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Bioorganic & Medicinal Chemistry Letters 15 (2005) 2149–2157
Bioorganic & Medicinal Chemistry Letters

The role of QSAR in dopamine interactions

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Received 7 January 2005; revised 4 February 2005; accepted 4 February 2005
Available online 16 March 2005

Abstract—Dopamine receptor blockers have been used for the treatment of schizophrenia for many years. We have developed 22 quantitative structure activity relationships (QSAR) for different sets of compounds to understand chemical–biological interactions governing their activities toward dopamine receptors.

1. Introduction

Neuropsychiatric illnesses such as schizophrenia remain a serious and yet not fully resolved problem for emotional and cognitive functions. The symptoms are poor speech, lack of sociability, depression, psychosis and anxiety, which affect about 1% of the population. For many years dopamine receptor blockers have been used in the treatment for schizophrenia. Many articles have been published using 'structure–activity analysis' to improve our understanding of chemicals reacting with dopamine receptors. There are five dopamine receptors: D1, D2, D3, D4, and D5. We report here 22 QSAR studies on (previously published) dopamine receptor ligands.

2. Materials and methods

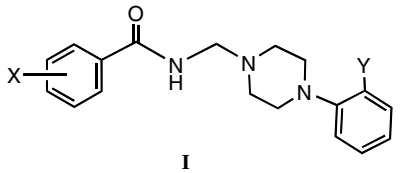
All the data have been collected from the literature (see individual QSAR for respective references). Physicochemical descriptors are auto-loaded, and multi-regression analyses (MRA) used to derive the QSAR were executed with the C-QSAR program.[1] The parameters used in this paper have already been discussed in detail along with their application.[2] Briefly, $C\log P$ is the calculated partition coefficient in octanol/water and is a measure of hydrophobicity, and π is the hydrophobic parameter for substituents. CMR is the calculated molar refractivity for the whole molecule. MR is calculated as we describe: $(n^2 - 1/n^2 + 2)(\mathrm{MW}/\delta)$, where n is the refractive index, MW is the molecular weight, and δ is the density of a molecule. MR is dependent on volume and polarizability. MR can be used for a substituent or for the whole molecule. There are three encountered electronic parameters: σ, σ^- and σ^+ that account for specific electronic effects of substituents on aromatic systems and known as Hammett parameters. B1 and B5 are Verloop's sterimol parameters for substituents. B1 is a measure of the width of the first atom of a substituent whereas B5 is an attempt to define width of the whole substituent. The indicator variable I is assigned the value of 1 or 0 for special features with special effects that cannot be parametrized and has been explained wherever used. Each regression equation includes 95% confidence limits for each term in parentheses.

In QSAR equations, n is the number of data points, r is the correlation coefficient, r^2 is the goodness of fit, q^2 is the goodness of prediction and s is the standard deviation. All the QSAR reported here are derived by us and were not given with the original data sets taken from the literature as referenced.

3. Results and discussion

3.1. Inhibition of human dopamine D4 receptor by I

Data from Glase et al.[3] (Table 1)



I

Keywords: Dopamine receptors; QSAR; Hydrophobicity; Molar refractivity; Verloop's sterimol parameters; Hammett parameters.
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doi:10.1016/j.bmcl.2005.02.012

Table 1. QSAR 1, 2, 3, and 4

	X	Y	log 1/K_i (Eq. 1)			log 1/K_i (Eq. 2)			log 1/K_i (Eq. 3)			log 1/K_i (Eq. 4)			$B1_{X,3}$	$B1_{X,4}$	$B5_{X,3}$	$B5_{X,4}$	*C*log *P*	$\sigma^+_{,Y}$
			Obsd	Pred	Δ	Obsd	Pred	Δ	Obsd	Pred	Δ	Obsd	Pred	Δ						
1	H	OMe	7.66	7.64	0.02	7.51	7.46	0.05	5.61	5.86	−0.25	5.73	5.92	−0.19	1.00	1.00	1.00	1.00	3.04	−0.78
2	H	Cl	7.49	7.40	0.10	6.97	7.18	−0.20	6.75	6.59	0.17	5.82	5.80	0.03	1.00	1.00	1.00	1.00	3.90	0.11
3	H	CN	7.57	7.67	−0.11	7.62	7.50	0.12	5.52	5.75	−0.23	5.38	5.35	0.02	1.00	1.00	1.00	1.00	2.91	0.66
4	3-Me	OMe	8.17	8.00	0.18	7.89	7.88	0.01	5.61	5.68	−0.07	6.08	6.04	0.04	1.52	1.00	2.04	1.00	3.54	−0.78
5	3-Me	Cl	7.57	7.73	−0.17	7.80	7.58	0.22	6.33	6.46	−0.12	5.88	5.93	−0.05	1.52	1.00	2.04	1.00	4.46	0.11
6	3-Me	CN	8.06	8.03	0.03	7.77	7.92	−0.15	5.55	5.57	−0.02	5.43	5.47	−0.05	1.52	1.00	2.04	1.00	3.41	0.66
7	4-Me	OMe	8.11	8.15	−0.03	8.47[a]	8.90	−0.43	6.76	6.28	0.48	6.54	6.49	0.04	1.00	1.52	1.00	2.04	3.54	−0.78
8	4-Me	Cl	7.92	7.89	0.03	6.66[a]	8.60	−1.93	7.31	7.06	0.25	6.33	6.39	−0.05	1.00	1.52	1.00	2.04	4.46	0.11
9	4-Me	CN	8.19	8.18	0.00	8.92	8.94	−0.02	6.42	6.17	0.25	5.94	5.93	0.01	1.00	1.52	1.00	2.04	3.41	0.66
10	3-Cl	OMe	7.82	7.76	0.06	7.82	8.05	−0.23	5.84	5.70	0.14	6.35	6.14	0.21	1.80	1.00	1.80	1.00	3.95	−0.78
11	3-Cl	Cl	7.39	7.50	−0.12	—	—	—	6.44	6.48	−0.05	5.62[a]	6.03	−0.41	1.80	1.00	1.80	1.00	4.88	0.11
12	3-Cl	CN	7.47[a]	7.80	−0.33	8.28	8.10	0.18	5.64	5.59	0.05	6.05[a]	5.57	0.47	1.80	1.00	1.80	1.00	3.82	0.66
13	4-Cl	OMe	7.85[a]	8.38	−0.53	8.46	8.39	0.06	6.57	6.63	−0.06	6.46	6.49	−0.03	1.00	1.80	1.00	1.80	3.95	−0.78
14	4-Cl	Cl	8.28	8.12	0.16	8.08	8.09	−0.02	7.18	7.41	−0.23	6.31	6.38	−0.07	1.00	1.80	1.00	1.80	4.88	0.11
15	4-Cl	CN	8.26	8.42	−0.16	8.41	8.43	−0.02	6.22	6.52	−0.30	6.03	5.92	0.11	1.00	1.80	1.00	1.80	3.82	0.66

[a] Data point not included in the derivation of Eqs. 1, 2 and 4.

$$\log 1/K_i = 0.48(\pm 0.24)B5_{X,3} + 1.25(\pm 0.36)B1_{X,4} - 0.28(\pm 0.15)C\log P + 6.77(\pm 0.66) \quad (1)$$

$n = 13$, $r^2 = 0.876$, $s = 0.129$, $q^2 = 0.701$

Outliers: X = 3-Cl, Y = CN; X = 4-Cl, Y = OMe.

The authors were trying to improve molecules for treating schizophrenia that had fewer side effects such as extra-pyramidal syndrome and tardive dyskinesia. The Verloop[4] parameters B5 and B1 are most significant. There is no high mutual correlation between $B1_{X,4}$ and $B5_{X,3}$ with respect to QSAR 1 ($r^2 = 0.354$, $q^2 = 0.157$).

3.2. Concentration increasing the uptake of [3H] thymidine by CHO cells expressing human dopamine D4 receptors by I

Data from Glase et al.[3] (Table 1)

$$\log 1/C = 1.12(\pm 0.45)B1_{X,3} + 1.54(\pm 0.37)B5_{X,4} - 0.33(\pm 0.23)C\log P + 5.79(\pm 0.96) \quad (2)$$

$n = 12$, $r^2 = 0.923$, $s = 0.166$, $q^2 = 0.825$

Outliers: X = 4-Me, Y = OMe; X = 4-Me, Y = Cl.

The interest was the same as in QSAR 1.

3.3. Inhibition of the binding of [3H] spiperone to human dopamine D2 receptors by I

Data from Glase et al.[3] (Table 1)

$$\log 1/K_i = -1.16(\pm 0.42)B1_{X,3} + 0.84(\pm 0.24) \times C\log P + 4.45(\pm 0.96) \quad (3)$$

$n = 15$, $r^2 = 0.864$, $s = 0.240$, $q^2 = 0.794$

3.4. Inhibition of the binding of [3H] spiperone to dopamine receptor D2 by I

Data from Glase et al.[3] (Table 1)

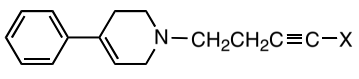
$$\log 1/K_i = 0.44(\pm 0.16)B5_{X,4} + 0.24(\pm 0.14)C\log P - 0.37(\pm 0.12)\sigma^+_{,Y} + 4.47(\pm 0.49) \quad (4)$$

$n = 13$, $r^2 = 0.933$, $s = 0.111$, $q^2 = 0.862$

Outliers: X = 3-Cl, Y = Cl; X = 3-Cl, Y = CN.

3.5. Binding affinity of II to dopamine D2 receptor from rat striatal membrane

Data from Glase et al.[5] (Table 2)



II

Table 2. QSAR 5

	X	log $1/K_i$ (Eq. 5)			*C*log *P*	CMR
		Obsd	Pred	Δ		
1	C_6H_5	6.55	6.54	0.01	4.95	9.41
2	4-OH–C_6H_4	7.27[a]	6.79	0.48	4.29	9.57
3	5-Indolyl	6.71	6.86	−0.15	4.94	10.53
4	4-Pyridinyl	7.49	7.48	0.02	3.46	9.20
5	3-Pyridinyl	7.43	7.48	−0.05	3.46	9.20
6	2-Pyridinyl	6.87[a]	7.40	−0.53	3.46	9.28
7	3-Quinolinyl	7.52	7.48	0.04	4.84	10.89
8	4-Isoquinolinyl	7.14[a]	7.59	−0.45	4.63	10.89
9	4-NH_2–C_6H_4	7.32	7.02	0.30	3.73	9.78
10	3-NH_2–C_6H_4	7.06	7.02	0.04	3.73	9.78
11	2-NH_2–C_6H_4	6.74	7.02	−0.28	3.73	9.78
12	2-NH_2-5-Pyridinyl	7.48	7.37	0.12	3.13	9.57
13	3-NH_2-6-Pyridinyl	7.20	7.34	−0.14	3.13	9.65
14	4-OMe–C_6H_4	6.49	6.49	0.00	4.87	10.03
15	3-$O(CH_2)_2O$–4-C_6H_3	6.90	6.82	0.07	4.88	10.47
16	5-Benzofuranyl	6.36	6.35	0.01	5.51	10.32

[a] Data point not included in the derivation of Eq. 5.

$$\log 1/K_i = -0.50(\pm 0.18)C\log P - 17.23(\pm 8.04)\mathrm{CMR} + 0.88(\pm 0.40)\mathrm{CMR}^2 + 93.41(\pm 40.13) \quad (5)$$

$n = 13$, $r^2 = 0.889$, $s = 0.162$, $q^2 = 0.821$

Outliers: X = $-C_6H_4$–4-OH, 2-pyridinyl, 4-isoquinolinyl.

Inversion point for CMR: 9.81 (9.55–9.97).

QSAR 5 is of special interest since it implies an allosteric reaction. That is, the receptor changes its shape[6] when CMR = 9.81. We have 109 such QSAR in our database (C-QSAR Program) on CMR and 125 based on *C*log *P*. With respect to QSAR Eq. 5, there is no high mutual correlation between *C*log *P* and CMR ($r^2 = 0.470$, $q^2 = 0.284$). Glase et al.[5] also evaluated the selected compounds **II** against human dopamine D3 and D4 receptors expressed in CHO K_1 cells. We derived QSAR 6 for the binding affinity of **II** to dopamine D4, but were unable to derive the same for dopamine D3.

3.6. Binding affinity of II to human dopamine D4 receptor

Data from Glase et al.[5] (Table 3)

$$\log 1/K_i = 3.02(\pm 1.52)\mathrm{MgVol} - 3.76(\pm 1.08) \quad (6)$$

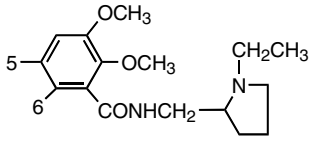
$n = 5$, $r^2 = 0.930$, $s = 0.061$, $q^2 = 0.835$

Table 3. QSAR 6

	X	log $1/K_i$ (Eq. 6)			MgVol
		Obsd	Pred	Δ	
1	3-Pyridinyl	6.17	6.20	−0.04	2.41
2	4-Pyridinyl	6.24	6.20	0.04	2.41
3	4-NH_2–C_6H_4	6.64	6.63	0.01	2.55
4	2-NH_2-5-Pyridinyl	6.56	6.50	0.05	2.51
5	3-NH_2-6-Pyridinyl	6.43	6.50	−0.07	2.51

3.7. Displacement of III from dopamine D2 receptor by [3H] spiperone

Data from Bishop et al.[7] (Table 4)



III

$$\log 1/C = 2.04(\pm 0.39)\mathrm{B1}_5 + 0.78(\pm 0.19)I + 5.15(\pm 0.59) \quad (7)$$

$n = 8$, $r^2 = 0.984$, $s = 0.101$, $q^2 = 0.967$

The indicator variable $I = 1$ for 6-OH. Many of such amides are inhibitors of dopamine and display potent dopamine D2 receptor side effects compared to haloperidol and butyrophenones.

3.8. Affinity of IV to dopamine D3 receptors

Data from Murray et al.[8] (Table 5)

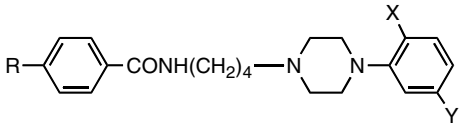
Table 4. QSAR 7

	Substituent	log $1/C$ (Eq. 7)			$B1_5$	I
		Obsd	Pred	Δ		
1	5-C_3H_6F	8.36	8.25	0.10	1.52	0.00
2	5-C_2H_4F	8.28	8.25	0.02	1.52	0.00
3	5-C_3H_6F, 6-OH	9.10	9.03	0.06	1.52	1.00
4	5-C_2H_4F, 6-OH	9.11	9.03	0.08	1.52	1.00
5	5-Br	9.12	9.13	−0.01	1.95	0.00
6	H	7.18	7.19	−0.01	1.00	0.00
7	5-C_3H_7	8.16	8.25	−0.10	1.52	0.00
8	5-C_3H_7, 6-OH	8.89	9.03	−0.14	1.52	1.00

Table 5. QSAR 8

	X	Y	R	pK_i (Eq. 8)			CMR
				Obsd	Pred	Δ	
1	H	H	Br	8.20	8.18	0.02	11.12
2	2′-OCH_3	H	Br	9.30[a]	8.43	0.87	11.73
3	2′-OCH_3	5′-OCH_3	Br	8.50	8.69	−0.19	12.35
4	2′-OCH_3	H	C_6H_4(4-$COCH_3$)	9.50	9.54	−0.04	14.43
5	2′-OCH_3	H	C_6H_4(4-SO_2CH_3)	9.50	9.70	−0.20	14.80
6	2′-OCH_3	H	C_6H_4(4-NH_2)	9.70	9.30	0.40	13.84

[a] Data point not included in the derivation of Eq. 8.



IV

$$pK_i = 0.41(\pm0.29)CMR + 3.60(\pm3.88) \quad (8)$$

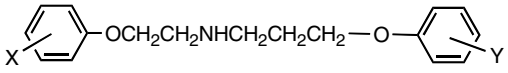
$n = 5$, $r^2 = 0.872$, $s = 0.281$, $q^2 = 0.744$

Outlier: X = 2′-OCH_3, Y = H, R = Br.

These compounds show a high affinity for dopamine D3 receptors, but low affinity for D1, D2, and D4 receptors. D3 shows its selective localization in the limbic areas of the brain, which suggests that D3 receptor might be an effective antipsychotic free from extrapyramidal side effects.

3.9. Binding affinity of V to cloned human dopamine D4 receptor via displacement of [3H] spiperone

Data from Unangst et al.[9] (Table 6)



V

$$\log 1/K_i = 0.77(\pm0.32)\pi_{X,4} - 1.65(\pm0.60)MR_{X,4} - 2.14(\pm0.41)MR_{Y,4} - 1.92(\pm0.44)B5_{X,2} + 11.78(\pm0.67) \quad (9)$$

$n = 20$, $r^2 = 0.927$, $s = 0.216$, $q^2 = 0.797$

Outlier: X = H, Y = H.

3.10. Binding affinity of V to cloned human dopamine D3 receptor via displacement of [3H] spiperone

Data from Unangst et al.[9] (Table 6)

$$\log 1/K_i = -2.06(\pm0.77)MR_{X,4} + 48.93(\pm17.75)CMR - 2.77(\pm1.00)CMR^2 - 207.87(\pm78.52) \quad (10)$$

$n = 13$, $r^2 = 0.883$, $s = 0.175$, $q^2 = 0.736$

Outliers: X = 4-Cl, Y = H; X = 3-Cl, 4-Me, Y = H; X = 3,4-Me_2, Y = H; X = H, Y = 4-Me.

3.11. Binding affinity of V to cloned human dopamine D2 receptor via displacement of [3H] spiperone

Data from Unangst et al.[9] (Table 6)

$$\log 1/K_i = -2.45(\pm0.51)MR_{X,4} - 1.39(\pm0.50)MR_{Y,4} + 8.04(\pm0.30) \quad (11)$$

$n = 16$, $r^2 = 0.912$, $s = 0.215$, $q^2 = 0.841$

Outliers: X = H, Y = H; X = 2-Cl, Y = H; X = 4-OH, Y = H; X = 4-Me, Y = 4-Me.

3.12. D2/D4 receptor binding selectivity of V

Data from Unangst et al.[9] (Table 6)

$$\log 1/K_i = -0.36(\pm0.29)\pi_{X,4} - 0.96(\pm0.40)MR_{X,4} + 0.77(\pm0.37)MR_{Y,4} + 7.07(\pm0.21) \quad (12)$$

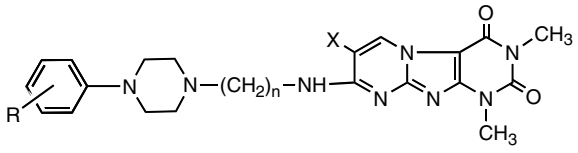
$n = 15$, $r^2 = 0.874$, $s = 0.148$, $q^2 = 0.739$

Outliers: X = 2-Cl, Y = H; X = 2-Me, Y = H; X = 4-OH, Y = H; X = 4-Cl, Y = 4-F; X = 4-Me, Y = 4-Me; X = 4-Me, Y = 4-Br.

A selective D4 receptor antagonist may show antipsychotic activity with a lower propensity for side effects. There is only one positive term in QSAR 9 so that increasing $\pi_{X,4}$ could yield more potent congeners.

3.13. Binding of VI to dopamine D2 receptor

Data from Jurczyk et al.[10] (Table 7)



VI

$$\log 1/K_i = 4.94(\pm2.54)C\log P - 0.58(\pm0.32) \times C\log P^2 - 3.65(\pm4.87) \quad (13)$$

Table 6. QSAR 9, 10, 11, and 12

	X	Y	log 1/K_i (Eq. 9)			log 1/K_i (Eq. 10)			log 1/K_i (Eq. 11)			log 1/K_i (Eq. 12)			$\pi_{X,4}$	$MR_{X,4}$	$MR_{Y,4}$	$B5_{X,2}$	CMR
			Obsd	Pred	Δ	Obsd	Pred	Δ	Obsd	Pred	Δ	Obsd	Pred	Δ					
1	H	H	8.70[a]	9.46	−0.77	6.87	6.72	0.14	6.60[a]	7.64	−1.04	6.90	7.05	−0.15	0.00	0.10	0.10	1.00	8.19
2	2-Cl	H	8.36	7.92	0.43	7.77	7.77	0.00	6.95[a]	7.64	−0.69	7.60[a]	7.05	0.55	0.00	0.10	0.10	1.80	8.69
3	2-Me	H	7.13	7.46	−0.33	—	7.75	—	7.70	7.64	0.05	9.57[a]	7.05	2.52	0.00	0.10	0.10	2.04	8.66
4	3-Cl	H	9.51	9.46	0.04	—	7.77	—	7.66	7.64	0.01	7.15	7.05	0.10	0.00	0.10	0.10	1.00	8.69
5	3-Me	H	9.34	9.46	−0.13	—	7.75	—	7.21	7.64	−0.43	6.88	7.05	−0.17	0.00	0.10	0.10	1.00	8.66
6	4-Me	H	9.28	9.13	0.15	6.77	6.80	−0.03	6.57	6.51	0.06	6.29	6.40	−0.11	0.56	0.56	0.10	1.00	8.66
7	4-OMe	H	8.27	8.32	−0.05	6.43	6.42	0.01	5.71	5.97	−0.26	6.44	6.40	0.04	−0.02	0.79	0.10	1.00	8.81
8	4-OH	H	8.51	8.65	−0.14	6.63	6.82	−0.19	6.25[a]	7.20	−0.94	6.75[a]	7.12	−0.37	−0.67	0.29	0.10	1.00	8.35
9	4-Cl	H	9.28	9.19	0.09	7.51[a]	6.74	0.76	6.64	6.42	0.22	6.37	6.31	0.06	0.71	0.60	0.10	1.00	8.69
10	4-NO_2	H	8.36	8.20	0.15	6.46	6.52	−0.06	5.85	6.09	−0.24	6.50	6.54	−0.04	−0.28	0.74	0.10	1.00	8.81
11	3-Cl–4-Me	H	9.28	9.13	0.15	8.41[a]	6.58	1.83	6.52	6.51	0.01	6.24	6.40	−0.16	0.56	0.56	0.10	1.00	9.15
12	3,4-Me_2	H	9.46	9.13	0.32	7.14[a]	6.63	0.51	6.84	6.51	0.33	6.39	6.40	−0.01	0.56	0.56	0.10	1.00	9.12
13	4-Cl	4-Me	8.25	8.20	0.05	6.75	6.50	0.25	5.88	5.77	0.11	6.63	6.67	−0.04	0.71	0.60	0.56	1.00	9.15
14	4-Cl	4-Br	7.42	7.51	−0.09	—	5.67	—	—	—	—	6.81	6.91	−0.10	0.71	0.60	0.89	1.00	9.46
15	4-Cl	4-F	9.08	9.21	−0.14	7.01	6.76	0.25	6.61	6.43	0.18	6.53[a]	6.30	0.23	0.71	0.60	0.09	1.00	8.70
16	H	4-Me	8.57	8.48	0.09	7.18[a]	7.75	−0.57	7.19	7.00	0.19	7.62	7.40	0.22	0.00	0.10	0.56	1.00	8.66
17	4-Me	2-Me	8.96	9.13	−0.18	6.42	6.63	−0.21	6.53	6.51	0.02	6.57	6.40	0.17	0.56	0.56	0.10	1.00	9.12
18	4-Me	3-Me	8.92	9.13	−0.21	6.72	6.63	0.09	6.53	6.51	0.02	6.61	6.40	0.21	0.56	0.56	0.10	1.00	9.12
19	4-Me	4-Me	7.96	8.15	−0.19	6.63	6.63	0.00	6.56[a]	5.87	0.69	7.60[a]	6.76	0.85	0.56	0.56	0.56	1.00	9.12
20	4-Me	4-Br	7.57	7.46	0.11	5.77	5.84	−0.07	5.24	5.42	−0.18	6.67[a]	7.01	−0.33	0.56	0.56	0.89	1.00	9.43
21	4-Me	4-F	9.02	9.16	−0.14	6.63	6.81	−0.18	6.41	6.53	−0.12	6.39	6.39	0.00	0.56	0.56	0.09	1.00	8.67

[a] Data points not included in the derivation of Eqs. 9–12.

Table 7. QSAR 13

	X	*n*	R	log $1/K_i$ (Eq. 13)			*C*log *P*
				Obsd	Pred	Δ	
1	H	2	3′-Cl	6.74	6.77	−0.03	3.83
2	H	2	2′-OCH_3	5.88	5.78	0.10	2.89
3	H	3	H	6.37	6.24	0.12	3.21
4	H	3	3′-Cl	7.03	6.87	0.16	4.10
5	H	3	2′-OCH_3	5.93	6.15	−0.22	3.14
6	Br	2	H	5.90[a]	6.77	−0.86	3.82
7	Br	2	3′-Cl	6.78	6.78	0.00	4.70
8	Br	2	2′-OCH_3	6.65	6.74	−0.09	3.76
9	Br	3	H	6.38[a]	6.87	−0.49	4.09
10	Br	3	3′-Cl	6.58	6.61	−0.03	4.97
11	Br	3	2′-OCH_3	6.49[a]	6.85	−0.36	4.01

[a] Data points not included in the derivation of Eq. 13.

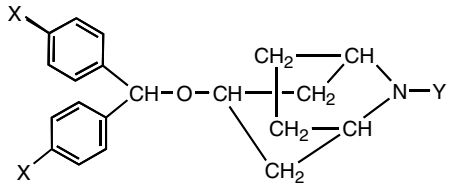
$n = 8$, $r^2 = 0.907$, $s = 0.148$, $q^2 = 0.784$,
optimum $C\log P = 4.27$ (4.09–4.77)

Outliers: X = Br, $n = 2$, R = H; X = Br, $n = 3$, R = H; X = Br, $n = 3$, R = 2′-OCH_3.

These compounds were tested on rats. They had marked anxiolytic-like activity in the Vogel test. The authors had deduced that more hydrophobic compounds should be more effective drugs. They varied *n* and R to achieve this goal. Since they did not employ QSAR, they did not realize that there was a limit to that objective.

3.14. Inhibition of dopamine uptake of receptor by VII

Data from Kulkarni et al.[11] (Table 8)



VII

$$\log 1/K_i = 3.35(\pm 1.42)C\log P - 0.36(\pm 0.17) \times C\log P^2 + 0.35(\pm 2.85) \quad (14)$$

$n = 10$, $r^2 = 0.895$, $s = 0.178$, $q^2 = 0.793$,
optimum $C\log P = 4.64$ (4.42–5.11)

Outliers: X = F, Y = $(CH_2)_4C_6H_5$; X = Cl, Y = CH_3; X = F, Y = $CH_2CH_2CH_2OC_6H_5$; X = F, Y = $(CH_2)_2$-OCH_2CH_2-N-morpholinyl.

QSAR 14 shows that the hydrophobicity of the molecules initially increases the inhibition activity of dopamine uptake up to an optimum $C\log P$ of 4.64 and then decreases. The authors compared these results with the binding at other receptors: SERT, DAT, NET and muscarinic M1. These compounds (**VII**) also showed good binding affinity at DAT with excellent selectivity over SERT, NET, and muscarinic receptors.

3.15. Binding of analogs of haloperidol to dopamine D2 receptor

Data from Lyles-Eggleston et al.[12] (Table 9)

$$\log 1/K_i = -82.47(\pm 39.67)\mathrm{CMR} + 4.10(\pm 1.95)\mathrm{CMR}^2 + 422.2(\pm 201) \quad (15)$$

$n = 5$, $r^2 = 0.984$, $s = 0.117$, $q^2 = 0.707$, inversion point: 10.07 (9.94–10.14)

$$\log 1/K_i = -3.73(\pm 1.91)C\log P + 23.31(\pm 7.82) \quad (16)$$

$n = 5$, $r^2 = 0.928$, $s = 0.184$, $q^2 = 0.639$

Outlier: compound 2.

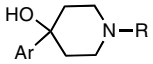
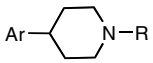
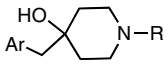
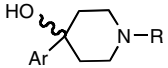
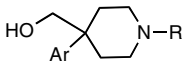
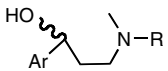
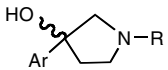
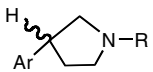
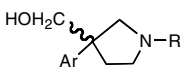
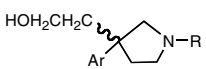
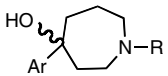
From the eleven data points of this data set, we were unable to derive a good QSAR due to the presence of six outliers, which is not acceptable. The presence of a large number of outliers may be due to their interaction with dopamine D2 receptor in a different mode. Thus, this data set was divided into two subsets on the basis of

Table 8. QSAR 14

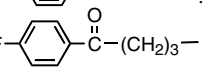
	X	Y	log $1/K_i$ (Eq. 14)			*C*log *P*
			Obsd	Pred	Δ	
1	F	CH_3	7.86	7.87	−0.01	3.81
2	F	$(CH_2)_4C_6H_5$	7.41[a]	6.66	0.75	6.64
3	Cl	CH_3	7.63[a]	8.08	−0.45	4.95
4	F	$CH_2CH_2OCH_2$-2-Thienyl	7.73	7.98	−0.25	5.26
5	F	$CH_2CH_2OCH_2C_6H_5$	7.65	7.77	−0.12	5.61
6	F	$CH_2CH_2CH_2OC_6H_5$	6.64[a]	7.46	−0.82	5.98
7	F	$CH_2CH_2OCH_2CH_2OH$	7.31	7.46	−0.15	3.29
8	F	$CH_2CH_2OCH_2CH_2$-N-Morpholinyl	6.18[a]	8.02	−1.84	4.12
9	F	$CH_2CH_2NH_2$	7.59	7.48	0.11	3.31
10	F	$CH_2CH_2NHCOC_6H_5$	8.19	8.11	0.08	4.76
11	F	$CH_2CH_2NHCH_2C_6H_5$	8.09	7.91	0.18	5.39
12	F	CH_2CH_2NHCO-3-Pyridyl	7.85	7.97	−0.13	4.01
13	F	$CH_2CH_2CONHC_6H_5$	8.30	8.07	0.23	5.00
14	Cocaine		6.63	6.58	0.05	2.57

[a] Data points not included in the derivation of Eq. 14.

Table 9. QSAR 15, 16, 17, 18, and 19

	Compound	log 1/K_i (Eqs. 15 and 16)					log 1/K_i (Eqs. 17 and 18)					log 1/K_i (Eq. 19)			*C*log *P*	CMR	MgVol
		Obsd	(Eq. 15)		(Eq. 16)		Obsd	(Eq. 17)		(Eq. 18)		Obsd	Pred	Δ			
			Pred	Δ	Pred	Δ		Pred	Δ	Pred	Δ						
1		9.05	—	—	8.97	0.08	8.34	8.31	0.03	—	—	7.98[a]	7.36	0.62	3.85	10.26	2.80
2		7.81[a]	—	—	2.34	5.47	7.34	—	—	7.32	0.02	7.59	7.56	0.03	5.63	10.11	2.74
3		8.10	—	—	8.12	−0.02	8.05	—	—	7.84	0.21	7.23[a]	6.89	0.34	4.08	10.72	2.94
4		7.62	—	—	7.45	0.17	7.11	6.96	0.15	—	—	6.91	6.89	0.02	4.26	10.72	2.94
5		7.81	—	—	7.78	0.03	6.96	7.26	−0.30	—	—	7.11	6.89	0.22	4.17	10.72	2.94
6		7.58	7.70	−0.12	—	—	6.79	6.80	−0.01	—	—	6.72	7.00	−0.28	4.31	10.44	2.91
7		7.48	7.42	0.06	—	—	6.70[a]	7.34	−0.64	—	—	7.98	7.84	0.14	4.14	9.80	2.66
8		7.81	7.86	−0.05	—	—	8.00	—	—	8.02	−0.02	7.82	8.04	−0.22	5.22	9.64	2.60
9		7.36	7.29	0.07	—	—	6.78	—	—	6.85	−0.07	7.62	7.36	0.26	3.61	10.26	2.80
10		7.64	—	—	7.90	−0.26	7.49	7.36	0.13	—	—	6.71	6.89	−0.18	4.14	10.72	2.94
11		8.96	8.92	0.04	—	—	8.07	—	—	8.21	−0.14	8.09[a]	6.89	1.20	4.41	10.72	2.94

Ar = 

R = 

[a] Data points not included in the derivation of Eqs. 16, 17, and 19.

Table 10. QSAR 20, 21, and 22

	R	R_1	*n*	log $1/K_i$ (Eq. 20)			log $1/K_i$ (Eq. 21)			log $1/K_i$ (Eq. 22)			*C*log *P*	CMR
				Obsd	Pred	Δ	Obsd	Pred	Δ	Obsd	Pred	Δ		
1	H	H	1	7.71	7.49	0.21	7.76	7.88	−0.11	8.08	8.15	−0.07	3.84	8.58
2	F	H	1	8.11	7.91	0.21	8.07	8.35	−0.28	8.57	8.50	0.06	4.01	8.59
3	Cl	H	1	8.72	8.57	0.15	9.37	9.19	0.17	8.70	9.11	−0.41	4.58	9.07
4	Br	H	1	8.47	8.45	0.02	9.35	9.11	0.24	9.60	9.03	0.57	4.73	9.35
5	H	CHO	1	5.37	5.42	−0.05	5.87	5.62	0.25	6.99	6.45	0.54	3.43	9.08
6	H	CH_2OH	1	5.76[a]	3.51	2.25	6.07[a]	3.48	2.59	6.95[a]	4.84	2.10	2.81	9.19
7	H	CH_2O–$CH(CH_3)_2$	1	5.12	5.08	0.03	5.42	5.54	−0.12	6.56	6.32	0.24	4.34	10.58
8	H	CH=N–OH	1	—	—	—	—	—	—	5.37	6.02	−0.65	3.63	9.69
9	H	CH_3	1	7.15	7.99	−0.84	6.90[a]	8.53	−1.63	7.74[a]	8.61	−0.87	4.34	9.04
10	Cl	H	2	8.23	7.97	0.26	8.46	8.61	−0.15	8.37	8.65	−0.28	4.67	9.53

[a] Data points not included in the derivation of Eqs. 20–22.

outliers and derived two Eqs. 15 and 16 with good statistics.[13]

Eq. 15 is based on only five data points. However, we have included it because it is a very sharp correlation defining an allosteric reaction. It is interesting that the inversion point of QSAR 15 is near that of QSAR 5. Apparently, the dopamine receptor undergoes a structural change rather easily.

3.16. Binding of haloperidol analogs to dopamine D3 receptor

Data from Lyles-Eggleston et al.[12] (Table 9)

$$\log 1/K_i = -3.31(\pm 1.86)C\log P + 21.07(\pm 7.70) \quad (17)$$

$n = 5$, $r^2 = 0.915$, $s = 0.208$, $q^2 = 0.827$

Outlier: compound 7.

$$\log 1/K_i = 11.39(\pm 8.5)C\log P - 1.21(\pm 0.91) \times C\log P^2 - 19.33(\pm 18.52) \quad (18)$$

$n = 5$, $r^2 = 0.945$, $s = 0.189$, $q^2 = 0.506$ optimum *C*log *P*: 4.72 (4.47–5.15)

This data set was also divided into two subsets due to the same reason as mentioned above, resulting in two QSAR Eqs. 17 and 18.

3.17. Binding of haloperidol analogs to dopamine D4 receptor

Data from Lyles-Eggleston et al.[12] (Table 9)

$$\log 1/K_i = -3.37(\pm 1.48)\mathrm{MgVol} + 16.78(\pm 4.18) \quad (19)$$

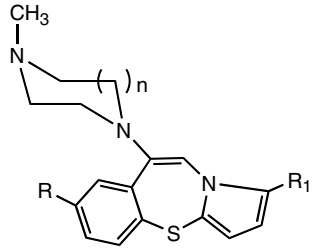
$n = 8$, $r^2 = 0.837$, $s = 0.221$, $q^2 = 0.688$

Outliers: compounds 1, 3, and 11.

3.18. Binding of VIII to dopamine D1 receptor

Data from Campiani et al.[14] (Table 10)

$$\log 1/K_i = 2.68(\pm 1.04)C\log P - 1.69(\pm 0.72)\mathrm{CMR} + 10.89(\pm 7.23) \quad (20)$$



VIII

$n = 8$, $r^2 = 0.925$, $s = 0.450$, $q^2 = 0.874$

Outlier: compound 6, Table 10.

The same compounds employed in QSAR 20 were tested by the same authors on the D2 receptor to yield QSAR 21.

$$\log 1/K_i = 3.09(\pm 0.49)C\log P - 1.73(\pm 0.34)\mathrm{CMR} + 9.85(\pm 3.37) \quad (21)$$

$n = 7$, $r^2 = 0.990$, $s = 0.194$, $q^2 = 0.946$

Outliers: compounds 6 and 9, Table 10.

Eqs. 20 and 21 are very similar. The same set was also tested on the D3 receptor to obtain QSAR 22.

$$\log 1/K_i = 2.33(\pm 1.10)C\log P - 1.36(\pm 0.81)\mathrm{CMR} + 10.11(\pm 8.61) \quad (22)$$

$n = 8$, $r^2 = 0.891$, $s = 0.535$, $q^2 = 0.682$

Outliers: compounds 6 and 9, Table 10.

Again, we see the same two parameters with slightly different coefficients.

4. Conclusion

An analysis of our QSAR results of dopamine interactions brings up a number of points of interest. On considering the most important factor, that is, hydrophobicity for this paper containing 22 individual

biological QSAR, only 7 QSAR lack the hydrophobic term. Nine QSAR (Eqs. 3, 4, 9, 13, 14, 18, 20, 21, and 22) have a positive hydrophobic term. The role of hydrophobicity is brought out by three QSAR (Eqs. 13, 14, and 18) where we get parabolic $C\log P$ term. Optimum $C\log P$ of these equations is 4.27, 4.64, and 4.72, respectively. It is interesting that Eqs. 5 and 15 bring out an allosteric reaction in terms of CMR that means, at first, activity declines as CMR increases, but then the exponential term takes over and activity begins to increase. This implies a change in the receptor structure or the binding mode. Verloop's parameters (B1 and B5) are also important parameters and present in six QSAR (Eqs. (1)–(4), (7), (and) (9)). The electronic parameter (σ^+) of substituents is present in one QSAR (Eq. 4). QSAR 13 is an encouraging example for dopamine D2 receptors, where we get a parabolic model in the $C\log P$ term. This means the binding activity of ligands **VI** to dopamine D2 receptor increases with the increase in hydrophobicity up to $C\log P = 4.27$ and then decreases. We believe that this will be the predictive model to narrow the synthetical challenges in order to yield very specific drugs. On the other hand, QSAR 6 and 19 suggest that MgVol of the compound should be important for the binding to dopamine D4 receptor.

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