mixture was added to monolayer cultures of mouse L cells (5×10^5 cells), and the incubation was stopped after 30 min by adding the stabilized diazonium salt Garnet GBC (1 mL, 1 mg/mL) in 1 M acetic acid buffer at pH 4.2, containing 10% Tween 20. The mixture was left at room temperature for 15 min and centrifuged, and its absorbance was measured at 525 nm.

Antinociceptive Activity. Antinociception was evaluated in mice by means of the tail-flick test,[30] immersing the tail into water at 52 °C, using a cutoff time of 10 s. The observer was blind to the compound injected. Results were expressed as percentage change in reaction time vs predrug score (1.9–2.5 s). A group of mice injected with saline was also tested in parallel. Saline administration had no effect on the tail-flick latency at any time postinjection.

Acknowledgment. The present work has been supported by Comisión Interministerial de Ciencia y Tecnología (Plan Nacional Project FAR 88-0298). We thank Francisco Caballero for help in typing this manuscript.

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Development of High-Affinity 5-HT_3 Receptor Antagonists. 1. Initial Structure–Activity Relationship of Novel Benzamides

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This report describes the development of novel benzamides which are orally active, highly potent, specific antagonists of 5-HT_3 receptors. Described in this first report are the structure–activity relationships that led to novel structures with improved potency and selectivity. From this series of compounds, (*S*)-**28** was identified and selected for further evaluation as a 5-HT_3 receptor antagonist. Compared with 5-HT_3 antagonists such as GR 38032F, BRL 43694, and metoclopramide, (*S*)-**28** was most active in (a) inhibiting binding to 5-HT_3 receptor binding sites in rat entorhinal cortex with an K_i value of 0.19 nM and (b) blocking cisplatin-induced emesis in the ferret with an ED_{50} value determined to be 9 μg/kg po.

Introduction

In the past decade there have been significant advances in our understanding of the biochemistry and physiology of the neurotransmitter serotonin (5-HT). Much of this progress was stimulated by the discovery of multiple 5-HT receptor subtypes and by the subsequent design of pharmacological agents selective for these sites. During recent years, there has been intense effort aimed at identification and functional characterization of 5-HT receptor subtypes and preparation of ligands with both potent binding affinity and receptor subtype specificity. One of these receptor subtypes is the 5-HT_3 receptor through which 5-HT acts to excite enteric neurons.[1] Ligand-binding and functional studies have shown that the 5-HT_3 receptor is found in both the peripheral[2] and central nervous system.[3] In enteric neurons and in autonomic neurons, activation of 5-HT_3 receptors produces depolarization and causes neurotransmitter release.[4] A somewhat selective 5-HT_3 agonist, 2-methylserotonin has been described[4a] and 5-HT_3 antagonists have been described which exhibit a variety of pharmacological effects. Several have displayed potent antagonism of chemotherapy or radiation-induced emesis in man.[5] In various animal models there has been some indication that these drugs may have utility in the treat-

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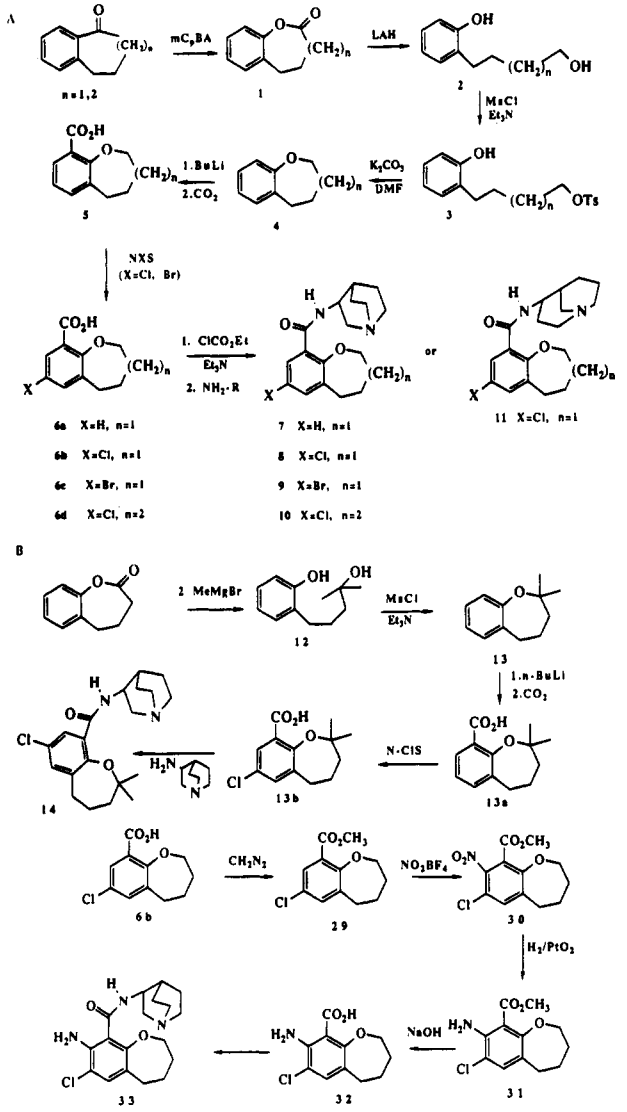
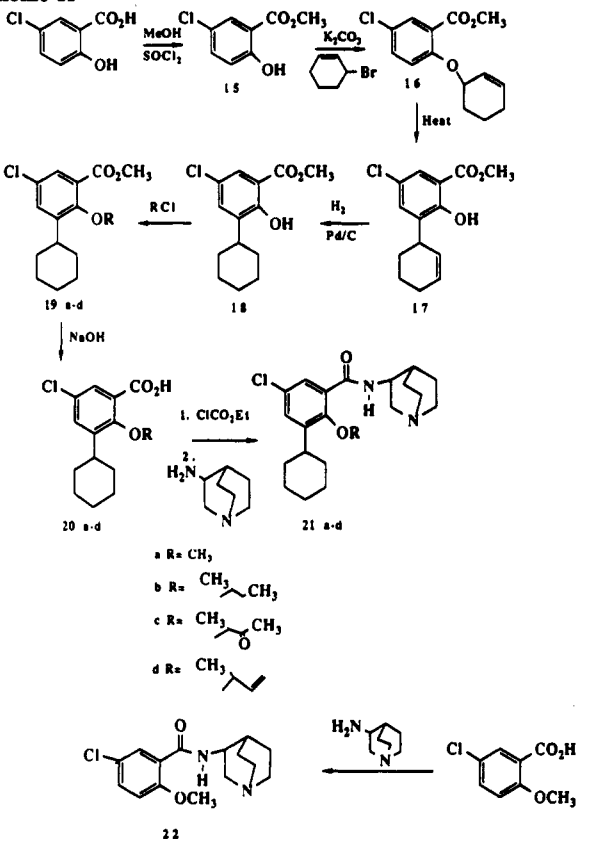
Scheme I



ment of psychosis,[6] anxiety,[7] migraine,[8] and pain[8] (peripheral analgetic).

One of the most prominent side effects of current chemotherapeutic agents is the emesis or nausea experienced during and following such therapy. At present, metoclopramide is the drug most often used to block the emesis produced by such agents. Although originally thought to exert its antiemetic action via dopamine receptor blockade, the antiemetic action of this drug has now been linked to antagonism of 5-HT_3 receptors, an action first reported for metoclopramide in isolated rabbit hearts.[10] In this regard,

Scheme II



relatively high doses of metoclopramide must be administered to block emesis produced by antineoplastic agents,[11] but this is due to the fact that metoclopramide is a relatively weak 5-HT_3 antagonist.[3] Recently, more potent and selective 5-HT_3 receptor antagonists (e.g. BRL 43694, GR 38032F) have proven effective in preventing emesis induced by cytotoxic drugs.[5,6,12-14] In this series of papers, we describe the development of novel chemical compounds which eventually led us to potent and selective 5-HT_3 receptor antagonists with remarkable potency in vivo in blocking antineoplastic induced emesis in the ferret.

It has been reported that derivatives of benzofuran- and benzopyrancarboxamides have demonstrated varying degrees of antiemetic activity.[15,16] The antiemetic activity of the benzofurancarboxamide derivatives[15,16] has been correlated to binding affinity for 5-HT_3 receptors. Thus,

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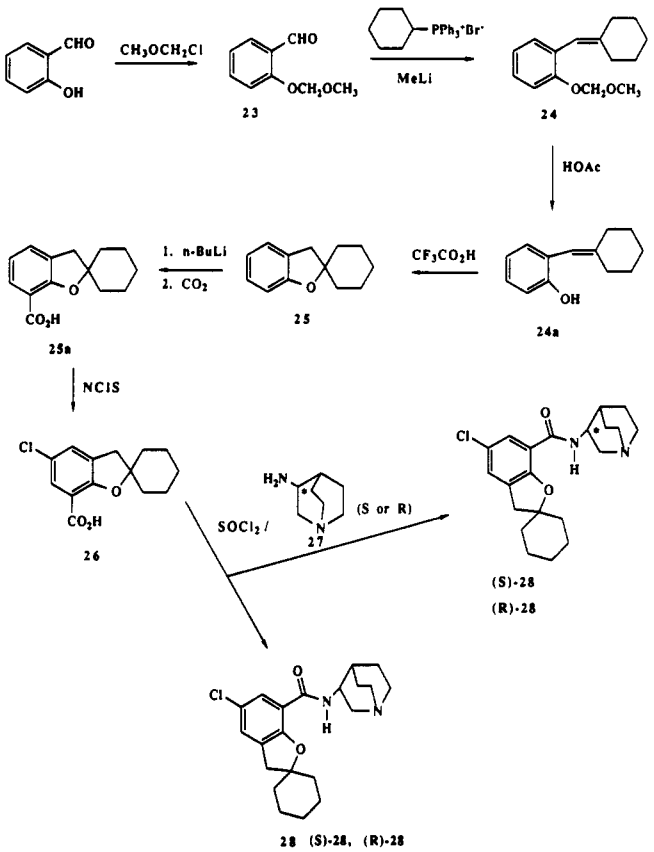
Scheme III



we chose to examine the structure–activity relationships of benzamides with an expanded or modified ring system.

Chemistry

Benzoxepin and benzoxocin derivatives were synthesized as shown in Scheme I. Baeyer–Villager oxidation of the appropriate ketone gave the corresponding lactone **1**, which could be reduced to the desired diol **2**, in a straightforward fashion. Monoderivatization of the primary alcohol, followed by intramolecular displacement with the phenoxide anion, yielded the benzoxepin (**4**, n = 1) or benzoxocin (**4**, n = 2) ring system. Direct reduction of lactone **1** to ether **4** could not be accomplished in reasonable yield.

With the desired seven- or eight-membered ring ether in hand, the oxygen atom was used to direct the metalation of the aromatic ring at the ortho position. Quenching of the lithium anion with carbon dioxide provided the expected carboxylic acid **5**. As anticipated, electrophilic addition to the aromatic ring occurred para to the oxygen atom (**6**). Amide formation with either the appropriate aminoquinuclidine or bicyclo[3.3.1]nonane then gave the desired analogues **7–11**.

Synthesis of the dimethyl derivative was accomplished by the addition of 2 equiv of methylmagnesium bromide to lactone **1** (n = 1). Acid-catalyzed cyclization of diol intermediate **12** provided the desired ring system **13**, which was subjected to the sequence described above to obtain amide **14**.

Esterification, followed by nitronium tetrafluoroborate nitration of **6b** provided **30**, whose structure was confirmed by single-crystal X-ray analysis. Catalytic reduction of the nitro group and basic hydrolysis of the ester function, followed by amidation using 3-aminoquinuclidine, led to **33**.

The 3-alkylated benzamides were synthesized as shown in Scheme II. Starting with 5-chlorosalicylic acid, esterification followed by O-alkylation with 3-bromocyclohexene provided compound **16**. Claisen rearrangement of **16** gave **17**, which on hydrogenation led to **18**. Intermediate **18** was O-alkylated with the appropriate alkyl halide to give **19a–d** deesterified with base and coupled with 3-aminoquinuclidine to provide **21a–d**. Amidation of 2-methoxy-5-chlorobenzoic acid with 3-aminoquinuclidine gave **22**.

The synthesis of the novel spirobenzamide **28** and its optical isomers is shown in the Scheme III. The overall yield of **28** was much improved when the starting salicylaldehyde was protected as its methoxymethyl ether **23**. Reaction of **23** with the appropriate Wittig reagent gave **24**. Acid hydrolysis of **24**, followed by treatment with trifluoroacetic acid, provided tricyclic **25**. Carboxylation and chlorination as usual led to **26**. Coupling of **26** with racemic or optically active 3-amionoquinuclidine[17] **27** provided the appropriate spirobenzamide **28**, (*S*)-**28**, or (*R*)-**28**.

Table I. Antagonism of [^{3}H] GR 65630 Binding by Various Agents

compd	n^a	K_i ± SE	compd	n^a	K_i ± SE
7	1	13.8 ± 3.40	**28**	1	1.07 ± 0.57
8	1	1.22 ± 1.04	(*S*)-**28**	3	0.19 ± 0.04
9	1	2.16 ± 0.30	(*R*)-**28**	1	0.89 ± 0.57
10	1	4.70 ± 0.48	**33**	1	>100
11	1	63.0 ± 26.1	BRL 43694	3	1.72 ± 0.03
14	1	15.6 ± 2.30	GR 38032F	3	6.16 ± 2.1
21a	1	6.09 ± 1.42	ICS 205-930	5	1.66 ± 0.28
21b	1	>30	metoclopramide	3	995 ± 226
22	1	46.8 ± 13.6	zacopride	3	1.5 ± 0.36

[a] n = number of experiments. In each experiment compounds were tested in six-point competition experiments with triplicate replication.

Biological Results

Data for the displacement of the 5-HT$_3$ receptor ligand [^{3}H]GR 65630 from rat brain cortical membranes[18] by compounds reported in this paper are illustrated in Table I. The parent unsubstituted benzoxepincarboxamide **7** demonstrated a 5-HT$_3$ receptor binding affinity of 13.80 nM. Substitution of a bromine atom at the 3-position (**9**) improved the binding affinity 6-fold, while 3-substitution with a chlorine atom (**8**) further enhanced the activity by 11-fold (K_i = 1.22 nM). Encouraged by this result, compound **8** was chosen for further derivatization. Amination of **8** at the 4-position (**33**) essentially eliminated the binding affinity of the molecule. Similarly, *gem*-dimethyl substitution at 6-position (**14**) led to a substantial loss in binding affinity (K_i = 15.60 nM).

Replacement of the quinuclidine of the carboxamide of **8** with the azabicyclo[3.3.1]nonane moiety resulted in a compound (**11**) that displayed one of the weakest binding affinities among the compounds tested in this series.

Expansion of the benzoxepin ring system of **8** by one carbon atom gave the corresponding 3-chlorobenzoxocin **10**, which displayed appreciable activity as a ligand for the 5-HT$_3$ receptor (K_i = 4.70), but was not as potent as benzoxepin **8** (K_i = 1.22).

A comparison of the relative binding affinity of the compounds **8**, **21a**, and **22** illustrates the importance of a fused ring in this system. To further examine the binding affinity of other fused ring systems, tricyclic carboxamide **28** was synthesized. This compound was found to be one of the most potent 5-HT$_3$ receptor antagonists with a K_i

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Table II. Antiemetic Activity against Cisplatin-Induced Emesis in the Ferret: Intravenous Administration

compd[a]	dose required to reduce emetic episodes to 50% of control value: ED_{50},[b] μg/kg (95% confidence limits)	dose required to increase latency to first emetic bout by 100%: ED_{100}, μg/kg (95% confidence limits)
28	2 (0.2, 21)	6 (2, 20)
(*S*)-**28**	9 (2, 54)	5 (1, 28)
(*R*)-**28**	99 (8, 1301)	55 (24, 126)
metoclopramide	1450 (190, 10900)	2100 (380, 11600)
BRL 43694	226 (100, 510)	82 (37, 180)
GR 38032F	8 (7, 9)	15 (6, 34)

[a] Administered 30 min prior to cisplatin, or 30 min before and 45 min after cisplatin. The mean number of emetic episodes in control (0.5% methylcellulose) treated animals ranged from 8.5 to 15.6, while the mean latency to the first emetic bout ranged from 50 to 68 min. [b] Determined from 4–10 animals per dose and at least 3 doses per compound.

value of 0.77 nM. Moreover, compound **28** failed to potently displace [^{3}H]spiroperidol from D_2 binding sites, indicating negligible potential for dopaminergic antagonist activity. The K_i value for metoclopramide at the D_2 binding site was determined to be 233 nM as compared to 10448 nM for **28**.

Since compound **28** is racemic, it was decided to synthesize each of the enantiomers and compare their binding affinities for the 5-HT_3 receptor and their antiemetic activity against cisplatin-induced emesis in the ferret.[19] In ^{3}H-ligand binding assays, (*S*)-**28** potently displaced [^{3}H]GR 65630 binding from rat cortical tissue with a K_i value of 0.19 nM. The K_i value of this isomer was 9.0-, 32.4-, and 8.7-fold lower than those derived for BRL 43694, GR 38032F, and ICS 205-930, respectively. It was also 4.0-fold lower than the K_i value of the (*R*)-**28** isomer.

(*S*)-**28** was the most potent and effective isomer in both reducing emetic episodes and increasing the latency to the first emetic episode produced by cisplatin in the ferret following either intravenous or oral administration as illustrated in Tables II and III, respectively. After iv administration, (*S*)-**28** was equipotent to GR 38032F, but was clearly more potent than BRL 43694, metoclopramide, and (*R*)-**28**. However, following oral administration, (*S*)-**28** had the lowest ED_{50} value (9 μg/kg) among those desired for all these agents. A comparison of the po/iv ratio of ED_{50} values further suggests that (*S*)-**28** (1.0) is readily bioavailable. A comparison of the antiemetic activity of (*S*)-**28**, BRL 43694, GR 38032F, and metoclopramide following po administration is shown in Table III. A significant correlation ($r = 0.9994$, $p < 0.001$) between ED_{50} values for 50% reduction in emetic episodes and K_i values for binding to the $5HT_3$ receptor for these compounds was determined.

Experimental Section

All melting points were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus using open capillaries and are uncorrected. Analytical results are indicated by the elements' symbols and are within ±0.4% of the theoretical values. ^{1}H NMR spectra were recorded on a Varian EM-390 instrument using tetramethylsilane as an internal standard and are consistent with the assigned structures.

4,5-Dihydro-1-benzoxepin-2(3*H*)-one (1, *n* = 1). To a solution of mCpBA (236 g, 1.368 mol) in chloroform (1 L) at 0 °C was added α-tetralone (100 g, 0.684 mol) as a solution in chloroform (250 mL), dropwise, via an addition funnel. After the addition was complete the reaction mixture was allowed to come to room temperature. Stirring was continued for 5 days at room temperature. Saturated aqueous sodium carbonate (1 L) was carefully added and the mixture transferred to a separatory funnel. The aqueous layer was discarded and the organic layer was carefully washed with saturated aqueous sodium bicarbonate and water, dried over magnesium sulfate, filtered, and concentrated in vacuo. Vacuum distillation provided the desired lactone as a low-melting white solid: ^{1}H NMR ($CDCl_3$) δ 7.30–7.00 (m, 4 H), 2.80 (t, 2 H), 2.60–2.00 (m, 4 H).

3,4,5,6-Tetrahydro-2*H*-1-benzoxocin-2-one (1, *n* = 2). When benzosuberone is used in place of α-tetralone under similar conditions, 1-benzoxocin-2-one 1 is obtained: ^{1}H NMR ($CDCl_3$) δ 7.30–7.00 (m, 4 H), 2.80 (t, 2 H), 2.50–1.90 (m, 4 H).

4-(2-Hydroxyphenyl)-1-butanol (2, *n* = 1). To a solution of lithium aluminum hydride (17.5 g, 461 mmol) in ether (1 L) was added lactone 1 ($n = 1$) (74.7 g, 461 mmol) as a solution in ether (200 mL), dropwise, via an addition funnel at 0 °C. The ice bath was removed and stirring was continued for 1 h at room temperature. The reaction mixture was cooled to 0 °C and excess LAH was decomposed by the sequential addition of water (17.5 mL), 15% aqueous sodium hydroxide (17.5 mL), and water (53 mL). The reaction mixture was filtered through Celite and the filtrate was dried over magnesium sulfate, filtered, and concentrated in vacuo to provide diol **2** ($n = 1$): ^{1}H NMR ($CDCl_3$) δ 7.50–7.10 (m, 4 H), 4.21 (t, $J = 3.6$ Hz, 2 H), 3.00 (t, $J = 3.8$ Hz, 2 H), 2.10–1.70 (m, 6 H).

5-(2-Hydroxyphenyl)-1-pentanol (2, *n* = 2). When lactone **2** ($n = 1$) is used in place of lactone 1 ($n = 1$) under similar reaction conditions diol **2** ($n = 2$) is obtained: ^{1}H NMR ($CDCl_3$) δ 7.50–7.10 (m, 4 H), 4.10 (t, $J = 3.6$ Hz, 2 H), 3.00 (t, $J = 3.8$ Hz, 2 H), 2.10–1.70 (m, 6 H).

4-(2-Hydroxyphenyl)-1-(tosyloxy)butane (3, *n* = 1). To a solution of the diol (3.6 g, 21.7 mmol) in dichloromethane (20 mL) was added triethylamine (4.5 mL, 32.5 mmol) in a single portion at room temperature. A solution of tosyl chloride (4.1 g, 21.7 mmol) in dichloromethane (10 mL) was added dropwise via an addition funnel at room temperature. Stirring was continued for 48 h at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give tosylate **3** ($n = 1$): ^{1}H NMR ($CDCl_3$) δ 8.00 (d, $J = 4.5$ Hz, 2 H), 7.60 (d, $J = 4.5$ Hz, 2 H), 7.40–7.20 (m, 4 H), 3.81 (t, $J = 3.8$ Hz, 2 H), 2.70 (s, 3 H), 2.68 (t, $J = 4.3$ Hz, 2 H), 1.85–1.50 (m, 4 H).

5-(2-Hydroxyphenyl)-1-(tosyloxy)pentane (3, *n* = 2). When the $n = 2$ diol **2** is used in place of the $n = 1$ diol **2** under similar reaction conditions, tosylate **3** ($n = 2$) is obtained: ^{1}H NMR ($CDCl_3$) δ 8.00 (d, $J = 4.6$ Hz, 2 H), 7.60 (d, $J = 4.6$ Hz, 2 H), 7.40–7.20 (m, 4 H), 3.85 (t, $J = 3.8$ Hz, 2 H), 2.70 (s, 3 H), 2.70 (t, $J = 4.2$ Hz, 2 H), 1.90–1.50 (m, 6 H).

2,3,4,5-Tetrahydro-1-benzoxepin (4, *n* = 1). To a suspension of sodium hydride (936 mg, 23.4 mmol, 60% dispersion) in tetrahydrofuran (10 mL) was added tosylate **3** ($n = 1$) (7.5 g, 23.4 mmol) as a solution in tetrahydrofuran (5 mL), dropwise, via an addition funnel at room temperature. Stirring was continued for

Table III. Antiemetic Activity against Cisplatin-Induced Emesis in the Ferret: Oral Administration

compd[a]	dose required to reduce emetic episodes to 50% of control value: ED_{50},[b] μg/kg (95% confidence limits)	dose required to increase latency to first emetic bout by 50%: ED_{50}, μg/kg (95% confidence limits)
(*S*)-**28**	9 (3, 25)	4 (1, 21)
BRL 43694	119 (28, 510)	117 (30, 470)
GR 38032F	280 (57, 1390)	31 (10, 110)
metoclopramide	6170 (670, 56600)	>5000[c]

[a] Administered 60 min before cisplatin. The mean emetic episodes in control (0.5% methylcellulose) treated ferrets ranged from 6.9 to 11.7, while the mean emetic latency period ranged from 55 to 81 min. [b] Determined from 3–12 animals per dose and at least 3 doses per compound. [c] Increase in emetic latency was 23% at 5 mg/kg (highest dose tested).

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24 h at room temperature. Water (1 L) was added and the reaction mixture diluted with ethyl acetate and washed with brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (10% ethyl acetate/hexanes) provided benzoxepin **4**, (n = 1) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.05 (m, 4 H), 3.95 (t, J = 6.5 Hz, 2 H), 2.80 (t, J = 7.2 Hz, 2 H), 2.0–1.5 (m, 4 H).

3,4,5,6-Tetrahydro-2*H*-1-benzoxocin (4, *n* =2). When the n = 2 tosylate **3** is used in place of the n = 1 tosylate **3** under similar reaction conditions, benzoxocin **4** (n = 2) is obtained: ^{1}H NMR ($CDCl_3$) δ 7.30–6.80 (m, 4 H), 3.98 (t, J = 6.5 Hz, 2 H), 2.80 (t, J = 7.0 Hz, 2 H), 2.00–1.50 (m, 6 H).

5-(2-Hydroxyphenyl)-2-methyl-2-hydroxypentane (12). To a solution of lactone **1** (n = 1) (5 g, 31 mmol) in ether (50 mL) was added methylmagnesium bromide (7.38 g, 62 mmol) as a 3 M solution in ether, dropwise, via an addition funnel at 0 °C. Stirring was continued for 1 h at 0 °C. Hydrochloric acid (1 N, 20 mL) was added at 0 °C and stirring continued for 15 min. The reaction mixture was diluted with water and extracted with ether. The organic extracts were dried over magnesium sulfate, filtered, and concentrated to give the diol: ^{1}H NMR ($CDCl_3$) δ 7.10–6.70 (m, 4 H), 2.60 (t, 2 H), 1.70–1.40 (m, 4 H), 1.20 (s, 6 H).

2,2-Dimethyl-2,3,4,5-tetrahydro-1-benzoxepin (13). To a solution of diol (4.8 g, 24.7 mmol) in chloroform (100 mL) was added *p*-toluenesulfonic acid (94 g, 4.94 mmol) in a single portion at room temperature. The reaction mixture was heated at reflux for 2 h. The reaction mixture was washed with saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (10% ethyl acetate/hexanes) provided the desired product: ^{1}H NMR ($CDCl_3$) δ 7.20–6.90 (m, 4 H), 2.90–2.70 (m, 2 H), 1.80–1.60 (m, 4 H), 1.30 (s, 6 H).

2,3,4,5-Tetrahydro-1-benzoxepin-9-carboxylic Acid (5, *n* = 1). Tetramethylethylenediamine (1.1 mL, 7.4 mmol) was added to a solution of butyllithium in hexanes (3 mL of 2.5 M solution), dropwise, via a syringe at room temperature. Benzoxepin **4** (n = 1) (1.0 g, 6.7 mmol) was added neat, via a syringe at room temperature. Stirring was continued for 18 h at room temperature. The reaction mixture was cooled to 0 °C and carbon dioxide gas was bubbled into the solution via a cannula from another flask containing dry ice. Hexanes were added, and bubbling was continued for another 20 min at 0 °C. Water was added and the aqueous layer separated and washed with ether. The aqueous layer was acidified to about pH 2 with 3 N hydrochloric acid and extracted with dichloromethane. The organic extracts were dried over magnesium sulfate, filtered, and concentrated to provide carboxylic acid **5** (n = 1) as a low-melting solid: ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 4.8 Hz, 1 H), 7.35 (d, J = 4.8 Hz, 1 H), 7.20 (dd, J = 4.8, 5.2 Hz, 1 H), 4.20 (t, J = 5.0 Hz, 2 H), 2.80 (t, J = 4.6 Hz, 2 H), 1.90–1.60 (m, 4 H).

3,4,5,6-Tetrahydro-2*H*-1-benzoxocin-10-carboxylic Acid (5, *n* = 2). When the n = 2 benzoxocin **4** is used in place of the n = 1 benzoxepin **4** under similar reaction conditions, acid **5** (n = 2) is obtained: ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 4.5 Hz, 1 H), 7.40 (d, J = 4.6 Hz, 1 H), 7.20 (dd, J = 4.5, 4.8 Hz, 1 H), 4.25 (t, J = 5.0 Hz, 2 H), 2.80 (t, 4.6 Hz, 2 H), 1.90–1.20 (m, 4 H).

2,2-Dimethyl-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylic Acid (13a). To a solution of 23.18 mmol (1.2 equiv) of *n*-butyllithium (9.3 mL of 2.5 M solution in hexanes) is added 3.45 mL (23.18 mmol) of tetramethylethylenediamine, dropwise at room temperature. To this resulting solution is added 3.4 g (19.32 mmol) of 2,2-dimethyl-2,3,4,5-tetrahydro-1-benzoxepin (**13**). After stirring for 18 h, the reaction mixture is cooled to 0 °C, hexanes (20 mL) are added, and gaseous carbon dioxide is bubbled into the mixture for 1 h. At this time sufficient water is added to dissolve all the salts. The hexanes are then removed, and the aqueous layer is washed with hexanes. The aqueous layer is acidified to about pH 2 with 3 N hydrochloric acid and extracted with methylene chloride.

The combined organic extracts are dried over magnesium sulfate, filtered, and concentrated to dryness to obtain 2,2-dimethyl-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylic acid as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.10 (br d, 1 H), 7.50–7.10 (m, 2 H), 2.85 (br t, 2 H), 2.10–1.80 (m, 4 H), 1.40 (s, 6 H).

7-Chloro-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylic Acid (6b). To a solution of carboxylic acid **5** (n = 1) (5.14 g, 26.8 mmol) in dimethylformamide (20 mL) was added *N*-chlorosuccinimide (4.3 g, 32.16 mmol) in a single portion at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (30% ethyl acetate/hexanes) provided the desired product: ^{1}H NMR ($CDCl_3$) δ 7.9 (s, 1 H), 7.3 (s, 1 H), 4.2 (t, J = 6.8 Hz, 2 H), 2.90 (m, 2 H), 2.20–1.70 (m, 4 H).

7-Bromo-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylic Acid (6c). When *N*-bromosuccinimide is used in place of *N*-chlorosuccinimide under similar reaction conditions, acid **6c** is obtained: ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1 H), 7.30 (s, 1 H), 4.30 (t, J = 6.4 Hz, 2 H), 2.80 (br t, 2 H), 2.10–1.70 (m, 4 H).

8-Chloro-3,4,5,6-tetrahydro-2*H*-1-benzoxocin-10-carboxylic Acid (6d). When the n = 2 acid **5** is used in place of the n = 1 acid **5** under similar reaction conditions, chloro acid **6d** is obtained: ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1 H), 7.4 (s, 1 H), 4.2 (t, J = 7.0 Hz, 2 H), 2.80 (t, J = 7.0 Hz, 2 H), 1.9 (m, 6 H).

2,2-Dimethyl-7-chloro-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylic Acid (13b). To a solution of 2,2-dimethyl-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylic acid (3.6 g, 16.4 mmol) in dimethylformamide (20 mL) is added *N*-chlorosuccinimide (2.6 g, 19.7 mmol) in one portion at room temperature. The resulting solution is stirred for 3.5 days. The reaction mixture is then diluted with ethyl acetate and washed with water, and the organic layer is dried over magnesium sulfate, filtered, and concentrated to obtain 2,2-dimethyl-7-chloro-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylic acid (**13b**): ^{1}H NMR ($CDCl_3$) δ 7.90 (br d, 1 H), 7.30 (br d, 1 H), 2.70 (br t, 2 H), 2.00–1.60 (m, 4 H), 1.30 (s, 6 H).

Methyl 7-Chloro-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylate (29). A solution of carboxylic acid **6b** (1.0 g, 4.4 mmol) in tetrahydrofuran (5 mL) was added, with stirring, to a large excess of diazomethane (Diazald, Aldrich). Glacial acetic acid was added dropwise to decompose excess diazomethane. All solvents were removed in vacuo to give **29**: ^{1}H NMR ($CDCl_3$) δ 8.10 (br s, 1 H), 7.50 (br s, 1 H), 4.00 (t, 2 H), 3.80 (s, 3 H), 2.80 (t, 2 H), 2.30–1.80 (m, 4 H).

Methyl 7-Chloro-8-nitro-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylate (30). To a solution of ester **29** (100 mg, 0.42 mmol) in sulfolane (1.5 mL) was added nitronium tetrafluoroborate (56 mg, 0.42 mmol) as a 0.5 M solution in sulfolane, dropwise, via a syringe, at such a rate that the temperature of the reaction mixture did not rise above 25 °C. Stirring was continued for 1 h at room temperature. Ice was added and the reaction mixture diluted with ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (10% ethyl acetate/hexanes) provided the desired product **30**. The structure was confirmed by single-crystal X-ray analysis: ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 1 H), 4.10 (t, J = 7.0 Hz, 2 H), 3.7 (s, 3 H), 3.00–2.80 (m, 2 H), 2.10–1.60 (m, 4 H).

Methyl 8-Amino-7-chloro-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylate (31). A solution of nitro derivative **30** (630 mg, 2.2 mmol) in ethyl acetate (10 mL) containing 10% w/w platinum oxide (63 mg) was shaken under a positive pressure of hydrogen (50 psi) for 24 h. The reaction mixture was filtered through Celite and concentrated in vacuo. Flash chromatography (10% ethyl acetate/hexanes) provided the desired product **31**: ^{1}H NMR ($CDCl_3$) δ 7.10 (s, 1 H), 4.05 (t, J = 6.9 Hz, 2 H), 3.80 (s, 3 H), 3.80–3.65 (m, 2 H), 2.00–1.50 (m, 4 H).

8-Amino-7-chloro-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylic Acid (32). To a solution of ester **31** (100 mg, 0.4 mmol) in methanol (4 mL) was added 10% aqueous sodium hydroxide (1 mL). The solution was heated at 65 °C for 2 h. Methanol was removed in vacuo. Water was added and the solution was acidified to about pH 2 with 1 N hydrochloric acid. The white precipitate **32** was filtered and dried: ^{1}H NMR ($CDCl_3$) δ 7.20 (s, 1 H), 4.10 (t, J = 7.4 Hz, 2 H), 2.80–2.75 (m, 2 H), 2.20–1.70 (m, 4 H).

General Procedure for the Preparation of the *N*-(1-Azabicyclo[2.2.2]oct-3-yl) Carboxamides. To a solution of the carboxylic acid (3.1 mmol) in pyridine (4 mL) at 0 °C was added dicyclohexylcarbodiimide (3.41 mmol) in a single portion. Stirring was continued for 1 h at 0 °C. 3-Aminoquinuclidine (3.1 mmol) was then added, the reaction mixture was allowed to come to room temperature, and stirring was continued for 17 h. Sodium hydroxide (1 N, 4 mL) was added and stirring continued for 30 min.

The reaction mixture was then filtered and the filtrate diluted with dichloromethane and washed with water. The organic layer was dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (30% ethyl acetate/hexanes, followed by methanol) provided the crude amide, which was recrystallized from the solvent indicated.

N-(1-Azabicyclo[2.2.2]oct-3-yl)-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxamide (7): oily product from chloroform/hexanes; ^{1}H NMR ($CDCl_3$) δ 8.35 (d, 1 H), 7.60–7.30 (m, 3 H), 4.0 (m, 4 H), 4.20–3.80 (m, 4 H), 3.60–3.30 (m, 6 H), 2.90–2.50 (m, 6 H), MS m/z = 300 (M^+). Anal. ($C_{18}H_{24}N_2O_2 \cdot {}^1/_2H_2O$) H, N; C: calcd, 69.58; found, 70.20.

7-Chloro-N-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxamide (8): white crystals; crystallized from ethyl acetate/hexane; mp 133–4 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, 1 H), 7.60 (d, 1 H), 7.20 (d, 1 H), 3.95 (m, 4 H), 3.51 (m, 2 H), 3.12 (m, 2 H), 2.76 (m, 6 H), 1.25 (m, 6 H); MS m/z = 334 (M^+). Anal. ($C_{18}H_{23}ClN_2O_2$) H, N; C: calcd, 64.56; found, 64.01.

2,2-Dimethyl-7-chloro-N-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxamide (14): white crystals; crystallized from methanol/ether; mp 55–6 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, 1 H), 7.91 (d, 1 H), 7.42 (d, 1 H), 4.40–4.10 (m, 2 H), 3.60–3.30 (m, 4 H), 3.10–2.80 (m, 6 H), 1.90–1.70 (m, 6 H), 1.30 (s, 6 H); MS m/z = 362 (M^+). Anal. ($C_{20}H_{27}ClN_2O_2 \cdot {}^1/_4H_2O$) C, H; N: calcd, 7.62; found 7.00.

8-Amino-7-chloro-N-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxamide (33): white crystals from methanol; mp 89–91 °C; ^{1}H NMR (DMSO) δ 8.30 (d, 1 H), 7.31 (s, 1 H), 6.30 (s, 2 H), 4.30–3.90 (m, 4 H), 3.50–3.30 (m, 2 H), 3.00–2.50 (m, 6 H), 2.10–1.50 (m, 6 H); MS m/z = 349 (M^+). Anal. ($C_{18}H_{24}ClN_3O_2 \cdot H_2O$) C, H, N.

8-Chloro-N-(azabicyclo[2.2.2]oct-3-yl)-3,4,5,6-tetrahydro-2H-1-benzoxocin-10-carboxamide (10): white solid from ethyl acetate/hexane; mp 139–40 °C; MS m/z = 348 (M^+). Anal. ($C_{19}H_{25}ClN_2O_2$) C, H, N.

7-Bromo-N-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxamide (9): off-white crystals from ethyl acetate/hexane; mp 80–1 °C; ^{1}H NMR ($CDCl_3$) δ 8.41 (d, 1 H), 7.62 (d, 1 H), 7.40 (d, 1 H), 4.20–3.80 (m, 4 H), 3.60–3.20 (m, 4 H), 2.90–2.50 (m, 6 H), 2.20–1.60 (m, 6 H); MS m/z = 379 (M^+). Anal. ($C_{18}H_{23}BrN_2O_2 \cdot {}^3/_4H_2O$) C, H; N: calcd, 7.13; found, 6.52.

7-Chloro-N-(1-azabicyclo[3.3.1]nonan-4-yl)-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxamide (11). To a solution of 7-chloro-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylic acid (**6b**) (100 mg, 0.4 mmol) in chloroform (3 mL) was added triethylamine (0.073 mL, 52 mmol) in one portion at room temperature. The solution was cooled to 0 °C and ethyl chloroformate (0.042 mL, 0.44 mmol) was added dropwise. Stirring was continued for 1 h at 0 °C. 4-Amino-1-azabicyclo[3.3.1]nonane dihydrochloride (852 mg, 4.0 mmol) was dissolved in saturated aqueous potassium carbonate (3 mL) and the resulting solution was cooled to 0 °C. The cold aqueous solution was added in one portion to the chloroform solution with vigorous stirring. The reaction mixture was allowed to come to room temperature and stirred overnight. The reaction mixture was diluted with water and extracted with chloroform. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (10% methanol/chloroform) removed the impurities to afford 7-chloro-N-(1-azabicyclo[3.3.1]nonan-4-yl)-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxamide (**11**): mp 166–7 °C; ^{1}H NMR (DMSO) δ 8.40 (d, 1 H), 7.68 (d, 1 H), 7.52 (d, 1 H), 4.40–4.10 (m, 4 H), 3.50–2.80 (m, 8 H), 2.30–1.70 (m, 10 H); MS m/z = 348 (M^+). Anal. ($C_{19}H_{25}ClN_2O_2$) C, H, N.

Methyl 5-Chlorosalicylate (15). Thionyl chloride (900.0 g, 7.56 mol) was added dropwise to methanol (1977.0 g, 61.72 mol) at 20 °C over a period of 1.5 h, with maintenance of the temperature between 15 and 25 °C with an ice bath. The cooling bath was removed and 5-chlorosalicylic acid (1000.0 g, 5.8 mol) was added in one portion and then slowly heated to reflux. On completion of the reaction the solution was cooled to −5 °C for 1 h. The methyl 5-chlorosalicylate was filtered and washed with cold (−5 °C) methanol (150 mL) and deionized water (2 × 1.0 L). The solid was dried under house vacuum at 30 °C for 24 h to give 934.1 g (86%) of **15**: mp 44–6 °C; ^{1}H NMR ($CDCl_3$) δ 10.63 (s, 1 H, OH), 7.68 (m, 1 H, H_6), 7.32 (m, 1 H, H_4), 6.86 (d, 1 H, H_3), 3.98 (s, 3 H, OCH_3); HPLC 97.87%. Anal. ($C_8H_7ClO_3$) C, H; Cl: calcd, 19.00; found, 18.50.

Methyl 5-Chloro-2-(3′-cyclohexenyl)salicylate (16). A mixture of methyl 5-chlorosalicylate (**15**) (550.0 g, 2.95 mol), 3-bromocyclohexene (597.4 g, 3.71 mol), finely grounded potassium carbonate (815.0 g, 5.90 mol), and acetone (4860.0 g, 83.7 mol) was slowly heated to reflux and maintained at reflux for 24 h. The mixture was cooled to 30–40 °C, the solids were filtered and washed with acetone, and the filtrate was concentrated to dryness to give 810.0 g of **16** as an amber oil: ^{1}H NMR ($CDCl_3$) δ 7.73 (m, 1 H, H_6), 7.34 (m, 1 H, H_4), 6.95 (d, 1 H, H_3), 5.91 (m, 2 H, CH=CH), 4.76 (br s, 1 H, COH), 3.86 (s, 3 H, OCH_3), 1.6–2.05 (m, 6 H, CH_2); HPLC 95.3%. Anal. ($C_{14}H_{15}ClO_3$) C, H, Cl.

Methyl 5-Chloro-3-(3′-cyclohexenyl)salicylate (17). A slurry of **16** (603.6 g, 2.26 mol) and cesium carbonate (33.5 g, 0.1 mol) was heated, under a nitrogen blanket, to 155–175 °C, for about 4 h. On completion of the reaction the mixture was cooled to 80 °C and toluene (500 mL) added. The mixture was stirred for 1 h, and the solids were removed by filtration. The filter cake was washed with toluene (2 × 65 mL). The filtrates were combined and concentrated to dryness to give 557.3 g (92%) of **17** as a brown oil. The oil was crystallized from denatured ethanol (550 mL). The solid was filtered, washed with cold denatured ethanol, and dried under house vacuum at 40 °C overnight to give 429.6 g (71.2%) of **17** as a tan solid: mp 59–61 °C; ^{1}H NMR ($CDCl_3$) δ 11.03 (s, 1 H, OH), 7.62 (d, 1 H, ArH), 7.30 (d, 1 H, ArH), 5.96 (m, 1 H, CH=CH), 5.94 (m, 1 H, CH=CH), 3.92 (s, 3 H, OCH_3), 3.84 (m, 1 H, COH), 1.34–2.2 (m, 6 H, CH_2); HPLC 99.79%. Anal. ($C_{14}H_{15}ClO_3$) C, H, Cl.

Methyl 5-Chloro-3-cyclohexylsalicylate (18). A solution of methyl 5-chloro-3-(3′-cyclohexenyl)salicylate (**17**) (6.0 g, 22.5 mmol) in methanol (30 mL) was reduced on a Parr shaker at 25 psi of H_2 pressure with platinum dioxide as catalyst (100 mg). After filtration and evaporation of methanol, there was obtained product **18** (5.2 g, 86% yield) as a white fluffy solid: ^{1}H NMR ($CDCl_3$) δ 0.9–2.3 (m, 10 H), 3.0 (m, 1 H), 3.9 (s, 3 H), 7.3 (d, 1 H), 7.8 (d, 1 H).

Methyl 5-Chloro-3-cyclohexyl-2-(2′-oxo-1′-methylpropoxy)benzoate (19c). A mixture of methyl-5-chloro-3-cyclohexylsalicylate (**18**) (6.0 g, 22 mmol), 3-bromo-2-butanone (3.7 g, 24.5 mmol), and potassium carbonate (3.7 g, 27 mmol) in dimethylformamide (30 mL) was heated at 80 °C for 4 h. The reaction mixture was filtered from salts, diluted with water, and extracted with ethyl acetate. The organic solution was washed well with water, dried with magnesium sulfate, and evaporated. The crude product was purified through a flash silica gel column with 10% ethyl acetate/hexane to give 5.1 g (67% yield) of **19c** as a light amber oil: ^{1}H NMR ($CDCl_3$) δ 1.0–2.0 (m, 13 H), 2.4 (s, 3 H), 3.0 (m, 1 H), 3.9 (s, 3 H), 4.2–4.5 (m, 1 H), 7.4 (d, 1 H), 7.8 (d, 1 H).

5-Chloro-3-cyclohexyl-2-(2′-oxo-1′-methylpropoxy)benzoic Acid (20c). A solution of methyl-5-chloro-3-cyclohexyl-2-(2′-oxo-1′-methylpropoxy)benzoate (**19c**) (5.1 g, 15 mmol) in methanol (20 mL) and aqueous 1 N sodium hydroxide (20 mL) was stirred at room temperature overnight. The methanol was stripped and the alkaline residue diluted with water and then extracted with ethyl acetate, which was dried with magnesium sulfate and evaporated to dryness to give 3.9 g (80% yield) of **20c** as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.9–1.7 (m, 13 H), 2.4 (s, 3 H), 3.0 (m, 1 H), 4.2–4.5 (m, 1 H), 7.4 (d, 1 H), 7.8 (d, 1 H), 10.3 (s, 1 H).

5-Chloro-3-cyclohexyl-2-(2′-oxo-1′-methylpropoxy)-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamide (21c). Thionyl chloride (2.2 g, 18.5 mmol) was added to a solution of 5-chloro-3-cyclohexyl-2-(2′-oxo-1′-methylpropoxy)benzoic acid (**20c**) (1.5 g, 4.6 mmol) in dichloromethane (25 mL) and stirred at reflux for 2 h and then evaporated to dryness with three washings of dichloromethane. The weight of the resulting acid chloride was 1.5 g as an amber oil. This was dissolved in chloroform (20.0 mL) and to it was added a solution of 3-aminoquinuclidine (0.6 g, 4.8 mmol) free base in chloroform (5.0 mL) and the solution refluxed for 1 h.

The reaction mixture was washed with 1 N sodium hydroxide and then water, dried with magnesium sulfate, filtered, and evaporated to dryness to give 2.0 g of crude product as amber crystals. This was purified through a flash silica gel column with

10% methanol/chloroform to give 1.1 g (55% yield) of **21c** as white crystals: mp 60–1 °C; ^{1}H NMR ($CDCl_3$) δ 1.0–2.1 (m, 13 H), 2.3 (s, 3 H), 2.6–4.6 (m, 15 H), 7.2 (d, 1 H), 7.6 (d, 1 H). Anal. ($C_{24}H_{23}ClN_2O_3 \cdot 2H_2O$) C, N; H: calcd, 7.95; found, 7.46.

Methyl 5-Chloro-3-cyclohexyl-2-(1′-methallyloxy)benzoate (19d). A mixture of methyl 5-chloro-3-cyclohexylsalicylate (**18**) (4.6 g, 17 mmol), 3-chloro-1-butene (1.7 g, 18.8 mmol) and potassium carbonate (4.7 g, 33.9 mmol) in dimethylformamide (20 mL) was heated at 80 °C for 4 h. The reaction mixture was filtered from salts, diluted with water, and extracted with ethyl acetate. The organic solution was washed well with water, dried with magnesium sulfate, and evaporated to an oil. The oil was dissolved in a little *n*-hexane and put onto a bed of silica gel (for dry column), washed with *n*-hexane, and then eluted with ethyl acetate, which had been dried with magnesium sulfate. Evaporation gave 3.3 g of **19d** as an amber oil: ^{1}H NMR ($CDCl_3$) δ 0.9–2.1 (m, 13 H), 2.7–3.2 (m, 1 H), 3.9 (s, 3 H), 4.1–6.2 (m, 4 H), 7.4 (d, 1 H), 7.6 (d, 1 H).

Methyl 5-Chloro-3-cyclohexyl-2-isobutoxybenzoate (19b). A solution of methyl 5-chloro-3-cyclohexyl-2-(1′-methallyloxy)-benzoate (**19d**) (3.3 g, 10.2 mmol) in methanol (30 mL) containing platinum oxide catalyst (0.6 g) was hydrogenated at 35 psi for 1 h. After filtration through Celite the filtrate was evaporated to dryness to give 2.8 g of crude light amber oil. This crude oil was purified by flash chromatography (silica gel, 5% ethyl acetate/hexane) to give **19b** as a white oil (0.8 g, 25% yield): ^{1}H NMR ($CDCl_3$) δ 0.8–2.1 (m, 18 H), 3.0 (m, 1 H), 3.7–4.0 (d, 4 H), 7.4 (d, 1 H), 7.6 (d, 1 H).

5-Chloro-3-cyclohexyl-2-isobutoxybenzoic Acid (20b). A solution of methyl 5-chloro-3-cyclohexyl-2-isobutoxybenzoate (**19b**) (0.8 g, 2.5 mmol) in methanol (10 mL) and 1 N aqueous sodium hydroxide (5 mL) was refluxed for 1 h. The methanol was stripped and the alkaline residue was diluted with water then extracted with ethyl acetate. The alkaline layer was acidified to pH 2 with concentrated hydrochloric acid and extracted with ethyl acetate, which was dried and evaporated to give **20b** as a white solid (0.6 g, 79% yield): ^{1}H NMR ($CDCl_3$) δ 0.7–2.1 (m, 18 H), 2.8–4.2 (m, 2 H), 7.4 (d, 1 H), 7.8 (d, 1 H).

5-Chloro-3-cyclohexyl-2-isobutoxy-*N*-(1-azabicyclo-[2.2.2]oct-3-yl)benzamide (21b). Thionyl chloride (0.9 g, 7.6 mmol) was added to a solution of 5-chloro-3-cyclohexyl-2-isobutylbenzoic acid (**20b**) (0.6 g, 1.9 mmol) in dichloromethane (10 mL) and stirred at reflux for 32 h and then evaporated to dryness and washed three times with dichloromethane. The resulting acid chloride oil was dissolved in chloroform (10 mL) and to it was added a solution of 3-aminoquinuclidine free base (0.6 g, 7.9 mmol) in chloroform (5 mL) and the solution refluxed for 1 h. The reaction mixture was washed with 1 N aqueous sodium hydroxide and then water, dried with magnesium sulfate, and evaporated to dryness to give the crude product as an oil. The oil was purified by flash chromatography (silica gel, 10% methanol/chloroform) to give **21b** as a white crystalline solid (0.3 g, 38% yield): mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 0.8–4.3 (m, 33 H), 7.3 (d, 1 H), 7.9 (d, 1 H). Anal. ($C_{24}H_{35}ClN_2O_2 \cdot {}^1/_2H_2O$) C, N; H: calcd, 8.48; found, 7.95.

Methyl 5-Chloro-3-cyclohexyl-2-methoxybenzoate (19a). A mixture of 5-chloro-3-cyclohexylsalicylate (**18**) (9.5 g, 35.4 mmol), methyl iodide (5.5 g, 38.6 mmol), sodium iodide (1.1 g, 7.3 mmol), and potassium carbonate (14.6 g, 105.7 mmol) in dimethylformamide (137 mL) was heated at 60 °C overnight. The reaction mixture was filtered from salts, diluted with water, and extracted with ethyl acetate. The organic solution was washed with water, dried with magnesium sulfate, filtered, and concentrated to dryness to give **19a** as an amber oil (9.9 g, 99% yield), which was used in the next synthetic step without further purification.

5-Chloro-3-cyclohexyl-2-methoxybenzoic Acid (20a). A mixture of methyl 5-chloro-3-cyclohexyl-2-methoxybenzoate (**19a**) (9.9 g, 35 mmol) in methanol (40 mL) and 1 N aqueous sodium hydroxide (40 mL) was stirred at room temperature for 20 h. The methanol was stripped and the alkaline portion was extracted with ethyl acetate and then acidified with concentrated hydrochloric acid to pH 2 and again extracted with ethyl acetate. The ethyl acetate was dried with magnesium sulfate, filtered, and evaporated to dryness and the residue triturated with *n*-hexane. After filtering and air-drying there was obtained **20a** as a white solid (7.1 g, 76% yield): ^{1}H NMR ($CDCl_3$) δ 1.1–2.1 (m, 10 H), 2.6–3.1 (m, 1 H), 3.8 (s, 3 H), 7.4 (d, 1 H), 7.8 (d, 1 H).

5-Chloro-3-cyclohexyl-2-methoxy-*N*-(1-azabicyclo[2.2.2]-oct-3-yl)benzamide (21a). A solution of 5-chloro-3-cyclohexyl-2-methoxybenzoic acid (**20a**) (7.1 g, 26.4 mmol) in chloroform (111 mL) containing triethylamine (4.0 g, 39.5 mmol) was prepared. The mixture was cooled in an ice bath and ethyl chloroformate (3.0 g, 27.2 mmol) was added dropwise. This was stirred at ice/water bath temperature; then a solution of potassium carbonate (111 g, 803 mmol) in water (111 mL) containing 3-aminoquinuclidine dihydrochloride (26.2 g, 131.7 mmol) was added. After stirring overnight and allowing the mixture to warm to room temperature it was separated from the salts and the chloroform layer separated. The chloroform was washed several times with water and then dried with magnesium sulfate and concentrated to dryness. Treatment of the residue with several portions of hot *n*-hexane and decanting each time, followed by the evaporation of the combined *n*-hexane extracts to dryness, gave product **21a** as white crystals (4.1 g, 41% yield): mp 50 °C; ^{1}H NMR ($CDCl_3$) δ 1.2–3.2 (m, 22 H), 3.8 (s, 3 H), 4.1–4.4 (q, 2 H), 7.4 (d, 1 H), 7.9 (d, 1 H); MS m/z = 376. Anal. ($C_{21}H_{29}ClN_2O_2 \cdot {}^1/_2H_2O$) C, H, N.

2-(Methoxymethoxy)salicylaldehyde (23). To a solution of salicylaldehyde (30.5 g, 0.25 mol) in acetonitrile (200 mL) cooled to ~5 °C was added potassium *tert*-butoxide (28 g, 0.25 mol) in portions, and the temperature was kept below 15 °C. Precipitation occurred and acetonitrile (100 mL) was added to facilitate stirring. To this mixture, at 3 °C, was added 18-crown-6-ether (7.3 g, 27.5 mmol), followed by chloromethyl methyl ether (22.6 mL, 0.3 mol), dropwise over 10 min. The reaction mixture was stirred at room temperature for about 1 h and filtered, and the solid washed with acetonitrile (100 mL). The filtrate was concentrated to dryness to give an amber oil, which was dissolved in methylene chloride (200 mL), washed with water (2 × 200 mL), 5% aqueous sodium hydroxide (2 × 200 mL), water (2 × 200 mL), and saturated aqueous sodium chloride (2 × 200 mL), dried with sodium sulfate, filtered, and evaporated to dryness to give **23** as a brown oil (35.7 g, 86%). A sample (4.7 g) of this product was purified by repeatedly extracting the oil with hexanes (300 mL): ^{1}H NMR ($CDCl_3$) δ 10.51 (s, 1 H, COH), 7.84 (dd, 1 H, aryl), 7.52 (m, 1 H, aryl), 7.15 (m, 2 H, aryl), 5.30 (s, 2 H, OCH_2), 3.52 (s, 3 H, OCH_3). MS m/z = 167 (M + 1).

2-(Cyclohexylidenemethyl)phenyl Methoxymethyl Ether (24). To a stirred suspension of triphenylphosphine cyclohexyl bromide (76.7 mL, 0.18 mol) in tetrahydrofuran (750 mL) cooled to ~0 °C was added under nitrogen a 1.4 mol solution of methyllithium in ether (130 mL) over a period of 10 min. A solution of **23** (30 g, 0.18 mol) in tetrahydrofuran (50 mL) was added, over 15 min, between 7 and 9 °C. The ice bath was removed and the reaction allowed to warm to room temperature over 1.5 h. Water (100 mL) was added portionwise and the mixture extracted with ethyl acetate. The ethyl acetate was washed with water, dried with sodium sulfate, filtered, and evaporated to dryness to give a brown solid (71.0 g). Repeated extraction of the solid with hexanes and evaporation to dryness gave product **24** as an oil (29.5 g): ^{1}H NMR ($CDCl_3$) δ 6.8–7.4 (m, 4 H, aryl), 6.23 (s, 1 H, CH), 5.17 (s, 2 H, OCH_2), 3.47 (s, 3 H, OCH_3), 2.27 (m, 4 H, CH_2), 1.58 (m, 6 H, CH_2).

2-(Cyclohexylidenemethyl)-1-phenol (24a). A mixture of 2-(cyclohexylidenemethyl)phenyl methoxymethyl ether (**24**) (28 g, 0.113 mol), water (240 mL), and acetic acid (30 mL) was heated to reflux and the reaction monitored by TLC. After 24 h only a small amount of product had formed, so acetic acid (10 mL) was added and heating continued for 6 h, when more acetic acid (10 mL) was added and the reaction refluxed for a further 48 h. TLC showed practically no starting material. The reaction was extracted wtih ethyl acetate (250 mL), and the organic layer was washed with saturated aqueous sodium chloride (250 mL) and aqueous sodium bicarbonate (3 × 200 mL) and dried with sodium sulfate. Filtration and concentration to dryness gave the product as a brown oil (23.5 g). This material was used as is in the ring-closure step.

Spiro[benzofuran-2(3*H*),1′-cyclohexane] (25). A mixture of 2-(cyclohexylidenemethyl)phenol (**24a**) (20.0 g, 0.106 mol) and trifluoroacetic acid was heated to reflux for 2 h and then concentrated to dryness to give a dark oil. The oil was treated with methylene chloride (200 mL) and washed with water (2 × 100

mL), followed by saturated aqueous sodium bicarbonate (2 × 200 mL). The methylene chloride was dried with sodium sulfate, filtered, and evaporated to dryness to give an oil. This oil was purified by filtering a hexane solution of the oil through a silica plug to give the desired compound **25** as an oil (10.1 g): ^{1}H NMR ($CDCl_3$) δ 7.0–7.2 (m, 2 H, aryl), 6.6 (m, 2 H, aryl), 2.91 (s, 2 H, CH_2), 1.2–1.9 (m, 10 H, CH_2).

Spiro[benzofuran-2(3*H*),1′-cyclohexane]-7-carboxylic Acid (25a). To a solution of *n*-butyllithium (2.5 M in hexane, 26.3 mL), was added, under nitrogen, tetramethylethylenediamine (10 mL). The mixture was allowed to stir at room temperature for 30 min, when spiro[benzofuran-2(3*H*),1′-cyclohexane] (**25**) (9.5 g, 0.05 mol) in hexane (15 mL) was added dropwise. The mixture was allowed to stir overnight, carbon dioxide was bubbled through the reaction for about 1 h, and then the reaction was quenched with water (200 mL). The hexane layers were discarded, while the aqueous layer was acidified with aqueous hydrochloric acid to a pH of 2 to give a white solid which was filtered, washed with a little water, and air-dried (4.1 g).

This crude mixture was recrystallized from acetonitrile (13 mL) to give 2.1 g of the desired product **25a**: mp 138–42 °C; ^{1}H NMR ($CDCl_3$) δ 10.31 (br s, 1 H, OH), 7.80 (m, 1 H, aryl), 7.36 (m, 1 H, aryl), 6.92 (m, 1 H, aryl), 3.03 (s, 2 H, CH_2), 1.4–2.0 (m, 10 H, CH_2); MS m/z = 232. Anal. ($C_{14}H_{16}O_3$) H; C: calcd, 72.41; found 71.90.

5-Chlorospiro[benzofuran-2(3*H*),1′-cyclohexane]-7-carboxylic Acid (26). To a stirred solution of spiro[benzofuran-2(3*H*),1′-cyclohexane]-7-carboxylic acid (**25a**) (2.4 g, 0.01 mol) in dimethylformamide (7.5 mL) was added *N*-chlorosuccinimide (3.6 g, 0.026 mol) and the mixture stirred over 2 days. The reaction was quenched with water (200 mL) and extracted with ethyl acetate (2 × 150 mL). The ethyl acetate was washed with water (2 × 100 mL), dried with sodium sulfate, filtered, and concentrated to dryness to give an oil which solidified on standing. The solid (3.7 g) was recrystallized from acetonitrile (5.0 mL) to give 1.93 g of the desired compound **26**: mp 139–41 °C; ^{1}H NMR ($CDCl_3$) δ 10.53 (br s, 1 H, OH), 7.76 (d, 1 H, aryl), 7.29 (d, 1 H, aryl), 3.02 (s, 2 H, CH_2), 1.4–2.0 (m, 10 H, CH_2). MS m/z 267 (M + 1). Anal. ($C_{14}H_{15}ClO_3$) C, H.

***N*-(1-Azabicyclo[2.2.2]oct-3-yl)-5-chlorospiro[benzofuran-2(3*H*),1′-cyclohexane]-7-carboxamide (28).** 5-Chlorospiro[benzofuran-2(3*H*),1′-cyclohexane]-7-carboxylic acid (**26**) (0.5 g) is dissolved in chloroform (2.5 mL) and triethylamine (0.39 g). The solution is cooled in an ice bath, ethyl chloroformate (0.22 mL) is added over a period of 5 min and the solution is stirred at 0 °C for 1.5 h. Chloroform (2.5 mL) is added followed by a solution of 3-aminoquinuclidine hydrochloride (1.86 g) in 50% (w/w) aqueous potassium carbonate solution (6.0 mL) and water (3.0 mL) which had been cooled to 0 °C. This mixture is stirred at 0 °C for 30 min, then at room temperature for 18 h. The mixture is partitioned between ethyl acetate (50 mL) and water (50 mL). The ethyl acetate layer is washed with water and brine, dried over sodium sulfate, filtered, and evaporated to the crude product, which is crystallized from ethyl acetate to give 0.45 g of the desired compound **28**: mp 160–2 °C; MS m/z = 374.

***N*-(1-Azabicyclo[2.2.2]oct-3(*S*)-yl)-5-chlorospiro[benzofuran-2(3*H*),1′-cyclohexane]-7-carboxamide [(*S*)-28].** Spiro[benzofuran-2(3*H*),1′-cyclohexane]-5-chloro-7-carboxylic acid (**26**) (1.2 g, 0.0045 mol) in chloroform (5.0 mL) was heated to about 40 °C and thionyl chloride (0.45 mL) was added dropwise. The mixture was stirred at about 40 °C for 3 h and then concentrated to dryness to give an oil which was treated with toluene (4.0 mL). To this solution was added a solution of 3(*S*)-aminoquinuclidine (0.6 g, 0.005 mol) in toluene (4.0 mL) and the reaction mixture stirred at room temperature for 2 h. The reaction was quenched with a solution of 50% aqueous sodium hydroxide (0.4 g) in methanol (11.2 mL) to give a hazy solution. Water (40 mL) was added and the mixture extracted with toluene (2 × 20 mL). The toluene was dried with sodium sulfate, filtered, and concentrated to dryness to give a semisolid, which on trituration with ethyl acetate (5.0 mL) gave an off-white solid. The mixture was heated to reflux and filtered hot to remove a small amount of insolubles, and the filtrate cooled to room temperature. The precipitated solid was filtered, washed with ethyl acetate (2.0 mL), and dried in vacuo to give the desired compound (*S*)-**28** (250 mg): mp 143–6 °C. ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1 H, NH), 7.86 (d, 1 H, aryl), 7.19 (d, 1 H, aryl), 4.17 (br m, 1 H), 3.44 (dd, 1 H), 3.00 (s, 2 H, CH_2), 2.7–3.0 (m, 4 H), 2.5–2.6 (dd, 1 H), 1.3–2.1 (m, 14 H); MS m/z = 374. Anal. ($C_{21}H_{27}ClN_2O_2$) H, N; C: calcd, 67.27; found, 66.21.

***N*-(1-Azabicyclo[2.2.2]oct-3(*R*)-yl)-5-chlorospiro[benzofuran-2(3*H*),1′-cyclohexane]-7-carboxamide [(*R*)-28].** The same procedure was utilized as that for the preparation of (*S*)-**28** starting with (1.19 g, 0.0045 mol) of spiro acid **26** and 0.8 g (0.006 mol) of 3(*R*)-aminoquinuclidine to give 0.25 g of the title compound (*R*)-**28** as an off-white solid: mp 149–55 °C; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1 H, NH), 7.85 (d, 1 H, aryl), 7.18 (d, 1 H, aryl), 4.16 (br s, 1 H), 3.44 (dd, 1 H), 3.00 (s, 2 H, CH_2), 2.7–3.0 (m, 4 H), 2.5–2.6 (dd, 1 H), 1.3–2.1 (m, 14 H); MS m/z = 374. Anal. ($C_{21}H_{27}ClN_2O_2$) H, N; C: calcd, 67.27; found, 66.16.

Bioassays. 5-HT$_3$ Receptor Binding Assay. Binding to a rat cortex [^{3}H]GR-65630-labeled 5HT$_3$ site was performed according to the methods of Kilpatrick et al.[3] with modifications. Whole frozen rat brains (Pel-Freeze Biologicals, Rogers, AR) were thawed and the entorhinal portion of the cortex dissected on an ice-cold surface. Tissues were homogenized (Polytron, setting 7, for 15 s) and centrifuged (Sorvall, SS-34) at 40000*g* for 10 min in a Hepes-cation assay buffer consisting of 25 mM HEPES, 180 nM NaCl, 5 mM $CaCl_2$, and 1.2 mL of mM $MgCl_2$, pH 7.4. The crude membranes pellet was resuspended in assay buffer and a quantity of membranes proportional to 9 mg wet weight of tissue added to assay tubes. Assay tubes contained, in a total volume of 1 mL, 0.2 nM [^{3}H]GR-65630 (Du Pont NEN Research Products, Boston, MA) assay buffer and competitors or 100 nM ICS 205-930 (in nonspecific binding tubes). Tubes were incubated for 30 min at 23 °C, and the contents aspirated and washed three times with 50 nM Tris buffer, pH 7.7, using a Brandel cell harvester. Filters were placed in scintillating vials, equilibrated, and filter-retained radioactivity quantitated by liquid scintillation spectroscopy. Drug competition binding assays at four to six concentrations were performed with triplicate replication. K_d and IC_{50} value estimates were calculated from saturation and competition curves using the Ligand program (Biosoft, Elsevier). Resulting IC_{50} values were converted to K_i values using the Cheng–Prusoff correction: $K_i = IC_{50}/(1 + S/K_d)$.

Cisplatin-Induced Emesis Assay. Nonfasted Fitch castrated males (1–2 kg; Marshall Farms, North Rose, NY) were used. The animals were anesthetized with sodium pentobarbital (30 mg/kg ip) and an indwelling jugular vein catheter was implanted at least 48 h before subsequent use in emesis studies. One emetic study was conducted per ferret. Three to 12 ferrets were used per dose of drug and each dose was tested on at least two separate occasions. Vehicle-treated animals were run in tandem with drug-treated ferrets in these experiments. Test drugs were dissolved in 0.9% saline and given in a dose volume of 2 mL/kg (iv studies) or dissolved/suspended in 0.5% methylcellulose and given in a no. 5 gelatin capsule (po studies). These agents were given (iv studies) 30 min before and 45 min after cisplatin (3 mg/kg iv). For po studies, compounds were given 60 min before cisplatin. In the duration of action studies, (*S*)-**28** was administrated at various time points (1–6 h) before cisplatin. Ferrets were observed for 4 h post-cisplatin and the emetic latency, as well as the number of emetic episodes, were recorded. The percentage of inhibition of cisplatin-induced emesis (no. of episodes) was calculated as follows:

$$\frac{\text{emetic episodes (vehicle)} - \text{emetic episodes (drug)}}{\text{emetic episodes (vehicle)}} \times 100$$

Likewise, the percentage of increase in the emetic latency period was calculated by

$$\frac{\text{emetic latency (drug)} - \text{emetic latency (vehicle)}}{\text{emetic latency (vehicle)}} \times 100$$

The ED_{100} value reported for the test drugs is that dose which increased the mean emetic latency period by 100%.

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Registry No. 1 (n = 1), 3041-17-6; 1 (n = 2), 73345-01-4; 2 (n = 1), 103386-91-0; 2 (n = 2), 112998-54-6; 3 (n = 1), 138572-42-6; 3 (n = 2), 138572-63-1; 4 (n = 1), 6169-78-4; 4 (n = 2), 51060-43-6; 5 (n = 1), 31457-17-7; 5 (n = 2), 138572-64-2; **6b**, 124794-82-7; **6c**, 138572-65-3; **6d**, 138572-66-4; **7**, 138572-43-7; **8**, 138572-44-8; **9**, 138572-45-9; **10**, 138572-46-0; **11**, 124911-57-5; **12**, 138572-47-1; **13**, 124773-73-5; **13a**, 124773-72-4; **13b**, 124773-75-7; **14**, 138572-48-2; **15**, 4068-78-4; **15** (acid), 321-14-2; **16**, 138572-49-3; **17**, 138572-50-6; **18**, 138572-51-7; **19a**, 138572-52-8; **19b**, 138572-67-5; **19c**, 138572-68-6; **19d**, 138605-33-1; **20a**, 138572-53-9; **20b**, 138605-34-2; **20c**, 138572-69-7; **20d**, 138572-70-0; **21a**, 138572-54-0; **21b**, 138572-71-1; **21c**, 138572-72-2; **21d**, 138572-73-3; **22**, 138663-20-4; **23**, 5533-04-0; **24**, 138572-55-1; **24a**, 138572-74-4; **25**, 182-50-3; **25a**, 138572-75-5; **26**, 138572-56-2; (±)-**27**, 76883-48-2; (*S*)-**27**, 120570-05-0; (*R*)-**27**, 123536-15-2; (±)-**28**, 138572-57-3; (*S*)-**28**, 138663-21-5; (*R*)-**28**, 138663-22-6; **29**, 138572-58-4; **30**, 138572-59-5; **31**, 138572-60-8; **32**, 138572-61-9; **33**, 138572-62-0; CH_3OCH_2Cl, 107-30-2; NO_2BF_4, 13826-86-3; α-tetralone, 529-34-0; benzosuberone, 826-73-3; triphenylphosphine cyclohexyl bromide, 7333-51-9; 3-bromocyclohexene, 1521-51-3; 3-bromo-2-butanone, 814-75-5; 3-chloro-1-butene, 563-52-0; salicylaldehyde, 90-02-8; 2-methoxy-5-chlorobenzoic acid, 3438-16-2.

Development of High-Affinity 5-HT_3 Receptor Antagonists. 2. Two Novel Tricyclic Benzamides

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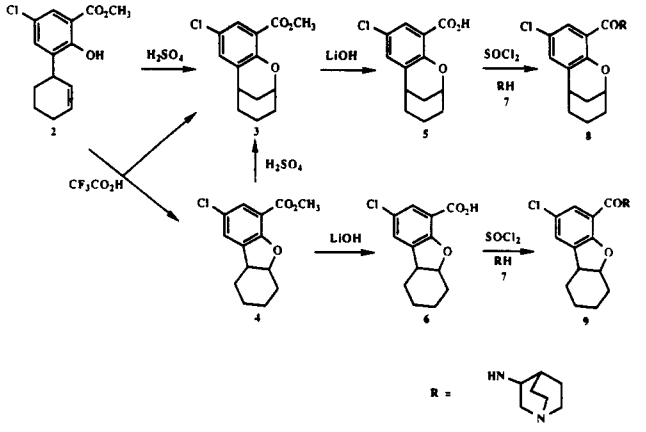
Two new classes of potent 5-HT_3 agents have been developed and examined as inhibitors of cytotoxic drug induced emesis in the ferret and dog. The absolute configuration of the most active molecules **10** and **18** have been determined by X-ray crystallography. These two compounds are more potent than known 5-HT_3 receptor antagonists both in vivo and in vitro in blocking 5-HT_3 receptor activation and preventing chemotherapeutic induced emesis. Compared with 5-HT_3 antagonists, such as GR 38032F, zacopride, BRL 43694, and ICS 205-930, compound **10** was more potent in (1) inhibiting binding to 5-HT_3 receptor binding sites in rat cortex (K_i = 0.17 nM), (2) blocking the von Bezold–Jarisch effect in the rat (lowest effective dose, 1 μg/kg iv), and (3) inhibiting 5-HT-induced contraction of guinea pig ileum (lowest effective concentration, 10^{-9} M). This novel agent was as effective given po as when given iv in reducing cisplatin-induced emetic episodes in the ferret (ED_{50} = 4 μg/kg iv or po). A 1 mg/kg po dose of **10** virtually abolished cisplatin-induced emesis for 10 h in the ferret. However, it was inactive against apomorphine or copper sulfate-induced vomiting. These data, coupled with receptor binding studies of ligands for D_2-dopamine, a_1, a_2, 5-HT_1, 5-HT_2, and muscarinic receptors demonstrate that **10** is a highly selective 5-HT_3 receptor antagonist with remarkable potency in vivo.

Introduction

An unfortunate side effect of chemotherapeutic treatment of cancer is nausea and vomiting which has stimulated efforts to discover an effective and safe antiemetic agent to block this side effect of neoplastic agents. 5-HT_3 antagonists have demonstrated potent antagonism of chemotherapy- or radiation-induced emesis in man.[1] Metoclopramide, which was originally thought to block emesis via antagonism of dopamine D_2 receptors, is the drug most often used to inhibit the emesis produced by such agents. It has been found to be a relatively weak 5-HT_3 antagonist,[2] requiring high dosage, and it suffers from the fact that it exerts D_2-dopamine receptor blocking side effects.[3] Recently several compounds exhibiting high affinity for 5-HT_3 receptor have been identified as potent antiemetic agents. Members of this class of compounds, which include ICS 205-930,[4] MLD 72222,[5] BRL 43674,[6] GR 38032F,[7] and aromatic thiazoles[8] have been shown effective clinically in the treatment of chemotherapy-induced emesis.[9] 5-HT_3 receptor binding sites have been indicated in the ferret area postrema and the nucleus tractus solitarius.[9] Injection of GR 38032F directly into this region of the ferret brain has completely prevented cisplatin-induced emesis.[10,11]

Previously,[12] we have described the initial structure–activity relationships of a series of bicyclic and tricyclic benzamides as 5-HT_3 receptor antagonists leading to a tricyclic benzamide (**1**) as the most potent 5-HT_3 receptor antagonist. In this paper we describe the synthesis and properties of two new classes of tricyclic benzamides that

Scheme I



are potent antagonists of chemotherapy-induced emesis in animals and exhibit high affinity for 5-HT_3 receptor

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