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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 5-HETEROARYL BENZODIAZEPINES : ANALOGUES OF YM022

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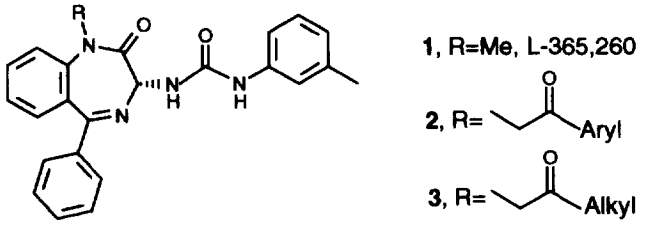
Abstract: A novel series of analogues of the potent gastrin/CCK-B receptor antagonist YM022 have been prepared which incorporate 5- and 6-membered heteroaromatic rings in the benzodiazepine 5-position. The 5-(2-pyridyl) derivatives in particular retained good *in vitro* and *in vivo* potency and one such compound **9i** was shown to inhibit acid secretion after oral dosing in dogs. Improved bioavailability for **9i** over the 5-phenyl analogue, **9h** was demonstrated in rats.

Urea derivatives of 3-amino-5-phenyl-1,4-benzodiazepin-2-ones (e.g., L-365,260, **1**) have been known for some time to be antagonists of the gastrin/CCK-B receptor.[1] Incorporation of aryl- (**2**) or alkylcarbonylmethyl groups (**3**) at the benzodiazepine 1-position improves both potency and selectivity of receptor binding and efficacy *in vivo*.[2,3]

Figure 1 Structures of gastrin/CCK-B antagonists



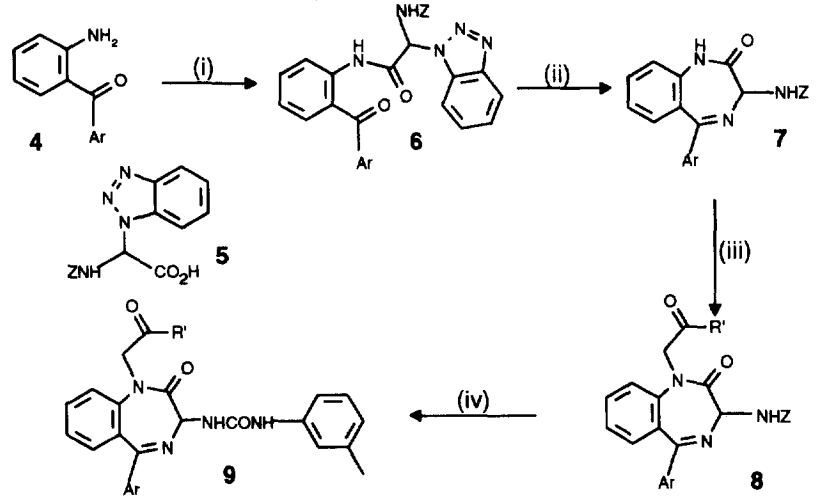
Compounds of type **1** however, have been shown to be sparingly soluble in water and consequently have limited oral bioavailability.[4] Aqueous solubility has been increased by introducing acid groups onto the aryl urea portion of the molecule,[5] and we have shown that incorporation of a *tert*-butylcarbonylmethyl group at the 1-position (**3**, Alkyl = t-butyl) provides a significant increase in absorption.[3]

An alternative approach to improving bioavailability has been to introduce substituents other than phenyl into the 5-position of the parent benzodiazepine. This has been achieved by incorporation of either a cyclohexyl group[6] or a saturated cyclic amino

group to form an amidino functionality.[7] We now wish to report the structure-activity relationships of a series of derivatives of YM022 and related compounds, in which five- and six-membered aromatic nitrogen containing heterocycles have been incorporated at this position.

The benzodiazepine derivatives were synthesised using the benzotriazole mediated ring synthesis reported recently[8,9] (Figure 2). The intermediates **7** were typically crystalline and could all be selectively alkylated at the 1-position with the requisite bromomethyl ketone derivative to provide **8**. Deprotection of the 3-amino substituent and resolution of the intermediate amine where appropriate,[9b] followed by reaction with m-tolyl isocyanate, provided the target compounds **9**. In the examples where the 5-heteroaryl group was a diazole, a (trimethylsilyl)ethoxymethyl (SEM) protecting group was employed throughout the synthesis to prevent side reactions on the ring nitrogen. In these cases the Z group in **8** was removed by hydrogenolysis and the SEM group removed after the urea formation step by acid hydrolysis. For each of the six-membered nitrogen containing heterocycles however, attempted hydrogenolysis of the Z group in **8** resulted in concomitant reduction of the benzodiazepine imine bond and so in these cases deprotection was carried out by treatment with dry HBr in DCM.

Figure 2: Synthesis of 5-heteroaryl substituted benzodiazepine analogues.



Reagents and Conditions: (I) WSC, **5**, 0°C-r.t., (ii) a) NH_3/MeOH, b) AcOH, (iii) a) NaH, DMF b) $R'COCH_2Br$ (iv) a) either H_2/5% Pd on C or HBr in DCM, 0°C b) (3-Me)-PhNCO

The structure-activity relationships for the 5-heteroaryl benzodiazepines prepared are shown in the Table. In the 1-cyclopentylcarbonylmethyl series, the isomeric 5-substituted 3- (**9g**) and 4-pyridyl (**9e**) derivatives exhibited significantly reduced affinity for the gastrin/CCK-B receptor in comparison to the parent phenyl compound (**9d**). In contrast, the insertion of a 2-pyridyl substituent at the 5-position gave a compound with affinity for the gastrin/CCK-B receptor comparable to that of the 5-phenyl analogue. This pattern was repeated in the YM022 series and the 1-*tert*-butylcarbonylmethyl series. In addition, these 2-pyridyl compounds (**9c** and **9i**) showed improved selectivity for the gastrin/CCK-B receptor over CCK-A.

Table: Structure-Activity relationships for substituted benzodiazepines (95% confidence limits).

No.	R¹	Ar	Config.[a]	CCK-B[b] (nM)	CCK-A[c] (nM)	ED₅₀[d] (μmol/kg)
9a (YM022)	2-MePh		R	0.11 (0.10-0.11)	146 (120-170)	7.8
9b	2-MePh		RS	18 (13-25)	670 (390-1200)	37% @ 0.1 μmol/kg
9c	2-MePh		RS	0.13 (0.10-0.17)	980 (940-1040)	16.7
9d			RS	0.23 (0.17-0.30)	n.d.	15.5
9e			RS	48 (33-70)	>10,000	15% @ 0.1 μmol/kg
9f			RS	0.12 (0.10-0.15)	2600 (2400-2800)	18.9
9g			RS	1.6 (1.3-1.8)	80 (75-85)	34% @ 0.1 μmol/kg
9h			R	0.52 (0.43-0.63)	111 (85-146)	5.7
9i			R	0.44 (0.33-0.59)	470 (361-611)	16.0
9j			RS	0.88 (0.70-1.11)	1356 (1051-1772)	55% @ 0.1 μmol/kg
9k			RS	4.52 (2.83-7.24)	844 (721-989)	49% @ 0.1 μmol/kg
9l			RS	8.0 (5.02-12.6)	2615 (1507-4539)	14% @ 0.1 μmol/kg
9m			RS	26.1 (13.5-41.2)	232 (171-316)	25% @ 0.1 μmol/kg
9n			RS	>100	105 (88-124)	18% @ 0.1 μmol/kg
9o			RS	0.8 (0.68-0.94)	433 (369-509)	58% @ 0.1 μmol/kg

a) Absolute configuration at the benzodiazepine 3-position.
b) IC_{50} value for displacement of [^{125}I]-CCK-8 from Gastrin/CCK-B receptors from rat brain.
c) IC_{50} value for displacement of [^{3}H]-L-364,718 from CCK-A receptors from rat pancreas.
d) *In Vivo* data : i.v. dose required to inhibit pentagastrin induced gastric acid secretion in rats by 50 %. (For full experimental details see ref. 2).

Having established that a 2-heterosubstituted 6-membered ring was well tolerated, we attempted to further increase the predicted water solubility by adding a second heteroatom to the 5-substituent. However, the insertion of a second nitrogen into the ring to give the 5-(2-pyrazine) derivative **9j** resulted in a decrease in potency.

We next turned our attention to a series of 5-membered heteroaromatic ring substituents each containing two heteroatoms. As can be seen from the Table however,

only the 5-(2-thiazole) derivative **9o** retained any significant affinity, whereas all the diazole analogues tested were much poorer ligands for the gastrin/CCK-B receptor.

In our *in vivo* functional screen, the 5-(2-pyridyl) compounds again proved to be comparable to the analogous 5-phenyl derivatives in their ability to antagonise the effects of pentagastrin-induced gastric acid secretion in rats following i.v. administration (Table). None of the weaker gastrin/CCK-B ligands showed such good levels of efficacy in this *in vivo* test.

We further examined the gastrin antagonist properties of one of our 5-(2-pyridyl) analogues **9i**, after oral administration in Heidenhain pouch dogs.[10] **9i** inhibited pentagastrin-induced gastric acid secretion in dogs by 97% at a dose of 3μmol/kg (p.o.) and peptone meal induced gastric acid secretion by 64% at the same dose.

Significantly improved oral bioavailability for the 5-(2-pyridyl) series was clearly demonstrated in a preliminary pharmacokinetic study. Following an oral dose of 10mg/kg in rats the 5-phenyl derivative **9h** gave a maximum plasma concentration (C_{max}) of 80.7 ng/mL, whereas the same dose of the 5-(2-pyridyl) analogue **9i** achieved a C_{max} of 570.5 ng/mL.

Together these data show **9i** to be a highly potent and orally active gastrin/CCK-B antagonist. Thus incorporation of a 5-(2-pyridyl) group into the parent structure provides compounds with a major advantage over other known benzodiazepine based gastrin/CCK-B antagonists.

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