# Novel 5-HT$_3$ Antagonists: Indol-3-ylspiro(azabicycloalkane-3,5′(4′*H*)-oxazoles)

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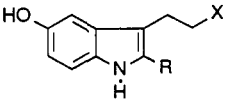
The synthesis and biochemical evaluation of a series of spirofused indole oxazoline 5-HT$_3$ antagonists is described in which the oxazoline ring acts as a bioisosteric replacement for esters and amides. The effect of substitution about the indole ring has shown the steric limitations of the aromatic binding site. Incorporation of a variety of azabicyclic systems within the rigid spirofused framework has allowed the definition of a binding model which incorporates a number of known antagonists and agonists. In this model steric constraints limit substitution around the indole ring although there is some bulk tolerance at the 1- and 2-positions. The importance of constraining the basic nitrogen within an azabicyclic system is underlined by comparison with the monocyclic piperidine. The highest affinity was observed for those compounds in which the basic nitrogen occupies a bridgehead position, the most potent analogue in this group being the azabicyclic [3.3.1] system (pIC$_{50}$ = 8.95), suggesting lipophilic interactions may play a role in increasing affinity. A suggested model for agonist binding is included in which the basic nitrogens are superimposed and the 5-hydroxyl group of 5-HT is superimposed on the H-bond-accepting atom of the heterocyclic linking group.

## Introduction

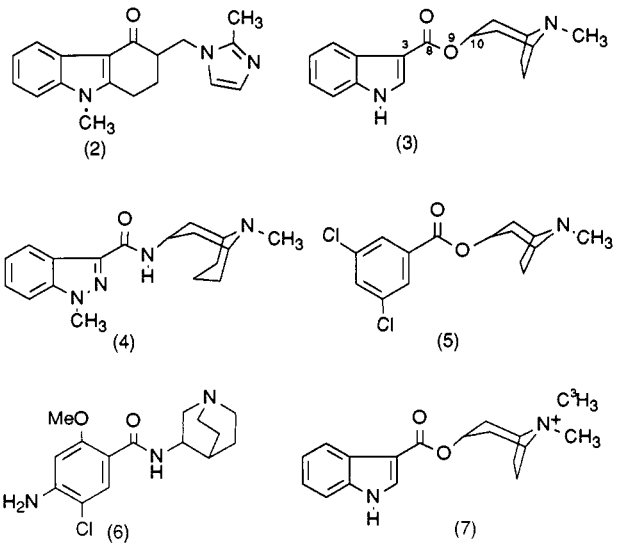
Serotonin (5-HT) (**1a**) has been shown to be a neurotransmitter involved in a wide range of pharmacological effects, and characterization of multiple 5-HT receptors has given impetus to the search for novel subtype-selective 5-HT ligands. 5-HT receptors can be broadly classified into four types (5-HT$_1$, 5-HT$_2$, 5-HT$_3$, and 5-HT$_4$).[1a-d] While the 5-HT$_2$ receptor population appears homogeneous, there is ample evidence for heterogeneity within 5-HT$_1$ (5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, 5-HT$_{1D}$);[1c] recent evidence also suggests that there may be heterogeneity within 5-HT$_3$ receptors.[2] A number of 5-HT$_3$ antagonists have been reported (GR 38032F (**2**),[3] ICS 205-930 (**3**),[2] BRL 43694 (**4**),[4] MDL 72222 (**5**),[5] zacopride (**6**)[6] (Chart I), and these compounds have shown activity in models thought to be predictive of therapeutic roles in the control of cancer chemotherapy-induced emesis,[7,8] migraine,[9] schizophrenia,[10] and anxiety.[11] However, to date the clinical efficacy of 5-HT$_3$ antagonists in all but the first indication remains unproven.

A program of molecular modeling based on structures of known 5-HT$_3$ antagonists (**2–6**) was initiated to define the pharmacophore of the 5-HT$_3$ antagonist binding site. When undertaking such a program it is desirable to choose the most rigid member of the group of ligands under investigation as the reference molecule. However, since the known 5-HT$_3$ antagonists have at least two rotatable bonds, it was necessary to consider all reasonable low-energy conformers within 2–3 kcal of the global energy minima. The technique adopted to investigate the conformational properties of these molecules is illustrated by reference to ICS 205-930 (**3**) using the MACROMODEL[12] program. First the structure was built and the bond angles and lengths idealized; sequential 30° increment rotations about each of the three rotatable bonds (C3-C8, C8-O9, O9-C10) (Chart I) generated a number of conformations which were then independently minimized using the MM2 force field[13] with block diagonal Newton–Raphson minimization. As a result four minimum-energy conformations were identified (Table I); apart from the two rotamers about the conjugated ester linkage, there are only two reasonable conformations, which correspond to rotations of ±50° about the O9-C10 bond and are thus mirror images of each other. However, some flexibility of these precise conformations is possible, since rotation of up to 20° about the O9-C10 bond incurs a penalty of less than 2 kcal mol$^{-1}$.

**Chart I.** Structures of 5-HT$_3$ Receptor Ligands



(1a); R = H, X = NH$_2$
(1b); R = CH$_3$, X = NH$_2$
(1c); R = H, X = $^+$NMe$_3$ X$^-$



(2) (3) (4) (5) (6) (7)

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§ Department of Biophysical Chemistry, Rahway, New Jersey.

(1) (a) Richardson, B. P.; Engel, G. The Pharmacology and Functions of 5-HT$_3$ Receptors. *Trends Neurosci.* **1986**, *9*, 424–428. (b) *Serotonin: Actions, Receptors, Pathophysiology; Proceedings of the 1987 IUPHAR Congress Satellite Meeting, Heron Island, Australia*; Mylecharane, E. J., de la Lande, I. S., Angus, J. A., Humphrey, P. P. A., Eds.; MacMillan: London, 1987. (c) Peroutka, S. J. 5-Hydroxytryptamine Receptor Subtypes: Molecular, Biochemical, and Physiological Characterisation. *Trends Neurosci.* **1988**, *11*, 496–500. (d) Clarke, D. E.; Craig, D. A.; Fozard, J. R. The 5-HT$_4$ Receptor: Naughty but Nice. *Trends Pharmacol. Sci.* **1989**, *10*, 385–386.
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(3) Butler, A.; Hill, J. M.; Ireland, S. J.; Jordan, C. C.; Tyers, M. B. Pharmacological Properties of GR38032F, a Novel Antagonist at 5-HT$_3$ Receptors. *Br. J. Pharmacol.* **1988**, *94*, 397–412.

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**Table I.** Conformational Analysis of ICS 205-930 (**3**)

| conformer | dihedral angle,[a] deg | | | energy, kcal/mol |
|---|---|---|---|---|
| | C3–C8 | C8–O9 | O9–C10 | |
| 1 | −2.6 | 1.6 | −49.7 | 38.41 |
| 2 | 2.9 | −1.8 | 49.9 | 38.41 |
| 3 | −169.9 | −1.2 | −50.0 | 38.98 |
| 4 | −169.9 | 0.8 | 50.2 | 38.98 |

[a] For numbering, see Chart I.

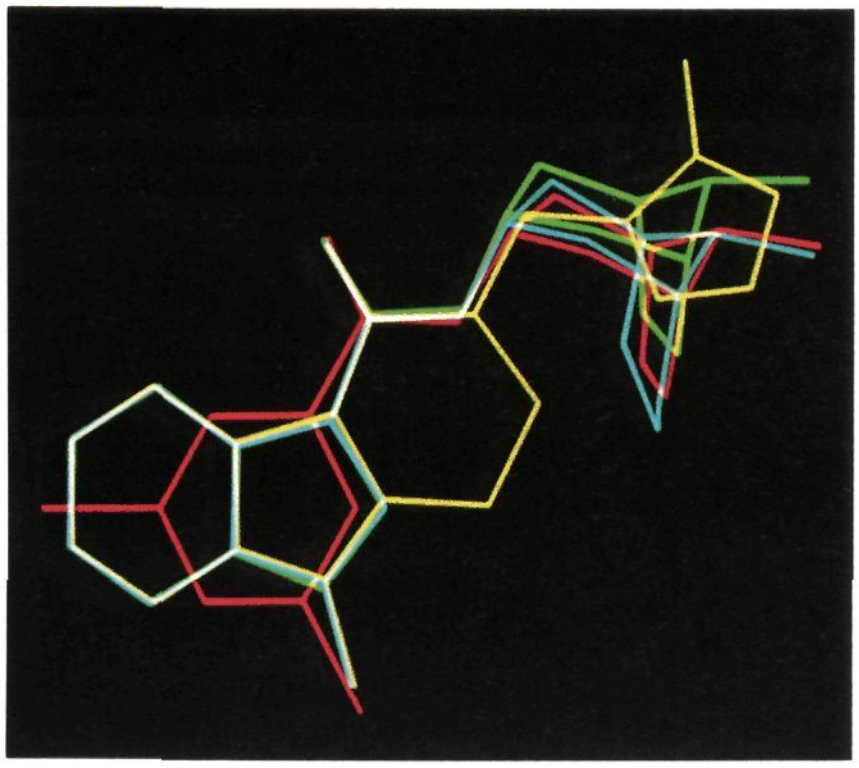


**Figure 1.** Superimposition of ICS 205-930 (**3**) (green), GR 38032F (**2**) (yellow), BRL 43694 (**4**) (blue), and MDL 72222 (**5**) (red).

Each of the 5-$HT_3$ antagonists was then treated analogously with similar results, except in the case of GR 38032F (**2**), where two groups of low-energy conformers of the cyclohexenone ring were identified, one in which the side-chain adopts a pseudoaxial position, the other where the side chain adopts a pseudoequatorial position. Each of the fully minimized low-energy conformations was then compared with all the conformers identified for each of the known ligands. Superimpositions were attempted using the least-squares fitting routine within CHEMX,[14] the important common atoms for GR 38032F (**2**), ICS 205-930 (**3**), and BRL 43694 (**4**) were assumed to be a dummy atom at the center of the benzene ring, C3 of the indole or indazole ring, and both the carbon and oxygen of the carbonyl group. For MDL 72222 (**5**) the atoms chosen for this superimposition were the carbon and both oxygens of the ester linkage and the nitrogen of the tropane. The choice of these atoms was based on electrostatic modeling of the appropriate indole amides and esters and the SAR observed in a series of indole oxadiazoles[15] in which the heteroatoms were thought to be involved in hydrogen-bonding interactions. The result of this superimposition is shown (Figures 1 and 2); none of the low-energy conformers of GR 38032F (**2**) having a pseudoaxial side chain on the cyclohexenone ring gave satisfactory fits (Figure 2).

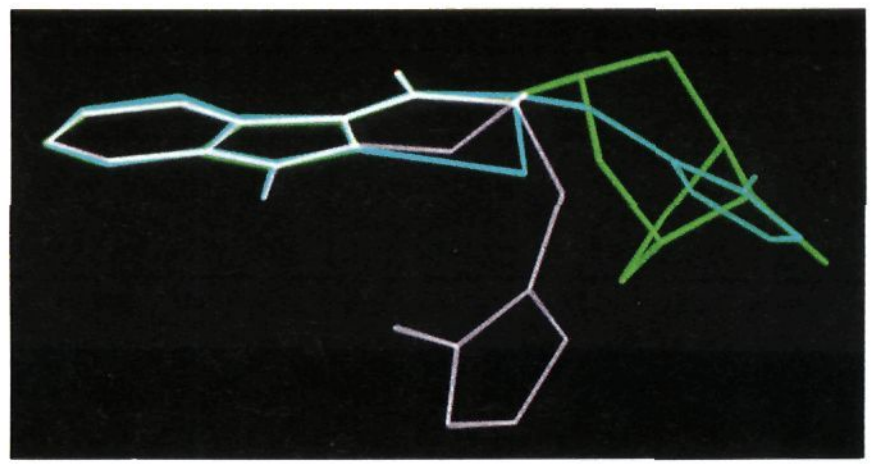
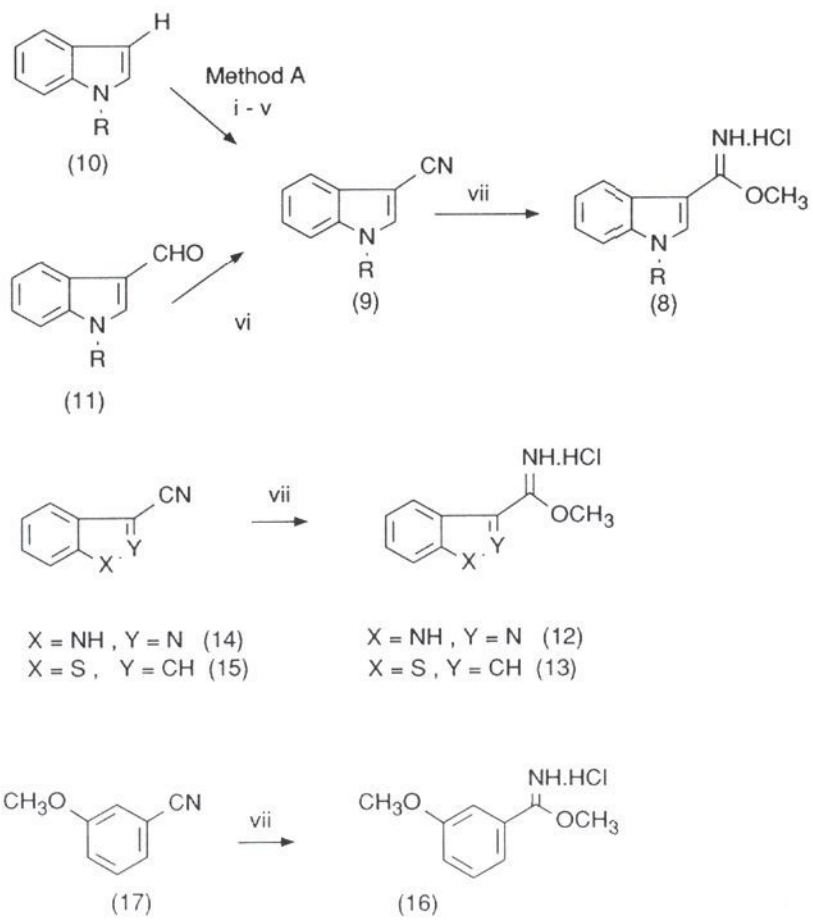


**Figure 2.** Superimposition of ICS 205-930 (**3**) (green) with equatorial (blue) and axial (purple) side-chain conformers of GR 38032F (**2**).

**Scheme I**[a]




[a] Reagents: (i) TFAA; (ii) NaOH, reflux; (iii) $(COCl)_2$, THF; (iv) $NH_3$; (v) TFAA, dioxane; (vi) KCN, $(NH_4)H_2PO_4$; (vii) MeOH, HCl.

(4) Sanger, G. J.; Nelson, D. R. Selective and Functional 5-Hydroxytryptamine$_3$ Receptor Antagonism by BRL 43694 (granisetron). *Eur. J. Pharmacol.* **1989**, *159*, 113–124.
(5) Fozard, J. R. MDL 72222: A Potent and Highly Selective Antagonist at Neuronal 5-Hydroxytryptamine Receptors. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1984**, *326*, 36–44.
(6) Smith, W. W.; Sancilio, L. F.; Owera-Atepo, J. B.; Naylor, R. J.; Lamberg, L. Zacopride, a Potent 5-$HT_3$ Antagonist. *J. Pharm. Pharmacol.* **1988**, *40*, 301–302.
(7) Leibundgut, U.; Lancranjan, I. First Results with ICS 205-930 (5-$HT_3$ Receptor Antagonist) in Prevention of Chemotherapy-Induced Emesis. *Lancet* **1987**, *i*, 1198.
(8) Andrews, P. L. R.; Rapeport, W. G.; Sanger, G. J. Neuropharmacology of Emesis Induced by anti-Cancer Therapy. *Trends Pharmacol. Sci.* **1988**, *9*, 334–341.
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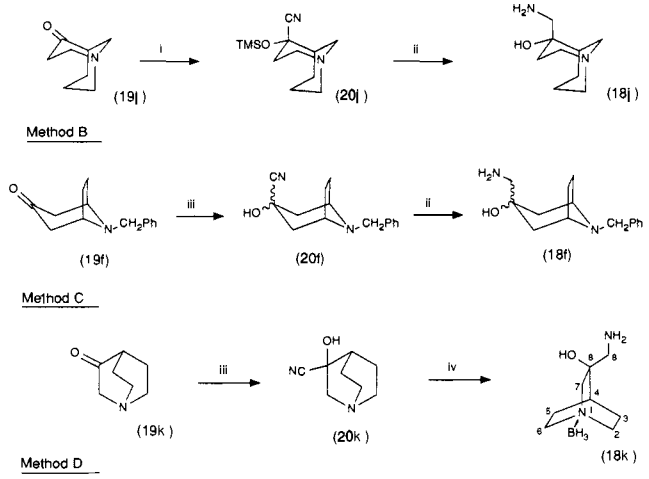
(10) Costall, B.; Domeney, A. M.; Naylor, R. J.; Tyers, M. B. Effects of the 5-$HT_3$ Receptor Antagonist, GR 38032F, on Raised Dopaminergic Activity in the Mesolimbic System of the Rat and Marmoset Brain. *Br. J. Pharmacol.* **1987**, *92*, 881–894.
(11) Jones, B. J.; Costall, B.; Domeney, A. M.; Kelly, M. E.; Naylor, R. J.; Oakley, N. R.; Tyers, M. B. The Potential Anxiolytic Activity of GR 38032F, a 5-$HT_3$-Receptor Antagonist. *Br. J. Pharmacol.* **1988**, *93*, 985–993.
(12) Still, C. MACROMODEL; Columbia University: New York.
(13) Allinger, N. L. Conformational Analysis. 130. MM2. A Hydrocarbon Force Field Utilizing $V_1$ and $V_2$ Torsional Terms. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(14) CHEMX; Chemical Design Ltd.: Oxford, U.K.
(15) Swain, C. J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G.; Beer, M.; Stanton, J.; Watling, K. J. Novel 5-$HT_3$ Antagonists. Indole Oxadiazoles. *J. Med. Chem.* **1991**, *34*, 140–151.

**Scheme II**[a]




[a] Reagents: (i) TMSCN, $ZnI_2$, $(CH_2Cl)_2$; (ii) $LiAlH_4$, THF; (iii) HCl, NaCN; (iv) $BH_3$·THF.

This analysis demonstrates several common structural features among this group of 5-$HT_3$ antagonists. The superimposition (Figure 1) places all of the basic nitrogens in the same region of space, and notably places the methyl substituent on the imidazole of GR 38032F (**2**) in a position that might be occupied by a quaternary methyl analogue of ICS 205-930 (**3**). This observation together with the ease of synthesis and favorable physicochemical properties led to the use of [$^3$H]Q-ICS 205-930 (**7**)[16] as a selective radioligand for the 5-$HT_3$ recognition site. The superimposition emphasizes three features that may contribute toward binding: an aromatic, lipophilic, or $\pi$-stacking interaction, a hydrogen bond to the acyl functionality, and an electrostatic interaction with the basic nitrogen. Using this model it is possible to design novel ligands which accommodate all of these features within a rigid framework.

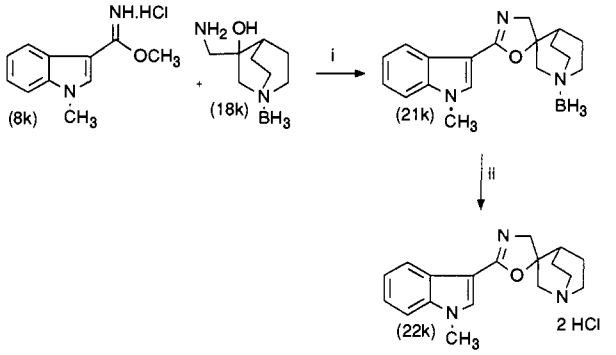
This paper describes the synthesis, receptor binding properties, and molecular modeling studies of a series of indole oxazolines spirofused to an azacyclic ring. By virtue of the spiro center the relative positions of the key pharmacophoric elements can be precisely defined and modified to provide novel ligands for the 5-$HT_3$ receptor that could critically probe the issue of heterogeneity.

## Results

**Synthetic Chemistry.** A general procedure was used to prepare all of the compounds described; this involved the reaction of an imino ether hydrochloride with a 1,2-amino alcohol. The indole-substituted imino ethers **8** were prepared from the corresponding indole-3-carbonitriles **9** according to Scheme I. Nitriles **9** were prepared from parent indoles **10** (method A) or from the corresponding indole-3-carboxaldehydes **11** where available. Methyl indazole-3-carboximidate (**12**) and methyl benzo[*b*]thiophen-3-ylimidate (**13**) were prepared from the corresponding nitriles **14** and **15** obtained via literature procedures.[17] Methyl 3-methoxybenzenecarboximidate (**16**) was prepared from 3-methoxybenzonitrile (**17**) (Scheme I).

1,2-Amino alcohols **18** were obtained from the appropriate ketones **19** by one of three general methods: Method B is illustrated in Scheme II for the synthesis of **18j** in which ketone **19j** was treated with trimethylsilyl cyanide, yielding the TMS-protected cyanohydrin **20j**; subsequent reduction with lithium aluminium hydride afforded amino alcohol **18j**. Method C is illustrated by the reaction of ketone **19f** with potassium cyanide, giving cyanohydrin **20f**, and subsequent reduction with lithium aluminium hydride provided amino alcohol **18f** (Scheme II). Method D is illustrated by the reaction of ketone **19k** with potassium cyanide to form cyanohydrin **20k**, subsequent reduction with borane–tetrahydrofuran complex afforded the borane complex of amino alcohol **18k** (Scheme II).

**Scheme III**[a]




[a] Reagents: (i) MeOH, reflux; (ii) MeOH, HCl.

**Table II.** Displacement of [$^3$H]Q-ICS 205-930 (**7**) Binding to 5-$HT_3$ Recognition Sites in Rat Brain Membranes by Known 5-$HT_3$ Antagonists

| no. | name | $pIC_{50} \pm SD$[a] |
|---|---|---|
| **1b** | 2-methyl-5-HT | 6.19 ± 0.07 |
| **2** | GR 38032F | 8.71 ± 0.24 |
| **3** | ICS 205-930 | 8.90 ± 0.25 |
| **5** | MDL 72222 | 7.66 ± 0.39 |

[a] SD, standard deviation from $n \geq 3$.

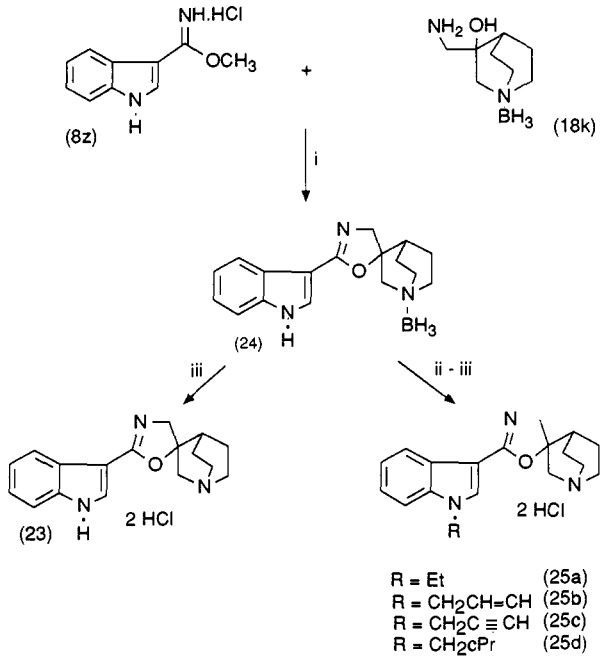
The key spirofused oxazoline ring was generated by the general reaction of an imino ether hydrochloride with the appropriate 1,2-amino alcohol. This is illustrated schematically for the synthesis of oxazoline **22k** (Scheme III). Heating a methanolic solution of imino ether **8k** and the borane-protected amino alcohol **18k** at reflux afforded oxazoline **21k** in good yield. Treatment with methanolic hydrogen chloride removed the borane protection and afforded **22k** as the dihydrochloride salt. Compounds **22a,b,d,f,h–j** (Table III) were prepared in a similar manner. Catalytic hydrogenation of **22f** afforded the secondary amine **22g**. Treatment of **22b,d,l,m** with excess methyl iodide in acetone at reflux gave quaternary salts **22c,e,n,o** (Table III). *N*-Oxide **22p** was prepared from **22k** by oxidation using 3-chloroperoxybenzoic acid. Analogue **23**, unsubstituted at the indole nitrogen, was prepared from the reaction of methyl indole-3-carboximidate (**8z**) with the borane-protected amino alcohol **18k** in methanol at reflux. This afforded the borane complex **24** which was deprotected by treatment with methanolic hydrogen chloride (Scheme IV). Treatment of borane complex **24** with sodium hydride and subsequent reaction with a variety of electrophiles allowed regioselective alkylation of the indole nitrogen (N1). Use of the borane complex avoided reaction at the highly nucleophilic nitrogen of the azabicycle. The azabicyclic nitrogen was then deprotected with methanolic hydrogen chloride to give **25a–d** (Table IV).

It is known that oxazolines direct metalation to the ortho position of an aromatic ring and this fact was exploited in the preparation of the substituted analogues **26a–c** (Scheme V). Treatment of **22k** with 2 equiv of *t*-BuLi yielded regiospecific lithiation at C2. Subsequent reaction

(16) *The Peripheral Actions of 5-Hydroxytryptamine*; Fozard, J. R., Ed.; Oxford University Press: New York, 1989.

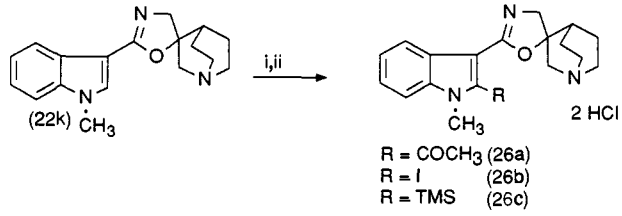
(17) Watling, K. J.; Aspley, S.; Swain, C. J.; Saunders J. [$^3$H]Quaternised ICS 205-930 Labels 5-$HT_3$ Receptor Binding Sites in Rat Brain. *Eur. J. Pharmacol.* **1988**, *149*, 397–398.

**Scheme IV**[a]




[a] Reagents: (i) MeOH, reflux; (ii) NaH, RX, THF; (iii) MeOH, HCl.

**Scheme V**[a]



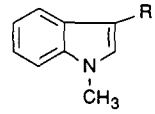

[a] Reagents: (i) *t*-BuLi (2 equiv), $Ac_2O$ (**26a**), $I_2$ (**26b**), TMSCl (**26c**); (ii) MeOH, HCl.

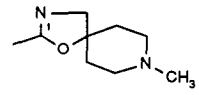
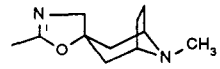
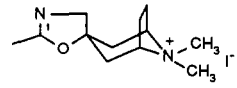
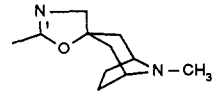
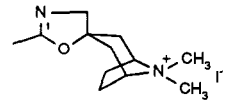
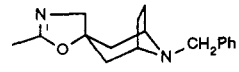
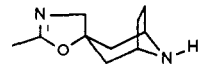
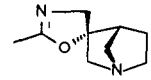
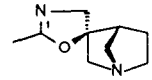
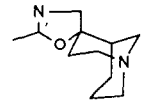
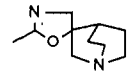
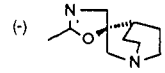
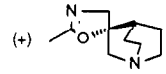
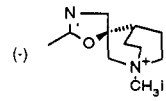
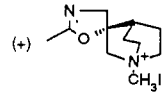
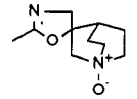
with a variety of electrophiles afforded the substituted products **26a–c** (Table IV). The 5- and 7-substituted indoles **27–29**, **31**, and **33** were prepared by the reaction of the appropriate imino ethers with the borane-protected amino alcohol **18k** in methanol at reflux. Catalytic reduction of 5-nitro derivative **29** gave 5-amino derivative **30**. 5-Methoxy analogue **31** was deprotected with boron tribromide to give 5-hydroxyindole **32**. The benzo[*b*]-thiophene (**34**), indazole (**35**), and 3-methoxyphenyl (**36**) derivatives were prepared from the reaction of imino ethers **12**, **13**, and **16**, respectively with amino alcohol **18k** according to the example illustrated in Scheme III.

The racemic spiro quinuclidine **22k** was resolved by preparation of the diastereomeric salts using *O,O'*-dibenzoyl-D-tartrate, followed by fractional crystallization to constant rotation. (+)-*O,O'*-Dibenzoyl-D-tartrate afforded **22l** after liberation of the free base and conversion to the dihydrochloride salt; similarly (−)-*O,O'*-dibenzoyl-D-tartrate afforded **22m** after liberation of the free base and conversion to the dihydrochloride salt.

**X-ray Crystallography.** The resolved enantiomer **22l** crystallizes as the (+)-*O,O'*-dibenzoyl-D-tartrate acid salt with two ions of $[C_{18}H_{22}N_3O]^+$ for each doubly charged tartrate molecule. Interestingly, the cation is observed as two rotational isomers (Figure 3), one with the oxazoline ring oriented such that N2 is trans to C17 (extended rotamer) and the other where these atoms are cis. The bond distances and angles within the ions are all within the normal ranges for such bonds (selected interatomic distances and angles are presented in Table V and a full

**Table III.** Displacement of [$^3$H]Q-ICS 205–930 (**7**) Binding to 5-$HT_3$ Recognition Sites in Rat Brain Membranes by Indole Oxazolines



| no. | R | mp, °C | method[c] | $pIC_{50}$ ± SEM[d] |
|---|---|---|---|---|
| **22a** |  | 238–240[a] | D | 6.80 |
| **22b** |  | 252–253[a] | B | 8.34 ± 0.03 |
| **22c** |  | 253–254 | | 8.30 |
| **22d** |  | 209–210[b] | B | 8.20 |
| **22e** |  | 252–253 | | 8.48 |
| **22f** |  | 185–187[a] | C | 6.76 |
| **22g** |  | 196–198[a] | | 7.95 ± 0.06 |
| **22h** |  | 215–217[a] | D | 8.46 |
| **22i** |  | 258–260[a] | D | 8.51 |
| **22j** |  | 259–261[a] | B | 8.95 |
| **22k** |  | 264–265[a] | D | 8.50 ± 0.07 |
| **22l** | (-)  | 261–262[a] | | 8.54 ± 0.04 |
| **22m** | (+)  | 261–262[a] | | 8.59 ± 0.28 |
| **22n** | (-)  | 198–200 | | 7.37 ± 0.08 |
| **22o** | (+)  | >150 | | 7.99 ± 0.14 |
| **22p** |  | 177–180 | | 5.58 |

[a] Salt formed with methanolic hydrogen chloride. [b] Salt formed with ethereal oxalic acid. [c] Methods B, C, D refer to the preparation of the 1,2-amino alcohols and are illustrated in Scheme II. [d] SEM, standard error of the mean from $n \geq 3$; when SEM is not quoted, the figures are the mean of two independent determinations, typically with individual values ±10% of the mean.

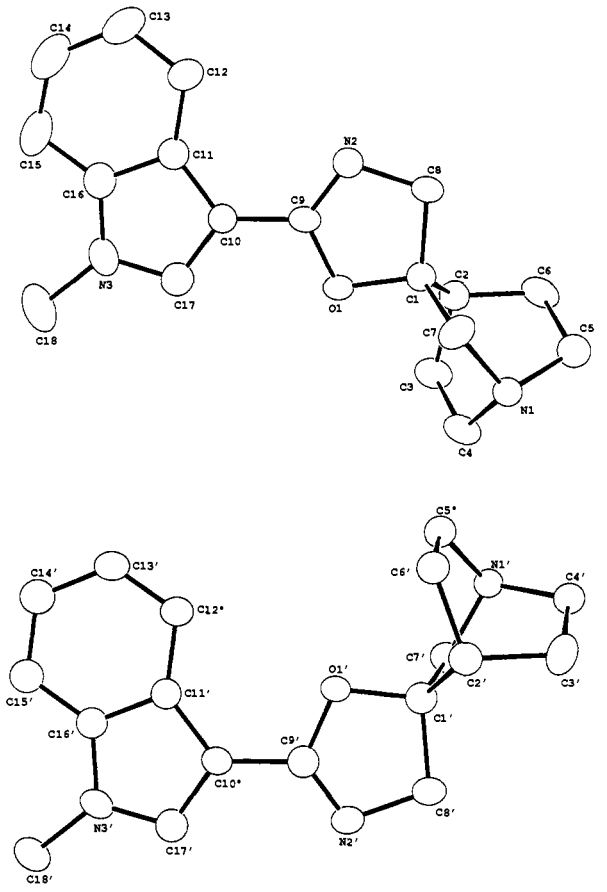



**Figure 3.** Perspective view of the two rotamers present in the crystal structure of 22l showing the crystallographic numbering scheme. Rotamer 1 (the extended form) has atom labels without primes while the folded form (rotamer 2) has primed labels. The atoms are drawn as 20% probability ellipsoids and the H atoms have been omitted for clarity. The depicted relationship between the two molecules is arbitrary and does not represent the crystallographic orientation.

listing is available as supplementary material). The two conformers of the base have differences in some bond lengths presumably related to the difference in orientation of the substituted oxazoline with respect to the indole. For instance, as a result of the differing degrees of delocalization the C9–C10 [1.441 (8) and 1.469 (8) Å] distance is significantly shorter (2.5$\sigma$) in one conformer than the other. Differences in the bond lengths associated with the bicyclic quinuclidine ring are harder to rationalize but are presumably the result of different environments of this moiety. In the crystal the two basic molecules interact electrostatically with the tartrate. The geometrical nature of this interaction is shown in Figure 4. That each N is strongly interacting with only one O atom of the two in each carboxylate is shown by the asymmetry in the N–O distances and in the C=O and C–O distances within the carboxylate groups (Table V). Besides the interactions between the ions there appears to be nothing other than normal van der Waals forces between molecules in a unit cell. Since the absolute stereochemistry of (+)-*O,O'*-dibenzoyl-D-tartrate is known the stereochemistry of the spirocenter of the indole oxazoline was determined to be *R*.

**NMR Studies.** The novel ligands described in this paper accommodate within a rigid framework three elements that may be important for receptor binding: an aromatic group, a hydrogen-bond-accepting group and a basic nitrogen. The precise conformation of the azabicyclic ring will control the relative positions of the aromatic group

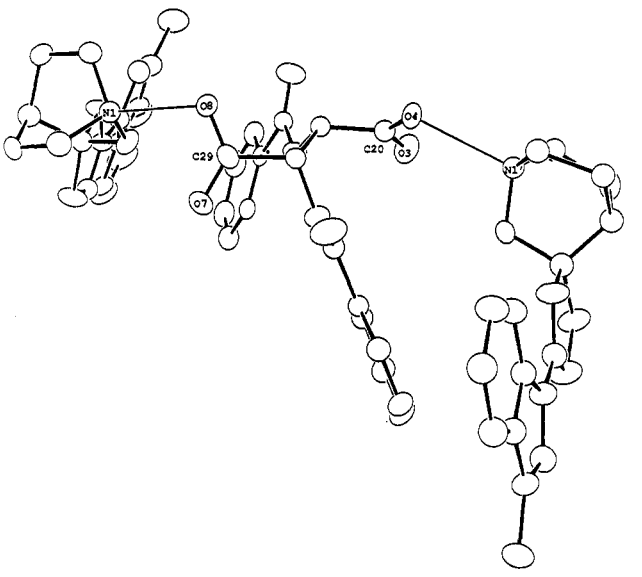
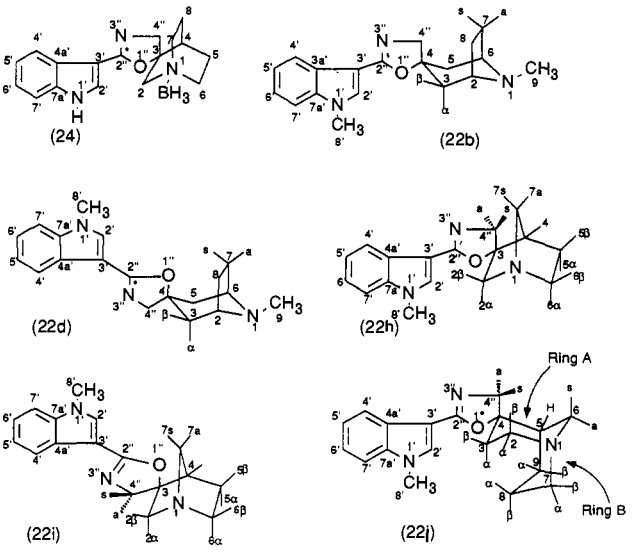



**Figure 4.** A perspective view of the interaction between the tartrate anion and the two independent cations of 22l. The two hydrogen bonds between N1 and O8 and N1′ and O4 are shown as thin lines.

**Chart II.** Structures and Numbering Schemes of Selected Compounds Used in NMR Analysis

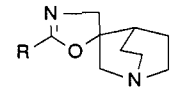


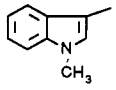
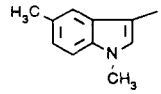
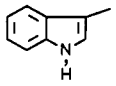
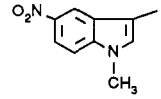
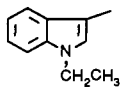
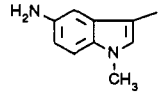
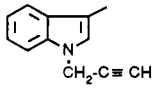
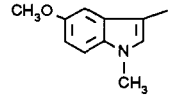
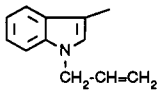
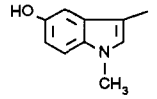
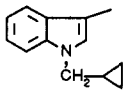
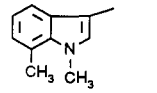
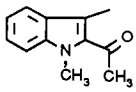
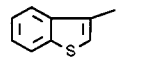
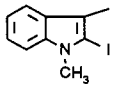
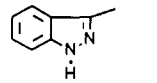
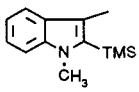
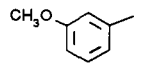
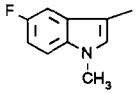

and the basic nitrogen. In order to include these ligands in molecular modeling studies we felt it was necessary to determine the conformation of the various azabicyclic ring systems in solution. Detailed NMR studies were performed to establish the relative stereochemistry at the spiro center and the conformation of the azabicyclic rings. NMR studies also confirmed the site of borane complexation in some of the intermediates used in the synthetic section.

The site of borane complexation in **18k** (Scheme II) was established from a detailed analysis of the $^1H$ and $^{13}C$ NMR data of **18k** and the corresponding free base and unambiguous assignment by COSY and HCCOSY, which revealed a downfield shift of ca. 6 ppm for C6 and C7 and ca. 4 ppm for C2, while C3 and C9 were only slightly perturbed. This is consistent with borane-complex formation with the quinuclidine nitrogen. Similar downfield shifts were seen for C2 (ca. 2 ppm) and C6 and C7 (ca. 6 ppm) of the borane complex **24** (Chart II).

Examination of the 1-D and 2-D (COSY-45) $^1H$ NMR data for the [2.2.1] azabicycles **22h** and **22i** gave a complete and unambiguous assignment of all protons (see Chart II

**Table IV.** Displacement of [$^3$H]Q-ICS 205-930 (7) Binding to 5-HT$_3$ Recognition Sites in Rat Brain Membranes by Substituted Aryloxazolines



| no. | R | mp, °C | pIC$_{50}$ ± SEM[c] | no. | R | mp, °C | pIC$_{50}$ ± SEM[c] |
|---|---|---|---|---|---|---|---|
| **22k** |  | 264–265[a] | 8.50 ± 0.07 | **28** |  | 242–243[a] | 6.88 ± 0.10 |
| **23** |  | 220–222[a] | 8.32 | **29** |  | 245–250[a] | 6.64 |
| **25a** |  | 260 dec[a] | 7.87 ± 0.14 | **30** |  | 260 dec[a] | 6.24 |
| **25b** |  | 200–202[a] | 8.21 ± 0.17 | **31** |  | 210–214[a] | 6.58 |
| **25c** |  | 215–217[a] | 8.10 | **32** |  | 215 dec[a] | 6.71 ± 0.05 |
| **25d** |  | 199–200[a] | 7.88 | **33** |  | 204–206[a] | 8.05 ± 0.10 |
| **26a** |  | 206 dec[a] | 8.19 | **34** |  | 167–170[a] | 7.57 |
| **26b** |  | 188 dec[a] | 7.57 | **35** |  | 187–189[a] | 7.58 |
| **26c** |  | 202–204[a] | 6.81 | **36** |  | 239–240[a] | 6.39 |
| **27** |  | 175–178[b] | 7.83 | | | | |

[a] Salt formed with methanolic hydrogen chloride. [b] Salt formed with ethereal oxalic acid. [c] SEM, standard error of the mean from $n \geq 3$; when SEM is not quoted, the figures are the mean of two independent determinations, typically with individual values ±10% of the mean.

for numbering). The presence of an oxazoline ring was inferred from the appearance of a characteristic AB system: two sharp doublets for H4″a and H4″s at δ 4.28/4.52 and δ 4.41/4.58. Stereochemical assignment of the resonances associated with the protons of the azabicyclic system depended on $^4J$ couplings between trans antiperiplanar protons. These were identified in **22h** and **22i** between H2α and H7a, H2β and H6β, H5α and H7s, and also H6α and H7s. The relative stereochemistry at the spiro carbon (C3) was then determined from NOE data derived by irradiation of the oxazoline methylene protons H4″a and H4″s and the azabicyclic protons H5α and H5β (Table VI).

The stereochemistry at the spiro carbon (C4) of tropane **22b** was demonstrated by an NOE experiment (see Chart II for numbering). Irradiation of H4″ resulted in enhancements at H7s, H8s, H3β, and H5β, which also confirmed that the six-membered ring was in a chair conformation. Similarly, irradiation of epimeric tropane **22d** at H4″ resulted in enhancements at H3α, H3β, H5α, and H5β, consistent with the other epimer at the spiro carbon (C4) and a chair conformation for the six-membered ring.

Analysis of the $^1$H NMR and COSY data provided a complete assignment for the [3.3.1] azabicyclic compound **22j** (see Chart II for numbering). The relative stereochemistry at the spiro carbon (C4) and the stereochemical assignment of H4″a/H4″s were determined from 1-D NOE and NOESY data as follows: irradiation of H4″a resulted in enhancements at H4″s, H5, and H6s; similarly irradiation of H4″s enhances H4″a, H2β, H3β, and H6s. This data and the observation that H2α and H6a are trans-antiperiplanar ($^4J_{2\alpha,6a}$) defines a chair conformation for ring A. The presence of a long-range coupling ($^4J$) between H6s and H9α suggests that ring β also has a chair conformation; this is confirmed by an NOE (NOESY) between H9α (equatorial) and H4$^1$ of the indole, consistent with a chair conformation for both rings A and B.

**Biology.** The affinity of each of the new compounds (**22a–p, 23, 25a–d, 26a–c, 27–36**) for the 5-HT$_3$ antagonist binding site in rat cortical membranes was measured by its ability to displace the specific binding of the radiolabeled antagonist [$^3$H]Q-ICS 205-930 (**7**)[17] (Tables III and IV). The affinities of a number of representative known ligands are shown (Table II). All compounds displaced the radioligand with a mass action profile and a Hill coefficient close to unity. All compounds behaved as antagonists in a variety of pharmacological models (von Bezold–Jarisch reflex, isolated rabbit heart, rat vagus nerve, and rat su-

Table V. Selected Interatomic Distances (Å) and Angles (deg)[a]

| | | | |
|---|---|---|---|
| O1–C1 | 1.446 (7) | N1′–C4′ | 1.477 (6) |
| O1–C9 | 1.369 (7) | N1′–C5′ | 1.489 (7) |
| N1–C4 | 1.482 (7) | N1′–C7′ | 1.489 (7) |
| N1–C5 | 1.499 (7) | N2′–C8′ | 1.448 (8) |
| N1–C7 | 1.475 (7) | N2′–C9′ | 1.256 (8) |
| N2–C8 | 1.445 (8) | C1′–C2′ | 1.502 (8) |
| N2–C9 | 1.271 (7) | C1′–C7′ | 1.511 (8) |
| C1–C2 | 1.514 (8) | C1′–C8′ | 1.573 (9) |
| C1–C7 | 1.526 (8) | C2′–C3′ | 1.558 (8) |
| C1–C8 | 1.561 (9) | C2′–C6′ | 1.547 (9) |
| C2–C3 | 1.534 (9) | C3′–C4′ | 1.528 (8) |
| C2–C6 | 1.523 (8) | C5′–C6′ | 1.539 (8) |
| C3–C4 | 1.516 (9) | C9′–C10′ | 1.469 (8) |
| C5–C6 | 1.482 (9) | O3–C20 | 1.226 (7) |
| C9–C10 | 1.441 (8) | O4–C20 | 1.267 (7) |
| O1′–C1′ | 1.443 (7) | O7–C29 | 1.232 (7) |
| O1′–C9′ | 1.361 (7) | O8–C29 | 1.255 (7) |
| C1–O1–C9 | 107.1 (4) | C4′–N1′–C5′ | 110.1 (4) |
| N1′–O4–C20 | 110.7 (3) | C4′–N1′–C7′ | 108.6 (4) |
| N1–O8–C29 | 107.6 (3) | C5′–N1′–C7′ | 110.2 (4) |
| C4–N1–C5 | 107.6 (5) | C8′–N2′–C9′ | 107.6 (6) |
| C4–N1–C7 | 111.6 (4) | C16′–N3′–C17′ | 108.3 (5) |
| C5–N1–C7 | 108.7 (5) | C16′–N3′–C18′ | 124.4 (6) |
| C8–N2–C9 | 107.1 (5) | C17′–N3′–C18′ | 127.3 (6) |
| O1–C1–C2 | 110.2 | O1′–C1′–C2′ | 109.7 (5) |
| O1–C1–C7 | 108.8 (5) | O1′–C1′–C7′ | 108.5 (5) |
| O1–C1–C8 | 102.1 (5) | O1′–C1′–C8′ | 101.6 (5) |
| C2–C1–C7 | 108.5 (5) | C2′–C1′–C7′ | 108.4 (5) |
| C2–C1–C8 | 114.0 (5) | C2′–C1′–C8′ | 114.5 (6) |
| C7–C1–C8 | 113.1 (5) | C7′–C1′–C8′ | 113.9 (5) |
| C1–C2–C3 | 109.1 (5) | C1′–C2′–C3′ | 108.8 (5) |
| C1–C2–C6 | 107.7 (5) | C1′–C2′–C6′ | 110.0 (5) |
| C3–C2–C6 | 108.0 (6) | C3′–C2′–C6′ | 108.0 (5) |
| C2–C3–C4 | 108.7 (5) | C2′–C3′–C4′ | 108.0 (4) |
| N1–C4–C3 | 111.0 (5) | N1′–C4′–C3′ | 109.8 (4) |
| N1–C5–C6 | 109.5 (5) | N1′–C5′–C6′ | 110.3 (5) |
| C2–C6–C5 | 111.4 (5) | C2′–C6′–C5′ | 106.8 (5) |
| N1–C7–C1 | 111.1 (4) | N1′–C7′–C1′ | 110.4 (5) |
| N2–C8–C1 | 106.0 (5) | N2′–C8′–C1′ | 105.0 (5) |
| O1–C9–N2 | 117.7 (5) | O1′–C9′–N2′ | 117.9 (5) |
| O1–C9–C10 | 116.3 (5) | O1′–C9′–C10′ | 113.7 (6) |
| N2–C9–C10 | 126.0 (6) | N2′–C9′–C10′ | 128.4 (6) |
| C1′–O1′–C9′ | 107.4 (5) | | |

[a] Values in parentheses are the estimated deviations in the least-significant digit(s).

Table VI. NOE Data for **22h** and **22i**[a]

| no. | irradiate | NOE observed at |
|---|---|---|
| **22h** | H4″s | H4″a |
| | H4″a | H4″s, H4 |
| | H5α | H4, H5β |
| | H5β | H4, H5α, H7a |
| **22i** | H4″s | H4″a |
| | H4″a | H4″s, H4, H5α |
| | H5α | H4″a, H5β, H6α |
| | H5β | H4, H5α, H6β |

[a] See Chart II for numbering.

perior cervical ganglion), the results of which will be reported separately.

## Discussion

**Structure–Activity Relationships.** As described in the introduction the key pharmacophoric elements of the known 5-$HT_3$ ligands are a lipophilic binding region and an electrostatic interaction with a charged nitrogen; these are linked by an acyl functionality. It has previously been shown that the acyl group may be replaced with a heterocyclic linking group containing at least one H-bond acceptor.[15] In this investigation an oxazoline acted as the H-bond-acceptor group and the spirofusion served to constrain the relative positions of the H-bond acceptor and the basic nitrogen of the azacycle. The importance of constraining the basic nitrogen within an azabicyclic system has previously been demonstrated[15,16] and is underlined by the comparison of the monocyclic piperidine (**22a**, $pIC_{50}$ = 6.80) with a variety of azabicyclic systems (**22b–p**) (Table III). The environment of the nitrogen within the azabicycle had a small but significant effect on affinity; tertiary amines were slightly more potent than the corresponding secondary amines (compare **22g**, $pIC_{50}$ = 7.95, and **22b**, $pIC_{50}$ = 8.34). However, large groups on nitrogen reduced affinity (**22f**, $pIC_{50}$ = 6.76). The highest affinity was observed for those compounds in which the basic nitrogen occupies a bridgehead position (**22h–k**), allowing maximal electrostatic interaction combined with minimal steric demand. The most potent analogue in this group is the [3.3.1] system (**22j**, $pIC_{50}$ = 8.95), which suggests that lipophilic interactions may play a significant role in increasing affinity. Interestingly, both enantiomers of the quinuclidine [2.2.2] system were of comparable potency (**22l**, $pIC_{50}$ = 8.54, and **22m**, $pIC_{50}$ = 8.59), suggesting that the preferred position for the basic nitrogen would be coplanar with the aromatic ring. Quaternization resulted in a small reduction in affinity and also served to highlight some stereoselectivity in binding (**22n**, $pIC_{50}$ = 7.37, and **22o**, $pIC_{50}$ = 7.99). Oxidation of the azabicycle to produce amine oxide **22p** dramatically reduced activity ($pIC_{50}$ = 5.58). Interestingly, both isomers of the tropane system (**22b** and **22d**) show similar affinity, this is in contrast to the axial preference for ICS 205-930 (**3**).

As was demonstrated in the indole oxadiazole series,[15] steric constraints restrict substitution in the indole ring although there is some bulk tolerance at the 1- and 2-positions (Table IV). 1-Propargyl (**25b**, $pIC_{50}$ = 8.21) was accommodated but the increased steric demand of the cyclopropylmethyl derivative reduced affinity (**25d**, $pIC_{50}$ = 7.88). A methyl ketone substituent (**26a**, $pIC_{50}$ = 8.19) was accommodated at the 2-position but the bulky trimethylsilyl group was much less active (**26c**, $pIC_{50}$ = 6.81). While fluorine at the 5-position results in only a small decrease in affinity (**27**, $pIC_{50}$ = 7.83), larger substituents caused a considerable decrease in affinity (**28–31**, $pIC_{50}$ = 6.88–6.24). Interestingly, a 5-hydroxyl group is not tolerated (**32**, $pIC_{50}$ = 6.71), suggesting that the indole moiety of these antagonists is *not* binding in the same manner as the agonists 5-HT **1a** or 2-Me-5-HT **1b**. There is some bulk tolerance about the 7-position, as introduction of the 7-methyl substituent caused only a small decrease in affinity (**33**, $pIC_{50}$ = 8.05). Replacement of the indole with benzthiophene (**34**, $pIC_{50}$ = 7.57), indazole (**35**, $pIC_{50}$ = 7.58), or 3-methoxyphenyl (**36**, $pIC_{50}$ = 6.39) yielded compounds of reduced affinity. These results were somewhat unexpected given that such bioisosteric replacements for indole have previously proved successful.[21]

**Receptor Selectivity.** The pharmacological specificity of one of the compounds (**22k**) for central 5-HT recognition

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sites was examined by investigating the compound in a wide variety of central nervous system binding assays. These included assays for serotonin receptors (5-$HT_1$, [$^3$H]-8-OH-DPAT; 5-$HT_{1B}$, [$^{125}$I]cyanopindolol; 5-$HT_{1D}$, [$^3$H]-5-HT; 5-$HT_2$, [$^3$H]ketanserin), dopamine receptors ([$^3$H]SCH 23390, [$^3$H]spiperone), muscarinic receptors ([$^3$H]NMS, [$^3$H]Oxo-M), adrenergic receptors ([$^3$H]prazosin, [$^3$H]rauwolscine, [$^{125}$I]iodopindolol), histamine receptors ([$^3$H]pyrilamine), amino acid receptors ([$^3$H]glutamate, [$^3$H]kainate, [$^3$H]glycine, [$^3$H]AMPA, [$^3$H]GABA), channel blockers ([$^3$H]strychnine, [$^3$H]MK-801, [$^3$H]-ω-conotoxin, [$^{125}$I]charybdotoxin, [$^3$H]verapamil, [$^3$H]nitrendipine, [$^3$H]diltiazam, [$^3$H]fluspirilene), peptide receptors ([$^{125}$I]-BH-SP, [$^{125}$I]BH-ELE, [$^{125}$I]BH-CCK), and [$^3$H]Ro15-1788 (benzodiazepine), [$^3$H]DTG (σ), [$^3$H]forskolin, and [$^3$H]-imipramine recognition sites. The apparent affinities, measured as $IC_{50}$ values, for **22k** were all <5, demonstrating that the compound was inactive at displacing binding to a large number of central recognition sites.

**Modeling.** The ligands described in this paper have a single rotatable bond; however, rotation is restricted by conjugation, and the relative position of the pharmacophoric elements can be precisely defined. Two rotamers are possible and both are energetically acceptable (<0.5 kcal difference), supporting evidence coming from the X-ray structure in which both rotamers are present. The identification of the extended rotamer (rotamer 1, Figure 3) as the active conformer was based on the modeling of the known ligands described above, in particular the superimposition with GR 38032F (**2**) (Figure 2). Supporting evidence was derived from the lack of affinity of thiazole **37**[15] in which the hydrogen-bonding interaction to the nitrogen of the linking heterocycle is absent in the extended rotamer but would be present if the folded rotamer were the active form. Further support for this observation comes from indazole esters **38** and **39**.[21] Methylation at N2 caused a marked decrease in affinity, which was ascribed to an unfavorable steric interaction between the N2 methyl group and the amide N–H, rendering the extended conformation disfavored. The decrease in affinity of **39** could also be attributed to an unfavorable steric interaction with the receptor. However, the present work would suggest that since the 2-iodo (**26a**) and 2-acetyl (**26b**) derivatives show high affinity, a methyl group should be accommodated at the 2-position.

This model is in direct contrast to that previously described,[22] which proposed the folded conformation to be the active configuration. Interestingly, the binding site shows little stereoselectivity, the enantiomers **22l** and **22m** being of comparable potency. In addition, a variety of tertiary amines and their quaternary analogues are also accommodated. This suggests that the interaction between ligand and the receptor more closely resembles a simple electrostatic interaction (between the basic amine and e.g. a carboxylate group in the receptor), rather than a highly directional charge-reinforced hydrogen bond, and also suggests the carboxylate group lies close to the plane of the aromatic ring. It is possible to refine the model of the binding site using the active rotamer (rotamer 1, Figure 3) from the X-ray structure as the template. The active ligands (**22b, 22d, 22j–k, 26a**) and the inactive ligands (**22f, 26c, 28, 29**), together with **25d**, which shows reduced affinity, can now be superimposed, using the center of the aromatic ring, the heteroatoms of the oxazoline, and the basic nitrogen of the azacycle as the key points for the

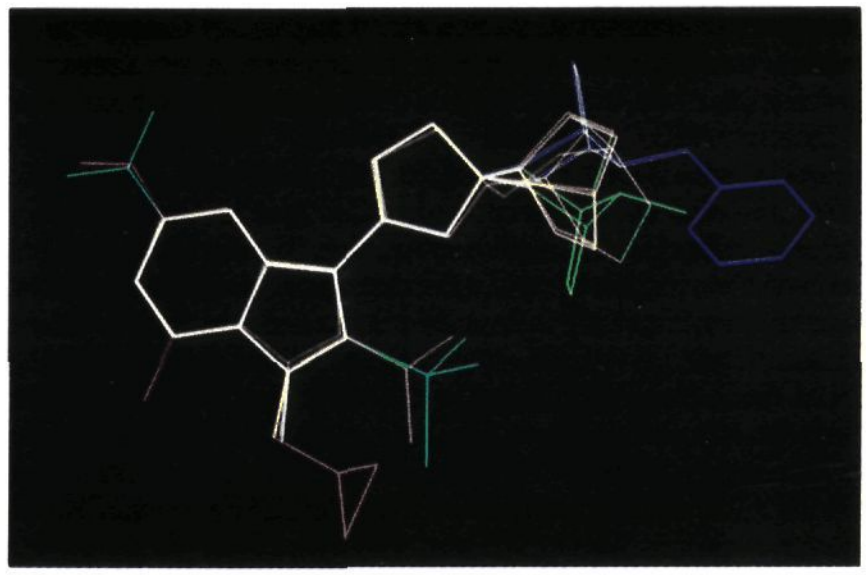
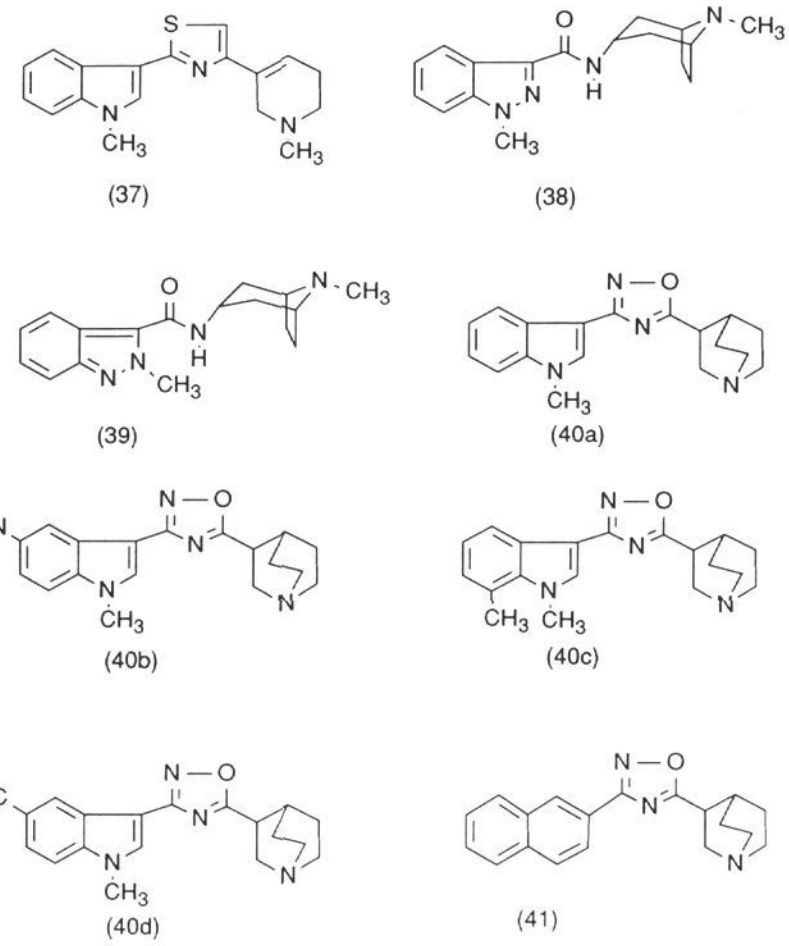


**Figure 5.** Superimposition of indole oxazolines.

**Chart III.** Structures of 5-$HT_3$ Receptor Ligands Used in Molecular Modeling Studies




superimposition (Figure 5). Each of the known ligands (**2–6**) and the indole oxadiazole **40a** can be fitted onto this template. The center of the benzene ring and the positions of the hydrogen bond and the basic nitrogen were used to define the superimposition for ICS 205-930 (**3**), BRL 43694 (**4**), and indole oxadiazole **40a**. For GR 38032F (**2**) the center of the benzene ring, the position of the hydrogen bond, and C2 of the imidazole were chosen; for MDL 72222 (**5**) the basic nitrogen and the hydrogen bond were used. In the case of zacopride (**6**) the rotamer shown was chosen because it was anticipated that a hydrogen bond between the methoxy and the amide N–H would favor this rotamer;[23] the points chosen for the superimposition were the basic nitrogen and the hydrogen bond. Using the same points to define the superimposition, a number of inactive compounds, the 5- and 7-substituted indole oxadiazoles (**40b,c**) and naphthyloxadiazole **41**, (Chart III) were also

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(23) King, F. D.; Dabbs, S.; Bermudez, J.; Sanger, G. J. Benzotriazinones as "Virtual Ring" Mimics of *o*-Methoxybenzamides. Novel and Potent 5-$HT_3$ Receptor Antagonists. *J. Med. Chem.* **1990**, *33*, 2942.

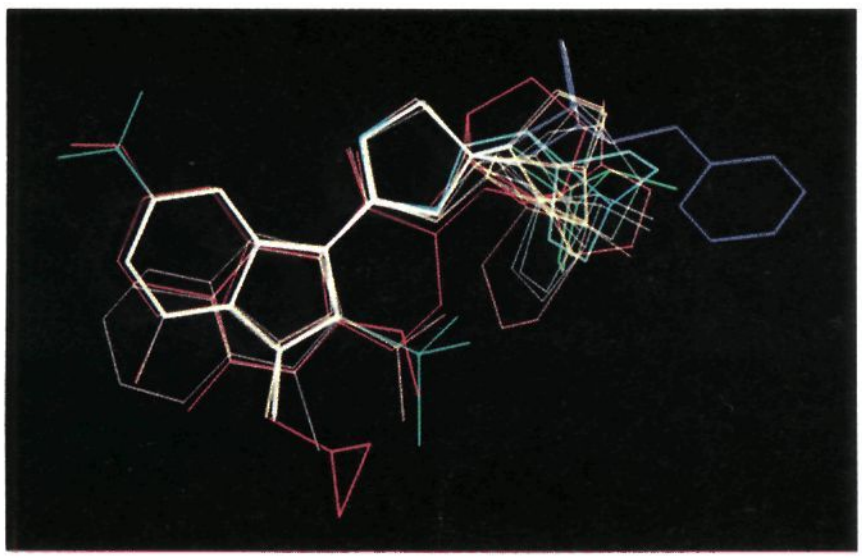

**Figure 6.** Superimposition of indole oxazolines, indole oxadiazoles, and known ligands GR 38032F (**2**), ICS 205-930 (**3**), BRL 43694 (**4**), and MDL 72222 (**5**).

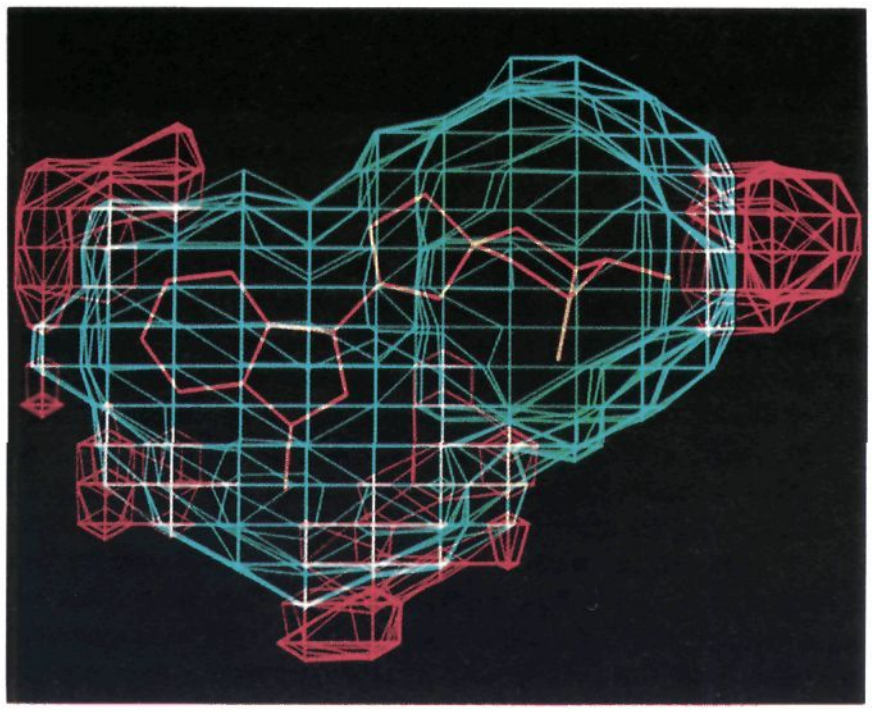

**Figure 7.** Total VDW map of the active ligands (shown in blue); the VDW difference map (red) showing volumes inaccessible to ligands.

included (Figure 6). A number of conclusions can be drawn from the resulting pharmacophore. Optimal activity is found in those compounds having an aromatic ring with a basic nitrogen approaching coplanarity and at a distance of 8.6–9.1 Å from the center of the ring. However, deviation from coplanarity of up to 1.2 Å is allowed, perhaps suggesting that an electrostatic interaction with either of the oxygens of the presumed carboxylate on the receptor is allowed. In addition, an atom capable of accepting a hydrogen bond coplanar with the aromatic ring at a distance of 4–4.5 Å from the center of the ring and 5–5.2 Å from the basic nitrogen is essential for activity.

It is now possible to define the volume accessible to ligands in the active site by generating a total VDW (van der Waals) map of all the active ligands (Figure 7, shown in blue). In addition, by generating the corresponding map for the inactive compounds and subtracting the volume occupied by the active ligands it is possible to define a VDW difference map displaying the areas of the recognition site inaccessible to ligands (Figure 7, shown in red). This clearly defines the limited space available about the benzo ring of the indole. Planar substituents can be accommodated at the 1- and 2-positions; however, an increase in the 3-D steric demand results in unfavorable interactions. Steric demand about the azabicyclic system is well-tolerated; however, large substituents on the nitrogen do reduce potency.

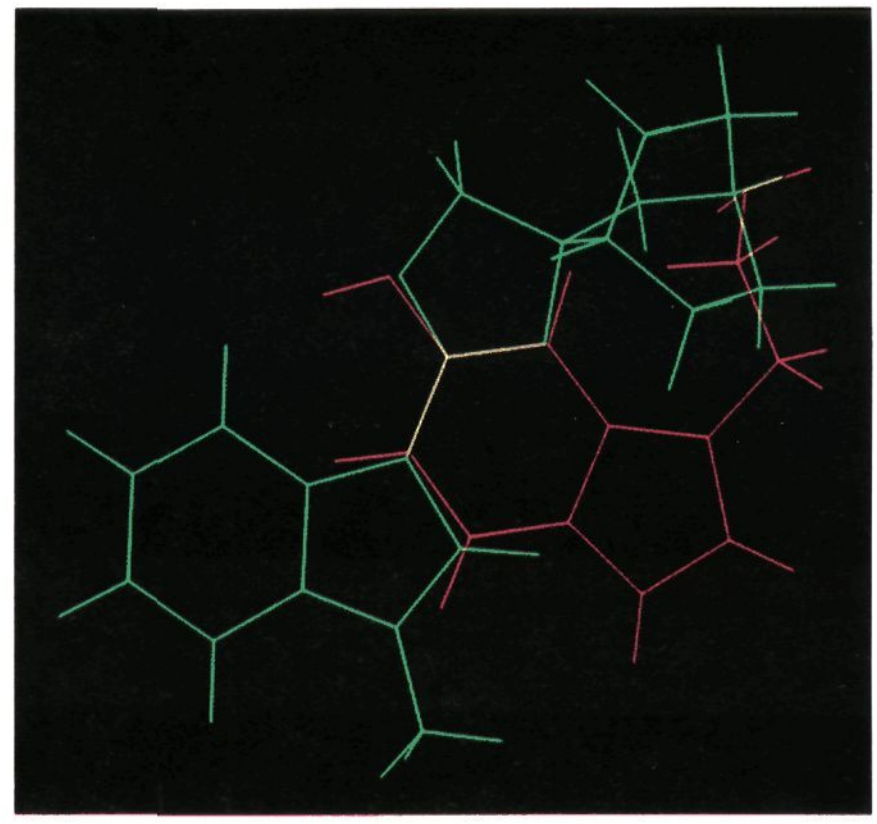

**Figure 8.** Superimposition of the antagonist **22l** and the agonist 5-HT (**1a**).

**Agonists.** In general it is unwise to attempt to incorporate a model of agonist binding on to a pharmacophore derived from data obtained from antagonist binding; however, in this case it may be possible to suggest a putative model. The observation that the quaternary ammonium analogue of 5-HT **1c** is a 5-$HT_3$ agonist[2] is intriguing given that the quinuclidine ring system has been demonstrated to be an excellent bioisosteric replacement for a quaternary ammonium moiety in the cholinomimetic area.[24] This suggests that the basic nitrogen in both agonists and antagonists occupies a common binding site. However, in the pharmacophore of the 5-$HT_3$ antagonist binding site the distance between the basic nitrogen and the center of the benzo ring of the indole is longer than is possible in 5-HT (**1a**). This and the poor affinity of the 5-hydroxy ligand **32** suggest that the indole moiety of the antagonists and agonists do not bind at the same site. Assuming the 5-hydroxyl of 5-HT participates in a hydrogen-bonding interaction, it is possible to superimpose 5-HT (**1a**) on to the antagonist pharmacophore by fitting the two basic nitrogens and the oxygen of the hydroxyl onto the hydrogen-bond-accepting heteroatom of the linking group and keeping the aromatic rings coplanar (Figure 8). This model would appear to be in direct contrast to that reported previously[25] in which the indole moiety of antagonists and agonists were superimposed; however, we have been assured by the authors that this superimposition was only intended to demonstrate a possible mode of binding and to highlight the difficulty in overlaying the basic nitrogens. Recently, an analogous conclusion was reached for a series of phenyl ureas[26] and amides.[27]

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## Conclusions

A novel series of indole oxazolines spirofused to an azacyclic ring have been shown to be potent ligands for the 5-$HT_3$ receptor. By virtue of the spiro center the relative positions of the key pharmacophoric elements can be defined and a detailed model of the 5-$HT_3$ antagonist binding site elucidated. The steric restriction surrounding the aromatic binding site is shown by the VDW difference map (Figure 7). Two key interactions have been identified; a basic nitrogen coplanar with and at a distance of 8.6–9.1 Å from the center of the aromatic ring, and an atom capable of accepting a hydrogen bond, coplanar with and at a distance of 4–4.5 Å from the center of the benzo ring and 5–5.2 Å from the basic nitrogen. However the position of the basic nitrogen is not rigidly defined; some deviation (1.2 Å) from coplanarity is allowable, perhaps reflecting the electrostatic nature of the interaction rather than a highly directional charge-reinforced hydrogen bond.

## Experimental Section

**Chemistry. General Directions.** Except where otherwise stated, the following procedures were adopted: $^1H$ (360 MHz) and $^{13}C$ (90 MHz) NMR spectra were recorded on a Bruker AM360 using a 5-mm dual probe. $^1H$ chemical shifts are expressed in ppm downfield from tetramethylsilane or sodium 3-(trimethylsilyl)propionate as internal standard. $^{13}C$ chemical shifts are reported relative to DMSO ($\delta$ = 39.4 ppm). Coupling constants were evaluated by first-order rules with an estimated accuracy of 0.5 Hz. $^1H$, $^1H$ and $^1H$, $^{13}C$ chemical shift correlations used standard Bruker microprograms. Nuclear Overhauser enhancements were measured by the NOE difference method using degassed samples. Mass spectra were recorded with a VG 70-250 mass spectrometer and infrared spectra on a Perkin-Elmer 782 IR spectrophotometer. Organic solvents were purified when necessary by the methods described by Perrin et al. (Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1986) or were purchased from Aldrich Chemical Co., Sureseal). All solutions were dried over anhydrous sodium sulfate and evaporated on a Büchi rotary evaporator, with a water bath temperature of 40 °C or below. Thin-layer chromatography and preparative chromatography were performed on silica, using plates (Merck Art. No. 5719) and gravity columns (Merck Art. No. 7734), or on alumina, using plates (Merck Art No. 5550) and gravity columns (Woelm Alumina Act. 2). Melting points are uncorrected.

**5-Nitro-1*H*-indole-3-carbonitrile. Method A.** This procedure illustrates the general method of preparation of substituted indole-3-carbonitriles **9**.

**(a) 5-Nitro-1*H*-indole-3-carboxylic Acid.** Trifluoroacetic anhydride (21.4 g, 0.2 mol) was added dropwise to a solution of 5-nitro-1*H*-indole (10.0 g, 0.09 mol) in dry dimethylformamide (150 mL) at 0 °C under a dry nitrogen atmosphere. The solution was allowed to warm to room temperature and then heated at reflux for 24 h. The reaction mixture was cooled and poured onto water (500 mL); the resulting brown solid was filtered and suspended in aqueous sodium hydroxide (50 g in 200 mL) until dissolution occurred. The solution was washed with ether (4 × 100 mL) and acidified to pH 2. The resulting solid was filtered and dried (19 g, 100%): mp 256–258 °C; $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.71 (d, $J$ = 7.0 Hz, 1 H, H-7), 7.90 (dd, $J$ = 7.0, 1.0 Hz, 1 H, ArH), 8.27 (s, 1 H, H-2), 8.89 (d, $J$ = 1.0 Hz, 1 H, H-4); MS $m/z$ 206 ($M^+$, 70), 123 (100).

**(b) 5-Nitro-1*H*-indole-3-carboxamide.** Oxalyl chloride (1.87 g, 14.7 mmol) was added to a solution of 5-nitro-1*H*-indole-3-carboxylic acid (3.06 g, 14.9 mmol) in dry tetrahydrofuran (80 mL). The solution was stirred at room temperature for 24 h and then evaporated to dryness. The residue was then dissolved in 1,2-dichloroethane (50 mL); anhydrous ammonia gas was passed through the solution for 1 h to afford the title compound as a bright yellow precipitate which was filtered and dried (3.2 g): mp 284–288 °C; $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.62 (d, $J$ = 7.0 Hz, 1 H, H-7), 8.04 (dd, $J$ = 7.0, 1.0 Hz, 1 H, H-6), 8.29 (s, 1 H, H-2), 9.08 (d, $J$ = 1.0 Hz, 1 H, H-4); MS $m/z$ 205 ($M^+$, 90), 189 (100).

**(c) 5-Nitro-1*H*-indole-3-carbonitrile.** 5-Nitro-1*H*-indole-3-carboxamide (2.0 g, 9.8 mmol) was suspended in dry dioxane (100 mL) containing triethylamine (7.8 g, 77.2 mmol). Trifluoroacetic anhydride (8.2 g, 39.0 mmol) was added dropwise to this solution at 0 °C and the reaction was stirred at room temperature overnight. The solution was then diluted with dichloromethane (200 mL), washed with water (3 × 100 mL), and dried, and the solvent was removed at reduced pressure. Recrystallization of the residue from ethyl acetate/hexane afforded the title compound (0.8 g, 46%): mp 186–190 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 7.58 (d, $J$ = 7.0 Hz, 1 H, H-7), 7.94 (d, $J$ = 1.0 Hz, 1 H, H-4), 8.16 (dd, $J$ = 7.0 Hz, 1.0 Hz, 1 H, H-6), 8.63 (s, 1 H, H-2); MS $m/z$ 187 ($M^+$, 100).

**1-Methyl-1*H*-indole-3-carbonitrile.** This procedure illustrates the general method of preparation of indole-3-carbonitriles **9** from the indole-3-carboxaldehydes **11**. A suspension of ammonium dihydrogen phosphate (220 g, 1.6 mol) in glacial acetic acid (300 mL) and nitropropane (900 mL) was placed in a 2-L three-necked round-bottomed flask equipped with a mechanical stirrer, condenser, and nitrogen inlet. The mixture was degassed with nitrogen for 10 min. 1-Methyl-1*H*-indole-3-carboxaldehyde (50 g, 0.3 mol) was added to the mixture which was then stirred vigorously at reflux under nitrogen for 12 h. The cooled dark red mixture was filtered to remove inorganic salts; the filtrate was washed thoroughly with ether to remove all product. Acetic acid and nitropropane were removed at reduced pressure. The resulting oil was dissolved in ether, washed with water (4 × 200 mL), dried, and evaporated. The oil was purified by chromatography on silica gel, using dichloromethane/hexane (70:30) as eluant. The product was recrystallized from ether/hexane (35 g, 75%): mp 60–61 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 3.80 (s, 3 H, $NCH_3$), 7.24–7.37 (m, 3 H, ArH), 7.48 (s, 1 H, ArH, H-2), 7.72 (dd, $J$ = 8.0, 1.0 Hz, 1 H, ArH); MS $m/z$ 156 ($M^+$, 100).

**Methyl 1-Methyl-1*H*-indole-3-carboximidate Hydrochloride (8k).** This illustrates the general procedure for the preparation of the indole imino ethers **8**. Dry hydrogen chloride gas was bubbled through a solution of 1-methyl-1*H*-indole-3-carbonitrile (1.7 g, 11 mmol) in dry methanol (30 mL). The solution was allowed to stand at room temperature for 24 h. Addition of dry ether (20 mL) gave the title compound as colorless needles (1.8 g, 72%): mp 156–158 °C; $^1H$ NMR (DMSO-$d_6$) $\delta$ 3.93 (s, 3 H, $NCH_3$), 4.30 (s, 3 H, $OCH_3$), 7.33 (dt, $J$ = 7.5, 1.0 Hz, 1 H, ArH), 7.38 (dt, $J$ = 8.0, 1.5 Hz, 1 H, ArH), 7.67 (d, $J$ = 7.8 Hz, 1 H, ArH), 7.94 (dd, $J$ = 6.5, 1.0 Hz, 1 H, ArH), 8.97 (s, 1 H, ArH, H-2); MS $m/z$ 188 ($M^+$).

**4-(Aminomethyl)-4-hydroxy-1-azabicyclo[3.3.1]nonane (18j). Method B.** This procedure illustrates the method of preparation of amino alcohols **18b,c,j**. Trimethylsilyl cyanide (3 mL, 22.5 mmol) was added dropwise to a stirred solution of 1-azabicyclo[3.3.1]nonan-4-one (2.5 g, 18.0 mmol) and zinc iodide (0.15 g, 0.5 mmol) in anhydrous dichloromethane (20 mL) and the resulting mixture was heated at reflux for 4 h. The mixture was cooled and the solvent was removed at reduced pressure. The residue was dissolved in dry tetrahydrofuran (20 mL) and was cooled to 0 °C. A solution of lithium aluminium hydride in tetrahydrofuran (1.0 M, 18 mL, 18 mmol) was then added and the resulting solution was stirred overnight at room temperature. Water (0.7 mL), followed by sodium hydroxide (0.7 mL of a 15% solution) and water (2.1 mL), was added to precipitate aluminium salts. These were removed by filtration, and evaporation of the filtrate furnished amino alcohol **18j** (2.2 g, 72%): $^1H$ NMR ($CDCl_3$) $\delta$ 1.20–1.30 (m, 2 H, $CH_2$), 1.30–1.36 (m, 1 H, C*H*H), 1.41 (dd, $J$ = 14.0, 5.0 Hz, 1 H, CH*H*), 1.54–1.66 (m, 2 H, $CH_2$), 1.70–1.74 (m, 1 H, C*H*H), 1.76–1.91 (m, 2 H, $CH_2$), 2.11–2.16 (m, 1 H, CH*H*), 2.67–2.98 (m, 8 H, $CH_2N$); MS $m/z$ 170 ($M^+$).

**3α-(Aminomethyl)-3β-hydroxy-8-benzyl-8-azabicyclo[3.2.1]octane Dihydrochloride (18f). Method C.** This procedure illustrates the preparation of amino alcohol **18f**. *N*-Benzylnortropanone hydrochloride (12.6 g, 0.05 mol) was dissolved in water (20 mL) and a solution of sodium cyanide (2.4 g, 0.05 mol) was added to the amine solution at 0 °C. This was stirred at 0 °C for 2 h and was then extracted into ether. The organic layer was washed with water, dried, and evaporated. The residue, which was a 1:1 mixture of 3α-cyano-3β-hydroxy-8-benzyl-8-

(27) King, F. D.; Sanger, G. J. 5-$HT_3$ Receptor Antagonists. *Drugs Future* **1989**, *14*, 875–889.

azabicyclo[3.2.1]octane and 3β-cyano-3α-hydroxy-8-benzyl-8-azabicyclo[3.2.1]octane was not purified. A solution of lithium aluminium hydride (1.0 M in tetrahydrofuran, 5.0 mL, 0.005 mol) in tetrahydrofuran (20 mL) was stirred at room temperature under nitrogen and the mixture of cyanohydrins (1.5 g, 0.006 mol) was added portionwise. The mixture was heated at reflux for 30 min. The mixture was cooled and water (0.38 mL) was added followed by sodium hydroxide (0.38 mL of 15% aqueous solution) and water (1.14 mL). The precipitated aluminium salts were removed by filtration, and the mother liquor was evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with dichloromethane/methanol/ammonia (90:10:1) affording the product (0.4 g). Treatment with methanolic hydrogen chloride afforded the title compound as a crystalline solid: mp 276–278 °C; $^1$H NMR ($D_2O$) δ 2.04–2.12 (m, 2 H, $CH_2$), 2.17–2.34 (m, 4 H, $CH_2$), 2.42–2.56 (m, 2 H, $CH_2$), 3.29 (s, 2 H, $CH_2NH_2$), 4.00–4.08 (m, 2 H, CH), 4.28 (br s, 2 H, $CH_2Ph$), 7.55 (s, 5 H, ArH); MS $m/z$ 247 ($M^+$ + H). Anal. ($C_{15}H_{22}N_2O$·2HCl) C, H, N, Cl.

**3-(Aminomethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane–Borane Complex (18k). Method D.** This procedure illustrates the preparation of the borane-protected amino alcohols **18a,h,i,k**.

**(a) 3-Cyano-3-hydroxyquinuclidine.** 3-Quinuclidinone hydrochloride (300 g, 1.86 mol) was dissolved in water (400 mL) and the solution was cooled to 0 °C. Sodium cyanide (90.97 g, 1.86 mol) in water (400 mL) was added dropwise to this solution, and the contents were stirred at 0 °C for 3 h. The resulting solid was isolated by filtration, washed with water, and dried under vacuum to afford the title compound (282 g, 99%): mp 153–157 °C (lit.[30] mp 152–155 °C).

**(b) 3-(Aminomethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane–Borane Complex (18k).** A solution of borane in tetrahydrofuran (266 mL of a 1.0 M solution, 0.26 mol) was added to a stirred solution of 3-cyano-3-hydroxyquinuclidine (40 g, 0.26 mol) in tetrahydrofuran (400 mL) under nitrogen. When the borane complex had formed (TLC monitor) two further equivalents of borane in tetrahydrofuran was added (534 mL of 1.0M solution), and the reaction was heated at reflux for 12 h. The mixture was cooled and ethanol (500 mL) was added slowly; the resulting solution was stirred at room temperature for 12 h. The solvents were removed at reduced pressure, and the residue was recrystallized from ethanol to afford the title compound as a white crystalline solid (32 g, 66%): mp (163–164 °C); $^1$H NMR ($CDCl_3$) δ 1.16–1.61 (m, 3 H, CH, $CH_2$), 1.86 (m, 1 H, C*H*H), 2.05 (m, 1 H, CH), 2.4–2.95 (m, 8 H, $CH_2N$); MS $m/z$ 157 ($M^+$); $^{13}$C NMR (DMSO-$d_6$) δ 20.60 ($CH_2$, C5), 21.87 ($CH_2$, C8), 28.17 (CH, C4), 48.89 ($CH_2$, C9), 52.38 ($CH_2$, C7), 53.12 ($CH_2$, C6), 66.14 ($CH_2$, C2), 70.37 (C, C3).

For comparison, the $^{13}$C NMR values of the corresponding free base are also included: δ 21.68 ($CH_2$, C5), 23.68 ($CH_2$, C8), 27.62 (CH, C4), 46.34 ($CH_2$, C7), 47.02 ($CH_2$, C6), 49.48 ($CH_2$, C9), 61.64 ($CH_2$, C2), 70.46 (C, C3).

**2′-(1-Methyl-1*H*-indol-3-yl)spiro(1-azabicyclo[2.2.2]octane-3,5′(4′*H*)-oxazole) Dihydrochloride (22k).** This represents the general procedure for synthesis of the oxazolines from the reaction of an amino alcohol and an imino ether and is illustrated in Scheme III. A solution of methyl 1-methyl-1*H*-indole-3-carboximidate hydrochloride (**8k**) (22.4 g, 0.1 mol) in anhydrous methanol (350 mL) was added to a stirred solution of 3-(aminomethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane–borane complex (**18k**) (20.4 g, 0.1 mol) in methanol (350 mL) under nitrogen over 75 min. The resulting solution was heated at reflux for 12 h and allowed to cool to room temperature. Saturated methanolic hydrogen chloride was added (100 mL) and the mixture heated at reflux for 12 h. The solvent was removed under reduced pressure and the residue dissolved in hydrochloric acid (50 mL of 2 N solution) and water (200 mL). The solution was washed with dichloromethane (250 mL), basified with ammonium hydroxide, and extracted with dichloromethane (3 × 100 mL). The combined extracts were dried, and the solvent was removed at reduced pressure. The residue was purified on silica gel using dichloromethane/methanol/ammonia solution (90:10:1) to afford the title compound as a viscous oil (19.5 g, 66%); treatment with methanolic hydrogen chloride furnished the dihydrochloride salt which was recrystallized from methanol: mp 262–263 °C; $^1$H NMR ($D_2O$) δ 2.00–2.30 (m, 3 H, CH), 2.46–2.56 (m, 1 H, CH), 2.70–2.74 (m, 1 H, CH), 3.42–3.48 (m, 2 H, CH), 3.54–3.70 (m, 2 H, CH), 3.84 (dd, $J$ = 13.0, 2.0 Hz, 1 H, C*H*H), 3.96 (s, 3 H, $NCH_3$), 4.09 (d, $J$ = 15.0 Hz, 1 H, CH*H*), 4.18 (d, $J$ = 12.0 Hz, 1 H, C*H*$H_{oxazoline}$), 4.46 (d, $J$ = 12.0 Hz, 1 H, CH*H*$_{oxazoline}$), 7.44–7.53 (m, 2 H, ArH), 7.67 (d, $J$ = 6.0 Hz, 1 H, ArH), (dd, $J$ = 8.0, 1.0 Hz, ArH), 8.34 (s, 1 H, ArH). Anal. ($C_{17}H_{21}N_3O$·2HCl) C, H, N, Cl.

**(+)- and (−)-2′-(1-Methyl-1*H*-indol-3-yl)spiro(1-azabicyclo[2.2.2]octane-3,5′(4′*H*)-oxazole) Dihydrochloride (22m and 22l).** To a solution of racemic **22k** free base (6.4 g, 21.7 mmol) in a minimum of ethanol was added a solution of (+)-*O*,*O*′-dibenzoyl-D-tartaric acid (1.93 g, 5.4 mmol). The solution was allowed to stand until crystallization occurred. This was filtered and recrystallized from ethanol to constant rotation [[α]$_D$ +11.6° (*c* = 0.5, methanol)]. The mother liquors from the original crystallization were evaporated to dryness, dissolved in dichloromethane (200 mL), and washed with aqueous sodium bicarbonate (3 × 100 mL). The organic phase was dried and concentrated. The residue was dissolved in the minimum amount of ethanol (20 mL) and treated with a solution of (−)-*O*,*O*′-dibenzoyl-L-tartaric acid (1.93 g, 5.4 mmol) in ethanol. The salt was recrystallized from ethanol to constant rotation [[α]$_D$ −12.4° (*c* = 0.5, methanol)]. The (+)-salt was suspended in dichloromethane (100 mL) and basified with dilute aqueous ammonia (3 × 100 mL) to liberate the free base. The organic phase was dried and concentrated and the residue treated with methanolic hydrogen chloride to furnish the dihydrochloride salt. Recrystallization from ethanol/ether gave the title compound: mp 261–262 °C; [α]$_D$ −43.3 (*c* = 0.5, methanol). The (−)-tartrate salt was treated in a similar fashion to give colourless crystals: mp 261–262 °C; [α]$_D$ +43.3° (*c* = 0.5, methanol). Anal. ($C_{17}H_{21}N_3O$) C, H, N, Cl.

**2′-(1*H*-Indol-3-yl)spiro(1-azabicyclo[2.2.2]octane-3,5′-(4′*H*)-oxazole)–Borane Complex (24).** To a solution of 3-(aminomethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane–borane complex (**18k**) (10.0 g, 0.059 mol) in anhydrous methanol (220 mL) was added dropwise a solution of methyl 1*H*-indole-3-carboximidate hydrochloride (10.9 g, 0.052 mol) in methanol (1000 mL). The reaction mixture was stirred at 50 °C for 12 h under nitrogen. The cooled mixture was basified with aqueous ammonia and was evaporated. The residue was purified by column chromatography on silica using dichloromethane/methanol (9:1), giving a white foam (14.2 g, 92%): mp 262–264 °C; $^1$H NMR (DMSO-$d_6$) δ 1.1–1.7 (br s, 3 H, $BH_3$), 1.69–1.75 (m, 3 H, $CH_2$), 2.04 (1 H, s, C*H*H), 2.14–2.16 (m, 1 H, CH), 2.86–1.95 (m, 2 H, $NCH_2$), 3.00–3.05 (m, 2 H, $NCH_2$), 3.08–3.11 (d, $J$ = 14.0 Hz, 1 H, NC*H*H), 3.12–3.17 (d, $J$ = 14.2 Hz, 1 H, NCH*H*), 3.82 (d, $J$ = 15.0 Hz, 1 H, C*H*H), 4.05 (d, $J$ = 15.0 Hz, 1 H, CH*H*), 7.18–7.25 (m, 2 H, ArH), 7.44 (m, 1 H, ArH), 7.9 (m, 1 H, ArH), 8.04 (m, 1 H, ArH), 11.69 (s, 1 H, NH); MS $m/z$ 281 ($M^+$, 20), 271 (100); $^{13}$C NMR (DMSO-$d_6$) δ 20.19 ($CH_2$, C5), 20.73 ($CH_2$), C8), 29.79 (CH, C4), 51.87 ($CH_2$, C7), 52.73 ($CH_2$, C6), 63.70 ($CH_2$, C4), 65.82 ($CH_2$, C2), 81.70 (C, C3), 103.49 (C, C3), 111.84 (CH, C7), 120.35 (CH, C5), 120.46 (CH, C4), 121.99 (CH, C6), 125.04 (C, C3a), 128.87 (CH, C2), 136.20 (C, C7a), 158.77 (C, C2). The values for the corresponding free base (prepared by heating (**24**) in methanolic hydrogen chloride at reflux and then the basifying with aqueous ammonia) are included for comparison: δ 21.28 ($CH_2$, C5), 22.11 ($CH_2$, C8), 30.60 (CH, C4), 45.66 ($CH_2$, C7), 46.34 ($CH_2$, C6), 62.08 ($CH_2$, C4), 64.08 ($CH_2$, C4), 64.20 ($CH_2$, C2), 83.03 (C, C3), 103.97 (C, C3), 111.83 (CH, C7), 120.24 (CH, C5), 120.57 (CH, C4), 121.90 (CH, C6), 125.14 (C, C3a), 128.47 (CH, C2), 136.19 (C, C7a), 159.19 (C, C2).

**2′-(1-Propyn-2-yl-1*H*-indol-3-yl)spiro(1-azabicyclo-[2.2.2]octane-3,5′(4′*H*)-oxazole) Hydrochloride (25b).** This procedure illustrates the preparation of N-substituted indoles. To a solution of **24** (0.5 g, 1.7 mmol) in tetrahydrofuran (40 mL) under nitrogen was added sodium hydride (0.09 g). The reaction mixture was stirred at room temperature for 30 min and propargyl bromide (0.16 mL, 1.7 mmol) was added. The mixture was stirred for 12 h and evaporated. The residue was treated with methanolic hydrogen chloride at 60 °C for 24 h to decompose the borane complex. The solvent was removed under reduced pressure and the residue was dissolved in water and extracted with dichloromethane. The aqueous layer was basified and extracted with dichloromethane (3 × 100 mL). The organic extracts were dried and evaporated at reduced pressure. The residue was dissolved in methanol and treated with ethereal hydrogen chloride. The title compound crystallized on standing (0.22 g, 33%): mp 200–230

°C; $^1$H NMR ($D_2O$) δ 2.09–2.28 (m, 3 H, CH), 2.50–2.52 (m, 1 H, CH), 2.74 (m, 1 H, CH), 2.98–2.99 (t, $J$ = 2.5 Hz, C≡CH), 3.38–3.46 (m, 2 H, CH), 3.55–3.66 (m, 2 H, $NCH_2$), 3.83–3.87 (dd, $J$ = 15.0, 2 Hz, 1 H, NC*H*H), 4.09–4.13 (d, $J$ = 15.0 Hz, 1 H, NCH*H*), 4.19–4.23 (d, $J$ = 12.0 Hz, C*H*H oxazoline), 4.48–4.51 (d, $J$ = 12.0 Hz, 1 H, CH*H* oxazoline), 5.18–5.19 (d, $J$ = 2.5 Hz, 2 H, $NCH_2C$≡CH), 7.45–7.55 (m, 2 H, ArH), 7.76–7.78 (dd, $J$ = 7.5, 1.0 Hz, 1 H, ArH), 7.94–7.97 (dd, $J$ = 7.5, 1.0 Hz, 1 H, ArH), 8.54 (s, 1 H, ArH, C2); MS $m/z$ 319 ($M^+$, 15), 225 (100). Anal. ($C_{20}H_{21}N_3O$·2HCl·1.5$H_2O$) C, H, N, Cl.

**2′-(2-Iodo-1-methyl-1*H*-indol-3-yl)spiro(1-azabicyclo-[2.2.2]octane-3,5′(4′*H*)-oxazole) Dihydrochloride (26b).** This procedure illustrates the synthesis of C2-substituted indoles **26a–c**. *tert*-Butyllithium (2 mL of 1.7 M solution in hexane, 3.4 mmol) was added dropwise to a stirred solution of free base **22k** (0.5 g, 1.7 mmol) in tetrahydrofuran (20 mL) at −78 °C under a nitrogen atmosphere. This was stirred for 1 h at −78 °C and iodine (0.5 g, 1.9 mmol) in tetrahydrofuran (10 mL) was added dropwise until the color persisted. The mixture was then allowed to warm to room temperature, diluted with water (100 mL), and extracted with chloroform (2 × 100 mL). The organic layer was dried and evaporated at reduced pressure to afford a white solid. Treatment with methanolic hydrogen chloride afforded a white crystalline solid which was recrystallized from methanol (0.5 g, 70%): mp 188 °C dec; $^1$H NMR ($D_2O$) δ 2.1–2.3 (m, 3 H, $CH_2CHH$), 2.6 (m, 1 H, C*H*H), 2.76 (1 H, m, CH), 3.46–3.72 (m, 4 H, $CH_2N$ × 2), 3.84 (s, 3 H, $NCH_3$), 3.93 (d, $J$ = 12.0 Hz, 1 H, C*H*HN), 4.12 (d, $J$ = 12.0 Hz, 1 H, CH*H*N), 4.25 (d, $J$ = 13.0 Hz, 1 H, C*H*H oxazoline), 4.52 (d, $J$ = 13.0 Hz, 1 H, CH*H* oxazoline), 7.4–7.47 (m, 2 H, ArH, H-5, H-6), 7.61 (d, $J$ = 7.0 Hz, ArH, H-7), 7.81 (d, $J$ = 7.0 Hz, 1 H, ArH, H-4); MS $m/z$ 421 ($M^+$, 30), 96 (100).

**2′-(5-Amino-1-methyl-1*H*-indol-3-yl)spiro(1-azabicyclo-[2.2.2]octane-3,5′(4′*H*)-oxazole) Trihydrochloride (30).** Nitroindole **29** (at the borane complex stage) (0.5 g, 1.4 mmol) was suspended in ethyl acetate (50 mL) and was hydrogenated over 10% Pd/C (50 mg) for 6 h at atmospheric pressure. The catalyst was removed by filtration and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethane/methanol/aqueous ammonia (90:10:1) as eluent. The product was then treated with methanolic hydrogen chloride and was heated at reflux for 1 h to decompose the borane–quinuclidine complex. After removal of solvent the residue was recrystallized from 2-propanol and was isolated as the trihydrochloride salt (140 mg, 24%): mp 260 °C dec; $^1$H NMR ($D_2O$) δ 2.17 (m, 3 H, $CH_2CH_2N$), 2.50 (m, 1 H, $CH_2CH_2N$), 2.73 (m, 1 H, $CHCH_2CH_2N$), 3.45 (t, $J$ = 9.5 Hz, 2 H, $CH_2CH_2N$), 3.64 (t, $J$ = 9.5 Hz, 2 H, $CH_2CH_2N$), 3.85 (d, $J$ = 12.0 Hz, $CH_2CH_2N$), 3.98 (s, 3 H, $NCH_3$), 4.00 (d, $J$ = 12.0 Hz, $CH_2CH_2N$), 4.20 (d, $J$ = 10.0 Hz, 1 H, C*H*H oxazoline), 4.50 (d, $J$ = 10.0 Hz, 1 H, CH*H* oxazoline), 7.40 (dd, $J$ = 11.0, 1.0 Hz, 1 H, H-6), 7.75 (d, $J$ = 11.0 Hz, 1 H, H-7), 7.90 (d, $J$ = 1.0 Hz, 1 H, H-4), 8.41 (s, 1 H, H-2); MS $m/z$ 310 ($M^+$, 100).

**2′-(5-Hydroxy-1-methyl-1*H*-indol-3-yl)spiro(1-azabicyclo[2.2.2]octane-3,5′(4′*H*)-oxazole) Trihydrochloride (32).** Methoxyindole **31** (prepared according to the procedure described for **22k**) (0.16 g, 0.5 mmol) was dissolved in dry dichloromethane (50 mL) and cooled to −78 °C under nitrogen. Boron tribromide (0.63 g, 2.5 mmol) was added and the solution was allowed to warm to room temperature over 3 h. The reaction was quenched with ice/water, basified to pH 7.5 with aqueous ammonia, and extracted with dichloromethane (2 × 100 mL). The organic extracts were dried and evaporated at reduced pressure, affording a yellow gum. Treatment with ethereal hydrogen chloride afforded a solid which was recrystallized, giving white needles (120 mg, 77%): mp 215–220 °C; $^1$H NMR ($D_2O$) 2.21 (m, 3 H, $CH_2CH_2N$), 2.48 (m, 1 H, $CH_2CH_2N$), 3.65 (m, 2 H, $CH_2CH_2N$), 3.84 (d, $J$ = 14.0 Hz, 1 H, C*H*HN), 3.90 (s, 3 H, $NCH_3$), 4.10 (d, $J$ = 14.0 Hz, 1 H, CH*H*N), 4.18 (d, $J$ = 14.5 Hz, 1 H, C*H*H oxazoline), 4.45 (d, $J$ = 14.5 Hz, 1 H, CH*H* oxazoline), 7.02 (dd, $J$ = 10.0 Hz, 1 H, H-7), 8.24 (s, 1 H, H-2); MS $m/z$ 311 ($M^+$, 40), 96 (100). The following data refers to the five compounds whose structures have been elucidated by detailed NMR analysis. The numbering schemes used here refer to those of Chart II.

**2′-(1-Methyl-1*H*-indol-3-yl)spiro((3(*R**),4(*R**))-1-azabicyclo[2.2.1]heptane-3,5′(4′*H*)-oxazole) dihydrochloride (22h):** $^1$H NMR ($D_2O$) δ 2.35 (1 H, dddd, $J$ = $J'$ = 13.3 Hz, $J''$ = 5.5 Hz, $J'''$ = 4.2 Hz, H-5β), 2.61 (1 H, m, H-5α), 3.50 (1 H, d, $J$ = 4.0 Hz, H-4), 3.60 (1 H, d, H-7a), 3.63 (1 H, d, H-7s), 3.70 (1 H, m, H-6α), 3.77 (1 H, dddd, $J$ = $J'$ = 11.9 Hz, $J''$ = 5.1 Hz, $J'''$ = 2.2 Hz, H-6β), 3.98 (3 H, s, H-8), 4.00 (1 H, dd, $J$ = 13.8 Hz, $J'$ = 1.9 Hz, H-2α), 4.03 (1 H, dd, $J$ = 13.8 Hz, $J'$ = 2.3 Hz, H-2β), 4.28 (1 H, d, $J$ = 12.0 Hz, H-4″s), 4.52 (1 H, d, $J$ = 12.0 Hz, H-4″a), 7.50 (1 H, ddd, $J$ = $J'$ = 7.7 Hz, $J''$ = 1.2 Hz, H-5), 7.53 (1 H, ddd, $J$ = $J'$ = 7.4 Hz, $J''$ = 1.3 Hz, H-6), 7.68 (1 H, dd, $J$ = 6.9 Hz, $J'$ = 1.4 Hz, H-7), 7.95 (1 H, dd, $J$ = 7.2 Hz, $J'$ = 1.8 Hz, H-4), 8.41 (1 H, s, H-2).

**2′-(1-Methyl-1*H*-indol-3-yl)spiro((3(*R**),4(*S**))-1-azabicyclo[2.2.1]heptane-3,5′(4′*H*)-oxazole) dihydrochloride (22i):** $^1$H NMR ($D_2O$) δ 2.03 (1 H, m, H-5α), 2.46 (1 H, m, H-5β), 3.46 (1 H, m, H-6α), 3.53 (1 H, d, $J$ = 5.0 Hz, H-4), 3.64 (1 H, m, H-6β), 3.67 (1 H, dd, $J$ = 10.1 Hz, $J'$ = 2.0 Hz, H-7a), 3.89 (1 H, dd, $J$ = 14.0 Hz, $J'$ = 2.3 Hz, H-2α), 3.96 (3 H, s, H-8), 3.98 (1 H, d, $J$ = 10.2 Hz, H-7s), 4.25 (1 H, dd, $J$ = 14.0 Hz, $J'$ = 2.5 Hz, H-2β), 4.41 (1 H, d, $J$ = 12.2 Hz, H-4″s), 4.58 (1 H, d, $J$ = 12.2 Hz, H-4″a), 7.49 (1 H, ddd, $J$ = $J'$ = 7.3 Hz, $J''$ = 1.1 Hz, H-5), 7.53 (1 H, ddd, $J$ = $J'$ = 7.1 Hz, $J$ = 1.2 Hz, H-6), 7.66 (1 H, dd, $J$ = 7.4 Hz, $J'$ = 1.2 Hz, H-7), 7.94 (1 H, dd, $J$ = 7.0 Hz, $J'$ = 1.5 Hz, H-4), 8.36 (1 H, s, H-2).

***syn*-2′-(1-Methyl-1*H*-indol-3-yl)spiro(8-methyl-8-azabicyclo[3.2.1]octane-3,5′(4′*H*)-oxazole) dihydrochloride (22b):** $^1$H NMR (DMSO-$d_6$) δ 2.12 (2 H, m, H-7s, H-8s), 2.24 (2 H, m, H-7a, H-8a), 2.24 (2 H, d, $J$ = 13.0 Hz, H-3β, H-5β), 2.48 (2 H, d, $J$ = 13.0 Hz, H-3α, H-5α), 2.72 (3 H, s, H-9), 3.84 (3 H, s, H-8), 4.03 (2 H, bs, H-2, H-6), 4.16 (2 H, s, H-4″), 7.17 (1 H, ddd, $J$ = $J'$ = 7.9 Hz, $J''$ = 1.1 Hz, H-5), 7.26 (1 H, ddd, $J$ = $J'$ = 7.8 Hz, $J''$ = 1.1 Hz, H-6), 7.51 (1 H, dd, $J$ = 8.0 Hz, $J$ = 1.1 Hz, H-7), 7.82 (1 H, s, H-2), 8.06 (1 H, dd, $J$ = 7.9 Hz, $J'$ = 1.1 Hz, H-4); $^{13}$C NMR (DMSO-$d_6$) δ 22.59 ($CH_2$, b, C3, C7, C8), 32.70 ($CH_3$, C8), 61.96 (CH, b, C2, C6), 66.53 ($CH_2$, C4″), 79.33 (C, C4), 101.84 (C, C3), 110.32 (CH, C7), 120.73 (2CH, C4, C5), 122.21 (CH, C6), 125.44 (C, C3a), 132.62 (CH, C2), 136.76 (C, C7a), 157.95 (C, C2″), 162.90 (C, $(CO_2H)_2$).

***anti*-2′-(1-Methyl-1*H*-indol-3-yl)spiro(8-methyl-8-azabicyclo[3.2.1]octane-3,5′(4′*H*)-oxazole) dihydrochloride (22d):** $^1$H NMR (DMSO-$d_6$) δ 2.15 (2 H, d, $J$ = 13.5 Hz, H-3β, H-5β), 2.31 (2 H, m, H-7a, H-8a), 2.37 (2 H, d, $J$ = 13.5 Hz, H-3α, H-5α), 2.49 (2 H, m, H-7s, H-8s), 2.75 (3 H, s, H-9), 3.74 (2 H, s, H-4″), 3.86 (3 H, s, H-8), 4.06 (2 H, bs, H-2, H-6), 7.19 (1 H, ddd, $J$ = $J'$ = 7.8 Hz, $J''$ = 1.1 Hz, H-5), 7.26 (1 H, ddd, $J$ = $J'$ = 7.7 Hz, $J''$ = 1.1 Hz, H-6), 7.52 (1 H, dd, $J$ = 8.1, $J'$ = 1.1, H-7), 7.97 (1 H, s, H-2), 8.05 (1 H, dd, $J$ = 7.7 Hz, $J'$ = 1.0 Hz, H-4); $^{13}$C NMR (DMSO-$d_6$) δ 23.77 ($CH_2$, b, C3, C5, C7, C8), 32.73 ($CH_3$, C8), 62.00 (CH, b, C2, C6), 66.25 ($CH_2$, C4), 79.12 (C, C4), 102.31 (C, C3), 110.38 (CH, C7), 120.46 (CH, C4), 120.78 (CH, C5), 122.19 (CH, C6), 125.35 (C, C3a), 133.11 (CH, C2), 136.85 (C, C7a), 158.85 (C, C2″), 163.01 (C, $(CO_2H)_2$).

**2′-(1-Methyl-1*H*-indol-3-yl)spiro(1-azabicyclo[3.3.1]nonane-3,5′(4′*H*)-oxazole) dihydrochloride (22j):** $^1$H NMR ($D_2O$) δ 2.12 (1 H, m, H-8β), 2.17 (1 H, m, H-9β), 2.47 (1 H, dm, $J$ = 14.3 Hz, H-9α), 2.52 (1 H, m, H-8α), 2.56 (1 H, dd, $J$ = 15.1 Hz, $J'$ = 5.3 Hz, H-3β), 2.73 (1 H, bs, H-5), 3.03 (1 H, ddd, $J$ = $J'$ = 14.9 Hz, $J''$ = 7.3 Hz, H-3α), 3.52 (1 H, d, $J$ = 13.7 Hz, H-6s), 3.68 (2 H, m, H-7α, H-7β), 3.69 (1 H, ddd, $J$ = $J'$ = 14.0 Hz, $J''$ = 5.8 Hz, H-2β), 3.70 (1 H, d, $J$ = 13.7 Hz, H-6a), 3.78 (1 H, dd, $J$ = 14.1 Hz, $J'$ = 7.8 Hz, H-2α), 3.94 (3 H, s, H-8), 4.21 (1 H, d, $J$ = 11.3 Hz, H-4″a), 4.32 (1 H, d, $J$ = 11.3 Hz, H-4″s), 7.47 (1 H, ddd, $J$ = $J'$ = 7.2 Hz, $J''$ = 1.2 Hz, H-5), 7.52 (1 H, ddd, $J$ = $J'$ = 7.3 Hz, $J''$ = 1.3 Hz, H-6), 7.64 (1 H, dd, $J$ = 7.1 Hz, $J'$ = 1.0 Hz, H-7), 7.90 (1 H, dd, $J$ = 7.0 Hz, $J'$ = 1.5 Hz, H-4), 8.30 (1 H, s, H-2).

**X-ray Experimental Data for 22l:** $2(C_{18}H_{21}N_3O)\cdot C_{18}H_{14}O_8$, $M_r$ = 949.08, monoclinic, $P2_1$, $a$ = 18.233 (2) Å, $b$ = 7.9201 (9) Å, $c$ = 18.847 (2) Å, β = 116.85 (1)°, $V$ = 2428 Å$^3$, $Z$ = 2, $D_x$ = 1.298 g cm$^{-3}$, monochromatized radiation λ(Cu Kα) = 1.54184 Å, $\mu$ = 0.70 mm$^{-1}$ $F(000)$ = 1004, $T$ = 273 K. Data collected on an Enraf-Nonius CAD4 diffractometer to a 2θ limit of 140° with 3491 observed, $I \geq 1\sigma(I)$, reflections out of 5129 measured. The structure was solved by direct methods using SHELXS-86[28] and

(28) Sheldrick, G. M. In *Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University Press: New York, 1985; pp 184–189.

refined using full-matrix least-squares on $F$. Final agreement statistics, based on 500 variables refined, are R = 0.063, $w_R$ = 0.072, $S$ = 1.84 $(\Delta/\sigma)_{max}$ = 0.02. Weighting scheme is $1/\sigma^2(I)$. Maximum peak height in final difference Fourier map is 0.24 (5) eÅ$^{-3}$ with no chemical significance. Full crystallographic details are presented in the supplementary material. All calculations performed on a Sun Microsystems computer using SDP-Plus[29] software. The molecular complex is depicted in Figure 3 with the numbering scheme employed.

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**Supplementary Material Available:** Microanalysis and NMR data for each of the final compounds described and tables of coordinates, thermal parameters, and bond distances and angles for **22l** (22 pages). Ordering information is given on any current masthead page.

(29) *Structure Determination Package*; Enraf-Nonius: Delft, The Netherlands, 1985.
(30) Grob, C. A.; Renk, E. *Helv. Chim. Acta* **1954**, *37*, 1689.