Substituted Benzamides. 1. Potential Nondopaminergic Antagonists of Chemotherapy-Induced Nausea and Emesis

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A series of new substituted benzamides has been synthesized and evaluated for dopamine antagonist activity and for antagonism of cisplatin-induced emesis in the dog and in the ferret. It was found that modification of the 2-methoxy substituent of metoclopramide was detrimental to dopaminergic D_2 antagonism but not necessarily to antagonism of cisplatin-induced emesis. A number of analogues having a β-keto, β-hydroxy, β-methoxy, β-imino, or β-unsaturated alkyloxy substituent instead of methoxy have shown equal or superior protection from emesis to that of metoclopramide. At the same time these compounds were found to be free of dopaminergic D_2 antagonism in both in vitro ([^{3}H]spiperone binding) and in vivo tests (rat catalepsy, antagonism of apomorphine-induced stereotypy in the rat, and apomorphine-induced emesis in the dog).

The rapidly growing field of chemotherapeutic treatment of cancer has stimulated efforts toward the discovery of effective agents capable of blocking chemotherapy-induced nausea and emesis. The clinical effectiveness of various substituted benzamides such as metoclopramide (**1**)[1] and alizapride (**2**),[2] the benzimidazole domperidone (**3**)[3] (shown in Chart I), various phenothiazines, dexamethasone, tetrahydrocannabinoids and their synthetic analogues, and various combinations thereof[4,5] has been evaluated. From these studies, high-dose, intravenous metoclopramide has emerged as the single most effective agent against cisplatin-induced nausea and emesis. Unfortunately the use of metoclopramide is limited by side effects such as extrapyramidal symptoms, which are a consequence of its dopaminergic D_2 receptor antagonist properties.[6]

In this paper we describe the synthesis and properties of a new series of benzamides that are highly effective antagonists of chemotherapy-induced emesis in animals and that are devoid of dopaminergic antagonist activity.

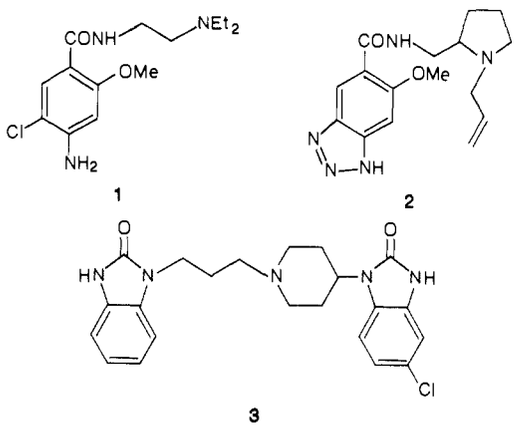
Chemistry

Most of the compounds **4–6**, **8**, and **9** shown in Table I were synthesized via reaction Scheme I by using general methods A–D, which are described in the Experimental Section. Ketoximes **7a**, **7b**, and **7c** were obtained by using method E and alcohols **8b** and **8g,h** by method F from the corresponding ketones **6a** and **6e**. Allylation of **6a** via method C gave the [(1-acetyl-3-butenyl)oxy] analogue **6i**.

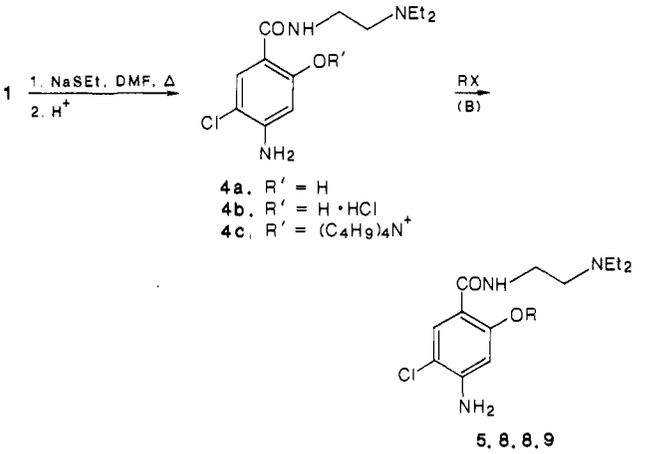
Diol **8l** was obtained by acid-catalyzed hydrolysis of acetal **9a**, methyl ether **8m** by MeONa treatment of epoxide **9b**, and tertiary alcohol **8p** by reduction of epoxide **9c**.

The enantiomeric alcohols **8e** and **8f** were synthesized by starting with the appropriate 2(*R*)- or 2(*S*)-[(methoxyethoxy)methoxy]-protected lactic acid methyl esters[7] as outlined in Scheme II. The homologous diasteriomeric alcohols **8g** and **8h** were prepared by chromatographic separation of the mixture of isomers **8i** and **8j** as shown in Scheme III. The stereochemical assignments were made on the basis of ^{1}H NMR (360 MHz) spectral data. In both erythro isomers, acetyl ester **8i** and alcohol **8g**, coupling constants J_{ab} were larger than in the corresponding threo isomers **8j** and **8h** as described in the Experimental Section. Although there are some exceptions, in general coupling constants in erythro isomers are found to be larger than in the corresponding threo isomers.[8]

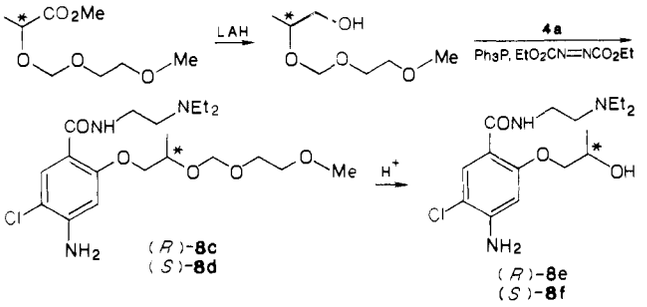
Chart I



Scheme I



Scheme II



Dihydroimidazole analogue **9i** was obtained by reaction of nitrile **5h** with ethylenediamine. In the substituted

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‡ Deceased.

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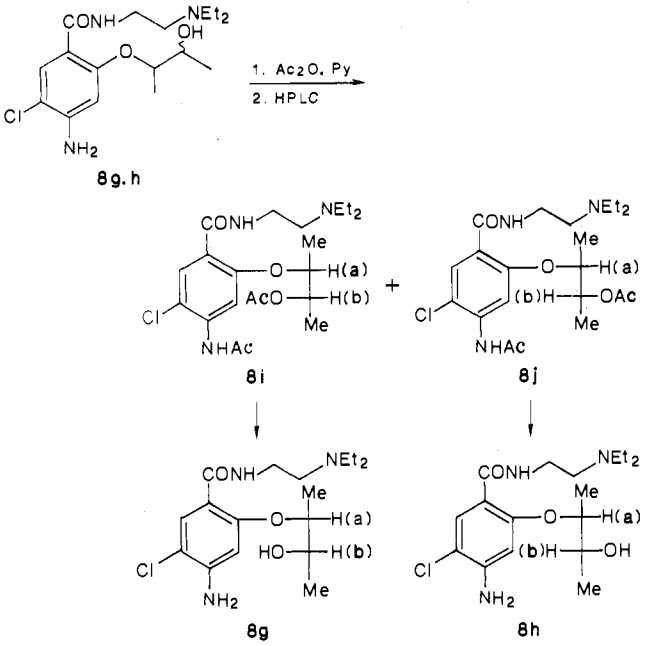
Scheme III



Scheme IV

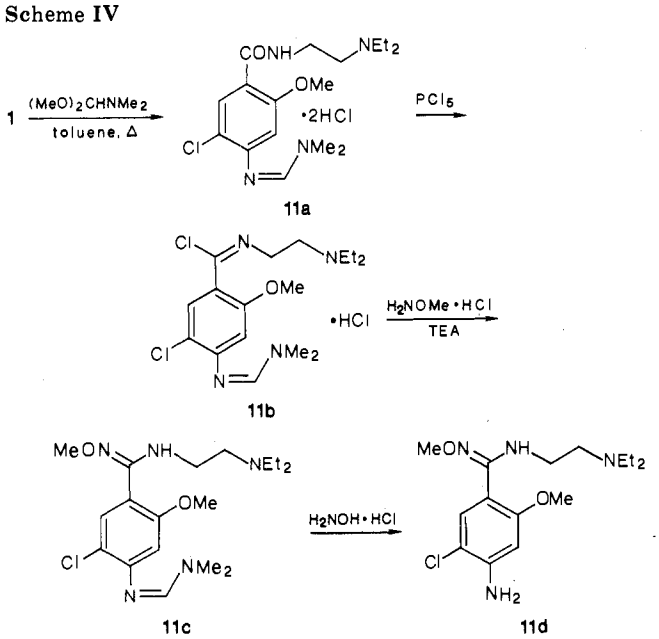
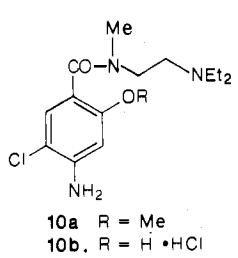
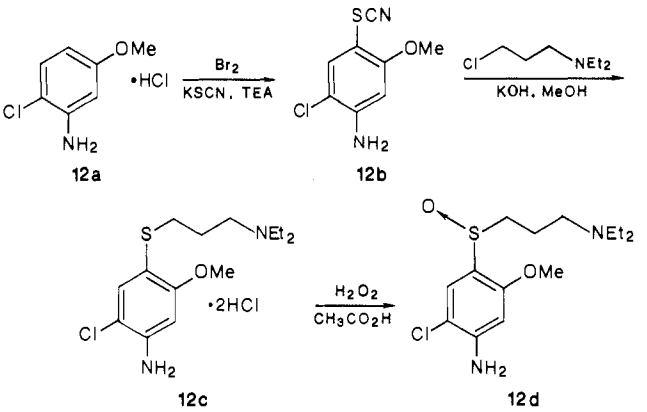


Chart II

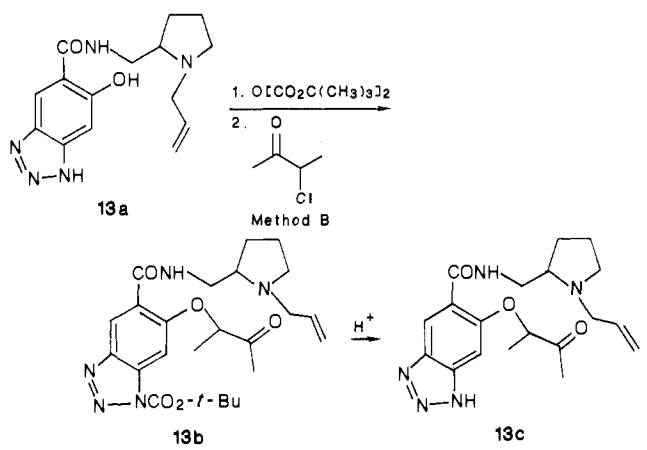


amide nitrogen series, the known compound **10a**[9] (Chart II) was demethylated via method A to give phenol **10b**.

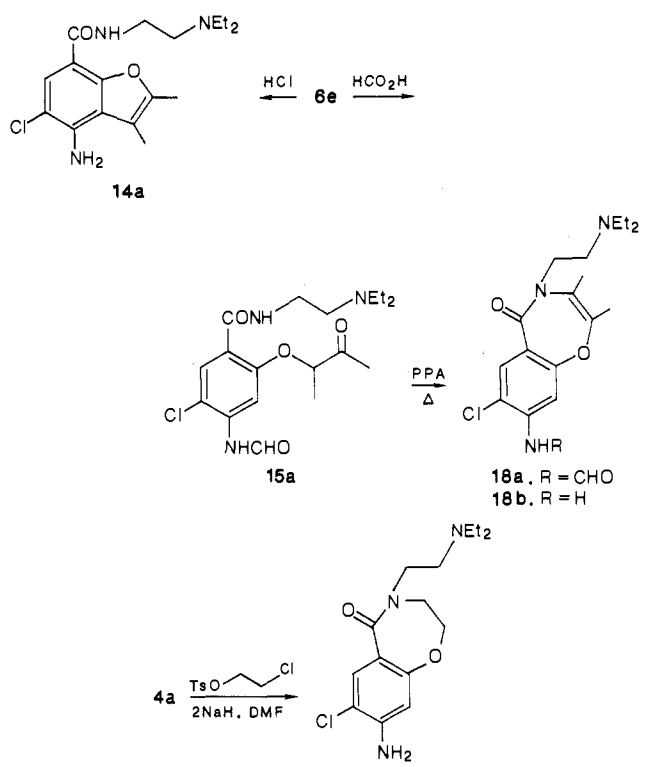
Scheme V



Scheme VI



Scheme VII



The amidoxime **11d** and sulfoxide **12d** were prepared as shown in Schemes IV and V, respectively. The synthesis

(1) Gralla, R. J.; Itri, L. M.; Pisko, S. E.; Squillante, A. E.; Kelsen, D. P.; Braun, D. W.; Bordin, L. A.; Brown, T. J.; Young, C. W. *N. Engl. J. Med.* **1981**, *305*, 905.
(2) Joss, R. A.; Galeazzi, R. L.; Bischoff, A. K.; Brunner, K. W. *Eur. J. Clin. Pharmacol.* **1985**, *27*, 721.
(3) Huys, J.; Troch, M.; Bourguignon, R. P.; Smets, Ph. *Curr. Med. Res. Opin.* **1985**, *9*, 400.
(4) Kris, M. G.; Gralla, R. J.; Tyson, L. B.; Clark, R. A.; Kelsen, D. P.; Reilly, L. K.; Groshen, S.; Bosl, J. G.; Kalman, L. A. *Cancer* **1985**, *55*, 527.

Table I. Structure and Physical Constants of 2-Substituted 4-Amino-5-chloro-*N*-[2-diethylamino)ethyl]benzamides 4–9

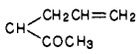
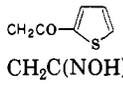
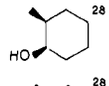
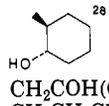
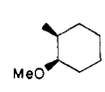
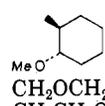
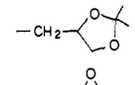
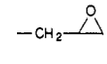
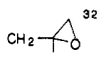
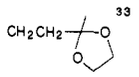
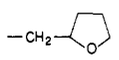
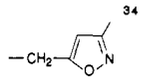
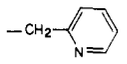
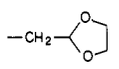
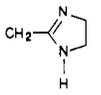
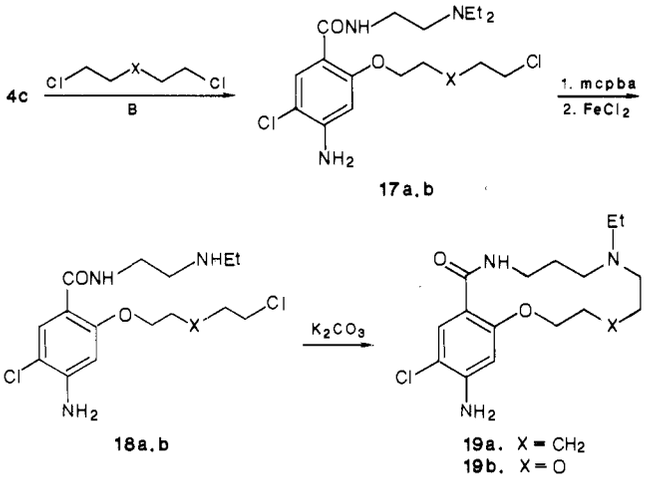
compd	R[a]	method	mp, °C	solvent[b]	yield, %	formula	anal.
4a	H	A	136.5–138.5	W	98	$C_{13}H_{20}ClN_3O_2$	C, H, N
5a	$CH_2CH{=}CH_2$	C	129–130	EE	54	$C_{16}H_{24}ClN_3O_2$	C, H, N
5b	$CH_2C{\equiv}CH$	C	111–112	CH_2Cl_2–P	43	$C_{16}H_{22}ClN_3O_2$	C, H, N, Cl
5c	$CH_2C(CH_3){=}CH_2$	B[c]	70–73	EE	27	$C_{17}H_{26}ClN_3O_2$	C, H, N
5d	$CH_2CH{=}CHCH_3$[d]	C	118–122	EE	48	$C_{17}H_{26}ClN_3O_2$	C,[e] H, N, Cl
5e	$(CH_2)_2CH{=}CH_2$	B[c]	114–116	EE–P	47	$C_{17}H_{26}ClN_3O_2$	C, H, N, Cl
5f	$(CH_2)_2CH_3$	B[c]	136–138.5	AC	75	$C_{16}H_{26}ClN_3O_2$	C, H, N, Cl
5g	$CH_2C_6H_5$	C	92–93	AC–H	51	$C_{20}H_{26}ClN_3O_2$	C, H, N, Cl
5h	CH_2CN	C	188–189	M	57	$C_{15}H_{21}ClN_4O_2$	C, H, N, Cl
5i	$CH(CH_3)CN$	B[c]	139–140	CH_2Cl_2–EE	84	$C_{16}H_{23}ClN_4O_2$	C, H, N, Cl[f]
5j	CH_2CO_2Me	C	94–95	CH_2Cl_2–EE	67	$C_{16}H_{24}ClN_3O_4$	C, H, N, Cl
6a	CH_2COCH_3	B	105–106.5	T	78	$C_{16}H_{24}ClN_3O_3$	C, H, N, Cl
6b	$CH_2COC_6H_5$	C	153–154	M	50	$C_{21}H_{26}ClN_3O_3$	C, H, N[g]
6c		D[h]	96–99	T	46	$C_{19}H_{28}ClN_3O_3$	C, H, N, Cl
6d		D[h]	89–90	EE	7	$C_{18}H_{26}ClN_3O_3$	C, H, N
6e	$CH(CH_3)COCH_3$	B	177–179	I–AT	81	$C_{17}H_{26}ClN_3O_3 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
6f	$CH_2COCH_2CH_3$	D	103–104.5	AC–W	86	$C_{17}H_{26}ClN_3O_3$	C, H, N, Cl
6g	$CH(C_2H_5)COCH_3$[23]	D	75–78	EE–P	22	$C_{18}H_{28}ClN_3O_3$	C, H, N, Cl
6h	$CH_2COCH_2CH_2CH_3$[23]	D	112–115	AC	10	$C_{18}H_{28}ClN_3O_3$	C, H, N
6i		C	171–173	AT–EE	13	$C_{19}H_{28}ClN_3O_3 \cdot HCl$	C, H, N, Cl
6j	$CH(CH_3)COCH_2CH_3$[24]	B[c]	100–102	I	63	$C_{18}H_{28}ClN_3O_3 \cdot HCl$	C, H, N, Cl
6k	$CH_2COCH(CH_3)_2$[25]	C	109–110	T	73	$C_{18}H_{28}ClN_3O_3$	C, H, N
6l	$CH_2COCH_2C_6H_5$[26]	D	138–139	AC	38	$C_{22}H_{28}ClN_3O_3$	C, H, N, Cl
6m	$C(CH_3)_2COCH_3$[27]	D	84–88	M–W	43	$C_{18}H_{28}ClN_3O_3 \cdot H_2O$	C, H, N, Cl
6n		D	135–139	AC	41	$C_{19}H_{24}ClN_3O_3S$	C, H, N, S
7a	$CH_2C(NOH)CH_3$	E	112–113	E–P	56	$C_{16}H_{25}ClN_4O_3 \cdot 0.25H_2O$	C, H, N, Cl
7b	$CH_2C(NOMe)CH_3$	E	121–123	CH_2Cl_2–P	70	$C_{17}H_{27}ClN_4O_3$	C, H, N, Cl
7c	$CH(CH_3)C(NOH)CH_3$	E	113–115	AC–P	34	$C_{17}H_{27}ClN_4O_3$	C, H, N, Cl
8a	CH_2CH_2OH	B[i]	144–146.5	AC	42.5	$C_{15}H_{24}ClN_3O_3$	C, H,[j] N, Cl
8b	$CH_2CHOHCH_3$	F	149–150	W	77	$C_{16}H_{26}ClN_3O_3$	C, H, N, Cl[k]
8e	(*R*)-$CH_2CHOHCH_3$		132–134	AC–CH_2Cl_2	77	$C_{16}H_{26}ClN_3O_3$	C, H, N
8f	(*S*)-$CH_2CHOHCH_3$		132–134	AC–CH_2Cl_2	77	$C_{16}H_{26}ClN_3O_3$	C, H, N
8g,h	$CH(CH_3)CHOHCH_3$	F	amorphous solid		42	$C_{17}H_{28}ClN_3O_3 \cdot 0.25H_2O$	C, H, N, Cl
8g	*erythro*-$CH(CH_3)CHOHCH_3$		amorphous solid		78	$C_{17}H_{28}ClN_3O_3$	C, H, N
8h	*threo*-$CH(CH_3)CHOHCH_3$		amorphous solid		78	$C_{17}H_{28}ClN_3O_3$	C, H, N, Cl[l]
8k	$CH_2CHOHCH_2C_6H_5$[26]	D[i]	155–157	AC	54	$C_{22}H_{30}ClN_3O_3$	C, H, N, Cl
8l	$CH_2CHOHCH_2OH$		heavy oil		74	$C_{16}H_{26}ClN_3O_4 \cdot 0.1MeOH$	C, H, N, Cl
8m	$CH_2CHOHCH_2OMe$[27]		70–73	AC	77	$C_{17}H_{28}ClN_3O_4$	C, H, N, Cl
8n			amorphous solid		22	$C_{19}H_{30}ClN_3O_3$	C, H, N
8o			amorphous solid		44	$C_{19}H_{30}ClN_3O_3$	C, H, N
8p	$CH_2COH(CH_3)_2$	F	87–89	CH_2Cl_2–P	59	$C_{17}H_{28}ClN_3O_3$	C, H, N, Cl
8q	$CH_2CH_2CHOHCH_3$	G	136.5–137.5	CH_2Cl_2–P	45	$C_{17}H_{28}ClN_3O_3$	C, H, N, Cl
8r	$CH_2CH_2OCH_3$	B[i]	108–110.5	AC	87	$C_{16}H_{26}ClN_3O_3$	C, H, N, Cl
8s	$CH_2CH(OMe)_2$	B[m]	64–70	AC–P	60	$C_{17}H_{28}ClN_3O_4$	C, H, N, Cl[n]
8t	$CH_2CH(OMe)CH_3$[29]	B	heavy oil		18	$C_{17}H_{28}ClN_3O_3$	C, H, N, Cl
8u		D	heavy oil		25	$C_{20}H_{32}ClN_3O_3 \cdot 0.75H_2O$	C, H, N,[o] Cl
8v		D	168–170	E–P	83	$C_{20}H_{32}ClN_3O_3 \cdot HCl \cdot 2H_2O$	C, H, N
8w	$CH_2OCH_2CH_2OCH_3$	C	79–81	EE	56	$C_{17}H_{28}ClN_3O_4$	C,[p] H, N
8x	$CH_2CH_2OCH_2CH_2OCH_3$	C	49–51	EE	24	$C_{18}H_{30}ClN_3O_4$	C, H, N
8y	$CH_2CH_2CH(OMe)CH_3$	G	76–80	T	76	$C_{18}H_{30}ClN_3O_3$	C, H, N, Cl
9a		B	76–78	CH_2Cl_2–P	45	$C_{19}H_{30}ClN_3O_4$	C, H, N, Cl
9b		D[h]	118–119	AC	48	$C_{16}H_{24}ClN_3O_3$	C, H, N, Cl

Table I (Continued)

compd	R[a]	method	mp, °C	solvent[b]	yield, %	formula	anal.
9c		B[c]	77.5–79	EE–P	27	$C_{17}H_{26}ClN_3O_3$	C, H, N, Cl
9d		C	84–86	CH_2Cl_2–P	44	$C_{19}H_{30}ClN_3O_4$	C, H, N
9e		D[g]	134–140	AC	83	$C_{18}H_{28}ClN_3O_3 \cdot 2HCl$	C, H, N, Cl
9f		D	109–111	AC	87	$C_{18}H_{25}ClN_4O_3$	C, H, N, Cl
9g		D	84–85	AC–H	77	$C_{19}H_{25}ClN_4O_2$	C, H, N, Cl
9h		C[r]	93–95	CH_2Cl_2–P	35	$C_{17}H_{26}ClN_3O_4$	C, H, N
9i			144–145	AC	76	$C_{17}H_{26}ClN_5O_2$	C, H, N, Cl

[a] Alkylating agents RX were obtained commercially or synthesized via referred literature procedures. [b] AC, acetonitrile; AT, acetone; E, ethanol; EE, diethyl ether; H, *n*-hexane; I, 2-propanol; M, methanol; P, *n*-pentane; T, toluene; W, water. [c] Additional stirring and heating at 60–70 °C for 4 h was applied. [d] The alkylating agent, 2-butynylmethane sulfonate was prepared in situ. [e] C: calcd, 60.44; found, 59.79. [f] Cl: calcd, 10.46; found, 9.64. [g] N: calcd, 10.40; found, 10.83. [h] Stirring was continued for 4 days. [i] Heating at reflux (150–160 °C) for 4 h was applied. [j] H: calcd, 7.33; found, 7.88. [k] Cl: calcd, 10.31; found, 9.80. [l] Cl: calcd, 9.91; found, 10.63. [m] Double amount of alkylating agent and 150–160 °C temperature for 6 h was used. [n] Cl: calcd, 9.48; found, 10.34. [o] Cl: calcd, 10.20; found, 9.76. [p] C: calcd, 54.60; found, 54.16. [q] Heating at 150–160 °C for 4 days was applied. [r] Heating at 80 °C for 30 h was applied.

Scheme VIII



of the 6-(1-methyl-2-oxopropoxy) analogue (**13c**) of alizapride is outlined in Scheme VI. Bicyclic compounds in the benzofuran series **14a** and 1,4-benzoxazepin-5-one series **16a** were synthesized via acid-catalyzed cyclizations of **6e** and **15a**, respectively. The saturated analogue **16c** was synthesized by double alkylation of **4a** with 2-(tosyloxy)ethyl chloride as shown in Scheme VII.

Cyclotridecenes **19a** and **19b** were synthesized by the reaction sequence shown in Scheme VIII. The key step was dealkylation of intermediates **17a** and **17b** to the corresponding desethyl compounds **18a** and **18b**.[10]

Biological Results and Discussion

Biological test procedures are described in the Experimental Section, and the results are presented in Table II.

The tests shown in the first four columns of Table II, viz. [^{3}H]spiperone binding, rat catalepsy, antagonism of apomorphine-induced stereotypy in the rat, and emesis in the dog, are associated with dopaminergic D_2 antagonism and are considered predictive of extrapyramidal side effects. The tests for antagonism of cisplatin-induced emesis in the dog and in the ferret in which metoclopramide is the most potent reference agent relate to projected therapeutic potential of the compounds.[11,12] In many cases the results in these two tests are from one screening dose level only. However, when promising protection against emesis was observed in the initial test, additional testing was done in order to obtain dose–response data. ED_{50} values for compound **6e** compared to metoclopramide are presented in Tables III and IV.

A number of observations based on the results in Table II can be summarized as follows:

i. Dopaminergic D_2 antagonism in vitro ([^{3}H]spiperone binding test) and in vivo (antagonism of apomorphine-induced emesis in the dog) in the metoclopramide series is highly sensitive to variation of the 2-substituent on the benzene ring. Irrespective of the nature of the substituent, if different from methoxy (we did not investigate ethoxy[13]), the activity is abolished. All the reference agents are active in these tests, domperidone being the most potent and

(5) Plezia, P. M.; Alberts, D. S.; Kessler, J.; Aapro, M. S.; Grahm, V.; Surwit, E. A. *Cancer Treat. Rep.* **1984**, *68*, 1493.
(6) *Med. Lett.* **1985**, *27*, 21.
(7) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180.
(8) Casey, A. F. In *PMR Spectroscopy in Medicinal and Biological Chemistry*; Academic: New York, 1971; Chapter 3, pp 93–132.
(9) Soc. d'Etudes Scientifiques et Ind. Paris; FR CAM86, 1965; *Chem. Abstr.* **1966**, *64*, 658.
(10) Monković, I.; Wong, H.; Bachand, C. *Synthesis* **1985**, 770.
(11) Gylys, J. A.; Doran, K. M.; Buyniski, J. P. *Res. Commun. Chem. Pathol. Pharmacol.* **1979**, *23*, 61.
(12) Florczyk, A. P.; Schurig, J. E.; Bradner, W. T. *Cancer Treat. Rep.* **1982**, *66*, 187.
(13) In the analogous series of 2-[(2,6-dialkoxybenzamido)-methyl]-1-ethylpyrrolidines, several 2-ethoxy compounds were found to be active as dopaminergic antagonists. See: Florwall, L.; Ogren, S.-O. *J. Med. Chem.* **1982**, *25*, 1280.

Table II. Inhibition of [^{3}H]Spiperone Binding, Catalepsy in the Rat, Antagonism of Apomorphine-Induced Stereotypy in the Rat and Emesis in the Dog, and Antagonism of Cisplatin-Induced Emesis in the Dog and Ferret

					antagonism of cisplatin-induced emesis							
					dog				ferret			
compd	[^{3}H]spiperone[b] binding: IC_{50}, nM	ED_{50}, mg/kg sc[a] rat catalepsy	rat stereotypy	dog emesis	dose mg/kg sc 2×	N[c]	emetic episodes,[d] mean ± SE	% protect.	dose mg/kg iv 2×	N	emetic episodes,[d] mean ± SE	% protect.
metoclopramide	565 (290–1085)	26 (15–51)	4.0 (3.6–4.4)	0.36 (0.12–0.84)	2.5	4	1.0 ± 0.7	92	2.5	5	0.6 ± 0.3	90
					0.8	3	1.0 ± 0.6	92	0.8	5	2.4 ± 1.3	73
					0.2	4	5.0 ± 0.9	58	0.2	4	5.5 ± 0.9	22
alizapride	200 (130–375)	>40	>40	0.3 (0.13–0.43)	3	3	4.3 ± 0.3	69	3	3	5.0 ± 1.2	27
					6	3	4.7 ± 0.9	66				
domperidone	5.2 (4.1–6.8)	>40	>40	0.08 (0.04–0.15)	6	3	9.7 ± 0.3	30	3	3	3.3 ± 0.7	50
4a	>1000	>40	>40	>1	6	2	2.0 ± 2.0	84	3	2		40
5a	>1000	>40	>40	>1	6	2	1.0 ± 0.0	90	3	3	0.3 ± 0.3	95
					1	2	3.5 ± 2.5	72	1	3	3.0 ± 2.1	56
									0.3	3	4.7 ± 0.3	30
5b	>1000	>40	>40	>1	6	2	2.0 ± 2.0	73	3	3	3.3 ± 1.8	50
					3	2	3.5 ± 1.5	72	1	3	4.3 ± 1.5	40
5c	>1000	>40	>40	>3	3	2	4.0 ± 4.0	68	3	3	2.3 ± 0.3	70
5d	>1000	>40	>40	>3	1	2	2.5 ± 2.5	80	3	3	0.7 ± 0.3	90
5e	>1000	>40	>40	>3	3	2	3.5 ± 2.5	71	3	3	3.7 ± 2.7	50
5f	>1000	>40	>40	>3	6	2	8.0 ± 3.6	40	3	3	2.0 ± 2.0	70
5g	>1000	>40	>40	>1[e]	NT				NT			
5h	>1000	>40	>40	>3	3	3	4.7 ± 4.2	63	3	3	0.7 ± 0.7	90
5i	>1000	>40	>40	>3	3	2	2.5 ± 1.5	80	3	3	2.7 ± 1.2	63
5j	>1000	>40	>40	>3	NT				3	3	5.0 ± 0.6	30
6a	>1000	>40	>40	>3	6	2	0.5 ± 0.5	96	3	3	0.7 ± 0.7	90
					1	2	1.5 ± 1.5	92	1	3	4.5 ± 1.3	38
					0.3	2	5.0 ± 1.0	60	0.3	3	4.0 ± 0.2	44
6b	>1000	>40	>40	>3	3	2	1.5 ± 1.5	88	3	3	0.0	100
6c	>1000	>40	>40	>3	1	2	0.0	100	3	3	0.0 ± 0.0	100
					0.3	2	1.5 ± 0.5	88	0.3	3	2.7 ± 1.5	62
6d	>1000	>40	>40	>3	1	2		87	1	3	5.7 ± 1.5	21
6e	>1000	>40	>40	>3	1	2	0.5 ± 0.5	96	3	3	0.3 ± 0.3	96
					0.3	2	1.5 ± 0.5	87	0.3	3	1.0 ± 0.6	90
					0.1	2	0.5 ± 0.3	60	0.1	3	3.3 ± 2.0	54
6f	>1000	>40	>40	>3	1	2	0.0	100	3	3	0.7 ± 0.3	90
					0.3	2	3.0 ± 1.0	76	0.3	3	7.3 ± 1.2	0
6g	>1000	>40	>40	>3	1	2	0.5 ± 0.5	96	1	3	2.3 ± 1.2	68
					0.3	2	3.0 ± 1.0	76				
6h	>1000	>40	>40	>3	0.3	2	2.0 ± 1.0	84	1	3	0.7 ± 0.7	90
6i	>1000	>40	>40	>3	1	2	6.0 ± 1.0	52	3	3	2.3 ± 1.5	68
									1	3	1.7 ± 0.7	76
6j	>1000	>40	>40	>3	0.3	2	2.0 ± 2.0	84	1	3	1.3 ± 0.9	82
6k	>1000	>40	>40	>3	0.3	2	3.0 ± 1.0	44	1	3	4.0 ± 0.6	44
6l	>1000	>40	>40	>3	0.3	2	13.0 ± 0.0	0	3	3	0.0 ± 0.0	100
6m	>1000	>40	>40	>3	0.3	3	2.7 ± 2.2	77	1	3	2.7 ± 1.2	62
6n	>1000	>40	>40	NT	1	2	3.0 ± 2.0	75	3	3	0.3 ± 0.3	95
7a	>1000	>40	>40	>3	1	2	2.5 ± 0.5	79	3	3	0.0	100
7b	>1000	>40	>40	NT	6	2	3.5 ± 1.5	71	3	3	0.7 ± 0.3	90
7c	>1000	>40	>40	>3	NT				1	3	4.3 ± 0.9	44
8a	>1000	>40	>40	>3	1	2	3.0 ± 3.0	76	3	3	2.3 ± 0.3	68
8b	>1000	>40	>40	>3	1	2	0.0	100	3	3	1.0 ± 0.6	86
					0.3	2	3.0 ± 1.0	68	1	3	4.5 ± 1.3	36
8e	>1000	>40	>40	>3	1	2	1.0 ± 1.0	92	1	3	2.0 ± 0.6	73
					0.3	2	6.5 ± 1.5	45	0.3	2	6.0 ± 1.0	18
8f	>1000	>40	>40	>3	1	2	0.0	100	1	3	5.7 ± 1.9	22
					0.3	2	2.0 ± 1.0	84	0.3	3	8.0 ± 0.6	0
8g,h	>1000	>40	>40	NT	0.3	2	0.5 ± 0.5	96	3	3	1.3 ± 0.7	80
									1	3	1.7 ± 0.3	75
8g	>1000	>40	>40	>3	1	2	0.0	100	3	3	1.0 ± 0.6	86
					0.3	2	0.0	100	1	3	1.3 ± 0.9	82
					0.1	2	4.5 ± 1.5	62	0.3	3	0.7 ± 0.9	49
8h	>1000	>40	>40	>3	1	2	3.0 ± 2.0	75	3	3	0.3 ± 0.3	95
					0.3	2	4.5 ± 0.5	60	1	3	2.3 ± 1.3	68
									0.3	3	4.7 ± 2.7	37
8k	>1000	>40	>40	>3	NT				1	3	3.3 ± 0.9	54
8l	>1000	>40	>40	>3	NT				3	3	6.3 ± 0.9	10
8m	>1000	>40	>40	>3	NT				3	3	3.3 ± 0.7	54
8n	>1000	>40	>40	NT	1	2	0.0	100	3	3	2.7 ± 0.7	64

Table II (Continued)

					antagonism of cisplatin-induced emesis							
					dog				ferret			
compd	[^{3}H]spiperone[b] binding: IC_{50}, nM	ED_{50}, mg/kg sc[a] rat catalepsy	rat stereotypy	dog emesis	dose mg/kg sc 2×	N[c]	emetic episodes,[d] mean ± SE	% protect.	dose mg/kg iv 2×	N	emetic episodes,[d] mean ± SE	% protect.
					0.3	2	4.5 ± 0.5	64				
8o	>1000	>40	>40	>3	1	2	4.0 ± 0	66	3	3	3.0 ± 0.6	60
8p	>1000	>40	>40	>3	NT				3	3	1.3 ± 0.6	84
									1	3	3.0 ± 1.5	57
8q	>1000	>40	>40	>3	0.3	2	8.0 ± 2.0	32	1	3	2.0 ± 1.0	73
8r	>1000	>40	>40	>3	1	2	1.5 ± 1.5	88	3	3	1.7 ± 0.7	76
									0.3	3	5.0 ± 1.2	10
8s	>1000	>40	>40	>3	1	2	1.5 ± 1.5	88	3	3	1.3 ± 0.3	82
									0.3	3	6.7 ± 0.2	0
8t	>1000	>40	>40	>3	ND				3	3	1.0 ± 2.0	86
									1	3	3.0 ± 0.6	57
8u	>1000	>40	>40	>3	1	2	0.0	100	3	3	1.3 ± 2.7	82
									0.3	3	1.7 ± 0.9	77
					0.3	2	3.5 ± 0.5	70	0.1	3	3.7 ± 0.9	49
8v	>1000	>40	>40	>3	1	2	10.0 ± 2.0	15	3	3	0.7 ± 0.3	91
									1	3	2.3 ± 0.9	69
									0.3	3	4.3 ± 0.7	42
8w	>1000	>40	>40	>3	1	2	3.5 ± 1.5	72	3	2	0.0	100
8x	>1000	>40	>40	>3	NT				3	3	1.7 ± 0.7	76
									1	3	4.3 ± 0.9	39
8y	>1000	>40	>40	>3	1	2	1.5 ± 1.5	88	3	3	1.3 ± 0.9	82
					0.3	2	8.5 ± 2.5	28	1	3	4.3 ± 0.9	42
9a	>1000	>40	>40	>3	3	2	4.0 ± 0.0	68	3	3	2.0 ± 0.6	72
9b	>1000	>40	>40	>3	NT				3	3	4.7 ± 0.9	44
9c	>1000	>40	>40	>3	NT				3	3	3.3 ± 0.9	53
9d	>1000	>40	>40	>3	NT				3	3	1.3 ± 0.3	80
9e	>1000	>40	>40	>3	NT				3	3	3.3 ± 0.9	54
9f	>1000	>40	>40	>3	NT				3	3	2.0 ± 1.2	72
9g	>1000	>40	>40	>3	NT				3	3	1.0 ± 0.6	86
									1	3	2.3 ± 0.9	67
9h	>1000	>40	>40	>3	NT				3	3	2.3 ± 0.9	67
									1	3	4.0 ± 0.0	43
9i	>1000	>40	>40	>3	1	2	1.5 ± 0.5	88	3	3	1.0 ± 0.6	86
10a	>1000	>40	>40	>3	NT				3	3	8.7 ± 0.3	0
10b	**10b**	>1000	>40	>40	>3	NT			3	3	5.0 ± 1.0	30
11d	>1000	>40	>40	>1	6	2	8.5 ± 2.5	34	3	3	8.3 ± 0.9	0
12d	>1000	>40	>40	>1	NT				3	3	2.0 ± 1.2	70
13a	>1000	>40	>40	>3	NT				3	3	8.0 ± 0.6	0
13c	>1000	>40	>40	>3	NT				3	3	5.7 ± 2.3	21
14a	>1000	>40	>40	>3	NT				3	3	3.3 ± 1.2	53
16a	>1000	>40	>40	>3	0.3	2	9.5 ± 3.5	25	3	3	0.0	100
									0.3	3	4.7 ± 2.3	32
16b	>1000	>40	>40	>3	0.3	2	7.5 ± 3.5	37	3	3	0.3 ± 0.3	95
									0.3	3	2.3 ± 0.7	67
16c	>1000	>40	>40	>3	NT				1	3	6.0 ± 0.4	14
19a	7.7 (5.2–10.2)	>40	10 (5–20)	>3	NT				3	3	2.3 ± 0.3	67
19b	>1000	>40	active at 40	>3	NT				3	3	11.7 ± 2.4	0

[a] ED_{50} values and 95% CL were obtained by probit analysis. [b] The IC_{50} values were obtained by log-logit regression analysis. [c] N = number of animals. [d] Percent protection is based on comparison of experimental results with the dynamic control value, which was obtained by pooling the mean historical control value with the one obtained in the actual experiment. [e] Emetogenic at higher doses.

metoclopramide the least potent. Metoclopramide is also active in the catalepsy test and antagonizes apomorphine-induced stereotypy in the rat.

ii. Among compounds **4a** and **5a–j**, all are effective as antagonists of cisplatin-induced emesis but only **5a** and **5d** are comparable in potency to metoclopramide.

iii. Compounds **6** and **7**, with few exceptions (**6k** in both species, **6l** and **6i** in the dog, **6d**, **6g**, and **7c** in the ferret), have shown high potency as antagonists of cisplatin-induced emesis.

iv. Various alcohols and ethers **8** were also found to be potent antiemetics generally comparable to ketones **6**. However, erythro (cis) isomers (**8g**, **8n**, and **8u**) were found to be more potent than the corresponding threo (trans) isomers (**8h**, **8o**, and **8v**). Optical isomer (*R*)-**8e** appears to be more potent than its enantiomer (*S*)-**8f** in the antagonism of cisplatin-induced emesis in the ferret, whereas both isomers showed a similar activity in the dog.

v. Most of compounds **9**, with a heterocyclic 2-substituent, have not been tested for antiemetic activity in the dog because of modest activity shown in the ferret. Exceptions are compounds **9d**, **9g**, and **9i**, which showed comparable activity to that of metoclopramide. Amide NMe analogues **10** and amide isosters amidoxime **11d** and sulfoxide **12d** did not show promising activity. The same applies for alizapride analogues **13a** and **13c**.

vi. Benzofuran **14a** showed marginal activity in the ferret and was not tested in the dog. Benzazepines **16a** and **16b** showed high potency in the ferret and were less active in the dog. Cyclotridecene **19a** showed moderate activity and **19b** was inactive in the ferret. Neither was tested in the dog. It is interesting to note that dopaminergic D_2 antagonist activity was restored with **19a** and to a lesser degree with **19b**.

Table III. Protection against Cisplatin-Induced Emesis in the Ferret

compound	mg/kg, iv × 2[a]	N[e]	emetic episodes, mean ± SE	% protection	ED_{50} (95% CL), mg/kg iv × 2
6e	0.1	3	3.3 ± 0.2[b]	53 (1/3)[d]	0.14 (0.05–0.25)
	0.3	6	2.5 ± 1.2[c]	64 (2/6)	
	0.9	6	0.5 ± 0.2[c]	93 (3/6)	
	2.7	3	0.3 ± 0.3[c]	96 (2/3)	
metoclopramide	0.2	4	5.5 ± 0.9	21	0.53 (0.24–1.0)
	0.8	5	2.4 ± 1.3[c]	66 (2/5)	
	2.5	5	0.6 ± 0.3[c]	91 (2/5)	
saline		49	7.0 ± 0.3		

[a] Treatment schedule: first dose 30 min before, followed by second dose, 120 min after cisplatin. [b] $p < 0.05$ vs saline. [c] $p < 0.01$ vs saline. [d] Complete protection/ferrets used; otherwise partial protection. [e] N = number of ferrets.

Table IV. Protection against Cisplatin-Induced Emesis in the Dog

compound	mg/kg, sc × 2[a]	N[d]	emetic episodes, mean ± SE	% protection	ED_{50} (95% CL), mk/kg sc × 2
6e	0.1	3	5.0 ± 1.7	58	0.05 (0.02–0.10)
	0.3	5	1.6 ± 0.4[b]	86	
	0.9	3	0 ± 0.0[b]	100 (3/3)[c]	
metoclopramide	0.2	4	5.0 ± 0.9[b]	58	0.18 (0.06–0.32)
	0.8	3	1.0 ± 0.6[b]	92 (1/3)	
	2.5	4	1.0 ± 0.7[b]	92 (2/4)	
saline		36	11.8 ± 0.6		

[a] Treatment schedule: first dose, 30 min before, second dose, 120 min after cisplatin. [b] $p < 0.01$ saline. [c] Complete protection/dogs used; otherwise partial protection. [d] N = number of dogs.

As indicated above, species variations have been observed with some compounds. However, good overall species correlation does seem to exist. We have used the ferret test as the initial screen for most of our compounds. Which of the two species is more predictive as far as clinical effectiveness is concerned remains an open question.

Metoclopramide, the most effective reference agent in the cisplatin-induced emesis tests, has shown uniform activity across the spectrum of tests presented in Table II, consistent with its dopaminergic D_2 antagonist profile. On the other hand, a number of our structural variants have been found to be selective, antiemetic agents with equal or better protection in cisplatin-induced emesis tests.

Overall, optimal antiemetic potency was found to be associated with appropriately substituted compounds (**5–9**), where R is a β-keto, β-hydroxy, β-methoxy, β-imino, or β-unsaturated alkyl substituent.

On the basis of these results, compound **6e** was selected for additional testing, and as shown in Tables III and IV, it compares favorably with metoclopramide in both dog and ferret models. Additional animal tests in both species have shown that **6e** is also effective in preventing emesis induced by cyclophosphamide, doxorubicin, and total body radiation.[14] Compound **6e** has been selected for clinical evaluation.

(14) Gylys, J. A.; Wright, R. N.; Nicolosi, W. D.; Buyniski, J. P.; Crenshaw, R. R. *J. Pharm. Exp. Ther.* **1988**, *244*, 830.

Our work demonstrates that dopaminergic D_2 blockade, while required for antagonism of apomorphine-induced emesis and responsible for undesirable side effects, is not necessary for antagonism of chemotherapy-induced emesis.[15] Clearly, another mechanism of action must be involved. However, **6e** had no activity in 5-HT_1, 5-HT_2, α or β adrenergic, cholinergic, or histaminergic H_1 receptor binding tests.[14]

Recently, antagonism of central "5-HT_M" sites,[16] now classified as 5-HT_3 receptors,[17] has been postulated as a mechanism of control of chemotherapy-induced emesis in the ferret. In the assay for 5-HT_3 antagonism (Bezold–Jarisch reflex), **4e** has shown moderate activity.[14] However, existence of 5-HT_3 receptors in the central nervous system (CNS) has yet to be demonstrated,[18] and more work remains to be done in order to elucidate both the exact location and nature of the receptor sites.[18a,b]

In summary, new potent compounds effective against chemotherapy-induced emesis in ferrets and dogs have been synthesized in the substituted benzamide series. These compounds act probably via a nondopaminergic mechanism. Antagonism at an as yet undefined subclass of 5-HT receptors may be involved. Compound **6e** shows potential advantage over clinically available antiemetic agents for chemotherapy by virtue of both selectivity and superior protection from emesis.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. ^1H NMR spectra were recorded on either a JEOL-FX90 (90 MHz) spectrometer or Bruker-AM360 (360 MHz) spectrometer. Mass spectral analysis were recorded on Du Pont DP-102, H-5985, and Kratos MS50TC mass spectrometers. Optical rotations were obtained in ethanol on a PE-241MC polarimeter. The elemental analyses were performed on a CEC elemental analyzer model 240-XP.

Analytical thin-layer chromatography was conducted with Analtec Uniplate silica gel GF precoated plates. All preparative chromatography on silica was conducted with ICN silica 32-63, deactivated by shaking a slurry in CH_2Cl_2 with NH_4OH in a ratio of 100:1.8 and gradient elution with a CH_2Cl_2–MeOH solvent system, containing 0.5% NH_4OH.

Method A. 4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-hydroxybenzamide Hydrochloride (4b). To a cooled (10 °C), stirred suspension of sodium hydride (57.44 g of 60%, 1.436 mol) in DMF (1275 mL) was added dropwise a cold solution of ethanethiol (89.22 g, 1.436 mol) in DMF (250 mL). After hydrogen evolution had ceased, 1[19] (287.0 g, 0.957 mol) was added,

(15) Since our work was completed, other workers have published on a similar finding in the 2-alkoxy-*N*-[(1-azabicyclo[2.2.2]octan-3-yl)amino]benzamide series. See: Smith, W. L.; Jackson, C. B.; Proakis, A. G.; Leonard, C. A.; Munson, H. R.; Alphin, R. S. *Proc. Am. Soc. Clin. Oncol.* **1986**, *5*, 260. See also ref 18a for other benzamides and related antiemetic compounds.

(16) Miner, W. D.; Sanger, G. J. *Br. J. Pharmacol.* **1986**, *88*, 497.

(17) Bradley, P. B.; Engel, G.; Feniuk, W.; Fozard, J. R.; Humphrey, P. P. A.; Middlemiss, D. N.; Mylecharane, E. J.; Richardson, B. P.; Saxena, P. R. *Neuropharmacology* **1986**, *25*, 563.

(18) Glennon R. A. *J. Med. Chem.* **1987**, *30*, 1. (a) For a recent review on newer 5-HT_3 antagonists, see: Fozard, J. R. *Trends Pharmacol. Sci.* **1987**, *8*, 44. (b) The evidence for existence of 5-HT_3 receptors in the brain was reported recently by Kilpatrick, G. J.; Jones, B. J.; Tyers, M. B. *Nature (London)* **1987**, *330*, 746.

(19) Thominet, M. L. U.S. Pat. 3 357 978, 1967.

(20) Creese, I.; Schneider, R.; Snyder, S. H. *Eur. J. Pharmacol.* **1977**, *46*, 377.

(21) Finney, D. J. *Probit Analysis*, 3rd ed.; University: Cambridge, England, 1971; pp 50–80 and 100–103. a. Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.

(22) Dunn, O. J. *J. Am. Stat. Assoc.* **1961**, *56*, 52.

and the mixture was heated in an oil bath at 100–105 °C for 90 min. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 (800 mL) and water (400 mL). The aqueous layer was washed with another portion of CH_2Cl_2, and the combined organic extracts were back-washed with water (150 mL). From the combined aqueous phase the free base **4a** can be isolated by neutralization with carbon dioxidie and extraction with CH_2Cl_2. Alternatively, treatment of the combined aqueous phase with concentrated HCl (200 mL) and cooling resulted in precipitation of a solid, which was collected by filtration and washed with MeOH (500 mL) to give 302.3 g (98%) of **4b**, mp 235–237 °C. Anal. ($C_{13}H_{20}ClN_3O_2$·HCl) H, N; calcd: C, 48.46; Cl, 22.00. Found: C, 47.67; Cl, 21.43.

Tetra-*n*-butylammonium Salt of 4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-hydroxybenzamide (4c). A solution of **4b** (10 g, 0.031 mmol), NaOH (5 g), and water (100 mL) was treated with tetra-*n*-butylammonium hydrogen sulfate (10.6 g, 0.031 mmol) with stirring. The crystals were collected, washed with water, and dried (14.7 g, 87%). Recrystallization from EtOAc gave the title compound containing 0.5 mol of water, mp 136.5–138 °C. Anal. ($C_{29}H_{55}ClN_4O_2$·0.5H_2O) C, H, N, H_2O.

Method B. A mixture of the 2-hydroxybenzamide **4a** (free base) or **4b** (HCl salt) (10 mmol), K_2CO_3 (two to three times excess), NaI (2 mmol), and the alkylating agent (10 mmol) in DMF (40 mL) was stirred at ambient temperature for 16 h. For less reactive alkylating agents, additional stirring and heating were applied as specified in Table I. The solvent was removed in vacuo, and the residue was partitioned between water and CH_2Cl_2. The products were isolated from CH_2Cl_2 by chromatography.

Method C. Method C is identical with method B except that NaH is used instead of K_2CO_3–NaI.

Method D. In method D, the preformed tetrabutylammonium phenolate **4c** was reacted directly with the alkylating agent, without the addition of a base, in acetonitrile or DMF, as exemplified by the synthesis of **6f**.

4-Amino-2-[(2-oxobut-1-yl)oxy]-5-chloro-*N*-[2-(diethylamino)ethyl]benzamide (6f). A solution of the tetrabutylammonium salt of 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-hydroxybenzamide (**4c**) (5.3 g, 10 mmol) in acetonitrile (100 mL) was treated with 1-bromo-2-butanone (1.5 g, 10 mmol) and stirred at 20 °C for 2 h. The residue after concentration was partitioned between water and ethyl acetate. The insoluble solid material was collected and combined with organic extracts. Concentration of this mixture gave sticky crystalline material, which was recrystallized from acetonitrile–water (4:1) to give 3.1 g (86%) of **6f**.

Method E. A mixture of the ketone (3 mmol) and hydroxylamine hydrochloride or methoxyamine hydrochloride (4.3 mmol) in methanol (20 mL) was stirred for 16 h. The solvent was removed in vacuo, and the residue was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The organic phase was dried and concentrated, and the residue was crystallized from an appropriate solvent.

Method F. A mixture of the ketone (4 mmol) and $NaBH_4$ (2.1 mmol) in absolute ethanol (45 mL) was heated to reflux for 30 min. Another portion of $NaBH_4$ (1.3 mmol) was added, and the mixture was heated for 10 min, cooled, and acidified with 2 N HCl. The mixture was concentrated in vacuo, and the residue was partitioned between water and ether. The aqueous phase was made basic with Na_2CO_3, and the product was isolated by either filtration or extraction into CH_2Cl_2.

Method G. To a suspension of the 2-hydroxybenzamide **4a** (6 mmol) in dry THF (50 mL) was added, in succession and equimolar amounts, triphenylphosphine, alcohol, and diethyl azodicarboxylate. The solution was stirred until the starting materials reacted completely, as determined by TLC. The product was isolated by chromatography and crystallized from an appropriate solvent.

(*R*)-4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-(2-hydroxypropoxy)benzamide (8e). To a stirred suspension of LAH (3.36 g, 89 mmol) in dry Et_2O (100 mL) was added dropwise (*R*)-2-[2-(methoxyethoxy)methoxy]propionic acid methyl ester[7] (12.7 g, 67 mmol) over a 15-min period. The mixture was allowed to stand for 16 h, and then excess hydride was destroyed with saturated aqueous Na_2SO_4 (20 mL). The mixture was filtered, and the solid was washed with Et_2O to give after drying and concentration in vacuo 10 g (91.5%) of (*R*)-2-[2-(methoxyethoxy)methoxy]propanol as a colorless oil. This was used in the next step without further purification to prepare (*R*)-4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-[2-(methoxyethoxy)propoxy]benzamide (**8c**) via method G as an oil (61%): NMR ($CDCl_3$) δ 8.05 (s, 1 H), 6.25 (s, 1 H), 4.75 (s, 2 H), 3.3 (s, 3 H), 3.2–4.5 (m, 11 H), 2.56 (q, 6 H, J = 6 Hz), 1.35 (d, 3 H, J = 6 Hz), 1.0 (t, 6 H, J = 6 Hz).

To a cooled (0 °C) stirred solution of **8c** (8.0 g 19 mmol) in CH_2Cl_2 (175 mL) was added $TiCl_4$ (17.65 g, 93 mmol) over a 20-min period. The mixture was allowed to stand for 2 h at 0 °C and then was partitioned between aqueous 10% NaOH (200 mL), water (50 mL), and CH_2Cl_2 (50 mL). The aqueous phase was extracted with 3 × 125 mL of CH_2Cl_2, and the combined organic phase was extracted with three 100-mL portions of 10% HCl. The extracts were back-washed with CH_2Cl_2, basified with 10% NaOH, and the product was extracted with CH_2Cl_2 to give after drying and concentration in vacuo 4.89 g of crude product. This was recrystallized from EtOAc and EtOAc–CH_2Cl_2 to give pure **8e**: $[\alpha]^{25}_D$ −6.8° (EtOH, c 2.3).

(*S*)-4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-(2-hydroxypropoxy)benzamide (8f), $[\alpha]^{25}_D$ 6.8° (EtOH, *c* 2.5), was prepared similarly, with (*S*)-2-[2-(methoxyethoxy)methoxy]-propionic acid methyl ester as the starting material.

***erythro*-4-Acetamido-5-chloro-*N*-[2-(diethylamino)-ethyl]-2-(2-acetoxy-1-methylpropoxy)benzamide (8i) and *threo*-4-Acetamido-5-chloro-*N*-[2-(diethylamino)ethyl]-2-(2-acetoxy-1-methylpropoxy)benzamide (8j).** A crude mixture of **8g** and **8h** obtained from **6e** by method F (30 g of 3:7 ratio) was crystallized from EtOAc–*n*-hexane to give 6.0 g of predominately **8h** (90% purity).

The mother liquors were evaporated to dryness, and the residual oil was dissolved in 200 mL of pyridine. Acetic anhydride (34.23 g, 0.335 mol) was added, and the solution was heated at 72–75 °C (oil bath temperature) for 1 h and at 100–105 °C for 2.5 h. The reaction mixture was concentrated at reduced pressure, and the residue was partitioned between aqueous NaOH and CH_2Cl_2. The aqueous phase was extracted with several portions of CH_2Cl_2, the combined extracts were dried, and the solvent was evaporated to give a mixture of the diacylated products **8i** and **8j** as a dark oil. This was first purified by flash chromatography on silica to give two fractions: 12.3 g of 88% threo isomer and 14.7 g of 56:44 ratio of erythro to threo isomers. Determination of the isomer ratio was done by analytical HPLC with a 10 μm Alltech silica 600 column and a mobil phase of CH_2Cl_2, 2-propanol, NH_4OH (800:8:4); UV detector at 280 nm.

The second fraction was chromatographed in six runs on a Waters Prep 500 HPLC System. Detector, refractive index; mobile phase, CH_2Cl_2 + 2–5% IPA + 0.5% NH_4OH to yield 4.44 g of amber oil that was 96.8% pure erythro isomer **8i**: NMR ($CDCl_3$) δ 8.30 (s, 1 H), 8.20 (s, 1 H), 5.15 (m, H_a), 4.56 (m, H_b, J_{ab} = 6.4 Hz), 3.4–3.7 (m, 2 H), 2.5–2.8 (m, 6 H), 2.24 (s, 3 H), 1.99 (s, 3 H), 1.0 (t, 6 H, J = 6.5 Hz).

Also isolated was threo isomer **8j** (6.74 g, 97% pure) as a heavy oil: NMR ($CDCl_3$) δ 8.30 (s, 1 H), 8.18 (s, 1 H), 5.13 (m, H_a), 4.60 (m, H_b, J_{ab} = 4.4 Hz), 3.4–3.6 (2 H, m) 2.5–2.7 (m, 6 H), 2.24 (s,

(23) Borrows, E. T.; Holland, D. O.; Kenyon, J. *J. Chem. Soc.* **1946**, 1083.
(24) McIntosh, J. M.; Masse, G. M. *J. Org. Chem.* **1975**, *40*, 1294.
(25) Gaudri, M.; Marquet, A. *Org. Synth.* **1976**, *55*, 24.
(26) Galons, H.; Girardeau, J. F.; Combet Farnoux, C.; Miocque, M.; Dupont, C.; Wepierre, J. *Eur. J. Med. Chem.* **1978**, *14*, 165.
(27) Gaudri, M.; Marquet, A. *Tetrahedron* **1970**, *26*, 5611.
(28) Emerson, W. S.; Patrick, T. M., Jr. *J. Org. Chem.* **1948**, *13*, 722.
(29) Dewael, A. *Bull. Soc. Chim. Belg.* **1930**, *39*, 395.
(30) Buck, K. W.; Foster, A. B.; Labib, A.; Webber, J. M. *J. Chem. Soc.* **1964**, 2846.
(31) Hardie, W. R.; Aaron, J. E., Jr. Fr 1,522,153; *Chem. Abstr.* **1969**, *71*, 3249*q*.
(32) Gravel, D.; Deziel, R.; Bordeleau, L. *Tetrahedron Lett.* **1983**, *24*, 699.
(33) Stowell, J. C.; King, B. T.; Hauck, H. F., Jr. *J. Org. Chem.* **1983**, *48*, 5381.
(34) Maier, R.; Mueller, E. Ger. Offen. 2,045,050, 1972.

3 H) 1.99 (s, 3 H), 1.38 (d, 3 H, J = 6.4 Hz), 1.31 (d, 3 H, J = 6.4 Hz), 1.0 (t, 6 H, J = 6.5 Hz).

***erythro*-4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-(2-hydroxy-1-methylpropoxy)benzamide (8g).** erythro-4-Acetamido-5-chloro-*N*-[2-(diethylamino)ethyl]-2-(2-acetoxy-1-methylpropoxy)benzamide (8i) (4.42 g, 10 mmol) was dissolved in MeOH (40 mL), treated with 15 mL of 4.0 N NaOH, and stirred at reflux for 1 h. The methanol was removed at reduced pressure, the residue was partitioned between water and CH_2Cl_2, and the combined extracts were dried and evaporated to dryness to give a yellow gum. This was purified by chromatography to give 2.81 g (78.5%) of **8g** as a yellow semisolid, contaminated with 3.5% of the threo isomer **8h**, as determined by ^1H NMR analysis: NMR ($CDCl_3$) δ 8.04 (s, 1 H), 6.25 (s, 1 H), 4.12 (m, 1 H) and 3.77 (m, 1 H, CONHCH_2), 3.64 (m, H_a), 3.42 (m, H_b, J_{ab} = 5.9 Hz) 2.55–2.75 (m, 6 H), 1.35 (d, 3 H, J = 6.6 Hz), 1.24 (d, 3 H, J = 6.6 Hz), 1.0 (t, 6 H, J = 6.6 Hz).

***threo*-4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-(2-hydroxy-1-methylpropoxy)benzamide (8h)** was similarly prepared from **8j** as a yellow gum contaminated with ca 2% of **8g**: NMR ($CDCl_3$) δ 8.08 (s, 1 H), 6.27 (s, 1 H), 4.09 (m, 1 H) and 4.25 (m, 1 H, CONHCH_2), 3.72 (m, H_a), 3.32 (m, H_b, J_{ab} = 2.2 Hz), 2.5–2.7 (m, 6 H), 1.30 (d, 3 H, J = 6.6 Hz), 1.14 (d, 3 H, J = 6.6 Hz).

4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-(2,3-dihydroxypropoxy)benzamide (8l). Compound **8l** was obtained by acid-catalyzed hydrolysis (MeOH–3 N HCl) of acetal **9a**.

4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-(2-hydroxy-3-methoxypropoxy)benzamide (8m). Compound **8m** was prepared by reaction of epoxide **9b** with sodium methoxide in methanol for 20 h and isolation via standard procedure.

4-Amino-5-chloro-*N*-[(2-diethylamino)ethyl]-2-[(2-hydroxycyclohexyl)oxy]benzamides (8n) and (8o). A 1:2 mixture of **8n** and **8o** was obtained by reduction of **6c** via method F as a heavy oil in 73% yield. Anal. ($C_{19}H_{30}ClN_3O_3$) C, H, N.

The isomers were separated via repeated chromatography on silica to give first **8o** as a gummy foam: NMR ($CDCl_3$) δ 8.4 (br s, 1 H), 8.0 (s, 1 H), 6.3 (s, 1 H), 4.3 (s, 2 H), 3.9 (m, H_a), 3.78 (m, H_b, J_{ab} = 8.7 Hz), 3.4 (m, 1 H), 2.7 (m, 6 H), 1.7 (br d, 1 H), 1.43–1.10 (br m, 8 H), 1.03 (t, 6 H); HRMS, m/z 383.1972 ($C_{19}H_{30}ClN_3O_3$ requires 383.1975).

The more polar isomer **8n** was obtained next as a gummy foam: NMR ($CDCl_3$) δ 8.7 (s, 1 H), 8.07 (s, 1 H), 6.27 (s, 1 H), 4.30 (br s, 2 H), 4.21 (m, H_a), 4.01 (m, H_b, J_{ab} = 4.3 Hz), 3.78 (br m, 1 H), 3.31 (br m, 1 H), 2.72 (br m, 6 H), 1.9–1.27 (br m, 9 H), 1.03 (t, 6 H); HRMS, m/z 383.1970 ($C_{19}H_{30}ClN_3O_3$ requires 383.1975).

4-Amino-5-chloro-*N*-2-[2-(diethylamino)ethyl]-2-[(1*H*-4,5-dihydro-2-imidazolyl)methoxy]benzamide (9i). A mixture of **5h** (3.25 g, 10 mmol) and 1,2-diaminoethane (0.60 g, 10 mmol) in MeOH (25 mL) was heated to reflux for 3 h. The mixture was concentrated and the residue recrystallized to give the product as a white solid.

4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-hydroxy-*N*-methylbenzamide (10b). Compound **10a**[9] was demethylated by method A to give **10b** as a HCl salt in 40% yield, mp 200 °C from MeOH. Anal. ($C_{14}H_{22}ClN_3O_2$·HCl·0.25H_2O) C, H, N, Cl.

4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxy-*O*-methylbenzamidoxime (11d). Compound **11d** was synthesized via reaction Scheme IV. (a) A mixture of metoclopramide (15 g, 50 mmol) and *N,N*-dimethylformamide dimethyl acetal (7.16 g, 60 mmol) in dry toluene was heated under reflux for 3 h and then concentrated in vacuo to give 17.5 g of solid 5-chloro-*N*-[2-(diethylamino)ethyl]-4-[[(dimethylamino)methylene]amino]-2-methoxybenzamide (**11a**), mp 90–91 °C. Anal. ($C_{17}H_{27}ClN_4O_2$) C, H, N.

(b) To a stirred solution of **11a** (10.62 g, 30 mmol) in 1,2-dichloroethane (350 mL) was added PCl_5 (6.8 g, 33 mmol). After 30 min, a crystalline solid was filtered off, washed with dry 1,2-dichloroethane, and dried in vacuo to give 6.15 g (51%) of 5-chloro-*N*-[2-(diethylamino)ethyl]-4-[[(dimethylamino)-methylene]amino]-2-methoxybenzenecarboximidoyl chloride hydrochloride (**11b**) as a highly hygroscopic white solid.

(c) To a suspension of **11b** (3.5 g, 8.58 mmol) and methoxylamine hydrochloride (0.79 g, 9.46 mmol) in CH_2Cl_2 (20 mL) was added dropwise TEA (2.62 g, 25.0 mmol), andd the resulting solution was heated under reflux for 4 h. The mixture was partitioned between aqueous Na_2CO_3 and CH_2Cl_2, and the product, 5-chloro-*N*-[2-(diethylamino)ethyl]-4-[[(dimethylamino)methylene]amino]-2-methoxy-*O*-methylbenzamidoxime (**11c**) was isolated by chromatography, to give 1.35 g (41%) of a white solid, mp 86–97 °C. Anal. ($C_{18}H_{30}ClN_5O_2$) C, H, N, Cl.

(d) To a solution of **11c** (1.2 g, 3.13 mmol) in MeOH (10 mL) was added hydroxylamine hydrochloride (0.5 g, 7.2 mmol), and the mixture was stirred for 30 min. The solvent was removed in vacuo, and the residue was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The organic phase was concentrated, and the residue was dissolved in 10 mL of 1 N HCl. The solution was heated to reflux for 2 min, cooled, neutralized with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was concentrated, and the residue was chromatographed on silica to give 0.81 g of **11d** (79%) as a heavy oil. Anal. ($C_{15}H_{25}ClN_4O_2$) H, Cl; calcd: C, 54.79; N, 17.04. Found: C, 54.10; N, 16.54.

4-Amino-5-chloro-2-methoxyphenyl Thiocyanate (12b). To a cooled (ice–water) stirred mixture of 6-chloro-*m*-anisidine hydrochloride (**12a**) (19.4 g, 0.1 mol), KSCN (11.67 g, 0.12 mol), and TEA (10.12 g 0.1 mol) in MeOH (100 mL) was added dropwise a solution of bromine (16.0 g 0.1 mol) in MeOH (30 mL) over 1 h. The mixture was stirred for 1 h at ambient temperature and filtered, and the filtrate was poured into 2 L of H_2O. This was stirred for 15 min, cooled at 0 °C for 2 h, and filtered, and the solid was dried and recrystallized from MeOH to give 12.1 g (56%) of the product **12b**: mp 100–102 °C; NMR ($CDCl_3$) δ 7.52 (s, 1 H), 6.44 (s, 1 H), 4.4 (b s, 2 H), 3.92 (s, 3 H).

3-[(4-Amino-5-chloro-2-methoxyphenyl)thio]-1-(diethylamino)propane Dihydrochloride (12c). To a stirred solution of KOH (9.4 g, 168 mmol) in MeOH (350 mL) was added **12b** (12.0 g, 55.9 mmol), and the mixture was heated to reflux for 45 min. Then 3-(diethylamino)-1-chloropropane hydrochloride (10.4 g, 55.9 mmol) was added, and heating was continued for 1.5 h. This was concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The organic phase was concentrated, and the residue was chromatographed on silica to give an oil, which was converted to dihydrochloride salt **12c** (8.8 g 42%), mp 150–153 °C from 2-PrOH. Anal. ($C_{14}H_{23}ClN_2OS$·2HCl) C, H, N, Cl.

3-[(4-Amino-5-chloro-2-methoxyphenyl)sulfinyl]-1-(diethylamino)propane (12d). A solution of **12c** (3.0 g, 8.0 mmol) and 30% H_2O_2 (0.82 mL, 8.0 mmol) in acetic acid (50 mL) was stirred for 24 h and concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 and aqueous K_2CO_3. The organic phase was concentrated, and the residue was chromatographed on silica to give 0.92 g of **12d** (29%) as a heavy oil. Anal. ($C_{14}H_{23}ClN_2O_2S$·0.5H_2O) C, H, N, Cl, S.

***N*-[(1-Allyl-2-pyrrolidinyl)methyl]-6-hydroxy-1*H*-benzotriazole-5-carboxamide (13a).** Compound **13a** was prepared by method A from **2**[35] in 46% yield, mp 125–133 °C from CH_2Cl_2–pentane. Anal. ($C_{15}H_{19}N_5O_2$·0.2H_2O) C, H, N, H_2O.

***N*-[(1-Allyl-2-pyrrolidinyl)methyl]-6-(1-methyl-2-oxopropoxy)-1*H*-benzotriazole-5-carboxamide (13c).** A solution of phenol **13a** (1.0 g, 3.3 mmol) and di-*tert*-butyl dicarbonate (0.92 g, 4.2 mmol) in DMF (13 mL) was stirred for 3 h and then concentrated in vacuo. The residue was then alkylated with 3-chloro-2-butanone via method B, and the product **13b**, an oil, was treated with 2 N aqueous HCl (20 mL) and MeOH (5 mL) at 60 °C for 10 min. The mixture was concentrated in vacuo, and the residue was partitioned between aqueous ammonia and CH_2Cl_2. The organic phase was concentrated, and the residue was chromatographed on silica to give 240 mg (19%) of a white solid **13c** as a semihydrate, mp 61–65 °C. Anal. ($C_{19}H_{25}N_5O_3$·0.5H_2O) C, H, N.

4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2,3-dimethyl-7-benzofurancarboxamide (14a). A solution of **6e** (5.0 g, 12.75 mmol) in 50 mL of concentrated HCl was heated at 54–56 °C for 7 h under nitrogen, cooled, and basified with ammonium hydroxide. The mixture was extracted with CH_2Cl_2, the extract was chromatographed on silica, and the product was recrystallized from CH_2Cl_2–Et_2O to give 1.25 g (26%) of **14a** as a light yellow solid: mp 119–120 °C; NMR ($CDCl_3$) δ 7.83 (s, 1 H), 4.6 (br s, 2 H), 3.3–3.8 (m, 2 H), 2.3–2.9 (m, 6 H), 2.33 (s, 6 H), 1.05 (t, 3

(35) Bulteau, G.; Acher, J.; Collignon, C.; Monier, J. C. U.S. Pat. 4 039 672, 1977.

H, J = 6 Hz). Anal. ($C_{17}H_{24}ClN_3O_2$) C, H, N, Cl.

7-Chloro-4-[2-(diethylamino)ethyl]-8-formamido-2,3-dimethyl-1,4-benzoxazepin-5(4*H*)-one (16a) and 8-Amino-7-chloro-4-[2-(diethylamino)ethyl]-2,3-dimethyl-1,4-benzoxazepin-5(4*H*)-one (16b). A mixture of **6e** (3.0 g, 7.65 mmol) and formic acid (22 mL of 97%) was heated under reflux for 10 min and concentrated in vacuo to give an oil, which was shown by ^{1}H NHR to be N-formylated **6e** (**15a**). To this was added polyphosphoric acid (22 g), and the mixture was heated at 70 °C for 18 h with occasional swirling. After cooling, the mixture was treated with ammonia–ice until all the acid was neutralized. The product was extracted into CH_2Cl_2. The extract was concentrated in vacuo, and the residue was chromatographed on silica to give first 1.2 g of a yellow oil, which crystallized from Et_2O. This was recrystallized from CH_2Cl_2–Et_2O to give 465 mg (17%) of a white solid **16a**: mp 134–135 °C; NMR ($CDCl_3$) δ 8.24 (br s, 1 H), 7.90 (s, 1 H), 3.6–3.9 (m, 2 H), 2.4–2.8 (m, 6 H), 1.95 (br s, 3 H), 1.82 (br s, 3 H), 1.2 (t, 6 H, J = 6 Hz). Anal. ($C_{18}H_{24}ClN_3O_3$) C, H, N, Cl.

Continued elution of the column gave a second fraction (820 mg), which was combined with the mother liquors of **16a** and concentrated, and the residue was treated with aqueous 1 N NaOH (4 mL) and MeOH (20 mL) at 45 °C for 30 min. This was concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The organic phase was chromatographed on alumina (eluent CH_2Cl_2; 0.35% MeOH), to give 860 mg (38%) of solid **16b**. This was recrystallized from CH_2Cl_2–Et_2O to give a pure sample: mp 160–161 °C; NMR ($CDCl_3$) δ 7.88 (s, 1 H), 4.2 (br s, 2 H), 3.6–4.0 (m, 2 H), 2.4–2.8 (m, 6 H), 1.95 (br s, 3 H), 1.82 (br s, 3 H), 1.04 (t, 6 H, J = 6 Hz). Anal. ($C_{17}H_{24}ClN_3O_2$) C, H, N, Cl.

8-Amino-7-chloro-4-[2-(diethylamino)ethyl]-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one (16c). Compound **16c** was prepared by method C as shown in Scheme VII in 25% yield, mp 82–83 °C from Et_2O. Anal. ($C_{15}H_{22}ClN_3O_2$) C, H, N.

14-Amino-13-chloro-7-ethyl-2,3,4,5,6,7,8,9-octahydro-10*H*-1,7,10-benzooxadiazacyclotridecen-11-one (19a) and 14-Amino-13-chloro-7-ethyl-2,3,6,7,8,9,10,11-octahydro-11*H*-1,4,7,10-benzodioxadiazacyclotridecen-11-one (19b). Compounds **19a** and **19b** were synthesized in three steps according to Scheme VIII. Intermediates **17a** [67%; mp 87–88 °C from CH_2Cl_2–Et_2O. Anal. ($C_{18}H_{29}ClN_3O_2$) C, H, N, Cl.] and **17b** [64%; mp 83–84 °C from CH_2Cl_2–Et_2O. Anal. ($C_{17}H_{27}Cl_2N_3O_3$) C, H, N, Cl.] were synthesized via method D. Intermediates **18a** [47%; mp 117–118 °C from CH_2Cl_2–Et_2O. Anal. ($C_{16}H_{25}Cl_2N_3O_2$) C, H, N, Cl.] and **18b** [50%; mp 97–98 °C, from CH_2Cl_2–Et_2O. Anal. ($C_{15}H_{23}Cl_2N_3O_3$) C, H, N, Cl.] were synthesized according to the recently described method for dealkylation of tertiary amines.[10] Compounds **19a** [50%; mp 255–256 °C from methoxyethanol; NMR ($CDCl_3$–Me_2SO-d_6, 10:1) δ 8.6 (s, 1 H), 7.8 (s, 1 H), 5.9 (br s, 2 H), 4.0 (m, 2 H), 3.5 (m, 2 H), 2.4–2.7 (m, 6 H), 1.4–2.0 (m, 6 H), 0.9 (t, 3 H, J = 6 Hz). Anal. ($C_{16}H_{24}ClN_3O_2$) C, H, N, Cl.] and **19b** [65%; mp 205–207 °C from methoxyethanol; NMR ($CDCl_2$–Me_2SO-d_6, 10:1) δ 8.8 (s, 1 H), 7.7 (s, 1 H), 6.5 (s, 1 H), 5.1 (br s, 2 H), 3.3–4.3 (m, 8 H), 2.5–2.8 (m, 6 H), 1.0 (t, 3 H, J = 6 Hz). Anal. ($C_{15}H_{22}ClN_3O_3$) C, H, N, Cl.] were synthesized from the corresponding **18a** and **18b** by method B.

Pharmacology: [^{3}H]Spiperone Binding.[20] Rat brain striatal membranes were prepared by differential centrifugation in 50 mM Tris buffer pH 7.4 at 4 °C. The membrane pellets were suspended in 50 volumes of Tris buffer; 10 mg of membrane protein were incubated for 15 min at 37 °C with 0.1 nM [^{3}H]spiperone in the presence of varying concentrations of the competing ligands. The assay mixture included 50 mM Tris·HCl pH 7.5, 0.1% ascorbic acid, 10 M pargyline, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$. Nonspecific binding was defined by the addition of 1 M (+)-butaclamol. After incubation, the membranes were filtered through Whatman GF/B glass fiber filters, which were dried and placed in vials with 5 mL of Instagel and were counted in a Beckman scintillation counter. The IC_{50} values were obtained by log–logit regression analysis.[21,21a]

Cataleptic Activity and Antagonism of Apomorphine Stereotypy in Rats.[13] Male Long Evans rats (275 g) were dosed sc with graded doses of test compounds dissolved in diluted aqueous HCl (pH 4.5–5.5). For the next 180 min, animals were observed for catalepsy, which was defined as a response when the animal remained stationary for at least 15 s on a template consisting of four corks. In stereotypy experiments rats were dosed sc with test compounds 30 min prior to apomorphine (1 mg/kg, sc). For the next 30 min, animals were observed for stereotypy at 10-min intervals. In both tests, animal responses were evaluated quantally, and ED_{50} and 95% confidence limits (CL) values were calculated according to probit analysis.

Apomorphine-Induced Emesis in Dogs. Test compounds were dosed sc 30 min prior to apomorphine (0.3 mg/kg, sc) as solutions in diluted aqueous HCl (pH 4.5–5.5) in male adult beagle dogs (Marshall Farms). The predose time for domperidone was 120 min. Dogs were observed and scored for emesis in a quantal fashion 30 min following administration of the emetogenic substance. Probit analysis was employed to obtain ED_{50} values and 95% confidence limits.

Cisplatin-Induced Emesis in Dogs and Ferrets. Nonfasted dogs (mature, male or female beagles, Marshall Farms) were administered test compounds or saline sc twice: 30 min prior to and 120 min after cisplatin dosing (3 mg/kg, iv). Cisplatin was dissolved in 0.9% warm saline with a final concentration of 3 mg/mL and used immediately. Dogs were observed for emesis for up to 5 h following cisplatin administration.

A similar procedure was used in cisplatin-induced emesis in ferrets (nonfasted Fitch castrated males, 1–1.5 kg, Marshall Farms). They were previously (at least 48 h prior) implanted, under general anesthesia, with in-dwelling jugular vein catheters employed for all drug administrations. Test compounds or saline were administered twice: 5 min prior to and 90 min after cisplatin dosing (12 mg/kg, iv). Cisplatin was dissolved in 0.9% warm saline with a final concentration of 12 mg/mL and used immediately. Ferrets were observed for emesis for up to 4 h after cisplatin administration. In antiemetic studies involving cytostatic agents, emesis was defined as an expulsion of stomach content; any combination of multiple emetic and retching events occurring within a period of 1 min in the ferret and 2 mins in the dog were considered as a single emetic episode.

The percent protection from cisplatin-induced emesis was calculated as follows:

$$\frac{\text{emetic frequency (saline)} - \text{emetic frequency (drug)}}{\text{emetic frequency (saline)}} \times 100$$

Probit analysis[21] was employed to obtain ED_{50} values and 95% confidence limits. The t test[22] was used to analyze the antiemetic responses of individual drug doses versus the saline control value.

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Registry No. 1, 364-62-5; **2**, 59338-93-1; **4a**, 38339-95-6; **4b**, 38059-78-8; **4c**, 102670-98-4; **5a**, 55304-07-9; **5b**, 89481-31-2; **5c**, 114614-35-6; **5d**, 114614-36-7; **5e**, 114614-37-8; **5f**, 114614-38-9; **5g**, 23205-22-3; **5h**, 102670-52-0; **5i**, 102670-53-1; **5j**, 102670-54-2; **6a**, 102670-44-0; **6b**, 102670-45-1; **6c**, 102670-48-4; **6d**, 114614-39-0; **6e**, 102670-59-7; **6f**, 102670-62-2; **6g**, 102670-61-1; **6h**, 102670-63-3; **6i**, 102670-60-0; **6j**, 102670-64-4; **6k**, 102670-65-5; **6l**, 102670-66-6; **6m**, 102670-67-7; **6n**, 102670-89-3; **7a**, 102670-49-5; **7b**, 102670-50-8; **7c**, 102670-70-2; **8a**, 102670-41-7; **8b**, 102670-51-9; **8c**, 114614-40-3; **8d**, 114614-41-4; **8e**, 114614-42-5; **8f**, 114614-43-6; **8g**, 102671-01-2; **8h**, 102670-78-0; **8i**, 114633-58-8; **8j**, 114633-59-9; **8k**, 102670-69-9; **8l**, 114614-44-7; **8m**, 114614-45-8; **8n**, 114614-46-9; **8o**, 114614-47-0; **8p**, 102671-16-9; **8q**, 114614-48-1; **8r**, 102670-40-6; **8s**, 102670-42-8; **8t**, 102671-15-8; **8u**, 114614-49-2; **8v**, 114614-50-5; **8w**, 102670-43-9; **8x**, 102670-83-7; **8y**, 114614-51-6; **9a**, 102685-89-2; **9b**, 114614-52-7; **9c**, 114614-53-8; **9d**, 102670-91-7; **9e**, 114614-54-9; **9f**, 102670-57-5; **9g**, 102670-82-6; **9h**, 114614-55-0; **9i**, 102670-88-2; **10a**, 114614-56-1; **10b**, 114614-57-2; **11a**, 114614-58-3; **11b**, 114614-59-4; **11c**, 114614-60-7; **11d**, 114614-61-8; **12a**, 85006-21-9; **12b**, 114614-62-9; **12c**, 114614-63-0; **12d**, 114614-64-1; **13a**, 114614-65-2; **13b**, 114614-66-3; **13c**, 114614-67-4; **14a**, 114614-68-5; **15a**, 114614-69-6; **16a**, 114614-70-9; **16b**, 114614-71-0; **16c**, 114614-72-1; **17a**, 114614-73-2; **17b**, 114633-60-2; **18a**, 114614-74-3; **18b**, 114633-61-3; **19a**, 114614-75-4; **19b**, 114614-76-5; $BrCH_2CH{=}CH_2$, 106-95-6;

$BrCH_2C{\equiv}CH$, 106-96-7; $BrCH_2C(CH_3){=}CH_2$, 1458-98-6; $BrCH_2CH{=}CHCH_3$, 4784-77-4; $Br(CH_2)_2CH{=}CH_2$, 5162-44-7; $Br(CH_2)_2CH_3$, 106-94-5; $BrCH_2C_6H_5$, 100-39-0; $BrCH_2CN$, 590-17-0; $BrCH(CH_3)CN$, 19481-82-4; $BrCH_2CO_2Me$, 96-32-2; $BrCH_2COCH_3$, 598-31-2; $BrCH_2COC_6H_5$, 70-11-1; $BrCH(CH_3)COCH_3$, 814-75-5; $BrCH_2COCH_2CH_3$, 816-40-0; $BrH(C_2H_5)COCH_3$, 815-48-5; $BrCH_2CO(CH_2)_2CH_3$, 817-71-0; $BrCH(COCH_3)CH_2CH{=}CH_2$, 114614-77-6; $BrCH(CH_3)COCH_2CH_3$, 815-52-1; $BrCH_2COCH(CH_3)_2$, 19967-55-6; $BrCH_2COCH_2C_6H_5$, 20772-12-7; $BrC(CH_3)_2COCH_3$, 2648-71-7; $Br(CH_2)_2OH$, 540-51-2; $BrCH_2CH(OH)CH_2C_6H_5$, 28988-98-9; $Br(CH_2)_2OCH_3$, 6482-24-2; $BrCH_2CH(OMe)_2$, 7252-83-7; $BrCH_2CH(OMe)CH_3$, 23465-33-0; $BrCH_2O(CH_2)_2OCH_3$, 100107-97-9; $Br(CH_2)_2O(CH_2)_2OMe$, 54149-17-6; $HO(CH_2)_2CH(OH)CH_3$, 107-88-0; $HO(CH_2)_2CH(OMe)CH_3$, 2517-43-3; $TsO(CH_2)_2Cl$, 80-41-1; $Cl_2(CH_2)_5$, 628-76-2; $Cl(CH_2)_2O(CH_2)_2Cl$, 111-44-4; (*R*)-2-[2-(methoxyethoxy)methoxy]propionic acid methyl ester, 114614-78-7; (*R*)-2-[2-(methoxyethoxy)methoxy]propanol, 114614-79-8; (*S*)-2-[2-(methoxyethoxy)methoxy]propionic acid methyl ester, 114614-80-1; (*S*)-2-[2-(methoxyethoxy)methoxy]propanol, 114614-81-2; 1,2-diaminoethane, 107-15-3; 3-(diethylamino)-1-chloropropane hydrochloride, 4535-85-7; *N*-[(1-allyl-2-pyrrolidinyl)methyl]-6-hydroxy-1-(*tert*-butyloxycarbonyl)benzotriazole-5-carboxamide, 114614-82-3; 3-chloro-2-butanone, 4091-39-8; 2-bromocyclohexanone, 822-85-5; 2-bromocyclopentanone, 21943-50-0; 2-(bromoacetyl)thiophene, 10531-41-6; *cis*-1-bromo-2-methoxycyclohexane, 51332-48-0; *trans*-1-bromo-2-methoxycyclohexane, 5927-93-5; 4-(bromomethyl)-2,2-dimethyl-1,3-dioxolane, 36236-76-7; (bromomethyl)oxirane, 3132-64-7; 2-(bromomethyl)-2-methyloxirane, 49847-47-4; 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 37865-96-6; 2-(bromomethyl)tetrahydrofuran, 1192-30-9; 5-(bromomethyl)-3-methylisoxazole, 36958-61-9; 2-(bromomethyl)pyridine, 55401-97-3; 2-(bromomethyl)-1,3-dioxolane, 4360-63-8; dompiridone, 57808-66-9.

Stereoisomers of Allenic Amines as Inactivators of Monoamine Oxidase Type B. Stereochemical Probes of the Active Site[1]

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The kinetics of inactivation of mitochondrial monoamine oxidase type B (MAO-B) by a series of 18 stereoisomers of tertiary α-allenic amines have been investigated in detail. The chirality of the allene group in *N*-methyl-*N*-aralkylpenta-2,3-dienamines was found to have a profound effect on the inactivation rate, with the (*R*)-allenes being up to 200-fold more potent than their (*S*)-allenic counterparts. The ability of (*S*)-allenes to inactivate MAO was severely compromised by the presence of *N*-phenethyl or *N*-α-substituted-aralkyl substituents. The opposing chiralities in both the allene and aralkyl groups of (*R*,*R*)- and (*S*,*S*)-*N*-methyl-*N*-(1,2,3,4-tetrahydro-1-naphthyl)-penta-2,3-dienamine resulted in a difference of more than 3 orders of magnitude in inactivation rates. The stereoselectivity of MAO-B was examined further with a series of reversible aralkylamine inhibitors; thus (*R*)-1,2,3,4-tetrahydro-1-naphthylamine was determined to be 150-fold more potent than its enantiomer.

As a result of its important role in psychopharmacology, the enzyme monoamine oxidase [amine: oxygen oxidoreductase (deaminating, flavin-containing); EC 1.4.3.4; MAO] has been the subject of active research for the last three decades.[2] A number of inhibitors of MAO have proved useful in clinical psychiatry for the treatment of depression; however, their effectiveness has been complicated by the "cheese effect", a serious hypertensive response to the tyramine present in common foodstuffs.[2] An attractive strategy for the development of MAO inhibitors that are devoid of such side effects focusses on the selective inhibition of the multiple forms of MAO, termed types A and B,[3] as it is believed that inhibitors that are selective for the B form should not exhibit the cheese effect.[4] However, while MAO-B selective inhibitors have found application in the L-DOPA treatment of Parkinson's disease,[5] the role of MAO-B in depression remains controversial;[6] one point of view holds that antidepressant agents should be directed to the selective inhibition of MAO-A.[7] The most widely investigated selective inhibitors are *l*-deprenyl (an irreversible MAO-B inhibitor) and clorgyline (an irreversible MAO-A inhibitor);[2] most recently, selective inhibitors such as 3-fluoro-2-arylallylamines[8] and oxazolidinones[9] have been reported. The MAO substrate and inhibitory activity of MPTP, a tetrahydropyridine that induces irreversible Parkinsonism, is also of current interest.[10]

Both reversible and irreversible stereoselective inhibitors of monoamine oxidase have been developed.[3,11-14] The

(1) Contribution No. 263 from the Institute of Bio-Organic Chemistry.
(2) (a) Ho, B. T. *J. Pharm. Sci.* **1972**, *61*, 821. (b) Blascho, H. *Rev. Physiol. Biochem. Pharmacol.* **1974**, *70*, 83. (c) *Monoamine Oxidase: Structure, Function, and Altered Functions*; Singer, T. P., Von Korff, R. W., Murphy, D. L., Eds.; Academic: New York, 1979. (d) Fowler, C. J.; Ross, S. B. *Med. Res. Rev.* **1984**, *4*, 323. (e) *Monoamine Oxidase and Disease: Prospects for Therapy with Reversible Inhibitors*; Tipton, K. F., Dostert, P., Benedetti, M. S., Eds.; Academic: New York, 1984.
(3) Fowler, C. J. *Drugs Future* **1982**, *7*, 501.
(4) Knoll, J. *Trends Neurosci.* **1979**, 111.
(5) Birkmayer, W.; Knoll, J.; Reiderer, P.; Youdim, M. B. H. *Mod. Probl. Pharmacopsychiatry* **1983**, *19*, 170.
(6) Frazee, W. J.; Ohnmacht, C. J.; Malick, J. B. *Annu. Rep. Med. Chem.* **1985**, *20*, 31.
(7) Neff, N. H.; Yang, H.-Y. T. *Life Sci.* **1974**, *14*, 2061.
(8) (a) McDonald, I. A.; Lacoste, J. M.; Bey, P.; Palfreyman, M. G.; Zreika, M. *J. Med. Chem.* **1985**, *28*, 186. (b) Bey, P.; Fozard, J.; Locoste, J. M.; McDonald, I. A.; Zreika, M.; Palfreyman, M. G. *J. Med. Chem.* **1984**, *27*, 9.
(9) (a) Dostert, P.; Benedetti, M. S.; Guffroy, C. *J. Pharm. Pharmacol.* **1983**, *35*, 661. (b) Fowler, C. J.; Benedetti, M. S. *J. Neurochem.* **1983**, 510. (c) Tipton, K. F.; Fowler, C. J.; McCrodden, J. M.; Benedetti, M. S. *Biochem. J.* **1983**, *209*, 235.
(10) (a) Kulkarni, S. K.; Mehta, A. K. *Drugs Future* **1986**, *11*, 384. (b) Fuller, R. W.; Hemrick-Luecke, S. K. *J. Pharmacol. Exp. Ther.* **1985**, *232*, 696. (c) Lewin, R. *Science (Washington, D.C.)* **1984**, *225*, 1460. (d) Snyder, S. H. *Nature (London)* **1984**, *311*, 514.
(11) Fuller, R. W.; Hemrick, S. K. *Res. Commun. Chem. Pathol. Pharmacol.* **1978**, *20*, 199.
(12) Fowler, C. J.; Oreland, L. *J. Pharm. Pharmacol.* **1981**, *33*, 403.

0022-2623/88/1831-1558$01.50/0