Pergamon

Bioorganic & Medicinal Chemistry 6 (1998) 535–550

BIOORGANIC & MEDICINAL CHEMISTRY

Theoretical Descriptors in Quantitative Structure–Affinity and Selectivity Relationship Study of Potent N4-Substituted Arylpiperazine 5-HT1$_A$ Receptor Antagonists

M. C. Menziani,[a,*] P. G. De Benedetti[a] and M. Karelson[b]

[a]*Dipartimento di Chimica, Universita' di Modena, V. Campi 183, 41100 Modena, Italy*
[b]*Department of Chemistry, University of Tartu, 2 Jakobi Str., Tartu, EE2400, Estonia*

Received 4 September 1997; accepted 4 November 1997

Abstract—The ability of ad hoc defined size and shape descriptors and theoretical descriptors derived on a single structure to give poweful interpretative and predictive QSAR models has been compared and evaluated with respect to the quality of the pharmacological data available for a series of structurally diverse 5-HT1$_A$ receptor antagonists, displaying selectivity towards the α1-adrenergic receptor.

Introduction

The techniques of computational chemistry are being applied increasingly in the generation of theoretical descriptors able to describe biologically active molecules in QSAR studies.[1] This implies that the bioactivity of a set of compounds, which might be expected to operate through a common mechanism, is reduced and translated into a theoretical chemical formalism, with great benefit to the physical interpretability of the QSAR model produced. Moreover, molecular series of non-congeneric compounds can be studied and their different bioactivity prototropic forms can be explicitly considered.

When dealing with the rationalization of biological responses (binding affinity, selectivity, and efficacy) of ligands for G-protein coupled receptors the crucial point of the large molecular diversity of the receptors and their subtypes, has to be faced. On one hand, there exists a general mode of interaction of bioamine ligands with their receptors, which has been strictly conserved through receptor evolution: that is, all ligands have a basic nitrogen function, protonated at physiological pH, therefore a long range electrostatic interaction has been hypothesized as recognition step. On the other hand, the large variation in the details of molecular interactions between the chemical signals (transmitters) and receptors exists, and few molecular determinants are responsible for discrimination of compounds among receptor classes, subtypes, or variants.

Thus, the ability to obtain good quantitative rationalization of the binding properties of highly affine and selective ligands showing a large variability of structural features depends primarily on the availability of descriptors able to capture the strict ligand-receptor complementarity criteria, which determine the biological properties of interest.

We have recently shown that theoretical QSAR analysis based on ad hoc size and shape descriptors defined, with respect to a reference supermolecule, on the ligand bioactive molecular form is a simple and very promising approach to rationalize the different activity and selectivity of the neuroactive protonated amines towards different receptors.[2] According to the ligand pharmacophore similarity-target receptor complementarity paradigm, this approach assumes that the volume obtained by superimposing the most structurally different ligands, which show the highest affinities for the same receptor, might reflect the overall shape and the conformational flexibility of the high affinity receptor binding site.

Key words: Theoretical descriptors; QSAR; CODESSA; 5-HT1$_A$ receptor antagonists; α_1-adrenoceptor selectivity.
*Corresponding author. Fax: 01139 59 373543; Tel: 01139 59 378463; E-mail: deben@unimo.it

0968-0896/98/$19.00
PII: S0968-0896(98)00008-X

Therefore, size and shape descriptors can be defined 'ad hoc', that is, within a specific molecular series and in connection with a specific bioactivity and this constitutes the main advantage over molecular descriptors defined and performed for a single structure and a single conformation. However, the large amount of information provided by quantum chemical calculations on the isolated molecules enlarges the probability to pinpoint the subtle causes of the observed variation in activity in some series of compounds, thus the versatility of molecular orbital (MO) derived molecular descriptors or of the ad hoc derived size and shape descriptors has to be evaluated in strict connection with the structural features characterizing the molecular series, which, in turn, is usually conditioned by the availability of biological data.

In the present study, theoretical descriptors derived by means of the program CODESSA[3] and ad hoc defined size and shape descriptors have been employed for deciphering, on a quantitative ground, the molecular features responsible for affinity and selectivity in a series of potent N4-substituted arylpiperazines antagonists acting at postsynaptic 5-HT1_A receptor and displaying a wide range of selectivity towards the α1-adrenoceptors.[4] The performance of the descriptors used has been evaluated with respect to the intrinsic nature of the pharmacological data available, which refer to binding measures on an individual receptor subtype in the case of the 5-HT1_A receptor and a generic population of α1-adrenoceptors containing at least three subtypes. Moreover, the ability of the CODESSA program to furnish a fast and adequate search for the best correlation equations for a given property has been exploited to obtain several QSAR models for predictive purposes.

Computational Procedure

Geometry optimization

Conformational analysis of the N4-protonated form of some simple arylpiperazine derivatives was recently perfomed.[5] The resulting absolute minimum structure of eltoprazine (1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine) was considered in this study as starting geometry to insert the N4 substituents in an extended conformation of the linker chain. Then, the protonated structures were fully optimized by means of molecular orbital calculations (AM1),[6] using the MOPAC 6.0 (QCPE 455) program.

Molecular superimposition

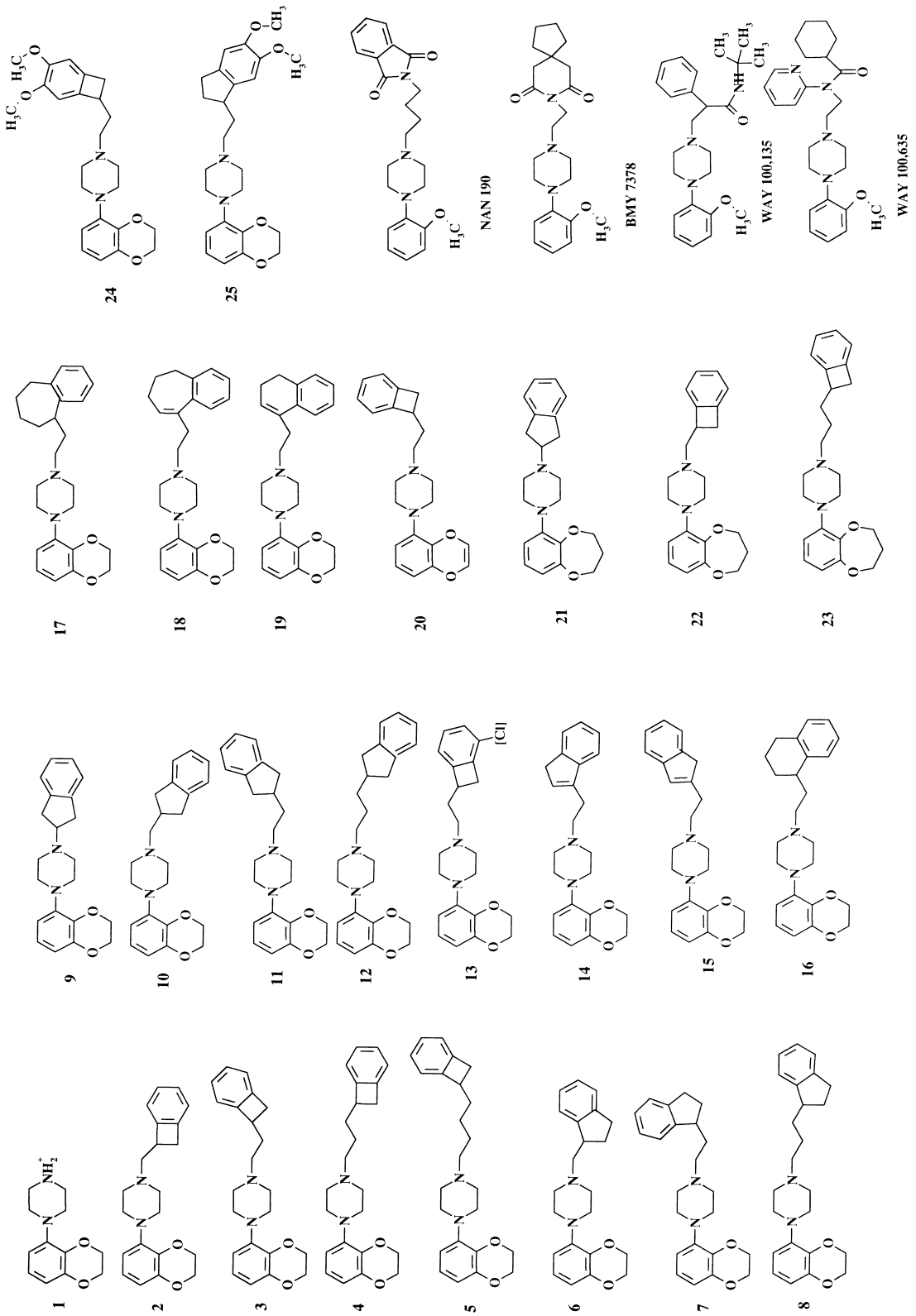
The most structurally different ligands, which show the highest affinity for the 5-HT1_A receptor (compounds **3**, **4**, **8**, and NAN190) and for the α_1 receptor (compounds **25** and NAN190), were chosen for the construction of the respective reference supermolecule, and were superimposed, by a rigid fit procedure, minimising the rms deviations with respect to three dummy atom pairs. The dummy atoms, reported below, were defined by taking into account the common structural features shared by all the ligands (i.e. the amine function in its protonated form) and the mutual orientation of two aromatic nuclei: (a) A dummy atom positioned 3.0 Å from the protonated nitrogen on the vector defined by the N–H$^+$ bond. For compound **1** (eltoprazine) of Scheme 1, which has a primary amine function, we considered the axial N–H$^+$ bond. (b) Two dummy atoms positioned, respectively, 3 Å above and below the centre of the aromatic plane of the phenyl ring attached to the piperazine. (c) Two dummy atoms positioned, respectively, 3 Å above and below the centre of the plane of the condensed rings.

All the other compounds were satisfactorily superimposed on the supermolecule using the same procedure, in their extended minimum conformer, or conformers whose energy is only 1 kcal/mol above.

The QUANTA 4.1[7] molecular modeling software was utilized for molecular comparisons, matching and computation of van der Waals volumes. The ad hoc defined size and shape descriptor, V_{dif}, is computed according to the following formula: $V_{dif} = V_{in} - V_{out}/V_{sup}$ where V_{sup} is the resultant van der Waals volume of the reference supermolecule. V_{in} and V_{out} are, respectively, the intersection and the outer van der Waals volume of the ligands considered with respect to the supermolecule.

Molecular descriptors and statistical treatment of data

Up to approximately one thousand global and fragment descriptors (constitutional, topological, electrostatic, geometrical, and quantum-chemical) were generated for each compound within the framework of the CODESSA[3] program. The ad hoc defined molecular size and shape parameters, described above, were added as external descriptors. The search for the best correlation equation was achieved by means of the heuristic method, which accomplished a preselection of descriptors on the basis of their statistical significance.[3,8] Default values for control parameters and criteria were used: minimum squared correlation coefficient to consider one-parameter correlation significant, $R^2\text{min} = 0.1$; t-test value to consider descriptor significant in one-parameter correlation, $t_1 = 1.5$, t-test value to consider descriptor significant in multi-parameter correlation, $t_2 = 3.0$; highest pair correlation coefficient of two descriptors scales, $r_{full} = 0.99$; significant intercorrelation

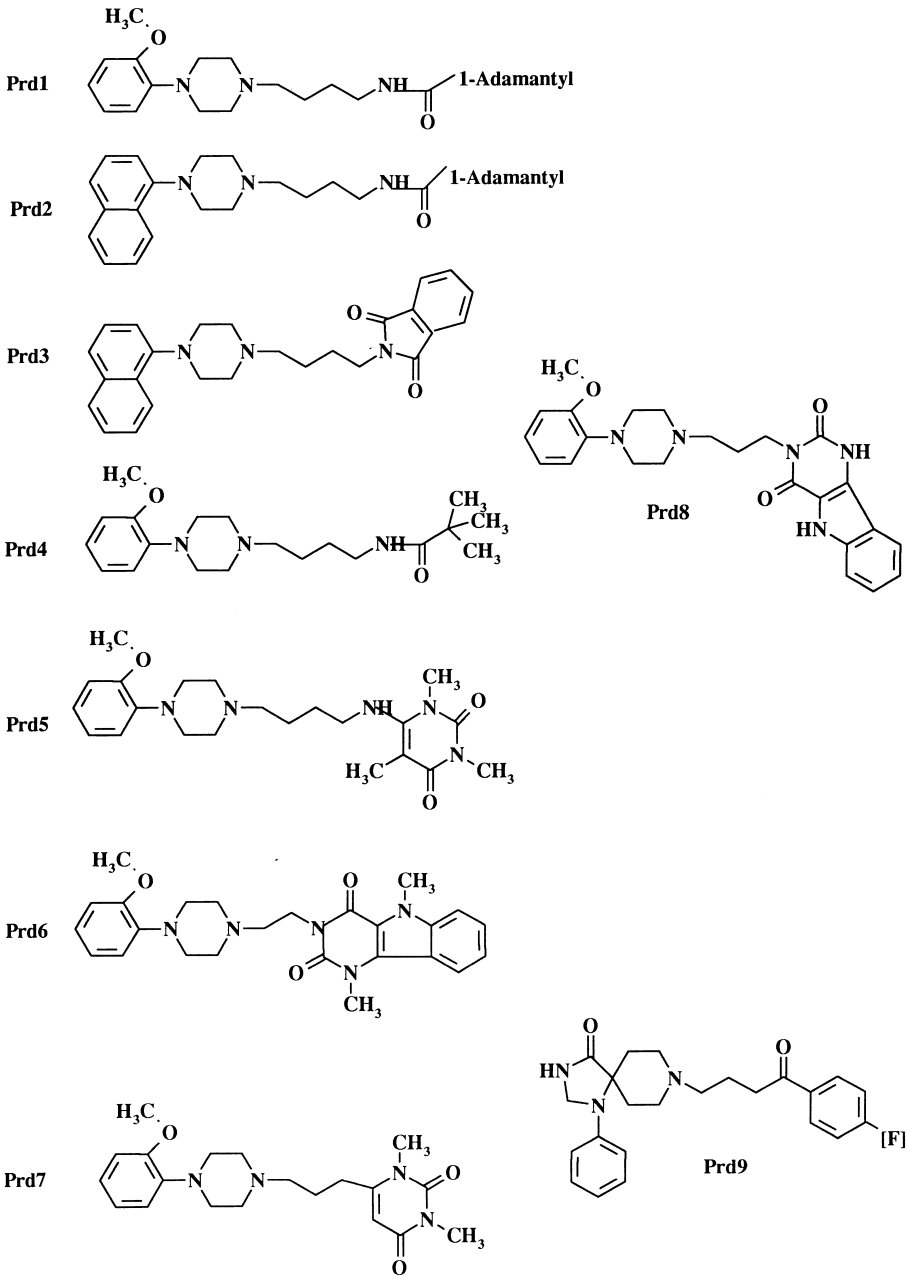


Scheme 1.

level, $r_{sig} = 0.80$. Evaluation of the best correlation models was carried out by validation of each model by cross-validation techniques and by prediction response values for test sets of structurally diverse molecules, reported in Scheme 2. As a final result the program lists the 10 correlations found with the highest squared correlation coefficient and the 10 correlations found with the highest *F*-test's values. The QSAR models reported in this paper were selected, among these, on the basis of the best statistical parameters and the largest diversity of the descriptors involved.

Definition of the descriptors used in the selected QSAR models[9]

qtot (N)	net atomic charge of the protonated nitrogen
qtot (H)	net atomic charge of the proton



Scheme 2.

Est (N)	minimum atomic state energy for the protonated nitrogen
Pσ-π (N–H)	σ–π bond order for the $(N–H)^+$ pair
Eexch (N–H)	electronic exchange energy for the $(N–H)^+$ pair
EC (N–H)	Coulomb interaction energy for the $(N–H)^+$ pair
ER (N–H)	resonance energy for the $(N–H)^+$ pair
Enn (N–H)	nuclear repulsion energy for the $(N–H)^+$ pair
Eee (N–H)	electronic repulsion energy for the $(N–H)^+$ pair
μh	total hybridization component of the molecular dipole
GAMMA	GAMMA polarizability (DIP)
I_A	principal moment of inertia A
PSA (N)	partial surface area of the protonated nitrogen atom
PNSA-1	partial negative surface area
DPSA-3	difference in CPSAs (PPSA-3-PNSA-3) [Zefirov's], where CPSA and PPSA are, respectively, the charged partial surface area and the partial positive surface area of the molecule considered
WNSA-3	surface weighted CPSA (PNSA-3*TMSA/1000) [Zefirov's]
FPSA-1	fractional CPSA (PNSA-1/TMSA) [Semi-MO]
f-PNSA-1	partial negative surface area [Semi-MO] of the bicyclic fragment
f-WNSA-1	surface weighted CPSA (PNSA-1*TFSA/1000) [Semi-MO] of the bicyclic fragment, where TFSA is the total fragment surface area
f-FNSA-1	fractional CPSA (PNSA-1/TFSA) [Semi-MO] of the bicyclic fragment
f-WNSA-1	surface weighted CPSA (PNSA-1*TFSA/1000) [Semi-MO] of the bicyclic fragment
f-WNSA-2	surface weighted CPSA (PNSA-2*TFSA/1000) [Semi-MO] of the bicyclic fragment

Results and Discussion

A recently reported SAFIR study on a series of arylpiperazines led to the characterization of several potent 5-$HT1_A$ antagonists displaying some selectivity towards the α1 receptors and marked selectivity towards the D2 receptors.[4]

The most informative molecules have been chosen in the present study for a quantitative rationalization of their affinity and selectivity properties. The main structural features shared by these ligands (Scheme 1) are the arylpiperazinic nucleus and a saturated or unsaturated bicyclic system. The two moieties are connected by a spacer of variable length, constitutes by a flexible alkyl chain.

Some reference compounds showing structurally diverse elements are also reported in the Scheme 1. They are: (1) NAN190, a weak partial agonist not selective versus the α_1-adrenergic receptor, (2) BMY7378, which exerts antagonistic action at 5-$HT1_A$ postsynaptic site but retains some agonist properties at 5-$HT1_A$ autoreceptors, and, (3) WAY100,135 and WAY100,635 which exert pre- and postsynaptic antagonistic action at 5-$HT1_A$ sites and display selectivity versus the α_1-adrenergic receptor.

The data values of the molecular descriptors effectively used in the selected correlation equations are listed in Table 1, together with the cologarthmic form of the 5-$HT1_A$ serotoninergic (p*K*i 5-$HT1_A$) and α_1 adrenergic (p*K*i α_1) binding affinity of the ligands considered. Their difference Δp*K*i is also reported in the Table and represents the selectivity of the compounds considered with respect to the two receptors, the higher the Δp*K*i values, the higher the selectivity of the ligands towards the 5-$HT1_A$ receptor.

A quantitative overview of the collinearities existing between the theoretical descriptors of Table 1 is shown in Table 2, were the respective intercorrelation coefficients are given.

Satisfactory linear correlations rationalize the variation in the 5-$HT1_A$ serotoninergic and α_1-adrenergic receptors binding affinity of these ligands by making use of ad hoc derived size and shape descriptors. The most significant QSAR models obtained involve V_{dif} in the case of the 5-$HT1_A$ serotoninergic receptor (eq (1), Table 3) and V_{out} and V_{dif} for the α_1-adrenergic receptor (eq (1) and (2), Table 4).

By assuming that the volume (V_{sup}) obtained by superimposing the most structurally different ligands which show the highest affinities might reflect the best size and shape complementarity towards the receptor considered, the higher binding affinities are realized by minimizing V_{out}, which may represent the repulsive interactions with the receptor. Similar results are obtained for the molecular descriptor V_{dif}, which, by taking into account in its formulation both the inner and outer molecular volumes of the ligands considered with respect to the reference volume of the supermolecule, indicates that, in these molecular series of compounds, the binding affinities are mainly modulated by the molecular shape of the bicyclic system though the optimization of dispersive and steric interactions.

Table 1. 5-HT1$_A$ serotoninergic and α_1-adrenergic binding affinities, selectivity and theoretical descriptors of the protonated form of the ligands reported in Scheme 1

Mol.	p*Ki*[a] 5-HT1$_A$	p*Ki*[a] α1	Δp*Ki*	V_{in} 5-HT1$_A$ (Å^3)	V_{out} 5-HT1$_A$ (Å^3)	V_{dif} 5-HT1$_A$	V_{in} α_1 (Å^3)	V_{out} α_1 (Å^3)	V_{dif} α_1	qtot (N)	qtot (H)	Est (N) (eV)	Pσ-π (N–H)	Eexch (NH) (eV)	Ec (N–H) (eV)	E_R (N–H) (eV)
1	8.03			180.38	15.12	0.30				3.70×10^{-4}	0.2534	182.474	1.50×10^{-5}	5.2017	5.5836	12.8505
2	8.75			257.75	44.25	0.39				-4.00×10^{-3}	0.2376	182.550	5.00×10^{-6}	5.1471	5.5666	12.7793
3	9.23	7.66	1.57	317.00	0.00	0.58	262.50	55.13	0.42	-4.30×10^{-3}	0.2345	182.542	6.00×10^{-6}	5.1650	5.5618	12.7888
4	9.35			334.38	0.00	0.61				-5.30×10^{-3}	0.2343	182.564	5.00×10^{-6}	5.1568	5.5592	12.7738
5	8.89	7.56	1.33	294.50	55.88	0.43	271.75	80.00	0.39	-5.10×10^{-3}	0.2347	182.562	6.00×10^{-6}	5.1589	5.5597	12.7803
6	8.76	7.75	0.80	265.75	50.38	0.39	260.25	55.88	0.42	-4.70×10^{-3}	0.2358	182.579	1.40×10^{-5}	5.1532	5.5692	12.7737
7	8.80			296.50	34.88	0.48				-6.00×10^{-3}	0.2341	182.586	5.00×10^{-6}	5.1534	5.5430	12.7553
8	9.21			349.00	0.00	0.64				-5.40×10^{-3}	0.2343	182.564	5.00×10^{-6}	5.1578	5.5594	12.7738
9	8.75	6.84	1.91	253.50	43.13	0.38	217.88	80.00	0.28	7.30×10^{-3}	0.2387	182.415	2.10×10^{-5}	5.1468	5.5877	12.7571
10	8.55			284.00	31.50	0.46				-5.70×10^{-3}	0.2327	182.584	6.00×10^{-6}	5.1597	5.5580	12.7723
11	9.18			296.00	34.75	0.48				-3.70×10^{-3}	0.2345	182.536	7.00×10^{-6}	5.1649	5.5629	12.7895
12	8.90			300.38	46.00	0.46				-4.20×10^{-3}	0.2343	182.548	6.00×10^{-6}	5.1614	5.5617	12.7829
13	8.65	7.19	1.46	291.25	35.50	0.47	240.50	85.50	0.32	-4.20×10^{-3}	0.2350	182.545	4.00×10^{-6}	5.1608	5.5621	12.7812
14	9.10			289.50	36.13	0.46				$-6.1O\times10^{-3}$	0.2326	182.574	4.00×10^{-6}	5.1617	5.5572	12.7780
15	9.27			312.50	12.75	0.55				-5.50×10^{-3}	0.2335	182.562	4.00×10^{-6}	5.1618	5.5589	12.7805
16	8.56			305.13	42.37	0.48				-4.30×10^{-3}	0.2345	182.549	5.00×10^{-6}	5.1586	5.5597	12.7761
17	8.18			270.50	93.63	0.32				-4.20×10^{-3}	0.2338	182.546	5.00×10^{-6}	5.1635	5.5598	12.7838
18	8.50			340.13	90.12	0.46				-5.40×10^{-3}	0.2316	182.566	4.00×10^{-6}	5.1670	5.5585	12.7861
19	8.70			289.50	52.13	0.43				-4.20×10^{-3}	0.2350	182.544	7.00×10^{-6}	5.1577	5.5655	12.7810
20	8.85			282.88	27.25	0.47				-4.30×10^{-3}	0.2352	182.546	5.00×10^{-6}	5.1604	5.5620	12.7829
21	8.42	6.68	1.82	269.50	45.00	0.41	216.25	95.13	0.25	7.20×10^{-3}	0.2389	182.416	1.90×10^{-5}	5.1464	5.5875	12.7570
22	8.10			244.63	72.62	0.31				-3.70×10^{-3}	0.2376	182.545	2.00×10^{-6}	5.1583	5.5649	12.7804
23	9.10			331.50	18.50	0.57				-6.20×10^{-3}	0.2359	182.576	2.00×10^{-6}	5.1534	5.5579	12.7710
24	8.50			320.75	115.63	0.37				-4.50×10^{-3}	0.2345	182.552	7.00×10^{-6}	5.1563	5.5609	12.7723
25	8.80	7.81	0.99	307.75	71.38	0.43	379.75	0.00	0.77	-6.00×10^{-3}	0.2337	182.583	6.00×10^{-6}	5.1568	5.5576	12.7718
BMY	8.71	6.74	1.97	291.25	61.75	0.42	253.88	98.00	0.32	1.70×10^{-3}	0.2396	182.478	4.50×10^{-5}	5.1521	5.5917	12.8024
NAN	9.15	9.09	0.06	345.75	0.00	0.63	347.00	0.00	0.71	-5.30×10^{-3}	0.2387	182.560	8.00×10^{-6}	5.1556	5.5826	12.8079
W135	7.49	5.94	1.55	244.63	126.62	0.22	203.13	171.00	0.07	-2.90×10^{-3}	0.2459	182.516	3.00×10^{-6}	5.2510	5.5796	12.7705
W635	9.20[b]	6.50[b]	2.70	301.50	84.00	0.40	266.63	127.75	0.26	2.17×10^{-4}	0.2459	182.124	6.59×10^{-4}	5.1075	5.4855	12.5796

Table 1—*contd*

Mol.	Enn(N–H) (eV)	Eee(N–H) (eV)	μh (Debye)	GAMMA	I_A (cm^{-1})	PSA(N) ($Å^2$)	PNSA-1 ($Å^2$)	DPSA-3 ($Å^2$)	WNSA-3 ($Å^2$)	FPSA-1	f-PNSA-1 ($Å^2$)	f-FNSA-1	f-WNSA-1 ($Å^2$)	f-WNSA-2 ($Å^2$)
1	53.3946	36.1049	1.334	2.64×10^4	0.0341	21.648	101.052	17.141	−3.133	0.777				
2	53.4006	36.0415	0.926	4.34×10^4	0.0235	0.802	148.106	17.945	−3.960	0.773	73.277	0.112	5.370	−41.287
3	53.3946	36.1870	1.047	5.47×10^4	0.0228	3.207	147.970	19.070	−4.604	0.779	71.207	0.106	5.070	−40.398
4	53.3946	36.2022	1.101	4.54×10^4	0.0211	1.604	149.445	19.432	−4.547	0.790	69.196	0.097	4.788	−41.961
5	53.3946	36.1860	0.971	5.30×10^4	0.0204	2.405	143.779	19.650	−4.654	0.804	72.636	0.099	5.276	−46.059
6	53.4148	36.1402	0.924	3.96×10^4	0.0206	0.802	142.523	17.984	−4.062	0.783	70.507	0.107	4.971	−46.447
7	53.3580	36.2040	0.944	4.82×10^4	0.0182	3.207	137.663	18.959	−4.433	0.798	57.210	0.084	3.273	−38.301
8	53.3946	36.2015	1.020	5.63×10^4	0.0173	2.405	152.244	20.013	−4.890	0.794	73.947	0.100	5.468	−53.762
9	53.3946	35.9151	0.796	4.65×10^4	0.0228	0.802	145.691	17.726	−3.776	0.771	71.325	0.112	5.087	−44.627
10	53.3946	36.2809	1.205	4.00×10^4	0.0182	2.405	138.616	18.409	−4.187	0.786	67.767	0.105	4.592	−43.855
11	53.3946	36.1820	1.024	4.58×10^4	0.0202	2.405	149.755	19.244	−4.603	0.788	71.266	0.101	5.079	−49.239
12	53.3946	36.1950	1.007	4.87×10^4	0.0215	1.604	139.665	19.903	−4.796	0.811	65.756	0.089	4.324	−47.829
13	53.3946	36.1649	0.952	4.78×10^4	0.0203	1.604	144.878	18.116	−4.357	0.796	64.238	0.090	8.612	−34.882
14	53.3946	36.2856	1.178	5.69×10^4	0.0163	2.405	144.050	18.828	−4.602	0.786	73.650	0.109	5.424	−47.560
15	53.3946	36.2433	1.145	8.14×10^4	0.0210	2.405	159.469	19.181	−4.669	0.772	81.349	0.116	6.618	−53.003
16	53.3900	36.1877	1.019	5.07×10^4	0.0166	3.207	155.072	19.662	−4.691	0.786	73.247	0.101	5.365	−58.781
17	53.3900	36.2182	1.152	5.51×10^4	0.0134	1.604	139.412	19.581	−4.624	0.808	58.521	0.081	3.425	−54.156
18	53.3946	36.3259	1.321	5.39×10^4	0.0125	4.811	146.219	19.038	−4.306	0.801	67.411	0.092	4.544	−59.504
19	53.4042	36.1703	0.944	5.70×10^4	0.0177	3.207	160.315	19.384	−4.861	0.775	82.108	0.115	6.742	−62.709
20	53.3946	36.1552	0.970	6.11×10^4	0.0230	0.802	180.508	17.806	−3.261	0.732	76.835	0.114	5.904	−44.181
21	53.3946	35.9068	1.050	5.10×10^4	0.0206	0.000	148.255	17.381	−3.956	0.776	74.825	0.113	5.599	−48.784
22	53.3946	36.0398	1.132	4.57×10^4	0.0202	1.604	143.663	17.080	−3.628	0.784	72.636	0.109	5.276	−41.734
23	53.3946	36.1363	0.878	5.24×10^4	0.0193	2.405	148.611	18.797	−4.392	0.799	73.395	0.099	5.387	−46.132
24	53.3946	36.1911	1.437	5.75×10^4	0.0141	2.405	159.865	24.922	−6.245	0.791	84.132	0.110	7.608	−78.101
25	53.3946	36.2376	0.888	6.23×10^4	0.0108	3.207	154.877	25.844	−6.949	0.803	74.569	0.095	6.030	−78.939
BMY	53.4361	35.9314	1.486	4.40×10^4	0.0199	2.405	140.086	25.730	−9.889	0.803	73.404	0.103	5.782	−106.146
NAN	53.4503	36.0247	1.356	6.12×10^4	0.0209	4.811	226.988	26.846	−11.834	0.697	149.345	0.199	24.206	−171.847
W135	53.4290	39.2091	1.973	4.85×10^4	0.0118	0.000	141.125	18.130	−5.025	0.809	72.581	0.098	5.612	−122.052
W635	53.0513	35.3480	0.605	7.85×10^4	0.0109	0.802	158.118	20.784	−6.693	0.797	85.920	0.110	7.440	−143.045

[a]Ref. 4.
[b]Ref. 10.

Table 2. Correlation matrix of the experimental binding affinities and molecular descriptors of Table 1

	V_{in} 5-HT1$_A$	V_{out} 5-HT1$_A$	V_{dif} 5-HT1$_A$	V_{in} α_1	V_{out} α_1	V_{dif} α_1	qtot (N)	qtot (H)	Pσ-π(N–H)	Est(N)	Eexch(NH)	Ec(N–H)	E_R (N–H)	Enn(N–H)	Eee(N–H)	μh	GAMMA	I_A	PSA (N)	PNSA-1	DPSA-3	WNSA-3	FPSA-1	f-PNSA-1	f-FNSA-1	f-WNSA-	f-WNSA-2
V_{in} SHT1$_A$	1.00																										
V_{out} SHT1	−0.22	1.00																									
V_{dif} SHTl$_A$	0.80	−0.76	1.00																								
V_{in} α1	0.77	−0.28	0.55	1.00																							
V_{out} α1	−0.67	0.68	−0.75	−0.82	1.00																						
V_{dif} α1	0.74	−0.50	0.68	0.95	−0.96	1.00																					
qtot(N)	−0.46	0.11	0.37	−0.58	0.38	−0.51	1.00																				
qtot (H)	−0.64	0.13	−0.50	−0.41	0.73	−0.60	0.52	1.00																			
Pσ-π(N–H)	0.03	0.22	−0.11	−0.01	0.34	−0.21	0.24	0.40	1.00																		
Est(N)	0.20	−0.23	0.27	0.28	−0.49	0.43	−0.64	−0.60	−0.89	1.00																	
Eexch(NH)	−0.38	0.21	−0.38	−0.28	0.36	−0.31	−0.12	0.32	−0.47	0.36	1.00																
Ec(N–H)	−0.31	−0.13	−0.12	−0.18	−0.17	0.02	0.32	0.09	−0.76	0.45	0.48	1.00															
E_R(N–H)	−0.17	−0.29	0.06	0.11	−0.40	0.29	−0.18	−0.12	−0.90	0.77	0.53	0.81	1.00														
Enn(N–H)	−0.04	−0.19	0.09	0.02	−0.33	0.21	−0.16	−0.29	−0.96	0.82	0.50	0.87	0.91	1.00													
Eee(N–H)	−0.19	0.39	−0.37	−0.31	0.48	−0.40	−0.16	0.18	−0.30	0.26	0.88	0.27	0.21	0.34	1.00												
μh	−0.14	0.35	−0.31	−0.21	0.33	−0.26	−0.05	0.25	−0.36	0.27	0.77	0.50	0.46	0.48	0.71	1.00											
GAMMA	0.54	0.08	0.31	0.47	−0.10	0.28	−0.18	−0.25	0.45	−0.28	−0.36	−0.54	−0.53	−0.45	−0.13	−0.23	1.00										
I_A	−0.45	−0.64	0.10	−0.26	−0.27	0.01	0.25	0.33	−0.31	0.11	0.09	0.47	0.52	0.32	−0.26	−0.08	−0.51	1.00									
PSA(N)	−0.40	−0.24	−0.11	0.80	−0.78	0.83	0.04	0.54	−0.09	0.02	0.32	0.19	0.44	0.09	−0.10	0.20	−0.39	0.55	1.00								
PNSA-1	0.58	−0.17	0.48	0.59	−0.55	0.59	−0.20	−0.26	0.07	0.04	−0.28	−0.04	−0.12	0.03	−0.12	−0.04	0.57	−0.22	−0.36	1.00							
DPSA-3	0.49	0.14	0.24	0.80	−0.55	0.70	−0.14	−0.09	0.10	0.02	−0.20	0.01	0.00	0.04	−0.14	0.20	0.33	−0.35	−0.03	0.51	1.00						
WNSA-3	−0.42	−0.04	−0.25	−0.59	0.37	−0.50	0.02	−0.08	−0.20	0.12	0.17	−0.06	0.06	0.00	0.08	−0.27	−0.30	0.26	0.06	−0.60	−0.90	1.00					
FPSA-1	−0.05	0.46	−0.32	−0.35	0.56	−0.47	−0.06	−0.08	0.10	4.04	0.13	−0.26	−0.20	−0.19	0.22	0.02	−0.16	−0.40	−0.12	−0.72	−0.14	0.29	1.00				
f-PNSA-1	0.35	−0.21	0.33	0.52	−0.45	0.51	−0.02	0.28	0.14	−0.11	−0.12	0.12	0.02	0.03	−0.11	0.17	0.38	0.07	0.35	0.92	0.57	−0.73	−0.77	1.00			
f-FNSA-1	0.20	−0.31	0.31	0.41	−0.47	0.46	0.07	0.25	0.05	−0.07	−0.14	0.23	0.09	0.12	−0.15	0.13	0.26	0.26	0.26	0.88	0.41	−0.61	−0.88	0.96	1.00		
f-WNSA-1	0.34	−0.23	0.33	0.50	−0.47	0.51	−0.06	0.23	0.07	−0.04	−0.07	0.15	0.09	0.09	−0.09	0.18	0.28	0.09	0.37	0.89	0.56	−0.74	−0.73	0.95	0.91	1.00	
f-WNSA-2	−0.19	−0.28	0.07	−0.35	−0.05	−0.15	−0.12	−0.65	−0.49	0.45	−0.06	0.11	0.32	0.28	−0.17	−0.37	−0.40	0.42	−0.16	−0.59	−0.66	0.83	0.29	−0.73	−0.60	−0.69	1

Table 3. Regression models for the correlation between molecular structure descriptors and the 5-HT1$_A$ serotoninergic receptor binding affinity

1.		$R^2=0.7048$ $n=29$ $F=64.46$ $s^2=0.0558$ R^2cv $=0.6490$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	7.1184	$2.0760e\times10^{-1}$	34.2892
	V_{dif} (5HTl$_A$)	3.6397	4.5333×10^{-1}	8.0289
2.		$R^2=0.8106$ $n=29$ $F=55.64$ $s^2=0.0371$ R^2cv $=0.7708$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	7.9475	$2.7576e\times10^{-1}$	28.8203
	V_{dif}	3.1798	3.8921×10^{-1}	8.1698
	μh	-5.6866×10^{-1}	1.4921×10^{-1}	−3.8112
3.		$R^2=0.7934$ $n=29$ $F=49.91$ $s^2=0.0405$ R^2cv $=0.7538$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	1.0932×10^{2}	3.0617×10^{1}	3.5707
	V_{dif}	3.7550	3.8804×10^{-1}	9.6768
	Enn (N–H)	−1.9154	5.7377×10^{-1}	−3.3382
4.		$R^2=0.7925$ $n=29$ $F=49.66$ $s^2=0.0407$ R^2cv $=0.4501$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	7.0191	1.7986×10^{-1}	39.0258
	V_{dif}	3.7903	3.8992×10^{-1}	9.7207
	Pσ-π (N–H)	1.0502×10^{3}	3.1668×10^{2}	3.3162
5.		$R^2=0.7850$ $n=29$ $F=47.48$ $s^2=0.0422$ R^2cv $=0.7050$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	4.4578×10^{1}	1.2026×10^{1}	3.7069
	V_{dif}	3.7147	3.9494×10^{-1}	9.4056
	E_R (N–H)	−2.9352	9.4217×10^{-2}	−3.1153
6.		$R^2=0.7728$ $n=29$ $F=44.21$ $s^2=0.0446$ R^2cv $=0.6756$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	4.0505×10^{1}	1.1971×10^{1}	3.3835
	V_{dif}	3.5015	4.0831×10^{-1}	8.5755
	Ec (N–H)	−5.9905	2.1478	−2.7892
7.		$R^2=0.8322$ $n=29$ $F=41.33$ $s^2=0.0342$ R^2cv $=0.7826$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	7.6639	3.0834×10^{-1}	24.8552
	V_{dif}	3.0010	3.8668×10^{-1}	7.7609
	μh	-5.3102×10^{-1}	1.4476×10^{-1}	−3.6684
	GAMMA	6.1792×10^{-6}	3.4451×10^{-6}	1.7936
8.		$R^2=0.8305$ $n=29$ $F=40.82$ $s^2=0.0346$ R^2cv $=0.7605$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	7.9858	2.6701×10^{-1}	29.9082
	V_{dif}	2.9298	4.0295×10^{-1}	7.2708
	μh	$-6.6778\times10^{1}\}$	1.5518×10^{-1}	−4.3032
	WNSA-3	-3.6304×10^{-2}	2.1216×10^{-2}	−1.7112
9.		$R^2=0.8300$ $n=29$ $F=40.68$ $s^2=0.0347$ R^2cv $=0.7783$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	7.6506	3.1929×10^{-1}	23.9614
	V_{dif}	2.9619	3.9759×1	17.4496
	μh	-6.4512×10^{-1}	1.5112×10^{-1}	−4.2690
	DPSA-3	2.4224×10^{-2}	1.4350×10^{-2}	1.6880
10.		$R^2=0.8295$ $n=29$ $F=40.54$ $s^2=0.0348$ R^2cv $=0.7679$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	3.3133×10^{1}	1.1091×10^{1}	2.9873
	V_{dif}	3.2752	4.2013×10^{-1}	7.7958
	Pσ-π (N–H)	5.6519×10^{2}	3.5674×10^{2}	1.5843
	Eexch. (N–H)	−5.0125	2.1289	−2.3545

Table 4. Regression models for the correlation between molecular structure descriptors and the α_1-adrenoceptor binding affinity

1.		$R^2=0.8263$ $n=11$ $F=42.82$ $s^2=0.1399$ R^2cv $=0.6837$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	8.4435	$2.1430\times1\text{-}^{-1}$	39.3993
	V_{out} (α_1)	-1.5462×10^{-2}	2.3628×10^{-3}	−6.5439
2.		$R^2=0.7649$ $n=11$ $F=29.28$ $s^2=0.1894$ R^2cv $=0.4980$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	5.8544	2.8953×10^{-1}	20.2208
	V_{dif} (α_1)	3.6612	6.7665×10^{-1}	5.4108
3.		$R^2=0.6967$ $n=11$ $F=20.67$ $s^2=0.2443$ R^2cv $=0.5261$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	6.4018	2.3893×10^{-1}	26.7941
	PSA (N)	4.6597×10^{-1}	1.0249×10^{-1}	4.5465
4.		$R^2=0.9495$ $n=11$ $F=75.26$ $s^2=0.0457$ R^2cv $=0.9038$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	3.9921×10^{1}	3.7807	10.5592
	f-PNSA-1	2.7725×10^{-2}	2.9097×10^{-3}	9.5285
	qtot (H)	-1.4640×10^{2}	1.5990×10^{1}	−9.1562
5.		$R^2=0.9424$ $n=11$ $F=65.50$ $s^2=0.0521$ R^2cv $=0.8888$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	4.1542×10^{1}	4.0600	10.2321
	f-WNSA-1	$3.4055\times1\text{-}^{-2}$	3.8403×10^{-3}	8.8676
	qtot (H)	1.5209×10^{2}	1.7193×10^{1}	−8.8464
6.		$R^2=0.9362$ $n=11$ $F=58.66$ $s^2=0.0578$ R^2cv $=0.8995$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	3.4102×10^{1}	4.2389	8.0449
	PNSA-1	2.5684×10^{-2}	3.0675×10^{-3}	8.3728
	qtot (H)	-1.2927×10^{2}	1.7772×10^{1}	−7.2741
7.		$R^2=0.9184$ $n=11$ $F=45.02$ $s^2=0.0739$ R^2cv $=0.7564$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	4.8953×10^{1}	5.0880	9.6214
	qtot (H)	-1.7809×10^{2}	2.1496×10^{1}	−8.2849
	f-WNSA-2	-6.9691×10^{-2}	9.5638×10^{-3}	−7.2870
8.		$R=0.9057$ $n=11$ $F=38.40$ $s=0.0855$ $R=0.5978$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	3.7657×10^{1}	5.1470	7.3162
	f-FNSA-1	2.0883×10^{1}	3.1183	6.6969
	qtot (H)	-1.3742×10^{2}	2.1702×10^{1}	−6.3322
9.		$R^2=0.8934$ $n=11$ $F=33.53$ $s^2=0.0966$ R^2cv $=0.7315$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	1.6562	7.0315×10^{-1}	2.3554
	V_{in}(α_1)	1.4185×10^{-2}	1.8673×10^{-3}	7.5968
	I_A	1.0053×10^{2}	2.1400×10^{1}	4.6979
10.		$R^2=0.8925$ $n=11$ $F=33.19$ $s^2=0.0974$ R^2cv $=0.7172$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	-7.3731×10^{1}	1.3357×10^{1}	−5.5201
	f-PNSA-1	2.5936×10^{-2}	4.2133×10^{-3}	6.1556
	Eee (N–H)	2.1934	3.7023×10^{-1}	5.9244

However, a significant improvement in the correlations is obtained by using extended set of descriptors developed in the CODESSA program.[3] The multilinear regression models which better describe the variation in the 5-HT1$_A$ receptor binding affinity involve molecular descriptors which can be related to: (a) the dipole–dipole (eq (2), Table 3) and dispersion interactions (eq (7), Table 3); (b) the propensity of the protonated nitrogen to act as a proton donor and to form charge reinforced hydrogen bonding interactions (eq (3)–(6) and (10), Table 3), (c) polar interactions whose features are encoded by charged partial surface area (CPSA) descriptors[11] (eq (8) and (9), Table 3). Thus, the essential nature of the interaction mode between the ligands considered and their receptors, which can be summarized in an electrostatic interaction between the protonated amine function and a primary nucleophilic site of the receptor, complemented by short-range attractive (polar and dispersive) and repulsive (steric) intermolecular interactions, is well accounted for by the molecular descriptors involved in the rationalization of the 5-HT1$_A$ receptor binding affinity. This result can be extended to the description of the α_1-adrenergic binding affinity variation. In fact, in this case, the long range interaction component is explicitly considered in eq (4)–(8) (Table 4) by means of the total electronic charge on the nitrogen proton and in eq (10) (Table 4) by means of the electronic repulsion energy for the N–H$^+$ pair. Specific and non specific polar interactions are represented, in the models obtained, by charged contact surface area descriptors computed on the saturated or unsaturated bicyclic substituents (eq (5), (7), (8) and (10), Table 4) or on the whole ligands (eq (6), Table 3). It is worth noting that, while V_{dif}(5-HT1$_A$) is an essential descriptor in all the regression models obtained for the 5-HT1$_A$ binding affinity, ad hoc derived size and shape descriptors do not seem to be essential in the bilinear models for the α_1 binding affinity variation in this class of compounds; in fact, $V_{in}(\alpha_1)$ (eq (9), Table 4) proved to be the only significant descriptor in a two parameter equation together with the moment of inertia (I_A) defined with respect to the main axis of the ligands. By considering that the ligands analyzed show a limited range of variation from medium to high affinity for the 5-HT1$_A$ receptor subtype, while a larger range from low to high affinity is accomplished for the generic α_1 receptor, the results obtained suggest that the need of descriptors which encode the strict complementarity requirements for receptor binding is strictly related to the nature of the pharmacological data to model. This statement is also supported by the high level of collinearity observed between the ad hoc size and shape descriptors defined on the α_1 supermolecule and some of the charged contact surface area descriptors (Table 2). These trends are not paralleled by ad hoc size and shape descriptors defined on the 5-HT1$_A$ supermolecule.

The challenging goal of describing selectivity is achieved, for this series of ligands, by the quantum-chemically derived dscriptors for the protonated nitrogen (the net atomic charge of the protonated nitrogen, qtot (N), and the atomic state energy for this atom, Est (N), cf. eq (1) and (2), Table 5). These descriptors are affected by the geometrical environment of the protonated nitrogen atom (cf. Table 1), in particular, by the absence of the tether between the two aromatic moieties (compds **9** and **21**) or showing a particularly crowded environment of the protonated nitrogen as in the case of BMY7378, WAY100,635, and WAY100,135, where a bulky substituent on a short chain is present. Notably, these compounds are characterized by the highest level of selectivity towards the α_1-adrenoceptor. Improvement of the correlation statistics is obtained by introducing charged contact surface area indexes computed on the whole ligands (eq (3), (6) and (10), Table 5) or on the bicyclic substituents (eq (4), (5), (7)–(9), Table 5).

The profusion of the models quickly obtained by the program for the rationalization of the biological responses facilitates the ultimate need to predict the activities of newly considered compounds. Assessment of the prediction power of the QSAR models obtained is given by the cross-validated correlation coefficient R^2cv, reported in Tables 3–4. Figures 1–3 report the comparison of the experimental and calculated biological activities for eq (7) (Table 3), eq (4) (Table 4) and eq (3) (Table 5), which can be considered, on the basis of their statistical quality and predictive power, the best QSAR equations to describe the 5-HT1$_A$ serotoninergic receptor binding affinity, the α_1-adrenergic receptor binding affinity and the receptors selectivity, respectively.

In order to challenge further the performance of the selected QSAR models when applied to new compounds, we performed a retrospective assessment on the set of structurally diverse ligands reported in Scheme 2. The molecular descriptors utilized in the predictions for this set of compounds are listed in Table 6 and the prediction results are reported in Table 7.

Satisfactory predictions of the 5-HT1$_A$ binding affinity are given in general, by considering a factor 2 tolerance in the concentration scale, for four out of six ligands tested. The main disagreement is observed for compounds **Prd1** and **Prd2** which carry the bulky adamantyl moiety. The value of the 5-HT1$_A$ binding affinities of these ligands is systematically underestimated. The descriptor V_{dif} is partly responsible of this effect, as the supermolecule is constituted by molecules of smaller size with respect to these compounds and an unrealistic negative contribute of the V_{out} component resulted.

Table 5. Regression models for the correlation between molecular structure descriptors and the 5-HT1_A serotoninergic receptor and α_1-adrenergic receptor selectivity

1.		$R^2=0.6268$ $n=11$ $F=15.11$ $s^2=0.1983$ R^2cv $=0.5113$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	1.4377	1.3452×10j1	10.6878
	qtot (N)	6.3949×10^{1}	1.6449×10^{1}	3.8877
2.		$R^2=0.6109$ $n=11$ $F=14.13$ $s^2=0.2068$ R^2cv $=0.4656$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	7.4025×10^{2}	1.9653×10^{2}	3.7667
	Est (N)	−4.0485	1.0769	−3.7592
3.		$R^2=0.9204$ $n=11$ $F=46.26$ $s^2=0.0476$ R^2cv $=0.8684$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	7.1132×10^{2}	9.4418×10^{1}	7.5337
	Est (N)	−3.8768	5.1754×10^{-1}	−7.4909
	PNSA-1	-1.5526×10^{-2}	2.7836×10^{-3}	−5.5776
4.		$R^2=0.9111$ $n=11$ $F=41.00$ $s^2=0.0531$ R^2cv $=0.8546$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	7.3531×10^{2}	9.9640×10^{1}	7.3796
	Est (N)	−4.0143	5.4603×10^{-1}	−7.3518
	f-PNSA-1	-1.6093×10^{-2}	3.0963×10^{-3}	−5.1976
5.		$R^2=0.9035$ $n=11$ $F=37.44$ $s^2=0.0577$ R^2cv $=0.7931$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	7.5248×10^{2}	1.0385×10^{2}	7.2458
	Est (N)	−4.1093	5.6906×10^{-1}	−7.2213
	f-WNSA-1	-1.9505×10^{-2}	3.9608×10^{-3}	−4.9243
6.		$R^2=0.8996$ $n=11$ $F=35.85$ $s^2=0.0600$ R^2cv $=0.8597$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	3.6935	4.8934×10^{-1}	7.5479
	qtot (N)	5.9540×10^{1}	9.0969	6.5450
	PNSA-1	-1.4631×10^{-2}	3.1375×10^{-3}	−4.6635
7.		$R^2=0.8988$ $n=11$ $F=35.51$ $s^2=0.0605$ R^2cv $=0.8572$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	2.7983	3.0276×10^{-1}	9.2426
	qtot (N)	6.1331×10^{1}	9.1046	6.7362
	f-FNSA-1	-1.2118×10^{1}	2.6140	−4.6358
8.		$R^2=0.8947$ $n=11$ $F=33$ 97 $s^2=0.0630$ R^2cv $=0.6000$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	7.1741×10^{2}	1.0858×10^{2}	6.6075
	Est (N)	−3.9157	5.9506×10^{-1}	−6.5803
	f-FNSA-1	-1.2367×10^{1}	2.6643	−4.6419
9.		$R^2=0.8915$ $n=11$ $F=32.86$ $s^2=0.0649$ R^2cv $=0.8481$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept	2.6503	2.8508×10^{-1}	9.2966
	qtot (N)	6.1660×10^{1}	9.4221	6.5442
	f-PNSA-1	-1.5134×10^{-2}	3.4260×10^{-3}	−4.4174
10.		$R^2=0.8855$ $n=11$ $F=30.93$ $s^2=0.0685$ R^2cv $=0.7155$		
	Descriptor	Regression coeff.	Std. dev. of regr. coeff.	t-test
	Intercept-	7.3650	2.0723	−3.5541
	qtot (N)	5.9252×10^{1}	9.7277	6.0910
	FPSA-1	1.1 238×10^{1}	2.6436	4.2510

Table 6. Experimental 5-HT1$_A$ serotoninergic and α_1-adrenergic binding affinities, selectivity ratio, and theoretical descriptors of the protonated form of the ligands reported in Scheme 2 and utilized for predictivity assessment of the QSAR models obtained

5-HT1$_A$ serotoninergic binding activity predictions

Mol.	p*Ki* 5HT1$_A$	V_{in} 5HT1$_A$ (Å^3)	V_{out} 5HT1$_A$ (Å^3)	V_{dif} 5HT1$_A$	Eexch(N–H) (eV)	$P_{\sigma\text{-}\pi}$(N–H)	Ec(N–H) (eV)	E_R(N–H) (eV)	Enn(N–H) (eV)	μh (Debye)	GAMMA	DPSA-3 (Å^2)	WNSA-3 (Å^2)
Prd1	9.40[a]	328.50	74.50	0.46	5.2773	1.20E-05	5.5944	12.8222	53.4681	1.842	5.46E+04	22.009	−6.231
Prd2	9.20[a]	329.38	93.25	0.43	5.2799	6.00E-06	5.5771	12.8059	53.4397	1.896	6.73E+04	21.506	−7.552
Prd3	9.00[a]	333.50	30.75	0.55	5.1560	1.00E-06	5.5725	12.7995	53.4361	1.272	7.03E+04	26.713	−13.612
Prd4	9.00[a]	317.63	22.00	0.54	5.2528	1.10E-05	5.5956	12.8116	53.4610	2.029	4.97E+04	19.753	−5.570
Prd5	9.50[b]	345.25	16.88	0.60	5.3136	2.93E-04	5.5829	12.7620	53.3793	1.035	6.23E+04	28.379	−10.551
Prd6	8.80	343.13	44.25	0.55	5.1425	2.10E-05	5.5770	12.7820	53.4006	1.307	9.08E+04	25.129	−9.123

α_1-Adrenergic binding affininity predictions

Mol.	p*Ki* α_1	V_{in} α_1 (Å^3)	V_{out} α_1 (Å^3)	V_{dif} α_1	qtot(H)	I_A (cm^{-1})	Eee(N–H) (eV)	PSA(N) (Å^2)	f-PNSA-1 (Å^2)	PNSA-1 (Å^2)	f-WNSA-1 (Å^2)	f-WNSA- (Å^2)
Prd1	7.20[a]	318.13	86.75	0.47	0.2404	0.0189	40.0273	1.6035	40.785	107.581	1.691	−65.983
Prd2	6.96[a]	314.75	107.00	0.43	0.2358	0.0155	40.1256	2.4053	36.906	158.837	1.436	−62.022
Prd3	7.70[a]	342.75	22.75	0.66	0.2368	0.0179	36.1186	4.0088	152.864	261.584	25.621	−181.546
Prd4	7.10[a]	309.63	27.12	0.58	0.2377	0.0250	39.5692	3.2070	46.370	125.849	2.150	−48.515
Prd7	7.07[d]	292.13	52.62	0.49	0.2407	0.0197	39.8479	1.6035	101.377	176.249	12.753	−161.714
Prd8	7.90[c]	265.50	102.75	0.33	0.2427	0.0129	36.4517	2.4053	160.887	231.255	31.062	−279.721
Prd9	8.14[b]	258.75	88.25	0.35	0.2363	0.0132	37.4184	2.4053	144.608	245.379	22.804	−106.464

5-HT1$_A$ serotoninergic/α_1-adrenergic selectivity predictions

Mol.	Δp*Ki*	qtot(N)	Est(N) (ev)	f-FNSA-1	FPSA-1	f-WNSA-1 (Å^2)	PNSA-1 (Å^2)	f-PNSA-1 (Å^2)
Prd1	2.20	−0.0028	182.5295	0.0506	0.867	1.691	107.581	40.785
Prd2	2.24	−0.0057	182.5682	0.0437	0.812	1.436	158.837	36.906
Prd3	1.30	−0.0071	182.5886	0.1976	0.662	25.621	261.584	152.864
Prd4	1.90	−0.0009	182.5089	0.0643	0.826	2.150	125.849	46.370

[a]Ref. 12.
[b]Ref. 13.
[c]Ref. 14.
[d]Ref. 15.

Table 7. Experimental binding affinities and prediction results obtained by the QSAR models reported in Tables 3–5

Mol.	Obs.	Calcd eq (1)	Δ	Calcd eq (2)	Δ	Calcd eq (3)	Δ	Calcd eq (4)	Δ	Calcd eq (5)	Δ	Calcd eq (6)	Δ	Calcd eq (7)	Δ	Calcd eq (8)	Δ	Calcd eq (9)	Δ	Calcd eq (10)	Δ	Average Calcd	Δ
												pKi 5-HT1$_A$											
Prd5	9.50	9.30	0.20	9.27	0.23	9.34	0.16	9.60	−0.10	9.35	0.15	9.16	0.34	9.30	0.19	9.44	0.06	9.45	0.05	8.63	0.87	9.28	0.22
Prd1	9.40	8.81	0.59	8.38	1.02	8.66	0.74	8.79	0.61	8.67	0.73	8.62	0.78	8.41	0.98	8.34	1.06	8.37	1.03	8.21	1.19	8.53	0.87
Prd2	9.20	8.69	0.51	8.24	0.96	8.59	0.61	8.66	0.54	8.59	0.61	8.61	0.59	8.37	0.83	8.26	0.94	8.23x	0.97	8.09	1.11	8.43	0.77
Prd3	9.00	9.13	−0.13	8.98	0.02	9.06	−0.06	8.11	0.89	9.07	−0.07	9.06	−0.06	9.08	−0.09	9.25	−0.25	9.12	−0.12	9.10	−0.10	9.00	0.00
Prd4	9.00	9.09	−0.09	8.51	0.49	8.96	0.04	9.08	−0.08	8.98	0.02	8.88	0.12	8.51	0.48	8.42	0.58	8.42	0.58	8.58	0.42	8.74	0.26
Prd6	8.80	9.11	−0.31	8.94	−0.14	9.09	−0.29	9.11	−0.31	9.09	−0.29	9.01	−0.21	9.17	−0.37	9.04	−0.24	9.04	−0.23	9.16	−0.36	9.07	−0.27
												p*Ki* α_1											
Prd9	8.14	7.08	1.06	7.13	1.01	7.52	0.62	9.33	−1.19	9.12	−0.98	9.85	−1.71	8.50	−0.36	9.40	−1.26	6.65	1.49	9.11	−0.97	8.36	−0.22
Prd8	7.90	6.85	1.05	7.07	0.83	7.52	0.38	8.84	−0.94	8.91	−1.01	6.67	1.23	10.52	−2.62	8.60	−0.70	6.72	1.18	9.10	−1.20	8.08	−0.18
Prd3	7.70	8.09	−0.39	8.26	−0.56	8.27	−0.57	9.49	−1.79	9.55	−1.85	10.20	−2.50	9.52	−1.82	9.24	−1.54	8.32	−0.62	9.46	−1.76	9.04	−1.34
Prd1	7.20	7.10	0.10	7.59	−0.39	7.15	0.05	5.85	1.35	6.10	1.10	5.79	1.41	6.38	0.82	5.48	1.72	8.07	−0.87	6.16	1.04	6.56	0.64
Prd4	7.10	8.02	−0.92	7.97	−0.87	7.90	−0.80	6.40	0.70	6.53	0.57	6.60	0.50	6.84	0.26	6.33	0.77	8.56	−1.46	6.54	0.56	7.16	−0.06
Prd7	7.07	7.63	−0.53	7.65	−0.58	7.15	−0.08	7.49	−0.42	7.51	−0.44	7.51	−0.44	7.98	−0.91	7.41	−0.34	7.78	−0.71	7.44	−0.37	6.81	0.26
Prd2	6.96	6.79	−0.17	7.41	−0.45	7.52	−0.56	6.42	0.54	6.74	0.22	7.70	−0.74	7.16	−0.20	6.16	0.80	7.68	−0.72	6.53	0.43	7.00	−0.04
												Δp*Ki*											
Prd2	1.30	0.98	0.32	1.04	0.26	−0.61	1.91	−0.12	1.42	−0.15	1.45	−0.56	1.86	−0.03	1.33	0.00	1.30	−0.10	1.40	−0.35	1.65	0.02	1.28
Prd1	1.90	1.38	0.52	1.37	0.53	1.81	0.09	1.91	0.01	1.83	0.07	1.80	0.10	1.96	−0.06	1.96	−0.06	1.89	0.01	1.86	0.04	1.78	0.12
Prd4	2.20	1.26	0.94	1.28	0.92	2.01	0.19	1.92	0.28	1.76	0.44	1.95	0.25	2.01	0.19	2.05	0.15	1.86	−0.01	2.21	−0.19	1.83	0.37
Prd3	2.24	1.07	1.17	1.12	1.12	1.07	1.17	1.82	0.42	1.63	0.61	1.03	1.21	1.91	0.33	1.98	0.26	1.74	0.50	1.42	0.82	1.48	0.76

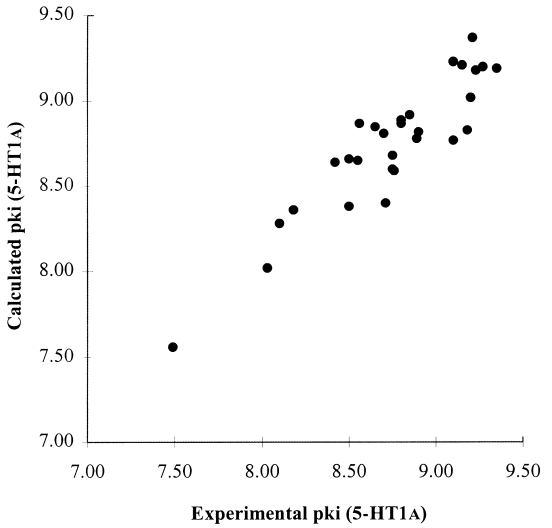


Figure 1. Calculated versus experimental 5-HT1$_A$ serotoninergic receptor binding affinity according to eq (7), Table 3.

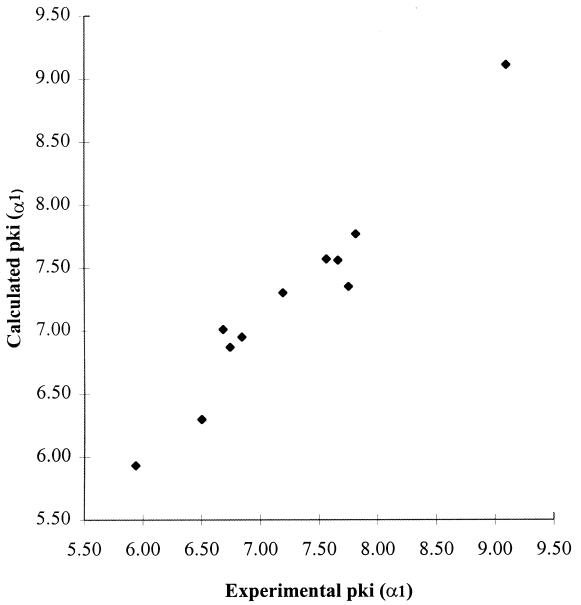


Figure 2. Calculated versus experimental α_1-adrenergic receptor binding affinity according to eq (4), Table 4.

It is worth noting that, because of the large structural diversity of the ligands considered not always the correspondence between the highest value of R^2cv and good prediction is respected. In this respect, the possibility to generate in a fast way a large pool of QSAR models able to describe a biological property assumes a fundamental importance in particular with respect to the prediction problem, in fact a gratifying agreement between the binding affinity data values averaged over all the ten models and the experimental data values is

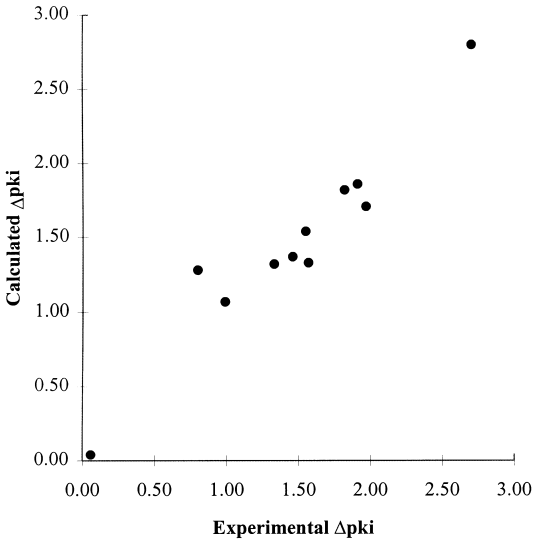


Figure 3. Calculated versus experimental receptor selectivity according to eq (3), Table 5.

observed. This is emphasized by the results obtained for the prevision of the α_1-adrenergic receptor binding affinity, where the averaged values agree well with the experimental values notwithstanding no more than two good predictions can be obtained by a single model.

Only four ligands present a selectivity ratio within the range covered by the QSAR models obtained. The best predictions are obtained by eq (7) and (8) of Table 5 which share the involvemet of the CPSA descriptor f-FNSA-1, computed on the bicyclic fragment and normalized with respect to the total surface area of the fragment itself.

Conclusions

Powerful predictive and interpretative theoretical QSAR models have been obtained in this study by means of the heuristic statistical treatment implemented in the CODESSA program.

The theoretical descriptors involved in the selected QSAR models can be classified as: (a) ad hoc size and shape descriptors defined with respect to a supermolecule of highly affine ligands, and (b) descriptors derived on a single structure, i.e. molecular orbital indexes and charged partial surface area descriptors).

On an interpretative ground, the complete scenario of key features for receptor binding is well depicted by all these indexes. In fact, the electrostatic interaction between the protonated amine function and a primary nucleophilic site of the receptor necessary for recognition

are described by the MO indexes localized on the $N–H^+$ group, while the short-range attractive and repulsive intermolecular interactions mainly responsible for the modulation of the binding affinities are described by MO indexes computed on the whole molecules (polar and dispersive forces), by CPSA descriptors computed on the whole molecules or on the bicyclic fragments (polar forces) and by ad hoc defined size an shape descriptors (dispersive and steric forces). However, the results obtained seems to suggest that the ad hoc defined size and shape descriptors, being derived to account for the strict complementarity requirements for receptor binding are more suitable to describe, in a series of non congeneric compounds, the range of high affinities and to be used in connection with pharmacological data referring to single population of receptor subtypes.

Moreover, the availability of a large pool of robust QSAR models quickly obtained by CODESSA has proven to be very useful in the prediction of the activities and selectivities of ligands structurally very diverse from those used in the QSAR modeling.

References

1. Karelson, M.; Lobanov, V. S.; Katritzky, A. R. *Chem. Rev.* **1996**, *96*, 1027, and refs therein.

2. De Benedetti, P. G.; Cocchi, M.; Menziani, M. C.; Fanelli, F. *J. Mol. Struct. (Theochem)* **1994**, *305*, 101, and refs therein.

3. Katritzky, A. R.; Lobanov, V. S.; Karelson, M. *Chem. Soc. Rev*. **1995**, 279.

4. Peglion, J. L.; Canton, H.; Bervoets, K.; Audinot, V.; Brocco, M.; Gobert, A.; Le Marouille-Girandon, S.; Millan, M. J. *J. Med. Chem*. **1995**, *38*, 4044.

5. Cocchi, M.; Fanelli, F.; Menziani, M. C.; De Benedetti, P. G. *J. Mol. Struct. (Theochem)* **1997**, *397*, 129.

6. Dewar, M. J. S.; Zoebisch, E. G.; Healey, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc*. **1985**, *107*, 3902.

7. QUANTA/CHARMm, 1995 Molecular Simulations Inc., 16 New England Executive Park, Burlington, MA 01803-5297, USA.

8. Katritzky, A. R.; Mu, L.; Lobanov, V. S.; Karelson, M. *J. Phys. Chem*. **1996**, *100*, 10400.

9. CODESSA User's Manual, University of Florida, Gainesville, FL 32601, 1994.

10. De Benedetti, P. G.; Fanelli, F; Menziani, M. C.; Cocchi, M,; Testa, R.; Leonardi, A. *Bioorg. & Med. Chem*. **1997**, *5*, 809.

11. Stanton, D.T.; Jurs, P.C. *Anal. Chem*. **1990**, *62*, 2323.

12. Raghupathi, R. K.; Rydelek-Fitzgerald, L.; Teitler, M.; Glennon, R. A. *J. Med. Chem*. **1991**, *34*, 2633.

13. Eltze, M.; Boer, R.; Sanders, K. H.; Kolassa, N. *Eur. J. Pharmacol*. **1991**, *202*, 33.

14. Russo, F.; Romeo, G.; Guccione, S.; De Blasi, A. *J. Med. Chem*. **1991**, *34*, 1850.

15. Yazawa, H.; Takanaschi, M.; Sudoh, K.; Inagaki, O.; Honda, K. *J. Pharmacol. Exp. Ther*. **1992**, *263*, 201.