Biological Activity of Analogues of YM022.[1] Novel (3-Amino Substituted Phenyl)urea Derivatives of 1,4-Benzodiazepin-2-one as Gastrin/Cholecystokinin-B Receptor Antagonists

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A series of (3-substituted phenyl)urea analogues of the potent gastrin/cholecystokinin (CCK)-B receptor antagonist YM022 has been prepared. Structure–activity relationship studies of this series suggested that a number of analogues retained good *in vitro* potency for gastrin/CCK-B receptor. In particular, the (3-amino substituted phenyl)urea derivatives (10—12) were more potent inhibitors of pentagastrin-induced gastric acid secretion in rats than YM022 on intraduodenal (i.d.) administration.

Key words gastrin/CCK-B receptor antagonist; YM022; structure–activity relationship; pentagastrin-induced gastric acid secretion; 1,4-benzodiazepin-2-one

Since the discovery of the nonpeptidal, potent and selective gastrin/cholecystokinin (CCK)-B receptor antagonist L-365,260 (**1**),[2] several urea derivatives of 3-amino-1,4-benzodiazepin-2-ones have been investigated as target molecules in this area.[3] We have recently reported that a 1-aroylmethyl derivative, YM022 (**2**), shows superior *in vitro* and *in vivo* potency.[1,4] Incorporation of alkylcarbonylmethyl groups at the 1-position of the benzodiazepine ring system has also been shown to result in retention of the gastrin/CCK-B receptor antagonistic activity.[5] In addition, the 5-(2-pyridyl) analogues demonstrated significantly improved oral activity.[6]

In our further search for analogues of YM022, we have recently prepared a series of (3-substituted phenyl)urea derivatives and evaluated their structure–activity relationships for gastrin/CCK-B receptor antagonistic activity.

Chemistry and Biology

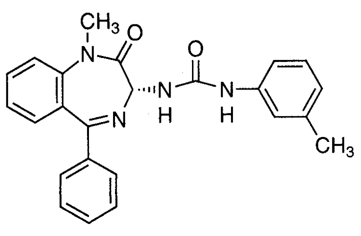
The target compounds (**4**—**13**, Table 1) were prepared from (*RS*)- or (*R*)-3-amino-1,3-dihydro-1-(2-methylphenacyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3**)[1] by reaction with the corresponding isocyanates, followed by further reactions (hydrolysis, deprotection, *etc.*), if necessary (Chart 1).

In vitro receptor binding assays were used to measure affinities at the CCK-B[7] and CCK-A[8] receptors. *In vivo* efficacy was measured in anesthetized rats by assaying gastric acid secretion[9] following intravenous (i.v.) or intraduodenal (i.d.) administration of a test compound 1 h after the start of pentagastrin infusion.

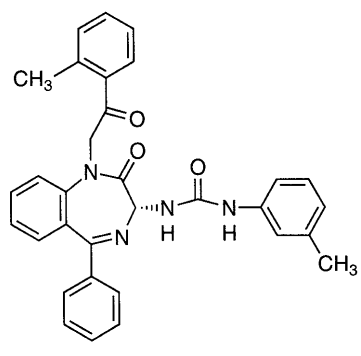
Results and Discussion

The structure–activity relationships for the (3-substituted phenyl)urea analogues of YM022 are shown in Table 1. The attachment of a carboxyl group to the 3-position (**4**) led to improved selectivity as well as retained affinity for the gastrin/CCK-B receptor compared to YM022, although the insertion of a carboxamide (**5**) or a nitrile (**6**) group resulted in reduced potency. Incorporation of nitrogen-substituents (**8**—**13**) proved to increase the selectivity for the gastrin/CCK-B receptor over the CCK-A receptor, with equipotent binding affinity to YM022, whereas a nitro function was less effective (**7**).

In our *in vivo* test, all the compounds were potent inhibitors of pentagastrin-induced gastric acid secretion in rats following i.v. administration, except for a cyclic amino analogue (**13**). The basic (3-amino substituted phenyl)urea analogues (**10**—**12**) showed stronger inhibition of acid secretion than YM022 after i.d. administration at a dose of 0.3 μmol/kg in rats. This result is similar to



L-365,260 (**1**)



YM022 (**2**)

Fig. 1

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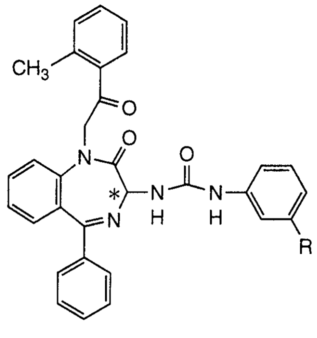
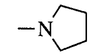
Table 1. Structure–Activity Relationships for (3-Substituted Phenyl)urea Analogues of YM022



Compound	R	C3-stereo	Binding assay: IC_{50} (nM)		Inhibition (%) of acid secretion at 0.1 μmol/kg i.v. in SD rats	Inhibition (%) of acid secretion at 0.3 μmol/kg i.d. in SD rats
			CCK-A[a)]	CCK-B[b)]		
YM022	CH_3	*R*	150	0.11	81 (at 0.03 μmol/kg)	16
4	CO_2H	*RS*	3210	0.40	77	10
5	$CONH_2$	*RS*	2680	4.24	73	8
6	CN	*RS*	1070	4.22	69	10
7	NO_2	*RS*	1310	5.59	62	0
8	NHCHO	*R*	360	0.09	89	18
9	$NH(CH_3)CHO$	*R*	660	0.04	65	NT
10	NH_2	*R*	450	0.24	74	50
11	$NHCH_3$	*R*	310	0.04	87	50
12	$N(CH_3)_2$	*R*	710	0.17	63	66
13		*RS*	> 10000	0.38	41	9

a) IC_{50} (nM) of [^{3}H]L-364,718 binding to rat pancreas membranes. *b)* IC_{50} (nM) of [^{125}I]CCK-8 binding to rat brain membranes. NT: not tested.

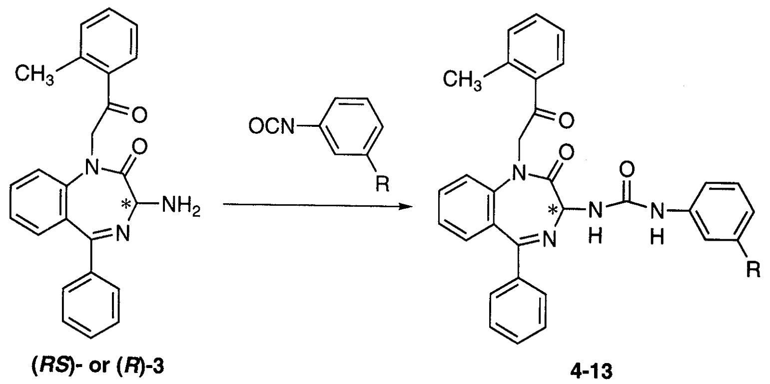


Chart 1

that in our preceding report,[6)] in which the 5-(2-pyridyl) analogues showed improved oral activity in dogs, and provides further evidence that the enhanced basicity of these gastrin/CCK-B receptor antagonists increases their i.d. activity by improving bioavailability.

Experimental

Melting points were determined on a Yanaco MP-500D and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNN-EX-400, or a JEOL JNN-GX-500 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL JMS DX-300 mass spectrometer. Elemental analysis was performed with a Yanaco MT-5. Column chromatography was performed on silica gel (Merck Kieselgel 60, 70—230 mesh).

3-[3-[2,3-Dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]ureido]benzoic Acid (4) Et_3N (113 mg, 1.12 mmol) was added to a solution of methyl isophthalate (202 mg, 1.12 mmol) and diphenylphosphoryl azide (DPPA, 339 mg, 1.23 mmol) in toluene (20 ml). The mixture was stirred at room temperature for 1 h, refluxed for 1.5 h and cooled. A solution of (*RS*)-3-amino-1,3-dihydro-1-(2-methylphenacyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3**)[1)] (142 mg, 0.37 mmol) in toluene (5 ml) was added and the stirring was continued at room temperature for 1 h. The reaction mixture was successively washed with saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 1) to give the methyl ester of the title compound (151 mg, 72%).

1 N NaOH (0.78 ml) was added to a solution of the above ester (145 mg, 0.26 mmol) in MeOH (4 ml), and the mixture was stirred at 50 °C for 6 h. Then 1 N HCl (0.78 ml) and water (10 ml) were added and the resultant precipitate was collected by filtration to give crude **4**. The crude **4** was purified by silica gel column chromatography ($CHCl_3$: MeOH = 93 : 7) to give **4** (42 mg, 30%) after crystallization from ether: mp 254—257 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.34 (3H, s, CH_3), 5.39 (3H, m, $C\underline{H}_2$COPh and C3-H), 7.26—8.04 (18H, m), 9.26 (1H, s). FAB-MS (Pos.) *m/z*: 547 $(M+1)^+$. *Anal.* Calcd for $C_{32}H_{26}N_4O_5 \cdot 0.4H_2O$: C, 69.40; H, 4.88; N, 10.12. Found: C, 69.37; H, 4.85; N, 10.11.

3-[3-[2,3-Dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzo-

diazepin-3-yl]ureido]benzamide (5) A solution of isobutyl chloroformate (74 mg, 0.54 mmol) in tetrahydrofuran (THF, 1 ml) was added to a solution of **4** (300 mg, 0.55 mmol) and *N*-methylmorpholine (62 mg, 0.61 mmol) in THF (3 ml). The mixture was stirred at room temperature for 15 min, then concentrated NH_4OH (0.3 ml) was added and the stirring was continued overnight. The resultant precipitate was collected by filtration and crystallized from MeOH to give **5** (86 mg, 29%): mp 271—275 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.34 (3H, s, CH_3), 5.39 (3H, m, C$\underline{H}_2$COPh, C3-H), 7.26—7.88 (20H, m), 9.16 (1H, s). FAB-MS (Pos.) *m*/*z*: 546 $(M+1)^+$. *Anal.* Calcd for $C_{32}H_{27}N_5O_4 \cdot 1.25H_2O$: C, 67.65; H, 5.23; N, 12.33. Found: C, 67.85; H, 4.83; N, 12.08.

3-[3-[2,3-Dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]ureido]benzonitrile (6) Et_3N (85 mg, 0.84 mmol) was added to a solution of 3-cyanobenzoic acid (124 mg, 0.84 mmol) and DPPA (254 mg, 0.92 mmol) in toluene (15 ml). The mixture was stirred at room temperature for 1 h, refluxed for 1 h and cooled. A solution of (*RS*)-**3**[1] (107 mg, 0.28 mmol) in toluene (4 ml) was added and the stirring was continued at room temperature for 1 h. The reaction mixture was successively washed with saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : AcOEt = 2 : 1) to give **6** (75 mg, 51%) after crystallization from AcOEt–hexane: mp 238—241 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s, CH_3), 5.37 (3H, m, C$\underline{H}_2$COPh, C3-H), 7.26—7.93 (18H, m), 9.41 (1H, s). FAB-MS (Pos.) *m*/*z*: 528 $(M+1)^+$. *Anal.* Calcd for $C_{32}H_{25}N_5O_3$: C, 72.85; H, 4.78; N, 13.27. Found: C, 72.94; H, 4.84; N, 13.29.

1-[2,3-Dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]-3-(3-nitrophenyl)urea (7) 3-Nitrobenzoic acid (167 mg, 1.00 mmol), Et_3N (101 mg, 1.00 mmol), DPPA (275 mg, 1.00 mmol) and (*RS*)-**3**[1] (107 mg, 0.28 mmol) were treated in the manner described for **6** to give **7** (100 mg, 65%): mp 222—224 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, CH_3), 5.15 (1H, d, J=20 Hz, one of C$\underline{H}_2$COPh), 5.30 (1H, d, J=20 Hz, one of C$\underline{H}_2$COPh), 5.80 (1H, d, J=5 Hz, C3-H), 7.16—7.69 (18H, m), 8.24 (1H, s). FAB-MS (Pos.) *m*/*z*: 548 $(M+1)^+$. *Anal.* Calcd for $C_{31}H_{25}N_5O_5 \cdot 0.5H_2O$: C, 66.90; H, 4.71; N, 12.58. Found: C, 66.98; H, 4.65; N, 12.72.

(*R*)-1-[2,3-Dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]-3-(3-formylaminophenyl)urea (8) 3-Formylaminobenzoic acid (308 mg, 1.86 mmol), Et_3N (189 mg, 1.87 mmol), DPPA (565 mg, 2.05 mmol) and (*R*)-**3**[1] (357 mg, 0.93 mmol) were treated in the manner described for **6** to give **8** (239 mg, 47%): mp 155 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, d, J=20 Hz, CH_3), 5.04 (1H, br, one of C$\underline{H}_2$COPh), 5.29 (1H, br, one of C$\underline{H}_2$COPh), 5.80 (1H, br s, C3-H), 6.51 (1H, br), 6.95—8.53 (18H, m). FAB-MS (Pos.) *m*/*z*: 546 $(M+1)^+$. $[\alpha]_D^{20}$ +122.7° (c=0.51, CH_2Cl_2). *Anal.* Calcd for $C_{32}H_{27}N_5O_4 \cdot 0.4H_2O$: C, 69.53; H, 5.07; N, 12.67. Found: C, 69.54; H, 5.11; N, 12.44.

(*R*)-1-[2,3-Dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]-3-[(*N*-formyl-*N*-methylamino)phenyl]urea (9) 3-(*N*-Formyl-*N*-methylamino)benzoic acid (285 mg, 1.59 mmol), Et_3N (161 mg, 1.59 mmol), DPPA (482 mg, 1.75 mmol) and (*R*)-**3**[1] (307 mg, 0.80 mmol) were treated in the manner described for **6** to give **9** (312 mg, 70%): mp 125 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s, PhC$\underline{H}_3$), 3.18 (3H, s, NC$\underline{H}_3$), 5.14 (1H, d, J=18 Hz, one of C$\underline{H}_2$COPh), 5.28 (1H, d, J=18 Hz, one of C$\underline{H}_2$COPh), 5.72 (1H, d, J=8 Hz, C3-H), 6.65 (1H, d, J=8 Hz), 7.02—7.62 (17H, m), 8.03 (1H, s), 8.37 (1H, s, NCHO). FAB-MS (Pos.) *m*/*z*: 560 $(M+1)^+$. $[\alpha]_D^{20}$ +123.4° (c=0.52, CH_2Cl_2). *Anal.* Calcd for $C_{33}H_{29}N_5O_4 \cdot 0.3H_2O$: C, 70.15; H, 5.28; N, 12.39. Found: C, 70.15; H, 5.32; N, 12.27.

(*R*)-1-(3-Aminophenyl)-3-[2,3-dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]urea (10) 4 N HCl (2 ml) was added to a solution of **8** (350 mg, 0.64 mmol) in acetone (5 ml) and the mixture was stirred at room temperature for 6 h. The solvent was evaporated *in vacuo*, and the residue was partitioned between CH_2Cl_2 (10 ml) and saturated aqueous $NaHCO_3$ (5 ml). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 2) to give **10** (220 mg, 65%) after crystallization from CH_2Cl_2–ether: mp 165—168 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s, CH_3), 5.09 (1H, d, J=18 Hz, one of C$\underline{H}_2$COPh), 5.30 (1H, d, J=18 Hz, one of C$\underline{H}_2$COPh), 5.67 (1H, d, J=8 Hz, C3-H), 6.34 (1H, dd, J=2, 8 Hz), 6.60 (1H, d, J=8 Hz), 6.84—7.60 (17H, m). FAB-MS (Pos.) *m*/*z*: 518 $(M+1)^+$. $[\alpha]_D^{20}$ +111.0° (c=0.39, $CHCl_3$). *Anal.* Calcd for $C_{31}H_{27}N_5O_3 \cdot 0.4H_2O$: C, 70.95; H, 5.34; N, 13.35. Found: C, 70.94; H, 5.40; N, 13.32.

(*R*)-1-[2,3-Dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]-3-(3-methylaminophenyl)urea (11) **9** (187 mg, 0.33 mmol) was treated in the manner described for **10** to give **11** (107 mg, 60%): mp 151—153 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s, PhC$\underline{H}_3$), 2.79 (3H, s, NC$\underline{H}_3$), 5.10 (1H, d, J=18 Hz, one of C$\underline{H}_2$COPh), 5.31 (1H, d, J=18 Hz, one of C$\underline{H}_2$COPh), 5.68 (1H, d, J=8 Hz, C3-H), 6.33 (1H, d, J=8 Hz), 6.58 (1H, d, J=8 Hz), 6.80—7.61 (17H, m). FAB-MS (Pos.) *m*/*z*: 532 $(M+1)^+$. $[\alpha]_D^{20}$ +128.5° (c=0.17, $CHCl_3$). *Anal.* Calcd for $C_{32}H_{29}N_5O_3 \cdot 0.3C_6H_{14}$: C, 72.82; H, 6.00; N, 12.56. Found: C, 72.61; H, 6.09; N, 12.32.

(*R*)-1-[2,3-Dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]-3-(3-dimethylaminophenyl)urea (12) 3-Dimethylaminobenzoic acid (165 mg, 1.00 mmol), Et_3N (101 mg, 1.00 mmol), DPPA (275 mg, 1.00 mmol) and (*R*)-**3**[1] (107 mg, 0.28 mmol) were treated in the manner described for **6** to give **12** (97 mg, 64%): mp 191—193 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s, PhC$\underline{H}_3$), 2.84 (6H, s, $N(CH_3)_2$), 5.37 (2H, s, C$\underline{H}_2$COPh), 6.32 (1H, d, J=10 Hz, C3-H), 6.58—7.85 (18H, m), 8.89 (1H, s). FAB-MS (Pos.) *m*/*z*: 546 $(M+1)^+$. $[\alpha]_D^{20}$ +128.0° (c=0.54, DMF). *Anal.* Calcd for $C_{33}H_{31}N_5O_3$: C, 72.64; H, 5.73; N, 12.84. Found: C, 72.42; H, 5.77; N, 12.86.

1-[2,3-Dihydro-1-(2-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]-3-[3-(1-pyrrolidinyl)phenyl]urea (13) 3-(1-Pyrrolidinyl)benzoic acid[10] (88 mg, 0.46 mmol), Et_3N (47 mg, 0.46 mmol), DPPA (139 mg, 0.51 mmol) and (*RS*)-**3**[1] (176 mg, 0.46 mmol) were treated in the manner described for **6** to give **13** (73 mg, 28%): mp 210 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.96 (4H, m, C3 and C4-H of pyrrolidine), 2.39 (3H, s, CH_3), 3.28 (4H, m, C2 and C5-H of pyrrolidine), 5.10 (1H, d, J=18 Hz, one of C$\underline{H}_2$COPh), 5.30 (1H, d, J=18 Hz, one of C$\underline{H}_2$COPh), 5.70 (1H, d, J=5 Hz, C3-H), 6.38 (1H, s), 6.55 (1H, d, J=10 Hz), 6.79—7.59 (17H, m). FAB-MS (Pos.) *m*/*z*: 572 $(M+1)^+$. *Anal.* Calcd for $C_{35}H_{33}N_5O_3$: C, 73.54; H, 5.82; N, 12.25. Found: C, 73.33; H, 6.11; N, 12.11.

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