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Quantitative structure – activity relationship studies on membrane receptors inhibition by antipsychotic drugs. Application to schizophrenia treatment

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Abstract There are presented six new QSAR models, which are correlating antipsychotic activity (pK_i values at dopamine D1–D4 and serotonine (5-HT2C, 5-HT2A) receptors) with physicochemical parameters. A large data set of typical and atypical antipsychotics already approved for clinical treatment including as well representatives with new chemical structures which are exhibiting antipsychotic activity (tetrahydrofuran-, benzamide-, 3-aminoethyl-1-tetralones-, piperazine-, benzothiazepine- and pyrrolobenzazepine-derivatives) were incorporated within this study. The appropriate 2D and internal-3D molecular descriptors could be generated by use of the computational software MOE (Molecular Operating Environment). Significant q^2 (0.63–0.76) and r^2 (0.70–0.78) correlation coefficients were obtained, indicating that the established equations can be used within a wide range of binding constants ($pK_i = 5$ to 9.76). By use of these linear models an assembly of new aripiprazole structures could be established. Some of them are showing significantly improved antipsychotic activity in comparison with the parent compound.

Keywords Antipsychotics; 2D-QSAR; Membrane receptors.

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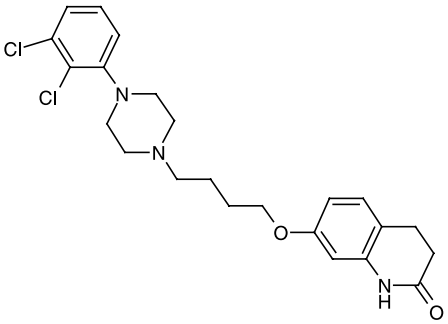
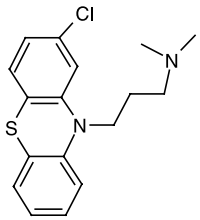
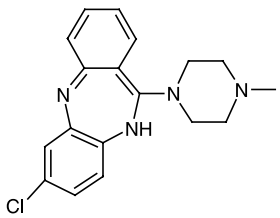
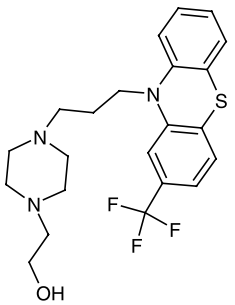
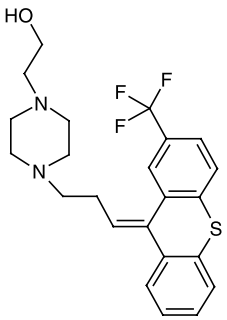
Introduction

Schizophrenia is a major mental disease affecting almost 1% of the general population [1, 2] and which generally is described by positive symptoms: (*e.g.*, delusions, hallucinations, grandiosity, hostility, and disorganization) and negative symptoms (apathy, attention impairment, affective disorder, poverty of speech) [3–7]. At present, the schizophrenia etiology is not very clear but it is considered that genetic [8–10], environmental [11, 12], prenatal, and perinatal risks are present [13–15]. Among the psychosocial factors that may induce schizophrenia are stress and lack of social support [12]. Economically, schizophrenia treatment requires high costs [16–18]. The direct healthcare and non-healthcare costs were estimated to be US$ 1.91 billion in 2004 [16] and also these costs were very high in Europe [18].

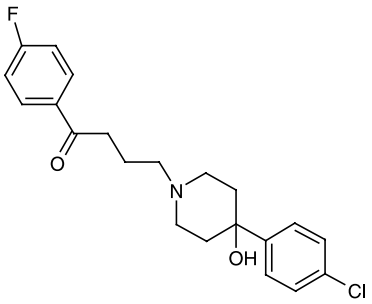
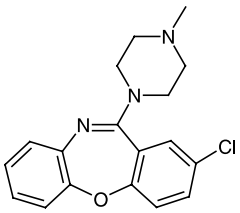
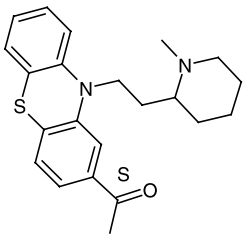
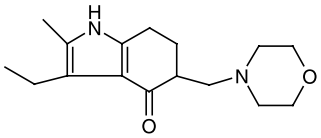
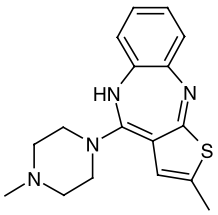
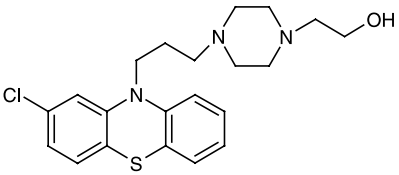
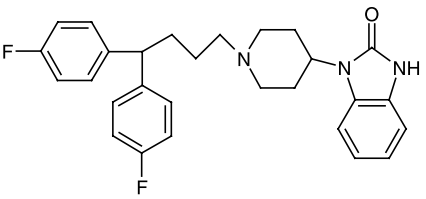
The antipsychotics are able to reduce the positive symptoms and also to prevent the relapse, but negative symptoms are poorly reduced. Usually, typical (*e.g.*, haloperidol, chlorpromazine) and atypical (*e.g.*, risperidone, olanzapine, sertindole, and quetiapine) antipsychotics are known [19–21], and recently, many other chemical structures having antipsychotic activities have been reported [22–28]. The high efficacy of antipsychotics against schizophrenia and their high affinity to D2 dopamine receptors have led to the ''dopamine hypothesis'' of schizophrenia

Table 1a Typical and atypical antipsychotics which are already approved for clinical treatment. References of the source of supply are given in brackets[†]

Compounds	Nr.	pK_i5HT2A	pK_i5HC	pK_iD2	pK_iD1	pK_iD3	pK_iD4
	**N1**	8.06 [46, 49]		9.18 [47]	5.70 [49]	8.52 [48]	6 [48]
	**N2**	8.09 [47]	7.6 [47]	8.39 [47]	7.13 [46]	8.20 [48]	7.61 [46, 48]
	**N3**	8.26 [47]	7.76 [47]		6.28 [28]	7.10 [48]	8.11 [48]
	**N4**	7.52 [47]	5.85 [47]	9.26 [47]			8.14 [48]
	**N5**	7.05 [51]		8.82 [48]	8.39 [46]	9.22 [48]	6.88 [48]

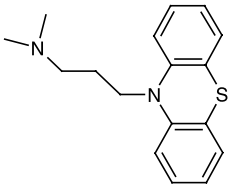
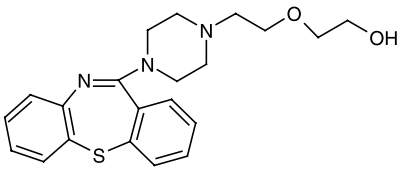
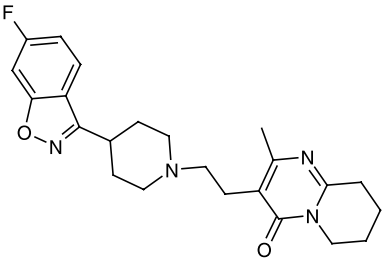
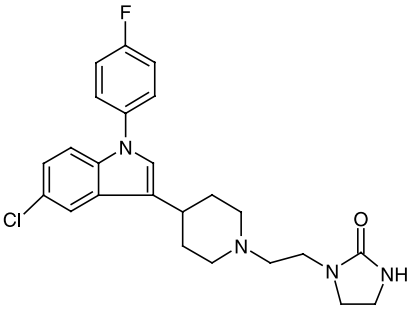
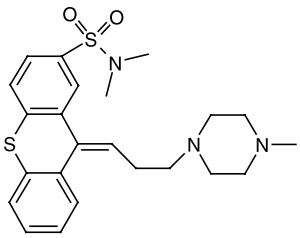
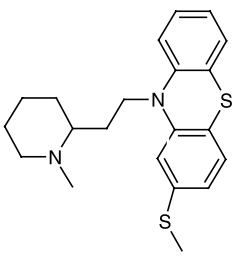
(*continued*)

Table 1a (*continued*)

Compounds	Nr.	pK_i5HT2A	pK_i5HC	pK_iD2	pK_iD1	pK_iD3	pK_iD4
	**N6**		5 [47]				
	**N7**	8.11 [47]	8.02 [47]	7.92 [47]		7.67 [50]	8.10 [50, 53]
	**N8**	8.31 [46]	6.8 [46]	7.72 [48]			8.04 [48]
	**N9**	6.49 [47]				7.29 [48]	8.25 [48]
	**N10**	8.69 [47]	8.16 [47]	7.47 [47]	6.92 [28]	7.85 [47]	7.50 [47]
	**N11**	8.25 [47]	6.87 [47]	8.85 [47]		9.63 [50]	7.49 [50]
	**N12**	7.72 [47]	5.47 [47]	9.18 [47]		9.52 [48]	8.74 [48]

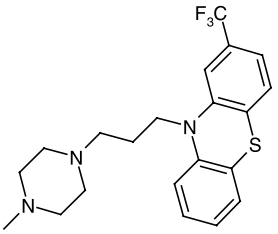
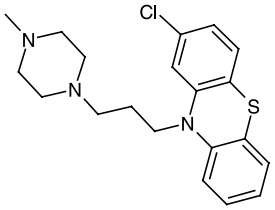
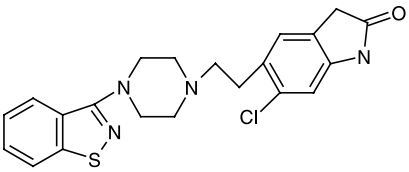
(*continued*)

Table 1a (*continued*)

Compounds	Nr.	pK_i5HT2A	pK_i5HC	pK_iD2	pK_iD1	pK_iD3	pK_iD4
	**N13**	7.79 [52]		6.79 [52]		6.79 [48]	
	**N14**	6.99 [47]			6.14 [46]	8.03 [48]	5.70 [50]
	**N15**	9.76 [47]	7.45 [47]	8.18 [47]	6.83 [28]	8.79 [48]	7.74 [48]
	**N16**			8.04 [48]		8.11 [48]	7.55 [48]
	**N17**	7.3 [47]	5.85 [47]	9.2 [47]	7.29 [46]	9.30 [48]	
	**N18**	8 [47]	7.22 [47]	7.95 [47]	7 [46]	8.13 [48]	8 [50]

(*continued*)

Table 1a (*continued*)

Compounds	Nr.	pK_i5HT2A	pK_i5HC	pK_iD2	pK_iD1	pK_iD3	pK_iD4
	**N19**	7.88 [47]	6.42 [47]	8.88 [47]		9.15 [50]	7.40 [50]
	**N20**	7.82 [52]	6.91 [46]	8.76 [48]		8.46 [48]	5.94 [48]
	**N21**	9.52 [47]	7.88 [47]	8.01 [47]	7.52 [46]	8.13 [48]	

† Within the following tables the chemical structures and biological activities of antipsychotics (pK_i) in interaction with dopamine (D1–D4) and serotonine (5HT2A, 5HT2C) receptors are given

[29], which assumes ''an over-activity of the dopamine neurons''. The typical and atypical antipsychotics do not block only dopamine but also muscarinic, alpha 1 adrenergic, histaminergic H1, and serotoninergic receptors within large brain areas with fewer side effects [30, 31] for atypical [32, 33] but not typical antipsychotics.

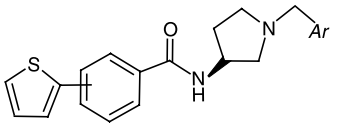
The study of interactions between membrane receptors and neuroleptics is not only important for psychiatry but also for many other scientific fields like pharmacology, computational chemistry, and biochemistry, as these receptors represent an attractive target for new drugs.

When neuroleptics are discussed, frequently the D2 dopaminergic [34] or serotoninergic receptors are considered but, unfortunately, their 3D structures are not yet available. Under these circumstances, the quantitative structure-activity relationship (QSAR) methods remain an optimal option, being useful especially in case of unknown 3D structures of the receptors or proteins involved.

At present, most QSAR studies are rather confined to small data sets and are using both, the classical quantitative structure-activity relationship (2D-QSAR) [23–25] and also 3D-QSAR approaches [35–42] giving rise to enhanced knowledge about antipsychotics drugs and their interactions with different membrane receptors. These studies have been reviewed elsewhere [43]. Generally, in many QSAR studies, the logarithm of the reciprocal constant of inhibition, K_i, was correlated with physicochemical descriptors like: steric *Taft* constants (Es) [44], *Connolly* Surface Area [45], ionization potentials, or dipole moments.

There is a high demand for better therapeutics, especially for patients resistant to neuroleptically active agents. In order to investigate their cognitive symptoms, we performed 2D-QSAR studies of: (i) typical and atypical antipsychotics already approved for clinical treatment (aripiprazole, chlorpromazine, clozapine, fluphenazine, fluphentixol, haldol, loxapine, mesoridazine, molindone, olanzapine, perhenazine, pimozide, quetiapine, promazine, risperidone, sertindole, thiothixene, thioridazine, trifluoperazine, compazine, and ziprazidone) [28, 46–53] as well as (ii) novel potential antipsychotic agents with favorable pharmacokinetic properties like: tetrahydrofuran- [28], benzamide- [27], 3-aminoethyl-1-

Table 1b Benzamide derivatives (the observed biological activity of compounds was taken from Ref. [27])



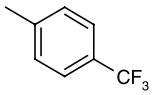
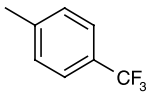
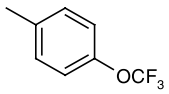
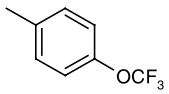
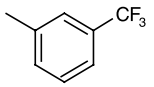
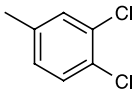
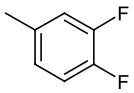
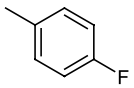
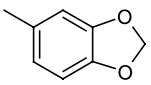
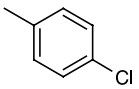
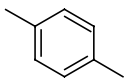
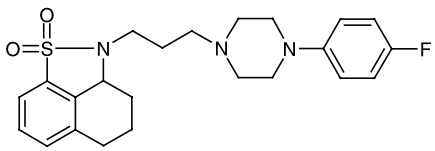
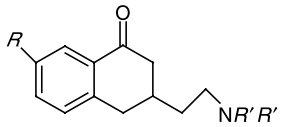
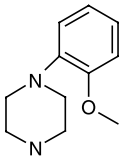
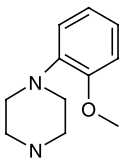
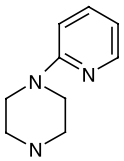
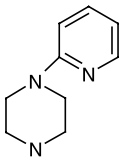
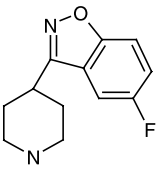
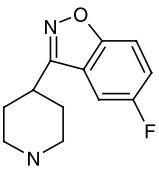
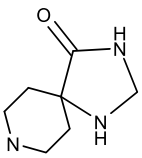
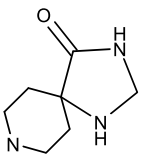
Compounds	Biarylisomer	Nr.	pK_i5HT2A	pK_iD2	pK_iD4
Ph	*para*	**N22**		6.0	8.52
Ph	*meta*	**N23**	6.33	7.22	8.82
	*para*	**N24**	6.88		7.85
	*meta*	**N25**	6.13	5.88	7.67
	*para*	**N26**	6.85		7.10
	*meta*	**N27**		6.30	7.28
	*para*	**N28**			7.65
	*para*	**N29**	7.65		7.82
	*para*	**N30**	7.79		
	*para*	**N31**	7.85		8.30
	*para*	**N32**			8.15
	*meta*	**N33**			7.79
	*meta*	**N34**	6.21	7.22	8.39
		**N35**	9.43		

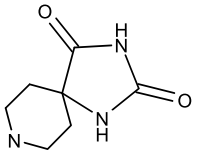
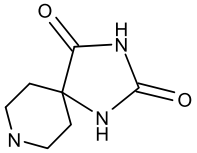
Table 1c 3-Aminoethyl-1-tetralone derivatives (the observed biological activity of compounds was taken from Ref. [26])

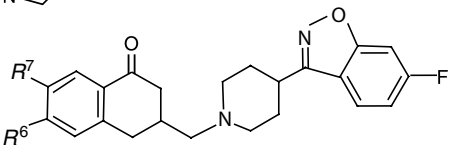


NR′R′	Residue *R*	Nr.	pK_i5HT2A	pK_iD2	pK_i5HT2C
	H	**N36**	6.59	6.97	6.35
	O*Me*	**N37**	6.65	6.55	5.72
	H	**N38**		5	5
	O*Me*	**N39**		5	5.81
	H	**N40**	8.29	5.98	7.06
	O*Me*	**N41**	8.23	7.04	6.89
	H	**N42**	5	5	5
	O*Me*	**N43**	5	5	5

(*continued*)

Table 1c (*continued*)

N$R'R'$	Residue R	Nr.	pK_i5HT2A	pK_iD2	pK_i5HT2C
	H	**N44**	6.15	5	7.05
	O*Me*	**N45**	5.98	5	6.90

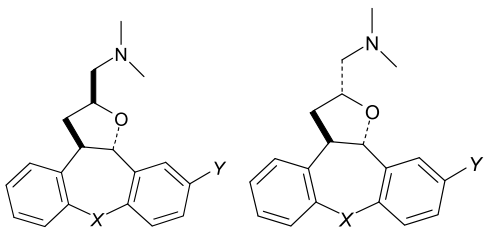


Nr.	R^6	R^7	pK_i5HT2A	pK_iD2	pK_i5HT2C
N46	H	H	8.57	–	6.89
N47	O*Me*	H	7.34	6.34	5.79
N48	O*Me*	O*Me*	8.02	6.82	6.83

tetralones- [26], piperazine- [22], benzothiazepine- [24, 25], and pyrrolobenzazepine- [23] derivatives, in their interactions with membrane receptors like dopamine D1–D4 and serotonine (5HT2A and 5HT2C).

Preliminary, *in vivo* studies [22–28] confirmed the superior pharmacological effects (significant reduction of spontaneous locomotor activity, a negligible increase of prolactin 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. The receptor affinity profile of these new compounds suggested a complex interaction with cortical receptors involved in regu-

Table 1d Tetrahydrofuran derivatives (the observed biological activity of compounds was taken from Ref. [28])



Nr.	Residues		pK_i5HT2A	pK_iD2	pK_i5HT2C	pK_iD1	pK_iD3
	X	Y					
N49	O	F	–	6.71	8.11	–	6.53
N50	O	F	–	7.49	8.36	–	7.50
N51	O	Cl	7.65	7.16	8.43	6.60	7.34
N52	O	Cl	8.22	–	8.61	7.08	6.60
N53	O	Br	7.42	6.43	7.76	–	–
N54	O	Br	7.82	7.18	8.05	6.81	7.02
N55	S	F	7.88	7.92	9.18	7.72	8.06
N56	S	F	9.25	–	–	8.52	–

lation of the activity in prefrontal cortical cells, like 5HT2A and also dopamine receptor subtypes [23–25].

We also correlated the biological activities (log $1/K_i$) using the smallest possible number of sensitive physicochemical descriptors, which were chosen from an initially large number of descriptors calculated by the MOE procedure. Furthermore, we used these validated models to predict new chemical structures with possible improved antipsychotic profiles. Following this way, we are able to present modified types of descriptors, which could give new insights for the profiling of new structures.

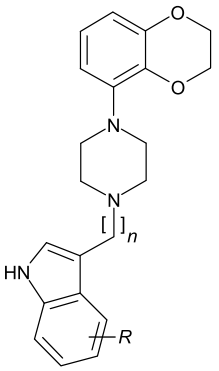
Also, in our attempt to obtain novel antipsychotics with fewer side effects and a higher affinity to the membrane receptors (especially for D1–D4) eighteen aripiprazole derivatives were modeled and their antipsychotic activities were predicted in accordance with estimated 2D-QSAR models.

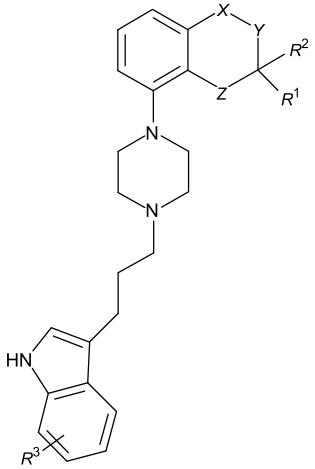
Results and discussion

MLR – equations

6 QSAR models have been generated, each of them containing a different number of antipsychotics interacting with membrane receptors (Table 2a). Due to the validation procedure of QSAR equations some compounds had to be considered as outliers and were finally excluded from the training set. (i) Serotonine 5HT2A (67 antipsychotics in the training set, the observed biological activity of compounds (pK_i)5HT2A is presented in col-

Table 1e Piperazine derivatives (the observed biological activity of compounds was taken from Ref. [22])

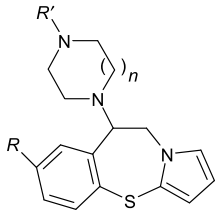


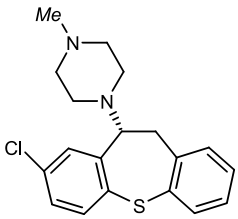


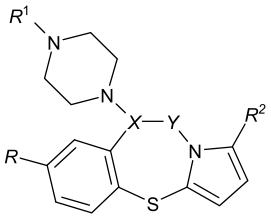
Nr.	Residues		pK_iD2	Nr.	Residues						pK_iD2
	n	*R*			*X*	*Y*	*Z*	R^1	R^2	R^3	
N57	1	H	7.20	**N73**	O	CH_2	CH_2	H	H	H	7.69
N58	2	H	7.34	**N74**	NH	CH_2	CH_2	H	H	H	7.94
N59	3	H	7.67	**N75**	NH	CH_2	CH_2	*Me*	H	H	7.82
N60	4	H	8.29	**N76**	NH	C(=O)	CH_2	H	H	H	7.94
N61	5	H	8.04	**N77**	NH	C(=O)	O	H	H	H	8.36
N62	3	4-F	8.09	**N78**	NH	C(=O)	O	*Me*	H	H	8.34
N63	3	5-F	7.72	**N79**	NH	C(=O)	O	*Me*	*Me*	H	8.13
N64	3	6-F	7.83	**N80**	NH	C(=O)	O	(*R*)-*Me*	H	H	8.06
N65	3	7-F	7.97	**N81**	NH	C(=O)	O	(S)-*Me*	H	H	9
N66	3	5-O*Me*	7.82	**N82**	NH	C(=O)	O	(*R*)-*Me*	H	5-F	8.16
N67	3	4-Cl	7.61	**N83**	NH	C(=O)	O	(S)-*Me*	H	5-F	8.32
N68	3	5-Cl	7.50	**N84**	NH	C(=O)	O	(*R*)-*Me*	H	7-F	8.27
N69	3	6-Cl	8.67	**N85**	NH	C(=O)	O	(S)-*Me*	H	7-F	9
N70	3	7-Cl	7.80								
N71	3	5-*Me*	7.97								
N72	3	7-*Me*	7.79								

umn 3 (Table 1a), column 4 (Tables 1d, f, g) and column 4 (Tables 1b, c)), outliers are: haldol (**N6**), 3-aminoethyl-1-tetralones derivatives **N38** and **N39**; (ii) serotonine 5HT2C (35 antipsychotics in the training set, the observed biological activity of compounds (pK_i)5HT2C are presented in col-

Table 1f Benzothiazepine derivatives (the observed biological activity of compounds was taken from Ref. [25] (upper subtable) and [24] (lower subtable))

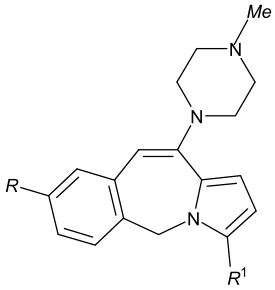


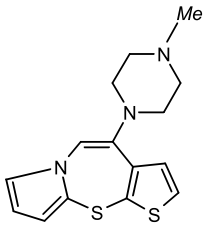
Nr.	Residue			pK_i5HT2-A	pK_iD2	pK_iD1	pK_iD3
	R	*n*	*R′*				
N86	Cl	1	*Me*	8.94	8.42	7.57	8.40
N87	H	1	*Me*	7.60	7.10	6.67	6.99
N88	F	1	*Me*	–	7.63	7.29	7.61
N89	Cl	1	*Et*	8.23	8.51	7.74	8.35
N90	Cl	1	CH_2 CH_2OH	8.06	8.23	7.57	8.44
N91	Cl	2	*Me*	7.27	7.53	7.27	–
N92	F	1	*Et*	8.36	8.02	7.51	7.74
N93	F	1	CH_2 CH_2OH	7.13	7.66	7.14	7.88
N94	Br	1	*Me*	7.92	8.44	7.84	8.44
N95	Br	1	*Et*	7.64	8.40	7.85	8.13
N96	Br	1	CH_2 CH_2OH	7.65	8.30	7.70	8.00
N97				–	–	8.64	8.62



Neuroleptic	Radical				pK_i5HT2-A	pK_iD2	pK_iD1	pK_iD3
	R	R^1	R^2	*X–Y*				
N98	Cl	2-(oxo-imidazolidinyl)*Et*	H	$CH–CH_2$	7.13	–	–	–
N99	H	*Me*	H	C=CH	9.18	7.76	7.70	8.08
N100	F	*Me*	H	C=CH	9.45	8.07	8.11	8.56
N101	Cl	*Me*	H	C=CH	9.46	–	–	8.69
N102	Br	*Me*	H	C=CH	9.08	9.34	–	–
N103	H	*Me*	CHO	C=CH	7.69	–	–	–
N104	H	*Me*	CH_2OH	C=CH	7.72	–	–	–
N105	H	*Me*	*Me*	C=CH	8.95	6.89	7.14	7.74

Table 1g Pyrrolobenzazepine derivatives (the observed biological activity of compounds was taken from Ref. [23])



Nr.	Residue		pK_i5HT2-A	pK_iD2	pK_iD1	pK_iD3
	R	R^1				
N106	H	H	8.13	6.23	6.90	6.64
N107	Cl	H	8.86	7.14	7.32	7.61
N108	H	*Me*	8.30	–	6.63	7.05
N109			8.66	8.07	8.30	7.60

umn 4 (Table 1a) and column 6 (Table 1d), outliers are: aripiprazole (**N1**), molindone (**N9**), sertindole (**N16**), and tetrahydrofuran derivative **N56**; (iii) dopamine D2 receptor (87 antipsychotics in the training set, the observed biological activity of compounds (pK_i)D2 is presented in column 4

Table 2a ANOVA results of the 2D-QSAR models with regard to interaction with dopamine D1–D4 and serotonine 5HT2A and 5HT2C receptors

Receptors	Q^2 (cross-validated r^2)	R^2		ANOVA results				
				df	SS	MS	*F*	Significance *F*
5HT2A	0.73	0.77	Regression	4	51.81	12.95	50.56	7.5E-19
			Residual	62	15.88	0.25		
			Total	66	67.69			
5HT2C	0.63	0.72	Regression	4	33.18	8.29	21.70	1.69208E-08
			Residual	30	11.46	0.38		
			Total	34	44.64			
D1	0.64	0.70	Regression	3	10.73	3.57	22.37	8.39992E-08
			Residual	30	4.79	0.15		
			Total	33	15.53			
D2	0.76	0.78	Regression	3	74.88	24.96	97.71	3.78211E-27
			Residual	83	21.20	0.25		
			Total	86	96.08			
D3	0.64	0.71	Regression	4	18.65	4.66	22.86	1.11E-09
			Residual	38	7.75	0.20		
			Total	42	26.41			
D4	0.68	0.75	Regression	3	12.44	4.14	25.50	8.91E-08
			Residual	25	4.06	0.16		
			Total	28	16.50			

Table 2b Coefficients, *p*-values and confidence limits (95%) of the 2D QSAR models with regard to interaction with dopamine D1–D4 and serotonine 5HT2A, 5HT2C receptor

Receptor	Descriptors	Coefficients	*p*-Value	Lower 95%	Upper 95%
5HT2A	Constant	9.552	9.26E-49	9.12	9.98
	PEOE_VSA + 1	−0.021	7.81E-08	−0.03	−0.01
	PEOE_VSA-4	0.023	0.001747	0.01	0.04
	SlogP_VSA4	−0.015	0.006946	−0.03	−0.004
	SMR_VSA2	−0.063	2.75E-12	−0.08	−0.05
5HT2C	Constant	11.637	1.62E-17	10.30	12.97
	Q_VSA_POS	0.012	7.74E-06	−0.02	−0.01
	SlogP_VSA4	−0.027	0.001	−0.04	−0.01
	SMR_VSA5	−0.012	0.0006	−0.02	−0.01
	E_{sol}	−0.020	0.000391	−0.03	−0.01
D1	Constant	8.958	5.43E-27	8.48	9.44
	PEOE_VSA + 1	−0.023	1.1E-06	−0.03	−0.02
	vsa_other	−0.045	6.67E-08	−0.06	−0.03
	SMR_VSA1	0.014	0.003978	0.004	0.02
D2	Constant	3.666	5.89E-09	2.54	4.79
	vsa_hyd	0.013	2.68E-11	0.01	0.02
	SlogP_VSA4	−0.050	2.58E-18	−0.06	−0.04
	SMR_VSA4	0.017	0.001	0.006	0.03
D3	Constant	3.374	3.07E-06	2.12	4.62
	PEOE_VSA + 1	−0.012	0.002	−0.02	−0.004
	Q_VSA_POS	0.005	0.024	0.00	0.01
	vsa_hyd	0.013	7.34E-07	0.01	0.02
	SMR_VSA1	0.009	0.079	−0.001	0.02
D4	Constant	16.741	6.23E-13	14.17	19.31
	SlogP_VSA8	0.007	0.020	0.00	0.01
	SMR_VSA5	0.011	4.45E-07	0.01	0.02
	ASA_H	−0.019	1.71E-08	−0.02	−0.01

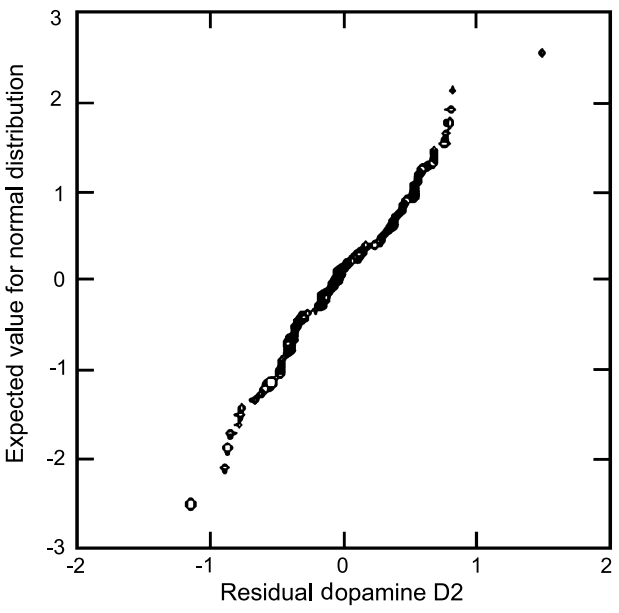


Fig. 1 Graphic representation of residual values *vs.* expected values for normal distribution of neuroleptics in interaction with dopamine D2 receptors

(Table 1e), column 5 (Tables 1a–d, g) and column 6 (Table 1f)), outliers are: clozapine (**N3**) and tetrahydrofuran derivatives **N52** and **N56**; (iv) dopamine D1 (34 antipsychotics in the training set, the observed biological activity of compounds (pK_i)D1 are presented in column 6 (Tables 1a, g) and column 7 (Tables 1d, f)), outliers are: **N6**, loxapine (**N7**), and benzothiazepine derivative **N102**; (v) dopamine D3 (43 antipsychotics in the training set, the observed biological activity of compounds (pK_i)D3 are presented in column 7 (Tables 1a, f, g) and column 8 (Table 1d)), outliers are: fluphenazine (**N4**) and benzothiazepine derivative **N91**; (vi) dopamine D4 (29 antipsychotics in the training set, the observed biological activity of compounds (pK_i)D4 are presented in column 8 (Table 1a) and column 6 (Table 1b)), outliers are benzamide derivatives **N30** and **N35**.

Coefficients, 95% confidence limits as well as ANOVA results of the best QSAR models using

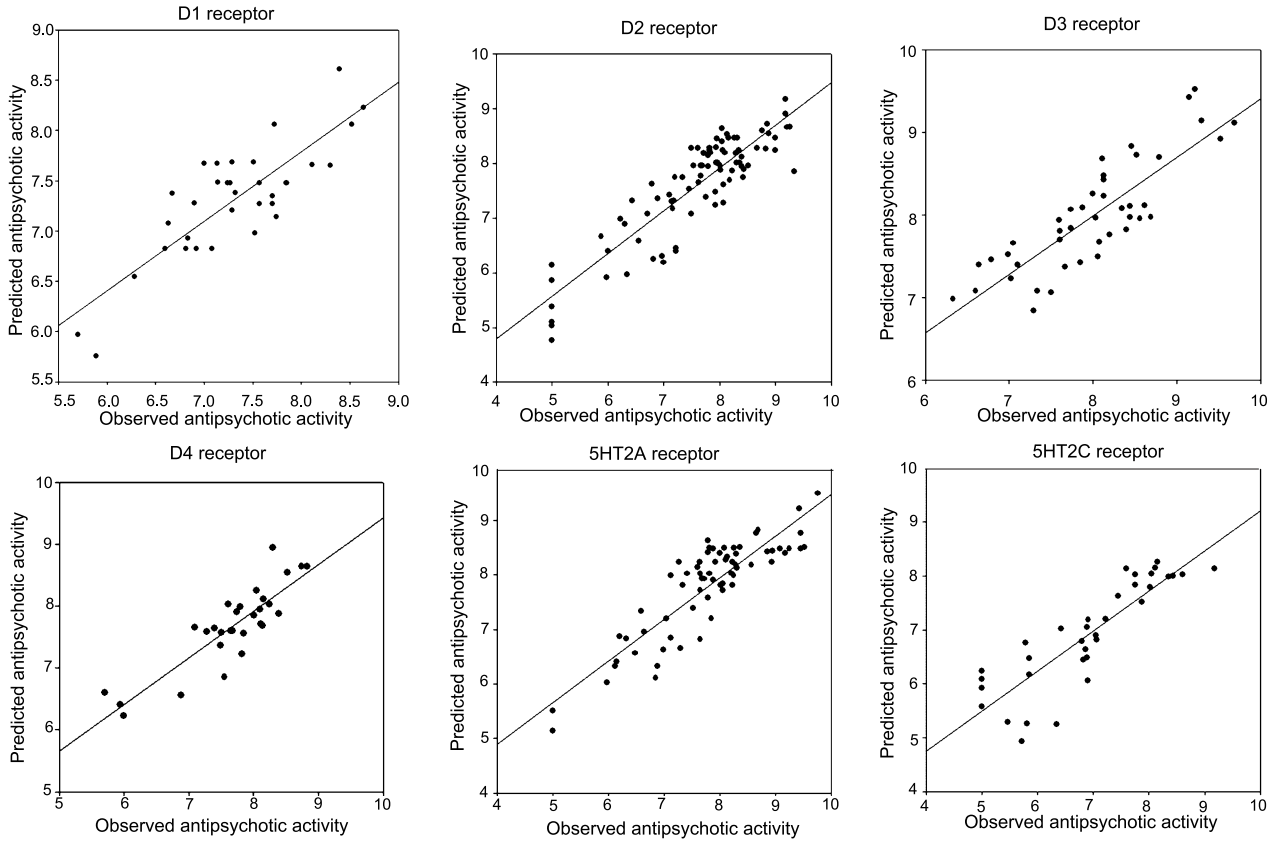


Fig. 2 The correlation between predicted and observed biological activity of neuroleptics in interaction with dopamine (D1–D4) and serotonine (5HT2A and 5HT2C) receptors

Table 3 The factor analysis performed for dopamine receptors D1–D4

Receptor	Rotated loading matrix				Eigenvalues			Explained variance (%)		
D1	Factor		1	2	FN	1	2	FN	1	2
	number (FN)					1.458	1.096		48.603	36.545
	PEOE_VSA + 1		0.813	−0.354						
	vsa_other		−0.029	0.969						
	SMR_VSA1		0.893	0.180						
D2	FN		1	2	FN	1	2	FN	1	2
	vsa_hyd		0.918	0.004		1.163	1.110		38.779	36.988
	SLOGP_VSA4		−0.565	0.480						
	SMR_VSA4		0.043	−0.937						
D4	(FN)		1	2	FN	1	2	FN	1	2
	SLOGP_VSA8		0.166	0.980		1.528	1.040		50.936	34.680
	SMR_VSA5		0.903	0.060						
	ASA_H		0.828	0.278						
D3	FN	1	2	3	FN 1	2	3	FN 1	2	3
	PEOE_VSA + 1	0.171	0.954	0.132	1.355	1.092	1.143	33.864	27.302	28.574
	Q_VSA_POS	0.764	−0.039	0.486						
	vsa_hyd	0.207	0.159	0.940						
	SMR_VSA1	0.836	0.394	0.072						

three to four descriptors, the *Fisher F* Statistics as well as the *Student*'s *p*-values are given in Tables 2a and b.

The MLR – calculations are showing that for each receptor domain a different set of descriptors was extracted from the system: (i) the hydrophobic descriptor SlogP, represented by SlogP_VSA4 (antagonist profile on serotonine 5HT2A and 5HT2C and also on dopamine D2 receptors) and SlogP_VSA8 (antagonist profile on dopamine D4 receptor) shows up within all domains with the exception of D1 and D3; (ii) the refractivity descriptor SMR is important for antipsychotic activity within all investigated receptor domains; (iii) the energy of solvation solely shows up within serotonine receptor domain 5HT2C; (iv) *van der Waals* area of hydrophobic substituents was important for the binding at dopamine receptors D1–D3 while the solvent accessible area is an important descriptor for the D4 receptor domain; and (v) electrostatic interaction of different types (POE_VSA + 1, POE_VSA-4, and QVSA_POS) seems to be important for the affinity at serotonine and dopamine D1–D3 receptors, but not for dopamine D2, D4 receptors. Predicted and observed inhibition properties of the data set within the domain of the investigated six receptors are grouped together in Fig. 2.

The best predictions of biological activity were obtained for: tetrahydrofuran derivative **N54** which blocks dopamine D1, (residual value = 0.01) and also serotonine 5HT2C receptors (residual value = 0.005) and **N51** which interacts with dopamine D2 receptor (residual value = 0.003); risperidone interacting with dopamine D3 receptor (residual value = 0.09), benzamide derivative **N22** interacting with D4 receptor (residual value = 0.02) and benzothiazepine

Table 4 Jackknived classification matrix and canonical discriminant function

Receptor	Group frequencies within the range of biological activity			% Correctly classified compounds (Jackknived method)			Canonical discriminant functions		
	1	2	3	1	2	3		1	2
5HT2A	23	35	9	>78	49	89	Constant	−1.815	−3.090
							PEOE_VSA + 1	0.010	0.060
							PEOE_VSA-4	−0.030	−0.006
							SLOGP_VSA4	0.037	0.004
							SMR_VSA2	0.114	−0.002
5HT2C	9	15	11	89	67	82	Constant	−9.096	−2.381
							Q_VSA_POS	0.025	0.003
							SLOGP_VSA4	0.049	−0.029
							SMR_VSA5	0.025	0.011
							E_{sol}	0.044	−0.043
D1	11	18	5	55	50	80	Constant	−4.255	−0.702
							PEOE_VSA + 1	0.064	0.033
							vsa_other	0.109	−0.051
							SMR_VSA1	−0.035	−0.016
D2	42	31	14	67	52	86	Constant	−3.567	−6.549
							vsa_hyd	0.014	0.017
							SLOGP_VSA4	−0.111	0.054
							SMR_VSA4	0.035	0.071
D3	8	25	10	75	72	90	Constant	8.363	−5.960
							PEOE_VSA + 1	0.042	0.007
							Q_VSA_POS	–	–
							vsa_hyd	−0.031	0.023
							SMR_VSA1	−0.058	−0.057
D4	13	13	3	62	54	100	Constant	23.448	4.617
							SLOGP_VSA8	0.017	0.031
							SMR_VSA5	0.026	−0.013
							ASA_H	−0.048	−0.005

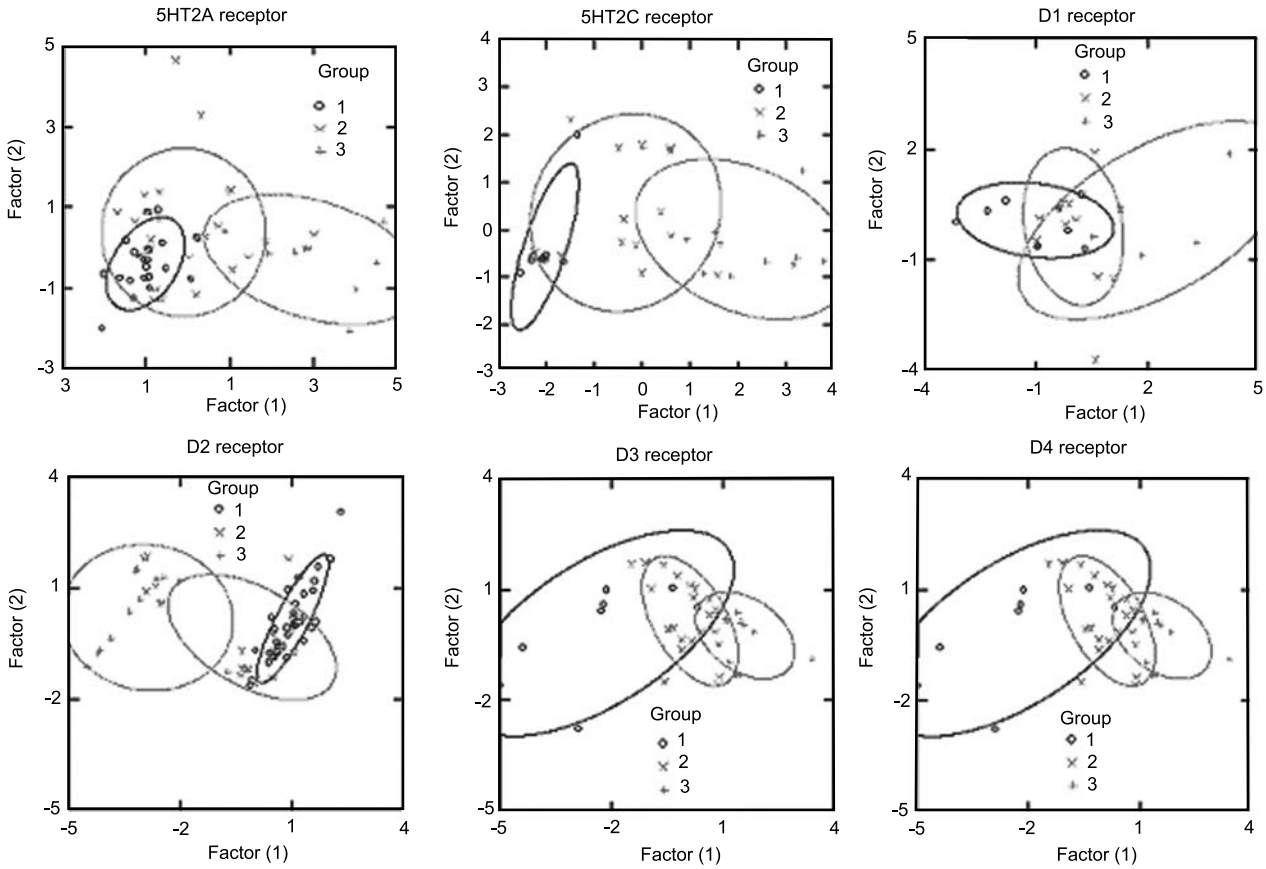


Fig. 3 The classification within the six receptors domains are visualized with the ''canonical scores plots''

derivative **N89** interacting with serotonine 5HT2A (residual value = 0.001).

Principal component analysis (PCA)

Further attempts were made to classify the molecules to active and inactive compounds by application of the principal component analysis on the descriptors data matrix. As summarized in Table 3, for the entire set of descriptors, the first two to three principal components (PCs) explain about 88% of variances in the descriptors data matrices. The varimax based PCs comprise the same set of descriptors, which was obtained by using the afore mentioned MLR – method, giving rise to the justified assumption that we are dealing with a relevant set of descriptors (Table 3).

Discriminant analysis (DA)

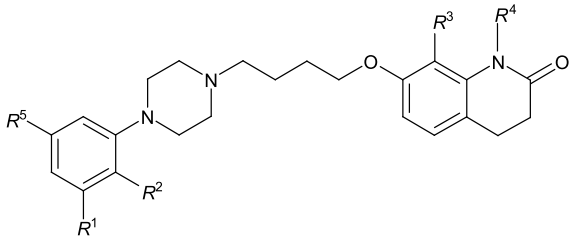
The Jackknived classification matrix and the canonical discriminant functions are summarized in Table 4.

The variables constituting the canonical discriminant functions are the same ones that were obtained by MLR – and PCA – analyses, thus giving us the opportunity to predict properly ranges of biological activity. The classification within the six receptors domains is visualized within the ''canonical scores plots'' (Fig. 3).

Novel structures of aripiprazole derivatives with enhanced antipsychotic profile

Due to their low affinities, the currently used atypical antipsychotics are suffering of the disadvantage of high dose administration with the exception of the partial agonist aripiprazole. With respect to the dopaminergic hypothesis of schizophrenia, a lot of chemical structures were proposed to act as antagonist at dopamine D2, D4, or D3 receptors. Presently, the major problem of using neuroleptics is governed by side effects that were already mentioned above. By using compounds with high affinity to the dopaminergic D3 receptor subtype (control of locomotion and motivation [43]), the above mentioned side effects, *i.e.*, extrapryamidal

Table 5 Biological activity pK_i and residual values (the biological activity for novel aripiprazole derivatives differences to the parent biological activity) (in the bracket) in interaction with dopamine D1–D4 receptors



Aripiprazole derivative	Substituent					pK_iD1	pK_iD2	pK_iD3	pK_iD4
	R^1	R^2	R^3	R^4	R^5				
M1	F	Cl	H	H	H	6.28 (0.58)	8.82 (−0.35)	8.79 (0.27)	7.13 (1.13)
M2	Br	Cl	H	H	H	6.07 (0.37)	9.06 (−0.11)	9.00 (0.48)	6.01 (0.01)
M3	allyl	Cl	H	H	H	5.77 (0.07)	9.08 (−0.09)	9.20 (0.68)	5.76 (−0.23
M4	O=C–NH_2	Cl	H	H	H	5.43 (−0.26)	7.56 (−1.61)	8.59 (0.07)	6.88 (0.88)
M5	Cl	Cl	allyl	H	H	5.76 (0.06)	9.39 (0.21)	9.45 (0.93)	5.59 (−0.40)
M6	Cl	Cl	*Et*	H	H	6.07 (0.37)	9.18 (0.01)	9.39 (0.87)	5.63 (−0.36)
M7	Cl	Cl	*i*-propyl	H	H	6.07 (0.37)	9.39 (0.21)	9.66 (1.14)	4.90 (−1.09)
M8	Cl	Cl	propyl	H	H	6.07 (0.37)	9.39 (0.21)	9.66 (1.14)	5.42 (−0.57)
M9	Cl	Cl	*t*-butyl	H	H	6.07 (0.37)	9.77 (0.59)	10.0 (1.56)	4.66 (−1.33)
M10	Cl	Cl	C_6H_5	H	H	5.56 (−0.13)	9.95 (0.77)	9.63 (1.11)	4.99 (−1.00)
M11	Cl	Cl	NH_2	H	H	5.76 (0.06)	8.73 (−0.44)	8.77 (0.25)	6.07 (0.07)
M12	Cl	Cl	OH	H	H	6.24 (0.54)	8.68 (−0.49)	8.99 (0.47)	6.46 (0.46)
M13	Cl	Cl	OH	*Et*	H	6.08 (0.38)	9.06 (−0.11)	9.75 (1.23)	5.42 (−0.57)
M14	Cl	Cl	H	*Me*	*Me*	6.07 (0.37)	9.11 (−0.06)	9.75 (1.23)	4.74 (−1.25)
M15	Cl	Cl	H	*Me*	O*Me*	5.33 (−0.36)	9.33 (0.15)	9.77 (1.25)	4.45 (−1.54)
M16	Cl	Cl	H	H	OH	5.84 (0.14)	8.68 (−0.49)	8.77 (0.25)	6.68 (0.68)
M17	Cl	Cl	H	H	O=C(NH_2)	5.47 (−0.22)	7.88 (−1.29)	8.86 (0.34)	6.15 (0.15)
M18	Cl	Cl	H	H	O=CH(NH)	5.76 (0.06)	9.41 (0.23)	9.25 (0.73)	6.21 (0.21)

syndrome, could be avoided: Aripiprazole shows high affinity to dopamine receptors as well as to serotonine – receptor subtypes [49].

Interestingly, it was discovered that the functional actions of aripiprazole at cloned human D2-dopamine receptors are cell-type selective, and that a range of actions (agonism, partial agonism, antagonism) at cloned D2-dopamine receptors are possibly depending of the cell type [49]. Due to the afore mentioned high importance of aripiprazole as a ''typical'' neuroleptic agent, we finally used a set of 18 potential new aripiprazole structures and calculated their theoretical binding constants by using our above presented equations (Table 5).

The reliably predicted neuroleptic activity at the membrane receptors allows us to design new aripiprazole derivatives which could be used as potential antipshychotics. In our opinion an important improvement of the antipsychotic activity could be obtained by facilitating the aripiprazoles membrane crossing as well as by generating more electrostatic contacts at the active site of the membrane receptors.

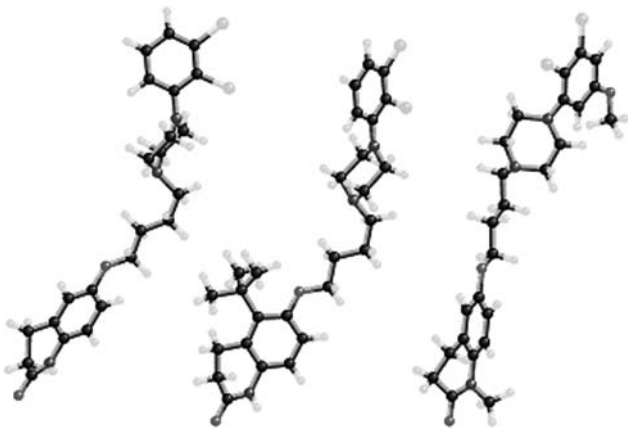


Fig. 4 Aripiprazole and its derivatives: left – aripiprazole, middle – aripiprazole **M9**, and right – aripiprazole **M9**

So, we enhanced the number of hydrophobic contacts of aripiprazole, by adding allyl, ethyl, *i*-propyl, propyl, *t*-butyl and C_6H_5 substituents as well as the number of hydrophilic contacts by adding halogen, hydroxyl, amino, or amide substituents. The calculated values are pointing to a real improvement of aripiprazole's activity within the D3 receptor for **M9** (pK_iD3 = 10.00, R^1 = Cl, R^2 = Cl, R^3 = *t*-butyl, R^4 = H, R^5 = H), **M13** (pK_iD3 = 9.75, R^1 = Cl, R^2 = Cl, R^3 = OH, R^4 = ethyl, R^5 = H), and **M15** (pK_iD3 = 9.77, R^1 = Cl, R^2 = Cl, R^3 = H, R^4 = *Me*, R^5 = O*Me*) (Fig. 4) There is no improvement for the aripiprazole **M14** (pK_iD4 = 4.74, R^1 = Cl, R^2 = Cl, R^3 = H, R^4 = *Me*, R^5 = *Me*) in interaction with D4 receptor and also for aripiprazole **M4** (pK_i = 7.56, R^1 = O = C–NH_2, R^2 = Cl, R^3 = H, R^4 = H, R^5 = H) in interaction with D2 receptor.

Conclusions

In our study, MLR-, Factor-Analyses, and Discriminant-Analyses were used to elucidate the most important physicochemical properties which are responsible for the binding properties of 109 antipsychotic agents out of different structural domains. An analysis of our QSAR results on neuroleptics interactions with various membrane receptors like dopamine D1–D4 and serotonine 5HT2A, 5HT2C brings up a number of points of interest. From a huge amount of possible variables three to four main descriptors for each receptor domain were extracted which are covering: hydrophobic and refractivity properties on subdivided Surface Areas (SlogP_VSA4, SlogP_VSA8, SlogP_VSA9 and SMR_VSA2, SMR_VSA5, SMR_VSA3, SMR_VSA4, SMR_VSA1, SMR_VSA7), electronic properties (PEOE_VSA + 1, PEOE_VSA-4, and 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. In agreement with the afore mentioned QSAR studies [44, 45], the important factors are hydrophobicity, refractivity, and also electronic properties. The influences of these descriptors to binding affinities could be laid down in four, respectively five QSAR equations. The results suggested that the lipophilicity is one of the most important parameters for the transport of the drug to the CNS. Thus the judicious modulation of the physicochemical properties, particularly lipophilic and electronic ones, may be very useful in designing new neuroleptic drugs. Considering the above set of 18 new potential aripiprazole structures, the established equations could be possibly used as a guidance to enhance or diminish K_i values according to the particular biological need. The comparable outcome of three different methodologies (MRLG, PCA, DA) gives rise to the justified assumption that we are dealing with sound correlations between structure and biological activity.

Methodology

The binding constants of 109 neuroleptically active compounds with regard to 4 dopamine (D1–D4) and 2 serotonine (5HT2A and 5HT2C) receptors were compiled out of Refs. [22–28, 46–53]. Although these constants are originating from different literature sources, they are mutually well comparable, which is shown with a few examples. Clozapine (pK_i5HT2A = 8. 26 [47], 8.00 [23–25], 8.20 [28], 8.04 [26]; pK_i5HT2C = 7.76 [47], 7.67 [28], 7.98 [26], pK_iD1 = 6.45 [23–25], 6.26 [28]; pK_iD3 = 7.10 [48], 6.61 [28], 6.50 [23–25], pK_iD2 = 6.59 [47], 6.60 [23–25], 6.84 [28], 6.65 [26]), or haldol (pK_iD2 = 8.39 [47], 8.60 [28], 8.32 [23–25], 9.00 [26], and 8.69 [27]). Thus, we had the possibility to combine the affinities data of different literature sources.

Our used set of compounds includes antipsychotics being already approved for clinical treatment (aripiprazole (**N1**), chlorpromazine (**N2**), clozapine (**N3**), fluphenazine (**N4**), fluphentixol (**N5**), haldol (**N6**), loxapine (**N7**), mesoridazine (**N8**), molindone (**N9**), olanzapine (**N10**), perhenazine (**N11**), pimozide (**N12**), quetiapine (**N14**), promazine (**N13**), risperidone (**N15**), sertindole (**N16**), thiothixene (**N17**), thioridazine (**N18**), trifluoperazine (**N19**), compazine (**N20**) and ziprazidone (**N21**)) [28, 46–53] as well as structurally new representatives in this domain, like: tetrahydrofuran (**N49**–**N56**) [28], benzamide (**N22**–**N35**) [27], 3-aminoethyl-1-tetralones (**N36**–**N48**) [26], piperazine (**N57**–**N85**) [22], benzothiazepine (**N86**–**N105**) [24, 25], and pyrrolobenzothiazepine (**N106**–**N109**) [23] derivatives. The list of studied compounds and 2D – structures are shown in Tables 1a–g.

The different data sets were selected due to the following criteria: (i) a large range of observed biological activities ($5 < pK_i < 9.76$) (ii) favorable pharmacokinetic properties covering the interactions with many subtypes of dopamine and serotonine receptors; and (iii) a big variety of substituents, covering as many as possible chemical classes of compounds.

Statistical calculations

Multiple linear regressions analysis (MLRA), principal component analysis (PCA) as well as discriminant analysis (DA) were used to select the descriptors in order to generate correlation models that relate the structural features to the inhibitory constants. The obtained equations consisting of three to four descriptors were calculated by use of SYSTAT-9 [54a] and MOE [54b] – software. It was

paid attention to high correlation coefficients (R) [55], low standard deviations (S) [55], and the least possible number of variables. In addition, the properties under consideration, in our case the K_i values, are shown to be normally distributed (Fig. 1).

To this end, feature selection was made objectively to eliminate these descriptors that provide minimal on redundant information. The correlation between biological activities and structural properties has been obtained by using the "backward" and "forward" variable selection of SYSTAT-9, which automatically selects the optimum number of descriptors and constructs the most relevant equation with highest predictive power. In proof of reliability, the set of equations was submitted to the "leave one out" technique and confirmed by the cross-validation coefficient Q^2 [2, 55].

Descriptors

There are preceding QSAR studies [64, 65] with the aim to model new structures with fewer side effects, such as extrapyramidal syndrome and tardive dyskinesia. Within these MLR studies *Verloop4* parameters [65], hydrophobic terms [65], lipophicility (RM and πR) [64], molar refractivity [64], partition coefficient water/octanol (logP) [64] or Subdivided Surface Area (SlogP_VSA8) [64], and globularity [64] were used.

In our study energy minimized conformations of typical and atypical antipshychotics were primarily established using the Maxim 2 minimization routine in *Sybyl* 7 [56] with the Tripos force field [56] and Conjugate-Gradient algorithm [57]. After having obtained the appropriate conformations the *Gasteiger-Marsili* partial charges of the compounds [58] were loaded on the chemical structures from the *Sybyl* 7 dictionary. These data were introduced to the MOE program where the calculation of the descriptors was performed. The emerging set of descriptors included both 2D and internal 3D ones.

Initially, a huge number of descriptors was calculated (200 MOE descriptors) like: (i) 2D descriptors including physical properties, subdivided surface areas, atom counts and bond counts, *Kier* and *Hall* connectivities [59, 60], kappa shape indices [61], adjacency and distance matrix descriptors [62], pharmacophore feature descriptors, and partial charge descriptors [58] and (ii) 3D molecular descriptors including potential energy descriptors, surface area, volume and shape descriptors, as well as conformation-dependent charge descriptors [63]. At the end, a set of descriptors was chosen, which was small enough to avoid redundancy and chance correlation, but large enough to allow an accurate validation of QSAR model (q^2- (cross-validated r^2) not less than 0.6, r^2 higher than 0.7 and number of principal components = 3). For different types of membrane receptors different combinations of the subsequently specified descriptors were used:

(i) Subdivided Surface Areas: SlogP_VSA4, SlogP_VSA8, SlogP_VSA9 (hydrophobicity descriptors, with L_i in different range) [54] and SMR_VSA2, SMR_VSA5, SMR_VSA3, SMR_VSA4, SMR_VSA1, SMR_VSA7 (refractivity descriptors with R_i in different ranges[54]). In MOE the descriptor based Subdivided Surface Areas are calculated on an approximate accessible *van der Waals* surface area for each atom, v_i along with some other atomic property, p_i. The v_i is calculated using a connection table approximation. Each descriptor in a series is defined to be the sum of the v_i over all atoms i such that p_i is in a specified range (a, b). In the descriptions to follow, L_i denotes the contribution to $\log P(o/w)$ for atom i as calculated in the SlogP descriptor. R_i denotes the contribution to molar refractivity for atom i as calculated in the SMR descriptor. The ranges were determined by a percentile subdivision over a large collection of compounds [54].

(ii) Partial Charges PEOE_VSA + 1, PEOE_VSA-4, PEOE_VSA-0, which are calculated according to the PEOE (Partial Equalization of Orbital Electronegativities method of *Gasteiger*). They are based on the iterative equalization of atomic orbital electronegativities and on Q_VSA_POS (positive *van der Waals* surface area), this is the sum of the v_i such that q_i is non-negative. The v_i are calculated using a connection table approximation [54].

(iii) Potential energy E_{sol} (Solvation energy).

(iv) Conformation-dependent charge ASA_H (Water accessible surface area of all hydrophobic ($|q_i| < 0.2$) atoms, q_i denote the partial charge of atom i).

(v) Pharmacophore feature vsa_hyd (Approximation to the sum of VDW surface areas of hydrophobic atoms).

Principal component analysis (PCA)

Using a large number of variables, one is dealing unavoidably with a lot of superfluous and overlapping information, which clearly turns out of the correlation matrix. The originally obtained correlation matrix was thus decomposed to a few principal components (also called factors), which are representing on their part a linear combination of the former variables. The varimax rotation algorithm was used to group related variables within one factor, thus giving the new (latent) variable a physical meaning.

Discriminant analyses

This type of statistical analysis is related to multiple regression analysis and provides a linear or quadratic function of the variables that "best" separate cases into two or more predefined groups. These groups (2 to 3) have to be established previously according to the values of the dependent variable (in our case pK_i) as: (i) dopamine D1 receptor: group 1 ($8.64 < pK_i < 7.58$), group 2 ($7.57 < pK_i < 6.64$), and group 3 ($6.63 < pK_i < 5.70$); (ii) dopamine D2 receptor: group 1 ($9.34 < pK_i < 7.90$), group 2 ($7.89 < pK_i < 6.46$), and group 3 ($6.45 < pK_i < 5$); (iii) dopamine D3 receptor: group 1 ($9.69 < pK_i < 8.57$), group 2 ($8.56 < pK_i < 7.45$), and group 3 ($7.44 < pK_i < 6.33$); (iv) dopamine receptor D4: group 1 ($8.82 < pK_i < 7.83$), group 2 ($7.82 < pK_i < 6.67$), and group 3 ($6.66 < pK_i < 5.70$); (v) serotonine receptor 5HT2A: group 1 ($9.76 < pK_i < 8.18$), group 2 ($8.17 < pK_i < 6.60$), and group 3 ($6.59 < pK_i < 5$); and (vi) serotonine receptor 5HT2C: group 1 ($9.18 < pK_i < 7.80$), group 2 ($7.79 < pK_i < 6.41$), and group 3 ($6.40 < pK_i < 5$).

The relevant variables can be selected in a "forward" or "backward" stepwise manner, either interactively or automatically by SYSTAT-9. Within a so-called "canonical scores plot", the compounds can be pictured within groups according

to their predefined activity. With the Jackknived classification, which can be seen as an approximate cross validation, the reliability of results was examined.

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