Novel Antagonists of the 5-HT_3 Receptor. Synthesis and Structure–Activity Relationships of (2-Alkoxybenzoyl)ureas

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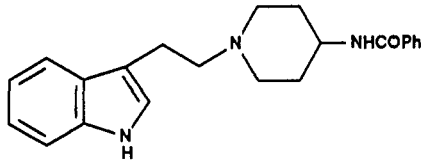
A series of benzoylureas derived from bicycle amines were prepared and evaluated for 5-HT_3 antagonist activity on the rat isolated vagus nerve. From among these compounds, those analogues which were ortho substituted by an alkoxy group on the benzoyl function were shown to be potent 5-HT_3 antagonists with similar or greater potency than the standard agent ondansetron. NMR and X-ray crystallography studies showed these *o*-alkoxy compounds to exist as a planar, hydrogen-bonded, tricyclic ring system. In molecular modeling studies on *endo*-*N*-[[(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)amino]carbonyl]-2-(cyclopropylmethoxy)benzamide (**30**) the central hydrogen-bonded ring was able to mimic an aromatic ring present in previously reported 5-HT_3 antagonists.

5-Hydroxytryptamine receptors have been classified into 5-HT_1, 5-HT_2, and 5-HT_3 subtypes on the basis of their pharmacological and physiological responses.[1] The 5-HT_3 receptor subtype was originally thought to be confined to the periphery. However, more recently animal behavioral studies[2,3] and binding studies on animal and human brain tissue have suggested a role for this receptor subtype within the CNS.[4,5] Several highly selective antagonists of the 5-HT_3 receptor have been described[6] and a number of these are the subject of clinical studies. In particular ondansetron (**1**), granisetron (**2**), and ICS 205-930 (**3**) (Chart I) have been shown to be highly effective inhibitors of cytotoxic drug induced emesis in man[7,8] and are now marketed for this therapeutic indication. Animal studies[6,9,10] suggest that this class of compound may also possess anxiolytic, antipsychotic, or cognition-enhancing activity. Preliminary clinical studies have provided support for these psychiatric uses in man.[11]

Many of the currently reported 5-HT_3 antagonists are aromatic amides or esters of appropriate bicyclic amines or alcohols; examples are granisetron (**2**),[12] ICS 205-930 (**3**), zacopride (**4**),[13] MDL 72222 (**5**),[14] MDL 73147 (**6**),[15] and LY278584 (**7**)[16] (Chart I). Where direct comparison of amides and esters have been reported the two functionalities appear to be equivalent in terms of potency.[16] Earlier work in these laboratories on benzamidopiperidines related to the antihypertensive agent indoramin (**8**) demonstrated that replacement of the benzamide function by benzoylurea gave compounds of equivalent or superior potency as antihypertensives to the corresponding benzamides.[17] Our previous experience prompted us to investigate benzoylurea and benzoylcarbamate analogues of the 5-HT_3 antagonist benzamides and benzoyl esters as potential 5-HT_3 antagonists. These studies have identified a new class of potent 5-HT_3 antagonists.



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Chemistry

The compounds listed in Table I were prepared by the two general methods illustrated in Scheme I. Both benzoylureas and benzoylcarbamates were readily prepared by reaction of benzoylisocyanates with an appropriate bicyclic amine or alcohol (method A). The intermediate benzoylisocyanates were available by treatment of a pri-

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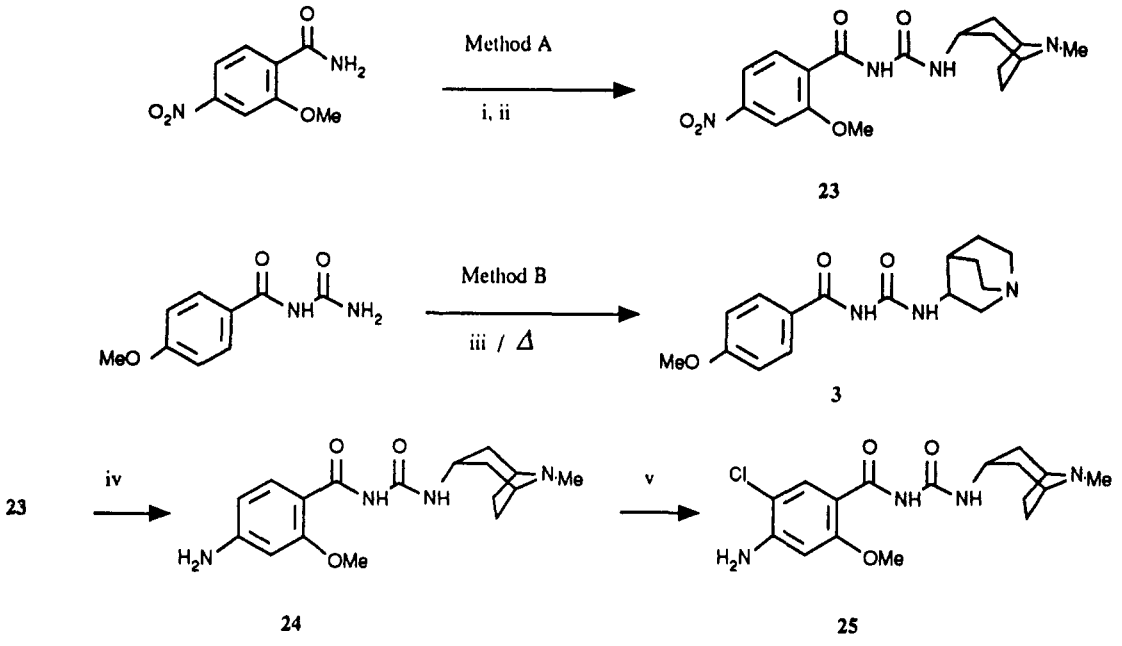
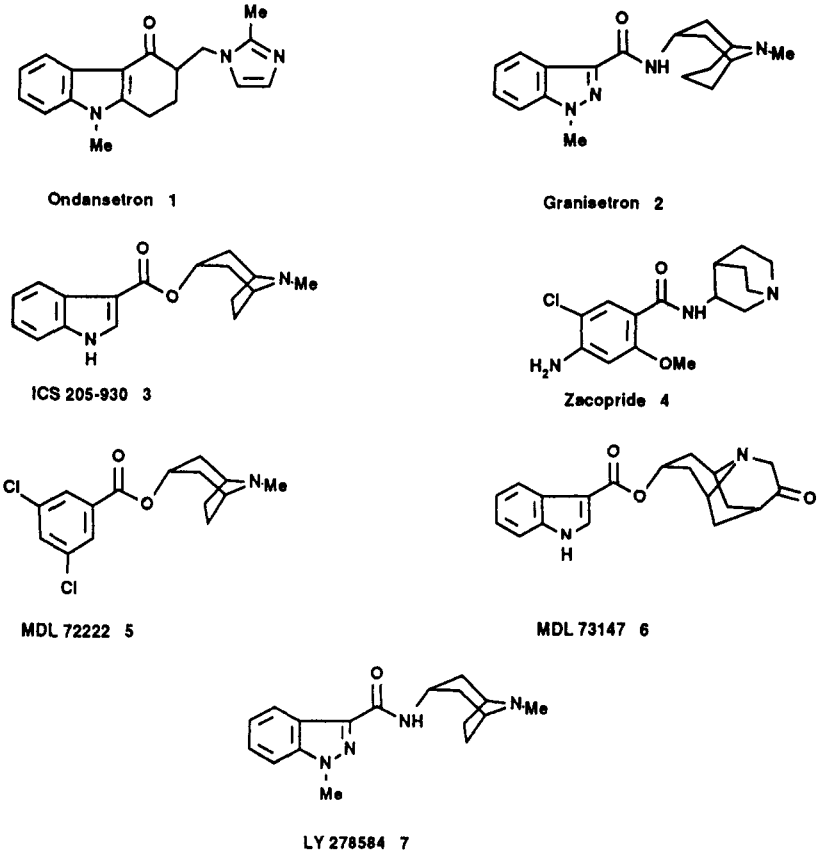
Scheme I[a]



[a] Reagents: (i) $(COCl)_2$; (ii) *endo*-3-aminotropane; (iii) 3-aminoquinuclidine, pyridine; (iv) H_2–Pd, AcOH; (v) iodobenzene dichloride.

Chart I



mary benzamide with oxalyl chloride. Benzoylureas were also prepared by thermal condensation of a primary benzoylurea with a bicyclic amine (method B). The bicyclic amines used in this work were commercially available or prepared by methods described previously.[18,19] Compounds **24** and **25** were prepared by further functionalization of **23** as illustrated in Scheme I.

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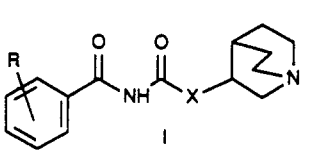
Table I



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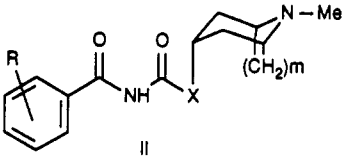


II

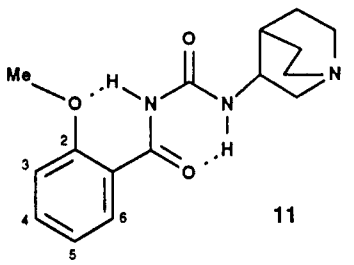
compound	R	I/II	X	*m*	crystn solv	mp, °C	method	% yield	formula[a]	pA_2 (95% limits)	*n*[b]
9	3,5-Cl_2	I	NH	–	EtOH	253–254	B	18	$C_{15}H_{17}Cl_2N_3O_2$·HCl	6.7 (6.3–7.1)	4
10	3,5-Cl_2	II	O	–	MeCN	175–177	A		$C_{16}H_{18}Cl_2N_2O_3$	6.9 (6.91–6.97)	4
11	2-MeO	I	NH	–	*i*-PrOH–EtOH	187–188	A	37	$C_{16}H_{21}N_3O_3$·$C_4H_4O_4$[c]	8.0 (7.6–8.7)	19
12	4-MeO	I	NH	–	*i*-PrOH	166–168	B	67	$C_{16}H_{21}N_3O_3$·$C_4H_4O_4$[d,e]	<6.5	3
13	2-Me	I	NH	–	*i*-PrOH	216–217	A	74	$C_{16}H_{21}N_3O_2$·$C_4H_4O_4$[c]	6.6	3
14	2-F	I	NH	–	EtOH	187–188	A	75	$C_{15}H_{18}FN_3O_2$·$C_4H_6O_4$[f]	<6.5	3
15	2-MeO	I	O	–	*i*-PrOH–MeOH	157–159	A	39	$C_{16}H_{20}N_2O_4$·$C_2H_2O_4$	7.44 (7.2–7.8)	13
16	2,6-MeO	I	NH	–	EtOH	159–161	B	10	$C_{17}H_{23}N_3O_4$·$C_4H_4O_4$[c,e]	<6.5	3
17	2-MeO	(*R*)-I[g]	NH	–	*i*-PrOH–EtOAc	158–159	A	48	$C_{16}H_{21}N_3O_3$·$C_4H_4O_4$[c]	8.15 (7.88–8.83)	11
18	2-MeO	(*S*)-I[h]	NH	–	*i*-PrOH–EtOAc	157–158	A	57	$C_{16}H_{21}N_3O_3$·$C_4H_4O_4$[c]	7.25 (7.01–7.75)	13
19	2-MeO	II	NH	2	*i*-PrOH–EtOH	230–231	A	30	$C_{17}H_{23}N_3O_3$·HCl	8.6 (8.3–9.0)	10
20	2-MeO	*exo*-II	NH	2	EtOH–MeOH	195–197	A	29	$C_{17}H_{23}N_3O_3$·$C_2H_2O_4$[j]	<7.5	3
21	2-MeO	II	NH	3	EtOH	228–230	A	70	$C_{18}H_{25}N_3O_3$·$C_7H_6O_3S$[k]	7.4 (7.2–7.7)	12
22	2-MeO,5-Cl	II	NH	2	*i*-PrOH	221–222	A	75	$C_{17}H_{22}ClN_3O_3$·HCl	7.33 (7.1–7.5)	3
23	2-MeO,4-NO_2	II	NH	2	EtOAc	unstable[l]	A	11	$C_{17}H_{22}N_4O_5$[e]	<7	4
24	2-MeO,4-NH_2	II	NH	2	EtOH–Et_2O	237–239		46	$C_{17}H_{24}N_4O_3$·HCl[m]	6.8 (6.1–7.5)	4
25	2-MeO,4-NH_2,5-Cl	II	NH	2	EtOH	212–223		5	$C_{17}H_{23}ClN_4O_3$·1.65HCl	7.1 (6.7–7.5)	4
26	2-EtO	II	NH	2	*i*-PrOH	188–191	A	77	$C_{18}H_{25}N_3O_3$·$C_4H_4O_4$[c]	8.69 (8.5–9.0)	9
27	2-*n*-PrO	II	NH	2	*i*-PrOH	202–203	A	77	$C_{19}H_{27}N_3O_3$·$C_2H_2O_4$[j]	8.9 (8.6–10.2)	9
28	2-*n*-BuO	II	NH	2	*i*-PrOH	190–192	A	57	$C_{20}H_{29}N_3O_3$·HCl	8.7 (8.4–9.6)	9
29	2-*n*-pentylO	II	NH	2	EtOAc–MeOH	183–184	A	26	$C_{21}H_{31}N_3O_3$·HCl[n]	7.5 (7.1–7.9)	3
30	2-c-$PrCH_2O$	II	NH	2	*i*-PrOH	162–164	A	72	$C_{20}H_{27}N_3O_3$·$C_4H_4O_4$[d]	8.9 (8.7–9.4)	14
31	2-*i*-PrO	II	NH	2	*i*-PrOH	161–164	A	77	$C_{19}H_{27}N_3O_3$·$C_4H_4O_4$[d]	9.2 (9.0–9.6)	12
32	2-*i*-$PrCH_2O$	II	NH	2	*i*-PrOH–EtOAc	165–168	A	61	$C_{20}H_{29}N_3O_3$·$C_4H_4O_4$[c,e]	8.5 (8.3–8.9)	8
33	2-*i*-$PrCH_2CH_2O$	II	NH	2	*i*-PrOH	180–182	A	66	$C_{21}H_{31}N_3O_3$·$C_2H_2O_4$[j,m]	8.2 (7.3–9.1)	4
34	2-HO	II	NH	2	EtOH	229–230	B	50	$C_{16}H_{21}N_3O_3$·HCl[m]	7.9 (7.7–8.2)	4
35	2-MeO	II	O	2	*i*-PrOH	157–161	A	35	$C_{17}H_{22}N_2O_4$·$C_4H_6O_4$[f,e]	7.77 (7.6–8.0)	13
1	ondansetron									8.7 (8.4–9.2)	18
4	zacopride									9.1 (8.9–9.3)	8
5	MDL 72222									7.8 (7.5–8.4)	8

[a] C, H, and N analyses were within ±0.4% of the theoretical values for the formulae given. [b] *n* = Number of determinations. [c] Fumarate. [d] Maleate. [e] Half hydrate. [f] Succinate. [g] (*R*)-(+)-Enantiomer. [h] (*S*)-(–)-Enantiomer. [i] Exo-isomer of **19**. [j] Oxalate. [k] Toluenesulfonate. [l] Unstable to light and heat, decomposes >50 °C. [m] Quarter hydrate. [n] Hydrate.

Results and Discussion

Antagonist activity at 5-HT$_3$ receptors in vitro was assessed from the pA_2 value for inhibition of 5-HT-induced depolarization of the rat isolated vagus nerve.[20] This depolarization has previously been shown to be antagonized by low concentrations of 5-HT$_3$ antagonists. Also the degree of antagonism of this response correlates well with binding affinities for central 5-HT receptors.[21] Test results are listed in Table I together with values for the 5-HT$_3$ antagonists ondansetron, zacopride, and MDL72222.

Initially we prepared the (3,5-dichlorobenzoyl)urea (**9**) and (3,5-dichlorobenzoyl)carbamate (**10**) as analogues of MDL72222. These compounds possessed only modest 5-HT$_3$ antagonist activity and were in fact less potent than MDL72222 itself. Nonetheless we felt that this initial result justified further exploration. Consequently we sought to enhance activity by systematic modification of the benzoyl ring substituents. The importance of *o*-alkoxy substitution in 5-HT$_3$ antagonists related to zacopride and also in a series of 5-HT$_3$ antagonist phenylureas, reported during the course of this work,[22] prompted the synthesis of the (2-methoxybenzoyl)urea (**11**) at an early stage in this study. This modification increased potency over **9** by 20-fold, an effect which was lost when the substituent was relocated to the 4-position (**12**) or replaced by substituents which are unable to act as hydrogen bond acceptors (**13** and **14**). These SAR suggest that the potency-enhancing effect of 2-methoxy substitution may be due to conformational restriction induced by intramolecular hydrogen-bond formation between the methoxy substituent and the benzamide N–H. This phenomenon is well known for 2-alkoxybenzamides.[23] The presence of intramolecular hydrogen bonding in **11** was also supported by ^{1}H NMR studies. For example, the chemical shift of both the amide and urea NH signals of **11** in $CDCl_3$ were independent of



11

Figure 1.

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concentration, a result consistent with a doubly intramolecularly hydrogen bonded structure (Figure 1). By contrast the spectra of **12** and **13** showed marked concentration dependence in the position of the amide NH while the urea NH still remained largely independent of concentration. The presence of a tricyclic planar system in **11** is also supported by the observed downfield shift of the 6-position ring proton (δ 8.16) relative to that observed for the equivalent proton in **12** (δ 7.9) and **13** (δ 7.5). This shift results from anisotropic deshielding of the 6-proton in **11** by the coplanar benzamide carbonyl. The (2-methoxybenzoyl)carbamate (**15**) lacks the second hydrogen bond formed between the amide carbonyl and urea NH present in **11**. This modification reduced potency, emphasizing the importance of the conformational restraints imposed by both hydrogen bonds in **11** for optimum activity.

2,6-Dimethoxy substitution (**16**) reduced activity, possibly reflecting non-coplanarity for **16** as is observed in the related 2,6-dimethoxybenzamide remoxipride.[24] The potency of **11** as a $5HT_3$ antagonist prompted the synthesis of its enantiomers. These were prepared from the corresponding (*R*)- and (*S*)-3-aminoquinuclidines.[25] Both enantiomers (**17** and **18**) behaved as antagonists on the rat vagus, with the (*R*)-enantiomer **17** being about 10-fold more potent than the (*S*)-enantiomer **18**. Previous studies in these laboratories on enantiomers of zacopride have shown both enantiomers to be 5-HT_3 antagonists in the rat while in the ferret (*S*)-zacopride behaves as a 5-HT_3 agonist and the (*R*)-enantiomer remains an antagonist.[26] This observation prompted us to examine **17** and **18** in the ferret, where we observed 5-HT_3 agonist like effects for the (*R*)-enantiomer **17**. We have also observed similar enantiomer-dependent functional activity for a number of quinuclidine derived 5-HT_3 antagonsts in the ferret.[27] Interestingly, agonst-like activity may be observed in either steroisomer depending on the chemical series, as illustrated by the enantiomers of **11** and zacopride above. The uncertain clinical implications of this interspecies variation in the functional activity of quinuclidine derived 5-HT_3 antagonists prompted us to seek an alternative achiral right-hand fragment for our series. Replacement of 3-aminoquinuclidine by *endo*-3-aminotropane gave the achiral compound **19** which showed no agonist effects in the ferret and was a more potent antagonist on the rat vagus nerve than the quinuclidine **11**. The *exo*-3-aminotropane- and granatane-substituted compounds (**20** and **21**, respectively) were less potent. Accordingly further studies concentrated on the *endo*-aminotropane series. Additional substitution (**22–24**) on the aromatic ring of **19** consistently led to marked reductions in activity. This observation even applied to **25** which bears the same aromatic ring substitution pattern as that found in zacopride. Compound **25** was less potent than **19** or zacopride. This result implies that the aromatic rings in **25** and zacopride serve different functions at the receptor and that the benzoylurea function is not a simple surrogate for benzamide. Replacement of the 2-methoxy substituent in **19** by higher straight-chain alkoxy substituents, **26–29**, produced compounds of similar high potency up to 4-

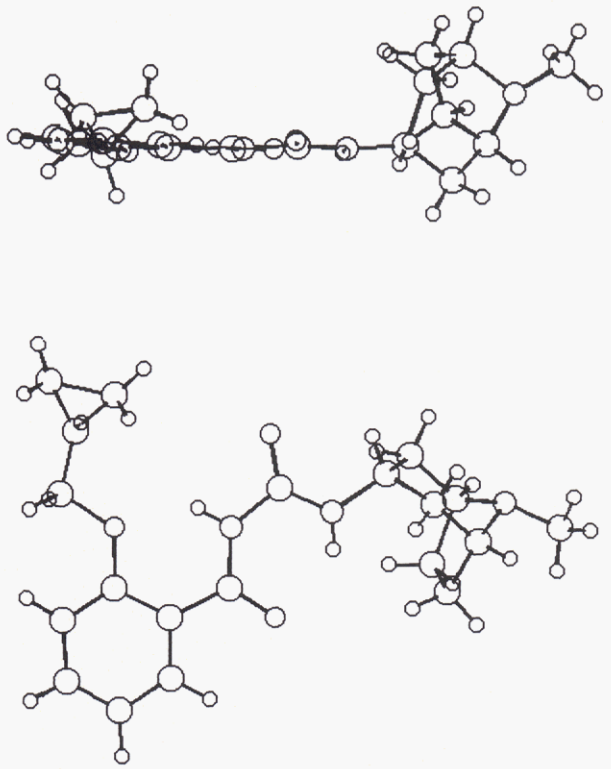

Figure 2. The solid-state conformation of **30** base shown from two different angles.

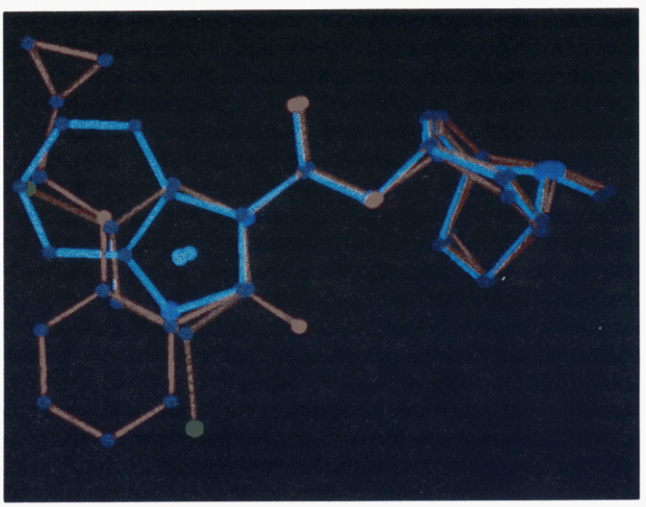

Figure 3. Rigid superimposition of **3** (light blue), **5** (yellow), and **30** (red) in their minimum energy conformations. Dummy atoms are shown in light blue.

carbon atoms, after which potency declined. Branched alkoxy substituents (**30–33**) were favored. The increased potency associated with these larger alkyl groups may reflect a hydrogen-bond-strengthening effect resulting from greater electron donation to the ortho oxygen. Alternatively, or additionally, the alkyl substituents may interact with a lipophilic pocket on the receptor which is limited in its capacity to accommodate larger substituents. The phenol **34** showed reduced activity relative to **19**, consistent with the expected hydrogen-bond-weakening effect of this modification.

As mentioned earlier, spectroscopic and SAR data within this series were consistent with the presence of intramolecular hydrogen bonding for the (2-alkoxybenzoyl)ureas (Figure 1). This structural assignment was confirmed by X-ray crystallographic analysis of **30**. The solid-state conformation of **30** is shown in Figure 2 and selected

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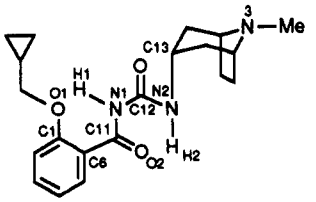
Table II. Crystallographic Data for Compound **30**



Torsion Angles, deg	
τ_1 C-1, C-6, C-11, N-1	2.36
τ_2 C-6, C-11, N-1, C-12	175.27
τ_3 C-11, N-1, C-12, N-2	5.72
τ_4 N-1, C-12, N-2, C-13	-179.87
τ_5 C-12, N-2, C-13, N-3	147.5
Distances to Benzene Ring Plane, Å	
C-11	0.062
N-1	0.151
C-12	0.306
N-2	0.264
N-3	1.636

crystallographic data are listed in Table II. The X-ray data show a near-planar configuration of the aromatic ring, amide, and urea groups with only minor deviations from 0° and 180° torsion angles for τ_1, τ_2, τ_3, and τ_4 and a maximum deviation from coplanarity with the aromatic ring of about 0.3 Å (C-12). Since the solid-state conformation may not correspond to the lowest energy conformer, or the bioactive conformer, it was of interest to subject the X-ray structure of **30** to minimization and comparison with other tropane derived 5-HT$_3$ antagonists. X-ray coordinates for **30** were used to build this structure with a μVAX 3900 and the CHEM-X molecular modeling program.[28] Charges were assigned by the Gasteiger method and the bond between N-2 and C-13 was rotated through 360° by 1-deg increments. The lowest energy conformer was then extracted. This process resulted in shifts of the torsion angle τ_5 from 147.5° to 134.5° and of the N-3 to benzene ring plane distance from 1.636 to -1.187 Å relative to the original crystal structure (Table II). This process was also carried out on ICS 205-930 and MDL72222. These structures were built from standard fragments for indole, benzene, and ester groups within the CHEM-X program combined with the tropane ring fragment obtained from the X-ray data for **30**. Rotations through 360° were carried out on the bond between the tropane ring and the ester oxygen. Since these standard agents have a plane of symmetry the low-energy conformer, having the tropane nitrogen below the plane of view, was selected for comparison in each case. A three-component pharmacophore for 5-HT$_3$ antagonists has been described previously in terms of the spatial relationship between a basic nitrogen, carbonyl oxygen, and the centroid of an aromatic ring. We considered that the central hydrogen-bonded ring (Figure 1) in our series might mimic an aromatic ring.[29] Accordingly we assigned dummy atoms at the centroids defined by O-1, C-1, C-6, C-11, N-1, and H-1 (Table II) in **30**, the pyrrole ring of **3**, and the benzene ring of **5**. A rigid superimposition of ICS 205-930 and MDL72222 was performed using the centroids defined above, the carbonyl oxygens, and tropane nitrogens as equally weighted fitting parameters, the results are shown in Figure 3. The mean deviation from exact superimposition of the fitting points on **3** and **5** on to the equivalent points on **30** was 0.148 Å. From the results of this superimposition it is evident that the central hydrogen-bonded ring in **30** is able to mimic the effect of an aromatic ring in other tropane derived 5-HT$_3$ antagonists. Also the benzene ring in **3**, one chlorine in **5**, and the cyclopropyl methyl ether function of **30** occupy the same region. All of these groups are lipophilic, and occupation of this region may account for the potency enhancing effect of alkyl loading on the 2-position in analogues of **30**. Finally it is interesting to note that the benzene ring in **30** occupies an aromatic acceptor region not previously exploited by other 5-HT$_3$ antagonists.

Table III. Crystal Data, Intensity Data, Collection Parameters, and Details of Refinement for Compound **30**

crystal data	
formula	$C_{20}H_{27}N_3O_3$
formula weight	357.446
a, Å	19.432 (4)
b, Å	7.481 (2)
c, Å	13.370 (2)
α, deg	90
β, deg	101.89 (1)
γ, deg	90
V, Å	1901.91
system	monoclinic
space group	$P2_1/a$
D_c, g cm^{-3}	1.25
$F(000)$	768
radiation	Mo Kα
λ	0.71069
μ, 1/cm	0.792
Z	4
data collection	
θ min, max	1.5, 25
temperature	room temp
total data measured	3824
total data unique	3331
total data observed	2212
significant test	$F_o > 3\sigma(F_o)$
refinement	
no. of parameters	343
absorption correction	φ-scan
g[a] (weighting scheme)	0.000018
final $R = (F)/(F_o)$	0.0410
final RG	0.0372

[a] $\bar{\omega} = 1/[\sigma(F_o) + gF_o]^2$.

Conclusion

A novel series of (2-alkoxybenozyl)ureas has been discovered with potent 5-HT$_3$ antagonist activity. Structural data and modeling studies show that these compounds exist as planar, hydrogen-bonded, tricyclic ring systems in which one of the hydrogen-bonded rings is able to mimic the aromatic ring present in previously reported 5-HT$_3$ antagonists. A number of compounds from this series were selected for more extensive studies, in particular we were interested to evaluate their potential as anxiolytic agents. These studies led to the identification of compound **30** (WAY-100289) as a highly selective antagonist in vivo and in vitro with a particularly favorable profile in a number of behavioral anxiolytic assays. The results of these studies will be reported elsewhere.[30]

Experimental Section

Melting points are uncorrected. IR spectra were obtained in nujol with a Perkin-Elmer model 983G spectrophotometer. NMR spectra were obtained on a Brucker WP200 instrument. C, H, and N analyses were within ±0.4% of theoretical values. Crystals

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of **30** base (mp 153–155 °C) suitable for X-ray diffraction studies were grown from acetonitrile. Crystal data were collected on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Mo Kα radiation. Crystal data, intensity data, collection parameters, and details of refinement are listed in Table III. Methods of structure solution and refinement were as described previously.[31]

***endo*-*N*-[[(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)amino]carbonyl]-2-methoxy-4-nitrobenzamide (23).** Oxalyl chloride (2.7 mL, 31 mmol) was added dropwise under N_2 to a stirred solution of 2-methoxy-4-nitrobenzamide (4.82 g, 24.6 mmol) in 120 mL of 1,2-dichloroethane. The solution was then heated at 70 °C for 19 h. The solvent was evaporated and the residue dissolved in toluene and reevaporated under vacuum to remove residual oxalyl chloride. The solid residue was suspended in 40 mL of toluene and added in one portion to a solution of *endo*-3-aminotropane base, prepared by addition of a solution of butyllithium (39 mL, 1.6 M, 54.6 mmol) in hexane to a suspension of the amine dihydrochloride (5.5 g, 25.8 mmol) in 200 mL of dry THF beneath N_2. The mixture was stirred overnight, excess isocyanate was destroyed by addition of MeOH, and the mixture was evaporated. The residue was partitioned between Et_2O and 1 M hydrochloric acid. The aqueous phase was separated, washed with ether, and basified with K_2CO_3, and the precipitated product was collected by filtration. This thermally unstable product was dried at room temperature under vacuum and purified by trituration with EtOAc to give 4.07 g (45.6%): mp 50 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.7–2.4 (8 H, m, CH_2), 2.39 (3 H, s, MeN), 3.18 (2 H, m, CH), 4.16 (3 H, s, MeO), 7.9–8.0 (2 H, m, Ar), 8.37 (1 H, d, Ar), 9.2 (1 H, d, NH), and 9.56 (1 H, s, NH); IR 3331, 3100, 1696, 1664, 1348, 1267, 805 cm^{-1}.

***endo*-*N*-[[(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)amino]carbonyl]-4-amino-2-methoxybenzamide (24).** A solution of **23** (4 g, 11.05 mmol) in 100 mL of AcOH was hydrogenated at 35 psi, and 28 °C over 5% Pd–C (0.4 g) for 2 h. The catalyst was removed by filtration and the filtrate evaporated. The residue was triturated with EtOH–HCl to give the crystalline hydrochloride 2.1 g (46.9%): mp 237–239 °C; ^{1}H NMR (DMSO-d_6) δ 1.9–2.6 (8 H, m, CH_2), 2.63 (3 H, d, MeN), 3.88 (3 H, s, MeO), 6.25–6.55 (5 H, m, Ar + NH_3^+), 7.7 (1 H, d, Ar), 9.3 (1 H, d, NH), 9.8 (1 H, s, NH), and 10.9 (1 H, b, NH^+); IR 3317, 2572, 1693, 1668, 1608, 1298, 1021, 774 cm^{-1}.

***endo*-*N*-[[(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)amino]carbonyl]-4-amino-5-chloro-2-methoxybenzamide (25).** A solution of iodobenzene dichloride (0.17 g, 0.62 mmol) in 4 mL of $CHCl_3$ was added to a stirred solution of **24** (0.2 g, 0.6 mmol) in 20 mL of $CHCl_3$ maintained at −5 °C. After addition was complete the mixture was stirred at 0 °C for 12 h, then washed twice with 5% aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residue was triturated with Et_2O–HCl to precipitate the hydrochloride which was recrystallized three times from ethanol to give pure product 0.015 g (5.8%): mp 212–223 °C; ^{1}H NMR (DMSO-d_6) δ 1.9–2.5 (8 H, m, CH_2), 2.5 (3 H, s, MeN), 3.9 (3 H, s, MeO), 6.45 (2 H, s, NH_2), 6.52 (1 H, s, Ar), 7.73 (1 H, s, Ar), 9.25 (1 H, d, NH), 9.25 (1 H, d, NH), 9.65 (1 H, s, NH), and 9.8 (1 H, b, NH^+).

(4-Methoxybenzoyl)urea. A mixture of 4-methoxybenzoyl chloride (8.5 g, 50 mmol) and urea (9 g, 150 mmol) was heated and stirred in a melt at 100–110 °C for 2 h. The mixture was then heated to reflux with 20 mL of H_2O, basified with $NaHCO_3$ solution, and ice-cooled, and the solid was collected. Recrystallization from a mixture of 60 mL of AcOH and 30 mL of H_2O gave the product (9 g, 93%), mp 215–17 °C.

***N*-[[(1-Azabicyclo[2.2.2]octan-3-yl)amino]carbonyl]-4-methoxybenzamide (12).** A mixture of (4-methoxybenzoyl)urea (0.97 g, 5 mmol), 3-aminoquinuclidine dihydrochloride (1 g, 5 mmol), diisopropylethylamine (1.29 g, 10 mmol), and 20 mL of pyridine was heated at reflux for 20 h. The solvent was evaporated and the residue partitioned between Et_2O and 1 M hydrochloric acid. The aqueous phase was separated, washed twice with Et_2O, and basified with K_2CO_3 to precipitate **12** base (1.12 g, 74%). The base was dissolved in 10 mL of *i*-PrOH and treated with a hot solution of maleic acid (0.42 g) in 10 mL of *i*-PrOH to precipitate the maleate (1.44 g, 67.3%): mp 166–168 °C; ^{1}H NMR (DMSO-d_6) δ 1.75–1.95 (4 H, m, CH_2), 2.15 (1 H, m, CH), 3.1–3.3 (4 H, m, CH_2), 3.84 (3 H, s, OMe), 4.1–4.25 (1 H, m, CH), 6.03 (2 H, s, maleic acid), 7.05 (2 H, dd, Ar 3,5-H), 8.0 (2 H, dd, Ar 2, 6-H), 9.1 (1 H, d, NH), and 10.76 (1 H, s, NH); IR 3250, 1686, 1258, 1175, 853, 768 cm^{-1}.

Estimation of 5-HT$_3$ Antagonism on the Rat Isolated Vagus Nerve. Male, Sprague-Dawley rats (250–350 g) were killed by a blow to the head and cervical dislocation. The cervical vagus nerves were dissected free and 10–20-mm lengths (without the nodose ganglion) excised and placed in Krebs solution. The connective tissue sheath was removed and the nerve placed in a two-compartment bath maintained at 27 °C. The nerve was passed from one compartment to the next through a grease-sealed gap. One compartment was perfused continuosly with Krebs solution to which 5-HT and test compound were added. The potential different between this compartment and the other (containing the vagus nerve in Krebs solution alone) was recorded using Ag/AgCl electrodes in saline–agar. Depolarizations evoked by 5-HT were displayed on a pen recorder. Noncumulative concentration–response curves to 5-HT (3×10^{-8} to 3×10^{-4} M) were constructed using a 4-min contact time and a 10–15-min washout. Concentration–response curves were repeated in the same tissue following equilibration (50 min) with test compound (3×10^{-9} to 3×10^{-8} M).

Schild plot data for the antagonism of 5-HT responses by test compounds were derived by linear regression analysis of pooled data.

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Registry No. (±)-**9**, 139655-39-3; (±)-**9** free base, 139655-40-6; **10**, 124808-45-3; (±)-**11**, 139756-52-8; (±)-**11** free base, 139686-66-1; (±)-**12**, 139632-20-5; (±)-**12** free base, 139632-19-2; (±)-**13**, 139632-22-7; (±)-**13** free base, 139632-21-6; (±)-**14**, 139632-24-9; (±)-**14** free base, 139632-23-8; (±)-**15**, 139632-26-1; (±)-**15** free base, 139632-25-0; (±)-**16**, 139632-28-3; (±)-**16** free base, 139632-27-2; **17**, 124809-04-7; **17** free base, 124808-67-9; **18**, 124809-03-6; **18** free base, 124808-66-8; **19**, 139632-29-4; **19** free base, 124808-63-5; **20**, 139632-31-8; **20** free base, 139632-30-7; **21**, 139632-33-0; **21** free base, 139632-32-9; **22**, 139632-34-1; **22** free base, 139632-35-2; **23**, 139632-36-3; **24**, 139655-41-7; **24** free base, 139632-37-4; **25**, 139632-38-5; **25** free base, 139632-39-6; **26**, 139632-41-0; **26** free base, 139632-40-9; **27**, 139632-43-2; **27** free base, 139632-42-1; **28**, 139632-44-3; **28** free base, 139632-45-4; **29**, 139632-46-5; **29** free base, 139632-47-6; **30**, 136013-70-2; **30** free base, 136013-69-9; **31**, 139632-49-8; **31** free base, 139632-48-7; **32**, 139632-51-2; **32** free base, 139632-50-1; **33**, 139655-42-8; **33** free base, 139632-52-3; **34**, 139632-53-4; **34** free base, 136013-77-9; **35**, 139632-55-6; **35** free base, 139632-54-5; 2-methoxy-4-nitrobenzamide, 62726-03-8; *endo*-3-aminotropane, 87571-88-8; 4-methoxybenzoyl chloride, 100-07-2; (4-methoxybenzoyl)urea, 51884-02-7; (±)-3-aminoquinuclidine, 76883-48-2.

Supplementary Material Available: All further information concerning the X-ray analysis of **30** (fractional atomic coordinates, anisotropic temperature factors, bond angles and bond distances) and atomic coordinates of the three structures displayed in Figure 3 (9 pages). Ordering information is given on any current masthead page.

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