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Development of 3D-QSAR Models in Cyclic Ureidobenzenesulfonamides: Human β_3-Adrenergic Receptor Agonist☆

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Abstract—Pharmacophoric mapping based on 3D-QSAR studies is performed on sixteen cyclic ureidobenzenesulfonamides for their β_3-adrenergic receptor agonistic activity. The best 3D-QSAR model (with $r^2 = 0.877$) which described the properties and distributions of 5-biophoric and 2-secondary biophoric sites, showed a good correlation between the observed and predicted activity both in training and test.

Obesity is a major challenge to human health at present and clinically relevant obesity is now at epidemic proportions in the US.[1–3] Among various approaches, one based on search for specific β_3-adrenoceptors agonist capable of increasing metabolic rates by selective activation of these receptors considered as a potentially effective approach for the treatment of obesity and diabetes in recent years.[4–6] Many series of compounds possessing β_3-adrenoceptor agonistic property have been reported in recent years.[7–10] The main problem with β_3-adrenoceptor agonists is their cross-reactivity at the β_1 and β_2-receptors. Since obesity is a chronic condition and drug therapy is likely to occur over a prolonged period of time, there is a need to have very selective β_3-adrenoceptor agonists, thus it is important to derive structure–activity relationships in terms of identification of important structural feature using the 3D-QSAR methods. Such studies may be useful in proposing new compounds with enhanced activity and selectivity profile for β_3-adrenoceptors. Since no such studies have been made for β_3-adrenergic receptor agonists, it appeared of interest to carry the logico-based 3D-QSAR analysis to the cyclic ureidobenzenesulfonamides and the results are described in this paper.[11–13]

Among the 15 cyclic ureidobenzenesulfonamides reported in the paper thirteen (Comp. no. **1**–**13**; Table 1) were taken into training set and the remaining two (Comp. no. **14** and **15**; Table 1) along with three β_3-adrenoceptor agonists covering similar range of activity of other paper were taken for test set (Comp. no. **16**–**18**; Table 1).[14] The molecular modeling and QSAR studies were carried out essentially according to the procedure described by us earlier.[15,16]

Among several 3D-pharmacophore models developed with different size and arrangements (center of aromatic rings, hydrophobicity, refractivity, hydrogen bond donor, hydrogen bond acceptor, hydrogen binding site etc.) this model of comparable probability was selected, based on RMSA (calculated root mean square error based on all compounds with degrees of freedom correction) = 0.34, RMSP (calculated root mean square error based on 'leave-one-out' with no degree of freedom correction) = 0.41, $r^2 = 0.877$, chance = 0.13, match value = 0.71, variable = 3 and number of compounds 13. This model described most accurately the distribution of the pharmacophore for β_3-adrenergic receptor agonists.[17] The model has five biophoric centers A, B, C, D and E corresponding to hydroxyl oxygen of ethanolamine chain, imidazolidinone nitrogen attached to benzene ring, imidazolidinone oxygen, lone pair of electron of hydroxyl oxygen of ethanolamine chain and lone pair of electron of imidazolidinone oxygen respectively and two secondary sites S_2 and S_3 in the vicinity of terminal

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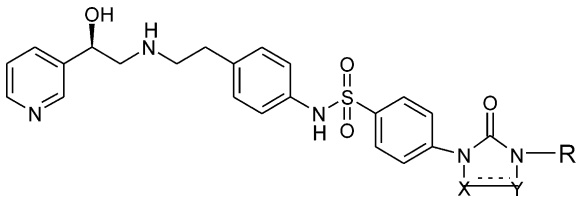
Table 1. In vitro activity (EC_{50}) of cyclic ureidobenzenesulfonamides as human β_3-adrenergic receptor; Compound no. **1–13** training set; Compound no. 14–18 test set and Parameter values for secondary sites S_2 and S_3 in model no. 1



Compd	R	X	Y	EC_{50}, nM	Observed -log EC_{50}	Calculated -log EC_{50}	Predicted -log EC_{50}	Model No. 1[a]	
								Hydrophobicity at S_2	Refractivity at S_3
1	Hex	CH_2	CH_2	18.00	−1.25	−1.31	−1.33	—	−4.21
2	Oct	CH_2	CH_2	2.20	−0.34	−0.45	−0.55	0.61	−4.21
3	Hex	CH	CH	14.00	−1.15	−1.16	−1.80	—	−3.49
4	Oct	CH	CH	3.40	−0.53	−0.76	−1.03	—	−3.49
5	Hex	CH	C-CH_3	81.00	−1.91	−2.15	−2.26	—	−4.21
6	Oct	CH	C-CH_3	60.00	−1.78	−1.29	−1.04	—	−3.49
7	Hex	N	CH	6.00	−0.78	−0.53	−0.35	0.86	−3.49
8	Hex	CH	N	100.00	−2.00	−1.61	−1.46	—	−4.33
9	Hex	C=O	CH_2	130.00	−2.44	−2.03	−2.00	0.86	−4.33
10	Oct	C=O	CH_2	16.00	−1.20	−1.42	−1.48	—	−4.33
11	Hex	CH_2	C=O	13.00	−1.11	−0.99	−0.96	0.86	−4.33
12	Oct	CH_2	C=O	4.90	−0.69	−0.99	−1.07	—	−3.25
13	Oct	N	C=O	100.00	−2.00	−1.71	−1.66	—	−4.33
Test Set									
14	Oct	N	CH	5.40	−0.73	—	−0.76	—	—
15	Oct	CH	N	15.00	−1.18	—	−1.29	—	—
16	$CF_3(CH_2)_3$	CH_3	CH_2	18.00	−1.26	—	−1.31	—	—
17	$(CH_2)_4NCO(CH_2)_2$	CH_2	CH_2	130.00	−2.11	—	−2.03	—	—
18	$CF_3CF_2(CH_2)_3$	CH_2	CH_2	14.00	−1.15	—	−1.31	—	—

[a](−) Indicates absence of property.

carbon atom of the side chain present in the imidazolidinone nitrogen and imidazolidinone nitrogen attached to support phenyl ring respectively as shown in Figure 1. The spatial disposition of the three biophoric sites A, B and C in the model involved in interaction with the specific receptor site in addition to two sites D and E most likely involved in hydrogen bonding depends not only on the properties of biophoric sites A (charge_HET: -0.317 ± 0.0; Don_01: 8.45 ± 0.0), B (pi-population: 0.505 ± 0.057; charge_HET: -0.329 ± 0.045) and C (pi-population: 0.924 ± 0.018; charge_HET: -0.407 ± 0.017; DON_01: 8.303 ± 0.064) but also on their spatial arrangement in terms of mean biophoric distances between site A–B (17.473 ± 0.5680), B–C (2.2798 ± 0.0173) and C–A (18.0708 ± 0.1570). In addition to the identification of the five common structural features described above as biophoric sites for all the molecules, 3D-QSAR equation was derived using the above pharmacophore as a template for superimposition.

$$\log EC_{50} = -0.630(\pm0.262)\ \text{Hydrophobicity} - 1.224(-0.326)\ \text{Hydrophobicity at S2} - 1.204\ (\pm0.274)\ \text{Refractivity at S3} + 2.184$$

$$n = 13;\ R^2 = 0.77;\ r = 0.877;\ F_{(3,9)} = 10.007;\ \text{Chance} = 0.13$$

This equation gives physicochemical properties of the total molecule (global) and of secondary sites S_2 and S3 as independent and the β3-adrenergic receptor agonists activity ($-\log EC_{50}$) as dependent parameter.

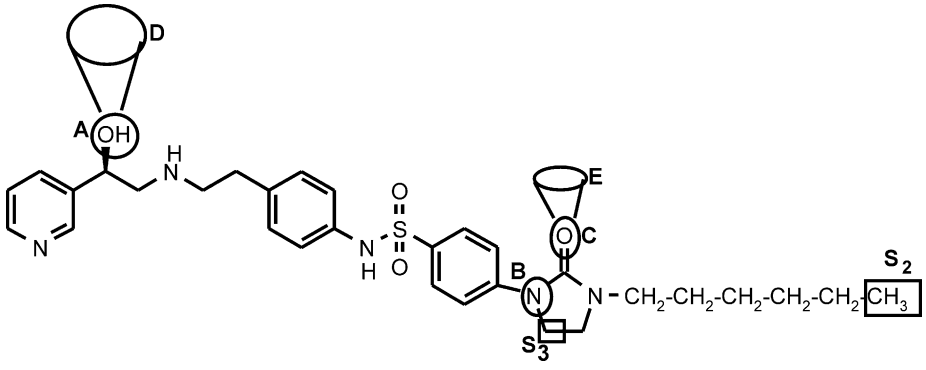


Figure 1. Pictorial representation of biophoric sites O (A,B,C,D,E) and secondary □ sites (S_2 and S_3) represented on the most active compound no. 2.

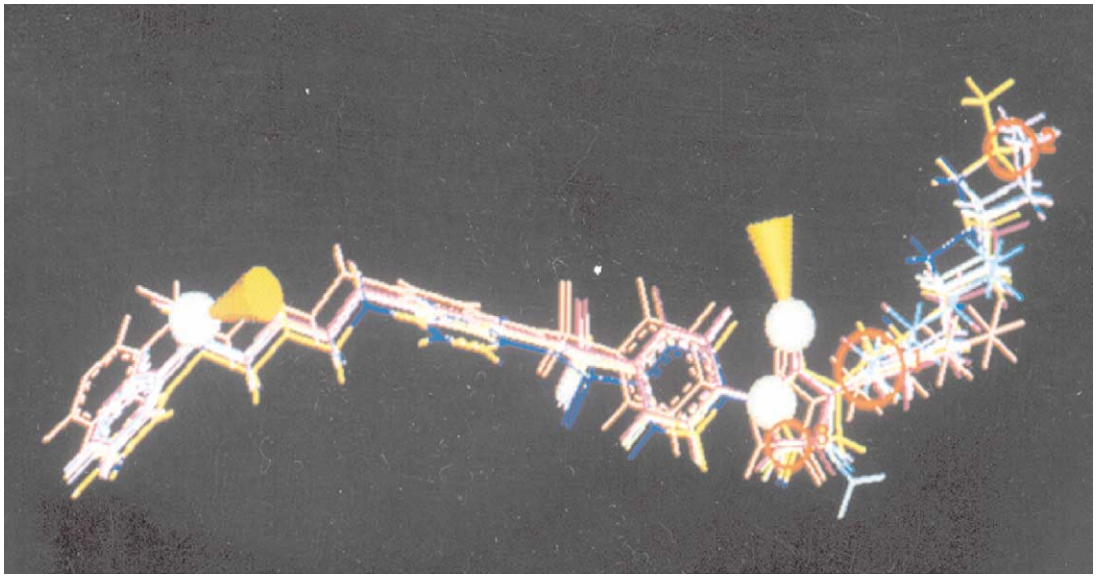


Figure 2. Photograph showing the superimposition of all the thirteen compounds (1–13) of the model with biophoric sites (solid sphere) and secondary sites (red circle).

The atomic hydrophobicity index at the hydrophobic site in the vicinity of R substituent (S_2) (18.04, 1.48, 3.49 Å being the distance from biophoric site A, B and C respectively) and atomic refractivity index at steric site S_3 (25.52, 11.18, 9.11Å being the distance from biophoric site A, B and C, respectively) in addition to the total hydrobhobicity of the molecules best described the observed variation in β3-adrenergic receptor agonistic activity on these molecules within good correlation coefficient ($r = 0.97$) of high statistical significance ($F_{3,9} = 10.00$) (eq. 1).

This 3D-QSAR model showed high match value (0.71) representing the 71% superimposition of all the molecules (Fig. 2) with low difference (0.07) between RMSA and RMSP variables which is also reflected in the comparison of experimental, calculated and predicted (Leave-One-Out) values of biological activity (Table 1). At sites S_2 and S_3 in the model increase in hydrophilicity at S_2 and decrease in bulk at site S_3 may lead to the improvement in activity (Table 1). This model was used to predict the biological activity of test set (Compd no. **14**–**18**) to check validity of the model where a high correlation (0.97) between observed and predicted activities for the test set compounds suggests that the model can be useful in designing the β_3-adrenoceptor agonistic molecules (Table 1).

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17. The 3D QSAR equations were derived with the occupancy set at 4, site radius at 1.10, sensitivity at 1.00 and the randomization value at 100. The primary biophoric centers and secondary sites were used to obtain equation to predict β_3-adrenoceptor agonist activity (EC_{50}). The biophoric sites were set to pi-population, charge, hydrogen donor, hydrogen acceptor, HOMO, LUMO, hydrophobicity and refractivity. The secondary sites were set to hydrogen acceptor, presence; hydrogen donor, presence; heteroatom, presence; ring, presence; hydrophobic, hydrophobicity; steric, refractivity. Quality of the each model was estimated from the observed R^2 (correlation cofficient), RMSA (calculated root mean square error based on all compounds with degrees of freedom correction), RMSP (calculated root mean square error based on 'leave-one-out' with no degree of freedom correction), chance statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.01 corresponds to 1% chance of fortuitous correlation) and match parameter (evaluated for the quality of superimposition for molecules having common biophores; a value of 1 corresponding to the best possible fit).