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# SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF HIGHLY POTENT DUAL HISTAMINE $H_2$ AND GASTRIN RECEPTOR ANTAGONISTS

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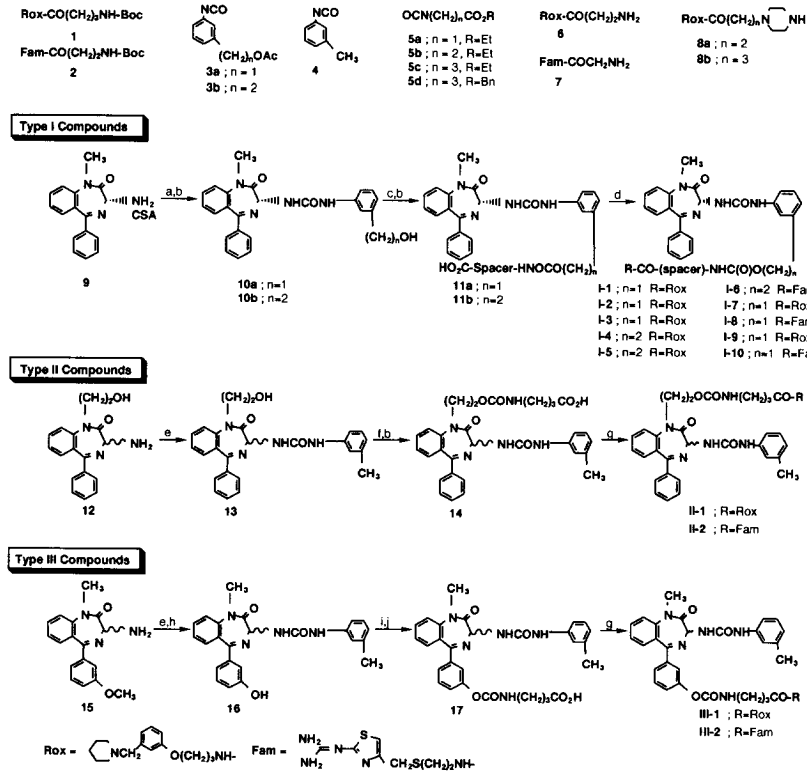
**Abstract:** The chemical modification of the dual histamine $H_2$ and gastrin receptor antagonists described in our preceding paper, particularly the modification of spacers as well as the alteration of their connecting bonds at the gastrin receptor antagonist site (GA) from the amide bond to the carbamate bond, significantly improved not only their dual activity but also the GA versus CCK-A receptor selectivity.


With the objective of alleviating the relapse problem frequently encountered in the chemotherapy of peptic ulceration with histamine $H_2$ receptor antagonists ($H_2A$),we reported in our preceding paper[1] the design, synthesis, and pharmacological evaluation of dual histamine $H_2$ and gastrin receptor antagonists. In that study, we designed as the dual antagonist, a joint type of hybrid molecule composed of a $H_2A$ moiety and a GA one which were selected from well-known $H_2As$, famotidine and roxatidine, and GA L-365,260, respectively. We found that to retain the dual activity, it was important to consider the spacers as well as the three sites of L-365,260 to which the $H_2A$ moieties could be attached, namely the $N_1$ methyl group, the *meta* methyl group on the $C_{3'}$ tolyl group, and the *meta* position of the phenyl group at $C_5$. Consequently, we obtained several compounds with the dual activity. However, they showed distinct disadvantages such as lower $H_2A$ and GA activities compared to famotidine and L-365,260, respectively, smaller gastrin versus CCK-A receptor selectivities than that of L-365,260, and decreased oral absorbability. To improve these compounds, we tried altering the connecting bond of the spacers at the GA sites from the amide bond to the carbamate bond as well as modifying the structure of the spacers.

We chose the carbamate bond as the binding function of the spacers at the GA sites in this study for three reasons. First, as we had observed the extremely high $pA_2$ values, 7.8 and 7.3, of $H_2A$ intermediate compounds **1** and **2** bearing the carbamate group, we predicted that the carbamate group, if properly located, would greatly potentiate the $H_2A$ activity of the hybrid compounds as well. Second, as the carbamate bond is less liable to enzymatic hydrolysis than the amide bond, its use as a binding function was expected to enhance the metabolic stability of hybrid molecules. Third, as the carbamate group is more hydrophobic than the amide group, its use might enhance the oral absorbability of the hybrid compounds.

The carbamate-type hybrid compounds[2] synthesized in this work are summarized in Scheme 1. These compounds can be classified into three types (Type I, II, III) depending upon the $H_2A$ connecting sites at L-365,260 as previously described. The general synthetic scheme is briefly summarized in Scheme 1. First, isocyanates such as **3a, b** and **4** were prepared using known methods. For the synthesis of Type I compounds, **3a** and **3b** were coupled with 3R-(+)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepine-2-one camphorsulfonic acid salt (CSA salt) **9**[3] followed by alkaline hydrolysis to afford




Scheme 1. (a) **3a** or **3b**, $Et_3N$ (b) aq.KOH in MeOH (c) **5a** or **5b** or **5c**, $[(n\text{-}Bu)_3Sn]_2O$ (d) **Rox-H** or **Fam-H** or **6** or **7** or **8a** or **8b**, WSCI-HOBt-$Et_3N$ (e) **4**, $Et_3N$ (f) **5c**, $[(n\text{-}Bu)_3Sn]_2O$ (g) **Rox-H** or **Fam-H**, WSCI-HOBt-$Et_3N$ (h) $BBr_3$ (i) **5d**, $[(n\text{-}Bu)_3Sn]_2O$ (j) $H_2$/Pd-C

the alcohol derivatives, **10a** and **10b**. For the syntheses of Type II and Type III compounds, the corresponding benzodiazepine amines, **12** and **15**, were prepared as racemates using essentially the same methods as those reported and condensed with isocyanate **4** to afford the corresponding alcohol derivatives, **13** and **16**, respectively. All the alcohols **10a**, **b**, **13**, **16** thus far prepared were allowed to react in the presence of bis tri-n-butyltin oxide catalysis with various spacer-coupled isocyanates **5a - d** which were easily prepared by known methods. The resultant products were hydrolyzed under alkaline conditions to afford intermediate carbamate derivatives **11a**, **b**, **14**, and **17**. These intermediates were subjected to coupling reactions with $H_2A$ amine moieties, **Rox-H**, **Fam-H**, **6**, **7**, **8a**, or **8b**, in the same way as previously reported, producing the desired spacers containing carbamate-type hybrid molecules as described above. All the hybrid compounds prepared with simple alkylene spacers are presented in Table 1 together with their *in vitro* biological activities. The significant features of their biological results are as follows: 1) Alteration of the spacer connecting bond from the amide bond to the carbamate bond significantly improved both the $H_2A$ and the GA activity of Type I hybrid compounds, particularly the latter. However, Type II and Type III compounds showed no or if any, only marginal, augmentation of these activities. 2) Most notably, the gastrin versus CCK-A receptor selectivity was highly improved by this structural modification (see Entry 3 vs 15). 3) The roxatidine type of hybrid compounds tended to show a higher $pA_2$ value than their famotidine counterparts.

In order to examine pharmacological effects of spacers with polar functional groups such as amino acid glycine or the piperazine group, hybrid compounds **I-7, I-8, I-9, I-10** were prepared. Their structures and biological activities are summarized in Table 1. The characteristics of the biological data are as follows: 1) Among these hybrid compounds, compound **I-7** with a glycine type of spacer showed the highest $pA_2$ value of 6.8 which obviously exceeded the value of cimetidine, 6.6. Its GA activity as well as gastrin versus CCK-A receptor selectivity were much better than those of the propylene compounds **I-3** and **I-5**. Although its $pA_2$ value is obviously lower than **I-7**, the famotidine type analogue **I-8** shows the highest GA activity, $IC_{50}$ = 4 nM, which is comparable to that of L-365,260. 2) The compounds with piperadine type spacers **I-9** and **I-10** show somewhat lower $pA_2$ values, 6.2 and 6.5, than compounds **I-7** and **I-8** but their GA activities are retained at quite high levels, being $IC_{50}$ = 7 nM and 9 nM, respectively. Thus, the most characteristic feature of the biological results here was the enhancement of both *in vitro* $H_2A$ and GA activities as well as the gastrin versus CCK-A receptor selectivity, the latter being approximately 100-fold better than that of the amide-type hybrid compounds.

Table 1. *In Vitro* Biological Activities

| Entry | No. | $(CH_2)_n$ n= | GA← spacers→$H_2B$ | $H_2B$ | (R,S) | Receptors $IC_{50}$ (nM) Gastrin | CCK-B | CCK-A | Ratio Gastrin/CCK-A | $pA_2$ His. $H_2$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **I-1** | 1 | $-CH_2-$ | Rox | R | 11 | 200 | 6100 | 555 | 6.1 |
| 2 | **I-2** | 1 | $-CH_2CH_2-$ | Rox | R | 36 | 160 | 310 | 9 | 6.5 |
| 3 | **I-3** | 1 | $-CH_2CH_2CH_2-$ | Rox | R | 26 | 94 | 3600 | 138 | 6.6 |
| 4 | **I-4** | 2 | $-CH_2CH_2-$ | Rox | R | 27 | 94 | 4200 | 156 | 5.9 |
| 5 | **I-5** | 2 | $-CH_2CH_2CH_2-$ | Rox | R | 23 | 180 | 5000 | 217 | 6.4 |
| 6 | **I-6** | 2 | $-CH_2CH_2CH_2-$ | Fam | R | 37 | 300 | 1300 | 35 | 6.1 |
| 7 | **II-1** | | $-CH_2CH_2CH_2-$ | Rox | RS | 135 | 4000 | 4600 | 34 | 6.0 |
| 8 | **II-2** | | $-CH_2CH_2CH_2-$ | Fam | RS | 17 | 930 | 4400 | 289 | 5.5 |
| 9 | **III-1** | | $-CH_2CH_2CH_2-$ | Rox | RS | 220 | 460 | 3800 | 17 | 6.3 |
| 10 | **III-2** | | $-CH_2CH_2CH_2-$ | Fam | RS | >1000 | >1000 | >10000 | 10 | 5.7 |
| 11 | **I-7** | 1 | $-CH_2CONHCH_2CH_2-$ | Rox | R | 19 | 103 | 8200 | 432 | 6.8 |
| 12 | **I-8** | 1 | $-CH_2CONHCH_2-$ | Fam | R | 4 | 75 | 3100 | 775 | 6.0 |
| 13 | **I-9** | 1 | $-H_2COCN\frown NCH_2CH_2-$ | Rox | R | 7 | 45 | 740 | 106 | 6.2 |
| 14 | **I-10** | 1 | $-H_2COCN\frown NCH_2CH_2CH_2-$ | Rox | R | 9 | 400 | 1650 | 183 | 6.5 |
| 15 | Amide type | 1 | $-CH_2CH_2CH_2-$ | Rox | R | 115 | 205 | 330 | 3 | 6.4 |
| 16 | **1** | | | Rox | | | | | | 7.8 |
| 17 | **2** | | | Fam | | | | | | 7.3 |
| 18 | Cimetidine | | | | | | | | | 6.6 |
| 19 | L-365,260 | | | | R | 4 | 29 | 11100 | 2775 | |

The *in vivo* gastric acid antisecretory activity of the most promising compound **I-7** was evaluated by three different methods, namely Schild's rat method[4] (i.d. route administration), rat pylorus ligation method[5] (p.o.), and canine Heidenhain pouch method[6] (i.v. and p.o.). When **I-7** was administered to Heidenhain pouch dog by i.v. route, it distinctly inhibited gastric acid secretion by 51% at 0.3 mg/kg dose. Nevertheless, it did not show any notable inhibition even at 30 mg/kg dose via oral administration. For Schild's rat method and rat pylorus ligation method, it inhibited histamine-stimulated gastric acid secretion only 77% at 30 mg/kg dose and less than 50% at 10 mg/kg dose in the former and only 54% at 10 mg/kg

dose in the latter. All these results suggested low oral absorbability of this compound in these animal species. Next, the *in vivo* GA activity of **I-7** was evaluated as the % inhibition of tetragastrin-induced histidine decarboxylase activity. Inhibition was statistically positive but low, being 32% at 30 mg/Kg dose by i.p. route. Because of the low oral absorbability of **I-7**, we could not evaluate its pharmacological effects as a typical compound for suppressing the rebound of gastric acid after cessation and thereby relapse of ulcer. Although the species dependency of the GA activity as well as the diminished oral absorbability of L-365,260 in higher animals have been documented[7], the present study strongly indicated that improvement of their diminished oral absorbability would be essential for the development of these novel dual histamine $H_2$ and gastrin antagonists as antiulcer agents for practical use.

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2. For a typical example of the general experimental procedure for the synthesis of hybrid molecules refer to the preceding paper. All three types of hybrid compounds were obtained in 50 - 70% yield by this method and gave satisfactory analytical data on elemental analysis. $^1$H NMR data [200 MHz, δ (ppm), J (Hz)] for selected hybrid compounds with glycine or piperadine spacers: **I-5** ; ($CD_3OD$) 1.60-2.05 (m, 8H, $4CH_2$), 2.16 (t, 2H, $CH_2$, J = 6 Hz), 2.80-3.00 (m, 4H, $2CH_2$), 3.08 (t, 2H, $CH_2$, J = 6 Hz), 3.30-3.60 (m, 6H, $3CH_2$), 3.51 (s, 3H, N-$CH_3$), 4.03 (t, 2H, $CH_2$, J = 6 Hz), 4.17 (s, 2H, $CH_2$), 4.17 (t, 2H, $CH_2$, J = 6 Hz), 5.37 (s, 1H, 3-H), 6.85-7.80 (m, 17H, Ar-H). **I-6** ; 1.60-1.80 (m, 2H, $CH_2$), 2.07-2.22 (m, 2H, $CH_2$), 2.57 (t, 2H, $CH_2$, J = 6 Hz), 2.85 (t, 2H, $CH_2$, J = 6 Hz), 3.07 (t, 2H, $CH_2$, J = 6 Hz), 3.25-3.37 (m, 2H, $CH_2$), 3.49 (s, 3H, $CH_3$), 3.63 (s, 2H, $CH_2$), 4.20 (t, 2H, $CH_2$, J = 6 Hz), 5.37 (s, 1H, 3-H), 6.52 (s, 1H, thiazole-CH), 6.85-7.75 (m, 13H, Ar-H). **I-7**; ($CDCl_3$) 1.35-1.66 (m, 6H, $3CH_2$), 1.79-1.96 (m, 2H, $CH_2$), 2.36-2.56 (m, 6H, $3CH_2$), 3.31-3.42 (m, 2H, $CH_2$), 3.40 (s, 3H, $CH_3$), 3.50 (s, 2H, $CH_2$), 3.75 (d, 2H, $CH_2$), 3.88-3.96 (m, 2H, $CH_2$), 5.00 (s, 2H, $CH_2$), 3.50 (d, 1H, 3-H, J = 8 Hz), 6.69-7.60 (m, 17H, Ar-H). **I-9** ; ($CD_3OD$) 1.35-1.68 (m, 6H, $3CH_2$), 1.69-1.88 (m, 2H, $CH_2$), 1.88-2.04 (m, 2H, $CH_2$), 2.24 (m, 2H, $CH_2$), 2.22-2.38 (m, 8H, $4CH_2$), 2.37-2.58 (m, 4H, $2CH_2$), 3.18-3.36 (m, 2H, $CH_2$), 3.45 (s, 3H, $CH_3$), 3.35-3.52 (m, 2H, $CH_2$), 3.55 (s, 2H, $CH_2$), 3.95 (d, 2H, $CH_2$, J = 5.6 Hz), 4.05 (m, 2H, $CH_2$), 5.04 (s, 2H, $CH_2$), 5.54 (d, 1H, 3-H, J = 8.2 Hz), 6.74-7.62 (m, 13H, Ar-H). **II-1** ; ($CD_3OD$) 1.40-1.70 (m, 8H), 1.98 (m, 4H), 2.28 (s, 3H), 2.40 (m, 4H), 2.83 (m, 2H), 3.34 (t, 2H, J = 7 Hz), 3.45 (s, 2H), 3.98 (t, 2H, J = 7 Hz), 3.90-4.20 (m, 3H), 4.71 (m, 1H), 5.38 (s, 1H), 6.75-7.80 (m, 17H). **III-1** ; ($CD_3OD$) 1.35-1.68 (m, 6H, $3CH_2$), 1.69-1.88 (m, 2H, $CH_2$), 1.88-2.04 (m, 2H, $CH_2$), 2.24 (m, 2H, $CH_2$), 2.22-2.38 (m, 8H, $4CH_2$), 2.37-2.58 (m, 4H, $2CH_2$), 3.18-3.36 (m, 2H, $CH_2$), 3.45 (s, 3H, $CH_3$), 3.35-3.52 (m, 2H, $CH_2$), 3.55 (s, 2H, $CH_2$), 3.95 (d, 2H, $CH_2$, J = 5.6 Hz), 4.05 (m, 2H, $CH_2$), 5.04 (s, 2H, $CH_2$), 5.54 (d, 1H, 3-H, J = 8.2 Hz), 6.74-7.62 (m, 13H, Ar-H).
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