# Ketanserin Analogues: Structure–Affinity Relationships for 5-HT<sub>2</sub> and 5-HT<sub>1C</sub> Serotonin Receptor Binding

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Ketanserin is the prototypic 5-HT<sub>2</sub> 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<sub>1C</sub> 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<sub>2</sub> 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<sub>2</sub> affinity. N-(4-Phenylbutyl)-4-(4-fluorobenzoyl)piperidine (39), for example, binds with nearly the same affinity  $(K_i = 5.3 \text{ nM})$  as ketanserin  $(K_i = 3.5 \text{ nM})$ . All of the compounds examined bind at 5-HT<sub>1C</sub> sites with lower affinity than ketanserin, and some of the simplified analogues bind with nearly 10 times the 5-HT<sub>2</sub> versus 5-HT<sub>1C</sub> 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<sub>2</sub> ligands.

5-HT<sub>2</sub> serotonin receptors are of significant clinical interest because of their potential involvement in cardiovascular function and in certain mental disorders.<sup>1-3</sup> Ketanserin (1) is the most widely used 5-HT<sub>2</sub> antagonist in preclinical pharmacological investigations, and [<sup>3</sup>H]ketanserin is the radioligand of choice for binding studies. Although ketanserin has been available for about a decade.<sup>4</sup> remarkably little has been published about its structureaffinity 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<sub>2</sub> affinity.<sup>5</sup> 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.<sup>6,7</sup> 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<sub>2</sub> affinity.<sup>7</sup> There is also a report that reduction of the 4-fluorobenzovl group to the corresponding benzylic alcohol reduces 5-HT<sub>2</sub> affinity by 680-fold.<sup>5</sup> Although the 4-fluorobenzoyl group is a standard feature among many ketanserin-related analogues. there are several analogues where the 4-fluorobenzovl 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 sp2-hybridized carbon atom (e.g. 3). A number of high-affinity 5-HT<sub>2</sub> 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<sub>2</sub> antagonist, but with the subsequent discovery of 5-HT<sub>1C</sub> receptors came the realization that it is also a 5-HT<sub>1C</sub> antagonist. Ketanserin has been reported to bind with as little as 2-fold<sup>8</sup> to as much as 140-fold<sup>9</sup> selectivity for 5-HT<sub>2</sub> versus 5-HT<sub>1C</sub> receptors. Thus, in addition to a lack of information on how specific structural features influence the 5-HT<sub>2</sub> affinity of ketanserin, almost nothing is known concerning how these same features impact on 5-HT<sub>2</sub> versus 5-HT<sub>1C</sub> selectivity.

5-HT<sub>2</sub> 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.<sup>10</sup> For comparison purposes amongst these

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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<sub>2</sub> agonists, partial agonists, or antagonists (depending upon their specific substituents), they possess a rather conformationallyconstrained and stereochemically-defined framework, and embedded within this framework can be found fragments of other known classes of serotonergic agents.<sup>10,11</sup> (+)-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<sub>2</sub> 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.<sup>10</sup>

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<sub>2</sub> binding, (b) to determine how these same structural features contribute to 5-HT<sub>1C</sub> 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<sub>2</sub> 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[2,3b]quinazolin-5-one (42d) (for 12, 13, 15-18; method B,



8-11,14 12,13,15-18

<sup>a</sup> (a) POCl<sub>3</sub>; (b) NaOH; (c)  $C_2H_4O/NaOH$ ; (d) HNR'R",  $\Delta$ .

Table I). Compound  $42d^{12}$  was prepared according to literature procedure from commercially available 2,4quinazolinedione (42a) by (a) conversion of 42a to 2,4dichloroquinazoline (42b) by treatment with POCl<sub>3</sub>,<sup>13</sup> (b) selective hydrolysis of the 4-chloro group with NaOH to afford 42c,<sup>14</sup> and (c) reaction of 42c with ethylene oxide in NaOH solution.<sup>15</sup> 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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Ketanserin Analogues

Table I. Physicochemical Properties of Ketanserin Analogues

no.ª	method	yield, %	RS⁵	mp (°C)	empirical formula <sup>c</sup>	
8	Α	24	MEď	197-199	C22H23N3O3-C4H4O4e,	
9	Α	26	AE	22 <del>9–</del> 231	C <sub>22</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub> ·C <sub>2</sub> H <sub>2</sub> O <sub>4</sub> / <i>s</i>	
10	Α	21	AE	227-229	C22H25N3O2•C4H4O4	
11	Α	22	$H^h$	240-243	C <sub>22</sub> H <sub>24</sub> FN <sub>3</sub> O <sub>2</sub> ·C <sub>2</sub> H <sub>2</sub> O <sub>4</sub> <sup><i>i</i></sup>	
12	В	23	AE	220222	C <sub>19</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> ·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	
13	В	22	AE	230–232	$C_{20}H_{23}N_3O_2C_2H_2O_4$	
14	A	18	Α	207-209.5	C <sub>20</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub> ·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> /	
15	$\mathbf{B}_{j}$	81	AE	315 dec	C <sub>10</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> ·HCl*	
16	Bj	72	AE	221–222 <sup>/</sup>		
17	$\mathbf{B}^m$	75	AE	275-277	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> ·HCl	
18	$\mathbf{B}^m$	61	AE	268-270	C <sub>15</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub> -2HCl <sup>4</sup>	
19		83	AE	223-226 <sup>n</sup>		
20	С	56	AE	217–219°		
21	D₽	72	AE	140–141 <sup>9</sup>		
22	E	87	AE	175–176	C <sub>14</sub> H <sub>20</sub> FNO·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	
23	F	41	AE	174–175	C <sub>12</sub> H <sub>16</sub> FN·HCl/	
25			AE	177 <b>-</b> 179'		
26	С	95 <sup>s</sup>	AE	160–161	C <sub>13</sub> H <sub>19</sub> N·HCl	
27	G	60	AE	265–267 <sup>t</sup>		
29	$\mathrm{D}^{p,\mu}$	36	MA	260-262	C <sub>12</sub> H <sub>17</sub> N <sub>2</sub> ·2HCl/	
32	$\mathbf{D}^{v}$	60	AE	17 <b>9–</b> 182	$C_{21}H_{23}FN_2O_2 C_2H_2O_4^{f}$	
33	$\mathbf{D}^{\boldsymbol{w}}$	37	AE	164-166	$C_{21}H_{24}FN_{3}O_{2}C_{2}H_{2}O_{4}i$	
34	D*	30	AE	235-237	C <sub>22</sub> H <sub>24</sub> FNO <sub>2</sub> ·HCl	
35	D*	60	AE	255–257 <sup>y</sup>		
36	$\mathbf{D}^{w}$	52	AE	100-102	C <sub>19</sub> H <sub>20</sub> FNO•C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>	
37	Н	50	AE	1 <b>66–168</b> ²	$C_{20}H_{22}FNO \cdot C_2H_2O_4$	
38	Н	72	Α	146148	C <sub>21</sub> H <sub>24</sub> FNO-C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>	
39	н	47	Α	1 <b>86</b> –189	C <sub>22</sub> H <sub>28</sub> FNO·C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>	
40	Н	36	A	152-154 <sup>aa</sup>	$C_{23}H_{28}FNO \cdot C_2H_2O_4$	

<sup>a</sup> Compounds 28, 30, 31 were on hand from previous studies; 24 was obtained from a commercial source (Janssen). <sup>b</sup> Recrystallization solvent: A = absolute EtOH, M = MeOH, E = anhydrous  $Et_2O$ , H =  $H_2O$ . <sup>c</sup> All compounds analyzed correctly for C, H, N within 0.4%. <sup>d</sup> Previous reported as free base; free base mp 217-219 °C (lit.<sup>32</sup> mp 214.5 °C). Maleate salt. / Crystallized with 0.25 mol of H<sub>2</sub>O. <sup>8</sup> Hydrogen oxalate salt. <sup>h</sup> Previously reported as free base; free base mp 192-194 °C (lit.<sup>32</sup> mp 193-194 °C). <sup>i</sup> Crystallized with 0.5 mol of H<sub>2</sub>O. <sup>j</sup> Reaction performed neat at 110 °C. <sup>k</sup> Crystallized with 1.0 mol of H<sub>2</sub>O. <sup>1</sup> Lit.<sup>33</sup> mp 219-221 °C. <sup>m</sup> Reaction time = 4 h. <sup>n</sup> Lit.<sup>16</sup> mp 222-224 °C. ° Lit.<sup>34</sup> mp 216-217 °C. <sup>*p*</sup> MeCN used as solvent; reaction time = 2 h.  $^{q}$  Lit.<sup>34</sup> mp 141-142 °C. <sup>*r*</sup> Hydrochloride salt prepared from commercially available (Janssen) free base. \* Yield of free base. <sup>t</sup> Lit.<sup>20</sup> mp 261-264 °C. <sup>u</sup> Using 1-methylpiperazine and 4-fluorobenzyl bromide as reactants. " Reaction was heated overnight at reflux using MeCN as solvent. " Dioxane was used as solvent; reaction time = 2 h. \* Reaction was heated overnight at reflux using dioxane as solvent. <sup>y</sup> Previously reported; lit.<sup>16</sup> mp 255-257 °C. <sup>2</sup> Previously reported as HCl salt;<sup>16</sup> we were unable to obtain a crystalline HCl salt. <sup>aa</sup> The HCl salt has been prepared,<sup>35</sup> 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<sup>17</sup> 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;<sup>18</sup> 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.<sup>19</sup> 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<sub>2</sub> receptors with high affinity ( $K_i = 3.5 \text{ nM}$ ; 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;  $K_i = 655 \text{ nM}$ ) 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.<sup>5</sup> 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 ( $K_i = 32 \text{ nM}$ ).

Examination of Ketanserin "Halves". The following studies were conducted in order to determine the relative importance to 5-HT<sub>2</sub> 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<sub>2</sub> 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).<sup>21</sup> Together, these results provide an estimation  $(\pm 0.5 \text{ bond lengths})$  of the aromaticto-amine distance that is typical for 5-HT<sub>2</sub> ligands. Ketanserin may be viewed as an amine separated from two aromatic moieties (i.e., a guinazolinone 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.<sup>22,23</sup> The benzoyl-to-amine distance can actually be as short as 5.7 Å.<sup>24</sup> Thus, either end of the ketanserin molecule (i.e., the benzoylpiperidine moiety, or the less likely phenyl-mimic,

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<sup>a</sup> (a) KOH/N<sub>2</sub>H<sub>4</sub>, diethylene glycol; (b) H<sub>3</sub>O<sup>+</sup>; (c) SiEt<sub>3</sub>; (d) H<sub>2</sub>C=O/HCOOH; (e) RX or RO-Ts; (f) LiAlH<sub>4</sub>.

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 benzovl end of the molecule) and the second series consisted of several benzovlpiperidines (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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> antagonist that binds with high affinity at 5-HT<sub>2</sub> receptors (IC50 = 3.4 nM).<sup>25</sup> Bøgesø et al.<sup>25</sup> 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<sub>2</sub> receptors. We have previously shown that simple N-benzoylpiperazines do not bind at 5-HT<sub>2</sub> receptors.<sup>26</sup> 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)<sup>25</sup> relative to that of, for example, 27 or 29 ( $K_i > 10000$  nM; Table II). Furthermore, the 4-fluorobenzoyl counterpart of irindalone (i.e., 45) does not bind at 5-HT2 receptors (IC50 = 58,000 nM).<sup>25</sup> Bøgesø et al.<sup>25</sup> 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

<sup>(24)</sup> Tollenaere and co-workers<sup>22</sup> have found that the benzoylpiperidine portion of ketanserin is structurally flexible about the piperidine-tocarbonyl and carbonyl-to-benzene bonds; when the carbonyl oxygen atom is cis  $(\pm 50^{\circ})$  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,<sup>36</sup> 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°)<sup>37</sup> 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 benzenecarbonyl (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 (Xray) pyrimidinedione-to-amine distance (5.2 Å)<sup>36</sup> 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.

<sup>(25)</sup> Bøgesø, K. P.; Arnt, J.; Boeck, V.; Vibeke Christensen, A.; Hyttel, J.; Jensen, K. G. Antihypertensive activity of a series of 1-piperazino-3-phenylindans with potent 5-HT<sub>2</sub> antagonist activity. J. Med. Chem. 1988, 31, 2247-2256.

<sup>(26)</sup> Lyon, R. A.; Titeler, M.; McKenney, J. D.; Magee, P. S.; Glennon, R. A. Synthesis and evaluation of phenyl and benzoylpiperazines as potential serotonergic agents. J. Med. Chem. 1986, 29, 630-635.



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.



These results suggest that the quinazolinone nucleus is not essential for 5-HT<sub>2</sub> 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.,<sup>25</sup> 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<sub>2</sub> binding.

Another recently described class of  $5\text{-HT}_2$  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  $5\text{-HT}_2$  receptors ( $K_i = 12.5$  nM and IC50 = 0.9 nM, respectively) relative to ketanserin ( $K_i = 3.2 \text{ nM}$ ).<sup>8,27</sup> 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, <sup>5</sup> 8 with 9, and 21 with 22) decreases  $5\text{-HT}_2$ 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.



5-HT<sub>1C</sub> Binding Studies. In general, all of the compounds bind at 5-HT<sub>1C</sub> sites with lower affinity than they display for 5-HT<sub>2</sub> receptors, and none binds with an affinity as high as ketanserin  $(5-HT_{1C}K_i = 50 \text{ nM}; \text{Table}$ II). In the present study, ketanserin binds with modest affinity and with 14-fold selectivity for 5-HT<sub>2</sub> sites. Although Levsen<sup>9</sup> 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<sub>1C</sub> affinity by only 4-fold and has no effect on selectivity. Replacement of the fluoro group by hydrogen decreases 5-HT<sub>1C</sub> affinity by more than 1 order of magnitude and results is greater selectivity (i.e. desfluoroketanserin, 8, 5-HT<sub>1C</sub>  $K_i$  = 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<sub>1C</sub> 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<sub>2</sub> receptors, binds with higher affinity than the quinazolinone ethylamine portion at 5-HT<sub>1C</sub> 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<sub>1C</sub> 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<sub>2</sub>-selective derivatives. Nevertheless, none of these agents is particularly selective for 5-HT<sub>2</sub> versus 5-HT<sub>1C</sub> receptors, and none displayed more than 10 times the selectivity of ketanserin.

Interestingly, as was previously reported for a series of phenylisopropylamine derivatives,<sup>28</sup> the simple benzoylpiperidines (e.g. 19–21) bind with little selectivity for 5-HT<sub>2</sub> versus 5-HT<sub>1C</sub> 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<sub>2</sub> versus 5-HT<sub>1C</sub> receptors.

#### Summary

Ketanserin (1) is a standard 5-HT<sub>2</sub> antagonist with relatively little selectivity for 5-HT<sub>2</sub> versus 5-HT<sub>1C</sub> receptors. Reduction of the 4-fluorobenzoyl carbonyl group to the alcohol (i.e.,  $8 \rightarrow 9$ ) reduces 5-HT<sub>2</sub> affinity by at

<sup>(27)</sup> Dudley, M. W.; Wiech, N. L.; Miller, F. P.; Carr, A. A.; Cheng, H. C.; Roebel, L. E.; Doherty, N. S.; Yamamura, H. I.; Ursillo, R. C.; Palfreyman, M. G. Pharmacological effects of MDL 11,939. Drug Dev. Res. 1988, 13, 29-43.

<sup>(28)</sup> Glennon, R. A.; Raghupathi, R.; Bartyzel, P.; Teitler, M.; Leonhardt, S. Binding of phenylalkylamine derivatives at 5-HT<sub>1C</sub> and 5-HT<sub>2</sub> serotonin receptors: Evidence for a lack of selectivity. J. Med. Chem. **1992**, 35, 734-740.

1able II. 5-F.	$11_2$ and $3-11_{1C}$	Dinaing Aminit	les of Keu	inserin Analogues		
no.	<u> </u>	Y		$5-\mathrm{HT}_2 K_i^a$	$5-\mathrm{HT}_{1\mathrm{C}}K_{\mathrm{i}}^{a}$	5- $\mathrm{HT}_{1\mathrm{C}} K_{\mathrm{i}}$ /5- $\mathrm{HT}_{2} K_{\mathrm{i}}$ ratio
			$\bigcirc$	Å N N N N N N N N N N N N N N N N N N N	K),	
1	O F			3.5 (0.5)	50 (8)	14
8				6.5 (0.3) 655 (100)	760 (40)	115
10	H.H	Ĥ		32 (5)	970 (190)	>15
11	H,H	F		12 (3)	200 (20)	17
no.	R			5-HT <sub>2</sub> $K_{i}^{a}$	5-HT <sub>1C</sub> $K_i^a$	5-HT <sub>1C</sub> $K_i$ /5-HT <sub>2</sub> $K_i$ ratio
12	NH-(CH <sub>2</sub> ) <sub>3</sub> -Ph			660 (20)	>10000	>10
13	N(Me)-(CH <sub>2</sub> ) <sub>3</sub> -Ph			640 (35)	1390 (325)	2
14	NH-(CH <sub>2</sub> ) <sub>4</sub> -Ph			180 (14)	>10000	>50
15 16				>10000	>10000	
17	N(CH <sub>3</sub> ) <sub>2</sub>			>10000	>10000	
		]				
18				>10000	>10000	
	۲ <u>ــــــــــــــــــــــــــــــــــــ</u>	/ /				
no.	Х	Y	R	5-HT <sub>2</sub> $K_i^a$	5-HT <sub>1C</sub> K <sub>i</sub> <sup>a</sup>	5-HT <sub>1C</sub> K <sub>i</sub> /5-HT <sub>2</sub> K <sub>i</sub> ratio
				y C NR		
19	0	F	H M-	430 (30)	1100 (115)	2
20	0	л Я	Ivie Et	125 (15) 260 (30)	1510 (140) 3160 (500)	12 19
22	й, он	F	Ēt	>10000	>10000	12
23	H, H	F	Н	1100 (70)	>10000	>9
24	0	H	H	3320 (280)	>10000	>3
25 26	п, п Н. Н	н Н	н Ме	>10000 3870 (90)	>10000 >10000	>9
no.			Y	B	5-HT. K.ª	5.HT.c.K.4
			-		0.1112.111	
27	0		F	Me	>10000	>10000
28	0		н	Me	>10000	>10000
29	H,	, Н	F	Me	>10000	>10000
30 31		н	н	н	>10000	>10000
	,					- 10000
no.	R		<u>5HT<sub>2</sub> K<sub>i</sub><sup>a</sup></u>	5-HT <sub>1C</sub> $K_i^a$	$5\text{-}\mathrm{HT}_{1\mathrm{C}}K_{\mathrm{i}}/5\text{-}\mathrm{HT}_{2}K_{\mathrm{i}}\mathrm{ratio}$	
				F		
32	$CH_2CH_2NHC(=0)-Ph$			16 (1)	1610 (480)	100
33	$CH_2CH_2NHC(=0)NH-Ph$		h	4.3 (0.8)	200 (6)	50
34 35	$CH_2CH_2CH_2C(=0)-Ph$		.н.	0.0 (1.9) 1 3 (0.5)	300 (40) 345 (6)	50
36	∪n₂∪n₂∪(==0)-4-r∪6H4 CH₀-Ph		4.0 (0.0) 25 (1)	340 (0)	120	
37	CH <sub>2</sub> CH <sub>2</sub> -Ph		8.5 (0.2)	145 (50)	15	
38	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -Ph			16 (2)	940 (380)	60
39	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -Ph			5.3 (1.0)	620 (20)	120
40	$CH_2CH_2CH_2CH_2CH_2$ -Ph			10 (2)	420 (30)	40

Table II. 5-HT<sub>2</sub> and 5-HT<sub>1C</sub> Binding Affinities of Ketanserin Analogues

<sup>a</sup>  $K_i$  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  $(1 \rightarrow 11)$  or the fluoro group  $(1 \rightarrow 8)$  have small effects on binding. Both the quinazolinone and the benzoylpiperidine portion of ketanserin contribute to its 5-HT<sub>2</sub> 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<sub>2</sub> receptors. On the other hand, benzoylpiperidines lacking the quinazolinone portion retain modest 5-HT<sub>2</sub> receptor affinity. Per se, the quinazolinone moiety of ketanserin is not essential for binding. The quinazolinone ring can be abbreviated to a

#### Ketanserin Analogues

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<sub>2</sub> affinity between 36-40. This feature may also influence 5-HT<sub>2</sub> versus 5-HT<sub>1C</sub> selectivity, but none of the derivatives are particularly selective for 5-HT<sub>2</sub> 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<sub>2</sub> receptors; at the very least, they indicate that the benzoyl portion is important for 5-HT<sub>2</sub> and 5-HT<sub>1C</sub> 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. <sup>1</sup>H-NMR and <sup>13</sup>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<sub>2</sub>O to a solution of the amine in anhydrous Et<sub>2</sub>O 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<sub>2</sub>O to a solution of the amine in anhydrous Et<sub>2</sub>O or absolute EtOH/Et<sub>2</sub>O. Flash chromatography was performed on silica gel (Merck, grade 60, 230-400 mesh, 60 Å) using 9:1 CHCl<sub>3</sub>/MeOH as eluent. MeCN was dried by distillation, THF was dried by distillation from LiAlH<sub>4</sub>, and CHCl<sub>3</sub> 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-guinazolinedione 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<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>O (10 mL,  $2 \times 5$  mL), acidified to pH 4 with dilute HCl, and made alkaline again with 10% NH<sub>4</sub>OH solution. The precipitated solids were removed by filtration, washed with H<sub>2</sub>O, and allowed to air-dry. The crude product was dissolved in anhydrous  $Et_2O(20 \text{ mL})$  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<sup>12</sup> (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<sub>2</sub>O (50 mL). The aqueous solution was made alkaline by the addition of 30% NaOH and extracted with Et<sub>2</sub>O (3 × 50 mL). The combined organic fractions were dried (MgSO<sub>4</sub>), 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<sup>16</sup> (19; 0.8 g, 3.9 mmol) and K<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>O (50 mL) was added and the suspension was washed with H<sub>2</sub>O (2 × 25 mL) and 10% NaHCO<sub>3</sub> (2 × 25 mL) and extracted into 10% HCl (2 × 30 mL). The combined acidic solutions were dried (MgSO<sub>4</sub>), and the solvent was prepared as described for 14. See Table I.

(±)-1-Ethyl-4-(4-fluoro- $\alpha$ -hydroxybenzyl)piperidine Maleate (22). Method E. A solution of 1-acetyl-4-(4-fluorobenzoyl)piperidine<sup>16</sup> (43; 1 g, 4 mmol) in dry THF (20 mL) was added dropwise to a stirred suspension of LiAlH<sub>4</sub> (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<sub>2</sub>O (2.5 mL), 10% NaOH (1.2 mL), and H<sub>2</sub>O (6 mL). The insoluble salts were removed by filtration and suspended in hot THF (50 mL). The organic filtrates were combined and dried (MgSO<sub>4</sub>), 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<sub>2</sub>O (3 × 30 mL), made alkaline by addition of 30% NaOH, and extracted with Et<sub>2</sub>O (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<sub>4</sub>), 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 1methylpiperazine (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<sub>3</sub> (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<sub>2</sub>O (30 mL) and extracted with  $\text{H}_2\text{O}$  (3 × 10 mL). The combined filtrates were washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>), and treated with a saturated solution of oxalic acid (150 mg) in anhydrous Et<sub>2</sub>O 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<sub>2</sub>O was added. The mixture was extracted with  $CHCl_3$  (4 × 100 mL), the combined organic portions were washed with  $H_2O(4 \times 100 \text{ mL})$  and dried (MgSO<sub>4</sub>), 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<sub>2</sub>O mixture: mp 123-124 °C; MS m/e 279 (M<sup>+</sup>); IR (KBr) 3127 (OH), 2916 (NH<sub>2</sub><sup>+</sup>), 1241 (COAr), 1127 (COC); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.40 (m, 2 H, CH<sub>2</sub>), 1.69 (m, 3 H, CH<sub>2</sub>, CH), 2.46 (d, 2 H, CH<sub>2</sub>), 2.77 (m, 2 H, CH<sub>2</sub>), 3.22 (m, 2 H, CH<sub>2</sub>), 3.50 (m, 4 H, OCH<sub>2</sub>), 3.74 (t, 2 H, OCH<sub>2</sub>), 4.06 (t, 2 H, OCH<sub>2</sub>), 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<sub>2</sub><sup>+</sup>); <sup>13</sup>C NMR  $(DMSO-d_6) \delta 157.07 (ArCO), 131.50 (ArCC), 130.13 (ArC), 114.42$ (ArC), 72.74 (CO), 69.23 (CO), 67.32 (CO), 60.50 (CO), 43.26 (CNH<sub>2</sub><sup>+</sup>) 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.<sup>29</sup> 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 icecold buffer solution (50 mM Tris-HCl, 0.5 mM EDTA, and 10 mM MgCl<sub>2</sub> at pH 7.4) and centrifuged at 3000g 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 3000g for 10 min (with resuspension between centrifugations). The final pellet was resuspended in buffer which also included 0.1% ascorbate and 10<sup>-5</sup> 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<sub>2</sub> receptor assays, and 10 mg wet weight of tissue and 1 nM [3H]mesulergine (75.8 Ci/mmol; Amersham) for 5-HT<sub>1C</sub> receptor assays. Cinanserin (1.0  $\mu$ M) was used to define nonspecific binding in the 5-HT<sub>2</sub> assay. In the 5-HT<sub>1C</sub> assays, mianserin (1.0  $\mu$ M) 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<sub>2</sub> 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<sup>30</sup> 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,  $K_{\rm D}^*$  is the equilibrium dissociation constant determined in saturation studies, and  $D^*$  is the concentration of radioactive ligand used in the competition assays.<sup>31</sup> Serotonin hydrogen oxalate and spiperone were obtained from Sigma (St. Louis, MO).

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