Prediction of Blood-Brain Barrier Penetration of *meta-/para*-Alkoxyphenylcarbamic Acid Esters Bearing Substituted *N*-Phenylpiperazine Fragment

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ABSTRACT: The present study deals with blood-brain barrier (*BBB*) passive penetration of the substances labelled as **7a–7d** and chemically referred to as 1-[3-(Y-alkoxyphenylcarbamoyloxy)-2-hydroxypropyl]-4-(2-methylphenyl) piperazinium chlorides. Following their chemical structures, they could be classified as prospective *α*-/*β*-adrenoceptor blockers. Such groups are known, among others, by their adverse reactions on central nervous system due to their transport across the *BBB*. The lipophilicity as the main parameter of the *BBB* permeability predictions is presented by the values of partition coefficient which was experimentally estimated using shake-flask method in two different partitions, *i.e.* in octan-1-ol/buffer and cyclohexane/buffer as well. The *in silico* models which were used are based on the correlation between the log *BB* and the Δ log *P* readouts (the log *P* value estimated in octan-1-ol/buffer minus the one estimated in cyclohexane/buffer) whereby log *BB* is primary transfer marker for such compounds entering brain from blood. Besides the log *BB* outputs, some other molecular physicochemical descriptors have to be generated. According to the results obtained by using Young, Kaliszan, Kelder, Clarks, Pan, Abraham, Feher and van de Waterbeemd models, probably none of the currently investigated compounds will permeate across the *BBB*.

Key words: *α*-/*β*-Blockers, slkoxyphenylcarbamates, partition coefficient, blood-brain barrier, lipophilicity

INTRODUCTION

β-Adrenergic receptor blockers (*β*-blockers; *β*-ARBs) are in general well tolerated and commonly used for variety of cardiovascular and non-cardiovascular disorders. Aimed group of the drugs is efficacious with relatively few accompanying side effects. Besides such fact, some of the *β*-ARBs are connected with serious CNS undesirable effects. Two key factors determine the extent of penetration through the blood-brain barrier. These are partition coefficient and the ability to bind to plasma proteins as well.[1] Current study is concerned only with partition coefficient. In terms of pharmacokinetics, relatively lipophilic *β*-ARBs cross the *BBB* more easily than the hydrophilic ones which can cause pharmacodynamic diversity within this therapeutic group and which leads to differences in clinical practice in the end.[2] The most frequently occurred undesirable side effects on CNS are headaches, depression, panic, sleeping disorders, nightmares and hallucinations as well which may occur due to the binding to CNS adrenergic and/or serotonergic receptors or *via* non-specific membrane stabilizing effects.[3] For example, last three side effects mentioned above are related to a depressed melatonin secretion. Norepinephrine stimulates synthesis and releasing of melatonin *via* β_1- and α_1-adrenergic receptors (ARs). It has been proved that *β*-ARBs have been able to reduce the production of melatonin *via* specific inhibition of β_1-AR.[4] For the evaluated series of the compounds labelled as **7a–7d** could be assumed such dualistic effect on both *α*- as well as *β*-ARs. Integrated 2-hydroxypropane-1,3-diyl fragment is primarily responsible for β_1-antagonistic activity

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whereas (substituted) *N*-phenylpiperazin-1-yl fragment controls their activity as vasodilatants.

MATERIALS AND METHODS

Characterization of the evaluated compounds. Synthesis, basic physicochemical properties as well as spectral characterization of the substances under the study **7a–7d** were previously published in paper.[5]

The SMILES codes. The SMILES (Simplified Molecular-Input Line-Entry Specification) notification is a comprehensive chemical language (a typographical method using printable characters) with its own rules which specifies molecules and reactions using ASCII characters to represent atom and bond symbols. The result is a line notation which comes into being from two-dimensional drawn pictures.[6] The ALOGPS program which has been used for the generation of SMILES strings is Java based server and it is one of the main parts of the VCCLAB site. The studied molecules were at first converted into the SMILES codes (in the form of bases and corresponding salts with hydrochloric acids) from their 2D-structures drawn in Java molecular editor and according to these codes specific parameters could be calculated.[7]

Estimation of partition coefficients. The logarithm of partition coefficients (the log P_{exp} data) were estimated experimentally in two mediums, octan-1-ol/phosphate buffer (log P_{expO}) and cyclohexane/phosphate (log P_{expC}) buffer, using well-known and generally accepted shake-flask method. Lipophilic phase was represented by octan-1-ol/cyclohexane and the aqueous one by phosphate buffer with pH = 7.4 prepared from disodium hydrogenphosphate, *p.a.* (Slavus, Slovak Republic) with c = 0.2 mol·l^{-1} and pure citric acid (Chemapol, Czech Republic) with c = 0.1 mol·l^{-1}. The process of the log P_{expO} estimation was described in detail within the paper.[5] The log P_{expC} readouts were estimated by applying the method described below. The amount 0.0020 g of particular investigated compound was dissolved in 50 ml of phosphate buffer with pH = 7.4 in volumetric flask. The volume of 5 ml of basic solution was weakened with phosphate buffer into 10 ml volumetric flask. The absorbance of such solution was measured (A_1). After adding 0.5 ml of cyclohexane (Mikrochem, Slovak Republic), the system was shaken and the absorbance (A_2) of aqueous phase was taken by the wavelength of second absorption maximum. Partition coefficient value(s) was (were) derived from the equations 1–3:

$$P_{\exp C} = \frac{(1000 \times g) - (a \times c_{H_2O} \times M_r)}{b \times c_{H_2O} \times M_r} \quad (1)$$

$$c_{H_2O} = \frac{A_2}{\varepsilon} \quad (2)$$

$$\varepsilon = \frac{A_1}{c} \quad (3)$$

where g is the weight of studied compound in grams in 10 ml of measured solution, a is number of mililiters of aqueous phase, b is number of mililiters of cyclohexane, M_r is molecular weight of studied compound, $_{c}H_2O$ is amount of inspected compound in aqueous phase after shaken, c is concentration of measured solution expressed in mol/l units.

The prediction of partition coefficient in system octan-1-ol/water. Partition coefficient in system octan-1-ol/„water“ was calculated for the substances **7a–7d** using two specific methods, the CLOGP 4.0 (an integral part of Bio-Loom 1.5 software) and MLOGP (an integral part of ALOGPS applet) which are based on different algorithms. The CLOGP 4.0 method is based on principles of constructionism developed by Hansch and Leo.[8] Fragmental system consists of exactly measured log *P* data of a small set of simple molecules whereby the other values were derived. This method is rule-based fragmental conception of isolating carbon (sp^3 carbon with at least two bonds linked directly to two another carbons). Consequently correction for branching was applied. 200 Fragments and 25 correction factors were defined. Chou and Jurs[9] adapted this method for computational use and called it CLOGP. The version 4.0 was upgraded with so-called FRAGCALC algorithm which is based on 600 fragments containing only aliphatic or aromatic bonds.[10]

The MLOGP approach reflects the relationship between the structure of compound or topological indices and the log *P* data. The set of 1230 organic molecules including general aliphatic, aromatic and heterocyclic structures which contains C, H, N, O, S P, F, Cl, Br and I atoms were used for deriving 13 parameters that are the basis for calculating log *P* values according to Moriguchi:[11]

$$\begin{aligned}\text{MLOGP} = &-1.041 + 1.244(\text{CX})^{0.6} - 1.017(\text{NO})^{0.9} + \\ &0.406(\text{PRX}) - 0.145(\text{UB})^{0.8} + 0.511(\text{HB}) + \\ &0.268(\text{POL}) - 2.215(\text{AMP}) + 0.912(\text{ALK}) - \\ &0.392(\text{RNG}) - 3.684(\text{QN}) + 0.474(\text{NO2}) + \\ &1.582(\text{NCS}) + 0.773(\text{BLM}) \qquad (4)\end{aligned}$$

Particular parameters presented witin the equation (4) are described in article.[11]

Distribution coefficient value(s) calculation. As the neutral and ionic species are diversely polarised, the log *P* readout of ionisable compounds is pH dependant.[12] General contribution of ionised and unionised form of compound in both phases water and non-aqueous is described as distribution coefficient (*D*). Providing that only neutral species are present in non-aqueous phase, for acidic compounds value of log *D* can be calculated according to the relationship if the activity corrections are neglected:[13]

$$\log D = \log P - \log\left(1 + 10^{pH - pK_a}\right) \qquad (5)$$

The calculation of some molecular descriptors used in particular models for the *BBB* penetration. Some important molecular properties as molecular (topological) polar surface area (*TPSA*), molecular volume and number of hydrogen bond acceptors (*n*ON) have to be generated. Using interactive property calculator Molinspiration Cheminformatics (Slovak Republic), they were obtained and summarized for both basic and salty forms of studied molecules applying the SMILES codes generated before.[14]

Molecular (topological) polar surface area (TPSA). Such descriptor is defined as a sum of fragment contributions of polar atoms and their hydrogens attached. It is a quick fragmental method, which is called topological *PSA*. The *TPSA* assigns also relatively good to blood-brain barrier penetration, intestinal absorption and transport properties. Particular fragment contributions were determined by least squares fitting to the single conformer three-dimensional *PSA* for 34810 drugs from the World Drug Index. According to this model, 43 polar fragments centered over C-, N-, P-, S-atoms were determined.[15]

Molecular volume. The volume of a compound is given by a sum of group contribution of particular fragments, which correspond to real three-dimensional volume. They were evaluated on the basis of set of 12000 molecules. Calculated volume is expressed in cubic Angstroems.[16]

Hydrogen bond acceptors (nON). Hydrogen bonds have importance in determining the interaction of drug with receptor. The simplest descriptor describing hydrogen bond is an indicator variable which has the value 1 if molecule or its substituent is able to create a hydrogen bond and value 0 if not. The OH-, NH_2- and COOH-groups have the value 1 for their donor and also acceptor ability whereas OCH_3-, $N(CH_3)_2$- and $COOCH_3$-groups have for donor ability the value 0 and for the acceptor one the value 1.[17]

The log BB values and in silico methods for the BBB penetration. The parameter of log *BB* is a common measure of the *BBB* penetration degree and it is defined as the ratio of steady-state total concentration of investigated compound in the brain (C_{brain}) to that in the blood (C_{blood}):[18]

$$\log BB = \frac{C_{brain}}{C_{blood}} \qquad (6)$$

The aim of current research was to calculate log *BB* values applying commonly used models and to determine whether or not will the studied molecules permeate through the *BBB*. Generally, they are not based on classic quantum chemical descriptors from 3D-drug modelling, but they are set up on physicochemical properties and specific molecular descriptors. The first *in silico* model for prediction

BBB permeation was Young model.[19] It is based on good correlation between the log *BB* and the $\Delta \log P$ outputs whereby the permeability increases with lower hydrogen-bonding ability:

$$\log BB = 0.889 - 0.485 \times \Delta \log P$$

$n = 20$, $r = 0.831$, $s = 0.439$, $F = 40.2$ (7)

Kaliszan et al. developed a model based on the Young's one in which they took into account also molecular weight of compounds:[20]

$$\log BB = -0.088 + 0.272 \times \Delta \log P - 0.00112 \times M_r n$$

$= 33$, $r = 0.947$, $s = 0.126$, $F = 131.1$ (8)

Kelder explained the role of *PSA* during penetration process of substances from blood to brain:[21]

$$\log BB = 1.330 - 0.032 \times PSA$$

$n = 45$, $r = 0.840$, $F = 229.0$ (9)

Clark used in his first model only *PSA* as a determinant, which was not applicable for the compounds without *PSA* (e.g. nonpolar):[22]

$$\log BB = -0.016 \times PSA + 0.550$$

$n = 57$, $r = 0.819$, $s = 0.455$, $F = 229.0$. (10)

From that reason it was necessary to implement another descriptor, which will distinguish non-polar substances. After an integration of the CLOGP value into the equation model B was suggested:[22]

$$\log BB = 0.139 - 0.148 \times PSA + 0.152 \times CLOGP$$

$n = 55$, $r = 0.790$, $s = 0.350$, $F = 95.8$ (11)

Using the MLOGP method instead of the CLOGP one, resulting model C provided slightly different statistic coefficients:[22]

$$\log BB = 0.131 - 0.145 \times PSA + 0.172 \times MLOGP$$

$n = 55$, $r = 0.770$, $s = 0.370$, $F = 86.0$ (12)

Pan´s method was based on the division of substances into the clusters according to their chemical structure. This method is quite easy to use but it dismissed some statistic parameters:[23]

$$\log BB = 0.064 + 0.200 \times \log P_{\exp O} - 0.00502 \times M_r$$

$n = 55$, $r = 0.770$, $s = 0.370$, $F = 86.0$ (13)

Abraham derived a relationship for the calculating log *BB* value which come from a solvatation equation used to analyze solubility of gases and vapours in water, blood and other biological liquids:[24]

$$\log BB = 0.119 + 0.350 \times \log P_{\exp O} - 0.00502 \times M_r$$

$n = 53$, $r = 0.852$, $s = 0.363$, $F = 66.2$ (14)

Hydrogen bonding ability represented by n_{acc} (number of atoms which are able to accept hydrogen bonds) was for Feher model given below essential:[25]

$$\log BB = 0.4275 - 0.3873 \times n_{acc} + 0.1092 \times \log P_{\exp O} - 0.0017 \times PSA$$

$n = 61$, $r = 0.854$, $s = 0.424$, $F = 51.0$ (15)

Last model used within current paper was based on Young's set of molecules. van de Waterbeemd found out that the log *BB* value can be calculated by an implementation of *PSA* and molecular volume V_m into the equation:[26]

$$\log BB = -0.021 \times PSA - 0.003 \times V_m + 1.643$$

$n = 20$, $r = 0.835$, $s = 0.448$, $F = 19.5$ (16)

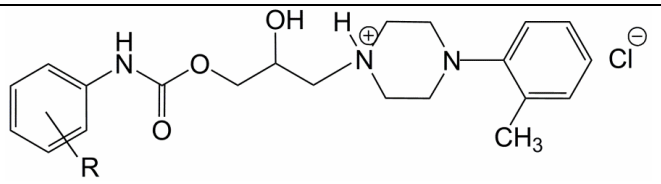
RESULTS AND DISCUSSION

The equilibrium of distribution substances between blood and brain is given by a ratio of steady-state concentrations of the compounds in brain and in blood or plasma. In form of algorithms, it is defined as log *BB*. The *BBB* is described as the specialized set of specific capillary endothelial cells, which main function is to protect brain from malign agents, toxins and viruses which can be present in blood circulation. The *BBB* can inhibit penetration of therapeutic agents into the brain but it has also the main role in supplying the brain with nutritive substances. In contradistinction to systemic circulation it's cells are characterized by a low degree of pinocytosis and membrane fenestration and that is the reason why exchange of substances between blood and brain is realized by transcellular way, i.e. by passive diffusion. The *BBB*

represents an enzyme barrier with higher concentrations of enzymes in brain microcapillaries. It also disposes of specific efflux transporters such as P-glycoprotein or another typical efflux mechanisms such as multi resistance protein or breast cancer resistant protein. Despite the assumption that passive diffusion through *BBB* is the most important process of permeation, more and more scientist support the idea that actively mediated transport and influx/efflux can be even more important.[27]

The aim of current paper was to predict the margin of permeation of the compounds with incorporated *N*-phenylpiperazine moiety, chemically 1-[3-(Y-alkoxyphenylcarbamoyloxy)-2--hydroxy-propyl]-4-(2-methylphenyl)piperazinium chlorides (Table 1), through *BBB* as potential drugs with supposed multireceptor activity. The descriptors used in specific models for the *BBB* permeation were calculated for both forms of studied molecules, i.e. for the bases and the salts as well. The term base(s) represents molecule in which the nitrogen atom of piperazin-1,4-diyl skeleton is 3-bond (unprotonated) whereas the term salt(s) represent(s) the monochloride(s) whereby in this case the nitrogen atom is 4-bond as positive charge carrier.

Table 1. General characterization of investigated compounds 7a–7d.



Entry	*R*	Formula	M_{rB} (Base)	M_{rS} (Salt)
7a	3-OCH_3	$C_{22}H_{30}ClN_3O_4$	399.49	435.95
7b	3-OC_2H_5	$C_{22}H_{32}ClN_3O_4$	413.52	449.98
7c	4-OCH_3	$C_{22}H_{30}ClN_3O_4$	399.49	435.95
7d	4-OC_2H_5	$C_{22}H_{32}ClN_3O_4$	413.52	449.98

Table 2. The SMILES codes of evaluated molecules generated for the form of base (B) and salt (S).

Entry	SMILES
7aB	C1=C(OC)C=CC=C1NC(OCC(CN3CCN(C2=C(C)C=CC=C2)CC3)O)=O
7aS	C1=C(OC)C=CC=C1NC(OCC(C[N+]3([H])CCN(C2=C(C)C=CC=C2)CC3)O)=O
7bB	C1=C(OCC)C=CC=C1NC(OCC(CN3CCN(C2=C(C)C=CC=C2)CC3)O)=O
7bS	C1=C(OCC)C=CC=C1NC(OCC(C[N+]3([H])CCN(C2=C(C)C=CC=C2)CC3)O)=O
7cB	C1=CC(OC)=CC=C1NC(OCC(CN3CCN(C2=C(C)C=CC=C2)CC3)O)=O
7cS	C1=CC(OC)=CC=C1NC(OCC(C[N+]3([H])CCN(C2=C(C)C=CC=C2)CC3)O)=O
7dB	C1=CC(OCC)=CC=C1NC(OCC(CN3CCN(C2=C(C)C=CC=C2)CC3)O)=O
7dS	C1=CC(OCC)=CC=C1NC(OCC(C[N+]3([H])CCN(C2=C(C)C=CC=C2)CC3)O)=O

As the most significant property is considered the partition coefficient estimated experimentally in two various lipohydrophilic systems, i.e. in octan-1-ol/buffer (log P_{expO}) and cyclohexane/buffer (log P_{expC}) as well. In octan-1-ol/buffer medium were estimated the values similar for *meta*- and *para*-methoxy derivatives (3.44 and 3.47, respectively; Table 3) just like for the *meta*- and *para*-ethoxy ones (3.60 and 3.65, respectively; Table 3). In the medium made up from cyclohexane and buffer were determined higher readouts for the substances containing the substituent *R* in *meta*-position (1.66 and 1.73, respectively; Table 3). One of the most important experimental parameter used within current paper is the value of $\Delta\log P_{expO–expC}$ characterizing distribution of the substances between two system with different lipophilic phase. As expected, higher outputs were acquired for ethoxy derivatives (Table 3).

The majority of therapeutically used drugs are ionisable substances which can be ionised into several degrees by the physiological pH. Positive and negative charged molecules are much more polar than the neutral ones. Therefore the degree of polarisation shows a significant influence on the lipophilicity of ionisable substances. The distribution coefficient is characterized as an effective lipophilicity measured by specific pH considering inner lipophilicity and the degree of ionisation.[28] Observed values are at interval from 1.31 to 3.42 in both used mediums. According to calculated results it can be assumed that investigated compounds will penetrate partially through the *BBB* (Table 3).

Polar surface area (*PSA*) is a prediction parameter of drug transport properties and it is formed of atoms which can accept hydrogen bonds – hydrogen bond acceptor (*n*ON). The value of *PSA* is defined as a sum of surfaces of polar atoms (usually oxygens and nitrogens) and hydrogens attached directly to these heteroatoms.[15]

Molecules with *PSA* higher than 140 Å^2 are usually absorbed badly from stomach and gastrointestinal tract whereas *PSA* readout about 60–70 Å^2 indicates relatively good gastrointestinal absorption as well as a passage through the *BBB*. The outputs of *PSA* for studied compounds in their basic form are lower of a contribution of hydrogen atom attached to nitrogen atom in form of salt. As in both cases, the values of *PSA* are higher than 70 Å^2 so it can be expected that the evaluated substances not to cross the *BBB* (Table 4).

Table 3. Some experimentally estimated and calculated parameters of the lipophilicity for inspected set of the compounds 7a–7d.

Entry	log P_{expO}	log P_{expC}	$\Delta\log P$	log $D_{o/w}$	log $D_{c/w}$
7a	3.44	1.66	1.78	3.23	1.45
7b	3.60	1.73	1.87	3.42	1.55
7c	3.47	1.62	1.85	3.20	1.35
7d	3.65	1.60	2.05	3.36	1.31

$\Delta\log P = \Delta\log P_{expO–expC}$

Table 4. Molecular descriptors generated by Molinspiration Cheminformatics, Bio-Loom 1.5 and ALOGPS applets for evaluated set of the compounds 7a–7d.

Entry	PSA_B	PSA_S	V_{mB}	V_{mS}	*n*ON	CLOGP 4.0		MLOGP	
						Base	Salt	Base	Salt
7a	74.27	75.47	378.312	381.425	7	3.53	3.73	1.58	-2.10
7b	74.27	75.47	395.114	398.227	7	4.06	4.26	1.80	-1.89
7c	74.27	75.47	378.312	381.425	7	3.53	3.73	1.58	-2.10
7d	74.27	75.47	395.114	398.227	7	4.06	4.26	1.80	-1.89

PSA_B/PSA_S = polar surface area calculated for bases/salts, *n*ON = hydrogen-bond acceptors (bases), V_{mB}/V_{mS} = calculated molecular volume for bases/salts

As the passage across the *BBB* is realized through passive transport, among lipophilicity, molecular volume as well as charge are considered some of the most important factors. Small molecules can cross the *BBB* easily while the relatively bulkier ones do not cross the barrier at all. The data about molecular volume were used lately in van de Waterbeemd and Kansy model.[29] Higher values are related to the compounds in form of salt (Table 4).

The partition coefficient in octan-1-ol/„water“ medium can be also calculated using *in silico* methods. Two approaches, CLOGP 4.0 and MLOGP, have been chosen within current paper. In the series of the substances under the study **7a–7d** were generated equivalent values for corresponding *meta*- and *para*-alkoxy positional isomers (Table 4).

The values of the log *BB* for the most of drugs used in practise range from –2.000 to 1.000.[30] The substances with the log *BB* data higher than 0.300 cross the *BBB* easily.[30] On the other hand, the compounds which showed lower log *BB* readout than –1.000 indicated their low concentration in the brain.

In present study, the *BBB* penetration of the compounds **7a–7d** has been predicted by applying ten models based on different principals. Using Young and Kaliszan models, the calculated log *BB* data were not higher than 0.300 (Table 5).

The values were either negative or just in two cases positive (for the compound **7a** in Young model, for **7d** in Kaliszan model, respectively). In remaining models, the log *BB* data were negative and not higher than –0.564. Even most of them were under the limit of –1.000.

Table 5. Calculated values of log *BB* using Young, Kaliszan and Kelder models.

Entry	Young		Kaliszan		Kelder	
	Base	Salt	Base	Salt	Base	Salt
7a	–	0.026	-0.051	-0.569	-1.047	-1.085
7b	–	-0.018	-0.043	-0.083	-1.047	-1.085
7c	–	-0.008	-0.032	-0.073	-1.047	-1.085
7d	–	-0.105	0.006	-0.034	-1.047	-1.085

Table 6. Calculated values of log *BB* using Clark (A, B, C) and Pan models.

Entry	Clark (A)		Clark (B)		Clark (C)		Pan	
	Base	Salt	Base	Salt	Base	Salt	Base	Salt
7a	-0,638	-0,658	-10,316	-10,464	-10,366	-11,173	-0,585	-0,606
7b	-0,638	-0,658	-10,236	-10,383	-10,329	-11,137	-0,553	-0,574
7c	-0,638	-0,658	-10,316	-10,464	-10,366	-11,173	-0,579	-0,600
7d	-0,638	-0,658	-10,236	-10,383	-10,329	-11,137	-0,543	-0,564

Table 7. Calculated values of log *BB* using Abraham, Feherand van de Waterbeemd models.

Entry	Abraham		Feher		van de Waterbeemd	
	Base	Salt	Base	Salt	Base	Salt
7a	-0.682	-0.865	-2.786	-2.788	-1.052	-2.730
7b	-0.697	-0.880	-2.803	-2.805	-1.102	-2.780
7c	-0.742	-0.855	-2.789	-2.791	-1.052	-2.730
7d	-0.679	-0.862	-2.808	-2.810	-1.102	-2.780

In conclusion, following the obtained results is can be assumed that the *BBB* will be impassable for all of currently investigated compounds **7a–7d** which could be classified as potential *α*-/*β*-AR blockers without any serious undesirable effects on CNS.

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