Substituted Benzamides with Conformationally Restricted Side Chains. 5. Azabicyclo[x.y.z] Derivatives as 5-HT$_4$ Receptor Agonists and Gastric Motility Stimulants

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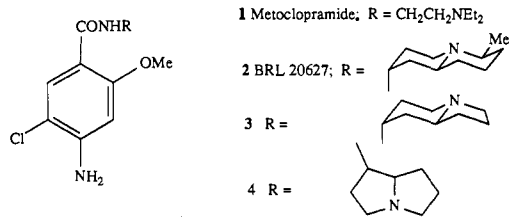
The syntheses of benzamides containing azabicyclo[x.y.z] side chains and their 5-HT$_4$ receptor agonist and 5-HT$_3$ receptor antagonist properties are described. These compounds were designed to mimic higher energy conformations of quinolizidine and indolizidine. High potency was achieved for both activities although an exactly paralleling SAR was not apparent. Introduction of O and S resulted in only marginal differences in potency which was more apparent for 5-HT$_3$ antagonism. The introduction of a methyl group α to the basic nitrogen resulted in a reduction in 5-HT$_4$ receptor agonist potency. Renzapride (**5f**) was identified for further evaluation for which both enantiomers had an identical pharmacological profile, as did an azatricyclic **9b**, which contained a combination of the steric bulk of the two separate enantiomers.

In part 1 of this series of papers we showed that conformational restriction of the (diethylamino)ethyl side chain of metoclopramide (**1**) led to the identification of the axial quinolizidine BRL 20627 (**2**) which retained the gastric motility stimulant properties of **1** but was effectively devoid of central and peripheral dopamine receptor antagonist activity.[1] It is this latter activity which is believed to be responsible for the occasional extrapyramidal side effects and hyperprolactinaemia seen with metoclopramide and related dopamine receptor antagonists.[2] Recently **2** has been shown to be a partial agonist at the serotonin 5-HT$_4$ receptor subtype,[3] a property which has now been correlated with gastric prokinetic activity.[4] The 5-HT$_4$ receptor has been identified in the central nervous system (CNS),[5] the heart,[6] and the gastrointestinal tract[7] which could indicate a wide therapeutic use for modulators of this receptor.



Although the quinolizidine ring of **2** is relatively conformationally restricted, there is still some degree of conformational freedom, although conformations other than chair–chair with a trans ring junction are higher in energy.[1] In a search for more potent compounds we synthesized and investigated the pharmacological properties of more conformationally restricted compounds which would both mimic the higher energy conformations of the quinolizidines and increase basicity. In particular we investigated azabicycles in which the second ring is "tied back". This would have the dual effect of both mimicking the unfavorable "cis" ring junction of the quinolizidines and reducing the bulk extending outwards from the basic nitrogen (Figure 1).

An indication that this approach could lead to more potent compounds was given by the observation that

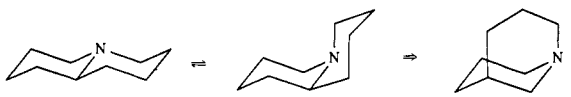
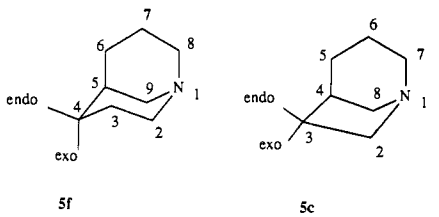


Figure 1.

greater potency was found with the indolizidine **3** and pyrrolizidine **4** in which the cis form of the ring junction is more favored.[8]

In this paper we describe the synthesis and pharmacological properties of the bridged azabicyclo[x.y.z] benzamides (compounds **5a–i** and **6**, Tables I and II), isosteric bridged azabicyclo derivatives which contain an additional hetero atom, either O (compound **7**) or S (compound **8**), and the azatricyclic derivatives, (compounds **9a,b**), which contain a combination of the steric elements of the separate enantiomers of **5e** and **5f**, respectively.



5f **5c**

Chemistry

The benzamides **5a–f** (Table I) were prepared by reaction of the appropriate amine **10a–f** with 4-(acetylamino)-5-chloro-2-methoxybenzoyl chloride in toluene followed by selective base hydrolysis of the *N*-acetyl group (Scheme I), similar to that described in our earlier paper.[1] The use of toluene was preferred as it was found that some of the amines **10** reacted rapidly with halogenated solvents, and even with ethyl acetate.

The amines **10a–f** were prepared by reduction of the oxime derivatives of the ketones **11** with sodium in amyl alcohol or lithium aluminum hydride (LAH) as appropriate. In general, dissolving metal reduction gave a thermodynamic product-controlled mixture of isomers whereas LAH gave mixtures dependent upon steric reagent-control. For the synthesis of **10f**, both methods gave almost exclusively the endo (equatorial) isomer. The

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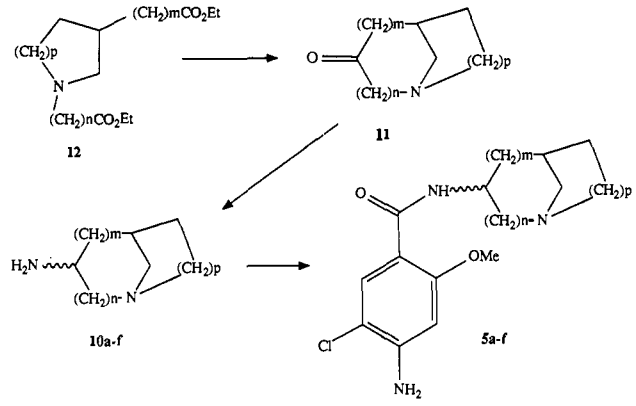
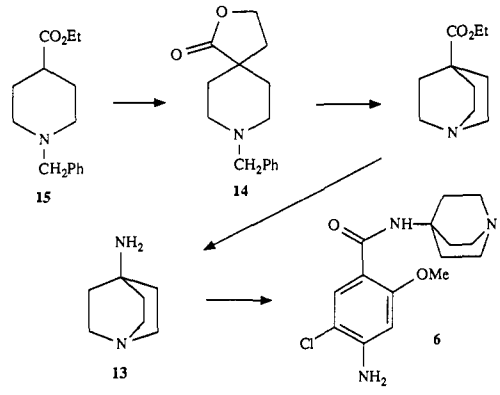
Scheme I. Synthesis of **5a-f**



Scheme II. Synthesis of **6**



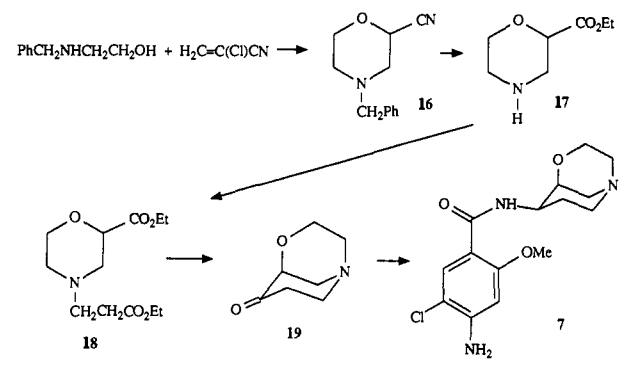
ketones **11** were prepared essentially by the literature procedures[9-11] from the diesters **12**, except that in every case potassium *tert*-butoxide was the base used for the Dieckmann cyclization. The (+) and (−) isomers of **5f** were prepared by resolution of the amine **10f** using the ditartrate salts of (−) and (+) tartaric acid, respectively. The exo isomer, **5e**, was isolated as a minor component from a large scale synthesis of **5f**. Treatment of a pentanol solution of the crude amine **10f** with CO_2 gave a solid complex of essentially pure endo isomer. The free amine could be regenerated by heating the complex in toluene. The mother liquors from the CO_2 treatment, on further treatment with Et_2O and CO_2, furnished an amine mixture enriched in the (exo) isomer **10e** as a 3:2 mixture of **10f**/**10e** from which **5e** was obtained. The methyl-substituted analogues of **5f**, compounds **5g-i** (Table II) were prepared similarly from the appropriately substituted ketones.

The 4-quinuclidinyl benzamide **6** was prepared from the amine **13**, which was prepared essentially by the literature procedure[12] except that the lactone **14** was prepared more efficiently and in fewer steps by addition of the anion of **15** to ethylene oxide, as recently adopted for the synthesis of the related azabicyclo[2.2.1]heptane[13] (Scheme II).

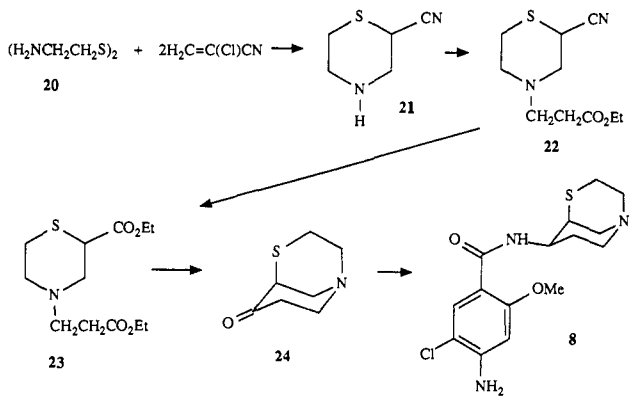
The synthesis of the oxa analogue **7** is shown in Scheme III. A full discussion on approaches to the synthesis of **7** has been reported in a preliminary communication,[14] however synthetic details are given in the Experimental Section. The (+) and (−) enantiomers of **7** were prepared by separation of the amine using (+) and (−) tartaric acid as described for **5f** except that the (+) tartaric acid now gave the (+) amine.

The thia analogue **8** was prepared as outlined in Scheme IV. The diester precursor to the Dieckmann cyclization (**23**) was prepared by a "one-pot" procedure of Michael

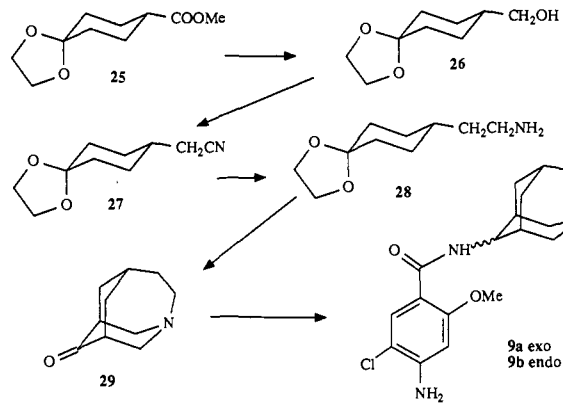
Scheme III. Synthesis of **7**



Scheme IV. Synthesis of **8**



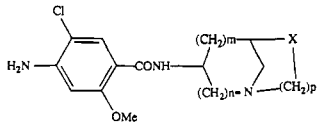
Scheme V. Synthesis of **9a,b**



addition of cystamine (**20**) to α-chloroacrylonitrile followed by disulfide reduction and cyclization to the 2-cyanothiomorpholine (**21**). The use of the disulfide was necessary as cysteamine ($HSCH_2CH_2NH_2$) undergoes preferential Michael addition of the more nucleophilic thiol and cyclization to the 3-isomer.[15] Neither use of *S*-trityl nor *S*-(trimethylsilyl)cysteamine gave any of the desired 2-cyanothiomorpholine. Michael addition of ethyl acrylate gave **22** which was converted to the ester **23**, the required Dieckmann precursor, using ethanolic sulfuric acid.

The azatricyclo derivatives **9a,b** were prepared from methyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (**25**)[16] by a procedure analogous to that used for 1-azaadamantan-4-one via a double Mannich reaction[17] (Scheme V). In contrast to **5f**, reduction of the oxime derivative of **29** by either dissolving metal or LAH gave an almost 1:1 mixture of endo and exo isomers. The benzamide isomers **9a,b** were separated by column chromatography. The stereochemistry of the benzamides was determined spectroscopically by the assignment, splitting pattern, and coupling constants of, and by the NOE enhancements by,

Table I. Structures of **5a–f**, **6–8**, and **9a,b** and Pharmacological Data



compd no.	isomer	m	n	p	X	ileum[a] EC_{20}, ng/mL	IGP[b] ED_{50}, mg/kg	HP dog[c] LAD, mg/kg	B–J[d] ID_{50}, μg/kg
1	metoclopramide					120 ± 70	1.0	0.25	500 ± 100
5a	exo	1	1	2	CH_2	2 ± 1	>1	>0.1	5.5 ± 1.6
5b	exo	0	1	2	CH_2	47 ± 42	NT	0.05	45 ± 10
5c	endo	0	1	2	CH_2	17 ± 15	0.06	0.01	3.0 ± 0.7
5d	endo	0	2	1	CH_2	0.4 ± 0.2	0.1	0.005	30[f]
5e	exo	0	2	2	CH_2	87 ± 75	NT	0.05	>100
5f	endo	0	2	2	CH_2	7 ± 5	0.1	0.01	3.3 ± 1.0
(+)**5f**	endo	0	2	2	CH_2	22 ± 19	NT	0.01	4.2 ± 1.7
(−)**5f**	endo	0	2	2	CH_2	32 ± 24	NT	0.01	3.9 ± 1.7
6[e]	–	–	–	–	–	NT[h]	NT	0.01	86[f]
7	endo	0	2	2	O	NT	0.1	0.01	19 ± 4
(+)**7**	endo	0	2	2	O	NT	0.1	0.01	18 ± 5
(−)**7**	endo	0	2	2	O	NT	0.1	0.01	32 ± 9
8	endo	0	2	2	S	NT	0.5	0.01	NT
9a[g]	exo	–	–	–	–	NT	NT	0.05	59[f]
9b[g]	endo	–	–	–	–	NT	NT	0.01	3.4 ± 1.3

[a] Isolated guinea pig ileum. [b] Stimulation of intragatric pressure in the rat, sc. [c] Heidenhain pouch dog, lowest active dose, iv. [d] Inhibition of Benzold–Jarisch reflex in the rat, iv. [e] Structure in Scheme II. [f] $n = 2$. [g] Structure in Scheme V. [h] NT = not tested.

the NMR signal for the proton at the point of attachment of the benzamide to the azabicycle.

For example in deuteriomethanol, the 4-exo proton of **5f** has a chemical shift of δ 4.46 and appears as a double-double-doublet with coupling constants of 4.5 Hz with proton H_5, 7 Hz with H_{3exo}, and 12 Hz with H_{3endo}, the latter being consistent with a trans diaxial orientation. For **5c**, a 2-D COSY proton spectrum showed a correlation between the signal at 4.66 ppm with those for H_2 at 3.61 and 2.60 and for H_4 at 2.31 ppm consistent with its assignment as H_3. An NOE difference experiment with irradiation of H_3 at 4.66 ppm produced an NOE at H_{5eq} at 2.95 ppm. This is consistent with the orientation of H_3 being exo, and hence of the amide endo. For the isomer **5b**, H_3 is coincident with the *O*-methyl resonance and therefore a selective irradiation could not be achieved. However, a similar 2-D COSY proton spectrum showed only two correlations with signals for H_2 at 3.50 and 2.78 ppm only and no correlation with the H_4 signal at 2.14 ppm. This would be consistent with a H_3–C_3–C_4–H_4 dihedral angle of approximately 90°. Furthermore, irradiation of H_3 produced NOE at H_{6endo}, H_{5endo}, and H_4. These results therefore show that for **5b**, H_3 is endo, opposite to that found in **5c**.

Results and Discussion

Compounds were tested for their potential as 5-HT$_4$ receptor agonists in vitro, by their relative ability to increase electrically evoked, cholinergically mediated contractions in guinea pig isolated ileum,[18] and as gastric prokinetics in vivo by their ability to stimulate intragastric pressure in the rat[19] and/or to increase rhythmic contractile activity in a canine Heidenhain pouch preparation when administered intravenously.[20] The 5-HT$_4$ receptor agonist activity in vitro was a well-maintained response which is qualitatively different from the 5-HT$_3$ response seen with high concentrations of 5-HT in the same preparation. Activities in vitro are expressed as the concentration required to increase contractions by 20%, a proportional increase which we believe correlates with clinical efficacy, and in vivo as the dose to produce a significant degree of stimulation of intragastric pressure in 50% of the rats or the lowest dose required to show a significant increase in contractile activity in half the number of dogs tested. The compounds were tested for their 5-HT$_3$ receptor antagonist potency by their ability to inhibit the reflex bradycardia, the Bezold–Jarisch reflex, induced by a bolus injection of 5-HT in the rat.[21]

Most of the simple azabicyclo compounds **5a–f** and **6** showed significant activity both in vitro and in vivo and were more potent than metoclopramide. In general a parallel degree of potency between the 5-HT$_4$ and gastric prokinetic test systems was observed (Table I). The major exception was **5a** for which a high potency was found in vitro but was inactive in vivo within the dose range tested. It is intriguing to speculate whether the in vitro activity is, in fact, mediated by 5-HT$_4$ receptor activation. In vivo, the endo (equatorial) isomers **5c,f** were more potent than the exo (axial) isomers **5b,e** which confirmed the trend observed in vitro. This order of activity was surprising considering that for the quinolizidines, the axial isomers were more potent than the equatorial.[1] The most potent gastro-prokinetics were the azabicyclo[3.2.1]octanes **5c** and **5d**. The increase in potency with the 5-membered ring correlates with that found for the indolizidine **3**. The good activity with **5b** and **5c** in which there is a 2-carbon distance between the amidic and basic nitrogen atoms is in direct contrast to the quinolizidines for which the 2-carbon distance compounds were very much less potent. Within the limits of experimental error, both the (+) and (−) isomers of **5f** were of equal activity to **5f** itself. This is in marked contrast to the related 3-quinuclidinyl benzamide, zacopride, for which it has been reported that there are major differences in pharmacological activity between the enantiomers.[22] The similarity between the activities of the enantiomers of **5f** prompted us to investigate the azatricyclic compounds **9a,b** which combine the geometries of the two enantiomers in one molecule, but with an increase in ring size (Figure 2).

The activites of both *exo*-**9a** and *endo*-**9b** were virtually identical to those of the equivalent racemic **5e** and **5f**. This further confirms that neither the 5-HT$_3$ nor the 5-HT$_4$ receptors have any enantioselectivity in the environment "above" the piperidinyl ring shown in bold (Figure 2).

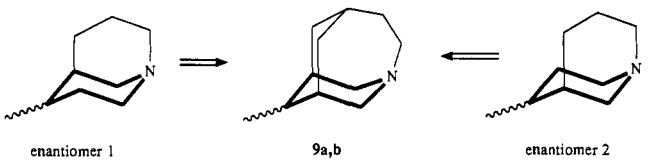


Figure 2.

Modeling studies suggested that the 4-quinuclidinyl benzamide **6** could approximate in terms of the relative position of the aromatic ring, the carbonyl group, and the basic nitrogen to that of **5f**. Indeed **6** was found to be as potent as **5f** as a potential prokinetic in the dog, though much less potent as a 5-HT_3 receptor antagonist and is, therefore, potentially a more selective 5-HT_4 receptor agonist.

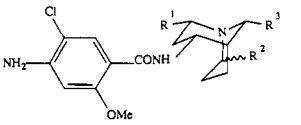
We have recently shown that the introduction of hetero atoms into **2** in the form of oxa- and thiaquinolizidines retained or improved gastric prokinetic potency despite a marked reduction in basicity.[23] Similar introduction of hetero atoms in the form of the novel 1-aza-4-oxa **7** and 1-aza-4-thia **8** nonane systems also retained high gastric prokinetic activity, both in the rat and dog. As for **5f**, the enantiomers of **7** showed no significant differences in activity. None of the compounds, **5a–f** or **6–8**, showed any evidence of significant dopamine receptor antagonist activity in the reversal of apomorphine-induced climbing behavior in mice[24] up to a dose of 50 mg/kg sc.

In addition to their gastric prokinetic activity, some of these compounds were also found to be potent 5-hydroxytryptamine 5-HT_3 receptor antagonists. In this model, compounds **5a**, **5c**, and **5f** were all of similar potency to GR 38032F (ondansetron, ID_{50} 3.6 μg/kg) and only about 5× less potent than BRL 43694 (granisetron, ID_{50} 0.7 μg/kg), two compounds recently introduced to the clinic as antiemetics for use in conjunction with cancer therapy.[25] 5-HT_3 receptor antagonism has been implicated as a possible mechanism for stimulation of gastric motility.[26] For this series of compounds, however, we believe that this property is only of secondary importance to an inherent "primary" stimulant activity.[27] Thus whereas **5e**, **6**, and **7** are potent gastric motility stimulants, they are relatively weak 5-HT_3 receptor antagonists. Additionally, **6** and **5f** are equipotent as gastric prokinetics in the dog, yet **6** is 26× less potent as a 5-HT_3 receptor antagonist. By contrast, **5a** is a potent 5-HT_3 receptor antagonist, 100× geater than **1**, yet less potent than **1** as a gastric prokinetic in vivo. From this it can also be concluded that the optimum geometries for the side chains for binding to the 5-HT_3 and 5-HT_4 receptors differ. This observation has also recently been noted in a series of pyrrolizidinyl benzamides.[28]

Substitution α to the basic nitrogen, as in **2**, retained good activity in the quinolizidine series,[1] although substitution in the other α positions resulted in a reduction in potency.[8] Similar α substitution was investigated with the bridged azabicycle of **5f** in order to determine the steric tolerance around the basic nitrogen. In contrast to the quinolizidines, all three compounds, **5g–i**, had a lower potency than **5f**, particularly **5g**, which implies a major steric intolerance in the region of R^1 (Table II).

From these compounds, **5f**, BRL 24924 (renzapride), was selected for further evaluation. The pharmacological properties of **5f** have been reviewed.[29] In the rat, **5f** has been shown to be a potent stimulant of gastric emptying, between 8–100× more potent than **1** depending upon the test system.[30] In a more detailed study in the dog, **5f** was approximately 50× more potent than **1** (ED_{50} 0.02 and 1.16 mg/kg, respectively).[20] The potential gastric motility stimulant activity and absence of dopamine receptor antagonist activity has been confirmed in man.[31,32] In addition, **5f** has been identified as a potent 5-HT_4 receptor agonist in the CNS,[3] the GI tract,[4,7] and the heart[6] and as a 5-HT_{1P} receptor antagonist,[33] though the physiological significance of this latter property is unknown.

Table II. Structure and Pharmacology of **5g–i**



compd no.	R^1	R^2	R^3	ileum[a] EC_{20}, ng/mL	HP dog[b] LAD, mg/kg
5g	Me	H	H	150 ± 120	0.25
5h	H	Me[c]	H	18 ± 7	0.05
5i	H	H	Me	56 ± 45	0.05

[a] Isolated guinea pig ileum. [b] Heidenhain pouch dog, lowest active dose, iv. [c] Mixture of isomers.

In conclusion, consideration of rigid azabicycles which mimic higher energy conformations of the quinolizidine **2** led to the identification of a number of highly potent gastric motility stimulants, some, but not all of which are also potent 5-HT_3 receptor antagonists. A separation between gastric motility stimulant and 5-HT_3 receptor antagonist activity has therefore been demonstrated.

Experimental Section

Chemistry. Melting points and boiling points are uncorrected. The elemental analyses indicated are within 0.4% of the theoretical values. ^1H NMR spectra were recorded on a JEOL GX 270 or Varian CFT-20 spectrometer with Me_4Si as internal standard and mass spectra were recorded on an AEI MS9 (70 eV) spectrometer. All evaporations were carried out under reduced pressure, and organic solvents were dried over K_2CO_3 unless specified otherwise. For column chromatography the silica gel used was Merck Kieselgel 60 and the alumina Camag neutral 100–250 mesh Brockman Type I. Light petroleum refers to the fraction boiling between 60 and 80 °C. All compounds containing chiral centers were prepared as mixtures of diastereoisomers unless specified otherwise.

General Procedure for the Preparation of Ketones 11. 1-Azabicyclo[3.2.1]octan-3-one. An efficiently stirred suspension of KOBu-t (37 g, 0.33 mol) in dry toluene (500 mL) was heated to reflux under N_2 and a solution of ethyl 1-[(ethoxycarbonyl)-methyl]piperidine-3-carboxylate (29 g, 0.12 mol) in dry toluene (100 mL) was added, dropwise, over a period of 1 h. Heating was continued for a further 2 h when the reaction mixture was cooled to room temperature and extracted with H_2O (2 × 100 mL). The combined aqueous extracts were acidified with 12 N HCl (200 mL) and heated under vigorous reflux for 14 h. The reaction mixture was concentrated by rotary evaporation and the residue basified and then saturated with solid K_2CO_3. The product was extracted into CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried, filtered, and concentrated to give the title product (11 g, 55%), as a pale yellow solid, used without further purification. 1-Azabicyclo[3.3.1]nonan-3-one, 1-azabicyclo[3.3.1]-nonan-4-one, 1-azabicyclo[3.2.1]octan-6-one, and the 2-, 8-, and 9-methyl-1-azabicyclo-[3.3.1]nonan-4-ones were prepared similarly from the appropriate diesters.

General Procedure for the Preparation of Amines 10a–i. ***exo*-1-Azabicyclo[3.3.1]nonan-3-amine (10a).** A solution of hydroxylamine hydrochloride (7.7 g, 0.11 mol), pyridine (15 mL), and 1-azabicyclo[3.3.1]nonan-3-one (11 g, 0.1 mol) in EtOH (200 mL) was heated under reflux for 2 h. The EtOH was removed by rotary evaporation, the residue dissolved in H_2O (100 mL) and basified with K_2CO_3, and the oxime extracted into CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried, filtered,

and concentrated to give the crude oxime (12 g, 80%), used without further purification. A stirred solution of the oxime (3.1 g, 0.02 mol) in pentanol (100 mL) was heated to reflux under N_2 and, after removing the heat source, Na (5.5 g 0.24 mol) was carefully added at such a rate as to maintain vigorous reflux. After completion of the addition of the Na, the heat source was replaced and the reaction mixture was heated under reflux until all the Na had dissolved. The reaction mixture was cooled to about 50 °C and carefully treated with 5 N HCl (100 mL) and EtOAc (150 mL). The aqueous layer was separated and the organic layer extracted with further 5 N HCl (50 mL). The combined aqueous extracts were washed with EtOAc (3 × 100 mL), basified, and then saturated with solid K_2CO_3 and the product was extracted into toluene (4 × 100 mL). The combined organic extracts were dried, filtered, and concentrated to give **10a** (2.4 g, 85%) as an oil, used without further purification.

General Procedure for the Preparation of Benzamides (5a–9b). *exo*-4-Amino-5-chloro-2-methoxy-*N*-(1-azabicyclo-[3.3.1]nonan-3-yl)benzamide (5a). A stirred solution of 4-(acetylamino)-5-chloro-2-methoxybenzoyl chloride (2.6 g, 0.01 mol) in dry toluene (100 mL) was treated with a solution of *exo*-1-azabicyclo[3.3.1]nonan-3-amine (**10a**) (1.4 g, 0.01 mol) and Et_3N (1.2 g, 0.012 mol) in toluene (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h and treated with 2.5 N NaOH (4 mL) in H_2O (50 mL), and the organic layer was separated and dried. Concentration of the filtered organic extracts gave the *N*-acetyl derivative of **5a** (2.4 g, 65%). A solution of the *N*-acetyl compound (2.4 g, 0.0065 mol) in EtOH (100 mL) and 2.5 N NaOH (5 mL) was heated under reflux for 2 h. The reaction mixture was concentrated by rotary evaporation, the residue treated with water (50 mL), and the product extracted into CH_2Cl_2 (3 × 50 mL). The dried and filtered organic extracts were concentrated and purified by column chromatography on alumina with preabsorption and elution with CH_2Cl_2 containing increasing proportions of MeOH to 5% to give the title compound (**5a**, 1.6 g 75%): mp 185–186 °C; ^{1}H NMR (monohydrochloride salt) [$(CD_3)_2SO$] δ 11.30 (brs 1 H), 7.78 (d, 1 H), 7.67 (s, 1 H), 6.51 (s, 1 H), 5.02–4.80 (m, 1 H), 3.85 (s, 3 H). Anal. ($C_{16}H_{22}ClN_3O_2 \cdot 0.25H_2O$) C, H, N.

The benzamides **5b–8** were prepared similarly, the separation of **5b** and **5c** being achieved at the *N*-acetyl stage by column chromatography on alumina, with preabsorption and elution with CH_2Cl_2 with increasing polarity through $CHCl_3$ to $CHCl_3$ + 1% MeOH. **5b**: mp 164–166 °C. Anal. ($C_{15}H_{20}ClN_3O_2$) C, H, N. **5c**: mp 181–182 °C. Anal. ($C_{15}H_{20}ClN_3O_2 \cdot 0.25H_2O$) C, H, N. **5d**: mp 235 °C dec. Anal. ($C_{15}H_{20}ClN_3O_2 \cdot 0.75H_2O$) C, H, N. **5e**: mp 181–231 °C dec; ^{1}H NMR (CD_3OD) δ 7.80 (s, 1 H), 6.52 (s, 1 H), 4.26–4.19 (m, 1 H), 4.96 (s, 3 H). Anal. ($C_{16}H_{22}ClN_3O_2 \cdot 0.25H_2O$) C, H; N: calcd, 12.8; found, 7.55 (95.4% purity by HPLC containing <1.5% **5f**). **5f**: mp >260 °C. Anal. ($C_{16}H_{22}ClN_3O_2$) C, H, N. (+)**5f**: mp 224 °C dec. Anal. ($C_{16}H_{22}ClN_3O_2$) C, H, N. (−)**5f**: mp 207 °C dec. Anal. ($C_{16}H_{22}ClN_3O_2$) C, H, N. **5g**: mp 100–102 °C. Anal. ($C_{17}H_{24}ClN_3O_2$) C, H, N. **5h**: mp 176–178 °C. Anal. ($C_{17}H_{24}ClN_3O_2 \cdot 0.75H_2O$) C, H, N. **5i**: mp 180–183 °C. Anal. ($C_{17}H_{24}ClN_3O_2 \cdot 0.25H_2O$) C, H, N. **6**: mp 251–253 °C (phase change) 275–281 °C dec. Anal. ($C_{15}H_{20}ClN_3O_2 \cdot 0.5H_2O$) C, H, N. **7**: mp 224–225 °C (monohydrochloride). Anal. ($C_{15}H_{20}ClN_3O_3 \cdot HCl$) C, H, N. (+)**7**: mp 234–235 °C. Anal. ($C_{15}H_{20}ClN_3O_3$) C, H, N. (−)**7**: mp 230–233 °C. Anal. ($C_{15}H_{20}ClN_3O_3$) C, H, N. **8**: mp 234–236 °C. Anal. ($C_{15}H_{20}ClN_3O_2S$) C, H, N.

Resolution of 10f. A solution of the amine **10f** (5.28 g, 38 mmol) in water (15 mL) was treated with (+) tartaric acid (11.3 g, 75 mmol) in water (20 mL). Ethanol (35 mL) was added from which the ditartrate salt crystallized overnight. The salt was collected (5.1 g) and recrystallized twice from water/ethanol (1:1) (yield 3.4 g, 20%). This salt was converted to the free (−) amine (1.1 g) by dissolving the salt in the minimum quantity of water, basifying with 40% NaOH, and extraction with *n*-BuOH. $[\alpha]^{20}_D = -14.2°$ (c = 1, MeOH). The amine was converted to (−) **5f** by the procedure described earlier $[\alpha]^{21}_D = -16.7°$ (c = 1, MeOH); optical purity 97.6% by chiral HPLC. Similar resolution using (−) tartaric acid gave (+) **5f** $[\alpha]^{21}_D = +17.8$ (c = 1, MeOH); optical purity >99.9% by chiral HPLC.

***exo*-4-Amino-5-chloro-2-methoxy-*N*-(1-azabicyclo[3.3.1]-nonan-4-yl)benzamide (5e).** The oxime hydrochloride of 1-azabicyclo[3.3.1]nonan-4-one (600 g, 3.15 mol) was reduced in pentanol (6 L) with Na (580 g, 25.2 mol) as described for **10a** except that, after the Na had dissolved and the reaction had cooled to 85 °C, ice (1 kg) was added followed by H_2O (2.5 L). After stirring for 1 h, the organic layer was separated, dried (K_2CO_3, 500 g), and filtered. The solid was washed with pentanol (500 mL) and EtOH (250 mL), and the combined organics were treated with an excess of solid CO_2 and left overnight. The solid CO_2 complex of the *endo*-amine (**10f**) was collected and washed with EtOH (500 mL), Et_2O (1 L), then resuspended in Et_2O (1.5 L), collected, and dried (424 g, 73%). The combined mother liquors were concentrated and retreated with Et_2O and CO_2. The solid was collected, suspended in toluene, and heated to reflux to break down the complex. Concentration afforded an oil which, from GC analysis consisted of a 3:2 mixture of *endo*- and *exo*-amines. A sample (10 g, 0.07 mol) of the amine mixture was converted into a mixture of the *N*-acetyl derivatives by the previously described general procedure (10.2 g, 40%). The mixture (5 g) was separated by column chromatography on Al_2O_3 eluting with EtOAc containing increasing quantities of MeOH up to 10% to give the pure exo isomer (0.5 g) and enriched mixture (1.3 g). The enriched mixture (1.3 g) was combined with a further 4 g of mixture and repurified as before to give a combined total of 1.8 g of exo isomer. The *N*-acetyl group was removed by base hydrolysis as previously described to give the title compound (**5e**, 0.66 g, 75%). HPLC (Hypersil, 250 × 5 mm, 98:2 CH_3CN/MeOH containing 0.05 M isobutylamine at 5 mL min^{-1}) indicated isomer purity >98.5%.

8-Benzyl-8-aza-2-oxaspiro[4.5]decan-1-one (14). A solution of diisopropylamine (11.5 g 0.113 mol) in dry Et_2O (200 mL) at −65 °C under N_2 was treated with 1.6 M *n*-butyllithium in hexane (70 mL, 0.112 mol) and the solution stirred for 0.25 h before treating with TMEDA (30 mL). After stirring for a further 10 min, the solution was treated dropwise over 15 min with a solution of ethyl 1-benzyl-4-piperidinecarboxylate (25 g 0.1 mol) in dry Et_2O (25 mL) and stirring was continued at −65 °C for 0.25 h. An excess of ethylene oxide (9 g, 0.2 mol) was then bubbled into the solution over 20 min and the mixture was allowed to warm to room temperature over 1 h and stirring was continued for a further 1 h. The reaction mixture was treated with saturated $NaHCO_3$ solution (150 mL), the organic layer separated, and the aqueous layer extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL) and brine (100 mL) and dried. Concentration and distillation of the residue afforded the title compound (17.2 g, 70%) bp 180–185 °C (1 mm).

4-Benzyl-2-cyanomorpholine (16). A solution of *N*-benzylethanolamine (15.1 g, 0.1 mol) and 2-chloroacrylonitrile (8.8 g, 0.1 mol) in Et_2O (100 mL) was stirred at room temperature for 5 days. The Et_2O was removed by rotary evaporation and the residue dissolved in dry DME (300 mL). The stirred solution was cooled to 0 °C and solid KOBu-t (12.3 g, 0.11 mol) was added in one portion. The reaction mixture was stirred at 0 °C for 2 h, heated to reflux for 1 h, and then cooled to room temperature. Saturated $NaHCO_3$ (100 mL) was added and the product was extracted into Et_2O (3 × 100 mL). The combined organic extracts were dried, filtered, evaporated, and distilled to give the title compound (16.4 g 81%), bp 125–135 °C (0.2 mm); ^{1}H NMR ($CDCl_3$) δ 7.20 (s, 5 H), 4.47 (t, 1 H), 4.20–3.70 (m, 2 H), 3.45 (2, 2 H), 2.90–2.20 (m, 4 H). On a larger scale synthesis, considerable decomposition occurred on distillation, and therefore the crude product was carried through to the next stage.

Ethyl Morpholine-2-carboxylate (17). A solution of 4-benzyl-2-cyanomorpholine (16.4 g, 0.081 mol) in EtOH (150 mL) and concentrated H_2SO_4 (24 mL) was heated under reflux for 48 h. The reaction mixture was cooled, concentrated to about half the original volume, and basified with aqueous K_2CO_3. The product was extracted into Et_2O (3 × 100 mL) and the combined organic extracts were dried, filtered, and concentrated to give ethyl 4-benzylmorpholine-2-carboxylate (15.9 g 79%): bp 140–150 °C (0.1 mm); ^{1}H NMR ($CDCl_3$) 7.70 (s, 5 H), 4.40–3.60 (m, 5 H including 4.13, q, 2 H), 3.47 (s, 2 H), 3.10–2.00 (m, 4 H), 1.23 (t, 3 H). A solution of the above ester (15.9 g, 0.064 mol) in EtOH (200 mL) and trifluoroacetic acid (5.5 mL) was shaken with 10% Pd/C (0.5 g) in an atmosphere of hydrogen until the uptake of hydrogen had ceased. The catalyst was removed by filtration and the filtrate concentrated by rotary evaporation. The residue

was dissolved in H_2O (10 mL), the solution basified and then saturated with solid K_2CO_3, and the product extracted into EtOAc (3 × 100 mL). The combined extracts were dried, filtered, concentrated, and distilled to give the title compound (8.9 g, 87%). ^1H NMR ($CDCl_3$) δ 4.24 (q, CH_2), 4.12 (dd, 2H-ax), 4.00 (dt, 6H-eq), 3.64 (ddd, 6H-ax), 3.20 (dd, 3H-eq), 2.97–2.79 (m, 3H-ax, 5H-ax, eq), 1.80 (s, NH), 1.30 (t, CH_3).

1-Aza-4-oxabicyclo[3.3.1]nonan-6-one (19). A mixture of ethyl morpholine-2-carboxylate (17) (8.9 g 0.056 mol) and ethyl acrylate (15 mL) was heated under reflux under N_2 for 12 h. The reaction mixture was cooled and the residue treated with Et_2O (100 mL). The mixture was extracted with 2 N HCl (3 × 30 mL), the combined aqueous extracts were basified with K_2CO_3, and the Michael adduct was extracted into CH_2Cl_2 (3 × 80 mL). The combined organic extracts were dried, filtered, and evaporated to give the diester for Dieckman cyclization (11.5 g 80%): ^1H NMR ($CDCl_3$) δ 4.5–3.3 (m, 7 H), 3.0–2.0 (m, 8 H), 1.27 (t, 3 H), 1.23 (t, 3 H). The diester was cyclized as described previously for 1-azabicyclo[3.3.1]octan-3-one to give **19** as an oil, used without further purification (3.5 g, 56%).

***endo*-1-Aza-4-oxabicyclo[3.3.1]nonan-6-amine** (intermediate to compound 7). The oxime derivative of 1-aza-4-oxabicycl-[3.3.1]nonan-6-one (**19**) was prepared by the previously described method: ^1H NMR ($CDCl_3$) δ 4.08 (s, 1 H), 3.93 (dt, 1 H), 3.65 (dd, 1 H), 3.59–3.42 (m, 2 H), 3.32–3.10 (m, 4 H), 3.00–2.83 (m, 2 H), 2.67–2.48 (m, 1 H). Concentrated H_2SO_4 (1 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.5 g) in dry THF (50 mL) at 0 °C under N_2. After stirring the reaction mixture at 0 °C for 1 h, a solution of the oxime derivative (2.1 g, 0.013 mol) in dry THF (100 mL) was added over 30 min and the whole was heated under reflux for 2.5 h before cooling to 0 °C. Sequential treatment with H_2O (1.5 mL), 10 N NaOH (2.2 mL), and H_2O (3.8 mL), filtration, and concentration of the filtrate gave the title compound (1.78 g 98%), used without further purification.

2-Cyanothiomorpholine (21). A solution of cystamine (7.4 g, 0.06 mol) and α-chloroacrylonitrile (8 mL, 0.1 mol) in DME (100 mL) was stirred at room temperature overnight. Sodium borohydride (4 g, 0.106 mol) was then added and the reaction was heated to reflux for 1 h. On cooling, K_2CO_3 (7 g, 0.05 mol) was added and the reaction reheated to reflux for a further 6 h. The cooled reaction mixture was carefully acidified with an excess of 5 N HCl and the product extracted into CH_2Cl_2 (3 × 200 mL), presumably as a borane complex. The solvent was removed and the residue heated under reflux in EtOH (100 mL) with TFA (20 mL) for 12 h. The solvent was removed and the residue partitioned between CH_2Cl_2 (300 mL) and an excess of aqueous K_2CO_3 solution. The dried organic extract was evaporated and the residue distilled under vacuum to give the title compound (3.2 g, 31%): bp 88–90 °C (0.2 mm); MS, *m/e* 128.0409 (M^+).

Ethyl 4-[2-(Ethoxycarbonyl)ethyl]thiomorpholine-2-carboxylate (23). A mixture of 2-cyanothiomorpholine (21) (3.2 g, 0.031 mol) and ethyl acrylate (4 mL) was stirred at room temperature for 3 days. A mixture of EtOH (60 mL) and concentrated H_2SO_4 (30 mL) was added and the reaction heated to reflux for 6 h. The reaction was cooled and poured into ice/water (100 mL) and the aqueous solution washed with Et_2O (2 × 200 mL). The aqueous layer was basified with K_2CO_3 and the product extracted into Et_2O (3 × 100 mL). Evaporation of the solvent afforded the title compound (4.9 g, 57%) used without further purification.

1-Aza-4-thiabicyclo[3.3.1]nonan-6-one (24). Following the procedure described for 1-aza-4-oxabicycl[3.3.1]nonan-6-one, **23** (4.1 g, 0.015 mol) was converted into the title compound (1.1 g, 47%), MS, *m/e* 157.0563 (M^+), used without further purification.

***endo*- and *exo*-4-Amino-5-chloro-2-methoxy-*N*-(1-azatricyclo[4.3.1.1^{3,7}]undecan-4-yl)benzamide (9a,b).** To a stirred suspension of LAH (1.2 g 0.03 mol) in dry Et_2O (100 mL) was added a solution of methyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (**25**) (9.6 g, 0.048 mol) in Et_2O (50 mL), and the reaction was stirred at ambient temperature for 5 h. Sequential addition of H_2O (1.2 mL), 2.5 N NaOH (2 mL), and H_2O (3 mL), filtration, concentration, and distillation of the filtrate gave 1,4-dioxaspiro[4.5]decane-8-methanol (**26**) (7.5 g, 90%), bp 80–86 °C (0.2 mm), used without further purification. A solution of **26** (7.5 g, 0.044 mol) and Et_3N (8 mL) in CH_2Cl_2 (200 mL) at 0 °C was treated with a solution of $MeSO_2Cl$ (5 g, 0.044 mol) in CH_2Cl_2 (10 mL) over 15 min and the reaction stirred at 0 °C for 2 h. The reaction mixture was washed with H_2O (100 mL), a saturated solution of $NaHCO_3$ (100 mL), and brine (100 mL) and the organic layer dried ($MgSO_4$). Concentration afforded the crude mesylate (10.8 g 100%) which was dissolved in DMSO (75 mL) and heated to 100 °C for 3 h with NaCN (2.5 g, 0.05 mol). The reaction mixture was cooled and poured into ice/H_2O (300 mL) and the product extracted into Et_2O (3 × 100 mL). The organic extracts were washed with H_2O (2 × 100 mL) and brine (100 mL) and dried. Concentration afforded the crude nitrile which, by IR, contained some deprotected ketone. The crude mixture was therefore heated under reflux in benzene (100 mL) with ethylene glycol (2 mL) and a catalytic quantity of tosic acid under Dean–Stark conditions for 2 h. The reaction mixture was cooled, washed with $NaHCO_3$ solution (50 mL), H_2O (2 × 50 mL), and brine (50 mL), and dried. Concentration afforded the crude nitrile **27** (7 g, 87%). The crude nitrile **27** (7 g, 0.039 mol) in Et_2O (50 mL) was added to a stirred suspension of LAH (1.2 g, 0.03 mol) in dry Et_2O (100 mL) over 15 min and the reaction was stirred at ambient temperatures for 2 h. Sequential workup as before gave 1,4-dioxaspiro[4.5]decane-8-ethanamine (**28**) (4.2 g, 60%) bp 95–99 °C (1 mm). A solution of **28** (2.3 g, 0.012 mol) in EtOH (5 mL) was added slowly to a gently boiling solution of paraformaldehyde (1.4 g) in 200 mL of 2% v/v H_2SO_4 over 1 h and the reaction heated under gentle reflux for a further 24 h. The reaction was concentrated to about 50 mL, CH_2Cl_2 (100 mL) added, and the aqueous layer basified and then saturated with K_2CO_3. The separated organic layer was dried and concentrated to give the crude ketone **29** (0.9 g) which was converted to its oxime derivative and purified by column chromatography on alumina, eluting with Et_2O (0.6 g, 29%) (attempted purification of the ketone by column chromatography on Al_2O_3 resulted in decomposition). The oxime (0.6 g, 3.3 mmol) was reduced to the amine (0.43 g, 78%) with LAH as previously described and converted to an endo and exo mixture of benzamides which were separated by column chromatography on SiO_2, eluting with $CHCl_3$ containing increasing proportions of MeOH up to 10%. The first isomer to elute was the endo isomer **9b** (0.09 g): mp 219–221 °C; ^1H NMR ($CDCl_3$) δ 8.26 (d, 1 H), 8.10 (s, 1 H), 6.32 (s, 1 H), 4.42 (brs, 2 H), 4.17–4.07 (m, 1 H), 3.95 (s, 3 H), 3.42 (d, 2 H), 3.17 (t, 2 H), 2.67 (d, 2 H), 2.32–2.10 (m, 3 H), 1.90 (brs, 4 H), 1.65 (d, 2 H). Anal. ($C_{18}H_{26}ClN_3O_2$) C, H, N. The second isomer was the exo isomer **9a** (0.08 g): mp 224–232 °C. ^1H NMR ($CDCl_3$) δ 8.20–8.05 (m, 2 H including 8.10, s, 1 H), 6.32 (s, 1 H), 4.41 (brs, 2 H), 4.20–4.10 (m, 1 H), 3.95 (s, 3 H), 3.40 (d, 2 H), 3.15 (t, 2 H), 2.83 (d, 2 H), 2.30–1.80 (m, 7 H), 1.42 (d, 2 H). Anal. ($C_{18}H_{26}ClN_3O_2$) C, H, N.

Pharmacology. In vitro activity was determined on distal ileum removed at least 10 cm proximal to the caecum from male guinea pigs (300–400 g) and longitudinal muscle–myenteric plexus preparations were prepared approximately 2–3 cm long. The muscle–nerve strips were suspended under a 0.5-g load in 10-mL tissue baths containing Krebs solutions, bubbled with 5% CO_2 in O_2 and maintained at 37 °C. Responses were registered and magnified 6–18 times with isotonic transducers. Bipolar rectangular pulses were passed between two Pt wire electrodes 25 mm long and 5 mm apart, suspended on either side of the muscle strip and insulated on entry to the bathing solution. Electrical field stimulation (EFS) was given as 0.5-ms pulses at 0.1-Hz frequency and at minimum voltage which evoked maximum muscle contractions (25–40 V). After obtaining consistent contractions, 10 min after washout and replacement of the bathing solution, cumulative concentration–response curves were constructed for the test compound by adding increasing concentrations at 5-min intervals. The effects on the EFS-evoked contractions were calculated as a % of the contraction heights measured before addition of the test compound and expressed as a mean of at least six determinations. Activity on gastric motility in the rat was determined in male Wistar rats (200–500 g) in which a chronic gastric fistula had previously been inserted. The rats were fasted overnight and then individually restrained in Bollman cages for the duration of the experiment. Gastric motility was assessed from the mean amplitude of pressure waves recorded via the gastric fistula for four 10-min periods before and after subcutaneous administration of the compound. Only

rats with a low pretreatment basal motility (mean amplitude <4 mmHg) were used. With groups of 8–10 animals, the lowest dose of a compound that showed a statistical increase ($p < 0.05$, Student's t test) in a greater number of rats than is encountered in a control (vehicle dosed) group was ascertained. Activity on gastric motility in the dog was determined by measurement of intraluminal pressure in the Heidenhain pouch. Pressure changes were recorded via a saline-filled catheter inserted, with airtight closure, into the fistula of a chronic Heidenhain pouch of a previously fasted and lightly restrained conscious dog. The catheter was connected to a physiological pressure transducer and pressure changes recorded on a hot wire pen recorder. Compounds were administered when the motility was in a phase of relatively low activity, and the dose range was determined which induced an increase in the amplitude of rhythmical contractions for a period of at least 4–5 min.

The compounds were evaluated for antagonism of the Bezold–Jarisch reflex evoked by 5-HT in the anesthetized rat. Male rats (260–290 g) were anaesthetized with urethane (1.25 g/kg ip) and blood pressure and heart rate recorded. A submaximal dose of 5-HT (6 μg/kg iv) was given repeatedly and the changes in heart rate were quantified. Compounds were given intravenously prior to administration of 5-HT and the dose required to reduce the 5-HT response to 50% of the control response (ID_{50}) was determined.

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