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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1-ALKYLCARBONYLMETHYL ANALOGUES OF YM022

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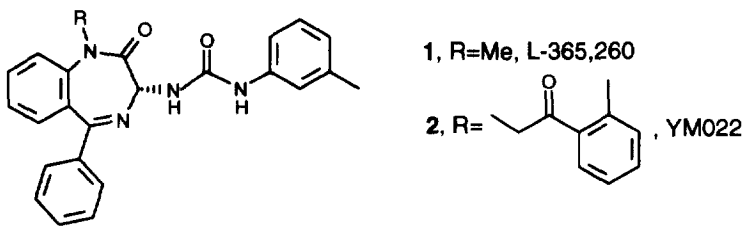
Abstract: A novel series of 1-alkylcarbonylmethyl analogues of the potent gastrin/CCK-B receptor antagonist YM022 have been prepared. A number of analogues retained good affinity for the gastrin/CCK-B receptor and one compound (**6d**) showed improved binding and enhanced selectivity for this receptor over CCK-A. A second compound (**6j**) gave improved *in vivo* inhibition of gastric acid secretion in rats. Both analogues were shown to have significantly better activity in the same model following i.d. dosing than either YM022 or L-365,260.

Urea derivatives of 3-amino-1,4-benzodiazepin-2-ones, such as L-365,260 (**1**), are potent and selective antagonists for gastrin and CCK-B receptors.[1] **1** has been shown to supress gastric acid secretion induced by either pentagastrin, histamine or bethanechol in rats,[2] and by pentagastrin in humans after oral dosing.[3]

Our own work in this area has shown that the incorporation of arylcarbonylmethyl substituents into the 1-position of the parent benzodiazepine (e.g. YM022, **2**) produces a series of antagonists with greatly increased affinity for the gastrin/CCK-B receptor which maintain selectivity over the CCK-A receptor. In addition, *in vivo* studies have shown that YM022 is more than 500 times as effective as L-365,260 as an inhibitor of pentagastrin induced gastric acid secretion in rats.[4]

Figure 1: Structures of Benzodiazepine Based CCK-B Ligands

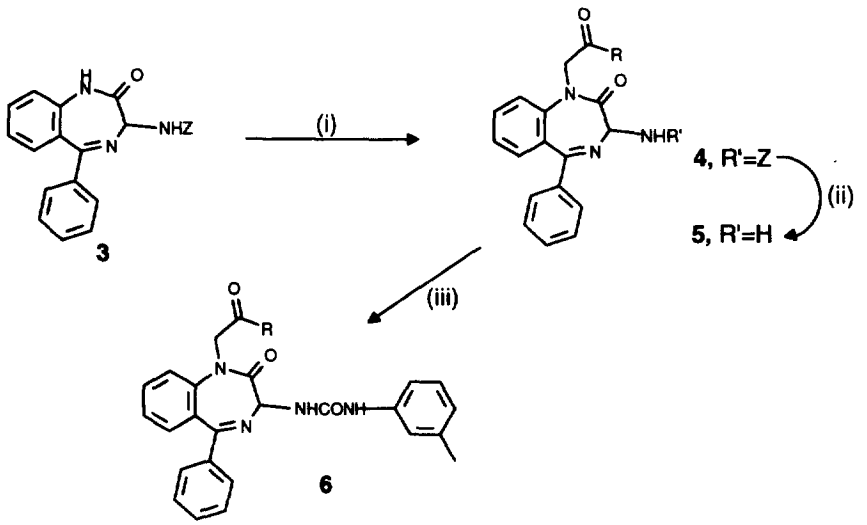


In our continuing search for novel antagonists of the gastrin/CCK-B receptor we have recently prepared a series of analogues of YM022 in which the arylcarbonylmethyl

group is replaced by a range of cyclic and branched alkylcarbonylmethyl groups. The synthesis of these compounds is outlined in figure 2.

The 3-benzyloxycarbonylamino benzodiazepine derivative **3** was prepared using the procedure of **Bock *et al.*[5]** or with minor modifications to the recent method of Sherrill and Sugg.[6] Alkylation at the benzodiazepine 1-position was readily achieved by treatment with sodium hydride in DMF followed by the appropriate bromide derivative. The requisite bromomethylketones were either commercially available or prepared by treatment of the appropriate acid chloride with diazomethane to form the diazomethylketone, followed by a saturated solution of HBr in ethyl acetate. The synthesis was completed by hydrogenolysis of the benzodiazepine **4**, to give the amino intermediate **5**, followed by reaction with m-tolyl isocyanate to provide the target benzodiazepine **6**.

Figure 2: Synthesis of analogues of YM022



Reagents: (i) (a) NaH, 0°C, 1h (b) $RCOCH_2Br$ (ii) H_2, 5%Pd on C (iii) (3-Me)-PhNCO.

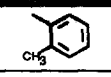
The compounds were examined for their affinity for CCK-A and gastrin/CCK-B receptors[4] and the results are shown in Table 1.

We initially prepared a series of cyclic 1-alkylcarbonylmethyl derivatives as saturated ring analogues of YM022. The cyclopentyl derivative **6c** contains the optimum ring size amongst this series, the four-, six- and seven-membered ring analogues having less affinity for the gastrin/CCK-B receptor.

The promising activity of the racemic cyclopentyl derivative prompted us to prepare the compound in optically pure form. The relevant intermediate amine (**5**,R=cyclopentyl) was resolved by a racemisation/resolution procedure,[7] the absolute configuration of the (+)-enantiomer of the target urea derivative being assigned as R by analogy with L-365,260. Consistent with previous observations, the R-enantiomer was the more active isomer, and this compound **6d**, was a more potent and selective ligand for gastrin/CCK-B receptors than YM022.

We next turned our attention to branched, acyclic 1-alkylcarbonylmethyl derivatives and observed that analogues with a quaternary carbon adjacent to the carbonyl group (e.g. **6j**, **6k**) showed greater affinity for the gastrin/CCK-B receptor than those with a methine group in the same position (e.g. **6h**, **6i**).

Table 1. Receptor binding affinity data for YM022 and its analogues, **6** (95% confidence limits).

2 (YM022)[4]		R	0.11 (0.10-0.11)	146 (120-170)
6a		RS	0.28 (0.26-0.31)	480 (310-750)
6b		RS	2.37 (1.53-3.67)	n.d.
6c		RS	0.23 (0.17-0.30)	n.d.
6d		R	0.07 (0.06-0.09)	440 (370-530)
6e		S	6.1 (4.71-7.89)	2500 (1900-3400)
6f		RS	0.4[d] (0.30-0.53)	n.d.
6g		RS	2.0[d] (1.41-3.42)	n.d.
6h		RS	2.1 (1.55-2.71)	1200 (1100-1400)
6i		RS	1.9 (1.60-2.32)	n.d.
6j		R	0.52 (0.43-0.63)	111 (85-146)
6k		RS	0.57 (0.46-0.69)	720 (680-770)
6l		RS	0.41 (0.30-0.55)	n.d.
6m		RS	0.10 (0.11-0.16)	293 (245-349)
6n		RS	0.38 (0.33-0.44)	>10,000
6o		RS	0.86 (0.51-1.46)	n.d.

n.d.=not determined

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. See Ref 4 for full experimental details.

d) Data determined by Novascreen (Baltimore, Md.).

This led us to prepare a series of analogues which combined both a carbocyclic ring and a quaternary centre adjacent to the carbonyl group resulting in the discovery of **6m**, a highly potent gastrin/CCK-B ligand. However, the improvement in potency obtained did not compensate for the increase in synthetic complexity in this series.

With a number of potent gastrin/CCK-B ligands in hand, we turned our attention to their *in vivo* effects by examining a selection of the compounds for their efficacy in

inhibiting pentagastrin induced gastric acid secretion in rats when given i.v (Table 2). All of the analogues of YM022 were shown to be significantly more potent antagonists of pentagastrin in this model than L-365,260. The most effective compound was the *tert*-butyl derivative **6j**. Despite showing weaker affinity for the gastrin/CCK-B receptor in our *in vitro* test system, this compound was more potent *in vivo* than either the cyclopentyl derivative **6c**, or the parent compound YM022 following i.v. administration. In addition **6j** was also a highly potent inhibitor of acid secretion when dosed i.d. This observation appears to indicate an advantage for this compound over both YM022, which shows weaker activity in this model, and L-365,260 which is known to suffer from poor bioavailability,[8,9] making these novel compounds worthy of further study. The results of these investigations will be reported in due course.

Table 2: *In vivo* data for analogues of YM022. Inhibition of pentagastrin induced gastric acid secretion in rats[4] after intravenous or intraduodenal administration.

1 (L-365,260)	**0**	**4230**[4]	n.d.
2 (YM022)	80	7.8[4]	16
6c	65.2	15.5	36
6d	79.9	n.d.	31
6f	67[b]	47	n.d.
6g	53.5	18	n.d.
6j	76.7	5.7	80

n.d.= not determined

a) I.v. dose required to inhibit pentagastrin induced gastric acid secretion in rats by 50%.

b) at 0.1μmol/kg.

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