a 25% increase in coronary flow. The EC_{25} was derived logarithmically from nonlinear regression logit analysis of concentration-response data for each heart with 95% confidence limits in parentheses.[23] The results summarized in Table III are the mean of 5-10 individual experiments.

Logarithms of the EC_{25} values were subjected to a Neuman-Keul multiple comparison test at the 0.05 significance level[24] to assess differences between the compounds tested.

Registry No. **3a**, 120225-61-8; **3b**, 120225-53-8; **3c**·HCl, 127258-32-6; **3d**·HCl, 127258-35-9; **3e**·HCl, 127258-37-1; **3f**, 120225-58-3; **3g**·HCl, 127258-40-6; **3h**·HCl, 124431-80-7; **3i**·HCl, 127258-42-8; **3j**·HCl, 127258-44-0; **3k**·HCl, 127258-46-2; **4**, 146-77-0; 4 acetonide derivative, 24639-06-3; **5**, 72209-19-9; **6a**, 127258-29-1; **6b**, 120225-75-4; **6c**, 127258-33-7; **7a**, 127258-30-4; **7b**, 72209-22-4; **8a**, 127258-31-5; **8b**, 120225-77-6; **8c**, 127258-34-8; **8d**, 127258-36-0; **8e**, 127258-38-2; **8f**, 127258-39-3; **8g**, 127258-41-7; **8h**, 120225-76-5; **8i**, 127258-43-9; **8j**, 127258-45-1; **9h**, 120225-79-8; **9i**, 124499-19-0; **9j**, 124499-20-3; **10h**, 16532-79-9; **10i**, 14191-95-8; **10j**, 33155-58-7; **11h**, 120225-74-3; **11j**, 116856-62-3.

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5-Hydroxytryptamine (5-HT_3) Receptor Antagonists. 1. Indazole and Indolizine-3-carboxylic Acid Derivatives

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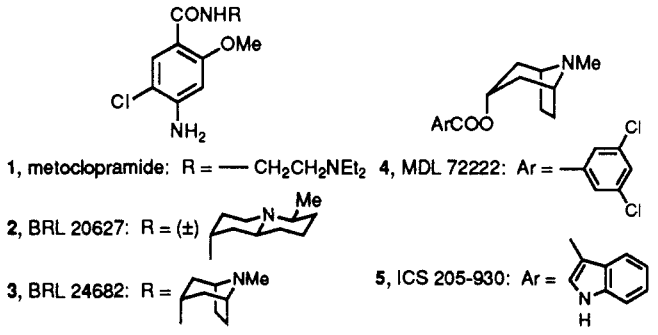
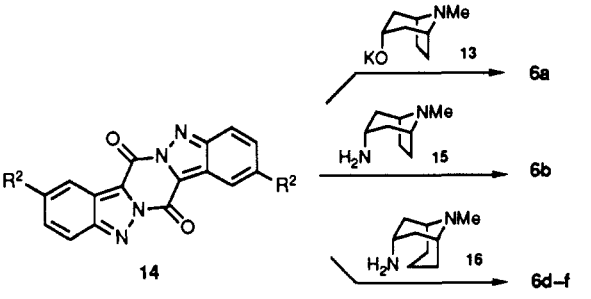
Metoclopramide (1) is a gastric motility stimulant and a weak dopamine and 5-HT_3 receptor antagonist. Conformational restriction of the (diethylamino)ethyl side chain of 1 in the form of the azabicyclic tropane gave **3**, a very potent gastric motility stimulant and 5-HT_3 receptor antagonist but devoid of significant dopamine receptor antagonist properties. Subsequent alteration of the aromatic nucleus led to the identification of indazoles **6a-h**, and 1- and 3-indolizines **7b-d** and **8**, and imidazo[1,5-*a*]pyridines **9** and **10**, as potent 5-HT_3 receptor antagonists devoid of either dopamine antagonist or gastric motility stimulatory properties. Further conformational restriction of the side chain identified quinuclidine **11** and isoquinuclidine **12** as potent 5-HT_3 receptor antagonists which mimic the distorted chair conformation of the tropane with, in the case of **11**, the *N*-methyl group axial. From these series, **6g** (BRL 43694) was found to be both potent and selective and has been shown to be a very effective antiemetic agent against cytotoxic drug induced emesis both in the ferret and in man.

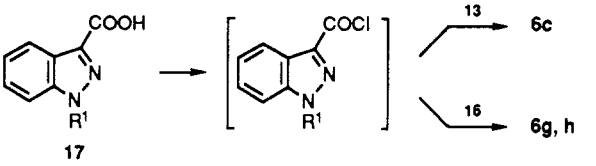
Metoclopramide (1) is a gastric prokinetic benzamide which is also a dopamine receptor antagonist.[1] In addition, 1 has been shown to be a relatively weak 5-hydroxytryptamine 5-HT_3 receptor antagonist.[2] We have recently correlated the 5-HT_3 receptor antagonist activity with the effectiveness of high-dose metoclopramide at inhibiting emesis evoked by cytotoxic agents used in cancer chemotherapy.[3] Antagonism of 5-HT_3 receptors has also been implicated for the treatment of migraine,[4] schizophrenia,[5] and anxiety.[6]



Scheme I. Synthesis of Indazoles **6a,b,d-f**



Scheme II. Synthesis of Indazoles **6c,g,h**



In earlier publications we showed that selectivity of action could be achieved by restricting the conformational freedom of the (diethylamino)ethyl side chain of 1.[7,8] In particular **2** (BRL 20627) was identified as a selective stimulant of upper gastrointestinal motility.[7] Subsequently, tropane **3** (BRL 24682), was identified as both a potent gastric motility stimulant (lowest active dose 0.1 mg/kg sc in rat, method of McClelland et al.[9]) and a potent

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(2) Fozard, J. R.; Mobarok Ali, A. T. M. *Eur. J. Pharmacol.* **1978**, *49*, 109.
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(7) Hadley, M. S.; King, F. D.; McRitchie, B.; Turner, D. H.; Watts, E. A. *J. Med. Chem.* **1985**, *28*, 1843.
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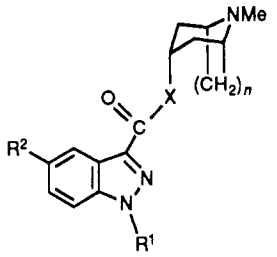
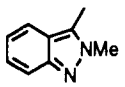
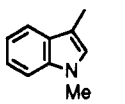
0022-2623/90/1833-1924$02.50/0

Table I. Inhibition of BJ Reflex: Indazoles **6a–h** and Related Compounds



no.	structure R¹	R²	n	X	antagonism of BF reflex: ID_{50}, μg/kg iv (mean ± SEM)	no. of rats
4	MDL 72222				35.0 ± 0.1	4
5	ICS 205-930				1.4 ± 0.4	5
22	GR 38032F				3.6 ± 1.1	4
6a[a]	H	H	2	O	5.3 ± 1.4	6
6b[a]	H	H	2	NH	1.2 ± 0.4	3
6c	Me	H	2	O	1.4 ± 0.1	3
6d	H	H	3	NH	1.1 ± 0.3	3
6e	H	F	3	NH	1.0 ± 0.2	3
6f	H	Cl	3	NH	12.4 ± 5.0	7
6g	Me	H	3	NH	0.7 ± 0.2	9
6h	Et	H	3	NH	0.6 ± 0.2	5
23	Me	H	2	NH	2.0[a]	–
18			3	NH	>100	3
21[b]			3	NH	6.8 ± 1.0	9

[a] Reference 29. **6a** = LY 211000. **6b** = LY 258458. [b] Reference 15.

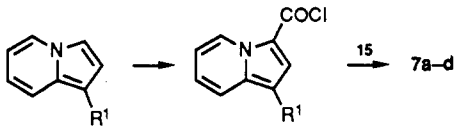
5-HT_3 receptor antagonist [ID_{50} 0.8 ± 0.2 μg/kg iv for inhibition of the 5-HT-evoked Bezold–Jarisch (BJ) reflex, method of Fozard[10]].

The reported 5-HT_3 receptor antagonist activity of tropane esters **4** (MDL 72222)[11] and **5** (ICS 205,930),[12] both structurally related to **3**, prompted us to reinvestigate alternative aromatic nuclei. We have identified indazoles **6a–h** (Table I), indolizines **7b–d** and **8**, and imidazopyridines **9** and **10** (Table II) as potent 5-HT_3 receptor antagonists. The present paper describes their synthesis and structure–activity relationships and highlights **6g**, a particularly potent and selective 5-HT_3 receptor antagonist which is currently being developed for the prevention of nausea and vomiting induced by anticancer treatments.

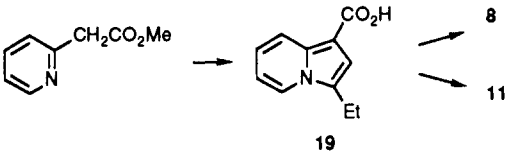
Chemistry

1-Unsubtituted indazole ester **6a** was prepared by the reaction of the potassium salt of tropine (**13**) with dimer **14** (Scheme I).[13] Similarly, reaction of **14** with tropaneamine **15**[14] gave **6b**, and reaction of the appropriately substituted **14** with granataneamine **16**[15] gave amides **6d–f**. 1-Substituted analogues **6c,g,h** were prepared from the appropriate acids **17** via their acid chloride (Scheme II).

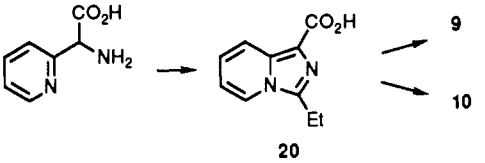
Scheme III. Synthesis of Indolizines **7a–d**



Scheme IV. Synthesis of Indolizines **8** and **11**

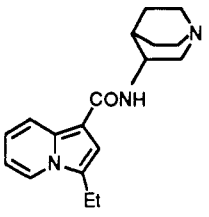


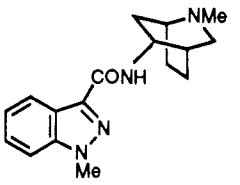
Scheme V. Synthesis of Imidazopyridines **9** and **10**



Isoquinuclidine **12** and 2-methyl analogue **18** were prepared similarly.

Indolizine-3-carboxamides **7a–d** were prepared from the parent indolizine by reaction with phosgene[16] followed by amine **15** (Scheme III). The isomeric indolizine-1-carboxamides **8** and **11** were prepared from acid **19** via the





acid chloride (Scheme IV). Acid **19** was prepared by condensation of methyl 2-pyridylacetate and 2-bromobutyraldehyde in the presence of 2,6-lutidine followed by base hydrolysis. Imidazo[1,5-*a*]pyridines **9** and **10** were prepared via acid **20** obtained by acylation of ethyl 2-pyridylglycine[17] with propionic anhydride with subsequent cyclization and dehydration with phosphoryl chloride (Scheme V).

The stereochemistry of the amides was confirmed by ^1H NMR. In $CDCl_3$, the 3-proton for all the tropane analogues appeared as a quartet which simplified to a triplet on deuterium exchange of the amide proton. This splitting pattern is consistent for a 3-exo proton and a distorted chair conformation in which the 3-exo proton is orthogonal to the 2- and 4-endo protons. By contrast, in deuteromethanol the 3-proton of **6g** appears as a triplet of triplets, with an 11.5 Hz coupling constant with the 2- and 4-endo protons. In addition, a coupling constant of 10.5 Hz observed for the interaction between the 2-exo and 1-protons is indicative of a near 0° dihedral angle, consistent with a 3-exo proton and a boat–chair conformation of the granatane.

The stereochemistry of isoquinuclidine **12** was determined by direct comparison with the ^1H NMR spectra of the 4-amino-5-chloro-2-methoxybenzamide derivatives for which stereochemical assignments had previously been

(9) McClelland, C. M.; McRitchie, B.; Turner, D. H. *Br. J. Pharmacol.* **1983**, *80*, 569P.
(10) Fozard, J. R. *Neuropharmacology* **1984**, *23*, 1473.
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(13) Smith, R. F.; Kirchner, F. K. *J. Org. Chem.* **1958**, *23*, 62.
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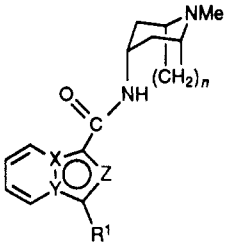
(16) Jones, G.; Stanger, J. *J. Chem. Soc. C* **1969**, 901.
(17) Van Zyl, G.; Devries, D. L.; Decker, R. H.; Niles, E. T. *J. Org. Chem.* **1963**, *26*, 3373.

Table II. Inhibition of BJ Reflex: Compounds **7a–d**, **8**, **9**, and **10**



no.	structure					antagonism of BF reflex	
	R^1	X	Y	Z	n	ID_{50}, μg/kg iv (mean ± SEM)	no. of rats
7a	H	N	C	CH	2	>10	3
7b	Me	N	C	CH	2	1.6 ± 0.2	4
7c	Et	N	C	CH	2	1.0 ± 0.2	3
7d	Ph	N	C	CH	2	4.7 ± 1.3	3
8	Et	C	N	CH	2	0.24 ± 0.03	6
9	Et	C	N	N	2	1.0 ± 0.3	3
10	Et	C	N	N	3	0.5 ± 0.2	4

made.[18] In the spectra of the 5-*endo*-benzamides, the 6-exo proton was identified at the unusually low position of δ 2.6 from the 'W' coupling to a 7-proton. The 6-exo proton also suffered a 10 Hz coupling to the 5-proton at δ 4.31, thus defining the 5-proton as coplanar and exo. The amide substituent is therefore endo. In addition, the effect of introducing a lanthanide shift reagent was both to markedly alter the position of the 6-aromatic proton for the benzamide derivative, which indicates that the lanthanide binding site is close to the amide carbonyl, and to alter the position of the 7-proton of the side chain, while having little effect on the position of the 2-protons. These results are again consistent with an endo assignment of the amide stereochemistry.

In the ^1H NMR spectrum of **12**, the position and splitting pattern of the isoquinuclidine side chain protons was identical in every respect with that of the *endo*-benzamide isomer.

Results

The relative potencies of the compounds as 5-HT_3 receptor antagonists were assessed by their ability to inhibit the 5-HT evoked reflex bradycardia [Bezold–Jarisch (BJ) reflex] in the rat. This effect is mediated by activation of 5-HT_3 receptors located in the wall of the right ventricle.[19] For direct comparison, all potencies reported are the results from standardized procedures performed within our laboratory.

Within the indazole series, high potency was found both with tropaneamide **6b** and with granataneamide **6d** (Table I). Although ester **6a** was significantly less potent, 1-methyl analogue **6c** retained the high potency of amide **6b**. The 1-methyl (6g) and 1-ethyl (6h) amides were slightly more potent than 1-unsubstituted **6d** and significantly more so than the equivalent, isosteric indole **21**. 2-Methyl isomer **18** was very much less potent. Although a small substituent in the 5-position of the indazole ring could be tolerated, for example the fluoro in **6e**, the presence of the larger chloro substituent in **6f** resulted in a marked reduction in potency. This lack of steric tolerance has been previously reported for indolyl esters.[20]

The high potency of the indazoles prompted us to investigate other aromatic 6,5-azaheterocycles, in particular indolizines and imidazopyridines. The possible beneficial effect of a 1-alkyl substituent seen with the indazoles was even more marked with the 3-indolizines (Table II). Whereas 1-H compound **7a** had relatively low potency, the 1-methyl (**7b**) and 1-ethyl (**7c**) analogues retained good 5-HT_3 receptor antagonist potency. However, introduction of the much larger phenyl substituent (**7d**) resulted in a marked reduction in potency. Isomeric 3-ethylindolizine-1-carboxamide **8** was found to be more potent than **7c** and in vivo is the most potent 5-HT_3 antagonist reported to date. Introduction of the additional nitrogen atom in **9** resulted in a 4-fold loss in potency. However, granatane **10** had twice the potency of tropane **9**. Both the conformationally more rigid quinuclidine **11** and isoquinuclidine **12** retained good 5-HT_3 receptor antagonist activity (inhibition of Bezold-Jarisch reflex, ID_{50} 1.3 ± 0.5 and 1.7 ± 0.6 μg/kg iv, respectively).

From these series **6g** was selected for further evaluation. The full pharmacological profile has been published elsewhere.[21-26] The 5-HT_3 receptor antagonist activity was confirmed by its ability to antagonize 5-HT evoked tachycardia of rabbit isolated heart (apparent pA_2 10.6 ± 0.3). In addition, **6g** showed a high affinity for central 5-HT_3 sites (K_i 0.59 nmol for displacement of [^3H]GR 65630)[27] but little affinity for other receptor sites, in particular for 5-HT_1 sites (K_i < 10000 nmol for displacement of [^3H]-5-HT) or 5-HT_2 cites (K_i > 1000 nmol for displacement of [^3H]ketanserin) in rat cortex.

The rationale behind the investigation of 5-HT_3 receptor antagonists was to find a potent and selective inhibitor of emesis evoked by the use of either cytotoxic drugs or

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(19) Paintal, A. S. *Physiol. Rev.* **1973**, *53*, 159.
(20) Giger, R. K. A.; Dontasch, P.; Engel, G.; Richardson, B.; Stadler, P. A. VIIIth Internation Symposium on Medicinal Chemistry Uppsala, August 27–31, 1984; Abstract L63.
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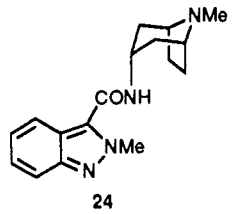
(23) Fake, C. S.; King, F. D.; Sanger, G. J. *Br. J. Pharmacol.* **1987**, *91*, 335P.
(24) Boyle, E. A.; Miner, W. D.; Sanger, G. J. *Br. J. Cancer* **1987**, *56*, 227.
(25) Boyle, E. A.; Miner, W. D.; Sanger, G. J. *Br. J. Pharmacol.* **1987**, *91*, 418P.
(26) Sanger, G. J.; Boyle, E. A.; McClelland, C. M.; Miner, W. D.; Moss, H. E. Xth International Congress of Pharmacology, Sydney, August 23–28, 1987; Abstract 0416.
(27) Kilpatrick, G. J.; Jones, B. J.; Tyers, M. B. *Nature* **1987**, *330*, 746.

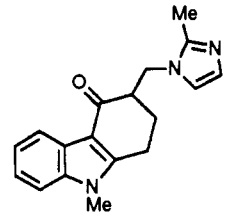
X-irradiation in anticancer therapy. In ferrets, **6g** at a dose of 2 × 0.5 mg/kg iv totally inhibited emesis evoked either by cisplatin (10 mg/kg iv) or by the combination of doxorubicin (6 mg/kg) and cyclophosphamide (8 mg/kg). In addition, again in ferrets, a single dose of 0.5 mg/kg iv similarly totally inhibited emesis evoked by whole-body X-irradiation (10.4-min exposure, 300 rd/min). Compound **6g** is therefore a very effective inhibitor of emesis evoked by anticancer therapies in animal models. This high effectiveness is being mirrored in the on-going clinical trials in man.[28]

Discussion

The common features of four potent 5-HT_3 receptor antagonists, **3**, **6g**, ester **5**, and carbazole **22**,[29] are an aromatic system connected via a five-atom, carbonyl-containing linkage to a basic nitrogen atom. A particular feature of benzamides such as **3** is the hydrogen bond between the amidic N–H and the *o*-methoxy group which holds the amide system in the same plane as, and hence in conjugation with, the aromatic ring, thus forming a planar "virtual ring".[8] Similarly, the carbonyl group in **22** would also be held in plane by its inclusion in a fused 6-membered ring. It would therefore be reasonable to conclude that both **6g** and **5** also adopt an "in plane" orientation of the carbonyl group at the 5-HT_3 receptor. This could account for the lack of potency of 2-methyl isomer **18** in which steric interactions would destabilize the "in plane" orientation. The X-ray structures of tropanes **23** (LY 278584) and **24** (LY 278989) have recently been published confirming that, whereas in the inactive 2-methyl isomer **24** the amide carbonyl is "out of plane", in the active 1-methyl isomer **23** planarity is maintained.[30]



24



22, GR 38032F

For both tropanes and granatanes, the endo-3-substituted ring could adopt either a chair or boat conformation, the preferred conformation depending upon the size of the 3-substituent.[31] In $CDCl_3$, the ^1H NMR spectra of tropanes **6a–c**, **7a–d**, **8**, and **9** show that they all exist primarily in a chair conformation with some distortion to reduce steric strain between the amide and the bismethylene bridge protons. The chair conformation of **23** has also been confirmed in the solid state by X-ray analysis.[30] From previous investigations on the conformation of 3-tropanylamides, the boat conformation is only observed when a large N-substituent, such as phenyl, is present.[31] With the high potency of the tropaneamides, it would be reasonable to conclude that the tropane side chain adopts a chair conformation at the 5-HT_3 receptor. The reported inactivity of equatorial isomers further substantiates this conclusion.[20] If the axially substituted tropanes adopted a boat conformation, the relative positions of the aryl amide group and the basic *N*-atom would be similar to that in the inactive equatorial isomers. It was therefore surprising that, although the conformation adopted by 3-substituted granatane **6g** in solution as the monohydrochloride is a boat, it retained the high potency of the tropanes. In order to rationalize this apparent anomaly, the energy required to convert the granatane to the chair form must be balanced by an inherently more energetically favored binding of the axial granatane to the 5-HT_3 receptor.

Upon the basis of the hypothesis that the axially substituted chair conformation is that adopted by the tropane at the 5-HT_3 receptor, quinuclidine **11** and isoquinuclidine **12**, which are both capable of mimicking this conformation, were prepared. Both compounds retained high potency, which provides further evidence for this conformational hypothesis. In addition, **11** mimics the tropane with an axially orientated *N*-methyl group. It has recently been reported that the methyl quaternary derivative of **5** is a potent 5-HT_3 receptor antagonist.[32] Therefore, for the free bases, activity is probably retained whether the *N*-methyl group is axial or equatorial.

Superimposition of the side chains and carbonyl linkages of **3** with either **6g** or **5** would superimpose the phenyl ring of **3** onto the 5-membered ring of the indazole or indole. This suggests that the aromaticity of the 5-membered ring is important for activity. However, recent work in our laboratories has shown that aromaticity in the 5-membered ring is not an essential requirement. This work will form the basis of our next paper in this series.

Experimental Section

Chemistry. Melting points are uncorrected. The elemental analyses indicated are within 0.4% of the theoretical values. For those compounds whose values fall outside this range, a high-resolution molecular mass ion value is quoted. ^1H NMR spectra were recorded on a JEOL GX270 or Varian CFT-20 instrument as indicated with Me_4Si as internal standard. Mass spectra were recorded on an AEI MS9 (70 eV) spectrometer. All evaporations of solvent were carried out under reduced pressure and organic extracts were dried over K_2CO_3 unless specified otherwise. For column chromatography, the alumina used was neutral Brockman Grade I and the compounds were preabsorbed prior to loading. Yields quoted are not optimized and generally refer to results of a single experiment. 5-fluoro-1*H*-indazole-3-carboxylic acid,[33] 5-chloro-1*H*-indazole-3-carboxylic acid,[34] 1-alkylindolizines,[35] and 1-phenylindolizine[36] were prepared by the literature methods.

***endo*-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 1*H*-Indazole-3-carboxylate (6a).** A solution of tropine (0.45 g, 3.2 mmol) and KO-*t*-Bu (0.36 g, 3.2 mmol) in dry DMF (50 mL) was stirred at room temperature for 30 min. The more volatile *t*-BuOH was removed by partial evaporation under reduced pressure and diindazolo[2,3-*a*,2′,3′-*d*]pyrazine-7,14-dione[13] (0.2 g, 0.7 mmol) was added. The reaction mixture was heated to 120 °C for 2 h and cooled and the solvent was removed by rotary evaporation. The residue was treated with saturated $NaHCO_3$ and the product was extracted into $CHCl_3$ (3 × 50 mL). The solvent was removed from the dried organic extracts and the residue was triturated with Et_2O to give title compound **6a**, which was recrystallised from EtOAc: 0.16 g (40%); mp 234–235 °C dec; ^1H NMR [$(CD_3)_2SO$] δ 13.55 (br s, 1, NH), 5.31 (t, 1, 3-H), 2.36 (s, 3, NCH_3). Anal. ($C_{16}H_{19}N_3O_2$) C, H, N.

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***endo*-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 1-Methyl-1*H*-indazole-3-carboxylate (6c).** A stirred suspension of 1-methyl-1*H*-indazole-3-carboxylic acid[37] (0.88 g, 5 mmol) in dry CH_2Cl_2 (50 mL) was treated with oxalyl chloride (0.46 g, 5 mmol) and 3 drops of DMF. After 1 h the effervescence had ceased and the solvent was removed by rotary evaporation to give the crude acid chloride. The potassium salt of tropine in DMF [50 mL, prepared as described for **6a** from tropine (0.7 g, 5 mmol)] was treated with a solution of the crude acid chloride in dry CH_2Cl_2 (20 mL) and the mixture was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, the residue was treated with saturated $NaHCO_3$, and the product was extracted into CH_2Cl_2 (3 × 50 mL). Evaporation of the dried extracts afforded crude **6c** which was converted into its monohydrochloride, monohydrate salt and was recrystallized from EtOH/Et_2O: 0.4 g (27%); mp 257–260 °C; ^1H NMR ($CDCl_3$) δ 5.55–5.30 (m, 1, 3-H), 4.18 (s, 3, NCH_3), 2.83 (s, 3, NCH_3). Anal. ($C_{17}H_{24}ClN_3O_3$) C, H, N.

General Procedure for the Preparation of the Indazoles 6b,d–f. A suspension of the appropriate diindazolo[2,3-*a*,2′,3′-*d*]pyrazine-7,14-dione (**14**, 2.5 mmol) in dry DMF (20 mL) was heated with the appropriate amine, **15** or **16** (5 mmol), at 100 °C for 2 h. The solvent was evaporated and the residue was partitioned between saturated $NaHCO_3$ (50 mL) and CH_2Cl_2 (100 mL). Concentration of the dried organic extracts afforded crude products **6b,d–f**, which were purified by column chromatography on alumina, eluting with CH_2Cl_2 containing increasing proportions of MeOH.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-1*H*-indazole-3-carboxamide (6b):** 28%; mp 234–235 °C dec; ^1H NMR ($CDCl_3$) δ 11.60 (br s, 1, NH), 4.38 (dt, 1, 3-H) 2.39 (s, 3, NCH_3). Anal. ($C_{16}H_{20}N_4O$) C, H, N.

***endo*-*N*-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-1*H*-indazole-3-carboxamide (6d):** 10%; mp 209–212 °C; ^1H NMR ($CDCl_3$) δ 13.01 (br s, 1, NH), 4.54 (dtt, 1, 3-H), 2.53 (s, 3, NCH_3). Anal. ($C_{17}H_{22}N_4O$) C, H, N.

***endo*-*N*-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-5-fluoro-1*H*-indazole-3-carboxamide (6e):** 19%; mp 264–267 °C dec; ^1H NMR [$(CD_3)_2SO$] δ 13.32 (br s, 1), 4.50 (m, 1), 2.50 (s, 3, NCH_3). Anal. ($C_{17}H_{21}FN_4O \cdot 0.5H_2O$) C, H, N.

***endo*-*N*-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-5-chloro-1*H*-indazole-3-carboxamide (6f):** 6%; mp 295–298 °C; HRMS *m/e* 332.1410, $C_{17}H_{21}ClN_4O$ requires 332.1404; ^1H NMR [$CDCl_3$ + $(CD_3)_2SO$] δ 13.50 (br s, 1, NH), 4.75–4.20 (m, 1, 3-H), 2.49 (s, 3, NCH_3). Anal. ($C_{17}H_{21}ClN_4O \cdot H_2O$) C, H; N: calcd, 6.60; found, 5.95.

***endo*-*N*-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-1-methyl-1*H*-indazole-3-carboxamide (6g).** A solution of 1-methylindazole-3-carbonyl chloride [prepared from the acid (0.88 g, 5 mmol) by the procedure described for **6c**] in CH_2Cl_2 (50 mL) was treated with a solution of **16** (0.7 g, 5 mmol) and Et_3N (0.55 g, 5.5 mmol) in CH_2Cl_2 (30 mL). The reaction was stirred for 2 h and washed with saturated $NaHCO_3$, and the organic layer was dried and concentrated. Purification of the residue by column chromatography on alumina, eluting with CH_2Cl_2, gave **6g**, which was converted to its monohydrochloride salt: 1.0 g (65%); mp 290–292 °C; ^1H NMR (CD_3OD) δ 4.63 (tt, 1, J = 11.5 Hz, 3-H), 4.15 (s, 3, NCH_3), 2.98 (s, 3, NCH_3). Anal. ($C_{18}H_{25}ClN_4O$) C, H, N, Cl.

The following compounds were prepared by the procedure described for **6g**.

***endo*-*N*-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-1-ethyl-1*H*-indazole-3-carboxamide (6h).** 1-Ethyl-1*H*-indazole-3-carboxylic acid[37] (0.95 g, 5 mmol) was converted to title compound **6h**: 1.1 g (70%); mp 143–144 °C; ^1H NMR ($CDCl_3$ + D_2O) δ 4.54 (tt, 1, 3-H), 4.44 (q, 2, NCH_2), 2.56 (s, 3, NCH_3), 1.53 (t, 3, CH_3). Anal. ($C_{19}H_{26}N_4O$) C, H, N.

***endo*-*N*-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-2-methyl-2*H*-indazole-3-carboxamide (18).** 2-Methyl-2*H*-indazole-3-carboxylic acid[35] (0.88 g, 5 mmol) was converted to title compound **18**, which was isolated as its monohydrochloride salt: 0.86 g (55%); mp 271–272 °C; ^1H NMR [$(CD_3)_2SO$] δ 11.25, 10.30 (2 br s, 1, NH), 4.95, 4.62 (2 m, 1, 3-H), 4.39 (s, 1, NCH_3), 2.99, 2.90 (2 d, 3, NCH_3). Anal. ($C_{18}H_{25}ClN_4O$) C, H, N.

General Procedure for the Preparation of Indolizine-3-carboxamides 7a–d. A solution of the appropriate indolizine (10 mmol) in dry toluene (10 mL) was added to a cooled and stirred solution of phosgene in toluene (10 mL, 12.5% solution) under nitrogen. The solution was kept overnight, the precipitated indolizine hydrochloride was removed by filtration, and the filtrate was evaporated under reduced pressure to give the crude indolizine-3-carboxylic acid chloride. This was dissolved in CH_2Cl_2 (50 mL) and a solution of **15** (1.2 g, 8 mmol) and Et_3N (1.6 g, 16 mmol) in CH_2Cl_2 (10 mL) was added with stirring and cooling. After 4 h, the reaction mixture was washed with 10% Na_2CO_3 solution, dried, and evaporated to dryness. The residue was purified by column chromatography as described previously for **6g** and the product was recrystallized from EtOAc/petroleum ether.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-indolizine-3-carboxamide (7a):** 55%; mp 102–103 °C; ^1H NMR ($CDCl_3$) δ 9.56 (d, 1), 7.45 (d, 1), 7.06 (d, 1), 6.92 (t, 1), 6.72 (t, 1), 6.45 (d, 1), 6.25 (br d, 1, NH), 2.34 (s, NCH_3). Anal. ($C_{17}H_{21}N_3O$) C, H, N.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-1-methylindolizine-3-carboxamide (7b):** 60%; mp 169–170 °C; ^1H NMR ($CDCl_3$) δ 9.52 (d, 1), 7.38 (d, 1), 6.88 (s, t, 2), 6.67 (t, 1), 6.17 (br d, 1, NH), 2.34 (s, 6, NCH_3, CH_3). Anal. ($C_{15}H_{23}N_3O$) C, H, N.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-1-ethylindolizine-3-carboxamide (7c):** 60%; mp 171–172 °C; ^1H NMR ($CDCl_3$) δ 9.53 (d, 1), 7.40 (d, 1), 6.89 (s, 1), 6.92–6.82 (m, 1), 6.67 (t, 1), 6.19 (br d, 1, NH), 2.76 (q, 2, CH_2), 2.33 (s, 3, NCH_3), 1.30 (t, 3, CH_3). Anal. ($C_{19}H_{25}N_3O$) C, H, N.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-1-phenylindolizine-3-carboxamide (7d):** 45%; mp 148 °C; ^1H NMR ($CDCl_3$) δ 9.15 (d, 1), 7.90–6.60 (m, 9 including 7.18, s, 1), 6.30 (br d, 1, NH), 2.34 (s, 3, NCH_3). Anal. ($C_{23}H_{25}N_3O$) C, H, N.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-3-ethylindolizine-1-carboxamide (8).** A solution of methyl 2-pyridylacetate (6 mL), 2,6-lutidine (6 mL), and 2-bromobutyraldehyde[38] (5.5 g, 36 mmol) in xylene (200 mL) was heated under reflux for 18 h, with removal of the H_2O produced by means of a Dean–Stark apparatus. The reaction mixture was cooled and washed with an excess of dilute citric acid solution, and the organic phase was dried (Na_2SO_4), concentrated, and purified by column chromatography on silica, eluting with CH_2Cl_2 to give methyl 3-ethylindolizine-1-carboxylate (4.6 g, 64%). A solution of this ester (4.6 g) in EtOH (100 mL) and 1 N NaOH (50 mL) was heated under reflux for 3 h. The cooled reaction mixture was concentrated and the aqueous residue was washed with ether (50 mL). Acidification of the aqueous layer gave 3-ethylindolizine-1-carboxylic acid (**19**, 3.0 g, 70%), used without further purification. Acid **19** was converted to title compound **8** by the procedure described for **6c**: 55%; mp 182–183 °C; ^1H NMR ($CDCl_3$) δ 8.33 (d, 1), 7.78, (d, 1), 6.95 (m, 1), 6.70 (t, 1), 6.60 (s, 1), 6.18 (br d, 1, NH) 2.82 (q, 2, CH_2) 2.32 (s, 3, NCH_3), 1.40 (t, 3, CH_3). Anal. ($C_{19}H_{25}N_3O$) C, H, N.

Prepared similarly was ***N*-(1-azabicyclo[2.2.2]octan-3-yl)-3-ethylindolizine-1-carboxamide (11):** 48%; mp 211–212 °C; ^1H NMR ($CDCl_3$) δ 8.33 (d, 1), 7.78 (d, 1), 6.96 (m, 1), 6.73 (s, 1), 6.70 (td, 1), 5.48 (br d, 1, NH), 4.27–4.15 (m, 1), 3.48 (ddm, 1). Anal. ($C_{18}H_{23}N_3O$) C, H, N.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-3-ethylimidazo[1,5-*a*]pyridine-1-carboxamide (9).** A solution of freshly distilled ethyl 2-pyridylglycine[17] (3.8 g, 21 mmol) and propionic anhydride (4 mL) in CH_2Cl_2 (25 mL) was stirred at room temperature for 18 h. The reaction mixture was evaporated to dryness and the residue was partitioned between EtOAc (100 mL) and 10% Na_2CO_3 solution (100 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated, and the residue was heated under reflux with $POCl_3$ (12 mL) in $ClCH_2CH_2Cl$ (100 mL) for 18 h. The reaction mixture was evaporated to dryness and the residue was partitioned between EtOAc (100 mL) and 10%

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Na_2CO_3 solution (100 mL). The organic phase was separated, dried, and concentrated to give the crude ethyl 3-ethylimidazo-[1,5-*a*]pyridine-1-carboxylate (4.0 g, 85%). This ester was hydrolyzed to acid **20** (2.5 g, 70%) by the method described for **19**. A suspension of **20** (0.22 g, 1.1 mmol) was stirred with $SOCl_2$ (3 mL) at room temperature for 3 h. The excess $SOCl_2$ was removed by evaporation; the residue was suspended in CH_2Cl_2 (10 mL) and treated with a solution of **15** (0.2 g, 1.4 mmol) and Et_3N (0.4 mL) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 18 h and washed with saturated $NaHCO_3$ (20 mL), and the lower organic phase was dried and concentrated. Purification of the residue by column chromatography on alumina, eluting with $CHCl_3$, gave **9**: 0.22 g (65%); mp 107–108 °C; ^1H NMR ($CDCl_3$) δ 8.25 (dm, 1), 7.77 (dm, 1), 7.71 (br d, 1, NH), 6.94 (dd, 1), 6.69 (tm, 1), 2.96 (q, 2, CH_2), 2.32 (s, 3, NCH_3), 1.46 (t, 3, CH_3). Anal. ($C_{17}H_{24}N_4O$) C, H, N.

***endo*-*N*-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-ethylimidazo[1,5-*a*]pyridine-1-carboxamide (10).** By following the procedure described for **9**, **20** (0.22 g, 1.1 mmol) was converted to **10**: 0.2 g (55%); mp 155–157 °C; ^1H NMR ($CDCl_3$) δ 8.28 (dm, 1), 7.77 (dm, 1), 6.96–6.85 (m, 2), 6.68 (tm, 1), 2.98 (q, 2, CH_2), 2.42 (s, 3, NCH_3), 1.44 (t, 3, CH_3). Anal. ($C_{18}H_{26}N_4O$) C, H, N.

***endo*-*N*-(2-Methyl-2-azabicyclo[2.2.2]octan-5-yl)-1-methyl-1*H*-indazole-3-carboxamide (12).** A mixture of *endo*- and *exo*-5-amino-2-methyl-2-azabicyclo[2.2.2]octane (0.3 g, 2.1 mmol) was converted to title compound **12**, which was separated from its exo isomer by column chromatography on alumina, eluting with CH_2Cl_2 containing increasing quantities of $CHCl_3$: 0.15 g (24%); mp 107–109 °C; ^1H NMR ($CDCl_3$) δ 8.36 (dt, 1), 7.05 (d, 1), 4.48–4.35 (m, 1, 5-H), 4.10 (s, 3, NCH_3), 2.79 (d, 2, J = 2 Hz), 2.76–2.67 (m, 1), 2.67–2.59 (m, 1). Anal. ($C_{16}H_{22}N_4O$) C, H, N.

Pharmacology. The compounds were evaluated for antagonism of the Bezold–Jarisch reflex evoked by 5-HT in the anesthetized rat by the method of Fozard et al.[10,39] Male rats (260–290 g) were anesthetized with urethane (1.25 g/kg ip) and blood pressure and heart rate were recorded. A submaximal dose of 5-HT (6 μg/kg iv) was given repeatedly and the changes in heart rate were quantified. Compounds were given intravenously prior to administration of 5-HT and the dose required to reduce the 5-HT evoked response to 50% of the control response (ID_{50}) was determined. The antiemetic activity was assessed in the ferret. Food was withdrawn 12 h before experimentation and emesis was induced by iv injection of either cisplatin (10 mg/kg) or by a combination of cyclophosphamide (80 mg/kg) and doxorubicin (6 mg/kg). To evoke emesis by X-irradiation, ferrets were exposed to X-rays derived from the tungsten anode of a Machlett Model OEG-50 operating at 50 kV and 20 mA through a beryllium window with a 0.18-mm aluminum filter placed about 25 cm above the ferret for 10.4 min. Compound **6g** was given either as a divided dose 30 min before and 45 min after cisplatin, 30 min before and 30 min after doxorubicin/cyclophosphamide, or as a single dose 5 min before exposure to X-irradiation. The latency period for the onset of emesis and the number of emetic episodes was compared with saline-based controls. Antagonism of 5-HT evoked contraction of guinea pig ileum and 5-HT-evoked tachycardia was assessed by the literature procedure.[39] pA_2 values were determined by the method of Arunlakshana and Schild.[40] Binding to 5-HT_1 and 5-HT_2 receptors was estimated by the methods of Bennett and Snyder[41] and Leysen et al.,[42] respectively, using rat cortical membranes, [^{3}H]-5-HT (4 nmol), and [^{3}H]ketanserin (0.5 nmol).

Acknowledgment. We thank A. Dunbar and W. D. Miner for biological testing and D. Smith for the NMR data.

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5-Hydroxytryptamine (5-HT_3) Receptor Antagonists. 2. 1-Indolinecarboxamides

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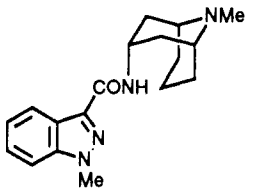
Indazole **1** has previously been shown to be a potent and selective 5-HT_3 receptor antagonist. A novel series of potent 5-HT_3 receptor antagonists, 1-indolinecarboxamides **2a–q** and 1-indolecarboxamides **3b,i,j,k**, is described. The activity of the indolines suggests that aromaticity of the 5-membered ring is not an essential requirement for potency provided that an "in plane" orientation of the carbonyl group is favored. Upon the basis of this hypothesis indene **9** was prepared in which the "in plane" orientation of the carbonyl group is maintained by conjugation with the aromatic ring through the sp^2 hybridized carbon. It was also found to be a potent 5-HT_3 receptor antagonist.

The first paper in this series described the synthesis and activity of a novel series of potent 5-hydroxytryptamine (5-HT_3) receptor antagonists from which indazole **1** (BRL



1 BRL 43694

43694), was highlighted,[1] which is currently undergoing clinical trials for the inhibition of emesis evoked by cancer therapy. In that paper we proposed that, for high potency, the carbonyl link must be in the same plane as the aromatic rings. We also speculated on the relative importance of the aromaticity of the two rings of the bicyclic indazole with respect to its activity. This paper describes our results obtained from compounds in which the 5-membered ring of a fused bicyclic system is nonaromatic, but in which a planar relationship of the amide and the aromatic ring is maintained with the sp^2 hybridization of an aromatic amide. The synthesis and activities of 1-indolinecarboxamides **2a–q** (Table I) are described, together with the closely related 1-indolecarboxamides **3b,i,j,k** (Table II). Upon the basis of the conclusions regarding structure–activity, indene **9** was also prepared and its activity was investigated.

Chemistry

1-Indolinecarboxamides **2a–q** were synthesized (Scheme I) from the appropriate indoline **4** and either *endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-amine or *endo*-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine[1] via trichloromethyl carbamate **5** (method 1), carbamoyl chloride **6**

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0022-2623/90/1833-1929$02.50/0