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Models of 5-Hydroxytryptamine Receptors. A Review

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The Types of 5-Hydroxytryptamine Receptors

Since the discovery of the neurotransmitter 5-hydroxytryptamine (5-HT, serotonin) in 1948, its role has been associated with many central nervous system-related activities (Zifa & Fillion 1992). 5-HT can bind to many 5-HT-nergic receptors located pre- and postsynaptically. 5-HT receptors can be divided into two major superfamilies: G-protein coupled and ion channels. The former can be further characterized according to their second messenger system: adenyl cyclase-coupled (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_4, 5-HT_{5A}, 5-HT_{5B}, 5-HT_6, 5- HT_7) or phosphoinositol-coupled (5-HT_{2A}—previously 5-HT_2, 5-HT_{2B} and 5-HT_{2C}—previously 5-HT_{1C}). The 5-HT_3 receptors belong to the superfamily of ion-channel receptors (Glennon & Dukat 1992, Matthes et al 1993, Monsma et al 1993, Hoyer et al 1994). The ligands of the receptors family have been recently reviewed by Glennon & Dukat (1992).

Most interest has been paid to the three sub populations of the receptors: 5-HT_{1A}, 5-HT_2 and 5-HT_3. The 5-HT_{1A}-receptor agonists have attracted considerable interest due to their potential use in the therapy of anxiety and depression (Traber & Glaser 1987; Fuller 1988). Of the different chemical classes which bind to the 5-HT_{1A} receptor buspirone (**2**) and ipsapirone (**3**) are effective anti-anxiety and antidepressant drugs (Nelson 1991).

The 5-HT_{2A} and 5-HT_{2C} receptors have a very similar pharmacological profiles and for many years they were hardly distinguished from each other (Glennon & Dukat 1992). It is known that a large number of psychotherapeutic agents, including certain antidepressants (e.g. the 5-HT_2 antagonist mianserin **4**) (Schoonover 1983) and antipsychotic agents display a high affinity for 5-HT_2 receptors (Lysen 1978; Bergsstrom & Kellar 1979; Peroutka & Snyder 1980; Peroutka et al 1981; Roth et al 1987; Meltzer et al 1989). It has also been found that typical and atypical antipsychotic agents apparently prefer the 5-HT_{2A} receptor to the 5-HT_{2C} (Roth et al 1992).

The 5-HT_3 receptor antagonists are a novel class of therapeutic agents that are highly effective as anti-emetics (Hamik & Peroutka 1989; Carpenter 1990; Sanger 1990) and exhibit a potential for treating secretory and mobility disorders of the gastrointestinal tract (Guslandi 1989; Costall & Naylor 1990). Moreover, some of them (e.g. ondansetron **5** or zacopride **6**) have been found effective in the control of cancer chemotherapy-induced emesis (Leibundgut 1987; Andrews et al 1988; Evans et al 1991). They are also promising in the treatment of central nervous system conditions such as anxiety, psychoses, pain and migraine (King & Sanger 1989; Watling 1989; Jones 1990).

Methods of Construction of Models of a Receptor-Binding Site

Pharmacore identification

Pharmacophore identification, described by Marshall et al (1979) as the active analogue approach (also known as the common template hypothesis or the common conformation hypothesis), consists in superimposition of key features in the low-energy three-dimensional structures of different ligands. These low-energy structures are statistically populated to a large extent under physiological conditions.

The general approach defined by Marshall was outlined by Hibert et al (1988) as four phases: critical examination of compounds active or inactive at the target receptor; computer-aided definition of the pharmacophore; three-dimensional graphics computer-assisted mapping of the recognition site; use of the previously defined pharmacophore and receptor map to design original putative optimized ligands.

In the construction of a pharmacophore model, different geometrical and electrical molecular descriptors such as the molecular electrostatic potential (MEP), Van der Waals volume and area, the planes containing selected atoms and normal to the planes, and specific interatomic distances, may be used.

Protein modelling

In this approach three-dimensional models of regulatory proteins are constructed. Such 3-D models have been constructed for several G-protein bound receptors from their sequence (Dahl et al 1991; Hibert et al 1991; Edvardsen et al 1992; Ijzerman & Van Galen 1992; Lewell 1992; Maloney-Huss & Lybrand 1992; Sylte et al 1993). Molecular modeling of a protein is based on the crystal structure (when available) or on the structure of homologous proteins. The experiments of Anfinsen (1973) suggested that all information needed to direct the folding of protein into its tertiary structure is contained in the amino acid sequence.

There are many experimental and computational methods (Rooman et al 1992, Rooman & Wodak 1992; Lecomte & Matthews 1993; Rackovsky 1993) for predicting tertiary protein structures but no generally applicable method has so far been available (Dahl & Edvardsen 1993).

Many of the receptor models have been constructed from a model of the membrane-spanning α-helices in bacteriorhodopsin, the membrane protein in *Halobacterium halobium*, whose three-dimensional structure has been examined by electron microscopic and electron diffraction techniques (Henderson & Unwin 1975; Henderson et al

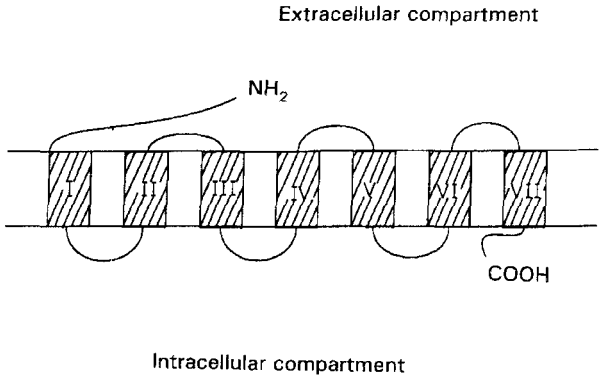

FIG. 1. Schematic representation of transmembrane domains of a G-protein coupled receptor.

1990; Subramanian 1993). The protein contains seven membrane-spanning α-helices linked by intracellular and extracellular loops, closely packed in an oval arrangement with the chromophore, retinal, located in the central pore between the helices. Schematic representation of putative transmembrane domains of a G-protein-coupled receptor is shown in Fig. 1.

The construction of G-protein coupled receptor model usually starts by building an α-helical model of each membrane-spanning segment from the amino acid sequence. The approximate locations of the putative membrane-spanning domains in receptor sequences are usually determined from hydropathicity indices which may be calculated by different methods (Hopp & Woods 1981; Kyte & Doolittle 1982). The seven-helix bundle is usually refined by molecular mechanics energy minimization. Molecular dynamic simulations may change the structure of a protein from an initial circular arrangement of the helices into a more bacteriorhodopsin-like shape during 20–25 ps simulation in-vacuo (Sylte et al 1993; Jähning & Edholm 1992). The addition of a ligand to the molecular dynamic simulations may show the putative binding domain arrangement.

To construct any of the models one needs to identify the ligands exhibiting affinity to a receptor and find out whether they promote certain biological responses. The affinity of a ligand for a receptor is usually expressed in terms of the dissociation constant K_I of the drug-receptor complex, conveniently measured by the inhibition of a radioligand binding (Hollenberg 1978):

$$K_I = IC50/(1 + L^*/K^*) \quad (1)$$

where IC50 is the concentration of unlabeled ligand that reduces the binding of labeled ligand by 50%, K* is the dissociation constant of the labelled ligand and L* is the concentration of labeled ligand.

The biological response of a ligand is usually expressed in terms of agonistic and antagonistic activity. A quantitative measure of the activity was proposed by Ariens (1954) and is known as an intrinsic activity (IA). It can be defined as the ratio of the maximal effect produced by a ligand to that produced by a full agonist (usually the endogenous agonist). Thus, for full agonists IA = 1, for full antagonists IA = 0 and for partial agonists $0 < IA < 1$.

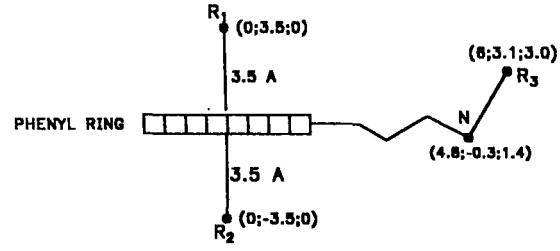

FIG. 2. Pharmacophore model for drugs acting on CNS according to Lloyd & Andrews (1986).

The Active Analogue Approach

A model of pharmacophore for drugs acting on the central nervous system (including 5-HT ligands) was proposed by Lloyd & Andrews (1986). Using computer graphics they established remarkable similarity in the topographical arrangement in the crystal structure of the following eight drugs: morphine (**7** an analgesic), LSD (**8** a hallucinogen), phenobarbitone (**9** a hypnotic), diazepam (**10** an anxiolytic), amphetamine (**11** a stimulant), imipramine (**12** an antidepressant), chlorpromazine (**13** an antipsychotic) and diphenylhydantoin (**14** an anticonvulsant). Analysing molecular similarities, they built onto the solid-state structures three receptor points R1, R2, and R3. The points R1 and R2 represented hydrophobic bonding and were placed 0·35 nm above and below the center of a phenyl ring as the origin. The R3 point, representing hydrogen bonding was located tetrahedrally 0·28 nm from the nitrogen atom. The three receptor points lay in the XOY plane, R1–R2 being the Y'OY axis, the center of the phenyl ring being the origin, and the nitrogen Z coordinate being positive (Fig. 2). It was then concluded that the presence of a phenyl ring and a nitrogen atom with defined topology is a common characteristic feature of CNS-active drugs.

Weinstein et al (1981) pointed out the importance of molecular electrostatic potential (MEP) as a criterion for binding to the 5-HT receptor. The binding of an 5-HT receptor ligand at the receptor depends on molecular rearrangement of the ligand required to align the electrostatic orientation vector of its indole portion relative to the recognition site in the receptor, in a direction parallel to that observed in 5-HT (**1**) which was chosen as a template. They also found similarities in the MEP characteristic of 5-HT and LSD (**8**) by showing that the local minimum in the electrostatic potential map of LSD generated by the C(9)=C(10) double bond, conferred the same reactivity properties as the minimum generated by the hydroxyl group in 5-HT. Compounds lacking the aforementioned double bond, such as dihydro-LSD and others, had lower affinity for that receptor (Weinstein et al 1987).

The 5-HT$_{1A}$ receptor ligands

Hibert et al (1988) attempted fitting of four 5-HT$_{1A}$ receptor antagonists and the partial agonist (*R*)-(−)-methiotepin (**16**), spiperone (**17**), (*S*)-(−)-propranolol (**18**) and buspirone (**2**). For each compound rotatable bonds were assigned and a conformational search was performed, allowing the bonds to rotate with a chosen stepwise increment of the dihedral angle. The obtained basic pharmacophore for the antagonist

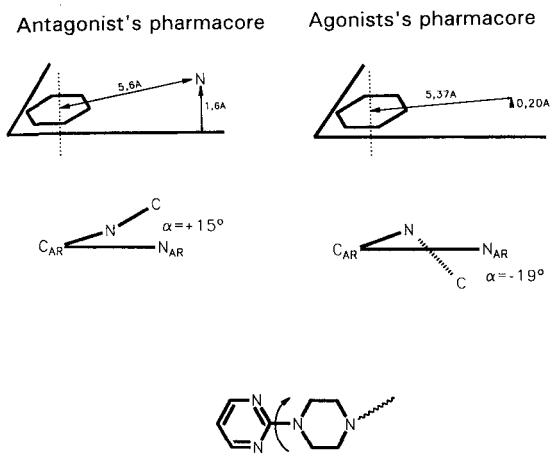

FIG. 3. Hibert's model of 5-HT_{1A} agonist and antagonist pharmacophores (Hibert et al 1988, 1989).

recognition site consisted of an aromatic nucleus and a basic nitrogen atom placed 0·56 nm from the aromatic ring centre and lying 0·16 nm above the plane defined by the reference ring (Fig. 3).

Following a similar procedure for LSD (**8**), 5-HT (**1**), 8-MeO-DPAT (**19**), buspirone (**2**), RU 24969 (**20**) the basic pharmacophore for the agonist recognition site was obtained (Hibert et al 1989). The agonist pharmacophore contained the same structural elements as those described for antagonists, the difference being in the distance and out-of-plane deviation between the aromatic ring and the basic nitrogen atom (0·537 nm and 0·02 nm, respectively). The proposed conformation of buspirone in the 5-HT_{1A} antagonist recognition site was different from its conformation in the 5- HT_{1A} agonist recognition site (Fig. 3). Thus the torsional angle defined by the four atoms N_{arom}-C_{arom}-N-C was −19 for the agonist conformer and + 15 for the antagonist conformer.

Hacksell and coworkers (Hacksell et al 1990; Mellin et al 1991; Valgårda et al 1993) employed molecular mechanics calculations of energies and geometries of several (**21**–**37**) analogues of 8-hydroxy-2-(dipropylamino)tetraline (8-OH-DPAT, **15**) to define a pharmacophore for potent and moderate agonists of the 5-HT_{1A} receptor. They divided their set of compounds into three subsets containing, respectively, potent agonists ($K_i < 32·3$ nM), moderately potent agonists (K_i between 38 and 394 nM), and compounds which lack agonistic properties. The proposed pharmacophore consisted of 2 elements: an aromatic site and a dummy atom located 2·6 nm from the nitrogen and aligned with the N+-H-vector (the dummy atom was supposed to mimic a carboxylate at the receptor site) the whole model being built on the template structure of JV-26 (**38**) (Fig. 4). To account for the differences in binding to the receptor between some of the compounds, allowed and excessive volume of the ligands was also considered.

The pharmacophore for potent and moderate agonists was defined by certain distances and angles, the respective values for the moderate agonist being less defined.

Application of the structure activity relationship (SAR) method for a set of 1-arylpiperazines (**39**, **40**) led to the hypothesis that not only coplanar conformations of piperazine and the aromatic rings might be responsible for their

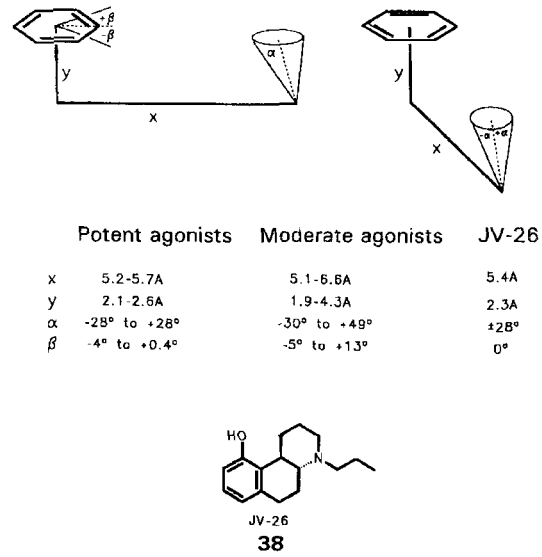

FIG. 4. 5-HT_{1A} agonist model according to Hacksell (Hacksell et al 1990; Mellin et al 1991; Valgårda et al 1993).

activity at 5-HT_{1A} receptors (Mokrosz et al 1992). Although the 1-arylpiperazines with a relatively low barrier of rotation may assume the coplanar conformations at the receptors, the others should adopt the twisted conformations with the lone pair of the N-1 atom placed approximately in the plane of the aromatic ring (Fig. 5).

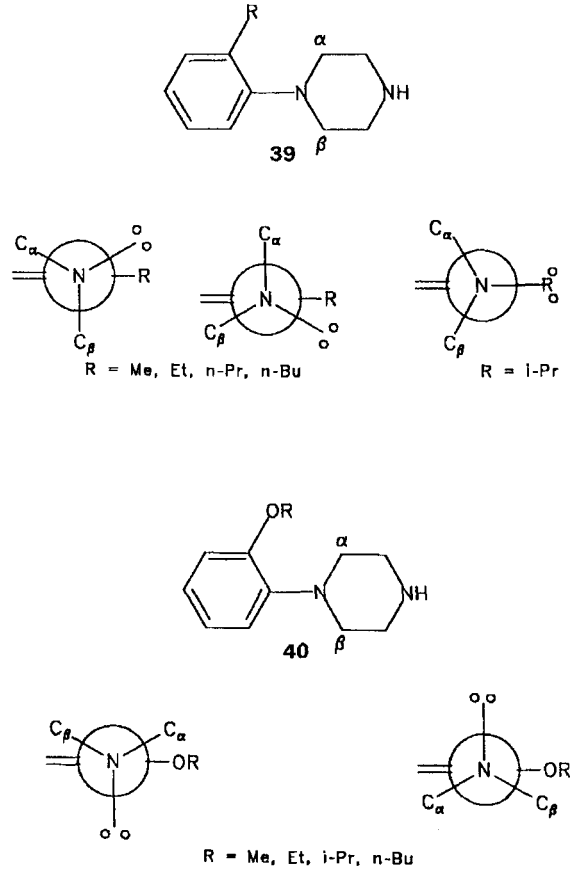

FIG. 5. Possible bioactive conformations of 5-HT_{1A}-receptor ligands according to Mokrosz et al (1992).

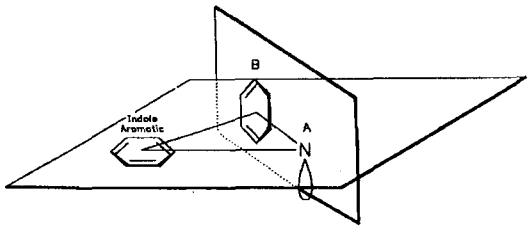

FIG. 6. Relative orientation of ligands with a nitrogen lone pair parallel to an aromatic ring plane at the 5-HT_{1A}-binding site (Mokrosz et al 1994).

Mokrosz et al (1994) using (+)-LSD as a template proposed a model for such 5-HT_{1A} ligands in which the lone pair of the basic nitrogen is fixed in a parallel position to the plane of the aromatic ring. In this model the nitrogen atom lone pair vectors of such ligands were considered as parallel to the lone pair of the (+)-LSD N-4 vector (Fig. 6—interaction site A) and aromatic ring of a ligand taking the position of the (+)-LSD amide side chain (interaction site B).

Agarwal & Taylor (1993) used comparative molecular field analysis (CoMFA) to examine the relationship between the intrinsic activity of several 5-HT_{1A} receptor ligands and their electrostatic (coulombic) and steric (Lennard-Jones) potentials. The obtained model suggested that both the agonist and the antagonist ligands were able to share some parts of a common binding site on the receptor; that is, the primary agonist binding region may also be occupied by antagonists, and the secondary binding site accommodates the excess bulk present in the side chain in many antagonists and partial agonists. The CoMFA steric field graph indicated that the agonists tended to be flatter (more coplanar) than the antagonists (Fig. 7).

The CoMFA electrostatic field graph suggested that, in the region surrounding the essential protonated amino

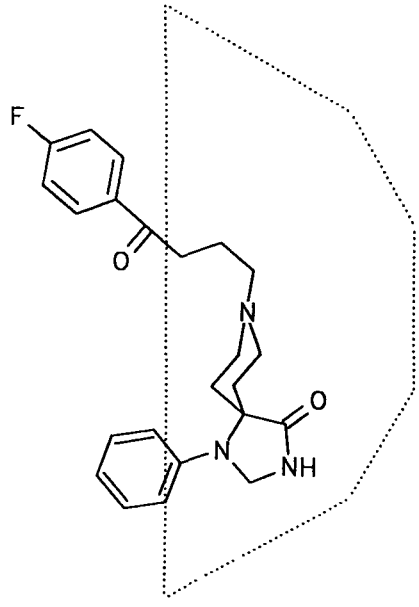

FIG. 7. Putative conformation of spiperone (**17** an antagonist) at 5-HT_{1A}-binding site (Agarwal & Taylor 1993).

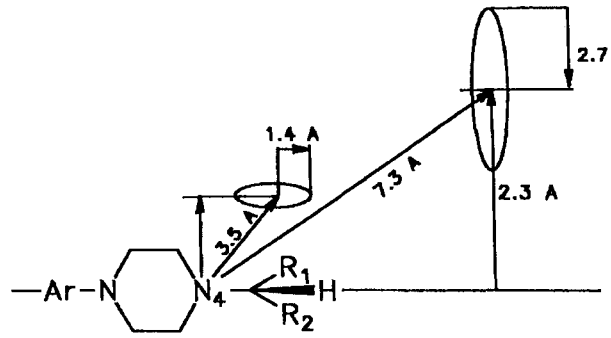

FIG. 8. Schematic representation of the CoMFA steric field graph for 5-HT_{1A}-binding site according to van Steen et al (1994).

group, the positive molecular electrostatic potential might be weaker in the antagonists than in the agonists. Together, the steric and electrostatic maps suggested that in the secondary binding site region the increased hydrophobic binding might enhance antagonist activity.

3-D QSAR-CoMFA was employed for two series of heterobicyclic ligands of 5-HT_{1A} receptor—4-aralkyl derivatives of 1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine (**41**) and 1-(benzo[b]furan-7-yl)piperazine (**42**) (van Steen 1994). According to the CoMFA, the nature of interaction between the ligands and the 5-HT_{1A} receptor can be explained using a 98:2 ratio for the steric versus the electrostatic field description. A positive bulk contribution was found as a hemisphere shaped contour level located 0·73 nm from the basic N4-nitrogen. The substituents located in that region reach the maximum hydrophobic interaction, resulting in a strong interaction with the 5-HT_{1A} receptor site. The steric bulk located 0·35 nm from the N4-nitrogen atom negatively influenced the affinity (Fig. 8). This effect on affinity was explained in terms of a steric hindrance caused by certain N4-substituents during the approach of ligand to the binding site.

The 5-HT_{2A} receptor ligands

Ergolines were used as templates for the 5-HT_{2A} receptor modelling. For comparison purposes they possess some advantages as templates. Although most ergolines are non-selective serotonergic agents they typically bind with high affinity. They can serve as 5-HT_{2A} agonists, partial agonists or antagonists (depending upon their specific substituents). They have a conformationally constrained and stereochemically defined framework and within this framework one can find embedded fragments of different classes of 5-HT-nergic agents (Glennon et al 1991; Glennon & Dukat 1991). (+)-Lysergic acid diethylamide (LSD **8**) is representative of this class of compounds.

The 5-HT_{2A} receptor topography appears to accept a wide array of structural types, with derivatives of nearly all classes of serotonergic agents displaying some affinity for the site. Glennon et al (1991) carried out molecular modeling studies that suggested that the structure of ketanserin (**43**) may be related to that of the LSD (**8**) in two completely different orientations: one in which the quinazoline portion may mimic the indole nucleus and the other—in which the benzoyl portion may do so. Modification of the ketanserin

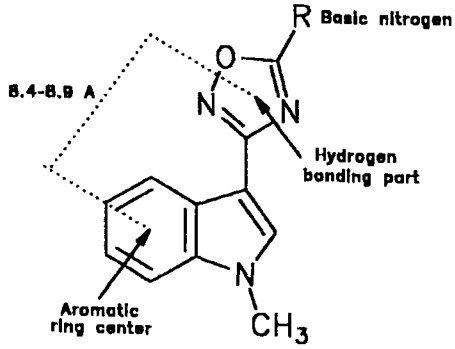

FIG. 9. Basic pharmacophore of 5-HT_3 receptor according to Swain et al (1991).

(**43**) structure and binding studies revealed that the fluoro and carbonyl groups of the 4-fluorobenzoyl portion make small contribution to the 5-HT_{2A} binding and that the intact benzoylpiperidine moiety is an important feature (Herdnon et al 1992). The obtained results suggested that it is the benzoyl portion of ketanserin (and not pyrimidinone portion of the quinazoline nucleus) that mimics the indolealkylamine portion of the ergolines upon binding at 5-HT_{2A} receptors. At the very least the results indicated that the benzoyl portion was important for 5-HT_{2A} and 5-HT_{2C} binding and that the piperidine nitrogen substituents might play a role in determining receptor selectivity.

The 5-HT_3 receptor ligands

Schmidt & Peroutka (1989), when comparing a list of potent 5-HT_3-receptor ligands, determined their chemical similarities and proposed a two-dimensional pharmacophore for the 5-HT_3-receptor site: a 6-aromatic ring separated from a nitrogen by the distance of 0·60–0·78 nm. The pharmacophore was obtained from superimposition of each ligand in an arbitrary conformation in which the nitrogen was placed in the same plane as the aromatic ring and conformational energy of the molecules was not considered.

Analysis of the structure-activity relationship for a series of indole oxadiazoles of general formula **44** (Swain et al 1991) led to definition of the 5-HT_3 antagonist basic pharmacophore consisting of a basic nitrogen, a linking group capable of H-bonding interactions, and an aromatic moiety. The optimum distance between the centre of the benzene ring of the indole and the basic nitrogen appears to be within the range 0·84–0·89 nm (Fig. 9).

A three-component pharmacophore computer model for the 5-HT_3 receptor antagonists binding, based on the structures of known potent ligands (ICS-205–930, **45**; ondansetron, **5**; zacopride, **6**; and 3-[2-(guanidinylmethyl)-4-thiazolyl]indol, **46**) of the receptor, has been elaborated (Rizzi et al 1990). The model suggests that the essential components of the 5-HT_3-receptor binding for reported agents involve two key electrostatic interactions; the ligand must have a domain capable of acting as a hydrogen-bond acceptor, and a corresponding appropriately located region which can donate a hydrogen bond. The optimum distance between the centres has been calculated to be 0·77 nm (Fig. 10). The third region of interaction is a

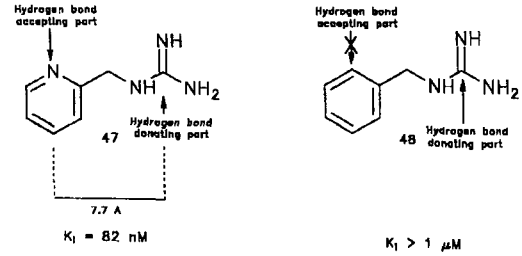

FIG. 10. Pharmacophore for 5-HT_3-receptor antagonist according to Rizzi et al (1990).

plane occupied by the lipophilic aromatic portion of the receptor ligands. Compound **47** represents the minimum structure requirement that maintains the necessary electrostatic interaction for binding activity. The aromatic nitrogens are responsible for the hydrogen-bond accepting interaction, and the protonated guanidine moiety for the hydrogen-bond donating interaction. Removal of the aromatic nitrogen eliminates the ability of the compound to accept a hydrogen bond and hence compound **48** does not exhibit significant 5-HT_3-receptor binding affinity at a concentration as high as 1·0 μM.

SAR calculations for a structurally novel class of potent and selective 5-HT_3-receptor antagonists of the general structure **49**, containing a thiazole moiety linking an aromatic group and a nitrogen-containing basic region, showed that an arrangement of the aryl and thiazole groups approaching planarity might be optimal for binding. Such a relationship could be enhanced by a group (such as in the methoxy compound **50**) which can contribute to the hydrogen bond accepting properties of the ligand (Fig. 11) (Rosen et al 1990).

Evans et al (1991) derived from computational techniques common geometrical features among the 5-HT_3-receptor ligands and described the three-dimensional pharmacophore for the 5-HT_3 recognition site. Studying a structurally unique subset of five ligands ICS 205–930 (**45**), MDL 72222 (**51**), BRL 43694 (granisetron, **52**), LY 278584 (**53**) and zacopride (**6**), they defined the chemical template containing the recognition elements (functional groups) for the receptor that consisted of an aromatic or heteroaromatic ring system, a coplanar carbonyl group and a nitrogen centre, interrelated by a well-defined distance: 0·35 nm between the aromatic ring centroid and the carbonyl oxygen, 0·51 nm between the oxygen and the nitrogen atom, and 0·71 nm between the nitrogen atom and the aromatic ring centroid (Fig. 12).

Two binding (or active) shapes arising from low-energy

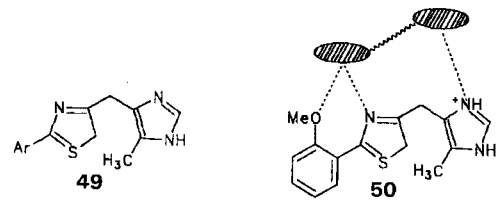

FIG. 11. Interaction of compound **50** with the 5-HT_3-receptor binding site enhancing the affinity of compounds with the general formula **49** to the receptor (Rosen et al 1990).

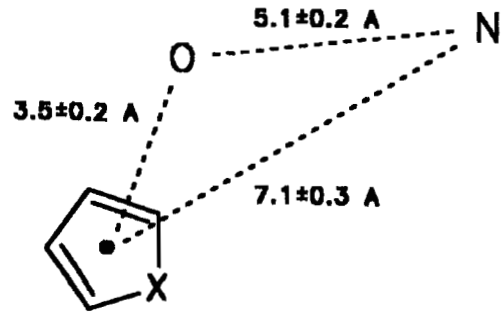

FIG. 12. 5-HT$_3$-receptor model according to Evans et al (1991).

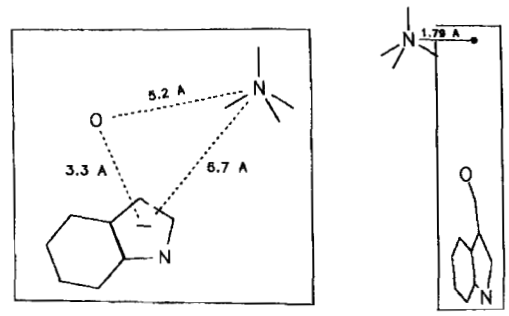

FIG. 14. Hibert's model of the 5-HT$_3$ receptor (Hibert et al 1992).

conformations which can be adopted by each ligand in the set studied have been identified. Both may be described as half-T in overall shape differing in spatial orientation around the bond to the group containing the nitrogen centre (Fig. 13).

Very similar results were obtained by Hibert et al (1990) based on a conformation-activity relationship study of 5-HT$_3$ receptor antagonists; a basic pharmacophore consisting essentially of a carbonyl group coplanar to a ring and a basic centre in the relative positions was defined as shown in Fig 14.

Different models of the 5-HT$_3$ receptor were recently discussed by Gozlan & Langlois (1992).

3-D models of Regulatory Proteins

Using molecular modeling of a protein, Sylte et al (1993) constructed a 3-D model of the human 5-HT$_{1A}$ receptor from its amino acid sequence by computer graphic techniques, molecular mechanics calculations and molecular dynamic simulations. The model has seven α-helical membrane-spanning domains which form a central core containing a putative ligand binding site. The electrostatic potentials 0·14 nm outside the water-accessible surface were mainly negative on the synaptic side of the receptor model and at the postulated ligand binding site, and positive in the cytoplasmic domains. The negative electrostatic potentials around the synaptic domains show that the positively charged molecules are attracted to the receptor by electrostatic forces. Molecular dynamic simulations of the receptor model with 5-hydroxytryptamine (**1**), ipsapirone (**3**), (*R*)-(−)- or (*S*)-(+)-methiotepin (**16**) in the central core suggested that up to 22 different amino acid residues may form a ligand binding pocket, and contribute to the specificity of ligand recognition and binding.

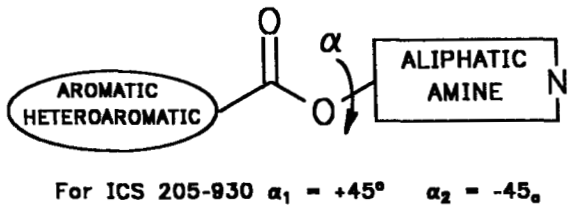

FIG. 13. Identification of a rotable bond enabling different spatial orientation of some ligands at the 5-HT$_3$-binding site (Evans et al 1991).

In a similar way a three-dimensional model of another subtype of the 5-HT receptors—5-HT$_{2A}$ has been constructed (Edvardsen et al 1992). The model also had 7 α-helical segments besides other similarities. Simulations with protonated ligands have shown that they neutralized the negative electrostatic potential around Asp 120 and Asp 155 in the central core of the receptor. 5-HT showed only a weak interaction with Asp 155 but a strong interaction with Asp 120 with the amino group of 5-HT tightly bound to the carboxylic side chain of Asp 120.

Using bacteriorhodopsin as a template, Hibert et al (1991) built and analysed three-dimensional models of the dopamine D$_2$, 5-HT$_{2A}$, noradrenaline α_2, adrenaline β_2 2 and acetylcholine m$_2$ receptors. The models were constructed using primary sequence comparison and hydrophobicity-hydrophilicity (hydropathicity) analyses. The authors proposed a schematic representation of the interactions between the receptors recognition sites and their corresponding neurotransmitters (Fig. 15).

The model was recently refined (Hibert et al 1994) by considering the structure of the bovine opsin receptor determined by Schertler et al (1993). Using molecular dynamic simulations Zhang & Weinstein (1993) investigated the mechanism of signal transduction that connects the ligand binding to the interaction of the G-protein-coupled receptor with the effector system. Their results show that the main differences in ligand-receptor complexes with the agonists as compared with those with the antagonists consist

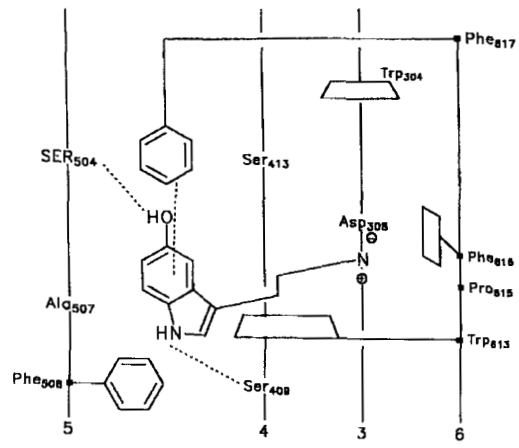

FIG. 15. Three-dimensional model of the 5-HT$_{2A}$ receptor according to Hibert et al (1991).

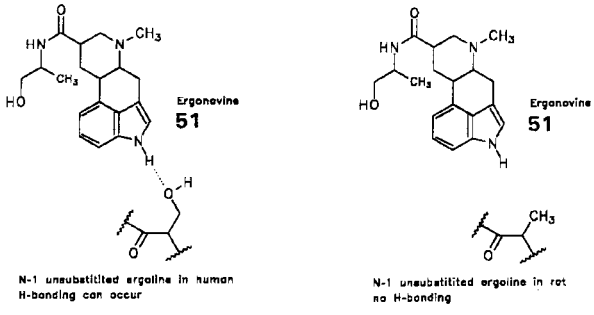

FIG. 16. The possible interaction of amino acid 242 of the 5-HT_{2A} receptor with indole-containing compounds (Johnson et al 1994).

in the intracellular side of the loop connecting transmembrane domains V and VI where the agonist seems to produce the largest change and in the group of the domains I-III. The intracellular loop V-VI has also been proposed in other studies (Dohlman et al 1991) to be important for the interaction of G-protein-coupled receptors with G-proteins. In principle, the validity of G-protein-coupled receptor models built using a model of bacteriorhodopsin as a template, depends both on the structural similarities between bacteriorhodopsin and the receptor, and on the accuracy of the bacteriorhodopsin model (Dahl & Edvardsen 1993). The bacteriorhodopsin model which has been used as a template for some of the recent receptor models, was based on structure maps with 0·35-nm resolution in directions parallel to the membrane plane but only 10-nm resolution in the direction perpendicular to the membrane plane (Henderson et al 1990). The use of bacteriorhodopsin as a template has also been questioned on the grounds of the limited amino acid sequence homology between bacteriorhodopsin and G-protein-coupled receptors (MaloneyHuss

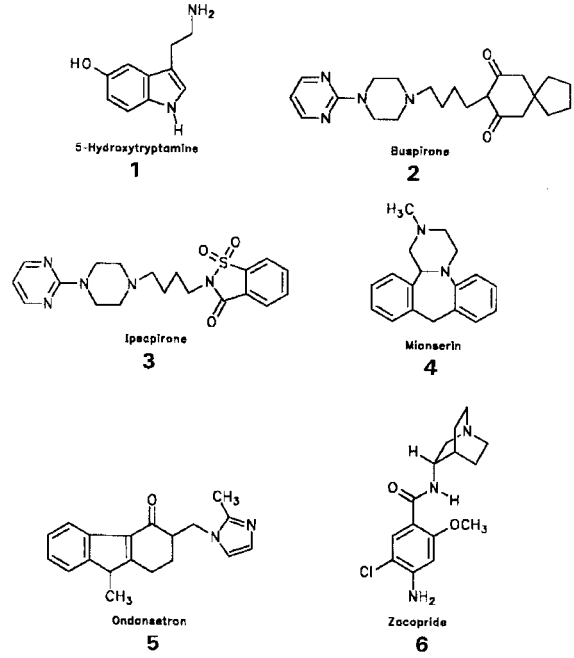

Chart 1. Structures of 5-HT (**1**), buspirone (**2**), ipsapirone (**3**), mianserin (**4**), ondansetron (**5**) and zacopride (**6**).

& Lybrand 1992; Pardo et al 1992). It has been suggested, based on the analysis of the amino acid sequences, that the sequential order of transmembrane helices in G-protein-coupled receptors may be different from that in bacteriorhodopsin, due to reshuffling of the helices during a proposed evolution of G-protein-coupled receptors from bacteriorhodopsin (Pardo et al 1992).

The proposed models may be corroborated by site-

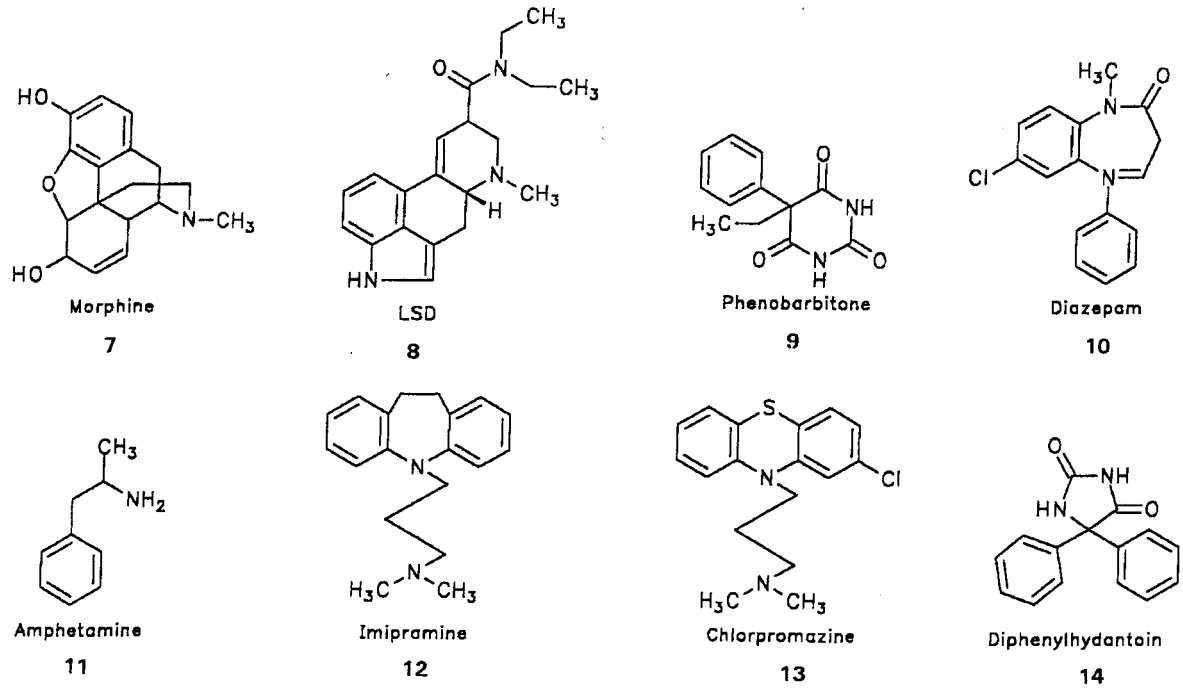

Chart 2. Structures of morphine (**7**), LSD (**8**), phenobarbitone (**9**), diazepam (**10**), amphetamine (**11**), imipramine (**12**), chlorpromazine (**13**), diphenylhydantoin (**14**).

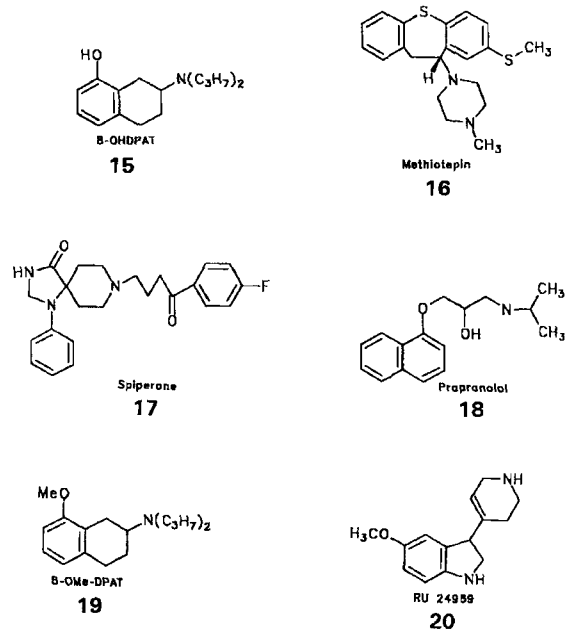

Chart 3. Structures of 8-OH-DPAT (**15**), methiotepin (**16**), spiperone (**17**), propranolol (**18**), 8-MeO-DPAT (**19**) and RU 24969 (**20**).

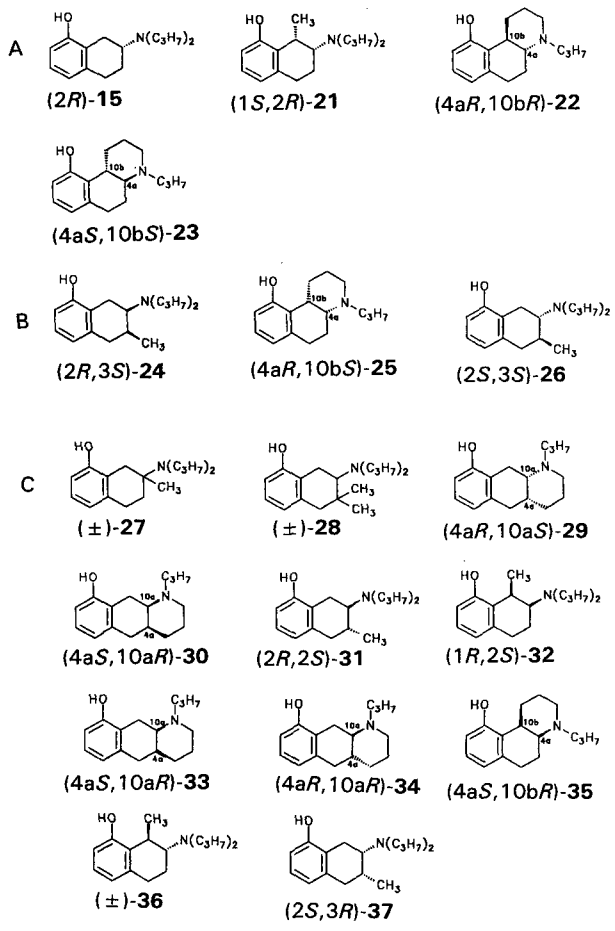

Chart 4. Compounds included by Hacksell et al (1990) to define a pharmacophore for agonists of the 5-HT_{1A} receptor. A. Potent agonists. B. Moderate agonists. C. Compounds lacking agonistic activity.

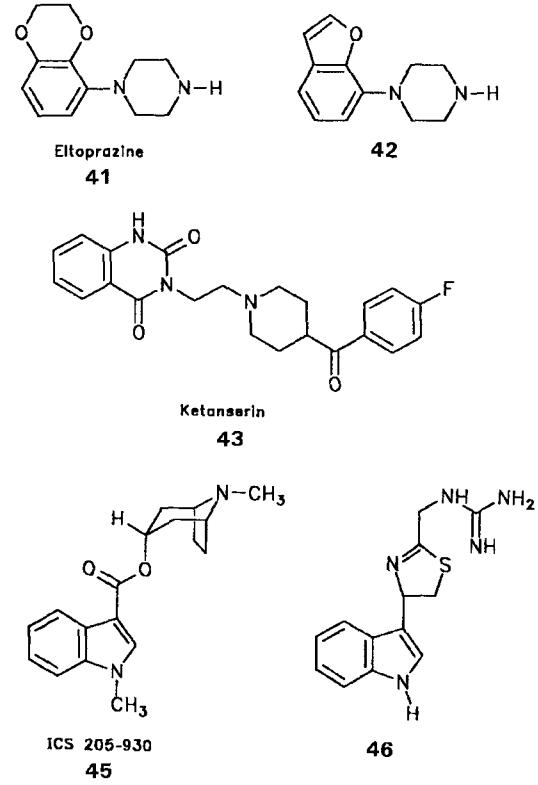

Chart 5. Structures of eltoprazine (**41**), compound **42**, ketanserin (**43**), ICS 205–930 (**45**) and compound **45**.

directed mutagenesis experiments. The G-protein-coupled neurotransmitter receptors have a common ligand binding site in the central core of the receptor. Site-directed mutagenesis experiments have suggested that Asp 113 is essential for the agonist and antagonist binding to the α_2-adrenergic

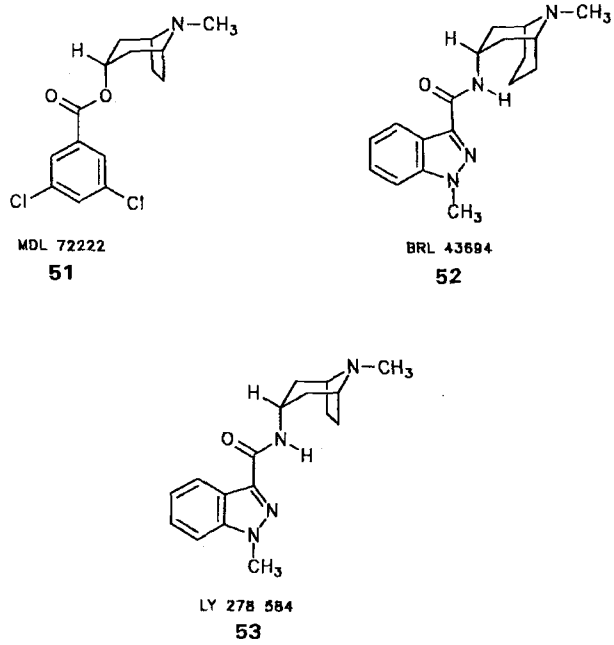

Chart 6. Structures of MDL 72222 (**51**), BRL 43694 (**52**) and LY 278 584 (**53**).

receptor, whereas the agonist binding or signal transduction involves Asp 79, Asp 130, Asn 318, Ser 204 and Ser 207, all located in putative transmembrane region of the receptor (Strader et al 1987, 1988, 1989 a, b; Fraser et al 1988). All known sequences of the neurotransmitter receptors have aspartic acid residues in positions corresponding to those of Asp 79, Asp 113 and Asp 130 in the β_2-adrenergic receptor. These correspond to Asp 82, Asp 116 and Asp 133 in the 5-HT_{1A} (Sylte et al 1993) and Asp 120, Asp 115 and Asp 172 in the 5-HT_{2A} receptor (Dahl et al 1991). Asn 318 in the β_2-receptor is conserved in the 5-HT_{1A} receptor whereas the 5-HT_{2C} receptor has a cysteine and 5-HT_{2A} a serine in the corresponding position. The 5-HT_{2C} and 5-HT_{2A} receptors have a serine residue corresponding to Ser 204 in the β_2-adrenergic receptor, and the 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors have an alanine in the position corresponding to Ser 207 in the β_2-adrenergic receptor. Substitution of Asp 82, Asp 116 and Ser 198 of the 5-HT_{1A} receptor resulted in decreased affinity of 5-HT to the receptor but did not affect the affinity for pindolol (Ho et al 1992). Substitution of one of the aspartic acid units (Asp 120, Asp 155, Asp 172) by asparagine in the 5-HT_{2A} receptor have shown that Asp 120 is necessary for allosteric activation of the guanine nucleotide binding protein and Asp 155 is necessary for high affinity binding, probably by acting as a counter-ion for the amino group of the ligand (Wang et al 1993).

Using site-directed mutagenesis, it was shown (Choudhary et al 1993) that a single-point mutation of a conserved phenylalanine residue (Phe 340) largely attenuates the ability of agonists, some ergots and selected antagonists to bind to the 5-HT_{2A} receptor. It was concluded that a specific interaction with the conserved aromatic residue (found in all G-protein-coupled 5-HT, catecholamine, and histamine receptors cloned so far) of the amino acid is essential for the binding to the receptor recognition site. The results were used to validate Hibert's (Hibert et al 1991) and Edvardsen's (Edvardsen et al 1992) models of the 5-HT_2 receptor providing evidence in favour of Hibert's model.

Site-directed mutagenesis was also used for explaining species differences in the pharmacology of 5-HT_{2A} receptor. Nelson et al (1993) found that N-1 unsubstituted ergolines and tryptamines exhibited higher affinity for the pig and human than that for the rat 5-HT_{2A} receptor. Johnson et al (1994) have shown that mutating the rat receptor Ala 242 to Ser 242 gave a pharmacological profile that was virtually identical to that of the human receptor and differed significantly from that of the rat receptor. This was explained as the human 5-HT_{2A} receptor and the rat A242S mutant having a potential hydrogen-bond acceptor in the hydroxyl group of Ser 242 that is not present in the rat. Therefore, a potential hydrogen bond can occur between the N-1 hydrogen of the indole and the oxygen of Ser 242 in the human receptor, but not with Ala 242 in the rat 5-HT_{2A} receptor (Fig. 16).

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