the parent 17-ketones, and they also could be conjugated and excreted as water-soluble 17-conjugates. Covey et al.[78] have already drawn attention to possible ways of circumventing this problem (cf. the use of *D*-secosteroids).

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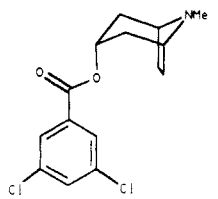
Registry No. Cytochrome P450, 9035-51-2; aromatase, 9039-48-9.

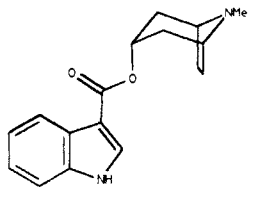
Communications to the Editor

Benzotriazinones as "Virtual Ring" Mimics of *o*-Methoxybenzamides: Novel and Potent 5-HT_3 Receptor Antagonists

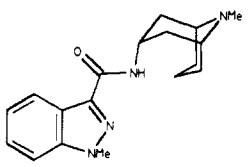
The majority of 5-HT_3 receptor antagonists can be regarded as falling into three structural classes. In the first are the benzoate esters in which the carbonyl is directly attached to the 6-membered aromatic ring and is typified by MDL 72222 (**1**).[1] In the second are the 6,5-heterobicyclic esters and amides in which the carbonyl is connected to the 6-membered aromatic ring via an sp^2 hybridized N or C atom, for example, ICS 205-930 (**2**),[2] granisetron (**3**),[3] and indoline **4**.[4] In the third class are the carbazoles such as ondansetron (**5**) in which the basic side chain nitrogen is provided by an aromatic imidazole.[5] Included in the first group are the *o*-methoxybenzamides such as zacopride (**6**)[6] and BRL 24682 (**7**).[3] A particular characteristic of these latter benzamides is the possible intramolecular hydrogen bond between the amide and the methoxy group which holds the carbonyl group both in plane, forming a "virtual ring", and in a particular orientation with respect to the other substituents on the benzene ring. Despite the proposal that this "virtual ring" is important for the activity of certain of these compounds as either gastric motility stimulants[7] or dopamine receptor antagonists,[8] little convincing evidence has been published demonstrating that compounds in which the "virtual ring" has been replaced by an actual ring retain either of these activities. We have recently suggested that it is this H bonding which is, in part, responsible for the exceptional potency of certain *o*-methoxybenzamides as 5-HT_3 receptor antagonists.[9] In this communication we show that the H-bonded system can be replaced by the cyclic aromatic system benzotriazinone with retention of 5-HT_3 receptor antagonist activity. A similar structure–activity relationship is also observed with respect to aromatic substitution between the two series.



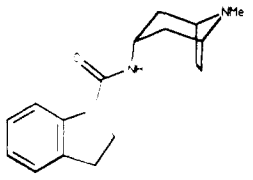
(1) MDL 72222



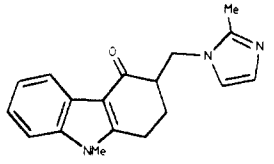
(2) ICS 205-930



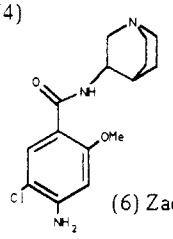
(3) Granisetron



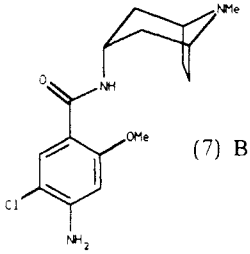
(4)



(5) Ondansetron

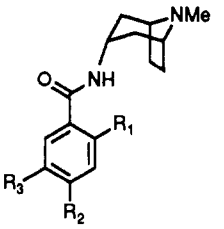


(6) Zacopride



(7) BRL 24682

Table I. Structure and Activity of Benzamides **8a–c**



no.	R_1	R_2	R_3	antagonism of B–J reflex: ID_{50}, μg/kg iv	antagonism of B–J reflex: no. of rats
1		MDL 72222		35.0 ± 0.1	4
2		ICS 205-930		1.4 ± 0.4	5
7	OMe	NH_2	Cl	0.8 ± 0.2	5
8a	H	NH_2	Cl	36.0 ± 5.0	3
8b	OMe	NH_2	H	16.0 ± 3.0	3
8c	OMe	H	Cl	15.0 ± 3.0	3

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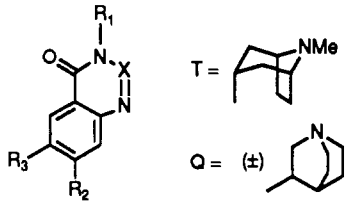
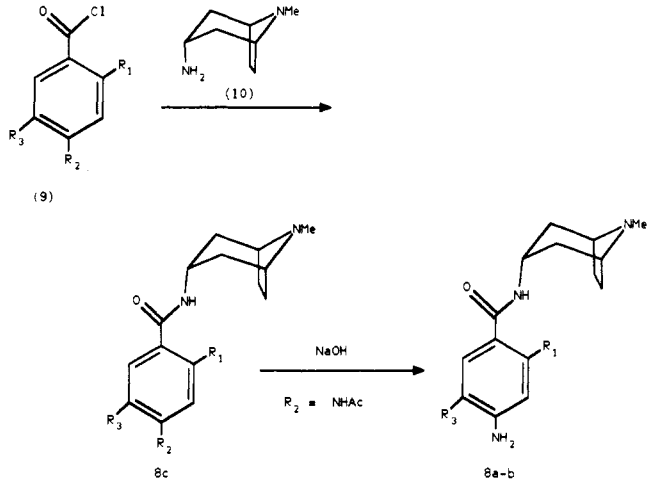
Table II. Structure and Activity of Benzotriazines 11a–d, 12a,b, and 13

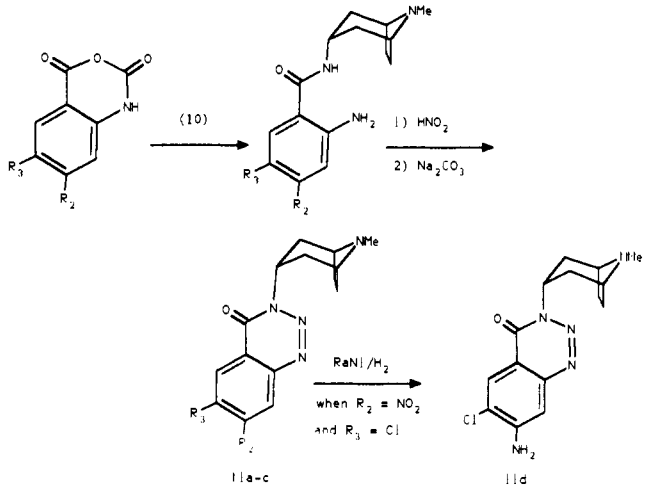


no.	R_1	R_2	R_3	X	antagonism of B-J reflex ID_{50}, μg/kg iv	antagonism of B-J reflex no. of rats
11a	T	H	H	N	>50	2
11b	T	H	Cl	N	12 ± 3.5	3
11c	T	NO_2	Cl	N	13 ± 3.0	3
11d	T	NH_2	Cl	N	0.17 ± 0.08	5
12a	Q	NO_2	Cl	N		
12b	Q	NH_2	Cl	N	3.6 ± 1.0	3
13	T	NH_2	Cl	CH	330 ± 30	3

Scheme I. Synthesis of Benzamides 8a–c



Scheme II. Synthesis of Benzotriazines 11a–d



Benzamides **8a–c** were prepared (Scheme I) by standard procedures from the appropriate acid chlorides (**9**) and *endo*-tropaneamine (**10**).[10] The benzotriazinones (**11a–c**) (Scheme II) and (**12a**) were prepared by nucleophilic ring opening of an appropriate isatoic anhydride by the appropriate amine[11] followed by diazotization and neutralization.[12] Yields of the intermediate anthranilamides were only moderate as attack at the 2-carbonyl appears to be more favored for more hindered amines.[11] 7-Amino compounds **11d** and **12b** were prepared from 7-nitro compounds **11c** and **12a**, respectively, by hydrogenation over Raney nickel. In a similar manner quinazoline **13** was prepared from the anthranilamide by cyclization with triethyl orthoformate followed by hydrogenation.[13]

Table I illustrates the 5-HT_3 receptor antagonist activities of benzamides **8a–c** as assessed by their ability to antagonize 5-HT-induced bradycardia, the von Bezold–Jarisch reflex (B–J reflex), in the anesthetized rat.[14] Included for comparison are our data for **1** and **2** as values in this model vary between laboratories and depend on whether 5-HT or 2-Me-5-HT is used as agonist. As previously reported, compound **7** is a highly potent 5-HT_3 receptor antagonist.[3] Removal of the *o*-methoxy group (**8a**) resulted in a 45-fold reduction in potency. This is larger than could be reasonably explained by the greater rotational freedom of the amide group, which can now adopt two energetically favorable orientations. Removal of either the 5-chloro (**8b**) or 4-amino (**8c**) substituents also resulted in a marked, but lower reduction of 20-fold. It may therefore be concluded that all three substituents are necessary for potent activity.

Results of similar testing of benzotriazinones **11a–d** are reported in Table II. The unsubstituted benzotriazinone (**11a**) was found to be inactive up to 50 μg/kg iv, the maximum dose tested. Introduction of a 6-chloro substituent (**11b**) resulted in 5-HT_3 receptor antagonist activity of the same order as that found for benzamide **8c** with a chloro substituent at the equivalent position. Similar potency was found with 6-chloro-7-nitro compound **11c**. However 6-chloro-7-amino compound **11d** was dramatically more potent than **11b**, the increase being similar to that originally seen in the benzamide series. This high potency has been confirmed in vitro (pK_i 10.0 for displacement of [^{3}H]BRL 43694 in rat cortical membranes).

The benzotriazines were originally chosen because our conception of antagonist–receptor interaction suggested that a large group at the 2-position of the aromatic "actual ring" would sterically hinder the optimum alignment of the azabicyclic side chain.[15] Our proposal was similar to

(10) For typical experimental details, see: Hadley, M. S.; King, F. D.; McRitchie, B.; Turner, D. H.; Watts, E. A. *J. Med. Chem.* **1985**, *28*, 1843.
(11) Staiger, R. P.; Wagner, F. C. *J. Org. Chem.* **1953**, *18*, 1427.
(12) For full experimental details, see: King, F. D. EP 315, 390, 1989.
(13) Spectra data for all new compounds (^{1}H NMR, high-resolution mass spectra, and/or C, H, N analysis) support their structural assignment.
(14) Sanger, G. J. *Br. J. Pharmacol.* **1987**, *91*, 77.
(15) King, F. D.; Sanger, G. J. *Drugs Future* **1989**, *14*, 875.

that of Hibert in which he more exactly defined the spatial geometry of molecules in their active conformation.[16,17] This concern regarding steric hindrance appears to be confirmed by 4-quinazolinone **13**. This compound contains a larger 2-functionality and was found to be almost 2000-fold less potent than **11d**. This steric intolerance at the 2-position may also explain the lower potency of quinuclidine **12b** compared with tropane **11d**. In the corresponding benzamides, tropane **7** and quinuclidine **6** are of approximately equal potency.[15] The quinuclidine, therefore, probably has a lower degree of steric tolerance than the tropane.

The results presented for the benzotriazines support the hypothesis that, in the active conformation of the benzamides, the orientation of the benzamide is as expected, with the carbonyl oxygen pointing toward the 6-position and the NH hydrogen bonded to the *o*-methoxy group. This is the exact opposite to the orientation recently proposed by Schmidt and Peroutka, where simple structural overlap criteria were applied without consideration of conformational energies.[18] Indeed it is physically impossible for the benzotriazines to adopt the conformation proposed for the benzamides by these authors. In contrast, the relative restriction of freedom, with consequential structural definition, is wholly consistent with our own and Hibert's model with regard to the orientation of the carbonyl and basic side chain. The positional requirements for the aromatic ring are less clear. There is no possible overlap between the aromatic rings of the benzotriazines and the indolines related to **4**. The necessary requirement of both a 5-chloro and 4-amino group in the benzamides, and equivalent substitution in the benzotriazines, therefore suggests that these functionalities are complimenting the structural requirements met by the benzo-fused ring in the 6,5-bicyclic and carbazole classes of highly potent 5-HT_3 receptor antagonists.

Acknowledgment. The authors are indebted to D. N. Nelson for the receptor binding studies on compound **11d**.

Supplementary Material Available: Spectral and physical data for **8a–c**, **11a–d**, **12b**, **13** (2 pages). Ordering information is given on any current masthead page.

(16) Hibert, M. F. *Actual. Chim. Ther.* **1988**, *16*, 37.
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(18) Schmidt, A. W.; Peroutka, S. J. *Mol. Pharmacol.* **1989**, *36*, 505.

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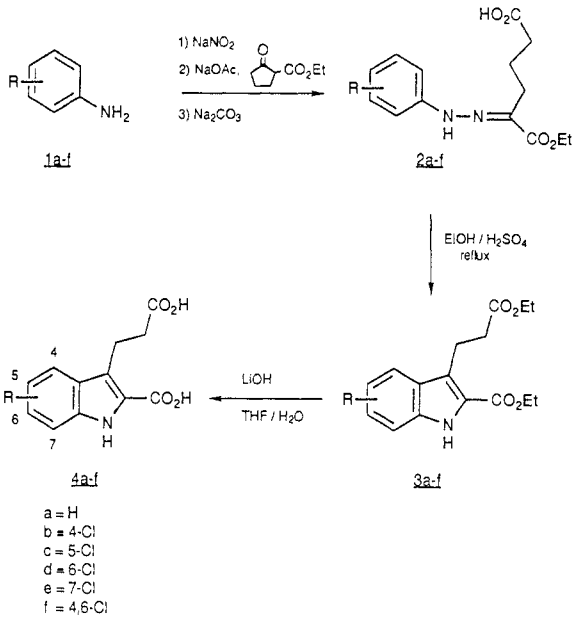
3-(2-Carboxyindol-3-yl)propionic Acid Derivatives: Antagonists of the Strychnine-Insensitive Glycine Receptor Associated with the *N*-Methyl-D-aspartate Receptor Complex

During the past 15 years evidence has accumulated implicating the acidic amino acids, glutamic acid and aspartic acid, as excitatory neurotransmitters in the mammalian central nervous system. Several distinct glutamate receptor complexes have been identified and classified according to the relatively selective ligands *N*-methyl-D-aspartic acid (NMDA), kainic acid, and α-amino-3-

Scheme I



hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). From a potential therapeutic point of view, the NMDA receptor complex has attracted considerable interest. Overstimulation of this receptor has been implicated in the etiology of several neurodegenerative disorders[1] and may play a role in human epilepsy.[2] This particular receptor complex possesses several allosteric binding sites which can alter cellular responses to glutamic acid. In particular, glycine acting at a strychnine-insensitive binding site has been shown to facilitate the action of glutamic acid[3] and, more recently, has been suggested as a cotransmitter required for activation of the NMDA receptor.[4-8] The role of glycine has largely been deduced from the actions of quinoline,[5,6] quinoxaline,[7] and aminopyrrolidinone,[8] or indole[9] antagonists which possess varying degrees of selectivity for the glycine site. A potent, selective antagonist of this glycine binding site, therefore, may have potential clinical applications as an anticonvulsant or neuroprotective agent. In this communication we report that 3-(4,6-dichloro-2-carboxyindol-3-yl)-propionic acid (**4f**) and other indolepropionic acid derivatives represent a new class of selective NMDA antagonists acting at the strychnine-insensitive glycine binding site.

Indoles **4a–f** were synthesized in good yields by utilizing the Japp–Klingemann reaction.[10] In general, hydrazones **2a–f** were prepared by condensation of 2-(ethoxycarbonyl)cyclopentanone with the corresponding benzenediazonium salt, isolated, and cyclized without further purification under Fischer indole reaction conditions

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