Bioorganic & Medicinal Chemistry Letters, Vol.2, No.9, pp 1147-1152, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

Substituted Benzamides with Conformationally Restricted Side Chains. 3. Azabicyclo[x.y.0] Derivatives as Gastric Prokinetic Agents.

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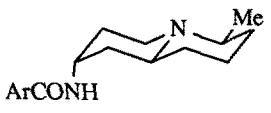
(*Received* 29 *May* 1992)

Abstract: The effect of alteration of ring size, introduction of alternative substituents and insertion of an exocyclic methylene group on the gastric prokinetic and dopamine antagonist activity of azabicyclic benzamides related to the serotonin 5-HT_4 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).[1,2]

(1) metoclopramide Ar $CONHCH_2CH_2NEt_2$

(2) BRL 20627 (±)



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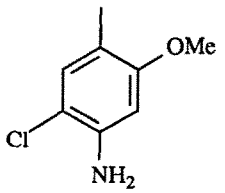
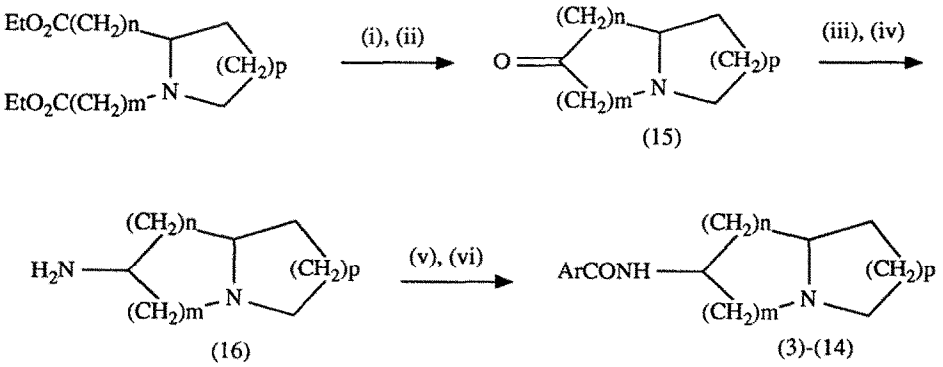


Recently both (1) and (2) have been shown to be partial agonists at the serotonin 5-HT_4 receptor[3] and it is this activity which has recently been correlated with gastric prokinetic activity.[4] The 5-HT_4 receptor has been identified in both the CNS[5] and the heart[6] and it is the renewed interest in modulators of this receptor[7] which has prompted this report on our wider study on azabicyclic benzamides related to (2). Our aim was to identify compounds which were more potent gastric prokinetics whilst retaining the selectivity of (2). Initially we investigated the effect of ring size on pharmacological profile. All the compounds (3-14) were prepared from the intermediate ketones (15) via LAH reduction of the oxime derivatives and conversion of the resultant isomeric mixture of amines (16) to the benzamides by the previously described route (Scheme I), with separation of the isomers by chromatography on silica.[1] The orientation of the amide group was assigned by NMR where possible. The intermediate ketones (15) were prepared by Dieckmann cyclisation of the appropriate diesters using KOBu-t in either Et_2O or toluene[8-10] except for the seven-membered ring ketones. For these, the cyclisation was performed using NaH in toluene under reflux at high dilution using a continuous extraction apparatus for which yields in excess of 60% were thus obtained.

For pharmacological evaluation, the measure used for gastric prokinetic activity was the

Scheme I; General synthesis of 3-14



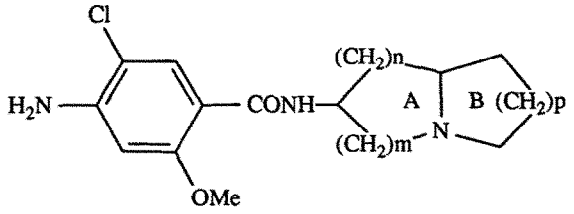
(i) KOBu-t in Et_2O or toluene or NaH in toluene; (ii) H^+; (iii) $H_2NOH.HCl$/pyridine; (iv) LAH/THF (v) N-Ac-ArCOCl; (vi) NaOH, then chromatography ($SiO_2/CHCl_3$ + 5-10% MeOH)

effectiveness of the compound to increase intra-gastric pressure in the rat by our previously described procedure.[1] For dopamine antagonist activity, the reversal of apomorphine-induced climbing behaviour was used.[1] The results for compounds (3)-(15) are shown in Table 1 with (1) and (2) included for comparison.

For the indolizidines (3-6), amide substitution β to the ring fusion (3,4 n = 1)) resulted in a loss in gastric prokinetic activity, though interestingly an increase in dopamine antagonist activity with the more polar isomer. In contrast, the isomers α to the ring fusion (5,6 n = 0) retained gastric prokinetic activity but with little selectivity. An increase in selectivity was observed with the pyrrolizidine (7) which prompted us to investigate the alternative indolizidines (8-11) in which reduction of the size of ring B may further increase the selectivity of (2). Unfortunately this did not prove to be the case although an increase in potency was observed with (9), but with no greater selectivity. Expansion of the A ring to 7-membered (12-14) resulted in two compounds, (12) and (13), which had good selectivity but with reduced potency.

Within the previously reported quinolizidines, good prokinetic activity and selectivity was retained with the methyl substitution as exemplified by (2).[1] We have also previously reported the effect of introduction of a phenyl substituent into the indolizidine system which either retained gastric prokinetic activity, or enhanced dopamine antagonist activity depending upon the orientation of the phenyl group.[11] We therefore investigated the effects of substituents in more detail for the most potent side chains, the 2-amido-quinolizidine and the 7-amido-indolizidine. The structures and results for compounds (17)-(32) are shown in Table II. Compounds (17) and (18) were prepared by routes analogous to that in Scheme I. Our previously reported tandem Michael addition/Mannich cyclisation to the intermediate ketones was used for compounds (23)-(25) and (27)-(30).[12] The syntheses of (19)-(22) are shown in Scheme II. Compound (26) was prepared similarly from the indolizidinone[13] as an inseparable mixture of isomers and (31) and (32) were prepared from the known 9-methyl alcohol.[14] For axial amines, the equatorial

Table I: Structure of 3-14 and pharmacological data



Cpd. No.	n	m	p	ring size A	ring size B	isomer*	IGP**	DA***	ratio
1	metoclopramide					-	1.0	0.8	0.8
2	BRL 20627			6	6	Ax	0.5	25	50
3	1	1	2	5	6	F1	>10	>10	-
4	1	1	2	5	6	F2	>10	0.1	-
5	0	2	2	5	6	F1	0.5	0.2	0.4
6	0	2	2	5	6	F2	1.0	1.8	1.8
7	0	2	1	5	5	-	0.5	7.5	15
8	1	2	1	6	5	Eq	5.0	6.0	1.2
9	1	2	1	6	5	Ax	0.2	12	60
10	0	3	1	6	5	Eq	>5	3.5	-
11	0	3	1	6	5	Ax	0.5	0.1	0.2
12	1	3	2	7	6	F1	1.0	38	38
13	1	3	2	7	6	F2	1.0	>50	>50
14	2	2	2	7	6	-	>25	>50	-

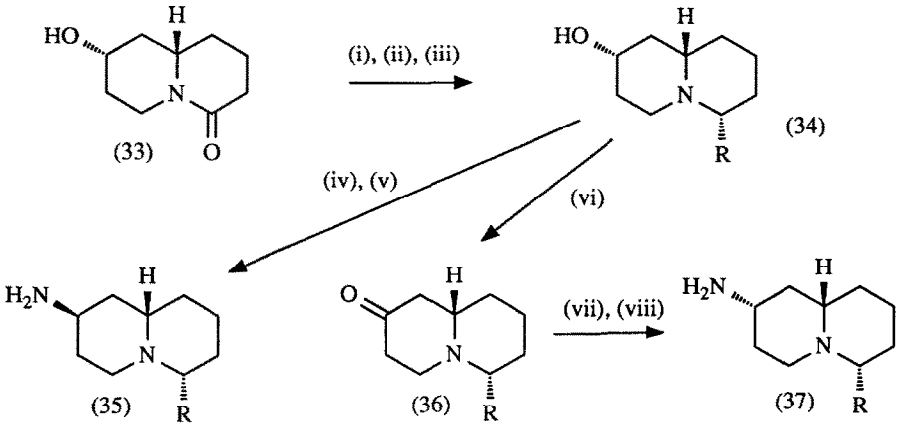
* F1 and F2 are the first and second fractions from the purification column; Eq = equatorial, Ax = axial; ** IGP = stimulation of intragastric pressure, lowest active dose, mg/kg sc; ***DA = inhibition of apomorphine-induced climbing, ED_{50} mg/kg sc.

alcohols were converted via an S_N2 displacement with azide by the Mitsunobu reaction followed by reduction. Alternatively, Oppenauer oxidation to the ketones and reduction of the oxime derivatives with Na in amyl alcohol afforded the equatorial amines.

Introduction of a 7-equatorial methyl substituent (17,18) resulted in a significant reduction in potency in both test models which would imply a severe steric constraint in this area of space. The effect of 6-substituents larger than Me (in 2) was difficult to rationalise, with a loss in activity with the 6-ethyl (19) but retention with the 6-n-propyl (20). The 6-phenyl compounds (21,22) were also ineffective as gastric prokinetic agents with little anti-dopaminergic activity. Introduction of either an equatorial (23,24) or an axial (25) methyl substituent in the 4-position also dramatically reduced activity. For the indolizidines, the 3-methyl substituted compound (26) retained similar activity and selectivity to (2), but showed no advantage over the unsubstituted compound (9). Gastric prokinetic activity was retained with the 5-methyl substituted compounds (27-29) which was surprising considering the effect of methyl substitution in the equivalent position in the quinolizidines (compounds 23-25). In addition, no activity was found with the 9-methyl isomers with either the equatorial (31) or axial (32) amides.

To date, all the compounds investigated had the amide substituent attached directly to the

Scheme II; Synthesis of amine intermediates to 19-22



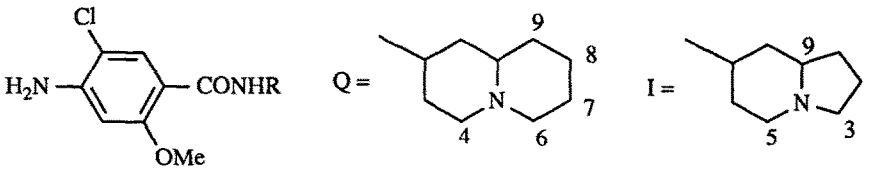
(i) $(Me_3Si)_2NH$; (ii) RMgBr or RLi; (iii) $H^+/NaBH_4$; (iv) DEAD/Ph_3P/$(PhO)_2PON_3$; (v) LAH (vi) KOBu-t/fluorenone; (vii) $HONH_2.HCl$/pyridine; (viii) $Na/C_5H_{11}OH$

azabicycle. This direct attachment severely restricts the conformational freedom of the molecule. In order to determine whether this severe restriction has a deleterious effect upon gastric prokinetic activity, we investigated the effect of inserting a methylene group between the amide and the azabicycle (Table III, compounds 38-44). The amine intermediates (46) for (38-41) and for (44) were prepared from the known hydroxymethyl compounds (45)[15-17] via displacement of the bromomethyl compounds by ammonia. The amine intermediate (48) for (42) and (43) was prepared by an intramolecular alkylation of the appropriate piperidinyl-acetonitrile (47) (Scheme III). The stereochemistry of (38) was determined by single crystal X-ray analysis.

For the quinolizidines (38-42), gastric prokinetic activity was retained only with the 3-isomer, β to the basic nitrogen. The axial isomer (38) had at least twice the potency of (2) with no significant dopamine antagonist activity. Interestingly, the 3-amide isomers connected directly to the ring were inactive.[1] For the indolizidines, the more polar isomer in the 3-position, now α to the basic nitrogen was highly potent, but with lower selectivity. Of additional interest is that neither (38) nor (43) possessed any $5\text{-}HT_3$ receptor antagonist activity as measured by their inability to inhibit the 5-HT-induced bradycardia, the Bezold-Jarisch reflex,[18] at doses up to 1 mg/kg iv. In addition (38) had only very weak dopamine D_2 receptor affinity (IC_{50} 3.9 μM for displacement of [^{125}I]-iodosulpiride from rat D_2 clones).[19] The 2-substituted analogue (44), obtained as an inseparable mixture of isomers, had no significant activity and was therefore not investigated further.

In conclusion, although reduction in ring size to indolizidine gave increased potency with compound (9), no increase in selectivity over dopamine receptor antagonism was achieved. However the introduction of limited extra flexibility with the methylene insertion did give a more potent and more selective gastric prokinetic agent, compound (38), BRL 24330, and by

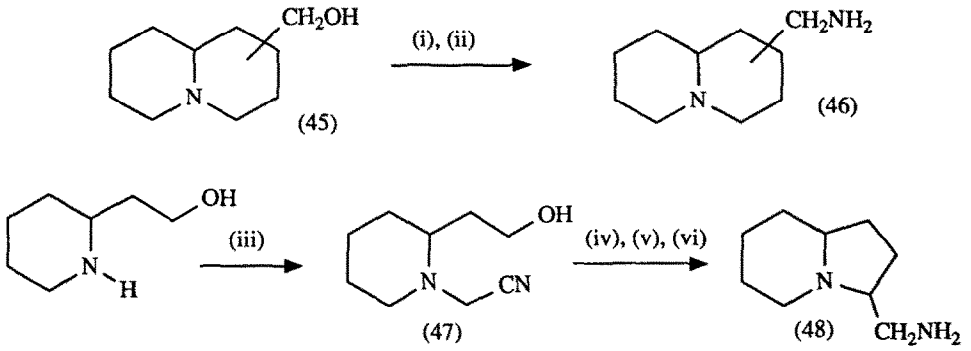
Table II: Structure of 17-32 and pharmacological data.



Cpd. No.	R	amide* isomer	substituent*	IGP*	DA*	ratio
2	Q	Ax	6-Eq-Me	0.5	25	50
17	Q	Eq	7-Eq-Me	>5	>10	-
18	Q	Ax	7-Eq-Me	5	>10	-
19	Q	Ax	6-Eq-Et	>5	-	-
20	Q	Ax	6-Eq-n-Pr	1	>10	>10
21	Q	Eq	6-Eq-Ph	-	5	-
22	Q	Ax	6-Eq-Ph	>5	5	-
23	Q	Eq	4-Eq-Me	>5	>30	-
24	Q	Ax	4-Eq-Me	>1	>30	-
25	Q	Eq	4-Ax-Me	>1	>30	-
26	I	Ax	3-Me	0.5	15	30
27	I	Eq	5-Eq-Me	1	10	10
28	I	Ax	5-Eq-Me	1	50	50
29	I	Eq	5-Ax-Me	1	34	34
30	I	Ax	5-Ax-Me	>1	>50	-
31	I	Eq	9-Me	>1	>30	-
32	I	Ax	9-Me	>1	>30	-

*Key: see Table I.

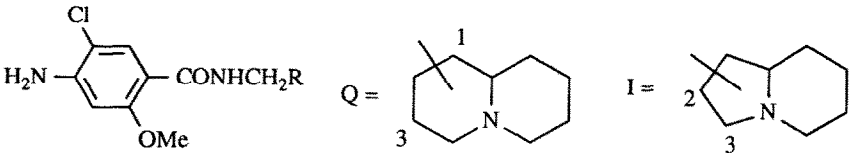
Scheme III; General procedure for amine intermediates to 38-44



(i) PBr_3; (ii) NH_3; (iii) $ClCH_2CN/K_2CO_3$; (iv) $SOCl_2$; (v) NaH; (vi) LAH

implication a more potent 5-HT_4 receptor agonist devoid of either significant dopamine or 5-HT_3 receptor antagonist activity.

Table III: Structure of 38-44 and pharmacological data.



Cpd. No.	R	amidomethyl* isomer	amidomethyl position	IGP*	DA*	ratio
38	Q	Ax	3	0.2	>25	>125
39	Q	Eq	3	5	-	-
40	Q	F1	1	>25	-	-
41	Q	F2	1	>25	-	-
42	I	F1	3	>1	20	-
43	I	F2	3	0.2	15	75
44	I	-	2	>25	-	-

*Key: see Table I.

Acknowledgement: We thank D. Eggleston and P. Baures for the X-ray structure determination of, and Dr. G. Riley for the D_2 binding data on, BRL 24330 (38).

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