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Modelling of adrenoceptor ligand targets based on novel medium- or macro-sized fused nitrogen heterocyclic systems

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Summary

Novel medium- and macro-sized heterocyclic compounds were assessed for their potential as subtype-selective adrenergic ligands. Their conformational flexibilities were investigated and their geometric shapes were compared to rigid lead compounds of known selectivity. In the case of α_{1A} selective antagonists, interesting potential targets for synthesis and evaluation were identified by 'opening up' various rings of the fused-ring lead compound **1** by shared-bond cleavage. For α_2 selective ligands, compound **6** was the lead compound and the possibility of mimicking the fused-ring system via intramolecular hydrogen bonding was investigated. None of the potential targets were closely enough related in this case to the lead compound to warrant synthesis.

Introduction

The design and synthesis of new compounds with specific pharmacological activity is an area of worldwide interest, and of both scientific and economic importance. There is a need for useful medicinal agents of more selective action, minimizing undesirable side effects, and also for more fundamental work in understanding the relationships between the structure of a compound and its pharmacological activity and the nature of the molecular events involved. So hand in hand with the search for new active lead compounds, preferably with new modes of biological activity, studies are directed towards a fundamental understanding of the molecular basis for activity, with the longer term goal of identifying new sites for drug development.

It is now well established that many receptors have a range of subtypes [1,2]. This offers the possibility for the development of highly selective antagonists with potentially fewer detrimental activities. However, the design principles involved in order to achieve such fine tuning for affinity still require further development, and this paper aims to explore possible principles in the case of α_1 and α_2 adrenoceptor subtype ligands. Compounds which block α_{1A} receptor sites selectively could be of value medicinally in the treatment of benign prostatic hyperplasia, while selective α_2 adrenergic antagonists are of interest as antidepressants [2].

One way of exploring possible design principles for the achievement of highly selective medicinal agents is by studying compounds that are structurally different from known drugs. In this connection, one aspect of our work is concerned with the design, synthesis and evaluation of novel medium-sized heterocyclic compounds that could act as ligands of adrenoceptors.

As a starting point we have studied, using computer-based modelling methods, the structural effects of progressively increasing ring size and flexibility (**2**–**4**) from a rigid starting ligand **1**.

The rigid compounds were based on the isoquinolino[8,1-*a,b*]carbazole system (**1**), a ring D indole analogue of the aporphine alkaloid skeleton [3,4]. The racemic derivatives (**1**) were shown to have high binding affinity at the α_1 adrenoceptor (rat *vas deferens*) using radioligand binding assays (J.B. Bremner, J.N. Pennefather and W. Lau, Department of Pharmacology, Monash University, Melbourne, Australia,

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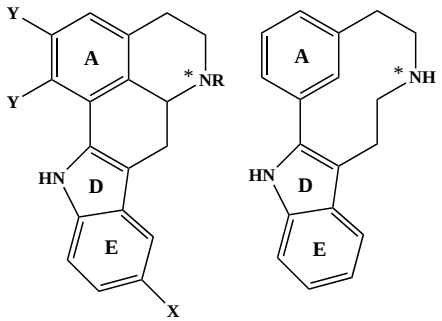
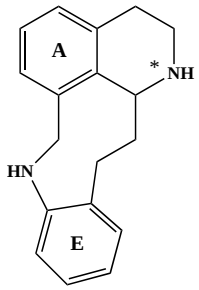
unpublished results). The *N*-*n*-propyl derivative (**1**, R=Pr, X=Y=OMe) had an especially high pK_i value (10.74) at the prazosin high affinity binding site (α_{1A}) relative to the low affinity binding site (pK_i 7.18). This compound has also recently been tested for affinity [5] on cloned expressed human α_1 receptor subtypes and its α_{1A} selectivity has been confirmed in these experiments (pK_i values for α_{1A}, α_{1B}, α_{1D} are 8.2, 6.9, 7.0, repectively). Also, these compounds showed reasonable selectivity over binding (pK_i 5.77) at the α_2 adrenoceptor (guinea pig uterus). A comparative pharmacophore model for antagonists at the α_{1A} and α_{1B} subtypes has been published [6] recently, but fails to fully account for the selectivity of compounds such as **1**, while at the same time predicting correctly the α_{1A} selectivity of dicentrine and analogues such as glaucine (**5**) [7]. One of the key features of this model is the distance between the basic nitrogen atom and the centre of the phenyl ring, which was found to be 5.2–5.8 Å for the α_{1A} subtype and 6.2–7.8 Å for the α_{1B} subtype.



(**1**)

(**2**)



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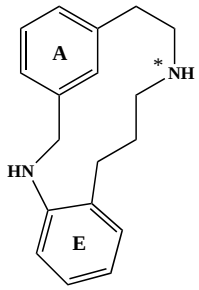


(**4**)

The target compounds **2**–**4** are chemically novel and will allow further exploration of the features and structural architecture required for α_1 adrenoceptor subtype binding. Structural analysis of their conformational flexibility will be presented in this paper and compared to **1**.

The same general theme has been pursued with compounds interacting at the α_2 adrenoceptor. The starting rigid compound in this case was the benzo[*b*]thieno derivative (**6**) (as the hydrochloride salt) which has a pK_i of 8.15 at the α_2 receptor (rat cortex). This compound will be compared with the target fused medium ring structures **7** and **8**.

The aim with **7** is to determine whether intramolecular hydrogen bonding using groups with relatively low steric demand can be used to control medium ring geometry and therefore binding to the receptor site. We have already investigated the effect of the transannular interaction between the nitrogen and the carbonyl group in **9** [8] and found this a very interesting means to subtly control the medium-sized ring.

Methods

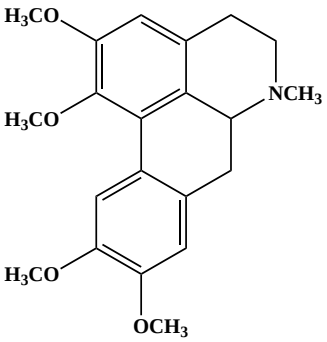
All calculations were performed in vacuo (on isolated molecules). The compounds were modelled using the Spartan program (v. 4.0) by Wavefunction Inc. on a Silicon Graphics Indy workstation.

Conformational searching was performed using the Osawa 'systematic searching' method for rings [9], whereby individual ring atoms are alternately 'puckered up' and 'puckered down'. The resulting structures were minimized using the Sybyl force field and duplicates were discounted upon geometrical checking. Default settings were used; notably the cutoffs for optimization were as follows: 0.0001 Å for the displacements, 0.00001 kcal/mol for the energy, 0.0003 kcal/Å for the gradients and 8.0 Å for the vdW interactions. All conformations for each compound were then re-submitted for minimization at a semi-empirical level, using the AM1 method, again with default settings (0.001 kcal/mol for the heat of formation, 0.0001 atomic units for the gradients, 0.0003 Å for the displacements).

The centres of aromatic rings were determined as the geometric (unweighted) centre of the six carbon atoms for phenyl rings and the four carbon atoms and the nitrogen atom for the five-membered ring in indoles.

Selected conformations were exported (using the Sybyl MOL2 file format) into the InsightII module

by MSI (Molecular Simulations Inc.) for superimpositions.



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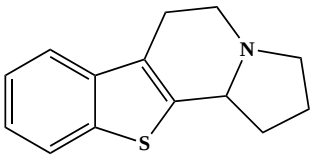
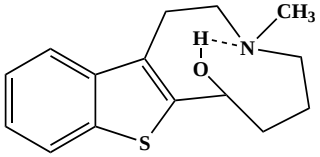
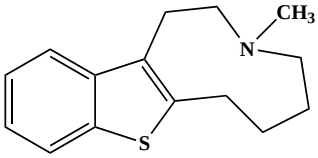


(**6**)



(**7**)



(**8**)

Results and discussion

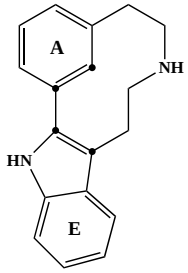
α_1 *adrenoceptor ligands*

Compound (*S*)-**1** (R=X=Y=H) showed two different low-energy conformations when the two non-aromatic rings were searched as described above. Both were very similar in energy (81.1 versus 80.0 kcal/mol), but the higher energy structure was in fact the enantiomer, resulting from change during the modelling calculations. They are fully optimized conformations and

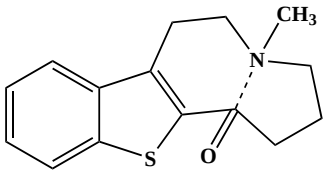
Table 1. Results of conformational searching and AM1 optimization for **2** and **3**

Number	Heat of formation (kcal/mol)	Distance[a] (Å)	Angle[b] (deg)	Dihedral[c] (deg)
2-1	85.5	6.40	137.0	−31.2
2-2	87.9	6.23	134.1	−53.2
2-3	90.2	5.76	131.0	−50.1
2-4	91.5	6.04	136.7	−30.5
3-1	52.3	5.87	87.4	–
3-2	54.7	5.87	79.5	–
3-3	53.2	5.91	88.0	–
3-4	56.4	6.20	98.7	–

[a] Distance between the basic nitrogen and the centre of phenyl ring E.
[b] Angle between the centre of phenyl ring A, the 'indole' nitrogen, and the centre of phenyl ring E.
[c] Dihedral angle as indicated below.



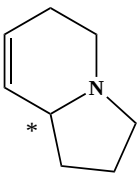
are therefore discussed here as two (slightly different) conformations. For the (*S*) stereochemistry, the heat of formation is 80.0 kcal/mol and the most basic amine hydrogen is axial. For the second (*R*) conformer, this hydrogen is equatorial. The top phenyl ring (A) is twisted out of the plane of the indole moiety by 12.5°. The distance between the more basic nitrogen (indicated by an ∗ in **1**–**4**) and the indole phenyl ring (ring E) is 6.47 Å and that between this nitrogen and the indole five-membered ring (ring D) is 4.85 Å for the lowest energy conformation (6.46 and 4.86 Å for the second conformer). The angle between the centre of ring A, the indole nitrogen and the centre of ring E is 136° in both cases.



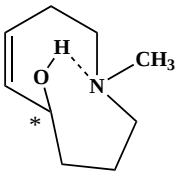
(**9**)

The modelling results for compounds **2** and **3** are summarized in Table 1, with **3** being modelled as the (*R*) enantiomer. Only four conformations were found for each of them. In both cases the energies of all conformers in Table 1 are very close together and, rather than considering only the conformation of lowest energy (the global minimum), all conformations are considered to be likely, given that solvation and the energetic effects of interacting with the receptor are greater than the differences between them. The heat of formation of compound **2** is considerably higher (85.5 kcal/mol) than for any of the other analogues. One reason for this can be found in the fact that the 10-membered ring in the cyclophane is very strained due to the large number of neighbouring carbons that are sp^2 hybridized. In fact, the phenyl ring A is buckled in all four conformations because of this strain, and the dihedral angle between the planes of the indole system and the A ring is enlarged (range −31° to −53°) compared to **1**. This is not a problem for compound **3**, where the planar carbon atoms are separated by sp^3-hybridized carbons, and this is reflected in a much lower heat of formation (52.3 kcal/mol). This molecule adopts a bent shape however, with the angle between the centre of phenyl ring A, the 'indole' nitrogen and the centre of the other phenyl ring (E) being in the range of 85°–100°. The corresponding angle for **1** is 136°, and for **2** it is also between 131° and 137°. The distance between the basic nitrogen and phenyl ring E is between 6.0 and 6.4 Å for **2** and between 5.9 and 6.2 Å for **3**.

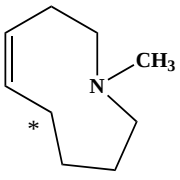
In contrast to the relative rigidity of **2** and **3**, 43 conformers were found for the macrocyclic compound **4**, with energies ranging from 40.5 to 50.3 kcal/mol. These are summarized in Table 2. Again, for reasons outlined above, all conformations are considered. The angles encountered between the two phenyl rings range from 89° to 152° and the distance between the basic nitrogen and phenyl ring E varies from 3.8 to 6.2 Å.



(**10**)



(**11**)



(**12**)

Table 2. Results of conformational searching and optimization for **4**

Number	Distance[a] (Å)	Angle[b] (deg)
1	5.68	96.7
2	4.88	92.3
3	3.98	91.9
4	5.14	91.6
5	5.92	99.2
6	5.80	114.6
7	5.87	140.6
8	5.71	96.3
9	5.22	89.8
10	5.90	144.7
11	5.57	100.0
12	6.10	109.7
13*	6.22	98.6
14	5.69	98.9
15	5.10	105.8
16	5.29	102.1
17	5.77	138.3
18	5.68	96.8
19	5.68	133.6
20	5.31	92.4
21*	6.15	138.2
22	5.71	105.4
23	4.80	115.7
24	5.69	99.1
25*	5.96	152.4
26	5.69	99.2
27	4.48	117.6
28	5.50	95.6
29*	6.22	123.6
30	6.21	101.2
31	5.78	108.7
32	4.32	95.5
33	4.60	120.9
34	5.53	106.2
35	5.80	116.5
36*	3.78	106.4
37*	4.11	89.1
38	6.15	101.7
39	6.10	138.4
40	6.11	139.4
41	5.74	110.6
42*	5.79	138.1
43	6.21	95.4

[a,b] As in Table 1.

* Conformation chosen for further investigation.

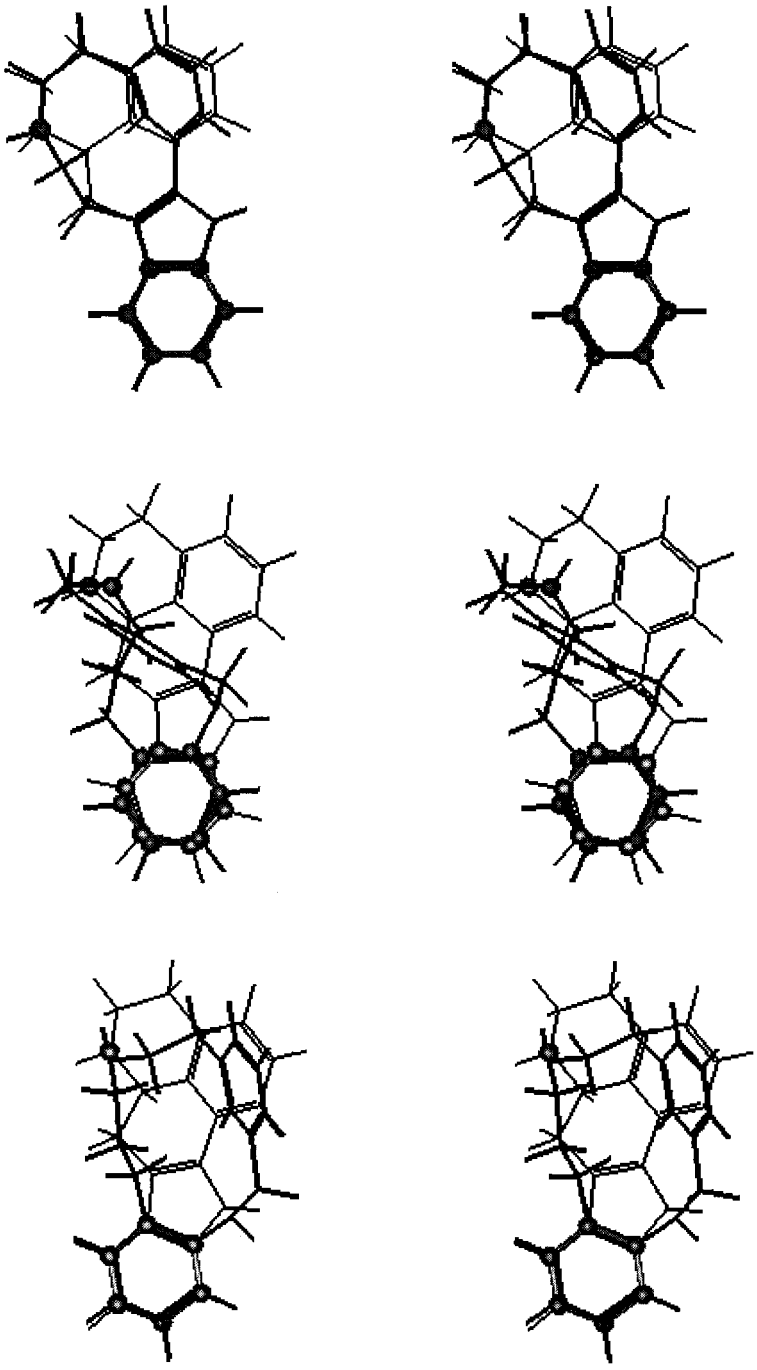


Figure 1. Stereopairs of superimpositions of selected conformers (best fit, see Table 3) of compounds **2** (top), **3** (middle) and **4** (bottom) onto compound (*R*)-**1** (R=X=Y=H; thin lines) using the carbon atoms of phenyl ring E and the more basic nitrogen atom (indicated by an ∗ in **1**–**4**).

Table 3. Superimposition of selected conformers of **2**, **3** and **4** onto **1** (R=X=Y=H) using the carbon atoms of phenyl ring E and the basic nitrogen atom

Conformer	Rms (Å)
2-1	0.075
2-2	0.257
2-3	0.463
2-4	0.198
3-1*	0.649
3-2*	0.605
3-3*	0.639
3-4*	0.493
4-13	0.482
4-21	0.331
4-25	0.368
4-29	0.282
4-36	1.225
4-37	1.095
4-42	0.459

*(*R*)-**1** (R=X=Y=H) used for superimposition.

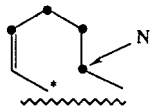
In order to predict how closely compounds **2**–**4** will be able to mimic compound **1** in its receptor binding, selected conformations were superimposed onto **1** using in all cases the carbon atoms of phenyl ring E and the basic nitrogen atom. The best results for **2**, **3** (compared to (*R*)-**1**) and **4** are shown in Figure 1, and the rms values for all conformations tested are given in Table 3. It is clear that compound **2**, with the indole ring system intact, would be an excellent mimic of **1**, and thus a suitable target for synthesis and adrenoceptor binding studies.

Compounds **3** and **4** are of interest because they lack the fused indolic moiety, with only the original ring E remaining. As a result, a bent shape arises (especially for **3**), which makes them much poorer mimics of **1**. Furthermore, most of the distances observed between the basic nitrogen and phenyl ring E for **3** are now in between the two ranges predicted by the pharmacophores to be important for α_{1A} versus α_{1B} selectivity. Compound **4** exhibits only 6 out of the 43 conformers with a distance long enough for the α_{1B} subtype, however, versus 21 with a distance in the α_{1A} range, 10 with a distance even shorter than 5.2 Å, and 6 in between 5.8 and 6.2 Å. This macrocyclic compound is therefore of some interest for future synthesis.

Table 4a. Results of conformational searching and optimization for **10**, **11**, and **12** as described in the Methods section

Number	Distance[a] (Å)	Dihedral[b] (deg)
10-1	1.5	44.6
10-2	1.5	−49.6
11-1	3.2	89.9
11-2	3.4	80.2
11-3	3.4	58.6
11-4	3.8	76.9
11-5	3.9	48.4
11-6	3.6	−45.6
11-7	4.1	90.1
11-8	3.6	42.0
12-1	3.2	89.4
12-2	3.4	79.1
12-3	3.8	78.1
12-4	3.4	−80.7
12-5	3.3	−57.8
12-6	3.8	46.5
12-7	3.6	−44.5
12-9	3.2	−31.5
12-10	3.5	30.9

[a] Distance between the carbon atom * and the nitrogen atom.
[b] Dihedral angle as indicated below.



Parameters employed in conformational searching

During the reviewing process, the authors were alerted to the fact that possibly not all relevant conformations were found using the Osawa search method with default parameters in Spartan. Upon reflection, the parameter setting which cuts off all conformers that are expected to be less than 10% as abundant as the lowest energy conformer seemed too stringent, especially since the ordering of conformers in terms of the heat of formation often gets changed upon reminimization with the AM1 method. The two parameters regulating this cutoff were therefore neutralized (MINPOP=SELPOP=ALL), so no conformers were removed on the grounds of the Boltzmann distribution alone.

The conformational searches were repeated and, again, all conformers found were reoptimized at the AM1 level. For the very rigid molecule **1** only the

Table 4b. Results of conformational searching and optimization for **10**, **11**, and **12** with the refined method for conformational searching (see text for details); conformers for **11** and **12** are ordered by increasing heats of formation

Number	Distance[a] (Å)	Dihedral[b] (deg)
10-1	1.5	44.6
10-2	1.5	−49.6
11-47	4.1	n.d.
11-11	3.7	n.d.
11-16	4.0	n.d.
11-5	3.4	57.8
11-3	3.4	80.4
11-1*	3.2	89.9
11-12	4.0	n.d.
11-27	4.0	n.d.
11-21	4.1	n.d.
11-15	3.7	n.d.
11-40	3.7	n.d.
11-7	3.6	n.d.
11-35	4.3	n.d.
11-9*	3.3	−34.7
11-13*	3.5@	−77.9
11-23	3.1	−71.7
11-8*	3.3@	−88.5
11-2	3.3@	−88.5
11-22	4.1	n.d.
11-25	4.1	n.d.
11-6	3.8	n.d.
11-34	4.1	n.d.
11-14	3.8	n.d.
11-29	4.1	n.d.
11-39	3.8	n.d.
11-28	3.8	n.d.
11-41	3.5@	−106.3
11-24	3.8	n.d.
11-4	3.8	n.d.
11-31	3.8	n.d.
11-33	3.7	n.d.
11-30	3.5	−113.4
11-32	3.5	−58.8
11-10	3.4	−59.0
11-17	3.8	n.d.
11-43	4.0	n.d.
11-38	3.9	n.d.
11-36	3.5	19.0
11-42	3.8	n.d.
11-45	3.8	n.d.
11-20	3.9	n.d.
11-46	3.6	n.d.
11-37*	3.0	−43.1
11-18	3.4	35.8
11-19*	3.0	−76.4
11-48	3.8	n.d.
11-44	3.6	n.d.
11-50	3.6	n.d.
11-49*	3.2@	72.3
11-26	3.2@	72.3
12-12	4.0	n.d.
12-16	4.0	n.d.
12-2	3.4	−79.9
12-1*	3.2	−90.9
12-9	4.0	n.d.
12-11	3.7	n.d.
12-22	3.7	n.d.
12-6	3.6	n.d.
12-4*	3.3	−57.9
12-14	4.1	n.d.
12-17	3.8	n.d.
12-24	3.8	n.d.
12-8	3.6	n.d.
12-5	3.8	n.d.
12-25	3.8	n.d.
12-3	3.9	n.d.
12-7*	3.3	n.d.
12-26	4.1	n.d.
12-20	4.0	n.d.
12-18	4.1	n.d.
12-15*	3.1	−72.0
12-19	3.5	−114.6
12-10*	3.1	−58.1
12-23	3.9	n.d.
12-13*	3.0	78.4
12-21*	3.0	−42.5

[a,b] As in Table 4a.
n.d.: not determined.
* Conformation chosen for further investigation.
@: hydrogen bond present across the ring.

same two conformations were found, while for **2** two additional conformers were found. For **3**, two additional conformers were found, but the highest energy conformer previously found (Table 1) was not found this time. For **4**, the results were very similar to the previous search, with the first 43 conformations identical to the first run, and seven more found. For none of these molecules, however, was the lowest energy con-

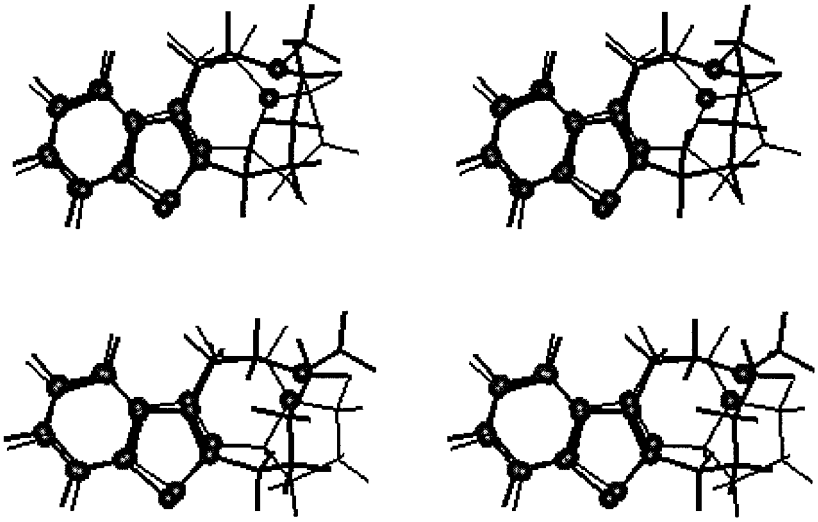


Figure 2. Stereopairs of superimpositions of selected conformers (best fit, see Table 6) of compounds **7** (top) and **8** (bottom) onto **6** (thin lines) using the heavy atoms of the benzo[*b*]thiophene system and the nitrogen atom.

Table 5. Results of AM1 optimization for **6**, **7** and **8**

Number	Heat of formation (kcal/mol)	Distance[a] (Å)	Dihedral[b] (deg)
6-1	40.9	1.5	44.8
6-2	42.5	1.5	−50.3
7-1	−10.6	3.2	90.7
7-9	−8.5	3.3	−31.2
7-23	−8.5	3.1	−74.5
7-8*	−10.4	3.3	−89.4
7-37	−4.6	3.0	−44.2
7-19	−4.3	3.0	−78.9
7-49*	−3.8	3.2	75.8
8-1	31.2	3.2	−90.8
8-4	31.8	3.4	−58.3
8-7	33.8	3.3	39.3
8-15	33.4	3.1	−73.3
8-10	32.8	3.9	−79.0
8-13	36.3	3.0	80.2
8-21	37.5	3.0	−43.7

[a,b] As in Table 4a.
* Hydrogen bond present across the ring.

former changed from the first run nor was a conformer found which fitted better on to the target molecule **1**.

α_2 *adrenoceptor ligands*

Because the sulphur atom in compounds **6**–**8** slowed down the computations considerably, a variety of starting geometries were created via conformational searching of the smaller systems **10**–**12**, where the benzo[*b*]thieno ring has been cut away.

Compounds **10**–**12** were subjected to the original searching strategy as defined in the Methods section and also to the refined conformational searching as described in the previous section (Osawa search with MINPOP=SELPOP=ALL and with Sybyl force field minimization, followed by reoptimization of all conformers using AM1).

For compound **10** two different conformations were found by the original method, eight different conformations for **11** and six for **12**. The energies of these (in kcal/mol) range from 9.1 to 10.0 for **10**, from −42.6 to −39.9 for **11**, and from 0.8 to 2.9 for **12**. Again, for each molecule the energetic spread of the conformers found is small and all of them are considered likely. These are summarized in Table 4a and characterized in terms of the distance between the carbon atom and the nitrogen atom across the ring (in **6** and **10** these two atoms are connected via a single bond) and also the dihedral angle measured along the double bond carbon-CH_2CH_2-N.

For these three molecules, contrary to what had been observed for **1**–**4**, changing the method of conformational searching led to quite different results for **11** and **12**. For **10** only the same two conformations were observed.

For **11**, we now report 50 conformations, and the additional conformations are not all higher in energy than those found previously. In fact, several conformers were found with lower heat of formation

Table 6. Superimposition of selected conformers of **6**, **7** and **8** using the heavy atoms of the benzothiophene system and the nitrogen atom

Pair of conformers	Rms (Å)
6-1 **7**-1	0.463
6-1 **7**-9	0.614
6-1 **7**-23	0.431
6-1 **7**-8	0.481
6-1 **7**-37	0.517
6-1 **7**-19	0.346
6-1 **7**-49	0.340
6-1 **8**-1	0.452
6-1 **8**-4	0.599
6-1 **8**-7	0.595
6-1 **8**-15	0.426
6-1 **8**-13	0.334
6-1 **8**-21	0.505
6-2 **7**-1	0.477
6-2 **7**-9	0.645
6-2 **7**-23	0.413
6-2 **7**-8	0.464
6-2 **7**-37	0.495
6-2 **7**-19	0.347
6-2 **7**-49	0.341
6-2 **8**-1	0.435
6-2 **8**-4	0.578
6-2 **8**-7	0.574
6-2 **8**-15	0.408
6-2 **8**-13	0.333
6-2 **8**-21	0.483

values than the lowest identified before (−43.8 versus −42.6 kcal/mol). Similarly, for **12** 26 conformations were now observed with the heats of formation as low as 0.42 kcal/mol (previously 0.79 kcal/mol). These results are detailed in Table 4b. Of all the conformers of **11** (Table 4b), only six show hydrogen bonding across the ring (as defined by the distance between the OH hydrogen and the nitrogen being below 2.5 Å) and, furthermore, the 14 lowest energy conformers do not display a hydrogen bond. Hydrogen bonding across the ring can therefore not be used in this system to control the geometry of the medium-sized ring. This finding must, however, be considered preliminary, because we have previously found that the AM1 method is not particularly suited to the calculation of the transannular amine–carbonyl interaction [8].

Selected conformations (indicated by an ∗ in Table 4b) were extracted, the benzo[*b*]thiophene moiety was built on to give compounds **6**–**8**, and then these were optimized using the AM1 method. Conformer selections from Table 4b were governed mainly by the distance between the nitrogen atom and carbon ∗: all conformers with this distance smaller than or equal to 3.3 Å were selected. This set was found to include conformations with the dihedral angle very close to that for **10** and was therefore considered sufficient. The results are summarized in Table 5. Comparison between the results in Tables 4b and 5 also demonstrates that **10**–**12** are excellent model systems for **6**–**8**. The double bond seems to be unable to twist in the medium rings **10**–**12**, even without the rigidity of the added rings. Upon converting the smaller molecules into the larger ones and reoptimization, the distances across the ring only change in one conformer (**8**-10). The dihedrals also change very little in each case, except for **8**-10. The ordering of energies, however, changes slightly for **7** and **8**.

The various conformations for **7** and **8** were then superimposed upon the two conformations for **6** using the heavy atoms of the benzo[*b*]thiophene moiety and the nitrogen atom (Table 6). As was already suspected from the values in Tables 4 and 5, only poor to moderate fits could be achieved. Figure 2 gives the best example in each case.

Compounds **7** and **8** would therefore not be expected to mimic the properties of **6** as an α_2 adrenoceptor ligand very convincingly, and further design in this area will need to be undertaken.

Conclusions

We have been able to design promising target adrenergic ligands which should be able to bind very well to the α_{1A} subtype, but not to the very closely related α_{1B} subtype. This has been achieved by modelling the conformational flexibility of various potential target molecules of increasing flexibility and comparing their geometry to that of a fused-ring lead compound of known selectivity. The same approach has been used in a series of potential α_2 selective ligands, but the intramolecular hydrogen bond examined proved unsatisfactory to hold the medium-sized ring together in the required ‘pinched’ conformation.

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