Development of Potent Serotonin-3 (5-HT_3) Receptor Antagonists. II.[1] Structure–Activity Relationships of *N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)carboxamides

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Our studies on 4-amino-5-chloro-2-ethoxybenzamides led to the discovery that the *N*-(1,4-dimethylhexahydro-1*H*-1,4-diazepin-6-yl)benzamide 9 and the 1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine analogue 10 are potent serotonin-3 (5-HT_3) receptor antagonists. Structure–activity relationship (SAR) studies on the influence of the aromatic nucleus of 9 and 10 upon inhibition of the von Bezold–Jarisch reflex in rats are described. Heteroaromatic rings such as pyrrole, thiophene, furan, pyridine, pyridazine, 1,2-benzisoxazole, indole, quinoline, and isoquinoline rings showed weak 5-HT_3 receptor antagonistic activity. Within this series, use of the 1*H*-indazole ring as an aromatic moiety led to a substantial increase of the activity; the 1*H*-indazolylcarboxamides 54, 57, 97, and 102 showed potent 5-HT_3 receptor antagonistic activity. The optimal compound identified *via* extensive SAR studies was *N*-(1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1*H*-indazole-3-carboxamide (54), whose effect was superior to that of the corresponding benzamide 10 and essentially equipotent to those of ondansetron (1) and granisetron (4).

Key words serotonin-3 antagonist; von Bezold-Jarisch reflex; hexahydro-1*H*-1,4-diazepine; *N*-(1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1*H*-indazole-3-carboxamide

Serotonin [5-hydroxytryptamine (5-HT)] is an important neurotransmitter that mediates a wide variety of physiological responses in both the peripheral and central nervous systems.[2] The past decade has seen the discovery of multiple 5-HT receptor subtypes and design of potent specific ligands for these sites. 5-HT receptors are currently classified into four types or groups, comprising 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4 receptors. The 5-HT_1 receptor class has been further subdivided into 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_{1D} subtypes.[3] During the past several years, one of these receptor subtypes, the 5-HT_3 receptor has generated considerable interest due to the pharmacological properties of 5-HT_3 receptor antagonists which made them very attractive for the treatment of a number of brain and gastrointestinal disorders.[4] Indeed, 5-HT_3 receptor antagonists including ondansetron[5] (**1**), tropisetron[6] (**2**), YM 060[7] (**3**), granisetron[8] (**4**), zacopride[9] (**5**), MDL 72222[10] (**6**), azasetron[11] (**7**), and zatosetron[12] (**8**) are clinically effective in the control of cancer chemotherapy-induced nausea and emesis.[13] Furthermore, 5-HT_3 receptor antagonists have been postulated to be potential agents for the treatment of pain,[14] schizophrenia,[15] migraine,[16] anxiety,[17] substance abuse,[18] and irritable bowel syndrome.[19]

We previously reported 5-HT_3 receptor antagonistic activity of 2-alkoxy-4-amino-5-chlorobenzamide derivatives bearing five- to seven-membered heteroalicyclic rings, *i.e.*, pyrrolizine, morpholine, 4*H*-1,4-thiazine, piperidine, piperazine, hexahydro-1,4-oxazepine, hexahydro-1,4-thiazepine, hexahydro-1*H*-azepine, and hexahydro-1*H*-1,4-

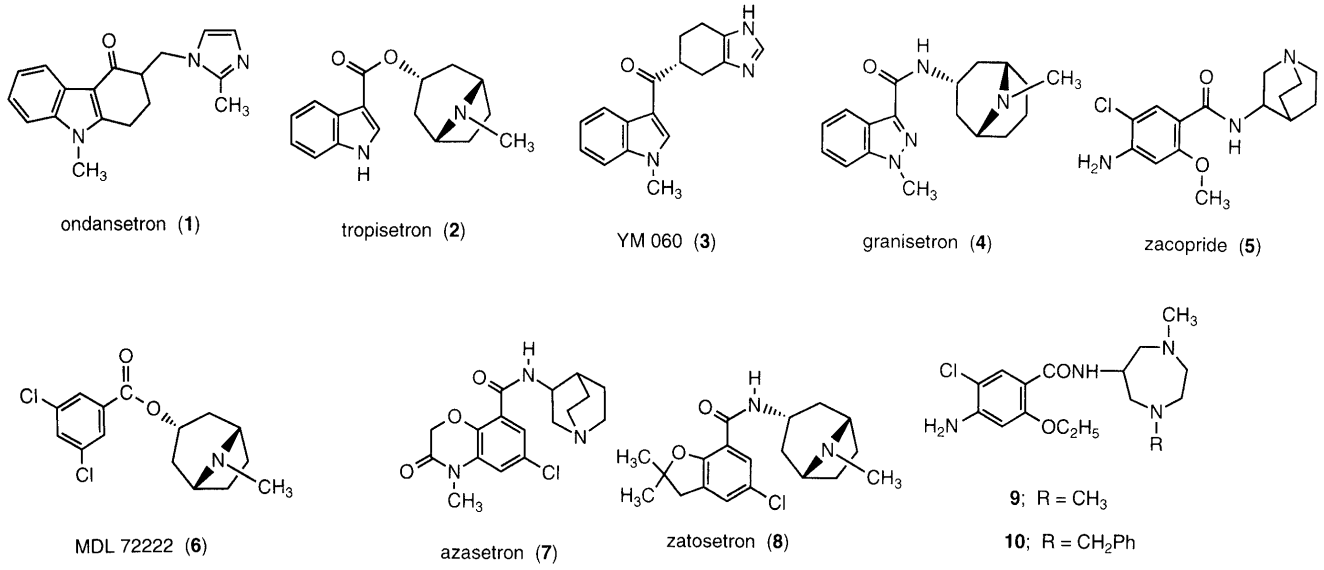

Fig. 1

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diazepine rings, in the amine moiety.[1] From the structure–activity relationships (SARs) of this series, use of the 1,4-diazepine ring gave a substantial increase of the activity compared with the other heteroalicyclic rings. In particular, 4-amino-5-chloro-*N*-(1,4-dimethylhexahydro-1*H*-1,4-diazepin-6-yl)-2-ethoxybenzamide (**9**) and the 1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine analogue **10** showed potent 5-HT_3 receptor antagonistic activity without 5-HT_4 receptor agonistic activity. The chemical structure of the aromatic moiety of the 5-HT_3 receptor antagonists described above has been categorized into three general classes: (1) indole ring, *e.g.*, **1**—**3**; (2) indazole ring as typified by **4**; (3) benzene ring, *e.g.*, **5**—**8**. The potent 5-HT_3 receptor antagonistic activity of compounds **1**—**4** having a heteroaromatic ring prompted us to examine the effect of modifying the aromatic moiety of **9** and **10**; the replacement of the benzene ring of **9** and **10** with alternative heteroaromatic nuclei containing indole and indazole rings, while keeping the 1,4-diazepine ring in the amine moiety constant, seemed worthwhile. We expected that the *N*-(hexahydro-1*H*-1,4-diazepin-6-yl)-3-indolecarboxamides and/or -1*H*-indazole-3-carboxamides would show potent 5-HT_3 receptor antagonistic activities. The present paper describes the synthesis of *N*-(1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)carboxamides and SARs concerning the influence of the aromatic moiety of 1,4-diazepinylcarboxamides upon 5-HT_3 receptor antagonistic activity.

Chemistry

The requisite 1,4-diazepinylamines and alcohols **30**,[20] **31**,[21] **35**,[20] and **36**[1] were prepared by the method reported previously, and the syntheses of the new amines **17** and **20** and the alcohol **15** are shown in Chart 1. Thus, the reaction of methyl β,β-dibromoisobutyrate (**11**) with *N*-benzyl-*N'*-methylethylenediamine (**12**) in the presence of Et_3N gave the 1,4-diazepinylester **14** in an excellent yield. The ester **14** was alternatively obtained by esterification of the 1,4-diazepine-6-carboxylic acid **13**, which was prepared from malonic acid, formaldehyde, and **12**. Reduction of the ester **14** with sodium bis(2-methoxyethoxy)aluminum hydride (Vitride®) furnished the 1,4-diazepinylmethanol **15**. The phthalimido analogue **16**, which was derived from **15** by using the Mitsunobu reaction,[22] was treated with hydrazine to give the desired 6-aminomethyl-1,4-diazepine **17** in a moderate yield. On the other hand, the alcohol **15** was allowed to react with $SOCl_2$, followed by treatment of the resultant 6-chloromethyl-1,4-diazepine **18** with KCN in the presence of 18-crown-6 to afford the 6-cyanomethyl-1,4-diazepine **19**. Hydrogenation of **19** in the presence of Raney Ni produced the target 6-(2-aminoethyl)-1,4-diazepine **20**.

The various carboxylic acids were obtained commercially or prepared according to the literature, except for the 5,6-difluoro-, 6-fluoro-, 6-chloro-, and 7-chloro-1*H*-indazole-3-carboxylic acids (**25a**—**d**) and 1-substituted 1*H*-indazole-3-carboxylic acids (**26b**—**j**). The synthesis of **25a**—**d** was achieved by the method of Snyder *et al.* (Chart

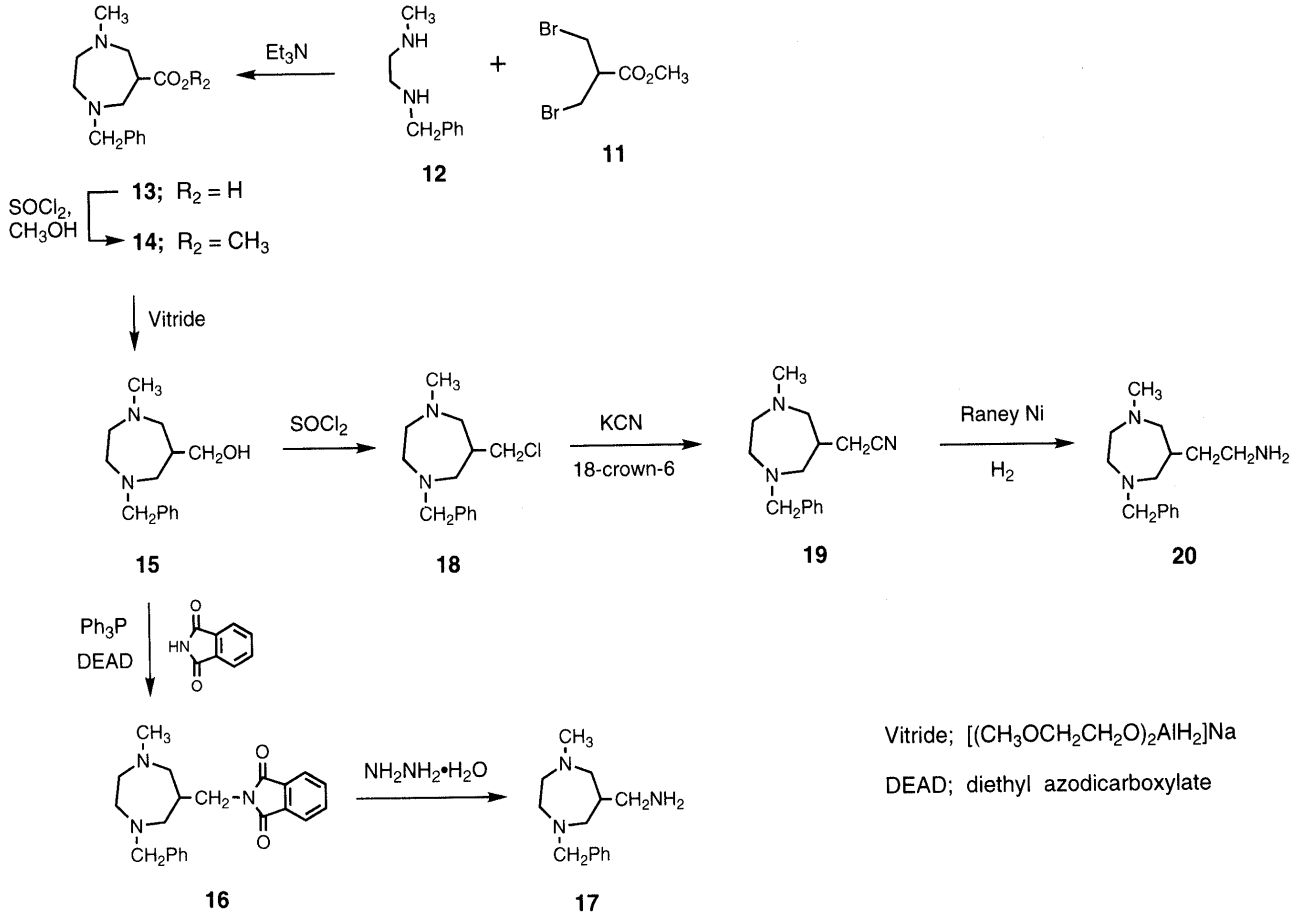


Chart 1

2).[23] The reaction of sodium (2-aminophenyl)glyoxylate derivatives (**22a—d**), which were readily prepared from the corresponding isatins (**21a—d**) and NaOH, with $NaNO_2$ in acidic aqueous solution, followed by reduction of the resulting diazonium salts (**23a—d**) to the hydrazino derivatives (**24a—d**) and spontaneous cyclization, afforded 1*H*-indazole-3-carboxylic acids (**25a—d**) in low yields. Fludzinski *et al.*[24] reported that 1*H*-indazole-3-carboxylic acid (**26a**) was treated with CH_3I in the presence of K_2CO_3 in *N*,*N*-dimethylformamide (DMF) at 50 °C for 4 h to afford a 4/1 mixture of *N*-1/*N*-2 methylated products as the corresponding methyl esters. In order to obtain 1-substituted 1*H*-indazole-3-carboxylic acids, we first applied this method; the treatment of methyl 1*H*-indazole-3-carboxylate (**27a**) with C_2H_5I in the presence of K_2CO_3 in DMF gave the *N*-1/*N*-2 ethylated products **27b**/**28b** in a ratio of 1.4/1 in 95% yield (Table 1, run 1). The separation of **27b** and **28b** by silica gel column chromatography, followed by hydrolysis of the ester moiety, furnished the corresponding carboxylic acids **26b** and **29b**, which were identical with the products reported previously,[25a] on the basis of melting point comparison. Furthermore, the structures of **26b** and **29b** were readily distinguished by ^{1}H-NMR and UV-absorption measurements. In the ^{1}H-NMR spectrum, signals due to the methylene proton of the ethyl group of **26b** appeared at higher field than those of **29b**. The UV-absorption peak of **26b** (299 nm) was observed at a shorter wavelength than that of **29b** (310 nm). To improve the regioselectivity of the ethylation of **27a** with C_2H_5I, we investigated the reaction conditions (Table 1). The ratio of the products (**27b** : **28b**) was determined from the relative intensity of the methylene signals (**27b**: δ 4.52, **28b**: δ 4.98) of the ethyl group in the ^{1}H-NMR spectrum. When NaH [hexamethylphosphoramide (HMPA), 5 °C→room temperature, run 2] or *n*-$Bu_4N^+F^-$ [tetrahydrofuran (THF), room temperature, run 8] was used, the ratio of **27b** and **28b** was essentially the same as that of run 1. On the other hand, the reaction in the presence of *tert*-BuOK as a base proceeded smoothly to give a good yield of the products and resulted in highly selective formation of the *N*-1 ethylated product **27b** (run 3). Addition of 18-crown-6 or tris(dioxa-3,6-heptyl)amine (TDA-1) (runs 4—6) did not further increase *N*-1 ethylation. The combination of K_2CO_3–18-crown-6 (run 7) was less effective. Overall, the reaction of **27a** with C_2H_5I in the presence of *tert*-BuOK

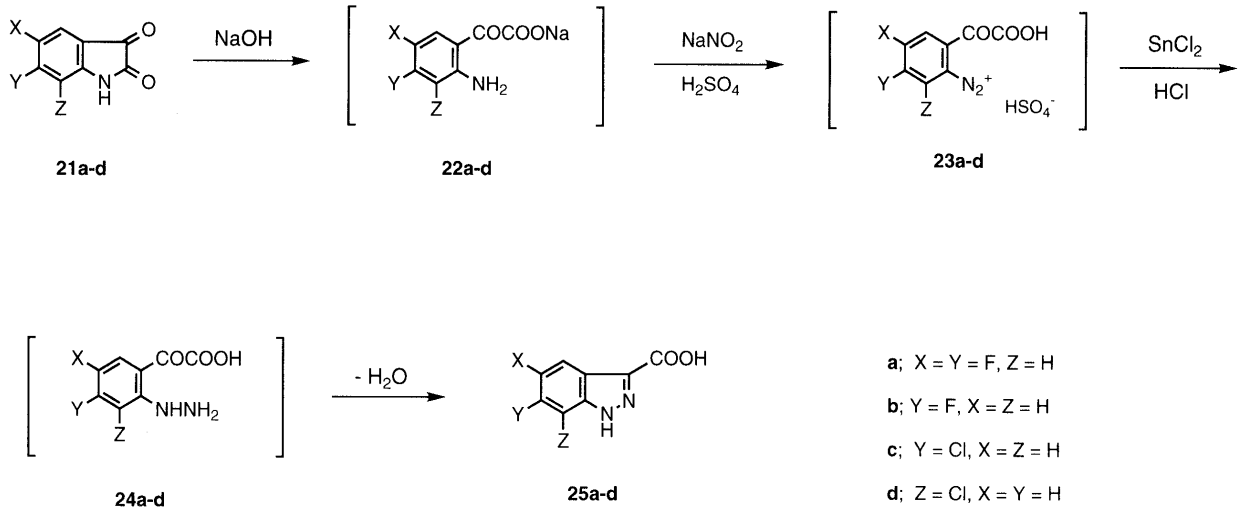
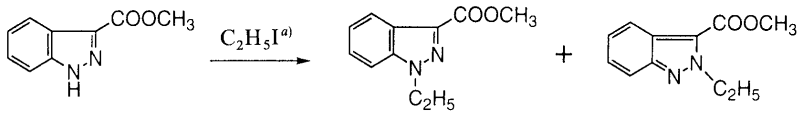


Chart 2

Table 1. Ethylation of Methyl 1*H*-Indazole-3-carboxylate (**27a**)



Run	Base (mol eq)	Solvent	Temp. (°C)	Ratio[b]
1	K_2CO_3 (3.0)	DMF	60	1.4 : 1
2	NaH (1.1)	HMPA[c]	5→room temperature[d]	1 : 1
3	*tert*-BuOK (1.1)	THF	5→room temperature	18 : 1
4	*tert*-BuOK (1.1)+18-crown-6 (0.1)	Et_2O	Room temperature	6 : 1
5	*tert*-BuOK (1.1)+18-crown-6 (0.1)	Et_2O	5→room temperature	9 : 1
6	*tert*-BuOK (1.1)+TDA-1[e] (0.1)	Et_2O	5→room temperature	9 : 1
7	K_2CO_3 (1.5)+18-crown-6 (0.1)	Et_2O	Room temperature	[f]
8	*n*-$Bu_4N^+F^-$ (3.0)	THF	Room temperature	8 : 7

a) 2.0 eq of **27a** was used. *b*) The ratios of **27b** and **28b** were determined by ^{1}H-NMR (see Experimental). *c*) Hexamethylphosphoramide. *d*) Reaction was initiated at *ca.* 5 °C and the mixture was allowed to warm to room temperature (see Experimental). *e*) Tris (dioxa-3,6-heptyl)amine. *f*) *Ca.* 40% of **27a** was recovered unchanged.

as a base afforded a satisfactory result. Under identical reaction conditions, **27a** was alkylated by using various alkyl halides to give the requisite methyl *N*-1-substituted 1*H*-indazole-3-carboxylates **27c—h**, which were hydrolyzed to furnish the corresponding carboxylic acids **26c—h**. On the other hand, in the case of iso-PrI and cyclopentyl bromide as an alkyl halide, the reaction did not proceed, presumably owing to steric hindrance and/or elimination of reagents. Compounds **26i** and **26j** were obtained by using the conditions of run 1; the reaction of **27a** with iso-PrI or cyclopentyl bromide in the presence of K_2CO_3 in DMF, followed by the separation of the mixture of **27i** and **27j** or **28i** and **28j**, and then hydrolysis of the methyl ester moieties of **27i** and **27j** gave the carboxylic acids **26i** and **26j**, respectively (Chart 3).

Various carboxamide derivatives **46—55**, **57—61**, **65—76**, **78—82**, and **91—119**, except for **67**, **73**, **78**, **101—106**, **117**, and **119**, were synthesized by the reaction of an appropriate carboxylic acid with the amine **17**, **20**, **30** or **31** in the presence of *N*,*N*′-carbonyldiimidazole (CDI, method A, Chart 4) or 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSC, method B, Chart 4) as a coupling reagent.

The indolyl and 1*H*-indazolylesters **56**, **62—64**, and

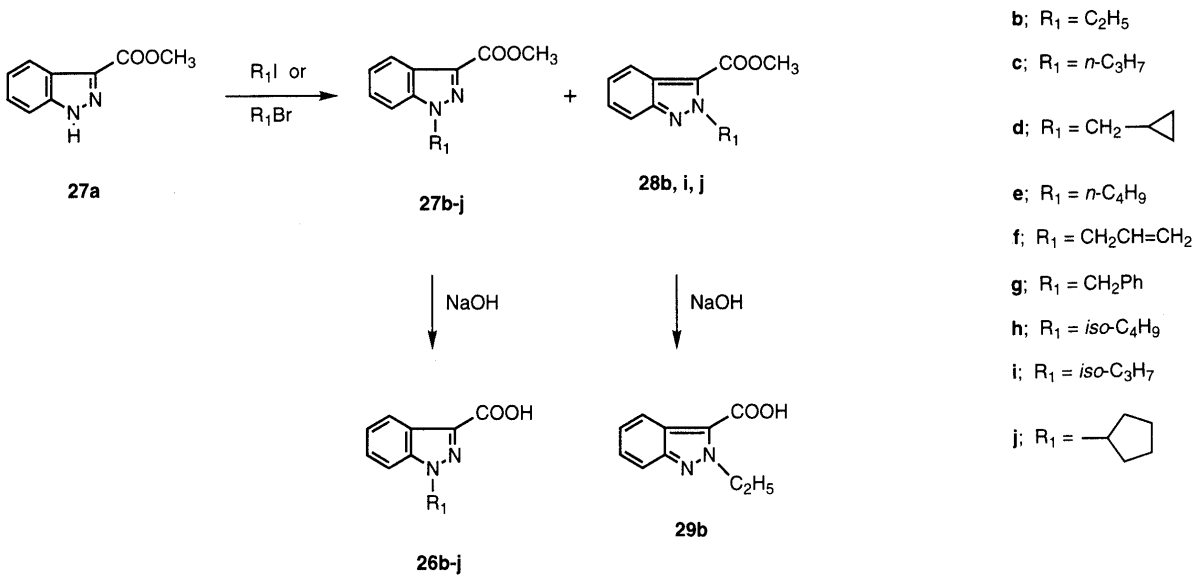


Chart 3

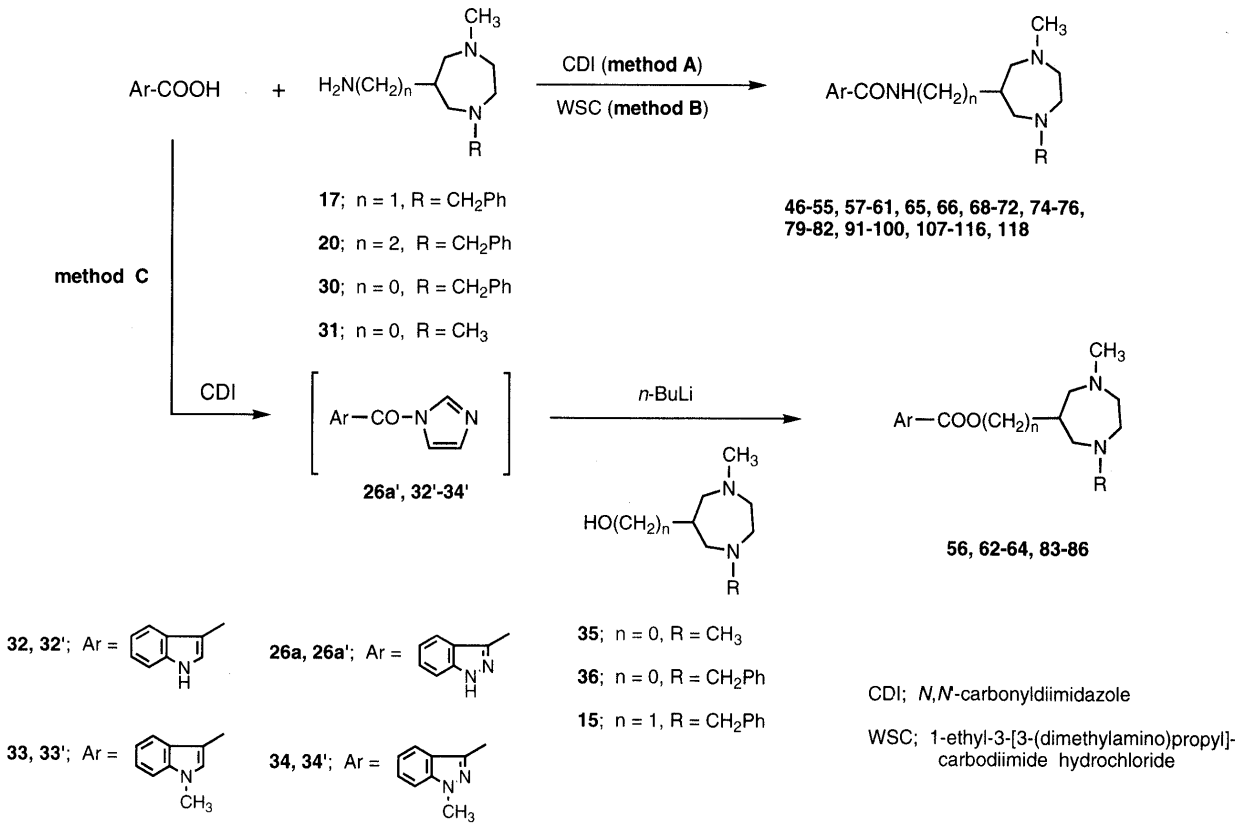


Chart 4

83—**86** were prepared as follows; the carboxylic acid **26a** or **32**—**34** was activated as the imidazolide **26a**′ or **32**′—**34**′, respectively, and then treated with the lithium 1,4-diazepinylalkoxide which was generated from the alcohol **35**, **36**, or **15** and *n*-BuLi (method C, Chart 4).

The treatment of the 1*H*-indazole-3-carboxamide **54** with a carboxylic anhydride or methyl chloroformate gave the corresponding 1-acyl- and 1-methoxycarbonyl-1*H*-indazole-3-carboxamides **101**—**103** and **104**, respectively. Similarly, the reaction of **54** with 3-chloro-2-butanone or 2-chloroethanol in the presence of *tert*-BuOK afforded the 1-alkyl-1*H*-indazole-3-carboxamides **105** as a diastereomeric mixture and **106**, respectively (method D, Chart 5). In this case, the formation of the regioisomer was not observed in the ^{1}H-NMR spectrum, presumably because of the steric hindrance of the 3 position of the 1*H*-indazole ring.

The 5-hydroxy- and 5-amino-1*H*-indazole-3-carboxamides **117** and **119** were obtained by demethylation of the methoxy group of **116** and hydrogenation of the nitro group of **118**, respectively (Chart 5).

The indoline-1-carboxamide **67** was obtained by the reaction of indoline with *N*,*N*′-disuccinimidyl carbonate (**37**) and subsequent treatment of the resulting carbamate

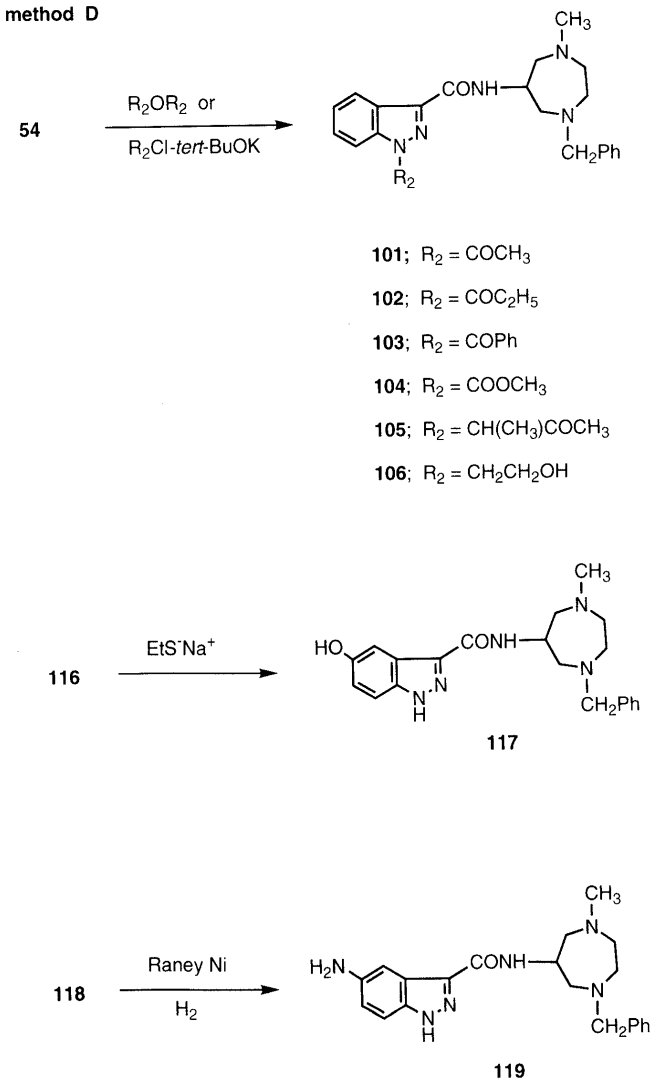


Chart 5

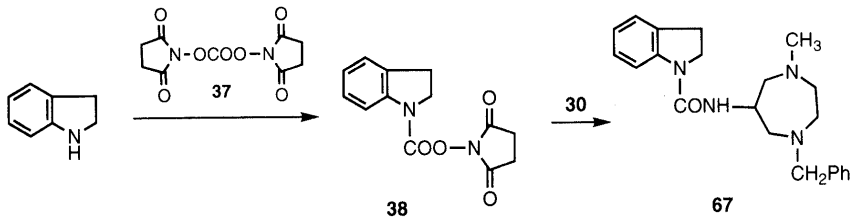
38 with the 6-amino-1,4-diazepine **30**. 4-Hydroxy-3-quinolinecarboxylic acid (**39**) was treated with $SOCl_2$, followed by reaction with the amine **30** in the presence of NaH to give the 4-chloro-3-quinolinecarboxamide **40**. The acid hydrolysis of **40** afforded the 4-hydroxy-3-quinolinecarboxamide **73**. The treatment of isatoic anhydride with **30**, followed by the reaction of the resultant 2-aminobenzamide **41** with $NaNO_2$ in diluted HCl, furnished the 1,2,3-benzotriazin-4-one derivative **77**. 6-Chloro-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-8-carboxylic acid (**42**) was allowed to react with $SOCl_2$, and subsequent treatment of the corresponding acid chloride with the amine **30** gave the target carboxamide **78** (Chart 6).

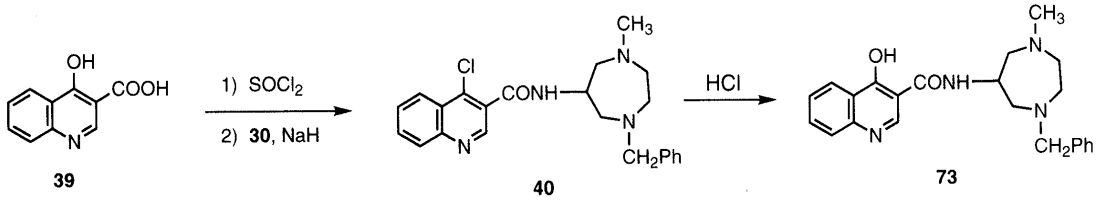
The thioamide **87** was obtained by the reaction of **54** with Lawesson's reagent in a moderate yield. The treatment of 1*H*-indazol-3-ol (**43**) with the 6-chloromethyl-1,4-diazepine **18** in the presence of NaH gave a mixture of the *O*-alkylated compound **88** and the *N*-alkylated product **44** in a ratio of 1 : 1 in 9.2% yield. The mixture was separated by column chromatography on silica gel, and the structure of each compound was proposed on the basis of their ^{1}H- and ^{13}C-NMR spectra. Thus, in the ^{1}H- and ^{13}C-NMR spectra of the less polar **88**, the C_6-methylene proton and carbon signals of the 1,4-diazepine ring were observed at δ 4.22 and at δ 70.16, respectively. On the other hand, those of the more polar **44** appeared at field than those of **88** (^{1}H-NMR: δ 3.84, 4.00; ^{13}C-NMR: δ 50.60). The reaction of 3-acetyl-1-methyl-1*H*-indazole (**45**) with the dihydrochloride of the ethylenediamine **12** in the presence of paraformaldehyde produced the carbonyl product **89**, which was treated with sodium borohydride to give the alcohol derivative **90** as a diasteromeric mixture (Chart 7). The structures of all compounds thus prepared were supported by their ^{1}H-NMR spectra and elemental analyses.

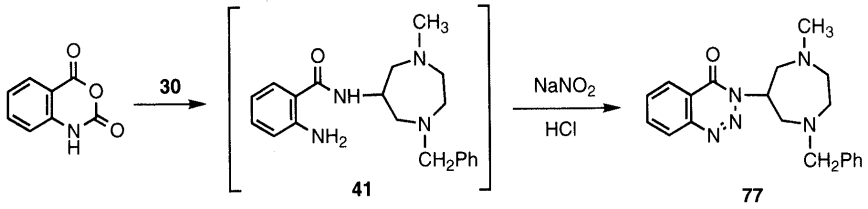
Biological Results and Discussion

Compounds **46**—**119** were evaluated for 5-HT_3 receptor antagonistic activity *in vivo* by measuring their ability to inhibit the von Bezold–Jarisch (B–J) reflex induced by 2-methyl-5-HT in rats. The effect is the result of reflex stimulation of the vagus nerve following activation of 5-HT_3 receptors located in the wall of the right ventricle.[26] The results are shown in Tables 2—4, and ED_{50} values (dose causing 50% inhibition of the bradycardia) are shown in Table 5 for the compounds with potent activity. Data for the benzamides **9** and **10**, ondansetron (**1**), tropisetron (**2**), and granisetron (**4**) are also included in Table 5 for comparison.

In order to identify the optimal aromatic ring, a number of compounds bearing five- and six-membered aromatic heterocycles and two and three fused heterocyclic ring systems, while keeping the 1,4-dimethyl or 1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine ring constant, were initially prepared (Table 2). In the series of five- and six-membered rings, none of the carboxamides prepared (**46**—**53**) showed potent 5-HT_3 receptor antagonistic activity. A six-membered aromatic ring displayed slightly more potent activity than a five-membered aromatic ring. A three-component pharmacophore for 5-HT_3 receptor







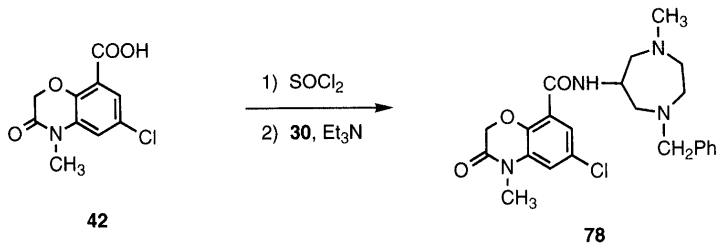
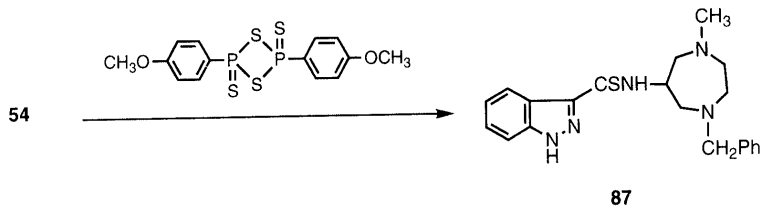
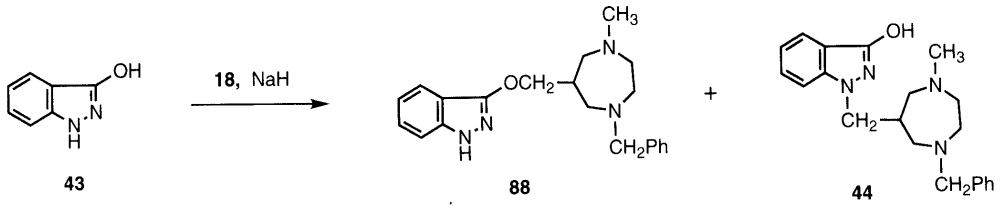


Chart 6





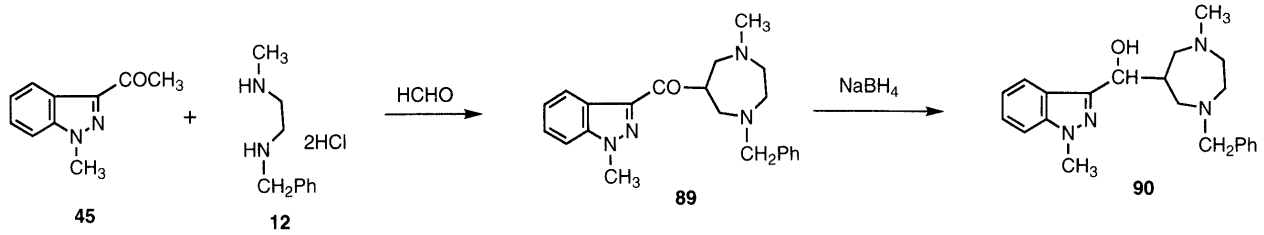
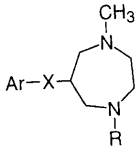


Chart 7

Table 2. Physical Data and 5-HT_3 Receptor-Antagonistic Activity for 1,4-Diazepine Derivatives **46**—**80**



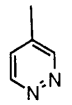
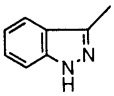
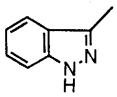
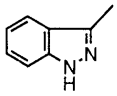
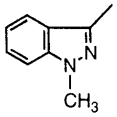
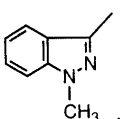
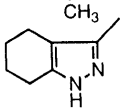
Compd.	Ar	X	R	mp (°C) (Recryst. solvent)	Yield[a] (%) Method	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of B–J reflex[b] (%) (μg/kg, i.v.)
46		CONH	$PhCH_2$	165—169 (EtOH)	30 A	$C_{18}H_{23}N_3O_2 \cdot 2C_2H_2O_4$[c]	53.55 (53.49)	5.52 (5.51)	8.52 (8.54)	0 (10)
47		CONH	$PhCH_2$	179—184 (EtOH)	51 A	$C_{18}H_{23}N_3OS \cdot 2C_2H_2O_4$[c,d]	51.86 (52.00)	5.34 (5.19)	8.25 (8.19)	0 (10)
48		CONH	$PhCH_2$	79—82 (Tri)[e]	65 A	$C_{18}H_{24}N_4O$	69.20 (69.09)	7.74 (7.82)	17.93 (17.79)	0 (10)
49		CONH	$PhCH_2$	88—92 (Tri)[e]	44 A	$C_{19}H_{24}N_4O \cdot 2C_2H_2O_4$[c] $\cdot 3/4H_2O$	53.33 (53.61)	5.72 (5.74)	10.82 (10.58)	15 (10)
50		CONH	CH_3	169—170 (EtOH)	33 A	$C_{13}H_{20}N_4O \cdot 3C_4H_4O_4$[f]	50.34 (50.25)	5.41 (5.71)	9.39 (9.27)	8 (1.0)
51		CONH	$PhCH_2$	80—82 (Tri)[e]	71 A	$C_{18}H_{23}N_5O$	66.44 (66.38)	7.12 (7.07)	21.52 (21.34)	7 (10)
52		CONH	CH_3	200—202 (EtOH)	21 A	$C_{12}H_{19}N_5O \cdot 2C_4H_4O_4$[f] $\cdot C_2H_5OH$[g] $\cdot 1/4H_2O$	49.67 (49.68)	6.35 (6.49)	13.16 (13.31)	0 (1.0)
53		CONH	CH_2Ph	140—143 (EtOH)	68 A	$C_{18}H_{23}N_5O \cdot 2C_2H_2O_4$[c] $\cdot 1/4H_2O$	51.81 (51.85)	5.44 (5.41)	13.73 (13.51)	5 (1.0)
54		CONH	$PhCH_2$	192—194 (EtOH)	49 A	$C_{21}H_{25}N_5O \cdot 1/2C_4H_4O_4$[f]	64.85 (65.02)	6.51 (6.76)	16.44 (16.26)	69 (1.0)
55		CONH	CH_3	153—155 (EtOH)	21 B	$C_{15}H_{21}N_5O \cdot 2C_4H_4O_4$[f] $\cdot 1/4H_2O$	52.72 (52.69)	5.67 (5.67)	13.37 (13.31)	3 (1.0)
56		COO	CH_3	184—185 (EtOH)	67 C	$C_{15}H_{20}N_4O_2 \cdot 5/2C_4H_4O_4$[f] $\cdot 1/4C_2H_5OH$[g]	51.91 (52.05)	5.38 (5.57)	9.50 (9.55)	17 (1.0)
57		CONH	$PhCH_2$	80—85 ($EtOH–Et_2O$)	46 B	$C_{22}H_{27}N_5O \cdot 3/2C_2H_2O_4$[c] $\cdot 1/4H_2O$	58.08 (58.27)	5.95 (6.31)	13.55 (13.60)	96 (1.0)
58		CONH	CH_3	176—180 (EtOH)	30 B	$C_{16}H_{23}N_5O \cdot 3/2C_4H_4O_4$[f]	55.57 (55.62)	6.15 (6.27)	14.73 (14.76)	33 (1.0)
59		CONH	$PhCH_2$	118—120 ($EtOH–Et_2O$)	35 A	$C_{21}H_{29}N_5O \cdot 1/4H_2O$	67.80 (67.65)	7.99 (7.97)	18.83 (18.79)	0 (10)

Table 2. (continued)

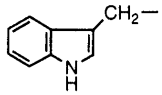
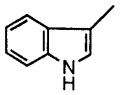
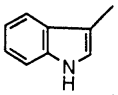
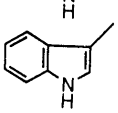
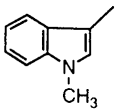
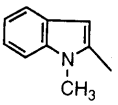
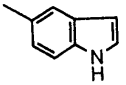
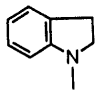
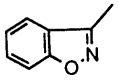
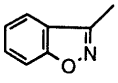
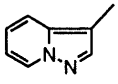
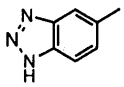
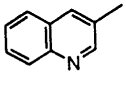
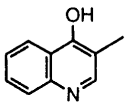
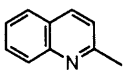
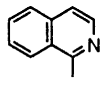
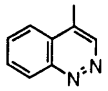
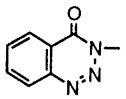
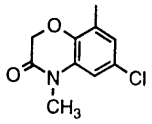
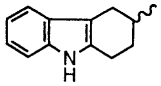
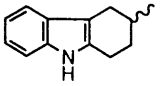
Compd.	Ar	X	R	mp (°C) (Recryst. solvent)	Yield[a] (%) Method	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of B–J reflex[b] (%) (μg/kg, i.v.)
60		CONH	CH_2Ph	175—176 (EtOH)	44 A	$C_{23}H_{28}N_4O \cdot 1/2C_4H_4O_4$[f]	69.10 (68.74	6.96 6.86	12.89 12.66)	7 (1.0)
61		CONH	CH_2Ph	191—194 (EtOH)	54 B	$C_{22}H_{26}N_4O \cdot 1/2C_4H_4O_4 \cdot 1/4C_2H_5OH$[f,g]	67.41 (67.61	6.93 7.21	12.83 12.55)	6 (1.0) 90 (100)
62		COO	CH_3	172—175 (AcOEt)	60 C	$C_{16}H_{21}N_3O_2$	66.88 (66.82	7.37 7.46	14.62 14.58)	3 (1.0)
63		COO	CH_2Ph	104—105 ($EtOH–Et_2O$)	18 C	$C_{22}H_{25}N_3O_2$	72.70 (72.32	6.93 7.03	11.56 11.49)	0 (10)
64		COO	CH_2Ph	207—109 (EtOH)	23 C	$C_{23}H_{27}N_3O_2 \cdot 2HCl \cdot 1/2H_2O$[h]	60.13 (60.15	6.58 6.42	9.15 9.02)	0 (10)
65		CONH	CH_2Ph	148—150 (EtOH)	52 A	$C_{23}H_{28}N_4O \cdot 2C_2H_2O_4$[c]	58.27 (58.34	5.80 5.72	10.07 9.97)	0 (10)
66		CONH	CH_2Ph	130—131 (MeCN)	37 A	$C_{22}H_{26}N_4O$	72.90 (72.83	7.23 7.24	15.46 15.52)	0 (10)
67		CONH	CH_2Ph	162—164 (MeOH)	[b]	$C_{22}H_{28}N_4O \cdot 2C_2H_2O_4$[c]	57.35 (57.07	5.92 5.88	10.29 10.20)	0 (10)
68		CONH	CH_2Ph	151—153 (EtOH)	22 B	$C_{21}H_{24}N_4O_2 \cdot 2.5C_4H_4O_4 \cdot 0.25H_2O$[f]	56.49 (56.88	5.28 5.24	8.50 8.56)	2 (1.0) 61 (100)
69		CONH	CH_3	159—161 (EtOH)	25 B	$C_{15}H_{20}N_4O_2 \cdot 2C_4H_4O_4$[f]	53.08 (52.97	5.42 5.58	10.76 10.83)	7 (1.0)
70		CONH	$PhCH_2$	128—131 (EtOH)	34 A	$C_{21}H_{25}N_5O \cdot 2.5C_2H_2O_4 \cdot 0.5H_2O$[c]	52.26 (52.29	5.23 5.40	11.72 11.64)	2 (10)
71		CONH	$PhCH_2$	125—129 ($EtOH–Et_2O$)	41 A[i]	$C_{20}H_{24}N_6O \cdot 1.5C_2H_2O_4 \cdot 0.75H_2O$[c]	53.85 (53.78	5.60 5.45	16.38 16.58)	7 (1.0)
72		CONH	$PhCH_2$	67—69 (Tri)[e]	75 A	$C_{23}H_{26}N_4O \cdot 0.25H_2O$	72.89 (72.86	7.05 6.82	14.78 14.81)	0 (10)
73		CONH	$PhCH_2$	164—165 (MeOH–EtOH)	[b]	$C_{23}H_{26}N_4O_2 \cdot 2C_2H_2O_4$[c]	56.84 (56.70	5.30 5.50	9.82 9.64)	0 (10)
74		CONH	$PhCH_2$	121—123 ($EtOH–Et_2O$)	46 A	$C_{23}H_{26}N_4O \cdot 2C_2H_2O_4$[c]	58.48 (58.69	5.45 5.56	10.10 10.22)	0 (10)
75		CONH	$PhCH_2$	121—124 (EtOH)	47 A	$C_{23}H_{26}N_4O \cdot 5/2C_2H_2O_4$[c]	56.09 (56.40	5.21 5.22	9.34 9.32)	0 (10)

Table 2. (continued)

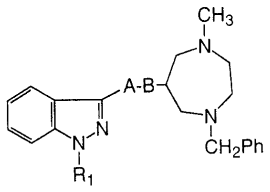
Compd.	Ar	X	R	mp (°C) (Recryst. solvent)	Yield[a] (%) Method	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of B–J reflex[b] (%) (μg/kg, i.v.)
76		CONH	$PhCH_2$	136—141 (EtOH)	60 A	$C_{22}H_{25}N_5O \cdot 5/2C_2H_2O_4$[c] $\cdot 3/4H_2O$	52.81 (52.76	5.17 5.47	11.41 11.28)	10 (10)
77		—	$PhCH_2$	229—231 (EtOH)	[b]	$C_{20}H_{23}N_5O \cdot 2HCl$[j]	56.88 (56.72	5.97 5.80	16.58 16.41)	5 (100)
78		CONH	$PhCH_2$	167—169 (MeOH)	79 [b]	$C_{23}H_{27}ClN_4O_3 \cdot 3/2C_2H_2O_4$[c,k]	53.00 (52.98	5.12 5.03	9.33 9.36)	100 (30)
79[l]		CONH	$PhCH_2$	229—230 (EtOH)	27 A	$C_{26}H_{32}N_4O \cdot 1/2C_2H_2O_4$[c] $\cdot 1/4H_2O$	69.58 (69.45	7.24 7.02	12.02 11.83)	28 (100)
80[m]		CONH	$PhCH_2$	114—116 ($MeOH-Et_2O$)	21 A	$C_{26}H_{32}N_4O \cdot 3/2C_2H_2O_4$[c] $\cdot 1/2H_2O$	62.13 (62.00	6.47 6.46	9.99 9.93)	2 (100)

a) Yields are given for the amine or alcohol condensation and were not optimized. *b*) See Experimental. *c*) Oxalic acid. *d*) Calcd for S: 6.29, Found: 6.14. *e*) Tri (trituration) refers to grinding of the solid to produce a fine powder. *f*) Fumaric acid. *g*) The presence of solvent of crystallization was shown by the ^{1}H-NMR spectrum. *h*) Calcd for Cl: 15.43, Found: 15.58. *i*) 4-Dimethylaminopyridine (0.5 eq of the carboxylic acid) was added. *j*) Calcd for Cl: 16.79, Found: 16.60. *k*) Calcd for Cl: 5.90, Found: 6.02. *l*) The mixture of **79** and **80** was separated by using silica gel column chromatography. More polar isomer. *m*) Less polar isomer.

antagonists has been described previously in terms of the spatial relationship between a basic nitrogen, carbonyl function, and the centroid of an aromatic ring.[27] Thus, the pharmacophore of compounds **46**—**53** is assumed to occupy a different relative orientation in space compared with that of the standard agents **1**, **2**, and **4**. Surprisingly, introduction of a 1*H*-indazole ring caused a remarkable increase in activity. In particular, *N*-(1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1*H*-indazole-3-carboxamide (**54**) and the 1-methyl-1*H*-indazole analogue (**57**) exhibited potent activity (ED_{50} 0.60 and 0.19 μg/kg, i.v., respectively). The activity of **57** was more potent than that of the benzamides **9** and **10**, ondansetron (**1**), tropisetron (**2**), and granisetron (**4**) (ED_{50} 0.37, 0.44, 1.10, 0.39, 0.26 μg/kg, i.v., respectively). A particular feature of benzamides such as **9** and **10** is the hydrogen bond between the amidic N–H and the *o*-ethoxy group which holds the amide system in the same plane as the aromatic ring, thus forming a "virtual ring" plane. It would therefore be reasonable to conclude that **54** and **57** also adopt an "in-plane" orientation of the carbonyl group at the 5-HT_3 receptor. On the other hand, replacement of the 1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine ring of **54** and **57** by the 1,4-dimethylhexahydro-1*H*-1,4-diazepine ring (giving compounds **55** and **58**, respectively) resulted in reduction in activity. The difference in the activity observed for the two compounds (**54** *vs.* **55** and **57** *vs.* **58**) may be due to an unfavorable conformation of compounds **55** and **58** at the 5-HT_3 receptor. Attempts to replace the amide linkage of **55** by an ester linkage (yielding **56**) and the 1*H*-indazole ring of **54** by a 4,5,6,7-tetrahydro-1*H*-indazole ring (giving **59**) caused a decrease in activity. Next, we expected that the indole analogues of **54** and **57** would show potent activity; the indole ring has been shown to be an excellent bioisosteric replacement for the 1*H*-indazole ring. Furthermore, tropisetron (**2**) and YM 060 (**3**), having an indole ring, are potent 5-HT_3 receptor antagonists. Therefore, carboxamides and esters with an indole ring in the aromatic moiety were prepared. 3-Indolylacetamide (**60**), indolylcarboxamides (**61**, **65**, **66**), and the esters (**62**—**64**) showed very weak activity as compared to the 1*H*-indazole congeners **54** and **57**, although the reason for this result is unknown. Formation of indolinyl- (**67**), 1,2-benzisoxazolyl- (**68**, **69**), 3-azapyrrocolinyl- (**70**), and 1,2,3-benzotriazolyl- (**71**) carboxamides failed to enhance the activity. Azasetron (**8**) and *endo*-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-hydroxy-3-quinolinecarboxamide[28] were reported to be potent 5-HT_3 receptor antagonists. Thus, the result prompted us to prepare the corresponding 1,4-diazepinylcarboxamide and the related carboxamides. The carboxamides **72**—**80** prepared did not display potent activity, except for **78**. Compound **78**, having the same aromatic moiety as that in **8**, exhibited moderate activity (ED_{50} = 2.30 μg/kg, i.v.). The loss of 5-HT_3 receptor activity observed with 6–(5)–6 membered ring systems such as the quinoline and tetrahydrocarbazole derivatives indicates that there is a limitation to the size of the aromatic moiety of 5-HT_3 receptor antagonists which can fit into the 5-HT_3 receptor. As a result of the SAR studies described above, the optimum heteroaromatic ring for 6-amino-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine was concluded to be a 1*H*-indazole ring.

SARs associated with modification of the amide moiety

Table 3. Physical Data and 5-HT_3 Receptor-Antagonistic Activity for 1,4-Diazepine Derivatives **81**—**90**



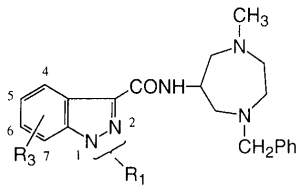
Compd.	R_1	A–B	mp (°C) (Recryst. solvent)	Yield[a] (%) Method	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition of B–J reflex[b] (%) (μg/kg, i.v.)
81	H	CO–$NHCH_2$	111—115 (EtOH)	59 A	$C_{22}H_{27}N_5O \cdot 2C_2H_2O_4$[c] $\cdot 1/2H_2O$	55.12 (54.98)	5.69 5.71	12.36 12.31)	12 (100)
82	H	CO–$NHCH_2CH_2$	115—118 (EtOH–Et_2O)	55 A	$C_{23}H_{29}N_5O \cdot 3/2C_2H_2O_4$[c] $\cdot 3/4H_2O$	57.82 (57.83	6.25 6.28	12.97 13.26)	26 (100)
83	H	CO–O	107—109 (MeOH–Et_2O)	46 C	$C_{21}H_{24}N_4O_2 \cdot 9/5HCl$ $\cdot 1/2H_2O$[d]	57.44 (57.16	6.15 6.12	12.76 12.69)	0 (10)
84	CH_3	CO–O	173—175 (EtOH)	44 C	$C_{22}H_{26}N_4O_2 \cdot 2HCl$ $\cdot 3/4H_2O$[e]	56.84 (56.88	6.40 6.41	12.05 11.70)	0 (10)
85	H	CO–OCH_2	111—114 (MeOH)	47 C	$C_{22}H_{26}N_4O_2 \cdot C_2H_2O_4$[c] $\cdot 1/2H_2O$	60.37 (60.64	6.12 6.14	11.73 11.67)	12 (10)
86	CH_3	CO–OCH_2	162—164 (EtOH)	41 C	$C_{23}H_{28}N_4O_2$ $\cdot 2HCl \cdot C_2H_5OH$[f,g]	58.71 (58.63	7.09 7.14	10.95 10.90)	0 (10)
87	H	CS–NH	123—124 (EtOH)	[b]	$C_{21}H_{25}N_5S$[h]	66.46 (66.29	6.64 6.53	18.45 18.36)	0 (10)
88	H	O–CH_2	107—110 (EtOH–Et_2O)	[b]	$C_{21}H_{26}N_4O \cdot 3/2C_2H_2O_4$[c] $\cdot 1/2H_2O$	58.29 (58.41	6.11 6.22	11.33 11.62)	0 (10)
89	CH_3	CO–	205—208 (EtOH–Et_2O)	[b]	$C_{22}H_{26}N_4O \cdot 3/2C_2H_2O_4$[c] $\cdot 3/4H_2O$	58.76 (58.84	6.02 6.11	10.96 11.11)	1 (10)
90[i]	CH_3	CH(OH)–	101—103 (EtOH–Et_2O)	[b]	$C_{22}H_{28}N_4O \cdot 2C_2H_2O_4$[c] $\cdot 1/4H_2O$	56.88 (56.59	5.97 6.06	10.20 10.40)	10 (10)

a) Yields are given for the amine or the alcohol condensation and were not optimized. *b*) See Experimental. *c*) Oxalic acid. *d*) Calcd for Cl, 14.53; Found: 14.54. *e*) Calcd for Cl, 15.25; Found: 15.10. *f*) Calcd for Cl: 13.86, Found; 13.56. *g*) The presence of solvent of crystallization was shown by the ^{1}H-NMR spectrum. *h*) Calcd for S, 8.45; Found: 8.41. *i*) Diastereomeric mixture.

of **54** and **57** were then studied (Table 3). Methylene and ethylene groups were incorporated into the amide linkage at the 6 position of the 1,4-diazepine ring of **54** (giving **81** and **82**, respectively). Furthermore, in order to examine the importance of the amide linkage of **54** and **57**, esters (**83**—**86**), thioamide (**87**), ether (**88**), carbonyl (**89**), and hydroxy (**90**) groups were introduced. None of the compounds prepared showed potent 5-HT_3 receptor antagonistic activity. Compounds **81** and **82**, which have three or four carbon atoms between the nitrogen atoms of the amide group and the 1,4-diazepine ring, exhibited much less potent activity than **54**. Furthermore, like the 1,4-dimethylhexahydro-1*H*-1,4-diazepinyl ester **56** described above, the 1-benzyl-4-methylhexahydro-1*H*-1,4-diazepinyl ester series **83**—**86** tended to be ineffective. The decreased activity of the esters *versus* amides may be due to hydrolysis of the ester group in an *in vivo* screening model such as the B–J reflex. From these results, it is reconfirmed that the pharmacophore for 5-HT_3 receptor antagonists can be regarded as an aromatic ring, a carbonyl group, and a basic nitrogen, and their location is crucial for the activity.

The influence of substituents of the indazole ring of **54** on inhibition of the B–J reflex was finally examined. As mentioned above, the 1-methyl-1*H*-indazolylcarboxamide **57** showed potent activity. On the other hand, the 2-methyl isomer **91** was inactive at the screening dose. A similar result has been observed for a series of indazolylcarboxamides with a granatane in the amine moiety, including granisetron (**4**).[15a] The lack of activity of the 2-methyl isomer **91** can be accounted for by presuming that the methyl group would destabilize the "in-plane" orientation of the carbonyl group owing to steric interactions. To examine the effect of variation of the *N*-1 substituent on activity, large alkyl, allyl, benzyl, acyl, and methoxycarbonyl substituents were introduced. All the *N*-1 substituted 1*H*-indazole-3-carboxamides (**92**—**106**) prepared retained good 5-HT_3 receptor antagonistic activity. The bulky cyclopentyl substituent (**99**) was tolerated. This relatively small difference in the activity of *N*-1 substituted indazolylamides *versus* unsubstituted carboxamide **54** might be accounted for by elimination of the *N*-1 substitution in this screening model. The isopropyl (**94**), cyclopropylmethyl (**96**), allyl (**97**), acetyl (**101**), and propionyl (**102**) derivatives (ED_{50} = 0.49, 0.47, 0.30, 0.30, 0.33 μg/kg, i.v., respectively) were essentially equipotent to the benzamides **9** and **10** and tropisetron (**2**). Next, the effect of substituents on the benzene moiety of the 1*H*-indazole ring was studied. In general, the substituents did not provide any improvement. Introduction of a chlorine atom (yielding compounds **107**—**110**) resulted in retention or a significant decrease of the activity. The activity decreased in the order of position 7 > 6 = 5 ≫ 4. The 5-fluoro (**111**) and 6-fluoro (**112**) analogues showed slightly increased activity compared with the chloro congeners **108** and **109**, whereas the 5,6-difluoro (**113**) and

Table 4. Physical Data and 5-HT_3 Receptor-Antagonistic Activity for *N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1*H*-indazole-3-carboxamides (**91**—**119**)



Compd.	R_1 or R_3	mp (°C) (Recryst. solvent)	Yield[a] (%) Method	Formula	Analysis (%) Calcd (Found) C	H	N	Halogen	Inhibition of B–J reflex[b] (%) 1.0 μg/kg, i.v.
91	2-CH_3	86—90 (EtOH–Et_2O)	48 B	$C_{22}H_{27}N_5O \cdot 3/2C_2H_2O_4$[c] $\cdot 3/4H_2O$	57.08 (57.13	6.04 6.25	13.31 13.33)		0
92	1-C_2H_5	135—137 (EtOH–Et_2O)	51 B	$C_{23}H_{29}N_5O \cdot C_2H_2O_4$[c] $\cdot 3/4H_2O$	57.82 (57.69	6.25 6.60	12.97 12.95)		41
93	1-*n*-C_3H_7	70—76 (EtOH–Et_2O)	56 B	$C_{24}H_{31}N_5O \cdot 3/2C_2H_2O_4$[c] $\cdot 1/2H_2O$	59.01 (59.01	6.42 6.43	12.74 12.82)		62
94	1-iso-C_3H_7	77—80 (EtOH–Et_2O)	61 B	$C_{24}H_{31}N_5O \cdot 3/2C_2H_2O_4$[c] $\cdot 3/4H_2O$	58.53 (58.51	6.46 6.65	12.64 12.54)		72
95	1-*n*-C_4H_9	69—74 (EtOH–Et_2O)	55 B	$C_{25}H_{33}N_5O \cdot 3/2C_2H_2O_4$[c] $\cdot 1/2H_2O$	59.67 (59.53	6.62 6.66	12.43 12.41)		70
96	1-CH_2—	72—75 (EtOH–Et_2O)	77 B	$C_{25}H_{31}N_5O \cdot 5/4C_2H_2O_4$[c] $\cdot 5/4H_2O$	59.77 (59.95	6.57 6.70	12.67 12.47)		75
97	1-$CH_2CH=CH_2$	73—77 (EtOH–Et_2O)	60 B	$C_{24}H_{29}N_5O \cdot 3/2C_2H_2O_4$[c] $\cdot 1/2H_2O$	59.22 (59.23	6.07 6.02	12.79 12.90)		79
98	1-$CH_2CH(CH_3)_2$	82—85 (EtOH–Et_2O)	50 B	$C_{25}H_{33}N_5O \cdot 3/2C_2H_2O_4$[c] $\cdot 1/2H_2O$	59.67 (59.75	6.62 6.58	12.43 12.39)		55
99	1- 	86—90 (EtOH–Et_2O)	37 B	$C_{26}H_{33}N_5O \cdot 3/2C_2H_2O_4$[c] $\cdot 1/4H_2O$	60.99 (60.98	6.44 6.55	12.26 12.27)		59
100	1-CH_2Ph	76—79 (EtOH–Et_2O)	61 B	$C_{28}H_{31}N_5O \cdot 3/2C_2H_2O_4$[c] $\cdot 1/4H_2O$	62.77 (62.61	5.86 5.97	11.81 11.86)		34
101	1-$COCH_3$	166—168 (EtOH)	83 D	$C_{23}H_{27}N_5O_2 \cdot C_4H_4O_4$[d] $\cdot 1/4H_2O$	61.64 (61.76	6.04 5.89	13.31 13.28)		89
102	1-COC_2H_5	185—187 (EtOH)	75 D	$C_{24}H_{29}N_5O_2 \cdot C_4H_4O_4$[d]	62.79 (62.58	6.21 6.29	13.08 12.86)		83
103	1-COC_6H_5	187—189 (EtOH)	78 D	$C_{28}H_{29}N_5O_2 \cdot C_4H_4O_4$[d] $\cdot 1/2H_2O$	64.85 (65.04	5.78 5.62	11.82 11.83)		50
104	1-$COOCH_3$	158—160 (EtOH)	88 D	$C_{23}H_{27}N_5O_3 \cdot C_4H_4O_4$[d]	60.33 (60.05	5.81 5.76	13.03 12.88)		64
105	1-$CH(CH_3)COCH_3$	97—100 (EtOH–Et_2O)	45 D	$C_{25}H_{31}N_5O_2 \cdot 3/2C_2H_2O_4$[c] $\cdot 1/4H_2O$	58.68 (58.65	6.07 6.16	12.22 12.31)		74
106	1-CH_2CH_2OH	84—89 (EtOH–Et_2O)	27 D	$C_{23}H_{29}N_5O_2 \cdot C_2H_2O_4$[c] $\cdot 1/2H_2O$	59.28 (59.12	6.37 6.12	13.83 13.60)		63
107	4-Cl	108—111 (EtOH–acetone)	58 B	$C_{21}H_{24}ClN_5O \cdot 2C_2H_2O_4$[c] $\cdot C_2H_5OH$[e]	51.97 (52.03	5.49 5.28	11.22 11.13	5.68 5.46)	0
108	5-Cl	142—146 (EtOH–acetone)	79 B	$C_{21}H_{24}ClN_5O \cdot 3/2C_2H_2O_4$[c] $\cdot 1/4C_2H_5OH$[e] $\cdot 1/2H_2O$	53.17 (53.18	5.37 5.18	12.65 12.51	6.41 6.62)	20
109	6-Cl	119—124 (EtOH–acetone)	44 B	$C_{21}H_{24}ClN_5O \cdot 2C_2H_2O_4$[c] $\cdot 1/4H_2O$	51.55 (51.26	4.93 4.90	12.02 12.04	6.09 6.19)	21
110	7-Cl	145—148 (EtOH–acetone)	33 B	$C_{21}H_{24}ClN_5O \cdot 2C_2H_2O_4$[c] $\cdot 1/2H_2O$	51.16 (50.87	4.98 4.89	11.93 11.91	6.04 6.13)	61
111	5-F	118—121 (EtOH–acetone)	69 B	$C_{21}H_{24}FN_5O \cdot 2C_2H_2O_4$[c] $\cdot 1/4C_2H_5OH$[e] $\cdot 1/4H_2O$	53.03 (52.84	5.24 5.22	12.13 11.89	3.29 3.21)	43
112	6-F	126—130 (EtOH–acetone)	55 B	$C_{21}H_{24}FN_5O \cdot 2C_2H_2O_4$[c]	53.48 (53.27	5.03 5.27	12.47 12.38	3.39 3.51)	31
113	5,6-diF	120—123 (EtOH–acetone)	91 B	$C_{21}H_{23}F_2N_5O \cdot 2C_2H_2O_4$[c] $\cdot 1/2C_2H_5OH$[e] $\cdot 3/4H_2O$	50.68 (50.68	5.15 4.78	11.37 11.72	6.17 5.81)	6
114	5-Br	188—189 (EtOH)	31 B	$C_{21}H_{24}BrN_5O$	57.02 (56.88	5.42 5.32	15.83 15.84	18.06 18.24)	1
115	5-CH_3	112—115 (EtOH–acetone)	64 B	$C_{22}H_{27}N_5O \cdot 2C_2H_2O_4$[c] $\cdot 3/4H_2O$	54.68 (54.86	5.74 5.74	12.26 12.01)		10
116	5-OCH_3	218—220 (EtOH)	47 B	$C_{22}H_{27}N_5O_2 \cdot 2HCl \cdot 1/4H_2O$	56.11 (56.22	6.31 6.27	14.87 14.58	15.06 14.86)	3
117	5-OH	223—225 (EtOH)	[b]	$C_{21}H_{25}N_5O_2 \cdot 1/4H_2O$	65.69 (65.50	6.69 6.60	18.24 17.95)		22
118	5-NO_2	262—264 (acetone)	64 B	$C_{21}H_{24}N_6O_3$	61.75 (61.62	5.92 5.67	20.58 20.63)		0
119	5-NH_2	152—155 (EtOH–Et_2O)	[b]	$C_{21}H_{26}N_6O \cdot 2C_2H_2O_4$[c]	55.76 (55.50	5.41 5.66	15.05 14.91)		1

a) Yields are given for the amine condensation and for the acylation or alkylation of **54**, and were not optimized. *b*) See Experimental. *c*) Oxalic acid. *d*) Fumaric acid. *e*) Diastereomeric mixture. *f*) The presence of solvent of crystallization was shown by the ^{1}H-NMR spectrum.

large 5-bromo (**114**) substituents showed poorer activity. A compound with a small substituent such as a fluorine atom at the 5 position of the indazole ring showed more potent activity than one with a large substituent such as a chlorine or bromine atom; this result indicates the steric limitations of the aromatic binding site. Introduction of an electron-donating group such as methyl, methoxy, hydroxy, and amino groups at the 5 position (yielding **115**, **116**, **117**, and **119**, respectively) resulted in significant reduction in activity. The compound with an electron-withdrawing nitro group was inactive at the dose of 1.0 mg/kg, i.v. Variation of the substituent at the 5 position caused a decrease of activity in the order $H > F > OH \geq Cl > CH_3 \gg OCH_3 = Br = NH_2 = NO_2$. Electronic influence on the 5-HT_3 receptor remains unclear.

On the basis of inhibition of the B–J reflex, compounds **54**, **57**, **97**, and **102** were selected for further biological assay, *i.e.*, acute toxicity test in mice (Table 5) and protection against cisplatin-induced emesis in ferrets (Table 6). In the acute toxicity test, all compounds showed a slight or moderate toxicity and were less toxic than ondansetron (**1**) and granisetron (**4**). In Table 6, the activities of **1**, **2**, **4**, and the benzamides **9** and **10** are included for comparison. Compounds **54**, **1**, **2**, and **4** inhibited the emetic episodes induced by cisplatin in a dose-dependent manner in the dose range from 0.01 to 0.1 mg/kg, i.v., and showed complete protection at a dose of 0.1 mg/kg, i.v. On the whole, the activity of **54** was somewhat more potent than that of compounds **57**, **97**, and **102** and the benzamides **9** and **10**, and compared very favorably with that of the reference 5-HT_3 receptor antagonists **1**, **2**, and **4**.

In order to examine the molecular shape of the potent

Table 5. Inhibition of B–J Reflex and Acute Toxicity in Mice of Selected Compounds **54**, **57**, **78**, **94**, **96**, **97**, **101**, and **102**

Compound	Inhibition of B–J reflex ED_{50} (95% C.L.) μg/kg, i.v.	Acute toxicity[a] 100 mg/kg, i.p.
54	0.60 (0.18—1.96)	0/5
57	0.19 (0.06—0.67)	2/5
78	2.30 (0.74—7.00)	NT
94	0.49 (0.14—1.76)	NT
96	0.47 (0.16—1.39)	NT
97	0.30 (0.09—0.95)	3/5
101	0.30 (0.10—0.93)	NT
102	0.33 (0.07—1.54)	1/5
9	0.37 (0.12—1.11)	NT
10	0.44 (0.11—1.77)	NT
Ondansetron (**1**)	1.10 (0.35—3.27)	5/5[b]
Tropisetron (**2**)	0.39 (0.11—1.34)	2/5
Granisetron (**4**)	0.26 (0.07—0.91)	5/5

a) Number of dead animals/animals used. *b*) 30 mg/kg, i.p. NT, not tested.

Table 6. Protection against Cisplatin-Induced Emesis in Ferrets

Compound	mg/kg, i.v. ×2[a]	Protection[b]	Latency to first emetic episode (min) Mean±S.E.	Number of emetic episodes Mean±S.E.
Saline		0/12	60.8± 2.5	11.3±1.3
54	0.01	0/4	78.8± 2.7[d]	9.0±0.4
	0.03	1/4	125.5±18.9[d]	5.0±2.1[c]
	0.1	4/4	>180[d]	0[d]
57	0.03	0/3	77.7± 6.2[c]	6.3±2.4
97	0.03	0/3	99.7± 7.1	5.3±0.3[c]
102	0.03	0/3	78.0± 0.6[d]	8.0±1.5
Ondansetron (**1**)	0.01	0/5	89.4± 6.1[d]	8.2±0.7
	0.03	3/6	148.2±14.6[d]	1.2±0.7[d]
	0.1	4/4	>180[d]	0[d]
Tropisetron (**2**)	0.01	0/4	92.3±10.8	14.5±3.8
	0.03	5/6	169.0±11.0[d]	1.2±1.2[d]
	0.1	4/4	>180[d]	0[d]
Granisetron (**4**)	0.01	0/4	85.8± 4.7[d]	6.8±2.1
	0.03	0/4	101.0± 9.5[d]	5.3±1.5[d]
	0.1	5/5	>180[d]	0[d]
Saline		0/6	57.5± 3.9	19.0±5.5
9	0.1	0/4	114.3± 5.5[d]	5.5±0.6[c]
10	0.1	2/4	156.3±14.4[d]	1.8±1.2[d]

a) Treatment schedule: first dose 30 min before, followed by second dose, 45 min after cisplatin. *b*) Number of ferrets completely protected/terrets used. A statistically significant difference from the saline control; *c*) $p<0.05$; *d*) $p<0.01$ (Williams–Wilcoxon's multiple test).

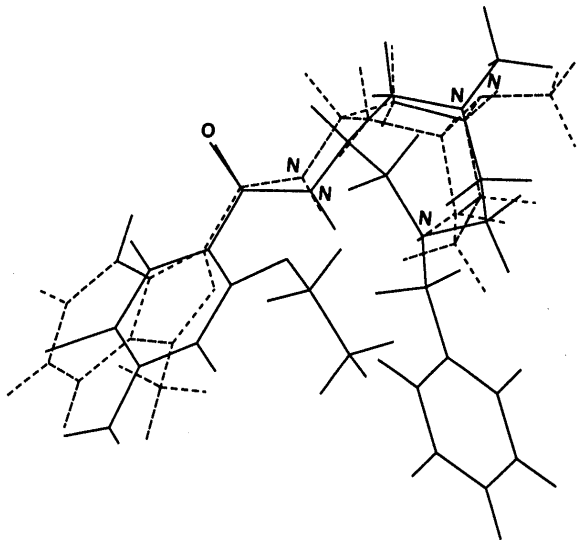


Fig. 2. Superposition of Granisetron (**4**) (Dotted Line) and **10** (Solid Line)

The centers of the five-membered ring in the indazole of **4** and the benzene ring of **10**, the oxygen atoms in the amide moiety, and the ring nitrogen atoms were subjected to a least-squares fit (RMS=0.216). The methyl substituted nitrogen atom was selected as a fitting point in the case of the diazepine ring.

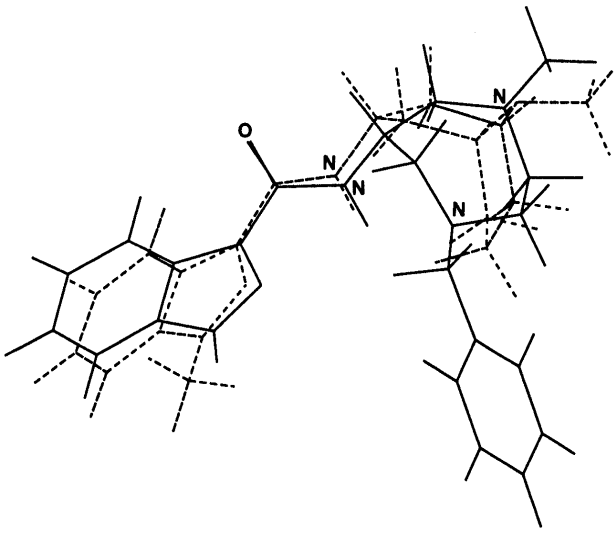


Fig. 3. Superposition of Granisetron (**4**) (Dotted Line) and **54** (Solid Line)

Fitting conditions are identical to those described in Fig. 2 except for the centroid of the five-membered ring in the structure **54** (RMS=0.189).

5-HT_3 receptor antagonists **10** and **54**, the benzamide **10** and the 1*H*-indazolylcarboxamide **54** were superposed on granisetron (**4**; bearing a 1-methyl-1*H*-indazole ring) used to refine the 5-HT_3 pharmacophore model. The superpositions are shown in Figs. 2 and 3. The benzamides **10** and **4** fit quite well except for the benzyl group. Similarly, the conformational resemblance between **54** and **4** is obvious except for the benzyl group; the lowest root mean square (RMS) values for the least-squares fit of compounds **10** and **54** upon **4**, indicating the degree of overlap, have a close relation to the overall molecular similarity. The RMS values of **10** and **54** *versus* **4** (0.216 and 0.189, respectively) show a good fit between the compounds. The role of the benzyl group in the 5-HT_3 receptor binding site is not clear. A detailed conformation–activity relationship study of 5-HT_3 receptor antagonists including **1**—**5** and a 1,4-diazepinylcarboxamide derivative like **54** will be reported elsewhere.

In conclusion, modification of the aromatic moiety of the *N*-(1,4-dimethylhexahydro-1*H*-1,4-diazepin-6-yl)benzamide **9** and the 1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine analogue **10** has led to the discovery of *N*-(1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1*H*-indazole-3-carboxamide (**54**). The representative compound **54** in this series showed a potent antagonistic activity on the B–J reflex and provided complete protection against cisplatin-induced emesis at a dose of 0.1 mg/kg, i.v.

Experimental

Chemistry All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Hitachi 260-10 spectrometer and a Shimadzu FTIR-8200PC spectrometer. Electron ionization and secondary ion mass spectra were obtained on a JEOL JMS D-300 or a Hitachi M-80-B spectrometer. ^{1}H-NMR spectra were taken at 80 MHz with a Varian FT-80A spectrometer, at 200 MHz with a Varian Gemini-200 spectrometer, and at 300 MHz with a Varian XL-300 spectrometer. ^{13}C-NMR spectra were measured with a Varian XL-300 spectrometer in $CDCl_3$ solution. Chemical shifts are expressed as δ (ppm) values with $SiMe_4$ as an internal standard, and coupling constants (J) are given in Hz. UV-visible absorption spectra were obtained on a Hitachi U-3210 spectrophotometer. Organic extracts were dried over anhydrous $MgSO_4$ or anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Merck Silica gel 60 (70—230 mesh) was used for column chromatography. The following known carboxylic acids and amines were prepared according to the cited literature: 1*H*-indazole-3-carboxylic acid[23,29] (**26a**), methyl 1*H*-indazole-3-carboxylate[25] (**27a**), 1-methylindole-3-carboxylic acid[30] (**33**), 1,2-benzisoxazole-3-carboxylic acid,[31] 1-methyl-1*H*-indazole-3-carboxylic acid[25] (**34**), 2-methyl-1*H*-indazole-3-carboxylic acid,[25] 4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylic acid,[32] 3-azapyrrocoline-1-carboxylic acid,[33] 5-chloro-1*H*-indazole-3-carboxylic acid,[34] 5-fluoro-1*H*-indazole-3-carboxylic acid,[34a] 5-bromo-1*H*-indazole-3-carboxylic acid,[34a] 5-methyl-1*H*-indazole-3-carboxylic acid,[35] 5-methoxy-1*H*-indazole-3-carboxylic acid,[36] 5-nitro-1*H*-indazole-3-carboxylic acid,[37] 4-chloro-1*H*-indazole-3-carboxylic acid,[38] 1,2,3,4-tetrahydrocarbazole-4-carboxylic acid,[39] 6-amino-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine[20] (**30**), and 6-amino-1,4-dimethylhexahydro-1*H*-1,4-diazepine[21] (**31**).

Methyl 1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepine-6-carboxylate (14) a) From Methyl β,β-Dibromoisobutyrate (11) A solution of **11**[40] (20.0 g, 77 mmol) in toluene (200 ml) was added dropwise to a solution of *N*-benzyl-*N'*-methylethylenediamine[41] (**12**, 12.6 g, 77 mmol) and Et_3N (17.1 g, 0.17 mol) in toluene (100 ml) at *ca.* 10 °C. The mixture was heated at 80 °C for 2 h, then cooled to room temperature, and washed successively with water and brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with ethyl acetate (AcOEt) to give 19.5 g (97%) of **14** as an oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.39 (s, 3H, NCH_3), 2.50—2.75 (m, 5H), 2.80—3.05 (m, 4H), 3.61 (s, 3H, $COOCH_3$), 3.67 (s, 2H, $C\underline{H}_2Ph$), 7.15—7.35 (m, 5H, arom. H). IR (neat) ν cm^{-1}: 2945, 2805, 1735. MS *m/z*: 262 (M^+), 91.

b) From Malonic Acid Malonic acid (31.4 g, 0.30 mol) was added portionwise to a solution of **12** (49.2 g, 0.30 mol) in CH_3CN (300 ml) at *ca.* 5 °C. The mixture was stirred at room temperature for 20 min, and then formaldehyde (37% solution in water, 60.0 g, 0.74 mol) was added. The mixture was stirred at room temperature for 20 h and concentrated to dryness. The oily residue was dissolved in a small amount of acetone, and the resulting precipitates were collected by filtration. The crystals obtained were recrystallized from iso-PrOH to give 58.0 g (77%) of 1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine-6-carboxylic acid (**13**). This compound was identical with a sample obtained in an alternative synthesis,[42] on the basis of melting point, IR, and ^{1}H-NMR comparisons.

Thionyl chloride (50 ml, 0.69 mol) was added dropwise to a stirred suspension of **13** (53.7 g, 0.22 mol) in MeOH (500 ml) kept at *ca.* 5 °C. The mixture was stirred at room temperature for 3 h and then concentrated to dryness. The residue was dissolved in water, basified with 20% aqueous NaOH, and then extracted with $CHCl_3$. The extract was washed with brine, and the solvent was evaporated to give 48.2 g (85%) of **14** as an oil. This compound was identical with the sample described above, on the basis of TLC, IR, and ^{1}H-NMR comparisons.

(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)methanol (15) A solution of **14** (10.0 g, 38 mmol) in toluene (50 ml) was added dropwise to a solution of Vitride® (70% solution in toluene; 22.0 g, 76 mmol) in toluene (100 ml) kept at 5 °C. The mixture was stirred at the same temperature for 0.5 h and at room temperature for 12 h. The excess of the reducing agent was decomposed by addition of water (100 ml) at 5 °C. The organic layer was separated, and the aqueous layer was extracted with toluene (300 ml × 2). The combined organic layer was washed with brine and then evaporated to give an oily residue, which was chromatographed on silica gel with $CHCl_3$: MeOH = 10 : 1 to afford 5.9 g (66%) of **15** as an oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.02 (m, 1H), 2.33 (s, 3H, NCH_3), 2.40—2.75 (m, 6H), 2.83—3.00 (m, 2H), 3.45—3.65 (m, 2H), 3.60 (s, 2H, $C\underline{H}_2Ph$), 4.57 (br s, 1H, OH), 7.11—7.40 (m, 5H, arom. H). IR (neat) ν cm^{-1}: 2916, 2810, 1454. MS *m/z*: 234 (M^+), 175, 91.

***N*-[(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)methyl]phthalimide (16)** A solution of diethyl azodicarboxylate (DEAD, 2.3 g, 13 mmol) in anhydrous THF (50 ml) was added dropwise to a stirred mixture of **15** (3.1 g, 13 mmol), triphenylphosphine (3.5 g, 13 mmol), phthalimide (1.9 g, 13 mmol), and anhydrous THF (100 ml) at 5 °C. The mixture was stirred at room temperature for 15 h. After solvent had been evaporated, the residue was dissolved in AcOEt and 10% HCl. The aqueous layer was separated, basified with 10% aqueous NaOH, and then extracted with AcOEt. The extract was washed with brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with $CHCl_3$: MeOH = 7 : 1 to give 2.5 g (52%) of **16** as an oil. ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 2.36 (s, 3H, NCH_3), 2.44—2.85 (m, 9H), 3.49 (d, J = 13, 1H, $C\underline{H}_2Ph$), 3.53 (d, J = 6, 2H, $CH_2N(CO)_2$), 3.72 (d, J = 13, 1H, $C\underline{H}_2Ph$), 7.06—7.40 (m, 5H, arom. H), 7.63—7.85, 7.85—7.87 (m, 4H, arom. H). IR (neat) ν cm^{-1}: 2820, 2790, 1760, 1710, 1380, 1350. MS *m/z*: 363 (M^+), 272 ($M^+ - CH_2Ph$), 91.

6-Aminomethyl-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine (17) A mixture of **16** (1.5 g, 4.1 mmol), 100% $NH_2NH_2 \cdot H_2O$ (327 mg, 6.5 mmol), and EtOH (30 ml) was heated to reflux for 1.5 h and then cooled to room temperature. The reaction mixture was diluted with $CHCl_3$ (50 ml), and the precipitates were filtered off. The filtrate was washed successively with small amounts of water and brine. The solvent was evaporated to give 930 mg (97%) of **17** as an oil. ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.05 (br s, 2H, NH_2), 1.84 (m, 1H), 2.35 (s, 3H, NCH_3), 2.23—2.85 (m, 10H), 3.57 (s, 2H, $C\underline{H}_2Ph$), 7.10—7.40 (m, 5H, arom. H). IR (neat) ν cm^{-1}: 3330, 2930, 2790, 1580, 1440. MS *m/z*: 233 (M^+), 91.

6-Chloromethyl-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine (18) A solution of **15** (4.4 g, 19 mmol) and $SOCl_2$ (4 ml, 55 mmol) in $CHCl_3$ (40 ml) was heated to reflux for 2 h and then cooled to room temperature. The mixture was concentrated to dryness, and the residue was taken up in water. The aqueous solution was basified with 10% aqueous NaOH and then extracted with $CHCl_3$. The extract was washed with brine, and the solvent was evaporated to give 4.3 g (91%) of **18** as an oil, which was used without further purification. ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.9—3.25 (m, 8H), 2.35 (s, 3H, NCH_3), 3.25—3.8 (m, 3H), 3.58 (s, 2H, $C\underline{H}_2Ph$), 7.10—7.40 (m, 5H, arom. H). MS *m/z*: 252 (M^+), 217 ($M^+ - Cl$),

91.

6-(2-Aminoethyl)-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine (20) A mixture of **18** (1.7 g, 6.7 mmol), KCN (2.9 g, 59 mmol), 18-crown-6 (0.2 g), and HMPA (20 ml) was stirred at room temperature for 48 h. The reaction mixture was diluted with water and then extracted with Et_2O. The extract was washed with brine and evaporated to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$: MeOH = 20 : 1 to give 1.6 g (98%) of (1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)acetonitrile (**19**) as an oil [IR (neat) ν cm^{-1}: 2240 (CN). MS *m/z*: 243 (M^+), 91]. A solution of **19** (1.6 g, 6.6 mmol) in a mixture of EtOH (40 ml) and 28% NH_4OH (4 ml) was hydrogenated over Raney Ni at room temperature, until no more hydrogen was consumed. The catalyst was filtered off, and the filtrate was evaporated to afford quantitatively 1.6 g of **20** as an oil, which was used without further purification to prepare the carboxamide **82**. MS *m/z*: 247 (M^+), 91.

5,6-Difluoro-, 6-Fluoro-, 6-Chloro-, and 7-Chloro-1*H*-indazole-3-carboxylic Acids (25a—d) A literature procedure[23] was adopted. A mixture of 5,6-difluoroisatin[43] (**21a**, 30.0 g, 0.16 mol), NaOH (6.8 g, 0.17 mol), and water (120 ml) was gently heated until the mixture became a pale yellow solution [formation of sodium (2-amino-4,5-difluorophenyl)glyoxylate (**22a**)]. The solution was cooled to 5 °C, and then a solution of $NaNO_2$ (12.4 g, 0.18 mol) in water (40 ml) was added at 5 °C. The whole was added dropwise to a vigorously stirred solution of concentrated H_2SO_4 (30.5 g, 0.31 mol) in water (390 ml) kept at 10 °C and then stirred at the same temperature for 30 min. A solution of anhydrous $SnCl_2$ (97%, 76.9 g, 0.39 mol) in concentrated HCl (150 ml) was added to the resulting solution including the diazonium salt **23a** at 5 °C and the whole was stirred at room temperature for 2 h. The precipitates including crude **25a** were collected by filtration, washed with a large amount of water, and dried. In order to purify it, the crude **25a** (*ca.* 23 g) was esterified; a mixture of the pale brown powder **25a**, concentrated H_2SO_4 (3 drops), and MeOH (500 ml) was heated to reflux for 3 h and cooled to room temperature. After the insoluble materials had been filtered off, the filtrate was concentrated to dryness. The residue was dissolved in $CHCl_3$, and the solution was washed successively with 10% aqueous NaOH, water, and brine. The solvent was evaporated to leave a solid, which was triturated with a small amount of acetone to give 17.0 g (49% yield from **21a**) of methyl 5,6-difluoro-1*H*-indazole-3-carboxylate as a pale yellow powder, mp 240—241 °C. ^{1}H-NMR [200 MHz, *N*,*N*-dimethylsulfoxide (DMSO)-d_6] δ: 3.94 (s, 3H, $COOCH_3$), 7.79 (dd, $J_{7H\text{-}5F}$ = 6.6, $J_{7H\text{-}6F}$ = 10.5, 1H, 7-H), 7.93 (dd, $J_{4H\text{-}6F}$ = 7.8, $J_{4H\text{-}5F}$ = 10.5, 1H, 4-H), 14.16 (br s, 1H, NH). IR (KBr) ν cm^{-1}: 3269, 1732, 1493, 1456. MS *m/z*: 213 (MH^+). *Anal.* Calcd for $C_9H_6F_2N_2O_2$: C, 50.95; H, 2.85; F, 17.91; N, 13.20. Found: C, 51.08; H, 2.83; F, 17.91; N, 13.14. A mixture of the methyl ester of **25a** (4.0 g, 19 mmol), THF (200 ml), and 2 N NaOH (20 ml) was heated to reflux for 3.5 h and cooled to room temperature. The solution was acidified with concentrated HCl, and the resulting precipitates were collected by filtration, washed with water, and dried to give 2.5 g (67%) of **25a** as a pale yellow powder, mp 288—293 °C. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 7.77 (dd, $J_{7H\text{-}5F}$ = 7.0, $J_{7H\text{-}6F}$ = 10.5, 1H, 7-H), 7.92 (dd, $J_{4H\text{-}6F}$ = 8.0, $J_{4H\text{-}5F}$ = 10.5, 1H, 4-H), 13.25 (br s, 1H, NH), 14.15 (br s, 1H, COOH). MS *m/z*: 199 (MH^+). In a similar manner to that described above, compounds **25b—d** were prepared. Starting materials, melting points, and spectral data are given below.

Compound **25b**: 6-Fluoroisatin[44] (**21b**), mp > 280 °C. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 7.18 (ddd, $J_{7H\text{-}5H}$ = 2.5, $J_{4H\text{-}5H}$ = 9.0, $J_{6F\text{-}5H}$ = 8.5, 1H, 5-H), 7.46 (ddd, $J_{5H\text{-}7H}$ = 2.5, $J_{6F\text{-}7H}$ = 8.5, $J_{4H\text{-}7H}$ = 0.4, 1H, 7-H), 8.10 (ddd, $J_{7H\text{-}4H}$ = 0.4, $J_{6F\text{-}4H}$ = 4.5, $J_{5H\text{-}4H}$ = 9.0, 1H, 4-H), 13.3 (br s, 1H, NH), 13.9 (br s, 1H, COOH). MS *m/z*: 181 (MH^+).

Compound **25c**: 6-Chloroisatin[45] (**21c**), mp > 280 °C. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 7.32 (dd, J = 1.8, 8.8, 1H, 5-H), 7.78 (dd, J = 0.5, 1.8, 1H, 7-H), 8.10 (dd, J = 0.5, 8.8, 1H, 4-H), 13.3, (br s, 1H, NH), 13.9 (br s, 1H, COOH). MS *m/z*: 197 (MH^+).

Compound **25d**: 7-Chloroisatin[46] (**21d**), mp 243—245 °C. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 7.30 (dd, J = 8.0, 8.0, 1H, 5-H), 7.56 (dd, J = 1.0, 8.0, 1H, 6-H), 8.06 (dd, J = 1.0, 8.0, 1H, 4-H), 14.30 (br s, 2H, COOH, NH). MS *m/z*: 197 (MH^+).

Methyl 1-Ethyl-1*H*-indazole-3-carboxylate (27b) and Methyl 2-Ethyl-2*H*-indazole-3-carboxylate (28b) (Table 1; run 1). A mixture of methyl 1*H*-indazole-3-carboxylate (**27a**, 5.0 g, 28 mmol), C_2H_5I (8.9 g, 57 mmol), anhydrous K_2CO_3 (11.7 g, 86 mmol), and DMF (100 ml) was heated at 60 °C for 4 h. The reaction mixture was poured into ice-water and extracted with Et_2O. The extract was washed with brine and concentrated to leave a residue, which was chromatographed on silica gel with AcOEt : *n*-hexane = 1 : 3 to give 2.3 g (40%) of **28b** as an oil and 3.2 g (55%) of **27b** as an oil in that order.

Compound **27b**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.54 (t, J = 7.0, 3H, $NCH_2C\underline{H}_3$), 4.03 (s, 3H, $COOCH_3$), 4.52 (q, J = 7.0, 2H, $NC\underline{H}_2CH_3$), 7.30 (ddd, J = 2.0, 8.0, 8.0, 1H, 5-H), 7.37—7.52 (m, 2H, arom. H), 8.23 (ddd, J = 1.0, 2.0, 8.0, 1H, 4-H). IR (neat) ν cm^{-1}: 1732, 1713, 1479, 1441, 1408. MS *m/z*: 205 (MH^+).

Compound **28b**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.54 (t, J = 7.0, 3H, $NCH_2C\underline{H}_3$), 4.04 (s, 3H, $COOCH_3$), 4.98 (q, J = 7.0, 2H, $NC\underline{H}_2CH_3$), 7.24—7.50 (m, 2H, arom. H), 7.79 (ddd, J = 1.0, 2.0, 8.0, 1H, 7-H), 8.02 (ddd, J = 1.0, 2.0, 8.0, 1H, 4-H). IR (neat) ν cm^{-1}: 1715, 1470, 1439. MS *m/z*: 205 (MH^+).

1-Ethyl-1*H*-indazole-3-carboxylic Acid (26b) a) A solution of **27b** (3.2 g, 16 mmol) in a mixture of 1 N aqueous NaOH (31 ml) and THF (30 ml) was stirred at room temperature for 20 h. The reaction mixture was washed with AcOEt, and the aqueous solution was acidified with concentrated HCl. The resulting precipitates were collected by filtration, washed with water, and dried to give 2.9 g (97%) of **26b**, mp 161—164 °C [lit.[25a] mp 162—163 °C (benzene–benzin)]. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.45 (t, J = 7.0, 3H, $NCH_2C\underline{H}_3$), 4.55 (q, J = 7.0, 2H, $NC\underline{H}_2CH_3$), 7.32 (ddd, J = 8.0, 8.0, 1.5, 1H, 5-H), 7.48 (ddd, J = 8.0, 8.0, 1.5, 1H, 6-H), 7.81 (ddd, J = 8.0, 1.5, 0.8, 1H, 7-H), 8.10 (ddd, J = 8.0, 1.5, 0.8, 1H, 4-H), 13.02 (s, 1H, COOH). IR (KBr) ν cm^{-1}: 1682, 1481. UV λ_{max} (EtOH) nm: 278 sh, 299. UV λ_{max} (EtOH + 10% aqueous NaOH) nm: 264, 272, 299, 310. *Anal.* Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.07; H, 5.28; N, 14.63.

b) (Table 1; run 3) A solution of **27a** (11.5 g, 65 mmol) in anhydrous THF (110 ml) was treated with *tert*-BuOK (8.0 g, 71 mmol) at 5 °C. The mixture was stirred at the same temperature for 1 h, then C_2H_5I (11.1 g, 71 mmol) was added. The whole was stirred at room temperature for 20 h and then concentrated to dryness. The residue was taken up in $CHCl_3$ and water, and the organic layer was separated and washed with brine. The solvent was evaporated to give 11.8 g of crude **27b** as an oil. In a similar manner to that described above, **27b** (11.8 g) was hydrolyzed with 1 N aqueous NaOH and recrystallized from toluene–*n*-hexane to give 9.6 g (77% yield from **27a**) of **26b**.

2-Ethyl-2*H*-indazole-3-carboxylic Acid (29b) In a similar manner to that described above, **28b** was hydrolyzed with 1 N aqueous NaOH to give **29b** in 84% yield. mp 185—188 °C [lit.[23a] mp 180—181 °C (H_2O)]. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.48 (t, J = 7.0, 3H, $NCH_2C\underline{H}_3$), 4.89 (q, J = 7.0, 2H, $NC\underline{H}_2CH_3$), 7.28 (ddd, J = 8.0, 8.0, 1.5, 1H, 5-H), 7.37 (ddd, J = 8.0, 8.0, 1.5, 1H, 6-H), 7.77 (ddd, J = 8.0, 1.5, 0.8, 1H, 7-H), 8.01 (ddd, J = 8.0, 1.5, 0.8, 1H, 4-H), 13.64 (s, 1H, COOH). IR (KBr) ν cm^{-1}: 1688, 1477. UV λ_{max} (EtOH) nm: 297, 310. UV λ_{max} (EtOH + 10% aqueous NaOH) nm: 306. *Anal.* Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.20; H, 5.28; N, 14.65.

General Procedures for Ethylation of Methyl 1*H*-Indazole-3-carboxylate (27a) in Table 1 Runs 4, 7, 8: A mixture of **27a** (2.0 g, 11 mmol), C_2H_5I (2.0 eq), solvent (20 ml), and *tert*-BuOK (1.1 eq)–18-crown-6 (0.1 eq), or anhydrous K_2CO_3 (1.5 eq)–18-crown-6 (0.1 eq), or *n*-$Bu_4N^+F^-$ (3.0 eq) was stirred at room temperature for 20 h. The solvent was evaporated to leave a residue, which was dissolved in $CHCl_3$. The solution was washed successively with water and brine. The solvent was evaporated to leave a solid, which was analyzed by ^{1}H-NMR spectroscopy. Runs 2, 5, 6: To a solution of **27a** (2.0 g, 11 mmol) in the solvent (20 ml) was added each base (1.1 eq) and 18-crown-6 (0.1 eq) or TDA-1 (0.1 eq) at 5 °C. The mixture was stirred at the same temperature for 1 h, and C_2H_5I (2.0 eq) was added. The whole was stirred at room temperature for 20 h. The reaction mixture was poured into ice-water and extracted with Et_2O or the organic layer was separated. The organic layer was washed with brine and concentrated to leave a residue, which were analyzed by ^{1}H-NMR spectroscopy.

1-Substituted 1*H*-Indazole-3-carboxylic Acids (26c—j) In a similar manner (Table 1, run 3) to that described for the preparation of **27b**, compounds **27c—h** were prepared by using **27a** and an appropriate alkyl halide or benzyl bromide. Compounds **27c—h** were hydrolyzed to produce the corresponding 1*H*-indazole-3-carboxylic acids **26c—h**.

In a similar manner (Table 1, run 1) to that described for the preparation of **27b**, compounds **27i** and **27j** were prepared by using **27a** and an appropriate alkyl halide. The mixture was separated into the less polar **28i**/**28j** and the more polar **27i**/**27j** by silica gel column chromatography, and the methyl esters **27i** and **27j** were hydrolyzed to

Table 7. Physical Data for the 1-Substituted 1*H*-Indazole-3-carboxylic Acids (**26c—j**)

Compd.	mp (°C)	^{1}H-NMR (200 MHz, ppm, in DMSO-d_6)	Formula	Analysis (%) Calcd (Found) C	H	N	MS (*m/z*)	IR (cm^{-1})
26c	126—129	0.83 (t, J=7.0, 3H, $CH_2CH_2C\underline{H}_3$), 1.89 (sex, J=7.0, 2H, $CH_2C\underline{H}_2CH_3$), 4.48 (t, J=7.0, 2H, $C\underline{H}_2CH_2CH_3$), 7.31 (ddd, J=8.0, 8.0, 1.5, 1H, 5-H), 7.47 (ddd, J=8.0, 8.0, 1.5, 1H, 6-H), 7.82 (ddd, J=8.0, 1.5, 0.8, 1H, 7-H), 8.09 (ddd, J=8.0, 1.5, 0.8, 1H, 4-H), 13.00 (s, 1H, COOH)	$C_{11}H_{12}N_2O_2$	64.69 (64.54	5.92 5.91	13.72 13.61)	205 (MH^+)	1627, 1508, 1483
26d	180—182	0.35—0.60 (m, 4H, CH_2CH_2), 1.33 (m, 1H, CH), 4.41 (d, J=7.3, 2H, $C\underline{H}_2CH$), 7.31 (ddd, J=8.0, 8.0, 1.5, 1H, 5-H), 7.47 (ddd, J=8.0, 8.0, 1.5, 1H, 6-H), 7.84 (ddd, J=8.0, 1.5, 0.8, 1H, 7-H), 8.10 (ddd, J=8.0, 1.5, 0.8, 1H, 4-H), 13.00 (s, 1H, COOH)	$C_{12}H_{12}N_2O_2$	66.65 (66.38	5.59 5.63	12.96 12.66)	217 (MH^+)	1672, 1508, 1483
26e	102—104	0.88 (t, J=7.0, 3H, $CH_2CH_2CH_2C\underline{H}_3$), 1.26 (sex, J=7.0, 2H, $CH_2CH_2C\underline{H}_2CH_3$), 1.85 (quint, J=7.0, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 4.51 (t, J=7.0, 2H, $C\underline{H}_2$-$CH_2CH_2CH_3$), 7.31 (ddd, J=8.0, 8.0, 1.5, 1H, 5-H), 7.48 (ddd, J=8.0, 8.0, 1.5, 1H, 6-H), 7.81 (ddd, J=8.0, 1.5, 0.8, 1H, 7-H), 8.10 (ddd, J=8.0, 1.5, 0.8, 1H, 4-H), 13.00 (s, 1H, COOH)	$C_{12}H_{14}N_2O_2$	66.04 (66.13	6.47 6.48	12.84 12.81)	219 (MH^+)	1730, 1485
26f	154—156	5.01—5.35 (m, 4H), 6.06 (m, 1H), 7.33 (ddd, J=8.0, 8.0, 1.5, 1H, 5-H), 7.48 (ddd, J=8.0, 8.0, 1.5, 1H, 6-H), 7.77 (ddd, J=8.0, 1.5, 0.8, 1H, 7-H), 8.11 (ddd, J=8.0, 1.5, 0.8, 1H, 4-H), 13.06 (s, 1H, COOH)	$C_{11}H_{10}N_2O_2$	65.34 (65.05	4.98 5.00	13.85 13.66)	203 (MH^+)	1672, 1510, 1481
26g	161—163	5.78 (s, 2H, CH_2Ph), 7.15—7.40 (m, 6H), 7.47 (ddd, J=8.0, 8.0, 1.5, 1H, 6-H), 7.85 (ddd, J=8.0, 1.5, 0.8, 1H, 7-H), 8.11 (ddd, J=8.0, 1.5, 0.8, 1H, 4-H), 13.12 (br s, 1H, COOH)	$C_{15}H_{12}N_2O_2$	71.42 (71.58	4.79 4.80	11.10 11.05)	253 (MH^+)	1684, 1508, 1485
26h	93—96	0.87 (d, J=6.7, 6H, $CH(C\underline{H}_3)_2$), 2.27 (m, 1H), 4.34 (d, J=7.5, 2H, $C\underline{H}_2CH(CH_3)_2$), 7.32 (ddd, J=8.0, 8.0, 1.5, 1H, 5-H), 7.48 (ddd, J=8.0, 8.0, 1.5, 1H, 6-H), 7.83 (ddd, J=8.0, 1.5, 0.8, 1H, 7-H), 8.12 (ddd, J=8.0, 1.5, 0.8, 1H, 4-H), 13.02 (s, 1H, COOH)	$C_{12}H_{14}N_2O_2$	66.04 (65.77	6.47 6.46	12.84 12.74)	219 (MH^+)	1682, 1508, 1483
26i	160—163	1.52 (d, J=6.7, 6H, $CH(C\underline{H}_3)_2$), 5.12 (hept, J=6.7, 1H, $C\underline{H}(CH_3)_2$), 7.31 (ddd, J=8.0, 8.0, 1.5, 1H, 5-H), 7.47 (ddd, J=8.0, 8.0, 1.5, 1H, 6-H), 7.84 (ddd, J=8.0, 1.5, 0.8, 1H, 7-H), 8.10 (ddd, J=8.0, 1.5, 0.8, 1H, 4-H), 12.98 (s, 1H, COOH)	$C_{11}H_{12}N_2O_2$	64.69 (64.67	5.92 5.90	13.72 13.64)	205 (MH^+)	1684, 1504, 1489
26j	117—119	1.60—2.40 (m, 8H), 5.27 (quint, J=7.0, 1H), 7.31 (ddd, J=8.0, 8.0, 1.5, 1H, 5-H), 7.47 (ddd, J=8.0, 8.0, 1.5, 1H, 6-H), 7.84 (ddd, J=8.0, 1.5, 0.8, 1H, 7-H), 8.09 (ddd, J=8.0, 1.5, 0.8, 1H, 4-H), 13.14 (br s, 1H, COOH)	$C_{13}H_{14}N_2O_2$	67.81 (67.54	6.13 6.08	12.17 12.08)	231 (MH^+)	1686, 1500, 1485

afford the corresponding 1*H*-indazole-3-carboxylic acids **26i** and **26j**. Physical and spectral data for compounds **26c—j** are listed in Table 7.

Method A. General Procedure A solution of carboxylic acid (1.0 g) and CDI (1.1 eq) in DMF (20 ml) was stirred at room temperature for 0.5 h. An amine **17**, **20**, **30**, or **31** (1.1 eq) was added to the solution, and the mixture was stirred at room temperature for 18 h. The solvent was evaporated to leave a residue, which was dissolved in AcOEt. The solution was washed successively with water, 10% aqueous NaOH, and brine. The solvent was evaporated to afford a crude product, which was chromatographed on silica gel. The product was crystallized from the solvent given in Tables 2 and 3 or converted to the oxalate or fumarate in the usual manner, followed by recrystallization from the solvent given in Tables 2 and 3.

Method B. General Procedure A mixture of carboxylic acid (1.0 g), amine (1.1 eq), WSC (1.2 eq), and CH_2Cl_2 (50 ml) was stirred at room temperature for 5 h. The reaction mixture was washed successively with water, 10% aqueous NaOH, water, and brine, and concentrated to dryness. Work-up similar to that described above gave the product.

Method C. (1,4-Dimethylhexahydro-1*H*-1,4-diazepin-6-yl) Indole-3-carboxylate (62) A solution of *n*-BuLi (1.6 M solution in hexane; 9.4 ml, 15 mmol) was added dropwise to a solution of **35**[20] (1.9 g, 13 mmol) in anhydrous THF (10 ml) at room temperature under nitrogen. The mixture was stirred at the same temperature for 30 min. To the reaction mixture was added dropwise a mixture containing the imidazolide **32'** prepared by the following method: CDI (2.0 g, 12 mmol) was added to a solution of indole-3-carboxylic acid (**32**, 2.0 g, 12 mmol) in anhydrous DMF (20 ml) at room temperature, and the mixture was heated at 80 °C for 4.5 h and then cooled to room temperature. The whole was heated to reflux for 1 h. The solvent was evaporated to leave a residue, which was diluted with water and extracted with Et_2O. The extract was concentrated to give an oily residue, which was chromatographed on silica gel with $CHCl_3$: MeOH = 9 : 1 to afford 2.1 g (60%) of **62** as a solid. The solid was recrystallized from AcOEt. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.44 (s, 6H, $CH_3 \times 2$), 2.63—2.92 (m, 4H), 2.95 (dd, J=5.8, 13.8, 2H, 5-$C\underline{H}_2$, 7-$C\underline{H}_2$), 3.11 (dd, J=5.8, 13.8, 2H, 5-$C\underline{H}_2$, 7-$C\underline{H}_2$), 5.38 (quint, J=5.8, 1H, 6-CH), 7.19—7.42 (m, 2H), 8.00 (d, J=3.2, 1H), 8.25 (m, 1H), 10.92 (br s, 1H, NH). IR (KBr) ν cm^{-1}: 2950, 1695, 1530, 1450. MS *m/z*: 288 (MH^+).

In a similar manner to that described above, the esters **56**, **63**, **64**, and **83—86** were prepared by using **32**, 1-methylindole-3-carboxylic acid (**33**), 1*H*-indazole-3-carboxylic acid (**26a**), and 1-methyl-1*H*-indazole-3-carboxylic acid (**34**) and the alcohols **15**, **35**, and **36**.[1]

Method D. a) 1-Acetyl-*N*-(1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1*H*-indazole-3-carboxamide Fumarate (101) A mixture of acetic anhydride (560 mg, 5.5 mmol), **54** (1.0 g, 2.8 mmol), and CH_2Cl_2 (10 ml) was stirred at room temperature for 16 h. The solution was washed successively with saturated aqueous $NaHCO_3$ and brine. The solvent was evaporated to leave an oil, which was chromatographed on silica gel with acetone to give 0.9 g of the base of **101** as an oil. The oil was converted to the fumarate in the usual manner. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 2.40 (s, 3H, NCH_3), 2.50—3.00 (m, 8H), 2.84 (s, 3H, $COCH_3$), 3.66 (s, 2H, C$\underline{H}_2$Ph), 4.25 (m, 1H, 6-CH), 6.60 (s, 2H), 7.00—7.80 (m, 7H, indazole 5-H, 6-H, arom. H), 8.10—8.50 (m, 3H, indazole 4-H, 7-H, CONH). IR (KBr) ν cm^{-1}: 1725, 1670, 1525, 1375, 1325. MS *m/z*: 406 (MH^+).

In a similar manner, compounds **102**—**104** were prepared by using propionic anhydride, benzoic anhydride, and methyl chloroformate, respectively.

b) *N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1-(2-butanon-3-yl)-1*H*-indazole-3-carboxamide 3/2Oxalate (105) A solution of **54** (1.0 g, 2.8 mmol) in anhydrous THF (20 ml) was treated with *tert*-BuOK (320 mg, 1.8 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 0.5 h, and then 3-chloro-2-butanone[47] (293 mg, 2.8 mmol) was added. The mixture was stirred at room temperature for 16 h and concentrated to dryness. The residue was dissolved in $CHCl_3$ and the solution was washed successively with water and brine. The solvent was evaporated to give a residue, which was chromatographed on silica gel with acetone to afford 540 mg (45%) of **105** as an oil. The oil was converted to the oxalate in the usual manner. ^{1}H-NMR (80 MHz, DMSO-d_6) δ: 1.76 (d, J=7, 3H, CHC$\underline{H}_3$), 2.02 (s, 3H, $COCH_3$), 2.80 (s, 3H, NCH_3), 2.50—3.50 (m, 8H), 3.75 (s, 2H, C$\underline{H}_2$Ph), 4.46 (m, 1H, 6-CH), 5.77 (q, J=7, 1H, C$\underline{H}$CH$_3$), 7.10—7.60 (m, 7H, indazole 5-H, 6-H, arom. H), 7.74 (d-like, J=8, 1H, indazole 7-H), 8.16 (d-like, J=8, 1H, indazole 4-H), 8.40 (d, J=8, 1H, CONH), 8.0—9.0 (oxalic acid). IR (KBr) ν cm^{-1}: 1720, 1650, 1530, 1490, 1400. MS *m/z*: 434 (MH^+).

In a similar manner, compound **106** was prepared by using **54** and 2-chloroethanol.

***N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1-indolinecarboxamide Dioxalate (67)** The method of Bermudez *et al.*[48] was adopted. A mixture of indoline (4.7 g, 39 mmol), *N*,*N*′-disuccinimidyl carbonate (**37**, 10.0 g, 39 mmol), and anhydrous toluene (190 ml) was stirred at room temperature for 18 h. The solvent was evaporated to leave a residue, which was dissolved in $CHCl_3$. The solution was washed successively with 20% HCl, 10% aqueous K_2CO_3, and brine. The solvent was evaporated to leave a solid, which was triturated with toluene to give 8.3 g (81%) of **38**, mp 209—211 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.87 (s, 4H, $NCOCH_2CH_2CON$), 3.23 (t, J=8.5, 2H, indoline 3-H), 4.25 (t, J=8.5, 2H, indoline 2-H), 7.05 (ddd, J=1.1, 7.3, 7.3, 1H), 7.16—7.28 (m, 2H), 7.74 (br d, J=8.2, 1H). IR (KBr) ν cm^{-1}: 1770, 1730, 1490, 1400, 1210. MS *m/z*: 261 (MH^+), 260 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.83; H, 4.61; N, 10.71.

A mixture of **38** (3.3 g, 13 mmol), **30** (2.8 g, 13 mmol), Et_3N (1.3 g, 13 mmol), and toluene (100 ml) was heated to reflux for 20 h and cooled to room temperature. The reaction mixture was washed successively with 10% aqueous K_2CO_3, water, and brine and then concentrated to dryness. The oily residue was chromatographed on silica gel with $CHCl_3$: MeOH = 9 : 1 to give 2.3 g (50%) of the free base of **67** as an oil. The oil was converted to the oxalate in the usual manner. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 2.65—3.05 (m, 4H), 2.85 (s, 3H, NCH_3), 3.10 (t, J=9, 2H, indoline 3-H), 3.20—3.35 (m, 2H), 3.43 (d, J=5, 2H), 3.75 (s, 2H, C$\underline{H}_2$Ph), 3.85 (t, J=9, 1H, indoline 2-H), 3.93 (t, J=9, 1H, indoline 2-H), 4.43 (m, 1H, 6-CH), 6.73 (d-like, J=8, 1H), 6.85 (t, J=8, 1H), 7.00—7.20 (m, 2H), 7.20—7.45 (m, 5H), 7.80 (d, J=8, 1H), 11.75 (br s, oxalic acid). IR (KBr) ν cm^{-1}: 3410, 1720, 1660, 1650, 1485. MS *m/z*: 365 (MH^+).

***N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-4-hydroxy-3-quinolinecarboxamide Dioxalate (73)** The method of Hayashi *et al.*[28] was adopted. A mixture of 4-hydroxy-3-quinolinecarboxylic acid[49] (**39**, 0.9 g, 4.8 mmol), $SOCl_2$ (5 ml, 69 mmol), and DMF (5 drops) was stirred at room temperature for 2 h and then concentrated to dryness. The residue was dissolved in THF, and the solution was added dropwise to a mixture prepared by the following method at room temperature; a solution of **30** (1.8 g, 8.2 mmol) in anhydrous THF (40 ml) was added to a stirred suspension of NaH (60% dispersion in mineral oil, 380 mg, 9.5 mmol) in anhydrous THF (30 ml) at room temperature, and the mixture was stirred at the same temperature for 1 h. The whole was stirred at room temperature for 1.5 h and concentrated to dryness. The residue was dissolved in 1 N HCl and washed twice with $CHCl_3$. The aqueous solution was basified with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine and evaporated to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$: MeOH = 12 : 1 to give 1.3 g (67%) of *N*-(1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-4-chloro-3-quinolinecarboxamide (**40**) as an oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.42 (s, 3H, NCH_3), 2.1—3.1 (m, 8H), 3.56 (d, J=11, 1H, C$\underline{H}_2$Ph), 3.71 (d, J=11, 1H, C$\underline{H}_2$Ph), 4.33 (m, 1H, 6-CH), 7.05—7.55 (m, 6H), 7.72 (ddd, J=1.6, 8.0, 8.0, 1H, quinoline 6-H), 7.85 (ddd, J=1.6, 8.0, 8.0, 1H, quinoline 7-H), 8.17 (ddd, J=0.6, 1.6, 8.0, 1H, quinoline 5-H), 8.33 (ddd, J=0.6, 1.6, 8.0, 1H, quinoline 8-H), 8.91 (s, 1H, quinoline 2-H). IR (neat) ν cm^{-1}: 3145, 2940, 1635, 1555, 1490, 1450, 1350. MS *m/z*: 409 (MH^+).

A stirred solution of **40** (1.3 g, 3.2 mmol) in 1 N HCl (150 ml) was heated at 80 °C for 15 h and then cooled to room temperature. The reaction mixture was washed with $CHCl_3$, then the aqueous solution was adjusted to a pH of 7.5 with $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine and evaporated to leave a residue, which was chromatographed on silica gel with $CHCl_3$: MeOH = 9 : 1 to give 0.7 g (56%) of the free base of **73** as an oil. The oil was converted to the oxalate in the usual manner. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 2.25—2.40 (m, 2H), 2.40—2.55 (m, 2H), 2.70—3.05 (m, 4H), 2.80 (s, 3H, NCH_3), 3.79 (s, 2H, C$\underline{H}_2$Ph), 4.42 (m, 1H, 6-CH), 7.20—7.40 (m, 3H), 7.45—7.58 (m, 3H), 7.70—7.85 (m, 2H), 8.31 (dd, J=1.2, 8.0, 1H, quinoline 8-H), 8.75 (d, J=4.2, 1H, quinoline 2-H), 10.54 (d, J=7.0, 1H), 13.05 (br s, 1H), 13.1 (br s, oxalic acid). IR (KBr) ν cm^{-1}: 3000, 1720, 1660, 1610, 1520. MS *m/z*: 391 (MH^+).

3-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1,2,3-benzotriazin-4(3*H*)-one Dihydrochloride (77) A mixture of isatoic anhydride (1.6 g, 9.8 mmol), **30** (2.2 g, 10 mmol), and DMF (5 ml) was stirred at room temperature for 18 h, then concentrated to dryness. The residue containing 2-amino-*N*-(1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)benzamide (**41**) was dissolved in concentrated HCl (2 ml). A solution of $NaNO_2$ (200 mg, 2.9 mmol) in H_2O (2 ml) was added to the cooled (0 °C) solution of **41**. The mixture was stirred at room temperature for 1 h. The resulting precipitates were collected, washed with water, dried, and recrystallized from EtOH to give 800 mg (23%) of **77**. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 2.52 (s, 3H, NCH_3), 2.70—3.55 (m, 8H), 3.75 (s, 2H, C$\underline{H}_2$Ph), 5.55 (m, 1H, 6-CH), 7.10—7.41 (m, 5H), 7.70—8.35 (m, 4H). IR (KBr) ν cm^{-1}: 1680. MS *m/z*: 350 (MH^+).

***N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-6-chloro-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-8-carboxamide 3/2Oxalate (78)** A mixture of 6-chloro-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-8-carboxylic acid[18] (**42**, 2.0 g, 8.3 mmol) and $SOCl_2$ (5 ml, 69 mmol) was heated to reflux for 1.5 h and then cooled to room temperature. The reaction mixture was concentrated to dryness. The residue was dissolved in $CHCl_3$ (100 ml), and the solution was added dropwise to a stirred solution of **30** (2.0 g, 9.1 mmol) and Et_3N (3.3 g, 33 mmol) in $CHCl_3$ (40 ml) kept at 5 °C. The mixture was stirred at room temperature for 3 h and then washed successively with water, 10% aqueous NaOH, and brine. The solvent was evaporated to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$: MeOH = 9 : 1 to give 2.9 g (79%) of the free base of **78** as an oil. The oil was converted to the oxalate in the usual manner. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 2.70—3.05 (m, 4H), 2.80 (s, 3H, NCH_3), 3.15—3.35 (m, 2H), 3.32 (s, 3H, NCH_3), 3.35—3.50 (m, 2H), 3.78 (s, 2H, C$\underline{H}_2$Ph), 4.40 (m, 1H, 6-CH), 4.77 (s, 2H, $NCOCH_2$), 7.20—7.45 (m, 7H, arom. H), 8.59 (d, J=8, 1H, CONH), 10.65 (br s, oxalic acid). IR (KBr) ν cm^{-1}: 3200, 1680, 1650, 1580, 1520. MS *m/z*: 443 (MH^+).

***N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1*H*-indazole-3-carbothioamide (87)** A mixture of **54** (1.0 g, 2.8 mmol), Lawesson's reagent [97%, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, 1.1 g, 2.8 mmol], and toluene (30 ml) was heated to reflux for 2 h and then cooled to room temperature. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with $CHCl_3$: MeOH = 10 : 1 to give 580 mg (56%) of **87** as an amorphous powder. An analytical sample of **87** was obtained by crystallization from EtOH. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.52 (s, 3H, NCH_3), 2.60—3.00 (m, 4H), 3.05—3.30 (m, 4H), 3.65 (d, J=13, 1H, C$\underline{H}_2$Ph), 3.75 (d, J=13, 1H, C$\underline{H}_2$Ph), 5.02 (m, 1H, 6-CH), 7.15—7.50 (m, 10H), 8.85 (d, J=8, 1H, CONH). IR (KBr) ν cm^{-1}: 3315, 2790, 1495, 1475, 1450. MS *m/z*:

380 (MH^+).

3-(Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)methoxy-1*H*-indazole 3/2Oxalate (88) Sodium hydride (60% dispersion in mineral oil, 540 mg, 14 mmol) was added portionwise to a solution of 1*H*-indazol-3-ol[50] (**43**, 1.9 g, 14 mmol) in DMF (20 ml) at room temperature. The mixture was stirred at room temperature for 1 h, and then **18** (3.2 g, 13 mmol) was added. The whole was heated at 50 °C for 2 h, poured into ice-water and extracted with AcOEt. The extract was washed successively with water and brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with $CHCl_3$: MeOH = 10 : 1 to give 230 mg (4.6%) of the free base of **88** as an oil and 230 mg (4.6%) of 1-[(benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)methyl]-1*H*-indazol-3-ol (**44**) as an oil in that order. ^{1}H-NMR (300 MHz, $CDCl_3$) 2.44 (s, 3H, NCH_3), 2.40—3.10 (m, 9H), 3.65 (s, 2H, $C\underline{H}_2Ph$), 4.22 (d, J = 6.0, 2H, CH_2O), 7.00—7.45 (m, 8H), 7.59 (d, J = 8, 1H), 10.03 (m, 1H). ^{13}C-NMR δ: 37.66 (C_6), 47.18 (NCH_3), 54.81, 56.53, 58.96, 59.41, 63.24 ($\underline{C}H_2Ph$), 70.16 (OCH_2), 109.67, 112.60, 119.70, 119.85, 127.02, 127.70, 128.25, 128.84, 139.12, 142.51, 157.39. MS m/z: 351 (MH^+). The oily free base of **88** was converted to the oxalate in the usual manner.

Compound **44**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.46 (s, 3H, NCH_3), 2.60—3.10 (m, 9H), 3.62 (s, 2H, $C\underline{H}_2Ph$), 3.84 (dd, J = 6.0, 12.0, 1H, $C\underline{H}_2N$), 4.00 (dd, J = 6.0, 12.0, 1H, $C\underline{H}_2N$), 6.90—7.41 (m, 9H), 7.73 (d, J = 8, 1H). ^{13}C-NMR δ: 36.79 (C6), 46.80 (NCH_3), 50.60 (NCH_2), 54.20, 57.25, 59.27, 59.39, 63.15 ($\underline{C}H_2Ph$), 108.68, 113.24, 119.13, 121.22, 127.31, 128.19, 128.37, 128.97, 138.38, 142.64, 157.05. MS m/z: 351 (MH^+).

1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl 1-Methyl-1*H*-indazol-3-yl Ketone 3/2Oxalate (89) A mixture of 3-acetyl-1-methyl-1*H*-indazole[51] (**45**, 2.0 g, 11 mmol), **12**·2HCl (2.7 g, 11 mmol), paraformaldehyde (760 mg), and acetic acid (20 ml) was heated at 120 °C for 2 h. The solvent was evaporated to give an oil, which was dissolved in water. The aqueous solution was neutralized with saturated aqueous $NaHCO_3$ and then extracted with $CHCl_3$. The extract was washed with brine and evaporated to leave a residue, which was chromatographed on silica gel with $CHCl_3$: MeOH = 20 : 1 to afford 1.0 g (24%) of the free base of **89** as an oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.65—3.90 (m, 9H), 2.85 (s, 3H, NCH_3), 3.67 (s, 2H, $C\underline{H}_2Ph$), 4.12 (s, 3H, NCH_3), 5.9 (br s, oxalic acid), 6.90—7.90 (m, 7H), 7.81 (d-like, J = 8, indazole 7-H), 8.16 (d-like, J = 8, 1H, indazole 4-H). MS m/z: 363 (MH^+). The oily free base of **89** was converted to the oxalate in the usual manner. IR (KBr) ν cm^{-1}: 3200, 1705, 1650, 1475.

1-Methyl-1*H*-indazole-3-(1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)methanol Dioxalate (90) To a solution of the free base of **89** (1.0 g, 2.8 mmol) in MeOH (20 ml) was added portionwise $NaBH_4$ (220 mg, 5.8 mmol) at *ca.* 10 °C. The mixture was stirred at room temperature for 1 h and concentrated to dryness. The residue was dissolved in $CHCl_3$ and water. The organic layer was separated and washed with brine. The solvent was evaporated to afford an oily residue, which was chromatographed on silica gel with $CHCl_3$: MeOH = 20 : 1 to give 800 mg (80%) of the free base of **90** as an amorphous solid. The amorphous solid was converted to the oxalate in the usual manner. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 2.4—3.0 (m, 5H), 2.75 (s, 3H, NCH_3), 3.0—3.6 (m, 5H), 3.65 (s, 2H, $C\underline{H}_2Ph$), 3.97 (s, 3H, NCH_3), 5.01 (d, J = 3.8, 1H), 7.05—7.9 (m, 7H, arom. H), 7.5 (br s, oxalic acid), 7.58 (d-like, J = 8, 1H), 7.84 (d-like, J = 8, 1H). IR (KBr) ν cm^{-1}: 3370, 1710, 1615, 1400. MS m/z: 365 (MH^+).

***N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-5-hydroxy-1*H*-indazole-3-carboxamide (117)** Ethanethiol (230 mg, 3.7 mmol) was added to a suspension of NaH (60% dispersion in mineral oil, 127 mg, 3.2 mmol)) in anhydrous DMF (5 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 0.5 h, and the free base of **116** (500 mg, 1.3 mmol) was added. The mixture was heated at 100 °C for 2 h and then cooled to room temperature. The solvent was evaporated, then the residue was taken up in water and the solution obtained was washed with $CHCl_3$. The aqueous solution was neutralized with 10% HCl and extracted with $CHCl_3$. The extract was washed with brine and evaporated. The residue was chromatographed on silica gel with $CHCl_3$: MeOH = 5 : 1 to give 90 mg (19%) of **117** as an amorphous powder. The powder was crystallized from EtOH to afford an analytical sample of **117**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.32 (s, 3H, NCH_3), 2.40—2.95 (m, 8H), 3.34 (s, H_2O), 3.60 (d, J = 13.5, 1H, $C\underline{H}_2Ph$), 3.69 (d, J = 13.5, 1H, $C\underline{H}_2Ph$), 4.16 (m, 1H, 6-CH), 6.95 (dd, J = 2.0, 9.0, 1H, indazole 6-H), 7.10—7.50 (m, 7H, indazole 4-H, 7-H, arom. H), 8.05 (d, J = 8.5, 1H, CONH), 9.33 (s, 1H, OH), 12.33 (s, 1H, NH). IR (KBr) ν cm^{-1}: 3170, 2810, 1625, 1540, 1485. MS m/z: 380 (MH^+).

5-Amino-*N*-(1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1*H*-indazole-3-carboxamide Dioxalate (119) A solution of **118** (900 mg, 2.2 mmol) in MeOH (200 ml) was hydrogenated over Raney Ni at room temperature, until no more hydrogen was consumed. The catalyst was filtered off, and the filtrate was evaporated to give 350 mg (42%) of the free base of **119** as an oil. The oil was converted to the oxalate in the usual manner. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 2.83 (s, 3H, NCH_3), 2.65—3.15, 3.15—3.60 (m, 10H), 3.76 (s, 2H, $C\underline{H}_2Ph$), 4.49 (m, 1H, C_6-H), 6.82 (dd, J = 2.0, 9.0, 1H, indazole 6-H), 6.5—7.9 (m, 7H, arom. H, indazole 4-H, 7-H), 7.2 (br s, oxalic acid), 7.36 (d, J = 8.5, 1H), 13.4 (br s, 1H, NH). IR (KBr) ν cm^{-1}: 3200, 1705, 1640, 1535, 1500. MS m/z: 379 (MH^+).

Molecular Modeling The molecular modeling of granisetron (**4**) and 1-benzyl-4-methylhexahydro-1*H*-diazepinyl amides **10** and **54** was performed with SYBYL Ver. 5.5[52] on a Silicon Graphics IRIS 4D/35TG workstation. Modeling procedures were as follows. All reference compounds and substructures mentioned below were retrieved from the Cambridge Structural Database[53] to get each starting geometry for molecular energy minimization. Initial atomic coordinates of structure **4** were obtained by replacement of the tropane ring in the X-ray crystal structure of 3-(3α-tropanylaminocarbonyl)-1-methylindazole (REFCODE: FIZXUH) by the three-dimensional substructure 9-azabicyclo[3.3.1]non-3-yl (REFCODE: FILJAL). The MM1[54] calculation with geometry optimization in MOPAC Ver. 5.0[55] for all geometric variables was carried out with the keyword "MMOK." This optimized structure was used as a template for molecular superposition with structures **10** and **54**. Molecular models of **10** and **54** were built up using three-dimensional fragments, a 4-amino-5-chloro-2-ethoxybenzamide moiety and 1-methylindazole-3-carboxamide in the X-ray crystal structure of metoclopramide (REFCODE: METPRA01) and FIZXUH, respectively. The coordinates of the seven-membered diazepine ring in both structures **10** and **54** were obtained from our X-ray analysis[56] of the 3-methylbenzyl analogue of **54**. The other remaining substructure was constructed with standard bond lengths and bond angles. After energy minimization using the MAXIMIN2 routine implemented in SYBYL with neglect of the electrostatic term of the Tripos force field,[57] semiempirical molecular orbital calculation of the energy-minimized structures using MOPAC/AM1 with full geometry optimization was done to refine our molecular models of compounds **10** and **54**. No attempt was made to seek any other stable conformer, and the conformations of the *N*-benzyl group in **10** and **54** adopted in Figs. 2 and 3 were arbitrary selected.

Molecular superposition was performed by least-squares fitting between the Cartesian coordinates of particular atoms and/or centroids with the FIT command in SYBYL. The values of the RMS distances are also shown in Figs. 2 and 3.

Biological Activities Male rats of the JCL SD strain (Nihon SLC Inc., Shizuoka, Japan) weighing 300—350 g, and male albino ferrets (Marshall Res. Animal Inc., N.Y., U.S.A.) weighing 1—1.5 kg were used. Compounds prepared were dissolved in saline at room temperature, and cisplatin was dissolved in saline at 70 °C.

B–J Reflex (2-Methyl-5-HT-Induced Bradycardia) Rats were anesthetized with urethane (1.2 g/kg, i.p.). The heart rate was derived from the electrocardiogram (lead II), which was recorded *via* electrodes s.c. inserted into the left forelimb and right hindlimb. The femoral vein was cannulated for i.v. injection of 2-methyl-5-HT and test compounds. Bolus i.v. injections of 2-methyl-5-HT (30—50 mg/kg) were given every 15 min. After the 2-methyl-5-HT-induced bradycardia had stabilized, a test compound was injected i.v. 3 min before administration of 2-methyl-5-HT. The ED_{50} values (dose causing 50% inhibition of the bradycardia) of compounds were obtained by Probit analysis.[58]

Cisplatin-Induced Emesis in Ferrets Under pentobarbital anesthesia (30 mg/kg, i.p.), a chronic indwelling jugular venous catheter was surgically implanted for i.v. injection of cisplatin and test compounds in ferrets, as reported by Florczyk and Schuring.[59] Two to three days after the operation, test compounds were administered i.v. twice at 30 min before and 45 min after administration of cisplatin (10 mg/kg, i.v.). The latency from administration of cisplatin to the first emetic episode and the number of emetic episodes induced were observed for 3 h after administration of cisplatin. The differences from the control group that were statistically significant were identified by means of the MUSCOT statistical analysis program (Yukms Co., Tokyo, Japan; Williams–

Wilcoxon's multiple range test).

Acute Toxicity Male Std-ddY mice, weighing 25—30 g, were used in groups of 10 animals each. The test compounds, dissolved or suspended in a 0.5% tragacanth solution, were administered intraperitoneally. The mortality was observed for 7 d after the administration.

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