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STUDY OF BLOOD-BRAIN BARRIER PERMEATION USING PARALLEL ARTIFICIAL MEMBRANE PERMEABILITY ASSAY AND QUANTITATIVE-STRUCTURE PERMEABILITY RELATIONSHIP MODELING

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INTRODUCTION

Imidazoline receptor ligands are a numerous family of biologically active compounds known to produce central hypotensive effect by interaction with both α_2-adrenoreceptors (α_2-AR) and imidazoline receptors (IRs) (1, 2).

The main aims of this study were to evaluate Blood-Brain Barrier (BBB) permeability (P_e) of 18 IRs/α-ARs ligands and 22 Central Nervous System (CNS) drugs using Parallel Artificial Membrane Permeability Assay (PAMPA) and Biopartitioning Micellar Chromatography (BMC), and than to develop the Quantitative-Structure-Permeability Relationship (QSPR) models useful for prediction BBB permeability of related IRs/α-ARs ligands.

MATERIALS AND METHODS

Effective permeability of 40 compounds (18 IRs/α-ARs ligands and 22 CNS drugs) was examined using PAMPA-BBB model based on porcine brain lipid extract, which was based on the BBB model described in literature (3).

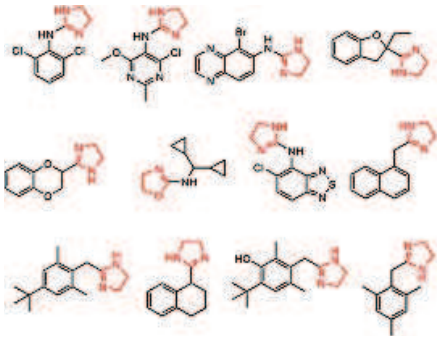

Figure 1. Chemical structures of selected IRs/α-ARs ligands.

The retention factors ($\log k_{BMC}$) of the ligands were also examined using BMC systems.

BMC analyses were performed on a Zorbax Extend-C18 column (150 mm × 4.6 mm, particle size 5 μm), with a flow rate of 1 ml/min, temperature of 36.5 °C, and detection wavelength on 210 nm. Micellar mobile phase was prepared by dissolving polyoxyethylene (23) lauryl ether Brij 35 in buffered solution at pH 7.40 to get a final surfactant concentration of 0.04 M (4).

Obtained $\log k_{BMC}$ retention factors were correlated with PAMPA permeability coefficients (Pe).

The geometry of dominant species at pH=7.4 have been performed using B3LYP/6–31G(d, p) basis set included in ChemBio3D Ultra 13.0 program (CambridgeSoft Corporation, 2013). Molecular parameters of optimized models were calculated using ChemBio3D Ultra 13.0, Dragon 6.0 (Talete srl, 2010) and ADMET Predictor 6.5 (Simulations Plus, Inc., 2013) programs.

The QSPR studies were applied to examine the correlations between effective BBB permeability (logPe) and $\log k_{BMC}$ retention factors of the examined ligands and their calculated constitutional, physicochemical, electronic, and geometrical descriptors by use

of the Partial Least Square (PLS), stepwise Multiple Regression (MLR), and Artificial Neural Networks (ANN) statistical methods.

RESULTS AND DISCUSSION

PAMPA-BBB method was used to assess effective permeability (Pe) of examined compounds, as parameter of the rate of blood brain permeation process.

The comparison of the optimal linear (MLR/QSPR-Model-3(logPe) and PLS/MLR-Model-3(logPe)) and non-linear (ANN/QSPR-Model-3(logPe)) methods showed the superiority of the ANN over PLS and stepwise MLR models. Even though MLR/QSPR-Model-3(logPe) and PLS/QSPR-Model-3(logPe) showed good predictive power, ANN/QSPR-Model-3(logPe) was chosen as optimal due to highest prognostic capabilities for external data set (R^2_{pred}= 0.770) (Figure 2). This means that relation between selected descriptors (P_VSA_LogP_4, HBDnch, MATS7e, Mor11s and Mor16m) and permeability (logPe) is not absolutely linear and there are some non-linear relationships in the system which may be modelled better with the ANN function. Analyzing descriptors in these QSPR(logPe) models, most significant molecular properties that influence BBB permeability were identified.

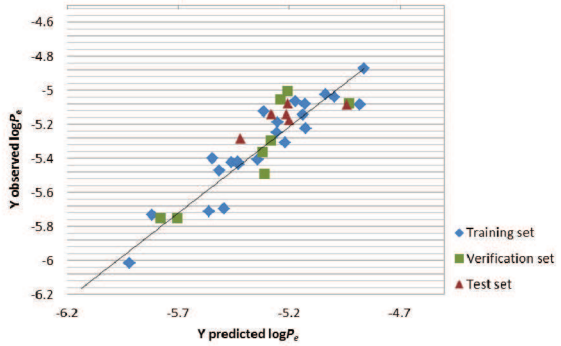

Fig. 2: Observed vs. predicted values in selected ANN/QSPR-Model-3

Significant correlations were obtained between logarithm of BMC-retention factor (logk_{BMC}) and effective permeability (Pe) (r = 0.83).

The comparison of statistical parameters of PLS/QSPR-logk_{BMC}, MLR/QSPR-logk_{BMC} and ANN/QSPR-logk_{BMC} indicates that PLS/QSPR-logk_{BMC} and MLR/QSPR-logk_{BMC} were superior over ANN/QSPR-logk_{BMC} model. The P_VSA_s_5, VE1_RG, P_VSA_p_2 and GATS1e parameters were selected descriptors with the most significant influence on logk_{BMC}, indicating on possible structural modifications which could enhance BBB penetration of related IRs/α-ARs ligands.

CONCLUSIONS

Based on the impact of descriptors in optimal ANN/QSPR-Model-3(logPe) was concluded that increase in van der Waals surface area (VSA) of certain atoms (bromine), presence of functional group that are characterized by high Sum of Estimated NPA Partial Atomic Charges on Nitrogen (guanidine, aminoguanidine) as well as presence of groups such as methyl or isobutyl have a negative influence on BBB permeability of α-AR/IR ligands and related compounds. On the other hand, presence of highly electronegative atoms located in aromatic moiety has a positive influence on BBB penetration.

Structural diversity of the examined drugs provide wide application domain of the QSPR models, which can be used as fast screening models for assessment of brain penetration of related IRs/α-ARs ligands.

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