QSAR Modeling and Prediction of Triptan Binding Affinities

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ABSTRACT

The purpose of this study was to use quantitative structure-activity relationships (QSARs) to identify new triptan molecules that selectively bind to h 5-HT1B and h 5-HT1D to a greater extent than to the similar h 5-HT1A receptor in order to identify novel compounds that could lead to an alternative and potentially superior migraine relief drug. Due to its possibility in migraine abortive properties, binding affinities to h 5-HT1F were also modeled. Binding affinities for 12 different triptan drugs and structurally similar substances were compiled from the literature, and descriptors were generated for those and other potential drug candidates using a variety of programs. The most significant descriptors were identified using a stepwise model, and the final QSARs were built for each activity with those descriptors, and a neural network. QSARs for all four activities were validated using a holdback method and were all found to be highly accurate. With these QSARs, activities of novel compounds similar to triptan drugs were predicted and three potential drug candidates were suggested.

KEYWORDS

Drug Discovery, Drug Screening, Migraine

INTRODUCTION

Triptans are a class of drugs which are selective agonists for the h 5-HT1B and (1B) h 5-HT1D (1D) serotonin receptors. Considerable scientific evidence supports these two receptors as the target of the triptans’ migraine abortive effects; however, 1B and 1D also cause vasoconstrictive side-effects (Reddy, 2013). Despite these effects, their safety profile is superior to the non-specific h 5-HT1 agonists, ergot alkaloids. Most likely due to triptans’ more selective 1B and 1D affinities, triptans lack many of the negative side effects of the older drugs. Although triptans’ main pathway is thought to be through the 1B and 1D receptors, it is theorized that the h 5-HT1F (1F) receptor, for which many triptans also have affinity, may have the potential to relieve migraines without the vasoconstriction caused by the 1B and 1D receptors (Vila-Pueyo, 2018).

To the best of the author’s knowledge, at the time of writing, no study has been performed using computational chemistry to model the binding affinities of triptan drugs. Thus, in order to identify novel compounds with potential migraine abortive effects, this study built quantitative structure-activity relationships (QSARs) for four serotonin h 5-HT1 receptors. The binding affinities for 1B and 1D receptors were modeled in order to identify compounds which can activate the primary targets for triptans’ anti-migraine effects. The binding affinity for h 5-HT1A (1A) receptor was modeled as a check to ensure that the potential drugs are selective 1B and 1D agonists and thus would be less likely to share the side effects caused by ergot alkaloids. The binding affinity for 1F receptor was modeled as a secondary potential criterion for identifying migraine-abortive drugs.

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METHODS

Descriptor Generation and Selection

The binding affinities of 12 different triptan migraine relief drugs and structurally similar substances to four serotonin receptors, 1B, 1D, h 5-HT\textsubscript{1A}, 1A, and 1F, were identified from published literature (John et al., 1999; Ramadan, Skljarevski, Phibus, & Johnson, 2003). Binding affinities for all four receptors were found for 9 of the compounds. For the other 3 molecules, data were only available for the 1B, 1D, and 1F receptors. Using a variety of programs, specifically, Spartan (Wavefunction Inc., 2020) using parametric method 3 (PM3), PhysChem (ACD/Labs, 2020), EPI Suite (EPA Office of Pollution Prevention Toxics, 2012), and E-Dragon (Tetko et al., 2005; Virtual Computational Chemistry Laboratory, 2005), 1708 descriptors were calculated. All descriptors with less than a 1\% standard deviation were eliminated as they were not indicative of the activity differences between the chemicals, leaving 1381 descriptors deemed significant. All molecular descriptors that were calculated can be found in the Supporting Information. These descriptors were entered into SAS JMP 15 (SAS Institute Inc., 2020). Using this program, a stepwise model for each activity was generated. The most significant descriptors by F Ratio before (initial) and after (final) building the model were ranked by highest F Ratio. A selection of this information is presented in Tables 2 and 3.

QSAR Model Creation

Using SAS JMP 15, multiple QSAR models were built for each of the four activities using four general approaches and randomly excluding three of the 12 molecules from the analysis for later validation:

1. A stepwise regression model with a minimum Akaike’s Information Criterion (AICc) stopping rule was created for each activity. Stepwise models such as these are able to automatically select the best descriptors to use. However, they are relatively simple linear models, and are thus not best suited for describing very complex relationships (Advances in QSAR modeling, 2017).

2. Sixteen NIPALS partial least square (PLS) models, four per activity, were created. Each model utilized four factors. The first of the four groups of PLS models was generated using all 1381 significant descriptors. From that model, all 1125 descriptors with a variable importance on projections (VIP) >0.8 were used to create the second group of PLS models. This process was repeated by first creating another four PLS models using the 422 descriptors which had an initial F Ratio of >4 for any activity and again, eliminated all descriptors with a VIP of \( \leq 0.8 \). This process resulted in 16 PLS QSARs, four per activity, each with a different set of descriptors chosen using different processes. These PLS models are able to utilize a very large number of descriptors, however, like stepwise models, they are linear and may share some of those models’ drawbacks (Advances in QSAR modeling, 2017).

3. Eight neural network models, two per activity, each with three hidden nodes, were created. The first four neural models were built using the most significant descriptors by initial F Ratio (Table 1). For the 1A model, due to the decreased size of the data set, only the top three descriptors were used. For each of the other models, 1B, 1D, and 1F, the top four descriptors were used. For activities which had two descriptors very similar descriptors, such as GATS5e and GATS5m, only the most significant one was used. The second four neural models were built in the same way as the first four models but using the most significant descriptors by final F Ratio (Table 2) in place of the initial F Ratio. While these Neural models are non-linear and can be highly accurate, their black-box nature can make them hard to easily interpret (Advances in QSAR modeling, 2017).

4. From the above three methods, nine consensus models were created, three per activity: the median of the best (see Section 2.3) model of the prior three methods, the median of the four groups of PLS models, and the median of the two groups of neural models. Consensus models can sometimes be better predictors than their component models, thus their creation is an important part of a QSAR study (Cherkasov et al., 2014).
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