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QSAR–CoMSIA applied to antipsychotic drugs with their dopamine D_2 and serotonine $5HT_{2A}$ membrane receptors

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Abstract: Antipsychotic drugs are psychiatric medication primarily used to manage psychosis (*e.g.*, delusions or hallucinations), particularly in schizophrenia and bipolar disorder. First and second generations of antipshychotics tend to block receptors in the brain's dopamine pathways, but antipsychotic drugs encompass a wide range of receptor targets. The inhibition constant, K_i, at the level of membrane receptors is a major determinant of their pharmacokinetic behavior and, consequently, it can affect their antipsychotic activity. Here, predicted inhibition constants, K_i for 71 antipsychotics, already approved for clinical treatment, as well as representative new chemical structures which exhibit antipsychotic activity, were evaluated using 3D-QSAR–CoMSIA models. Significant values of the cross-validated correlation q^2 (higher than 0.70) and the fitted correlation r^2 (higher than 0.80) revealed that these models have reasonable power to predict the biological affinity of the 15 new risperidone and 12 new olanzapine derivatives in interactions with dopamine D_2 and serotonin $5HT_{2A}$ receptors; these compounds are suggested for further studies.

Keywords: antipsychotic; CoMSIA; QSAR; membrane receptors; olanzapine; risperidone.

INTRODUCTION

Schizophrenia is a severe mental illness characterized by positive symptoms, such as delusions and hallucinations, and disorganized speech, and negative symptoms, such as affective flattening, social withdrawal in nature and deficits of attention.[1–5] Moreover, inhibition of inappropriate actions and irrelevant sensory

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information are also present.[6,7] Schizophrenia etiology indicates that many factors are involved, namely genetic factors,[8–10] alterations in chemical transmission (dopamine, serotonine, *etc*.),[11–13] obstetrical complications[14–17] and viral infections.[18] The neurobiology of schizophrenia has shown that an enlarged ventricular system accompanied by an overall reduction in brain volume[19] and a regional decrease in the hippocampus, thalamus and frontal lobes are present.[20,21] Neurons in these regions appear reduced in size with abnormal dendritic arborization and synaptic organization.[19,22] Currently there are many classes of chemical structures which can be regarded as typical antipsychotics (*e.g*., haloperidol and chlorpromazine) and atypical antipsychotics (risperidone, olanzapine and clozapine)[23–25] but recently many other chemical structures having antipsychotic activities have been reported.[26–32] A common feature of these drugs is not only their relatively high affinity for dopamine receptors,[33] but also for serotonin receptors.[34,35] In schizophrenia treatment, a strong correlation between therapeutic doses of neuroleptics and their binding affinity to D_2 receptor was noticed.[33,36,37] The important limitations of antipsychotic prescription are their critical side effects, such as extra-pyramidal symptoms (EPS),[38] increased plasma prolactin levels and decreasing tardive dyskinesia (TD),[39] which develop in about 70 % of patients.

Risperidone and olanzapine, two extremely potent antipsychotics, are included in empirical protocols for the treatment of psychosis with good tolerance in patients. They decrease the negative symptoms by acting on the serotonergic and noradrenergic receptors, while the positive symptoms are reduced by their effects on the dopaminergic pathway,[37] with lower side effects. There is currently much interest in the development of new derivatives starting from these antipsychotics.

Structure–activity relationship (QSAR) studies using the classical quantitative structure–activity relationship (2D-QSAR)[27–29,40,41] and a few 3D-QSAR––CoMFA and/or 3D-comparative molecular similarity analysis (3D-CoMSIA) approaches[42–48] have enhanced knowledge concerning the interactions of antipsychotics with different classes of membrane receptors.

In a previous study,[40] six new QSAR models were presented in which correlate the inhibition constants of antipsychotics at the dopamine D_1–D_4 and serotonine ($5HT_{2C}$, $5HT_{2A}$) receptors were correlated with their physicochemical parameters using MOE software (http://www.chemcomp.com/software.htm). In this previous study,[40] MLR-, factor-analyses and discriminant-analyses were used to elucidate the most important physico–chemical properties of the antipsychotics which are responsible for their binding properties, *i.e*., hydrophobic and refractivity properties on subdivided surface areas (SlogP_VSA4, SlogP_VSA8, SlogP_VSA9 (hydrophobicity descriptors, with L_i in different ranges; L_i denotes the contribution to log P(o/w) of atom i as calculated in the *S*log *P* descriptor,

http://www.chemcomp.com/software.htm) and SMR_VSA2, SMR_VSA5, SMR_VSA3, SMR_VSA4, SMR_VSA1, SMR_VSA7 (refractivity descriptors with R_i in different ranges; R_i denotes the contribution to molar refractivity of atom i as calculated in the SMR descriptor, http://www.chemcomp.com/ /software.htm), electronic properties (PEOE_VSA+1, PEOE_VSA-4, PEOE_VSA--0), energetic term E_{sol} (solvation energy), as well as properties due to the solvent accessible surface areas (ASA_H) and the pharmacophore feature vsa-hyd. The 71 antipsychotic drugs analyzed before were used to extend the study by developing new 3D-QSAR-CoMSIA models.

The aim of this study is to develop predictive 3D-QSAR models to observe which structural features are responsible for selective $5HT_{2A}$ antagonism *vs.* D_2 receptor binding.

An objective of this study was to use 3D-QSAR models to predict the effect of molecular properties, for example hydrogen bond donor/acceptor, hydrophobic, steric and electrostatic properties, on the inhibitor constant at dopamine and serotonin receptors of a large number of antipsychotics: *i*) typical and atypical antipsychotics already approved for clinical treatment,[32,49–55] and *ii*) novel potential antipsychotic agents, such as 3-aminoethyl-1-tetralones,[30] piperazine,[26] benzothiazepine[28,29] and pyrrolobenzazepine[27] derivatives, with favorable pharmacokinetic properties. Preliminary, studies[26–31] confirmed the superior pharmacological effects (significant reduction of spontaneous locomotor activity, a negligible increase of prolactine serum levels, therapeutic potential against cognitive and negative symptoms of schizophrenia) of these novel drugs which are administered in much lower doses compared to classical antipsychotics.

This encouraged the present study in which the above-mentioned molecular properties led to powerful 3D-QSAR models for K_i prediction, despite the large variety of chemical structures from different literature sources. The ultimate goal was to design selective, high affinity D_2 and $5HT_{2A}$ receptor antagonists with a superior clinical profile for schizophrenia treatment, with the assistance of the 3D-QSAR models developed herein. Therefore, new 15 risperidone and 11 olanzapine derivatives with possible higher affinity to dopamine D_2 and serotonin $5HT_{2A}$ membrane receptors were designed and their antipsychotic activities were predicted in accordance with the estimated 3D-QSAR models.

EXPERIMENTAL

Dataset for analysis

The inhibitor constant data, K_i, of 71 dopamine D_2 and serotonin $5HT_{2A}$ receptors antagonists (typical and atypical antipsychotics already approved for clinical treatment and novel potential antipsychotic agents) used in this study were collected from the literature.[26–32,49–55]

A large range of observed inhibition constant K_i (pK_i from 5 to 10), favorable pharmacokinetic properties covering the interactions with dopamine and serotonine receptors, various

substituents, covering as many as possible chemical classes of compounds (Tables I–V) were the selection criteria of the compounds considered in this study.

As a rule, a range in affinity of at least three logarithmic units is necessary to develop a statistically significant 3D-QSAR model. The $5HT_{2A}$ receptor affinities spread over a range of nearly five logarithmic units, whereas the D_2 ligands covered four logarithmic units.

Even if the values of the inhibition constants originated from different studies, they were mutually well comparable, as in following examples: clozapine (pK_{i5HT2A} = 8.26,[50] 8.00,[27–29] 8.20,[32] 8.04;[30] pK_{iD1} = 6.45,[27–29] 6.26;[32] pK_{iD2} = 6.59,[50] 6.60,[27–29] 6.84,[32] 6.65)[30] or haldol pK_{iD2} = 8.39,[50] 8.60,[32] 8.32,[27–29] 9.00).[30] This enabled the affinity data of the compounds to be combined in one set. The names of typical and atypical antipsychotics, corresponding to the observed and predicted pK_i values and also the 2D structures of potential antipsychotics are given in Tables I–V.

TABLE I. Typical and atypical antipsychotics which are already approved for clinical treatment[49–55]

Compound	$pK_{i5HT2Aobs}$	$pK_{i5HT2Apred}$	pK_{iD2obs}	$pK_{iD2pred}$
Clozapine (**N1**)	8.26	8.68	6.59	7.12
Flupentixol (**N2**)	7.05	7.24	8.82	8.63
Haloperidol (**N3**)	7.27	7.48	8.39	8.21
Loxapine (**N4**)	8.11	7.86	7.92	7.79
Mesoridazine (**N5**)	8.31	8.08	7.72	7.87
Olanzapine (**N6**)	8.69	8.73	7.46	7.27
Quetiapine (**N7**)	6.99	7.20	6.61	6.47
Risperidone (**N8**)	9.76	9.30	8.18	8.34
Sertindole (**N9**)	9.23	9.15	8.04	7.74
Thiothixene (**N10**)	7.30	7.47	9.20	8.07
Thioridazine (**N11**)	8.00	8.23	7.95	8.06
Campazine (**N12**)	7.82	7.61	8.76	8.00
Ziprazidone (**N13**)	9.52	9.26	8.01	8.07

Molecular modeling and minimum energy performed for antipsychotics

Three dimensional structures of studied compounds were obtained using of the build module from Sybyl 7 software.[56,57] In the first step, 2D structures of the antipsychotics that were automatically changed into 3D structures were saved in Sybyl specific files .mol2.

In this study, the conformation of the antipsychotics with the minimum potential energy was established using the Maxim 2 minimization routine in Sybyl 7, with Tripos force field, conjugate-gradient algorithm and convergence 0.01 without constraint. After energy minimization, the Gasteiger–Marsili partial charges of the compounds[57] were loaded on the chemical structures from the Sybyl 7 dictionary.

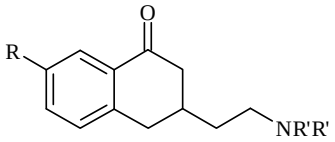
CoMSIA strategy and chemometric analyses

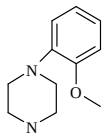
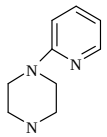
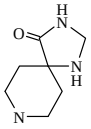
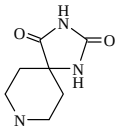
The CoMSIA method involves a "common scaffold". As all the inhibitors had a six-membered ring in common (*e.g.*, piperazine and piperidine), in this study, a "common scaffold" was obtained by the superposition of the common six-membered ring belonging to compounds and of the most active antagonist benzothiazepine (derivative, N66, pK_{iD2} = 9.36) to the dopamine D_2 receptor and risperidone, pK_{i5HT2A} = 9.76 to the serotonin $5HT_{2A}$ receptor.

The steric and electrostatic, hydrophobic and hydrogen bond donor/ acceptor properties of each inhibitor were calculated at the intersections of a regularly spaced (2 Å) grid in a grid-

-box ‘‘create automatically’’ in Sybyl. Lennard-Jones 6–12 potential and Coulombic potential functions, hydrophobicity, and hydrogen bond properties of compounds, within the Tripos force field, using a sp^3 carbon probe atom, with a +1 charge, were considered.[56,57]

TABLE II. 3-Aminoethyl-1-tetralones derivatives[30]



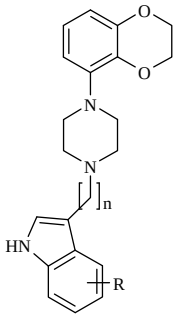
Compound	Radical R	NR’R’	p$K_{i5HT2Aobs}$	p$K_{i5HT2Apred}$	pK_{iD2obs}	p$K_{iD2pred}$
N14	H		6.59	6.39	6.97	6.11
N15	OCH_3		6.65	6.33	6.55	6.2
N16	H		–	–	5	5.07
N17	OCH_3		–	–	5	5.05
N18	H		8.29	8.35	5.98	7.23
N19	OCH_3		8.23	8.24	7.04	7.06
N20	H		5	5.94	5	5.15
N21	OCH_3		5	4.98	5	5.15
N22	H		6.15	5.98	5	4.83
N23	OCH_3		5.98	5.94	5	4.87

An energy cutoff of 30 kcal mol^{-1} was used for both the electrostatic and steric contributions. Regression analysis was performed by the partial least squares (PLS) algorithm within Sybyl 7.2. The leave-one-out cross-validation method using the SAMPLS method was employed to evaluate the predictable residual sum squares (*PRESS*), standard deviation (*SD*) and cross-validated correlation coefficient (q^2). The optimal number of orthogonal principal components was chosen based on t the highest q^2 value by the PLS using the leave-one-out cross-validation method.[56,57]

The minimum standard deviation threshold sigma was set to 2.0 kcal mol^{-1} and 2.0 for CoMSIA. Furthermore, the control criteria fitted correlation coefficient r^2, standard error of estimate (*SEE*) and Fisher test (*F*) were calculated using the CoMFA module by the non--cross-validated method.[56,57] In addition, the representation of the hydrophobic and hydrogen

bond acceptor descriptors as a 3D contour plot (the favorable and unfavorable area representation by polygons) formed just around the risperidone were performed in the Sybyl/ QSAR module.[56,57]

TABLE III. Piperazine derivatives[26]



Compound	Radicals		pK_{iD2obs}	$pK_{iD2pred}$
	n	R		
N24	1	H	7.20	7.07
N25	2	H	7.34	7.79
N26	3	H	7.67	7.87
N27	4	H	8.29	8.00
N28	5	H	8.04	7.99
N29	3	4-F	8.09	7.86
N30	3	5-F	7.72	7.86
N31	3	6-F	7.83	7.85
N32	3	7-F	7.97	7.88
N33	3	5-OMe	7.82	7.87
N34	3	4-Cl	7.61	7.87
N35	3	5-Cl	7.50	7.87
N36	3	6-Cl	8.67	7.86
N37	3	7-Cl	7.80	7.9
N38	3	5-Me	7.97	7.88
N39	3	7-Me	7.79	7.93

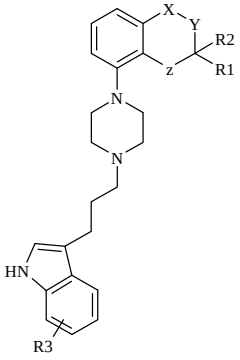
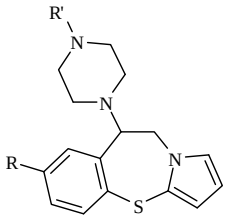


TABLE III. Continued

Compound	Radical						pK_{iD2obs}	$pK_{iD2pred}$
	X	Y	Z	R1	R2	R3		
N40	O	CH_2	CH_2	H	H	H	7.69	7.65
N41	NH	CH_2	CH_2	H	H	H	7.94	7.64
N42	NMe	CH_2	CH_2	H	H	H	7.04	7.62
N43	NH	CH_2	CH_2	Me	H	H	7.82	7.66
N44	NH	C(=O)	CH_2	H	H	H	7.94	8.19
N45	NH	C(=O)	O	H	H	H	8.36	8.56
N46	NH	C(=O)	O	Me	H	H	8.34	8.6
N47	NH	C(=O)	O	Me	Me	H	8.13	8.5
N48	NH	C(=O)	O	(*R*)–Me	H	H	8.06	8.25
N49	NH	C(=O)	O	(*S*)–Me	H	H	9.00	8.51
N50	NH	C(=O)	O	(*R*)–Me	H	5-F	8.16	8.31
N51	NH	C(=O)	O	(*R*)–Me	H	7-F	8.27	8.51
N52	NH	C(=O)	O	(*S*)–Me	H	7-F	9.00	8.63

TABLE IV. Benzothiazepine derivatives[28,29]



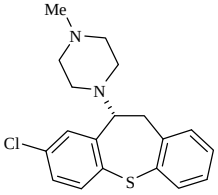
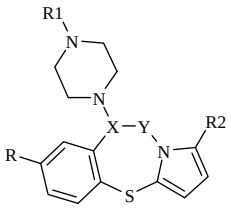
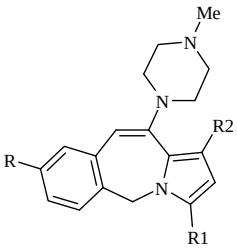
Compound	Radical			$pK_{i5HT2Aobs}$	$pK_{i5HT2Apred}$	pK_{iD2ob}	pK_{iD2pr}
	R	*n*	R’			s	ed
N53	Cl	1	Me	8.94	8.11	8.69	7.99
N54	H	1	Me	7.60	8.17	7.10	7.97
N55	F	1	Me	8.29	8.13	7.63	7.98
N56	Cl	1	Et	8.23	8.01	8.51	7.97
N57	Cl	1	CH_2CH_2OH	8.06	7.79	8.23	8.1
N58	F	1	Et	8.36	8.22	8.02	8.22
N59	F	1	CH_2CH_2OH	7.13	7.70	7.66	7.98
N60	Br	1	Me	7.92	8.40	8.44	8.42
N61	Br	1	Et	7.64	8.29	8.40	8.40
N62	Br	1	CH_2CH_2OH	7.65	7.84	8.30	8.21
N63				9.64	8.51	9.30	8.5

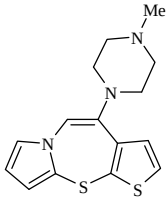
TABLE IV. Continued



Compound	Radical				$pK_{i5HT2Aobs}$	$pK_{i5HT2Apred}$	pK_{iD2obs}	$pK_{iD2pred}$
	R	R1	R2	X–Y				
N64	H	Me	H	C=CH	9.18	9.08	7.76	8.18
N65	F	Me	H	C=CH	9.45	9.11	8.07	8.29
N66	Cl	Me	H	C=CH	9.46	9.20	9.36	8.4
N67	Br	Me	H	C=CH	9.08	9.26	9.34	8.48
N68	H	Me	Me	C=CH	8.95	9.01	6.89	7.98

TABLE V. Pyrrolobenzazepine derivatives[27]



Compound	Radical		$pK_{i5HT2Aobs}$	$pK_{i5HT2Apred}$	pK_{iD2obs}	$pK_{iD2pred}$
	R	R1				
N69	H	H	8.13	8.67	6.23	7.50
N70	Cl	H	8.86	8.85	7.14	7.95
N71			8.66	8.65	8.07	8.21

Training and test sets in the QSAR models

The ability of CoMSIA to predict the biological activities of the antipsychotics to the dopamine D_2 and serotonin $5HT_{2A}$ receptors was evaluated by training and test sets in which a variable number of molecules were used (Tables I–V). Traditionally, external test sets are used to check the predictive power of models derived from training sets. The predicted binding affinities for the test sets are given in Tables I–V in bold numbers/characters.

Initially, to validate 3D-QSAR CoMSIA D_2 and $5HT_{2A}$ models, individual hydrophobic, hydrogen bond acceptor, hydrogen bond donor, steric and electrostatic fields in different com-

binations were considered. Finally, choosing a set of descriptors sufficient to enable an accurate validation of the QSAR models (q^2 (cross-validated r^2) not less than 0.6, r^2 higher than 0.9), two 3D-QSAR models were presented: *i*) the 3-QSAR-CoMSIA D_2 model contains 5 compounds in test set (thiothixene (**N10**), campazine (**N12**), 3-aminoethyl-1-tetralones derivative (**N18**), benzothiazepine derivative (**N68**) and pyrrolobenzazepine derivative (**N69**) and the other 66 compounds in the training set) assessed with hydrogen bond acceptor, hydrophobic, steric and electrostatic as descriptors; *ii*) the 3D-QSAR-CoMSIA $5HT_{2A}$ model contains 4 compounds in the test set (benzothiazepine derivatives: **N53**, **N54**, **N61** and **N63**) and the other 38 compounds in training set, assessed with hydrogen bond donor, hydrophobic and steric and electrostatic as descriptors.

Design of new D_2 and $5HT_{2A}$ antagonist derivatives from risperidone and olanzapine with possibly improvement in the antagonist potency

Taking into account the best correlations between the observed and predicted pK_i for risperidone and olanzapine to dopamine and serotonin receptors, 15 molecules derived from risperidone and another 11 derivatives from olanzapine were designed and proposed as possible antipsychotic drugs, and their pK_{iD2} and pK_{i5HT2A} values were evaluated. Molecular modeling of risperidone and olanzapine derivatives was performed under the above-described procedure. The risperidone and olanzapine derivatives were generated using the added atoms (Cl, F) and groups (ethyl, *iso*-propyl, cyclohexyl, *n*-butyl, methyl, $CH_3NC_2H_5$, OH, COOH, NH_2) from the Sybyl data base. The minimum potential energy for the risperidone and olanzapine derivatives was established using the Maxim 2 minimization routine in Sybyl 7, with Tripos force field, conjugate-gradient algorithm, and convergence 0.01. During energy minimization, only the specific substituents were allowed free movement while the rest of the molecule was kept rigid. After energy minimization, the Gasteiger–Marsili partial charges of the compounds[57] were loaded on the chemical structures from the Sybyl 7 dictionary. Prediction of inhibitor constants to dopamine D_2 and serotonin $5HT_{2A}$ receptors of the obtained derivatives was realized using QSAR models statistically validated during previous phases of the study.

RESULTS AND DISCUSSION

The 3D-QSAR-CoMSIA D_2 model predicted antagonist potency of 66 compound by the leave-one-out cross-validated PLS analysis running with four principal components led to a q^2 cross-validated correlation coefficient of 0.71 and by non-cross-validated PLS analysis, a fitted correlation coefficient r^2 = 0.86, standard error estimate of 0.40 and *F* value of 96.72 were obtained (Table VI).

The other goal of this study was to establish by 3D-QSAR/CoMSIA the contribution of molecular properties, such as hydrogen bond donor/acceptor property, hydrophobic and also steric/electrostatic fields, to the D_2 receptor antagonist potency.

The statistic parameters q^2 – cross-validated correlation coefficient, r^2 – fitted correlation coefficient and the standard error estimate (*SEE*) were statistically significant when the hydrogen bond acceptor, hydrophobic and steric and electrostatic fields were considered (Table VI). It was noticed that the hydrogen bond acceptor (1.397) and hydrophobic (0.60) properties contributed significantly more compared with the steric and electrostatic (0.283/ 0.496) properties.

When the antagonist potency of compounds referred were studied to the serotonin 5HT2A receptor, a second CoMSIA model was obtained and the statistic parameters q^2 cross-validated of 0.78, fitted correlation coefficient r^2 of 0.95 and *SEE* of 0.34 were evaluated (Table VI).

TABLE VI. Summary of the 3D-QSAR-CoMSIA statistical data

Statistical parameter	3D-QSAR D_2 model	3D-QSAR $5HT_{2A}$ model
Molecules	66	38
Q2 cv	0.71	0.78
Component used	4	3
*SEE*stimate	0.40	0.34
R squared	0.86	0.95
F value	96.72	250.53
Steric contribution	0.28	0.35
Electrostatic contribution	0.49	0.75
Acceptor contribution	1.39	–
Hydrophobic contribution	0.60	0.67
Donor contribution	–	0.77

Analysis of the contribution of the molecular descriptors showed that the significant statistical q^2 cross-validated and fitted correlation coefficient r^2 parameters were obtained when the descriptors steric and electrostatic, hydrophobic and hydrogen bond donor were considered (Table VI). Noteworthy is that three (electrostatic (0.75), hydrophobic (0.67) and hydrogen bond donor (0.77)) of the four descriptors had contributions higher than 0.65; the most involved descriptor in the interaction between the described compounds and the serotonine $5HT_{2A}$ receptors seemed to be hydrogen bond donor.

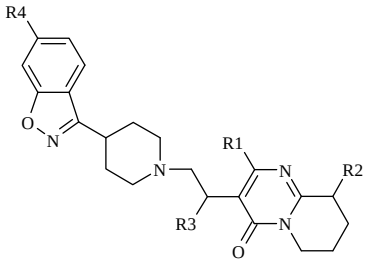
Modeling of new risperidone and olanzapine derivatives with potentially superior antagonist potency at the dopamine D2 and serotonin 5HT2A membrane receptors

Due to their low affinities, the currently used atypical antipsychotics suffer the disadvantage of high dose administration. Currently, the major problem of using antipsychotic drugs is governed by the above-mentioned side-effects. Due to the before-mentioned high importance of risperidone and olanzapine as antipsychotic agents, two sets of 15 new risperidone and 11 olanzapine derivatives were made in order to predict improved pK_i values for D_2 and $5HT_{2A}$ receptors using the above-presented 3D-QSAR models (Tables VII and VIII).

In designing the new risperidone and olanzapine derivatives, two strategies were followed: first, the number of hydrophobic contacts on *i*) risperidone by adding methyl, ethyl, *iso*-propyl, *n*-propyl, *n*-butyl, cyclohexyl and phenyl substituents at 2,6-diazabicyclo[4.4.0]deca-1,3-dien-5-one and ethyl chain and *ii*) olanzapine by adding methyl, ethyl, *iso*-propyl, *iso*-butyl and phenyl at piperazinyl and 10*H*-thieno rings, respectively.

Secondly, Cl, hydroxyl, carboxyl or amino substituents were generated on risperidone. In addition, Cl, F and hydroxyl were generated on olanzapine (Tables VII and VIII). The chemical structures of the risperidone and olanzapine derivatives, residual pK_i values (the difference between template antipsychotics and predicted pK_i derivatives) and the predicted pK_i values for the risperidone and olanzapine derivatives are presented in Tables VII and VIII.

TABLE VII. Antagonist potency pK_{iD2} and pK_{i5HT2A} for the risperidone derivatives and residual values (differences in the antagonist potency of the risperidone derivatives to the parent antagonist potency are given in brackets)



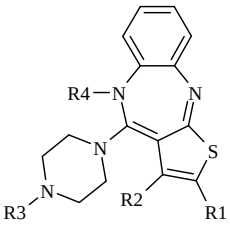
Risperidone derivate	Group				Predicted pK_{iD2}	Predicted pK_{i5HT2A}
	R1	R2	R3	R4		
1	C_2H_5	H	H	F	8.7 (0.54)	9.37(–0.39)
2	$(CH_3)_2CH$	H	H	F	8.74 (0.56)	9.46 (–0.3)
3	CH_3	$(CH_3)_2$	H	F	8.55 (0.37)	9.10 (–0.66)
4	$(CH_3)_2CH$	H	OH	F	8.60 (0.42)	9.41(–0.35)
5	C_6H_{13}	H	H	F	7.46 (–0.72)	8.41 (–1.35)
6	$H_3C–NH_2$	H	H	F	8.12 (–0.06)	9.30 (–0.46)
7	$CH_2N(CH_3)_2$	H	H	F	8.66 (0.48)	9.42 (–0.34)
8	OH	H	H	F	8.23 (0.05)	9.36 (–0.4)
9	C_4H_7	H	H	F	8.18 (0)	9.00 (–0.76)
10	C_4H_7	H	NH_2	F	8.27 (0.09)	8.94 (–0.82)
11	CH_3	H	C_6H_5	F	8.75 (0.57)	9.30 (–0.46)
12	C_4H_7	H	H	OH	8.25 (0.07)	9.52 (–0.24)
13	C_4H_7	H	H	Cl	8.27(0.09)	9.60 (–0.16)
14	C_4H_7	H	H	COOH	8.42 (0.24)	8.06 (–1.7)
15	C_4H_7	CH_3	H	F	7.42 (–0.76)	8.15 (–1.61)

In this study, good correlations between the observed and predicted antagonist potency of the compounds to the dopamine D_2 receptor (Tables I–V) were obtained. As examples, the correlation between the observed and predicted antagonist potency of compounds included in the training set were piperazine derivative **N40** ($pK_{iD2observed} - pK_{iD2predicted} = 0.04$), benzothiazepine **N60** ($pK_{iD2observed} - pK_{iD2predicted} = 0.02$) and **N61** ($pK_{iD2observed} - pK_{iD2predicted} = = 0.001$) derivatives. However, the residual value was not good when the anta-

gonist potency was predicted for the 3-aminoethyl-1-tetralones derivative **N18** ($pK_{iD2observed} - pK_{iD2predicted} = -1.03$).

Data presented in Tables I–V are illustrated by graphical presentations of the correlation between the observed and the predicted antagonist potency of the compounds to the dopamine D_2 membrane receptor in Fig. 1.

TABLE VIII. Antagonist potency pK_{iD2} and pK_{i5HT2A} for olanzapine derivatives and residual values (differences in the antagonist potency of the olanzapine derivatives to the parent antagonist potencyare given in brackets)



Olanzapine derivate	Group				Predicted pK_{iD2}	Predicted pK_{i5HT2A}
	R1	R2	R3	R4		
1	CH_3-CH_2	H	CH_3	H	7.31 (–0.15)	8.42 (–0.27)
2	CH_3	CH_3	CH_3	H	7.49 (0.03)	8.48 (–0.21)
3	CH_3	C_3H_7	CH_3	H	7.46 (0)	8.99 (0.30)
4	CH_3	isobutyl	CH_3	H	7.51(0.05)	8.94 (0.25)
5	CH_3	H	CH_3	CH_3	6.97 (–0.49)	8.69 (0)
6	C_6H_5	H	CH_3	H	7.30 (–0.16)	8.27 (–0.42)
7	CH_3	H	H_3C–CH_2	H	7.20 (–0.26)	8.15 (–0.54)
8	CH_3	H	C_3H_7	H	7.16 (–0.3)	8.10 (–0.59)
9	CH_3	H	CH_2F	H	7.26 (–0.2)	8.20 (–0.49)
10	CH_3	H	CH_2Cl	H	7.26 (–0.2)	8.65 (–0.04)
11	CH_3	H	CH_2OH	H	7.02 (–0.44)	7.95 (–0.74)

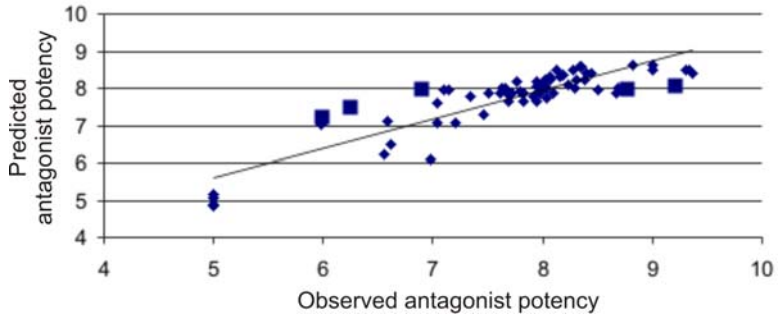


Fig. 1. Correlation between the observed and predicted antagonist potency pK_{iD2} of the antipsychotic drugs when the hydrophobic, hydrogen acceptor bond, electrostatic and steric properties are regarded as descriptors (the molecules from the test set are represented by the square shape).

The observed and predicted antagonist potency of serotonin $5HT_{2A}$ receptor for the training and test (bold letters) sets are shown in Tables I–V.

CoMSIA statistic validation in this case leads to a good correlation of observed and predicted antagonist potency for the pyrrolobenzazepine derivatives **N71** ($pK_{i5HT2Aobserved} - pK_{i5HT2Apredicted} = 0.01$) and **N70** ($pK_{i5HT2Aobserved} - - pK_{i5HT2Apredicted} = 0.01$). A graphical presentation of the correlation between the observed and predicted antagonist potency of the compounds in interaction with the serotonin $5HT_{2A}$ receptor is presented in Fig. 2.

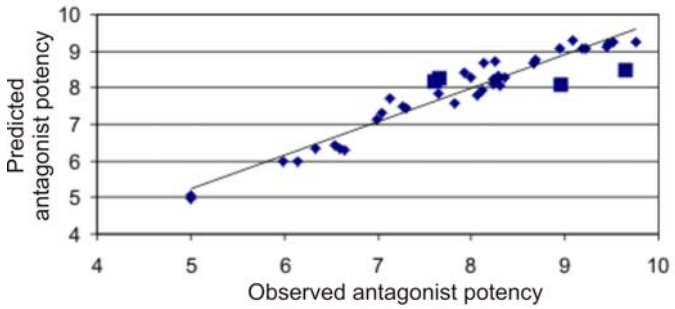


Fig. 2. Correlation between the observed and predicted antagonist potency pK_{i5HT2A} of the antipsychotic drugs belong to the training set when the hydrophobic, hydrogen donor bond, electrostatic and steric properties are regarded as descriptors (the molecules from the test set are represented by the square shape).

Graphical interpretation of the 3D-QSAR–CoMSIA models

The great advantage of the CoMSIA method is its ability to visualize the descriptor fields as 3D contour plots (the favorable and unfavorable descriptor areas are represented by polygons) formed just around the target molecule. Accordingly, in this study, with the contribution of the descriptors to the biological activity, CoMSIA contour maps of the hydrophobic field and hydrogen bond acceptor were used for graphical analysis.

The favorable hydrogen acceptor bond areas (white polygons) and the unfavorable hydrophobic areas (grey polygons) formed around risperidone when its antagonist potencies at the dopamine D_2 and setotonine $5HT_{2A}$ receptors were considered ($pK_{iD2} = 8.18$ and $pK_{i5HT2A} = 9.76$) are shown in Figs. 3–5.

The contour maps for hydrophobic property obtained from risperidone (Fig. 3) show that the presence of large unfavorable hydrophobic areas (2,6-diazabicyclo[4.4.0]deca-1,3-dien-5-one and also isoxazol-rings) could be responsible for the relatively low affinity of risperidone at D_2. On the contrary, the hydrophobic property distribution presented in Fig. 4 looks around risperidone and shows the presence of favorable areas (white areas) around the isoxazol ring and ethyl group, which might be a good explanation for the high antagonist potency of risperidone at $5HT_{2A}$ receptor.

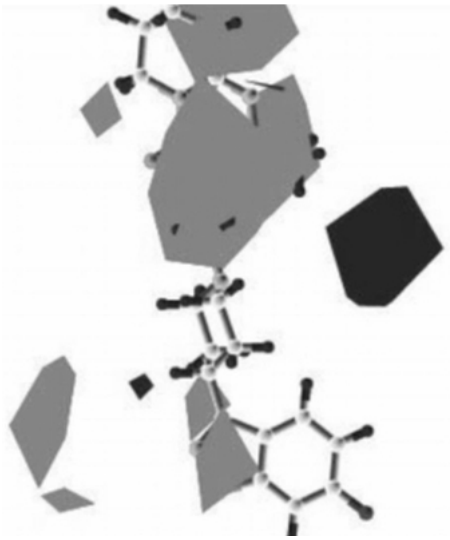


Fig. 3. Representation of the favorable (white polygons) and unfavorable (grey polygons) hydrophobic areas of risperidone (pK_{iD2} = 8.18) when its antagonist potency at dopamine D_2 receptor is considered.

Fig. 4. Representation of the favorable (white polyhedra) and unfavorable (grey polyhedra) hydrophobic areas of risperidone (pK_{i5HT2A} = 9.76) when its antagonist potency at the serotonin $5HT_{2A}$ receptor is considered.

CoMSIA maps showing the hydrogen acceptor bond property are depicted in Fig. 5; they correspond to regions of the putative protein environment which are capable of donating hydrogen bonds. The three favorable regions which formed around the 1,3-dien-5-one and piperidine rings could be important for the D_2 receptor affinity.

Following the employed design strategy, four risperidone derivatives with affinity for the dopamine D_2 receptor (**1** (R1=C_2H_6, R2=H, R3=H, R4=F, pK_{iresD2} = 0.54), **2** (R1=$(CH_3)_2CH$, R2=H, R3=H, R4=F, pK_{iresD2} = 0.56), **7** (R1=$CH_2N(CH_3)_2$, R2=H, R3=H, R4=F, pK_{iresD2} = 0.48) and **11** (R1=CH_3, R2=H,

R3=C_6H_5, R4=F, pK_{iresD2} = 0.57)) had higher predicted pK_{iD2} values than risperidone. It should be mentioned that the presence of additional hydrophobic contacts on R1 in 2,6-diazabicyclo-dione and R3, while simultaneously maintaining F on R4, lead to an increased affinity of the new risperidone derivatives to the dopamine D_2 receptor. The same observation could not be made if a substantial increase of the hydrophobic effect was obtained (derivatives **5** (R1=C_6H_{13}, R2=H, R3=H, R4=F, pK_{iresD2} = –0.72) and **15** (R1=C_4H_7, R2=CH_3, R3=H, R4=F, pK_{iresD2} = –0.76)). In the present study, it is interesting to note that an increased number of hydrophobic contacts on risperidone did not result in a higher affinity for the serotonin 5HT2A receptor and sometimes a decrease in affinity could be found (derivatives **5** (R1=C_6H_{13}, R2=H, R3=H, R4=F, p$K_{ires5HT2A}$ = –1.35), **14** (R1=C_4H_7, R2=H, R3=H, R4=COOH, p$K_{ires5HT2A}$ = –1.70) and **15** (R1=C_4H_7, R2=CH_3, R3=H, R4=F, p$K_{ires5HT2A}$ = –1.61)).

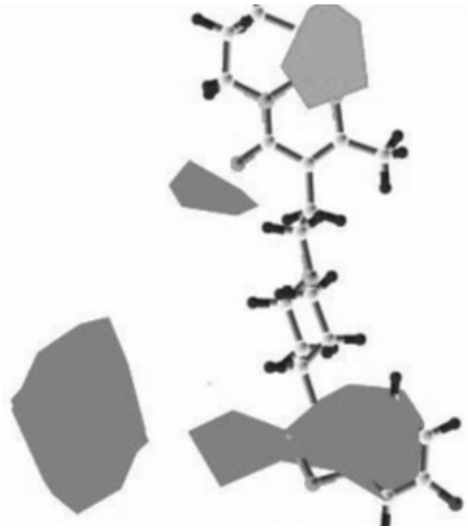


Fig. 5. Representation of the favorable (grey polyhedra) and unfavorable (black polyhedra) hydrogen acceptor bond areas of risperidone when its antagonist potency at the dopamine D2 receptor is considered.

Analysis of the antagonist potency of the olanzapine derivatives at the dopamine D_2 receptor led to the observation that ten had a lower antagonist potency, except derivative **3** (R1=CH_3, R2=C_3H_7, R3=CH_3, R4=H, pK_{iresD2} = 0), for which an identical pK_{iD2} was recorded The same observation could not be made when the affinity of the olanzapine derivate **3** at the serotonin $5HT_{2A}$ receptor was analyzed. The additional hydrophobic contacts on R2 led to clear affinity increases for derivative **3**, p$K_{ires5HT2A}$ = 0.30 and derivative **4** (R1=CH_3, R2= isobutyl, R3=CH_3, R4=H, p$K_{ires5HT2A}$ = 0.25). However, the addition of a hydrophobic contact on R4, *i.e.*, a methyl group, resulted in the same affinity as the template compound (derivative **5** (R1=CH_3, R2=H, R3=CH_3, R4=CH_3, p$K_{ires5HT2A}$ = 0.00).

CONCLUSIONS

3D-QSAR–CoMSIA models can give different information, for example reliable prediction of the affinity of compounds belonging to a data set and chemical interpretation of the results obtained. In this paper, alignment-dependent 3D-QSAR–CoMSIA studies using two QSAR models are reported of a series of 71 antipsychotic drugs already used in clinical practice, as well as representative new chemical structures which exhibit antipsychotic activity and 15 risperidone and 11 olanzapine derivatives proposed as possible antagonists of dopamine D_2 and serotonin $5HT_{2A}$ receptors. The models were used to elucidate the most important physico–chemical properties responsible for the antagonist potency of the chemical structures to dopamine D_2 and serotonin $5HT_{2A}$ receptors. In this study, hydrogen donor/acceptor and hydrophobic properties supplied by steric and electrostatic fields were considered.

Significant PLS results were obtained when a hydrogen acceptor bond and the simultaneous presence of hydrophobic, electrostatic and steric properties were considered in the study of the antagonist potency at the dopamine D_2 receptor. However, the serotonin $5HT_{2A}$ receptor affinity of the antipsychotics was governed by the hydrogen bond donor ability and the simultaneous presence of hydrophobic, electrostatic and steric properties.

Thus, judicious modulation of the physico–chemical properties, particularly hydrogen bond acceptor/donor and hydrophobic properties may be very useful for the design of new chemical structures as possible antagonists of D_2 and $5HT_{2A}$ receptors. Considering the above set of 15 risperidone and 11 olanzapine derivatives, the established equations could be used to enhance or reduce the antagonist potency pK_i, in accordance with the biological requirements.

It was noticed that additional hydrophobic contacts on R1 and R3 on risperidone rings, while simultaneously retaining F in R4, increased the antagonist potency of risperidone derivatives to the dopamine D_2 receptor. In addition, hydrophobic contacts on R2 resulted in a clearly enhanced antagonist potency of two olanzapine derivatives.

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ИЗВОД

QSAR–CoMSIA МОДЕЛИ ПРИМЕЊЕНИ НА АНТИПСИХОТИЧКЕ ЛЕКОВЕ И ЊИХОВЕ ДОПАМИН D_2 И СЕРОТОНИН $5HT_{2A}$ МЕМБРАНСКЕ РЕЦЕПТОРЕ

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Антипсихотици су лекови који се користе у терапији психоза, првенствено схизофреније и биполарног поремећаја. Антипсихотици делују на широк спектар рецептора који учествују у бројним системима трансмисије у мозгу, али главни терапијски ефекат остварују блокирајући допаминске рецепторе. Константа инхибиције, K_i, на нивоу мембранских рецептора је главна детерминанта фармакокинетике и дејства ових лекова. У раду су коришћењем 3D-QSAR–CoMSIA модела оцењене предсказане инхибиционе константе K_i за низ од 71 антипсихотика већ одобрених за клиничку праксу, као и за репрезентативне нове хемијске структуре које показују антипсихотичну активност. Значајне вредности унакрсне корелације q^2 (изнад 0,70) и фитоване корелације r^2 (изнад 0,80), показале су да ови модели могу да предвиде биолошке афинитете 15 нових респеридонских и 12 нових оланзапинских деривата за допаминске D_2 и серотонинске $5HT_{2A}$ рецепторе, те се ова једињења предлажу за даље испитивање.

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