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DESIGN, SYNTHESIS, AND PHARMACOLOGICAL EVALUATION OF DUAL HISTAMINE H$_2$ AND GASTRIN RECEPTOR ANTAGONISTS

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Abstract: The joint type of hybrid molecules composed of two pharmacophore moieties taken from histamine H$_2$ and gastrin receptor antagonists have been designed and synthesized to exhibit dual histamine H$_2$ and gastrin receptor antagonistic activities. Here we report the importance of spacers as well as binding sites of both pharmacophores for the dual activity.

Despite the epoch-making success of histamine H$_2$ receptor antagonists (H$_2$A) as a gastric acid antisecretagogue in the chemotherapy of peptic ulcer[1], the relatively high relapse rate after cessation of treatment has been found as a serious therapeutic shortcoming[2a]. Various causative factors have been implicated in the recurrence of ulceration[2a], namely, the rebound of gastric acid secretion after cessation of therapy[2b], the deterioration of defensive factors such as prostaglandins involved in fundic mucosa[2a] and smooth muscle, mucosal strain brought about by rapid ulcer healing[2a], and the proliferation of *Helicobacter pylori* during H$_2$A therapy[3]. We decided to focus on the rebound of gastric acid secretion for the following reasons. Mechanistically, H$_2$As as well as proton-pump inhibitors have been pointed out to have some possibilities of causing chronic hypergastrinemia which would, in turn, result in hyperplasia of oxyntic mucosal cells including gastrin-dependent histamine secretory Enterochromaphin-like cells (ECL cells) and cause the rebound of gastric acid secretion leading to the recurrence of ulceration after cessation of therapy[4].

The discovery of the potent and selective nonpeptide cholecystokinin-B (CCK-B) or gastrin receptor antagonist (GA) L-365,260 by the Merck group[5] provided an excellent tool for examining these hitherto unproved mechanistic speculations by blocking the signal transactions of gastrin through gastrin receptors located on ECL cells as well as on parietal cells. Our group disclosed in a patent the following results[6]. They orally administered potent H$_2$A famotidine (10 mg/kg/day) to male Sprague-Dawley rats (body weight 270-290 g, N = 4) for 7 days. A distinct augmentation of the daily total gastric acid output was observed from two days after cessation of the drug, strongly indicating a rebound of gastric acid secretion. Of importance to our study was the fact that this augmentation of the daily total gastric acid output was effectively attenuated by the oral co-administration of L- 365,260 (10 mg/kg/day) with famotidine (10 mg/kg/day). In another experiment, aspirin-induced gastric mucosal cell injury was found to be augmented from two days after cessation of famotidine and this augmentation could be effectively suppressed by oral co-administration of L-365,260.

As these preliminary results suggested a potential applicability of GA for alleviating the relapse problem in H_2A therapy, we decided to design and synthesize, for the first time to our knowledge, dual histamine H_2 and gastrin receptor antagonists (H_2 & G-A) in order to evaluate their pharmacological advantages as antiulcer agents. Here we report our preliminary results of these studies.

In our chemical design of these dual antagonists, we adopted a strategy of constructing hybrid molecules[7] from a known H_2A and GA with keeping their essential structural requirements for exhibiting dual H_2 & G-A activities. Among the two conceivable approaches shown in Figure 1, namely the joint type of hybrid molecules (Type A) and the overlapping type of hybrid molecules (Type B), we chose the type A in consideration of distinct structural and physicochemical differences of H_2A and GA, particularly the following one, that is the most H_2A are hydrophilic, whereas the gastrin antagonist L-365,260 is highly hydrophobic. With the aid of well documented structure-activity relationships (SARs) of H_2As[8] and L-365,260[9], the type A molecules were designed as follows. Two different amine moieties involved in famotidine and roxatidine (**4** and **5** shown in Scheme 1) were employed as the H_2A components in the hybrid molecules. Roxatidine was added to our series as it has been suggested to have a different binding site from those of the well-known H_2A such as cimetidine, ranitidine, and famotidine. Next, from the following computer analyses[10], we were able to predict three sites of L-365,260 to which the H_2A amine moieties could be connected while maintaining its GA activity, namely the methyl group at N_1, the *meta* methyl group on the C_3' tolyl group, and the *meta* position of the phenyl group at C_5 in the benzodiazepine ring as shown in Figure 2. In the analyses we first obtained the same folded conformation of N-acetyl-CCK-7 as the one proposed by Pincus et al.[11] and employed it as an active conformation of non-sulfated CCK-8 for the binding with the CCK-B and/or gastrin receptor, since the

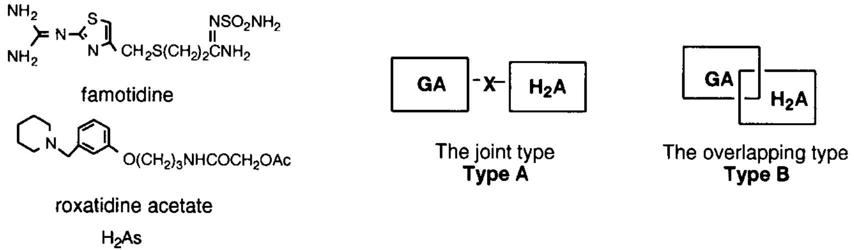
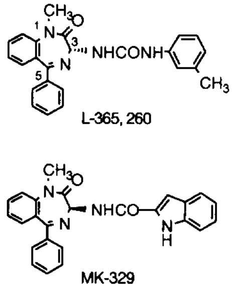


Figure 1.



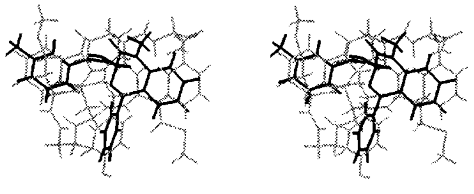
L-365, 260

MK-329

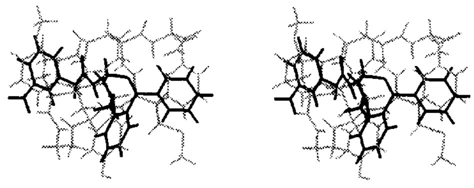
$\text{Ac-Tyr}^7\text{-Met}^6\text{-Gly}^5\text{-Trp}^4\text{-Met}^3\text{-Asp}^2\text{-Phe}^1\text{-NH}_2$

N-Ac-CCK-7

Figure 2.

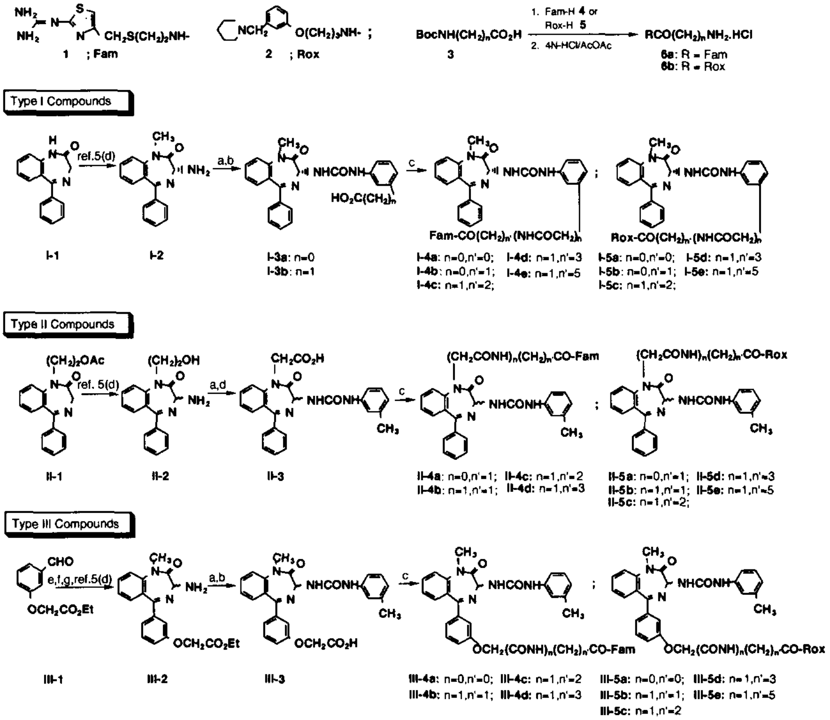


Stereo view of N-Ac-CCK-7 superimposed with the comformer **I**



Stereo view of N-Ac-CCK-7 superimposed with the comformer **II** same benzodiazepine substrates, MK-329 and L-365,260, could become a potent selective ligand for the CCK-A and CCK-B (or gastrin) receptor, respectively. Next, we calculated the two stable conformations of L-365,260 and superimposed them onto the folded conformation of N-acetyl-CCK-7 to obtain the following suggestions (see Figure 2). 1) The benzo, phenyl, and tolyl group of L-365,260 would correspond to two phenyl groups of Phe^1 and Tyr^7, and the indole group of Trp^4 of N-acetyl-CCK-7, respectively (See the more stable conformation I of L-365,260 shown in the upper part of Figure 2). 2) The N-acetyl group of CCK-7 representing the rest of the amino terminal residues of biogenetic CCKs larger than CCK-7 was shown to be located near the region of the N_1 methyl group of L-365,260, indicating this region would be sufficiently open for accommodating bulky groups including H_2A moieties attached to L-365,260. 3) There would be an another open space between the C_5 phenyl group and the $C_{3'}$ tolyl group of L-365,260, where a H_2A moiety attached to either the $C_{3'}$ tolyl group or the C_5 phenyl group of L-365,260 could be accommodated.

In this manner, three sites of L-365,260 were chosen as the coupling site with H_2A moieties. As the amide bond has a particular advantage for maintaining H_2A activity, as shown by many examples[1], we decided to first synthesize the joint type of hybrid molecules directly connecting each of the H_2A amine moieties selected with the three sites of L-365,260 by the amide bond. Subsequently, if necessary, we decided to examine the use of spacers, to improve the pharmacological activities as well as the pharmacodynamic properties of the type A compounds.



Scheme 1. (a) Isocyanate, Et_3N in CH_2Cl_2 (b) aq. NaOH in MeOH (c) 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride, 1-Hydroxybenzotriazol, Et_3N (d) Jones' oxidation (e) N-Methylaniline, BCl_3 (f) Chloroacetylchloride, and Jones' oxidation (g) $(NH_4)_2CO_3$, NaI

In accordance with this plan, we first synthesized three types of directly linked type A compounds by coupling each H_2A pharmacophor amines **4** and **5** with four carboxylic acid derivatives (**I-3a, b, II-3,** and **III-3**) of L-365,260 to form the amide bond as shown in Scheme 1. All the starting materials employed in these coupling reactions were prepared either by the reported methods or slightly modified procedures as shown in Scheme 1. All the directly connected type A compounds prepared[12] are summarized in Table 1 together with their *in vitro* 50% inhibitory concentration (IC_{50}) values determined for the gastrin, CCK-A, and CCK-B receptor, respectively, and pA_2 values for the histamine H_2 receptor antagonistic activity[13]. Surprisingly, none of the directly connected hybrid compounds (**I-4a** ~ **III-5a**) synthesized in the first stage showed any significant *in vitro* H_2A nor GA activities except for compound **II-4a** which bore the famotidine amine component at the N_1 methyl group and exhibited clear GA activity. Consequently, we deduced from these findings that the direct connection of the H_2A and GA moieties would mostly cause serious steric hindrance to the ligand bindings with the H_2A and GA receptor.

Table 1. *In Vitro* Biological Activities of Hybrid Compounds

No.	(R,S)	Receptors IC_{50} (nM)			Ratio Gastrin/CCK-A	pA_2
		Gastrin	CCK-B	CCK-A		His. H_2
I - 4a	R	380	440	380	1.0	<5.0
I - 4b	R	168	480	560	3.4	<5.0
I - 5a	R	550	600	2500	4.5	<5.0
I - 5b	R	230	160	4100	17.8	<5.0
II - 4a	R	3	35	4800	1600.0	<5.0
II- 5a	R	155	540	5700	36.8	<5.0
III - 4a	RS	135	350	5400	40.0	5.3
III - 5a	RS	570	1700	9200	16.1	5.3
I - 4c	R	80	200	120	1.5	6.4
I - 4d	R	240	330	330	1.4	6.3
I - 4e	R	45	255	190	4.2	6.0
I - 5c	R	136	290	190	1.4	6.6
I - 5d	R	115	205	330	2.9	6.4
I - 5e	R	110	92	340	3.1	6.2
II - 4b	RS	370	6800	760	2.1	5.4
II - 4c	RS	75	430	390	5.2	5.9
II - 4d	RS	190	6600	720	3.8	5.5
II - 5b	RS	790	3600	430	0.5	5.2
II - 5c	RS	185	2150	1300	7.0	6.1
II - 5d	RS	210	5000	900	4.3	6.1
II - 5e	RS	16	800	650	40.6	6.4
III - 4b	RS	12	310	1090	90.8	6.0
III - 4c	RS	25	400	2000	80.0	6.1
III - 4d	RS	14	215	2100	150.0	6.2
III - 5b	RS	63	550	5200	82.5	6.3
III - 5c	RS	200	760	15000	75.0	6.3
III - 5d	RS	60	290	9400	156.7	6.5
III - 5e	RS	32	320	3600	112.5	6.2
Cimetidine						6.6
L-365,260	R	4	29	11100	2775.0	

In order to examine the effects of spacers on these receptor bindings, the type A compounds incorporated with the alkylene type of spacers of different lengths were prepared. For synthetic convenience, we also used the amide bond as a linker of spacers at both H_2A and GA moieties (Scheme 1). This type of compounds prepared (**I-4c** ~ **III-5e**)[14] were summarized in Table 1 together with their *in vitro* biological activities. The significant features of the biological results are: 1) the incorporation of alkylene-type spacers significantly improved not only the H_2A activity but also the GA activity of all three types of the type A compounds. 2) The ethylene spacer brought about the maximum effect on pA_2 as shown by the pA_2 value of the most potent compound **I-5c** , which was the same value as that of the most well known H_2A, cimetidine. 3) On the other hand, as for GA activity, all the compounds prepared were less active than L-365,260, with the most active compound showing a potency of approximately one-third of it. 4) The CCK-A/gastrin receptor selectivities of these amide-type hybrid compounds were much lower than that of L-365,260. 5) As for *in vivo* gastric acid antisecretory activity[15], even the most active compound **I-5c** showed quite marginal activity when administered by i.d. route, suggesting poor oral absorbability of these hybrid compounds.

In conclusion, our present study has shown the feasibility of a chemical design of hybrid molecules with dual H_2A and GA activity. We have also briefly described the importance of the spacers as well as the coupling site of the GA moiety with the H2A one as preliminary studies. In the accompanying paper, we will report on another study which deals with how spacers as well as spacer-connecting bonds at the GA site from the amide bond were varied in order to improve the biological activities, particularly the GA activity as well as the oral absorbability of these dual antagonists.

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10. At first we assumed an initial molecular geometry of N-Ac-CCK-7 which resembled the folded conformation reported by Pincus et al.[11] and obtained from it the local energy minimized molecular conformation shown in Figure 2 by iteration of conformational modification and energy minimization using a computer program SYBYL Ver.5.5, Tripos Associates Inc.. Next, two stable conformations of L-365,260 , **I** and **II**, were also calculated using the same computer method. Their values of heat of

formation were 58.8 kcal/mol (**I**) and 59.7 kcal/mol (**II**), respectively by AM1 method (MOPAC). Each of these two conformations was superimposed onto the folded conformation of N-Ac-CCK-7 as shown in Figure 2 using the superimposition function of SYBYL Ver.5.5.

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12. A typical example for the general experimental procedure for the synthesis of hybrid molecules is as follows: Into a well stirred solution of the carboxylic acid derivative **I-3b** of L-365,260 (177 mg, 0.40 mmol) and roxatidine amine **2-H** (139 mg, 0.56 mmol) in 10 ml of dimethylformamide was added stepwise 1-hydroxybenzotriazol (54 mg, 0.40 mmol), Et_3N (0.112 ml, 0.80 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg, 0.52 mmol) under ice cooling. The reaction mixture was kept at room temperature for 16 h and concentrated well under vacuum. The residue was thoroughly washed with cold water at least three times until the residue was well solidified, washed twice with cold 0.1 N NaOH solution and once with cold water, and then well dried under vacuum. Column chromatography of the residue on silica gel using a solvent mixture $CHCl_3$/MeOH (15:1) as an eluent gave the pure product **I-5b** which was crystallized from EtOAc-$CHCl_3$ to afford a pure specimen (179 mg, yield 67%); mp 168-170°C. All three types of directly connected hybrid compounds were obtained in 50 - 70% yield by this method and gave satisfactory analytical data on elemental analysis. ^1H NMR data [200 MHz, δ (ppm), J (Hz)] for selected hybrid compounds with no spacers: **I-4b**; ($CDCl_3$) 2.60 (t, 2H, CH_2, J = 6 Hz), 3.34 (t, 2H, CH_2, J = 6 Hz), 3.45 (s, 2H, CH_2), 3.49 (s, 3H, N-CH_3), 3.60 (s, 2H, CH_2), 5.37 (s, 1H, 3-H), 6.46 (s, 1H, thiazole-CH), 6.90-7.75 (m, 13H, Ar-H). **I-5b**; ($CDCl_3$) 1.35-2.05 (m, 8H, 4CH_2), 2.35-2.50 (m, 4H, 2CH_2), 3.35-3.55 (m, 6H, 3CH_2), 3.47 (m, 3H, N-CH_3), 3.93 (t, 2H, CH_2, J = 6 Hz), 5.55 (d, 1H, 3-H, J = 9 Hz), 5.94 (m, 1H), 6.60-7.65 (m, 17H, Ar-H). **II-4a**; (CD_3OD) 2.29 (s, 3H, CH_3), 2.63 (d, 1H, J = 7 Hz), 3.41 (t, 2H, CH_2, J = 7 Hz), 3.66 (s, 2H, CH_2), 4.52 (d, 1H, J = 17 Hz), 4.66 (d, 1H, J = 17 Hz), 5.51 (s, 1H), 6.53 (s, 1H), 6.82 (d, 1H, d = 7 Hz), 7.10-7.70 (m, 12H, Ar-H), 7.86 (s, 1H). **III-4a**; ($CDCl_3$+CD_3OD) 2.30 (s, 3H, CH_3), 2.70 (t, 2H, J = 6.6 Hz), 3.30-3.55 (m, 2H, CH_2), 3.50 (s, 3H), 3.61 (s, 2H), 4.51 (s, 2H), 5.46 (s, 1H), 6.47 (s, 1H), 6.84 (m, 1H), 7.02 (m, 2H), 7.10-7.48 (m, 8H, Ar-H), 7.64 (s, 1H).
13. Binding assay: Guinea pig gastric glands (for gastrin binding) were suspended in binding assay buffer with [^{125}I] gastrin and the appropriate concentration of unlabeled compounds. The suspensions were incubated at 25 °C for 30 min. Mouse brain cortex (for CCK-B binding) and pancreas membranes (for CCK-A binding) were suspended in binding assay buffer with [^{3}H] CCK-8 and the appropriate concentration of unlabeled compounds. The suspensions were incubated at 25°C for 90 min. Incubation was terminated by filtration through glass fiber GF/B filters and washing three times with buffer. Specific binding was defined as the difference between total binding and nonspecific binding in the presence of 2 μM gastrin or 1 μM CCK-8. CCK-B receptors and CCK-A receptors: Saito A.; Goldfine, I. D.; Williams, J. A. *J. Neurochem.* **1980**, *37*, 483. Gastrin receptors: Chang, R. S. L.; Victor, J. L.; Maureen, E. K.; Kristie, A. K. *Biochem. Biophys. Res. Commun.* **1986**, *134*, 895.
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14. All three types of hybrid compounds with spacers were synthesized in the same way as described above. ^1H NMR data [200 MHz, δ (ppm), J (Hz)] for selected hybrid compounds: **I-4d**; (CD_3OD) 1.71-1.85 (m, 2H, CH_2), 2.18 (t, 2H, CH_2, J = 6 Hz), 2.58 (t, 2H, CH_2, J = 6 Hz), 3.18 (t, 2H, CH_2, J = 6 Hz), 3.25-3.40 (m, 2H, CH_2), 3.46 (s, 2H, CH_2), 3.49 (s, 3H, N-CH_3), 3.71 (s, 2H, CH_2), 5.36 (s, 1H, 3-H), 6.91 (s, 1H, thiazole-CH), 6.90-7.80 (m, 13H, Ar-H). **I-5d**; ($CDCl_3$) 1.30-2.20 (m, 12H, 6CH_2), 2.40-2.60 (m, 4H, 2CH_2), 3.10-3.35 (m, 4H, 2CH_2), 3.44 (s, 3H, N-CH_3), 3.45-3.55 (m, 2H, CH_2), 3.91 (t, 2H, CH_2, J = 6 Hz), 5.45 (d, 1H, 3-H, J = 8 Hz), 6.70-7.80 (m, 17H, Ar-H). **II-4d**; (CD_3OD) 1.77 (m, 2H), 2.18 (t, 2H, J = 7 Hz), 2.57 (t, 2H, J = 7 Hz), 3.23 (t, 2H, CH_2, J = 7 Hz), 3.62 (s, 2H, CH_2), 4.58 (s, 2H), 5.49 (s, 1H), 6.51 (s, 1H), 6.81 (d, 1H, J = 6 Hz), 7.05-7.70 (m, 13H, Ar-H). **III-4d**; ($CDCl_3$+CD_3OD) 1.84 (quint, 2H, J = 7 Hz), 2.18 (t, 2H, J = 7 Hz), 2.30 (s, 3H), 2.63 (t, 2H, J = 7 Hz), 3.33 (t, 2H, J = 7 Hz), 3.34 (t, 2H, J = 7 Hz), 3.48 (s, 3H), 3.60 (s, 2H), 4.51 (s, 2H), 5.48 (s, 1H), 6.44 (s, 1H), 6.83 (m, 1H), 7.07-7.47 (m, 10H, Ar-H), 7.63 (m, 1H).
15. Determination of gastric acid secretion in anesthetized rats: Gastric acid secretion was measured in anesthetized rats using Schild's rat method. Acid secretion was measured at pH 7.0 by the addition of 0.01 N NaOH. When basal acid secretion had stabilized, histamine 2 HCl (3 mg/kg/hr) was infused as acid via the vein. Test compounds were intraduodenally injected 90 min after the start of histamine infusion. Data are expressed as maximal inhibition.

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