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Relevance of Theoretical Molecular Descriptors in Quantitative Structure–Activity Relationship Analysis of α1-Adrenergic Receptor Antagonists

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Abstract—A quantitative structure–activity relationship (QSAR) study of a wide series of structurally diverse α_1-adrenergic receptor antagonists was performed using the CODESSA (Comprehensive Descriptors for Structural and Statistical Analysis) technique. Theoretical descriptors derived on a single structure and ad hoc defined size and shape descriptors were considered in the attempt of describing information relevant to receptor interaction. The relative effectiveness of these two classes of parameters in developing QSAR models for native (α_{1A} and α_{1B}) and cloned (α_{1a}, α_{1b}, and α_{1d}) adrenergic receptor binding affinity, functional activity of vascular and lower urinary tract tissues, and in vitro and in vivo selectivity was evaluated.

Introduction

Nowadays, the main challenge of a quantitive structure–activity relationship (QSAR) study is to discriminate successfully between subtly different types of activity. Protein biochemistry approaches combined with DNA cloning and sequencing techniques have demonstrated that receptors constitute families of proteins built on a common structural scheme, despite the wide molecular diversity of their ligands. Thus, few molecular determinants are responsible for discrimination of compounds among receptor classes, subtypes or variants, as well as for the agonistic or antagonistic character of the ligands.

A representative example is constituted by the class of monoamines acting at the α_1-adrenergic G protein-coupled receptors (α_1-AR). It is generally assumed that a common molecular recognition mechanism, strictly conserved through receptor evolution, is exploited to guide the cationic ligands into a productive interaction with the crucial aspartic acid residue of the thirth transmembrane domain. Therefore, the molecular determinants for the modulation of binding affinity, selectivity and efficacy rest, from the protein side, on accessory binding areas of the receptor and, from the drug side, on additional molecular moieties or functional groups.

The process of distinguishing the few functionalities that contribute to binding from those that are superfluous is complicated by the great diversity in size and chemical composition of the ligands. 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.[1–3] 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. Therefore, size and shape descriptors can

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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. Moreover, the use of a supermolecule instead of a single ligand for molecular similarity comparison allows the modeling of non congeneric series of compounds, where the most active ligands share little topological and topographical structural similarity.[4] 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.[5]

In the present work, a quantitative rationalization of the pharmacological properties of a wide series of non congeneric α_1-AR antagonists constituted by prototype of extensively investigated class of ligands has been attempted.

Ad hoc defined size and shape descriptors and a large variety of global and local theoretical molecular descriptors, which have been shown to characterize typical features of the electronic structure and/or of ligand reactivity,[6] have been employed in order to compare their performance in rationalizing high-quality binding affinity data values and to extend the results obtained in a recently published paper[3] to the modeling of in vitro and in vivo functional activities.[7]

The heuristic statistical treatment implemented in the CODESSA (Comprehensive Descriptors for Structural and Statistical Analysis) program[8,9] has been used to select a limited set of descriptors able to describe the molecular determinants for binding affinity of native (α_{1A} and α_{1B}) and cloned (α_{1a}, α_{1b}, and α_{1d}) adrenergic receptors, functional activity of vascular and lower urinary tract tissues, and, in vitro and in vivo subtype selectivity.

Computational Procedure

Geometry optimization

Conformational analysis of the protonated form of some 1,4 benzodioxane WB-4101-like derivatives[10] and of some quinazoline, piperazine and piperidine[11,12] derivatives was recently performed. In this work, we considered the resulting absolute minimum structure of the parent compounds as starting geometry. The substituents were constructed within the Editor module of the QUANTA96 program.[13] Then, the protonated structures were fully optimized by means of molecular orbital calculations (AM1),[14] using the MOPAC 6.0 (QCPE 455) program.

Ad hoc modeling

The ad hoc modeling consisted in comparing the van der Waals volume of the minimized structure of each ligand (in its extended minimum conformation) with the van der Waals volume of a supermolecule chosen as a template.[3] An automatic procedure to facilitate this goal has recently been published.[4]

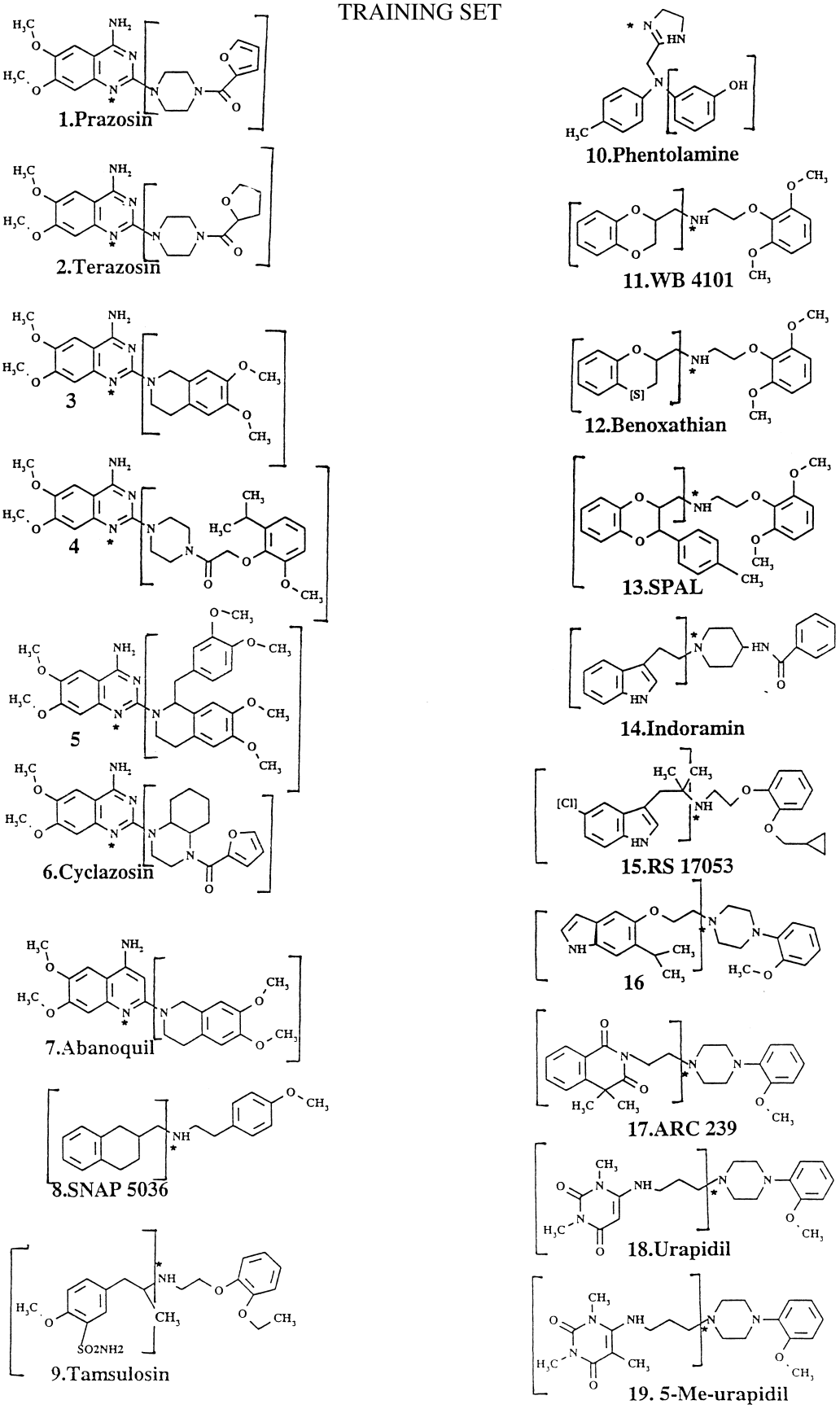
In the series of antagonists considered in this study, subsets of analogues can be identified as constituents of extensively investigated class of ligands such as quinazolines, *N*-arylpiperazines, imidazoline, phenylalkilamines, benzodioxans, indoles, 1-4 dihydropyridines, etc. (Scheme 1). Because of this structural heterogeneity, two criteria have to be satisfied contemporaneously from a ligand in order to be part of the tentative reference subtype supermolecule, that is, high affinity for the specific adrenergic receptor subtype and representativity of unique structural features. Therefore, the cutoff for the minimum in the binding affinity data value (p*K*) to be considered was fixed to 9 for the α_{1A}-AR, 8.9 for the α_{1B}- and α_{1b}-ARs, 9.2 for the α_{1a}-AR and 8.8 for the α_{1d}-AR.

The ligands chosen were superimposed, by a rigid fit procedure, minimizing the rms deviations with respect to three dummy atom pairs: (a) a dummy atom positioned 3.0 Å from the protonated nitrogen (marked with one star in Schemes 1 and 2) on the vector defined by the $N–H^+$ bond; (b) two dummy atoms positioned, respectively, 3 Å above and below the centre of the aromatic plane of the phenyl ring close to the protonated nitrogen; (c) two dummy atoms positioned, respectively, 3 Å above and below the centre of the average plane of the variable fragment enclosed in brackets in Scheme 1. For ligand 38 (SKF106686) only dummy atoms (a) and (c) were used. The volume of the resulting supermolecule was computed and redundant constituents were successively eliminated. Redundancy was judged by considering the minimum number of active compounds which contribute in an original way to the overall three-dimensional shape of the supermolecule.

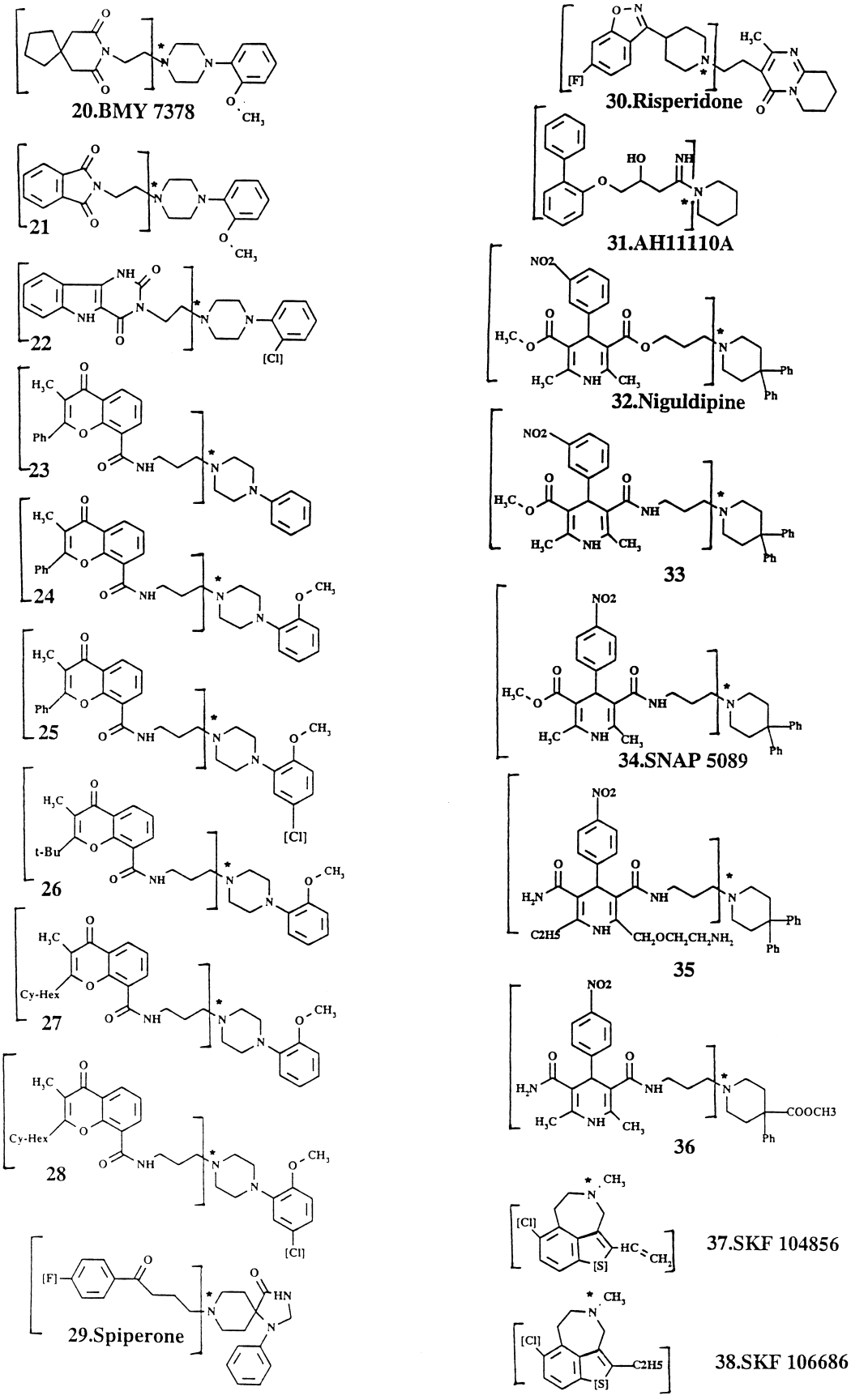
Thus, to model the pharmacological α_1-adrenergic subtype binding affinities compounds **1**, **3**, **9**, **15** and **28** were used for the α_{1A} supermolecule, whereas compounds **6**, **7** and **22** were used for the α_{1B} supermolecule. For the cloned α_1-adrenergic receptor binding affinity, the ligands used for the α_{1a} supermolecule are compounds **3**, **9**, **11**, **15**, **28** and **32** (compound **3** was preferred to compound **7** for consistency with the corresponding pharmacological supermolecule, since the two ligands have very similar volumes, they are perfectly interchangeable in the construction of the supermolecule); for the α_{1b} supermolecule: compounds **1**, **4**, **7**, **22**; and for the α_{1d} supermolecule: compounds **1**, **7**, **17**, **22**, **38**.

All the other compounds of the training and test sets were satisfactorily superimposed on the appropriate supermolecule using the same matching procedure, each ligand being superimposed on the analogue compound present in the supermolecule, or on its structurally closest compound.

TRAINING SET

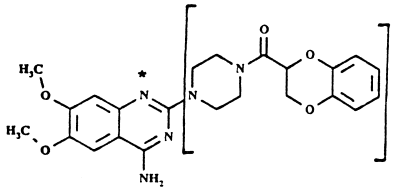


Scheme 1. Brackets enclose group of atoms assigned to the variable fragment in the computation of the theoretical descriptors. Stars mark the protonated nitrogen atom. *(Continued on next page.)*

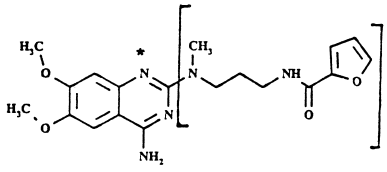


Scheme 1. *(continued).*

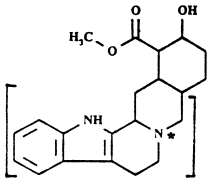
TEST SET



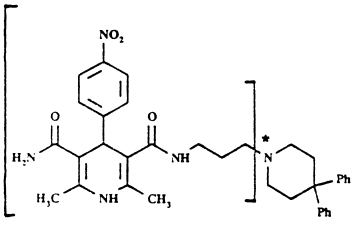
39.Doxazosin



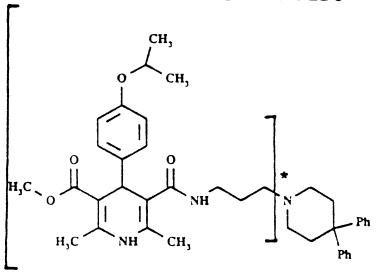
40.Alfuzosin



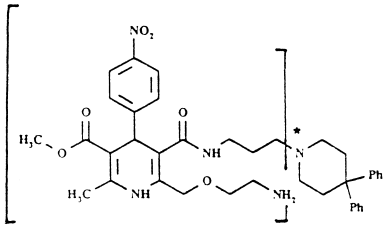
41.Corynanthine



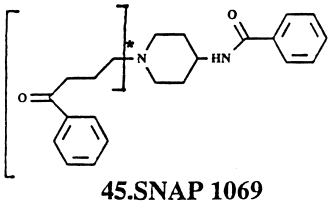
42.SNAP 5150



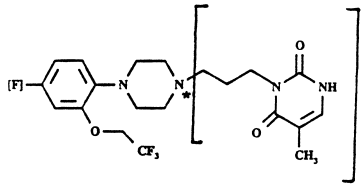
43



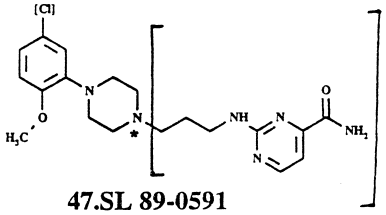
44.SNAP5399



45.SNAP 1069



46.RS 100,975



47.SL 89-0591

Scheme 2. Brackets enclose group of atoms assigned to the variable fragment in the computation of the theoretical descriptors. Stars mark the protonated nitrogen atom.

The QUANTA96[13] molecular modeling software was utilized for molecular comparison and computation of van der Waals volumes. We considered the ad hoc defined size and shape descriptors: V_{in} and V_{out} which are respectively the inner (intersection) and the outer van der Waals volume of the ligand considered with respect to the volume of the supermolecule (V_{sup}) and V_{dif} which is computed according to the formula $V_{dif} = (V_{in} - V_{out})/V_{sup}$.

Molecular descriptors and statistical treatment of data

The MOPAC output files were loaded into the CODESSA program[8] along with the experimental binding affinities and a large number of global and fragment descriptors (topological, electrostatic, geometrical and quantum-chemical) were generated for each compound.[6,15] The ad hoc defined molecular size and shape descriptors, described above, were added as external descriptors.[5]

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.[8,9] Default values for control parameters and criteria were used: minimum squared correlation coefficient to consider one-parameter correlation significant, $R_{min} = 0.1$; 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 level, $r_{sig} = 0.80$. Evaluation of the best correlation models was carried out by (a) validation of the stability of each regression model by cross-validation techniques (i.e. the sensitivity of the model to the elimination of any single data point) and (b) by prediction response value for test sets of structurally diverse molecules, reported in Scheme 2. The QSAR models reported in this paper were selected on the basis of the best statistical parameters and the largest diversity in the physical information content of the descriptors involved.

Results and Discussion

The large diversity in the structural features of the α_1-antagonists considered in this study is shown in Scheme 1.

The data values of global and local molecular descriptors involved in the correlations finally chosen are listed in Table 1 (ad hoc defined molecular descriptors) and Table 2 (theoretical descriptors derived on a single structure). The local theoretical descriptors have been defined either on a single atom (N), pairs of atoms (N–H, C–O and C–X, where X represents a nitrogen or oxygen atom) or group of atoms (f-). The groups of atoms chosen to represent the variable fragment (f-) for each α_1-AR antagonists are bracketed in Scheme 1.

The cologarithmic form of the α_1-adrenergic subtype binding affinities of the ligands considered are listed in Table 1.

Correlation analysis of subsets

According to the hybridization characteristics of the protonated nitrogen atom, which is the essential pharmacophoric element shared by all the ligands, the original set can be divided into three subsets: (a) sp^2 planar nitrogen, compounds **1**–**7** and **10**; (b) sp^3 secondary amine, compounds **8**, **9**, **11**–**13** and **15**; (c) sp^3 tertiary amine, compounds **14**, **16**–**38**.

Among the regression models obtained for the two most populated subsets (a) and (c), those showing the best statistical parameters are reported in Table 3.

The critical role of the protonated nitrogen atom of the prasozin-like ligands of subset (a) (compounds **1**–**7**) is well accounted for by the coulombic or total interaction energy for the $(N–H)^+$ pair.[14] Other intermolecular electrostatic interactions between the ligand and receptor are described, for the native α_{1A} binding affinity, by the accessible surface areas weighted charges of the negatively charged atoms of the fragment[16] (f-WNSA-3). Equation (4), obtained in a previous work[3] and reported here for comparative purposes, involves the V_{dif} descriptor computed with respect to the supermolecule conceived to represent a map of the target α_{1a}-AR binding site, and, therefore constituted by ligands representative of the whole heterogeneous set (i.e. ligands **3**, **9**, **11**, **15**, **28** and **32**, see Computational Procedure).

The molecular descriptors involved in the rationalization of the various binding affinity for subset (c) reflect different molecular peculiarities. The variation in the native α_{1A} receptor subtype binding affinity data values is explained by the XY Shadow index,[17] which codifies for the size of the molecules, while 77% of the variation in the native α_{1B} receptor subtype binding affinity data values is explained by FPSA-2, a charged partial surface area (CPSA) descriptors[16] which models polar intermolecular interactions.

It is worth noting that the best correlation for the cloned α_{1a}-AR binding affinity is obtained, also for this subset of ligands, with an ad hoc defined molecular descriptor (V_{in}, eq (3)). The positive slope of the correlation suggests that the volume of the ligands which show high affinity should be included as much as possible in that of the supermolecule, consistently with the assumption that the supermolecule might reflect the best size and shape complementarity towards the high affinity binding site of the receptor considered. The affinity for the cloned α_{1b}-AR subtypes is roughly interpreted by the electronic repulsion energy for the $(N–H)^+$ pair. Two parameters are necessary to obtain satisfactory correlation for the α_{1d}-AR binding affinity. These are codified for the structural features responsible for intermolecular hydrogen bonding[16] (FHBSA) and polarizability[6] (E_L–E_H) of the ligands.

The outliers for all the QSAR models obtained are ligands that show medium to low affinities for the specific α_1-AR subtype, with the exception of compounds **16** and **22** which are underestimated by the α_{1A} QSAR

Table 1. Experimental binding affinities[a] on native (pK_{1A} and pK_{1B}) and closed (pK_{1a}, pK_{ib} and pK_{id}) adrenergic receptors and ad-hoc defined molecular descriptors (V_{in}, V_{in}/V_{mol}, V_{out} and V_{dif})[b] of the antagonists reported in Scheme 1

mol[c]	pK_{1A}	V_{in}/V_{mol}	V_{out} (Å^3)	V_{dif}	pK_{1B}	V_{inb} (Å^3)	V_{inb}/V_{mol}	V_{dif}	pK_{1a}	V_{in} (Å^3)	V_{in}/V_{mol}	V_{dif}	pK_{1b}	V_{in} (Å^3)	V_{in}/V_{mol}	V_{dif}	pK_{1d}	V_{in} (Å^3)	V_{in}/V_{mol}	V_{dif}
1	**9.04**	1.0000	0.00	0.395	9.34	299.75	0.9588	0.474	9.15	289.75	0.9268	0.263	**9.30**	312.63	1.0000	0.459	**8.85**	312.63	1.0000	0.415
2	8.24	0.9708	1.75	0.399	8.45	292.50	0.8996	0.440	7.85	299.13	0.9200	0.269	7.85	301.25	0.9266	0.407	7.45	307.00	0.9442	0.383
3	**10.00**	1.0000	0.00	0.417	9.15	316.88	0.9448	0.502	**9.69**	335.38	1.0000	0.330	9.69	324.00	0.9661	0.459	9.69	322.25	0.9609	0.410
4	8.66	0.8015	75.50	0.334	8.96	316.25	0.7485	0.359	8.12	344.13	0.8145	0.262	**9.30**	422.50	1.0000	0.621	8.00	322.50	0.7633	0.295
5	6.29	0.6305	164.12	0.161	7.64	289.13	0.6267	0.203	6.37	311.63	0.6755	0.173	6.99	295.00	0.6982	0.184	6.20	289.88	0.6283	0.173
6	7.60	0.8458	46.37	0.337	**9.69**	358.25	1.0000	0.589	7.48	300.25	0.8142	0.228	9.15	297.38	0.8065	0.332	7.56	317.75	0.8617	0.354
7	9.69	0.9619	5.50	0.406	**10.00**	330.25	1.0000	0.543	10.00	331.13	0.9807	0.320	**10.00**	337.63	1.0000	0.496	**10.00**	337.63	1.0000	0.448
8									8.36	212.00	0.7488	0.139	7.14	182.13	0.6433	0.119	6.81	193.25	0.6825	0.137
9	**9.69**	1.0000	0.00	0.435	8.39	282.38	0.9974	0.366	**9.69**	350.50	1.0000	0.345	8.17	275.63	0.7864	0.295	8.74	298.00	0.8502	0.326
10	7.79	0.4993	68.50	0.135	7.05	170.25	0.4857	0.160	8.49	192.13	0.7735	0.134	7.05	168.75	0.6794	0.131	7.17	187.88	0.7564	0.169
11	8.87	0.9215	62.25	0.212	7.58	222.25	0.8948	0.252	**9.22**	296.13	1.0000	0.292	7.24	225.00	0.7598	0.226	8.20	236.75	0.7995	0.235
12	6.69	0.7843	63.38	0.215	7.24	224.75	0.7590	0.253	9.15	300.63	0.9938	0.294	7.26	230.13	0.7608	0.232	7.67	240.50	0.7950	0.237
13	7.35	0.6132	190.25	−0.006	6.20	177.75	0.5876	−0.033	8.39	338.25	0.8446	0.272	6.79	241.75	0.6036	0.122	6.85	268.13	0.6695	0.180
14	7.55	0.5215	96.12	0.143	7.37	206.50	0.5156	0.178	8.30	241.13	0.7637	0.164	7.62	215.88	0.6837	0.170	6.56	246.13	0.7795	0.234
15	**9.15**	1.0000	0.00	0.454					**9.52**	369.38	1.0000	0.364	7.85	261.63	0.7083	0.226	7.77	266.13	0.7205	0.216
16	8.72	0.8535	28.50	0.364	7.82	285.38	0.7726	0.373	9.22	334.50	0.9275	0.304	7.79	286.00	0.7931	0.311	7.39	211.63	0.5358	0.038
17									9.00	329.25	0.9120	0.293	8.69	263.00	0.7285	0.242	**9.39**	362.88	1.0000	0.481
18	6.56	0.7944	43.88	0.308	6.37	265.25	0.7355	0.329	6.54	319.50	0.9308	0.291	5.88	289.13	0.8423	0.345	5.78	291.38	0.8489	0.318
19	8.33	0.8535	35.12	0.347	6.66	292.25	0.8096	0.397	8.69	336.38	0.9341	0.308	6.11	326.75	0.9073	0.431	6.76	319.63	0.8875	0.370
20	6.37	0.8602	38.63	0.326	6.56	271.88	0.7921	0.345	6.30	322.38	0.9175	0.289	6.37	276.88	0.7880	0.297	8.24	295.75	0.8417	0.318
21									**7.37**	308.00	0.9720	0.294	5.98	292.25	0.9223	0.393	6.32	295.13	0.9314	0.363
22	9.09	0.7917	54.00	0.294	**8.92**	339.13	1.0000	0.558	8.92	324.13	0.9378	0.298	**8.92**	345.63	1.0000	0.508	**10.00**	345.63	1.0000	0.458
23	8.85	1.0960	29.62	0.452	8.49	268.50	0.7641	0.201	8.45	404.50	0.9577	0.381	7.92	298.38	0.7064	0.256	7.41	294.13	0.6964	0.220
24	8.89	1.3033	27.00	0.491	7.96	284.38	0.8974	0.212	9.52	429.13	0.9619	0.406	7.28	318.63	0.7142	0.281	7.62	311.38	0.6980	0.234
25	8.77	1.2336	28.37	0.506	7.87	294.00	0.8506	0.219	8.89	443.25	0.9589	0.418	8.29	324.38	0.7017	0.274	7.37	320.50	0.6933	0.237
26	9.04	0.9609	24.87	0.484	7.21	291.75	0.6907	0.251	9.39	426.00	0.9619	0.403	6.93	330.88	0.7471	0.322	7.85	320.88	0.7245	0.264
27	9.30	0.9529	20.50	0.514	7.69	296.38	0.6643	0.242	9.39	445.25	0.9619	0.421	7.36	330.88	0.7148	0.292	8.27	326.75	0.7059	0.253
28	**9.52**	1.0000	0.00	0.584	8.00	298.00	0.6447	0.224	**9.69**	484.38	1.0000	0.477	7.74	333.00	0.6875	0.267	8.12	333.13	0.6877	0.241
29	7.42	0.5792	79.13	0.225	8.79	271.88	0.6139	0.347	7.89	317.25	0.9186	0.285	8.15	273.75	0.7926	0.297	7.66	296.25	0.8578	0.328
30	8.33	0.6794	25.75	0.367	8.66	282.63	0.6106	0.370	8.55	331.38	0.9358	0.304	8.11	294.88	0.8327	0.346	7.60	302.88	0.8553	0.334
31									6.79	225.00	0.7296	0.139	7.37	199.75	0.6472	0.134	6.42	224.13	0.7262	0.185
32	8.19	0.7412	158.50	0.255	6.42	304.00	0.6276	0.149	**9.39**	522.00	1.0000	0.514	7.60	320.38	0.6138	0.175	7.08	335.75	0.6432	0.198
33									9.39	509.13	0.9993	0.501	6.64	316.75	0.6217	0.182	6.37	333.50	0.6546	0.209
34	8.58	1.0279	158.50	0.247	6.64	298.75	0.8650	0.135	9.30	482.50	0.9171	0.432	7.12	315.25	0.5992	0.153	6.33	339.50	0.6453	0.203
35									9.22	468.88	0.8070	0.351	6.49	314.13	0.5407	0.069	6.19	345.63	0.5949	0.146
36									9.09	443.63	0.9175	0.397	5.56	303.13	0.6269	0.180	5.35	322.75	0.6675	0.215
37									7.44	149.75	0.6749	0.076	7.53	119.00	0.5363	0.024	8.79	209.00	0.9420	0.260
38									7.23	149.75	0.6532	0.069	7.82	121.00	0.5278	0.019	**8.92**	229.25	1.0000	0.304

[a] Triated prasozin was utilized to assess the affinity for the native α_1-AR (rat cerebral cortex), the α_{1A} (rat hippocampus pretreated with CEC) and α_{1B} (rat liver) adrenergic subtypes, as well as for the recombinant bovine α_{1a}, hamster α_{1b}, and rat α_{1d} transiently expressed in COS-7 cells.[7]

[b] The ad hoc defined size and shape molecular descriptors are computed by comparing the volume of the ligand with respect to the volume of reference supermolecule constructed by superimposition of ligands **1**, **3**, **9**, **15**, **28** for the α_{1A}-AR , ligands **6**, **7** and **22** for the α_{1B}, ligands **3**, **9**, **11**, **15**, **28** and **32** for the α_{1a}-AR, ligands **1**, **4**, **7** and **22** for the α_{1b}-AR and ligands **1**, **7**, **17**, **22** and **38** for the α_{1d}-AR. The experimental binding affinity data values of the ligands constituting the supermolecules are in bold in the table.

[c] Numbers in italic, bold and underlined designate the ligand to be part of subset (a), (b) or (c), respectively, according to the hybridization characteristics of the nitrogen atom.

Table 2. Theoretical descriptors computed on the protonated form of the ligands reported in Scheme 1

mol	E_C (TOT) (eV)	E_T (N–H) (eV)	E_C (N–H) (eV)	E_{ee} (N–H) (eV)	f-Pπ-π (C–O)	f-Pσ–π (C–X)	1/2×BETA	E_L–E_H (eV)	XY Shadow (Å^2)	ABIC^2	f-WNSA-3 (Å^2)	f-WPSA-3 (Å^2)	f-RNCS (Å^2)	FPSA-2	FPSA-3	WPSA-1 (Å^2)	DPSA-1 (Å^2)	HASA (Å^2)	FHBSA
1	311.68	13.75	5.39	37.89	0.8234	0.0224	−124.14	7.27	130.32	0.7636	−15.05	21.90	6.57	3.03	0.1014	146.63	218.96	131.66	0.3394
2	318.81	13.75	5.39	37.90	0.8186	0.0213	−131.68	7.55	127.12	0.7723	−10.51	24.42	5.83	3.56	0.0998	217.32	371.57	109.81	0.2213
3	326.78	13.76	5.39	37.96	0.4873	0.0280	−558.43	6.54	131.60	0.7167	−7.17	22.27	0.00	3.22	0.0932	214.83	345.11	95.67	0.1984
4	406.70	13.73	5.39	37.81	0.8521	0.0287	−113.21	5.94	162.10	0.7412	−16.31	37.98	0.16	4.16	0.0939	368.92	466.07	92.62	0.1661
5	444.96	13.69	5.31	37.52	0.4886	0.0303	−313.22	5.88	169.74	0.6497	−30.03	39.64	1.93	3.96	0.0839	407.42	410.56	112.62	0.1777
6	358.02	13.73	5.42	37.87	0.8111	0.0236	−150.30	6.93	131.18	0.7803	−16.59	27.48	0.00	3.64	0.0979	215.20	312.82	105.53	0.2782
7	327.79	13.78	5.44	38.24	0.4823	0.0272	−582.25	6.33	131.46	0.7118	−7.81	20.00	0.60	3.16	0.0888	202.75	322.25	92.36	0.1986
8	252.74	12.54	5.52	36.14	0.4855	0.0088	−223.27	7.95	94.06	0.7302	−4.46	19.15	0.00	2.69	0.0968	155.25	332.90	26.32	0.0637
9	274.54	14.18	5.56	42.22	0.5007	0.0268	−178.25	7.55	132.34	0.7901	−59.42	36.44	7.34	4.61	0.1085	202.33	314.33	115.67	0.2364
10	237.73	13.54	5.34	35.83	0.4738	0.0120	−144.24	7.03	80.94	0.7468	−8.74	10.45	0.00	2.64	0.1116	63.07	267.12	40.28	0.1653
11	283.09	12.56	5.70	36.20	0.4558	0.0238	−36.68	7.64	103.52	0.7023	−7.97	20.07	0.94	2.60	0.0947	139.38	294.69	55.40	0.1053
12	277.45	12.51	5.54	35.90	0.5164	0.0220	231.18	6.40	104.56	0.7572	−7.35	34.48	0.42	3.33	0.1280	143.31	320.46	40.08	0.1148
13	356.38	12.56	5.57	36.08	0.4931	0.0254	9.92	8.32	119.90	0.7126	−13.56	31.70	1.19	3.14	0.0917	231.26	329.59	46.84	0.0761
14	292.55	13.77	5.71	38.96	0.6178	0.0175	−6.02	7.60	110.32	0.7385	−6.85	20.35	0.51	3.01	0.1068	128.36	266.22	31.94	0.1206
15	323.26	13.40	5.72	36.69	0.6133	0.0184	−105.29	7.60	133.12	0.7911	−6.28	21.48	0.56	3.14	0.0914	189.23	355.30	32.70	0.0997
16	333.52	13.48	5.70	37.19	0.6885	0.0194	−211.51	6.99	118.92	0.7878	−9.63	26.26	0.46	3.27	0.1021	204.87	409.76	14.79	0.0632
17	334.89	12.36	5.59	35.86	0.8442	0.0223	−131.93	8.17	125.94	0.7316	−17.93	23.53	2.94	3.53	0.0987	179.37	359.36	47.34	0.0754
18	326.98	13.22	5.41	40.02	0.7990	0.0230	65.87	7.28	122.54	0.7790	−22.97	26.21	1.92	3.79	0.1027	193.29	383.42	74.98	0.1246
19	336.23	13.25	5.58	40.29	0.8193	0.0219	−17.08	7.45	128.88	0.7892	−18.88	25.60	4.12	3.89	0.1014	206.08	414.53	69.30	0.1194
20	321.14	12.36	5.58	35.92	0.8724	0.0260	−56.04	8.17	118.60	0.7246	−15.93	21.86	0.37	3.83	0.1002	190.04	432.03	63.75	0.1009
21	297.64	12.36	5.59	35.97	0.8831	0.0236	−103.63	8.09	119.74	0.7045	−18.64	19.26	0.14	2.87	0.1007	110.88	246.89	76.45	0.1223
22	323.16	13.42	5.76	36.13	0.8041	0.0296	−468.34	7.14	130.68	0.7434	−26.67	28.75	5.15	2.82	0.1017	157.31	163.30	80.05	0.1766
23	391.92	13.69	5.46	38.69	0.8916	0.0289	−122.00	7.07	147.18	0.7017	−29.39	40.04	0.07	3.75	0.0986	284.31	334.39	65.10	0.0921
24	415.79	13.70	5.48	38.67	0.8919	0.0286	−125.72	7.22	148.14	0.7362	−30.89	41.62	0.07	3.99	0.0970	295.74	374.67	65.47	0.0864
25	416.99	13.65	5.48	38.48	0.8924	0.0282	−74.53	7.22	154.06	0.7639	−30.77	42.48	0.07	4.06	0.0919	301.22	424.20	63.49	0.0822
26	408.81	13.61	5.49	38.50	0.8898	0.0308	−170.61	7.33	146.14	0.7618	−24.61	34.33	0.00	4.27	0.0961	282.67	431.33	62.50	0.086
27	431.74	13.64	5.44	38.85	0.9199	0.0289	−82.55	7.64	153.10	0.7452	−24.30	39.12	0.07	4.59	0.0964	342.56	498.42	63.28	0.0842
28	427.83	13.64	5.54	38.83	0.8931	0.0279	−50.53	7.52	154.66	0.7632	−26.84	40.47	0.07	4.56	0.0904	343.28	522.48	67.01	0.084
29	316.31	13.71	5.64	37.41	0.9103	0.0175	−197.99	8.32	117.96	0.7411	−15.50	18.26	6.06	3.16	0.1015	124.97	224.03	69.41	0.1505
30	331.16	12.38	5.60	36.19	0.6986	0.0277	−117.95	8.41	125.86	0.8014	−7.81	27.97	1.68	3.33	0.0963	231.23	343.63	91.19	0.1656
31	290.18	12.53	5.82	36.60	1.0408	0.0202	−70.73	7.47	98.96	0.7352	−15.21	26.26	2.98	3.05	0.1071	180.10	337.92	44.19	0.1216
32	490.57	13.45	5.57	37.31	0.8084	0.0227	−277.44	7.43	148.86	0.7016	−47.76	66.47	1.27	5.10	0.1099	405.59	419.32	141.82	0.1632
33	481.34	13.73	5.56	38.85	0.8113	0.0195	−219.76	7.47	148.36	0.7317	−48.53	66.08	2.35	5.06	0.1136	378.92	407.16	154.26	0.1892
34	494.48	13.71	5.71	38.90	0.8098	0.0194	−151.02	7.40	144.92	0.7134	−44.47	65.12	1.08	5.30	0.1104	404.71	435.29	139.85	0.1658
35	546.55	14.03	5.57	43.25	0.7839	0.0187	−235.24	7.17	183.61	0.7483	−64.03	89.92	1.06	5.99	0.1123	563.61	515.85	179.44	0.2144
36	485.52	13.86	5.69	40.15	0.7955	0.0199	−214.76	7.35	138.98	0.7655	−52.35	62.5	0.37	5.03	0.1103	341.98	350.12	191.46	0.2655
37	171.54	12.31	5.56	35.43	0.9325	0.0103	−169.11	7.62	84.54	0.8753	−5.89	22.73	1.36	2.27	0.1489	99.98	263.94	4.81	0.0271
38	175.61	12.30	5.53	35.39	0.6055	0.0101	−189.88	7.77	82.38	0.8503	−3.54	24.73	1.13	2.55	0.1560	119.35	331.65	2.41	0.0211

Table 3. Regression models for the correlation between molecular structure descriptors and α_1-AR binding affinities for the subsets of antagonists

Subset a		
1.	$pK_{1A} = 10.7(\pm 0.5) + 0.15(\pm 0.03)$f-WNSA-3	$R^2 = 0.81$, $F = 21.39$, $s^2 = 0.37$, $n = 7$, $R^2cv = 0.72$
2.	$pK_{1A} = -511(\pm 113) + 37.8(\pm 8.2)E_T$ (N–H)	$R^2 = 0.80$, $F = 21.18$, $s^2 = 0.37$, $n = 7$, $R^2cv = 0.67$
3.	$pK_{1B} = -84.0(\pm 16.6) + 17.3(\pm 3.1)E_C$ (N–H)	$R^2 = 0.86$, $F = 31.31$, $s^2 = 0.10$, $n = 7$, $R^2cv = 0.80$
4.	$pK_{1a} = 2.49(\pm 1.01) + 21.8(\pm 3.7)V_{dif_a}$[a]	$R^2 = 0.88$, $F = 35.31$, $s^2 = 0.25$, $n = 7$, $R^2cv = 0.82$
5.	$pK_{1a} = -531(\pm 106) + 39.2(\pm 7.7)E_T$ (N–H)	$R^2 = 0.84$, $F = 26.03$, $s^2 = 0.33$, $n = 7$, $R^2cv = 0.76$
6.	$pK_{1b} = -105(\pm 33.8) + 21.0(\pm 6.3)E_C$ (N–H)	$R^2 = 0.69$, $F = 11.27$, $s^2 = 0.43$, $n = 7$, $R^2cv = 0.60$
7.	$pK_{1d} = -542(\pm 118) + 40.0(\pm 8.6)E_T$ (N–H)	$R^2 = 0.81$, $F = 21.72$, $s^2 = 0.41$, $n = 7$, $R^2cv = 0.72$
Subset c		
1.	$pK_{1A} = 0.12(\pm 1.53) + 0.06(\pm 0.01)$XY Shadow	$R^2 = 0.72$, $F = 28.93$, $s^2 = 0.29$, $n = 13$, $R^2cv = 0.60$ omitted: **14**, **16** and **22**
2.	$pK_{1B} = 11.5(\pm 0.63) - 0.89(\pm 0.15)$FPSA-2	$R^2 = 0.77$, $F = 33.24$, $s^2 = 0.16$, $n = 12$, $R^2cv = 0.67$ omitted: **14**, **18**, **19** and **20**
3.	$pK_{1a} = 6.51(\pm 0.33) + 0.0062(\pm 0.00009)V_{ina}$[a]	$R^2 = 0.72$, $F = 49.81$, $s^2 = 0.19$, $n = 21$, $R^2cv = 0.66$ omitted: **18**, **20** and **21**
4.	$pK_{1b} = 27.9(\pm 3.65) - 0.53(\pm 0.09)E_{ee}$ (N–H)	$R^2 = 0.65$, $F = 31.35$, $s^2 = 0.30$, $n = 19$, $R^2cv = 0.56$ omitted: **20**, **21**, **35**, **37** and **38**
5.	$pK_{1d} = 2.45(\pm 2.21) - 13.6(\pm 1.99)$ FHBSA $+ 0.86(\pm 0.29)E_L - E_H$	$R^2 = 0.75$, $F = 28.07$, $s^2 = 0.29$, $n = 22$, $R^2cv = 0.68$ omitted: **18** and **22**

[a] These descriptors are defined with respect to the supermolecule considered to represent a map of the binding site obtained by superimposition of compounds **3**, **9**, **11**, **15**, **28** and **32**.

model. The high affinity of compound **22** is, as well, misinterpreted by the α_{1d} QSAR model.

Modeling the binding affinity of the combined set

Any of the theoretical descriptors defined on a single molecule and involved in the reported correlation models for the subsets (Table 3) gives successful linear correlations when applied to the whole set. However, the native and cloned α_1-AR subtype binding affinities are satisfactorily rationalized by the ad hoc derived size and shape descriptors, as shown in Table 4.

The best linear correlations are obtained for the native and cloned α_{1B}-AR binding affinity and involve V_{dif} and V_{in}/V_{mol}. The linear models suggest that optimization of the binding affinity is realized by maximizing the amount of bulk in one ligand, in the van der Waals volume region delimited by V_{sup}. Intermolecular structural complementarity is then quantified by the extent and the balance of dispersion forces and steric interactions.

It is interesting to note that the statistical parameter values for one-parameter correlations involving analogue descriptors (for instance, eqs (1) and (8), and eqs (5) and (11), Table 4) are rather similar, suggesting the same mechanism for the antagonist–receptor interaction in the case of native and cloned receptors. However, the intensity and selectivity of the interaction might be different. In fact, despite the original inconsistency[18] between the pharmacological properties of the native and cloned subtypes, it is now clear that the recombinant α_{1a} and α_{1b}-ARs correlate closely with the α_{1A} and α_{1B}-AR subtypes that have been identified in native tissues and which mediate their functional responses.[7] A satisfactory agreement is observed between the native α_{1B} and cloned α_{1b} binding affinity data values for the set of compounds analyzed ($R^2 = 0.81$, $s = 0.46$, $n = 28$, slope $= 0.91$). Slightly worse statistics are obtained for the native α_{1A} versus cloned α_{1a} binding affinity data values ($R^2 = 0.69$, $s = 0.58$, $n = 28$, slope $= 0.86$). However, omission of compound **12**, which is the largest outlier, notably improves the correlation ($R^2 = 0.82$, $s = 0.43$, $n = 27$, slope $= 0.93$).

A significant improvement in the linear regressions is obtained by using theoretical molecular descriptors which represent the propensity of the ligands to give additional intermolecular interactions.[5] In fact, specific and non specific polar interactions are codified, in the models obtained, by charged contact surface area descriptors computed on the fragment (eqs (7) and (16), Table 4) or on the whole ligands (eqs (6), (13) and (15), Table 4). The hydrogen-bonding potential of the ligands is taken into account in eqs (3), (10) and (14) (Table 4) by the σ–π or π–π bond order of a C–O or C–N pair of atoms of the fragments, which modulates the availability of the lone electron pairs of the heteroatoms for intermolecular interactions. The average bonding information content[19] (order 2) (ABIC^2), which encodes the branching ratio and constitutional diversity of a molecule (eq 2 Table 4), adjusts the linear regression model of the α_{1A}-AR binding affinity.

The descriptors involved in the multilinear regressions reported in Table 4 are orthogonal: R^2 for the intercorrelations ranges from 0.01 to 0.38. The upper limit, which may still be considered an acceptable value,[20] is reached by V_{inb} versus WPSA-1.

It is worth noting that the critical role of the protonated nitrogen atom is not explicitly taken into account in the QSAR models obtained for the combined set of heterogeneous ligands. Therefore, a long range electrostatic interaction has to be hypothesized as preliminary recognition step. Once the main docking has been accomplished, the binding affinities might be modulated by the optimization of short-range intermolecular interactions and dispersion contributions of the various molecular regions. In fact, both strength and specificity arise from the cumulation and interplay of many weak forces between the ligand and its target receptor.

In this context, the theoretical indices involved in the rationalization of the various α_1-AR binding affinities suggest that dispersive and polar interactions are very important for stabilization of the ligand–receptor complexes of the cloned α_{1a}, α_{1b} and α_{1d} receptors and native α_{1B} receptor subtype. The native α_{1A}-AR seems to be more susceptible to steric factors, since most of the correlations obtained involve the V_{out} ad hoc defined molecular descriptor.

Table 4. Regression models for the correlation between molecular descriptors and α_1-AR binding affinities for the combined set of antagonists

	$x \pm \Delta x$	*t*-test	R^2	F	s^2	n	R^2cv
α_{1A} (omitted compounds: **12**, **13**, **18**, **20**, **32**, **34**)							
1.	2.97 ± 9.1e−01	3.25-Intercept					
	6.35 ± 1.02	6.24-V_{in_A}/V_{mol}	0.65	38.96	0.28	23	0.57
2.	1.58e + 01 ± 2.44	6.51-Intercept					
	−2.2e−02 ± 2.8e−03	−7.83-V_{out_A}					
	−8.50 ± 3.16	−2.69-ABIC^2	0.77	33.17	0.19	23	0.69
3.	8.15 ± 4.9e−01	16.6240-Intercept					
	−1.7e−02 ± 2.4e−03	−7.2983-V_{out_A}					
	4.697e + 01 ± 1.874e + 01	2.51-f-Pσ–π(c−x)	0.76	31.67	0.20	23	0.66
α_{1B} (omitted compounds: **18**, **19**, **20**, **23**)							
4.	6.21 ± 1.9019e−01	32.63-Intercept					
	5.99 ± 5.5539e−01	10.78-V_{dif_B}	0.84	116.21	0.17	24	0.81
5.	3.53 ± 5.3876e−01	6.55-Intercept					
	5.90 ± 6.9094e−01	8.53-V_{in_B}/V_{mol}	0.77	72.83	0.25	24	0.73
6.	8.62 ± 8.3e−01	10.43-Intercept					
	5.81 ± 4.8e−01	12.10-V_{dif_B}					
	−2.37e + 01 ± 7.94	−2.98-FPSA	0.89	83.44	0.12	24	0.86
7.	4.69 ± 4.73e−01	9.90-Intercept					
	1.8e−02 ± 1.7e−03	10.52-V_{in_B}					
	−5.4e−02 ± 6.1e−03	−8.81-f-WPSA-3	0.87	73.22	0.14	24	0.85
α_{1a} (omitted compounds: **5**, **18**, **20**, **21**)							
8.	3.72 ± 7.67e−01	4.86-Intercept					
	5.66 ± 8.51e−01	6.65-V_{in_a}/V_{mol}	0.58	44.21	0.27	34	0.53
9.	7.25 ± 2.7e−01	26.98-Intercept					
	5.00 ± 8.2e−01	6.10-V_{dif_a}	0.54	37.24	0.30	34	0.48
10.	8.61 ± 3.5e−01	24.68-Intercept					
	5.74 ± 6.5e−01	8.86-V_{dif_a}					
	−2.14 ± 4.4e−01	−4.83-f-Pπ–π(C–O)	0.74	43.24	0.17	34	0.68
α_{1b} (omitted compounds: **18**, **19**, **20**, **21**, **26**, **36**, **37**, **38**)							
11.	3.40 ± 4.8e−01	7.01-Intercept					
	5.92 ± 6.3e−01	9.43-V_{inb}/V_{mol}	0.76	88.94	0.21	30	0.72
12.	6.22 ± 1.9e−01	31.51-Intercept					
	5.81 ± 6.2e−01	9.35-V_{dif_b}	0.75	87.50	0.21	30	0.71
13.	5.59 ± 4.2e−01	13.18-Intercept					
	1.7e−02 ± 1.8e−03	9.42-V_{in_b}					
	−5.2e−03 ± 6.1e−04	−8.59-WPSA-1	0.79	52.26	0.19	30	0.75
α_{1d} (omitted compounds: **2**, **5**, [16], **18**, **19**, **21**, **36**)							
14.	1.06 ± 6.4e−01	1.66-Intercept					
	7.08 ± 6.8e−01	10.36-V_{in_d}/V_{mol}					
	5.218e + 01 ± 1.408e + 01	3.70-f-Pσ–π(C–X)	0.81	59.84	0.23	31	0.77
15.	−5.7e−02 ± 1.11	−0.05-Intercept					
	8.43 ± 9.4e−01	8.97-V_{in_d}/V_{mol}					
	3.5e−03 ± 1.39	32.50-DPSA-1	0.77	46.61	0.28	31	0.71
16.	5.89 ± 5.03e−01	11.71-Intercept					
	−1.7e−02 ± 1.6e−03	−10.55-E_C(TOT)					
	2.8e−02 ± 2.9e−03	9.81-V_{in_d}					
	−1.1−01 ± 4.7e−02	−2.39-f-RNCS	0.82	42.28	0.22	31	0.78

The discrepancy observed in the determinants for ligand binding to cloned and native α_{1A}-AR seems to reflect the discrepancy in the binding affinity data values that might be artificially induced by pretreatment of the rat hippocampus tissue with the alkylating agent chloroethilclonidine (CEC)[21] or provoked by the presence of interfering receptor subtypes.

Validation of the binding affinity QSAR models

Assessment of the prediction power of the QSAR models obtained for the combined set of compounds is given by the cross-validated correlation coefficient R^2cv, reported in Table 4. The comparison of the experimental and calculated biological activities for eqs (2), (6), (10), (13) and (16) (Table 4), which can be considered, on the basis of their statistical quality, the best QSAR equations to describe the α_1-AR binding affinity, is shown in Table 5.

Moreover, the predictive power of the QSAR models of Table 4 can be challenged further on the set of ligands reported in Scheme 2. The predicted binding affinities for the cloned α_1-AR subtypes are reported in Table 6, together with their experimental binding affinity data values. The descriptors used are listed in Table 7. The binding affinity data values of the training and test sets of compounds come from two different laboratories[7,22] and are measured on animal cloned and human cloned, respectively.

Very good predictions are obtained for the α_{1a}-AR subtype, by considering a factor of 0.7 tolerance, in a logarithmic scale.[23] The overestimation of compounds **43** and **44** given by eq (8) is ameliorated by introducing in the correlation the V_{dif} descriptor (eqs (9) and (10)). A systematic overestimation of the poor α_{1b} binding affinity of compound **41** is observed. The rigid structure of this ligand (corynanthine) is easily accommodated within the volume of the supermolecule and the unrealistic positive contribution of V_{in} (eqs (11) and (12)) is not balanced by the second descriptor (WPSA-1) involved in eq (13). The α_{1d}-AR QSAR models fail in the prediction of compounds **46** and **47**. Also in this case the systematic overestimation of compound **46** and underestimation of compound **47** is due to the relative weight of the descriptors V_{in} and V_{mol}. Only the introduction of DPSA-1 (eq (15)) corrects this trend. It is worth noting that because of the large structural diversity

Table 5. Experimental and predicted values for the most significant regressions of Table 4

	pK_{1A}		pK_{1B}		pK_{1a}		pK_{1b}		pK_{1d}	
mol	Obsd	Calcd (eq (2))	Obsd	Calcd (eq (6))	Obsd	Calcd (eq (10))	Obsd	Calcd (eq (13))	Obsd	Calc. (eq (16))
1	9.04	9.38	9.34	8.98	9.15	8.40	9.30	9.18	8.85	8.67
2	8.24	9.27	8.45	8.82	7.85	8.45	7.85	8.52	7.45	8.40
3	10.00	9.78	9.15	9.33	9.69	9.50	9.69	8.90	9.69	9.33
4	8.66	7.87	8.96	8.48	8.12	8.31	9.30	9.48	8.00	8.03
5	6.29	6.65	7.64	7.81	6.37	8.56	6.99	7.17	6.20	6.32
6	7.60	8.19	9.69	9.73	7.48	8.23	9.15	8.49	7.56	8.73
7	9.69	9.70	10.00	9.67	10.00	9.47	10.00	9.22	10.00	9.64
8					8.36	8.34	7.14	6.94	6.81	6.79
9	9.69	9.15	8.39	8.18	9.69	9.55	8.17	8.05	8.74	8.62
10	7.79	7.98	7.05	6.91	8.49	8.34	7.05	7.10	7.17	7.08
11	8.87	8.50	7.58	7.84	9.22	9.35	7.24	7.54	8.20	7.49
12	6.69	8.01	7.24	7.06	9.15	9.23	7.26	7.61	7.67	7.77
13	7.35	5.53	6.20	6.26	8.39	9.11	6.79	7.08	6.85	6.90
14	7.55	7.43	7.37	7.13	8.30	8.22	7.62	7.37	6.56	7.56
15	9.15	9.15		5.92	9.52	9.39	7.85	7.86	7.77	7.61
16	8.72	8.53	7.82	8.37	9.22	8.86	7.79	8.08	7.39	8.53
17					9.00	8.45	8.69	8.30	9.39	9.86
18	6.56	8.26	6.37	8.10	6.54	8.63	5.88	8.16	5.78	8.00
19	8.33	8.37	6.66	8.53	8.69	8.64	6.11	8.76	6.76	8.45
20	6.37	8.84	6.56	8.25	6.30	8.38	6.37	7.98	8.24	8.45
21					7.37	8.44	5.98	8.79	6.32	9.12
22	9.09	8.34	8.92	9.45	8.92	8.64	8.92	9.59	10.00	9.46
23	8.85	9.24	8.49	7.46	8.45	8.91	7.92	7.86	7.41	7.33
24	8.89	9.01	7.96	7.56	9.52	9.07	7.28	7.86	7.62	7.34
25	8.77	8.74	7.87	7.72	8.89	9.13	8.29	7.77	7.37	7.59
26	9.04	8.84	7.21	7.81	9.39	9.04	6.93	8.12	7.85	7.58
27	9.30	9.07	7.69	7.75	9.39	9.09	7.36	7.78	8.27	7.44
28	9.52	9.38	8.00	7.78	9.69	9.44	7.74	7.52	8.12	7.65
29	7.42	7.79	8.79	8.24	7.89	8.28	8.15	8.31	7.66	7.97
30	8.33	8.48	8.66	8.49	8.55	8.85	8.11	8.33	7.60	8.33
31					6.79	7.17	7.37	7.10	6.42	6.57
32	8.19	6.34	6.42	6.88	9.39	9.93	7.60	7.26	7.08	6.79
33					9.39	9.85	6.64	7.36	6.37	6.73
34	8.58	6.24	6.64	6.79	9.30	8.66	7.12	7.12	6.33	6.70
35					9.22	9.04	6.49	6.12	6.19	6.15
36					9.09	9.26	5.56	7.38	5.35	6.47
37					7.44	6.99	7.53	6.58	8.79	8.48
38					7.23	7.65	7.82	6.50	8.92	8.87

Table 6. Experimental binding affinities and prediction values, obtained by the QSAR models reported ion Table 4 for the ligands of Scheme 2

mol	pK_{1a}[a]				pK_{1b}[a]				pK_{1d}[a]			
	Obsd	Calcd (eq (8))	Calcd (eq (9))	Calcd (eq (10))	Obsd	Calcd (eq (11))	Calcd (eq (12))	Calcd (eq (13))	Obsd	Calcd (eq (14))	Calcd (eq (15))	Calcd (eq (16))
39	8.50	8.75	8.80	8.59	9.00	8.30	8.37	8.47	8.40	8.37	8.17	8.42
40	8.34	8.19	8.42	8.18	8.00	8.51	8.35	7.88	8.50	8.70	9.01	8.87
41	7.54	7.68	7.73	7.83	5.97	7.07	6.86	7.13	6.54	6.46	6.29	5.90
42	8.67	9.43	8.68	8.54	7.87	7.18	7.46	7.68	7.18	6.77	6.86	6.65
43	8.53[b]	9.74	8.60	8.40	6.76[b]	6.94	7.17	6.67	6.05[b]	6.54	7.17	6.34
44	8.35	10.00	8.43	8.20	6.49	6.90	7.16	7.14	6.20	6.32	6.50	5.47
45	8.07	7.76	8.18	7.70	6.70	7.01	6.84	7.16	6.10	7.00	6.68	6.34
46	8.62	7.88	8.68	8.49	7.10	7.67	7.59	8.39	7.00	8.23	7.56	7.75
47	8.69	7.96	8.74	8.57	7.90	8.08	7.91	7.29	8.60	7.92	8.04	7.38

[a] ref 22.
[b] ref. 7.

of the ligands considered not always the correspondence between the highest value of R^2cv and good prediction is respected. Therefore, 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.

Modeling of in vitro and in vivo potency and selectivity

α_1-Antagonistic activity data values are available in the literature[7] for a subset of representative ligands. The in vivo and in vitro potency measured on different organs are listed in Table 8, together with the binding selectivity (Δp$K(a–b)$ and Δp$K(a–d)$) for the cloned receptors. The α_{1b}/α_{1d} receptor subtype selectivity is poorly achieved in this subset of compounds.

p*K*b represents the functional affinity for the α_1-ARs of rat aorta (RA), rabbit aorta (RBA), rabbit urethra (RBU) and human prostata (HP). The functional properties of these tissues seem to be due to a pure population of α_{1d} receptors in RA, a prevalent population of α_{1b} in RBA and of α_{1a} in both RBU and HP.[7,22] pKb$_{(RBA/RBU)}$ is the selectivity ratio for the in vitro potency on rabbit aorta and urethra.

Finally, -log (DBU/UP) is the in vivo selectivity studied in a dog model, UP represents the doses active in inhibiting by 50% the urethral contractions induced by NA, and DBU the doses active in lowering diastolic blood pressure by 25%.

The QSAR analysis of functional activities for this set of compounds yields successful correlations.

The data values of the descriptors used are listed in Table 8. The molecular descriptors involved in the rationalization of the antagonistic potency measured on RA and RBA are physically diverse with respect to those involved in the corresponding receptor subtype binding affinities. They concern the reactivity of the molecular fragment nitrogen atom (eq (1), Table 9) and the total intramolecular electrostatic interaction (eq (2), Table 9). The variation in the antagonistic potency data values measured on RBU and HP is, on the contrary, very well explained by ad hoc defined (eq (3), Table 9) and CPSA (eq (4), Table 9) descriptors. It is worth noting that V_{in}/V_{mol} in eq (3) is computed with respect to the supermolecule which defines the overall shape of the native α_{1a}-AR subtype binding site, in agreement with the evident predominance of α_{1a} receptor subtype in this tissue.[7]

Molecular orbital descriptors computed on the protonated nitrogen or on the N–H$^+$ ionic pair are involved in the QSAR models obtained for the selectivity ratio of the cloned receptor subtypes (eqs (5)–(8), Table 9). The same theoretical descriptors, comprising information about the ligand propensity to hydrogen bonding or charge-reinforced hydrogen bonding intermolecular interactions, are able to rationalize the different functional effects exercised by the same ligand on two tissues (eqs (9) and (11), Table 9).

Table 7. Theoretical descriptors computed on the protonated form of the ligands reported in Scheme 2

mol	V_{in_a}/V_{mol}	V_{dif_a}	f-Pπ–π (C–O)	V_{in_b}/V_{mol}	V_{dif_b}	V_{in_b} (Å^3)	WPSA-1 (Å^2)	V_{in_d}/V_{mol}	V_{dif_d}	f-Pσ-π (C-X)	DPSA-1 (Å^2)	E_C (TOT) (eV)	V_{in_d} (Å^3)	f-RNCS (Å^2)
39	0.9091	0.3096	0.8394	0.8278	0.3691	302.75	421.38	0.8428	0.3486	0.0256	322.54	365.93	308.25	0.00
40	0.8473	0.2345	0.8282	0.8626	0.3646	281.75	441.51	0.9158	0.3771	0.0221	386.44	322.67	299.13	0.25
41	0.6577	0.0952	0.6201	0.6197	0.1093	183.75	288.30	0.6197	0.0977	0.0193	322.05	300.52	183.75	0.77
42	0.7760	0.2846	0.8017	0.6378	0.2132	320.63	657.84	0.6579	0.2195	0.0201	392.03	499.68	330.75	1.00
43	0.7449	0.2700	0.8205	0.5974	0.1622	323.13	844.85	0.6205	0.1787	0.0207	573.63	525.46	335.63	1.12
44	0.6990	0.2346	0.8202	0.5906	0.1609	340.63	857.44	0.5767	0.1227	0.0225	485.52	568.80	332.63	1.48
45	0.7872	0.1848	0.9224	0.6092	0.1049	190.00	338.59	0.6970	0.1681	0.0192	246.72	288.89	217.38	7.05
46	0.9019	0.2862	0.8228	0.7213	0.2353	249.13	324.28	0.8331	0.3196	0.0242	170.69	328.72	287.75	6.38
47	0.9467	0.2969	0.8134	0.7913	0.2902	256.00	444.41	0.7747	0.2462	0.0262	448.07	311.49	250.63	2.84

Table 8. In vivo and in vitro potency and selectivity[a] and theoretical molecular descriptors of selected α_1-AR antagonists[b]

mol	ΔpK (a–b)	ΔpK (a–d)	$pKb_{(RA)}$	$pKb_{(RBA)}$	$pKb_{(RBU)}$	$pKb_{(HP)}$	$pKb_{(RBA/RBU)}$	-log(DBU/UP)	f-S^n_{HOMO} (eV–1)	f-FNSA-2	μ_h (Debye)	V_{mol}/XYZ	(N)CPSA (Å^2)	E_R (N–H) (eV)	E_{LUMO} (eV)	HDSA (Å^2)	μ(N–H) (Debye)	q (N)
1	−0.15	0.30	9.90	9.00	8.11	8.25	0.89	−0.26	1.55E–04	−0.6031	0.6590	0.3309	0.8123	−13.58	−4.39	19.79	0.5291	−0.2583
2	0.00	0.40	8.58	7.92	6.95	7.38	0.96	−0.49	1.00E–03	−0.2754	0.7100	0.2944	1.3103	−13.58	−4.36	16.35	0.5307	−0.2604
4	−1.18	0.12	8.74	7.49	6.20		1.30	−0.45	1.39E–05	−0.4986	0.3610	0.3115	1.2257	−13.57	−4.52	15.69	0.5190	−0.2436
7	0.00	0.00				7.30			3.25E–05	−0.3136	0.8290	0.2752	1.2661	−13.52	−4.38	14.34	0.4768	−0.2013
9	1.52	0.95	9.35	9.54	9.31	9.20	0.23	−1.00	8.83E–09	−1.3926	0.8480	0.2844	0.4390	−12.91	−3.84	14.17	0.2952	−0.0365
15	1.67	1.75				6.89			6.84E–03	−0.3455	0.8950	0.3063	0.2951	−12.94	−3.56	9.73	0.2923	−0.0409
19	2.58	1.93	7.65	7.52	8.04	7.93	−0.52	−0.89	4.45E–03	−0.6273	0.3870	0.3085	0.0157	−12.80	−3.76	4.11	0.2598	−0.0049
24	2.24	1.90	8.62	7.70	8.64	8.57	−0.94	−2.00	6.21E–05	−1.1384	1.7810	0.2177	0.1402	−12.80	−3.83	2.49	0.2991	−0.0583
27	2.03	1.12	8.74	7.82	8.57	8.17	−0.75	−1.73	9.04E–05	−0.7734	1.7270	0.2239	0.0031	−12.62	−3.51	2.31	0.2637	−0.0039
34	2.18	2.97	6.65	5.00	5.53		−0.53	−1.00	5.05E–03	−1.2435	0.6980	0.2351	0.0016	−12.94	−3.42	5.36	0.2510	−0.0005

[a] ref 7.

[b] ΔpK (a–b) and ΔpK (a—d) are the binding selectivity for the cloned receptor, pKb represents the functional affinity for the α_1-ARs of rat aorta (RA), rabbit aorta (RBA), rabbit urethra (RBU) and human prostata (HP), $pKb_{(RBA/RBU)}$ is the selectivity ratio for the in vitro potency on rabbit aorta and urethra, and -log (DBU/UP) is the in vivo selectivity studied in a dog model. UP represents the doses active in inhibiting by 50% the urethral contractions induced by NA, and DBU the doses active in lowering diastolic blood pressure by 25%.

Table 9. Regression models for the correlation between molecular structure descriptors and in vitro and in vivo potency and selectivity

1.	$pKb_{(RA)} = 9.08 \pm 2.2e{-}01 + -4.1350e+02 \pm 8.984e+01 f\text{-}S^{N}_{HOMO}$	$R^2 = 0.78$,	$F = 21.18$,	$s^2 = 0.25$,	$n = 8$,	$R^2cv = 0.59$
2.	$pKb_{(RBA)} = 1.346e+01 \pm 1.45 + -1.5e{-}02 \pm 3.8e{-}03 E_C(tot)$	$R^2 = 0.73$,	$F = 16.01$,	$s^2 = 0.57$,	$n = 8$,	$R^2cv = 0.43$
3.	$pKb_{(RBU)} = -7.90 \pm 1.99 + 1.703e+01 \pm 2.18\ V_{in_\alpha}/V_{mol}$[a]	$R^2 = 0.91$,	$F = 61.12$,	$s^2 = 0.18$,	$n = 8$,	$R^2cv = 0.87$
4.	$pKb_{(HP)} = 6.77 \pm 2.05e{-}01 + -1.74 \pm 2.6e{-}01 f\text{-}FNSA\text{-}2$	$R^2 = 0.88$,	$F = 43.99$,	$s^2 = 0.07$,	$n = 8$,	$R^2cv = 0.81$
5.	ΔpK (a–b) $= 4.78 \pm 4.5e{-}01 + -9.92 \pm 1.16\mu(N\text{–}H)$	$R^2 = 0.90$,	$F = 72.77$,	$s^2 = 0.19$,	$n = 10$,	$R^2cv = 0.83$
6.	ΔpK (a–b) $= 2.27 \pm 2.14e{-}01 + 1.066e+01 \pm 1.38q(N)$	$R^2 = 0.88$,	$F = 59.74$,	$s^2 = 0.22$,	$n = 10$,	$R^2cv = 0.81$
7.	ΔpK (a–d) $= 9.15 \pm 1.65 + 2.02 \pm 4.1e{-}01 E_{LUMO}$	$R^2 = 0.75$,	$F = 23.73$,	$s^2 = 0.27$,	$n = 10$,	$R^2cv = 0.60$
8.	ΔpK (a–d) $= 1.98 \pm 2.4e{-}01 + -1.51 \pm 3.2e{-}01(N)CPSA$	$R^2 = 0.73$,	$F = 21.95$,	$s^2 = 0.28$,	$n = 10$,	$R^2cv = 0.59$
9.	$pKb_{(RBA/RBU)} = -6.6e{-}01 \pm 1.5e{-}01 + 1.50 \pm 2.1e{-}01(N)CPSA$	$R^2 = 0.89$,	$F = 50.20$,	$s^2 = 0.09$,	$n = 8$,	$R^2cv = 0.81$
10.	$pKb_{(RBA/RBU)} = -1.08 \pm 2.0e{-}01 + 1.1e{-}01 \pm 1.6e{-}02HDSA$	$R^2 = 0.89$,	$F = 48.92$,	$s^2 = 0.10$,	$n = 8$,	$R^2cv = 0.81$
11.	$pKb_{(RBA/RBU)} = -2.640e+01 \pm 4.05 + -2.02 \pm 3.1e{-}01 E_R(N\text{–}H)$	$R^2 = 0.88$,	$F = 42.80$,	$s^2 = 0.11$,	$n = 8$,	$R^2cv = 0.81$
12.	$-\log(DBU/UP) = 2.12 \pm 3.6e{-}01 + -9.4 \pm 1.07 V_{dif_a}$[a]	$R^2 = 0.93$,	$F = 76.94$,	$s^2 = 0.03$,	$n = 8$,	$R^2cv = 0.85$
13.	$-\log(DBU/UP) = -9.1e{-}02 \pm 2.2e{-}01 + -9.8e{-}01 \pm 2.1e{-}01 \mu_h$	$R^2 = 0.78$,	$F = 20.97$,	$s^2 = 0.10$,	$n = 8$,	$R^2cv = 0.65$
14.	$-\log(DBU/UP) = -4.44 \pm 7.2e{-}01 + 1.26e+01 \pm 2.59 V_{mol}/XYZ$	$R^2 = 0.80$,	$F = 23.60$,	$s^2 = 0.09$,	$n = 8$,	$R^2cv = 0.64$

[a] These descriptors are defined with respect to the supermolecule considered to represent a map of the binding site obtained by superimposition of compounds **3, 9, 11, 15, 28** and **32**.

Finally, in vivo selectivity is described by theoretical indices related to the molecular volume (eqs (12) and (14), Table 9) and to dipole–dipole interactions (eq (13)). The best statistical parameters are obtained by correlating the in vivo selectivity with the V_{dif} descriptor defined with respect to the α_{1a}–AR supermolecule. It is worth noting that α_{1a} is the adrenergic receptor subtype of functional relevance for the urethra tissue (dog model).[7] Thus, ligands showing high potency and selectivity for the lower urinary tract (compounds **24** and **27**) are those which better fit the volume of the supermolecule, which represents the binding site of the α_{1a}-AR subtype.

Conclusions

Several problems are connected with the attempt to rationalize in quantitative terms the pharmacological data which concern receptors. Cells expressing cloned receptors constitute useful tools for drug screening and facilitate the establishment of precise structure–affinity relationships. However, the ultimate goal is to generalize the information obtained on a pure population of receptors to the native receptors in order to design tissue-selective drugs.

Given the high flexibility of its structure, the same receptor can accommodate very diverse ligands. On the other hand, subtle molecular determinants might be responsible of the selectivity towards different receptor subtypes, and apparently small chemical modifications of a ligand can change its pharmacological phenotype dramatically. Therefore, it is the rule in this field to deal with series of non-congeneric compounds, showing a large variability in their structural features, and the task of deciphering the information relevant for ligand–receptor interaction can only be accomplished with key molecular descriptors able to perceive non-intuitive differences among ligands.

The results presented in this work show that the heuristic statistical treatment implemented in the CODESSA program is a valuable tool to select, from a large pool, the theoretical molecular descriptors which give powerful predictive and interpretative QSAR models for different types of pharmacological data.

Molecular orbital indexes describing the small variation of molecular electronic structure which contributes to the recognition step (electrostatic interaction between the protonated amine function and a primary nucleophilic site of the receptor) are more suitable for rationalizing the binding affinity of subsets of congeneric ligands or to be used in connection to selectivity data.

Moreover, the strict requirements for shape complementarity between the ligand and receptor are encoded by ad hoc defined size and shape descriptors. These indexes proved to be very useful in the rationalization of pharmacological data referring to a single population of receptor subtypes (binding affinity on cloned receptors) or animal and human tissues assumed to express a predominance of specific receptor subtypes (potency and in vivo or in vitro selectivity).

Other important receptor recognition features are encoded in the charged partial surface area descriptors which might be considered to reflect the polarity map of the receptor binding site. The QSAR models obtained with these two classes of descriptors pointed out that the main determinants for the modulation of the α_{1a} and α_{1b}-AR binding affinity are mainly related to dispersive and polar interactions, respectively.

Finally, molecular orbital indexes describing the reactivity characteristics of specific atoms can be introduced to adjust the linear models improving their predictivity power, as demonstrated by the ability of the QSAR model selected to classify correctly the binding affinity of functionally related ligands whose structures cover a large expanse of chemical space.

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