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A molecular modelling study of the interaction of noradrenaline with the β_2-adrenergic receptor

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SUMMARY

A model of the β_2-adrenergic receptor binding site is built from the primary structure of the receptor, experimental evidence for key binding residues and analogy with a homologous protein of partially determined structure. It is suggested that residues Trp-109, Thr-110 and Asp-113 are involved in ligand binding. Noradrenaline is successfully docked into this model, and the results of an INDO molecular orbital calculation on the complex indicate that a charge transfer interaction between Trp-109 and noradrenaline is possible.

INTRODUCTION

Considerations of how a molecule may react with the adrenergic receptor [1–9] have so far been based on circumstantial evidence concerning the structure of the receptor. Recently, the gene and cDNA for the hamster lung β_2-adrenergic receptor have been cloned, and the amino acid sequence deduced from the nucleotide sequence [10]. The β_2-adrenergic receptor is found to be very similar in sequence and hydrophobicity profile [11,12] to rhodopsin [13,14] and it has been reported that the enzyme which phosphorylates rhodopsin (rhodopsin kinase) is also capable of phosphorylating the β_2-adrenergic receptor, and that β_2-adrenergic receptor kinase can also phosphorylate rhodopsin [15]. Also the fact that both rhodopsin and the β_2-adrenergic receptor are involved in signal transduction mechanisms that involve interaction with the guanine nucleotide regulatory proteins, transducin [16] and G_S [17] is strong evidence to suggest that rhodopsin and β_2-adrenergic receptor have similar secondary structures.

Electron diffraction has been used to indicate that bacterio-rhodopsin consists of seven α-helical rods which span the cell membrane [18–21]. The primary structure of ovine [22] and bovine rhodopsin [23] is very similar to bacterio-rhodopsin, hence it is very probable that rhodopsin and

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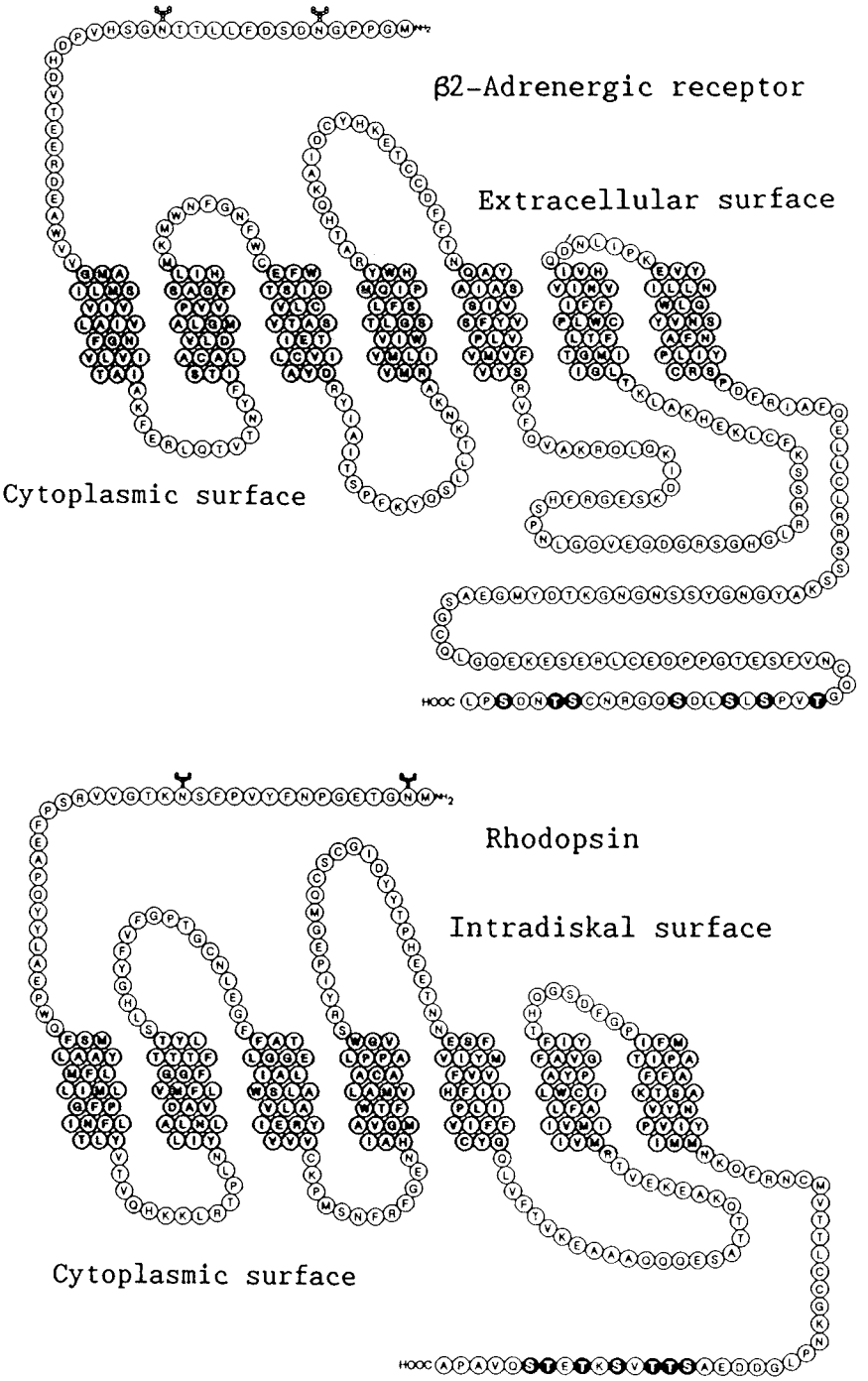

Fig. 1. Postulated arrangements of the α-helices of rhodopsin and the β_2-adrenergic receptor. Single letter codes for residues used in this study are: W = tryptophan, T = threonine, S = serine, I = isoleucine, D = aspartate.
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the β_2-adrenergic receptor have a similar structure consisting of seven α-helices which traverse the cell membrane. The amino acid sequence of other receptors including the α_2-adrenergic [24,25], β_1-adrenergic [26] and several subtypes of acetylcholine, muscarinic [27–31] and the serotonin [32] receptor have been recently deduced and are found to be homologous with the β_2-adrenergic receptor in both sequence and hydrophobicity. The sequence of the human β_2-adrenergic receptor has also been recently reported [33–35] and it is found to be about 90% homologous with the hamster β_2-receptor. It is thought that these receptors also consist of seven membrane spanning α-helices. Other similarities between this family of membrane-bound neuro-transmitter receptors which suggest that these proteins evolved from a similar ancestor are the fact that they all contain two possible N-glycosylation sites near the amino-terminal regions of the molecules. These sites in rhodopsin are known to be glycosylated [23]. Also the carboxyl-terminal regions of these proteins contain several serine residues which are possible sites for phosphorylation [15]. Phosphorylation has been shown to play an important role in the regulation of rhodopsin [23] and the β_2-adrenergic receptor [36]. The postulated arrangements of the α-helices of rhodopsin and the β_2-adrenergic receptor are shown in Fig 1.

It has been proposed that adrenergic agents interact with the β-$_2$ adrenergic receptor in a similar manner to the binding of retinal to opsin [37] in that they intercalate among the hydrophobic transmembrane helices and hence determine whether the receptor is in its active or inactive conformation.

Retinal is known to form a Schiff base with a lysine residue in helix VII of opsin [37]. There is no analogous lysine in the same helix of the β_2-adrenergic receptor, but it is interesting to note that the sequenced adrenergic, muscarinic and serotonin receptors all possess two buried aspartate residues, one in helix II and the other in helix III, which have been suggested as possible agonist binding sites [28]. The fact that a nitrogen atom which is protonated at physiological pH is a feature of all adrenergic agents implies that the mode of binding of these molecules is to a negatively charged region of the receptor. It has been found that labelling the binding site of purified rat brain muscarinic receptor, with the irreversible antagonist propylbenzilylcholine mustard, followed by digestion yields two peptides whose properties suggest that they are labelled on acidic residues in hydrophobic regions, predominantly in helix III [38–40]. As one of these peptides is glycosylated it is likely that it comes from the amino-terminal half of the receptor. The β-adrenergic, muscarinic and serotonin receptors also conserve a tryptophan residue in helix III, and there is experimental evidence of a trypthophan residue being involved in the binding of adrenergic agents [41]. An oligonucleotide-directed mutagenesis study [42] of the hamster lung β_2-receptor indicated that Asp-113, on helix III, is involved in agonist and antagonist binding. Mutagenisis experiments have also shown that Asp-79 (on helix II) is involved in agonist binding [43] and that Asp-130 (on helix III) is involved in coupling to adenylyl cyclase [44]. An earlier molecular modelling study [45] of this system concentrated on helix VII.

The aim of the work described here is to investigate how molecular modelling techniques can be used to gain some more information about the binding of the natural substrate, noradrenaline, to the β_2-adrenergic receptor.

RESULTS AND DISCUSSION

The COSMIC molecular modelling package [46] is used to generate models of helices II and III,

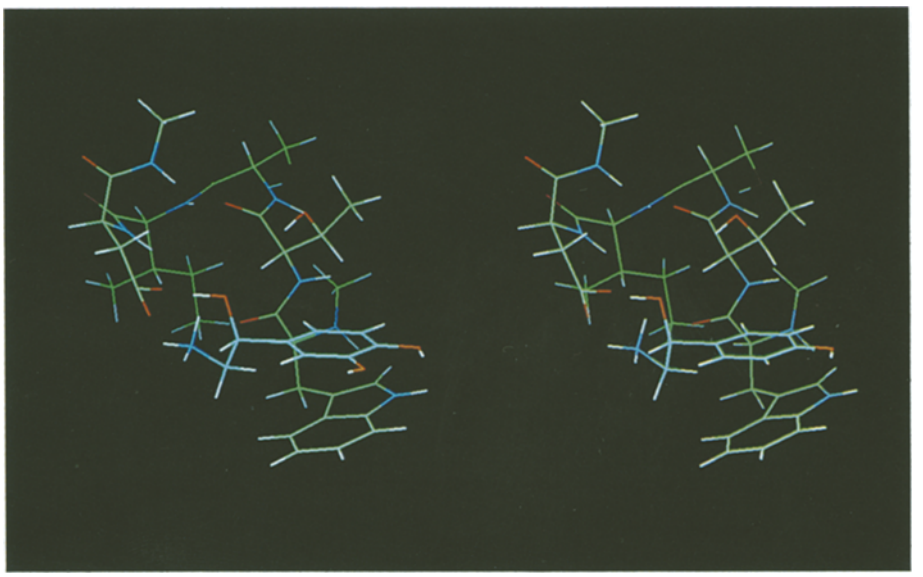

Fig. 2. The proposed β_2-adrenergic receptor model. The CH_3-Trp-Thr-Ser-Ile-Asp-$NHCH_3$ penta-peptide α-helix minimised by molecular mechanics. Internal coordinates are listed in Appendix 1.

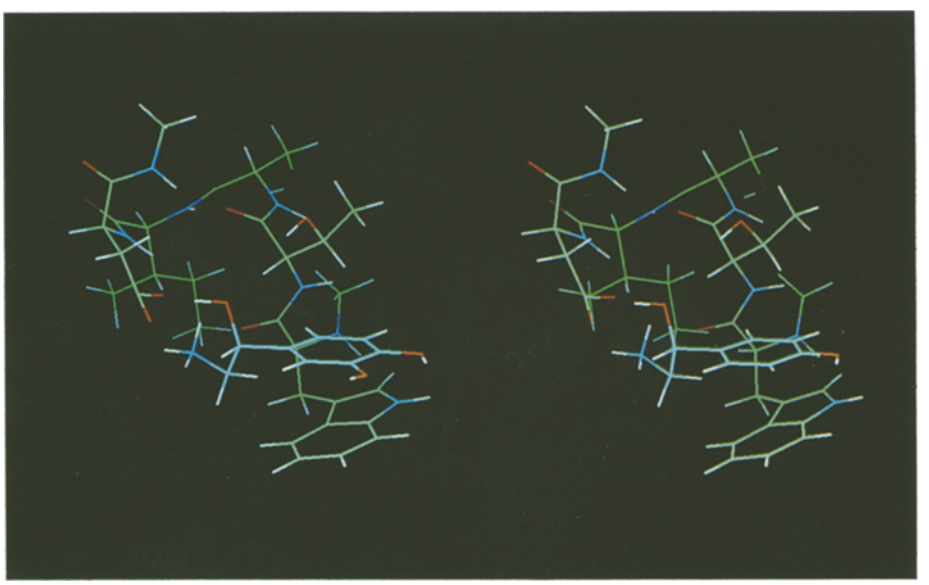

Fig. 3. Noradrenaline docked into the proposed β_2-adrenergic receptor model. Internal coordinates are listed in Appendix 2.

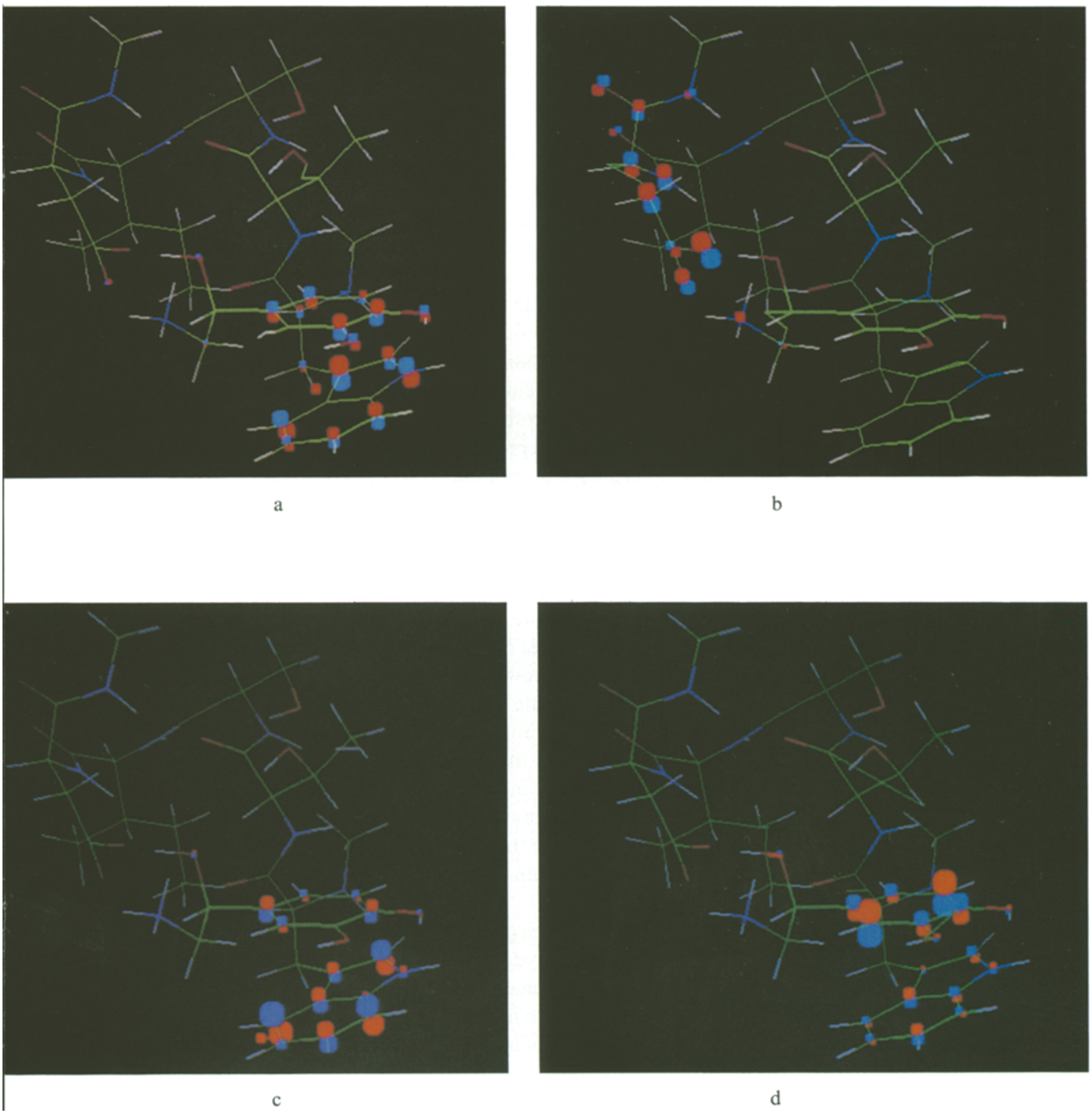

Fig. 4. The (a) NHOMO, (b) HOMO, (c) LUMO and (d) NLUMO of the noradrenaline–$ß_2$-adrenergic receptor model complex. Calculated by INDO and displayed using the program 'ORBIT' [53]. Molecular orbital energies are (a) −0.4054, (b) −0.3641, (c) 0.0968 and (d) 0.1172.

using Φ and Ψ values of $-59°$ and $-44°$, respectively, as suggested by Blundell et al. [47] for an α-helix in a hydrophobic environment.

The regions around the aspartate residues are examined for any group which might interact with the phenyl ring of noradrenaline. As can be seen from the representation in Fig. 1, the residues around the aspartate in helix II are largely alkyl, hence unlikely to strongly interact with noradrenaline. The surroundings of the aspartate in helix III appear to be much more interesting, especially the tryptophan unit which is four residues ($\approx$ 1 turn) away from the aspartate. It is thought possible that noradrenaline could bind to this region of the receptor with the ammonium head of the molecule involved in an electrostatic interaction with the aspartate while the phenyl ring of noradrenaline overlaps the tryptophan indole ring.

To model this region of the receptor, the sequence CH_3-Trp-Thr-Ser-Ile-Asp-$CONH_3$ is built using the COSMIC package, with the Φ, Ψ and Ω torsion angles set to $-59°$, $-44°$ and $180°$, respectively. The aspartate carboxyl proton is removed as it is assumed that noradrenaline will interact in its protonated form with a negatively charged receptor. Partial atomic charges are calculated by Abraham's method [48–50] with the calculated charges on the aspartate carboxyl oxygen atoms (-0.8265 and -0.3954) being replaced by the average of these charges (-0.6110).

The orientation of the side chains of the peptide model are optimised using the COSMIC MIN01 [46] torsion angle searching facility. The minimum energy conformation from this procedure is then subjected to 100 cycles of molecular mechanics minimisation to give the structure shown in Fig. 2. It can be seen that the tryptophan indole ring and the aspartate carboxyl group are in suitable positions to interact with both the amino and phenyl groups of noradrenaline.

The X-ray crystallographic structure of noradrenaline [51] is placed in the receptor model so that the ammonium head is oriented towards the aspartate carboxyl group and the phenyl ring overlaps the tryptophan indole ring. The complex is then subjected to 100 cycles of molecular mechanics minimisation. The resulting structure shows that the amino head and side chain hydroxyl of noradrenaline are still directed at the aspartate group and that the indole ring of the receptor has moved away from the noradrenaline phenyl ring, so that the two rings still overlap but the interplanar distance between the two rings is 3.2 Å. It could also be seen that the threonine hydroxyl group, although directed away from the noradrenaline unit, could come into hydrogen bonding distance with the noradrenaline side chain hydroxyl if the threonine Cα-Ca and Cβ-O bonds are rotated. These bonds are thus rotated so that the threonine hydroxyl hydrogen is as close as possible to the oxygen of the noradrenaline side chain hydroxyl. The distance of closest approach is 2.74 Å.

This structure is again minimised by 100 cycles of molecular mechanics minimisation to ensure that the threonine hydroxyl can maintain the hydrogen bond with noradrenaline. This is in fact the case, the resulting threonine O-H to noradrenaline O-H distance being 2.84 Å. This final noradrenaline β_2-adrenergic receptor model is shown in Fig. 3.

The interaction between the noradrenaline amino and side chain hydroxyl and the receptor carboxyl groups is very similar to the model proposed in Ref. 52. In this study, a formate unit was used as a model for the receptor interaction. The fact that the threonine residue may also be involved in the binding of noradrenaline to the β_2-adrenergic receptor can be used to explain why the *S*-form of noradrenaline, with the chirality at the β-carbon inverted, is much less active than *R*-noradrenaline. With the side chain hydroxyl group in the *S*-configuration it is still able to interact with the aspartate carboxyl group, but is too distant from the threonine residue to form the additional hydrogen bond.

An INDO molecular orbital calculation is performed on the noradrenaline-β_2-adrenergic receptor model to investigate whether a charge–transfer interaction is possible between tryptophan and noradrenaline. The two highest lying occupied (NHOMO and HOMO) and lowest lying unoccupied orbitals (LUMO and NLUMO) are shown in Fig. 4. The HOMO of the complex is oriented around the aspartate carboxyl group. This is not surprising as this carboxyl group carries an overall unit negative charge. The NHOMO and LUMO are found to be distributed over the noradrenaline and tryptophan aromatic rings and the NLUMO is found to be predominant over the noradrenaline phenyl ring. The fact that the high lying occupied and low lying unoccupied orbitals are found to be distributed around the noradrenaline phenyl and tryptophan indole rings means that, from this calculation, there is very strong evidence for the suggested charge transfer interaction.

CONCLUSION

Using the described experimental data, we have been able to generate a model of the β_2-adrenergic receptor. This model has enabled a detailed study of the interaction of noradrenaline with the β_2-adrenergic receptor to be carried out. A possible binding site has been identified using this information, and molecular modelling techniques are successfully used to show that noradrenaline would fit this site. The results of the INDO calculation on the noradrenaline–receptor model complex indicate that an interaction involving high lying occupied and low lying unoccupied orbitals may indeed be involved in binding.

The 'extra' hydrogen bond between the receptor model threonine residue and the noradrenaline side chain hydroxyl is not expected from initial investigations of the model, but proves to be a useful explanation of why chirality is very important amongst adrenergic agents.

It is interesting to note that the way in which the α_2-receptor differs from the β_2-receptor is the substitution of a tyrosine for tryptophan-109. Thus a difference between α_2-specific and β_2-specific ligand may be in their preferred interactions with tyrosine and tryptophan, respectively. This is supported by some recent experimental evidence [54] that a tyrosine residue is directly involved in the binding of ligands to the α_2-adrenergic receptor.

ACKNOWLEDGEMENTS

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APPENDIX 1

Internal coordinates for the β_2-adrenergic receptor model

A	B	C	D	A-B	B-C	C-D	ABC	BCD	ABCD
C-1	- N1	- CA1	- CB1	1.451	1.453	1.530	121.4	111.0	176.6
C-1	- N1	- CA1	- C1	1.451	1.453	1.530	121.4	108.0	–59.0
N1	- CA1	- CB1	- CG1	1.453	1.530	1.530	111.0	114.0	60.0
N1	- CA1	- C1	- O1	1.453	1.530	1.230	108.0	120.4	136.0
N1	- CA1	- C1	- N2	1.453	1.530	1.345	108.0	116.6	–44.0
CB1	- CA1	- C1	- O1	1.530	1.530	1.230	113.0	120.4	–100.8
CB1	- CA1	- C1	- N2	1.530	1.530	1.345	113.0	116.6	79.2
C1	- CA1	- CB1	- CG1	1.530	1.530	1.530	113.0	114.0	–61.5
CA1	- CB1	- CG1	- CD11	1.530	1.530	1.340	114.0	128.0	–90.0
CA1	- CB1	- CG1	- CD21	1.530	1.530	1.443	114.0	126.6	90.0
CA1	- C1	- N2	- CA2	1.530	1.345	1.453	116.6	122.0	–180.0
O1	- C1	- N2	- CA2	1.230	1.345	1.453	123.0	122.0	0.0
CB1	- CG1	- CD11	- NE11	1.530	1.340	1.380	128.0	111.5	180.0
CB1	- CG1	- CD21	- CE31	1.530	1.443	1.406	126.6	130.3	0.0
CB1	- CG1	- CD21	- CE21	1.530	1.443	1.380	126.6	108.3	–180.0
CD11	- CG1	- CD21	- CE31	1.340	1.443	1.406	105.4	130.3	–180.0
CD11	- CG1	- CD21	- CE21	1.340	1.443	1.380	105.4	108.3	0.0
CD21	- CG1	- CD11	- NE11	1.443	1.340	1.380	105.4	111.5	0.0
CG1	- CD11	- NE11	- CE21	1.340	1.380	1.390	111.5	107.4	0.0
CG1	- CD21	- CE31	- CZ31	1.443	1.406	1.401	130.3	114.7	180.0
CG1	- CD21	- CE21	- NE11	1.443	1.380	1.390	108.3	107.4	0.0
CG1	- CD21	- CE21	- CZ21	1.443	1.380	1.400	108.3	123.2	–180.0
CE31	- CD21	- CE21	- NE11	1.406	1.380	1.390	121.4	107.4	180.0
CE31	- CD21	- CE21	- CZ21	1.406	1.380	1.400	121.4	123.2	0.0
CE21	- CD21	- CE31	- CZ31	1.380	1.406	1.401	121.4	114.7	0.0
CD21	- CE31	- CZ31	- CH21	1.406	1.401	1.390	114.7	124.6	0.0
CD21	- CE21	- NE11	- CD11	1.380	1.390	1.380	107.4	107.4	0.0
CD21	- CE21	- CZ21	- CH21	1.380	1.400	1.400	123.2	116.4	0.0
NE11	- CE21	- CZ21	- CH21	1.390	1.400	1.400	129.4	116.4	–180.0
CZ21	- CE21	- NE11	- CD11	1.400	1.390	1.380	129.4	107.4	180.0
CE31	- CZ31	- CH21	- CZ21	1.401	1.390	1.400	124.6	119.7	0.0
CE21	- CZ21	- CH21	- CZ31	1.400	1.400	1.390	116.4	119.7	0.0
C1	- N2	- CA2	- CB2	1.345	1.453	1.530	122.0	108.0	176.5
C1	- N2	- CA2	- C2	1.345	1.453	1.530	122.0	110.4	–59.0
N2	- CA2	- CB2	- CG2	1.453	1.530	1.530	108.0	112.5	180.0
N2	- CA2	- CB2	- OG2	1.453	1.530	1.425	108.0	104.1	–67.9
N2	- CA2	- C2	- O2	1.453	1.530	1.230	110.4	120.4	136.0
N2	- CA2	- C2	- N3	1.453	1.530	1.345	110.4	116.6	–44.0
CB2	- CA2	- C2	- O2	1.530	1.530	1.230	113.4	120.4	–102.7
CB2	- CA2	- C2	- N3	1.530	1.530	1.345	113.4	116.6	77.3
C2	- CA2	- CB2	- CG2	1.530	1.530	1.530	113.4	112.5	57.3
C2	- CA2	- CB2	- OG2	1.530	1.530	1.425	113.4	104.1	169.4
CA2	- CB2	- OG2	- HG2	1.530	1.425	0.960	104.1	109.5	–12.2
CG2	- CB2	- OG2	- HG2	1.530	1.425	0.960	104.1	109.5	105.8
CA2	- C2	- N3	- CA3	1.530	1.345	1.453	116.6	122.0	–180.0
O2	- C2	- N3	- CA3	1.230	1.345	1.453	123.0	122.0	0.0

A	B	C	D	A-B	B-C	C-D	ABC	BCD	ABCD
C2	- N3	- CA3	- CB3	1.345	1.453	1.530	122.0	111.1	178.6
C2	- N3	- CA3	- C3	1.345	1.453	1.530	122.0	110.0	–59.0
N3	- CA3	- CB3	- OG3	1.453	1.530	1.425	111.1	112.0	60.0
N3	- CA3	- C3	- O3	1.453	1.530	1.230	110.0	120.4	136.0
N3	- CA3	- C3	- N4	1.453	1.530	1.345	110.0	116.6	–44.0
CB3	- CA3	- C3	- O3	1.530	1.530	1.230	110.3	120.4	–101.1
CB3	- CA3	- C3	- N4	1.530	1.530	1.345	110.3	116.6	78.9
C3	- CA3	- CB3	- OG3	1.530	1.530	1.425	110.3	112.0	–62.3
CA3	- CB3	- OG3	- HG3	1.530	1.425	0.960	112.0	109.5	109.6
CA3	- C3	- N4	- CA4	1.530	1.345	1.453	116.6	120.0	180.0
O3	- C3	- N4	- CA4	1.230	1.345	1.453	123.0	120.0	0.0
C3	- N4	- CA4	- CB4	1.345	1.453	1.530	120.0	110.5	175.2
C3	- N4	- CA4	- C4	1.345	1.453	1.530	120.0	109.3	–59.0
N4	- CA4	- CB4	- CG24	1.453	1.530	1.530	110.5	111.0	–180.0
N4	- CA4	- CB4	- CG14	1.453	1.530	1.530	110.5	111.0	–54.7
N4	- CA4	- C4	- O4	1.453	1.530	1.230	109.3	120.4	136.0
N4	- CA4	- C4	- N5	1.453	1.530	1.345	109.3	116.6	–44.0
CB4	- CA4	- C4	- O4	1.530	1.530	1.230	113.7	120.4	–100.0
CB4	- CA4	- C4	- N5	1.530	1.530	1.345	113.7	116.6	80.0
C4	- CA4	- CB4	- CG24	1.530	1.530	1.530	113.7	111.0	56.7
C4	- CA4	- CB4	- CG14	1.530	1.530	1.530	113.7	111.0	–178.1
CA4	- CB4	- CG14	- CD4	1.530	1.530	1.530	111.0	111.0	–180.0
CG24	- CB4	- CG14	- CD4	1.530	1.530	1.530	112.0	111.0	–55.3
CA4	- C4	- N5	- CA5	1.530	1.345	1.453	116.6	122.0	–180.0
O4	- C4	- N5	- CA5	1.230	1.345	1.453	123.0	122.0	0.0
C4	- N5	- CA5	- CB5	1.345	1.453	1.530	122.0	111.1	–178.1
C4	- N5	- CA5	- C5	1.345	1.453	1.530	122.0	109.3	–59.0
N5	- CA5	- CB5	- CG5	1.453	1.530	1.530	111.1	115.0	–60.0
N5	- CA5	- C5	- O5	1.453	1.530	1.230	109.3	120.4	136.0
N5	- CA5	- C5	- N+1	1.453	1.530	1.345	109.3	116.6	–44.0
CB5	- CA5	- C5	- 05	1.530	1.530	1.230	108.0	120.4	–103.0
CB5	- CA5	- C5	- N+1	1.530	1.530	1.345	108.0	116.6	77.0
C5	- CA5	- CB5	- CG5	1.530	1.530	1.530	108.0	115.0	–179.9
CA5	- CB5	- CG5	- OD15	1.530	1.530	1.290	115.0	115.0	150.0
CA5	- CB5	- CG5	- OD25	1.530	1.530	1.240	115.0	121.0	–30.0
CA5	- C5	- N+1	- C+1	1.530	1.345	1.450	116.6	119.5	–180.0
O5	- C5	- N+1	- C+1	1.230	1.345	1.450	123.0	119.5	0.0

APPENDIX 2

Internal coordinates for noradrenaline docked into the β_2-adrenergic receptor model

A	B	C	D	A-B	B-C	C-D	ABC	BCD	ABCD
C-1	- N1	- CA1	- CB1	1.455	1.457	1.529	120.7	110.9	168.8
C-1	- N1	- CA1	- C1	1.455	1.457	1.508	120.7	112.4	–65.2
N1	- CA1	- CB1	- CG1	1.457	1.529	1.504	110.9	114.8	56.8
N1	- CA1	- C1	- O1	1.457	1.508	1.220	112.4	118.7	176.4
N1	- CA1	- C1	- N2	1.457	1.508	1.347	112.4	117.7	–3.8
CB1	- CA1	- C1	- O1	1.529	1.508	1.220	111.8	118.7	–58.1
CB1	- CA1	- C1	- N2	1.529	1.508	1.347	111.8	117.7	121.7
C1	- CA1	- CB1	- CG1	1.508	1.529	1.504	111.8	114.8	–69.5
CA1	- CB1	- CG1	- CD11	1.529	1.504	1.349	114.8	126.6	–52.0
CA1	- CB1	- CG1	- CD21	1.529	1.504	1.515	114.8	123.5	128.9
CA1	- C1	- N2	- CA2	1.508	1.347	1.463	117.7	120.3	177.8
O1	- C1	- N2	- CA2	1.220	1.347	1.463	123.6	120.3	–2.4
CB1	- CG1	- CD11	- NE11	1.504	1.349	1.353	126.6	108.0	179.9
CB1	- CG1	- CD21	- CE31	1.504	1.515	1.394	123.5	137.1	0.0
CB1	- CG1	- CD21	- CE21	1.504	1.515	1.377	123.5	101.7	–179.8
CD11	- CG1	- CD21	- CE31	1.349	1.515	1.394	109.9	137.1	–179.2
CD11	- CG1	- CD21	- CE21	1.349	1.515	1.377	109.9	101.7	1.0
CD21	- CG1	- CD11	- NE11	1.515	1.349	1.353	109.9	108.0	–0.8
CG1	- CD11	- NE11	- CE21	1.349	1.353	1.405	108.0	109.7	0.4
CG1	- CD21	- CE31	- CZ31	1.515	1.394	1.403	137.1	116.9	–175.7
CG1	- CD21	- CE21	- NE11	1.515	1.377	1.405	101.7	110.7	–0.7
CG1	- CD21	- CE21	- CZ21	1.515	1.377	1.393	101.7	122.9	176.6
CE31	- CD21	- CE21	- NE11	1.394	1.377	1.405	121.2	110.7	179.4
CE31	- CD21	- CE21	- CZ21	1.394	1.377	1.393	121.2	122.9	–3.3
CE21	- CD21	- CE31	- CZ31	1.377	1.394	1.403	121.2	116.9	4.1
CD21	- CE31	- CZ31	- CH21	1.394	1.403	1.404	116.9	121.4	–1.9
CD21	- CE21	- NE11	- CD11	1.377	1.405	1.353	110.7	109.7	0.3
CD21	- CE21	- CZ21	- CH21	1.377	1.393	1.400	122.9	116.4	0.1
NE11	- CE21	- CZ21	- CH21	1.405	1.393	1.400	126.3	116.4	176.9
CZ21	- CE21	- NE11	- CD11	1.393	1.405	1.353	126.3	109.7	–176.9
CE31	- CZ31	- CH21	- CZ21	1.403	1.404	1.400	121.4	121.1	–1.2
CE21	- CZ21	- CH21	- CZ31	1.393	1.400	1.404	116.4	121.1	2.1
C1	- N2	- CA2	- CB2	1.347	1.463	1.526	120.3	109.9	147.1
C1	- N2	- CA2	- C2	1.347	1.463	1.505	120.3	112.7	–90.6
N2	- CA2	- CB2	- CG2	1.463	1.526	1.522	109.9	112.5	70.7
N2	- CA2	- CB2	- OG2	1.463	1.526	1.469	109.9	109.4	–169.5
N2	- CA2	- C2	- O2	1.463	1.505	1.221	112.7	120.7	138.5
N2	- CA2	- C2	- N3	1.463	1.505	1.346	112.7	116.3	–40.0
CB2	- CA2	- C2	- O2	1.526	1.505	1.221	109.5	120.7	–98.9
CB2	- CA2	- C2	- N3	1.526	1.505	1.346	109.5	116.3	82.6
C2	- CA2	- CB2	- CG2	1.505	1.526	1.522	109.5	112.5	–53.5
C2	- CA2	- CB2	- OG2	1.505	1.526	1.469	109.5	109.4	66.3
CA2	- CB2	- OG2	- HG2	1.526	1.469	0.954	109.4	110.4	56.1
CG2	- CB2	- OG2	- HG2	1.522	1.469	0.954	107.8	110.4	178.8
CA2	- C2	- N3	- CA3	1.505	1.346	1.453	116.3	120.0	177.2
O2	- C2	- N3	- CA3	1.221	1.346	1.453	123.0	120.0	–1.2

A	B	C	D	A-B	B-C	C-D	ABC	BCD	ABCD
C2	- N3	- CA3	- CB3	1.346	1.453	1.520	120.0	107.1	165.6
C2	- N3	- CA3	- C3	1.346	1.453	1.505	120.0	109.7	–74.0
N3	- CA3	- CB3	- OG3	1.453	1.520	1.471	107.1	107.8	64.9
N3	- CA3	- C3	- O3	1.453	1.505	1.221	109.7	121.7	–116.3
N3	- CA3	- C3	- N4	1.453	1.505	1.341	109.7	113.7	58.2
CB3	- CA3	- C3	- O3	1.520	1.505	1.221	110.9	121.7	1.9
CB3	- CA3	- C3	- N4	1.520	1.505	1.341	110.9	113.7	176.3
C3	- CA3	- CB3	- OG3	1.505	1.520	1.471	110.9	107.8	–54.8
CA3	- CB3	- OG3	- HG3	1.520	1.471	0.958	107.8	107.5	60.1
CA3	- C3	- N4	- CA4	1.505	1.341	1.452	113.7	121.4	–178.3
O3	- C3	- N4	- CA4	1.221	1.341	1.452	124.4	121.4	–4.1
C3	- N4	- CA4	- CB4	1.341	1.452	1.528	121.4	110.4	94.9
C3	- N4	- CA4	- C4	1.341	1.452	1.503	121.4	104.5	–145.5
N4	- CA4	- CB4	- CG24	1.452	1.528	1.524	110.4	108.9	–177.1
N4	- CA4	- CB4	- CG14	1.452	1.528	1.526	110.4	110.1	–55.2
N4	- CA4	- C4	- O4	1.452	1.503	1.219	104.5	121.0	113.6
N4	- CA4	- C4	- N5	1.452	1.503	1.343	104.5	114.1	–57.1
CB4	- CA4	- C4	- O4	1.528	1.503	1.219	111.2	121.0	–127.3
CB4	- CA4	- C4	- N5	1.528	1.503	1.343	111.2	114.1	61.9
C4	- CA4	- CB4	- CG24	1.503	1.528	1.524	111.2	108.9	67.5
C4	- CA4	- CB4	- CG14	1.503	1.528	1.526	111.2	110.1	–170.6
CA4	- CB4	- CG14	- CD4	1.528	1.526	1.521	110.1	111.8	–175.5
CG24	- CB4	- CG14	- CD4	1.524	1.526	1.521	111.0	111.8	–54.8
CA4	- C4	- N5	- CA5	1.503	1.343	1.451	114.1	121.6	168.8
O4	- C4	- N5	- CA5	1.219	1.343	1.451	124.2	121.6	–1.6
C4	- N5	- CA5	- CB5	1.343	1.451	1.526	121.6	107.8	172.3
C4	- N5	- CA5	- C5	1.343	1.451	1.504	121.6	110.5	–71.3
N5	- CA5	- CB5	- CG5	1.451	1.526	1.500	107.8	113.1	–29.8
N5	- CA5	- C5	- O5	1.451	1.504	1.220	110.5	120.3	142.9
N5	- CA5	- C5	- N+1	1.451	1.504	1.347	110.5	115.9	–42.4
CB5	- CA5	- C5	- O5	1.526	1.504	1.220	106.8	120.3	–100.1
CB5	- CA5	- C5	- N+1	1.526	1.504	1.347	106.8	115.9	74.6
C5	- CA5	- CB5	- CG5	1.504	1.526	1.500	106.8	113.1	–148.6
CA5	- CB5	- CG5	- OD1	1.526	1.500	1.302	113.1	117.8	–172.9
CA5	- CB5	- CG5	- OD2	1.526	1.500	1.218	113.1	119.4	47.7
CA5	- CB5	- CG5	- N9X*	1.526	1.500	2.579	113.1	160.2	109.2
CA5	- C5	- N+1	- C+1	1.504	1.347	1.454	115.9	119.4	–173.8
O5	- C5	- N+1	- C+1	1.220	1.347	1.454	123.5	119.4	0.7
CB5	- CG5	- N9X	- C8X*	1.500	2.579	1.466	160.2	132.0	53.4
OD1	- CG5	- N9X	- C8X*	1.302	2.579	1.466	59.9	132.0	–35.5
OD2	- CG5	- N9X	- C8X*	1.218	2.579	1.466	52.9	132.0	127.0
C3X	- C2X	- C1X	- C6X	1.397	1.397	1.397	120.0	119.6	0.2
C3X	- C2X	- C1X	- C7X	1.397	1.397	1.529	120.0	120.5	179.8
C1X	- C2X	- C3X	- C4X	1.397	1.397	1.397	120.0	120.1	0.9
C1X	- C2X	- C3X	- O3X	1.397	1.397	1.302	120.0	119.9	–178.9
C2X	- C3X	- C4X	- C5X	1.397	1.397	1.394	120.1	120.1	–0.9

A	B	C	D	A-B	B-C	C-D	ABC	BCD	ABCD
C2X	- C3X	- C4X	- O4X	1.397	1.397	1.298	120.1	119.9	–179.4
C2X	- C3X	- O3X	- H3X	1.397	1.302	0.949	119.9	109.6	–5.8
C4X	- C3X	- O3X	- H3X	1.397	1.302	0.949	120.0	109.6	174.4
O3X	- C3X	- C4X	- C5X	1.302	1.397	1.394	120.0	120.1	178.9
O3X	- C3X	- C4X	- O4X	1.302	1.397	1.298	120.0	119.9	0.4
C3X	- C4X	- C5X	- C6X	1.397	1.394	1.397	120.1	119.6	–0.1
C3X	- C4X	- O4X	- H4X	1.397	1.298	0.954	119.9	106.4	–3.1
C5X	- C4X	- O4X	- H4X	1.394	1.298	0.954	120.0	106.4	178.4
O4X	- C4X	- C5X	- C6X	1.298	1.394	1.397	120.0	119.6	178.3
C4X	- C5X	- C6X	- C1X	1.394	1.397	1.397	119.6	120.6	1.2
C5X	- C6X	- C1X	- C2X	1.397	1.397	1.397	120.6	119.6	–1.2
C5X	- C6X	- C1X	- C7X	1.397	1.397	1.529	120.6	119.9	179.1
C2X	- C1X	- C7X	- C8X	1.397	1.529	1.520	120.5	109.6	–122.8
C2X	- C1X	- C7X	- O7X	1.397	1.529	1.469	120.5	109.8	117.9
C6X	- C1X	- C7X	- C8X	1.397	1.529	1.520	119.9	109.6	56.8
C6X	- C1X	- C7X	- O7X	1.397	1.529	1.469	119.9	109.8	–62.5
C1X	- C7X	- C8X	- N9X	1.529	1.520	1.466	109.6	109.1	–143.5
C1X	- C7X	- O7X	- H7X	1.529	1.469	0.969	109.8	109.6	–173.5
C8X	- C7X	- O7X	- H7X	1.520	1.469	0.969	108.6	109.6	66.6
O7X	- C7X	- C8X	- N9X	1.469	1.520	1.466	108.6	109.1	–23.4
C7X	- C8X	- N9X	- CG5*	1.520	1.466	2.579	109.1	132.0	–18.0

* CG5 – Noradrenaline N9X 'bond' included to define one position of noradrenaline with respect to the receptor.

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