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ORIGINAL PAPER

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Quantitative structure–activity relationships of α_1 adrenergic antagonists

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Abstract A quantitative structure–activity relationship study with respect to selectivity for α_1 adrenoreceptor subtypes (α_{1a}, α_{1b} and α_{1d}) of a wide series of structurally heterogeneous α_1 adrenoreceptor antagonists has been performed. A large variety of molecular descriptors have been calculated and then analyzed by a heuristic method. The orthogonalization of the descriptors has been applied to build the QSAR equations. Ad hoc defined shape descriptors calculated by the Connolly algorithm with respect to reference supermolecules have also been considered in the rationalization of the mechanism of the activity of the ligands acting as antagonists on all three subtypes of α_1 adrenoreceptors.

Keywords QSAR · α_1 adrenergic antagonists · Molecular descriptors

Introduction

The α_1 adrenergic receptors (α_1 AR) are members of the superfamily of G-protein-coupled receptors (GPCR) that transduce signals across the cell membrane. Molecular biology techniques allowed the identification of cDNAs encoding three α_1 adrenoreceptors (α_{1a}, α_{1b} and α_{1d}). The recombinant α_1 adrenoreceptors correlate with the three α_1 adrenoreceptor subtypes that were identified in native tissues mediating their functional responses (α_{1A}, α_{1B} and α_{1D}). [1] There is also evidence for an additional α_1 adrenoreceptor population, designated as α_{1L} adrenoreceptors. [2]

Considerable recent interest in subtypes of α_1 adrenoreceptors has resulted from the realization that differences in the distribution of subtypes of these receptors between the cardiovascular system and prostate gland could be of therapeutic importance. For example, a number of nonsubtype-selective compounds have been used in the treatment of benign prostate hypertrophy, although cardiovascular complications of these agents have been attributed to their equivalent blockade of all α_1 adrenoreceptors. [3]

There are many types of chemical structures that have the ability to act as α_1 adrenoreceptor antagonists. However, for a wide range of chemical structures to interact at the same receptor, they must possess certain regions of similar shape and electronic character, which in the case of α_1 adrenergic antagonists have been postulated as an aromatic region, a basic nitrogen atom with at least one available protonation site and a semipolar region. [4] There is also evidence that some of the compounds can discriminate between discovered α_{1a}, α_{1b} and α_{1d} adrenoreceptor subtypes, but there are still insufficient compounds available with significant subtype selectivity to be able to draw definitive conclusions about structure–activity relationships with regard to their selectivity. Therefore, to discriminate successfully between subtly different types of activity represents a challenge for a quantitative structure–activity relationship study (QSAR).

Recently, a QSAR analysis of α_1 adrenoreceptors based on ad hoc size and shape descriptors, which include measuring of van der Waals volumes with respect to a reference supermolecule, has been shown to be a promising approach to rationalize the different activity and selectivity of α_1 adrenoreceptors. [5, 6]

In order to design selective antagonists, a ligand-based drug design methodology has also been performed using a pharmacophore hypothesis to predict the activity of the compounds. [7, 8, 9, 10] Molecular descriptors in QSAR of congeneric and noncongeneric α_1 adrenergic antagonists have also been presented. [11, 12, 13] A variety of

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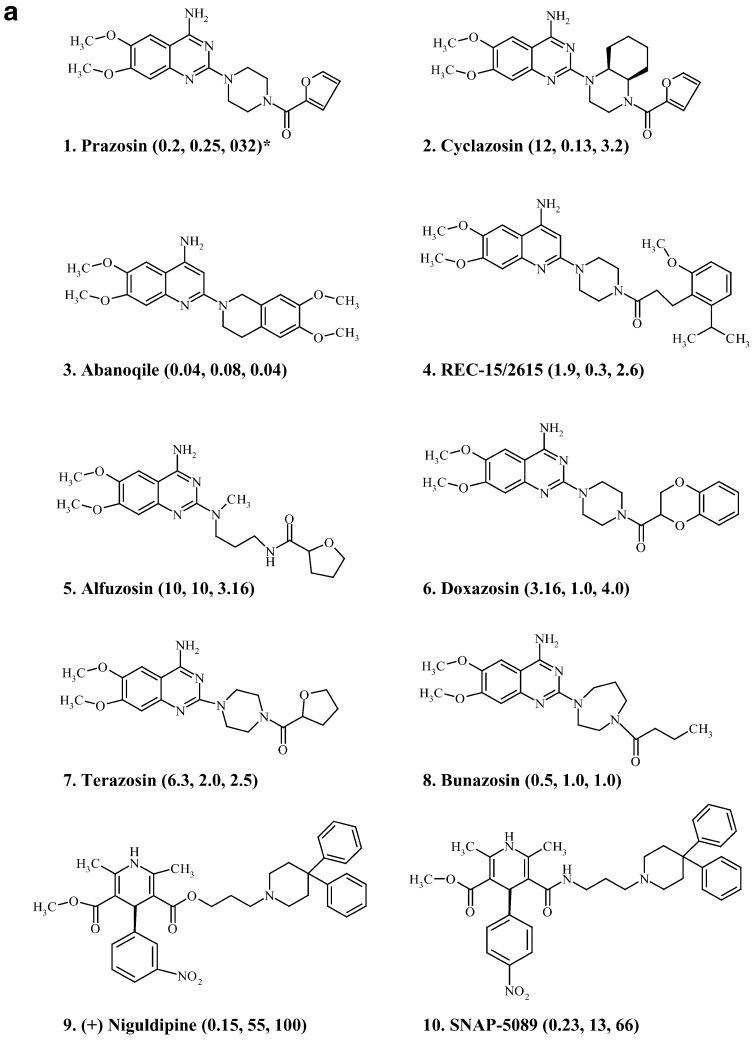


Fig. 1 Structures of α_1 adrenergic antagonists. (Ki values (nM) for α_{1a}, α_{1b}, α_{1d} AR antagonists, respectively, are given in parentheses for all compounds)

chemometric tools has been applied to build the QSAR equations. [14, 15, 16, 17]

Binding affinities of the compounds toward cloned subtypes have also been estimated, [18] as well as molecular-dynamic simulations, which allowed a structural/dynamic analysis of α-helix-bundle models of the α_1 adrenoreceptor subtypes in order to rationalize, at a molecular level, the antagonist selectivity. [19] Approaches based on receptor docking and evaluation of small molecule ligands for selective binding to the α_1 adrenoreceptor subtypes have also been used. [20]

In the present work we have investigated the possibility of generating statistically-based correlative models between experimentally determined selectivity for a set of compounds with a wide variety of chemical structures and theoretical molecular descriptors. A large number of molecular descriptors have been calculated and then a heuristic method applied for the choice of the descriptors, which were analyzed by multilinear regression method (MLR). Ad hoc defined shape descriptors calculated by the Connolly algorithm with reference to a supermolecule modeled for all three subtypes of α_1 adrenoreceptors have also been employed for considering the molecular features responsible for selectivity in a series of noncongeneric antagonists toward α_{1a}, α_{1b} and α_{1d} AR.

Materials and methods

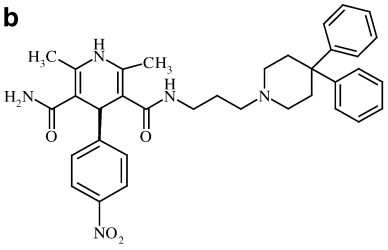
The set (Fig. 1) of 38 α_1 adrenergic antagonists [7] showing a large diversity of chemical structures was used in this study. The biological data were expressed as activities (–log Ki (nM)) for α_{1a}, α_{1b} and α_{1d} subtypes and selectivities (–log Ki α_{1a}/α_{1b}, –log Ki α_{1a}/α_{1d} and –log Ki α_{1b}/α_{1d}). Chemical structures and Ki values (nM) of all compounds investigated are given in Fig. 1.

The structures were constructed using the Spartan program package. [21] Complete geometry optimization was performed for the N1-protonated forms of the compounds investigated taking the most extended conformations as starting geometries and assuming all the aromatic rings to be planar. Molecular orbital calculations (AM1) of the protonated structures were performed using the MOPAC 6.0 program.

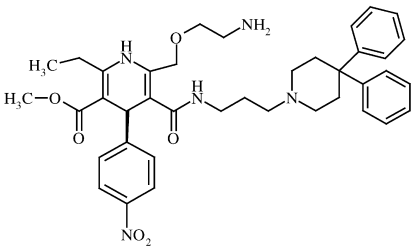
For the superimposition of the molecules with regard to their selectivity and high activity for the different subtypes, the most active molecule (abanoquile, compound **3**) for all three subtypes of adrenoreceptors was chosen as the reference compound. Each compound considered in the subset was superimposed onto molecule 3 by a fitting procedure that minimized the r.m.s.

Fig. 1 (continued)

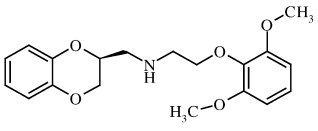
b



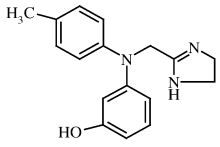
11. SNAP-5399 (0.65, 324, 631)



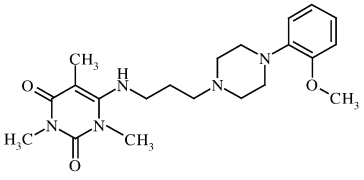
12. SNAP-5150 (1.9, 331, 400)



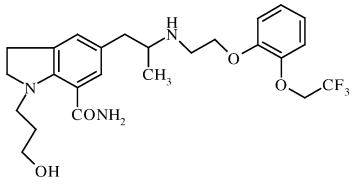
13. WB-4101 (0.16, 2.5, 0.25)



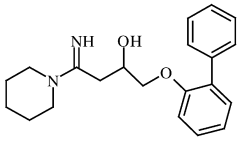
14. Phentolamine (1.6, 7.9, 7.9)



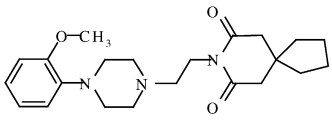
15. 5-Methyluropidil (0.63, 40, 10)



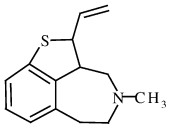
16. KMD-3213 (0.04, 20, 2.0)



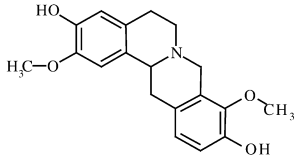
17. AH-11110A (2500, 76, 2750)



18. BMY (250, 630, 6.3)



19. SKF - 104856 (44, 63, 5.2)



20. Discretamine (616, 360, 25)

deviations of their respective position using three points: the protonated nitrogen atom, the center of the aromatic region and the center of the semipolar region, which have been determined previously. Computations of Connolly surfaces were performed with respect to a reference supermolecule obtained by superimposition of molecules in the set. [22, 23, 24]

The calculation of a large number of molecular descriptors was performed using the CODESSA (Comprehensive Descriptors for Structural and Statistical Analysis) software as a multipurpose program for developing quantitative structure–activity or structure–property relationships. [25]

All descriptors were divided into five groups: constitutional (reflecting the molecular composition of the compounds), topological (describing the atomic connectivity in a molecule), geometric (calculated from 3D atomic coordinates of the molecule), electrostatic (reflecting characteristics of the charge distribution in the molecule) and quantum chemical (divided into three groups: charge-distribution related descriptors, valency related descriptors, and quantum mechanical energy related descriptors).

For selection of descriptors, we used the heuristic method implemented in CODESSA, which accomplished a preselection of descriptors on the basis of their statistical significance. First, descriptors with missing or constant values for the set of structures were discarded from the original set. Further selection of descriptors was accomplished on the basis of the statistical parameters: r^2, F-test, and t-test for the one-parameter equations with the descriptors. The default values, which were kept constant throughout the calculations, were set as follows: r^2_{min}=0.01, r^2_{max}=0.99 and t_1=0.1.

After selection of the descriptors, MLR analysis was applied for developing QSAR models.

For statistical improvement of the models obtained, the Randic method for orthogonalization of the descriptors was used. [26, 27] Orthogonal δ_1–δ_n were derived from nonorthogonal molecular descriptors D_1–D_n in a stepwise procedure, using D_1 as the first orthogonal descriptor δ_1. The second orthogonal descriptor δ_2 was

Fig. 1 (continued)

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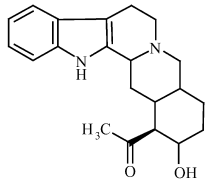
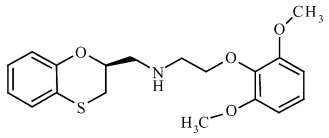
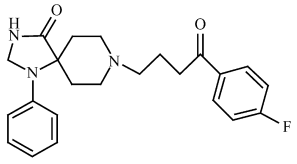


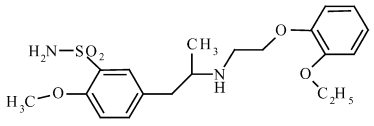
21. Coryanthine (142, 517, 253)



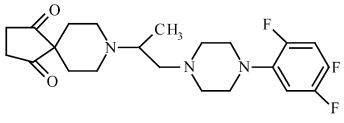
22. Benzoxathian (0.2, 4.0, 0.4)



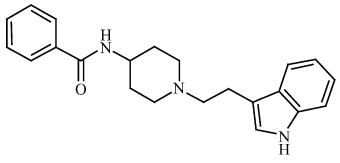
23. Spiperone (7.9, 0.5, 13)



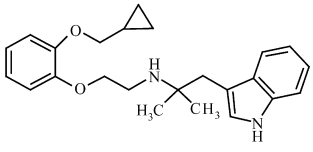
24. (+) YM -617 (4.3, 96, 22)



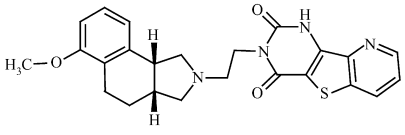
25. SNAP -8719 (294, 191, 1.6)



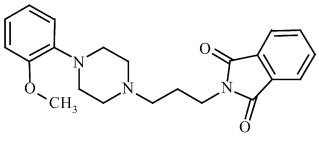
26. Indoramin (4.0, 40, 160)



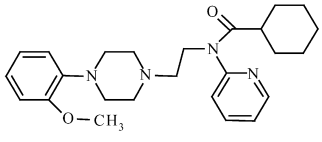
27. RS -17053 (0.6, 16, 16)



28. A -131701 (0.22, 6.95, 0.97)



29. NAN -190 (2.0, 15. 0.8)



30. WAY -100635 (144, 186, 63)

constructed as a simple regression between D_2 and δ_1, where δ_1 is independent and D_2 a dependent variable. New D_2(calc) were calculated and the difference between D_2 and D_2(calc) is the residual, which represents our new descriptor δ_2. This procedure was performed until all descriptors were orthogonal. Finally, the MLR method was applied to develop regression models for orthogonal descriptors.

Results and discussion

It is assumed in general that few molecular determinants are responsible for the discrimination of the compounds among receptor classes or subtypes. However, the elucidation of functionalities that contribute to binding is complicated by the great diversity in size and chemical structure of the ligands. The availability of descriptors able to capture the strict ligand–receptor complementarity criteria is the primary objective for obtaining a good quantitative rationalization of the binding properties of highly active and selective ligands.

The focus of the present work was twofold: (a) to construct good predictive models for selectivity between all three subtypes and to examine the differences in molecular descriptors chosen by a heuristic method to be informative for the subtype selectivity and (b) computation of the shape descriptors of the compounds with respect to a reference supermolecule and correlation with

Fig. 1 (continued)

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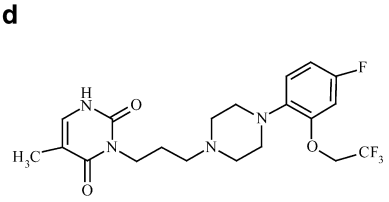
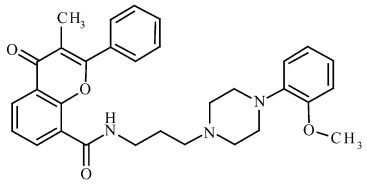
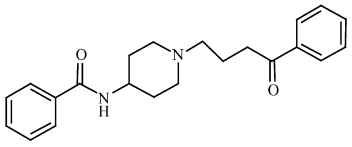


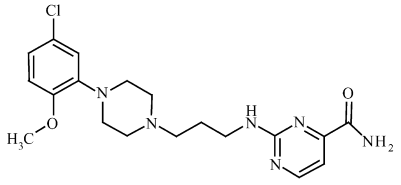
31. RS -100,975 (1.0, 79, 100)



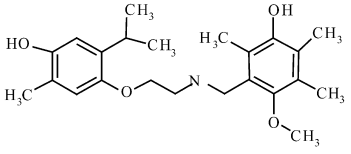
32. REC -15/2739 (1.0, 32, 2.5)



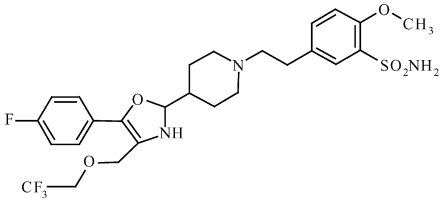
33. SNAP -1069 (16, 200, 790)



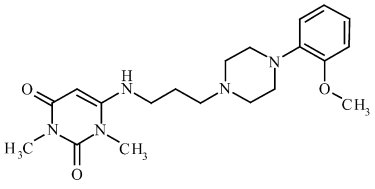
34. SL -89.0591 (2.5, 13, 2.5)



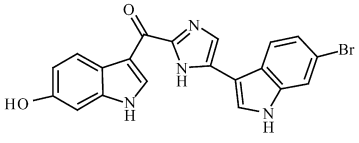
35. JHT -601 (0.4, 1.2, 1.2)



36. GG -818 (0.2, 16, 25)



37. Uropidil (288, 1320, 1660)



38. Bromotopsentin (12000, 740, -)

selectivity for all subtypes was the object of the search as well.

The results obtained in the work of Menziani et al. [13] showed that the heuristic method implemented in CODESSA is a valuable tool for selecting from a large pool of theoretical molecular descriptors to obtain powerful predictive and interpretative QSAR models.

The selection of the five best descriptors by a heuristic method for all three subtypes is shown in Table 1. They are calculated by one-parameter correlations inside each group of descriptors and sorted by descending value of correlation coefficient and *F*-test.

On the basis of the results obtained, it could be assumed that the following information content about the structure–selectivity relationship for the α_{1a}/α_{1b} and α_{1a}/α_{1d} selectivity could be presented in all groups of the descriptors as follows: r^2=0.3292–0.4408 for constitutional, r^2=0.2838–0.3550 for topological, r^2=0.3872–0.4401 for geometrical, r^2=0.4440–0.4980 for electrostatic and r^2=0.2892–0.4562 for quantum chemical descriptors. For the selectivity α_{1d}/α_{1b}, only electrostatic (r^2= 0.1147–0.1158) and quantum chemical descriptors (r^2= 0.2868–0.3977) were found to be significant.

Searching the one-parameter correlation of molecular descriptors with the activity (–log Ki) for α_{1a}, α_{1b} and α_{1d} adrenoreceptor subtypes for the same set of compounds, it was shown that all groups of descriptors have an influence on the α_{1a} adrenergic activity (r^2=0.1226–0.2180 for constitutional, r^2=0.1811–0.1922 for topological, r^2= 0.1378–0.1822 for geometrical, r^2=0.1911–0.2224 for electrostatic and r^2=0.1746–0.2139 for quantum chemical descriptors), while for α_{1b} activity (r^2=0.0328–0.0797 for constitutional, r^2=0.0336–0.0488 for topological, r^2= 0.0365–0.0661 for geometrical, r^2=0.1611–0.2426 for electrostatic and r^2=0.2348–0.3083 for quantum chemical descriptors) and α_{1d} activity (r^2=0.0.1071–0.1935 for constitutional, r^2=0.1020–0.1149 for topological and r^2= 0.0435–0.0755 for geometrical, r^2=0.1063–0.1990 for

Table 1 Selection of five best descriptors from each group of descriptors according to correlation coefficients for one-parameter correlations with regard to selectivity on α_{1a}/α_{1b}, α_{1a}/α_{1d} and α_{1b}/α_{1d} AR subtypes

Selectivity α_{1a}/α_{1b}			Selectivity α_{1a}/α_{1d}			Selectivity α_{1b}/α_{1d}		
	r^2	F		r^2	F		r^2	F
Constitutional descriptors[a]								
N_C	0.2722	13.465	N_C	0.4401	28.297	N_{AB}	0.1456	6.184
N_A	0.2696	13.286	N_A	0.4343	27.643	N_{SB}	0.0685	2.6465
N_{SB}	0.2585	12.547	MW	0.4208	26.155	N_{BR}	0.0615	2.358
MW	0.2571	12.461	G_{AP}	0.4060	24.602			
N_H	0.2454	11.710	N_H	0.3872	22.744			
Topological descriptors[b]								
W	0.3384	18.414	W	0.4980	35.710	$^2BIC_A$	0.0710	2.7534
$^3\kappa$	0.3206	16.989	$^3\kappa$	0.4826	33.582	^2IC_A	0.0699	2.7072
$^2\kappa$	0.3083	16.045	$^2\kappa$	0.4742	32.467	^0IC_A	0.0652	2.5092
Φ	0.2962	15.152	$^1\kappa$	0.4509	29.564	^0IC	0.0558	2.128
$^1\kappa$	0.2902	14.717	^0IC	0.4440	28.744			
Geometrical descriptors[c]								
MSA	0.2576	12.492	MSA	0.4063	24.639	S_1	0.0392	1.4691
S_2	0.2563	12.409	S_2	0.3714	31.266			
S_1	0.2075	9.423	S_1	0.3354	18.169			
S_3	0.1549	6.599	S_3	0.2892	14.644			
Electrostatic descriptors[d]								
^{E}WNSA-1	0.4408	28.379	^{E}WNSA-1	0.4780	32.959	PC'$_N$	0.1158	4.714
^{E}WNSA-2	0.4210	26.173	^{E}WNSA-2	0.4468	29.077	^{E}DPSA-1	0.1147	4.665
^{E}PNSA-2	0.3988	23.884	^{E}PNSA-2	0.4234	26.433	^{E}PPSA-1	0.0829	3.256
^{E}PNSA-1	0.3654	20.728	^{E}PNSA-1	0.4110	25.123	PC_H	0.0747	2.907
^{E}FNSA-2	0.3292	17.669	^{E}FNSA-2	0.3758	21.671	^{E}FNSA-2	0.0721	2.799
Quantum chemical descriptors[e]								
E′ee(N)	0.3550	19.811	E′ee(N)	0.4580	30.424	Eex(HN)	0.3977	23.772
^{Q}WNSA-1	0.3403	18.568	^{Q}WNSA-1	0.4564	30.221	Er(HN)	0.3298	17.718
^{Q}WNSA-2	0.3309	17.799	^{Q}WNSA-2	0.4551	30.071	P_N	0.3032	15.667
^{Q}PNSA-2	0.2873	14.510	^{Q}PNSA-2	0.4383	28.089	Enn(HN)	0.2897	14.683
^{Q}TMSA	0.2838	14.265	^{Q}TMSA	0.4376	28.009	Ett(HN)	0.2868	14.480

[a] N_C, number of C atoms; N_A, number of atoms; N_{SB}, number of single bonds; MW, molecular weight; N_H, number of H atoms; G_{AP}, gravitational index (all pairs); N_{AB}, number of aromatic bonds; N_{BR}, number of benzene rings

[b] W, Wiener index; $^3\kappa$, Kier shape index (order 3); $^2\kappa$, Kier shape index (order 2); Φ, Kier flexibility index; $^1\kappa$, Kier shape index (order 1); ^0IC, complementarity information content (order 0); $^2BIC_A$, average bonding information content (order 2); ^2IC_A, average complementarity information content (order 2); ^0IC_A, average bonding information content (order 0); ^0IC, bonding information content (order 0)

[c] MSA, molecular surface area; S_1, *XY* shadow; S_2, *YZ* shadow; S_3, *ZX* shadow

[dE] WNSA-1, weighted ^{E}PNSA-1 (Zefirov); ^{E}WNSA-2, weighted ^{E}PNSA-2 (Zefirov); ^{E}PNSA-2, total charge weighted ^{E}PNSA-1 (Zefirov); ^{E}PNSA-1, partial negative surface area (Zefirov); ^{E}FNSA-2, fractional ^{E}PNSA-2 (Zefirov); PC'$_N$, minimum partial charge for an N atom; ^{E}DPSA-1, difference in ^{E}PPSA-1 and ^{E}PNSA-1 (Zefirov); ^{E}PPSA-1, partial positive surface area (Zefirov); PC_H, maximum partial charge for an H atom

[e] E′ee(N), minimum e–e repulsion for an N atom; ^{Q}WNSA-1, weighted ^{Q}PNSA-1 (semi MO); ^{Q}WNSA-2, weighted ^{Q}PNSA-2 (semi MO); ^{Q}PNSA-2, total charge weighted ^{Q}PNSA-1 (semi MO); ^{Q}PNSA-1, partial negative surface area (semi MO); ^{Q}TMSA, total molecular surface area (semi MO); Eex(HN), maximum exchange energy for an H–N bond; Er(HN), maximum resonance energy for an H–N bond; P_N, average bonding order for an N atom; Enn(HN), maximum n–n repulsion for an H–N bond; Ett(HN), maximum total interaction for an H–N bond

electrostatic and r^2=0.2379–0.3673 for quantum chemical descriptors), mostly electrostatic and quantum chemical descriptors could give the useful information.

The correlation of the five best descriptors of each group of descriptors (the best descriptor of each group was chosen) with receptor selectivity was also performed but the regression coefficients obtained were not found to be satisfactory (r^2=0.5434 for selectivity α_{1a}/α_{1b}, r^2= 0.5167 for selectivity α_{1a}/α_{1d} and r^2=0.4456 for selectivity α_{1b}/α_{1d}).

The QSAR equations for all three types of selectivity were obtained using a heuristic method for the selection and the first five best descriptors (yielding the best regression coefficients) were correlated using the MLR method.

According to the chemical features of the protonated nitrogen atom at physiological pH (Fig. 1), the α_1 AR antagonists partitioned into training and test set can be subdivided into several subsets: (a) quinazolinic and quinolinic, compounds **1**–**8**, (b) aminic, compounds **13**, **16**, **22**, **24**, **27** and **35**, (c) piperazinic, compounds **15**, **18**, **25**, **29**–**32**, **34** and **37**, (d) piperidinic, compounds **9**–**12**, **23**, **26**, **28**, **33** and **36** and (e) a few compounds of different structures, compounds **14**, **19**–**21** and **38**.

The linear QSAR models generated have been validated by predicting selectivity of test sets containing the

compounds from each subset determined on the basis of the protonated nitrogen. For the selectivity α_{1a}/α_{1b} and α_{1a}/α_{1d}, compounds: **2**, **5**, **7**, **10**, **18**, **19**, **24**, **28**, **32** and **36** have been chosen for test sets, while for the selectivity α_{1b}/α_{1d}, compounds **3**, **6**, **11**, **20**, **25**, **26**, **31**, **35** and **36** were used.

The following equations were obtained:

$$-\log \alpha_{1a}/\alpha_{1b} = 3.568 + 0.5121\,{}^{3}\kappa - 0.3341\,\mathrm{Eex(CN)} - 11.767\ \mathrm{E'r1 - e} + 0.4394\ E_{\mathrm{HOMO-1}}$$
$$\left(n = 28,\ r^2 = 0.6827,\ F = 12.37, S^2 = 0.5054\right)$$
for selectivity α_{1a}/α_{1b} (1)

$$-\log \alpha_{1a}/\alpha_{1d} = 83.839 - 0.0273\,\mathrm{E'e - n(N)} + 0.3778\,\mathrm{Ett(HN)} - 14.864\,{}^{\mathrm{Q}}\mathrm{RNCG} - 0.0152\ \mathrm{HDSA - 1} - 0.7631\ \mathrm{E'st(C)}\left(n = 28,\ r^2 = 0.8476,\ F = 24.47,\right.$$
$$\left.S^2 = 0.1998\right)$$ for selectivity α_{1a}/α_{1d} (2)

$$-\log \alpha_{1b}/\alpha_{1d} = 63.214 - 0.420\,\mathrm{Est(C)} + 4.199\,\mathrm{Ee - e(H)} + 20.59\,{}^{0}\mathrm{BIC} + 9.703\,\mathrm{Er1 - e(C)} - 0.7029\,\mathrm{Eex(HN)}$$
$$\left(n = 29, r^2 = 0.7493, F = 13.75, S^2 = 0.2272\right)$$
for selectivity α_{1b}/α_{1d} (3)

The correlation graphics of training and test sets showing experimental versus predicted selectivity α_{1a}/α_{1b}, α_{1a}/α_{1d} and α_{1b}/α_{1d}, respectively, are shown in Fig. 2.

As can be observed, for all the equations the parameters correlating best with bioactivity belong to the group of electrostatic and quantum chemical descriptors, which is in accordance with previous works studying QSAR of α_1 adrenergic antagonists. [14]

The intercorrelations of descriptors involved in Eqs. (1), (2) and (3) are presented in Table 2. The results of MLR analysis in Eqs. (1), (2) and (3) with values of the *t*-test, which reflects the significance of the parameter within a particular model, are shown in Table 3.

Orthogonalization of the descriptors was performed to demonstrate the differences between the use of nonorthogonal and orthogonal descriptors in the development of a QSAR model. As an example, the data of selectivity α_{1a}/α_{1d} were used for the estimation. Heuristic optimization was applied to generate the ten best parameters used for regression models. The statistical parameters r^2, S^2 and *F*-test were used for the evaluation of the quality of the models obtained. Comparison of the regression equations derived from nonorthogonal and from orthogonal descriptors is shown in Tables 4 and 5. It is known that orthogonalization of the descriptors does not alter the values of the correlation coefficients (r^2), standard deviations (s^2) and *F* values, [26] which is also shown in Table 5. From data presented in Table 4 it could be concluded that introduction of a new descriptor to nonorthogonal models introduces fluctuation of the coefficients in the regression equations, while the corresponding coefficients in orthogonal models remain constant.

In Table 6 we show the relative standard deviations of regression coefficients. It can be observed that, in the case of orthogonalized descriptors, at each successive step of regression introduction of a new descriptor decreases the relative standard deviation of all the descriptors already used. This is generally not the case with the relative standard deviation of regression coefficients in the nonorthogonalized model. For example, the relative standard deviation for D_1 in one parameter regression model equals RSD_{D1}=–0.4102, in four-parameter regression RSD_{D1}=19.3456 and in ten-parameter regression RSD_{D1}=–0.3748, while the standard deviations for δ_1 are decreased by introducing each new descriptor into the model (in one-parameter regression $\mathrm{RSD}_{\delta 1}$=–0.4102, in ten-parameter regression $\mathrm{RSD}_{\delta 1}$=–0.1383).

Therefore, the advantages of orthogonalized MLR justify the use of the proposed method to build the QSAR equations, as also shown in previous work. [27]

A pharmacophore for antagonists at the α_1 adrenoreceptors has been reported previously. [28] The resulting pharmacophore had three features including an aromatic region, a basic nitrogen atom and a semipolar region or a lipophilic area. This early study did not consider specific requirements for α_1 AR subtypes.

Bremner et al. have developed pharmacophore models for α_{1a} and α_{1b} subtypes using the Apex-3D software of MSI and these models were the first subtype-specific α_1 pharmacophores reported. [29] The only differences between the two subtypes were the distance between the aromatic rings and the amine function. This distance was shorter for the α_{1a} subtype. In their next study, the structural features of the new selective antagonists included were investigated by the same authors. [7] Pharmacophores for selective antagonists at the α_{1a} and α_{1b} adrenoreceptor sites were developed together with a preliminary antagonist pharmacophore for the α_{1d} adrenoreceptor. These pharmacophores were found to be useful for designing ligands based on the aporphine skeleton. Pharmacological α_1 adrenergic subtype binding affinities were modeled by Menziani et al. [13] and satisfactory correlations of ad hoc defined size and shape descriptors with pharmacological data of all three subtypes indicated the strict requirements for shape complementarity between the ligand and the receptor subtypes.

The next step in our work was to superimpose the most selective and most active compounds fitted by the criteria of protonated nitrogen atom and centers of aromatic and semipolar regions previously constructed in the SPARTAN program. Three supermolecules were obtained for α_{1a}, α_{1b} and α_{1d} subtypes (Fig. 3). All compounds were superimposed on abanoquile, a component chosen as reference because of its high activity for all three subtypes. The α_{1a} supermolecule (subset 1) consisted of the following compounds: **1**, **3**, **9** (compounds **10**, **11** and **12**, being very similar to compound **9**, were not superimposed), **15**, **16**, **26**, **27**, **33** and **36**, while the supermolecule for α_{1b} (subset 2) consisted of compounds **2**, **3**, **4**, **17** and **23** and the supermolecule for α_{1d} subtype (subset3) consisted of compounds **3**, **18**, **19** and **25**.

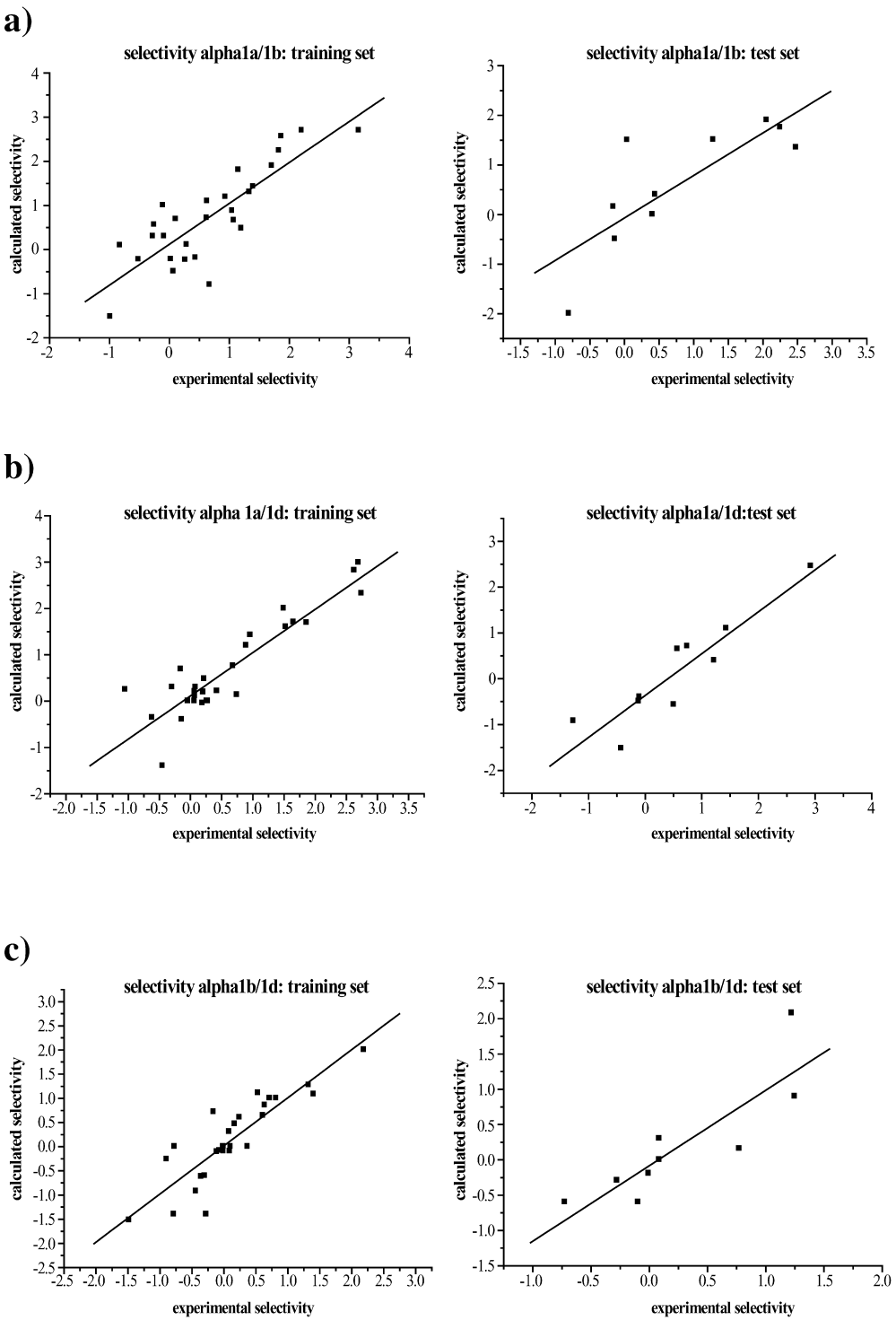


Fig. 2 Correlations between experimental and calculated selectivity for the training and test sets: **a** α_{1a}/α_{1b}; **b** α_{1a}/α_{1d}; **c** α_{1b}/α_{1d}. For selectivity α_{1a}/α_{1b} and α_{1a}/α_{1d}, compounds of test sets are: **2**, **5**, **7**, **10**, **18**, **19**, **24**, **28**, **32** and **36**. For selectivity α_{1b}/α_{1d}, compounds of test set are: **3**, **6**, **11**, **20**, **25**, **26**, **31**, **35** and **36**. Correlation coefficients between experimental and calculated selectivity for test sets are: r=0.6372 (n=10), r=0.8363 (n=10) and r=0.7317 (n=9), for α_{1a}/α_{1b}, α_{1a}/α_{1d} and α_{1b}/α_{1d}, respectively

Widely used algorithms for calculating the molecular and accessible surfaces developed by Connolly [22, 23, 24] were used to compute the following parameters: surface areas, surface volumes, contact areas, reactant areas and total areas. The fact that these descriptors were highly intercorrelated prompted us to choose only the correlation of surface areas with selectivity of α_1 adrenergic antagonists for further consideration and the following regression coefficients were obtained:

– For α_{1a}/α_{1b} selectivity: (compounds of subset 1 (and compounds 10, 11 and 12) and subset 2): (n=16), r^2=0.4261, F=14.425, S^2=0.4201.

Table 2 Correlation matrices for descriptors used in Eqs. (1–3)

Eq. (1)[a]					
	$^3\kappa$	Eex(CN)	E′r1-e	E_{HOMO-1}	
$^3\kappa$	1.0000				
Eex(CN)	–0.0746	1.0000			
E′r1-e	–0.2230	0.0321	1.0000		
E_{HOMO-1}	–0.5078	0.0456	0.4864	1.0000	
Eq. (2)[b]					
	E′e-n(N)	Ett(HN)	^{Q}RNCG	HDSA-1	E′st (C)
E′e-n(N)	1.0000				
Ett(HN)	0.0702	1.0000			
^{Q}RNCG	0.2570	–0.0084	1.0000		
HDSA-1	0.0091	–0.3988	0.1982	1.0000	
E′st (C)	0.3934	0.3182	–0.1017	–0.7062	1.0000
Eq. (3)[c]					
	Est(N)	Ee-e(H)	^{0}BIC	Er1-e(C)	Eex(HN)
Est(C)	1.0000				
Ee-e(H)	0.3787	1.0000			
^{0}BIC	0.3547	–0.1152	1.0000		
Er1-e(C)	0.0581	0.1543	–0.2266	1.0000	
Eex(HN)	0.4246	–0.1608	–0.0401	–0.0524	1.0000

[a] $^3\kappa$, Kier shape index (order 3); Eex(CN), maximum exchange energy for a C–N bond; E′r1-e, minimum 1-electron reactivity index for a C atom; E_{HOMO-1}, HOMO-1 energy

[b] E′e-n(N), minimum e–n attraction for an N atom; Ett(HN), minimum total interaction for an H–N bond; ^{Q}RNCG, relative negative charge (semi MO); ^{E}HDSA-1, HA dependent HDSA-1 (Zefirov); E′st (C), minimum atomic state energy for a C atom

[c] Est(C), maximum atomic state energy for a C atom; Ee-e(H), maximum e–e repulsion for an H atom; ^{0}BIC, average bonding information content; Er1-e(C), maximum 1-electron reactivity index for a C atom; Eex(HN), maximum exchange energy for an H–N bond

Table 3 t-values of regression coefficients in QSAR models

Eq. (1)		Eq. (2)		Eq. (3)	
Descriptor	*t*-test	Descriptor	*t*-test	Descriptor	*t*-test
$^3\kappa$	5.8402	E′e-n(N)	–3.1279	Est(N)	–4.6295
Eex(CN)	–3.2978	Ett(HN)	2.3317	Ee-e(H)	4.2851
E′r1-e	–3.7646	^{Q}RNCG	–2.8135	^{0}BIC	5.5096
E_{HOMO-1}	2.2153	HDSA-1	–4.5009	Er1-e(C)	4.0303
		E′st (C)	–5.0596	Eex(HN)	–2.0488

Table 4 Regression coefficients in QSAR models with regard to selectivity α_{1a}/α_{1d} for nonorthogonal (D_i) and orthogonal descriptors (δ_i)

D_1	D_2	D_3	D_4	D_5	D_6	D_7	D_8	D_9	D_{10}
–11.0831									
–0.4468	–1.1409								
95.7293	–0.3830	–2.8102							
0.0266	44.4508	–0.2749	–4.0610						
–31.8461	0.0291	27.0546	–0.2170	–5.0228					
5.8987	–35.9313	0.0316	38.7218	–0.1909	–8.1285				
20.9049	5.4769	–37.0707	0.0272	46.1227	–0.2124	–8.7759			
–0.6626	11.1993	7.2469	–32.0819	0.0376	55.8052	–0.1188	–8.4427		
–2.2859	–0.6156	–27.2440	9.2984	–39.5124	0.0399	91.0995	–0.1081	–8.2796	
–34.0906	–2.0972	–0.5701	–25.531	10.3556	–67.4058	0.0397	101.0103	–0.1272	–8.1792
δ_1	δ_2	δ_3	δ_4	δ_5	δ_6	δ_7	δ_8	δ_9	δ_{10}
–11.0831									
–11.0831	–0.4468								
–11.0831	–0.4468	95.7293							
–11.0831	–0.4468	95.7293	0.0266						
–11.0831	–0.4468	95.7293	0.0266	–31.846					
–11.0831	–0.4468	95.7293	0.0266	–31.846	5.8986				
–11.0831	–0.4468	95.7293	0.0266	–31.846	5.8986	20.9049			
–11.0831	–0.4468	95.7293	0.0266	–31.846	5.8986	20.9049	–0.6626		
–11.0831	–0.4468	95.7293	0.0266	–31.846	5.8986	20.9049	–0.6626	–2.2859	
–11.0831	–0.4468	95.7293	0.0266	–31.846	5.8986	20.9049	–0.6626	–2.2859	–34.0906

Table 5 Statistical parameters in QSAR models with regard to selectivity α_{1a}/α_{1d} for nonorthogonal (D_i) and orthogonal descriptors (δ_i)

Descriptor	Constant	r^2	s^2	F
(i) Nonorthogonal model				
D_1	0.2185	0.1417	1.0122	0.1178
D_1, D_2	1.7457	0.4837	0.7962	0.4542
D_1, D_2, D_3	–0.4029	0.5546	0.7503	0.5153
D_1, D_2, ..., D_4	–8.0116	0.6008	0.7210	0.5524
D_1, D_2, ..., D_5	22.2116	0.6129	0.7209	0.5525
D_1, D_2, ..., D_6	13.8757	0.6309	0.7153	0.5595
D_1, D_2, ..., D_7	16.6097	0.6941	0.6619	0.6227
D_1, D_2, ..., D_8	40.7898	0.7937	0.5529	0.7368
D_1, D_2, ..., D_9	49.5993	0.9075	0.3767	0.8778
D_1, D_2, ..., D_{10}	70.5264	0.9268	0.3412	0.8997
(ii) Orthogonal model				
δ_1	0.2185	0.1417	1.0122	0.1178
δ_1, δ_2	0.2185	0.4837	0.7962	0.4542
δ_1, δ_2, δ_3	0.2185	0.5546	0.7503	0.5153
δ_1, δ_2, ..., δ_4	0.2185	0.6008	0.7210	0.5524
δ_1, δ_2, ..., δ_5	0.2185	0.6129	0.7209	0.5525
δ_1, δ_2, ..., δ_6	0.2185	0.6309	0.7153	0.5595
δ_1, δ_2, ..., δ_7	0.2185	0.6941	0.6619	0.6227
δ_1, δ_2, ..., δ_8	0.2185	0.7937	0.5529	0.7368
δ_1, δ_2, ..., δ_9	0.2185	0.9075	0.3767	0.8778
δ_1, δ_2, ..., δ_{10}	0.2185	0.9268	0.3412	0.8997

– For α_{1a}/α_{1d} selectivity: (compounds of subset 1 (and compounds 10, 11 and 12) and subsets 3): (n=15), r^2=0.6408, F=23.19, S^2=0.3680.

For α_{1b}/α_{1d} selectivity (compounds of subset 2 and subset 3, n=8) the correlations with these descriptors were not found to be significant. (r^2=0.1002, F=13.425, S^2=0.3201). The results suggest that the descriptors

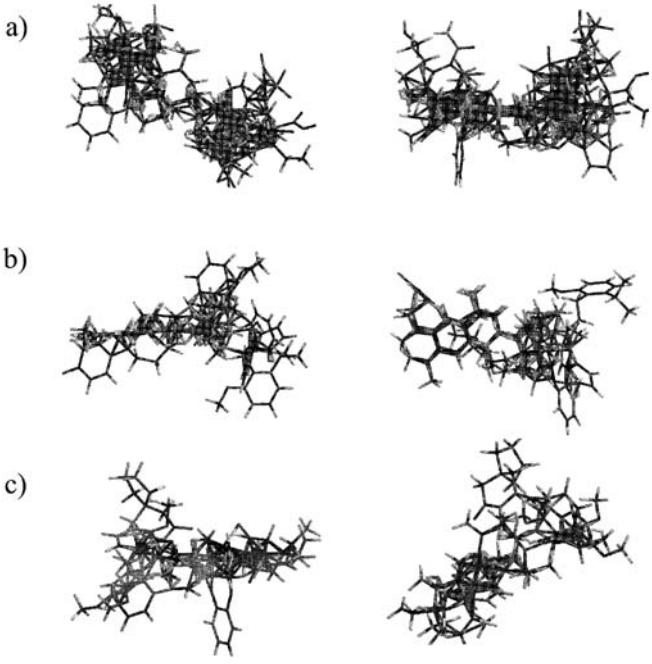


Fig. 3 Frontal and side views of supermolecules obtained by superimposing the most selective and active compounds for the following subtypes. **a** α_{1a} adrenenoreceptor subtype (compounds **1**, **3**, **9**, **15**, **16**, **26**, **27**, **33** and **36**). The resultant surface area and volume calculated by the Connolly algorithm are 992.55 Å^2 and 1,615.94 Å^3. **b** α_{1B} adrenenoreceptor subtype (compounds **2**, **3**, **4**, **17** and **23**). The resultant surface area and volume calculated by the Connolly algorithm 833.86 Å^2 and 1,263.01 Å^3. **c** α_{1d} adrenenoreceptor subtype (compounds **3**, **18**, **19** and **25**). The resultant surface area and volume calculated by the Connolly algorithm are 708.35 Å^2 and 1,068.48 Å^3

Table 6 Relative standard deviations of regression coefficients in nonorthogonal models (i) and orthogonal models (ii)

(i) Nonorthogonal model

RSD_{D1}	RSD_{D2}	RSD_{D3}	RSD_{D4}	RSD_{D5}	RSD_{D6}	RSD_{D7}	RSD_{D8}	RSD_{D9}	$>RSD_{D10}$	RSDc
–0.4102										1.6176
–0.7483	3.6189									0.2416
0.4330	–1.3698	–4.8836								–2.4955
19.3456	1.0678	–0.3783	–0.9495							–0.5009
–1.0406	0.4762	1.8678	–0.5482	–0.7910						1.3694
0.8138	–0.8821	0.3804	1.3178	–0.6285	–0.5761					2.2291
0.4017	0.8117	–0.7913	0.4765	1.0258	–0.5239	–0.4947				1.7246
–0.2673	0.6236	0.5165	–0.7649	0.2972	0.7097	–0.8103	–0.4269			0.6076
–0.1703	–0.1964	–0.3045	0.2768	–0.4243	0.1912	0.3034	–0.6074	–0.2985		0.3418
–0.3748	–0.1715	–0.1945	–0.2954	0.2284	–0.2735	0.1739	0.2506	–0.4709	–0.2737	0.2445

(ii) Orthogonal model

$RSD_{\delta1}$	$RSD_{\delta2}$	$RSD_{\delta3}$	$RSD_{\delta4}$	$RSD_{\delta5}$	$RSD_{\delta6}$	$RSD_{\delta7}$	$RSD_{\delta8}$	$RSD_{\delta9}$	$RSD_{\delta10}$	RSDc
–0.4102										1.6176
–0.3226	–0.2077									1.2723
0.3040	–0.1957	0.4298								1.1989
–0.2922	–0.1881	0.4131	0.5120							1.1522
–0.2921	–0.1880	0.4130	0.5119	0.9976						1.1521
–0.2899	–0.1866	0.4098	0.5079	–0.9897	0.8138					1.1431
0.2682	–0.1648	0.3792	0.4700	–0.9159	0.7531	0.4017				1.0578
–0.2241	–0.1442	0.3167	0.3926	–0.7650	0.6291	0.3355	–0.2673			0.8835
–0.1532	–0.0982	0.2158	0.2688	–0.5212	0.4286	0.2286	–0.1821	–0.1703		0.6019
–0.1383	–0.0890	0.1955	0.2423	–0.4722	0.3882	0.2071	–0.1649	–0.1543	–0.3747	0.5453

Table 7 Selection of best descriptors from each group of descriptors according to correlation coefficients for one-parameter correlations with regard to selectivity on α_{1a}/α_{1b}, α_{1a}/α_{1d} and α_{1b}/α_{1d} adrenoreceptor subtypes of subsets 1, 2 and 3

Subset 1 and 2 selectivity α_{1a}/α_{1b}			Subset 1 and 3 selectivity α_{1a}/α_{1d}			Subset 2 and 3 selectivity α_{1b}/α_{1d}		
	r^2	F		r^2	F		r^2	F
Constitutional descriptors[a]								
MW	0.3374	8.1475	N_C	0.5633	20.6357	N_{AR}	0.5815	9.7279
$^{R}N_R$	0.3041	6.9912	N_A	0.5508	19.6217	$^{R}N_{SB}$	0.4094	4.8517
N_A	0.2933	6.6409	MW	0.5373	18.5801	N_{BR}	0.3487	3.7471
Topological descriptors[b]								
^{3}Sw	0.5781	21.9199	$^{2}\kappa$	0.6235	26.4939	$^{1}IC_A$	0.1278	1.0258
Φ	0.4406	12.6031	W	0.5702	21.2231	$^{2}BIC_A$	0.1255	1.0048
W	0.3706	9.4219	$^{1}\chi$	0.5692	21.1417			
Geometrical descriptors[c]								
MSA	0.3575	8.9035	MSA	0.6097	24.9931	I_A	0.2462	2.2867
I_C	0.3502	8.6229	MV	0.5692	21.1424	S_2	0.1929	1.6733
MV	0.3176	7.4462	S_3	0.5355	18.4458			
Electrostatic descriptors[d]								
^{E}WNSA-1	0.5995	23.9525	^{E}TMSA	0.5839	22.4478	PC_H	0.2626	2.4922
^{E}PNSA-1	0.5865	22.6914	^{E}WNSA-1	0.5372	18.5716	^{E}FNSA-3	0.2433	2.2510
^{E}FNSA-2	0.4672	14.0297	PC_N	0.4946	15.6551	PC'_N	0.2240	2.0206
Quantum chemical descriptors[e]								
^{Q}WNSA-1	0.4788	14.6960	RI(C)	0.6055	24.5575	E′st(H)	0.7718	23.6707
^{Q}PNSA-1	0.4353	12.3342	^{Q}TMSA	0.5839	22.4478	FHACA	0.7145	17.5211
Ev(N)	0.4083	11.0399	$Etot_{2\text{-}c}$	0.5702	21.2302	Eex(HN)	0.7070	16.8868
Eee(HN)	0.3880	10.1429	Eex(HN)	0.5498	19.5393	Enn(HN)	0.6656	13.9352
			Nel	0.5461	19.2492	HACA	0.6621	13.7132

[a] $^{R}N_R$, relative number of rings; N_{AR}, number of aromatic bonds; $^{R}N_{SB}$, relative number of single bonds; see footnote [a] of Table 1
[b] ^{3}Sw, Wiener shape index (order 3); $^{1}\chi$, Randic index (order 1); $^{1}IC_A$, average information content (order 1); see footnote [b] of Table 1
[c] I_C, moment of inertia C; MV, molecular volume; I_A, moment of inertia A; see footnote [c] of Table 1
[d] ^{E}TMSA, total molecular surface area (Zefirov); PC_N, maximum partial charge for an N atom; ^{E}FNSA-3, fractional atomic charge weighted ^{E}PNSA-1 (Zefirov); see footnote [d] of Table 1
[e] Ev(N), maximum valency of an N atom; RI(C), average electrophilic reaction index for an C atom; $Etot_{2\text{-}c}$, total molecular 2-center resonance energy; Eee(HN), maximum e–e repulsion for an H–N bond; Nel, number of occupied electronic levels; E′st(H), minimum atomic state energy for an H atom; FHACA, fractional HACA; HACA, hydrogen acceptor charged surface area; see footnote [e] of Table 1

obtained by the Connolly algorithm could give useful information in the estimation of the α_{1a}/α_{1b} and α_{1a}/α_{1d} selectivity of the compounds investigated.

The compounds of subset 1, subset 2 and subset 3 were further investigated and the correlation of molecular descriptors with selectivity of the compounds present in subsets is given in Table 7.

It is interesting to note that the molecular descriptors in one-parameter correlations are different for the different subtype selectivity, suggesting a different mechanism for the receptor–antagonist interaction for α_{1a}, α_{1b} and α_{1d} subtypes. The theoretical indices involved in the rationalization of various α_1 AR-binding selectivity indicate that electrostatic and quantum chemical interactions are crucially important for ligand–receptor complexes.

Menziani et al. [13] have developed two classes of parameters in their development of QSAR models for native (α_{1A} and α_{1B}) and cloned (α_{1a}, α_{1b} and α_{1d}) adrenoreceptor subtypes. A large number of global and fragmental descriptors were generated for each compound. The ad hoc defined size and shape descriptors were added. The results presented in their work showed that the heuristic statistical method implemented in CODESSA is a valuable tool for selecting the theoretical molecular descriptors from a large pool to give powerful predictive and interpretative QSAR models. It was also shown that the requirements for shape complementarity between the ligand and the receptor are encoded by ad hoc defined size and shape descriptors and these indexes are very useful in the rationalization of pharmacological data to express a predominance of specific receptor subtypes. Good predictive QSAR models for adrenergic activities of compounds related to prazosin with a restricted pool of informative theoretical descriptors were obtained by Cocchi et al., [14] in which both congeneric and noncongeneric molecular series were modeled satisfactorily. Theoretical descriptors allowed well-defined physico-chemical information and were considered in the rationalization of the structural heterogeneity of the molecules examined as differences in the complementarity intermolecular interactions of the studied ligands towards receptor.

Conclusion

A comprehensive set of 38 α_1 AR antagonists has been used to determine quantitative relationships between their chemical structure and selectivity for three subtypes of α_1 adrenoreceptors. The molecular descriptors chosen by a heuristic method indicated the different structural features required for binding of antagonists for α_{1a}, α_{1b} and α_{1d} subtypes of the adrenoreceptor. Use of orthogonalization of the descriptors provided the stability of coefficients of

the regression models as well as a decrease in the relative standard deviations of regression models when introducing more descriptors into the model. The computation of ad hoc shape descriptors confirmed the usefulness of these descriptors in the rationalization of the mechanism of the adrenergic activity with respect to selectivity for α_{1a}, α_{1b}, and α_{1d} subtypes.

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