Synthesis of a New Class of 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic Acid Derivatives as Highly Potent 5-HT_3 Receptor Antagonists

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A series of 2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic acid esters and amides containing a basic azacyclo- or azabicycloalkyl moiety has been synthesized and evaluated for 5-HT_3 antagonistic activity in a radioligand binding assay ([^{3}H]ICS 205930) and in the 5-HT-induced von Bezold-Jarisch reflex in the rat. It was found that endo-substituted azabicycloalkyl derivatives (e.g. **7a**, **12a**, **12b**) were much more active than the corresponding exo analogues (e.g. **7b**, **12h**, **12i**) or azacycloalkyl compounds. Amidic derivatives **12a**, **12b**, **12c**, **12e**, **13b**, and **13c** proved to be about 10 times more active than the corresponding ester derivatives **7a**, **11a**, **7c**, **7d**, **8a**, and **8b**. In particular, compound **12a** (DA 6215) showed a K_i = 3.8 nM in the binding test and an ED_{50} = 1 nM/kg iv in the von Bezold-Jarisch reflex assay, an activity comparable to that of the reference compound **2** (ICS 205930, K_i = 2 nM, ED_{50} = 2.1 nM/kg). IR spectroscopy studies in the solid state and in $CHCl_3$ solution revealed the existence of an intramolecular hydrogen bond in **13b**, taken as a model compound for this class of substances. A molecular modeling study showed that **12a**, in its internal hydrogen-bound conformation, well matches a recently proposed pharmacophoric model for 5-HT_3 antagonist activity.

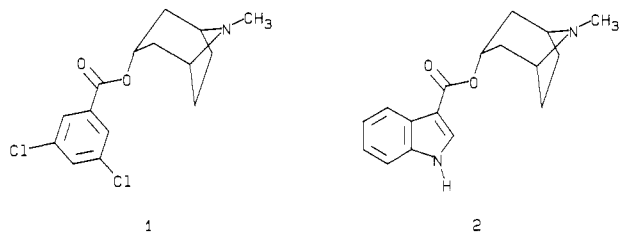
The heterogeneity of serotonin (5-HT) receptors has been recognized since 1957, when Gaddum and Picarelli obtained pharmacological evidence for the existence of two subtypes that were defined as D and M receptors.[1]

Only recently, however, the availability of radioligand-binding techniques did allow a more accurate classification into 5-HT_1 and 5-HT_2 sites.[2] The former are not homogeneous and could be further subdivided into four additional subtypes. While the D receptor was demonstrated to correspond to the 5-HT_2 binding site, a more precise designation of the functional M receptor, which is of neither the 5-HT_1 nor 5-HT_2 type, was hampered by the lack of specific agonists or antagonists.

The development of new antagonists specific for the neuronal M receptor was an achievement of two separate research groups which synthesized two series of selective serotonin antagonists, typified by compounds MDL 72222 (**1**)[3] and ICS 205930 (**2**)[4] respectively (Chart I). These substances were used as tools to study and, then, to redesignate the M receptor of the functional classification into the 5-HT_3 category. From a clinical standpoint these compounds, as well as other 5-HT_3 receptor antagonists including GR-38032F,[5] BRL-43694,[6] and zacopride,[7] have demonstrated high efficacy as antiemetics in the management of the severe nausea and vomiting associated with anticancer therapy.[8] Moreover, evidence strongly suggests that 5-HT_3 receptors are functionally active in the central nervous system CNS,[9] and the potential of some antagonistic compounds in the clinical treatment of anxiety and psychoses is currently being investigated.[10]

Chemically both **1** and **2** possess structural features reminiscent of ACh antimuscarinic compounds, since they contain a tropane ester moiety typical of the naturally occurring muscarine antagonists atropine and derivatives. In the course of our studies aimed at finding selective antimuscarinic agents, we had been synthesizing a class of compounds containing this pharmacophoric group linked to a benzimidazolone moiety through an ester or amide functionality. The apparent analogy between our structures and the two prototypes **1** and **2** prompted us to submit the new substances to a screening for 5-HT_3 antagonism. This report describes the synthesis and biological activity of the new derivatives. Conformational properties of a representative member of this class are also discussed in relation to a pharmacophore recently proposed

Chart I



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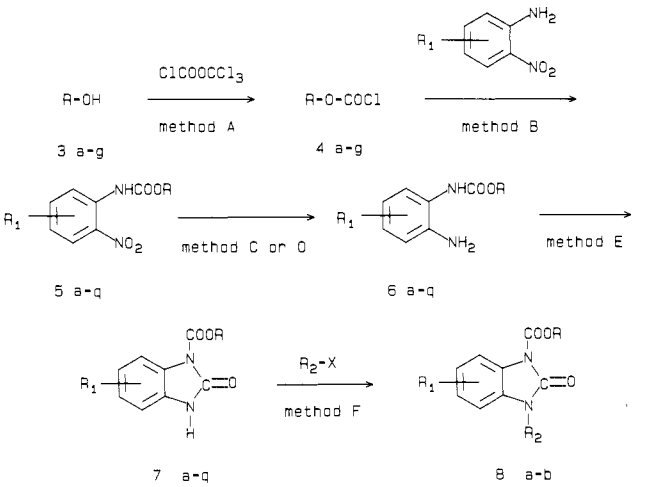
Scheme I



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(1) Gaddum, J. H.; Picarelli, Z. P. *Br. J. Pharmacol.* **1957**, *12*, 323.
(2) 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*, 163.
(3) Fozard, J. R.; Gittos, M. W. *Br. J. Pharmacol.* **1983**, *80*, 511P.
(4) Richardson, B. P.; Engel, G.; Donatsch, P.; Stadler, P. A. *Nature (London)* **1985**, *316*, 126.
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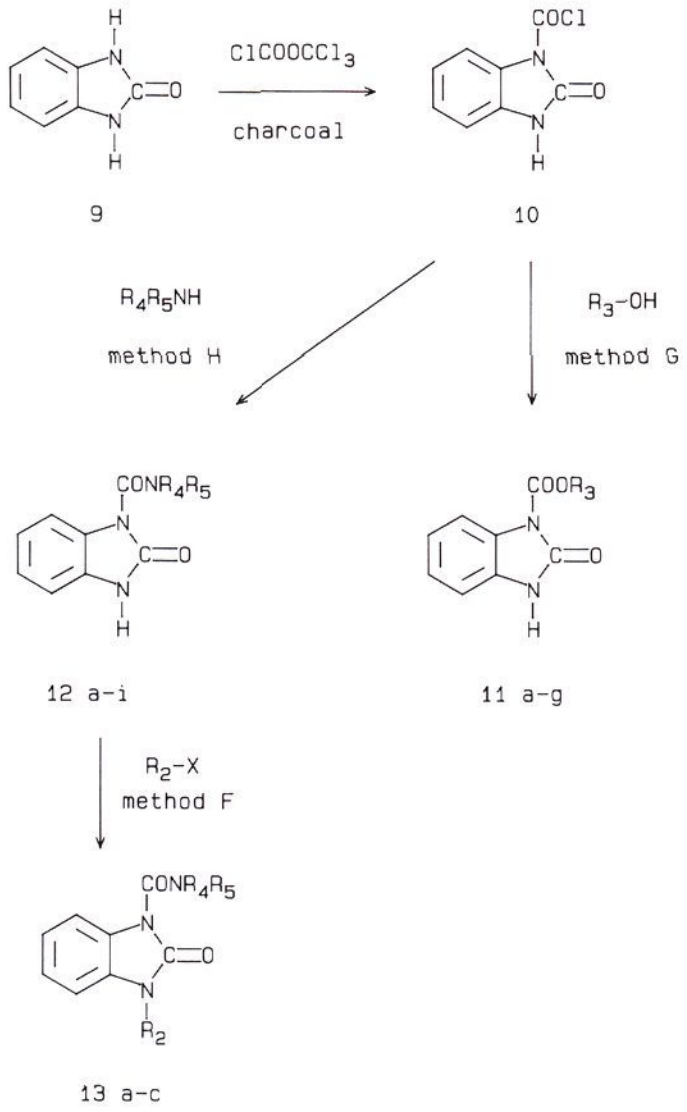
Scheme II



for 5-HT_3 receptor antagonists.[11]

Chemistry

Synthesis of most 2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic acid esters and amides (**7**, **8**, and **11**–**13**) was accomplished following the two general pathways shown in Schemes I and II. According to Scheme I, chloroformates **4** of azacycloalkanols **3** were smoothly prepared by the action of trichloromethyl chloroformate. Reaction of **4** with the properly substituted *o*-nitroanilines afforded nitrocarbamates **5** which, after reduction to aminocarbamates **6**, were cyclized at room temperature with trichloromethyl chloroformate to give benzimidazolones **7**. N-Substituted compounds **8** were prepared by alkylation of **7** with the proper halides using sodium hydride as a deprotonating agent. Compounds which either did not form stable chloroformates or did not easily couple with *o*-nitroanilines were prepared according to Scheme II.

The synthesis of chlorocarbonyl derivative **10** was carried out by employing trichloromethyl chloroformate in the presence of activated charcoal in refluxing THF; the method did not require the drastic experimental conditions and the large amount of highly toxic phosgene as previously reported.[12] Coupling with azacycloalkanols R_3OH or azacycloalkylamines R_4R_5NH was accomplished in *o*-dichlorobenzene at high temperatures or in THF at room temperature, respectively. N-Alkylated compounds **13** were prepared similarly to **8**. Preparation of compound **16** was performed according to Scheme III by direct condensation of tropine chloroformate hydrochloride **4a** with the diamine **14**, followed by cyclization of carbamate **15** with trichloromethyl chloroformate.

The physicochemical data for 2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic acid esters and amides (**7**, **8**, **11**–**13**, **16**, and **17**) are reported in Tables I, II, and III; the

Scheme III

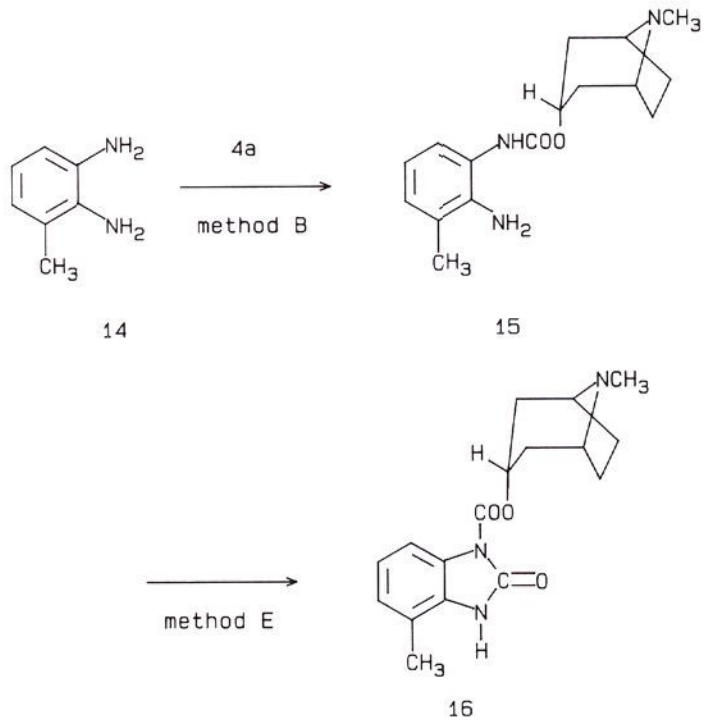
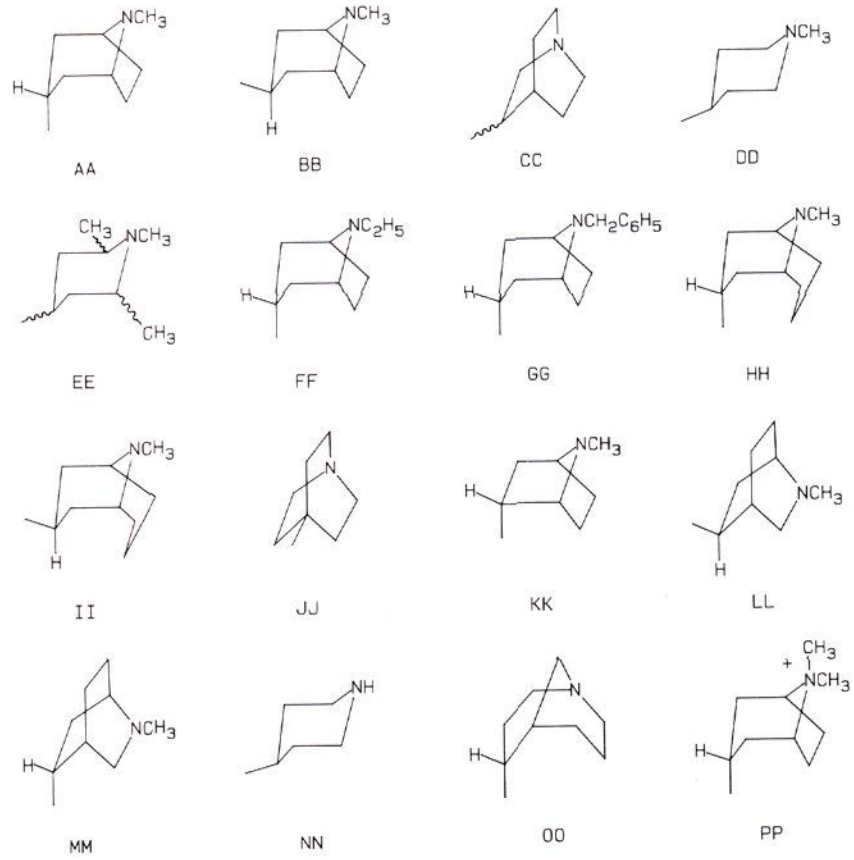


Chart II



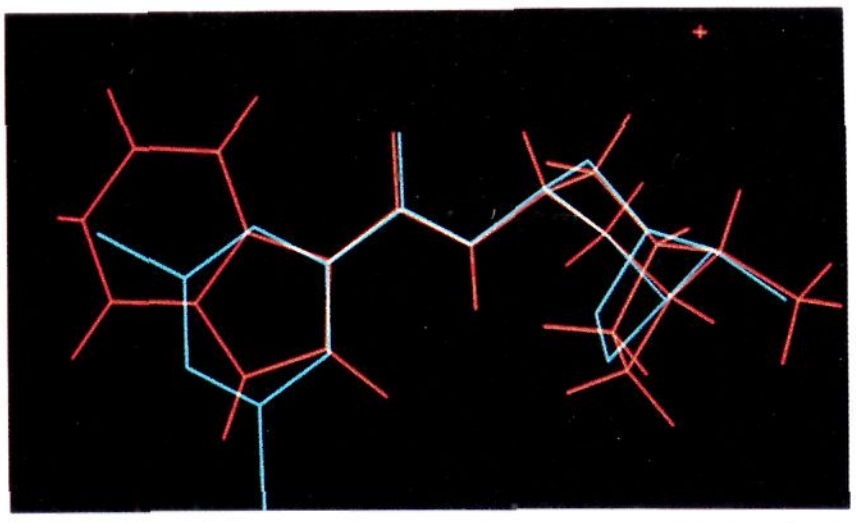


Figure 1. Superimposition of compounds 1 (light blue) and **12a** (orange), as obtained by using the MULTIFIT option within SYBYL. RMS = 0.17 Å.

(9) Barnes, J. M.; Barnes, N. M.; Costall, B.; Naylor, R. J.; Tyers, M. B. *Nature (London)* **1989**, *338*, 762.
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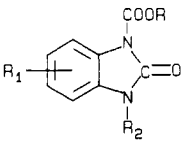
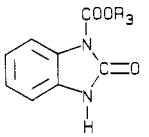
Table I. Physical Data for 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic Acid Esters **7**, **8**, **16** and **17**



compd	R[a]	R_1	R_2	method[b]	% yield	mp, °C	crystn solvent	formula
7a	AA	H	H	E	47	191–192	CH_3CN	$C_{16}H_{19}N_3O_3$
7b	BB	H	H	E	68	255–256	*i*-PrOH	$C_{16}H_{19}N_3O_3$·HCl
7c	CC	H	H	E	33	259–261	EtOH/Et_2O	$C_{15}H_{17}N_3O_3$·HCl
7d	DD	H	H	E	44	219–220	EtOH	$C_{14}H_{17}N_3O_3$·HCl
7e	EE	H	H	E	84	250–252	EtOH/Et_2O	$C_{16}H_{21}N_3O_3$·HCl
7f	FF	H	H	E	64	258–260	EtOH	$C_{17}H_{21}N_3O_3$·HCl
7g	GG	H	H	E	87	219–220	*i*-PrOH/(*i*-Pr)$_2$O	$C_{22}H_{23}N_3O_3$[c]
7h	AA	5-OCH_3	H	E	43	177–178	CH_3CN	$C_{17}H_{21}N_3O_4$
7i	AA	5-CH_3	H	E	27	187–189	CH_3CN	$C_{17}H_{21}N_3O_3$
7j	AA	5-Cl	H	E	46	236–238	EtOH	$C_{16}H_{18}ClN_3O_3$·HCl
7k	AA	6-F	H	E	80	261–263	EtOH/Et_2O	$C_{16}H_{18}FN_3O_3$·HCl
7l	AA	5,6-$(CH_3)_2$	H	E	53	268–270	EtOH	$C_{18}H_{23}N_3O_3$·HCl
7m	AA	5-F	H	E	47	257–258	EtOH/Et_2O	$C_{16}H_{18}FN_3O_3$·HCl[d]
7n	AA	7-CH_3	H	E	55	250–251	EtOH	$C_{17}H_{21}N_3O_3$·HCl
7o	AA	5-CF_3	H	E	37	222–224	*i*-PrOH	$C_{17}H_{18}F_3N_3O_3$·HCl
7p	AA	6-OCH_3	H	E	65	265–267	EtOH/Et_2O	$C_{17}H_{21}N_3O_4$·HCl
7q	AA	6-$COCH_3$	H	E	74	>270	EtOH	$C_{18}H_{21}N_3O_4$·HCl
8a	AA	H	CH_3	F	46	265–267	EtOH/Et_2O	$C_{17}H_{21}N_3O_3$·HCl
8b	AA	H	C_2H_5	F	38	250 dec.	$(CH_3)_2CO$	$C_{18}H_{23}N_3O_3$·HCl[e]
16	AA	4-CH_3	H	E	75	>270	EtOH	$C_{17}H_{21}N_3O_3$·HCl
17	PP	H	H	*f*	35	>270	EtOH	$C_{17}H_{22}BrN_3O_3$

[a] See Chart II for symbols' explanation. [b] Methods are as described in Schemes I–III. [c] C: calcd, 70.00; found, 69.35. [d] N: calcd, 11.81; found, 11.71. [e] C: calcd, 59.09; found, 58.69. N: calcd, 11.48; found, 11.39. Cl: calcd, 9.69; found, 9.84. [f] See the Experimental Section.

Table II. Physical Data for 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic Acid Esters **11**



compd	R_3[a]	% yield	mp, °C	crystn solvent	formula
11a	HH	38	252–254	EtOH	$C_{17}H_{21}N_3O_3$·HCl
11b	II	18	77–80	EtOAc	$C_{17}H_{21}N_3O_3$·$C_6H_8O_7$[b,c]
11c	JJ	12[d]	254–256	EtOH/Et_2O	$C_{15}H_{17}N_3O_3$·HCl
11d	KK	35[d]	175–178	*i*-PrOH/(*i*-Pr)$_2$O	$C_{15}H_{17}N_3O_3$
11e	LL	10	208–211	EtOH/Et_2O	$C_{16}H_{19}N_3O_3$·HCl
11f	MM	5	73–75[e]		$C_{16}H_{19}N_3O_3$·$C_6H_8O_7$[b,f]
11g	NN	33	>270	EtOH	$C_{13}H_{15}N_3O_3$·HCl

[a] See Chart II for symbols' explanation. [b] Citric acid salt. [c] C: calcd, 54.43; found, 53.87. N: calcd, 8.28; found, 7.91. [d] The reaction was carried out without solvent. [e] Freeze-dried. [f] C: calcd, 53.55; found, 52.96. H: calcd, 5.52; found, 5.64. N: calcd, 8.52; found, 8.39.

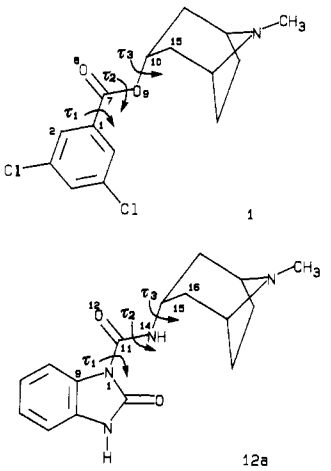
structural formulas of the basic azacycloalkyl groups present in the new compounds are shown in Chart II.

Molecular Modeling

A molecular modeling study was performed in order to verify whether **12a**, a selected representative of the present class of compounds, might fit the pharmacophore model recently proposed by Hibert and co-workers for the 5-HT$_3$ recognition site.[11] Compound **1**, one of the four antagonists used to define the pharmacophore, was chosen as reference compound for superimposition. First, a systematic conformational analysis was carried out for **1** and **12a** in order to evaluate the putative global minimum energy. Rotatable bonds were assigned to both compounds (Scheme IV) and then they were allowed to rotate with defined stepwise increments of the dihedral angles. The energy of each conformer was finally calculated and the global minimum energy was located.

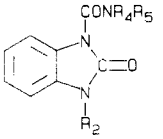
Superimposition was performed with the MULTIFIT program within SYBYL.[13,14] This method is particularly helpful to evaluate a possible three-dimensional arrangement of significant molecular structural features and to verify whether this arrangement is energetically feasible. In fact the method, which is based on molecular mechanics, forces the selected structural features to an optimized fit at the cost of some conformational energy. After the MULTIFIT process each molecule was relaxed to the closest minimum, thus giving the energy of the putative active conformer. The energy difference between the active conformer and the global minimum energy gave a measure as to whether the active conformation was energetically accessible. The structural features taken into account for the matching process were the centroid of the phenyl ring, the ester carbonyl group, the ester oxygen atom, and the tropane nitrogen atom for compound **1**; and the centroid of the imidazole ring, the amide carbonyl group, the amide

Scheme IV



(13) Tripos Associates, St. Louis, MO 63117.
(14) Labanowski, J.; Motoc, I.; Naylor, C.; Mayer, D.; Dammkoehler, R. *Quant. Struct.-Act. Relat.* **1986**, *5*, 138.

Table III. Physical Data for 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxamides 12 and 13



compd	R_2	R_4	R_5[a]	method[b]	% yield	mp, °C	crystn solvent	formula
12a	H	H	AA	H	75	205–207	CH_3CN	$C_{16}H_{20}N_4O_2$
12b	H	H	HH	H	53	269–270	EtOH	$C_{17}H_{22}N_4O_2$·HCl
12c	H	H	CC	H	36	196–198	*i*-PrOH/(*i*-Pr)$_2$O	$C_{15}H_{18}N_4O_2$
12d	H	H	OO	H	8	245–248	EtOH/Et_2O	$C_{16}H_{20}N_4O_2$
12e	H	H	DD	H	18	194–197	CH_3CN	$C_{14}H_{18}N_4O_2$
12f	H	CH_3	HH	H	68	198–200	EtOH	$C_{18}H_{24}N_4O_2$
12g	H	H	GG	H	43	210–211	EtOH	$C_{22}H_{24}N_4O_2$[c]
12h	H	H	BB	H	59	>270	EtOH	$C_{16}H_{20}N_4O_2$·HCl
12i	H	H	II	H	93	220–222	CH_3CN	$C_{17}H_{22}N_4O_2$
13a	CH_3	H	HH	F	47	175–176	EtOH	$C_{18}H_{24}N_4O_2$
13b	CH_3	H	AA	F	16	107–109	(*i*-Pr)$_2$O	$C_{17}H_{22}N_4O_2$
13c	C_2H_5	H	AA	F	46	242–244	$(CH_3)_2CO$	$C_{18}H_{24}N_4O_2$·HCl

[a] See Chart II for symbols' explanation. [b] Methods are as described in Scheme II. [c] N: calcd, 14.88; found, 14.69.

Table IV. Torsional Angles, Relative Energy, and Fitting Index of Representative Conformers

compound	torsional angles,[a] deg			global minimal energy,[b] kcal/mol	ΔE,[c] kcal/mol	RMS,[d] Å
1 (lowest energy conformer)	178.9	185.4	190.7	15.808		
(active conformer)	180.0	185.1	191.0	15.808	0.000	0.00
12a (lowest energy conformer)	180.5	181.6	193.9	45.931		
(active conformer)	180.7	181.5	193.8	47.116	1.185	0.17

[a] See the Experimental Section for definition of the torsional angles. [b] Total energy is the sum of bond stretching, angle bending, torsional, out of plane bending, and van der Waals energy terms (MAXIMIN 2). [c] Difference between the active conformer energy and the global minimum energy. [d] Root mean square index.

nitrogen atom, and the tropane nitrogen atom for compound **12a**. These structural features were chosen according to the 5-HT_3 pharmacophore model.[11]

Results of the fitting experiment are shown in Figure 1 and in Table IV.

Biological Results and Discussion

As seen from the data reported in Table V members of this class of compounds displayed 5-HT_3 antagonistic properties. This was shown by the ability of these molecules to displace binding of the specific 5-HT_3 ligand [^{3}H]ICS 205930[15] in rat brain tissues and from their ability to inhibit the 5-HT_3-mediated component of the von Bezold–Jarisch reflex in rat heart.[16] Interestingly, the ligand studies agreed with the functional in vivo results. The linear regression of the pK_i (−log K_i) values derived from binding experiments with the negative logarithms of the ED_{50} values (−log ED_{50}) obtained in the von Bezold–Jarisch reflex experiments is shown in Figure 2.

The specificity of interaction with 5-HT_3 receptors was also investigated for compounds **7a**, **7h**, **8a**, **8b**, **11a**, **12a**, **12b**, **12c**, **13a**, and **13c**. Interaction with 5-HT_{1A}, 5-HT_2, DA_2, and benzodiazepine receptors occurred with affinities in the range of 10^{-4}–10^{-6} M in radioligand binding assays, and similarly, no significant effect on monoamine reuptake was observed in synaptosomal preparations.[17] Some antimuscarinic activity was detectable only for parent compound **7a**, which displayed some affinity (K_i = 400 nM)

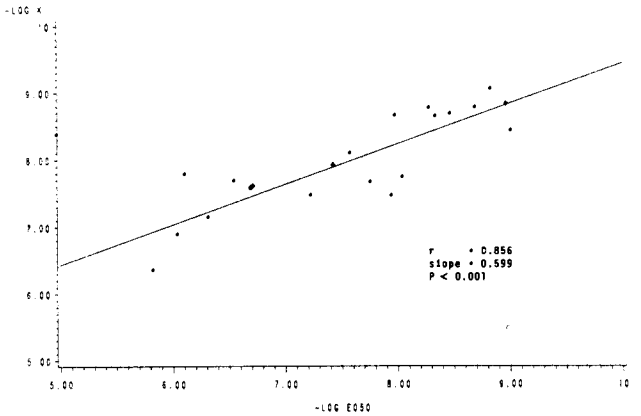


Figure 2. Correlation between the binding affinities (−log K_i) and the activities in the von Bezold–Jarisch reflex (−log ED_{50}).

in the displacement of bound [^{3}H]-*N*-methylscopolamine in the cortex tissue.[18]

The antagonistic potency of the described compounds was very sensitive to the stereochemistry of the azabicycloalkyl substituents. Endo-substituted azabicycloalkyl derivatives such as **7a**, **11a**, **11f**, **12a**, and **12b** proved to be up to 1000 times more potent than the corresponding exo isomers **7b**, **11b**, **11e**, **12h**, and **12i**. Also, the presence of substituents on the phenyl ring of the benzimidazole nucleus was critical for 5-HT_3 affinity: the introduction of any substituent in the positions 5, 6, and 7 depressed affinity, as shown by compounds **7h–q**, in comparison with the unsubstituted analogue **7a**. The fact that this decrement of affinity is less pronounced for compounds bearing a small fluorine substituent (**7k**, **7m**) suggests a steric constraint by the 5-HT_3 receptor. The presence of a

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(16) Paiutal, A. S. *Physiol. Rev.* **1973**, *53*, 159.
(17) Bechtel, C.; Mierau, J., Biochemistry Dept., Boehringer Ingelheim, Ingelheim, personal communication.
(18) Schiavi, G. B., Biochemistry Dept., Istituto De Angeli, Milan, personal communication.

Table V

compd	5-HT$_3$ binding affinity[a] for rat cortex: K_i,[c] nM	Bezold–Jarisch reflex:[b] ED_{50},[d] nM/kg iv
7a	21.4 (±2.90)	17.9 (12.6–25.9)
7b	>1000	3982 (1125–14230)
7c	16.3 (±1.00)	800 (348–1838)
7d	>1000	>3000
7e	>1000	>3000
7f	>1000	>3000
7g	>1000	>3000
7h	>1000	>3000
7i	>1000	>3000
7j	>1000	>3000
7k	33.9 (±11.02)	62 (31.3–122.1)
7l	>1000	>3000
7m	26.2 (±3.65)	204 (103.2–1024)
7n	306 (±74)	>3000
7o	>1000	>3000
7p	>1000	nd[e]
7q	>1000	>3000
8a	12.0 (±2.94)	38 (28.5–47.6)
8b	18.0 (±4.10)	9.7 (7.6–12.8)
11a	2.17 (±0.56)	10.8 (6.0–18.7)
11b	>1000	>3000
11c	>1000	>3000
11d	>1000	>3000
11e	>1000	>3000
11f	nd[e]	18.9 (14.9–24.2)
11g	72.4 (±20.04)	487 (205–1162)
12a	3.75 (±0.97)	1 (0.67–1.66)
12b	1.53 (±0.33)	1.1 (0.54–2.4)
12c	2.07 (±0.36)	3.5 (2.1–5.6)
12d	20.2 (±0.22)	289 (210–399)
12e	436 (±75)	1520 (1028–2249)
12f	>1000	>3000
12g	>1000	>3000
12h	>1000	>3000
12i	130 (±26)	905 (496–1650)
13a	0.89 (±0.42)	1.5 (0.85–2.56)
13b	1.70 (±0.43)	5.4 (3.1–9.2)
13c	2.30 (±0.66)	5.1 (4.1–6.5)
16	7.94 (±0.89)	30.1 (19.3–46.9)
17	33.6 (±9.50)	9.3 (6.1–14.1)
1 (MDL-72222)	24.4 (±5.80)	195 (173–219)
2 (ICS 205930)	1.71 (±0.29)	2.1 (1.5–2.8)

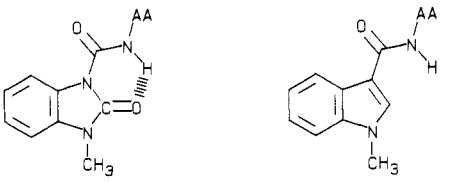
[a] [^{3}H]ICS 205930 labeled 5-HT$_3$ sites. [b] Antagonism of bradycardia induced by bolus iv injection of 20 μg/kg 5-HT. [c] K_i is defined as the concentration of compound that inhibited 50% of the specific binding (±SEM in brackets) and was determined as described in the Experimental Section. [d] ED_{50}, i.e. the dose of antagonist causing 50% reduction of serotonin effect, was calculated by linear-regression analysis. Values shown are the means ±95% CL. [e] Not determined.

substituent in position 4 as in **16** had no influence on activity; similarly, substituents in position 3 are well tolerated.

Compounds bearing a carboxamido moiety between the benzimidazolone and the basic side chain showed an antagonistic activity about 10 times more pronounced than that of the corresponding derivatives bearing an ester moiety as seen from the activity values obtained for **12a**, **12b**, **12c**, **12e**, **13b**, and **13c** in comparison with **7a**, **11a**, **7c**, **7d**, **8a**, and **8b**, respectively.

The presence of an intramolecular hydrogen bond in carboxamido derivatives between the amide nitrogen and the carbonyl group of the benzimidazolone was revealed by infrared spectroscopic studies. Shifts of the frequencies relative to the amide N–H stretching of the model compounds **13b** and **19**[19] (Chart III) measured in the solid state (Nujol) and $CHCl_3$ solution (1% w/v) were compared. The

Chart III



13b 19

frequency shift to a higher wavelength was consistently lower for **13b** (20 cm^{-1}) in comparison to that of **19** (105 cm^{-1}), which cannot form the intramolecular hydrogen bond. These results are in agreement with those found in *o*-methoxy-substituted benzamides, a class of substances known to exist in a strongly hydrogen-bound conformation.[20] The hydrogen-bound conformation found for **13b** was confirmed in the crystalline state for **12a** by single-crystal X-ray diffraction analysis.[21]

1,3-Diacylbenzimidazolones are known to exist with the endocyclic and exocyclic carbonyls in an antiperiplanar conformation in order to minimize the repulsive dipole–dipole interaction;[22] rotation about the bond between the endocyclic nitrogen and the exocyclic carbonyl carbon atoms is restricted. In our carboxamido derivatives the intramolecular hydrogen bond may further stabilize that particular conformation of carbonyls by formation of a pseudo six-membered ring; the higher 5-HT$_3$ receptor affinity and activity in comparison to ester derivatives might therefore find a reasonable explanation.

Molecular modeling studies showed that this hydrogen-bound conformation might be the bioactive one in the interaction of **12a** with the 5-HT$_3$ receptor, since it fit quite well, as measured by the RMS index, when superimposed on the reference compound **1**, one of the antagonists used to define the 5-HT$_3$ pharmacophore model (Figure 1). Coplanarity of the imidazole ring with the amide group is evident from the values of the torsional angles. Both **1** and **12a** show the same distance (7.2 Å) between the tropane nitrogen atoms and the centers of the reference rings, and between the same nitrogen atoms and the oxygen atoms of the ester and amide carbonyl groups (5.3 Å). The distance between the tropane nitrogen atom and the plane defined by the reference ring is 2.0 Å for **1** and 1.8 Å for **12a**. These values favorably agree with those reported (6.7, 5.3, and 1.6 Å, respectively) for the proposed 5-HT$_3$ pharmacophore.[11] Moreover, the active conformations of both compounds are easily accessible from the respective lowest energy conformers (Table IV). The distance between the amide hydrogen atom and the oxygen atom of the benzimidazolone carbonyl (2.0 Å), the distance between the donor and acceptor groups (2.7 Å), and the D–H–A angle (142.3°) are indicative of an intramolecular hydrogen bond in **12a**. In conclusion, the data presented demonstrate that this class of compounds is endowed with a high antagonistic activity on 5-HT$_3$ receptors, together with a high selectivity toward other receptor systems. In order to assess the potential therapeutic usefulness of this class of substances, compounds **8b**, **12a**, **12b**, and **13c** are undergoing deeper pharmacological evaluation as antiemetics in pharmacological models of chemotherapy-induced emesis.

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Experimental Section

Chemistry. Starting materials that were not commercially available were prepared according to already published procedures: *exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol,[23] 1,2,6-trimethylpiperidin-4-ol,[24] *endo*-8-ethyl-8-azabicyclo[3.2.1]octan-3-ol,[25] *endo*-8-benzyl-8-azabicyclo[3.2.1]octan-3-ol,[25] 5-fluoro-2-nitroaniline,[26] 5-methoxy-2-nitroaniline,[27] 5-acetyl-2-nitroaniline,[28] *endo*-9-methyl-9-azabicyclo[3.3.1]nonan-3-ol,[29] *exo*-9-methyl-9-azabicyclo[3.3.1]nonan-3-ol,[29] 1-azabicyclo[2.2.2]octan-4-ol,[30] *endo*-7-methyl-7-azabicyclo[2.2.1]heptan-2-ol,[31] *cis*-2-methyl-2-azabicyclo[2.2.2]octan-5-ol,[32] *trans*-2-methyl-2-azabicyclo-[2.2.2]octan-5-ol,[32] *endo*-8-azabicyclo[3.2.1]octan-3-ol,[33] *endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-amine,[34] *endo*-9-methyl-9azabicyclo[3.3.1]nonan-3-amine,[35] *endo*-1-azabicyclo[3.3.1]nonan-4-amine,[36] 1-methylpiperidin-4-amine,[37] *endo*-8-benzyl-8-azabicyclo[3.2.1]octan-3-amine,[38] *exo*-8-methyl-8-azabicyclo-[3.2.1]octan-3-amine.[38]

Melting points are uncorrected and were obtained on a Büchi capillary melting point apparatus. Infrared spectra were run in Nujol or as 2.5% $CHCl_3$ solutions in KBr cells (0.1 mm) on a Perkin-Elmer 337 spectrophotometer; selected compounds were run as 1% $CHCl_3$ solutions. ^1H NMR spectra were recorded on either a Varian T-60 (60-MHz) spectrometer or a Varian VXR 200 (200-MHz) spectrometer: chemical shift values are given in ppm (δ) against the internal standard tetramethylsilane. The new compounds were analyzed for C, H, N and the analytical data were within ± 0.4% of the theoretical values. The indicated yields have not been optimized. The physical data for the intermediates **5** and **6** were reported elsewhere.[39]

Progress of the reactions as well as purity of the compounds were monitored by thin-layer chromatography (TLC) on silica gel 60 F-254 plates (Merck) eluted by appropriate solvents. Column chromatographies were performed on silica gel 60 (Merck, 70–230 mesh) and were eluted by appropriate solvents.

Method A. *endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl Chloroformate Hydrochloride (4a). To a stirred suspension of tropine hydrochloride (43.0 g, 0.242 mol) in dry CH_3CN (440 mL) was added trichloromethyl chloroformate (62.23 g, 0.314 mol) dropwise at 0 °C. The reaction mixture was stirred at this temperature for 30 min and, then, at room temperature for 24 h more until a clear solution was obtained. The solvent was removed under vacuum and the residue was triturated with Et_2O to afford **4a** (56.8 g, 98%), sufficiently pure to be used in the following step, mp 132–136 °C. Anal. ($C_9H_{14}ClNO_2$·HCl) C, H, Cl, N. The following compounds were prepared similarly: *exo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl chloroformate hydrochloride (**4b**) [95%, mp 137–140 °C. Anal. ($C_9H_{14}ClNO_2$·HCl) C, H, Cl, N.], 1-azabicyclo[2.2.2]oct-3-yl chloroformate hydrochloride (**4c**) [97%, mp 130–132 °C. Anal. ($C_8H_{12}ClNO_2$·HCl) C, H, Cl, N.], 1-methylpiperidin-4-yl chloroformate hydrochloride (**4d**) [98%, mp 152–153 °C. Anal. ($C_7H_{12}ClNO_2$·HCl) C, H, Cl, N.], 1,2,6-trimethyl-piperidin-4-yl chloroformate hydrochloride (**4e**) [89%, mp 141–143 °C. Anal. ($C_9H_{16}ClNO_2$·HCl) C, H, Cl, N.], *endo*-8-ethyl-8-azabicyclo[3.2.1]oct-3-yl chloroformate hydrochloride (**4f**) (90%, mp 145–147 °C. Anal. ($C_{10}H_{16}ClNO_2$·HCl) C, H, Cl, N.], *endo*-8-benzyl-8-azabicyclo[3.2.1]oct-3-yl chloroformate hydrochloride (**4g**) [93%, mp 152–153 °C. Anal. ($C_{15}H_{18}ClNO_2$·HCl) C, H, Cl, N.].

Method B. *endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl *N*-(2-Nitrophenyl)carbamate Hydrochloride (5a). 2-Nitroaniline (5.0 g, 36 mmol) was dissolved in dry pyridine (75 mL) at room temperature and **4a** (8.7 g, 36 mmol) was then added portionwise with stirring. Once the initial exothermic reaction had subsided, the mixture was heated to 80 °C and stirred for 4 h. Upon cooling, pure **5a** hydrochloride crystallized as yellow needles; it was recovered by filtration and washed with a little pyridine and Et_2O: yield 6.5 g, IR (Nujol) ν 1720, 1605, 1590, 1520, 1350, 1250–1220 cm^{-1}; ^1H NMR (DMSO-d_6/$CDCl_3$ 5:2) δ 10.22 (b, 1 H), 9.86 (s, 1 H), 7.97 (dd, 1 H), 7.76–7.52 (m, 2 H), 7.31 (m, 1 H), 4.90 (bt, 1 H), 3.87 (bs, 2 H), 2.69 (d, 3 H), 2.8–1.9 (m, 8 H).

Method C. *endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl *N*-(2-Aminophenyl)carbamate (6a). A solution of **5a** (6.5 g, 19 mmol) in 70% aqueous EtOH (200 mL) was hydrogenated in the presence of 10% Pd/C (0.3 g) at room temperature and atmospheric pressure. After hydrogen uptake stopped, the reaction mixture was filtered and concentrated to dryness. The residue was taken up into water, washed with 2 × 100 mL of Et_2O, made basic with NaOH, and extracted with EtOAc. The organic phase was dried over $MgSO_4$, the solvent was evaporated to dryness, and crude **6a** was crystallized from diisopropyl ether: yield 4.4 g; IR (Nujol) ν 3430, 3260, 1680, 1605, 1690, 1540, 1250–1230 cm^{-1}; ^1H NMR (DMSO-d_6/$CDCl_3$ 5:2) δ 8.19 (bs, 1 H), 7.07 (d, 1 H), 6.92–6.35 (m, 3 H), 4.75 (t, 1 H), 4.69 (s, 2 H), 2.96 (bs, 2 H), 2.14 (s, 3 H), 2.19–1.51 (m, 8 H).

Method D. *endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl *N*-(2-Amino-5-fluorophenyl)carbamate (6k). To a stirred suspension of **5k**·HCl (2.0 g, 5.5 mmol) in 17% HCl (120 mL) was added iron powder (1.55 g, 27.8 mmol) at room temperature. Stirring was continued for 30 min, then the reaction mixture was filtered and the filtrate was made basic with aqueous NaOH. The product which separated was extracted into CH_2Cl_2 and purified by a flash chromatography technique (eluent CH_2Cl_2/MeOH/32% NH_4OH 80:20:2) and 1.2 g of pure **6k** was obtained: IR (Nujol) ν 3440, 3340, 1690, 1605, 1530, 1250–1220 cm^{-1}; ^1H NMR (DMSO-d_6/$CDCl_3$ 5:2) δ 8.38 (s, 1 H), 7.14 (bd, 1 H), 6.7–6.6 (m, 2 H), 4.82 (bt, 1 H), 4.66 (bs, 2 H), 3.01 (bs, 2 H), 2.20 (s, 3 H), 2.20–1.56 (m, 8 H).

Method E. *endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxylate (7a). A solution of **6a** (4.14 g, 15 mmol) and triethylamine (2.5 mL) in dry CH_2Cl_2 (65 mL) was slowly added to a cooled (5 °C) solution of trichloromethyl chloroformate (3.26 g, 16.5 mmol) in the same solvent (20 mL) with stirring. When the addition was over (1 h), the temperature was allowed to reach 25 °C while stirring was continued for another 60 min. Diluted HCl was then added and the organic phase was discarded. The aqueous phase was made basic with saturated Na_2CO_3 and extracted with CH_2Cl_2. After the usual workup, the title compound **7a** (2.2 g) was obtained as a white solid: IR (Nujol) ν 1760, 1715, 1630, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94 (dd, 1 H), 7.25–6.91 (m, 3 H), 5.26 (t, 1 H), 3.19 (bs, 2 H), 2.35 (s, 3 H), 2.49–1.87 (m, 8 H). The proton in position 3 was not detected.

Method F. *endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2,3-Dihydro-3-ethyl-2-oxo-1*H*-benzimidazole-1-carboxylate Hydrochloride (8b). Sodium hydride as an 80% dispersion in mineral oil (0.26 g, 8.6 mmol) was added portionwise to a stirred suspension of **7a** (2.6 g, 8.6 mmol) in dry DMF at room temperature. After hydrogen evolution subsided (90 min), ethyl iodide (1.36 g, 8.7 mmol) was added and the reaction mixture was stirred for 2 h more. The solvent was removed under vacuum and the residue was taken up into diluted HCl and washed with EtOAc

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Upon addition of saturated Na_2CO_3, a solid separated which was recovered by filtration. Crude **8b** was purified by crystallization of the hydrochloride salt: yield 1.2 g; IR (Nujol) ν 1760–1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.45 (b, 1 H), 7.99 (dd, 1 H), 7.29–6.87 (m, 3 H), 5.45 (t, 1 H), 3.91 (q, 2 H), 3.78 (bs, 2 H), 2.78 (d, 3 H), 3.31–2.07 (m, 8 H), 1.35 (t, 3 H).

2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carbonyl Chloride (10). In a well-ventilated hood, 2,3-dihydro-1*H*-benzimidazole-2-one (**9**; 170 g, 1.27 mol) and activated charcoal (3.0 g) were suspended in dry THF (3.4 L); trichloromethyl chloroformate (115 mL, 0.95 mol), dissolved in the same solvent (200 mL), was added dropwise at room temperature under stirring. The reaction apparatus was equipped with a gas-outlet tube dipping into a trap containing concentrated NH_4OH. The reaction mixture was refluxed for 12 h, then heating was removed while stirring was continued for 5 h more. The solid was removed by filtration. Evaporation of the solvent left an oily crude material which was triturated with cold Et_2O (500 mL). Compound **10** (167.4 g, 67%) was used as such in the next reactions, mp 193–197 °C dec (lit.[12] 179–184 °C).

Method G. *endo*-9-Methyl-9-azabicyclo[3.3.1]non-3-yl 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxylate Hydrochloride (11a). A suspension of **10** (0.56 g, 2.8 mmol) and *endo*-9-methyl-9-azabicyclo[3.3.1]nonan-3-ol hydrochloride (0.5 g, 2.6 mmol) in *o*-dichlorobenzene (5 mL) was heated to 110 °C under stirring for 3 h while HCl evolution took place. After cooling the white solid was recovered by filtration, washed with Et_2O, and crystallized to afford 0.35 g of pure **11a**: IR (Nujol) ν 3100, 1760–1740, 1635, 1610 cm^{-1}; ^1H NMR (DMSO-d_6/$CDCl_3$ 5:2) δ 11.19 (s, 1 H), 10.7 (b, 1 H), 7.75 (dd, 1 H), 7.20–6.97 (m, 3 H), 5.30 (t, 1 H), 3.52 (bs, 2 H), 2.84 (bs, 3 H), 3.10–1.17 (m, 10 H).

Method H. *endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxamide (12a). To a solution of *endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (5.0 g, 35.7 mmol) in THF (100 mL) was added 2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carbonyl chloride (**10**; 9.6 g, 49 mmol) portionwise under stirring at room temperature. The temperature of the suspension rose spontaneously up to 45 °C, then decreased. Stirring was continued for 3 h, then the reaction mixture was concentrated to dryness and the residue was taken up into diluted HCl. The acid phase was washed with EtOAc and upon addition of diluted NaOH a solid separated which was recovered by filtration. Crystallization from CH_3CN afforded 8.1 g of the title compound: IR (Nujol) ν 3250, 3220, 1730, 1690, 1620, 1610, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.25 (d, 1 H), 8.19 (m, 1 H), 7.25–6.87 (m, 3 H), 4.20 (dt, 1 H), 3.26 (bs, 2 H), 2.37 (s, 3 H), 2.53–1.69 (m, 8 H). The proton in position 3 of the benzimidazole moiety was not detected. Colorless crystals of the hydrochloride were obtained from a solution of the corresponding base in EtOH, by adding anhydrous HCl, mp 270 °C. Anal. ($C_{16}H_{20}N_4O_2$·HCl) C, H, Cl, N.

***endo*-*N*,9-Dimethyl-9-azabicyclo[3.3.1]nonan-3-amine (18).** To a solution of 9-methyl-9-azabicyclo[3.3.1]nonan-3-one (pseudopelletierine;[40] 1.7 g, 11.1 mmol) in anhydrous EtOH (30 mL) was added methylamine (10 mL of a 33% solution in EtOH) and the resulting mixture was left aside for 4 days in a stoppered flask. The mixture was then transferred into a hydrogenation flask containing 0.2 g of reduced PtO_2, ammonium acetate (1.0 g), and EtOH (40 mL). The mixture was hydrogenated overnight at room temperature and atmospheric pressure, then it was filtered from the catalyst and concentrated to dryness. It was taken up into water (50 mL), made strongly basic with NaOH, and extracted once with EtOAc (30 mL). The aqueous phase was saturated with solid K_2CO_3 and again extracted with CH_2Cl_2. Evaporation of the combined organic layers left 1.4 g (75%) of the title compound as slightly yellow liquid which was used without further purification: ^1H NMR ($CDCl_3$) δ 3.03 (bd, 2 H), 2.93 (m, 1 H), 2.46 and 2.43 (2 s, 6 H), 2.35 (m, 2 H), 2.07 (bs, 1 H), 2.00–1.94 (m, 3 H), 1.44 (bd, 1 H), 1.12 (m, 2 H), 0.96 (m, 2 H).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl *N*-(2-Amino-3-methylphenyl)carbamate (15).** This was prepared according to method B starting from 2,3-diaminotoluene (**14**) and **4a**, using pyridine as solvent. Compound **15** was purified by a flash chromatography technique (eluent CH_2Cl_2/MeOH/32% NH_4OH 90:10:1): yield 17%; oil; IR (Nujol) ν 3440, 3360, 3220, 1710–1690, 1610, 1530, 1250–1220 cm^{-1}; ^1H NMR (DMSO-d_6/$CDCl_3$ 5:2) δ 8.28 (bs, 1 H), 6.99 (d, 1 H), 6.80 (d, 1 H), 6.46 (dd, 1 H), 4.79 (bt, 1 H), 4.43 (bs, 2 H), 3.06 (bs, 2 H), 2.22 (s, 3 H), 2.11 (s, 3 H), 2.22–1.56 (m, 8 H). Anal. ($C_{16}H_{23}N_3O_2$) C, H, N.

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2,3-Dihydro-4-methyl-2-oxo-1*H*-benzimidazole-1-carboxylate Hydrochloride (16).** This was prepared according to method E: IR (Nujol) ν 3170, 3120, 1745, 1635, 1610 cm^{-1}; ^1H NMR (DMSO-d_6/$CDCl_3$ 5:2) δ 11.34 (s, 1 H), 10.95 (b, 1 H), 7.64 (m, 1 H), 6.99–6.96 (m, 2 H), 5.20 (bt, 1 H), 3.88 (bs, 2 H), 2.69 (d, 3 H), 2.90–2.52 (m, 4 H), 2.30 (s, 3 H), 2.30–2.11 (m, 4 H).

***endo*-3-[[(2,3-Dihydro-2-oxo-1*H*-benzimidazol-1-yl)-carbonyl]oxy]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Bromide (17).** A solution of **7a** (0.5 g, 1.6 mmol) in acetone (60 mL) was added in 40 min to a stirred solution of methyl bromide (3.8 g, 40 mmol) in a 1:1 mixture of acetone and Et_2O at 0.5 °C. The reaction flask was closed and left at room temperature overnight. Pure **17** (0.22 g) crystallized and was recovered by filtration. IR (Nujol) ν 1730, 1620, 1610, cm^{-1}; ^1H NMR (DMSO-d_6/$CDCl_3$ 5:2) δ 11.23 (s, 1 H), 7.82 (dd, 1 H), 7.19–7.00 (m, 3 H), 5.32 (t, 1 H), 3.94 (s, 2 H), 3.22 (s, 3 H), 3.11 (s, 3 H), 2.75–2.08 (m, 8 H).

Molecular Modeling. Molecular modeling studies were performed on an Evans and Sutherland PS 390 color raster graphics terminal coupled to a VAX 8250 computer. The molecules were superimposed, displayed, and manipulated by using the SYBYL program, version 5.22.[13]

Atomic coordinates of **1**, as the *p*-toluenesulfonate salt monohydrate, and **12a**, as the hydrochloride salt, were taken from X-ray data.[21,41] The solid-state conformation of each compound was chosen as the starting conformation and was optimized with the MAXIMIN 2 program within SYBYL. Conformational analyses were performed by employing the SEARCH option within SYBYL by allowing the selected rotatable bonds of each compound to rotate with stepwise increments of the dihedral angles. These were defined as τ_1 [C(2)–C(1)–C(7)–O(9)], τ_2 [C(1)–C(7)–O(9)–C(10)], and τ_3 [C(7)–O(9)–C(10)–C(15)] for compound **1** and τ_1 [C(9)–N(1)–C(11)–N(14)], τ_2 [N(1)–C(11)–N(14)–C(15)], and τ_3 [C(11)–N(14)–C(15)–C(16)] for compound **12a**. Selected increments for compound **1** were τ_1, 180°; τ_2, 5°; τ_3, 5°; and for compound **12a** they were τ_1, 180°; τ_2, 180°; τ_3 5° (Scheme IV). The resulting conformers were optimized by using the MAXIMIN 2 program.

A spring force constant of 20 mdyn/Å was used for each atomic set during the MULTIFIT analysis. The number of iterations used for fitting was 120. Hydrogen atoms were included during the optimization process but omitted for display.

Radioligand-Binding Assay. The 5-HT_3 serotonin receptor in the rat cerebral cortex (P2 fraction) was labeled with [^{3}H]ICS 205930 (82.7 Ci/mmol; New England Nuclear). Tissue was homogenated in 50 mM TRIS·HCl buffer pH 7.4 containing 0.1% ascorbate, 4 mM $CaCl_2$, and 10 μM pargyline and diluted to have a final protein concentration of about 500 μg/mL. The experiments were performed by incubating the homogenate (450 μL) in the presence of 0.5–2.0 nM [^{3}H]ICS 205930 and different concentrations of the tested compounds dissolved in the assay buffer (50 μL), at 30 °C for 30 min. Nonspecific binding was determined in the presence of 10 μM compound **1**. To separate bound from free radioligand, an automatic filtration technique (SKATRON) was employed with GF/B filters. All the experiments were performed in triplicate and the data were evaluated by computer fit analysis.

Pharmacology. The antagonism of 5-HT-induced von Bezold–Jarisch reflex was measured according to the following method.

The femoral artery of urethane-anesthetized rats was cannulated and connected to a pressure transducer. Heart rate was derived from the arterial blood pressure signal using a tachometer. Bolus intravenous infusion of 20 μg/kg serotonin repeated every

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15 min reproducibly elicited the von Bezold–Jarisch reflex. Antagonists were injected iv 5 min prior serotonin, and their effect was expressed as percent inhibition of serotonin response. ED_{50} were calculated by linear regression analysis. Values shown are the means ± 95% CL.

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Registry No. **4a**·HCl, 123259-23-4; **4b**·HCl, 123259-28-9; **4c**·HCl, 123259-24-5; **4d**·HCl, 127595-09-9; **4e**·HCl, 123259-26-7; **4f**·HCl, 123259-25-6; **4g**·HCl, 123259-27-8; **5a**·HCl, 123259-36-9; **5k**·HCl, 123259-43-8; **6a**, 123259-35-8; **6b**, 123259-52-9; **6c**, 123259-51-8; **6d**, 123279-50-5; **6e**, 123259-53-0; **6f**, 123259-54-1; **6g**, 127595-15-7; **6h**, 123259-49-4; **6i**, 123259-50-7; **6j**, 123259-55-2; **6k**, 123279-51-6; **6l**, 123259-56-3; **6m**, 123259-57-4; **6n**, 123259-58-5; **6o**, 123259-59-6; **6h**, 123259-60-9; **6q**, 123259-61-0; **7a**, 127595-10-2; **7b**, 127595-22-6; **7b**·HCl, 123258-88-8; **7c**, 127595-23-7; **7c**·HCl, 123258-87-7; **7d**, 127595-24-8; **7d**·HCl, 123258-89-9; **7e**, 127595-25-9; **7e**·HCl, 123258-90-2; **7f**, 127595-26-0; **7f**·HCl, 123258-91-3; **7g**, 123279-46-9; **7h**, 123279-43-6; **7i**, 123279-44-7; **7j**, 127595-27-1; **7j**·HCl, 123258-92-4; **7k**, 127595-28-2; **7k**·HCl, 123258-93-5; **7l**, 127595-29-3; **7l**·HCl, 123258-94-6; **7m**, 127595-30-6; **7m**·HCl, 123279-45-8; **7n**, 127595-31-7; **7n**·HCl, 123258-96-8; **7o**, 127595-32-8; **7o**·HCl, 123258-97-9; **7p**, 127595-33-9; **7p**·HCl, 123258-98-0; **7q**, 127595-34-0; **7q**·HCl, 123258-95-7; **8a**, 127595-35-1; **8a**·HCl, 123259-05-2; **8b**, 127595-36-2; **8b**·HCl, 127595-11-3; **9**, 615-16-7; **10**, 65657-53-6; **11a**, 123259-00-7; **11a**·HCl, 127595-12-4; **11b**, 127595-16-8; **11b**·$C_6H_8O_7$, 127595-17-9; **11c**, 127595-38-4; **11c**·HCl, 123259-02-9; **11d**, 123259-03-0; **11e**, 127642-62-0; **11e**·HCl, 127595-18-0; **11f**, 123288-60-8; **11f**·$C_6H_8O_7$, 123288-61-9; **11g**, 127595-39-5; **11g**·HCl, 127595-19-1; **12a**, 123258-84-4; **12a**·HCl, 127618-28-4; **12b**, 123258-83-3; **12b**·HCl, 123259-06-3; **12c**, 123259-07-4; **12d**, 123259-08-5; **12e**, 123259-09-6; **12f**, 123259-12-1; **12g**, 123259-13-2; **12h**, 127595-40-8; **12h**·HCl, 127595-20-4; **12i**, 127595-21-5; **13a**, 123259-10-9; **13b**, 127595-42-0; **13c**, 127595-41-9; **13c**·HCl, 127595-43-1; **14**, 2687-25-4; **15**, 127595-13-5; **16**, 127595-37-3; **16**·HCl, 127595-14-6; **17**, 123259-14-3; **18**, 123259-33-6; AA-OH·HCl, 2292-08-2; BB-OH, 135-97-7; JJ-OH, 26458-74-2; FF-OH, 1748-08-9; GG-OH, 18717-73-2; 2-$NO_2C_6H_4NH_2$, 88-74-4; HH-OH·HCl, 60205-58-5; AA-NH_2, 87571-88-8; II-OH, 6376-00-7; KK-OH, 99445-15-5; LL-OH, 16576-15-1; MM-OH, 37778-50-0; NN-OH, 5382-16-1; HH-NH_2, 76272-56-5; CC-NH_2, 6238-14-8; OO-NH_2, 127642-61-9; DD-NH_2, 41838-46-4; GG-NH_2, 76272-35-0; BB-NH_2, 81487-04-9; II-NH_2, 76272-41-8; 1-methyl-4-piperidinol, 106-52-5; 1,2,6-trimethyl-4-piperidinol, 90226-91-8; pseudopelletierine, 552-70-5.

Supplementary Material Available: The atomic coordinates of compounds **1** and **12a** in their active conformations (Figure 1) are available (2 pages). Ordering information is given on any current masthead page.

Synthesis and Biological Evaluation of New Antimuscarinic Compounds with Amidine Basic Centers. A Useful Bioisosteric Replacement of Classical Cationic Heads

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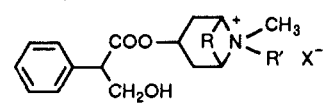
Amidines (guanidine, formamidine, and acetamidine) were introduced as substitutes for the cationic heads present in atropine, scopolamine, and corresponding quaternary derivatives. Amidine systems are intermediate in structure between tertiary amines and quaternary compounds, at least as regards ionization and electronic properties, but differ from the latter in shape (planar not tetrahedral). They have additional binding opportunities on account of their hydrogen-bond-forming capacity. The effect of the introduction of these cationic heads on the affinity for different muscarinic acetyl choline receptor (m-AcChR) subtypes was investigated in vitro, in binding displacement studies, and in functional tests on isolated organs. All new compounds (**3a,b–5a,b**) showed high affinity for the m-AcChR considered, comparable or slightly inferior to that of the parent drugs (**1a–e**). The new amidine derivatives proved effective as spasmolytic agents, with little tendency to cause central effects. However, no separation was achieved of spasmolytic and other untoward effects, like inhibition of salivation. Thus, amidine moieties are effective bioisosteric substitutes for conventional cationic heads present in antimuscarinic agents. Their unusual physical–chemical properties make them useful tools when modulation of pharmacokinetic or pharmacodynamic effects is required.

Muscarinic antagonists have long been employed in the treatment of several diseases in which it is useful to limit the effects of the natural transmitter acetylcholine. Their efficacy in the treatment of gastrointestinal disorders such as peptic ulcer and smooth-muscle spasms has led to the bothersome, sometimes troublesome side effects produced by their lack of selectivity in blocking muscarinic receptors (m-AcChR) in different organs.[1] Quaternization of the tertiary amino function is a commonplace chemical manipulation in this class of substances, widely utilized to control untoward effects especially in the central nervous system (CNS). Even though the inherent character of quaternary compounds negatively affects their absorption from the gastrointestinal tract, and hence their oral

Chart I. Classical Antimuscarinic Agents of Both Tertiary Amino and Quaternary Ammonium Type



1a: R = $-CH_2CH_2-$ R' = H (atropine)
b: R = $-CH(O)CH-$ R' = H (scopolamine)
c: R = $-CH_2CH_2-$ R' = CH_3 (atropine *N*-methyl bromide)
d: R = $-CH(O)CH-$ R' = CH_3 (scopolamine *N*-methyl bromide)
e: R = $-CH(O)CH-$ R' = $(CH_2)_3CH_3$ (scopolamine *N*-butyl bromide)

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