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Modeling Promiscuity Based on in vitro Safety Pharmacology Profiling Data

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This study describes a method for mining and modeling binding data obtained from a large panel of targets (in vitro safety pharmacology) to distinguish differences between promiscuous and selective compounds. Two naïve Bayes models for promiscuity and selectivity were generated and validated on a test set as well as publicly available drug databases. The model shows a higher score (lower promiscuity) for marketed drugs than for compounds in early development or compounds that failed during clinical development. Such models can be used in triaging high-throughput screening data or for lead optimization.

Introduction

One of the main goals of a drug-discovery project is to develop highly selective compounds for a therapeutically relevant target while avoiding side effects or adverse drug reactions (ADRs). There are a few exceptional cases for which the design of compounds with multiple activities in a given pathway may be desirable. These include some well-known examples in depression, schizophrenia,[1] and Alzheimer's disease,[2] but also in oncology,[3] showing that a weaker selectivity is key to the efficacy of a significant number of approved drugs. However, promiscuity in these cases is often limited to a particular subclass of targets (for example, kinases). New paradigms to selectively modulate several molecular targets are also emerging, despite the challenge of this multitarget approach for medicinal chemists.[4–6] Compounds with "off-target" activity (effects at various targets unrelated to the therapeutic target) carry ADR liabilities and could severely restrict the use of the drug or prevent its entry into the clinic. Therefore, there is clear interest to evaluate compound promiscuity or selectivity at the earliest possible phase of drug discovery.

As described earlier, a broad panel of in vitro safety pharmacology profiling assays have been implemented at Novartis to screen compounds for potential unwanted or adverse effects well before the first clinical stage.[7,8] This in vitro safety pharmacology profile is essentially composed of noncellular binding assays that target a diverse set of receptors (GPCRs highly represented), nuclear receptors, transporters, enzymes, and binding sites on ion channels with well-documented associations to clinical ADRs.[9,10] The in vitro safety pharmacology assay set is used as an initial screen of compound scaffolds during lead selection and early optimization. If selected compounds hit a particular unwanted target, regular testing of that target may need to be incorporated into the drug-discovery project flow chart as a possible source of clinical liability to be addressed regularly. If the initial screen is clean, the safety pharmacology screen is used only at decision points where changes in chemical design might introduce new unexpected liabilities. The project team integrates the results of this in vitro safety profile together with the results on the primary target, physicochemical, and ADME properties for making decisions on the optimization of further compounds. The assumption is that increased selectivity for the desired target correlates with the decrease of ADR frequency resulting from binding to "off-target" binding sites: the unwanted effects that may arise from binding to the secondary targets selected in this in vitro safety profile. To obtain a reliable answer in all the profiling assays, full IC_{50} determinations are systematically carried out, and a large set of profiling data is now available.

We have already shown, by using a large set of safety pharmacology profiling data, that the percentage of compounds displaying promiscuous properties during the lead-optimization stage was significant, and in the range of 20–30% (according to the cut-off used).[7] This finding supports the importance of assessing compound promiscuity early in the drug-discovery process. In the present study, we further expanded this set of data to 3138 compounds tested on up to 79 targets, all selected for their known link with potential safety issues.

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Some recent articles describe in silico approaches to discuss promiscuity and its linkage to side effects (using mainly the Cerep Bioprint dataset).[11–15] Besides the pharmacological activity associated with competitive binding, promiscuity can also be linked to some physicochemical properties of molecules such as aggregation.[16]

We compared the chemical properties of the compounds showing promiscuous properties in this panel of assays with the selective compounds in order to design a naïve Bayesian model[17–20] that can predict compound promiscuity or selectivity. Herein we describe the setup and validation of this model and its potential use in the drug-discovery process.

Results and Discussion

Dataset and hit-rate parameters

We used a total of 3138 compounds that have been tested in at least 50 out of 79 assays. The targets tested are mainly GPCRs (serotoninergic, adrenergic, dopaminergic, muscarinic, neurokinin, opiate, histaminic), but also include ion channels (calcium N- and L-type, potassium), transporters (DAT, NET, 5-HT, adenosine), nuclear receptors (glucocorticoid, estrogen, progesterone), and enzymes (COX-1, COX-2, PDE4, PDE3). The full panel of targets can be found in work published previously.[7]

The data were split randomly into 2512 compounds for modeling and 626 compounds for testing the models. In addition to the test set, 119 known drugs were also profiled and kept separate for testing the models. All sets were checked visually to ensure that no chemical classes were over-represented in one set or the other.

The target hit-rate parameter (THR) was defined in order to assign to each compound its selectivity or promiscuity across the whole panel of assays. THR is defined as the ratio of the number of targets hit (>50% inhibition) by a compound to the number of targets tested at a given concentration.

In the training and test sets, the compounds were flagged according to their target hit-rate at 10 μM (THR_{10}). Compounds with $THR_{10} \geq 20\%$ were flagged as promiscuous (P); 604 (24%) P compounds were found. Compounds with $THR_{10} \leq 5\%$ were flagged as selective hits (S); 1171 (47%) S compounds were identified. Other compounds with THR_{10} values between 5 and 20% were flagged as medium promiscuous (MP); 737 (29%) MP compounds were found.

Overall, a considerable number of compounds lacking specificity ("promiscuous compounds") were found, even if the vast majority of these were at the lead-optimization stage. Activity below 5 μM was shown by 21% of the compounds toward at least eight different targets (Figure 1). This number is biased, however, because the projects that encounter pharmacological promiscuity submit more compounds than others. Nevertheless, these data show the importance of assessing the pharmacological profile of the compounds well before the last steps of the drug-discovery process.

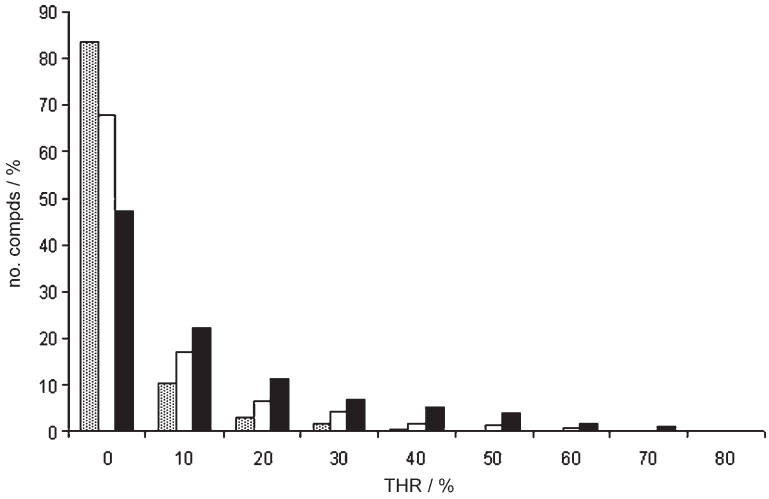

Figure 1. Distribution of compounds by their target hit-rate THR for various IC_{50} thresholds; gray: $IC_{50} < 1$ μM, white: $IC_{50} < 3$ μM, black: $IC_{50} < 10$ μM.

Data analysis

The chemical profiles of all the promiscuous compounds were compared with the selective compounds by using classical 2D molecular descriptors. The mean values and standard deviations are reported in Table 1.

The calculated log*P* (Alog*P*) and molecular weight (M_r) were significantly higher for the promiscuous compounds than for the selective compounds. Recently, Hopkins et al.[4] showed an inverse correlation between M_r and promiscuity. The authors' explanation for the correlation was that M_r could be a gross es-

Table 1. Average and standard deviation (SD) of calculated molecular descriptors.[a]

Descriptors	All		P		MP		S	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
M_r	460	142	493	99	472	177	436	130
Alog*P*	3.7	1.7	4.4	1.3	3.9	1.7	3.3	1.8
H-bond acceptors	5.2	2.4	5.4	2.1	5.2	3.1	5.2	2.1
H-bond donors	2.0	1.8	2.1	1.5	2.1	2.7	1.9	1.3
O count	3.0	2.2	2.5	1.7	2.8	2.6	3.3	2.0
N count	4.0	2.3	4.6	2.0	4.2	2.8	3.6	1.9
Rotatable bonds	7.0	4.2	7.7	3.0	7.2	5.7	6.6	3.5
Ring count	4.0	1.3	4.6	1.2	4.3	1.2	3.6	1.2
Ring assemblies	3.2	1.1	3.6	0.9	3.4	1.1	2.8	1.0
Terminal rotomers	0.4	0.7	0.2	0.5	0.3	0.7	0.6	0.7
Chain assemblies	4.9	2.0	5.3	1.8	4.8	1.9	4.7	2.1

[a] P: promiscuous compounds, MP = medium-promiscuous compounds, S: selective compounds.

timate for complexity defined in Hann's model.[21] Indeed, the model states that more complex molecules are more active because they lead to a larger number of specific binding events. In our case, compounds with higher M_r exhibit, on average, higher promiscuity (Figure 2), at least for compounds with $M_r < 600$ Da. The same correlation was observed if promiscuity was defined with THR_1 or THR_3 ($IC_{50} < 1$ μmol or 3 μmol).

The number of nitrogen atoms was also higher for promiscuous compounds, whereas the number of oxygen atoms was lower than for nonpromiscuous compounds. The number of H-bond donor or acceptor atoms did not differ significantly between the compound groups.

Table 2. Functional group frequency.[a]

Functional Group	Frequency			Percentage			
	P	MP	S	P [%]	MP [%]	S [%]	S−P [%][b]
Benzoic acid	0	8	50	0	14	86	86
Aliphatic carboxylic acid	8	48	208	3	18	79	76
Nitro	2	6	21	7	21	72	66
Sulfone	6	7	36	12	14	73	61
Nitrile	20	37	99	13	24	63	51
Sulfonamide	53	91	216	15	25	60	45
Ester	25	39	78	18	27	55	37
Primary amine	38	39	95	22	23	55	33
Imidazole	52	98	134	18	35	47	29
Pyrazole	31	44	71	21	30	49	27
Hydroxy in R–OH	94	142	216	21	31	48	27
Amide	345	413	701	24	28	48	24
Tetrazole	7	25	15	15	53	32	17
Secondary amine	488	538	726	28	31	41	14
Tertiary amine	451	458	530	31	32	37	5
Piperidine	155	131	135	37	31	32	−5
Piperazine	148	122	79	42	35	23	−20
Indole	174	114	72	48	32	20	−28
Furan	56	20	15	62	22	16	−45

[a] P: promiscuous compounds, MP = medium-promiscuous compounds, S: selective compounds. [b] Percent difference between selective and promiscuous compounds.

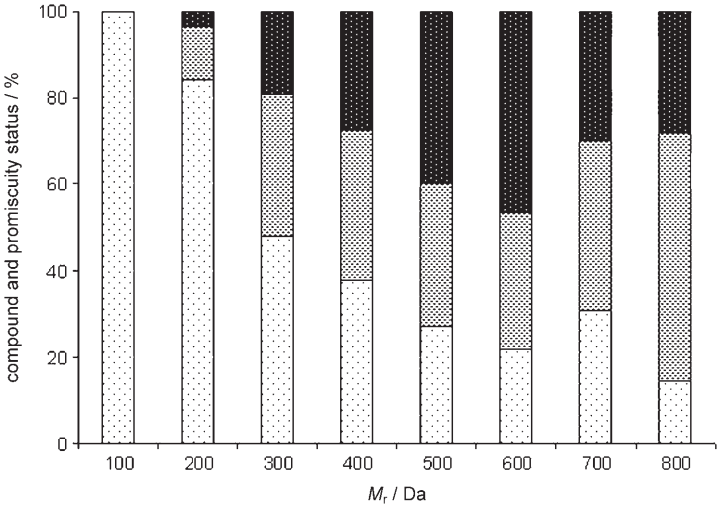

Figure 2. Correlation of molecular weight with promiscuity; black: promiscuous (P), gray: medium promiscuous (MP), white: selective (S).

To further investigate the influence of O and N atoms, functional groups were counted for each set of compounds. The results are reported in Table 2. It appears that the indole substructure is highly represented in promiscuous compounds relative to selective compounds. Furan and piperazine rings also have a greater presence in promiscuous compounds. As the profiling panel contains a large number of GPCR targets, previously published work suggested to find such privileged substructures in promiscuous compounds.[22–24]

Other substructures were checked, but were not significantly prominent in one group or the other. Carboxylic acids show a high selectivity that is probably due to the possible negative charge of the carboxylate group which can lead to unfavorable interactions with most targets of the current in vitro safety panel. Its benefit for avoiding hERG channel binding was recently shown as a magic SAR switch[25] (other acidic groups such as tetrazole or sulfonamide do not show such a large difference). In combining the differences observed above between promiscuous (P) and selective (S) compounds, we can confirm that small hydrophilic compounds with carboxylic groups are less promiscuous in the profiling panel, and that bulky and hydrophobic amines are most likely to be promiscuous.

Naïve Bayesian (NB) modeling

To generalize these observations, we used naïve Bayesian modeling, a technique that compares frequencies of features between selective and promiscuous sets of compounds. Bayesian classification has been applied in many studies and was recently compared with other machine-learning techniques.[18–21]

To classify promiscuous from selective compounds, we used the Bayesian modeling protocol available in Pipeline Pilot (SciTegic).[26] A large number of models were built using different sets of descriptors. We chose mainly to use structural fingerprints and classical descriptors used for the definition of general drug-likeness. We also used descriptors that were found in the above structure–activity relationships for promiscuity (Tables 1 and 2). The outcome of such naïve Bayesian models is the normalized probability of features present in the compound training set. For instance, the fingerprint of a carboxylic acid will contribute largely to the probability of selective compounds, as mentioned above.

To compare the predictabilities of such models, a test set was used to predict promiscuous and selective compounds. The specificity and sensitivity of each model is reported in Table 3. The optimal naïve Bayesian probability threshold was determined by plotting selectivity (SE) and specificity (SP) for different scores applied to the test set. In general, the models trained on only SciTegic fingerprints (models 1 and 2) perform better than the other models.

Table 3. Sensitivity and specificity of the naïve Bayesian (NB) classifiers.

Model[a]	NB Probability[b]	Sensitivity	Specificity
1. NB for Selectivity	−22.0	0.84	0.86
2. NB for Promiscuity	4.0	0.87	0.83
3. NB for Selectivity	−1.5	0.76	0.78
4. NB for Promiscuity	1.0	0.81	0.78

[a] Models 1 and 2 use fingerprint descriptors, and models 3 and 4 use property-based descriptors. [b] Optimal threshold.

The best models were applied to the test set, and the result of the top-ranked promiscuous or selective compounds are reported in Tables 4 and 5. A relatively high enrichment was observed for both models, although the selectivity model appears more accurate than the promiscuity model. Combining the models did not improve their sensitivity.

Table 4. Top-ranking scores with NB model 1 applied to the test set.

Model 1 for Selectivity	S [%]	MP [%]	P [%]
Top 5%	97	3	0
Top 10%	97	3	0
Top 20%	89	11	0
Top 30%	85	14	1
No Ranking	46	28	25

Table 5. Top-ranking scores with NB model 2 applied to the test set.

Model 2 for Promiscuity	S [%]	MP [%]	P [%]
Top 5%	0	6	94
Top 10%	5	6	89
Top 20%	6	20	74
Top 30%	14	24	61
No Ranking	46	28	25

Table 6. Top-ranking scores with NB model 1 applied to known drugs set.

Model 1 for Selectivity	S [%]	MP [%]	P [%]
Top 5%	100	0	0
Top 10%	100	0	0
Top 20%	92	8	0
Top 30%	92	6	3
No Ranking	71	13	17

Table 7. Top-ranking scores with NB model 2 applied to known drugs set.

Model 2 for Promiscuity	S [%]	MP [%]	P [%]
Top 5%	50	0	50
Top 10%	25	17	58
Top 20%	38	13	50
Top 30%	42	22	36
No Ranking	71	13	17

Application to known drugs

We included 119 known drugs in the test set. Of these, 71% were highly selective, 13% were medium-promiscuous, and 17% were highly promiscuous. The top-ranking scores for tested drugs are reported in Tables 6 and 7. The whole panel of compounds without the known drugs have a distribution of 46, 28, and 25%, respectively, for S, MP, and P. The majority of those compounds are "lead-like" or are in the "hit-to-lead" phase. As expected, the drug panel seems to have a higher number of selective compounds relative to the leads. Also as expected, most of the drugs predicted as promiscuous by the model are CNS drugs (Tables 8 and 9).

Promiscuity and attrition rate

The high attrition rate of new chemical entities (NCEs) in preclinical and clinical phases is due to many factors. According to Kola and Landis,[27] NCEs fail mainly due to insufficient efficacy, bioavailability, safety, toxicological issues, and economic reasons. As all these factors are somehow interrelated, a less soluble drug might be less bioactive and thus less efficient. The attrition rate also depends on the discovery stage and the therapeutic area. In the areas of CNS and oncology, it seems that

Table 8. Examples of the best predicted as selective drugs.

Drug	Model 1 Score	Model 2 Score	Exptl THR_{10} [%]	Activity Class
Cyclosporin A	34.7	−58.28	1.8	Immunosuppressive
Finasteride	11.4	−24.0	0.0	Antiandrogenic
Eprosartan	11.2	−42.4	1.5	Antihypertensive
Bumetanide	11.1	−39.5	0.0	Diuretic
Amoxicillin	10.6	−32.7	0.0	Antibiotic
Folic acid	10.1	−27.0	2.9	(Vitamin B)
Enalapril	9.0	−32.6	0.0	Antihypertensive
Acarbose	8.4	−14.7	0.0	Antidiabetic
Bicalutamide	8.1	−17.6	0.0	Anticancer
Hydrochlorothiazide	8.1	−20.8	1.4	Antihypertensive

Table 9. Examples of highly predicted promiscuous drugs.

Drug	Model 1 Score	Model 2 Score	Exptl THR_{10} [%]	Activity Class
Sumatriptan	−30.03	13.32	3.4	Serotoninergic
Rizatriptan	−27.06	10.93	3.1	Serotoninergic
Carvedilol	−19.63	10.34	41.7	Beta blocker
Serzone	−15.6	9.41	42.9	Antidepressant
Risperidone	−18.18	7.72	27.4	Neuroleptic
Iprindole	−11.32	5.51	30.8	Antidepressant
Chlorpheniramine	−16.35	5.39	16.4	Antihistaminic
Doxepin	−11.72	4.63	39.7	Antidepressant
Diphenhydramine	−6.36	3.73	26.2	Antihistaminic

compounds tend to fail more than in other therapeutic areas.[27]

To investigate whether promiscuity correlates with the attrition rate of compounds during development, we applied the models (models 1 and 2) to our in-house database, where all compounds are represented and classified as 1) terminated, 2) in development, or 3) in clinical use or launched. The results of the top best score of the database are shown in Figure 3. Interestingly, compounds in terminated programs are ranked 15% above the average in the promiscuity model and 15% below the average in the selectivity model. We cannot link these observations directly to real safety pharmacology because we do not have access to the reasons for the terminations. However, it is clear that a lower proportion of compounds predicted promiscuous by the model reached the clinic.

To further investigate this observation, we applied the models to the MDL Drug Data Report database (MDDR)[28] to compounds in different drug-discovery phases. The database was previously filtered free of any antipsychotic drugs. Because antipsychotic drugs are usually known as promiscuous,[1] we scored them separately, and the results of their average scores are listed in Table 10. For both promiscuity models 2 and 4, the average score for promiscuity tends to decrease from the lead-optimization phase to launch phase. The trend is the opposite for selectivity models 1 and 3 (Table 11).

Because the number of compounds in each phase is quite different, the comparison of their scores is difficult. Therefore, we decided to decrease the number of compounds randomly for each phase to fit the lowest number of compounds in phase III (in the case of non-antipsychotic drugs, the lowest number was 250 for compounds in phase III). The resulting dataset of 1500 compounds (250 from each phase) was then scored. Models 3 and 4 were the best to confirm a logical trend from lead optimization to launched drugs. Indeed, as shown in Figure 4, 20% of the best-scored compounds were checked for the phase in which

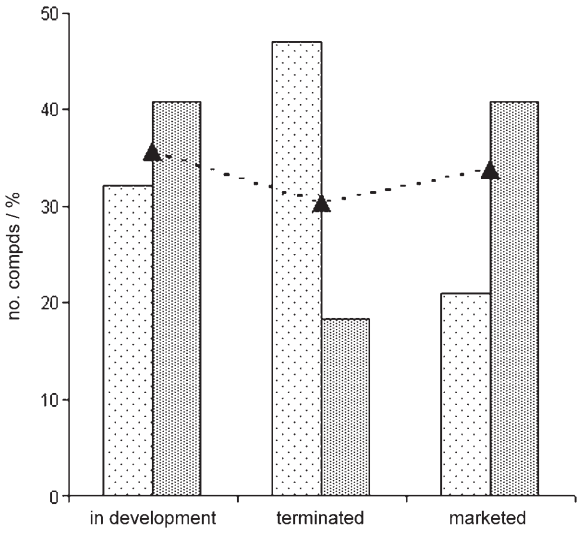

Figure 3. Top 20% ranked compounds for different stages of drug discovery at Novartis; white: top 20% ranked with promiscuity model, gray: top 20% ranked with selectivity model, -----▲-----: 20% picked randomly.

Table 10. Average NB scores for MDDR antipsychotic compounds.

Phase	Total Antipsychotic Drugs	Model 1 for Selectivity	Model 2 for Promiscuity	Model 3 for Selectivity	Model 4 for Promiscuity
Lead optimization	21594	−7.6	−5.9	0.2	−1.7
Preclinical	1389	−6.1	−7.8	0.4	−2.2
Phase I	107	−5.0	−7.9	0.6	−2.4
Phase II	182	−8.1	−6.8	0.4	−2.0
Phase III	47	−5.5	−7.2	0.7	−2.7
Launched	273	−4.5	−8.8	1.1	−3.4

Table 11. Average NB scores for MDDR non-antipsychotic compounds.

Phase	Total Other Drugs	Model 1 for Selectivity	Model 2 for Promiscuity	Model 3 for Selectivity	Model 4 for Promiscuity
Lead optimization	121898	−0.7	15.3	0.3	2.0
Preclinical	7572	−0.6	15.8	0.4	2.3
Phase I	616	−0.5	17.0	0.5	2.5
Phase II	830	−0.3	17.1	0.6	2.6
Phase III	250	0.2	15.9	0.8	3.1
Launched	863	−0.1	14.6	1.1	3.5

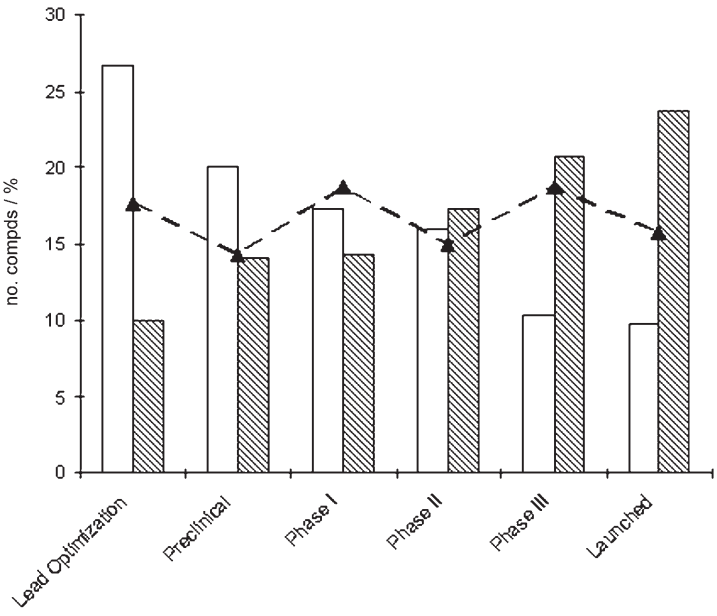

Figure 4. Top 20% best-scored compounds in MDDR after filtering antipsychotic drugs; white: top 20% ranked with promiscuity model, gray: top 20% ranked with selectivity model, -----▲-----: 20% picked randomly.

they belong, and the average scores suggest the trend that more compounds predicted promiscuous are found in the lead-optimization phase than in the launched phase. On the other hand, more compounds predicted selective are in the launched phase than in the lead-optimization phase. For comparison, we also picked 20% of the compounds randomly without ranking them.

Conclusions

In vitro safety pharmacology profiling is becoming an essential tool for successful drug development. The observation that compounds are active against multiple biological targets is a property often observed for compounds identified at the lead-selection phase of a drug-discovery program.

High-throughput screening of targets with libraries of compounds numbering in the millions inevitably identifies a significant number of promiscuous compounds. The selection of a scaffold at the early phase of drug discovery is now based on broad-scale profiling for drug-like characteristics, including a minimal occurrence of ADRs. This can be done by introducing the in vitro safety pharmacology profile, as has been reported by several research groups.[1,7,8]

By mining the profiling data, we were able to define some general rules and structure–activity relationships to distinguish between promiscuous and selective compounds. We have developed a simple scoring model for promiscuity and selectivity based on naïve Bayesian classification. Interestingly, when applied to a large database of compounds at different phases of the drug-discovery process, the model shows a higher score (lower promiscuity) for marketed drugs than for compounds in early development or those that failed during clinical development. Although the failure of drugs can originate from various factors, we found a clear correlation between the promiscuity and attrition rate of compounds. This demonstrates the usefulness of this predictive model of promiscuity and the importance of having a "clean profile" in the in vitro safety pharmacology panel. Such a model can be used for virtual screening and lead optimization.

Computational Section

From the training set of 2512 compounds, four naïve Bayesian classifiers were built using Pipeline Pilot software: two models for promiscuous and two models for selective compounds. The molecular descriptors used for models 1 and 2 were a combination of chemical fingerprints such as extended-connectivity fingerprints (ECFP_4) and functional-connectivity fingerprints (FCFP_4).[29–31] The combination of both fingerprints gives the best sensitivity (SE) and specificity (SP) (see definitions below). For models 3 and 4, we used mainly physicochemical descriptors such as calculated log P (Alog P), molecular weight (M_r), number of H-bond donor and acceptor atoms, and number of rotatable bonds. We also used the following descriptors that have a large difference, on average, between promiscuous and selective compounds: number of ring systems, number of nitrogen atoms, presence of carboxylic groups, presence of indole rings, number of terminal rotomers.

The output from the naïve Bayesian is a normalized probability, which is a standard Laplacian-modified Bayesian score. For the training set of molecules (promiscuous), the descriptors are calculated (chemical fingerprints or physicochemical properties). The Bayesian statistics are then applied to assign the probability for each individual descriptor (fingerprint bit or property range) of a molecule's likelihood to be a member of the promiscuous or selective class. The Bayesian score is a measure of how different this is from the hit rate as a whole, which is the ratio that would be expected if the features occur at random across the promiscuous and selective compounds. The score also takes into account the total number of occurrences of the feature, ensuring more weight is placed on features that are observed more often and less weight on those for which there are only very few occurrences.

To validate the classification models, the sensitivity (SE) and specificity (SP) of an individual model were evaluated by the equations:

$$SE_i = TP_i/(TP_i + FN_i) \quad (1)$$

$$SP_i = TN_i/(TN_i + FP_i) \quad (2)$$

for which TP_i, TN_i, FP_i, and FN_i represent the number of true positives, true negatives, false positives, and false negatives, respectively. TP_i, TN_i, FP_i, and FN_i are the four different possible outcomes of a single prediction for a two-class case with classes "1" ("yes") and "0" ("no"). A false positive is when the outcome is incorrectly classified as "yes" (or "positive"), when it is in fact "no" (or "negative"). A false negative is when the outcome is incorrectly classified as negative when it is, in fact,

positive. True positives and true negatives are clearly correct classifications.

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