Application of ionic liquids for the determination of lipophilicity parameters using TLC method, and QSRR analysis for the antipsychotic drugs

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Abstract: The application of ionic liquids for the determination of lipophilicity parameters of the antipsychotic drugs as well as their QSRR analysis have been studied. The properties under consideration have been either determined empirically (experimental parameters of lipophilicity), by reversed-phase liquid chromatography (TLC and HPLC technique) with or without addition of mobile phase additives (ionic liquids), or calculated (theoretically computed lipophilicity parameters as logPs indices) with the use of established theoretical medicinal chemistry software (VCCLAB). Chromatographic techniques allowed to determine the retention constants and $\log_{kw}$ that characterize lipophilicity of compounds. Considering potential pharmaceutical importance of antipsychotic drugs, we examined the retention behavior in the reversed-phase liquid chromatography (RP-LC) systems, in both planar and column LC, as well as both in the presence and absence of ionic liquids, and determined the relationships between chromatographic data and selected structural features of analytes using QSRR studies. Significant relationships were found between the retention constants, (with addition of ionic liquids) and $\log_{kw}$, and the in silico calculated logPs indices. Therefore, the and $\log_{kw}$ values of the investigated compounds have been recommended for description of their lipophilicity.

Keywords: antipsychotic drugs, lipophilicity parameters, molecular descriptors, QSRR, quantitative structure-retention relationships, retention parameters

1. INTRODUCTION

Evaluation of relationships between retention data and structural descriptors (physiochemical, quantumchemical, topochemical, etc.) of solutes in a specific chromatographic system has been a subject of academic studies for many years. Initial works in this research area, known also under the acronym QSRR: quantitative structure-retention relationship date back to 1977, in the studies of Prof. Kaliszan [1, 2]. Nowadays, QSRR supported by chemometrics is an useful analytical technique capable of relating chromatographic (retention) parameters and structural informative descriptors of multiple analytes [3, 4]. Despite the benefits arising of retention prediction and identification the most informative descriptors for the known and/or unknown compounds or newly synthesized derivatives, QSRR technique can also provide principal information about the molecular mechanism regarding their chromatographic separation and evaluate their physicochemical properties that can also affects biological activity [3, 5].

One of the compound`s most recognizable and studied property in QSRR is its lipophilicity parameter, broadly expressed as a n-octanol-water partition coefficient (logP) or distribution coefficient for ionizable compounds (logD) [6]. It is an substantial parameter in drug and pesticides design and development, as well as in pharmacokinetics, pharmacodynamics, and toxicology in both pharmaceutical and environmental sciences being responsible for compound`s ADMET properties [7, 8]. The reference system of $logP_{o/w}$ or $logD_{o/w}$ assessment is a shake-flask technique [9, 10]. However, traditional shake-flask method possess certain drawbacks as it is time- and solvent-consuming, and it is not recommended for routine analysis of a large series of compounds [11]. Hence, to overcome these problems recently reversed-phase

chromatographic methods like RP-TLC and RP-HPLC are widely used in a lipophilicity parameters estimation [12-15].

RP-LC techniques are commonly considered as relatively relevant and reliable methods. Nevertheless, despite many advantages, these techniques may not be imperfect especially in the case of basic drugs due to the strong silanophilic interactions in the partition mechanism impending the elution of analytes [16, 17]. In this aspect, ionic liquids (ILs) may be a convenient solution for suppressing noxious effect of free residuals of silanol groups, allowing to remodel the stationary/mobile phase system and thus improve lipophilicity assessment process [18]. Till today, there are only few studies dealing with the usefulness of the ILs in the lipophilicity determination studies of different drugs, and both of them with different results and conclusions [18, 19].

Hence, the aim of the following study was to evaluate insights into the retention behavior of series of basic antipsychotics using various RP-LC systems and compare them with data derived from the RP-TLC systems modified with ionic liquid as a mobile phase additives. In this study we have also evaluated lipophilicity parameters using experimental chromatographic techniques (expressed as and $\log_{kw}$, derived from chromatography, which are equivalent to logP) and compared them with various computed logP values (established from theoretical medicinal chemistry software (VCCLAB)) in order to contribute the analysis of quantitative structure retention-relationships.

2. MATERIAL AND METHODS

2.1. Chemicals

Reference compounds of investigated antipsychotics were provided as follows: amisulpiride, benperidol, bromperidol, chlorpromazine, clozapine, cis-(Z)-flupentixol dihydrochloride, fluphenazine hydrochloride, haloperidol, pimozide, quetiapine, risperidone, sertindole, thioridazine, trifluoperazine hydrochloride, triflupromazine hydrochloride were from Sigma-Aldrich (Steinheim, Germany), perazine dimalonate was from LGC Standards GmbH (Wesel, Germany), whereas zuclopentixol hydrochloride standard was purchased from British Pharmacopeia Commission Laboratory (Teddington, UK). Mobile phase components such as methanol, acetonitrile (both LC-MS grade) and 1-ethyl-3-methylimidazolium tetrafluoroborate ([emim][BF_4]) were obtained from Sigma-Aldrich (Steinheim, Germany). Purified, deionized water used in this study was obtained using a Milli-Q Water Purification System from Millipore (Bedford, MA, USA).

2.2. Chromatography

Thin-layer chromatographic separation of selected diverse antipsychotics was carried out at 20 ± 2ºC on aluminium coated RP-18 silica gel plates, 10x20 cm (Merck KGaA, Darmstadt, Germany) in a chromatographic chamber (Desaga, Wiesloch, Germany), previously saturated with mobile phases vapors: (i) methanol-water (with increasing content of methanol from 40-90% v/v), (ii) acetonitrile-water (acetonitrile content from 40-90% v/v) and in two systems modified with 1.5% addition (v/v) of [emim][BF_4]: (iii) methanol-water-[emim][BF_4] (methanol content in the range 40-90% v/v) and (iv) acetonitrile-water-[emim]

[BF_4] (acetonitrile range 40-90% v/v). In each of these systems the content of organic part varied by 10% v/v. Reference standards solutions (1 mg/mL) were prepared using methanol as a solvent and 2 µL aliquots of each solutes were spotted onto the RP-18 silica plates. Mean time for chromatogram development was 15 min ± 5 min. Further, developed plates (at a distance of 90 mm) were dried at ambient temperature and subjected to detection under UV lamp (254nm) by Desaga CabUV-VIS apparatus (Wiesloch, Germany) combined with the appropriate software of this company. Each separation process was run in triplicate and mean R_F values were calculated. Documentation process was performed with special camera connected with the aforementioned apparatus.

An HPLC instrument (Shimadzu, Kyoto, Japan) equipped with two pumps LC20AD (Shimadzu, Kyoto, Japan), degasser DGU20A3 (Shimadzu, Kyoto, Japan), autosampler SIL-20A (Shimadzu, Kyoto, Japan) column oven CTO-20AC (Shimadzu, Kyoto, Japan) and diode-array detector (Shimadzu, Kyoto, Japan) was used during HPLC analysis. Separation and quantification (at 254nm) of examined antipsychotics were carried out in triplicate in isocratic mode on reversed-phase Dionex Acclaim™ C18 column (Thermo Fisher Scientific, Waltham, MA, USA) (50mm x 4.6 mm i.d., 3 µm particle size with a pore size 300Å). The mobile phase consisted of different mixtures of methanol-water in the range 40-90% v/v. Experiment was performed with the mobile phase flow set at 0.4 mL/min, column oven temperature 30ºC, and sample injection volume 5 µL.

2.3. Calculations

2.3.1. Chromatographic data

Reversed-phase TLC can provide a variety of indices that can be used as lipophilicity determinants. In contrast to time- and cost-consuming experimental methods (including shake-flask method) chromatographic methods can provide relatively fast measurement of expanded lipophilicity range. In thin-layer chromatography the most popular one are based on the retention parameter (R_F), according to the equation defined by Bate-Smith and Westall [20]:

R_F-*1)* (1)

For each examined antipsychotic drug and in each TLC system (i-iv), lipophilicity parameter in the (intercept) form were derived as an extrapolated value corresponding to 0% of organic additive in a mobile phase system, using the Soczewiński-Wachtmeister equation [21]:

(2)

where *S* was the slope of the linear plot, while was the volume fraction of organic modifier used in chromatographic system.

In HPLC, respectively, retention data were usually derived by calculating $\log_{kw}$ as a mean value obtained from the chromatographic separation of investigated compound(s), according to the equation shown below [5]

(3)

where was a retention time of analyzed compound(s) and was a dead-time of chromatographic separation.

In reversed-phase HPLC system, chromatographic lipophilicity parameter expressed as $\log_{kw}$ was calculated from the 4. equation (analogically to from the 2. equation), taking the form of an equation analogically for the needs of high-performance liquid chromatography

(4)

where and has the same role as in the case of RP-TLC from the 2. equation.

Calculated and indices of investigated antipsychotics based on the above-mentioned equations are presented in the Table 1.

2.3.2. Computational method

A large number of theoretical lipophilicity indices has been computed and compared using various theoretical procedures and different software. All chemical structures were first drawn with the HyperChem Professional software version 8.0.7 (Hybercube, Gainseville, FL, USA). Then, hydrogens were added to the drawn structures and a models were constructed. In order to obtain molecular descriptors, given structures has been subjected to pre-optimization with the Molecular Mechanics Force Field (MM+) procedure. Then, computed geometries were further optimized by means of semi-empirical Austin Model 1 (AM1) method, using Polak-Ribiere algorithm with gradient limit set at 0.01 kcal/mol. The optimized geometries for each compound were loaded into Dragon 5.0 software (Talete, Milano, Italy) in order to calculate molecular descriptors, which were further used in our QSRR studies.

In our study, we have also derived a set of theoretical lipophilicity indices based on different theoretical procedures (ALOGPs, AC logP, miLogP, ALOGP, MLOGP, XLOGP2, XLOGP3,

Average LogP) using the on-line applet provided by Virtual Computational Chemistry Laboratory (http://www.vcclab.org/).

Values of computed lipophilicity parameters as logPs indices and molecular descriptors being crucial in QSRR models of investigated antipsychotics are presented in the Table 2.

2.3.3. Statistical analysis

QSRR analysis was performed by stepwise multiple linear regression (MLR) procedure available in Statistica 12.5 software package (StatSoft, Tulsa, OK, USA). The significance of obtained QSRRs has been evaluated by statistical F-test. Other important statistical parameters, such as multiple correlation coefficient (R), the standard error of estimate (S) and the significance level of each term and for whole equation (p) were calculated.

Additionally, for data set of 17 analyzed antipsychotic drugs to build QSRR equations, no more than three most statistically significant independent variables have been used. Moreover, correlations were limited to the value of regression coefficient $R \geq 0.8$, and additional criterion, as relevance of particular independent variables, was established at significance level $p \leq 0.05$.

3. RESULTS AND DISCUSSIONS

The group of seventeen antipsychotic drugs (Figure 1) were subjected to initial chemical screening of their retention behaviour and evaluation of their lipophilicity. In the studied group representatives from butyrophenone (benperidol, bromperidol, haloperidol), diphenylbutylpiperidine (pimozide), indole (sertindole) and thioxanthene derivatives were

distinguished. Also, compounds from the group of phenothiazines (chlorpromazine, trifluopromazine, fluphenazine, perazine, trifluoperazine, thioridazine), dibenzodiazepines (clozapine) and other structurally diverse heterocyclic compounds (quetiapine, risperidone) were used.

Reversed-phase TLC and HPLC were carried out in the aforementioned conditions, and in the case of TLC the R_F values employed were averages of at least three measurements, but for subsequent analyses the mean values were used, as calculated from the equations (1-2). Various TLC systems were tested - one with the use of ionic liquid ([emim][BF_4]), and the other one without any additive. Preliminary chromatographic experiments using concentration of ionic liquid below 1.5% did not substantially improve chromatography of most of the selected antipsychotics, thus to ensure proper separation this concentration was kept throughout all TLC separations. In HPLC, instead of the corresponding parameter - $\log_{kw}$ - was calculated as a mean of three determinations according to the equations (3-4). The coefficients of the linear relationships between retention and the volume fraction of organic modifier in the mobile phase as well as lipophilicity parameters determined for antipsychotic drugs using experimental chromatographic techniques as TLC (with or without addition of ionic liquids) and expressed as compared to HPLC and expressed $\log_{kw}$ are listed in Table 1, and were used for the further correlations and QSRR studies. The calculated the and $\log_{kw}$ values were different for individual compounds due to their differences in chemical structures.

Correlations between determined in methanol-water vs. determined in acetonitrile-water (with or without addition of ionic liquids) analysis were performed. Obtained results showed significant correlation between determined in methanol-water and determined in acetonitrile-water with the addition of [emim][BF_4] (see Figure 2A). On the other hand, lack of correlation

was observed in the case determined in methanol-water vs. determined in acetonitrile-water without addition of ionic liquids (Figures 2B-D). The large difference between the correlation coefficients can be clearly explained by the effect of suppression of undesired interactions in reversed-phase system between the analytes and alkyl-bonded stationary phase when ILs are utilized (their role will be later discussed at work).

Moreover, values determined using TLC and methanol or acetonitrile as organic modifier with or without addition of ionic liquids were correlated against $\log_{kw}$ values determined with the use of HPLC (Figures 3A-D). Similar as demonstrated above, a significant correlation was also found between indices determined with the addition of [emim][BF_4] (see Figures 3A-B) compared to indices determined without addition of IL (see Figures 3C-D) which characterized lack of linear relationship between and $\log_{kw}$ values.

Additionally, correlation analysis between experimentally determined lipophilicity indices (and $\log_{kw}$) and calculated logP values had also been performed (see Table 3). The obtained correlation coefficients showed that generally $\log_{kw}$ correlates relatively poor (R near or below 0.85 for the most cases) with calculated lipophilicity (logPs). However, the best relationships (R over 0.90) obtained are between ALOGP and the retention constants and $\log_{kw}$. Moreover, statistical relevance of particular correlation coefficients was established at significance level $p \leq 0.05$ and all determined R values fulfill this criteria are presented in bold type. And it is important to note, that similar as demonstrated above, a significant correlation was only found for indices determined with addition of 1-ethyl-3-methylimidazolium tetrafluoroborate.

Differences between results of proposed TLC system (using IL additive) and conventional TLC (without any additive) are most probably a consequence of applied imidazolium class ionic liquid. Addition of [emim][BF_4] in most cases significantly improved resolution, drugs

spot shape and/or reduced compound`s band tailing. Alteration in elution affecting the lipophilicity of the antipsychotics, when compared with conventional mobile phases, may occur[22]. Therefore, it should be noted that [emim][BF_4] remarkably impacts the hydrophobicity of the mobile phases and analytes. This phenomena is attributed mainly with the complexity of interactions that ILs participate in. Among which, ion-pairing, ion-exchange and hydrophobic partitioning seems to be the most important ones that contribute the retention of basic compounds upon addition of [emim][BF_4] [17]. As reported by other authors [23, 24], both $[emim]^+$ and $[BF_4]^-$ can participate in these interactions and form ion-mobile and ion-stationary phase effects and thus as a consequence efficiently block acidic residual silanols on octadecyl-silica stationary phases, displacing basic compounds from these connections and improving their separation, which may be problematic under normal conditions. Furthermore, ILs like [emim][BF_4] may also be considered as a “green” additives as they allow to obtain notable improvement of spot shape and retention, without the increase of mobile phase organic modifier content. Therefore, the utilization of IL in our study provides for reliable data of lipophilicity of antipsychotic drugs.

It has been known that quantitative structure-retention relationships (QSRR) are among the most extensively studied procedures by which molecular chemical structure is quantitatively correlated with a well-defined physicochemical property of analytes, such as chromatographic retention data as and $\log_{kw}$ lipophilicity parameters. Therefore, QSRR approach was also performed for the analysis of the studied antipsychotic drugs. As a result of the QSRR analysis, six statistically significant QSRR models were developed (Table 4, equations (5-10)). These equations were characterized by three statistically significant independent variables where eqs. (5,7 and 9) were derived only on the basis of molecular

descriptors while for building of QSRRs as eqs. (6, 8 and 10) computed parameters of lipophilicity (logPs) were taken into account. The eq. (5) is characterized predominantly by descriptor (VE1_B(s) defined as Randic-like eigenvector-based index from Burden matrix weighted by I-State form 2D matrix-based classes of descriptor calculated based on the two-dimensional geometry of the molecule, CATS2D_04_AL defined as CATS2D Acceptor-Lipophilic at lag 04 from CATS descriptor class calculated based on the lipophilicity of the molecule, and HOMT descriptor defined as HOMA total belonging to classes of Geometrical descriptors. Equation (6) showed relationship between $\log_{kw}$ and a molecular descriptors: ALOGP and CATS2D_04_AL (both characterized lipophilicity of molecule), and G(N..O) defined as sum of geometrical distances between N..O from class of 3D Atom Pairs characterized geometry of molecule. Equation (7) connected (1,5IL MeOH:H20) parameter with molecular descriptors TPSA(NO), HOMT and QXXm (first from class of Molecular properties and others from class of Geometrical descriptors, respectively). These descriptors characterized: topological polar surface area using N,O polar contributions, HOMA total and quadrupole x-component value/weighted by mass, respectively. In equation (8) the major parameters were ALOGP as lipophilicity parameter and CATS2D_06_LL defined as CATS2D Lipophilic-Lipophilic at lag 06 from CATS descriptor class calculated based on the lipophilicity of the molecule. Equation (9) showed relationship between (1,5IL ACN:H20) and a molecular descriptors: QXXm (from class of Geometrical descriptors defined as quadrupole x-component value/weighted by mass), TPSA(NO) (from class of Molecular properties defined as topological polar surface area using N,O polar contributions) and VAR (from class of Topological indices and characterized variation of molecule). In equation (10) the major parameters were ALOGP as lipophilicity parameter, CATS2D_04_LL defined as

CATS2D Acceptor-Lipophilic at lag 04 from CATS descriptor class calculated based on the lipophilicity of the molecule, and VAR descriptor (from class of Topological indices and characterized variation of molecule). Moreover, calculated QSRR equations (5-10) were characterized by very good value of regression coefficients (R=0.9872-0.9303). Also, statistical significance level ($p < 0.05$) for of each equation variable and, for whole equation (see details in Table 4) has been assessed as very good.

Moreover, compound's structure had a great impact on its behavior during chromatographic separation process using both TLC or HPLC techniques. Based on the obtained QSRR models, comparison between experimental and calculated or log k_w was made (see Figure 4, Plots A to F). As it can be observed on the presented plot, coefficient of regression for the equation reached the values of R^2 = 0.8655-0.9747. All presented data fit well to straight line, presented linear relationship determining linear relationship between experimental vs. predicted lipophilicity properties.

4. CONCLUSIONS

In the presented study the usefulness of the commonly available 1-ethyl-3-methylimidazolium ionic liquid ([emim][BF_4]) has been proved in a chromatographic separation of basic drugs, such as presented antipsychotics. As reported elsewhere, it is due to the suppression effect of free silanols on octadecyl-silica stationary phases, which in standard conditions may cause difficulties in chromatography of base-attracting compounds/drugs. These modifiers provide enhanced optimization of separation conditions (symmetrical peaks without tailing) and reproducible estimation of lipophilicity indices from TLC systems, similar to those from standard HPLC. Moreover, the obtained correlation coefficients showed that lipophilicity

parameters from TLC systems without the addition of ionic liquids additives correlates very poor (R below 0.7) with calculated logPs indices, whereas the lipophilicity indices from the traditional HPLC and TLC systems (with the additive of imidazolium tertrafluoroborate ionic liquid) were clearly better (R over 0.8). Thus, the and $\log_{kw}$ values of the investigated compounds have been recommended for description of their lipophilicity.

On the other hand, QSRR analysis performed for these experimentally obtained lipophilicity parameters shown significant relationships between the retention constants (as and $\log_{kw}$ lipophilicity parameters) and the *in silico* calculated physico-chemical molecular descriptors which generally characterized geometry and lipophilicity properties of molecular structures of analyzed antipsychotic compounds. Additionally, derived QSRR models showed that they may be helpfully in searching (or predicting) HPLC or TLC retention factor for the new/other antipsychotic drugs.

5. CONFLICT OF INTEREST

The authors declare no conflict of interest.

6. ACKNOWLEDGEMENTS

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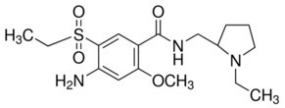
Figure **1**. Chemical structures of analyzed antipsychotic drugs.



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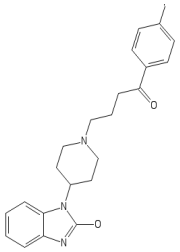

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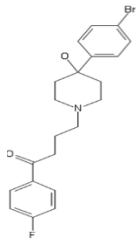

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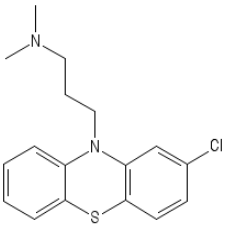

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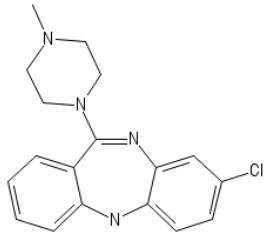

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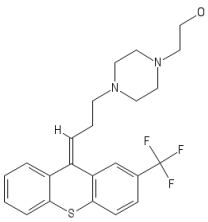

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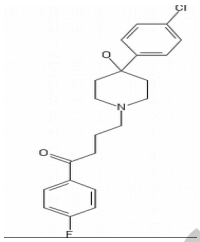

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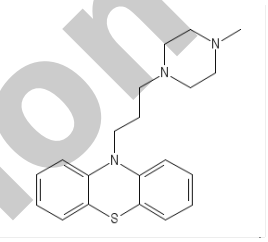
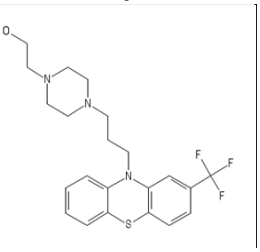
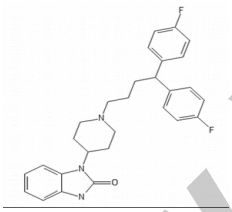


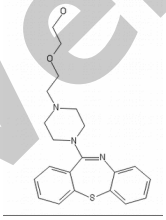
Perazine



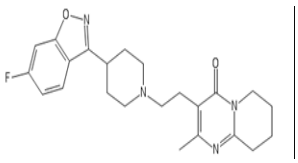
Fluphenazine



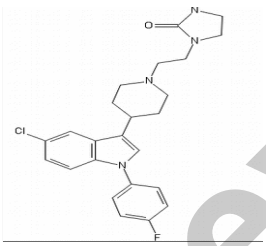
Pimozide



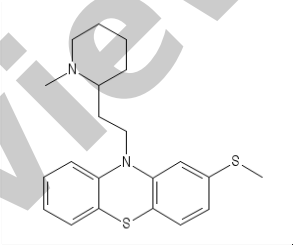
Quetiapine



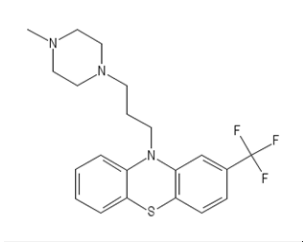
Risperidone



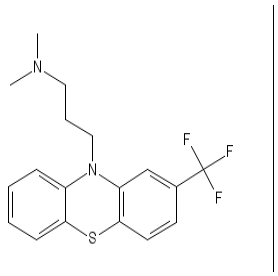
Sertindole



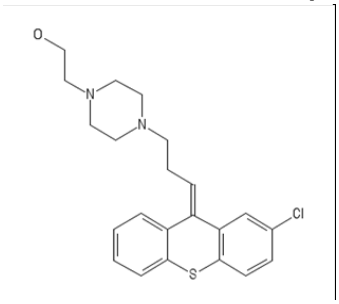
Thioridazine



Trifluoperazine



Triflupromazine



Zuclopenthixol

Figure **2**. Correlations between determined in methanol-water vs. determined in acetonitrile-water (with or without addition of ionic liquids).

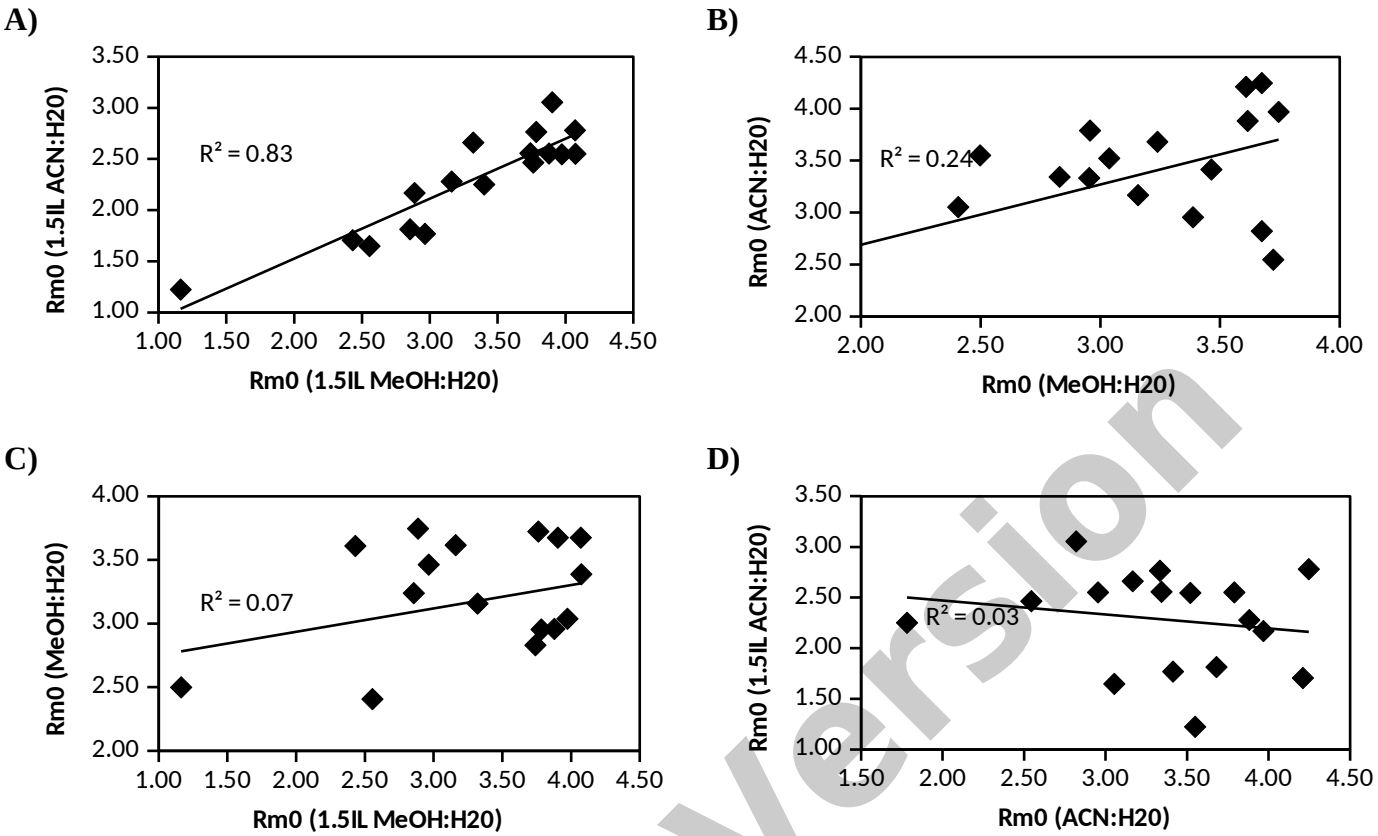


Figure **3**. Correlations between $\log_{kw}$ and determined with (panel A and B) or without (panel C and D) addition of ionic liquids.

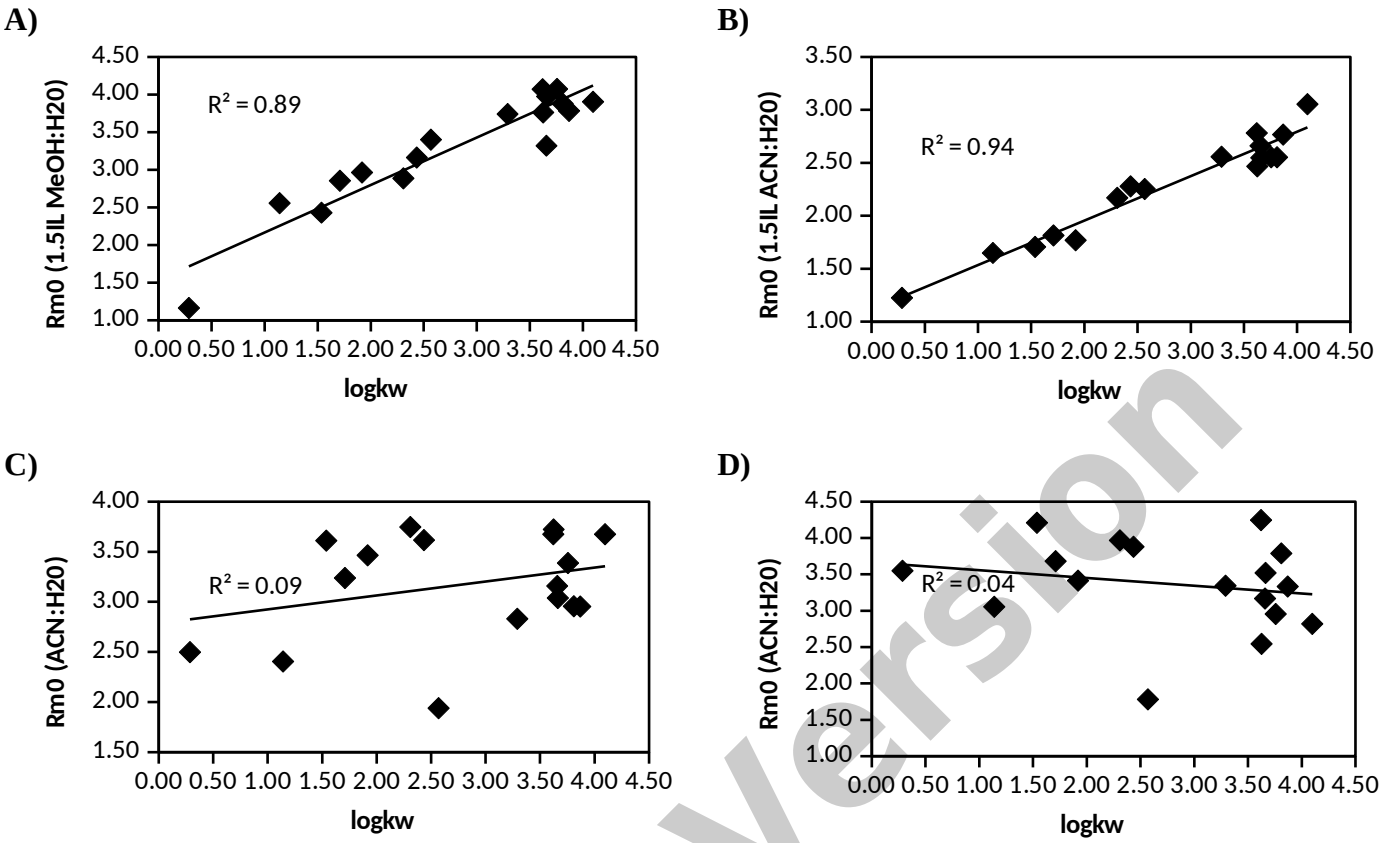


Figure **4**. Correlation between the experimental data and predicted data from obtained multiple regression QSRR equations. The experimentally obtained lipophilicity parameters as $\log_{kw}$ and determined with addition of ionic liquids ((1.5IL MeOH:H20) and (1.5IL ACN:H20)) in relative to the predicted values ($\log_{kw\ pred.I}$ or $\log_{kw\ pred.II}$) (panel **A** and **B**) and ($(1.5IL\ MeOH:H20)_{pred\ I}$ or $(1.5IL\ MeOH:H20)_{pred\ II}$) (panel **C** and **D**) and $(1.5IL\ ACN:H20)_{pred\ I}$ or $(1.5IL\ MeOH:H20)_{pred\ II}$) (panel **E** and **F**) using data according to eqs. (5)-(10) from Table 4; $\log_{kw\ pred.I}$ and $\log_{kw\ pred.II}$ - predicted on the basis eqs. (5) and (6) from Table 4, respectively; $(1.5IL\ MeOH:H20)_{pred\ I}$ or $(1.5IL\ MeOH:H20)_{pred\ II}$ - predicted on the basis eqs. (7) and (8) from Table 4, respectively; $(1.5IL\ ACN:H20)_{pred\ I}$ or $(1.5IL\ ACN:H20)_{pred\ II}$ - predicted on the basis eqs. (9) and (10) from Table 4, respectively.

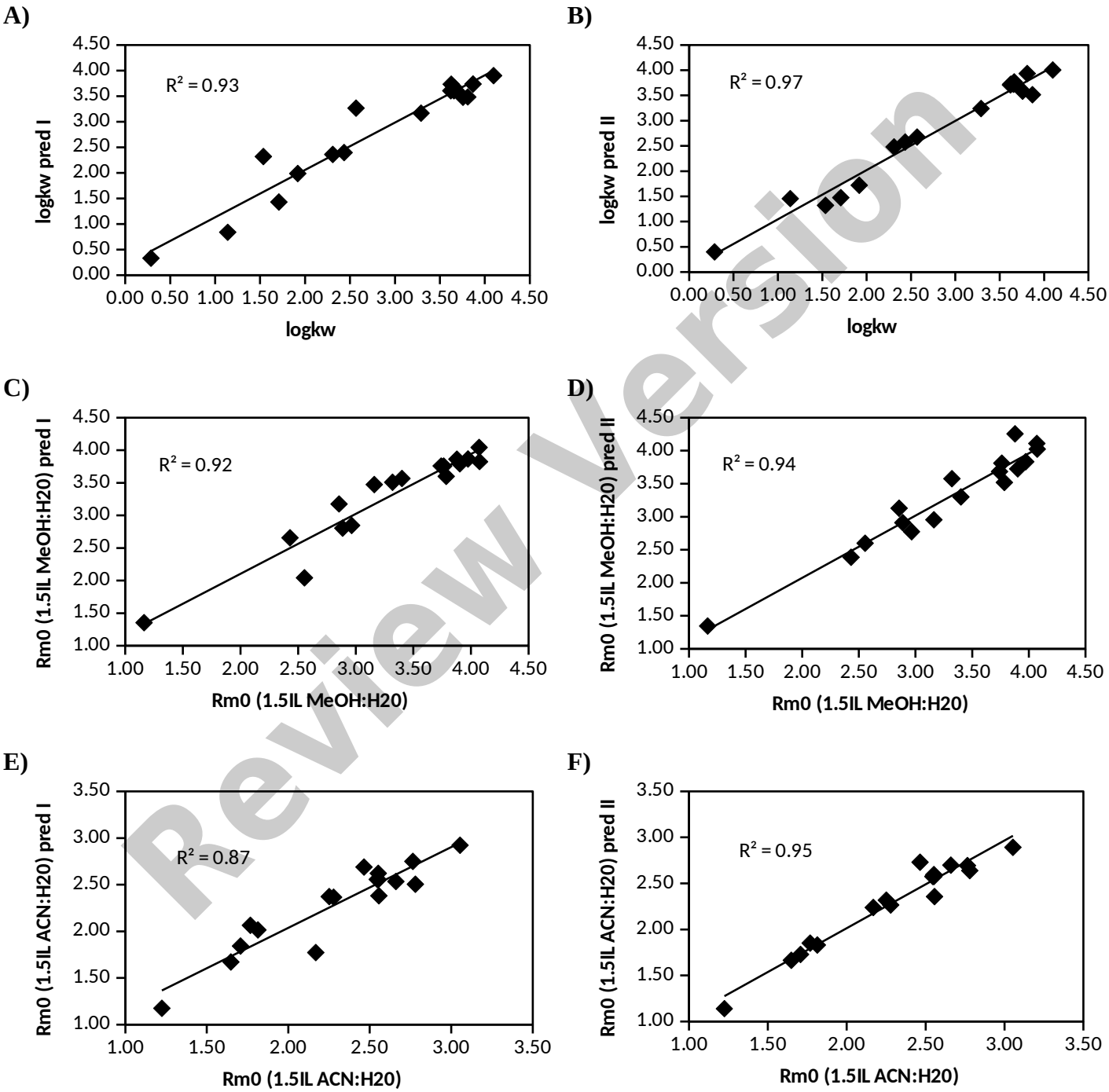


Table **1**. Lipophilicity parameters determined for antipsychotic drugs using experimental chromatographic tec
addition of ionic liquids) compared to HPLC $\log_{kw}$.

Analyte	Chromatographic system										
	TLC										
	methanol-water (+1.5% [emim][BF_4] v/v)			methanol-water			acetonitrile-water (+1.5% [emim][BF_4] v/v)			acetonitril	
	R_M^0	S	R	R_M^0	S	R	R_M^0	S	R	R_M^0	S
Amisulpiride	1.1643	-2.5040	0.9982	2.4983	-2.6245	0.9611	1.2241	-2.7807	0.9978	3.5499	-4.471
Benperidol	2.4306	-3.6105	0.9991	3.6095	-4.1204	0.9857	1.7069	-3.2821	0.9963	4.2102	-5.221
Bromperidol	3.1614	-4.3170	0.9967	3.6164	-4.1201	0.9941	2.2785	-3.8454	0.9970	3.8812	-4.918
Chlorpromazine	3.7408	-4.1924	0.9969	2.8306	-2.1782	0.9893	2.5569	-3.9658	0.9939	3.3430	-3.527
Clozapine	2.8551	-3.5970	0.9954	3.2386	-3.0431	0.9943	1.8137	-3.1262	0.9978	3.6802	-4.075
Flupenthixol	3.9029	-4.5764	0.9981	3.6745	-3.0270	0.9843	3.0537	-4.2330	0.9515	2.8202	-2.923
Haloperidol	2.8875	-4.0056	0.9980	3.7455	-4.3455	0.9904	2.1687	-3.7150	0.9971	3.9683	-4.990
Perazine	3.4008	-3.8940	0.9890	1.9391	-1.0912	0.9983	2.2510	-2.3527	0.9565	1.7815	-1.286
Fluphenazine	3.7846	-4.4957	0.999	2.9533	-2.5569	0.9820	2.7650	-3.1976	0.9790	3.3329	-3.594
Pimozide	4.0708	-5.2778	0.9968	3.6745	-3.9018	0.9805	2.7797	-4.4094	0.9938	4.2461	-5.407
Quetiapine	2.9651	-3.9270	0.9935	3.4637	-3.7291	0.9899	1.7679	-3.2875	0.9991	3.4143	-3.953
Risperidone	2.5550	-3.6325	0.9944	2.4060	-2.2700	0.9874	1.6486	-3.1725	0.9988	3.0527	-3.387
Sertindole	4.0744	-4.9061	0.9947	3.3877	-2.9196	0.9391	2.5520	-3.6991	0.9683	2.9540	-2.506
Thioridazine	3.8788	-4.5728	0.9979	2.9570	-2.3476	0.9801	2.5525	-3.6250	0.9915	3.7896	-4.239
Trifluoperazine	3.7625	-4.1924	0.9954	3.7228	-4.1179	0.9954	2.4651	-3.0566	0.9909	2.5449	-3.229
Triflupromazine	3.9740	-4.8084	0.9972	3.0373	-2.4982	0.9784	2.5456	-3.7613	0.9929	3.5206	-3.895
Zuclopenthixol	3.3205	-3.8188	0.9955	3.1577	-2.5239	0.9744	2.6600	-2.8958	0.9651	3.1666	-2.959

In Thin-layer Chromatography (TLC): R_M^0 – lipophilicity parameter in TLC (intercept); **S** – slope of the linear plot; **R** – coefficient of correlation (ac
In High Performance Chromatography (HPLC): $\log_{kw}$- lipophilicity parameter in HPLC (intercept); **S** – slope of the linear plot; **R** – coefficient of co

Table 2. Values of theoretically computed lipophilicity parameters (expressed as some logPs indices) as well a
in designated QSRR models for analyzed antipsychotic drugs.

Analyzed drugs	Lipophilicity parameters								Molecul			
	ALOGPs	AC logP	miLogP	XLOGP2	XLOGP3	Average LogP	MLOGP	ALOGP	VE1_B(s)	CATS2D_04_AL	HOMT	G(N..O)
Amisulpride	1.50	1.01	1.55	1.87	1.48	1.39	1.198	1.127	3.353	5	4.181	63.1
Benperidol	3.52	3.76	3.41	3.00	3.37	3.38	3.145	3.040	3.862	7	10.308	33.31
Bromperidol	3.78	4.72	4.43	4.16	3.29	4.07	4.113	3.972	3.548	3	11.213	7.448
Chlorpromazine	5.18	5.03	5.03	4.92	5.19	4.84	3.768	4.740	3.818	3	11.228	0
Clozapine	3.67	3.21	4.14	3.74	3.08	3.54	2.965	3.947	3.544	7	10.400	0
Flupentixol	4.56	4.45	4.91	4.42	4.51	4.51	3.892	4.820	3.938	1	11.103	9.174
Fluphenazine	4.40	4.70	4.51	4.16	4.36	4.22	2.955	4.436	3.950	2	11.154	15.22
Haloperidol	3.70	4.63	4.30	3.98	3.23	3.96	4.006	3.888	3.530	3	11.295	7.268
Perazine	4.19	4.45	4.27	3.94	4.15	3.97	2.732	4.033	3.784	2	11.153	0
Pimozide	6.36	6.15	5.62	5.60	6.30	5.81	5.108	5.522	3.918	6	16.207	10.13
Quetiapine	2.93	2.80	3.49	2.83	2.14	2.82	2.360	3.181	3.723	7	10.725	42.68
Risperidone	2.41	3.37	2.96	3.07	2.72	3.07	3.613	3.318	3.683	9	6.737	43.70
Sertindole	4.29	4.52	3.84	4.10	4.07	4.18	3.773	4.680	3.839	3	12.857	16.05
Thioridazine	5.93	5.89	5.68	5.94	5.90	5.57	4.059	5.563	4.008	4	11.149	0
Trifluoperazine	4.87	5.22	5.14	4.87	5.03	4.81	3.550	4.975	3.948	2	11.168	0
Triflupromazine	4.95	5.18	5.25	5.23	5.19	4.55	4.115	5.018	3.925	2	11.148	0
Zuclopentixol	4.46	4.30	4.69	4.12	4.31	4.29	3.577	4.542	3.836	1	11.062	10.2

Table **3**. Correlation matrix between experimentally obtained and theoretically computed lipophilicity parame
expressed as correlation coefficient (R).

Experimentally obtained lipophilicity parameters	Theoretically computed lipophilicity parameter						
	ALOGPs	AC logP	miLogP	XLOGP2	XLOGP3	Average LogP	M
	0.8596	**0.8250**	**0.8581**	**0.8358**	**0.8471**	**0.8586**	
(1.5IL MeOH:H20)	**0.8771**	**0.8753**	**0.8811**	**0.8654**	**0.8516**	**0.8915**	
(MeOH:H20)	0.2784	0.3030	0.3345	0.2356	0.1633	0.3144	
(1.5IL ACN:H20)	**0.8401**	**0.8204**	**0.8492**	**0.8133**	**0.8280**	**0.8545**	
(ACN:H20)	0.0538	0.0385	0.0140	0.0446	-0.0217	0.0369	

Table **4**. Multiple regression QSRR equations derived for experimentally obtained and theoretically computed analyzed antipsychotic drugs (dependent variable = $k_0 + k_1A + k_2B + k_3C$).

Eq. no.	Dependent variable	Coefficients and statistically significant molecular descriptors					
		k_0	k_1	A	k_2	B	k_3
(5)		-8.804±2.045 $p = 8.54*10^{-4}$	2.839±0.585 $p = 3.17*10^{-4}$	VE1_B(s)	-0.207±0.038 $p = 1.08*10^{-4}$	CATS2D_04_AL	0.156±0.044 $p = 3.41*10^{-3}$
(6)		-1.371±0.422 $p = 6.32*10^{-3}$	1.112±0.085 $p = 1.10*10^{-7}$	ALOGP	-0.221±0.025 $p = 1.10*10^{-6}$	CATS2D_04_AL	0.0257±0.005 $p = 3.21*10^{-4}$
(7)	(1.5IL MeOH:H20)	1.910±0.420 $p = 5.52*10^{-4}$	-0.015±0.003 $p = 3.55*10^{-4}$	TPSA(NO)	0.116±0.033 $p = 3.91*10^{-3}$	HOMT	0.0035±0.0010 $p = 4.60*10^{-3}$
(8)	(1.5IL MeOH:H20)	0.605±0.199 $p = 8.80*10^{-3}$	0.545±0.064 $p = 1.31*10^{-6}$	ALOGP	0.062±0.022 $p = 1.21*10^{-2}$	CATS2D_06_LL	-
(9)	(1.5IL ACN:H20)	1.577±0.238 $p = 1.61*10^{-5}$	0.003±0.001 $p = 3.30*10^{-3}$	QXXm	-0.012±0.002 $p = 1.64*10^{-4}$	TPSA(NO)	0.005±0.002 $p = 1.53*10^{-2}$
(10)	(1.5IL ACN:H20)	0.843±0.199 $p = 9.64*10^{-4}$	0.317±0.031 $p = 1.11*10^{-6}$	ALOGP	-0.076±0.014 $p = 1.10*10^{-4}$	CATS2D_04_AL	0.004±0.001 $p = 2.85*10^{-3}$

[a]**R (R^2)** – multiple correlation coefficient (determination coefficient). [b]**S** – standard error of estimate. [c]**F** – value of the F-test of si