Thiazole as a Carbonyl Bioisostere. A Novel Class of Highly Potent and Selective 5-HT_3 Receptor Antagonists

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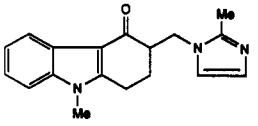
A novel structural class of highly potent and selective 5-HT_3 receptor antagonists is described. The compounds in this new series contain a thiazole moiety linking an aromatic group and a nitrogen-containing basic region; the thiazole group appears to be acting as a carbonyl bioisostere in this system. An optimized member of this series, 4-(2-methoxyphenyl)-2-[[4(5)-methyl-5(4)-imidazolyl]methyl]thiazole (**5**), exhibits oral activity in the Bezold-Jarisch reflex paradigm comparable to or better than the standard agents ondansetron (1) and ICS-205-930 (**2**). Several of the structure-activity relationships are rationalized in terms of a computer pharmacophore model for 5-HT_3 receptor binding.

Introduction

During recent years, there has been intense effort aimed at the identification and functional characterization of serotonin (5-HT) receptor subtypes and the preparation of ligands with potent binding affinity and receptor subtype specificity.[1] The presence of a receptor subtype in the periphery that has now been classified as 5-HT_3 has been known for some time,[2] while more recent data have suggested the existence of 5-HT_3 binding sites in the brain.[3] Several compounds exhibiting high affinity for this receptor have been identified. Members of this class of agents, typified by 1 (ondansetron)[4] and 2 (ICS-205-930),[5]



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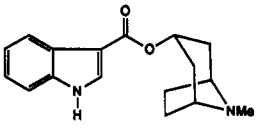

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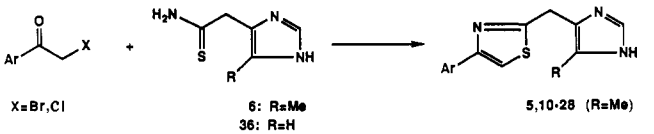
have been shown to be highly effective clinically for the blockade of chemotherapy-induced emesis,[6] an event suggested to be modulated by 5-HT_3 receptors in the *area postrema*.[7] More exciting, perhaps, have been pharmacological, behavioral, and neurochemical results suggesting that 5-HT_3 receptor antagonists may play a useful role in the amelioration of central nervous system disorders such as schizophrenia or anxiety, through the selective modulation of mesolimbic dopaminergic pathways,[8] or memory disorders, as 5-HT_3 receptors also have been shown to modulate cholinergic neurons.[9]

The selective 5-HT_3 receptor antagonists reported to date may be represented by the general structure shown below, in which a lipophilic aromatic group is linked by a carbonyl-containing side chain to a nitrogenous basic moiety.

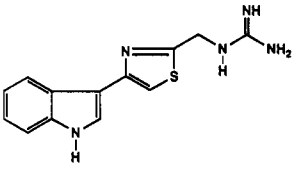
Scheme I



X=Br,Cl 6: R=Me 36: R=H 5,10-28 (R=Me)

Ar----(carbonyl)-----base

During the course of screening for a 5-HT_3 receptor antagonist lead structure for psychotherapeutic use, guanidine **3** was discovered to possess high affinity binding for 5-HT_3 receptors as well as show potent inhibition of serotonin-induced bradycardia in rats [Bezold-Jarisch (B-J) reflex], a demonstration of 5-HT_3 receptor antagonist activity. However, compound **3** was found to exhibit mixed agonist/antagonist properties as evidenced by its own ability to induce a transient bradycardia in rat upon iv administration, which could be blocked by prior administration of the selective 5-HT_3 receptor antagonist **2**. Furthermore, the highly polar guanidine substituent reduces the probability of achieving effective penetration of the blood-brain barrier and consequently diminishes the potential of achieving psychotherapeutic efficacy. A synthesis and screening program around **3**, examining several basic replacements for the guanidine moiety, led to the preparation of the imidazole **4**, a novel, less polar compound devoid of agonist character and possessing moderate 5-HT_3 receptor binding affinity.[10]



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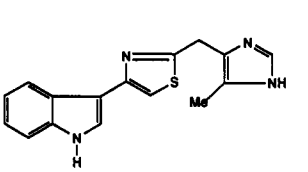

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Herein, we report the synthesis of a series of highly potent 5-HT_3 receptor antagonists related to **4** which, like the original lead **3**, lack a carbonyl group and instead contain a thiazole bridge between the aryl and basic substituents. Structure-activity relationships (SAR) for the aryl substituent, which diverge from related compounds

(1) Peroutka, S. J. *Annu. Rev. Neurosci.* **1988**, *11*, 45 and references therein.
(2) Gaddum, J. H.; Picarelli, Z. P. *Br. J. Pharmacol. Chemother.* **1957**, *12*, 323.
(3) Kilpatrick, G. J.; Jones, B. J.; Tyers, M. B. *Nature* **1987**, *330*, 746.
(4) Butler, A.; Hill, J. M.; Ireland, S. J.; Jordan, C. C.; Tyers, M. B. *Br. J. Pharmacol.* **1988**, *94*, 397.
(5) Richardson, B. P.; Engel, G.; Donatsch, P.; Stadler, P. A. *Nature* **1985**, *316*, 126.
(6) Cunningham, D.; Pople, A.; Ford, H. T.; Hawthorn, J.; Gazet, J. C.; Challoner, T. *Lancet* **1987**, *i*, 1461.
(7) Higgins, G. A.; Kilpatrick, G. J.; Bunce, K. T.; Jones, B. J.; Tyers, M. B. *Br. J. Pharmacol.* **1989**, *97*, 247 and references therein.
(8) For a review of this area, see: Trickelbank, M. D. *Trends Pharmacol. Sci.* **1989**, *10*, 127.
(9) Barnes, J. M.; Barnes, N. M.; Costall, B.; Naylor, R. J.; Tyers, M. B. *Nature* **1989**, *338*, 762.
(10) Nagel, A. A.; Rosen, T.; Rizzi, J.; Daffeh, J.; Guarino, K.; Nowakowski, J.; Vincent, L. A.; Heym, J.; McLean, S.; Seeger, T.; Connolly, M.; Schmidt, A. W.; Siok, C. *J. Med. Chem.* **1990**, *33*, 13.

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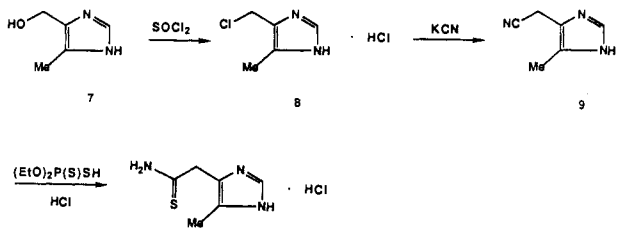
Scheme II



Scheme III

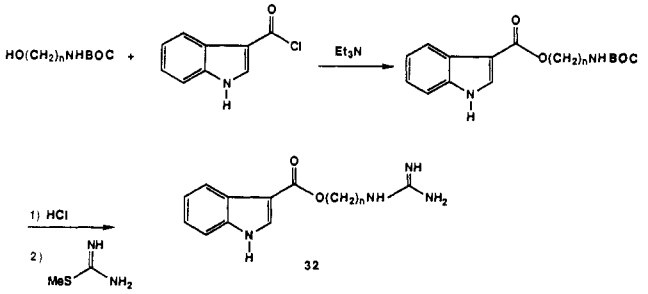
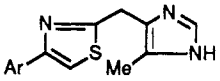


Table I. Structures of Compounds



no.[a]	Ar	formula	mp, °C
4	indol-3-yl	$C_{16}H_{14}N_4S$	oil
5	*o*-$MeOC_6H_4$	$C_{15}H_{15}N_3OS \cdot {}^1/_4H_2O$	159–161
10	C_6H_5	$C_{14}H_{13}N_3S$	138–143
11	quinolin-8-yl	$C_{17}H_{15}N_4S \cdot HCl$	>245
12	*o*-FC_6H_4	$C_{14}H_{12}FN_3S$	oil
13	*o*-$EtOC_6H_4$	$C_{16}H_{17}N_3OS$	oil
14	*o*-HOC_6H_4	$C_{14}H_{13}N_3OS$	181–183
15	*o*-MeC_6H_4	$C_{15}H_{15}N_3S$	131
16	*o*-$CF_3C_6H_4$	$C_{15}H_{12}F_3N_3S \cdot {}^3/_8H_2O$	oil
17	*m*-ClC_6H_4	$C_{14}H_{12}ClN_3S \cdot {}^5/_8H_2O$	186–187
18	*m*-$MeOC_6H_4$	$C_{15}H_{15}N_3OS \cdot {}^2/_3H_2O$	oil
19	*m*-FC_6H_4	$C_{14}H_{12}FN_3S \cdot 2H_2O$	178–179
20	*m*-BrC_6H_4	$C_{14}H_{12}BrN_3S$	200
21	*p*-FC_6H_4	$C_{14}H_{12}FN_3S$	196–200
22	*p*-MeC_6H_4	$C_{15}H_{15}N_3S$	
23	*p*-BrC_6H_4	$C_{14}H_{12}BrN_3S$	
24	*p*-$MeOC_6H_4$	$C_{15}H_{15}NO_3S \cdot {}^1/_2H_2O$	165–166
25	*p*-ClC_6H_4	$C_{14}H_{12}ClN_3S$	195
26	1-methoxynaphth-2-yl	$C_{19}H_{17}N_3OS \cdot {}^1/_2H_2O$	oil
27	2-methoxynaphth-1-yl	$C_{19}H_{17}N_3OS \cdot {}^1/_2H_2O$	245–247
28	2,6-$(MeO)_2C_6H_3$	$C_{16}H_{17}N_3O_2S \cdot 1.1H_2O$	oil

[a] All compounds have high-field ^1H NMR spectra, mass spectra, combustion analysis (C, H, N ± 0.4% of theoretical value) and/or high-resolution mass spectra that are consistent with the indicated structures. Compounds for which high-resolution mass spectral data were obtained were homogeneous by thin-layer chromatographic analysis.

such as **2**, are also discussed. Compounds in this study were evaluated for 5-HT_3 receptor binding affinity by using displacement of [^{3}H]-**2** binding to NG-108-15 cells and for 5-HT_3 receptor antagonist activity by examining their ability to block the serotonin-induced Bezold–Jarisch reflex in rats. Several of the structure–activity relationships developed in this series may be rationalized by using a three-component pharmacophore computer model for 5-HT_3 receptor binding that was developed based on the structures of known potent 5-HT_3 receptor ligands.[11]

Results and Discussion

Chemistry. The primary compounds in this study were prepared in a highly convergent manner, involving the condensation of an appropriately substituted α-halo ketone and imidazolethioamide **6** (Scheme I). The synthesis of the key reagent **6**[10] is outlined in Scheme II. Treatment of 4-methyl-5-imidazolemethanol with thionyl chloride provides (chloromethyl)imidazole **8**.[12] Displacement of chloride is accomplished by exposure of **8** to potassium cyanide. Subsequent reaction of nitrile **9**[13] with diethyl dithiophosphate[14] in the presence of hydrochloric acid provides the desired thioamide **6**, as its hydrochoride salt. This hygroscopic salt is used in subsequent condensation reactions (Scheme I) without futher purification. The compounds prepared in this manner are shown in Table I. The related desmethylimidazole analogues **33–35** were prepared in a similar fashion employing the corresponding thioamide **36**.[10]

The guanidine ester derivatives **32** were prepared by acylation of the appropriate *N*-(*tert*-butoxycarbonyl)amino alcohol with 3-(chlorocarbonyl)indole followed by acidic cleavage of the nitrogen protecting group and guanidine formation using 2-methyl-2-thiopseudourea sulfate (Scheme III).

Table II. 5-HT_3 Receptor Binding Affinity[a] versus [^{3}H]-**2** in Neuroblastoma–Glioma NG-108-15 Cells

no.	K_i ± SEM, nM	no.	K_i, nM
4	12 ± 1	20	2.0 ± 1
5	0.42 ± 0.1	21	4.9 ± 0.5
10	1.8 ± 0.4	22	110 ± 60
11	1.0 ± 0.2	23	270 ± 30
12	1.94 ± 0.3	24	390 ± 60
13	0.95 ± 0.6	25	34 ± 9
14	1.5 ± 0.5	26	95 ± 20
15	8.7 ± 3	27	400 ± 20
16	61 ± 10	28	430 ± 50
17	0.88 ± 0.4	1 (ondansetron)	16.2 ± 5.7
18	2.0 ± 0	2 (ICS-205-930)	2.7 ± 0.3
19	3.7 ± 2		

[a] Unless noted otherwise, all data represent a minimum of two determinations.

Table III. Inhibition of Bezold–Jarisch Reflex[a] by 5-HT_3 Receptor Antagonists

no.	dose, $\mu g\ kg^{-1}$ iv	*n*	% inhibition ± SEM
4	100	3	45.2 ± 5.5
5	100	1	100
	5	1	88.5
	2	3	57.9 ± 9.3
10	100	1	100
	20	2	85.6 ± 0.6
	2	3	10.7 ± 9.4
11	20	1	91.9
	2	2	43.0 ± 13.9
12	2	1	66.4
1	20	4	89.7 ± 3.8
	2	6	42.7 ± 8.0
2	2	10	77.5 ± 3.1

[a] Serotonin was administered at a dose of 100 $\mu g\ kg^{-1}$ iv 1 min posttreatment with drug at the specified dose.

Biological Evaluation of Compounds

Structure–Activity Relationships. Compounds **4**, **5**, and **10–28** were evaluated for 5-HT_3 receptor binding affinity versus [^{3}H]ICS-205-930 in neuroblastoma–glioma NG-108-15 cells.[15] The K_i values are shown in Table II.

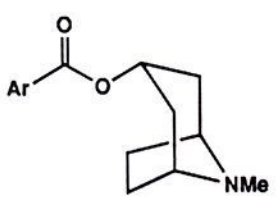
(11) Rizzi, J. P.; Nagel, A. A.; Rosen, T.; McLean, S.; Seeger, T. *J. Med. Chem.*, following paper in this issue.
(12) Bagley, J. R.; Riley, T. N. *J. Heterocycl. Chem.* **1981**, *19*, 485.
(13) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Roe, A. M.; Slater, R. A. *J. Med. Chem.* **1976**, *19*, 923.
(14) Shabana, R.; Meyer, H. J.; Lawesson, S. O. *Phosphorus Sulfur* **1985**, *25*, 297.

Table IV. Receptors at Which Compound **10** Exhibits ≫1 μM Binding Affinity (K_i)

receptor	radioligand
D_1	[^{3}H]SCH 23390
D_2	[^{3}H]spiperone
5-HT_{1A}	[^{3}H]-8-HODPAT
5-HT_{1B}	[^{3}H]-5-HT (rat cortex)
5-HT_{1C}	[^{3}H]mesulergine
5-HT_{1D}	[^{3}H]-5-HT (bovine caudate)
5-HT_2	[^{3}H]ketanserin
α_1	[^{3}H]prazosin
α_2	[^{3}H]-*p*-aminoclonidine (PAC)
β	[^{3}H]dihydroalprenolol (DHA)
H_1	[^{3}H]mepyramine
M-cholinergic	[^{3}H]QNB
benzodiazepine	[^{3}H]flunitrazepam
σ	[^{3}H]-(+)-3-(3-hydroxyphenyl)-*N*-1-propyl-piperidine ((+)-3-PPP)
μ opiate	[^{3}H]naloxone

The corresponding values for **1** and **2** are provided for comparison. Selected compounds were examined in the B–J reflex assay for their ability to block serotonin-induced bradycardia.[16] This assay was employed as a secondary screen to further profile in vitro binding leads, since it is a sensitive in vivo measure of 5-HT_3 functional activity. The data from these experiments are shown in Table III; the results for **1** and **2** are also provided. All of these compounds exhibit full antagonist activity in this functional assay.

Replacement of the indole moiety in **4** with a phenyl substituent results in a significant increase in binding affinity (K_i = 12 nM → K_i = 1.8 nM) as well as improved potency in the B–J reflex assay.[10] This finding is quite interesting, as a simlar modification to the structure of **2** (to give **29**) results in a greater than 100-fold reduction in



2: Ar=indol-3-yl, K_i=2.7nm
29: Ar=phenyl, Ki=329 nM

binding affinity. On the basis of this result, several substituted-phenyl analogues of **10** were synthesized in order to optimize 5-HT_3 receptor binding affinity. Several structure–activity features emerge. Modifications at the 2-position of the phenyl ring are generally well tolerated. Introduction of a 2-methoxy substituent provides compound **5**, the agent with the best overall properties in this study. This compound shows improved binding affinity (K_i = 0.42 nM) with respect to **10** as well as the standard agents **2** (K_i = 2.7 nM) and **1** (K_i = 16 nM). Upon iv administration, the rank order of potency in the B–J reflex assay is **2** > **5** > **1**. Results for the oral evaluation of these agents in this paradigm are discussed below.

Substitution at the 3-position of the phenyl ring (**17–20**) is well-tolerated, although none of the analogues prepared exhibit significantly improved potency relative to the unsubstituted congener. In contrast, 5-HT_3 receptor binding affinity is quite sensitive to modifications at the 4-position (**21–25**) of the phenyl ring. The deleterious effect seems

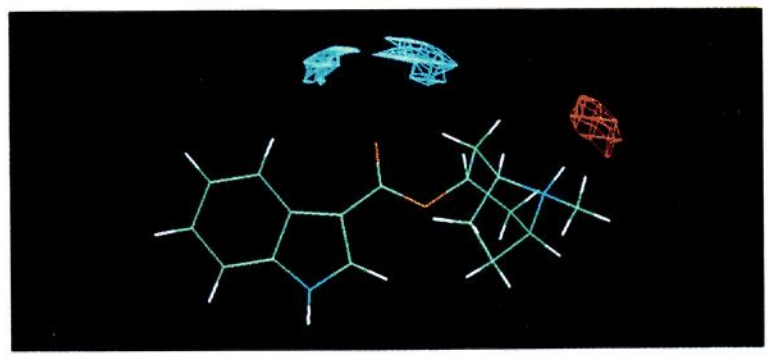


Figure 1. Proposed regions of electrostatic interaction for **2** and the 5-HT_3 receptor.

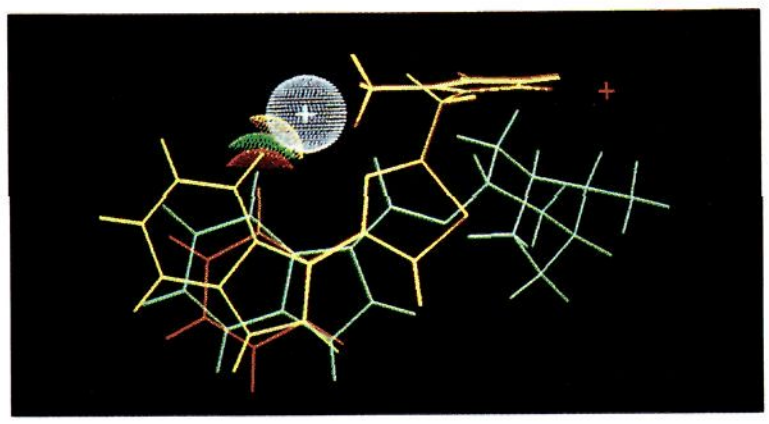


Figure 2. Overlap of the pharmacophore regions of compound **4** (yellow), compound **10** (red), and compound **2**, (green).

to be primarily steric in nature; introduction of a 4-fluoro substituent (**21**, K_i = 4.9 nM) results in the least reduction of binding affinity. All larger substituents investigated result in significantly reduced activity. The related methoxynaphthyl deriatives **26** and **27** also exhibit reduced 5-HT_3 receptor binding affinity.

Compound **10**, a representative member of this new class of 5-HT_3 receptor antagonists, was evaluated in a battery of standard receptor binding assays. The results, summarized in Table IV, indicate a high degree of receptor selectivity.

The most potent binding agents in this study (**5**, **10–12**) all show excellent in vivo activity in the Bezold–Jarisch reflex assay. A three-component pharmacophore computer model for 5-HT_3 receptor binding, based on the structures of known potent 5-HT_3 receptor ligands, has been described.[11] This model suggests that essential components of 5-HT_3 receptor binding for reported agents involve two key electrostatic interactions: the ligand must have a domain capable of acting as a hydrogen-bond acceptor and a corresponding appropriately located region which can donate a hydrogen bond. The third region of interaction is a plane occupied by the lipophilic aromatic portions of the receptor ligands. Figure 1 illustrates the electrostatic receptor–ligand interactions for **2**. The optimum distance between the centers of these two regions has been calculated to be 7.7 Å. On the basis of this model, it appears that the thiazole nitrogen in this new series of compounds is acting as a replacement for the carbonyl portions of previously reported 5-HT_3 receptor antagonists and the basic regions (guanidine or imidazole), which are presumably protonated under physiological conditions, are situated at an appropriate distance to act analogously to the corresponding basic portions of earlier compounds. Several of the structure–activity relationships observed in this study may be interpreted in terms of this model. The molecular conformation of **4** in which the pharmacophoric regions are in an optimal relationship for receptor binding (Figure 2) leads to a steric interaction between the 4-hydrogen on the indole ring in **4** and the proposed receptor hydrogen-bond donating site (1.40 Å distance); the alleviation of this unfavorable van der Waals interaction results

(15) (a) Hoyer, D.; Neijt, H. C. *Eur. J. Pharmacol.* **1987**, *143*, 291. (b) Neijt, H. C.; Karpf, A.; Schoeffter, P.; Engel, G.; Hoyer, D. *Arch. Pharmacol.* **1988**, *337*, 493.

(16) (a) Krayer, O. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1961**, *240*, 361. (b) Paintal, A. S. *Physiol. Rev.* **1973**, *53*, 159. (c) Fozard, J. R.; Host, M. *Br. J. Pharmacol.* **1982**, *77*, 520P.

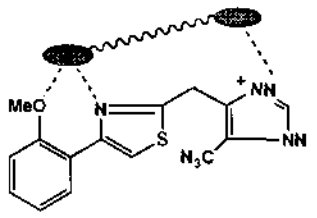
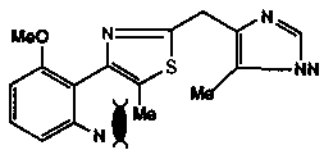


Figure 3. Proposed mode of enhancement in 5-HT_3 receptor binding by a 2-methoxy substituent.

in a molecular conformation in which the spatial relationship of the thiazole and protonated amine functions are no longer optimal for receptor binding, and a decrease in binding affinity is observed. Figure 2, which shows an overlap of the hydrogen bond accepting regions of **4** (in its calculated optimal binding conformation) and **2**, illustrates this point. The analogous ortho hydrogen in **2**, in its optimal binding conformation, is at an acceptable distance (1.85 Å) from the proposed region of receptor–ligand interaction. Similarly, the ortho hydrogen in **10** is located at a 2.15 Å distance from this binding site. This figure also shows the comparable spatial relationship between the phenyl group in **10** and the 6-membered ring of the indole moiety in **2**; it is proposed that the phenyl group in **29** (phenyl analogue of **2**) cannot interact with the receptor analogous to the corresponding aryl regions of **4** and **2** (which have lipophilic character at a distance from the pharmacophoric regions that extends beyond the phenyl group in **29**) while still maintaining an optimal relationship with the two important electrostatic binding regions, thus accounting for the markedly reduced binding affinity of **29** relative to **2**. The deleterious effect of para substituents in this series is somewhat surprising, as there would appear to be toleration to volume in this region of the molecule, based on the proposed mode of receptor binding for ondansetron in the pharmacophore model.[11] These results suggest that ondansetron may not be binding in its minimum-energy conformation.

The SAR results suggest that an arrangement of the aryl and thiazole groups approaching planarity may be optimal for binding. Such a relationship could be enhanced by a group (such as methoxy, compound **5**) which can contribute to the hydrogen bond accepting properties of the ligand (Figure 3). A similar interaction with the quinoline ring nitrogen may account for the excellent binding affinity of **11**. The 2-methyl substituent present in **15** cannot act in such a manner and would tend to decrease the planarity of the system relative to the unsubstituted congener, and this analogue is greater than **1** order of magnitude less active than **5**. The 2,6-dimethoxy analogue **28**, in which a planar arrangement of the aryl rings would necessitate an interaction between the 4-position hydrogen on the thiazole moiety and the 6-methoxy group, shows a large relative decrease in receptor binding affinity. Similarly, introduction of a methyl substituent at the 4-position of the thiazole moiety (compound **30**)[17] also results in a decrease in activity (K_i = **110 ± 10** nM).



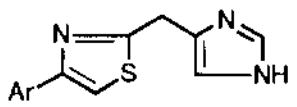
30

(17) Compound **30** was prepared analogously to compounds shown in Scheme I by condensation of α-bromo-2-methoxy-5-bromopropiophenone and thioamide **6** followed by hydrogenolysis (10% Pd–C/methanol); α-bromo-2-methoxy-5-bromopropiophenone is obtained by bromination (Br_2/methanol) of 2-methoxypropiophenone.

Table V. 5-HT_3 Receptor Binding Affinity of Guanidine Derivatives

no.	K_i ± SEM, nM
3	3.3 ± 1.3
32a, n = 2	7.1 ± 2
32b, n = 3	27 ± 2
32c, n = 4	29 ± 1

Table VI. 5-HT_3 Receptor Binding Affinities of 4-Desmethyl Analogues **33–35**



Ar	no.	K_i ± SEM, nM
phenyl	**33**	1.0 ± 0.1
2-methoxyphenyl	**34**	0.29 ± 0.1
quinolin-8-yl	**35**	0.31 ± 0.2

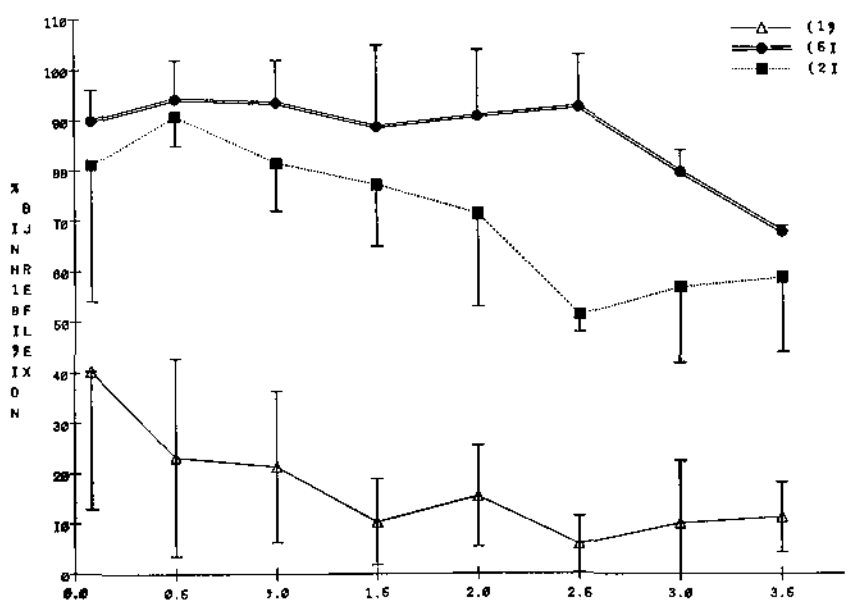
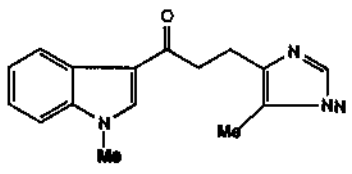


Figure 4. Comparative oral efficacies of 5-HT_3 receptor antagonists in the Bezold–Jarish reflex assay–time course study (error bars represent SEM).

The apparent isosteric relationship between the thiazole substituent and carbonyl group is supported by the structural similarity between compounds in this series and the ondansetron-related analogue **31** (GR-65630).[3] Furthermore, replacement of the (guanidinylmethyl)thiazole moiety in the lead structure **3** with guanidinylalkyl ester substituents (compounds of structure **32a–c**) affords agents with moderately potent 5-HT_3 receptor binding affinity (Table V), an observation again consistent with a thiazole–carbonyl bioisosteric relationship.



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A final SAR point, which has been introduced previously[10] and merits note, is the functional effect associated with the 4-methyl substituent on the imidazole ring in this series of compounds. The desmethyl analogues **33–35**, analogous to their corresponding methylated derivatives, show highly potent 5-HT_3 receptor binding affinity (Table VI). However, these compounds do not exhibit pure antagonist properties in the B–J reflex functional assay, inducing a transient bradycardia upon bolus injection analogous to serotonin, the serotonin agonist 2-methylserotonin, and **3**. The molecular basis or the pharmaco-

logical ramifications of this interesting observation are presently unknown.

Oral Evaluation of Compound 5 in B–J Reflex Assay. Compounds **5**, **1**, and **2** were compared for oral efficacy in inhibiting the Bezold–Jarisch reflex in rats. These agents were evaluated in a time-course study so that each compound was administered to rats at a fixed dose of 0.5 mg kg^{-1} po, and serotonin was administered (100 μg kg^{-1} iv) at varying time intervals as indicated in Figure 4. The comparative results of these studies, illustrated in Figure 4, indicate a rank order of oral potency as follows: compound **5** ~ **2** > **1**.

Summary of Results

A novel series of highly potent 5-HT_3 receptor antagonists has been discovered in which a thiazole substituent appears to exhibit bioisosteric properties with the carbonyl function in related agents. Compound **10**, which is a prototypical member of this series, was also found to be essentially inactive (K_i values greater than 1 μM) at other serotonin receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_2) as well as D_1, D_2 α_1, α_2, β, H_1, cholinergic, μ opiate, σ, and benzodiazepine receptors. Structure–activity studies led to the identification of compound **5** and the related analogues **11** and **12** which exhibit 5-HT_3 receptor binding affinity and activity in the B–J reflex assay (iv and po) comparable to or better than the standard agents **1** and **2**. Furthermore, **5** shows excellent oral activity in the B–J reflex functional paradigm, and recent studies utilizing ^3H-labeled compound **5** have shown that this agent, as well as **11** and **12**, effectively penetrates the blood–brain barrier.[18,19] Finally, the related desmethyl derivatives **33–35** show excellent 5-HT_3 receptor binding affinity but exhibit mixed functional characteristics in the B–J reflex assay, unlike ligands for the 5-HT_3 receptor reported previously, and thus merit further pharmacological evaluation.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. α-Halo ketones were either commerically available or obtained by bromination of the corresponding methyl ketone. Melting points are uncorrected. Thin-layer chromatographic analysis was performed with Analtech silica gel GF (250 μm) TLC plates with methanol/chloroform solvent systems as the eluant, and compound visualization was effected with a UV lamp (254 nM) or a 2–5% solution of concentrated sulfuric acid in ethanol. ^1H NMR spectra were determined on a Varian XL-300 spectrometer operating at 299.9 MHz. Significant ^1H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Mass spectra were obtained with an A.E.I. MS-30 mass spectrometer or a Finnigan 4510 instrument. Column chromatography was done with J. T. Baker silica gel for flash column chromatography (40 μM average particle diameter) or Silica Woelm 32-63 (particle size 32–63 μM). Elemental analyses were performed by the Microanalytical Laboratory, operated by the Analytical Department, Pfizer Central Research, Groton, CT.

A full experimental procedure is provided for the condensation of thioamide **6** and 2-bromo-2′-methoxyacetophenone to give thiazole **5**, and this protocol is representative of the general procedure for the preparation of the thiazoles in this study. ^1H NMR spectral data for other thiazole derivatives are also provided. The overall yields for the preparation of these derivatives are provided with the spectral data and are nonoptimized.

General Biological Methods. Binding affinities were determined by employing the radioligand [^3H]-**2** and NG-108-15 cells and the protocol described by Hoyer et al.[15]

The Bezold–Jarisch reflex assay was carried out according to the reported[5,16] procedure, with the following exceptions. Intravenous injections of test compounds, as well as serotonin, were made through a cannula placed in the right femoral vein. For determination of oral activity, test compounds were administered by oral gavage in unfasted, urethane-anesthetized animals in a total volume of 1.5 mL.

4(5)-Methyl-5(4)-(2-amino-2-thioxoethyl)imidazole Hydrochloride (6). Under a nitrogen atmosphere, in a round-bottom flask was placed 50 mL of thionyl chloride. To this stirring liquid was added slowly 20 g (134 mmol) of 4-methyl-5-imidazolemethanol hydrochloride in portions. The reaction mixture was stirred at room temperature for 3.5 h, and chloroform was added to the system. The resulting solid was collected by suction filtration and rinsed with chloroform to obtain 22.4 g (quantitative yield) of (chloromethyl)imidazole **8**[12] hydrochloride: ^1H NMR (DMSO-d_6) δ 2.34 (s, 3 H), 4.92 (s, 2 H), 9.04 (s, 1 H).

Under a nitrogen atmosphere, in a round-bottom flask equipped with a pressure-equalizing addition funnel were placed 42.9 g (659 mmol) of KCN and 100 mL of water. To this solution was added dropwise a solution of 22.0 g (132 mmol) of the imidazole hydrochloride prepared above in 450 mL of ethanol, over a period of 1.75 h; the temperature of the reaction mixture was maintained at −2 to 0 °C. The reaction mixture was stirred at 0 °C for a period of 1 h, and solids were removed by suction filtration. To the filtrate was added 120 mL of saturated aqueous sodium carbonate, and the mixture was concentrated with a rotary evaporator. The resulting solids were washed with ethyl acetate and dissolved in water. The aqueous solution was extracted with two portions of ethyl acetate. The ethyl acetate solutions were dried (Na_2SO_4) and concentrated with a rotary evaporator to afford a solid/oil mixture; trituration with chloroform afforded 4.51 g of **9**[13] as a white solid. The combined trituration mother liquors were subjected to flash column chromatography (320 g of silica gel) using 1:9 methanol/chloroform containing 0.1% of 14.8 M aqueous ammonia as the eluant to obtain an additional 2.09 g of **9**[13] (overall yield: 6.60 g, 42%): ^1H NMR (DMSO-d_6) δ 2.18 (s, 2 H), 3.75 (s, 2 H), 7.47 (s, 1 H).

Under a nitrogen atmosphere, in a three-neck round-bottom flask were placed 6.6 g (55 mmol) of nitrile **9**[13] prepared above and 200 mL of ethyl acetate. To this stirring suspension was added 9.15 mL (55 mmol) of diethyl dithiophosphate. HCl gas was bubbled into the resulting solution, upon which a precipitate formed. The internal temperature of the reaction mixture rose from 22 to 30 °C, and the addition of HCl was discontinued when the temperature of the medium had decreased to 28 °C. The mixture was stirred at room temperature for 5.5 h, and the hygroscopic white solid was collected by suction filtration, rinsed with ether, and concentrated from toluene to afford 8.6 g (82% yield) of thioamide **6** hydrochloride; mp 149–154 °C. This material was used in subsequent transformations without further purification: ^1H NMR ($CDCl_3$) δ 2.26 (s, 3 H), 3.95 (s, 2 H), 7.45 (m, 1 H), 7.80 (br s, 2 H), 8.90 (br s, 1 H).

4-(2-Methoxyphenyl)-2-[[4(5)-methyl-5(4)-imidazolyl]methyl]thiazole (5). Under a nitrogen atmosphere, in a round-bottom flask equipped with a reflux condenser were placed 1.44 g (6.3 mmol) of 2-bromo-2′-methoxyacetophenone and 1.2 g (6.3 mmol) of thioamide **6** hydrochloride in 15 mL of 2-propanol. The reaction mixture was heated at 80 °C for 3 h and concentrated in vacuo. The resulting foam was partitioned between water and chloroform, and the precipitate was collected by suction filtration and rinsed with chloroform. This solid (1.25 g) was partitioned between saturated aqueous sodium bicarbonate and chloroform, the layers were separated, and the aqueous phase was extracted with two portions of chloroform. The combined chloroform solutions were dried and concentrated with a rotary evaporator to obtain 860 mg (48% yield) of pure **5** as a white solid: mp 159–161 °C; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H,) 3.93 (s, 3 H), 4.32 (s, 2 H), 7.00 (d, 1 H, J = 7), 7.06 (t, 1 H, J = 7), 7.30 (t, 1 H, J = 7), 7.52 (s, 1 H), 7.78 (s, 1 H), 8.18 (d, 1 H, J = 7); exact mass calcd for $C_{15}H_{15}N_3OS$ 285.0936, found 285.0922. Anal. ($C_{15}H_{15}N_3OS \cdot {}^1/_4H_2O$) C, H, N.

(18) Seeger, T., unpublished results.
(19) The preparation of ^3H-labeled compound **5** will be reported elsewhere.

^{1}H NMR spectral data for 4-aryl-2-[[4(5)-methyl-5(4)-imidazolyl]methyl]thiazoles and 4(5)-desmethyl derivatives and yields for their preparation are as follows.

4 (29%): ($CDCl_3$) δ 2.20 (s, 3 H), 4.25 (s, 2 H), 7.0–7.4 (m, 4 H), 7.45 (s, 1 H), 7.65 (s, 1 H), 7.90 (m, 1 H).

10 (20%): ($CDCl_3$) δ 2.12 (s, 3 H), 4.26 (s, 2 H), 7.26 (s, 1 H), 7.3–7.4 (m, 3 H), 7.52 (s, 1 H), 7.76 (m, 2 H), 8.18 (br s, 1 H).

11·HCl (31%): (DMSO-d_6) δ 2.14 (s, 3 H), 4.38 (s, 2 H), 7.55 (m, 2 H), 7.83 (m, 1 H), 8.36 (m, 2 H), 8.65 (s, 1 H), 8.76 (s, 1 H), 8.90 (m, 1 H).

12 (57%): ($CDCl_3$) δ 2.24 (s, 3 H), 4.39 (s, 2 H), 7.14 (m, 3 H), 7.46 (s, 1 H), 7.55 (d, 1 H, J = 2), 8.12 (t, 1 H, J = 6).

8·HCl: (DMSO-d_6) δ 2.14 (s, 3 H), 4.38 (s, 2 H), 7.55 (m, 2 H), 7.83 (m, 1 H), 8.36 (m, 2 H), 8.65 (s, 1 H), 8.76 (s, 1 H), 8.90 (m, 1 H).

13 (12%): ($CDCl_3$) δ 1.48 (t, 3 H, J = 7), 2.24 (s, 3 H), 4.14 (q, 2 H, J = 7), 4.28 (s, 2 H), 6.92 (d, 1 H, J = 7), 7.00 (t, 1 H, J = 6), 7.23 (t, 1 H, J = 6), 7.46 (s, 1 H), 7.80 (s, 1 H), 8.19 (d, 1 H, J = 6).

14 (58%): (DMSO-d_6) δ 2.21 (s, 3 H), 4.26 (s, 2 H), 6.92 (m, 2 H), 7.20 (t, 1 H, J = 5), 7.48 (s, 1 H), 7.95 (d, 1 H, J = 7), 8.01 (s, 1 H).

15 (45%): ($CDCl_3$) δ 2.26 (s, 3 H), 2.45 (s, 3 H), 4.34 (s, 2 H), 7.11 (s, 1 H), 7.26 (m, 3 H), 7.46 (s, 1 H), 7.56 (d, 1 H, J = 6).

16 (9%): ($CDCl_3$) δ 2.20 (s, 3 H), 4.26 (s, 2 H), 7.19 (s, 1 H), 7.44 (s, 1 H), 7.51 (m, 3 H), 7.70 (d, 1 H, J = 7).

17 (19%): ($CDCl_3$) δ 2.27 (s, 3H), 4.29 (s, 2 H), 7.27 (m, 2 H), 7.30 (s, 1 H), 7.49 (s, 1 H), 7.70 (d, 1 H, J = 7), 7.85 (s, 1 H).

18 (55%): ($CDCl_3$) δ 2.20 (s, 3 H), 3.80 (s, 3 H), 4.22 (s, 2 H), 6.80 (d, 1 H, J = 6), 7.22 (m, 2 H), 7.36 (m, 2 H), 7.45 (s, 1 H).

19 (34%): ($CDCl_3$) δ 2.28 (s, 3 H), 4.30 (s, 2 H), 6.99 (m, 1 H), 7.34 (s, 1 H), 7.35 (m, 1 H), 7.51 (m, 1 H), 7.6 (m, 2 H).

20 (71%): (DMSO-d_6) δ 2.16 (s, 3 H), 4.15 (s, 2 H), 7.36 (t, 1 H, J = 6), 7.45 (m, 2 H), 7.90 (d, 1 H, J = 6), 8.02 (s, 1 H), 8.09 (s, 1 H).

21 (32%): (DMSO-d_6) δ 2.36 (s, 3 H), 4.53 (s, 2 H), 7.27 (t, 2 H, J = 9), 7.94 (d, 1 H, J = 6), 7.96 (d, 1 H, J = 6), 8.02 (s, 1 H), 8.99 (s, 1 H).

24 (38%): ($CDCl_3$) δ 2.36 (s, 3 H), 3.93 (s, 3 H), 4.38 (s, 2 H), 7.00 (d, 2 H, J = 9), 7.32 (s, 1 H), 7.57 (s, 1 H), 7.85 (d, 2 H, J = 9).

25 (40%): ($CDCl_3$) δ 2.28 (s, 3 H), 4.26 (s, 2 H), 7.26 (m, 4 H), 7.79 (d, 2 H, J = 6).

26 (14%): ($CDCl_3$) δ 2.34 (s, 3 H), 3.86 (s, 3 H), 4.39 (s, 2 H), 7.54 (m, 3 H), 7.71 (d, 1 H, J = 8), 7.89 (d, 1 H, J = 8), 7.96 (s, 1 H), 8.24 (m, 2 H).

27 (31%): ($CDCl_3$) δ 2.27 (s, 3 H), 3.89 (s, 3 H), 4.38 (s, 2 H), 7.26 (m, 4 H), 7.43 (s, 1 H), 7.54 (d, 1 H, J = 7), 7.74 (d, 1 H, J = 7), 7.84 (d, 1 H, J = 7).

28 (32%): (CD_3OD) δ 2.23 (s, 3 H), 3.86 (s, 6 H), 4.92 (s, 2 H), 6.82 (d, 2 H, J = 7), 7.50 (t, 1 H, J = 7), 7.98 (s, 1 H), 8.93 (s, 1 H).

30: ($CDCl_3$) δ 2.20 (s, 3 H), 2.22 (s, 3 H), 3.77 (s, 3 H), 4.18 (s, 2 H), 6.95 (m, 2 H), 7.30 (m, 2 H), 7.40 (s, 1 H).

33 (18%): ($CDCl_3$) δ 4.27 (s, 2 H), 6.84 (s, 1 H), 7.21 (s, 1 H), 7.48 (s, 1 H), 7.2–7.8 (m, 5 H).

34·HCl (56%): (DMSO-d_6) δ 3.88 (s, 3 H), 4.52 (s, 2 H), 6.98 (m, 1 H), 7.09 (d, 1 H, J = 2.5), 7.28 (m, 1 H), 7.60 (s, 1 H), 7.98 (s, 1 H), 8.07 (d, 1 H, J = 2.5), 9.07 (s, 1 H).

35 (41%): ($CDCl_3$) δ 4.28 (s, 2 H), 6.94 (s, 1 H), 7.44 (m, 1 H), 7.52 (s, 1 H), 7.64 (m, 1 H), 7.80 (d, 1 H, J = 2.5), 8.21, (d, 1 H, J = 2.5), 8.55 (d, 1 H, J = 2.5), 8.57 (s, 1 H), 8.98 (d, 1 H, J = 2.5).

3-Guanidinylpropyl Indole-3-carboxylate (32b). Under a nitrogen atmosphere, in a round-bottom flask were placed 525 mg (3 mmol) of *N*-(*tert*-butyoxycarbonyl)-3-aminopropanol and 1 mL of tetrahydrofuran (THF). To the system were added 0.42 mL (3.0 mmol) of triethylamine and 540 mg (3 mmol) of 3-(chlorocarbonyl)indole, and the reaction mixture was stirred at room temperature for ca. 1.5 h and partitioned between chloroform and saturated aqueous sodium bicarbonate. A white solid was removed by suction filtration, the layers were separated, and the organic phase was dried (Na_2SO_4) and concentrated with a rotary evaporator to obtain 1 g of viscous oil. This oil was subjected to flash column chromatography (50 g of silica gel) using 2:1 ethyl acetate/hexanes as the eluant to obtain 490 mg (51% yield) of *N*-(*tert*-butoxycarbonyl)-3-aminopropyl indole-3-carboxylate as a colorless viscous oil which partially crytallized upon standing under vacuum. This protected amine (402 mg, 1.26 mmol) was dissolved in 8 mL of dioxane saturated with HCl. The solution was stirred at room temperature for 1 h and concentrated with a rotary evaporator to obtain 314 mg (98% yield) of 3-aminopropyl indole-3-carboxylate: ^{1}H NMR (DMSO-d_6) δ 2.03 (m, 2 H), 2.60 (m, 2 H), 4.29 (t, 2 H, J = 7), 7.17 (m, 2 H), 7.48 (m, 1 H), 7.94 (m, 1 H), 8.08 (m, 1 H); exact mass calcd for $C_{12}H_{14}N_2O_2$ 218.1055, found 218.1041. Anal. ($C_{12}H_{14}N_2O_2$·HCl) C, H, N.

Under a nitrogen atmosphere, in a round-bottom flask equipped with a reflux condenser were placed 304 mg (1.2 mmol) of the amine prepared above, 1.59 g (5.7 mmol) of 2-methyl-2-thiopseudourea sulfate, 980 mg (12 mmol) of sodium acetate, and 40 mL of 2-propanol. The reaction mixture was heated at reflux overnight, and the solvent was removed with a rotary evaporator. The crude material was passed through a small plug of silica gel in a fritted glass funnel, eluting with 2:3 methanol/chloroform, and the eluant was concentrated. Attempts to form a solid hydrochloride salt from the residue (HCl/ethanol) were not successful. After concentration, the hydrochloride salt was treated with saturated aqueous sodium bicarbonate. Scratching of the flask afforded **32c** as a white solid which was collected (120 mg, 38% yield) by suction filtration: mp 154–155 °C dec; ^{1}H NMR (CD_3OD) δ 2.20 (m, 2 H), 3.41 (t, 2 H, J = 8), 4.41 (t, 2 H, J = 8), 7.21 (m, 2 H), 7.46 (m, 1 H), 8.00 (s, 1 H), 8.06 (m, 1 H); mass spectrum, m/z 260 (parent); exact mass calcd for $C_{13}H_{16}N_4O_2$ – C(NH)NH 218.1055, found 218.1025.

Compounds **32a** and **32c** were prepared in similar manner, employing the appropriate *N*-(*tert*-butoxycarbonyl)amino alcohol in the initial esterification of 3-(chlorocarbonyl)indole and have the following spectral and physical properties.

32a (29%): mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 3.46 (m, 2 H), 4.24 (m, 2 H), 7.16 (m, 2 H), 7.48 (m, 1 H), 7.96 (m, 1 H), 8.16 (s, 1 H); mass spectrum, m/z 246 (parent); exact mass calcd for $C_{12}H_{14}N_4O_2$ 246.1093, found 246.1124.

32c (52%): mp 155–160 °C; ^{1}H NMR (DMSO-d_6) δ 2.70 (m, 4 H), 3.15 (m, 2 H), 4.26 (m, 2 H), 7.18 (m, 2 H), 7.52 (m, 1 H), 7.97 (m, 1 H), 8.08 (s, 1 H); mass spectrum, m/z 274 (parent); exact mass calcd for $C_{14}H_{18}N_4O_2$ 274.1429, found 274.1402.