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Substituted Benzamides with Conformationally Restricted Side Chains.4. Hetero-azabicyclo[x.y.0] Derivatives as Gastric Prokinetic Agents.

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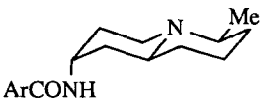
Abstract: The gastric prokinetic and dopamine receptor antagonist activity of diazabicyclo[4.3.0], [4.4.0] and oxa- and thia-azabicyclo[4.4.0] benzamides related to the serotonin 5-HT_4 receptor agonist BRL 20627 (2) is described.

In part 1 of this series we described how conformational restriction of the diethylaminoethyl side chain of metoclopramide (1) in the form of quinolizidine gave BRL 20627 (2) as a gastric prokinetic agent effectively devoid of the central dopamine receptor antagonist activity which gives rise to the extrapyramidal side effects occasionally seen with (1).[1]

(1) metoclopramide Ar $CONHCH_2CH_2NEt_2$

(2) BRL 20627 (±)



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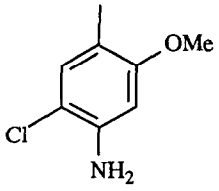
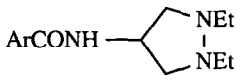


(3) Dazopride

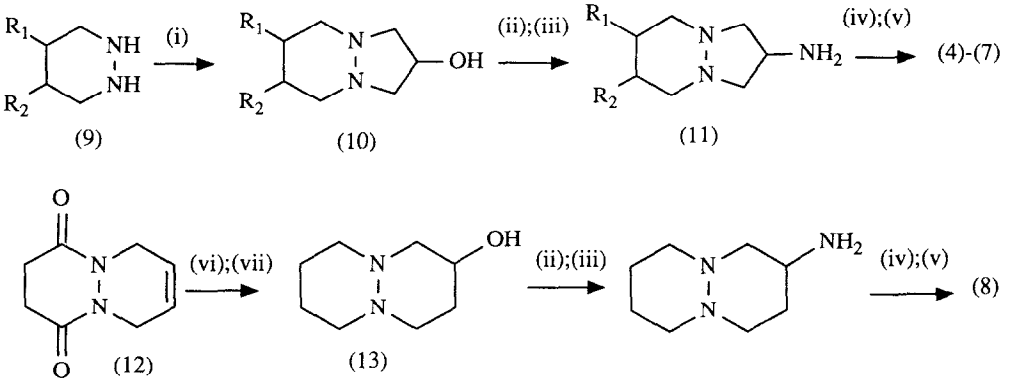


Recently both (1) and (2) have been shown to be partial agonists at the serotonin 5-HT_4 receptor[2] and it is this activity which has recently been correlated with gastric prokinetic activity.[3] The 5-HT_4 receptor has been identified in both the CNS[4] and the heart[5] and it is the renewed interest in modulators of this receptor which has prompted this report on our wider study on fused azabicyclic benzamides related to (2). Our aim was to identify compounds which were more potent gastric prokinetics whilst retaining the selectivity of (2). We have recently reported our results on a wider SAR investigation of azabicycles related to the quinolizidine (2).[6] In this communication we now describe the effects on the pharmacological profile of the introduction of hetero atoms into the azabicycle. All compounds which contain assymetry were prepared and tested as racemates.

Initially we introduced a second nitrogen atom into the ring fusion to form bicyclic hydrazine derivatives (4-8, Table I). These compounds can be regarded as cyclised analogues of the gastric

prokinetic, dazopride (3).[7] The effect of the second nitrogen is to increase the conformational freedom of the azabicycle and to remove the differentiation between the axial and equatorial orientation of the benzamide which in the quinolizidines was essential for gastric prokinetic selectivity.[1] Their general synthesis is shown in Scheme 1.[8]

Scheme 1. General synthesis of compounds (4)-(8)



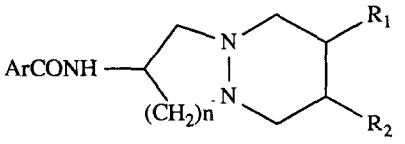
Reagents; (i) $ClCH_2$  ; (ii) DEAD/Ph_3P/$(PhO)_2PON_3$; (iii) LAH; (iv) N-Ac-ArCOCl; (v) NaOH; (vi) BH_3; (vii) H_2O_2

The 5,6-diazabicyclic system in compounds (4-7) was prepared from the appropriately substituted hexa- or tetra-hydro-pyridazine (9) by reaction with epichlorohydrin, conversion of the alcohol (10) to the amine (11) using Mitsunobu methodology followed by acylation by the previously reported standard procedure.[1] The 6,6-diazabicyclic system was prepared from the dione[9] (12) by concomitant reduction and hydroboration with diborane followed by oxidation to the alcohol (13). The alcohol was converted to (8) using the same methodology as described for compounds (4-7).

The structures and pharmacological properties of (4)-(8) are shown in Table I. For the assessment of gastric prokinetic activity their ability to increase intragastric pressure in the rat by our previously reported method was used.[1] Their ability to inhibit apomorphine-induced climbing behaviour was used to assess dopamine receptor antagonist activity.[1]

Both the simple 5,6-diazabicyclic (4) and 6,6-diazabicyclic (8) compounds retained gastric prokinetic activity of the same order of potency as metoclopramide and BRL 20627. However, an increase in conformational restraint by introduction of unsaturation (5) or an increase in bulk and lipophilicity by either benzo-fusion (6) or introduction of a phenyl substituent (7) resulted in loss of prokinetic activity, although both (6) and (7) retained some dopamine receptor antagonist activity. The activity and selectivity of (4) was surprising considering that the equivalent

Table I. Structure and activies of compounds 4-8.



Cpd. No.	n	R_1	R_2	IGP*	DA**	ratio
1	-	metoclopramide		1.0	0.8	0.8
2	-	BRL 20627		0.5	25	50
4	1	H	H	0.5	10	20
5	1	DOUBLE BOND		>1	>50	-
6	1	=CH-CH=CH-CH=		>1	10	-
7	1	Ph	H	>1	5	-
8	2	H	H	1	30	30

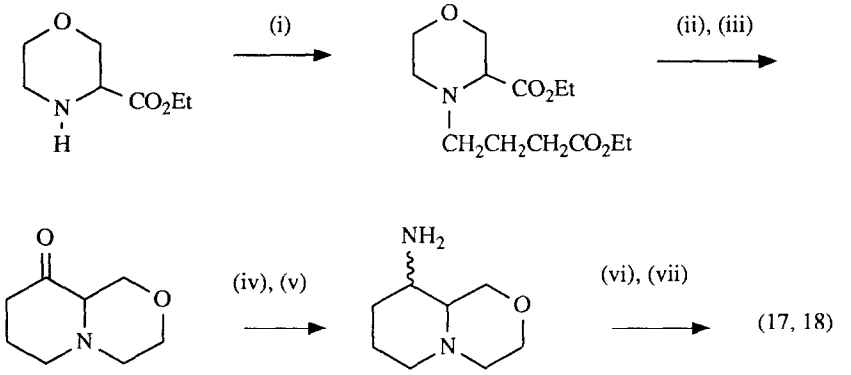
* Intragastric pressure, lowest active dose mg/kg sc; ** inhibition of apomorphine climbing, ED_{50} mg/kg sc.

indolizidine was reported to be inactive as a gastric prokinetic.[6] In conclusion, the introduction of the second nitrogen atom, which effectively eliminates the differentiation between axial and equatorial isomers, both retained and even introduced gastric prokinetic activity with the simplest examples, but with no advantage in terms of potency over the quinolizidine (2), though both (4) and (8) were significantly more selective than metoclopramide. It would be expected that, for (8), the thermodynamically more stable isomer would be with the orientation of the benzamide equatorial. However (8) is much more selective than the equivalent equatorial quinolizidine.[1] Therefore a major effect of the introduction of the second nitrogen is to reduce the dopamine receptor antagonist potency.

In addition to the fused diaza systems, we also investigated the effect of the introduction of an oxygen or sulfur atom into the quinolizidine system and their structure and pharmacological properties are described in Table II. For stability reasons, the additional hetero atom was introduced β to the basic nitrogen. Syntheses of the 2-oxa-8-benzamides (14,15) and the 4-methyl-substituted analogue (16) have been previously described.[10] The 9-isomers (17, 18) were prepared as outlined in Scheme 2 from ethyl morpholine-3-carboxylate[11] by Dieckmann cyclisation, conversion of the ketone to an isomeric mixture of amines which was acylated by the previously described procedure.[1] The isomers were separated by column chromatography on silica, eluting with $CHCl_3$ containing an increasing proportion of MeOH.

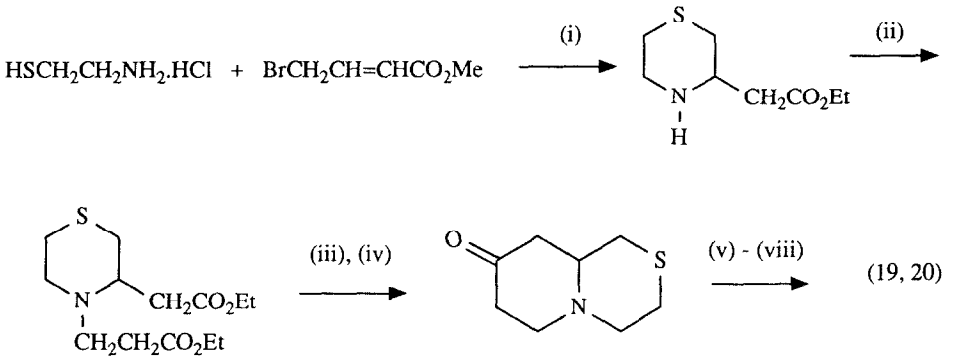
The equivalent thia analogues, compounds (23) and (24), were prepared similarly from ethyl

Scheme 2. Synthesis of compounds 17 and 18.



Reagents. (i) $K_2CO_3/BrCH_2CH_2CH_2CO_2Et$; (ii) KOBu-t/$Et_2O$; (iii) H^+;
(iv) $HONH_2.HCl$/pyridine; (v) $LiAlH_4$; (vi) N-Ac-ArCOCl; (vii) NaOH

Scheme 3. Synthesis of compounds 19 and 20.

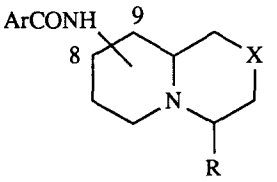


Reagents. (i) $Et_3N/CHCl_3$; (ii) $H_2C{=}CHCO_2Et$; (iii) KOBu-t/Et_2O; (iv) H^+;
(v) $HONH_2.HCl$/pyridine; (vi) $LiAlH_4$; (v) N-Ac-ArCOCl; (vi) NaOH

thiomorpholine-3-carboxylate.[12] The 2-thia-8-benzamides (19, 20) were also prepared via the Dieckmann cyclisation of the appropriate thiomorpholine diester, prepared from methyl 4-bromocrotonate and cystamine[13] and conversion of the ketone as described for (17) and (18) (Scheme 3).

The sulfoxides (21) and (22) were prepared by sodium periodate[14] oxidation of (19) and (20) respectively.

Table II. Structure and pharmacological activities of compounds 14-24



Cpd. No.	amide* isomer	X	R	IGP**	DA***	ratio
14	8A	O	H	0.2	70	350
15	8E	O	H	1	30	30
16	8A	O	Me	0.2	40	200
17	9A	O	H	>5	30	-
18	9E	O	H	1	>25	-
19	8A	S	H	1	>25	-
20	8E	S	H	1	-	-
21	8A	SO	H	5	>10	-
22	8E	SO	H	1	-	-
23	9A	S	H	>5	5	-
24	9E	S	H	1	30	30

* A = axial, E = equatorial; ** Intragastric pressure, lowest active dose mg/kg sc;

*** inhibition of apomorphine-induced climbing, ED_{50} mg/kg sc.

In contrast to the diaza compounds, the hetero-containing quinolizidines (14)-(24) retained the differentiation between axial and equatorial orientation of the benzamide. Both (14) and (15) were more potent than the previously reported analogous quinolizidines[1] though the same order of potency and selectivity, axial>equatorial, was maintained. Indeed (14) was at least twice as potent as BRL 20627 with an even lower potency as a dopamine receptor antagonist. Introduction of a methyl substituent to give (16), the direct analogue of BRL 20627, retained the high gastric prokinetic potency, but with a marginally lower selectivity from dopamine receptor antagonism. However, in contrast to the quinolizidines, the 9-equatorial compound (18) retained good prokinetic activity and selectivity, though the 9-axial isomer (17) was effectively inactive. Good prokinetic activity was also retained with the thia compounds (19)-(22), although now the beneficial axial orientation of the benzamide for potency was no longer apparent. Indeed, the axial sulphoxide (21) was now less potent than its equatorial isomer (22). The activities of the 9-isomers, (23) and (24) almost exactly match that of the oxa compounds (17) and (18), though (23) is a much more potent dopamine receptor antagonist. Although neither (20) nor (22) were assessed for their ability to inhibit apomorphine-induced climbing behaviour in the rat, neither

compound was effective at inhibiting apomorphine-induced emesis in the dog up to a dose of 10 mg/kg sc.

The major effect of the introduction of the hetero-atom common to all the compounds prepared is to reduce the basicity of the bridgehead nitrogen.[10] The results presented here indicate that, whereas the reduced basicity has little effect, or can even enhance gastric prokinetic potency, a significant reduction in dopamine antagonist activity is observed. Thus binding of this class of dopamine antagonist to the dopamine receptor may be relatively sensitive to the basicity of the side chain nitrogen atom.

In conclusion, the introduction of a second nitrogen to give the diaza-fused systems (compounds 4 and 8) retained gastric prokinetic activity and selectivity from dopamine antagonism despite losing the differentiation between axial and equatorial isomers. However no compound better than BRL 20627 was identified. In contrast the introduction of an oxygen atom into the quinolizidine system did provide compounds (14 and 16) which were both more potent, and more selective gastric prokinetics than BRL 20627. The equivalent sulfur analogues (compounds 19 and 21) were less potent. Both (14) and (16) also have good 5-HT_3 receptor antagonist potency which has been reported separately.[10]

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