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Abstract- In recent years, *in silico* pharmaceutical tools have a notable impact of drug discovery as complementary methods for *in vitro* and *in vivo* assays. Such procedures help to optimize pharmacokinetic and pharmaceutical properties of (not only) drug-like candidates. Following the Lipinski´s Rule of Five concept and experimental partition coefficients data as well, the majority of currently in silico investigated compounds, 8aB–8iB, which structure contained so-called privileged structure, 4-(3-trifluoromethylphenyl)piperazin-1-yl fragment, would be regarded as the drugs with the physicochemical properties that could be convenient in terms of their pharmacokinetic and metabolic profiles. In addition, their ability to cross blood–brain barrier was *in silico* inspected. In general, the CNS drugs tend to be more lipophilic, be less polar, have shown less flexibility, had lower molecular weight and smaller molecular volume as well than the drugs applied for other therapeutic indications. Following the calculated (molecular weight, topological polar surface area, hydrogen-bond acceptors count, hydrogen-bond donors count, rotatable bonds count, CLOGP data) and experimentally estimated (log P_{exp}) readouts, it was suggested that concerned derivatives would probably not cross blood–brain barrier by passive diffusion, thus they could not affect CNS processes.

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I. Introduction

More than ten years have passed since the research paper concerning the Rule of Five (RO5) by Lipinski et al. (2001) was published[1]. Assuming the evaluation of potentially orally active compounds, in the discovery setting, the RO5 predicted[1,2] that poor absorption or permeation was more likely when there were more than five hydrogen-bond donors (OH plus NH count), more than ten hydrogen -bond acceptors (O plus N atoms), the molecular weight (MW) was greater than 500 and the calculated log *P* value for the system octan-1-ol/water using CLOGP approach[3] was more than 5 or higher than 4.15 when applied Moriguchi MLOGP predictive method[4], respectively. In other words, these physicochemical parameters were connected with acceptable aqueous solubility and intestinal permeability and comprised the first steps of oral bioavailability. The RO5 was deliberately created to be a conservative predictor in an area where medicinal chemistry produced too many compounds with poor physicochemical properties[2]. Veber et al.[5] later suggested that the commonly applied MW cutoff at 500 did not itself significantly separate compounds with poor oral bioavailability from those with acceptable values. Taking into account the fact that molecular rigidity was a much more complex issue than the simple counting of rotatable bonds, their conclusions[5] also pointed out that the compounds which met only two criteria, i.e. ten or fewer rotatable bonds and the value of polar surface area (PSA) equal to or less than 140 Å^2 (or 12 or fewer hydrogen-bond donors and acceptors), would have a high probability of good oral bioavailability. Nevertheless, it is important to emphasize the limitations of these rules: (i) the RO5 applies only to the compounds which are delivered by the oral route, (ii) the RO5 applies only to the compounds which are absorbed by passive mechanisms, (iii) there are important exceptions (MW>500 and reduced molecular flexibility and constrained PSA; natural products), (iv) passing the RO5 is no guarantee that a compound is drug-like, (v) the RO5 says nothing about specific chemistry structural features found in drugs or non-drugs[2,6,7].

From chemical viewpoint, currently *in silico* investigated molecules, labelled as **8aB–8iB**, could be regarded as *ortho*-/*meta*-/*para*-alkoxyphenylcarbamic acid-based derivatives as well as *N*-arylpiperazine -based structures (Figure). It was previously found out that some of them (all the investigated molecules were prepared and tested as the salts with hydrochloric acid) have shown relatively promising antimicrobial profile[8,9]. In general, the *N*-arylpiperazine moiety was regarded as so-called privileged structure[10] – it represented a class of the molecules capable of binding to multiple receptors with high affinity, inter alia by displaying key physicochemical characteristics that facilitated their ability to bind to them. The use of such fragment should allow the medicinal chemists to rapidly discover biologically active compounds across a broad range of therapeutic areas[11]. Following mentioned, the principal objective of current paper was to evaluate if these derivatives **8aB–8iB** could potentially exhibit convenient physicochemical properties, which would be

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related to their favorable pharmacokinetic profiles, in terms of RO5.

II. Materials and Methods

Currently *in silico* studied compounds **8aB–8iB**, chemically 3-[4-(3-trifluoromethylphenyl)piperazin-1-yl]--2-hydroxypropyl (2-/3-/4-alkoxyphenyl) carbamates (Figure), were previously *in vitro* antimicrobially screened against Gram-positive *Staphylococcus aureus* ATCC 6538, Gram-negative *Escherichia coli* CNCTC 377/79 and *Candida albicans* CCM 8186, a yeast, respectively, as the salts with hydrochloric acid[8,9], i.e. **8a–8i**, chemically 1-[3-(2-/3-/4-alkoxyphenylcarba-moyloxy)-2-hydroxypropyl]-4-(3-trifluoromethylphenyl)pi- perazinium chlorides. Although they contained stereogenic centre, they were prepared and tested as racemates. The letter „**B**" in the entry (Table) meant the „base".

The data, which characterized molecular weight (MW), hydrogen-bond acceptors count (*n*ON), hydrogen-bond donors count (*n*OHNH), topological polar surface area[12] (TPSA), rotatable bonds count (*n*rotb) and the predicted logarithms of partition coefficient for the system octan-1-ol/water by applying miLogP 2.2 substructure approach, of investigated compounds **8aB–8iB** were calculated by using interactive applet of Molinspiration Cheminformatics software tool (Molinspiration Cheminformatics, Slovak Republic). The CLOGP 4.0 readouts were generated by using ChemBioDraw Ultra 11.0 program package (CambridgeSoft, USA). The outputs of log *P* calculated by Moriguchi method (MLOGP) were obtained by an interactive applet of Virtual Computational Chemistry Laboratory (VCChL)[13]. The ALOGP procedure of log *P* prediction was calculated using VCChL applet based on the approach developed by Ghose and Crippen[14].

The readouts of partition coefficient logarithms, which were experimentally estimated in octan-1-ol/buffer (p*H*=7.0) medium, were adopted from the research paper[15] of Sedlárová et al. (2007).

The observed differences between calculated (CLOGP 4.0, MLOGP, miLogP 2.2 and ALOGP, respectively) and experimentally estimated (log P_{exp}) log *P* values were expressed by the Absolute Average Residual Sums (AARS). If the AARS output was in the range of 0.000–0.490, the MLOGP, CLOGP 4.0, miLogP 2.2 and ALOGP approach, respectively, was qualified as acceptable, while AARS value within the area of 0.500–0.999 indicated that respect predictor tool was viewed as disputable and, finally, if calculated AARS readout exceeded 1.000, it was then classified as an unacceptable predictive procedure[16].

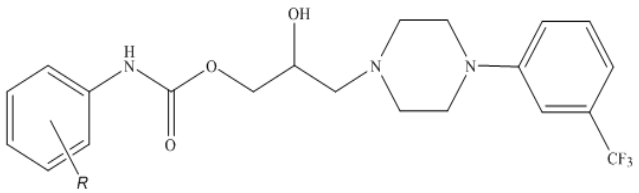

Figure : General chemical structure of currently *in silico* investigated compounds **8aB–8iB**; **8aB**: *R*=2-OCH_3, **8bB**: *R*=2-OC_2H_5, **8cB**: *R*=3-OCH_3, **8dB**: *R*=3-OC_2H_5, **8eB**: *R*=3-OC_3H_7, **8fB**: *R*=4-OCH_3, **8gB**: *R*=4-OC_2H_5, **8hB**: *R*=4-OC_3H_7, **8iB**: *R*=4-OC_4H_9.

Table : The descriptors which characterized currently *in silico* inspected derivatives **8aB–8iB**

Entry	MW	*n*ON	*n*OHNH	*n*rotb	CLOGP 4.0	MLOGP	ALOGP	miLogP 2.2	logP_{exp}
8aB	453.46	7	2	9	4.21	3.16	3.78	3.72	3.57
8bB	467.49	7	2	10	4.74	3.65	4.13	4.10	3.63
8cB	453.46	7	2	9	4.21	3.16	3.78	3.75	3.53
8bD	467.49	7	2	10	4.74	3.65	4.13	4.12	3.61
8eB	481.52	7	2	11	5.27	4.14	4.65	4.63	4.06
8fB	453.46	7	2	9	4.21	3.16	3.78	3.77	3.60
8gB	467.49	7	2	10	4.74	3.65	4.13	4.15	3.71
8hB	481.52	7	2	11	5.27	4.14	4.65	4.65	3.90
8iB	495.54	7	2	12	5.80	4.64	5.11	5.21	3.98

III. Results and Discussion

Presently *in silico* calculated outputs revealed that almost all the inspected molecules completely met the RO5 (Table). In detail, the substances **8aB–8iB** have shown MW less than 500, *n*ON=7 and *n*OHNH=2 as well. The calculation of PSA in a classical way, however, was rather time consuming, because of the necessity to

generate a reasonable 3D molecular geometry and to determine the surface itself. Additionally, such calculations required specialized software to generate the 3D molecular structures and to determine the surface. The methodology for the calculation of used TPSA was described in details in the paper[12]. Briefly, such procedure was based on the summation of tabulated surface contributions of polar fragments (atoms regarding also their environment). These fragment contributions were determined by least squares fitting to the single conformer 3D PSA for 34,810 drugs from the World Drug Index. Topological polar surface area (TPSA) provided results of practically the same quality as the classical 3D PSA, the calculations, however, were two to three orders of magnitude faster. The values of TPSA for all studied compounds **8aB–8iB** were 74.27 Å^2.

As suggested by Clark[17], the criterion for poor absorption of PSA>140 Å^2 appeared to be an efficient method of computationally screening large numbers of compounds. Following given, all the studied derivatives fulfilled the requirement for good absoprtion.

Palm and coworkers[18] found out that excellent correlation could be obtained between dynamic polar van der Waals´ surface areas (PSA_d) and Caco-2 permeabilities when evaluated a series of antagonists of β-adrenergic receptors (ARs). However, the major drawback of such parameter, it was computationally expensive, made it inappropriate for large database screening.

However, the RO5 violation was clearly indicated in terms of the rotatable bonds count for the compounds bearing *meta-*/*para*-propoxy or *para*-butoxy side chain, namely **8eB**, **8hB** and **8iB**, respectively. Such descriptor was a widely used filter following the finding that greater than ten rotatable bonds correlated with decreased oral bioavailability in animal models[5].

Additionally, the same derivatives have shown the predicted values of log *P* by CLOGP 4.0 approach higher than 5. Following the AARS readouts, the CLOGP 4.0 method was considered unacceptable because of providing ARRS=1.067. The main disadvantage of using such relatively unconvenient (but required, actually) fragmental-based procedure for current investigation of homological series **8aB–8iB** was that it did not take into account the position of alkoxy side chain attached to lipophilic aromatic ring – identical values were observed when *in silico* evaluated corresponding positional isomers (Table).

Similar situation was encountered when analyzing the data related to Moriguchi MLOGP. Given fragmental approach did not reflect the position of attached alkoxy side string, as expected. Surprisingly, calculated output of AARS=0.258 identified this *in silico* procedure as an acceptable tool for the prediction of log *P*. It was also documented that MLOGP>4.15 was generated for *para*-butoxy derivative (**8iB**) only.

Ghose and Crippen proposed that the qualifying range of calculated log *P* for drug-like molecules was from -0.4 to 5.6 by fragmental ALOGP procedure. The mean ALOGP was set to 2.3 and the preferred interval was 1.3–4.1, as published in[14]. Following given, propoxy- and butoxysubstituted derivatives were out of the range. In addition, the AARS for ALOGP was 0.506 so this procedure was considered disputable.

When inspecting the AARS readout assigned to miLogP 2.2, relatively conventient value was indicated (0.478). It seemed that, except for the MLOGP procedure, the miLogP 2.2 could be considered an acceptable prediction method for the *in silico* investigation of concerned compounds.

From structural viewpoint, currently studied derivatives could be also regarded as arylcarbamoyloxy-aminopropanols, i.e. a class of the compounds which act as the antagonists of β-ARs. Side effects of these drugs, which are connected with their central nervous system (CNS) activity, are well-known; for instance lethargy, depressions, psychoses[19,20] or visual hallucinations[21], respectively. Early assessment of the physicochemical properties of potentially active CNS drugs in terms of their ability to cross blood–brain barrier is extremely important.

Kelder et al.[22] previously found out that non-CNS drugs transported passively and transcellurlarly needed a PSA of 120 Å^2 or less, whereas the drugs can be targeted to the CNS with a PSA less than 60–70 Å^2. On the other hand, following the van de Waterbeemd research[23], the cutoff for PSA cutoff for CNS penetration was set to 90 Å^2 or below and molecular weight cutoff of 450. Levin suggested the molecular weight cutoff 400 or lower[24]. It was also previously documented that PSA value was dependent upon hydrogen bonding and donating atoms[25,26]. Because the hydrogen bonding was primarily associated with oxygen (O) and nitrogen (N) moieties in a molecule, then, if the sum of the N and O atoms in the structure was five or less, the compound has shown a high probability of entering the CNS. Moreover, if following difference CLOGP – (N+O) was higher than 0, then the compound had a high probability of entering the CNS.

Additionally, CNS active drugs have shown notably fewer rotatable bonds count (five or less) than other drug classes[26].

Considering the log *P* data (log P_{exp}), Hansch and Leo[27] found out that blood–brain barrier penetration was optimal when mentioned readout was within the interval of 1.5–2.7.

For the complexity of information, in paper[26] were summarized some essential attributes of successful CNS drugs. Some of them were as follows: MW<450, CLOGP<5, *n*OHNH<3, *n*ON<7, *n*rotb<8, hydrogen bonds<8 and PSA<60–70 Å^2, respectively.

Following current *in silico* calculated outputs and previously estimated data[15] as well, the compounds under the study **8aB–8iB** probably would not permeate cross blood–brain barrier so they would not probably involve the CNS side effects.

IV. Conclusion

Rather than trying to predict absorption-related quantities, researchers tried to find out general principles to distinguish drug-like from non-drug-like molecules by inspecting the drugs and non-drugs databases. Current article was focused on the *in silico* evaluation of some highly lipophilic *N*-arylpiperazine based compounds containing 2-hydroxypropan-1,3-diyl connecting chain and substituted alkoxyphenylcarbamoyloxy fragment as well, in terms of their drug-like properties. It seemed that majority of all the substances inspected successfully met the criteria which were previously pioneered especially by Christopher Lipinski in his famous Rule of Five and Daniel Veber, respectively. It could be assumed that focused compounds would potentially shown good absorption and permeation after an oral administration. In addition, following the molecular weight, PSA (TPSA), hydrogen-bond acceptors count, rotatable bonds count, CLOGP 4.0 readouts and estimated log P_{exp} data as well, it could be hypothesized that all currently inspected derivatives would not be able to cross blood–brain barrier passively and consequently not to involve CNS-related side effects.

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