Phenylimidazolidin-2-one Derivatives as Selective 5-HT_3 Receptor Antagonists and Refinement of the Pharmacophore Model for 5-HT_3 Receptor Binding

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Received January 31, 1997[⊗]

A possible bioisosterism between the benzamido and the phenylimidazolidin-2-one moieties has been suggested on the basis of the similarity between the molecular electrostatic potential (MEP) of metoclopramide, a D_2 receptor antagonist with weak 5-HT_3 receptor antagonist properties, and zetidoline, a D_2 receptor antagonist. Starting from this premise, a series of phenylimidazolidin-2-one derivatives bearing a basic azabicycloalkyl or an imidazolylalkyl moiety were synthesized and evaluated for 5-HT_3 receptor radioligand binding affinity ([^{3}H]-GR 43694). *In vitro* 5-HT_3 receptor antagonist activity was tested in the guinea pig ileum assay (GPI). A number of high-affinity ligands were shown to be potent 5-HT_3 receptor antagonists *in vivo* as determined by inhibition of the Bezold−Jarisch reflex in the anesthetized rat. In general, the imidazolylalkyl derivatives were found to be more active than azabicycloalkyls. 1-(3,5-Dichlorophenyl)-3-[(5-methyl-1*H*-imidazol-4-yl)methyl]imidazolidin-2-one (**58**), in particular, displayed very high affinity for the 5-HT_3 receptor (K_i of 0.038 nM) with a K_b of 5.62 nM in the GPI assay, being more potent than the reference compounds (ondansetron, tropisetron, granisetron, and BRL 46470) tested. **58** showed an ID_{50} comparable to that of ondansetron (2.2 μg/kg iv) in the Bezold−Jarisch reflex. A molecular modeling study based on this structurally novel series of compounds allowed the refinement of previously reported 5-HT_3 receptor antagonist pharmacophore models.

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) acts as a neurotransmitter, neuromodulator, and hormone, exhibiting profound pharmacological activities both in the central nervous system and in the periphery. 5-HT is involved in numerous physiological and pathological processes interacting with various distinct membrane receptors. Four main 5-HT receptorial subclasses, 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4, are characterized.[1] These receptor subtypes have been confirmed by molecular biology techniques. Molecular cloning studies have revealed the existence of additional receptor subtypes such as 5-HT_5, 5-HT_6, and 5-HT_7, but very little pharmacological data are available, and their physiological relevance is not yet clear.[2] The majority of the 5-HT receptors belongs to a G-protein-paired receptor family. The 5-HT_3 receptors, on the other hand, are coupled directly to a cation channel and are present within the central and peripheral nervous system.[3] Electrophysiological analysis of 5-HT_3 receptor function reveals that agonist interaction mediates the opening of an ion channel permeable to monovalent cations.[4] The development of selective antagonists of the 5-HT_3 receptor subtype has attracted considerable attention in recent years.[5] For example, the 5-HT_3 receptor antagonists, such as ondansetron[6] and granisetron,[7] represent a major improvement in the pharmacotherapy of emesis, which is a frequent, severe, and sometimes incapacitating syndrome, associated with cancer chemotherapy and anesthesia. Although the only well-established therapeutic indication of 5-HT_3 receptor antagonists is as antiemetics, several lines of evidence suggest a role of 5-HT_3 receptor antagonists in the treatment of central nervous system disorders such as anxiety, schizophrenia, drug abuse and withdrawal, and age-associated memory impairments.[8] The aim of this study was to design novel and potent 5-HT_3 receptor antagonists, combining a molecular modeling and traditional medicinal chemistry approach to develop potential therapeutic agents for the treatment of chemotherapy-induced emesis and CNS disorders.

Before the introduction of potent and selective 5-HT_3 antagonists, metoclopramide was the drug of choice to alleviate chemotherapy-induced nausea and vomiting. Dopamine (D_2) receptor blockade was originally thought to underlie metoclopramide's antiemetic activity.[9] Subsequently, the antiemetic action for this drug has been linked to its relatively weak antagonism of 5-HT_3 receptors, an action first reported for metoclopramide in isolated rabbit heart.[10] Modification of the basic side chain of metoclopramide with the introduction of a quinuclidine ring in place of the (diethylamino)ethyl moiety led to the identification of the potent and selective 5-HT_3 receptor antagonist zacopride,[11] which is also endowed with potent antiemetic properties.[12]

Molecular modeling studies indicated that the molecular electrostatic potential (MEP) of metoclopramide shows a remarkable similarity with that of zetidoline, a potent dopamine D_2 receptor antagonist, in a nearly extended conformation.[13] The close electronic similarity between metoclopramide and zetidoline has been proposed to account for their common D_2 receptor antagonist properties. We observed that substructure A (benzamide group) of metoclopramide can be considered bioisoster of substructure B (phenylimidazolidin-2-one

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[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1997.

S0022-2623(97)00060-5 CCC: $14.00

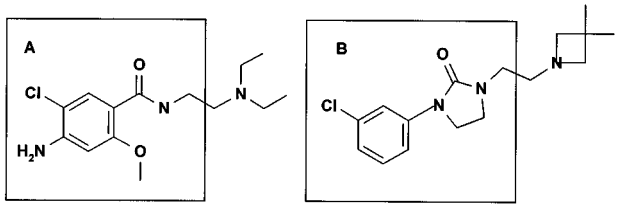


Figure 1. Substructures of metoclopramide (A) and zetidoline (B).

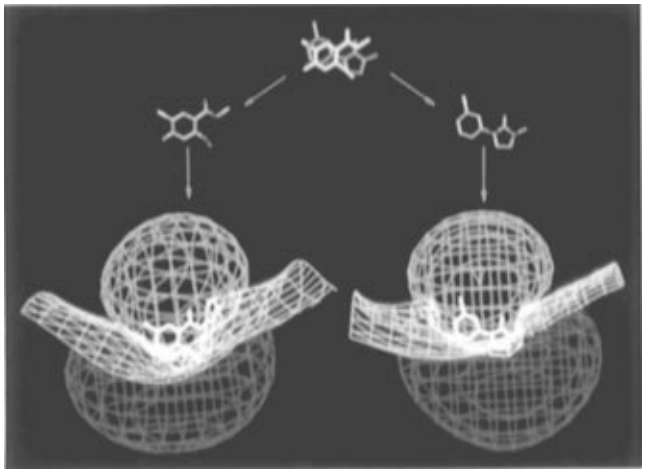
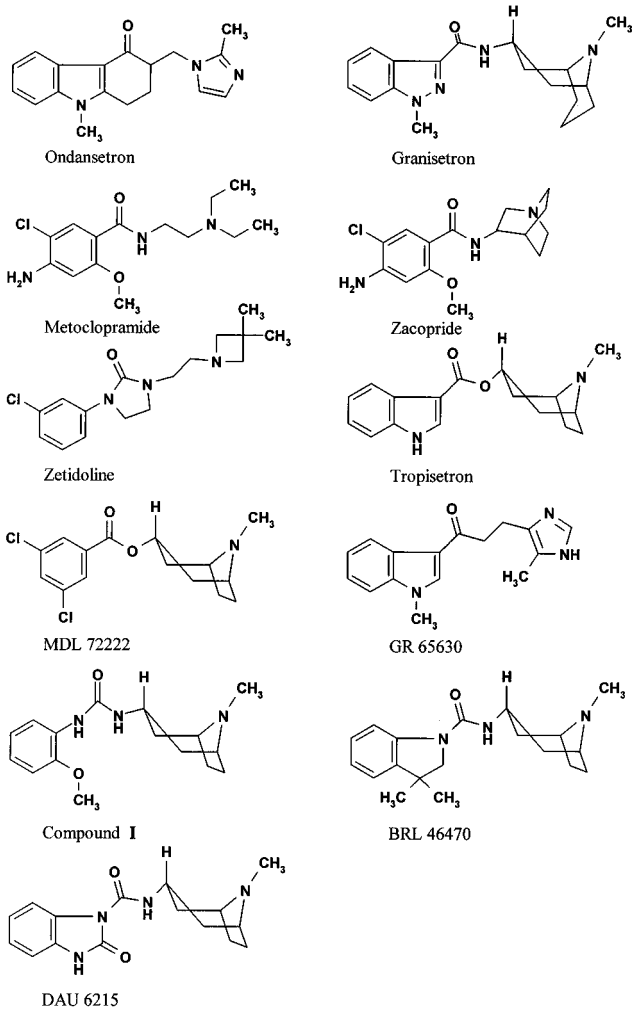


Figure 2. Electrostatic isopotential maps of substructure A (bottom left) and substructure B (bottom right). Negative fields are presented in cyan, neutral fields in yellow, and positive fields in red. The superposition of substructure A (yellow) and substructure B (red) at the top of the picture were obtained by maximizing the surface overlap of the MEPs. For clarity the two structures in the middle of the picture are reported color coded by atom type in the same orientation of the bottom pair. In both compounds the chloro and the carbonyl groups are the main responsible for the definition of the negative part (cyan) of the MEP in which the largest part of both molecules is enveloped. Only the methyl of the metoxy group in A and the *N*-methyl in B appear in the positive volume (red).

group) of zetidoline (Figure 1). This assumption was supported by a qualitative comparison of the isopotential maps obtained through the semiempirical computer modeling of substructures A and B (Figure 2).

These relationships led to the working hypothesis that 5-HT_3 receptor antagonist properties should be conferred to the molecule by linking the phenylimidazolidin-2-one group (substructure B) to the quinuclidine ring. Compound **21** was synthesized to test this hypothesis. This compound showed an affinity (K_i) of 2 ± 0.16 nM to the 5-HT_3 receptor and an ID_{50} of 79.9 μg/kg, after iv administration, in the Bezold−Jarisch reflex response. These results encouraged us to explore further other basic moieties such as tropane, granatane, and (5-methyl-1*H*-imidazol-4-yl)methyl, which are known to be present in different 5-HT_3 antagonists such as tropisetron and MDL 72222, granisetron, and GR 65630, respectively.[14,15] In addition, the phenylimidazolidin-2-one group can be viewed as a cyclized phenylurea moiety, which is present in several 5-HT_3 antagonists, such as compound **I**,[16] BRL 46470,[17] and DAU 6215.[18]

We report on the synthesis and the pharmacological properties of phenylimidazolidin-2-one derivatives bearing a basic imidazolylalkyl or an azabicycloalkyl moiety. The endo/exo configuration and the conformation of the azabicycloalkyl compounds were assigned by means of coupling constants in ^{1}H-NMR spectra and verified



through ^{13}C-NMR and NOE experiments. A structure−activity (SAR) study of the present set of compounds allowed the refinement of the reported pharmacophore model for 5-HT_3 receptor binding.

Chemistry

The synthesis of 1-azabicyclo-3-phenylimidazolidin-2-ones (**21-39**) (Table 3) is shown in Scheme 1. Reductive amination of quinuclidin-3-one, tropinone or pseudopelletierine with the appropriate *N*-phenyl-1,2-diaminoethane in presence of $NaBH_3CN$ as reducing agent in refluxing methanol at pH 6 provided the intermediates **1**−**20** (Table 1). Tropinone and pseudopelletierine afforded a mixture of endo and exo derivatives that were separated by column chromatography. Imidazolidinone ring closure was achieved employing 1,1′-carbonyldiimidazole in refluxing THF, except for compound **40** (Table 3). In this case, the concomitant steric hindrance of the 2,5-disubstituted aromatic ring and of the [3.3.1]azabicyclic moiety did not allow the cyclization. Ring closure was carried out via the carbamate intermediate **20a** and cyclization in refluxing pyridine (Scheme 2). The endo/exo configuration assignment of 3′-substituted granatanes and tropanes was performed by means of ^{1}H-NMR. This aim was complicated by conformational flexibility of these bicyclic rings. Indeed, while the exo-3′-substituted ring adopts a chair conformation, the endo-3′-substituted ring could adopt a conformation varying from the normal chair to boat depending on the size of the 3′-substituent in order to

Scheme 1

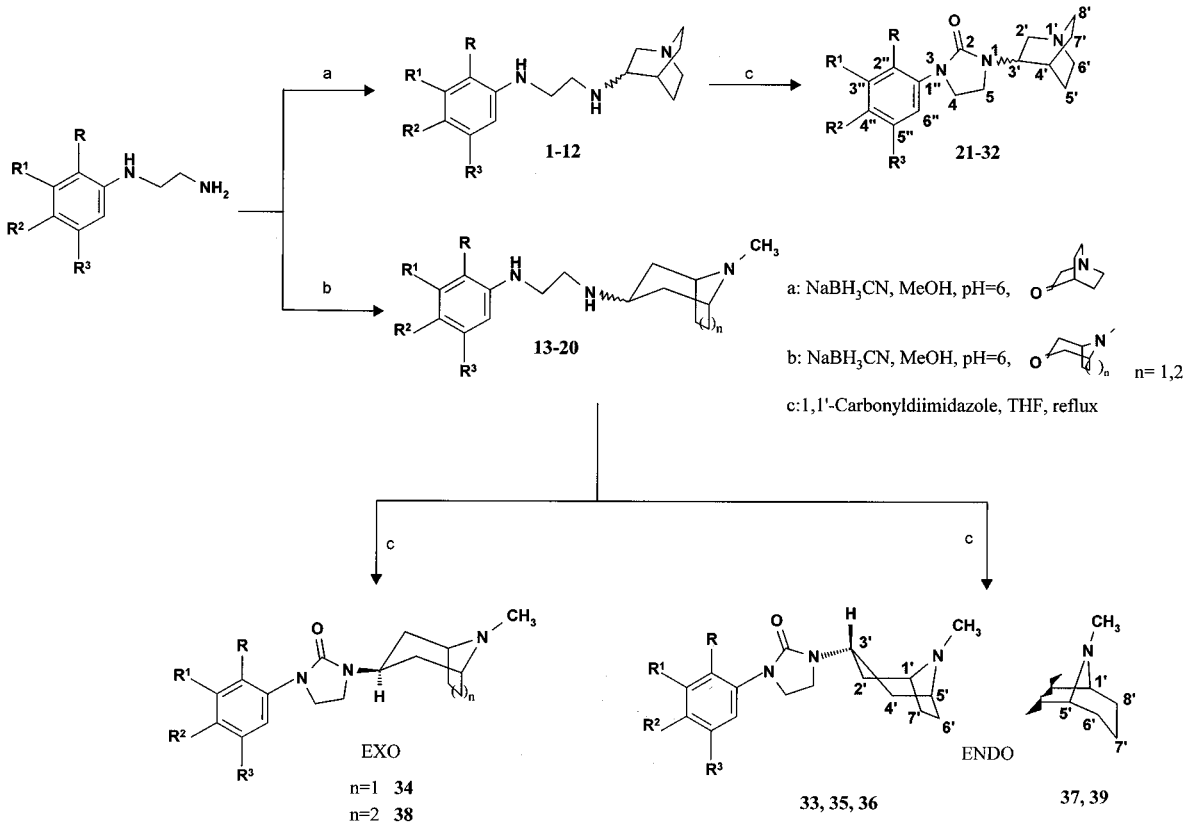
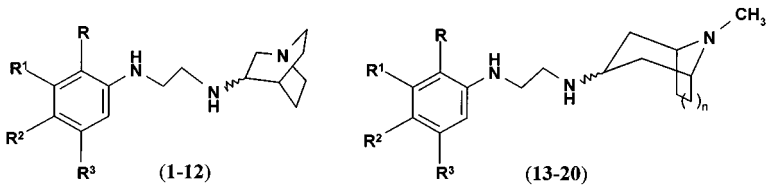


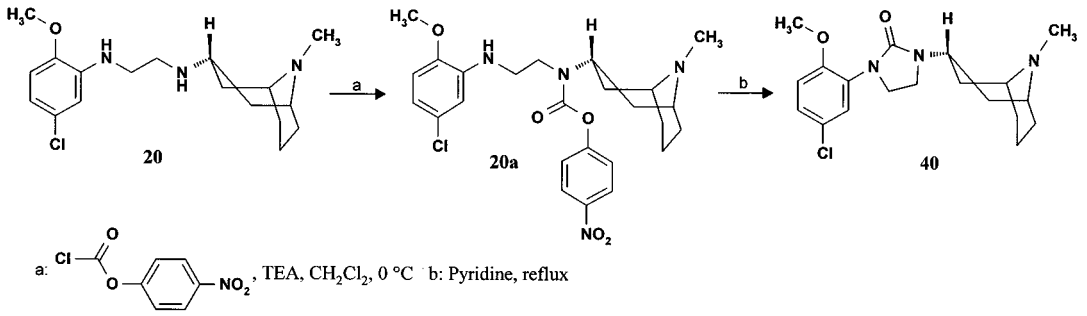
Table 1. Physicochemical Data of Intermediates of **1**−**20**



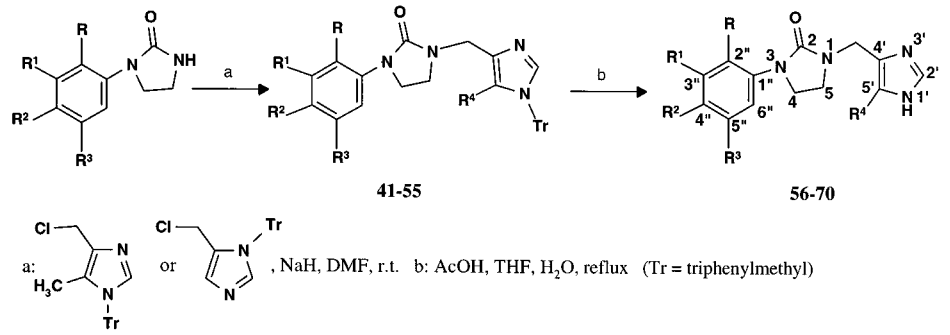
compd	R	R^1	R^2	R^3	endo/exo	n	% yield	mp, °C	formula
1	H	Cl	H	H			40	oil	$C_{15}H_{22}ClN_3$
2	OCH_3	H	H	Cl			62	oil	$C_{16}H_{24}ClN_3O$
3	H	OCH_3	H	H			41	oil	$C_{16}H_{25}N_3O$
4	H	CH_3	H	H			55	oil	$C_{16}H_{25}N_3$
5	H	H	Cl	H			51	oil	$C_{15}H_{22}ClN_3$
6	H	SCH_3	H	H			50	oil	$C_{16}H_{25}N_3S$
7	H	CN	H	H			48	oil	$C_{16}H_{22}N_4$
8	H	Cl	H	Cl			64	oil	$C_{15}H_{21}Cl_2N_3$
9	H	H	H	H			48	oil	$C_{15}H_{23}N_3$
10	H	CF_3	H	H			55	oil	$C_{16}H_{22}F_3N_3$
11	H	NO_2	H	H			48	oil	$C_{15}H_{22}N_4O_2$
12	H	Br	H	H			50	oil	$C_{15}H_{22}BrN_3$
13	H	Cl	H	H	endo	1	40	82.5−85.5	$C_{16}H_{24}ClN_3$
14	H	Cl	H	H	exo	1	20	62−64	$C_{16}H_{24}ClN_3$
15	OCH_3	H	H	Cl	endo	1	47	45−48	$C_{17}H_{26}ClN_3O$
16	H	H	H	H	endo	1	45	60−63	$C_{16}H_{25}N_3$
17	H	Cl	H	H	endo	2	42	oil	$C_{17}H_{26}ClN_3$
18	H	Cl	H	H	exo	2	20	oil	$C_{17}H_{26}ClN_3$
19	H	H	H	H	endo	2	48	oil	$C_{17}H_{27}N_3$
20	OCH_3	H	H	Cl	endo	2	56	oil	$C_{18}H_{28}ClN_3O$

relieve transannular steric interactions of the substituent with C6′/C7′ (tropanes) or C7′ (granatanes) hydrogens in the chair conformation.[19,20] A complete stereochemical study is possible through analysis of H3′ and H1′/H5′ coupling constants, but we also verified the endo/exo assignment through ^{13}C-NMR (granatanes)[21] and NOE (granatanes and tropanes) data. To our knowledge, no one has verified the stereochemistry of these bicyclic systems by NOE experiments. Free base spectra of our tropane derivatives (**33**−**36**) show H3′ as a triple triplet with coupling constants J = 8.1, 8.1 Hz (quintet like signal) for one stereoisomer (**33**, **35**, **36**) and J = 5.9, 11.8 Hz (septet like signal) for the other (**34**). The signal of the bridgehead protons H1′/H5′ is a multiplet from which J values could not be extracted but with half-bandwidth larger for **33**, **35**, and **36** than

Scheme 2



Scheme 3



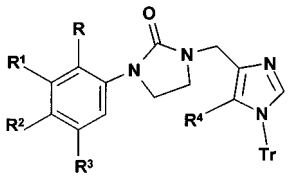
for **34** ($\Delta\nu_{1/2}$ = 17 and 9 Hz, respectively). These data suggest that **34** is an exo isomer in a normal chair conformation, while **33**, **35**, and **36** are endo isomers in a slightly flattened boat conformation (Scheme 1) in which H3′ is placed in pseudo axial-axial and pseudo-axial−equatorial relationship with C2′ and C4′ protons and H1′/H5′ having a large coupling constant with H2′β/H4′β protons due to an almost zero degree dihedral angle between these protons. Steady state 1D-NOE experiments performed on the *N*,*N*-dimethyl quaternary ammonium iodide derivatives of **33** and **34** (**75** and **76** respectively) confirmed configuration assignment. In fact, irradiation of the *N*-methyl signal overlooking C6′/C7′ (3.00 ppm in both compounds) enhances H6′β/H7′β and H1′/H5′ signals in both **75** and **76**; irradiation of the *N*-methyl signal overlooking C3′ (3.12 ppm for **75**, 3.29 ppm for **76**) causes NOE enhancements of H1′/H5′ and H2′β/H4′β signals in both stereoisomers but of the H3′ signal only in the case of endo derivative (**75**). ^{1}H-NMR spectra of all granatane derivatives (**37**−**40**) show H3′ as a triple triplet with coupling constants J = 6.2, 12.4 Hz, but H1′/H5′ signal is a narrow multiplet in the case **38** and a broad doublet ($J \cong$ 10 Hz) in the case of **37**, **39**, and **40**. This pattern of coupling constants, as in the case of tropanes, suggests that **38** is an exo isomer in a "chair−chair" conformation and **37**, **39**, and **40** are endo isomers in a "chair−boat"conformation[20] (Schemes 1 and 2). Stereochemistry assignment was verified by means of ^{13}C-NMR and NOESY experiments performed on compounds **38** and **37** as free bases. The ^{13}C-NMR spectra show C7′ chemical shifts at lower field for the exo isomer **38** (20.0 ppm) with respect to the endo isomer **37** (14.1 ppm) as previously reported,[21] and the NOESY spectra display H3′/H7′α cross peak for **38** and H7′α/H2′α-H4′α cross peak for **37** in agreement with the proposed configuration and conformation (Scheme 1).

The 1-(imidazolylalkyl)-3-phenylimidazolidin-2-ones (**56**−**70**) (Table 3) were prepared according to the procedure outlined in Scheme 3. The intermediates **41**-**55** (Table 2) were prepared by alkylating the appropriate 1-phenylimidazolidin-2-one with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1*H*-imidazole [5-(chloromethyl)-1-(triphenylmethyl)-1*H*-imidazole to obtain **55**] in the presence of NaH at room temperature. Mild deprotection of trityl derivatives in AcOH/H_2O/THF at reflux afforded **56**−**70**. The two pairs of regioisomers **71**, **72**, and **73**, **74** (Table 3) were prepared according to Scheme 4 by direct alkylation of **59** in DMF at 0 °C in the presence of NaH as base and the appropriate alkyl halide. The imidazole substitution pattern was assigned using steady state 1D-NOE experiments through irradiation of imidazole ring substituents. Irradiation of the CH_2 signal caused NOE enhancements of the NCH_3 and CH_3 signals for **73** and only of the CH_3 signal for **74**. Irradiation of the CH_3 signal enhances the CH_2 signal in **73** and the CH_2 and NCH_3 signals in **74**. Similar results were obtained for **71** and **72**.

Molecular Modeling

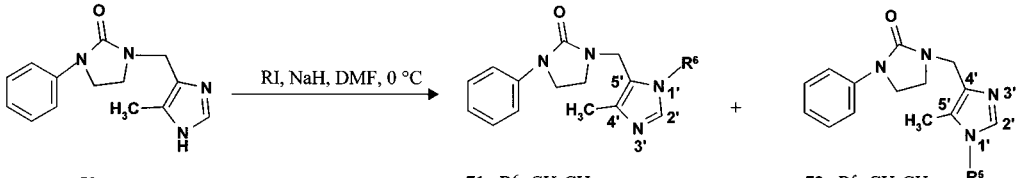
Many pharmacophore models for the 5-HT_3 receptor antagonism have already been reported in the literature. However, substantial discrepancies between these pharmacophore models can be noted because of the different 5-HT_3 compounds chosen and the different methods used to build them. Bull et al.[22] proposed three necessary components for high 5-HT_3 receptor affinity on the basis of a critical examination of five pharmacophore models:[23−27] an aromatic ring, a carbonyl group directly attached to the aromatic ring, and a basic nitrogen. The aromatic ring may be the benzene of a benzoate or benzamide, or the five-atom ring of an indole or indazole compound. The carbonyl group may be substituted by a bioisosteric equivalent function, such as a 1,2,4-oxadiazole ring.[28] Clark et al.[29] proposed a pharmacophore model where the alignment of the receptor element that interacts with the basic nitrogen was judged to be a more critical factor than the alignment of the nitrogen itself. In this pharmacophore model, it is the lone pair of the nitrogen atoms and not the nitrogens themselves, that is used for the superposi-

Table 2. Physicochemical Data of Intermediates **41**−**55**



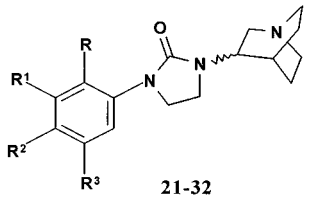
product	R	R^1	R^2	R^3	R^4	% yield	mp, °C	formula
41	H	Cl	H	H	CH_3	51	189−191	$C_{33}H_{29}ClN_4O$
42	H	Br	H	H	CH_3	56	215−217	$C_{33}H_{29}BrN_4O$
43	H	Cl	H	Cl	CH_3	60	199−202	$C_{33}H_{28}Cl_2N_4O$
44	H	H	H	H	CH_3	47	196−198	$C_{33}H_{30}N_4O$
45	H	CN	H	H	CH_3	59	180−183	$C_{34}H_{29}N_5O$
46	H	SCH_3	H	H	CH_3	60	206 dec	$C_{34}H_{32}N_4OS$
47	H	CH_3	H	H	CH_3	65	178−180	$C_{34}H_{32}N_4O$
48	H	CH_3	H	CH_3	CH_3	45	165−168	$C_{35}H_{34}N_4O$
49	H	H	Cl	H	CH_3	40	180−183	$C_{33}H_{29}ClN_4O$
50	Cl	H	H	H	CH_3	60	133−135	$C_{33}H_{29}ClN_4O$
51	H	CF_3	H	H	CH_3	58	174−176	$C_{34}H_{29}F_3N_4O$
52	H	NO_2	H	H	CH_3	55	185−187	$C_{33}H_{29}N_5O_3$
53	H	F	H	H	CH_3	58	173−176	$C_{33}H_{29}FN_4O$
54	H	OCH_3	H	H	CH_3	60	170−173	$C_{34}H_{32}N_4O_2$
55	H	H	H	H	H	68	162−166	$C_{32}H_{28}N_4$

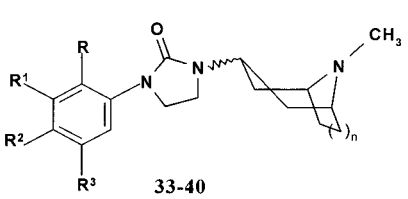
Scheme 4

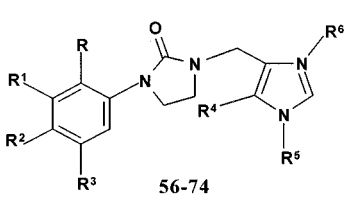


tion of the molecules. In this case the lone pairs would point to a specific atom on the receptor, but their direction is not necessarily the same for all the compounds. A molecular modeling study was performed in order to verify whether the pharmacophore models cited might be used for SAR study of the present class of compounds. These compounds were submitted to a systematic conformational analysis, and the distances between the pharmacophore features described previously were measured during the complete scanning of the torsional angles. No conformation of even the most active structure of this series could be properly fitted into any of the models proposed. For example, in the reference model of Hibert et al.,[24] the distance between the centroid of the aromatic ring and the oxygen of the carbonyl group, and the distance between the centroid of the aromatic ring and the basic nitrogen, are 3.3 and 6.7 Å, respectively. On the other hand, we measured 4.1 and 7.0−8.8 Å in the case of compound **58**, or 4.1 and 8.3−8.9 Å for the compound **28** of our series. In addition, the substitution of the phenyl ring in the present series is a crucial factor that can increase the potency several times. This fact cannot be explained by the previously reported models. An automated pharmacophore builder, the APEX-3D, was used to avoid any bias with the models cited. A set of four 5-HT$_3$ antagonists was used to represent the major different chemical classes of the 5-HT$_3$ antagonists: zacopride, ondansetron, granisetron, and tropisetron. Compound **58** was chosen as representative of our series of molecules. While the computational methodology described in the experimental molecular modeling section did not yield any meaningful pharmacophore model when applied to the five structures, the same procedure, applied only to zacopride, ondansetron, granisetron, and tropisetron yielded a model that seems to be a compromise between the models cited by Hibert et al.[24] and Clark et al.[29] The elements of the pharmacophore are as follows: the basic nitrogen, the receptor element that interacts with the basic nitrogen, the carbonyl group, and the aromatic ring. In spite of this good technical result, the problem of the SAR remained still unsolved because no structure of our series of compounds could be fitted into this model. However, we envisaged that this automatically generated model could be used as a starting point for modeling studies if the rigorous requirement for the aromatic ring (and/or its centroid surrogate marker) was eliminated. Indeed, with this proviso we found that many other known 5-HT$_3$ antagonists could be superimposed to this revised model, which uses only the carbonyl group and the basic nitrogen with its lone pair pointing to the receptor atom as key points for superimposition. In particular, the 5-HT$_3$ antagonists MDL 72222, DAU 6215, BRL 46470, and compound **I** were added in the superimposition of the model previously defined by zacopride, ondansetron, granisetron, and tropisetron. Notably, BRL 46470 and compound **I** have never been included in literature models cited before. The analysis of this putative model of bioactive conformations of eight compounds suggested that, in addition to the features used for the superimposition, the presence of two hydrophobic sites could refine the 5-HT$_3$ antagonist pharmacophore model to account for the activities of the training set (Figure 3). The hydrophobic site, described already by Clark et al.[29]

Table 3. Pharmacological Data of Compounds **21**−**40**, and **56**−**74**[a]







compd	R	R^1	R^2	R^3	R^4	R^5	R^6	*n*	endo/exo	[^{3}H]BRL 43694 K_i nM (±SEM)	GPI K_b, nM (±SEM)	Bezold−Jarisch reflex 5-HT, 30 μg/kg iv: % of inhibn at 100 μg/kg iv	Bezold−Jarisch reflex 5-HT, 30 μg/kg iv: ID_{50} μg/kg iv (95% C. L.)
21	H	Cl	H	H						2 (±0.16)	30.9 (±12)	60	79.94 (54−98)
22	OCH_3	H	H	Cl						40 (± 2.81)		−11	nc
23	H	OCH_3	H	H						6 (±0.48)	33.1 (±8.4)	37	nc
24	H	CH_3	H	H						4 (±0.23)	12 (±6.3)	75	37.6 (31−46)
25	H	H	Cl	H						210 (±12)		8	nc
26	H	SCH_3	H	H						6 (±0.62)	214 (±93)	28	nc
27	H	CN	H	H						30 (±1.51)		43	nc
28	H	Cl	H	Cl						1 (±0.08)	45 (±12)	76	20.6 (11−31)
29	H	H	H	H						8 (±0.63)	21.4 (±9.5)	71	67.1 (34−93)
30	H	CF_3	H	H						98 (±7.00)		14	nc
31	H	NO_2	H	H						10 (±0.60)	75.2 (±14)	5	nc
32	H	Br	H	H						3 (±0.18)	38.3 (±16)	77.7	nc
33	H	Cl	H	H				1	endo	25 (±0.95)		27	nc
34	H	Cl	H	H				1	exo	>10000		0	nc
35	OCH_3	H	H	Cl				1	endo	400 (±12)		−22	nc
36	H	H	H	H				1	endo	12 (±0.97)		56	nc
37	H	Cl	H	H				2	endo	250 (±15)		15	nc
38	H	Cl	H	H				2	exo	360 (±39)		−21	nc
39	H	H	H	H				2	endo	190 (±12)		22	nc
40	OCH_3	H	H	Cl				2	endo	>10000		5	nc
56	H	Cl	H	H	CH_3	H	H			0.5 (±0.02)	12 (±1.6)	87	5.26 (4.5−6.1)
57	H	Br	H	H	CH_3	H	H			0.62 (±0.03)	10.4 (±4.2)	89	6.5 (4.6−8.4)
58	H	Cl	H	Cl	CH_3	H	H			0.038 (±0.001)	5.62 (±8.1)	93	2.2 (1.9−2.6)
59	H	H	H	H	CH_3	H	H			3.4 (±0.12)	26.9 (±10)	95	3.9 (2.2−5.4)
60	H	CN	H	H	CH_3	H	H			2.7 (±0.18)	134 (±45)	88	32.2 (23−44)
61	H	SCH_3	H	H	CH_3	H	H			1.6 (±0.98)	120 (±79)	88	28.6 (19−35)
62	H	CH_3	H	H	CH_3	H	H			0.93 (±0.04)	45.7 (±12)	86	3.1 (2.5−3.9)
63	H	CH_3	H	CH_3	CH_3	H	H			0.42 (±0.02)	50.1 (±27)	86	3.4 (2.2−5.4)
64	H	H	Cl	H	CH_3	H	H			19 (±2.00)		29	nc
65	Cl	H	H	H	CH_3	H	H			290 (±18)		5	nc
66	H	CF_3	H	H	CH_3	H	H			9.7 (±1.00)	68.5 (±12)	39	nc
67	H	NO_2	H	H	CH_3	H	H			6.6 (±0.51)	125 (±21)	95	54 (46−64)
68	H	F	H	H	CH_3	H	H			3.7 (±0.12)	88.3 (±17)	84	17.6 (12−24)
69	H	OCH_3	H	H	CH_3	H	H			3.6 (±0.18)	67.8 (±31)	92	15.4 (12−19)
70	H	H	H	H	H	H	H			4 (±0.39)	45.4 (±23)	56	nc
71	H	H	H	H	CH_3	H	C_2H_5			67 (±3.00)		38	nc
72	H	H	H	H	CH_3	C_2H_5	H			85 (±2.00)		21	nc
73	H	H	H	H	CH_3	H	CH_3			55 (±1.00)		45	nc
74	H	H	H	H	CH_3	CH_3	H			8.5 (±0.63)	63.8 (±27)	77	28.5 (18−41)
Ondansetron										1 (±0.09)	19.4 (±8.2)	90	2.25 (1.6−2.9)
Tropisetron										1.57 (±0.08)	9.33 (±6.8)	90	1.0 (0.9−1.2)
Granisetron										0.35 (±0.02)	12.9 (±3.6)	95	0.88 (0.6−1.1)
BRL 46470										0.26 (±0.01)	22.0 (±7.4)	90.5	0.89 (0.3−4.7)

[a] None of the compounds showed affinity for D_1, D_2, α_1, α_2, M_{1+2}, 5-HT_1, 5-HT_{1A}, 5-HT_2, and 5-HT_4 receptor binding sites (IC_{50} >10 μM), or agonistic (EC_{50} >1 μM) or antagonistic activity (K_b > 1 μM) on rat oesophagus preparation (5-HT_4 receptor).

and located below the aromatic ring, is not shared by all compounds.

The presence of the aromatic ring linked to the carbonyl group does not appear to be essential for affinity. As suggested by Bermudez et al.,[17] this may act as a "spacer" unit to ensure the optimal spatial orientation of the other features. As we noted, the five-atom aromatic ring of tropisetron may be substituted by an imidazolone group (DAU 6215), by a urea group (compound **I**), or by an aliphatic group (BRL 46470). The affinity value of BRL 46470 toward 5-HT_3 receptor increased 6-fold with respect to tropisetron (Table 3). The phenylimidazolidin-2-one derivatives lent support to a model that qualitatively accounted for a structure−activity relationship. The most potent antagonists could be easily superimposed on this model. The compounds from either imidazole and quinuclidine series, occupying the two hydrophobic pockets with halogens or alkyl groups (**28**, **58**, and **63**), display the highest potency. Compounds with only one hydrophobic substituent on the phenyl ring in a meta position from the imidazole and quinuclidine series have a greater potency than the corresponding unsubstituted structures (compare **21** and **29**; **56** and **59**). The same pattern of activity has been reported for 5-HT_3 receptor antagonists, belonging to other chemical series.[30,31] However, among the compounds we prepared, the meta-substituted molecules have a potency lower than that of the corre-

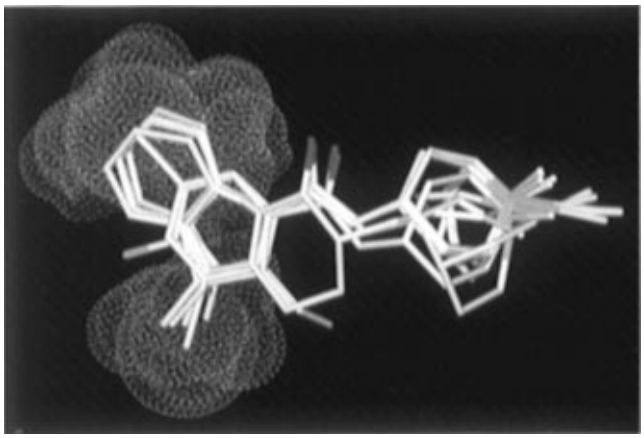


Figure 3. Superposition (without hydrogen) of zacopride, ondansetron, granisetron, tropisetron, MDL 72222, DAU 6215, BRL 46470, and compound **I**. The lone pair of the nitrogen pointing at the receptor atoms are shown in yellow, the nitrogen atoms in blue, and the carbonyl groups in red. The hydrophobic sites (van der Waals surface) are in green. In this model the direction of the lone pair is nearly perpendicular to the plane of the aromatic rings.

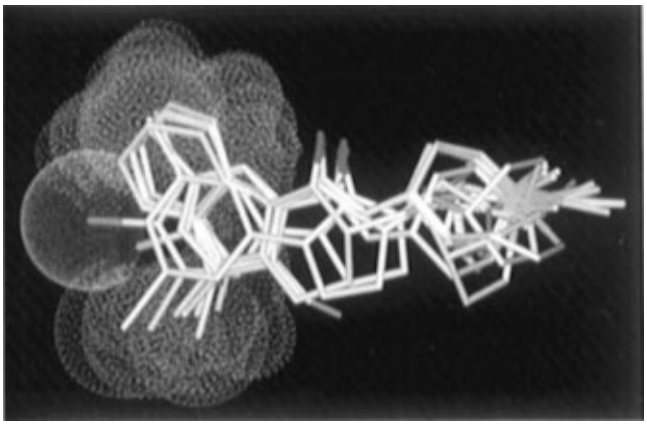


Figure 4. Superposition (without hydrogen) of zacopride, ondansetron, granisetron, tropisetron, MDL 72222, DAU 6215, BRL 46470, compound **I**, and compounds **28**, **58**, **63**, and **64**. The lone pair of the nitrogen pointing at the receptor atoms are shown in yellow, the nitrogen atoms in blue, and the carbonyl groups in red. The hydrophobic sites (van der Waals surface) are in green. The van der Waals surface of the chloro atom of compound **64** is shown in magenta.

sponding double-meta-substituted ones (**28, 58,** and **63**). In our model, the chloro atom of the para-substituted inactive compounds **25** and **64** occupies the space located between the two hydrophobic sites (Figure 4). As the amino group of the benzene of zacopride is located in this site, it is possible to formulate the hypothesis that the presence of a receptor residue is able to give a polar interaction with the ligand. The inactivity of the compound bearing a chloro atom in the ortho position to the phenyl ring (**65**) may be explained by the fact that this substituent prevents the planarity between the phenyl ring and the carbonyl group. As a consequence, the halogen occupies a region out of the pharmacophoric hydrophobic sites. The compounds of this series with a tropane or granatane ring, and particularly the exo derivatives when compared with the endo derivatives, do not fit this model because of the greater distance between the basic nitrogen and hydrophobic regions, and this is in agreement with their lack of or low level of affinity. It must be observed that this model does not preclude those reported in the literature, which, of course fit the molecules from which they were derived, but represents a redefined pharmacophore model incorporating features of the others. The most relevant improvements of our model with respect to the models reported in the literature previously are the definition of the two important hydrophobic sites, and the fact that the phenyl ring acts as a "spacer" unit and not as a group interacting with the receptor.

Pharmacological Results

As shown in Table 3, several compounds of this series were selective 5-HT$_3$ receptor antagonists displaying a noticeable *in vitro* and *in vivo* activity. All of the active molecules displaying high affinity for the 5-HT$_3$ receptor showed no affinity (IC_{50} > 10 μM) for adrenergic, dopaminergic, muscarinic, and the other serotoninergic receptors. In particular, no affinity was found for the 5-HT$_4$ binding site in the rat striatum, and neither 5-HT$_4$ agonist nor antagonist activity was detected in the rat oesophagus preparation test (see the Experimental Section). 1-(Imidazolylalkyl)-3-phenyl derivatives were found to be more active than the corresponding azabicycloalkane analogs. N-Alkylation of either 5-methyl-1*H*-imidazol-4-yl nitrogens as well as removal of the 5-methyl substituent on the imidazolyl ring led to a decrease in potency (compare analogs **71**−**74** to the unalkylated analog **59** and **59** to **70**, respectively). Within the azabicycloalkane compounds, the quinuclidine and tropane (n = 1) basic moieties led to more potent compounds than the granatane (n = 2) moiety. Among the compounds tested, the exo compounds were inactive (**34**) or less active (**38**) than the endo compounds (**33, 37**), respectively. The ortho and para ring monosubstitution decreased 5-HT$_3$ receptor antagonist activity (**25**, **64**, and **65**). The meta substitution generally increased both *in vitro* and *in vivo* 5-HT$_3$ receptor activity compared to the unsubstituted compounds (**29**, **36**, **39**, and **59**). 2,5-disubstitution led to weak activity (**22**, **35**, and **40**), while the 3,5-disubstituted compounds (**28**, **58**, and **63**) were the most potent compounds of this series. 1-(3,5-Dichlorophenyl)-3-[(5-methyl-1*H*-imidazol-4-yl)methyl]imidazolidin-2-one (**58**) was one of the most potent 5-HT$_3$ receptor antagonists reported so far. This compound was a more potent 5-HT$_3$ receptor antagonist *in vitro* than the reference compounds tested and showed *in vivo* activity comparable to that of ondansetron (Table 3).

Conclusions

Starting from the observation of the close electronic similarity between the substructures of metoclopramide and zetidoline, the substructure of the latter was linked to basic moieties present in different 5-HT$_3$ antagonists. This work revealed novel and potent 5-HT$_3$ receptor antagonists as potential candidates as antiemetics or psychotropic drugs. This new series of compounds helped to refine a 5-HT$_3$ antagonist pharmacophore model that was used to perform a structure−activity relationship study of the present class of compounds and of some known 5-HT$_3$ antagonists. The model obtained in this study could be a useful tool for a rational design of new potential 5-HT$_3$ antagonists.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries on a Buchi apparatus and are not corrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian VXR-

200 or VXR-400S spectrometer using the solvent as internal standard. Chemical shifts are expressed in parts per million (ppm). The complete ^{1}H-NMR spectrum is listed for one representative compound of each structural class, and only signals of the differing parts are reported for the other derivatives. When spectra were registered in different conditions (solvent, hydrochloride, free base) within a structural class, one full spectrum is reported for each experimental condition. Steady state 1D-NOE (preirradiation time 4 s) and NOESY (mixing time 0.5 s) experiments were performed on a Varian VXR-400 at 27 °C in DMSO-d_6 as solvent. Positive ion fast bombardment (FAB), field desorption (FD), and electronic impact (EI) mass spectra (MS) were obtained on a Varian MAT 311-A and on a Finnigan TSQ 70 instrument. Some compounds have been tested by direct exposure probe technique (DEP) in order to increase the molecular ion intensity. Elemental analyses were performed for new compounds by a Carlo Erba 1106 instrument.Where elemental analyses are indicated, the results were within 0.4% of the theoretical values. Yields refer to the purified products and are not optimized. Column chromatography was carried out using silica gel 60, 230−400 mesh (Carlo Erba). Starting materials that were not commercially available were prepared according to procedures already published.

General Procedure for the Preparation of 1-Arylimidazolidin-2-ones.[32] **(1) *N*-Aryl-1,2-diaminoethanes.**[32] A mixture of 2-bromoethylamine hydrobromide (0.1 mol) and the aniline derivative (0.2 mol) in 40 mL of toluene was heated at reflux temperature for 16 h and then cooled. A solution of 60 mL of water and 20 mL of 50% aqueous KOH was added, and the layers were separated. The aqueous layer was saturated with NaCl and extracted three times with toluene. The combined organic layers were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. Column chromatography gave the pure compounds.

(2) 1-Arylimidazolidin-2-ones.[32] To a solution of *N*-aryl-1,2-diaminoethane derivative (0.3 mol) in 40 mL of anhydrous THF, 1,1-carbonyldiimidazole (0.33 mol) was added under nitrogen atmosphere. The solution was refluxed for 4 h and then evaporated to dryness; the residue was taken up in ethyl acetate, washed with saturated NaCl solution, and dried over anhydrous Na_2SO_4. After filtration and evaporation to dryness, the products were purified by crystallization from a suitable solvent.

General Procedure for the Preparation of Intermediates 1−20. This procedure is illustrated for the preparation of *N*-[*endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-*N*′-(3-chlorophenyl)-1,2-diaminoethane (**13**) and *N*-[*exo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-*N*′-(3-chlorophenyl)-1,2-diaminoethane (**14**). Tropinone (1.53 g, 0.01 mol) was added to a stirred solution of *N*-(3-chlorophenyl)-1,2-diaminoethane (2.06 g, 0.01 mol) in 50 mL of anhydrous methanol kept under nitrogen atmosphere. The pH was adjusted to 6 by addition of AcOH. $NaBH_3CN$ (1.26 g, 0.02 mol) was added, and the reaction mixture was refluxed 8 h, then cooled, and filtered. After evaporation, the residue was taken up with water, basified with 20% NaOH solution, and extracted three times with ethyl acetate. The organic layer was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated to dryness after filtration. The residue was purified by silica gel chromatography (CH_2Cl_2−MeOH−30% NH_4OH, 150:50:5) as eluant, to give 1.2 g of the endo product **13** as a white solid followed by 0.52 g of the exo compound **14** as a white solid. **13**: ^{1}H-NMR (200 MHz, $CDCl_3$) 1.4−2.2 (m, 8H, CH_2-2′ + CH_2-4′ + CH_2-6′ + CH_2-7′), 2.26 (s, 3H, NCH_3), 2.83 (m, 3H, ArNHCH$_2$*CH*$_2$ + H3′), 3.0−3.2 (m, 4H, ArNH*CH*$_2$-CH_2 + H1′ + H5′), 4.3 (br s, 1H, Ar*NH*), 6.4−6.7 (m, 3H, H2″ + H4″ + H6″), 7.06 (t, J = 7.9 Hz, 1H, H5″); MS (EI) *m*/*z* (rel intensity) 293 (M^+, 8), 153 (88), 140 (15), 124 (100), 96 (18). Anal. ($C_{16}H_{24}ClN_3$) C, H, Cl, N.

14: ^{1}H-NMR (200 MHz, $CDCl_3$) 1.3−1.6 (m, 4H, H2′β + H4′β + H6′α + H7′α), 1.77 (ddd, J = 13.2, 5.6, 3.4 Hz, 2H, H2′α + H4′α), 1.97 (m, 2H, H6′β + H7′β), 2.27 (s, 3H, NCH_3), 2.73 (tt, J = 5.6, 11.2 Hz, 1H, H3′), 2.83 (m, 2H, ArNHCH$_2$*CH*$_2$), 3.0−3.2 (m, 4H, ArNH*CH*$_2$CH$_2$ + H1′ + H5′), 4.3 (br s, 1H, Ar*NH*), 6.4−6.7 (m, 3H, H2″ + H4″ + H6″), 7.04 (t, J = 7.9 Hz, 1H, H5″); MS (EI) *m*/*z* (rel intensity) 293 (M^+, 293), 153 (94), 140 (12), 124 (100), 96 (9). Anal. ($C_{16}H_{24}ClN_3$) C, H, Cl, N.

Compounds **1**−**12** and **15**−**20** were similarly prepared. Yields and analytical data are reported in Table 1. The ^{1}H NMR spectra and MS data are consistent with the assigned structures.

General Procedure for Cyclization of 1,2-Diaminoethanes to Imidazolidin-2-ones 21−39. The procedure is reported for the preparation of **1**-[1-azabicyclo[2.2.2]oct-3-yl]-3-(3-chlorophenyl)imidazolidin-2-one hydrochloride (**21**). 1,1-Carbonyldiimidazole (2.04 g, 0.0125 mol) was added to a stirred solution of **1** (2.7 g, 0.0097 mol) in 10 mL of anhydrous THF. The reaction mixture was refluxed for 8 h under nitrogen atmosphere. After evaporation, the residue was taken up in ethyl acetate, washed with saturated NaCl solution, and dried over anhydrous Na_2SO_4. After filtration and evaporation to dryness, the crude product was purified by silica gel chromatography (CH_2Cl_2−MeOH-30% NH_4OH, 180:20:2) as eluant, followed by treatment with an excess of a solution of HCl in EtOH. The crude salt was collected by filtration and recrystallized from anhydrous EtOH to give 2.3 g (69.3% yield) of the desired product (mp 234−239 °C): ^{1}H-NMR (200 MHz, DMSO-d_6) 1.7−2.1 (m, 4H, CH_2-5′ + CH_2-7′), 2.22 (m, 1H, H4′), 3.1−3.3 (m, 4H, CH_2-6′ + CH_2-8′), 3.3−3.6 (m, 2H, CH_2-2′), 3.6−3.9 (m, 4H, CH_2-4 + CH_2-5), 3.99 (m, 1H, H3′), 7.0−7.5 (m, 3H, H4″ + H5″ + H6″), 7.74 (t, J = 2.1 Hz, 1H, H2″); MS (EI) *m*/*z* (rel intensity) 305 (M^+, 10), 235 (13), 222 (12), 153 (7), 109 (100), 96 (24). Anal. ($C_{16}H_{20}ClN_3O$·HCl) C, H, Cl, N.

Compounds **22**−**39** were prepared as hydrochlorides or free bases according to the procedure described for **21** starting from the appropriate intermediate (**2**−**19**).

1-[1-Azabicyclo[2.2.2]oct-3-yl]-3-(5-chloro-2-methoxyphenyl)imidazolidin-2-one, hydrochloride (22): 75% yield (mp 209−215 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 3.78 (s, 3H, OCH_3), 7.09 (d, J = 8.7 Hz, 1H, H3″), 7.2−7.4 (m, 2H, H4″ + H6″); MS (EI) *m*/*z* (rel intensity) 335 (M^+, 4), 265 (3), 252 (2), 168 (3), 109 (100), 96 (19). Anal. ($C_{17}H_{22}ClN_3O_2$·HCl) C, H, Cl, N.

1-[1-Azabicyclo[2.2.2]oct-3-yl]-3-(3-methoxyphenyl)imidazolidin-2-one (23): 63% yield (mp 120−133 °C); ^{1}H-NMR (200 MHz, $CDCl_3$) 1.4−1.9 (m, 4H, CH_2-5′ + CH_2-7′), 2.00 (sestet, J = 3.0 Hz, 1H, H4′), 2.7−3.1 (m, 5H, CH_2-6′ + CH_2-8′ + H2′a), 3.30 (ddd, J = 14.1, 9.7, 2.1 Hz, 1H, H2′b), 3.60 (m, 2H, CH_2-5), 3.80 (s, 3H, OCH_3), 3.82 (m, 3H, CH_2-4 + H3′), 6.57 (m, 1H, H4″), 6.95 (m, 1H, H6″), 7.20 (t, J = 8.3 Hz, 1H, H5″), 7.34 (t, J = 2.2 Hz, 1H, H2″); FD MS 301. Anal. ($C_{17}H_{23}N_3O_2$) C, H, N.

1-[1-Azabicyclo[2.2.2]oct-3-yl]-3-(3-methylphenyl)imidazolidin-2-one (24): 64% yield (mp 122−126 °C); ^{1}H-NMR (200 MHz, $CDCl_3$): 2.33 (s, 3H, CH_3), 6.84 (d, J = 7.0 Hz, 1H, H4″), 7.1−7.3 (m, 2H, H5″ + H6″), 7.43 (s, 1H, H2″); FD MS 285. Anal. ($C_{17}H_{23}N_3O$) C, H, N.

1-[1-Azabicyclo[2.2.2]oct-3-yl]-3-(4-chlorophenyl)imidazolidin-2-one (25): 66% yield (mp 175−178 °C); ^{1}H-NMR (200 MHz, $CDCl_3$): 7.26 (m, 2H, H3″ + H5″), 7.47 (m, 2H, H2″ + H6″); FD MS 305. Anal. ($C_{16}H_{20}ClN_3O$) C, H, Cl, N.

1-[1-Azabicyclo[2.2.2]oct-3-yl]-3-[3-(methylthio)phenyl]-imidazolidin-2-one, hydrochloride (26): 62% yield (mp 205 °C dec.). ^{1}H-NMR (200 MHz, DMSO-d_6) 2.44 (s, 3H, SCH_3), 6.90 (m, 1H, H4″), 7.25 (m, 2H, H5″ + H6″), 7.54 (s, 1H, H2″); MS (EI) *m*/*z* (rel intensity) 317 (M^+, 17), 247 (7), 234 (11), 193 (9), 109 (100), 96 (20). Anal. ($C_{17}H_{23}N_3OS$·HCl) C, H, Cl, N, S.

1-[1-Azabicyclo[2.2.2]oct-3-yl]-3-(3-cyanophenyl)imidazolidin-2-one (27): 58% yield (mp 163−167 °C); ^{1}H-NMR (200 MHz, $CDCl_3$): 7.2−7.5 (m, 2H, H4″ + H5″), 7.7−7.9 (m, 2H, H2″ + H6″); FD MS 296. Anal. ($C_{17}H_{20}N_4O$) C, H, N.

1-[1-Azabicyclo[2.2.2]oct-3-yl]-3-(3,5-dichlorophenyl)-imidazolidin-2-one, hydrochloride hydrate (28): 72% yield (mp 248.5−254 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 7.21 (t, J = 1.7 Hz, 1H, H4″), 7.64 (t, J = 1.7 Hz, 2H, H6″ + H2″); MS (EI) *m*/*z* (rel intensity) 339 (M^+, 12), 269 (8), 256 (11), 109 (100), 96 (20). Anal. ($C_{16}H_{19}Cl_2N_3O$·HCl·H_2O) C, H, Cl, N.

1-[1-Azabicyclo[2.2.2]oct-3-yl]-3-phenylimidazolidin-2-one (29): 83% yield (mp 140−143 °C); ^{1}H-NMR (200 MHz, $CDCl_3$): 7.01 (m, 1H, H4″), 7.31 (m, 2H, H3″ + H5″), 7.52 (m, 2H, H2″ + H6″); FD MS 271. Anal. ($C_{16}H_{21}N_3O$) C, H, N.

1-[1-Azabicyclo[2.2.2]oct-3-yl]-3-[3-(trifluoromethyl)-phenyl]imidazolidin-2-one (30): 81% yield (mp 130.5−134.5 °C); ^{1}H-NMR (200 MHz, $CDCl_3$): 7.27 (d, J = 7.9 Hz, 1H, H4″), 7.42 (t, J = 7.9 Hz, 1H, H5″), 7.76 (m, 2H, H2″ + H6″); MS (EI) m/z (rel intensity) 339 (M^+, 26), 269 (16), 256 (19), 109 (100), 96 (17). Anal. ($C_{17}H_{20}F_3N_3O$) C, H, N.

1-[1-Azabicyclo[2.2.2]oct-3-yl]-3-(3-nitrophenyl)imidazolidin-2-one, hydrochloride (31): 52% yield (mp 220 °C dec); ^{1}H-NMR (200 MHz, DMSO-d_6) 7.62 (t, J = 8.2 Hz, 1H, H5″), 7.85 (m, 2H, H4″ + H6″), 8.63 (t, J = 2.2 Hz, 1H, H2″), 9.8 (br s, 1H, NH^+); MS (EI) m/z (rel intensity) 316 (M^+, 19), 286 (2), 246 (18), 233 (23), 109 (100), 96 (23). Anal. ($C_{16}H_{20}N_4O_3$·HCl) C, H, Cl, N.

1-[1-Azabicyclo[2.2.2]oct-3-yl]-3-(3-bromophenyl)imidazolidin-2-one (32): 72% yield (mp 132−136 °C); ^{1}H-NMR (200 MHz, $CDCl_3$): 7.0−7.3 (m, 2H, H4″ + H5″), 7.47 (m, 1H, H6″), 7.70 (s, 1H, H2″); FD MS 349. Anal. ($C_{16}H_{20}BrN_3O$) C, H, N.

***endo*-1-[8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-3-(3-chlorophenyl)imidazolidin-2-one, hydrochloride (33):** 68% yield (mp 264−268 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 2.0−2.5 (m, 8H, CH_2-2′ + CH_2-4′ + CH_2-6′ + CH_2-7′), 2.62 (d, J = 4.9 Hz, 3H, NCH_3), 3.50 (m, 2H, CH_2-5), 3.81 (m, 5H, CH_2-4 + H1′ + H5′ +H3′), 7.0−7.5 (m, 3H, H4″ + H5″ + H6″), 7.76 (t, J = 2.1 Hz, 1H, H2″), 9.7 (br s, 1H, NH^+); ^{1}H-NMR (200 MHz, $CDCl_3$, free base) 1.4−1.6 (m, 4H, H6′α + H7′α + H2′α + H4′α), 2.10 (m, 2H, H6′β + H7′β), 2.20 (s, 3H, NCH_3), 2.33 (dt, J = 14.0, 8.1 Hz, 2H, H2′β + H4′β), 3.19 (m, $\Delta\nu_{1/2}$ = 17 Hz, 2H, H1′ + H5′), 4.11 (tt, J = 8.1, 8.1 Hz, 1H, H3′), 6.9−7.5 (m, 3H, H4″ + H5″ + H6″), 7.54 (t, J = 2.1 Hz, 1H, H2″); MS (EI) m/z (rel intensity) 319 (M^+, 19), 223 (13), 196 (6), 124 (44), 96 (97), 82 (100). Anal. ($C_{17}H_{22}ClN_3O$·HCl) C, H, Cl, N.

***exo*-1-[8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-3-(3-chlorophenyl)imidazolidin-2-one, hydrochloride hydrate (34):** 70% yield (mp 239−243 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 1.75 (m, 2H, H2′β + H4′β), 1.95 (m, 2H, H6′α + H7′α), 2.2−2.5 (m,4H, H2′α + H4′α + H6′β + H7′β), 2.64 (d, J = 4.9 Hz, 3H, NCH_3), 3.45 (m, 2H, CH_2-5), 3.81 (m, 2H, CH_2-4), 3.90 (m, 2H, H1′ + H5′), 4.17 (tt, J = 5.9, 11.8 Hz, 1H, H3′), 6.9−7.5 (m, 3H, H4″ + H5″ + H6″), 7.55 (t, J = 2.1 Hz, 1H, H2″); ^{1}H-NMR (200 MHz, $CDCl_3$, free base) 1.58 (ddd, J = 12.8, 5.9, 3.3 Hz, 2H, H2′α + H4′α), 1.7−1.9 (m, 4H, H6′α + H7′α + H2′β + H4′β), 2.07 (m, 2H, H6′β + H7′β), 2.28 (s, 3H, NCH_3), 3.22 (m, $\Delta\nu_{1/2}$ = 9 Hz, 2H, H1′ + H5′), 3.43 (m, 2H, CH_2-5), 3.73 (m, 2H, CH_2-4), 4.20 (tt, J = 11.8, 5.9 Hz, 1H, H3′), 6.9−7.5 (m, 3H, H4″ + H5″ + H6″), 7.60 (t, J = 2.1 Hz, 1H, H2″); MS (EI) m/z (rel intensity) 319 (M^+, 12), 223 (18), 196 (5), 124 (88), 96 (80), 82 (100). Anal. ($C_{17}H_{22}ClN_3O$·HCl·H_2O) C, H, Cl, N.

***endo*-1-[8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-3-(5-chloro-2-methoxyphenyl)imidazolidin-2-one, hydrochloride (35)**: 41% yield (mp 224−228 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 6.80 (d, J = 7.9 Hz, 1H, H3″), 7.12 (dd, J = 7.9, 2.5 Hz, 1H, H4″), 7.36 (d, J = 2.5 Hz, 1H, H6″); MS (EI) m/z (rel intensity) 349 (M^+, 32), 253 (17), 170 (10), 124 (100), 96 (70), 82 (66). Anal. ($C_{18}H_{24}ClN_3O_2$·HCl) C, H, Cl, N.

***endo*-1-[8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-3-phenylimidazolidin-2-one, hydrochloride (36):** 68% yield (mp 252−257 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 6.99 (m, 1H, H4″), 7.30 (m, 2H, H3″ + H5″), 7.54 (m, 2H, H2″ + H6″); MS (EI) m/z (rel intensity) 285 (M^+, 11), 189 (41), 162 (10), 124 (64), 96 (85), 82 (100). Anal. ($C_{17}H_{23}N_3O$·HCl) C, H, Cl, N.

***endo*-1-[9-Methyl-9-azabicyclo[3.3.1]non-3-yl]-3-(3-chlorophenyl)imidazolidin-2-one, hydrochloride (37):** 62% yield (mp 243−249 °C); ^{1}H-NMR (400 MHz, DMSO-d_6) 1.3−1.6 (m, 3H, H6′α + H8′α + H7′β), 1.8−2.3 (m, 7H, CH_2-2′ + CH_2-4′ + H6′β + H8′β + H7′α), 2.79 (s, 3H, NCH_3), 3.53 (m, 2H, CH_2-5), 3.64 (br d, J = 10.6 Hz, 2H, H1′ + H5′), 3.82 (m, 2H, CH_2-4), 4.56 (tt, J = 12.4, 6.2 Hz, 1H, H3′), 6.9−7.4 (m, 3H, H4″ + H5″ + H6″), 7.74 (t, J = 2.0 Hz, 1H, H2″), 9.9 (br s, 1H NH^+); ^{1}H-NMR (400 MHz, DMSO-d_6, free base): 0.95 (m, 2H, H6′α + H8′α), 1.43 (m, 1H, H7′β), 1.56 (ddd, J = 13.0, 13.0, 2.8 Hz, H2′α + H4′α), 1.8−2.1 (m, 5H, H6′β + H8′β + H7′α + H2′β + H4′β), 2.40 (s, 3H, NCH_3), 3.02 (br d, J = 11.1 Hz, 2H, H1′ + H5′), 3.47 (m, 2H, CH_2-5), 3.76 (m, 2H, CH_2-4), 4.20 (tt, J = 12.4, 6.2 Hz, 1H, H3′), 6.9−7.4 (m, 3H, H4″ + H5″ + H6″), 7.74 (t, J = 2.1 Hz, 1H, H2″); ^{13}C-NMR (50 MHz, $CDCl_3$, free base) 14.1 (C7′), 24.4 (C6′ + C8′), 28.5 (C2′ + C4′), 40.1 (NCH_3), 38.8, 42.6 (C4 + C5), 44.9 (C3′), 51.5 (C1′ + C5′), 115.1, 117.1, 121.9, 129.7 (C2″ + C4″ + C5″ + C6″), 134.5, 141.8 (C1″ + C3″), 156.9 (C2); MS (EI) m/z (rel intensity) 333 (M^+, 21), 235 (3), 223 (7), 138 (100), 110 (70), 96 (82). Anal. ($C_{18}H_{24}ClN_3O$·HCl) C, H, Cl, N.

***exo*-1-[9-Methyl-9-azabicyclo[3.3.1]non-3-yl]-3-(3-chlorophenyl)imidazolidin-2-one (38):** 58% yield (mp 157.5−161.5 °C); ^{1}H-NMR (400 MHz, DMSO-d_6) 1.3−1.5 (m, 4H, H6′α + H8′α + H2′α + H4′α), 1.62 (m, 1H, H7′β), 1.75 (m, 1H, H7′α), 1.8−2.1 (m, 4H, H6′β + H8′β + H4′β + H2′β), 2.39 (s, 3H, NCH_3), 2.83 (narrow m, 2H, H1′ + H5′), 3.44 (m, 2H, CH_2-5), 3.77 (m, 2H, CH_2-4), 4.56 (tt, J = 12.4, 6.2 Hz, 1H, H3′), 6.9−7.4 (m, 3H, H4″ + H5″ + H6″), 7.77 (t, J = 2.1 Hz, 1H, H2″); ^{13}C-NMR (50 MHz, $CDCl_3$) 20.0 (C7′), 25.0 (C6′ + C8′), 30.2 (C2′ + C4′), 36.0, 42.5 (C4 + C5), 40.5 (NCH_3), 45.5 (C3′), 53.3 (C1′ + C5′), 114.9, 117.2, 122.0, 129.7 (C2″ + C4″ + C5″ + C6″), 134.5, 141.7 (C1″ + C3″), 156.8 (C2); MS (EI) m/z (rel intensity) 333 (M^+, 16), 235 (2), 223 (4), 138 (100), 110 (33), 96 (58). Anal. ($C_{18}H_{24}ClN_3O$) C, H, N.

***endo*-1-[9-Methyl-9-azabicyclo[3.3.1]non-3-yl]-3-phenylimidazolidin-2-one, hydrochloride (39)**: 63% yield (mp 243−245.5 °C); ^{1}H-NMR (400 MHz, DMSO-d_6) 6.98 (m, 1H, H4″), 7.30 (m, 2H, H3″ + H5″), 7.54 (m, 2H, H2″ + H6″); FAB-MS m/z 300 (M + H)$^+$. Anal. ($C_{18}H_{25}N_3O$·HCl) C, H, Cl, N.

***N*-[*endo*-9-Methyl-9-azabicyclo[3.3.1]non-3-yl]-*N*′-[(4-nitrophenoxy)carbonyl]-*N*′-(5-chloro-2-methoxyphenyl)-1,2-diaminoethane (20a)**. A solution of 4-nitrophenylchloroformate (1.3 g, 0.0065 mol) in 5 mL of dichloromethane was dropped at 0 °C to a solution of **20** (2 g; 0.0059 mol) and triethylamine (0.99 mL, 0.0071 mol) in 30 mL of dichloromethane. The mixture was stirred at 0 °C for 4 h, washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated to dryness after filtration. The crude product was purified by silica gel chromatography (EtOAc−MeOH−TEA, 80:15:5) as eluant to give 2.54 g (86% yield) of an amorphous yellow solid (mp 57−64 °C); ^{1}H-NMR (200 MHz, $CDCl_3$): 0.8−2.3 (m, 10H, CH_2-2′ + CH_2-4′ + CH_2-6′ + CH_2-7′ + CH_2-8′), 2.47 (s, 3H, NCH_3), 3.07 (d, J = 10.9 Hz, 2H, H2′ + H5′), 3.3−3.7 (m, 4H, $NHCH_2CH_2$), 3.81 (s, 3H, OCH_3), 4.1−4.7 (m, 2H, H3′ + $NHCH_2CH_2$), 6.5−6.7 (m, 3H, H3″ + H4″ + H6″), 7.37,8.27 (two m, 4H, $PhNO_2$); MS (EI) m/z (rel intensity) 502 (M^+, 3), 363 (22), 320 (34), 138 (100). Anal ($C_{25}H_{31}ClN_4O_5$) C, H, Cl, N.

***endo*-1-[9-Methyl-9-azabicyclo[3.3.1]non-3-yl]-3-(5-chloro-2-methoxyphenyl)imidazolidin-2-one, Hydrochloride (40).** A solution of **20a** (2.5 g; 0.005 mol) in 60 mL of anhydrous pyridine was refluxed 56 h. The solution was evaporated to dryness then purified by silica-gel chromatography (EtOAc−MeOH−TEA, 80:15:5) as eluant followed by treatment with an excess of a solution of HCl in EtOH. The crude salt was ground with anhydrous EtOH to give 1.1 g (61% yield) of an amorphous solid (mp 95−103 °C): ^{1}H-NMR (400 MHz, DMSO-d_6) 7.06 (d, J = 8.8 Hz, 1H, H3″), 7.23 (dd, J = 8.8, 2.6 Hz, 1H, H4″), 7.29 (d, J = 2.6 Hz, 1H, H6″); FD MS 363. Anal. ($C_{19}H_{26}ClN_3O_2$·HCl) C, H, Cl, N.

The quaternary ammonium iodide salts **75** and **76** were prepared by addition of an excess of methyl iodide to a solution of the corresponding free bases of **33** and **34** in MeOH. The resulting precipitates were collected by filtration and ground with acetone to give white solids.

***endo*-1-[8-Dimethyl-8-azabicyclo[3.2.1]octyl]-3-(3-chlorophenyl)imidazolidin-2-one, iodide (75):** ^{1}H-NMR (400 MHz, DMSO-d_6) 2.10 (m, 2H, H6′α + H7′α), 2.21 (d, J = 17.0 Hz, 2H, H2′α + H4′α), 2.33 (m, 2H, H6′β + H7′β), 2.58 (ddd, J = 16.7, 9.4, 4.8 Hz, 2H, H2′β + H4′β), 3.00, 3.12 (two s, 6H, $N(CH_3)_2$), 3.60 (m, 2H, CH_2-5), 3.79 (m, 2H, CH_2-4), 3.84 (m, 2H, H1′ + H5′), 4.14 (t, J = 9.2 Hz, 1H, H3′), 7.0−7.5 (m, 3H, H4″ + H5″ + H6″), 7.77 (t, J = 2.1 Hz, 1H, H2″). Anal. ($C_{18}H_{25}ClIN_3O$) C, H, N.

***exo*-1-[8-Dimethyl-8-azabicyclo[3.2.1]oct-yl]-3-(3-chlorophenyl)imidazolidin-2-one, iodide (76):** ^{1}H-NMR (400 MHz, DMSO-d_6) 1.84 (dd, J = 13.4, 6.6 Hz, 2H, H2′α + H4′α), 2.07 (m, 2H, H6′α + H7′α), 2.35 (m, 2H, H6′β + H7′β), 2.52 (m, 2H, H2′β + H4′β), 3.00, 3.29 (two s, 6H, $N(CH_3)_2$), 3.55 (m, 2H, CH_2-5), 3.80 (m, 2H, CH_2-4), 3.90 (m, 3H, H3′ + H1′ + H5′), 7.0−7.4 (m, 3H, H4″ + H5″ + H6″), 7.72 (t, J = 2.1 Hz, 1H, H2″). Anal. ($C_{18}H_{25}ClIN_3O$) C, H, N.

General Procedure for the Preparation of Intermediates 41−54. The procedure is reported for the preparation of 1-[(5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl)methyl]-3-(3-chlorophenyl)imidazolidin-2-one (**41**). 50% NaH (0.3 g,0.0062mol) was added at 0 °C to a stirred solution of 1-(3-chlorophenyl)imidazolidin-2-one (1.2 g, 0.0061 mol) in 20 mL of anhydrous DMF kept under nitrogen atmosphere. The solution was stirred for 1 h at 60 °C, and then 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1*H*-imidazole (2.3 g, 0.0061 mol) was added at room temperature. The mixture was stirred 6 h at 90 °C, cooled, poured into water, and extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated to dryness after filtration. The residue was purified by silica gel chromatography (EtOAc as eluant) to give 2.1 g of the desired product as a white solid. ^{1}H-NMR (200 MHz, $CDCl_3$) 1.47 (s, 3H, CH_3-5′), 3.52 (m, 2H, CH_2-5), 3.74 (m, 2H, CH_2-4), 4.36 (s, 2H, CH_2-4′), 6.9−7.5 (m, 19H, 3-Ph + H2′ + H4″ + H5″ + H6″), 7.57 (t, J = 2.1 Hz, 1H, H2″).; FD MS 532. Anal. ($C_{33}H_{29}ClN_4O$) C, H, Cl, N.

Compounds **42**−**54** were similarly prepared starting from related 1-arylimidazolidin-2-ones. Compound **55** was prepared employing 5-chloromethyl-1-(triphenylmethyl)-1*H*-imidazole as alkylating agent. Yields and analytical data are given in Table 2. The ^{1}H NMR spectra and MS data were consistent with the assigned structures.

Typical Deprotection Procedure of Trityl Derivatives to 1-(Imidazolylalkyl)-3-phenylimidazolidin-2-ones (56−70). The procedure is reported for the preparation of 1-(3-chlorophenyl)-3-[(5-methyl-1*H*-imidazol-4-yl)methyl]imidazolidin-2-one (**56**). A solution of **41** (2 g; 0.0038 mol) in AcOH (30 mL), H_2O (30 mL), and THF (30 mL) was heated at reflux for 1 h. The solution was cooled and poured into 1 N HCl (100 mL) and washed with ethyl acetate. The aqueous layer was basified with K_2CO_3 to pH 9 and then extracted with CH_2Cl_2. The organic phase was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and, after filtration, evaporated to dryness. The residue was ground with dry Et_2O to obtain 0.8 g (73% yield) of the product as a white solid (mp 229.5−232.5 °C dec): ^{1}H-NMR (200 MHz, $CDCl_3$) 2.28 (s, 3H, CH_3-5′), 3.50 (m, 2H, CH_2-5), 3.75 (m, 2H, CH_2-4), 4.35 (s, 2H, CH_2-4′), 6.9−7.5 (m, 3H, H4″ + H5″ + H6″), 7.47 (s, 1H, H2′), 7.58 (t, J = 2.1 Hz, 1H, H2″); MS (EI) m/z (rel intensity) 290 (M^+, 6), 275 (2), 209 (3), 196 (10), 140 (16), 96 (83), 95 (100). Anal. ($C_{14}H_{15}ClN_4O$) C, H, Cl, N.

The following compounds were also prepared by the general procedure described above.

1-(3-Bromophenyl)-3-[(5-methyl-1*H*-imidazol-4-yl)-methyl]imidazolidin-2-one (57): 88% yield (mp 233−238.5 °C); ^{1}H-NMR (400 MHz, DMSO-d_6) 2.15 (s, 3H, CH_3-5′), 3.36 (m, 2H, CH_2-5), 3.73 (m, 2H, CH_2-4), 4.22 (s, 2H, CH_2-4′), 7.1−7.5 (m, 3H, H4″ + H5″ + H6″), 7.43 (s, 1H, H2′), 7.92 (t, J = 2.1 Hz, 1H, H2″), 11.8 (br s, 1H, NH-1′); FAB-MS m/z 335 (M + H)$^+$. Anal. ($C_{14}H_{15}BrN_4O$) C, H, Br, N.

1-(3,5-Dichlorophenyl)-3-[(5-methyl-1*H*-imidazol-4-yl)-methyl]imidazolidin-2-one (58): 86% yield (mp 242−249 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 7.14 (t, J = 1.8 Hz, 1H, H4″), 7.62(d, J = 1.8 Hz. 2H, H2″ + H6″); MS (EI) m/z (rel intensity) 324 (M^+, 12), 309 (5), 243 (4), 230 (9), 174 (15), 96 (100), 95 (92). Anal. ($C_{14}H_{14}Cl_2N_4O$) C, H, Cl, N.

1-[(5-Methyl-1*H*-imidazol-4-yl)methyl]-3-phenylimidazolidin-2-one (59): 84% yield (mp 207−210.5 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 6.96 (m, 1H, H4″), 7.29 (m, 2H, H3″ + H5″), 7.54 (m, 2H, H2″ + H6″); MS (EI) m/z (rel intensity) 256 (M^+, 58), 241 (13), 175 (15), 162 (94), 106 (71), 96 (94), 95 (100). Anal. ($C_{14}H_{16}N_4O$) C, H, N.

1-(3-Cyanophenyl)-3-[(5-methyl-1*H*-imidazol-4-yl)-methyl]imidazolidin-2-one (60): 84% yield (mp 221−226 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 7.3−7.6 (m, 2H, H4″ + H5″), 7.85 (m, 1H, H6″), 8.00 (t, J = 1.8 Hz, 1H, H2″); MS (EI) m/z (rel intensity) 281 (M^+, 2), 200 (12), 187 (18), 96 (88), 95 (100). Anal. ($C_{15}H_{15}N_5O$) C, H, N.

1-[(5-Methyl-1*H*-imidazol-4-yl)methyl]-3-[3-(methylthio)phenyl]imidazolidin-2-one (61): 89% yield (mp 185−190 °C); ^{1}H-NMR (200 MHz, $CDCl_3$): 2.49 (s, 3H, SCH_3), 6.93 (m, 1H, H4″), 7.24 (m, 2H, H5″ + H6″), 7.54 (m, 1H, H2″); MS (EI) m/z (rel intensity) 302 (M^+, 76), 287 (8), 221 (11), 208 (76), 152 (50), 96 (100), 95 (80). Anal. ($C_{15}H_{18}N_4OS$) C, H, N, S.

1-[(5-Methyl-1*H*-imidazol-4-yl)methyl]-3-(3-methylphenyl)imidazolidin-2-one (62): 88% yield (mp 216−221 °C); ^{1}H-NMR (400 MHz, DMSO-d_6) 2.26 (s, 3H, CH_3-3″), 6.78 (d, J = 7.5 Hz, 1H, H4″), 7.16 (t, J = 7.5 Hz, 1H, H5″), 7.35 (m, 2H, H2″ + H6″); MS (EI) m/z (rel intensity) 270 (M^+, 35), 255 (6), 189 (7), 176 (43), 120 (50), 96 (72), 95 (100). Anal. ($C_{15}H_{18}N_4O$) C, H, N.

1-(3,5-Dimethylphenyl)-3-[(5-methyl-1*H*-imidazol-4-yl)-methyl]imidazolidin-2-one (63): 83% yield (mp 246−249 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 2.22 (s, 6H, CH_3-3″ + CH_3-5″), 6.61 (s, 1H, H4″), 7.17 (s, 2H, H2″ + H6″); MS (EI) m/z (rel intensity) 284 (M^+, 20), 269 (2), 203 (3), 190 (39), 134 (51), 96 (90), 95 (100). Anal. ($C_{16}H_{20}N_4O$) C, H, N.

1-(4-Chlorophenyl)-3-[(5-methyl-1*H*-imidazol-4-yl)-methyl]imidazolidin-2-one (64): 77% yield (mp 230−234 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 7.33 (m, 2H, H3″ + H5″), 7.57 (m, 2H, H2″ + H6″); MS (EI) m/z (rel intensity) 290 (M^+, 12), 275 (2), 209 (2), 196 (16), 140 (18), 96 (80), 95 (100). Anal. ($C_{14}H_{15}ClN_4O$) C, H, Cl, N.

1-(2-Chlorophenyl)-3-[(5-methyl-1*H*-imidazol-4-yl)-methyl]imidazolidin-2-one (65): 70% yield (mp 159.5−167.5 °C); ^{1}H-NMR (400 MHz, DMSO-d_6) 7.2−7.6 (m, 4H, H3″ + H4″ + H5″ + H6″); MS (EI) m/z (rel intensity) 290 (M^+, 54), 275 (21), 209 (13), 196 (25), 140 (18), 96 (75), 95 (100). Anal. ($C_{14}H_{15}ClN_4O$) C, H, Cl, N.

1-[(5-Methyl-1*H*-imidazol-4-yl)methyl]-3-(trifluoromethyl)imidazolidin-2-one (66): 84% yield (mp 205−209 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 7.2−7.7 (m, 3H, H4″ + H5″ + H6″), 8.12 (s, 1H, H2″); MS (EI) m/z (rel intensity) 324 (M^+, 33), 309 (6), 243 (6), 230 (13), 174 (19), 96 (78), 95 (100). Anal. ($C_{15}H_{15}F_3N_4O$) C, H, N.

1-[(5-Methyl-1*H*-imidazol-4-yl)methyl]-3-(3-nitrophenyl)-imidazolidin-2-one (67): 88% yield (mp 227−231 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 7.57 (dd, J = 9.0, 7.4 Hz, 1H, H5″), 7.80 (m, 2H, H6″ + H4″), 8.62 (t, J = 2.3 Hz, 1H, H2″); MS (EI) m/z (rel intensity) 301 (M^+, 20), 286 (4), 220 (3), 207 (5), 151 (6), 96 (86), 95 (100). Anal. ($C_{14}H_{15}N_5O_3$) C, H, N.

1-(3-Fluorophenyl)-3-[(5-methyl-1*H*-imidazol-4-yl)-methyl]imidazolidin-2-one (68): 90% yield (mp 220.5−223.5 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 6.78 (m, 1H, H4″), 7.1−7.7 (m, 3H, H5″ + H6″ + H2″); FAB-MS m/z 275 (M + H)$^+$. Anal. ($C_{14}H_{15}FN_4O$) C, H, N:

1-(3-Methoxyphenyl)-3-[(5-methyl-1*H*-imidazol-4-yl)-methyl]imidazolidin-2-one (69): 84% yield (mp 183−187 °C); ^{1}H-NMR (200 MHz, DMSO-d_6) 6.55 (ddd, J = 8.1, 2.4, 0.9 Hz, 1H, H4″), 7.03 (ddd, J = 8.1, 2.0, 0.9 Hz, 1H, H6″), 7.1−7.5 (m, 2H, H2″ + H5″); FAB-MS m/z 287 (M + H)$^+$. Anal. ($C_{15}H_{18}N_4O_2$) C, H, N.

1-[(1*H*-Imidazol-4-yl)methyl]-3-phenylimidazolidin-2-one (70): 72% yield (mp 201−203 °C); ^{1}H-NMR (400 MHz, DMSO-d_6) 3.38 (m, 2H, CH_2-5), 3.74 (m, 2H, CH_2-4), 4.27 (s, 2H, CH_2-4′), 6.97 (m, 1H, H4″), 7.01 (s, 1H, H5′), 7.30 (m, 2H, H3″ + H5″), 7.56 (m, 3H, H2′ + H6″ + H2″); MS (EI) m/z (rel intensity) 242 (M^+, 100), 175 (3), 162 (64), 106 (86), 82 (90), 81 (79). Anal. ($C_{13}H_{14}N_4O$) C, H, N.

Preparation of 1-[(1-Ethyl-4-methyl-1*H*-imidazol-5-yl)-methyl]-3-phenylimidazolidin-2-one, Hydrochloride (71) and 1-[(1-Ethyl-5-methyl-1*H*-imidazol-4-yl)methyl]-3-phenylimidazolidin-2-one, Hydrochloride (72). 50% NaH (0.198 g, 0.0041 mol) was added at 0 °C to a solution of **59** (1 g; 0.0039 mol) in 20 mL of anhydrous DMF kept under nitrogen atmosphere. After 15 min, ethyl iodide (0.33 mL, 0.0041 mol) was dropped. Stirring was continued for 1 h at room temperature. The mixture was poured into H_2O and extracted with CH_2Cl_2. The organic layer was washed with

saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated to dryness after filtration. The residue was purified by silica gel chromatography using EtOAc−MeOH−30% NH_4OH (190:10:1) as eluant. Both the first eluted and second eluted compounds were treated with an excess of a solution of HCl in EtOH. The crude salts were collected by filtration and recrystallized from anhydrous EtOH to afford 0.13 g of **71** (white solid, 10% yield, mp 227−230 °C) and 0.57 g of **72** (white solid, 40% yield, mp 225−230 °C).

71: ^{1}H-NMR (400 MHz, DMSO-d_6) 1.37 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.34 (s, 3H, CH_3-4′), 3.36 (m, 2H, CH_2-5), 3.78 (m, 2H, CH_2-4), 4.16 (q, J = 7.3 Hz, 2H, CH_2CH_3), 4.50 (s, 2H, CH_2-5′), 6.9−7.6 (m, 5H, Ph), 9.13 (s, 1H, H2′); MS (DEP) *m/z* (rel intensity) 284 (M^+, 54), 269 (5), 255 (6), 175 (11), 162 (5), 123 (100), 95 (27). Anal. ($C_{16}H_{20}N_4O$·HCl) C, H, Cl, N .

72: ^{1}H-NMR (400 MHz, DMSO-d_6) 1.37 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.32 (s, 3H, CH_3-5′), 3.47 (m, 2H, CH_2-5), 3.78 (m, 2H, CH_2-4), 4.11 (q, J = 7.3 Hz, 2H, CH_2CH_3), 4.44 (s, 2H, CH_2-4′), 6.9−7.6 (m, 5H, Ph), 9.11 (s, 1H, H2′); MS (DEP) *m/z* (rel intensity) 284 (M^+, 41), 269 (2), 255 (3), 124 (100), 95 (39). Anal. ($C_{16}H_{20}N_4O$·HCl) C, H, Cl, N.

Following the general procedure described above 1-[(1,4-dimethyl-1*H*-imidazol-5-yl)methyl]-3-phenylimidazolidin-2-one, hydrochloride hemihydrate (**73**) (white solid, mp 219−223 °C, 8% yield) and 1-[(1,5-dimethyl-1*H*-imidazol-4-yl)methyl]-3-phenylimidazolidin-2-one, hydrochloride (**74**) (white solid, mp 250−270 °C dec, 47% yield) were obtained starting from **59** and employing methyl iodide as alkylating agent.

73: ^{1}H-NMR (400 MHz, DMSO-d_6) 2.33 (s, 3H, CH_3-4′), 3.37 (m, 2H, CH_2-5), 3.78 (m, 5H, CH_2-4 + NCH_3), 4.49 (s, 2H, CH_2-5′), 6.9−7.6 (m, 5H, Ph), 8.98 (s, 1H, H2′); MS (EI) *m/z* 270 (M^+, 13), 255 (1), 175 (1), 110 (100), 109 (53). Anal. ($C_{15}H_{18}N_4O$·HCl) C, H, Cl, N.

74: ^{1}H-NMR (400 MHz, DMSO-d_6) 2.29 (s, 3H, CH_3-5′), 3.43 (m, 2H, CH_2-5), 3.72 (s, 3H, NCH_3), 3.78 (m, 2H, CH_2-4), 4.43 (s, 2H, CH_2-4′), 6.9−7.6 (m, 5H, Ph), 8.97 (s, 1H, H2′); MS (EI) *m/z* (rel intensity) 270 (M^+, 10), 255 (1), 175 (4), 162 (5), 109 (100). Anal. ($C_{15}H_{18}N_4O$·HCl) C, H, Cl, N.

Pharmacology. Binding Assays. *In vitro* affinity of compounds for central 5-HT$_3$ receptor sites was determined by their ability to displace the radioligand [^{3}H]BRL 43694 in the rat entorhinal cortex according to the method of Nelson et al.[33] The interaction with 5-HT$_4$ receptor site was evaluated by their ability to displace the radioligand [^{3}H]GR113808 in the rat striatum according to Grossman et al.[34] Affinity for α_1, α_2, D_1, D_2, 5-HT$_{1A}$, 5-HT$_2$ and M_{1+2} binding site was also assessed in rat brain membrane using [^{3}H]prazosin, [^{3}H]-yohimbine, [^{3}H]SCH23390, [^{3}H]-8-OH-DPAT, [^{3}H]ketanserine, and [^{3}H]QNB as ligands according to established methods. The analysis of binding data was carried out by the "Ligand" computer program of Munson et al.[35] Average K_i (±SEM) values were calculated from at least three determinations of displacement curves, each consisting of 10 concentrations in triplicate.

Isolated Tissues. Serotonin 5-HT$_3$ and 5-HT$_4$ activities were evaluated in the guinea pig ileum (GPI) according to Eglen et al.[36] and in rat tunica muscularis mucosae precontracted by carbachol as reported by Baxter et al.[37] respectively. The antagonist potency expressed as K_b (±SEM) values was estimated in the GPI assay for ondansetron, tropisetron, granisetron, and BRL 46470 by the method of Arunlakshana et al.[38] The K_b (±SEM) for the remaining compounds were estimated by the method of Furchgot[39] using a single concentration of antagonist.

***In Vivo* 5-HT$_3$ Activity.** The compounds were evaluated for antagonism of the Bezold Jarisch reflex evoked by 30 μg/kg iv of 5-HT in ethylurethane (1.25 g/kg ip) anesthetized rats according to Fozard.[40] The rapid and transient drop in heart rate due to the administration of 5-HT was quantified in the absence and presence of antagonist compounds. The dose required to reduce the 5-HT-evoked response to 50% of the control response (ID_{50}) was determined by the regression analysis, and confidence limits for p = 95 (95% CL) were calculated.

Molecular Modeling. The three-dimensional structures of the compounds reported in Figures 3 and 4 were either built from available structural fragments of the INSIGHTII version 2.3 software package (Biosym) or by referring to Cambridge Structural Database. The database was accessed by the substructure search feature of ISIS-Base (MDL). The built structures were energy minimized by DISCOVER, version 2.9, with molecular mechanics using gradient method and cvff.frc force fields. The minimization was carried out until the rms of gradients was less than 0.001 kcal/(mol A). The structures were then submitted to a complete torsional angle search with increment of 30°, for the bonds free to rotate, discarding the conformations above 5 kcal/mol. The distance between the pharmacophoric features of the present class of compounds was measured in the Analysis module (Biosym). The conformations of the compounds used for the generation of automated pharmacophoric pattern were submitted to the APEX-3D software (Biosym) in MDL format. The alignment of compounds to the pharmacophore model generated by APEX-3D were done using the Search-Compare module of INSIGHTII.

The three-dimensional structures of the substructures A and B were obtained by referring to fragments of compounds reported in Cambridge Structural Database. The atomic charges were computed by the program MOPAC using AM1 semiempirical method. The electrostatic isopotential surfaces were calculated with DelPhi, version 2.3 (Biosym). The potentials were expressed in kcal/mol, and the value of +1 was represented in red, −1 in cyan, and 0 in yellow.

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JM970060O