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QSAR STUDIES OF CALCIUM CHANNEL BLOCKERS

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ABSTRACT

In India, there is an alarmingly high prevalence of hypertension as well as concomitant conditions including metabolic syndrome, diabetes mellitus, and chronic renal disease. However, it comes with a number of drawbacks, such as reflex tachycardia and pedal edema. Therefore, for the comprehensive care of hypertension in the nation, a potent antihypertensive drug that does not have these side effects and offers end-organ protection is needed. Numerous approaches, including partial least squares (PLS), heuristic method (HM), multiple linear regression (MLR), and various artificial neural networks can be used for QSAR development.

Genetic function approximation (GFA), has recently grown in prominence in QSAR research. Using 2D-QSAR modeling, it is possible to identify the molecular components that may be changed to improve affinity and efficacy, which is helpful advice for the drug discovery process. These models are helpful for rationalizing a large number of experimental findings, allowing for time and cost savings throughout the drug design process, and they represent a development in the in-silico discovery of effective CCBs.

Keywords: QSAR, CCB, Hypertension, Genetic function approximation

INTRODUCTION

Using structural and molecular data from a chemical library, quantitative structure-activity relationship (QSAR) modeling involves creating prediction models of biological activities. The idea of QSAR is frequently applied in the drug research and development process and has found widespread usage in comparing molecular data to various physical as well as biological aspects. QSAR is a commonly utilized prediction and diagnostic method to identify relationships between chemical structures and biological activity. The goal of QSAR is to satisfy the

requirement and desire of medicinal chemists to anticipate biological reactions.1 It gradually made its way into the practice of medicinal chemistry, agrochemistry, and most other aspects of chemistry.[1]

Modeling significant drug characteristics like ADMET has made substantial use of QSAR techniques. Designing novel, safe medications requires minimizing toxicity and optimizing pharmacokinetics; inaccurate assessment of these parameters can have unintended side effects and impair in vivo efficacy, eventually leading to the failure of a therapeutic candidate. The therapeutic index, or the ratio of the effective dose (ED50) that produces the desired therapeutic effect in 50% of research subjects to the drug dose (TD50) that produces the undesirable therapeutic effect in 50% of subjects, is a crucial component of any drug. It should be noted that almost any chemical is toxic at a sufficiently high dose. Therefore, it should not come as a surprise that even exceedingly hazardous substances, such as the toxins found in snake venom, may be effective as diagnostic probes, drug leads, or even therapeutic agents when used in adequate amounts. Here, we've incorporated recent and emerging trends in a number of fields of study where statistical data modeling has started to take center stage and where lessons learned and broadly applicable QSAR modeling strategies might spark the discovery of novel insights. We anticipate that both data modeling experts and experimental researchers wishing to add computational data analysis methods to their toolkits will find value in our joint effort. [2]

Calcium channel blockers are a diverse class of substances with unique pharmacological properties and chemical compositions. These medications are frequently used to treat supraventricular arrhythmias, persistent coronary ischemia, and hypertension. Phenylalkylamines (for example, verapamil), benzothiazepines (for example, diltiazem), and dihydropyridines (for example, nifedipine, amlodipine, and isradipine) are three different subclasses of CCBs. There seems to be some variation in the relative efficacy of the compounds that make up this family of CCBs, much of which is related to half-life and drug-delivery system properties. Dihydropyridine CCB monotherapy does not offer the best defense against chronic renal disease and/or heart failure. Instead, using substances from this class has a positive effect on occurrences related to both coronary artery disease and stroke.[3]

LITERATURE REVIEW

D.C. Juvale et al (2005) investigated the 1,4-dihydropyridine series substituted at the 2-position with a preferred basic side chain for the QSAR analysis of amlodipine analogs. The link between the physicochemical characteristics and the biological activity was investigated using multiple linear regression analysis. The relevance of electronic, spatial, and steric characteristics was discovered by the QSAR models that were created. It was discovered that the interaction with the receptor site depends on the spatial orientations of the side chains at the 2-position and the 4-substituted phenyl group.[4]

Munikumar Reddy Doddareddy et al (2004) reported the 3D QSAR investigations on T-type calcium channel blockers utilizing CoMFA and CoMSIA on a number of isoxazolyl compounds as effective T-type calcium channel blockers. Three of the most active compound's template structures were derived using Catalyst pharmacophore modeling, while one was discovered utilizing the SYBYL random search option. The cross-validated r2 (q2) values of all CoMFA and CoMSIA models were greater than 0.5, while the conventional r2 values were all greater than 0.85. An external test set of 10 chemicals was used to verify the models' predictive

power; these results showed that all models had adequate pred r2 values ranging from 0.577 to 0.866. The CoMFA standard model of Conformer No. 3 alignments produced the best predictions (q2=0.756, r2=0.963), yielding a predicted r2 value of 0.866 for the test set. The structural characteristics of the ligands accounting for the activity in terms of positively contributing physicochemical parameters, such as steric, electrostatic, hydrophobic, and hydrogen bonding fields, were examined using CoMFA and CoMSIA contour maps.[5]

M. A. Safarpour et al (2003) reported a Study of several recently synthesized C-3 and C-5 ester-substituted 4-(nitro imidazolyl) 1,4-dihydropyridine derivatives using quantum chemistry and QSAR. The ab-initio approach with gaussian98 at RHF/6-21G level was used to compute several quantum chemical descriptors, including atomic charges, electrostatic potentials, HOMO and LUMO energies, electronegativity, electrophilicity, hardness, and softness indices. Using a genetic algorithm as a method for variable selection, multiple linear regression was utilized to simulate the correlations between molecular descriptors and the biological activity of molecules (GA-MLR). The result was a superior multiparametric QSAR model. The prediction of activity of the chemicals in the prediction set, which had no bearing on model construction, was used to assess the predictive power of the generated models. The physicochemical factors were added to the electrical properties of the molecules, which improved the models' capacity for prediction. A genetic algorithm for feature selection in combination with an artificial neural network (GA-ANN) was also used to simulate nonlinear structure-activity correlations. The findings demonstrated that ANN produced QSAR models that were more suitable than those produced by MLR. The best MLR and ANN models, which employed six descriptors as predictor variables, had root means square error of prediction values of 0.60 and 0.21, respectively. Additionally, these models had squared correlation coefficients of 0.874 and 0.988, respectively.[6]

Xiaojun Yao et al (2005) reported the least squares support vector machine-based QSAR and classification investigation of 1,4-dihydropyridine calcium channel antagonists. Calculated structure descriptors that encode constitutional, topological, geometrical, electrostatic, and quantum-chemical characteristics were used to describe each molecule. The descriptor space was then searched using the heuristic technique to identify the descriptors in charge of the activity. With mean-square errors of 0.2593, a projected correlation coefficient (R(2)) of 0.8696, and a cross-validated correlation coefficient (R(cv)(2)) of 0.8167, quantitative modeling yields a nonlinear, seven-descriptor model based on LSSVM. The percentage (%) of right predictions based on leaving one out cross-validation was 91.1%, yielding the best classification results when employing LSSVM.[7]

Hong Zong Si et al (2006) investigated the gene expression-based QSAR analysis of 1,4-dihydropyridine calcium channel antagonists. The descriptor space was searched and the activity-related descriptors were chosen using the heuristic technique. Gene expression programming was used to put up a nonlinear, six-descriptor model with mean-square errors of 0.19 and a projected correlation coefficient (R2) of 0.92.[8]

Bahram Hemmateenejad et al (2004) reported that Utilizing GA-MLR and PC-GA-ANN techniques, ab initio theory is used for a QSAR investigation of calcium channel blockers based on 1,4-dihydropyridine. 45 known-active dihydropyridine compounds were employed as a data set. A model of an artificial neural network combined with principle component analysis for dimension reduction and a genetic algorithm for factor selection (PC-GA-ANN) were used, as well as multiple linear regressions mixed with a genetic algorithm for

variable selection. For several classes of dihydropyridine derivatives, certain multiparametric MLR equations with excellent statistical quality were found. The obtained equations revealed that the conformation of the molecules as well as the electronic characteristics of the atoms that make up their backbone had an impact on how these molecules bind to their receptor. In the PC-GA-ANN, the principal components of the descriptors data matrix were utilized as the neural network's input, and a genetic algorithm was then used to choose the principal components that were the most pertinent. Five chosen primary components were derived from two ANN models. These highly statistical models can accurately predict molecular activity with prediction errors of approximately five percent.[9]

Bahram Hemmateenejad et al (2003) evaluated the Genetic Algorithm used to apply principal component artificial neural networks to the selection of variables in a QSAR analysis of the calcium channel antagonist activity of 1,4-dihydropyridines (analogous to nifedipine). In this investigation, 124 1,4-dihydropyridines with known Ca^{2+} channel binding affinities and various ester substituents at the C-3 and C-5 locations of the dihydropyridine ring as well as nitro imidazolyl, phenyl imidazolyl, and methyl sulfonyl imidazolyl groups at the C-4 position were used as the data set. For every molecule, 837 descriptors were computed among ten distinct sets. The descriptor groups were compressed into principal components using principal component analysis. Each set's most important descriptors were chosen and utilized as ANN input. The optimal set of extracted principal components was chosen using a genetic algorithm (GA). The nonlinear connection between the major components of interest and the biological activity of the dihydropyridines was processed using a feed-forward artificial neural network with a back-propagation of error technique. Comparing PC-GA-ANN to standard PC-ANN reveals that the first model has superior predictive power.[10]

Christiaan Jardínezet al (2016) investigated the 1, 4-dihydropyridine compounds with possible antihypertensive effects as a unique use of the Reduced density gradient for calculating QSAR descriptors. The association between the log IC50 and the highest molecular orbital energy (E HOMO), molecular volume (V), partition coefficient (log P), non-covalent interactions (NCI) (H4-G), and the dual descriptor [f(r)] is highlighted by the QSAR model. The following four internal analytical validations—DK=0.076, DQ=-0.006, R P=0.056, and R N=0.000—as well as the external validation Q 2boot=64.26—were used to confirm the model's output values of R 2=79.57 and Q 2=69.67. The discovered QSAR model may be utilized to accurately predict biological activity in novel compounds based on a DHP series.[11]

Amol S Sherikar et al (2021) reported the Determination and Study of Calcium Channel Blocking Chalcone Derivatives. After performing pharmacophore modeling and docking analysis, potential scaffolds were found. On adult goat pulmonary veins, lead compounds were in vitro screened for calcium channel-blocking activity, IC50 values were calculated, and 3D QSAR was carried out. Hydrophobic groups, hydrogen bond donors, and hydrogen bond acceptors are significant characteristics for calcium channel blocking action, according to the pharmacophore modeling. The docking investigation identified interactions between amino acid residues and ligands known as Vander Wall's, hydrophobic, and hydrogen bonds. When tested in vitro, the compounds AI6, Ca2, and D8 yielded IC50 values of 4.756, 3.608, and 5.211 M, respectively, while the reference drug Nifedipine had an IC50 value of 1.304 M. The significance of various steric and electrostatic factors and their association

with L-type calcium channel-blocking activity were elucidated by the 3D QSAR analysis. This research demonstrated the potential of the chalcone scaffold as a NO donor for the development of new calcium channel blockers for the treatment of vascular diseases.[12.]

Peter Ayoub Sidhom et al (2017) evaluated the Synthesis, Docking Simulation, Biological Evaluations, and 3D-QSAR Study of 1,4-Dihydropyridines as Calcium Channel Blockers. the synthesis of two series of nifedipine analogs where the ortho- or a meta-nitrophenyl ring is retained was done. A pre-synthetic molecular docking study with a receptor model followed by molecular alignment has been performed on synthesized compounds to predict the most active member. The IC_{50} values revealed that some of the compounds are similar to or more active than nifedipine. Substitution of groups at the 3- and 5-positions of the dihydropyridine (DHP) ring gave 3k, which is more active than nifedipine. The valid three-dimensional quantitative structure–activity relationship (3D-QSAR) model prefigures the influence of lipophilicity, bulkiness, and chelating effects of the C3 and C5 substituents. Bulky groups reduce the effectiveness of lengthening the hydrocarbon chain of esters at the 3- and 5-positions of the DHP ring as a strategy to increase activity. Bulky groups also prevent ring-to-ring hydrophobic contact with tyrosine (Tyr)4311. Strong binding to the receptor is made possible by the chelating substituent on the phenyl ring at the 4-position of the DHP ring, which also stabilizes the closed-channel conformation. The validation of the 3D-QSAR model showed that it was capable of foretelling the activity of novel compounds from the same chemical class.[13]

Maryam Hosseini et al (2008) reported New 1,4-Dihydropyridine Derivatives: Synthesis, QSAR, and Calcium Channel Antagonist Activity Using guinea-pig ileum longitudinal smooth muscle to contain 1-Methyl-4,5-dichloroimidazolyl Substituents. IR, (1)H-NMR, and mass spectra were used to confirm the structure of every molecule that was synthesized. According to the calcium-channel antagonist activity of the various compounds, compound 10b was the most active, and compound 10f was the least active. The most effective substance with unsymmetrical diesters 12a–k was the ethyl, phenethyl derivative. By using QSAR analysis to analyze the structural characteristics of calcium-channel antagonist activity, a linear association between the -log IC (50) values of these compounds and their constitutional and topological features was discovered.[14]

CONCLUSION

Both as initial monotherapy and in combination with other antihypertensive drugs, calcium channel blockers are potent antihypertensive medications. The treatment of chronic, stable angina, variable angina, and supraventricular arrhythmias is also successful with these medications. In doing so, they lower intracellular calcium concentration and relax and dilate arterial smooth muscle. They also function to decrease calcium entrance into both vascular and cardiac cells. Myocardial contractility is decreased, and cardiac conduction is suppressed. The atrioventricular (AV) node, where this impact is most noticeable, decreases the pace of the heartbeat. Calcium channel blockers have the effect of lowering myocardial oxygen demand by reducing cardiac activity, contractility, and afterload; as a result, they serve as the prophylactic against angina. Verapamil, a non-dihydropyridine, is more cardioselective than dihydropyridines like nifedipine, which are more selective for the vasculature.

QSAR development can use a variety of strategies, including partial least squares (PLS), heuristic methods, multiple linear regression (MLR), and several forms of artificial neural networks (ANN). In QSAR research, genetic function approximation (GFA) has recently become quite well-liked. In a statistical study, the GFA approach, created by Rogers and Hopfinger, is used to choose the pertinent descriptors and produce several QSAR models. The best model created may then be used to forecast test set molecules that weren't in the training set molecules after doing a sensitivity analysis of QSAR models. The model's correct validation is guaranteed by randomization tests conducted on it at various intervals of confidence levels.

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