CHAPTER 2

STRUCTURE-ACTIVITY RELATIONSHIPS

2.1 Introduction.

When the structure of the molecular target is unknown, predictions of the activity of different molecules have to rely on indirect models. The development of such a model may be based on the recognition of key features common to sets of active molecules, the pharmacophore. The identification of a pharmacophore may provide insight into the mechanism of the drug-receptor interaction.

Drug-receptor interactions can be divided into two different events. The recognition by the receptor of the ligand, agonist or antagonist, is expressed in its affinity for the receptor. The binding of an agonist induces a change in the drug-receptor complex that eventually leads to a measurable response. The inability of antagonist to induce a response may be related to different receptor interactions as compared to those of the agonists and thus, the use of both agonists and antagonists when developing a model, i.e. by using only affinity data, may be misleading.

Several attempts to correlate structural features of dopaminergic and serotonergic agents with their activity have been made [1,2,3,4]. However, the lack of comparable pharmacological data and the limited access to enantiomerically pure test compounds have in some cases resulted in less relevant models [5,6].

2.2 Structure-Activity Relationships of Dopamine Agonists

Drug design is, in spite of the recent developments in molecular biology, up to now an empirical exercise. The true design of new active structures is still virtually impossible at the present state of the art. Thus, one finds that all dopamine agonists which have been developed as a result of design processes originated in one of two ways. They represent either structural dissection efforts, or they attempt to incorporate the structure of dopamine into a rigid framework.

Typical of the former approach would be the dissection of the semi-natural product apomorphine 1 (Scheme 2.1) to yield first, linear benzo[g]quinolines (2), and with further dissection 2-amino-5,6-dihydroxytetrahydronaphthalenes (3).
Scheme 2.1. Dissection of the semi-natural product apomorphine (1).

Incorporation of the dopamine moiety into a rigid framework essentially represents the converse process.

Scheme 2.2. Incorporation of the dopamine moiety in a variety of ring systems.

One of the great challenges in dopaminergic structure-activity relationship studies
(SAR’s) is that the elements of the dopamine molecule can be incorporated within the matrix of a variety of ring systems, with retention of a high degree of potency and activity itself. Scheme 2.2 illustrates some representative ring systems that have been studied [1,2,3,7].

There have been many studies of the structure-activity relationships (SAR) of central and peripheral DA receptor agonists [1-3,7,8].

The purpose of this section is to give a brief summary of the structure-activity relationships of dopaminergic 2-aminotetralins and related compounds.

2.2.1 2-Aminotetralins

In addition to the apomorphine and ergot analogues, the 2-aminotetralin derivatives have been one of the most important groups of compounds which have increased our understanding of the neurobiology of dopaminergic systems. Interest in the dopaminergic activity of this class of compounds arose as a result of the report of Woodruff et al. [9] on the pharmacological profile of 6,7-ADTN (5). In the aminotetralins, the dopamine moiety can be incorporated in two ways, the so-called α- and β-rotameric form (Fig. 2.1) [2]. In the 2-aminotetralins, both the α-conformer and β-conformer of the dopamine moiety retain at least a portion of the spectrum of dopaminergic agonism.

![Chemical structures of the rotamers of dopamine and its aminotetralin analogues.](image)

Figure 2.1. Chemical structures of the rotamers of dopamine and its aminotetralin analogues.

In the 2-aminotetralins, differences in metabolic pathways and in rates of metabolism seem at least as important as structural parameters in determining spectrum and sites of dopaminergic effects. One of the main problems with 5 is its very limited ability to pass the blood-brain barrier. Improved permeation and prolonged duration of action by ester formation of the catechol OH groups in aminotetralins [10] has facilitated and controlled absorption and distribution of these dopaminergic agonists. The
resorcinolic 5,7-dihydroxy substitution pattern led to compounds that were, in general, less active than the catechols.

![Figure 2.2. Dibenzoyl ester of 6,7-ADTN (6).](image)

A catechol group is not necessary for activity. The discovery of the high potency of 5-hydroxy-2-dipropylaminotetralin (7) was particularly interesting. As compared to the catechols, this compound could be expected to have a higher chemical and metabolic stability and consequently a longer duration of action. Since the chemotrigger zone of the emetic centre is considered to be located outside of the blood brain barrier, there is also a possibility that a more lipophilic compound, i.e. with large N-substituents, could be relatively less emetic. Based on these considerations we and other groups have synthesized and tested a large number of N-alkyl-5-hydroxyaminotetralins [11-14].

Tertiary amines are generally more potent than the secondary amines. Potency and activity in phenylethylamines, certain 2-aminotetralins, apomorphine, chromanamines and the octahydrobenzo[f]quinolines are maximal with n-propyl or di-n-propyl substitution on the nitrogen. Higher alkyl substitution results in complete or almost complete loss of activity [2]. The n-propyl group seems to have a special effect at the receptor side, not exclusively due to its lipophilic character. The observations regarding the structural specificity for the N-substituents of DA-agonists seem to indicate that at least one of the N-substituents must fit into a cavity, which because of its size, can maximally accommodate an n-propyl group. Smaller groups like methyl or ethyl can also fit this pocket although these groups probably give less efficient binding. The second N-substituent is allowed to vary within wide limits. The only restriction that is found is that this substituent should not be branched at the carbon next to the nitrogen. In fig 2.3 some potent agonists of the 2-aminotetralin group are shown.

When the hydroxyl group is moved from C5 to the other positions, interesting effects are observed. 6-OH-DPAT (8) has lost most of its dopaminergic potency whereas 7-OH-DPAT (9) is a potent DA receptor ligand. 8-OH-DPAT (10) is not a DA receptor agonist but rather a potent and selective 5-HT1A receptor agonist (see also section 2.3).
Figure 2.3. Chemical structures of some potent dopaminergic 2-aminotetralins. 5-OH-DPAT (7), 6-OH-DPAT (8), 7-OH-DPAT (9), 8-OH-DPAT (10), N-0437 (11), N-0434 (12).

The potent selective D₂ receptor agonist 2-(N-n-propyl-N-2-thienylethylamino)-5-hydroxytetralin ((*)-N-0437, 11) is of special interest, because it is the first example of a 2-ATN derivative, which has reached the stage of clinical evaluation for the treatment of Parkinson's disease. The enantiomers of this potent and D₂ selective agonist have been extensively tested for their pharmacological action on D₂ autoreceptors, in vivo, by measuring DA release by microdialysis during local administration of both drugs and in vitro, by measuring their effects on the electrically stimulated release of [³H]DA from striatal slices [15]. In both experiments (-)-N-0437 acted as agonist on receptors controlling the DA release. The (+)-enantiomer of N-0437 displayed partial agonistic activity at DA D₂ receptors. (+)-N-0437 showed agonistic activity in a DA synthesis model (GBL-model), while in the microdialysis release model it showed antagonistic activity. The (+)-enantiomer also acted as a weak antagonist at postsynaptic receptors in the in vitro [³H]-acetylcholine release model and in some behavioural models [16,17]. This spectrum of activity is similar to that of (-)-3-(3-hydroxyphenyl-N-n-propylpiperidine ((-)3-PPP, 13), which indicates that (+)-N-0437 may have potential antipsychotic activity [18].

In a series of ring-halogenated mono and di-OH-ATN analogues, Weinstock and associates have found that the 8-chloro and 8-fluoro-6,7-dihydroxy aminotetralins 14 were selective D₁ agonists [19]. However, this is in contrast to findings of Murray and Waddington [20], who found no selectivity for a receptor subtype. Replacement of the 6- or 7-OH group by a halogen reduced the dopaminergic activity.
Introduction of a methyl group in the 1-position has produced some interesting compounds [21]. The putative DA autoreceptor antagonist cis-(1S,2R)-5-methoxy-1-methyl-2-(n-propylamino)tetralin ((+)AJ76, 15a) and its dipropyl analogue (+)-UH 232 (15b) have about 4 times higher affinity for D₃ than for D₂ receptors [22]. The C₁-methylated phenolic compounds were less active as antagonists at central DA receptors as compared with the non-methylated analogues. However, cis-(+)-(1S,2R)-5-OH-1-CH₃-DPAT ((+)-UH242, 16) was the DA receptor antagonist with preferential action on DA autoreceptors that was first discovered [23].

2.2.2 The McDermed Receptor Concept

A key discovery was that the stereoisomers of 5-hydroxy and 7-hydroxy ATN derivatives, which have high affinity D₂ receptor binding, and which show pharmacological activity in functional assays of dopaminergic activity, have the opposite absolute configuration. The active enantiomer of 5-hydroxy-2-(di-n-propyl)amino)tetralin has the (2S) configuration. This enantiomer is more potent than its antipode in a number of dopaminergic test systems. In sharp contrast, 7-hydroxy-2-(di-n-propylamino)tetralin and 7,8-dihydroxy-2-(di-n-propylamino)tetralin exhibit the opposite stereochemical requirement; their (2R)(+) enantiomers are more potent than their optical antipodes. These stereochemical differences have been elegantly rationalized in a simple manner by McDermed et al. [24]. They suggested that the two most important binding sites in the DA receptor interact with the amino nitrogen and the
hydroxyl group meta to the ethylamine side chain (Fig 2.6). Thus, although the (2S)-(−)-5-OH-DPAT and (6aS)-(−)-apomorphine both bind in a similar way to the receptor, (2R)-(−)-7-OH-DPAT and (2R)-(−)-6,7-OH-DPAT must be rotated with respect to the other two compounds in order to fit this model.

![Figure 2.6. Orientation of (2S)-5-OH-ATN (7) and (2R)-7-OH-ATN (9) towards the two proposed major binding sites of the D2 receptor.](image)

McDermed has also included a boundary in the receptor preventing the interaction with compounds having steric bulk in this region (Fig 2.7).

![Figure 2.7. Interaction of (2S)-SOH-ATN with conceptual receptor model of McDermed.](image)

Thus, this model not only rationalizes the activity of many DA receptor agonists, but it is also of predictive value. Although it is conceivable that the exact receptor preferred conformation of DA might be different at D1 and D2 receptors, it is possible to reach some general conclusions which can be applicable for both receptors.

This so-called "McDermed flip" has been the start of several hypothetical dopamine receptor models, some of which will be discussed in this chapter.

In an extension of this model by Wikström et al. [25,26], applied to the dopaminergic monohydroxylated 3-phenylpiperidines 13 and the octahydrobenzo[f]quinolines 17 and 18, they have found that there is a relationship between the absolute configuration, the ring position of the hydroxyl group and the size of the N-alkyl substituent. There are now two different directions possible for the N-alkyl...
substituents, namely upwards- and downwards (Fig 2.8). An assumption they made is that, due to the different directions in which the N-substituents point, the space

![Chemical structures](image)

**Figure 2.8.** Wikström's modification of McDermed's model. The structures of 7- and 9-OHB[t]Q's superimposed.

available for the N-substituent of compound 18 might be more restricted than for the corresponding isomer 17. And indeed, they have found that the N-substituent downwards is sterically restricted to maximally a propyl group, whereas the upwards direction has less restricted demands.

![Diagram](image)

**Figure 2.9** Topographical model for dopamine receptors: Grol's model [27,28].

Grol et al [27,28] have postulated two binding sites, P and M, complementary to the p-OH and m-OH groups of agonists; X and Y are putative electronegative sites complementary to different amino binding sites for α- and β-rotameric compounds (Fig 2.9). The two sites have been proposed to rationalize the activity of agonists in which the m-OH to N distance varies between 5.5 and 7.4 Å. In their view, these two nitrogen-binding sites correspond with the distance (~2.4 Å) between the two oxygen atoms of the carboxylate anion of likely the aspartic acid (Grol, personal communication). π1 is an interaction place for an aromatic ring and π2 is an accessory site for the 1-aryl group.
of 3-benzazepines. This model was developed from a different approach, using molecular orbital calculations as the basis.

The graphic representation of a dopamine receptor proposed by McDermid [24] and modified by Liljefors and Wikström [25,26] (Fig 2.8), as well as similar models proposed by Grol and Rollema [27,28] (Fig 2.9), Seeman [29], Kaiser and Jain [1,30] and by Seiler and Markstein [31], have provided some insights into structural requirements for dopaminergic agonism, and have permitted rationalization of the activity of some molecules and of the inactivity of other molecules; but this work has been largely retrospective.

No extant receptor model seems to explain adequately the agonist actions of all categories of dopaminergic agents and to rationalize the observed inactivity of all the molecules for which dopaminergic agonism may have predicted. None of the proposed models take into consideration all the subpopulations of DA receptors currently under discussion in the literature.

2.2.3 Chromanamines

Isosteric replacement of the C4 in the aminotetralins by an oxygen atom yields the 3-chromanamines. 6,7-Dihydroxy-3-chromanamine (19) was found to have in vivo activity similar to that of the parent compound, but its in vitro activity was much less pronounced [32]. We and other groups have demonstrated that the 6- and 8-monoxygenated chromanamines are potent agonists at the DA receptor [33-37]. The behavioural effects on locomotion in naive and reserpine pretreated rats suggest that these compounds do have selectivity for autoreceptor sites [35]. 8-Hydroxy-N,N-di-n-propylchromanamine (21), which contains the DA pharmacophore in an α-conformation was more potent than the 6-OH analogue 20, which exists in the β-conformation. Comparing the general structure of an aminotetralin and an aminochroman in their preferred conformations according to MMP2 calculations, the compounds appear very similar in size and shape [37] and the difference between the two structures, when tested in biological assays, should therefore be related to electronic factors. An additional oxygen will have an electronically donating effect and, therefore an enhanced electron density over the aromatic ring. And indeed, Thorberg [37] and we (Chapter 6) have shown that the phenolic group is less acidic (~ 1 pKₐ unit), as compared to that of the aminotetralins. It also displays a weakened electron density over the aliphatic nitrogen. Maybe these differences are the reasons for the better CNS penetration. The 5-hydroxy isomer 22 showed, by analogy to the 2-aminotetralins, 5HT₁A activity.
Fig 2.10. Structures of 6,7-dihydroxy-3-chromanamine (19); 6-OH (20), 8-OH (21) and 5-OH-3-(di-n-propylamino)-2H-1-benzopyrans (22).

2.2.4 Octahydrobenzo[f]quinolines

This group of DA-agonists can be looked upon as aminotetralin analogues with one propyl group fixed on the non-aromatic ring of the tetralin. The trans-fused monophenolic 7- and 9-OH-octahydrobenzo[f]quinolines (OHB[f]Qs) have been found to possess potent dopaminergic activity. The nitrogen must be properly substituted. For trans-9-OH in the 'downwards' direction the substituent must be ≤ n-propyl and any size in 'upwards' direction for trans-7-OH-OHB[f]Q (see also section 2.2.2) [25]. By analogy to the 2-aminotetralins, the 10-OH showed 5-HT1A receptor activity (Fig 2.11).

Figure 2.11. Structures of OHB[f]Q's (17 and 18), naphthoxazines (23), benzopyranopyridines (24) and the benzopyranoxazines (25).

2.2.5 Hexahydronaphthoxazines

Due to difficulties involved in the preparation of the active trans-isomers of these compounds, the isosteric ring system containing an oxygen, the trans-hexahydro-4H-[1,2b][1,4]oxazines (23) have been prepared (see Chapter 5). The 9-hydroxy trans-N-propyl analogue (23) (N-0500) was found to be a very potent and selective D2 agonist [38,39]. The (+)-enantiomer (PHNO) has been found to be active in cases of Parkinson's disease [40]. The absolute configuration of the (+)-enantiomer has been shown to be R for C4a, thus, the absolute configuration of (+)-PHNO and (+)-7-OH-DPAT are comparable.
2.2.6 Tetrahydrobenzopyranoxazines and Hexahydrobenzopyranopyridines

Replacement of a methylene group in the naphthoxazines by oxygen produced compound 25, which was much less active in both in vitro and in vivo tests of DA receptor activation (see Chapter 6). This low activity, compared with hexahydronaphthoxazines (23), may result from inadequate protonation of the compound at physiological pH due to its low pKₐ value. Previous work, employing both dopamine agonists and antagonists, suggests that it is the charged species of the dopaminergic ligand which actually binds to the DA D₂ receptor [41]. CGS 15855A (24) (R = n-propyl) a rigid trans-hexahydrobenzopyranopyridin-9-ol was reported as an auto-receptor agonist which produces a dose dependent decrease in 3-methoxytyramine levels in both mouse and the rat. Weak behavioural stereotypies have been observed with 25 only at doses 20 times the ED₅₀ for activity in the GBL model. The behavioural effects appear to be confined to the (+)-enantiomer [42,43,44].

2.2.7 The Significance of the Charge on the Nitrogen Atom of Dopamine Agonists.

Although catecholamines can exist in a variety of forms at physiological pH, a basic question arises as to which of these species is/are involved in the binding and activation of dopamine receptors.

![Figure 2.12 Possible charged and uncharged species of dopamine that could interact with dopamine receptors.](image)

Some reports indicate that an uncharged nitrogen atom is required for the activation of the DA receptor [45,46], whereas others have reported that the charged form of the nitrogen atom is a prerequisite for activity [41,47]. Nichols [48] has suggested that the real importance of this atom lies in the orientation of its unshared
electron pair, whether free or protonated. However, the introduction of a second oxygen atom at the 6-position in the hexahydronaphthoxazines led to compounds which are only protonated to an extent of 2% under physiological conditions (pH ~ 7.4), and which are very weak DA agonists. This decrease in activity has led to the hypothesis that DA agonists probably bind to their receptors through the charged rather than the non-protonated nitrogen atom (chapter 6). Further evidence for this assumption is afforded by Miller and Uretsky [49,50,51], who have synthesized analogues of dopamine and ADTN in which the amine group was replaced with either a neutral methylsulfide, a methylselenide or a sulfoxide group.

![Figure 2.13. Some permanently uncharged (26, 29) and charged (27, 28, 30) sulfide, sulfoxide and sulfonium analogues of dopamine and 6,7-dihydroxy-2-aminitetralin (28), and uncharged 31 and charged 32 sulfur analogues of DA antagonist sulpiride.](image)

These analogues were tested for D2 activity. None of these permanently uncharged analogues activated the DA D2 receptor regulating the depolarization-induced release of [3H]acetylcholine. However, the permanently charged dimethylsulfonium, dimethylselenonium and trimethylammonium analogues of dopamine exert D2 receptor activity. They have also synthesized and examined the biological activity of permanently uncharged and permanently charged analogues of the dopamine antagonist sulpiride. And again, only the permanently charged compounds have shown to be active as dopamine antagonists [52].

In all cases, the activity of these compounds is less than that of the parent compounds. The lower activity of the permanently charged compounds may be due to
their lack of hydrogen at the charged center. Without a hydrogen atom these analogues are not capable of forming a reinforced ionic bond with the receptor, but are only capable of forming an ionic bond. Since an ionic bond has approximately one half the bond strength of a reinforced ionic bond (5 kcal/mol vs. 10 kcal/mol) and since the interaction of the amine nitrogen with the dopamine receptor is thought to be a major contributor to the binding of agonists and antagonists to the dopamine receptor, the lower activity of the permanently charged analogues may be due the inability of these compounds to form a reinforced ionic bond with an anionic site on the dopamine receptor [53,54].

2.3 Structure-Activitivity Relationships of Serotonin Agonists

2.3.1 The SAR of 2-Aminotetralins at the 5-HT₁A Binding Sites.

The ergoline skeleton contains, in its rigid structural framework the key elements of both dopamine and 5-HT. It has been exploited by medicinal chemists, who have designed and synthesized potent and selective rigid dopamine analogues belonging to the aminotetralin class. The 8-hydroxy-2-N,N-di-n-propylaminotetralin (8-OH-DPAT, 10) was independently synthesized by Feenstra et al. [55] and Arvidsson et al. [56]. According to both groups, the compound did not have any effect on dopamine receptors. In 1980, Arvidsson [56], showed that 8-OH-DPAT possessed very potent 5-HT receptor stimulant properties both in behavioral and biochemical tests. As mentioned above, 8-OH-DPAT became a very important pharmacological tool to characterize 5-HT receptor subtypes. The compound possesses a very high affinity for the 5-HT₁A sites and a low affinity for the 5-HT₁B, 5HT₁C and 5-HT₂ sites.

Extensive structure-activity relationship studies of the aminotetralins have been performed [56,57]. The main conclusions are the following:

- (R)-(+)8-OH-DPAT is the most potent compound in the series, the (S)(-) enantiomer being two times less active. The 8-methoxy analogue is six times less active compared to its parent compound.
- The 5-, 6- and 7-hydroxy analogues of 8-OH-DPAT are practically inactive at 5-HT₁A receptor sites [58,59].
- The N-substituents are important for 5-HT₁A activity. The N,N-diethyl and N,N-di-n-propyl-substituted aminotetralins are equipotent, whereas longer branched chains reduced the potency. However, one of the N-propyl groups may be exchanged for a considerable larger substituent.
- By introducing methyl groups in the non-aromatic ring of the tetralin skeleton, steric and bulk conformational requirements of the receptors can be examined.
Hjorth et al. [60] have found that the activity of the cis 1-methylated 8-OH-DPAT analogue (+)-ALK-3 was comparable to the parent compound in reducing the 5-HT output from rat ventral hippocampus. In comparison, both the (-)-ALK-3 and the trans diasteromers were inactive, whereas the two enantiomers of 8-OH-DPAT strongly reduced 5-HT release. ALK-3 is highly stereoselective and may therefore represent a useful probe in further characterization of the 5-HT$_{1A}$ receptor mediated mechanisms and functions. This study defines some of the sterochemical requirements for 5-HT$_{1A}$ receptor interaction, emphasizing the importance of the receptor region complementary to C$_1$ and C$_2$ carbons of the 8-OH-DPAT molecule.

Fig 2.14. Chemical structures of serotonin (5-HT), LSD (33), 8-OH-DPAT (10), UH301 (34) and the amide and thiomethyl derivatives of 8-OH DPAT (36).

Introduction of fluorine in the aromatic ring in the selective 5-HT$_{1A}$-receptor agonist 8-OH-DPAT (10) has been shown to alter dramatically the pharmacological profile. 5-F-8-OH-DPAT (UH 301, 34) is stereoselective whereas 8-OH-DPAT is not. The enantiomers of 5-fluoro-8-hydroxy-2-(dipropylamino)tetralin have opposite activities, and the R-enantiomer is a 5-HT$_{1A}$ agonist, although of slightly lower potency than 8-OH-DPAT, whereas the S-enantiomer behaves as a 5-HT$_{1A}$ antagonist [61,62]. Fluorine differs only little in size from hydrogen, and its effect on the acidity should be minimal. The NMR experiments and molecular mechanics calculations indicate that the fluorine does not induce any conformational change. Thus, the major difference between 10 and 34 may be related to their electronic distribution. Consequently, these results indicate that the efficacy may be further modified by
changing the the electronic properties of the aromatic ring.

Compounds 36 showed high 5-HT<sub>1A</sub> receptor binding affinity, indicating that 8-methoxy or 8-hydroxy substituents are not necessary for efficient binding [63,64].

Glennon et al. [65] have demonstrated that the introduction of the large N-(phthalimidobutyl) group is not only tolerated but can result in significantly enhanced affinities at the 5-HT<sub>1A</sub> sites. This group is also tolerated by members of every major class of agents known to display significant affinity for 5-HT<sub>1A</sub> sites.

8-OH-DPAT has been used as a template to construct a photoaffinity label for 5-HT<sub>1A</sub> receptors. The label 37 binds with high affinity to 5-HT<sub>1A</sub> sites in rat hippocampus. In addition to its importance as a biological tool, this agent demonstrates that, just like by the dopaminergic 2-aminotetralins, one of the propyl groups may be modified substantially while maintaining high affinity and selectivity for the 5-HT<sub>1A</sub> receptor [66].

![Figure 2.15](image)

### 2.3.2. Chromanamines

The chromane analogue of 8-OH-DPAT, where an oxygen atom replaces the carbon C-4 of the aminotetralin skeleton, has been described [67,68]. This agent, 5-hydroxy-3-N,N-di-n-propylaminochromane (5-OH-DPAC, 38), possesses an affinity comparable to 8-OH-DPAT for the 5-HT site, but is claimed to be 10 to 20 times less active at the presynaptic sites in the striatum. The 5-MeO-DPAC also acts in the nM range on 5-HT<sub>1A</sub> sites, but in contrast to 8-OH-DPAT did it scarcely binds to presynaptic striatal slices. These presynaptic sites are possibly associated with 5-HT reuptake in serotonergic terminals [69]. The electronic enrichment which results from isosteric O-substitution mimics that created by a double bond in two other preferential 5-HT<sub>1A</sub> ligands such as LSD and BAY R 1531. Boyer et al. [70] described a selective tricyclic 5-HT<sub>1A</sub> ligand in which electronic enrichment in the same position of the molecule is provided by an oxygen as in 5-MeO-DPAC. So, comparison of the chemical structures of 5-MeO-DPAC and other 5-HT<sub>1A</sub> ligands suggests that electronic enrichment due to isosteric displacement of carbon by an oxygen may play an important
role in the selective recognition of the 5-HT\textsubscript{1A} receptor by these drugs.

### 2.3.3 Tricyclic 2-Aminotetralin Congeners

![Figure 2.16 Structures of tricyclic 5-HT\textsubscript{1A} agonists. 10-OH OHBQ (39), CGS 18102A (40) and the tetrahydro-benzopyranopyridine (41)](image)

Analogously to the 2-aminotetralins, the 10-hydroxy octahydrobenzo[f]-quinoline showed 5-HT-like activity. The relatively low potency has been explained on conformational grounds [71]. Potent and selective ligands for 5-HT\textsubscript{1A} receptors may be obtained by appropriate modification, from compounds related to the 3-aminochromanes, namely the hexahydro-benzopyranopyridines 40 and the tetrahydro-benzopyranopyridines 41 [78]. Compound 40 (GCS18102A) is relative selective for 5-HT\textsubscript{1A} and 5-HT\textsubscript{2} receptors. Compounds 40 and 41 may be viewed as tricyclic analogues of lysergic acid (33) in which the pyrrole ring has been eliminated and an oxygen has been introduced at the former 3-position of the indole moiety.

### 2.3.4 Receptor Model

X-ray analysis and conformational studies of 5-HT do not provide conclusive information regarding the receptor-bound conformer of 5-HT, since numerous side chain conformations are separated only by low energy barriers. Consequently, scientists have turned to rigid active molecules to investigate receptors. In this respect, (+)-LSD proved to be an important compound. Models based on the structure of (+)-LSD have been proposed and it has been claimed that the A-ring and the aliphatic nitrogen atom are essential for the binding to the receptor. In addition, it has been suggested that the pyrrole function and the C9-C10 double bond in (+)-LSD are of importance for an electrostatic interaction, and that the phenol group on 5-HT and 8-OH-DPAT should correspond to the double bond in terms of electronic properties. The importance of the phenolic group for serotonergic activity was supported by the fact that 2-aminotetralins with hydroxy substituents in other positions of the aromatic ring apparently lack 5-HT activity and instead show dopaminergic properties. According to Hibert [58], the minimal structural parameters necessary for 5-HT\textsubscript{1A}-receptor stimulation is one
aromatic ring and one amino group and its lone pair of electrons in the relative position shown in Fig 2.17a. The mean distance between the center of the common aromatic ring and the nitrogen atom is 5.3-5.6 Å, and the nitrogen lies at 0.2 Å above the plane defined by the reference ring and the electron lone pair is almost perpendicular to the plane of the aromatic ring. Nevertheless, these two primary points of binding are probably not always sufficient and additional binding groups are presumably required to stabilize the receptor-ligand complex. It seems reasonable to assume that the 8-hydroxy or 8-methoxy and the N-di-n-propyl substituents of the aminotetralin moiety seems to be required to offset the lack of the indole nucleus and to obtain compounds with high affinity and selectivity for the 5-HT_{1A} recognition site [58]. According to this model, the stereochemical requirements of the 5-HT_{1A} and α-adrenoceptor are identical. Interestingly, the height of the nitrogen atom above the plane defined by the aromatic ring, as well as the directions in which the nitrogen lone pair of electrons point are different in the model for antagonistic and agonistic activity, respectively [58]. This may allow comparison of the active and inactive conformation of the 5-HT_{1A} receptor induced during the fitting process by agonists and antagonists.

Because it was not possible to obtain a reasonable fit with conformationally restrained, but active derivatives of 8-OH DPAT, a second model has been proposed by the group of Hacksell [76]. This model describes the minimal structural parameters necessary for agonists at the 5-HT_{1A} receptor. Since the non-phenolic 2-(propylamino)tetralin possesses fairly high affinity for the 5-HT_{1A} receptor [77], the phenol group is omitted in this model. The pharmacophore model consists of two elements 1) an aromatic site; 2) a dummy atom-nitrogen site. This dummy atom, located 2.6 Å from the nitrogen and aligned with the N-H bond vector, was supposed to mimic a cation binding site (most likely, a carboxylate) at the receptor. The model defines limits within which the relative position of an aromatic nucleus and a nitrogen-dummy atom vector may vary (Fig 2.17b). It also defines a partial 5-HT_{1A}-receptor-excluded volume. Just as the model of Hibert et al., this model also does not take into account the electronic properties of the aromatic moiety.

Figure 2.17. Pharmacophore of the 5-HT_{1A} agonist recognition site as proposed by a) Hibert et al. [58], and b) Mellin et al. [76]. All the distances in the models are in Å: y = 2.1 - 2.6; x = 5.2 - 5.7; α = (-) 28° - (+)-28°; β = (-)-4° - (+) 0.4°
Because a large N-(phthalimidobutyl) group is tolerated and also seems to enhance affinity, Glennon [65] postulated that these agents probably utilize a common aryl, terminal amine and a phthalimido site.

An extensive study of the molecular electrostatic potential of ligands with other substituents which may contribute to the ligand-receptor complex stability by interacting directly with electropositive or hydrogen bond donor residues of the recognition site remains to be performed (see chapter 9).

2.4 References


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(London) 347 146
24. McDermed JD, Freeman HS, Ferris RM (1979) in Catecholamines: Basic and
Clinical Frontiers eds Usdin E, Kopin IJ, Barchas J Pergamon Press Vol I, 568
29. Seeman P, Watanabe M, Grigoriadis D, Tedesco JI, George SR, Svensson U,
Chem 27, 1340
33. Dijkstra D, Mulder TBA, Rollema H, Tepper PG, Van der Weide J, Horn AS
35. Wise L, DeWald HA, Hawkins ES, Reynolds DM, Heffter TG, Meltzer LT,
36. Neirabeysaeh MA, Reinaud D, Podona T, Ou L, Perdicakis C, Goudert G,
Suec 24, 169.
GF, Randall WC, Martin GE, Williams M, Hirshfield JM, Smith G, Lumma PK
and Psychiatry 52, 732

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