Pharmacology Biochemistry & Behavior, Vol. 40, pp. 1041–1051. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Structure-Activity Relationships at 5-HT_{1A} Receptors: Binding Profiles and Intrinsic Activity

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NELSON, D. L. *Structure-activity relationships at 5-HT_{1A} receptors: Binding profiles and intrinsic activity.* PHARMACOL BIOCHEM BEHAV **40**(4) 1041–1051, 1991.—The 5-HT_{1A} receptor has been one of the most studied 5-HT receptor subtypes in terms of its pharmacologic profile. Comparisons of various studies of structure-activity relationships (SAR) at this receptor shows an emerging profile for this receptor's pharmacophore. The present discussion focuses on the findings generated with relatively small molecules that can be considered as analogs of serotonin itself and that illustrate some of the structural properties that are important for high-affinity recognition by the receptor. Most of the SAR work has been based on the affinities of compounds for the receptor as determined by the radioligand-binding technique, which has a significant limitation in that it cannot define the intrinsic activity of compounds at the receptor. This problem can be addressed by functional assays, and an example of SAR at the 5-HT_{1A} receptor-coupled adenylate cyclase system is provided.

Serotonin 5-HT Serotonin$_{1A}$ receptors 5-HT_{1A} receptors Structure-activity relationships

AMONG all the serotonin (5-hydroxytryptamine, 5-HT) receptor subtypes, the 5-HT_{1A} has been one of the most widely studied, and specifically, within the 5-HT_1 class, there is much more known about the structure activity relationships (SAR) for the 5-HT_{1A} receptor than for any of the other 5-HT_1 subtypes. This receptor was initially defined as a binding site for [^{3}H]5-HT, with the basis for its distinction being regional differences in the sensitivity of [^{3}H]5-HT binding to rather nonselective pharmacologic agents, such as spiperone and butaclamol (34,35). The crucial event that facilitated the study of 5-HT_{1A} receptors was the development of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) as a serotonergic agonist (2), followed by the later discoveries that this compound was very selective for the 5-HT_{1A} receptor (31) and that [^{3}H]8-OH-DPAT could be used to measure 5-HT_{1A} receptors in ligand-binding assays (17,28). This then resulted in a very specific tool to study the pharmacology of the 5-HT_{1A} receptor independent of the other 5-HT receptor subtypes.

The availability of a selective agonist for the 5-HT_{1A} receptor has resulted in a substantial body of knowledge about this receptor and its actions. In the central nervous system, the 5-HT_{1A} receptor is broadly distributed and occurs both postsynaptically and as a somaldendritic autoreceptor [for reviews, see (11,39)]; it couples to multiple effector systems, e.g., the inhibition and stimulation of adenylate cyclase, the stimulation of potassium channels, and the inhibition of carbachol-stimulated phosphatidylinositol turnover [for reviews, see (8, 11, 39)], and drugs that affect it may be useful for treating certain conditions, such as anxiety and depression [for reviews, see (12,42)]. While it is outside the scope of the present discussion to thoroughly describe the properties of the 5-HT_{1A} receptor, the recent reviews noted above will provide the interested reader with extensive information regarding its properties.

Over the years, a wide variety of compounds has been examined at the 5-HT_{1A} receptor, giving clues to the structural requirements for recognition by this receptor. However, in many cases, the compounds have represented a single or only a few examples from any given chemical class so that it has not been possible to determine the relative importance of particular structural features for recognition by the receptor. In other cases, the size of the compounds and/or the number of different possible conformations has made it impossible to determine either the regions of the molecules that are important for binding to the receptor or the likely conformations that the receptor might recognize. Therefore, for the present discussion, the groups of compounds that will be considered have been limited primarily to those classes where multiple structures have been made and studied and those classes that represent relatively small molecules, especially those that can be viewed as rigid or partially rigid homologs of 5-HT itself. Examples of these include the indoleethylamines, aminotetralins, tetrahydropyridylindoles, arylpiperazines, and tricyclic partial ergolines. Representative examples of well-documented 5-HT_{1A} agonists from these classes are shown in Fig. 1.

A standard description of the fundamental or most basic pharmacophore for monoamine receptors consists of two primary parts: 1) an aromatic nucleus and 2) an amino function at a specified distance and orientation from the aromatic nucleus [see for example (26)]. Based on this approach, the initial discussion of the groups of compounds represented in Fig. 1 will be to consider how structural alterations on or around the aromatic indole nucleus (or its equivalent) and the ethylamino group affect the recognition of the structures by the 5-HT_{1A} receptor. The measure of goodness of fit to the receptor is defined in this case as the affinity (i.e., dissociation constant, K_d) for the receptor as determined by the radioligand-binding technique, using [^{3}H]8-OH-DPAT as the ligand. A limit to SAR analysis based on this measure is that it does not provide information on the structural

TABLE 1

EFFECT ON 5-HT_{1A} AFFINITY BY SUBSTITUTIONS AT THE INDOLE C5 POSITION OF INDOLEETHYLAMINES

Compound	R	R_1	K_i* (nM)	Reference
Tryptamine	H	H	125	(44)
5-HT	OH	H	3	(19)
5-MeOT	OCH_3	H	9	(19)
5-CT	$CONH_2$	H	0.2	(19)
5-BOT	$OCH_2C_6H_5$	H	60	(33)
DMT	H	CH_3	170†	(28)
5-OH-DMT	OH	CH_3	4.9†	(28)
5-MeO-DMT	OCH_3	CH_3	6.5†	(28)

*$K_i = K_d$ = dissociation constant.

†Values given as IC_{50} rather than K_i. IC_{50} = concentration of drug producing 50% inhibition of binding of the radioligand.

determinants that define the ability of a compound to activate the receptor, i.e., agonist versus antagonist activity. This concern will be addressed in more detail in the last section of this paper.

SAR OF COMPOUNDS BINDING TO THE 5-HT_{1A} RECEPTOR

Effects of Substitutions at the Indole C5 (or Equivalent) Position

The 5-hydroxy group of 5-HT has long been considered an important feature for its ability to be recognized by and for its activation of the various 5-HT receptor subtypes. Over the years, many different tryptamines have been synthesized with different substituents at this position for testing at 5-HT receptors. Interestingly, most of the SAR work with these indoleethylamines appears to have been carried out before the development of specific assays for the 5-HT_{1A} receptor; thus there is less information about the C5 substituents for this class of compounds than for more recently developed classes, such as the tetrahydropyridylindoles or aminotetralins. Examples of the effects of sub-

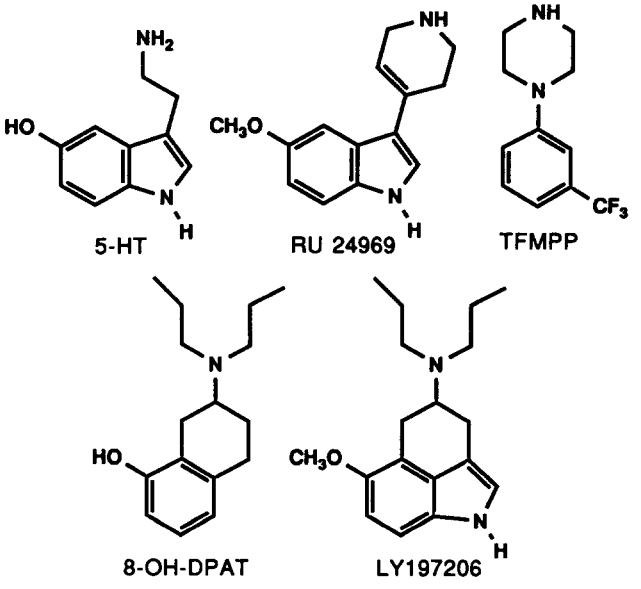
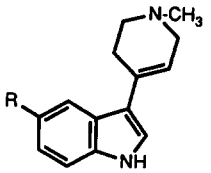


FIG. 1. Examples of classes of 5-HT_{1A} receptor ligands.

TABLE 2

EFFECT ON 5-HT_{1A} AFFINITY BY SUBSTITUTIONS AT THE INDOLE C5 POSITION OF TETRAHYDROPYRIDYLINDOLES

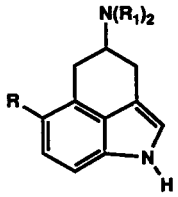


Compound	R	K_i (nM)
SN-1	H	146
SN-3	OCH_3	21.1
SN-2	Br	15
SN-21	Cl	26.2
SN-14	F	67.9
SN-26	$CONH_2$	5.31
SN-11	$COOCH_3$	19.4
SN-7	$COOC_2H_5$	36.1
SN-25	$OOCCH_3$	80.5
SN-4	CH_3	31.8
SN-5	NO_2	36.8
SN-17	CN	55.0
SN-20	OH	61.7
SN-6	$OCH_2C_6H_5$	111
SN-15	phthalimido	377

From (45).

TABLE 3

EFFECT ON 5-HT_{1A} AFFINITY BY SUBSTITUTIONS AT THE C6 POSITION OF A SERIES OF TRICYCLIC PARTIAL ERGOLINES

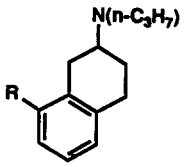


Compound	R	R_1	K_i (nM)	Reference
RU27849	H	H	326	(44)
RU28306	H	Me	329	(44)
LY178208	CN	Propyl	22	(41)
LY178209	NO_2	Propyl	19	(41)
LY197205	Br	Propyl	1.3	(41)
LY178210	$CONH_2$	Propyl	0.67	(41)
LY197206	OCH_3	Propyl	1.3	(41)
LY254089	$COOCH_3$	Propyl	0.89	(41)

stituents at the C5 position of indoleethylamines are shown in Table 1. Even within this small series of indoleethylamines, the importance of the C5 substituent can be seen. Thus the unsubstituted compounds tryptamine and DMT have much lower affinity for the receptor than the compounds with the C5 substitutions. Similar effects have also been seen with a series of tetrahydropyridylindoles, as shown in Table 2.

TABLE 4

EFFECT ON 5-HT_{1A} AFFINITY BY SUBSTITUTIONS AT THE C8 POSITION OF A SERIES OF AMINOTETRALINS



Compound	R	IC_{50} (nM)*
LY133610	H	32
8-OH-DPAT	OH	2.7
8-OMe-DPAT	OCH_3	4.9
LY198354	F	84
LY198342	Cl	9.7
LY190533	Br	19
LY246261	I	13
LY198743	CH_3	44
LY198968	CO_2CH_3	2.6
LY161610	$CONH_2$	8.3
8-DMK-DPAT	$COCHN_2$	19†
LY190512	CN	39
LY232067	SCH_3	1.2
LY233583	SC_2H_5	40
LY233877	SC_6H_5	13
LY233178	$SCH_2C_6H_5$	12
LY209418	S(*p*-Me)C_6H_5	35

*From (37); †from (25).

A third example of indole-containing 5-HT_{1A} ligands is the tricyclic partial ergoline class. The number of these compounds that have been reported on is small, but the findings support the importance of the substituent at the C5 indole position for affinity at the 5-HT_{1A} receptor, as shown in Table 3.

As noted above, 8-OH-DPAT has become the pharmacologic standard for defining 5-HT_{1A} receptors. For this relatively rigid analog of 5-HT, substitutions at the C8 position have been assumed to be equivalent to the C5 position of the indoles. Examples of 8-OH-DPAT analogs having various C8 substituents are shown in Table 4.

Among the indole-containing compounds shown in Tables 1–3, it can be seen that a variety of groups substituted at C5 result in higher affinity than the unsubstituted homologs. This site appears to tolerate relatively large groups, with substitutions as large as 5-benzyloxy resulting in compounds that retain relatively good affinity. It is also interesting to note that, among the groups tested, the carboxamido group resulted in the highest affinity for all three classes of compounds. The 8-OH-DPAT analogs show similar effects of substitutions at the C8 position of the aminotetralin. However, there are significant differences compared to the indole-containing compounds. For example, the unsubstituted compound (i.e., 8-H) has relatively higher affinity at the 5-HT_{1A} site than the unsubstituted indoles. Also, 8-car-

TABLE 5

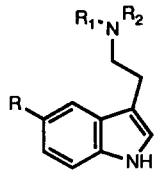
EFFECT ON 5-HT_{1A} AFFINITY OF SUBSTITUTIONS ON THE BENZO RING OF SOME INDOLEETHYLAMINES

Compound	IC_{50} (nM)
5-OH-N,N-dimethyltryptamine	4.9
4-OH-N,N-dimethyltryptamine	190
5-MeO-N-methyl,N-isopropyltryptamine	87
4-OH-N-methyl,N-isopropyltryptamine	4900
6-MeO-N-methyl,N-isopropyltryptamine	>10,000
5,6-diMeO-N-methyl,N-isopropyltryptamine	>10,000

From (28).

TABLE 6

EFFECT ON 5-HT_{1A} AFFINITY OF SUBSTITUTIONS ON THE AMINO GROUP OF SOME INDOLEETHYLAMINES



Compound	R	R_1	R_2	K_i (nM)	Reference
Tryptamine	H	H	H	125	(44)
DMT	H	Me	Me	245	(44)
5-HT	OH	H	H	6.6*	(17)
Bufotenine	OH	Me	Me	21*	(17)
5-MeOT	OCH_3	H	H	1.8	(38)
5-MeODMT	OCH_3	CH_3	CH_3	1.9	(38)
5-CT	$CONH_2$	H	H	0.2	(19)
DP-5-CT	$CONH_2$	*n*-propyl	*n*-propyl	0.3	(19)
5-HT	OH	H	H	1.7	(16)
DiPS	OH	*n*-propyl	*n*-propyl	7.1	(16)
5-OMeT	OCH_3	H	H	3.2	(16)
5-OMe-DMT	OCH_3	CH_3	CH_3	7.8	(16)
5-OMe-DiPS	OCH_3	*n*-propyl	*n*-propyl	4.0	(16)
5-MeODMT	OCH_3	CH_3	CH_3	10	(13)
—	OCH_3	H	NBP†	20	(13)
BDT	OCH_3	H	MBD‡	28	(43)

*These are given as IC_{50} values.
†NBP = N-(4-phthalimidobutyl).
‡MBD = 2-methyl-1,4-benzodioxane.

boxamido-DPAT has relatively lower affinity compared to the other substituents than the 5-carboxamido-indoles. This could reflect slight differences in the fit of the aminotetralins versus the indoles within the receptor or differences in the electronic effects of the indole system on the substituents compared to tetralin. Resolution of this will require further study.

In addition to substitutions at the indole C5 position, the effects of substitutions at other portions of the benzo ring of indole are of interest. This does not appear to have been systematically examined for the 5-HT_{1A} receptor, but the limited studies that are available suggest that substitutions at positions C4 or C6 are detrimental to affinity (Table 5).

Effects of Substitutions at the Amino Group

Examinations of substitutions at the amino group have begun to provide some insights into how these can affect recognition by the 5-HT_{1A} receptor. Examples of these are shown in Table 6. The data show that symmetrical substitutions up to N,N-di-*n*-propyl have no significant effect on affinity. For monosubstitutions, relatively larger substituents can be tolerated quite well, and this appears to be a function of the alkyl chain length separating the amino group from the substituent (13).

Substitutions at the amino group have been most extensively studied for the aminotetralins. Examples of these are summarized in Table 7. Unlike the indoleethylamines, the aminotetralins appear to require substitution on the amino group to achieve optimal affinity for the 5-HT_{1A} receptor. For symmetrical alkyl substitutions, the di-*n*-propyl substitution seems optimal, with affinity dropping off significantly for the di-*n*-butyl substitution. There also appears to be an interesting enantiomeric selectivity with regard to the effects of the alkyl substitutions. For di-*n*-methyl and di-*n*-ethyl substitutions, the (*R*)-enantiomer has the highest affinity; for the di-*n*-propyl, there is no significant difference in the affinities of the two enantiomers; and for the di-*n*-butyl compounds, the (*S*)-enantiomer has the highest affinity. For monosubstitution at amino group (or where one substituent is limited to a methyl group), it can be seen that relatively large substituents can be tolerated, depending on the alkyl chain length that links them to the amino group.

Effects of Substitutions on the Pyrrole Ring

Substitution on the pyrrole ring is one of the least explored areas for interaction of indole-containing compounds with the 5-HT_{1A} receptor. From the data available, it would appear that adding a methyl substituent at the indole C2 position results in a large decrease in 5-HT_{1A} affinity (Table 8). It is unclear, however, as to what the effects of N1 substitutions might be. For the tetrahydropyridylindoles, at least, addition of a benzyl group at this position dramatically decreased 5-HT_{1A} affinity. No equivalent indoleethylamine has been reported, nor have smaller substituents been evaluated at the N1 indole position.

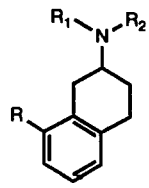
While there is limited SAR information on the effects of substitutions at the pyrrole ring, it does appear clear that this ring itself is not necessary for high affinity at the 5-HT_{1A} receptor. This can be seen especially in the aminotetralins (Tables 4 and 7), which lack this ring, compared to the tricyclic partial ergolines (Table 3). Likewise, the phenylcyclopropylamine shown in Table 9 also shows relatively high affinity for the 5-HT_{1A} receptor.

Miscellaneous Structural Modifications

In addition to the semisystematic structural modifications of 5-HT-like molecules described above, there is a plethora of other

TABLE 7

EFFECT ON 5-HT_{1A} AFFINITY OF SUBSTITUTIONS ON THE AMINO GROUP OF AMINOTETRALINS



Compound	R	R_1	R_2	K_i (nM)	Reference
8-MeO-AT	OCH_3	H	H	177	(19)
8-MeO-PAT	OCH_3	H	*n*-propyl	4.8	(19)
8-MeO-DPAT	OCH_3	*n*-propyl	*n*-propyl	2.6	(19)
LY103384	Cl	H	H	374*	(37)
LY178295	Cl	CH_3	CH_3	310*	(37)
LY190228	Cl	C_2H_7	C_2H_7	25*	(37)
LY198342	Cl	*n*-propyl	*n*-propyl	9.7*	(37)
LY233039	Cl	*n*-butyl	*n*-butyl	620*	(37)
LY254362	SCH_3	CH_3	CH_3	23*	(37)
LY232067	SCH_3	*n*-propyl	*n*-propyl	1.2*	(37)
(*R*)-8-OH-DMAT	OH	CH_3	CH_3	75*	(3)
(*S*)-8-OH-DMAT	OH	CH_3	CH_3	675*	(3)
(*R*)-8-OH-DEAT	OH	C_2H_7	C_2H_7	9.7*	(3)
(*S*)8-OH-DEAT	OH	C_2H_7	C_2H_7	115*	(3)
(*R*)-8-OH-DPAT	OH	*n*-propyl	*n*-propyl	4.8*	(3)
(*S*)-8-OH-DPAT	OH	*n*-propyl	*n*-propyl	6.5*	(3)
(*R*)-8-OH-DBAT	OH	*n*-butyl	*n*-butyl	109*	(3)
(*S*)-8-OH-DBAT	OH	*n*-butyl	*n*-butyl	46*	(3)
—	H	H	*n*-propyl	19	(32)
—	OCH_3	H	H	53	(32)
—	OCH_3	H	*n*-propyl	2.3	(32)
—	OCH_3	CH_3	*n*-propyl	2.1	(32)
—	OCH_3	CH_3	CH_2Ph†	78	(32)
—	OCH_3	H	$(CH_2)_2$Ph	44	(32)
—	OCH_3	CH_3	$(CH_2)_2$Ph	7.9	(32)
—	OCH_3	H	$(CH_2)_3$Ph	2.5	(32)
—	OCH_3	H	$(CH_2)_4$Ph	5.6	(32
—	H	H	$(CH_2)_3$Ph	13	(32)
—	OH	H	$(CH_2)_3$Ph	1.9	(32)
—	OCH_3	CH_3	$(CH_2)_3$Ph	2.0	(32)
—	OBenzyl	H	$(CH_2)_3$Ph	10	(32)
—	OCH_3	H	$(CH_2)_2$PTH‡	250	(13)
—	OCH_3	H	$(CH_2)_3$PTH	48	(13)
—	OCH_3	H	$(CH_2)_4$PTH	11	(13)

*IC_{50} values.
†Ph = phenyl.
‡PTH = 2-phthalimido.

structures that have been examined at the 5-HT_{1A} receptor. There are many more of these than can be addressed in a review of this size; however, selected examples are shown below to give some feel for the range of small molecule structures that can interact with high affinity at the 5-HT_{1A} receptor.

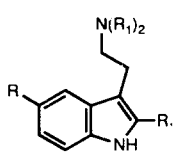
8-OH-DPAT analogs. The compounds in Table 9 show a sampling of 8-OH-DPAT-related structures and serve to illustrate certain spatial restrictions for recognition by the 5-HT_{1A} receptor. They also serve to emphasize the importance of studying resolved enantiomers when characterizing SAR.

Arylpiperazines. Over the years, a number of arylpiperazines has been shown to be active at a variety of 5-HT receptor subtypes. Aside from the naphthylpiperazines, the most active 5-HT_{1A} compounds have a second aryl, heteroaryl, or heterocyclic moiety attached through an alkyl chain to the piperazine (see Table 10). There are many compounds that have high affinity for the 5-HT_{1A} receptor that share this common characteristic, i.e., two aryl, polycyclic aryl, heteroaryl, or heterocyclic moieties coupled by alkyl chains of varying lengths. A possible explanation of their affinities could be that one region of the molecule binds within the active site of the receptor (i.e., the site 5-HT binds to), while the other region of the molecule binds to an accessory site. It is outside the scope of this review to discuss the many compounds that fit this mold; however, examples can be found in the following references: (1, 13, 18).

Beta-adrenergic antagonist-like structures. Certain β-adrenergic receptor antagonists, such as propranolol (36) and pindolol (22), also have relatively high affinity for the 5-HT_{1A} receptor.

TABLE 8

EFFECT ON 5-HT_{1A} AFFINITY OF SUBSTITUTIONS ON THE PYRROLE RING OF CERTAIN INDOLE-CONTAINING COMPOUNDS



Structure 1

Structure 2

Compound	R	R_1	R_2	K_i (nM)	Reference
Structure 1	OH	H	—	2	(23)
Structure 1	OH	CH_3	—	1200	(23)
Structure 1	OCH_3	CH_3	—	1300	(23)
Structure 2	H	H	H	146	(45)
Structure 2	H	CH_3	H	1783	(45)
Structure 2	OCH_3	H	H	11	(45)
Structure 2	OCH_3	CH_3	H	345	(45)
Structure 2	H	H	Benzyl	>10000	(45)

Table 11 shows an exploration of the 5-HT_{1A} affinities of a series of propranolol-like structures. These compounds are of particular interest not only because some of them have reasonably high affinity for the 5-HT_{1A} receptor, but because they also have relatively low affinity for the β-adrenergic receptors and may act as antagonists at the 5-HT_{1A} receptor.

Summary of the SAR of 5-HT_{1A} Binding Sites

It is hoped that the selected groups of compounds discussed above provide a general feel for the structural requirements for recognition by the 5-HT_{1A} receptor. Certainly, enough compounds have been studied at the 5-HT_{1A} receptor to begin to build a picture of the pharmacophore for this site. One area not addressed in this review is the selectivity or specificity of the compounds for the 5-HT_{1A} receptor relative to other 5-HT receptor subtypes and other neurotransmitter receptors. Given the structural similarities among the many G protein-coupled receptors, it is not surprising that many of the compounds that interact with 5-HT_{1A} receptors also interact with other receptor types. Examples of this are given in the introductory paper by Glennon and Dukat. For most of the compounds discussed in this review, there have been only limited, if any, comparisons at other receptor subtypes. Selectivity must be addressed on a case by case basis, and for any given compound the degree of selectivity can only be expressed among the different receptor subtypes that have actually been experimentally evaluated.

While the literature provides information on the 5-HT_{1A} affinity of a wide variety of structural types, there is a need for someone to incorporate all this information into a large comprehensive SAR or quantitative SAR assessment. Such an effort would likely lead to a much more accurate assessment of the 5-HT_{1A} pharmacophore and facilitate the design of optimal ligands for this receptor.

INTRINSIC ACTIVITY OF 5-HT_{1A} LIGANDS

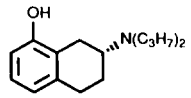
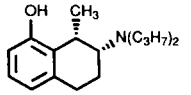
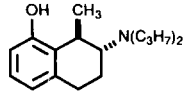
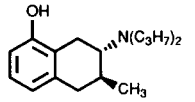
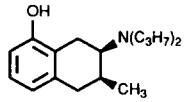
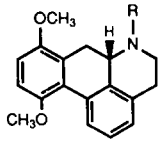
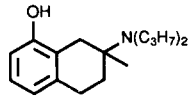
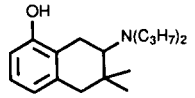
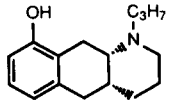
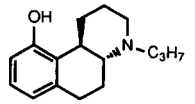
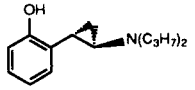
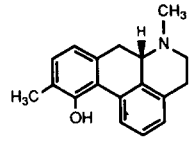
Most of the work examining SAR at the 5-HT_{1A} receptors has focused on the binding affinity of compounds. While such information is of great importance in defining the optimal structures for recognition by the 5-HT_{1A} receptor, it does not provide information about efficacy, i.e., whether a compound is a full agonist, partial agonist, or antagonist [for a review of the definitions of efficacy, intrinsic activity, etc., see (24)]. Such information is important for the use of 5-HT_{1A} ligands both as research tools and therapeutic agents. For example, of special concern currently is the need for a very selective, high-affinity full antagonist at the 5-HT_{1A} receptor. Current 5-HT_{1A} antagonists are plagued by either lack of specificity, by having some partial agonist activity, or both.

When tested for 5-HT_{1A} functional activity, most compounds have been examined in vivo. While this can provide qualitative information regarding agonist versus antagonist activities, it is difficult to determine relative efficacies and potencies of compounds, especially between different chemical classes. For example, pharmacokinetic differences, e.g., distribution, metabolism, compartmentalization, etc., may result in different concentrations of drug reaching the receptors even when the different compounds are given in equivalent doses. This could obviously lead to erroneous conclusions regarding SAR. Also, the type of response measured, e.g., behavioral, neurochemical, electrophysiologic, etc., may give different conclusions regarding efficacy, depending on whether the 5-HT_{1A} response is characterized by having a significant receptor reserve or not. An example of this can be illustrated by the effects of the high-affinity agent NAN-190 (see Table 10 for structure). When examined in certain in vivo tests, NAN-190 appears to be a full antagonist at 5-HT_{1A} receptors (14, 15, 21); however, at somal-dendritic autoreceptors, where there is apparently a large receptor reserve (29), NAN-190 exhibits partial agonist activity (21). Thus information regarding the agonist/antagonist profile of 5-HT_{1A} compounds must be evaluated in the context of the tests that are used.

Another method of testing functional activity at 5-HT_{1A} receptors is to examine effects against forskolin-stimulated adenylate cyclase activity in rat hippocampal membranes, a system that has been well characterized as a measure of the 5-HT_{1A} receptor (9,10). This in vitro system provides access of the compound to the receptors under conditions that are similar to the binding assay and that alleviate some of the access problems that occur

TABLE 9

5-HT$_{1A}$ RECEPTOR AFFINITIES OF A GROUP OF 8-OH-DPAT ANALOGS

Structure	Enantiomer	K_i (nM)
	(2*R*)-	4.1
	(2*S*)-	6.1
	(1*S*,2*R*)-	21
	(1*R*,2*S*)	2920
	(±)-	1037
	(2*S*,3*S*)-	50
	(2*R*,3*R*)-	1389
	(2*R*,3*S*)-	394
	(2*S*,3*R*)-	2021
	(*R*)-	
	R=CH_3	8.6*
	R=n-C_3H_7	240*
	(±)-	1130
	(±)-	>10000
	(4a*R*,10a*S*)-	>10000
	(4a*S*,10a*R*)-	151
	(4a*R*,10b*R*)-	33
	(4a*S*,10b*S*)-	3.9
	(1*R*,2*S*)-	8
	(1*S*,2*R*)-	923
	(*R*)-	3.7†

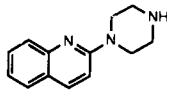
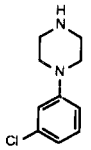
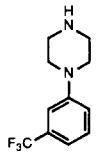
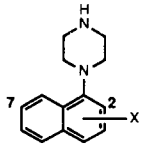
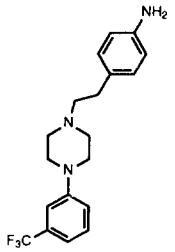
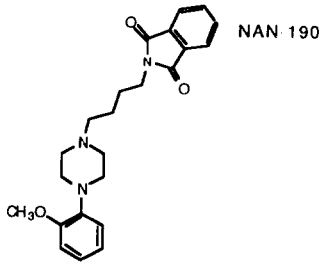
*From (5); †from (6).
All other compounds from (29).

with in vivo studies. Because of difficulties in carrying out the measurements of 5-HT-mediated inhibition of forskolin-stimulated adenylate cyclase, this technique has not yet been widely applied to the screening of compounds for SAR analyses, but advances in the assay should result in its broader application.

Table 12 illustrates the effects, as measured by the cyclase assay, of certain relatively small ligands at the 5-HT$_{1A}$ receptor. As can be seen from these examples, slight changes in structure or configuration can have dramatic effects on intrinsic activity that would not have been predicted from examining the binding

TABLE 10

5-HT_{1A} RECEPTOR AFFINITIES OF A SERIES OF ARYLPIPERAZINES

Structure		K_i (nM)
	Quipazine	3240*
	mCPP	245*
	TFMPP	288*
	X=H	39*
	X=2-OMe	34†
	X=7-OMe	3.3†
	PAPP	6.2*
	NAN-190	0.6*

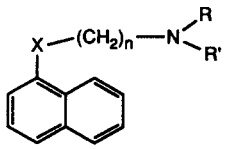
*From (40); †from (13).

affinity alone. For example, the two enantiomers of 8-OH-DPAT show no significant difference in affinity for the 5-HT_{1A} receptor; yet, one is a full agonist while the other is a partial agonist with only about 50% intrinsic activity (note that intrinsic activity in this system is defined relative to the native neurotransmitter 5-HT as the full agonist). Certain DPAT analogs, e.g., (2*R*,3*R*)-CM-12 and (*S*)-UH-301, produced no detectable agonist activity, but rather antagonized the activity of 5-HT at the cyclase. In fact, (*S*)-UH-301 has been shown to act as a 5-HT_{1A} antagonist in a variety of in vivo tests as well, with no indication of agonist activity (4,20). TD-59 and TD-60 are an example of another 5-HT_{1A} ligand class, the tetrahydropyridylindoles, where a slight structural difference translates into a rather large difference in intrinsic activity.

In the future, it is hoped that more SAR and quantitative SAR studies will focus on defining not only those structural features that define optimal affinity and selectivity for the 5-HT_{1A} receptor, but also how various structural properties affect the ability of small molecules to activate the receptor. Such information should result in the design of compounds having the de-

TABLE 11

AFFINITIES AT THE 5-HT_{1A} RECEPTOR OF A SERIES OF PROPRANOLOL-LIKE COMPOUNDS



X	n	R	R′	K_i (nM)
O	3	CH_3	CH_3	345
O	3	n-C_3H_7	n-C_3H_7	450
O	3	n-C_4H_9	n-C_4H_9	225
O	3*	n-C_3H_7	n-C_3H_7	1325
O	2	CH_3	CH_3	80
O	2	CH_3	n-C_3H_7	45
O	2	CH_3	benzyl	95
O	2	C_2H_5	n-C_4H_9	39
CO	2	C_2H_5	n-C_4H_9	3530
CH_2	2	C_2H_5	n-C_4H_9	300

*Hydroxylated chain (-$CH_2CH(OH)CH_2$-).
From (36).

sired degree of selectivity and intrinsic activity to serve as tools to probe selected parts of the serotonergic systems, as well as serving as prototypes for new therapeutic agents.

SUMMARY

The intent of this paper was not to provide an exhaustive review of the hundreds of compounds that have been tested at 5-HT_{1A} receptors, but rather to use selected examples to show the importance of various structural features of relatively small 5-HT-like molecules. From these kinds of studies, an emerging picture of the 5-HT_{1A} pharmacophore can be seen. Thus the importance of the substituent at the C5 indole (and equivalent) position is beginning to be clear, as are the constraints for substituents on the amino group. Less clear, and an area where additional work is needed, are the effects of substituents on the pyrrole nitrogen. While much information has been gained regarding the structural features that determine optimal binding to the 5-HT_{1A} receptor, there is still much work to be done to determine those properties that confer specificity for this receptor type compared to other 5-HT receptor subtypes and other neurotransmitter receptors. The ligand-binding technique has been instrumental in developing the SAR for the 5-HT_{1A} receptor, but it is clear from functional studies that SAR studies must ultimately include not only binding affinity, but measures of intrinsic activity as well. At present, there is a significant lack of information regarding the intrinsic activities of homologous series of compounds at the 5-HT_{1A} receptor. In addition, there is the question of accessory binding sites on the 5-HT_{1A} receptor and how these might be used to influence affinity and selectivity. Lastly, better knowledge will have to be developed regarding the structure of the 5-HT_{1A} receptor and where in the receptor the different classes of ligands are binding.

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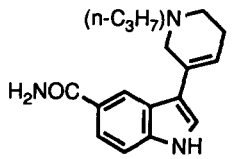
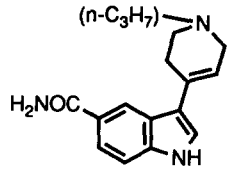
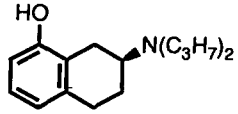
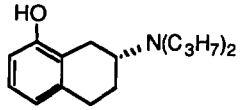
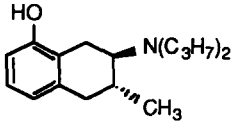
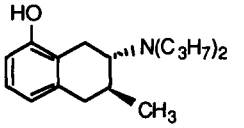
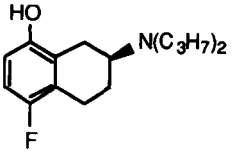
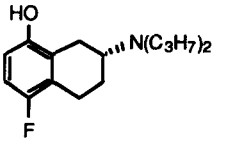
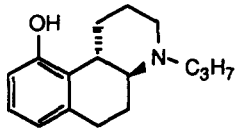
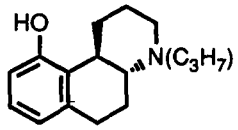
TABLE 12

AFFINITIES AND INTRINSIC ACTIVITIES OF VARIOUS LIGANDS AT THE 5-HT_{1A} RECEPTOR

Compound	Structure	Affinity K_i (nM)*	Potency EC_{50} (nM)†	Intrinsic Activity‡
TD-59		4.4	203	100
TD-60		17	—§	20
(*S*)8-OH-DPAT		6.1	135	47
(*R*)8-OH-DPAT		4.1	57.4	101
(2*R*,3*R*) CM-12		1389	—§	NS¶
(2*S*,3*S*) CM-12		49.6	643	78
(*S*)UH-301		126	—§	NS¶
(*R*)UH-301		32.7	356	47
(4a*S*,10b*S*) JV-26		3.9	47.13	82
(4a*R*,10b*R*) JV-26		32.3	—§	28

Values are from (7). TD-59 and TD-60 were synthesized in the laboratory of A. R. Martin, Dept. of Pharmaceutical Sciences, University of Arizona. The remaining compounds were synthesized in the laboratory of U. Hacksell, Dept. of Organic Pharmaceutical Chemistry, Uppsala University.

*5-HT_{1A} binding affinity against [^{3}H]8-OH-DPAT.

†EC_{50} determined in the forskolin-stimulated cyclase assay as calculated by nonlinear regression analysis.

‡Percent inhibition of the 5-HT-sensitive component of forskolin-stimulated adenylate cyclase.

§An accurate EC_{50} could not be calculated due to low intrinsic activity.

¶No statistically significant inhibition of cyclase detected.

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