Russian Chemical Reviews **70** (4) 333 – 355 (2001) © 2001 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2001v070n04ABEH000654

Physiologically active compounds interacting with serotonin (5-hydroxytryptamine) receptors

O N Zefirova, N S Zefirov

Contents

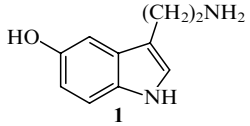
I.	Introduction	333
II.	Classification of serotonin receptors	333
III.	Ligands of serotonin 5-HT_{1A} subtype receptors	334
IV.	Ligands of serotonin 5-HT_{1B} and 5-HT_{1D} subtype receptors	338
V.	Ligands of serotonin receptors of other 5-HT_1 subtypes	341
VI.	Ligands of serotonin 5-HT_2 subtype receptors	342
VII.	Ligands of serotonin 5-HT_3 subtype receptors	346
VIII.	Ligands of serotonin 5-HT_4 subtype receptors	349
IX.	Ligands of serotonin receptors of other subtypes	350

Abstract. The data on the structures of organic compounds active with respect to serotonin (5-hydroxytryptamine) receptors are systematised. Various aspects of their design are considered. The bibliography includes 296 references.

I. Introduction

The problems connected with the design of physiologically active compounds are discussed in the literature in terms of medicinal chemistry;† therefore, they are usually not very well known to a broad circle of organic chemists. The present review is aimed at the systematisation of the published data on the design of physiologically active compounds interacting with serotonin receptors and the analysis of effects of their chemical structures on their activities.

It is known that the physiological role of serotonin (5-hydroxytryptamine) (**1**, 5-HT) in the human brain consists in the regulation of various psychoemotional reactions. In addition, serotonin controls thermal regulation, sensory perception (particularly, pain sensitivity), *etc*. Recent studies have shown that disturbances in serotonin metabolism and/or functional activities of serotonin regulators are related to the pathogenesis of schizophrenia, depressive and anxiety states, alcoholism, drug abuse, *etc*.



1

These findings have stimulated the interest that emerged over the past decade in the design of chemical compounds involved in the neurotransmission mediated by serotonin.

O N Zefirova, N S Zefirov Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119899 Moscow, Russian Federation. Fax (7-095) 939 30 26. Tel. (7-095) 939 48 78.
E-mail: olgaz@org.chem.msu.ru (O N Zefirova)
Tel. (7-095) 939 16 20. E-mail: zefirov@org.chem.msu.ru, zefirov@org.chem.msu.su (N S Zefirov)

Received 22 January 2001
Uspekhi Khimii **70** (4) 382 – 407 (2001); translated by R L Birnova

We hope that this review, which generalises structural approaches to the design of compounds interacting with serotonin receptors, will inspire synthetic chemists to make a radically new contribution to this branch of medicinal chemistry.

II. Classification of serotonin receptors

Serotonin (**1**) is a biogenic amine which manifests an extremely broad range of biological activities with respect to the central nervous system and other body organs and tissues. In the human central nervous system, it acts as a neurotransmitter, *i.e*., a chemical compound which transmits information from one nerve cell to another.[3] In the course of transmission, neurotransmitter molecules are released into the space separating membranes of the interacting cells where they bind to the corresponding receptors on the surfaces of target cells. It is this event that represents perception of information. The specificity of neurotransmitter – receptor interactions is determined by the structures of both the receptor and the neurotransmitter.

Serotonin receptors represent proteins incorporated into cell plasmatic membranes, which transform molecular signals from serotonin and its analogues into specific cell responses. The capability of chemical compounds of binding to their specific receptors underlies their effects on serotoninergic transmission. The effects of the majority of compounds presently used for the treatment of mental disorders, anxiety, schizophrenia, obesity, migraine, *etc*., are thought to be based on their involvement in serotoninergic transmission. These compounds act as agonists (activators) or antagonists (blockers) of the corresponding receptors. It should be noted that the interactions of chemical compounds with receptors are considered from the standpoint of both affinity (*i.e*., binding ability) and intrinsic activity (*i.e*., the ability to produce a biological response by means of structural or conformational changes in the receptor). (Affinity is numerically expressed by the reverse value of the equilibrium dissociation constant of the ligand – receptor complex. Apparently, antagonists possess no intrinsic activities.) The existence of partial

† The subject of medicinal chemistry is the search for, and the structural design [1,2] of, physiologically active compounds (drugs), the elucidation of chemical structure – activity relationships and, finally, the solution of the opposite structure – activity problem, *viz*., the design of compounds with predetermined properties.

agonists, *i.e.*, those which cannot produce maximum activation of their specific receptors and, as a consequence, maximum biological effect irrespective of their concentrations, is also possible.

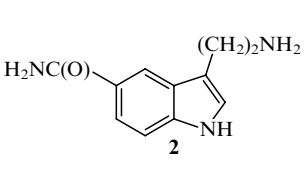
The discovery of an immense variety of serotonin receptors of different subtypes in the past decade has brought about significant changes in their classification and nomenclature. Here, we shall adhere to the classification proposed by a special IUPAC commission according to which the 14 presently known subtypes of serotonin receptors are further divided into seven groups ($5HT_1 - 5HT_7$) depending on their amino acid sequences and the similarity of their signal transmission mechanisms.[4–6] Activation of serotonin receptors triggers the mechanism which involves a cascade of membrane proteins interacting sequentially with one another. In a definite step, signal transmission involves secondary messengers, *i.e.*, molecules or ions endowed with the ability of inducing conformational changes in the proteins involved in specific cellular processes. $5HT_3$ receptors which form ionic channels and transmit signals directly from nervous cells by ionic currents are the only exception.

The discovery of various subtypes of serotonin receptors led to the conclusion that the majority of presently known drugs, influencing serotoninergic transmission, act simultaneously on several subtypes of 5-HT receptors. Therefore, the design of selective ligands aimed at more efficient treatment with minimum side effects has been and still remains the problem of paramount importance, to say nothing of the fact that the design of selective ligands may culminate in the elaboration of radically new treatment schedules.

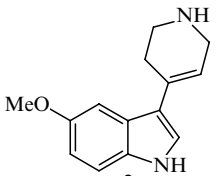
III. Ligands of serotonin 5-HT_{1A} subtype receptors

High concentrations of 5-HT_{1A} subtype serotonin receptors were found in the brain cortex where they are thought to play a crucial role in the processes associated with emotions. It has presently been demonstrated that these receptors are involved in the pathogenesis of various mental diseases, whereas ligands (especially agonists) interacting with these receptors were recommended as candidates for the treatment of various anxiety states, phobias, depressions, Alzheimer's disease (senile dementia), as analgesics, *etc.*[7–9] It is of note that 5-HT_{1A} receptors display a high degree of similarity to other receptor systems of the organism, such as adrenergic and dopaminergic systems, which significantly complicates the search for their selective ligands.

The simplest structural modifications of the serotonin molecule, *viz.*, the introduction of substituents into the benzene ring or restriction of the conformational mobility of the side chain, afforded several high-affinity 5-HT_{1A} agonists, *e.g.*, amines **2** and **3**. However, like serotonin itself, these compounds are not selective and interact with different subtypes of serotonin receptors (predominantly, with 5-HT_{1B}, 5-HT_{1D} and 5-HT_{2C}).[10,11]

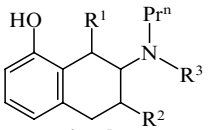


2



3

8-Hydroxy-2-dipropylaminotetralin (**4a**) was among the first most active and selective agonists of 5-HT_{1A} receptors,[12,13] the (+)-(*R*)-enantiomer being fully agonist and manifesting the highest affinity. The main structure–activity regularities for compounds of the type **4** are as follows. The presence of the hydroxy group in position 8 is essential for the binding and provides 500-fold higher selectivity with respect to serotonin receptors in comparison with dopamine receptors (the shift of the OH group into positions 5 or 7 sharply decreases the selectivity), while the hydroxy group in position 8 may be replaced by OMe, Ac or other groups (but not the carboxy group) without any loss in the affinity and selectivity, although the agonistic activity sometimes decreases noticeably, as in substitution by Ac.[14] The presence of two propyl substituents at the nitrogen atom is an optimum for affinity, selectivity and agonistic activity, although some variations in substituents, *e.g.*, replacement of one Pr^n group by $CH_2CH=CHI$ (compound **4b**),[15] enhance significantly the binding of the ligand to the receptor.

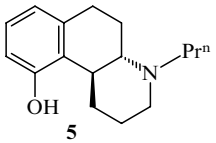


4a–d

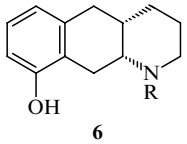
$R^1 = R^2 = H$: $R^3 = Pr^n$ (**a**),
$CH_2CH=CHI$ (**b**);
$R^1 = Me$, $R^2 = H$, $R^3 = Pr^n$ (**c**);
$R^1 = H$, $R^2 = Me$, $R^3 = Pr^n$ (**d**).

The introduction of small substituents (*e.g.*, Me) into positions 1 (compound **4c**)[16] or 3 (compound **4d**)[17] of the alicyclic fragment of the molecule results in compounds manifesting different activities. The tetralin (1*S*,2*R*)-isomer **4c** displays nearly the same affinity as compound **4a**, but is much inferior to the latter with regard to intrinsic activity and is a weak partial agonist. The derivatives containing a methyl group in position 3 bind less effectively to 5-HT_{1A} receptors, although some of them, *e.g.*, the (2*S*,3*S*)-isomer of the tetralin **4d**, manifest high intrinsic activities.[18]

The transition to tricyclic structures afforded several potent 5-HT_{1A} agonists (*e.g.*, the *trans*-isomer **5**),[19] whereas the synthesis of rigid octahydrobenzo[*g*]quinolines yielded weak 5-HT_{1A} agonists, among which the amine **6** was the most active compound.[17] Notice that these cyclic analogues were used for the preparation of pharmacophore models of compounds interacting with 5-HT_{1A} receptors.‡



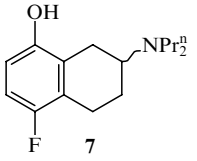
5



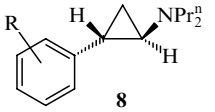
6

And, finally, it should be noted that the introduction of a fluorine atom into position 5 of compound **4a**, which gives compound **7**, changes quite unexpectedly the binding pattern. Thus the (*R*)-isomer of the tetralin **7**, is a full agonist and is somewhat less active than compound **4a**, while the (*S*)-isomer of compound **7** is a strong antagonist of 5-HT_{1A} receptors and its affinity is nearly an order of magnitude lower than that of the (*R*)-enantiomer.[20–22]

The amine **4a** was used as a prototype for the design of yet another structural class of 5-HT_{1A} agonists, *viz., trans*-(arylcyclopropyl)amines **8**.[16,23] The analysis of the structure–activity relationships in this series of compounds revealed that the introduction of electron-withdrawing substituents into the phenyl ring decreases the affinity for 5-HT_{1A} receptors, whereas electron donor or aromatic substituents (with the exception of bulky ones), *e.g.*, 2- or 3-thienyl substituents, enhance the affinity. Unlike the aminotetralin **4a**, compounds of this series are highly stereoselective, only (1*R*,2*S*)-isomers manifesting high activities.



7

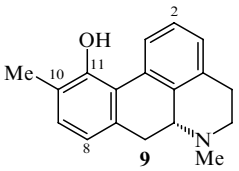


8

Yet another class of 5-HT_{1A} agonists, *viz.*, (*R*)-apomorphine analogues structurally close to aminotetralins **4** are known.

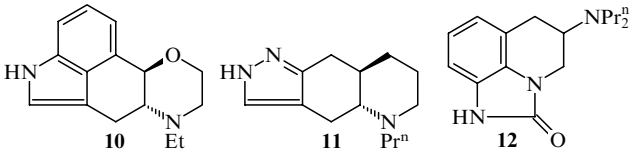
‡ The pharmacophore entails specific spatial arrangement of the binding groups essential for the optimum interaction with the receptor and causing (or blocking) a specific biological reaction. It is a purely structural concept which is neither a genuine molecule nor a genuine association of functional groups.

(*R*)-Apomorphine is a non-selective agonist of dopamine receptors. Structure–activity studies of its derivatives resulted in compounds which do not interact with dopamine receptors but are selective towards serotonin receptors. 11-Hydroxy-10-methylaporphine (**9**) with a methyl group in position 10 (instead of the hydroxy group in aporphine) is the most potent and selective compound. It is of note that only the (*R*)-enantiomer manifests agonistic activity, whereas the variations of substituents in positions 10, 11 and at the nitrogen atom reduce this activity in comparison with the amine **9**. These findings suggest that a hydrogen bond is formed between the hydroxy group in position 11 and serine-168 in the receptor protein and that a 'pocket' for the methyl group in position 10 exists in the binding site of the 5-HT_{1A} receptor.[24,25]



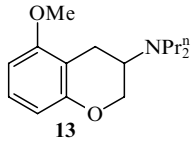
9

Compounds **10**–**12** provide other examples of cyclic systems that interact with 5-HT_{1A} receptors. Although these compounds are not selective, being active with respect to other receptors, they have been used for the construction of computer models of the ligand-binding site of 5-HT_{1A} receptors.[26–28]



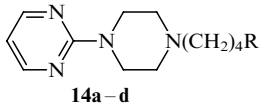
10 **11** **12**

Other structural variations in compound **4a** included the introduction of heteroatoms into the bicyclic fragment. For example, the 5-methoxy derivative **13** manifests the same high reactivity as aminotetralin (**4a**) and, which is more important, is more selective towards the 5-HT_{1A} receptor.[29] The main structure–affinity relationships for this class of compounds can be summarised as follows. Tertiary amines manifest higher affinity for the receptor than secondary and primary amines; substituents at the nitrogen atom can be rather bulky and the presence of MeO, CO_2Me and $CONH_2$ groups in position 5 provides both tight binding and the selectivity towards 5-HT_{1A} receptors.[30]

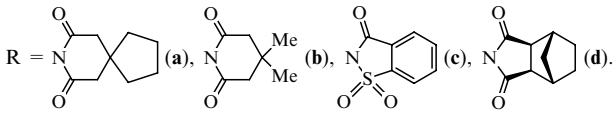


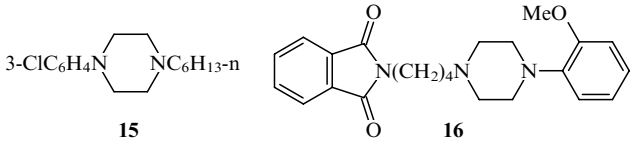
13

Buspirone derivatives constitute a large and very important structural class of 5-HT_{1A} receptor ligands.[31–33] Buspirone (**14a**) manifests high affinity for 5-HT_{1A} receptors and is endowed with agonistic activity. This is the only known compound specific for this subtype of receptor that has been recommended for clinical application as an antidepressant drug. Structural modifications of the imide and piperazine fragments and variations in the lengths of the alkyl chains were carried out aimed at a search for more active and selective buspirone analogues. These studies showed that the imide fragment of compound **14a** can be replaced by bioisosteric groups,§ *e.g.*, like those in gepirone (**14b**), ipsapirone (**14c**), tandospirone (**14d**), *etc.*[34–36] These groups should be lipophilic,[37–39] although the role of steric effects may also be significant.[40] Interestingly, some compounds, *e.g.*, substituted piperazine (**15**),[41] devoid of the cyclic amine fragment in the side chain, also manifest agonistic activities towards 5-HT_{1A} receptors. Heterocyclic substituents at the second nitrogen atom of the piperazine rings of buspirone and its analogues can be replaced by the phenyl substituent either non-substituted or containing an electron-withdrawing substituent in the *o*- or *m*-position to ensure higher affinity, *e.g.*, compound **16**.[42,43]



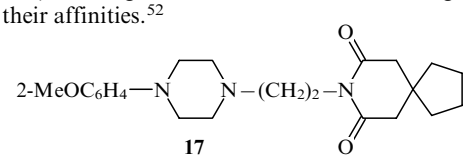
14a–d



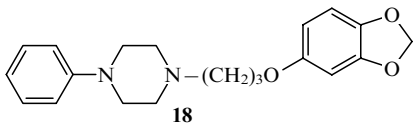


15 **16**

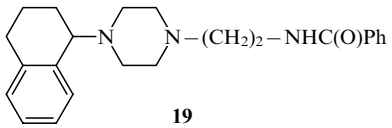
The optimum number of methylene groups in the linker needed for manifestation of maximum affinities of buspirone analogues for 5-HT_{1A} receptors is four, although some compounds with three and even two (less frequently) methylene groups also manifest noticeable affinities, *e.g.*, compound **17**.[44–46] Moreover, high affinity can persist upon substitution of heteroatoms for some methylene groups in the chain as is the case with ether **18**[47,48] or amide **19**.[49] Variations in the chain length and structure strongly affect its selectivity towards serotonin receptors in comparison with adrenoceptors and dopaminergic receptors.[50,51] Thus the selectivities of the bicyclohydantoin derivatives **20a**,**b** for 5-HT_{1A} can be improved by reducing the length of the intermediate alkyl chain to one methylene group ($n = 1$), although such modification causes a significant decrease in their affinities.[52]



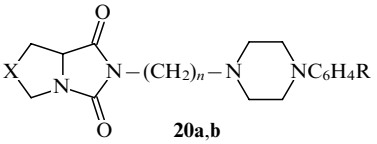
17



18



19



20a,**b**

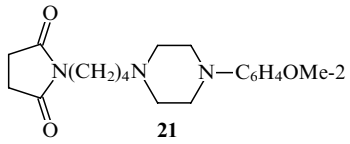
$n = 1–4$; X = CH_2 (**a**), $(CH_2)_2$ (**b**).

Computer simulation studies aimed at rationalisation of such an increase in the selectivities of the bicyclohydantoin derivatives **20a**,**b** revealed[53] that compounds with $n = 1$ and $n = 4$ bind differently to the receptor. The fact that the derivatives with $n = 1$ manifest agonistic activities towards 5-HT_{1A} receptors (albeit rather weakly) suggests[53] that the protein molecule has a 'non-pharmacophoric' pocket (*i.e.*, the site docking 'non-essential' fragments of the ligand molecule rather than the pharmacophore group), which docks the imide group of the ligand

§ A bioisoster is a compound prepared by the replacement of an atom or a group of atoms (*e.g.*, a functional group) by other structural fragments with 'preserved' biological activity. The bioisosteric equivalence rules were established experimentally and are widely used in medicinal chemistry.

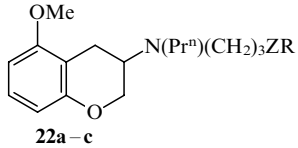
containing one methylene bridge. Its selectivity is attributed to the fact that adrenoceptors have no such pocket.

It is noteworthy that the majority of buspirone analogues mentioned above and buspirone itself, despite their high affinities for 5-HT_{1A} receptors, do not manifest any high intrinsic activities and are thus partial agonists. Moreover, some of them, *e.g.*, compounds **17** and **18** or the succinimide analogue **21** [54, 55] are sometimes classified as antagonists due to their very low intrinsic activities.

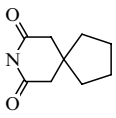
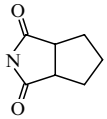


21

Studies aimed at the design of 5-HT_{1A} agonists containing simultaneously the groups constituting the essential fragments of the two main classes of 5-HT_{1A} ligands, *viz.*, aminotetralin (**4a**) and buspirone (**14a**) analogues, have become very popular in the past decade. An imide or a bioisosteric group, such as substituents R in buspirone (**14a**), gepirone (**14b**), ipsapirone (**14c**), *etc.*, were attached to the amino group of the benzopyran fragment of compound **13** through an alkyl chain, resulting in compounds **22**. Studies of structure–affinity relationships of these compounds revealed that compounds **22a–c** containing imide or sulfanylamide substituents manifested the highest activities and selectivities, whereas the preferred length of their side chains was four methylene groups, although sulfonylamide derivatives are also active even if their chains contain two methylene groups.[56]

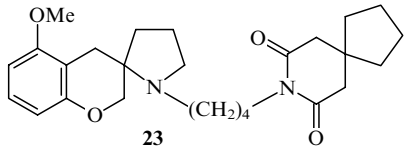


22a–c

Z = CH_2: R =  (**a**),  (**b**);

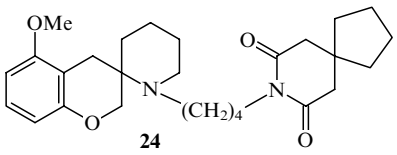
Z = CH_2NHSO_2, R = C_6H_4Me-4 (**c**).

High activities and selectivities of analogues of compounds **22** with limited mobilities of their side chains due to incorporation of the alkylamino groups into ring structures were predicted using the pharmacophore model of 5-HT_{1A} receptor agonists [17] and QSAR.¶ It should be noted that in many cases the restriction of conformational mobilities of functional groups is a classical approach in medicinal chemistry, since this allows stabilisation of the conformation which is the most suitable for the interaction with the receptors. The spiropyrrolidine- and spiropiperidinebenzopyrans **23** and **24** synthesised manifest high agonistic activities and selectivities with respect to 5-HT_{1A} receptors, though not exceeding those of compounds **22a–c**. In our opinion, it is expedient to carry out a detailed analysis of other types of restriction of conformational mobility in the side chains of such compounds. It is also noteworthy that compounds **23** and **24** are partial agonists of 5-HT_{1A} receptors and manifested the properties of antidepressant and anxiolytic drugs *in vivo*.[60]



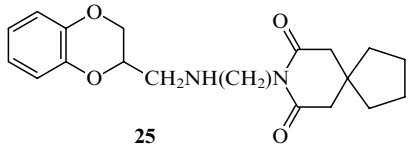
23

¶ QSAR is the abbreviation for 'quantitative structure–activity relationships'. This branch of medicinal chemistry is aimed at establishing the relationships between the properties (activities) and structural parameters of compounds (see, *e.g.*, Refs 2, 57–59).

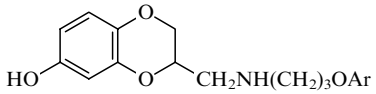


24

Benzodioxane derivatives which constitute another structural class of effective 5-HT_{1A} receptor ligands are being studied intensively. Compound **25** is one of the most potent and selective partial agonists.[61–63]



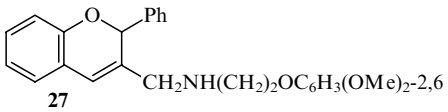
25



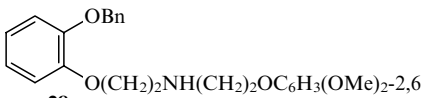
26

Ar = C_6H_4R, Het.

In such structures, as in any other buspirone (**14a**) analogues, the bridging chain may be elongated and modified, as in the case of the high-affinity partial agonists **26**, although such modification sometimes causes significant reduction in their selectivities.[64] Therefore, the search for structural modifications of benzodioxanes which might afford compounds endowed with the ability to distinguish among the binding sites of adrenoceptors and dopaminergic 5-HT_{1A} receptors was continued. It was found [65] that benzopyran (**27**), the unsaturated analogue of benzodioxanes, manifests high affinity for 5-HT_{1A} receptors and partial agonistic activity; the presence of a double bond in its ring and the absence of the oxygen atom in position 1 strongly depress its binding to adrenoceptors, which makes this compound more selective with respect to serotonin receptors. The acyclic benzodioxane analogue (compound **28**) is, contrariwise, less selective towards 5-HT_{1A} receptors than compounds **26**, although they retain their high affinities for these receptors.

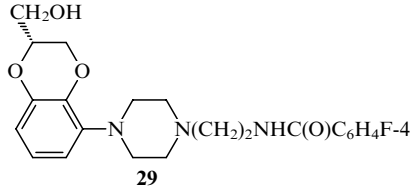


27



28

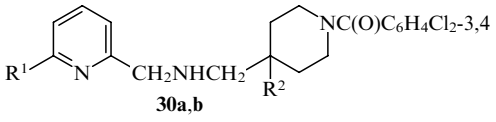
Benzodioxane derivatives with substituents in the benzene rings, *e.g.*, flesinoxan (**29**), also manifest high selectivities and agonistic activities.[66] Studies of structure–affinity relationships revealed that the main contribution to the binding of compound **29** to the receptor is made by the lipophilic substituent at the N(4) atom (the 4-fluorophenyl fragment may be replaced by the phenyl, thiophene or cyclohexane fragment without any loss in activity, but not by polar five- or six-membered heterocyclic substituents). Also, the amide group hardly takes part in the binding to the receptor but, rather, acts as a bridge and may therefore be replaced by other fragments. Structural modifications may also involve the



29

aryl substituent at N(1); these affect not only the affinities of the analogues but also their selectivities in comparison with dopamine receptors.[66]

An intensive search for 5-HT_{1A} receptor ligands characterised by high intrinsic activities is now in progress, since the majority of the known ligands are partial agonists. Full 5-HT_{1A} agonists were found in a new class of compounds, *viz*., 6-substituted pyridylmethylamine derivatives **30**. These ligands were selected using a special model of 5-HT_{1A} receptor activation according to which the intrinsic activities of 5-HT_{1A} ligands depend on their abilities to stabilise the positive charge generated on the receptor protein upon its binding to the agonist. The pyridine ring was chosen as a group endowed with this ability. Therefore, the pyridine derivatives of the type **30** were constructed in order to obtain full agonists of 5-HT_{1A} receptors.

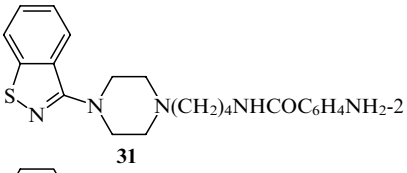


30a,**b**

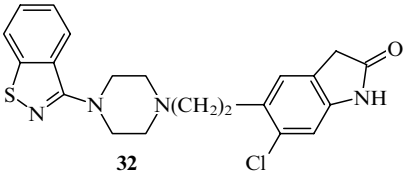
R^1 = , R^2 = H (**a**); R^1 = , R^2 = H (**b**).

The results of QSAR studies suggest that the abilities of compounds to activate the corresponding receptors strongly depend on the nature and position of substituents in the pyridine ring. Thus a substituent (preferrably an electron-donor substituent) should be present in position 6. Compounds **30a**,**b** were finally found to be full agonists of 5-HT_{1A} receptors and possess the highest affinities and selectivities.[67] Moreover, the agonistic activities and selectivities of these compounds and some of their pharmacological characteristics can be improved by introducing the fluorine atom (R^2 = F).[68]

As shown above, structure–activity studies of 5-HT_{1A} receptor ligands are mainly directed at the search for selective compounds. However, special mention should be made of other relevant tasks, such as the search for compounds acting simultaneously as dopaminergic receptor antagonists and serotonin 5-HT_{1A} agonists. These compounds hold much promise in the therapy of schizophrenia and other mental disorders; some of them, *e.g*., the piperazine derivative **31**, are undergoing clinical trial.[69] Certain structurally related compounds, *e.g*., ziprasidone (**32**), manifest antagonistic activities towards 5-HT_2 receptors.[70]

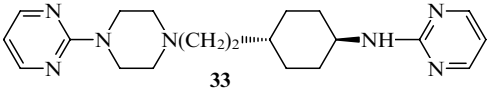


31



32

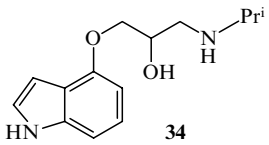
Since this review is aimed at the structural analysis of serotonin receptor ligands, their affinities, intrinsic activities and selectivities, we shall not dwell on the search for ligands for the related types of receptors, although in these studies 5-HT-selective ligands can also be found. Thus the search for ligands of dopaminergic receptors revealed that compound **33** possessed affinity and selectivity exclusively with respect to 5-HT_{1A} receptors.[71]



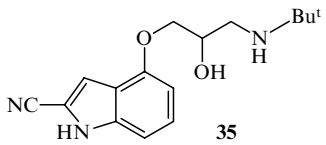
33

To complete the consideration of problems related to the design of 5-HT_{1A} agonists, it should be noted that although such ligands are rather numerous, all of them belong to a limited set of structural classes of compounds. Moreover, only some of these ligands interact with 5-HT_{1A} receptors in a selective manner and very few of them are full agonists. In this context, a search for agonists among novel classes of compounds is a very important task, since it helps elucidation of the structure–activity relationships for ligands and sheds more light on the structural peculiarities and functional roles of the corresponding receptors.

Antagonists of 5-HT_{1A} receptors have been studied in lesser detail, although they could in principle be used for the treatment of various diseases of the central nervous system. Some presently known β-adrenoceptor blockers, *e.g*., pindolol (**34**),[72,73] cyanopindolol (**35**),[74,75] *etc*., manifest antagonistic activities towards 5-HT_{1A} receptors, the (−)-(*S*)-enantiomers being more active. These compounds are also active with respect to other subtypes of serotonin receptors.

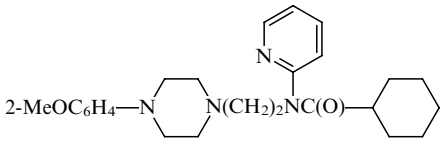


34

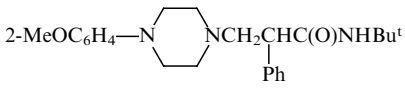


35

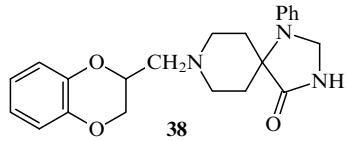
Numerous studies aimed at a search for selective antagonists of 5-HT_{1A} receptors have led to compounds **7** and **36**.[76,77] It was also found that many compounds previously assigned to 5-HT_{1A} antagonists, *e.g*., the piperazine derivative **37**,[78] spiroxatrine **38**,[79,80] *etc*., are in fact not genuine antagonists but manifest partial agonistic and low intrinsic activities.† It should be noted that the main approach to the design of compounds **36**–**38** consists in the introduction of bulky lipophilic substituents into the structures of 5-HT_{1A} receptor agonists. This approach is widely used in medicinal chemistry for the construction of antagonists, since the presence of additional hydrophobic interactions between the ligand and the receptor in the vicinity of the binding site increases the strength of binding to such an extent that the receptor appears to be completely blocked by the compound.



36



37

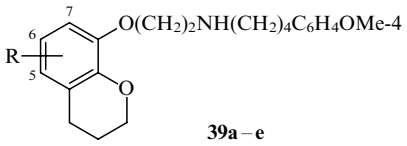


38

Until recently, there was no evidence in the literature concerning the differences in the structural requirements for agonists or antagonists of 5-HT_{1A} receptors.[18] Special mention should be made of investigations into effects of substituents on the intrinsic activities of chromanes of the type **39** which, like benzodioxanes **26**, represent high-affinity 5-HT_{1A} ligands.[81,82] Modifications of the benzene ring in their side chains revealed that the *p*-methoxy group plays a crucial role in both affinity and antagonistic activity of compound **39a**, whereas other substituents diminish both the

† The term 'silent antagonist' was specially introduced to distinguish among genuine antagonists, *i.e*., those devoid of agonistic activity, and partial agonists.

binding and the blocking properties. Modifications of the chromane ring showed that the introduction of F, Cl and OMe (but not OH and Me) into position 6 results in strong antagonists (compounds **39b**,**c**,**d**), whereas the introduction of analogous substituents into positions 5 and 7 yields partial agonists. The differences in the antagonistic activities of this series of compounds cannot be explained by different distribution of their electron densities, since the introduction of both electron-donor (*e.g.*, OMe) and electron-withdrawing groups (*e.g.*, Cl) affords full antagonists, whereas compound **39e** containing the hydroxy group manifests the properties of a partial agonist.



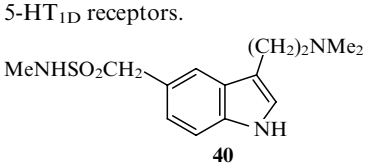
39a–e

R = H (**a**), 6-F (**b**), 6-Cl (**c**), 6-OMe (**d**), 6-OH (**e**).

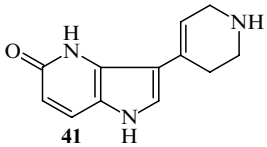
In all probability, the antagonistic properties of the majority of structural classes of 5-HT_{1A} ligands depend on many factors and not necessarily depend on those factors which determine the strength of binding of the ligand to the receptor, *i.e.*, affinity. This circumstance and the fact that even minor structural modifications of 5-HT_{1A} receptor antagonists often cause significant reduction in their affinities, selectivities and antagonistic activities call for further investigations using computer simulation of the receptor structure and ligand docking (in this context, docking is a molecular simulation technique aimed at a search for the optimum matching of the ligand to the binding site).[83] On the whole, the search for selective antagonists of 5-HT_{1A} receptors is a complicated but very urgent task, since no preparations of this class have been recommended for the clinical use thus far.

IV. Ligands of serotonin 5-HT_{1B} and 5-HT_{1D} subtype receptors

Serotonin 5-HT_{1B} and 5-HT_{1D} subtype receptors are rather densely localised in the human brain. They contain extremely similar amino acid sequences despite being encoded by two different genes. These two subtypes can pharmacologically be separated using several non-selective 5-HT_2 antagonists (*e.g.*, ketanserin, see below);[53,84–86] however, their functional roles in the organism have not been established yet because only a very small number of selective ligands to these receptors are known. It is known that blocking of 5-HT_{1B} receptors results in coronary vasodilation,[87] therefore, their selective antagonists can be used for the treatment of various cardiovascular disorders. They are also recommended for use as effective fast-acting antidepressant drugs.[88,89] Agonists of 5-HT_{1D} receptors are putative antimigraine drugs, since their activation causes the brain vasodilation, diminishes pulsation, *etc*. In recent years, 5-HT_{1B} and 5-HT_{1D} subtype ligands have attracted considerable attention in connection with the design of an efficient antimigraine drug sumatriptan (**40**), which appeared to be a 5-$HT_{1B/1D}$ receptor agonist.[90–93] Sumatriptan has very few side effects, but causes coronary vasodilation, which is controlled by 5-HT_{1B} receptors (see above). This, too, calls for the design of selective agonists of 5-HT_{1B} and 5-HT_{1D} receptors.

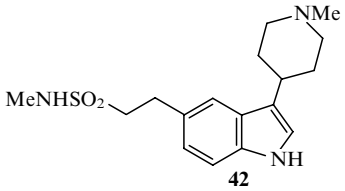


40

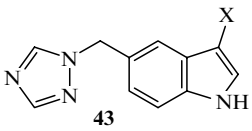


41

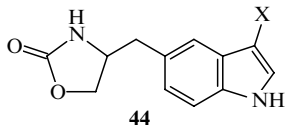
A fairly large group of 5-HT_{1B} and 5-HT_{1D} receptor agonists includes serotonin or tryptamine derivatives, such as amines **2** and **3**, which represent non-selective agonists of 5-$HT_{1B/1D}$ and 5-HT_{1A} receptors. Interestingly, the amine **41**,[94–96] which is a close analogue of compound **3**, is much more active and selective towards the 5-HT_{1B} receptor. Close serotonin analogues include sumatriptan (**40**) itself and its numerous derivatives, such as naratriptan (**42**),[97,98] rizatriptan (**43**),[97,99,100] zolmitriptan (**44**),[101,102] eletriptan,[103] avitriptan,[104] almotriptan[97,105] and frovotriptan (**45**).[85,106] The majority of these compounds are candidates for antimigraine drugs and have passed clinical trials or are in the final stages. Their structures vary largely by changing substituents in the indole fragment or by restricting conformational mobility of the side chain containing an amino group.



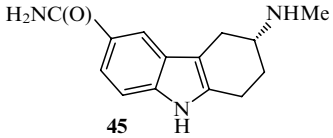
42



43



44

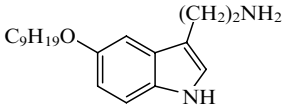


45

X = $(CH_2)_2NMe_2$.

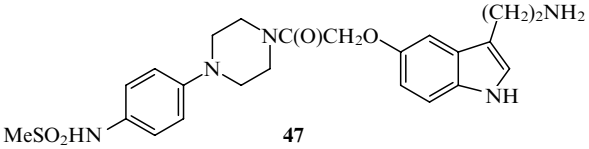
Compounds **42**–**45** possess high affinities for 5-HT_{1D} receptors. However, they are non-selective and only 1.5–3-fold less active with respect to 5-HT_{1B} receptors. Comparison of the structures obtained suggest that the basic amine, the indole fragment and the substituent in position 5 involved in the formation of a hydrogen bond as an acceptor or a donor are the key groups needed for their efficient binding to the receptor. QSAR studies aimed at improving the activities and selectivities of serotonin and tryptamine derivatives towards 5-HT_{1D} receptors included variations of substituents at the C(5) atom.

It was found[43] that in the case of alkoxy substituents the optimum length of the alkyl chain needed for the binding to 5-$HT_{1B/1D}$ receptors is 8 or 9 carbon atoms; with shorter chains, the selectivity is lost, while with longer chains, the affinity is decreased. Thus 5-nonyloxytryptamine (**46**) represents a high-affinity agonist, which is more selective towards 5-HT_{1B} than towards 5-HT_{1D} receptors and is practically inactive towards 5-HT_{1A} receptors. It should be noted, however, that no compounds capable of distinguishing 5-HT_{1B} and 5-HT_{1D} receptors with a high degree of selectivity could thus far be obtained by changing the lengths and degree of ramification of the alkoxy substituents.[43]

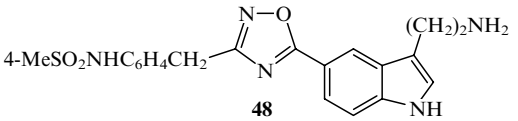


46

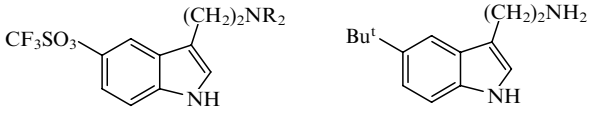
The variations in the substituents in position 5 revealed that the latter can be rather bulky as in the case of compounds **47**,[88,107] **48**[108–110] and **49**,[111–112] which are more selective towards 5-HT_{1D} than towards 5-HT_{1B} receptors. This is suggests the existence of a deep pocket in the binding site of 5-$HT_{1D/1B}$ receptor proteins adjacent to C(5) of the serotonin molecule. According to some data, it is in the size of this domain that 5-$HT_{1D/1B}$ receptors differ from the 5-HT_{1A} receptor,[113] although some of compounds mentioned, as expected, manifest low affinities for the latter.



47



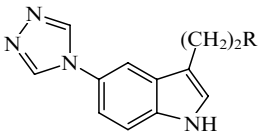
It is noteworthy that the introduction of a triflate group (compounds **50**), which is bioisosteric to the carboxy or the methoxy group,[114] increases the selectivity towards 5-HT_{1D} receptors 10–15-fold in comparison with 5-HT_{1B} receptors.[115]



R = Me, Et.

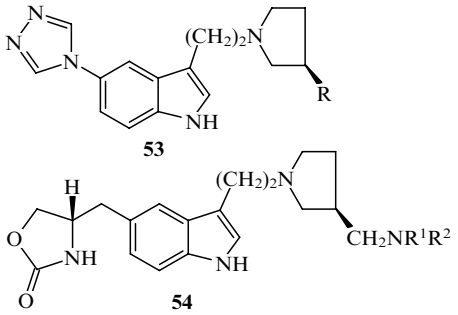
It is of note that until recently the ability of the substituent in position 5 to be involved in the formation of a hydrogen bond was thought to be a necessary prerequisite for high affinity, since virtually all presently known 5-HT_{1D} receptor agonists have at least one heteroatom (N, O or S) in this position. However, the recently discovered 5-alkyltryptamine analogues devoid of heteroatoms in position 5 possess high affinities for 5-HT_{1D} receptors. This affinity increases as the size of the lipophilic group increases, reaching a maximum in the *tert*-butyl derivative **51**.[85] The resulting compounds are not highly selective, *viz*., their maximum selectivities towards 5-HT_{1D} receptors are only four times greater than towards 5-HT_{1B} receptors. The fact that the formation of a hydrogen bond involving the substituent at the C(5) atom of serotonin is not critical for the manifestation of its high affinity for 5-HT_{1D} receptors points to the hydrophobicity of the spacious pocket in the vicinity of C(5). This finding allows one to expand significantly the range of possible substituents at this atom.

The variations in substituents in position 3 are much less documented. However, there are recent data to show that the selectivity towards 5-HT_{1B} and 5-HT_{1D} receptors can be enhanced by introduction of structurally more complex substituents in this position. Thus it was shown that the tryptamine analogue **52a** containing the pyrrolidine ring possesses an order of magnitude higher affinity for 5-HT_{1D} receptors than for 5-HT_{1B} receptors. On the other hand, the analogous *N*,*N*-dimethylamino derivative **52b** is non-selective.[116, 117]

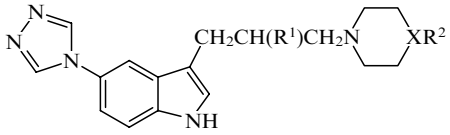


R =  (**a**), NMe_2 (**b**).

It is thought that the region in the receptor which binds the fragment at the C(3) atom contains an aspartic acid residue.[117] The steric requirements for the binding to this domain in both types of receptors can be determined by modifying this fragment.[117] Studies of series of compounds **53** and **54** revealed that 5-HT_{1D} receptors can bind bulky groups. It was therefore assumed that this domain contains a spacious binding pocket. At the same time, compounds containing smaller substituents bind more effectively to 5-HT_{1B} receptors. For example, compounds **53** or **54** which are full agonists of 5-HT_{1D} receptors manifest 100- and 140-fold higher selectivities towards them. Hence, the selectivity towards each of these two receptor subtypes can be provided by a correct choice of a substituent in the structural domain responsible for the binding to the aspartate residue. It is of note that the presence of a bulky substituent at C(3) can in principle increase the affinities for 5-HT_{1A} receptors (see above). However, the above-mentioned series includes compounds (*e.g*., **54**, $R^1 = CH_2Ph$, $R^2 = H$) which are selective with respect to both 5-HT_{1B} and 5-HT_{1A} receptors.[117]

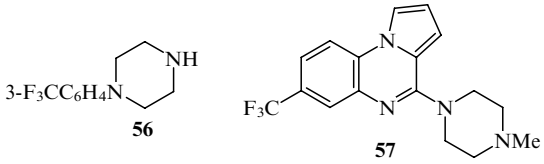


Many (3-piperazinopropyl)indoles, *e.g*., compound **55a**, also manifest high (up to 200-fold) selectivities towards 5-HT_{1D} *vs*. 5-HT_{1B} receptors.[118] The selectivity increases 300- to 500-fold upon introduction of the hydroxy group or the fluorine atom into the propyl chain (compound **55b**).[119] The distal nitrogen atom of piperazine does not seem to be essential for the binding to this receptor, since the corresponding piperidine analogues, *e.g*., compound **55c**, also manifest high affinities.[120] The distal nitrogen atom can also be displaced into the exocyclic position without any loss of its affinity,[120] as in the case of the 4-aminopiperidine derivative **55d**.[116] The selectivities of the ligands **55a**–**d** towards 5-HT_{1D} receptors suggest that these are less sensitive to changes in the position of the nitrogen atom than 5-HT_{1B} receptors despite close homology of these two proteins. This circumstance can further be used in the structural design.

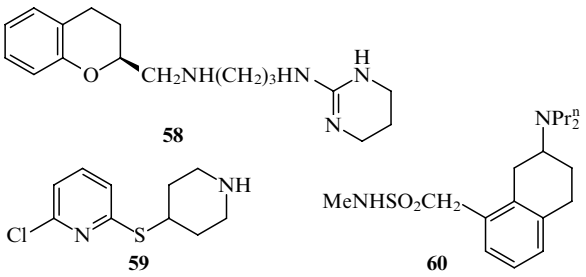


R^1 = H, X = N, R^2 = $(CH_2)_2C_6H_4F$-3 (**a**); R^1 = OH, F; X = N, R^2 = Ph, C_6H_4F-3 (**b**); R^1 = H, X = CH, R^2 = Bn (**c**); R^1 = H, X = CH, R^2 = N(Me)Bn (**d**).

Among other full and partial agonists of 5-HT_{1B} and 5-HT_{1D} receptors structurally different from tryptamine, special mention should be made of arylpiperazines, *e.g*., compounds **56**[121, 122] and **57**,[121, 123] which display very low selectivities towards 5-HT_{1B} subtype receptors. As expected, these compounds possess high

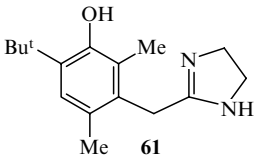


affinities with respect to the 5-HT_{1A} receptor. More recently synthesised compounds of this series include alniditane (**58**)[124] as well as compounds **59**[125] and **60**.[126]



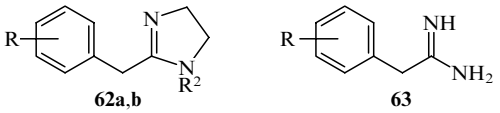
The adrenoceptor agonist oxymethazoline (**61**) manifests agonistic activity towards both 5-HT_{1B} and 5-HT_{1D} receptors

and is among the most promising lead compounds ‡ for the design of 5-$HT_{1D/1B}$ agonists.[127]



61

However, an analysis of structural requirements for the binding of benzylimidazolines of the general formula **62** to these receptors revealed that far from all substituents in the aromatic ring of compound **61** are necessary for the manifestation of high affinity. Thus the hydroxy group in position 3 of compounds **62** can be removed without any noticeable decrease in their affinities for 5-HT_{1D} subtype receptors. However, such modification decreases 50-fold the affinity for 5-HT_{1B} subtype receptors. Moreover, the contribution of the bulky substituent at the C(4) atom to the binding to 5-HT_{1D} receptors is greater. Therefore, some structural modifications of compounds **62** (*cf.*, *e.g.*, compounds **62a**,**b**) lead to a 100-fold increase in the selectivities towards 5-HT_{1D} receptors. Compounds **62a**,**b** are agonists, their affinities for adrenergic receptors are lower than that of compound **61**. It should be noted that the transition to amidines **63** decreases both their affinities and selectivities towards 5-HT_{1D} subtype receptors.[113]

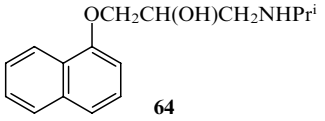


62a,**b** **63**

R^1 = 4-Bu^t (**a**), 6-Me (**b**).

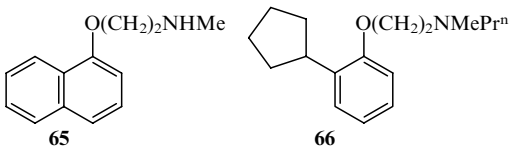
Thus, the overwhelming majority of agonists of 5-HT_{1B} and 5-HT_{1D} receptors represent tryptophan analogues; therefore, these types of new lead compounds could be useful in the search for the next generation of agonists able to distinguish between these two subtypes of receptors.

The main efforts of chemists engaged in the search for antagonists are directed at the synthesis of compounds more selective towards 5-$HT_{1B/1D}$ subtype receptors in comparison with other serotonin receptors. As mentioned above, some aryloxyalkylamines, such as the well-known β-adrenoceptor antagonist propranolol (**64**), are characterised also by low affinities for 5-HT_{1A} and 5-HT_{1B} receptors and usually represent antagonists or very weak partial agonists of these receptors.

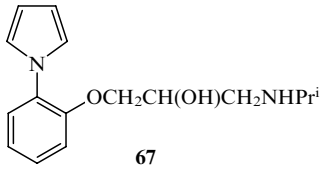


64

Studies of binding of their analogues to 5-$HT_{1D/1B}$ receptors [128] revealed that the presence of the hydroxy group in the side chain is not necessary, whereas the substitution of the CH_2 group for the oxygen atom in the ether group results in the loss of affinity. The affinity for 5-HT_{1B} subtype receptors can be increased by reducing the length of the side chain to two CH_2 groups or by using a primary or a secondary amine with smaller alkyl groups, *e.g.*, compound **65**. Replacement of the naphthalene fragment by a substituted phenyl ring is also possible, but in this case the affinity will decrease by an order of magnitude as in compounds **66** and **67**.[129] In our opinion, the structures of these lead compounds are not very suitable for the design of antagonists, since the compounds obtained interact with adrenoceptors, but are virtually non-selective towards 5-HT_{1B} subtype receptors in comparison with 5-HT_{1D} subtype receptors. Moreover, some high-affinity compounds, *e.g.*, compound **65**, lose their antagonistic properties and behave as agonists towards the corresponding receptors.

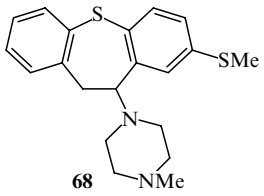


65 **66**



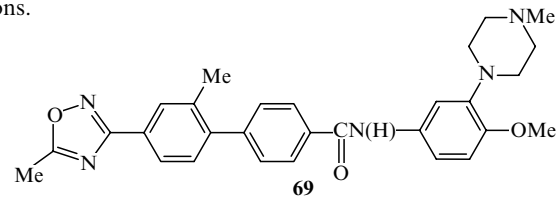
67

It is of note that until recently virtually no selective 5-$HT_{1B/1D}$ antagonists existed and studies into receptor binding were carried out with other compounds, *e.g.*, methiothepin (**68**), which interacts with other serotonin, dopaminergic and adrenergic receptors.



68

Benzanilide (**69**) is the first example of a selective 5-$HT_{1D/1B}$ antagonist, although it does not discriminate between the subtypes. This finding has played a crucial role in the characterisation of 5-$HT_{1D/1B}$ receptors. However, subsequent studies using cloned human receptors revealed that compound **69** is not a full antagonist, it rather acts as a partial agonist.[130,131] Therefore, the construction of selective antagonists required further investigations.

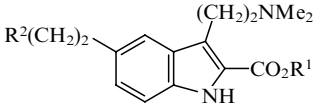


69

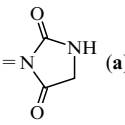
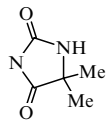
Sumatriptan (**40**), zolmitriptan (**44**) and other tryptamine analogues were used for the design of 5-$HT_{1B/1D}$ antagonists based on the corresponding selective agonists. QSAR studies of the factors affecting both the activity and selectivity as well as simulation using pharmacophore models of 5-$HT_{1D/1B}$ receptors [132] revealed that certain geometrical and conformational restrictions can result in the displacement of the indole nucleus from the site (which is arbitrarily termed as the aromatic binding site) specific, *e.g.*, for zolmitriptan (**44**). It was demonstrated that the retention of high affinity can be accompanied by a significant decrease in intrinsic activity. Later, it was shown that the antagonistic effect is manifested if only the pyrrole moiety of tryptamine (rather than the whole indole nucleus) is displaced. In other words, it was necessary to modify the structure of the agonist in such a fashion that the interaction of the pyrrole double bond with the π-electrons of the receptor in their specific domain would be blocked and the agonistic response would correspondingly be prevented. To achieve this, it was proposed to design an electron-deficient aromatic system by introducing electron-withdrawing substituents into position 2 of zolmitriptan (**44**). The presence of a substituent in position 2 not only makes the indole system electron-deficient, but also restricts the conformational mobility of the side chain. The alkyl chain in position 5 was also varied in order to confer greater mobility on this substituent.[132]

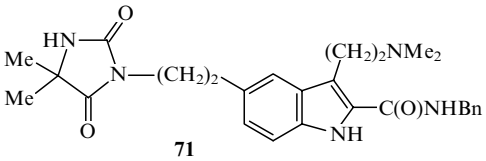
‡ The 'lead compound' is one of the basic concepts in medicinal chemistry which denotes a structural prototype for the future drug. The lead compound manifests definite physiological activity and its structure serves as the basis for the design of a new drug.[2]

This approach was successful, *viz*., the resulting tryptamine derivatives of the type **70** contain heterocyclic substituents comprising the carbonyl group R^2 (this group is critical for selectivity as compared with that of 5-HT_{2A} receptors)[133] and represent highly active full antagonists of 5-HT_{1B} receptors. These are also selective towards other serotonin receptors including sometimes compounds **70a**,**b** 5-HT_{1D} subtype receptors. Substitution of the amide group for the ester group in position 2 afforded less active and less selective antagonists; high affinities and selectivities were restored only after the introduction of bulky substituents to the nitrogen atom, *e.g*., compound **71**. It is believed[134] that this substituent can occupy the aromatic binding site in the receptor by pushing the indole nucleus out from this site.



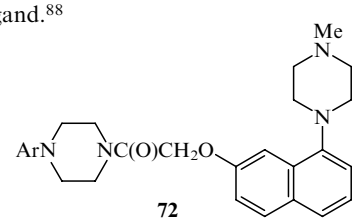
70a,**b**

R^1 = Et: R^2 =  (**a**),  (**b**).



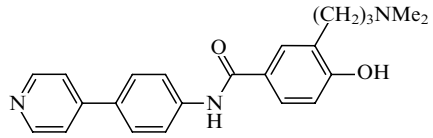
71

Yet another example is the design of 5-$HT_{1D/1B}$ receptor antagonists from the corresponding agonists.[88] Assuming that the tryptamine fragment in compound **47** is responsible for the intrinsic activity (by analogy with serotonin), while the arylpiperazine moiety is mainly responsible for the binding to the receptor, it was suggested to replace the tryptamine fragment in compound **47** by a non-selective ligand manifesting antagonistic activity towards 5-$HT_{1D/1B}$ receptors (in this particular case, the 1-naphthylpiperazine fragment) which would result in their selective antagonists. This was the case, *e.g*., for compounds **72**. Studies of these compounds showed that they are indeed selective towards 5-$HT_{1D/1B}$ receptors and many of them are full antagonists. However, the antagonistic activity depends on the aryl substituent of the arylpiperazine side chain and is maximum for Ar = 2-MeC_6H_4 or 2,3-$Me_2C_6H_3$. This suggests that the binding of this fragment also contributes to the intrinsic activity of the ligand.[88]

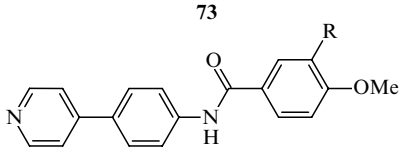


72

Recently, a series of antagonists based on the above-mentioned partial agonist **69**, which was successfully used as the lead compound in the design of compounds selectively blocking 5-HT_{1D} and 5-HT_{1B} subtype receptors, have been synthesised. These include primarily benzamide (**73**),[112,135] the structural analogue of compound **69**, which is a strong antagonist much more selective towards 5-HT_{1B} subtype receptors. Variations in the substituent R of its methylated analogues **74a**–**d** revealed that all these compounds bind to the receptor to approximately the same degree and in the same manner (like compound **73**) and manifest low affinities for 5-HT_{1A} and 5-HT_{1D} subtype receptors; their agonistic activities depend critically on the conformation of their side chains. Compound **74a** and the (*Z*)-alkenyl derivative **74b** act as strong antagonists resembling compound **73**, whereas the alkynyl derivative **74d** and the (*E*)-alkenyl derivative **74c** manifest pronounced agonistic activities.[89]



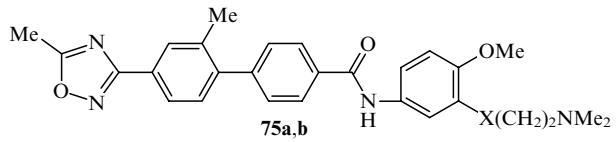
73



74a–**d**

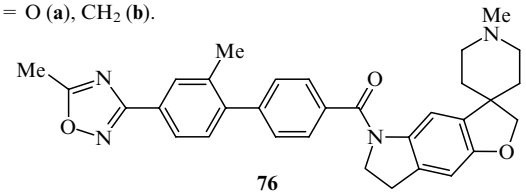
R = $(CH_2)_3NMe_2$ (**a**), (*Z*)-CH=$CHCH_2NMe_2$ (**b**), (*E*)-CH=$CHCH_2NMe_2$ (**c**), C≡CCH_2NMe_2 (**d**).

It should be noted that substitution of the flexible aminoalkyl side chain for the piperazine ring in compound **69** (compounds **75a**,**b**) decreases their intrinsic activities with respect to 5-HT_{1B} receptors.[89,136] These data demonstrate the significant role of the spatial orientation of the aminoalkyl fragment in the design of 5-HT_{1B} antagonists, although it is still impossible to describe this notion in terms of conformation, since some conformationally rigid analogues of compounds **69** can also act as full antagonists. Thus compound **76** is a selective 5-HT_{1B} antagonist; its design was based on the use of a computer model of 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A} and 5-HT_{2C} receptors.[86,137]



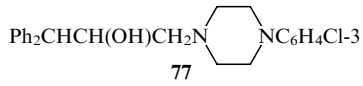
75a,**b**

X = O (**a**), CH_2 (**b**).



76

In conclusion, we shall refer to the structure of compound **77**, the recently discovered selective antagonist of 5-HT_{1D} receptors.[138] This compound possesses 60-fold higher affinity with respect to 5-HT_{1D} subtype receptors than to 5-HT_{1B} subtype receptors and is virtually inactive with respect to other serotonin receptors.



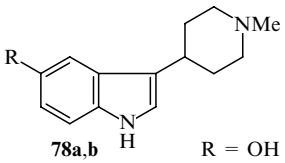
77

It is necessary to stress again that only a few compounds are known which interact with each of the above-mentioned subtypes with high selectivities, which is due to the structural similarity of 5-HT_{1B} and 5-HT_{1D} receptors. However, the present-day structural requirements for the design of such ligands are becoming more and more understandable and their number will be increasing.

V. Ligands of serotonin receptors of other 5-HT_1 subtypes

The 5-HT_{1E} and 5-HT_{1F} subtype receptors have been studied to a much lesser degree than those of other 5-HT_1 subtypes. It is known that they are present in large concentrations in brain and display high structural similarity as regards their amino acid sequences. The non-selective 5-HT_1 agonist, *viz*., the amine **2**, manifests *ca*. 1000-fold lower affinity for 5-HT_{1E} subtype recep-

tors than for the 5-HT_{1B} subtype receptors.[139,140] This is explained by the presence of the lysine–glutamic acid pair in the binding site of the 5-HT_{1E} receptor protein instead of the less polar isoleucine–serine (5-HT_{1B}) pair or the valine–serine pair (5-HT_{1D}). Presumably, this results in the formation of a salt bridge between lysine and the aspartate residue which plays the key role in the ligand binding. Compound **78a** is the agonist of 5-$HT_{1E/1F}$ receptors but does not discriminate between them and possesses low affinity. No selective or highly active ligands of 5-HT_{1E} receptors have been identified so far and the function of these receptors still remains to be established.



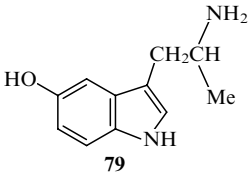
78a,b R = OH (**a**), 4-$FC_6H_4CONH_2$ (**b**).

Recently, studies of the functions and ligands for 5-HT_{1F} receptors have attracted the attention of many research groups due to the detection of high affinity of sumatriptan (**40**) for 5-HT_{1F} receptors (which was about an order of magnitude lower than for 5-HT_{1D} receptors). It was assumed that some (probably all) effects of sumatriptan in the alleviation of migraine symptoms are due to its binding to these receptors. The recently discovered indole derivative **78b** is their first and the only selective agonist;[141–143] no antagonists of 5-HT_{1F} receptors have been identified yet.

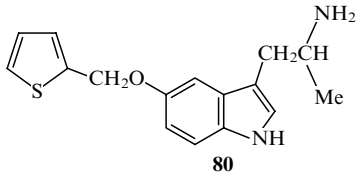
VI. Ligands of serotonin 5-HT_2 subtype receptors

The family of serotonin 5-HT_2 receptors is classified into three subtypes, *viz*., 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. The first two subtypes occur widely in peripheral tissues where they regulate muscle contraction; therefore, their ligands are used in the therapy of cardiovascular diseases. As for 5-HT_{2C} subtype receptors, they are localised exclusively in the central nervous system; their ligands produce psychotropic effects, *e.g*., their antagonists are used as anxiolytic and sedative drugs.

A series of 5-HT_2 receptor agonists were obtained by the simplest modifications of the serotonin structure. Thus α-methyl-5-hydroxytryptamine (**79**)[48,144,145] is a full high-affinity agonist of 5-HT_{2B} subtype receptors which manifests 10- and 100-fold lower affinities for 5-HT_{2C} and 5-HT_{2A} receptors, respectively. Similar selectivity profiles hold following the introduction of the thienylmethoxy substituent into position 5 (compound **80**).[146–148]

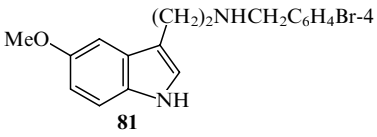


79



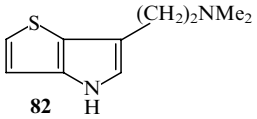
80

5-Methoxytryptamine also manifests higher affinity for 5-HT_{2B} receptors than for 5-HT_{2A} and 5-HT_{2C} receptors (25- and 400-fold, respectively), although it is non-selective towards other serotonin receptors. The introduction of a bulky bromobenzyl substituent into the amino group of 5-methoxytryptamine results in the ligand **81** which possesses high affinity and selectivity with respect to 5-HT_{2A} receptors,[149] but manifests the properties of a partial agonist.

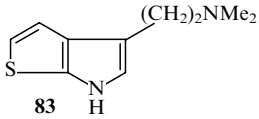


81

Bioisosteric substitution of thienepyrrole fragments for the tryptamine indole nucleus was undertaken in an attempt to design 5-HT_2 agonists. However, the resulting compounds **82** and **83** displayed somewhat lower activities towards 5-HT_2 receptors than the corresponding indole analogues (compound **82** is nearly 4 times more selective with respect to 5-HT_{2C} receptors than to 5-HT_{2A} and 5-HT_{2B} receptors). Moreover, this transformation increased significantly the affinity for 5-HT_{1A} receptors.[150] On the whole, these data corroborate the fact that different subtypes of serotonin receptors are highly sensitive to minor changes in the electronic characteristics of the aromatic systems.

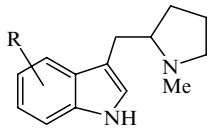


82

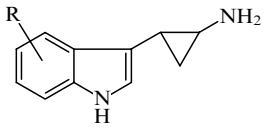


83

Studies of restriction of conformational mobility in the aminoethyl side chain of serotonin have led to the *N*-methylpyrrolidine derivative **84** (R = 5-OMe) and its analogues which manifested very high agonistic activities, being more selective towards 5-HT_{2A} subtype receptors. The activities of these compounds strongly depend on their stereochemistry, *viz*., (*R*)-enantiomers manifest *ca*. 30-fold higher affinities than (*S*)-enantiomers.[151,152]



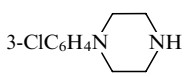
84



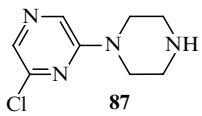
85

It is of note that conformationally rigid serotonin analogues containing cyclopropane fragments (**85**) in their side chains are somewhat more selective towards 5-HT_{2C} receptors, the fluoro derivative (**85**, R = 5-F) being the most active compound.[153,154] Noteworthy, the electron-withdrawing fluorine atom in the benzene ring not only decreases the affinity of this compound for 5-HT_{1A} receptors (see above) but also seems to be responsible for higher selectivity towards 5-HT_{2C} receptors in comparison with 5-HT_{2A} receptors. A similar dependence was demonstrated for other fluorotryptamines.[155]

The agonists manifesting higher selectivities towards 5-HT_{2C} subtype receptors were identified among halogeno derivatives of other structural classes, *e.g*., of piperazine. The diamine **86**, a partial agonist of 5-HT_{2C} receptors, which possesses 10-fold lesser affinity for 5-HT_{2A} receptors, is the most popular among them.[48,156–159] Structural variations in its molecule revealed that substitution of the pyrazine ring for the benzene ring increased significantly its selectivity and intrinsic activity; thus, the affinity of compound **87**,[160,161] a full agonist of 5-HT_{2C} subtype receptors, is 25 times higher than for 5-HT_{2A} subtype receptors.

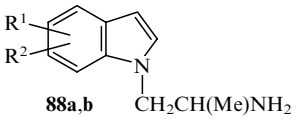


86

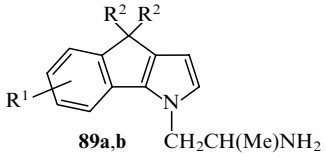


87

Agonists of 5-HT_{2C} receptors have recently been identified among indole derivatives manifesting high selectivities towards 5-HT_{2A} subtype receptors. Earlier, it was found[162] that isotryptamines (**88**) with the 2-aminopropyl side chain attached to the nitrogen atom are bioisosteric to the corresponding tryptamines as regards their binding to serotonin receptors. Affinity studies of a series of isotryptamines **88** and their analogues, *viz*., indenopyrroles **89**, revealed[155] that many of them, *e.g*., compounds **88a,b** and **89a,b**, are high-affinity full agonists of 5-HT_{2C} receptors which are 20- to 100-fold more selective towards 5-HT_{2A} receptors. It is noteworthy that the selectivities of *S*-isomers are higher than those of the corresponding *R*-isomers.[155] It should be noted that tryptamine structural isomers of some of these derivatives manifest nearly identical affinities but much lower selectivities with respect to 5-HT_{2C} receptors.



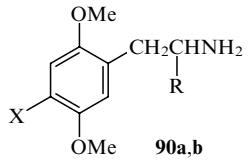
88a,**b**



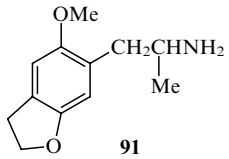
89a,**b**

R^1 = 5-F: R^2 = H (**a**), 6-Cl (**b**). R^1 = 7-OMe: R^2 = H (**a**), Me (**b**).

Phenylisopropylamines **90a** and phenylethylamines **90b** [163–165] which constitute a large group of high-affinity 5-$HT_{2A/2C}$ receptors have been the subjects of in-depth studies into the structure–activity relationships aimed at establishing the topologies of the binding sites of this particular subtype of serotonin receptors (see, *e.g.*, Refs 166–169). These studies demonstrated that high affinities for 5-$HT_{2A/2C}$ receptors require that certain structural requirements are fulfilled, such as the presence of a two-carbon chain between the amino group and the phenyl ring, the presence of methoxy groups in positions 2 and 5 of the aromatic ring and the presence of the hydrophobic substituent X in position 4. Assuming that the methoxy groups in compounds **90a**,**b** bind to two serine residues in the receptor protein, Nichols *et al.*[166,170] synthesised the cyclic derivatives **91**–**94** in order to study the geometry of this binding. It was found that compound **91** having a '*syn*-conformation' of the tetrahydrofuran ring relative to the aminoalkyl chain is practically inactive towards 5-$HT_{2A/2C}$ receptors, whereas the activity of the analogous compound **92** with the '*anti*-orientation' of these fragments is as active as that of the acyclic analogue **90a**.

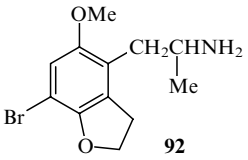


90a,**b**



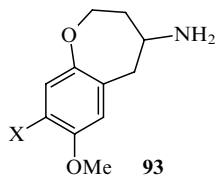
91

R = Me (**a**), H (**b**);
X = Alk, Hal, AlkS, F_3C *etc*.

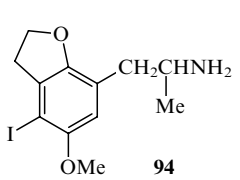


92

Substitution of the oxygen-containing heterocycle for the methoxy group in position 2 produces an opposite effect, *viz*., the '*anti*-analogues' of the type **93** compounds are inactive, whereas compound **94** is a potent agonist. As expected, structurally rigid compounds, *e.g*., compound **95** with two dihydrofuran fragments mimicking effectively active binding conformations of the methoxy groups in compounds **90a**,**b**, appeared to be high-affinity agonists of 5-$HT_{2A/2C}$ receptors. In this case, benzodihydrofuran-containing compounds represent effective conformationally restricted bioisosteres of aromatic methoxy groups.[169]

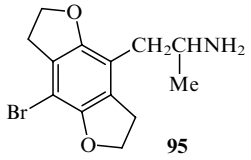


93

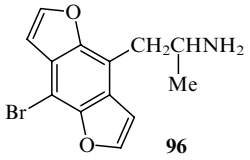


94

Substitution of furan fragments (see, *e.g*., compound **96**)[169] for dihydrofuran fragments made it possible to enhance also the agonistic activity with respect to 5-$HT_{2A/2C}$ receptors by an order of magnitude. Compounds of the type **96** manifest the highest affinities among other known ligands. Unfortunately, none of these compounds discriminate between 5-HT_{2A} and 5-HT_{2C} subtype receptors; the affinities of these compounds for 5-HT_{2B} receptors are severalfold lower because of similarities of the binding domains of the corresponding receptors.



95

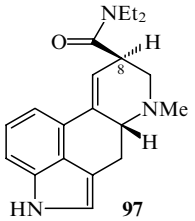


96

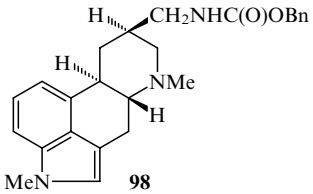
The attempts to lock the geometry of the aminopropyl side chain in compounds **90a**,**b** showed that its incorporation into the aminotetralin or the aminoindan rings results in the loss of activity towards 5-$HT_{2A/2C}$ receptors, whereas its introduction into the side chain of the cyclopropane ring, as in *trans*-2,5-dimethoxy-4-methylphenylcyclopropylamine, enhances the activity.[154,171]

As can be seen from the above survey, the structural classes of 5-HT_2 agonists are not very diverse and their design is poorly documented in the literature. This can probably be attributed to the strong hallucinogenic effect of these agonists,[172] which makes them unsuitable as therapeutics. Antagonists of 5-HT_2 subtype receptors can be used as drugs in treatment of ischemia and other vascular disorders.[173]

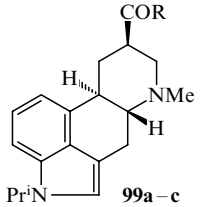
So far, several structural classes of 5-HT_2 antagonists have been identified. The most prominent position is occupied by ergolines and related compounds which manifest the properties of partial agonists or antagonists with respect to the corresponding receptors [174] [the former include the classical hallucinogenic agent, *viz*., lysergic acid diethylamide (LSD, **97**)].[174–176] Numerous antagonists of 5-HT_2 receptors have been synthesised based on ergolines and related compounds; the main strategy consisted in the introduction of various substituents [most frequently, at C(8)] assuming that this might enhance the antagonistic activity due to their additional binding to the receptor. This resulted in potent 5-HT_2 antagonists, such as compounds **98**,[177,178] **99a**–**c**, *etc*.[176,179–182]



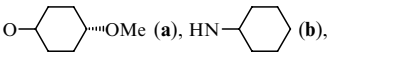
97



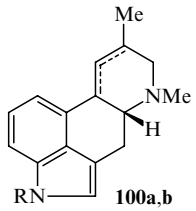
98



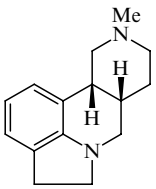
99a–**c**

R =  (**a**),  (**b**),  (**c**).

Subsequent computer simulation of the binding of ergolines to 5-HT_2 receptors [174] showed that the presence of an aromatic ring in the vicinity of phenylalanine-340 of the receptor is an essential structural feature which ensures high-affinity binding owing to π- or hydrophobic interactions. This prompted synthesis of a series of ergolines and related compounds of the type **100a**,**b** devoid of the acyl fragment at C(8). Indeed, the resulting compounds manifested high affinities for 5-HT_2 antagonists and high selectivities as regards other subtypes of serotonin receptors. Thus, the ergoline structure of 5-HT_2 antagonists can in principle be reduced to a simple tetracyclic indoloquinoline system without any detriment to the affinity and antagonistic activity.[182]



100a,b



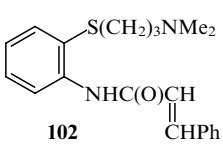
101

R = H (**a**), Pr^i (**b**).

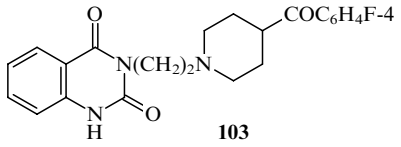
Other structural modifications of ergoline analogues included variations of substituents at the nitrogen atom of the indole moiety. It was shown that the introduction of small alkyl substituents, including branched ones, into this position is possible.§ In some cases, the antagonistic activity is enhanced due to the presence of a double bond in positions 9 and 10 present also in lysergic acid.[182] The literature data on the role of substituents in position 4 of the cyclohexane ring are controversial: in some cases, the methoxy group at C(4) of the cyclohexane ring significantly enhances the antagonistic activity,[187] but has no effect in other cases.[182]

The majority of ergoline derivatives are active with respect to serotonin 5-HT_1, adrenergic and other receptors, but are non-selective towards 5-HT_2 subtype receptors. However, recent systematic screening of ergoline-related compounds disclosed the naphthyridine (**101**),[188–190] a highly selective antagonist of 5-$HT_{2B/2C}$ receptors which does not interact with 5-HT_1 receptors. This compound will probably serve as a prototype for the design of novel selective ligands.

Distant analogues of the long-known non-selective ligand **102**,[191,192] such as ketanserin (**103**)[193,194] and its derivatives which manifest certain selectivities towards 5-HT_{2A} receptors, constitute another large structural class of 5-HT_2 antagonists.[191,192] Ketanserin (**103**) is used in the clinical practice as an antihypertensive drug.

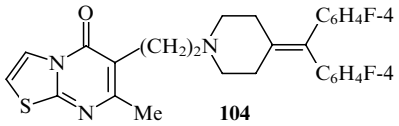


102

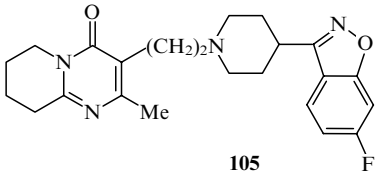


103

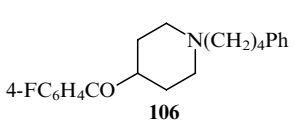
Studies of the structure–activity relationships in ketanserin derivatives have revealed the following features. The carbonyl group in position 2 of quinazoline can be replaced by the thiocarbonyl group, and a phenolic hydroxy group can be introduced into position 6. The two-carbon side chain can be replaced by the $(CH_2)_4$, but not by the $(CH_2)_3$ chain, which decreases the activity 100-fold.[195] Piperidine ring-opening also decreases the affinity. Although the 4-fluorobenzoyl group is present in the majority of ketanserin analogues, it can be replaced by the benzylidene [as in the case of ritanserin (**104**)] or a similar group. However, the benzylic carbon atom should be sp^2-hybridised [*cf.* the carbonyl group in ketanserin (**103**) or the double bond in ritanserin (**104**) and risperidone (**105**)]. Although a certain role in the affinity for 5-HT_{2A} receptors is played by the quinazoline-2,4-dione fragment,[195] this may be replaced by the pyridopyrimidine or thiazolopyrimidine fragment[196] or structurally simplified, as in compound **106**.[197] The latter modification is more appropriate because it affords 120-fold enhancement of selectivity towards 5-HT_{1C} receptors for which ketanserin manifests high affinity. It is of note that some ketone **106** analogues having a shortened bridging chain, *e.g.*, compound **107**,[198] are also potent selective antagonists of 5-HT_2 receptors. However, none of the above-mentioned compounds distinguish among different subtypes of 5-HT_2 receptors.



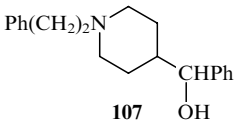
104



105

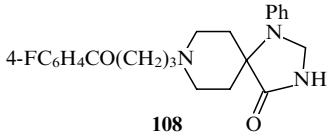


106



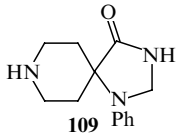
107

Variations in the quinazolidinedione fragment of ketanserin analogues have led to a large family of 5-HT_2 antagonists, *viz.*, triazaspirodecanones; their classical representative is spiperone (**108**).[197,199] This compound manifests rather high affinity for dopaminergic and 5-HT_{1A} receptors, and is also one of the few ligands binding more selectively (*ca.* 1000-fold) to 5-HT_{2A} subtype receptors than to 5-HT_{2C} subtype receptors.

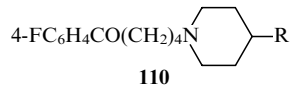


108

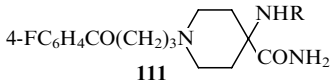
Molecular 'dissection' of this compound into its two basic fragments revealed that 1,3,8-triazaspirodecanone (**109**) is absolutely inactive towards 5-HT_1 and 5-HT_2 receptors, while the piperidine derivative **110** (R = H) manifests moderate affinity for 5-HT_{2A} receptors, which is 150-fold lower than that of spiperone (**108**), but is inactive towards 5-HT_1 and 5-HT_{2C} receptors. The introduction of the anilino group into position 4 of piperidine (**110**, R = NHPh) increases its affinity for 5-HT_{2A} receptors; however, the resulting compound manifests 150-fold lower selectivity towards 5-HT_{2C} receptors than spiperone (**108**).[200] These findings are suggestive of the important role of the imidazolidinone fragment in the reactivity and selectivity of spiperone (**108**). This conclusion is corroborated by the fact that the spiperone derivatives **111** containing geminal amino groups and an amide group instead of an imidazolidine ring are less selective towards 5-HT_{2A} receptors. Moreover, the affinities of some spiperone analogues decrease dramatically after the removal of the lactam carbonyl group, which points to its significance for the binding to the receptor.



109



110

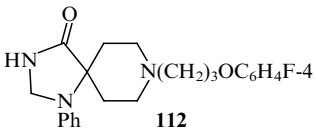


111

Other modifications of the spiperone (**108**) structure showed that substitution of the cyclohexyl fragment for the phenyl substituent at the N(1) atom increases its affinity twofold, whereas the substitution of alkyl groups decreases it. However, the

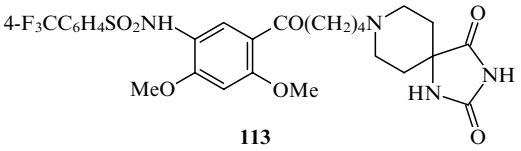
§ It should be noted that ergolines non-substituted at N(1) manifest higher affinities for human 5-HT_2 receptors than for the corresponding rat receptors,[183,184] although the only structural difference between these receptors is associated with the amino acid 242 residue (serine in humans and alanine in rats).[185,186] Presumably, serine and the NH group of indole in non-substituted ergolines form a hydrogen bond, whereas hydrophobic interactions occur between alanine and the alkyl group of the substituted ergolines.

selectivity towards 5-HT_{2A} subtype receptors increases in comparison with 5-HT_{2C}, 5-HT_{1A} and dopaminergic receptors.[201] Contrariwise, analogous substituents at the N(3) atom significantly decrease the selectivity.[201,202] It was shown also that the carbonyl group in the spiperone (**108**) molecule may be replaced by the ether group (compound **112**) with the preservation of activity and a small increase in the selectivity towards 5-HT_{2A} receptors in comparison with 5-HT_{2C} receptors. Such analogues can further be used as new structural prototypes in the search for affinity ligands to 5-HT_{2A} receptors.[200,201]



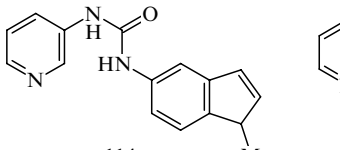
112

The sulfonylamide derivative **113** assayed recently among spiperone analogues (**108**) is attractive, because unlike compound **108** it manifested antagonistic activity and 100-fold higher selectivity towards 5-HT_{2C} receptors in comparison with 5-HT_{2A} and 5-HT_{2B} receptors. Moreover, this compound virtually did not bind to other serotonin receptors.[203,204]

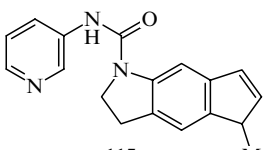


113

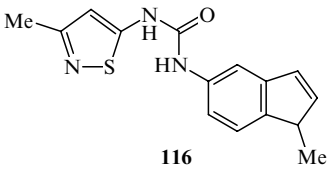
Progress has also been achieved in the design of selective antagonists of 5-HT_{2B} receptors. It was found that the indole derivative **114** manifests 150-fold higher affinity for 5-HT_{2B} receptors than for 5-HT_{2A} receptors, but is non- selective with respect to 5-HT_{2C} receptors.[205] The selectivity to the latter was virtually unenhanced upon partial restriction of conformational mobility of the linking chain (compound **115**); however, this approach makes it possible to increase the affinity for 5-HT_{2B} receptors and to decrease the affinity for 5-HT_{2A} receptors. A highly selective antagonist of 5-HT_{2B} receptors was obtained by substitution of the methylisothiazole fragment for the pyrimidine fragment (**114** → **116**), but the activity of the resulting compound is not very high.[206,207]



114

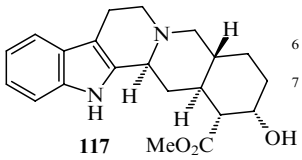


115

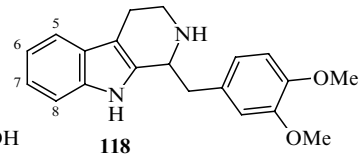


116

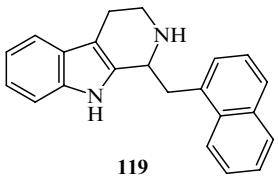
More active and selective (with respect to 5-HT_{2B} receptors) compounds were prepared based on the alkaloid yohimbine (**117**), which exhibits low affinity for this type of receptor itself. Elucidation of the key elements essential for the antagonistic activity of this alkaloid towards 5-HT_{2B} receptors was carried out by sequential simplification of its structure, resulting in high-affinity derivatives **118** and **119**. The affinities of these compounds and some of their analogues for 5-HT_{2B} receptors were 100–200-fold higher than for 5-HT_{2A} and 5-HT_{2C} receptors; these were practically inactive with respect to adrenergic receptors (in contrast to the original alkaloid **117**).[173] Structure–activity studies revealed an unusual and interesting fact, namely, it was found that the introduction of the methoxy substituent into position C(6) of compound **118** [which corresponds to position C(5) of the serotonin molecule] decreases the affinity, whereas the introduction of two methyl substituents into positions C(7) and C(8) increases it to a unique extent.[173] This suggests that the direct structural analogies of serotonin and the corresponding fragments of compounds **118** and **119** do not reflect their actual orientation during their binding to the receptor and demands further investigation.



117



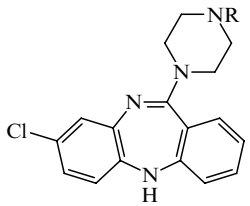
118



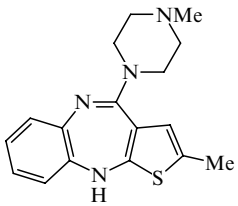
119

A new structural class of 5-HT_2 antagonists based on 5-HT_{2A} agonists of the type **90a** has recently been found. Compound **90a** (X = $CH_2CH_2CH_2Ph$) containing a phenylpropyl substituent in position 4 has become the first representative of this class. Structure–activity studies of some of its analogues established a surprising fact, *viz*., that the presence of methoxy groups in the ring is not a necessary prerequisite for their high affinities. However, this feature holds only for antagonists (for agonists, see above). This indicates that the phenylpropyl substituent can change the binding profile to the receptor.[165,208] Further developments in this field can be expected in the nearest future.

And finally, there exists a vast class of compounds manifesting nearly identical antagonistic activities towards serotonin 5-HT_2 and dopamine receptors which can be used as efficient antischizophrenic drugs. The neuroleptic drug clozapine (**120a**) is a classical representative of these compounds.[165,209,210] This possesses somewhat higher selectivity towards serotonin receptors of the 5-HT_{2A} subtype, whereas its desmethyl derivative **120b** manifests higher affinity for 5-HT_{2C} receptors.[211,212] A large number of their presently known analogues comprise a lipophilic tricyclic system,[213] which may contain additional heteroatoms (*e.g*., compound **121**) or be devoid of them (*e.g*., compound **122**).[214,215] Tetracyclic analogues such as mianserin (**123**) are also known.[216,217] A detailed survey of the work devoted to the design of compounds similar to compounds **120**–**123** or mixed-type antipsychotic drugs belonging to other structural classes is beyond the scope of the present review, which considers only compounds selective towards serotonin receptors.

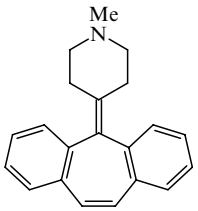


120a,**b**

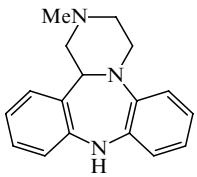


121

R = Me (**a**), H (**b**).



122



123

It should be stressed that the selectivities of antagonists towards serotonin 5-HT_2 receptors as opposed to dopaminergic (D_2) receptors are difficult to achieve. This problem was the central issue in special studies aimed at comparative structural analysis of binding sites of both types of receptors (see, *e.g.*, Ref. 218). Although the structural requirements for the affinities of both receptors are very close, they have certain steric differences, which makes it possible to predict the selectivities of various compounds to 5-HT_2 receptors.

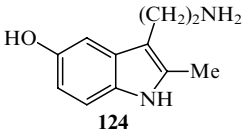
To conclude this chapter, it should be emphasised that the search for 5-HT_2 ligands employed mainly simple screening procedures, without recourse to computer simulation or pharmacophore hypotheses. Nevertheless, the design of such ligands entails efficient structural approaches. Moreover, the use of pharmacophore and receptor models developed in the last few years and modern QSAR methods [174, 218, 219] leaves hope that progress in this area will finally be achieved.

VII. Ligands of serotonin 5-HT_3 subtype receptors

Receptors of the 5-HT_3 subtype are the only serotonin receptors that form ion channels penetrable for monovalent cations and calcium ions. The ligands interacting with this type of receptor have been in the focus of attention in the past decade, primarily in connection with the design of antagonists, some of which proved to be efficient antiemetic drugs. Antagonists of 5-HT_3 receptors can also be used for the treatment of schizophrenia and other mental disorders. The putative therapeutic role of 5-HT_3 agonists is based on their ability to control the release of the neuromediator acetylcholine in the brain, which makes these compounds promising for the treatment of neurodegenerative diseases associated with cholinergic transmission disturbances. In addition, 5-HT_3 agonists can be used as antidepressant and analgesic drugs.

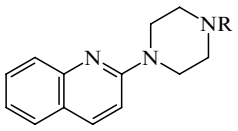
Since the mechanism of signal transmission by 5-HT_3 receptors is different from those of other serotonin receptors, its ligands often possess unique structures and manifest high selectivity. Thus quaternary amines of the type *N*,*N*,*N*-trimethyl-5-hydroxytryptamine do not bind to any other subtypes of serotonin receptors.

Agonists of 5-HT_3 receptors have been studied less thoroughly than their antagonists and are less numerous. The most well-known of them is 5-hydroxy-2-methyltryptamine (**124**) which possesses lower affinity than serotonin but much higher selectivity towards 5-HT_3 subtype receptors and preserves simultaneously agonistic activity.[145, 220, 221]

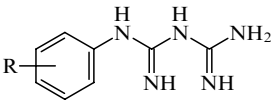


124

The other two structural groups of 5-HT_3 subtype agonists include arylpiperazines and arylbiguanides; their classical representatives are quipazine (**125a**) [222, 223] and 1-phenylbiguanide (**126**, R = H).[224] These compounds had been neglected for a long time, apparently because of the high selectivity but low affinity of phenylbiguanide for 5-HT_3 receptors. At the same time, arylpiperazines of the general formula **127** display higher affinities for 5-HT_2 receptors but are less selective and are active with respect to a vast variety of other serotonin receptors (see above). The number of publications devoted to the design of arylpiperazine and arylbiguanide analogues has increased markedly over the past decade; studies in this field were designed to increase the affinities of arylbiguanides and the selectivities of arylpiperazines.

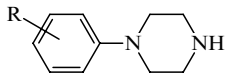


125a,**b**



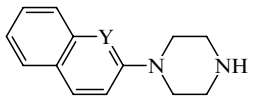
126

R = H (**a**), Me (**b**).

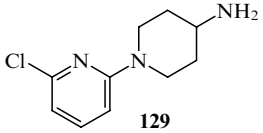


127

For the first trend, the key hypothesis was that both classes of compounds occupy the same aromatic binding site on 5-HT_3 receptors; therefore, the structure–activity dependences for arylpiperazines **127** can be extrapolated to arylbiguanides. The main structure–activity regularity for arylpiperazines **127** is that the chlorine atom in the *m*-position of the benzene ring is the only substituent (R) studied which produces a significant increase in affinity. This cannot be replaced by any other electron-withdrawing substituent (*e.g.*, CF_3). Substitution of the naphthyl substituent (compound **128a**) for the phenyl substituent, the introduction of the nitrogen atom into the benzene or the naphthalene fragment (compound **128b**) and the conversion of the NH group of piperazine into an exocyclic amino group (compound **129**) also affords high-affinity compounds.[225–227] It should be noted that the majority of these compounds manifest pronounced antagonistic activities and behave as partial agonists.¶



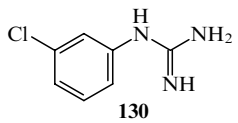
128a,**b**



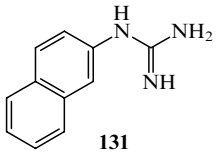
129

Y = CH (**a**), N (**b**).

In contrast, all the arylbiguanide derivatives under study are full agonists of 5-HT_3 receptors and manifest high selectivities towards them. As in the case of piperazine compounds, the introduction of the chlorine atom into the *m*-position affords the high-affinity compound **126** (R = 3-Cl), and 2-naphthylbiguanide binds 100 times more effectively than 1-phenylbiguanide.[229–233] These data unambiguously demonstrate the validity of the hypothesis about the similarity of binding profiles (or binding sites) of arylpiperazines **127** and arylbiguanides **126**. It is of note that the affinities of 3-chlorophenyl- (**130**) and 2-naphthylguanides (**131**) which also act as 5-HT_3 receptor agonists manifest the highest (by one or two orders of magnitude) affinities among other structurally related arylguanides [233] and can thus be regarded as representatives of a new structural class of serotonin receptor agonists.



130



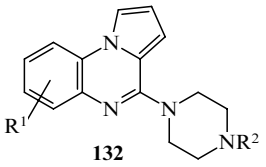
131

Investigations into the increase in the selectivities of arylpiperazines towards 5-HT_3 receptors have led to the synthesis of a vast variety of effective ligands endowed with a broad range of intrinsic activities, *viz.*, from full agonists to full antagonists. In the majority of studies, quipazine (**125a**) was used as the structural lead; its simplest modifications showed that the *N*-methyl analogue **125b** [225] manifests nearly identical affinity for 5-HT_3 recep-

¶ Some arylpiperazine derivatives manifest complex activity profiles with respect to 5-HT_3 subtype receptors. Thus the intrinsic activity of quipazine (**125a**) depends on the type of the cells comprising these receptors. It was shown that quipazine behaves as an agonist for some of these receptors and an antagonist for other receptors.[228]

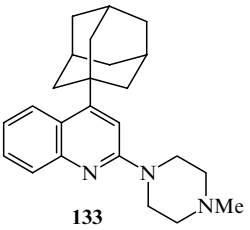
tors but does not bind to 5-HT_{1B} receptors (according to more recent data, the *N*-methyl substituent is the most suitable substituent for many quipazine analogues [234]).

Earlier, it was shown that the 5-HT_{1B} receptor ligand **57** which contains a pyrrole ring and is inactive towards 5-HT_3 receptors acquires high affinity for these receptors upon removal of the trifluoromethyl group. Therefore, a vast majority of studies aimed at modification of the quipazine structure include the introduction of a condensed pyrrole ring into the quinoline system.[234–236] Among compounds of the general formula **132**, the derivatives manifesting the highest affinities for 5-HT_3 receptors possess the properties of partial (R^1 = H, 6-, 7- or 9-F; R^2 = H, Alk, CH_2 = $CHCH_2$) and full (R^1 = 9-Me, R^2 = Me; R^1 = 7-OH, R^2 = Me) agonists, the latter being the strongest 5-HT_3 agonists presently known.[237]

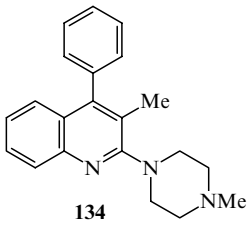


132

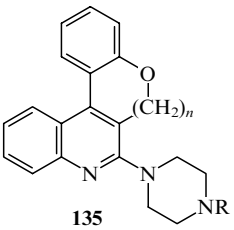
The introduction of lipophilic groups into the quipazine molecule yields the derivatives **133**–**135**, which behave as antagonists of the corresponding receptors or partial agonists endowed with low intrinsic activities, *e.g.*, compound **136**.[228]



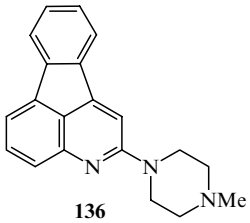
133



134



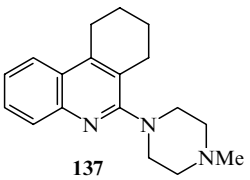
135



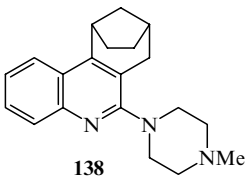
136

n = 0–2, R = H, Alk.

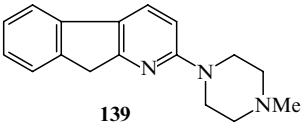
QSAR studies of quipazine derivatives containing various heteroaromatic fragments revealed several compounds (*e.g.*, compounds **137**–**139**) manifesting high activities, high selectivities and different intrinsic activities with respect to 5-HT_3 receptors. Thus compound **137** is the partial agonist, compound **138** is the antagonist, while compound **139** is the agonist of the corresponding receptors.[238]



137

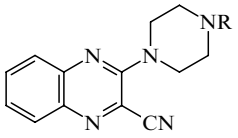


138



139

This finding was used in the design of a binding model of quipazine derivatives (both agonists and antagonists) to 5-HT_3 receptors.[238, 239] According to this model, the high-affinity interaction with the receptor involves the formation of a hydrogen bond between the protonated terminal nitrogen atom of piperazine and the carboxylate anion of the amino acid residue in 5-HT_3 receptors (there is conformational restriction for the bulk of the substituent at this nitrogen atom), the formation of a hydrogen bond between the nitrogen atom in the heterocycle and the corresponding hydrogen bond donor in the receptor and, finally, the specific interaction between the aromatic ring and the corresponding amino acid residue of the receptor (there is a size restriction of substituents in the region of aromatic ring fusion). Presumably, the first two interactions make a weighty contribution to affinity.[240] Moreover, favourable van der Waals interactions which are supposed [238] to be critical for the modulation of intrinsic activities with respect to 5-HT_3 receptors (*cf.* structures **137**–**139**) can be triggered in that domain of the receptor molecule which corresponds to the quinoline fragment. However, the structural determinants responsible for the intrinsic activities of quipazine derivatives are in fact more complicated, since the changes in their activities can be provoked even by any apparently insignificant changes in the heterocyclic backbone of quipazine. Thus compounds **140a**,**b** which contain neither bulky, nor lipophilic substituents in their nuclei behave nevertheless as 5-HT_3 antagonists.[240, 241]

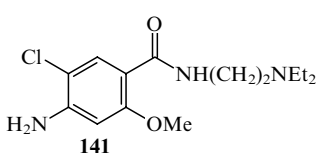


140a,**b** R = H (**a**), CH_2 = $CHCH_2$ (**b**).

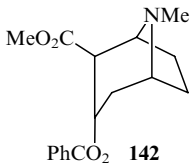
QSAR studies aimed at the search for effective 5-HT_3 agonists and antagonists based on quipazine give an insight into the molecular fragments essential for the strong binding of the ligands to the receptors and allow the prediction of novel high-affinity compounds. However, elaboration of structural requirements for their agonistic and antagonistic activities is hardly possible without detailed computer simulation studies.

As indicated above, the main progress in the design of 5-HT_3 ligands is associated with the synthesis of its selective antagonists some of which have already found application in clinical practice. The majority of 5-HT_3 antagonists represent aryl- or hetarylamide derivatives. We shall briefly summarise the main concepts and results of structure–activity studies of 5-HT_3 antagonists with special emphasis on the latest data.

The first potent and selective 5-HT_3 antagonists prepared were based on the non-selective dopamine receptor ligand metoclopramide (**141**), which had long been used as an antiemetic drug. Studies from the early 1980's showed that metoclopramide and some cocaine (**142**) analogues manifest relatively weak antagonistic activities towards one of the serotonin subtype receptors [242] further identified as 5-HT_3.[243] This activity is responsible for the antiemetic effect of metoclopramide. Further modifications of metoclopramide structure as well as of the structures of analoguous and lead compounds consisted in conformational restriction of the side chain, modification of the amide fragment and substitution of an oxygen-containing ring for the *o*-alkoxy group.



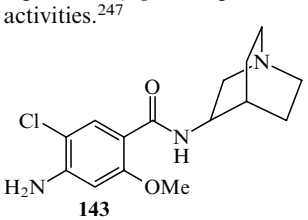
141



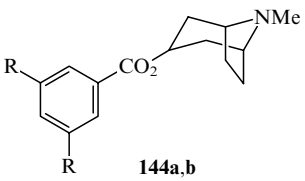
142

The introduction of the quinuclidine residue into the side chain of metoclopramide (**141**) afforded zacopride (**143**), which is a potent selective antagonist of 5-HT_3 receptors.[244, 245] Modifications including the introduction of a tropane fragment and variations of substituents in the ring give compound **144a** which is also a potent selective antagonist of this subtype of receptors.[246] Its analogue **144b** containing two methyl groups possesses virtually the same activity. It should be noted that side chain

modifications included the variations in its 'mobile' fragment. Thus phenylurea derivatives containing an alkoxy group in the *o*-position (*e.g.*, compound **145**) manifested high antagonistic activities.[247]

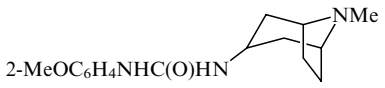


143



144a,b

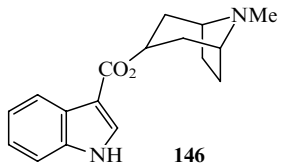
R = Cl (**a**), Me (**b**).



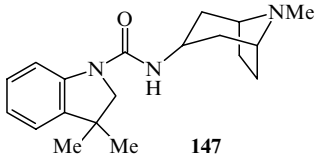
145

The benzene ring of these compounds was subjected to structural modification. Thus substitution of the indole ring for the disubstituted benzene ring in compounds **144a,b** which affords tropisetron (**146**) [144] significantly increases the affinity. A similar effect is observed upon the replacement of the aryl substituent in the urea derivative **145** by hetaryl substituents (compounds **147** and **148**).[248, 249]

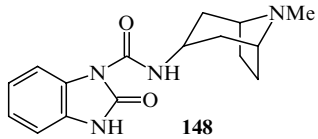
Tropisetron (**146**) is a selective 5-HT_3 ligand used in clinical practice as an antiemetic drug, like its more active structural analogue granisetron (**149**) containing a 9-azabicyclo[3.3.1]nonane residue in the side chain.[250]



146

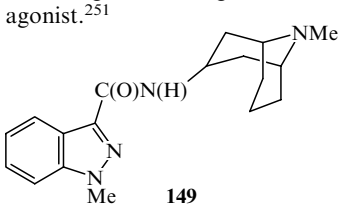


147

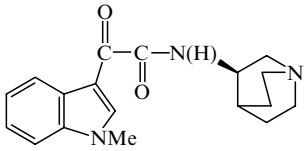


148

Modification of the 'mobile' fragment of the side chain resulted in the ketoamide (**150**), a high-affinity and selective 5-HT_3 ligand although manifesting the properties of a partial agonist.[251]

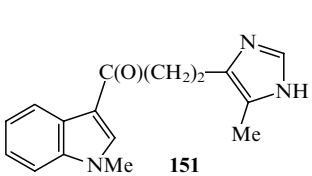


149

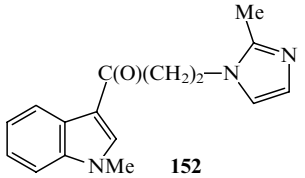


150

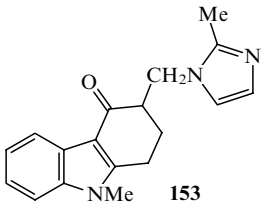
It is of note that these modifications were carried out together with the search for effective 5-HT_3 ligands among indole derivatives. Thus compounds **151** and **152** containing an imidazole fragment in their side chains were synthesised [252] and ondansetron (**153**),[253] the conformationally rigid analogue of compound **152**, a potent selective antagonist of 5-HT_3 receptors. Ondansetron (**153**) is the most well-known 5-HT_3 antagonist widely used as an antiemetic drug in combined therapy of tumour diseases.[254]



151

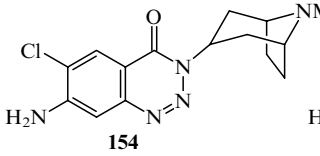


152

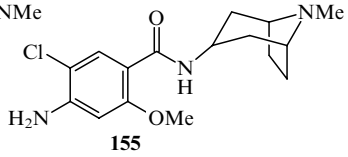


153

A modification of the amide group of metoclopramide (**141**) included the formation of the benzotriazine fragment (compound **154**). Since this modification increases the activity in comparison with the 'open' analogues of the type **155**, it is assumed that the active conformation of benzamides in the 5-HT_3 receptor should involve a planar arrangement of the carbonyl group.[255] Similar results were obtained for a series of ondansetron analogues (**153**) in which ketones fused to the indole fragment were 4 times as active as the non-cyclic analogue **152**.[255]

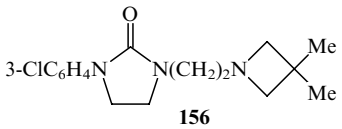


154

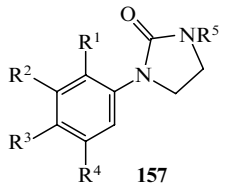


155

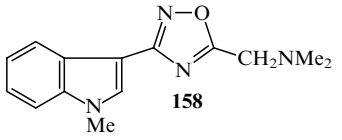
Yet another version of cyclisation is the incorporation of an amide group into a new ring in the side chain. The idea of this transformation stems from bioisosterism of benzamide and phenylimidazolidin-2-one fragments. Comparison of the structures of metoclopramide (**141**) and the dopamine receptor antagonist zetidoline (**156**) prompted an idea about the introduction of azabicyclic or other equivalent structural fragments of 5-HT_3 antagonists into the phenylimidazolidinonalkyl group. Indeed, several high-affinity antagonists of the 5-HT_3 receptor were identified among a series of compounds of the general formula **157**, and a compound with $R^1 = R^3 = R^6 = R^7 = H$, $R^2 = R^4 = Cl$, $R^8 = Me$ is characterised by unusually high affinity.[256] It should be noted also that the indole derivative **158** containing an oxadiazole residue mimicking the amide group instead of the bicyclic substituent is a specific antagonist of 5-HT_3 receptors.[257]



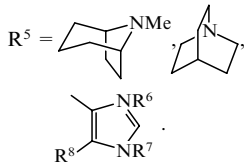
156



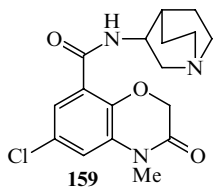
157



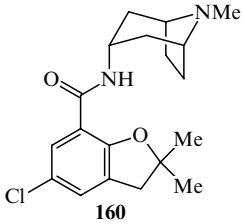
158



Substitution of a fused oxygen heterocycle for the *o*-alkoxy group is also a modification of the metoclopramide (**141**) structure. This modification resulted in several high-affinity selective 5-HT_3 antagonists, *e.g.*, the quinuclidine derivative **159** [258, 259] and zatosetron **160**.[260] In all these cases, the presence of the chlorine atom is a necessary prerequisite for the high activities of these compounds.

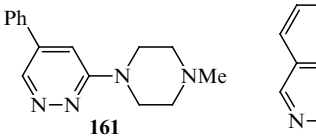


159

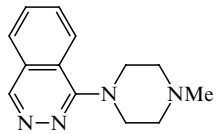


160

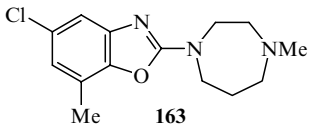
Many pharmacophore models have been suggested for 5-HT_3 antagonists. The differences between them originate from different models and different 5-HT_3 ligands used in their development. Critical analysis of five pharmacophore models [247, 248, 251, 261–263] disclosed the following essential components required for manifestation of high affinity, *vis*., the presence of an aromatic ring, the carbonyl group directly attached to the aromatic ring and a basic amine. The aromatic ring can represent a structural element of benzoate, benzamide, indole or imidazole fragments. As mentioned above, the carbonyl group can be replaced by an equivalent bioisosteric group, *e.g*., the 1,2,4-oxadiazole or the imidazolidin-2-one fragment. The presence and accessibility of the amine nitrogen plays a significant role in certain models,[261–263] although the details of this binding are still unknown.[264] It should be stressed, however, that some antagonists (*e.g*., compound **157**) do not fit into these structural models. The lack of correlation brought forth the necessity for modification of the binding profile of the receptor, *viz*., two additional hydrophobic binding sites were identified in the domain surrounding the aromatic ring.[257, 265] Pharmacophore models have proved to be a useful tool for the rational design of 5-HT_3 antagonists. Thus these models were used to predict high affinities of 3-aminopyridazines **161** and **162** containing a piperazine fragment for 5-HT_3 receptors.[265]



161



162



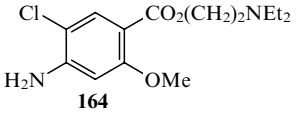
163

It should finally be noted that the number of publications devoted to the design of 5-HT_3 antagonists has presently lessened, presumably due to progress already achieved in this area. Nevertheless, the search for novel structural classes of 5-HT_3 antagonists is a vital problem in the endeavour to go far beyond the scope of tryptamine, metoclopramide and arylpiperazine derivatives. In novel compounds, such as compound **163** containing a seven-membered ring, modifications involve the same fragments. Compound **163** is a high-affinity partial agonist of 5-HT_3 receptors with low intrinsic activity.[266, 267]

VIII. Ligands of serotonin 5-HT_4 subtype receptors

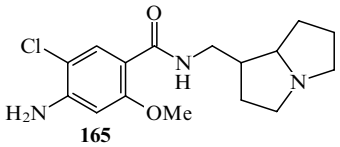
Serotonin 5-HT_4 subtype receptors were discovered in the late 1980's and cloned in 1995;[268] their molecular structures and some functional characteristics have not been described until very recently.[269] Various therapeutic applications for their agonists and antagonists, *e.g*., in the treatment of intestinal disorders, arrhythmias and diseases associated with the loss of the cognitive ability, are based on the localisation of this receptor in gastrointestinal tract, atrium and urinary bladder tissues as well as in the central nervous system.

Some non-selective antagonists of serotonin receptors, mostly of 5-HT_3 receptors, *e.g*., metoclopramide (**141**), possess partial agonistic activities towards 5-HT_4 receptors. Therefore, metoclopramide (**141**) and its ester analogue **164**[270] manifesting the properties of a weak antagonist and 30-fold selectivity towards 5-HT_4 receptors than to 5-HT_3 receptors were used as the lead compounds in the design of more selective 5-HT_4 ligands.

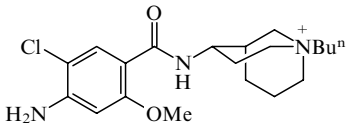


164

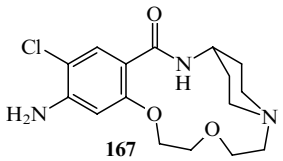
The general scheme of the design of these ligands resembles in many features that for 5-HT_3 antagonists and includes, in the first place, different versions of restriction of conformational mobility and modification of the amine side chain. The agonist **165**[271] and the antagonist **166** (a quaternised butyl analogue of renzapride (which is a partial agonist of the 5-HT_3 receptor) were among the first compounds manifesting somewhat higher selectivity towards 5-HT_4 receptors in comparison with 5-HT_3 receptors. This modification is based on a significant decrease in the activities of quaternary salts of 5-HT_3 antagonists with substituents bulkier than the methyl group at the nitrogen atom.[272, 273] Special mention should also be made of the original macrocyclic benzamide (**167**) which represents a partial agonist twice as selective towards 5-HT_4 receptors as towards 5-HT_3 receptors, which does not interact with other receptors.[274]



165

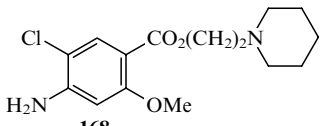


166

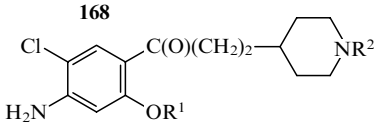


167

The close structural analogues of compound **164**, *viz*., the piperidine derivatives **168** and **169a**,**b**, are potent selective partial agonists of 5-HT_4 receptors (their intrinsic activities are 50% – 60%).[275–277] The classical approach to decrease the intrinsic activity of compound **169b** by introducing bulky lipophilic substituents proved to be successful. Thus the derivative **169c**[275, 278] manifests high antagonistic activity and 100-fold higher selectivity towards 5-HT_4 receptors than towards other serotonin receptors. It is of note that the changes in the structural activity of compound **168** from the agonistic to the antagonistic one is achieved by less significant structural modification, *viz*., through the introduction of two methyl groups into positions 3 and 5 of the piperidine ring. For the derivative **169a**, the decrease in the intrinsic activity is achieved through structural simplification, whereas the analogue **170** containing an additional carbon atom in the side chain but devoid of the lipophilic butyl substituent is a full 5-HT_4 antagonist manifesting high affinity and noticeable selectivity.[279, 280]

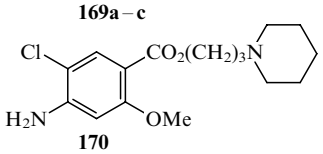


168



169a–c

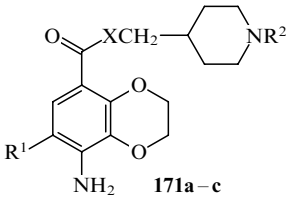
R^1 = Me: R^2 = Bu (**a**), $(CH_2)_2NHSO_2Me$ (**b**); R^1 = $CH_2C_6H_3(OMe)_2$-3,5, R^2 = $(CH_2)_2NHSO_2Me$ (**c**).



170

These and some other examples of this kind, *e.g*., the fact that metoclopramide (**141**) is a partial agonist of 5-HT_4 receptors and its ester analogue **164** is a 5-HT_4 antagonist, suggest that even minor structural changes may provoke dramatic changes in the intrinsic activities of 5-HT_4 ligands. A hypothesis of the existence of two binding sites in the 5-HT_4 receptor was developed to rationalise this fact.[277]

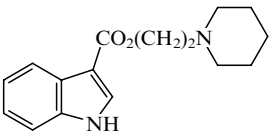
Substitution of an oxygen-containing ring for the *o*-alkoxy group in the piperidine-substituted metoclopramide derivatives (**141**) was efficient in the design of both 5-HT_3 and 5-HT_4 antagonists. Thus chlorine-substituted benzodioxanes **171a**,**b**[281] and the iodo derivative **171c**[282,283] proved to be selective 5-HT_4 antagonists with affinities exceeding that of compound **164** 1000-fold and even more.



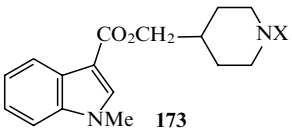
171a–c

R^1 = Cl, R^2 = Bu^n, X = O (**a**); R^1 = Cl, R^2 = $(CH_2)_3C_6H_3(OMe)_2$-3,4, X = CH_2 (**b**); R^1 = I, R^2 = Bu^n, X = O (**c**).

Substitution of the indole fragment for the benzene rings in many metoclopramide derivatives mentioned above was also effective. Compounds **172** and **173**[284,285] and their tricyclic analogue **174**[285] proved to be high-affinity selective 5-HT_4 antagonists. The attempts to modify the indole fragment revealed that benzoimidazoles **175** containing the piperazine fragment in their side chains manifest high affinities for 5-HT_4 receptors. Interestingly, compound **175** (where R = cyclo-C_3H_5) behaved as a potent antagonist, whereas that with R = Pr^i was a partial agonist manifesting very high intrinsic activity.[286] This is yet another example of reversal of the pharmacological profile of structurally related compounds, which provides additional evidence in favour of the hypothesis postulating the existence of two binding sites in the 5-HT_4 receptor.

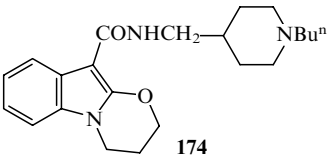


172

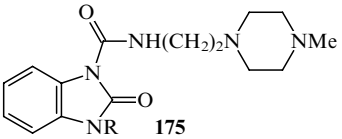


173

X = $(CH_2)_2NHSO_2Me$.



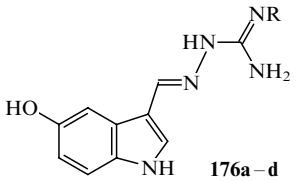
174



175

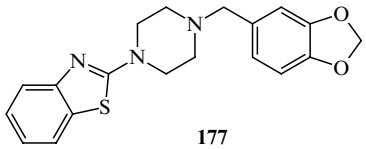
Conformational analysis of serotonin and zacopride (**143**) which also manifests agonistic activity towards its receptor disclosed very potent and selective 5-HT_4 agonists among indole derivatives close to serotonin and made it possible to propose a model of a binding site for 5-HT_4 agonists corresponding to the serotonin analogue **176a**. The latter appeared to be a high-affinity full agonist of 5-HT_4 receptors towards which it was more selective than to other serotonin and dopaminergic receptors.[287,288] The affinity of this compound can be increased through the introduction of lipophilic substituents into the side chain. Thus the derivatives **176b**,**c** are full agonists with the affinities exceeding that of serotonin severalfold. Compound **176d** binds to the receptor 300 times more effectively than serotonin but manifests the properties of a partial agonist. These compounds are among the most potent and selective 5-HT_4 agonists presently available.[287,288]

Some 5-HT_4 ligands were found among the derivatives of quipazine (**125a**), which also represents a 5-HT_3 ligand. The majority of compounds of this kind, *e.g.*, compound **177**, manifest partial agonistic activity towards 5-HT_4 receptors and simultaneously act as 5-HT_3 antagonists[289] which makes them promising candidates for gastrokinetic agents.



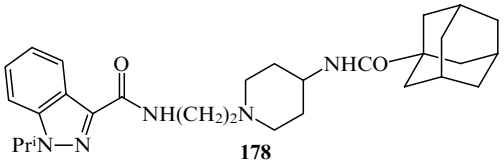
176a–d

R = H (**a**), C_5H_{11} (**b**), $(CH_2)_2Ph$ (**c**), $(CH_2)_2C_6H_3Cl_2$-3,4 (**d**).



177

It should be stressed in conclusion that despite the construction of a fairly large number of potent and sufficiently selective 5-HT_4 ligands, they manifest predominantly antagonistic activities. Full selective agonists are fewer in number, but are therapeutically more valuable. Moreover, very many 5-HT_4 ligands do not possess high pharmacodynamic characteristics needed for their clinical application. It is for this reason that the main attention has presently been focussed on those modifications of the ligand structure which might improve their pharmacodynamic characteristics. To this end, amide, carbamate or ketone groups are introduced into the side chains of compounds **170** instead of ester groups.[290,291] Among compounds with improved pharmacodynamic characteristics, compounds **171b** and **174** and the recently prepared compound **178**,[290,292] a long-acting, potent and selective 5-HT_4 antagonist, deserve special mentioning.

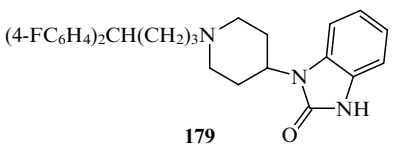


178

IX. Ligands of serotonin receptors of other subtypes

Among other subtypes of serotonin receptors, 5-HT_5 (further classified into 5-HT_{5A} and 5-HT_{5B}), 5-HT_6 and 5-HT_7 receptors are the least known. Highly selective ligands to 5-HT_5 and 5-HT_6 receptors have not been identified yet; therefore, their functional and, perhaps, therapeutic values have been studied relatively little. It is suggested that 5-HT_7 receptors play a role in the pathophysiology of certain sleep disturbances, depressive states and schizophrenia; also their stimulation causes vasodilation.

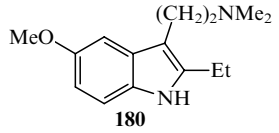
Studies of the effects of many classical ligands of serotonin receptors on these subtypes revealed that 5-carboxamidotryptamine (**2**) and LSD (**97**) manifested high, whereas compound **4a** manifested moderate, affinities for 5-HT_{5A} and 5-HT_7 receptors.[293] Many non-selective 5-HT_2 antagonists, such as methiothepin (**68**), methergoline (**98**), ritanserin (**104**), *etc.*, bind to 5-HT_6 and 5-HT_7 receptors manifesting high or moderate affinities. Very strong binding is observed in the interaction of some mixed-action antipsychotic drugs, *e.g.*, clozapine (**120a**) and pimozide (**179**), with these receptors.[294]



179

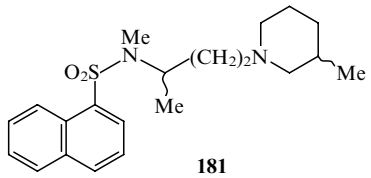
It is not until very recently that a series of studies devoted to the design of selective ligands of some of the above-mentioned receptor groups have been published.[295,296] Thus it was found that 5-HT_6 receptors match small alkyl substituents in position 2 of the indole ring of serotonin. The ethyl derivative **180** which represents

a full 5-HT_6 agonist manifests the highest affinity and binds to the receptor 5 times more strongly than serotonin. Compound **180** manifests only moderate affinity for some other types of serotonin receptors, being the most selective 5-HT_6 agonist known so far. Substitution of the phenyl group for the ethyl substituent does not influence the affinity but decreases dramatically the intrinsic activity. These data suggest that 2-substituted tryptamines can be used in the design of both selective agonists and antagonists of 5-HT_6 receptors.[296]

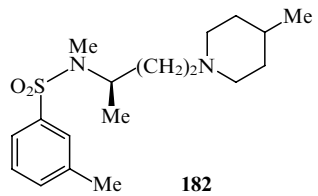


180

A selective ligand of 5-HT_7 receptors was prepared based on sulfamide **181**, which has been found as a result of wide screening and manifesting moderate affinity and weak selectivity towards 5-HT_7 receptors; its *R*,*R*-configuration was found to be important for binding. Modifications of compound **181** revealed that the methyl group in the piperidine ring may be shifted to position 4, whereas the naphthalene ring may be replaced by other aromatic substituents. Thus sulfamide **182** appeared to be two orders of magnitude more selective towards 5-HT_7 receptors than to other serotonin receptors. Compound **182** is the first example of an effective selective ligand endowed with 5-HT_7 antagonistic activity, although its affinity for these receptors is not very high.[295]



181



182

* * *

A vast variety of compounds interacting with serotonin receptors with high affinity have been prepared by the methods employed in medicinal chemistry. Selectivity is the major problem in the design of new ligands, since the family of serotonin receptors is characterised by a large set of structurally similar subclasses. Although this problem can successfully be overcome for some of 5-HT subtypes, for other 5-HT receptors, particularly for 5-HT_{1E}, 5-HT_{1F}, 5-HT_{5A}, 5-HT_{5B}, 5HT_6 and 5-HT_7, the design of selective ligands presents a challenge. Its successful solution will help better understanding of the functional roles of receptors in the organism. Obviously, progress in the search for ligands to serotonin receptors will depend on further advances in X-ray diffraction analysis, which will provide a basis for refining of computer models and docking studies of ligands pertaining to different structural classes.

References

1. O N Zefirova, N S Zefirov *Vestn. Mosk. Univ., Ser. 2, Khim.* **41** 43 (2000) [a]
2. O N Zefirova, N S Zefirov *Vestn. Mosk. Univ., Ser. 2, Khim.* **41** 103 (2000) [a]
3. O N Zefirova, N S Zefirov *Zh. Org. Khim.* **36** 1273 (2000) [b]
4. D Hoyer, G R Martin *Behav. Brain Res.* **73** 263 (1996)
5. D Hoyer, G Martin *Neuropharmacology* **36** 419 (1997)
6. L Uphouse *Neurosci. Biobehav. Rev.* **21** 679 (1997)
7. P Blier, C de Montigny *Trends Pharmacol. Sci.* **15** 220 (1994)
8. A Fletcher, I A Cliffe, C T Dourish *Trends Pharmacol. Sci.* **14** 41 (1993)
9. M Hamon *Trends Pharmacol. Sci.* **15** 36 (1994)
10. M S Beer, J A Stanton, Y Bevan, N S Chauhan, D N Middlemiss *Eur. J. Pharmacol.* **213** 193 (1992)
11. E Zifa, G Fillion *Pharmacol. Rev.* **44** 401 (1992)
12. D N Middlemiss, J R Fozard *Eur. J. Pharmacol.* **90** 151 (1983)
13. D R Helton, W E Colbert *J. Pharm. Pharmacol.* **46** 902 (1994)
14. H Yu, Y Liu, U Hacksell, T Lewander *Eur. J. Pharmacol.* **231** 69 (1993)
15. Z-P Zhuang, M-P Kung, H F Kung *J. Med. Chem.* **36** 3161 (1993)
16. L-E Arvidsson, A M Johansson, U Hacksell, J L Nilsson, K Svensson, S Hjorth, T Magnusson, A Carlsson, B Andersson, H Wikström *J. Med. Chem.* **30** 2105 (1987)
17. C Mellin, J Vallgarda, D L Nelson, L Björk, H Yu, N-E Anden, I Csöregh, L-E Arvidsson, U Hacksell *J. Med. Chem.* **34** 497 (1991)
18. L J Cornfield, G Lambert, L E Arvidsson, C Mellin, J Vallgarda, U Hacksell, D L Nelson *Mol. Pharmacol.* **39** 780 (1991)
19. H Wikström, B Andersson, T Elebring, J Jacyno, N L Allinger, K Svensson, A Carlsson, S Sundell *J. Med. Chem.* **30** 1567 (1987)
20. B B Höök, L Cortizo, A M Johansson, A Westlind-Danielsson, N Mohell, U Hacksell *J. Med. Chem.* **39** 4036 (1996)
21. L Björk, L J Cornfield, D L Nelson, S E Hillver, N E Anden, T Lewander, U Hacksell *J. Pharmacol. Exp. Ther.* **258** 58 (1991)
22. S-E Hillver, L Björk, Y-L Li, B Svensson, S Ross, N-E Anden, U Hacksell *J. Med. Chem.* **33** 1541 (1990)
23. J Vallgarda, U Appelberg, L E Arvidsson, S Hjorth, B E Svensson, U Hacksell *J. Med. Chem.* **39** 1485 (1996)
24. M H Hedberg, T Linnanen, J M Jansen, G Nordvall, S Hjorth, L Unelius, A M Johansson *J. Med. Chem.* **39** 3503 (1996)
25. M H Hedberg, J M Jansen, G Nordvall, S Hjorth, L Unelius, A M Johansson *J. Med. Chem.* **39** 3491 (1996)
26. G S Baxter, D A Craig, D E Clarke *Naunyn Schmiedebergs Arch. Pharmacol.* **343** 439 (1991)
27. R D Titus, E C Kornfeld, N D Jones, J A Clemens, E B Smalstig, R W Fuller, R A Hahn, M D Hynes, N R Mason, D T Wong, M M Foreman *J. Med. Chem.* **26** 1112 (1983)
28. R F Heier, L A Dolak, J N Duncan, D K Hyslop, M F Lipton, I J Martin, M A Mauragis, M F Piercey, N F Nichols, P J K D Schreur, M W Smith, M W Moon *J. Med. Chem.* **40** 639 (1997)
29. J M Cossery, H Gozlan, U Spampinato, C Perdicakis, G Guillaumet, L Pichat, M Hamon *Eur. J. Pharmacol.* **140** 143 (1987)
30. E Hammarberg, G Nordvall, R Leideborg, M Nylof, S Hanson, L Johansson, S-O Thorberg, B R Tolf, E Jerning, G T Svantesson, N Mohell, C Ahlgren, A Westlind-Danielsson, I Csöregh, R Johansson *J. Med. Chem.* **43** 2837 (2000)
31. K L Goa, A Ward *Drugs* **32** 114 (1986)
32. A Gobert, J-M Rivet, L Cistarelli, C Melon, M J Millan *Neuroscience* **93** 1251 (1999)
33. B J Cao, R J Rodgers *Psychopharmacology (Berlin)* **139** 185 (1998)
34. D P Taylor, S L Moon *Neuropeptides* **19** (Suppl.) 15 (1991)
35. K Ishizumi, A Kojima, F Antoku *Chem. Pharm. Bull.* **39** 2288 (1991)
36. I van Wijngaarden, M T M Tulp, W Soudijn *Eur. J. Pharmacol.* **188** 301 (1990)
37. M Abou-Gharbia, U R Patel, M B Webb, J A Moyer, T H Andree, E A Muth *J. Med. Chem.* **31** 1382 (1988)
38. R K Raghupathi, L Rydelek-Fitzgerald, M Teitler, R A Glennon *J. Med. Chem.* **34** 2633 (1991)
39. B J van Steen, I van Wijngaarden, M T M Tulp, W Soudijn *J. Med. Chem.* **36** 2751 (1993)
40. B J van Steen, I van Wijngaarden, M T M Tulp, W Soudijn *J. Med. Chem.* **37** 2761 (1994)
41. J L Mokrosz, M Pietrasiewicz, B Duszynska, M T Cegla *J. Med. Chem.* **35** 2369 (1992)
42. R A Glennon, S -S Hong, M Dukat, M Teitler, K Davis *J. Med. Chem.* **37** 2828 (1994)
43. R A Glennon, S S Hong, M Bondarev, H Law, M Dukat, S Rakhit, P Power, E Fan, D Kinneau, R Kamboj, M Teitler, K Herrick-Davis, C Smith *J. Med. Chem.* **39** 314 (1996)

44. J M Greuel, T Glaser *Eur. J. Pharmacol.* **211** 211 (1992)
45. T Sharp, L I Backus, S Hjorth, S R Bramwell, D G Grahame-Smith *Eur. J. Pharmacol.* **176** 331 (1990)
46. H T Yang, M Endoh *Br. J. Pharmacol.* **122** 1541 (1997)
47. T Matsuda, Y H Seong, H Aono, T Kanda, A Baba, K Saito, A Tobe, H Iwata *Eur. J. Pharmacol.* **170** 75 (1989)
48. G Baxter, G Kennett, F Blaney, T Blackburn *Trends Pharmacol. Sci.* **16** 105 (1995)
49. Y El Ahmad, E Laurent, P Maillet, A Talab, J F Teste, R Dokhan, G Tran, R Ollivier *J. Med. Chem.* **40** 952 (1997)
50. A Orjales, L Alonso-Cires, L Labeaga, R Corcostegui *J. Med. Chem.* **38** 1273 (1995)
51. J-L Peglion, H Canton, K Bervoets, V Audinot, M Brocco, A Gobert, S Le Marouille-Girardon, M J Millan *J. Med. Chem.* **38** 4044 (1995)
52. M L Lopez-Rodriguez, M L Rosado, B Benhamu, M J Morcillo, A M Sanz, L Orensanz, M E Beneitez, J A Fuentes, J Manzanares *J. Med. Chem.* **39** 4439 (1996)
53. M L Lopez-Rodriguez, M J Morcillo, T K Rovat, E Fernandez, B Vicente, A M Sanz, M Hernandez, L Orensanz *J. Med. Chem.* **42** 36 (1999)
54. G Griebel, R J Rodgers, G Perrault, D J Sanger *Psychopharmacology (Berlin)* **144** 121 (1999)
55. G Griebel, R J Rodgers, G Perrault, D J Sanger *Neuropharmacology* **39** 1848 (2000)
56. T Podona, B Guardiola-Lemaitre, D -H Caignard, G Adam, B Pfeiffer, P Renard, G Guillaumet *J. Med. Chem.* **37** 1779 (1994)
57. R T Kroemer, E Koutsilieri, P Hecht, K R Liedl, P Riederer, J Kornhuber *J. Med. Chem.* **41** 393 (1998)
58. H Kubinyi *QSAR: Hansch Analysis and Related Approaches.* (Eds R Mannhold, P Krogsgaard-Larsen, H Timmerman) (Weinheim: VCH, 1993)
59. H Kubinyi, in *The Quantitative Analysis of Structure-Activity Relationships* Vol. 1 (Ed. M E Wolff) (New York: Wiley, 1995) p. 497
60. C Comoy, C Marot, T Podona, M-L Baudin, L Morin-Allory, G Guillaumet, B Pfeiffer, D-H Caignard, P Renard, M -C Rettori, G Adam, B Guardiola-Lemaitre *J. Med. Chem.* **39** 4285 (1996)
61. S Buisson-Defferier, M van den Buuse *Eur. J. Pharmacol.* **223** 133 (1992)
62. S E Gartside, P J Cowen, S Hjorth *Eur. J. Pharmacol.* **191** 391 (1990)
63. P van den Hooff , M Galvan *Eur. J. Pharmacol.* **196** 291 (1991)
64. R E Mewshaw, J Kavanagh, G Stack, K L Marquis, X Shi, M Z Kagan, M B Webb, A H Katz, A Park, Y H Kang, M Abou-Gharbia, R Scerni, T Wasik, L Cortes-Burgos, T Spangler, J A Brennan, M Piesla, H Mazandarani, M I Cockett, R Ochalski, J Coupet, T H Andree *J. Med. Chem.* **40** 4235 (1997)
65. W Quaglia, M Pigini, A Piergentili, M Giannella, G Marucci, E Poggesi, A Leonardi, C Melchiorre *J. Med. Chem.* **42** 2961 (1999)
66. W Kuipers, C G Kruse, I van Wijngaarden, P J Standaar, M T M Tulp, N Veldman, A L Spek, A P Ijzerman *J. Med. Chem.* **40** 300 (1997)
67. B Vacher, B Bonnaud, P Funes, N Jubault, W Koek, M-B Assie, C Cosi *J. Med. Chem.* **41** 5070 (1998)
68. B Vacher, B Bonnaud, P Funes, N Jubault, W Koek, M-B Assie, C Cosi, M Kleven *J. Med. Chem.* **42** 1648 (1999)
69. A M Birch, P A Bradley, J C Gill, F Kerrigan, P L Needham *J. Med. Chem.* **42** 3342 (1999)
70. H R Howard, J A Lowe III, T F Seeger, P A Seymour, S H Zorn, P R Maloney, F E Ewing, M E Newman, A W Schmidt, J S Furman, G L Robinson, E Jackson, C Johnson, J Morrone *J. Med. Chem.* **39** 143 (1996)
71. D Wustrow, T Belliotti, S Glase, S R Kesten, D Johnson, N Colbry, R Rubin, A Blackburn, H Akunne, A Corbin, M D Davis, L Georgic, S Whetzel, K Zoski, T Heffner, T Pugsley, L Wise *J. Med. Chem.* **41** 760 (1998)
72. E M Clifford, S E Gartside, V Umbers, P J Cowen, M Hajos, T Sharp *Br. J. Pharmacol.* **124** 206 (1998)
73. R Corradetti, N Laaris, N Hanoun, A M Laporte, E Le Poul, M Hamon, L Lanfumey *Br. J. Pharmacol.* **123** 449 (1998)
74. H Giles, S J Lansdell, M L Bolofo, H L Wilson, G R Martin *Br. J. Pharmacol.* **117** 1119 (1996)
75. A Hoey, C Jackson, G Pegg, M Sillence *Br. J. Pharmacol.* **117** 712 (1996)
76. A Fletcher, E A Forster, D J Bill, G Brown, I A Cliffe, J E Hartley, D E Jones, A McLenachan, K J Stanhope, D J Critchley, K J Childs, V C Middlefell, L Lanfumey, R Corradetti, A M Laporte, H Gozlan, M Hamon, C T Dourish *Behav. Brain Res.* **73** 337 (1996)
77. E A Forster, I A Cliffe, D J Bill, G M Dover, D Jones, Y Reilly, A Fletcher *Eur. J. Pharmacol.* **281** 81 (1995)
78. I A Cliffe, C I Brightwell, A Fletcher, E A Forster, H L Mansell, Y Reilly, C Routledge, A C White *J. Med. Chem.* **36** 1509 (1993)
79. D B Bylund, H S Blaxall, L J Iversen, M G Caron, R J Lefkowitz, J W Lomasney *Mol. Pharmacol.* **42** 1 (1992)
80. D L Nelson, E W Taylor *Eur. J. Pharmacol.* **124** 207 (1986)
81. T Yasunaga, R Naito, T Kontani, S Tsukamoto, T Nomura, T Yamaguchi, T Mase *J. Med. Chem.* **40** 1252 (1997)
82. T Yasunaga, T Kimura, R Naito, T Kontani, F Wanibuchi, H Yamashita, T Nomura, S Tsukamoto, T Yamaguchi, T Mase *J. Med. Chem.* **41** 2765 (1998)
83. M J Mokrosz, B Duszynska, A J Bojarski, J L Mokrosz *Bioorg. Med. Chem.* **3** 533 (1995)
84. J M Zgombick, L E Schechter, S A Kucharewicz, R L Weinshank, T A Branchek *Eur. J. Pharmacol.* **291** 9 (1995)
85. Y-C Xu, J M Schaus, C Walker, J Krushinski, N Adham, J M Zgombick, S X Liang, D T Kohlman, J E Audia *J. Med. Chem.* **42** 526 (1999)
86. L M Gaster, F E Blaney, S Davies, D M Duckworth, P Ham, S Jenkins, A J Jennings, G F Joiner, F D King, K R Mulholland, P A Wyman, J J Hagan, J Hatcher, B J Jones, D N Middlemiss, G W Price, G Riley, C Roberts, C Routledge, J Selkirk, P D Slade *J. Med. Chem.* **41** 1218 (1998)
87. J Longmore, C M Boulanger, B Desta, R G Hill, W N Schofield, A A Taylor *Br. J. Clin. Pharmacol.* **42** 431 (1996)
88. C Jorand-Lebrun, P J Pauwels, C Palmier, C Moret, P Chopin, M Perez, M Marien, S Halazy *J. Med. Chem.* **40** 3974 (1997)
89. M Lamothe, P J Pauwels, K Belliard, P Schambel, S Halazy *J. Med. Chem.* **40** 3542 (1997)
90. M D Ferrari, P R Saxena *Trends Pharmacol. Sci.* **14** 129 (1993)
91. K L Dechant, S P Clissold *Drugs* **43** 776 (1992)
92. C M Perry, A Markham *Drugs* **55** 889 (1998)
93. K W Weitzel, M L Thomas, R E Small, J V Goode *Pharmacotherapy* **19** 957 (1999)
94. R N Iyer, C W Bradberry *J. Pharmacol. Exp. Ther.* **277** 40 (1996)
95. M D Lee, V J Aloyo, S J Fluharty, K J Simansky *Psychopharmacology (Berlin)* **136** 304 (1998)
96. A C Trillat, I Malagie, K Scearce, D Pons, M C Anmella, C Jacquot, R Hen, A M Gardier *J. Neurochem.* **69** 2019 (1997)
97. M J Gawel *Can. J. Clin. Pharmacol.* **6** 20A (1999)
98. R Salonen *Int. J. Clin. Pract.* **53** 552 (1999)
99. L J Street, R Baker, W B Davey, A R Guiblin, R A Jelley, A J Reeve, H Routledge, F Sternfeld, A P Watt, M S Beer, D N Middlemiss, A J Noble, J A Stantor, K Scholey, R J Hargreaves, B Sohal, M I Graham, V G Matassa *J. Med. Chem.* **38** 1799 (1995)
100. D Deleu, Y Hanssens *J. Clin. Pharmacol.* **40** 687 (2000)
101. C M Spencer, N S Gunasekara, C Hills *Drugs* **58** 347 (1999)
102. R M Gallagher, G Dennish, E L Spierings, R Chitra *Headache* **40** 119 (2000)
103. A Al Shekhlee, R Reed *Neurology* **55** 735 (2000)
104. P R Saxena, P De Vries, W Wang, J P Heiligers, v A Maassen, W A Bax, F D Yocca *Naunyn Schmiedebergs Arch. Pharmacol.* **355** 295 (1997)
105. H C Diener, H Kaube, V Limmroth *J. Neurol.* **246** 515 (1999)
106. A A Parsons, R Valocik, P Koster, P Raval, R Gagnon, N Tilford, G Feuerstein *J. Cardiovasc. Pharmacol.* **32** 995 (1998)
107. M Perez, C Fourrier, I Sigogneau, P J Pauwels, C Palmier, G W John, J-P Valentin, S Halazy *J. Med. Chem.* **38** 3602 (1995)
108. M S Beer, J A Stanton, Y Bevan, A Heald, A J Reeve, L J Street, V G Matassa, R J Hargreaves, D N Middlemiss *Br. J. Pharmacol.* **110** 1196 (1993)
109. A Heald, J A Stanton, S A Osborne, D N Middlemiss, M S Beer *Eur. J. Pharmacol.* **264** 213 (1994)
110. L J Street, R Baker, J L Castro, M S Chambers, A R Guiblin, S C Hobbs, V G Matassa, A J Reeve, M S Beer, D N Middlemiss, A J Noble, J A Stanton, K Scholey, R J Hargreaves *J. Med. Chem.* **36** 1529 (1993)

111. S J Starkey, M Skingle *Neuropharmacology* **33** 393 (1994)
112. J W Clitherow, D I Scopes, M Skingle, C C Jordan, W Feniuk, I B Campbell, M C Carter, E W Collington, H E Connor, G A Higgins, D Beattie, H A Kelly, W C Mitchell, A W Oxford, A H Wadsworth, M B Tyers *J. Med. Chem.* **37** 2253 (1994)
113. H Law, M Dukat, M Teitler, D K H Lee, L Mazzocco, R Kamboj, V Rampersad, T Prisinzano, R A Glennon *J. Med. Chem.* **41** 2243 (1998)
114. C Sonesson, T Barf, J Nilsson, D Dijkstra, A Carlsson, K Svensson, M W Smith, I J Martin, J N Duncan, L J King, H Wikström *J. Med. Chem.* **38** 1319 (1995)
115. T A Barf, P de Boer, H Wikström, S J Peroutka, K Svensson, M D Ennis, N B Ghazal, J C McGuire, M W Smith *J. Med. Chem.* **39** 4717 (1996)
116. J L Castro, L J Street, A R Guiblin, R A Jelley, M G Russell, F Sternfeld, M S Beer, J A Stanton, V G Matassa *J. Med. Chem.* **40** 3497 (1997)
117. F Sternfeld, A R Guiblin, R A Jelley, V G Matassa, A J Reeve, P A Hunt, M S Beer, A Heald, J A Stanton, B Sohal, A P Watt, L J Street *J. Med. Chem.* **42** 677 (1999)
118. M S Chambers, L J Street, S Goodacre, S C Hobbs, P Hunt, R A Jelley, V G Matassa, A J Reeve, F Sternfeld, M S Beer, J A Stanton, D Rathbone, A P Watt, A M MacLeod *J. Med. Chem.* **42** 691 (1999)
119. M B van Niel, I Collins, M S Beer, H B Broughton, S K F Cheng, S C Goodacre, A Heald, K L Locker, A M MacLeod, D Morrison, C R Moyes, D O'Connor, A Pike, M Rowley, M G N Russell, B Sohal, J A Stanton, S Thomas, H Verrier, A P Watt, J L Castro *J. Med. Chem.* **42** 2087 (1999)
120. J L Castro, I Collins, M G N Russell, A P Watt, B Sohal, D Rathbone, M S Beer, J A Stanton *J. Med. Chem.* **41** 2667 (1998)
121. P Schoeffter, D Hoyer *Naunyn Schmiedebergs Arch. Pharmacol.* **339** 675 (1989)
122. F Chaouloff, S Aguerre, P Mormede *Neuropharmacology* **37** 1159 (1998)
123. R F Neale, S L Fallon, W C Boyar, J W Wasley, L L Martin, G A Stone, B S Glaeser, C M Sinton, M Williams *Eur. J. Pharmacol.* **136** 1 (1987)
124. J E Leysen, W Gommeren, L Heylen, W H Luyten, I van de Weyer, P Vanhoenacker, G Haegeman, A Schotte, P van Gompel, R Wouters, A S Lesage *Mol. Pharmacol.* **50** 1567 (1996)
125. E Schlicker, U Werner, M Hamon, H Gozlan, B Nickel, I Szelenyi, M Gothert *Br. J. Pharmacol.* **105** 732 (1992)
126. M A Petty, J Elands, M P Johnson, M D Linnik, E Hamel, M A Moskowitz, W S Lee, D R McCarty, M Hibert, B M Baron *Eur. J. Pharmacol.* **336** 127 (1997)
127. P Schoeffter, D Hoyer *Eur. J. Pharmacol.* **196** 213 (1991)
128. A M Ismaiel, M Dukat, H Law, R Kamboj, E Fan, D K H Lee, L Mazzocco, D Buekschkens, M Teitler, M E Pierson, R A Glennon *J. Med. Chem.* **40** 4415 (1997)
129. P C Waldmeier, M Williams, P A Baumann, S Bischoff, M A Sills, R F Neale *Naunyn Schmiedebergs Arch. Pharmacol.* **337** 609 (1988)
130. P J Pauwels, F C Colpaert *Neuropharmacology* **34** 235 (1995)
131. J M Watson, M J Burton, G W Price, B J Jones, D N Middlemiss *Eur. J. Pharmacol.* **314** 365 (1996)
132. R C Glen, G R Martin, A P Hill, R M Hyde, P M Woollard, J A Salmon, J Buckingham, A D Robertson *J. Med. Chem.* **38** 3566 (1995)
133. G P Moloney, A D Robertson, G R Martin, S MacLennan, N Mathews, S Dodsworth, P Y Sang, C Knight, R Glen *J. Med. Chem.* **40** 2347 (1997)
134. G P Moloney, G R Martin, N Mathews, A Milne, H Hobbs, S Dodsworth, P Y Sang, C Knight, M Williams, M Maxwell, R C Glen *J. Med. Chem.* **42** 2504 (1999)
135. M R MacLean, R A Clayton, A G Templeton, I Morecroft *Br. J. Pharmacol.* **119** 277 (1996)
136. C Roberts, G W Price, L Gaster, B J Jones, D N Middlemiss, C Routledge *Neuropharmacology* **36** 549 (1997)
137. I T Forbes, S Dabbs, D M Duckworth, P Ham, G E Jones, F D King, D V Saunders, F E Blaney, C B Naylor, G S Baxter, T P Blackburn, G A Kennett, M D Wood *J. Med. Chem.* **39** 4966 (1996)
138. E Schlicker, K Fink, G J Molderings, G W Price, M Duckworth, L Gaster, D N Middlemiss, J Zentner, J Likungu, M Gothert *Naunyn Schmiedebergs Arch. Pharmacol.* **356** 321 (1997)
139. S Leonhardt, K Herrick-Davis, M Titeler *J. Neurochem.* **53** 465 (1989)
140. E M Parker, D G Izzarelli, L Lewis-Higgins, D Palmer, R A Shapiro *J. Neurochem.* **67** 2096 (1996)
141. S Shepheard, L Edvinsson, M Cumberbatch, D Williamson, G Mason, J Webb, S Boyce, R Hill, R Hargreaves *Cephalalgia* **19** 851 (1999)
142. D S Dupuis, F C Colpaert, P J Pauwels *Br. J. Pharmacol.* **124** 283 (1998)
143. K W Johnson, J M Schaus, M M Durkin, J E Audia, S W Kaldor, M E Flaugh, N Adham, J M Zgombick, M L Cohen, T A Branchek, L A Phebus *Neuroreport* **8** 2237 (1997)
144. B P Richardson, G Engel, P Donatsch, P A Stadler *Nature (London)* **316** 126 (1985)
145. H Wilson, W J Coffman, M L Cohen *J. Pharmacol. Exp. Ther.* **252** 683 (1990)
146. M S Duxon, G A Kennett, S Lightowler, T P Blackburn, K C Fone *Neuropharmacology* **36** 601 (1997)
147. G A Kennett, K Ainsworth, B Trail, T P Blackburn *Neuropharmacology* **36** 233 (1997)
148. G A Kennett, B Trail, F Bright *Neuropharmacology* **37** 1603 (1998)
149. R A Glennon, M Dukat, M El-Bermawy, H Law, J De los Angeles, M Teitler, A King, K Herrick-Davis *J. Med. Chem.* **37** 1929 (1994)
150. J B Blair, D Marona-Lewicka, A Kanthasamy, V L Lucaites, D L Nelson, D E Nichols *J. Med. Chem.* **42** 1106 (1999)
151. M Gerasimov, D Marona-Lewicka, D M Kurrasch-Orbaugh, A M Qandil, D E Nichols *J. Med. Chem.* **42** 4257 (1999)
152. J E Macor, J Blake, C B Fox, C Johnson, B K Koe, L A Lebel, J M Morrone, K Ryan, A W Schmidt, D W Schulz, S H Zorn *J. Med. Chem.* **35** 4503 (1992)
153. S Vangveravong, D E Nichols *J. Org. Chem.* **60** 3409 (1994)
154. S Vangveravong, A Kanthasamy, V L Lucaites, D L Nelson, D E Nichols *J. Med. Chem.* **41** 4995 (1998)
155. M Bös, F Jenck, J R Martin, J L Moreau, A J Sleight, J Wichmann, U Widmer *J. Med. Chem.* **40** 2762 (1997)
156. G Curzon, G A Kennett *Trends Pharmacol. Sci.* **11** 181 (1990)
157. K C Fone, R H Austin, I A Topham, G A Kennett, T Punhani *Br. J. Pharmacol.* **123** 1707 (1998)
158. I Lucki, H R Ward, A Frazer *J. Pharmacol. Exp. Ther.* **249** 155 (1989)
159. Y Sugimoto, J Yamada, T Yoshikawa, K Horisaka *Eur. J. Pharmacol.* **307** 75 (1996)
160. P J Conn, E Sanders-Bush *J. Pharmacol. Exp. Ther.* **242** 552 (1987)
161. S K Hemrick-Luecke, R W Fuller *Eur. J. Pharmacol.* **311** 207 (1996)
162. R A Glennon, J M Jacyno, R Young, J D McKenney, D Nelson *J. Med. Chem.* **27** 41 (1984)
163. R A Glennon, R Raghupathi, P Bartyzel, M Teitler, S Leonhardt *J. Med. Chem.* **35** 734 (1992)
164. D E Nichols, S Frescas, D Marona-Lewicka, X Huang, B L Roth, G A Gudelsky, J F Nash *J. Med. Chem.* **37** 4346 (1994)
165. M R Seggel, M Y Yousif, R A Lyon, M Titeler, B L Roth, E A Suba, R A Glennon *J. Med. Chem.* **33** 1032 (1990)
166. A P Monte, D Marona-Lewicka, M A Parker, D B Wainscott, D L Nelson, D E Nichols *J. Med. Chem.* **39** 2953 (1996)
167. A P Monte, S R Waldman, D Marona-Lewicka, D B Wainscott, D L Nelson, E Sanders-Bush, D E Nichols *J. Med. Chem.* **40** 2997 (1997)
168. A P Monte, D Marona-Lewicka, M M Lewis, R B Mailman, D B Wainscott, D L Nelson, D E Nichols *J. Med. Chem.* **41** 2134 (1998)
169. M A Parker, D Marona-Lewicka, V L Lucaites, D L Nelson, D E Nichols *J. Med. Chem.* **41** 5148 (1998)
170. D E Nichols, S E Snyder, R Oberlender, M P Johnson, X Huang *J. Med. Chem.* **34** 276 (1991)
171. M P Johnson, C A Mathis, A T Shulgin, A J Hoffman, D E Nichols *Pharmacol. Biochem. Behav.* **35** 211 (1990)
172. R A Glennon, M Titeler, J D McKenney *Life Sci.* **35** 2505 (1984)
173. J E Audia, D A Evrard, G R Murdoch, J J Droste, J S Nissen, K W Schenck, P Fludzinski, V L Lucaites, D L Nelson, M L Cohen *J. Med. Chem.* **39** 2773 (1996)

174. M S Choudhary, N Sachs, A Uluer, R A Glennon, R B Westkaemper, B L Roth *Mol. Pharmacol.* **47** 450 (1995)
175. R A Glennon *Neuropsychopharmacology* **3** 509 (1990)
176. M L Cohen, C J Parli, R W Fuller *J. Pharmacol. Exp. Ther.* **251** 1006 (1989)
177. C S Aulakh, J L Hill, D L Murphy *J. Pharmacol. Exp. Ther.* **263** 588 (1992)
178. G Bagdy, A F Sved, D L Murphy, K Szemeredi *Eur. J. Pharmacol.* **210** 285 (1992)
179. M L Cohen, R W Fuller, K D Kurz, C J Parli, N R Mason, D B Meyers, J K Smallwood, R E Toomey *J. Pharmacol. Exp. Ther.* **244** 106 (1988)
180. M L Cohen, D W Robertson, W E Bloomquist, H C Wilson *J. Pharmacol. Exp. Ther.* **261** 202 (1992)
181. J W Misner, W L Garbrecht, G Marzoni, K R Whitten, M L Cohen *J. Med. Chem.* **33** 652 (1990)
182. H H Pertz, H -C Milhahn, E Eich *J. Med. Chem.* **42** 659 (1999)
183. M P Johnson, J E Audia, J S Nissen, D L Nelson *Eur. J. Pharmacol.* **239** 111 (1993)
184. D L Nelson, V L Lucaites, J E Audia, J S Nissen, D B Wainscott *J. Pharmacol. Exp. Ther.* **265** 1272 (1993)
185. M P Johnson, R J Loncharich, M Baez, D L Nelson *Mol. Pharmacol.* **45** 277 (1994)
186. H T Kao, N Adham, M A Olsen, R L Weinshank, T A Branchek, P R Hartig *FEBS Lett.* **307** 324 (1992)
187. W L Garbrecht, G Marzoni, K R Whitten, M L Cohen *J. Med. Chem.* **31** 444 (1988)
188. H O Kalkman, V Neumann, J Nozulak, M D Tricklebank *Eur. J. Pharmacol.* **343** 201 (1998)
189. P O Mora, C F Netto, F G Graeff *Pharmacol. Biochem. Behav.* **58** 1051 (1997)
190. J Nozulak, H O Kalkman, P Floersheim, D Hoyer, P Schoeffter, H R Buerki *J. Med. Chem.* **38** 28 (1995)
191. J E Leysen, F Awouters, L Kennis, P M Laduron, J Vandenberk, P A Janssen *Life Sci.* **28** 1015 (1981)
192. P A Pierce, J Y Kim, S J Peroutka *Naunyn Schmiedebergs Arch. Pharmacol.* **346** 4 (1992)
193. Z Razzaque, J Longmore, R G Hill *Eur. J. Pharmacol.* **283** 199 (1995)
194. J M Van Nueten, P A Janssen, J Van Beek, R Xhonneux, T J Verbeuren, P M Vanhoutte *J. Pharmacol. Exp. Ther.* **218** 217 (1981)
195. Y Watanabe, H Usui, S Kobayashi, H Yoshiwara, T Shibano, T Tanaka, Y Morishima, M Yasuoka, M Kanao *J. Med. Chem.* **35** 189 (1992)
196. F Darchen, D Scherman, P M Laduron, J P Henry *Mol. Pharmacol.* **33** 672 (1988)
197. J L Herndon, A Ismaiel, S P Ingher, M Teitler, R A Glennon *J. Med. Chem.* **35** 4903 (1992)
198. C J Schmidt, V L Taylor, G M Abbate, T R Nieduzak *J. Pharmacol. Exp. Ther.* **256** 230 (1991)
199. P Seeman, H H van Tol *Trends Pharmacol. Sci.* **15** 264 (1994)
200. A M Ismaiel, J De los Angeles, M Teitler, S Ingher, R A Glennon *J. Med. Chem.* **36** 2519 (1993)
201. K A Metwally, M Dukat, C T Egan, C Smith, A DuPre, C B Gauthier, K Herrick-Davis, M Teitler, R A Glennon *J. Med. Chem.* **41** 5084 (1998)
202. R H Mach, J R Jackson, R R Luedtke, K J Ivins, P B Molinoff, R L Ehrenkaufer *J. Med. Chem.* **35** 423 (1992)
203. D W Bonhaus, K K Weinhardt, M Taylor, A DeSouza, P M McNeeley, K Szczepanski, D J Fontana, J Trinh, C L Rocha, M W Dawson, L A Flippin, R M Eglen *Neuropharmacology* **36** 621 (1997)
204. D W Bonhaus, C L Rocha, M W Dawson, R M Eglen *Ann. N.Y. Acad. Sci.* **861** 269 (1998)
205. I T Forbes, G A Kennett, A Gadre, P Ham, C J Hayward, R T Martin, M Thompson, M D Wood, G S Baxter, A Glen, O E Murphy, B A Stewart, T P Blackburn *J. Med. Chem.* **36** 1104 (1993)
206. I T Forbes, P Ham, D H Booth, R T Martin, M Thompson, G S Baxter, T P Blackburn, A Glen, G A Kennett, M D Wood *J. Med. Chem.* **38** 2524 (1995)
207. I T Forbes, G E Jones, O E Murphy, V Holland, G S Baxter *J. Med. Chem.* **38** 855 (1995)
208. C S Dowd, K Herrick-Davis, C Egan, A DuPre, C Smith, M Teitler, R A Glennon *J. Med. Chem.* **43** 3074 (2000)
209. A Y Deutch, B Moghaddam, R B Innis, J H Krystal, G K Aghajanian, B S Bunney, D S Charney *Schizophr. Res.* **4** 121 (1991)
210. H Y Meltzer *Psychopharmacology (Berlin)* **99** (Suppl.) S18 (1989)
211. S Fox, J Brotchie *Eur. J. Pharmacol.* **301** 27 (1996)
212. M Kuoppamaki, E Syvalahti, J Hietala *Eur. J. Pharmacol.* **245** 179 (1993)
213. G Campiani, V Nacci, S Bechelli, S M Ciani, A Garofalo, I Fiorini, H Wikstrlm, P de Boer, Y Liao, P G Tepper, A Cagnotto, T Mennini *J. Med. Chem.* **41** 3763 (1998)
214. D Hoyer, D E Clarke, J R Fozard, P R Hartig, G R Martin, E J Mylecharane, P R Saxena, P P Humphrey *Pharmacol. Rev.* **46** 157 (1994)
215. A Moran, C Velasco, T Salvador, M L Martin, L San Roman *Br. J. Pharmacol.* **113** 1358 (1994)
216. B E Leonard *Adv. Biochem. Psychopharmacol.* **31** 301 (1982)
217. R A Newton, J M Elliott *J. Neurochem.* **69** 1031 (1997)
218. K Andersen, T Liljefors, K Gundertofte, J Perregaard, K P Bögesö *J. Med. Chem.* **37** 950 (1994)
219. T Borowski, M Krol, E Broclawik, T C Baranowski, L Strekowski, M J Mokrosz *J. Med. Chem.* **43** 1901 (2000)
220. A M Ismaiel, M Titeler, K J Miller, T S Smith, R A Glennon *J. Med. Chem.* **33** 755 (1990)
221. D A Craig, R M Eglen, L K Walsh, L A Perkins, R L Whiting, D E Clarke *Naunyn Schmiedebergs Arch. Pharmacol.* **342** 9 (1990)
222. S J Peroutka, A Hamik *Eur. J. Pharmacol.* **148** 297 (1988)
223. N A Sharif, E H Wong, D N Loury, E Stefanich, A D Michel, R M Eglen, R L Whiting *Br. J. Pharmacol.* **102** 919 (1991)
224. S J Ireland, M B Tyers *Br. J. Pharmacol.* **90** 229 (1987)
225. R A Glennon, A M Ismaiel, B G McCarthy, S J Peroutka *Eur. J. Pharmacol.* **168** 387 (1989)
226. A Bachy, M Heaulme, A Giudice, J C Michaud, I A Lefevre, J Souilhac, L Manara, M B Emerit, H Gozlan, M Hamon *Eur. J. Pharmacol.* **237** 299 (1993)
227. E Edwards, E Hampton, C R Ashby, J Zhang, R Y Wang *Brain Res.* **733** 21 (1996)
228. M Anzini, A Cappelli, S Vomero, G Giorgi, T Langer, M Hamon, N Merahi, B M Emerit, A Cagnotto, M Skorupska, T Mennini, J C Pinto *J. Med. Chem.* **38** 2692 (1995)
229. G J Kilpatrick, A Butler, J Burridge, A W Oxford *Eur. J. Pharmacol.* **182** 193 (1990)
230. M I Sepulveda, S C Lummis, I L Martin *Br. J. Pharmacol.* **104** 536 (1991)
231. F G Boess, M I Sepulveda, S C Lummis, I L Martin *Neuropharmacology* **31** 561 (1992)
232. M I Niemeyer, S C Lummis *Br. J. Pharmacol.* **123** 661 (1998)
233. M Dukat, A A Abdel-Rahman, A M Ismaiel, S Ingher, M Teitler, L Gyermek, R A Glennon *J. Med. Chem.* **39** 4017 (1996)
234. G Campiani, A Cappelli, V Nacci, M Anzini, S Vomero, M Hamon, A Cagnotto, C Fracasso, C Uboldi, S Caccia, S Consolo, T Mennini *J. Med. Chem.* **40** 3670 (1997)
235. H Prunier, S Rault, J-C Lancelot, M Robba, P Renard, P Delagrange, B Pfeiffer, D-H Caignard, R Misslin, B Guardiola-Lemaitre, M Hamon *J. Med. Chem.* **40** 1808 (1997)
236. S Rault, J-C Lancelot, H Prunier, M Robba, P Renard, P Delagrange, B Pfeiffer, D-H Caignard, B Guardiola-Lemaitre, M Hamon *J. Med. Chem.* **39** 2068 (1996)
237. G Campiani, E Morelli, S Gemma, V Nacci, S Butini, M Hamon, E Novellino, G Greco, A Cagnotto, M Goegan, L Cervo, F D Valle, C Fracasso, S Caccia, T Mennini *J. Med. Chem.* **42** 4362 (1999)
238. A Cappelli, M Anzini, S Vomero, L Mennuni, F Makovec, E Doucet, M Hamon, G Bruni, M R Romeo, M C Menziani, P G de Benedetti, T Langer *J. Med. Chem.* **41** 728 (1998)
239. A Cappelli, A Donati, M Anzini, S Vomero, P G de Benedetti, M C Menziani, T Langer *Bioorg. Med. Chem.* **4** 1255 (1996)
240. A Cappelli, M Anzini, S Vomero, L Canullo, L Mennuni, F Makovec, E Doucet, M Hamon, M C Menziani, P G de Benedetti, G Bruni, M R Romeo, G Giorgi, A Donati *J. Med. Chem.* **42** 1556 (1999)
241. A Monge, J A Palop, J C Del Castillo, J M Caldero, J Roca, G Romero, J Del Rio, B Lasheras *J. Med. Chem.* **36** 2745 (1993)

242. J R Fozard, A T Mobarok Ali *Eur. J. Pharmacol.* **49** 109 (1978)
243. V Derkach, A Surprenant, R A North *Nature (London)* **339** 706 (1989)
244. W L Smith, R S Alphin, C B Jackson, L F Sancilio *J. Pharm. Pharmacol.* **41** 101 (1989)
245. W W Smith, L F Sancilio, J B Owera-Atepo, R J Naylor, L Lambert *J. Pharm. Pharmacol.* **40** 301 (1988)
246. J R Fozard *Naunyn Schmiedebergs Arch. Pharmacol.* **326** 36 (1984)
247. J Bermudez, S Dabbs, F D King *J. Med. Chem.* **33** 1932 (1990)
248. J Bermudez, S Dabbs, K A Joiner, F D King *J. Med. Chem.* **33** 1929 (1990)
249. M Turconi, M Nicola, M G Quintero, L Maiocchi, R Micheletti, E Giraldo, A Donetti *J. Med. Chem.* **33** 2101 (1990)
250. J Bermudez, C S Fake, G F Joiner, K A Joiner, F D King, W D Miner, G J Sanger *J. Med. Chem.* **33** 1924 (1990)
251. R D Clark, J M Muchowski, K K Weinhardt, M P Dillon, C-H Lee, K R Bley, D W Bonhaus, E H F Wong, R M Eglen *Bioorg. Med. Chem. Lett.* **5** 1853 (1995)
252. G J Kilpatrick, K T Bunce, M B Tyers *Med. Res. Rev.* **10** 441 (1990)
253. A Butler, J M Hill, S J Ireland, C C Jordan, M B Tyers *Br. J. Pharmacol.* **94** 397 (1988)
254. M A Liberman, S Howe, M Lane *Am. J. Surg.* **179** 60 (2000)
255. F D King (Ed.) *Medicinal Chemistry: Principles and Practice* (Cambridge: Royal Society of Chemistry, 1994)
256. F Heidempergher, A Pillan, V Pinciroli, F Vaghi, C Arrigoni, G Bolis, C Caccia, L Dho, R McArthur, M Varasi *J. Med. Chem.* **40** 3369 (1997)
257. C J Swain, R Baker, C Kneen, J Moseley, J Saunders, E M Seward, G Stevenson, M Beer, J Stanton, K Watling *J. Med. Chem.* **34** 140 (1991)
258. T Fukuda, M Setoguchi, K Inaba, H Shoji, T Tahara *Eur. J. Pharmacol.* **196** 299 (1991)
259. K Haga, K Inaba, H Shoji, Y Morimoto, T Fukuda, M Setoguchi *Jpn. J. Pharmacol.* **63** 377 (1993)
260. D W Robertson, W B Lacefield, W Bloomquist, W Pfeifer, R L Simon, M L Cohen *J. Med. Chem.* **35** 310 (1992)
261. T Rosen, A A Nagel, J P Rizzi, J L Ives, J B Daffeh, A H Ganong, K Guarino, J Heym, S McLean, J T Nowakowski, A W Schmidt, T F Seeger, C J Sick, L A Vincent *J. Med. Chem.* **33** 2715 (1990)
262. A W Schmidt, S J Peroutka *Mol. Pharmacol.* **36** 505 (1989)
263. C J Swain, R Baker, C Kneen, R Herbert, J Moseley, J Saunders, E M Seward, G I Stevenson, M Beer, J Stanton, K Watling, R G Ball *J. Med. Chem.* **35** 1019 (1992)
264. R D Clark, A B Miller, J Berger, D B Repke, K K Weinhardt, B A Kowalczyk, R M Eglen, D W Bonhaus, C H Lee, A D Michel *J. Med. Chem.* **36** 2645 (1993)
265. Y Rival, R Hoffmann, B Didier, V Rybaltchenko, J -J Bourguignon, C G Wermuth *J. Med. Chem.* **41** 311 (1998)
266. Y Sato, M Yamada, S Yoshida, T Soneda, M Ishikawa, T Nizato, K Suzuki, F Konno *J. Med. Chem.* **41** 3015 (1998)
267. M Yamada, Y Sato, K Kobayashi, F Konno, T Soneda, T Watanabe *Chem. Pharm. Bull.* **46** 445 (1998)
268. C Gerald, N Adham, H T Kao, M A Olsen, T M Laz, L E Schechter, J A Bard, P J Vaysse, P R Hartig, T A Branchek *EMBO J.* **14** 2806 (1995)
269. O Blondel, M Gastineau, Y Dahmoune, M Langlois, R Fischmeister *J. Neurochem.* **70** 2252 (1998)
270. K H Buchheit, R Gamse, H J Pfannkuche *Naunyn Schmiedebergs Arch. Pharmacol.* **345** 387 (1992)
271. D L Flynn, D L Zabrowski, D P Becker, R Nosal, C I Villamil, G W Gullikson, C Moummi, D-C Yang *J. Med. Chem.* **35** 1486 (1992)
272. T P Blackburn, G S Baxter, G A Kennet, F D King, D C Piper, G I Sanger, D R Thomas, N Upton, M D Wood *Psychopharmacology* **110** 357 (1993)
273. F D King, M S Hadley, K T Joiner, R T Martin, G J Sanger, D M Smith, G E Smith, P Smith, D H Turner, E A Watts *J. Med. Chem.* **36** 683 (1993)
274. M Langlois, D Yang, B Bremont, S Shen *Bioorg. Med. Chem. Lett.* **5** 795 (1995)
275. R M Eglen, D W Bonhaus, L G Johnson, E Leung, R D Clark *Br. J. Pharmacol.* **115** 1387 (1995)
276. S Elz, A Keller *Arch. Pharm. (Weinheim)* **328** 585 (1995)
277. D Yang, J-L Soulier, S Sicsic, M Mathe-Allainmat, B Bremont, T Croci, R Cardamone, G Aureggi, M Langlois *J. Med. Chem.* **40** 608 (1997)
278. S S Hegde, D W Bonhaus, L G Johnson, E Leung, R D Clark, R M Eglen *Br. J. Pharmacol.* **115** 1087 (1995)
279. R M Eglen, E H Wong, A Dumuis, J Bockaert *Trends Pharmacol. Sci.* **16** 391 (1995)
280. R M Eglen, K Bley, D W Bonhaus, R D Clark, S S Hegde, L G Johnson, E Leung, E H F Wong *Br. J. Pharmacol.* **110** 119 (1993)
281. R D Clark, A Jahangir, L A Flippin, J A Langston, E Leung, D W Bonhaus, E H Wong, L G Jonhnson, R M Eglen *Bioorg. Med. Chem. Lett.* **5** 2119 (1995)
282. A J Kaumann, L M Gaster, F D King, A M Brown *Naunyn Schmiedebergs Arch. Pharmacol.* **349** 546 (1994)
283. L M Gaster, A J Jennings, G F Joiner, F D King, K R Mulholland, S K Rahman, S Starr, P A Wyman, K A Wardle, E S Ellis, K J Sanger *J. Med. Chem.* **36** 4121 (1993)
284. J D Gale, C J Grossman, J W Whitehead, A W Oxford, K T Bunce, P P Humphrey *Br. J. Pharmacol.* **111** 332 (1994)
285. L M Gaster, G F Joiner, F D King, P A Wyman, J M Sutton, S Bingham, E S Ellis, G J Sanger, K A Wardle *J. Med. Chem.* **38** 4760 (1995)
286. I Tapia, L Alonso-Cires, P L Lopez-Tudanca, R Mosquera, L Labeaga, A Innerarity, A Orjales *J. Med. Chem.* **42** 2870 (1999)
287. K-H Buchheit, R Gamse, R Giger, D Hoyer, F Klein, E Kllppner, H-J Pfannkuche, H Mattes *J. Med. Chem.* **38** 2326 (1995)
288. K-H Buchheit, R Gamse, R Giger, D Hoyer, F Klein, E Klöppner, H-J Pfannkuche, H Mattes *J. Med. Chem.* **38** 2331 (1995)
289. A Monge, M del Carmen Pena, J A Palop, J M Caldero, J Roca, E Garcia, G Romero, J del Rio, B Lasheras *J. Med. Chem.* **37** 1320 (1994)
290. J M Schaus, D C Thompson, W E Bloomquist, A D Susemichel, D O Calligaro, M L Cohen *J. Med. Chem.* **41** 1943 (1998)
291. J-L Soulier, D Yang, B Bremont, T Croci, U Guzzi, M Langlois *J. Med. Chem.* **40** 1755 (1997)
292. M-L Cohen, W Bloomquist, J M Schaus, D C Thompson, A D Susemichel, D O Calligaro, I Cohen *J. Pharmacol. Exp. Ther.* **277** 97 (1996)
293. M Wood, M Chaubey, P Atkinson, D R Thomas *Eur. J. Pharmacol.* **396** 1 (2000)
294. B L Roth, S C Craigo, M S Choudhary, A Uluer, F J Monsma Jr, Y Shen, H Y Meltzer, D R Sibley *J. Pharmacol. Exp. Ther.* **268** 1403 (1994)
295. I T Forbes, S Dabbs, D M Duckworth, A J Jennings, F D King, P J Lovell, A M Brown, L Collin, J J Hagan, D N Middlemiss, G J Riley, D R Thomas, N Upton *J. Med. Chem.* **41** 655 (1998)
296. R A Glennon, M Lee, J B Rangisetty, M Dukat, B L Roth, J E Savage, A McBride, L Rauser, S Hufeisen, D K H Lee *J. Med. Chem.* **43** 1011 (2000)

[a] — *Moscow Univ. Bull. (Engl. Transl.)*
[b] — *Russ. J. Org. Chem. (Engl. Transl.)*