

INTEGRATING THE VALUES OF MOLECULAR DESCRIPTORS IN THE PREDICTION OF BIOPHARMACEUTICAL PROPERTIES FOR NEW COMPOUNDS WITH DIBENZOTHIEPINE STRUCTURE

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Abstract

The paper presents the results of *in silico* evaluations performed on a group of 127 compounds with dibenzothiepine structure. The predictions were focused on molecular descriptors relevant for quantitative estimation of penetration across various biological barriers. The results indicated a low solubility together with high permeability profile, with considerable impact of gastro-intestinal, endogenous tensioactives. The predicted pharmacokinetic characteristics are favorable for expressing a potential psychotropic activity.

Rezumat

Lucrarea prezintă rezultatele evaluărilor *in silico* efectuate asupra unui grup de 127 de compuși cu structură dibenzotiepinică. Predicțiile au vizat descriptori moleculari relevanți pentru estimarea cantitativă a traversării prin diferite bariere biologice. Rezultatele au indicat un profil de tip solubilitate redusă - permeabilitate crescută, cu un impact considerabil al tensioactivilor endogeni prezenți la nivelul tractului gastro-intestinal. Caracteristicile farmacocinetice prefigurate teoretic sunt favorabile pentru exprimarea unei potențiale activități psihotrope.

Keywords: molecular descriptors, logBB (BB= the brain/ blood concentration ratio), biopharmaceutics, dibenzothiepinines

Introduction

After administration, the molecular entities with potential therapeutic effect have to overpass consecutive biological barriers that limit the rate and extent of *in vivo* exposure. Although the safety and efficacy profile could be accurate for human use, there are several cases where the

failure of the lengthy and expensive process of drug development resides on the biopharmaceutical properties. Currently, the emerging concept of drugability assessment [1] encloses several rules (named after the number of correlated molecular descriptors [2,3]), for accurate selection of candidate structure with optimal pharmacokinetic profile [4]. The particularities of the administration pathways, the effective dose and the correlated, solubility and permeability driven processes across a specific succession of membrane interfaces represent key issues. Many of the kinetic parameters characterizing absorption, distribution, metabolism and elimination process (ADME) have been described using as main underlying parameter the lipophilicity, estimated by the *n*-octanol/ water partition coefficient [5]. Since many non-correlations are always reported [6], the possible involvement of several types of transporters, as well as other structural characteristics have been considered as essential contributors, even though no clear information are available in literature. Nevertheless, the role of lipophilicity seems to be overestimated, especially since drug development is oriented lately toward larger, intensely hydrophobic molecules. The biological complexity of living organisms generates many distinct interactions with compounds having essentially similar chemical structure or physico-chemical properties [7,8]. Linear dependence between one or more structure-based predictors and the *in vivo* resultant remains the main target, but in reality it proves to be difficult to achieve. The integration of particular cases mentioned by the literature or developed *in-house* by the pharmaceutical companies gives more or less the accuracy of prediction for the biopharmaceutical properties, with further implication in selecting the right drug candidate, with the accurate dose in terms of prospected extent and level of exposure.

The introduction of the Biopharmaceutical Classification System (BCS) [9] and, more important, its acceptance by the main drug regulatory agencies [10] can be considered as one of the turning points in drug discovery. By the integration of two parameters relevant for oral absorption pattern (solubility and permeability), and most important, by considering the administered dose, it offers a good basis for further critical decision on the pathway of drug product registration. Chemical and metabolic stability, as well as the affinity for several transporter systems must be considered [11]. It is a known fact that class IV drugs according to BCS (characterized by limitation or pH-dependence of both solubility and permeability) are frequently discarded, since the variability of drug exposure will give a variability of safety and efficacy profiles. Therefore, the clinical data will be difficult to use as a support for registration. Nevertheless, BCS or, more specifically, its strict limitations, have been contested [12]. The lack of biological relevance for the evaluation of solubility

in water or non-physiological buffer systems is frequently mentioned. The simulated gastro-intestinal (GI) fluids recommended by Federation International Pharmaceutique (FIP) [13] led to several reports of good *in vitro* – *in vivo* correlations, suggesting the essential role of endogenous components in the overall dissolution and absorption processes of lipophilic drugs. The composition was furthermore subject for continuous changes, by considering the particularities of fluid secretion in several GI segments [14]. Since the solubility and consequently, the availability of drugs for absorption can be subject for a complex modulation by means of pharmaceutical formulation factors, the permeability could be considered as the central determinants of both absorption and distribution profiles (if the feature of active transport is neglected). Therefore, the approach of Fagerholm U. [15], based on effective permeability (Permeability Based Classification System, PCS), becomes an accurate alternative approach.

Several *in silico* screening platforms are available [16], offering good estimations of solubility in water and buffer systems (including physiological media), ionization constants, permeability across various types of membranes and interfaces, as well as biorelevant molecular descriptors, included in several formulas used for estimating the penetration through biological barriers. The current paper deals with these issues, by considering a group of new molecular entities with dibenzothiepine structure.

The antimicrobial potential of dibenzothiepine derivatives against various bacterial and fungal strains was presented in several previous works. The compounds tested revealed good antibacterial and antifungal activity against both reference and clinical multidrug resistant strains [17-20].

Materials and Methods

A number of 127 new dibenzothiepine entities with prospected pharmacological activity were included in the analysis, the chemical structures being presented in figure 1. This library of compounds was designed in a previous work [21].

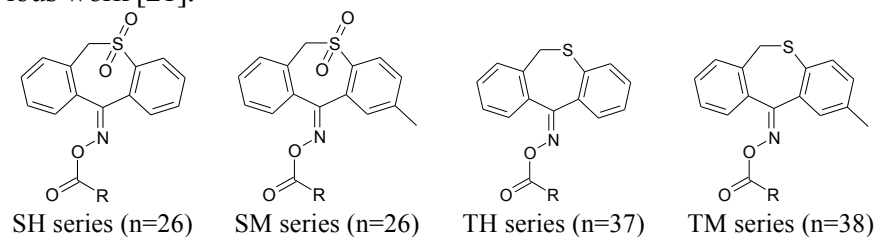


Figure 1

The molecular structure of the evaluated chemical entities
(four series, noted SH, SM, TH, TM)

Within each of the four series, the compounds differed by the nature of the side chain substituent: R= alkyl, heterocyclic ring, aromatic ring substituted with methyl, ethyl, methoxy, halogen, nitro groups.

MedChem Designer (TM) version 1.1.2.2. was used for drawing and for the preliminary characterization of molecular entities. The chemical structures were processed as batch using ADMET Predictor software, version 5.0.5.5, Simulation Plus Inc.. Estimated values for the following molecular descriptors were generated: molecular weight (MW, g/mol) and volume (MV, cm³/mol); *n*-octanol/ water partition coefficient (LogP); distribution coefficient at physiological pH=7.4 (LogD)(also calculated using Pallas program [22]); acid and base ionization constants, pKa or pKb; number of freely rotatable bounds (FRB); topological polar surface area (PSA (Å²)); number of H-bond donors (HBD); number of H-bond acceptors (HBA).

The predictions were extended to solubility profile, estimated in water (Sw, mg/ mL) and simulated GI fluids (fasted state simulated gastric and intestinal fluid, FaSSGF and FaSSIF; fed state simulated intestinal fluid, FeSSIF). The *in silico* protocol also included the estimated penetration through various types of model membranes: human jejunal effective permeability (Peff, cm/s·10⁴), apparent permeability in Madin-Darby Canine Kidney Cells (MDCK, cm/s·10⁷) and rabbit cornea (P_{cornea}, cm/s·10⁷).

The platform was also used for prediction of essential parameters for *in vivo* distribution: apparent volume of distribution, Vd, (L/kg); fraction unbound to plasma proteins, Fu, (%) and for the transfer across two types of biological barriers: log BB (defined as the logarithm of brain to blood concentration ratio) and logKp (penetration of *stratum corneum*). The last parameter was calculated using various relationships described in the literature, based on MW and logP [23]:

$$\log Kp = -2.184 + 0.851 \log P - 0.012 MW \quad (1)$$

$$\log Kp = -2.44 + 0.514 \log P - 0.0050 MW \quad (2)$$

$$\log Kp = -2.61 + 0.067 \log P - 0.0061 MW \quad (3)$$

$$\log Kp = -2.8 + 0.74 \log P - 0.006 MW \quad (4)$$

$$\log Kp = -2.72 + 0.71 \log P - 0.0061 MW \quad (5)$$

$$\log Kp = \log(0.00284 + 0.000256 \log P) - 0.0059 MW \quad (6)$$

Results and Discussion

The values of molecular descriptor underlined the typical character of a BCS class II drug. The *in vivo* ADME profile is dominated by the low solubility and high permeability (with an accentuated lipophilic character, induced by the dibenzothiepine core). The estimated logP values increased dramatically from SH to TM compound series, with a correlated reduction in the PSA value. The descriptors presented in table I are the main determinants of

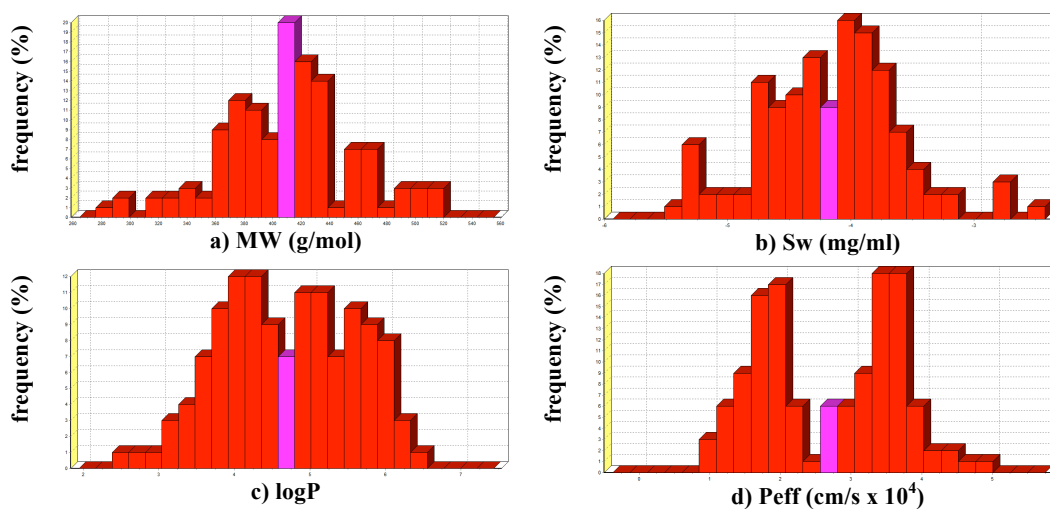
passive diffusion across phospho-lipidic membranes. The ionization constants indicated a low impact of the physiological pH values on the fraction of unionized and therefore, permeable species.

Table I

The main molecular descriptors with biological relevance
(mean values with standard deviation)

Series	MW (g/mol)	MV (cm ³ /mol)	logP	PSA (Å ²)	HBD	HBA	FRB
SH	425.54 (40.44)	311.50 (21.80)	3.73 (0.40)	81.99 (15.57)	0	5.65 (0.98)	2.50 (0.86)
SM	437.76 (42.70)	330.88 (22.80)	4.01 (0.52)	80.71 (13.68)	0	5.58 (0.90)	2.46 (0.81)
TH	387.45 (43.93)	297.97 (29.00)	5.10 (0.56)	46.31 (13.64)	0	3.59 (0.90)	2.62 (1.01)
TM	400.89 (42.84)	316.11 (23.89)	5.39 (0.61)	47.70 (14.86)	0	3.63 (0.91)	400.89 (42.84)

The low water solubility profile must be considered as one of the main absorption risks, according to currently implemented criteria. The variation range is considerable, starting from 3.44 mg/mL for SH1 derivative (R=CH₃) and decreasing to 3.28 µg/mL for the dichloro-phenyl derivative in the TM compound series. The effective jejunal permeability (P_{eff}) was estimated to be higher than the $20 \cdot 10^{-6}$ cm/s threshold proposed in the PCS [15] (Figure 2). Therefore, complete absorption at the intestinal level can be forecasted, as well as an increased distribution within hepatocytes with further considerable hepatic clearance.

**Figure 2**

Frequency histograms for BCS-based parameters and some correlated molecular descriptors

The interplay of endogenous tensioactives (e.g. sodium taurocholate) is underlined by the three fold increase of solubility from water to FeSSIF, almost independent on the considered series (figure 3). It is to be mentioned the possible contribution of biliary excretion for compounds with MW higher than 450 (including their conjugates), which theoretically will lead to a prolonged absorption with consecutive double peak in plasma concentration profile.

The extent of predicted hepatic biotransformation, as well as the intercompartmental partition, must be scaled with the value of unbound fraction, lower than 8% for all the considered structures. This fact indicates a small amount involved in any of the post-absorption processes, with plasma representing a central storage compartment. The mean value for the volume of distribution was 1.3 L/kg.

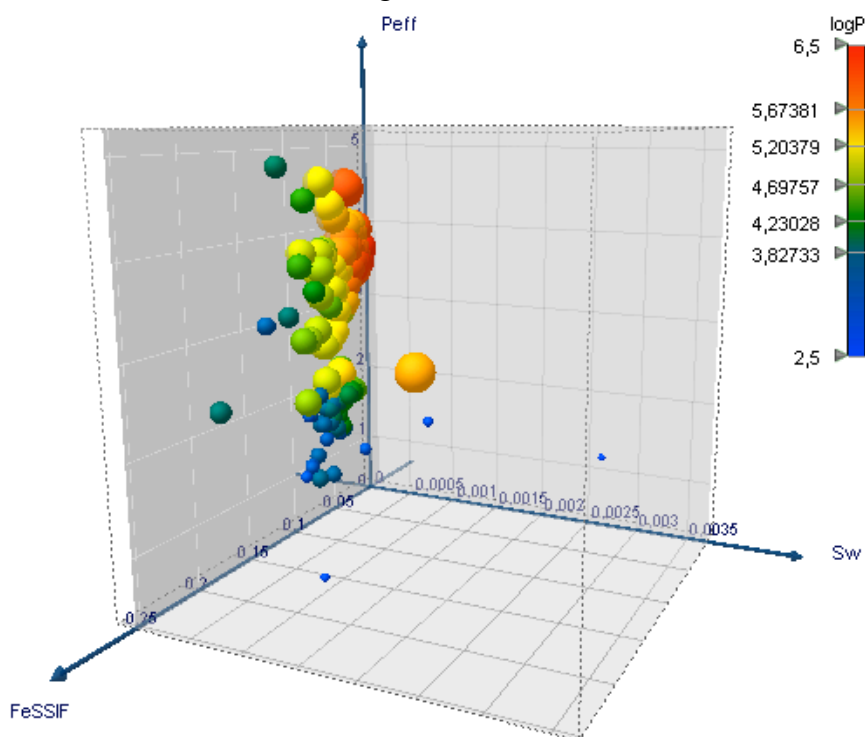


Figure 3

The dependence of solubility and effective jejunal permeability on logP.
The interplay of endogenous tensioactives

Concerning the penetration across various types of biological barriers, all the estimated values are under the control of the high lipophilicity of the drugs considered (table II).

Table II

The permeability across biological barriers (mean values with standard deviation)

Series	Pe _{eff} (cm/s · 10 ⁴)	MDCK (cm/s · 10 ⁷)	P _{cornea} (cm/s · 10 ⁷)	LogBB	logK _p (cm/h)
SH	1.69 (0.29)	273.15 (57.60)	135.75 (38.22)	0.24 (0.17)	-3.28 (0.27)
SM	1.64 (0.33)	281.70 (56.30)	142.43 (35.23)	0.41 (0.22)	3.04 (1.46)
TH	3.49 (0.59)	413.50 (31.37)	221.71 (64.13)	0.46 (0.16)	1.95 (1.22)
TM	3.29 (0.54)	412.28 (32.52)	218.09 (66.65)	0.47 (0.24)	1.96 (1.19)

For blood brain barrier and *stratum corneum*, an optimal logP interval of 1 to 3 is frequently specified. Values higher than 3 indicate a possible preferential distribution into lipidic tissues, with a consequent low release and elimination patterns. The presence of the methyl group on the tricycle ring has a dramatic impact on logK_p values only for the S series. This fact can be associated with the estimated values of logD for individual series, e.g. compounds noted 25 (TH 25, TM 25, SH 25, SM 25, R= -C₆H₅Fp) have the following values of logD for pH=7.5, calculated with Pallas program [22]:

4.95 (TH25); 5.74 (TM25); 2.81 (SH25) and 3.25 (SM25).

Our data outlined that the compound SH25 is the only compound with values of distribution coefficient below the limit of 3.

A high lipophilicity could be associated with a rapid, quantitatively significant process of accumulation in the more profound stratus of the skin.

The logBB value suggests a rapid distribution at the level of central nervous system (CNS), all compounds being classified as highly permeable (figure 4).

It is to be mentioned that the structurally similar compound, Dosulepine (Prothiaden[®]), is currently available for clinical use as antidepressant agent. Dosulepine is used to treat depression especially where an anti-anxiety effect is required.

Taking into account the presence of dibenzothiepine ring as potent psychotropic pharmacophore, it is highly possible that these new dibenzothiepine compounds may have potential antipsychotic/antidepressant profiles.

If the inhibitory effect of serotonin and norepinephrine reuptake will be proved by further studies, the pharmacokinetic profile, determined by the

correlated, above mentioned molecular descriptors will be advantageous, considering the safety profile of this particular class of therapeutic agents.

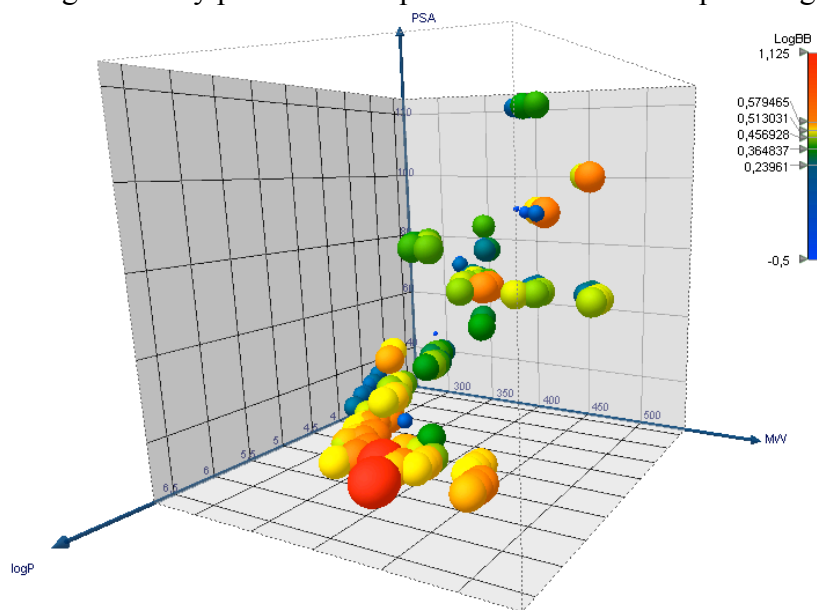


Figure 4

Graphical presentation of logBB and its molecular determinants (molecular weight, MW; topological surface area, PSA; *n*-octanol/ water partition coefficient, logP) for dibenzothiepine entities

Conclusions

The values of several biorelevant molecular descriptors and biopharmaceutical parameters for compounds with dibenzothiepine structure were estimated using available *in silico* platforms. The results indicated a low solubility - high permeability profile, with considerable impact of gastro-intestinal, endogenous tensioactives. The distribution profile seems to be dominated by the low protein-unbound fraction, with a rapid and extensive distribution across the blood-brain barrier. The predicted pharmacokinetic pattern is favorable for expressing a potential psychotropic activity.

Acknowledgements

The authors acknowledge the financial support offered by the National Authority for Scientific Research of Romania, through the Joint Research Project Romania- Slovakia 465/ 2011. This paper was partially supported by the Sectoral Operational Programme Human Resources Development,

financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/89/1.5/S/64153.

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Manuscript received: December 20th 2010