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Chemical Proteomics Reveals the Target Landscape of Clinical Kinase Inhibitors

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Abstract

Protein kinases are key signaling molecules in the cell and catalyze the phosphate group transfer of ATP to their respective substrates. They have emerged as major drug target class, as they are often aberrant in diseases like cancer or inflammation. Small molecule kinase inhibitors provide one treatment option. Over 250 of these molecules are currently evaluated in clinical trials; over 30 have already been approved for human therapy. Most of them mimic ATP, thus targeting the ATP-binding pocket of kinases and preventing signal transduction via phosphate-transfer. As the ATP-binding pocket is quite conserved across the 518 protein kinases, many inhibitors can bind to more than one target protein. This polypharmacology can be advantageous and lead to the use of one drug in more than one indication. It might also lead to side effects and has influence on the mode of action of a drug. Therefore, thorough evaluation of the target space of a kinase inhibitor and its selectivity is necessary.

In this study, 242 small molecule inhibitors currently tested in clinical trials have been subjected to competitive Kinobeads profiling in a dose dependent manner followed by LC-MS/MS readout. The Kinobeads technology allows enrichment of over 300 kinases from cell or tissue lysate by binding of the ATP pocket. Competition with a free inhibitor for the ATP pocket leads to a dose dependent decrease of potential targets on the beads. Thus, drug-protein interaction profiles for each drug and all proteins bound by Kinobeads can be obtained. These allow determination of effective concentrations for half-maximal inhibition EC_{50} values and apparent binding constants. The selectivity of the investigated panel ranges from very selective drugs to unselective, multi-kinase inhibitors. Selective inhibition is desirable for unambiguous drug-protein interaction studies in basic research and thus, these inhibitors might be directly used as chemical probes, whereas more unselective inhibitors might be beneficial for the therapeutic success of a drug. Kinase inhibitor selectivity can be influenced by a number of factors. No major difference between inhibitors targeting the 'DFG-in' confirmation of kinases (type 1) and those binding the 'DFG-out' confirmation (type 2) inhibitors could be observed, whereas the allosteric (type 3) inhibitors could be confirmed as selective MAP2K1 and MAP2K2 drugs. Irreversible EGFR inhibitors were not necessarily more selective than their reversible counterparts. Reversible inhibitors can have no further additional targets; irreversible inhibitors are often more affine for EGFR than their off-targets. The observed additional off-targets of some drugs can explain adverse effects or generate rational hypotheses for drug repositioning. This work raises many opportunities for both cases. A set of six inhibitors was examined further for their additional NTRK1 inhibition in colon cancer and the approved MET-inhibitor Cabozantinib was evaluated in FLT3-ITD driven acute myeloid leukemia. Another important finding was the non-kinase off-target Ferrochelatase for 12% of all inhibitors. The protoporphyrin pocket of this enzyme could be determined as the binding site for some of these inhibitors and inhibition is likely linked to the side effect of photosensitivity in some patients receiving these inhibitors, as observed in Vemurafenib therapy.

To conclude, this work revealed the target landscape of small molecule inhibitors with the use of chemical proteomics. This thesis offers new insights into inhibitor selectivity and the druggable kinome. It can help to understand the molecular mode of actions of inhibitors and molecular reasons for side effects. Furthermore, new possibilities for drug repurposing as well as inhibitor design can be generated. It can be anticipated that this study will have impact on multiple disciplines like basic research, medicinal chemistry, cell biology, and medicine.

Zusammenfassung

Kinasen spielen eine wichtige Rolle in zellulären Signalübertragungswegen. Da sie in der Krankheitsentstehung von z.B. Krebs und Entzündung involviert sind, sind sie ein wichtiges Ziel von Medikamenten. Niedermolekulare Kinasehemmer, wie Imatinib oder Erlotinib, finden zunehmend mehr Anwendung in diesen Krankheiten. Weltweit werden über 250 dieser Moleküle in klinischen Versuchen getestet, über 30 davon sind für die Therapie zugelassen. Die Molekülstruktur ähnelt ATP, weswegen sie Kinasen in ihrer ATP-Bindetasche binden und die Signalübertragung von einer Phosphatgruppe auf ein Substrat blockieren. Die Struktur der ATP-Bindetasche ist innerhalb der Kinase-Familie konserviert, weshalb ein Molekül oft mehrere Zielproteine binden kann. Die daraus resultierende Polypharmakologie hat Vor- und Nachteile. Zum einen ermöglicht es die Anwendung des gleichen Medikamentes in einem anderen Krankheitsbild, zum anderen kann es zu Nebenwirkungen führen. Auch Schlussfolgerungen bezüglich der Wirkweise eines Moleküls oder eines Phänotyps nach gezielter Behandlung werden von der Selektivität der verwendeted Substanz beeinflusst. Um molekulare Ursachen zu erklären, ist eine genaue Kenntnis der Zielproteine eines Medikamentes nötig.

Mithilfe von Kinobeads und Massenspektrometrie wurden 242 niedermolekulare, klinische Kinaseinhibitoren dosisabhängig evaluiert. Kinobeads binden ebenfalls die ATP-Tasche von Kinasen, was in Kombination mit freien Inhibitormolekülen zu einer dosisabhängigen Abnahme von Zielproteinen führt. Damit kann die Wechselwirkung zwischen jedem Molekül und anderen Proteinen untersucht werden, sowie die effektive Konzentration bei halb-maximaler Inhibition (EC_{50}) und die Bindungskonstante für jedes Protein bestimmt werden. Es gibt viele unselektive Inhibitoren aber auch selektive Substanzen, welche gute Kandidaten für chemische Sonden darstellen. Zwischen Inhibitoren die vor allem die ‚DFG-in' Konformation der Kinase binden (Typ 1) und solcher, die die ‚DFG-out' Konformation blockieren (Typ 2) konnte kein signifikanter Unterschied bezüglich ihrer Selektivität beobachtet werden. Allosterische Typ 3 Inhibitoren jedoch konnten als sehr selektive MAP2K1 und MAP2K2 Inhibitoren bestätigt werden. Irreversible EGFR Inhibitoren waren nicht zwingend selektiver als reversible; einige reversible Inhibitoren binden nur EGFR, während hingegen die Affinität der irreversiblen für EGFR oftmals gegenüber andere Kinasen überwiegt.

Einige Moleküle zeigten zusätzliche Inhibition von NTRK1 und wurden daher in Hinsicht auf eine mögliche Wachstumsinhibition von NTRK1 abhängigen Darmkrebszellen näher untersucht. Des weiteren wird auf eine mögliche Indikation von Cabozantinib in FLT3-ITD mutierter, akuter myeloider Leukämie hingewiesen. Eine weitere Entdeckung dieser Arbeit war, dass 12% aller Kinaseinhibitoren an Ferrochelatase, ein Protein ohne Nukleotidbindungstasche, binden können. Die Protoporphyrinbindungstasche wurde als mögliche Bindestelle für einige dieser Inhibitoren identifiziert. Eine Hemmung von Ferrochelatase führt zu erhöhter Photosensitivität, die auch als Nebenwirkung in Patienten, zum Beispiel bei Gabe von Vemurafenib, detektiert wurde.

Zusammenfassend evaluiert diese Arbeit das Targetspektrum klinischer Kinaseinhibitoren und dient als eine Grundlage für neue Fragestellungen. Zudem kann diese Studie auch dazu beitragen, den molekularen Wirkmechanismus sowie Ursachen für Nebenwirkungen zu verstehen. Desweiteren können auf Basis dieser Arbeit neue Konzepte für die Repositionierung von Inhibitoren als auch für das Design neuer Moleküle generiert werden. Diese Informationen können nun sowohl in der Grundlagenforschung und Inhibitorentwicklung aber auch in der Medizin verwendet werden.

1 Introduction

1.1 Kinases as drug targets

1.1.1 The human kinome

All living organisms rely on manifold biological processes that are simultaneously or subsequently active. These processes are mainly carried out by proteins, which react to external and internal stimuli, catalyze cellular reactions and regulate development, growth, division, and death of a cell. One important group of proteins involved in these processes is protein kinase family. They are organized in signaling cascades and responsible for the transmission of external stimuli from the cell membrane anchored receptor tyrosine kinases to substrate kinases eventually resulting in gene transcription, cell division, cell growth or apoptosis (as exemplarily shown for EGFR, Figure 1a). This signal transmission is characterized by a tight interplay of phosphorylation and dephosphorylation events. Kinases catalyze the transfer of the γ-phosphate group of adenosine triphosphate (ATP) to a substrate, which activates this protein. The phosphate group can again be removed by phosphatases resulting in a reversible control mechanism (Figure 1b). This tightly controlled process allows the cell to alter enzyme activity and react to external and internal changes[1, 2]. Its discovery by Edmond Fischer and Edwin Krebs was awarded with the Nobel Prize in Physiology or Medicine.

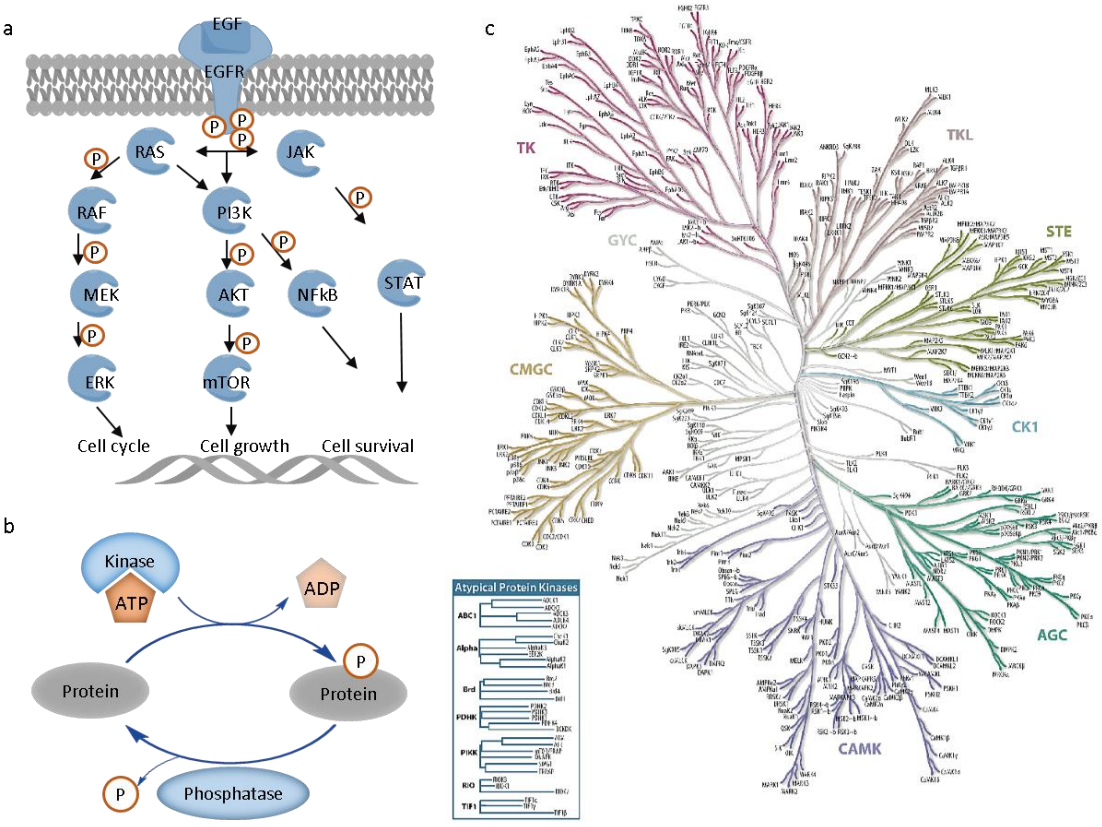

Figure 1: The human kinome. *a) Schematic of EGFR-signaling cascade. b) Schematic representation of protein phosphorylation by kinases and dephosphorylation by phosphatases. c) Phylogenetic tree of human kinases (Courtesy of Cell Signaling Technologies).*

To date, 518 protein kinases have been identified in man, also referred to as the human kinome. It represents almost 2% of the known genome and, therefore, is one of the largest gene families encoded by eukaryotes. Protein kinases can be classified according to the sequence of their catalytic center, the kinase domains. This is often represented as phylogenetic tree (Figure 1c). The major groups are tyrosine kinases (TK, divided into receptor TK and non-receptor TK), 'tyrosine kinase like' kinases (TKL), sterile 20 kinases (STE), AGC family containing PKA, PKG and PKC, calcium/calmodulin dependent kinases (CAMK), casein kinases 1 (CK1) and a group comprised of cyclin dependent kinases, MAP kinases, glycogen synthase kinase and casein kinase 2 (CMGC). Kinases that cannot be grouped into these major groups are attributed to the so-called 'other' group. The kinome is completed by atypical kinases that do not share sequence similarity with the kinases in the major groups but have shown protein kinase activity[3-6]. Besides tyrosine, most kinases phosphorylate a serine or threonine[4]. Roughly 10% of all kinases are non-catalytic (pseudo-kinases). They can still bind ATP and may execute important regulatory functions like scaffolding or allosteric regulation of kinases[7-9]. Apart from protein kinases, phosphatidylinositol kinases (PI) play central roles in signaling pathways. They phosphorylate lipids in the cell membrane, which then again recruit protein kinases.

1.1.2 Structural insights into the kinase domain

A kinase has to be structurally flexible allowing simultaneous binding of both protein substrate and ATP to exert its catalytic function. During the phosphate group transfer, the kinase domain changes its conformation, which has been investigated in crystallization studies by several groups (Figure 2)[10-12].

The protein kinase domain consists of two structurally and functionally different lobes, the N- and C- lobe. Both lobes are connected via a hinge region, which forms a cleft - the active site (Figure 2a, b). Here, ATP or other nucleotides can be bound, hydrolyzed and released again.
The motif between the first two β-strands of the N-lobe is called glycine-rich loop (Gly-rich loop). It can fold over ATP and positions the phosphate group for catalysis (see top left of Figure 2b). The AxK-motif in the β3-strand pairs the ATP-phosphates to the αC-helix. The N-terminus of the αC -helix is connected with the activation loop, therefore the positioning of the αC -helix is a crucial step for the activation of a kinase and its catalytic activity[13]. The C-lobe mainly consists of helices and acts as anchoring surface for protein or peptide substrates. Its beta-subdomain comprises motifs necessary for the catalytic transfer of the phosphate group from ATP to the substrate. This includes the magnesium-binding loop (at the beginning of the activation loop) containing the DFG-motif, a conserved sequence of aspartate (D), phenylalanine (F) and glycine (G). The aspartate (D) interacts with all three ATP phosphates by polar interactions or through coordinating atoms of magnesium. The phenylalanine (F) contacts the αC-helix and the conserved HRD-motif (histidine, arginine, aspartate) of the catalytic loop and thereby alters the position of the DFG-motif. The glycine (G) acts as 'bipositional switch' between inactive and active conformation and leads to proper positioning of the aspartate[11]. The activation loop is interrupted by the β9-strand, forming an antiparallel β-sheet with the β6-strand in the catalytic loop. Within inactive kinases, this formation is often disordered and therefore considered important for proper magnesium-binding loop configuration. Most protein kinases are activated by phosphorylation of a residue in the activation loop (P-loop), the most variable and diverse part of a kinase, leading to rearrangement of the loop and an increase in enzymatic activity.

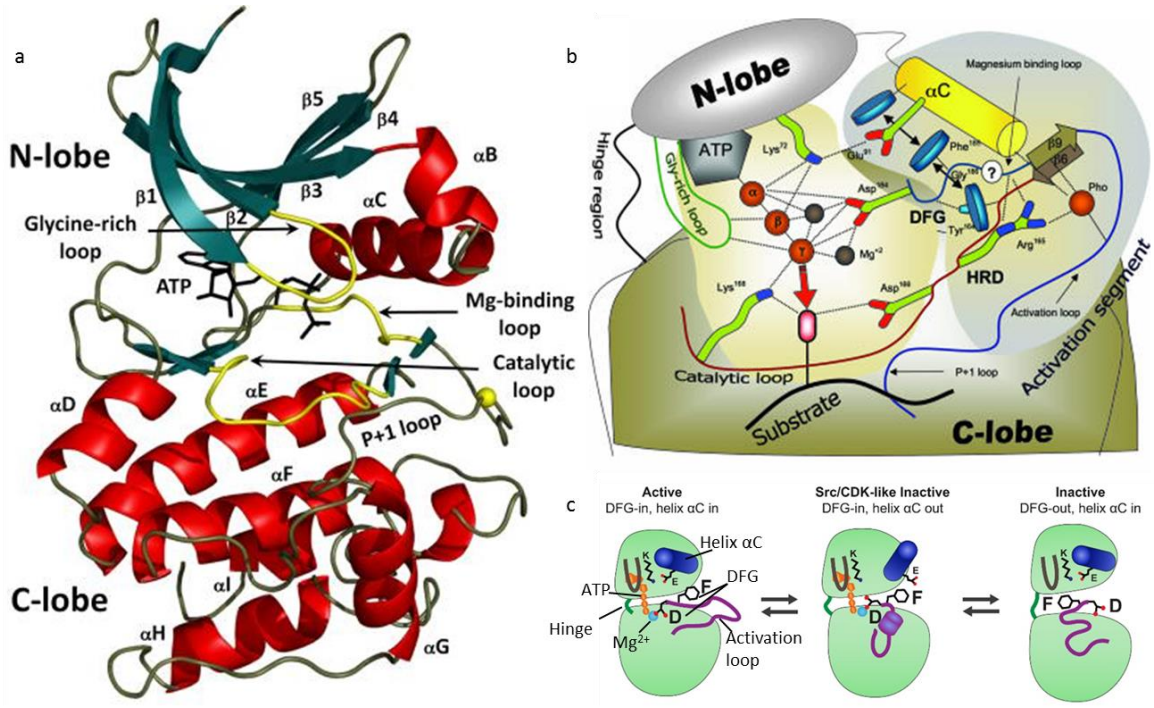

Figure 2: Structure of the kinase domain. *a) Ribbon view on the catalytic center of the kinase highlighting the relevant residues and structures (from [10]). b) Schematic of kinase domain with ATP in the active conformation (from [11]). c) Conformational changes in active or inactive conformation as well as the SRC/CDK like inactive DFG-in, helix αC out conformation (from [9]).*

In the active, so-called 'DFG-in' conformation, the D coordinates with magnesium and the F points in the direction of the αC-helix. In this position, the αC-helix can then interact with the ß3-strand. When D and F switch positions, the bulky phenyl ring of the F prevents binding of the nucleotide and induces conformational changes in the activation loop. This is referred to as 'DFG-out' or the inactive conformation. Besides the 'DFG-out' inactive conformation, another inactive conformation exists. Here, the αC-helix is turned away from the lysine, with the DFG-motif still pointing inwards. The activation loop then rearranges in a short helix. This inactive state has been discovered for SRC and CDKs and has been found for other kinases as well (Figure 2c)[7, 9, 14].

1.1.3 Kinases in disease

Miss-regulation of protein kinases has been found to be involved in various diseases like cancer, immunological, neurological, metabolic and infectious disorders because of their key function in cellular signaling[15, 16]. Pioneering studies by Collet and Erikson, who found that the rous sarcoma virus transforming factor was a protein kinase[17], as well as the discovery of tumor-promoting phorbol esters as activators of protein kinase C by Castagna and colleagues[18] implicated an important role of kinase activity in tumor biology. The role of kinases in the development of cancer is also reflected in the hallmarks of cancer. They are directly involved in sustained proliferative signaling, evasion of growth suppression, induction of angiogenesis as well as invasion and metastasis[19, 20]. Looking at the distribution of drugs across various protein families, protein kinases have become the second major target class after G-protein coupled receptors[21].

Kinase inhibition directly interferes with the signaling cascade and, thus, can lead to a real physiological response. Targeting kinase deregulation in cancer can be divided into three groups depending on their involvement in cellular pathways. In the first group, the kinases have undergone genetic mutation or translocation and are therefore unaffected by normal cellular regulatory

mechanisms. Often, they are constitutively active, which makes them indispensable for the survival and proliferation of a cell. This so-called oncogene addiction makes the cancer susceptible for appropriate kinase inhibitors[22, 23]. Inhibition of the mutated kinase has direct impact on tumor survival. Well-known examples for this are BCR-ABL in chronic myeloid leukemia (CML)[24], EGFR and/or ALK mutations in lung cancer[25, 26], BRAF(V600E) in malignant melanoma[27], or PIK3CA in various cancers[28]. These mutations can be easily identified by DNA sequencing[29] and represent addressable targets as inhibition prevents oncogenic signaling[22, 23].

The next group consists of kinases, which are essential for cell survival and/or proliferation. Usually, these kinases are downstream of the oncogenic kinases mentioned before. Examples here are MEK1/2 (MAP2K1, MAP2K2), mTOR, RPS6K, CDKs, Aurora kinases or PLK. Inhibition of these kinases is synthetically lethal to the tumor in combination with a cancer-driving mutation[30].

The last group of kinases is relevant for tumor formation and interaction of cancer cells with the human host. Examples are VEGFR, FGFR or NTRK2. They can promote vessel growth towards the tumor[31] and are required for metastasis development[32]. Targeting the two latter groups interferes with healthy cell signaling and has to be carefully evaluated in the specific disease background[33].

1.2 Small molecule kinase inhibitors

As outlined above, kinases have emerged as interesting targets to tackle diseases dependent on the function of these proteins. In light of personalized medicine, specific targeting of kinases has moved in the focus of research supporting conventional chemotherapy[34]. The arsenal of molecular targeting techniques comprises monoclonal antibodies, small molecule inhibitors, peptide mimetics or gene therapy with antisense oligonucleotides[35]. Antibodies interact with cancer-specific proteins expressed on the cell surface, interfere with ligand-receptor interactions and activate the immune system. Targets of antibodies currently approved include HER2, VEGFR, TNFα and antigens (CD20, CD25, CD33, CD52). Whereas antibodies are large biomolecules (around 150 kDa) and are administered intravenously, small molecule inhibitors are small synthetic chemicals (around 500 Da) and can be taken orally. The latter can not only target proteins on the cell surface but also interact with kinases inside the cell and further downstream of signaling cascades by interrupting signal transduction[36]. The following work will focus on small molecule kinase inhibitors, which will therefore be described in more detail.

1.2.1 Small molecule kinase inhibitors in clinical trials

The first medicinal chemistry efforts in the development of small molecule inhibitors were based on lead compounds like the natural molecule Staurosporine and synthetic tyrphostins[37, 38]. Fasudil, targeting Rho-kinase, was the first inhibitor approved in Japan in 1995 for treatment of cerebral vasospasm[39]. Four years later, the allosteric inhibitor Rapamycin, was approved for immunosuppression after organ transplants[40]. It targets the protein kinase mTOR (mammalian target of Rapamycin), which was discovered in 1993[41] and is a component of the PI3K/mTOR pathway resulting in protein translation.

In 2001, Imatinib (Gleevec, STI-571) was approved for inhibition of BCR-ABL positive chronic myeloid leukemia (CML). It was the first rational, target-based kinase inhibitor and has been very successful since then[42]. Besides BCR-ABL, also KIT and PDGFR are inhibited by the drug[43]. This polypharmacology of Imatinib led to application in gastro-intestinal stromal tumors (GIST), hyper-eosinophilic syndrome (HES) and other indications[44]. CML and GIST have been fatal diagnoses before the use of Imatinib, but application of the drug turned them into manageable diseases. This success encouraged pharmaceutical companies to invest more into the design of protein and lipid kinase inhibitors in light of targeted therapies[45, 46]. Around 50-70% of today's cancer drug discovery efforts concentrate on protein kinase inhibitors[47]. The timeline in Figure 3 showing the FDA approval of small molecule kinase inhibitors is representative for the clinical success of these molecules[48]. In 2015, another three small molecule inhibitors received FDA approval, namely Alectinib, Osimertinib and Cobimetinib[49]. Currently, 37 inhibitors are approved worldwide; Imatinib, Nilotinib, Dasatinib, Bosutinib and Ponatinib are indicated for CML, but only Ponatinib can target the T315I Imatinib resistant gatekeeper mutation[50]. Lapatinib and Palbociclib are used for the treatment of HER2 positive breast cancer, Ibrutinib and Idelalisib for various types of blood cancers. Gefitinib, Erlotinib, Icotinib, Afatinib and Osimertinib are applied in non-small cell lung cancer (NSCLC) with activating EGFR mutations, whereas ALK-translocations in NSCLC are treated with Ceritinib, Crizotinib or Alectinib. Sorafenib, Sunitinib, Everolimus, Temsirolimus, Axitinib and Pazopanib are used in renal cell cancer. Sunitinib and Imatinib as well as Regorafenib can also be applied in GIST.

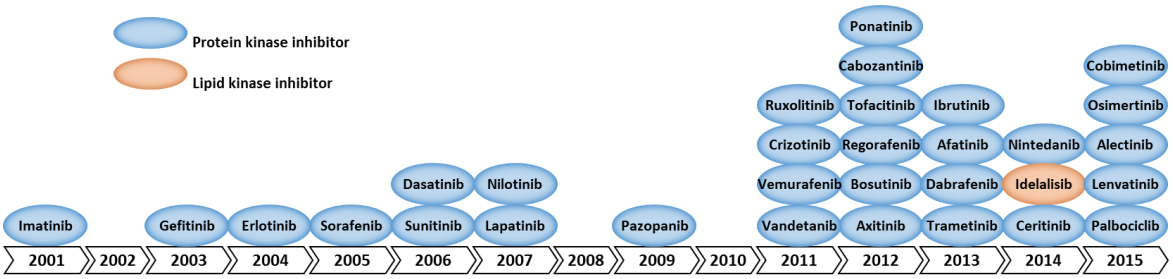

Figure 3: Approved small molecule inhibitors. *Timeline for FDA approval of small molecule inhibitors (adapted from[48]). The increasing number of approved molecules in recent years indicates clinical success of these molecules.*

Cabozantinib, Lenvatinib and Vandetanib treat medullary thyroid carcinoma. BRAF(V600E) mutated metastatic melanoma can be managed with either Vemurafenib or Dabrafenib alone or in combination with the MEK-inhibitors Trametinib or Cobimetinib. Besides oncology, kinase inhibitors can also be applied in other diseases; Tofacitinib is approved for rheumatoid arthritis, Ruxolitinib for myeloid fibrosis, Rapamycin as immunosuppressive in organ transplants, Fasudil for cerebral vasospasm and Nintedanib for idiopathic pulmonary fibrosis. Masitinib is a KIT inhibitor with orphan drug status in Europe for pancreatic cancer in human and mast-cell tumors in dogs[48, 49]. Additionally, more than 300 small molecules are tested in clinical trials for various indications nowadays, ranging from oncology to transplantation or infectious diseases (www.clinicaltrials.gov)[47, 49, 51].

1.2.2 Kinase binding of small molecule inhibitors

With a few exceptions - MEK-inhibitors and analogues of Rapamycin (rapalogs) - most of the inhibitors described above target the structurally conserved ATP-binding pocket. They interact with amino acids in the hinge region, simulating the hydrogen bond, which is formed by the adenine ring upon ATP binding[52, 53]. Small molecule kinase inhibitors can be categorized akin to their mode of binding to their kinase target (Figure 4a, reviewed in[48, 49, 54]). The following classification scheme is based on Roskoski[55]. Kinase inhibitors binding to the active conformation of a kinase are so-called type 1 inhibitors. In the active conformation, the D of the DFG-motif points into the ATP binding pocket (‘DFG-in’). Selectivity is achieved by variation of shape and size of the inhibitor and interactions with the gatekeeper residue at the entrance of the ATP-binding pocket as well as non-conserved residues at the solvent exposed sites (Erlotinib, Figure 4b)[56]. A subtype are the type 1.5 inhibitors, the kinase is also fixed in a ‘DFG-in’ position but the αC-helix is pointing outwards (C-helix-out). This is the case for BRAF bound by Vemurafenib and has also been found in other kinases (Vemurafenib, Figure 4b)[7, 14]. Inhibitors locking the kinase in its inactive state, with the DFG-motif pointing outwards, are termed type 2 inhibitors. The ‘DFG-out’ conformation exposes a hydrophobic pocket next to the ATP-binding site, which can be targeted by these type 2 molecules (Sorafenib, Figure 4b). Furthermore, C-helix, activation and P-loop are also more flexible in the inactive conformation, which therefore can vary between kinases. This is why type 2 inhibitors seem to be more selective for a specific kinase than the type 1 inhibitors binding the more conserved active conformation[7, 57].

Other molecules bind the kinase non-ATP competitively on an allosteric site. Inhibitors in clinical trials of the type 3 binding mode are mainly MEK1/2 inhibitors. These drugs exploit a unique binding pocket adjacent to the ATP-binding site, only present in these proteins. Inhibitor binding leads to

conformational changes and blocks the kinase in its inactive state (i.e. TAK-733, Figure 4b)[58]. Inhibitors binding to the substrate-binding site or other motifs along the kinase are called type 4 inhibitors (MK-2206, in Figure 4b) or type 5 inhibitors if exploiting two different binding sites along the kinase.

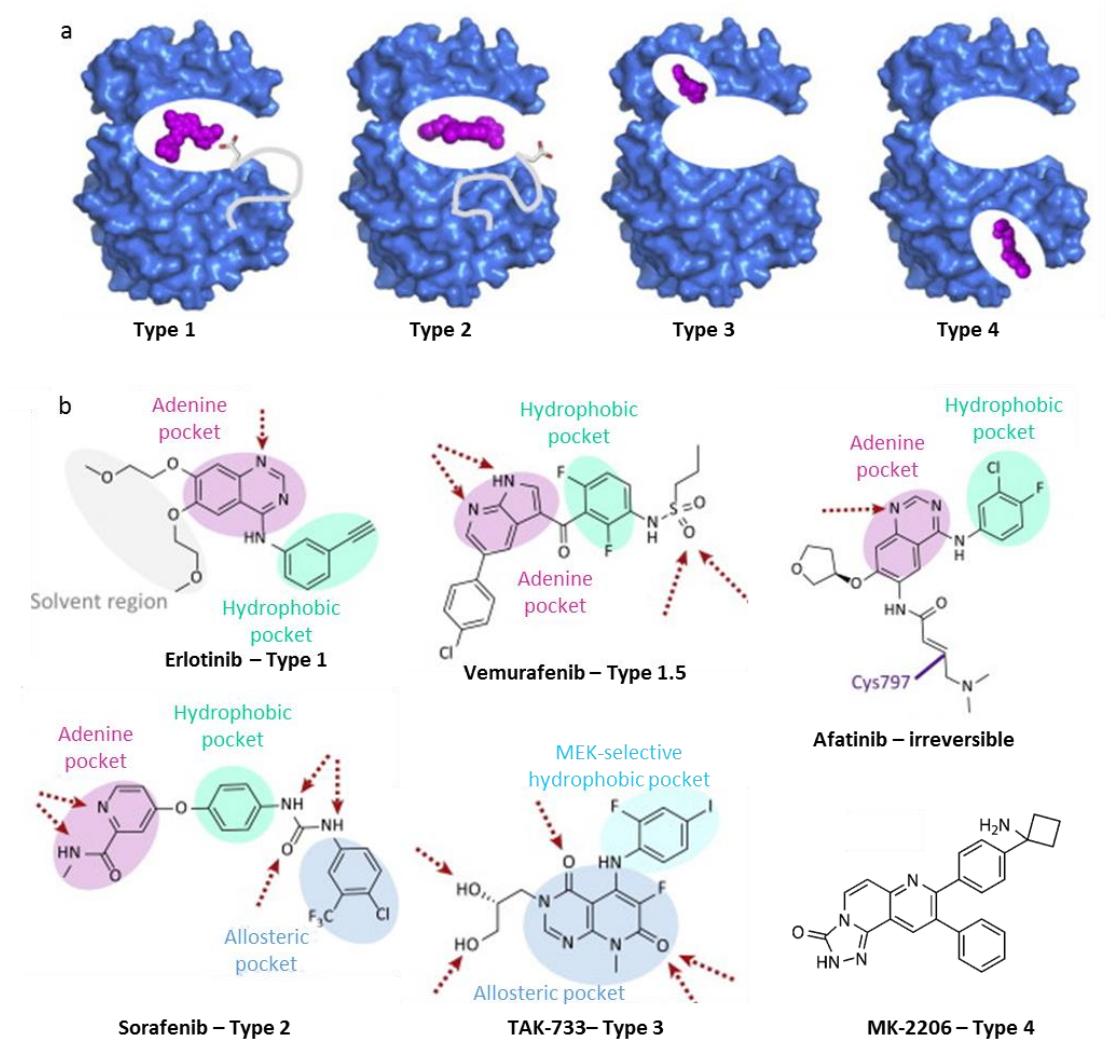

Figure 4: Kinase inhibitor binding modes. *a) Overview of possible small molecule binding types to kinases (modified from). b) Example kinase inhibitors for different binding modes. Chemical moieties targeting the adenine, hydrophobic, allosteric or MEK-selective pocket are highlighted. Arrows indicate direct kinase-drug interactions. Erlotinib is an example for type 1 EGFR binding; Vemurafenib inhibits BRAF in DGF-in helix αC out conformation. Afatinib irreversibly interacts with Cys797 of EGFR after Michael-addition with the double bound. Sorafenib binds to VEGFR in type 2 binding mode whereas TAK-733 exploits the MEK selective pocket for binding. MK-2206 is an example for an allosteric inhibitor targeting the pleckstrin homolog domain (modified after[48]).*

Some inhibitors (*e.g.* Afatinib, Ibrutinib, Osimertinib) can bind to their target covalently (sometimes referred to as type 6 inhibitors). They bind to a lysine or cysteine, either in the ATP binding pocket or in close proximity to it (Afatinib, Figure 4b). Most irreversible inhibitors in clinical evaluation today are targeting a cysteine in the active center of EGFR and BTK[59]. They feature a Michael acceptor site in their structure. Ibrutinib, Afatinib and Osimertinib are approved by the FDA.

1.2.3 Evaluating selectivity and affinity of small molecules

As the ATP-binding pocket is structurally conserved, these 'ATP-mimetics' potentially interact with more than one kinase. This promiscuity might lead to toxicity[60] or can be used for repositioning of a drug in another disease setting, pioneered by the use of Imatinib for GIST (see above). The hitherto known target landscape of small molecule kinase inhibitors revealed that only about 80 protein and lipid kinases can be successfully targeted[61]. These inhibitors are mainly indicated for oncology and there are several inhibitors against one target in one indication[54].

The selectivity and efficacy of drugs is often influenced by their binding affinity towards a target. Common measures for ligand-receptor interactions include the half maximal inhibitory concentration (IC_{50}), the half maximal effective concentration (EC_{50}), the inhibition constant (K_i) and the equilibrium dissociation constant (K_d). The IC_{50} value describes the concentration that leads to 50% inhibition and is dependent on factors like substrate concentration, target accessibility, duration of incubation, or cell permeability[62]. EC_{50} describes the drug concentration needed to achieve 50% of the maximum effect. For inhibitors, this value is halfway between the baseline and maximum of a measured effect. Cheng and Prusoff introduced the inhibition constant (K_i), which describes the inhibitor concentration at 50% inhibition[63]. This constant is an absolute value for any inhibitor-protein combination, whereas the IC_{50} can vary between experiments. K_i can be calculated as shown in equation (1). [S] refers to the concentration of substrate and the Michaelis-Menten constant K_m is the substrate concentration (for kinase inhibitors ATP) at which velocity of the reaction is half-maximal.

$$K_i = \frac{IC_{50}}{1 + \frac{[S]}{K_m}} \quad (1)$$

For competitive inhibitors, K_i equals K_d of the kinase-inhibitor complex. However, affinity is not the only parameter for assessing effectiveness. Another important parameter is residence time, the time how long a receptor-ligand complex exists. It is affected by the association (k_{on}) and dissociation (k_{off}) rates. Especially the k_{off} rate influences this time. In closed systems (used in the laboratory to investigate drug-target interactions), affinity is determined in equilibrium. Here, k_{on} can often be neglected and thus, K_d correlates strongly with k_{off} (with $K_d = k_{on}/k_{off}$). In open systems like the human body, the pharmacodynamics of a drug (efficacy and duration of efficacy) are subject to drug distribution, drug absorption and metabolism in the body (pharmacokinetics). Here, the actual residence time of a drug-protein complex is an important factor to be considered. Moreover, K_d and residence time also influence drug selectivity and thus off-target toxicity. Higher affinity of a drug towards its intended target and longer residence time at this target result in better safety characteristics as less drug can be used, whereas long residence time at an off-target might lead to toxicity[64, 65]. Upon irreversible binding, residence time is very high. In this binding mode, inhibitor potency is dependent on reversible binding first (K_i) and then on the efficiency of the covalent bond formation (K_{inact}, rate of inactivation). The IC_{50} of irreversible inhibitors decreases over time, because maximal inhibition might only be reached after longer incubation time[66]. The targeted proteins need to be expressed *de novo* in order to perform their function again. Hence, also lower amounts of drug are sufficient to achieve a pharmacological effect[67].

1.3 Chemical proteomics for studying drug-protein interactions

As outlined above, small molecule kinase inhibitor targeting the conserved ATP-binding site can be quite unselective. Determining the full target spectrum of a kinase inhibitor still remains a challenge[33, 68]. Nevertheless, this information is crucial to understand the molecular mechanisms for tumor response as well as potential toxicities upon drug treatment. Various methods have been developed over the years to address this issue. Traditional methods employ *in vitro* screening panels that contain large numbers of recombinant kinases. Here, kinase inhibitors are tested for inhibition of activity by measuring the transfer of a radioactively labeled phosphate group of ATP to a substrate. This has successfully been performed with smaller numbers of up to 65 inhibitors against 80 kinases[69-71]. Anastassiadis *et al.* expanded it to 178 kinase inhibitors against 300 kinases[72] and recently, 183 inhibitors were tested against mutant kinase variants applying the same technology[73]. Other groups use DNA-tagged recombinant kinases to assess binding of free inhibitors in competition with an immobilized ligand. Binding affinity is then determined by a qPCR readout[74-76]. Nowadays, new compounds are often evaluated in recombinant assays against selected kinases in the intended target's family.

Recombinant kinase assays are quite powerful and provide good insight into the target spectrum of a drug, but do not take all molecular characteristics of endogenous target proteins like posttranslational modifications, cofactors, or interaction partners in the cell into account. Most drugs target proteins, which are part of complex networks and pathways in a cellular environment and may change depending on their physiological or functional context. Therefore, it seems natural to investigate the effect of a drug on the whole proteome. Proteomics has developed several methods during the last years to evaluate the target spectrum of a drug of interest[77].

1.3.1 Target deconvolution on sub-proteome level

Chemical proteomic technologies often employ protein affinity chromatography approaches with immobilized small molecules, like kinase inhibitors, followed by protein identification via mass spectrometry[78]. Classical methods directly immobilize the compound of interest to beads. Therefore, the molecule often needs to be modified to facilitate covalent linking to chromatography resin. Simultaneously, protein binding capabilities should not be affected. Inhibitor-protein binding sites might be deduced from available co-crystal structures or inferred from structure-activity relationship data[78-80]. First efforts in chemical proteomics at the beginning of the millennium identified RPS6KA3 as target of bisindolylmaleimide[81] and investigated targets of CDK inhibitors[82, 83]. Back then, target identification was biased towards highly abundant cellular kinases, but could be improved by altering biochemical conditions during enrichment and elution[79, 84]. By using excess of free inhibitor, the targets of the compound are competed from the beads, whereas background binding stays the same. This approach reduces false positive identifications (Figure 5a).

Cravatt and colleagues developed the so-called activity-based protein profiling (ABPP) approach. Here, the compound is modified as reactive probe, which covalently attaches to the active site of a target protein. The covalent interaction occurs with suitable amino acids inside or in close proximity of the catalytic/reactive site. These molecules feature chemical moieties like biotin for streptavidin enrichment, or can be linked to fluorescent tags for monitoring proteins in vitro or fluorescent gels (Figure 5b). This technology is often applied for serine hydrolases but has also been used to study HDACs and kinases[85-87]. The technology can also be used for competitive profiling of an inhibitor of choice. The active site of the enzyme is then blocked and cannot be assessed by the probe[88].

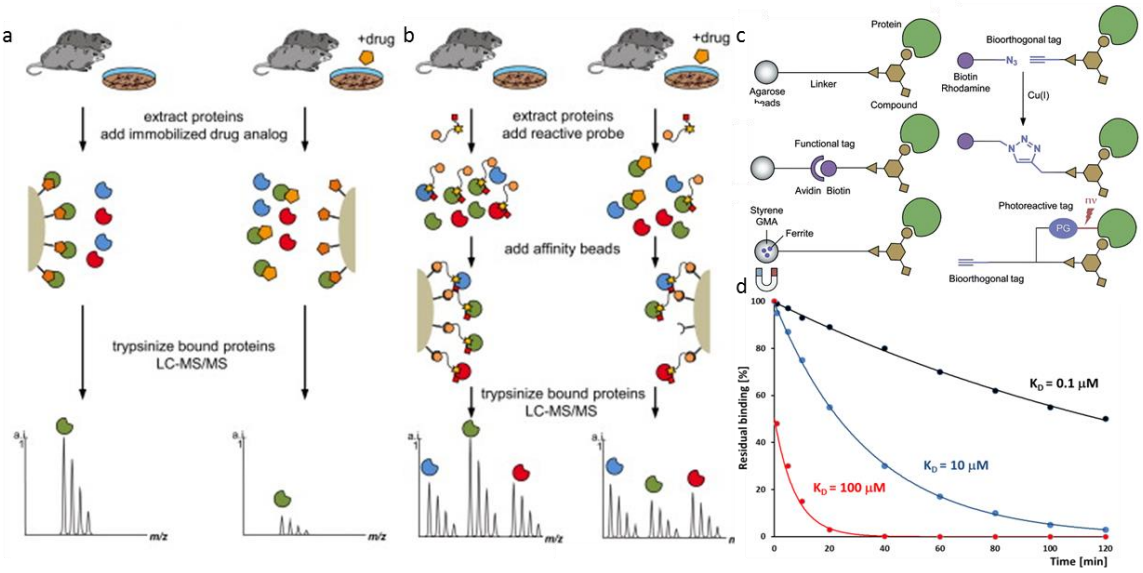

Figure 5: Chemical Proteomic strategies. *a) Affinity-based profiling: the compound of interest or a functional derivative is immobilized. Subsequent incubation with cell or tissue lysate enriches for target proteins, which are then identified by mass spectrometry. Competition with free inhibitor prevents target proteins from binding. b) Activity-based profiling: a reactive probe binds the active site of the enzyme, followed by affinity enrichment and MS analysis. c) Strategies for affinity pulldowns. d) Influence of affinity and time on residual binding (adapted from [77, 89, 90].*

Various ways exist to immobilize the compound on a solid support like agarose beads or magnetic particles. Besides the use of a direct linker, the compound can be modified with an alkyne handle and then be 'clicked' to an azide bearing support. Trifunctional probes not only reversibly interact with the target but are also equipped with a reactive group that stabilizes this interaction after photo activation, for instance. A common sorting function (*e.g.* biotin or alkyne handle) then allows affinity enrichment of the drug target complex (Figure 5c)[77, 89].
In each of these methods, the compound of interest needs to be chemically modified to a functionalized analog, to be immobilized on beads or to covalently bind to the target. This might hamper target identification as the compound doesn't reflect the true inhibitor anymore and its synthesis is a time consuming step.

In 'binding mode centric' profiling approaches, the immobilized probe or a mixture of probes is constructed in a way that a particular protein target class (kinases) can be enriched from a lysate[77]. This requires a conserved and druggable binding site in the target class. Besides enriching subproteomes for closer and more complete coverage, this approach can also be used for selectivity profiling of a compound of interest. The compound of interest competes with the affinity matrix for the active site of the enzymes present in the lysate. If the protein is a target of the particular inhibitor, its binding site is blocked for enrichment by the beads. Bead-bound proteins are eluted and can subsequently be analyzed by immunodetection (if looking for known targets) or mass spectrometry (unbiased target identification). Target proteins should then show reduced amounts of signal intensity. Competition with a range of inhibitor concentrations leads to a dose dependent decrease of target proteins enabling the determination of affinity values (EC_{50}) of each protein in the lysate towards the free drug. This approach combines the identification of off-targets and allows ranking of targets according to their affinity. In 2007, Bantscheff and coworkers introduced the concept of Kinobeads[91] that represent such an affinity matrix for kinases. In the original version,

seven unselective small molecule inhibitors were immobilized on Sepharose beads and mixed, leading to the identification of novel targets for the small molecule inhibitors Imatinib, Dasatinib and Bosutinib. Médard *et al.* optimized these Kinobeads to an improved version, featuring only five immobilized inhibitors with greater kinase coverage by using a mixture of four different cancer cell lines[92]. Other groups employed similar strategies to profile kinases in breast cancer and leukemia[93, 94].

Kinases and nucleotide binding proteins can also be enriched using modified ATP or ADP. In the KiNativ technology, biotinylated acyl phosphates of ATP and ADP react irreversibly with conserved lysine residues in the ATP-binding site, thus, labeling the protein with biotin. Upon prior inhibitor treatment, the reactive ATP-probe cannot bind anymore. After digestion and streptavidin enrichment, mass spectrometry readout allows for identification and quantification of target proteins[95, 96]. The use of only one peptide per protein (containing the active site labeled residue) for identification and quantification reduces sample complexity but can lead to less accurate measurements. Compared to the Kinobeads technology, these ATP-probes generally enrich more nucleotide binding proteins[97].

These so-called chemical proteomic methods are powerful, as they investigate the target proteins and the inhibitors close to physiological conditions; the proteins are at endogenous expression levels, contain their natural modification status and can be investigated in a cell line or tissue lysate of interest. Combined with mass spectrometry, not only kinases are investigated as targets but the inhibitor is also profiled against various other proteins binding to ATP-like molecules. These approaches identify direct targets of bioactive molecules. Furthermore, selective targeting of protein complexes is possible, providing insight into regulatory mechanisms of protein-protein interactions[98].

Using either of such assays, many novel and sometimes quite surprising protein-drug interactions have been identified in recent years. To name a few, FLT3 or MAP4K4 appear to be frequently hit by kinase inhibitors[72], DDR1 was discovered as a new target for Imatinib and other BCR-ABL inhibitors[91, 99] and Pazopanib as well as Ponatinib were identified as inhibitors of cellular necroptosis[100]. Interestingly, enantiomers of kinase inhibitors can also have different targets. Huber and co-workers have found that the (S)-enantiomer of the approved MET/ALK inhibitor Crizotinib selectively inhibits the 7,8-dihydro-8-oxoguanine triphosphatase MTH1 while the actual (R)-enantiomer drug does not[101].

1.3.2 Parameters influencing competition binding assays

The success of competition binding assays with reversible inhibitors is dependent on several biochemical factors: (i) the affinity of the target protein to the immobilized probe (Figure 5d); (ii) the concentration of the probe; (iii) the concentration of the target protein (*e.g.* kinase) or its expression/abundance in the tissue/cell line used; (iv) the concentration and affinity of the free compound; (v) the k_{off}-rate of the enriched protein from the beads. The first three factors are different from experiment to experiment and vary between proteins, ligands, and lysates. Diminishing the influence of (i)-(iii) in a competition experiment results in IC_{50} values that are close to 'true' dissociation constants (K_d).

$$K_d = \frac{K_{d(probe)}}{K_{d(probe)} + [probe]}\ x\ IC_{50} \qquad (2)$$

with $[probe] \ll K_{d(probe)}$

$$K_d = IC_{50} \tag{3}$$

Equation (3) shows that by using concentrations of the immobilized compounds ([probe]) below the affinity of a protein towards the immobilized probe ($K_{d(probe)}$), the binding constant K_d of protein and free compound are independent of $K_{d(probe)}$[76, 102].

In competition experiments, depletion of a protein from the lysate is defined as the fraction of this protein bound to the immobilized probe. It influences the correct determination of an EC_{50} value and shifts it to higher values. Depletion can be avoided using nanomolar concentrations of immobilized compounds. Moreover, large amounts of lysate reduce the influence of individual protein expression levels. Immobilized compounds with low nanomolar to picomolar affinity towards their targets also result in depletion and underestimation of EC_{50}s. If the depletion of protein is higher than 40%, competition experiments will not be possible anymore[91]. Contrary to assuming that there should be no depletion in the case of unselective Kinobead-probes, experimental evidence shows otherwise. To correct for this, Sharma *et al.* introduced a correction factor[103] which was slightly modified for Kinobeads. It allows the correction of the obtained EC_{50} values by multiplication with the correction factor *r* to an apparent binding constant K_d^{app}. Therefore, two subsequent pulldowns of the vehicle treated lysate are performed. For each protein, a depletion factor can be calculated by determining the ratio (*r*) of the MS1 intensity in the second pulldown divided by the MS1 intensity in the first enrichment step[97].

$$\mathrm{r} = \frac{incubation\ 2}{incubation\ 1} = \frac{f(T - f(T))}{f(T)} = \frac{intensity\ (PD2)}{intensity\ (PD1)} \tag{4}$$

$$K_d(probe) = \frac{[probe] * [T]}{[probe * T]} = [probe] * \frac{r}{1-r} \tag{5}$$

$$K_d(\mathrm{inhibitor}) = \frac{K_{d(probe)}}{K_{d(probe)} + [probe]}\ x\ EC_{50} \tag{6}$$

with (5) in (6):

$$K_d(\mathrm{inhibitor}) = \frac{[probe] * \frac{r}{1-r}}{[probe] * \frac{r}{1-r} + [probe]}\ x\ EC_{50} = \frac{\frac{r}{1-r}}{\frac{r}{1-r} + 1}\ x\ EC_{50}\ = r *\ EC_{50} \tag{7}$$

with T being the total amount of a target and f being the fraction of captured target that remains constant over subsequent pulldowns.

Some studies characterized interactions with affinities of up to 40 mM[104], but generally nanomolar potencies for free compounds are needed for target identification. Moreover, washing of the beads after enrichment and the time needed for the whole affinity purification process limit the recovery of certain proteins (Figure 5d). Improved sensitivity and accuracy of mass spectrometers also help the detection of low abundant proteins and more robust quantification leads to better determination of binding constants[77].

1.3.3 Target deconvolution on proteome wide level

The methods described above are still limited to sub-proteomes and rely on competition of the compound at the same site as the immobilized compounds. This can lead to an incomplete view on the target spectrum of a drug. Recent advances have enabled target deconvolution on a proteome-wide level. They make use of differences in biophysical properties upon drug binding. In drug affinity responsive target stability (DARTS) measurements, target identification is based on the idea that a protein has reduced protease digestion susceptibility upon drug binding[105]. Protein oxidation as a function of denaturation by hydrogen peroxide reduces thermodynamic stability as well and can be assessed by SPROX (stability of proteins from rates of oxidation)[106]. A protein's thermal stability changes upon addition of a ligand and has been used extensively in drug discovery programs[107]. Here, purified proteins are heated with increasing temperatures in the presence or absence of a ligand, being it a small molecule, DNA or RNA molecule or even another protein. Upon heat denaturation, the protein unfolds and exposes its hydrophobic parts. This can be measured with the use of a fluorescent dye; the difference in melting is then dependent on the ligand's affinity towards the protein[108]. Martinez-Molina *et al.* discovered that this principle can also be used in living cells or whole cell lysate without a dye and named it cellular thermal shift assay (CETSA). Upon drug-protein interaction, a target protein is stabilized and, thus, precipitates later compared to vehicle control treated samples. However, they only showed this for target proteins of interest, followed by western blot readout[109]. Combination of this method with multiplexed quantitative mass spectrometry allows investigation of protein thermal stability on a proteome wide level[110]. This allows the determination of melting temperatures for every protein identified in the sample. Furthermore, target engagement can be assessed in a cellular context and enables unbiased target and off-target identification. A variant of the CETSA is the isothermal dose response (ITDR). Here, living cells or lysate are heated to the same temperature (the half-melting temperature) but are treated with increasing concentrations of inhibitor. The protein's stability will increase with increasing compound concentrations enabling the determination of affinity values for half maximal stabilization[109].

It has to be noted that most of the chemoproteomic approaches mentioned above measure binding and, therefore, only generate target hypotheses. Such identified targets then require further validation with purified proteins or cell culture models to investigate the influence on a desired phenotype[77].

1.4 Mass spectrometry based proteomics

Research in the twenty first century is shifting towards integrative approaches investigating the whole interaction network of biomolecules and biochemical reactions instead of focusing on genes or proteins in isolation. These systems biology approaches aim to understand the tight interaction of genes and proteins in complex biological systems at the molecular level. 'Omic'-techniques, especially genomics, transcriptomics, proteomics and metabolomics, are needed for achieving this holistic view of functional living systems[111]. Whereas genomics and transcriptomics analyze the DNA and RNA content of a cell, proteomics investigates the complement of proteins including abundance, structure, function, modifications, interactions, and influences of the environment. All 'omic'-techniques are in need of high throughput analytical tools, which can identify and measure the respective parts of the system. Genomics has benefited significantly from the development of gene sequencing. The first human genome has been sequenced in 2001 and contains 20.000-25.000 genes[112, 113]. With technical improvement, it is nowadays possible to analyze a complete genome in less than a day. Genome sequencing has already found its way into medicine. Therefore, sequencing of a patient's cancer genome can improve possibilities for personalized therapy based on individual alterations on the gene level.

Contrary to static genomes, proteomes are dynamic, change during the lifetime of a cell and react to external influences. Alternative splice events and posttranslational modifications lead to various protein-isoforms and proteoforms. This increases the complexity of the proteome. As external influences (*e.g.* drugs) mainly act on the proteome, proteomics completes the investigation of organisms on a system level. Advances in mass spectrometry based techniques have contributed to a better and thorough understanding of the proteome[114, 115]. This led to the first draft of the human proteome in 2014[116, 117].

1.4.1 Bottom up proteomics workflow

Proteomic questions can be answered using different workflows. The three technological setups used nowadays are called top-down, middle-down and bottom-up. The first one deals with the analysis of purified, intact proteins by mass spectrometry (MS), whereas the second one investigates large polypeptides like histone variants[118-120]. Bottom up or shotgun proteomics is the most widely distributed approach, offering targeted approaches, data independent (DIA) and data dependent approaches (DDA). Shotgun approaches are less time consuming and therefore suited for comprehensive proteomic analysis of large-scale studies. Figure 6 shows a standard shotgun bottom up proteomics workflow as used in this project.

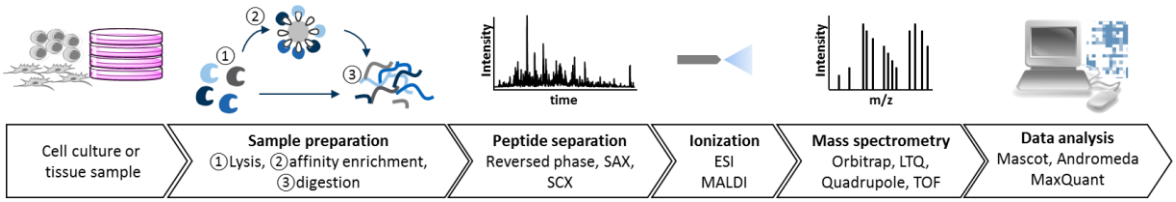

Figure 6: Standard bottom-up proteomics workflow *(adapted from [121]). Proteins are extracted from cell culture or tissue samples, subjected to affinity enrichments (if applied) and digested to peptides. Peptides are then separated, ionized and analyzed in the mass spectrometer. Data analysis identifies and quantifies peptides and proteins present in the sample.*

Proteomes derived from cell cultures or tissue samples are first lysed and homogenized. The choice of lysis buffer substances and addition of detergents influences the lysis efficiency as well as the state of proteins. Subsequent affinity enrichments like Kinobead-pulldowns require functional proteins. Cells should be lysed under 'essentially physiological conditions' conserving the native three-dimensional protein structure, as well as posttranslational modifications and stable protein-complexes[122]. (Enriched) proteins are then digested to peptides by proteases. Samples can be digested in solution, with the help of membrane filters[123] or out of SDS-gels[124, 125], with the latter two methods allowing the use of detergents like SDS. The most widely used protease in proteomics is trypsin because of high specificity and the generation of short peptides (7-20 amino acids in length) with the basic amino acids Arginine or Lysine at the C-terminus facilitating downstream analysis[121]. Recently, it has been shown that the use of alternative proteases like chemotrypsin, LysC, LysN, AspN, GluC or ArgC enables better sequence coverage of the proteome[126-128]. Digestion of over 10,000 proteins present in bottom-up experiments results in thousands of peptides challenging thorough analysis of proteomes. Chromatographic peptide separation prior to mass spectrometric analysis reduces sample complexity and, thus, helps to improve proteome coverage by permitting better sequence coverage and higher peak capacity. Common setups separate complex peptide mixtures by ion-pairing reversed phase liquid chromatography (LC). The separation power of this type of chromatography is generated by interactions of nonpolar side chains of peptides with the nonpolar stationary phase (C18). Upon elution with increasing concentrations of organic solvent (*e.g.* acetonitrile), peptides are separated according to hydrophobicity, influenced by the size and polarity of peptides[129-131]. With coupling of the LC to the MS (online-coupling), peptides are directly ionized after chromatography and enter the mass spectrometer subsequently[132]. Increasing the length of the elution gradient promotes deeper coverage of the analyzed proteome. A robust LC-MS setup also facilitates better quantification especially for the MS1 based methods (see below), where retention time stability and narrow peaks lead to less signal-to-noise ratios and better comparison between runs[133]. For deep proteome coverage, two-dimensional separation techniques are often used. The first dimension, often offline, should apply an orthogonal separation principle to the second ion pairing reversed phase chromatography. Common techniques include strong anion exchange chromatography (SAX)[131, 134] or strong cation exchange chromatography (SCX)[135] and separate peptides according to their charge. However, a combination of reversed phase and high pH elution followed by reversed phase with low pH was recently shown to have good separation strength as well[136]. After LC separation, peptides have to be ionized to be applicable for MS analysis. Thereafter, data analysis then identifies and quantifies peptides and proteins present in the sample. These relevant parts of the mass spectrometric workflow applied in this project will now be described in more detail.

1.4.2 Mass Spectrometry

A mass spectrometer can be seen as a small scale determining the mass of molecular analytes. Contrary to macroscopic objects, the mass of biomolecules like proteins and peptides cannot be measured as a response to gravity. In fact, mass spectrometers assess the influence of electromagnetic forces on ions with differing mass[137]. Therefore, the biomolecules need to be ionized, which makes them susceptible to electric and magnetic fields, guiding the path through the mass analyzer and enabling measurement of mass to charge (*m/z*) ratios of these ions at the detector. This results in spectra with increasing m/z-values plotted against the intensity of these

ions. In bottom up proteomics, peptides and peptide fragments analyzed by mass spectrometry can be used for the identification of proteins.

Electrospray ionization

Earlier 'hard' ionization methods lead to physical destruction of biomolecules, hampering identification of proteins and peptides by mass spectrometry. The development of 'soft' ionization techniques (awarded with the Nobel Prize in 2002) was a huge step, which made the routine mass spectrometric analysis of large polar organic molecules like proteins and peptides possible[138]. The two used methods nowadays are matrix assisted laser desorption ionization (MALDI) and electrospray ionization (ESI).

In MALDI, peptides are co-crystallized with suitable matrix molecules and subsequently hit by a laser. Upon contact with the laser, the matrix layer is heated, expands, and desorbs in the vacuum. In this process, ions are generated and transferred first to matrix molecules and eventually to the analyte[139, 140]. MALDI commonly leads to singly charged species.

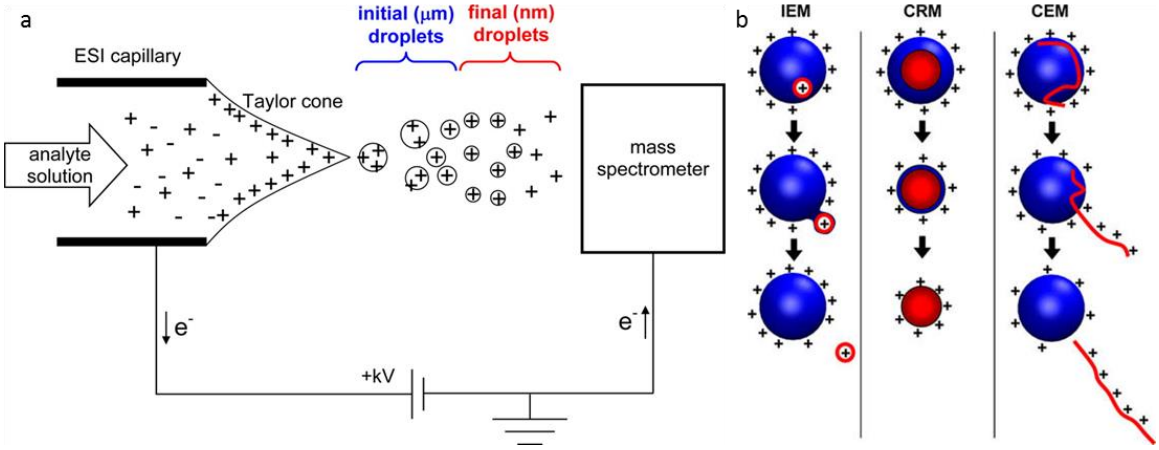

Figure 7: Electrospray ionization. *a) Schematic overview of the electrospray ionization process. Surface tension and electric force on the droplet lead to formation of a Taylor cone eventually resulting in droplet fission. b) Three models explain the transfer of a charge onto the analyte (modified from [141])*

ESI is more suited for online coupling of liquid chromatography and mass spectrometry[142, 143]. For the projects described in this thesis, a nano-ESI source was used. It is suited for flow rates down to <10 nL/min, leads to less sample consumption with increased sensitivity and enhanced ionization efficiency[144]. ESI-ion sources operate at atmospheric pressure[145]. The mobile phase carrying the peptides for that chromatographic fraction is exiting the analytical column of the LC through a spray capillary. An electric potential is applied to this capillary resulting in a charged liquid. In positive ion mode, electrons are conducted towards the anode and positive ions accumulate at the capillary tip forming a droplet because of surface tension. With increasing voltage in the electric field, the electric force on the droplet reaches the amount of surface tension leading to the formation of a cone-shaped stream (Taylor Cone)[146]. After reaching a certain voltage threshold, a jet of liquid is emitted from the cone. These small droplets are subject to rapid solvent evaporation leading to high charge density. At the Rayleigh limit[147], surface tension and Coulomb repulsion are in balance. Repeated fission and/or evaporation events ultimately result in highly charged nanodroplets[148, 149] (Figure 7a). Three models describe how charged peptides can then be generated[141]. Low molecular weight analytes likely follow the ion evaporation model (IEM). Charge repulsion on the droplet surface leads to an active ion generation process called ion evaporation (Figure 7b)[150]. The charged

residue model (CRM) is a passive process, where the charge ends up on the analyte due to subsequent solvent evaporation. This model might apply to large globular species[151]. Another mechanism called chain ejection model (CEM) has been described for unfolded proteins. Briefly, polymer chains of a protein are subsequently emitted from the droplet[152]. The charged peptides can then enter the mass analyzer. Electrospray ionization leads to multiply charged ions, facilitating the detection of large molecules with mass spectrometers of limited *m/z* range and enabling ion dissociation for tandem MS measurements[142]. Recently, it has been shown that addition of low percentages of dimethylsulfoxide (DMSO) to LC solvents enhances ionization of peptides. The lower surface tension of DMSO might help faster and more efficient generation of charged nanodroplets. This increases the ESI response and consequently improves sensitivity of proteomic measurements[153].

Mass analyzers - LTQ-Orbitrap Elite

The charged peptide ions generated by ESI then enter the mass spectrometer. Electric fields direct the peptides towards the mass analyzer where they are separated depending on their *m/z* ratio. The mass analyzer should (i) determine the true mass of the analyte with high accuracy, (ii) be able to separate two similar masses (mass resolution) and (iii) detect even low amount of ions (sensitivity). Furthermore, the analyzers can only detect the (iv) abundance of ions in a certain range (dynamic range), are (v) limited in the m/z range they can acquire and (vi) vary in scan speeds. Table 1 gives an overview of the four most commonly used analyzers for proteomic experiments today.

Table 1: Properties of mass analyzers used for proteomics *(adapted from [154, 155]).*

Analyzer	*Mass accuracy*	*Mass resolution*	*Sensitivity*	*m/z range*	*scan speed*	*dynamic range*
Orbitrap	<2 ppm	>200,000	+++	200-4000	moderate	10^4
2D Ion Trap	0.1-0.5 Da	2000	++	50-2000	moderate	10^4
Quadrupole	0.1-1 Da	1000	+++	200-4000	moderate	10^5
TOF	<5 ppm	>20,000	++	>50,000	fast	10^3

Time of flight (TOF) mass analyzers measure the time an ion needs to travel a certain distance within a vacuum. At the beginning, the ions all have the same kinetic energy, for analytes with equal charge, the flight time is dependent of the mass and therefore directly proportional to the square root of *m/z*[156].

Quadrupoles possess four parallel rods around a common axis. Two opposing rods are always electrically paired, resulting in helicoidal motion of ions through the quadrupole. With changing radio frequency applied to the rods only ions with a defined (range of) *m/z* value(s) have stable trajectories through the quadrupole and therefore make their way to a detector or further analysis, other ions will fall out along the way. It is mostly used as mass filter in hybrid instruments[137, 157]. By adding two additional electrodes on both ends, ions can be trapped inside the quadrupole, also called linear (2D) ion trap (LTQ). Ions can spread out axially which leads to high ion capacity inside the linear trap. Besides radial confinement, main radio frequency (RF) now induces 'secular' ion motion, which is proportional to the main RF amplitude and the mass. Smaller ions move more than larger ones. Whether an ion can be kept in the trap or falls out, hence, depends on its *m/z*–ratio at a given main RF amplitude. Ions can then be ejected depending on their *m/z*-ratio by applying an

additional 'resonance ejection' current at the exit rods. During a scan, the main RF is constantly increased and different ions can be measured. For isolation of an ion of interest, the exit rod current is superimposed (isolation waveform) so that all ions, except the desired one are ejected. Quadrupoles and ion traps determine *m/z*-ratios in relation to ion stability in an electromagnetic field[137, 158].

A further development is the Orbitrap. Here, ions are radially trapped by oscillation around a spindle shaped electrode. This electrode is covered by an outer barrel-like electrode. Electromagnetic forces induce ion oscillation along the z-axis as well as radial movement around the central spindle electrode (Figure 8a, b). Dependent on their *m/z* ratios, ions differ in their oscillation frequency independent of energy and spatial spread. During a scan, the frequency of the whole ion population is assessed simultaneously. Fast Fourier Transformation of recorded transients then de-convolutes the time domain oscillation data and enables the generation of mass spectra. The longer ions are allowed to move around the central spindle, the higher is the resolution of the masses[159-162].

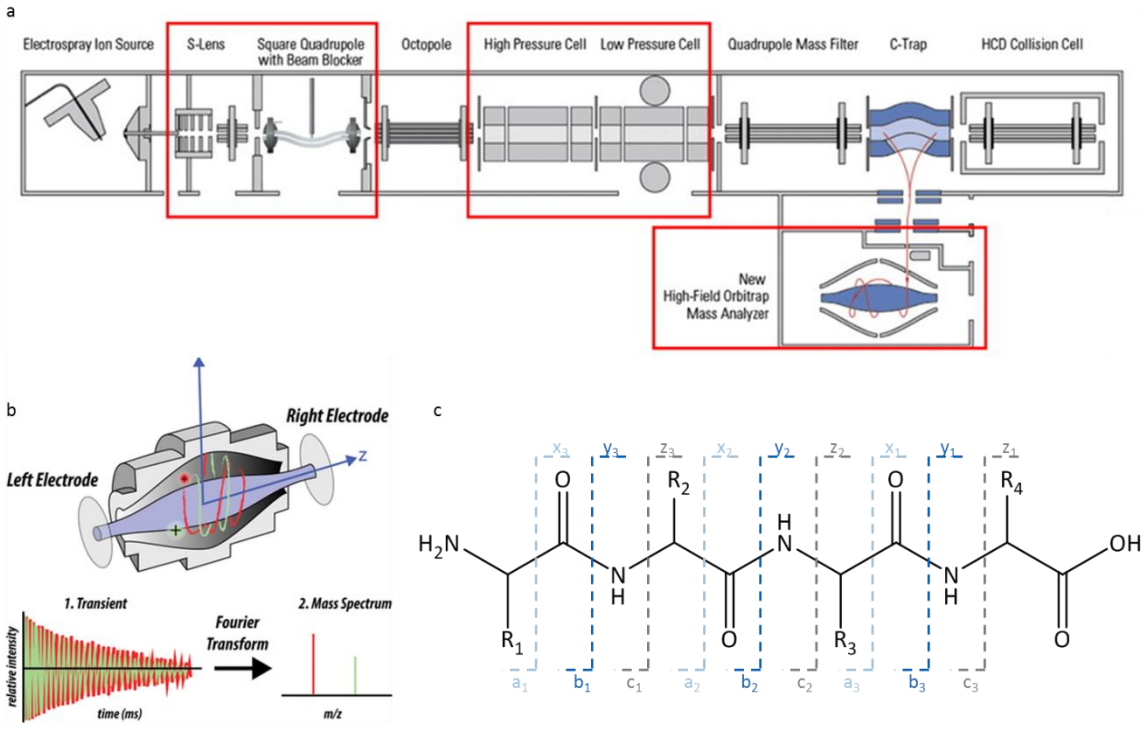

Figure 8: Tandem mass spectrometry. *a) Schematic of a LTQ-Orbitrap Elite mass spectrometer [163]. Novel elements compared with previous versions of LTQ-Orbitraps are highlighted in red. Improvements in the ion optics introduced a rotated square quadrupole with a beam blocker to prevent neutral and low charged ions from transferring further. The dual ion trap can now cover higher dynamic ranges and the high-field Orbitrap has increased resolving power. b) Orbitrap mass analyzer[137]. c) Peptide fragment nomenclature after Roepstorff-Fohlman[164].*

Mass spectrometers employing a combination of the above-mentioned mass analyzers are very common. One popular combination is employed in the LTQ-Orbitrap Elite (Thermo Scientific, Figure 8a) and was mainly used for this study. It is the latest addition to an instrument family of Orbitrap mass analyzer with a preceding ion trap. Ions are transferred via improved ion optics to the ion trap. The ion optics employ a bent transfer quadrupole with a neutral blocker to prevent transfer of uncharged species. In the ion trap, ions are trapped until a certain amount of charges is collected (standard = 10^6). Those are then further moved to the C-trap where ions are focused and transmitted to the improved high-field Orbitrap and subsequently analyzed[163, 165, 166]. This

arrangement combines the high sensitivity of ion traps with very high resolution and mass accuracy of the orbitrap[167].
Another successful combination features a quadrupole in front of the Orbitrap[168]. With an ultra-high-field Orbitrap, this type of mass spectrometer is capable of deep proteome analysis in shorter time than the LTQ-Orbitrap combination[169].

Tandem mass spectrometry for peptide sequencing

Edman degradation was long the only method to determine the amino acid sequences in peptides and proteins[170, 171]. With the introduction of soft ionization techniques and routine measurements of peptides and proteins in mass spectrometry, it is nowadays also possible to define a peptide sequence by mass spectrometry. This is realized in tandem mass spectrometry approaches. After obtaining a MS1 spectrum, single precursor ions are selected and subjected to a collision cell where peptides are fragmented. Then, fragments are again transferred to the mass analyzer and their *m/z*-ratio is again determined (MS/MS or MS2)[172-174]. Ideally, the peptide breaks in a way that fragments differ by the mass of one amino acid. According to Roepstorff and Fohlman, resulting fragments containing the N-terminus of the peptide are called a, b or c, depending on the position of bond breakage. Respective C-terminal fragments are referred to as x, y or z-ions (Figure 8c)[164]. There are different techniques to obtain fragment ions. In collision induced dissociation (CID), isolated ions are fragmented with neutral gas molecules (helium, argon or nitrogen)[173, 175]. This can take place in an ion trap where the isolated ions are brought into resonance, but not ejected. They will then collide with inert helium-atoms, leading to vibrational excitation and finally breakage. Unfortunately, MS2 spectra readout in ion traps lacks resolution and mass accuracy and suffers from a cutoff of small fragments. Higher energy C-trap dissociation (HCD) was developed in the C-trap leading to a hardware addition of an octopole collision cell (HCD-cell) in the rear end of the LTQ-Orbitrap devices. In this cell, ions are accelerated by current offsets (beam type activation), are then collided with nitrogen-atoms (or other gases) and are subsequently readout in the Orbitrap. This generates tandem mass spectra with better mass accuracy and resolution and improves the detection of peptide modifications[167]. In CID and HCD, the breakage mainly occurs at the peptide bond, generating y- and b- ions. Another method (not used in this thesis) is electron transfer dissociation (ETD). Here, fragments are generated by the influence of electrons. The transfer of an electron onto the positively charged peptide leads to an unstable positive radical ion and eventually fragmentation of the peptide at the N-Cα-bond. ETD mainly generates c- and z- ions (Figure 8c)[176].
The LTQ Orbitrap Elite allows two ways of obtaining MS/MS spectra. Ions are collected in the ion trap, which now acts as a mass filter and only keeps the desired *m/z*-ratio stable. They can now either be fragmented in the ion trap by CID and readout by the detectors (multipliers) of the ion trap (high-low) or the filtered ions can be transferred to the HCD collision cell, where they are colliding with nitrogen atoms. Fragments are then subsequently read out in the Orbitrap (high-high)[166].

The possibility to measure fragment ions led to the development of different acquisition approaches. In classical DDA, the mass spectrometer switches between scanning peptide ions (MS1) and sequencing of peptide derived fragment ions (MS2). Peptides of the MS1 scan are selected for MS2 often dependent on their intensity[177]. This process is limited by reproducibility, sensitivity and speed by which the mass spectrometer can acquire these spectra[178, 179]. In DIA approaches, fragment ions for MS2 spectra are grouped into *m/z*-dependent sections and subsequently measured. Spectra are then compared to a spectral library for identification[180].

1.4.3 Protein identification and quantification

After data acquisition, peptide *m/z*-ratios and fragments need to be identified and attributed to a protein sequence. In DDA shotgun measurements, mainly fragment spectra are used for identification. Several search algorithms have been developed, the most common ones are Mascot, Sequest or Andromeda[181]. They employ different ways and means on how to assign a spectrum to a peptide sequence, which are all based on similar principles. First, several search parameters need to be specified. Spectra are searched against one or more protein databases of the respective organism (of the sample). If the sample was digested with an enzyme, the protease can be specified. Furthermore, peptide modifications of interest or those expected due to respective sample preparation are included. They can be fixed, meaning that they have to occur in a peptide, which is reflected by the addition of this mass to each peptide mass. They can also be defined as variable, which leads to an increase in search space as each peptide is searched in modified and unmodified version. The database is now digested *in silico* to generate potential peptides, which are expected to occur in the sample. This leads to theoretical spectra that are then compared with the actual, acquired data. Mascot and Andromeda compute a probability if the detected matches between theoretically calculated and experimentally determined fragment masses might be a random hit. A peptide spectrum match (PSM) is then assigned to the protein, which contains this peptide. Some peptides can occur in several proteins which makes protein identification difficult. A peptide occurring in only one protein is called unique. Peptides preferentially occurring in one protein group are called razor.

As the whole data analysis is based on heuristic and probability scores, quality of peptide and protein identifications is evaluated by the so-called false discovery rate (FDR). The rate is an estimation of the percentage of false matches in an experiment. Therefore, spectra are also searched against a decoy database, i.e. a database containing reversed or scrambled peptide sequences. If fragment spectra match one of these decoy-hits, it has to be a false hit by definition. A common assumption is that random hits in the target space occur at a similar rate like the decoy hits[182]. Then, the proportion of decoy hits in all PSMs is determined. This is continued until a defined fraction of decoy hits is reached (often 1%). All matches counted so far are accepted, all other PSMs are discarded as false positives. The same principle applied on peptide and protein level allows local and global FDR calculation[183-185]. The classic approach in the community leads to an overestimation in large data sets, why currently efforts are made to overcome this issue[186, 187].

The search engine Andromeda was used for this thesis and is implemented in the MaxQuant software[181, 185, 188]. The implementation of Andromeda into MaxQuant combines easy and robust peptide and protein identification and quantification in one user interface and is, therefore, easily applicable for large-scale datasets. Scoring is based on binominal distributions that can also be applied to decide on the probable localization of a peptide side-chain modification. The more fragment masses of the actual experiment spectrum match the theoretically calculated masses, the lower is the probability of this being a random hit[189]. The Andromeda score is then defined as -10x $\log_{10}$ of the probability of matching a least number of experimentally determined fragment masses out of the theoretical masses by chance. This also takes the highest intensity peaks per 100 Da *m/z* window into account. The higher the score, the more likely it is that the peptide spectrum match did not occur by chance. Moreover, Andromeda can also distinguish co-fragmented peptides (e.g. one spectrum with information on two peptide series) by a second peptide search option[181].

Quantification

Accurate quantification of peptides and proteins by mass spectrometry, even though still facing challenges, has been implemented in many workflows[133, 190]. Proteolytic digestion and ionization influence the abundance of peptides and, therefore, potentially alter the true quantitative amounts in cells or organisms. Direct comparison of individual peptides between experiments addresses this challenge. Various options exist in proteomic workflows (Figure 9). The metabolic labeling approach is very popular. In this approach, stable isotopes are incorporated into the proteome of cells or small organisms. Samples can then be combined in the earliest possible point in the workflow so that errors/variations downstream of cell lysis affect all samples leading to high quantification accuracy and precision. Stable isotopes behave identically during chromatography and mass spectrometric analysis. The mass analyzer can then differentiate the two peptides due to their mass difference between heavy and light amino acids. Similar abundant peptides should then show comparable intensities/peak areas whereas peptides of changing proteins show different intensities allowing relative quantification. Stable isotope labeling with amino acids in cell culture (SILAC) is the most applied metabolic labeling technique in proteomics. In a typical SILAC experiment, isotope-labeled arginine and lysine (^{13}C, ^{15}N) are used, rendering each tryptic peptide with at least one labeled amino acid[191]. As the variety of useful isotope-combinations is limited to three, the multiplexing capabilities of metabolic labeling strategies are narrow. Besides SILAC, also ^{15}N labeling can be used, but incorporation of ^{15}N fluctuates between peptides making data analysis rather complicated[133, 192]. However, metabolic labeling strategies are only applicable to cell culture systems and some smaller organisms.

Another use of stable isotopes is employed in the chemical labeling approach. Either proteins or peptides can get labeled after lysis and digestion, be combined, and then subsequently processed as one sample. The quantification channel can either occur on the MS1 level or on the MS2 level. For the first variant, many options exist, ranging from ^{18}O-incorporation during digestion[193] to dimethyllabeling[194]. For the later variant, isobaric tags have been designed[195]. They all have the same mass but different distribution of isotopes in their structure. The tags can be coupled to free amines in lysines and peptide/protein N-termini by NHS-reaction. Samples are combined afterwards and analyzed by mass spectrometry. As each tag has the same mass (isobaric), complexity in the MS1 spectrum is not increased (a problem in MS1 based labeling approaches). Only in MS2 mode, the tag fragments and gives rise to different ions, whose intensity then reflects the quantity of peptide per condition. The two most popular ones are tandem mass tags (TMT) and isobaric tags for relative and absolute quantification (iTRAQ). TMT allows multiplexing of up to ten samples in one experiment and MS run, iTRAQ is suited for eight conditions[196-199]. One major drawback in MS2 based methods is the phenomenon of ratio compression leading to underestimation of the true abundance of a peptide. This occurs due to potential co-isolation and co-fragmentation of peptides as well as overlapping isotopic patterns of the tags themselves[200, 201]. Further fragmentation of fragment ions and a third MS measurement (MS3) can reduce this effect[202].

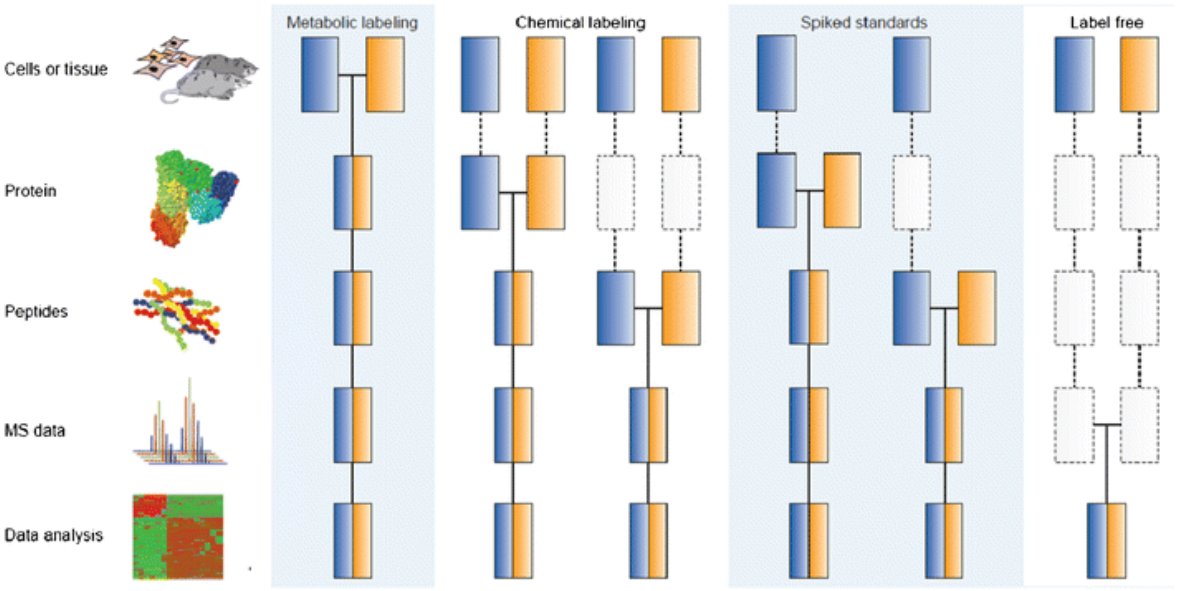

Figure 9: Overview of relative quantification strategies in proteomics. *Blue and yellow boxes refer to different experimental conditions (taken from[133]).*

Another option is the addition of spike-in peptides with known quantities that can also serve as relative measure of peptide abundance.

A simple and economic method to determine the relative abundance of peptides and proteins can be realized with label-free quantification. Here, samples are only compared on the data analysis level, assuming robust and reproducible sample processing steps and mass analysis. It is not limited by the sample type or number of conditions compared. With the routine application of high-resolution mass spectrometers, it has become possible to compare intensities or areas under the curve directly between samples, similar to isotope-labeled quantification methods. Therefore, the peptide peak is integrated over the whole area of elution from the analytical column, the extracted ion chromatogram (XIC). It correlates well with the concentration of a peptide and covers a high dynamic range of at least four orders of magnitude[203, 204]. Only high mass resolution enables the accurate determination of XICs for a respective peptide. A second approach correlates the number of MS2 spectra per peptide to its abundance based on the assumption that peptides of a more abundant protein should also be selected for sequencing events more often (spectral counting). However, today's instrument methods in DDA mode often apply a dynamic exclusion list. A peptide sequenced once is not fragmented anymore for a specific amount of time to enable sequencing of low intensity peptides and, thus, a deeper coverage of the proteome. Therefore, the MS1 intensity based approach with high resolution instruments is nowadays superior to spectral counting[205]. Most DDA-methods embrace a compromise between the number of MS1 spectra needed for proper determination of chromatographic elution profiles for quantification and the number of MS2 spectra for deeper proteome coverage[133]. The MaxQuant platform employs a sophisticated algorithm for label-free quantification termed MaxLFQ. It features a 'delayed normalization' for up front separated samples assuming that abundance of most proteins is not changing and extracts the 'maximum ratio information for peptide signals' for accurate quantification. A protein is quantified by first determining pairwise peptide ratios and then calculating the median of peptide ratios present in both samples[206]. For increased coverage across samples, MaxQuant employs a 'match between runs' algorithm. If the information from the raw file is insufficient for identification of a feature, because it was not measured or is of too low intensity, MaxQuant matches the MS/MS

and sequence information through aligning the different runs within a tight retention time and mass window. A peptide is then still identified in a search containing more samples, compared to a single search of the specific run[185].
Besides relative quantification across samples, absolute quantification methods have been developed and applied in various biological questions. These approaches either use stable isotope-labeled standards (AQUA, QconCAT, or absolute SILAC) or are based on label-free methods with respective algorithms and scoring strategies (PAI, APEX, IBAQ) (reviewed in [133]).

1.5 Objective and outline

Kinases are important key regulators in cellular signaling and are often involved in the development and progression of disease. Small molecule kinase inhibitors often target the conserved ATP-binding kinase domain and are quite successful molecularly targeted therapies. Over 30 drugs are approved for various indications and over 250 inhibitors are currently evaluated in clinical trials. Due to their chemical nature, these inhibitors can be rather unselective and not only act on their intended target but also inhibit other proteins. This polypharmacology does not necessarily lead to toxic side effects but can also open up new therapeutic opportunities where an inhibitor can be administered. So far, the target landscape of these drugs has not been evaluated in a systematic manner. Chemoproteomic approaches, like Kinobeads, offer valuable insights into drug-protein interactions in close to endogenous settings and can evaluate the effect of one drug on multiple proteins in one experiment. Therefore, this method should be applied to profile the selectivity of clinical kinase inhibitors systematically. The resulting target spectra can then be used to deduce insights into inhibitor mode of action, propose repositioning possibilities and identify off-targets leading to side effects.

This thesis presents an improved workflow to apply Kinobeads in a higher throughput setting enabling the screening of over 200 molecules (3.1). With this, 242 small molecule inhibitors were profiled for their selectivity resulting in the druggable kinome (3.2). The use of this resource is then demonstrated in the following paragraphs. Selectivity could be evaluated across drugs, binding modes or targets (3.3). Selected targets and inhibitors were then characterized concerning their mode of action or new uses for the respective drug (3.4). Finally, the discovery of a non-kinase off-target was characterized further (3.5).

2 Experimental procedures

Cell culture, reagents and affinity matrices

The cell lysate mixture (cell line mix) used to profile all kinase inhibitors in this study was generated from K-562, COLO 205 and MV4-11 cells grown in RPMI1640 medium (Biochrom GmbH), SK-N-BE(2) cultured in DMEM/HAM's F-12 medium (Biochrom GmbH). All were supplemented with 10% FBS (Biochrom GmbH) and 1% antibiotic solution (Sigma). For MET-inhibitor profiling, Caki-1 cells were cultured in IMDM (Biorad) with 10% FBS. For EGFR-inhibitor profiling, BT-474 cells were grown in DMEM/HAM's F-12 supplemented with 15% FBS (Biochrom). KM-12 and HEK-293 cells were grown in IMDM-medium (Biochom GmbH) in the presence of 10% FBS. For phosphorylated SK-N-BE(2) cell lysate, cells were treated with 100 µM pervanadate for 15 min.

Affinity matrices were produced in house as published previously[92]. PPIX was coupled to beads by first reversing NHS-beads with aminoethanol (4:1 mixture), ethylendiamine and triethylamine in DMSO for 20 h on an end-over-end shaker at r.t. in the dark. PPIX was coupled to the beads at a coupling density of 1 µmol/mL in the presence of Hünig's base, triethylamine and PyBrOP in DMF for 20 h on an end-over-end shaker at r.t. in the dark. Remaining free residues on the beads were blocked with NHS-activated acetic acid[92]. Small molecule inhibitors were purchased from Selleckchem, MedChemExpress, Active Biochem, Abmole, Merck or LC Labs (a complete list of inhibitors can be found in the Appendix I). Hemin and Protoporphyrin IX (PPIX) were obtained from Sigma Aldrich (H9039 and 25385). The stable and soluble recombinant FECH R115L mutant was a gift from Vipul Gupta (Tokyo Institute of Technology, Tokyo). It was expressed and purified as described previously[207].

Binding profiling using affinity matrices

Kinobeads selectivity profiling, as well as profiling with PPIX affinity matrices, was performed as described previously[92].

For affinity pulldowns, cells were lysed in so called 1x CP buffer (50 mM Tris/HCl pH7.5, 5% Glycerol, 1.5 mM $MgCl_2$, 150 mM NaCl, 1 mM Na_3VO_4, 25 mM NaF, 1 mM DTT) with 0.8% NP40 (Igepal-CA630, Sigma Aldrich) supplemented with Protease inhibitor (SigmaFast (S8820-20TAB) and Phosphatase inhibitor I (2.5 mM (-)-p-Bromotetramisole oxalate (190047, Sigma Aldrich), 500 µM Cantharidin (C7632, Sigma Aldrich), 500 nM Mirocystin LR (ALX-350-012-C050, Enzo)), II (200 mM Imidazole, 100 mM NaF, 115 mM $NaMoO_4$, 100 mM Na_3VO_4, 400 mM Sodium tartrate dehydrate), III (20 µM Calyculin A (C-3987, LC Laboratories)).

For kinase or protein enrichment, a protein mixture of the four cell lines or a single cell line were ultra-centrifuged at 52,000 rpm (167,177 xg) at 4°C for 20 min and diluted with 1x CP buffer with Protease and Phosphatase inhibitors to a 0.4% NP40 concentration in the lysate. This was then equally distributed into wells of a 96 deep well plate and adjusted to 5 mg/mL. Kinase inhibitors of interest were spiked into 1 mL cell lysates in increasing concentrations(3 nM, 10 nM, 30 nM, 100 nM, 300 nM, 1 µM, 3 µM, 30 µM and vehicle control) in suggested solvent (mostly DMSO) or as single compound dose (5 µM) and incubated for 45 min at 4°C. The preincubation step was followed by incubation with kinobeads or other affinity matrices (35 µl settled beads) for 30 min at 4 °C. Unbound proteins were washed away by first applying 3 mL of 1x CP buffer with 0.4% NP40 to the filter plate, followed by 2 mL of 1x CP buffer with 0.2% NP40. Bound proteins were eluted with

2xLDS sample buffer (NuPAGE, Invitrogen) containing 50 mM DTT by heating to 50°C for 30 min at 700 rpm.

For the calculation of a correction factor, the unbound fraction of the DMSO control was incubated with fresh beads for a second time (pull down of pull down).

For pulldowns using recombinant FECH protein, 1 µg FECH were spiked into 1 mL of 1x CP buffer with 0.4% NP40. (Competition) pulldowns were performed following the procedure described above.

Protein digestion

Reduced eluates were alkylated with chloroacetamide (55 mM) for 30 min in the dark and the proteins were concentrated by a short electrophoresis on a 4-12% Bis-Tris NuPAGE gel (Invitrogen) at 200 V for 5 min. Gels were stained with Coomassie or silver nitrate following standard procedures to visualize protein bands. In-gel digestion was performed according to standard procedures by technical assistants at the Chair of Proteomics, Technical University of Munich.

TMT labeling

Dried peptides were dissolved in 20 µl 50 mM TEAB (pH 8.5) and incubated for 10 min at 20 °C and 400 rpm. Up to 12 mM TMT labeling reagent (60 mM in anhydrous ACN) was added to each sample and incubated for 1 h at 20 °C and 400 rpm according to manufacturer's instructions. The labeling reaction was stopped by adding 2 µl 5% hydroxylamine for 14 min at 20 °C and 400 rpm. 75 µl of differentially labeled peptides were then combined in equal amounts by adding 50 µl 0.1% FA in H_2O to each sample.

StageTip desalting

After TMT labeling, peptides were desalted using StageTips[123, 208]. Five disks of Empore™ C18 47 mm SPE extraction disks (Supelco) were packed into the end of 200 µl pipet tip. Disks were equilibrated by first soaking the material with up to 100 µl of ACN and subsequent washing with 2x 100 µl 0.1% FA in H_2O and centrifugation of the tip at 2,000 rpm. Acidified samples (pH 2) were loaded onto the micro-column and washed with 2x 100 µl 0.1% FA in H_2O. Peptides were eluted in 100 µL 60% ACN/0.1% FA in H_2O and dried in a vacuum concentrator centrifuge.

High pH reverse phase fractionation

For high pH reverse phase fractionation, five disks of Empore™ C18 47 mm SPE extraction disks (Supelco) were packed into the end of 200 µl pipet tip, soaked with ACN and equilibrated with 25 mM NH_4FA. Samples were dissolved in 100 µl 25 mM NH_4FA and sonicated three times for 1 min with 1 min on ice after each step. They were then loaded onto the micro-column with reloading the first flowthrough. The second flowthrough was collected and desalted. Peptides on the micro-column were then washed with 2 x 40 µl 25 mM NH_4FA and sequentially eluted with 40 µl of elution buffer with increasing ACN concentrations (5%, 12.5%, 15%, 50%). Peptides in the flowthrough were pooled with the 50% fraction and dried in a vacuum concentrator centrifuge.

LC MS/MS analysis

Peptides generated by in-gel trypsin digestion were analyzed via LC-MS/MS on a nanoLC-Ultra 1D+ (Eksigent) coupled to a LTQ-Orbitrap Elite mass spectrometer (Thermo Scientific). Peptides were delivered to a trap column (75 µm × 2 cm, self-packed with Reprosil-Pur C18 ODS-3 5 µm resin, Dr. Maisch) at a flow rate of 5 µL/min in solvent A_0 (0.1% formic acid in water). Peptides were separated

on an analytical column (75 µm × 40 cm, self-packed with Reprosil-Gold C18, 3 µm resin, Dr. Maisch) using a 100 min linear gradient from 4-32% solvent B (0.1% formic acid, 5% DMSO in acetonitrile) and solvent A_1 (0.1% formic acid, 5% DMSO in water)[153] at a flow rate of 300 nL/min. The mass spectrometer was operated in data dependent mode, automatically switching between MS and MS2 spectra. MS1 spectra were acquired over a mass-to-charge (*m/z*) range of 360-1300 *m/z* at a resolution of 30,000 (at m/z 400) in the Orbitrap using an automatic gain control (AGC) target value of 1e6 or maximum injection time of 100 ms. Up to 15 peptide precursors were selected for fragmentation by higher energy collision-induced dissociation (HCD; isolation width of 2 Th, maximum injection time of 100 ms, AGC value of 2e5) using 30% normalized collision energy (NCE) and analyzed in the Orbitrap (7,500 resolution). A previous-experimentally obtained inclusion list containing approximately 1,000 kinase peptide *m/z* and retention time values was enabled in the data acquisition regime. Dynamic exclusion was 20 s and singly charged precursors were excluded.

Profiles of EGFR inhibitors in BT-474 cells were obtained using a Dionex Ultimate 3000 nano HPLC coupled to a Q Exactive HF mass spectrometer. Peptides were delivered to a trap column as described above and separated on an analytical column using a 60 min gradient from 4-32% solvent B in solvent A_1. MS1 spectra were acquired at a resolution of 60,000 (at *m/z* 200) using a maximum injection time of 10 ms and an AGC target value of 3e6. Up to 12 peptide precursors were isolated (isolation width of 1.7 Th, maximum injection time of 75 ms, AGC value of 2e5), fragmented by HCD using 25% NCE and analyzed at a resolution of 15,000. Precursor ions that were singly-charged, unassigned or with charge states >6+ were excluded. The dynamic exclusion duration of fragmented precursor ions was 30 s.

Peptide and protein identification and quantification

For label-free quantification of Kinobeads selectivity profiles, peptide and protein identification and quantification was performed using MaxQuant (version 1.5.3.30)[188] by searching the tandem MS data against a human Swissprot reference database (human proteins only, 20,193 entries, downloaded 22.03.16, internally annotated with PFAM domains) using the embedded search engine Andromeda[181]. Carbamidomethylated cysteine was specified as fixed modification; phosphorylation of serine, threonine, and tyrosine, oxidation of methionine, and N-terminal protein acetylation were variable modifications. Trypsin/P was specified as the proteolytic enzyme and up to two missed cleavage sites were allowed. Precursor tolerance was set to 10 ppm and fragment ion tolerance to 20 ppm. Label-free quantification[206] and match between runs (alignment window 1 min) were enabled within MaxQuant. Search results were filtered for a minimum peptide length of seven amino acids, 1% peptide and protein FDR as well as common contaminants and reverse identifications. For consistent peptide identification and protein grouping, the MS data for each compound was supplemented with 15 standard controls. Each compound was analyzed separately.

TMT labeled samples were searched with MaxQuant (version 1.5.2.8) against a human UniProt reference database (88,354 entries, downloaded 22.07.13, internally annotated with PFAM domains). TMT10 reporter ions were specified for quantification, other parameters were set the same as for the label-free analysis. Furthermore, TMT data was also analyzed using the phyton package isobarQuant in combination with the Mascot search engine. Therefore, relative TMT intensities were extracted directly from the raw files, whereas protein identification was performed by Mascot with the same search parameters as for MaxQuant.

Data analysis

For competition binding assays, protein intensities were normalized to the respective DMSO control. IC_{50} and EC_{50} values were deduced by a four-parameter, log-logistic regression using an internal pipeline that utilizes the 'drc' package[209] in R. A K_d^{app} was then calculated by multiplying the estimated EC_{50} with a protein-dependent correction factor (depletion factor) that was limited to a maximum value of 1. The correction factor cf for a protein is defined as the ratio of the amount of protein captured from two consecutive pull downs of the same DMSO control lysate[92, 97]. In this study, protein-dependent correction factors were set to the median of correction factors across all experiments using the same lysate and beads. Representative dose dependent inhibition curves were analyzed using GraphPadPrism (version 5.03).

Target annotation

Targets were manually annotated. A protein was considered a high-confidence target if the binding curve showed a sigmoidal shape with a dose-dependent decrease in binding to the Kinobeads. Proteins that only showed an effect at the highest inhibitor dose where not annotated as targets. The number of unique peptides and MSMS spectra were also included as target selection criteria. Peptide intensity in DMSO controls and MS/MS data quality was also taken into account. Proteins with low peptide counts, MS/MS spectral counts or MS1 intensity that nonetheless showed a reasonable dose response curve fit were considered as potential targets. In addition, if an inhibitor also interacted with similar kinases (*e.g.* CDK family) it was also considered as a potential target. Low-confidence targets were excluded from further analysis. Note that for some targets, curve fitting with our data processing pipeline was not possible resulting in no or very high K_d^{app} values. Targets were considered as direct Kinobeads binders if annotated in UniProt.org as a protein or lipid kinase. Furthermore, nucleotide binders, helicases, ATPases and GTPases, FAD (*e.g.*, NQO2) and heme (*e.g.*, FECH) containing proteins were also considered as potential direct binders. Most other target proteins are interaction partners/adaptor proteins of the kinases and are termed indirect Kinobeads binders.

All high confidence targets will from now on be referred to as targets, used for analysis and shown in figures if not stated otherwise.

Comparison of kinase inhibitor profiles/targets to other published data

To compare kinase inhibitor profiles to published screening data and major online databases, only targets annotated as either direct Kinobeads binders or kinases were considered. Datasets obtained from CHEMBL[210], LINCS[211], Anastassiadis *et al.*[72] and Metz *et al.*[212] were filtered for compounds used in the Kinobeads drug screen and protein names were annotated according to gene names as used in UniProt. Dose response data was filtered for half-maximal response at 30 µM or lower if the assay threshold concentration was lower. Single concentration data was filtered for a minimum of 25% inhibition of binding or activity.

Kinase activity assays

Kinases activity assays where performed at Reaction Biology Corporation. IC_{50}s were determined using 10 concentrations in semi-log steps. Kinases of interest were measured at an ATP concentration corresponding to the apparent K_m for ATP of the corresponding kinase.

Cell viability assays

Cell viability was measured using the alamarBlue cell viability assay (DAL1100, Invitrogen). For KM12 viability, 1,000 cells were seeded per well in IMDM Medium with 10% FBS (Biochrom). Cells were allowed to attach overnight. On the following day, the cells were exposed to increasing concentrations of a specific inhibitor (final inhibitor concentration: 10 µM, 3 µM, 1 µM, 300 nM, 100 nM, 30 nM, 10 nM, 3 nM) to the cells, as well as a DMSO control. The cells were incubated for 72 h at 37 °C and 5% CO_2. Cell viability assays were performed by adding 10% alamarBlue reagent to each well. The reduction from resazurin to resorufin was measured after 4 h using a fluorescence spectrophotometer (BMG Labtech) at 544 nm (excitation) and 584 nm (emission). Each compound was measured in a technical triplicate.

MV4-11 viability was measured using the Cell Proliferation Kit II (XTT, Cat. No. 11465 015 001, Roche) according to manufacturer's procedure. Briefly, 10^4 cells were seeded per well and allowed to attach overnight. Cells were exposed to increasing concentrations of each inhibitor (1 µM, 100 nM, 30 nM, 10 nM, 3 nM, 1 nM, 300 pM, 100 pM). The cells were incubated for 72 h at 37 °C and 5% CO_2. Cell viability assays were performed by adding XTT reagent to each well. The metabolite formazan 4 h using an absorbance spectrophotometer (Tecan) at 492 nm. Each compound was measured in a technical triplicate.

Viability was then assessed by calculating the reduction in fluorescence of each inhibitor dose compared to the DMSO control. Graphs were generated in GraphPadPrism (version 5.03).

Immunodetection for NTRK1 signaling

After separation of up to 40 µg of previously treated KM12 lysate, immunoblots were performed using the Xcell II Blot Modul (Invitrogen) and PVDF Membranes (Biorad) according to manufacturer's instructions. Downstream targets of NTRK1 signaling were detected with the respective antibodies: phospho-AKT (S473, (D9E) XP™, Cell Signaling Technology), pan AKT (C67E7, Cell Signaling Technology), phospho-p44/41 Erk1/2 (Thr202/Tyr204, (D13.14.4E) XP™, Cell Signaling Technology) and p44/41 Erk1/2 (137F5, Cell Signaling Technology). ß-actin (C4, sc-47778, Santa Cruz Biotechnology) was used as loading control. Secondary antibodies used were IRDye 800CW Goat-anti-Rabbit Antibody and IRDye 680LT Donkey-anti-Mouse antibody (LICOR Biosciences). Detected protein was readout with the Odyssey infrared imaging system (LI-COR Biosciences).

Cellular thermal shift (CETSA) and isothermal dose response assay (ITDR)

Cellular shift and isothermal dose response assays were performed as described before[110]. For CETSA, K562 cell lysate was incubated with up to 10 µM of drug for 30 min. Compound treated lysate was then distributed into PCR-tubes à 50 µl and heated to increasing temperatures from 40-70 °C for 3 min, followed by a 3 min cooling phase at 25 °C.

For ITDR, K562 cells were incubated with increasing concentrations of drug for 1h at 37 °C. Then, cells were washed with PBS and heated to 55 °C for 3 min followed by a 3 min cooling phase at 25 °C. After heating, cells were lysed by freeze thaw cycles in liquid N_2.

After CETSA or ITDR, denatured proteins were precipitated by centrifugation at 20,000 xg for 30 min. Supernatants were reduced in LDS Sample buffer and proteins were separated in a 4-12% NuPAGE gel (Invitrogen) at 200 V for 45 min. FECH protein was detected by immunoblotting with a mouse monoclonal antibody (sc-271434, Santa Cruz Biotechnology) in a 1:400 dilution in 0.2% BSA in 1x TBS-T for at least 16 h at 4 °C. For secondary detection IRDye 800CW conjugated goat anti-mouse (LI-COR Biosciences) was used (1:5000 in 0.2% BSA and 0.02% SDS in 1x TBS-T, 1 h, RT). Detected protein was quantified with the Odyssey infrared imaging system (LI-COR Biosciences).

The data are normalized with the quantity of soluble target at highest compound concentration, reflecting maximum thermal stabilization, set to 100%. Dose dependent stabilization curves were analyzed using GraphPadPrism (version 5.03) and EC_{50}-values were calculated using nonlinear regression analysis.

FECH activity assay

For cell viability measurements, differentiated K562 cells were incubated with 1 µM of drug for up to 6 days and the amount of live cells was quantified using the alamarBlue assay (Thermo Scientific). Experiments were performed in triplicates for each compound. The activity assay was modified based on Smith et al.[213] Briefly, differentiated K562 cells were incubated with 1 µM drug for up to 6 days, washed with PBS and lysed using only ddH2O for 4 hours. Cell debris were pelleted by centrifugation at 20,000 xg at 4 °C for 10 min. Heme was measured from these cleared supernatants by LC-MS, using an Agilent 1100 HPLC system and a Triart C18 (10 x 1mm I.D., 3 µm resin, YMC Europe GmbH) column, applying a 60-95% gradient of solvent B (0.1% FA in acetonitrile) in solvent A_0 (0.1% FA in water) coupled online to an Amazon ion trap (Bruker). For quantification of heme content, the area under the curve of the UV trace at 400 nm was determined and normalized to the protein content of the sample. The change in heme content was calculated with respect to the vehicle treated sample.

Cell-free FECH enzymatic assay

Inhibition of FECH enzymatic activity was performed as described previously.[207] Recombinant FECH R115L mutant was used for the assay because it is more stable and better soluble than the wild type enzyme and this mutant has also been used in the literature including the reported crystal structure (see below).

Docking studies

Docking was performed by Bjoern Oliver Gohlke (Structural Bioinformatics Group, Charité-Universitätsmedizin, Berlin, Germany). The X-ray structure of Ferrochelatase (PDB: 3w1w) was selected for all docking studies. In this structure, salicylic acid as well as cholic acid were co-crystallized with the protein. For docking, hydrogens were added and ligands as well as possible side chain rotamers removed from the protein. Docking studies were carried out using GOLD 5.2[214] by applying a radius of 10.0 Å around the respective coordinates, using standard parameters and the ChemScore scoring function for ranking the docking poses. This set of parameters was kept for every docking step to guarantee reproducibility. Separate docking experiments were performed for the dimerization region and protoporphyrin site. For the dimerization site, residues around salicylic acid were defined as active site and docking was performed by using standard parameters and applying the ChemScore scoring function to rank the results. For the protoporphyrin site, compounds were docked in an iterative process based on the known binding mode of cholic acid. Cholic acid was removed from the complex, whereas the definition of the binding site for every of the three steps was based on the coordinates of the corresponding cholic acid molecule. To consider intermolecular interactions to the previously docked compounds, the best docking position for every compound was placed in the protoporphyrin site and kept for the next docking step.

3 Results and Discussion

3.1 Assay development

The primary aim of this thesis was to assess the target space of small molecule kinase inhibitors. To systematically profile the selectivity of 242 kinase inhibitors currently evaluated in clinical trials, the Kinobeads technology should be used. Briefly, Kinobeads enrich kinases and other binding proteins out of cell or tissue lysates and combined with mass spectrometry bound proteins can be identified and quantified (Figure 10a). In-lysate competition using one of the 242 unmodified commercially available inhibitors in increasing concentrations leads to a dose dependent loss of specific protein binding to the beads. The more protein bound by an inhibitor in solution, the less can bind to Kinobeads and the lower is the intensity of the respective peptides detected by the mass spectrometer (Figure 10b). The current version of Kinobeads (Kinobeads γ, from now on referred to as Kinobeads) consists of five broad spectrum kinase inhibitors immobilized on beads which are mixed in equal amounts (Figure 10c)[92] and can enrich over 300 human protein kinases. Using mass spectrometry readout proteins bound to Kinobeads can be identified and quantified for each dose of competitor (or vehicle). The relative binding of proteins to the beads at each inhibitor concentration combined with non-linear regression analysis enables the generation of binding curves and target identification. The inhibitor concentration at the inflection point of the curve is the effective concentration for half-maximal inhibition (EC_{50}). The apparent dissociation constant K_d^{app} is obtained after correction for depletion with a correction factor (cf)[97, 103].

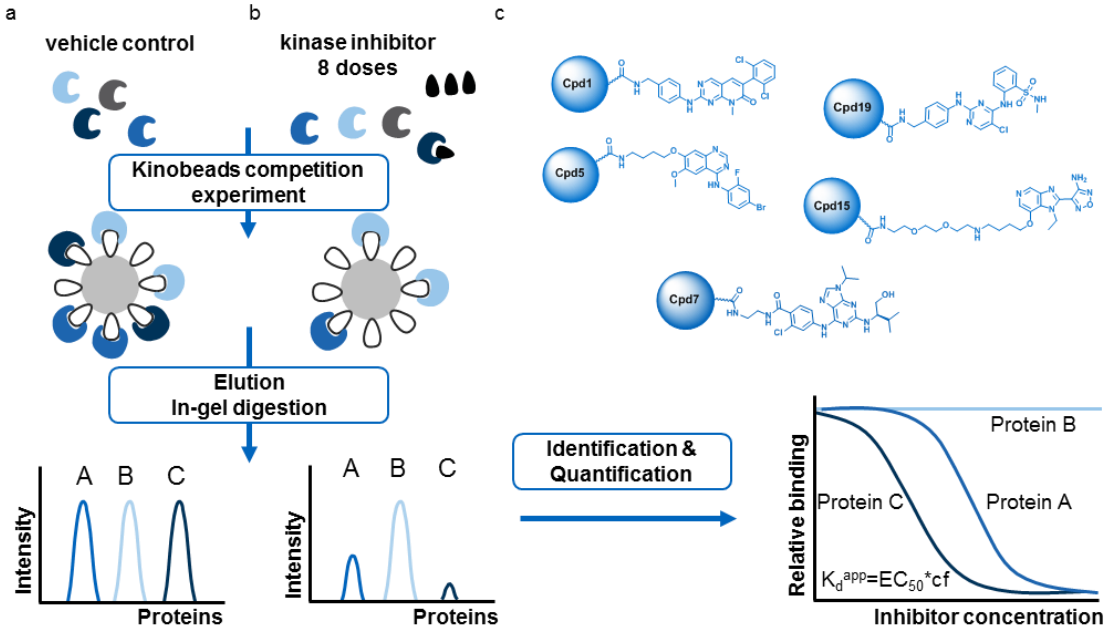

Figure 10: Kinobeads workflow used for this study. *a) Kinobeads enrich kinases out of cell lysate. b) In-lysate competition with kinase inhibitor of interest and Kinobeads. Target proteins of the inhibitor cannot bind to Kinobeads anymore and show reduced intensity in the mass spectrum. c) Unselective, broad-spectrum kinase inhibitors immobilized on γ-version of Kinobeads. d) Residual binding of protein to the beads dependent on inhibitor concentration combined with nonlinear regression analysis allows generation of binding curves. EC_{50}s can be converted to K_d^{app} by using a correction factor (cf) for every protein identified.*

3.1.1 Downscaling for high throughput pulldowns

Since the state of the art Kinobeads pulldown protocol performed affinity enrichment in 5-15 mL reaction vessels with up to 10 mg protein followed by bead washing on spin-columns (now referred to as spin-column based protocol), it enabled pulldown experiments for about 8-10 concentrations of one inhibitor or different conditions in parallel per day[91, 215, 216]. This throughput had to be enhanced for profiling of over 200 kinase inhibitors. A robust protocol was needed that would allow for reproducible Kinobeads enrichments across all inhibitors with eight increasing compound concentrations, a DMSO control and a pulldown of pulldown for depletion factor calculation. Moreover, reduced sample input material (especially lysate and Kinobeads) was also desirable. One goal was to use 96-well filter plates instead of single spin-columns to perform more pulldowns in parallel. Therefore, the bead amount would need downscaling. Furthermore, washing conditions might also influence the recovery and identification of kinases. Protein amount and unspecific binding were also considered important parameters that would need evaluation. Lastly, the MS-acquisition parameters have to be optimized to facilitate reasonable measurement throughput.
Becher *et al.* employed a protocol in spin-column format with 35 µl beads, 5mg/mL protein input and 1 mL washing buffer to profile nucleotide cofactors[217]. These lower input amounts were used as starting point to convert the spin-column setup to a 96-well assay format. All experiments were performed as singlicate with 35 µl beads, 5 mg/ml protein of the four cell line mix in a 96-well filter plate and measured on the Orbitrap Elite with a 215 min gradient, unless stated otherwise.
First, different bead washing conditions were evaluated. Washing of beads in the spin column based protocol used an iterative washing step of 10 mL 1x CP+0.4% NP40 followed by 5 mL of 1x CP+0.2% NP40 whereas the published downscaled protocol employed 1 mL of 1x CP+0.2% NP40. The composition of buffers was not changed but the effect of increasing volume was evaluated to assess number of kinases and the effect of unspecific background. Figure 11a plots the number of quantifiable kinases (no zero value in LFQ-intensity) in Kinobeads pulldowns with different washing steps after incubation of the beads with the lysate. Apart from using only 1 mL 1x CP+0.2 NP40 buffer, volume was increased up to 5 mL as a combination of 1x CP+0.4% NP40and 1x CP+0.2% NP40. When using 1 mL 1x CP+0.2% NP40, 144 kinases could be identified, whereas the number of kinases increased to 196 and 191 after washing with a 3 mL or 2 mL combination of 1x CP+0.4% NP40 and 1x CP+0.2% NP40, respectively. Washing with 5 mL buffer yielded slightly less kinases (n=186), which might be due to loosing kinases with less affinity to Kinobeads. By washing, unspecific binding is reduced, which facilitates higher kinase peptide intensity in the MS-run (blue line). Apparently, with 1 mL buffer, relative kinase intensity in the MS1 is 15%, whereas washing with 3 mL 1x CP+0.4% NP40 followed by 2 mL 1x CP+0.2% NP40 could reduce binding of many background proteins, so that more than 50% of the total MS1 intensity was contributed by kinase peptides. Overall, higher washing buffer volumes increased both the number of kinases and the relative kinase intensity. Therefore, the 5 mL washing condition was chosen for all subsequent pulldown experiments as it provided a rational balance of kinase identifications and reduced intensity of background proteins.

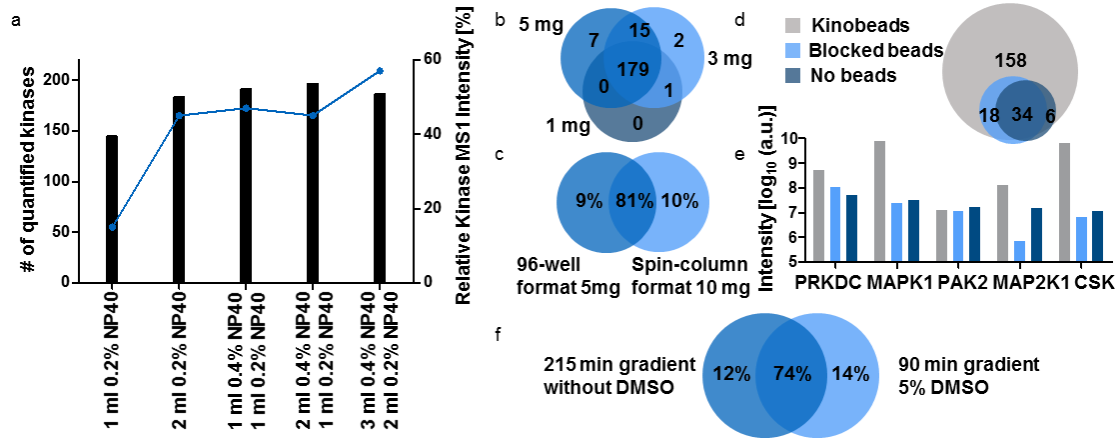

Figure 11: Protocol downscaling for high throughput pulldowns. *a) Number of identified kinases and relative intensity of kinases using different washing buffer volumes and combinations after bead incubation. Washing with at least 2 mL increased number of quantified kinases and reduced background binding. b) Number of identified kinases using different amounts of protein per 1 mL. 5 mg/mL yielded highest number of identified kinases. c) Overlap of identified kinases in 5 mg and the 96-well assay compared to 10 mg protein in the spin-column format. Downscaling maintained assay performance by applying less input material. d) Background kinase binding by beads (blocked beads) and plastic (no beads) compared to kinases identified in a Kinobeads experiment. e) MS1 intensity distribution of kinases identified in Kinobeads, blocked beads and no beads-experiments. These kinases showed the highest intensity in the no beads-experiment. f) Overlap of identified kinases when using a 215 min gradient or a 90 min gradient and 5% DMSO in the LC-MS/MS buffers. LC-MS/MS measurement time could be successfully reduced.*

Higher protein amounts and concentration improve identification of kinase and reduce the influence of individual protein expression levels on EC_{50} determination[91]. 180 kinases could be identified using 1 mg of protein per mL, whereas 197 and 201 protein kinases could be enriched from 3 mg and 5 mg cell mix in 1 mL, respectively (Figure 11b). Notably, kinases like CDK4 or NTRK1 were only identified in the 5 mg experiment. To ensure robust and reproducible kinase coverage in the drug screen, 5 mg of protein were used per experimental condition; however, the optimized 96-well protocol can also be used with less protein amounts. The number of identified kinases is comparable to the spin-column based format (Figure 11c) by using half the amount of protein. To assess unspecific binding to plastic ware and beads, the workflow was performed using Kinobeads, blocked beads (all NHS sites reacted with aminoethanol without immobilized probe) and no beads. Indeed, 34 protein kinases overlapped in a Kinobeads pulldown, a pulldown using blocked beads or when incubating lysate without beads. Eighteen more kinases might bind to sepharose beads alone whereas another six kinases might bind to plastic (Figure 11d). The absolute numbers might vary as this experiment has only been performed once, but have to be acknowledged for data interpretation in certain cases. However, these kinases are among the most abundant ones and the intensity in the two negative controls is often lower than in the pulldown with Kinobeads (Figure 11e). In this project, drug-protein interactions are characterized by dose responses after competition with Kinobeads, which provides clear specificity in data interpretation. From now on, pulldown experiments could be performed in 96-well plates allowing simultaneous competition profiling of eight inhibitors with eight increasing free compound concentrations and a vehicle (DMSO) control for each inhibitor. The second pulldown (pulldown of pulldown) of the DMSO control flowthrough had to be performed separately after the first enrichment step of the DMSO-treated lysate. The lowest dose of inhibitor was chosen to be 3 nM as most inhibitors showed no lower affinities in published values. As endpoint, 30 µM was selected to ensure complete

competition from the beads. The concentration ranges were than chosen such that semi logarithmic steps enabled meaningful curve fitting (3 nM, 10 nM, 30 nM, 100 nM, 300 nM, 1 µM, 3 µM, 30 µM).

Previous pulldowns were measured in 215 min gradients per sample[215, 216, 218], which would result in over 40 h measurement for a full dose response of one inhibitor. Due to the addition of DMSO to LC-MS/MS buffers[153], gradient time could be reduced to 90 min whilst keeping the identification of kinases comparable to the 215 min gradient (Figure 11f). Carryover of kinases in blank runs in-between dose response samples was identified to be 0.2% compared to the intensity of kinases in the sample. Therefore, samples could be run sequentially, starting from the pulldown of pulldown samples and the highest inhibitor concentration (expecting the lowest protein content) to the lowest inhibitor concentration and ending with the DMSO control, which should show the highest protein amount. With these changes, a full dose response of an inhibitor could be measured in less than a day.

Summarizing these results, the downscaling of the kinobeads pulldown assay was successful. The now established 96-well setup for selectivity profiling of 242 clinical kinase inhibitors employed 5 mg of protein in a reaction volume of 1 mL. Kinobeads were used with 35 µL per well. Background proteins were reduced by washing with 3 mL 1x CP+0.4% NP40 and 2 mL 1x CP+0.2% and bound proteins were subsequently analyzed using 90 min gradients and DMSO in the LC-MS/MS buffers.

3.1.2 Quantification using label-free or isotope-labeled approaches

Assessing the EC_{50} of a given drug-protein interaction depends on residual binding ratios after competition profiling for each dose. Therefore, reliable and reproducible quantification is needed. The original publication[91] suggested labeling with iTRAQ or TMT and multiplexing of the samples. A new labeling reagent for MS2 based quantification (TMT10) allows labeling of 10 samples and then combining them for subsequent measurement[199]. This matched the experimental setup regarding the number of increasing compound concentrations plus DMSO control and pulldown of pulldown sample. Multiplexing was appealing, as it would reduce the measurement time per compound by a factor ten and result in quantitative values across all dosage points for every peptide sequenced. This might suffer from less identified peptides and proteins. Another option was relative quantification with no label at all. In label-free quantification, MS1 intensities are used as measure of abundance and can be directly compared between samples. However, each experimental condition for one compound needs to be measured in a separate MS-run increasing the measurement time for one competition experiment. Moreover, peptides might not be quantified in each run because of the statistical nature in DDA MS measurements resulting in less peptides and proteins with meaningful dose responses. A dose dependent competition with the multi-kinase inhibitor Golvatinib in the four cell line mix was used for evaluation of label-free or TMT-labeled quantification. For TMT evaluations five dose-response pulldowns of Golvatinib were labeled and pooled to one mix. The pulldown for label-free quantification was performed separately. For TMT measurements, 2.5x more peptide was injected than in the label-free run.

Label-free MS-runs were performed on the Orbitrap Elite using a 2 h gradient and up to 15 precursors per MS1 run were selected for MS2 measurement and isolated with a window of 2 Th in the ion trap (see Experimental Procedures). Over 1800 proteins, including 230 kinases, were identified in this experiment (Figure 12).

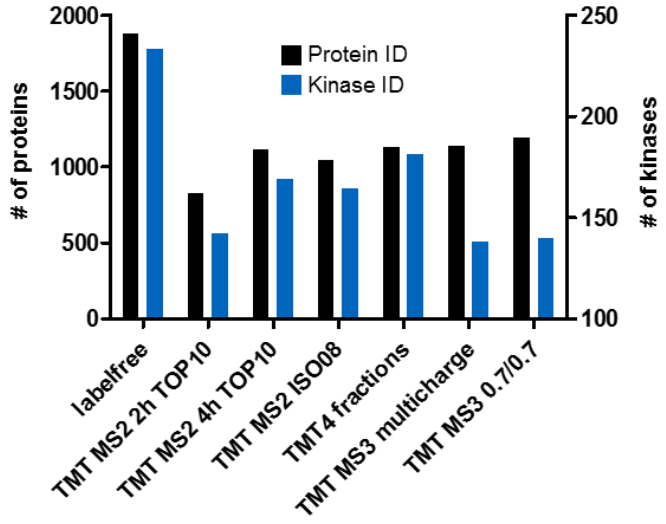

Figure 12: Protein identification in label-free or TMT quantification*. Number of protein (left y-axis) and kinase (right y-axis) identifications influenced by quantification and measurement method. Label-free quantification yields more proteins and kinases than TMT labeled samples. Less kinases were identified in the TMT MS3 acquisition, whereas similar numbers could be identified in TMT MS2 methods*

DDR2, EPHA2, RIPK2, and ZAK were selected as example targets. All four proteins showed a dose dependent decrease in residual binding to the beads and showed no residual binding at higher doses (light blue line/points, Figure 13).

For TMT-labeled samples, these MS-parameters had to be varied to find a potential optimal solution. The first method used a 2 h-gradient and subjected the 10 most intense precursors for MS2 measurement with an isolation width of 1.3 Th in the ion trap (2h Top 10; dark grey line/points, Figure 13). With this method, 825 proteins and 142 kinases were identified. For DDR2, no curve could be fitted; the other targets show a decrease in residual binding to 0.8 at the highest compound concentration. A prolonged gradient (4h Top 10; light grey line/points, Figure 13) also did not improve curve fits but yielded slightly more total protein and kinase identifications (1115 and 169, respectively, Figure 12).

The plateau of the dose response curves can be attributed to ratio compression, partially due to co-isolation and co-fragmentation of other peptides[201]. Therefore, the isolation width was decreased from 1.3 to the lowest possible window (0.8 Th; iso 0.8; black line/points, Figure 13) to reduce the impact of co-isolation. Similar numbers of proteins and kinases were identified (Figure 12). The curve shape for potential targets did not change much compared to prior acquisition methods. The residual binding remained at a least ratio of 0.5 for DDR2, RIPK2 and EPHA2 and no competition could be observed for ZAK. To diminish the effect of potential co-isolation further, peptides were fractionated with high pH reversed phase after TMT-labeling. The four resulting fractions were then measured using the 2 h gradient and fragmenting the 10 most intense precursors in MS2 (dark grey line/pyramid, Figure 13). For DDR2, no residual binding could be observed for higher doses, but for other targets minimum residual binding was 0.5 and did not change compared to the other methods. Moreover, measurement time increased to at least 8 h per sample also leading to an increased number of identified kinases (181) compared to non-fractionated TMT samples. However, identification numbers are still lower than in the label-free measurement and its 20 h.

Another option for less ratio compression is the use of a MS3 method. Peptides were isolated and fragmented for MS2 with the TMT reporter ion remaining at the fragment ion. TMT reporter ions

were then read out in a third MS measurement (MS3) and simultaneously fragmented after isolation of up to five fragment ions (from one peptide). This measurement method is now implemented in the new generation of tribrid mass spectrometer and the samples were measured on a Fusion Lumos (Thermo Scientific, demo lab). If fragments were isolated with isolation widths of 0.7 Th for both MS2 and MS3 (MS3 2h 0.7/0.7, blue line/square, Figure 13), residual binding for EPHA2 and RIPK2 decreased similarly to that of the label-free curve, but could not improve for ZAK. DDR2 was not identified. Lastly, fragment ions were isolated for MS3 using isolation windows dependent on the charge of the fragment (1.3 Th for 2+, 1.0 Th for 3+, 0.8 Th for 4+ and 0.7 Th for 5-7+ ions, MS3 2h multicharge, grey line/square, Figure 13). Again, residual binding of EPHA2 and RIPK2 almost decreased to zero at higher doses, resembling the curve of the label-free measurement and, therefore, providing the only suitable alternative to label-free quantification. Reduced ratio compression in MS3 comes at the cost of identified proteins and kinases. For example, DDR2 could not be identified in these measurements. Roughly, half of the proteins identified in the label-free measurement were found in MS3 measurements and less than 150 kinases could be measured (Figure 12).

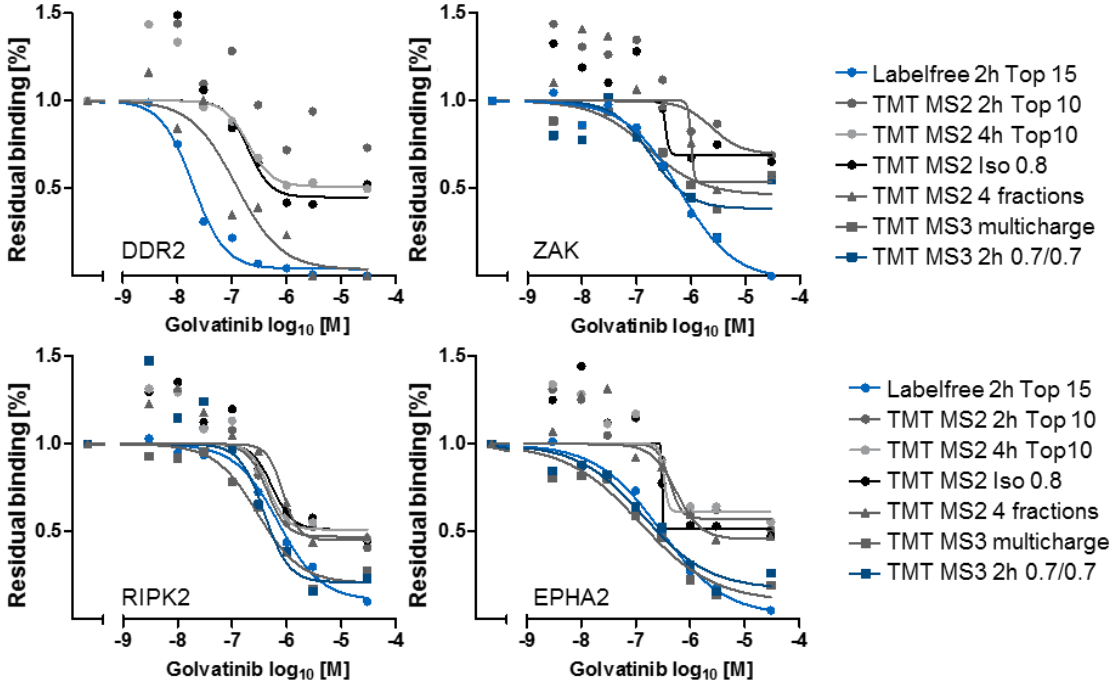

Figure 13: Evaluation of quantification options. *Exemplary dose response curves for the selected targets DDR2, ZAK, RIPK2 and EPHA2 of Golvatinib after label-free or TMT quantification. Label-free quantification shows characteristic dose response. TMT quantification suffers from ratio compression in the MS2 acquisition mode. The impact of ratio compression is reduced in the TMT-MS3 methods.*

The best method was selected based on possible target identification and curve shape of selected Golvatinib targets (Figure 13). Therefore, the Kinobeads drug screen was performed using label-free quantification.

To conclude, TMT quantification could not compete with the label-free measurement. Only in the latter, more proteins and kinases were identified and targets could be determined unambiguously as residual binding completely decreased to zero. The impact of ratio compression was very high in the TMT-labeled samples. This led to underestimation of protein competition off the beads and would hamper proper annotation of previously unknown targets. Label-free quantification overall yields more proteins and kinases as well as better conditions for target identification at the cost of longer measurement time.

3.1.3 Improved data analysis for selectivity profiling of kinase inhibitors

With this established assay in hand, 242 small molecule kinase inhibitors were profiled (Figure 14) in a lysate mix of the four cell lines Colo 205, SK-N-BE(2), K-562 and MV4-11. The inhibitor set contained 37 approved molecules (plus the active metabolite Hydroxyfasudil), 35 drugs in phase III, 4 in phase II/III, 69 in phase II, 16 in Phase I/II and 80 phase I compounds (clinical status as of February 2016; a complete list of inhibitors can be found in the appendix). These inhibitors should target 201 kinases according to the respective supplier. Every compound was profiled in eight concentrations, plus a DMSO control and a pulldown of pulldown, resulting in at least 2420 pulldowns. The whole dataset was measured on the Orbitrap Elite with 20 h per compound and label-free quantification. This generated roughly 5000 h of LC-MS/MS time and over 2400 raw files for the project.

The results presented in this thesis, were finally searched with MaxQuant (v. 1.5.3.30) and a Swissprot database for human proteins containing 20205 entries (internally annotated with PFAM domains). All isoform and TREMBL entries were discarded, facilitating single gene identification and, therefore less protein grouping issues. Fifteen DMSO controls (out of 242 pulldown experiments) were selected for most diverse kinase expression and high intensities. These runs, from now on referred to as standard DMSO controls, were included in every MaxQuant search per inhibitor akin to the concept of spectral libraries in DIA approaches[180]. Exploiting the 'Match-between-runs' feature, also weakly expressed proteins like EGFR and MET could now be identified and quantified in almost every experiment. After identification and quantification by MaxQuant, residual binding of each protein per dose of inhibitor compared to the DMSO control was calculated. IC_{50} and EC_{50} values were inferred by non-linear regression using an internal pipeline (implemented by Mathias Wilhelm, Chair of Proteomics and Bioanalytics, see Experimental Procedures).

Furthermore, if LFQ intensities were only available for the protein in the DMSO control but not in the remaining experimental conditions due to lacking spectral information, residual binding was calculated using raw intensity. This was often the case for potent EGFR or MET inhibitors.

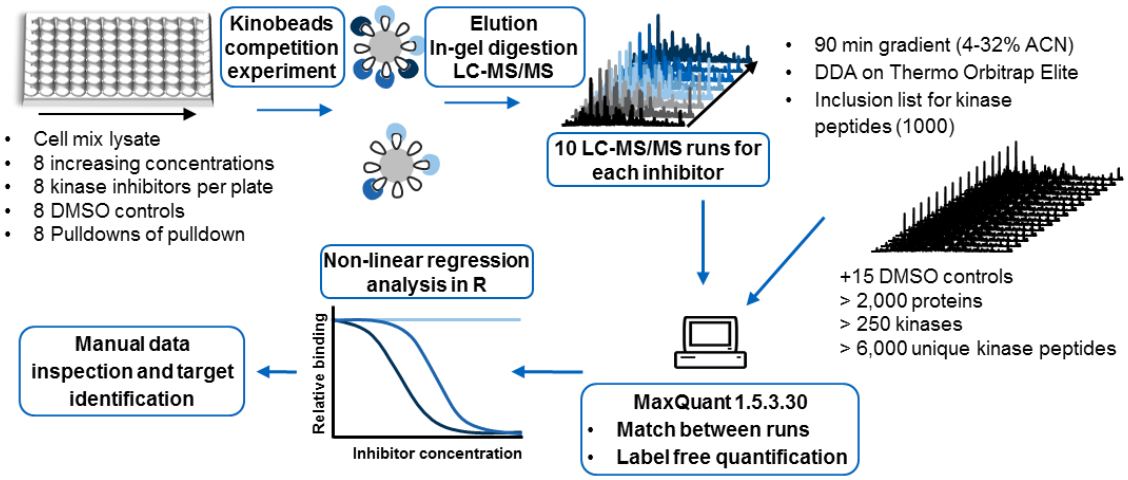

Figure 14: Workflow used for the Kinobeads profiling of 242 inhibitors. *After Kinobeads competition experiments, eluates were digested and analyzed by LC-MS/MS. LC-MS/MS runs for each inhibitor were searched with 15 standard DMSO controls. After identification and quantification, dose response curves were generated and EC_{50} values were deduced by non-linear regression. Targets were annotated manually.*

EC_{50} values could be converted to K_d^{app} values by multiplication with a correction factor (cf) specific to every kinase. This was assessed by a second pulldown (pulldown of pulldown) of the DMSO sample flowthrough. The ratio of the intensity of a kinase found in the pulldown of pulldown to the DMSO intensity for that protein constitutes the cf for the respective protein. Plotting all correction factors across 242 experiments revealed that this ratio varies due to experimental variation. Theoretically, depletion should be similar across all 242 pulldowns, since all parameters were kept constant. The large amount of data facilitated analysis of the depletion in systematic manner. Figure 15 shows this distribution of cf for kinases of the Tyr and STE group, which spans a wide range of possible correction factors for each kinase. Despite always using the same composition of cell mix, protein content in the cell lysates might vary in different lysate batches. The EC_{50} is not influenced too much by this, as the curve fit should correct for outliers in intensities of the single concentration steps. The cf relies on only two values (pulldown of pulldown and DMSO control). Hence, the median correction factor per kinase was used for the final calculation of K_d^{app} in the whole dataset, acknowledging, that this might not correct for the true depletion in the respective experiment. However, a median cf reduces the risk of overestimation of K_ds due to technical variation.

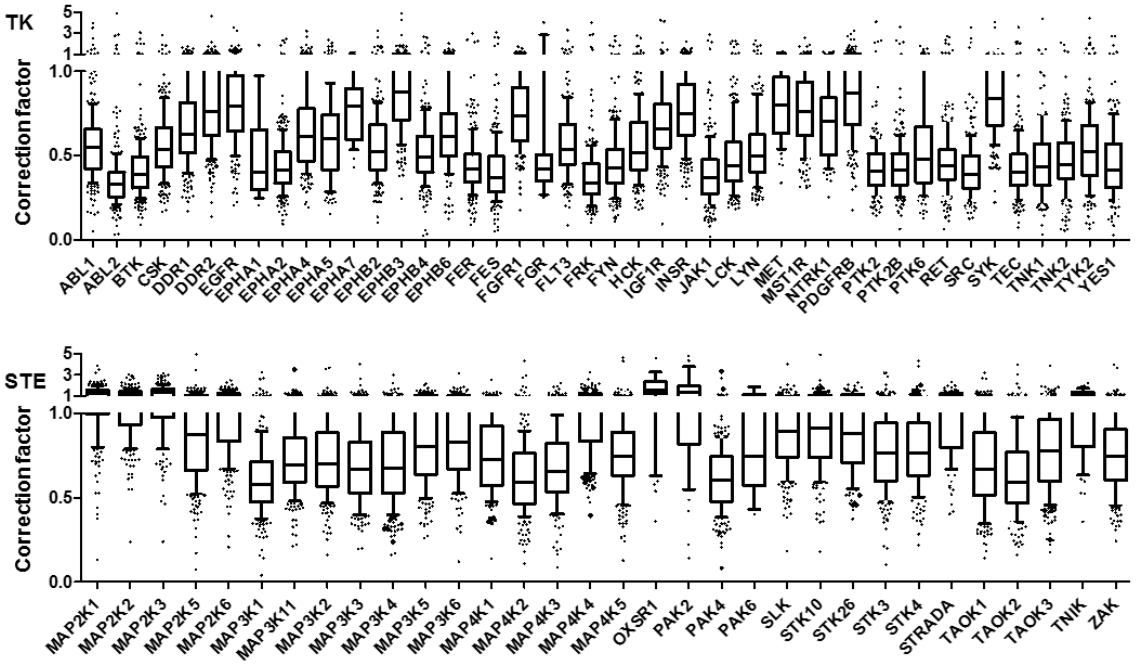

Figure 15: Correction factors for kinases across 242 experiments. *The spread of correction factors for kinases of the tyrosine kinase group (TK) and STE-group depicted as box plots. Whiskers span the 10-90 percentile. A median correction factor of 242 experiments was determined for each kinase and used for EC_{50} to K_d^{app} conversion to eliminate influence of experimental variation of the pulldown of pulldown.*

With this improved data analysis, a total of 357 kinases and 5267 protein groups could be identified across all pulldowns. The average number per inhibitor is 228 and 1974 kinases and protein groups, respectively. To conclude, around 2000 binding curves were obtained per inhibitor describing the target interactions of the respective drug. Overall, this study assesses almost 500,000 drug-protein interactions in dose responses and is one of the largest chemical proteomics studies undertaken so far.

3.2 Target landscape of clinical kinase inhibitors

3.2.1 The druggable Kinome

Chemical proteomics profiling of 242 inhibitors identified 221 kinases as targets of small molecules. Unsupervised clustering of the inhibitors and their respective kinase targets as a heat map revealed the druggable kinome from a chemical proteomics point of view (Figure 16). Each dot represents a drug-kinase interaction colored according to its affinity (pK_d^{app}=-$\log_{10}$ (K_d^{app} [M])). Information on proteins that are either not a target or have not been identified in the respective experiment are shown in white.

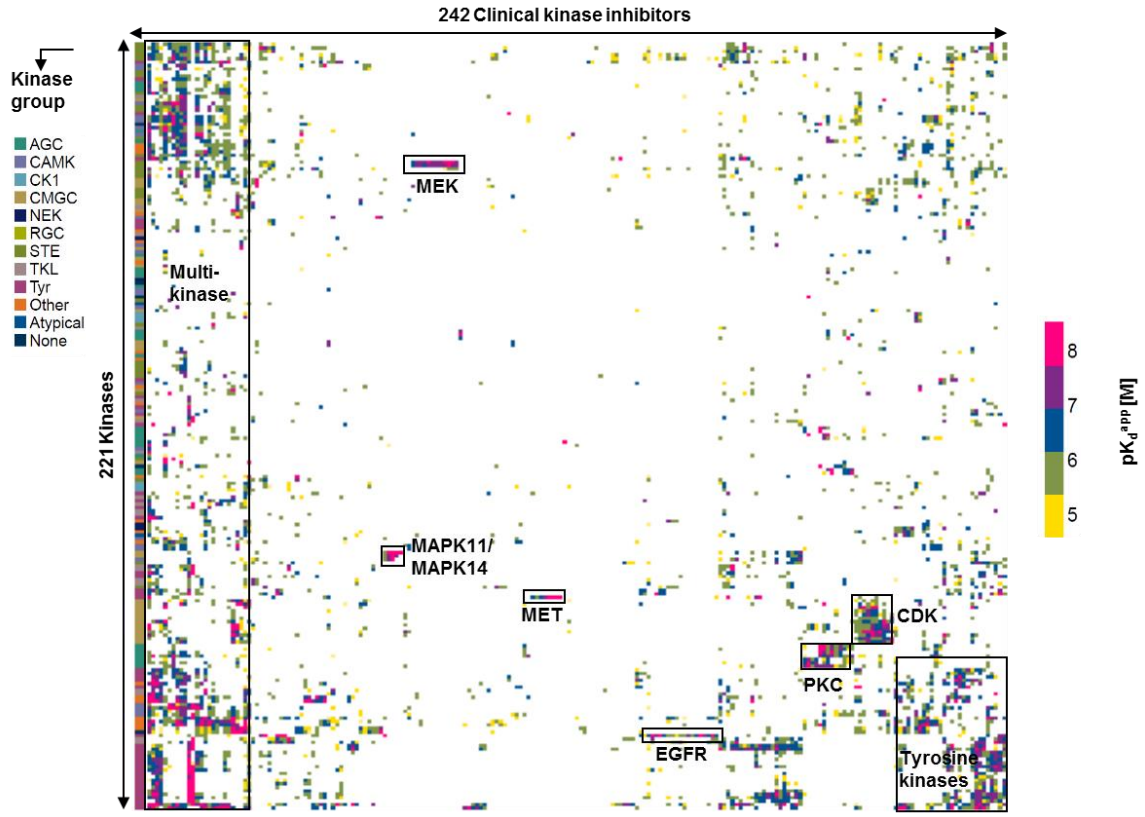

Figure 16: View on the druggable kinome. *Unsupervised clustering of kinase inhibitors and their kinase targets. 221 kinases were identified as targets of 242 inhibitors. The color of the dot reflects pK_d^{app} of the respective drug-kinase interaction. Distinct clusters can be attributed to multi-kinase inhibitors, tyrosine kinase inhibitors, CDK and PKC inhibitors and quite selective EGFR, MEK, MET or p38 inhibitors.*

Unsupervised hierarchical clustering showed that inhibitors have no obvious preference for a particular kinase group. Inhibitors targeting protein kinase C and CDK family such as Ruboxistaurin or Enzastaurin and Alvocidib, AT-7519 or PHA-79387 were relatively selective for their phylogenetic kinase group as most of the targets of these inhibitors cluster together. Many of the 221 kinases are bound by a group of potent multi-kinase inhibitors like Danusertib and Dasatinib. Furthermore, a huge group of inhibitors mainly targets the tyrosine kinase class. Other clusters highlight selective inhibitors against MEK, p38, MET or EGFR. With this drug-protein interaction map in hand, targets of one inhibitor can be assessed at a glance. Furthermore, this dataset can also help choose an inhibitor for a certain target of interest. These results will now be further characterized either on full dataset level or highlighted by selected examples for proteins and compounds.

3.2.2 Compound centric evaluation

In drug discovery, it is always valuable to know the target space of a particular inhibitor. The screen can be analyzed in this regard. For each compound, the target space in this assay can be investigated. Besides kinases, other nucleotide binders and other proteins can be targets of small molecules and results show such interaction. This data is collected and summarized in a PDF for each inhibitor, with an example file in Appendix II (all files can be accessed at http://proteomecentral.proteomexchange.org with the dataset identifier PXD005336 or at www.proteomicsdb.org using the identifier PRDB004257). The kinase targets of PF-3758309 are an example of data available for each inhibitor. PF-3758309 was designed against PAK4 and is currently evaluated in a Phase I trial. Over 92 proteins showed a dose response, thereof 78 kinases. The kinome wide distribution of targets is represented on a phylogenetic kinome tree, where the diameter of the dots is inversely proportional to the K_d^{app} (Figure 17a). Each drug-protein interaction is characterized by a dose response curve plotting residual binding against increasing inhibitor concentration. These intensity-based dose responses are supported by the number of identified peptides and the number of fragmented peptides (MS/MS counts).

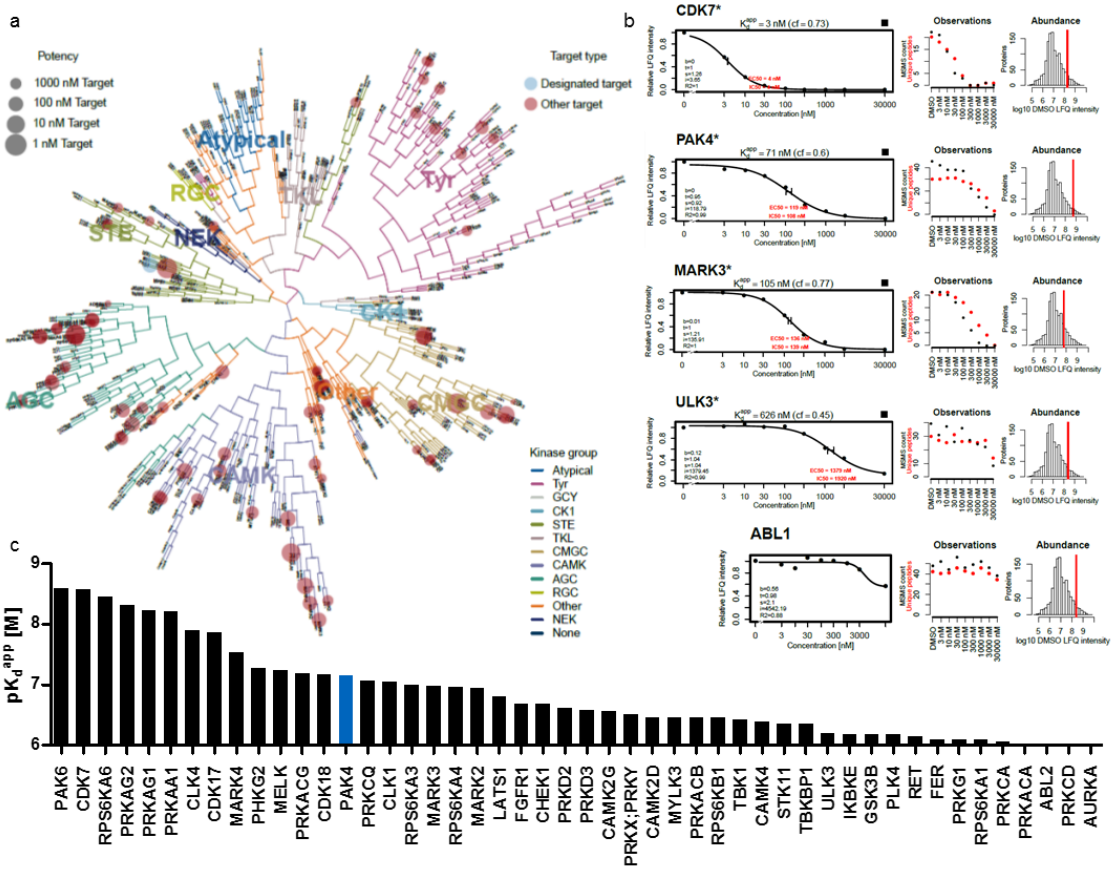

Figure 17: Compound centric evaluation of PF-3758309, a designated PAK4 inhibitor. *a) 78 kinase targets are represented in the kinome tree, blue dots represent designated targets, and red dots mark kinase off-targets. Size of the dots is proportional to affinity. b) Dose response plots, peptide and MS/MS counts per dose point as well as overall intensity abundance of the particular protein across all identified proteins. CDK7, PAK4, MARK3 and ULK3 were annotated as targets, whereas ABL1 is an example for an unaffected kinase. c) Kinase targets below 1 µM ranked according to their pK_d^{app}. PAK4 is marked in blue.*

The protein's intensity in the DMSO control across the overall intensity distribution in the sample reflects the abundance and, thus, the MS-quality of the underlying protein data. With this, CDK7,

PAK4, MARK3 or ULK3 could be identified as clear PF-3758309 binders, whereas for instance ABL1 is not a target as binding to the beads is not affected by this inhibitor (Figure 17b). Profiling of all potential target proteins in one experiment also enabled ranking of the targets according to their K_d^{app}. For PF-3758309, PAK6 was the most potently inhibited kinase, followed by CDK7 and RPSKA6 (Figure 17c). A full list of all inhibitors and their targets is attached in Appendix III.

Of the 242 evaluated inhibitors, 21 compounds (Amuvatinib, AXL-1717, AZD-6482, Buparlisib, Certican, Copanlisib, Dactolisib, Deforolimus, Gedatolisib, GSK-2636771, HMN-214, Idelalisib, KX2-391, Perifosine, Pilaralisib, Rapamycin, Sonolisib, Tideglusib, Torisel, Triciribine and XL-765) showed no targets in the Kinobeads screen. Certican, Deforolimus, Perifosine, Rapamycin, Tideglusib, Torisel and KX2-391 are allosteric inhibitors and their binding to kinases might does not alter the ATP-binding pocket. Targets of those inhibitors still bind to Kinobeads and are thus not competed. AXL-1717 is an inhibitor of IGF1R autophosphorylation, also not affecting the ATP-binding site[219]. HMN-214 is a prodrug and rapidly converted to its active metabolite HMN-176 in living cells. Therefore, it might not bind to PLK in its parental form present in the assay. Unfortunately, HMN-176 was not available for testing. Triciribine, which is dependent on its phosphorylated form[220], presents a similar case. Amuvatinib might be mutant sensitive[221], the main targets c-Kit and PDGFRα were not present in the used cell mix lysate and FLT3 is present in an ITD mutant isoform from MV4-11 cells. AZD-6482, Buparlisib, Copanlisib, Dactolisib, Gedatolisib, GSK-2636771, Idelalisib, Pilaralisib, Sonolisib, and XL-765 are designed against the ATP-binding pocket of the mTOR/PI3K kinase family. The absence of these targets might be explained by an alternative binding mechanism of lipid kinases to the Kinobeads. The development of novel probes, *e.g.* immobilization of such a PI3K inhibitor, enables profiling of this inhibitor class as well[222]. However, the data of the Kinobeads experiments could identify off-targets for some of these mTOR-inhibitors, Apitolisib and Pictilisib targeted 12 and 3 additional proteins, for instance.
The absence of targets in the screen thus indicates quite selective inhibitors with no additional kinase targets.

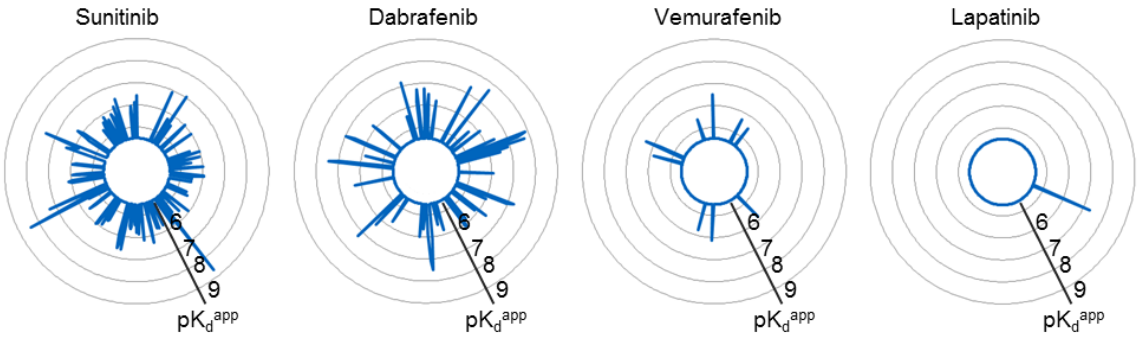

Figure 18: Targets of clinical inhibitors. *Sunitinib and Dabrafenib are multikinase inhibitors with varying affinities for their targets. Vemurafenib has fewer targets with low affinities; Lapatinib only targets EGFR.*

The screen revealed up to 134 targets for AT-9283 (Phase II) or 114 targets for Cyc-116 (Phase I). AT-9283 is known to target over 60 kinases below 300 nM[223], whereas Cyc-116 inhibited activity of ten kinases and has been described as potent Aurora inhibitor[224]. Sunitinib, an approved drug, has over 80 targets (Figure 18). Contrary, 64 inhibitors of the screened panel target only one or two proteins. A closer look on Sunitinib targets (Figure 18) exposed that the majority of proteins have K_d^{app}s below 1 µM, whereas only few proteins are targeted with low nanomolar binding affinities. Dabrafenib, approved for the treatment of malignant melanoma, targets over 40 proteins, many

thereof with high binding affinity (<100 nM, Figure 18). Vemurafenib, also approved for treatment of malignant melanoma, targets ten proteins and most of them with micromolar affinity. Lapatinib, approved for breast cancer therapy, only hit EGFR in the screen.

The screen also contained some pro-drugs and active metabolites thereof. The target spectrum and potency of such pairs varied considerably (Figure 19). Fasudil had many more targets than the active metabolite Hydroxyfasudil. Conversely, the VEGFR pro-drug TG-100801 had far fewer and less potent targets than the active drug TG-100572. As similarly observed with Barasertib, the active metabolite of the SYK inhibitor Fostamatinib had a very different kinase binding profile compared to the precursor molecule. Careful target profiling of an inhibitor, the formulation and metabolites thereof should generally be performed to comprehensively understand the mechanisms by which a clinical drug might exert its *in vivo* effect.

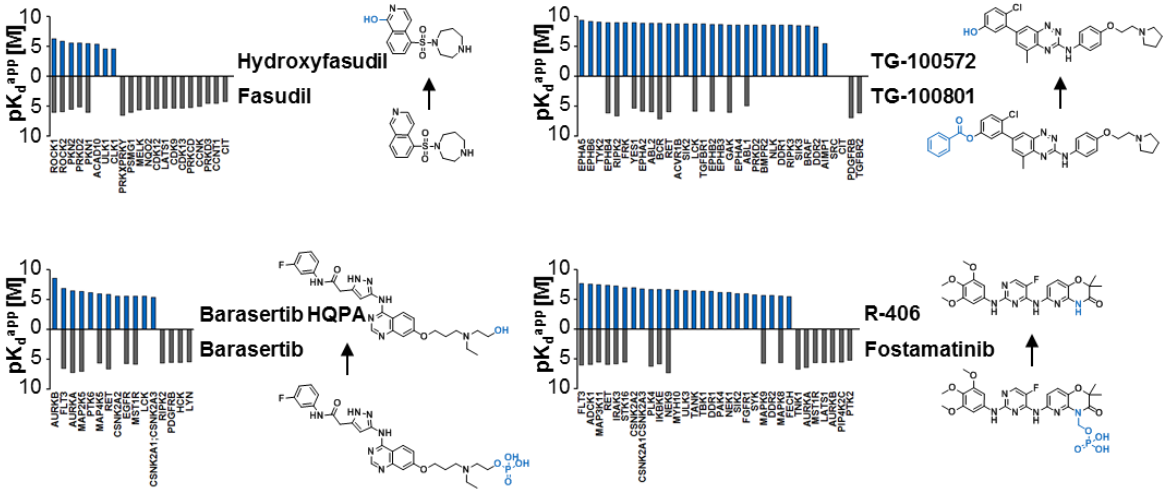

Figure 19: Pro-drugs and their active metabolites. *Number of targets and their potency varies between pro-drugs and the respective active drug. Fasudil targets many more proteins as its metabolite, whereas TG-100801 has fewer and less potent targets than the active drug. Barasertib and Fostamatinib target additional proteins that could not be identified for their active metabolites.*

3.2.3 Protein centric evaluation

One advantage of this large-scale selectivity profiling approach is that one cannot only investigate the number of targets of one drug but also look at the number of drugs against one target. Based on the range of available inhibitors and their additional targets, the most appropriate one can then be chosen for an experiment. A closer analysis of the druggable kinome revealed that all kinase groups can be targeted with clinical drugs (Figure 20a, b). The most often hit protein is RET, a target of 88 compounds (Figure 20c). This is followed by FLT3, another tyrosine kinase targeted by 61 inhibitors. Both kinases are well-studied and implicated in disease (over 200 citations in pubmed.gov since the early 2000s). STK10 in the STE family was identified as target of 58 compound profiles (Figure 20d). Other frequent hitters include GAK (other, 55 drugs), ABL (Tyr, 54 drugs), BMP2K (other, 53 drugs) and DDR1 (Tyr, 50 drugs). The majority of identified inhibitor targets can be found in the tyrosine kinase group. Out of historic reasons, drug discovery has long focused on this kinase group. Moreover, most chemical scaffolds are quite similar suggesting a preference for the inhibition of the same kinases[61]. Members of the AGC, STE or CMGC group are also prominently represented in the target space, whereas only a small number of atypical kinases are targets of the tested inhibitors. Potency against these kinases varies and can/has to be taken into account when

selecting a molecule against this target. Binding constants below 1 µM (light grey, Figure 20b) could be determined for several inhibitors in almost all kinase groups. Inhibition below 100 nM was often observed in the tyrosine and other kinase group (blue, Figure 20b). The radar plot of K_d^{app} of all inhibitors against RET shows that 29 inhibitors can bind to RET with an affinity of less than 100 nM (Figure 20c). On the contrary, members of the remaining kinase groups are not always bound with this affinity. STK10, for example, is targeted by many compounds but only five have a binding affinity below 100 nM (Figure 20c). It is a common off-target of kinase inhibitors and implicated in side effects during therapy. Previous studies linked STK10 and SLK inhibition to adverse effects in Erlotinib therapy by upregulation of lymphocytic responses[225]. For a big part of inhibitors, the main target VEGFR could not be identified as the VEGFR-family is rarely found in cell lines[226]. The use of tissue expressing these proteins, like placenta tissue, provides an option here[218].

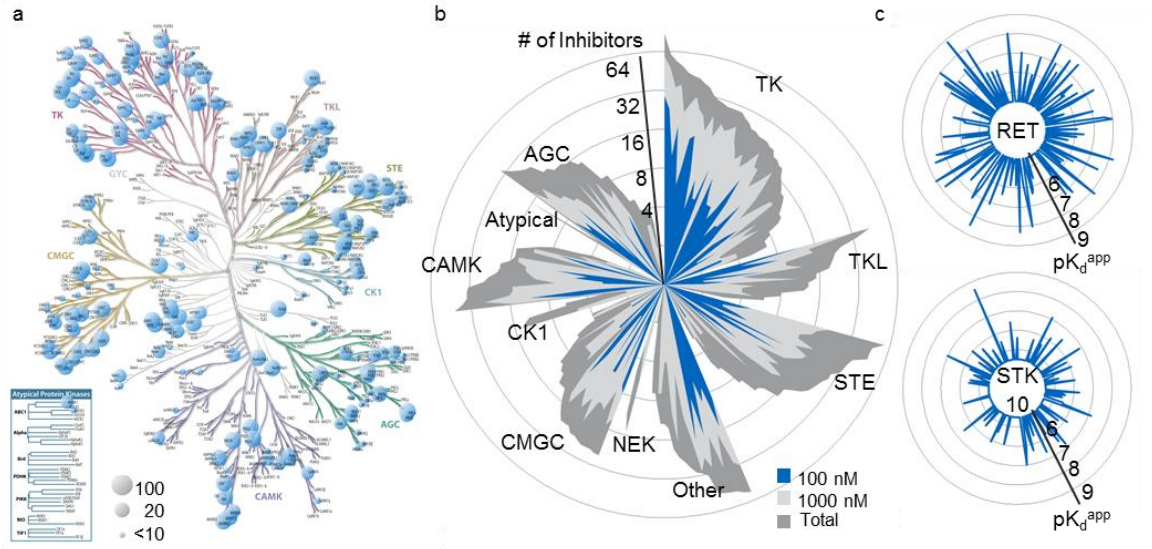

Figure 20: Protein centric evaluation. *a) Kinometree representation of all targeted kinases (courtesy of Cell Signaling Technologies). With this inhibitor set, 40% of the kinome can be addressed. b) Radar plot for number of inhibitors against one kinase. Kinase are sorted according to kinase group and color reflects affinity of the target (blue<100 nM, light grey<1000 nM, dark grey for total number). A majority of compounds is designed against tyrosine kinases, but all other kinase groups are also represented in the target space. c) Radar plots for 88 and 58 inhibitors targeting RET (top panel) and STK10 (bottom panel), respectively. Inhibitors are sorted alphabetically and length of the spikes reflects pK_d^{app}. RET can be bound with high affinity, whereas STK10 is often targeted with lower potency.*

As expected, the vast majority of compounds interacted with protein or lipid kinases. The study also revealed binding to seven metabolic kinases, 19 other nucleotide binders, five FAD binders (ACAD10, ACAD11, ACOX3, DHCR24 and NQO2), and the heme binding enzyme FECH. These unanticipated interactions can potentially lead to desired consequences, but can also represent mechanisms of drug toxicity. The off-target FECH will be further investigated in paragraph 3.5 of this thesis.

3.2.4 Comparison to existing datasets

As outlined in the beginning, good characterization of clinical molecules is desirable to evaluate drug effects and off-target effects. The community already engaged in several approaches and efforts to help this characterization. Anastassiadis *et al.* profiled 178 inhibitors at a single dose against 300 recombinant kinases[72], 25 of these inhibitors are also present in our clinical inhibitor

set. Kinase inhibitors have also been investigated using the KinomeScan technology[76]. The published datasets include 20 compounds (16 clinical) against 119 phage-displayed-kinases[76], 38 compounds against 317 recombinant kinases[75] with 28 inhibitors overlapping to our set and 72 kinase inhibitors against 442 kinases[74], thereof 52 clinical drugs. This data collection is ongoing in the LINCS database which currently includes 161 kinase inhibitors (67 clinical) and 440 kinase domains including mutant variants[211]. The results of the Kinobeads selectivity profiling were compared to these datasets for overlapping drug-protein interactions. Furthermore, the comprehensive activity data analysis of Metz *et al.*[212] (3800 inhibitors (42 clinical) against 172 kinases) as well as all relevant entries in CHEMBL database[210] were included in the comparison.

The size of the black dots in Figure 21a reflects the number of newly identified targets for each inhibitor. Inhibitors are grouped according to their clinical status and the Kinobeads screen still identified new targets even for approved drugs. Notably, selectivity profiling of the approved inhibitor Ponatinib revealed 40 protein-drug interactions not present in the screening literature or databases. Fauster *et al.* performed pulldowns with immobilized Ponatinib and could identify several of these previously unknown off-targets[100]. The compound with the highest number of novel targets is AT-9283, originally designed to inhibit JAK2/3 and Aurora kinases, followed by PF-3758309, a designated PAK4 inhibitor, with 77 new targets.

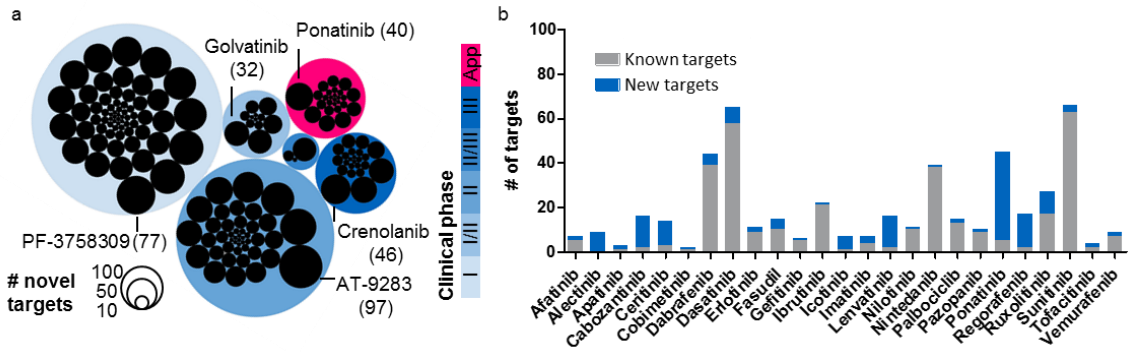

Figure 21: Novel targets of kinase inhibitors compared to literature. *a) Novel targets identified by Kinobeads, which were not reported as target in the screening literature. Inhibitors are grouped by clinical phase, each drug is shown as black circle and the size of the circle is proportional to the number of undescribed targets (in brackets). b) Closer view on novel targets of approved inhibitors.*

This analysis shows, that even compounds that are available for quite some time and already routinely used for therapy are not yet fully characterized as part of large-scale studies and commonly used databases (Figure 24b).

3.3 Characterization of clinical kinase inhibitor selectivity

3.3.1 Global selectivity of clinical kinase inhibitors

The assessment of selectivity of kinase inhibitors has always been subject of discussions. Most clinical kinase inhibitors are claimed to be potent and selective, because they are discovered in target based drug discovery. Moreover, selectivity seems to be desired in therapy to rule out off-target toxicities and to ensure target directed efficacy. It has been found, that unselective drugs might also have some benefits[227]. Polypharmacology on the one hand can explain off-target toxicities, on the other hand it can also be beneficial as more proteins are hit with one drug and the inhibitor can be used in another disease setting. Nevertheless, small molecule inhibitors are also applied in basic research and often, phenotypic effects are attributed to the inhibition of the designated target with a 'selective' inhibitor[228].

Assessing selectivity of a compound for a target or target class is not trivial as the full range of targets of a given compound is rarely known or measured. Drug selectivity for a given target also depends on the applied dose and the qualitative and quantitative expression of the target proteins in a particular cell type. Selectivity can be measured in various ways; *e.g.* using the selectivity score[74, 75]; the selectivity entropy[229], the Gini-coefficient[230], or the partition index[231]. Each of these metrics has their advantages but also several shortcomings. As all compounds in this project were profiled in a dose dependent fashion and at near thermodynamic equilibrium in cellular lysates, a novel selectivity measure (Concentration and Target Dependent Selectivity: CATDS) was developed by Stephanie Heinzlmeir and Mathias Wilhelm in-house. Briefly, CATDS measures the reduction of binding of a particular protein to Kinobeads at a particular compound concentration relative to the summed reduction of binding of all proteins at that concentration. A CATDS of 1 means no additional target, whereas a CATDS close to zero represents unselective inhibitors. The CATDS is very versatile and can be used to answer multiple questions concerning selectivity.

Global selectivity of the whole panel was investigated after calculating the CATDS for the most potent target of each inhibitor at its K_d^{app} against all other targets. The 242 profiled inhibitors range from very selective compounds to very unselective multi-kinase inhibitors (Figure 22a). Rabusertib, Capmatinib or Lapatinib appear to be very selective compounds and can be used to selectively target CHEK1, MET or EGFR, respectively. Compounds like TAK-901, Midostaurin or XL-228 on the other hand target multiple kinases and show very poor selectivity.

Some inhibitors have been previously annotated as selective chemical probes in thorough evaluation by others[232]. However, the rank plot shows that inhibitors like Palbociclib or Ruxolitinib are not selective according to Kinobeads results (Figure 20a, blue dots). Ruxolitinib, for example, has been tested against a commercial panel of 26 kinases across the kinome and was not found to inhibit any other targets than the JAK family[233]. It was concluded, that concentrations up to 1 µM can be used without off-target effects. In the Kinobeads profile, six other kinases are hit with a K_d^{app} below 1 µM indicating potential off-target effects when used at this concentration. The same is true for Palbociclib; it is described as a selective inhibitor[234] but showed several off-targets in the Kinobeads screen. Here, systematic reprofiling of clinical inhibitors improved target space knowledge and contributed to better characterization of potential chemical probes. This is a prerequisite for drawing conclusions when using these inhibitors as chemical probes[235].

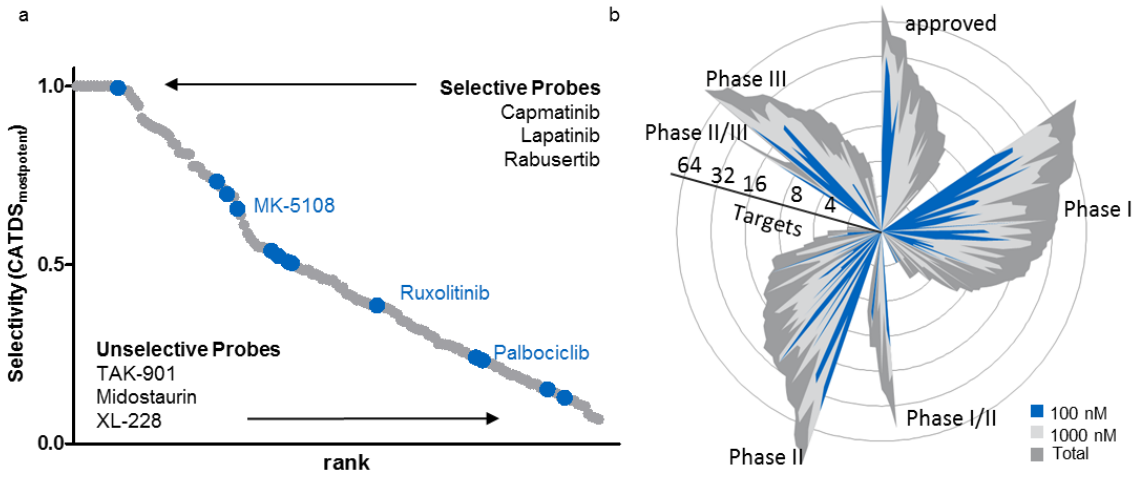

Figure 22: Selectivity distribution of clinical kinase inhibitors. *a) Global selectivity distribution. A CATDS score of 1.0 means high selectivity, a CATDS close to 0 identifies unselective inhibitors. Clinical kinase inhibitors span a wide range of selectivity, multiple drugs are very selective, but also several unselective molecules are successful in clinical evaluation. Blue dots mark inhibitors that qualified as chemical probes according to chemicalprobes.org[232]. b) Number of targets of inhibitors sorted according to clinical phase. Color reflects affinity (blue<100 nM, light grey<1000 nM, dark grey for total number). Drugs in Phase I trials are not more selective than inhibitors, which are already longer under clinical evaluation.*

Inhibitors were sorted in regard to their clinical status (as of February 2016) and their number of targets up to 100 nM (blue), 1 µM (light grey) and the total number of targets (dark grey) were plotted in a radar plot (Figure 22b). The distribution of compound selectivity in a clinical phase ranges from very promiscuous to very selective inhibitors and more advanced compounds do not show higher selectivity than those in earlier trials. This reinforces the notion that selectivity is not a strict requirement for progressing compounds in the clinic.

3.3.2 Selectivity across binding types

A common classification of kinase inhibitors considers the binding mode to the kinase main target. Out of the 242 molecules, 137 inhibitors had available binding mode information. The investigated data set contained 66 type 1 inhibitors that bind to the designated target kinase in the 'DFG-in'-conformation, 17 inhibitors were classified as having a type 2 binding mode, thus targeting the 'DFG-out' conformation. Only inhibitors were considered whose main target was identified. Selectivity was calculated according to the most potent designated target of each inhibitor at the respective K_d^{app}. Both inhibitor-type groups contain very selective (CATDS=1) but also very unselective (CATDS≥0) inhibitors (Figure 23a). The median CATDS of both groups showed no notable difference (median CATDS of 0.3 for type 1 vs 0.4 for type 2). Hence, type 2 inhibitors are not more selective than type 1 inhibitors, a fact that has already been found by others using screening panels[74]. Up to 80 and 60 targets were identified for type 1 and type 2 binding modes, respectively. Another 12 inhibitors bind to a cavity adjacent to the ATP binding pocket in MEK1 and MEK2-kinases. This cavity can be targeted by small molecule inhibitors of the type 3 binding mode and results in very selective inhibitors[58]. The median CATDS of these inhibitors was higher compared to type 1 and 2 inhibitors (median CATDS of 0.7). Indeed, most type 3 inhibitors only target MEK1 and MEK2 with differing selectivity for one or the other protein (Figure 23b). For inhibitors with off-targets, MEK1 or MEK2 were still inhibited with a better K_d^{app} than the off-targets. RDEA-436 showed the most off-targets, including the non-kinases S-adenosylmethionine synthase MAT2A and the oxidoreductase NQO2. NQO2 is also an off-target of Binimetinib and has been previously

identified as off-target of some other kinase inhibitors as well[91, 99]. MAP2K5 (MEK5) is bound by three of the 12 inhibitors. Its structure is highly similar to MEK1/2 but lacks the copper binding sites of MEK1/2 involved in cell signaling. MEK5 might promote copper independent MEK-ERK signaling and can render tumor cells resistant towards potential copper-chelator therapy in BRAF(V600E) melanoma[236].

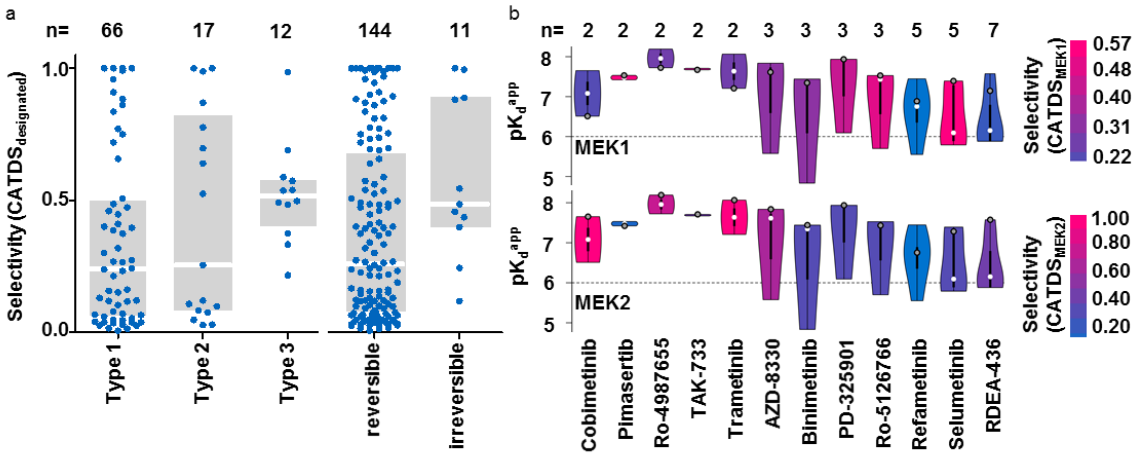

Figure 23: Selectivity across binding types. *a) Selectivity analysis of 137 kinase inhibitors with annotated binding type according to $CATDS_{designated}$ (selectivity for the most potent designated target of a compound at its K_d^{app}). Type 1 and 2 inhibitors do not differ in median selectivity, whilst type 3 inhibitors were generally more selective. Irreversible and reversible inhibitors spanned a broad range of selectivity, albeit highly selective molecules were apparent in both. 'n' states the number of inhibitors. b) Violin plots depicting the number of targets (n) and binding affinity (expressed as pK_d^{app}) of MEK1 (top panel) and MEK2 (bottom panel) inhibitors (MEK, grey circle). The color code for the violins is according to selectivity for MEK1 or MEK2, respectively (expressed as $CATDS_{MEK}$ at the respective K_d^{app}). MEK inhibitors are very selective and potent for either MEK1, MEK2 or both.*

The last category comprises allosteric inhibitors. They were included in the panel to evaluate if the binding modifies the ATP site enough to result in reduced binding to the Kinobeads. This was observed for MK-2206, which is indeed very selective towards its intended target AKT. It has one further off-target, FECH (see 3.5). No other type 4 allosteric inhibitors in the panel scored in the assay, thus the design of their pharmacophores is orthogonal to that of ATP-binding inhibitors.

Most of the inhibitors in the panel are reversible ATP-competitors, but a few inhibitors in clinical trials nowadays are irreversible by design. The median CATDS of 0.6 compared to 0.4 for reversible inhibitors might indicate higher selectivity of covalent inhibitors but this was not universally the case. It will be discussed in more detail in the next paragraph.

3.3.3 Irreversible and reversible inhibitors

Another option in drug design is the addition of a chemical group enabling a covalent, irreversible interaction with the target. The use of irreversible inhibitors has always been evaluated carefully, as specific and unspecific irreversible reactions might lead to unpredictable side effects. However, the cellular potency of ATP-competitive inhibitors is affected by intracellular ATP levels, so even if kinase binding can be observed *in vitro*, the inhibitor might not be able to compete with ATP inside the cell[237]. Here, irreversible inhibitors offer a solution, as covalent, irreversible inhibition increases residence time at the target protein. Irreversible inhibitors have gained considerable attention as three inhibitors have been approved recently (Afatinib and Osimertinib for EGFR inhibition in

NSCLC, Ibrutinib for treatment of mantle cell lymphoma and chronic lymphatic leukemia). In our set, nine inhibitors target the EGF-receptor and two are directed against BTK (Bruton tyrosine kinase). They can bind covalently to a cysteine in the active center of these kinases (C797 in EGFR and C481 in BTK) and are considered more selective than their reversible counterparts. These inhibitors might also bind reversibly to other kinases and are expected to be irreversible for all proteins having a cysteine at this position in the active site[238]. Druggable cysteines in kinases have been separated into different groups, depending on their position within the kinase domain[33, 239]. K_d^{app} values for irreversible inhibitors lack the influence of kinetic behavior of this binding mode[63], therefore their binding affinities need to be evaluated with care. For comparison to reversible inhibitors, K_d^{app} values were used as the relative ranking of targets did not change, whereas EC_{50} values were considered for characterization of Pelitinib binding kinetics.

Figure 24 depicts the distribution of targets and their pK_d^{app}s of reversible and irreversible EGFR inhibitors after 45 min pre-incubation prior the Kinobeads enrichment. The only two designated BTK-inhibitors in clinical trials are irreversible; therefore, they are also included in this plot. Ibrutinib profiling revealed 23 additional targets, whereas the structurally similar compound Ono-4059 analogue is very selective with only two targets. Since EGFR/HER2 inhibitors represent the majority of this binding type in the panel, 24 EGFR inhibitors will be discussed further. At first sight, there was no obvious difference in proteins binding to the inhibitors. Both binding types can have many or few targets. Notably, the reversible inhibitors AC-480, Lapatinib and TAK-285 showed no additional targets in the profiling using the four cell line mix. 24 EGFR-inhibitors were also profiled in BT-474 lysate, a breast cancer cell line driven by HER2 expression and with high EGFR levels[240]. In this more disease relevant setting, the inhibitors showed comparable selectivity to the profiles obtained in the four cell line mix. Also, the K_d^{app}s were comparable. However, HER2 could not be identified as target, suggesting a different binding mechanism to the Kinobeads. Here, MAP2K5 and STK17A were identified for AC-480 and TAK-285, respectively, albeit with lower potency. MAP2K5 was identified as low confidence target of both inhibitors in the four cell line mix and thus not considered in the analysis. EGFR was always the most potent target, except for Neratinib and Rociletinib in the cell mix. In the BT-474 cell line, the determined EC_{50} was slightly better than that of the off targets. This is likely due to higher EGFR expression levels that led to better EGFR quantification and thus better curve fitting. The multi-kinase inhibitors that bind EGFR reversibly showed no trend towards higher K_d^{app}s for EGFR in a systematic manner. The difference in K_d^{app} between EGFR and other targets is more than two log_{10}-units for the reversible Sapitinib (and AC-480 in BT-474) and for the irreversible Afatinib, AV-412, Canertinib, Dacomitinib and Poziotinib. These inhibitors can thus be very selective for EGFR if choosing the right dosage window. Icotinib and Vandetanib have very poor affinity towards EGFR, which could be due to the unique compound structure of Icotinib, whereas Vandetanib is a designated VEGFR-inhibitor with known less potency towards EGFR[241]. GAK (Cyclin G associated kinase, grey dot) was identified as a common off-target of EGFR inhibitors. It was hit by reversible and irreversible inhibitors alike with comparable potency to EGFR for reversible inhibitors. GAK is a negative regulator of EGFR signaling and its down regulation might promote tumorigenesis[242]. Moreover, GAK inhibition might be one molecular reason for the side effect of pulmonary alveolar dysfunction observed in Gefitinib therapy[243]. Therefore, GAK inhibition should be carefully evaluated in drug design and therapy, as this might lead to undesired consequences.

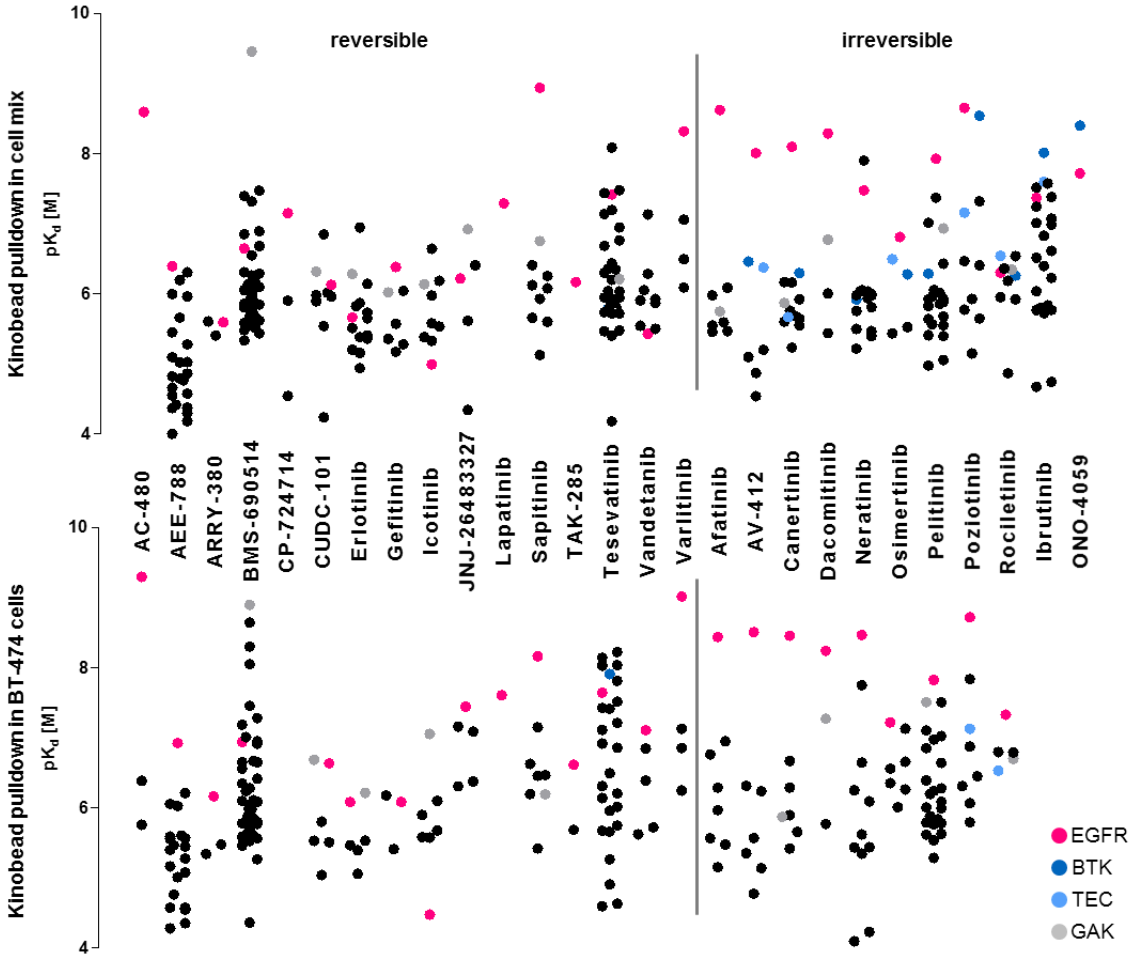

Figure 24: Reversible and irreversible EGFR inhibitors. *Scatter dot plots for targets of designated reversible and irreversible inhibitors against EGFR or BTK. EGFR inhibitors were also profiled in BT-474 cell lines (bottom panel). EGFR is marked in pink, BTK in blue and TEC in light blue; they have a cysteine in the same position as EGFR. GAK (grey) seems to be a common off-target of EGFR inhibitors. Irreversible and reversible inhibitors do not necessarily differ in their selectivity. Some reversible inhibitors can be quite selective (e.g. AC-480, Lapatinib, TAK-285). The main target of irreversible inhibitors often shows the most potent inhibition and spans a wide affinity range to the next off-target (e.g. Afatinib).*

Remarkably, BTK is commonly targeted by all irreversible inhibitors, but not by Afatinib and Dacomitinib. Except for Poziotinib, the designated EGFR inhibitors were more potent towards EGFR. For designated BTK inhibitors the expected preference for BTK was observed. Interestingly, irreversible inhibitors do not bind to BTK in BT-474 cells. BT-474 cells express a different transcript variant of BTK with an alternative promoter and an additional sequence at the N-terminus[244]. Tesevatinib, which is the only reversible inhibitor targeting BTK as well, also binds to the kinase in BT-474 lysate. One might speculate that the reactive cysteine in the alternative transcript cannot be reached by irreversible inhibitors anymore, whereas Tesevatinib interacts with different residues in the kinase domain. EGFR, BTK and TEC all have a highly nucleophilic cysteine in the hinge binding region, especially facilitating electrophilic reactions[33, 239]. For that reason not only BTK, but also TEC-kinase is targeted by this set of irreversible inhibitors and is often amongst the top three hits of an inhibitor.

Afatinib for example has quite a few targets but spans a wide range of K_d^{app}s. The K_d^{app} for EGFR is around 8 nM (after 45 min preincubation), whereas the next target is only targeted with a potency of around 1 µM. At the respective dosage, Afatinib can thus also be considered a selective inhibitor.

Selectivity for the main target is not only dependent on affinity but also on the residence time of the drug at the target. This often results in the application of lower dosing concentrations, with which these drugs can be applied.

The irreversible inhibitor Pelitinib was investigated further concerning irreversibly and reversibly bound off-targets. Therefore, incubation times of the drug with the lysate were extended to 6 h, 14 h and 20 h prior to the 30 min Kinobeads incubation. Figure 25 shows the inhibition curves for selected targets of Pelitinib and their time dependence. EGFR as main target shows an EC_{50} of 22 nM after 45 min, which improves to 6 nM and 5 nM for the 6-14 h and 20 h time points. The same behavior can be observed for BTK, with an EC_{50} of 7551 nM after 45 min and 212 nM after 20 h. GAK shows the opposite behavior, with 57 nM at 45 min increasing to an EC_{50} of 562 nM after 20 h incubation. Therefore, the obtained EC_{50} values in the screen should be compared carefully, as irreversible inhibitors show better potency over time confirming the irreversible binding behavior[239]. This was especially severe for BTK, where no real curve fit and EC_{50} determination was possible for the earliest time point.

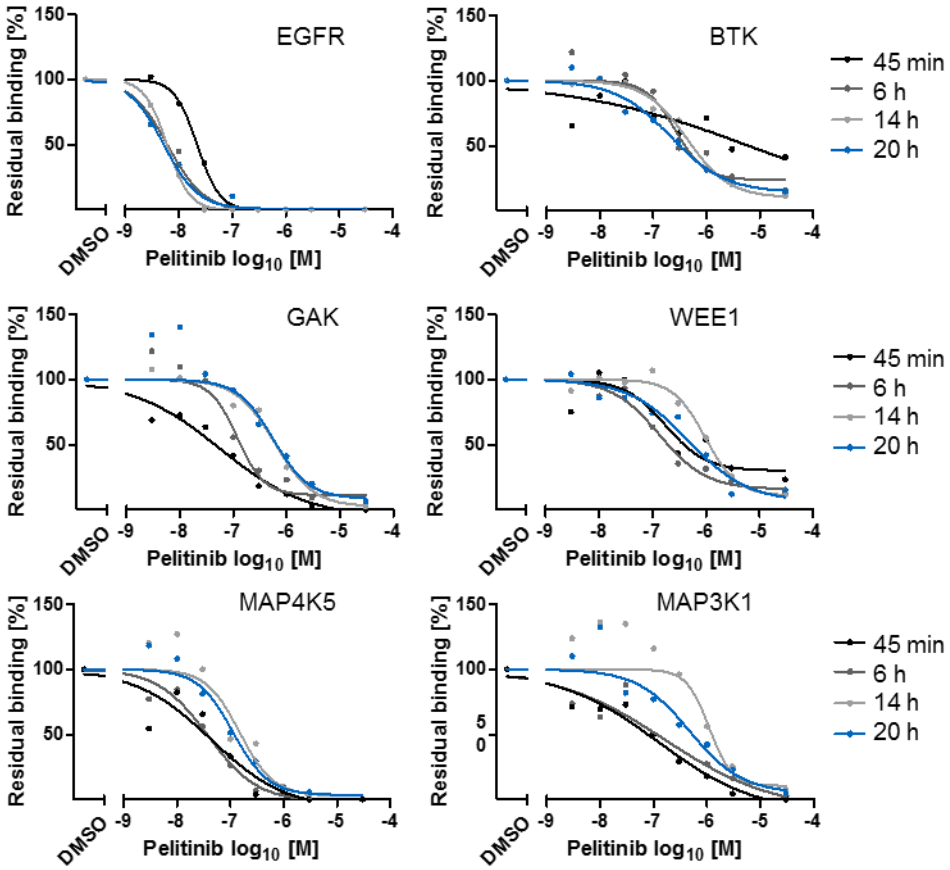

Figure 25: Time dependence of obtained EC_{50} values for the irreversible EGFR inhibitor Pelitinib. *Irreversible binding mechanisms, e.g. EGFR and BTK, improve in their EC_{50} upon longer incubation, whereas the EC_{50} of targets bound reversibly (GAK, WEE1, MAP4K5, MAP3K1) is not affected or decreases over time.*

The other targets of Pelitinib do not have a cysteine at the respective position of EGFR[238]. They are therefore likely binding reversibly and this binding should therefore not be influenced by incubation time. The kinase WEE1 shows similar binding curves for 45 min, 6 h and 20 h (EC_{50} between 174 nM to 470 nM). MAP4K5 and MAP3K1 have similar EC_{50}s for the two earlier time points (~40 nM and

~140 nM, respectively), which increase for the two latter time points (~130 nM and 1091/475 nM). Members of the SRC-family of kinases as well as the non-kinase protein FECH (see 3.5), showed binding at higher doses for the 45 min time point but were not competed after 20 h. Therefore, targets with no cysteine in the active center (MAP4K5 and MAP3K1) or at a distinct position from the EGFR/BTK cysteine group (e.g. WEE1, GAK) showed no difference in EC_{50} or decreased binding affinities over time[238]. The shift towards less potent EC_{50}s for reversible targets at longer time points might be an artefact of the experiment itself. One potential explanation is given by potential side reactions of the irreversible inhibitor with DTT, diminishing the effective concentration of free inhibitor present in the lysate. Experiments with lower DTT concentrations, however, did not show severe differences (data not shown). Moreover, with longer incubation times, more drug will be bound irreversibly by the main target. Unspecific binding to cysteines in other proteins might also occur. This might affect the pool of free inhibitor as well.

In conclusion, selective EGFR inhibitors can be designed that inhibit only their designated target or show increased potency because of longer residence time in the irreversible binding mode. Irreversible inhibitors can be profiled with Kinobeads, but the kinetic aspect of their mode of action and therefore, influence on the target profile, has to be considered.

3.3.4 Selectivity is not dependent on the designated target

Many inhibitors in the panel have been designed against the same target. The selectivity for that target amongst these inhibitors varies. Similar to the EGFR inhibitors shown above, inhibitors can be very selective for their intended target or possess several off-targets. This can be a selection criterion, when more inhibitors for one target are available. Here, the MET receptor and its inhibitors are used as an example. The screening panel includes 15 inhibitors against MET-receptor, and 12 were used for the comparison. MET-receptor competition in the used four cell line mix suffered from low expression, thus, the underlying MS data was often poor. This hampered comparison of potential off-target effects. To overcome this issue, additional Kinobeads pulldowns were performed for designated MET inhibitors in the four cell line mix plus an additional cell line with higher MET expression (CAKI-1, renal cancer)[245]. The addition of CAKI-1 enabled the identification of MET in all pulldowns and thus, generation of dose-response curves for MET.

Figure 26 displays the targets of MET inhibitors profiled in cell mix (grey) and cell mix plus CAKI (blue). Target profiles of the two experiments per drug overlapped quite well. Pulldowns in cell mix + CAKI lysate could detect a few additional targets like AXL, which were not identified in cell mix alone. Moreover, the plots clearly show that selective MET inhibitors can be designed. Capmatinib, PF-04217903 and Tivantinib seemed to be selective for MET in the evaluated settings and should be good chemical probes to investigate MET-biology. The high selectivity of PF-04217903 can be explained by unique interactions with residues in the auto-inhibited ATP-pocket[246]. To a lesser extent, also AMG-208, JNJ-38877605 and Tepotinib can be considered selective within the kinome. However, Tepotinib and JNJ-38877605 target NQO2, a quinone reductase. Off-targets of AMG-208 include PRKCSH (Glucosidase 2 subunit beta), MAP4 (microtubule-associated protein 4), and FLNB (Filamin B). MET was identified in the Volitinib profile, but a curve fit and thus determination of an EC_{50}/K_d^{app} was not possible as it could only be quantified in the DMSO control. This might be due to very high affinity of Volitinib to MET. Profiling with inhibitor doses below 3 nM might overcome this issue and enable curve-fitting. Besides its designated target MET, binding of AXL was observed with micromolar affinity. BMS-777607, Cabozantinib, Crizotinib, Foretinib and Golvatinib target up to 42

proteins and, thus, are unselective, multi-kinase inhibitors. Cabozantinib and BMS-777607 have fewer targets within the TK kinase group compared to Foretinib and Golvatinib. Crizotinib targets more TKL and STE group members as well as members of the CAMK family. Despite their common main target, these inhibitors span a wide range of selectivity. This analysis reveals that it is possible to design selective inhibitors for MET when addressing certain residues.

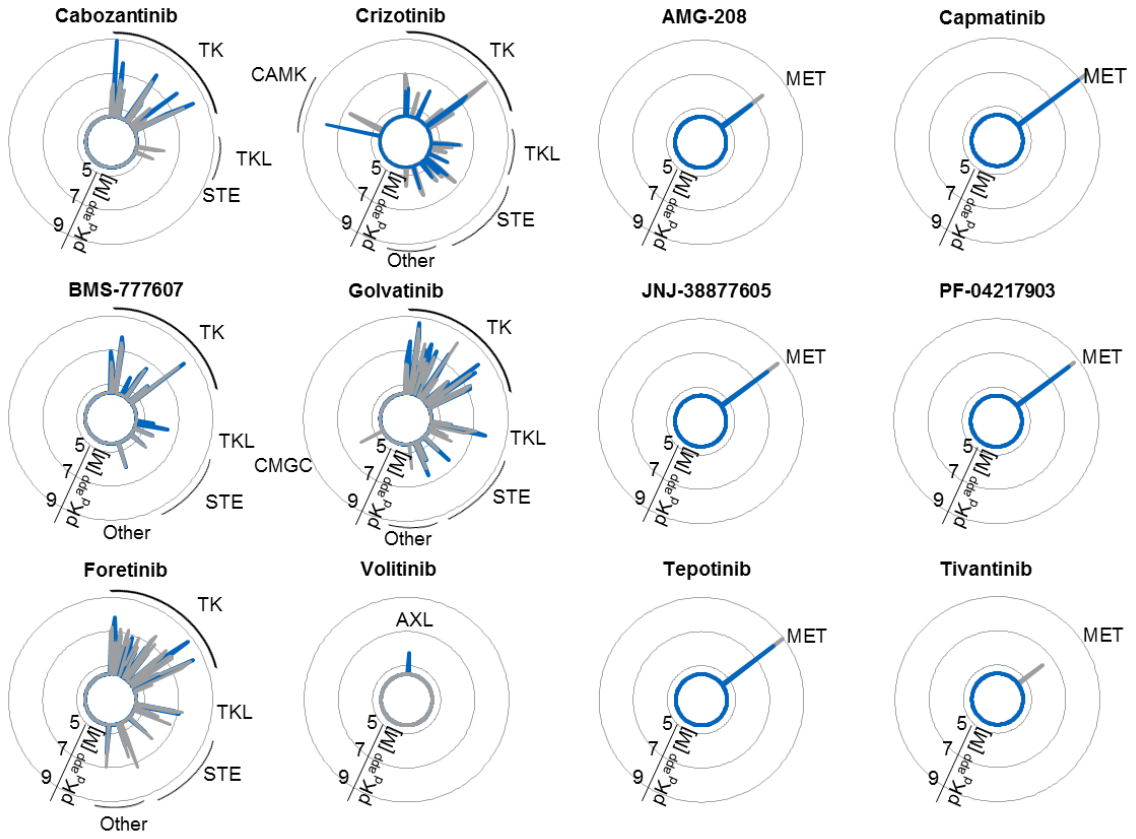

Figure 26: Selectivity of MET-inhibitors. *Targets of MET inhibitors across the kinome after profiling in four cell line mix (grey) or cell line mix plus CAKI-1 lysate (blue). Cabozantinib, Crizotinib, BMS-777607, Golvatinib and Foretinib target many kinases, whereas AMG-208, JNJ-38877605, Volitinib and Tepotinib have few kinase or non-kinase off-targets. Capmatinib, PF-04217903 and Tivantinib are selective for MET.*

Other interesting examples are clinical inhibitors against protein kinase C (PKC, AGC group). Notably, they are all derived from the same core compound structure of Staurosporine (Midostaurin, Enzastaurin, Ruboxistaurin, Sotrastaurin and UCC-01). Staurosporine is not in clinical trials itself, but is often applied as positive control in activity assays as it was found to be a potent multi-kinase inhibitor. Interestingly, they differ in their selectivity among the kinome (Figure 27). UCN-01 was found to target the most kinases, whereas Enzastaurin only targeted the PKC-kinases (α, ß, γ) and GSK3α/ß. Enzastaurin and Midostaurin have lower affinity towards their targets compared to Staurosporine, whereas Ruboxistaurin, Sotrastaurin and UCN-01 retained potency. Target space knowledge for similar compounds like this could help in inhibitor design for PKC inhibitors and give guidance for potential structure activity relationships of compounds, akin to what has been published by Heinzlmeir *et al.* They recently showed, that the results of the Kinobeads screen described in this thesis can be combined with structural data (NMR and X-ray) and kinome-wide sequence alignment to generate guidance for medicinal chemistry campaigns[247].

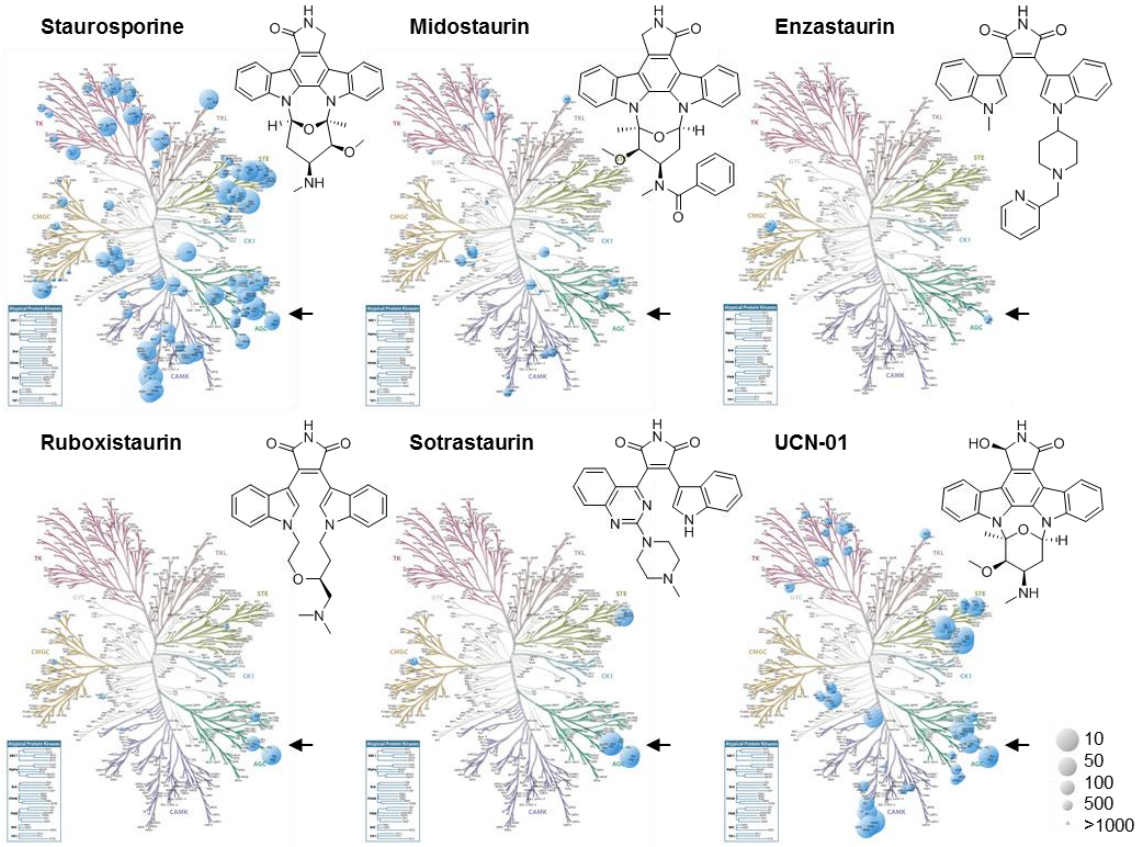

Figure 27: Selectivity of PKC inhibitors across the kinome. *Inhibitors are all derived from the same compound core structure of Staurosporine but differ in selectivity. Dot size is inversely proportional to the respective* K_d^{app} *(Kinometree representation is courtesy of Cell Signaling Technologies). The arrow indicates PKC.*

3.4 Characterization of selected inhibitors and (novel) targets

3.4.1 Co-competition of protein complex partners

Some kinases form relatively stable complexes and some members of such complexes are hence enriched on Kinobeads together with the kinases they can bind to. Their drug response curves overlap with the one of the kinase and the whole complex can therefore be assayed for drug binding in endogenous environment.

One example is the KEOPS complex (Figure 27a). LAGE3, OSGEP and TPRKB are known interactors of TP53-regulating kinase (TP53RK). Their dose response is, thus, likely due to co-enrichment and co-competition and these proteins are no direct targets of the assayed drug. The complex is involved in tRNA modification and TP53RK acts as ATPase inside the complex. Inhibition of TBK1 and IKBKE by *e.g.* PF-03814735 resulted in the identification of TBKBP1, TANK and AZI2 as target, a complex that is involved in regulating inflammatory response. Members of the clathrin-mediated endocytosis AP2 complex, namely AAK1, AP2B1, AP2S1, and AP2M1, were frequently observed to be co-competed by kinase inhibitors (*e.g.* PF-03814735) as well. The group of CDK complexes is prevalently observed. CDKs are usually paired with a cyclin, which is also reflected in their curve shape and affinity. Transferring a CDK (CDK1/2/4/6) in the cell cycle process to another cyclin starts a new phase of the cell cycle. In activity assays, CDKs are always profiled with a respective cyclin, as they are otherwise not active. CDK7 interacts with CCNH, MNAT1 and ERCC1, when regulating translation. Other translational CDKs were also identified with their respective cyclins, whereas CCND (in complex with CDK4/6) was not identified in any pulldown[248, 249].

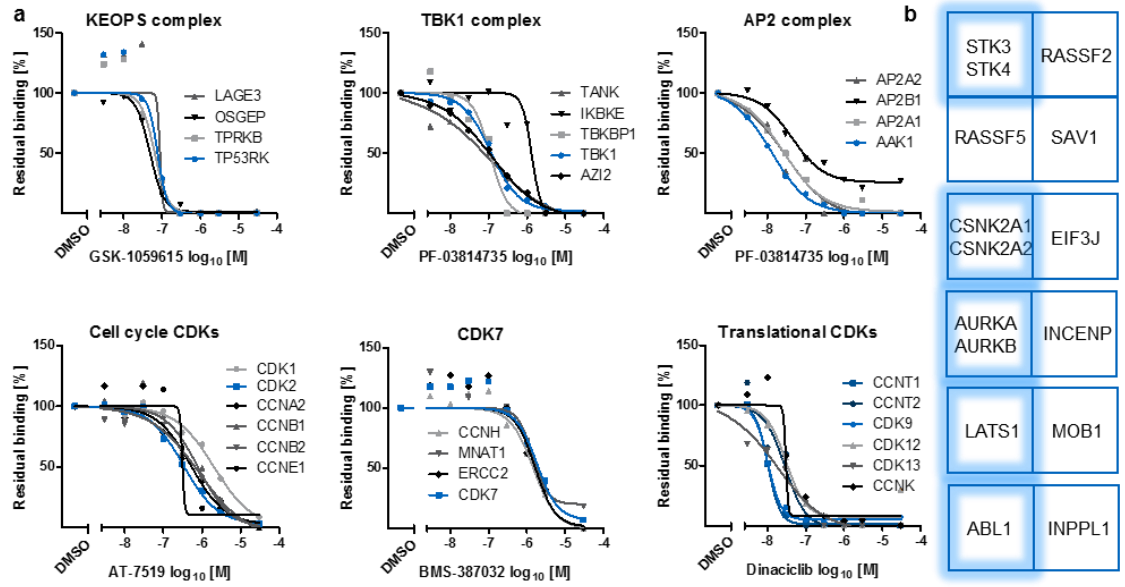

Figure 28: Complexes enriched on Kinobeads. *a) Example dose response curves for co-competed protein members of the KEOPS, TBK1 and AP2 complex as well as CDK-cyclin complexes involved in cell cycle and translation. b) Other co-occurring inhibitions of scaffolding or signaling modules with their respective kinase.*

Other examples include common kinase interactors such as scaffolding proteins like INPPL1 and INCENP interacting with ABL1 and Aurora kinases, respectively. Moreover, co-competed signaling modules like EIF3J or MOB1 were often observed as well (Figure 28b) with CSNK2A1/A2 or LATS1 binding of kinase inhibitors.

The target space of these inhibitors obtained in Kinobeads pulldowns needs to be properly evaluated and characterized to rule out these complex members as direct binders of the compound. It is unlikely that a few proteins exhibit the same binding affinity and dose response characteristics towards one drug, as observed for a range of kinase inhibitors in this screen. Inhibitors disrupting protein-protein interactions of CDKs and cyclins could be evaluated with this assay. One might also be able to identify differently regulated complex competitions, especially for different variants of CDK-cyclin combinations. However, the screen revealed no clear pattern in this regard as this possibility might only be available when treating cells with compound *in vivo* and then pulldown kinases from the lysate.

3.4.2 Dabrafenib is a multi-kinase inhibitor

Dabrafenib (Tafinlar®, GSK-2118436) is an approved inhibitor for the treatment of malignant melanoma in patients with a BRAF(V600E) mutation. Despite the general notion as selective BRAF(V600E) inhibitor[250], Kinobeads profiling in cell mix not only revealed its known target BRAF but also showed binding to 47 other targets. Thereof, 30 proteins are kinases and show binding affinities below 1 µM. Figure 29a depicts the distribution of kinases across the kinome, the size of the dots is proportional to the potency of the inhibition. Kinase targets of Dabrafenib cannot only be found in the tyrosine kinase like branch where BRAF is located but are also distributed across the tyrosine kinase family, the CAMK and the CMGC group. Studies on Dabrafenib activity only report on selective BRAF inhibition with a few related kinases inhibited (Figure 29b)[250, 251]. KinomeScan data published on the LINCS database (Dataset 20131, LINCS[211]) obtains similar binding results to the Kinobeads data. Here, off-targets were also identified in the TK and CMGC branch of the kinome (Figure 29c). This confirmed the obtained binding data as well as the suitability of Kinobeads for selectivity profiling.

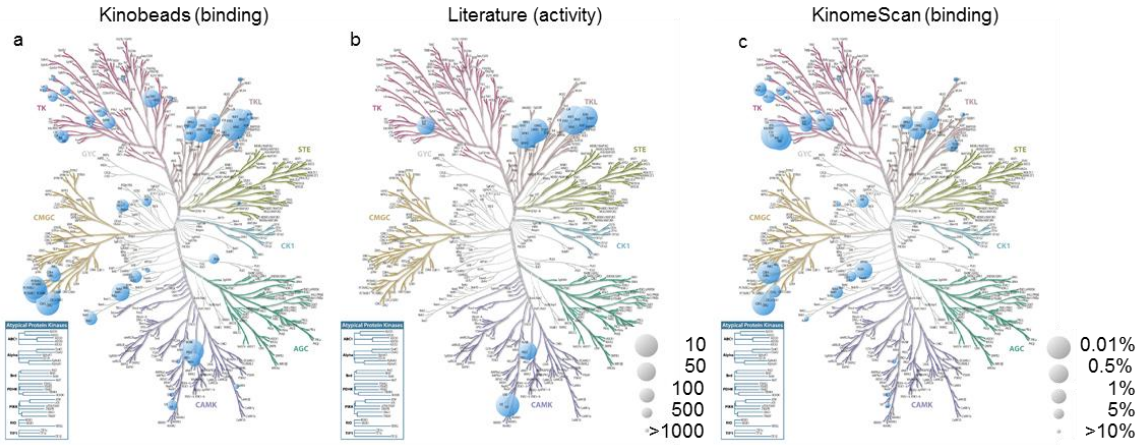

Figure 29: Dabrafenib target space. *Kinome tree representation of Dabrafenib targets (courtesy of Cell Signaling Technologies). a) Targets identified in the Kinobeads screen. Size of the dots is proportional to affinity in nM. b) Reported activity [nM] for Dabrafenib and selected kinases in literature.c) Reported KinomeScan data for Dabrafenib (Dataset 20131, LINCS). Size of dots is proportional to % control after 10 µM compound treatment.*

As the discrepancy between binding data and known activity inhibition for Dabrafenib was so large, the additional targets were subjected to recombinant activity assays. These were performed at Reaction Biology Corporation, monitoring phosphorylation activity of recombinant kinases and radioisotope labeled ATP. In general, most of the identified kinases that bound to Dabrafenib also

showed reduction in activity of the respective kinase (Figure 30a, b). Besides binding to ARAF and BRAF in the proteomics assay, Dabrafenib could inhibit the activity of the whole RAF-family with IC_{50} values of 0.14 nM for ARAF, 0.63 nM for BRAF, 0.51 nM for RAF1 and 4.05 nM for the mutant version BRAF(V600E) in the recombinant panel. At these low doses, the effect on selective BRAF(V600E) inhibition in the clinic is supposedly due to the inhibition of the cancer driving mutation, whereas wildtype BRAF melanomas are not dependent on BRAF. Reduced activity could also be confirmed for the actin filament regulatory kinases LIMK1 and LIMK2, ULK1 involved in autophagy, as well as for RIPK2, RIPK3, SIK2, SIK3, ULK1 and ZAK, which take part in immune regulatory pathways. Binding inhibition of some members of the SRC-family (LCK, LYN, FYN, FGR, FRK) as well as other tyrosine kinases also led to loss of kinase activity. ABL1, IRAK1 and TGFBR1 showed the weakest EC_{50}s and, thus, might only be fully inhibited upon higher dosage (Figure 30, Table 2).

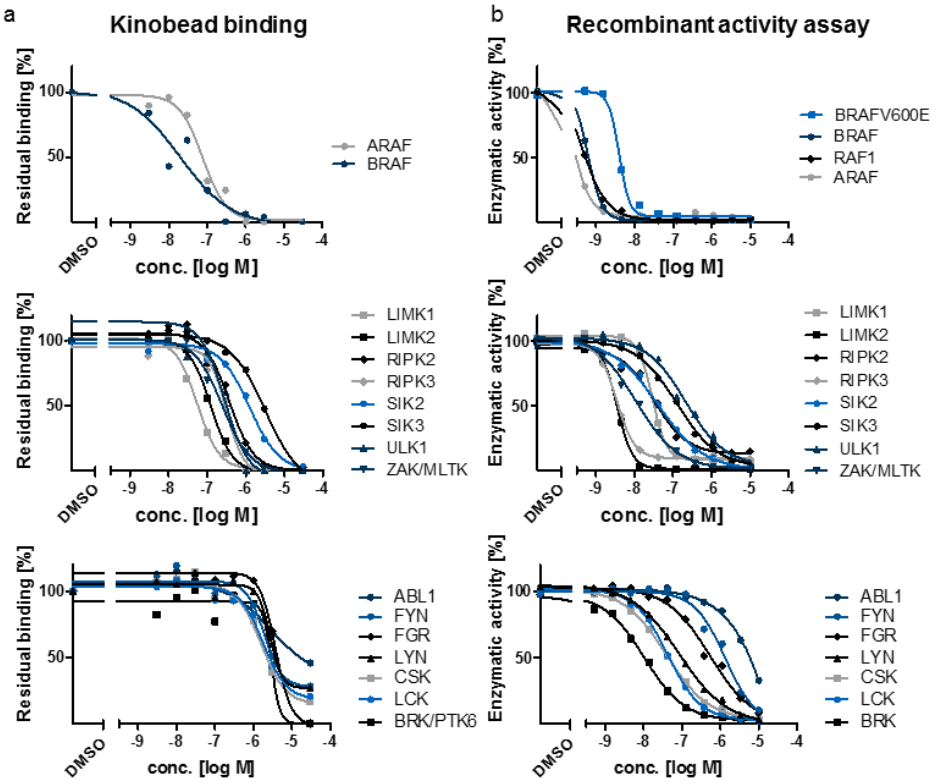

Figure 30: Confirmation of Dabrafenib targets. *a) Dose response curves of the Kinobeads competition experiment with Dabrafenib for several kinases. b) Recombinant kinase activity assays confirm inhibition of novel Dabrafenib targets. Besides ARAF, BRAF and RAF1, also several kinases involved in immune regulatory pathways (e.g. RIPK2, SIK2) and members of the SRC-family could be confirmed as targets.*

Notably, the binding profile revealed several interactions with CDK-family members. Besides potent CDK16 and CDK17 binding, Dabrafenib could bind to all cyclin-dependent kinases directly involved in cell cycle progression (CDK1, CDK2, CDK4, CDK5 and CDK6, Figure 31b). For further investigation, Dabrafenib was also incubated with MALME 3M lysate, a melanoma cancer cell line expressing the BRAF(V600E) mutation. Subsequent Kinobeads pulldowns confirmed binding to CDK2, CDK4, CDK5 and CDK6 but not to CDK1 (Figure 31b).

In activity assays, CDK-activity is assessed with the help of a cyclin. Various CDK-cyclin combinations are available for testing representing known CDK-cyclin interactions in the cell. The potent

inhibition of Dabrafenib on CDK16, a kinase involved in vesicle mediated transport and exocytosis, was confirmed in combination with cyclin Y. CDK4 in combination with CCND1 and D3, as well as CDK6 with CCND3 could also be reduced in their activity, even though with slightly less potent EC_{50}s than anticipated from the Kinobeads pulldown. Interestingly, CDK6 together with CCND1 showed no inhibition (Figure 31c). The binding of Dabrafenib to CDK5 at 1 µM was also reflected in 3-5 µM EC_{50}s in the activity assay for the respective CDK5-p25/p35 combinations. CDK1 inhibition could be partially confirmed by inhibition of CDK1 together with CCNE or CCNB1 but not with CCNA2. Surprisingly, no CDK2-cyclin combination tested (CCNE, CCNO, CCN2) had reduced activity upon Dabrafenib treatment, but CDK2 alone was detected as target in both the Kinobeads and KinomeScan data.

As kinobeads pull down protein-protein complexes, also potential CDK-interacting cyclins were identified in the Dabrafenib screen. Contrary to other CDK inhibitors in the screen, only CCNB2 showed a dose response profile similar to their respective CDK interaction partner CDK1 in the cell mix and was also co-competed in the MALME-3M lysate, whereas CCNA2, CCNB1 and CCNE1/2 showed no effect. CCNA2 and CCNE1/2 are the known interaction partners of CDK2 in the cell cycle. One can now speculate whether CDK2 interacts with CCNB2 (known to interact with CDK1), which could not be assessed in commercial activity assays, or whether it can bind to Dabrafenib alone or in combination with an unknown cyclin not detected in the screen and not available for testing in an activity assay. This prevented clear assessment of potential CDK inhibition by Dabrafenib.

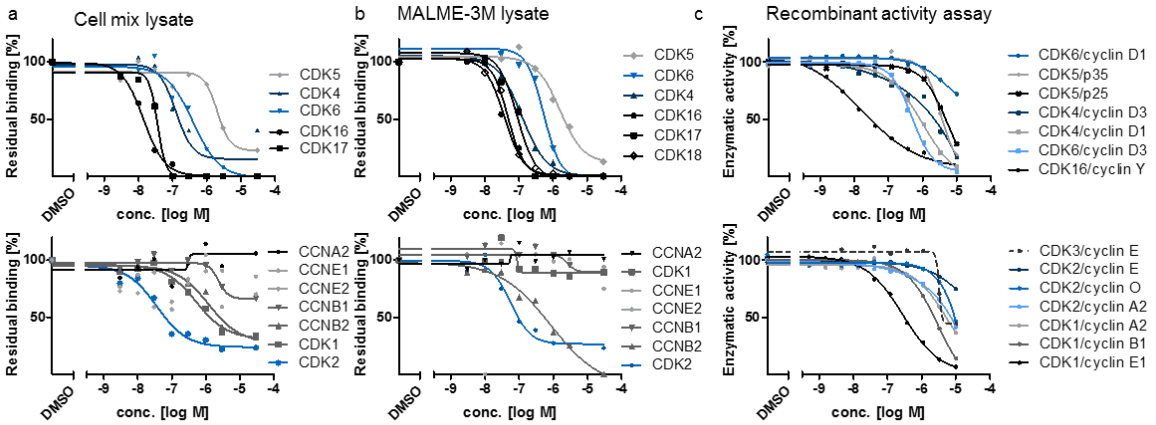

Figure 31: Binding and activity assays for Dabrafenib and CDK. *a) Kinobeads competition for several CDKs and their cyclins in cell mix. All CDKs show inhibition, whereas only CCNB1 shows a similar dose respons. b) Kinobeads competition of CDKs and cyclins in MALME-3M lysate. c) Recombinant kinase assays for CDK/cyclin pairs. The potent inhibition of CDK2 in the Kinobeads experiments could not be confirmed.*

Activity assays for Dabrafenib also revealed a general concordance between targets identified in a binding assay and affected activity (Table 2). Except for the CDK-targets, all targets identified in the binding assay also show impaired activity upon Dabrafenib treatment. Hence, Dabrafenib in fact needs to be considered as a multi-kinase inhibitor, with potential off-target toxicities because of multiple kinase inhibition.

Table 2: Binding and activity data for Dabrafenib. *K_d^{app} and EC_{50} values for kinase targets of Dabrafenib in the Kinobeads screen (binding) and in recombinant kinase assays (activity, performed at Reaction Biology Corporation).*

KINASE	BINDING K_d^{app} [nM]	ACTIVITY EC_{50}[nM]	KINASE	BINDING K_d^{app} [nM]	ACTIVITY EC_{50}[nM]
ARAF	47	0.14	**CDK1**	364	n.a.
BRAF	22	0.63	**CDK1/ CYCLIN A2**	n.a.	5693
BRAF(V600E)	n.a.	4.05	**CDK1/ CYCLIN B1**	n.a.	2220
CRAF	n.a.	0.51	**CDK1/ CYCLIN E**	n.a.	292
ABL1	1545	5186	**CDK2**	19	n.a.
TGFBR1/ALK5	2384	2942	**CDK2/ CYCLIN A2**	n.a.	n.i.
PTK6/BRK	1414	11.28	**CDK2/ CYCLIN O**	n.a.	n.i.
LIMK1	33	32.15	**CDK2/ CYCLIN E**	n.a.	n.i
LIMK2	82	3.59	**CDK4**	126	n.a.
RIPK2	106	41.32	**CDK4/ CYCLIN D1**	n.a.	852
RIPK3	283	4.08	**CDK4/ CYCLIN D3**	n.a.	1835
SIK2	649	42.25	**CDK5**	1068	n.a.
SIK3	2005	137.5	**CDK5/P35**	n.a.	3709
ULK1	188	240.3	**CDK5/P25**	n.a.	4918
ZAK/MLTK	184	12.16	**CDK6**	318	
FYN	817	1298	**CDK6/ CYCLIN D1**	n.a.	n.i.
FRK	727	396.7	**CDK6/ CYCLIN D3**	n.a.	537
FGR	1549	534.5	**CDK16**	13	
LYN	1353	85.65	**CDK16/CYCLIN y**		29
CSK	851	42.42			
LCK	783	45.02			
PRKD2	34	123.4			
IRAK1	1564	3389			
TNK	66	37.78			

3.4.3 Ceritinib binds to the phosphorylated version of IGF1-receptor

Ceritinib (Zykadia®, LDK-378) was approved for ALK positive NSCLC in 2014. Besides ALK, IGF1R, InsR and STK22D were discovered as targets of Ceritinib with IC_{50} values of 8, 7, and 23 nM[252]. However, in the Kinobeads pulldown in cell mix IGF1R and InsR could only be identified with low affinity (K_d^{app} of 4 µM and 20 µM, respectively), differing substantially from the expected, published values. Some kinases might escape detection, if the inhibitor only targets a specific conformation of the kinase whereas the Kinobeads can bind to various and other conformations. Only the proportion of kinase in that particular conformation will be blocked by the inhibitor. The remaining protein in the lysate is still available for binding to the beads, thus leading to no visible effect in the mass spectrum and subsequent data analysis. Activity and binding to beads has been subject to discussions. Other groups claimed, that by using type-1 inhibitors as probes, the resulting enriched kinases should only be targeted in their active state[253]. However, a thorough analysis evaluated this for the published setup as well as for Kinobeads and proved that this is rarely the case[254]. This activity analysis also revealed that IGF1R is enriched by Kinobeads in both confirmations.

To evaluate a potential activity effect on Ceritinib binding to IGF1R, Kinobeads pulldowns in differently treated lysates were performed. For this evaluation, SK-NB-E(2) cells were used as they

show stable IGF1R expression. On the one hand, pervanadate treatment prevents dephosphorylation in cell culture, rendering most of the proteins in the lysate in their phosphorylated form. On the other hand, serum starvation should lead to decreased phosphorylation of kinases. The volcano plot shows the fold change in intensity of proteins of pervanadate treated samples to those in serum starved cell lysate as fished by Kinobeads against the $-\log_{10}$ p-value (t-test) of a triplicate analysis (Figure 32a). IGF1R (blue dot) had a positive fold change, indicating preference for Kinobeads binding to the active form of IGF1R. However, this was not significant (p-value > 0.05). Therefore, Kinobeads bound both the phosphorylated and non phosphorylated form of IGF1R in the used setup. The differentially treated lysate was subjected to competitive Kinobeads pulldowns with Ceritinib.

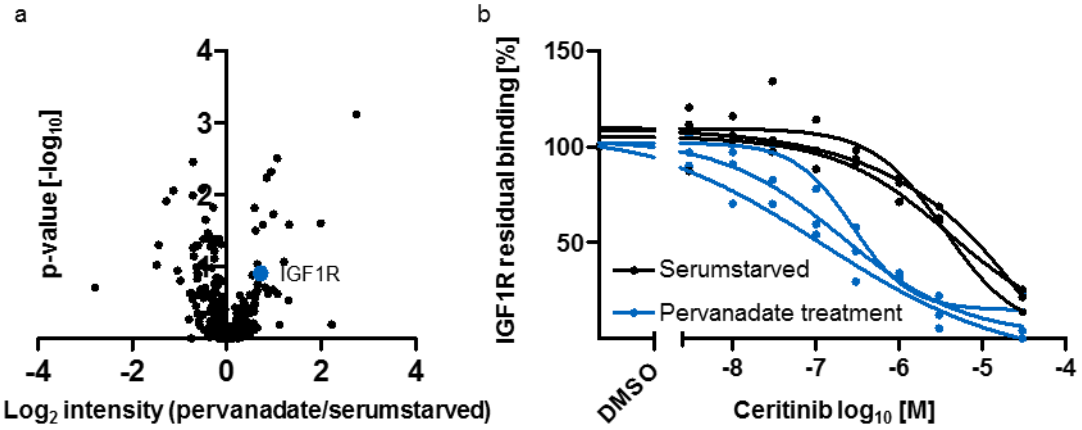

Figure 32: IGF1R binding by Ceritinib. *a) Volcano plot with log_2 Intensity fold change of pervanadate samples and serum starved samples against a p-value of biological triplicates. Kinobeads have no significant preference for the phosphorylated or non-phosphorylated form of the receptor. b) Dose response curves for IGF1R in triplicate pervanadate treated cell lysates (blue) or serum starved cell lysates (black). Ceritinib preferentially binds to phosphorylated IGF1R, whereas non-phosphorylated IGF1R shows lower affinity towards the drug.*

Competition in active (blue) and inactive (black) SKNBE-2 lysate revealed a different binding curve for IGF1R depending on the condition (Figure 32b). Phosphorylated IGF1R could be competed with lower inhibitor concentrations (median K_d^{app} of 121 nM), whereas the competition of the non-phosphorylated receptor showed lower K_d^{app} values close to no inhibition. This indicated that the activated IGF1 receptor is bound by Ceritinib, whilst the non-phosphorylated receptor is not affected to that extent.

To summarize, binding to phosphorylated kinases can be shown for selected cases in an environment chosen for the particular question. This could be differentially treated lysate like it was done for Ceritinib and IGF1R. Notably, only IGF1R binding was affected by the phosphorylation state of the kinase, whereas all other Ceritinib targets were identified with comparable affinities in both treatment conditions. One can also choose one specific probe, which enriches the protein of interest in a preferred conformation. From the before mentioned analysis, it is known, that compound 7 of the Kinobeads preferentially binds the active IGF1R, providing a good probe to study IGF1R inhibition dependent on activity. With these options in hand, other missing targets could be investigated that might have escaped detection as target because of an activity dependent binding.

3.4.4 Validation of the off-target NTRK1 in the KM12 colon cancer cell line

The off-targets identified in the screen can furthermore be investigated in light of potential novel applications for these drugs. One example is NTRK1, which has been identified as new target in several inhibitors. NTRK1 (TrkA) is known to be involved in pain response and has been a rising target in oncology in recent years. In some lung and colon cancers, it is expressed as a fusion protein TPM3-NTRK1[255, 256]. In the Kinobeads screen, 20 inhibitors were identified to target NTRK1 with varying potencies from nanomolar to micromolar affinities (Figure 33a).

To assess NTRK1 inhibition, ENMD-2076 (206 nM), Foretinib (49 nM), Golvatinib (601 nM), Lestaurtinib (561 nM) and TAK-901 (843 nM) were evaluated in cell culture. LY-2801653 was also included, as NTRK1 was annotated as low confidence target.

The human colon cancer KM12 cell line is a known model cell line expressing the TPM3-NTRK1 fusion and being dependent on it[255]. In fact, treatment for 72 h with increasing concentrations of the six inhibitors showed clear reduction in cell viability compared to Gefitinib, which is not inhibiting NTRK1. Lestaurtinib, Foretinib, LY-2801653 and TAK-901 showed the most potent effect (Figure 33b). Golvatinib and ENMD-2076 had less influence on growth inhibition. HEK-293 cells served as control cell line. Lestaurtinib and TAK-901 could also reduce the viability of this cell line. However, growth inhibition is not affected in the same potency range as for the KM12 cell line. Lestaurtinib and TAK-901 are multi-kinase inhibitors, which could explain the effect on HEK-293 cells. The other evaluated inhibitors had no effect on survival of this cell line.

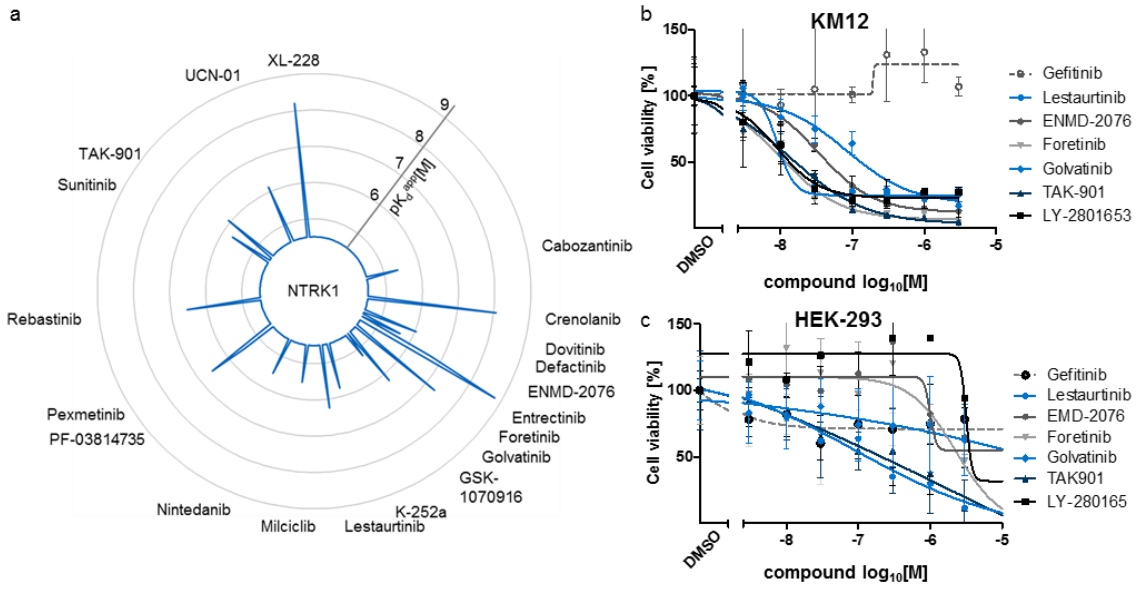

Figure 33: Validation of NTRK1 inhibition in cell culture. *a) Radar plot for NTRK1 inhibitors, length of spikes depict K_d^{app}. b) Cell viability of KM12 cells after treatment with NTRK1 inhibitors (error bars show standard deviation of technical triplicates). All NTRK1 inhibitors reduced cell viability of TPM3-NTRK1 fusion dependent KM12 cells. Gefitinib was used as negative control and had no influence on KM12 viability. c) HEK-293 viability after treatment with NTRK1 inhibitors (technical replicates, error bars depict standard deviation). Lestaurtinib and TAK-901 could reduce cell viability at higher compound concentrations due to multikinase inhibition.*

The inhibitory effect on KM12 cells of these inhibitors can very likely be attributed to NTRK1 inhibition. For further target engagement validation, the influence on TrkA signaling was monitored. Cells were treated with increasing concentrations (50 nM, 250 nM, 500 nM, 1 µM, DMSO) of ENMD-2076, Golvatinib, TAK-901, LY-2801653, Foretinib or Lestaurtinib for 4 hours. Effects on the

downstream targets of NTRK1, namely the phosphorylation of AKT or ERK1/2 were analyzed by Western Blot analysis. ENMD-2076 showed decreased AKT phosphorylation but no clear inhibition of ERK1/2 phosphorylation was detectable (Figure 34a). Similar behavior could be observed for Foretinib and Lestaurtinib (Figure 34c). Golvatinib treatment led to decreased phosphorylated AKT and ERK1/2 upon later doses (Figure 34a). This effect was even more pronounced in TAK-901 and LY-2801653 (Figure 34c). 1 µM Gefitinib was added as control, which shows no effect on phosphorylation of AKT, but little reduction for ERK1/2. Gefitinib is an EGFR inhibitor, inhibition of EGFR will also inhibit ERK phosphorylation. ß-actin served as loading control, indicating a little more protein loaded in the 50 nM Golvatinib lane.

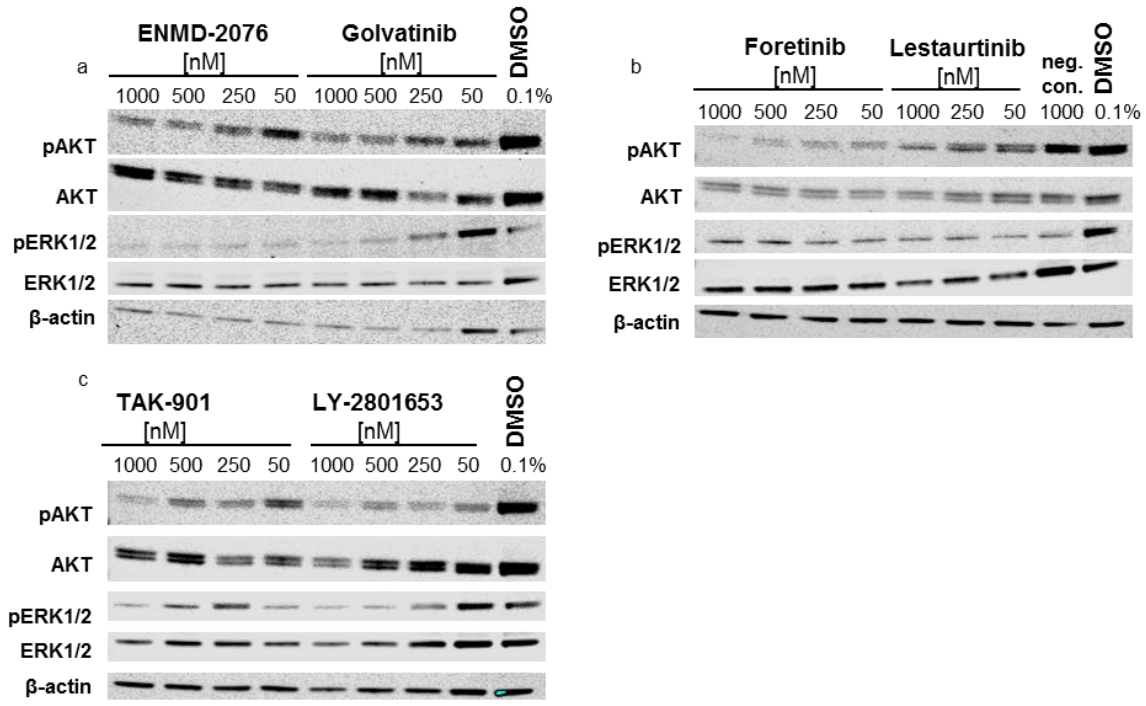

Figure 34: Analysis of NTRK1 downstream signaling. *KM12 cells were treated with increasing doses of ENMD-2076, Golvatinib, TAK-901, LY-2801653, Foretinib or Lestaurtinib and decrease in pAKT, AKT, pERK and ERK was assessed by immune blot analysis. Gefitinib (1 µM) was used as negative control. NTRK1 inhibition led to decreased phosphorylation of AKT and ERK.*

The promising results on KM12 cell lines as well as the inhibition of downstream signaling indicate an inhibitory effect through NTRK1 inhibition, which could make these inhibitors valuable candidates for medicinal chemistry lead compounds. In addition, LY-2801653 treatment interfered with KM12 cell growth and TrkA signaling, thus its low confidence target NTRK1 in the drug screen could be confirmed. For direct use of these inhibitors in an NTRK1 dependent disease setting, further preclinical evaluation is recommended. In 2015, the first designated selective NTRK1 inhibitor Entrectinib entered clinical trials and was granted orphan drug status in Europe and the United States for the treatment of Neuroblastoma, NSCLC and CRC. It was so far the only inhibitor in clinical trials demonstrating activity against CNS metastases and is currently evaluated in a phase 2 basket trial (NCT02568267). It is the most potent NTRK1 inhibitor in the examined panel with an affinity of 1.6 nM, followed by XL-228 (6.1 nM) and Crenolanib (8.5 nM). In addition, it has no additional off-targets in our screen, making it a valuable chemical probe to investigate NTRK1. However, before Entrectinib, no designated, selective NTRK1 inhibitor was available. The drug screen could identify potential new inhibitors for this previously undrugged kinase and many

others, which will hopefully result in increased clinical, chemical and biological research activity for these proteins. In fact, a clinical trial just started in November 2015 that is recruiting patients for evaluating the MET inhibitor Merestinib (LY-2801653) in lung cancer and solid tumors because of its MET and NTRK1 inhibition (NCT02920996).

3.4.5 Repositioning of Cabozantinib in AML

A further example for inhibitor off-targets and a potential new indication for that inhibitor is FLT3, which was identified as additional target in Cabozantinib (Cobimetriq®, XL-184). It is an approved inhibitor for medullary thyroid cancer and advanced renal carcinoma, making it a valuable candidate for further indications. It is originally designated against MET and VEGFR, but has been known to inhibit other kinases as well[257]. In the pulldown with four cell line mix, Cabozantinib binds to 18 proteins, which mainly belong to the tyrosine kinase and tyrosine kinase like family (Figure 35a). FLT3 was the most potently inhibited protein (pK_d^{app} = 53 nM), followed by RET (pK_d^{app} = 86 nM). MET suffered from low MS1 intensity and could not be quantified (also see 3.3.4). The selectivity profiling in CAKI-1 cells confirmed FLT3 and RET as targets and furthermore enabled detection of the known targets MET and AXL (Figure 35b).

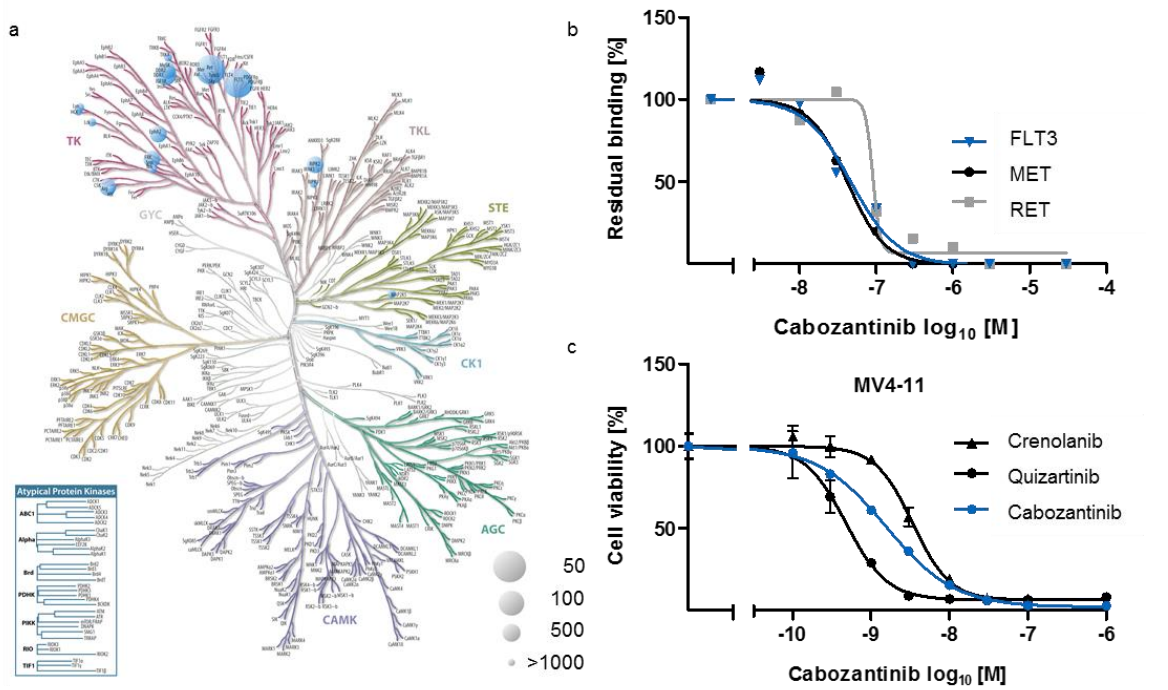

Figure 35: Cabozantinib is a potent FLT3 inhibitor. *a) Kinometree representation of Cabozantinib targets in four cell line mix profiling (courtesy of Cell Signaling Technologies). Cabozantinib is mainly targeting the TK family. b) Residual binding of MET, RET and FLT3 after Kinobeads competition experiment in four cell line mix with CAKI cells. FLT3 shows similar potency as the designated target MET. c) Cell viability assay with the designated FLT3 inhibitors Quizartinib, Crenolanib, and the MET inhibitor Cabozantinib in the MV4-11 cell line, which carries a FLT3-ITD mutation that leads to constitutive phosphorylation of the receptor.*

FLT3 is often mutated in acute myeloid leukemia (AML)[258], which renders the receptor constitutively active. It is a common target of clinical inhibitors in the screen (61 compounds) and Cabozantinib is the most interesting potential candidate for repositioning as the drug is already approved. A cell viability assay in the AML cell line MV4-11, which carries a FLT3-ITD mutation was performed in

comparison with Quizartinib (AC-220, Phase 2) and Crenolanib (CP-868596, Phase 3). Cabozantinib showed similar cellular IC_{50}s to the designated FLT3 inhibitors (Figure 35c).

Therefore, Cabozantinib was preclinically evaluated for AML treatment in collaboration with Binje Vick, Katrin Reiter and Harald Polzer in the hematology groups of Irmela Jeremias, Philipp Greif and Karsten Spiekermann at the Department of Gene Vectors at the Helmholtz Center Munich and the Department of Internal Medicine III at the Ludwig-Maximilians-Universität Munich. These results are briefly mentioned for completeness of this project. It exemplifies potential translational value of the dataset obtained in this thesis.

The effect of Cabozantinib was tested in a panel of AML cell lines (MOLM-13, MV4-11, MONO-MAC5, Kasumi-1, OCI-AML3, HL-60, KG-1a, and THP-1). Only FLT3-ITD and KIT mutated cell lines were sensitive towards Cabozantinib and the FLT3 inhibitors Quizartinib and Crenolanib with similar cellular IC_{50}s. FLT3 wildtype cell lines showed no reduced viability and proliferation upon drug treatment. This indicates potential use of these inhibitors in a FLT3-ITD stratified cohort of patients.

Immune-fluorescent staining of FLT3 wildtype and FLT3-ITD transfected U2OS cells showed, that Cabozantinib treatment can restore the membrane localization of FLT3-ITD similar to what has been shown for Quizartinib[259]. Furthermore, immunoblot analysis revealed decreased phosphorylation of STAT5 in MV4-11 cells upon inhibitor treatment indicating that Cabozantinib treatment has an effect on downstream signaling in FLT3-ITD mutated cells.

Finally, Cabozantinib treatment was also evaluated in a xenograft mouse model with MOLM-13 (FLT3-ITD) and OCI-AML3 (FLT3-WT) cells. Drug treatment led to significantly decreased tumor burden in mice injected with FLT3-ITD cells and showed a statistically significant, positive effect on survival.

Collectively, this pre-clinical data and recent results[260] are in support of initiating a phase II clinical trial of Cabozantinib in FLT3-ITD stratified AML patients.

3.5 Characterization of Ferrochelatase as kinase inhibitor off-target by chemical proteomics

3.5.1 Kinobeads profiling identifies FECH as an off-target binder of many inhibitors

The Kinobeads profiling technology can also reveal non-kinase proteins that can bind to small molecule inhibitors. One such case is the last enzyme in the heme biosynthesis pathway, Ferrochelatase (FECH). FECH was first identified as off-target of Vemurafenib as it shows the same K_d^{app} value as its cognate target BRAF (about 1 µM) (Figure 36a). To rule out indirect FECH binding as part of a protein complex with BRAF, the selectivity of Dabrafenib, another approved BRAF inhibitor, was examined for FECH binding. The screen revealed potent interaction with BRAF (K_d^{app} = 60 nM, Figure 36b) but no FECH binding, excluding the possibility of co-purification of a BRAF-FECH complex.

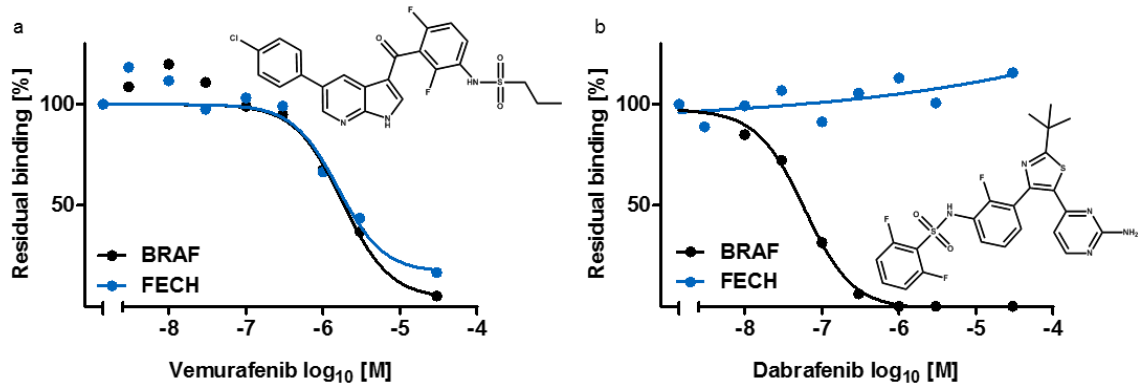

Figure 36: FECH is an off-target of Vemurafenib. *Dose response curves for Vemurafenib (a) and Dabrafenib (b) for the main drug target BRAF (black line) and the off-target FECH (blue line).*

Extending this to 242 inhibitors reveals FECH binding in 26 kinase inhibitors with binding constants in the range of 1 to 12 µM (Figure 37a).

Clear interactions occur between FECH and the inhibitors AEW-541, Arry-380, Axitinib, AZD-8055, BGT-226, BI-2536, BI-847325, Cabozantinib, Crenolanib, CUDC-101, Cyc-116, Erlotinib, Gefitinib, GSK-1070916, GSK-690693, Lenvatinib, Linsitinib, MK-2206, MK-2461, Neratinib, Nilotinib, OSI-027, Pelitinib, R-406, Rigosertib and Vemurafenib. Figure 37b shows the full dose response data for five selected inhibitors. In this assay, Cyc-116 was found to be the most potent FECH inhibitor, followed by MK-2206 and Vemurafenib.

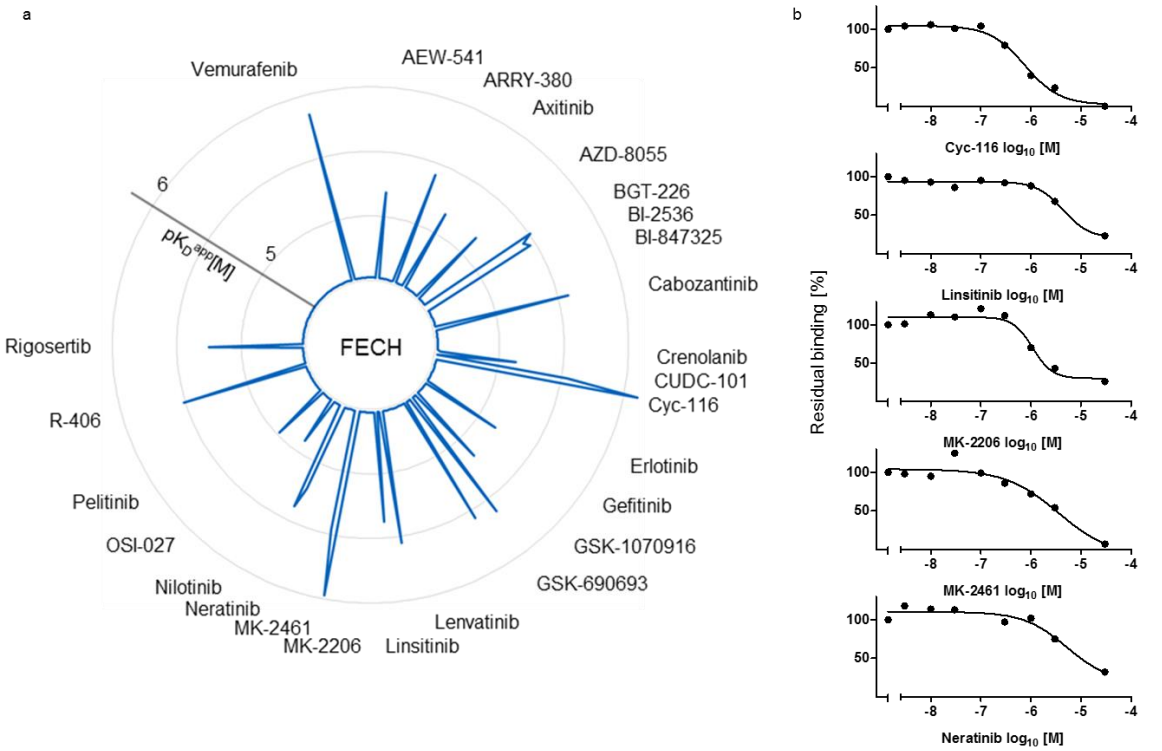

Figure 37: FECH binding across 242 clinical kinase inhibitors. *a) Radar plot showing K_d^{app} values for FECH binding determine for 242 small molecule kinase inhibitors using the Kinobeads assay. Drugs that show no inhibition of FECH binding populate the inner circle. b) Full dose response curves for five selected kinase inhibitors: Cyc-116, Linsitinib, MK-2206, MK-2461 and Neratinib.*

As the potency for FECH is quite low, the Kinobeads binding results were verified by performing cellular thermal shift assays (CETSA). Here, K-562 (cell line expressing FECH) lysate was incubated with 10 µM of Vemurafenib, MK-2461, Neratinib or DMSO as control and subsequently heated to increasing temperature (40-70 °C). As drug binding leads to protein stabilization, unbound FECH precipitates during centrifugation after its melting temperature was reached. The actual protein stabilization was then measured by quantifying the amount of soluble protein using Western Blot analysis with an anti-FECH antibody (Figure 38a). In the DMSO control, FECH amount starts to decrease at around 50 °C, whereas in the drug incubated samples FECH can be detected at least towards 67 °C hinting a stabilizing effect. This is not apparent when calculating fractions of soluble FECH (Figure 38b).

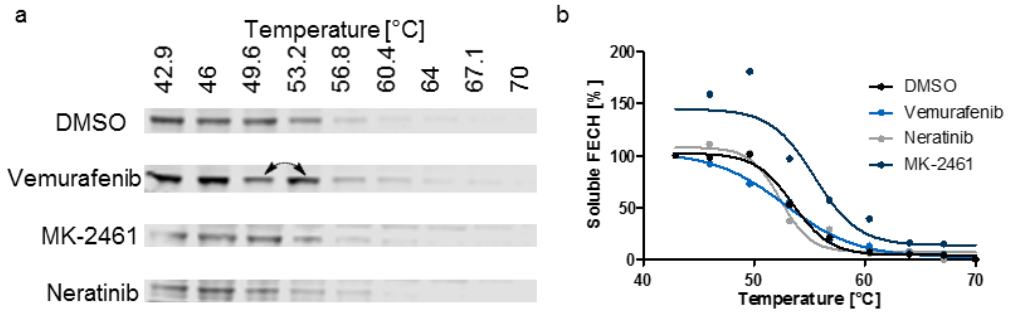

Figure 38: Validation of Kinobeads binding data using cellular thermal shift assay*. a) Immunoblot analysis for soluble FECH after heating K-562 lysate incubated with Vemurafenib, MK-2461 and Neratinib to increasing temperatures. Arrow indicates switched samples of temperature points 49.6°C and 53.2 °C in the CETSA experiment with Vemurafenib. b) Curve fit of quantified immune blot band intensity for soluble FECH. Identification of thermal shift upon drug binding compared to DMSO control is not clearly visible.*

Apparently, CETSA in lysate combined with Western blot quantification made it very difficult to determine a clear, visible thermal shift to verify drug-protein binding. Readout with MS seems to result in a more accurate quantification that clearly enables determination of a thermal shift[110].

Another variant of thermal shift assay is the so-called isothermal dose response profiling. In this assay, cells are treated with increasing compound concentrations and then all heated to the same temperature with the biggest difference between drug and control sample (55 °C) in the CETSA experiment. Again using Western Blot readout, binding of FECH to 11 compounds was confirmed (Figure 39). The ITDR data was mostly well aligned with the affinities determined by the Kinobeads assay. Strong stabilization was detected for all inhibitors except for Dabrafenib, which was used as negative control. Alectinib, which was negative in the Kinobeads assay, scored by ITDR, confirming earlier results for this drug and its interaction with FECH[110].

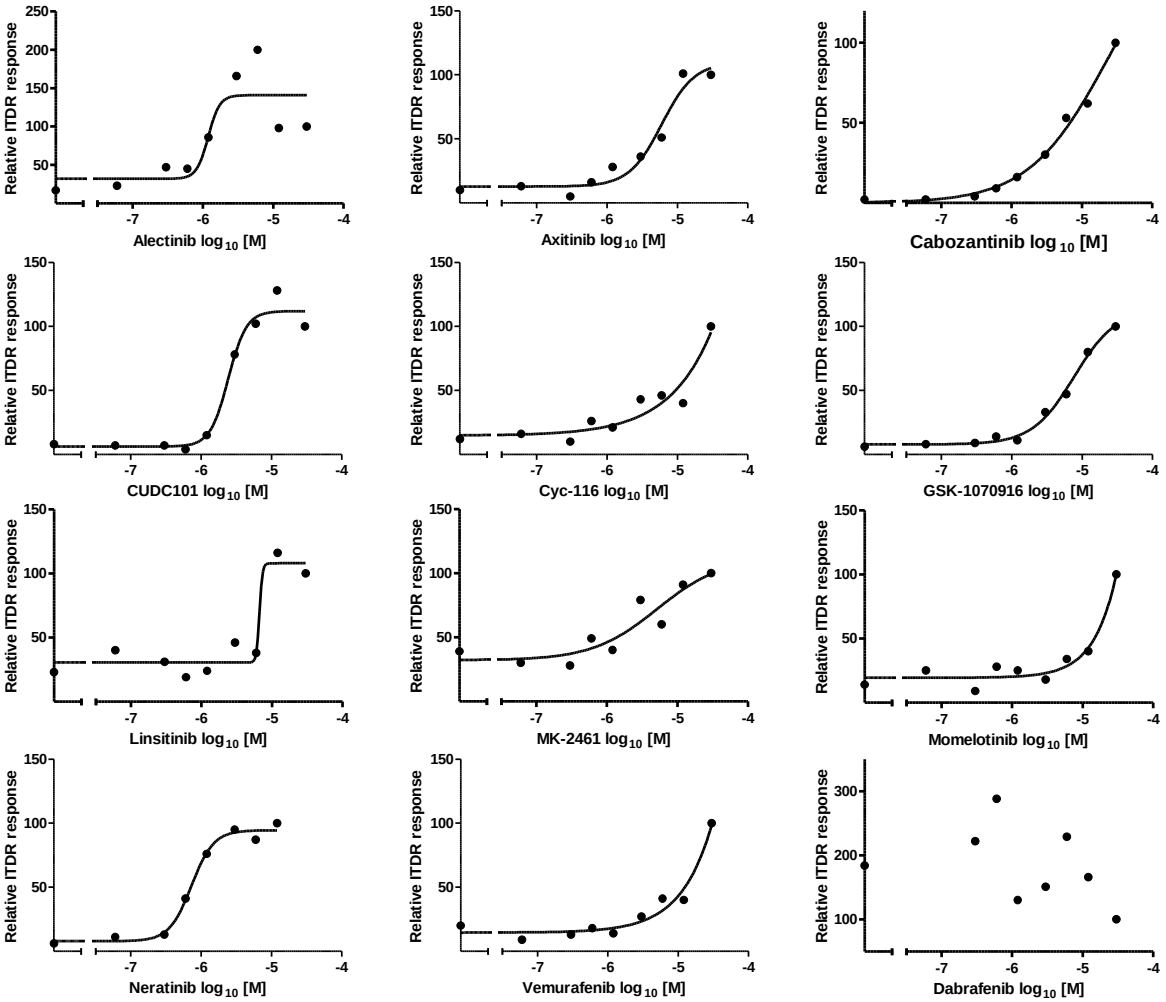

Figure 39: Validation of Kinobeads binding data using isothermal dose response assays*. K-562-cells were treated with increasing concentrations of inhibitor and heated to 55 °C Alectinib, Axitinib, Cabozantinib, CUDC101, Cyc-116, GSK-1070916, Linsitinib, MK-2461, Momelotinib, Neratinib and Vemurafenib show concentration-dependent thermal stabilization of FECH. Dabrafenib is shown as a negative control as it does not bind to FECH.*

3.5.2 FECH inhibition leads to heme reduction in K562 cells

As binding not always leads to loss of enzymatic activity, an assay was developed to measure FECH activity. The human erythroleukemic K-562 cell line is capable of heme biosynthesis[261]. These cells contain active FECH and can therefore serve as cellular system for measuring FECH inhibition by kinase inhibitors[262]. Four compounds (MK-2461, Neratinib, Linsitinib and Vemurafenib) were amenable to this experiment whereas the other seven drugs (Alectinib, Axitinib, Cabozantinib, CUDC-101, Cyc-116, GSK-1070916 and, Nilotinib) tested were too toxic to the cells over the period of the experiment of about one week (Figure 40a). Following exposure of differentiated K562 cells (K562*, which are slightly red owing to an elevated heme content compared to the parental K562 cells) to the respective kinase inhibitors, the heme content of the cells was measured by LC-MS[213].

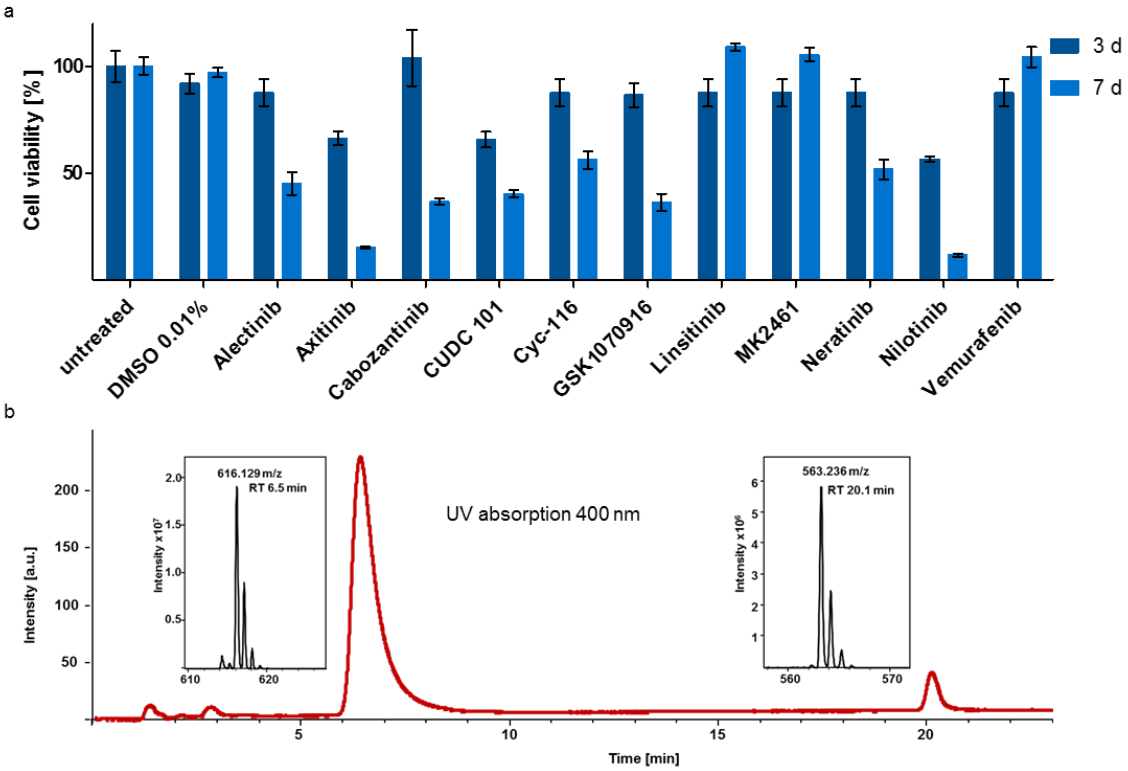

Figure 40: FECH activity assay. *a) Cell viability of K-562 cells upon treatment with potential FECH-inhibitors for up to 7 days. Only Linsitinib, MK-2461, Neratinib and Vemurafenib were amenable to the assay (error bars depict standard deviation of technical triplicates). b) UV-absorption trace of heme (616 m/z) and protoporphyrin IX (563 m/z) in LC-MS. Both can be clearly separated over time.*

This allowed clear separation and independent detection of heme and PPIX in the same assay (Figure 40b). The UV absorption trace for heme (400 nm; as well as the MS trace of m/z 616) in Figure 41b shows the analytical evidence for the assay; it is evident that K-562* cells produced heme whereas HEK-293 control cells did not. Hemin alone or parental K-562 cells spiked with the compound showed the same elution profile as untreated K-562* cells, indicating functioning heme synthesis in K-562* cells. Following treatment of cells with Vemurafenib (1 or 3 µM), the heme content of the cells decreased in a dose dependent fashion (Figure 41b). However, PPIX accumulation could not be observed as it accumulates in the mitochondria, which are not lysed under the assay conditions. MK-2461, Neratinib and Linsitinib were then subjected to the same assay (1 µM for 6 days) and each drug clearly led to reduced heme levels indicating inhibition of

FECH activity in K-562 cells with Neratinib showing the most potent effect (60% reduction, Figure 41c).

As cellular heme changes may also be due to secondary effects, FECH activity was evaluated in a cell-free assay using the FECH R115L mutant because of its better stability and solubility *in vitro* (performed in collaboration with Vipul Gupta, Tokyo Institute of Technology, Tokyo)[207, 263]. Indeed, increasing concentrations of Vemurafenib led to inhibition of FECH (Figure 41d), showing that Vemurafenib inhibits FECH activity in-vitro and in cells.

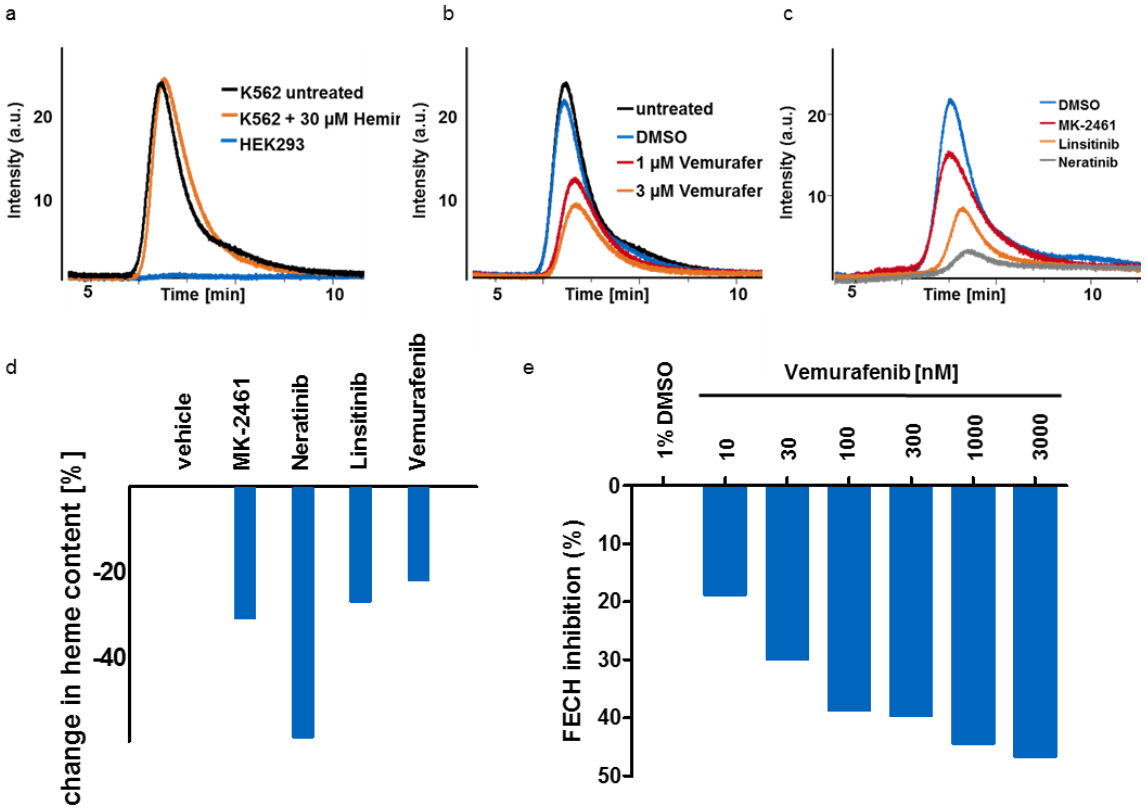

Figure 41: FECH activity for Vemurafenib, MK-2461, Linsitinib and Neratinib. *a) Chromatograms for heme absorption at 400 nm for K-562 lysates. Differentiated K-562* cells (black line) contain high amounts of hemin, undifferentiated K-562 lysates spiked with 30 µM hemin (orange line) and lysates of HEK 293 (blue line) cells show that hemin can be detected in cells with active heme biosynthesis. b) Increasing Vemurafenib concentrations decrease the amount of heme in K-562 cells. c) 1 µM MK-2461, Linisitinib and Neratinib also decrease amount of heme in K-562 cells. d) Change in K562 cells heme content after 6 days of treatment with 1 µM MK-2461, Neratinib, Linsitinib and Vemurafenib relative to vehicle treated cells. e) Inhibition of recombinant FECH in vitro with increasing concentrations of Vemurafenib.*

3.5.3 Kinase inhibitors inhibit FECH by blocking the protoporphyrin binding site

FECH is not a kinase and has no obvious nucleotide binding site. Hence the question arises as to where a small molecule kinase inhibitor binds the protein. First, I studied the PPIX binding site because binding of inhibitors in this area would completely shut down the catalytic activity of the enzyme. In a published crystal structure of FECH, the PPIX site is occupied by three cholate molecules[264]. The presence of cholate was found to be required in order to keep the purified protein soluble. A Kinobeads competition experiment using cholate and recombinant FECH R115L enzyme

showed a decrease in binding at increasing concentrations of cholate (Figure 42a) indicating that kinobeads bind FECH via its active site.

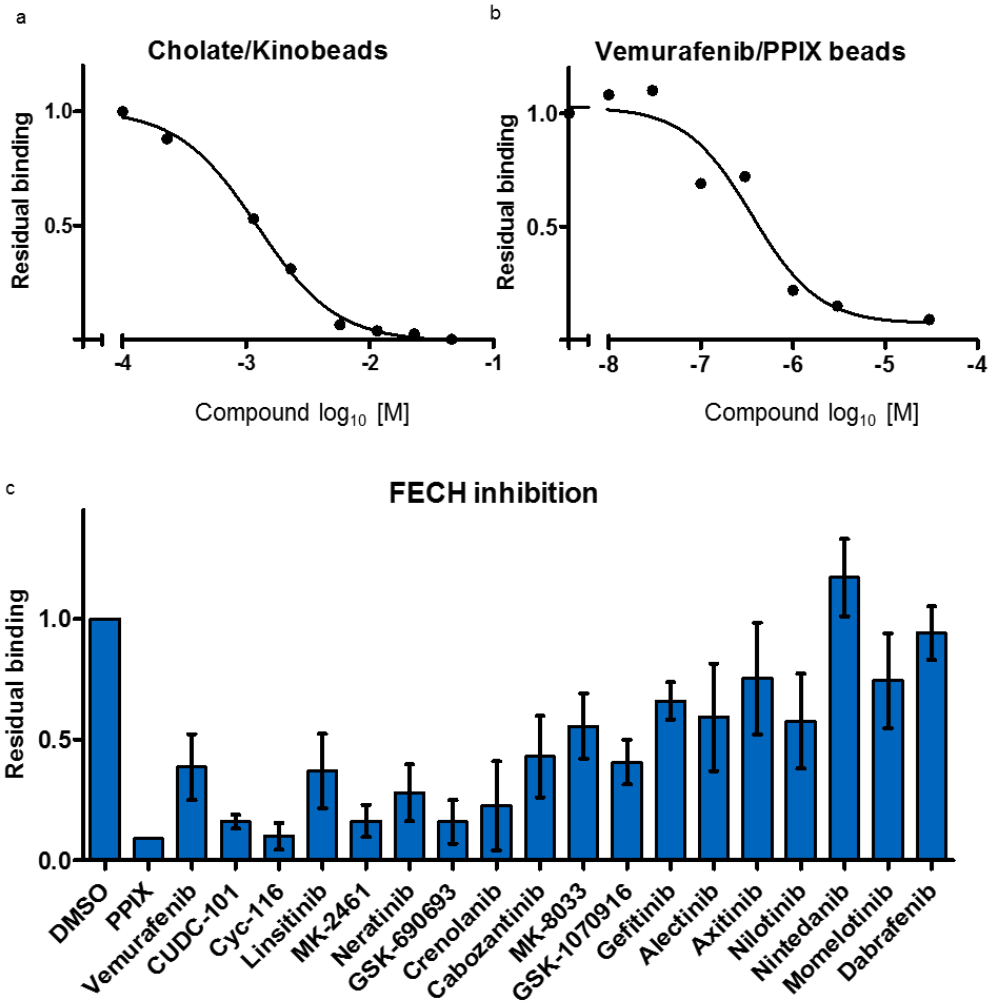

Figure 42: FECH binding of kinase inhibitors. *(a) Increasing concentrations of cholate reduce binding of FECH to kinobeads. (b) Increasing Vemurafenib concentrations can compete FECH binding to PPIX immobilized on beads, demonstrating that Vemurafenib binds in the PPIX pocket of FECH. (c) Analogous binding site determination experiments for 18 kinase inhibitors in triplicates. PPIX is included as a positive control and Dabrafenib serves as a negative control. While Vemurafenib, CUDC-101, Cyc-116, Linsitinib, MK-2461, Neratinib, GSK-690693, Cabozantinib, Crenolanib, MK-8033 and GSK-1070916 show decreased binding of FECH to PPIX beads, Gefitinib, Alectinib, Axitinib, Nilotinib, Nintedanib and Momelotinib do not, implying the presence of an alternative binding site for these inhibitors on FECH. Error bars depict the standard error of the mean (SEM).*

Given that kinobeads comprise immobilized kinase inhibitors, the aforementioned kinase inhibitors that bind and/or inhibit FECH may act by the same mechanism. To follow up on this hypothesis, PPIX was immobilized onto sepharose beads and a competition pulldown experiment using Vemurafenib as the competitor was performed. FECH binding to the PPIX beads was monitored by Western Blotting and the results clearly show a dose dependent decrease of FECH binding to PPIX beads, demonstrating that Vemurafenib indeed binds to the PPIX site in FECH (Figure 42b). To evaluate the binding mode of further FECH inhibitors identified in this study, pulldowns from K-562 cell lysates were performed using PPIX beads in competition with the respective drugs (5 µM) or PPIX (5 µM) as positive and Dabrafenib (5 µM) as negative control. In line with the K_d values

obtained from Kinobeads experiments, Vemurafenib, CUDC 101, Cyc-116, Linsitinib, MK-2461, Neratinib, GSK-690693, and Crenolanib reduced FECH binding to the PPIX beads by 50% or more compared to the DMSO control. This data clearly indicate that the PPIX binding site of FECH can be targeted by kinase inhibitors (Figure 42c). However, the binding data were not entirely conclusive for the compounds Cabozantinib, MK-8033, GSK-1070916, Gefitinib, Alectinib, Axitinib, Nilotinib, Nintedanib and Momelotinib raising the possibility that there may be one or several other sites in the FECH structure to which these inhibitors may bind.

Unfortunately, co-crystallization FECH with kinase inhibitors failed since high cholate concentrations are required for protein stabilization and cholate molecules are direct competitors of the kinase inhibitors (see above). Therefore, docking studies were performed in collaboration with Bjoern-Oliver Gohlke (Structural Bioinformatics Group, Charité-Universitätsmedizin, Berlin, Germany)[263] for all FECH inhibitors identified in the study based on the published crystal structure of FECH[207] (PDB 3w1w). In this structure, three cholate molecules occupy the active site and one salicylic acid molecule is found in the dimer interface. Interestingly, for Vemurafenib, Neratinib, Linsitinib, MK-2461 and CUDC-101 up to three drug molecules could be docked into the active site akin to the three cholate molecules in the original structure (Figure 43a, b). For other kinase inhibitors, GSK1070916, Gefitinib, Alectinib, Axitinib, Nilotinib, Nintedanib and Momelotinib, no reasonable docking results could be obtained for the PPIX site, suggesting that these molecules may bind to an alternative site. The prime candidate for such a site is the dimerization region because active FECH is a dimer and the crystal structure of the dimer accommodates a salicylic acid molecule.

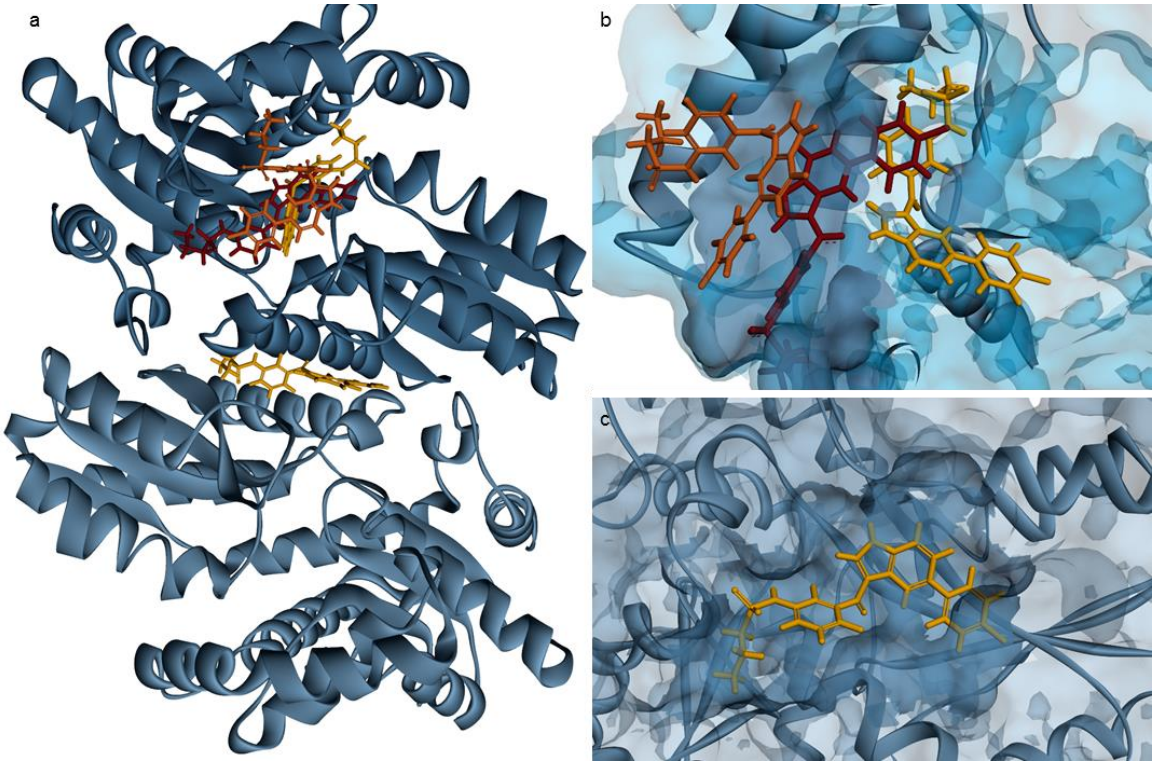

Figure 43: Docking studies using the crystal structure of FECH. *(a) Structure of the FECH dimer with both the PPIX and dimerization sites occupied by Vemurafenib. Three Vemurafenib molecules can be placed into the PPIX binding site. The first molecule docked into the PPIX site is shown in gold, the second molecule when the first is already in place is shown in red and orange depicts the third and final molecule of Vemurafenib in the PPIX binding pocket (b) Detail of the PPIX binding site with three molecules of Vemurafenib stacked inside the pocket. (c) Detail of the dimerization site with Vemurafenib docked at the dimer interface.*

Hence, additional docking studies for this dimerization site were performed (Figure 43c). Overall, FECH binders showed higher docking scores compared to those kinase inhibitors that showed no binding. Axitinib showed the highest docking score for the dimerization site and did not compete FECH binding in the PPIX pulldown assay indicating that it may indeed bind to the dimerization site. Alectinib, Gefitinib, GSK-1070916, Nilotinib and Momelotinib also scored higher at the dimerization site than kinase inhibitors that showed no FECH binding raising the possibility that some molecules actually exert their FECH inhibitory effect by disrupting the dimerization site or inducing a conformational change that renders the enzyme inactive[207]. Docking data also indicate that some inhibitors, including MK-2461 or Cyc-116, appear to fit into both potential binding sites, possibly suggesting a mixed mode of FECH binding and inhibition. However, further biochemical and structural experimentation will be required to substantiate the significance of the presumed second binding site for kinase inhibitors on FECH.

3.5.4 Clinical implications of FECH inhibition

Biochemical follow-up studies could confirm FECH as a general off-target of kinase inhibitors. Potential implications of FECH inhibition shall now be discussed in more detail.

The discovery that other kinase inhibitors can also inhibit FECH was unexpected and the fact that more than 10% of all clinically used kinase inhibitors show this off-target effect was even more surprising. This raises the question if FECH inhibition by kinase inhibitors is also of clinical relevance. Partial FECH deficiency in humans leads to the development of a disease called erythropoietic protoporphyria (EPP)[265, 266], which is characterized by cutaneous signs of acute and painful photosensitivity[267, 268]. Photosensitivity also occurs in at least 50% of all patients receiving Vemurafenib therapy[269-271], whereas photosensitivity is a much lesser issue in patients treated with Dabrafenib[272]. The fact that Vemurafenib is a FECH inhibitor and Dabrafenib is not, makes FECH inhibition a strong candidate for a molecular mechanism explaining the photosensitive phenotype observed in Vemurafenib patients. It has been shown that decreased FECH activity leads to protoporphyrin accumulation in a number of tissues and cell types including erythrocytes[265, 273]. Protoporphyrin IX is an endogenous photosensitizer as it absorbs light in a range from 320 to 595 nm and can induce the production of reactive oxygen species (ROS) that, in turn, may contribute to pro-inflammatory processes[274]. Vemurafenib patients also show elevated PPIX levels after UVA-radiation[275, 276,277] further substantiating the link between FECH as an off-target and the clinical phenotype. Further evidence comes from the pharmacology of Vemurafenib. With a dose of 960 mg twice daily and a reported plasma concentration of $AUC_{0\text{-}24}$ of 1741±639 µM x h[270], the Vemurafenib concentration in the human body is certainly high enough to inhibit FECH completely and systemically. It is therefore not far-fetched to speculate that FECH inhibition by Vemurafenib is the molecular mechanism that explains the photosensitive phenotype in patients treated with this drug.

Based on this rational and the data presented above, photosensitivity due to FECH inhibition may also be a relevant issue for Cabozantinib for which plasma concentrations in the mid micromolar range have been reported[257]. Similar considerations may apply to Crenolanib[278], Alectinib[279], Axitinib[280], or Nilotinib[281] for which photosensitivity has also been described as a clinical side effect. For other kinase inhibitors such as Neratinib or MK-2461, FECH inhibition may be irrelevant as the clinical doses of these compounds do not reach the levels required for FECH inhibition *in-vivo*[282].

Cyc-116 is currently the most potent FECH inhibitor (K_d^{app} = 0.7 µM) but no plasma concentrations have been reported so far and there are also no reports yet on clinical observations from a completed Phase I clinical trial. Notably, the photosensitizing effect of small molecule inhibitors can also be used for photodynamic therapy of cancer. For example, the heme precursor 5-aminolevulinic acid (ALA) is a commonly used prodrug to upregulate PPIX content in cancer cells. Upon light excitation, PPIX forms reactive oxygen species that kill nearby tumor cells[283, 284]. It has been shown that not only ALA treatment but also FECH inhibition leads to PPIX accumulation[285]. Therefore, on a more speculative note, a kinase inhibitor that is also a FECH inhibitor may be useful for photodynamic therapy, in case the kinase inhibitor is otherwise very well tolerated.

Since the photosensitive phenotype characteristic for patients with genetic FECH deficiency resembles that of Vemurafenib treated skin cancer patients, FECH inhibition by this drug is a likely molecular mechanism by which this toxicity occurs. Given that about 13% of all kinase inhibitors are also FECH inhibitors, it would seem prudent to consider including a FECH assay in the pre-clinical development of kinase inhibitor drugs in general.

4 General Discussion

Molecular targeted therapies including small molecule kinase inhibitors have shown great success over the years. As these inhibitors are mostly directed towards the ATP-binding pocket of a kinase, they are not always only acting on their intended target. With the rising use of kinase screening panels, selectivity and off-targets of inhibitors can nowadays be assessed kinome-wide and in routine manner[71, 72, 74, 75, 286, 287]. However, the available assays often concentrate on recombinant protein kinases in an artificial environment. Kinobeads, a chemical proteomic technology, can be used to profile protein binding to these inhibitors in endogenous conditions without prior modification of the compound of interest. Using this setup, 242 inhibitors currently in clinical trials were profiled against the proteome of four cell lines. This enabled the identification of 221 kinases and 32 other nucleotide, FAD or heme binders as targets of small molecules.

The presented study is the most thorough, systematic selectivity evaluation of small molecule inhibitors currently evaluated in humans. Other large-scale screens profiled a smaller number of clinical molecules against over 400 recombinant kinases[72, 74] or focused on large tool compound libraries[287]. Moreover, these studies mostly profiled one or two concentrations of a compound and determined remaining residual activity. The Kinobeads profiling was performed with eight concentrations of inhibitors, enabling the generation of dose-response curves, as well as EC_{50} and K_d^{app} values. This dose dependent evaluation has allowed to rank targets according to their affinity and to better estimate therapeutic windows in several applications. Furthermore, a dose response generates more solid target hypotheses than one single data point alone. As chemical proteomics assays measure mostly binding and generate target hypotheses, recombinant activity assays are needed to confirm these assumptions. Correlation of recombinant activity assays and binding assays is often poor due to screening activity on kinase domain level only[288]. The screen was performed in native lysate; hence the setup is closer to natural occurring protein abundances, their proteoforms and their influences on specific drug-protein interactions. The native biological settings are better represented than when inhibition is evaluated on proteins in isolation[77, 90]. As shown for Dabrafenib, activity data confirmed the results of the binding assay. CDK2 binding of Dabrafenib was identified both in the Kinobeads assay and the KinomeScan profiling (Dataset 20131, LINCS[211]) and, so far, remains the only case, where binding seems not to be affecting activity. The reason for this might be that CDK2, when paired with a cyclin to measure activity or performing its function *in vivo*, is not affected by Dabrafenib anymore.

Kinobeads profiling is, of course, dependent on the provided protein resource and the used immobilized compounds. The dataset is lacking information on kinases, which are not expressed in the used cell lines. As shown for MET- and EGFR-inhibitor profiling, additional cell lines or use of tissue can give further insights into the target space. Despite an already good kinome coverage with the current version of Kinobeads[92] and a mix of four cell lines, some kinases like ALK, LRRK2, VEGFR or lipid kinases could not be enriched or competed in this screen. Further improvements in the design of such immobilized probes can help to overcome this issue. Mass spectrometric readout in the applied bottom-up approach also cannot determine the mutation status of the underlying protein[289], thus, compounds that might specifically interact with mutant versions of one protein[73] cannot be distinguished in this setup. Hence, conclusions on inhibited mutants can only be inferred from RNAseq data for the respective cell line or tissue used. These shortcomings of proteomic technologies are compensated by other interesting discoveries not possible with recombinant

kinases assays. Chemical proteomics and cellular thermal shift assays facilitate the detection of non-kinase off-targets. Using Kinobeads, other ATP-binding proteins can be profiled but also proteins completely lacking a respective ATP-binding site. Previous studies already described NQO2 as an off-target of kinase inhibitors[91, 99, 290]. With the screen, nine more inhibitors could be identified, binding to NQO2 with nanomolar affinity (30 inhibitors up to 1 µM). The physiological relevance of this common off-target remains unclear. It might provide a therapeutic benefit in some cases as NQO2 inhibition can lead to a reduction of NFκB activation[291]. A more recent such case is Ferrochelatase which has been identified as an off-target of the approved BRAF inhibitor Vemurafenib[110] that is used for the treatment of unresectable or metastatic melanoma carrying a BRAF(V600E) mutation[292]. The present study has shown that a substantial number of clinically used kinase inhibitors (26 compounds) also target the enzyme Ferrochelatase (FECH). Biochemical and structural data revealed that several inhibitors bind to the protoporphyrin site in the enzyme whereas others potentially interact with the protein in the dimerization domain. FECH deficiency leads to erythropoietic protoporphyria, which is accompanied by severe photosensitivity[267, 268]. Photosensitivity is also a side effect in Vemurafenib therapy[276, 277], thus FECH inhibition is likely the underlying molecular reason for this side effect. The photosensitivity phenotype can be prevented by application of sunscreen, the effect of protoporphyrin IX accumulation in lipid tissues, however, is not fully assessed yet[265]. As about 12% of all drugs in clinical trials target this protein, inclusion of potential FECH binding in the preclinical evaluation of a promising inhibitor candidate, therefore, seems rational to estimate off-target toxicities. Besides these two now well-characterized biomolecules, the screen also revealed further less studied non-kinase proteins to be targets of these compounds. Several kinase inhibitors, like Alisertib and Crizotinib, were potent binders of the Acetyl-CoA dehydrogenases ACAD10 and ACAD11. They might bind inhibitors via their FAD co-factor binding site. The information on ACAD function is sparse, but they presumably play a role in fatty-acid metabolism. ACAD11 has been shown to be involved in oxidative phosphorylation and tumor survival under conditions of glucose starvation. In this case, ACAD inhibition might provide therapeutic opportunities and a beneficial effect when targeted as an off-target during cancer therapy[293].

Still, the majority of the 242 clinical inhibitors targeted mainly kinases. These 221 kinases identified in the drug screen represent more than 40% of the kinome that can be addressed by drugs, which is a considerable improvement to the known target space just a few years ago[61]. On the one hand, this highlights a Kinobeads point of view on the druggable kinome[232]; on the other hand, it enables improved characterization of potential off-targets and selectivity of these inhibitors.

The polypharmacology of inhibitors is of great interest during the drug development process. The analysis of inhibitors in clinical trials revealed no specific trend towards either more selective or less selective inhibitors. Benefits of one group over the other are still disputed. Selective inhibitors, so called ‘magic bullets’[294], have shown potential, but also might lack efficacy in specific cancers if their target is not important for survival or if signaling can be reconstituted by other proteins. Reasonable selectivity has to be a criterion, when drugs are administered chronically or in other indications than cancer[237]. Some unselective inhibitors target a defined subset of kinases. These selectively unselective inhibitors, also referred to as ‘magic shotguns’[294], are often more efficacious in clinical settings[295]. One reason could be that partial inhibition of multiple targets might be more effective than selective and complete inhibition of one target[296]. However, these multi-kinase inhibitors might lead to more side effects, which need to be considered in rational drug design and monitored in clinical trials. In fact, therapeutic effects in some cancers are dependent on targeting multiple

targets at once which could either be achieved by one multi-kinase inhibitor or a combination of several selective molecules[35, 297]. Here, combinations of a variety of selective drugs seem to offer a more effective and flexible approach than the application of multi-kinase inhibitors. Despite successful results for selected examples like BRAF and MEK inhibitors, many combination therapies suffer from dosing errors and drug-drug interactions[298].

Overall, targeted therapies require patient stratification based on the molecular tumor subtype to ensure treatment success with kinase inhibitors. These efforts are now increasing in personalized cancer therapy and medical oncology[299]. Advances in routine DNA or RNA sequencing of cancer cell lines or patient tissue revealed a huge variety of kinases mutated in tumors[300, 301].

Apart from known and well-studied proteins involved in disease, also previously uncharacterized proteins can be potential drug targets. How these kinases interfere with signaling and whether they might be a suitable therapeutic target is still a matter of ongoing research. Even with the rise of genome wide studies, most of protein research is still focused on the same 10% of proteins[302]. Molecular tools like antibodies or small molecules are needed to study the function and implications of a protein. Each molecule needs to be thoroughly characterized to confirm, that it is suitable to be used as chemical probe against the intended target[235, 303]. The results of the drug screen may help to identify potential inhibitors for kinases that have so far lacked interest in drug discovery. Furthermore, these structures can serve as scaffold for the generation of new inhibitors with increased selectivity for a kinase, also facilitating thorough evaluation in basic research. The drug screen already identified highly selective molecules (e.g. Lapatinib, Capmatinib or Rabusertib) that might be used as chemical probes for the investigation of their target proteins.

Another problem in targeting cancer with small molecules is tumor resistance. After a few months of treatment, the tumor often adopts to the treatment by mutation of the targeted protein such that the drug cannot bind anymore or by upregulation of an alternative pathway. For example, the BRAF(V600E) inhibitors Vemurafenib and Dabrafenib show very promising results, but after two to twelve months the tumor developed resistance against these inhibitors[270, 304]. Elevated CRAF levels have been observed in some studies, indicating a circumvention of BRAF signaling[305]. Combination therapy with inhibitors targeting the downstream signaling node MEK has significantly prolonged survival and postponed tumor resistance[250]. Other known resistance mechanisms include higher levels of c-MET and EPHA2[306] or mutations of the oncogene, like observed for BCR-ABL (*e.g.* T315I)[50] and EGFR (*e.g.* T790M)[307] and lead to the administration of another drug. The screen can also identify potential useful combination treatments or alternative drugs to overcome resistance.

The molecular characterization of tumors also identifies certain drug targets involved in various entities. Here, polypharmacology of drugs can have advantage as an already well-known drug can also be of use in other indications. The additional use of Imatinib in gastro intestinal stromal tumors (GIST) due to its additional KIT-inhibition has paved the way for so-called kinase inhibitor repurposing[43, 44]. Drug repositioning in general can reduce research and economic efforts that arise with the development of a new drug against a new target[308]. The compounds used in this study are all in clinical evaluation, making them easy candidates for repurposing. They have already been optimized in preclinical studies and have been tested for toxicity or are currently in such a phase I trial. Therefore, another phase 1 safety trials can be skipped and the drug can directly be evaluated for efficacy in a phase II trial. Often, many drugs are applied and evaluated in off-label uses by practicing physicians[309].

The potential of repositioning drugs for personalized therapy is already reflected in clinical trial design. Basket trials are based on molecular subtyping of cancers and patients are then grouped into the trial based on their genetic phenotype rather than their cancer entity[310, 311]. This was firstly evaluated for Imatinib and patients expressing Imatinib sensitive targets[312]. Furthermore, patients with various cancers driven by a BRAF(V600E) mutation could be successfully treated with Vemurafenib[313]. Of course, certain entities showed better response than others, but rare diseases with no further treatment option (e.g. Erdheim-Chester) showed promising response. This 'basket' design of clinical studies provides a good option for evaluation of molecularly targeted therapies and is rapidly adaptable for novel biomarkers. Several such trials are now active and investigate BRAF or MET inhibitors but also hedgehog inhibitors or PD-1 antagonists.
The resource presented here now provides further drug candidates and molecular rationales for repurposing drugs. This can be achieved by either using the drug against the same drug target in another disease setting or by using the drug because of an off-target effect. The screen provides opportunities for either ways. Ozanne et al. discovered that Dasatinib and Bosutinib inhibit SIK2 and thus induce anti-inflammatory macrophages. This effect could be of advantage in the treatment of chronic inflammatory diseases[314]. The screen of 242 clinical inhibitors revealed 25 inhibitors for SIK2, which can now also be investigated in regard to inflammation. Another rising target of interest is NTRK1 (TrkA). Sequencing revealed a TPM3-NTRK1 fusion in colorectal cancer (CRC) and non-small cell lung cancer (NSCLC) patients as tumor driving mutation[255, 256]. At the beginning of this project, no selective inhibitor was known to target NTRK1. Besides the known TrkA inhibitors Lestaurtinib and Entrectinib, selectivity profiling revealed 18 additional compounds that can bind to NTRK1 with nanomolar affinity. As these inhibitors are all targeting many other kinases as well, it might be more likely that they serve as starting point for medicinal chemistry approaches trying to develop selective NTRK1 inhibitors. Another promising example for drug repositioning is the here presented example of Cabozantinib. FLT3 inhibition was already described for Cabozantinib[257] and potent FLT3 inhibition could be confirmed in the Kinobeads pulldown. FLT3 represents a therapeutic target in acute myeloid leukemia (AML)[258] and FLT3 internal tandem duplications (ITD) were observed in patients[315]. Treatment of AML is still lacking personalized medicine approaches and selective inhibition of FLT3-ITD might provide one therapeutic option. The convincing *in vitro* and *in vivo* data of a joint study conducted based on the results of this screen as well as other studies[260] strongly supports a clinical evaluation of Cabozantinib in AML.

In summary, the target landscape of kinase inhibitors currently evaluated in clinical trials was successfully profiled using the Kinobeads technology. This work provides a rich resource of data describing the molecular landscape of clinically evaluated small molecule kinase inhibitors and targets thereof. Examples on how this information can be used were highlighted. Besides the aspects on selectivity, selected inhibitors and targets were further characterized. Noteworthy is the discovery of the non-kinase off-target FECH, whose inhibition most likely is one molecular reason for the observed side effect of photosensitivity. The most exciting aspect of the study is the demonstration that re-purposing kinase drugs is feasible and can be approached in a systematic fashion. In order to facilitate further exploitation of the data, the derived target profiling information will be made publicly available. It can help the community to improve the understanding of the mode-of-action of cancer drugs and aid in accelerating the development of novel therapeutic regimens.

Abbreviations

ABPP activity based protein profiling
ACN acetonitrile
AGC protein kinase A, G, C group
AML acute myeloid leukemia
ATP adenine triphosphate
AUC area under the curve
CAMK calcium/calmodulin dependent kinase group
CATDS concentration and target dependent selectivity
CETSA cellular thermal shift assay
CEM chain ejection model
CID collision induced dissociation
CK1 casein kinase group
CMGC cyclin dependent kinase, MAP kinase, GSK kinase, casein kinase 2 group
CML chronic myeloid leukemia
CRM charged residue model
Da Dalton (unit)
DDA data dependent acquisition
DIA data independent acquisition
DMSO Dimethylsulfoxide
DTT Dithiothreitol
EC_{50} effective concentration for half maximal inhibition
ESI electrospray ionization
ETD electron transfer dissociation
FDR false discovery rate
FECH Ferrochelatase
GIST Gastro-intestinal stroma tumor
HCD Higher collision cell induced dissociation
iBAQ intensity based absolute quantification
IC_{50} inhibitory concentration for half maximal inhibition
IEM ion evaporation model
ITD internal tandem duplication
ITDR isothermal dose response
K_d dissociation constant
K_d^{app} apparent dissociation constant
LC liquid chromatography
LFQ label-free quantification
LTQ linear trapped quadrupole (2D ion trap)
MALDI matrix assisted laser desorption ionization
MAP mitogen-activated protein
MS mass spectrometry
MS/MS tandem mass spectrometry
m/z mass to charge ratio
NCT national clinical trial
NHS N-hydroxysuccinimide
NSCLC non-small cell lung cancer
PPIX Protoporphyrin IX
ppm parts per million
PSM peptide spectrum match
RF radio frequency
r.t. room temperature
SAX strong anion exchange chromatography
SCX strong cation exchange chromatography
SDS sodium dodecyl sulfate
SILAC stable isotope labeling with amino acids in cell culture
STE sterile 20 kinase group
Th Thomson unit
TK tyrosine kinase group
TKL tyrosine kinase like group
TMT tandem mass tag
WT wildtype
XIC extracted ion chromatogram

Proteins and gene names are based on UniProt and HUGO accessions
(Exceptions: MEK1/2 MAP2K1/MAP2K2
p38 MAPK11/MAPK14)

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Education

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Scholarship

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German A-levels (Abitur), Grade: 1.2

Languages

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Extracurricular activities

Apr. 2009 – Oct. 2012 Member and leadership tasks of the "Biolloquium"–team at the department biosciences at the Technical University of Munich – organization of lecture-series on actual topics in life-science

May – Nov. 2011 Participation in the iGEM (international Genetically Engineered Machine)-competition for synthetic biology with an interdisciplinary student team of the Technical University of Munich, prize: participation in the world jamboree in Boston, MA and gold medal.

Conference contributions and publications

Conferences

Munich Cancer Retreat 2016	Target Landscape of Clinical Kinase Inhibitors, Highlight Talk (Best Talk Award)
ASMS 2016	Selectivity Profiling of Kinase Inhibitors – From Label Free DDA Quantification to Spectral Libraries for Sub-Proteomes, poster
HUPO 2015	Selectivity Profiling of 200 Clinical Kinase Inhibitors Using Chemical Proteomics, oral presentation and poster
Munich Cancer Retreat 2015	Preclinical evaluation of Cabozantinib in AML, poster
DKTK Retreat 2015	Identification of Ferrochelatase as a common off target of small molecule kinase inhibitors, poster
Munich Cancer Retreat 2014	Selectivity profiling of BRAF inhibitors using chemical proteomics, poster
DKTK Retreat 2014	Selectivity profiling of BRAF inhibitors using chemical proteomics, poster

Publications

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(*contributed equally)

Appendix I

Table of all inhibitors used in this study:

Drug	Name of the drug
Synonyms	Synonyms of drug names
Designated targets	Designated targets according to supplier
Other targets	Other targets according to supplier
Binding type	Binding mode to designated target
Clinical Phase	Clinical phase as of 2/2016
Supplier	Supplier of compound used in this study
Supplier order number	Oder number at supplier

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
Abemaciclib	LY-2835219	CDK4,CDK6		0	Phase III	Selleckchem	S7158
AC-480	BMS-599626	EGFR,ERBB2	ERBB4	0	Phase I	Selleckchem	S1056
ACTB-1003		FGFR1	KDR,TEK,RPS6KA1,RPS6KA2,RPS6KA3,RPS6KB1,RPS6KB2	0	Phase I	MedChem Express	HY-16025
AEE-788	NVP-AEE788, GNF-Pf-5343	EGFR,ERBB2	KDR,ABL1,SRC,FLT1,CSF1R,ERBB4,PDGFRB,FLT4,FLT3,RET,KIT	1	Phase I/II	Selleckchem	S1486
AEW-541	NVP-AEW541	IGF1R,INSR	FLT3,TEK,FLT1	1	Phase I	Active Biochem	A-1911
Afatinib	Afatinib Dimaleate, BIBW2992-MA2, BIBW-2992	EGFR	ERBB2	1 (covalent)	approved	Selleckchem	S1011
Alectinib	AF-802, CH-5424802, AF-802, CH-5424802	ALK	INSR	1	approved	MedChem Express	HY-13011
Alisertib	MLN-8237, MLN-8237-004, Alisertib Sodium	AURKA	AURKB	0	Phase II	Selleckchem	S1133
Alvocidib	HL-275, HMR-1275, L-868275, L-86-8275, NSC-649890, MDL-107826A, Flavopiridol, Alvocidib HCl	CDK1,CDK2,CDK4,CDK6	CDK7,EGFR,PRKACA,PRKACB,PRKACG	1	Phase II	Selleckchem	S1230
AMG-208		MET		1	Phase I	Selleckchem	S1316
AMG-900		AURKA,AURKB,AURKC	MAPK14,TYK2,MAPK9,MET,TEK	2	Phase I	Selleckchem	S2719
Amuvatinib	HPK56, HPK-56, MP-470, MP-470.HCl, Amuvatinib HCl	KIT,PDGFRA,FLT3		0	Phase II	Selleckchem	S1244
Apatinib	YN-968D1	KDR	RET,KIT,SRC	2	approved	Selleckchem	S2221
Apitolisib	RG-7422, G-038390, GDC-0980.1, G-038390.1, GDC-0980	PIK3CA,PIK3CB,PIK3CD,PIK3CG,MTOR		0	Phase II	Active Biochem	A-1069
ARRY-380	ONT-380, Irbinitinib, Tucatinib	ERBB2	EGFR	0	Phase I	Selleckchem	S2752

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
ASP-3026		ALK		0	Phase I	MedChem Express	HY-13326
AT-13148		AKT1,AKT2,AKT3,RPS6KB1,RPS6KB2,PRKACA,PRKACB,PRKACG,ROCK1,ROCK2	SGK3,RPS6KA1,CHEK2	0	Phase I	Selleckchem	S7563
AT-7519		CDK1,CDK2,CDK4,CDK5,CDK6,CDK9,CDK3	CDK7,GSK3B	1	Phase II	Selleckchem	S1524
AT-9283		JAK2,JAK3	AURKA,AURKB,ABL1,GSK3B,FGFR2,FLT4,MERTK,RET,RPS6KA3,RPS6KA2,TYK2,YES,STK17A,FGFR1,FGFR3,FLT1,FLT3,PDGFRA,PDPK1,PRKD1,RPS6KA6,SRC,KDR	1	Phase II	Selleckchem	S1134
AV-412	MP-412	EGFR,ERBB2		0 (covalent)	Phase I	MedChem Express	HY-10346A
Axitinib	AG-013736, Inlyta, AG-13736	FLT1,KDR,FLT4	PDGFRB,KIT,PDGFRA,CSF1R	2	approved	Selleckchem	S1005
AXL-1717	Picropodophyllin, Picropodophyllotoxin	IGF1R	INSR,FGFR1,FGFR2,FGFR3,FGFR4,PDGFRA,PDGFRB,EGFR	0	Phase II	MedChem Express	HY-15494
AZD-1208		PIM1,PIM2,PIM3		0	Phase I	MedChem Express	HY-15604
AZD-1480		JAK2	JAK3,TYK2,JAK1	1	Phase I	Selleckchem	S2162
AZD-2014		MTOR	PIK3CA,PIK3CB,PIK3CD,PIK3CG	0	Phase II	MedChem Express	HY-15247
AZD-4547	KB-74810	FGFR1,FGFR2,FGFR3	KDR,IGF1R	1	Phase II/III	Selleckchem	S2801
AZD-5363		AKT1,AKT2,AKT3	RPS6KB1,RPS6KB2,PRKACA,PRKACB,PRKACG,ROCK1,ROCK2	1	Phase II	Selleckchem	S8019
AZD-5438		CDK1,CDK2,CDK9	CDK5,CDK6,GSK3B	0	Phase I	Selleckchem	S2621

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
AZD-6482		PIK3CB	PIK3CA,PIK3CD,PIK3CG,PRKDC	0	Phase I	MedChem Express	HY-10344
AZD-7762		CHEK1	CHEK2,YES,FYN,LYN,HCK,LCK	1	Phase I	Selleckchem	S1532
AZD-8055	AZ-12600000	MTOR		0	Phase I	Selleckchem	S1555
AZD-8186		PIK3CB,PIK3CD	PIK3CA,PIK3CG	0	Phase I	Active Biochem	A-1610
AZD-8330	ARRY-704, ARRY-424704	MAP2K1,MAP2K2		3	Phase I	Selleckchem	S2134
Bafetinib	CNS-9, NS-187, INNO-406	ABL1,LYN	PDGFRA,PDGFRB,KIT	2	Phase II	MedChem Express	HY-12039
Barasertib	AZD-1152	AURKB		2	Phase II/III	MedChem Express	HY-10127
Barasertib_HQPA	AZD-1152-HQPA	AURKB		2	Phase III	MedChem Express	HY-10126
Baricitinib	INCB-28050, LY-3009104, INCB-028050	JAK1,JAK2	JAK3,TYK2	1	Phase III	MedChem Express	HY-15315
BGT-226	NVP-BGT226	PIK3CA,PIK3CB,PIK3CG,MTOR		0	Phase I/II	Selleckchem	S2749
BI-2536		PLK1	PLK2,PLK3	1	Phase II	Selleckchem	S1109
BI-847325		MAP2K1,MAP2K2,AURKA,AURKB,AURKC		0	Phase I	Selleckchem	S7843
Binimetinib	ARRY-162, MEK-162, NVP-MEK162, ARRY-438162	MAP2K1,MAP2K2		3	Phase II	Active Biochem	A-1128
BMS-387032	SNS-032	CDK2,CDK7,CDK9	CDK1,CDK4,CDK6,GSK3A,CDK5,GSK3B	1	Phase I	Selleckchem	S1145
BMS-690514		EGFR,ERBB2,ERBB4,FLT1,KDR,FLT4		0	Phase II	MedChem Express	HY-10333

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
BMS-754807		IGF1R,INSR	MET,AURKA,AURKB,NTRK1,NTRK2,MST1R,FLT3,JAK2,GSK3B,CDK2,MAPKAPK2	1	Phase II	Active Biochem	A-1013
BMS-777607		MET,AXL,MST1R,TYRO3	LCK,KDR,NTRK1,NTRK2,MERTK,FLT3,AURKB,PRKACA,PRKACB,PRKACG	2	Phase I/II	Selleckchem	S1561
BMS-911543		JAK2	JAK1,JAK3,LYN,CSF1R	1	Phase I/II	Active Biochem	A-1175
Bosutinib	Bosulif, SKI-606, Bosutinib Monohydrate	SRC,ABL1		1	approved	LC Laboratories	B-1788
Brivanib	BMS-540215	KDR	FGFR1,FLT1	1	Phase III	Selleckchem	S1084
Brivanib-alaninate	BMS-582664	KDR	FGFR1,FLT1	1	Phase III	Selleckchem	S1138
Buparlisib	BKM-120, BKM120-NX, Buparlisib HCl, NVP-BKM120, BKM120-AAA	PIK3CA,PIK3CB,PIK3CD,PIK3CG		0	Phase III	Selleckchem	S2247
BYL-719	Alpelisib, NVP-BYL719	PIK3CA	PIK3CB,PIK3CD,PIK3CG	0	Phase II	MedChem Express	HY-15244
Cabozantinib	BMS-907351, Cometriq, Cabozantinib S-Malate, XL-184	KDR	MET,KIT,FLT1,FLT3,FLT4,AXL,TEK,MST1R,PDGFRB,FGFR1	2	approved	Selleckchem	S1119
Canertinib	PD-0183805, PD-183805, Canertinib Dihydrochloride, CI-1033, SN-26606	EGFR,ERBB2		1 (covalent)	Phase II	Selleckchem	S1019
Capmatinib	NVP-INC280, INC-280, INCB-28060	MET		0	Phase II	Selleckchem	S2788
CC-401		MAPK8,MAPK9,MAPK10		0	Phase I	MedChem Express	HY-13022
Cediranib	AZD-2171, ZD-2171, Recentin, Cediranib Maleate	KDR	KIT,FLT1,FLT4,PDGFRB,FGFR1,PDGFRA,CSF1R,SRC,ABL1	1	Phase III	Selleckchem	S1017
CEP-32496		BRAF,CRAF	KIT,LCK,PDGFRB,ABL1,RET,KDR,CSF1R,EPHA2,EGFR,MET	0	Phase I/II	MedChem Express	HY-15200

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
Cerdulatinib	PRT-2070, PRT-062070	JAK1,JAK2,JAK3, TYK2,SYK	STK4,NUAK1,MAP3K9,CSF1R,PRKAA1,PRKAA2,JAK2,JAK3,TBK1,MARK1,JAK1,MARK2,TSSK1B,TSSK2,TSSK3,TSSK4,TSSK6,STK3,MAPK10,RPS6KA3,RPS6KA6,SYK,CHEK1,FLT4,FLT3,RET,ITK	0	Phase I	MedChem Express	HY-15999
Ceritinib	NVP-LDK378-NX	ALK	IGF1R,INSR,TSSK1B,TSSK3,FLT3,FGFR2,RET,FGFR3,LCK,JAK2,AURKA,LYN,EGFR,FGFR4	1	approved	MedChem Express	HY-15656
Certican	RAD001, Afinitor, Zortress, Everolimus, Afinitor Disperz	MTOR		0	approved	Selleckchem	S1120
CH-5183284		FGFR1,FGFR2,FGFR3,FGFR4		1	Phase I	Active Biochem	A-1332
Cobimetinib	RG-7420, GDC-0973, Cobimetinib Fumarate, XL-518, RG-7420, RG-7421, GDC-0973	MAP2K1		3	approved	Active Biochem	A-1180
Copanlisib	BAY 84-1236, BAY-80-6946, BAY 80-6946, Copanlisib hydrochloride	PIK3CA,PIK3CB,PIK3CD,PIK3CG		0	Phase I	MedChem Express	HY-15346
CP-547632	OSI-632	KDR,FGFR1	EGFR,PDGFRB	0	Phase II	Axon Medchem	Axon 1662
CP-724714		ERBB2	EGFR,INSR,IGF1R,PDGFRA,PDGFRB,KDR,ABL1,SRC,MET,MAPK9,MAPK10,ZAP70,CDK2,CDK5	0	Phase II	Selleckchem	S1167
Crenolanib	ARO-002-26, CP-868596, ARO-002, Crenolanib Besylate, 596-26, CP-868	PDGFRA,PDGFRB	KIT,KDR,TEK,FGFR2,EGFR,ERBB2,SRC,FLT3	0	Phase III	Selleckchem	S2730
Crizotinib	Xalkori, PF-2341066	MET,ALK		1	approved	Selleckchem	S1068
CUDC-101		EGFR,ERBB2		0	Phase I	Selleckchem	S1194

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
Cyc-116		AURKA,AURKB	KDR,FLT3,CDK2,CDK9,RPS6KB1,RPS6KB2,SRC	1	Phase I	Selleckchem	S1171
Dabrafenib	GSK2118436A, GSK2118436B, Dabrafenib Mesylate	BRAF	CRAF	1	approved	MedChem Express	HY-14660
Dacomitinib	PF-00299804, PF-00299804-03	EGFR	ERBB2,ERBB4	1 (covalent)	Phase III	Selleckchem	S2727
Dactolisib	BEZ-235, NVP-BEZ235, NVP-BEZ235-NX, NVP-BEZ235-ANA, Dactolisib Tosylate	PIK3CA,PIK3CB,PIK3CD,PIK3CG,MTOR	ATR	0	Phase II	Selleckchem	S1009
Danusertib	PHA-739358	AURKA,AURKB,AURKC	ABL1,NTRK1,RET,FGFR1,LCK,KDR,FLT4,KIT,CDK2	1	Phase II	Selleckchem	S1107
Dasatinib	Sprycel, BMS-354825-03, BMS-354825	ABL1,SRC	KIT	1	approved	Selleckchem	S1021
Decernotinib	Adelatinib, VX-509, VRT-831509	JAK3	JAK1,JAK2,TYK2	1	Phase I	MedChem Express	HY-12469
Defactinib	PF-04554878, VS-6063, Defactinib Hydrochloride	PTK2		0	Phase II	MedChem Express	HY-12289
Deforolimus	MK-8669, AP-23573, Ridaforolimus	MTOR		0	Phase III	Selleckchem	S1022
Dinaciclib	MK-7965, SCH-727965	CDK2,CDK5,CDK1,CDK9		1	Phase III	Selleckchem	S2768
Dovitinib	TKI-258, CHIR-258, Dovitinib Lactate, NVP-TKI258, GFKI-258	FLT3,KIT	INSR,EGFR,MET,EPHA2,TEK,IGF1R,ERBB2,FGFR1,FGFR3,FLT1,KDR,FLT4,PDGFRB,CSF1R,PDGFRA	1	Phase III	Selleckchem	S1018
Encorafenib	NVP-LGX818, LGX-818, NVP-LGX818-NXA	BRAF		0	Phase II	Selleckchem	S7108
ENMD-2076		AURKA,FLT3	RET,AURKB,KDR,FLT4,FGFR1,FGFR2,SRC,NTRK1,CSF1R,LCK,PTK2,PDGFRA,BLK,YES1,ABL1,FYN,JAK2,KIT	0	Phase II	Selleckchem	S1181
Entrectinib	RXDX-101, NMS-E628	NTRK1,NTRK2,NTRK3,ROS1,ALK		1	Phase I	MedChem Express	HY-12678

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
Enzastaurin	LY-317615, Enzastaurin HCl	PRKCB	PRKCA,PRKCG,PRKCE	0	Phase III	Selleckchem	S1055
Erlotinib	RG-1415, Tarceva, OSI-774, R-1415, CP-358774, Ro-508231, CP-35877401, CP-358774-01, Erlotinib HCl	EGFR		1	approved	Selleckchem	S1032
Fasudil	HA-1077, AT-877, ZK-258594	ROCK2,PRKACA, PRKACB,PRKACG ,PRKCA,PRKCB,P RKCZ,PRKCH,PRK CG,PRKCD,PRKCI ,PRKCE,PRKG1,P RKG2,MYLK	1	reversible	Selleckchem	S1573	
Fedratinib	SAR-302503, TG-101348, TG-101348, TG101348, SAR-302503	JAK2	JAK1,JAK3,FLT3,RET	1	Phase I	Selleckchem	S2736
Filgotinib	G-146034, GLPG-0634, G-146034_101, Filgotinib hydrochloride	JAK1	JAK2,JAK3,TYK2	1	Phase II	MedChem Express	HY-18300
Foretinib	GSK089, XL-880, EXEL-2880, GSK1363089, GSK1363089G	MET,KDR	MST1R,FLT1,FLT3,FLT4,KIT,PDGFR A,PDGFRB,TEK,FGFR1	2	Phase II	Selleckchem	S1111
Fostamatinib	R-788, R-935788, R-788 Sodium, R-788 Free acid, R-935788 Sodium, R-935788 Free acid, Fostamatinib Disodium	SYK	FLT3	0	Phase III	Selleckchem	S2625
Galunisertib	LY-2157299	TGFBR1		0	Phase II/III	Selleckchem	S2230
GDC-0994		MAPK3,MAPK1		1	Phase I	Selleckchem	S7554
Gedatolisib	PKI-587, PF-05212384	PIK3CA,PIK3CG, MTOR		0	Phase II	Selleckchem	S2628

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
Gefitinib	Iressa, ZD-1839	EGFR		1	approved	Selleckchem	S1025
Gilteritinib	Gilteritinib fumarate, ASP-2215 HEMIFUMARATE, ASP-2215	FLT3,AXL		0	Phase III	MedChem Express	HY-12432
Golvatinib	E7050, E-7050, Golvatinib Tartrate, ER-396901-08	MET,KDR		2	Phase I/II	MedChem Express	HY-13068
GSK-1059615	GSK615	PIK3CA,PIK3CB,PIK3CD,PIK3CG,MTOR		0	Phase I	Selleckchem	S1360
GSK-1070916		AURKB,AURKC	AURKA,FLT1,TEK,SIK1,FLT4,FGFR1	0	Phase I	Selleckchem	S2740
GSK-2110183	GSK2110183B, Afuresertib, GSK2110183, GSK2110183C, Afuresertib HCl	AKT1,AKT2,AKT3		0	Phase II	GlaxoSmithKline	
GSK-2636771	GSK2636771	PIK3CB		0	Phase I	Selleckchem	S8002
GSK-461364	GSK461364, GSK461364A	PLK1	PLK2,PLK3	1	Phase I	Selleckchem	S2193
GSK-690693		AKT1,AKT2,AKT3	PRKACA,PRKACB,PRKACG,PRKX,PRKCA,PRKCB,PRKCZ,PRKCH,PRKCG,PRKCD,PRKCI,PRKCE	1	Phase I	GlaxoSmithKline	
HMN-214	VX-214	PLK1		0	Phase I	Selleckchem	S1485
Hydroxyfasudil		ROCK2,PRKACA,PRKACB,PRKACG,PRKCA,PRKCB,PRKCZ,PRKCH,PRKCG,PRKCD,PRKCI,PRKCE,PRKG1,PRKG2,MYLK	1	reversible	Merck	390602	
Ibrutinib	CRA-032765, PCI-32765-00, PCI-32765	BTK	BMX,CSK,FGR,PTK6,HCK,EGFR,YES,ERBB2,JAK3,BLK,ITK,FRK,LCK,RET,F	1(covalent)	approved	Selleckchem	S2680

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
			LT3,TEC,ABL1,FYN,RIPK2,SRC,LYN, PDGFRA				
Icotinib	BPI-2009	EGFR		0	approved	MedChem Express	HY-15164
Idelalisib	GS-1101, CAL-101, GS-11CAL-101	PIK3CD	PIK3CA,PIK3CB,PIK3CG,PIK3C3	0	approved	Selleckchem	S2226
Imatinib	Gleevec, Imatinib mesylate, STI-571	ABL1,KIT,PDGFRA,PDGFRB		2	approved	Selleckchem	S2475
IMD-0354		IKBKB		0	Phase I	Selleckchem	S2864
JANEX-1	WHI-P131	JAK3		0	Phase I	MedChem Express	HY-15508
JNJ-26483327		EGFR,ERBB2,ERBB4,LYN,YES,FYN, LCK,SRC,FLT4		0	Phase I	Active Biochem	A-1357
JNJ-38877605		MET		0	Phase I	Selleckchem	S1114
K-252a	SF 2370	PRKCA,PRKCB,PRKCZ,PRKCH,PRKCG,PRKCD,PRKCI, PRKCE	1	reversible	LC Laboratories	K-2151	
KW-2449		FLT3	FGFR1,ABL1,AURKA,PDGFRB,IGF1R,EGFR,JAK2,KIT,SRC	1	Phase I	Selleckchem	S2158
KX2-391		SRC		4	Phase II	Selleckchem	S2700
Lapatinib	GW-2016, GW-572016, GW572016F, Lapatinib Ditosylate, Tykerb, Lapatinib ditosylate monohydrate	EGFR,ERBB2	ERBB4	1	approved	Selleckchem	S1028
Lenvatinib	E7080, ER-203492-00, Lenvatinib Mesylate	KDR,FLT4	FLT1,FGFR1,PDGFRA,PDGFRB,KIT	1	approved	Selleckchem	S1164
Lestaurtinib	CEP-701, SP-924, KT-555, SP924, KT-5555, A-	JAK2,FLT3,NTRK1		1	Phase III	LC Laboratories	L-6307

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
Linifanib	1544750, SPM-924, A-154475 ABT-869, RG-3635, AL-39324	KDR,CSF1R,FLT1, FLT3	PDGFRB,KIT,TEK,FLT4,SGK1	2	Phase III	Selleckchem	S1003
Linsitinib	OSI-906, ASP-7487, OSI-906AA	IGF1R	INSR,INSRR	0	Phase III	Selleckchem	S1091
Losmapimod	GSKAHAB, GW856553, GW856553X	MAPK14,MAPK11		0	Phase II	Selleckchem	S7215
Lucitanib	E-3810, AL-3810, CO-3810, S-80881	FLT1,KDR,FLT4,FGFR1,FGFR2,FGFR3	PDGFRA,PDGFRB	1	Phase III	MedChem Express	HY-15391
LY-2584702		RPS6KB1,RPS6KB2		0	Phase I	Selleckchem	S7698
LY-2801653	Merestinib	MET	MST1R,FLT3,AXL,MERTK,TEK,ROS1,DDR1,DDR2,MKNK1,MKNK2	2	Phase I	Active Biochem	A-1182
Masitinib	AB-1010	KIT,PDGFRA,PDGFRB	LYN	2	Phase III	Selleckchem	S1064
MGCD-265		MET,FLT1,KDR,FLT4	MST1R,TEK	0	Phase I	Selleckchem	S1361
Midostaurin	PKC-412, CGP-41251, NVP-PKC412	PRKCA,PRKCB,PRKCG,SYK,KDR,AKT1,AKT2,AKT3,PRKACA,PRKACB, PRKACG,KIT,FGR,SRC,FLT3,PDGFRB,FLT1,KDR	CDK1	1	Phase III	LC Laboratories	P-7600
Milciclib	PHA-848125	CDK2	CDK1,CDK4,CDK5,CDK7,NTRK1	1	Phase II	Selleckchem	S2751
MK-1775	AZD-1775	WEE1		0	Phase II	Active Biochem	A-1117
MK-2206		AKT1,AKT2,AKT3		4	Phase II	Selleckchem	S1078
MK-2461		MET	FGFR1,FGFR2,FGFR3,PDGFRB,KDR, FLT3,FLT4,NTRK1,NTRK2,MST1R,FL	0	Phase I/II	Selleckchem	S2774

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
			T1,MERTK,STK17A,JAK2,IRAK4,MELK,RET				
MK-5108	VX-689	AURKA	AURKB,AURKC,NTRK1	1	Phase I	Selleckchem	S2770
MK-8033		MET,MST1R		0	Phase I	Active Biochem	A-1107
MLN-2480		ARAF,BRAF,RAF1		0	Phase I	Active Biochem	A-1192
MLN-8054		AURKA	AURKB	1	Phase I	Selleckchem	S1100
Momelotinib	CYT-387, Momelotinib Dihydrochloride, CYT-11387, GS-0387	JAK1,JAK2	JAK3	0	Phase III	Selleckchem	S2219
Motesanib	AMG-706, Motesanib Diphosphate	FLT1,KDR,FLT4	PDGFRA,PDGFRB,RET,KIT	2	Phase I/II	Selleckchem	S1032
Mubritinib	TAK-165	ERBB2		0	Phase I	Selleckchem	S2216
Neratinib	CDP-820, HKI-272, WAY-179272	ERBB2,EGFR	KDR	1 (covalent)	Phase III	Selleckchem	S2150
Nilotinib	AMN-107, Tasigna, Nilotinib Hydrochloride Monohydrate	ABL1		2	approved	Selleckchem	S1033
Nintedanib	BIBF-1120, Nintedanib Esylate	FLT1,KDR,FLT4,FGFR1,FGFR2,FGFR3,PDGFRA,PDGFRB	LCK,FLT3,SRC,LYN,FGFR4	2	approved	Selleckchem	S1010
NMS-1286937		PLK1		1	Phase I	MedChem Express	HY-15828
Omipalisib	GSK2126458	PIK3CA,PIK3CB,PIK3CD,PIK3CG	MTOR	0	Phase I	Selleckchem	S2658
ONO-4059 analogue		BTK		0 (covalent)	Phase I	MedChem Express	HY-18951
Orantinib	TSU-68, SU-6668	PDGFRA,PDGFRB	IGF1R,MET,SRC,LCK,ZAP70,ABL1,CDK2	1	Phase I	Selleckchem	S1470

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
OSI-027		MTOR	PIK3CG,PRKDC	0	Phase I	Selleckchem	S2624
OSI-930		KIT,KDR,CSF1R	FLT1,CRAF,LCK	2	Phase I	Selleckchem	S1220
Osimertinib	AZD-9291, Osimertinib mesylate, AZD-9291 mesylate	EGFR		1 (covalent)	approved	Selleckchem	S7297
P-276-00	P-27600	CDK1,CDK4,CDK9	CDK2	0	Phase II	Selleckchem	S8058
Pacritinib	ONX-0803, SB-1518, SB1518	JAK2,FLT3	TYK2,JAK3	0	Phase III	MedChem Express	HY-16379
Palbociclib	PD-0332991, PF-0008066573, Palbociclib Isethionate, PD-03329910054	CDK4,CDK6		1	approved	Selleckchem	S1116
Pazopanib	GW786034, Votrient, Pazopanib HCl, GW786034B	FLT1,KDR,FLT4	PDGFRA,FGFR1,FGFR2,FGFR3,FGFR4,KIT,CSF1R	1	approved	Selleckchem	S1035
PD-325901	PD-0325901	MAP2K1,MAP2K2		3	Phase II	Selleckchem	S1036
Pelitinib	EKB-569, WAY-EKB-569	EGFR	SRC,MAP2K1,MAP2K2,MAPK3,MAPK1	0 (covalent)	Phase II	Selleckchem	S1392
Perifosine	KRX-0401	AKT1		0	Phase III	Selleckchem	S1037
Pexidartinib	PLX-3397	CSF1R	KIT,FLT3	2	Phase II	Selleckchem	S7818
Pexmetinib	ARRY-614	MAPK14,MAPK11,MAPK12,MAPK13,TEK		0	Phase I	Selleckchem	S7799
PF-03814735		AURKA,AURKB	FLT3,PTK2,NTRK1,MET,FGFR1,FLT1	1	Phase I	Selleckchem	S2725
PF-04217903		MET		1	Phase I	Selleckchem	S1094

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
PF-04691502		PIK3CA,PIK3CB,PIK3CD,PIK3CG,MTOR	PIK3C3,AKT,PDK1,RPS6KB1,RPS6KB2,MAP2K1,MAP2K2,MAPK3,MAPK1,MAPK14,MAPK11,MAPK12,MAPK13,MAPK8,MAPK9,MAPK10	0	Phase II	Selleckchem	S2743
PF-3758309	PF-03758309	PAK4	PAK1,PAK6,PAK5,PAK4,PAK3,PAK2	1	Phase I	MedChem Express	HY-13007
PF-477736	PF-00477736	CHEK1	KDR,AURKA,FGFR3,FLT3,CSF1R,RET,YES,CHEK2	0	Phase I	MedChem Express	HY-10032
PF-562271	PF-00562271	PTK2	PTK2B,CDK2,CDK3,CDK1,CDK7,FLT3,GSK3A,CDK5,GSK3B,AURKA,CDK2,YES,MAPK1,FYN,LCK,IGF1R,SRC,PRKACA,PRKACB,PRKACG,SRC	1	Phase I	Selleckchem	S2672
PH-797804	PHA-797804	MAPK14	MAPK11	1	Phase II	Selleckchem	S2726
PHA-793887		CDK2,CDK5,CDK7	CDK1,CDK4,CDK9,GSK3B	1	Phase I	Selleckchem	S1487
Pictilisib	RG-7321, GDC-0941	PIK3CA,PIK3CD	PIK3CB,PIK3CG,MTOR,PIK3C2B	0	Phase II	Selleckchem	S1065
Pilaralisib	XL-147, SAR-245408	PIK3CA,PIK3CD,PIK3CG	PIK3CB	0	Phase I/II	Selleckchem	S1118
Pimasertib	AS-703026, MSC-1936369B, EMD 1036239	MAP2K1,MAP2K2		3	Phase II	Selleckchem	S1475
Ponatinib	AP-24534 HCl, AP-24534, Iclusig, Ponatinib HCl	ABL1	PDGFRA,KDR,FGFR1,SRC,KIT	2	approved	Selleckchem	S1490
Poziotinib	HM-781-36B, NOV-120101	EGFR,ERBB2,ERBB4		0 (covalent)	Phase II	Selleckchem	S7358
Quizartinib	AC220, AC-220, Quizartinib Dihydrochloride, AC010220.2HCl, AC010220, ASP-2689	FLT3	KIT,PDGFRA,PDGFRB,RET,CSF1R	2	Phase III	Selleckchem	S1526
R-406		SYK	FLT3	1	Phase II	Selleckchem	S1533

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
R-547	RG-547	CDK1,CDK2,CDK4	CDK2,GSK3A,GSK3B	1	Phase I	MedChem Express	HY-10014
Rabusertib	IC-83, LY-2603618	CHEK1		2	Phase II	Selleckchem	S2626
RAF-265	CHIR-265, NVP-RAF265	CRAF,BRAF,KDR		2	Phase II	Selleckchem	S1361
Rapamycin	Rapamune, AY-22989, Sirolimus, WY-090217	MTOR		0	approved	Selleckchem	S1039
RDEA-436		MAP2K1,MAP2K2		3	Phase I	Active Biochem	A-1038
Rebastinib	DP-1919, DCC-2036, Rebastinib Tosylate	ABL1	SRC,LYN,FGR,HCK,KDR,FLT3,TEK,KIT,PDGFRA,PDGFRB	2	Phase I	Selleckchem	S2634
Refametinib	RDEA-119, BAY-86-9766	MAP2K1,MAP2K2		3	Phase II	Active Biochem	A-1036
Regorafenib	Stivarga, BAY-73-4506, BAY-734506 monohydrate	KDR,RET,RAF1	FLT1,FLT4,PDGFRB,KIT,BRAF,FGFR1,TEK	2	approved	Selleckchem	S1178
RGB-286638		CDK9,CDK1,CDK2,CDK4,CDK3,CDK5	CDK6,CDK7,GSK3B,MAP3K7,PRKAA1,PRKAA2,JAK2,MAP2K1	0	Phase I	MedChem Express	HY-15504A2
Ribociclib	LEE-011, NVP-LEE011	CDK4,CDK6		1	Phase III	Selleckchem	S7440
Rigosertib	Rigosertib Sodium, ON-01910.Na, ON-01910	PLK1	PLK2	4	Phase III	Selleckchem	S1362
Ripasudil	K-115	ROCK1,ROCK2		0	Phase II	MedChem Express	HY-15685
Ro-4987655	CH-4987655	MAP2K1		3	Phase I	MedChem Express	HY-14719
Ro-5126766	RG-7304, CKI-27	BRAF,CRAF,MAP2K1		3	Phase I	Active Biochem	A-1085
Rociletinib	AVL-301, CNX-419, CO-1686	EGFR		0 (covalent)	Phase III	MedChem Express	HY-15729
Ruboxistaurin	LY-333531	PRKCB		1	Phase III	Axon Medchem	Axon 1401

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
Ruxolitinib	INCB-018424, Jakafi, Ruxolitinib Phosphate, INCB-018424 Salt	JAK1,JAK2	JAK3	1	approved	Selleckchem	S1378
Sapanisertib	TAK-228, MLN0128, INK128, MLN-0128	MTOR	PIK3CA,PIK3CD,PIK3CG	0	Phase II	Selleckchem	S2811
Sapitinib	AZD-8931	EGFR,ERBB2,ERBB3	MKNK1,FLT1	0	Phase II	Selleckchem	S2192
SAR-407899		ROCK1	ROCK2	0	Phase II	MedChem Express	HY-15687
Saracatinib	AZ-10353926, Saracatinib Difumarate, AZD-0530 difumarate, AZD-0530	SRC	YES,FYN,LYN,BLK,FGR,LCK,ABL1,EGFR,KIT,EPHA2	1	Phase II/III	Selleckchem	S1006
SB-1317	TG02, TG-02	CDK1,CDK2,CDK7,CDK9,JAK2,FLT3		0	Phase I	MedChem Express	HY-15166
SCH-900776	MK-8776	CHEK1	CDK2	0	Phase II	Active Biochem	A-1202
Seliciclib	Rosovitine, CYC-202, AL-39256	CDK1,CDK2,CDK5		1	Phase II	Selleckchem	S1153
Selumetinib	AZD-6244 HYD-SULFATE, ARRY-886, ARRY-142886, AZD-6244 Hydrogen sulfate, AZD-6244, Selumetinib Sulfate	MAP2K1		3	Phase III	Selleckchem	S1008
SGI-1776		PIM1	PIM2,PIM3,FLT3,GSG2	0	Phase I	MedChem Express	HY-13287
SGX-523		MET		1	Phase I	MedChem Express	HY-12019
Silmitasertib	CX-4945	CSNK2A1,CSNK2A2	FLT3,PIM1,CDK1	1	Phase I/II	MedChem Express	HY-50855
SNS-314		AURKA,AURKB,AURKC	NTRK1,NTRK2,FLT4,CSF1R,AXL,CRAF,DDR2	1	Phase I	Selleckchem	S1154

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
Sonolisib	PX-866	PIK3CA,PIK3CD,PIK3CG		0	Phase II	LC Laboratories	P-7501
Sorafenib	[11C]-Sorafenib, Sorafenib Tosylate, BAY-54-9085, BAY-43-9006, Nexavar	RAF1,BRAF	KDR,FLT4,PDGFRB,FLT3,KIT,FGFR1	2	approved	Selleckchem	S1040
Sotrastaurin	AEB071, AEB-071, Sotrastaurin Acetate, NVP-AEB071	PRKCQ	PRKCA,PRKCB,PRKCZ,PRKCH,PRKCG,PRKCD,PRKCI,PRKCE	1	Phase I/II	Selleckchem	S2791
SU-14813	SU-014813	FLT1,KDR,FLT4,PDGFRA,PDGFRB,KIT,FLT3		1	Phase II	MedChem Express	HY-10501
Sunitinib	SU-11248, Sutent, Sunitinib Malate	KDR,PDGFRB	KIT	1	approved	Selleckchem	S1042
TAK-285		ERBB2,EGFR	ERBB4	1	Phase I	Selleckchem	S2784
TAK-593		KDR	FLT1,FLT4,PDGFRA,PDGFRB	0	Phase I	MedChem Express	HY-15506
TAK-733		MAP2K1		3	Phase I	Selleckchem	S2617
TAK-901		AURKA,AURKB	JAK3,SRC,FGR,YES,LRRK2,FLT3,FYN,ABL2,AXL,HCK,SIK2,RET,NTRK1,LCK,PTK5,CSF1R,FGFR2,EPHB1,ABL,EPHA1,NUAK1,ITK,ALK2,CDK7,BLK,JAK2,EPHB2,STK16,EPHA2,PTK6,EPHB4,TNK2,FGFR1,EPHA4,STK33,CLK1,PRKAA2,PRKAA1,FES,SLK,CHEK2,TYK2,BTK,PTK2,KIT,KDR,FGFR3,TGFBR1,MAP3K9,CLK3,JAK1	0	Phase I	Selleckchem	S2718
Talmapimod	SCIO-469	MAPK14,MAPK11,MAPK12,MAPK13		1	Phase II	Axon Medchem	Axon 1671
Tandutinib	MLN-518, CT-53518, MLN-0518	FLT3	PDGFRA,PDGFRB,KIT	2	Phase II	Selleckchem	S1043

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
Tanzisertib	CC-930, JNK-930	MAPK8,MAPK9, MAPK10		1	Phase II	MedChem Express	HY-15495
Telatinib	BAY-57-9352, BAY-579352	KDR,FLT4,KIT	PDGFRA	0	Phase II	Selleckchem	S2231
Tepotinib	MSC-2156119J, MSC-2156119, EMD-1214063	MET	IRAK4	1	Phase I/II	Active Biochem	A-1087
Tesevatinib	KD-019, KD-020, XL-647, Tesevatinib tosylate	EGFR	ERBB2,KDR,EPHB4	0	Phase II	MedChem Express	HY-13314
TG-100115	TG100-115	PIK3CD,PIK3CG		1	Phase I/II	Selleckchem	S1352
TG-100572		SRC,KDR	FLT1,FGFR1,FYN	0	Phase II	MedChem Express	HY-10185
TG-100801	TG100-801	SRC,KDR	FLT1,FGFR1,FYN	0	Phase II	MedChem Express	HY-10186
Tideglusib	NP-031112, NP-12	GSK3B		4 (covalent)	Phase II	Selleckchem	S2823
Tivantinib	ARQ-197	MET	MST1R	2	Phase III	Selleckchem	S2753
Tivozanib	AV-951, KRN-951, Kil8951, Tivozanib HCl, Kil-8951, ASP-4130	FLT1,KDR,FLT4	PDGFRA,PDGFRB,KIT,EPHB2,TEK,EPHB4,FGFR1,MET,ABL1,SRC	2	Phase III	Selleckchem	S1207
Tofacitinib	Tasocitinib, Tofacitinib Citrate, CP-690, Xeljanz, CP-690550-10, Tasocitinib Citrate, CP-690550	JAK3	JAK2,JAK1	1	approved	Selleckchem	S5001
Torisel	CCI-779, Temsirolimus	MTOR		0	approved	Selleckchem	S1044
Tozasertib	VX-68, MK-045, Tozasertib Lactate, MK-0457, VX-680	AURKA	AURKB,AURKC,FLT3,ABL1	1	Phase II	Selleckchem	S1048
Trametinib	GSK1120212, GSK1120212B, Trametinib Dimethyl Sulfoxide	MAP2K1,MAP2K2		3	approved	Selleckchem	S2673

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
Triciribine	Phosphate Salt Of Tricyclic Nucleoside, Triciribine Phosphate, VQD-002	AKT1		0	Phase I/II	MedChem Express	HY-15457
UCN-01	UCN-02, KRX-0601, KW-2401	PRKCA,PRKCB,PRKCZ,PRKCH,PRKCG,PRKCD,PRKCI,PRKCE,PRKCQ	MAPKAPK2	1	Phase II	Merck	539644
Ulixertinib	BVD-523, VRT-752271	MAPK3,MAPK1		0	Phase I	Selleckchem	S7854
Uprosertib	GSK2141795, GSK2141795C	AKT1		0	Phase II	Active Biochem	A-1504
Vandetanib	Caprelsa, GNF-Pf-2188, Zactima, ZD-64, ZD-6474	KDR		1	approved	Selleckchem	S1046
Varlitinib	ARRY-543, ASLAN-001, AR-00334543, ARRY-334543, Varlitinib Tosylate	EGFR,ERBB2		0	Phase I	Selleckchem	S2755
Vatalanib	PTK787, PTK-787, K-222584, CGP-79787, BAY-86-5127, ZK-222584, CGP-79787D, NVP-PTK787	KDR	FLT1,FLT4,PDGFRB,KIT	0	Phase III	Selleckchem	S1101
Vemurafenib	PLX-4032, Ro-5185426, RG-7204, Zelboraf	BRAF	SRMS,TNK2,CRAF,MAP4K5,FGR,LCK,BRK,NEK11,BLK,LYN,YES,WNK3	1	approved	LC Laboratories	V-2800
Volasertib	BI-6727, BI-6727-CL3, Volasertib Trihydrochloride	PLK1	PLK2,PLK3	1	Phase III	Selleckchem	S2235
Volitinib	AZD-6094, Savolitinib	MET		0	Phase II	Active Biochem	A-1316
VX-702		MAPK14	MAPK11,MAPK12,MAPK13	0	Phase II	Selleckchem	S6005
X-396		ALK		0	Phase I/II	Abmole	M1743

Drug	Synonyms	Designated targets	Other targets	Binding type	Clinical phase	Supplier	Supplier order #
XL-019		JAK2	JAK1,JAK3,TYK,PDGFRB,FLT3,KIT,RPS6KB1,RPS6KB2,MAP3K9,IKBKB,KDR,PDGFRA,FLT4,FLT1	1	Phase I	MedChem Express	HY-13775
XL-228		IGF1R,AURKA,AURKB,AURKC,FGFR1,FGFR2,FGFR3,ABL1,ALK,SRC,YES,FYN,FGR,LCK,HCK,BLK,LYN,FRK	0	reversible	MedChem Express	HY-15749	
XL-413	BMS-863233	CDC7	CSNK2A1,CSNK2A2,PIM1	1	Phase I/II	MedChem Express	HY-15260A
XL-765	SAR-245409, Voxtalisib	PIK3CG	PIK3CA,PIK3CB,PIK3CD,MTOR,PRKDC	0	Phase II	Selleckchem	S1523
Y-39983	Y-33075	ROCK1	PRKCA,PRKCB,PRKCZ,PRKCH,PRKCG,PRKCD,PRKCI,PRKCE,PRKCQ,CAMK2A,CAMK2B,CAMK2D,CAMK2G	0	Phase I	MedChem Express	HY-10069

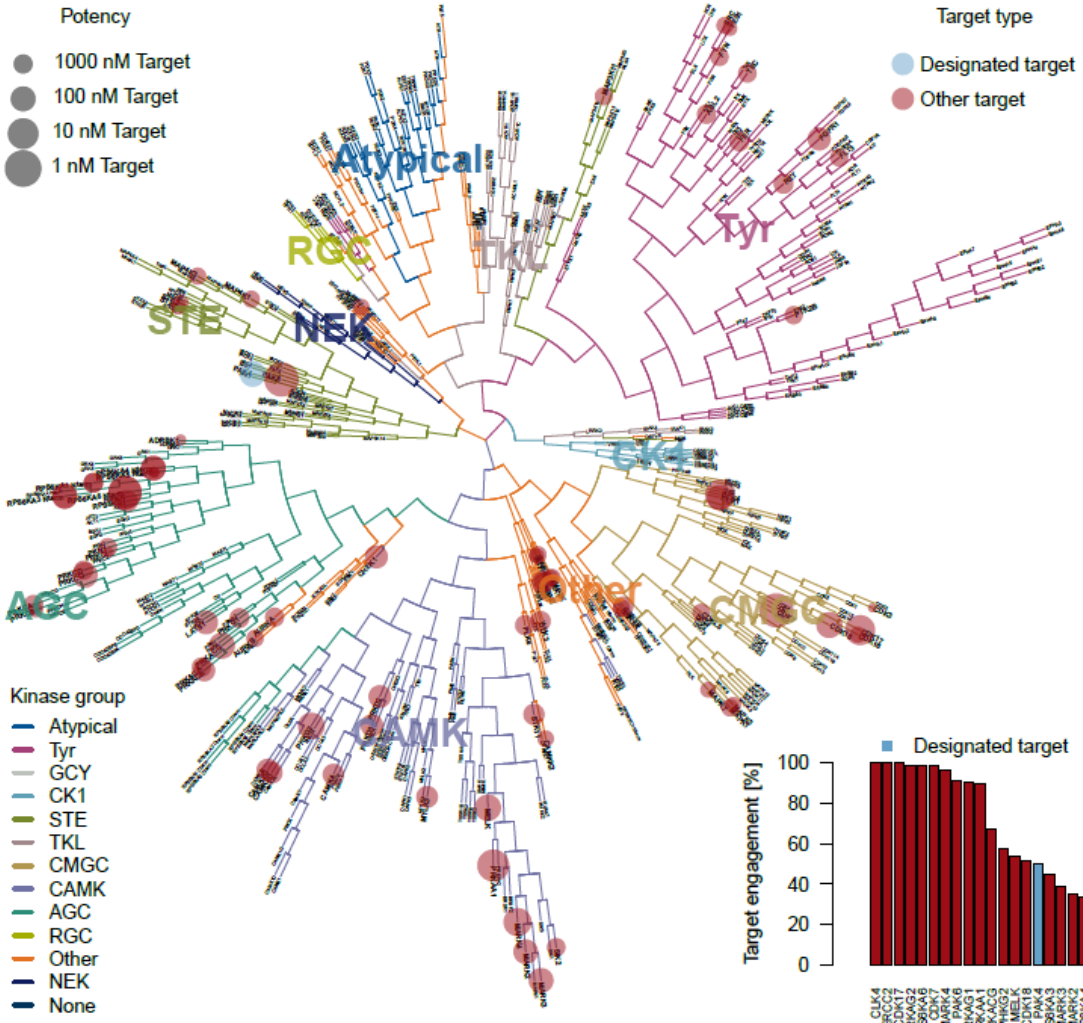
Appendix II

Data collection and summary for PF-3758309.

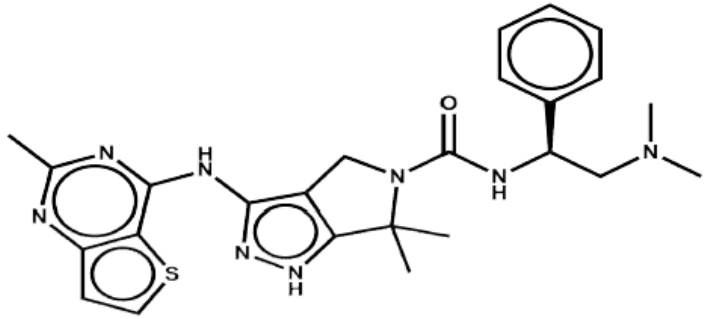
First 30 pages (of 264) containing data summary for proteins identified in a Kinobeads pulldown with PF-3758309 (also described in Figure 17, paragraph 3.2.2). The first page shows the distribution of targets on a phylogenetic kinome tree, metadata for the compound, the selectivity of the compound compared to all 242 inhibitors according to $CATDS_{(most\ potent\ target)}$ and the predicted target engagement at the K_d^{app} of the designated target (here PAK4). The following pages show underlying dose response data, as well as MSMS counts and number of unique peptides (observations) and the DMSO intensity in respect of all protein intensities in the experiment (abundance). Proteins marked with an asterisk (*) or hashtag (**#**) are classified as either high or low confidence targets, respectively. Black, grey or empty squares (top right corner) indicate that the current target is either a protein kinase, a direct binder of the beads or an indirect binder (e.g. complex partner). The last column shows dose dependent characteristics of target engagement, selectivity and dose optimum according to CATDS).

Profiling of PF−3758309 in 4 cell line mix lysate using Kinobeads

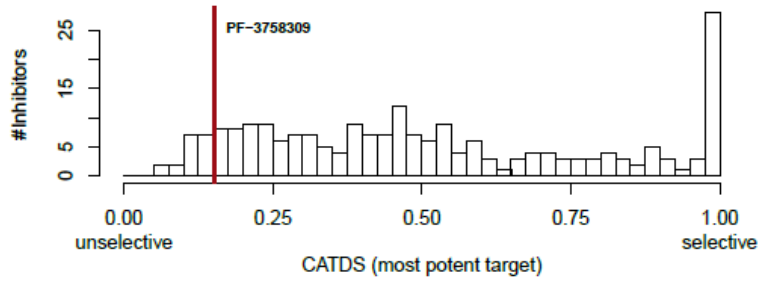
Designated targets: PAK4
Synonyms: PF−03758309
CAS:
ChEMBL ID: CHEMBL3128043
PubChem CID: 25227462
SMILES: CN(C)C[C@@H](NC(=O)N1Cc2c(Nc3nc(C)nc4ccsc34)n(nH)c2C1(C)C)c5ccccc5



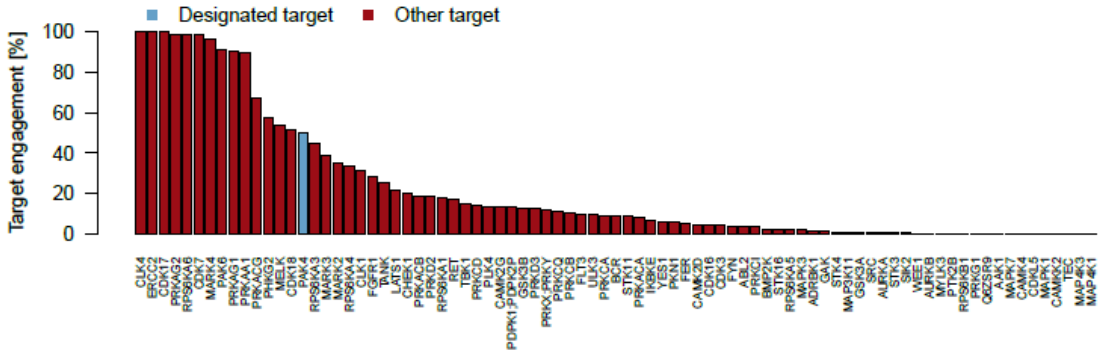
Structure



Selectivity distribution over 242 inhibitors



Predicted target engagement at 71 nM



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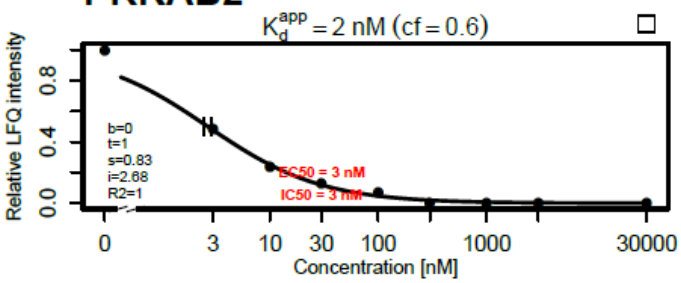
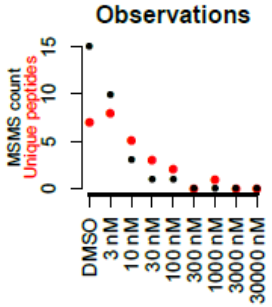
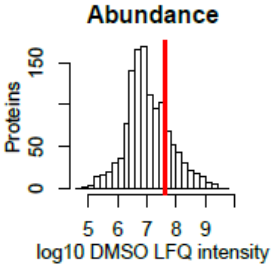


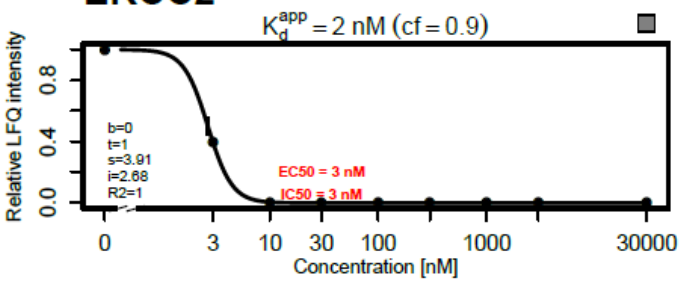


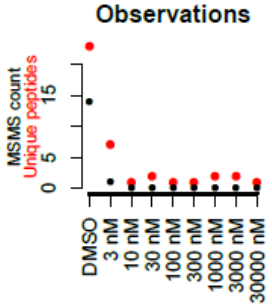


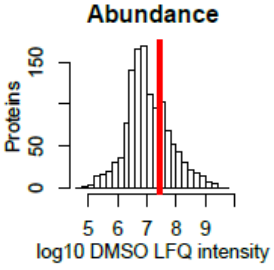
Predicted effects

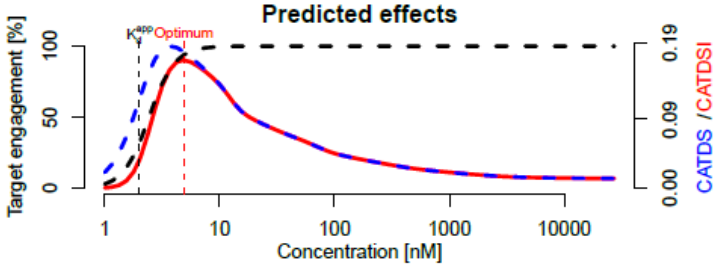
n.a.

ERCC2*









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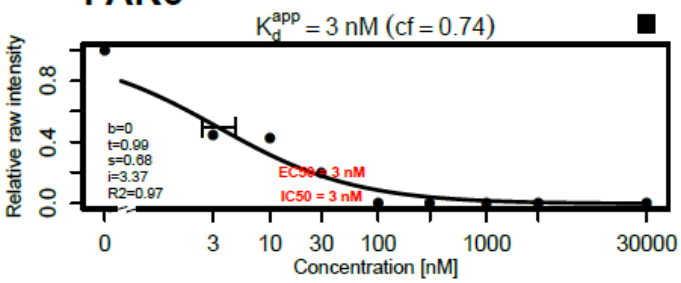

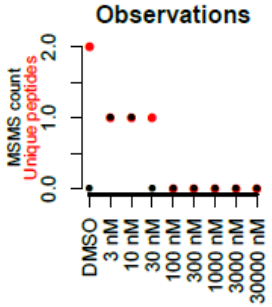

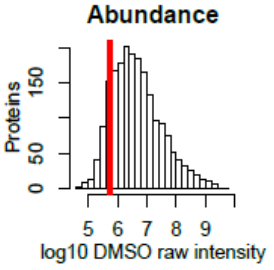

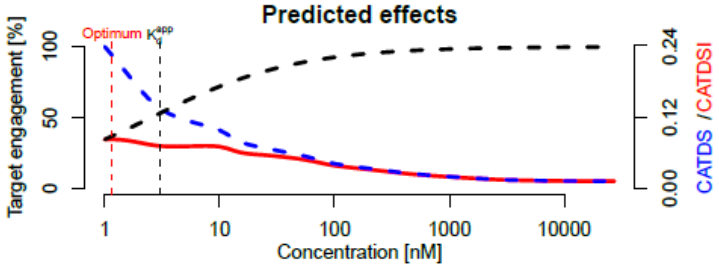

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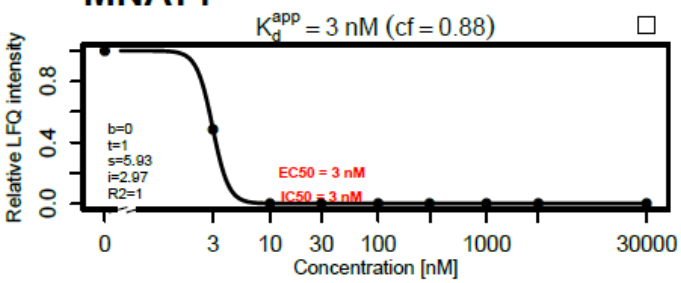
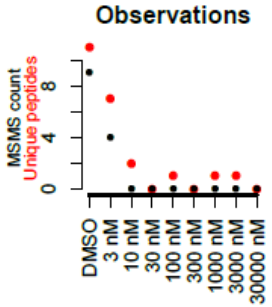
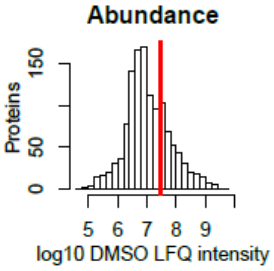


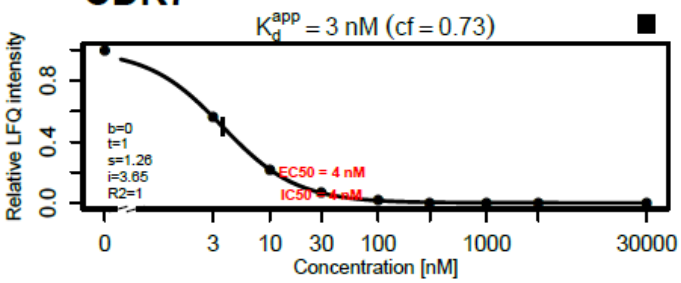


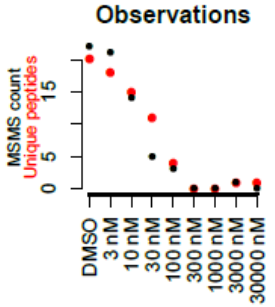


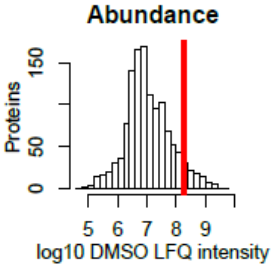
Predicted effects

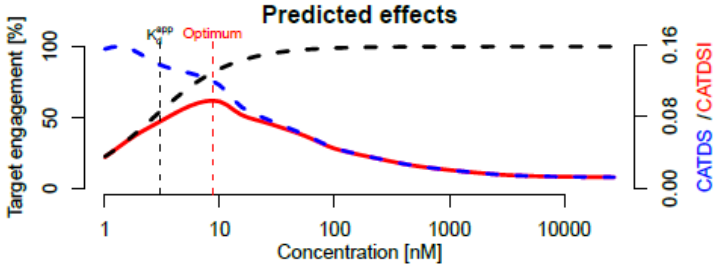
n.a.

CDK7*









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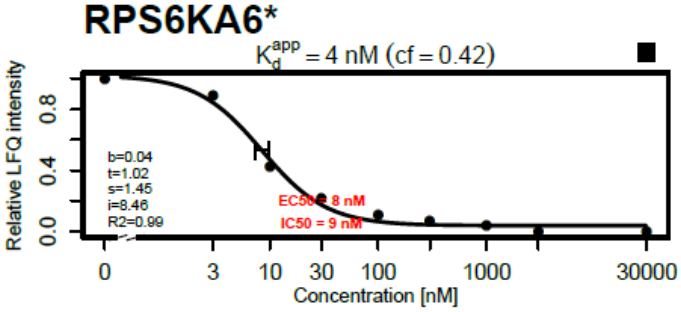

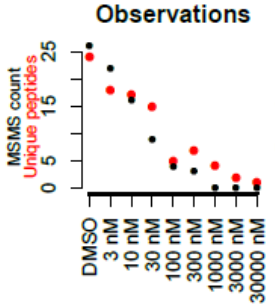

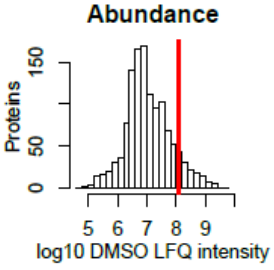

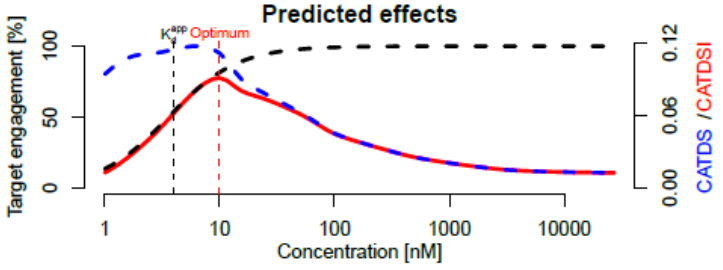

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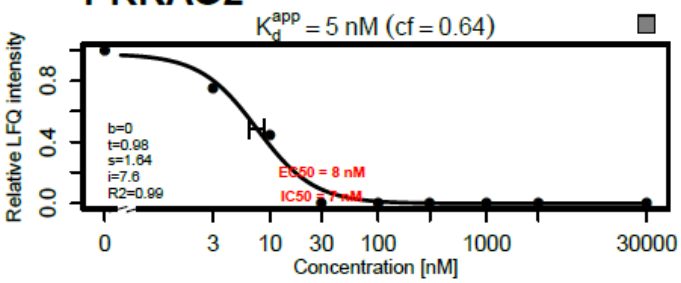

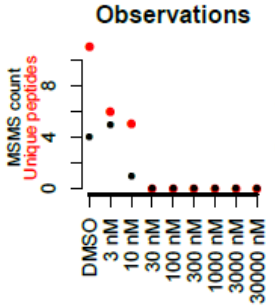

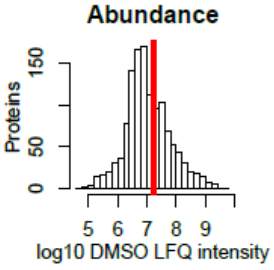

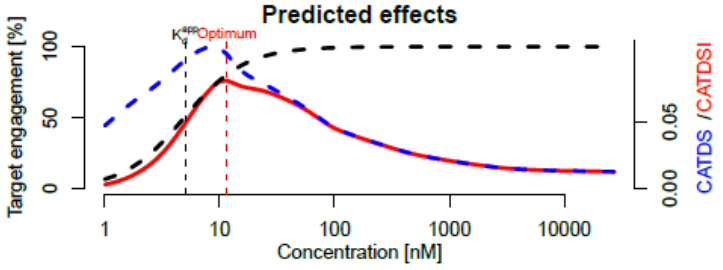

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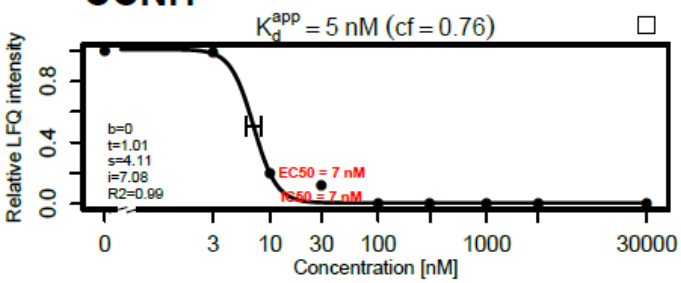
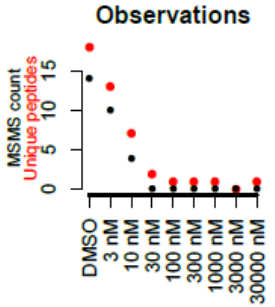
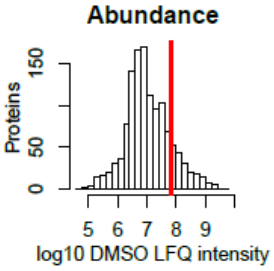


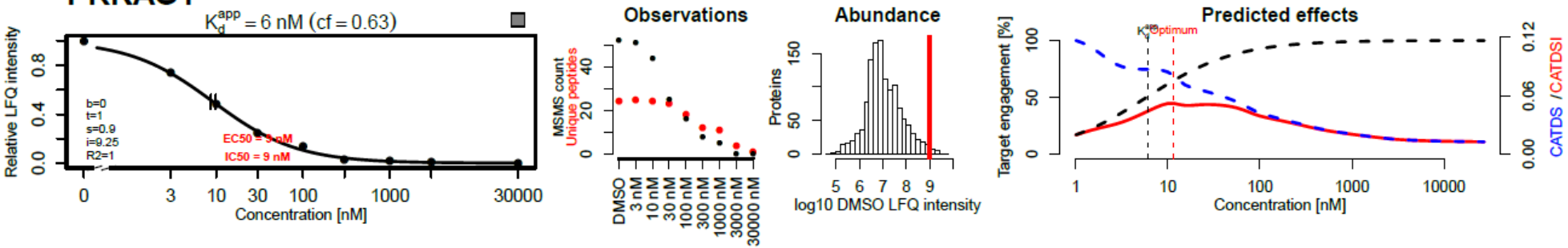




Predicted effects

n.a.

PRKAG1*



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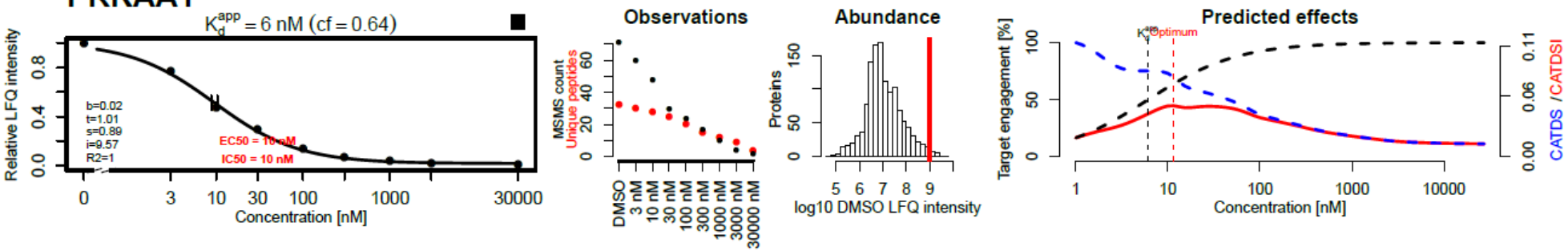

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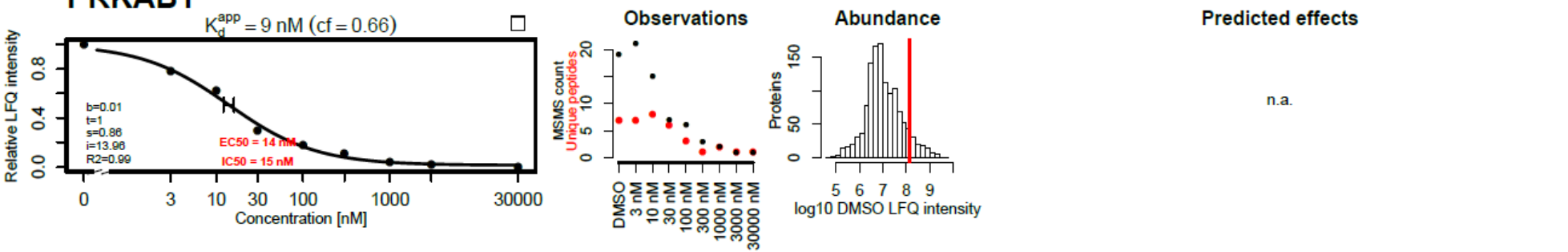

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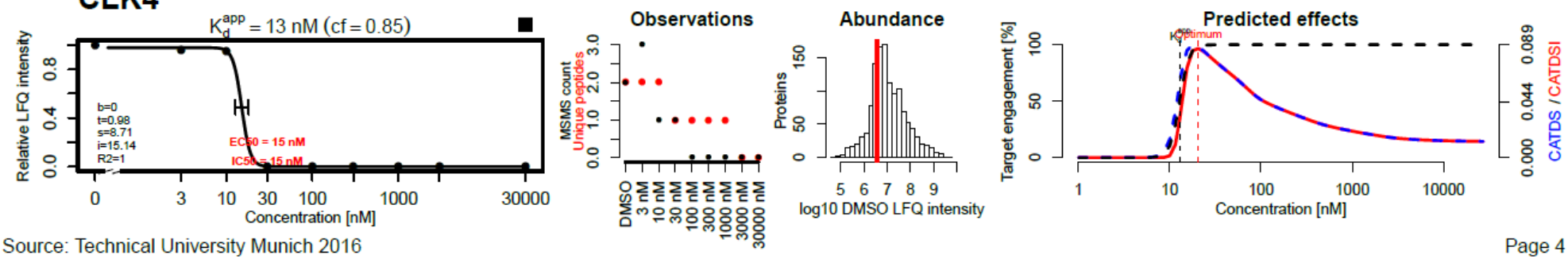
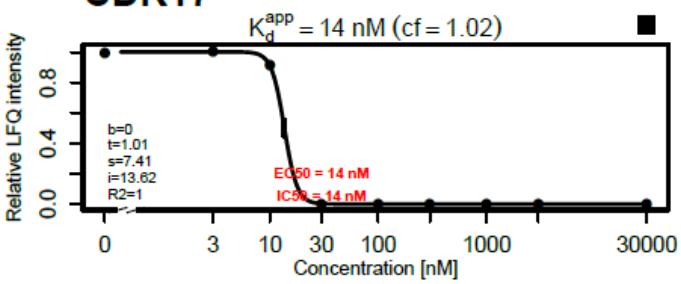
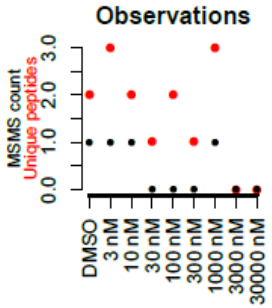
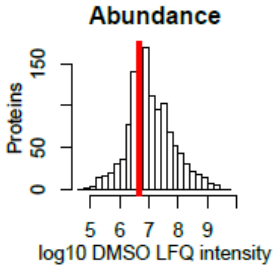
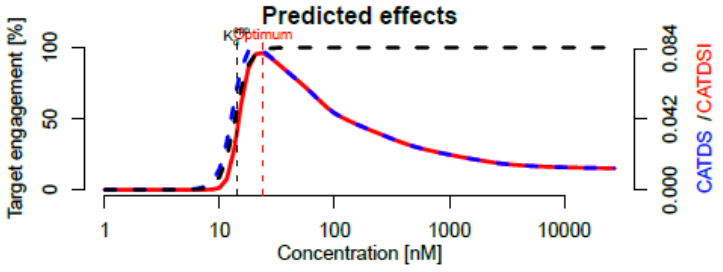


CDK17*

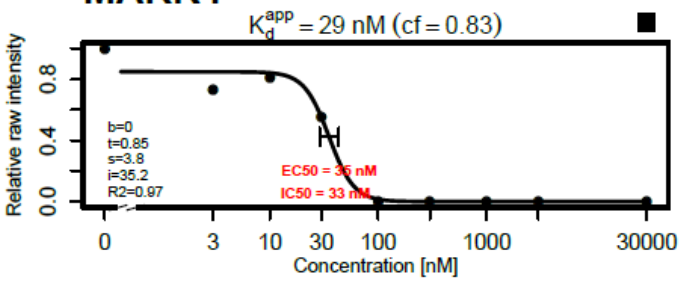


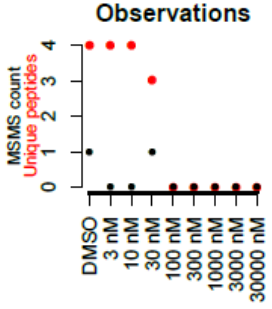


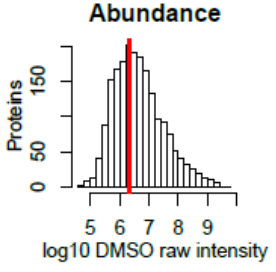


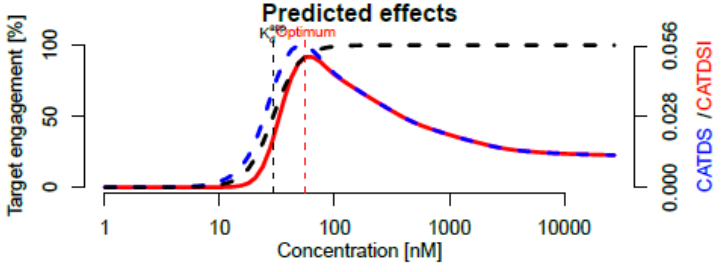


MARK4*

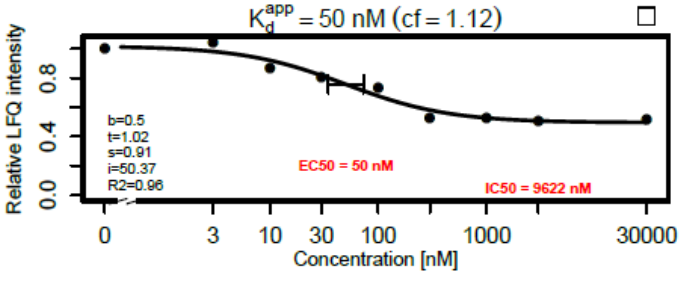


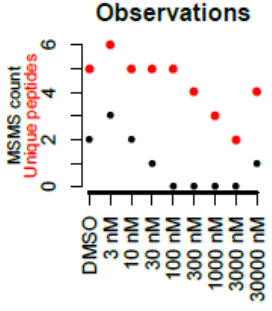


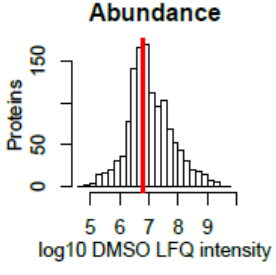




CAB39*



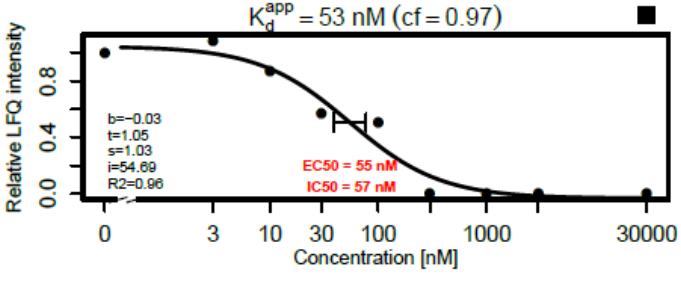


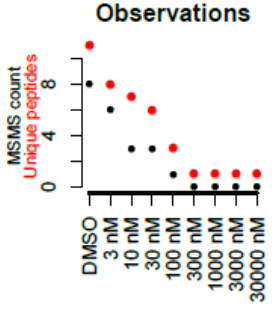


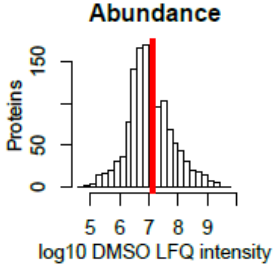
Predicted effects

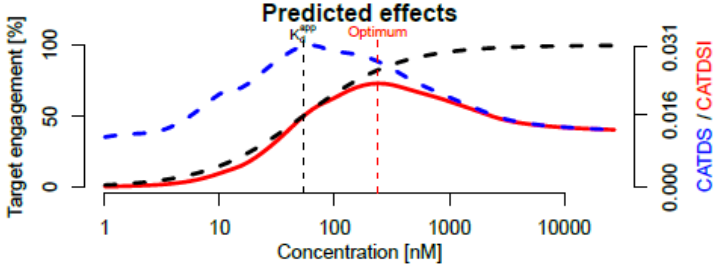
n.a.

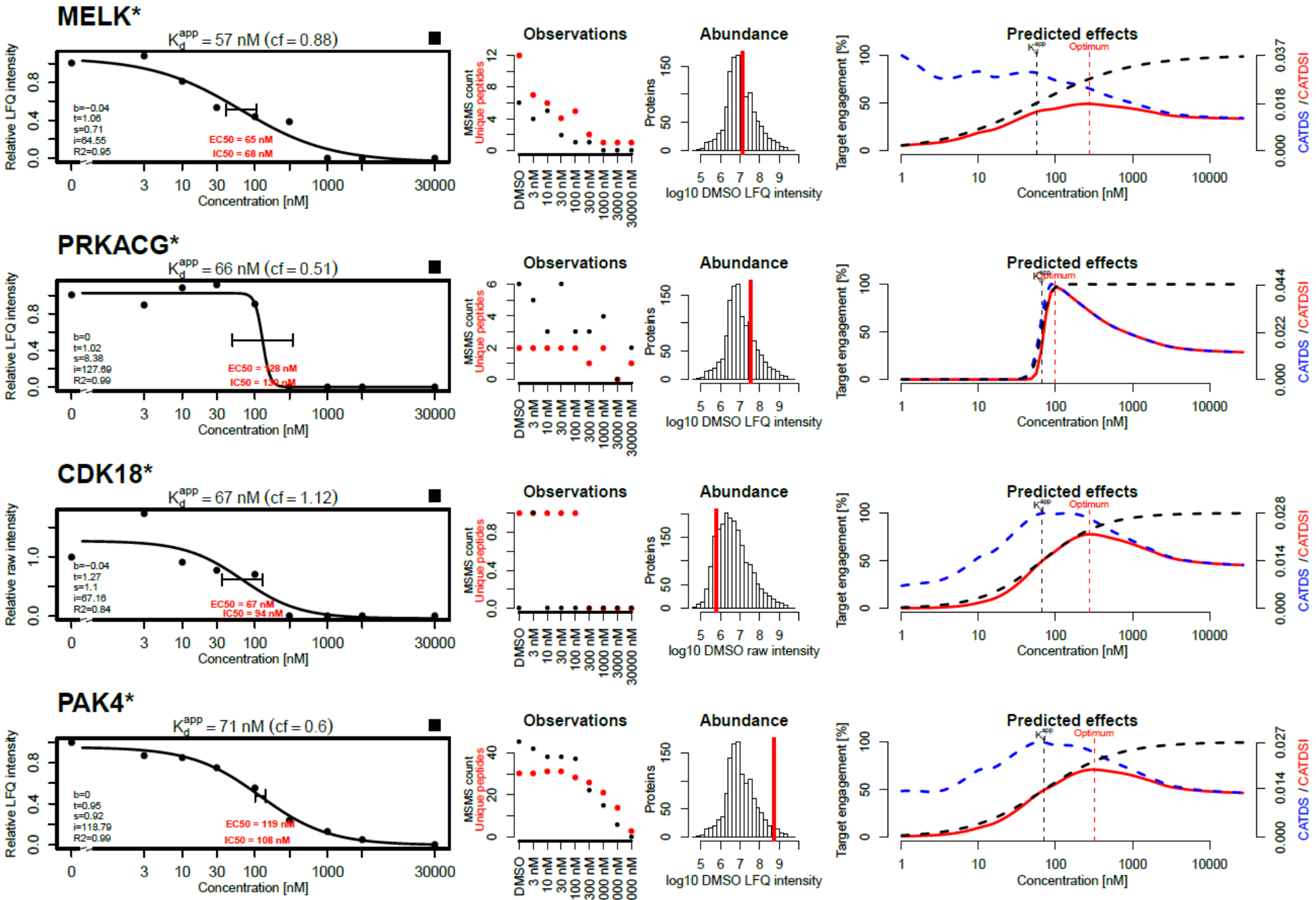
PHKG2*

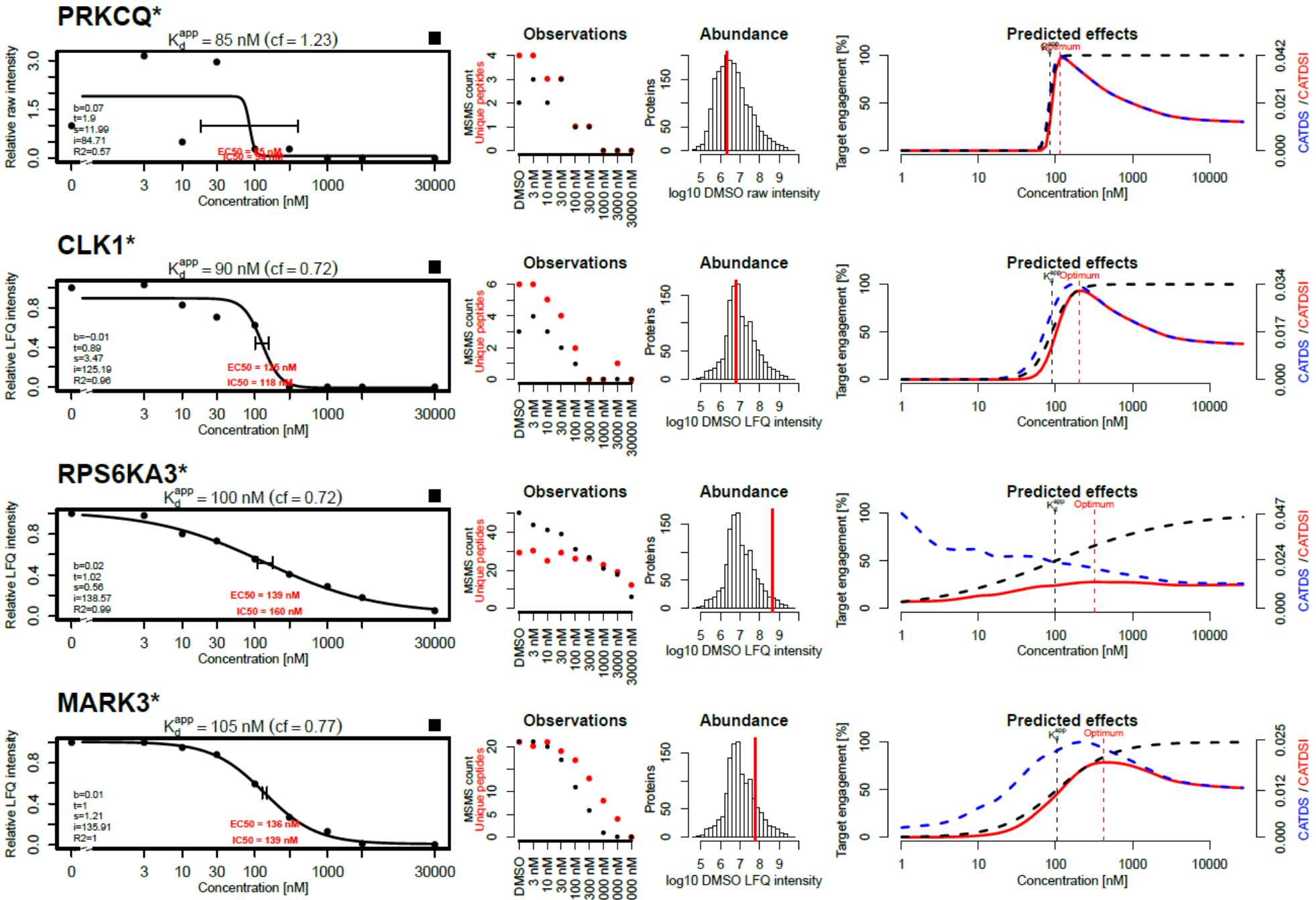


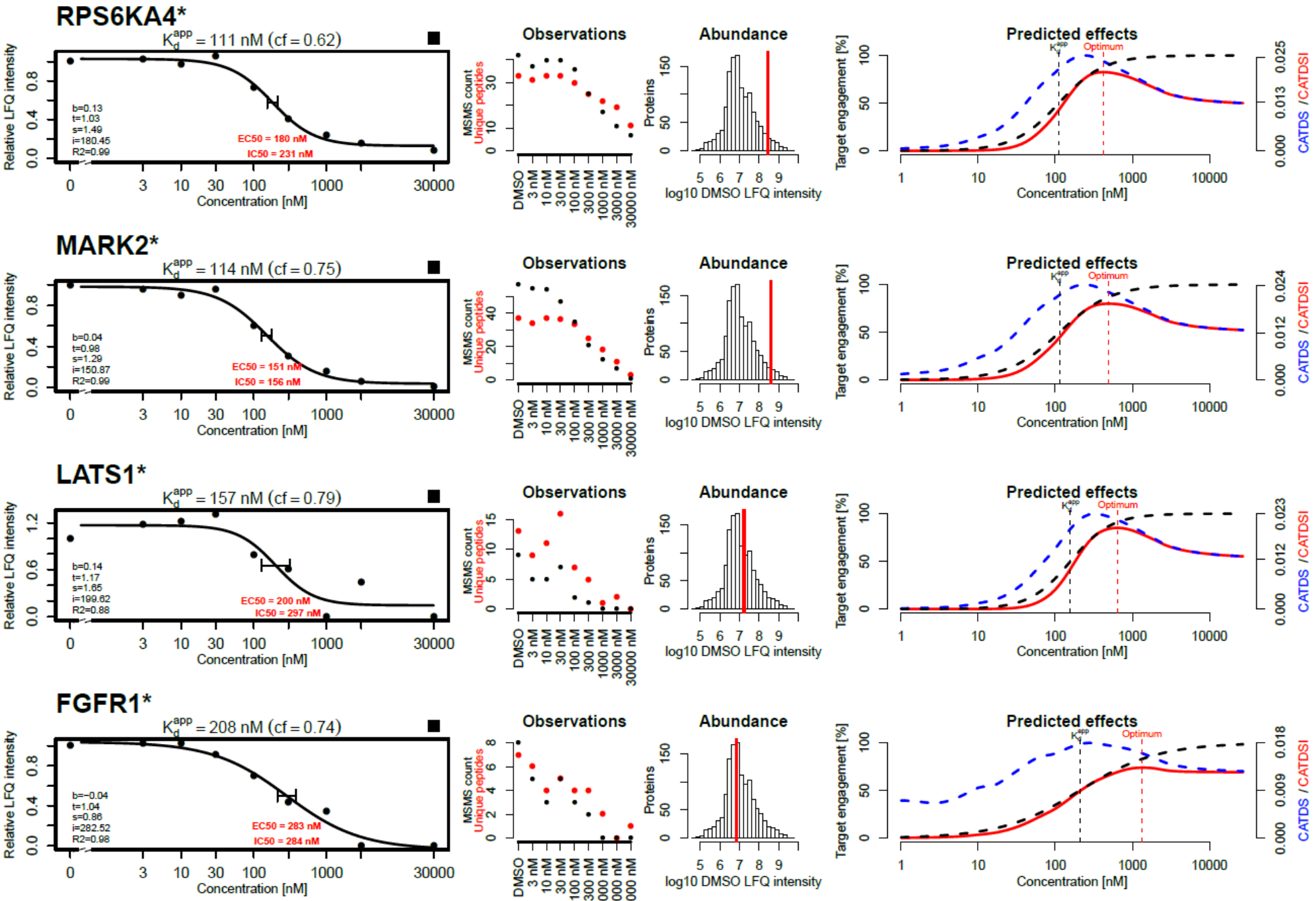


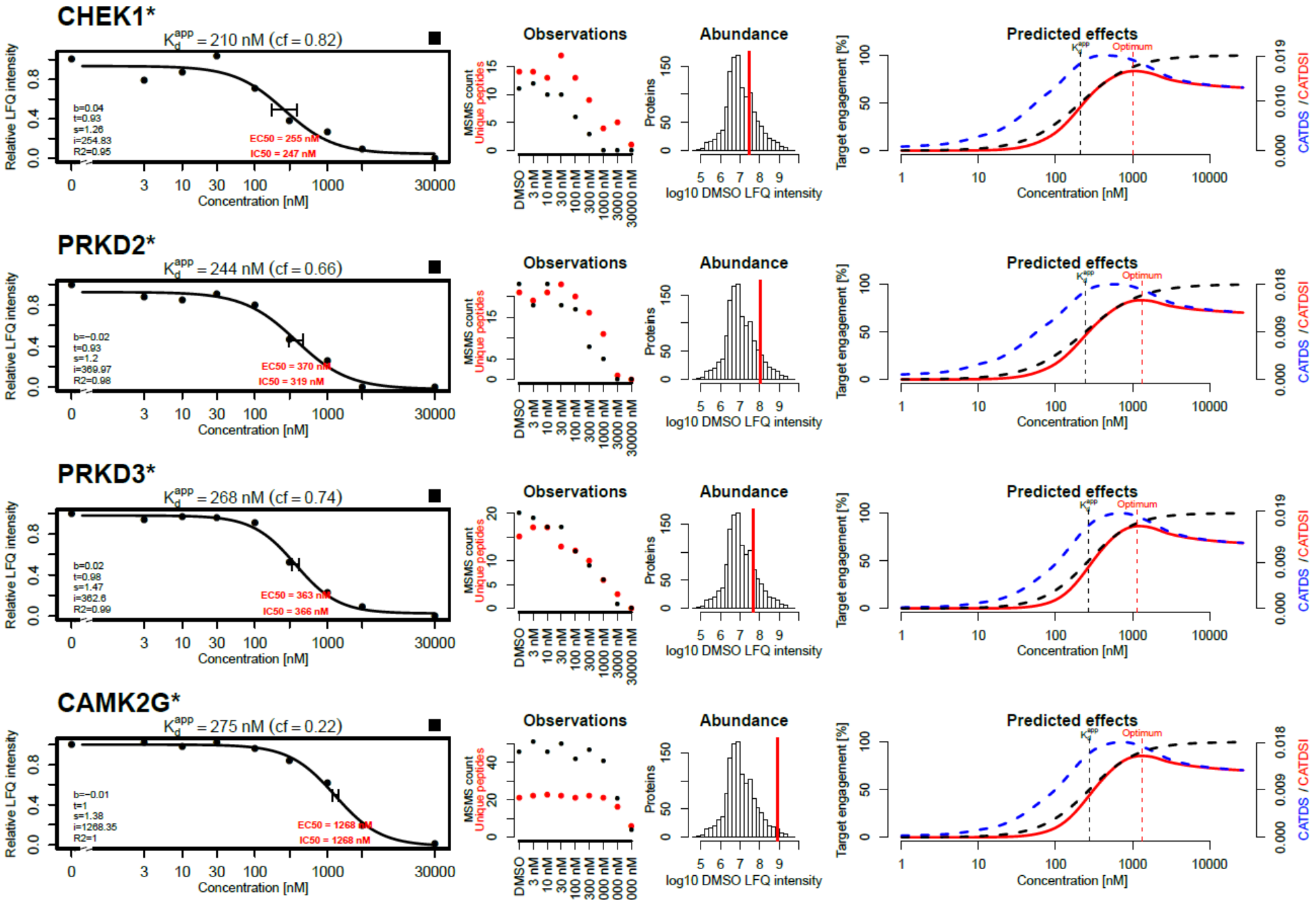


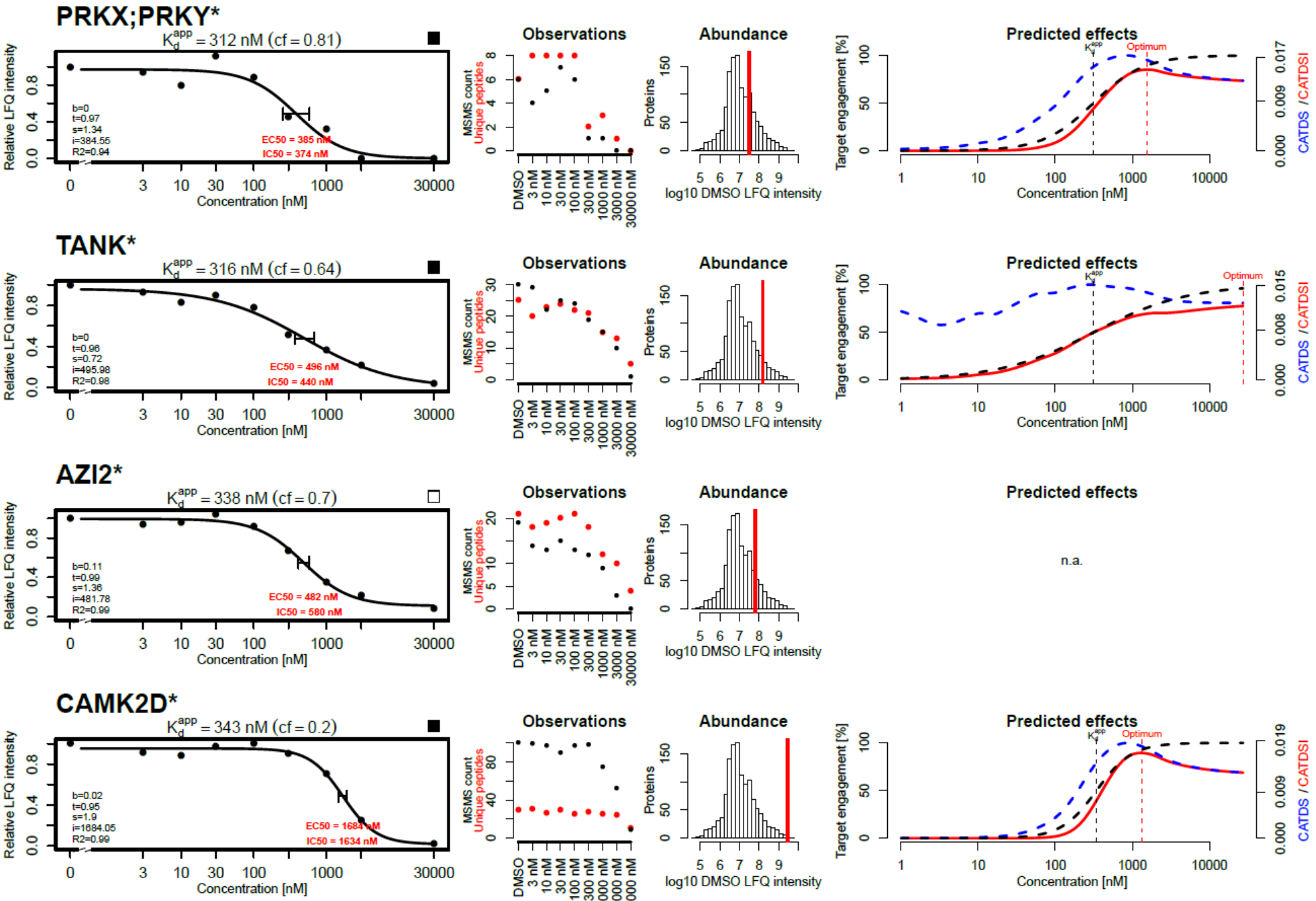


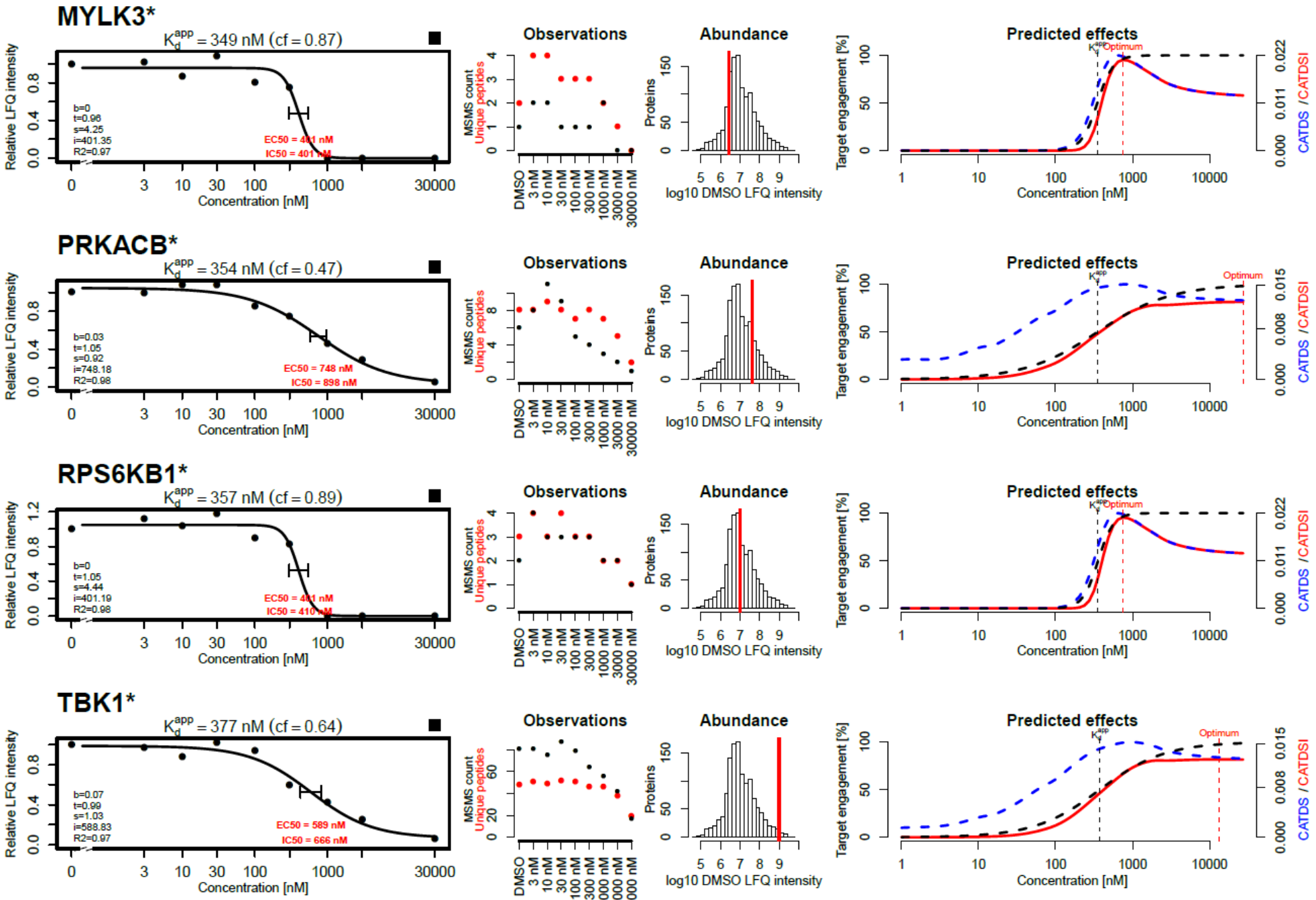

MELK*
K_d^{app} = 57 nM (cf = 0.88)
Relative LFQ intensity
b=−0.04
t=1.06
s=0.71
i=64.55
R2=0.95
EC50 = 65 nM
IC50 = 68 nM
Concentration [nM]
Observations
MSMS count
Unique peptides
DMSO
3 nM
10 nM
30 nM
100 nM
300 nM
1000 nM
3000 nM
30000 nM
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
CATDS / CATDSI
Optimum
PRKACG*
K_d^{app} = 66 nM (cf = 0.51)
b=0
t=1.02
s=8.38
i=127.69
R2=0.99
EC50 = 128 nM
IC50 = 130 nM
CDK18*
K_d^{app} = 67 nM (cf = 1.12)
Relative raw intensity
b=−0.04
t=1.27
s=1.1
i=67.16
R2=0.84
EC50 = 67 nM
IC50 = 94 nM
log10 DMSO raw intensity
PAK4*
K_d^{app} = 71 nM (cf = 0.6)
b=0
t=0.95
s=0.92
i=118.79
R2=0.99
EC50 = 119 nM
IC50 = 108 nM


PRKCQ*
K_d^{app} = 85 nM (cf = 1.23)
b=0.07
t=1.9
s=11.99
i=84.71
R2=0.57
EC50 = 95 nM
IC50 = 94 nM
Relative raw intensity
Concentration [nM]
Observations
MSMS count
Unique peptides
Abundance
Proteins
log10 DMSO raw intensity
Predicted effects
Target engagement [%]
CATDS /CATDSI
Optimum
CLK1*
K_d^{app} = 90 nM (cf = 0.72)
b=-0.01
t=0.89
s=3.47
i=125.19
R2=0.96
EC50 = 125 nM
IC50 = 118 nM
Relative LFQ intensity
log10 DMSO LFQ intensity
RPS6KA3*
K_d^{app} = 100 nM (cf = 0.72)
b=0.02
t=1.02
s=0.56
i=138.57
R2=0.99
EC50 = 139 nM
IC50 = 160 nM
MARK3*
K_d^{app} = 105 nM (cf = 0.77)
b=0.01
t=1
s=1.21
i=135.91
R2=1
EC50 = 136 nM
IC50 = 139 nM
DMSO
3 nM
10 nM
30 nM
100 nM
300 nM
1000 nM
3000 nM
30000 nM

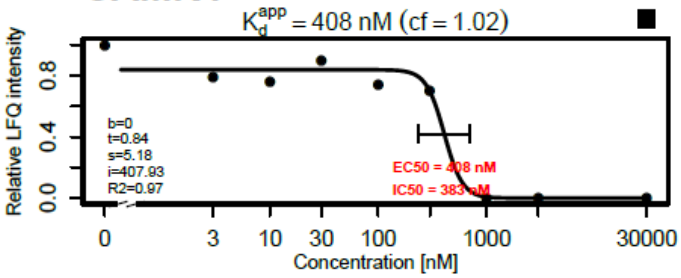

RPS6KA4*
K_d^{app} = 111 nM (cf = 0.62)
b=0.13
t=1.03
s=1.49
i=180.45
R2=0.99
EC50 = 180 nM
IC50 = 231 nM
Relative LFQ intensity
Concentration [nM]
Observations
MSMS count
Unique peptides
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Optimum
Target engagement [%]
CATDS /CATDSI
MARK2*
K_d^{app} = 114 nM (cf = 0.75)
b=0.04
t=0.98
s=1.29
i=150.87
R2=0.99
EC50 = 151 nM
IC50 = 156 nM
LATS1*
K_d^{app} = 157 nM (cf = 0.79)
b=0.14
t=1.17
s=1.65
i=199.62
R2=0.88
EC50 = 200 nM
IC50 = 297 nM
FGFR1*
K_d^{app} = 208 nM (cf = 0.74)
b=-0.04
t=1.04
s=0.86
i=282.52
R2=0.98
EC50 = 283 nM
IC50 = 284 nM

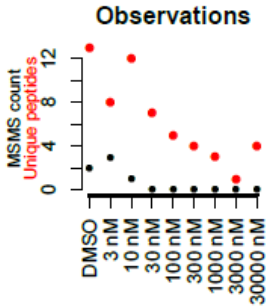

CHEK1*
K_d^{app} = 210 nM (cf = 0.82)
b=0.04
t=0.93
s=1.26
i=254.83
R2=0.95
EC50 = 255 nM
IC50 = 247 nM
Relative LFQ intensity
Concentration [nM]
Observations
MSMS count
Unique peptides
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
CATDS /CATDSI
Optimum
PRKD2*
K_d^{app} = 244 nM (cf = 0.66)
b=-0.02
t=0.93
s=1.2
i=369.97
R2=0.98
EC50 = 370 nM
IC50 = 319 nM
PRKD3*
K_d^{app} = 268 nM (cf = 0.74)
b=0.02
t=0.98
s=1.47
i=362.6
R2=0.99
EC50 = 363 nM
IC50 = 366 nM
CAMK2G*
K_d^{app} = 275 nM (cf = 0.22)
b=-0.01
t=1
s=1.38
i=1268.35
R2=1
EC50 = 1268 nM
IC50 = 1268 nM

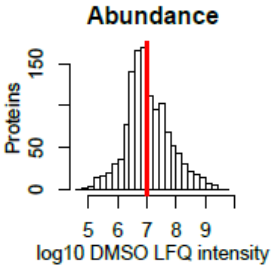

PRKX;PRKY*
K_d^{app} = 312 nM (cf = 0.81)
Relative LFQ intensity
b=0
t=0.97
s=1.34
i=384.55
R2=0.94
EC50 = 385 nM
IC50 = 374 nM
Concentration [nM]
Observations
MSMS count
Unique peptides
DMSO
3 nM
10 nM
30 nM
100 nM
300 nM
1000 nM
3000 nM
30000 nM
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
Optimum
CATDS / CATDSI
TANK*
K_d^{app} = 316 nM (cf = 0.64)
b=0
t=0.96
s=0.72
i=495.98
R2=0.98
EC50 = 496 nM
IC50 = 440 nM
AZI2*
K_d^{app} = 338 nM (cf = 0.7)
b=0.11
t=0.99
s=1.36
i=481.78
R2=0.99
EC50 = 482 nM
IC50 = 580 nM
n.a.
CAMK2D*
K_d^{app} = 343 nM (cf = 0.2)
b=0.02
t=0.95
s=1.9
i=1684.05
R2=0.99
EC50 = 1684 nM
IC50 = 1634 nM

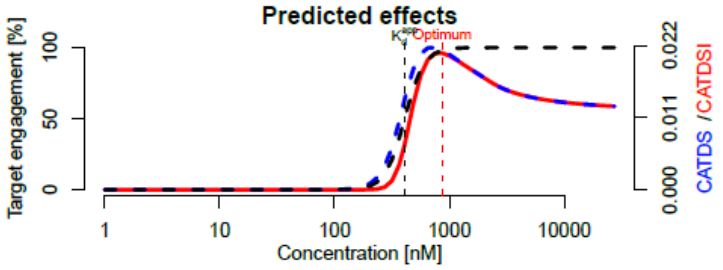

MYLK3*
K_d^{app} = 349 nM (cf = 0.87)
Relative LFQ intensity
b=0
t=0.96
s=4.25
i=401.35
R2=0.97
EC50 = 401 nM
IC50 = 401 nM
Concentration [nM]
Observations
MSMS count
Unique peptides
DMSO
3 nM
10 nM
30 nM
100 nM
300 nM
1000 nM
3000 nM
30000 nM
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
CATDS / CATDSI
Optimum
PRKACB*
K_d^{app} = 354 nM (cf = 0.47)
b=0.03
t=1.05
s=0.92
i=748.18
R2=0.98
EC50 = 748 nM
IC50 = 898 nM
RPS6KB1*
K_d^{app} = 357 nM (cf = 0.89)
b=0
t=1.05
s=4.44
i=401.19
R2=0.98
EC50 = 401 nM
IC50 = 410 nM
TBK1*
K_d^{app} = 377 nM (cf = 0.64)
b=0.07
t=0.99
s=1.03
i=588.83
R2=0.97
EC50 = 589 nM
IC50 = 666 nM

CAMK4*

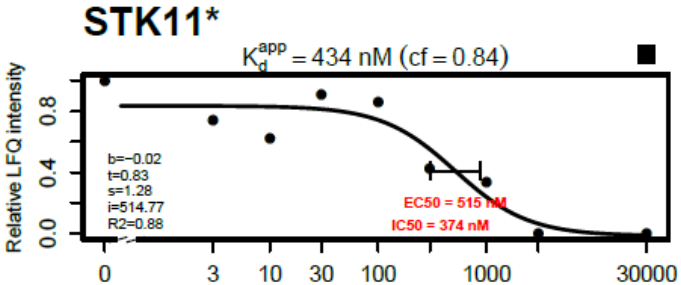


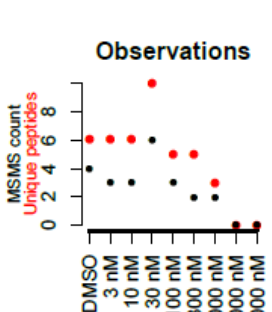


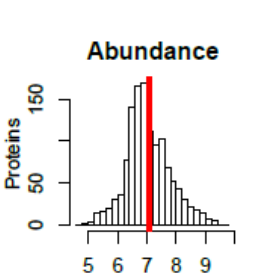


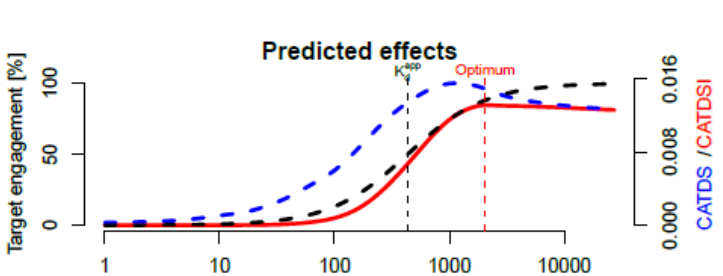


STK11*

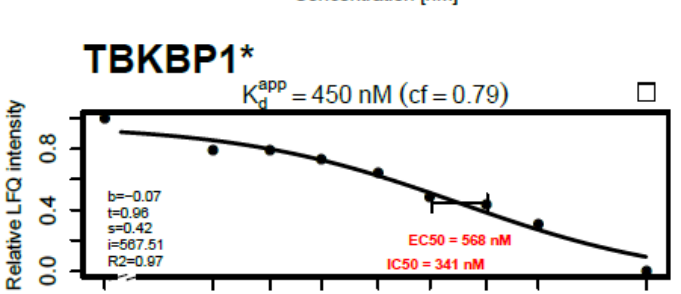


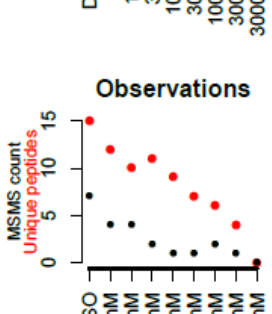


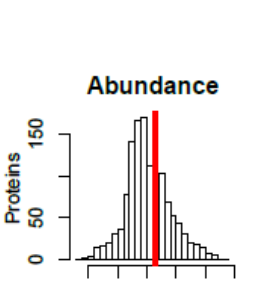




TBKBP1*



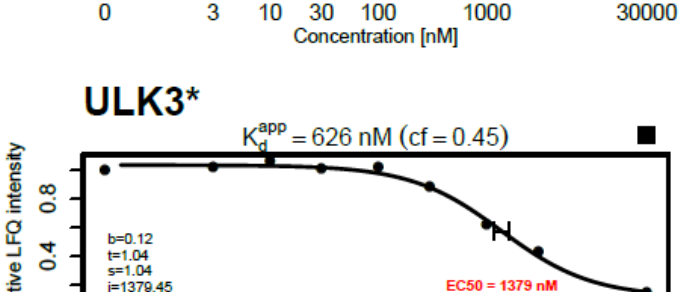


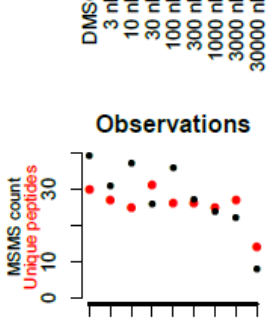


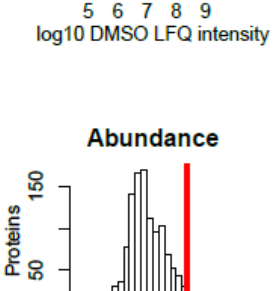
Predicted effects

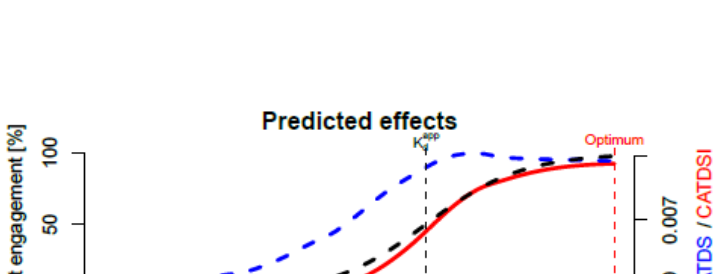
n.a.

ULK3*

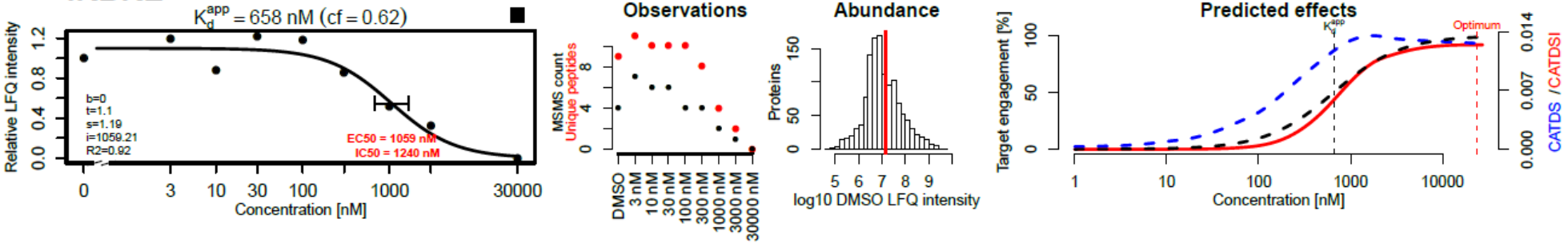




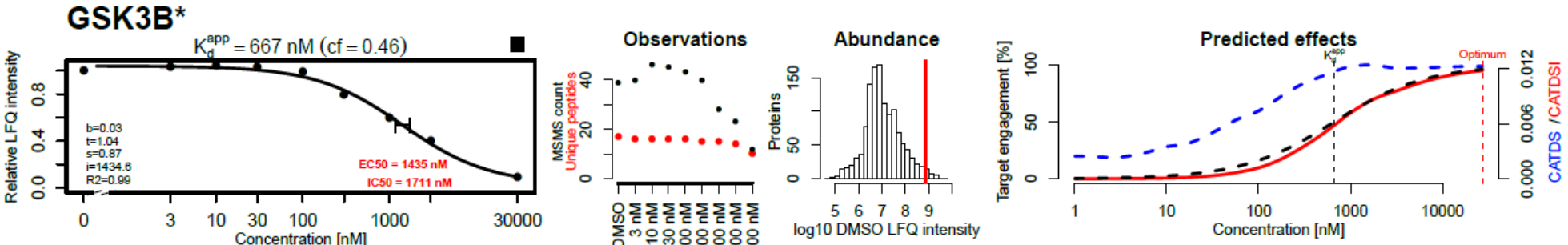




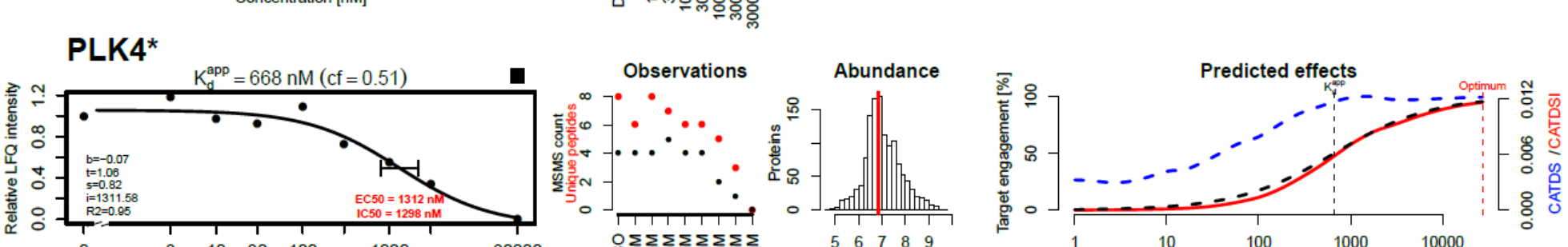
IKBKE*



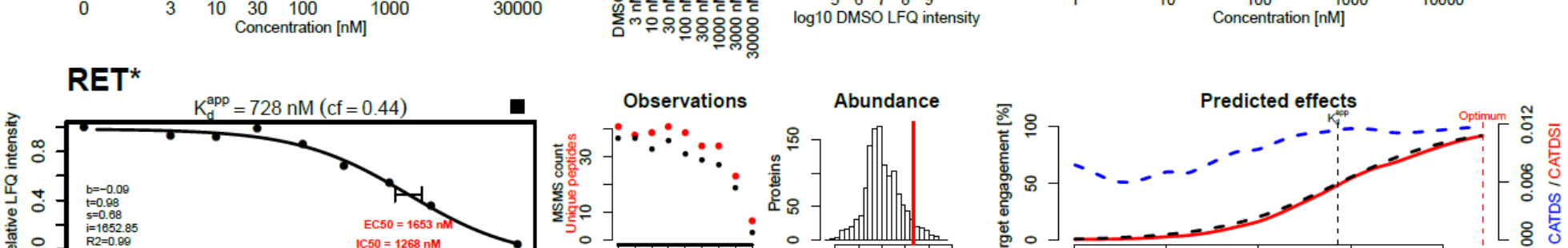
GSK3B*

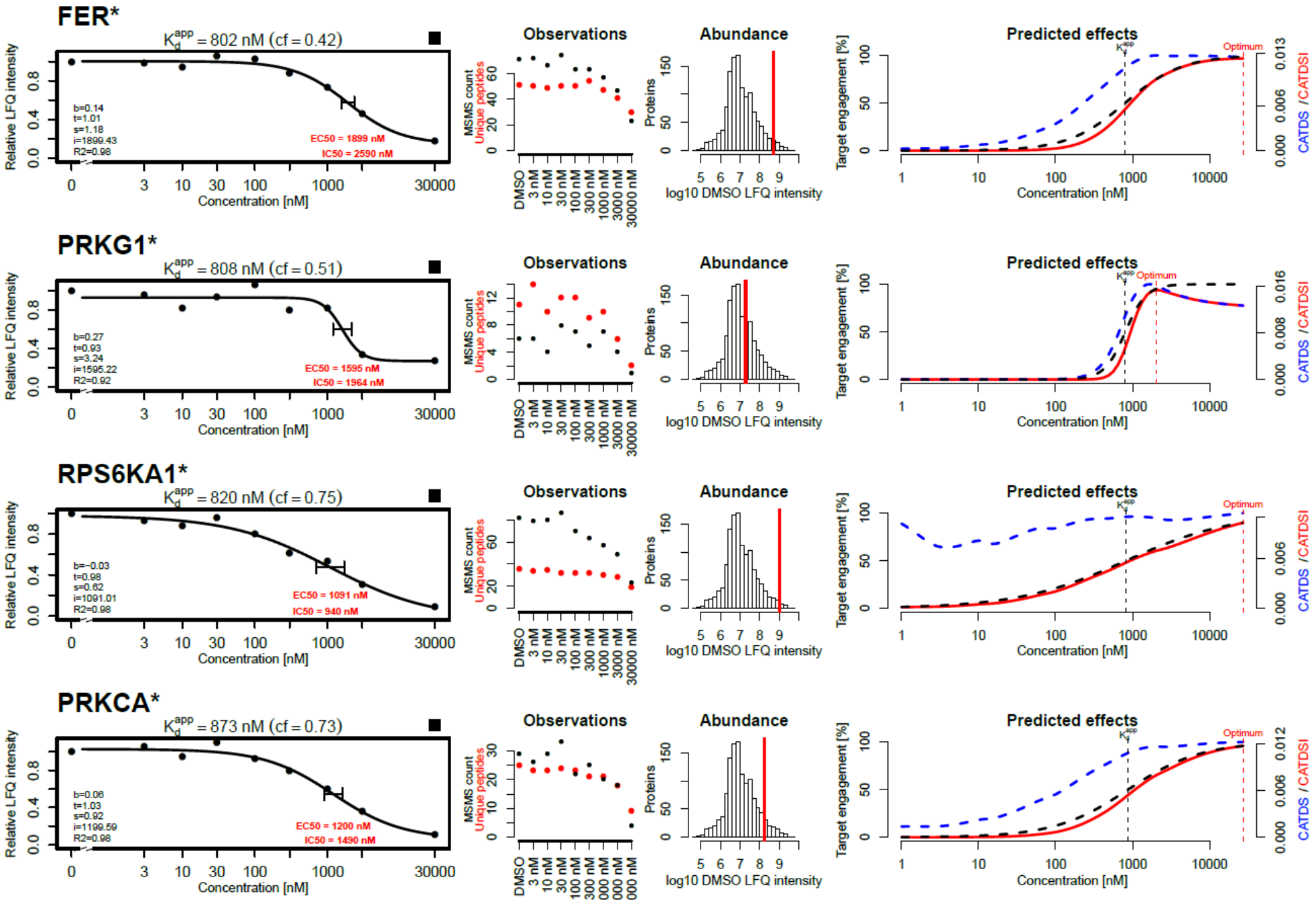


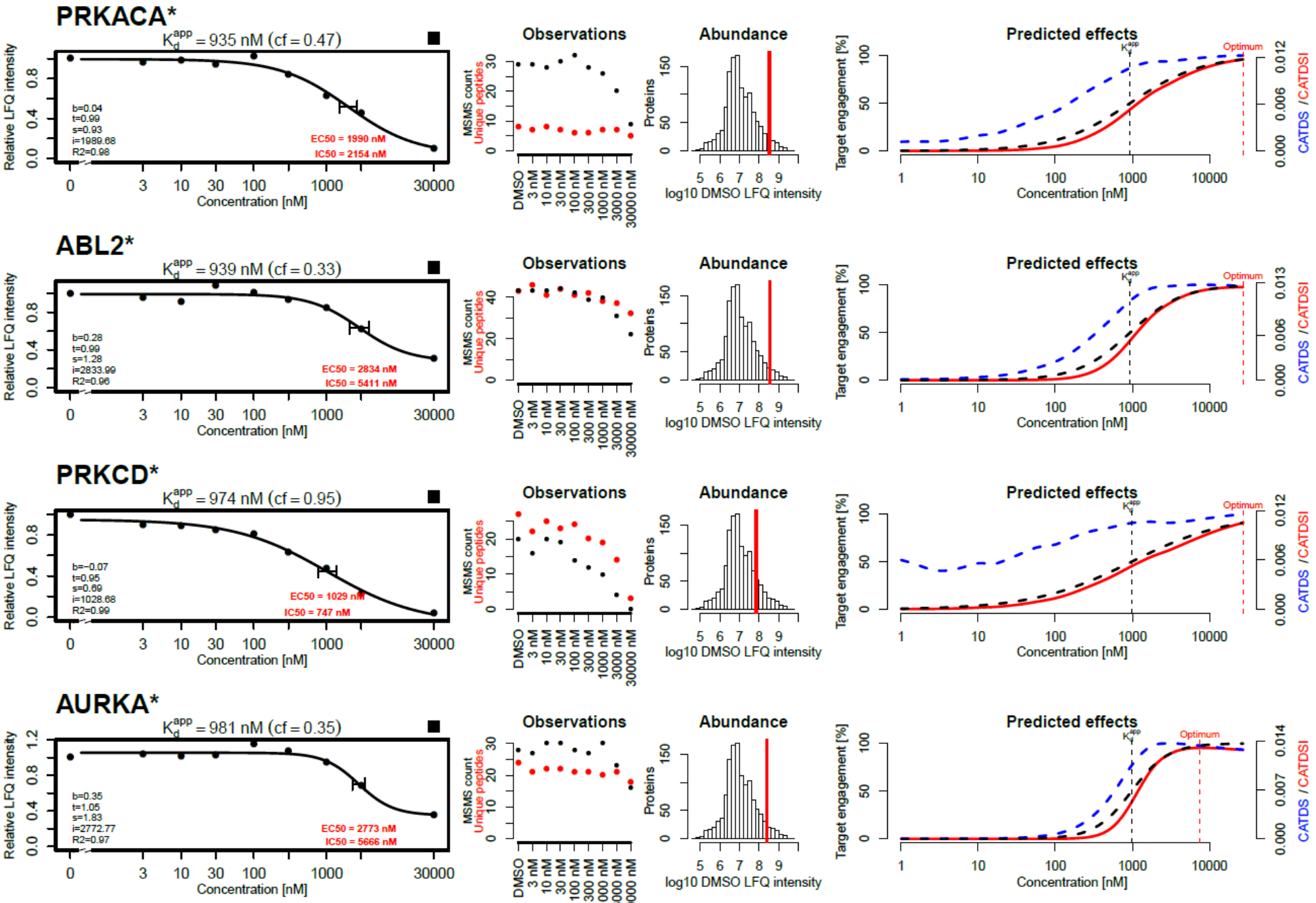
PLK4*

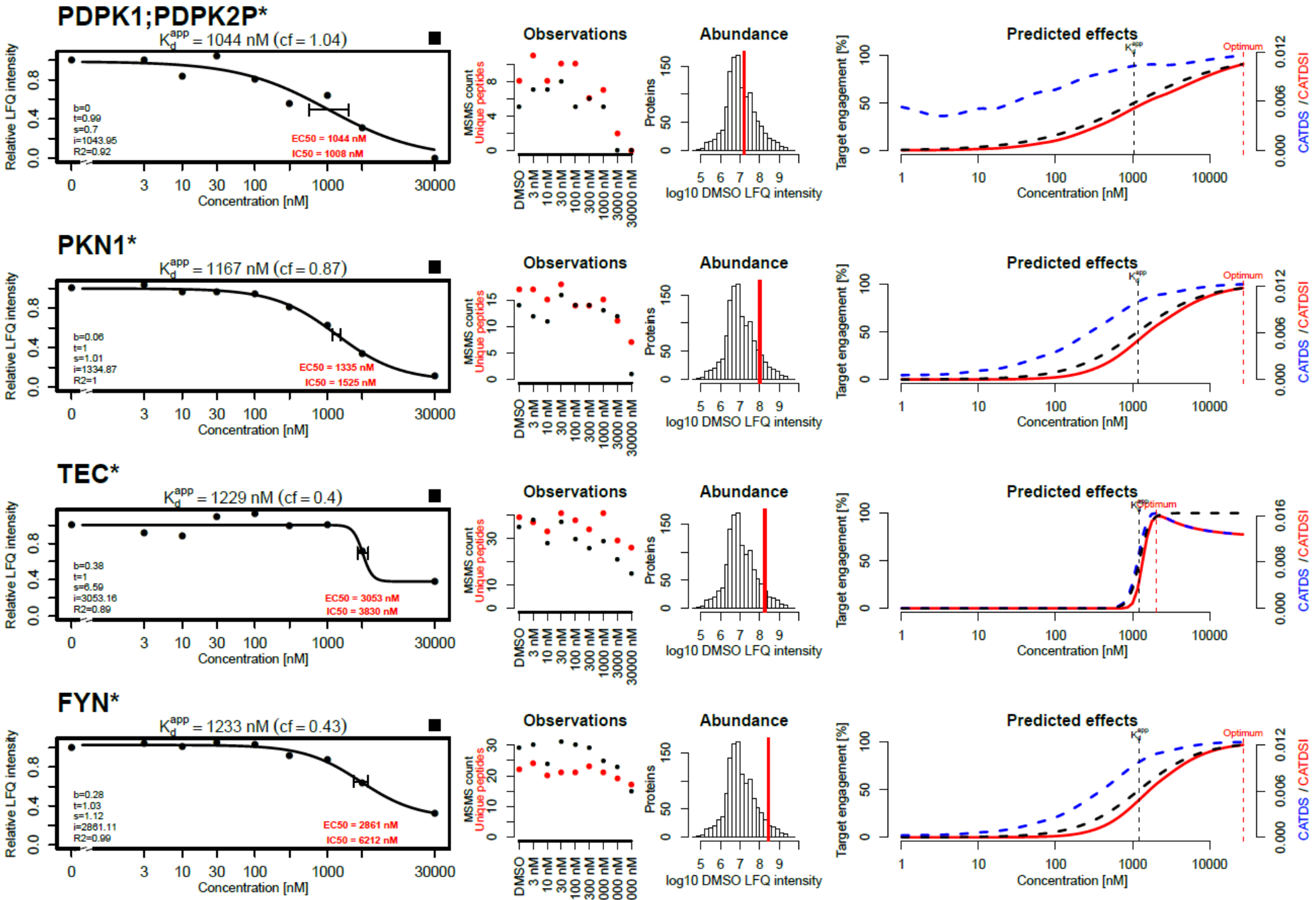


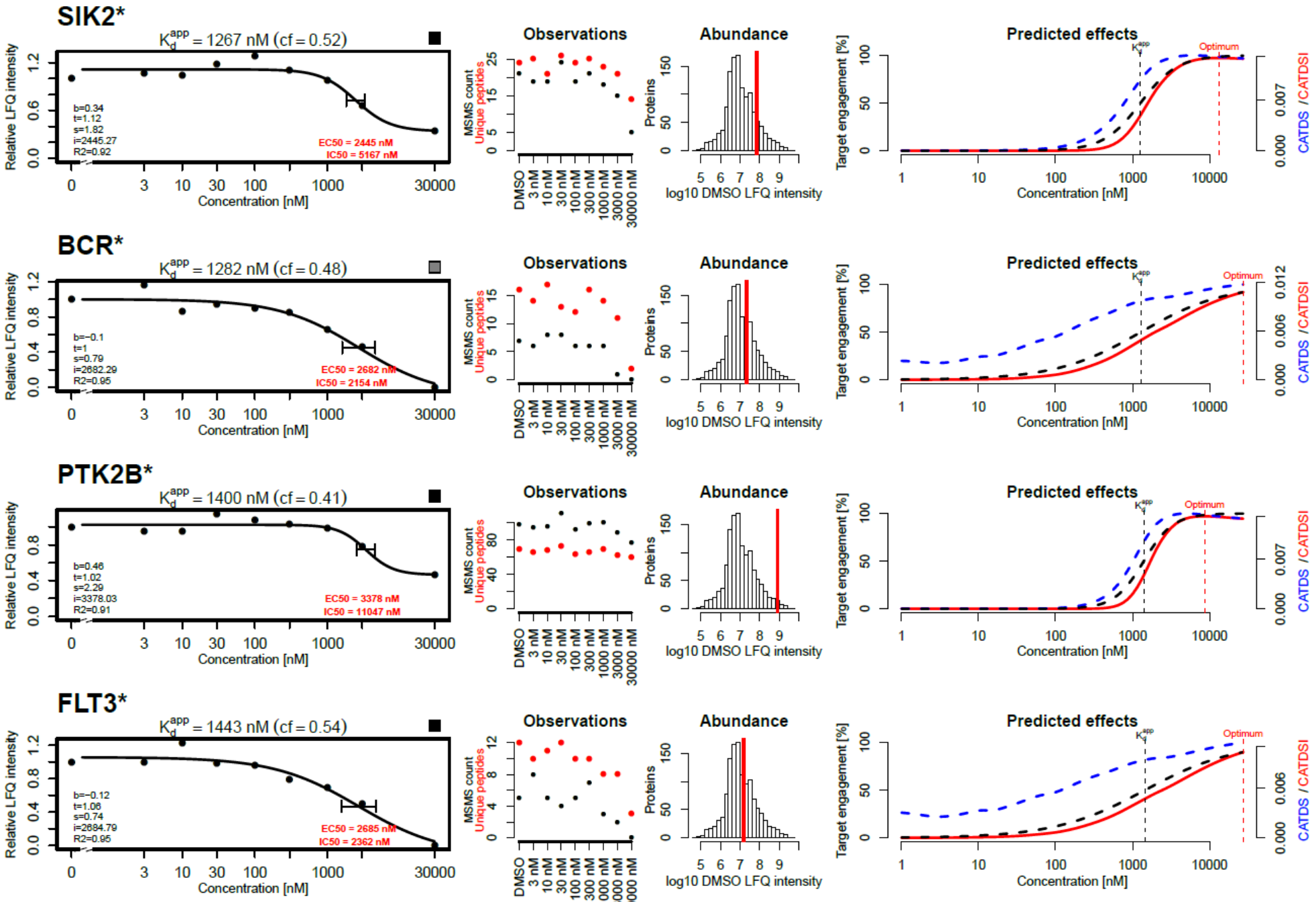
RET*



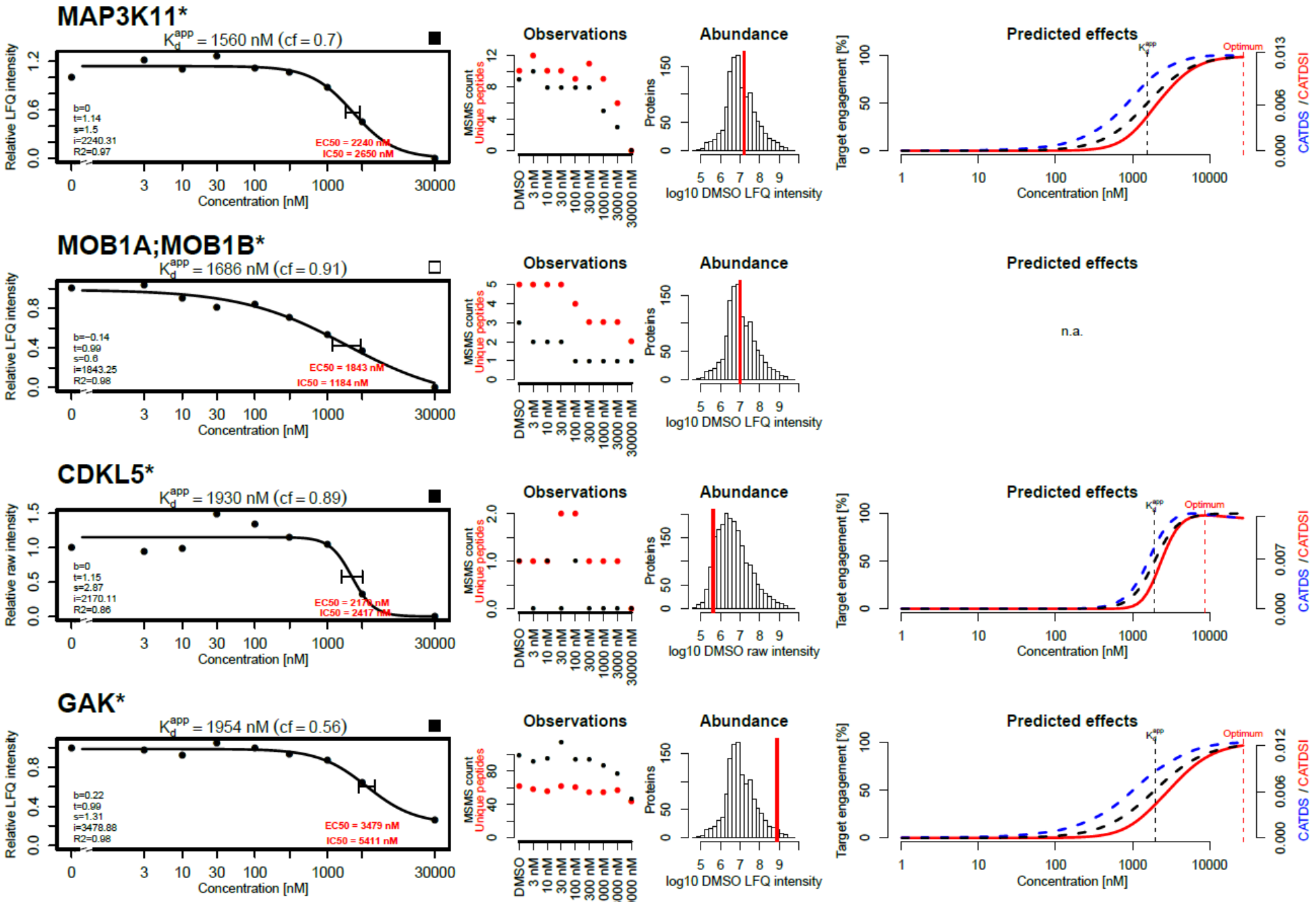

FER*
K_d^{app} = 802 nM (cf = 0.42)
b=0.14
t=1.01
s=1.18
i=1899.43
R2=0.98
EC50 = 1899 nM
IC50 = 2590 nM
Relative LFQ intensity
Concentration [nM]
Observations
MSMS count
Unique peptides
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
Optimum
CATDS / CATDSI
PRKG1*
K_d^{app} = 808 nM (cf = 0.51)
b=0.27
t=0.93
s=3.24
i=1595.22
R2=0.92
EC50 = 1595 nM
IC50 = 1964 nM
RPS6KA1*
K_d^{app} = 820 nM (cf = 0.75)
b=−0.03
t=0.98
s=0.62
i=1091.01
R2=0.98
EC50 = 1091 nM
IC50 = 940 nM
PRKCA*
K_d^{app} = 873 nM (cf = 0.73)
b=0.06
t=1.03
s=0.92
i=1199.59
R2=0.98
EC50 = 1200 nM
IC50 = 1490 nM

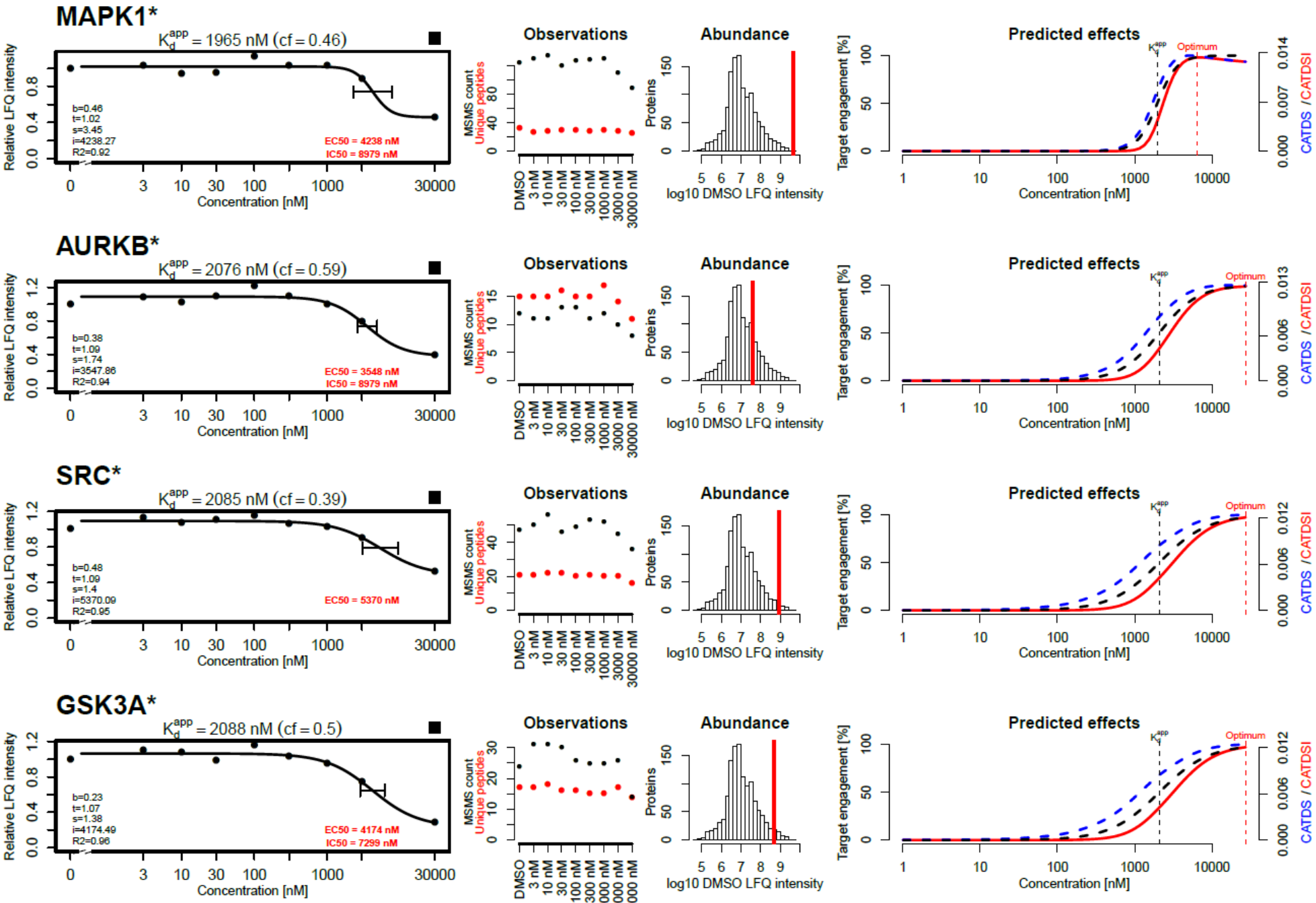

PRKACA*
K_d^{app} = 935 nM (cf = 0.47)
b=0.04
t=0.99
s=0.93
i=1989.68
R2=0.98
EC50 = 1990 nM
IC50 = 2154 nM
Relative LFQ intensity
Concentration [nM]
Observations
MSMS count
Unique peptides
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
CATDS /CATDSI
Optimum
ABL2*
K_d^{app} = 939 nM (cf = 0.33)
b=0.28
t=0.99
s=1.28
i=2833.99
R2=0.96
EC50 = 2834 nM
IC50 = 5411 nM
PRKCD*
K_d^{app} = 974 nM (cf = 0.95)
b=−0.07
t=0.95
s=0.69
i=1028.68
R2=0.99
EC50 = 1029 nM
IC50 = 747 nM
AURKA*
K_d^{app} = 981 nM (cf = 0.35)
b=0.35
t=1.05
s=1.83
i=2772.77
R2=0.97
EC50 = 2773 nM
IC50 = 5666 nM

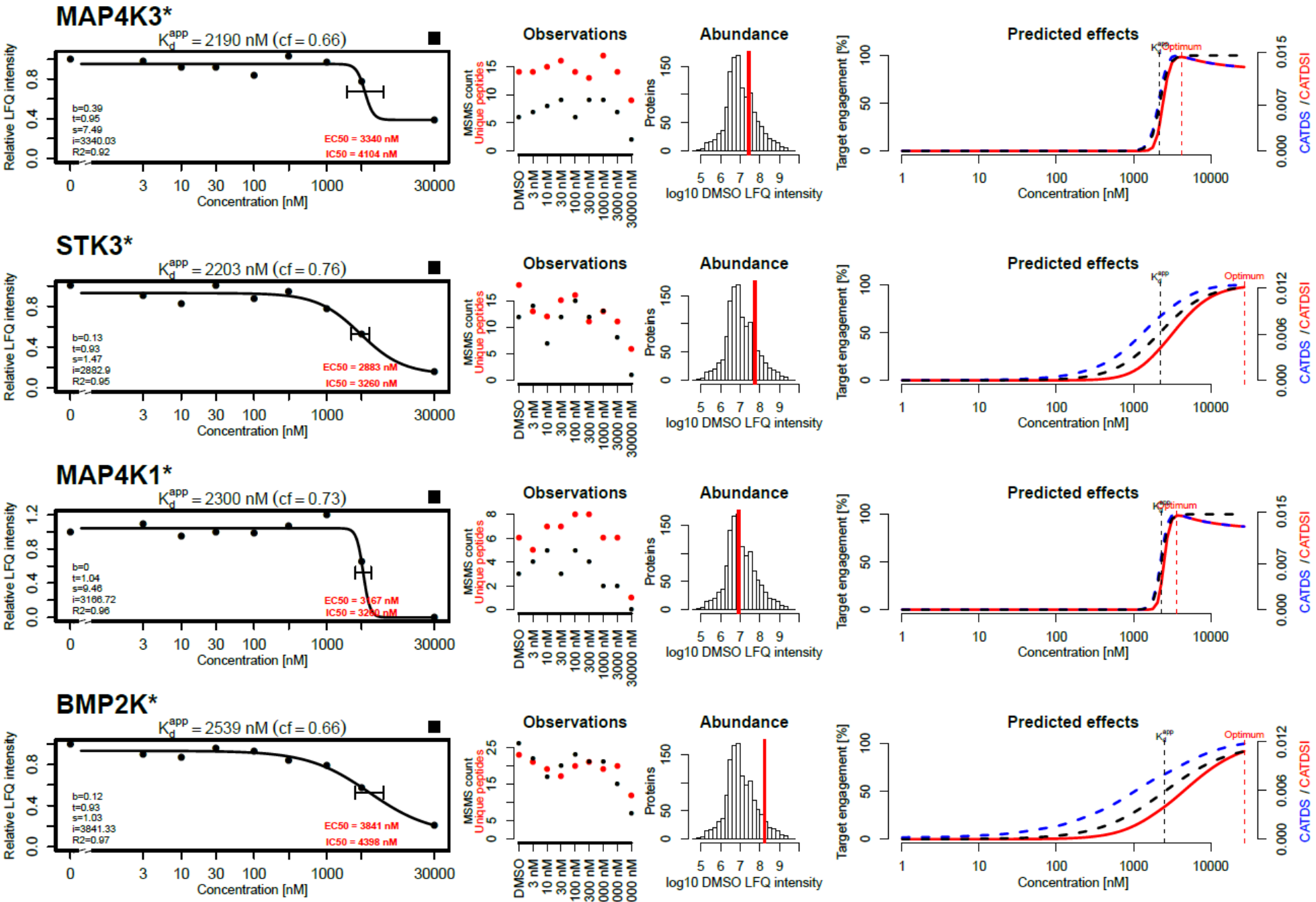

PDPK1;PDPK2P*
K_d^{app} = 1044 nM (cf = 1.04)
Relative LFQ intensity
b=0
t=0.99
s=0.7
i=1043.95
R2=0.92
EC50 = 1044 nM
IC50 = 1008 nM
Concentration [nM]
Observations
MSMS count
Unique peptides
DMSO
3 nM
10 nM
30 nM
100 nM
300 nM
1000 nM
3000 nM
30000 nM
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
Optimum
CATDS / CATDSI
PKN1*
K_d^{app} = 1167 nM (cf = 0.87)
b=0.06
t=1
s=1.01
i=1334.87
R2=1
EC50 = 1335 nM
IC50 = 1525 nM
TEC*
K_d^{app} = 1229 nM (cf = 0.4)
b=0.38
t=1
s=6.59
i=3053.16
R2=0.89
EC50 = 3053 nM
IC50 = 3830 nM
FYN*
K_d^{app} = 1233 nM (cf = 0.43)
b=0.28
t=1.03
s=1.12
i=2861.11
R2=0.99
EC50 = 2861 nM
IC50 = 6212 nM

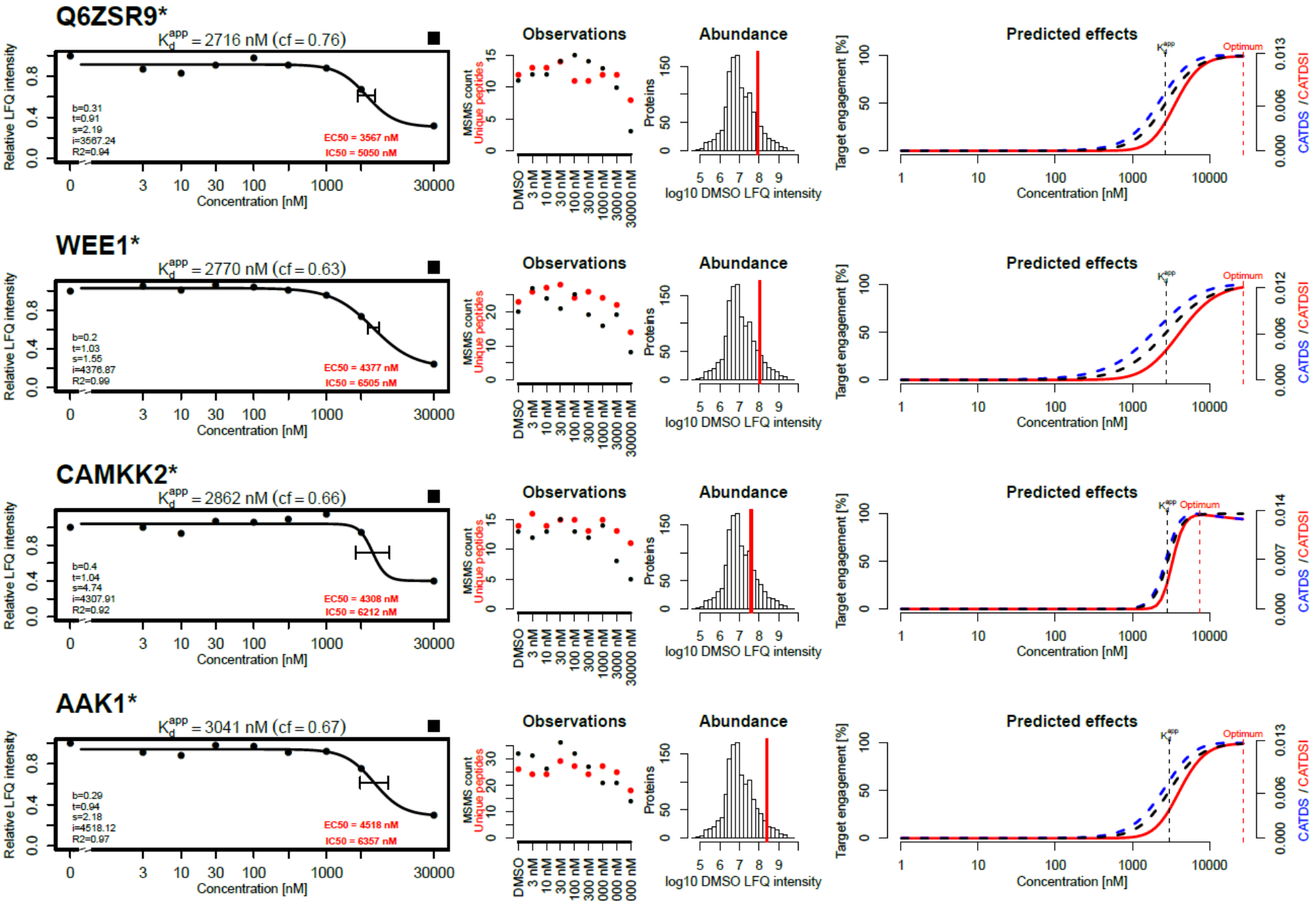


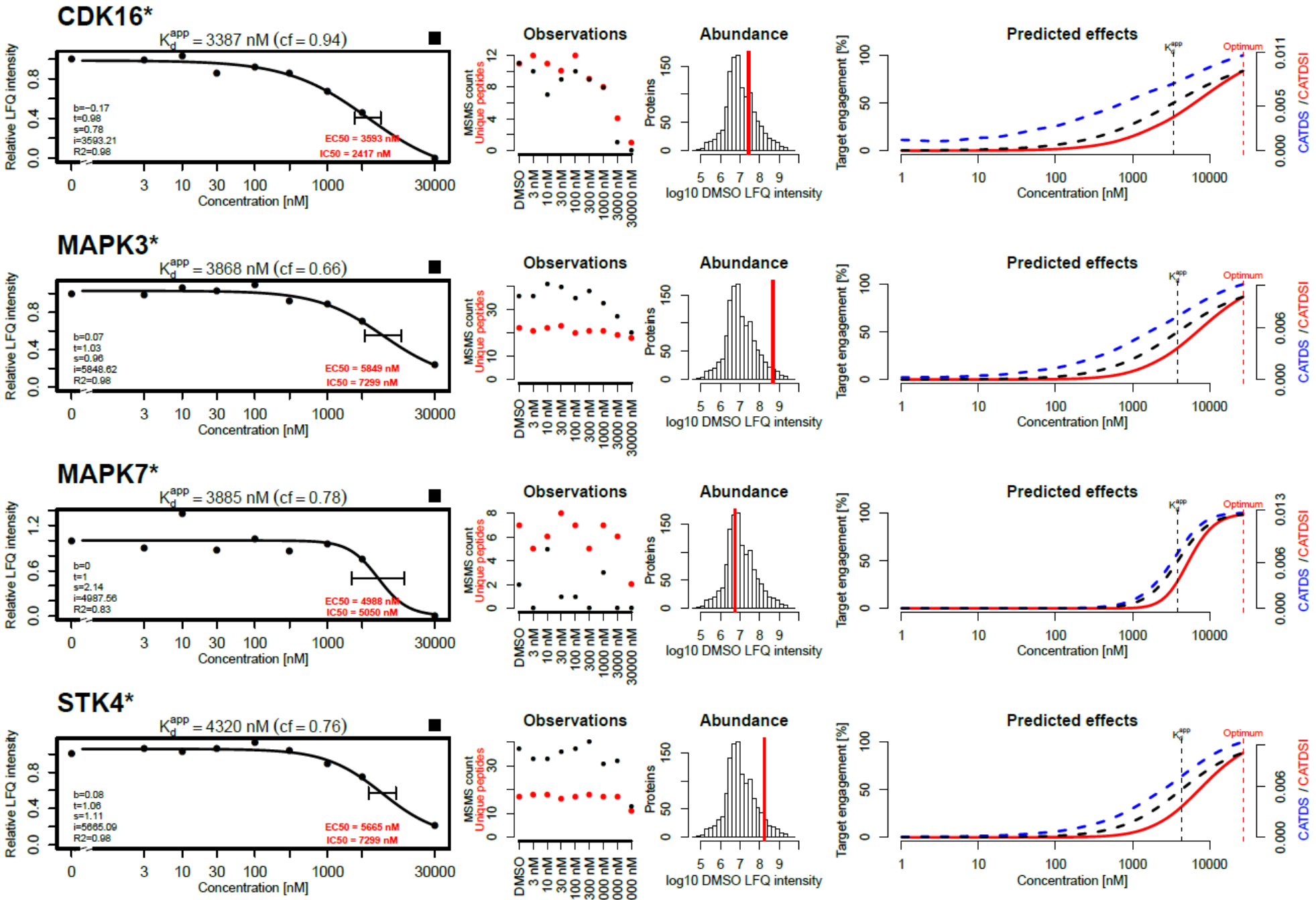
Source: Technical University Munich 2016

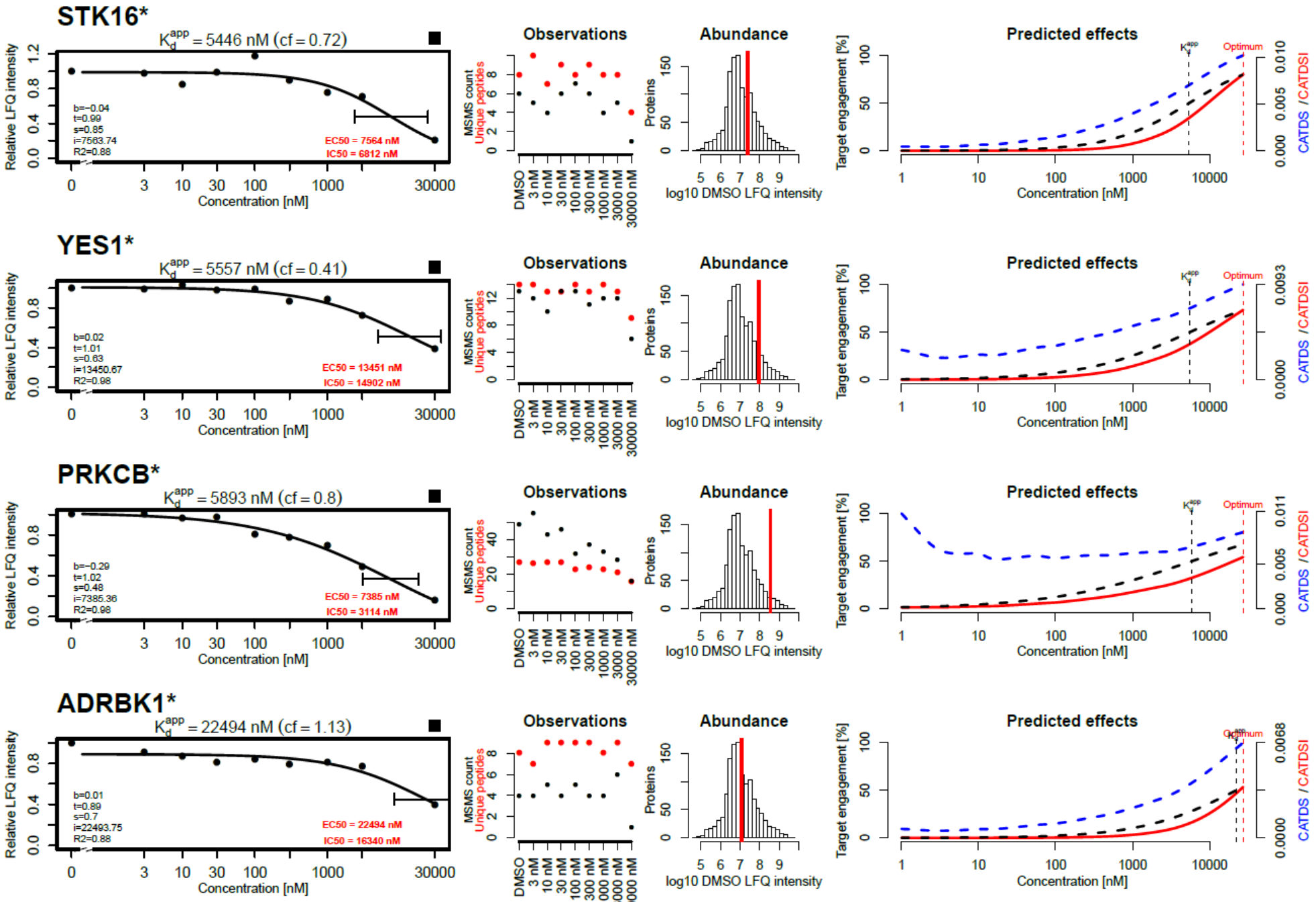

MAP3K11*
K_d^{app} = 1560 nM (cf = 0.7)
Relative LFQ intensity
b=0
t=1.14
s=1.5
i=2240.31
R2=0.97
EC50 = 2240 nM
IC50 = 2650 nM
Concentration [nM]
Observations
MSMS count
Unique peptides
DMSO
3 nM
10 nM
30 nM
100 nM
300 nM
1000 nM
3000 nM
30000 nM
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
Optimum
CATDS / CATDSI
MOB1A;MOB1B*
K_d^{app} = 1686 nM (cf = 0.91)
b=-0.14
t=0.99
s=0.6
i=1843.25
R2=0.98
EC50 = 1843 nM
IC50 = 1184 nM
n.a.
CDKL5*
K_d^{app} = 1930 nM (cf = 0.89)
Relative raw intensity
b=0
t=1.15
s=2.87
i=2170.11
R2=0.86
log10 DMSO raw intensity
GAK*
K_d^{app} = 1954 nM (cf = 0.56)
b=0.22
t=0.99
s=1.31
i=3478.88
R2=0.98
EC50 = 3479 nM
IC50 = 5411 nM


MAPK1*
K_d^{app} = 1965 nM (cf = 0.46)
Relative LFQ intensity
b=0.46
t=1.02
s=3.45
i=4238.27
R2=0.92
EC50 = 4238 nM
IC50 = 8979 nM
Concentration [nM]
Observations
MSMS count
Unique peptides
DMSO
3 nM
10 nM
30 nM
100 nM
300 nM
1000 nM
3000 nM
30000 nM
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
Optimum
CATDS / CATDSI
AURKB*
K_d^{app} = 2076 nM (cf = 0.59)
b=0.38
t=1.09
s=1.74
i=3547.86
R2=0.94
EC50 = 3548 nM
IC50 = 8979 nM
SRC*
K_d^{app} = 2085 nM (cf = 0.39)
b=0.48
t=1.09
s=1.4
i=5370.09
R2=0.95
EC50 = 5370 nM
GSK3A*
K_d^{app} = 2088 nM (cf = 0.5)
b=0.23
t=1.07
s=1.38
i=4174.49
R2=0.96
EC50 = 4174 nM
IC50 = 7299 nM

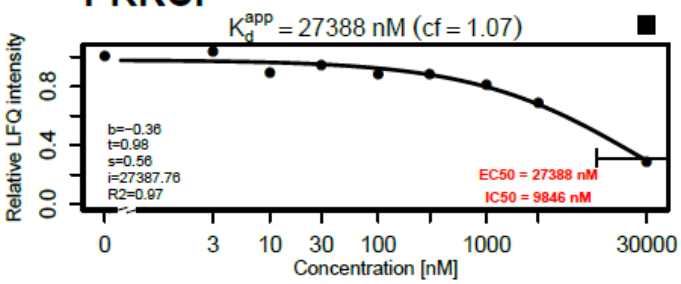

MAP4K3*
K_d^{app} = 2190 nM (cf = 0.66)
b=0.39
t=0.95
s=7.49
i=3340.03
R2=0.92
EC50 = 3340 nM
IC50 = 4104 nM
Relative LFQ intensity
Concentration [nM]
Observations
MSMS count
Unique peptides
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
CATDS / CATDSI
Optimum
STK3*
K_d^{app} = 2203 nM (cf = 0.76)
b=0.13
t=0.93
s=1.47
i=2882.9
R2=0.95
EC50 = 2883 nM
IC50 = 3260 nM
MAP4K1*
K_d^{app} = 2300 nM (cf = 0.73)
b=0
t=1.04
s=9.46
i=3166.72
R2=0.96
BMP2K*
K_d^{app} = 2539 nM (cf = 0.66)
b=0.12
t=0.93
s=1.03
i=3841.33
R2=0.97
EC50 = 3841 nM
IC50 = 4398 nM

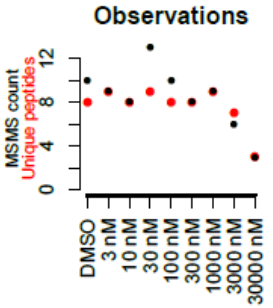

Q6ZSR9*
K_d^{app} = 2716 nM (cf = 0.76)
b=0.31
t=0.91
s=2.19
i=3567.24
R2=0.94
EC50 = 3567 nM
IC50 = 5050 nM
Relative LFQ intensity
Concentration [nM]
Observations
MSMS count
Unique peptides
DMSO
3 nM
10 nM
30 nM
100 nM
300 nM
1000 nM
3000 nM
30000 nM
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
Optimum
CATDS / CATDSI
WEE1*
K_d^{app} = 2770 nM (cf = 0.63)
b=0.2
t=1.03
s=1.55
i=4376.87
R2=0.99
EC50 = 4377 nM
IC50 = 6505 nM
CAMKK2*
K_d^{app} = 2862 nM (cf = 0.66)
b=0.4
t=1.04
s=4.74
i=4307.91
R2=0.92
EC50 = 4308 nM
IC50 = 6212 nM
AAK1*
K_d^{app} = 3041 nM (cf = 0.67)
b=0.29
t=0.94
s=2.18
i=4518.12
R2=0.97
EC50 = 4518 nM
IC50 = 6357 nM

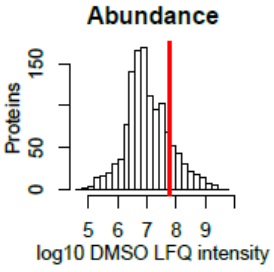

CDK16*
K_d^{app} = 3387 nM (cf = 0.94)
b=−0.17
t=0.98
s=0.78
i=3593.21
R2=0.98
EC50 = 3593 nM
IC50 = 2417 nM
Relative LFQ intensity
Concentration [nM]
Observations
MSMS count
Unique peptides
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
CATDS / CATDSI
Optimum
MAPK3*
K_d^{app} = 3868 nM (cf = 0.66)
b=0.07
t=1.03
s=0.96
i=5848.62
R2=0.98
EC50 = 5849 nM
IC50 = 7299 nM
MAPK7*
K_d^{app} = 3885 nM (cf = 0.78)
b=0
t=1
s=2.14
i=4987.56
R2=0.83
EC50 = 4988 nM
IC50 = 5050 nM
STK4*
K_d^{app} = 4320 nM (cf = 0.76)
b=0.08
t=1.06
s=1.11
i=5665.09
R2=0.98
EC50 = 5665 nM
IC50 = 7299 nM
DMSO
3 nM
10 nM
30 nM
100 nM
300 nM
1000 nM
3000 nM
30000 nM

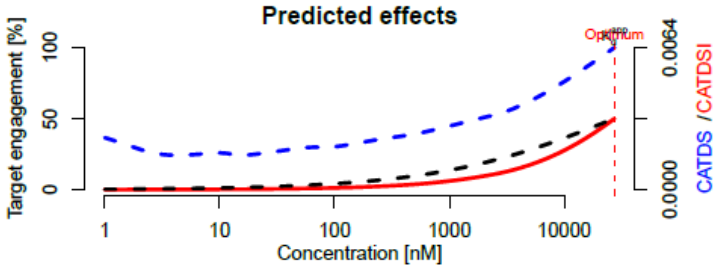

STK16*
K_d^{app} = 5446 nM (cf = 0.72)
Relative LFQ intensity
b=−0.04
t=0.99
s=0.85
i=7563.74
R2=0.88
EC50 = 7564 nM
IC50 = 6812 nM
Concentration [nM]
Observations
MSMS count
Unique peptides
DMSO
3 nM
10 nM
30 nM
100 nM
300 nM
1000 nM
3000 nM
30000 nM
Abundance
Proteins
log10 DMSO LFQ intensity
Predicted effects
Target engagement [%]
Optimum
CATDS / CATDSI
YES1*
K_d^{app} = 5557 nM (cf = 0.41)
b=0.02
t=1.01
s=0.63
i=13450.67
R2=0.98
EC50 = 13451 nM
IC50 = 14902 nM
PRKCB*
K_d^{app} = 5893 nM (cf = 0.8)
b=−0.29
t=1.02
s=0.48
i=7385.36
R2=0.98
EC50 = 7385 nM
IC50 = 3114 nM
ADRBK1*
K_d^{app} = 22494 nM (cf = 1.13)
b=0.01
t=0.89
s=0.7
i=22493.75
R2=0.88
EC50 = 22494 nM
IC50 = 16340 nM

PRKCI*

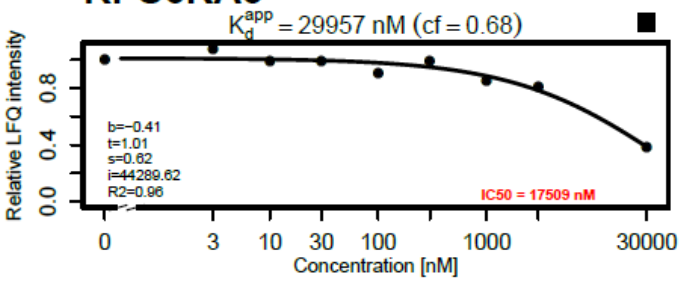


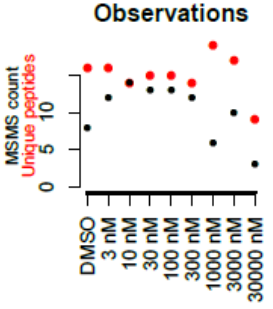


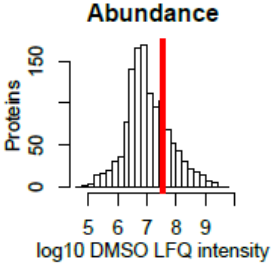


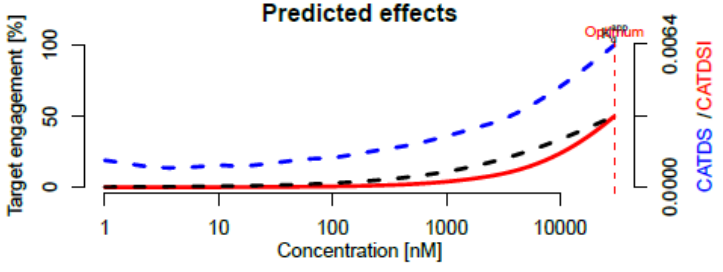


RPS6KA5*

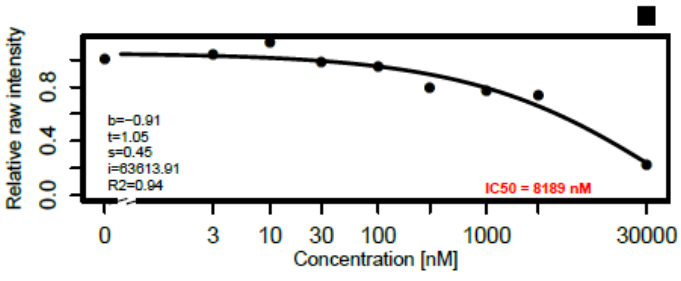


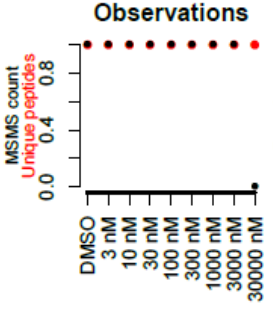


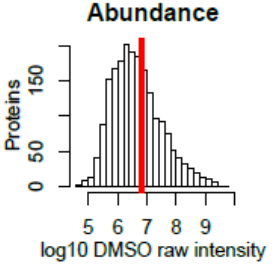


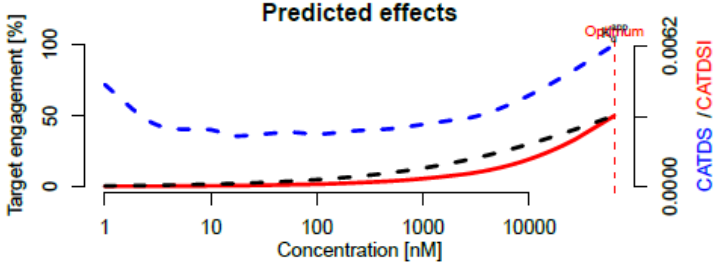


CDK3*

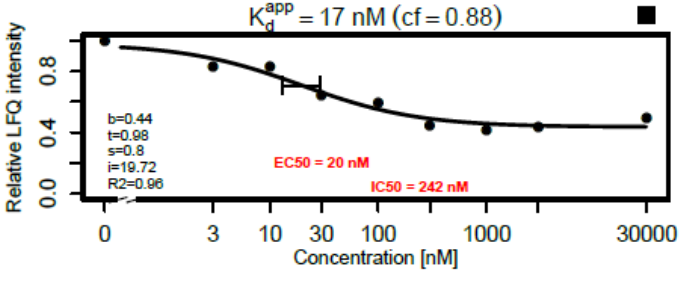


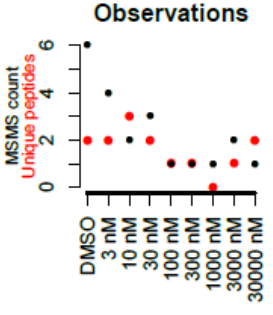


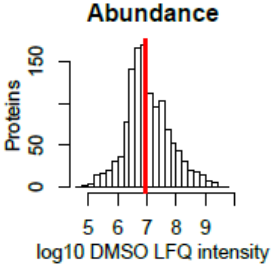




STK26#



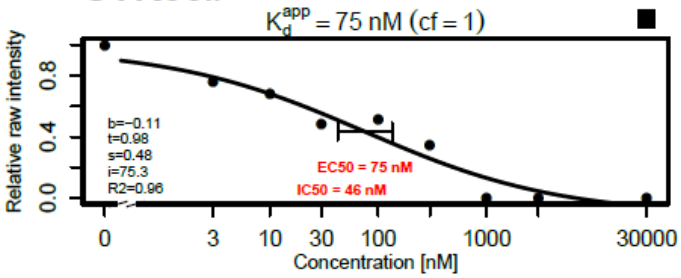


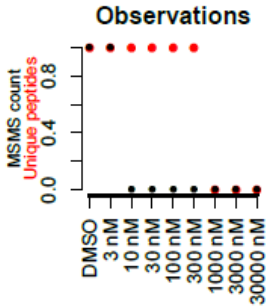


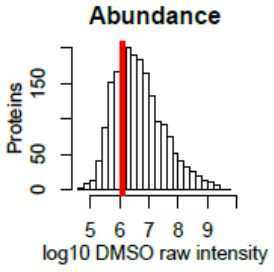
Predicted effects

n.a.

STK38#



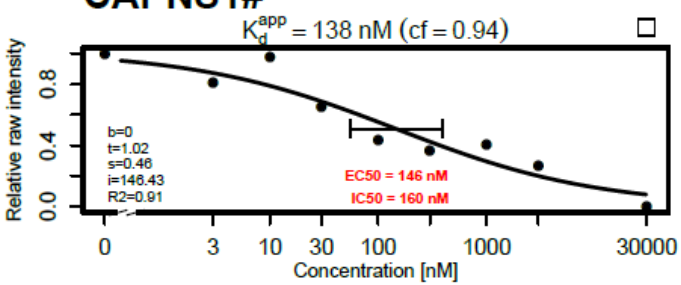


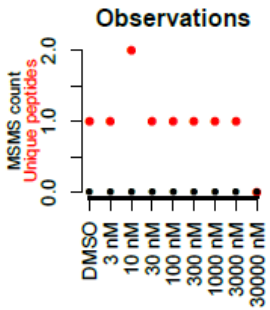


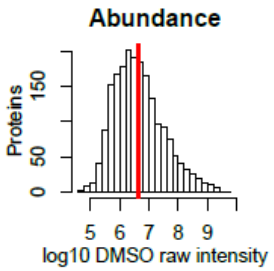
Predicted effects

n.a.

CAPNS1#



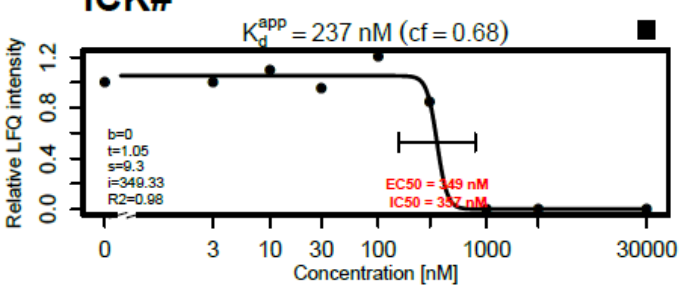


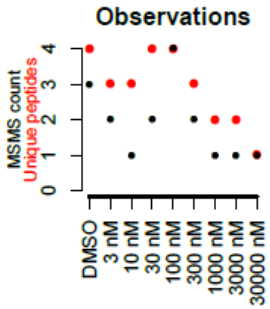


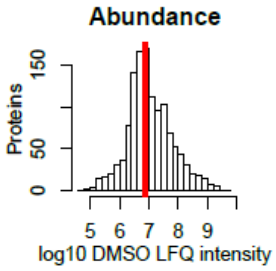
Predicted effects

n.a.

ICK#



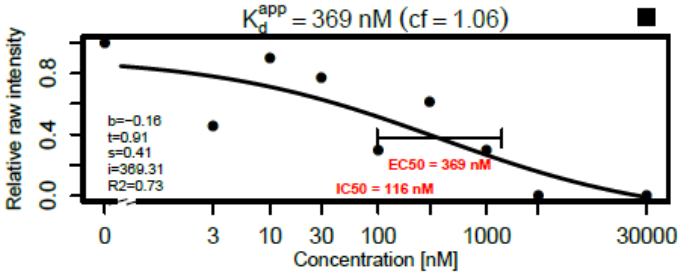


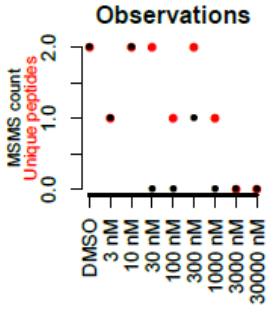


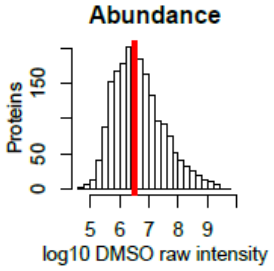
Predicted effects

n.a.

STK24#





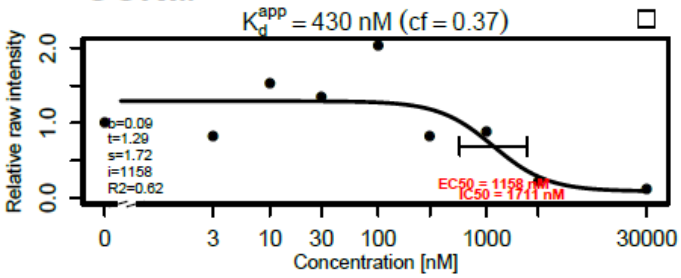


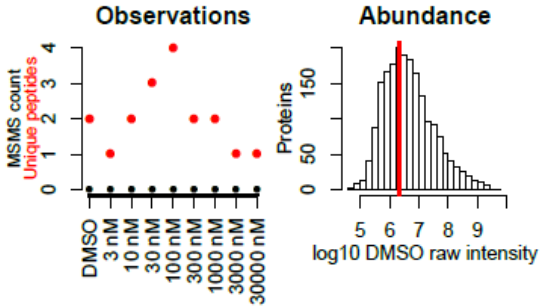
Predicted effects

n.a.

Source: Technical University Munich 2016

CCNI#





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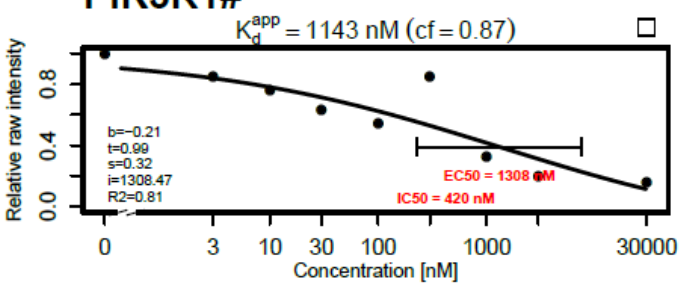
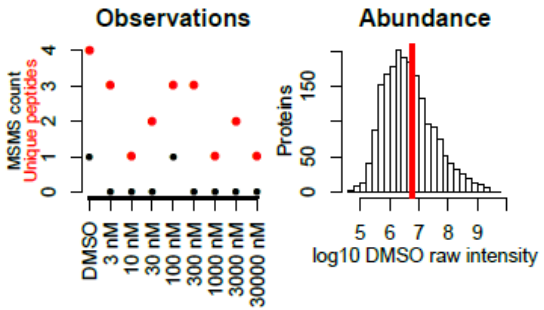
PIK3R1#





Predicted effects

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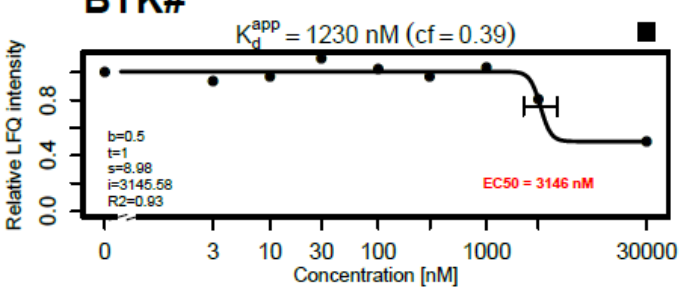

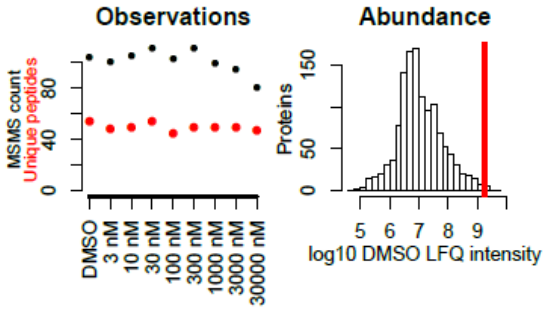

Predicted effects

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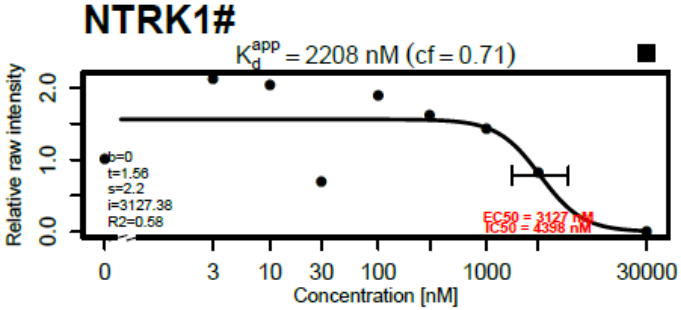

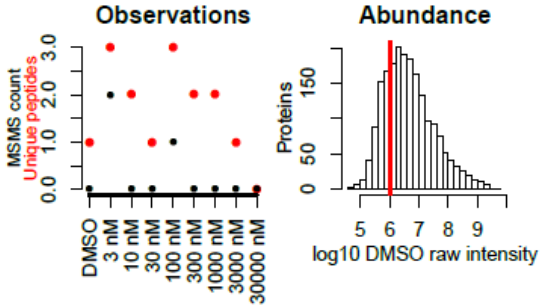

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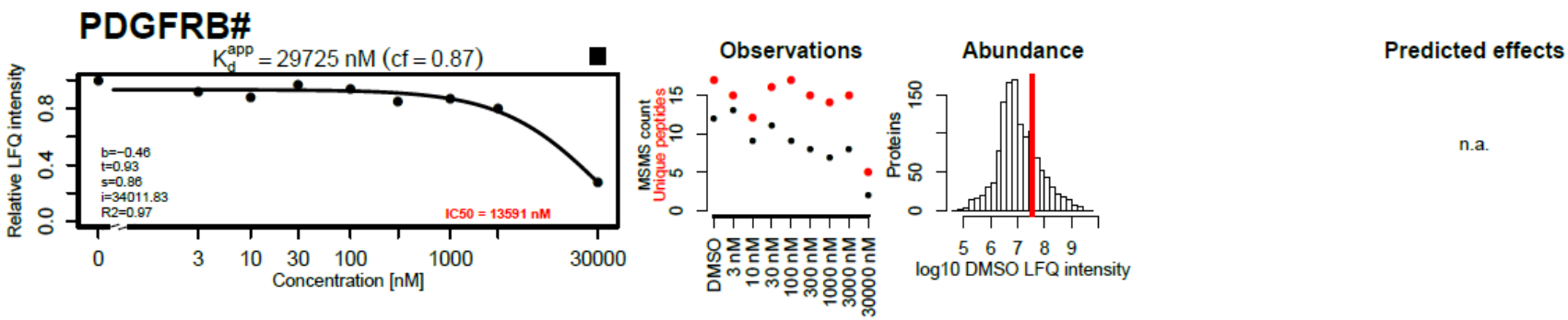

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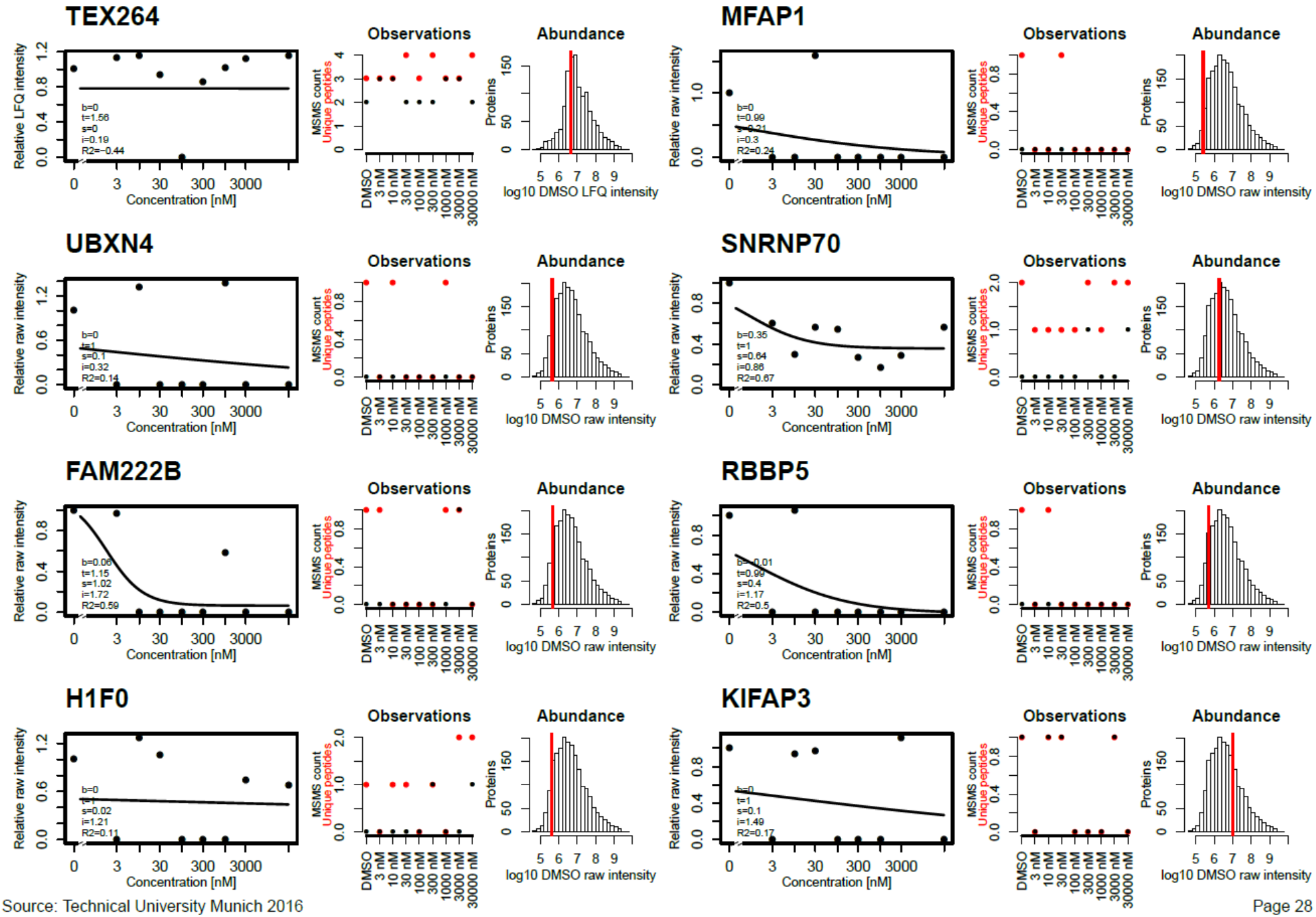
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Unique peptides
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10 nM
30 nM
100 nM
300 nM
1000 nM
3000 nM
30000 nM
Abundance
Proteins
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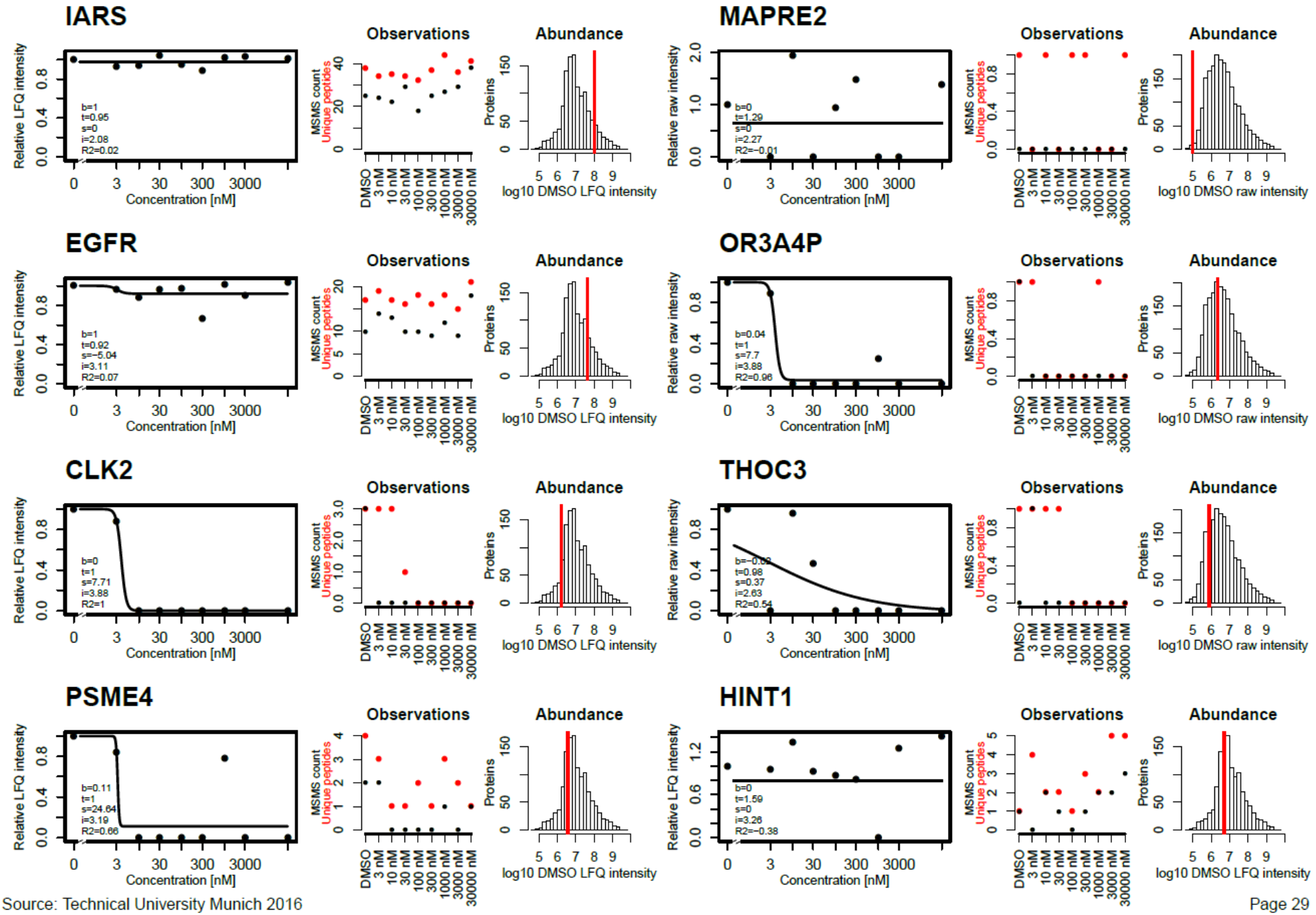
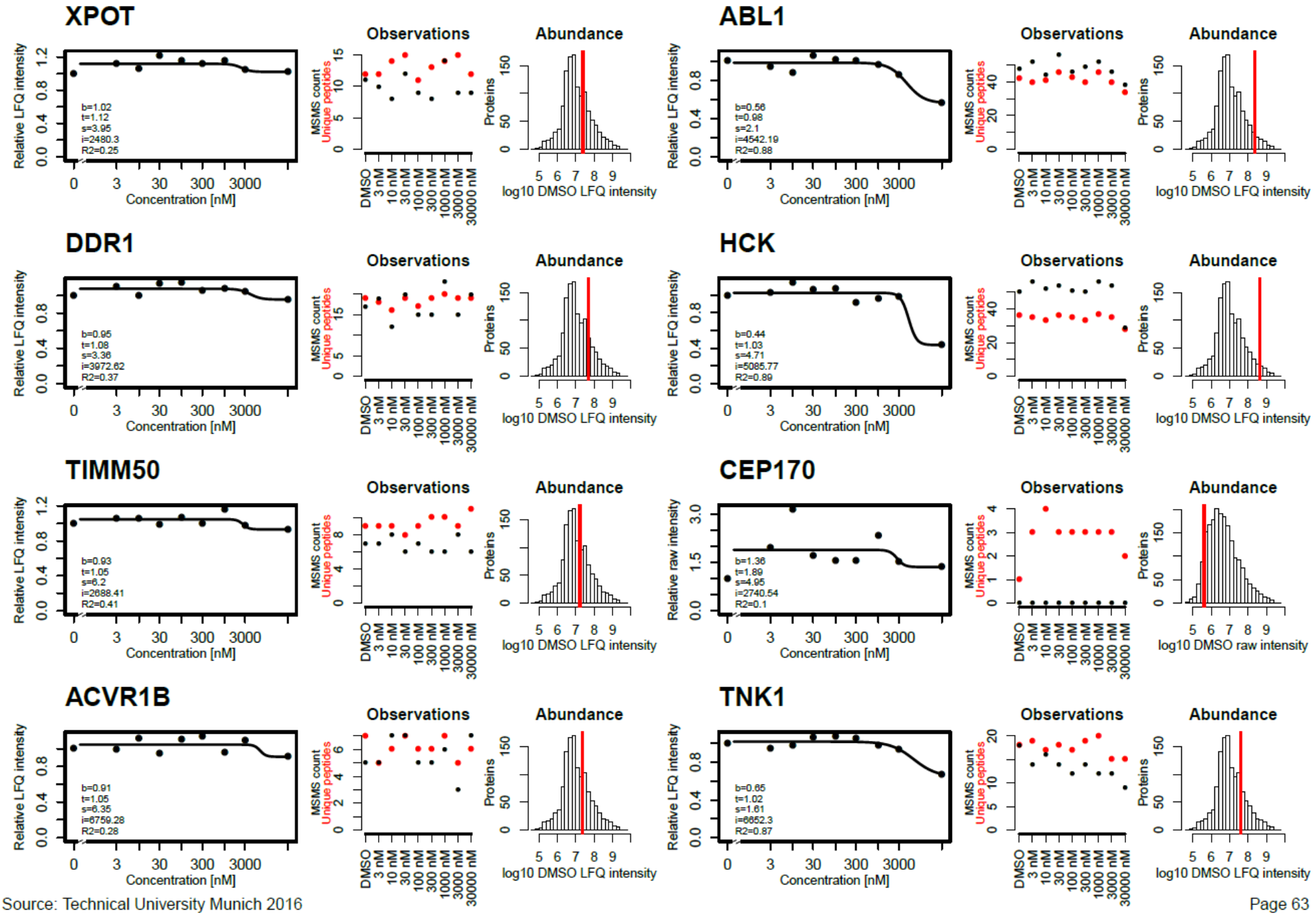


Source: Technical University Munich 2016



Source: Technical University Munich 2016

Appendix III

Table of all inhibitors and their targets

Drug	Name of the drug
Gene names	Name of the target protein
EC50	EC_{50} of respective target
Correction factor	Factor used for correction of EC_{50} to K_d^{app} for respective target
Apparent Kd	K_d^{app} of respective target
R2	R^2 for respective curve-fit
Target classification	High or low confidence target (as defined in Experimental Procedures)

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Abemaciclib	CSNK2A1	4	1.02	4	0.99	High confidence	Abemaciclib	PRKD3	2488	0.74	1841	0.88	High confidence
Abemaciclib	CLK1	9	0.72	7	0.69	High confidence	Abemaciclib	PRKD2	3131	0.66	2064	0.97	High confidence
Abemaciclib	PIM1	17	0.43	7	0.96	High confidence	Abemaciclib	GAK	3907	0.56	2194	0.96	High confidence
Abemaciclib	GSK3B	28	0.46	13	0.96	High confidence	Abemaciclib	STK10	2698	0.92	2470	0.83	High confidence
Abemaciclib	CLK4	16	0.85	13	0.69	Low confidence	Abemaciclib	CAMKK2	3911	0.66	2598	0.91	High confidence
Abemaciclib	GSK3A	27	0.50	13	0.99	High confidence	Abemaciclib	MAPK8	5796	0.65	3756	0.88	High confidence
Abemaciclib	CAMK2G	82	0.22	18	0.94	High confidence	Abemaciclib	EIF2AK1	5247	0.92	4836	0.78	High confidence
Abemaciclib	CSNK2A2	20	0.96	19	1.00	High confidence	Abemaciclib	CDK2	19695	0.53	10487	0.85	High confidence
Abemaciclib	CAMK2D	95	0.20	19	0.99	High confidence	Abemaciclib	BMP2K	84774	0.66	56032	0.94	High confidence
Abemaciclib	DCAF7	43	0.90	39	0.94	High confidence	AC-480	EGFR	3	0.79	3	1.00	High confidence
Abemaciclib	ADCK1	64	0.62	40	0.98	High confidence	AC-480	MAP2K5	6768	0.88	5927	0.46	Low confidence
Abemaciclib	CSNK2B	44	1.08	44	0.87	High confidence	ACTB-1003	FGFR1	55	0.74	40	0.57	High confidence
Abemaciclib	CDK16	53	0.94	50	0.95	High confidence	ACTB-1003	RET	211	0.44	93	0.87	High confidence
Abemaciclib	ICK	79	0.68	53	0.87	High confidence	ACTB-1003	DDR1	501	0.63	314	0.97	High confidence
Abemaciclib	CDK6	71	0.82	59	0.95	High confidence	ACTB-1003	FLT3	865	0.54	465	0.93	High confidence
Abemaciclib	EIF3J	86	1.11	86	0.77	High confidence	ACTB-1003	TNK1	2924	0.43	1265	0.88	High confidence
Abemaciclib	Q6ZSR9	115	0.76	88	0.96	High confidence	ACTB-1003	MAPK9	2157	0.70	1510	0.79	High confidence
Abemaciclib	CDK4	97	1.00	97	0.79	High confidence	ACTB-1003	FRK	5486	0.34	1864	0.96	High confidence
Abemaciclib	AAK1	151	0.67	102	0.99	High confidence	ACTB-1003	RPS6KA6	6372	0.42	2688	0.85	High confidence
Abemaciclib	TAOK1	162	0.66	107	0.76	High confidence	ACTB-1003	MAP3K11	4340	0.70	3023	0.96	High confidence
Abemaciclib	IRAK1	206	0.61	126	0.96	High confidence	ACTB-1003	DDR2	4265	0.76	3250	0.98	High confidence
Abemaciclib	CCNT2	150	0.88	132	0.85	High confidence	ACTB-1003	RPS6KA1	5499	0.75	4135	0.88	High confidence
Abemaciclib	CDK9	245	0.71	174	0.99	High confidence	ACTB-1003	MAP4K2	7052	0.59	4161	0.95	High confidence
Abemaciclib	DYRK1A	218	0.93	204	0.96	High confidence	ACTB-1003	BCR	8802	0.48	4206	0.68	High confidence
Abemaciclib	CCNT1	240	0.98	236	0.97	High confidence	ACTB-1003	PRKCD	5359	0.95	5076	0.92	High confidence
Abemaciclib	PIGT	240	1.09	240	0.91	Low confidence	ACTB-1003	RPS6KA3	7318	0.72	5305	0.90	High confidence
Abemaciclib	STK16	688	0.72	495	0.79	High confidence	AEE-788	GRB2	515	0.62	321	0.87	High confidence
Abemaciclib	PRKCA	728	0.73	530	0.88	High confidence	AEE-788	EGFR	508	0.79	403	0.99	High confidence
Abemaciclib	CCNA2	679	0.86	585	0.88	High confidence	AEE-788	BCR	1035	0.48	495	0.85	High confidence
Abemaciclib	PRKCD	839	0.95	795	0.88	High confidence	AEE-788	INPPL1	1197	0.48	578	0.94	High confidence
Abemaciclib	CIT	798	1.21	798	0.84	High confidence	AEE-788	LIMK1	1063	0.59	632	0.61	High confidence
Abemaciclib	CCNE1	1224	0.73	892	0.60	Low confidence	AEE-788	TNK2	2234	0.45	1006	0.92	High confidence
Abemaciclib	CCNB1	1658	0.77	1270	0.94	High confidence	AEE-788	ABL1	1990	0.55	1091	0.93	High confidence
Abemaciclib	EIF4G1	1304	1.48	1304	0.72	High confidence	AEE-788	MAP3K4	3259	0.67	2189	0.83	High confidence
Abemaciclib	MAP4K4	1322	1.01	1322	0.74	High confidence	AEE-788	MAP4K2	5990	0.59	3534	0.94	High confidence
Abemaciclib	PRKCB	2035	0.80	1624	0.81	High confidence	AEE-788	DDR1	8327	0.63	5223	0.97	High confidence
Abemaciclib	TAOK3	2224	0.77	1721	0.89	High confidence	AEE-788	MAP4K4	7979	1.01	7979	0.71	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
AEE-788	PDGFRB	10736	0.87	9383	0.85	High confidence	AEW-541	FECH	6534	0.99	6501	0.78	High confidence
AEE-788	MAP2K5	10768	0.88	9430	0.80	High confidence	AEW-541	IGF1R	14762	0.66	9769	0.92	High confidence
AEE-788	ZAK	18340	0.74	13638	0.93	High confidence	AEW-541	ROCK2	20949	0.87	18265	0.88	High confidence
AEE-788	ABL2	45036	0.33	14924	0.97	High confidence	AEW-541	RET	52557	0.44	23155	0.91	High confidence
AEE-788	ACVR1	33675	0.48	16121	0.97	High confidence	AEW-541	CSNK1E	70796	0.85	60523	0.76	High confidence
AEE-788	YES1	41513	0.41	17152	0.89	High confidence	Afatinib	EGFR	3	0.79	2	1.00	High confidence
AEE-788	LIMK2	32841	0.66	21770	0.97	High confidence	Afatinib	MET	196	0.80	157	0.52	Low confidence
AEE-788	EPHB4	53350	0.49	26399	0.88	High confidence	Afatinib	MAPKAPK2	1131	0.72	817	0.96	High confidence
AEE-788	DDR2	36994	0.76	28192	0.96	High confidence	Afatinib	UNC119	1159	0.73	841	0.81	Low confidence
AEE-788	NEK3	44562	0.85	38088	0.81	High confidence	Afatinib	MAPK14	2044	0.51	1047	0.98	High confidence
AEE-788	SIK2	80646	0.52	41795	0.93	High confidence	Afatinib	GAK	3154	0.56	1771	0.99	High confidence
AEE-788	STK10	46479	0.92	42550	0.97	High confidence	Afatinib	GRB2	3828	0.62	2388	0.92	High confidence
AEE-788	MAP4K5	67480	0.74	50214	0.92	High confidence	Afatinib	MAPK9	3633	0.70	2543	0.96	High confidence
AEE-788	WEE1	1E+05	0.63	65158	0.93	High confidence	Afatinib	MAPK11	3884	0.72	2811	0.84	High confidence
AEE-788	SLK	1E+05	0.89	99232	0.93	High confidence	Afatinib	PHKG2	3490	0.97	3384	0.88	High confidence
AEW-541	ATR	5	1.11	5	1.00	Low confidence	Afatinib	ADK	3493	1.12	3493	0.88	High confidence
AEW-541	PKN3	23	1.06	23	0.67	Low confidence	Afatinib	MYLK	37923	0.83	31599	0.76	Low confidence
AEW-541	MAP2K5	167	0.88	146	0.98	High confidence	Alectinib	EPHA1	480	0.40	193	0.80	High confidence
AEW-541	YES1	816	0.41	337	0.72	High confidence	Alectinib	BRD4	200	1.20	200	0.98	Low confidence
AEW-541	RIPK2	1266	0.28	355	0.87	High confidence	Alectinib	OSBPL8	255	1.08	255	0.97	Low confidence
AEW-541	HCK	1201	0.52	623	0.91	High confidence	Alectinib	GAK	461	0.56	259	0.99	High confidence
AEW-541	ADCK3	938	0.89	835	0.95	High confidence	Alectinib	ACOX1	271	1.28	271	0.56	Low confidence
AEW-541	ACVR1	2511	0.48	1202	0.81	High confidence	Alectinib	RET	839	0.44	369	0.96	High confidence
AEW-541	BMPR1B	2349	0.61	1442	0.80	High confidence	Alectinib	CSNK1G2	588	0.88	514	0.81	Low confidence
AEW-541	PTK6	4014	0.48	1939	0.82	High confidence	Alectinib	PHKA1	637	0.97	617	0.96	Low confidence
AEW-541	LYN	4871	0.50	2445	0.89	High confidence	Alectinib	CLK3	1397	1.03	1397	0.66	High confidence
AEW-541	MAP4K5	3351	0.74	2494	0.97	High confidence	Alectinib	PHKG2	1765	0.97	1711	0.93	High confidence
AEW-541	MAP2K1	3326	1.23	3326	0.78	High confidence	Alectinib	CLK2	3586	0.65	2320	0.83	High confidence
AEW-541	SRC	9155	0.39	3555	0.84	High confidence	Alectinib	ACOX3	3919	0.66	2602	0.99	High confidence
AEW-541	STK4	4949	0.76	3774	0.88	High confidence	Alectinib	FER	8899	0.42	3758	0.92	High confidence
AEW-541	LATS1	4926	0.79	3879	0.98	High confidence	Alectinib	CLK1	41764	0.72	29881	0.80	High confidence
AEW-541	INSR	5382	0.75	4041	0.69	High confidence	Alectinib	CAMKK2	53525	0.66	35559	0.93	High confidence
AEW-541	COMT	4103	1.23	4103	0.92	High confidence	Alisertib	AURKA	15	0.35	5	1.00	High confidence
AEW-541	MOB1A	4991	0.91	4564	0.91	High confidence	Alisertib	ACAD10	82	0.96	78	0.95	High confidence
AEW-541	MAP4K2	7754	0.59	4575	0.94	High confidence	Alisertib	GNAI2	201	0.92	184	0.89	Low confidence
AEW-541	MAP2K2	5762	1.17	5762	0.82	High confidence	Alisertib	AURKB	333	0.59	195	0.67	High confidence
AEW-541	RIPK3	7217	0.89	6453	0.70	High confidence	Alisertib	PDPK1	289	1.04	289	0.90	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Alisertib	EPHA2	749	0.41	309	0.97	High confidence
Alisertib	PSMA7	405	1.21	405	0.97	Low confidence
Alisertib	EPHA4	737	0.62	455	0.95	High confidence
Alisertib	MCM4	629	1.29	629	0.98	Low confidence
Alisertib	DNAJA1	962	1.02	962	0.71	High confidence
Alisertib	ABL2	3044	0.33	1009	0.93	High confidence
Alisertib	PLK4	2313	0.51	1178	0.81	High confidence
Alisertib	EPHB4	2556	0.49	1265	0.95	High confidence
Alisertib	TNK1	2936	0.43	1270	0.97	High confidence
Alisertib	RAB10	1348	1.60	1348	0.91	Low confidence
Alisertib	PTK2	3679	0.41	1501	0.94	High confidence
Alisertib	GRB2	3914	0.62	2441	0.66	High confidence
Alisertib	EIF3J	3107	1.11	3107	0.87	High confidence
Alisertib	CSNK2A1	3834	1.02	3834	0.92	High confidence
Alisertib	NDUFA13	3920	1.11	3920	0.90	Low confidence
Alisertib	CSNK2A2	5749	0.96	5535	0.88	High confidence
Alisertib	HCK	30854	0.52	15993	0.96	High confidence
Alisertib	CSNK2B	18334	1.08	18334	0.94	High confidence
Alvocidib	AFF4	2	1.01	2	0.94	High confidence
Alvocidib	AFF1	3	0.93	3	1.00	Low confidence
Alvocidib	CCNT2	4	0.88	3	1.00	High confidence
Alvocidib	CCNT1	5	0.98	5	1.00	High confidence
Alvocidib	CDK17	6	1.02	6	0.98	High confidence
Alvocidib	CDK9	9	0.71	7	0.99	High confidence
Alvocidib	EIF2AK1	63	0.92	58	0.75	Low confidence
Alvocidib	CDK5	204	0.52	107	0.97	High confidence
Alvocidib	CDK12	157	1.12	157	0.94	High confidence
Alvocidib	CCNB1	406	0.77	311	0.98	High confidence
Alvocidib	CCNB2	496	0.70	348	0.91	High confidence
Alvocidib	FIBP	975	0.57	556	0.86	High confidence
Alvocidib	CCNK	580	1.11	580	0.91	High confidence
Alvocidib	CDK7	930	0.73	675	0.95	High confidence
Alvocidib	CIT	738	1.21	738	0.73	High confidence
Alvocidib	GSK3B	1591	0.46	740	0.87	High confidence
Alvocidib	MNAT1	954	0.88	838	0.85	High confidence
Alvocidib	PRKD3	1157	0.74	857	0.93	High confidence
Alvocidib	DYRK1A	975	0.93	910	0.88	High confidence
Alvocidib	ERCC2	1018	0.90	921	0.96	High confidence
Alvocidib	GSK3A	1941	0.50	971	0.93	High confidence
Alvocidib	C2CD5	1819	0.55	992	0.91	High confidence
Alvocidib	CCNH	1367	0.76	1037	0.94	High confidence
Alvocidib	CDK16	1158	0.94	1092	0.84	High confidence
Alvocidib	PRKD2	1997	0.66	1316	0.94	High confidence
Alvocidib	CDK2	2511	0.53	1337	0.83	High confidence
Alvocidib	CAMKK2	2076	0.66	1379	0.96	High confidence
Alvocidib	GSKIP	1744	0.84	1460	0.92	High confidence
Alvocidib	CDK1	2209	0.69	1516	0.96	High confidence
Alvocidib	PRKCD	1681	0.95	1592	0.94	High confidence
Alvocidib	CDK13	1814	1.25	1814	0.82	High confidence
Alvocidib	TBK1	3048	0.64	1949	0.89	High confidence
Alvocidib	DCAF7	2219	0.90	1989	0.83	High confidence
Alvocidib	PYGL	2121	1.08	2121	0.96	High confidence
Alvocidib	RPS6KA1	3111	0.75	2339	0.83	Low confidence
Alvocidib	ADK	2441	1.12	2441	0.82	Low confidence
Alvocidib	TANK	4348	0.64	2766	0.85	High confidence
Alvocidib	PIP4K2C	3137	0.91	2845	0.82	Low confidence
Alvocidib	CSNK2A1	3104	1.02	3104	0.91	High confidence
Alvocidib	TAOK1	4896	0.66	3255	0.78	Low confidence
Alvocidib	CDK6	3976	0.82	3259	0.90	High confidence
Alvocidib	CSNK2B	3320	1.08	3320	0.92	Low confidence
Alvocidib	AZI2	4844	0.70	3400	0.76	High confidence
Alvocidib	TYK2	6652	0.52	3468	0.87	High confidence
Alvocidib	PYGB	3569	1.07	3569	0.90	High confidence
Alvocidib	TBKBP1	4683	0.79	3716	0.93	High confidence
Alvocidib	CAB39	3965	1.12	3965	0.85	Low confidence
Alvocidib	TAOK3	5571	0.77	4310	0.80	Low confidence
Alvocidib	KLHL6	5869	0.74	4348	0.81	Low confidence
Alvocidib	CCNA2	5684	0.86	4899	0.84	High confidence
Alvocidib	CAMK4	5460	1.02	5460	0.86	High confidence
Alvocidib	CSNK2A2	6837	0.96	6582	0.87	High confidence
Alvocidib	CABLES1	15894	0.55	8734	0.79	High confidence
Alvocidib	PKN1	10981	0.87	9598	0.89	High confidence
Alvocidib	EIF3J	11698	1.11	11698	0.85	High confidence
Alvocidib	CDC42BPA	14597	0.96	14020	0.80	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Alvocidib	CDC42BPB	51456	0.97	50005	0.74	High confidence
AMG-208	PRKACG	4	0.51	2	1.00	Low confidence
AMG-208	FAM83B	6	1.06	6	1.00	Low confidence
AMG-208	MET	35	0.80	28	0.99	High confidence
AMG-208	FLNB	232	0.96	223	0.93	Low confidence
AMG-900	AURKA	19	0.35	7	0.98	High confidence
AMG-900	AURKB	34	0.59	20	0.99	High confidence
AMG-900	DDR1	176	0.63	110	0.98	High confidence
AMG-900	FES	345	0.37	127	0.97	High confidence
AMG-900	MAP4K2	315	0.59	186	0.99	High confidence
AMG-900	ULK1	284	0.67	190	0.56	High confidence
AMG-900	DDR2	391	0.76	298	0.92	High confidence
AMG-900	MAPK14	1435	0.51	735	0.97	High confidence
AMG-900	PTCD3	746	1.22	746	0.97	Low confidence
AMG-900	PAG1	2185	0.49	1077	0.98	High confidence
AMG-900	PRKCD	1153	0.95	1092	0.84	High confidence
AMG-900	RET	2586	0.44	1139	0.95	High confidence
AMG-900	MFAP1	1142	1.01	1142	0.87	Low confidence
AMG-900	CLK3	1479	1.03	1479	0.66	High confidence
AMG-900	INPPL1	3391	0.48	1639	0.96	High confidence
AMG-900	IPO7	1690	1.22	1690	0.72	High confidence
AMG-900	MAP4K5	2298	0.74	1710	0.94	High confidence
AMG-900	TAOK3	2283	0.77	1766	0.84	High confidence
AMG-900	CAMK4	1817	1.02	1817	0.87	High confidence
AMG-900	TAOK1	2853	0.66	1896	0.74	High confidence
AMG-900	ABL1	3466	0.55	1899	0.92	High confidence
AMG-900	PRKD3	2582	0.74	1912	0.94	High confidence
AMG-900	MAP3K2	2815	0.70	1966	0.94	High confidence
AMG-900	BCR	4119	0.48	1968	0.84	High confidence
AMG-900	RPS6KA4	3352	0.62	2069	0.90	High confidence
AMG-900	RPS6KA5	3183	0.68	2153	0.71	High confidence
AMG-900	OSBPL3	2636	0.83	2186	0.82	High confidence
AMG-900	CERS2	2248	1.14	2248	0.89	High confidence
AMG-900	CSNK2B	2335	1.08	2335	0.85	High confidence
AMG-900	NEK1	2884	0.83	2381	0.88	High confidence
AMG-900	CLK1	3435	0.72	2458	0.92	High confidence
AMG-900	BRAF	2482	1.11	2482	0.96	High confidence
AMG-900	CDK13	2507	1.25	2507	0.73	Low confidence
AMG-900	DKC1	2524	1.48	2524	0.89	Low confidence
AMG-900	TOP2B	2597	1.20	2597	0.94	Low confidence
AMG-900	GAPVD1	2650	0.99	2636	0.74	Low confidence
AMG-900	MAPKAPK2	3716	0.72	2686	0.89	High confidence
AMG-900	THRAP3	2746	1.08	2746	0.72	Low confidence
AMG-900	MAP3K3	4093	0.67	2747	0.73	High confidence
AMG-900	FAM83B	2774	1.06	2774	0.92	High confidence
AMG-900	MAP3K5	3488	0.80	2792	0.92	High confidence
AMG-900	GRAMD1A	3469	0.85	2955	0.85	High confidence
AMG-900	CDK12	2977	1.12	2977	0.90	Low confidence
AMG-900	STK26	3441	0.88	3023	0.91	High confidence
AMG-900	CLK2	4975	0.65	3218	0.91	High confidence
AMG-900	MAP2K1	3314	1.23	3314	0.93	High confidence
AMG-900	NQO2	3353	1.07	3353	0.90	High confidence
AMG-900	MAP2K2	3488	1.17	3488	0.89	High confidence
AMG-900	Q6ZSR9	4670	0.76	3556	0.68	High confidence
AMG-900	PRKD2	8607	0.66	5673	0.94	High confidence
AMG-900	NCL	33065	1.36	33065	0.93	Low confidence
Amuvatinib	CBR1	2	1.51	2	1.00	Low confidence
Amuvatinib	PYCR2	2	3.55	2	1.00	Low confidence
Apatinib	RET	252	0.44	111	0.99	High confidence
Apatinib	RIPK3	2654	0.89	2373	0.93	High confidence
Apatinib	ZAK	6402	0.74	4760	0.93	High confidence
Apitolisib	JAK1	69	0.37	26	0.89	High confidence
Apitolisib	TEC	1417	0.40	570	0.95	High confidence
Apitolisib	ULK3	1588	0.45	721	0.92	High confidence
Apitolisib	ABL1	1486	0.55	814	0.88	High confidence
Apitolisib	PAK4	1504	0.60	904	0.95	High confidence
Apitolisib	FER	3544	0.42	1497	0.89	High confidence
Apitolisib	BTK	3979	0.39	1555	0.94	High confidence
Apitolisib	PRKCA	2931	0.73	2134	0.94	High confidence
Apitolisib	STK10	2479	0.92	2269	0.94	High confidence
Apitolisib	MAP2K5	4083	0.88	3576	0.68	High confidence
Apitolisib	EGFR	6146	0.79	4874	0.91	High confidence
Apitolisib	SLK	11418	0.89	10170	0.95	High confidence
ARRY-380	MYH14	257	0.73	188	0.78	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
ARRY-380	RIPK3	1191	0.89	1065	0.79	Low confidence	ASP-3026	NQO2	6363	1.07	6363	0.64	High confidence
ARRY-380	NQO2	2463	1.07	2463	0.87	High confidence	ASP-3026	INSR	10530	0.75	7906	0.74	High confidence
ARRY-380	EGFR	3196	0.79	2534	0.92	High confidence	ASP-3026	CAMKK2	13742	0.66	9130	0.84	High confidence
ARRY-380	FECH	3932	0.99	3912	0.95	High confidence	ASP-3026	IGF1R	14691	0.66	9722	0.91	High confidence
ASP-3026	TNK2	11	0.45	5	1.00	High confidence	ASP-3026	ERN1	14972	0.81	12201	0.89	High confidence
ASP-3026	GTPBP4	9	1.25	9	0.90	Low confidence	ASP-3026	EIF3J	12461	1.11	12461	0.58	Low confidence
ASP-3026	TNK1	76	0.43	33	0.94	High confidence	ASP-3026	EGFR	26261	0.79	20827	0.88	High confidence
ASP-3026	PTK6	126	0.48	61	0.99	High confidence	ASP-3026	STK10	25889	0.92	23701	0.98	High confidence
ASP-3026	PLK4	137	0.51	70	1.00	High confidence	ASP-3026	CSNK2B	29018	1.08	29018	0.62	Low confidence
ASP-3026	PTK2	180	0.41	74	0.96	High confidence	ASP-3026	SLK	40765	0.89	36309	0.98	High confidence
ASP-3026	AURKB	171	0.59	100	0.96	High confidence	AT-13148	PKN2	12	0.82	9	0.65	High confidence
ASP-3026	SIK2	237	0.52	123	0.94	High confidence	AT-13148	PRKACB	30	0.47	14	0.73	High confidence
ASP-3026	PTK2B	658	0.41	273	0.95	High confidence	AT-13148	PRKACA	31	0.47	15	0.75	High confidence
ASP-3026	FER	860	0.42	363	0.96	High confidence	AT-13148	PKN1	28	0.87	25	0.73	High confidence
ASP-3026	FRK	1149	0.34	390	0.79	High confidence	AT-13148	ROCK2	30	0.87	26	0.71	High confidence
ASP-3026	BTK	1264	0.39	494	0.91	High confidence	AT-13148	ROCK1	29	0.91	27	0.72	High confidence
ASP-3026	FLT3	1167	0.54	627	0.76	High confidence	AT-13148	LATS1	34	0.79	27	0.75	High confidence
ASP-3026	CAMK2D	3450	0.20	704	0.97	High confidence	AT-13148	PRKCD	46	0.95	44	0.60	High confidence
ASP-3026	YES1	1891	0.41	781	0.78	High confidence	AT-13148	ADRBK1	170	1.13	170	0.77	High confidence
ASP-3026	Q6ZSR9	1079	0.76	822	0.93	High confidence	AT-7519	AFF1	1	0.93	1	0.99	High confidence
ASP-3026	TEC	2545	0.40	1024	0.76	High confidence	AT-7519	PTMA	1	1.55	1	0.97	Low confidence
ASP-3026	FES	3036	0.37	1122	0.84	High confidence	AT-7519	CTTN	3	0.88	3	0.90	Low confidence
ASP-3026	HCK	2405	0.52	1247	0.88	High confidence	AT-7519	CDK9	10	0.71	7	1.00	High confidence
ASP-3026	EPHA2	3032	0.41	1252	0.78	High confidence	AT-7519	CDK17	7	1.02	7	0.74	High confidence
ASP-3026	LCK	2895	0.44	1275	0.79	High confidence	AT-7519	CCNT2	9	0.88	8	0.99	High confidence
ASP-3026	AAK1	1969	0.67	1325	0.95	High confidence	AT-7519	CDK16	8	0.94	8	1.00	High confidence
ASP-3026	CAMK2G	6512	0.22	1414	0.90	High confidence	AT-7519	BRD4	8	2.17	8	0.90	Low confidence
ASP-3026	FYN	3556	0.43	1533	0.83	High confidence	AT-7519	CCNT1	10	0.98	10	1.00	High confidence
ASP-3026	BMPR1B	2969	0.61	1823	0.95	High confidence	AT-7519	CLK3	12	1.03	12	0.57	Low confidence
ASP-3026	PRKD2	4051	0.66	2670	0.94	High confidence	AT-7519	AFF4	22	1.01	22	0.91	High confidence
ASP-3026	GAK	5022	0.56	2820	0.97	High confidence	AT-7519	GSK3A	65	0.50	33	0.99	High confidence
ASP-3026	LIMK1	6690	0.59	3978	0.86	High confidence	AT-7519	CCNE1	67	0.73	49	0.57	High confidence
ASP-3026	DDR1	6440	0.63	4040	0.86	High confidence	AT-7519	GSK3B	125	0.46	58	0.99	High confidence
ASP-3026	PAG1	8921	0.49	4395	0.75	High confidence	AT-7519	CCNK	67	1.11	67	0.97	High confidence
ASP-3026	ABL1	9596	0.55	5258	0.76	High confidence	AT-7519	GEMIN4	73	1.15	73	0.74	Low confidence
ASP-3026	LIMK2	8004	0.66	5306	0.66	High confidence	AT-7519	CCNI	257	0.37	95	0.51	Low confidence
ASP-3026	EPHB3	6280	0.88	5500	0.85	High confidence	AT-7519	CDK4	131	1.00	131	0.66	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
AT-7519	CDK2	318	0.53	169	0.99	High confidence	AT-9283	PLK4	41	0.51	21	1.00	High confidence
AT-7519	CCNE2	227	0.76	173	0.52	Low confidence	AT-9283	BMPR1B	34	0.61	21	0.67	High confidence
AT-7519	CDK13	203	1.25	203	0.97	High confidence	AT-9283	Q6ZSR9	31	0.76	24	0.94	High confidence
AT-7519	CDK12	250	1.12	250	0.83	High confidence	AT-9283	FGFR1	33	0.74	25	0.88	High confidence
AT-7519	MAPK7	325	0.78	253	0.97	High confidence	AT-9283	AP2A1	31	0.92	28	0.90	High confidence
AT-7519	CCNA2	442	0.86	381	0.94	High confidence	AT-9283	SIK2	58	0.52	30	0.99	High confidence
AT-7519	CCNB1	693	0.77	531	0.94	High confidence	AT-9283	CDK16	34	0.94	32	0.85	High confidence
AT-7519	CCNB2	828	0.70	581	0.99	High confidence	AT-9283	PRKAG1	54	0.63	34	0.97	High confidence
AT-7519	TAOK2	1251	0.59	737	0.97	High confidence	AT-9283	BMP2K	52	0.66	34	0.96	High confidence
AT-7519	TAOK1	1404	0.66	933	0.78	High confidence	AT-9283	PRKAB1	63	0.66	42	0.97	High confidence
AT-7519	DYRK1A	1177	0.93	1098	0.91	High confidence	AT-9283	BMPR2	51	0.84	43	0.91	High confidence
AT-7519	DCAF7	1312	0.90	1176	0.96	High confidence	AT-9283	LATS1	57	0.79	45	0.97	High confidence
AT-7519	CDK6	1592	0.82	1305	0.94	High confidence	AT-9283	ULK3	99	0.45	45	0.95	High confidence
AT-7519	CDK1	2049	0.69	1406	0.99	High confidence	AT-9283	MAP2K5	54	0.88	47	0.98	High confidence
AT-7519	CDK5	2794	0.52	1463	0.95	High confidence	AT-9283	PRKAA1	79	0.64	50	0.96	High confidence
AT-7519	FIBP	3490	0.57	1990	0.91	High confidence	AT-9283	KLHL6	72	0.74	53	0.97	High confidence
AT-7519	CABLES1	3967	0.55	2180	0.82	High confidence	AT-9283	AZI2	77	0.70	54	0.97	High confidence
AT-7519	CDK7	5598	0.73	4061	0.92	High confidence	AT-9283	MAP3K11	80	0.70	56	0.93	High confidence
AT-7519	CLK1	6242	0.72	4466	0.75	High confidence	AT-9283	PRKAG2	96	0.64	62	0.93	High confidence
AT-7519	CCNH	6092	0.76	4618	0.97	High confidence	AT-9283	FLT3	119	0.54	64	0.98	High confidence
AT-7519	TAOK3	8267	0.77	6396	0.92	High confidence	AT-9283	CSNK2A2	67	0.96	65	0.98	High confidence
AT-9283	PRKACG	5	0.51	3	0.96	High confidence	AT-9283	RPS6KA4	119	0.62	73	0.96	High confidence
AT-9283	GSK3A	12	0.50	6	0.99	High confidence	AT-9283	EIF3J	77	1.11	77	0.96	High confidence
AT-9283	MET	8	0.80	7	0.85	High confidence	AT-9283	TGFBR1	112	0.69	77	0.94	High confidence
AT-9283	GSK3B	15	0.46	7	1.00	High confidence	AT-9283	ACVR1	163	0.48	78	0.86	High confidence
AT-9283	EPHA7	10	0.79	8	0.99	High confidence	AT-9283	STK10	90	0.92	82	0.94	High confidence
AT-9283	CDK10	9	1.35	9	0.85	Low confidence	AT-9283	CHEK1	102	0.82	84	0.96	High confidence
AT-9283	INCENP	12	0.89	11	1.00	High confidence	AT-9283	PDPK1	88	1.04	88	0.99	High confidence
AT-9283	RET	25	0.44	11	0.98	High confidence	AT-9283	BUB1	94	1.04	94	0.99	High confidence
AT-9283	EPHB6	20	0.61	12	1.00	High confidence	AT-9283	TBK1	160	0.64	102	0.95	High confidence
AT-9283	ACVRL1	15	1.23	15	0.97	High confidence	AT-9283	CSNK2B	103	1.08	103	0.95	High confidence
AT-9283	AURKA	44	0.35	16	1.00	High confidence	AT-9283	MOB1A	113	0.91	103	0.93	High confidence
AT-9283	RPS6KA6	38	0.42	16	0.98	High confidence	AT-9283	CSNK2A1	106	1.02	106	0.98	High confidence
AT-9283	AURKB	28	0.59	17	0.99	High confidence	AT-9283	RPS6KA3	148	0.72	108	0.96	High confidence
AT-9283	PRKAB2	28	0.60	17	0.94	High confidence	AT-9283	MAP4K4	108	1.01	108	0.96	High confidence
AT-9283	AAK1	26	0.67	17	0.99	High confidence	AT-9283	PAK4	183	0.60	110	0.97	High confidence
AT-9283	AP2B1	20	1.01	20	0.94	High confidence	AT-9283	SYK	138	0.84	116	0.96	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
AT-9283	RPS6KB1	132	0.89	117	0.99	High confidence	AT-9283	TNIK	801	1.02	801	0.91	High confidence
AT-9283	TANK	194	0.64	124	0.93	High confidence	AT-9283	ACVR1B	1907	0.43	811	0.93	High confidence
AT-9283	MYLK3	149	0.87	129	0.95	High confidence	AT-9283	LCK	2020	0.44	890	0.84	High confidence
AT-9283	TEC	335	0.40	135	0.95	High confidence	AT-9283	PRKACB	1961	0.47	927	0.90	High confidence
AT-9283	CDK6	171	0.82	140	0.84	High confidence	AT-9283	DCAF7	1094	0.90	980	0.88	High confidence
AT-9283	ACAD10	150	0.96	144	0.59	Low confidence	AT-9283	PRKX	1228	0.81	998	0.91	High confidence
AT-9283	BCR	326	0.48	156	0.95	High confidence	AT-9283	CABLES1	1857	0.55	1021	0.73	High confidence
AT-9283	MAPK8	243	0.65	157	0.92	High confidence	AT-9283	GRB2	1671	0.62	1043	0.88	High confidence
AT-9283	PTK6	389	0.48	188	0.86	High confidence	AT-9283	ABL2	3265	0.33	1082	0.92	High confidence
AT-9283	PAK6	286	0.74	213	0.74	High confidence	AT-9283	INPPL1	2276	0.48	1100	0.61	High confidence
AT-9283	MAP4K1	295	0.73	214	0.88	High confidence	AT-9283	CDK17	1148	1.02	1148	0.91	High confidence
AT-9283	IKBKE	347	0.62	215	0.91	High confidence	AT-9283	RPS6KA5	1847	0.68	1249	0.69	High confidence
AT-9283	FAM58A	318	0.72	230	0.89	High confidence	AT-9283	STK16	1779	0.72	1281	0.90	High confidence
AT-9283	CCNT2	264	0.88	233	0.83	High confidence	AT-9283	CDK4	1287	1.00	1287	0.95	High confidence
AT-9283	PRKD2	370	0.66	244	0.89	High confidence	AT-9283	AFF1	1461	0.93	1354	0.70	High confidence
AT-9283	MAP3K2	397	0.70	277	0.95	High confidence	AT-9283	MARK2	1810	0.75	1364	0.90	High confidence
AT-9283	TYK2	534	0.52	279	0.91	High confidence	AT-9283	MARK3	1777	0.77	1370	0.88	High confidence
AT-9283	FER	726	0.42	307	0.93	High confidence	AT-9283	TGFBR2	1840	0.75	1384	0.86	High confidence
AT-9283	ABL1	574	0.55	315	0.92	High confidence	AT-9283	CDK5	2645	0.52	1385	0.85	High confidence
AT-9283	MAP3K3	514	0.67	345	0.95	High confidence	AT-9283	MAP3K1	2424	0.58	1399	0.85	High confidence
AT-9283	MAPK10	425	0.84	358	0.87	High confidence	AT-9283	LYN	2828	0.50	1420	0.85	High confidence
AT-9283	JAK1	988	0.37	368	0.91	High confidence	AT-9283	EPHA2	3460	0.41	1429	0.75	High confidence
AT-9283	TBKBP1	487	0.79	386	0.91	High confidence	AT-9283	CSK	2737	0.54	1473	0.84	High confidence
AT-9283	BMPR1A	735	0.53	388	0.90	High confidence	AT-9283	NEK9	3472	0.44	1532	0.82	High confidence
AT-9283	SLK	451	0.89	402	0.91	High confidence	AT-9283	FGR	3663	0.42	1537	0.94	High confidence
AT-9283	RPS6KA1	627	0.75	471	0.90	High confidence	AT-9283	PRKCA	2119	0.73	1543	0.86	High confidence
AT-9283	MAPK9	727	0.70	509	0.82	High confidence	AT-9283	C2CD5	2876	0.55	1568	0.82	High confidence
AT-9283	CDC7	555	0.92	511	0.87	Low confidence	AT-9283	GAK	2867	0.56	1610	0.83	High confidence
AT-9283	FYN	1187	0.43	511	0.93	High confidence	AT-9283	CDK9	2305	0.71	1640	0.91	High confidence
AT-9283	PRKD3	718	0.74	532	0.92	High confidence	AT-9283	LIMK1	2845	0.59	1692	0.91	High confidence
AT-9283	BTK	1374	0.39	537	0.94	High confidence	AT-9283	FIBP	3049	0.57	1739	0.87	Low confidence
AT-9283	ADCK1	898	0.62	559	0.88	High confidence	AT-9283	MELK	2031	0.88	1795	0.99	High confidence
AT-9283	YES1	1390	0.41	574	0.94	High confidence	AT-9283	CCNT1	1944	0.98	1911	0.85	High confidence
AT-9283	MAPKAPK5	634	0.93	589	0.84	High confidence	AT-9283	DYNLL2	3585	0.55	1959	0.77	Low confidence
AT-9283	SRC	1524	0.39	592	0.88	High confidence	AT-9283	CLK1	2858	0.72	2045	0.84	High confidence
AT-9283	U2AF1	794	0.83	658	0.91	High confidence	AT-9283	NEK3	2404	0.85	2055	0.82	High confidence
AT-9283	HCK	1281	0.52	664	0.90	High confidence	AT-9283	MAP4K5	2979	0.74	2217	0.79	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
AT-9283	TAOK1	3337	0.66	2219	0.88	High confidence	Axitinib	AAK1	3208	0.67	2159	0.96	High confidence
AT-9283	DYRK1A	2622	0.93	2447	0.76	High confidence	Axitinib	BMP2K	3364	0.66	2223	0.96	High confidence
AT-9283	AFF4	2661	1.01	2661	0.89	High confidence	Axitinib	Q6ZSR9	3019	0.76	2299	0.98	High confidence
AT-9283	PKN2	3391	0.82	2767	0.80	High confidence	Axitinib	STK10	2964	0.92	2713	0.93	High confidence
AT-9283	PKN1	3533	0.87	3088	0.76	High confidence	Axitinib	MAP4K5	3675	0.74	2735	0.92	High confidence
AT-9283	PRKACA	6788	0.47	3191	0.83	High confidence	Axitinib	MYLK3	4486	0.87	3904	0.88	High confidence
AT-9283	PRKCB	4235	0.80	3380	0.79	High confidence	Axitinib	ZAK	6206	0.74	4615	0.97	High confidence
AT-9283	MAP2K6	3545	1.01	3545	0.64	High confidence	Axitinib	SLK	6692	0.89	5960	0.91	High confidence
AT-9283	SIK3	5018	0.82	4108	0.84	High confidence	Axitinib	FECH	6875	0.99	6840	0.92	High confidence
AT-9283	LIMK2	6686	0.66	4432	0.83	High confidence	AXL-1717	TOP2A	505	0.96	486	0.75	Low confidence
AT-9283	DYNLL1	25433	0.50	12740	0.56	Low confidence	AZD-1208	PIM1	3	0.43	1	0.98	High confidence
AT-9283	GRK6	13552	1.03	13552	0.60	Low confidence	AZD-1208	PTPN1	4	1.08	4	1.00	Low confidence
AT-9283	MAP3K5	28947	0.80	23168	0.68	High confidence	AZD-1208	CSNK2A2	3134	0.96	3017	0.74	High confidence
AT-9283	EPHA4	71266	0.62	43942	0.67	High confidence	AZD-1208	EIF3J	3086	1.11	3086	0.57	Low confidence
AV-412	EGFR	12	0.79	10	0.98	High confidence	AZD-1208	CSNK2A1	3505	1.02	3505	0.82	High confidence
AV-412	BTK	882	0.39	345	0.89	High confidence	AZD-1208	CSNK2B	5990	1.08	5990	0.73	High confidence
AV-412	TEC	1048	0.40	422	0.83	High confidence	AZD-1480	COG1	57	1.12	57	0.90	Low confidence
AV-412	YES1	15169	0.41	6267	0.42	High confidence	AZD-1480	PTK2	469	0.41	191	0.89	High confidence
AV-412	MAP3K1	13791	0.58	7960	0.89	High confidence	AZD-1480	RET	540	0.44	238	0.96	High confidence
AV-412	SLK	15063	0.89	13417	0.75	High confidence	AZD-1480	AURKA	865	0.35	306	0.97	High confidence
AV-412	STK10	31288	0.92	28643	0.81	High confidence	AZD-1480	PLK4	605	0.51	308	0.90	High confidence
Axitinib	INPPL1	46	0.48	22	0.63	High confidence	AZD-1480	STRADA	316	1.02	316	0.71	Low confidence
Axitinib	RET	239	0.44	105	0.93	High confidence	AZD-1480	RASSF5	384	0.98	377	0.96	High confidence
Axitinib	BCR	394	0.48	188	0.95	High confidence	AZD-1480	SAV1	461	0.87	399	0.85	High confidence
Axitinib	AURKB	403	0.59	236	0.97	High confidence	AZD-1480	TNK2	1144	0.45	515	0.87	High confidence
Axitinib	FGFR1	363	0.74	268	0.96	High confidence	AZD-1480	FER	1225	0.42	517	0.87	High confidence
Axitinib	AURKA	1056	0.35	374	0.95	High confidence	AZD-1480	SLK	770	0.89	686	0.91	High confidence
Axitinib	PDGFRB	462	0.87	404	0.94	High confidence	AZD-1480	STK11	847	0.84	714	0.48	Low confidence
Axitinib	INCENP	542	0.89	484	0.91	High confidence	AZD-1480	STK10	795	0.92	728	0.98	High confidence
Axitinib	FGR	1531	0.42	642	0.98	High confidence	AZD-1480	FGFR1	1055	0.74	777	0.91	High confidence
Axitinib	PLK4	1417	0.51	721	0.95	High confidence	AZD-1480	STK3	1126	0.76	860	0.88	High confidence
Axitinib	ABL1	1653	0.55	906	0.94	High confidence	AZD-1480	STK4	1130	0.76	861	0.93	High confidence
Axitinib	ABL2	3137	0.33	1039	0.94	High confidence	AZD-1480	CDK3	942	2.15	942	0.86	Low confidence
Axitinib	TNIK	1770	1.02	1770	0.59	High confidence	AZD-1480	INCENP	1315	0.89	1174	0.75	Low confidence
Axitinib	MAP4K4	1812	1.01	1812	0.94	High confidence	AZD-1480	TNK1	2923	0.43	1264	0.93	High confidence
Axitinib	TNK1	4322	0.43	1870	0.67	Low confidence	AZD-1480	AURKB	2663	0.59	1559	0.84	High confidence
Axitinib	AP2A1	2282	0.92	2096	0.90	High confidence	AZD-1480	FLT3	3135	0.54	1685	0.77	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
AZD-1480	PTK2B	4544	0.41	1884	0.76	High confidence	AZD-5363	LIMK2	719	0.66	477	0.99	High confidence
AZD-1480	PAK4	3136	0.60	1884	0.90	High confidence	AZD-5363	CLK4	608	0.85	513	0.79	High confidence
AZD-1480	CSNK2B	3485	1.08	3485	0.83	High confidence	AZD-5363	ROCK1	776	0.91	706	0.97	High confidence
AZD-1480	CSNK2A2	4109	0.96	3956	0.86	High confidence	AZD-5363	FGFR1	1174	0.74	865	0.83	Low confidence
AZD-1480	EIF3J	4059	1.11	4059	0.83	High confidence	AZD-5363	PRKX	1082	0.81	879	0.97	High confidence
AZD-1480	CSNK2A1	4868	1.02	4868	0.91	High confidence	AZD-5363	PRKAB2	1517	0.60	912	0.61	High confidence
AZD-2014	ETF1	15	1.25	15	0.52	Low confidence	AZD-5363	RET	2513	0.44	1107	0.96	High confidence
AZD-2014	FAH	58	1.15	58	0.92	Low confidence	AZD-5363	PKN1	1804	0.87	1577	0.95	High confidence
AZD-2014	PFKP	983	1.39	983	0.81	High confidence	AZD-5363	PRKCA	2380	0.73	1733	0.94	High confidence
AZD-4547	FGFR1	2	0.74	2	0.98	High confidence	AZD-5363	PRKAA1	2855	0.64	1821	0.93	High confidence
AZD-4547	MAP4K5	8	0.74	6	0.99	High confidence	AZD-5363	MAP4K3	2898	0.66	1900	0.89	High confidence
AZD-4547	PHKA1	12	0.97	12	1.00	Low confidence	AZD-5363	MAP3K11	2870	0.70	1999	0.90	High confidence
AZD-4547	RET	67	0.44	29	0.98	High confidence	AZD-5363	PRKAB1	3101	0.66	2053	0.65	High confidence
AZD-4547	MAP4K3	75	0.66	49	0.90	High confidence	AZD-5363	PRKD3	2982	0.74	2207	0.87	High confidence
AZD-4547	DDR1	90	0.63	56	0.89	High confidence	AZD-5363	PRKD2	3407	0.66	2246	0.94	High confidence
AZD-4547	MAP4K2	187	0.59	110	0.98	High confidence	AZD-5363	PRKCB	3047	0.80	2431	0.92	High confidence
AZD-4547	TNK2	330	0.45	148	0.89	Low confidence	AZD-5363	PRKAG1	3863	0.63	2445	0.68	High confidence
AZD-4547	EIF2AK1	184	0.92	170	0.86	High confidence	AZD-5363	AKT2	2906	0.86	2490	0.80	High confidence
AZD-4547	SGTA	268	0.96	256	0.83	Low confidence	AZD-5363	PRKAG2	4204	0.64	2711	0.90	High confidence
AZD-4547	PDGFRB	329	0.87	288	0.88	High confidence	AZD-5363	PRKCD	2966	0.95	2809	0.87	High confidence
AZD-4547	MAP4K1	487	0.73	354	0.94	High confidence	AZD-5363	AKT1	4317	0.90	3883	0.75	High confidence
AZD-4547	TNIK	1387	1.02	1387	0.55	Low confidence	AZD-5363	PRKCQ	4246	1.23	4246	0.94	High confidence
AZD-4547	INCENP	1858	0.89	1659	0.90	High confidence	AZD-5363	ADRBK1	4859	1.13	4859	0.94	High confidence
AZD-4547	AURKB	2857	0.59	1672	0.91	Low confidence	AZD-5363	LATS1	17908	0.79	14103	0.95	High confidence
AZD-4547	NTRK1	3191	0.71	2252	0.92	Low confidence	AZD-5438	CCNT1	1	0.98	1	0.93	High confidence
AZD-4547	MARK2	6584	0.75	4960	0.98	High confidence	AZD-5438	GSK3A	111	0.50	55	0.86	High confidence
AZD-4547	STK26	5689	0.88	4996	0.91	High confidence	AZD-5438	GSK3B	133	0.46	62	0.88	High confidence
AZD-4547	MARK3	11705	0.77	9024	0.94	High confidence	AZD-5438	AAK1	339	0.67	228	0.85	High confidence
AZD-4547	ZAK	12829	0.74	9540	0.89	High confidence	AZD-5438	C2CD5	502	0.55	274	0.97	High confidence
AZD-4547	DDR2	16926	0.76	12899	0.97	High confidence	AZD-5438	CDK9	450	0.71	320	0.75	High confidence
AZD-4547	MAP3K11	37327	0.70	25999	0.86	Low confidence	AZD-5438	CDK5	1197	0.52	627	0.76	High confidence
AZD-5363	PRKACB	506	0.47	239	0.82	High confidence	AZD-5438	FIBP	1131	0.57	645	0.63	High confidence
AZD-5363	PRKG1	586	0.51	297	0.96	High confidence	AZD-5438	CDK2	1355	0.53	721	0.78	High confidence
AZD-5363	ROCK2	372	0.87	324	0.99	High confidence	AZD-5438	IRAK3	1797	0.43	771	0.75	High confidence
AZD-5363	LIMK1	600	0.59	357	0.97	High confidence	AZD-5438	BMP2K	1250	0.66	826	0.89	High confidence
AZD-5363	PRKACA	822	0.47	387	0.92	High confidence	AZD-5438	CSNK1D	1421	0.82	1169	0.72	High confidence
AZD-5363	CLK1	664	0.72	475	0.96	Low confidence	AZD-5438	EIF3J	1179	1.11	1179	0.90	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
AZD-5438	CSNK2A1	1527	1.02	1527	0.82	High confidence	AZD-7762	PAK4	276	0.60	166	0.95	High confidence
AZD-5438	MAPK8	2586	0.65	1676	0.40	High confidence	AZD-7762	GRB2	286	0.62	178	0.85	High confidence
AZD-5438	CSNK2A2	1955	0.96	1882	0.85	High confidence	AZD-7762	BMP2K	275	0.66	181	0.74	High confidence
AZD-5438	MAPK9	2712	0.70	1898	0.72	High confidence	AZD-7762	MAP4K5	265	0.74	197	0.83	High confidence
AZD-5438	CDK1	2903	0.69	1992	0.46	Low confidence	AZD-7762	GAK	359	0.56	202	0.82	High confidence
AZD-5438	PRKD2	3511	0.66	2314	0.90	High confidence	AZD-7762	ACVR2B	379	0.67	253	0.98	High confidence
AZD-5438	CDK7	3215	0.73	2332	0.66	High confidence	AZD-7762	FYN	658	0.43	284	0.95	High confidence
AZD-5438	CSNK2B	2345	1.08	2345	0.77	High confidence	AZD-7762	IRAK4	393	0.77	304	0.97	High confidence
AZD-5438	CSNK1A1	3506	0.92	3238	0.42	High confidence	AZD-7762	CSK	582	0.54	313	0.94	High confidence
AZD-5438	YWHAG	3470	0.98	3412	0.74	Low confidence	AZD-7762	FES	862	0.37	319	0.84	High confidence
AZD-5438	PRKD3	5E+13	0.74	4E+13	0.91	High confidence	AZD-7762	MARK3	416	0.77	321	0.91	High confidence
AZD-6482	PGD	151	1.53	151	0.49	Low confidence	AZD-7762	STK10	393	0.92	360	0.94	High confidence
AZD-6482	DDX6	4103	1.12	4103	0.80	Low confidence	AZD-7762	MAP4K3	554	0.66	363	0.85	High confidence
AZD-7762	ERLIN2	3	1.07	3	0.89	Low confidence	AZD-7762	PRKAB2	640	0.60	385	0.93	High confidence
AZD-7762	CHEK1	6	0.82	5	0.89	High confidence	AZD-7762	PAG1	806	0.49	397	0.89	High confidence
AZD-7762	SIK2	13	0.52	7	1.00	High confidence	AZD-7762	PRKX	506	0.81	411	0.96	High confidence
AZD-7762	INPPL1	28	0.48	13	0.66	High confidence	AZD-7762	YES1	1052	0.41	435	0.79	High confidence
AZD-7762	RET	53	0.44	23	0.95	High confidence	AZD-7762	MARK2	587	0.75	442	0.95	High confidence
AZD-7762	MAP4K4	35	1.01	35	0.92	High confidence	AZD-7762	MARK4	571	0.83	475	0.83	High confidence
AZD-7762	SIK3	53	0.82	43	0.99	High confidence	AZD-7762	LYN	957	0.50	480	0.94	High confidence
AZD-7762	MAP4K2	85	0.59	50	0.91	High confidence	AZD-7762	PDGFRB	632	0.87	552	0.83	High confidence
AZD-7762	STK4	74	0.76	56	0.94	High confidence	AZD-7762	AP2M1	554	1.03	554	0.96	Low confidence
AZD-7762	AAK1	108	0.67	73	0.87	High confidence	AZD-7762	PDCD10	581	1.07	581	0.60	High confidence
AZD-7762	MAP3K11	117	0.70	81	0.99	High confidence	AZD-7762	PRKAG1	928	0.63	587	0.92	High confidence
AZD-7762	MAP4K1	114	0.73	83	0.74	Low confidence	AZD-7762	PTK2B	1467	0.41	608	0.85	High confidence
AZD-7762	FER	200	0.42	85	0.94	High confidence	AZD-7762	ABL1	1113	0.55	610	0.91	High confidence
AZD-7762	BCR	177	0.48	85	0.98	High confidence	AZD-7762	PRKAB1	1000	0.66	662	0.92	High confidence
AZD-7762	STK3	111	0.76	85	0.95	High confidence	AZD-7762	AURKB	1221	0.59	715	0.78	High confidence
AZD-7762	TNIK	94	1.02	94	0.80	High confidence	AZD-7762	PLK4	1419	0.51	722	0.69	High confidence
AZD-7762	HCK	199	0.52	103	0.96	High confidence	AZD-7762	PRKAA1	1195	0.64	762	0.96	High confidence
AZD-7762	SRC	280	0.39	109	0.97	High confidence	AZD-7762	EGFR	1019	0.79	808	0.69	High confidence
AZD-7762	PDPK1	111	1.04	111	0.87	High confidence	AZD-7762	RPS6KA4	1424	0.62	879	0.94	High confidence
AZD-7762	RASSF5	116	0.98	114	0.96	High confidence	AZD-7762	PRKAG2	1388	0.64	895	0.90	High confidence
AZD-7762	ULK1	173	0.67	115	0.98	High confidence	AZD-7762	ABL2	2713	0.33	899	0.82	High confidence
AZD-7762	Q6ZSR9	158	0.76	120	0.87	High confidence	AZD-7762	PRKCD	980	0.95	928	0.74	Low confidence
AZD-7762	CDK3	139	2.15	139	0.97	High confidence	AZD-7762	PTK2	2322	0.41	948	0.84	High confidence
AZD-7762	MAP2K5	168	0.88	147	0.92	High confidence	AZD-7762	DCAF7	1147	0.90	1028	0.87	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
AZD-7762	TNK2	2424	0.45	1091	0.88	High confidence	Bafetinib	BCR	30	0.48	15	0.84	High confidence
AZD-7762	SLK	1228	0.89	1093	0.89	High confidence	Bafetinib	GRB2	30	0.62	18	0.97	High confidence
AZD-7762	PRKD2	1761	0.66	1161	0.67	High confidence	Bafetinib	MAPKAPK3	28	0.83	23	0.98	High confidence
AZD-7762	FRK	3555	0.34	1207	0.82	High confidence	Bafetinib	ABL1	48	0.55	26	0.90	High confidence
AZD-7762	MAP2K2	1217	1.17	1217	0.79	High confidence	Bafetinib	DDR2	63	0.76	48	0.99	High confidence
AZD-7762	LCK	2941	0.44	1295	0.82	High confidence	Bafetinib	ZAK	88	0.74	65	0.99	High confidence
AZD-7762	PTK6	2832	0.48	1368	0.83	High confidence	Bafetinib	EPHA2	218	0.41	90	0.95	High confidence
AZD-7762	SYK	1770	0.84	1484	0.97	High confidence	Bafetinib	LYN	475	0.50	239	0.99	High confidence
AZD-7762	RPS6KA6	3587	0.42	1513	0.91	High confidence	Bafetinib	LCK	667	0.44	294	1.00	High confidence
AZD-7762	DYRK1A	1801	0.93	1680	0.84	High confidence	Bafetinib	MAPKAPK2	421	0.72	304	0.96	High confidence
AZD-7762	ULK3	3940	0.45	1789	0.84	High confidence	Bafetinib	EPHA5	577	0.60	345	0.74	Low confidence
AZD-7762	MAP2K1	2039	1.23	2039	0.90	High confidence	Bafetinib	FRK	1259	0.34	428	0.97	High confidence
AZD-7762	PRKD3	2885	0.74	2136	0.83	High confidence	Bafetinib	RIPK3	566	0.89	506	0.97	High confidence
AZD-7762	PKN1	2471	0.87	2159	0.85	High confidence	Bafetinib	MAPK14	1047	0.51	536	0.98	High confidence
AZD-7762	KLHL6	3207	0.74	2375	0.97	Low confidence	Bafetinib	BRAF	1135	1.11	1135	0.99	High confidence
AZD-7762	TEC	6485	0.40	2609	0.85	High confidence	Bafetinib	MYLK	1451	0.83	1209	0.73	Low confidence
AZD-7762	CSNK2A1	2985	1.02	2985	0.80	High confidence	Bafetinib	EPHB4	2626	0.49	1299	0.96	High confidence
AZD-7762	BTK	7843	0.39	3066	0.85	High confidence	Bafetinib	FYN	3351	0.43	1444	0.97	High confidence
AZD-7762	PKN2	3793	0.82	3095	0.71	High confidence	Bafetinib	RIPK2	5236	0.28	1469	0.96	High confidence
AZD-7762	CSNK2A2	3276	0.96	3153	0.89	High confidence	Bafetinib	MAPK11	2381	0.72	1723	0.59	Low confidence
AZD-7762	MYLK3	4191	0.87	3647	0.76	Low confidence	Bafetinib	CDC23	1925	1.01	1925	0.73	Low confidence
AZD-7762	JAK2	4609	0.80	3678	0.83	High confidence	Bafetinib	EPHA4	3212	0.62	1980	0.81	High confidence
AZD-7762	EIF3J	3768	1.11	3768	0.82	High confidence	Bafetinib	IRAK1	3374	0.61	2059	0.87	Low confidence
AZD-7762	MELK	5129	0.88	4533	0.81	High confidence	Bafetinib	CSK	4002	0.54	2154	0.86	High confidence
AZD-7762	CSNK2B	4829	1.08	4829	0.85	High confidence	Bafetinib	RET	5483	0.44	2416	0.90	High confidence
AZD-8055	CNOT2	33	1.38	33	0.95	Low confidence	Bafetinib	ARAF	4644	0.62	2893	0.90	High confidence
AZD-8055	FECH	6931	0.99	6896	0.96	High confidence	Bafetinib	PDGFRB	3584	0.87	3132	0.87	High confidence
AZD-8186	NPM1	482	1.31	482	0.88	High confidence	Bafetinib	EPHB3	5190	0.88	4546	0.97	High confidence
AZD-8186	TOP2B	936	1.20	936	0.85	High confidence	Bafetinib	PIP4K2C	6818	0.91	6185	0.86	Low confidence
AZD-8186	ERN2	1915	0.78	1500	0.80	Low confidence	Bafetinib	NQO2	6869	1.07	6869	0.85	Low confidence
AZD-8330	MAP2K2	15	1.17	15	0.99	High confidence	Bafetinib	MAP2K5	13008	0.88	11392	0.85	High confidence
AZD-8330	MAP2K1	24	1.23	24	0.92	High confidence	Bafetinib	EPHB2	1E+05	0.52	53198	0.99	High confidence
AZD-8330	EIF2AK1	1976	0.92	1821	0.95	Low confidence	Barasertib	RAB6A	33	1.62	33	0.87	Low confidence
AZD-8330	MAP2K5	3034	0.88	2657	0.80	High confidence	Barasertib	AURKA	138	0.35	49	0.92	High confidence
Bafetinib	ABL2	30	0.33	10	0.92	High confidence	Barasertib	MAP2K5	93	0.88	82	0.79	High confidence
Bafetinib	INPPL1	28	0.48	14	0.99	High confidence	Barasertib	RET	475	0.44	209	0.92	High confidence
Bafetinib	DDR1	23	0.63	14	0.99	High confidence	Barasertib	FLT3	478	0.54	257	0.67	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Barasertib	MST1R	1858	0.76	1416	0.81	High confidence
Barasertib	DYRK1A	1821	0.93	1699	0.93	Low confidence
Barasertib	EGFR	2187	0.79	1734	0.82	High confidence
Barasertib	RIPK2	6591	0.28	1850	0.84	High confidence
Barasertib	CSNK2A2	2022	0.96	1947	0.66	Low confidence
Barasertib	CSNK2B	2044	1.08	2044	0.73	Low confidence
Barasertib	CSNK2A1	2071	1.02	2071	0.75	Low confidence
Barasertib	EIF3J	2094	1.11	2094	0.61	Low confidence
Barasertib	MAP4K5	3005	0.74	2236	0.91	High confidence
Barasertib	PDGFRB	3080	0.87	2692	0.90	High confidence
Barasertib	HCK	5568	0.52	2886	0.89	High confidence
Barasertib	LYN	7239	0.50	3633	0.95	High confidence
Barasertib_HQPA	AURKB	4	0.59	2	1.00	High confidence
Barasertib_HQPA	FLT3	237	0.54	127	0.95	High confidence
Barasertib_HQPA	AURKA	806	0.35	285	0.93	High confidence
Barasertib_HQPA	MAP2K5	462	0.88	405	0.97	High confidence
Barasertib_HQPA	PTK6	1130	0.48	546	0.95	High confidence
Barasertib_HQPA	MAP4K5	1210	0.74	900	0.98	High confidence
Barasertib_HQPA	RET	2902	0.44	1278	0.95	High confidence
Barasertib_HQPA	CSNK2A2	2303	0.96	2217	0.89	High confidence
Barasertib_HQPA	EGFR	2844	0.79	2255	0.78	High confidence
Barasertib_HQPA	KLHL6	3149	0.74	2333	0.81	Low confidence
Barasertib_HQPA	MST1R	3291	0.76	2508	0.81	High confidence
Barasertib_HQPA	LCK	6112	0.44	2692	0.89	High confidence
Barasertib_HQPA	EIF3J	2909	1.11	2909	0.81	High confidence
Barasertib_HQPA	CSNK2B	3170	1.08	3170	0.78	High confidence
Barasertib_HQPA	CSNK2A1	3747	1.02	3747	0.92	High confidence
Barasertib_HQPA	EIF2AK1	4695	0.92	4326	0.81	Low confidence
Baricitinib	EWSR1	19	1.65	19	0.97	Low confidence
Baricitinib	AP2A2	32	0.94	30	0.83	High confidence
Baricitinib	AAK1	69	0.67	46	0.97	High confidence
Baricitinib	PPP4R2	56	1.14	56	0.94	Low confidence
Baricitinib	DNAJB11	56	1.59	56	0.87	Low confidence
Baricitinib	Q6ZSR9	103	0.76	78	0.94	High confidence
Baricitinib	9-Sep	84	1.43	84	0.85	Low confidence
Baricitinib	AP2A1	103	0.92	95	0.96	High confidence
Baricitinib	PKN1	119	0.87	104	0.92	High confidence
Baricitinib	MARK3	135	0.77	104	0.95	High confidence
Baricitinib	MARK2	166	0.75	125	0.98	High confidence
Baricitinib	PIP4K2A	145	0.87	126	0.81	High confidence
Baricitinib	AP2B1	153	1.01	153	0.90	High confidence
Baricitinib	KLHL6	267	0.74	198	0.95	Low confidence
Baricitinib	BMP2K	327	0.66	216	0.99	High confidence
Baricitinib	CAMK2G	1118	0.22	243	0.98	High confidence
Baricitinib	CSNK1G2	302	0.88	265	0.98	Low confidence
Baricitinib	PKN2	330	0.82	269	0.96	High confidence
Baricitinib	CAMK2D	1530	0.20	312	0.98	High confidence
Baricitinib	EIF2AK1	364	0.92	335	0.96	High confidence
Baricitinib	ROCK1	530	0.91	482	0.97	High confidence
Baricitinib	TNK1	1437	0.43	622	0.88	Low confidence
Baricitinib	ROCK2	867	0.87	756	0.96	High confidence
Baricitinib	CLK1	1087	0.72	778	0.50	Low confidence
Baricitinib	ULK1	1213	0.67	810	0.85	High confidence
Baricitinib	RET	2209	0.44	973	0.79	High confidence
Baricitinib	PRKCD	1135	0.95	1075	0.81	High confidence
Baricitinib	CSNK1G1	2026	0.87	1753	0.88	Low confidence
Baricitinib	MAP3K1	3277	0.58	1891	0.77	High confidence
Baricitinib	PRKCA	2844	0.73	2071	0.91	High confidence
Baricitinib	CSNK2B	2521	1.08	2521	0.81	High confidence
Baricitinib	PDPK1	3315	1.04	3315	0.98	High confidence
Baricitinib	PRKACA	7651	0.47	3597	0.93	High confidence
Baricitinib	CIT	4361	1.21	4361	0.92	High confidence
Baricitinib	GAK	8658	0.56	4862	0.90	High confidence
Baricitinib	PRKCB	32991	0.80	26324	0.90	High confidence
BGT-226	GLO1	0.38	1.27	0.38	0.99	Low confidence
BGT-226	SNAP29	3	1.11	3	1.00	Low confidence
BGT-226	CLK1	344	0.72	246	0.98	High confidence
BGT-226	TPRKB	762	0.95	721	0.81	High confidence
BGT-226	OSGEP	758	0.96	727	0.71	High confidence
BGT-226	DYRK1A	988	0.93	922	0.91	High confidence
BGT-226	TP53RK	1009	1.05	1009	0.84	High confidence
BGT-226	MYLK3	1270	0.87	1105	0.90	High confidence
BGT-226	DCAF7	1609	0.90	1442	0.85	High confidence
BGT-226	LAGE3	1856	0.95	1764	0.76	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
BGT-226	FECH	3124	0.99	3108	0.66	High confidence
BGT-226	GSK3A	6802	0.50	3403	0.73	High confidence
BGT-226	MELK	4617	0.88	4081	0.81	High confidence
BGT-226	PIP4K2C	5285	0.91	4795	0.75	High confidence
BGT-226	CSNK2B	5237	1.08	5237	0.57	High confidence
BGT-226	CAPZA1	5559	0.98	5446	0.60	Low confidence
BGT-226	CSNK2A1	7667	1.02	7667	0.66	High confidence
BGT-226	CSNK2A2	8815	0.96	8487	0.86	High confidence
BI-2536	EIF3M	11	1.29	11	0.99	Low confidence
BI-2536	CAMKK2	388	0.66	258	0.98	High confidence
BI-2536	PDXK	387	1.43	387	0.98	High confidence
BI-2536	PTK2	1072	0.41	437	0.98	High confidence
BI-2536	ADK	1163	1.12	1163	0.90	Low confidence
BI-2536	PRKD2	2942	0.66	1939	0.94	High confidence
BI-2536	PHKG2	2163	0.97	2097	0.78	High confidence
BI-2536	PIP4K2C	2690	0.91	2440	0.81	High confidence
BI-2536	FECH	3820	0.99	3801	0.86	High confidence
BI-2536	GAK	8577	0.56	4816	0.89	High confidence
BI-2536	CSNK1E	8435	0.85	7211	0.78	High confidence
BI-847325	MDH1	3	1.39	3	1.00	Low confidence
BI-847325	CDKL5	23	0.89	20	0.86	High confidence
BI-847325	RNPEP	26	1.20	26	0.94	Low confidence
BI-847325	AURKA	167	0.35	59	1.00	High confidence
BI-847325	AURKB	102	0.59	59	0.97	High confidence
BI-847325	INCENP	73	0.89	65	0.96	High confidence
BI-847325	UNC119	122	0.73	89	0.84	High confidence
BI-847325	YES1	227	0.41	94	0.90	High confidence
BI-847325	LYN	193	0.50	97	0.98	High confidence
BI-847325	LCK	260	0.44	115	0.95	High confidence
BI-847325	STK10	148	0.92	136	0.99	High confidence
BI-847325	FLT3	275	0.54	148	0.97	High confidence
BI-847325	MAP2K5	202	0.88	177	0.99	High confidence
BI-847325	MAP2K2	181	1.17	181	0.98	High confidence
BI-847325	FYN	434	0.43	187	0.93	High confidence
BI-847325	RET	514	0.44	227	0.86	High confidence
BI-847325	MAP2K1	279	1.23	279	1.00	High confidence
BI-847325	TBKBP1	356	0.79	282	0.89	High confidence
BI-847325	PLK4	653	0.51	333	0.89	High confidence
BI-847325	FER	911	0.42	385	0.97	High confidence
BI-847325	IKBKE	658	0.62	408	0.93	High confidence
BI-847325	DDR1	747	0.63	469	0.85	High confidence
BI-847325	SRC	1266	0.39	491	0.93	High confidence
BI-847325	BTK	1505	0.39	588	0.95	High confidence
BI-847325	ULK3	1349	0.45	612	0.95	High confidence
BI-847325	LATS1	806	0.79	635	0.96	High confidence
BI-847325	RPS6KA3	1013	0.72	734	0.95	High confidence
BI-847325	FRK	2166	0.34	736	0.88	High confidence
BI-847325	TBK1	1187	0.64	759	0.97	High confidence
BI-847325	TANK	1202	0.64	765	0.95	High confidence
BI-847325	RPS6KA1	1062	0.75	799	0.96	High confidence
BI-847325	AZI2	1188	0.70	834	0.91	High confidence
BI-847325	MAP4K1	1205	0.73	875	0.71	High confidence
BI-847325	TEC	2199	0.40	885	0.92	High confidence
BI-847325	CDK3	897	2.15	897	0.95	High confidence
BI-847325	HCK	1736	0.52	900	0.91	High confidence
BI-847325	MELK	1038	0.88	918	0.97	High confidence
BI-847325	CDK16	1163	0.94	1096	0.97	High confidence
BI-847325	PDGFRB	1266	0.87	1107	0.93	High confidence
BI-847325	MAPKAPK5	1199	0.93	1114	0.82	Low confidence
BI-847325	DDR2	1526	0.76	1163	0.95	High confidence
BI-847325	STK4	1659	0.76	1265	0.85	High confidence
BI-847325	MDN1	1315	1.27	1315	0.98	Low confidence
BI-847325	MAP4K5	1824	0.74	1357	0.95	High confidence
BI-847325	RPS6KA4	2364	0.62	1459	0.96	High confidence
BI-847325	ABL2	4467	0.33	1480	0.80	High confidence
BI-847325	SLK	1677	0.89	1494	0.97	High confidence
BI-847325	TNK2	3442	0.45	1549	0.92	High confidence
BI-847325	ABL1	2906	0.55	1592	0.92	High confidence
BI-847325	FGFR1	3410	0.74	2511	0.93	High confidence
BI-847325	PRKAG2	4264	0.64	2749	0.68	High confidence
BI-847325	CDK6	3621	0.82	2968	0.79	High confidence
BI-847325	PRKAA1	4783	0.64	3050	0.82	High confidence
BI-847325	PDPK1	3284	1.04	3284	0.89	High confidence
BI-847325	FECH	3498	0.99	3481	0.86	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
BI-847325	SIK2	6778	0.52	3513	0.96	High confidence	BMS-387032	STRADA	2807	1.02	2807	0.75	Low confidence
BI-847325	CDC7	4335	0.92	3993	0.86	High confidence	BMS-387032	DCAF7	3226	0.90	2892	0.84	High confidence
BI-847325	STK3	6605	0.76	5048	0.87	High confidence	BMS-387032	CABLES1	5460	0.55	3000	0.74	High confidence
Binimetinib	MAP2K2	36	1.17	36	0.95	High confidence	BMS-387032	PRKD3	4241	0.74	3139	0.85	High confidence
Binimetinib	MAP2K1	45	1.23	45	0.96	High confidence	BMS-387032	DYRK1A	3690	0.93	3443	0.96	High confidence
Binimetinib	NQO2	14700	1.07	14700	0.95	High confidence	BMS-387032	CSNK1D	4642	0.82	3819	0.83	High confidence
BMS-387032	MLLT1	2	1.30	2	1.00	Low confidence	BMS-387032	CDK4	3964	1.00	3964	0.85	High confidence
BMS-387032	CDK17	2	1.02	2	0.99	High confidence	BMS-387032	CDK5	7605	0.52	3982	0.93	High confidence
BMS-387032	AFF1	8	0.93	7	1.00	High confidence	BMS-387032	MAPK7	5665	0.78	4413	0.51	High confidence
BMS-387032	CCNT1	10	0.98	10	0.97	High confidence	BMS-387032	FAM83B	5116	1.06	5116	0.83	High confidence
BMS-387032	GSKIP	13	0.84	11	1.00	High confidence	BMS-690514	GAK	1	0.56	0	1.00	High confidence
BMS-387032	CCNT2	29	0.88	25	0.99	High confidence	BMS-690514	RET	77	0.44	34	0.95	High confidence
BMS-387032	AFF4	29	1.01	29	0.91	High confidence	BMS-690514	ABL2	121	0.33	40	0.97	High confidence
BMS-387032	CDK9	48	0.71	34	1.00	High confidence	BMS-690514	SIK2	93	0.52	48	0.98	High confidence
BMS-387032	CCNE1	93	0.73	68	0.89	High confidence	BMS-690514	ABL1	233	0.55	128	0.96	High confidence
BMS-387032	CDK16	120	0.94	113	0.96	High confidence	BMS-690514	PRKD2	213	0.66	140	0.87	High confidence
BMS-387032	FAM58A	183	0.72	132	0.89	High confidence	BMS-690514	TNK2	461	0.45	208	0.86	High confidence
BMS-387032	CDK6	173	0.82	142	0.95	High confidence	BMS-690514	EGFR	284	0.79	225	0.96	High confidence
BMS-387032	CDK12	167	1.12	167	0.88	High confidence	BMS-690514	ZAK	380	0.74	282	0.94	High confidence
BMS-387032	GSK3A	387	0.50	193	0.98	High confidence	BMS-690514	PRKD3	665	0.74	493	0.93	High confidence
BMS-387032	CDK2	385	0.53	205	0.98	High confidence	BMS-690514	LCK	1166	0.44	514	0.95	High confidence
BMS-387032	CCNK	295	1.11	295	0.93	High confidence	BMS-690514	MAP3K3	814	0.67	546	0.92	High confidence
BMS-387032	GSK3B	644	0.46	299	0.95	High confidence	BMS-690514	FYN	1353	0.43	583	0.98	High confidence
BMS-387032	CDK13	356	1.25	356	0.96	High confidence	BMS-690514	CAMK2D	3447	0.20	703	0.94	High confidence
BMS-387032	CKS1B	628	0.69	434	0.82	High confidence	BMS-690514	HCK	1374	0.52	712	0.97	High confidence
BMS-387032	MNAT1	934	0.88	820	0.84	High confidence	BMS-690514	CAMK2G	3399	0.22	738	0.93	High confidence
BMS-387032	CCNH	1252	0.76	949	0.98	High confidence	BMS-690514	FRK	2342	0.34	795	0.79	High confidence
BMS-387032	CDK7	1382	0.73	1002	0.97	High confidence	BMS-690514	LYN	1767	0.50	887	0.94	High confidence
BMS-387032	CCNA2	1244	0.86	1072	0.90	High confidence	BMS-690514	PRKACA	1949	0.47	916	0.91	High confidence
BMS-387032	ERCC2	1225	0.90	1108	0.96	High confidence	BMS-690514	MAP2K5	1109	0.88	972	0.90	High confidence
BMS-387032	CDK1	1790	0.69	1228	0.95	High confidence	BMS-690514	YES1	2484	0.41	1026	0.92	High confidence
BMS-387032	CCNB1	1755	0.77	1345	0.96	High confidence	BMS-690514	MAP3K2	1509	0.70	1054	0.98	High confidence
BMS-387032	MET	2069	0.80	1663	0.85	High confidence	BMS-690514	SRC	2969	0.39	1153	0.90	High confidence
BMS-387032	CLK1	2573	0.72	1841	0.79	High confidence	BMS-690514	PRKACB	2563	0.47	1212	0.95	High confidence
BMS-387032	CCNB2	2683	0.70	1882	0.95	High confidence	BMS-690514	TGFBR1	1773	0.69	1229	0.86	High confidence
BMS-387032	C2CD5	3893	0.55	2123	0.93	High confidence	BMS-690514	STK10	1399	0.92	1281	0.97	High confidence
BMS-387032	FIBP	4866	0.57	2775	0.96	High confidence	BMS-690514	PKN1	1537	0.87	1344	0.97	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
BMS-690514	CSNK1A1	1485	0.92	1371	0.89	High confidence
BMS-690514	Q6ZSR9	1822	0.76	1388	0.90	High confidence
BMS-690514	AAK1	2100	0.67	1414	0.98	High confidence
BMS-690514	PRKCA	2138	0.73	1557	0.97	High confidence
BMS-690514	MARK3	2207	0.77	1701	0.98	High confidence
BMS-690514	BMP2K	2591	0.66	1712	0.95	High confidence
BMS-690514	CSK	3190	0.54	1717	0.83	High confidence
BMS-690514	PRKCD	1839	0.95	1741	0.97	High confidence
BMS-690514	PKMYT1	2527	0.73	1854	0.83	High confidence
BMS-690514	CHEK1	2264	0.82	1867	0.98	High confidence
BMS-690514	FLT3	3743	0.54	2011	0.92	High confidence
BMS-690514	MAP4K5	2784	0.74	2071	0.90	High confidence
BMS-690514	MARK2	2886	0.75	2174	0.96	High confidence
BMS-690514	SLK	2717	0.89	2420	0.89	High confidence
BMS-690514	PRKCI	2422	1.07	2422	0.97	High confidence
BMS-690514	MAP3K11	3739	0.70	2604	0.66	High confidence
BMS-690514	EPHB3	3028	0.88	2652	0.96	High confidence
BMS-690514	CIT	2780	1.21	2780	0.73	Low confidence
BMS-690514	ROCK1	3097	0.91	2816	0.87	High confidence
BMS-690514	CSNK2A2	2969	0.96	2859	0.86	High confidence
BMS-690514	EIF3J	3023	1.11	3023	0.95	High confidence
BMS-690514	CSNK2A1	3105	1.02	3105	0.84	High confidence
BMS-690514	DYRK1A	3528	0.93	3292	0.97	High confidence
BMS-690514	CSNK1E	4259	0.85	3641	0.89	High confidence
BMS-690514	PHKG2	4761	0.97	4618	0.84	High confidence
BMS-690514	CSNK2B	10612	1.08	10612	0.89	Low confidence
BMS-754807	IGF1R	7	0.66	5	1.00	High confidence
BMS-754807	PLK4	20	0.51	10	0.96	Low confidence
BMS-754807	PTK2	28	0.41	11	0.99	High confidence
BMS-754807	MET	18	0.80	14	0.80	Low confidence
BMS-754807	INSR	26	0.75	20	0.98	High confidence
BMS-754807	AURKA	214	0.35	76	0.98	High confidence
BMS-754807	PTK2B	236	0.41	98	0.98	High confidence
BMS-754807	TNK1	351	0.43	152	0.95	High confidence
BMS-754807	AURKB	263	0.59	154	0.99	High confidence
BMS-754807	PRKAG2	422	0.64	272	0.98	High confidence
BMS-754807	PRKAG1	646	0.63	409	0.94	High confidence
BMS-754807	DYNLL1	843	0.50	423	0.85	High confidence
BMS-754807	PRKAB1	831	0.66	550	0.89	High confidence
BMS-754807	NEK9	1482	0.44	654	0.99	High confidence
BMS-754807	RET	1533	0.44	675	0.90	High confidence
BMS-754807	FER	1893	0.42	799	0.97	High confidence
BMS-754807	PRKAA1	1357	0.64	865	0.98	High confidence
BMS-754807	EPHA2	3268	0.41	1350	0.95	High confidence
BMS-754807	FES	4787	0.37	1769	0.94	High confidence
BMS-754807	FLT3	3346	0.54	1798	0.91	High confidence
BMS-754807	DDR1	3799	0.63	2383	0.98	High confidence
BMS-777607	MET	13	0.80	11	0.98	High confidence
BMS-777607	DDR1	62	0.63	39	0.96	High confidence
BMS-777607	DDR2	85	0.76	65	0.94	High confidence
BMS-777607	FLT3	425	0.54	228	1.00	Low confidence
BMS-777607	PLK4	592	0.51	301	0.45	Low confidence
BMS-777607	FRK	971	0.34	330	0.91	High confidence
BMS-777607	ABL1	954	0.55	523	0.93	High confidence
BMS-777607	AURKB	1833	0.59	1073	0.96	High confidence
BMS-777607	ABL2	4551	0.33	1508	0.97	High confidence
BMS-777607	LCK	3566	0.44	1571	0.88	High confidence
BMS-777607	MAP4K2	3516	0.59	2075	0.99	High confidence
BMS-777607	MAP2K5	2380	0.88	2085	0.81	High confidence
BMS-911543	NQO2	5864	1.07	5864	0.95	High confidence
Bosutinib	INPPL1	5	0.48	2	0.98	Low confidence
Bosutinib	BCR	7	0.48	3	1.00	High confidence
Bosutinib	MAP4K5	21	0.74	16	0.96	High confidence
Bosutinib	ABL1	34	0.55	19	0.99	High confidence
Bosutinib	ABL2	62	0.33	20	0.99	High confidence
Bosutinib	TNIK	23	1.02	23	0.95	Low confidence
Bosutinib	BTK	65	0.39	25	0.99	High confidence
Bosutinib	STK24	25	1.06	25	0.78	Low confidence
Bosutinib	FRK	80	0.34	27	0.93	High confidence
Bosutinib	LCK	78	0.44	35	0.98	High confidence
Bosutinib	GAK	75	0.56	42	0.98	High confidence
Bosutinib	MAP4K3	88	0.66	58	0.90	High confidence
Bosutinib	EPHA4	96	0.62	59	0.90	High confidence
Bosutinib	LYN	125	0.50	63	0.96	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Bosutinib	MAP4K2	131	0.59	77	0.93	High confidence	Bosutinib	CSNK1D	4176	0.82	3436	0.74	Low confidence
Bosutinib	FANCI	100	0.97	96	0.92	High confidence	Bosutinib	MAP2K1	3668	1.23	3668	0.83	High confidence
Bosutinib	EPHB4	200	0.49	99	0.99	High confidence	Brivanib	VDAC3	4	1.26	4	0.91	Low confidence
Bosutinib	MAP3K1	185	0.58	107	0.97	High confidence	Brivanib	CALM1	82	1.10	82	0.80	Low confidence
Bosutinib	PAG1	239	0.49	118	0.94	High confidence	Brivanib	DDR1	1625	0.63	1019	0.97	High confidence
Bosutinib	EPHA2	285	0.41	118	0.97	High confidence	Brivanib	STRADA	1137	1.02	1137	0.92	Low confidence
Bosutinib	HCK	262	0.52	136	0.98	High confidence	Brivanib	PDGFRB	2902	0.87	2537	0.87	High confidence
Bosutinib	TNK2	306	0.45	138	0.70	High confidence	Brivanib	SLK	3077	0.89	2741	0.98	High confidence
Bosutinib	SIK3	196	0.82	160	0.95	Low confidence	Brivanib	RET	6491	0.44	2860	0.95	High confidence
Bosutinib	SRC	434	0.39	168	0.92	High confidence	Brivanib	STK10	11098	0.92	10160	0.97	High confidence
Bosutinib	YES1	416	0.41	172	0.90	High confidence	Brivanib	MAP4K4	22757	1.01	22757	0.98	High confidence
Bosutinib	FYN	414	0.43	179	0.93	High confidence	Brivanib_alaninate	NUAK2	3	0.77	3	0.81	Low confidence
Bosutinib	CSK	363	0.54	195	0.96	High confidence	Brivanib_alaninate	DDR1	1656	0.63	1039	0.95	High confidence
Bosutinib	SIK2	397	0.52	206	0.96	High confidence	Brivanib_alaninate	PDGFRB	2165	0.87	1892	0.95	High confidence
Bosutinib	EPHB2	494	0.52	259	0.91	High confidence	Brivanib_alaninate	FGFR1	5291	0.74	3896	0.89	High confidence
Bosutinib	CLK1	836	0.72	598	0.81	Low confidence	Brivanib_alaninate	RET	16986	0.44	7483	0.95	High confidence
Bosutinib	MAP3K2	931	0.70	650	0.86	High confidence	Brivanib_alaninate	STK10	9223	0.92	8443	1.00	High confidence
Bosutinib	FER	1816	0.42	767	0.90	High confidence	Brivanib_alaninate	SLK	10652	0.89	9488	0.68	High confidence
Bosutinib	MAP4K1	1129	0.73	820	0.89	High confidence	Brivanib_alaninate	MAP4K4	46183	1.01	46183	0.84	High confidence
Bosutinib	IKBKE	1350	0.62	838	0.92	High confidence	BYL-719	PRKACG	3875	0.51	1990	0.79	High confidence
Bosutinib	BMP2K	1316	0.66	870	0.92	High confidence	BYL-719	GAK	8847	0.56	4968	0.70	High confidence
Bosutinib	SLK	981	0.89	873	0.96	High confidence	Cabozantinib	FLT3	99	0.54	53	0.92	High confidence
Bosutinib	PKMYT1	1194	0.73	876	0.96	High confidence	Cabozantinib	RET	195	0.44	86	0.95	High confidence
Bosutinib	STK10	958	0.92	877	0.87	High confidence	Cabozantinib	DDR1	334	0.63	209	0.92	High confidence
Bosutinib	TBK1	1598	0.64	1022	0.80	High confidence	Cabozantinib	BCR	717	0.48	342	0.85	High confidence
Bosutinib	ZAK	1631	0.74	1213	0.92	High confidence	Cabozantinib	DDR2	658	0.76	501	0.79	High confidence
Bosutinib	MAP2K2	1223	1.17	1223	0.85	High confidence	Cabozantinib	FRK	1648	0.34	560	0.86	High confidence
Bosutinib	TANK	1929	0.64	1227	0.92	High confidence	Cabozantinib	EPHA2	1806	0.41	746	0.90	High confidence
Bosutinib	MAP3K3	1953	0.67	1311	0.88	High confidence	Cabozantinib	RIPK2	2735	0.28	767	0.79	High confidence
Bosutinib	Q6ZSR9	1783	0.76	1357	0.80	High confidence	Cabozantinib	ABL2	2771	0.33	918	0.79	High confidence
Bosutinib	AAK1	2186	0.67	1471	0.82	Low confidence	Cabozantinib	LCK	2372	0.44	1045	0.82	High confidence
Bosutinib	EPHB3	1746	0.88	1529	0.81	High confidence	Cabozantinib	ABL1	2004	0.55	1098	0.88	High confidence
Bosutinib	MAP3K4	2435	0.67	1636	0.86	High confidence	Cabozantinib	HCK	2119	0.52	1098	0.80	High confidence
Bosutinib	MAP2K5	1906	0.88	1669	0.81	High confidence	Cabozantinib	LYN	2657	0.50	1333	0.87	High confidence
Bosutinib	WEE1	3201	0.63	2026	0.92	High confidence	Cabozantinib	PTK6	3649	0.48	1763	0.77	High confidence
Bosutinib	TBKBP1	2741	0.79	2176	0.65	High confidence	Cabozantinib	MAP2K5	2726	0.88	2388	0.80	High confidence
Bosutinib	PDGFRB	2917	0.87	2550	0.82	Low confidence	Cabozantinib	RIPK3	2751	0.89	2459	0.91	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Cabozantinib	FECH	2641	0.99	2628	0.83	High confidence	CC-401	CSNK2A2	607	0.96	584	0.98	High confidence
Cabozantinib	PIP4K2C	3198	0.91	2901	0.80	High confidence	CC-401	MAPK8	982	0.65	636	0.99	High confidence
Cabozantinib	NTRK1	5819	0.71	4108	0.78	High confidence	CC-401	CSNK2B	741	1.08	741	0.99	High confidence
Canertinib	EGFR	10	0.79	8	0.86	High confidence	CC-401	CSNK2A1	747	1.02	747	0.99	High confidence
Canertinib	BTK	1289	0.39	504	0.93	High confidence	CC-401	EIF3J	784	1.11	784	0.99	High confidence
Canertinib	RIPK2	2421	0.28	679	0.86	High confidence	CC-401	KLHL6	1059	0.74	785	0.97	Low confidence
Canertinib	BCR	1438	0.48	687	0.84	High confidence	CC-401	GAPVD1	1068	0.99	1063	0.84	Low confidence
Canertinib	INPPL1	2071	0.48	1001	0.56	Low confidence	CC-401	NQO2	1413	1.07	1413	0.97	High confidence
Canertinib	EPHA7	1502	0.79	1190	0.51	High confidence	CC-401	GAK	2606	0.56	1464	0.98	High confidence
Canertinib	GAK	2406	0.56	1351	0.89	High confidence	CC-401	BMP2K	2219	0.66	1467	0.99	High confidence
Canertinib	EPHA5	2906	0.60	1741	0.57	High confidence	CC-401	AP2B1	1597	1.01	1597	0.97	Low confidence
Canertinib	CSNK1G2	2127	0.88	1862	0.88	Low confidence	CC-401	AP2A1	2482	0.92	2280	0.97	Low confidence
Canertinib	EPHB4	4209	0.49	2083	0.76	High confidence	CC-401	TNIK	2343	1.02	2343	0.70	High confidence
Canertinib	TEC	5299	0.40	2132	0.76	High confidence	CC-401	Q6ZSR9	3322	0.76	2529	0.94	High confidence
Canertinib	UNC119	3103	0.73	2253	0.66	Low confidence	CC-401	AAK1	3874	0.67	2608	0.97	High confidence
Canertinib	RIPK3	2521	0.89	2254	0.86	High confidence	CC-401	MAPK10	3858	0.84	3243	0.86	High confidence
Canertinib	RET	5640	0.44	2485	0.65	High confidence	CC-401	MAP4K4	4172	1.01	4172	0.87	High confidence
Canertinib	ZAK	3790	0.74	2819	0.96	High confidence	CC-401	CSNK1A1	5588	0.92	5161	0.98	High confidence
Canertinib	STK10	6357	0.92	5820	0.65	High confidence	CC-401	FECH	32549	0.99	32384	0.95	High confidence
Capmatinib	MET	0.42	0.80	0.34	1.00	High confidence	Cediranib	ACSL5	8	1.06	8	0.92	Low confidence
Capmatinib	SEC16A	1726	1.18	1726	0.94	Low confidence	Cediranib	DDR1	30	0.63	19	0.94	High confidence
Capmatinib	CDKL5	2296	0.89	2042	0.97	Low confidence	Cediranib	PDGFRB	22	0.87	19	0.77	High confidence
Capmatinib	LMAN1	2992	1.47	2992	0.63	Low confidence	Cediranib	RET	62	0.44	27	0.95	High confidence
CC-401	FAM83B	2	1.06	2	0.82	Low confidence	Cediranib	FGFR1	743	0.74	547	0.79	High confidence
CC-401	DCAF7	31	0.90	28	0.96	High confidence	Cediranib	STK10	960	0.92	879	0.94	High confidence
CC-401	CALR	40	1.42	40	0.60	Low confidence	Cediranib	DDR2	1312	0.76	1000	0.92	High confidence
CC-401	PRKD2	84	0.66	56	0.97	High confidence	Cediranib	PTK6	2523	0.48	1219	0.90	High confidence
CC-401	PRKD3	121	0.74	90	0.97	High confidence	Cediranib	SLK	2212	0.89	1970	0.91	High confidence
CC-401	CSNK1G3	124	0.79	97	0.96	High confidence	Cediranib	TGFBR1	2960	0.69	2052	0.76	High confidence
CC-401	CSNK1G2	120	0.88	105	0.96	High confidence	Cediranib	BCR	4841	0.48	2313	0.81	High confidence
CC-401	DYRK1A	172	0.93	161	0.97	High confidence	Cediranib	MAP4K5	3329	0.74	2477	0.84	High confidence
CC-401	MELK	245	0.88	217	0.94	High confidence	Cediranib	SKIV2L2	2607	1.14	2607	0.78	Low confidence
CC-401	CSNK1G1	326	0.87	282	0.96	High confidence	Cediranib	EGFR	3447	0.79	2733	0.80	High confidence
CC-401	CSNK1E	333	0.85	285	1.00	High confidence	Cediranib	INPPL1	5711	0.48	2761	0.88	High confidence
CC-401	CSNK1D	348	0.82	287	0.98	High confidence	Cediranib	EIF2AK1	3573	0.92	3292	0.73	High confidence
CC-401	MAPK9	486	0.70	340	0.99	High confidence	Cediranib	MET	6119	0.80	4916	0.64	High confidence
CC-401	MYLK3	555	0.87	483	0.93	High confidence	Cediranib	GRB2	9888	0.62	6167	0.85	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Cediranib	ABL1	24552	0.55	13453	0.87	High confidence	Cerdulatinib	RASSF5	34	0.98	34	0.95	Low confidence
CEP-32496	RET	25	0.44	11	0.97	High confidence	Cerdulatinib	STK3	81	0.76	62	0.98	High confidence
CEP-32496	INPPL1	58	0.48	28	0.89	Low confidence	Cerdulatinib	JAK1	209	0.37	78	0.95	High confidence
CEP-32496	ABL2	92	0.33	30	0.95	High confidence	Cerdulatinib	INCENP	111	0.89	99	0.60	Low confidence
CEP-32496	BCR	86	0.48	41	0.71	High confidence	Cerdulatinib	STK4	134	0.76	102	0.96	High confidence
CEP-32496	ABL1	91	0.55	50	0.92	High confidence	Cerdulatinib	SIK2	246	0.52	128	0.98	High confidence
CEP-32496	S100A6	110	1.29	110	0.82	Low confidence	Cerdulatinib	PDGFRB	232	0.87	203	0.66	High confidence
CEP-32496	DDR1	197	0.63	124	0.94	High confidence	Cerdulatinib	LATS1	332	0.79	261	0.78	High confidence
CEP-32496	EPHA2	348	0.41	144	0.96	High confidence	Cerdulatinib	TANK	440	0.64	280	0.93	High confidence
CEP-32496	MAPK9	212	0.70	148	0.98	High confidence	Cerdulatinib	MAP3K5	356	0.80	285	0.85	High confidence
CEP-32496	GRB2	275	0.62	172	0.97	High confidence	Cerdulatinib	TBK1	468	0.64	299	0.88	High confidence
CEP-32496	DDR2	240	0.76	183	0.85	High confidence	Cerdulatinib	MARK2	402	0.75	302	0.92	High confidence
CEP-32496	RIPK3	274	0.89	245	0.74	Low confidence	Cerdulatinib	MARK3	397	0.77	306	0.90	High confidence
CEP-32496	MAPK10	450	0.84	378	0.60	Low confidence	Cerdulatinib	MAPK10	367	0.84	308	0.79	High confidence
CEP-32496	EPHA5	670	0.60	401	0.70	Low confidence	Cerdulatinib	MAPK8	549	0.65	356	0.98	High confidence
CEP-32496	RIPK2	1574	0.28	442	0.96	High confidence	Cerdulatinib	AZI2	574	0.70	403	0.98	High confidence
CEP-32496	MAPKAPK2	678	0.72	490	0.97	High confidence	Cerdulatinib	BUB1	437	1.04	437	0.95	High confidence
CEP-32496	FLT3	1023	0.54	550	0.87	High confidence	Cerdulatinib	SYK	525	0.84	440	0.95	High confidence
CEP-32496	MAPK14	1106	0.51	566	0.97	High confidence	Cerdulatinib	RPS6KA6	1080	0.42	455	0.96	High confidence
CEP-32496	LYN	1536	0.50	771	0.97	High confidence	Cerdulatinib	MAP3K6	573	0.83	473	0.78	High confidence
CEP-32496	FRK	2502	0.34	850	0.97	Low confidence	Cerdulatinib	GAK	982	0.56	552	0.87	High confidence
CEP-32496	MAPK11	1205	0.72	872	0.86	High confidence	Cerdulatinib	ULK3	1444	0.45	655	0.99	High confidence
CEP-32496	FER	2321	0.42	980	0.94	High confidence	Cerdulatinib	MAP2K5	749	0.88	656	0.98	High confidence
CEP-32496	ZAK	1342	0.74	998	0.98	High confidence	Cerdulatinib	CHEK1	849	0.82	701	0.86	High confidence
CEP-32496	MAPK8	2270	0.65	1471	0.95	High confidence	Cerdulatinib	TBKBP1	932	0.79	740	0.74	High confidence
CEP-32496	MYLK	3220	0.83	2683	0.93	High confidence	Cerdulatinib	MAP3K2	1069	0.70	747	0.96	High confidence
CEP-32496	MAP4K2	4783	0.59	2822	0.95	High confidence	Cerdulatinib	PAK4	1416	0.60	851	0.94	High confidence
CEP-32496	BRAF	2852	1.11	2852	0.86	High confidence	Cerdulatinib	PRKD3	1431	0.74	1059	0.85	High confidence
CEP-32496	EPHB4	19841	0.49	9818	0.81	High confidence	Cerdulatinib	MAP3K3	1622	0.67	1089	0.93	High confidence
CEP-32496	MAP4K5	27017	0.74	20104	0.93	High confidence	Cerdulatinib	NEK3	1293	0.85	1105	0.90	High confidence
Cerdulatinib	Q6ZSR9	1	0.76	1	0.97	High confidence	Cerdulatinib	PDPK1	1201	1.04	1201	0.95	High confidence
Cerdulatinib	BMP2K	1	0.66	1	0.99	High confidence	Cerdulatinib	PRKD2	1832	0.66	1207	0.92	High confidence
Cerdulatinib	AAK1	2	0.67	1	0.98	High confidence	Cerdulatinib	RET	2793	0.44	1231	0.91	High confidence
Cerdulatinib	SARNP	10	1.11	10	0.99	Low confidence	Cerdulatinib	IKBKE	2079	0.62	1291	0.95	High confidence
Cerdulatinib	STK26	33	0.88	29	0.99	Low confidence	Cerdulatinib	MAPK9	2044	0.70	1430	0.95	High confidence
Cerdulatinib	TYK2	61	0.52	32	0.79	High confidence	Cerdulatinib	MAP2K3	1480	1.32	1480	0.87	High confidence
Cerdulatinib	MAP4K3	50	0.66	33	1.00	High confidence	Cerdulatinib	FLT3	2791	0.54	1500	0.95	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Cerdulatinib	PRKAB1	2365	0.66	1566	0.93	High confidence
Cerdulatinib	MAP3K11	2600	0.70	1811	0.88	High confidence
Cerdulatinib	PRKAG2	3050	0.64	1967	0.78	High confidence
Cerdulatinib	TAOK1	3270	0.66	2174	0.72	High confidence
Cerdulatinib	TAOK2	3767	0.59	2221	0.95	High confidence
Cerdulatinib	INPPL1	4934	0.48	2385	0.92	High confidence
Cerdulatinib	ULK1	4217	0.67	2818	0.78	Low confidence
Cerdulatinib	MAP4K4	3056	1.01	3056	0.95	High confidence
Cerdulatinib	EIF2AK1	4041	0.92	3724	0.72	Low confidence
Cerdulatinib	AURKB	6477	0.59	3791	0.97	High confidence
Cerdulatinib	PRKCD	4035	0.95	3821	0.81	High confidence
Cerdulatinib	BMPR2	5773	0.84	4861	0.85	High confidence
Cerdulatinib	RPS6KA3	8127	0.72	5891	0.91	High confidence
Cerdulatinib	PRKAB2	11783	0.60	7082	0.83	High confidence
Cerdulatinib	PRKAG1	12286	0.63	7776	0.87	High confidence
Cerdulatinib	TAOK3	10675	0.77	8258	0.95	High confidence
Cerdulatinib	PRKAA1	16890	0.64	10773	0.96	High confidence
Cerdulatinib	SIK3	16563	0.82	13559	0.85	High confidence
Cerdulatinib	CSNK2A1	15518	1.02	15518	0.85	High confidence
Cerdulatinib	CSNK2A2	16982	0.96	16348	0.84	High confidence
Cerdulatinib	MAP4K5	25742	0.74	19155	0.85	High confidence
Cerdulatinib	EIF3J	25029	1.11	25029	0.68	High confidence
Cerdulatinib	CSNK2B	32749	1.08	32749	0.83	High confidence
Ceritinib	TNK1	62	0.43	27	0.94	High confidence
Ceritinib	FER	507	0.42	214	1.00	High confidence
Ceritinib	PTK2	533	0.41	218	0.97	High confidence
Ceritinib	CAMK4	635	1.02	635	0.96	High confidence
Ceritinib	TNK2	2064	0.45	929	0.97	High confidence
Ceritinib	CLK1	1480	0.72	1059	0.93	Low confidence
Ceritinib	FES	4714	0.37	1742	0.96	High confidence
Ceritinib	INSR	5177	0.75	3887	0.84	High confidence
Ceritinib	FLT3	7919	0.54	4255	0.69	High confidence
Ceritinib	CAMKK2	8172	0.66	5429	0.94	High confidence
Ceritinib	PLK4	13942	0.51	7100	0.65	High confidence
Ceritinib	MAPK7	12647	0.78	9851	0.65	High confidence
Ceritinib	PTK2B	44277	0.41	18357	0.88	High confidence
Ceritinib	IGF1R	29038	0.66	19217	0.88	High confidence
Ceritinib	RPS6KA1	28460	0.75	21402	0.91	High confidence
CH-5183284	INPPL1	2	0.48	1	0.99	Low confidence
CH-5183284	FGFR1	4	0.74	3	0.65	High confidence
CH-5183284	EPHB6	12	0.61	7	0.91	Low confidence
CH-5183284	MAPKAPK2	24	0.72	18	0.70	Low confidence
CH-5183284	RET	1776	0.44	783	0.92	High confidence
CH-5183284	PDXK	2110	1.43	2110	0.88	High confidence
Cobimetinib	MAP2K2	22	1.17	22	0.79	High confidence
Cobimetinib	ACTR3	36	1.05	36	0.91	Low confidence
Cobimetinib	MAP2K1	309	1.23	309	0.92	High confidence
Copanlisib	RAB27A	4493	1.49	4493	0.95	Low confidence
CP-547632	ACVR1B	10	0.43	4	0.97	High confidence
CP-547632	TGFBR1	7	0.69	5	0.99	High confidence
CP-547632	DDR1	107	0.63	67	0.99	High confidence
CP-547632	MAP3K1	234	0.58	135	1.00	High confidence
CP-547632	EPHB6	368	0.61	226	0.93	High confidence
CP-547632	SLK	301	0.89	268	0.99	High confidence
CP-547632	ADCK1	452	0.62	281	0.99	High confidence
CP-547632	RET	774	0.44	341	0.97	High confidence
CP-547632	FGFR1	538	0.74	396	0.95	High confidence
CP-547632	STK10	562	0.92	515	0.98	High confidence
CP-547632	FRK	1847	0.34	627	0.87	High confidence
CP-547632	DDR2	878	0.76	669	0.96	High confidence
CP-547632	MAP4K2	1309	0.59	772	0.94	High confidence
CP-547632	MST1R	1017	0.76	775	0.86	Low confidence
CP-547632	YES1	2132	0.41	881	0.91	High confidence
CP-547632	FLT3	1665	0.54	894	0.82	High confidence
CP-547632	SIK2	1745	0.52	904	0.94	High confidence
CP-547632	RIPK2	3415	0.28	958	0.89	High confidence
CP-547632	PDGFRB	1312	0.87	1146	0.95	High confidence
CP-547632	LCK	2754	0.44	1213	0.90	High confidence
CP-547632	MAPKAPK2	1693	0.72	1224	0.79	High confidence
CP-547632	MAP4K5	1854	0.74	1380	0.97	High confidence
CP-547632	TESK1	1922	0.74	1417	0.99	High confidence
CP-547632	CSNK1E	1714	0.85	1465	0.87	Low confidence
CP-547632	AURKB	2568	0.59	1503	0.91	High confidence
CP-547632	SIK3	1911	0.82	1564	0.96	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
CP-547632	PTK6	4226	0.48	2042	0.85	High confidence
CP-547632	ABL1	3949	0.55	2164	0.92	High confidence
CP-547632	INCENP	2637	0.89	2354	0.85	High confidence
CP-547632	BCR	5432	0.48	2596	0.93	High confidence
CP-547632	MAP4K3	4248	0.66	2785	0.86	High confidence
CP-547632	INPPL1	5985	0.48	2893	0.94	High confidence
CP-547632	ADCK3	3428	0.89	3053	0.72	Low confidence
CP-547632	EIF2AK1	3876	0.92	3572	0.95	High confidence
CP-547632	MAP4K4	8111	1.01	8111	0.94	High confidence
CP-547632	PLK4	16487	0.51	8397	0.63	Low confidence
CP-724714	EGFR	89	0.79	71	0.90	High confidence
CP-724714	MAP2K5	1433	0.88	1255	0.97	High confidence
CP-724714	OSBPL3	2312	0.83	1918	0.95	High confidence
CP-724714	FECH	28716	0.99	28570	0.84	High confidence
Crenolanib	SIK3	3	0.82	2	0.96	High confidence
Crenolanib	SAE1	3	1.45	3	0.91	Low confidence
Crenolanib	CMPK1	3	1.43	3	0.96	High confidence
Crenolanib	LSM3	5	0.73	4	0.97	Low confidence
Crenolanib	SARNP	7	1.11	7	0.99	Low confidence
Crenolanib	OLA1	7	1.07	7	0.99	Low confidence
Crenolanib	SUCLA2	7	1.06	7	0.97	Low confidence
Crenolanib	NTRK1	12	0.71	8	0.95	High confidence
Crenolanib	HBG1	9	1.21	9	0.95	Low confidence
Crenolanib	DBI	10	1.59	10	0.97	Low confidence
Crenolanib	ETFB	12	1.32	12	0.87	Low confidence
Crenolanib	STK26	14	0.88	13	0.91	High confidence
Crenolanib	GFPT1	16	1.30	16	0.94	Low confidence
Crenolanib	SIK2	31	0.52	16	0.98	High confidence
Crenolanib	FLT3	33	0.54	18	0.96	High confidence
Crenolanib	TRRAP	21	1.05	21	0.99	High confidence
Crenolanib	MARK4	30	0.83	25	0.95	High confidence
Crenolanib	APRT	29	1.38	29	0.97	Low confidence
Crenolanib	P4HB	30	1.37	30	0.92	Low confidence
Crenolanib	NQO2	40	1.07	40	0.99	High confidence
Crenolanib	GARS	40	1.34	40	0.91	High confidence
Crenolanib	MAP2K5	47	0.88	41	0.95	High confidence
Crenolanib	UGGT1	43	1.28	43	0.88	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Crenolanib	STK24	57	1.06	57	0.76	High confidence
Crenolanib	PPIB	81	1.57	81	0.88	Low confidence
Crenolanib	PDGFRB	121	0.87	106	0.98	High confidence
Crenolanib	TNIK	107	1.02	107	0.67	Low confidence
Crenolanib	CDK2	240	0.53	128	0.98	High confidence
Crenolanib	CAMKK2	203	0.66	135	0.98	High confidence
Crenolanib	PKN1	189	0.87	165	0.95	High confidence
Crenolanib	RASSF5	191	0.98	188	1.00	High confidence
Crenolanib	MARK3	286	0.77	220	0.92	High confidence
Crenolanib	MAP4K4	282	1.01	282	0.98	High confidence
Crenolanib	MARK2	399	0.75	300	0.99	High confidence
Crenolanib	CDK5	599	0.52	313	0.98	High confidence
Crenolanib	CCNB1	498	0.77	382	0.98	High confidence
Crenolanib	MAP4K3	619	0.66	406	0.94	High confidence
Crenolanib	PIGK	449	1.19	449	0.90	Low confidence
Crenolanib	MAP4K5	611	0.74	455	0.97	High confidence
Crenolanib	PRPH	2159	0.23	496	0.91	Low confidence
Crenolanib	AFF4	507	1.01	507	0.85	Low confidence
Crenolanib	CCNB2	932	0.70	654	0.85	High confidence
Crenolanib	CCNT2	757	0.88	666	0.90	High confidence
Crenolanib	STK4	921	0.76	702	0.99	High confidence
Crenolanib	STK3	972	0.76	743	0.92	High confidence
Crenolanib	CAMK2G	3525	0.22	766	0.94	High confidence
Crenolanib	IRAK4	1005	0.77	778	0.99	High confidence
Crenolanib	PRKAB1	1220	0.66	808	0.96	High confidence
Crenolanib	RET	1840	0.44	810	0.99	High confidence
Crenolanib	CAMK2D	4027	0.20	821	0.94	High confidence
Crenolanib	ULK1	1256	0.67	839	0.96	High confidence
Crenolanib	PRKAB2	1414	0.60	850	0.84	High confidence
Crenolanib	DCAF7	997	0.90	894	0.84	High confidence
Crenolanib	CDK9	1388	0.71	988	0.96	High confidence
Crenolanib	PAK4	1676	0.60	1007	0.91	High confidence
Crenolanib	CDK3	1066	2.15	1066	0.81	High confidence
Crenolanib	HNRNPH3	1380	0.84	1159	0.96	Low confidence
Crenolanib	BMP2K	1816	0.66	1200	0.97	High confidence
Crenolanib	PKN2	1489	0.82	1215	0.96	High confidence
Crenolanib	TAOK1	1863	0.66	1239	0.92	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Crenolanib	PYCR1	1245	1.49	1245	0.97	Low confidence
Crenolanib	PRKAA1	1956	0.64	1247	0.99	High confidence
Crenolanib	RIPK2	4677	0.28	1312	0.93	High confidence
Crenolanib	ILK	1329	1.04	1329	0.94	Low confidence
Crenolanib	CDK1	2008	0.69	1378	0.97	High confidence
Crenolanib	IRAK3	3511	0.43	1506	0.96	High confidence
Crenolanib	CCNT1	1617	0.98	1590	0.96	High confidence
Crenolanib	PRKAG2	2749	0.64	1772	0.93	High confidence
Crenolanib	RPS6KA6	4696	0.42	1981	0.90	High confidence
Crenolanib	PRKAG1	3154	0.63	1996	0.96	High confidence
Crenolanib	MOB1A	2411	0.91	2205	0.88	High confidence
Crenolanib	C2CD5	4178	0.55	2278	0.89	High confidence
Crenolanib	GAK	4286	0.56	2407	0.92	High confidence
Crenolanib	HSP90AB2P	2566	1.27	2566	0.91	High confidence
Crenolanib	GRB2	4210	0.62	2626	0.93	High confidence
Crenolanib	LATS1	3514	0.79	2768	0.95	High confidence
Crenolanib	FIBP	4871	0.57	2778	0.96	High confidence
Crenolanib	PRKCD	3156	0.95	2989	0.96	High confidence
Crenolanib	PRKCQ	3063	1.23	3063	0.87	High confidence
Crenolanib	MAP3K11	4402	0.70	3066	0.95	High confidence
Crenolanib	YARS	3316	1.89	3316	0.86	Low confidence
Crenolanib	STK10	3745	0.92	3428	0.94	High confidence
Crenolanib	CCNA2	4168	0.86	3592	0.86	High confidence
Crenolanib	MELK	4783	0.88	4227	0.84	High confidence
Crenolanib	TXN	4421	1.34	4421	0.86	Low confidence
Crenolanib	DYRK1A	5323	0.93	4966	0.96	High confidence
Crenolanib	PHKG2	5172	0.97	5016	0.89	High confidence
Crenolanib	FECH	7392	0.99	7354	0.83	High confidence
Crenolanib	PDPK1	12602	1.04	12602	0.95	High confidence
Crenolanib	PRKD3	19951	0.74	14768	0.86	High confidence
Crenolanib	CABLES1	30972	0.55	17020	0.95	High confidence
Crenolanib	LCK	54985	0.44	24221	0.96	High confidence
Crizotinib	ALK	4	0.85	3	1.00	Low confidence
Crizotinib	MET	10	0.80	8	1.00	High confidence
Crizotinib	MST1R	100	0.76	76	0.87	High confidence
Crizotinib	TRAF7	93	0.98	91	0.90	Low confidence
Crizotinib	MAP4K2	309	0.59	182	0.97	High confidence
Crizotinib	ABL2	1288	0.33	427	0.91	High confidence
Crizotinib	AURKA	1455	0.35	514	0.94	High confidence
Crizotinib	EPHB6	886	0.61	545	0.99	High confidence
Crizotinib	PTK2	1457	0.41	595	0.89	High confidence
Crizotinib	IRAK3	1453	0.43	623	0.96	High confidence
Crizotinib	ABL1	1466	0.55	803	0.97	High confidence
Crizotinib	PRKD3	1172	0.74	867	0.76	High confidence
Crizotinib	MAP4K5	1520	0.74	1131	0.97	High confidence
Crizotinib	SLK	1324	0.89	1179	0.96	High confidence
Crizotinib	AURKB	2118	0.59	1240	0.97	High confidence
Crizotinib	EPHA2	3065	0.41	1266	0.89	High confidence
Crizotinib	LCK	3210	0.44	1414	0.95	High confidence
Crizotinib	MAP3K1	3235	0.58	1867	0.94	High confidence
Crizotinib	LIMK1	3179	0.59	1890	0.91	High confidence
Crizotinib	ACAD11	1950	0.98	1916	0.92	High confidence
Crizotinib	MAP4K1	2710	0.73	1968	0.97	High confidence
Crizotinib	GRB2	3229	0.62	2014	0.77	High confidence
Crizotinib	TANK	3845	0.64	2446	0.79	High confidence
Crizotinib	BCR	5200	0.48	2485	0.94	High confidence
Crizotinib	MAP4K3	3944	0.66	2587	0.94	High confidence
Crizotinib	IKBKE	4394	0.62	2728	0.78	High confidence
Crizotinib	STK10	3084	0.92	2823	0.95	High confidence
Crizotinib	TGFBR1	5038	0.69	3492	0.76	High confidence
Crizotinib	IRAK1	6459	0.61	3942	0.90	High confidence
Crizotinib	LIMK2	6546	0.66	4340	0.79	High confidence
Crizotinib	PRKD2	9843	0.66	6488	0.89	High confidence
CUDC-101	NME2	142	1.46	142	0.92	High confidence
CUDC-101	GAK	858	0.56	482	0.99	High confidence
CUDC-101	EGFR	932	0.79	739	0.91	High confidence
CUDC-101	BUB1	961	1.04	961	0.91	High confidence
CUDC-101	AK2	1036	1.22	1036	0.85	High confidence
CUDC-101	RIPK2	3884	0.28	1090	0.89	High confidence
CUDC-101	MAP3K1	2215	0.58	1278	0.90	High confidence
CUDC-101	FECH	2882	0.99	2867	0.89	High confidence
CUDC-101	OSBPL3	3492	0.83	2896	0.96	High confidence
CUDC-101	STK10	62758	0.92	57453	0.93	High confidence
Cyc-116	KLHL6	2	0.74	1	1.00	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Cyc-116	AP2A1	3	0.92	2	0.92	Low confidence	Cyc-116	MAPK9	821	0.70	575	0.94	High confidence
Cyc-116	AAK1	9	0.67	6	1.00	High confidence	Cyc-116	MST1R	755	0.76	575	0.80	High confidence
Cyc-116	CDK17	7	1.02	7	0.98	High confidence	Cyc-116	CLK1	819	0.72	586	0.84	High confidence
Cyc-116	NUAK2	8	0.77	7	1.00	Low confidence	Cyc-116	NQO2	648	1.07	648	0.99	High confidence
Cyc-116	Q6ZSR9	9	0.76	7	0.96	High confidence	Cyc-116	IKBKE	1110	0.62	689	0.96	High confidence
Cyc-116	BMP2K	11	0.66	7	1.00	High confidence	Cyc-116	ACAD10	747	0.96	716	0.98	Low confidence
Cyc-116	CSNK2B	9	1.08	9	0.98	High confidence	Cyc-116	FECH	787	0.99	783	0.99	High confidence
Cyc-116	STK26	14	0.88	13	1.00	Low confidence	Cyc-116	ULK3	1765	0.45	801	0.97	High confidence
Cyc-116	CSNK2A2	16	0.96	15	1.00	High confidence	Cyc-116	NEK3	971	0.85	830	0.96	High confidence
Cyc-116	TTK	16	1.07	16	0.87	Low confidence	Cyc-116	CSNK1E	983	0.85	841	0.94	High confidence
Cyc-116	EIF3J	22	1.11	22	0.99	High confidence	Cyc-116	FGFR1	1288	0.74	949	0.90	High confidence
Cyc-116	INCENP	40	0.89	36	0.98	High confidence	Cyc-116	CSNK1A1	1037	0.92	958	0.97	High confidence
Cyc-116	PLK4	85	0.51	43	0.60	Low confidence	Cyc-116	LIMK1	1656	0.59	984	0.97	High confidence
Cyc-116	CSNK2A1	49	1.02	49	1.00	High confidence	Cyc-116	TYK2	1958	0.52	1021	0.88	High confidence
Cyc-116	CSNK1G1	61	0.87	53	1.00	High confidence	Cyc-116	CIT	1097	1.21	1097	0.98	High confidence
Cyc-116	IRAK3	133	0.43	57	0.99	High confidence	Cyc-116	NEK1	1331	0.83	1099	0.90	High confidence
Cyc-116	LATS1	83	0.79	66	0.87	High confidence	Cyc-116	PRKD2	1694	0.66	1117	0.94	High confidence
Cyc-116	PIP4K2C	74	0.91	67	0.95	High confidence	Cyc-116	TBK1	1816	0.64	1162	0.97	High confidence
Cyc-116	AURKB	115	0.59	68	0.99	High confidence	Cyc-116	PRKD3	1571	0.74	1163	0.92	High confidence
Cyc-116	EPHB6	119	0.61	73	0.97	Low confidence	Cyc-116	ACVR1B	2984	0.43	1269	0.90	High confidence
Cyc-116	MOB1A	109	0.91	99	0.97	High confidence	Cyc-116	AZI2	1929	0.70	1354	0.94	High confidence
Cyc-116	BUB1	111	1.04	111	0.99	High confidence	Cyc-116	SIK2	2711	0.52	1405	0.94	High confidence
Cyc-116	AURKA	335	0.35	118	0.98	High confidence	Cyc-116	MAP2K5	1688	0.88	1478	0.86	High confidence
Cyc-116	NEK9	301	0.44	133	0.99	High confidence	Cyc-116	TBKBP1	1936	0.79	1536	0.92	High confidence
Cyc-116	GAPVD1	137	0.99	136	0.88	High confidence	Cyc-116	MARK3	2051	0.77	1581	0.98	High confidence
Cyc-116	MAPK10	175	0.84	147	0.83	High confidence	Cyc-116	CDK6	2093	0.82	1716	0.76	High confidence
Cyc-116	DYNLL1	341	0.50	171	0.99	High confidence	Cyc-116	TANK	2973	0.64	1891	0.97	High confidence
Cyc-116	GAK	350	0.56	196	0.99	High confidence	Cyc-116	TNIK	2135	1.02	2135	0.89	High confidence
Cyc-116	STK16	291	0.72	210	0.94	High confidence	Cyc-116	RET	4943	0.44	2178	0.95	High confidence
Cyc-116	FLT3	513	0.54	276	0.86	High confidence	Cyc-116	PRKAB1	3575	0.66	2367	0.88	High confidence
Cyc-116	MAPK8	460	0.65	298	0.99	High confidence	Cyc-116	FAM83B	2385	1.06	2385	0.87	High confidence
Cyc-116	TGFBR2	398	0.75	300	0.97	High confidence	Cyc-116	LIMK2	3842	0.66	2547	0.96	High confidence
Cyc-116	CSNK1D	419	0.82	344	0.99	High confidence	Cyc-116	RASSF5	2630	0.98	2586	0.92	High confidence
Cyc-116	MINK1	348	1.00	348	0.84	High confidence	Cyc-116	DCAF7	2978	0.90	2670	0.83	High confidence
Cyc-116	ACVR1	827	0.48	396	0.69	High confidence	Cyc-116	MAP4K3	4354	0.66	2855	0.86	High confidence
Cyc-116	FAM83A	459	0.88	404	0.83	High confidence	Cyc-116	IRAK1	4896	0.61	2988	0.91	High confidence
Cyc-116	ADCK1	876	0.62	545	0.95	High confidence	Cyc-116	PDPK1	2992	1.04	2992	0.94	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Cyc-116	MARK2	4178	0.75	3147	0.93	High confidence	Cyc-116	SIK3	12604	0.82	10318	0.76	High confidence
Cyc-116	RIPK2	11733	0.28	3292	0.92	High confidence	Cyc-116	PTK2	31957	0.41	13039	0.89	High confidence
Cyc-116	MAP4K4	3303	1.01	3303	0.78	High confidence	Cyc-116	PKN1	15054	0.87	13159	0.86	High confidence
Cyc-116	PRKAR2A	3455	1.26	3455	0.92	High confidence	Cyc-116	BMPR2	17076	0.84	14377	0.73	High confidence
Cyc-116	EPHA4	5613	0.62	3461	0.84	High confidence	Cyc-116	CCNT1	16423	0.98	16146	0.85	High confidence
Cyc-116	CDK16	3940	0.94	3714	0.92	High confidence	Cyc-116	STK3	22932	0.76	17526	0.95	High confidence
Cyc-116	CLK2	5943	0.65	3844	0.87	High confidence	Cyc-116	MELK	26287	0.88	23232	0.86	High confidence
Cyc-116	EPHA2	9520	0.41	3931	0.76	High confidence	Cyc-116	PAK4	50541	0.60	30371	0.91	High confidence
Cyc-116	STK10	4324	0.92	3958	0.95	High confidence	Cyc-116	CAMKK2	79547	0.66	52847	0.93	High confidence
Cyc-116	MAP3K11	5811	0.70	4048	0.93	High confidence	Cyc-116	ADCK3	73311	0.89	65302	0.94	High confidence
Cyc-116	CDK2	7948	0.53	4232	0.93	High confidence	Cyc-116	SLK	101943	0.89	90800	0.96	High confidence
Cyc-116	TGFBR1	6149	0.69	4262	0.87	High confidence	Dabrafenib	CDK16	14	0.94	13	1.00	High confidence
Cyc-116	EPHB4	9313	0.49	4608	0.81	High confidence	Dabrafenib	CDK2	36	0.53	19	0.96	High confidence
Cyc-116	RIPK3	5391	0.89	4820	0.87	High confidence	Dabrafenib	BRAF	22	1.11	22	0.92	High confidence
Cyc-116	ABL1	9229	0.55	5057	0.89	High confidence	Dabrafenib	LIMK1	55	0.59	33	0.99	High confidence
Cyc-116	SYK	6045	0.84	5068	0.93	High confidence	Dabrafenib	PRKD2	52	0.66	34	0.91	High confidence
Cyc-116	DYRK1A	5749	0.93	5364	0.94	High confidence	Dabrafenib	CDK17	36	1.02	36	0.99	High confidence
Cyc-116	JAK1	14464	0.37	5389	0.89	High confidence	Dabrafenib	ARAF	76	0.62	47	0.98	High confidence
Cyc-116	PRKAA1	8623	0.64	5500	0.95	High confidence	Dabrafenib	DYNLL1	102	0.50	51	0.98	High confidence
Cyc-116	CCNA2	7144	0.86	6158	0.81	High confidence	Dabrafenib	NEK9	121	0.44	53	0.99	High confidence
Cyc-116	RPS6KA4	10335	0.62	6381	0.91	High confidence	Dabrafenib	TNK1	153	0.43	66	0.97	High confidence
Cyc-116	CCNT2	7269	0.88	6397	0.86	Low confidence	Dabrafenib	LIMK2	124	0.66	82	1.00	High confidence
Cyc-116	IRAK4	8678	0.77	6719	0.98	High confidence	Dabrafenib	RIPK2	376	0.28	106	0.98	High confidence
Cyc-116	ZAK	9197	0.74	6839	0.87	High confidence	Dabrafenib	DYNLL2	205	0.55	112	0.97	High confidence
Cyc-116	STK4	9404	0.76	7171	0.92	High confidence	Dabrafenib	ERN2	148	0.78	116	0.91	Low confidence
Cyc-116	CSNK1G3	9585	0.79	7536	0.90	High confidence	Dabrafenib	PRKD3	162	0.74	120	0.98	High confidence
Cyc-116	PTK2B	18187	0.41	7540	0.85	High confidence	Dabrafenib	CDK4	126	1.00	126	0.89	High confidence
Cyc-116	EPHB2	14430	0.52	7565	0.75	High confidence	Dabrafenib	ZAK	248	0.74	184	0.99	High confidence
Cyc-116	BCR	16924	0.48	8087	0.88	High confidence	Dabrafenib	ULK1	282	0.67	188	0.93	High confidence
Cyc-116	CCNB1	10623	0.77	8140	0.90	High confidence	Dabrafenib	RIPK3	316	0.89	283	0.98	High confidence
Cyc-116	MAP3K1	14135	0.58	8159	0.79	High confidence	Dabrafenib	ABL2	919	0.33	305	0.99	High confidence
Cyc-116	ROCK2	10191	0.87	8885	0.95	High confidence	Dabrafenib	CDK6	388	0.82	318	0.97	High confidence
Cyc-116	WEE1	14111	0.63	8931	0.93	High confidence	Dabrafenib	CDK1	530	0.69	364	0.97	High confidence
Cyc-116	CDK9	13916	0.71	9901	0.93	High confidence	Dabrafenib	EPHB6	670	0.61	412	0.95	High confidence
Cyc-116	HCK	19375	0.52	10043	0.90	High confidence	Dabrafenib	NEK1	578	0.83	477	0.87	High confidence
Cyc-116	PRKAG1	16136	0.63	10212	0.88	High confidence	Dabrafenib	PLK4	1021	0.51	520	0.99	High confidence
Cyc-116	MAP4K5	13782	0.74	10255	0.90	High confidence	Dabrafenib	PAG1	1150	0.49	567	0.87	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Dabrafenib	ACVR1B	1414	0.43	601	0.95	High confidence
Dabrafenib	SIK2	1252	0.52	649	0.98	High confidence
Dabrafenib	UBASH3B	1322	0.49	653	0.90	High confidence
Dabrafenib	EPHA1	1752	0.40	705	0.54	Low confidence
Dabrafenib	FRK	2139	0.34	727	0.94	High confidence
Dabrafenib	LCK	1778	0.44	783	0.97	High confidence
Dabrafenib	FYN	1897	0.43	817	0.96	High confidence
Dabrafenib	CSK	1581	0.54	851	0.97	High confidence
Dabrafenib	CCNB2	1217	0.70	854	0.95	High confidence
Dabrafenib	EIF2AK1	1030	0.92	949	0.90	High confidence
Dabrafenib	MAP3K11	1451	0.70	1011	0.95	High confidence
Dabrafenib	CDK5	2040	0.52	1068	0.93	High confidence
Dabrafenib	YES1	3089	0.41	1276	0.85	Low confidence
Dabrafenib	LYN	2695	0.50	1353	0.97	High confidence
Dabrafenib	PTK6	2926	0.48	1414	0.95	High confidence
Dabrafenib	ERN1	1783	0.81	1453	0.87	High confidence
Dabrafenib	ULK3	3260	0.45	1480	0.90	Low confidence
Dabrafenib	ABL1	2820	0.55	1545	0.94	High confidence
Dabrafenib	FGR	3692	0.42	1549	0.95	High confidence
Dabrafenib	IRAK1	2562	0.61	1564	0.94	High confidence
Dabrafenib	MET	2034	0.80	1634	0.91	Low confidence
Dabrafenib	HCK	3176	0.52	1646	0.88	Low confidence
Dabrafenib	MELK	2055	0.88	1816	0.96	High confidence
Dabrafenib	SIK3	2449	0.82	2005	0.99	High confidence
Dabrafenib	CAMK4	2274	1.02	2274	0.79	High confidence
Dabrafenib	MAP2K5	2620	0.88	2294	0.96	High confidence
Dabrafenib	TGFBR1	3439	0.69	2384	0.91	High confidence
Dabrafenib	TGFBR2	3368	0.75	2534	0.92	High confidence
Dabrafenib	JAK2	4039	0.80	3223	0.91	High confidence
Dabrafenib	CDK18	NA	1.12	NA	NA	Low confidence
Dacomitinib	EGFR	7	0.79	5	0.96	High confidence
Dacomitinib	GAK	300	0.56	168	0.97	High confidence
Dacomitinib	RIPK2	3520	0.28	988	0.90	High confidence
Dacomitinib	INPPL1	2576	0.48	1245	0.79	High confidence
Dacomitinib	RIPK3	4068	0.89	3637	0.81	High confidence
Danusertib	INPPL1	4	0.48	2	0.96	High confidence
Danusertib	GRB2	5	0.62	3	0.92	High confidence
Danusertib	PLK4	9	0.51	5	0.97	High confidence
Danusertib	BCR	10	0.48	5	1.00	High confidence
Danusertib	RET	14	0.44	6	0.99	High confidence
Danusertib	ABL2	30	0.33	10	0.99	High confidence
Danusertib	AURKA	31	0.35	11	0.62	High confidence
Danusertib	EPHB4	37	0.49	18	0.99	High confidence
Danusertib	FAM58A	33	0.72	24	0.85	Low confidence
Danusertib	ABL1	43	0.55	24	0.99	High confidence
Danusertib	FYN	56	0.43	24	0.97	High confidence
Danusertib	EPHA2	59	0.41	24	0.94	High confidence
Danusertib	NUAK2	33	0.77	25	0.80	Low confidence
Danusertib	PTK2	81	0.41	33	1.00	High confidence
Danusertib	EPHA7	50	0.79	40	0.91	High confidence
Danusertib	UNC119	61	0.73	44	0.98	High confidence
Danusertib	TNK1	114	0.43	49	0.92	High confidence
Danusertib	PTK2B	120	0.41	50	1.00	High confidence
Danusertib	PRKAB2	87	0.60	52	0.89	High confidence
Danusertib	SRC	137	0.39	53	1.00	High confidence
Danusertib	YES1	134	0.41	55	0.98	High confidence
Danusertib	TNK2	132	0.45	59	0.92	High confidence
Danusertib	EPHB2	119	0.52	63	0.99	High confidence
Danusertib	PRKAA1	108	0.64	69	1.00	High confidence
Danusertib	PRKAG1	124	0.63	79	0.99	High confidence
Danusertib	FGFR1	110	0.74	81	0.96	High confidence
Danusertib	EPHA5	148	0.60	88	0.92	High confidence
Danusertib	PRKAG2	144	0.64	93	0.98	High confidence
Danusertib	CCNH	129	0.76	97	1.00	High confidence
Danusertib	PRKAB1	157	0.66	104	0.97	High confidence
Danusertib	CDK7	149	0.73	108	0.99	High confidence
Danusertib	FRK	331	0.34	112	0.97	High confidence
Danusertib	ERCC2	148	0.90	134	0.99	High confidence
Danusertib	HCK	265	0.52	137	0.99	High confidence
Danusertib	AURKB	238	0.59	139	0.95	High confidence
Danusertib	DDR1	227	0.63	142	0.95	High confidence
Danusertib	MNAT1	173	0.88	152	0.99	High confidence
Danusertib	JAK2	192	0.80	153	0.99	High confidence
Danusertib	EPHA4	258	0.62	159	0.91	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Danusertib	EPHB6	271	0.61	167	0.76	High confidence
Danusertib	EPHB3	200	0.88	175	0.94	High confidence
Danusertib	MAP4K1	271	0.73	196	0.91	High confidence
Danusertib	MARK4	278	0.83	232	0.95	High confidence
Danusertib	MAP4K2	435	0.59	256	0.97	High confidence
Danusertib	INCENP	303	0.89	271	0.97	High confidence
Danusertib	LCK	642	0.44	283	0.98	High confidence
Danusertib	MARK3	469	0.77	361	0.97	High confidence
Danusertib	MARK2	485	0.75	365	0.98	High confidence
Danusertib	MAPK7	545	0.78	425	0.74	High confidence
Danusertib	LYN	920	0.50	462	0.96	High confidence
Danusertib	RASSF2	517	0.93	480	0.91	High confidence
Danusertib	MAP3K1	882	0.58	509	0.97	High confidence
Danusertib	CAMKK2	785	0.66	521	0.99	High confidence
Danusertib	ACVR1B	1233	0.43	524	0.97	High confidence
Danusertib	ACVR1	1102	0.48	527	0.98	High confidence
Danusertib	FES	1608	0.37	594	0.91	High confidence
Danusertib	STK4	835	0.76	636	0.98	High confidence
Danusertib	LIMK1	1178	0.59	701	0.94	High confidence
Danusertib	FER	1659	0.42	701	0.96	High confidence
Danusertib	MAP4K5	964	0.74	718	0.97	High confidence
Danusertib	NTRK1	1085	0.71	766	0.74	Low confidence
Danusertib	DDR2	1115	0.76	850	0.97	High confidence
Danusertib	TGFBR2	1147	0.75	863	0.89	High confidence
Danusertib	SLK	971	0.89	865	0.98	High confidence
Danusertib	CDK3	866	2.15	866	0.95	High confidence
Danusertib	RASSF5	992	0.98	976	0.98	High confidence
Danusertib	STK26	1275	0.88	1120	0.97	High confidence
Danusertib	TEC	2846	0.40	1145	0.91	High confidence
Danusertib	MAP4K3	1819	0.66	1193	0.88	High confidence
Danusertib	SIK2	2422	0.52	1255	0.68	High confidence
Danusertib	FLT3	2637	0.54	1417	0.50	High confidence
Danusertib	BTK	3737	0.39	1461	0.96	High confidence
Danusertib	TGFBR1	2823	0.69	1957	0.91	High confidence
Danusertib	NEK9	4611	0.44	2034	0.97	High confidence
Danusertib	DYNLL1	4082	0.50	2045	0.95	High confidence
Danusertib	STK3	2726	0.76	2083	0.91	High confidence
Danusertib	STK10	3362	0.92	3078	0.95	High confidence
Danusertib	LIMK2	5670	0.66	3758	0.89	High confidence
Danusertib	CCNE1	6458	0.73	4707	0.96	High confidence
Danusertib	SYK	6207	0.84	5205	0.90	High confidence
Danusertib	PHKG2	7737	0.97	7503	0.81	High confidence
Danusertib	STK16	11579	0.72	8337	0.90	Low confidence
Danusertib	PRKD2	15761	0.66	10389	0.84	High confidence
Danusertib	CSNK2B	21838	1.08	21838	0.55	High confidence
Danusertib	MELK	33870	0.88	29933	0.70	High confidence
Danusertib	MAP4K4	62772	1.01	62772	0.88	High confidence
Dasatinib	SRC	7	0.39	3	1.00	High confidence
Dasatinib	PAG1	7	0.49	4	0.92	High confidence
Dasatinib	ABL2	11	0.33	4	1.00	High confidence
Dasatinib	EPHA5	6	0.60	4	1.00	High confidence
Dasatinib	EPHB4	7	0.49	4	1.00	High confidence
Dasatinib	YES1	9	0.41	4	1.00	High confidence
Dasatinib	FYN	9	0.43	4	1.00	High confidence
Dasatinib	EPHB2	8	0.52	4	1.00	High confidence
Dasatinib	FRK	14	0.34	5	0.94	High confidence
Dasatinib	ABL1	9	0.55	5	1.00	High confidence
Dasatinib	BCR	10	0.48	5	0.99	High confidence
Dasatinib	FGR	12	0.42	5	0.97	High confidence
Dasatinib	BTK	13	0.39	5	1.00	High confidence
Dasatinib	EPHA2	14	0.41	6	1.00	High confidence
Dasatinib	UNC119	9	0.73	7	0.90	Low confidence
Dasatinib	EPHA4	12	0.62	7	0.98	High confidence
Dasatinib	LCK	17	0.44	7	0.99	High confidence
Dasatinib	LYN	16	0.50	8	1.00	High confidence
Dasatinib	EPHA1	37	0.40	15	1.00	High confidence
Dasatinib	RIPK2	71	0.28	20	1.00	High confidence
Dasatinib	CSK	41	0.54	22	1.00	High confidence
Dasatinib	SIK2	48	0.52	25	0.97	High confidence
Dasatinib	TNK2	59	0.45	27	0.99	High confidence
Dasatinib	EPHB3	33	0.88	29	0.97	High confidence
Dasatinib	HCK	56	0.52	29	0.95	High confidence
Dasatinib	EPHB6	56	0.61	34	0.99	High confidence
Dasatinib	TEC	106	0.40	43	0.99	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Dasatinib	DDR1	69	0.63	43	0.99	High confidence	Dasatinib	ACVR2B	3727	0.67	2485	0.90	High confidence
Dasatinib	PTK6	123	0.48	59	0.95	High confidence	Dasatinib	CSNK1E	2920	0.85	2496	0.77	High confidence
Dasatinib	KIT	64	0.94	60	0.99	High confidence	Dasatinib	STK10	3090	0.92	2828	0.83	High confidence
Dasatinib	TESK1	89	0.74	65	0.93	High confidence	Dasatinib	TGFBR2	4148	0.75	3121	0.93	High confidence
Dasatinib	DDR2	92	0.76	70	0.99	High confidence	Dasatinib	BRAF	3231	1.11	3231	0.81	High confidence
Dasatinib	MYLK	86	0.83	72	0.86	High confidence	Dasatinib	MAP2K2	3370	1.17	3370	0.78	High confidence
Dasatinib	SIK3	180	0.82	147	0.90	High confidence	Dasatinib	MAP4K4	3871	1.01	3871	0.96	High confidence
Dasatinib	GAK	285	0.56	160	0.99	High confidence	Dasatinib	WEE1	7286	0.63	4611	0.72	Low confidence
Dasatinib	MINK1	209	1.00	209	0.95	Low confidence	Decernotinib	CCNT2	37	0.88	32	0.90	High confidence
Dasatinib	ZAK	291	0.74	217	0.99	High confidence	Decernotinib	TNK1	106	0.43	46	0.76	Low confidence
Dasatinib	NLK	388	0.66	258	0.92	High confidence	Decernotinib	SLK	65	0.89	58	1.00	High confidence
Dasatinib	PDGFRB	335	0.87	292	0.99	High confidence	Decernotinib	TOP2A	66	0.96	64	0.89	Low confidence
Dasatinib	PKN1	411	0.87	359	0.85	High confidence	Decernotinib	PRKCD	71	0.95	67	0.85	High confidence
Dasatinib	MAPKAPK2	744	0.72	538	0.97	High confidence	Decernotinib	STK10	78	0.92	71	0.99	High confidence
Dasatinib	TNK1	1568	0.43	678	0.71	High confidence	Decernotinib	MET	117	0.80	94	0.98	Low confidence
Dasatinib	PRKCQ	711	1.23	711	0.97	High confidence	Decernotinib	CDC42BPB	120	0.97	116	0.99	High confidence
Dasatinib	PAK4	1241	0.60	746	0.84	Low confidence	Decernotinib	PRKCA	161	0.73	117	0.98	High confidence
Dasatinib	MAPK14	1845	0.51	945	0.95	High confidence	Decernotinib	CDK17	139	1.02	139	0.88	High confidence
Dasatinib	MAP4K5	1284	0.74	955	0.97	High confidence	Decernotinib	TOP2B	148	1.20	148	0.60	High confidence
Dasatinib	RET	2168	0.44	955	0.96	High confidence	Decernotinib	PRKCB	534	0.80	426	0.92	High confidence
Dasatinib	LIMK2	1456	0.66	965	0.94	High confidence	Decernotinib	CDC42BPA	584	0.96	561	0.91	High confidence
Dasatinib	LIMK1	1906	0.59	1133	0.96	High confidence	Decernotinib	MARK3	730	0.77	562	0.97	High confidence
Dasatinib	ACVR1B	2726	0.43	1159	0.93	High confidence	Decernotinib	ABL1	1537	0.55	842	0.82	Low confidence
Dasatinib	PRKACB	2569	0.47	1215	0.90	High confidence	Decernotinib	STK26	1292	0.88	1135	0.95	High confidence
Dasatinib	PKMYT1	1673	0.73	1227	0.97	High confidence	Decernotinib	CDK9	2628	0.71	1870	0.97	High confidence
Dasatinib	TNIK	1262	1.02	1262	0.86	Low confidence	Decernotinib	PLK4	3851	0.51	1961	0.91	High confidence
Dasatinib	MAP3K1	2189	0.58	1263	0.96	High confidence	Decernotinib	MARK2	3066	0.75	2310	0.95	High confidence
Dasatinib	TYK2	2687	0.52	1401	0.95	High confidence	Decernotinib	Q6ZSR9	3472	0.76	2644	0.96	High confidence
Dasatinib	MAP2K5	1636	0.88	1432	0.90	High confidence	Decernotinib	TP53RK	2830	1.05	2830	0.98	High confidence
Dasatinib	TGFBR1	2486	0.69	1723	0.89	High confidence	Decernotinib	CSNK2A2	3354	0.96	3229	0.76	High confidence
Dasatinib	MAP4K2	2931	0.59	1729	0.93	High confidence	Decernotinib	OSGEP	3416	0.96	3279	0.80	High confidence
Dasatinib	EGFR	2372	0.79	1881	0.87	High confidence	Decernotinib	EIF3J	3405	1.11	3405	0.98	High confidence
Dasatinib	MAP3K2	3008	0.70	2100	0.96	High confidence	Decernotinib	TAOK1	5126	0.66	3407	0.94	High confidence
Dasatinib	MAP4K3	3232	0.66	2119	0.89	High confidence	Decernotinib	AAK1	6319	0.67	4253	0.85	High confidence
Dasatinib	MAP4K1	2921	0.73	2122	0.88	High confidence	Decernotinib	MAP3K2	6366	0.70	4445	0.85	High confidence
Dasatinib	SLK	2458	0.89	2189	0.83	High confidence	Decernotinib	BMP2K	8706	0.66	5754	0.99	High confidence
Dasatinib	SYK	2927	0.84	2455	0.94	High confidence	Decernotinib	CSNK2B	6473	1.08	6473	0.91	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Decernotinib	ABL2	21339	0.33	7071	0.95	High confidence
Decernotinib	TAOK3	10172	0.77	7870	0.92	High confidence
Decernotinib	ROCK1	14804	0.91	13462	0.92	High confidence
Decernotinib	CAMK2G	65625	0.22	14254	0.94	Low confidence
Decernotinib	CCNT1	14937	0.98	14686	0.96	High confidence
Decernotinib	CAMK2D	99556	0.20	20301	0.95	High confidence
Decernotinib	PKN1	56988	0.87	49813	0.93	High confidence
Decernotinib	ROCK2	64306	0.87	56066	0.96	High confidence
Defactinib	PTK2	1	0.41	0	1.00	High confidence
Defactinib	CDKL5	19	0.89	16	0.77	Low confidence
Defactinib	KIAA0195	31	0.66	21	0.98	High confidence
Defactinib	FAM58A	327	0.72	237	0.87	High confidence
Defactinib	MOB1A	348	0.91	318	0.96	High confidence
Defactinib	FLT3	632	0.54	340	0.93	High confidence
Defactinib	CABLES1	676	0.55	371	0.96	High confidence
Defactinib	FIBP	710	0.57	405	0.82	High confidence
Defactinib	PTK2B	1021	0.41	423	0.96	High confidence
Defactinib	NUAK2	588	0.77	454	0.92	Low confidence
Defactinib	KLHL6	667	0.74	494	0.77	Low confidence
Defactinib	AURKA	1759	0.35	622	0.92	High confidence
Defactinib	CDK12	730	1.12	730	0.93	High confidence
Defactinib	STK16	1240	0.72	893	0.56	High confidence
Defactinib	MELK	1015	0.88	897	0.85	High confidence
Defactinib	MAP3K11	1295	0.70	902	0.94	High confidence
Defactinib	NTRK1	1300	0.71	918	0.97	High confidence
Defactinib	CSNK2A1	1039	1.02	1039	0.83	High confidence
Defactinib	EIF3J	1064	1.11	1064	0.82	High confidence
Defactinib	CSNK2A2	1247	0.96	1201	0.87	High confidence
Defactinib	C2CD5	2215	0.55	1208	0.97	High confidence
Defactinib	FER	3085	0.42	1303	0.88	High confidence
Defactinib	GSK3B	2844	0.46	1322	0.80	High confidence
Defactinib	CCNK	1360	1.11	1360	0.94	High confidence
Defactinib	DYNLL1	2735	0.50	1370	0.59	High confidence
Defactinib	CDK5	2700	0.52	1414	0.90	High confidence
Defactinib	GSK3A	2924	0.50	1462	0.82	High confidence
Defactinib	AURKB	2501	0.59	1464	0.74	High confidence
Defactinib	PDPK1	1540	1.04	1540	0.92	High confidence
Defactinib	CSNK2B	1569	1.08	1569	0.90	High confidence
Defactinib	CCNT2	1825	0.88	1606	0.85	High confidence
Defactinib	CDK2	3111	0.53	1656	0.69	Low confidence
Defactinib	CDK7	2404	0.73	1744	0.93	High confidence
Defactinib	CDK9	2516	0.71	1790	0.91	High confidence
Defactinib	CCNH	2612	0.76	1980	0.84	High confidence
Defactinib	CDK1	2936	0.69	2014	0.37	Low confidence
Defactinib	CCNT1	2231	0.98	2194	0.92	High confidence
Defactinib	ERCC2	2497	0.90	2259	0.80	High confidence
Defactinib	STK4	3213	0.76	2450	0.90	High confidence
Defactinib	MARK2	3453	0.75	2601	0.91	High confidence
Defactinib	WEE1	4114	0.63	2604	0.83	High confidence
Defactinib	MNAT1	3277	0.88	2877	0.86	High confidence
Defactinib	CDK13	3107	1.25	3107	0.97	High confidence
Defactinib	MAP4K1	4317	0.73	3135	0.80	High confidence
Defactinib	TAOK1	4854	0.66	3227	0.91	High confidence
Defactinib	MARK3	5824	0.77	4490	0.94	High confidence
Defactinib	STK3	6476	0.76	4950	0.78	High confidence
Defactinib	LATS1	11492	0.79	9050	0.93	High confidence
Defactinib	DYRK1A	9776	0.93	9121	0.82	High confidence
Defactinib	TAOK3	13907	0.77	10759	0.84	High confidence
Defactinib	TNK1	26051	0.43	11269	0.93	High confidence
Defactinib	CCNB1	21042	0.77	16123	0.79	Low confidence
Defactinib	CCNA2	21119	0.86	18204	0.79	Low confidence
Defactinib	PAK4	36527	0.60	21950	0.93	High confidence
Defactinib	RET	62514	0.44	27542	0.91	High confidence
Defactinib	SLK	46037	0.89	41005	0.77	High confidence
Deforolimus	DYRK1B	1328	0.95	1262	0.87	Low confidence
Dinaciclib	AFF1	2	0.93	2	0.81	High confidence
Dinaciclib	CHD4	3	1.47	3	0.92	Low confidence
Dinaciclib	CCNI	10	0.37	4	0.83	Low confidence
Dinaciclib	AFF4	6	1.01	6	0.94	High confidence
Dinaciclib	CDK9	10	0.71	7	1.00	High confidence
Dinaciclib	C2CD5	13	0.55	7	1.00	High confidence
Dinaciclib	CABLES1	18	0.55	10	0.93	High confidence
Dinaciclib	CCNT1	10	0.98	10	1.00	High confidence
Dinaciclib	FIBP	18	0.57	10	0.93	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Dinaciclib	KIAA0195	21	0.66	14	0.96	High confidence	Dovitinib	BMP2K	98	0.66	65	1.00	High confidence
Dinaciclib	FAM58A	26	0.72	19	0.73	High confidence	Dovitinib	Q6ZSR9	136	0.76	104	0.99	High confidence
Dinaciclib	CDK13	21	1.25	21	0.98	High confidence	Dovitinib	MINK1	105	1.00	105	0.97	High confidence
Dinaciclib	CCNT2	24	0.88	21	0.94	High confidence	Dovitinib	MAP4K1	148	0.73	108	0.97	High confidence
Dinaciclib	CCNE1	35	0.73	26	0.97	High confidence	Dovitinib	MAP4K4	179	1.01	179	0.96	High confidence
Dinaciclib	CCNK	30	1.11	30	0.97	High confidence	Dovitinib	AAK1	310	0.67	209	1.00	High confidence
Dinaciclib	CDK12	32	1.12	32	0.95	High confidence	Dovitinib	FGFR1	329	0.74	243	0.94	High confidence
Dinaciclib	CDK6	39	0.82	32	0.93	High confidence	Dovitinib	AP2B1	281	1.01	281	0.77	High confidence
Dinaciclib	CDK2	169	0.53	90	0.91	High confidence	Dovitinib	JAK1	967	0.37	360	0.99	High confidence
Dinaciclib	CDK5	174	0.52	91	0.94	High confidence	Dovitinib	RPS6KA4	681	0.62	420	0.99	High confidence
Dinaciclib	STK26	111	0.88	98	0.98	High confidence	Dovitinib	SRC	1500	0.39	582	0.92	High confidence
Dinaciclib	CDK16	133	0.94	125	0.88	High confidence	Dovitinib	YES1	1430	0.41	591	0.97	High confidence
Dinaciclib	CCNA2	235	0.86	203	0.86	High confidence	Dovitinib	LCK	1615	0.44	712	0.94	High confidence
Dinaciclib	ICK	400	0.68	271	0.96	High confidence	Dovitinib	ULK1	1080	0.67	721	0.70	High confidence
Dinaciclib	GSKIP	417	0.84	349	0.97	High confidence	Dovitinib	FYN	1787	0.43	770	0.87	High confidence
Dinaciclib	CCNH	483	0.76	366	0.93	High confidence	Dovitinib	LYN	1566	0.50	786	0.96	High confidence
Dinaciclib	CAB39	379	1.12	379	0.95	High confidence	Dovitinib	MAP4K3	1282	0.66	841	0.97	High confidence
Dinaciclib	CDK7	566	0.73	411	0.90	High confidence	Dovitinib	DYNLL1	1718	0.50	861	0.96	High confidence
Dinaciclib	STK11	589	0.84	497	0.91	High confidence	Dovitinib	AURKB	1555	0.59	910	0.97	High confidence
Dinaciclib	MNAT1	617	0.88	542	0.93	High confidence	Dovitinib	PRKAG1	1469	0.63	930	0.99	High confidence
Dinaciclib	ERCC2	619	0.90	560	0.94	High confidence	Dovitinib	LATS1	1212	0.79	955	0.91	High confidence
Dinaciclib	CLK1	997	0.72	714	0.82	High confidence	Dovitinib	ULK3	2132	0.45	968	0.97	High confidence
Dinaciclib	CCNB1	937	0.77	718	0.98	High confidence	Dovitinib	MARK4	1174	0.83	976	0.98	High confidence
Dinaciclib	CDK17	778	1.02	778	0.96	High confidence	Dovitinib	MAP4K5	1356	0.74	1009	1.00	High confidence
Dinaciclib	CDK4	1145	1.00	1145	0.90	High confidence	Dovitinib	ABL2	3144	0.33	1042	0.97	High confidence
Dinaciclib	CCNB2	1665	0.70	1168	0.78	High confidence	Dovitinib	HCK	2085	0.52	1081	0.95	High confidence
Dinaciclib	CDK1	1773	0.69	1216	0.91	High confidence	Dovitinib	TBK1	1741	0.64	1114	0.99	High confidence
Dinaciclib	GSK3B	3076	0.46	1430	0.79	High confidence	Dovitinib	PRKAG2	1741	0.64	1123	0.98	High confidence
Dinaciclib	GSK3A	2950	0.50	1475	0.80	High confidence	Dovitinib	STK4	1490	0.76	1136	0.98	High confidence
Dinaciclib	CKS1B	2495	0.69	1725	0.78	High confidence	Dovitinib	PRKAA1	1789	0.64	1141	0.96	High confidence
Dinaciclib	TAOK2	3786	0.59	2233	0.93	High confidence	Dovitinib	PRKAB2	1998	0.60	1201	0.91	High confidence
Dinaciclib	TAOK3	3152	0.77	2439	0.98	High confidence	Dovitinib	RASSF2	1319	0.93	1225	0.93	High confidence
Dinaciclib	TAOK1	26874	0.66	17866	0.93	High confidence	Dovitinib	PRKAB1	1928	0.66	1276	0.97	High confidence
Dovitinib	FLT3	0.49	0.54	0.27	0.99	High confidence	Dovitinib	MAP3K11	1842	0.70	1283	0.97	High confidence
Dovitinib	CAMK1G	3	0.40	1	1.00	Low confidence	Dovitinib	TANK	2029	0.64	1291	0.96	High confidence
Dovitinib	RET	52	0.44	23	0.99	High confidence	Dovitinib	CSNK2A2	1391	0.96	1339	0.99	High confidence
Dovitinib	PDGFRB	41	0.87	35	0.98	High confidence	Dovitinib	KLHL6	1982	0.74	1469	0.80	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Dovitinib	CDK3	1479	2.15	1479	0.96	High confidence
Dovitinib	IKBKE	2433	0.62	1510	1.00	High confidence
Dovitinib	MAP2K5	1825	0.88	1598	0.98	High confidence
Dovitinib	TBKBP1	2278	0.79	1808	0.87	High confidence
Dovitinib	CSNK2A1	1816	1.02	1816	0.99	High confidence
Dovitinib	EIF3J	1845	1.11	1845	0.98	High confidence
Dovitinib	GAK	3344	0.56	1878	0.97	High confidence
Dovitinib	RASSF5	1981	0.98	1947	0.97	High confidence
Dovitinib	AP2A1	2151	0.92	1976	0.97	High confidence
Dovitinib	CSNK2B	1999	1.08	1999	0.99	High confidence
Dovitinib	INCENP	2251	0.89	2009	0.93	High confidence
Dovitinib	NEK9	4649	0.44	2051	0.98	High confidence
Dovitinib	IRAK4	2746	0.77	2126	0.95	High confidence
Dovitinib	MOB1A	2406	0.91	2200	0.96	High confidence
Dovitinib	STK3	2922	0.76	2233	0.94	High confidence
Dovitinib	NTRK1	3172	0.71	2239	0.89	High confidence
Dovitinib	RPS6KA1	3189	0.75	2398	0.98	High confidence
Dovitinib	MAP2K1	2420	1.23	2420	0.98	High confidence
Dovitinib	ABL1	4672	0.55	2560	0.94	High confidence
Dovitinib	PDPK1	2641	1.04	2641	0.96	High confidence
Dovitinib	MAP2K2	2782	1.17	2782	0.98	High confidence
Dovitinib	CDK6	3457	0.82	2835	0.94	High confidence
Dovitinib	CHEK1	3470	0.82	2862	0.94	High confidence
Dovitinib	MELK	3313	0.88	2928	0.95	High confidence
Dovitinib	NQO2	3011	1.07	3011	0.95	High confidence
Dovitinib	MAP4K2	5376	0.59	3172	0.96	High confidence
Dovitinib	AZI2	5244	0.70	3680	0.95	High confidence
Dovitinib	NUAK2	5497	0.77	4242	0.49	Low confidence
Dovitinib	RPS6KA3	6860	0.72	4973	0.92	High confidence
Dovitinib	MARK2	10258	0.75	7728	0.97	High confidence
Dovitinib	WEE1	13701	0.63	8671	0.98	High confidence
Dovitinib	PKN1	10290	0.87	8994	0.98	High confidence
Dovitinib	MARK3	13487	0.77	10397	0.95	High confidence
Dovitinib	BCR	36337	0.48	17364	0.79	High confidence
Encorafenib	LIMK1	43	0.59	26	0.92	High confidence
Encorafenib	FANCD2	36	1.15	36	0.98	Low confidence
Encorafenib	COX6C	38	1.19	38	0.99	Low confidence
Encorafenib	PCYT1A	41	1.08	41	0.99	Low confidence
Encorafenib	SNRPF	45	1.17	45	0.97	High confidence
Encorafenib	EXOC4	46	1.08	46	1.00	Low confidence
Encorafenib	ADSL	49	1.23	49	0.90	Low confidence
Encorafenib	DNAJC9	57	1.51	57	0.99	Low confidence
Encorafenib	CKAP5	65	1.46	65	0.94	High confidence
Encorafenib	LIMK2	145	0.66	96	0.95	High confidence
Encorafenib	CDK4	112	1.00	112	0.94	High confidence
Encorafenib	BRAF	124	1.11	124	0.94	High confidence
Encorafenib	PGRMC1	204	1.15	204	0.97	Low confidence
Encorafenib	IRAK1	405	0.61	247	0.94	High confidence
Encorafenib	RIPK2	1151	0.28	323	0.90	High confidence
Encorafenib	GSK3B	915	0.46	425	0.93	High confidence
Encorafenib	NLK	1101	0.66	732	0.92	High confidence
Encorafenib	ZAK	1055	0.74	785	0.94	High confidence
Encorafenib	MAP3K11	1166	0.70	812	0.94	High confidence
Encorafenib	MAPK9	1307	0.70	915	0.97	High confidence
Encorafenib	RIPK3	1081	0.89	967	0.91	High confidence
Encorafenib	GSKIP	1431	0.84	1199	0.93	High confidence
Encorafenib	MAP3K4	2139	0.67	1437	0.68	High confidence
Encorafenib	MAPK8	2878	0.65	1865	0.94	High confidence
Encorafenib	TAOK3	4298	0.77	3325	0.83	High confidence
Encorafenib	CSNK1A1	3610	0.92	3334	0.84	High confidence
Encorafenib	GSK3A	10513	0.50	5259	0.75	High confidence
Encorafenib	MAPKAPK2	20399	0.72	14742	0.77	High confidence
ENMD-2076	FLT3	15	0.54	8	0.95	High confidence
ENMD-2076	SRPR	8	1.29	8	0.97	Low confidence
ENMD-2076	AURKA	227	0.35	80	0.92	High confidence
ENMD-2076	PLK4	253	0.51	129	0.88	High confidence
ENMD-2076	NTRK1	292	0.71	206	0.80	High confidence
ENMD-2076	AURKB	418	0.59	245	0.91	High confidence
ENMD-2076	FGFR1	555	0.74	409	0.82	High confidence
ENMD-2076	YES1	1068	0.41	441	0.56	High confidence
ENMD-2076	ULK3	1048	0.45	476	0.89	High confidence
ENMD-2076	RET	1105	0.44	487	0.83	High confidence
ENMD-2076	STK16	976	0.72	702	0.81	High confidence
ENMD-2076	DDR1	1204	0.63	755	0.77	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
ENMD-2076	TYK2	2294	0.52	1196	0.72	High confidence	Erlotinib	ACAD11	4222	0.98	4147	0.95	High confidence
ENMD-2076	BMP2K	2252	0.66	1488	0.88	High confidence	Erlotinib	ABL1	7896	0.55	4327	0.89	High confidence
ENMD-2076	SRC	4786	0.39	1858	0.87	High confidence	Erlotinib	BMP2K	9423	0.66	6228	0.91	High confidence
ENMD-2076	PRKAB1	2818	0.66	1866	0.69	High confidence	Erlotinib	FECH	6940	0.99	6905	0.78	High confidence
ENMD-2076	TGFBR2	3121	0.75	2348	0.92	High confidence	Erlotinib	RIPK2	40741	0.28	11433	0.91	High confidence
ENMD-2076	DYNLL1	5227	0.50	2618	0.72	High confidence	Fasudil	PKN3	99	1.06	99	0.70	Low confidence
ENMD-2076	PRKAG1	4661	0.63	2950	0.72	High confidence	Fasudil	CLK1	213	0.72	152	0.75	Low confidence
ENMD-2076	LCK	6725	0.44	2962	0.76	High confidence	Fasudil	PRKX	304	0.81	247	0.96	High confidence
ENMD-2076	NEK9	6747	0.44	2977	0.91	High confidence	Fasudil	INA	1406	0.28	388	0.94	Low confidence
ENMD-2076	FYN	6999	0.43	3016	0.91	High confidence	Fasudil	PSMG1	789	1.06	789	0.82	High confidence
ENMD-2076	DYNLL2	5763	0.55	3149	0.76	High confidence	Fasudil	PKN1	963	0.87	841	0.98	High confidence
ENMD-2076	DDR2	4489	0.76	3421	0.88	High confidence	Fasudil	ROCK1	996	0.91	906	0.98	High confidence
ENMD-2076	MAP4K5	5084	0.74	3783	0.91	High confidence	Fasudil	ROCK2	1082	0.87	943	0.98	High confidence
ENMD-2076	CSNK2A2	4585	0.96	4414	0.86	High confidence	Fasudil	AFF4	1674	1.01	1674	0.90	Low confidence
ENMD-2076	CSNK2A1	5575	1.02	5575	0.82	High confidence	Fasudil	MELK	2175	0.88	1922	0.88	High confidence
ENMD-2076	CSNK2B	9143	1.08	9143	0.92	High confidence	Fasudil	NQO2	2451	1.07	2451	0.93	High confidence
ENMD-2076	EIF3J	9851	1.11	9851	0.91	High confidence	Fasudil	PKN2	3186	0.82	2599	0.94	High confidence
Entrectinib	NTRK1	2	0.71	2	0.91	High confidence	Fasudil	CDK12	3480	1.12	3480	0.84	High confidence
Entrectinib	TNK2	932	0.45	420	0.97	High confidence	Fasudil	LATS1	5295	0.79	4170	0.96	High confidence
Entrectinib	TNK1	3435	0.43	1486	0.95	High confidence	Fasudil	CDK9	5975	0.71	4251	0.93	High confidence
Enzastaurin	GSK3B	409	0.46	190	0.98	High confidence	Fasudil	CDK13	4518	1.25	4518	0.96	High confidence
Enzastaurin	GSK3A	492	0.50	246	0.97	High confidence	Fasudil	PRKCD	5056	0.95	4789	0.92	High confidence
Enzastaurin	PRKCA	720	0.73	524	0.86	High confidence	Fasudil	PRKD2	9734	0.66	6416	0.96	High confidence
Enzastaurin	PRKCD	2660	0.95	2519	0.68	High confidence	Fasudil	CCNK	7356	1.11	7356	0.82	High confidence
Enzastaurin	PRKCB	3630	0.80	2897	0.78	High confidence	Fasudil	PRKD3	31532	0.74	23341	0.92	High confidence
Erlotinib	BUB1	113	1.04	113	0.83	High confidence	Fasudil	CCNT1	26103	0.98	25663	0.90	High confidence
Erlotinib	GAK	921	0.56	517	0.97	High confidence	Fasudil	BMP2K	51120	0.66	33788	0.95	Low confidence
Erlotinib	STK10	787	0.92	721	0.97	High confidence	Fasudil	CIT	48876	1.21	48876	0.93	High confidence
Erlotinib	INPPL1	1740	0.48	841	0.84	High confidence	Fedratinib	GAK	82	0.56	46	0.70	High confidence
Erlotinib	RET	3062	0.44	1349	0.95	High confidence	Fedratinib	PTK2	422	0.41	172	0.65	High confidence
Erlotinib	SLK	1674	0.89	1491	0.98	High confidence	Fedratinib	AP2B1	181	1.01	181	0.97	High confidence
Erlotinib	BCR	3835	0.48	1832	0.98	High confidence	Fedratinib	ADCK1	372	0.62	231	0.71	High confidence
Erlotinib	GRB2	3421	0.62	2134	0.93	High confidence	Fedratinib	Q6ZSR9	364	0.76	277	0.60	High confidence
Erlotinib	EGFR	2729	0.79	2164	0.47	High confidence	Fedratinib	AP2A1	379	0.92	348	0.90	High confidence
Erlotinib	MAP3K1	3892	0.58	2247	0.96	High confidence	Fedratinib	AAK1	533	0.67	359	0.66	High confidence
Erlotinib	DCTPP1	3262	0.94	3054	0.91	High confidence	Fedratinib	INCENP	417	0.89	372	0.87	High confidence
Erlotinib	MAP2K5	4460	0.88	3906	0.91	High confidence	Fedratinib	BMP2K	784	0.66	519	0.68	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Fedratinib	STK16	787	0.72	566	0.71	High confidence
Fedratinib	FLT3	1247	0.54	670	0.79	High confidence
Fedratinib	SIK2	1945	0.52	1008	0.44	High confidence
Fedratinib	ACVR1	2737	0.48	1310	0.44	High confidence
Fedratinib	MAPK7	1683	0.78	1311	0.51	High confidence
Fedratinib	IRAK3	3299	0.43	1415	0.37	High confidence
Fedratinib	TNK2	3152	0.45	1419	0.42	High confidence
Fedratinib	MAPK9	2244	0.70	1571	0.62	High confidence
Fedratinib	NEK9	3705	0.44	1634	0.47	High confidence
Fedratinib	RET	3717	0.44	1638	0.40	High confidence
Fedratinib	BCR	3613	0.48	1727	0.28	High confidence
Fedratinib	WEE1	3082	0.63	1951	0.47	High confidence
Fedratinib	PLK4	3836	0.51	1954	0.49	High confidence
Fedratinib	AZI2	3079	0.70	2161	0.44	High confidence
Fedratinib	TANK	3420	0.64	2176	0.46	High confidence
Fedratinib	MAPK8	3430	0.65	2223	0.69	High confidence
Fedratinib	TBK1	3488	0.64	2230	0.44	High confidence
Fedratinib	IKBKE	3646	0.62	2264	0.73	High confidence
Fedratinib	AURKB	3975	0.59	2327	0.51	High confidence
Fedratinib	TBKBP1	2983	0.79	2368	0.43	High confidence
Fedratinib	CSNK2A2	2721	0.96	2619	0.76	High confidence
Fedratinib	CSNK2A1	3248	1.02	3248	0.72	High confidence
Fedratinib	CSNK2B	3590	1.08	3590	0.72	High confidence
Fedratinib	NQO2	4314	1.07	4314	0.50	High confidence
Fedratinib	EIF3J	5484	1.11	5484	0.67	High confidence
Filgotinib	STK10	2089	0.92	1912	0.92	High confidence
Filgotinib	ADCK1	3258	0.62	2028	0.81	High confidence
Filgotinib	MAPK10	2547	0.84	2140	0.71	High confidence
Filgotinib	CAMKK2	5469	0.66	3633	0.67	High confidence
Filgotinib	Q6ZSR9	5757	0.76	4384	0.77	High confidence
Filgotinib	AP2A1	5051	0.92	4640	0.74	Low confidence
Filgotinib	IRAK1	7724	0.61	4714	0.55	High confidence
Filgotinib	AAK1	7413	0.67	4990	0.72	High confidence
Filgotinib	BMP2K	9970	0.66	6590	0.81	High confidence
Filgotinib	SLK	10411	0.89	9273	0.77	High confidence
Filgotinib	CSNK2A1	10519	1.02	10519	0.74	High confidence
Foretinib	EPHA7	6	0.79	5	0.88	Low confidence
Foretinib	RET	15	0.44	6	1.00	High confidence
Foretinib	FRK	81	0.34	28	0.93	High confidence
Foretinib	SRC	72	0.39	28	0.90	High confidence
Foretinib	LCK	93	0.44	41	0.98	High confidence
Foretinib	NTRK1	69	0.71	49	0.95	High confidence
Foretinib	ZAK	72	0.74	53	0.93	High confidence
Foretinib	RIPK2	191	0.28	54	0.98	High confidence
Foretinib	ABL2	163	0.33	54	0.99	High confidence
Foretinib	FLT3	112	0.54	60	0.98	High confidence
Foretinib	EPHA2	153	0.41	63	0.99	High confidence
Foretinib	DDR1	105	0.63	66	0.99	High confidence
Foretinib	HCK	127	0.52	66	1.00	High confidence
Foretinib	GRB2	141	0.62	88	0.93	High confidence
Foretinib	MST1R	120	0.76	91	1.00	High confidence
Foretinib	MET	117	0.80	94	0.96	High confidence
Foretinib	ABL1	191	0.55	104	0.99	High confidence
Foretinib	BCR	222	0.48	106	0.97	High confidence
Foretinib	PLK4	209	0.51	106	0.94	High confidence
Foretinib	PIP4K2C	120	0.91	109	0.86	High confidence
Foretinib	LYN	224	0.50	112	0.97	High confidence
Foretinib	MAP2K5	183	0.88	160	0.97	High confidence
Foretinib	RIPK3	180	0.89	161	0.98	High confidence
Foretinib	DDR2	239	0.76	182	0.98	High confidence
Foretinib	EPHA5	365	0.60	219	0.95	High confidence
Foretinib	INPPL1	552	0.48	267	0.99	High confidence
Foretinib	AURKB	469	0.59	275	0.94	High confidence
Foretinib	FER	861	0.42	364	0.97	High confidence
Foretinib	BTK	1081	0.39	423	0.99	High confidence
Foretinib	PTK6	913	0.48	441	0.90	High confidence
Foretinib	MAP4K5	665	0.74	495	0.98	High confidence
Foretinib	EPHB6	928	0.61	570	0.96	High confidence
Foretinib	PTK2B	1595	0.41	661	0.96	High confidence
Foretinib	EPHB4	1624	0.49	804	0.98	High confidence
Foretinib	EPHA4	1508	0.62	930	0.95	High confidence
Foretinib	INCENP	1179	0.89	1052	0.95	High confidence
Foretinib	MAP2K2	1099	1.17	1099	0.93	High confidence
Foretinib	EPHA1	3601	0.40	1448	0.89	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Foretinib	TNK1	6132	0.43	2653	0.96	High confidence
Foretinib	TNIK	3787	1.02	3787	0.84	High confidence
Foretinib	MAP2K1	3933	1.23	3933	0.97	High confidence
Foretinib	EPHB2	9592	0.52	5029	0.95	High confidence
Foretinib	EPHB3	7318	0.88	6410	0.94	High confidence
Fostamatinib	DYNLL1	58	0.50	29	0.99	High confidence
Fostamatinib	NEK9	93	0.44	41	0.99	High confidence
Fostamatinib	TNK1	371	0.43	160	0.96	High confidence
Fostamatinib	AURKA	847	0.35	300	0.97	High confidence
Fostamatinib	PLK4	1119	0.51	570	0.98	High confidence
Fostamatinib	FLT3	1568	0.54	843	0.92	High confidence
Fostamatinib	ADCK1	1720	0.62	1071	0.94	High confidence
Fostamatinib	RET	2604	0.44	1147	0.97	High confidence
Fostamatinib	IRAK3	3008	0.43	1290	0.93	High confidence
Fostamatinib	IKBKE	2126	0.62	1320	0.91	High confidence
Fostamatinib	MAPK9	2191	0.70	1533	0.98	High confidence
Fostamatinib	MAPK8	3104	0.65	2011	0.98	High confidence
Fostamatinib	MST1R	2799	0.76	2132	0.86	High confidence
Fostamatinib	LATS1	2738	0.79	2157	0.97	High confidence
Fostamatinib	STK16	3450	0.72	2484	0.88	High confidence
Fostamatinib	MAP3K11	3598	0.70	2506	0.92	High confidence
Fostamatinib	AURKB	4356	0.59	2550	0.95	High confidence
Fostamatinib	PIP4K2C	2905	0.91	2635	0.97	High confidence
Fostamatinib	MOB1A	4152	0.91	3797	0.92	High confidence
Fostamatinib	PTK2	13236	0.41	5400	0.92	High confidence
Galunisertib	RIPK3	13	0.89	11	0.95	High confidence
Galunisertib	ACVR1B	38	0.43	16	0.97	High confidence
Galunisertib	MINK1	18	1.00	18	0.73	Low confidence
Galunisertib	RIPK2	136	0.28	38	1.00	High confidence
Galunisertib	TGFBR1	114	0.69	79	0.96	High confidence
Galunisertib	FAM83B	287	1.06	287	0.77	Low confidence
Galunisertib	GAK	881	0.56	495	0.98	High confidence
Galunisertib	GAPVD1	943	0.99	938	0.89	High confidence
Galunisertib	TNIK	1208	1.02	1208	0.54	Low confidence
Galunisertib	MAP4K4	1693	1.01	1693	0.89	High confidence
Galunisertib	CSNK1E	9244	0.85	7903	0.93	High confidence
Galunisertib	ADCK3	13750	0.89	12248	0.97	Low confidence
Galunisertib	CSNK1D	19631	0.82	16150	0.96	High confidence
Galunisertib	CSNK1A1	20954	0.92	19352	0.95	High confidence
GDC-0994	MAPK3	28	0.66	19	0.94	High confidence
GDC-0994	MAPK1	47	0.46	22	0.99	High confidence
GDC-0994	CAMK1G	292	0.40	117	0.91	High confidence
GDC-0994	TAOK1	346	0.66	230	0.47	High confidence
GDC-0994	MET	470	0.80	378	0.75	High confidence
GDC-0994	AAK1	596	0.67	401	0.92	High confidence
GDC-0994	Q6ZSR9	612	0.76	466	0.80	High confidence
GDC-0994	GSK3B	1288	0.46	599	0.78	High confidence
GDC-0994	PSMD7	628	1.30	628	0.89	Low confidence
GDC-0994	FIBP	1557	0.57	888	0.81	High confidence
GDC-0994	CABLES1	3205	0.55	1761	0.77	High confidence
GDC-0994	IGF2BP3	1988	1.30	1988	0.92	Low confidence
GDC-0994	KIAA0195	3085	0.66	2039	0.83	Low confidence
GDC-0994	GSK3A	4371	0.50	2186	0.81	High confidence
GDC-0994	BMP2K	4516	0.66	2985	0.65	High confidence
GDC-0994	PDGFRB	4563	0.87	3988	0.92	High confidence
GDC-0994	CDK13	5744	1.25	5744	0.85	High confidence
GDC-0994	ACVR1	12239	0.48	5859	0.58	High confidence
GDC-0994	ADRBK1	17728	1.13	17728	0.68	High confidence
GDC-0994	GAK	48283	0.56	27114	0.93	High confidence
GDC-0994	C2CD5	88312	0.55	48154	0.94	High confidence
Gefitinib	EGFR	521	0.79	413	0.84	High confidence
Gefitinib	RIPK2	3220	0.28	903	0.89	High confidence
Gefitinib	GAK	1693	0.56	951	0.93	High confidence
Gefitinib	FAM83A	1220	0.88	1075	0.93	High confidence
Gefitinib	RIPK3	2980	0.89	2664	0.90	High confidence
Gefitinib	MET	5441	0.80	4372	0.74	High confidence
Gefitinib	STK10	5720	0.92	5236	0.95	High confidence
Gefitinib	FECH	6716	0.99	6682	0.84	High confidence
Gefitinib	ACAD10	35261	0.96	33795	0.79	Low confidence
Gilteritinib	ULK3	14	0.45	6	0.99	High confidence
Gilteritinib	FLT3	13	0.54	7	1.00	High confidence
Gilteritinib	IRAK3	17	0.43	7	0.99	High confidence
Gilteritinib	GAK	15	0.56	9	0.99	High confidence
Gilteritinib	Q6ZSR9	15	0.76	11	0.99	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Gilteritinib	PLK4	36	0.51	18	0.99	Low confidence
Gilteritinib	AAK1	38	0.67	25	0.99	High confidence
Gilteritinib	TNK1	89	0.43	39	0.86	High confidence
Gilteritinib	ACVR1	82	0.48	39	0.99	High confidence
Gilteritinib	BMP2K	69	0.66	46	0.99	High confidence
Gilteritinib	PHKG2	49	0.97	48	0.99	Low confidence
Gilteritinib	RET	114	0.44	50	0.85	High confidence
Gilteritinib	FDPS	62	1.23	62	0.87	Low confidence
Gilteritinib	SLK	77	0.89	68	0.98	High confidence
Gilteritinib	DDB1	79	1.14	79	0.85	High confidence
Gilteritinib	MAP4K1	149	0.73	108	0.99	Low confidence
Gilteritinib	BMPR1A	229	0.53	121	0.96	High confidence
Gilteritinib	TPRKB	129	0.95	122	0.93	High confidence
Gilteritinib	STK10	163	0.92	149	0.87	High confidence
Gilteritinib	ADCK1	244	0.62	152	0.94	High confidence
Gilteritinib	CAMK2G	779	0.22	169	0.99	High confidence
Gilteritinib	AURKA	520	0.35	184	0.89	Low confidence
Gilteritinib	MYLK	225	0.83	188	0.92	High confidence
Gilteritinib	FER	445	0.42	188	0.96	High confidence
Gilteritinib	BUB1	191	1.04	191	0.97	High confidence
Gilteritinib	CYC1	202	1.23	202	0.96	Low confidence
Gilteritinib	MAP4K4	202	1.01	202	0.87	High confidence
Gilteritinib	CAMK2D	1016	0.20	207	0.99	High confidence
Gilteritinib	ACSL5	208	1.06	208	0.99	Low confidence
Gilteritinib	RPS4X	211	1.40	211	0.93	High confidence
Gilteritinib	CTTN	248	0.88	219	0.81	Low confidence
Gilteritinib	LATS1	280	0.79	221	0.94	High confidence
Gilteritinib	STK24	230	1.06	230	0.87	Low confidence
Gilteritinib	EPHB6	392	0.61	241	0.91	Low confidence
Gilteritinib	MAP4K2	413	0.59	244	0.97	High confidence
Gilteritinib	NEK2	355	0.69	247	0.95	Low confidence
Gilteritinib	MAPK15	532	0.49	263	0.91	Low confidence
Gilteritinib	AP1B1	316	0.86	270	0.92	Low confidence
Gilteritinib	STK16	409	0.72	295	0.88	High confidence
Gilteritinib	TMEM33	297	1.18	297	0.96	Low confidence
Gilteritinib	AP1G1	302	1.22	302	0.96	High confidence
Gilteritinib	SSR1	331	1.03	331	0.96	Low confidence
Gilteritinib	RPL31	336	1.91	336	0.95	Low confidence
Gilteritinib	CSNK2B	340	1.08	340	0.90	High confidence
Gilteritinib	RPL35A	373	1.52	373	0.95	High confidence
Gilteritinib	SYNGR2	399	1.16	399	0.97	High confidence
Gilteritinib	AP2M1	402	1.03	402	0.93	High confidence
Gilteritinib	CAMK4	421	1.02	421	0.91	High confidence
Gilteritinib	MAPK9	615	0.70	430	0.89	High confidence
Gilteritinib	DHCR24	432	1.09	432	0.87	High confidence
Gilteritinib	YES1	1076	0.41	445	0.91	High confidence
Gilteritinib	FANCI	465	0.97	449	0.92	Low confidence
Gilteritinib	SLC25A5	451	1.13	451	0.82	High confidence
Gilteritinib	TUFM	464	1.27	464	0.79	Low confidence
Gilteritinib	RIPK2	1716	0.28	482	0.95	High confidence
Gilteritinib	SLC25A6	495	1.11	495	0.89	Low confidence
Gilteritinib	MAP2K2	502	1.17	502	0.93	High confidence
Gilteritinib	EIF3J	508	1.11	508	0.84	High confidence
Gilteritinib	PDGFRB	584	0.87	510	0.87	High confidence
Gilteritinib	PTK2B	1231	0.41	510	0.95	High confidence
Gilteritinib	MAPK10	609	0.84	512	0.77	High confidence
Gilteritinib	MAP3K2	767	0.70	536	0.92	High confidence
Gilteritinib	BMPR1B	932	0.61	572	0.94	High confidence
Gilteritinib	PRKCA	812	0.73	591	0.98	High confidence
Gilteritinib	MAP3K11	861	0.70	600	0.91	High confidence
Gilteritinib	MAP4K3	923	0.66	605	0.86	High confidence
Gilteritinib	ADD2	1869	0.35	661	0.90	Low confidence
Gilteritinib	RPL10	710	1.40	710	0.94	High confidence
Gilteritinib	MAPK8	1135	0.65	736	0.84	High confidence
Gilteritinib	ACP1	748	1.06	748	0.88	Low confidence
Gilteritinib	RAN	759	1.45	759	0.79	Low confidence
Gilteritinib	MST1R	1055	0.76	804	0.97	High confidence
Gilteritinib	CSNK2A1	811	1.02	811	0.84	High confidence
Gilteritinib	CSNK2A2	997	0.96	960	0.85	High confidence
Gilteritinib	DYNLL2	2081	0.55	1137	0.87	High confidence
Gilteritinib	STK26	1302	0.88	1143	0.93	High confidence
Gilteritinib	RIPK3	1458	0.89	1304	0.88	High confidence
Gilteritinib	SNRNP200	1382	1.20	1382	0.93	High confidence
Gilteritinib	IKBKE	2365	0.62	1468	0.87	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Gilteritinib	HCK	3075	0.52	1594	0.85	High confidence	Golvatinib	PSMD12	150	1.30	150	0.93	Low confidence
Gilteritinib	TBKBP1	2022	0.79	1604	0.94	High confidence	Golvatinib	RIPK3	190	0.89	170	0.93	High confidence
Gilteritinib	NQO2	1701	1.07	1701	0.88	High confidence	Golvatinib	RET	397	0.44	175	0.99	High confidence
Gilteritinib	IRAK4	2269	0.77	1757	0.92	High confidence	Golvatinib	STK24	207	1.06	207	0.97	Low confidence
Gilteritinib	MAP2K6	1895	1.01	1895	0.94	High confidence	Golvatinib	EPHA5	357	0.60	214	0.93	High confidence
Gilteritinib	CDK4	1955	1.00	1955	0.84	High confidence	Golvatinib	EPHB6	415	0.61	255	0.98	High confidence
Gilteritinib	MAP2K5	2329	0.88	2040	0.99	High confidence	Golvatinib	TESK1	388	0.74	286	0.99	High confidence
Gilteritinib	TAOK2	3548	0.59	2092	0.89	High confidence	Golvatinib	UNC119	409	0.73	297	0.92	Low confidence
Gilteritinib	AZI2	3297	0.70	2314	0.98	High confidence	Golvatinib	EPHB2	576	0.52	302	0.98	High confidence
Gilteritinib	CIT	2346	1.21	2346	0.89	High confidence	Golvatinib	LCK	1190	0.44	524	0.96	High confidence
Gilteritinib	SLC16A3	2592	1.14	2592	0.79	High confidence	Golvatinib	NTRK1	852	0.71	601	0.94	High confidence
Gilteritinib	CAMKK2	3985	0.66	2648	0.97	High confidence	Golvatinib	ABL1	1152	0.55	631	0.98	High confidence
Gilteritinib	RPS6KA3	3672	0.72	2661	0.90	High confidence	Golvatinib	ZAK	935	0.74	695	0.94	High confidence
Gilteritinib	TP53RK	2716	1.05	2716	0.91	High confidence	Golvatinib	BCR	1471	0.48	703	0.87	High confidence
Gilteritinib	MAP2K1	2755	1.23	2755	0.91	High confidence	Golvatinib	ABL2	2179	0.33	722	0.99	High confidence
Gilteritinib	NEK3	3323	0.85	2840	0.97	High confidence	Golvatinib	PDGFRB	1037	0.87	907	0.87	Low confidence
Gilteritinib	EPHA7	3764	0.79	2980	0.92	High confidence	Golvatinib	ERN2	1259	0.78	986	0.95	Low confidence
Gilteritinib	MAP4K5	4187	0.74	3115	0.96	High confidence	Golvatinib	PTK2B	2427	0.41	1006	0.93	High confidence
Gilteritinib	TNK2	6994	0.45	3149	0.90	High confidence	Golvatinib	EPHA4	1675	0.62	1033	0.89	High confidence
Gilteritinib	PRKX	4222	0.81	3429	0.79	High confidence	Golvatinib	HCK	2065	0.52	1070	0.99	High confidence
Gilteritinib	RPS6KA1	4572	0.75	3438	0.89	High confidence	Golvatinib	EIF2AK1	1172	0.92	1080	0.90	High confidence
Gilteritinib	EGFR	4416	0.79	3502	0.95	High confidence	Golvatinib	MAP3K1	1916	0.58	1106	0.97	High confidence
Gilteritinib	OSGEP	3671	0.96	3523	0.80	Low confidence	Golvatinib	MAPK14	2169	0.51	1111	0.95	High confidence
Gilteritinib	SYK	4822	0.84	4043	0.91	High confidence	Golvatinib	RRP8	1360	1.25	1360	0.72	Low confidence
Gilteritinib	RABL3	4842	1.00	4830	0.87	Low confidence	Golvatinib	LYN	3043	0.50	1527	0.97	High confidence
Gilteritinib	PAICS	5481	1.39	5481	0.91	Low confidence	Golvatinib	TAOK2	3597	0.59	2121	0.87	High confidence
Gilteritinib	ACTR3	5511	1.05	5511	0.86	High confidence	Golvatinib	MAP4K5	2968	0.74	2209	0.99	High confidence
Gilteritinib	GHITM	6091	1.31	6091	0.80	Low confidence	Golvatinib	LIMK1	4023	0.59	2392	0.91	High confidence
Golvatinib	FLT3	8	0.54	4	0.95	High confidence	Golvatinib	MAP2K5	2800	0.88	2452	0.94	High confidence
Golvatinib	DDR1	8	0.63	5	0.99	High confidence	Golvatinib	EPHB3	5508	0.88	4824	0.99	High confidence
Golvatinib	MST1R	33	0.76	25	0.98	High confidence	Golvatinib	FRK	31904	0.34	10837	0.95	High confidence
Golvatinib	EPHA2	72	0.41	30	0.97	High confidence	GSK-1059615	CLK2	1	0.65	0	0.98	High confidence
Golvatinib	DDR2	51	0.76	39	1.00	High confidence	GSK-1059615	TAOK1	4	0.66	2	0.96	High confidence
Golvatinib	PTK6	109	0.48	53	1.00	High confidence	GSK-1059615	KLHL6	12	0.74	9	0.97	Low confidence
Golvatinib	EPHA7	97	0.79	77	0.83	Low confidence	GSK-1059615	EIF3J	10	1.11	10	0.99	High confidence
Golvatinib	RIPK2	345	0.28	97	0.98	High confidence	GSK-1059615	CSNK2A2	18	0.96	17	0.99	High confidence
Golvatinib	EPHB4	220	0.49	109	0.98	High confidence	GSK-1059615	CSNK2A1	20	1.02	20	0.99	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
GSK-1059615	CLK1	35	0.72	25	0.88	High confidence
GSK-1059615	CSNK2B	30	1.08	30	0.69	High confidence
GSK-1059615	AAK1	51	0.67	35	0.97	High confidence
GSK-1059615	TPRKB	50	0.95	47	0.98	High confidence
GSK-1059615	OSGEP	50	0.96	48	1.00	High confidence
GSK-1059615	TP53RK	58	1.05	58	0.97	High confidence
GSK-1059615	Q6ZSR9	102	0.76	78	0.97	High confidence
GSK-1059615	LAGE3	86	0.95	82	0.97	High confidence
GSK-1059615	AP2A1	94	0.92	87	0.92	High confidence
GSK-1059615	PIM1	481	0.43	205	0.91	High confidence
GSK-1059615	DYRK1A	337	0.93	314	0.97	High confidence
GSK-1059615	STK10	347	0.92	317	0.95	High confidence
GSK-1059615	PIP4K2C	365	0.91	331	0.64	Low confidence
GSK-1059615	BMP2K	608	0.66	402	0.91	High confidence
GSK-1059615	RPS6KA4	808	0.62	499	0.98	High confidence
GSK-1059615	DCAF7	788	0.90	706	0.97	High confidence
GSK-1059615	CSNK1G2	1106	0.88	968	0.89	High confidence
GSK-1059615	CSNK1G3	3639	0.79	2861	0.95	High confidence
GSK-1059615	SLK	4844	0.89	4315	0.95	High confidence
GSK-1059615	MAP2K2	5248	1.17	5248	0.90	High confidence
GSK-1059615	GAK	13252	0.56	7442	0.97	High confidence
GSK-1059615	IRAK3	20223	0.43	8673	0.96	High confidence
GSK-1059615	CSNK1G1	20175	0.87	17463	0.71	High confidence
GSK-1059615	MAP2K1	18457	1.23	18457	0.79	High confidence
GSK-1059615	CSNK1D	26169	0.82	21528	0.90	High confidence
GSK-1070916	DDR1	13	0.63	8	0.95	High confidence
GSK-1070916	FLT3	98	0.54	53	0.98	High confidence
GSK-1070916	RET	151	0.44	67	0.92	High confidence
GSK-1070916	AURKA	201	0.35	71	0.99	High confidence
GSK-1070916	MYLK3	119	0.87	104	0.98	High confidence
GSK-1070916	BMP2K	255	0.66	169	0.93	High confidence
GSK-1070916	AURKB	633	0.59	371	0.95	High confidence
GSK-1070916	TNK1	1238	0.43	536	0.94	High confidence
GSK-1070916	PLK4	1129	0.51	575	0.86	High confidence
GSK-1070916	RIPK2	2179	0.28	611	0.96	High confidence
GSK-1070916	SIK2	1321	0.52	685	0.98	High confidence
GSK-1070916	INCENP	777	0.89	693	0.97	High confidence
GSK-1070916	TANK	1437	0.64	914	0.94	High confidence
GSK-1070916	FGFR1	1299	0.74	957	0.95	High confidence
GSK-1070916	IKBKE	1598	0.62	992	0.98	High confidence
GSK-1070916	TRAF2	1284	0.83	1069	0.81	Low confidence
GSK-1070916	ACAD10	1159	0.96	1111	0.98	High confidence
GSK-1070916	ACVR1B	2838	0.43	1207	0.93	High confidence
GSK-1070916	MAP4K4	1223	1.01	1223	0.82	High confidence
GSK-1070916	DDR2	1668	0.76	1271	0.94	High confidence
GSK-1070916	MAP3K4	2130	0.67	1431	0.89	High confidence
GSK-1070916	PRKD2	2219	0.66	1463	0.96	High confidence
GSK-1070916	PDPK1	1770	1.04	1770	0.97	High confidence
GSK-1070916	MAP2K5	2203	0.88	1929	0.98	High confidence
GSK-1070916	PRKD3	2612	0.74	1933	0.87	High confidence
GSK-1070916	TGFBR1	2798	0.69	1940	0.96	High confidence
GSK-1070916	DCK	2163	1.16	2163	0.99	High confidence
GSK-1070916	ROCK2	2755	0.87	2402	0.98	High confidence
GSK-1070916	FECH	2427	0.99	2415	0.85	High confidence
GSK-1070916	CIT	2890	1.21	2890	0.95	High confidence
GSK-1070916	AKT3	3639	0.90	3289	0.84	High confidence
GSK-1070916	ACVR1	7784	0.48	3726	0.84	High confidence
GSK-1070916	EPHB6	6137	0.61	3772	0.81	High confidence
GSK-1070916	NTRK1	8423	0.71	5946	0.84	High confidence
GSK-1070916	PTK6	16947	0.48	8187	0.79	High confidence
GSK-1070916	MAPK14	16598	0.51	8500	0.83	High confidence
GSK-1070916	ACVR2B	14852	0.67	9900	0.83	High confidence
GSK-1070916	MAPKAPK2	13945	0.72	10078	0.98	High confidence
GSK-1070916	MAP3K11	25820	0.70	17984	0.93	High confidence
GSK-1070916	CSNK1D	22362	0.82	18396	0.91	High confidence
GSK-1070916	ADCK1	36536	0.62	22747	0.90	High confidence
GSK-2110183	AKT3	8	0.90	7	0.86	High confidence
GSK-2110183	AKT1	70	0.90	63	0.82	Low confidence
GSK-2110183	PRKACA	282	0.47	133	0.97	High confidence
GSK-2110183	PRKACB	446	0.47	211	0.90	High confidence
GSK-2110183	PKN1	1007	0.87	880	0.85	High confidence
GSK-2110183	ROCK1	2358	0.91	2144	0.93	High confidence
GSK-2110183	AKT2	3268	0.86	2800	0.77	Low confidence
GSK-2110183	PRKD2	5933	0.66	3911	0.79	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
GSK-2110183	CIT	4258	1.21	4258	0.90	High confidence
GSK-2110183	ROCK2	5429	0.87	4733	0.78	High confidence
GSK-2110183	PRKCB	6115	0.80	4879	0.88	High confidence
GSK-2110183	PRKCA	29324	0.73	21352	0.88	High confidence
GSK-461364	MAP3K1	184	0.58	106	0.98	High confidence
GSK-461364	SPAG9	1229	2.90	1229	0.79	Low confidence
GSK-461364	STK10	1735	0.92	1588	0.98	High confidence
GSK-461364	ADK	2507	1.12	2507	0.98	High confidence
GSK-461364	SLK	2832	0.89	2522	0.93	High confidence
GSK-461364	PIP4K2C	3127	0.91	2837	0.81	High confidence
GSK-461364	EIF3J	2952	1.11	2952	0.81	High confidence
GSK-461364	CSNK2B	3139	1.08	3139	0.93	High confidence
GSK-461364	PRKX	4210	0.81	3419	0.95	High confidence
GSK-461364	BMP2K	5879	0.66	3886	0.93	High confidence
GSK-690693	PRKCQ	10	1.23	10	0.68	High confidence
GSK-690693	PRKX	28	0.81	23	0.87	Low confidence
GSK-690693	PRKACB	75	0.47	36	0.78	High confidence
GSK-690693	PKN1	45	0.87	39	0.95	High confidence
GSK-690693	PAK4	81	0.60	49	0.78	High confidence
GSK-690693	PRKAR2A	52	1.26	52	0.76	Low confidence
GSK-690693	DNAJC3	67	1.27	67	0.89	Low confidence
GSK-690693	PRKCD	77	0.95	73	0.92	High confidence
GSK-690693	LATS1	94	0.79	74	0.91	High confidence
GSK-690693	PRKAG2	121	0.64	78	0.89	Low confidence
GSK-690693	MOB1A	86	0.91	79	0.90	High confidence
GSK-690693	PRKG1	174	0.51	88	0.70	High confidence
GSK-690693	PAK6	208	0.74	155	0.64	Low confidence
GSK-690693	MARK3	264	0.77	204	0.79	High confidence
GSK-690693	GSK3A	550	0.50	275	0.89	High confidence
GSK-690693	PRKCB	389	0.80	310	0.90	High confidence
GSK-690693	MARK2	466	0.75	351	0.88	High confidence
GSK-690693	AKT2	416	0.86	356	0.92	High confidence
GSK-690693	GSK3B	920	0.46	428	0.92	High confidence
GSK-690693	AKT1	616	0.90	554	0.81	High confidence
GSK-690693	PRKCA	778	0.73	566	0.80	High confidence
GSK-690693	DCTPP1	612	0.94	573	0.83	High confidence
GSK-690693	CIT	793	1.21	793	0.74	High confidence
GSK-690693	RPS6KA4	1379	0.62	851	0.64	High confidence
GSK-690693	PKN2	1094	0.82	892	0.86	High confidence
GSK-690693	ROCK2	1097	0.87	956	0.70	High confidence
GSK-690693	PASK	1157	0.92	1067	0.89	Low confidence
GSK-690693	SMC2	1106	1.15	1106	0.96	High confidence
GSK-690693	AKT3	1297	0.90	1173	0.78	High confidence
GSK-690693	MAPK15	2440	0.49	1205	0.89	Low confidence
GSK-690693	CDC42BPB	1776	0.97	1726	0.57	High confidence
GSK-690693	PRKCI	1982	1.07	1982	0.91	High confidence
GSK-690693	NEK7	2758	0.77	2126	0.87	High confidence
GSK-690693	ROCK1	2943	0.91	2676	0.63	High confidence
GSK-690693	FECH	2714	0.99	2701	0.77	High confidence
GSK-690693	PDPK1	2910	1.04	2910	0.84	High confidence
GSK-690693	EPHA5	6773	0.60	4057	0.70	Low confidence
HMN-214	MET	1733	0.80	1393	0.96	Low confidence
HMN-214	SLC2A1	2998	1.13	2998	0.73	Low confidence
Hydroxyfasudil	ROCK1	586	0.91	532	0.98	High confidence
Hydroxyfasudil	ROCK2	1547	0.87	1349	0.95	High confidence
Hydroxyfasudil	PKN2	2769	0.82	2260	0.93	High confidence
Hydroxyfasudil	PRKD2	3854	0.66	2541	0.94	High confidence
Hydroxyfasudil	PKN1	3346	0.87	2925	0.96	High confidence
Hydroxyfasudil	PRKX	3780	0.81	3070	0.83	Low confidence
Hydroxyfasudil	ACAD10	4129	0.96	3957	0.89	High confidence
Hydroxyfasudil	ULK1	34837	0.67	23273	0.89	High confidence
Hydroxyfasudil	CLK1	33623	0.72	24056	0.92	High confidence
Ibrutinib	UNC119	8	0.73	6	0.94	High confidence
Ibrutinib	BTK	25	0.39	10	0.99	High confidence
Ibrutinib	TEC	63	0.40	25	0.99	High confidence
Ibrutinib	YES1	65	0.41	27	0.95	High confidence
Ibrutinib	PTK6	63	0.48	31	0.98	High confidence
Ibrutinib	HCK	80	0.52	42	1.00	High confidence
Ibrutinib	EGFR	54	0.79	43	0.98	High confidence
Ibrutinib	RIPK2	204	0.28	57	1.00	High confidence
Ibrutinib	RIPK3	95	0.89	85	0.97	High confidence
Ibrutinib	SRC	251	0.39	97	0.97	High confidence
Ibrutinib	LCK	234	0.44	103	0.99	High confidence
Ibrutinib	LYN	296	0.50	148	1.00	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Ibrutinib	MAP2K5	277	0.88	243	0.90	High confidence	Imatinib	CSNK2A1	3783	1.02	3783	0.96	High confidence
Ibrutinib	PAG1	505	0.49	249	0.85	High confidence	Imatinib	CSNK2A2	3991	0.96	3843	0.98	High confidence
Ibrutinib	FYN	707	0.43	305	0.99	High confidence	Imatinib	PIP4K2C	4786	0.91	4342	0.73	High confidence
Ibrutinib	CSK	742	0.54	399	0.98	High confidence	IMD-0354	MAP4K5	1968	0.74	1464	0.89	High confidence
Ibrutinib	FRK	1735	0.34	589	0.98	High confidence	IMD-0354	MYLK	3870	0.83	3224	0.82	Low confidence
Ibrutinib	ABL2	2774	0.33	919	0.95	High confidence	JANEX-1	AAK1	1589	0.67	1069	0.91	High confidence
Ibrutinib	MOB1A	1188	0.91	1086	0.96	Low confidence	JANEX-1	EGFR	1466	0.79	1163	0.94	High confidence
Ibrutinib	BCR	3052	0.48	1459	0.57	High confidence	JANEX-1	FLT3	2443	0.54	1313	0.87	High confidence
Ibrutinib	FLT3	2936	0.54	1578	0.94	High confidence	JANEX-1	Q6ZSR9	2025	0.76	1542	0.83	High confidence
Ibrutinib	ABL1	3092	0.55	1694	0.92	High confidence	JANEX-1	STK10	2877	0.92	2634	0.97	High confidence
Ibrutinib	ZAK	2293	0.74	1705	0.96	High confidence	JANEX-1	SLK	4909	0.89	4373	0.92	High confidence
Ibrutinib	LATS1	2392	0.79	1884	0.96	High confidence	JANEX-1	RPS6KA6	13982	0.42	5898	0.75	High confidence
Ibrutinib	RET	40969	0.44	18050	0.92	High confidence	JANEX-1	RIPK2	21163	0.28	5939	0.82	High confidence
Ibrutinib	LIMK1	35467	0.59	21089	0.97	High confidence	JANEX-1	RET	49679	0.44	21887	0.94	High confidence
Icotinib	STK10	248	0.92	227	0.96	High confidence	JANEX-1	GAK	51021	0.56	28651	0.95	High confidence
Icotinib	CARS	652	1.07	652	0.99	High confidence	JANEX-1	IRAK4	44100	0.77	34145	0.91	High confidence
Icotinib	GAK	1291	0.56	725	0.96	High confidence	JNJ-26483327	AKT3	7	0.90	6	0.74	Low confidence
Icotinib	SLK	1180	0.89	1051	0.96	High confidence	JNJ-26483327	GAK	214	0.56	120	0.91	High confidence
Icotinib	RIPK2	9362	0.28	2627	0.82	High confidence	JNJ-26483327	RIPK2	1391	0.28	390	0.84	High confidence
Icotinib	SMARCC1	2652	1.34	2652	0.95	High confidence	JNJ-26483327	EGFR	759	0.79	602	0.88	High confidence
Icotinib	OSBPL3	3252	0.83	2697	0.83	Low confidence	JNJ-26483327	RET	5484	0.44	2416	0.59	High confidence
Icotinib	BUB1	2912	1.04	2912	0.70	High confidence	JNJ-26483327	FECH	3995	0.99	3974	0.40	Low confidence
Icotinib	MAP3K1	7158	0.58	4131	0.91	High confidence	JNJ-26483327	STK10	49316	0.92	45148	0.80	High confidence
Icotinib	PIP4K2C	5141	0.91	4663	0.91	High confidence	JNJ-38877605	MET	3	0.80	2	1.00	High confidence
Icotinib	EGFR	12771	0.79	10128	0.78	High confidence	JNJ-38877605	FAM92B	227	0.34	78	0.87	Low confidence
Imatinib	HIST2H2BE	4	1.58	4	0.93	Low confidence	JNJ-38877605	PIP4K2C	353	0.91	320	0.84	High confidence
Imatinib	BCR	14	0.48	7	0.93	High confidence	JNJ-38877605	NQO2	323	1.07	323	0.99	High confidence
Imatinib	GRB2	26	0.62	16	0.98	High confidence	K-252a	NEK7	3	0.77	3	1.00	Low confidence
Imatinib	DDR1	35	0.63	22	0.90	High confidence	K-252a	AAK1	7	0.67	5	0.95	High confidence
Imatinib	NQO2	41	1.07	41	0.99	High confidence	K-252a	AP2B1	6	1.01	6	0.96	Low confidence
Imatinib	ABL2	193	0.33	64	0.98	High confidence	K-252a	IRAK4	12	0.77	9	0.94	High confidence
Imatinib	INPPL1	193	0.48	93	0.93	High confidence	K-252a	CLK1	14	0.72	10	0.99	High confidence
Imatinib	ABL1	193	0.55	106	0.99	High confidence	K-252a	TNIK	10	1.02	10	0.99	High confidence
Imatinib	DDR2	237	0.76	181	0.97	High confidence	K-252a	CDK4	14	1.00	14	0.72	Low confidence
Imatinib	DDX3X	435	1.02	435	0.97	Low confidence	K-252a	CLK4	17	0.85	15	1.00	High confidence
Imatinib	EIF3J	3188	1.11	3188	0.90	High confidence	K-252a	ERN1	23	0.81	19	1.00	High confidence
Imatinib	CSNK2B	3730	1.08	3730	0.90	High confidence	K-252a	MAP4K4	19	1.01	19	0.93	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
K-252a	AURKA	56	0.35	20	0.99	High confidence	K-252a	MAP3K6	406	0.83	335	0.97	High confidence
K-252a	Q6ZSR9	28	0.76	21	0.94	High confidence	K-252a	INCENP	382	0.89	341	0.97	High confidence
K-252a	AP2A1	23	0.92	21	0.94	High confidence	K-252a	PAK4	573	0.60	344	0.99	High confidence
K-252a	SAV1	29	0.87	25	0.93	High confidence	K-252a	PRKAG1	556	0.63	352	0.98	High confidence
K-252a	MARK4	33	0.83	28	0.90	High confidence	K-252a	AURKB	604	0.59	353	0.99	High confidence
K-252a	STK4	37	0.76	29	1.00	High confidence	K-252a	PKN2	443	0.82	361	0.92	High confidence
K-252a	PRKD2	45	0.66	30	1.00	High confidence	K-252a	MARK3	498	0.77	384	0.81	High confidence
K-252a	TTK	30	1.07	30	0.96	Low confidence	K-252a	CDK6	487	0.82	399	0.95	High confidence
K-252a	RASSF5	32	0.98	31	0.93	High confidence	K-252a	RPS6KA4	699	0.62	432	0.99	High confidence
K-252a	CDK3	32	2.15	32	0.98	High confidence	K-252a	MAP4K1	623	0.73	452	0.99	High confidence
K-252a	MOB1A	40	0.91	36	1.00	High confidence	K-252a	FER	1078	0.42	455	0.98	High confidence
K-252a	PDPK1	38	1.04	38	0.98	High confidence	K-252a	PRKAA1	722	0.64	461	1.00	High confidence
K-252a	PRKD3	52	0.74	38	0.98	High confidence	K-252a	MAP2K2	474	1.17	474	0.97	High confidence
K-252a	MERTK	51	0.80	41	0.80	Low confidence	K-252a	STK10	526	0.92	481	0.99	High confidence
K-252a	STK3	56	0.76	43	0.99	High confidence	K-252a	IKBKE	795	0.62	494	0.93	High confidence
K-252a	SIK2	113	0.52	58	0.99	High confidence	K-252a	RIPK2	1875	0.28	526	0.97	High confidence
K-252a	LATS1	85	0.79	67	0.99	High confidence	K-252a	SYK	650	0.84	545	0.88	High confidence
K-252a	PLK4	144	0.51	73	0.96	High confidence	K-252a	MAPK8	850	0.65	551	0.98	High confidence
K-252a	MELK	94	0.88	83	0.95	High confidence	K-252a	MAP3K11	822	0.70	572	0.96	High confidence
K-252a	MAP2K6	88	1.01	88	0.98	High confidence	K-252a	RET	1519	0.44	669	0.98	High confidence
K-252a	BMP2K	136	0.66	90	0.99	High confidence	K-252a	MARK2	934	0.75	704	0.98	High confidence
K-252a	MYLK3	113	0.87	98	0.98	High confidence	K-252a	PRKAG2	1347	0.64	868	0.95	High confidence
K-252a	CDK2	189	0.53	101	0.99	High confidence	K-252a	ERN2	1160	0.78	908	0.92	High confidence
K-252a	ULK3	236	0.45	107	0.99	High confidence	K-252a	CDK5	1740	0.52	911	0.99	High confidence
K-252a	CHEK1	148	0.82	122	0.97	High confidence	K-252a	MAPK9	1409	0.70	986	0.85	High confidence
K-252a	MAP4K2	222	0.59	131	0.95	High confidence	K-252a	PDGFRB	1151	0.87	1006	0.79	High confidence
K-252a	PRKAB1	245	0.66	162	0.98	High confidence	K-252a	TBK1	1809	0.64	1157	0.97	High confidence
K-252a	PHKA1	171	0.97	166	0.94	Low confidence	K-252a	AZI2	1667	0.70	1170	0.99	High confidence
K-252a	MAPK15	337	0.49	167	0.98	High confidence	K-252a	LAGE3	1258	0.95	1196	0.94	High confidence
K-252a	CAMK2G	794	0.22	173	0.98	High confidence	K-252a	GAK	2259	0.56	1269	0.97	High confidence
K-252a	MAP3K5	228	0.80	182	0.90	High confidence	K-252a	PTK2B	3280	0.41	1360	0.94	High confidence
K-252a	CAMK2D	930	0.20	190	0.99	High confidence	K-252a	TANK	2168	0.64	1379	0.96	High confidence
K-252a	MAP4K5	259	0.74	193	0.97	High confidence	K-252a	BTK	4010	0.39	1567	0.92	High confidence
K-252a	FLT3	422	0.54	227	0.90	High confidence	K-252a	PRKAB2	2804	0.60	1685	0.89	High confidence
K-252a	IRAK3	592	0.43	254	0.99	High confidence	K-252a	TNK2	3813	0.45	1717	0.96	High confidence
K-252a	PKN1	302	0.87	264	0.99	High confidence	K-252a	NTRK1	2464	0.71	1739	0.92	High confidence
K-252a	TNK1	662	0.43	287	0.95	High confidence	K-252a	MAP2K1	1747	1.23	1747	0.96	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
K-252a	TBKBP1	2372	0.79	1882	0.95	High confidence	KW-2449	Q6ZSR9	375	0.76	285	0.83	High confidence
K-252a	MAP2K5	2322	0.88	2033	0.89	High confidence	KW-2449	TNIK	291	1.02	291	0.98	High confidence
K-252a	STK38L	2137	1.04	2137	0.85	High confidence	KW-2449	AAK1	472	0.67	318	0.93	High confidence
K-252a	TGFBR1	3143	0.69	2179	0.98	High confidence	KW-2449	KLHL6	442	0.74	328	0.92	Low confidence
K-252a	RPS6KA6	5171	0.42	2181	0.93	High confidence	KW-2449	RET	919	0.44	405	0.92	High confidence
K-252a	CAMKK2	3428	0.66	2277	0.98	High confidence	KW-2449	AURKA	1329	0.35	470	0.80	High confidence
K-252a	PRKCA	3131	0.73	2280	0.97	High confidence	KW-2449	CSNK2A2	532	0.96	512	0.90	High confidence
K-252a	MAP4K3	3620	0.66	2374	0.95	High confidence	KW-2449	EIF3J	734	1.11	734	0.88	High confidence
K-252a	PRKX	3000	0.81	2436	0.93	High confidence	KW-2449	CSNK2B	763	1.08	763	0.86	High confidence
K-252a	RPS6KA3	4126	0.72	2990	0.98	High confidence	KW-2449	STK16	1188	0.72	855	0.87	High confidence
K-252a	RPS6KA1	3982	0.75	2994	0.95	High confidence	KW-2449	CSNK2A1	858	1.02	858	0.87	High confidence
K-252a	PHKG2	3364	0.97	3263	0.99	High confidence	KW-2449	MAP4K2	1461	0.59	862	0.87	High confidence
K-252a	SLK	3711	0.89	3305	0.97	High confidence	KW-2449	PDPK1	907	1.04	907	0.85	High confidence
K-252a	DCAF7	4017	0.90	3601	0.94	High confidence	KW-2449	ULK3	2304	0.45	1046	0.85	High confidence
K-252a	CCNB1	4849	0.77	3716	0.92	High confidence	KW-2449	PLK4	2160	0.51	1100	0.86	High confidence
K-252a	CLK2	5889	0.65	3809	0.96	High confidence	KW-2449	TRAF2	1404	0.83	1168	0.89	Low confidence
K-252a	TP53RK	3840	1.05	3840	0.95	High confidence	KW-2449	BCR	2665	0.48	1274	0.99	High confidence
K-252a	SIK3	4920	0.82	4027	0.96	High confidence	KW-2449	SIK2	2500	0.52	1296	0.82	High confidence
K-252a	NQO2	4031	1.07	4031	0.98	High confidence	KW-2449	ACVR2B	1950	0.67	1300	0.99	High confidence
K-252a	MAP3K2	5897	0.70	4118	0.94	High confidence	KW-2449	JAK1	3541	0.37	1319	0.73	High confidence
K-252a	OSGEP	4682	0.96	4493	0.97	High confidence	KW-2449	MAP4K1	1966	0.73	1428	0.92	High confidence
K-252a	DYRK1A	5200	0.93	4852	0.96	High confidence	KW-2449	DYNLL1	2926	0.50	1466	0.86	High confidence
K-252a	ADCK1	9781	0.62	6090	0.84	High confidence	KW-2449	NEK9	3381	0.44	1492	0.87	High confidence
K-252a	RPS6KA5	21673	0.68	14659	0.96	High confidence	KW-2449	MARK3	1972	0.77	1520	0.87	High confidence
K-252a	ACVR1B	35882	0.43	15258	0.84	High confidence	KW-2449	MAP4K3	2324	0.66	1524	0.88	High confidence
K-252a	TAOK1	28214	0.66	18757	0.86	High confidence	KW-2449	IRAK3	3653	0.43	1567	0.72	High confidence
KW-2449	OLA1	3	1.07	3	0.99	Low confidence	KW-2449	MELK	1861	0.88	1645	0.88	High confidence
KW-2449	PAK2	4	1.34	4	0.97	High confidence	KW-2449	CHEK1	2030	0.82	1674	0.82	High confidence
KW-2449	FLT3	68	0.54	37	0.82	High confidence	KW-2449	PDGFRB	2054	0.87	1795	0.80	High confidence
KW-2449	BMP2K	69	0.66	45	1.00	High confidence	KW-2449	DYNLL2	3420	0.55	1869	0.82	High confidence
KW-2449	MARK4	86	0.83	72	0.80	High confidence	KW-2449	TBK1	3074	0.64	1966	0.85	High confidence
KW-2449	AP2A1	88	0.92	81	0.94	High confidence	KW-2449	MAP4K5	2654	0.74	1975	0.89	High confidence
KW-2449	AURKB	203	0.59	119	0.95	High confidence	KW-2449	MAPK9	2837	0.70	1985	0.78	High confidence
KW-2449	AP2B1	127	1.01	127	0.96	High confidence	KW-2449	MARK2	2685	0.75	2023	0.84	High confidence
KW-2449	MAP4K4	143	1.01	143	0.99	High confidence	KW-2449	MAPK8	3129	0.65	2027	0.80	High confidence
KW-2449	AP2M1	194	1.03	194	0.97	High confidence	KW-2449	TANK	3199	0.64	2035	0.82	High confidence
KW-2449	GRB2	381	0.62	237	0.92	High confidence	KW-2449	ABL1	3758	0.55	2059	0.85	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
KW-2449	TBKBP1	2655	0.79	2107	0.86	High confidence
KW-2449	MAP3K1	3691	0.58	2130	0.77	High confidence
KW-2449	DCAF7	2401	0.90	2152	0.71	High confidence
KW-2449	IGF1R	3319	0.66	2196	0.82	High confidence
KW-2449	PRKD2	3387	0.66	2232	0.84	High confidence
KW-2449	CAMKK2	3511	0.66	2333	0.72	High confidence
KW-2449	AZI2	3331	0.70	2338	0.84	High confidence
KW-2449	CLK1	3287	0.72	2351	0.92	High confidence
KW-2449	STK10	2588	0.92	2370	0.92	High confidence
KW-2449	CCNH	3137	0.76	2378	0.75	High confidence
KW-2449	PRKD3	3389	0.74	2509	0.85	High confidence
KW-2449	INSR	3446	0.75	2588	0.77	High confidence
KW-2449	IKBKE	4219	0.62	2620	0.84	High confidence
KW-2449	MNAT1	3014	0.88	2647	0.92	High confidence
KW-2449	CSNK1G3	3462	0.79	2722	0.79	High confidence
KW-2449	ULK1	4111	0.67	2746	0.93	High confidence
KW-2449	MAP3K11	3955	0.70	2755	0.90	High confidence
KW-2449	DYRK1A	2969	0.93	2770	0.93	High confidence
KW-2449	SLK	3149	0.89	2804	0.87	High confidence
KW-2449	CLK2	4451	0.65	2879	0.78	High confidence
KW-2449	ERCC2	3461	0.90	3131	0.86	High confidence
KW-2449	CSNK1G1	3792	0.87	3282	0.72	High confidence
KW-2449	FGFR1	4484	0.74	3302	0.95	High confidence
KW-2449	PHKG2	3471	0.97	3366	0.82	High confidence
KW-2449	CDK7	4688	0.73	3401	0.83	High confidence
KW-2449	NQO2	3597	1.07	3597	0.72	High confidence
Lapatinib	EGFR	65	0.79	51	0.92	High confidence
Lenvatinib	RET	20	0.44	9	0.97	High confidence
Lenvatinib	RIPK2	41	0.28	11	0.89	High confidence
Lenvatinib	DDR1	73	0.63	46	0.88	High confidence
Lenvatinib	MAPKAPK2	87	0.72	63	0.59	High confidence
Lenvatinib	PTK6	359	0.48	173	0.92	Low confidence
Lenvatinib	MAPK14	424	0.51	217	0.81	High confidence
Lenvatinib	DDR2	286	0.76	218	0.86	High confidence
Lenvatinib	RIPK3	353	0.89	316	0.95	High confidence
Lenvatinib	PDGFRB	362	0.87	316	0.97	High confidence
Lenvatinib	TNIK	565	1.02	565	0.92	High confidence
Lenvatinib	MAP4K2	980	0.59	578	0.75	High confidence
Lenvatinib	STK10	866	0.92	793	0.73	High confidence
Lenvatinib	NQO2	1523	1.07	1523	0.77	High confidence
Lenvatinib	MAP3K6	1908	0.83	1575	0.98	Low confidence
Lenvatinib	INCENP	1848	0.89	1649	0.44	High confidence
Lenvatinib	AURKB	3043	0.59	1781	0.62	High confidence
Lenvatinib	ERN1	2751	0.81	2242	0.57	Low confidence
Lenvatinib	FECH	2820	0.99	2806	0.78	High confidence
Lenvatinib	MAP2K5	3323	0.88	2910	0.62	High confidence
Lenvatinib	RASSF5	3161	0.98	3108	0.87	Low confidence
Lenvatinib	MAP4K5	4189	0.74	3117	0.65	High confidence
Lenvatinib	ABL1	6882	0.55	3771	0.72	High confidence
Lenvatinib	SLK	4323	0.89	3851	0.60	High confidence
Lenvatinib	BCR	8608	0.48	4113	0.23	High confidence
Lestaurtinib	PDPK1	11	1.04	11	0.99	High confidence
Lestaurtinib	RASSF3	14	1.13	14	0.92	High confidence
Lestaurtinib	RASSF2	24	0.93	22	0.88	High confidence
Lestaurtinib	AURKA	70	0.35	25	0.99	High confidence
Lestaurtinib	LATS1	32	0.79	25	0.99	High confidence
Lestaurtinib	MAPK10	33	0.84	28	0.88	High confidence
Lestaurtinib	PAK4	48	0.60	29	0.99	High confidence
Lestaurtinib	STK3	39	0.76	30	0.90	High confidence
Lestaurtinib	MOB1A	34	0.91	31	0.94	High confidence
Lestaurtinib	CDK3	37	2.15	37	0.97	High confidence
Lestaurtinib	MINK1	41	1.00	41	0.94	High confidence
Lestaurtinib	ERN1	51	0.81	42	0.98	High confidence
Lestaurtinib	STK4	59	0.76	45	0.98	High confidence
Lestaurtinib	PRKD2	69	0.66	46	0.97	High confidence
Lestaurtinib	PRKD3	71	0.74	53	0.88	High confidence
Lestaurtinib	SIK2	106	0.52	55	0.97	High confidence
Lestaurtinib	PHKB	61	1.15	61	0.97	Low confidence
Lestaurtinib	MAP4K2	107	0.59	63	0.92	High confidence
Lestaurtinib	TNK2	143	0.45	64	0.91	High confidence
Lestaurtinib	AAK1	97	0.67	66	0.94	High confidence
Lestaurtinib	RASSF5	73	0.98	72	0.90	High confidence
Lestaurtinib	CHEK1	87	0.82	72	0.96	High confidence
Lestaurtinib	NUAK2	94	0.77	72	0.85	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Lestaurtinib	MARK4	88	0.83	73	0.98	High confidence	Lestaurtinib	INCENP	520	0.89	464	0.91	High confidence
Lestaurtinib	AP2A1	84	0.92	77	0.98	High confidence	Lestaurtinib	NTRK1	795	0.71	561	0.91	High confidence
Lestaurtinib	Q6ZSR9	105	0.76	80	0.94	High confidence	Lestaurtinib	MAP2K2	569	1.17	569	0.91	High confidence
Lestaurtinib	MAP2K6	87	1.01	87	0.95	High confidence	Lestaurtinib	MAP3K5	788	0.80	631	0.98	High confidence
Lestaurtinib	IRAK4	114	0.77	88	0.95	High confidence	Lestaurtinib	IKBKE	1034	0.62	642	0.85	High confidence
Lestaurtinib	PLK4	177	0.51	90	0.94	High confidence	Lestaurtinib	ACVR1B	1551	0.43	660	0.86	High confidence
Lestaurtinib	MAP4K4	91	1.01	91	0.87	Low confidence	Lestaurtinib	GAK	1237	0.56	694	0.95	High confidence
Lestaurtinib	MYLK3	109	0.87	95	0.95	High confidence	Lestaurtinib	SLK	842	0.89	750	0.90	High confidence
Lestaurtinib	STK10	107	0.92	98	0.97	High confidence	Lestaurtinib	MAPK8	1208	0.65	783	0.89	High confidence
Lestaurtinib	MARK3	134	0.77	103	0.94	High confidence	Lestaurtinib	MAP2K4	790	1.09	790	0.64	Low confidence
Lestaurtinib	SAV1	123	0.87	107	0.85	High confidence	Lestaurtinib	TBKBP1	1009	0.79	801	0.90	High confidence
Lestaurtinib	TNK1	250	0.43	108	0.94	High confidence	Lestaurtinib	PRKAA1	1316	0.64	840	0.89	High confidence
Lestaurtinib	MAP2K3	120	1.32	120	0.96	High confidence	Lestaurtinib	SIK3	1036	0.82	848	0.81	High confidence
Lestaurtinib	PHKG2	126	0.97	122	0.80	High confidence	Lestaurtinib	TANK	1343	0.64	854	0.85	High confidence
Lestaurtinib	FLT3	227	0.54	122	0.91	High confidence	Lestaurtinib	CDK4	866	1.00	866	0.90	High confidence
Lestaurtinib	AURKB	223	0.59	131	0.94	High confidence	Lestaurtinib	PRKAG1	1399	0.63	885	0.83	High confidence
Lestaurtinib	IRAK3	343	0.43	147	0.94	High confidence	Lestaurtinib	PRKAG2	1380	0.64	890	0.97	High confidence
Lestaurtinib	MAP3K11	221	0.70	154	0.96	High confidence	Lestaurtinib	TGFBR1	1393	0.69	966	0.87	High confidence
Lestaurtinib	MARK2	209	0.75	157	0.93	High confidence	Lestaurtinib	AZI2	1379	0.70	968	0.92	High confidence
Lestaurtinib	TRAF2	194	0.83	162	0.99	Low confidence	Lestaurtinib	TBK1	1528	0.64	977	0.90	High confidence
Lestaurtinib	PKN2	201	0.82	164	0.89	High confidence	Lestaurtinib	RPS6KA6	2326	0.42	981	0.82	High confidence
Lestaurtinib	MAP4K5	233	0.74	173	0.95	High confidence	Lestaurtinib	PTK2B	2624	0.41	1088	0.77	Low confidence
Lestaurtinib	CLK1	251	0.72	179	0.83	High confidence	Lestaurtinib	MAP2K1	1162	1.23	1162	0.96	High confidence
Lestaurtinib	MELK	209	0.88	185	0.95	High confidence	Lestaurtinib	BTK	3015	0.39	1179	0.87	High confidence
Lestaurtinib	PKN1	227	0.87	198	0.97	High confidence	Lestaurtinib	PRKAB1	1791	0.66	1186	0.86	High confidence
Lestaurtinib	RET	466	0.44	205	0.83	High confidence	Lestaurtinib	FES	3209	0.37	1186	0.77	Low confidence
Lestaurtinib	ULK3	466	0.45	212	0.91	High confidence	Lestaurtinib	TGFBR2	1701	0.75	1280	0.79	High confidence
Lestaurtinib	BMP2K	323	0.66	214	0.93	High confidence	Lestaurtinib	PRKX	1575	0.81	1282	0.89	High confidence
Lestaurtinib	FER	557	0.42	235	0.96	High confidence	Lestaurtinib	PKN3	1374	1.06	1374	0.76	Low confidence
Lestaurtinib	MAP4K1	347	0.73	252	0.86	High confidence	Lestaurtinib	CAMKK2	2079	0.66	1381	0.76	High confidence
Lestaurtinib	SYK	316	0.84	265	0.96	High confidence	Lestaurtinib	CDK5	2987	0.52	1564	0.84	High confidence
Lestaurtinib	ERN2	373	0.78	292	0.98	High confidence	Lestaurtinib	MAP4K3	2386	0.66	1565	0.90	High confidence
Lestaurtinib	CAMK2G	1410	0.22	306	0.92	High confidence	Lestaurtinib	MAPK9	2470	0.70	1729	0.80	High confidence
Lestaurtinib	RPS6KA4	525	0.62	324	0.91	High confidence	Lestaurtinib	PDGFRB	1985	0.87	1735	0.87	High confidence
Lestaurtinib	CDK2	619	0.53	330	0.94	High confidence	Lestaurtinib	CDK6	2143	0.82	1757	0.81	Low confidence
Lestaurtinib	CAMK2D	1628	0.20	332	0.94	High confidence	Lestaurtinib	MAP2K5	2048	0.88	1794	0.95	High confidence
Lestaurtinib	MAP3K6	458	0.83	378	0.98	High confidence	Lestaurtinib	PRKCA	2471	0.73	1799	0.87	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Lestaurtinib	DYRK1A	1991	0.93	1858	0.83	High confidence
Lestaurtinib	ACVR1	4071	0.48	1949	0.61	High confidence
Lestaurtinib	CCNI	5305	0.37	1971	0.71	Low confidence
Lestaurtinib	DCAF7	2213	0.90	1984	0.79	High confidence
Lestaurtinib	RPS6KA3	2789	0.72	2022	0.87	High confidence
Lestaurtinib	PRKAB2	3519	0.60	2115	0.75	High confidence
Lestaurtinib	MAP3K2	3236	0.70	2260	0.85	High confidence
Lestaurtinib	MAP3K3	3555	0.67	2386	0.69	Low confidence
Lestaurtinib	RPS6KA1	3294	0.75	2477	0.84	High confidence
Lestaurtinib	NQO2	3257	1.07	3257	0.91	High confidence
Lestaurtinib	PTK6	29590	0.48	14295	0.63	Low confidence
Linifanib	CMPK1	6	1.43	6	0.94	Low confidence
Linifanib	FLT3	261	0.54	140	0.97	High confidence
Linifanib	RET	3265	0.44	1438	0.96	High confidence
Linifanib	PDGFRB	1775	0.87	1551	0.86	High confidence
Linifanib	AURKB	3078	0.59	1801	0.82	High confidence
Linifanib	INCENP	3379	0.89	3016	0.79	High confidence
Linsitinib	TRRAP	4	1.05	4	1.00	Low confidence
Linsitinib	MAPK11	14	0.72	10	0.99	Low confidence
Linsitinib	MAP4K2	114	0.59	67	0.92	High confidence
Linsitinib	IGF1R	208	0.66	138	0.96	High confidence
Linsitinib	LATS1	247	0.79	195	0.96	High confidence
Linsitinib	INSR	269	0.75	202	0.94	High confidence
Linsitinib	ADCK5	207	0.97	202	0.72	Low confidence
Linsitinib	MOB1A	335	0.91	307	0.98	High confidence
Linsitinib	FLT3	574	0.54	308	0.68	High confidence
Linsitinib	MAP2K1	352	1.23	352	0.88	High confidence
Linsitinib	MET	491	0.80	395	0.81	High confidence
Linsitinib	MAP4K5	826	0.74	614	0.96	High confidence
Linsitinib	MAP2K2	1137	1.17	1137	0.93	High confidence
Linsitinib	RIPK2	4862	0.28	1364	0.97	High confidence
Linsitinib	AURKB	3046	0.59	1783	0.77	High confidence
Linsitinib	MAPK9	3070	0.70	2149	0.90	High confidence
Linsitinib	FECH	4235	0.99	4213	0.98	High confidence
Linsitinib	INCENP	5050	0.89	4508	0.82	High confidence
Linsitinib	PIP4K2C	6143	0.91	5572	0.94	High confidence
Linsitinib	RIPK3	6771	0.89	6054	0.79	High confidence
Linsitinib	MAP2K5	7488	0.88	6558	0.99	High confidence
Linsitinib	MAP4K3	23538	0.66	15435	0.87	High confidence
Losmapimod	MAPK14	17	0.51	9	1.00	High confidence
Losmapimod	STK24	11	1.06	11	0.99	Low confidence
Losmapimod	MAPKAPK2	37	0.72	27	0.88	High confidence
Losmapimod	MAPK11	40	0.72	29	0.97	High confidence
Losmapimod	ACSL5	1690	1.06	1690	0.80	Low confidence
Losmapimod	BUB1	1921	1.04	1921	0.98	Low confidence
Losmapimod	PRKACG	95984	0.51	49278	0.92	High confidence
Lucitanib	RET	11	0.44	5	0.99	High confidence
Lucitanib	DDR1	22	0.63	14	0.82	High confidence
Lucitanib	DDR2	124	0.76	94	0.89	High confidence
Lucitanib	RIPK2	709	0.28	199	0.97	High confidence
Lucitanib	PDGFRB	318	0.87	278	0.63	Low confidence
Lucitanib	LYN	5507	0.50	2764	0.89	High confidence
Lucitanib	PDXK	16404	1.43	16404	0.93	High confidence
Lucitanib	AURKB	39045	0.59	22852	0.61	High confidence
LY-2584702	RPS6KB1	17	0.89	15	0.55	High confidence
LY-2801653	DDR1	277	0.63	174	0.98	High confidence
LY-2801653	MST1R	304	0.76	232	0.88	Low confidence
LY-2801653	FLT3	576	0.54	309	0.98	High confidence
LY-2801653	DDR2	1192	0.76	908	0.98	High confidence
LY-2801653	NTRK1	1463	0.71	1033	0.41	Low confidence
LY-2801653	RET	3137	0.44	1382	0.97	High confidence
LY-2801653	PLK4	3161	0.51	1610	0.83	High confidence
LY-2801653	CAMK4	3256	1.02	3256	0.84	High confidence
Masitinib	DDT	6	1.05	6	0.99	Low confidence
Masitinib	SLC25A6	6	1.11	6	1.00	Low confidence
Masitinib	EIF2B1	7	2.15	7	0.99	Low confidence
Masitinib	INPPL1	17	0.48	8	0.93	High confidence
Masitinib	ACOX1	14	1.28	14	0.95	Low confidence
Masitinib	GRB2	79	0.62	49	0.99	High confidence
Masitinib	BCR	163	0.48	78	0.93	High confidence
Masitinib	ABL2	1070	0.33	354	0.89	High confidence
Masitinib	NQO2	469	1.07	469	0.96	High confidence
Masitinib	ABL1	1083	0.55	593	0.95	High confidence
Masitinib	FRK	1894	0.34	643	0.82	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Masitinib	DDR1	1784	0.63	1119	0.94	High confidence
Masitinib	SLC25A11	3782	1.40	3782	0.75	Low confidence
Masitinib	DDR2	5191	0.76	3956	0.92	High confidence
Masitinib	PDGFRB	5427	0.87	4743	0.84	High confidence
MGCD-265	UNC119	118	0.73	86	0.99	High confidence
MGCD-265	LCK	209	0.44	92	1.00	High confidence
MGCD-265	MET	124	0.80	99	0.97	High confidence
MGCD-265	FLT3	333	0.54	179	0.99	High confidence
MGCD-265	ABL1	440	0.55	241	0.97	High confidence
MGCD-265	HCK	546	0.52	283	0.99	High confidence
MGCD-265	ABL2	952	0.33	315	0.98	High confidence
MGCD-265	SRC	868	0.39	337	0.98	High confidence
MGCD-265	DDR1	875	0.63	549	0.99	High confidence
MGCD-265	MAP4K4	600	1.01	600	0.62	Low confidence
MGCD-265	BCR	1796	0.48	858	0.95	High confidence
MGCD-265	LYN	1774	0.50	890	0.98	High confidence
MGCD-265	PTK6	2035	0.48	983	0.95	High confidence
MGCD-265	FRK	3250	0.34	1104	0.97	High confidence
MGCD-265	FYN	2874	0.43	1239	0.98	High confidence
MGCD-265	PLK4	2797	0.51	1425	0.89	High confidence
MGCD-265	DDR2	1960	0.76	1493	0.99	High confidence
MGCD-265	TNK1	3457	0.43	1495	0.93	High confidence
MGCD-265	MST1R	3045	0.76	2320	0.83	High confidence
MGCD-265	SYK	3193	0.84	2677	0.94	High confidence
MGCD-265	PDGFRB	3176	0.87	2776	0.74	High confidence
MGCD-265	GRB2	6085	0.62	3796	0.93	High confidence
Midostaurin	AZI2	105	0.70	74	0.97	High confidence
Midostaurin	TBKBP1	127	0.79	101	0.96	High confidence
Midostaurin	TANK	276	0.64	176	0.99	High confidence
Midostaurin	TBK1	294	0.64	188	0.99	High confidence
Midostaurin	PKN1	216	0.87	189	0.90	High confidence
Midostaurin	PLK4	418	0.51	213	0.99	High confidence
Midostaurin	Q6ZSR9	385	0.76	293	0.96	High confidence
Midostaurin	TNK2	674	0.45	303	0.96	High confidence
Midostaurin	FLT3	635	0.54	341	0.62	High confidence
Midostaurin	CAMK2G	1751	0.22	380	0.97	High confidence
Midostaurin	AAK1	613	0.67	413	0.92	High confidence
Midostaurin	RPS6KA6	994	0.42	419	0.95	High confidence
Midostaurin	IKBKE	713	0.62	443	0.83	High confidence
Midostaurin	AURKA	1348	0.35	477	1.00	High confidence
Midostaurin	BMP2K	798	0.66	528	0.96	High confidence
Midostaurin	CAMK2D	2883	0.20	588	0.99	High confidence
Midostaurin	MARK2	1008	0.75	759	0.97	High confidence
Midostaurin	MAP3K11	1147	0.70	799	0.98	High confidence
Midostaurin	TNK1	1995	0.43	863	0.98	High confidence
Midostaurin	MARK3	1414	0.77	1090	0.86	High confidence
Midostaurin	SIK2	2218	0.52	1149	0.97	High confidence
Midostaurin	PRKAG1	1846	0.63	1168	0.95	High confidence
Midostaurin	EIF2AK1	2221	0.92	2047	0.84	High confidence
Midostaurin	AURKB	4117	0.59	2409	0.93	High confidence
Midostaurin	FER	7069	0.42	2985	0.91	High confidence
Midostaurin	RPS6KA3	4825	0.72	3497	0.92	High confidence
Midostaurin	CAMKK2	5444	0.66	3616	0.88	High confidence
Midostaurin	IRAK3	8765	0.43	3759	0.83	High confidence
Midostaurin	PRKAG2	14155	0.64	9128	0.73	High confidence
Midostaurin	SYK	11003	0.84	9226	0.98	High confidence
Midostaurin	PRKAA1	20136	0.64	12843	0.96	High confidence
Midostaurin	PRKAB1	25025	0.66	16568	0.78	High confidence
Midostaurin	RET	44991	0.44	19822	0.89	High confidence
Milciclib	GAK	5	0.56	3	1.00	High confidence
Milciclib	CLK1	12	0.72	8	1.00	High confidence
Milciclib	WEE1	20	0.63	13	1.00	High confidence
Milciclib	CLK4	21	0.85	18	0.97	High confidence
Milciclib	FLT3	101	0.54	54	0.71	High confidence
Milciclib	DCAF7	92	0.90	83	0.98	High confidence
Milciclib	DYRK1A	112	0.93	105	0.99	High confidence
Milciclib	SIK2	213	0.52	110	0.98	High confidence
Milciclib	PRKD3	183	0.74	135	0.99	High confidence
Milciclib	PRKD2	217	0.66	143	1.00	High confidence
Milciclib	EPHA5	245	0.60	147	0.77	High confidence
Milciclib	GAPVD1	175	0.99	174	0.83	High confidence
Milciclib	MAP4K1	292	0.73	212	0.95	High confidence
Milciclib	CSNK1D	286	0.82	236	0.99	High confidence
Milciclib	FAM83B	260	1.06	260	0.87	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Milciclib	SIK3	325	0.82	266	0.93	High confidence	Milciclib	FIBP	2680	0.57	1528	0.90	High confidence
Milciclib	CCNH	368	0.76	279	0.99	High confidence	Milciclib	DCTPP1	1703	0.94	1594	0.96	High confidence
Milciclib	CDK7	393	0.73	285	0.99	High confidence	Milciclib	CDK6	2102	0.82	1724	1.00	High confidence
Milciclib	IRAK3	679	0.43	291	0.95	High confidence	Milciclib	ULK1	2616	0.67	1748	0.89	High confidence
Milciclib	ERCC2	364	0.90	329	0.97	High confidence	Milciclib	CCNB1	2378	0.77	1822	0.92	High confidence
Milciclib	MNAT1	376	0.88	330	0.98	High confidence	Milciclib	Q6ZSR9	2443	0.76	1860	0.90	High confidence
Milciclib	TAOK1	515	0.66	342	0.83	High confidence	Milciclib	CCNB2	2751	0.70	1929	0.87	High confidence
Milciclib	MYLK3	402	0.87	350	0.90	High confidence	Milciclib	MST1R	2612	0.76	1990	0.93	High confidence
Milciclib	TBKBP1	443	0.79	351	0.91	High confidence	Milciclib	CABLES1	3674	0.55	2019	0.90	High confidence
Milciclib	CSNK1E	428	0.85	366	0.94	High confidence	Milciclib	MAP4K3	3137	0.66	2057	0.90	High confidence
Milciclib	ACVR1	997	0.48	477	0.97	High confidence	Milciclib	IRAK1	3382	0.61	2064	0.89	High confidence
Milciclib	PDGFRB	586	0.87	512	0.95	High confidence	Milciclib	TBK1	3264	0.64	2088	0.91	High confidence
Milciclib	CDK16	558	0.94	526	0.97	High confidence	Milciclib	MARK2	3139	0.75	2365	0.98	High confidence
Milciclib	LCK	1419	0.44	625	0.97	High confidence	Milciclib	NEK3	2796	0.85	2390	0.95	High confidence
Milciclib	EPHA2	1600	0.41	661	0.89	High confidence	Milciclib	TANK	3861	0.64	2456	0.89	High confidence
Milciclib	LATS1	864	0.79	681	0.98	High confidence	Milciclib	MAP3K11	3566	0.70	2484	0.96	High confidence
Milciclib	BCR	1434	0.48	685	0.85	High confidence	Milciclib	EPHB3	2966	0.88	2598	0.93	High confidence
Milciclib	CDK2	1387	0.53	739	0.96	High confidence	Milciclib	MAPK10	3143	0.84	2642	0.89	High confidence
Milciclib	EPHB2	1462	0.52	767	0.97	High confidence	Milciclib	BUB1	2709	1.04	2709	0.95	High confidence
Milciclib	ICK	1274	0.68	863	0.90	High confidence	Milciclib	GRB2	4378	0.62	2731	0.96	High confidence
Milciclib	TNK2	1999	0.45	900	0.92	High confidence	Milciclib	MELK	3174	0.88	2805	0.98	High confidence
Milciclib	INPPL1	1880	0.48	909	0.97	High confidence	Milciclib	NTRK1	4196	0.71	2962	0.86	High confidence
Milciclib	CSNK1A1	1077	0.92	995	0.94	High confidence	Milciclib	IKBKE	4778	0.62	2966	0.99	High confidence
Milciclib	EPHB4	2173	0.49	1075	0.98	High confidence	Milciclib	AZI2	4229	0.70	2968	0.94	High confidence
Milciclib	STK16	1520	0.72	1095	0.82	High confidence	Milciclib	ADCK3	3381	0.89	3012	0.93	High confidence
Milciclib	C2CD5	2125	0.55	1159	0.95	High confidence	Milciclib	FRK	8901	0.34	3023	0.95	High confidence
Milciclib	ABL1	2130	0.55	1167	0.81	High confidence	Milciclib	EIF3J	3111	1.11	3111	0.99	High confidence
Milciclib	CDK17	1177	1.02	1177	0.95	High confidence	Milciclib	DYNLL2	5707	0.55	3118	0.96	High confidence
Milciclib	CAMKK2	1864	0.66	1238	0.99	High confidence	Milciclib	CSNK2A1	3389	1.02	3389	0.93	High confidence
Milciclib	TNIK	1247	1.02	1247	0.58	High confidence	Milciclib	MARK3	4467	0.77	3443	0.96	High confidence
Milciclib	CCNA2	1488	0.86	1282	0.87	High confidence	Milciclib	CSNK2A2	3631	0.96	3496	0.95	High confidence
Milciclib	HCK	2539	0.52	1316	0.95	High confidence	Milciclib	LYN	7045	0.50	3536	0.99	High confidence
Milciclib	RET	3002	0.44	1322	0.99	High confidence	Milciclib	ABL2	11328	0.33	3754	0.92	Low confidence
Milciclib	CDK5	2576	0.52	1349	0.93	High confidence	Milciclib	YES1	9170	0.41	3789	0.95	High confidence
Milciclib	FGFR1	1930	0.74	1421	0.94	High confidence	Milciclib	MAP3K4	5988	0.67	4021	0.94	High confidence
Milciclib	PIP4K2C	1578	0.91	1432	0.96	High confidence	Milciclib	CSNK2B	4103	1.08	4103	0.91	High confidence
Milciclib	FYN	3338	0.43	1439	0.96	High confidence	Milciclib	CDK4	4116	1.00	4116	0.89	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Milciclib	DDR1	6656	0.63	4175	0.88	High confidence	MK-1775	IKBKE	3313	0.62	2057	0.98	High confidence
Milciclib	DDR2	5628	0.76	4289	0.97	High confidence	MK-1775	CDK16	2830	0.94	2668	0.73	High confidence
Milciclib	TAOK2	8898	0.59	5246	0.94	High confidence	MK-1775	ABL1	6341	0.55	3474	0.95	High confidence
Milciclib	SRC	13684	0.39	5313	0.97	High confidence	MK-2206	AKT1	12	0.90	11	0.99	High confidence
Milciclib	MOB1A	6073	0.91	5554	0.94	Low confidence	MK-2206	AKT2	25	0.86	21	0.98	High confidence
Milciclib	TNK1	13138	0.43	5684	0.95	High confidence	MK-2206	AKT3	235	0.90	213	0.97	High confidence
Milciclib	DYNLL1	11375	0.50	5698	0.80	Low confidence	MK-2206	FECH	1074	0.99	1069	0.95	High confidence
Milciclib	AAK1	11013	0.67	7413	0.96	High confidence	MK-2461	SARNP	49	1.11	49	0.91	Low confidence
Milciclib	AURKB	12876	0.59	7536	0.93	Low confidence	MK-2461	MST1R	364	0.76	278	0.99	High confidence
Milciclib	EPHA4	13186	0.62	8131	0.91	High confidence	MK-2461	IRAK3	1170	0.43	502	0.87	High confidence
Milciclib	MAP4K5	13435	0.74	9997	0.97	High confidence	MK-2461	PDGFRB	621	0.87	543	0.62	Low confidence
Milciclib	TAOK3	13721	0.77	10615	0.98	High confidence	MK-2461	PIP4K2C	1132	0.91	1027	0.96	High confidence
Milciclib	MAP4K2	23801	0.59	14043	0.96	High confidence	MK-2461	IRAK4	1904	0.77	1475	0.79	High confidence
Milciclib	PHKG2	19139	0.97	18561	0.80	Low confidence	MK-2461	MAPK9	2760	0.70	1931	0.78	High confidence
Milciclib	NEK9	44467	0.44	19617	0.99	High confidence	MK-2461	Q6ZSR9	3401	0.76	2590	0.89	High confidence
Milciclib	IRAK4	33740	0.77	26123	0.99	High confidence	MK-2461	FECH	3435	0.99	3418	0.93	High confidence
MK-1775	WEE1	19	0.63	12	1.00	High confidence	MK-2461	AAK1	5418	0.67	3647	0.94	High confidence
MK-1775	ADK	13	1.12	13	1.00	High confidence	MK-2461	MAPK10	5594	0.84	4701	0.74	High confidence
MK-1775	MAP3K4	77	0.67	52	0.96	High confidence	MK-2461	NQO2	52632	1.07	52632	0.99	High confidence
MK-1775	AKR1C3	80	1.36	80	0.89	Low confidence	MK-5108	AURKA	0.34	0.35	0.12	0.99	High confidence
MK-1775	EPHB6	549	0.61	337	0.99	High confidence	MK-5108	TNK1	13	0.43	6	0.99	High confidence
MK-1775	CSNK2B	387	1.08	387	0.95	High confidence	MK-5108	BCR	24	0.48	11	0.97	High confidence
MK-1775	CSNK2A2	428	0.96	412	0.99	High confidence	MK-5108	GRB2	35	0.62	22	0.95	High confidence
MK-1775	GAK	745	0.56	418	0.97	High confidence	MK-5108	IRAK3	56	0.43	24	0.97	High confidence
MK-1775	EIF3J	500	1.11	500	0.89	High confidence	MK-5108	JAK2	31	0.80	25	0.95	High confidence
MK-1775	CSNK2A1	627	1.02	627	0.99	High confidence	MK-5108	ABL1	113	0.55	62	0.99	High confidence
MK-1775	INPPL1	1473	0.48	712	0.85	High confidence	MK-5108	ABL2	233	0.33	77	0.96	High confidence
MK-1775	NEK3	980	0.85	837	0.99	High confidence	MK-5108	INPPL1	217	0.48	105	0.96	High confidence
MK-1775	AZI2	1749	0.70	1227	0.73	High confidence	MK-5108	ACVR1	254	0.48	121	0.94	High confidence
MK-1775	PKMYT1	1964	0.73	1440	0.99	High confidence	MK-5108	AURKB	281	0.59	164	0.77	High confidence
MK-1775	TBK1	2547	0.64	1629	0.96	High confidence	MK-5108	PLK4	359	0.51	183	0.98	High confidence
MK-1775	GRB2	2710	0.62	1690	0.74	High confidence	MK-5108	EPHA2	488	0.41	202	0.96	High confidence
MK-1775	TBKBP1	2182	0.79	1732	0.97	High confidence	MK-5108	PTK2B	827	0.41	343	0.90	High confidence
MK-1775	TANK	2868	0.64	1825	0.98	High confidence	MK-5108	RET	880	0.44	388	0.92	High confidence
MK-1775	ADCK1	3045	0.62	1896	0.81	High confidence	MK-5108	ACVR1B	1001	0.43	425	0.97	High confidence
MK-1775	BCR	3990	0.48	1907	0.95	High confidence	MK-5108	TNK2	1050	0.45	473	0.91	High confidence
MK-1775	MAP3K11	2905	0.70	2023	0.94	High confidence	MK-5108	TEC	1758	0.40	707	0.86	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
MK-5108	FRK	2132	0.34	724	0.98	High confidence
MK-5108	PTK6	1741	0.48	841	0.78	High confidence
MK-5108	STK10	1192	0.92	1091	0.98	High confidence
MK-5108	MAPK8	1772	0.65	1148	0.99	High confidence
MK-5108	DDR1	1938	0.63	1216	0.85	High confidence
MK-5108	FER	3653	0.42	1543	0.82	High confidence
MK-5108	IRAK1	2590	0.61	1581	0.85	High confidence
MK-5108	TGFBR1	2455	0.69	1702	0.93	High confidence
MK-5108	MAP4K2	3137	0.59	1851	0.78	High confidence
MK-5108	STK3	2970	0.76	2270	0.84	High confidence
MK-5108	STK4	3113	0.76	2374	0.92	High confidence
MK-5108	ACAD10	2579	0.96	2472	0.76	High confidence
MK-5108	SAV1	2985	0.87	2588	0.66	High confidence
MK-5108	MAPK10	3660	0.84	3076	0.92	High confidence
MK-5108	RASSF5	3511	0.98	3452	0.91	High confidence
MK-5108	LIMK1	8552	0.59	5085	0.84	High confidence
MK-8033	MET	201	0.80	161	0.77	High confidence
MK-8033	TEX264	598	0.98	587	0.82	Low confidence
MK-8033	MST1R	1255	0.76	956	0.92	High confidence
MK-8033	FECH	32806	0.99	32640	0.87	High confidence
MLN-2480	DDR1	101	0.63	63	0.98	High confidence
MLN-2480	INPPL1	145	0.48	70	0.96	High confidence
MLN-2480	ABL2	297	0.33	99	0.99	High confidence
MLN-2480	GRB2	158	0.62	99	0.90	Low confidence
MLN-2480	MAP2K4	146	1.09	146	0.93	Low confidence
MLN-2480	FRK	506	0.34	172	0.97	High confidence
MLN-2480	DDR2	297	0.76	227	1.00	High confidence
MLN-2480	WEE1	398	0.63	252	0.80	High confidence
MLN-2480	BCR	620	0.48	296	0.92	High confidence
MLN-2480	MAPK14	699	0.51	358	0.99	High confidence
MLN-2480	ZAK	606	0.74	450	0.94	High confidence
MLN-2480	ABL1	909	0.55	498	0.99	High confidence
MLN-2480	MAPK11	945	0.72	684	0.99	High confidence
MLN-2480	EPHA2	1955	0.41	807	0.98	High confidence
MLN-2480	CLK1	1316	0.72	942	0.89	High confidence
MLN-2480	LIMK1	1717	0.59	1021	0.93	High confidence
MLN-2480	EPHA1	2653	0.40	1067	0.44	Low confidence
MLN-2480	TGFBR2	2182	0.75	1641	0.51	Low confidence
MLN-2480	RIPK3	2013	0.89	1800	0.93	High confidence
MLN-2480	MAP3K1	3621	0.58	2090	0.97	High confidence
MLN-2480	DYRK1A	3449	0.93	3218	0.86	High confidence
MLN-2480	EPHB6	5440	0.61	3344	0.94	High confidence
MLN-2480	BRAF	3772	1.11	3772	0.96	High confidence
MLN-2480	MYLK	5288	0.83	4406	0.89	Low confidence
MLN-2480	EPHB4	19065	0.49	9434	0.96	High confidence
MLN-2480	PDGFRB	12708	0.87	11107	0.98	High confidence
MLN-8054	AURKA	6	0.35	2	1.00	High confidence
MLN-8054	PRKAB2	63	0.60	38	0.87	High confidence
MLN-8054	AURKB	180	0.59	105	0.98	High confidence
MLN-8054	INCENP	194	0.89	173	0.96	High confidence
MLN-8054	MELK	362	0.88	320	0.77	Low confidence
MLN-8054	EPHA2	1516	0.41	626	0.98	High confidence
MLN-8054	PLK4	1603	0.51	816	0.75	Low confidence
MLN-8054	EPHB4	2247	0.49	1112	0.93	High confidence
MLN-8054	TEC	3112	0.40	1252	0.93	High confidence
MLN-8054	ABL2	3903	0.33	1293	0.95	High confidence
MLN-8054	BCR	2975	0.48	1421	0.94	High confidence
MLN-8054	ABL1	2711	0.55	1485	0.95	High confidence
MLN-8054	MAP3K4	2810	0.67	1887	0.96	High confidence
MLN-8054	BMPR1B	3520	0.61	2161	0.85	High confidence
MLN-8054	EPHA5	3979	0.60	2384	0.88	High confidence
MLN-8054	EIF3J	2874	1.11	2874	0.91	High confidence
MLN-8054	ACAD11	3213	0.98	3156	0.95	High confidence
MLN-8054	EPHA4	5311	0.62	3275	0.93	High confidence
MLN-8054	PDPK1	4300	1.04	4300	0.88	High confidence
MLN-8054	IRAK3	10746	0.43	4609	0.92	High confidence
MLN-8054	CSNK2B	6699	1.08	6699	0.93	High confidence
MLN-8054	CSNK2A2	11357	0.96	10934	0.95	High confidence
MLN-8054	GRB2	41569	0.62	25929	0.87	High confidence
MLN-8054	CSNK2A1	64960	1.02	64960	0.95	High confidence
Momelotinib	Q6ZSR9	4	0.76	3	0.94	High confidence
Momelotinib	AAK1	5	0.67	4	0.93	High confidence
Momelotinib	IKBKE	322	0.62	200	0.85	High confidence
Momelotinib	ADCK1	348	0.62	217	0.86	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Momelotinib	ROCK2	251	0.87	219	0.93	High confidence
Momelotinib	NEK3	335	0.85	286	0.93	High confidence
Momelotinib	ULK3	642	0.45	291	0.94	High confidence
Momelotinib	CSNK2A2	313	0.96	302	0.74	High confidence
Momelotinib	CIT	313	1.21	313	0.98	High confidence
Momelotinib	TYK2	770	0.52	401	0.89	High confidence
Momelotinib	MARK3	541	0.77	417	0.91	High confidence
Momelotinib	BMP2K	638	0.66	422	0.99	High confidence
Momelotinib	EIF3J	470	1.11	470	0.81	Low confidence
Momelotinib	TANK	742	0.64	472	0.81	High confidence
Momelotinib	NEK9	1075	0.44	474	0.95	High confidence
Momelotinib	CSNK2B	503	1.08	503	0.77	High confidence
Momelotinib	PRKD2	805	0.66	531	0.92	High confidence
Momelotinib	TBK1	879	0.64	562	0.87	High confidence
Momelotinib	CSNK2A1	584	1.02	584	0.81	High confidence
Momelotinib	AZI2	849	0.70	596	0.81	High confidence
Momelotinib	CAMK2G	2748	0.22	597	0.83	High confidence
Momelotinib	MAPK8	925	0.65	599	0.92	High confidence
Momelotinib	MARK2	814	0.75	614	0.88	High confidence
Momelotinib	PLK4	1215	0.51	619	0.90	Low confidence
Momelotinib	PRKD3	877	0.74	650	0.81	High confidence
Momelotinib	CAMK2D	3266	0.20	666	0.81	High confidence
Momelotinib	TBKBP1	861	0.79	683	0.85	High confidence
Momelotinib	OPA1	705	1.02	705	0.86	Low confidence
Momelotinib	CCNT2	807	0.88	711	0.84	High confidence
Momelotinib	DYNLL1	1434	0.50	718	0.93	High confidence
Momelotinib	ICK	1062	0.68	720	0.64	Low confidence
Momelotinib	CDK9	1041	0.71	741	0.96	High confidence
Momelotinib	SIK2	1525	0.52	790	0.95	High confidence
Momelotinib	GAK	1463	0.56	822	0.92	High confidence
Momelotinib	SIK3	1050	0.82	859	0.55	High confidence
Momelotinib	CLK1	1283	0.72	918	0.89	Low confidence
Momelotinib	CCNT1	1004	0.98	987	0.93	High confidence
Momelotinib	TRAF2	1221	0.83	1015	0.88	Low confidence
Momelotinib	MAPK9	1624	0.70	1137	0.88	High confidence
Momelotinib	CDK16	1232	0.94	1162	0.95	High confidence
Momelotinib	MAPK10	1417	0.84	1191	0.98	High confidence
Momelotinib	STK16	1778	0.72	1281	0.89	High confidence
Momelotinib	ROCK1	1498	0.91	1362	0.85	High confidence
Momelotinib	CDK17	1382	1.02	1382	0.76	Low confidence
Momelotinib	CCNA2	2249	0.86	1939	0.84	High confidence
Momelotinib	CDK2	3967	0.53	2113	0.81	High confidence
Momelotinib	CDK6	4093	0.82	3356	0.76	Low confidence
Motesanib	MAP4K1	2	0.73	1	1.00	Low confidence
Motesanib	GSPT2	3	1.24	3	1.00	Low confidence
Motesanib	RET	184	0.44	81	0.99	High confidence
Motesanib	ZAK	158	0.74	117	0.96	High confidence
Motesanib	RIPK3	1168	0.89	1044	0.94	High confidence
Mubritinib	MINK1	1766	1.00	1766	0.93	High confidence
Neratinib	RPL13	9	2.51	9	0.87	Low confidence
Neratinib	RPL6	9	2.08	9	0.83	Low confidence
Neratinib	MAP4K5	17	0.74	13	0.97	High confidence
Neratinib	EGFR	42	0.79	34	0.84	High confidence
Neratinib	RPL35	35	1.92	35	0.87	Low confidence
Neratinib	RPL4	43	2.05	43	0.92	High confidence
Neratinib	RPL28	47	1.88	47	0.85	Low confidence
Neratinib	YWHAQ	238	0.95	227	0.94	Low confidence
Neratinib	ADCK5	817	0.97	796	0.68	Low confidence
Neratinib	MAP3K4	1318	0.67	885	0.92	High confidence
Neratinib	MAP4K2	1562	0.59	922	0.79	High confidence
Neratinib	STK26	1054	0.88	926	0.97	High confidence
Neratinib	LCK	2283	0.44	1005	0.79	High confidence
Neratinib	SLK	1171	0.89	1043	0.98	High confidence
Neratinib	HCK	2038	0.52	1056	0.87	High confidence
Neratinib	MAP4K4	1159	1.01	1159	0.98	High confidence
Neratinib	BTK	3090	0.39	1208	0.96	High confidence
Neratinib	LYN	3079	0.50	1545	0.85	High confidence
Neratinib	MAP4K3	2673	0.66	1753	0.84	High confidence
Neratinib	MAP2K1	3173	1.23	3173	0.85	High confidence
Neratinib	STK10	3695	0.92	3382	0.62	High confidence
Neratinib	MAP2K2	4007	1.17	4007	0.90	High confidence
Neratinib	FECH	6060	0.99	6029	0.95	High confidence
Nilotinib	ILK	20	1.04	20	0.93	Low confidence
Nilotinib	DDR1	183	0.63	115	0.94	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Nilotinib	GRB2	279	0.62	174	0.88	High confidence	Nintedanib	STK3	997	0.76	762	0.87	High confidence
Nilotinib	ABL2	877	0.33	291	0.90	High confidence	Nintedanib	STK10	899	0.92	823	0.99	High confidence
Nilotinib	ABL1	550	0.55	301	0.98	High confidence	Nintedanib	YES1	2344	0.41	969	0.91	High confidence
Nilotinib	PHKG2	342	0.97	331	0.92	Low confidence	Nintedanib	AURKB	1678	0.59	982	0.98	High confidence
Nilotinib	DDR2	455	0.76	347	0.99	High confidence	Nintedanib	AZI2	1550	0.70	1088	0.96	High confidence
Nilotinib	INPPL1	1073	0.48	519	0.76	Low confidence	Nintedanib	TNIK	1130	1.02	1130	0.92	High confidence
Nilotinib	FRK	1649	0.34	560	0.84	High confidence	Nintedanib	MAP4K4	1373	1.01	1373	0.91	High confidence
Nilotinib	BCR	1362	0.48	651	0.82	High confidence	Nintedanib	ACVR1	2956	0.48	1415	0.85	High confidence
Nilotinib	EPHA2	1869	0.41	772	0.92	High confidence	Nintedanib	INCENP	1629	0.89	1454	0.87	High confidence
Nilotinib	MAPK14	1810	0.51	927	0.79	High confidence	Nintedanib	MAP3K2	2149	0.70	1501	0.93	High confidence
Nilotinib	ZAK	1415	0.74	1052	0.97	High confidence	Nintedanib	HCK	2900	0.52	1503	0.91	Low confidence
Nilotinib	RIPK3	1424	0.89	1274	0.87	High confidence	Nintedanib	FYN	3851	0.43	1660	0.87	Low confidence
Nilotinib	NQO2	1484	1.07	1484	0.86	High confidence	Nintedanib	TGFBR1	2692	0.69	1866	0.93	High confidence
Nilotinib	LYN	3201	0.50	1607	0.91	High confidence	Nintedanib	FGFR1	2584	0.74	1903	0.97	High confidence
Nilotinib	MAPK11	5171	0.72	3743	0.83	High confidence	Nintedanib	RPS6KA1	2689	0.75	2022	0.89	High confidence
Nilotinib	FECH	4159	0.99	4138	0.85	High confidence	Nintedanib	PRKAA1	3675	0.64	2344	0.93	Low confidence
Nilotinib	PTPN1	4750	1.08	4750	0.92	High confidence	Nintedanib	TANK	3840	0.64	2443	0.94	High confidence
Nintedanib	RET	7	0.44	3	0.98	High confidence	Nintedanib	BMP2K	3951	0.66	2611	0.93	High confidence
Nintedanib	FLT3	7	0.54	4	0.98	High confidence	Nintedanib	STK26	3098	0.88	2721	0.85	High confidence
Nintedanib	DDR2	21	0.76	16	0.89	High confidence	Nintedanib	MINK1	2831	1.00	2831	0.62	High confidence
Nintedanib	DDR1	32	0.63	20	0.96	High confidence	Nintedanib	PDPK1	2876	1.04	2876	0.79	High confidence
Nintedanib	PDGFRB	35	0.87	31	0.97	High confidence	Nintedanib	NTRK1	4160	0.71	2936	0.91	High confidence
Nintedanib	MELK	60	0.88	53	0.99	High confidence	Nintedanib	BTK	8776	0.39	3430	0.85	High confidence
Nintedanib	LCK	156	0.44	69	1.00	High confidence	Nintedanib	MAP4K5	4693	0.74	3492	0.90	High confidence
Nintedanib	JAK2	131	0.80	105	0.98	High confidence	Nintedanib	SLK	4284	0.89	3815	0.94	High confidence
Nintedanib	SIK2	235	0.52	122	0.99	High confidence	Nintedanib	CHEK1	5437	0.82	4485	0.86	High confidence
Nintedanib	CDK3	145	2.15	145	0.86	Low confidence	Nintedanib	FER	11429	0.42	4826	0.89	High confidence
Nintedanib	STK4	222	0.76	169	0.98	High confidence	Nintedanib	TBK1	8297	0.64	5306	0.96	High confidence
Nintedanib	SAV1	197	0.87	171	0.91	High confidence	Nintedanib	MAP3K3	7971	0.67	5349	0.78	High confidence
Nintedanib	IKBKE	279	0.62	173	0.96	High confidence	Nintedanib	MYLK3	11978	0.87	10424	0.72	High confidence
Nintedanib	MAP2K5	206	0.88	180	0.98	High confidence	Nintedanib	LATS1	13628	0.79	10733	0.82	High confidence
Nintedanib	INPPL1	468	0.48	226	0.98	High confidence	NMS-1286937	IMPDH2	27	1.11	27	0.53	Low confidence
Nintedanib	BCR	631	0.48	301	0.94	High confidence	NMS-1286937	KLHL6	51	0.74	38	0.84	Low confidence
Nintedanib	RASSF5	328	0.98	323	0.97	High confidence	NMS-1286937	CSNK2A1	233	1.02	233	0.98	High confidence
Nintedanib	GRB2	741	0.62	462	0.97	High confidence	NMS-1286937	GAPVD1	587	0.99	584	0.79	Low confidence
Nintedanib	TBKBP1	721	0.79	572	0.80	High confidence	NMS-1286937	CSNK2B	748	1.08	748	0.94	High confidence
Nintedanib	ABL1	1078	0.55	591	0.96	High confidence	NMS-1286937	EIF3J	796	1.11	796	0.91	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
NMS-1286937	CSNK2A2	1691	0.96	1628	0.95	High confidence	Orantinib	RPS6KA4	2248	0.62	1388	0.67	High confidence
NMS-1286937	CSNK1E	2101	0.85	1796	0.88	High confidence	Orantinib	IKBKE	2303	0.62	1430	0.73	High confidence
NMS-1286937	RPS6KA4	3977	0.62	2455	0.82	Low confidence	Orantinib	ULK3	3205	0.45	1455	0.81	High confidence
NMS-1286937	MYLK3	3377	0.87	2939	0.92	High confidence	Orantinib	STK4	2054	0.76	1567	0.89	High confidence
NMS-1286937	BMP2K	4847	0.66	3203	0.97	High confidence	Orantinib	EIF3J	1632	1.11	1632	0.79	High confidence
NMS-1286937	PIP4K2C	4426	0.91	4015	0.85	Low confidence	Orantinib	CSNK2A1	1779	1.02	1779	0.91	High confidence
NMS-1286937	CSNK1D	5860	0.82	4821	0.94	High confidence	Orantinib	STK3	2367	0.76	1809	0.85	High confidence
NMS-1286937	MELK	5846	0.88	5166	0.90	High confidence	Orantinib	TBK1	3100	0.64	1982	0.80	High confidence
NMS-1286937	DYRK1A	48133	0.93	44909	0.86	High confidence	Orantinib	MAP4K1	2775	0.73	2015	0.87	High confidence
Omipalisib	PIP4K2C	1512	0.91	1372	0.66	High confidence	Orantinib	GAK	3721	0.56	2090	0.87	High confidence
Omipalisib	IRAK3	7072	0.43	3033	0.76	High confidence	Orantinib	CSNK2A2	2185	0.96	2103	0.92	High confidence
ONO-4059	BTK	10	0.39	4	0.97	High confidence	Orantinib	MAP4K2	3858	0.59	2276	0.72	High confidence
ONO-4059	SRC	11	0.39	4	0.76	Low confidence	Orantinib	CSNK2B	2465	1.08	2465	0.85	High confidence
ONO-4059	YES1	11	0.41	5	0.90	Low confidence	Orantinib	AP2A1	2775	0.92	2549	0.73	High confidence
ONO-4059	FYN	12	0.43	5	0.75	Low confidence	Orantinib	TANK	4055	0.64	2580	0.87	High confidence
ONO-4059	LCK	12	0.44	5	0.74	Low confidence	Orantinib	RPS6KA1	3520	0.75	2647	0.82	High confidence
ONO-4059	TEC	14	0.40	6	0.79	Low confidence	Orantinib	MAP3K11	3819	0.70	2660	0.90	High confidence
ONO-4059	LYN	11	0.50	6	0.72	Low confidence	Orantinib	LATS1	3823	0.79	3011	0.77	High confidence
ONO-4059	HCK	12	0.52	6	0.82	Low confidence	Orantinib	RPS6KA5	4609	0.68	3117	0.90	High confidence
ONO-4059	CSK	13	0.54	7	0.65	Low confidence	Orantinib	MAP2K2	3225	1.17	3225	0.89	High confidence
ONO-4059	RIPK2	26	0.28	7	0.70	Low confidence	Orantinib	AURKA	9200	0.35	3254	0.87	High confidence
ONO-4059	EGFR	24	0.79	19	0.83	High confidence	Orantinib	TBKBP1	4252	0.79	3374	0.68	High confidence
ONO-4059	PTK6	51	0.48	25	0.58	Low confidence	Orantinib	MAP2K1	3426	1.23	3426	0.92	High confidence
Orantinib	FGFR1	0.47	0.74	0.35	0.86	Low confidence	Orantinib	PRKAB1	6690	0.66	4429	0.62	High confidence
Orantinib	FLT3	2	0.54	1	1.00	High confidence	Orantinib	MAP2K5	5639	0.88	4938	0.85	High confidence
Orantinib	TNIK	12	1.02	12	0.84	Low confidence	OSI-027	RET	130	0.44	57	0.96	High confidence
Orantinib	BMPR2	22	0.84	19	0.85	High confidence	OSI-027	ACVR1B	1291	0.43	549	0.83	High confidence
Orantinib	BMP2K	458	0.66	303	0.83	High confidence	OSI-027	TGFBR1	1125	0.69	780	0.88	High confidence
Orantinib	RET	716	0.44	316	0.85	High confidence	OSI-027	RIPK2	4145	0.28	1163	0.97	High confidence
Orantinib	PDPK1	637	1.04	637	0.89	High confidence	OSI-027	NQO2	1390	1.07	1390	0.96	High confidence
Orantinib	PDGFRB	852	0.87	744	0.62	High confidence	OSI-027	CSNK2A1	1478	1.02	1478	0.97	High confidence
Orantinib	AURKB	1594	0.59	933	0.92	High confidence	OSI-027	CSNK2A2	1666	0.96	1604	0.96	High confidence
Orantinib	RASSF5	1125	0.98	1106	0.90	High confidence	OSI-027	MAPK10	1923	0.84	1617	0.96	Low confidence
Orantinib	INCENP	1247	0.89	1113	0.86	High confidence	OSI-027	EIF3J	1864	1.11	1864	0.92	High confidence
Orantinib	AAK1	1744	0.67	1174	0.85	High confidence	OSI-027	BMPR2	2491	0.84	2097	0.58	Low confidence
Orantinib	Q6ZSR9	1553	0.76	1183	0.74	High confidence	OSI-027	S100A8	3124	0.73	2273	0.92	High confidence
Orantinib	NAT10	1240	1.32	1240	0.59	Low confidence	OSI-027	CSNK2B	3125	1.08	3125	0.81	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
OSI-027	NLK	5010	0.66	3331	0.86	Low confidence
OSI-027	MAP2K5	5612	0.88	4914	0.83	High confidence
OSI-027	PIP4K2C	5483	0.91	4974	0.91	Low confidence
OSI-027	FECH	12675	0.99	12611	0.90	High confidence
OSI-930	RET	881	0.44	388	0.87	High confidence
OSI-930	RIPK3	1897	0.89	1696	0.76	High confidence
OSI-930	ZAK	10396	0.74	7731	0.54	High confidence
Osimertinib	PSMB6	3	1.32	3	1.00	Low confidence
Osimertinib	CARS	12	1.07	12	0.99	Low confidence
Osimertinib	EGFR	196	0.79	155	0.88	High confidence
Osimertinib	TEC	798	0.40	321	0.89	High confidence
Osimertinib	BTK	1344	0.39	525	0.89	High confidence
Osimertinib	PIP4K2C	3277	0.91	2973	0.90	High confidence
Osimertinib	NQO2	3658	1.07	3658	0.83	High confidence
P-276-00	DDX42	2	1.53	2	1.00	Low confidence
P-276-00	CCNT2	6	0.88	6	0.95	High confidence
P-276-00	CCNT1	8	0.98	8	0.98	High confidence
P-276-00	PLK1	23	0.92	21	1.00	Low confidence
P-276-00	CDKL5	27	0.89	24	0.92	Low confidence
P-276-00	CDK9	40	0.71	28	0.98	High confidence
P-276-00	ICK	1316	0.68	892	0.93	High confidence
P-276-00	CAMK2G	6149	0.22	1336	0.93	High confidence
P-276-00	NLK	2229	0.66	1482	0.48	Low confidence
P-276-00	CCNB1	2623	0.77	2010	0.88	High confidence
P-276-00	PRKCD	2528	0.95	2394	0.80	High confidence
P-276-00	PRKD3	3431	0.74	2539	0.72	High confidence
P-276-00	CCNB2	3653	0.70	2561	0.86	High confidence
P-276-00	GSK3B	5854	0.46	2722	0.79	High confidence
P-276-00	CDK12	3162	1.12	3162	0.77	High confidence
P-276-00	CDK16	3990	0.94	3762	0.88	High confidence
P-276-00	CDK1	6160	0.69	4226	0.81	High confidence
P-276-00	CCNK	4855	1.11	4855	0.94	High confidence
P-276-00	AKT3	6552	0.90	5922	0.82	Low confidence
P-276-00	MET	8297	0.80	6667	0.64	Low confidence
Pacritinib	STK11	3	0.84	3	1.00	Low confidence
Pacritinib	NQO2	4	1.07	4	1.00	High confidence
Pacritinib	ACVR1	46	0.48	22	0.85	High confidence
Pacritinib	ADCK1	54	0.62	33	0.98	High confidence
Pacritinib	IRAK3	82	0.43	35	0.91	High confidence
Pacritinib	TYK2	74	0.52	38	0.83	High confidence
Pacritinib	BMP2K	58	0.66	39	1.00	High confidence
Pacritinib	AAK1	62	0.67	42	0.99	High confidence
Pacritinib	Q6ZSR9	68	0.76	52	0.97	High confidence
Pacritinib	AP2A1	75	0.92	69	0.88	Low confidence
Pacritinib	TNIK	89	1.02	89	0.71	Low confidence
Pacritinib	CCNT2	128	0.88	113	0.69	Low confidence
Pacritinib	CLK1	192	0.72	138	0.99	Low confidence
Pacritinib	MAP4K1	220	0.73	160	0.72	Low confidence
Pacritinib	FLT3	424	0.54	228	0.94	High confidence
Pacritinib	EIF3J	232	1.11	232	0.98	High confidence
Pacritinib	IRAK1	422	0.61	258	0.98	High confidence
Pacritinib	ICK	399	0.68	270	0.60	High confidence
Pacritinib	MAP4K4	293	1.01	293	0.82	High confidence
Pacritinib	CSNK2B	370	1.08	370	0.87	High confidence
Pacritinib	CSNK2A2	410	0.96	394	0.96	High confidence
Pacritinib	DYNLL2	1155	0.55	631	0.98	High confidence
Pacritinib	AURKB	1096	0.59	641	0.55	High confidence
Pacritinib	CSNK2A1	673	1.02	673	0.94	High confidence
Pacritinib	GAK	1201	0.56	674	0.96	High confidence
Pacritinib	IKBKE	1151	0.62	715	0.97	High confidence
Pacritinib	CCNT1	749	0.98	736	0.97	High confidence
Pacritinib	TNK1	2053	0.43	888	0.85	High confidence
Pacritinib	PRKCA	1283	0.73	934	0.92	High confidence
Pacritinib	CDK9	1414	0.71	1006	0.93	High confidence
Pacritinib	DYNLL1	2700	0.50	1352	0.70	High confidence
Pacritinib	PRKG1	2995	0.51	1516	0.55	High confidence
Pacritinib	NEK9	4034	0.44	1780	0.96	High confidence
Pacritinib	STK16	2592	0.72	1867	0.72	High confidence
Pacritinib	MAPK8	3019	0.65	1957	0.91	High confidence
Pacritinib	TAOK1	3301	0.66	2195	0.87	High confidence
Pacritinib	PDGFRB	3050	0.87	2666	0.90	High confidence
Pacritinib	AZI2	3889	0.70	2730	0.85	High confidence
Pacritinib	STK10	3189	0.92	2919	0.98	High confidence
Pacritinib	ZAK	4005	0.74	2978	0.68	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Pacritinib	TANK	4711	0.64	2997	0.95	High confidence	Palbociclib	Q6ZSR9	35897	0.76	27334	0.96	Low confidence
Pacritinib	CDK16	3285	0.94	3097	0.93	High confidence	Palbociclib	TAOK2	47442	0.59	27973	0.95	Low confidence
Pacritinib	TAOK2	5724	0.59	3375	0.88	High confidence	Pazopanib	DDR2	159	0.76	121	0.94	High confidence
Pacritinib	FER	8668	0.42	3660	0.97	High confidence	Pazopanib	DDR1	211	0.63	132	0.97	High confidence
Pacritinib	MAP4K2	6301	0.59	3718	0.91	High confidence	Pazopanib	RET	663	0.44	292	0.99	High confidence
Pacritinib	GSK3A	10372	0.50	5188	0.88	High confidence	Pazopanib	PDGFRB	492	0.87	430	0.95	High confidence
Pacritinib	LCK	14839	0.44	6537	0.92	High confidence	Pazopanib	RIPK3	2076	0.89	1856	0.56	Low confidence
Pacritinib	PRKCB	9078	0.80	7244	0.92	High confidence	Pazopanib	MAP3K11	2744	0.70	1911	0.93	High confidence
Pacritinib	CAMKK2	11581	0.66	7694	0.94	High confidence	Pazopanib	LIMK1	3880	0.59	2307	0.82	High confidence
Pacritinib	TNK2	20734	0.45	9334	0.81	High confidence	Pazopanib	RIPK2	27314	0.28	7665	0.91	High confidence
Pacritinib	TBK1	77558	0.64	49601	0.96	High confidence	Pazopanib	FLT3	24369	0.54	13095	0.61	Low confidence
Pacritinib	LIMK2	78529	0.66	52056	0.95	High confidence	Pazopanib	LIMK2	23572	0.66	15626	0.91	High confidence
Pacritinib	FECH	68260	0.99	67914	0.89	High confidence	Pazopanib	ADCK1	26049	0.62	16218	0.88	High confidence
Pacritinib	DDR1	113962	0.63	71484	0.96	High confidence	Pazopanib	IRAK3	59644	0.43	25581	0.95	High confidence
Palbociclib	CDK6	93	0.82	76	0.95	High confidence	PD-325901	MAP2K2	12	1.17	12	0.99	High confidence
Palbociclib	PIP4K2A	217	0.96	208	0.89	High confidence	PD-325901	MAP2K1	12	1.23	12	0.99	High confidence
Palbociclib	CLK1	386	0.72	276	0.93	High confidence	PD-325901	MAP2K5	923	0.88	808	0.98	High confidence
Palbociclib	CSNK2B	448	1.08	448	0.98	High confidence	PD-325901	KLHL6	4151	0.74	3075	0.81	Low confidence
Palbociclib	CSNK2A2	507	0.96	488	0.98	High confidence	Pelitinib	EGFR	15	0.79	12	0.91	High confidence
Palbociclib	CDK4	572	1.00	572	0.91	High confidence	Pelitinib	MAP4K5	57	0.74	42	0.99	High confidence
Palbociclib	EIF3J	701	1.11	701	0.98	High confidence	Pelitinib	MAP3K1	168	0.58	97	0.95	High confidence
Palbociclib	CSNK2A1	760	1.02	760	0.95	High confidence	Pelitinib	GAK	208	0.56	117	0.99	High confidence
Palbociclib	MAP2K4	1251	1.09	1251	0.70	Low confidence	Pelitinib	MAP3K4	550	0.67	369	0.91	High confidence
Palbociclib	CDK17	1272	1.02	1272	0.91	High confidence	Pelitinib	BTK	1314	0.39	514	0.98	High confidence
Palbociclib	CCNT2	1892	0.88	1665	0.70	High confidence	Pelitinib	GRB2	869	0.62	542	0.96	High confidence
Palbociclib	PIP4K2C	1897	0.91	1721	0.94	High confidence	Pelitinib	INPPL1	1663	0.48	804	0.78	High confidence
Palbociclib	CCNT1	2721	0.98	2676	0.91	High confidence	Pelitinib	ZAK	1176	0.74	875	0.91	High confidence
Palbociclib	CDK16	2947	0.94	2778	0.97	High confidence	Pelitinib	WEE1	1528	0.63	967	0.96	High confidence
Palbociclib	MAPK9	4080	0.70	2856	0.88	High confidence	Pelitinib	MAP4K1	1510	0.73	1096	0.69	High confidence
Palbociclib	MED23	3023	0.99	2998	0.77	Low confidence	Pelitinib	HCK	2277	0.52	1180	0.87	High confidence
Palbociclib	AAK1	6264	0.67	4216	0.96	Low confidence	Pelitinib	BCR	2496	0.48	1193	0.80	High confidence
Palbociclib	PRKD2	8530	0.66	5623	0.98	High confidence	Pelitinib	TNIK	1300	1.02	1300	0.91	High confidence
Palbociclib	CDK9	13341	0.71	9492	0.94	High confidence	Pelitinib	CAMKK2	2093	0.66	1390	0.87	High confidence
Palbociclib	STK16	13846	0.72	9969	0.92	High confidence	Pelitinib	CSNK1E	1736	0.85	1484	0.96	High confidence
Palbociclib	TAOK3	20490	0.77	15852	0.92	Low confidence	Pelitinib	MAP3K3	3121	0.67	2094	0.63	High confidence
Palbociclib	PRKD3	22014	0.74	16296	0.89	High confidence	Pelitinib	MAP4K2	3864	0.59	2280	0.94	High confidence
Palbociclib	BMP2K	40042	0.66	26466	0.94	High confidence	Pelitinib	MAP2K2	2724	1.17	2724	0.97	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Pelitinib	BMP2K	4253	0.66	2811	0.85	High confidence	Pexmetinib	EPHA7	4183	0.79	3312	0.82	High confidence
Pelitinib	CSNK1D	4715	0.82	3879	0.84	High confidence	Pexmetinib	CDK5	7935	0.52	4155	0.94	High confidence
Pelitinib	STK10	4370	0.92	4001	0.90	High confidence	Pexmetinib	IRAK1	7154	0.61	4366	0.93	High confidence
Pelitinib	MAP2K1	8773	1.23	8773	0.94	High confidence	Pexmetinib	EPHB4	10530	0.49	5210	0.95	Low confidence
Pelitinib	FECH	10599	0.99	10545	0.94	High confidence	Pexmetinib	BRAF	5233	1.11	5233	0.94	High confidence
Pexidartinib	PRKCQ	6	1.23	6	1.00	Low confidence	Pexmetinib	EPHB3	32151	0.88	28160	0.91	Low confidence
Pexidartinib	FLT3	103	0.54	55	0.96	High confidence	Pexmetinib	PTK2B	73360	0.41	30414	0.99	High confidence
Pexidartinib	Q6ZSR9	1907	0.76	1452	0.77	High confidence	PF-03814735	BMPR2	9	0.84	8	0.65	Low confidence
Pexidartinib	AAK1	20371	0.67	13711	0.77	High confidence	PF-03814735	AAK1	13	0.67	9	1.00	High confidence
Pexmetinib	MAPK14	82	0.51	42	0.99	High confidence	PF-03814735	MARK4	11	0.83	9	0.98	High confidence
Pexmetinib	INPPL1	117	0.48	57	0.82	High confidence	PF-03814735	Q6ZSR9	13	0.76	10	1.00	High confidence
Pexmetinib	MAPKAPK2	93	0.72	67	0.96	High confidence	PF-03814735	SIK2	21	0.52	11	0.98	High confidence
Pexmetinib	MYLK	97	0.83	81	0.94	Low confidence	PF-03814735	AURKA	38	0.35	14	1.00	High confidence
Pexmetinib	MAPK11	265	0.72	192	0.98	High confidence	PF-03814735	BMP2K	22	0.66	15	1.00	High confidence
Pexmetinib	MAPK10	231	0.84	195	0.51	Low confidence	PF-03814735	RET	39	0.44	17	0.99	High confidence
Pexmetinib	ABL1	386	0.55	211	0.93	High confidence	PF-03814735	ULK3	41	0.45	19	1.00	High confidence
Pexmetinib	MAP4K4	222	1.01	222	0.94	High confidence	PF-03814735	STK24	19	1.06	19	0.93	Low confidence
Pexmetinib	MAPK9	446	0.70	312	0.96	High confidence	PF-03814735	AURKB	34	0.59	20	0.99	High confidence
Pexmetinib	ABL2	1058	0.33	351	0.99	High confidence	PF-03814735	NUAK2	32	0.77	24	0.98	High confidence
Pexmetinib	DDR1	579	0.63	363	0.99	High confidence	PF-03814735	AP2A1	28	0.92	25	0.99	High confidence
Pexmetinib	CDK17	402	1.02	402	0.75	High confidence	PF-03814735	ULK1	42	0.67	28	1.00	High confidence
Pexmetinib	RIPK3	740	0.89	662	0.96	High confidence	PF-03814735	AP2A2	30	0.94	28	0.94	High confidence
Pexmetinib	BCR	1426	0.48	681	1.00	High confidence	PF-03814735	INCENP	33	0.89	29	1.00	High confidence
Pexmetinib	UNC119	1331	0.73	966	0.55	Low confidence	PF-03814735	FLT3	69	0.54	37	0.92	High confidence
Pexmetinib	DDR2	1493	0.76	1138	1.00	High confidence	PF-03814735	AP2B1	40	1.01	40	0.98	High confidence
Pexmetinib	RET	2723	0.44	1200	0.98	High confidence	PF-03814735	MAP3K11	71	0.70	50	0.98	High confidence
Pexmetinib	ZAK	1686	0.74	1254	0.97	High confidence	PF-03814735	PTK2	142	0.41	58	0.99	High confidence
Pexmetinib	FRK	4559	0.34	1548	0.96	High confidence	PF-03814735	TBKBP1	97	0.79	77	0.96	High confidence
Pexmetinib	TNK1	3840	0.43	1661	0.84	High confidence	PF-03814735	TANK	122	0.64	78	0.98	High confidence
Pexmetinib	FYN	4965	0.43	2140	0.95	Low confidence	PF-03814735	TBK1	122	0.64	78	1.00	High confidence
Pexmetinib	LYN	4973	0.50	2496	0.99	High confidence	PF-03814735	AZI2	123	0.70	86	1.00	High confidence
Pexmetinib	PCBP2	2539	1.22	2539	0.93	Low confidence	PF-03814735	C2CD5	176	0.55	96	0.95	High confidence
Pexmetinib	EPHA2	6210	0.41	2565	0.98	High confidence	PF-03814735	FER	244	0.42	103	1.00	High confidence
Pexmetinib	EPHA1	6575	0.40	2644	0.95	High confidence	PF-03814735	MYLK3	125	0.87	109	0.97	High confidence
Pexmetinib	FGFR1	3632	0.74	2675	0.93	High confidence	PF-03814735	PDPK1	114	1.04	114	0.95	High confidence
Pexmetinib	MERTK	3516	0.80	2810	0.97	Low confidence	PF-03814735	FIBP	257	0.57	147	0.95	High confidence
Pexmetinib	NTRK1	4428	0.71	3126	0.82	High confidence	PF-03814735	RPS6KA4	252	0.62	156	0.99	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
PF-03814735	KIAA0195	236	0.66	156	0.84	High confidence	PF-03814735	STK16	1727	0.72	1243	0.89	High confidence
PF-03814735	MAP3K2	235	0.70	164	1.00	High confidence	PF-03814735	PRKAG2	1946	0.64	1255	0.89	High confidence
PF-03814735	CABLES1	332	0.55	182	0.89	High confidence	PF-03814735	STK3	1661	0.76	1270	0.99	High confidence
PF-03814735	MAP3K3	367	0.67	246	0.98	High confidence	PF-03814735	MAP3K5	1590	0.80	1273	0.97	High confidence
PF-03814735	NTRK1	373	0.71	263	0.80	High confidence	PF-03814735	FGFR1	1742	0.74	1282	0.92	High confidence
PF-03814735	PTK2B	644	0.41	267	0.99	High confidence	PF-03814735	JAK1	3474	0.37	1294	0.96	High confidence
PF-03814735	PLK4	544	0.51	277	0.98	High confidence	PF-03814735	INPPL1	2750	0.48	1329	0.97	High confidence
PF-03814735	RPS6KA6	668	0.42	282	0.99	High confidence	PF-03814735	MAP4K2	2298	0.59	1356	0.95	High confidence
PF-03814735	STK10	338	0.92	309	0.99	High confidence	PF-03814735	TNK2	3017	0.45	1358	0.98	High confidence
PF-03814735	PRKAA1	549	0.64	350	1.00	High confidence	PF-03814735	RPS6KA3	1920	0.72	1392	1.00	High confidence
PF-03814735	MARK3	473	0.77	364	0.95	High confidence	PF-03814735	PRKAG1	2265	0.63	1433	0.96	High confidence
PF-03814735	TNK1	853	0.43	369	0.87	High confidence	PF-03814735	UBAP2L	1446	1.08	1446	0.97	Low confidence
PF-03814735	RASSF5	407	0.98	400	0.98	High confidence	PF-03814735	CDK3	1534	2.15	1534	0.91	High confidence
PF-03814735	LATS1	516	0.79	406	0.98	High confidence	PF-03814735	WEE1	2509	0.63	1588	0.92	High confidence
PF-03814735	CHEK1	505	0.82	417	0.94	High confidence	PF-03814735	GAK	3136	0.56	1761	0.49	High confidence
PF-03814735	PRKAB1	706	0.66	468	0.98	High confidence	PF-03814735	CDK2	3334	0.53	1775	0.93	High confidence
PF-03814735	RASSF2	505	0.93	470	0.87	Low confidence	PF-03814735	TYK2	3578	0.52	1866	0.96	High confidence
PF-03814735	CDK5	907	0.52	475	0.97	High confidence	PF-03814735	IRAK4	2613	0.77	2023	0.98	High confidence
PF-03814735	MARK2	770	0.75	580	0.99	High confidence	PF-03814735	TAOK2	3470	0.59	2046	0.97	High confidence
PF-03814735	SYK	812	0.84	681	0.99	High confidence	PF-03814735	CDK6	2539	0.82	2081	0.74	High confidence
PF-03814735	SLK	771	0.89	687	0.99	High confidence	PF-03814735	MAP3K1	3783	0.58	2184	0.90	Low confidence
PF-03814735	TNIK	746	1.02	746	0.92	High confidence	PF-03814735	CAMKK2	3295	0.66	2189	0.98	High confidence
PF-03814735	MAP4K3	1168	0.66	766	0.99	High confidence	PF-03814735	DYNLL2	4162	0.55	2274	0.96	High confidence
PF-03814735	IKBKE	1282	0.62	796	0.94	High confidence	PF-03814735	TEC	5764	0.40	2319	0.97	High confidence
PF-03814735	PRKD3	1110	0.74	822	0.96	High confidence	PF-03814735	INSR	3193	0.75	2398	0.92	High confidence
PF-03814735	PRKAB2	1376	0.60	827	0.85	High confidence	PF-03814735	TAOK3	3105	0.77	2402	0.87	High confidence
PF-03814735	STK4	1086	0.76	828	0.98	High confidence	PF-03814735	RPS6KA1	3199	0.75	2406	0.99	High confidence
PF-03814735	MAP4K5	1206	0.74	897	0.99	High confidence	PF-03814735	ABL1	4620	0.55	2532	1.00	High confidence
PF-03814735	PRKD2	1408	0.66	928	0.99	High confidence	PF-03814735	CSNK2A2	2737	0.96	2635	0.93	High confidence
PF-03814735	SAV1	1150	0.87	997	0.93	High confidence	PF-03814735	IGF1R	4101	0.66	2714	0.94	High confidence
PF-03814735	MET	1299	0.80	1044	0.95	High confidence	PF-03814735	CCNB1	3731	0.77	2859	0.96	High confidence
PF-03814735	MAP3K6	1284	0.83	1060	0.91	High confidence	PF-03814735	PKN1	3364	0.87	2940	0.97	High confidence
PF-03814735	MOB1A	1202	0.91	1099	0.96	High confidence	PF-03814735	MAPK7	3807	0.78	2965	0.91	Low confidence
PF-03814735	MAP2K5	1365	0.88	1196	0.97	High confidence	PF-03814735	EIF3J	3051	1.11	3051	0.96	High confidence
PF-03814735	MINK1	1221	1.00	1221	0.86	Low confidence	PF-03814735	GRB2	4963	0.62	3096	0.79	High confidence
PF-03814735	FES	3339	0.37	1234	0.94	High confidence	PF-03814735	CSNK2B	3192	1.08	3192	0.97	High confidence
PF-03814735	PAK4	2059	0.60	1237	0.99	High confidence	PF-03814735	MAP4K4	3362	1.01	3362	0.94	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
PF-03814735	ERN1	4470	0.81	3643	0.97	High confidence	PF-3758309	LATS1	200	0.79	157	0.88	High confidence
PF-03814735	MNAT1	4213	0.88	3700	0.93	Low confidence	PF-3758309	FGFR1	283	0.74	208	0.98	High confidence
PF-03814735	CSNK2A1	4310	1.02	4310	0.93	High confidence	PF-3758309	CHEK1	255	0.82	210	0.95	High confidence
PF-03814735	MST1R	5985	0.76	4560	0.96	High confidence	PF-3758309	ICK	349	0.68	237	0.98	Low confidence
PF-03814735	SIK3	11786	0.82	9648	0.84	High confidence	PF-3758309	PRKD2	370	0.66	244	0.98	High confidence
PF-03814735	BCR	22644	0.48	10820	0.96	High confidence	PF-3758309	PRKD3	363	0.74	268	0.99	High confidence
PF-04217903	MET	3	0.80	2	0.99	High confidence	PF-3758309	CAMK2G	1268	0.22	275	1.00	High confidence
PF-04691502	CSNK2A2	1603	0.96	1543	0.89	High confidence	PF-3758309	PRKX	385	0.81	312	0.94	High confidence
PF-3758309	PRKAB2	3	0.60	2	1.00	High confidence	PF-3758309	TANK	496	0.64	316	0.98	High confidence
PF-3758309	ERCC2	3	0.90	2	1.00	High confidence	PF-3758309	AZI2	482	0.70	338	0.99	High confidence
PF-3758309	PAK6	3	0.74	3	0.97	High confidence	PF-3758309	CAMK2D	1684	0.20	343	0.99	High confidence
PF-3758309	MNAT1	3	0.88	3	1.00	High confidence	PF-3758309	MYLK3	401	0.87	349	0.97	High confidence
PF-3758309	CDK7	4	0.73	3	1.00	High confidence	PF-3758309	PRKACB	748	0.47	354	0.98	High confidence
PF-3758309	RPS6KA6	8	0.42	4	0.99	High confidence	PF-3758309	RPS6KB1	401	0.89	357	0.98	High confidence
PF-3758309	PRKAG2	8	0.64	5	0.99	High confidence	PF-3758309	STK24	369	1.06	369	0.73	Low confidence
PF-3758309	CCNH	7	0.76	5	0.99	High confidence	PF-3758309	TBK1	589	0.64	377	0.97	High confidence
PF-3758309	PRKAG1	9	0.63	6	1.00	High confidence	PF-3758309	CAMK4	408	1.02	408	0.97	High confidence
PF-3758309	PRKAA1	10	0.64	6	1.00	High confidence	PF-3758309	CCNI	1158	0.37	430	0.62	Low confidence
PF-3758309	PRKAB1	14	0.66	9	0.99	High confidence	PF-3758309	STK11	515	0.84	434	0.88	High confidence
PF-3758309	CLK4	15	0.85	13	1.00	High confidence	PF-3758309	TBKBP1	568	0.79	450	0.97	High confidence
PF-3758309	CDK17	14	1.02	14	1.00	High confidence	PF-3758309	ULK3	1379	0.45	626	0.99	High confidence
PF-3758309	STK26	20	0.88	17	0.96	Low confidence	PF-3758309	IKBKE	1059	0.62	658	0.92	High confidence
PF-3758309	MARK4	35	0.83	29	0.97	High confidence	PF-3758309	GSK3B	1435	0.46	667	0.99	High confidence
PF-3758309	CAB39	50	1.12	50	0.96	High confidence	PF-3758309	PLK4	1312	0.51	668	0.95	High confidence
PF-3758309	PHKG2	55	0.97	53	0.96	High confidence	PF-3758309	RET	1653	0.44	728	0.99	High confidence
PF-3758309	MELK	65	0.88	57	0.95	High confidence	PF-3758309	FER	1899	0.42	802	0.98	High confidence
PF-3758309	PRKACG	128	0.51	66	0.99	High confidence	PF-3758309	PRKG1	1595	0.51	808	0.92	High confidence
PF-3758309	CDK18	67	1.12	67	0.84	High confidence	PF-3758309	RPS6KA1	1091	0.75	820	0.98	High confidence
PF-3758309	PAK4	119	0.60	71	0.99	High confidence	PF-3758309	PRKCA	1200	0.73	873	0.98	High confidence
PF-3758309	STK38	75	1.00	75	0.96	Low confidence	PF-3758309	PRKACA	1990	0.47	935	0.98	High confidence
PF-3758309	PRKCQ	85	1.23	85	0.57	High confidence	PF-3758309	ABL2	2834	0.33	939	0.96	High confidence
PF-3758309	CLK1	125	0.72	90	0.96	High confidence	PF-3758309	PRKCD	1029	0.95	974	0.99	High confidence
PF-3758309	RPS6KA3	139	0.72	100	0.99	High confidence	PF-3758309	AURKA	2773	0.35	981	0.97	High confidence
PF-3758309	MARK3	136	0.77	105	1.00	High confidence	PF-3758309	PDPK1	1044	1.04	1044	0.92	High confidence
PF-3758309	RPS6KA4	180	0.62	111	0.99	High confidence	PF-3758309	PIK3R1	1308	0.87	1143	0.81	Low confidence
PF-3758309	MARK2	151	0.75	114	0.99	High confidence	PF-3758309	PKN1	1335	0.87	1167	1.00	High confidence
PF-3758309	CAPNS1	146	0.94	138	0.91	Low confidence	PF-3758309	TEC	3053	0.40	1229	0.89	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
PF-3758309	BTK	3146	0.39	1230	0.93	Low confidence
PF-3758309	FYN	2861	0.43	1233	0.99	High confidence
PF-3758309	SIK2	2445	0.52	1267	0.92	High confidence
PF-3758309	BCR	2682	0.48	1282	0.95	High confidence
PF-3758309	PTK2B	3378	0.41	1400	0.91	High confidence
PF-3758309	FLT3	2685	0.54	1443	0.95	High confidence
PF-3758309	MAP3K11	2240	0.70	1560	0.97	High confidence
PF-3758309	MOB1A	1843	0.91	1686	0.98	High confidence
PF-3758309	CDKL5	2170	0.89	1930	0.86	High confidence
PF-3758309	GAK	3479	0.56	1954	0.98	High confidence
PF-3758309	MAPK1	4238	0.46	1965	0.92	High confidence
PF-3758309	AURKB	3548	0.59	2076	0.94	High confidence
PF-3758309	SRC	5370	0.39	2085	0.95	High confidence
PF-3758309	GSK3A	4174	0.50	2088	0.96	High confidence
PF-3758309	MAP4K3	3340	0.66	2190	0.92	High confidence
PF-3758309	STK3	2883	0.76	2203	0.95	High confidence
PF-3758309	NTRK1	3127	0.71	2208	0.58	Low confidence
PF-3758309	MAP4K1	3167	0.73	2300	0.96	High confidence
PF-3758309	BMP2K	3841	0.66	2539	0.97	High confidence
PF-3758309	Q6ZSR9	3567	0.76	2716	0.94	High confidence
PF-3758309	WEE1	4377	0.63	2770	0.99	High confidence
PF-3758309	CAMKK2	4308	0.66	2862	0.92	High confidence
PF-3758309	AAK1	4518	0.67	3041	0.97	High confidence
PF-3758309	CDK16	3593	0.94	3387	0.98	High confidence
PF-3758309	MAPK3	5849	0.66	3868	0.98	High confidence
PF-3758309	MAPK7	4988	0.78	3885	0.83	High confidence
PF-3758309	STK4	5665	0.76	4320	0.98	High confidence
PF-3758309	STK16	7564	0.72	5446	0.88	High confidence
PF-3758309	YES1	13451	0.41	5557	0.98	High confidence
PF-3758309	PRKCB	7385	0.80	5893	0.98	High confidence
PF-3758309	ADRBK1	22494	1.13	22494	0.88	High confidence
PF-3758309	PRKCI	27388	1.07	27388	0.97	High confidence
PF-3758309	PDGFRB	34012	0.87	29725	0.97	Low confidence
PF-3758309	RPS6KA5	44290	0.68	29957	0.96	High confidence
PF-3758309	CDK3	63614	2.15	63614	0.94	High confidence
PF-477736	CHEK1	0.30	0.82	0.24	0.99	High confidence
PF-477736	AAK1	3	0.67	2	1.00	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
PF-477736	AP2A1	3	0.92	2	0.89	Low confidence
PF-477736	Q6ZSR9	3	0.76	2	1.00	High confidence
PF-477736	BMP2K	9	0.66	6	0.99	High confidence
PF-477736	RET	22	0.44	10	0.97	High confidence
PF-477736	MERTK	22	0.80	18	0.90	Low confidence
PF-477736	PAK6	25	0.74	19	0.95	Low confidence
PF-477736	MINK1	20	1.00	20	0.96	Low confidence
PF-477736	GAK	41	0.56	23	0.97	High confidence
PF-477736	MYLK3	36	0.87	31	0.99	Low confidence
PF-477736	PLK4	63	0.51	32	0.92	High confidence
PF-477736	MARK4	44	0.83	36	0.85	Low confidence
PF-477736	SIK2	92	0.52	47	0.94	High confidence
PF-477736	FLT3	94	0.54	50	0.98	High confidence
PF-477736	PAK4	88	0.60	53	0.96	High confidence
PF-477736	PDGFRB	115	0.87	100	0.93	High confidence
PF-477736	INCENP	113	0.89	101	0.93	High confidence
PF-477736	PKN1	137	0.87	119	0.88	High confidence
PF-477736	AURKB	206	0.59	120	0.97	High confidence
PF-477736	LIMK1	224	0.59	133	0.86	High confidence
PF-477736	AURKA	398	0.35	141	0.95	High confidence
PF-477736	TGFBR2	194	0.75	146	0.98	High confidence
PF-477736	FGFR1	261	0.74	192	0.85	High confidence
PF-477736	LIMK2	309	0.66	205	0.98	High confidence
PF-477736	TNIK	251	1.02	251	0.55	Low confidence
PF-477736	LYN	660	0.50	331	0.97	High confidence
PF-477736	LATS1	460	0.79	363	0.84	High confidence
PF-477736	SIK3	471	0.82	386	0.96	High confidence
PF-477736	MARK3	502	0.77	387	0.98	High confidence
PF-477736	HCK	841	0.52	436	0.99	High confidence
PF-477736	PDPK1	458	1.04	458	0.91	High confidence
PF-477736	MARK2	652	0.75	491	0.95	High confidence
PF-477736	ABL1	1065	0.55	584	0.90	High confidence
PF-477736	YES1	1509	0.41	623	0.92	High confidence
PF-477736	PRKAB2	1177	0.60	707	0.98	High confidence
PF-477736	CIT	725	1.21	725	0.96	High confidence
PF-477736	PRKAG1	1239	0.63	784	0.99	High confidence
PF-477736	BMPR1A	1542	0.53	814	0.92	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
PF-477736	PRKAB1	1379	0.66	913	0.97	High confidence
PF-477736	RPS6KA4	1710	0.62	1055	0.94	High confidence
PF-477736	BCR	2320	0.48	1108	0.89	High confidence
PF-477736	ULK3	2571	0.45	1167	0.96	High confidence
PF-477736	PRKAG2	1963	0.64	1266	0.94	High confidence
PF-477736	PRKAA1	2075	0.64	1324	0.91	High confidence
PF-477736	FYN	3102	0.43	1337	0.95	High confidence
PF-477736	ABL2	4140	0.33	1372	0.84	High confidence
PF-477736	LCK	3136	0.44	1381	0.92	High confidence
PF-477736	SRC	3618	0.39	1405	0.92	High confidence
PF-477736	EPHB6	2480	0.61	1525	0.94	Low confidence
PF-477736	MAP4K3	2353	0.66	1543	0.92	High confidence
PF-477736	EGFR	2171	0.79	1722	0.96	High confidence
PF-477736	JAK1	4774	0.37	1779	0.85	High confidence
PF-477736	MAP3K1	3129	0.58	1806	0.74	High confidence
PF-477736	PRKX	2267	0.81	1841	0.96	High confidence
PF-477736	MAP3K11	2676	0.70	1864	0.96	High confidence
PF-477736	BMPR1B	3278	0.61	2013	0.66	High confidence
PF-477736	MAP2K5	2505	0.88	2194	1.00	High confidence
PF-477736	RPS6KA6	5633	0.42	2376	0.86	High confidence
PF-477736	RPS6KB1	2671	0.89	2379	0.80	High confidence
PF-477736	IRAK4	3368	0.77	2607	0.96	High confidence
PF-477736	MAP4K5	3546	0.74	2639	0.95	High confidence
PF-477736	BTK	7264	0.39	2839	0.94	High confidence
PF-477736	MAPK3	4848	0.66	3206	0.98	High confidence
PF-477736	ADRBK1	3558	1.13	3558	0.94	High confidence
PF-477736	STK11	5187	0.84	4375	0.88	High confidence
PF-477736	ADCK1	7223	0.62	4497	0.95	High confidence
PF-477736	EIF3J	4573	1.11	4573	0.86	High confidence
PF-477736	WEE1	7673	0.63	4856	0.85	High confidence
PF-477736	RPS6KA1	6917	0.75	5202	0.84	Low confidence
PF-477736	CSNK2A1	8572	1.02	8572	0.96	High confidence
PF-477736	CSNK2A2	15329	0.96	14757	0.97	High confidence
PF-477736	MELK	51705	0.88	45694	0.90	High confidence
PF-477736	CSNK2B	46390	1.08	46390	0.92	High confidence
PF-562271	PTK2	2	0.41	1	1.00	High confidence
PF-562271	PRKCQ	1	1.23	1	0.96	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
PF-562271	STK26	14	0.88	12	0.85	Low confidence
PF-562271	CABLES1	95	0.55	52	0.91	High confidence
PF-562271	INCENP	66	0.89	59	0.89	High confidence
PF-562271	C2CD5	114	0.55	62	0.99	High confidence
PF-562271	FIBP	132	0.57	76	0.94	High confidence
PF-562271	PTK2B	191	0.41	79	0.91	High confidence
PF-562271	KIAA0195	122	0.66	81	0.96	High confidence
PF-562271	CDK17	89	1.02	89	0.59	High confidence
PF-562271	STK16	192	0.72	138	0.93	High confidence
PF-562271	MARK4	168	0.83	140	0.71	High confidence
PF-562271	CSNK2B	156	1.08	156	0.96	High confidence
PF-562271	MAP4K4	230	1.01	230	0.61	Low confidence
PF-562271	CCNB1	460	0.77	352	0.87	High confidence
PF-562271	CLK1	507	0.72	363	0.81	High confidence
PF-562271	KLHL6	533	0.74	395	0.98	Low confidence
PF-562271	MAP3K11	637	0.70	444	0.89	High confidence
PF-562271	CDK5	915	0.52	479	0.79	High confidence
PF-562271	CCNT2	665	0.88	585	0.91	High confidence
PF-562271	STK11	742	0.84	626	0.70	High confidence
PF-562271	AURKA	1772	0.35	627	0.65	High confidence
PF-562271	GSK3B	1520	0.46	707	0.82	High confidence
PF-562271	EIF3J	714	1.11	714	0.89	High confidence
PF-562271	FER	1928	0.42	814	0.77	High confidence
PF-562271	GSK3A	1689	0.50	845	0.77	High confidence
PF-562271	NME2P1	862	1.32	862	0.67	Low confidence
PF-562271	CCNA2	1021	0.86	880	0.89	High confidence
PF-562271	CSNK2A2	1036	0.96	998	0.88	High confidence
PF-562271	AURKB	1771	0.59	1036	0.80	High confidence
PF-562271	CDK2	2014	0.53	1073	0.82	High confidence
PF-562271	CSNK2A1	1095	1.02	1095	0.87	High confidence
PF-562271	CCNH	1628	0.76	1234	0.86	High confidence
PF-562271	MAPK1	2667	0.46	1237	0.73	High confidence
PF-562271	PAK4	2062	0.60	1239	0.79	High confidence
PF-562271	FLT3	2463	0.54	1324	0.82	High confidence
PF-562271	CDK7	1839	0.73	1334	0.81	High confidence
PF-562271	CDK9	1903	0.71	1354	0.80	High confidence
PF-562271	CCNT1	1470	0.98	1445	0.88	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
PF-562271	MAPK15	2969	0.49	1466	0.64	Low confidence
PF-562271	CDK1	2202	0.69	1510	0.90	High confidence
PF-562271	CCNB2	2278	0.70	1598	0.86	High confidence
PF-562271	MNAT1	1885	0.88	1655	0.74	High confidence
PF-562271	MELK	1931	0.88	1706	0.78	High confidence
PF-562271	CSNK1G2	1955	0.88	1711	0.60	High confidence
PF-562271	MAP2K6	1934	1.01	1934	0.77	High confidence
PF-562271	CDK16	2115	0.94	1994	0.93	High confidence
PF-562271	MET	2512	0.80	2018	0.67	High confidence
PF-562271	PRKD2	3155	0.66	2080	0.76	High confidence
PF-562271	MARK2	3041	0.75	2290	0.79	High confidence
PF-562271	MARK3	3001	0.77	2314	0.86	High confidence
PF-562271	ERCC2	2915	0.90	2637	0.84	High confidence
PF-562271	IRAK4	3478	0.77	2693	0.67	High confidence
PF-562271	CCNK	2813	1.11	2813	0.89	High confidence
PF-562271	STK3	3722	0.76	2845	0.84	High confidence
PF-562271	BMP2K	4475	0.66	2958	0.68	High confidence
PF-562271	MAPK7	3854	0.78	3002	0.66	Low confidence
PF-562271	CDK3	3428	2.15	3428	0.65	High confidence
PF-562271	MAP4K1	5486	0.73	3984	0.82	High confidence
PF-562271	PDPK1	4497	1.04	4497	0.90	High confidence
PF-562271	CDK13	4503	1.25	4503	0.86	High confidence
PF-562271	STK4	7779	0.76	5932	0.90	High confidence
PF-562271	SLK	8746	0.89	7790	0.79	High confidence
PF-562271	PKN1	9106	0.87	7959	0.91	High confidence
PF-562271	TAOK3	15366	0.77	11888	0.89	High confidence
PF-562271	PRKCD	14057	0.95	13314	0.76	Low confidence
PH-797804	MAPK14	10	0.51	5	1.00	High confidence
PH-797804	MAPK11	141	0.72	102	0.97	High confidence
PH-797804	STRADA	672	1.02	672	0.58	Low confidence
PHA-793887	FARSB	3	1.16	3	1.00	Low confidence
PHA-793887	CCNE1	6	0.73	4	0.99	High confidence
PHA-793887	CCNE2	9	0.76	7	0.92	Low confidence
PHA-793887	CLK2	11	0.65	7	0.83	Low confidence
PHA-793887	CCNH	10	0.76	7	0.97	High confidence
PHA-793887	CDK7	11	0.73	8	0.98	High confidence
PHA-793887	CDK3	8	2.15	8	0.96	High confidence
PHA-793887	CCNI	22	0.37	8	0.82	Low confidence
PHA-793887	KIAA0195	13	0.66	9	0.89	High confidence
PHA-793887	CKS1B	13	0.69	9	0.85	High confidence
PHA-793887	ERCC2	11	0.90	10	0.97	High confidence
PHA-793887	GSK3B	25	0.46	12	0.88	High confidence
PHA-793887	CABLES1	23	0.55	13	0.93	High confidence
PHA-793887	FIBP	29	0.57	16	0.93	High confidence
PHA-793887	AFF4	19	1.01	19	0.99	High confidence
PHA-793887	C2CD5	36	0.55	20	0.92	High confidence
PHA-793887	MNAT1	30	0.88	26	0.93	High confidence
PHA-793887	GSK3A	59	0.50	29	0.87	High confidence
PHA-793887	PRKD3	88	0.74	65	0.92	High confidence
PHA-793887	CDK2	185	0.53	98	0.85	High confidence
PHA-793887	PRKD2	156	0.66	103	0.91	High confidence
PHA-793887	CCNT2	133	0.88	117	0.98	High confidence
PHA-793887	CDK5	258	0.52	135	0.89	High confidence
PHA-793887	CCNA2	160	0.86	138	0.88	High confidence
PHA-793887	STK26	199	0.88	175	0.69	Low confidence
PHA-793887	FAM58A	269	0.72	194	0.85	High confidence
PHA-793887	CDK9	307	0.71	218	0.85	High confidence
PHA-793887	MAPK15	535	0.49	264	0.78	High confidence
PHA-793887	CCNB1	382	0.77	293	0.75	High confidence
PHA-793887	CCNT1	312	0.98	307	0.89	High confidence
PHA-793887	CDK16	471	0.94	444	0.93	High confidence
PHA-793887	CCNK	444	1.11	444	0.82	High confidence
PHA-793887	CCNB2	1147	0.70	805	0.77	High confidence
PHA-793887	ULK1	1254	0.67	838	0.83	Low confidence
PHA-793887	PAK4	1437	0.60	864	0.75	High confidence
PHA-793887	PHKG2	1033	0.97	1002	0.88	High confidence
PHA-793887	CAB39	1091	1.12	1091	0.97	Low confidence
PHA-793887	CLK1	3052	0.72	2184	0.70	High confidence
PHA-793887	MAPK3	3523	0.66	2330	0.72	High confidence
PHA-793887	PRKCQ	2341	1.23	2341	0.83	High confidence
PHA-793887	CDK1	3739	0.69	2565	0.74	High confidence
PHA-793887	PDCD10	3091	1.07	3091	0.77	Low confidence
PHA-793887	CDK13	3582	1.25	3582	0.82	High confidence
PHA-793887	CDK12	3657	1.12	3657	0.85	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Pictilisib	S100A6	9	1.29	9	0.76	Low confidence
Pictilisib	NQO2	1028	1.07	1028	0.98	High confidence
Pictilisib	CCNE2	3532	0.76	2685	0.97	Low confidence
Pictilisib	CSNK2A2	3555	0.96	3422	0.98	High confidence
Pictilisib	CSNK2B	3546	1.08	3546	0.96	High confidence
Pictilisib	CSNK2A1	4181	1.02	4181	0.95	High confidence
Pictilisib	EIF3J	4358	1.11	4358	0.99	High confidence
Pimasertib	PSMD6	9	1.15	9	0.83	Low confidence
Pimasertib	IARS2	11	1.32	11	0.89	Low confidence
Pimasertib	MAP2K1	29	1.23	29	0.89	High confidence
Pimasertib	MAP2K2	38	1.17	38	0.99	High confidence
Pimasertib	PRKCZ	11230	0.92	10378	0.78	Low confidence
Ponatinib	FLT3	13	0.54	7	0.99	High confidence
Ponatinib	EPHA5	13	0.60	8	0.98	High confidence
Ponatinib	INPPL1	37	0.48	18	0.94	High confidence
Ponatinib	DDR1	29	0.63	18	1.00	High confidence
Ponatinib	UBASH3B	39	0.49	19	1.00	High confidence
Ponatinib	ABL2	59	0.33	20	0.99	High confidence
Ponatinib	GRB2	36	0.62	22	0.57	High confidence
Ponatinib	RIPK3	26	0.89	23	0.83	Low confidence
Ponatinib	LCK	55	0.44	24	1.00	High confidence
Ponatinib	RET	57	0.44	25	0.99	High confidence
Ponatinib	EPHA2	65	0.41	27	0.99	High confidence
Ponatinib	LYN	54	0.50	27	0.99	High confidence
Ponatinib	FYN	84	0.43	36	1.00	High confidence
Ponatinib	ABL1	66	0.55	36	0.98	High confidence
Ponatinib	FGR	90	0.42	38	0.83	Low confidence
Ponatinib	ZAK	55	0.74	41	0.97	High confidence
Ponatinib	MAP4K2	70	0.59	41	0.91	High confidence
Ponatinib	PAG1	86	0.49	42	0.94	Low confidence
Ponatinib	BCR	104	0.48	50	0.98	High confidence
Ponatinib	HCK	158	0.52	82	0.99	High confidence
Ponatinib	RIPK2	294	0.28	83	0.98	High confidence
Ponatinib	TNK1	194	0.43	84	0.82	High confidence
Ponatinib	DDX1	86	1.20	86	0.88	Low confidence
Ponatinib	DDR2	115	0.76	87	0.98	High confidence
Ponatinib	FRK	277	0.34	94	0.99	High confidence
Ponatinib	MYLK	118	0.83	99	0.87	High confidence
Ponatinib	MAPK14	300	0.51	154	0.99	High confidence
Ponatinib	YES1	527	0.41	218	0.92	High confidence
Ponatinib	PTK2B	711	0.41	295	0.99	High confidence
Ponatinib	MAP4K4	307	1.01	307	0.95	High confidence
Ponatinib	CSK	585	0.54	315	1.00	High confidence
Ponatinib	CDK17	335	1.02	335	0.93	High confidence
Ponatinib	SRC	946	0.39	367	0.99	High confidence
Ponatinib	TNIK	385	1.02	385	0.90	High confidence
Ponatinib	MAPKAPK2	647	0.72	468	0.96	High confidence
Ponatinib	MAP3K1	855	0.58	493	0.98	High confidence
Ponatinib	EPHB3	625	0.88	547	0.78	High confidence
Ponatinib	IRAK1	1132	0.61	691	0.99	High confidence
Ponatinib	MAP4K1	1059	0.73	769	0.92	High confidence
Ponatinib	MAPK11	1398	0.72	1012	0.66	High confidence
Ponatinib	EPHA1	2835	0.40	1140	0.94	High confidence
Ponatinib	BRAF	1194	1.11	1194	0.97	High confidence
Ponatinib	EPHB4	3018	0.49	1493	0.97	High confidence
Ponatinib	ULK3	3789	0.45	1720	0.97	Low confidence
Ponatinib	CDK16	1834	0.94	1729	0.75	High confidence
Ponatinib	CAMKK2	2659	0.66	1766	0.99	High confidence
Ponatinib	TGFBR2	2364	0.75	1779	0.81	High confidence
Ponatinib	BTK	4709	0.39	1841	0.98	Low confidence
Ponatinib	EPHB2	3542	0.52	1857	0.97	High confidence
Ponatinib	GAK	3316	0.56	1862	0.99	High confidence
Ponatinib	TAOK3	2761	0.77	2136	0.99	High confidence
Ponatinib	PPP1CA	2142	1.15	2142	0.90	Low confidence
Ponatinib	IRAK4	2829	0.77	2190	0.96	High confidence
Ponatinib	MAP2K5	3371	0.88	2952	0.85	High confidence
Ponatinib	MELK	3380	0.88	2987	0.91	Low confidence
Ponatinib	PDGFRB	3759	0.87	3285	0.89	High confidence
Ponatinib	MAPK9	11466	0.70	8025	0.82	Low confidence
Ponatinib	EPHA4	27818	0.62	17152	0.96	High confidence
Poziotinib	EGFR	3	0.79	2	1.00	High confidence
Poziotinib	BTK	7	0.39	3	0.97	High confidence
Poziotinib	RIPK2	170	0.28	48	0.99	High confidence
Poziotinib	TEC	172	0.40	69	0.92	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Poziotinib	EPHB4	688	0.49	340	0.95	High confidence	R-406	NEK1	711	0.83	587	0.95	High confidence
Poziotinib	RIPK3	439	0.89	392	0.63	High confidence	R-406	AZI2	842	0.70	591	0.86	High confidence
Poziotinib	MET	988	0.80	794	0.50	Low confidence	R-406	IRAK1	1060	0.61	647	0.92	Low confidence
Poziotinib	RET	2691	0.44	1185	0.92	High confidence	R-406	SIK2	1718	0.52	890	0.81	High confidence
Poziotinib	TNK1	3889	0.43	1682	0.88	High confidence	R-406	FGFR1	1211	0.74	892	0.60	High confidence
Poziotinib	EPHB2	4265	0.52	2236	0.92	High confidence	R-406	SYK	1692	0.84	1419	0.86	High confidence
Poziotinib	EPHA4	11446	0.62	7057	0.84	High confidence	R-406	MAPK9	2610	0.70	1827	0.69	High confidence
Quizartinib	FLT3	190	0.54	102	0.85	High confidence	R-406	DDR2	2510	0.76	1913	0.75	High confidence
Quizartinib	RET	390	0.44	172	0.82	High confidence	R-406	MAPK8	3599	0.65	2332	0.71	High confidence
Quizartinib	MYH10	3971	0.19	758	0.74	High confidence	R-406	FECH	3096	0.99	3080	0.80	High confidence
Quizartinib	BMPR1B	3750	0.61	2302	0.64	Low confidence	R-547	CDK2	10	0.53	5	0.99	High confidence
R-406	INCENP	15	0.89	14	0.83	Low confidence	R-547	CCNT1	6	0.98	6	0.98	High confidence
R-406	FLT3	33	0.54	18	0.95	High confidence	R-547	CDK5	23	0.52	12	0.99	High confidence
R-406	ADCK1	38	0.62	24	0.93	High confidence	R-547	MAPK15	36	0.49	18	0.97	Low confidence
R-406	MAP3K11	42	0.70	29	0.94	High confidence	R-547	CCNB2	26	0.70	18	0.99	High confidence
R-406	RET	88	0.44	39	0.95	High confidence	R-547	CABLES1	36	0.55	20	1.00	Low confidence
R-406	IRAK3	100	0.43	43	0.91	High confidence	R-547	CDK9	35	0.71	25	0.99	High confidence
R-406	CSNK2B	74	1.08	74	0.94	High confidence	R-547	CCNT2	36	0.88	31	0.99	Low confidence
R-406	STK16	132	0.72	95	0.91	High confidence	R-547	C2CD5	100	0.55	55	0.98	High confidence
R-406	EIF3J	98	1.11	98	0.90	High confidence	R-547	CDK1	112	0.69	77	1.00	High confidence
R-406	DYNLL1	198	0.50	99	0.90	Low confidence	R-547	CCNA2	126	0.86	109	0.94	High confidence
R-406	EPHA7	129	0.79	102	0.92	Low confidence	R-547	FIBP	191	0.57	109	0.90	High confidence
R-406	CSNK2A2	107	0.96	103	0.95	High confidence	R-547	SLK	176	0.89	157	0.95	High confidence
R-406	CSNK2A1	140	1.02	140	0.91	High confidence	R-547	CCNK	418	1.11	418	0.96	High confidence
R-406	PLK4	340	0.51	173	0.90	High confidence	R-547	CDK7	642	0.73	466	0.87	High confidence
R-406	TNK1	400	0.43	173	0.99	Low confidence	R-547	MNAT1	1140	0.88	1001	0.70	High confidence
R-406	IKBKE	284	0.62	176	0.92	High confidence	R-547	CDK12	1208	1.12	1208	0.94	High confidence
R-406	NEK9	407	0.44	180	0.92	High confidence	R-547	STK10	1401	0.92	1282	0.92	High confidence
R-406	CLK4	240	0.85	203	0.84	Low confidence	R-547	CCNH	1855	0.76	1407	0.88	High confidence
R-406	MYH10	1201	0.19	229	0.84	High confidence	R-547	GSK3A	78009	0.50	39022	0.90	High confidence
R-406	ULK3	600	0.45	272	0.87	High confidence	Rabusertib	CHEK1	52	0.82	43	0.97	High confidence
R-406	TANK	438	0.64	279	0.88	High confidence	Rabusertib	FECH	3844	0.99	3824	0.75	Low confidence
R-406	DYNLL2	611	0.55	334	0.75	High confidence	RAF-265	TAOK2	4113	0.59	2425	0.94	High confidence
R-406	TBK1	540	0.64	345	0.92	High confidence	RDEA-436	MAP2K2	27	1.17	27	0.97	High confidence
R-406	TBKBP1	510	0.79	404	0.94	High confidence	RDEA-436	MAP2K1	72	1.23	72	0.91	High confidence
R-406	DDR1	665	0.63	417	0.90	High confidence	RDEA-436	NQO2	370	1.07	370	0.99	High confidence
R-406	PAK4	935	0.60	562	0.81	High confidence	RDEA-436	AURKB	1204	0.59	705	0.94	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
RDEA-436	ACVR1	2641	0.48	1264	0.86	High confidence	Rebastinib	FLT3	1515	0.54	814	0.87	High confidence
RDEA-436	MAT2A	1285	1.16	1285	0.94	High confidence	Rebastinib	INPPL1	1848	0.48	894	0.95	High confidence
RDEA-436	ADCK1	2119	0.62	1319	0.95	High confidence	Rebastinib	MAPK9	1400	0.70	980	0.96	High confidence
RDEA-436	CDK17	1780	1.02	1780	0.67	Low confidence	Rebastinib	MAP4K2	1799	0.59	1062	0.99	High confidence
RDEA-436	EIF2S3	2147	1.41	2147	0.81	Low confidence	Rebastinib	CDK1	1559	0.69	1070	0.98	High confidence
RDEA-436	RAC1	2388	1.55	2388	0.79	Low confidence	Rebastinib	RET	2757	0.44	1215	0.99	High confidence
RDEA-436	ACADVL	5313	1.24	5313	0.71	Low confidence	Rebastinib	BTK	3118	0.39	1219	0.98	High confidence
RDEA-436	BMP2K	11563	0.66	7643	0.94	Low confidence	Rebastinib	FER	2896	0.42	1223	0.97	High confidence
Rebastinib	TESK2	4	0.57	2	1.00	Low confidence	Rebastinib	RIPK3	1434	0.89	1282	0.94	High confidence
Rebastinib	CDK17	7	1.02	7	0.73	High confidence	Rebastinib	FYN	3080	0.43	1328	0.95	High confidence
Rebastinib	TNK1	126	0.43	55	0.97	High confidence	Rebastinib	YES1	3488	0.41	1441	0.94	High confidence
Rebastinib	MAPK10	86	0.84	72	0.79	Low confidence	Rebastinib	CDK5	2860	0.52	1498	0.99	High confidence
Rebastinib	PAG1	217	0.49	107	0.97	High confidence	Rebastinib	CDK4	1562	1.00	1562	0.52	Low confidence
Rebastinib	MET	157	0.80	126	0.80	High confidence	Rebastinib	FRK	4799	0.34	1630	0.98	High confidence
Rebastinib	ABL2	409	0.33	135	0.99	High confidence	Rebastinib	SYK	2180	0.84	1828	0.99	High confidence
Rebastinib	HCK	340	0.52	176	0.99	High confidence	Rebastinib	TNIK	1881	1.02	1881	0.55	High confidence
Rebastinib	LCK	408	0.44	180	0.99	High confidence	Rebastinib	CLK1	2990	0.72	2139	0.95	High confidence
Rebastinib	CDK2	374	0.53	199	0.98	High confidence	Rebastinib	MYLK	2616	0.83	2180	0.73	High confidence
Rebastinib	UNC119	359	0.73	260	0.94	Low confidence	Rebastinib	IRAK1	3773	0.61	2303	0.75	High confidence
Rebastinib	DDR1	434	0.63	272	0.97	High confidence	Rebastinib	CLK4	2992	0.85	2528	0.44	Low confidence
Rebastinib	MAPK15	559	0.49	276	0.88	High confidence	Rebastinib	CDK3	2652	2.15	2652	0.78	High confidence
Rebastinib	NTRK1	396	0.71	280	0.91	High confidence	Rebastinib	CKS1B	3896	0.69	2694	0.96	High confidence
Rebastinib	UBASH3B	609	0.49	300	0.95	High confidence	Rebastinib	MAP4K4	2711	1.01	2711	0.99	High confidence
Rebastinib	CDK16	333	0.94	314	1.00	High confidence	Rebastinib	MAPK14	5396	0.51	2763	0.98	High confidence
Rebastinib	ABL1	578	0.55	317	0.99	High confidence	Rebastinib	ERN1	3733	0.81	3042	0.91	High confidence
Rebastinib	BCR	797	0.48	381	0.99	High confidence	Rebastinib	MAP3K11	4392	0.70	3059	0.98	High confidence
Rebastinib	ZAK	521	0.74	388	0.97	High confidence	Rebastinib	LIMK2	5287	0.66	3505	0.97	High confidence
Rebastinib	CSK	762	0.54	410	0.99	High confidence	Rebastinib	MAP4K5	5096	0.74	3792	0.98	High confidence
Rebastinib	LYN	900	0.50	452	0.99	High confidence	Rebastinib	PLK4	8028	0.51	4088	0.94	High confidence
Rebastinib	LIMK1	900	0.59	535	0.95	High confidence	Rebastinib	JAK2	5586	0.80	4457	0.88	High confidence
Rebastinib	MAP4K1	780	0.73	566	0.96	High confidence	Rebastinib	MAPKAPK2	6491	0.72	4691	0.98	High confidence
Rebastinib	CCNB2	818	0.70	574	0.96	High confidence	Rebastinib	SRC	15073	0.39	5852	1.00	High confidence
Rebastinib	GRB2	1010	0.62	630	0.87	High confidence	Rebastinib	PTK2B	22287	0.41	9240	0.99	High confidence
Rebastinib	EIF2AK1	723	0.92	666	0.76	High confidence	Rebastinib	STK3	15847	0.76	12111	0.89	High confidence
Rebastinib	FES	1819	0.37	672	0.98	High confidence	Rebastinib	RPS6KA4	20776	0.62	12827	0.95	Low confidence
Rebastinib	MST1R	961	0.76	732	0.95	High confidence	Rebastinib	TAOK3	18350	0.77	14196	0.91	High confidence
Rebastinib	DDR2	1056	0.76	805	0.96	High confidence	Rebastinib	ACOX3	24251	0.66	16101	0.96	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Rebastinib	IRAK4	29956	0.77	23194	0.98	High confidence
Rebastinib	STK4	33969	0.76	25902	0.94	High confidence
Rebastinib	BRAF	26018	1.11	26018	0.91	High confidence
Rebastinib	MAPK8	40213	0.65	26059	0.93	High confidence
Rebastinib	ARAF	54014	0.62	33655	0.87	High confidence
Refametinib	MAPK10	43	0.84	36	0.95	High confidence
Refametinib	MAP2K1	130	1.23	130	0.96	High confidence
Refametinib	MAP2K2	176	1.17	176	0.97	High confidence
Refametinib	CHEK1	533	0.82	439	0.63	High confidence
Refametinib	ADCK1	1249	0.62	778	0.85	Low confidence
Refametinib	PRKAG2	4369	0.64	2817	0.75	High confidence
Refametinib	PRKAG1	28099	0.63	17783	0.50	Low confidence
Regorafenib	EPHA1	17	0.40	7	0.69	Low confidence
Regorafenib	RET	286	0.44	126	0.93	High confidence
Regorafenib	ZAK	369	0.74	274	0.96	High confidence
Regorafenib	DDR1	571	0.63	358	0.95	High confidence
Regorafenib	RIPK3	412	0.89	368	0.96	High confidence
Regorafenib	DDR2	552	0.76	421	0.77	High confidence
Regorafenib	MAP3K1	806	0.58	465	0.93	High confidence
Regorafenib	INPPL1	995	0.48	481	0.89	High confidence
Regorafenib	FLT3	1046	0.54	562	0.77	High confidence
Regorafenib	LIMK1	1036	0.59	616	0.77	High confidence
Regorafenib	MAPKAPK2	944	0.72	682	0.76	High confidence
Regorafenib	MAPK14	1377	0.51	705	0.84	High confidence
Regorafenib	CDK17	719	1.02	719	0.57	High confidence
Regorafenib	BCR	1546	0.48	739	0.75	High confidence
Regorafenib	ABL1	1375	0.55	753	0.76	High confidence
Regorafenib	RIPK2	2732	0.28	767	0.83	High confidence
Regorafenib	EPHA2	2014	0.41	832	0.73	High confidence
Regorafenib	EPHA5	1874	0.60	1123	0.45	Low confidence
Regorafenib	GRB2	2232	0.62	1392	0.92	High confidence
Regorafenib	MAPK11	2641	0.72	1911	0.76	High confidence
Regorafenib	CLK1	2945	0.72	2107	0.84	High confidence
Regorafenib	BRAF	3125	1.11	3125	0.79	High confidence
Regorafenib	TTK	3923	1.07	3923	0.80	Low confidence
RGB-286638	CLK4	2	0.85	2	1.00	Low confidence
RGB-286638	CLK1	3	0.72	2	1.00	Low confidence
RGB-286638	GSKIP	3	0.84	2	1.00	High confidence
RGB-286638	CDK16	3	0.94	3	1.00	High confidence
RGB-286638	GAK	8	0.56	4	1.00	High confidence
RGB-286638	KLHL6	7	0.74	5	0.99	Low confidence
RGB-286638	GSK3A	13	0.50	7	0.97	High confidence
RGB-286638	EIF3J	7	1.11	7	0.99	High confidence
RGB-286638	CCNE1	10	0.73	7	0.97	High confidence
RGB-286638	GSK3B	16	0.46	8	0.90	High confidence
RGB-286638	ICK	12	0.68	8	0.99	High confidence
RGB-286638	BMP2K	12	0.66	8	0.96	High confidence
RGB-286638	CSNK2A2	9	0.96	8	1.00	High confidence
RGB-286638	MNAT1	10	0.88	9	0.77	High confidence
RGB-286638	CSNK2B	9	1.08	9	0.99	High confidence
RGB-286638	MAPK10	13	0.84	11	0.82	Low confidence
RGB-286638	CSNK2A1	12	1.02	12	0.98	High confidence
RGB-286638	CLK2	27	0.65	18	0.89	High confidence
RGB-286638	CCNT1	19	0.98	19	0.99	High confidence
RGB-286638	Q6ZSR9	29	0.76	22	0.99	High confidence
RGB-286638	AAK1	33	0.67	22	0.99	High confidence
RGB-286638	DCAF7	29	0.90	26	0.95	High confidence
RGB-286638	CDK9	46	0.71	33	0.98	High confidence
RGB-286638	DYRK1A	37	0.93	34	0.96	High confidence
RGB-286638	CCNT2	40	0.88	35	0.98	High confidence
RGB-286638	CABLES1	75	0.55	41	0.97	High confidence
RGB-286638	PIM2	42	1.14	42	0.88	High confidence
RGB-286638	C2CD5	98	0.55	54	0.99	High confidence
RGB-286638	AP2A1	65	0.92	60	0.95	Low confidence
RGB-286638	FIBP	123	0.57	70	0.91	High confidence
RGB-286638	CDK2	135	0.53	72	0.98	High confidence
RGB-286638	TGFBR2	107	0.75	80	0.89	High confidence
RGB-286638	MAP4K4	127	1.01	127	0.84	Low confidence
RGB-286638	JAK1	373	0.37	139	0.88	High confidence
RGB-286638	BMPR2	182	0.84	153	0.70	Low confidence
RGB-286638	CDK7	212	0.73	154	0.91	High confidence
RGB-286638	PRKD2	296	0.66	195	0.97	High confidence
RGB-286638	CCNH	260	0.76	197	0.99	High confidence
RGB-286638	SIK2	399	0.52	207	0.94	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
RGB-286638	MAP3K11	381	0.70	265	0.98	High confidence	RGB-286638	CSNK1G1	3674	0.87	3180	0.96	High confidence
RGB-286638	CCNB2	404	0.70	283	0.96	High confidence	RGB-286638	EIF2AK1	4127	0.92	3803	0.93	High confidence
RGB-286638	PRKD3	402	0.74	297	0.99	High confidence	RGB-286638	CSNK1A1	8741	0.92	8073	0.85	High confidence
RGB-286638	CDK5	608	0.52	318	0.95	High confidence	RGB-286638	CSNK1G3	24542	0.79	19295	0.77	Low confidence
RGB-286638	FLT3	602	0.54	323	0.88	High confidence	Ribociclib	CAMK2G	1137	0.22	247	0.88	High confidence
RGB-286638	MAPK9	529	0.70	370	0.81	High confidence	Ribociclib	CAMK2D	1435	0.20	293	0.96	High confidence
RGB-286638	CCNA2	433	0.86	373	0.87	High confidence	Ribociclib	CDK6	606	0.82	497	0.87	High confidence
RGB-286638	FAM83A	445	0.88	392	0.89	Low confidence	Ribociclib	GAK	1172	0.56	658	0.96	High confidence
RGB-286638	ERCC2	504	0.90	456	0.90	High confidence	Ribociclib	DCAF7	2080	0.90	1865	0.85	High confidence
RGB-286638	CCNB1	651	0.77	498	0.95	High confidence	Ribociclib	SIK2	4809	0.52	2492	0.82	High confidence
RGB-286638	STK16	716	0.72	515	0.77	Low confidence	Ribociclib	CDK9	5211	0.71	3708	0.94	High confidence
RGB-286638	MAP2K5	611	0.88	535	0.94	High confidence	Ribociclib	CDK16	4079	0.94	3845	0.65	Low confidence
RGB-286638	TPRKB	566	0.95	536	0.51	High confidence	Ribociclib	CCNT1	4485	0.98	4410	0.92	High confidence
RGB-286638	INPPL1	1305	0.48	631	0.88	High confidence	Ribociclib	Q6ZSR9	12227	0.76	9311	0.89	High confidence
RGB-286638	CCNK	689	1.11	689	1.00	High confidence	Ribociclib	FECH	12370	0.99	12308	0.74	Low confidence
RGB-286638	OSGEP	734	0.96	704	0.92	High confidence	Ribociclib	MAP3K1	21611	0.58	12473	0.89	High confidence
RGB-286638	MAPK8	1128	0.65	731	0.93	High confidence	Ribociclib	PRKD2	37957	0.66	25019	0.88	High confidence
RGB-286638	CIT	763	1.21	763	0.95	High confidence	Rigosertib	CLK3	40	1.03	40	0.98	Low confidence
RGB-286638	CDK12	947	1.12	947	0.88	High confidence	Rigosertib	MET	1170	0.80	940	0.91	High confidence
RGB-286638	CDK13	1012	1.25	1012	0.91	High confidence	Rigosertib	PLA2G2A	3139	1.53	3139	0.95	High confidence
RGB-286638	CDC42BPB	1049	0.97	1020	0.96	High confidence	Rigosertib	FECH	5605	0.99	5577	0.86	High confidence
RGB-286638	STK26	1198	0.88	1052	0.90	High confidence	Rigosertib	NQO2	15224	1.07	15224	0.99	High confidence
RGB-286638	CDC42BPA	1139	0.96	1094	0.88	High confidence	Ripasudil	ROCK1	37	0.91	33	0.96	High confidence
RGB-286638	ZAK	1497	0.74	1113	0.94	High confidence	Ripasudil	ROCK2	95	0.87	83	0.98	High confidence
RGB-286638	CSNK1D	1487	0.82	1223	0.90	High confidence	Ripasudil	PKN2	350	0.82	285	0.95	High confidence
RGB-286638	BCR	2585	0.48	1235	0.85	High confidence	Ripasudil	PKN1	476	0.87	416	0.99	High confidence
RGB-286638	CDK1	1950	0.69	1337	0.89	High confidence	Ripasudil	PRKX	703	0.81	571	0.93	High confidence
RGB-286638	PDGFRB	1561	0.87	1364	0.89	Low confidence	Ripasudil	PRKAB2	1582	0.60	951	0.72	High confidence
RGB-286638	MELK	1649	0.88	1458	0.94	High confidence	Ripasudil	AURKB	1968	0.59	1152	0.90	High confidence
RGB-286638	TP53RK	1716	1.05	1716	0.91	High confidence	Ripasudil	PRKAG1	2855	0.63	1807	0.68	High confidence
RGB-286638	IKBKE	3064	0.62	1902	0.96	High confidence	Ripasudil	PRKCD	2608	0.95	2470	0.97	High confidence
RGB-286638	MAP2K6	1952	1.01	1952	0.93	High confidence	Ripasudil	PRKAB1	4282	0.66	2835	0.70	High confidence
RGB-286638	TBK1	3138	0.64	2007	0.94	High confidence	Ripasudil	MAP2K3	3079	1.32	3079	0.59	High confidence
RGB-286638	TANK	3220	0.64	2048	0.96	High confidence	Ripasudil	MAP4K3	4910	0.66	3219	0.77	Low confidence
RGB-286638	LAGE3	2260	0.95	2147	0.71	High confidence	Ripasudil	PRKAA1	5125	0.64	3269	0.94	High confidence
RGB-286638	AZI2	3108	0.70	2181	0.82	High confidence	Ripasudil	NQO2	3699	1.07	3699	0.88	High confidence
RGB-286638	PIP4K2C	2408	0.91	2184	0.69	Low confidence	Ripasudil	PRKD2	5617	0.66	3703	0.98	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Ripasudil	MARK2	7988	0.75	6017	0.97	High confidence
Ripasudil	PLK4	15986	0.51	8141	0.97	High confidence
Ripasudil	CCNK	8204	1.11	8204	0.91	High confidence
Ripasudil	TAOK3	15251	0.77	11799	0.90	High confidence
Ripasudil	CDK9	18663	0.71	13279	0.85	Low confidence
Ripasudil	MARK3	75548	0.77	58240	0.97	High confidence
Ro-4987655	MAP2K2	6	1.17	6	0.92	High confidence
Ro-4987655	MAP2K1	19	1.23	19	1.00	High confidence
Ro-4987655	MAP2K5	34809	0.88	30484	0.75	High confidence
Ro-5126766	BRAF	7	1.11	7	0.96	Low confidence
Ro-5126766	MAP2K1	30	1.23	30	0.99	High confidence
Ro-5126766	MAP2K2	37	1.17	37	0.98	High confidence
Ro-5126766	MAP2K5	2279	0.88	1996	0.89	High confidence
Rociletinib	TEC	716	0.40	288	0.97	High confidence
Rociletinib	TNK1	667	0.43	289	0.89	High confidence
Rociletinib	PTK2	1061	0.41	433	0.97	High confidence
Rociletinib	GAK	802	0.56	450	0.98	High confidence
Rociletinib	EGFR	628	0.79	498	0.99	High confidence
Rociletinib	BTK	1401	0.39	547	0.98	High confidence
Rociletinib	CLK1	910	0.72	651	0.65	High confidence
Rociletinib	FER	2629	0.42	1110	0.97	High confidence
Rociletinib	FES	3230	0.37	1194	0.97	High confidence
Rociletinib	EIF3J	3937	1.11	3937	0.86	High confidence
Rociletinib	CSNK2A1	13533	1.02	13533	0.86	High confidence
Ruboxistaurin	PRKCA	32	0.73	23	0.98	High confidence
Ruboxistaurin	PRKCD	70	0.95	67	0.84	High confidence
Ruboxistaurin	PRKCB	248	0.80	198	0.94	High confidence
Ruboxistaurin	RPS6KA6	653	0.42	276	0.93	High confidence
Ruboxistaurin	PDPK1	410	1.04	410	0.96	High confidence
Ruboxistaurin	DYRK1A	1182	0.93	1103	0.58	High confidence
Ruboxistaurin	Q6ZSR9	1722	0.76	1311	0.93	High confidence
Ruboxistaurin	AAK1	2194	0.67	1476	0.95	High confidence
Ruboxistaurin	BMP2K	3326	0.66	2199	0.99	High confidence
Ruboxistaurin	SLK	2542	0.89	2264	0.93	High confidence
Ruboxistaurin	STK10	3044	0.92	2787	0.88	High confidence
Ruboxistaurin	PIM1	8916	0.43	3799	0.95	High confidence
Ruboxistaurin	GSK3B	10887	0.46	5063	0.86	High confidence
Ruboxistaurin	GSK3A	14405	0.50	7206	0.89	High confidence
Ruboxistaurin	RPS6KA1	30221	0.75	22726	0.89	High confidence
Ruboxistaurin	RPS6KA3	51880	0.72	37605	0.92	High confidence
Ruxolitinib	JAK2	6	0.80	5	1.00	High confidence
Ruxolitinib	CAMK4	196	1.02	196	0.93	High confidence
Ruxolitinib	Q6ZSR9	258	0.76	196	0.92	High confidence
Ruxolitinib	CAMK2G	1192	0.22	259	0.92	High confidence
Ruxolitinib	CAMK2D	1520	0.20	310	0.90	High confidence
Ruxolitinib	CLK2	580	0.65	375	0.71	Low confidence
Ruxolitinib	AP2A1	626	0.92	575	0.93	High confidence
Ruxolitinib	ROCK1	900	0.91	819	0.87	High confidence
Ruxolitinib	CSNK1G1	983	0.87	851	0.61	Low confidence
Ruxolitinib	PLK1	1291	0.92	1187	0.91	High confidence
Ruxolitinib	AAK1	2008	0.67	1351	0.94	High confidence
Ruxolitinib	RET	3537	0.44	1558	0.90	High confidence
Ruxolitinib	TNK2	3548	0.45	1597	0.88	Low confidence
Ruxolitinib	MAP3K11	2728	0.70	1900	0.76	High confidence
Ruxolitinib	DYRK1A	3101	0.93	2893	0.80	High confidence
Ruxolitinib	PKN1	3489	0.87	3050	0.80	High confidence
Ruxolitinib	MAPKAPK5	3355	0.93	3118	0.80	Low confidence
Ruxolitinib	CSNK2A1	3187	1.02	3187	0.84	High confidence
Ruxolitinib	CLK1	4519	0.72	3233	0.80	High confidence
Ruxolitinib	STRADA	3672	1.02	3672	0.81	Low confidence
Ruxolitinib	CSNK2A2	3943	0.96	3796	0.86	High confidence
Ruxolitinib	PDPK1	4123	1.04	4123	0.86	High confidence
Ruxolitinib	PHKG2	4541	0.97	4404	0.94	High confidence
Ruxolitinib	EIF3J	5587	1.11	5587	0.72	High confidence
Ruxolitinib	BMP2K	8893	0.66	5878	0.82	High confidence
Ruxolitinib	ROCK2	6821	0.87	5947	0.92	High confidence
Ruxolitinib	RPS6KA1	11383	0.75	8560	0.73	High confidence
Ruxolitinib	TAOK1	14726	0.66	9790	0.72	Low confidence
Ruxolitinib	MARK2	14739	0.75	11103	0.87	High confidence
Ruxolitinib	TAOK2	21950	0.59	12942	0.71	High confidence
Ruxolitinib	MARK3	19235	0.77	14828	0.80	High confidence
Ruxolitinib	CIT	15995	1.21	15995	0.86	High confidence
Ruxolitinib	PRKCA	22652	0.73	16494	0.87	High confidence
Ruxolitinib	NEK3	34943	0.85	29867	0.74	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Sapanisertib	PKN3	13	1.06	13	0.99	Low confidence
Sapanisertib	TESK2	31	0.57	18	0.95	Low confidence
Sapanisertib	ACVR1	83	0.48	40	0.86	High confidence
Sapanisertib	BMPR1B	201	0.61	123	0.74	High confidence
Sapanisertib	DDR2	182	0.76	139	0.98	High confidence
Sapanisertib	CSNK1D	185	0.82	152	0.96	High confidence
Sapanisertib	CSNK1E	185	0.85	158	0.98	High confidence
Sapanisertib	RIPK2	634	0.28	178	0.97	High confidence
Sapanisertib	INCENP	225	0.89	201	0.81	Low confidence
Sapanisertib	FAM83B	375	1.06	375	0.98	High confidence
Sapanisertib	NLK	675	0.66	449	0.86	High confidence
Sapanisertib	ACVR1B	1803	0.43	767	0.95	High confidence
Sapanisertib	DDR1	1405	0.63	881	0.96	High confidence
Sapanisertib	ACVR2B	1352	0.67	901	0.58	High confidence
Sapanisertib	MAP3K1	1827	0.58	1055	0.92	High confidence
Sapanisertib	TAOK1	1645	0.66	1094	0.79	High confidence
Sapanisertib	BMPR1A	2426	0.53	1281	0.93	High confidence
Sapanisertib	RET	3639	0.44	1603	0.83	High confidence
Sapanisertib	TAOK2	2941	0.59	1734	0.81	High confidence
Sapanisertib	LIMK1	3112	0.59	1850	0.87	High confidence
Sapanisertib	MAP2K2	1922	1.17	1922	0.97	High confidence
Sapanisertib	STK16	2795	0.72	2013	0.97	High confidence
Sapanisertib	PTK6	4342	0.48	2098	0.89	High confidence
Sapanisertib	STK26	2494	0.88	2190	0.74	High confidence
Sapanisertib	RIPK3	2657	0.89	2375	0.89	High confidence
Sapanisertib	TGFBR1	3568	0.69	2473	0.97	High confidence
Sapanisertib	MAP2K1	3007	1.23	3007	0.88	High confidence
Sapanisertib	STK10	3552	0.92	3252	0.91	High confidence
Sapanisertib	CSNK1A1	3577	0.92	3304	0.90	High confidence
Sapanisertib	MAP2K5	3901	0.88	3416	0.92	High confidence
Sapanisertib	CLK3	3498	1.03	3498	0.85	High confidence
Sapanisertib	PDGFRB	4129	0.87	3609	0.81	High confidence
Sapanisertib	MAP3K11	5355	0.70	3730	0.79	High confidence
Sapanisertib	FGFR1	5129	0.74	3777	0.92	High confidence
Sapanisertib	MAP4K4	3840	1.01	3840	0.70	High confidence
Sapanisertib	CAMK4	5955	1.02	5955	0.88	High confidence
Sapanisertib	DCK	6175	1.16	6175	0.93	Low confidence
Sapanisertib	FLT3	13109	0.54	7044	0.90	High confidence
Sapanisertib	MELK	9295	0.88	8215	0.94	High confidence
Sapanisertib	MAP4K2	26933	0.59	15891	0.93	High confidence
Sapanisertib	PRKCA	29902	0.73	21773	0.93	High confidence
Sapitinib	EGFR	1	0.79	1	0.99	High confidence
Sapitinib	EPHA1	38	0.40	15	0.51	Low confidence
Sapitinib	GAK	314	0.56	176	0.92	High confidence
Sapitinib	RET	885	0.44	390	0.96	High confidence
Sapitinib	EPHB4	1123	0.49	556	0.98	High confidence
Sapitinib	RIPK2	2677	0.28	751	0.96	High confidence
Sapitinib	EPHA5	1394	0.60	835	0.90	High confidence
Sapitinib	RIPK3	1310	0.89	1171	0.93	High confidence
Sapitinib	ADK	1404	1.12	1404	0.54	Low confidence
Sapitinib	PTK6	4558	0.48	2202	0.87	High confidence
Sapitinib	EPHB2	4353	0.52	2282	0.87	Low confidence
Sapitinib	LYN	4939	0.50	2479	0.91	High confidence
Sapitinib	EPHA4	11999	0.62	7399	0.64	High confidence
Sapitinib	EPHA2	19852	0.41	8198	0.90	Low confidence
SAR-407899	PRKG1	8	0.51	4	0.78	Low confidence
SAR-407899	PDPK1	6	1.04	6	0.82	High confidence
SAR-407899	PRKX	10	0.81	8	0.97	High confidence
SAR-407899	PKN2	10	0.82	8	0.91	High confidence
SAR-407899	CDC42BPA	11	0.96	10	0.84	High confidence
SAR-407899	AAK1	17	0.67	12	0.89	High confidence
SAR-407899	BMP2K	19	0.66	13	0.81	Low confidence
SAR-407899	PRKACA	27	0.47	13	0.80	Low confidence
SAR-407899	Q6ZSR9	17	0.76	13	0.92	High confidence
SAR-407899	ROCK2	18	0.87	16	1.00	High confidence
SAR-407899	CDC42BPB	17	0.97	16	0.75	High confidence
SAR-407899	ROCK1	18	0.91	17	1.00	High confidence
SAR-407899	PKN1	22	0.87	19	0.99	High confidence
SAR-407899	PRKCD	22	0.95	21	0.88	High confidence
Saracatinib	RIPK2	6	0.28	2	1.00	High confidence
Saracatinib	ACVR1	9	0.48	4	0.99	High confidence
Saracatinib	INPPL1	13	0.48	6	0.92	High confidence
Saracatinib	LCK	20	0.44	9	0.96	High confidence
Saracatinib	EPHA1	26	0.40	10	0.55	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Saracatinib	BCR	32	0.48	16	1.00	High confidence
Saracatinib	BMPR1B	47	0.61	29	0.45	Low confidence
Saracatinib	GRB2	59	0.62	37	0.95	High confidence
Saracatinib	ABL1	96	0.55	53	1.00	High confidence
Saracatinib	BMPR1A	113	0.53	60	0.98	High confidence
Saracatinib	PAG1	141	0.49	69	0.74	Low confidence
Saracatinib	ABL2	273	0.33	91	1.00	High confidence
Saracatinib	YES1	230	0.41	95	0.95	High confidence
Saracatinib	FYN	227	0.43	98	0.97	High confidence
Saracatinib	HCK	193	0.52	100	1.00	High confidence
Saracatinib	GAK	193	0.56	108	1.00	High confidence
Saracatinib	LYN	226	0.50	113	0.99	High confidence
Saracatinib	SRC	341	0.39	132	0.99	High confidence
Saracatinib	FLT3	260	0.54	140	0.82	Low confidence
Saracatinib	ACVR1B	333	0.43	142	0.88	High confidence
Saracatinib	SRSF2	162	1.59	162	0.83	Low confidence
Saracatinib	RET	404	0.44	178	0.87	Low confidence
Saracatinib	TGFBR1	284	0.69	197	0.92	High confidence
Saracatinib	ADCK3	309	0.89	275	0.94	High confidence
Saracatinib	PTK6	1171	0.48	566	0.85	Low confidence
Saracatinib	PDGFRB	722	0.87	631	0.95	High confidence
Saracatinib	EPHA2	1765	0.41	729	0.99	High confidence
Saracatinib	EPHA4	1488	0.62	917	0.91	High confidence
Saracatinib	FGR	2279	0.42	956	0.92	High confidence
Saracatinib	UBASH3B	2188	0.49	1079	0.90	High confidence
Saracatinib	MAP4K4	1121	1.01	1121	0.98	High confidence
Saracatinib	TNIK	1375	1.02	1375	0.94	High confidence
Saracatinib	SIK2	2716	0.52	1407	0.99	High confidence
Saracatinib	RIPK3	1978	0.89	1768	0.96	High confidence
Saracatinib	FRK	6858	0.34	2330	0.89	High confidence
Saracatinib	EPHA5	3975	0.60	2381	0.84	High confidence
Saracatinib	ZAK	4014	0.74	2985	0.94	High confidence
Saracatinib	EPHB6	5860	0.61	3602	0.84	High confidence
Saracatinib	ACVR2B	5817	0.67	3878	0.82	High confidence
Saracatinib	EPHB4	7837	0.49	3878	0.99	High confidence
Saracatinib	DDR1	7015	0.63	4401	0.84	High confidence
Saracatinib	TNK2	10330	0.45	4650	0.99	High confidence
Saracatinib	SIK3	5926	0.82	4851	0.92	High confidence
Saracatinib	EPHB2	17958	0.52	9415	0.90	High confidence
Saracatinib	BTK	25974	0.39	10153	0.90	High confidence
Saracatinib	STK10	12760	0.92	11681	0.98	High confidence
Saracatinib	MAP4K5	36403	0.74	27088	0.91	Low confidence
Saracatinib	SLK	35604	0.89	31713	0.98	High confidence
Saracatinib	CSK	73493	0.54	39553	0.99	High confidence
Saracatinib	DDR2	55481	0.76	42280	0.99	High confidence
SB-1317	CDK9	1	0.71	1	1.00	High confidence
SB-1317	CCNT1	6	0.98	6	0.87	High confidence
SB-1317	ADCK1	36	0.62	23	0.58	Low confidence
SB-1317	CDK16	37	0.94	35	0.99	High confidence
SB-1317	PKN2	173	0.82	141	0.84	Low confidence
SB-1317	FECH	244	0.99	243	0.92	Low confidence
SB-1317	CDK2	456	0.53	243	0.97	High confidence
SB-1317	IRAK3	666	0.43	286	0.94	High confidence
SB-1317	STK3	407	0.76	311	0.82	High confidence
SB-1317	ERCC2	353	0.90	319	0.53	Low confidence
SB-1317	FLT3	778	0.54	418	0.49	Low confidence
SB-1317	GSK3B	960	0.46	447	0.84	High confidence
SB-1317	CDK7	652	0.73	473	0.99	High confidence
SB-1317	PRKD2	719	0.66	474	0.94	High confidence
SB-1317	CCNK	475	1.11	475	0.94	High confidence
SB-1317	PRKD3	753	0.74	557	0.89	High confidence
SB-1317	GSK3A	1157	0.50	579	0.94	High confidence
SB-1317	CCNA2	740	0.86	637	0.90	High confidence
SB-1317	CCNH	999	0.76	757	0.72	High confidence
SB-1317	MAP4K3	1297	0.66	850	0.96	High confidence
SB-1317	MNAT1	1007	0.88	884	0.84	Low confidence
SB-1317	PRKCA	1216	0.73	885	0.97	High confidence
SB-1317	CDK5	1776	0.52	930	0.86	High confidence
SB-1317	CCNB2	1362	0.70	955	0.92	High confidence
SB-1317	PRKCD	1052	0.95	996	0.99	High confidence
SB-1317	TAOK2	1815	0.59	1070	0.75	High confidence
SB-1317	MAPK15	2173	0.49	1073	0.88	High confidence
SB-1317	INPPL1	2289	0.48	1107	0.67	Low confidence
SB-1317	SIK3	1588	0.82	1300	0.97	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
SB-1317	MAP4K2	2312	0.59	1364	0.90	High confidence	SCH-900776	MAP3K1	2173	0.58	1254	0.87	Low confidence
SB-1317	MAPK8	2248	0.65	1457	0.82	High confidence	SCH-900776	RPS6KA6	3009	0.42	1269	0.95	High confidence
SB-1317	CDK6	1948	0.82	1597	0.85	Low confidence	SCH-900776	PRKCD	1733	0.95	1641	0.92	High confidence
SB-1317	EIF3J	1663	1.11	1663	0.89	High confidence	SCH-900776	MARK3	2506	0.77	1932	0.69	High confidence
SB-1317	PKN1	1932	0.87	1689	0.88	High confidence	SCH-900776	SLK	2341	0.89	2085	0.94	High confidence
SB-1317	FER	4014	0.42	1695	0.95	Low confidence	SCH-900776	NQO2	2359	1.07	2359	0.96	High confidence
SB-1317	STK4	2363	0.76	1802	0.94	High confidence	SCH-900776	MAP2K2	2364	1.17	2364	0.64	High confidence
SB-1317	JAK1	5398	0.37	2011	0.96	High confidence	SCH-900776	RET	5786	0.44	2549	0.91	Low confidence
SB-1317	TAOK1	3216	0.66	2138	0.59	Low confidence	SCH-900776	BMP2K	4049	0.66	2676	0.61	Low confidence
SB-1317	CSNK2A2	2392	0.96	2302	0.69	High confidence	SCH-900776	PAK4	4827	0.60	2900	0.85	Low confidence
SB-1317	MAPK9	3297	0.70	2307	0.89	High confidence	SCH-900776	RPS6KA4	5519	0.62	3407	0.93	Low confidence
SB-1317	CSNK1D	2894	0.82	2381	0.79	High confidence	SCH-900776	IRAK4	5184	0.77	4014	0.90	Low confidence
SB-1317	TAOK3	3691	0.77	2856	0.90	High confidence	SCH-900776	STK10	4798	0.92	4392	0.83	High confidence
SB-1317	CSNK2B	3078	1.08	3078	0.84	Low confidence	SCH-900776	LATS1	5862	0.79	4616	0.95	High confidence
SB-1317	PRKCB	5415	0.80	4321	0.86	High confidence	SCH-900776	MELK	5313	0.88	4695	0.92	High confidence
SB-1317	MAP4K5	6837	0.74	5087	0.94	High confidence	SCH-900776	TGFBR2	6281	0.75	4725	0.93	High confidence
SB-1317	DYRK1A	6025	0.93	5622	0.92	Low confidence	SCH-900776	PRKD2	9726	0.66	6411	0.84	High confidence
SB-1317	CDK12	5635	1.12	5635	0.78	High confidence	SCH-900776	PIM1	45331	0.43	19316	0.88	High confidence
SB-1317	SLK	7152	0.89	6370	0.92	High confidence	SCH-900776	PRKCI	51018	1.07	51018	0.88	High confidence
SB-1317	STK10	10873	0.92	9954	0.90	High confidence	Seliciclib	CCNT2	1139	0.88	1002	0.83	High confidence
SB-1317	C2CD5	23489	0.55	12808	0.94	High confidence	Seliciclib	FAM83B	1825	1.06	1825	0.83	High confidence
SB-1317	RET	49614	0.44	21858	0.93	Low confidence	Seliciclib	CCNH	3377	0.76	2560	0.87	High confidence
SB-1317	ABL1	58767	0.55	32200	0.94	Low confidence	Seliciclib	CABLES1	5421	0.55	2979	0.96	High confidence
SB-1317	CDC42BPB	48308	0.97	46945	0.93	Low confidence	Seliciclib	CCAR2	3261	1.28	3261	0.91	High confidence
SB-1317	ROCK2	67645	0.87	58977	0.95	Low confidence	Seliciclib	CDK7	5107	0.73	3705	0.86	High confidence
SB-1317	EGFR	100792	0.79	79933	0.90	Low confidence	Seliciclib	MNAT1	4707	0.88	4133	0.92	High confidence
SB-1317	ROCK1	109126	0.91	99233	0.93	Low confidence	Seliciclib	FIBP	7510	0.57	4283	0.68	High confidence
SCH-900776	PSMC4	5	1.27	5	0.84	Low confidence	Seliciclib	CDK9	6831	0.71	4860	0.79	High confidence
SCH-900776	CHEK1	13	0.82	11	1.00	High confidence	Seliciclib	PAK4	8360	0.60	5024	0.76	High confidence
SCH-900776	CSNK2B	132	1.08	132	0.93	High confidence	Seliciclib	CCNT1	7494	0.98	7368	0.92	High confidence
SCH-900776	MYLK3	217	0.87	189	0.84	High confidence	Seliciclib	ERCC2	13288	0.90	12022	0.85	High confidence
SCH-900776	CSNK2A1	228	1.02	228	0.97	High confidence	Seliciclib	CSNK1E	14515	0.85	12409	0.79	High confidence
SCH-900776	SIK2	521	0.52	270	0.95	High confidence	Seliciclib	GAPVD1	12697	0.99	12632	0.91	High confidence
SCH-900776	CSNK2A2	290	0.96	279	0.79	High confidence	Seliciclib	DYRK1A	43184	0.93	40291	0.81	High confidence
SCH-900776	EIF3J	324	1.11	324	0.91	High confidence	Selumetinib	MAP2K1	41	1.23	41	0.99	High confidence
SCH-900776	PDPK1	391	1.04	391	0.96	High confidence	Selumetinib	MAP2K2	52	1.17	52	1.00	High confidence
SCH-900776	MAP2K5	695	0.88	609	0.90	High confidence	Selumetinib	KLHL6	266	0.74	197	0.94	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Selumetinib	SMC2	209	1.15	209	0.93	Low confidence
Selumetinib	SMC1A	365	1.21	365	0.70	Low confidence
Selumetinib	Q6ZSR9	1059	0.76	807	0.86	High confidence
Selumetinib	AP2A1	1205	0.92	1107	0.95	High confidence
Selumetinib	AAK1	1901	0.67	1279	0.90	High confidence
Selumetinib	BMP2K	2457	0.66	1624	0.78	High confidence
Selumetinib	CSNK2A2	2916	0.96	2807	0.77	Low confidence
SGI-1776	PRKAG2	36	0.64	23	0.71	Low confidence
SGI-1776	IRAK3	61	0.43	26	0.93	High confidence
SGI-1776	PIM1	100	0.43	43	0.85	High confidence
SGI-1776	FLT3	267	0.54	143	0.88	High confidence
SGI-1776	ACVR1	956	0.48	458	0.71	High confidence
SGI-1776	CAB39	841	1.12	841	0.73	Low confidence
SGI-1776	PDGFRB	1839	0.87	1607	0.83	High confidence
SGI-1776	STK10	2358	0.92	2159	0.97	High confidence
SGI-1776	RET	7301	0.44	3217	0.77	High confidence
SGI-1776	SLK	4028	0.89	3588	0.62	High confidence
SGI-1776	SIK2	11817	0.52	6124	0.65	High confidence
SGI-1776	CSNK2A2	8231	0.96	7924	0.56	High confidence
SGI-1776	BMP2K	12913	0.66	8535	0.84	High confidence
SGI-1776	GAK	15375	0.56	8634	0.84	High confidence
SGI-1776	RPS6KA6	56336	0.42	23762	0.92	High confidence
SGI-1776	PKN1	40526	0.87	35424	0.86	High confidence
SGX-523	NQO2	124	1.07	124	0.82	High confidence
Silmitasertib	CSNK2B	0.15	1.08	0.15	0.94	High confidence
Silmitasertib	CSNK2A1	0.31	1.02	0.31	0.73	High confidence
Silmitasertib	EIF3J	1	1.11	1	0.93	High confidence
Silmitasertib	CSNK2A2	1	0.96	1	0.88	High confidence
Silmitasertib	KLHL6	2	0.74	1	0.84	Low confidence
Silmitasertib	CLK3	10	1.03	10	1.00	High confidence
Silmitasertib	CLK1	20	0.72	14	0.99	High confidence
Silmitasertib	PIP4K2A	18	0.87	16	0.99	Low confidence
Silmitasertib	MAPKAPK3	31	0.83	26	0.86	High confidence
Silmitasertib	DCAF7	34	0.90	31	0.98	High confidence
Silmitasertib	DYRK1A	35	0.93	33	0.96	High confidence
Silmitasertib	STK10	105	0.92	96	0.95	High confidence
Silmitasertib	CCNI	380	0.37	141	0.79	High confidence
Silmitasertib	CCNB1	227	0.77	174	0.88	High confidence
Silmitasertib	SLK	247	0.89	220	0.99	High confidence
Silmitasertib	PRKAG2	534	0.64	344	0.91	High confidence
Silmitasertib	CDK5	983	0.52	514	0.99	High confidence
Silmitasertib	PLK1	731	0.92	672	0.92	High confidence
Silmitasertib	ICK	1304	0.68	884	0.94	High confidence
Silmitasertib	LAGE3	1075	0.95	1022	0.92	High confidence
Silmitasertib	BMPR2	1254	0.84	1056	0.97	High confidence
Silmitasertib	PIP4K2C	1226	0.91	1112	0.94	High confidence
Silmitasertib	CDK16	1287	0.94	1213	0.92	High confidence
Silmitasertib	PIM1	2903	0.43	1237	0.90	High confidence
Silmitasertib	TP53RK	1241	1.05	1241	0.97	High confidence
Silmitasertib	PRKAG1	2537	0.63	1606	0.86	High confidence
Silmitasertib	EIF2AK1	1803	0.92	1661	0.97	High confidence
Silmitasertib	CDK2	3171	0.53	1688	0.95	High confidence
Silmitasertib	STK26	1950	0.88	1713	0.48	Low confidence
Silmitasertib	OSGEP	2010	0.96	1929	0.99	High confidence
Silmitasertib	TAOK1	3129	0.66	2080	0.92	High confidence
Silmitasertib	RIPK3	2435	0.89	2177	0.60	High confidence
Silmitasertib	TYK2	4568	0.52	2382	0.96	High confidence
Silmitasertib	CCNB2	3751	0.70	2630	0.85	High confidence
Silmitasertib	OSBPL3	3325	0.83	2757	0.82	High confidence
Silmitasertib	MAP3K11	4257	0.70	2965	0.96	High confidence
Silmitasertib	CDK1	4444	0.69	3049	0.97	High confidence
Silmitasertib	PRKAB1	4708	0.66	3117	0.90	High confidence
Silmitasertib	MARK2	4227	0.75	3184	0.81	High confidence
Silmitasertib	PRKAB2	5482	0.60	3295	0.95	High confidence
Silmitasertib	RPS6KA6	8117	0.42	3424	0.93	High confidence
Silmitasertib	PHKG2	3614	0.97	3504	0.94	High confidence
Silmitasertib	ULK1	5483	0.67	3663	0.40	High confidence
Silmitasertib	GSK3B	10429	0.46	4850	0.94	High confidence
Silmitasertib	GAK	9180	0.56	5155	0.95	High confidence
Silmitasertib	MAPKAPK2	7331	0.72	5298	0.90	High confidence
Silmitasertib	RPS6KA1	7872	0.75	5920	0.97	High confidence
Silmitasertib	CHEK1	7477	0.82	6167	0.96	High confidence
Silmitasertib	CDK7	9819	0.73	7124	0.97	High confidence
Silmitasertib	PRKAA1	24127	0.64	15389	0.96	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Silmitasertib	GSK3A	34587	0.50	17301	0.96	High confidence	SU-14813	PDGFRB	5	0.87	4	0.98	High confidence
Silmitasertib	PKN1	23354	0.87	20414	0.89	High confidence	SU-14813	MYLK3	23	0.87	20	0.98	High confidence
Silmitasertib	CCNH	36791	0.76	27893	0.95	High confidence	SU-14813	RET	75	0.44	33	1.00	High confidence
Silmitasertib	MNAT1	69119	0.88	60700	0.88	Low confidence	SU-14813	BMP2K	118	0.66	78	0.99	High confidence
SNS-314	ETF1	1	1.25	1	0.98	Low confidence	SU-14813	INCENP	97	0.89	87	0.90	High confidence
SNS-314	ACOX3	39	0.66	26	0.96	High confidence	SU-14813	MAP4K1	129	0.73	93	0.95	High confidence
SNS-314	INCENP	117	0.89	104	0.89	High confidence	SU-14813	JAK1	407	0.37	152	0.93	High confidence
SNS-314	AURKA	333	0.35	118	0.94	High confidence	SU-14813	RASSF5	210	0.98	206	0.97	High confidence
SNS-314	DDR1	222	0.63	140	0.94	High confidence	SU-14813	KLHL6	287	0.74	213	0.92	Low confidence
SNS-314	AURKB	439	0.59	257	0.96	High confidence	SU-14813	AAK1	375	0.67	253	0.97	High confidence
SNS-314	DDR2	555	0.76	423	0.97	High confidence	SU-14813	RPS6KA4	441	0.62	272	0.97	High confidence
SNS-314	LASP1	913	1.58	913	0.89	High confidence	SU-14813	RPS6KB1	445	0.89	396	0.99	Low confidence
Sonolisib	PRKACG	13	0.51	7	0.99	Low confidence	SU-14813	ULK3	953	0.45	433	0.95	High confidence
Sonolisib	SIK3	14	0.82	11	0.99	Low confidence	SU-14813	BMPR2	802	0.84	675	0.90	High confidence
Sorafenib	RET	266	0.44	117	0.87	High confidence	SU-14813	STK4	906	0.76	691	0.98	High confidence
Sorafenib	ZAK	980	0.74	729	0.95	High confidence	SU-14813	MAP2K2	803	1.17	803	0.96	High confidence
Sorafenib	DDR1	2617	0.63	1641	0.77	High confidence	SU-14813	Q6ZSR9	1242	0.76	945	0.93	High confidence
Sorafenib	FLT3	3273	0.54	1759	0.82	High confidence	SU-14813	MAP4K4	953	1.01	953	0.90	High confidence
Sorafenib	DDR2	2559	0.76	1950	0.95	High confidence	SU-14813	PHKG2	1130	0.97	1096	0.91	Low confidence
Sorafenib	MAP3K1	6555	0.58	3783	0.96	High confidence	SU-14813	RASSF2	1320	0.93	1227	0.86	High confidence
Sotrastaurin	PRKCD	5	0.95	5	1.00	High confidence	SU-14813	TBK1	2079	0.64	1330	0.94	Low confidence
Sotrastaurin	PRKCQ	13	1.23	13	0.96	High confidence	SU-14813	STK3	1750	0.76	1338	0.99	High confidence
Sotrastaurin	PRKCA	18	0.73	13	1.00	High confidence	SU-14813	MELK	1560	0.88	1379	0.76	Low confidence
Sotrastaurin	PRKCE	23	0.71	16	0.90	High confidence	SU-14813	TRAF2	1706	0.83	1419	0.92	Low confidence
Sotrastaurin	PRKCB	30	0.80	24	1.00	High confidence	SU-14813	TANK	2419	0.64	1539	0.94	High confidence
Sotrastaurin	TNIK	38	1.02	38	0.43	Low confidence	SU-14813	CSNK1G2	1889	0.88	1653	0.94	Low confidence
Sotrastaurin	MINK1	41	1.00	41	0.59	High confidence	SU-14813	EIF3J	1656	1.11	1656	0.87	High confidence
Sotrastaurin	CLK2	187	0.65	121	0.59	Low confidence	SU-14813	IKBKE	3276	0.62	2034	0.86	High confidence
Sotrastaurin	GSK3B	1525	0.46	709	0.91	High confidence	SU-14813	MAP2K1	2330	1.23	2330	0.93	Low confidence
Sotrastaurin	GSK3A	2401	0.50	1201	0.94	High confidence	SU-14813	TBKBP1	3365	0.79	2670	0.96	High confidence
Sotrastaurin	RPS6KA6	3727	0.42	1572	0.95	High confidence	SU-14813	GAK	4812	0.56	2702	0.93	Low confidence
Sotrastaurin	MAP4K4	1580	1.01	1580	0.77	High confidence	SU-14813	IRAK4	4105	0.77	3178	0.97	High confidence
Sotrastaurin	PKN1	3379	0.87	2954	0.99	Low confidence	SU-14813	CSNK1E	4572	0.85	3908	0.91	Low confidence
Sotrastaurin	ICK	9867	0.68	6689	0.58	Low confidence	SU-14813	PRKAA1	6294	0.64	4015	0.95	High confidence
Sotrastaurin	GTPBP4	8198	1.25	8198	0.89	Low confidence	SU-14813	MARK2	5983	0.75	4507	0.92	Low confidence
Sotrastaurin	PIM1	20751	0.43	8842	0.70	Low confidence	SU-14813	AZI2	7137	0.70	5009	0.94	High confidence
SU-14813	FLT3	3	0.54	2	1.00	High confidence	SU-14813	STK10	5546	0.92	5077	0.94	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
SU-14813	CSNK2B	8073	1.08	8073	0.99	High confidence	Sunitinib	PRKD2	1706	0.66	1125	0.98	High confidence
SU-14813	RPS6KA1	22521	0.75	16936	0.90	Low confidence	Sunitinib	ULK3	2479	0.45	1125	0.90	High confidence
SU-14813	SLK	21310	0.89	18981	0.93	Low confidence	Sunitinib	PRKAG1	1802	0.63	1140	0.89	High confidence
SU-14813	MARK3	34528	0.77	26617	0.87	High confidence	Sunitinib	PRKAB2	1915	0.60	1151	0.69	High confidence
SU-14813	MAP4K5	100297	0.74	74634	0.90	Low confidence	Sunitinib	MNAT1	1323	0.88	1162	0.97	High confidence
Sunitinib	FLT3	4	0.54	2	1.00	High confidence	Sunitinib	MAP4K5	1604	0.74	1194	0.94	High confidence
Sunitinib	PDGFRB	4	0.87	4	1.00	High confidence	Sunitinib	CDK7	1657	0.73	1202	0.94	High confidence
Sunitinib	RET	75	0.44	33	0.95	High confidence	Sunitinib	ERCC2	1354	0.90	1225	0.97	High confidence
Sunitinib	PHKA2	49	1.58	49	0.96	High confidence	Sunitinib	GAK	2292	0.56	1287	0.90	High confidence
Sunitinib	BMP2K	132	0.66	87	0.96	High confidence	Sunitinib	STK4	1742	0.76	1329	0.93	High confidence
Sunitinib	AP2A1	132	0.92	121	0.93	High confidence	Sunitinib	MELK	1531	0.88	1353	0.82	High confidence
Sunitinib	UBE3C	189	0.99	186	0.83	Low confidence	Sunitinib	LYN	2821	0.50	1416	0.82	High confidence
Sunitinib	MAP4K1	342	0.73	249	0.96	High confidence	Sunitinib	UNC119	1964	0.73	1426	0.78	Low confidence
Sunitinib	MAP4K4	268	1.01	268	0.89	High confidence	Sunitinib	PDPK1	1430	1.04	1430	0.90	High confidence
Sunitinib	AAK1	539	0.67	363	0.92	High confidence	Sunitinib	LCK	3323	0.44	1464	0.73	Low confidence
Sunitinib	TNIK	387	1.02	387	0.91	High confidence	Sunitinib	RASSF5	1505	0.98	1480	0.97	High confidence
Sunitinib	Q6ZSR9	565	0.76	431	0.90	High confidence	Sunitinib	KLHL6	2003	0.74	1484	0.87	Low confidence
Sunitinib	CLK1	614	0.72	440	0.93	Low confidence	Sunitinib	TBK1	2349	0.64	1502	0.96	High confidence
Sunitinib	JAK1	1276	0.37	475	0.93	High confidence	Sunitinib	FGR	3618	0.42	1518	0.65	Low confidence
Sunitinib	MAP4K3	805	0.66	528	0.96	High confidence	Sunitinib	GAPVD1	1531	0.99	1524	0.91	High confidence
Sunitinib	RPS6KA4	927	0.62	572	0.98	High confidence	Sunitinib	GRK6	1615	1.03	1615	0.95	Low confidence
Sunitinib	PHKG2	681	0.97	661	0.93	High confidence	Sunitinib	PRKD3	2223	0.74	1645	0.94	High confidence
Sunitinib	LATS1	943	0.79	743	0.90	High confidence	Sunitinib	MAP2K2	1677	1.17	1677	0.97	High confidence
Sunitinib	PRKAB1	1136	0.66	752	0.81	High confidence	Sunitinib	RPS6KA3	2340	0.72	1696	0.87	High confidence
Sunitinib	YES1	1836	0.41	758	0.96	High confidence	Sunitinib	IKBKE	2788	0.62	1731	0.97	High confidence
Sunitinib	RASSF2	830	0.93	771	0.64	High confidence	Sunitinib	PRKAG2	2690	0.64	1734	0.86	High confidence
Sunitinib	TEX264	820	0.98	806	0.93	High confidence	Sunitinib	AURKB	3105	0.59	1817	0.88	High confidence
Sunitinib	CSNK1E	991	0.85	848	0.93	High confidence	Sunitinib	INPPL1	3842	0.48	1857	0.75	High confidence
Sunitinib	CSNK1D	1057	0.82	869	0.97	High confidence	Sunitinib	NTRK1	2749	0.71	1940	0.67	High confidence
Sunitinib	CAMK2G	4136	0.22	898	0.85	High confidence	Sunitinib	HCK	3749	0.52	1943	0.78	High confidence
Sunitinib	CLK2	1425	0.65	922	0.94	High confidence	Sunitinib	FER	4734	0.42	1999	0.82	Low confidence
Sunitinib	RASSF3	939	1.13	939	0.85	High confidence	Sunitinib	ULK1	3248	0.67	2170	0.79	High confidence
Sunitinib	MOB1A	1079	0.91	987	0.97	High confidence	Sunitinib	TANK	3475	0.64	2211	0.94	High confidence
Sunitinib	CDK3	1024	2.15	1024	0.87	High confidence	Sunitinib	STK26	2543	0.88	2234	0.77	High confidence
Sunitinib	PRKAA1	1691	0.64	1079	0.92	High confidence	Sunitinib	CDK16	2497	0.94	2353	0.67	Low confidence
Sunitinib	CCNH	1437	0.76	1089	0.95	High confidence	Sunitinib	MAP3K2	3418	0.70	2387	0.84	High confidence
Sunitinib	RPS6KA5	1659	0.68	1122	0.67	High confidence	Sunitinib	STK3	3144	0.76	2403	0.82	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Sunitinib	FAM83A	2740	0.88	2414	0.91	High confidence
Sunitinib	MARK3	3330	0.77	2567	0.95	High confidence
Sunitinib	MAP2K1	2580	1.23	2580	0.86	High confidence
Sunitinib	BMPR2	3098	0.84	2608	0.86	High confidence
Sunitinib	IRAK4	3391	0.77	2625	0.85	High confidence
Sunitinib	RPS6KA1	3558	0.75	2675	0.83	High confidence
Sunitinib	TBKBP1	3470	0.79	2754	0.88	High confidence
Sunitinib	EIF3J	2875	1.11	2875	0.88	High confidence
Sunitinib	CDK17	2880	1.02	2880	0.57	High confidence
Sunitinib	CSNK1G3	3747	0.79	2946	0.89	High confidence
Sunitinib	CAMK4	2970	1.02	2970	0.92	High confidence
Sunitinib	MARK2	4000	0.75	3013	0.89	High confidence
Sunitinib	MAP3K11	4446	0.70	3097	0.95	High confidence
Sunitinib	CSNK2A1	3110	1.02	3110	0.91	High confidence
Sunitinib	CSNK2B	3117	1.08	3117	0.92	High confidence
Sunitinib	PDCD10	3157	1.07	3157	0.79	High confidence
Sunitinib	SLK	3575	0.89	3184	0.88	Low confidence
Sunitinib	CSNK2A2	3325	0.96	3201	0.86	High confidence
Sunitinib	MAP3K3	4864	0.67	3264	0.83	High confidence
Sunitinib	CHEK1	3994	0.82	3294	0.95	High confidence
Sunitinib	CSNK1G1	3899	0.87	3374	0.87	High confidence
Sunitinib	BUB1	3507	1.04	3507	0.67	Low confidence
Sunitinib	MAP2K5	4025	0.88	3525	0.86	High confidence
Sunitinib	FGFR1	4882	0.74	3595	0.93	High confidence
Sunitinib	DYRK1A	3939	0.93	3675	0.87	High confidence
Sunitinib	STK10	4331	0.92	3965	0.97	High confidence
Sunitinib	NQO2	4022	1.07	4022	0.91	High confidence
Sunitinib	STK24	4084	1.06	4084	0.67	High confidence
Sunitinib	AZI2	8149	0.70	5719	0.95	High confidence
Sunitinib	PDXK	6021	1.43	6021	0.71	Low confidence
Sunitinib	EGFR	8559	0.79	6788	0.85	High confidence
Sunitinib	CSNK1A1	7947	0.92	7339	0.86	High confidence
TAK-285	EGFR	853	0.79	677	0.92	High confidence
TAK-285	NLK	1227	0.66	816	0.85	Low confidence
TAK-285	BMPR1B	2655	0.61	1630	0.91	Low confidence
TAK-285	EPHB6	3008	0.61	1849	0.85	Low confidence
TAK-593	INPPL1	2	0.48	1	1.00	High confidence
TAK-593	RET	22	0.44	10	0.96	High confidence
TAK-593	BCR	73	0.48	35	0.99	High confidence
TAK-593	PDGFRB	104	0.87	91	0.64	High confidence
TAK-593	NEK1	442	0.83	365	0.85	High confidence
TAK-593	YES1	1025	0.41	423	0.87	High confidence
TAK-593	Q6ZSR9	1142	0.76	869	0.97	High confidence
TAK-593	ABL1	1676	0.55	918	0.98	High confidence
TAK-593	AAK1	3626	0.67	2441	0.99	High confidence
TAK-593	ABL2	12247	0.33	4058	0.91	High confidence
TAK-593	BMP2K	16513	0.66	10914	0.93	High confidence
TAK-593	DDR1	23398	0.63	14677	0.95	High confidence
TAK-593	DDR2	25312	0.76	19290	0.91	High confidence
TAK-733	MAP2K2	20	1.17	20	0.99	High confidence
TAK-733	MAP2K1	21	1.23	21	0.99	High confidence
TAK-733	MAP2K5	3823	0.88	3348	0.68	Low confidence
TAK-901	YES1	54	0.41	22	0.99	High confidence
TAK-901	EPHA4	36	0.62	22	0.82	High confidence
TAK-901	AURKA	67	0.35	24	0.99	High confidence
TAK-901	IRAK3	62	0.43	27	0.91	High confidence
TAK-901	PLK4	81	0.51	41	0.91	High confidence
TAK-901	AURKB	74	0.59	44	0.92	High confidence
TAK-901	INCENP	55	0.89	49	0.77	High confidence
TAK-901	SRC	237	0.39	92	0.99	High confidence
TAK-901	FYN	221	0.43	95	0.99	High confidence
TAK-901	LCK	239	0.44	105	1.00	High confidence
TAK-901	RET	252	0.44	111	0.95	High confidence
TAK-901	SIK2	223	0.52	115	0.99	High confidence
TAK-901	BCR	278	0.48	133	0.97	High confidence
TAK-901	INPPL1	281	0.48	136	0.98	High confidence
TAK-901	HCK	275	0.52	143	1.00	High confidence
TAK-901	CCNH	223	0.76	169	1.00	High confidence
TAK-901	EPHA2	430	0.41	178	0.98	High confidence
TAK-901	PTK6	374	0.48	180	0.97	High confidence
TAK-901	PTK2B	459	0.41	190	0.98	High confidence
TAK-901	GRB2	306	0.62	191	0.94	High confidence
TAK-901	TGFBR1	284	0.69	197	0.99	High confidence
TAK-901	CDK7	283	0.73	205	1.00	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
TAK-901	FRK	653	0.34	222	0.99	High confidence	TAK-901	IRAK4	2755	0.77	2133	0.99	High confidence
TAK-901	ERCC2	272	0.90	246	0.99	High confidence	TAK-901	MELK	2602	0.88	2300	0.48	Low confidence
TAK-901	ACVR1	521	0.48	249	0.94	High confidence	TAK-901	PRKAA1	3623	0.64	2310	0.99	High confidence
TAK-901	PTK2	647	0.41	264	0.97	High confidence	TAK-901	DDR2	3059	0.76	2331	0.97	High confidence
TAK-901	TNK2	625	0.45	281	0.96	High confidence	TAK-901	MARK2	3096	0.75	2332	0.96	High confidence
TAK-901	TEC	700	0.40	282	0.98	High confidence	TAK-901	EPHB3	2682	0.88	2349	0.98	High confidence
TAK-901	MNAT1	338	0.88	296	0.97	High confidence	TAK-901	MARK3	3135	0.77	2416	0.96	High confidence
TAK-901	ABL1	566	0.55	310	0.99	High confidence	TAK-901	MAP3K11	3641	0.70	2536	0.87	High confidence
TAK-901	BTK	839	0.39	328	0.99	High confidence	TAK-901	TANK	4333	0.64	2756	0.94	High confidence
TAK-901	PRKAG1	560	0.63	355	0.96	High confidence	TAK-901	STK3	3610	0.76	2759	0.93	High confidence
TAK-901	LYN	711	0.50	357	0.99	High confidence	TAK-901	TBK1	4319	0.64	2762	0.92	High confidence
TAK-901	ABL2	1275	0.33	422	0.98	High confidence	TAK-901	PKN1	3413	0.87	2983	0.92	High confidence
TAK-901	EPHB6	734	0.61	451	0.61	Low confidence	TAK-901	RPS6KA4	4865	0.62	3004	0.93	High confidence
TAK-901	EPHA5	849	0.60	508	0.81	High confidence	TAK-901	DCAF7	3547	0.90	3180	0.85	High confidence
TAK-901	PRKAG2	790	0.64	509	0.83	High confidence	TAK-901	RPS6KA1	4542	0.75	3416	0.96	High confidence
TAK-901	PRKAB1	817	0.66	541	0.97	High confidence	TAK-901	ACAD10	3569	0.96	3420	0.56	Low confidence
TAK-901	FLT3	1032	0.54	554	0.68	Low confidence	TAK-901	STK4	4531	0.76	3455	0.95	High confidence
TAK-901	TNK1	1290	0.43	558	0.60	Low confidence	TAK-901	RASSF5	3545	0.98	3485	0.89	High confidence
TAK-901	FER	1360	0.42	574	0.96	High confidence	TAK-901	CDK9	5073	0.71	3609	0.29	High confidence
TAK-901	EPHA7	777	0.79	615	0.84	High confidence	TAK-901	CCNT2	4132	0.88	3636	0.44	High confidence
TAK-901	EPHB4	1325	0.49	656	0.95	High confidence	TAK-901	MAP2K2	3951	1.17	3951	0.97	High confidence
TAK-901	EPHB2	1275	0.52	669	0.95	High confidence	TAK-901	AZI2	5661	0.70	3973	0.93	High confidence
TAK-901	TRAF2	819	0.83	681	0.50	Low confidence	TAK-901	PDGFRB	5254	0.87	4592	0.92	High confidence
TAK-901	BMP2K	1051	0.66	695	0.98	High confidence	TAK-901	PDPK1	4637	1.04	4637	0.95	High confidence
TAK-901	NUAK2	914	0.77	705	0.92	High confidence	TAK-901	SYK	5560	0.84	4662	0.96	High confidence
TAK-901	PRKAB2	1236	0.60	743	0.83	High confidence	TAK-901	CCNT1	4791	0.98	4711	0.42	High confidence
TAK-901	NTRK1	1194	0.71	843	1.00	High confidence	TAK-901	MAP4K5	7198	0.74	5356	0.94	High confidence
TAK-901	STK16	1180	0.72	849	0.95	High confidence	TAK-901	RPS6KA3	8273	0.72	5997	0.93	High confidence
TAK-901	RPS6KA6	2131	0.42	899	0.96	High confidence	TAK-901	GSK3B	13265	0.46	6168	0.90	High confidence
TAK-901	STK10	1037	0.92	949	0.98	High confidence	TAK-901	MAP2K5	7762	0.88	6797	0.98	High confidence
TAK-901	MARK4	1245	0.83	1035	0.62	High confidence	TAK-901	MAP4K3	14160	0.66	9285	0.92	Low confidence
TAK-901	GRK6	1189	1.03	1189	0.79	Low confidence	TAK-901	DDR1	21946	0.63	13766	0.95	High confidence
TAK-901	SLK	1514	0.89	1348	0.95	High confidence	TAK-901	GSK3A	45067	0.50	22543	0.95	High confidence
TAK-901	FGFR1	1885	0.74	1388	0.97	High confidence	TAK-901	CSNK2A1	28533	1.02	28533	0.99	High confidence
TAK-901	EGFR	1851	0.79	1468	0.57	High confidence	TAK-901	CSNK2A2	29990	0.96	28872	0.99	High confidence
TAK-901	PRKCA	2209	0.73	1609	0.93	High confidence	TAK-901	NQO2	88903	1.07	88903	0.94	High confidence
TAK-901	CHEK1	2116	0.82	1745	0.91	High confidence	Talmapimod	ACTR2	4	1.02	4	0.96	Low confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Talmapimod	MAPK14	16	0.51	8	0.99	High confidence	Tesevatinib	EPHB6	422	0.61	259	0.93	Low confidence
Talmapimod	MAPKAPK2	26	0.72	19	0.66	Low confidence	Tesevatinib	RIPK3	410	0.89	366	0.94	High confidence
Talmapimod	NQO2	9918	1.07	9918	0.94	High confidence	Tesevatinib	EPHA4	714	0.62	440	0.98	High confidence
Tandutinib	FARSB	6	1.16	6	0.99	Low confidence	Tesevatinib	EPHB2	854	0.52	448	0.92	High confidence
Tandutinib	9-Sep	10	1.43	10	0.64	Low confidence	Tesevatinib	EPHA2	1213	0.41	501	0.92	High confidence
Tandutinib	FLT3	29	0.54	15	0.99	High confidence	Tesevatinib	GAK	1095	0.56	615	0.94	High confidence
Tandutinib	IRAK3	6900	0.43	2959	0.80	High confidence	Tesevatinib	ABL2	1895	0.33	628	0.91	High confidence
Tanzisertib	MAPK10	2	0.84	1	1.00	High confidence	Tesevatinib	MAP4K5	1220	0.74	908	0.89	High confidence
Tanzisertib	MAPK9	3	0.70	2	1.00	High confidence	Tesevatinib	ABL1	1681	0.55	921	0.96	High confidence
Tanzisertib	MAPK8	26	0.65	17	0.98	High confidence	Tesevatinib	CSNK1E	1189	0.85	1017	0.93	Low confidence
Tanzisertib	GAK	277	0.56	156	0.98	High confidence	Tesevatinib	SRC	2903	0.39	1127	0.83	High confidence
Tanzisertib	MAPK14	1424	0.51	729	0.90	High confidence	Tesevatinib	LYN	2251	0.50	1130	0.90	High confidence
Tanzisertib	MAPKAPK2	1293	0.72	934	0.94	High confidence	Tesevatinib	HCK	2240	0.52	1161	0.79	High confidence
Tanzisertib	MAPK1	2660	0.46	1233	0.85	High confidence	Tesevatinib	IRAK4	1517	0.77	1174	0.94	High confidence
Tanzisertib	ERN1	1664	0.81	1356	0.90	High confidence	Tesevatinib	MAPKAPK2	2102	0.72	1519	0.95	High confidence
Tanzisertib	LIMK2	2776	0.66	1840	0.96	High confidence	Tesevatinib	DDR2	1999	0.76	1523	0.91	High confidence
Tanzisertib	LIMK1	3654	0.59	2173	0.78	High confidence	Tesevatinib	BTK	4153	0.39	1623	0.78	High confidence
Tanzisertib	MYLK	3150	0.83	2625	0.81	Low confidence	Tesevatinib	MAP3K1	3020	0.58	1743	0.81	High confidence
Tanzisertib	SIK3	3642	0.82	2981	0.87	High confidence	Tesevatinib	MAP4K3	2774	0.66	1819	0.81	High confidence
Tanzisertib	MAPK3	5581	0.66	3692	0.90	High confidence	Tesevatinib	STK10	2080	0.92	1905	0.93	High confidence
Telatinib	NCKAP1L	17	1.14	17	0.93	Low confidence	Tesevatinib	MAP4K4	1907	1.01	1907	0.84	High confidence
Telatinib	ILK	32	1.04	32	0.66	Low confidence	Tesevatinib	TGFBR1	4784	0.69	3316	0.88	High confidence
Telatinib	ZAK	641	0.74	477	0.69	Low confidence	Tesevatinib	SLK	3841	0.89	3421	0.87	High confidence
Telatinib	PDGFRB	635	0.87	555	0.82	High confidence	Tesevatinib	YES1	9527	0.41	3936	0.98	High confidence
Tepotinib	MET	1	0.80	1	1.00	High confidence	Tesevatinib	MAP2K5	74995	0.88	65677	0.93	High confidence
Tepotinib	NQO2	875	1.07	875	0.89	High confidence	TG-100115	DCK	12	1.16	12	1.00	High confidence
Tesevatinib	MAPKAPK3	2	0.83	2	0.81	Low confidence	TG-100115	FLT3	83	0.54	44	0.51	Low confidence
Tesevatinib	EPHA1	20	0.40	8	0.99	High confidence	TG-100115	AP1B1	73	0.86	62	0.71	Low confidence
Tesevatinib	EPHA7	27	0.79	22	0.79	Low confidence	TG-100115	GAPVD1	418	0.99	416	0.69	Low confidence
Tesevatinib	RIPK2	118	0.28	33	0.97	High confidence	TG-100115	ACADVL	1689	1.24	1689	0.89	Low confidence
Tesevatinib	EPHB4	74	0.49	37	0.99	High confidence	TG-100115	S100A6	1869	1.29	1869	0.79	Low confidence
Tesevatinib	EGFR	48	0.79	38	0.93	High confidence	TG-100115	RIPK2	7009	0.28	1967	0.88	Low confidence
Tesevatinib	RET	145	0.44	64	0.94	High confidence	TG-100115	MAP3K1	4239	0.58	2447	0.83	High confidence
Tesevatinib	DDR1	116	0.63	73	0.99	High confidence	TG-100115	Q6ZSR9	3960	0.76	3015	0.99	High confidence
Tesevatinib	BCR	236	0.48	113	0.96	High confidence	TG-100115	AAK1	4969	0.67	3345	0.98	High confidence
Tesevatinib	PTK6	356	0.48	172	0.93	High confidence	TG-100115	RIPK3	4102	0.89	3668	0.88	Low confidence
Tesevatinib	LCK	470	0.44	207	0.92	High confidence	TG-100115	PDXK	5251	1.43	5251	0.83	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
TG-100115	PIP4K2A	7324	0.96	7017	1.00	Low confidence
TG-100115	BMP2K	21090	0.66	13940	0.95	High confidence
TG-100572	EPHA5	1	0.60	0	0.99	High confidence
TG-100572	EPHB6	1	0.61	1	0.80	High confidence
TG-100572	TYK2	1	0.52	1	0.96	High confidence
TG-100572	EPHB4	2	0.49	1	0.99	High confidence
TG-100572	RIPK2	3	0.28	1	0.99	High confidence
TG-100572	FRK	3	0.34	1	0.91	High confidence
TG-100572	YES1	3	0.41	1	0.96	High confidence
TG-100572	EPHA2	3	0.41	1	0.98	High confidence
TG-100572	ABL2	4	0.33	1	0.98	High confidence
TG-100572	BCR	3	0.48	1	0.99	High confidence
TG-100572	RET	3	0.44	1	0.99	High confidence
TG-100572	ACVR1B	3	0.43	1	0.94	High confidence
TG-100572	SIK2	3	0.52	2	0.94	High confidence
TG-100572	LCK	4	0.44	2	0.94	High confidence
TG-100572	TGFBR1	2	0.69	2	0.97	High confidence
TG-100572	EPHB2	4	0.52	2	0.98	High confidence
TG-100572	EPHB3	2	0.88	2	0.91	High confidence
TG-100572	GAK	4	0.56	2	0.96	High confidence
TG-100572	EPHA4	4	0.62	2	0.98	High confidence
TG-100572	ABL1	4	0.55	2	0.98	High confidence
TG-100572	PRKD2	4	0.66	3	0.95	High confidence
TG-100572	BMPR2	3	0.84	3	0.75	High confidence
TG-100572	NLK	4	0.66	3	0.61	High confidence
TG-100572	DDR1	4	0.63	3	0.90	High confidence
TG-100572	RIPK3	3	0.89	3	0.92	High confidence
TG-100572	SIK3	3	0.82	3	0.92	High confidence
TG-100572	BRAF	3	1.11	3	0.79	High confidence
TG-100572	PRKD3	4	0.74	3	0.81	Low confidence
TG-100572	DDR2	6	0.76	4	0.92	High confidence
TG-100572	GRB2	4008	0.62	2500	0.56	Low confidence
TG-100572	AIMP1	3181	1.25	3181	0.61	High confidence
TG-100572	SRC	9E+22	0.39	4E+22	0.69	High confidence
TG-100572	CIT	7E+26	1.21	7E+26	0.69	High confidence
TG-100801	BCR	137	0.48	65	0.94	High confidence
TG-100801	PDGFRB	125	0.87	109	0.78	High confidence
TG-100801	INPPL1	332	0.48	160	0.96	High confidence
TG-100801	RIPK2	685	0.28	192	0.97	High confidence
TG-100801	ACVR2B	629	0.67	419	0.77	Low confidence
TG-100801	GRB2	956	0.62	597	0.96	High confidence
TG-100801	TGFBR2	935	0.75	703	0.97	High confidence
TG-100801	EPHB4	1436	0.49	711	0.94	High confidence
TG-100801	GAK	1468	0.56	824	0.97	High confidence
TG-100801	RET	2333	0.44	1028	0.97	High confidence
TG-100801	ABL2	3120	0.33	1034	0.97	High confidence
TG-100801	EPHA2	2877	0.41	1188	0.86	High confidence
TG-100801	EPHB2	2472	0.52	1296	0.88	High confidence
TG-100801	LCK	3328	0.44	1466	0.86	High confidence
TG-100801	DDR1	2750	0.63	1725	0.77	Low confidence
TG-100801	EPHA4	3131	0.62	1930	0.88	Low confidence
TG-100801	YES1	10735	0.41	4435	0.83	High confidence
TG-100801	ABL1	19541	0.55	10707	0.96	High confidence
Tivantinib	OPA1	17	1.02	17	0.91	Low confidence
Tivantinib	CCDC47	29	1.15	29	0.90	Low confidence
Tivantinib	RANGAP1	52	0.89	47	0.91	Low confidence
Tivantinib	HMOX2	119	1.02	119	0.91	Low confidence
Tivantinib	EIF5B	232	1.38	232	0.80	Low confidence
Tivantinib	MET	636	0.80	511	0.91	High confidence
Tivozanib	PEBP1	3	1.38	3	0.95	Low confidence
Tivozanib	NUCKS1	7	2.29	7	0.95	Low confidence
Tivozanib	RET	28	0.44	12	1.00	High confidence
Tivozanib	FRK	426	0.34	145	0.95	High confidence
Tivozanib	EPHA2	355	0.41	147	0.93	High confidence
Tivozanib	BCR	335	0.48	160	0.98	High confidence
Tivozanib	INPPL1	343	0.48	166	0.89	High confidence
Tivozanib	DDR1	303	0.63	190	0.93	High confidence
Tivozanib	ABL1	356	0.55	195	0.95	High confidence
Tivozanib	GRB2	314	0.62	196	0.92	High confidence
Tivozanib	PAG1	509	0.49	251	0.72	Low confidence
Tivozanib	INCENP	285	0.89	254	0.56	Low confidence
Tivozanib	ABL2	911	0.33	302	0.88	High confidence
Tivozanib	EPHB4	626	0.49	310	0.93	High confidence
Tivozanib	EPHB2	854	0.52	448	0.98	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Tivozanib	DDR2	777	0.76	592	0.98	High confidence	Tozasertib	ABL1	874	0.55	479	0.94	High confidence
Tivozanib	EPHA5	1004	0.60	601	0.84	High confidence	Tozasertib	Q6ZSR9	659	0.76	502	0.98	High confidence
Tivozanib	PTK6	1628	0.48	787	0.76	High confidence	Tozasertib	BCR	1057	0.48	505	0.97	High confidence
Tivozanib	RIPK2	2853	0.28	801	0.93	High confidence	Tozasertib	PLK4	1005	0.51	512	0.90	High confidence
Tivozanib	RIPK3	1506	0.89	1346	0.90	High confidence	Tozasertib	MET	1238	0.80	995	0.73	High confidence
Tivozanib	AURKB	2669	0.59	1562	0.90	High confidence	Tozasertib	MAP4K5	2120	0.74	1577	0.85	High confidence
Tivozanib	LYN	4023	0.50	2019	0.92	High confidence	Tozasertib	MINK1	1810	1.00	1810	0.73	Low confidence
Tivozanib	LCK	4956	0.44	2183	0.93	High confidence	Trametinib	MAP2K2	9	1.17	9	0.90	High confidence
Tivozanib	MAP4K2	4025	0.59	2375	0.76	High confidence	Trametinib	MAP2K1	62	1.23	62	0.97	High confidence
Tivozanib	PDGFRB	2756	0.87	2409	0.97	High confidence	Trametinib	BRD4	1915	1.20	1915	0.95	Low confidence
Tivozanib	STK10	5049	0.92	4622	0.83	High confidence	UCN-01	STK10	3	0.92	3	0.99	High confidence
Tivozanib	MET	6725	0.80	5403	0.94	Low confidence	UCN-01	PAK6	5	0.74	4	0.82	High confidence
Tivozanib	EPHB3	6203	0.88	5433	0.70	High confidence	UCN-01	PKN1	9	0.87	8	0.97	High confidence
Tivozanib	EPHA4	9022	0.62	5563	0.87	High confidence	UCN-01	MARK4	10	0.83	8	0.99	High confidence
Tofacitinib	INCENP	38	0.89	34	0.99	High confidence	UCN-01	PDPK1	8	1.04	8	1.00	High confidence
Tofacitinib	PKN1	66	0.87	58	0.96	High confidence	UCN-01	SIK2	21	0.52	11	1.00	High confidence
Tofacitinib	MAP2K1	429	1.23	429	0.88	Low confidence	UCN-01	MARK2	18	0.75	13	1.00	High confidence
Tofacitinib	AURKB	896	0.59	525	0.92	High confidence	UCN-01	MARK3	21	0.77	16	1.00	High confidence
Tofacitinib	TNK2	2359	0.45	1062	0.74	Low confidence	UCN-01	PRKCB	24	0.80	19	0.98	High confidence
Tofacitinib	TNK1	3890	0.43	1683	0.84	Low confidence	UCN-01	PRKAG2	39	0.64	25	0.98	High confidence
Tofacitinib	ROCK1	3002	0.91	2730	0.91	Low confidence	UCN-01	PAK4	42	0.60	25	0.97	High confidence
Tofacitinib	ROCK2	3415	0.87	2977	0.94	Low confidence	UCN-01	CAMKK2	46	0.66	30	0.94	High confidence
Tofacitinib	MARK2	8796	0.75	6626	0.98	High confidence	UCN-01	RASSF5	33	0.98	33	1.00	High confidence
Tofacitinib	PRKCD	9720	0.95	9206	0.86	Low confidence	UCN-01	CHEK1	40	0.82	33	0.94	High confidence
Tofacitinib	MARK3	13986	0.77	10782	0.93	High confidence	UCN-01	PRKCA	48	0.73	35	0.99	High confidence
Tofacitinib	EIF3J	24107	1.11	24107	0.94	High confidence	UCN-01	PRKCD	41	0.95	38	0.97	High confidence
Tofacitinib	PRKCA	38588	0.73	28098	0.86	Low confidence	UCN-01	STK3	59	0.76	45	0.96	High confidence
Tozasertib	AURKA	16	0.35	6	0.98	High confidence	UCN-01	SIK3	68	0.82	56	0.93	High confidence
Tozasertib	MYLK3	17	0.87	15	0.92	High confidence	UCN-01	PDCD10	61	1.07	61	0.89	High confidence
Tozasertib	INCENP	19	0.89	17	0.93	Low confidence	UCN-01	PDCD11	63	1.31	63	0.98	High confidence
Tozasertib	AURKB	183	0.59	107	0.97	High confidence	UCN-01	FLT3	125	0.54	67	0.94	High confidence
Tozasertib	INPPL1	601	0.48	290	0.62	High confidence	UCN-01	PRKAB2	135	0.60	81	0.92	High confidence
Tozasertib	ABL2	1048	0.33	347	0.94	High confidence	UCN-01	SLK	100	0.89	89	0.91	High confidence
Tozasertib	AAK1	525	0.67	353	0.97	High confidence	UCN-01	CDC42BPB	113	0.97	110	0.99	High confidence
Tozasertib	BMP2K	586	0.66	387	0.98	High confidence	UCN-01	STK4	149	0.76	114	0.98	High confidence
Tozasertib	RET	969	0.44	427	0.92	High confidence	UCN-01	RPS6KA6	335	0.42	141	0.90	High confidence
Tozasertib	FLT3	858	0.54	461	0.81	High confidence	UCN-01	PKN2	175	0.82	142	0.84	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
UCN-01	TNK2	360	0.45	162	0.95	High confidence	UCN-01	WEE1	1739	0.63	1101	0.65	Low confidence
UCN-01	PTK2B	462	0.41	191	0.90	High confidence	UCN-01	MAP3K6	1435	0.83	1185	0.92	High confidence
UCN-01	SYK	259	0.84	217	0.98	High confidence	UCN-01	AP2B1	1330	1.01	1330	0.96	High confidence
UCN-01	CDC42BPA	264	0.96	254	0.89	High confidence	UCN-01	TAOK3	1824	0.77	1411	0.80	High confidence
UCN-01	CDC42BPG	269	1.02	269	0.98	High confidence	UCN-01	PRKCQ	1984	1.23	1984	0.93	High confidence
UCN-01	MAP3K11	435	0.70	303	0.94	High confidence	UCN-01	ERN1	2450	0.81	1997	0.54	Low confidence
UCN-01	PRKAA1	501	0.64	319	0.96	High confidence	UCN-01	FES	6261	0.37	2314	0.87	High confidence
UCN-01	AZI2	531	0.70	373	0.84	High confidence	UCN-01	PRKD2	6427	0.66	4236	0.91	High confidence
UCN-01	BTK	988	0.39	386	0.93	Low confidence	Ulixertinib	MAPK3	242	0.66	160	0.99	High confidence
UCN-01	TBK1	614	0.64	393	0.93	High confidence	Ulixertinib	MAPK1	395	0.46	183	0.98	High confidence
UCN-01	STK38L	414	1.04	414	0.86	Low confidence	Ulixertinib	TAOK1	584	0.66	388	0.91	High confidence
UCN-01	FER	1019	0.42	430	0.90	High confidence	Ulixertinib	PRKD2	9613	0.66	6336	0.87	High confidence
UCN-01	PTK2	1068	0.41	436	0.82	Low confidence	Uprosertib	PRKACA	21	0.47	10	0.96	High confidence
UCN-01	PDGFRB	499	0.87	436	0.94	High confidence	Uprosertib	CDK16	38	0.94	36	0.97	Low confidence
UCN-01	TANK	690	0.64	439	0.93	High confidence	Uprosertib	PRKACB	104	0.47	49	0.98	High confidence
UCN-01	CAMK2D	2552	0.20	520	0.96	High confidence	Uprosertib	PKN1	87	0.87	76	0.94	High confidence
UCN-01	RET	1182	0.44	521	0.83	High confidence	Uprosertib	DYRK1A	255	0.93	238	0.91	Low confidence
UCN-01	IKBKE	851	0.62	528	0.96	High confidence	Uprosertib	MELK	272	0.88	240	0.76	Low confidence
UCN-01	EXOC4	544	1.08	544	0.98	High confidence	Uprosertib	MNAT1	417	0.88	366	0.93	High confidence
UCN-01	HCK	1198	0.52	621	0.91	Low confidence	Uprosertib	AKT1	490	0.90	440	0.88	High confidence
UCN-01	AAK1	925	0.67	623	0.80	High confidence	Uprosertib	AKT2	1040	0.86	891	0.91	Low confidence
UCN-01	MAP4K2	1069	0.59	631	0.96	High confidence	Uprosertib	CDK7	1554	0.73	1127	0.97	High confidence
UCN-01	9-Sep	635	1.43	635	0.96	Low confidence	Uprosertib	ROCK1	1267	0.91	1152	0.90	High confidence
UCN-01	AURKB	1145	0.59	670	0.89	Low confidence	Uprosertib	PRKCB	1479	0.80	1180	0.96	High confidence
UCN-01	MAP4K3	1076	0.66	706	0.87	High confidence	Uprosertib	PRKD2	1802	0.66	1188	0.87	High confidence
UCN-01	NTRK1	1044	0.71	737	0.92	High confidence	Uprosertib	PRKCI	1230	1.07	1230	0.85	High confidence
UCN-01	MAP2K6	792	1.01	792	0.64	Low confidence	Uprosertib	CCNH	1992	0.76	1510	0.94	High confidence
UCN-01	CAMK2G	3791	0.22	823	0.90	High confidence	Uprosertib	PRKCA	2289	0.73	1667	0.91	High confidence
UCN-01	BMP2K	1259	0.66	832	0.84	High confidence	Uprosertib	CSNK1A1	1821	0.92	1682	0.90	High confidence
UCN-01	MAP4K4	832	1.01	832	0.53	Low confidence	Uprosertib	MARK2	2754	0.75	2075	0.90	High confidence
UCN-01	MAP4K5	1123	0.74	836	0.93	High confidence	Uprosertib	MARK3	2707	0.77	2087	0.69	Low confidence
UCN-01	IRAK4	1156	0.77	895	0.82	Low confidence	Uprosertib	ROCK2	2612	0.87	2277	0.87	High confidence
UCN-01	MET	1166	0.80	937	0.83	High confidence	Uprosertib	PRKD3	3565	0.74	2639	0.85	High confidence
UCN-01	ROCK1	1050	0.91	955	0.90	High confidence	Uprosertib	LATS1	4562	0.79	3592	0.88	Low confidence
UCN-01	Q6ZSR9	1262	0.76	961	0.75	High confidence	Vandetanib	RIPK2	263	0.28	74	0.97	High confidence
UCN-01	CCNT1	987	0.98	970	0.91	Low confidence	Vandetanib	RET	1175	0.44	518	0.86	High confidence
UCN-01	ROCK2	1257	0.87	1096	0.92	High confidence	Vandetanib	INPPL1	1322	0.48	639	0.90	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Vandetanib	BCR	1839	0.48	879	0.98	High confidence	X-396	MET	39	0.80	32	0.74	Low confidence
Vandetanib	GRB2	1609	0.62	1003	0.93	High confidence	X-396	MAP4K2	207	0.59	122	0.98	High confidence
Vandetanib	ABL1	2159	0.55	1183	0.96	High confidence	X-396	MAP3K1	3789	0.58	2187	0.99	High confidence
Vandetanib	PTK6	2561	0.48	1237	0.94	High confidence	X-396	Q6ZSR9	4414	0.76	3361	0.96	High confidence
Vandetanib	DDR1	2151	0.63	1349	0.86	High confidence	X-396	MAP4K5	28041	0.74	20866	0.94	High confidence
Vandetanib	STK10	3115	0.92	2852	0.94	High confidence	X-396	AAK1	33039	0.67	22238	0.95	High confidence
Vandetanib	LCK	7153	0.44	3151	0.95	High confidence	XL-019	AAK1	9	0.67	6	1.00	High confidence
Vandetanib	EGFR	4717	0.79	3741	0.36	High confidence	XL-019	Q6ZSR9	9	0.76	7	0.99	High confidence
Varlitinib	EGFR	6	0.79	5	0.99	High confidence	XL-019	BMP2K	30	0.66	20	0.94	High confidence
Varlitinib	RIPK3	98	0.89	88	0.95	High confidence	XL-019	NLK	41	0.66	27	0.96	Low confidence
Varlitinib	YES1	777	0.41	321	0.92	High confidence	XL-019	GAK	88	0.56	50	0.99	High confidence
Varlitinib	YTHDF3	649	1.47	649	0.81	Low confidence	XL-019	MYLK3	112	0.87	98	0.69	Low confidence
Varlitinib	RIPK2	2888	0.28	810	0.90	High confidence	XL-019	DYNLL1	321	0.50	161	0.84	High confidence
Varlitinib	FECH	76802	0.99	76413	0.94	Low confidence	XL-019	ADCK1	325	0.62	202	0.98	High confidence
Vatalanib	PDGFRB	5026	0.87	4393	0.77	High confidence	XL-019	SIK3	252	0.82	206	0.81	High confidence
Vatalanib	FLNB	5718	0.96	5495	0.90	Low confidence	XL-019	ULK3	654	0.45	297	0.98	High confidence
Vemurafenib	ZAK	425	0.74	316	0.96	High confidence	XL-019	SIK2	578	0.52	300	0.97	High confidence
Vemurafenib	RIPK2	1522	0.28	427	0.88	High confidence	XL-019	IKBKE	551	0.62	342	0.97	High confidence
Vemurafenib	MAP2K5	838	0.88	734	0.98	High confidence	XL-019	NEK3	413	0.85	353	0.98	High confidence
Vemurafenib	PTK6	2920	0.48	1411	0.92	High confidence	XL-019	MAPKAPK2	490	0.72	354	0.97	High confidence
Vemurafenib	FECH	1427	0.99	1419	0.96	High confidence	XL-019	BUB1	390	1.04	390	0.88	High confidence
Vemurafenib	MAP4K5	2419	0.74	1800	0.96	High confidence	XL-019	AZI2	743	0.70	521	0.99	High confidence
Vemurafenib	RIPK3	2325	0.89	2079	0.98	High confidence	XL-019	TANK	873	0.64	555	0.96	High confidence
Vemurafenib	ARAF	3431	0.62	2138	0.92	High confidence	XL-019	TBK1	877	0.64	561	0.96	High confidence
Vemurafenib	BRAF	3386	1.11	3386	0.95	High confidence	XL-019	MAPK8	1303	0.65	844	0.94	High confidence
Vemurafenib	TGFBR2	4514	0.75	3396	0.95	High confidence	XL-019	TBKBP1	1111	0.79	882	0.95	High confidence
Volasertib	PTMA	3	1.55	3	0.94	Low confidence	XL-019	PLK4	1783	0.51	908	0.89	High confidence
Volasertib	CAMKK2	293	0.66	195	0.95	High confidence	XL-019	PDGFRB	1279	0.87	1118	0.97	High confidence
Volasertib	PDXK	286	1.43	286	0.94	High confidence	XL-019	RET	3015	0.44	1328	0.94	High confidence
Volasertib	PTK2	1473	0.41	601	0.87	High confidence	XL-019	INPPL1	3075	0.48	1487	0.92	High confidence
Volasertib	NEK3	3469	0.85	2965	0.85	High confidence	XL-019	PIP4K2C	1759	0.91	1595	0.85	High confidence
Volitinib	NQO2	206	1.07	206	0.98	High confidence	XL-019	MARK3	2087	0.77	1609	0.96	High confidence
VX-702	MAPKAPK2	0.47	0.72	0.34	0.90	High confidence	XL-019	DYNLL2	3518	0.55	1922	0.94	High confidence
VX-702	ALK	3	0.85	2	0.99	Low confidence	XL-019	NEK9	4955	0.44	2186	0.93	High confidence
VX-702	MYLK	4	0.83	3	0.95	Low confidence	XL-019	EIF3J	2867	1.11	2867	0.97	High confidence
VX-702	MAPK11	6	0.72	5	1.00	High confidence	XL-019	PRKD3	3995	0.74	2957	0.96	High confidence
VX-702	MAPK14	13	0.51	7	0.98	High confidence	XL-019	CSNK2A1	3138	1.02	3138	0.87	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification	Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
XL-019	MARK2	4248	0.75	3200	0.96	High confidence	XL-228	FER	248	0.42	105	0.98	High confidence
XL-019	LIMK1	5453	0.59	3242	0.79	Low confidence	XL-228	PTK2B	285	0.41	118	0.97	High confidence
XL-019	CIT	3619	1.21	3619	0.92	High confidence	XL-228	MARK3	173	0.77	133	0.96	High confidence
XL-019	LATS1	4813	0.79	3790	0.94	High confidence	XL-228	SLK	155	0.89	138	0.80	High confidence
XL-019	ROCK2	4558	0.87	3974	0.86	High confidence	XL-228	AAK1	205	0.67	138	0.93	High confidence
XL-019	PDPK1	5376	1.04	5376	0.90	High confidence	XL-228	INSR	191	0.75	144	0.99	High confidence
XL-019	CSNK2A2	7426	0.96	7149	0.92	High confidence	XL-228	LCK	376	0.44	166	0.94	High confidence
XL-019	FLT3	23248	0.54	12492	0.78	High confidence	XL-228	EPHA4	270	0.62	167	0.88	High confidence
XL-019	CSNK2B	29169	1.08	29169	0.86	High confidence	XL-228	YES1	414	0.41	171	0.83	High confidence
XL-019	PRKD2	101422	0.66	66852	0.97	High confidence	XL-228	TNIK	184	1.02	184	0.60	Low confidence
XL-228	BCR	6	0.48	3	0.97	High confidence	XL-228	MARK2	261	0.75	196	0.81	High confidence
XL-228	AURKA	8	0.35	3	1.00	High confidence	XL-228	BMPR1A	384	0.53	203	0.97	High confidence
XL-228	PLK4	6	0.51	3	0.98	High confidence	XL-228	Q6ZSR9	268	0.76	204	0.95	High confidence
XL-228	TNK1	7	0.43	3	0.99	High confidence	XL-228	TBKBP1	258	0.79	204	0.92	High confidence
XL-228	AURKB	6	0.59	4	1.00	High confidence	XL-228	BMPR1B	345	0.61	212	0.99	High confidence
XL-228	CDK17	5	1.02	5	0.84	Low confidence	XL-228	DDR1	352	0.63	221	0.99	High confidence
XL-228	EPHA1	12	0.40	5	1.00	High confidence	XL-228	STK4	300	0.76	229	0.99	High confidence
XL-228	ACVR1	10	0.48	5	0.86	High confidence	XL-228	TGFBR1	334	0.69	231	0.86	High confidence
XL-228	FLT3	10	0.54	5	0.94	High confidence	XL-228	EPHB4	591	0.49	292	0.97	High confidence
XL-228	NTRK1	9	0.71	6	0.94	High confidence	XL-228	MAP4K2	597	0.59	352	0.92	High confidence
XL-228	ABL2	25	0.33	8	0.99	High confidence	XL-228	STK10	414	0.92	379	0.98	High confidence
XL-228	RET	20	0.44	9	1.00	High confidence	XL-228	PRKAA1	596	0.64	380	0.97	High confidence
XL-228	FGFR1	12	0.74	9	0.99	High confidence	XL-228	CDK3	429	2.15	429	0.79	Low confidence
XL-228	PKN1	12	0.87	11	0.93	High confidence	XL-228	SRC	1181	0.39	459	0.92	High confidence
XL-228	BMP2K	21	0.66	14	0.99	High confidence	XL-228	STK3	604	0.76	462	0.94	High confidence
XL-228	MAP4K1	21	0.73	15	0.96	High confidence	XL-228	ULK3	1084	0.45	492	0.90	High confidence
XL-228	EPHA7	22	0.79	17	0.84	High confidence	XL-228	MAP4K3	802	0.66	526	0.95	High confidence
XL-228	PTK2	55	0.41	22	0.99	High confidence	XL-228	MAP4K5	740	0.74	551	0.97	High confidence
XL-228	FYN	53	0.43	23	0.99	High confidence	XL-228	IGF1R	1139	0.66	754	0.97	High confidence
XL-228	EPHB6	42	0.61	26	0.63	High confidence	XL-228	MNAT1	1065	0.88	935	0.90	High confidence
XL-228	EPHA2	77	0.41	32	0.97	High confidence	XL-228	ERCC2	1053	0.90	953	0.97	High confidence
XL-228	INPPL1	74	0.48	36	0.78	High confidence	XL-228	TANK	1611	0.64	1025	0.95	High confidence
XL-228	TEC	111	0.40	45	0.98	High confidence	XL-228	CDK16	1119	0.94	1055	0.94	High confidence
XL-228	ABL1	138	0.55	75	0.99	High confidence	XL-228	SMARCE1	1078	1.16	1078	0.84	Low confidence
XL-228	TNK2	168	0.45	76	0.98	High confidence	XL-228	TBK1	1749	0.64	1118	0.99	High confidence
XL-228	IRAK3	187	0.43	80	0.95	High confidence	XL-228	CCNH	1567	0.76	1188	0.79	High confidence
XL-228	EPHA5	135	0.60	81	0.87	High confidence	XL-228	LYN	2646	0.50	1328	0.79	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
XL-228	PRKD2	2074	0.66	1367	0.75	High confidence
XL-228	IKBKE	2234	0.62	1387	0.98	High confidence
XL-228	CDK7	1982	0.73	1438	0.93	High confidence
XL-228	AZI2	2425	0.70	1702	0.89	High confidence
XL-228	SIK2	3465	0.52	1796	0.80	High confidence
XL-228	PRKD3	2508	0.74	1857	0.96	High confidence
XL-228	LIMK1	3476	0.59	2067	0.84	High confidence
XL-228	PRKCA	3125	0.73	2275	0.97	High confidence
XL-228	CAMKK2	3521	0.66	2339	0.73	High confidence
XL-228	MST1R	3106	0.76	2366	0.94	High confidence
XL-228	PHKG2	2482	0.97	2407	0.80	High confidence
XL-228	CSNK2A2	2530	0.96	2435	0.74	High confidence
XL-228	EPHB2	4780	0.52	2506	0.92	High confidence
XL-228	EIF3J	2619	1.11	2619	0.80	High confidence
XL-228	MAP3K11	4166	0.70	2902	0.98	High confidence
XL-228	CSNK2B	2906	1.08	2906	0.89	High confidence
XL-228	STK11	3647	0.84	3077	0.80	Low confidence
XL-228	EIF2AK1	3626	0.92	3342	0.78	High confidence
XL-228	CDK9	4935	0.71	3512	0.86	High confidence
XL-228	CCNT1	3778	0.98	3714	0.85	High confidence
XL-228	PRKAG1	6387	0.63	4042	0.81	High confidence
XL-228	MAP2K2	4212	1.17	4212	0.91	Low confidence
XL-228	DDR2	6513	0.76	4963	0.85	High confidence
XL-228	PRKAB1	7659	0.66	5070	0.86	High confidence
XL-228	CSNK2A1	5964	1.02	5964	0.69	High confidence
XL-228	HCK	12335	0.52	6394	0.90	High confidence
XL-228	MAP2K1	7032	1.23	7032	0.90	Low confidence
XL-228	BTK	40462	0.39	15816	0.92	Low confidence
XL-228	PAK4	83934	0.60	50438	0.88	Low confidence
XL-413	KLHL6	10	0.74	7	0.99	Low confidence
XL-413	CSNK2A1	9	1.02	9	0.99	High confidence
XL-413	CSNK2A2	23	0.96	22	0.97	High confidence
XL-413	PIM1	52	0.43	22	0.87	High confidence
XL-413	CSNK2B	26	1.08	26	0.96	High confidence
XL-413	EIF3J	35	1.11	35	0.96	High confidence
XL-413	DYRK1A	43	0.93	40	0.94	Low confidence
XL-413	TAOK3	2963	0.77	2292	0.91	High confidence
XL-413	CIT	3659	1.21	3659	0.94	High confidence
XL-413	GSK3B	18911	0.46	8793	0.82	Low confidence
Y-39983	ROCK1	9	0.91	8	1.00	High confidence
Y-39983	ROCK2	11	0.87	9	1.00	High confidence
Y-39983	CLK1	25	0.72	18	0.85	High confidence
Y-39983	PKN2	34	0.82	28	0.98	High confidence
Y-39983	CIT	33	1.21	33	0.98	High confidence
Y-39983	PRKCD	36	0.95	34	0.94	High confidence
Y-39983	CDC42BPB	35	0.97	34	0.96	High confidence
Y-39983	SIK3	86	0.82	71	0.95	High confidence
Y-39983	PRKCQ	90	1.23	90	0.92	High confidence
Y-39983	Q6ZSR9	140	0.76	106	0.95	High confidence
Y-39983	AAK1	181	0.67	122	0.97	High confidence
Y-39983	BMP2K	271	0.66	179	0.99	High confidence
Y-39983	PKN1	290	0.87	253	0.97	High confidence
Y-39983	CCNT1	264	0.98	259	0.90	High confidence
Y-39983	BMPR1A	643	0.53	340	0.82	Low confidence
Y-39983	AP2A1	565	0.92	519	0.79	Low confidence
Y-39983	PRKD2	868	0.66	572	0.98	High confidence
Y-39983	PRKD3	1030	0.74	762	0.97	High confidence
Y-39983	CSNK1A1	829	0.92	766	0.93	High confidence
Y-39983	CSNK1G3	994	0.79	782	0.81	High confidence
Y-39983	GSK3B	1988	0.46	924	0.68	High confidence
Y-39983	DCAF7	1052	0.90	943	0.86	High confidence
Y-39983	MAP4K4	946	1.01	946	0.78	High confidence
Y-39983	GSK3A	2205	0.50	1103	0.65	High confidence
Y-39983	AP2B1	1337	1.01	1337	0.96	Low confidence
Y-39983	CDK9	1904	0.71	1355	0.96	High confidence
Y-39983	TAOK1	3053	0.66	2030	0.88	High confidence
Y-39983	CSNK2B	2255	1.08	2255	0.92	High confidence
Y-39983	CSNK2A2	2850	0.96	2744	0.86	High confidence
Y-39983	PRKCA	4499	0.73	3276	0.91	High confidence
Y-39983	EIF3J	4861	1.11	4861	0.92	High confidence
Y-39983	PRKCB	7560	0.80	6032	0.93	High confidence
Y-39983	CSNK2A1	13148	1.02	13148	0.89	High confidence
Y-39983	PRKACA	49447	0.47	23245	0.81	High confidence
Y-39983	MARK3	49886	0.77	38457	0.95	High confidence

Drug	Gene Name	EC50	Correction Factor	Apparent Kd	R2	Target Classification
Y-39983	MAP3K5	63142	0.80	50536	0.82	High confidence