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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(40) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol. Chemother.* **1959**, *14*, 48.

(41) Bennett, J. P.; Snyder, S. H. *Mol. Pharmacol.* **1976**, *16*, 373.

(42) Leysen, J. E.; Niemegeers, J. E.; Van Neuten, J. M.; Laduron, P. M. *Mol. Pharmacol.* **1982**, *21*, 301.

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

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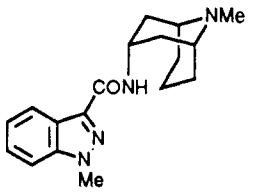
Indazole 1 has previously been shown to be a potent and selective 5-HT_3 receptor antagonist. A novel series of potent 5-HT_3 receptor antagonists, 1-indolinecarboxamides **2a–q** and 1-indolecarboxamides **3b,i,j,k**, is described. The activity of the indolines suggests that aromaticity of the 5-membered 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**

(1) Bermudez, J.; Fake, C. S.; Joiner, G. F.; Joiner, K. A.; King, F. D.; Sanger, G. J. *J. Med. Chem.* Preceding paper in this issue.

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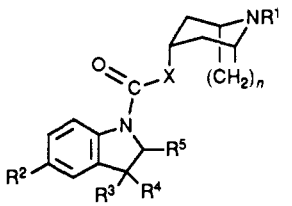
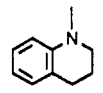
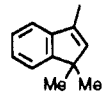
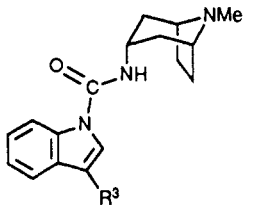
Table I. Structure and Analytical and Pharmacological Data of **2a–q**, **8**, and **9**



no.	R^1	R^2	R^3	R^4	R^5	X	*n*	method[a]	% yield[b]	formula	mp, °C	anal.	inhibn of BJ reflex ID_{50}, μg/kg iv (± SEM)	inhibn of BJ reflex no. of rats
1[d]			BRL 43694										0.7 ± 0.2	9
2a	Me	H	H	H	H	NH	3	1	52	$C_{18}H_{25}N_3O{\cdot}0.5H_2O$	176–178	C,H,N	12.5 ± 2.5	3
2b	Me	H	H	H	H	NH	2	1	48	$C_{17}H_{23}N_3O$	153–154	C,H,N	1.4 ± 0.1	6
2c	Et	H	H	H	H	NH	2	1	25	$C_{18}H_{25}N_3O$	140–141	C,H,N	>10	3
2d	Me	H	H	H	H	O	2	*a*	31	$C_{17}H_{22}N_2O_2$	133–134	C,H;N[c]	4.3 ± 1.3	3
2e	Me	F	H	H	H	NH	2	3	18	$C_{17}H_{22}FN_3O$	299–300	C,H,N	>10	3
2f	Me	Cl	H	H	H	NH	2	2	19	$C_{17}H_{22}ClN_3O$	149–150	C,N,Cl	>10	3
2g	Me	MeO	H	H	H	NH	2	1	45	$C_{18}H_{25}N_3O_2{\cdot}H_2O$	142–145	C,H,N	>10	3
2h	Me	NO_2	H	H	H	NH	2	1	62	$C_{17}H_{22}N_4O_3$	176–178	C,H,N	>10	3
2i	Me	H	Me	H	H	NH	2	3	23	$C_{18}H_{25}N_3O{\cdot}HCl$	268–270	C,H,N	3.0 ± 0.4	3
2j	Me	H	Et	H	H	NH	2	1	76	$C_{19}H_{27}N_3O{\cdot}HCl{\cdot}H_2O$	263–264	C,H,N	1.5 ± 0.5	3
2k	Me	H	Ph	H	H	NH	2	2	91	$C_{23}H_{27}N_3O{\cdot}HCl$	319–320	C,H,N	1.8 ± 0.2	3
2l	Me	H	H	H	Me	NH	2	2	78	$C_{19}H_{25}N_3O{\cdot}HCl$	292–293	C,H,N	0.8 ± 0.3	3
2m	Me	H	Me	H	Me	NH	2	2	35	$C_{19}H_{27}N_3O$	134–136	C,H,N	0.5 ± 0.2	4
2n	Me	H	Me	Me	Me	NH	2	2	50	$C_{20}H_{29}N_3O{\cdot}HCl$	225–226	C,H,N	1.4 ± 0.4	4
2o	Me	H	$-(CH_2)_2-$		H	NH	2	2	23	$C_{19}H_{25}N_3O$	196–197	C,H,N	3.5 ± 1.0	3
2p	Me	H	$-(CH_2)_4-$		H	NH	2	2	49	$C_{21}H_{29}N_3O$	191–193	C,H,N	1.2 ± 0.6	3
2q	Me	H	$-(CH_2)_5-$		H	NH	2	2	35	$C_{22}H_{31}N_3O$	188–189	C,H,N	3.6 ± 1.0	3
8	Me					NH	2	2	75	$C_{18}H_{25}N_3O{\cdot}HCl$	269–271	C,H,N	>100	3
9	Me					NH	2	*a*	86	$C_{20}H_{27}ClN_3O$	>300	C,H,N	1.0 ± 0.2	4

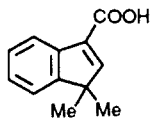
[a] See the Experimental Section. [b] Yield for final stage only. [c] H: calcd, 7.74; found, 8.19. [d] Reference 1.

Table II. Structure and Analytical and Pharmacological Data of **3b,i,j,k**



no.	R^3	formula	mp, °C	anal.	% yield	inhibn of BJ reflex ID_{50}, μg/kg iv (± SEM)	no. of rats
3b	H	$C_{17}H_{21}N_3O{\cdot}HCl{\cdot}0.4H_2O$	258–260	C, H, N	68	7.1 ± 1.7	3
3i	Me	$C_{18}H_{23}N_3O{\cdot}HCl{\cdot}H_2O$	158–161	C, H, N	40	1.6 ± 0.2	3
3j	Et	$C_{19}H_{25}N_3O{\cdot}HCl{\cdot}0.25H_2O$	210–213	C, H, N	40	2.0 ± 0.7	4
3k	Ph	$C_{23}H_{25}N_3O{\cdot}HCl$	264–265	C, H, N	40	5.1 ± 1.3	3

(method **2**), or *N*-succinimidyl carbamate **7** (method **3**). 1,2,3,4-Tetrahydroquinoline **8** was prepared similarly by method 2. When R^4 = H, 1-indolinecarboxamides **2b,i,j,k** were dehydrogenated with DDQ[2] to give indoles **3b,i,j,k**. Indene **9** was prepared from acid **10** via the acid chloride.[4]



10

Results and Discussion

The 5-HT_3 receptor antagonist potency of the compounds was assessed by their ability to antagonise the 5-HT-evoked reflex bradycardia [Bezold–Jarisch (BJ) reflex] in rats.[5] This effect is mediated by activation of 5-HT_3 receptors located in the wall of the right ventricle.[6]

The low potency of granatane **2a** (Table I) and the high potency of tropane **2b** parallels the structure–activity relationship of the 3-indolecarboxamides rather than that

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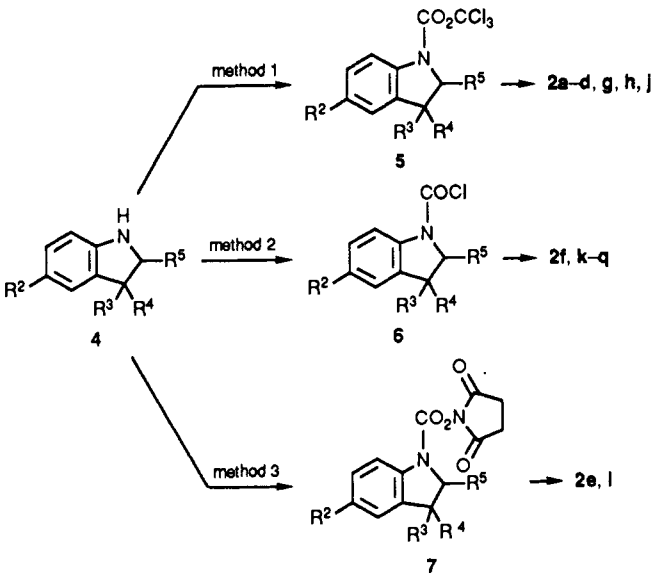
(3) Yoneda, R.; Terada, T.; Harusawa, S.; Kurihara, T. *Heterocycles* **1985**, *23*, 557.
(4) Fozard, J. R. *Neuropharmacol.* **1984**, *23*, 1473.
(5) Paintal, A. S. *Physiol. Rev.* **1973**, *53*, 159.
(6) Giger, R. K. A.; Donatsch, P.; Engel, G.; Richardson, B.; Stadler, P. A. *Proceedings of the VIIIth International Symposium on Medicinal Chemistry*, Uppsala, 1984; p 133.

Scheme I. Synthesis of Indolines **2a–q**



of the 3-indazolecarboxamides.[1] *N*-Ethyltropane **2c** was much less potent than the *N*-methyl analogue **2b**. A similar steric constraint has been previously observed for indole esters.[7] Carbamate **2d** was also less potent than urea **2b**. For the previously reported indazole series, substitution in the benzo ring with groups larger than F resulted in a marked reduction in potency. Steric intolerance was even more marked in this series with all the 5-substituted analogues **2e–h** being much less potent than **2b**. The related 1,2,3,4-tetrahydroquinolinyl urea **8** was inactive within the dose range tested. This may be a consequence of the greater steric interaction between the urea linkage and both the peri-8H atom and the two 2H atoms of the tetrahydro ring which would destabilize the "in plane" orientation of the carbonyl. Alternatively this lack of activity may result from the different relative orientation of the benzo ring and the tropane side chain.

The introduction of a 3-methyl in **2i** or the larger 3-phenyl in **2k** failed to increase potency. It was previously reported that the 2-methylindazoles were very much less potent than the 1-methyl isomers.[1] In marked contrast, 2-methylindolines retained high potency. 3-Unsubstituted **21**, 3-monomethyl **2m**, and 3,3-dimethyl **2n** were all found to be potent 5-HT_3 receptor antagonists. These results can still be rationalized in terms of the "in plane" hypothesis for the linking carbonyl. At the nonaromatic sp^3 hybridized 2-C atom of the indoline, the 2-methyl substituent can sit below the plane of the ring. This would allow a favored "in plane" orientation of the carbonyl link. For the fully aromatic indazoles, the 2-methyl substituent is held in the plane of the aromatic ring by the sp^2 hybridization, which would result in a considerable steric hindrance to the "in plane" orientated link.[1] 3,3-spiro compounds **2o,p,q** were less potent with potency being maximal for 5-membered **2p**. Although indole analogue **3b** was less potent than its indoline counterpart **2b**, reasonable potency was maintained for the 3-substituted indoles **3i** and **3j** (Table II).

Assuming that the indolines retain the "in plane" orientation of the carbonyl link via the sp^2 hybridization of the N atom, a similarly favored "in plane" orientation could be achieved by attaching the linking carbonyl via a nonaromatic sp^2 hybridized C atom. This was achieved with indene **9**, in which the 3,3-dimethyl substitution maintains the double bond in the 1,2-position. It was subsequently found to be a highly potent 5-HT_3 receptor antagonist (Table I).

In conclusion, the results with indolines **2b,d,i–q** and indene **9** show that aromaticity in the 5-membered ring of the bicyclic aromatic nucleus is not essential for potency. This would imply that the 5-membered ring is merely acting as a "spacer" unit to ensure the optimal angular and spacial orientation of the carbonyl linkage, the basic side chain, and the aromatic ring. Further work in our laboratories has shown that the active geometry can be retained in a monocyclic aromatic derivative; this will form the basis of the next paper in the series.

Experimental Section

Chemistry. Melting points are uncorrected. Elemental analyses indicated are within 0.4% of the theoretical values unless specified. All evaporations of solvent were carried out by rotary evaporation under reduced pressure and organic extracts were dried over Na_2SO_4 unless specified. For chromatography the alumina and silica used was Fluka TLC type H. Light petroleum refers to the fraction boiling between 60 and 80 °C. The yields quoted are nonoptimized and generally refer to the result of a single experiment. Indolines **4** were either commercially available or prepared by standard synthetic procedures which have been described in detail elsewhere.[7]

General Procedure for the Preparation of the 1-Indoline Ureas 2a–c,e–q and 8. Method 1. A solution of trichloromethyl chloroformate (3.7 g, 0.02 mol) in dry CH_2Cl_2 (20 mL) was added dropwise to a cooled solution of the appropriate indoline (0.02 mol) and Et_3N (2.0 g, 0.02 mol) in dry CH_2Cl_2 (100 mL). The reaction was stirred at room temperature for 2 h, washed with H_2O (5 mL) and 5 N HCl (5 mL), and dried. The solvent was removed and the residue was purified by filtration through a short alumina column, eluting with CH_2Cl_2 to give the appropriate trichloromethyl carbamate **5**. A solution of **5** (0.01 mol) and the appropriate diamine (0.01 mol) in dry toluene (100 mL) was heated under reflux for 24 h. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 (200 mL) and saturated K_2CO_3 (40 mL). The organic phase was separated, dried, and concentrated, and the residue was purified by column chromatography on alumina, eluting with $CHCl_3$, to give the appropriate carboxamides, which were either crystallized from EtOAc or converted to their hydrochloride salt.

Method 2. A solution of the appropriate indoline or 1,2,3,4-tetrahydroquinoline (0.02 mol) and Et_3N (2.0 g, 0.02 mol) in dry CH_2Cl_2 (20 mL) was added, dropwise, to a cooled and stirred solution of $COCl_2$ (18 mL of 12.5% w/w solution in toluene) in dry CH_2Cl_2 (30 mL). The reaction was stirred at 0 °C for 1 h, poured into pentane (400 mL), washed with 5 N H_2SO_4 (30 mL) and brine (30 mL), and dried. The solvent was evaporated to give carbamoyl chloride **6**, which was used without further purification. A solution of **6**, (0.01 mol) the appropriate diamine (0.01 mol) and Et_3N (1.0 g, 0.01 mol) in dry CH_2Cl_2 (100 mL) was stirred at room temperature for 18 h. The solvent was evaporated and the residue was partitioned between Et_2O (50 mL) and 5 N HCl (20 mL). The aqueous phase was separated and basified with K_2CO_3, and the product was extracted into CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried and concentrated and the residue was purified by filtration through a short alumina column, eluting with $CHCl_3$. The product was either crystallized from EtOAc or converted to its hydrochloride salt.

Method 3. A solution of the appropriate indoline (0.02 mol) and *N,N*-disuccinimidyl carbonate (5.1 g, 0.02 mol) in dry toluene (100 mL) was stirred at room temperature for 18 h. The solvent was evaporated, the residue was dissolved in CH_2Cl_2 (100 mL), and the solution was washed with 5 N HCl (10 mL), saturated K_2CO_3, and finally brine (30 mL). The organic phase was dried and concentrated, and the residue was purified by filtration through a short silica column, eluting with CH_2Cl_2, to give carbamate **7**. A solution of **7** (0.01 mol) and *endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (1.4 g, 0.01 mol) in dry toluene (100 mL) was heated under reflux for 18 h. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 (200 mL) and saturated K_2CO_3 (40 mL). The organic phase was dried, and concentrated, and the residue was purified by chromatography

(7) Joiner, K. A.; King, F. D. *European* Patent 0247,266, 1987.

on alumina, eluting with $CHCl_3$. The product was either crystallized from EtOAc or converted into its hydrochloride salt.

***endo*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl) 1-Indolinecarboxylate (2d).** A solution of tropine (1.13 g, 8 mmol) and KO-*t*-Bu (0.94 g, 8.4 mmol) in dry diglyme (50 mL) was stirred at room temperature for 1 h and then evaporated. The residue was treated with a solution of carbamate **5** (2.4 g, 8.5 mmol) in dry diglyme (50 mL) and heated under reflux for 36 h. The solvent was evaporated and the residue was partititoned between 5 N HCl (10 mL) and Et_2O (30 mL). The aqueous phase was separated and basified with K_2CO_3 and the product was extracted into CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried and concentrated and the residue was purified by column chromatography on alumina, eluting with CH_2Cl_2. Crystallization from Et_2O afforded **2d** (0.7 g).

General Procedure for Preparation of 1-Indolecarboxamides 3b,i,j,k. A solution of the monohydrochloride salt of the appropriate 1-indolinecarboxamide **2b,i,j,k** (1.6 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.41 g, 1.8 mmol) in dry $CHCl_3$ (100 mL) was heated under reflux for 6 h. The cooled reaction mixture was washed with saturated K_2CO_3 (20 mL), dried, and concentrated. The residue was filtered through a short alumina column, eluting with $CHCl_3$ to give the appropriate indole-1-carboxamide, which was converted into its hydrochloride salt.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-3,3-dimethyl-1-indenecarboxamide Hydrochloride (9).** A stirred solution of 3,3-dimethylindene-1-carbonyl chloride (1.1 g, 5.3 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was treated with a solution of *endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (0.8 g, 5.7 mmol) in dry CH_2Cl_2 (50 mL). After 2 h the reaction mixture was diluted with ether (300 mL) to give **9** (1.6 g): ^1H NMR (DMSO-d_6) δ 8.20 (br s 1 H), 7.80–7.70 (m, 1 H), 7.48–7.38 (m, 1 H), 7.30–7.15 (m, 2 H), 7.03 (s, 1 H), 2.64 (s, 3 H), 1.32 (s, 6 H).

Pharmacology. The compounds were evaluated for antagonism of the BJ reflex evoked by 5-HT in the anesthetised rat by the method of Fozard.[4,8] 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.

Acknowledgment. We thank C. S. Fake and G. J. Sanger for their help and support.

(8) Sanger, G. J. *Br. J. Pharmacol.* **1987**, *91*, 77.

5-Hydroxytryptamine (5-HT_3) Receptor Antagonists. 3. Ortho-Substituted Phenylureas

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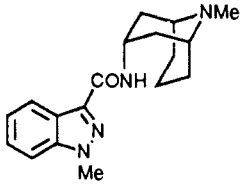
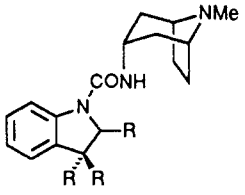
A novel series of potent 5-HT_3 receptor antagonists, ortho-substituted phenylureas **6a–z**, is described in which the 5-membered ring of the previously reported indazoles and indolines has been replaced by an intramolecular hydrogen bond. High potency was found both for carbamate **6a** and urea 6b. Granatane **6c** was less potent than the equivalent tropane. Phenylurea **11c** lacking the ortho substituent was inactive. Whereas further substitution could not be tolerated in the aromatic ring, activity was retained with a range of *O*-alkyl groups, compounds **6k–t**. In addition, good activity was found for ortho ester **6u** and sulfonamide **6x**. The ortho-substituted phenylureas can therefore be regarded as bioisosteres of the 6,5-heterocycles indole, indazole, and indoline.

In part 1 of this series of papers indazole **1** (BRL 43694) was shown to be a potent and selective 5-hydroxytrypt-



1 BRL 43694



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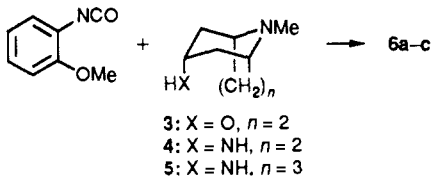
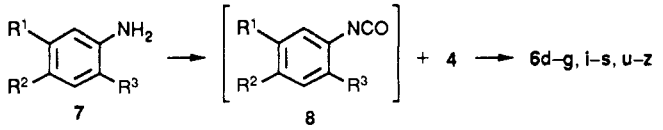
amine 5-HT_3 receptor antagonist.[1] It was also shown to be a highly effective inhibitor of cytotoxic drug and X-irradiation induced emesis in ferrets and is currently being developed as an antiemetic for use in conjunction with anticancer therapy in man. In part 2 we showed that high potency was retained with indolines of general formula **2**.[1] It was concluded that, provided an "in plane" orientation of the carbonyl linkage was not disfavored, aromaticity in the fused 5-membered ring was not necessary. It was therefore considered possible that the 5-membered ring could be replaced by a "pseudo" ring in the form of a hydrogen-bonded system. Although a 5-membered cyclic hydrogen bonded system is weak,[2] the stabilization afforded under suitable conditions may be sufficient to favor an "in plane" orientation of a strategically placed carbonyl linkage.

Scheme I. Synthesis of Ureas 6a–c



Scheme II. Synthesis of Ureas 6d–g,i–s,u–z



The present paper describes the synthesis and 5-HT_3 receptor antagonist activity of a series of ortho-substituted phenylureas, **6a–z**, which are capable of forming an intramolecular hydrogen bond.

(1) *J. Med. Chem.* Preceding papers in this issue.

(2) Blaney, F. E.; Clark, M. S. G.; Gardner, D. V.; Hadley, M. S.; Middleton, D.; White, T. J. *J. Med. Chem.* **1983**, *26*, 1747.

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