

Rational Design of M1-Muscarinic Antagonists using Combinatorial Transformation

M.B. Bolger¹

R. Fraczek¹, D. Miller¹, J. Crison¹, W.S. Woltosz¹

¹ *Simulations Plus, Inc., Lancaster, CA, U.S.A.*

Purpose. To develop an in silico process for de-novo design from high throughput screening (HTS) data.

Methods. HTS data for 61,044 M1-muscarinic antagonists (PubChem AID 628) were filtered and classified by ClassPharmer™ (Simulations Plus, Inc., Lancaster, CA). A categorical Support Vector Machine Ensemble (SVME) model for an N-phenylpiperazine chemical class with 168 members was generated using ADMET Predictor™ (AP). SVME performance accuracy: 91% TP, 88% TN, with only 5% FP, and 5% FN. We automatically generated 10,000 bioisosteres of the lowest molecular weight active molecule in this class using the Combinatorial Transformation feature in ClassPharmer. The new compounds were filtered using AP rules for ADMET properties and for M1-antagonist activity. Finally, the resulting data was exported and loaded into ClassPharmer for final class generation.

Results. 10,000 potential antagonists produced 6 molecules predicted to be active and with only one adverse ADMET characteristic. The most active class (phenyl-perhydrodiazepines) had 226 members with 68% of the molecules predicted to be active based on the SVM categorical model. Three of the molecules with the lowest ADMET Risk score had no hits in a substructure search of Chemical Abstracts registry indicating novel composition of matter. These molecules scored three hits in the ADMET Risk scale indicating potential interaction with the estrogen receptor, potential toxicity on the fat-head minnow LD50 scale, and potential inhibitory activity at the hERG potassium channel.

Conclusions. Classification, activity modeling, and ADMET property estimation for HTS data, combined with Combinatorial Transformation feature in ClassPharmer, are a powerful set of tools for the rational design of novel M1-muscarinic receptor antagonists

1. May, L.T. and A. Christopoulos, Allosteric modulators of G-protein-coupled receptors. *Curr Opin Pharmacol*, 2003. 3(5): p. 551-6.
2. Gasparini, F., R. Kuhn, and J.P. Pin, Allosteric modulators of group1 metabotropic glutamate receptors: novel subtype-selective ligands and therapeutic perspectives. *Curr Opin Pharmacol*, 2002. 2(1): p. 43-9.
3. Spalding, T.A., et al., Discovery of an ectopic activation site on the M(1) muscarinic receptor. *Mol Pharmacol*, 2002. 61(6): p. 1297-302.