# 2-(Quinuclidin-3-yl)pyrido[4,3-*b*]indol-1-ones and Isoquinolin-1-ones. Potent Conformationally Restricted 5-HT$_3$ Receptor Antagonists†

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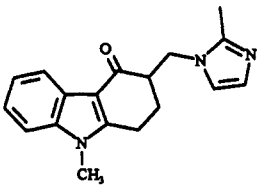
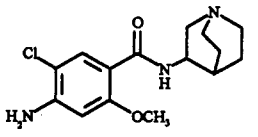
Several series of *N*-(quinuclidin-3-yl)aryl and heteroaryl-fused pyridones were synthesized and evaluated for 5-HT$_3$ receptor affinity. In the heteroaryl series, 2-(quinuclidin-3-yl)tetrahydropyrido-[4,3-*b*]indol-1-one (**8a**) and the 4,5-alkano-bridged analogues (**14** and **15**) displayed high 5-HT$_3$ receptor affinity with p$K_i$ values >9. The (3*S*)-quinuclidinyl isomers had >10 fold higher affinity than the (3*R*)-isomers. In a series of 2-quinuclidin-3-yl)isoquinolin-1-ones, derivatives substituted with small lipophilic groups (**25b–e**) and with 4,5-alkano-bridges (**34–36**) also displayed high affinity. In particular, the hexahydro-1*H*-benz[*de*]isoquinolinone (*S*,*S*)-**37** was the highest affinity 5-HT$_3$ receptor ligand prepared (p$K_i$ 10.4). A number of the high affinity ligands were shown to be potent 5-HT$_3$ receptor antagonists in vivo as determined by inhibition of the B-J reflex in the anesthetized rat. Again, (*S*,*S*)-**37** was the most active agent tested ($ID_{50}$ 0.02 μg/kg iv), and this compound was also potent in blocking cisplatin-induced emesis in both the ferret and the dog. Computer modeling studies were performed, and previously reported 5-HT$_3$ receptor antagonist pharmacophore models were refined to include a key lipophilic binding domain.

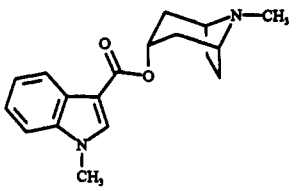
A number of 5-HT$_3$ receptor antagonists have been reported, and several are now in clinical use for the treatment of cancer chemotherapy-induced emesis.[1a,b] Investigation into the application of these compounds for the treatment of various CNS disorders is also being pursued.[1c] The chemical structures of these antagonists have been categorized as belonging to three general classes:[2a] (1) substituted imidazoles as typified by GR 38032F (ondansetron, **1**);[1a,3,4] (2) benzamides, e.g., zacopride (**2**);[5,6] and (3) esters, amides, and bioisosteric replacements of indole and related heterocycles, e.g., ICS 205-930 (tropisetron, **3**)[7] and BRL 43694 (granisetron, **4**).[8,9] In reviewing the structures of the first two classes, it is apparent that a certain degree of conformational restraint is present in both; imposed by the rigid carbazolone ring system of **1** and by the strong intramolecular hydrogen bonding which locks the amide into a "virtual ring" in **2**. This "virtual ring" has been converted into an actual ring in a series of benzotriazinones[2a] and naphthalimides.[2b,c] These conformational restraints define the spacial relationships between the aromatic rings, the carbonyl groups, and the basic-nitrogen-containing side chains of these antagonists, and consideration of these relationships, and others, has led to the development of pharmacophore models for 5-HT$_3$ receptor antagonists.[10,11] In this paper we report the synthesis and pharmacological evaluation of conformationally restricted analogues of the third structural class (related to **3** and **4**) which are potent 5-HT$_3$ receptor antagonists and serve to corroborate the established pharmacophore models.



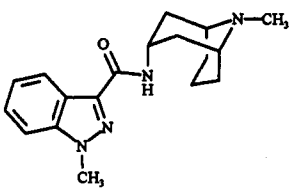
1 (Ondansetron)



2 (Zacopride)



3 (Tropisetron)



4 (Granisetron)

## Chemistry

The general route for the synthesis of the compounds in Tables II and III is exemplified by the preparation of the pyrido[4,3-*b*]indolones **8a,b** described in Scheme I.[12] Treatment of the *N*-quinuclidin-3-yl amides **6a,b** with 2 equiv of *n*-BuLi produced the dilithio derivatives which were quenched with *N*,*N*-dimethylformamide to provide the amidals **7a,b**. Without isolation, these labile intermediates were dehydrated by treatment with aqueous HCl to furnish **8a,b**. Catalytic hydrogenation of **8a** (X = H) afforded the dihydro derivative **9**. The *endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl and the 1-azabicyclo[3.3.1]-non-4-yl congeners **10** and **11**, respectively, were similarly prepared.

The 4,5-alkano-bridged pyrido[4,3-*b*]indolones **14** and **15**, pyrrolo[3,2-*c*]pyridinone **17**, tetrahydropyrrolo[3,2,1-*ij*][1,6]naphthyridinone **19**, and the benzofurano- and

† We dedicate this paper to Dr. John Edwards upon the occasion of his retirement as Director of the Institute of Organic Chemistry, Syntex Research.

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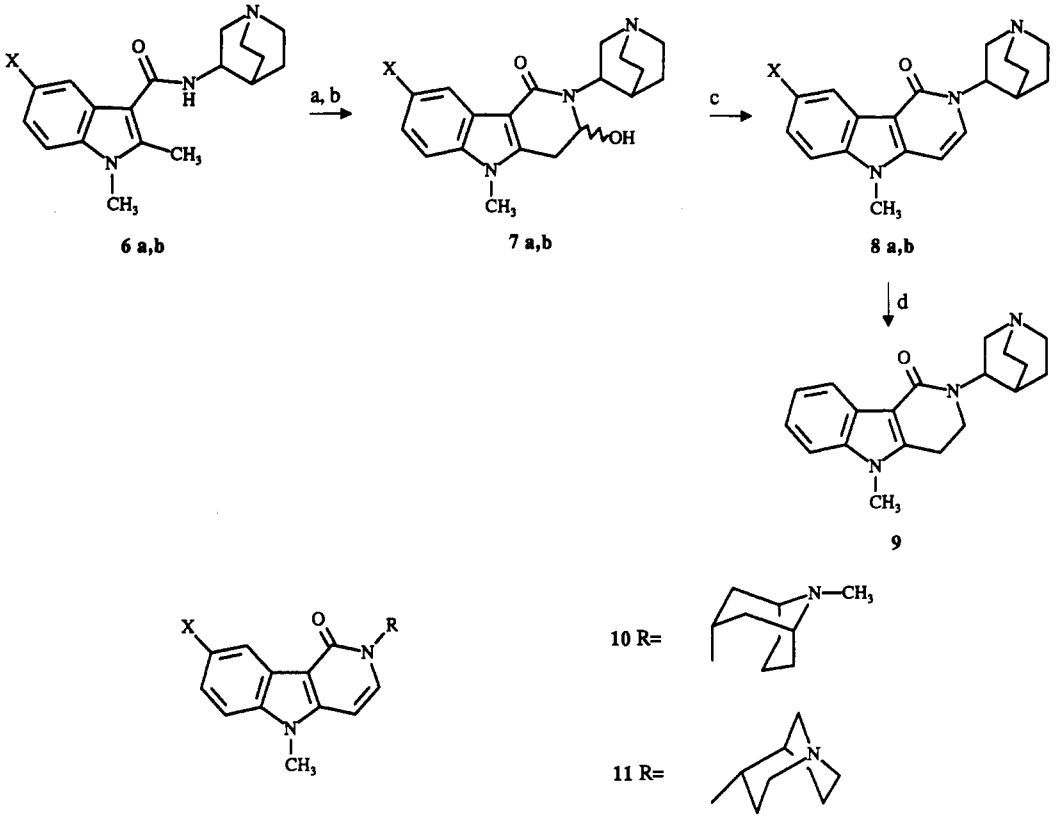
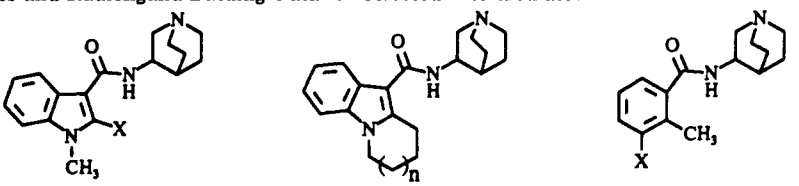
**Scheme I**[a]




[a] (a) *n*-BuLi (2 equiv); (b) DMF; (c) HCl; (d) $H_2$, Pd/C.

**Table I.** Physical Properties and Radioligand Binding Data for Selected Intermediates



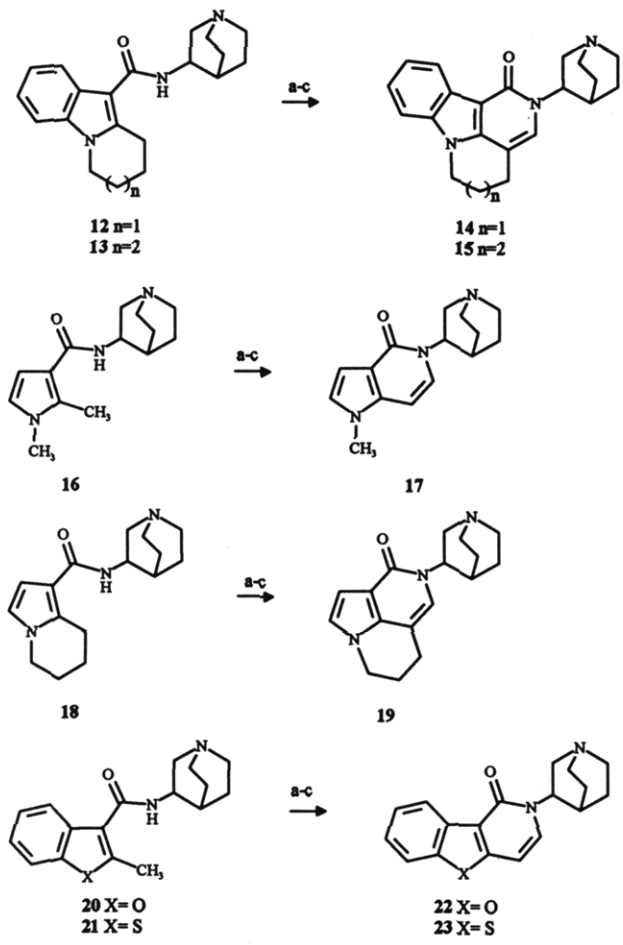

| compd | X | *n* | recryst solvent | mp, °C | formula[a] | radioligand binding:[b] 5-$HT_3$, p$K_i$ ± SEM |
|---|---|---|---|---|---|---|
| **5** | H | | EtOH–$Et_2O$ | >300 | $C_{17}H_{21}N_3O$·HCl | 8.7 ± 0.2 |
| (*S*)-**5** | H | | EtOH–acetone | 247–249 | $C_{17}H_{21}N_3O$·HCl·0.25$H_2O$ | 9.4 ± 0.1 |
| **6a** | $CH_3$ | | EtOH–$Et_2O$ | >250 | $C_{18}H_{23}N_3O$·HCl·1.5$H_2O$ | 7.4 |
| (*S*)-**12** | | 1 | EtOH–$Et_2O$ | 273–274 | $C_{20}H_{25}N_3O$·HCl·0.75$H_2O$[c] | 8.6 ± 0.1 |
| (*R*)-**12** | | 1 | EtOH–$Et_2O$ | 253–255 | $C_{20}H_{25}N_3O$·HCl·0.25$H_2O$ | 7.9 |
| (*S*)-**13** | | 2 | EtOH–$Et_2O$ | 175–176 | $C_{21}H_{27}N_3O$ | 8.3 ± 0.1 |
| **24a** | H | | EtOH–$Et_2O$ | 230–231 | $C_{15}H_{20}N_2O$·HCl·0.25$H_2O$ | 6.2 ± 0.2 |
| (*S*)-**24b** | $CH_3$ | | EtOH–$Et_2O$ | 263–265 | $C_{16}H_{22}N_2O$·HCl·0.5$H_2O$[d] | 6.8 ■ 0.1 |
| (*S*)-**24c** | $CH_2CH_3$ | | EtOH–$Et_2O$ | 260–261 | $C_{17}H_{24}N_2O$·HCl | 6.3 ± 0.1 |
| (*S*)-**24d** | $OCH_3$ | | EtOH–$Et_2O$ | 259–261 | $C_{16}H_{22}N_2O_2$·HCl·0.75$H_2O$[e] | 6.4 ± 0.1 |
| (*S*)-**32a** | (Scheme IV) | | EtOH–$Et_2O$ | 268–269 | $C_{18}H_{24}N_2O$·HCl | 6.7 ± 0.1 |

[a] Elemental analyses for C, H, and N were within 0.4% of the theoretical values unless otherwise noted. [b] Determined in rat brain cortical membranes using [$^3$H]quipazine. Values are means of at least three separate determinations ± SEM. Values without SEM are means of two determinations. [c] C: Calcd, 74.27; found, 73.34. [d] N: Calcd, 9.22; found, 8.58. [e] N: Calcd 8.64; found, 9.21.

benzothieno[3,2-c]pyridinones **22** and **23** were prepared as depicted in Scheme II. 2-(Quinuclidin-3-yl)- and 2-(*endo*-tropanyl)isoquinolin-1(2*H*)-ones **25a–e**, **30a–c**, and **27**, respectively, were synthesized from the requisite 2-alkylbenzamides (Scheme III). Catalytic hydrogenation of **25a–d** and **27** furnished the dihydroisoquinolin-1(2*H*)-ones and **26a–d** and **28**, respectively.

The 4,5-alkano-bridged isoquinolin-1(2*H*)-ones **34–36** and **39** were prepared in analogous fashion (Scheme IV). Catalytic hydrogenation of the hydrochloride salt of (*S*)-**35a** (X = Y = H, *n* = 1) afforded a mixture of diastereomers (*S,S*)-**37** and (*R,S*)-**38** in a ratio of ca. 57:43. The major diastereomer, (*S,S*)-**37**, was obtained in pure form (~99% by HPLC) by crystallization of the hydrochloride salt. The minor isomer (*R,S*)-**38** was obtained by crystallization of the mother liquors. Commencing with (*R*)-**35a** and performing the same sequence of operations, the isomers (*S,R*)-**38** and (*R,R*)-**37** were obtained. The absolute stereochemistry of (*S,S*)-**37** was determined by single-crystal X-ray crystallography of the HCl salt (Figure 1). Since the absolute configuration of the enantiomers of 3-aminoquinuclidine[13] has been previously established,[6g] this X-ray determination served to rigorously define the absolute stereochemistry of the four isomers of **37** and **38**.

**Scheme II**[a]




[a] (a) *n*-BuLi (2 equiv); (b) DMF; (C) HCl.

Since (*S,S*)-**37** was the most active isomer (Table III), it was of interest to determine if the hydrogenation conditions could be modified to further enhance production of that diastereomer. After evaluating a variety of solvent/catalyst combinations, it was eventually found that hydrogenation of the free base of (*S*)-**35a** in tetrahydrofuran or ethyl acetate with 10% Pd–C improved the diastereomeric ratio of (*S,S*)-**37**/(*R,S*)-**38** to 75:25. This ratio was reversed when the reduction was carried out on the 10-camphorsulfonic acid (10-CSA) salt of (*S*)-**35a**.

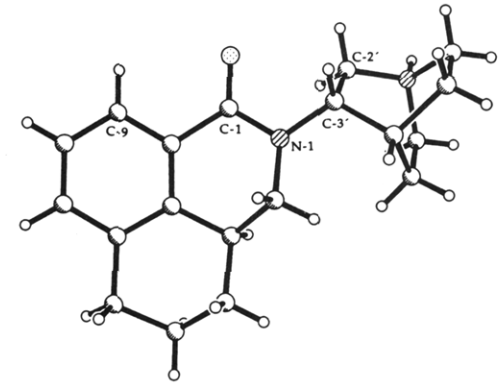



**Figure 1.** X-ray structures of (*S,S*)-**37**·HCl.

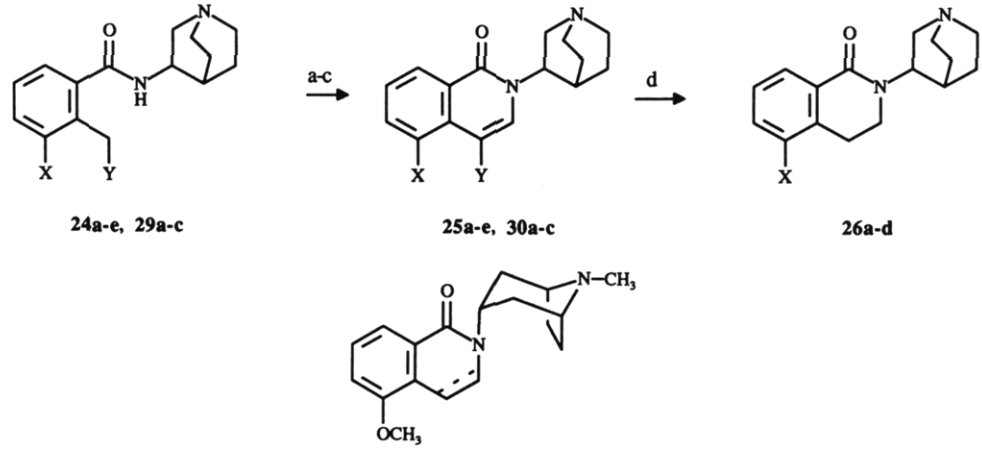
Interestingly, the same 25:75 ratio of (*S,S*)-**37**/(*R,S*)-**38** was obtained regardless of which enantiomer of 10-CSA was used, implying that the diastereoselectivity of the hydrogenation was influenced more by steric factors than by enantioselective interaction in the acid–base association.

The amide starting materials in Schemes I–IV were generally obtained from known acids or esters, using standard methodology (Experimental Section). The preparation of amide **24c** is outlined in Scheme V.

## Results and Discussion

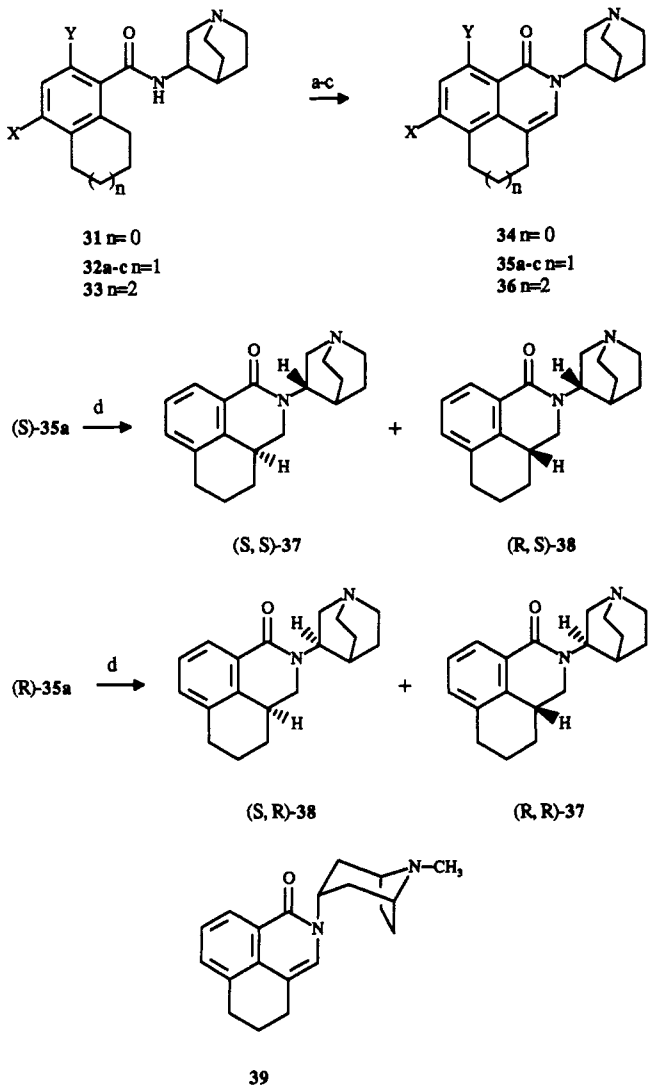
The 5-HT$_3$ receptor affinity of test compounds was determined in rat cerebrocortical membranes by measurement of displacement of the radioligand [$^3$H]quipazine[14] (Tables I–III). As a starting point, the racemic 3-quinuclidinyl amide of 1-methylindole-3-carboxylic acid (**5**) was prepared and found to have high affinity (p$K_i$ 8.7) for the 5-HT$_3$ receptor (Table I). The (*S*)-enantiomer had higher affinity than the racemate, a result which is in accord with subsequently published data on other amides of 3-aminoquinuclidine.[6f,g,15] The 2-methyl analogue **6a** had a lower affinity relative to the parent **5**. The same trend was previously noted for the indazole carboxamides **42** and **43** in that the 2-methyl derivative **43** was much less active as a 5-HT$_3$ antagonist.[9b] The X-ray structures of these compounds showed that, whereas the tropanyl amide side chain adopts an extended conformation (as depicted) in **42**, the 2-methyl group of **43** forces the side chain into a folded conformation in which the indazole-carbonyl bond

**Scheme III**[a]



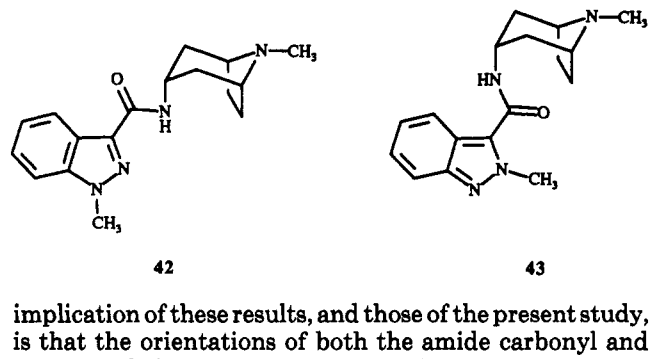

[a] (a) *n*-BuLi (2 equiv); (b) DMF; (c) HCl; (d) H$_2$, Pd/C.

**Scheme IV**[a]




[a] (a) *n*-BuLi (2 equiv); (b) DMF; (c) HCl; (d) $H_2$, Pd/C.

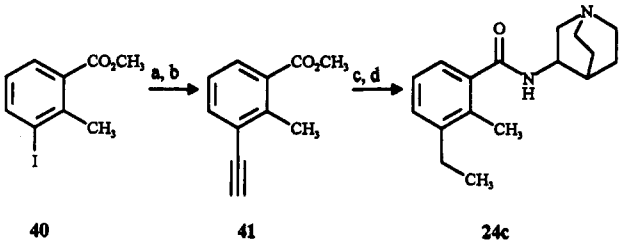
is twisted ca. 120° relative to the orientation in **43**. The




implication of these results, and those of the present study, is that the orientations of both the amide carbonyl and the appended tertiary amine group relative to the aromatic nucleus are critical determinants of 5-$HT_3$ receptor affinity. This was more conclusively demonstrated by cyclization of **6a** to the pyrido[4,3-*b*]indolone **8a** which resulted in a 100-fold increase in affinity (Table II).

Evaluation of the enantiomers of **8a** showed that, as previously noted, the (*S*)-isomer had higher 5-$HT_3$ receptor affinity than the (*R*)-isomer. The racemic dihydro derivative **9** had the same affinity as the parent **8a**. However, the 8-methoxy analogue (*S*)-**8b** had a much lower affinity ($pK_i$ 6.5). A similar loss of 5-$HT_3$ receptor affinity was observed upon substitution at the 5-position of indole esters and indazole amides[8] and at the 6-position of

**Scheme V**[a]




[a] (a) TMS-acetylene, $(Ph_3P)_2PdCl_2$; (b) $K_2CO_3$, $CH_3OH$; (c) $H_2$, Pd/C; (d) 3-aminoquinuclidine, $Me_3Al$, toluene.

tetrahydrocarbazolones[1b] (which correspond to the 8-position of **8a**) and indicates a region of steric inaccessibility at the receptor. Two other azabicyclo systems were evaluated (**10** and **11**), and as a significant reduction in affinity was observed, quinuclidine was subsequently adopted as the amine substituent of choice.

Addition of 3- or 4-methylene bridges from the 4-position to the indole nitrogen of **8a** afforded tetracycles **14** and **15**, both of which retained high affinity. In both instances, a ca. 1.2 log order increase in affinity was noted relative to the "ring-opened" progenitors **12** and **13** (Table I) which, as was noted above for **6a**, reflects the steric effect of the alkyl substituent on the orientation of the amide side chain. Removal of the benzene ring from **8a** and **14** resulted in greater than 10-fold reduction in affinity (**17** and **19**). The benzofurano and benzothieno analogues **22** and **23**, respectively, had slightly less affinity than **8a**.

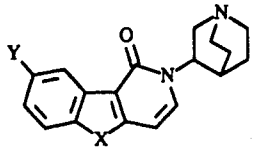
On the basis of the high 5-$HT_3$ receptor affinity of the pyrido[4,3-*b*]indolone series, it was of interest to evaluate the corresponding isoquinolones (Table III). Whereas the parent (*S*)-2-(quinuclidin-3-yl)isoquinolinone [(*S*)-**25a**] displayed moderate affinity ($pK_i$ 8.4), substitution at the 5-position with small lipophilic groups led to enhanced activity. Thus, the 5-methyl [(*S*)-**25b**], 5-ethyl [(*S*)-**25c**], and 5-methoxy [(*S*)-**25d**] analogues had $pK_i$ values between 9.2 and 9.8. The significantly lower affinity of the 2-methylbenzamide precursors **24a–d** was in accord with the results obtained on **6a**, **12**, and **13**. As in the pyrido[4,3-*b*]indolone series, saturation of the 3,4-double bond had essentially no effect on the high affinity of these compounds. In the one example in which a different amine was evaluated, the *endo*-tropanyl derivative **27** had less than one-tenth the affinity of the corresponding (*S*)-*N*-quinuclidin-3-yl analogue ((*S*)-**25d**).

Alkano-bridged isoquinolones **34–36** had $pK_i$ values of >9 with the 3-methylene congener (*S*)-**35a** marginally displaying the highest affinity ($pK_i$ 9.8). Methoxy groups on the benzene ring of this compound were detrimental [(*S*)-**35b,c**]. The low affinity of (*S*)-**35c** is significant since the methoxy group of this compound is in the same position previously claimed to enhance binding through a bidentate interaction with the receptor.[4c,6g]

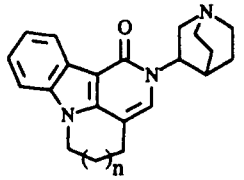
Of the two diastereomers produced by saturation of the double bond of (*S*)-**35a**, isomer (*S,S*)-**37** had approximately 10-fold higher affinity than the (*R,S*)-**37** isomer. As was the consistent trend, both of these isomers, which contain the (*S*)-3-aminoquinuclidine moiety, had higher affinity than their enantiomers [(*R,R*)-**37** and (*S,R*)-**38**] which have the (*R*)-configuration of the quinuclidine. Of the compounds in either the pyridoindolone or isoquinolone series, (*S,S*)-**37**, with a $pK_i$ of 10.4, was the highest affinity 5-$HT_3$ receptor ligand.

In vivo 5-$HT_3$ receptor antagonist activity was determined for a number of the high-affinity ligands by

**Table II.** Physical Properties and Radioligand Binding Data for Pyrido[4,3-*b*]indolones and Related Compounds



**8a-c, 22,23**



**14,15**

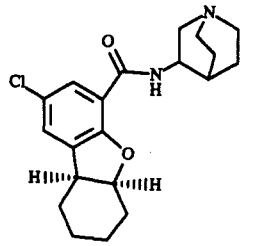
| compd | X | Y | *n* | recryst solvent | mp, °C | formula[a] | radioligand binding:[b] 5-HT$_3$, p$K_i$ ± SEM |
|---|---|---|---|---|---|---|---|
| **8a** | N-$CH_3$ | H | | EtOH-$Et_2O$ | >270 | $C_{19}H_{21}N_3O$·HCl | 9.4 |
| (*S*)-**8a** | N-$CH_3$ | H | | EtOH-$Et_2O$ | 254–255 | $C_{19}H_{21}N_3O$·HCl·0.75$H_2O$ | 10.0 ± 0.1 |
| (*R*)-**8a** | N-$CH_3$ | H | | EtOH-$Et_2O$ | 252–253 | $C_{19}H_{21}N_3O$·HCl·0.25$H_2O$ | 8.8 ± 0.1 |
| (*S*)-**8b** | N-$CH_3$ | $OCH_3$ | | 2-PrOH | 267–268 | $C_{20}H_{23}N_3O_2$·HCl·0.25$H_2O$ | 6.5 |
| **9** | (Scheme I) | | | EtOH-$Et_2O$ | >260 | $C_{19}H_{23}N_3O$·HCl | 9.4 |
| **10** | (Scheme I) | | | EtOH | 331–333 | $C_{21}H_{25}N_3O$·HCl·0.5$H_2O$ | 7.4 |
| **11** | (Scheme I) | | | EtOH-$Et_2O$ | 360 | $C_{20}H_{23}N_3O$·HCl | 8.5 |
| (*S*)-**14** | | | 1 | EtOH | 256–259 | $C_{21}H_{23}N_3O$·HCl·$H_2O$ | 9.8 ± 0.1 |
| (*R*)-**14** | | | 1 | EtOH-$Et_2O$ | 260–261 | $C_{21}H_{23}N_3O$·HCl·).5$H_2O$ | 8.4 ● 0.1 |
| (*S*)-**15** | | | 2 | EtOH-$Et_2O$ | >280 | $C_{22}H_{25}N_3O$·HCl | 9.5 ● 0.1 |
| **17** | (Scheme II) | | | EtOH-$Et_2O$ | 178–180 | $C_{15}H_{19}N_3O$·HCl·0.75$H_2O$ | 7.8 |
| (*S*)-**19** | (Scheme II) | | | EtOH-$Et_2O$ | 178–180 | $C_{17}H_{21}N_3O$·HCl | 8.5 |
| **22** | O | H | | EtOH-$Et_2O$ | >270 | $C_{18}H_{18}N_2O_2$·HCl·0.25$H_2O$ | 8.6 |
| **23** | S | H | | EtOH-$Et_2O$ | >265 | $C_{18}H_{18}N_2OS$·HCl·0.25$H_2O$ | 8.9 |

[a] Elemental analyses for C, H, and N were within 0.4% of the theoretical values unless otherwise noted. [b] Determined in rat brain cortical membranes using [$^3$H]quipazine. Values are means of at least three separate determinations ± SEM. Values without SEM are means of two determinations.

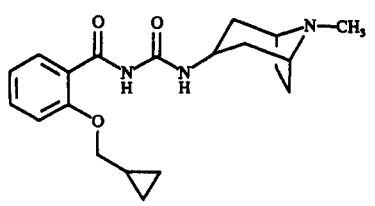
measuring their ability to antagonize 2-methyl-5-hydroxytryptamine induced bradycardia (von Bezold–Jarisch reflex, B–J reflex) in the anesthetized rat.[3,7] The results obtained upon intravenous administration are presented in Table IV. There was no evidence for 5-HT$_3$ receptor agonist activity for any of the compounds tested. This was important since several quinuclidine-containing amides and ureas have been reported to demonstrate receptor agonist activity.[6f,16] In the case of zacopride, this property has been linked to emetic activity.[16,17] The data in Table IV is generally consistent with the 5-HT$_3$ receptor affinities determined in the ligand binding assay and confirms the high potency of many of these compounds. In particular, (*S*,*S*)-**37**, the highest affinity 5-HT$_3$ receptor ligand of this study, was also the most potent compound at inhibiting the B–J reflex ($ID_{50}$ 0.02 μg/kg iv). This compound was also highly effective in the inhibition of cisplatin-induced emesis in both the ferret and dog by either iv or po administration (Table V).

With the above results in mind, we sought further definition of the 5-HT$_3$ receptor pharmacophore and binding site using computer modeling techniques. A number of pharmacophore models and alignments of antagonists binding to the 5-HT$_3$ receptor have recently been presented.[2,6f-h,9c,e,f,10,11,18,19] All of the previous models are in general agreement as to which pharmacophoric elements are important for significant binding affinity. The three-dimensional arrangement of these key elements and the methods used to determine them have differed somewhat in these models. The present work expands on what has been presented thus far and offers additional information regarding this receptor.

The modeling approach taken here centers around the highest affinity ligand presented in this study, (*S*,*S*)-**37** with a p$K_i$ of 10.4. An affinity of this magnitude could only be associated with a compound that binds at or near its global minimum. An X-ray structure of (*S*,*S*)-**37** reveals the conformation as seen in Figure 1 with the torsional angle defined by C-1, N-1, C-3′, C-2′ equal to −60.3°. Other known 5-HT$_3$ antagonists could not be "overlapped" with this conformation. However, this torsional bond has a 3-fold potential, and the other two conformations were also investigated. The conformation with a torsional angle of −133.8 after rotation and minimization with the TRIPOS force field was found to overlap with other known antagonists and will be discussed below. Both the X-ray and "overlap" conformations of (*S*,*S*)-**37** were subjected to the addition of hydrogens and minimization with both the TRIPOS force field[20] and the MM2(87) force field.[21,22] The TRIPOS force field gave an energy for the crystal structure conformation 1.58 kcal/mol lower than the "overlap" conformation, whereas using the MM2 force field, the "overlap" conformation was the more stable by 0.79 kcal/mol. Both sets of calculated minima were root mean square (RMS) fit using all heavy atoms, and the geometries of these two sets were almost identical with RMS values of 0.075 and 0.078, respectively. Since the geometries of these sets are almost identical, the force constants and torsional parameters are the root of the energy difference. The MM2 force field is the more sophisticated of the two and, therefore, the crystal structure may indeed not be the global minimum in the in vacuo environment. Needless to say, both are local minima and equally valid conformations that would be available in solution. In fact, a crystal structure of another 5-HT$_3$ antagonist (**44**)[6g] has the conformation of the quinuclidine ring system in a similar conformation to the "overlap" conformation of (*S*,*S*)-**37**.



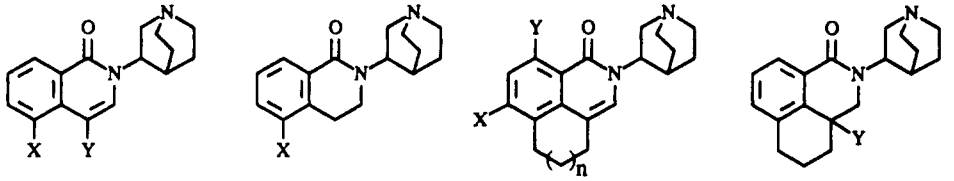
**44** (RG 12915)



**45**

Several other known 5-HT$_3$ antagonists were used to determine the alignment of the pharmacophore. For each

**Table III.** Physical Properties and Radioligand Binding Data for Isoquinolinones and Related Compounds



25a-e, 30a-c 26a-d 34-36 37-38

| compd | X | Y | n | recryst solvent | mp, °C | formula[a] | radioligand binding:[b] 5-HT$_3$, p$K_i$ ± SEM |
|---|---|---|---|---|---|---|---|
| **25a** | H | H | | MeOH–$Et_2O$ | 130–131 | $C_{16}H_{18}N_2O$·HCl·0.4$H_2O$ | 8.0 ± 0.1 |
| (*S*)-**25a** | H | H | | EtOH–$Et_2O$ | 239–240 | $C_{16}H_{18}N_2O$·HCl·0.4$H_2O$ | 8.4 ± 0.1 |
| (*S*)-**25b** | $CH_3$ | H | | EtOH–$Et_2O$ | 265–266 | $C_{17}H_{20}N_2O$·HCl·EtOH | 9.2 ± 0.1 |
| (*S*)-**25c** | $CH_2CH_3$ | H | | EtOH–$Et_2O$ | >290 | $C_{18}H_{22}N_2O$·HCl·0.5$H_2O$ | 9.7 ± 0.1 |
| (*S*)-**25d** | $OCH_3$ | H | | EtOH–$Et_2O$ | 275–277 | $C_{17}H_{20}N_2O_2$·HCl·$H_2O$ | 9.8 ± 0.2 |
| (*S*)-**25e** | Cl | H | | EtOH–$Et_2O$ | 287–288 | $C_{16}H_{17}ClN_2O$·HCl | 8.6 ± 0.1 |
| **26a** | H | H | | EtOH–$Et_2O$ | 230–232 | $C_{16}H_{20}N_2O$·HCl·0.25$H_2O$ | 8.0 |
| (*S*)-**26b** | $CH_3$ | H | | EtOH | >300 | $C_{17}H_{22}N_2O$·HCl | 9.5 ± 0.2 |
| (*S*)-**26c** | $CH_2CH_3$ | H | | EtOH | >290 | $C_{18}H_{24}N_2O$·HCl·0.25$H_2O$ | 9.7 ± 0.1 |
| (*S*)-**26d** | $OCH_3$ | H | | EtOH–$Et_2O$ | >290 | $C_{17}H_{22}N_2O_2$·HCl·0.5$H_2O$ | 9.7 ± 0.1 |
| **27** | (Scheme III) | | | EtOH–$Et_2O$ | 273–275 | $C_{18}H_{22}N_2O_2$·HCl·0.25$H_2O$ | 8.6 ± 0.1 |
| **28** | (Scheme III) | | | EtOH–$Et_2O$ | 265–267 | $C_{18}H_{24}N_2O_2$·HCl | 8.0 ± 0.1 |
| **30a** | $CH_3$ | $CH_3$ | | EtOH | >275 | $C_{18}H_{22}N_2O$·HCl·0.5$H_2O$ | 9.0 |
| (*S*)-**30b** | H | $CH_2CH_2CH_3$ | | acetone–$Et_2O$ | 155 | $C_{19}H_{24}N_2O$·HCl·$H_2O$ | 8.3 |
| (*S*)-**30c** | H | Ph | | MeOH–$Et_2O$ | 241–242 | $C_{22}H_{22}N_2O$·HCl·$H_2O$ | 8.6 |
| (*S*)-**34** | H | H | 0 | EtOH–$Et_2O$ | >285 | $C_{18}H_{20}N_2O$·HCl·0.5$H_2O$ | 9.2 ± 0.1 |
| (*R*)-**34** | H | H | 0 | EtOH–$Et_2O$ | >280 | $C_{18}H_{20}N_2O$·HCl | 7.6 ± 0.1 |
| (*S*)-**35a** | H | H | 1 | 2-PrOH–$Et_2O$ | >270 | $C_{19}H_{22}N_2O$·HCl | 9.8 ± 0.1 |
| (*R*)-**35a** | H | H | 1 | EtOH | >275 | $C_{19}H_{22}N_2O$·HCl | 8.1 ± 0.1 |
| (*S*)-**35b** | $OCH_3$ | H | 1 | EtOH | 296–297 | $C_{20}H_{24}N_2O_2$·HCl·0.25$H_2O$ | 7.9 ± 0.1 |
| (*S*)-**35c** | H | $OCH_3$ | 1 | EtOH–$Et_2O$ | 270–271 | $C_{20}H_{24}N_2O_2$·HCl·0.25$H_2O$ | 6.8 ± 0.1 |
| (*S*)-**36** | H | H | 2 | EtOH | >280 | $C_{20}H_{24}N_2O$·HCl·0.25$H_2O$ | 9.4 ± 0.2 |
| (*S,S*)-**37** | | α-H | | EtOH | >290 | $C_{19}H_{24}N_2O$·HCl | 10.4 ± 0.2 |
| (*R,R*)-**37** | | β-H | | EtOH | >280 | $C_{19}H_{24}N_2O$·HCl·0.25$H_2O$[c] | 8.4 ± 0.1 |
| (*R,S*)-**38** | | β-H | | EtOH–$Et_2O$ | 272–274 | $C_{19}H_{24}N_2O$·HCl·0.5$H_2O$ | 9.5 ± 0.1 |
| (*S,R*)-**38** | | α-H | | EtOH–$Et_2O$ | 275–276 | $C_{19}H_{24}N_2O$·HCl | 8.6 ± 0.1 |
| **39** | (Scheme IV) | | | EtOH–$Et_2O$ | 269–270 | $C_{20}H_{24}N_2O$·HCl | 9.1 ± 0.1 |
| ondansetron | | | | | | | 8.5 ± 0.2 |
| tropisetron | | | | | | | 8.7 ± 0.2 |
| granisetron | | | | | | | 9.1 ± 0.1 |
| (*S*)-zacopride | | | | | | | 9.6 ± 0.1 |
| (*R*)-zacopride | | | | | | | 8.5 ± 0.1 |

[a] Elemental analyses for C, H, and N were within 0.4% of the theoretical values unless otherwise noted. [b] Determined in rat brain cortical membranes using [$^3$H]quipazine. Values are means of at least three separate determintions ± SEM. Values without SEM are means of two determinations. [c] N: Calcd, 8.30; found, 7.70.

**Table IV.** Inhibition of B–J Reflex in Anesthetized Rats

| compd | antagonism of B–J reflex: $ID_{50}$, μg/kg iv (95% confidence limits) | no. of rats |
|---|---|---|
| (*S*)-**8a** | 0.13 (0.10–0.17) | 8 |
| (*S*)-**14** | 0.05 (0.03–0.07) | 9 |
| (*R*)-**14** | >2.41 | 5 |
| (*S*)-**25b** | 0.10 (0.10–0.14) | 8 |
| (*S*)-**25c** | 0.13 (0.09–0.19) | 8 |
| (*S*)-**25d** | 0.03 (0.02–0.05) | 8 |
| (*S*)-**26b** | 0.13 (0.07–0.24) | 8 |
| (*S*)-**26c** | 0.18 (0.13–0.25) | 8 |
| **30a** | 0.25 (0.18–0.35) | 8 |
| (*S*)-**34** | 0.18 (0.12–0.26) | 9 |
| (*S*)-**35a** | 0.10 (0.07–0.14) | 9 |
| (*R*)-**35a** | 2.00 (0.7–6.0) | 4 |
| (*S*)-**36** | 0.09 (0.05–0.16) | 8 |
| (*S,S*)-**37** | 0.02 (0.017–0.023) | 8 |
| **39** | 0.65 (0.47–0.88) | 8 |
| ondansetron | 2.6 (1.5–4.7) | 9 |
| tropisetron | 0.40 (0.24–0.77) | 8 |
| granisetron | 0.10 (0.01–0.19) | 11 |

of the molecules examined, the torsional angles were manually set for maximum overlap with (*S,S*)-**37**. After minimization, a lone pair atom was added to the basic nitrogen of each compound, and the bond length was adjusted to 2.8 Å. This length was chosen to reflect the 1.0 Å distance representing the length of the quaternary hydrogen atom that would presumably exist at physiological pH and an additional 1.8 Å representing the distance of the hydrogen to the cationic receptor element. An RMS fit was done using this lone pair atom, the carbonyl oxygen, and several aromatic carbon atoms. This overlap is shown in Figure 2. The receptor element interacting with the basic center of the antagonists would be the dominating binding interaction of the complex and the inclusion of this "dummy" lone pair was important from two perspectives. First, the presumed salt bridge that occurs with the receptor would not require the alignment of the antagonists' basic nitrogens to overlap in the same position in space. What would be required is that the basic nitrogens be in close proximity to the cationic receptor element. Secondly, although the interaction between the presumed quaternary center of the antagonists and the receptor element is ionic in nature, it has been shown in proteins that the addition of hydrogen-bonding characteristics is important in increasing the strength of salt bridges.[23a-d] This addition is denoted with the use of this "dummy" lone-pair atom and reflects the ability of the high-affinity ligands to direct the quaternary hydrogen toward the cationic receptor element. This allows, if nothing else, the two opposite charges to come in closer contact which would be important for high-affinity binding.

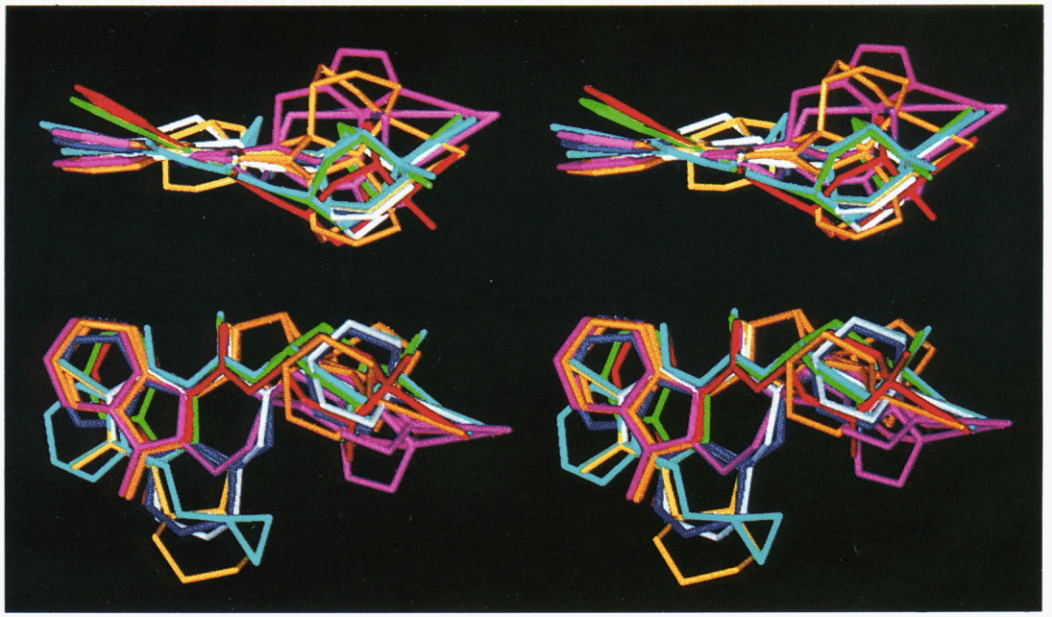


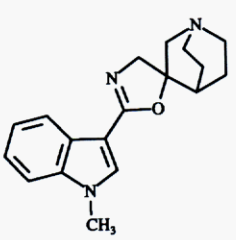
**Figure 2.** The superposition (without hydrogens) of ondansetron (**1**) (both enantiomers in magenta), (*S*)-zacopride (**2**) (green-blue), tropisetron (**3**) (green), granisetron (**4**) (red), (*S,S*)-**37** (white), (*S*)-**14** (blue), RG 12915 (**44**) (yellow), **45** (cyan), **46** (both enantiomers in orange), and YM060 (**47**) (red-orange) from two different viewpoints. Long bonds are lone pair atoms which have an extended bond length of 2.8 Å (see discussion).

**Table V.** Protection Against Cisplatin–Induced Emesis

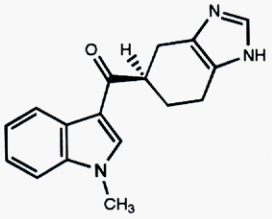
| | | iv | | | |
|---|---|---|---|---|---|
| | | in ferrets | | in dogs | |
| compd | dose,[a] mg/kg | $n^b$ | no. of emetic episodes | $n^b$ | no. of emetic episodes |
| control | | 4 | 16.00 ± 2.71 | 6 | 13.50 ± 5.89 |
| (*S,S*)-**37** | 0.001 | 9 | 9.67 ± 2.87*** | 6 | 7.17 ± 4.26* |
| | 0.003 | 5 | 0.60 ± 0.89*** | 6 | 4.33 ± 4.03** |
| | 0.01 | 6 | 0.00 ± 0.00*** | 6 | 4.50 ± 5.24** |
| | 0.03 | 5 | 0.00 ± 0.00*** | 6 | 1.33 ± 1.21** |
| | 0.1 | 6 | 0.17 ± 0.41*** | 6 | 1.17 ± 1.84** |
| ondansetron | 0.01 | | | 6 | 13.33 ± 3.01 |
| | 0.03 | | | 6 | 8.33 ± 3.20 |
| | 0.1 | | | 6 | 4.83 ± 2.40** |
| | 0.3 | | | 6 | 1.00 ± 2.00** |
| | 1.0 | | | 6 | 1.17 ± 0.41** |
| | | po | | | |
| | | in ferrets | | in dogs | |
| compd | dose,[a] mg/kg | $n^b$ | no. of emetic episodes | $n^b$ | no. of emetic episodes |
| control | | 5 | 14.20 ± 5.49 | 6 | 14.17 ± 7.99 |
| (*S,S*)-**37** | 0.001 | 6 | 15.17 ± 4.26 | 6 | 12.83 ± 4.70 |
| | 0.003 | 6 | 7.17 ± 6.08* | 6 | 16.17 ± 5.12 |
| | 0.01 | 6 | 2.17 ± 2.72*** | 6 | 4.00 ± 3.80** |
| | 0.03 | 5 | 1.80 ± 1.79*** | 6 | 2.67 ± 1.75** |
| | 0.1 | 5 | 0.80 ± 1.30*** | 6 | 0.00 ± 0.00** |
| ondansetron | 0.01 | | | 6 | 12.67 ± 3.01 |
| | 0.03 | 5 | 11.20 ± 4.15 | 6 | 18.33 ± 8.43 |
| | 0.1 | 5 | 2.20 ± 1.80** | 6 | 10.50 ± 3.15 |
| | 0.3 | 5 | 4.20 ± 5.76** | 6 | 3.17 ± 1.33** |
| | 1.0 | | | 6 | 2.00 ± 2.10** |

[a] Animals were pretreated with one dose of a test compound. [b] Number of animals. *$p < 0.05$. **$p < 0.01$. ***$p < 0.005$ vs control (Dunnett's $t$ test).

This pharmacophoric overlap incorporates many diverse ligands from our study and from the literature. Well-known antagonists tropisetron (**3**), (*S*)-zacopride (**2**), and granisetron (**4**) all fit the pharmacophore. Both enantiomers of ondanstron (**1**) are known to be equally potent from binding studies,[4a] and both are able to satisfy the model. Also both enantiomers of the spiro compound **46** are able to fit into the model equally well, and the affinity of these two compounds is nearly equal.[9e] YM060 (**47**)[4e] which is structurally diverse from previous antagonists was also able to fit the model, and the alignment of this compound along with the alignments of **46** suggest that steric tolerance may exist on both sides of the antagonist's aromatic plane.



**46**



**47** (YM060)

From the structure–reactivity relationship (SAR) of the compounds in this study, it is clear that the area around C-9 of (*S,S*)-**37** is either sterically occluded from any group or is a "narrow" pocket that will only accept a planar moiety. Also from the model, there is a suggestion of a lipophilic pocket "below" the aromatic system which increases the affinity of the compounds. These data suggest that the alignment of other known antagonists needs to be reexamined. Youssefyeh et al.[6g] had the original alignment of **44** so the oxygen in the fused tetrahydrofuran ring system was interacting with the same part of the receptor as the carbonyl oxygen to justify its greater affinity. From the data in this study, it is apparent that the increased interaction is probably not due to a double polar interaction, but from a lipophilic interaction that lies "beneath" the aromatic system (Figure 3). Also, Bradley et al.[6h] had the alignment for **45** with the methoxycyclopropyl chain protruding into the space similar to the space above C-9 of (*S,S*)-**37**. From our SAR data, this alignment is probably incorrect since this would protrude into the same space as the methoxy group of compound (*S*)-**35c** which lowers affinity by a factor of 3 log units (6.8 vs 9.8). The alignment of this stuctural class is shown in Figure 3 which has the methyoxycyclopropyl chain of **45** in the lipophilic area. The authors proposed

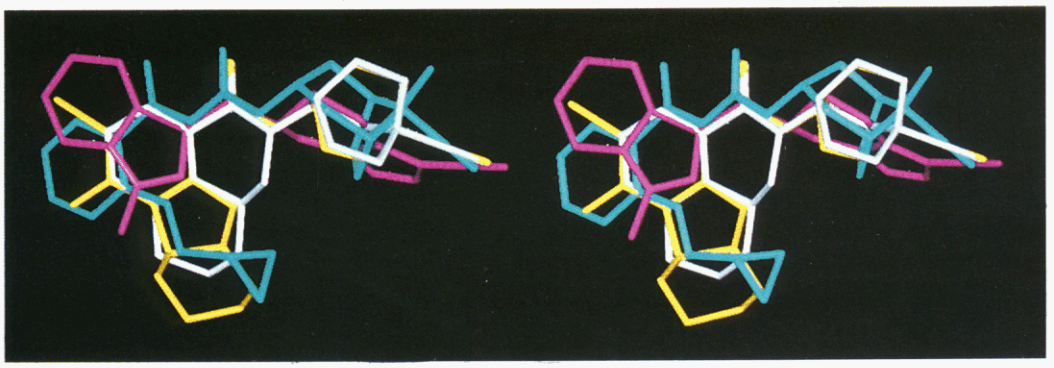


**Figure 3.** Superposition (without hydrogens) of (*S,S*)-**37** (white), RG 12915 (**44**) (yellow), **45** (cyan), and YM060 (**47**) (magenta). Long bonds are lone pair atoms which have an extended bond length of 2.8 Å (see discussion).

that another lipophilic interaction may have been the reason that the affinity increased.[6h] Both the 3-(*R*)- and 3-(*S*)-aminoquinuclidines in this structural class can be accommodated as well as the tropane which was found to be equipotent in their assay. The proposed conformation of this structural class allows all three of these basic nitrogen ring systems to interact equally well with the cationic receptor element where no other conformation allows all three to have the additional strength of the hydrogen-bonding characteristics. The aromatic system of **45** has been somewhat shifted in relation to the other antagonists; however, the aromatic ring protrudes into an area where there is no data suggesting this is not feasible, therefore, this alignment seems appropriate.

It is hard to quantitate activity from this type of modeling study because all of the compounds have not been assayed using the same system. Qualitatively however, all of the compounds with lesser binding affinity have the plane of their aromatic system somewhat askew to the reference compound (*S,S*)-**37**, whereas the more active compounds have their aromatic systems in the same plane. It is somewhat unrealistic to believe that all of the aromatic systems will be forced into the exact same place in the receptor. Since the charge–charge interaction would likely be the most important to the ligand–receptor complex, the more stringent alignment of this site would seem the most prudent. Figure 4 gives an outline of our proposed 5-$HT_3$ receptor antagonist pharmacophore. This model has all of the previous elements that others have presented and seeks to redefine the pharmacophore using the putative three-dimensional position of the receptor element that interacts with the basic nitrogen. Using (*S,S*)-**37** as a reference, this receptor element is 7.2 Å away from the carbonyl oxygen, 9.5 Å from the center of the aromatic ring system, and lies 2.0 Å above the aromatic plane. For comparison to the model by Hibert et al.,[10] the distances in (*S,S*)-**37** of the carbonyl oxygen to the basic nitrogen, center of the aromatic ring to the basic nitrogen, and height above the plane of the basic nitrogen were 5.2, 7.4, and 0.2 Å, respectively. Although the distance of the carbonyl oxygen to the basic nitrogen is equal (5.2 Å), the other distances are different. The distance from the center of the aromatic system to the basic nitrogen is somewhat longer (7.4 vs 6.7 Å), and the height above the plane is much less (0.2 vs 1.7 Å) and on the opposite side of the aromatic plane. But as discussed above, it is the position to the receptor element that is the most critical factor and not the position of the nitrogen. From this perspective, the interaction is on the same side of the aromatic plane as the model of Hibert et al.[10] The distances of our alignment fall very close to the modeling of Evans et al.[19] where their distances were 5.1 Å for the carbonyl–basic nitrogen distance and 7.1 Å for the aromatic ring–basic nitrogen distance. The alignment of Evans et al. is somewhat different from this study in that the overlap of the nitrogens remained the critical element in their model and not optimization of the ionic interaction. Some SAR work still is required to fully understand if the position above C-9 of (*S,S*)-**37** can accommodate planar functionality or is completely occluded. Also the space adjacent to C-7 and C-8 needs to be explored, since it is clear that these positions can accommodate a variety of groups.

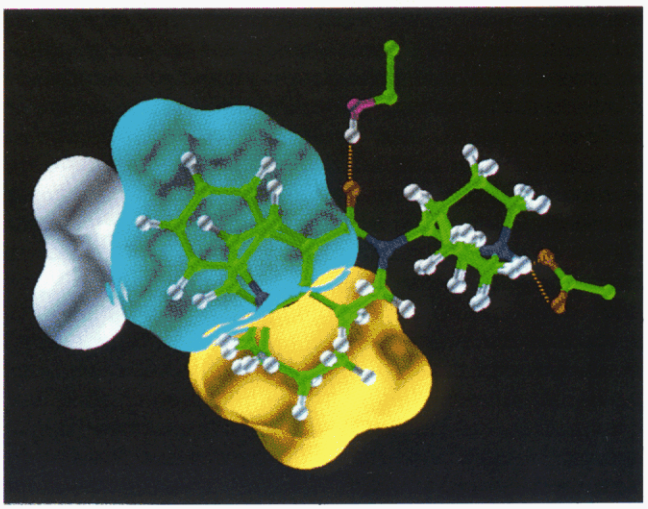


**Figure 4.** Hypothetical model of 5-$HT_3$ antagonist binding site using (*S,S*)-**37** and (*S*)-14 as model compounds. Proposed electrostatic interactions occur between the carbonyl of the antagonists with a polar hydrogen of the receptor, and between the basic nitrogen of the antagonists with cationic element in the receptor. Cyan area represents aromatic interactions, yellow area represents a lipophilic pocket, and the white area is fully undetermined.

In conclusion, we have prepared a number of highly potent 5-$HT_3$ receptor antagonists. The well-established principle of conformational restraint was used to maximize binding affinity as was the exploitation of an apparent lipophilic binding pocket at the receptor. Computer modeling studies based on previously reported 5-$HT_3$ receptor antagonists and on the SAR of the high affinity ligand (*S,S*)-**37** have led to further refinement of the 5-$HT_3$ receptor antagonist pharmacophore model. In addition to the potent antiemetic activity of (*S,S*)-**37**, several of the other 5-$HT_3$ antagonists reported in this paper demonstrate interesting activity in various animal behavioral models. For example, (*S*)-**35a** has been shown to possess potent anxiolytic activity in a large number of animal models of anxiety.[24a] Tritiated (*S*)-**35a** has also been proven to be a useful radioligand for 5-$HT_3$ receptor binding studies.[24b,c]

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Silica gel chromatography was performed under medium pressure with 230–400 mesh Merck Kieselgel. Microanalyses were performed by the Syntex Analytical Department, and, where analyses are indicated only by symbols of the elements, results were within ±0.4% (for C, H, and N) of the theoretical values unless otherwise noted. Optical rotations were meausred on a Perkin-Elmer model 141 polarimeter. $^1$H NMR spectra were measured on a Bruker WM 300 spectrometer. Optical purity of selected final compounds was determined by HPLC using a 100 × 4 mm Chiral AGP, $\alpha_1$-acid glycoprotein 5-$\mu$m column (LKB); mobile phase 4 mM phosphate buffer (pH 4.0)–acetonitrile–2-propanol, 97:2:1 (v,v,v); flow rate 0.5 mL/min; detection at 249 nm.

The following carboxylic acids and esters, which were converted to the amides in Schemes I–IV, were obtained from commercial sources or were prepared as described in the literature: ethyl 1,3-dimethylindole-3-carboxylate,[25] ethyl 5,6,7,8-tetrahydroindolizine-1-carboxylate,[26] 2-methylbenzo[*b*]furan-3-carboxylic acid,[27] 2-methylbenzo[*b*]thiophene-3-carboxylic acid,[28] 2,3-dimethyl- and 2-benzylbenzoic acid (Aldrich Chemical Co.), 3-methoxy-2-methylbenzoic acid,[29] 3-chloro-2-methyl-benzoic acid,[30] and indan-1-carboxylic acid and benzosuberane-1-carboxylic acid.[31] Ethyl 1,2-dimethyl-5-methoxyindole-3-carboxylate and ethyl 1,2-dimethylpyrrole-3-carboxylate were obtained by methylation (NaH, DMF, $CH_3I$) of ethyl 2-methyl-5-hydroxyindole-3-carboxylate[32] and ethyl 2-methylpyrrole-3-carboxylate,[33] respectively. 2-Ethyl-3-methylbenzoic acid and 2-butylbenzoic acid were prepared by alkylation of the corresponding toluic acid dianion according to the procedure of Creger.[34] 2-Methoxy- and 4-methoxy-5,6,7,8-tetrahydronaphthoic acid were prepared from 1-cyano-2-methoxy- and 1-cyano-4-methoxynaphthalene (Aldrich Chemical Co.) by hydrolysis to the acid followed by catalytic hydrogenation. The carboxylic acids were converted to amides via the acid chlorides. Esters were converted to amides by the Weinreb procedure.[35] All compounds had $^1$H NMR spectra in accord with the assigned structures, and spectral details are given for representative examples in each series.

**Typical Procedure for Preparation of Amides from Acid Chlorides. *N*-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-5,6,7,8-tetrahydronaphthylene-1-carboxamide [(*S*)-32a].** A solution of 5,6,7,8-tetrahydro-1-naphthylenecarboxylic acid[36] (179 g, 1.02 mol), thionyl chloride (85 mL, 1.17 mol), and DMF (1 mL) in 550 mL of toluene was stirred for 1 h at room temperature followed by 1 h at 50 °C. The mixture was concentrated in vacuo and then diluted with 1 L of ethyl acetate. The solution of the acid chloride was added to a solution of (*S*)-3-aminoquinuclinine[6g,13] (129 g, 1.02 mol) in 950 mL of toluene and 400 mL of ethyl acetate over 30 min, allowing the temperature of the mixture to reach 60 °C. The resulting suspension was stirred 18 h at room temperature. Aqueous sodium hydroxide (1 L of 2.5 M) was added, and the organic layer was separated. The aqueous layer was extracted 2× 1 L of ethyl acetate and the combined organic layers were dried ($Na_2SO_4$) and filtered. The filtrate was concentrated in vacuo, 2.75 L of hexane was added, and the product was allowed to cystallize for 1 h. Filtration afforded 269 g (93%) of (*S*)-**32a**: mp 159–160 °C; $[\alpha]^{25}_D$ –43.1° (*c* 0.6, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.52 (m, 1H), 1.60–1.74 (m, 3H), 1.74–1.86 (m, 4H), 2.05 (m, 1H), 2.52 (ddd, 1H, *J* = 1.8, 5.2, 14.2 Hz), 2.74–2.94 (m, 8H), 3.42 (ddd, 1H, *J* = 1.0, 9.5, 14.2 Hz), 4.14 (m, 1H), 5.92 (br d, 1H, exchanges with $D_2O$), 7.08–7.18 (m, 3H). HCl salt: mp 268–269 °C (ethanol–ether); $[\alpha]^{25}_D$ –10.0° (*c* 0.2, ethanol). Anal. ($C_{18}H_{24}N_2O$·HCl) C, H, N.

The following compounds were similarly prepared. Compound **24a**: yield 55%. Compound (*S*)-**24b**: yield 65%; HCl salt, $[\alpha]^{25}_D$ –16.0° (*c* 0.2, $H_2O$). Compound (*S*)-**24d**: yield 90%; HCl salt, $[\alpha]^{25}_D$ –13.8° (*c* 0.2, $H_2O$). Compound **20**: yield 72%; mp 154–155 °C (ethyl acetate–hexane). Anal. ($C_{17}H_{20}N_2O_2$) C, H, N. Compound **21**: yield 85%; mp 207–208 °C (ethyl acetate). Anal. ($C_{17}H_{20}N_2OS$) C, H, N.

***N*-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-1,2-dimethylindole-3-carboxamide [(*S*)-5].** 1,2-Dimethylindole-3-carboxylic acid was prepared from the ethyl ester[25] by hydrolysis with KOH in methanol–water and converted via the acid chloride to (*S*)-**5** according to the procedure given for (*S*)-**32a** (70% yield): mp 176–177 °C (ethyl acetate); $[\alpha]^{25}_D$ –51.9° (*c* 0.2, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.56 (m, 1H), 1.72 (m, 2H), 1.84 (m, 1H), 2.08 (m, 1H), 2.66 (m, 1H), 2.74 (s, 3H), 2.80–2.98 (m, 4H), 3.48 (m, 1H), 3.70 (s, 3H), 4.22 (m, 1H), 6.12 (br d, 1H, NH), 7.20–7.30 (m, 2H), 7.35 (m, 1H), 7.68 (m, 1H). Anal. ($C_{18}H_{23}N_3O$) C, H, N.

***N*-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-10-carboxamide [(*S*)-12].** A solution of 6,7,8,9-tetrahydropyrido[1,2-*a*]indole[37] (1.55 g, 9 mmol) in 20 mL of dichloromethane was added dropwise to an ice-cooled solution of phosgene in toluene (1.9 M, 5.7 mL, 10.8 mmol). The resulting solution was stirred 30 min at 0 °C, and a solution of (*S*)-3-aminoquinuclidine (1.26 g, 10 mmol) and triethylamine (1.9 mL, 13.6 mmol) in 20 mL of dichloromethane was then added. The mixture was stirred 30 min at 0 °C and then concentrated in vacuo. The residue was partitioned between ethyl acetate and 10% HCl, and the aqueous layer was basified with $NH_4OH$ and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated to a solid which was crystallized from ethyl acetate to afford 1.5 g (52%) of (*S*)-**12**: mp 164–165 °C; $[\alpha]^{25}_D$ –50.0° (*c* 0.3, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.56 (m, 1H), 1.70–2.00 (m, 5H), 2.04–2.16 (m, 3H), 2.65 (m, 1H), 2.80–3.00 (m, 4H), 3.34 (t, 2H, *J* = 6.5 Hz), 3.48 (m, 1H), 4.10 (t, 2H, *J* = 6.2 Hz), 4.20 (m, 1H), 6.10 (br d, exchanges with $D_2O$, NH), 7.24 (m, 2H), 7.34 (m, 1H), 7.70 (m, 1H). HCl salt: mp 273–274 °C; $[\alpha]^{25}_D$ –39.1° (*c* 0.5, $H_2O$). Anal. ($C_{20}H_{25}N_3O$·HCl·0.75$H_2O$) H,N; C: calcd, 74.27; found 73.34.

The following compounds were similarly prepared. Compound (*R*)-**12**: yield 65%; mp 164–165 °C (ethyl acetate); $[\alpha]^{25}_D$ +44.0° (*c* 0.4, $CHCl_3$). Compound (*S*)-**13**: yield 70%; mp 174–175 °C (ethyl acetate); $[\alpha]^{25}_D$ –45.9° (*c* 0.3, $CH_2Cl_2$).

**Typical Procedure for Preparation of Amides from Esters. *N*-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-5,6,7,8-tetrahydroindolizine-1-carboxamide [(*S*)-18].** To a solution of (*S*)-3-aminoquinuclidine (235 mg, 1.86 mmol) in 5 mL of toluene was added a solution of trimethylaluminum in toluene (0.93 mL of 2 M, 1.86 mmol), and the resulting solution was stirred for 1 h. A solution of ethyl 5,6,7,8-tetrahydroindolizine-1-carboxylate[26] (300 mg, 1.55 mmol) was added, and the mixture was heated to reflux for 3 h and then cooled in an ice bath. Water (1 mL) was added dropwise, and the resulting precipitate was filtered off. Evaporation of the filtrate and silica gel chromatography (10% methanol–dichloromethane, 1% $NH_4OH$) afforded 280 mg (66%) of (*S*)-**18** as an oil which was used directly in the next step: $^1$H NMR ($CDCl_3$) $\delta$ 1.50 (m, 1H), 1.64–2.00 (m, 8H), 2.54 (dd, 1H, *J* = 3.5, 14 Hz), 2.78–2.94 (m, 4H), 3.12 (t, 2H, *J* = 6 Hz), 3.40 (dd, 1H *J* = 10, 14 Hz), 3.93 (d, 2H, *J* = 6 Hz), 4.08 (m, 1H), 5.76 (br d, exchanges with $D_2O$, NH), 6.26 (d, 1H, *J* = 3 Hz), 6.46 (d, 1H, *J* = 3 Hz).

Compound **16** was similarly prepared: yield 58%; HCl salt, mp 278–280 °C (ethanol–ether). Anal. ($C_{14}H_{21}N_3O$·HCl·0.5$H_2O$) C, H, N.

***N*-[(S)-1-Azabicyclo[2.2.2]octan-3-yl]-3-ethyl-2-methylbenzamide Hydrochloride [(*S*)-24c].** Methyl 2-methyl-3-iodobenzoate (**40**)[38] was converted to methyl 3-ethynyl-2-methylbenzoate (**41**) according to the procedures of Austin et al.[39] in 55% overall yield. Catalytic hydrogenation followed by treatment with (*S*)-3-aminoquinuclidine and trimethylaluminum as described above afforded (*S*)-**24c** in 70% yield. HCl salt: mp 260–261 °C (ethanol–ether); $[\alpha]^{25}_D$ –13.6° (*c* 0.1, $H_2O$); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.16 (t, 3H, *J* = 7.6 Hz), 1.62 (m, 1H), 1.92 (m, 2H), 2.05 (m, 1H), 2.20 (m, 1H), 2.25 (s, 3H), 2.64 (q, 2H, *J* = 7.6 Hz), 3.05 (m, 1H), 3.14–3.28 (m, 4H), 3.66 (m, 1H), 4.32 (m, 1H), 7.14–7.26 (m, 2H), 8.62 (d, 1H, *J* = 6.4 Hz), 10.4 (br s, 1H, exchanges with $D_2O$). Anal. ($C_{17}H_{24}N_2O$·HCl).

**Typical Procedure for Conversion of Amides to Fused Pyridones. 2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one Hydrochloride [(*S*)-35a].** A solution of (*S*)-**32a** (118.8 g, 0.42 mol) in 1.3 L of tetrahydrofuran was cooled to –22 °C (under $N_2$) and a solution of *n*-BuLi in hexanes (530 mL of 1.6 M, 0.85 mol) was added at such a rate as to maintain the internal temperature between –22 and –14 °C. The resulting deep red solution was stirred at –22 °C for 30 min and DMF (37 mL, 0.48 mol) was added at a temperature below –14 °C (internal). After the addition was complete, the solution was stirred at –22 °C for 30 min. Hydrochloric acid (332 mL of 6 N, 2.0 mol) was slowly added, keeping the temperature below 5 °C. The mixture was concen-

trated in vacuo to remove most of the tetrahydrofuran and hexanes. The mixture was made basic with aqueous sodium hydroxide (ice bath) and extracted 4× with ethyl acetate. The combined extract was dried ($MgSO_4$), filtered, and evaporated to yield the crude base as a thick oil. This was dissolved in 290 mL of 2-propanol, and a solution of 2-propanol containing 17 g (0.47 mol) of HCl was added. After having been stirred overnight, the mixture was filtered to afford the crude HCl salt. Recrystallization from 1 L of 2-propanol and 32 mL of water (subsequently concentrated to 850 mL) afforded 106 g (77%) of (*S*)-**35a**·HCl: mp >270 °C; $[\alpha]^{25}_D$ −8.4° (*c* 0.5, $H_2O$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.74–2.10 (m, 6H), 2.32 (m, 1H), 2.80 (br t, 2H), 2.94 (br t, 2H), 3.20–3.40 (m, 3H), 3.60–3.72 (m, 2H), 3.84 (m, 1H), 5.20 (m, 1H), 7.42 (dd, 1H, *J* = 6.4, 7.0 Hz), 7.52 (dd, 1H, *J* = 0.9, 6.4 Hz), 7.54 (s, 1H), 8.06 (dd, 1H, *J* = 0.9, 7.0 Hz), 11.0 (br s, 1H, exchanges with $D_2O$); MS *m/e* 294 ($M^+$ − HCl), 236, 211, 185, 110, 109; chiral HPLC 99.9%. Anal. ($C_{19}H_{22}N_2O$·HCl).

**(*S*)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,3-dihydro-5-methyl-1*H*-pyrido[4,3-*b*]indol-1-one Hydrochloride [(*S*)-8a].** The free base was obtained in 55% yield after crystallization from ethyl acetate: mp 250–252 °C; $[\alpha]^{25}_D$ +59.6° (*c* 0.4, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.40 (m, 1H), 1.58–1.72 (m, 2H), 1.85 (m, 1H), 2.02 (m, 1H), 2.90–3.16 (m, 5H), 3.54 (m, 1H), 3.80 (s, 3H), 5.34 (m, 1H), 6.50 (d, 1H, *J* = 7.6 Hz), 7.30–7.46 (m, 3H), 7.62 (d, 1H, *J* = 7.6 Hz), 8.42 (m, 1H). Anal. ($C_{19}H_{21}N_3O$) C, H, N.

The HCl salt was crystallized from ethanol: mp 254–255 °C; $[\alpha]^{25}_D$ −67.1° (*c* 0.3, $H_2O$); chiral HPLC 99.7%. Anal. ($C_{19}H_{21}N_3O$·HCl·0.75$H_2O$) C, H, N.

**(*R*)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,3-dihydro-5-methyl-1*H*-pyrido[4,3-*b*]indol-1-one Hydrochloride [(*R*)-8a].** The free base was obtained in 85% yield after crystallization from ethyl acetate: mp 250–251 °C; $[\alpha]^{25}_D$ −60.2° (*c* 0.4, $CHCl_3$); $^1H$ NMR identical to (*S*)-**8a**. Anal. ($C_{19}H_{21}N_3O$) C, H, N.

The HCl salt was crystallized from ethanol: 252–253 °C; $[\alpha]^{25}_D$ +66.2° (*c* 0.3, $H_2O$); chiral HPLC 99.7%. Anal. ($C_{19}H_{21}N_3O$·HCl·0.25$H_2O$) C, H, N.

**(*S*)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*]naphthyridin-1-one Hydrochloride [(*S*)-14].** This compound was obtained from (*S*)-**12** in 70% yield: mp 256–259 °C; $[\alpha]^{25}_D$ −14.7° (*c* 0.3, $H_2O$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.80 (m, 1H), 1.90–2.10 (m, 3H), 2.18 (m, 2H), 2.28 (m, 1H), 2.88 (broad t, 2H), 3.20–3.40 (m, 3H), 3.65 (m, 2H), 3.87 (m, 1H), 4.22 (broad t, 2H), 5.35 (m, 1H), 7.26 (t, 1H, *J* = 8 Hz), 7.37 (t, 1H, *J* = 8 Hz), 7.58 (d, 1H, *J* = 8 Hz), 7.77 (s, 1H), 8.10 (d, 1H, *J* = 8 Hz), 10.8 (broad s, exchanges with $D_2O$). Anal. ($C_{21}H_{23}N_3O$·HCl·$H_2O$) C, H, N.

**2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-1,2,4,5,6,7-hexahydro-2,7a-diazacyclohepta[*jk*]fluoren-1-one [(*S*)-15].** The free base was obtained in 88% yield after silica gel chromatography (6% methanol–dichloromethane, 1% $NH_4OH$). HCl salt: mp >280 °C; $[\alpha]^{25}_D$ −13.3° (*c* 0.2, $H_2O$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.80 (m, 1H), 1.80–2.20 (m, 7H), 2.28 (m, 1H), 3.05 (m, 2H), 3.15–3.40 (m, 3H), 3.70 (m, 2H), 3.82 (m, 2H), 4.42 (m, 2H), 5.35 (m, 1H), 7.25 (dd, 1H, *J* = 7.4, 7.5 Hz), 7.37 (dd, 1H, *J* = 7.4, 8.2 Hz), 7.64 (d, 1H, *J* = 8.2 Hz), 7.73 (s, 1H), 8.20 (d, 1H, *J* = 7.5 Hz), 11.1 (br s, 1H, exchanges with $D_2O$). Anal. ($C_{22}H_{25}N_3O$·HCl) C, H, N.

**2-(1-Azabicyclo[2.2.2]oct-3-yl)-5-methylpyrrolo[3,2-*c*]pyridin-1(2*H*)-one Hydrochloride (17).** This compound was obtained in 65% yield from **16**: mp 178–180 °C; MS *m/e* 257 ($M^+$), 201, 174, 173, 148, 110, 109; $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.80–2.10 (m, 4H), 2.25 (m, 1H), 3.20–3.36 (m, 3H), 3.50–3.68 (m, 2H), 3.74 (s, 3H), 3.85 (m, 1H), 5.20 (m, 1H), 6.52 (d, 1H, *J* = 3 Hz), 6.63 (d, 1H, *J* = 8 Hz), 7.09 (d, 1H, *J* = 3 Hz), 7.60 (d, 1H, *J* = 8 Hz), 10.6 (br s, 1H, exchanges with $D_2O$). Anal. ($C_{15}H_{19}N_3O$·HCl·0.75$H_2O$) C, H, N.

**2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,7,8,9-tetrahydro-3*H*-pyrrolo[3,2,1-*ij*][1,6]naphthyridin-3-one Hydrochloride [(*S*)-19].** This compound was prepared in 30% yield according to the procedure described for (*S*)-**35a** except that *s*-BuLi was used instead of *n*-BuLi: mp 178–180 °C (ethanol–ether); $[\alpha]^{25}_D$ −9.7° (*c* 0.2, $H_2O$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.80 (m, 1H), 1.84–2.12 (m, 5H), 2.24 (m, 1H), 2.76 (br t, 2H), 3.16–3.35 (m, 3H), 3.50–3.68 (m, 2H), 3.82 (m, 1H), 4.06 (br t, 2H), 5.26 (m, 1H), 6.48 (d, 1H, *J* = 3 Hz), 7.12 (d, 1H, *J* = 3 Hz), 7.40 (s, 1H), 10.7 (br s, 1H, exchanges with $D_2O$). Anal. ($C_{17}H_{21}N_3O$·HCl).

**2-(1-Azabicyclo[2.2.2]oct-3-yl)-1,2-dihydrobenzofurano[3,2-*c*]pyridin-1-one Hydrochloride (22).** This compound was obtained in 10% yield after purification by silica gel chromatography: mp >270 °C (ethanol); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.80–2.16 (m, 4H), 2.40 (m, 1H), 3.20–3.40 (m, 3H), 3.50–3.70 (m, 2H), 3.92 (m, 1H), 5.26 (m, 1H), 6.92 (d, 1H, *J* = 8 Hz), 7.40–7.52 (m, 2H), 7.74 (dd, 1H, *J* = 1.7, 7 Hz), 8.05 (dd, 1H, *J* = 1.6, 6 Hz), 8.14 (d, 1H, *J* = 8 Hz), 10.5 (br s, 1H, exchanges with $D_2O$). Anal. ($C_{18}H_{18}N_2O_2$·HCl·0.25$H_2O$) C, H, N.

**2-(1-Azabicyclo[2.2.2]oct-3-yl)-1,2-dihydrobenzothieno[3,2-*c*]pyridin-1-one Hydrochloride (23).** This compound was obtained in 20% yield after purification by silica gel chromatography: mp >265 °C (ethanol–ether); MS *m/e* 310 ($M^+$ − HCl), 227, 226, 201, 184, 110, 109; $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.80–2.20 (m, 4H), 2.42 (m, 1H), 3.20–3.40 (m, 3H), 3.50–3.70 (m, 2H), 3.95 (m, 1H), 5.32 (m, 1H), 7.12 (d, 1H, *J* = 7.4 Hz), 7.46–7.58 (m, 2H), 8.05 (m, 2H), 8.75 (dd, 1H, *J* = 1.8, 7.4 Hz), 10.6 (br s, exchanges with $D_2O$). Anal. ($C_{18}H_{18}N_2OS$·HCl·0.25$H_2O$) C, H, N.

**2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]isoquinolin-1(2*H*)-one Hydrochloride [(*S*)-25a].** This compound was obtained in 65% yield: mp 239–240 °C (ethanol–ether); $[\alpha]^{25}_D$ −23.6° (*c* 1.1, methanol); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.78–2.15 (m, 4H), 2.38 (m, 1H), 3.20–3.40 (m, 3H), 3.54–3.66 (m, 2H), 3.86 (m, 1H), 5.20 (m, 1H), 6.70 (d, 1H, *J* = 7.5 Hz), 7.52 (m, 1H), 7.66–7.76 (m, 2H), 7.76 (d, 1H, *J* = 7.5 Hz), 8.24 (d, 1H, *J* = 7.6 Hz), 10.9 (br s, 1H, exchanges with $D_2O$). Anal. ($C_{16}H_{18}N_2O$·HCl·0.4$H_2O$) C, H, N.

**2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-5-methoxyisoquinolin-1(2*H*)-one Hydrochloride [(*S*)-25d].** The yield of the free base was 93%. The HCl salt was crystallized from ethanol: mp 275–277 °C; $[\alpha]^{25}_D$ −19.5° (*c* 0.2, $H_2O$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.76–2.10 (m, 4H), 2.36 (m, 1H), 3.20–3.40 (m, 3H), 3.50–3.64 (m, 2H), 3.88 (m, 1H), 3.94 (s, 3H), 5.16 (m, 1H), 6.80 (d, 1H, *J* = 7.8 Hz), 7.27 (d, 1H, *J* = 7.9 Hz), 7.46 (dd, 1H, *J* = 7.9, 8.0 Hz), 7.72 (d, 1H, *J* = 7.8 Hz), 7.81 (d, 1H, *J* = 8.0 Hz), 10.7 (br s, exchanges with $D_2O$). Anal. ($C_{17}H_{20}N_2O_2$·HCl·$H_2O$) C, H, N.

**2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-1,2,4,5-tetrahydrocyclopenta[*de*]isoquinolin-1(2*H*)-one Hydrochloride [(*S*)-34].** The yield of the free base was 81%. HCl salt: mp >285 °C (ethanol–ether); $[\alpha]^{25}_D$ −12.8°; $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.80 (m, 1H), 1.90–2.16 (m, 2H), 2.30 (m, 1H), 3.15 (m, 2H), 3.20–3.40 (m, 5H), 3.54–3.70 (m, 2H), 3.96 (m, 1H), 5.25 (m, 1H), 7.46 (dd, 1H, *J* = 7.2, 7.9 Hz), 7.57 (dd, 1H, *J* = 0.8, 7.2 Hz), 7.60 (s, 1H), 7.82 (dd, 1H, *J* = 0.8, 7.9 Hz), 10.6 (br s, 1H, exchanges with $D_2O$). Anal. ($C_{18}H_{20}N_2O$·HCl·0.5$H_2O$) C, H, N.

**2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-4,5,6,7-tetrahydrocyclohepta[*de*]isoquinolin-1(2*H*)-one Hydrochloride [(*S*)-36].** The yield of the free base was 30%. HCl salt: mp >280 °C (ethanol); $[\alpha]^{25}_D$ −3.4° (*c* 0.3, $H_2O$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.75–2.10 (m, 8H), 2.34 (m, 1H), 2.95 (m, 2H), 3.10 (m, 2H), 3.20–3.40 (m, 3H), 3.58–3.70 (m, 2H), 3.80 (m, 1H), 5.15 (m, 1H), 7.36 (dd, 1H, *J* = 7.6, 7.9 Hz), 7.44 (s, 1H), 7.48 (dd, 1H, *J* = 0.5, 7.9 Hz), 8.14 (dd, 1H, *J* = 0.5, 7.6 Hz), 10.8 (br s, 1H, exchanges with $D_2O$). Anal. ($C_{20}H_{24}N_2O$·HCl·0.25$H_2O$) C, H, N.

The following were also prepared by the above general procedure. Compound (*S*)-**8b**: yield 70%; HCl salt, $[\alpha]^{25}_D$ −57.0° (*c* 0.2, $H_2O$). Compound **10**: yield 50%. Compound **11**: yield 25%. Compound (*R*)-**14**: yield 85%; HCl salt, $[\alpha]^{25}_D$ +18.2° (*c* 0.9, $H_2O$). Compound (*S*)-**25b**: yield 85%; HCl salt, $[\alpha]^{25}_D$ −23.3° (*c* 0.5, $H_2O$). Compound (*S*)-**25c**: yield 81%; HCl salt, $[\alpha]^{25}_D$ −38.9° (*c* 0.2, $H_2O$). Compound (*S*)-**25e**: yield 70%; HCl salt, $[\alpha]^{25}_D$ −22.4° (*c* 0.3, $H_2O$). Compound **27**: yield 52%. Compound **28**: yield 73%. Compound (*S*)-**30b**: yield 25%; HCl salt, $[\alpha]^{25}_D$ −37.3° (*c* 0.5, $H_2O$). Compound (*S*)-**30c**: yield 20%; HCl salt, $[\alpha]^{25}_D$ −12.2° (*c* 0.6, $H_2O$). Compound (*R*)-**34**: yield 77%; HCl salt, $[\alpha]^{25}_D$ +17.1° (*c* 0.6, $H_2O$). Compound (*R*)-**35a**: yield 68%; HCl salt, $[\alpha]^{25}_D$ +6.8° (*c* 0.6, $H_2O$). Compound (*S*)-**35b**: yield 85%; HCl salt, $[\alpha]^{25}_D$ −8.0° (*c* 0.5, $H_2O$). Compound (*S*)-**35c**: yield 15%; HCl salt, $[\alpha]^{25}_D$ −21.1° (*c* 0.6, $H_2O$). Compound **39**: yield 35%.

**2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,3,4,5-tetrahydro-5-methyl-1*H*-pyrido[4,3-b]indol-1-one Hydrochloride (9).**[40] A mixture of the hydrochloride salt of racemic **8a** (300 mg, 0.87 mmol) in 8 mL of acetic acid and 3 drops of 70% aqueous perchloric acid was hydrogenated in the presence of 20% Pd–C (100 mg) for 18 h at 50 psi and 75 °C. The cooled mixture was filtered, and the

filtrate was concentrated in vacuo, diluted with water, and basified with aqueous NaOH. The crude product obtained by extraction with ethyl acetate was purified by silica gel chromatography (10% methanol–dichloromethane, 1% $NH_4OH$) to give 50 mg (17%) of the free base **9**. The hydrochloride salt was crystallized from ethanol–ether: mp >260 °C; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.81 (m, 1H), 1.92 (m, 2H), 2.06 (m, 1H), 2.22 (m, 1H), 3.08 (m, 2H), 3.20–3.48 (m, 3H), 3.66 (broad t, 2H), 3.73 (s, 3H), 3.84 (m, 1H), 4.65 (m, 1H), 7.14–7.21 (m, 2H), 7.50 (d, 1H, $J$ = 7.8 Hz), 7.92 (d, 1H, $J$ = 7.8 Hz), 10.3 (br s, 1H, exchanges with $D_2O$); MS *m/e* 309 ($M^+$ – Cl), 199, 171, 143, 109. Anal. ($C_{19}H_{23}N_3O$·HCl) C, H. N.

**2-(1-Azabicyclo[2.2.2]oct-3-yl)-3,4-dihydroisoquinolin-1-(2*H*)-one Hydrochloride (26a).** A mixture of racemic **25a**·HCl (600 mg, 2.1 mmol) and 2 g of 20% $Pd(OH)_2$ on carbon (Pearlman's catalyst) in ethanol (50 mL to which 5 mL of 10% ethanolic HCl was added) was hydrogenated at 50 psi for 16 h. The catalyst was filtered off, and the filtrate was evaporated. Crystallization of the residue from ethanol–ether afforded 505 mg (82%) of **26a**: mp 230–232 °C; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.76–2.10 (m, 4H), 2.24 (m, 1H), 2.96 (m, 2H), 3.14–3.30 (m, 3H), 3.42 (m, 2H), 3.56–2.70 (m, 2H), 3.75 (m, 1H), 4.76 (m, 1H), 7.20–7.30 (m, 2H), 7.48 (dd, 1H, $J$ = 7.8, 8 Hz), 7.90 (d, 1H, $J$ = 8 Hz), 10.9 (br s, 1H, exchanges with $D_2O$). Anal. ($C_{16}H_{20}N_2O$·HCl·0.25$H_2O$) C, H, N.

The following compounds were similarly prepared. (*S*)-**26b**: yield 85%; HCl salt, $[\alpha]^{25}_D$ –44.2° (*c* 0.4, $H_2O$). (*S*)-**26c**: yield 80%; HCl salt, $[\alpha]^{25}_D$ –40.3° (*c* 0.4, $H_2O$). (*S*)-**26d**: yield 87%; HCl salt, $[\alpha]^{25}_D$ –45.7° (*c* 0.4, $H_2O$).

**(3a*S*)-[2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one Hydrochloride [(*S,S*)-37].** A mixture of (*S*)-**35a**·HCl (2.25 g, 6.8 mmol), 20% $Pd(OH)_2$ on carbon (0.5 g), and 0.5 mL of 70% perchloric acid in 30 mL of acetic acid was hydrogenated at 50 psi and 65–70 °C for 4 h. The cooled mixture was filtered, and HPLC analysis (4.6- × 250-mm Zorbay silica gel column; eluent, $CH_2Cl_2$–MeOH–aqueous $NH_4OH$, 90:10:04 v/v/v; flow 2 mL/min) showed two products, $t_R$ 11.1 and 12.6 min, in a 43:57 ratio. The filtrate was evaporated, and the residue was partitioned between aqueous NaOH and dichloromethane. Evaporation of the dichloromethane afforded 2.0 g of a foam which was converted to the HCl salt (ethanol/HCl–ether): yield 1.0 g. HPLC analysis showed a 12:88 ratio of the short to long retention time components. Recrystallization of the salt from ethanol gave the major component in 98% purity: yield 580 mg (26%); mp >290 °C; $[\alpha]^{25}_D$ –94.1° (*c* 0.4, $H_2O$); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.30 (br q, 1H), 1.60–2.15 (m, 7H), 2.22 (m, 1H), 2.70–2.94 (m, 2H), 3.04 (m, 1H), 3.15–3.30 (m, 4H), 3.46 (m, 2H), 3.64 (m, 1H), 3.80 (dd, 1H, $J$ = 4.6, 11.7 Hz), 4.80 (m, 1H), 7.26 (m, 2H), 7.72 (dd, 1H, $J$ = 2.1, 6.8 Hz), 10.9 (br s, 1H, exchanges with $D_2O$). Anal. ($C_{19}H_{24}N_2O$·HCl) C, H, N.

This compound was shown to be (*S,S*)-**37** by X-ray crystallographic analysis.

**X-ray Structure Determination of (*S,S*)-37.** X-ray crystallographic data were obtained on (*S,S*)-**37**·HCl, $C_{19}H_{25}ClN_2O$, FW = 332.87. Crystals were obtained from ethanol. A clear, colorless prism, 0.3 × 0.3 × 0.5 mm was used for the structural determination. Diffraction photographs showed monoclinic symmetry, and accurate lattice constants of $a$ = 8.996(2) Å, $b$ = 7.555(1) Å, $c$ = 12.624(2) Å, and $\beta$ = 98.080(1)° were determined. The space group was $P21$, $Z$ = 2, $V$ = 849.5(2) Å$^3$, and $D_{calcd}$ = 1.309 g/cm$^3$. All unique diffraction maxima with $2\theta \leq 116°$ were collected on a computer-controlled diffractomer (Siemens R3m/V, SHELXTL PLUS (VMS)) with graphite monochromated Cu K$\alpha$ radiation ($\lambda$ = 1.5418 Å) and variable speed $2\theta - \theta$ scans. After correction for Lorentz, polarization, and background effects, 1248 of the 1262 independent reflections were judged observed. A phasing model was found by using direct methods, and full-matrix least-squares refinements with anisotropic heavy atoms and fixed isotropic riding hydrogens converged to give final $R$ factors of $R$ = 0.0455 and $R_w$ = 0.0619.

**Hydrogenation of the Free Base of (*S*)-35a.** A mixture of (*S*)-**35a** free base (1.14 g, 3.86 mmol) and 10% Pd–C (1.5 g, 62% $H_2O$ w/w) in 25 mL of tetrahydrofuran was stirred under a hydrogen atmosphere for 15 days. HPLC analysis indicated a 30:70 ratio of the two diastereomers. The mixture was filtered and concentrated in vacuo. The residue was dissolved in 10 mL of ethanol, and 1.5 mL of 7 M (10.5 mmol) of ethanolic HCl was added. After stirring overnight the mixture was filtered to afford 0.7 g (61%) of (*S,S*)-**37**; HPLC 99%.

**(3a*R*)-[2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*]isoquinolin-1-one Hydrochloride [(*R,S*)-38].** The mother liquor from the crystallization of (*S,S*)-**37** was evaporated, and the residue was chromatographed on silica gel (10% methanol–dichloromethane, 1% $NH_4OH$). A pure fraction of the less polar component was obtained which was evaporated to afford the free base of (*R,S*)-**38**. The HCl salt was crystallized from ethanol: mp 272-274 °C; $[\alpha]^{25}_D$ +80° (*c* 0.2, $H_2O$); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.30 (br q, 1H), 1.60–2.16 (m, 7H), 2.25 (m, 1H), 2.68–2.90 (m, 2H), 3.08 (m, 1H), 3.18–3.30 (m, 4H), 3.48 (m, 2H), 3.62 (m, 1H), 3.70 (dd, 1H, $J$ = 4.8, 11.8 Hz), 4.78 (m, 2H), 7.28 (m, 2H), 7.67 (dd, 1H, $J$ = 2.1, 6.8 Hz), 11.0 (br s, 1H, exchanges with $D_2O$); HPLC 99.6%. Anal. ($C_{19}H_{24}N_2O$·HCl·0.5$H_2O$) C, H, N.

**(3a*R*)-[2-[(*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one Hydrochloride [(*R,R*)-37].** This compound was obtained from (*R*)-**35a** as described for the preparation of (*S,S*)-**37**: mp >280 °C (ethanol–ether); $[\alpha]^{25}_D$ +94.7° (*c* 0.2, $H_2O$); $^1$H NMR identical to (*S,S*)-**37**; HPLC 98%. Anal. ($C_{19}H_{24}N_2O$·HCl·0.25$H_2O$) C, H; N: calcd, 8.30; found, 7.70.

**(3a*S*)-[2-[(*R*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one Hydrochloride [(*S,R*)-38].** Chromatography of the concentrated mother liquor from crystallization of (*R,R*)-**37** afforded a fraction enriched in the less polar component. This was evaporated, and the residue was crystallized from ethyl acetate to give the free base of (*S,R*)-**38**. The HCl salt was crystallized from ethanol–ether: mp 275–276 °C; $[\alpha]^{25}_D$ –67.6° (*c* 0.3, $H_2O$); $^1$H NMR identical to (*R,S*)-**38**; HPLC 95%. Anal. ($C_{20}H_{24}N_2O$·HCl) C, H, N.

**Von Bezold–Jarisch Reflex in Anesthetized Rats.** A modification of the procedure of Butler et al.[3] and Richardson et al.[7] was followed. Male Sprague–Dawley rats, 250–380 g, obtained from Charles River Breeding Laboratories were used. After the rats were anesthetized with urethane (1.5 g/kg, ip), they were cannulated (trachea, right and left femoral veins). Heart rate was recorded using ECG/Biotech amplifiers. After at least 30-min equilibration, each rat was titrated (iv) with 2-methyl-5-hydroxytryptamine (2-methyl-5-HT), and a lowest dose that induced a sufficient and consistent bradycardia was chosen. The rat was then challenged with the selected dose of 2-methyl-5-HT every 12 min. Test compounds were administered intravenously in increasing doses 5 min before each injection of 2-methyl-5-HT, until the response to 2-methyl-5-HT was blocked or until a sufficiently high dose of the test compound was administered. A separate group of rats receiving vehicle (saline) were similarly tested. Heart rate (beats/min) was recorded continuously for the duration of the study. The peak decrease in heart rate evoked by 2-methyl-5-HT was monitored. The change in responses to 2-methyl-5-HT before and after administration of the vehicle or test compound was calculated. This was expressed as percent inhibition from the predose value. The $ID_{50}$, the dose that inhibited 50% of the bradycardiac effect induced by 2-methyl-5-HT, and the 95% confidence interval were obtained by performing a four-parameter, modified seemingly unrelated nonlinear regression.

**5-HT$_3$ Receptor Radioligand Binding Assay.** The affinity of test compounds for 5-HT$_3$ receptors of the rat cerebral cortex radiolabeled with [$^3$H]quipazine[14] was measured using the method previously described by Sharif et al.[41]

Membranes were prepared from the cerebral cortices of rat brains homogenized in 50 mM Tris buffer (pH 7.4 at 4 °C) using a Polytron P10 tissue disrupter (setting 10, 2 × 10-s bursts). The homogenate was centrifuged at 48 000*g* for 12 min and the pellet obtained was washed, by resuspension and centrifugation, three times in homogenizing buffer. The tissue pellets were resuspended in the assay buffer, and were stored under liquid nitrogen until used.

The binding assays were conducted using a Tris-Krebs assay buffer of the following composition (mM): NaCl, 154; KCl, 5.4; $KH_2PO_4$, 1.2; $CaCl_2$·2$H_2O$, 2.5; $MgCl_2$, 1.0; glucose, 11; Tris, 10. Assays were conducted at 25 °C at 7.4 in a final volume of 0.25 mL. Racemic zacopride (1.0 $\mu$M) was used to define the nonspecific binding. 5-HT$_3$ receptors present in rat cortical membranes were labeled using 0.3–0.7 nM [$^3$H]quipazine (specific

activity 50–66 Ci/mmol; New England Nuclear) in the presence of 0.1 μM paroxetine to prevent [$^3$H]quipazine binding to 5-HT$_3$ uptake sites. The rat cortex membranes were incubated with [$^3$H]quipazine in the presence of 10 different concentrations of test compound ranging from $1 \times 10^{-12}$ to $1 \times 10^{-4}$ M. Incubations were conducted for 45 min at 25 °C and were terminated by vacuum filtration over Whatman GF/B glass fiber filters using a Brandel 48-well cell harvester. After filtration the filters were washed for 8 s with 0.1 M NaCl. The filters were pretreated with 0.3% poly(ethyleneimine) 18 h prior to use in order to reduce filter binding of the radioligand. Radioactivity retained on the filters was determined by liquid scintillation counting.

The $IC_{50}$ (concentration of test compound producing 50% inhibition of radioligand binding) was determined by an iterative curve fitting procedure. The inhibitory constant ($K_i$) was calculated from the $IC_{50}$ by using the equation of Cheng and Prusoff.[42] Hill coefficients were essentially unity for all compounds tested.

**Inhibition of Cisplatin-Induced Emesis.** The inhibition of emesis induced by iv administration of cisplatin (10 mg/kg) in the ferret and the dog (3 mg/kg) was determined by a modification of the procedure of Gylys et al.[43] Test compounds were administered iv as aqueous solutions through a jugular vein cannula 30 min prior to iv cisplatin treatment. Animals were observed continuously for 5 h following cisplatin administration for the number of emetic episodes. Oral administration of compounds in the ferret was by gavage of an aqueous solution. Test compounds were administered orally to the dogs by liquid gelatin capsules. Oral administration was 30 min prior to iv cisplatin treatment, and the number of emetic episodes was monitored for 5 h following cisplatin. Results were expressed as mean ±SE, and Dunnett's $t$ test was performed to determine statistical significance.

**Computer Modeling.** The calculations used in this study were carried out with SYBYL 5.5. When using the TRIPOS force field, a cutoff of 8 Å and a MIN-ENERGY-CHANGE of 0.00001 kcals were used as the termination criteria for minimization. The calculations were carried out using electrostatic charges calculated by the Gasteiger and Marsili method.[44,45] The MM2(87) calculations were carried out using the standard termination criteria.

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**Supplementary Material Available:** Tables of atomic coordinates, bond lengths, bond angles, anisotropic displacement coefficients, and H-atom coordinates for the hydrochloride salt of (*S,S*)-37 (4 pages). Ordering information is given on any current masthead page.

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