Ketanserin Analogues: Structure-Affinity Relationships for 5-HT_2 and 5-HT_{1C} Serotonin Receptor Binding

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Received August 26, 1992

Ketanserin is the prototypic 5-HT_2 serotonin antagonist; although it has been an important tool for the study of serotonin pharmacology, it has had relatively little impact on drug design because remarkably little is known about its structure-affinity relationships. Furthermore, ketanserin also binds at 5-HT_{1C} receptors and even less is known about the influence of its structural features on 5-HT_{1C} receptor affinity. The present study reveals that the fluoro and carbonyl groups of the 4-fluorobenzoyl portion of ketanserin make small contributions to 5-HT_2 binding and that the intact benzoylpiperidine moiety is an important feature. Ring-opening of the piperidine ring reduces affinity. Although the quinazoline-2,4-dione moiety also contributes to binding, it appears to play a smaller role and can be structurally simplified with retention of 5-HT_2 affinity. N-(4-Phenylbutyl)-4-(4-fluorobenzoyl)piperidine (**39**), for example, binds with nearly the same affinity (K_i = 5.3 nM) as ketanserin (K_i = 3.5 nM). All of the compounds examined bind at 5-HT_{1C} sites with lower affinity than ketanserin, and some of the simplified analogues bind with nearly 10 times the 5-HT_2 versus 5-HT_{1C} selectivity of ketanserin; however, none displays >120-fold selectivity. Several of the compounds, such as the amide **32** and the urea **33** represent examples of new structural classes of 5-HT_2 ligands.

5-HT_2 serotonin receptors are of significant clinical interest because of their potential involvement in cardiovascular function and in certain mental disorders.[1-3] Ketanserin (**1**) is the most widely used 5-HT_2 antagonist in preclinical pharmacological investigations, and [^{3}H]-ketanserin is the radioligand of choice for binding studies. Although ketanserin has been available for about a decade,[4] remarkably little has been published about its structure-affinity relationships. What little information is available is limited primarily to the following observations: the quinazoline 2-position carbonyl group can be replaced with a thiocarbonyl group, a phenolic hydroxyl moiety can be introduced at the 6-position, the ethyl side chain can be extended to butyl, and the quinazoline nucleus can be replaced by a pyridopyrimidine (e.g. pirenperone, **2**) or a thiazolopyrimidine (e.g. setoperone), all with less than 2-fold effect on 5-HT_2 affinity.[5] More recent reports suggest that replacement of the quinazoline nucleus with other ring systems (with the exception of thienopyrimidines and pyridopyrimidines) results in dramatic decreases in affinity.[6,7] Furthermore, in contrast to what was seen with the butyl derivative, extension of the ethyl side chain of ketanserin to a propyl side chain results in a >100-fold decrease in 5-HT_2 affinity.[7] There is also a report that reduction of the 4-fluorobenzoyl group to the corresponding benzylic alcohol reduces 5-HT_2 affinity by 680-fold.[5] Although the 4-fluorobenzoyl group is a standard feature among many ketanserin-related analogues, there are several analogues where the 4-fluorobenzoyl portion has been replaced by a benzylidene or similar moiety (e.g. ritanserin, **3**). In each case though, the benzylic carbon is typically a carbonyl group (e.g. **1**), a masked carbonyl group (e.g. risperidone, **4**) or is an sp^2-hybridized carbon atom (e.g. **3**). A number of high-affinity 5-HT_2 antagonists are now available (e.g. **1-6**; Chart I) however, to date, a systematic structure-affinity investigation of ketanserin has not been reported.

Ketanserin is not only a 5-HT_2 antagonist, but with the subsequent discovery of 5-HT_{1C} receptors came the realization that it is also a 5-HT_{1C} antagonist. Ketanserin has been reported to bind with as little as 2-fold[8] to as much as 140-fold[9] selectivity for 5-HT_2 versus 5-HT_{1C} receptors. Thus, in addition to a lack of information on how specific structural features influence the 5-HT_2 affinity of ketanserin, almost nothing is known concerning how these same features impact on 5-HT_2 versus 5-HT_{1C} selectivity.

5-HT_2 receptor topography appears to accept a wide array of structural types, with derivatives of nearly all classes of serotonergic agents displaying some affinity for these sites.[10] For comparison purposes amongst these

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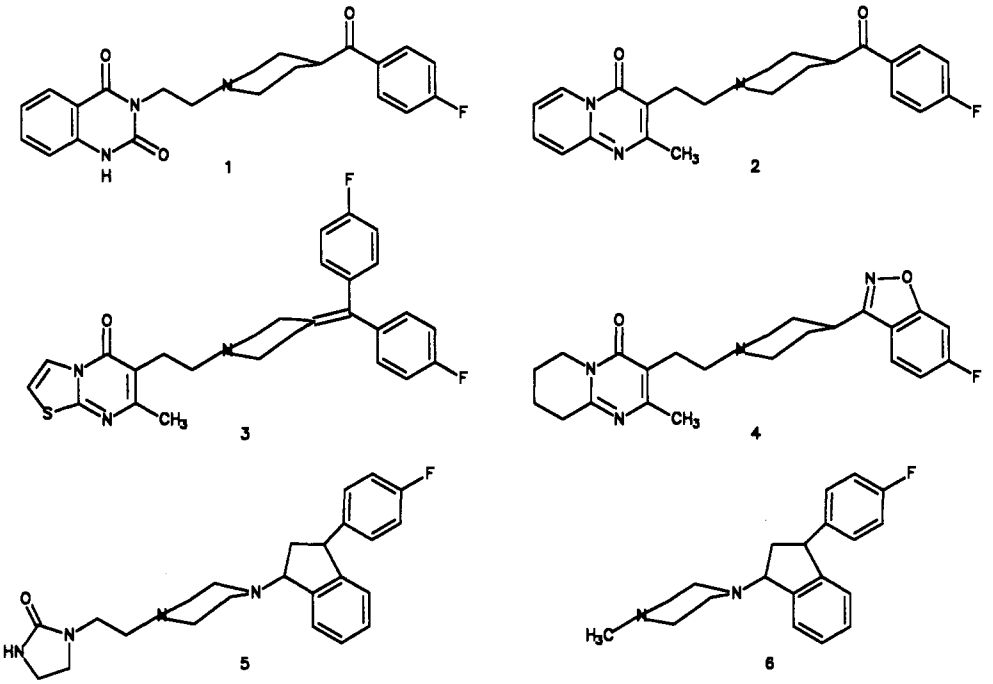
Chart I



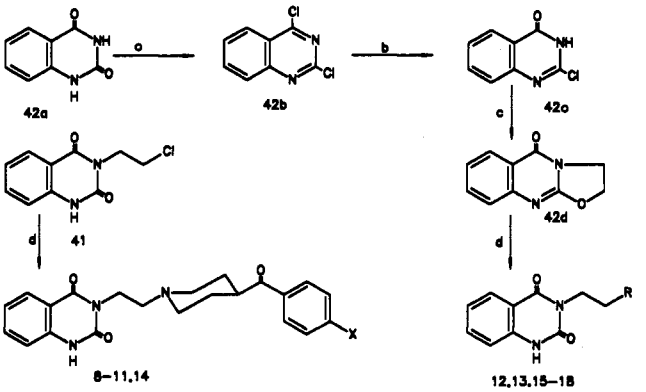
different classes of agents, the ergolines possess some advantages as templates. Although most ergolines are nonselective serotonergic agents, they typically bind with high affinity, they can serve as 5-HT_2 agonists, partial agonists, or antagonists (depending upon their specific substituents), they possess a rather conformationally-constrained and stereochemically-defined framework, and embedded within this framework can be found fragments of other known classes of serotonergic agents.[10,11] (+)-Lysergic acid diethylamide (LSD, 7) is representative of this class of compounds. In order to define the manner in which ketanserin binds at 5-HT_2 receptors relative to the ergolines, we conducted molecular modeling studies that suggest that the structure of ketanserin may be related to that of LSD in two completely different orientations: one in which the quinazolinone portion, and another in which the benzoyl portion, may mimic the indole nucleus.[10]

The purpose of the present investigation was threefold: (a) to determine what structural aspects of the ketanserin molecule are necessary for, and how they influence, 5-HT_2 binding, (b) to determine how these same structural features contribute to 5-HT_{1C} binding, and (c) to determine how the structure of ketanserin might be related to that of the ergolines by synthesis and evaluation of what might be considered each of the two halves of the ketanserin molecule. Hopefully, these studies will allow us to relate the structure of ketanserin to certain other 5-HT_2 antagonists and may lend some insight to the subsequent design and synthesis of more selective agents.

Chemistry

The quinazolinone derivatives were prepared by one of two methods (Scheme I): reaction of the appropriate amine either with 3-(2-chloroethyl)quinazoline-2,4-dione (**41**) (for **8–11, 14**; method A), or with 2,3-dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-one (**42d**) (for **12, 13, 15–18**; method B,

Scheme I[a]



[a] (a) $POCl_3$; (b) NaOH; (c) C_2H_4O/NaOH; (d) HNR′R″, Δ.

Table I). Compound **42d**[12] was prepared according to literature procedure from commercially available 2,4-quinazolinedione (**42a**) by (a) conversion of **42a** to 2,4-dichloroquinazoline (**42b**) by treatment with $POCl_3$,[13] (b) selective hydrolysis of the 4-chloro group with NaOH to afford **42c**,[14] and (c) reaction of **42c** with ethylene oxide in NaOH solution.[15] Shortly after these studies began, compound **41** became commercially available.

The 4-(4-fluorobenzoyl)piperidines **19–21** and the 4-(4-fluorobenzyl)piperidines **22** and **23**, were prepared via the common intermediate *N*-acetyl-4-(4-fluorobenzoyl)piperidine (**43**)[16] (Scheme II). Acid hydrolysis of **43** provided **19**; compound **21** was obtained by alkylation of **19** with

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Table I. Physicochemical Properties of Ketanserin Analogues

no.[a]	method	yield, %	RS[b]	mp (°C)	empirical formula[c]
8	A	24	ME[d]	197–199	$C_{22}H_{23}N_3O_3 \cdot C_4H_4O_4$[e,f]
9	A	26	AE	229–231	$C_{22}H_{25}N_3O_3 \cdot C_2H_2O_4$[f,g]
10	A	21	AE	227–229	$C_{22}H_{25}N_3O_2 \cdot C_4H_4O_4$
11	A	22	H[h]	240–243	$C_{22}H_{24}FN_3O_2 \cdot C_2H_2O_4$[i]
12	B	23	AE	220–222	$C_{19}H_{21}N_3O_2 \cdot C_4H_4O_4$
13	B	22	AE	230–232	$C_{20}H_{25}N_3O_2 \cdot C_2H_2O_4$
14	A	18	A	207–209.5	$C_{20}H_{23}N_3O_2 \cdot C_4H_4O_4$[f]
15	B[j]	81	AE	315 dec	$C_{10}H_{11}N_3O_2 \cdot HCl$[k]
16	B[j]	72	AE	221–222[l]	
17	B[m]	75	AE	275–277	$C_{15}H_{19}N_3O_2 \cdot HCl$[f]
18	B[m]	61	AE	268–270	$C_{15}H_{20}N_4O_2 \cdot 2HCl$[i]
19		83	AE	223–226[n]	
20	C	56	AE	217–219[o]	
21	D[p]	72	AE	140–141[q]	
22	E	87	AE	175–176	$C_{14}H_{20}FNO \cdot C_4H_4O_4$
23	F	41	AE	174–175	$C_{12}H_{16}FN \cdot HCl$[f]
25			AE	177–179[r]	
26	C	95[s]	AE	160–161	$C_{13}H_{19}N \cdot HCl$
27	G	60	AE	265–267[t]	
29	D[p,u]	36	MA	260–262	$C_{12}H_{17}N_2 \cdot 2HCl$[f]
32	D[v]	60	AE	179–182	$C_{21}H_{23}FN_2O_2 \cdot C_2H_2O_4$[f]
33	D[w]	37	AE	164–166	$C_{21}H_{24}FN_3O_2 \cdot C_2H_2O_4$[i]
34	D[x]	30	AE	235–237	$C_{22}H_{24}FNO_2 \cdot HCl$
35	D[x]	60	AE	255–257[y]	
36	D[w]	52	AE	100–102	$C_{19}H_{20}FNO \cdot C_2H_2O_4$
37	H	50	AE	166–168[z]	$C_{20}H_{22}FNO \cdot C_2H_2O_4$
38	H	72	A	146–148	$C_{21}H_{24}FNO \cdot C_2H_2O_4$
39	H	47	A	186–189	$C_{22}H_{26}FNO \cdot C_2H_2O_4$
40	H	36	A	152–154[aa]	$C_{23}H_{26}FNO \cdot C_2H_2O_4$

[a] Compounds 28, 30, 31 were on hand from previous studies; 24 was obtained from a commercial source (Janssen). [b] Recrystallization solvent: A = absolute EtOH, M = MeOH, E = anhydrous Et_2O, H = H_2O. [c] All compounds analyzed correctly for C, H, N within 0.4%. [d] Previous reported as free base; free base mp 217–219 °C (lit.[32] mp 214.5 °C). [e] Maleate salt. [f] Crystallized with 0.25 mol of H_2O. [g] Hydrogen oxalate salt. [h] Previously reported as free base; free base mp 192–194 °C (lit.[32] mp 193–194 °C). [i] Crystallized with 0.5 mol of H_2O. [j] Reaction performed neat at 110 °C. [k] Crystallized with 1.0 mol of H_2O. [l] Lit.[33] mp 219–221 °C. [m] Reaction time = 4 h. [n] Lit.[16] mp 222–224 °C. [o] Lit.[34] mp 216–217 °C. [p] MeCN used as solvent; reaction time = 2 h. [q] Lit.[34] mp 141–142 °C. [r] Hydrochloride salt prepared from commercially available (Janssen) free base. [s] Yield of free base. [t] Lit.[20] mp 261–264 °C. [u] Using 1-methylpiperazine and 4-fluorobenzyl bromide as reactants. [v] Reaction was heated overnight at reflux using MeCN as solvent. [w] Dioxane was used as solvent; reaction time = 2 h. [x] Reaction was heated overnight at reflux using dioxane as solvent. [y] Previously reported; lit.[16] mp 255–257 °C. [z] Previously reported as HCl salt;[16] we were unable to obtain a crystalline HCl salt. [aa] The HCl salt has been prepared,[35] but not characterized.

EtI. Reduction of **43** with $LiAlH_4$ afforded **22**. A single attempt to obtain **23** directly from **43** by Huang-Minlon modification of the Wolff–Kishner reduction[17] gave (in addition to ketone reduction and amide hydrolysis) an unexpected displacement of fluorine by diethylene glycol to afford 4-[4-[2-(2-hydroxyethoxy)ethoxy]benzyl]piperidine (**44**). A review of the literature provides precedence for displacement of activated halogens and cleavage of phenolic ethers and thioethers using this procedure;[18] however, using these conditions, examples of formation of phenolic ethers by direct substitution of fluoride were not found. No attempts were made to modify the reaction conditions; rather, compound **23** was obtained by reduction of **19** with triethylsilane using the conditions of West and co-workers.[19] Eschweiler–Clarke methylation of **19** provided **20**, and of **23** provided **26** (Scheme II). As with **21**, **32–36** were prepared by reaction of **19** with the appropriate alkyl halides; compounds **37–40** were obtained by reaction of **19** with the crude *O*-tosyl derivatives of the appropriate alcohols (see Table I).

Acylation of 1-methylpiperazine with 4-fluorobenzoyl chloride gave compound **27**,[20] whereas alkylation with 4-fluorobenzyl bromide gave **29**.

Results and Discussion

Alteration of the 4-Fluorobenzoyl Portion of Ketanserin. Ketanserin (**1**) binds at 5-HT_2 receptors with high affinity (K_i = 3.5 nM; Table II). The fluoro group seems to play a small role in binding; replacement of the fluoro group by hydrogen (compare **1** and **8**, or **11** with **10**) results only in about a 2–3-fold decrease in affinity. The benzoyl carbonyl group seems to influence binding; reduction to a hydroxyl group (i.e., **9**; K_i = 655 nM) results in a 100-fold decrease in affinity as compared with **8** (K_i = 6.5 nM). This finding is qualitatively consistent with the results of Darchen and co-workers.[5] Complete removal of the carbonyl oxygen (compare **1** with **11**, or **8** with **10**) decreases affinity by less than 5-fold. Compounds **12–14** represent ring-open (non-piperidine) analogues of **10**; each of these compounds binds with somewhat lower affinity than **10** itself (K_i = 32 nM).

Examination of Ketanserin "Halves". The following studies were conducted in order to determine the relative importance to 5-HT_2 binding of the quinazolinone versus the benzoyl portion of ketanserin. The relatively rigid nature of the ergolines provides a convenient framework for determining the interatomic distances tolerated by 5-HT_2 receptors. Using the small molecule building and optimization feature of SYBYL, the calculated distance from the center of the benzene ring to the basic nitrogen of the ergoline (+)-LSD is 5.2 Å; likewise, the distance between the center of the pyrrole ring and the basic nitrogen atom is 4.8 Å. The values compare favorably to those measured in an X-ray crystal structure of (+)-LSD (i.e., 5.5 and 4.9 Å, respectively).[21] Together, these results provide an estimation (±0.5 bond lengths) of the aromatic-to-amine distance that is typical for 5-HT_2 ligands. Ketanserin may be viewed as an amine separated from two aromatic moieties (i.e., a quinazolinone moiety on one end and a benzoyl moiety on the other) by calculated distances of 5.1 Å (amine to center of pyrimidinedione ring) and 6.7 Å (amine to center of benzoyl ring). In contrast to the ergolines, ketanserin is a fairly flexible molecule and the aromatic-to-amine portions may exist in any one of several accessible conformations.[22,23] The benzoyl-to-amine distance can actually be as short as 5.7 Å.[24] Thus, either end of the ketanserin molecule (i.e., the benzoylpiperidine moiety, or the less likely phenyl-mimic,

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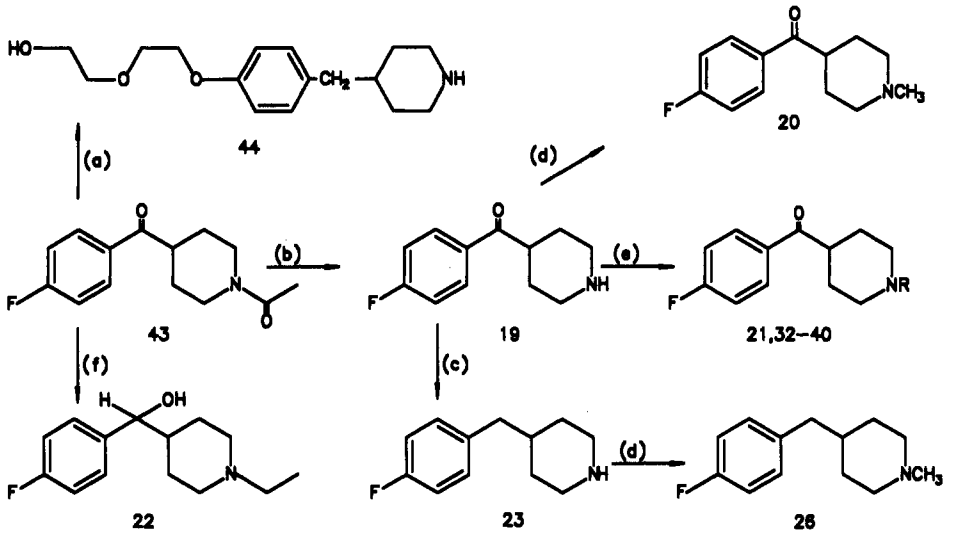
Scheme II[a]



[a] (a) KOH/N_2H_4, diethylene glycol; (b) H_3O^+; (c) $SiEt_3$; (d) $H_2C{=}O/HCOOH$; (e) RX or RO–Ts; (f) $LiAlH_4$.

the pyrimidinedione moiety) might mimic the indolealkylamine portion of the ergolines.

In order to determine which end of the ketanserin molecule might better mimic the indolealkylamine portion of the ergolines, we prepared two series of compounds. The first series consisted of several quinazolinone ethylamines (i.e., **15–18**; ketanserin fragments lacking the benzoyl end of the molecule) and the second series consisted of several benzoylpiperidines (i.e., **19–21**; ketanserin fragments lacking the quinazolinone portion). As shown in Table II, the benzoyl piperidines bind with higher affinity than the quinazolinone ethylamines. The primary amine **15** (K_i > 10 000 nM) does not bind at 5-HT_2 sites; likewise, the tertiary amines **16** and **17** do not bind. Compound **17** may be viewed as an analogue of ketanserin that simply lacks the 4-fluorobenzoyl group; this compound binds with >3000-fold lower affinity than ketanserin. The piperazine analogue **18** also lacks affinity for 5-HT_2 receptors. The benzoyl fragments **19–21** bind with somewhat higher affinity (K_i = 125–430 nM). Theoretically, modifications of this portion of the molecule should have an effect on affinity similar to those seen with the ketanserin analogs **8–11**. Indeed, removal of the fluoro group (i.e., **24–26**), reduction of the carbonyl group to an alcohol (i.e., **22**), and elimination of the carbonyl oxygen (**23**, **25**, **26**) all result in decreased affinity relative to **19–21**.

Irindalone (**5**) is a 5-HT_2 antagonist that binds with high affinity at 5-HT_2 receptors (IC50 = 3.4 nM).[25] Bøgesø et al.[25] have suggested on the basis of molecular modeling studies that irindalone (**5**) and ketanserin (**1**) bind at 5-HT_2 receptors in such a manner that the piperazine and piperidine rings are superimposed and the indan portion of irindalone mimics the 4-fluorobenzoyl portion of ketanserin. If this is the case, piperazine counterparts of **20** should retain affinity for 5-HT_2 receptors. We have previously shown that simple *N*-benzoylpiperazines do not bind at 5-HT_2 receptors.[26] This prompted us to verify our earlier results by examining or re-examining several additional piperazine derivatives; in each case (i.e., **27–31**; Table II, K_i > 10 000 nM) the piperazine derivatives are inactive. These results are particularly confounding in light of the high affinity of (+)-**6** (IC50 = 4.9 nM)[25] relative to that of, for example, **27** or **29** (K_i > 10 000 nM; Table II). Furthermore, the 4-fluorobenzoyl counterpart of irindalone (i.e., **45**) does not bind at 5-HT_2 receptors (IC50 = 58,000 nM).[25] Bøgesø et al.[25] have attempted to explain the difference in affinity between **5** and **45** by invoking an auxiliary binding site that binds the 4-fluorophenyl ring (present in **5** and **6**, but not in **45**). Perhaps this aromatic binding feature compensates for the presence of the second nitrogen atom found in the piperazines.

N-Substituted Benzoylpiperidine Derivatives. Because the quinazolinone portion of ketanserin has been replaced with other structurally related heterocycles, such as in pirenperone (**2**), it is evident that the quinazolinone moiety per se is not specifically required for high affinity. In order to determine how much of the quinazolinone ring

(24) Tollenaere and co-workers[22] have found that the benzoylpiperidine portion of ketanserin is structurally flexible about the piperidine-to-carbonyl and carbonyl-to-benzene bonds; when the carbonyl oxygen atom is cis (±50°) to the nitrogen lone-pair electrons, the benzene ring can assume any of a number of equienergetic orientations, and when the carbonyl oxygen is trans to the lone pair, the benzene ring tends to align itself 90° to the carbonyl group so as to minimize steric interactions between the ortho hydrogen atoms and the C_3 and C_5 methylene hydrogen atoms of the piperidine ring. Systematic conformational searches performed using the SYBYL molecular modeling package, beginning with the crystal structure of ketanserin,[36] confirm these results but reveal (a) smaller energy differences between the various conformations and (b) an additional equienergetic conformation in which the benzene ring and carbonyl group are coplanar with the carbonyl oxygen trans to the nitrogen lone pair. The differences may arise from the use, in the earlier study, of rigid rotation about the key rotatable bonds without further all-atom refinement, and a larger (10° versus 1°)[37] step size for the rotations. The energy values for the trans conformations are −2.7 and −2.8 kcal/mol for the planar benzene–carbonyl (trans-planar) and the orthogonal benzene–carbonyl (trans-orthogonal) arrangements, respectively. The values compare favorably ($\Delta E \lesssim 3$ kcal/mol) to the −5.8 kcal/mol calculated for the crystal-derived structure. The distance between the center of the benzene ring and the piperidine nitrogen atom in the energy-minimized trans-planar conformation is 5.7 Å. With regard to the aminoethyl side shain of the quinazolinone fragment, there appears to be limited structural flexibility as determined by theoretical calculations (PCILO) and by experiment (NMR).[23] And, because the experimentally determined (X-ray) pyrimidinedione-to-amine distance (5.2 Å)[36] lies within the range of the aromatic-to-amine distance of the ergolines, further conformational refinement was considered unnecessary. For representations of the different structural relationships between the ergolines and ketanserin, see ref 10.

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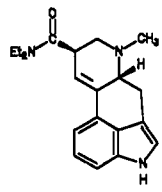

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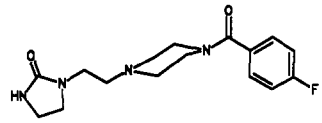
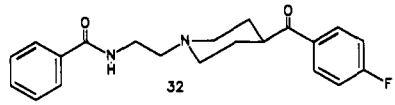


45

is necessary for binding, we prepared and examined the amide **32** (ketanserin minus the cyclic amide moiety) and **33** (ketanserin minus the quinazolinone 4-position carbonyl group). Compound **32** binds with high affinity (K_i = 16 nM); compound **33** (K_i = 4.3 nM) binds with an affinity similar to that of ketanserin (**1**). Compound **34** (K_i = 6.5 nM), in which the amide nitrogen of **32** has been replaced with a methylene group, binds with nearly the affinity of ketanserin (**1**). Compound **39**, an analogue of **34** in which the carbonyl oxygen has been eliminated, retains affinity (**39**; K_i = 5.3 nM). Shortening (i.e., **37**, **38**) or lengthening (i.e., **40**) the alkyl chain of **39** has a relatively small effect on affinity.



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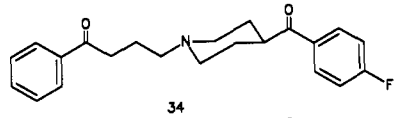

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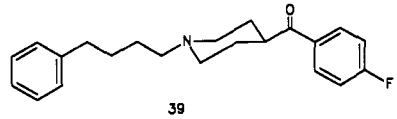

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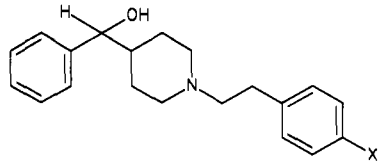
These results suggest that the quinazolinone nucleus is not essential for 5-HT_2 binding since it can be rather dramatically simplified. As compared with the structure of ketanserin (**1**), ring-opening to the simple amide **32**, conversion to the ketone **34**, and elimination of the carbonyl oxygen to yield the alkyl derivative **39** have little effect on affinity. These results also suggest that in addition to the auxiliary aromatic binding site proposed by Bøgesø et al.,[25] there is likely a binding site that accommodates the benzene portion of the quinazolinone ring. Further, the pyrimidinedione portion of the quinazolinone does not appear responsible for the high affinity of these agents because it can be removed (as with **32–40**) with little effect on 5-HT_2 binding.

Another recently described class of 5-HT_2 antagonists, the piperidinemethanols, are typified by MDL 11,939 (**46**, X = H) and MDL 28161 (**46**, X = F). These two compounds bind with high affinity, and in a stereoselective fashion, at 5-HT_2 receptors (K_i = 12.5 nM and IC50 = 0.9 nM, respectively) relative to ketanserin (K_i = 3.2 nM).[8,27] There is an obvious structural similarity between **46** and **37**, and **37** binds with high affinity (K_i = 8.5 nM; Table II). In view of the present finding that reduction of the benzoyl carbonyl group to an alcohol (comparing **1** with its hydroxy counterpart,[5] **8** with **9**, and **21** with **22**) decreases 5-HT_2 receptor affinity in a rather dramatic fashion, **46** must bind in an altogether different manner relative to the reduced analogues examined in the present study.



46

5-HT_{1C} Binding Studies. In general, all of the compounds bind at 5-HT_{1C} sites with lower affinity than they display for 5-HT_2 receptors, and none binds with an affinity as high as ketanserin (5-HT_{1C} K_i = 50 nM; Table II). In the present study, ketanserin binds with modest affinity and with 14-fold selectivity for 5-HT_2 sites. Although Leysen[9] has suggested that the 4-fluorobenzoyl carbonyl group may contribute to selectivity, replacement of the carbonyl oxygen atom with hydrogens (compare **1** and **11**) decreases 5-HT_{1C} affinity by only 4-fold and has no effect on selectivity. Replacement of the fluoro group by hydrogen decreases 5-HT_{1C} affinity by more than 1 order of magnitude and results is greater selectivity (i.e. desfluoroketanserin, **8**, 5-HT_{1C} K_i = 760 nM; 120-fold 5-HT_2 selectivity); this trend is also seen with the benzoyl derivatives (compare **19** and **24**). Little effect is observed, however, in the absence of the carbonyl oxygen (compare **10** and **11**). The piperidine ring-opened compounds **12** and **14** bind with very low affinity at 5-HT_{1C} sites (K_i > 10 000 nM); interestingly, however, the tertiary amine analog of **12** (i.e., **13**) binds with higher affinity and lower selectivity than **12** itself. The benzoylpiperidine portion of ketanserin, as at 5-HT_2 receptors, binds with higher affinity than the quinazolinone ethylamine portion at 5-HT_{1C} receptors (compare **19–21** with **14–17**). Unfortunately, most of the derivatives bind with too low an affinity to allow comment about structure–affinity relationships or selectivity. The piperazine derivatives **18** and **27–31** do not bind at 5-HT_{1C} receptors. The N-substituted 4-fluorobenzoyl piperidines **32** and **39** bind with slightly higher affinity than **19–21** but, due to their high 5-HT_2 receptor affinity, are among the more 5-HT_2-selective derivatives. Nevertheless, none of these agents is particularly selective for 5-HT_2 versus 5-HT_{1C} receptors, and none displayed more than 10 times the selectivity of ketanserin.

Interestingly, as was previously reported for a series of phenylisopropylamine derivatives,[28] the simple benzoylpiperidines (e.g. **19–21**) bind with little selectivity for 5-HT_2 versus 5-HT_{1C} receptors. However, introduction of the piperidine nitrogen substituent (e.g., as with **32–26**, **38–40**) seems to enhance the selectivity of these agents. Thus it could be this portion of ketanserin-related molecules that determines the selectivity of such agents for 5-HT_2 versus 5-HT_{1C} receptors.

Summary

Ketanserin (**1**) is a standard 5-HT_2 antagonist with relatively little selectivity for 5-HT_2 versus 5-HT_{1C} receptors. Reduction of the 4-fluorobenzoyl carbonyl group to the alcohol (i.e., **8** → **9**) reduces 5-HT_2 affinity by at

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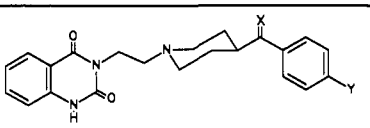
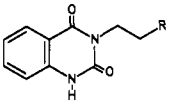
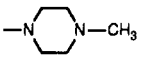
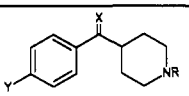
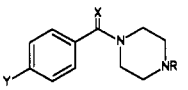
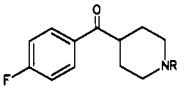
Table II. 5-HT_2 and 5-HT_{1C} Binding Affinities of Ketanserin Analogues

no.	X	Y	5-HT_2 K_i[a]	5-HT_{1C} K_i[a]	5-HT_{1C} K_i/5-HT_2 K_i ratio
					
1	O	F	3.5 (0.5)	50 (8)	14
8	O	H	6.5 (0.3)	760 (40)	115
9	H, OH	H	655 (100)	>10000	>15
10	H,H	H	32 (5)	970 (190)	30
11	H,H	F	12 (3)	200 (20)	17

no.	R	5-HT_2 K_i[a]	5-HT_{1C} K_i[a]	5-HT_{1C} K_i/5-HT_2 K_i ratio
				
12	NH-$(CH_2)_3$-Ph	660 (20)	>10000	>10
13	N(Me)-$(CH_2)_3$-Ph	640 (35)	1390 (325)	2
14	NH-$(CH_2)_4$-Ph	180 (14)	>10000	>50
15	NH_2	>10000	>10000	
16	$N(CH_3)_2$	>10000	>10000	
17		>10000	>10000	
18		>10000	>10000	

no.	X	Y	R	5-HT_2 K_i[a]	5-HT_{1C} K_i[a]	5-HT_{1C} K_i/5-HT_2 K_i ratio
						
19	O	F	H	430 (30)	1100 (115)	2
20	O	F	Me	125 (15)	1510 (140)	12
21	O	F	Et	260 (30)	3160 (500)	12
22	H, OH	F	Et	>10000	>10000	
23	H, H	F	H	1100 (70)	>10000	>9
24	O	H	H	3320 (280)	>10000	>3
25	H, H	H	H	>10000	>10000	
26	H, H	H	Me	3870 (90)	>10000	>2

no.	X	Y	R	5-HT_2 K_i[a]	5-HT_{1C} K_i[a]
					
27	O	F	Me	>10000	>10000
28	O	H	Me	>10000	>10000
29	H, H	F	Me	>10000	>10000
30	O	H	H	>10000	>10000
31	H, H	H	H	>10000	>10000

no.	R	5HT_2 K_i[a]	5-HT_{1C} K_i[a]	5-HT_{1C} K_i/5-HT_2 K_i ratio
				
32	$CH_2CH_2NHC(=O)$-Ph	16 (1)	1610 (480)	100
33	$CH_2CH_2NHC(=O)NH$-Ph	4.3 (0.8)	200 (6)	50
34	$CH_2CH_2CH_2C(=O)$-Ph	6.5 (1.9)	350 (40)	50
35	$CH_2CH_2CH_2C(=O)$-4-FC_6H_4	4.3 (0.5)	345 (6)	80
36	CH_2-Ph	25 (1)	3000 (230)	120
37	CH_2CH_2-Ph	8.5 (0.2)	145 (50)	15
38	$CH_2CH_2CH_2$-Ph	16 (2)	940 (380)	60
39	$CH_2CH_2CH_2CH_2$-Ph	5.3 (1.0)	620 (20)	120
40	$CH_2CH_2CH_2CH_2CH_2$-Ph	10 (2)	420 (30)	40

[a] K_i values (nM) are followed by SEM except for values > 10 000 nM.

least 100-fold (ref 5 and Table II); removal of the carbonyl oxygen (1 → 11) or the fluoro group (1 → 8) have small effects on binding. Both the quinazolinone and the benzoylpiperidine portion of ketanserin contribute to its 5-HT_2 receptor affinity. However, although the quinazolinone moiety enhances the affinity of benzoylpiperidines, quinazolinone ethylamines themselves do not bind (K_i > 10 000 nM) at 5-HT_2 receptors. On the other hand, benzoylpiperidines lacking the quinazolinone portion retain modest 5-HT_2 receptor affinity. Per se, the quinazolinone moiety of ketanserin is not essential for binding. The quinazolinone ring can be abbreviated to a

structurally simpler amide (e.g. **32**), urea (e.g. **33**), or ketone (e.g. **34**), and the carbonyl group can be eliminated as in **39**. Evidence suggests that there exists a receptor feature capable of binding the benzene ring portion of the quinazolinone nucleus. This binding feature, which probably accounts for the higher affinity of N-substituted benzoylpiperidines relative to their unsubstituted counterparts, allows for a certain amount of spatial latitude as noted by the relatively small difference in 5-HT_2 affinity between **36–40**. This feature may also influence 5-HT_2 versus 5-HT_{1C} selectivity, but none of the derivatives are particularly selective for 5-HT_2 receptors. The results of this study suggest that the benzoyl portion, and not the (pyrimidinone portion of the) quinazolinone nucleus, of ketanserin mimics the indolealkylamine portion of the ergolines upon binding at 5-HT_2 receptors; at the very least, they indicate that the benzoyl portion is important for 5-HT_2 and 5-HT_{1C} binding and that the piperidine nitrogen substituents may play a role in determining receptor selectivity.

Experimental Section

Synthesis. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 5ZDX FT-IR, and proton magnetic resonance (NMR) spectra on a JEOL FX90Q FT-NMR spectrometer at 89.55 MHz. ^{1}H-NMR and ^{13}C-NMR spectra for **44** were obtained using a GE QE-300 at 300.64 and 75.61 MHz, respectively. GC/MS analysis was performed using a Hewlett-Packard 5988A gas chromatograph/mass spectrometer at 70 eV ionization potential. All spectral data are consistent with assigned structures. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA) and values are within 0.4% of theory. Unless otherwise stated, salts were prepared by the following general procedure: (a) maleates and oxalates, by the dropwise addition of a molar equivalent solution of maleic acid or oxalic acid in anhydrous Et_2O to a solution of the amine in anhydrous Et_2O or a mixture of absolute EtOH and anhydrous Et_2O, (b) hydrochlorides, by the dropwise addition, until cessation of salt formation, of a saturated solution of HCl in anhydrous Et_2O to a solution of the amine in anhydrous Et_2O or absolute EtOH/Et_2O. Flash chromatography was performed on silica gel (Merck, grade 60, 230–400 mesh, 60 Å) using 9:1 $CHCl_3$/MeOH as eluent. MeCN was dried by distillation, THF was dried by distillation from $LiAlH_4$, and $CHCl_3$ was dried by distillation from P_2O_5; all solvents (except for Et_2O) were stored over 3-Å or 4-Å molecular sieves.

3-[2-[(4-Phenylbutyl)amino]ethyl]-2,4-quinazolinedione Maleate (14). The preparation of this compound typifies method A. A mixture of 3-(2-chloroethyl)-2,4-quinazolinedione (112 mg, 0.5 mmol), 4-phenylbutylamine (80 mg, 0.5 mmol), anhydrous K_2CO_3 (70 mg, 0.5 mmol), and a few crystals of KI in MeCN (10 mL) was heated at reflux for 7 h. The reaction mixture was filtered hot and the solvent evaporated under reduced pressure; the residue was suspended in H_2O (10 mL), and the suspension was treated with 10% NaOH (10 mL) and then filtered. The alkaline filtrate was extracted with Et_2O (10 mL, 2 × 5 mL), acidified to pH 4 with dilute HCl, and made alkaline again with 10% NH_4OH solution. The precipitated solids were removed by filtration, washed with H_2O, and allowed to air-dry. The crude product was dissolved in anhydrous Et_2O (20 mL) and treated with a saturated solution of maleic acid (50 mg) in Et_2O to afford the maleate salt. See Table I.

3-[2-[(3-Phenylpropyl)amino]ethyl]-2,4-quinazolinedione Maleate (12). Preparation of this compound is typical of method B. A mixture of 2,3-dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-one[12] (188 mg, 1 mmol) and 3-phenylpropylamine (137 mg, 1 mmol) in toluene (2 mL) was allowed to stir overnight at 80–90 °C in a closed screw-cap vial. The solvent was removed under reduced pressure and the crude product was treated in the same manner as described for **14**. See Table I.

4-Benzyl-1-methylpiperidine Hydrochloride (26). This procedure is typical for method C. A stirred mixture of 4-benzylpiperidine (2.0 g, 11.4 mmol), 97% formic acid (1.3 g, 28.5 mmol), and 35% formaldehyde (0.9 g, 12.5 mmol) was heated at reflux for 18 h. After addition of concentrated HCl (1 mL), the volatiles were removed under reduced pressure and the resulting oil was dissolved in H_2O (50 mL). The aqueous solution was made alkaline by the addition of 30% NaOH and extracted with Et_2O (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give 2.1 g of the free base as a liquid. The free base, but not the hydrochloride salt, has been previously reported. See Table I.

1-Ethyl-4-(4-fluorobenzoyl)piperidine Maleate (21). Synthesis of **21** typifies method D. A solution of EtI (0.6 g, 3.9 mmol) in MeCN (10 mL) was added dropwise to a stirred slurry of 4-(4-fluorobenzoyl)piperidine[16] (**19**; 0.8 g, 3.9 mmol) and K_2CO_3 (1.1 g, 7.8 mmol) in MeCN (20 mL). The resulting mixture was heated at reflux with stirring for 2 h. The suspended solids were removed by filtration, and the solvent was evaporated under reduced pressure to afford a crude white solid material. Et_2O (50 mL) was added and the suspension was washed with H_2O (2 × 25 mL) and 10% $NaHCO_3$ (2 × 25 mL) and extracted into 10% HCl (2 × 30 mL). The combined acidic solutions were dried ($MgSO_4$), and the solvent was removed to afford a white waxy solid material. The maleate salt was prepared as described for **14**. See Table I.

(±)-1-Ethyl-4-(4-fluoro-α-hydroxybenzyl)piperidine Maleate (22). Method E. A solution of 1-acetyl-4-(4-fluorobenzoyl)-piperidine[16] (**43**; 1 g, 4 mmol) in dry THF (20 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.2 g, 32 mmol) in THF (15 mL) at 0 °C under positive nitrogen pressure. The reaction mixture was heated at reflux for 15 h, cooled to 0 °C on an ice bath, and quenched by the sequential dropwise addition of H_2O (2.5 mL), 10% NaOH (1.2 mL), and H_2O (6 mL). The insoluble salts were removed by filtration and suspended in hot THF (50 mL). The organic filtrates were combined and dried ($MgSO_4$), and solvent was removed under reduced pressure to afford a crude oil. The oil was dissolved in 10% HCl (50 mL), and the solution was washed with Et_2O (3 × 30 mL), made alkaline by addition of 30% NaOH, and extracted with Et_2O (2 × 40 mL). The product was isolated as the maleate salt; see Table I.

4-(4-Fluorobenzyl)piperidine Hydrochloride (23). Method F. Triethylsilane (2.0 g, 17 mmol) was slowly added to a solution of **19** (0.44 g, 2.12 mmol) in trifluoroacetic acid (25 mL) and the resulting reaction mixture was allowed to stir for 3 d. The solvent was removed under reduced pressure and the orange residue was dissolved in Et_2O (30 mL). The solution was extracted into 10% HCl (3 × 30 mL), and the combined extracts were made basic by the addition of 30% NaOH solution. The basic solution was extracted with Et_2O (3 × 40 mL), the combined filtrates were dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford 0.17 g of **23** as the free base. The crude product was isolated as the hydrochloride salt; see Table I.

1-(4-Fluorobenzoyl)-4-methylpiperazine Hydrochloride (27). This procedure typifies method G. A solution of 1-methylpiperazine (1 g, 10 mmol) in dry THF (10 mL) was added to a stirred mixture of 4-fluorobenzoyl chloride (1.6 g, 10 mmol) and NEt_3 (1.1 g, 10 mmol) in THF (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature with continued stirring for 2 h. Filtration and removal of solvent under reduced pressure afforded a pale yellow oil that was purified (first eluate) by flash chromatography. The final product was isolated as the hydrochloride salt; see Table I.

4-(4-Fluorobenzoyl)-1-(2-phenylethyl)piperidine Hydrogen Oxalate (37). This procedure is typical of method H. A mixture of 4-fluorobenzoylpiperidine (200 mg, 0.97 mmol) and crude 2-phenylethanol *p*-toluenesulfonate (prepared by the treatment of the alcohol with *p*-toluenesulfonyl chloride) (280 mg, 1.0 mmol) was heated neat at 95–100 °C for 2 h. When the mixture had cooled to room temperature, it was triturated with absolute EtOH (20 mL) and filtered. The ethanolic filtrate was treated with H_2O (30 mL) and extracted with Et_2O (3 × 10 mL). The combined filtrates were washed with H_2O, dried ($MgSO_4$), and treated with a saturated solution of oxalic acid (150 mg) in anhydrous Et_2O to afford the desired product; see Table I.

4-[4-[2-(2-Hydroxyethoxy)ethoxy]benzyl]piperidine Hydrochloride (44). This compound was the sole product isolated from the Huang-Minlon reduction of **43**. *N*-Acetyl-4-(4-fluorobenzoyl)piperidine (*43*) (1 g, 4 mmol) was added to a stirred solution of KOH (7 g, 125 mmol) and 97% hydrazine (12.5 mL) in diethylene glycol (30 mL) heated at 155 °C. The orange solution became clear, with the evolution of gas, over the period of continued heating (1.5 h). The reaction mixture was chilled to 0 °C and 200 mL of H_2O was added. The mixture was extracted with $CHCl_3$ (4 × 100 mL), the combined organic portions were washed with H_2O (4 × 100 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford 0.8 g (74%) of a crude product as a pale yellow oil. The oil, which formed a waxy solid upon standing, was distilled (Kugelrohr, bath temperature 56–70 °C at 0.06 mmHg) and the distillate was treated with HCl gas to yield **44** as white crystals after recrystallization from an absolute EtOH/anhydrous Et_2O mixture: mp 123–124 °C; MS *m/e* 279 (M^+); IR (KBr) 3127 (OH), 2916 (NH_2^+), 1241 (COAr), 1127 (COC); ^1H NMR (DMSO-d_6) δ 1.40 (m, 2 H, CH_2), 1.69 (m, 3 H, CH_2, CH), 2.46 (d, 2 H, CH_2), 2.77 (m, 2 H, CH_2), 3.22 (m, 2 H, CH_2), 3.50 (m, 4 H, OCH_2), 3.74 (t, 2 H, OCH_2), 4.06 (t, 2 H, OCH_2), 4.63 (s, 1 H, OH), 6.84 (d, 2 H, ArH, J = 8.6 Hz), 7.07 (d, 2 H, ArH, J = 8.6 Hz), 8.90 (br s, 2 H, NH_2^+); ^{13}C NMR (DMSO-d_6) δ 157.07 (ArCO), 131.50 (ArCC), 130.13 (ArC), 114.42 (ArC), 72.74 (CO), 69.23 (CO), 67.32 (CO), 60.50 (CO), 43.26 (CNH_2^+) 41.08, 35.46, 28.29 (benzylic and piperidine C). Anal. ($C_{16}H_{25}NO_3$·HCl) C, H, N.

Radioligand Binding. Radioligand binding assays were performed as previously reported in detail.[29] Briefly, frontal cortical regions of male Sprague–Dawley rats (200–250 g, Charles River) were dissected on ice and homogenized (1:10 w/v) in ice-cold buffer solution (50 mM Tris·HCl, 0.5 mM EDTA, and 10 mM $MgCl_2$ at pH 7.4) and centrifuged at 3000*g* for 15 min. The pellet was resuspended in buffer (1:30 w/v), incubated at 37 °C for 15 min and then centrifuged twice more at 3000*g* for 10 min (with resuspension between centrifugations). The final pellet was resuspended in buffer which also included 0.1% ascorbate and 10^{-5} M pargyline.

Assays were performed in triplicate in a 2.0-mL volume containing 5 mg wet weight of tissue and 0.4 nM [^3H]ketanserin (76 Ci/mmol; New England Nuclear) for 5-HT_2 receptor assays, and 10 mg wet weight of tissue and 1 nM [^3H]mesulergine (75.8 Ci/mmol; Amersham) for 5-HT_{1C} receptor assays. Cinanserin (1.0 μM) was used to define nonspecific binding in the 5-HT_2 assay. In the 5-HT_{1C} assays, mianserin (1.0 μM) was used to define nonspecific binding, and 100 nM spiperone was added to all tubes to block the binding of the tritiated radioligand to 5-HT_2 receptors. Tubes were incubated for 15 min at 37 °C, filtered on Schliecher and Schuell (Keene, NH) glass fiber filters (presoaked in poly(ethylene imine)), and washed with 10 mL of ice-cold buffer. The filters were counted at an efficiency of 50%.

Saturation and competition experiments were analyzed using an updated version of the program EBDA[30] to obtain equilibrium dissociation constants (K_D), B_{max}, Hill coefficients, and IC50 values. K_i values for competition experiments were obtained using the equation K_i = IC50/1 + (D^*/K_D^*) where IC50 is the experimentally observed concentration of competing drug that inhibits 50% of specific binding, K_D^* is the equilibrium dissociation constant determined in saturation studies, and D^* is the concentration of radioactive ligand used in the competition assays.[31] Serotonin hydrogen oxalate and spiperone were obtained from Sigma (St. Louis, MO).

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