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Fischer, Peter M. (2017) Approved and experimental small-molecule oncology kinase inhibitor drugs: a mid-2016 overview. *Medicinal Research Reviews*, 37 (2). pp. 314-367. ISSN 1098-1128

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Approved and experimental small-molecule oncology kinase inhibitor drugs: a mid-2016 overview

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Abstract. Kinase inhibitor research is a comparatively recent branch of medicinal chemistry and pharmacology and the first small-molecule kinase inhibitor, imatinib, was approved for clinical use only 15 years ago. Since then, 33 more kinase inhibitor drugs have received regulatory approval for the treatment of a variety of cancers and the volume of reports on the discovery and development of kinase inhibitors has increased to an extent where it is now difficult –even for those working in the field– easily to keep an overview of the compounds that are being developed, as currently there are 231 such compounds, targeting 38 different protein and lipid kinases (not counting isoforms), in clinical use or under clinical investigation. The purpose of this review is thus to provide an overview of the biomedical rationales for the kinases being targeted on the one hand, and the design principles, as well as chemical, pharmacological, pharmaceutical, and toxicological kinase inhibitor properties, on the other hand. Two issues that are especially important in kinase inhibitor research, target selectivity and drug resistance, as well as the underlying structural concepts, are discussed in general terms and in the context of relevant kinases and their inhibitors.

Keywords: cancer, oncology, kinase inhibitor, experimental drug, drug design, clinical trials

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Introduction

Kinases are now one of the most important drug development target classes in several therapeutic indications, but until very recently all kinase inhibitors that were approved for clinical use were anticancer drugs, with the exception of fasudil, a (diazepanesulfonyl)isoquinoline ROCK inhibitor (for protein kinase nomenclature refer to Table S1).¹ Fasudil has been approved for some years in Japan for the treatment of certain cardiovascular indications² but even this agent –and ROCK inhibitors in general– may in fact also have potential uses in oncology.³ However, the situation changed with the U.S. Food and Drug Administration (FDA) approval in 2012 of the pyrrolopyrimidine JAK inhibitor tofacitinib for the treatment of rheumatoid arthritis.⁴ Again JAK inhibitors are also relevant in cancer, as we shall see later. At the time it was expected that the first kinase inhibitor approval outside oncology would act as a watershed and that pharmaceutical companies would accelerate kinase inhibitor development for a range of different therapeutic indications. In fact kinase inhibitors are undergoing clinical development in inflammatory, cardiovascular, neurodegenerative, liver, and metabolic diseases⁵ but since the approval of tofacitinib there has been only one additional approval outside oncology: nintedanib, a multi-targeted kinase inhibitor (MTKI), in idiopathic pulmonary fibrosis (IPF).⁶ Interestingly this compound was also approved in the European Union for lung cancer patients with advanced adenocarcinoma after first-line chemotherapy. Here we shall confine our discussion to kinase inhibitors in oncology, not only approved agents (Figure 1), but all compounds currently undergoing clinical development.

According to an analysis of new anticancer therapeutics that entered the clinic during the period 1990-2006, kinase inhibition was the most prevalent mode of action of experimental agents, whereas previously interference with DNA replication was the most common mechanism.⁷ A different analysis of new clinical oncology agents during a similar period (1995-2007) noted that while clinical development attrition was high (82%) overall, kinase inhibitors performed significantly better (53% attrition).⁸

Only a few years ago it was easy for those working in the field to keep track of the kinase inhibitor oncology drugs under development but the sheer number of agents that have recently entered clinical studies now renders this difficult. The main purpose of the present review is therefore to provide an up-to-date summary of some of approved and experimental (as verified in relevant publicly accessible literature, corporate disclosures, and <https://clinicaltrials.gov/>) kinase inhibitor cancer drugs. Salient points regarding kinase inhibitor targets, selectivity, medicinal chemistry, pharmacology, and toxicology will be discussed. Biological agents, including antibodies and antisense oligonucleotides, are not included but the focus is on small-molecule agents.

Selectivity

Following the success with the first approved small-molecule kinase inhibitor anticancer drug, imatinib (Figure 1),⁹ especially in the treatment of chronic myelogenous leukaemia (CML), highly specific targeted kinase inhibitors rapidly became a desirable goal in oncology drug discovery. However, demonstration of clear-cut clinical efficacy has been much more elusive with a range of other experimental kinase inhibitor drugs, and this situation has led to the on-going dispute about selective *versus* so-called multi-targeted agents.

The question is whether 'magic bullets' are preferable to 'magic shotguns'¹⁰ and arises not so much because one might be superior to the other, but because upon closer examination even the most carefully designed small-molecule kinase inhibitors often inadvertently turn out to be multi-targeted. In the early days of kinase inhibitor development it was not possible to profile the kinase selectivity of candidate molecules extensively, and unexpected kinase targets were frequently discovered for drugs late in the development process. This situation has changed with the advent of kinase panel¹¹ and chemical proteomics¹² technologies that permit kinome-wide analysis of candidate molecules.

Nevertheless, multi-targeted agents are frequently more efficacious than selective ones,¹³ although this may be due to selective drugs lacking efficacy because they block targets that are inappropriate *per se* or inappropriate for a specific cancer. Furthermore, network models suggest that partial inhibition of a small number of targets can be more efficient than the complete inhibition of a single target.¹⁴ Certainly the task of devising a kinase inhibitor that exclusively inhibits a range of predetermined kinases –which may not necessarily be structurally related– would appear to be formidable. Although strategies for the rational design of multi-targeted agents by multiple structure-based design and pharmacophore combination^{15,16} have been described, these have not yet been implemented widely for the design of kinase inhibitors with predetermined multiple selectivity.

Active versus inactive kinases. Because the vast majority of small-molecule kinase inhibitors target the ubiquitous ATP-binding site, target selectivity represents the biggest challenge for kinase inhibitor drug design and development. Protein and lipid kinases catalyse the transfer of the γ -phosphoryl group of ATP to their specific macromolecular substrates. This requires an architectural arrangement of the kinase to allow simultaneous binding of both substrates and positioning of the catalytic residues for productive phosphoryl-transfer. For protein kinases this canonical arrangement can be illustrated using PKA as an example (Figure 2). ATP is bound in a cleft between the N- and C-lobes of the kinase. These lobes are connected by the hinge region, which contains the so-called gatekeeper residue. The adenine portion of ATP forms H-bonds with the main-chain peptide bonds of the two hinge residues distal to the gatekeeper. The activation (A) loop adopts a conformation that supports binding of the macromolecular substrate and in which the side

chain of the Asp residue of the conserved DFG motif is positioned towards the ATP γ -phosphate (DFG in). Furthermore, the active (*i.e.* catalytically competent) kinase architecture is characterised by a near-linear arrangement of the regulatory (R) spine, which is composed of five residues (R0–R4) that interlock through H-bonding (R0–R1), CH– π (R1–R2–R3), and hydrophobic (R3–R4) interactions. Distortion of the linear spine, which contains residues from both the N- (R3 and R4) and C-lobes (R0, R1, and R2), is characteristic of inactive kinase architectures and can result from tilting of the kinase lobes about the hinge, by conformational preferences of the A-loop as a result of its phosphorylation status, or movement of the α C-helix or the catalytic (C) loop.

Classification of kinase inhibitors. Kinase inhibitors are classified using various criteria and several classification systems are in use. Here we shall use the integrated system recently proposed by Roskoski:¹⁷ Type-I inhibitors bind to the active kinase conformation with DFG-Asp in (towards the ATP-binding site), the α C-helix in, and with the R-spine in a linear configuration. Type-I½ inhibitors bind to kinases with an inactive (distorted R-spine) conformation with DFG-Asp in but α C-helix out. Type-II inhibitors also bind to inactive kinase conformations, but with DFG-Asp out. By division of the ATP-binding cleft into a front cleft and a back cleft (see below), type-I and type-II inhibitors can be further separated into A and B subtypes, where subtype A extends into the back cleft and subtype B does not. Allosteric inhibitors of type III bind in the cleft between the small and large kinase lobes but adjacent to the ATP-binding pocket, whereas type-IV inhibitors bind outside of the cleft and the phosphoryl-acceptor region. Allosteric ligands that span two regions of the protein kinase domain are type-V inhibitors. Compounds that form covalent adducts with a kinase are type-VI inhibitors.

X-ray crystal structures of complexes with type-I inhibitors generally show an active-like kinase conformation with the inhibitors bound at the same site as ATP but making contacts with kinase residues beyond those involved in binding of ATP. Such inhibitors also frequently recapitulate the hinge H-bonding pattern observed with ATP, using a variety of heterocyclic systems.¹⁸ Whereas binding of ATP does not usually depend on interactions with the gatekeeper, binding of inhibitors generally does. In type-I inhibitors selectivity arises from interactions of the inhibitor with non-conserved residues at the front (solvent-exposed; hydrophobic pocket I) and the back (towards gatekeeper; hydrophobic pocket II) of the binding cleft.

Type-II inhibitors are still ATP-competitive and bind to the ATP-binding pocket in a similar manner as type-I inhibitors but they bind to kinases with inactive architectures (disrupted R spine). These architectures possess altered A-loop conformations, where the DFG Asp residue side chain points away from the ATP γ -phosphate (DFG out) and the DFG Phe residue (R2) projects into the ATP-binding site. As a result, the R spine is disrupted and the kinase is not catalytically competent. Such a movement of the R2 side chain opens up

a new binding pocket (sometimes called the back cleft) beyond the gatekeeper and towards the α C-helix. Type-II inhibitors, which are typically larger than type-I inhibitors, usually extend into this pocket, which differs significantly between kinases.

Selectivity based on kinase inhibition potency. Inhibitor selectivity between kinase pairs is commonly expressed as a ratio (Figure 3a; selectivity index 1, SI_1) between measures of potency, such as half-maximal inhibition values (IC_{50}), inhibition constants (K_i), or dissociation constants (K_d). Biochemical kinase activity assays are generally used to determine IC_{50} values but it is important to remember that selectivity ratios for ATP-competitive inhibitors based on IC_{50} values can be misleading unless kinase assays are performed at ATP concentrations that give half-maximal reaction velocities for the kinases in question (*i.e.* $[ATP] = K_{M(ATP)}$). It is known that the ATP Michaelis constants ($K_{M(ATP)}$) for different kinases vary over a range of 3 orders of magnitude from low μ M to mM values.¹⁹ This is important because in cells, where the ATP concentration is typically as high as 1-5 mM, the potency of an inhibitor against a given kinase is highly dependent on the $K_{M(ATP)}$ of that kinase. For this reason K_i values are more useful for selectivity measurements, since these take into account $K_{M(ATP)}$: $K_i = IC_{50} / (1 + ([ATP] / K_{M(ATP)}))$.²⁰ K_d values are typically determined using biophysical binding assays rather than functional kinase assays. Provided assay conditions are similar (concentrations of protein and substrates) then K_d and K_i values are also numerically similar.

It is sometimes stated that type-II inhibitors are not ATP competitive and that for this reason the drop-off in cellular potency from biochemical potency is frequently smaller than is the case for type-I inhibitors.²¹ This is not entirely correct, since inactive forms of kinases can still bind ATP, although the difference in $K_{M(ATP)}$ between inactive and activated (phosphorylated) kinase forms can be large.¹⁹ The ratio of biochemical and cellular potency of a kinase inhibitor will therefore depend on whether it competes with ATP for the active or an inactive state of the target kinase, and in the latter case on the $K_{M(ATP)}$ of the inactive state. Regardless of inhibition mode, the relationship between biochemical and cellular potency is of course also affected by factors such as solubility, protein binding, and membrane permeability.

Selectivity based on receptor occupancy. For kinase inhibitor drugs we are interested not so much in selectivity based on differential kinase affinity under equilibrium conditions (SI_1), but in selectivity under physiological conditions *in vivo*. Here we need to take into account that the magnitude of physiological responses is proportional to the amount of inhibitor bound by a particular kinase over time. To assess true selectivity of kinase inhibitors it is therefore more useful to look at fractional kinase (receptor) occupancy as a function of time (f_{o_t}). Based on this we can formulate a second selectivity index (Figure 3a; SI_2).

For a type-I kinase inhibitor that reversibly binds a kinase by mechanism A, f_{o_t} depends on ligand concentration and K_d as shown in Figure 3a. To illustrate the relationship between SI_1 and SI_2 , let us assume that we have kinase inhibitors that all bind a particular on-target kinase with a K_d value of 10 nM but that bind an undesirable (leading to toxicity) off-target kinase with K_d values of 50 nM ($SI_1 = 5$), 250 nM ($SI_1 = 25$), 1 μ M ($SI_1 = 100$), and 10 μ M ($SI_1 = 1,000$), respectively. If we assume that these hypothetical kinase inhibitors have identical pharmacokinetic profiles and are dosed repeatedly so as to achieve continuous exposure, measured as the concentration of free drug fraction at steady state (C_{ssf}), then we can substitute C_{ssf} for $[L]_t$ in the expression for f_{o_t} and evaluate SI_2 as a function of C_{ssf} . This analysis (Figure 3b) shows that at $C_{ssf} = K_{d(\text{on-target})} = 10$ nM we have approximately 50% on-target receptor occupancy. At that C_{ssf} value we have SI_2 values of 3, 13, 50, and 500 for the inhibitors with SI_1 values of 5, 25, 100, and 1,000, respectively. Depending on how physiological responses are coupled to on-target kinase occupancy, we may require much higher f_o to achieve efficacy. If 90% occupancy is required ($f_{o_{\text{on-target}}} = 0.9$, $C_{ssf} = 90$ nM), then the SI_2 values for our inhibitors are 1.4 ($SI_1 = 2.5$), 3.4 ($SI_1 = 25$), 11 ($SI_1 = 50$), and 100 ($SI_1 = 1,000$), respectively. Depending on how off-target kinase occupancy is coupled to toxicity, the drop-off from SI_1 to SI_2 may be smaller or larger but the relationship between selectivity in terms of binding *versus* occupancy as a function of C_{ssf} clearly shows that an inhibitor with an SI_1 value of < 100 is unlikely to provide a useful margin between on- and off-target activities *in vivo*.

Selectivity based on residence time. High-affinity kinase inhibitors, especially those of type II, frequently exhibit slow binding kinetics. This is due to induced-fit binding, where the kinase undergoes a time-dependent change from a conformation R to a conformation R*, where the latter has higher affinity for the ligand L than the former (Figure 3a; mechanism B). Here dissociation (off-rate) and residence time are not defined by a single rate constant as in mechanism A, but by a composite of rate constants, where k_4 (and sometimes k_2) are limiting for dissociation. For inhibitors that bind kinases in inactive-like conformations, mechanism C is sometimes invoked, especially when these inhibitors selectively bind the kinase in its A-loop non-phosphorylated state. There are currently insufficient kinetic data to distinguish clearly between inhibitors that act by mechanisms B and C, however.²²

In any case, the situation often arises where an inhibitor exhibits kinase residence time that is significant in comparison to its *in vivo* elimination half-life. Under these conditions receptor occupancy can be maintained at levels leading to pharmacological responses even after a drug has been largely eliminated from systemic circulation. Under these circumstances we need to take the dynamics of binding into account when assessing selectivity. To illustrate this point let us assume that we have a kinase inhibitor that interacts with 3

target kinases and that the rate constants k_1 ($1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, *i.e.* 10-fold below the diffusional limit), k_2 (1 s^{-1}), and k_3 ($6 \times 10^{-3} \text{ s}^{-1}$) are identical in each case, and that only k_4 varies: $8.5 \times 10^{-3} \text{ s}^{-1}$ (target 1), $2.8 \times 10^{-4} \text{ s}^{-1}$ (target 2), and $1.26 \times 10^{-5} \text{ s}^{-1}$ (target 3), *i.e.* typical values for type-I, type-II, and covalent reversible type-VI inhibitors.^{17,23} With these values we have residence times τ of 2 min (target 1), 1 h (target 2), and 22 h (target 3). If we further assume that the inhibitor was dosed orally once, reaching a maximum plasma concentration (C_{max}) of 10 μM and being eliminated with a half-life of 3 h, then we can calculate free plasma levels, as well as f_{ot} with respect to the 3 targets, as a function of time as shown (Figure 3c). This analysis reveals that here selectivity is not driven by apparent affinity under equilibrium, but by residence time. Thus > 50% receptor occupancy is maintained for up to 12 h (target 1), 24 h (target 2), and 36 h (target 3). For targets 2 and 3, significant receptor occupancy persists at a time when plasma levels would be undetectable using conventional bioanalysis methods (24 h, $C_{\text{f}} = 4.2 \times 10^{-10} \text{ M}$). Because the inhibitor dissociates from target 3 much more slowly than for targets 1 and 2, it can be expected to be functionally selective for target kinase 3. Again the exact situation will depend on the magnitude and duration of receptor occupancy required to elicit physiological responses from the 3 targets, but it is clear that residence time is important in terms of selectivity and should be considered in the drug discovery process.²⁴

Target validity

It is important to remember that the pioneer kinase inhibitor drug imatinib itself is not mono-selective for BCR-ABL, the oncogenic kinase uniquely present in chronic myelogenous leukaemia (CML), but also inhibits a range of other kinases with high potency. Clearly the therapeutic effectiveness of imatinib in CML is not principally a result of drug selectivity, but the vital dependence of CML cells on BCR-ABL kinase activity. So for the narrow *versus* broad drug selectivity discussion to make any sense, we need to consider target validity.

If pharmacological modulation of a specific cellular component is sufficient to eradicate a diagnostically distinct cancer type, then surely an agent highly selective for that target should be preferable to a more promiscuous one on basic pharmacological grounds. If, on the other hand, the viability of a particular cancer type only appears susceptible to interference with two or more aberrant components, then multi-targeted agents would seem to be called for. Because we want to devise new cancer therapies that are inherently less toxic than conventional chemotherapies, the important thing is specificity for cancerous cells rather than inherent target selectivity.

If we accept the premise that at least for some cancer indications modulation of multiple targets is necessary to achieve the desired therapeutic effect, then the question that poses itself is whether it would be better to employ an appropriate cocktail of highly selective

drugs or a single multi-targeted drug.^{25,26} Considering the complexity of human cancers, one would expect that the availability of a range of highly targeted agents would allow a more effective and modular approach to personalised therapy than multi-targeted agents. However, combination therapies are prone to dosing errors and drug–drug interactions.²⁷ Furthermore, highly targeted drugs by definition will not find broad chemotherapeutic application but will only work in the (perhaps small) subset of cancers that possess the specific targeted molecular lesion, whereas multi-targeted drugs may find wider therapeutic use, *i.e.* they may be preferable commercial propositions for pharmaceutical companies.

As it turns out, the main clinical indication for imatinib, CML, is unusual since most cancers, especially non-haematological tumours, including *e.g.* common epithelial neoplasms of the lung, breast, colon, and prostate, display a much more complex transformed genotype than CML and may lack the critical vulnerability centred on a single cellular component characteristic of early-stage CML. In fact mouse models suggest that the *BCR-ABL* translocation is the only genetic abnormality required to cause CML.²⁸ It thus follows that imatinib probably represents an exception rather than a new paradigm in the area of kinase inhibitors.²⁹

However, target validation work in several areas suggests that there are probably many other cancers that may also possess therapeutic Achilles heels. Typically this situation arises as a result of oncogene addiction, *i.e.* the apparently paradoxical dependence of a tumour cell for sustained proliferation and survival on a single oncogenic pathway or protein, despite the presence of numerous genetic alterations.³⁰ A number of such oncogene addictions have been identified and frequently the relevant oncogene products are kinases.^{31,32} Such kinases are attractive as cancer drug targets, and several are now being targeted with experimental drugs, *e.g.* BRAF in melanoma, HER2 in breast cancer, HER1 in non-small cell lung cancer (NSCLC), MET in gastric cancer, and ARK in colon cancer. However, unlike in the case of CML, these addictions are not usually present in all cancers of a particular histological type, but the potentially responsive cancers need to be identified by examination of appropriate biomarkers.

Drug resistance

Although not themselves mutagenic like many conventional chemotherapy agents, kinase inhibitor drugs, just like most anticancer drugs, are nevertheless prone to both intrinsic and acquired resistance. The manifestation of drug resistance in at least a proportion of cases involves direct mutation of the target kinase in such a way that function is preserved, while inhibition by the drug is circumvented. Although it remains unclear how these mutations are caused, it is likely that genetic selection for insensitive target kinase mutants under the influence of the kinase inhibitor drug plays a role. This phenomenon was first

observed with imatinib and is in part responsible for the current emphasis on MTKIs, which may not be vulnerable to the same extent to this selection pressure.³³

In the case of the HER1 inhibitors gefitinib and erlotinib, which are used for the treatment of NSCLC with certain somatic mutations in the *HER1* Tyr kinase or with amplified wild-type *HER1*, it has also been observed that all patients eventually develop resistance, either through a secondary *HER* mutation T790M in about half of all cases, by *MET* oncogene amplification, or *via* other mechanisms.³⁴ The *HER1* T790M mutation concerns the gatekeeper residue (Thr in most Tyr kinases), which is not required for the binding of the natural cofactor ATP, but which is almost invariably involved in the recognition of ATP-antagonist kinase inhibitors. Resistance to HER2 inhibitors in breast cancer are also frequent and also develops through multiple mechanisms but unlike for HER1 inhibitors, *e.g.* lapatinib resistance due to the HER2 gatekeeper T798I mutation, appears to be less prevalent.³⁵ Resistance mutations corresponding to those observed with HER Tyr kinase inhibitors are known to be important in the case of many other kinases and their inhibitors, as we shall see later.

It has long been known that cancer cells can develop drug resistance much more rapidly than would be predicted from the rates of conventional mutation, by differential utilisation of the genome, while normal cells in the same organism remain sensitive. There is now much evidence that not only point mutations, but also deletions, translocations, amplifications, epigenetic changes, and even altered microRNA levels, can generate cancer cell progeny tolerant to individual or multiple drugs.³⁶ It is also now believed that clonal karyotype alterations are generated auto-catalytically by cancer-specific aneuploidy and that these specific chromosomal alterations cause drug resistance by changing the stoichiometry and integrity of multigenic transcriptomes.³⁷ Even in the case of imatinib over half of all resistance cases are associated with clonal karyotype alterations rather than kinase mutations.³⁸

Toxicology

For the discussion of kinase inhibitor toxicology we need to return to the question of selectivity. Provided a hypothetical mono-selective kinase inhibitor anticancer drug does not give rise to toxic metabolites, one would expect such a compound to possess a clean toxicology profile. Obviously this will only be the case, however, if on-target effects in tissues other than the tumour can be tolerated. Again we can use the pioneer kinase inhibitor drug imatinib to illustrate this point. Although one of the targets of imatinib, BCR-ABL, is uniquely present in transformed granulocytes as a result of an oncogenic chromosomal translocation, the normal non-fused ABL kinase, which is widely expressed in the body, is of course also inhibited by imatinib. This kinase turns out to be especially important for cardiomyocyte function and survival, and ABL inhibition has been identified as the root

cause of the cardiotoxicity of imatinib.³⁹ Similarly, hypo-phosphataemia is probably another on-target toxicity of imatinib, resulting from inhibition of PDGFR kinase activity in osteoclasts.⁴⁰

Various other toxicities are target-related, such as the skin toxicity of HER inhibitors.⁴¹ Dermatological toxicities are also a feature of the multi-targeted kinase inhibitor sorafenib, currently approved for the treatment of metastatic clear-cell renal cell carcinoma and hepatocellular carcinoma, but it is not understood if this is target-related.⁴² Animal studies show that chronic pharmacologic inhibition of HER leads to cardiac dysfunction.⁴³ Cardiac toxicity –drugs causing heart muscle valve damage or potentially fatal arrhythmias– has been implicated in 28% of drug withdrawals in the USA over the last 30 years. That cardiac and skin-related toxicities have been observed for many Tyr kinase inhibitors both in oncology and other indications suggests the possibility of a class effect.⁴⁴ Another on-target toxicity is hyperglycaemia, which has often been reported as a side effect of agents targeting IGF-IR, PI3K, AKT, and mTOR. All these kinases are important components of the insulin signalling pathway and their inhibition leads to altered hepatic glycogen metabolism and blockage of peripheral glucose uptake. It was shown recently, however, that drug-induced hyperglycaemia might be attenuated by decreasing liver glycogen storage using fasting, combined with a low-carbohydrate diet.⁴⁵

Approved and experimental kinase inhibitor drugs

An overview of approved and experimental oncology kinase inhibitor drugs is given in Figure 4 and individual agents are discussed below by the kinases they act on. Details for compounds are summarised in Tables S2-S29.

BCR-ABL kinase. The *BCR-ABL* oncogene is generated in CML by the so-called Philadelphia chromosome that results from a reciprocal translocation that juxtaposes the Abelson murine leukaemia viral oncogene homolog 1 (*ABL*) gene with the breakpoint cluster region (*BCR*) gene.⁴⁶ Since its approval, the first ABL kinase inhibitor imatinib has been used successfully in the control of progression from CML chronic phase to blast crisis. Whereas median survival in CML was 3 to 6 years prior to the clinical use of imatinib, a 10-year survival rate of 68% has been reported for patients with CML who receive imatinib after failure of interferon.⁴⁷

A 2nd generation of ABL inhibitors has now been approved: dasatinib and nilotinib, predominantly because many patients with CML undergo clinical relapse due to resistance to imatinib while these new agents are effective against most imatinib-resistant *BCR-ABL* mutants (Figure 5).⁴⁸ Neither imatinib nor the 2nd-generation ABL inhibitors are selective, but also inhibit a range of other kinases, especially PDGFR and SCFR. In fact some of these agents have been used in the treatment of dermatofibroma sarcoma protuberans (DFSP)

and gastrointestinal stromal tumours (GIST), in which disorders PDGFR and SCFR, respectively, are implicated.⁴⁹

Bosutinib is a 3rd generation ABL inhibitor. Like the 2nd-generation inhibitors, it is also active against the majority of imatinib-resistant *BCR-ABL* mutants, but it is a much more selective inhibitor, with only SRC kinases as significant additional targets.⁵⁰ The other approved 3rd-generation inhibitor, ponatinib, on the other hand, is a multi-targeted kinase inhibitor, but it is the only approved ABL inhibitor that has activity against the imatinib-resistant T315I gatekeeper BCR-ABL mutant kinase (Figure 5).⁵¹ Another BCR-ABL inhibitor, radotinib (structurally closely related to imatinib), was approved in South Korea in 2012.

Although there are currently six approved ABL inhibitors used successfully for the treatment of CML, there are at least another two ABL inhibitors at various stages of clinical development, including flumatinib (another compound closely related to imatinib) and ABL 001, an allosteric (type IV) inhibitor that targets the myristoyl-binding site in the SH1 catalytic kinase domain (Table S2).

SRC kinases. A number of ABL kinase inhibitors approved in CML, such as dasatinib, nilotinib, bosutinib, and ponatinib also inhibit the closely related SRC kinases. SRC family kinases are cytosolic Tyr kinases that have a multitude of functions in cellular signal transduction, whose activated forms are aberrantly expressed in many solid tumours, especially metastatic cancers.⁵² This has led to clinical evaluation of such dual ABL and SRC agents, including saracatinib and AZD 0424 (closely related compounds that share the (6-chloro-2*H*-[1,3]dioxolo[4,5-*b*]pyridin-7-yl)aminoquinazolin-7-yl substructure), in advanced solid tumours such as NSCLC, as well as in lymphomas.⁵³ Saracatinib is also currently being evaluated in Alzheimer's disease as an inhibitor of the SRC family kinase FYN, which is implicated in the pathogenesis of this disease.⁵⁴ The most SRC-selective experimental kinase inhibitor drug (Table S3) appears to be a compound known as KX 01, which is a type-III kinase inhibitor, *i.e.* a peptidomimetic of SRC kinase substrate peptides (Figure 6).

To date, therapeutic success in clinical trials of SRC kinase inhibitors has been limited and it has been postulated that a paradigm shift is required in clinical trial design for such agents in terms of patient selection, biomarker development, and rational design of combinatorial regimens with SRC inhibitors.⁵⁵ However, recent insights suggest that highly selective SRC kinase inhibitors may possess significant advantages over dual ABL/SRC inhibitors, since tumour suppressor signalling through ABL appears to occur at least in some cancers.⁵⁶ Inhibitors that are highly selective for SRC over ABL have recently been reported, and the clinical development of such compounds may overcome this issue, as well as the cardiotoxicity associated with ABL inhibition.⁵⁷

Epidermal growth factor receptor kinases. The EGFR Tyr kinase family consists of four transmembrane receptors, HER1–4, and signalling through this receptor family is important for many cell functions and for cell survival. At least HER1–3 are involved in tumorigenesis, and hetero-dimerisation of these receptors plays an important role in their function.⁵⁸ Inhibitors of the EGFR Tyr kinase family have been studied mostly in breast cancers and NSCLCs driven by HER2 and HER1, respectively. As a consequence, activating mutations in *e.g.* *EGFR* (such as exon 19 in-frame deletions and L858R point mutations) serve not only as the rationale for the use of EGFR Tyr kinase inhibitors, but also as biomarkers for patient selection.⁵⁹ Of the approved EGFR inhibitors, both gefitinib and erlotinib (Figure 7b) are HER1-specific and are used in NSCLCs, many of which overexpress HER1.⁶⁰

The trend in new EGFR Tyr kinase inhibitors is now towards pan-HER-targeted compounds, including the approved agent lapatinib (Figure 7d), which inhibits both HER1 and HER2 and is used for the treatment of advanced HER2-positive breast cancer.⁶¹ Icotinib, which is approved in China, is also an inhibitor of both HER1 and HER2. Although HER2 lacks an extracellular ligand-binding domain, it is nevertheless involved in hetero-dimerisation with other ligand-bound EGFR partners. Because EGFR signalling that affects cell proliferation and survival depends on both HER1 and HER2, inhibitors that block the catalytic activity of both have been sought, in the hope of enhanced clinical efficacy. However, clinical studies of pan-HER inhibitors have been difficult due to a narrow therapeutic margin with such agents, with dose-limiting on-target pan-HER toxicities such as diarrhoea and skin rash.⁶² Although the HER2-specific antibody drug trastuzumab has been used successfully in HER2-overexpressing breast cancer for some time,⁶³ it is perhaps surprising that more progress has not been achieved to date with HER2-selective small-molecule kinase inhibitors. Highly HER2-selective inhibitors are in fact known (Figure 7c),⁶⁴ but none seem to be under clinical evaluation at present.

Both acquired and innate drug resistance appear to play an important role in limiting the response rates to EGFR Tyr kinase inhibitor drugs. The comparatively unique presence of an unpaired Cys residue in the ATP-binding pocket of the EGFR Tyr kinases has allowed the development of irreversible ATP-site inhibitors.⁶⁵ In preclinical studies it has been shown that cancers that have become resistant to gefitinib and erlotinib through the secondary *EGFR* T790M mutation (in *ca.* 60% of cases) remain sensitive to 2nd-generation type-VI inhibitors.⁶⁶ This, and the observation that such inhibitors may be less likely to induce drug-resistant kinase mutants, might be due to the fact that covalent inhibitors can still block a mutant kinase that has reduced affinity for non-covalent inhibitors, because with covalent binders inhibition is rate- rather than affinity-driven.⁶⁷ Two such agents that can overcome T790M mutation, afatinib (Figure 7f) and osimertinib (Figure 7g), were re-

cently approved in metastatic NSCLC. Afatinib is a pan-HER inhibitor that blocks the catalytic activity of HER1, HER2, and HER4, as well as phosphorylation of the EGFR-transsignalling partner HER3,⁶⁸ which is itself kinase-inactive.⁶⁹ Osimertinib, on the other hand, is selective for T790M-mutant HER1, as well as L858R and exon-19 deletion mutant forms of HER1. Because osimertinib spares wild-type HER1, it may have reduced toxicity compared to afatinib and other EGFR inhibitors used in NSCLC.^{70,71}

Apart from the six small-molecule EGFR Tyr kinase inhibitors already approved, no fewer than four type-VI inhibitors are currently in late-stage clinical development, including dacomatinib and neratinib (pan-HER and T790M HER1), as well as ASP 8273 and rociletinib (T790M HER1-selective). At least another 16 agents, with varying selectivity profiles, are undergoing clinical development (Table S4).

CSF1/PDGF receptor subfamily kinases (Table S5). The CSF1/PDGF Tyr kinase subfamily contains a number of closely related kinases that are relevant to cancer, including CSF1R, VEGFR/FLT, PDGFR, and SCFR (c-Kit). Vascular endothelial growth factors (VEGFs) act on three main receptor Tyr kinase receptors, *i.e.* VEGFR1, VEGFR2, and VEGFR3, whereas platelet-derived growth factors (PDGFs) act on the PDGFR α and PDGFR β receptors, which contain similar Tyr kinase domains. Both VEGFRs and PDGFRs activate cellular proliferation and survival signalling pathways, such as the RAF–MAP–MEK–ERK and the PI3K–AKT pathways. These receptors are implicated in tumour angiogenesis, metastasis, and progression.^{72,73}

All currently approved (and many of the late-stage development) compounds that inhibit CSF1/PDGF Tyr kinases are MTKIs and contain some of the original kinase inhibitor core templates,⁷⁴ *e.g.* sunitinib and nintedanib are 3-methylidene-2-oxo-1*H*-indoles, vandetanib is a 4-(anilino)quinazoline, and pazopanib is a bis(arylamino)pyrimidine. These agents are variously used in the treatment of advanced renal cell carcinoma (sunitinib, axitinib, pazopanib), gastrointestinal stromal tumours (sunitinib), advanced or metastatic pancreatic neuroendocrine tumours (sunitinib), advanced soft tissue sarcoma (pazopanib), late-stage medullary thyroid cancer (MTC; vandetanib), and progressive, radio-iodine-refractory differentiated thyroid cancer (lenvatinib). Nintedanib is another approved MTKI with activity against CSF1/PDGF kinases. It received its first global approval not in oncology but for the treatment of IPF. The activity in this indication may be linked to the ability of nintedanib, amongst other kinases, potently to inhibit FGFR Tyr kinases, as aberrant FGFRs appear to contribute to the pathogenesis of IPF (see below).⁷⁵ Nintedanib is also now used for the treatment of advanced, metastatic NSCLC in combination with docetaxel. Numerous additional VEGFR inhibitors with varying selectivity profiles are now being developed. *E.g.* fruquitinib and cediranib are selective pan-VEGFR/PDGFR inhibitors.

Although there is abundant evidence that angiogenesis inhibitors can suppress tumour development in preclinical models, recent findings show that pharmacological as well as genetic VEGFR suppression can in fact alter tumour development by increasing invasion and metastasis.^{76,77} In the clinic, the response to VEGFR inhibitors is often limited and followed by disease progression that is at least in part due to tumour escape as a result of VEGFR inhibition. For these reasons research and clinical trialling of drug combination strategies that may prevent such escape mechanisms are on-going.⁷⁸

Closely related to the VEGFR Tyr kinases is FLT3, which is commonly overexpressed in most B-lineage leukaemias (acute lymphocytic leukaemia, ALL; acute myelogenous leukaemia, AML), in subsets of T-cell ALL, and CML in blast crisis. Furthermore, FLT3 activating mutations are present in about a third of AML patients.⁷⁹ A number of multi-targeted CSF1/PDGF TK inhibitors with activity against FLT3 are being developed, *e.g.* midostaurin, AKN 028, and PLX 7486. Quizartinib, a benzo[*d*]imidazo[2,1-*b*]thiazol-2-yl)phenyl)urea compound, is an example of a late-stage selective type-II⁸⁰ FLT3 inhibitor being trialled in the treatment of ALL.⁸¹ Unusually for a type-I TK inhibitor, crenolanib has high selectivity for FLT3, SCFR, and PDGFR kinases, including resistance-conferring kinase domain mutant forms.⁸² This finding supports the emerging notion that type-II inhibitors may not necessarily be intrinsically more selective than type-I inhibitors, as has been thought in the past.⁸³

Among the CSF1/PDGF Tyr kinases is SCFR. Oncogenic signalling from mutant *KIT* is especially common in GIST⁸⁴ and currently the standard therapy for unresectable or metastatic GISTs is first-line imatinib, second-line sunitinib, and third-line regorafenib.⁸⁵ All three of these agents are MTKIs that were originally developed for alternative indications, but more selective SCFR inhibitors are also now being developed, *e.g.* crenolanib and PLX 9486. The D816V *KIT* activating mutation occurs in > 90% of patients with systemic mastocytosis and whereas imatinib is not efficacious in this indication, dasatinib has been shown to be active.⁸⁶

CSF1R is a cell-surface receptor for both macrophage colony-stimulating factor-1 (CSF1) and interleukin-34. It plays an important role as a regulator of tissue and tumour-associated macrophages.⁸⁷ Because CSF1R activation promotes tumour progression through suppression of the anti-tumour immune response, as well as promotion of angiogenesis and metastasis, CSF1R inhibitors may be particularly useful in many cancer indications. In fact many MTKIs from the CSF1/PDGF class also inhibit CSF1R and this activity may contribute to their efficacy. However, selective CSF1R inhibitors are also now under development, *e.g.* pexidartinib and ARRY 382 (undisclosed structure).

Fibroblast growth factor receptor kinases. The four isoforms (FGFR1-4) of this receptor Tyr kinase family are structurally and functionally related to the HER family and bind

diverse FGF ligands. FGFR signalling appears to be implicated in the pathogenesis of several cancers and *FGFR* aberrations are frequent (7.1% of cancers), especially in urothelial, breast, endometrial, and lung cancers. Apart from finding potential therapeutic application against tumours with *FGFR* genetic alterations, FGFR inhibitors may also be useful to overcome resistance against HER inhibitors, as alternative signalling through the FGFR pathway apparently represents an important escape mechanism when HER signalling is suppressed. Conversely, FGFR kinase inhibitors may be able to potentiate HER inhibition.⁸⁸

Many of the approved MTKIs in the CSF1/PDGF class also inhibit FGFR kinases but more selective FGFR kinase inhibitors are also now under development. AZD 4547, infigratinib, and erdafitinib (Figure 8a) are potent and selective pan-FGFR inhibitors currently undergoing phase-II trials in a range of cancers. Another 7 FGFR kinase inhibitors (structures not disclosed) are currently in phase-I trials (Table S6). At least two of these are irreversible inhibitors (PRN 1371; TAS 120, refer Figure 8e), whereas another is an isoform-selective FGFR4 inhibitor (FGF 401).

One of the mechanisms of acquired resistance to FGFR inhibition is gatekeeper mutation. Thus V561M mutation in FGFR1 confers significant resistance to *e.g.* lucitanib (Figure 8c) but not dovitinib (Figure 8d). Interestingly AZD 4547 retains affinity for the V561M mutant FGFR1 by adopting an alternative binding mode in which the flexible dimethoxyphenethyl group –which is in contact with the wild-type V561 gatekeeper– is able to bend away from the larger M561 gatekeeper in the mutant kinase.⁸⁹

Hepatocyte growth factor receptor kinase (HGFR or MET). The MET Tyr kinase is a cell-surface receptor for hepatocyte growth factor, whose downstream signalling pathways are important for invasive growth in terms of motility, proliferation, and protection from apoptosis. These processes are important in embryonic development and tissue morphogenesis but often become reactivated in cancer, especially in tumour metastasis. Constitutive *MET* activation is a feature of many cancers,³² including NSCL carcinomas with acquired resistance to EGFR inhibitors.⁹⁰ *MET* amplification can be a primary or secondary transformation event and *e.g.* in some patients with colorectal carcinomas, *MET* amplification has been observed not in primary tumours, but in liver metastases.⁹¹

The first MET Tyr kinase inhibitor to be approved for the treatment of patients with progressive metastatic MTC is cabozantinib, a MTKI with MET and VEGFR2 as its main targets.⁹² A range of functionally different (Figure 9) selective and MTKI MET inhibitors are currently under clinical evaluation in a number of cancers, including NSCLC resistant to EGFR inhibitors.⁹³ The most advanced of these is tivantinib, a highly selective MET inhibitor. Second-generation inhibitors that are active against mutant forms of MET, such as tepotinib, are also being developed (Table S7).

Anaplastic lymphoma kinase (Table S8). ALK is a receptor Tyr kinase in the insulin receptor family and *ALK* rearrangement is second only to *HER* mutation as an oncogene addition in NSCLC. Modification of *ALK* is present in only a small proportion of NSCLC patients but specific targeting of this population for treatment with ALK inhibitors is particularly effective.⁹⁴ The first ALK inhibitor approval in NSCLC was crizotinib, a MTKI originally discovered and developed as a MET inhibitor and now prescribed successfully as first- or second-line therapy in ALK-positive NSCLC. *ALK* rearrangements also occur in > 50% of anaplastic large cell lymphomas (ALCLs) and crizotinib has been shown to have clinical activity in advanced chemoresistant ALCL.⁹⁵

The development of acquired resistance is the main reason why patients with ALK-positive NSCLC eventually relapse on crizotinib. Secondary resistance mutations in the ATP-binding site have been identified⁹⁶ and one of the main drivers for the development of second-generation ALK inhibitors has been to overcome crizotinib resistance.⁹⁷ Ceritinib was approved later and is a more potent ALK inhibitor that overcomes the most common secondary mutation to crizotinib (gatekeeper L1196M), as does the recently approved selective ALK inhibitor alectinib.

These second-generation ALK inhibitors also show activity against brain metastases, which is important, as almost half of ALK-positive NSCLC patients on crizotinib exhibit such metastases, even when systemic disease is under control.⁹⁸ Three more third-generation ALK inhibitors are currently undergoing clinical evaluation: brigatinib, belizatinib, and lorlatinib. At least the latter compound was designed specifically to have high CNS penetrance (Figure 10).⁹⁹

IGF1R and IR. The insulin-like growth factor 1 (IGF1) signalling pathway regulates many aspects of the proliferation, differentiation, and growth of normal cells. However, its receptor, IGF1R, as well as its ligands and adaptor proteins, are highly expressed in many malignancies. Furthermore, the IGF1 pathway is also implicated in carcinogenesis and cancer risk. IGF1R activates the RAS-RAF-MAPK and PI3K-AKT-mTOR pathways, both of which are associated with cancer cell proliferation and survival. For these reasons IGF1R inhibitors have been developed, especially in NSCLC.¹⁰⁰ The first generation of IGF1R inhibitors that have been tested in clinical trials are humanised monoclonal antibodies that block ligand binding to IGF1R. Although early results were promising, later studies using combinations with chemotherapy or EGFR inhibitors in NSCLC have been disappointing.^{101,102} Currently the only clinical small-molecule IGF1R inhibitor targeted at the Tyr kinase activity of this receptor is the phenylquinoline compound linsitinib, a dual IGF1R and insulin receptor (IR) inhibitor (Table S29).

Tropomyosin receptor kinase (Table S9). TRK was originally identified as an oncogene product that arises as a result of mutations and rearrangements of the *NTRK* genes and has been detected in various tumours, especially in the colon, the lung, and the thyroid

gland.¹⁰³ The three isoforms of wild-type TRK are expressed predominantly in neurons, however, where their activation by neurotrophins plays important roles in cell development, maintenance, and function. It is now clear that TRKs also regulate processes in non-neuronal cells. Furthermore, activation of cell survival pathways through TRKs contributes to tumorigenesis and resistance to cytotoxic chemotherapy not only in neuroblastoma, but also in many other cancers.¹⁰⁴ The TRKs belong to the same insulin receptor Tyr kinase subfamily as ALK and ROS, and entrectinib, a pan-TRK inhibitor with additional potent ALK and ROS inhibitory potency, is currently undergoing phase-II trials in colorectal carcinoma and NSCLC.¹⁰⁵ Another agent at a similar stage of development is LOXO 101, a selective pan-TRK inhibitor. Entrectinib and LOXO 101 are structurally related, the former contains an indazole, the latter a pyrazolo[1,5-*a*]pyrimidine core, both compounds containing a *meta*-difluorophenyl substituent.

AXL belongs to the TYRO3, AXL, and MERTK (TAM) family of receptor Tyr kinases and although it does not appear to be a strong oncogenic driver, it is overexpressed in many tumours and overexpression correlates with poor prognosis. Aberrant TAM signalling in cancer suggests that AXL inhibitors may confer anti-tumour immunity and tumour cell survival, as well as enhance chemosensitivity and suppress metastases.¹⁰⁶ It is somewhat difficult to decide which development compounds should be designated as AXL inhibitors, since several MTKIs, including approved agents such as cabozantinib, bosutinib, crizotinib, and sunitinib, are also potent AXL inhibitors.¹⁰⁷ One of the most potent AXL inhibitors (sub-nM IC₅₀) is the pyrazinecarboxamide gilteritinib, which also potently inhibits FLT3 and ALK.¹⁰⁸ The first selective (at least in terms of cell-based kinase inhibition activity) AXL inhibitor to enter the clinic is BGB 324, a substituted triazole-3,5-diamine that contains two instances of the unusual tetrahydrobenzannulene substructure (Table S10).

RET (REarranged during Transfection) is a receptor Tyr kinase whose activity supports cell survival and proliferation, as well as cell migration, differentiation, and chemotaxis. Activating mutations in *RET* (C634W and M918T) and a number of different gene translocations leading to oncogenic fusions involving *RET* occur in various cancers, particularly in MTC and NSCLC.¹⁰⁹ RET is closely related to other receptor Tyr kinases, especially VEGFR, and many MTKIs possess RET-inhibitory activity (refer Tables S5, S7, S9). As we have seen, vandetanib, lenvatinib, and cabozantinib are approved for use in MTC and the activity of these agents in thyroid cancers –as well as in some lung cancers– is probably due to a large extent because they inhibit RET.¹¹⁰⁻¹¹³ However, the efficacy of MTKIs, especially those that also block VEGFR activity, is limited by toxicities¹¹⁴ and selective RET inhibitors are highly desirable for the treatment of cancers that are driven by RET activation. Although research aimed at the discovery of such agents is under way,^{115,116} there do not appear to be any RET-specific kinase inhibitors under clinical evaluation at present.

Transforming growth factor- β receptor. A range of cellular responses, including proliferation, differentiation, motility, and survival, are elicited upon activation by the TGF- β cytokines of the three TGFR isoforms through receptor hetero-dimerisation. However, in normal cells TGF- β actually functions as a tumour suppressor but TGF- β signalling is hijacked by cells during tumour development and is particularly important during the epithelial-mesenchymal transition.¹¹⁷ TGFRs contain Ser/Thr kinase domains and signal transduction occurs through TGFR heterodimer-mediated phosphorylation of cellular proteins such as SMADs, which activate the TGF- β signalling pathway.¹¹⁸ Drugs, including antisense oligonucleotides, antibodies, and small molecules targeting this pathway have been under development in both neoplastic and non-neoplastic indications, especially in fibrosis.¹¹⁹ Two TGFR1 kinase inhibitors are currently being developed in oncology, galunisertib and TEW 7197, both of which contain the 2-methyl-6-(4*H*,5*H*,6*H*-pyrrolo[1,2-*b*]pyrazol-2-yl)pyridine substructure (Table S11).

Janus kinases. The JAK family includes the 3 cytoplasmic Tyr kinases JAK1, JAK2, and JAK3, as well as the non-receptor Tyr kinase TYK2. These kinases transmit signalling from a number of cytokines and growth factors important in haematopoiesis and cellular immune functions. Whereas JAK3, which is critical to signal transduction *via* common γ -chains of interleukin receptors, is pursued primarily as a drug target in inflammation, especially JAK2 is also an oncology drug target. The interest in JAK2 inhibitors stems from the discovery that many myeloproliferative neoplasms display an activating mutation (V617F) in the *JAK2* gene.¹²⁰

Ruxolitinib, a JAK1/2-selective compound,¹²¹ is the first JAK inhibitor in oncology, approved for the treatment of myelofibrosis. A recent survey of the clinical use of this agent concluded that ruxolitinib, currently the only approved therapy for myelofibrosis, is associated with a survival benefit and has changed the treatment landscape for this disease.¹²² Nevertheless, clinical responses have been attenuated and the original hope of curative effects with JAK2 inhibition similar to those seen with imatinib in CML, has not been fulfilled. It has recently been suggested that this may be due to an intrinsic resistance to JAK2 inhibition in myelofibrosis.¹²³

A number of other (structurally diverse) compounds (Table S12), including pacritinib (JAK2/FLT3-selective), momelotinib (JAK1-3-selective), are also currently undergoing clinical development in myeloproliferative neoplasms.¹²⁴ It is not as yet clear how these agents will be differentiated from ruxolitinib and if they will have to be compared to ruxolitinib in randomised studies for the purposes of approval.¹²²

Bruton tyrosine kinase. BTK is a non-receptor kinase in the B-cell antigen receptor (BCR) signalling cascade that mediates B-cell activation, proliferation, migration, and survival. In B-cell non-Hodgkin's lymphomas (NHL) constitutive BCR activation through BTK supports cell proliferation and survival, rendering BTK a relevant pharmacological target in NHL.

This is especially attractive in terms of specificity, since the phenotype of loss-of-function BTK, as occurs in the human disease X-linked agammaglobulinaemia, is restricted to B-cells.¹²⁵

The first potent and selective type-VI inhibitors of BTK were reported in 2007 and it took only 6 years before the first inhibitor of this type, ibrutinib, obtained initial global regulatory approval in the treatment of mantle cell lymphoma. The first BTK inhibitors of any kind were actually reported already in 1999: terreic acid (a quinone epoxide)¹²⁶ and leflunomide metabolite analogues (2-cyano-3-hydroxybut-2-enamides).¹²⁷ Since these compounds possess highly electrophilic functions, it is likely that they are also type-VI inhibitors that react covalently with the thiol of C481, an unpaired Cys residue in the ATP-binding site of BTK (corresponding to C773 in HER kinases), although this was not apparently realised at the time of their discovery. Interestingly, terreic acid was originally studied in the context of mast cell activation and it was realised that BTK inhibitors may find therapeutic application in immunology and inflammation, whereas leflunomide metabolite analogues were reported as anti-leukaemic drug leads. Ibrutinib, too, was discovered in a rheumatoid arthritis drug discovery programme,¹²⁸ and was later repositioned in B-cell malignancies.¹²⁹

Apart from ibrutinib (a pyrazolo[3,4-*d*]pyrimidine) there are currently five additional BTK inhibitors under clinical development in cancer (Table S13). Of these the chemical structures of two are in the public domain and both are structurally closely related to ibrutinib. Acalabrutinib is an imidazo[1,5-*a*]pyrazine derivative with a reactive but-2-enoyl function, whereas GS 4059 is a purin-8-one derivative with –like ibrutinib– an acryloyl electrophile.

Focal adhesion kinase. FAK1 is a cytoplasmic non-receptor Tyr kinase that transmits cell motility, survival, and proliferation signals from integrin-mediated cell extracellular matrix attachment and growth factor receptors. Because metastatic propensity and poor clinical outcomes of many cancers are correlated with enhanced FAK1 expression and activity, FAK1 is a promising target for cancer therapy.¹³⁰

A number of FAK1 inhibitors have been under clinical investigation in the past,¹³¹ but currently only three remain active (Table S14). GSK 2256098 and VS 4718 are selective FAK1 inhibitors, whereas defactinib is a dual FAK1 and FAK2 inhibitor. Such dual selectivity is believed to be potentially beneficial due to functional overlap and redundancy of these two closely related kinases.¹³² All three compounds are structurally related ATP-competitive (presumably type-I) inhibitors, but allosteric FAK1 inhibitors have also been reported,¹³³ although these have not yet reached clinical evaluation.

Spleen tyrosine kinase. SYK is a cytoplasmic non-receptor Tyr kinase expressed predominantly in haematopoietic cells. Phosphorylation of cytoplasmic immunoreceptor tyrosine-based activation motifs (ITAMs) leads to recruitment of SYK, which propagates signalling by activation of downstream pathways, including PI3K, MAPK, and BTK.¹³⁴ Because

SYK mediates cellular responses to antigens and antigen-immunoglobulin complexes it is especially relevant as a drug target to suppress the consequences of acute and chronic inflammation.¹³⁴ However, SYK, together with BTK, is also involved in dysregulation of BCR signalling in haematological malignancies such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and chronic lymphocytic leukaemia (CLL).¹³⁵

A number of SYK inhibitors have been evaluated clinically, mainly for the treatment of immune disorders, but were found to exhibit dose-limiting toxicities attributed predominantly to lack of sufficient selectivity for SYK.¹³⁶ The first of these was fostamatinib (a methylene phosphate oral prodrug of a poorly soluble dianilinopyrimidine compound), which failed in phase-III trials in rheumatoid arthritis and has also been trialled in B- and T-cell lymphoma, but apparently has not progressed.¹³⁷ Second-generation SYK inhibitors with improved kinome selectivity profiles have now been developed and entered the clinic (Table S15). The most advanced of these is entospletinib, a highly SYK-selective oral di-substituted imidazo[1,2-*a*]pyrazine compound, currently in phase-II studies in both inflammation and cancer (haematological malignancies). Cerdulatinib is a dual JAK and SYK inhibitor (Table S12) that has activity in autoimmunity and B-cell cancers like other SYK inhibitors.¹³⁸

PI3K pathway kinases (Table S16). The PI3K pathway regulates protein synthesis, cell growth, and cell proliferation in response to nutrient availability and mitogenic growth factors. Activation of this pathway has long been associated with malignant transformation and anti-apoptotic signalling.¹³⁹ Amplification or mutation of many receptor Tyr kinases, mutation of downstream signalling components, including PI3K itself, loss or mutation of the PTEN tumour suppressor protein, as well as mutation and amplification of *AKT*, can lead to pro-survival signalling through the PI3K–AKT–mTOR–eIF4E pathway in cancer cells. At least four kinases in this pathway, PI3K itself (*i.e.* the class-I PI3K isoforms α – δ), *AKT*, its activating kinase *PDK1*, and *mTOR*, are being actively pursued as oncology drug targets. The first generation *mTOR* inhibitors are derived from the macrolide rapamycin (sirolimus), a natural product from a fungus indigenous to the Easter Island (Rapa Nui). Studies based on the observation that rapamycin inhibited the proliferation of T-cells led to the discovery of the *mTOR* (mechanistic or mammalian target of rapamycin) genes and the development of sirolimus as a targeted drug. Although the anticancer activities of rapamycin had been known for a long time, sirolimus was first developed as an immunosuppressive agent. However, a rapalogue (rapamycin analogue), temsirolimus, was approved for the use in advanced renal cell carcinoma (RCC). Objective responses of kidney cancer patients to rapalogues had been observed already in phase-I studies¹⁴⁰ and the demonstration that loss of the von Hippel-Lindau tumour suppressor gene (*VHL*) sensitises kidney cancer cells to *mTOR* inhibitors subsequently enabled biomarker-driven development of temsirolimus in RCC.¹⁴¹ Another rapalogue, everolimus, was approved later for the same indication .

mTOR participates in at least two functionally distinct multiprotein complexes termed mTORC1/RAPTOR and mTORC2/RICTOR. Rapalogues, which block mTOR activity indirectly in complex with the immunophilin receptor known as FK506-binding protein-12 (FKBP12), specifically inhibit mTORC1.¹⁴² It was reported recently that the rapalogue everolimus can also act as a MET inhibitor (refer section on hepatocyte growth factor receptor kinase), since MET -like mTOR- also requires FKBP12 binding for full activity.¹⁴³ Because of the presence of mTORC1-dependent negative feedback loops *via* the mTOR phosphorylation substrate ribosomal protein S6 kinase β -1 (S6K1) leading to upregulation of PI3K and RAS activities, inhibition of mTORC1 can lead to activation of AKT- and MAPK-dependent survival pathways.¹⁴⁴ For this reason, selective ATP-antagonist mTOR inhibitors, which block both mTOR complexes, were developed and are also now entering clinical trials. Clinical compounds belonging to this group include vistusertib, sapanisertib, and CC 223.

Unsurprisingly considering the similarity of mTOR and PI3K, the majority of ATP-antagonist mTOR inhibitors turned out to inhibit PI3K as well, or they were designed to possess dual specificity. Again several compounds of this type are being developed, *e.g.* the dual pan-class I PI3K and mTOR kinase inhibitors voxtalisib, LY 3023414, PQR 309, gedatolisib, and VS 5584.

Inhibitors that do not modulate mTOR at all but inhibit various combinations of class-I PI3K isoforms are also now being pursued. This appears to be a valid approach as all four functionally non-redundant isoforms can generate the signalling molecule phosphatidylinositol-3,4,5-trisphosphate (PIP₃), which recruits AKT to the cell membrane, and because all are oncogenic in model systems.¹⁴⁵ Furthermore, all four isoforms are frequently genetically altered in a variety of cancers.¹⁴⁶ At present it remains unclear what PI3K/mTOR inhibition selectivity (Figure 11) will be therapeutically optimal. It is likely that the preferred class-I PI3K target will depend on the cellular context.¹⁴⁷ The main driver for seeking isoform-selective PI3K inhibitors is probably because broad selectivity may limit the therapeutic margin of an mTOR/PI3K inhibitor, due to the important role of the PI3K pathways in normal cells. Currently there are several pan-class-I PI3K inhibitors undergoing clinical trials, including buparlisip, copanlisip, pictilisib, ZSTK 474, and SF 1126, the latter being a vascularly targeted prodrug.

That PI3K δ is only expressed in haematopoietic cells provides the therapeutic rationale for the use of the PI3K δ -selective compounds in haematological cancers¹⁴⁸ and this concept has now led to the first approval of a PI3K δ -selective inhibitor, idelalisib as monotherapy for follicular and small lymphocytic lymphoma. Another compound, duvelisib, with a similar selectivity profile (10- to 40-fold selectivity over PI3K γ and higher over other PI3Ks) is in late-stage development. Other clinical compounds with more or less pronounced PI3K δ selectivity include AMG 319, HMPL 689, INCB 050465, and CDZ 173. A recent study showed that PI3K δ (and PI3K γ) is important for T-cell-mediated immune tolerance to cancer and

PI3K δ inhibitors may therefore find therapeutic applications not just in blood cancers but perhaps much more widely.¹⁴⁹

Apart from PI3K δ -selective inhibitors, a growing number of experimental PI3K inhibitor drugs with a range of PI3K isoform selectivity profiles are being investigated. The interest in PI3K α -selective agents stems predominantly from the observation that the gene encoding this isoform is mutated particularly frequently in certain cancers (*e.g.* HER2- and KRAS-driven tumours).¹⁵⁰ The most advanced PI3K α -selective compounds are alpelisib and talisib; others include MLN 1117 and AZD 8835. Because PI3K α specifically regulates glucose haemostasis, this must be carefully managed with PI3K α -selective inhibitors in the clinical setting.¹⁵¹ Dependence on PI3K β has been observed in certain PTEN-deficient tumours and the first PI3K β -selective agent, GSK 2636771 is now being trialled in this setting. Other PI3K β -selective clinical compounds include AZD 8186 and KA 2237.

Because of the importance of the PI3K pathway to cancer cell survival, it was originally thought that PI3K inhibitors might have anticancer efficacy in monotherapy, but with the clinical experience amassed so far with over 20 different PI3K/mTOR inhibitors, it is increasingly becoming clear that this is unlikely to be the case. Like most kinase inhibitors, PI3K inhibitors will probably work best in combination with other anticancer drugs.¹⁵²

AKT (also known as PKB) is a Ser/Thr kinase that acts downstream of PI3K and is activated by recruitment to the cell membrane by interaction with PIP₃ through its PH (pleckstrin homology) domain. Once activated, AKT mediates downstream responses by phosphorylation of multiple proteins. The lipid phosphatase PTEN, which is frequently inactivated in human tumours, negatively regulates AKT by dephosphorylation of PIP₃, whereas AKT is amplified or overexpressed in many tumours.¹⁵³

Until recently the clinically most advanced AKT inhibitor was the alkylphospholipid perifosine. It is not a direct kinase inhibitor but interferes with membrane localisation of AKT.¹⁵⁴ Phase-II clinical trials of perifosine as a single agent in several tumour types failed to show objective responses.¹⁵³ Although promising activity in patients with RCC, who have failed prior Tyr kinase inhibitor therapy, was reported,¹⁵⁵ perifosine does not appear to be under development any longer. Several type-I pan-AKT inhibitors, including AZD 5363, ipatasertib (Figure 12a,c), LY 2780301, and afuresertib are now in phase-II clinical studies and several more compounds are in early stage trials (Table S17), including the allosteric (type-III) AKT inhibitor MK 2206 (Figure 12a). This compound binds to an AKT site formed only in the presence of the PH domain and binding of the inhibitor promotes the formation of an inactive kinase conformation.¹⁵⁶ MK 2206 is similar to compound VIII of ref.¹⁵⁷, whose experimental binding mode is known (Figure 12b,c). ARQ 092 and BAY 1125976 are also allosteric AKT inhibitors. The structure of the latter compound has not yet been disclosed but the compound series that encompasses ARQ 092 is structurally related to compound VIII and MK 2206.¹⁵⁸

PDK1 plays an important role in the PI3K–AKT pathway. It activates AKT, as well as a number of other related AGC kinases, thus controlling several signalling pathways important in proliferation, apoptosis, and angiogenesis. Like PI3K, PDK1 is upregulated in more than half of all tumours due to constitutive growth factor receptor activation and *PTEN* mutations. As expected, transgenic mice expressing low levels of PDK1 are protected from tumourigenesis that normally results from loss of *PTEN*. The search for potent and selective PDK1 inhibitors has been pursued for some time but as with many other kinases, achieving selectivity in inhibitors has proven challenging.¹⁵⁹ Nevertheless, the first PDK1 inhibitor, AR 12, recently entered clinical trials (Table S29). This compound was designed from celecoxib, a cyclooxygenase-2 (COX2) inhibitor, following the assignation of tumour-preventive properties of celecoxib to PDK inhibition. However, the activity and selectivity with which AR 12 inhibits PDK1 is actually uncertain.¹⁵⁹

Protein kinase C. PKC overexpression has been linked to several types of cancer, with the PKC β isoform believed to be involved in VEGF-induced tumour development and angiogenesis and in the apoptosis-regulating PI3K–AKT pathway. The macrocyclic bisindolylmaleimide enzastaurin selectively inhibits PKC β at low concentrations, and also inhibits other PKC isozymes at higher concentrations that are reached or surpassed in clinical trials.¹⁶⁰ Anti-tumour activity of enzastaurin has been primarily attributed to the inhibition of AKT and its downstream targets, but its precise mechanism of action is not well understood.¹⁶¹ Both PKC and AKT are activated by PDK, and several PKC isozymes can also directly phosphorylate AKT at Ser⁴⁷³, which is essential for AKT activity. It was recently reported that a phase-III clinical trial of enzastaurin in monotherapy in diffuse large B-cell lymphoma failed to show a statistically significant increase compared to placebo in disease-free survival in patients at high risk of relapse following rituximab-based chemotherapy,¹⁶² and apparently development of this compound has been discontinued.

Enzastaurin is not the first staurosporin derivative to undergo clinical development, *e.g.* UCN-01 (7-hydroxystaurosporin) and midostaurin, which also inhibit PKC but have been developed as MTKIs (main targets are CHK1 and PDK1 for UCN-01, and FLT3 and other CSF-1/PDGF receptor subfamily kinases for midostaurin).^{163,164} Other staurosporine derivatives are being developed in non-oncology indications.¹⁶⁵ The only PKC inhibitor that remains under clinical study appears to be LXS 196, an oral compound whose structure or properties have not yet been disclosed (Table S29).

Choline kinase- α . CK is a lipid kinase that phosphorylates free choline to give phosphocholine, enabling the formation of phosphatidylcholine, the main phospholipid in mammalian cell membranes, through the Kennedy pathway. Many tumours display altered lipid metabolism during development and as a consequence of chemotherapy CK is up-regulated in many tumours and is associated with various malignant phenotypes.¹⁶⁶ Further-

more, CK was recently reported as an androgen receptor chaperone and potentially valuable drug target in prostate cancer.^{167,168} TCD 717 is the first CK inhibitor to have recently entered clinical trials in solid tumours (Table S29). It inhibits CK by virtue of competing with the substrate choline; its structure has not been disclosed but is related to hemicholinium-3 ((2*S*,2'*S*)-2,2'-biphenyl-4,4'-diylbis(2-hydroxy-4,4-dimethylmorpholin-4-ium), a choline re-uptake inhibitor.¹⁶⁹

Casein kinase II is a constitutively active hetero-tetrameric Ser/Thr kinase that sustains many cellular signalling pathways. Although CK II function is not apparently altered in cancer cells by mutation, it is nevertheless overexpressed in many different cancers.¹⁷⁰ Tumour cells often exhibit CK II-driven non-oncogene addiction¹⁷¹ and it has been shown that ablation of CK II through antisense oligonucleotides has profound anti-proliferative and pro-apoptotic effects in a rodent xenograft model.¹⁷² A number of small-molecule CK II inhibitors with anticancer activity have been reported and the first such compound, silmitasertib, an CK II-selective ATP-competitive benzo[*c*][2,6]naphthyridine-8-carboxylic acid compound, has recently entered clinical evaluation (Table S29).¹⁷³

MELK is an AMPK family kinase with several cellular functions related to survival and proliferation and it is overexpressed in many tumours. These functions appear to be especially important in cancer stem cells, *i.e.* undifferentiated cancer cells. The first clinical MELK inhibitor is OTS 167, a disubstituted (naphthyridin-3-yl)ethanone compound, whose binding mode was reported recently.¹⁷⁴ Another clinical compound, the (indol-3-ylidene)methylpyrrole amcasertib, also targets (undisclosed) cancer stem cell pathway kinases (Table S29).

PIM. The proviral insertion in murine (PIM) lymphoma family of Ser/Thr kinases (PIM1-3) is expressed predominantly in haematopoietic cells and signals downstream from ABL, JAK2, and FLT3. PIM kinases contribute to the regulation of the cell cycle, apoptosis, and the proliferation and migration of cells. All three isoforms have oncogenic potential and are aberrantly expressed in various tumours.¹⁷⁵ Although mouse knock-out of any of the three PIM kinases results in mild phenotypes, deficient PIM1 signalling is associated with cardiac function and PIM triple knock-out mice develop heart failure by 6 months. These observations may be relevant to the withdrawal of the first-in-class clinical PIM inhibitor SGI 1776 due to cardiotoxicity.¹⁷⁶ Despite this observation it would appear that both PIM inhibitors currently undergoing clinical development, *i.e.* INCB 053914 and PIM 447 (Table S18) are pan-selective PIM inhibitors. PIM kinases are somewhat unusual insofar as they recognise ATP, as well as most inhibitors, in a manner that does not involve the typical H-bonding interactions between the kinase hinge region and the ligand, due to the presence of two Pro residues in the PIM hinge, which imparts an atypical conformation to this region.¹⁷⁷ This unusual recognition mode may explain the high kinome-wide selectivity of compounds such as PIM 447.

Mitogen-activated protein kinase pathway kinases. The RAS–RAF–MEK–ERK MAPK pathway is one of the main signalling pathways that cancer cells use for the purposes of proliferative and survival advantages. Activation of the MAPK pathway, through activating mutations in either NRAS or BRAF, is particularly common in melanoma.¹⁷⁸ Below we shall discuss clinical RAF (Table S19) and MEK inhibitors (Table S20), which have recently been joined by the first ERK inhibitors (Table S21).

Currently there are two RAF kinase inhibitors approved for the treatment of unresectable or metastatic melanoma with *BRAF* V600E mutation, vemurafenib and dabrafenib. Both compounds display selectivity for V600E BRAF over other kinases, and to a lesser extent over wild-type RAF kinase isoforms.^{179,180} With these compounds, inhibition of the MAPK pathway is specific to tumour cells with mutant *BRAF* and this is likely due to their selectivity. In the majority of melanoma patients treated with vemurafenib or dabrafenib significant tumour regression and progression-free survival have been observed, a result that compares favourably with previously available therapies for metastatic melanoma.¹⁷⁸

Neither agent is indicated for the treatment of patients with wild-type BRAF melanoma due to the potential risk of tumour promotion, and both were approved concurrently with assays for the detection of *BRAF* V600E mutations. This contra-indication is due to paradoxical activation of the MAPK pathway by RAF inhibitors in cells with wild-type BRAF. MAPK pathway activation occurs as a result of RAS-dependent MEK phosphorylation by homo- and hetero-dimerised RAF isoforms. In mutant BRAF melanoma cells, in which MEK activation is driven by BRAF, RAF inhibition is effective because of increased affinity of BRAF V600E for ATP and lack of CRAF activation. Paradoxical MAPK pathway activation in cells with normal *BRAF*, where RAS signalling occurs predominantly through CRAF, is thought to arise due to binding of type-I RAF inhibitors to wild-type RAF isoforms, which leads to their loss of auto-inhibition in a manner that is independent of kinase inhibition, enhanced RAF dimerisation, membrane localisation, and eventually RAS-dependent MEK activation.^{181,182} The same phenomenon, *i.e.* paradoxical MAPK pathway activation in healthy keratinocytes, is probably responsible for the significant cutaneous toxicities observed with RAF inhibitors.¹⁸³

Despite the approval of vemurafenib and dabrafenib, a whole range of additional RAF kinase inhibitors are currently being developed in advanced melanoma and other solid tumours (Table S19).¹⁸⁴ The first RAF inhibitor studied in melanoma, however, was sorafenib, a type-II MTKI with pan-RAF activity. This compound, which also has activity against several CSF1/PDGF receptor subfamily kinases (Table S5), was being developed –and is now approved in– advanced RCC at the time when the *BRAF* V600E mutation, which is present in over half of all malignant melanomas, was first discovered.¹⁸⁵ Despite several clinical trials of sorafenib in melanoma, it was not possible to show significant patient benefit,

however. Presumably this was because at the maximum tolerated dose, defined by toxicities emanating from inhibition of kinases other than RAF, there was insufficient MAPK pathway inhibition.¹⁷⁸

The first MEK inhibitor (Table S20) approval was trametinib in the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or *BRAF* V600K mutation as detected by an FDA-approved test. This offers another treatment modality in this disease, although it is not as yet clear what the best treatment options with RAF and MEK inhibitors are.¹⁸⁶ Nevertheless, acquired resistance to RAF inhibitors occurs frequently and through multiple genetic mechanisms, which suggests that simultaneous inhibition of MEK and mutant RAF kinases may be a better strategy in terms of overall efficacy, prevention of MEK-driven acquired resistance, and modulation of toxicity emanating from paradoxical MAPK-pathway activation with RAF-inhibitor monotherapy.¹⁸⁷ On this basis cobimetinib was recently approved for the treatment of mutant BRAF melanoma in combination with vemurafenib.

The selectivity of trametinib and cobimetinib, as well as other MEK inhibitors under clinical development,¹⁸⁸ including rafametinib, selumetinib, pimasertib, PD-0325901, binimetinib, RG 7304, and TAK 733, is probably because these compounds target a non-conserved allosteric site in MEK1 and MEK2 (Figure 13).

Although treatment of advanced melanoma with both RAF and MEK inhibitors has been observed to be effective initially, resistance to both inhibitor types eventually occurs.¹⁸⁹ The main mechanisms of acquired resistance appear to be reactivation of the MAPK pathway in a number of ways, as well as compensatory signalling through the parallel PI3K pathway.¹⁷⁸ The latter observation has led to the initiation of clinical trials in melanoma and other solid tumours, where RAF/MEK and PI3K inhibitors are used in combination.¹⁹⁰

Direct targeting of ERK1/2 in order to block signalling through the RAS–RAF–MEK–ERK pathway has lagged behind the upstream inhibition strategies, but may be of benefit in several ways.¹⁹¹ Thus it has been demonstrated that dual pharmacological inhibition of MEK and ERK can be synergistic by inhibiting the emergence of resistance and overcoming acquired resistance to MEK inhibitors.¹⁹² There are currently three ERK1/2 inhibitors under clinical evaluation (Table S21), the most advanced being ulixertinib. Both ulixertinib and GDC 0994 contain the *N*-((1*S*)-2-hydroxy-1-phenylethyl)formamide substructure, whereas the chemical structure of CC 90003 has not been disclosed.

p38 MAPK. Several different MAPK signalling pathways are used by cells to respond to extracellular stimuli. Apart from the RAS–RAF–MEK–ERK we have just discussed, another important MAPK pathway is the p38 MAPK pathway, which mediates stress responses and responses to cytokines, chemokines, hormones, and growth factors. The four p38 Ser/Thr kinase isoforms p38 α (MAPK14), p38 β (MAPK11), p38 δ (MAPK13), and p38 γ (MAPK12)

can be activated in a number of ways involving both posttranslational modification and protein interactions, thus integrating many different signals. In turn the p38 kinases have numerous downstream targets and can activate different transcriptional programmes in a spatially and temporally controlled manner.¹⁹³

p38 MAPK is pursued mainly as a drug target in chronic inflammatory disorders, especially p38 α , which is over-activated in inflamed tissues. Many different p38 MAPK inhibitors are being developed in such disorders, including rheumatoid arthritis, atherosclerosis, and asthma.^{194,195} However, p38 MAPKs also play important roles in the responses of cancer cells to oncogenic stress, radiation, and chemotherapy and altered expression of p38 MAPKs is frequently observed in tumours, where they promote tumourigenesis.¹⁹⁶ Currently two structurally related p38 MAPK inhibitors are under clinical investigation in oncology indications: ralimetinib and pexmetinib (Table S22).

MNK. The Ser/Thr kinases MNK1 and MNK2 are activated through the mitogen- and stress-activated MAP kinase pathways and they phosphorylate the eukaryotic translation initiation factor 4E (eIF4e). Genetic studies indicate that whereas MNK activity is required for eIF4E-mediated oncogenic cell transformation, such activity is dispensable for normal development.¹⁹⁷ Until recently very few MNK inhibitors were known but selective type-I/II and type-VI MNK inhibitors have now been reported.^{198,199} The first MNK inhibitor to reach phase-I clinical trial is BAY 1143269 (Table S29; undisclosed structure).

Cyclin-dependent kinases (Table S23). The CDKs comprise a large group of Ser/Thr kinases involved predominantly in the control of the cell cycle and the regulation of transcription. Recruitment into and progression through the cell cycle are tightly regulated and the interphase CDKs control the first gap phase (G₁; CDK4, CDK6, CDK1, CDK2) by activating E2F-responsive genes required for entry to the DNA synthesis phase (S-phase), as well as the second gap phase (G₂; CDK1, CDK2) by activating the FoxM1 gene programme required for execution of mitosis. Similarly, the different phases of RNA polymerase II (RNAPII)-based transcription are regulated by CDKs. Here sequential phosphorylation of the C-terminal domain of RNAPII occurs: by CDK7 and CDK8 in transcription initiation, and by CDK9 in RNA elongation. Additionally, CDK activity is required (at least CDK11) for RNA processing (splicing).²⁰⁰ However, our understanding of CDK biology is still incomplete due to extensive functional overlap and redundancy between the many CDK–cyclin pairs, not only in the cell cycle and RNAPII transcription, but also between the two.

Because cancer is characterised by uncontrolled cell division, interference with CDKs as key regulators of the cell cycle appears attractive as a therapeutic strategy. However, the complexity of CDK–cyclin biology has confounded interpretable genetic target validation of CDKs. As a result uncertainty exists about which CDK function(s) should be blocked to achieve effective and specific anticancer activity in a therapeutic setting, and this has long

beset the development of CDK inhibitor drugs. A large number of CDK inhibitors had been trialled clinically in the past – mostly with disappointing results.²⁰¹

Nevertheless, the first CDK inhibitor, palbociclib, has now been granted FDA approval for use in combination with letrozole (a non-steroidal aromatase inhibitor) in ER-positive, HER2-negative metastatic breast cancer. Palbociclib is a highly CDK4/6-selective agent and preclinical studies with this and several other CDK4/6-selective compounds show anticancer activity in a range of models, with this activity being contingent on the presence of functional retinoblastoma protein (pRb; the CDK4/6 phosphorylation substrate), and leading to cytostatic G₁ arrest. Rapidly reversible neutropenia is the main dose-limiting toxicity of palbociclib, as one would expect on mechanistic grounds.²⁰¹

Other CDK inhibitors that remain under clinical development include two more CDK4/6-selective agents: ribociclib, abemaciclib, as well as number of pan-CDK-selective compounds: dinaciclib, AT 7519, milciclib, roniciclib, and CYC 065. Additionally, MTKIs that may be classed as CDK-inhibitors are TG 02 and RGB 286638.

The kinase inhibitor that probably has a longer clinical development history than any other is alvocidib (flavopiridol). This compound has been difficult to develop due to target promiscuity and limitations in formulation and disposition, but marked efficacy was observed some time ago in CLL, and this activity was ascribed to potent CDK9 inhibition by alvocidib. CLL –and many other cancers– are known selectively to depend on efficient RNA synthesis in order to support anti-apoptotic signalling, which in turn requires CDK9 activity.²⁰² Alvocidib has now re-entered clinical development, based on promising activity in AML, also likely due to potent CDK9 inhibition. The first selective CDK9 inhibitor, BAY 1143572, has also now entered clinical trials. This compound contains the unusual sulfoximine solubilising substructure.²⁰³

Aurora kinases. ARKs are a group of mitotic Ser/Thr kinases and in humans there are three homologues. ARK-A regulates mitotic entry, spindle assembly, alignment of metaphase chromosomes, and completion of cytokinesis. ARK-B and ARK-C, on the other hand, are chromosomal passenger proteins predominantly involved in chromosomal bi-orientation. ARKs play important roles in the maintenance of genetic stability and their aberrant expression leads to genomic instability or aneuploidy. Because ARKs are overexpressed in many cancers, thus generating aggressive tumours, they are regarded by many as attractive targets for cancer therapy.²⁰⁴

There is an on-going debate in the field about what ARK selectivity is optimal in terms of efficacy and on-target toxicity. Currently six ARK inhibitors (Table S24) with different selectivity profiles are being trialled in a variety of solid tumours and blood cancers. Compounds selective for ARK-A are alisertib and TAS 119, whereas barasertib is selective for ARK-B. Danusertib is a selective pan-ARK inhibitor. ENMD 2076 and ilorasertib, on the

other hand, are multi-targeted ARK inhibitors. An answer regarding desirable selectivity may therefore emerge. At this stage, however, this questions remains open.

Whereas some therapeutic effects have been seen with most experimental ARK inhibitor drugs, it would appear that all of them suffer the same limitations as classical antimetabolic agents, *i.e.* cytostatic or cytotoxic effects against proliferating cells only, without good discrimination between transformed and normal cells, which manifest clinically as neutropenia and other haematological toxicities. Interestingly, several ARK inhibitors have been found to be effective against imatinib- and 2nd-generation Tyr kinase inhibitor-resistant forms of the BCR-ABL kinase, especially the T315I mutant form. Some ARK inhibitors are now being tested clinically in patients with imatinib-resistant CML.²⁰⁵

Polo-like kinases. PLK1 is one of four related Ser/Thr kinases associated with cell proliferation, especially in the mitotic phase of the cell cycle. Most cancers exhibit higher PLK1 expression than corresponding normal tissues, and PLK1 inhibition results in G₂-M phase arrest, activation of the mitotic checkpoint, spindle dysfunction, and apoptosis in cancer cells. To date several PLK inhibitors have entered clinical evaluation, so far with disappointing results in terms of efficacy and with neutropenia as the most prominent toxicity.²⁰⁶ The most advanced experimental PLK inhibitor drug is volasertib, a potent and selective PLK1 inhibitor with pronounced anti-tumour activity in preclinical models, including taxane-resistant colorectal cancer. One of the possible reasons for the limited anticancer activity observed with this agent in humans may be its limited bioavailability in tumours compared to normal tissues.²⁰⁷ Using a genome-wide synthetic lethality screen it was shown recently that KRAS-driven tumours are selectively sensitive to PLK1 inhibition.²⁰⁸ This finding might be used profitably to guide patient selection in efficacy trials of experimental PLK1 inhibitor drugs. PLK4, which is involved in centriole duplication, has not as yet received significant attention as an oncology target, but a selective PLK4 inhibitor, CFI 400945, has recently entered clinical evaluation (Table S25).

DNA damage response pathway kinases. The PI3K-related kinase (PIKK) family includes ATM, ATR, DNA-PK, hSMG1, mTOR (discussed above under PI3K pathway inhibitors), and TRRAP, all large proteins that contain a C-terminal kinase domain closely related to the lipid kinase PI3K, but which function as Ser/Thr kinases, whereas CHK1 and CHK2 are Ser/Thr kinases in the CAMK family (NIM1 subfamily). Several PIKKs, including ATM, ATR, and DNA-PK, as well as the CHK kinases, are implicated in DNA replication and damage checkpoint pathways.

The DNA damage response helps cells to maintain genomic stability and the two main signalling routes are the ATM-CHK2 pathway, which controls DNA double-strand break repair, and the ATR-CHK1 pathway, which responds primarily to single-stranded DNA. DNA-PK, on the other hand, plays a role in DNA repair by non-homologous end joining. ATM and ATR act on their CHK substrates, which in turn promote cell-cycle arrest to allow

time for repair, as well as on numerous other components involved in DNA repair, apoptosis, and the cell cycle. Since efficient DNA repair allows cancer cells to tolerate not only oncogenic replication stress, but also exogenous genotoxic stress from radio- and chemotherapy, the DNA response pathway may represent a promising target for cancer therapy. At least ATR and CHK1 inhibitors are believed to be potentially useful for monotherapy of certain cancers, *e.g.* those with p53 and other DNA damage response deficiencies, whereas ATM, ATR, CHKs, and DNA-PK inhibitors are all potentially valuable as radio- and chemosensitising agents.²⁰⁹

Although a number of CHK inhibitors had been clinically evaluated in the past,²¹⁰ currently only the CHK1 inhibitors prexasertib and GDC 0575 remain under active development (Table S26). The first selective ATR inhibitors to enter the clinic are VX 970, VX 803, and AZD 6738 (Table S27). Additionally, the ATM inhibitor AZD 0156 (Table S29) and the DNA-PK inhibitors VX 984 and M 3814 (Table S28) are in early clinical trials. Finally the first-in-class WEE1 inhibitor AZD 1775 (Table S29) should be mentioned here, as WEE1 is another kinase associated with cell cycle checkpoint control following DNA damage.

CDC7. CDC7 is a Ser/Thr kinase that is involved in regulation of the S-phase and mitosis during the cell cycle. CDC7 inhibition has been reported to block DNA replication without activation of the S-phase checkpoint and directly to induce cellular apoptosis in transformed cells but not in normal cells.²¹¹ A number of CDC7 inhibitors have been reported and several have undergone early clinical evaluation.²¹² However, at present the only CDC7 inhibitor in the clinic is TAK 931 (Table S29; undisclosed structure).

Medicinal chemistry

Of the 231 (at the time of writing) clinical kinase inhibitor anticancer drugs, chemical structures for 172 are in the public domain. These molecules display structural and physicochemical properties as summarised and compared to those of all currently approved small-molecule drugs in Table 1.

In terms of physicochemical properties, it can be seen that on average oncology kinase inhibitors are significantly larger (by almost a third; M_r) and more lipophilic (by around two thirds; $\log P$, $\log D$) than small-molecule drugs in general, and they have much lower (predicted) intrinsic water solubility (by almost half; $\log S$). Increased lipophilicity and lower solubility stem predominantly from relatively abundant aliphatic and aromatic systems (nAr) present in oncology kinase inhibitors. Furthermore, kinase inhibitors are comparatively more flexible ($nRot$) and contain more polar functionalities for H-bonding interactions ($TPSA$, HBA , HBD) than approved drugs in general. Structurally, kinase inhibitors on average contain more cyclic systems ($nRing$, nAr) but fewer chiral centres ($nChir$) than other drugs, presumably because kinase inhibitors, unlike many other drugs, are less frequently derived from natural products.

Correlation of logP and logS (Figure 14) shows that most of the kinase inhibitor drugs are expected to be highly permeable but poorly soluble, some of them with exceptionally low (predicted) intrinsic aqueous solubility. With very few exceptions kinase inhibitor drugs are being developed as immediate release products for administration by the oral route and while the physicochemical properties in Table 1 are consistent with oral bioavailability,^{213,214} average M_r and logS suggest an average thermodynamic aqueous solubility of about 2 $\mu\text{g/mL}$ (75 $\mu\text{g/mL}$ for all approved drugs), which is only expected to be consistent with very low clinical doses, and provided permeability is high.²¹⁵ For many oncology kinase inhibitors absorption is likely to be variable and *in vivo* drug dissolution rate-limiting. It can therefore be expected that many kinase inhibitor drugs will be challenging to develop from a formulation viewpoint.

As can be seen from Figure 15, both the maximum and average structural dissimilarity amongst oncology kinase inhibitors is significantly lower than that of all approved drugs, indicating that many kinase inhibitors, which generally target the conserved ATP-binding site, are pharmacophorically related. As expected, dissimilarity of compounds that are targeted to subgroups or individual kinases is diminished compared to that of all experimental kinase inhibitors. The groups of kinase inhibitors with the highest and lowest average structural dissimilarity are the PI3K and CSF-1/PDGF inhibitors on the one hand, and the BCR-ABL inhibitors on the other.

Another way of looking at structural similarity of oncology kinase inhibitor drugs is to assess the frequency at which common substructures occur in these compounds (Figure 16). This shows that by far the most common substructure is the formamide group (31 instances). This is probably not a distinguishing structural feature of kinase inhibitors, as this group occurs frequently in many different drug classes. The next most frequent substructure, however, is the quinazoline group (14 instances), a commonly used kinase inhibitor core, which occurs in several approved drugs and many experimental agents, especially in EGFR inhibitors. Other substructures that occur more than three times in the 172 oncology kinase inhibitors are the ethoxybenzene (11), 2-anilinopyrimidine (10), benzamide (8), indole (8), benzimidazole (5), chromene (4), 4-(pyrimidin-4-yl)morpholine (4), (3-fluorophenyl)methanamine (4), 2-phenylethylamine (4), and *N*,4-dimethylpyrimidin-2-amine (4). Again some of these substructures are not specific to kinase inhibitors but it is notable that 3 of these substructures contain the pyrimidine heterocycle. Of the substructures that occur twice or three times a number of N-containing bicyclic heterocycles, including purines, 3-methyleneoxindoles, pyrrolo[2,3-*d*]pyrimidines are especially associated with kinase inhibitors.

Whereas kinase inhibitor lead compounds were frequently discovered using high throughput screening in the past, a much more common current strategy is structure-based redesign of known kinase inhibitor templates, as is evident from the preceding similarity and

property comparisons of clinical kinase inhibitors. More recently fragment-based drug discovery has started to play an increasingly important role in the design of kinase inhibitors and the first approved kinase inhibitor arrived at by this strategy is vemurafenib.²¹⁶ A more recent example is AZD 5363 (Figure 17).

Using a virtual screen of fragment compounds ($M_r < 250$) against a model of AKT based on a crystallographic complex of an active form of that protein, followed by crystallography of putative binding fragments with a PKA–AKT chimera construct, 7-azaindole was identified as an AKT hinge-binding fragment (Figure 17a).²¹⁷ The binding mode of the isoquinoline-5-sulfonamide AKT inhibitor CCT 077373 discovered earlier²¹⁸ suggested that determinants for AKT inhibition activity other than hinge binding were a basic amine group interacting with acidic groups in the ribose-binding regions, as well as a lipophilic group (chlorophenyl) interacting with the G-loop (Figure 17f). For synthetic ease the azaindole was replaced with purine, which was arylated at the 6-position to afford benzylamine intermediate 1 as one of the most active and ligand-efficient derivatives (Figure 17b). Replacement of the phenyl group in that intermediate with piperidine gave rise to compounds with improved polar interactions with the acidic residues in the ribose-binding region and intermediate 2 (Figure 17c) was identified as a compound with improved activity and excellent lipophilic ligand efficiency.²¹⁹ However, this compound was too polar and lacked cellular activity. Polarity was modulated by replacement of the azaindole core with pyrrolo[2,3-*d*]pyrimidine, repositioning of the primary amine group, and extension with a 4-chlorophenyl group to give rise to intermediate 3 (Figure 17d), a highly potent AKT inhibitor with well-balanced physicochemical properties.^{219,220} Intermediate 3 was subsequently further elaborated in terms of kinase selectivity, hERG activity, and *in vivo* disposition properties to afford AZD 5363 (Figure 17e).²²¹

Conclusions

Kinase inhibitor discovery is a comparatively recent medicinal chemistry endeavour and has progressed almost exponentially over the last ~25 years. Whereas early kinase inhibitor approvals were for MTKIs, the preponderance of more selective agents has increased gradually and now predominates. The advent of kinome-wide kinase assays and associated molecular pharmacology technologies, and the ever-expanding knowledge of how kinase inhibitors engage their molecular targets at the atomic level, now permit the rational design and validation of highly selective agents. This, together with modern clinical investigation strategies incorporating patient diagnosis, prognosis, and stratification based on genetic and mechanistic biomarkers, will continue to expand the oncologist's arsenal of highly specific kinase inhibitor drugs and will hopefully permit truly effective, modular, personalised treatments of cancers with less reliance on toxic chemotherapy. Because in general highly target-selective agents are also highly specific *in vivo*, it is hoped that progress can be

made to optimise the therapeutic margin (therapeutic *versus* toxic effects) of kinase inhibitor drugs, not only in oncology, but also in other therapeutic indications with unmet medical need. Based on current information it is likely that this may not be achievable in many cases with inhibitors that target the catalytic activity of kinases, except in those cases where a particular cancer is addicted completely to the activity of a given kinase. In principle pharmacological modulation of kinase activities is also possible by allosteric means, as we have seen. This is especially attractive if the possibility of such allostery arises in a manner that is specific for a particular context in terms of kinase environment and location, *e.g.* through specific disease-associated interactions of a kinases, but such approaches remain challenging. Maximisation of kinase inhibitor efficacy by these or other means is highly important in order to avoid emergence of drug resistance, which is a feature of many current kinase inhibitors, especially those with high target selectivity. As we have seen, the first kinase inhibitors for inflammatory disease have now been approved and several kinase inhibitors are under clinical investigation in indications other than cancer. A major challenge will be to apply what we have learned from oncology kinase inhibitors to other major disorders that currently lack effective therapies, such as neurodegeneration and (drug-resistant) microbial and viral infections.

Abbreviations. For kinase abbreviations refer to Table S1. Other abbreviations: ALCL, anaplastic large cell lymphoma; ALL, acute lymphocytic leukaemia; AML, acute myelogenous leukaemia; BCR, B-cell antigen receptor; CLL, chronic lymphocytic leukaemia; CML, chronic myelogenous leukaemia; C_{ssf} , concentration of free drug fraction at steady state; DLBCL, diffuse large B-cell lymphoma; DFSP, dermatofibroma sarcoma protuberans; FDA, U.S. Food and Drug Administration; fo_t , receptor occupancy as a function of time; GIST, gastrointestinal stromal tumour; IPF, idiopathic pulmonary fibrosis; MTC, medullary thyroid cancer; MTKI, multi-targeted kinase inhibitor; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; PH, pleckstrin homology; PIP₃, phosphatidylinositol-3,4,5-trisphosphate; RCC, renal cell carcinoma; RNAPII, RNA polymerase II; SI, selectivity index.

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Figure 1. Historical overview of kinase inhibitor approvals in oncology.

Figure 2. Active and inactive kinase architectures. An active, *i.e.* catalytically competent, form of PKA (PDB entry 1ATP), bound to ATP, Mn^{2+} (purple spheres; under physiological conditions the corresponding metal cations are Mg^{2+}), and a peptide substrate is shown, with key H-bonds indicated as broken black lines. The side chains of the Phe (R2) and Asp residues of the DFG motif in the A-loop are shown as sticks. The residues making up the regulatory spine are labelled R0 to R4 and the linear arrangement of this spine in active kinase conformations is indicated by a broken line (wheat) connecting these residues. This – and subsequent figures showing 3-dimensional protein structures – were constructed using PyMOL (The PyMOL Molecular Graphics System, Version 1.7, Schrödinger, LLC.).

Figure 3. Kinase inhibition mechanisms and selectivity. (a) Receptor–ligand interaction mechanisms, kinetic parameters, and selectivity indices (adapted from ref.²²; refer main text for explanations). (b) Relationship between C_{ssf} and on-target f_0 for type-I kinase inhibitors that all bind a particular on-target kinase with a K_d value of 10 nM but that bind an off-target kinase with K_d values of 50 nM ($SI_1 = 5$), 250 nM ($SI_1 = 25$), 1 μ M ($SI_1 = 100$), and 10 μ M ($SI_1 = 1,000$). (c) Relationship between time post C_{max} and blood levels (C_f) following *p.o.* administration of a kinase inhibitor (C_{max} of 10 μ M and $t_{1/2}$ of 3 h) that interacts with 3 target kinases with variable rate constants k_4 of $8.5 \times 10^{-3} s^{-1}$ (target 1), $2.8 \times 10^{-4} s^{-1}$ (target 2), and $1.26 \times 10^{-5} s^{-1}$ (target 3) and identical k_1 of $1 \times 10^8 M^{-1} s^{-1}$, k_2 of $1 s^{-1}$, and k_3 of $6 \times 10^{-3} s^{-1}$, giving residence times (τ) of 2 min (target 1), 1 h (target 2), and 22 h (target 3).

Figure 4. Small-molecule kinase inhibitors in the clinic. The numbers of approved agents and those currently undergoing clinical evaluation is summarised by kinase.

Figure 5. Molecular basis of BCR-ABL resistance. (a) The chemical structures of 1st (imatinib), 2nd (dasatinib), and 3rd generation (ponatinib) ABL inhibitors. (b) The ABL kinase (green) binding mode of the type-II inhibitor imatinib (grey;) shows an H-bond interaction (dashed line) with the gatekeeper residue T315 (yellow; secondary mutation sites Y253 & E255 in the Gly-rich loop are indicated in purple).²²² (c) The binding of ATP does not involve the T351 residue, hence the catalytic competence of the T315I mutant.²²³ (d) Second-generation drugs such as the type-I compound dasatinib are not effective against T315I mutant kinase, as they also make polar interactions with T315.²²⁴ (e) The recently approved ponatinib, which also inhibits the T315I mutant, evades the altered gatekeeper (Ile) through the placement of an ethynyl linkage between its front- and back-pocket binding portions.²²⁵ Constructed from PDB entries 1IEP, 2SRC, 2GQG, and 3IK3.

Figure 6. Non-ATP-dependent SRC kinase inhibition. (a) The substrate peptide SRC kinase inhibitor KX 01 was shown by saturation transfer difference NMR spectroscopy, using an ATP site-binding paramagnetic spin-labelled pyrazolopyrimidine probe containing the 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO) radical, to bind to SRC kinases in an ATP non-competitive manner.²²⁶ (b) An X-ray crystal structure (PDB entry 3KXZ) of this probe (green) bound to the SRC-family kinase LCK (surface with electrostatic potential colouring) is shown. The extended substrate-binding cavity, where KX-01 (cyan, modelled (Schrödinger Glide, <https://www.schrodinger.com/Glide>) binding pose) is likely to bind, is evident proximal to the ATP-binding site.

Figure 7. Inhibition of EGFR Tyr kinases. (a) Chemical structures of inhibitors. (b) Erlotinib (cyan) is a HER1-selective inhibitor; it binds to HER1 (grey cartoon; G-loop in blue) with the protein in an active-like conformation, with an extended A-loop (yellow) and inward position of the α C-helix (magenta).²²⁷ The phenylacetyle group of erlotinib interacts with the side chain of M766 (magenta stick model) at the base of the α C-helix, as well as the gatekeeper residue T790 (green). (c) Similarly, the HER2-selective compound SYR 127063 binds to HER2 in a way that involves an active-like conformation of that protein. Here the ligand trifluoromethylphenyl and chloro groups interact with M766 (EGFR numbering) and T790, respectively.²²⁸ It is evident that in active HER2 the inward position of the α C-helix is less pronounced than in active HER1. In active HER2 the cavity proximal to the gatekeeper is thus larger than in active HER1 and can accommodate the larger bis(aryl)ether group of SYR 127063, whereas the phenylacetyle group of erlotinib would be unable to make contacts with the α C-helix in HER2. Conversely the bis(aryl)ether group of SYR 127063 is too large to fit the gatekeeper- α C-helix cavity of active EGFR. (d) Dual HER1 and HER2 inhibitors such as lapatinib are generally observed to bind preferentially to inactive forms of the protein (HER1 shown), in which a short α -helix in the A-loop supports an outward position of the α C-helix.²²⁹ (e) TAK 285 is the only EGFR inhibitor for which crystal complexes with both HER1 (ligand and coloured protein elements in light colouring) and HER2 (dark colouring) have been solved.^{228,230} Although similar in structure to SYR 127063, TAK 285 inhibits HER1 and HER2 with similar potency. It can be seen that it binds to inactive forms of both kinases, which are highly similar. (f) Second-generation type-VI inhibitors are active against T790M mutant kinase forms and *e.g.* afatinib binds to wild-type (ligand and coloured protein elements in light colouring) and the T790M form of HER1 (dark colouring) in a very similar manner, with slight repositioning of the substituted aniline to optimise interactions with T790 or T790M.⁶⁸ (g) Osimertinib, on the other hand, is a type-VI inhibitor that selectively binds to the T790M mutant EGFR kinase. It was observed that the main determinant for this selectivity in the design of osimertinib was the indole N-methyl group, which can be observed to interact closely with the thiomethyl group of M790, an interaction that is not possible with T790 (modelled pose from docking using the Schrödinger Glide programme with the covalent docking protocol, using the 3IKA HER1 structure as the receptor).²³¹ Constructed from PDB entries 1M17, 3PP0, 1XKK, 3POZ, 3RCD, 4G5J, and 4G5P.

Figure 8. Experimental binding modes of FGFR inhibitors. (a) Chemical structures of inhibitors. (b) The three clinically most advanced selective FGFR inhibitors AZD 4547 (cyan), infigratinib (magenta), and erdafitinib (green) all contain 3,5-dimethoxyphenyl groups that make identical interactions with the kinase. (c) Lucatinib (green) and dovitinib (cyan) are MTKIs that also inhibit FGFR kinases with high potency. Lucatinib makes contacts with the V561 gatekeeper residue (spheres), whereas dovitinib does not. (d) For this reason dovitinib inhibits both wild-type (cyan) and V561M-mutated (green) forms of the kinase, whereas lucatinib is inactive against V561M FGFR.⁸⁹ (e) BLU 9931 (green) is an isoform-selective type-VI FGFR4 inhibitor²³² by virtue of targeting C552, which is unique in FGFR4 (Tyr in FGFR1-3), whereas FIIN-2²³³ is a selective dual inhibitor of FGFR and HER kinases, both of which contain Cys residues at the same position in the G-loop (C447 in FGFR, C797 in HER). Figure constructed from PDB entries 4RWJ, 5EW8, 3TT0, 4RWL, 4RWI, 5AM6, 5AM7, 4XCU, and 4QQC.

Figure 9. Inhibitors of active and inactive forms of MET. (a) Chemical structures of inhibitors. (b) The G-loop in the N-terminal lobe of the apo-form of MET²³⁴ is shown in cyan, the α C-helix, which contains key catalytic residues, is shown in magenta, and the A-loop, which is important for substrate recognition, in yellow, with the Phe residue of the DFG motif shown as a stick model. An example of an inhibitor that is selective for A-loop-phosphorylated active form of MET is the derivative of MK 2461. It is a type-I inhibitor and the shape of the ATP-binding site in its complexed structure (c) is similar to that of the apo-form, except that the G-loop folds over the ligand.²³⁴ The late-stage development Met inhibitor tivantinib is an unusual type-II inhibitor, which does not bind deep into the cavity formed by the DFG-out conformation, but it induces a major shape change in the kinase,

involving both the A-loop and the α C-helix (**d**).²³⁵ Like tivantinib, merestinib is selective for unphosphorylated inactive MET; it is a conventional type-II inhibitor (**e**).²³⁶ Constructed from PDB entries 3Q6U, 3Q6W, 3RHK, and 4EEV.

Figure 10. ALK inhibitors. (**a**) Chemical structures of crizotinib and lorlatinib, a macrocyclic derivative with high lipophilic efficiency and CNS bioavailability. (**b**) Crizotinib (green) and lorlatinib display highly similar ALK binding modes (crystallographic water molecules shown as spheres, H-bonds as broken lines).^{99,237} Constructed from PDB entries 2XP2 and 4CLI.

Figure 11. The basis of selectivity of PI3K and mTOR inhibitors. (**a**) Chemical structures of inhibitors. (**b**) The PI3K δ -selective idelalisib²³⁸ (green) binds to PI3K δ through H-bonding interactions (broken lines) with the backbone amide bonds of the hinge region (cyan). Its selectivity derives predominantly from induced-fit binding of the quinazolinone substructure between the side chains of M752 and W760 (spheres). (**c**) An apo structure of PI3K δ ²³⁹ shows that the residues that differ between the four PI3K isoforms (magenta) are quite remote from the ligand in the PI3K δ -idelalisib complex (and other ligands in other complexes) and that the slot between the M752 and W760 residues is closed. Although the residues corresponding to M752 and W760 are conserved in all 4 PI3K isoforms, induced-fit binding as observed with idelalisib appears to be a selectivity feature of PI3K δ -selective compounds.²³⁹ (**d**) The PI3K α -selective alpelisib²⁴⁰ interacts closely (broken lines) with the side chain of Q859, one of the few residues around the ATP-binding pocket that are not conserved across the PI3Ks. (**e**) The pan-PI3K-selective buparlisip²⁴¹ binds to PI3K γ in a similar mode as alpelisib binds to PI3K δ but any selectivity-imparting features are absent. (**f**) The mTOR-selective compound torin 2²⁴² binds to mTOR without any of the usual hinge-region H-bonds. Its selectivity is probably due in large part to interaction of the naphthyridinone substructure with the indole of W2239 in the hinge, which is not conserved in PI3Ks.²⁴³ (**g**) The dual mTOR- and pan-PI3K inhibitor PI 103²⁴⁴ interacts with mTOR through polar interactions involving the morpholine O and the phenol OH groups.²⁴³ Similar interactions are also possible with any of the PI3K isoforms. Furthermore, PI 103 adopts an almost completely planar conformation, which can be accommodated in the mTOR and the PI3K ATP-binding sites, regardless of the width of the binding clefts. Constructed from PDB entries 4XE0, 2WXR, 4JPS, 3SD5, 4JSX, and 4JT6.

Figure 12. Type-I and type-III AKT inhibitors. (**a**) AZD 5363 and ipatasertib are type-I inhibitors, whereas inhibitor VIII¹⁵⁷ and MK 2206 are type-III inhibitors. (**b**) Compound VIII (salmon) binds to AKT (N-lobe dark cyan, C-lobe magenta, PH domain yellow) in an inactive conformation compared to the active state as represented by the superposed complex between AMP-PNP (green) and AKT1 (N-lobe light cyan, C-lobe grey). Compound VIII binds at a site adjacent to the ATP-binding site composed of portions of the N- and C-lobes, as well as the PH domain. Binding induces or stabilises an inactive kinase conformation with disordered α C-helix, altered N- and C-lobes, and an A-loop conformation that projects the F293 side chain of the DFG motif into the ATP-binding site (Phe side chain as spheres). (**c**) AZD 5363 (magenta) and ipatasertib (cyan) bind to active AKT conformations and in complex with AKT occupy the same space as ATP (AMP-PNP; green). MK 2206 (yellow; predominant pose obtained from Schrödinger Glide docking shown) probably binds in a very similar manner to AKT as compound VIII (salmon). Constructed from PDB entries 3O96, 4EKK, 4EKL, and 4GV1.

Figure 13. Structural basis of MEK inhibition. MEK1 and MEK2 are comparatively unique insofar as these kinases contain an allosteric binding site adjacent to, but not overlapping, with the ATP-binding pocket. This exosite is evident in ATP/Mg²⁺-bound structures (**a**), as well as in complexes with type-I inhibitors (e.g. K252a,

b).²⁴⁵ A number of ATP non-competitive MEK inhibitors have been discovered that occupy this exosite, thus distorting the catalytic site and inactivating the enzyme (e.g. rafametinib (grey), superposed with ATP (cyan), **c).**²⁴⁶ The 2-fluoro-4-iodo-aniline system of rafametinib has high shape complementarity with the lipophilic back-pocket of the exosite (**d**) and is in fact present in most known type-III MEK inhibitors, including 7 of 8 current clinical MEK inhibitors (**e**). Protein structures are shown as green surfaces or meshes; ATP and related nucleosides are shown as cyan sticks (Mg^{2+} as green spheres), allosteric inhibitors as grey sticks, and K252a as yellow sticks. Constructed from PDB entries 1S9J, 2P55, 3DV3, 3DY7, 3E8N, 3EQB, 3EQC, 3EQD, 3EQF, 3EQG, 3EQH, 3EQI, 3MBL, 3ORN, 3OS3, 3PP1, 3SLS, 3V01, 3V04, 4AN2, 4AN3, 4AN9, 4ANB, and 1S9I.

Figure 14. Predicted biopharmaceutical properties of kinase inhibitors compared to all approved drugs. According to the Biopharmaceutics Classification System (BCS),²⁴⁷ oral drugs belong to class I if they are highly permeable and highly soluble, class II if highly permeable but of low solubility, class III if poorly permeable but highly soluble, and class IV if both poorly permeable and soluble. For the purposes of bioequivalence and other preclinical and clinical drug development studies class boundaries are based on solubility of the highest dose strength and permeability as assessed by pharmacokinetic comparison of oral and intravenous dosing. Here an attempt is made to predict such classifications based on calculated solubility (logS derived from intrinsic aqueous molar solubility) and permeability (logP; predicted octanol–water partition coefficient). LogS and logP values of -4.52 ($30 \mu M$) and 1.35 , respectively, were used to set the class boundaries.²⁴⁸ It can be seen that using this approximation it is predicted that the majority of kinase inhibitors fall into class II, some into class I, a few into class III, and very few into class IV.

Figure 15. Chemical similarity of oncology kinase inhibitors and all approved drugs. Dissimilarity was calculated using Tanimoto distances based on ChemAxon chemical fingerprints (CF; <http://www.chemaxon.com/jchem/doc/user/>). Only inhibitor groups of ≥ 5 compounds are included in the analysis.

Figure 16. Maximum common substructure (MCS) clustering of clinical kinase inhibitors. The chemical structures of the 172 experimental kinase inhibitor drugs were submitted to hierarchical MCS clustering using the LibMCS programme (www.chemaxon.com). The dendrogram shows that this analysis results in 44 top-level clusters, of which 1 has 5 levels, 10 have 3 levels, 25 have 2 levels, and 7 have 1 level. For top-level clusters containing 3 or more common substructures, these are shown.

Figure 17. Fragment-based discovery of the AKT inhibitor AZD 5363. **(a)** Fragment screening against AKT2 identified 7-azapurine as a promising hinge-binding starting point. **(b)** Fragment growing led to the benzylamine-substituted purine intermediate 1 and **(c)** replacement of the phenyl group with piperidine afforded the hydrophilic intermediate 2. **(d)** Modulation of polarity and further fragment growing yielded the highly active intermediate 3, from which **(e)** AZD 5363 itself was derived. **(f)** Fragment growing was guided by the known binding mode of the pharmacophorically related isoquinoline-5-sulfonamide CCT 077373. pIC_{50} values refer to AKT2 inhibition. Predicted logP values were calculated using Instant JChem (www.chemaxon.com). Ligand efficiency (LE) was calculated from pIC_{50} values and lipophilic ligand efficiency (LLE) values were calculated from pIC_{50} and predicted logP.²⁴⁹ Binding mode illustrations were constructed from PDB entries 2JDO, 2UVX, 2UVY, 2VNW, 2X39, and 4GV1. Ligands are shown as cyan stick models, H-bonds as broken yellow lines, and ligand H-bonded water molecules as red spheres. Hinge-region residues involved in ligand H-bonding, charged residues in the ribose-binding region involved in polar ligand interactions, as well as a mobile Phe residue in the G-loop are shown as line models.

Table 1. Comparative structural and physicochemical properties of kinase inhibitor experimental drugs.^a

Parameter ^b	Oncology kinase inhibitors ^c	All approved drugs ^d
M_r	475 ± 95 (464)	374 ± 121 (351)
nRot	6.2 ± 2.6 (6)	5.6 ± 3.9 (5)
HBA	6.1 ± 2.0 (6)	4.7 ± 2.9 (4)
HBD	2.2 ± 1.0 (2)	1.9 ± 1.9 (1)
TPSA (Å ²)	100 ± 31 (94)	82 ± 54 (73)
nRing	4.5 ± 1.1 (4)	2.9 ± 1.5 (3)
nAr	3.4 ± 1.0 (3)	1.6 ± 1.1 (2)
nChir	0.7 ± 1.8 (0)	2.1 ± 3.0 (1)
logP	3.4 ± 1.6 (3.5)	2.1 ± 2.8 (2.5)
logD _{6.5}	2.6 ± 1.7 (2.7)	0.7 ± 3.5 (1.2)
logS	-5.4 ± 1.3 (-5.4)	-3.7 ± 2.0 (-3.8)

^aValues are average ± standard deviation (median). ^bnRot, number of nonterminal rotatable bonds; HBA, number of H-bond acceptors; HBD, number of H-bond donors; TPSA, topological polar surface area; nRing, number of rings; nAr, number of aromatic rings; nChir, number of chiral centres; log P, predicted octanol–water partition coefficient; log D_{6.5}, predicted octanol–water distribution coefficient at pH = 6.5; log S, predicted intrinsic molar aqueous solubility. ^cOncology kinase inhibitors, n = 172; ^dall approved drugs, n = 1,478 (data from <http://www.drugbank.ca/>), for small-molecule drugs with 200 < M_r < 800, excluding inorganics, nutraceuticals, and illicit drugs). TPSA, logP, logD, and logS were predicted using the Instant JChem application (<https://www.chemaxon.com/products/instant-jchem-suite/instant-jchem/>).

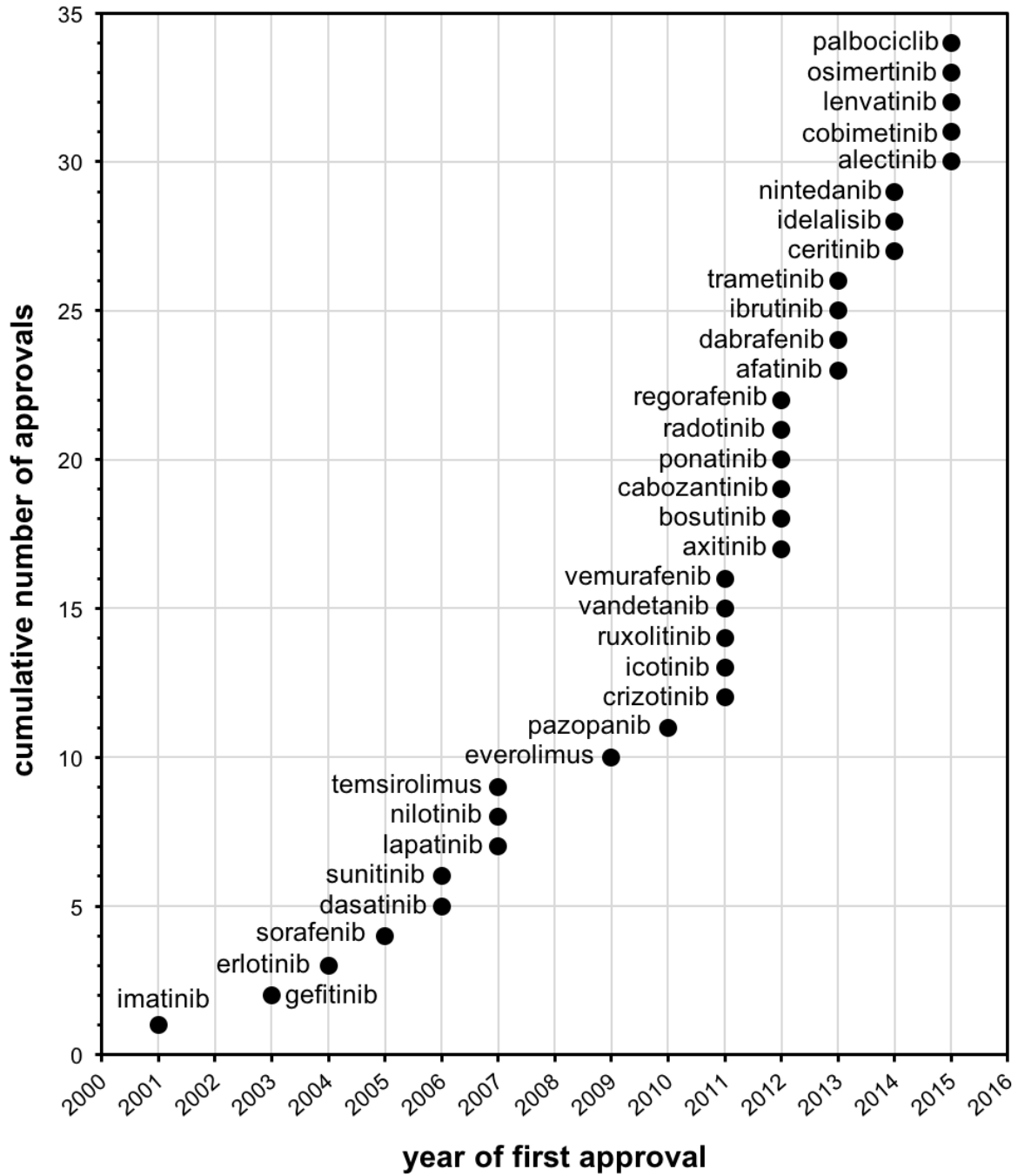


Figure 1

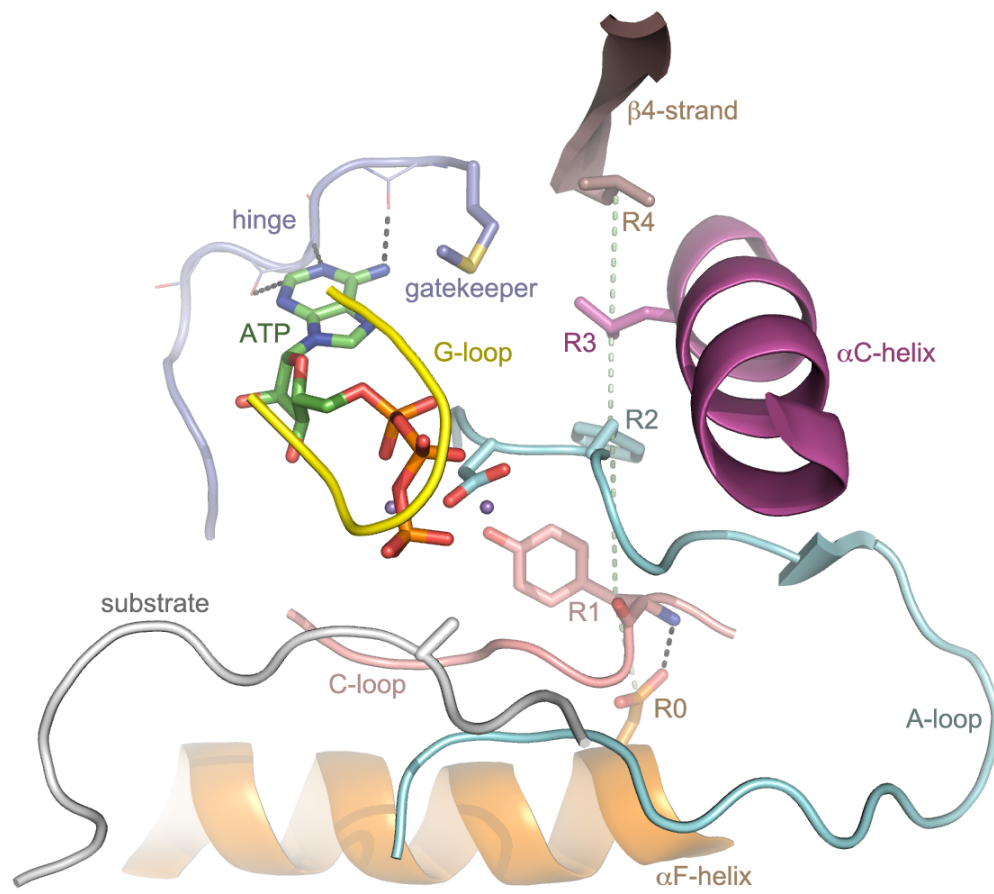


Figure 2

a

receptor (R) – ligand (L) interactions				
mechanism	equation	dissociation constant	residence time	receptor occupancy
A	$R + L \xrightleftharpoons[k_2]{k_1} RL$	$K_d = \frac{k_2}{k_1}$	$\tau = \frac{1}{k_2}$	$f_{o_t} = \frac{[L]_t}{[L]_t + K_d}$
B	$R + L \xrightleftharpoons[k_2]{k_1} RL \xrightleftharpoons[k_4]{k_3} R^*L$	$K_d^* = \frac{K_d}{1 + \frac{k_3}{k_4}}$	$\tau = \frac{k_2 + k_3 + k_4}{k_2 k_4}$	$f_{o_t} = \frac{[L]_t}{[L]_t + \frac{k_2}{k_1 + \frac{k_1 k_3}{k_4}}}$
C	$R \xrightleftharpoons[k_2]{k_1} R^* \xrightleftharpoons[k_4]{k_3 [L]} R^*L$	$K_d^* = \frac{k_4}{k_3}$	$\tau = \frac{1}{k_4}$	
selectivity indices (SI)				
based on receptor affinity		based on receptor occupancy		
$SI_1 = \frac{K_d(\text{off-target})}{K_d(\text{on-target})}$		$SI_2 = \frac{f_{o_{\text{on-target}}}}{f_{o_{\text{off-target}}}} = \frac{\frac{C_{\text{ssf}}}{K_d(\text{on-target}) + C_{\text{ssf}}}}{\frac{C_{\text{ssf}}}{K_d(\text{off-target}) + C_{\text{ssf}}}} = \frac{K_d(\text{off-target}) + C_{\text{ssf}}}{K_d(\text{on-target}) + C_{\text{ssf}}}$		

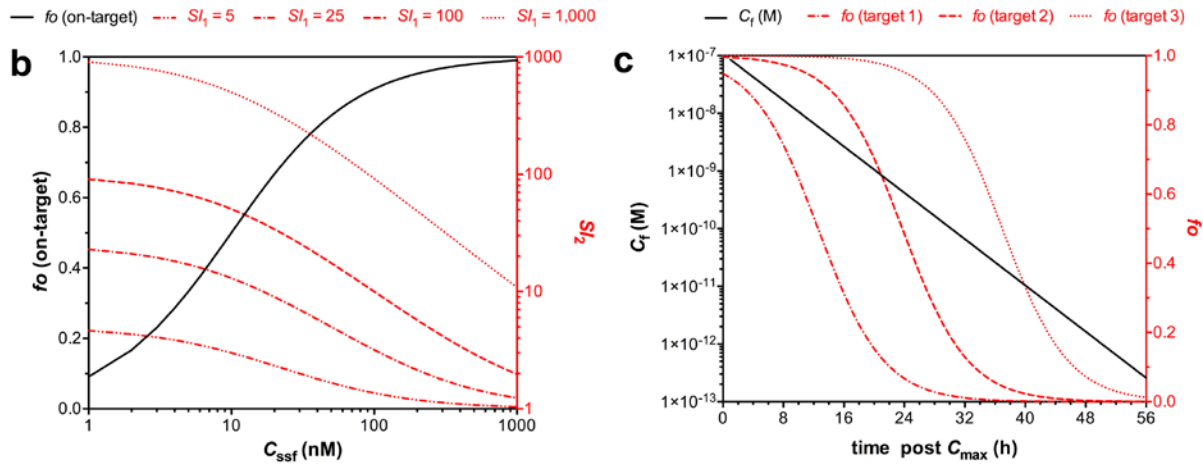


Figure 3

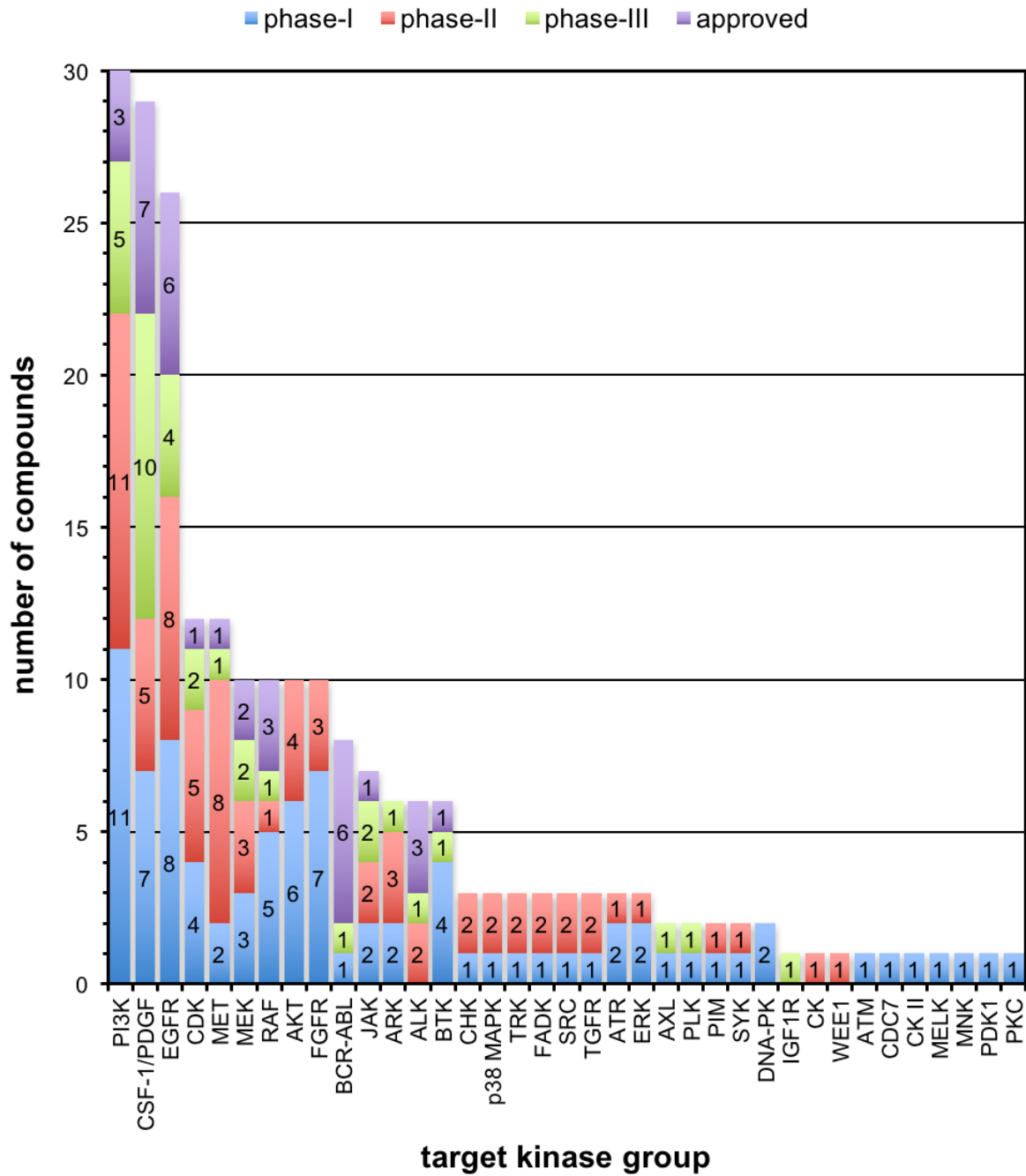


Figure 4

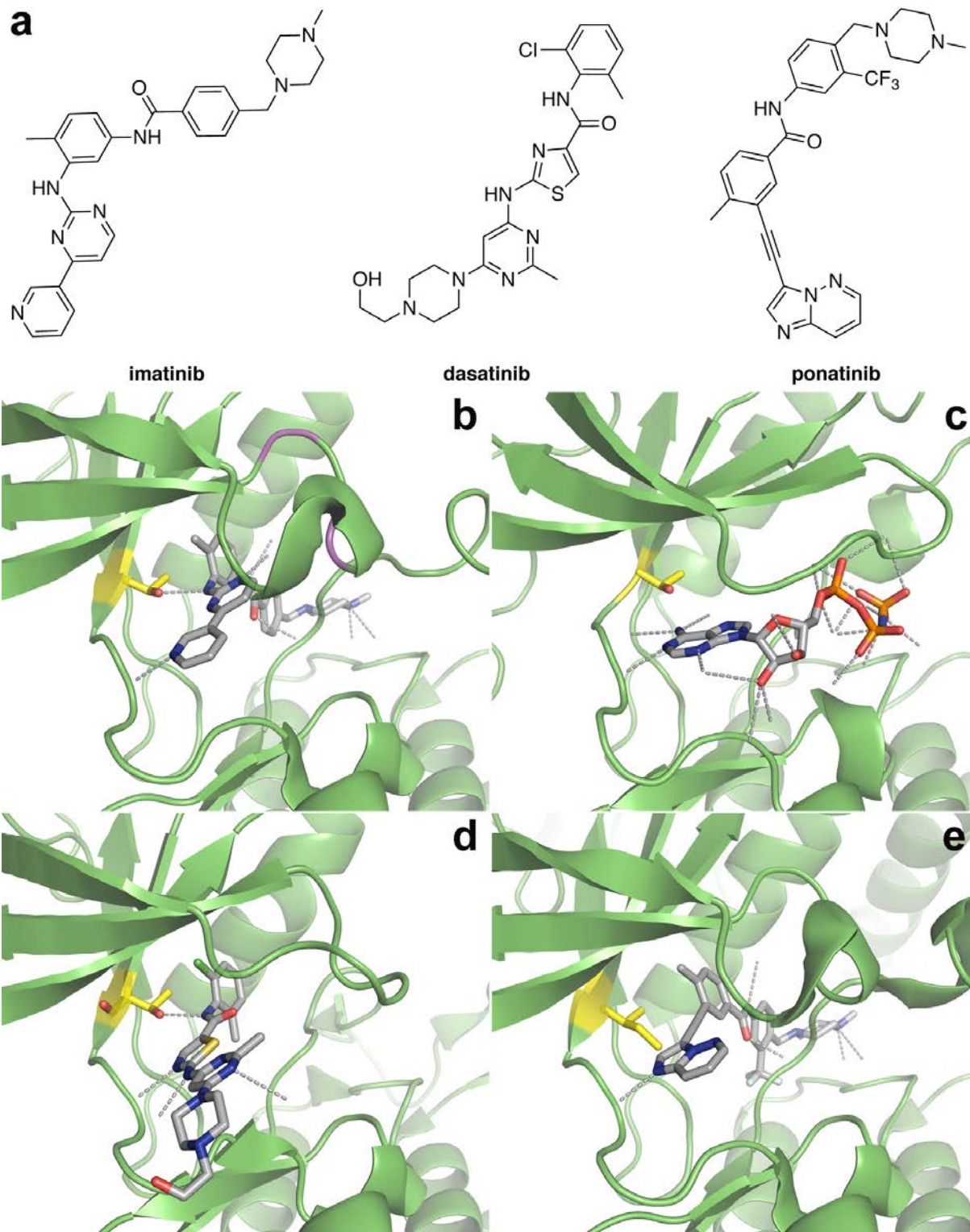


Figure 5

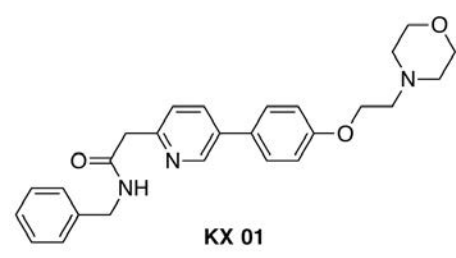
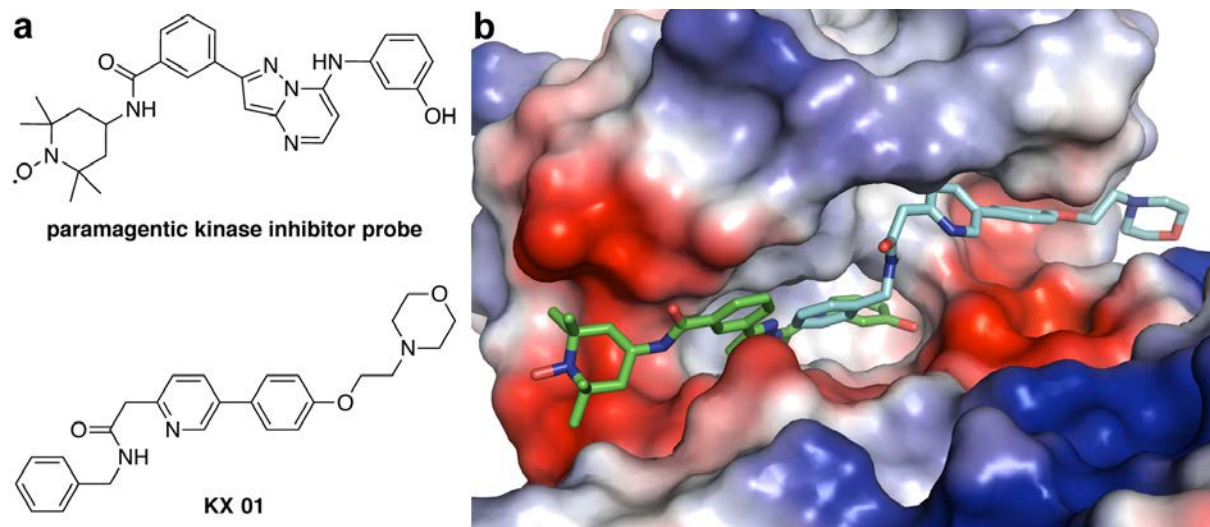


Figure 6

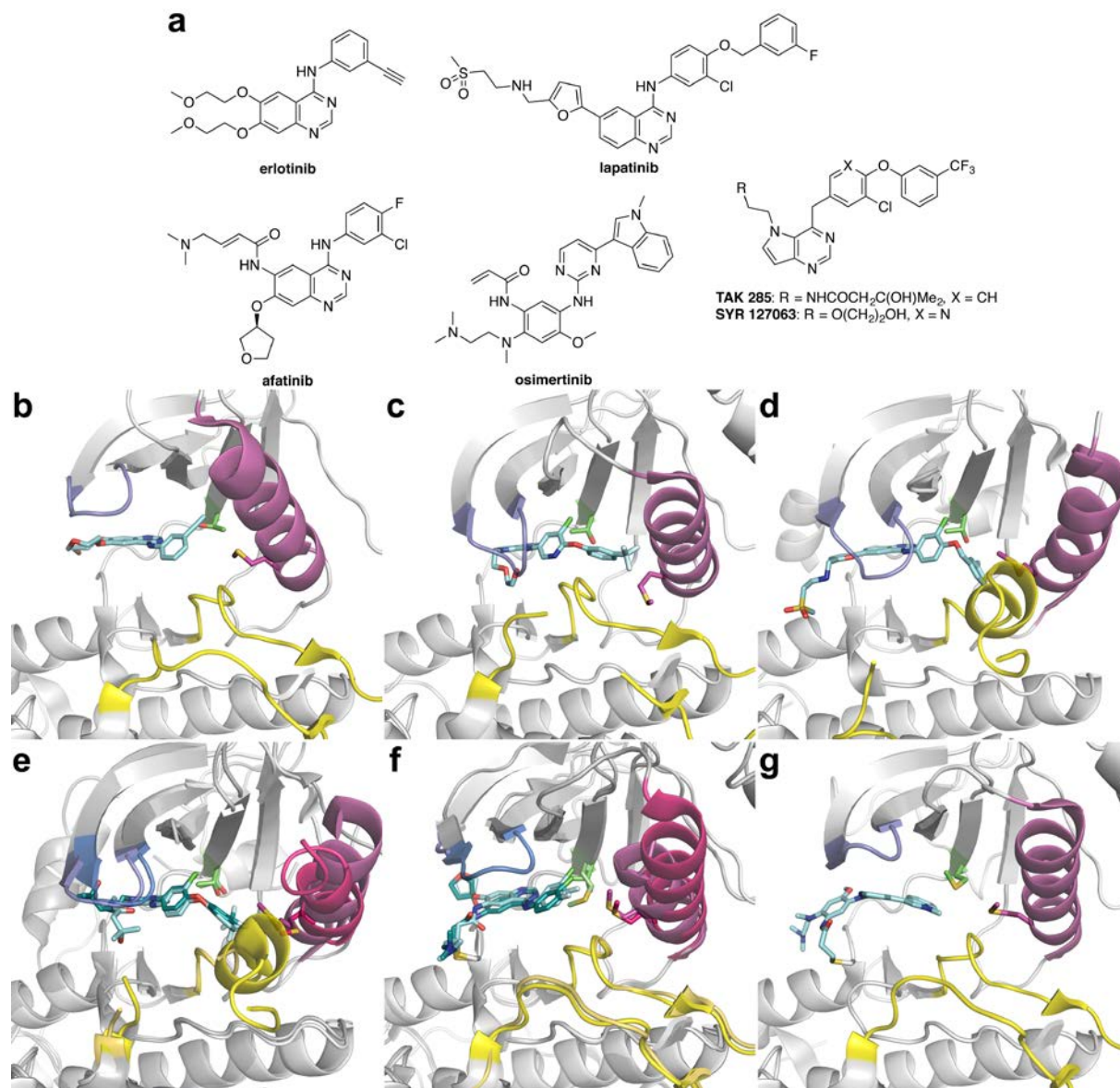


Figure 7

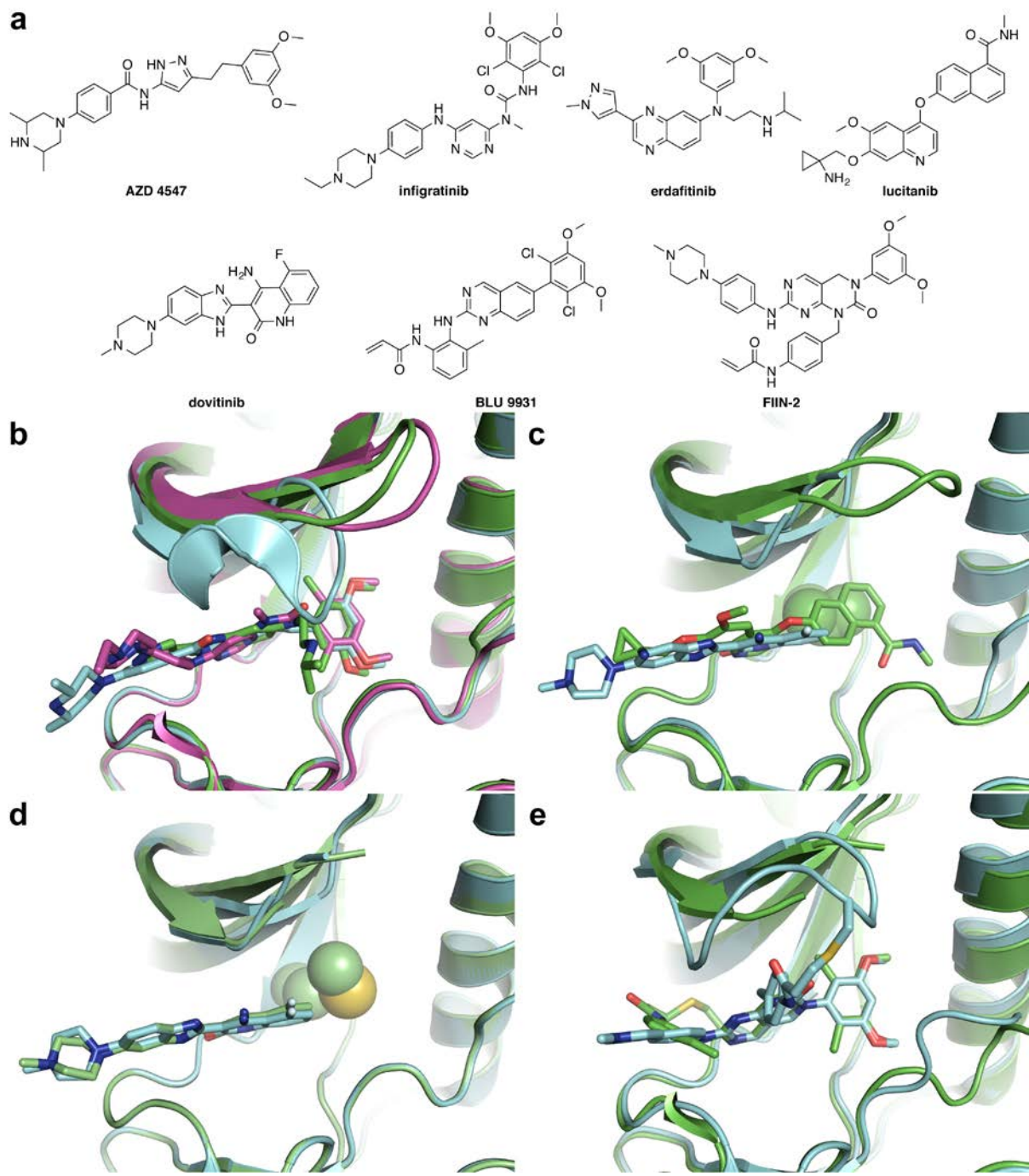


Figure 8

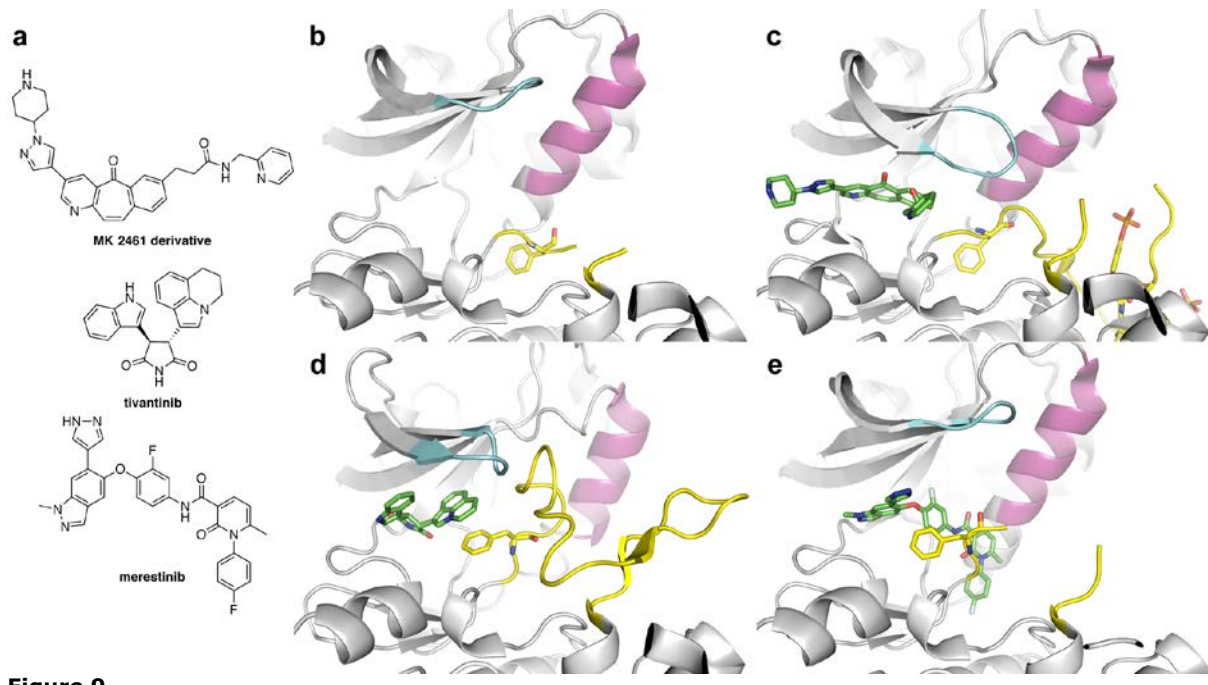
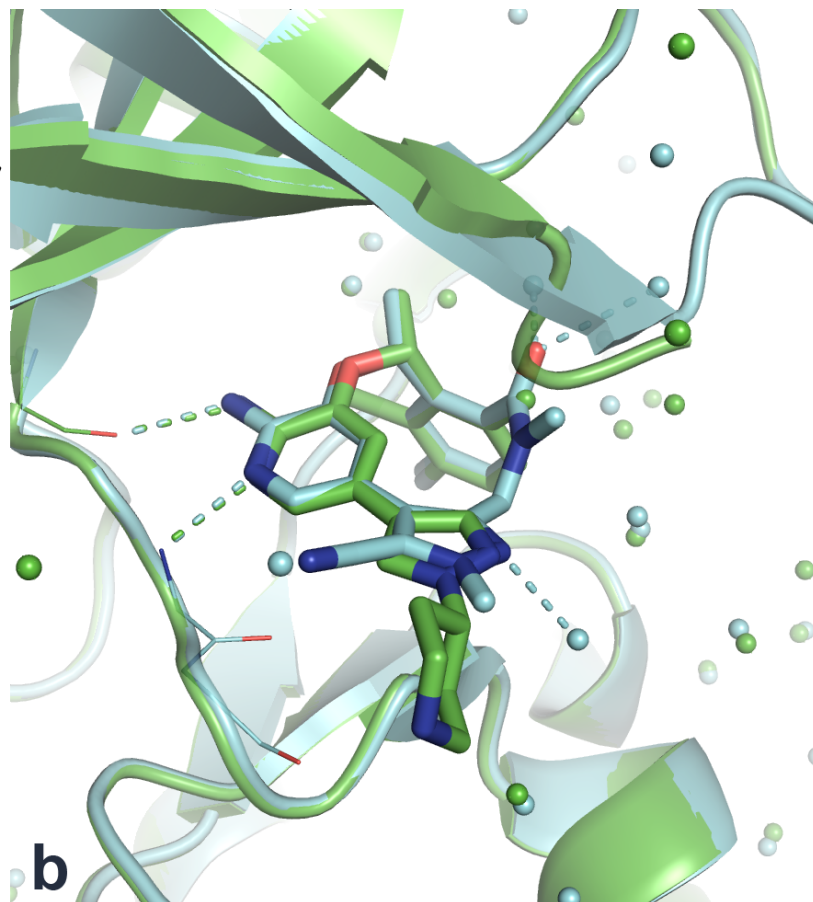
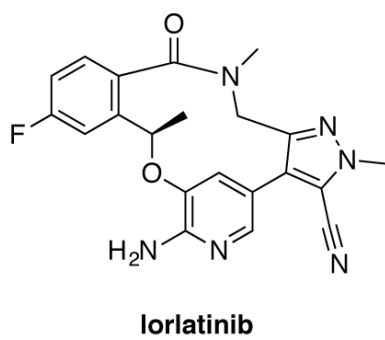
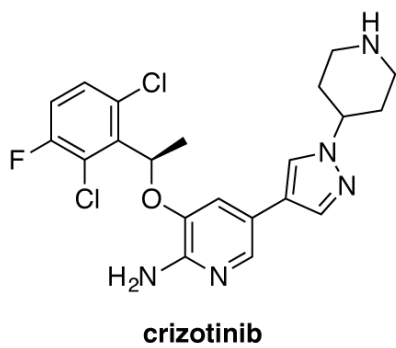


Figure 9



a
Figure 10

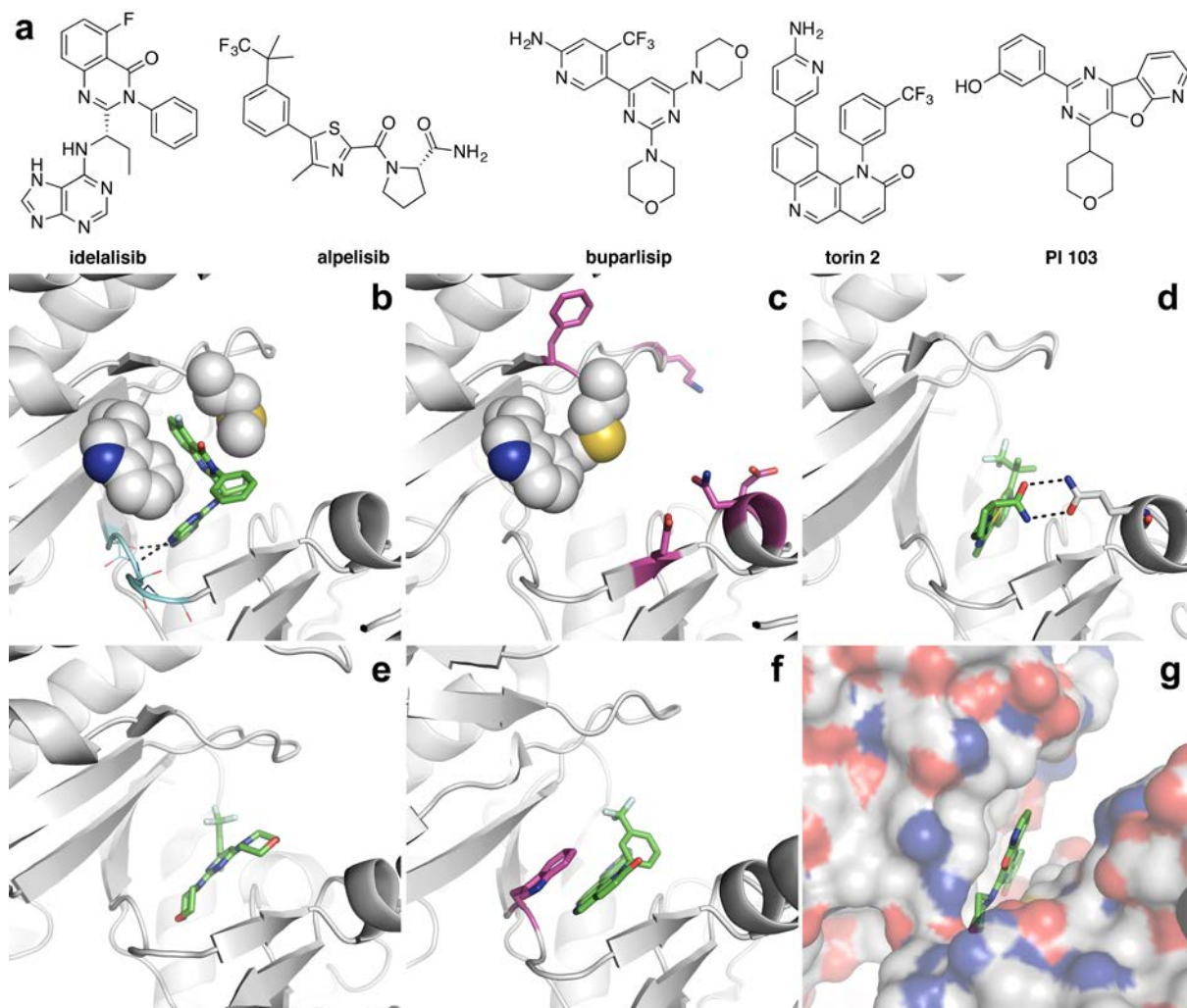


Figure 11

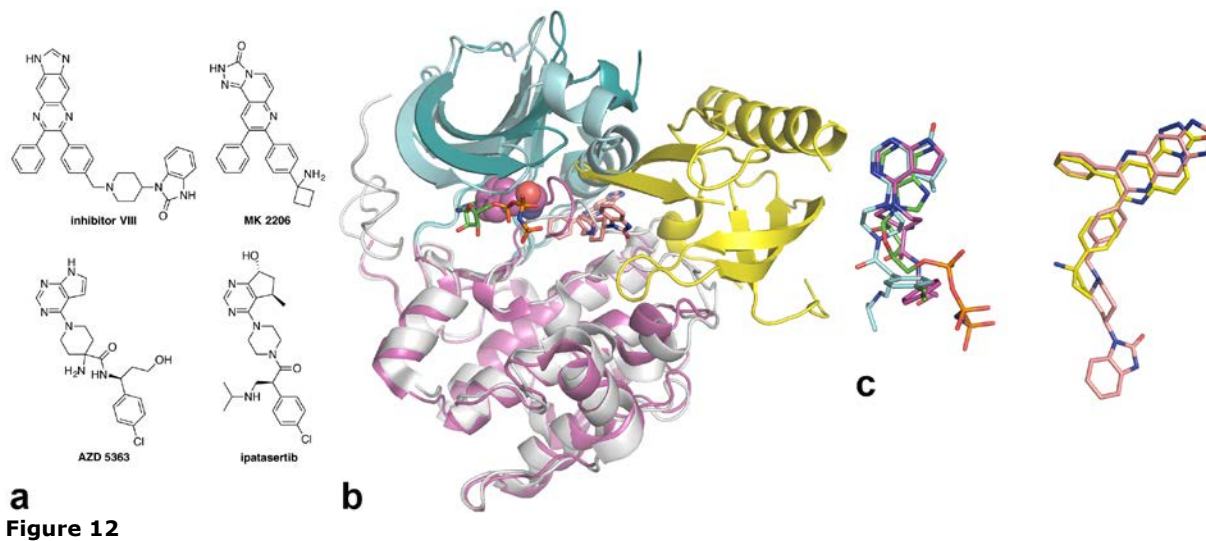


Figure 12

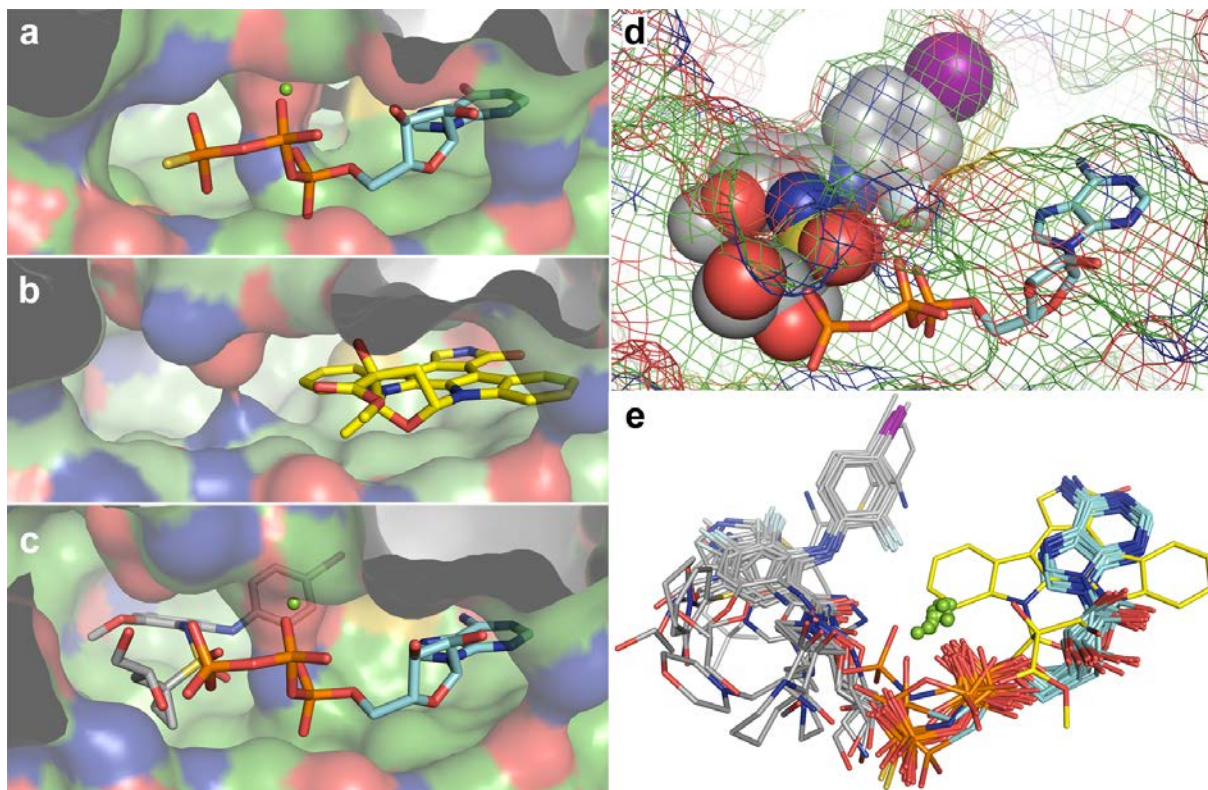


Figure 13

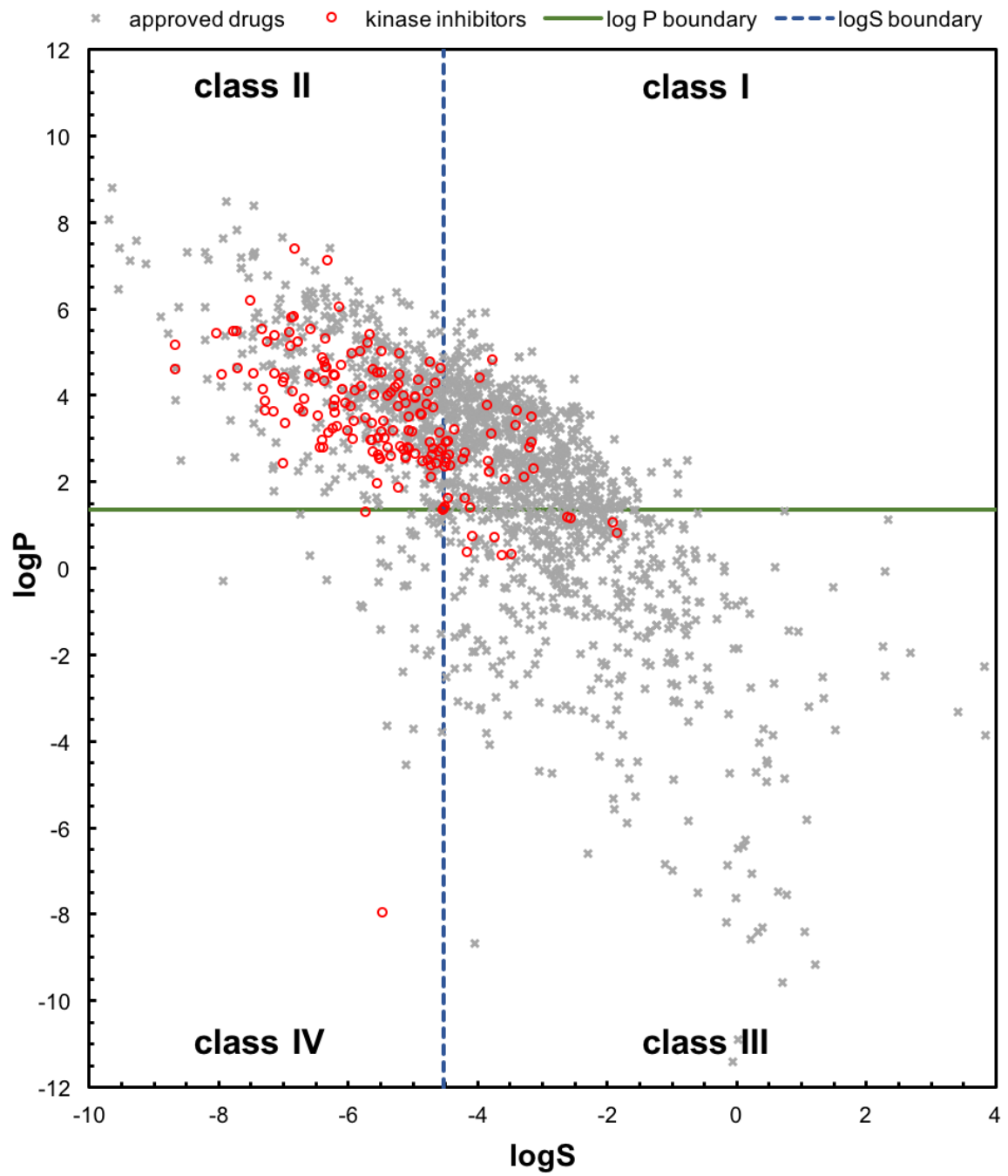


Figure 14

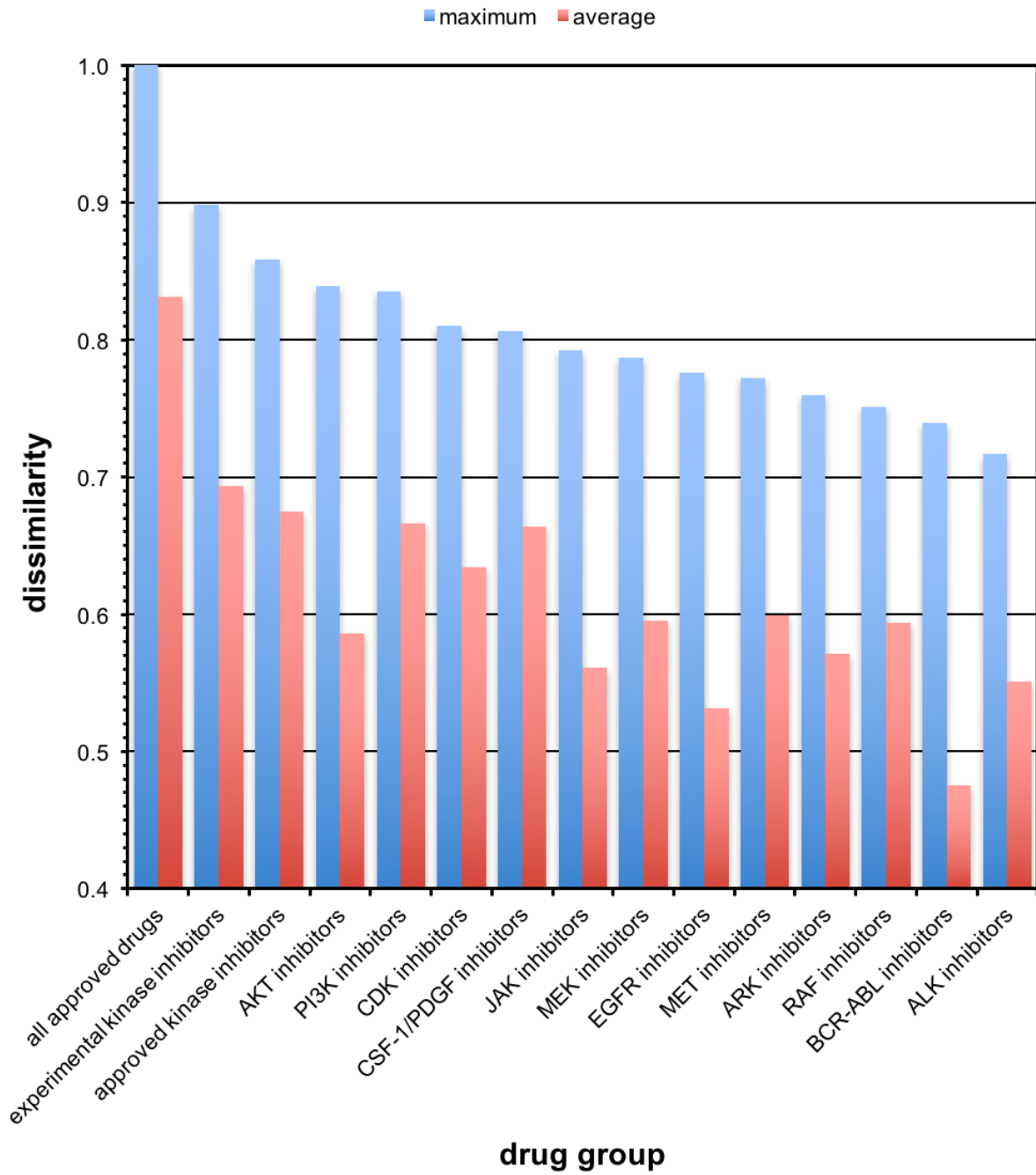


Figure 15

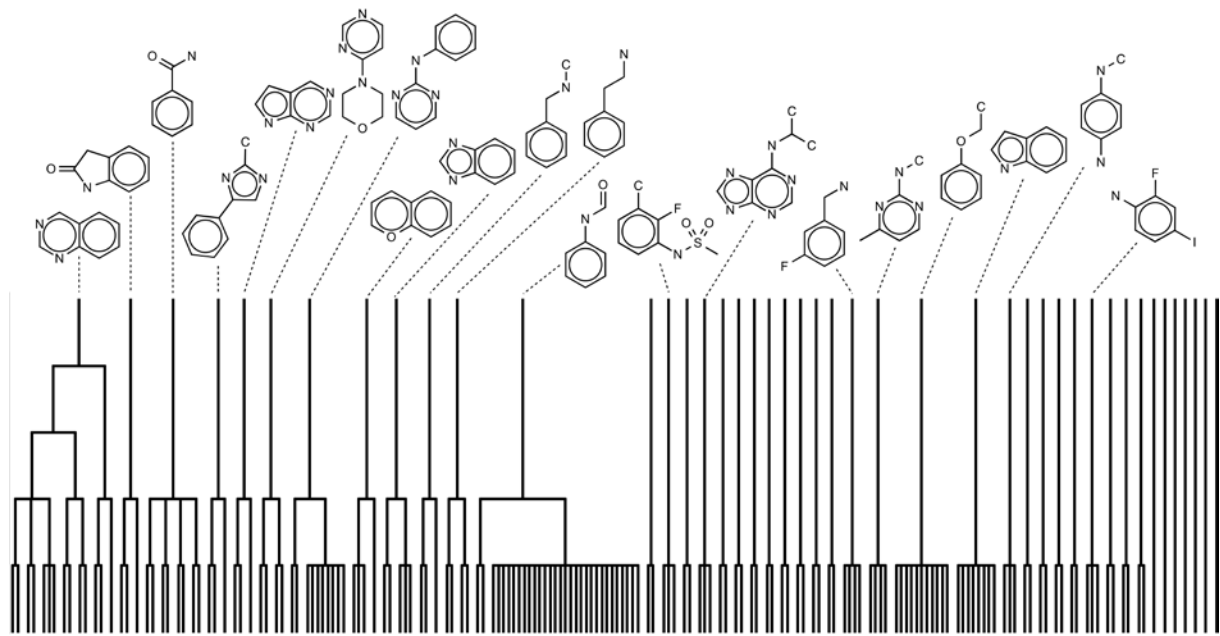


Figure 16

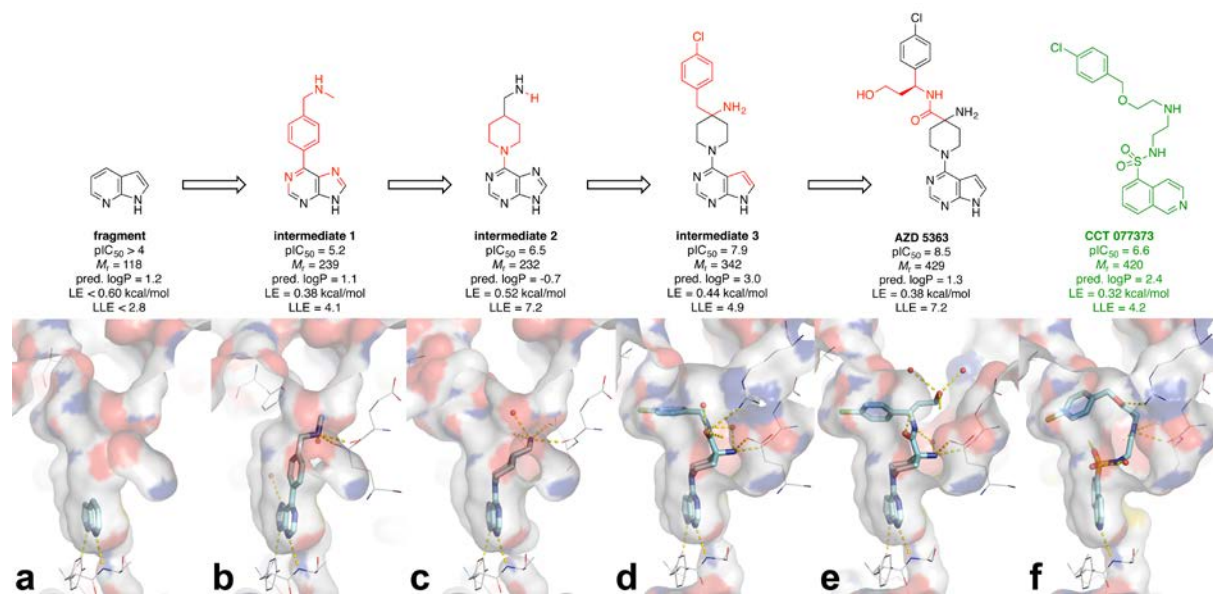


Figure 17

Table S1. Protein kinase nomenclature.

Name	Abbreviation	Synonyms	Gene	UniProtKB entry ^a
Tyrosine-protein kinase ABL1	ABL1	c-Abl	ABL1 (ABL, JTK7)	P00519
Tyrosine-protein kinase ABL2	ABL2	ARG	ABL2 (ABLL, ARG)	P42684
RAC-alpha serine/threonine-protein kinase, protein kinase B alpha	AKT1	PKB α	AKT1	P31749
RAC-beta serine/threonine-protein kinase, protein kinase B beta	AKT2	PKB β	AKT2	P31751
ALK tyrosine kinase receptor, anaplastic lymphoma kinase	ALK		ALK	Q9UM73
Aurora kinase A, aurora 2	ARK1		AURKA, ARK1, AURA	O14965
Aurora kinase B, aurora 1	ARK2	STK1	AURKB, ARK2, STK1	Q96GD4
Aurora kinase C, aurora 3	ARK3		AURKC, ARK3	Q9UQB9
Serine-protein kinase ATM, ataxia telangiectasia mutated	ATM		ATM	Q13315
Serine/threonine-protein kinase ATR, ataxia telangiectasia and Rad3-related protein, FRAP-related protein 1	ATR		ATR, FRP1	Q13535
Tyrosine-protein kinase receptor UFO, AXL oncogene	AXL		AXL, UFO	P30530
Serine/threonine-protein kinase A-Raf	A-RAF	PKS	ARAF1 (PKS, PKS2)	P10398
Serine/threonine-protein kinase B-Raf	B-RAF		BRAF1, RAFB1	P15056
Tyrosine-protein kinase BTK, Bruton tyrosine kinase	BTK	ATK	BTK, AGMX1, ATK, BPK	Q06187
Cell division cycle 7-related protein kinase	CDC7			O00311
Cyclin-dependent kinase 1	CDK1		CDK1, CDC2, CDKN1	P06493
Cyclin-dependent kinase 2	CDK2		CDK2, CDKN2	P24941
Cyclin-dependent kinase 4	CDK4		CDK4	P11802
Cyclin-dependent kinase 6	CDK6		CDK6, CDKN6	Q00534
Cyclin-dependent kinase 7	CDK7		CDK7, CAK, CDKN7, MO15, STK1	P50613
Cyclin-dependent kinase 9	CDK9		CDK9, CDC2L4, TAK	P50750
Serine/threonine-protein kinase Chk1, checkpoint kinase-1	CHK1		CHEK1, CHK1	O14757
Serine/threonine-protein kinase Chk2, checkpoint kinase-2	CHK2		CHEK2, CDS1, CHK2, RAD53	O96017
Choline kinase alpha	CK	CHETK- α	CHKA, CHK, CKI	P35790
Casein kinase II subunit alpha	CK II α		CSNK2A1, CK2A1	P68400
RAF proto-oncogene serine/threonine-protein kinase	C-RAF	RAF-1	RAF1	P04049
Proto-oncogene tyrosine-protein kinase Src	C-SRC		SRC	P12931
Macrophage colony-stimulating factor 1 receptor	CSF1R	c-Fms	CSF1R (FMS)	P07333
DNA-dependent protein kinase catalytic subunit	DNA-PKcs	DNAPK1, p460	PRKDC, HYRC, HYRC1	P78527
Epidermal growth factor receptor	EGFR	ErbB1, HER1	EGFR (ERBB, ERBB1, HER1)	P00533
Receptor tyrosine-protein kinase erbB-2	ERBB2	MLN19, NEU, HER2	ERBB2 (HER2, MLN19, NEU, NGL)	P04626
Receptor tyrosine-protein kinase erbB-3	ERBB3	HER3	ERBB3 (HER3)	P21860
Receptor tyrosine-protein kinase erbB-4	ERBB4	HER4	ERBB4 (HER4)	Q15303
Focal adhesion kinase 1	FADK1		PTK2, FAK, FAK1	Q05397
Protein-tyrosine kinase 2-beta, focal adhesion kinase 2	FADK2	CADTK	PTK2B, FAK2, PYK2, RAFTK	Q14289
Basic fibroblast growth factor receptor 1, Fms-like tyrosine kinase 2	FGFR1	bFGF-R-1, FLT1	FGFR1	P11362
Fibroblast growth factor receptor 2, Keratinocyte growth factor receptor	FGFR2	K-sam	FGFR2	P21802
Fibroblast growth factor receptor 3	FGFR3		FGFR3	P22607
Fibroblast growth factor receptor 4	FGFR4		FGFR4	P22455
Receptor-type tyrosine-protein kinase FLT3	FLT3	FLK2, STK1	FLT3 (CD135, FLK2, STK1)	P36888
Hepatocyte growth factor receptor	HGFR	MET	MET	P08581

Insulin-like growth factor 1 receptor	IGF1R		IGFR1	P08069
Insulin receptor	IR	CD220	ISNR	P06213
Tyrosine-protein kinase JAK1, Janus kinase 1	JAK1		JAK1 (JAK1A, JAK1B)	P23458
Tyrosine-protein kinase JAK2, Janus kinase 2	JAK2		JAK2	O60674
Tyrosine-protein kinase JAK3, Janus kinase 3	JAK3	LJAK	JAK3	P52333
Tyrosine-protein kinase Lck, leukocyte C-terminal Src kinase	LCK	LSK, p56-LCK	LCK	P06239
Mitogen-activated protein kinase 1, extracellular signal-regulated kinase 2	MAPK1	ERK2, MAPK2, p42-MAPK	MAPK1	P28482
Mitogen-activated protein kinase 3, extracellular signal-regulated kinase 1	MAPK3	ERK1, MAP2K, p44-MAPK	MAPK3	P27361
Dual specificity mitogen-activated protein kinase kinase 1	MAPKK1	MKK1, MEK1	MAP2K1 (MEK1, PRKMK1)	Q02750
Dual specificity mitogen-activated protein kinase kinase 2	MAPKK2	MEK2	MAP2K2 (MEK2, MKK2, PRKMK2)	P36507
Mitogen-activated protein kinase 14; Mitogen-activated protein kinase p38- α	MAPK14	p38- α	MAPK14, CSBP, MXI2, SAPK2A	Q16539
Maternal embryonic leucine zipper kinase	MELK		MELK	Q14680
MAP kinase-interacting serine/threonine-protein kinase 1	MNK1		MKNK1, MNK1	Q9BUB5
MAP kinase-interacting serine/threonine-protein kinase 2	MNK2		MKNK2, GPRK7, MNK2	Q9HBH9
Serine/threonine-protein kinase mTOR	mTOR	mTOR1	MTOR (FRAP, FRAP1, FRAP2, RAFT1, RAPT1)	P42345
Platelet-derived growth factor receptor alpha	PDGFR α	PDGFR2	PDGFR2 (PDGFR2, RHEPDGFRA)	P16234
Platelet-derived growth factor receptor beta	PDGFR β	PDGFR1	PDGFRB (PDGFR, PDGFR1)	P09619
3-Phosphoinositide-dependent protein kinase 1	PDK1	PDPK1	PDPK1 (PDK1)	O15530
Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform	PI3K α	p110 α	PIK3CA	P42336
Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta isoform	PI3K β	p110 β	PIK3C1	P42338
Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta isoform	PI3K δ	p110 δ	PIK3CD	O00329
Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma isoform	PI3K γ	p110 γ	PI3CG	P48736
cAMP-dependent protein kinase catalytic subunit alpha	PKA C- α		PRKACA	P17612
Protein kinase C beta type	PKC β		PRKCB, PKCB	P05771
Serine/threonine-protein kinase pim-1	PIM1		PIM1	P11309
Serine/threonine-protein kinase pim-2	PIM2		PIM2	Q9P1W9
Serine/threonine-protein kinase pim-3	PIM3		PIM3	Q86V86
RAC-alpha serine/threonine-protein kinase, protein kinase B	PKB	PKB α , c-Akt	AKT1 (PKB, RAC)	P31749
Serine/threonine protein kinase PLK1, polo-like kinase 1	PLK1	STPK13	PLK1, PLK	P53350
Serine/threonine protein kinase PLK4, polo-like kinase 4	PLK4	SAK	PLK4, SAK	O00444
Proto-oncogene tyrosine-protein kinase receptor Ret	RET			P07949
Rho-associated protein kinase 1	ROCK-I	p160ROCK	ROCK1	Q13464
Rho-associated protein kinase 2	ROCK-II	p164 ROCK-2	ROCK2	O75116
Mast/stem cell growth factor receptor Kit	SCFR	c-Kit	KIT (SCFR)	P10721
Serine/threonine-protein kinase SMG1	SMG1		SMG1, ATX, KIAA0421, LIP	Q96Q15
Tyrosine-protein kinase SYK, spleen tyrosine kinase	SYK		SYK	P43405
Angiopoietin-1 receptor; tunica interna endothelial cell kinase	TEK	TIE2		Q02763
Transforming growth factor-beta receptor type I	TGFR1	ALK5, SKR4	TGFBR1 (ALK5, SRK4)	P36897
High affinity nerve growth factor receptor, tropomyosin-related kinase A	TRK1	TRKA	NTRK1, MTC, TRK, TRKA	P04629
BDNF/NT-3 growth factors receptor, tropomyosin-related kinase B	TRK2	TRKB	NTRK2, TRKB	Q16620
NT-3 growth factor receptor	TRK3	TRKC	NTRK3, TRKC	Q16288
Transformation/transcription domain-associated protein	TRRAP	STAF40	TRRAP, PAF400	Q9Y4A5
Non-receptor tyrosine-protein kinase TYK2	TYK2		TYK2	P29597
Vascular endothelial growth factor receptor 1	VEGFR1	FLT1, FRT	FLT1 (FLT, FRT, VEGFR1)	P17948
Vascular endothelial growth factor receptor 2	VEGFR2	KDR, FLK1	KDR (FLK1, VEGFR2)	P35968

Vascular endothelial growth factor receptor 3	VEGFR3	FLT4	FLT4 (VEGFR3)	P35916
Wee1-like protein kinase	WEE1	WEE1A	WEE1	P30291

^a <http://www.uniprot.org/>

Table S2. BCR-ABL inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
Gleevec	Imatinib	STI 571	Novartis	ABL, PDGFR, SCFR, SRC	Approved MAY 2001	1
Sprycel	Dasatinib	BMS 354825	BMS	ABL, mutant ABL, SRC (MTKI)	Approved JUN 2006	2
Tasigna	Nilotinib	AMN 107	Novartis	ABL, mutant ABL, PDGFR, SRC	Approved OCT 2007	3
Bosulif	Bosutinib	SKI 606	Pfizer	ABL, mutant ABL, SRC	Approved SEP 2012	4
Iclusig	Ponatinib	AP 24534	Ariad	ABL, mutant ABL, SRC, VEGFR, PDGFR, FGFR (MTKI)	Approved DEC 2012	5
Supect	Radotinib	IY 5511	Il-Yang Pharmaceutical	ABL, mutant ABL	Approved OCT 2012 (S. Korea)	6
	Flumatinib		Jiangsu Hansoh Pharmaceutical	ABL, mutant ABL, PDGFRF, SCFR, SRC	Phase-III	7
		ABL 001	Novartis	ABL	Phase-I	8

Table S3. SRC kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
		KX 01	Thenex & Hanmi	SRC	Phase-II	9
	Saracatinib	AZD 0530	AstraZeneca	SRC, ABL	Phase-II	10
		AZD 0424	AstraZeneca	SRC, ABL	Phase-I	11

Table S4. Epidermal growth factor receptor tyrosine kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
Iressa	Gefitinib	AZD 1839	AstraZeneca	HER1	Approved JUL 2003	12
Tarceva	Erlotinib	OSI 744	OSI	HER1	Approved NOV 2004	13
Tykerb	Lapatinib	GSK 572016	GSK	HER2, HER1	Approved MAR 2007	14
Conmana	Icotinib	BPI-2009H	BettaPharma	HER1, HER2	Approved JUN 2011 (China)	15
Gilotrif	Afatinib	BIBW 2992	Boehringer-Ingelheim	HER1, HER2, HER4, T790M HER1	Approved JUL 2013	16
Tagrissa	Osimertinib	AZD 9291	AstraZeneca	T790M HER1	Approved NOV 2015	17
	Neratinib	HKI 272	Puma Biotechnology	HER1, HER2, T790M HER1	Phase-III	18
	Dacomitinib	PF 299804	Pfizer	HER1, HER2, HER4, T790M HER1	Phase-III	19
		ASP 8273	Astellas	T790M HER1	Phase-III	20
	Rociletinib	CO 1686	Clovis Oncology	T790M HER1	Phase-III	21
	Sapitinib	AZD 8931	AstraZeneca	HER1, HER2	Phase-II	22
	Tesevatinib	KD 019	Kadmon	HER1, T790M HER1	Phase-II	23
	Varlitinib	ASLAN 001	Aslan & Array	HER1, HER2	Phase-II	24
		AZD 3759	AstraZeneca	HER1, HER2	Phase-II	25
	Poziotinib	HM781-36B	Spectrum & Hanmi Pharmaceutical	HER1, HER2, HER4, T790M HER1	Phase-II	26
		HM 61713	Hanmi Pharmaceuticals & Boehringer Ingelheim	T790M HER1	Phase-II	27
		EGF 816	Novartis	T790M HER1	Phase-II	28

	Tarloxotinib	TH 4000	Threshold Pharmaceuticals	HER1, HER2, T790M HER1	Phase-II	29
		S 222611	Shionogi	HER1, HER2, HER4	Phase-I	30
	Tucatinib	ONT 380	Oncothyreon	HER2	Phase-I	NCT02614794
		PF 06747775	Pfizer	T790M HER1	Phase-I	NCT02349633
	Epitinib	HMPL 813	Hutchison MediPharma	HER1	Phase-I	31
	Theliatinib	HMPL 309	Hutchison MediPharma	HER1	Phase-I	NCT02601274
	Avitinib		Acea Bio (Hangzhou)	T7980M HER1	Phase-I	32
	Pyrotinib		Jiangsu HengRui	HER1, HER2	Phase-I	33
	Pirotinib	KBP 5209	SihuanPharm	HER1, HER2, T790M HER1	Phase-I	NCT02442414

Table S5. Inhibitors of tyrosine kinases in the CSF-1/PDGFR receptor subfamily.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
Sutent	Sunitinib	SU 11248	Pfizer	VEGFR, PDGFR, FLT3, SCFR, RET (MTKI)	Approved JAN 2006	34
Votrient	Pazopanib	GW 786034B	GSK	VEGFR, PDGFR, FGFR, SCFR, FMS (MTKI)	Approved OCT 2010	35
Caprelsa	Vandetanib	AZD 6474	AstraZeneca	VEGFR, EGFR, PDGFR, FGFR, RET (MTKI)	Approved APR 2011	36
Inlyta	Axitinib	AG 013736	Pfizer	VEGFR, PDGFR, SCFR (MTKI)	Approved JAN 2012	37
Stivarga	Regorafenib	BAY 73-4506	Bayer	VEGFR, SCFR, RAF, PDGFR, FGFR, KIT (MTKI)	Approved SEP 2012	38
Vargatef (Ovef)	Nintedanib	BIBF 1120	Boehringer-Ingelheim	VEGF, PDGF, FGFR (MTKI)	Approved NOV 2014	39
Lenvima	Lenvatinib	E 7080	Eisai	VEGFR, FGFR, PDGFR, SCFR, RET (MTKI)	Approved FEB 2015	40
	Midostaurin	PKC 412	Novartis	FLT3 (MTKI)	Phase-III	41
Masivet	Masitinib	AB 1010	AB-Science	KIT, PDGFR, SCFR, FGFR (MTKI)	Phase-III	42
	Tivozanib	AV 951	Aveo & Kyowa Hakko Kirin	VEGFR (MTKI)	Phase-III	43
	Motesanib	AMG 706	Amgen & Millenium-Takeda	VGFR, PDGFR, SCFR (MTKI)	Phase-III	44
	Crenolanib	CP 868,596	Arog	PDGFR, SCFR, FLT3 (selective)	Phase-III	45
	Fruquintinib	HMPL 013	Hutchison MediPharma	VEGFR (selective)	Phase-III	46
	Quizartinib	AC 220	Daiichi	FLT3 (selective)	Phase-III	47
Recentin	Cediranib	AZD 2171	AstraZeneca	VEGFR, PDGFR (selective)	Phase-III	48
	Pexidartinib	PLX 3397	Daiichi & Plexxikon	CSF1R, SCFR, FLT3 (selective)	Phase-III	49
	Sulfatinib	HMPL 012	Hutchison MediPharma	VEGFR, FGFR	Phase-III	NCT02589821
	Apatinib	YN 968D1	LSK BioPharma	VEGF	Phase-II	50
	Lucitanib	E 3810	Clovis Oncology & Servier	VEGFR, CSF1R, FGFR (selective)	Phase-II	51
		X 82	Tyrogenex	VEGFR, PDGFR	Phase-II	NCT02146222
	Anlotinib	AL 3818	Advenchen	VEGFR, FGFR	Phase-II	NCT02649361
		AKN-028	Akinion	FLT3 (selective)	Phase-II	52
	Linifanib	ABT 869	Abbott	VEGFR, FLT3 (MTKI)	Phase-I	53
		PLX 9486	Plexxikon	KIT	Phase-I	NCT02401815
		PLX 7486	Plexxikon & Daiichi Sankyo	FLT3, pan-TRK	Phase-I	NCT01804530
		ARRY 382	Array	CSF1R	Phase-I	54
	Dovitinib	TKI 258	Novartis	VEGFR, FLT3, FGFR (MTKI)	Phase-I	55
	Sitravatinib	MGCD 516	Mirati	MTKI	Phase-I	56
	Tafetinib	SIM 010603	Nanjing Yoko Biomedical	MTKI	Phase-I	57

Table S6. Fibroblast growth factor receptor kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
		AZD 4547	AstraZeneca	Pan-FGFR	Phase-II	58
	Infigratinib	BGJ 398	Novartis	pan-FGFR	Phase-II	59
	Erdafitinib	JNJ 42756493	Jansen	pan-FGFR	Phase-II	60
		E 7090	Eisai	pan-FGFR	Phase-I	61
		BAY 1163877	Bayer	pan-FGFR	Phase-I	62
		ARQ 087	ArQule	FGFR	Phase-I	63
		INCB 054828	Incyte	FGFR	Phase-I	64
		PRN 1371	Principia Biopharma	FGFR	Phase-I	65
		FGF 401	Novartis	FGFR4	Phase-I	NCT02325739
		TAS 120	Taiho Pharmaceutical	pan-FGFR	Phase-I	66

Table S7. Hepatocyte growth factor receptor kinase (MET) inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
Cometriq	Cabozantinib	XL 184	Exelixis	MET, RET, VEGFR	Approved NOV 2012	67
	Tivantinib	ARQ 197	ArQule & Daiichi	MET	Phase-III	68
	Foretinib	GSK 1363089	GSK & Exelixis	MET, VEGFR	Phase-II	69
		ASLAN 002	Aslan	MET	Phase-II	70
		MGCD 265	Mirati	MET (MTKI)	Phase-II	NCT02544633
	Savolitinib	AZD 6094	AstraZeneca & Hutchison MediPharma	MET	Phase-II	71
	Tepotinib	EMD 1214063	Merck Serono	MET	Phase-II	72
		AMG 337	Amgen	MET	Phase-II	73
	Capmatinib	INC 280	Novartis & Incyte	MET	Phase-II	74
	Merestinib	LY 2801653	Eli Lilly	MET (MTKI)	Phase-II	75
	Altiratinib	DCC 2701	Deciphera	MET (MTKI)	Phase-I	76
		SAR 125844	Sanofi	MET	Phase-I	77

Table S8. ALK tyrosine kinase receptor inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
Xalkori	Crizotinib	PF 02341066	Pfizer	ALK (c-MET)	Approved AUG 2011	78
Zykadia	Ceritinib	LDK 378	Novartis	ALK	Approved APR 2014	79
Alecensa	Alectinib	AF-802	Roche	ALK	Approved DEC 2015	80
	Brigatinib	AP 26113	Ariad	ALK (HER)	Phase-III	81
	Lorlatinib	PF 06463922	Pfizer	ALK (ROS1)	Phase-II	82
	Belizatinib	TSR 011	Tesaro	ALK	Phase-II	NCT02048488

Table S9. TRK inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
	Entrectinib	RXDX 101	Ignyta & Nerviano Medical Sciences	Pan-TRK (ROS1, ALK)	Phase-II	83
		LOXO 101	Loxo Oncology & Array	Pan-TRK	Phase-II	84
		DS 6051b	Daiichi Sankyo	Pan-TRK (ROS1)	Phase-I	NCT02279433

Table S10. AXL inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
	Gilteritinib	ASP 2215	Astellas	AXL, FLT3	Phase-III	85
		BGB 324	BerGenBio	AXL	Phase-I	86

Table S11. TGFR kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
	Galunisertib	LY2157299	Eli Lilly	TGFR1	Phase-II	87
		TEW 7197	MedPacto	TGFR1	Phase-I	88

Table S12. JAK2 kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
Jakafi	Ruxolitinib	INC 424	Novartis & Incyte	JAK2	Approved NOV 2011	89
	Pacritinib	SB 1518	CTI BioPharma	JAK2 (FLT3)	Phase-III	90
		NS-018	Nippon Shinyaku	JAK2	Phase-II	91
	Momelotinib	CYT 387	Gilead	JAK1, JAK2	Phase-III	92
	Cerdulatinib	PRT 062070	Portola	JAK (SYK)	Phase-II	93
		INCB 052793	Incyte	JAK1	Phase-I	94
		INCB 039110	Incyte	JAK1	Phase-I	95

Table S13. Bruton kinase BTK inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
Imbruvica	Ibrutinib	PCI-32765	Pharmacyclics	BTK	Approved NOV 2013	96
	Acalabrutinib	ACP 196	AstraZeneca	BTK	Phase-III	97
		HM 71224	Hanmi Pharmaceutical & Eli Lilly	BTK	Phase-I	NCT01765478
		GS 4059	Gilead	BTK	Phase-I	98
		BGB 3111	BeiGene	BTK	Phase-I	99
		PRN 1008	Principia Biopharma	BTK	Phase-I	65

Table S14. Focal adhesion kinase 1 inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
		GSK 2256098	GSK	FAK	Phase-II	100
	Defactinib	VS 6063	Verastem	FAK, PYK2	Phase-II	101
		VS 4718	Verastem	FAK	Phase-I	102

Table S15. SYK inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
	Entospletinib	GS-9973	Gilead	SYK	Phase-II	103
		TAK 659	Millenium	SYK	Phase-I	104

Table S16. Phosphatidylinositol-3-kinase pathway inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
Torisel	Temsirolimus	CCI 779	Pfizer	mTOR	Approved MAY 2007	105

Afinitor	Everolimus	RAD001	Novartis	mTOR	Approved MAR 2009	106
Zydelig	Idelalisib	GS 1101	Gilead	PI3K δ	Approved JUL 2014	107
	Duvelisib	INK 1197	Infinity & AbbVie	PI3K δ , PI3K γ	Phase-III	108
	Buparlisib	BKM 120	Novartis	Pan-PI3K	Phase-III	109
	Alpelisib	BYL 719	Novartis	PI3K α	Phase-III	110
	Copanlisib	BAY 80-6946	Bayer	Pan-PI3K	Phase-III	111
	Taselisib	GDC 0032	Genentech	PI3K α	Phase-III	112
	Voxtalisis	XL 765	Exelixis, Sanofi	Pan-PI3K, mTOR	Phase-II	113
	Vistusertib	AZD 2014	AstraZeneca	mTOR	Phase-II	114
		SF 1126	SignalRX Pharmaceuticals	PI3K (MTKI)	Phase-II	115
	Sapanisertib	MLN 0128	Millenium	mTOR	Phase-II	116
		AMG 319	Amgen	PI3K δ	Phase-II	117
		CC 223	Celgene	mTOR	Phase-II	118
		CC 115	Celgene	mTOR (DNA-PK)	Phase-II	119
		GSK 2636771	GSK	PI3K β	Phase-II	120
		CUDC 907	Curis	PI3K (HDAC)	Phase-II	121
		LY 3023414	Eli Lilly	Pan-PI3K, mTOR	Phase-II	122
		PQR 309	Piqur	mTOR, PI3K	Phase-II	NCT02723877
	Pictilisib	GDC-0941	Genentech	PI3K	Phase-I	123
	Gedatolisib	PF-05212384	Pfizer	PI3K, mTOR	Phase-I	124
		ZSTK 474	Zenyaku Kogyo	PI3K	Phase-I	125
		MLN 1117	Millenium	PI3K α	Phase-I	NCT02625259
		AZD 8186	AstraZeneca	PI3K β , PI3K δ	Phase-I	126
		AZD 8835	AstraZeneca	PI3K α , PI3K δ	Phase-I	127
		HMPL 689	Hutchison MediPharma	PI3K δ	Phase-I	NCT02631642
		INCB 050465	Incyte	PI3K δ	Phase-I	128
		VS 5584	Verastem	Pan-PI3K, mTOR	Phase-I	129
		KA 2237	Karus Therapeutics	PI3K β , PI3K δ	Phase-I	NCT02679196
		CDZ 173	Novartis	PI3K δ	Phase-I	NCT02435173

Table S17. RAC-alpha serine/threonine-protein kinase, protein kinase B inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
		AZD 5363	AstraZeneca & Astex	AKT	Phase-II	130
	Ipatasertib	GDC 0068	Genentech & Array	AKT	Phase-II	131
		LY 2780301	Lilly	AKT (p70S6)	Phase-II	132
	Afuresertib	ASB 183	Novartis	Pan-AKT	Phase-II	133
		ARQ 092	ArQule	AKT	Phase-I	134
		MK 2206	Merck	AKT	Phase-I	135
		M 2698	Merck Serono	AKT (p70S6)	Phase-I	NCT01971515
		AT 13148	Astex	AKT (MTKI)	Phase-I	136
		BAY 1125976	Bayer	AKT1, AKT2	Phase-I	137

Table S18. PIM inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
		PIM 447 (LGH 447)	Novartis	Pan-PIM	Phase-I	138
		INCB 053914	Incyte	PIM	Phase-II	139

Table S19. RAF kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
Nexavar	Sorafenib	BAY 43-9006	Bayer & Onyx	RAF (MTKI)	Approved DEC 2005	140
Zelboraf	Vemurafenib	PLX 4032	Plexxikon & Roche	Mutant BRAF	Approved AUG 2011	141
Tafinlar	Dabrafenib	GSK 2118436	GSK	ARAF, BRAF, CRAF	Approved MAY 2013	142
	Encorafenib	LGX 818	Novartis & Array	Mutant RAF	Phase-III	143
		PLX 8394	Plexxikon & Daiichi Sankyo	Mutant B-RAF	Phase-II	144
		RXDX 105	Ignyta	RAF (RET)	Phase-I	145
		MLN 2480	Millenium	RAF	Phase-I	146
		HM 95573	Hanmi Pharmaceutical	Pan-RAF	Phase-I	NCT02405065
		LY 3009120	Eli Lilly	Pan-RAF	Phase-I	147
		BGB 283	Merck Serono & BeiGene	Pan-RAF	Phase-I	148

Table S20. Mitogen-activated protein kinase kinase kinase (MEK) inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
Mekinist	Trametinib	GSK 1120212	GSK	MEK1, MEK2	Approved MAY 2013	149
Cotellic	Cobimetinib	GDC 0973	Genentech & Exelixis	MEK	Approved NOV 2015	150
	Selumetinib	AZD 6244	Array & AZ	MEK1, MEK2 (AKT)	Phase-III	151,152
	Binimetinib	MEK 162	Novartis & Array	MEK1, MEK2	Phase-III	153
	Refametinib	BAY 869766	Bayer & Ardea	MEK	Phase-II	154
	Pimasertib	AS703026	Merck Serono	MEK	Phase-II	155
		PD 325901	Pfizer	MEK	Phase-II	156
		TAK 733	Millenium-Takeda	MEK	Phase-I	157
		RG 7304	Roche	MEK1 (pan-RAF)	Phase-I	158
		E 6201	Strategia Therapeutics	MEK	Phase-I	159

Table S21. ERK inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
	Ulixertinib	BVD 523	BioMed Valley Discoveries	ERK1, ERK2	Phase-II	160
		GDC 0994	Genentech & Array	ERK1, ERK2	Phase-I	161
		CC 90003	Celgene	ERK	Phase-I	NCT02313012

Table S22. p38 MAP kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
	Ralimetinib	LY 2228820	Lilly	p38 MAPK	Phase-II	162
	Pexmetinib	ARRY-614	Array	p38 MAPK	Phase-I	163

Table S23. Cyclin-dependent kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
Ibrance	Palbociclib	PD 332991	Pfizer	CDK4, CDK 6	Approved FEB 2015	164
	Ribociclib	LEE 011	Astex & Novartis	CDK4, CDK6	Phase-III	165
	Abemaciclib	LY 2835219	Eli Lilly	CDK4, CDK6	Phase-III	166
	Dinaciclib	SCH 727965	Merck	CDK1, CDK2, CDK5, CDK9	Phase-II	167
		AT 7519	Astex	Pan-CDK	Phase-II	168
	Milciclib	PHA 848125	Nerviano Medical Sciences & Tiziana Life Sciences	CDK1, CDK2, CDK4 (TRKA)	Phase-II	169

	Alvocidib	HMR 1275	Tolero Pharmaceuticals	CDK9, pan-CDK	Phase-II	170
	Roniciclib	BAY 1000394	Bayer	Pan-CDK	Phase-II	171
		TG 02	Tragara	CDKs and JAK2, FLT3, ERK5 (MTKI)	Phase-I	172
		RGB 286638	Agennix	CDK, MTKI	Phase-I	173
		BAY 1143572	Bayer	CDK9	Phase-I	174
		CYC 065	Cyclacel	Pan-CDK	Phase-I	175

Table S24. Aurora kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
	Alisertib	MLN 8237	Millenium-Takeda	ARK-A	Phase-III	176
		ENMD 2076	CASI Pharmaceuticals	ARK (MTKI)	Phase-II	177
	Ilorasertib	ABT 348	AbbVie	ARK (MTKI)	Phase-II	178
	Danuseritib	PHA 739358	Nerviano Medical Sciences	Pan-ARK (ABL)	Phase-II	179
	Barasertib	AZD 2811	Bind Therapeutics & Astra-Zeneca	ARK-B	Phase-I	180
		TAS 119	Taiho Pharma	ARK-A	Phase-I	181

Table S25. Polo-like kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase target	Development stage	Refs.
	Volasertib	BI 6727	Boehringer-Ingelheim	PLK1	Phase-III	182
		CFI 400945	University Health Network, Toronto	PLK4	Phase-I	183

Table S26. Checkpoint kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
	Prexasertib	LY 2606368	Eli Lilly & Array	CHK1	Phase-II	184
		GDC 0575	Genentech	CHK1	Phase-I	185

Table S27. ATR inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
		VX 970	Vertex	ATR	Phase-II	186
		VX 803	Vertex	ATR	Phase-I	NCT02278250
		AZD 6738	AstraZeneca	ATR	Phase-I	187

Table S28. DNAPK inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
		VX 984	Vertex	DNAPK	Phase-I	NCT02644278
		M 3814	Merck Serono	DNAPK	Phase-I	NCT02316197

Table S29. New first-in-class kinase inhibitors.

Proprietary name	USAN / INN	Corporate code	Sponsor	Main kinase targets	Development stage	Refs.
	Linsitinib	OSI 906	Astellas	IGF-1R & IR	Phase-III	188
		AZD 1775	AstraZeneca	WEE1	Phase-II	189
	Silmitasertib	CX 4945	Senhwa Biosciences	CK2	Phase-II	190
	Amcasertib	BBI 503	Boston Biomedical	Cancer stem cell pathway kinases	Phase-II	191

	TCD-717	TCD Pharma	CK	Phase-I	192
	TAK 931	Millenium	CDC7	Phase-I	NCT02699749
	LXS 196	Novartis	PKC	Phase-I	NCT02601378
	AR 12	Arno Therapeutics	PDK1	Phase-I	193
	AZD 0156	AstraZeneca	ATM	Phase-I	NCT02588105
	BAY 1143269	Bayer	MNK1	Phase-I	194
	OTS 167	OncoTherapy Science	MELK	Phase-I	195

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