

An In Silico Approach to Rational Antipsychotic Drug Design

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ABSTRACT

Spectral Data Activity Relationship (SDAR) modeling is a computational method that uses the steric and electronic characteristics of small molecules (that determine their biological activity), as measured through spectral data, by which accurate models of a molecule's biological activity can be created. SDAR modeling can be used to screen molecules for a particular activity (e.g., efficacy, toxicity) or to design novel drugs having a set of desired characteristics with a high degree of accuracy. The present program's purpose was to use spectral modeling to create a series of atypical antipsychotic drug candidates predicted to have targeted characteristics that meet unmet medical needs in the treatment of schizophrenia. Spectral models were created using a random 10% cross-validation process and published human experimental data. Highly accurate spectral models were created for D₂ ($q^2_{10\%} = 0.96$) and 5-HT_{2A} ($q^2_{10\%} = 0.99$) receptor binding affinities, antipsychotic activity, agranulocytosis activity, agranulocytosis relative risk ($q^2_{10\%} = 0.98$), and hERG inhibition ($q^2_{10\%} = 1.0$). Data extracted from the spectral models were used to create 125 new atypical antipsychotic drug candidates. When screened against the spectral models, 83 drug candidates were predicted to have antipsychotic activity (confidence >80%), 21 of those 83 had the desired receptor binding profiles, and after toxicity prediction, 12 were selected for synthesis and further development. The drug development process through the lead selection stage usually takes years and hundreds of millions of dollars. Using spectral modeling and rational drug design principles, the entire process took 3 months. These time and cost savings realized through spectral modeling could have positive ramifications for the economics of the pharmaceutical industry.

INTRODUCTION

While the amount of money spent by the pharmaceutical industry on R&D has increased almost 10-fold over the past 20 years, productivity (as measured by new approvals), having peaked in the mid 1990s, is now in decline and stands at a level which is similar to that of 20 years ago¹¹. The average time and costs for drug development are estimated to be 12 years and \$1 billion¹². The inability to predict toxicity early in the drug discovery process carries a considerable financial toll, which was estimated at approximately \$8 billion in 2003¹³. The pharmaceutical industry as it is currently performing cannot be sustained in its present form. Earlier and more accurate prediction of drug candidate activities, especially toxicities, can save time and costs.

Spectral Data Activity Relationship (SDAR) is a computational method initially developed at FDA's National Center for Toxicological Research that has been shown to accurately predict toxic equivalency factors¹⁴ and estrogenic activity^{15,16} *in silico* screening purposes. Currently, LITMUS Molecular Design, LLC (LMD) holds exclusive worldwide rights to the commercialization and development of SDAR technology. SDAR utilizes computer-based *mathematical methods* to analyze spectral data for identification of spectral attributes that are highly predictive of a molecule's biological, chemical, and physical activities. Further development and refinement of computational techniques has allowed LMD to extend the application of SDAR to exploitation of computational results for designing structures with targeted activities and to potentially reduce side effects.

There is a tremendous unmet medical need for improved antipsychotic drugs. No antipsychotic drug has equaled the clinical efficacy of clozapine, however, clozapine is relegated for use in only certain patient populations because of a high risk of agranulocytosis. The goal of this project was to use spectral modeling to create an antipsychotic with clozapine-like activity at Dopamine 2 (D₂) and Serotonin 2A (5-HT_{2A}) receptors but without the risk for agranulocytosis. Spectral models have been used to design a series of antipsychotic drugs that have receptor-binding affinities similar to clozapine. Predictive models for two serious antipsychotic-associated adverse effects, hERG inhibition and agranulocytosis have also been created.

METHODS

SDAR Models of key biological characteristics of atypical antipsychotic drugs have been created to predict antipsychotic activity (human D₂ and 5-HT_{2A} receptor affinity) and toxicity (hERG inhibition and agranulocytosis risk). Once suitable data sets had been selected, we employed *in silico* methods to determine the most significant relationships between molecular architecture and biological responses by generating formalisms that describe the activity of interest as a function of the spectral attributes of the antipsychotic drugs used in the model. These SDAR models have been subjected to leave-10%-out cross-validation and were further tested by double-blind data approximately equal in magnitude to 20% of the original data set.

By identifying key molecular attributes of the evaluated antipsychotic drugs, we were able to change and/or maintain certain receptor affinities while simultaneously reducing antipsychotic-related toxicities. These *in silico* methods allow elucidation of the molecular features that are important for atypical antipsychotic drug activity and to reducing antipsychotic-related toxicities. From the results, 125 new antipsychotic drug candidates were created. The new drug candidates were then screened against the specific antipsychotic models. Candidates that exhibited the desired biological properties *in silico* were selected for synthesis and for *in vitro* and *in vivo* confirmation.

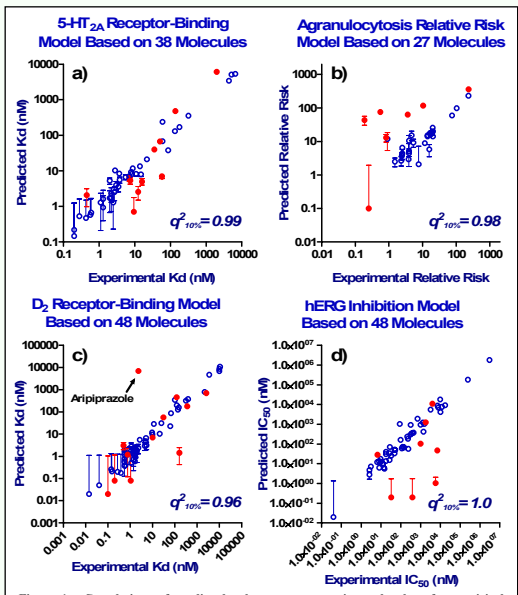


Figure 1. Correlations of predicted values versus experimental values for empirical models. The error bars represent the standard error of the mean for multiple predictions. The blue symbols represent molecules in the 10% cross-validation data set. The red symbols represent validation molecules.

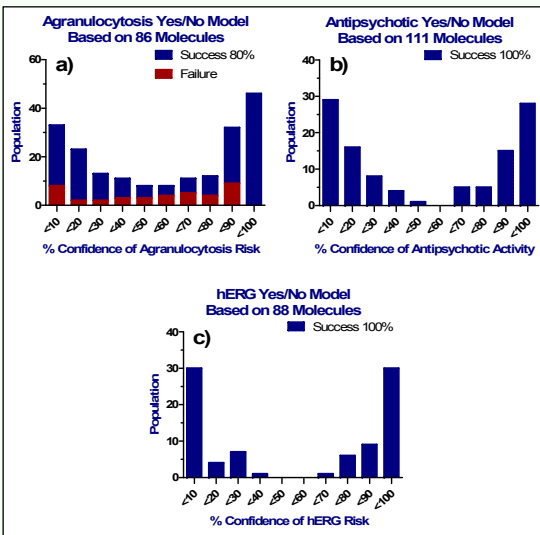


Figure 2. Confidence and accuracy of predicted categorical values. The horizontal axis represents the confidence interval of predictions. A prediction of over 50% confidence represents a "yes" response from the model. The vertical axis represents the population and accuracy of predicted values. The overall predictive accuracies are (a) 80%, (b) 100%, and (c) 100%. The agranulocytosis risk model (a) represents the total predictions made for 86 molecules during a 10% cross-validation analysis and for 115 additional validation molecules. Antipsychotic activity (b) and hERG risk (c) represent predictions made during 10% cross-validation analysis of 111 and 88 molecules respectively.

LMD Drug Candidate	Antipsychotic Yes/No (% Confidence of Yes)	Predicted mean D ₂ Kd (nM ± s.e.m.)	Predicted mean 5-HT _{2A} Kd (nM ± s.e.m.)	D ₂ /5-HT _{2A} ratio	Agranulocytosis Yes/No (% Confidence of Yes)	Predicted mean Agranulocytosis Relative Risk (relative risk ± s.e.m.)	Predicted mean hERG IC ₅₀ (nM ± s.e.m.)
LMD-00031	81.4%	77.6 ± 1.0	172.4 ± 1.1	0.5	37.6%	-2.1 ± 4.5	37.7 ± 1.1
LMD-00039	91.3%	73.2 ± 1.1	3.5 ± 1.0	21.1	20.5%	322.0 ± 23.9	0.3 ± 1.1
LMD-00058	90.9%	82.2 ± 1.1	4.1 ± 1.1	20.1	9.3%	124.9 ± 13.6	2.0 ± 1.1
LMD-00060	80.0%	96.9 ± 1.1	6.7 ± 1.1	14.4	23.4%	307.5 ± 23.5	9.6 ± 1.1
LMD-00074	94.6%	76.6 ± 1.1	1.5 ± 1.1	51.0	37.1%	124.9 ± 13.6	29.7 ± 1.1
LMD-00076	91.9%	92.6 ± 1.1	2.5 ± 1.1	36.4	60.0%	307.5 ± 23.5	158.7 ± 1.1
LMD-00083	93.9%	68.9 ± 1.2	6.9 ± 1.0	10.0	84.5%	-22.8 ± 4.8	17.6 ± 1.1
LMD-00085	89.3%	42.9 ± 1.1	14.7 ± 1.1	2.9	4.9%	21.1 ± 6.1	131.3 ± 1.1
LMD-00091	91.3%	87.7 ± 1.2	122.1 ± 1.1	0.7	22.4%	-77.3 ± 16.5	7.3 ± 1.1
LMD-00094	94.1%	85.0 ± 1.1	5.2 ± 1.1	16.4	53.6%	81.2 ± 9.4	50.7 ± 1.1
LMD-00096	72.8%	6.1 ± 1.1	0.2 ± 1.1	29.8	59.7%	-93.8 ± 20.1	2.0 ± 1.1
LMD-00102t	90.1%	14.6 ± 1.2	0.2 ± 1.1	58.3	4.7%	-7.8 ± 3.2	262.1 ± 1.1

Table 1. Selection criteria for twelve drug candidates chosen for *in vitro* and *in vivo* characterization. The standard error of the mean is represented as s.e.m. Data extracted from the spectral models was used to design 125 atypical antipsychotic drug candidates. These 125 drug candidates were submitted to the fleet of spectral models for prediction of desired characteristics. Of these 125 drug candidates, 83 were predicted to be antipsychotics with > 80% confidence and 21 had desirable receptor binding profiles. After screening for toxicities, 12 drug candidates were selected for *in vitro* and *in vivo* characterization.

RESULTS

An In Silico Approach to Rational Antipsychotic Drug Design - Highly accurate *in silico* models have been created for predicting antipsychotic activity (Figure 2b), D₂ and 5-HT_{2A} receptor affinities (Figures 1a and 1c), agranulocytosis relative risk (Figure 1b), agranulocytosis risk (Figure 2a), hERG inhibition (Figure 1d), and hERG risk (Figure 2c) of new drug candidates. The $q^2_{10\%}$ values shown in Figure 1 are a measure of the model's ability to randomly and blindly predict all of its substituents in 10% increments. The validation molecules (Figure 1) (red symbols) are random selections having published data that are used to verify the predictive value of the models. The predictive accuracies of the yes/no models in Figure 2 are demonstrated in the form of % confidence of yes and the % success of all outcomes. The models in Figure 1 allow assessment of empirical relationships among compounds. The models in Figure 2 allow assessment of the propensity of a compound to exhibit activity or risk.

Empirical Modeling - Predictions of D₂ and 5-HT_{2A} binding affinities, agranulocytosis relative risk, and hERG inhibition are correlated with experimental values. Results in Figure 1 show strong correlations ($q^2_{10\%} > 0.90$) that remain significant when validation samples are evaluated. The 5-HT_{2A} binding affinity model (Figure 1a) is highly accurate ($q^2_{10\%} = 0.99$), and remains significant ($r^2 = 0.80$ at $P < 0.0001$) when 11 validation samples are included in the correlation. The agranulocytosis relative risk model (Figure 1b) yields a high correlation ($q^2_{10\%} = 0.98$), and remains significant ($r^2 = 0.62$ and $P < 0.0001$) when 7 validation samples are included in the correlation. The D₂ binding affinity model (Figure 1c) is highly accurate ($q^2_{10\%} = 0.96$) and remains significant ($r^2 = 0.79$ at $P < 0.0001$) when 12 validation samples are included in the correlation. Results show that removing the only partial agonist (apiprazole) from the D₂ validation set (Figure 1c) yields a high correlation ($r^2 = 0.95$ at $P < 0.0001$) including 11 validation samples. The hERG IC₅₀ model (Figure 1d) yields ($q^2_{10\%} = 1.0$), and is highly significant ($r^2 = 1.0$ at $P < 0.0001$) when 8 validation samples are included in the correlation. Results show that removing the only partial agonist (apiprazole) from the D₂ validation set (Figure 1c) yields a high correlation ($r^2 = 0.95$ at $P < 0.0001$) including 11 validation samples. The hERG IC₅₀ model (Figure 1d) yields ($q^2_{10\%} = 1.0$), and is highly significant ($r^2 = 1.0$ at $P < 0.0001$) when 8 validation samples are included in the correlation. Results show that removing the only partial agonist (apiprazole) from the D₂ validation set (Figure 1c) yields a high correlation ($r^2 = 0.95$ at $P < 0.0001$) including 11 validation samples. 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