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Quantitative structure activity relationships (QSAR) of substituded (*S*)-phenylpiperidines as preferential dopamine autoreceptor antagonists*

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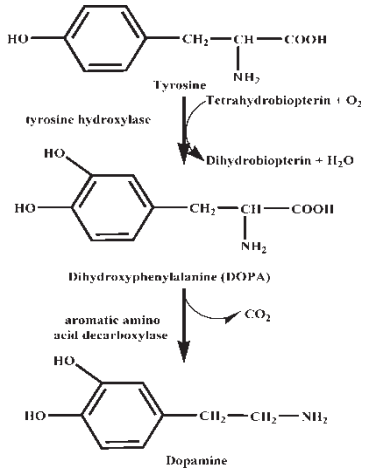
Abstract

A QSAR analysis for substituted (*S*)-phenylpiperidines as dopamine (DA) antagonists is described. The studied derivatives differ at the nitrogen substitutent (R) and at the substitutents (X) of the phenyl-ring. The analysis was done using the C-QSAR suite program (Biobyte) through the Internet. Clog *P*, CMR, M_{Vol}, B_1 and L (the Verloop's sterimol parameters for the substitutents) were used as parameters. In all the three studied cases clog *P* plays a significant part in the QSAR of DA antagonists, followed by the steric factors. In one case the electronic effect contributes significantly.

Keywords: *Quantitative structure activity relationships, (S)*-phenylpiperidines, dopamine antagonists, QSAR

Introduction

Dopamine (DA) is the major neurotransmitter within the mammalian central nervous system (CNS) and is biosynthesised from tyrosine. Tyrosine is taken up into the brain by a low-affinity amino acid transport system and subsequently from brain extracellular fluid into dopaminergic neurons by specific amino acid transporters. Once tyrosine has entered the neuron, it is first hydroxylated into L-DOPA. The cytosolic enzyme, tyrosine hyroxylase, catalyses this conversion and is normally the rate-limiting step in dopamine biosynthesis. Subsequently, aromatic amino acid decarboxylase



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Receptor subfamily	Location	Action	Therapeutic potential
Central			
D_1 and D_2	substantia nigra and striatum	motor control	agonists – Parkinson's disease
D_1 and D_2	limbic cortex and associated structures	information processing	antagonists – schizophrenia
D_2	anterior pituitary	inhibits prolactin release	agonists – hyperprolactinaemia
Peripheral			
D_1	blood vessels	vasodilatation	agonists – congestive
D_1	proximal tubule cells	natriuresis	heart failure and
D_2	sympathetic nerve terminals	decreases release	hypertension

Effects *mediated by dopamine receptor subfamilies, which have therapeutic potential.*[5]

(dopa-carboxylase) catalyses the cytosolic conversion of L-DOPA to dopamine.

DA mediates its neurochemical and physiological actions via membrane receptor proteins. DA receptors are found on postsynaptic neurons in brain regions that are DA-enriched. In addition, they reside presynaptically on DA neuronal cell bodies and dendrites in the midbrain as well as on their terminals in the forebrain. Stimulation of these 'autoreceptors' inhibits DA synthesis by blocking the activity of tyrosine hydroxylase, the rate-limiting enzymatic step in catecholamine synthesis [1,2].

All DA receptor proteins belong to a superfamily of large peptides that are coupled to G-proteins. There are at least five dopamine receptors (D_1, D_2, D_3, D_4, D_5) and they may be divided into two subfamilies whose pharmacological and biochemical properties resemble those of D_1 and D_2 receptors. The two subfamilies are often termed D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) receptors prossessing similarity (homology) of the amino acid sequences in the transmembrane domains [3]. D_1 receptors were characterized initially as mediating the stimulation of cAMP production. D_2 receptors, which inhibit the production of cAMP, were pharmacologically characterized based on the ability of only some DA agents to block adenylyl cyclase activity, and on the ability of catecholamines including DA to inhibit the release of prolactin *in vivo* and *in vitro* in a cAMP-independent fashion [4].

The D_1 receptors in the brain are linked to episodic memory, emotion, and cognition. Both D_1-like receptors (D_1, D_5) show a high affinity for benzazepine ligands which are selective antagonists for these subtypes. Thioxanthines and phenothiazines also show high affinity but are not selective for D_1-like over D_2-like receptors. The D_1-like receptors also show moderate affinities for typical dopamine agonists such as apomorphine [5].

The D_2-like receptors (D_2, D_3, and D_4) exhibit pharmacological properties similar to those of the D_2 receptor. The D_2-like receptors show high affinities for most of the drugs used to treat schizophrenia and Parkinson's disease. The distribution of the D_3 and D_4 receptors in limbic brain regions has made them particularly attractive targets for the design of potential selective antipsychotic drugs [5]

Dopamine *agonists* bind to dopamine receptors in place of dopamine and directly stimulate those receptors and some are currently used to treat Parkinson's disease, hyperprolactinaemia and congestive heart failure hypertension. These drugs can stimulate dopamine receptors even in someone without dopamine neurons. In contrast, dopamine *antagonists* bind but don't stimulate dopamine receptors and can prevent or reverse the actions of dopamine by keeping dopamine from attaching to receptors [6].

For the treatment of neurological diseases, a number of dopamine analogues (protoberberine alkaloids, tetrahydroisoquinolines, benzazepines and benzodiazepines) have been synthesised and tested for agonist and/or antagonist activities [4] (Figure 1).

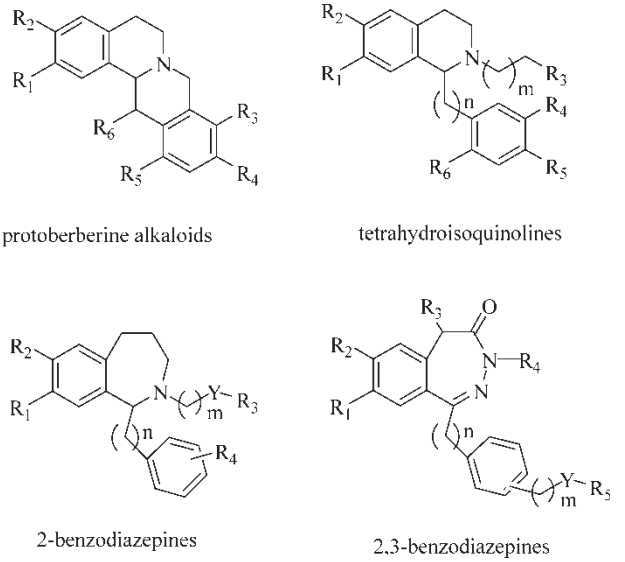

Figure 1. *Some dopamine analogues.*[4]

QSAR-reported results on dopamine antagonists

QSAR is a useful means for maximising the potency of a new lead compound. In the lead optimisation phase of the synthetic project, various QSAR procedures with the aid of computer technology have been used. Among them, the classical Hansch approach has been widely used leading to several successful examples. In the QSAR approach, the optimisation of the lead structure is inferred from mathematical equations correlating variations in physical organic properties in the congeneric molecules. Several researchers [7–9] have performed a small number of QSAR studies on all categories of dopamine receptor antagonists as follows.

1. A test series of 32 phenylpiperazines [7] (Figure 2) with affinity to 5-HT_{1A} and α_1 receptors was subjected to QSAR analysis using artificial neural networks (ANNs), in order to get insight into the structural requirements that are responsible for 5-HT_{1A}/α_1 selectivity. Good models and predictive power were obtained for 5-HT_{1A} and α_1 receptors. A comparison of both analysis gives an additional understanding for 5-HT_{1A}/α_1 selectivity: a) High *F* values increase the binding affinity for 5-HT_{1A} receptors and decrease the affinity for α_1 sites, b) the lipophilicity at the *meta* position is only influential for the α_1 receptor and c) the *meta* position seems to be implicated in 5-HT_{1A}/α_1 selectivity. A good way to improve 5-HT_{1A}/α_1 selectivity would be by the synthesis of long chain derivatives bearing bulky substitutents with high F values and low π values at the *meta* position [7].

2. A multiway 3D QSAR analysis by Nilsson *et al.* [8] using the multilinear PLS method was made for a set of (*S*)-*N*-[(-1-ethyl-2-pyrrodinyl)methyl]-6-methoxybenzamides (Figure 2), with affinity towards the dopamine D_2 receptor subtype. After exhaustive conformational analysis on the ligands, the active analogue approach was employed to align them in their

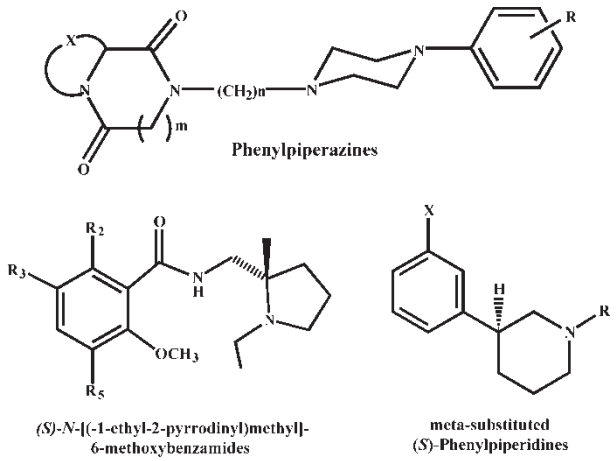

Figure 2. *QSAR analysed series.*

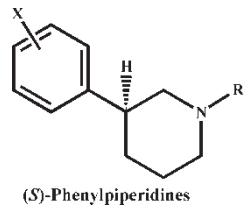

Figure 3. *QSAR analysed (S)-phenylpiperidines.*

presumed pharmacologically active conformations, using (−)-piquindone as a template. Descriptors were then generated in the GRID program, and 40 calibration compounds and 18 test compounds were selected by means of a principal component analysis in the descriptor space. The final model was validated with different types of cross-validation experiments. The cross-validated Q^2 was 62% for all experiments, confirming the stability of the model. The prediction of the test set with a predicted Q^2 of 62% also established the predicted ability [8].

3. A quantitative structure activity relationships study by Hansson *et al.* [9] (Figure 2) using partial least squares regression analysis (PLS) for a series of meta-substituted (*S*)-phenylpiperidines, has been described. For the computation of PLS regression models, SIMCA-S was used. All variables used in these computations were initially scaled to zero mean and unit variance (auto scaling). This was followed by an optimisation of the variable scaling to improve on the predictive properties of the models. The statistical significance of the models obtained was judged by their cross validated R^2 (cumulated Q^2 or R^2_{CV} based on PRESS statistics) using three different sizes of the cross validation groups.

Here for a series of substituted (*S*)-phenylpiperidines synthesized by Sonesson *et al.* [13]. A QSAR analysis has been done. The substituted compounds differ at the nitrogen substitutents (R) and at the substituetnts (X) of the phenyl-ring. (Figure 3)

QSAR methodology

Our analysis was done using the C-QSAR suite program (Biobyte) through the Internet [10]. Clog *P* is the calculated octanol/water partition coefficient for the whole molecule and π is the lipophilic contribution of the substitutent. Clog *P* applies to the neutral form of partially ionized compounds. B_1 and L are Verloop's sterimol parameters for the substitutents. Both are taken from the literature [11]. CMR is the calculated molar refractivity value for the whole molecule and it has been scaled by 0.1. σ_m the Hammet's electronic constant has been taken from the literature [12]. MgVol is the molar volume calculated by the methods of McGowan [10].

In all equations, n represents the number of data points, r the correlation coefficient, r^2 is the squared correlation coefficient, s is the standard deviation of

Table I. The parameters used to derive Equation (1).

No	X	R	Calcd.[a] log1/K_i	Δ log1/K_i	Obsd. log1/K_i	clog *P*	CMR	Ipr	L_3
1⋆	3-OH	n-Pr	5.76	1.24	7.00	3.33	6.74	1	2.74
2	3-OCH_3	n-Pr	5.79	−0.33	5.46	3.92	7.21	1	3.98
3	3-OCH_2CF_3	n-Pr	5.92	−0.14	5.78	4.71	7.72	1	5.23
4	3-OSO_2CH_3	n-Pr	5.47	−0.09	5.38	3.11	8.08	1	4.66
5	3-OSO_2CF_3	n-Pr	6.21	0.18	6.39	5.22	8.13	1	5.23
6	3-CO_2CH_3	n-Pr	5.73	−0.07	5.66	3.97	7.71	1	4.73
7⋆	3-CH_2OH	n-Pr	5.40	0.98	6.39	2.96	7.21	1	3.97
8	3-CN	n-Pr	5.51	0.43	5.94	3.43	7.07	1	4.23
9	3-NH_2	n-Pr	5.56	0.14	5.70	2.77	6.96	1	2.78
10	3-Br	n-Pr	6.25	0.02	6.27	4.86	7.37	1	3.82
11	3-$SO_2N(CH_3)_2$	n-Pr	5.60	−0.13	5.47	3.19	8.76	1	4.83
12	3-S-CH_3	n-Pr	6.11	−0.04	6.07	4.56	7.86	1	4.30
13	3-SO_2CH_3	n-Pr	5.27	−0.07	5.20	2.36	7.93	1	4.11
14	3-CH═O	n-Pr	5.65	0.30	5.95	3.35	7.09	1	3.53
15	3-CH_2CN	n-Pr	5.65	0.26	5.91	3.42	7.53	1	3.99
16	3-C≡CH	n-Pr	5.81	0.34	6.15	4.27	7.39	1	4.66
17	3-H	n-Pr	6.17	−0.34	5.83	4.00	6.59	1	2.06
18	3-CH_3	n-Pr	6.27	−0.24	6.03	4.50	7.05	1	2.87
19	3-(3-thienyl)	n-Pr	·	·	6.12	5.53	8.91	1	·
20	3-$COCH_3$	n-Pr	5.65	−0.47	5.18	3.44	7.55	1	4.06
21	3-$CH_2CH_2CH_3$	n-Pr	6.39	0.02	6.41	5.55	7.98	1	4.92
22	3-CN	H	5.02	0.55	5.57	1.93	5.68	0	4.23
23	3-CN	Me	5.29	−0.21	5.08	2.37	6.14	0	4.23
24	3-CN	Et	5.60	0.03	5.63	2.90	6.60	0	4.23
25	3-CN	i-Pr	5.82	0.32	6.14	3.21	7.07	0	4.23
26	3-CN	allyl	5.79	−0.07	5.72	3.15	7.04	0	4.23
27	3-CN	n-Bu	6.23	−0.02	6.21	3.96	7.53	0	4.23
28	3-CN	s-Bu	6.14	−0.16	5.98	3.74	7.53	0	4.23
29	3-CN	cyclopropylmethyl	5.96	−0.45	5.51	3.39	7.39	0	4.23
30	3-CN	2-phenylethyl	6.62	0.36	6.98	4.15	9.12	0	4.23
31	3-CN	3-phenylpropyl	6.93	0.17	7.10	4.68	9.58	0	4.23
32	3-CN	3-(2-ethyl)thiophene	6.84	0.15	6.99	4.77	8.92	0	4.23
33	3-CN	$(CH_2)_3N(CH_3)_2$	5.99	−0.36	5.63	2.75	8.83	0	4.23
34⋆	3-OSO_2CF_3	Me	6.00	−1.07	4.93	4.16	7.20	0	5.23
35	3-OSO_2CF_3	Et	6.31	−0.38	5.93	4.69	7.66	0	5.23
36	3-OSO_2CF_3	2-phenylethyl	7.33	0.07	7.40	5.93	10.17	0	5.23
37	2-OSO_2CF_3	n-Pr	6.81	0.23	7.04	4.82	8.13	1	2.06
⋆data omitted from the derivation of Equation (1); [a]calculated according to Equation (1)									
38[#]	4-OSO_2CF_3	n-Pr	6.98	−2.05	4.93	5.22	8.13	1	2.06
39[#]	3,4-di-OSO_2CF_3	n-Pr	7.08	−1.88	5.20	6.58	9.66	1	5.23

[#]data not included in Equation (1).

the regression equation, q^2 defines the cross-validated r^2 while *F* is the *F*-statistics-significance level. Each regression-equation also includes the 95% confidence limits for each term in the parentheses. For drugs acting as dopamine antagonists, lipophilicity should be an important property.

New QSAR results and discussion

a) In vitro binding data for D_2 receptors: [13]

The compounds were tested for their *in vitro* binding affinity to the rat striatial D_2 receptors utilizing [3H]-spiperone as ligand (Table I). The K_i values represent the displacement of the dopamine D_2 receptor antagonist spiperone. From these data we have formulated correlation 1:

$$\begin{aligned}\log 1/K_i = {} & 0.411(\pm 0.133)\,\text{clog}\,P \\ & + 0.201\,(\pm 0.139)\,\text{CMR} \\ & - 0.410\,(\pm 0.219)\,I_{pr} \\ & - 0.243\,(\pm 0.144)\,L_3 + 4.110\,(\pm 0.948)\end{aligned} \quad (1)$$

$$n = 33,\ r = 0.889,\ r^2 = 0.791,\ q^2 = 0.702,\ s = 0.285,\ F_{4,28} = 26.446,\ \alpha = 0.01,$$

$$F_{1,31} = 38.924,\ \alpha = 0.01,\ F_{1,30} = 9.626,\ \alpha = 0.01,\ F_{1,29} = 6.388,\ \alpha = 0.05,\ F_{1,28} = 8.798,\ \alpha = 0.01$$

clog *P* ⟩ I_{pr} ⟩ L_3⟩ CMR (order for parameter significance)

Correlation Matrix

Parameters	clog *P*	CMR	I_{pr}	L_3
clog *P*	·	0.383	0.039	0.033
CMR	·	·	0.000	0.108
I_{pr}	·	·	·	0.056
L_3	·	·	·	·

From the stepwise development of Equation (1), it seems that the lipophilicity and the steric effects play an important role. Lipophilicity is the most significant term, followed by indicator variable I_{pr}. I_{pr} is an indicator variable for the examples where a propyl group is present at the nitrogen atom of the piperidinyl group. The presence of the N-propyl group does not improve the antagonistic activity (negative sign). L_3 represents the length of the first atom of the substitutent at the 3-position of the phenyl-ring (Verloop's sterimol parameter). I_{pr} and L_3 indicate that steric interactions at the 3-position of the aromatic ring and at the nitrogen of the piperidinyl ring are unfavorable. No parameterization has been done for the rest of the R substituents on the nitrogen (except for the propargyl). However they all fit the pattern of QSAR 1. In the above equation CMR refers to the overall molar refractivity:

$$\mathrm{CMR} = [(n^2 - 1)/(n^2 + 2)] \cdot \mathrm{MW/d}$$

Since the refractive index (n) of organic compounds slightly varies, CMR is primarily a measure of volume with a small component of polarizability, the positive coefficient suggesting that in an approximate way the larger that CMR is the higher the affinity of the compounds to rat striatial D_2 receptors. The whole molecule with its substitutents does appear to reach a hydrophobic surface. The correlation matrix shows that CMR, L_3, I_{pr} and clog *P* are reasonably independent vectors. This data set is not ideal for exploration of electronic effects ($r = 0.005$). We tried to improve Equation (1) by removing derivatives **1**, **7**, and **34**, which behave as outliers. Compounds **1** and **7** are the only OH derivatives and it seems that the presence of a phenyolic –OH (3-OH, **1**) or of a CH_2OH group (**7**) in position-3 does not increase the biological response. In this analysis we did not include compounds **38** and **39**. Since compound **38** is the only analogue with a 4- substitutent and **39** the only one with 3-,4- substitution. An attempt to include both compounds in the derivation of Equation (1) did not give a better correlation. Under the circumstances of our analysis both compounds were found to be outliers. It is possible that both compounds present their biological response through a definite "different mode" and thus there is a need for some more 3-,4- and 4- analogues in order to have better defined results.

b) In vitro binding data for D_3 receptor: [13]

The K_i values represent the displacement of the dopamine receptor D_3 antagonist [^{3}H]-spiperone. Data were obtained from cloned mammalian receptors and the correlation is derived for them (Table II):

$$\begin{aligned}\log 1/K_i = {} & 0.508(\pm 0.166)\,\mathrm{clog}\,P \\ & - 0.007\,(\pm 0.003)\,\mathrm{MgVol} \\ & + 1.107\,(\pm 0.501)\sigma_m \\ & + 0.338\,(\pm 0.153)\,\mathrm{MR_{-R}} \\ & + 5.186\,(\pm 0.456) \qquad (2)\end{aligned}$$

$n = 26,\ r = 0.919,\ r^2 = 0.844,\ q^2 = 0.753,$
$s = 0.249,\ F_{4,21} = 28.392,\ \alpha = 0.01$

$F_{1,24} = 26.673,\ \alpha = 0.01,$
$F_{1,23} = 4.398,\ \alpha = 0.05,\ F_{1,22} = 5.389,\ \alpha = 0.05,$
$F_{1,21} = 21.147,\ \alpha = 0.01$

$\mathrm{MR_{-R}} \rangle$ clog *P* $\rangle$ MgVol $\rangle$ σ_m(order for parameter significance)

Correlation Matrix

Parameters	clog *P*	MgVol	MR_{-R}	σ_m
clog *P*	·	0.482	0.001	0.054
MgVol	·	·	0.131	0.054
MR_{-R}	·	·	·	0.044
σ_m	·	·	·	·

From the stepwise development of Equation (2), it seems that the molar refractivity MR of the substitutent R rationalizes 53.6% of the variance in the data, followed by clog *P* (theoretically overall calculated lipophilicity). The fact that clog *P*has been used to model hydrophobicity, implies that for all the parts whose substitutents have been entered, hydrophobic contacts have been made. The positive coefficient with MR_{-R} suggests that in an approximate way the larger that R is the higher the displacement of the dopamine receptor D_3 antagonist [^{3}H]-spiperone. The contribution of the molar volume MgVol is negative (MgVol is a measure of the bulk of the whole molecule). The larger that MgVol is the lower the displacement of the D_3 antagonist [^{3}H]-spiperone. The electronic effect, as the σ_m Hammet constant for the X-substituent at the *m*-position of the phenyl-ring slightly ($r^2 = 0.157$) contributes to Equation (2). We had to remove four compounds (**1**, **13**, **19**, **21**) to derive Equation (2). Although the correlation was not exceedingly sharp, compound **1** is the only derivative with a 3-OH group. For compound **13** (Table II) the observed value is

Table II. The parameters used to derive Equation (2).

No	X	R	Calcd.[a] log1/Ki	Δ log1/K_i	Obsd. log1/K_i	clog *P*	MgVol	σ_m	MR_{-R}
1*	3-OH	n-Pr	6.08	0.80	6.88	3.33	219.36	0.12	1.50
2	3-OCH_3	n-Pr	6.28	−0.40	5.88	3.92	233.39	0.12	1.50
3	3-OCH_2CF_3	n-Pr	·	·	5.85	4.71	301.39	·	1.50
4	3-OSO_2CH_3	n-Pr	5.75	0.26	6.01	3.11	297.46	0.39	1.50
5	3-$OSO_2C_6H_4CH_3$	n-Pr	·	·	7.04	5.44	373.56	·	1.50
6	3-OSO_2CF_3	n-Pr	·	·	7.17	5.22	351.43	·	1.50
7	3-CH_2OH	n-Pr	5.67	0.17	5.84	2.96	233.39	0.00	1.50
8	3-CN	n-Pr	6.56	0.04	6.60	3.43	228.37	0.56	1.50
9	3-Br	n-Pr	6.74	0.03	6.77	4.86	282.25	0.39	1.50
10	3-$SO_2N(CH_3)_2$	n-Pr	·	·	6.77	3.19	310.51	·	1.50
11	3-S-CH_3	n-Pr	6.54	0.32	6.86	4.56	249.46	0.15	1.50
12	3-SO_2CH_3	n-Pr	5.71	0.17	5.88	2.36	281.46	0.60	1.50
13*	3-CH═O	n-Pr	6.27	0.81	7.08	3.35	231.37	0.35	1.50
14	3-CH_2CN	n-Pr	6.02	0.27	6.29	3.42	242.40	0.16	1.50
15	3-C≡CH	n-Pr	6.60	−0.13	6.47	4.27	227.38	0.21	1.50
16	3-H	n-Pr	6.39	−0.28	6.11	4.0	203.36	0.00	1.50
17	3-CH_3	n-Pr	6.47	−0.23	6.24	4.50	217.39	−0.07	1.50
18	3-(3-thienyl)	n-Pr	6.66	0.45	7.11	5.53	285.49	0.03	1.50
19*	3-$COCH_3$	n-Pr	6.25	−0.58	5.67	3.44	245.40	0.38	1.50
20	3-$CH_2CH_2CH_3$	n-Pr	6.83	0.24	7.07	5.55	245.45	−0.07	1.50
21*	3-CN	H	5.60	0.60	6.20	1.93	186.28	0.56	1.50
22	3-CN	Me	5.89	−0.13	5.76	2.37	200.31	0.56	1.50
23	3-CN	Et	6.22	0.07	6.29	2.90	214.34	0.56	1.50
24	3-CN	i-Pr	6.44	0.13	6.57	3.21	228.37	0.56	1.50
25	3-CN	allyl	6.45	−0.27	6.18	3.15	226.35	0.56	1.56
26	3-CN	s-Bu	6.78	0.20	6.98	3.74	242.40	0.56	1.96
27	3-CN	cyclopropylmethyl	6.55	−0.27	6.28	3.39	240.38	0.56	1.79
28	3-CN	2-phenylethyl	7.20	0.03	7.23	4.15	290.44	0.56	3.51
29	3-CN	3-phenylpropyl	7.53	−0.09	7.44	4.68	304.47	0.56	3.98
30	3-CN	3-(2-ethyl)thiophene	7.41	−0.16	7.25	4.77	296.47	0.56	3.32
31	3-OSO_2CF_3	2-phenylethyl	7.55	0.17	7.72	5.93	413.50	0.79	3.51
32	2-OSO_2CF_3	n-Pr	5.83	−0.32	5.51	4.82	351.43	0.00	1.50
33	4-OSO_2CF_3	n-Pr	6.04	−0.09	5.95	5.22	351.43	0.00	1.50
34	3,4-di-OSO_2CF_3	n-Pr	6.64	−0.17	6.47	6.58	499.50	0.79	1.50

*data omitted from the derivation of Equation (2); [a]calculated using Equation (2).

higher than the predicted affinity while that for compound **19** is overestimated.

c) In vitro binding data for 5-HT_{1A} receptors: [13]

The K_i values represent the *in vitro* binding affinity of the compounds at 5-HT_{1A} using rat striatal membrane and [^{3}H]-8-OH-DPAT as ligand (Table III). From these data Equation (3) has been formulated.

$$\begin{aligned}\log 1/K_i = &-1.341(\pm 0.740)\,\mathrm{clog}\,P \\ &+ 0.231(\pm 0.095)\,\mathrm{clog}\,P^2 \\ &+ 0.190(\pm 0.181)\,MR_{-X-3} \\ &+ 0.224(\pm 0.138)\,MR_{-R} \\ &+ 6.697(\pm 1.345)\end{aligned} \qquad (3)$$

optimum clog *P* 2.906 (±0.522) from 2.191 to 3.235

$n = 30,\ r = 0.916,\ r^2 = 0.839,\ q^2 = 0.752,$
$s = 0.275,\ F_{4,25} = 32.663,\ \alpha = 0.01,$

$F_{1,25} = 4.639,\ \alpha = 0.05,\ F_{1,26} = 7.398,\ \alpha = 0.05,$
$F_{1,27} = 41.692,\ \alpha = 0.01$

$MR_{-R} \rangle$ clog $P \rangle MR_{-X-3}$ (order for parameter significance)

The ± data, within parenthesis associated with the coefficient of MR_{-X-3} in Equation (3) is not within permissible limits of statistical significance thus we had to reject this equation. The replacement Equation (4) was derived which included the clog *P*(parabolic model) parameter and MR_{-R}.

$$\begin{aligned}\log 1/K_i = &-1.249\,(\pm 0.916)\,\mathrm{clog}\,P \\ &+ 0.218\,(\pm 0.118)\,\mathrm{clog}\,P^2 \\ &+ 0.284\,(\pm 0.150)\,MR_{-R} \\ &+ 6.634\,(\pm 1.658)\end{aligned} \qquad (4)$$

$n = 31,\ r = 0.879,\ r^2 = 0.772,\ q^2 = 0.699,$
$s = 0.288,\ F_{3,27} = 30.545,\ \alpha = 0.01,$

$F_{1,27} = 15.071,\ \alpha = 0.01,\ F_{2,28} = 25.478,\ \alpha = 0.01$

optimum clog *P* 2.860 (±0.821) from 1.632 to 3.274

Correlation Matrix

parameters	clog *P*	MR_{-R}	MR_{-X-3}
clog *P*	·	0.001	0.128
MR_{-R}	·	·	0.001
MR_{-X-3}	·	·	·

Molar refractivity MR for substitutents R is the most significant term. Hydrophilicity should be taken into consideration as an important variable for this dataset (clog *P* with negative sign). The optimum hydrophobic character is very close to the value reported for the anticonvulsant activity [14] and to the log P_o value of benzene-boronic acids [15] estimated for penetration into the mouse brain. No term appears for the nitrogen piperidinyl-substituents. Adding a term in σ to Equation (3) does not improve the correlation so that the electronic effect appears unimportant. The parameters are reasonably orthogonal.

Two compounds **5** and **6** have been omitted which are less active than predicted. Equation (4) is not sharp in terms of r (0.879) but gives some information for the physicochemical properties implicated in this biological response.

General conclusions

Our study shows that in all the three studied cases clog *P* plays a significant part in the QSAR of DA antagonists. Although the substituents variation are not nearly as good as they should be, it appears that most of the molecules must be interacting with a hydrophobic portion of the receptor. Kaufman and Koski (1975) [16] concluded after several physicochemical, quantum mechanical and other theoretical studies that the pharmacological effectiveness of CNS agents is governed by lipophilicity and by the topographical and electronic structures of the pharmacophore.

The existence of linear correlations between activity and log *P* (Equations 1, 2) simply suggests that log *P* values were not great enough to establish the upper limit for the rate of penetration. Early on, QSAR and SAR analysis seemed to depend heavily on their relative

Table III. The parameters used to derive Equation (4).

No	X	R	Calcd.[a] $\log 1/K_i$	Δ $\log 1/K_i$	Obsd. $\log 1/K_i$	clog *P*	MR_{-R}	MR^{b}_{-X-3}
1	3-OH	n-Pr	5.38	−0.28	5.10	3.33	1.50	0.29
2	3-OCH_3	n-Pr	5.62	−0.18	5.44	3.92	1.50	0.79
3	3-OCH_2CF_3	n-Pr	6.13	−0.21	5.92	4.71	1.50	1.20
4	3-OSO_2CH_3	n-Pr	5.32	0.54	5.86	3.11	1.50	1.70
5*	3-$OSO_2C_6H_4CH_3$	n-Pr	6.78	−0.98	5.80	5.44	1.50	4.08
6*	3-OSO_2CF_3	n-Pr	6.56	−0.74	5.82	5.22	1.50	1.61
7	3-CO_2CH_3	n-Pr	5.65	0.15	5.80	3.97	1.50	1.29
8	3-CH_2OH	n-Pr	5.29	0.33	5.62	2.96	1.50	0.72
9	3-$CONH_2$	n-Pr	5.23	0.07	5.30	2.51	1.50	0.98
10	3-NH_2	n-Pr	5.26	0.01	5.27	2.77	1.50	0.54
11	3-Br	n-Pr	6.25	−0.15	6.10	4.86	1.50	0.89
12	3-$SO_2N(CH_3)_2$	n-Pr	5.34	−0.25	5.09	3.19	1.50	2.24
13	3-S-CH_3	n-Pr	6.01	0.04	6.05	4.56	1.50	1.38
14	3-SO_2CH_3	n-Pr	5.23	0.36	5.59	2.36	1.50	1.35
15	3-CH=O	n-Pr	5.39	−0.30	5.09	3.35	1.50	0.69
16	3-CH_2CN	n-Pr	5.41	0.08	5.49	3.42	1.50	1.01
17*	3-C≡CH	n-Pr	5.82	0.69	6.51	4.27	1.50	0.96
18	3-H	n-Pr	5.66	0.03	5.69	4.00	1.50	0.10
19	3-CH_3	n-Pr	5.97	−0.05	5.92	4.50	1.50	0.56
20	3-(3-thienyl)	n-Pr	6.87	−0.07	6.80	5.53	1.50	0.40
21	3-$COCH_3$	n-Pr	5.42	−0.04	5.38	3.44	1.50	1.12
22	3-$CH_2CH_2CH_3$	n-Pr	6.89	−0.02	6.87	5.55	1.50	1.50
23	3-CN	H	5.26	−0.16	5.10	1.93	0.10	0.63
24	3-CN	allyl	5.33	−0.31	5.02	3.15	1.56	0.63
25	3-CN	n-Bu	5.64	−0.25	5.39	3.96	1.96	0.63
26	3-CN	s-Bu	5.54	−0.45	5.09	3.74	1.96	0.63
27	3-CN	cyclopropylmethyl	5.40	−0.20	5.20	3.39	1.79	0.63
28	3-CN	2-phenylethyl	5.75	1.17	6.92	4.15	3.51	0.63
29	3-CN	3-phenylpropyl	6.10	0.65	6.75	4.68	3.98	0.63
30	3-CN	3-(2-ethyl)thiophene	6.17	0.33	6.50	4.77	3.32	0.63
31	3-CN	$(CH_2)_3N(CH_3)_2$	5.26	−0.11	5.15	2.75	2.76	0.63
32	3-OSO_2CF_3	Me	5.75	−0.10	5.65	4.16	0.57	1.61
33	3-OSO_2CF_3	Et	6.11	−0.13	5.98	4.69	1.03	1.61
34	2-OSO_2CF_3	n-Pr	6.21	−0.47	5.74	4.82	1.50	0.10

*data omitted from the derivation of Equation (4); [a] calculated using Equation (4); [b] parameter referred to in Equation (3).

hydrophobicity and the log *P* for a variety of data sets fell in the range found for non-specific CNS depressants [15]. This is certainly associated with the transport process and it is likely related to the binding at the site of action. The finding of active sites by drugs can be regarded as a random walk process in which molecules must cross many membranes. The log *P* value of 2.5 can be said to be the ideal lipophilic character to design into a neutral molecule for passive penetration into the CNS.

In Equation (3) where the relationship between log $1/K_i$ and log *P* is well approximated by a parabolic model then the role of the lipophilic character of DA antagonists can be at least roughly separated from their electronic and steric characteristics.

For some structural features e.g. the presence of a propyl-group, we had to use an indicator variable as a device to account for the effect of a specific feature that could not be accounted for by a more specific parameter. The electronic effect was found to be significant only for the in vitro binding data for the D_2-receptors.

In all cases the steric factors were found to be important. This suggests that the receptors possess a special stereochemical feature e.g. the aromatic ring and the nitrogen moieties are the primary binding groups.

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