Reconciling Selectivity Trends from a Comprehensive Kinase Inhibitor Profiling Campaign with Known Activity Data

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ABSTRACT: Kinase inhibitors are among the most intensely investigated compounds in medicinal chemistry and drug development. Profiling experiments and kinome screens reveal binding characteristics of kinase inhibitors and lead to better understanding of selectivity and promiscuity patterns. However, only limited amounts of profiling data are publicly available. By contrast, a large body of activity data for inhibitors of human kinases has become available from medicinal chemistry. In this study, we have correlated selectivity assessment of clinical kinase inhibitors from the most comprehensive profiling campaign reported to date with systematic mining of activity data from other sources. The results of our comparative analysis reveal consistency of orthogonal approaches in the study of kinase inhibitor selectivity versus promiscuity and stress the importance of taking alternative data confidence criteria into account. Moreover, it is also shown that there are little if any detectable differences in selectivity between type I and II kinase inhibitors and that inhibitors designated as chemical probes have very different target profiles.

1. INTRODUCTION

Kinase inhibitors are prime candidates for drug development in different therapeutic areas such as oncology, inflammatory diseases, and so forth.1−16 To better understand their binding characteristics and target profiles, kinase inhibitors have been—and continue to be—subjected to profiling experiments including various panel assays and kinome screens.5−12 Because the majority of current kinase inhibitors bind to the conserved adenosine 5′-triphosphate (ATP) site in kinases, or regions proximal to this site,12−14 selectivity versus promiscuity of kinase inhibitors is still an intensely debated issue.5−8,12−16 with important implications for therapeutic applications and clinical performance.5,17

Recently, Klaeger et al. have reported the most comprehensive kinase inhibitor profiling study available to date,18 yielding a variety of binding, functional, and structural data for a set of 243 kinase inhibitors at different stages of clinical evaluation and development, including marketed drugs. The authors primarily applied a chemoproteomics approach. “Kinobeads”, that is, nonspecific kinase inhibitors immobilized on the solid phase, were used to extract bound target proteins from mixed lysates of different cancer cell lines. Target binding was then determined using quantitative mass spectrometry. Using loaded kinobeads from lysates, dose-dependent competition assays with clinical kinase inhibitors were carried out to identify their targets and determine apparent dissociation constants.18 The set of clinical kinase inhibitors was found to interact with a total of 253 kinases, comprising nearly half of the human kinome. A key finding of this study has been that the investigated clinical kinase inhibitors covered a wide spectrum of binding characteristics ranging from selective to highly promiscuous compounds.

Given this extensive in vivo-oriented target identification effort for clinical kinase inhibitors and the variety of target profiles that were observed, we were interested in evaluating how some of the findings of Klaeger et al. might relate to the promiscuity assessment of kinase inhibitors on the basis of currently available activity data. We reasoned that comparison with literature data from medicinal chemistry might often provide complementary or orthogonal views of inhibitor selectivity versus promiscuity, given the many different assays these compounds were tested in. Klaeger et al. also searched the kinase inhibitor literature and retrieved biological activity annotations from ChEMBL,19 the major public repository of compounds and activity data from medicinal chemistry sources. They noted that no bioactivity records were deposited for 35 of the clinical kinase inhibitors under investigation.18

We have systematically collected all activity data available in ChEMBL for the clinical kinase inhibitors studied by Klaeger et al. and organized these data according to different confidence criteria. Then target annotations were identified and promiscuity degrees (PDs) of inhibitors were calculated at different data confidence levels. We also identified kinase inhibitors that were most and least selective on the basis of the data of Klaeger et al. and separately determined the target profiles for these inhibitors. The comparison of our findings with results of Klaeger et al. is reported herein.

Received: February 8, 2018
Accepted: March 5, 2018
Published: March 14, 2018
2. MATERIALS AND METHODS

2.1. Clinical Kinase Inhibitors and Data Confidence Level Criteria. ChEMBL identifiers and SMILES representations of clinical kinase inhibitors were taken from the supplementary information of Klaeger et al. and mapped to ChEMBL (release 23, accessed in Jan 2018). Only human targets were considered to conform with Klaeger et al. For inhibitors annotated with human targets, activity data were collected at two different confidence levels including levels 1 (intermediate) and 2 (high). For confidence level 1, the highest assay confidence was required for ChEMBL data, and for level 2, the highest assay and, in addition, highest measurement confidence were required for ChEMBL data. Accordingly, activity data were only selected from direct inhibition assays (assay relationship type “D”) for single targets with the highest assay confidence score (“9”). In addition, only unambiguously specified \( K_i \) or \( IC_{50} \) measurements with standard activity unit (“nM”) and consistent “activity comments” were considered. To address the compound concentration dependence of target annotations and identify weak inhibitory interactions, we also generated results for comparison after applying a \(<10 \mu M\) activity (potency) threshold to both data confidence levels.

2.2. Selectivity Scores and Promiscuity Degrees. Klaeger et al. introduced the “Concentration- And Target-Dependent Selectivity” (CATDS) score for the analysis of their experiments. The CATDS score quantifies the reduction in binding of a given target to kinobeads at a particular inhibitor concentration relative to the summed reduction in binding of all available targets. As defined, CATDS scores of inhibitors are target-dependent. Scores approaching 1 are characteristic of a selective kinase inhibitor (i.e., the compound almost exclusively inhibits a single target), whereas scores close to 0 are usually indicative of a nonselective (highly promiscuous) inhibitor. For each clinical kinase inhibitor found in ChEMBL, we selected the largest available CATDS score as a selectivity measure. Furthermore, we calculated the “promiscuity degree” (PD) of an inhibitor as the number of its unique targets on the basis of the activity records from ChEMBL that qualified for confidence levels 1 or 2 in the presence or absence of the \(<10 \mu M\) activity threshold.

2.3. Kinase Inhibitor Types and Chemical Probes. A subset of clinical kinase inhibitors was assigned by Klaeger et al. to type I or type II inhibitor category on the basis of the available structural data and binding mode information. Type I kinase inhibitors bind to the conserved ATP site in the active form of the kinase, whereas type II inhibitors bind to the inactive form and less conserved regions adjacent to the ATP site. Therefore, type II inhibitors are often expected to be more selective than type I inhibitors. We separately analyzed PDs for inhibitors with type I or II binding mode. Furthermore, a subset of clinical kinase inhibitors were designated chemical probes on the basis of reports from the Chemical Probes Portal. For such probe compounds used in chemical biology, a high degree of selectivity is generally required. Therefore, we also separately analyzed PD values of the designated chemical probes among clinical kinase inhibitors.

3. RESULTS AND DISCUSSION

3.1. Clinical Kinase Inhibitors and Data Confidence Levels. Structures of 3 of the 243 clinical kinase inhibitors were not found in ChEMBL. In addition, 38 inhibitors were not annotated with human targets, leaving 202 inhibitors with at least one known human target for activity data confidence analysis. For confidence level 1, the highest assay confidence was required, and for the more stringent level 2, the highest assay plus highest measurement confidence were required.
These data confidence levels were established to exclude target annotations from the analysis that were only weakly supported experimentally (e.g., target annotations from cell-based assays lacking confirmation of direct target engagement).

Confidence level 1 was met by activity data of 185 of 202 clinical kinase inhibitors available in ChEMBL. These 185 inhibitors were active against a total of 394 human kinases and 218 nonkinase targets. After applying the <10 μM activity threshold, 172 inhibitors were available for confidence level 1 that were active against 379 kinases and 64 nonkinase targets. Furthermore, 166 of the 185 inhibitors qualified for confidence level 2, which were active against 122 human kinases and 66 nonkinase targets. After applying the <10 μM activity threshold to confidence level 2, 164 inhibitors were obtained with activity against 122 kinases and 52 nonkinase targets. Hence, there was a sharp decline in target numbers at increasing data confidence. For comparison, at confidence level 1, clinical inhibitors were active against a total of 394 human kinases on the basis of the currently available data (379 human kinases after applying the activity threshold), while Klaeger et al. identified 253 kinase targets. The human kinome comprises 518 kinases.21

Although a significant number of nonkinase targets were identified, the majority of the clinical kinase inhibitors were predominantly active against kinases. After applying the <10 μM activity threshold to both data confidence levels, the number of nonkinase target annotations notably reduced by 154 targets for confidence level 1 and by 14 targets for confidence level 2, much more so than the number of human kinase annotations (with 15 kinases for confidence level 1 and 0 for confidence level 2). For statistical considerations, we also calculated fractional kinase PD values, defined as (#kinase targets/#targets). On average, these values were very close to 1. Therefore, for the purpose of our statistical analysis, it was not required to further distinguish between kinase and nonkinase targets.

3.2. Global Promiscuity Degrees. Figure 1 shows the distribution of PD values for the inhibitor subsets at confidence levels 1 and 2. At level 1, a broad distribution was observed with inhibitors in the upper quartile having hundreds of target annotations. However, although supported by in vitro assay confidence, many of these PDs were most likely artificially high because it is hardly conceivable that a clinical compound might indeed act in vivo on hundreds of targets. Of course, at high—or artificially high—compound concentrations, more activities might be detected. When the activity threshold was applied to level 1, the distribution became much more narrow, and the median PD was reduced from 7 to 4, whereas the distribution for level 2 remained nearly unchanged. In this context, it should be noted that Klaeger et al. detected 494 transcribed kinases including mutant forms in their experiments and 363 translated kinases, 253 of which were bound to kinobeads.18

Hence, on the basis of medicinal chemistry data, the 185 inhibitors qualifying for confidence level 1 (172 after applying the activity threshold) were annotated with a larger fraction of the human kinome (394 kinases, 379 after applying the threshold) than that was accessible to the 243 inhibitors during proteomics profiling.

However, Figure 1 also shows that many inhibitors at confidence level 1 had only low PD values, especially after applying the activity threshold. Taken together, these findings were consistent with the identification of selective to highly promiscuous inhibitors by Klaeger et al.

At confidence level 2, the distribution of the PD values was narrow, with a median of 3, and an upper quartile range of 3–5, with only a limited number of statistical outliers having PD values larger than 10 (there were only little differences when applying the activity threshold). Thus, the comparison in Figure...
1 revealed a strong influence of data confidence criteria on the
global distribution of PDs. Hence, analyzing activity data and
target annotations at different confidence levels yielded a
differentiated view of the target space of kinase inhibitors
charted under varying experimental stringency. It also provides
a meaningful framework for evaluating the results of profiling
experiments.

3.3. Most and Least Selective Kinase Inhibitors. Next,
we analyzed the distribution of CATDS scores reported by
Klaeger et al. to determine subsets of the most and least
selective inhibitors according to this scoring scheme. Therefore,
a score histogram was generated, and the resulting distribution
was fitted to a normal distribution, yielding a mean value \( m \)
and standard deviation \( \sigma \) of 0.510 and 0.285, respectively. Then
subsets of the most and least selective inhibitors were defined
by applying score thresholds of \( 1 \sigma \) above and below the mean,
respectively. The resulting most selective (CATDS \( \geq m + \sigma \);
CATDS \( \geq 0.795 \)) and least selective (CATDS \( \leq m - \sigma \);
CATDS \( \leq 0.225 \)) subsets contained 39 and 36 inhibitors,
respectively.

Figure 2 shows the distribution of PD values for these
subsets at confidence levels 1 and 2. At confidence level 1,
broad distributions were observed for both subsets, similar to
that of Figure 1, with median PD values of 6.5 and 8 for the
most and least selective inhibitors, respectively. Thus, differ-
ces in selectivity between these subsets were only small. The
distributions became very narrow after applying the activity
threshold, and the median PD values were reduced. However,
the distribution for the most selective inhibitors contained
compounds with hundreds of target annotations, more so than
the distribution for least selective inhibitors, indicating that this
data confidence level was inappropriate to reconcile differences
in selectivity suggested by CATDS scoring. A different picture
emerged for distributions generated at confidence level 2. In
this case, the distributions were narrow, in the presence or
absence of the activity threshold, similar to that of Figure 1,
yielding mean PD values of 2 and 4 (or 3) for the most and
least selective inhibitors, respectively. Thus, at high activity data
confidence, differences in selectivity between these subsets were
also small, taking into account that the most selective inhibitor
subset was defined by a CATDS score threshold of nearly 0.8,
and the least selective subset was defined by a CATDS score
threshold of less than 0.23. Thus, these observations suggested
that similar target profiles might yield CATDS scores of
different magnitudes, dependent on the relative binding
contributions of different targets and that CATDS scoring
and PDs might reflect selectivity in different ways.

Examples are given in Figure 3 that shows two clinical kinase
inhibitors, capmatinib and lapatinib, which both belonged to
the subset of most selective inhibitors. At confidence levels
2 and 1, capmatinib was only active against its primary kinase
target on the basis of the literature data, also reflecting high
selectivity. By contrast, lapatinib was active against 5 and 389
targets at confidence levels 2 and 1, respectively. After applying
the activity threshold, lapatinib was annotated with against 3
and 13 targets at confidence levels 2 and 1, respectively. Thus,
in this case, application of the activity threshold balanced the
view of lapatinib promiscuity at data confidence level 1.

3.4. Different Binding Modes. Clinical kinase inhibitors
available in ChEMBL included 85 compounds that were
categorized as type I and 27 as type II inhibitors on the basis of
the binding mode information. Figure 4 shows the PD value
distributions of type I and II inhibitors. Because the number of
type II inhibitors was much smaller than that of type I
inhibitors, statistical assessment was limited in this case, and it
was difficult to directly compare the distributions. However, at
confidence level 1, at least half of the designated type II
inhibitors were highly promiscuous, with a median PD of 295.5,
which was much larger than the median PD of 48 obtained for
type I inhibitors. Similar trends were observed after applying
the activity threshold, with PD median values of 9 and 26 for
type I and type II inhibitors, respectively. At confidence level 2,
the results were similar for type I and II inhibitors, with PD median values of 4 and 3, respectively, and outliers present in
both cases. While only a limited number of type II were
available, these findings did not provide evidence for often
assumed greater selectivity of type II versus type I inhibitors,
consistent with the results and conclusions of Klaeger et al. and
earlier proposals.14

It should also be noted that 16 type I and 4 type II inhibitors
belonged to the most selective inhibitor subset according to
Figure 2, whereas 22 type I and 4 type II inhibitors belonged to
the least selective subset. Hence, there was no notable relative
enrichment of the designated type II over type I inhibitors
in the most selective subset.

3.5. Chemical Probes. Clinical kinase inhibitors classified
as chemical probes represented another interesting subset
for our analysis, given that compounds used as probes typically
have rather stringent requirements for selectivity. The 164
clinical kinase inhibitors meeting data confidence level 2 in the
presence of the activity threshold were found to contain 13
designated chemical probes that are shown in Figure 5. For
each of these inhibitors, the CATDS score is provided,
revealing the presence of a large scoring range for these
putative probes. In fact, only two of these compounds belonged
to the most selective subset (having a CATDS score of 1),
whereas two others belonged to the least selective subset (with
scores of 0.15 and 0.22, respectively). However, at high data
confidence (level 2), all 13 probes were selective (with one or
two targets) or at least moderately selective (with four, six, or
nine targets). By contrast, at confidence level 1, a clear
separation was observed, as also shown in Figure 5. In this case,
only four inhibitors retained PD values of 2, and three others
had PD values of 14, 16, and 38, whereas the remaining six
inhibitors were each annotated with more than 370 or 380

Figure 3. Examples of the most selective clinical kinase inhibitors. Two
kinase inhibitors belonging to the most selective CATDS score-based
subset are shown. For each inhibitor, the PD value on the basis of
ChEMBL data is reported at confidence levels 2 (red background) and
1 (blue background) and after applying the <10 \( \mu \)M activity threshold
(level 2, red outline; level 1, blue outline).
targets, thus calling probe characteristics into question. There were only 4 of 13 inhibitors with PD values of 2 at both confidence levels 1 and 2, which could be considered meaningful chemical probes applying stringent criteria. However, when the activity threshold was applied to confidence level 1, the number of target annotations for chemical probes was significantly reduced, resulting in four highly promiscuous inhibitors (with 32, 37, 81, and 121 annotations) and nine others with less than 10 targets per probe. Taken together, these observations also corroborated findings by Klaeger et al. that clinical inhibitors with assumed selectivity were often promiscuous. Figure 6 shows the two designated chemical probes having the maximal CATDS score of 1, AZD-2014 and SGX-523. Inhibitor AZD-2014 was only active against two probes having the maximal CATDS score of 1, AZD-2014 and SGX-523. Inhibitor AZD-2014 was only active against two targets at data confidence levels 1 and 2 (only one after applying the activity threshold) and belonged to the group of four preferred chemical probes referred to above. By contrast, SGX-523 was active against a single kinase at confidence level 2, but annotated with 376 targets at confidence level 1, making it difficult to support its use as a probe on the basis of available activity data. After applying the activity threshold at level 1, SGX-523 was left with eight targets. However, weak activities against a variety of targets were likely in this case. This comparison illustrates the importance of comprehensive activity data analysis for evaluating putative chemical probes.

4. CONCLUSIONS

In this study, we have—to our knowledge for the first time—correlated results of an extensive cell-based kinase inhibitor profiling campaign with those obtained by systematic mining of compound activity data from different sources. Given the limited availability of profiling data in the public domain, this analysis was of high interest to us, especially considering the exploration of kinase inhibitor selectivity versus promiscuity. The analysis was focused on kinase inhibitors at different stages of clinical development, which are typically well characterized experimentally. At varying activity data confidence levels substantial differences in inhibitor promiscuity were observed. The clinical inhibitors covered a wide spectrum of target profiles, ranging from selective to highly promiscuous compounds, as revealed by both chemoproteomics profiling and data mining. A subset of inhibitors was annotated with more kinases on the basis of the activity data than were expressed under the conditions of the profiling experiment. In some instances, in vitro assays yielded hundreds of target annotations for kinase inhibitors, which could not possibly translate into in vivo settings for clinically viable compounds, thus highlighting the likely limitations of assay relevance. It was also of interest to determine the target profiles of kinase inhibitors with different binding modes thought to cause differences in selectivity. However, neither experimental profiling nor activity data mining revealed notable differences between type I and II kinase inhibitors. Moreover, we analyzed kinase inhibitors that were considered chemical probes, which also complemented the results of experimental profiling. For putative chemical probes, very different target profiles were observed and the majority of these compounds were non-selective at different data confidence levels. Main findings of the analysis can be summarized as follows:

(i) Cell-based kinase inhibitor profiling and mining of available kinase activity data from medicinal chemistry was complementary and revealed similar trends.
(ii) In part, significant differences in promiscuity were detected for clinical kinase inhibitors.
(iii) The analysis revealed the importance of considering activity data extracted from databases at different confidence levels.
(iv) At data confidence level 1, application of an activity threshold significantly reduced PDs and balanced the view of kinase inhibitor promiscuity.
Often assumed differences in selectivity between type I and II kinase inhibitors could not be confirmed by cell-based profiling or systematic compound data mining. Even clinical kinase inhibitors regarded as chemical probes showed notable difference in PDs and contained a subset of highly promiscuous.

In summary, correlating the results of experimental profiling and compound data mining has further advanced our understanding of binding characteristics of currently most advanced kinase inhibitors, clearly showing that there are no simple relationships between clinical performance and selectivity versus promiscuity of these compounds. We conclude by emphasizing that the data made available by Klaeger et al. provide a rich source for different types of follow-up analysis. Herein, we have focused on compound selectivity, given the applicability domain of compound data mining. However, there are many more functional data provided by Klaeger et al. that can be further explored via other computational or experimental approaches.

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The study was carried out and the manuscript was written with contributions from all authors. All authors have approved the final version of the manuscript.

**Notes**
The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**
Klaeger et al. are gratefully acknowledged for making their data publicly available.

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**Author Contributions**
The study was carried out and the manuscript was written with contributions from all authors. All authors have approved the final version of the manuscript.

**Notes**
The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**
Klaeger et al. are gratefully acknowledged for making their data publicly available.

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