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Current kinase inhibitors cover a tiny fraction of fragment space

Hongtao Zhao, Amedeo Caflisch

Department of Biochemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland



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ABSTRACT

We analyze the chemical space coverage of kinase inhibitors in the public domain from a fragment point of view. A set of 26,668 kinase inhibitors from the ChEMBL database of bioactive molecules were decomposed automatically by fragmentation at rotatable bonds. Remarkably, about half of the resulting 10,302 fragments originate from inaccessible libraries, as they are not present in commercially available compounds. By mapping to the established kinase pharmacophore models, privileged fragments in sub-pockets are identified, for example, the 5681 ring-containing fragments capable of forming bi-dentate hydrogen bonds with the hinge region in the ATP binding site. Surprisingly, hinge-binding fragments in current kinase inhibitors cover only 1% of the potential hinge-binders obtained by decomposing a library of nearly 7.5 million commercially available compounds, which indicates that a large fraction of chemical space is unexplored.

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Kinases have been among the most intensively pursued classes of drug targets, mainly for the treatment of cancer.¹ In addition, deregulation of kinase activity has been implicated in a variety of disorders including immunological, neurological, metabolic, and infectious diseases. More than 20 years of intensive research has already generated more than two dozens of kinase inhibitors approved as drugs. The majority of kinase inhibitors target the ATP binding site with the so-called activation loop in the active conformation (type I) while a minority bind to an inactive conformation (type II).² In addition, type I_{1/2} inhibitors bind to the DFG-in conformation but extend to the so-called back pocket establishing some characteristic type II interactions.³ Type III and IV inhibitors bind to regions distal to the ATP site, and act through more or less pronounced allosteric effects.⁴ With nearly 30,000 kinase inhibitors accumulated in the public domain, however, little is known about the coverage of chemical space. It is crucial to evaluate such coverage and find unexplored area for highly pursued targets in drug discovery projects.

Fragment-based drug discovery has progressed over years as a popular method in both pharmaceutical industry and academia.⁵ Fragment-based high-throughput virtual screening approaches have yielded novel kinase inhibitors^{6,7} as well as ligands for emerging therapeutic targets, for example, bromodomains (Table S1).^{8,9} Verification of binding modes by X-ray and lead elaboration further emphasize the unique merits of the in silico fragment-based

approaches.^{6,8,10,11} Here we provide an analysis of the chemical space coverage of kinase inhibitors from a fragment perspective. Furthermore, we analyze the influence of phenol on cellular activity of three distinct inhibitors.

From the latest version of ChEMBL (Kinase SARfari, version 6.0), compounds with K_i , K_d , or IC_{50} value below 10 μ M and molecular weight below 600 Da were extracted. This gives 26,668 kinase inhibitors with 70,273 activity data. About three quarters of the kinase inhibitors have inhibitory activity below 1 μ M and half of them below 0.2 μ M. In the ChEMBL database, 88 kinases out of the 367 kinases used for screening have more than 100 inhibitors with VEGFR2 (3,347 compounds), p38 α (2,817), EGFR (2,534), CDK2 (2,023), SRC (1,848), GSK3 β (1,273), LCK (1,271), CDK1 (1,205), ChK1 (1,130), PDGFR β (1,114), HER2 (1,051), and CDK4 (1,014) being the most pursued targets. The properties of the inhibitors are analyzed (Fig. 1, black histograms) with particular interest on ring systems,¹² which constitute the essential core of a drug.¹³ Most inhibitors have three to eight rotatable bonds, and two to four ring systems. Interestingly, 75% of the kinase inhibitors contain fused rings, which can offer a larger number of favorable interactions (van der Waals contacts and hydrogen bonds) with the binding site of the target than multiple non-fused rings of similar molecular weight.

The 26,668 kinase inhibitors are decomposed by an automatic fragmentation algorithm that was developed for fragment-based design by high-throughput docking.⁶ Firstly, all rotatable bonds of a molecule are broken to obtain initial ring systems. Secondly, each ring system is extended at the cut(s) until it reaches another

E-mail addresses: h.zhao@bioc.uzh.ch (H. Zhao), caflisch@bioc.uzh.ch (A. Caflisch)

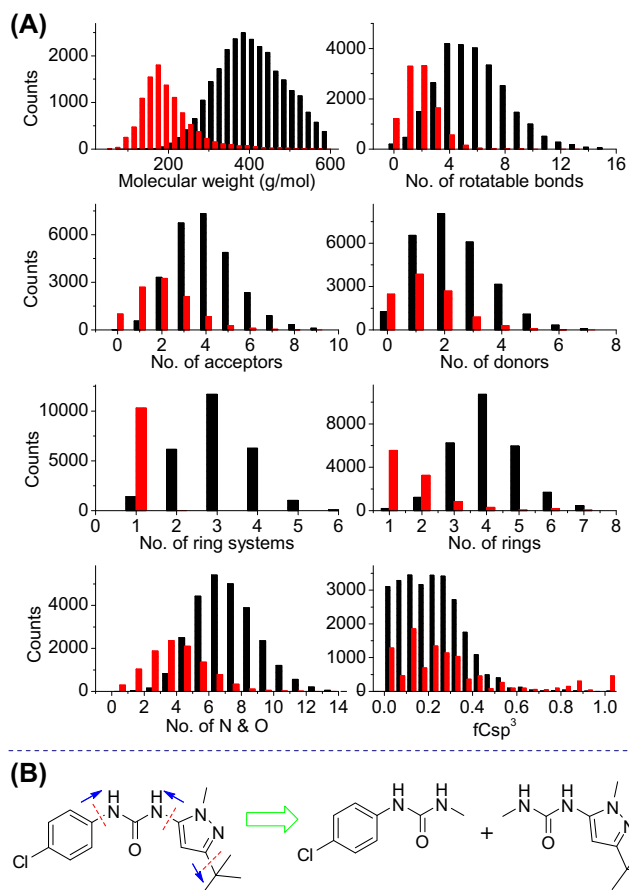


Figure 1. (A) Distributions of molecular properties of 26,668 kinase inhibitors (black) and their 10,302 unique ring-containing fragments (red) obtained by automatic decomposition. Distributions of molecular properties of the ZINC Drugs-Now 7.5 million compounds and their ring-containing fragments are shown in Figure S1. (B) Illustration of the fragmentation algorithm. (Left) The directions of elongation at the cuts (red dashed segments) are emphasized (blue arrows). (Right) Fragments obtained by automatic decomposition using the program described in Ref. 6. The cuts at rotatable bonds generate fragments with at least one ring and a single Murcko ring system.

ring or the length of the extension, that is, number of non-hydrogen atoms, reaches two. In case the atom on the second level is not an sp^3 carbon, the elongation goes further until it reaches an sp^3 carbon or a ring (Fig. 1B). In this way, 10,302 unique ring-containing fragments (i.e., Murcko ring systems¹² with rich chemical decorations) are extracted from the 26,668 kinase inhibitors. The molecular properties of the fragments are shown in Figure 1A (red histograms). Most of them consist of a single ring or fused

two rings, and have one or two rotatable bonds in the functional group(s) attached to the ring(s). Remarkably, 53% of these fragments are not present in the 477,617 unique fragments obtained by automatic decomposition (using the same fragmentation algorithm as above) of the nearly 7.5 million compounds in the ZINC Drugs-Now library (Table 1).¹⁴ To check for robustness, this analysis was repeated with Murcko ring systems,¹² that is, upon removal of ring decorations. About 40% of 2394 Murcko ring systems from kinase inhibitors are not present in the 81,715 Murcko ring systems from the ZINC Drugs-Now library. Both analyses of decorated fragments and Murcko ring systems show that a large portion of kinase fragments originates from compounds in proprietary libraries.

The most frequent fragments are six-member rings and pyrazole (Fig. 2A). They belong to four categories: (1) (substituted) benzene ring; (2) (substituted) pyridine or pyrimidine; (3) piperazine or morpholine; (4) benzamide or phenylurea. Fragments of top occurrence can be individually mapped to the binding site according to the pharmacophores² and the large amount of available crystal structures of kinase/inhibitor complexes (Fig. 2B). For example, pyridine and pyrimidine are known hinge-binding motifs, benzene is a preferred hydrophobic motif in the back pocket, piperazine and morpholine are solvent exposed motifs attached either to the hinge-binding motif (as in Gefitinib; PDB code 2ITY) or to the hydrophobic motif in the allosteric site (Gleevec; 1OPJ) to address solubility issue, and both benzamide and phenylurea are linkers to connect the hinge-binding motif and the hydrophobic motif in the allosteric site. Specifically, phenol is a privileged motif known to generate type $I_{1/2}$ inhibitors (see below)^{3,6,10,11,15}, whose binding modes are exemplified in Figure S2.

It is interesting to focus on the hinge-binding fragment space since such fragments are anchoring blocks suitable for lead elaboration. As the majority of kinase inhibitors form two to three hydrogen bonds with the hinge region, all fragments were filtered by the following two criteria: (1) at least one hydrogen bond acceptor, that is, sp^2 nitrogen or oxygen, and one donor including acidic CH;¹⁶ and (2) geometry of acceptor and donor groups allows for bi-dentate hydrogen bonds with the hinge region.¹⁷ Halogen bonds^{18,19} are not considered because of their strict dependence on directionality which makes their analysis very difficult. More than half (precisely 5681) of the ring-containing fragments in kinase inhibitors satisfy both criteria. By applying the same criteria to the 477,617 fragments obtained from the decomposition of the ZINC Drugs-Now library,¹⁴ a total of 196,904 potential hinge-binders are retrieved. Surprisingly, only 1% (precisely 1954) of the putative hinge-binding fragments in commercially available drug-like compounds are covered by those in kinase inhibitors (Table 1), which indicates that a large part of publically accessible chemical space remains unexplored.

Table 1
Coverage of chemical space by fragments of kinase inhibitors

	All fragments	Putative hinge-binding fragments		
		Monocyclic	Bicyclic	Multicyclic
In ZINC compounds ^a	477,617 (81,715)	102,097 (6902)	69,856 (17,694)	24,951 (12,669)
In kinase inhibitors ^b	10,302 (2394)	2031 (330)	2353 (678)	1297 (631)
ZINC coverage ^c	1.0% (1.8%)	1.0% (4.2%)	1.2% (2.7%)	0.4% (1.0%)
Proprietary ^d	53% (40%)	50% (12%)	64% (30%)	92% (80%)

^a Number of unique ring-containing fragments obtained by automatic decomposition of the nearly 7.5 million compounds in the ZINC Drugs-Now library. Values in parentheses correspond to Murcko ring systems throughout this table.

^b Same as above for the 26,668 current kinase inhibitors.

^c Fraction of putative hinge-binding fragments in the ZINC Drugs-Now library that are present in kinase inhibitors. As an example, 36% of the 2353 bicyclic putative hinge-binding fragments in known kinase inhibitors are present in the 69,856 bicyclic putative hinge-binding fragments in ZINC, which gives a coverage of 1.2% ($0.36 \times 2353 / 69,856$).

^d Fraction of kinase inhibitor fragments that are not found in the ZINC Drugs-Now library.

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