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RELATIONSHIP BETWEEN DIHEDRAL ANGLES OF N1 AND C9 SUBSTITUENTS IN 1,4-BENZODIAZEPINES AND DUAL CHOLECYSTOKININ-A AND -B ANTAGONISTIC ACTIVITIES

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Abstract

Introduction of a methyl moiety to the C9 position of a 1,4-benzodiazepine ring system afforded dual CCK-A and -B antagonistic activity. Novel derivatives having ethyl, isopropyl and chloro substituents at C9 were prepared in order to obtain more potent antagonistic activities. AM1(MOPAC93) calculations of the dihedral angles between the N1 and C9 substituents indicated that dihedral angles for dual antagonistic activities were between 50^{o} and 60^{o}. A methyl moiety was selected as the most suitable C9 substituent in this series for potent dual CCK-A and -B receptor antagonistic properties.

Keywords : 1,4-benzodiazepine; dual CCK-A and -B antagonist; dihedral angle; AM1(MOPAC93) calculation

Introduction

We described earlier the discovery of a potent orally active cholecystokinin CCK-A selective antagonist, FK480 (**1**),[1] and a potent CCK-B selective antagonist, FR175985/NF127 (**2**),[2] respectively, whose chemical structures are shown in Figure1. In the research process leading to **1** and **2**, some compounds displayed antagonistic properties against both CCK-A and CCK-B receptors, *i.e.* non-selective antagonists were obtained. We were very interested in these compounds possessing a new profile and postulated that these non-selective, dual antagonists of the CCK-A and -B receptors might be more efficacious for the treatment of pancreatitis than CCK-A selective receptor antagonists, based on the following reasons. CCK-A receptor antagonists inhibit pancreatic exocrine secretion on the one hand, whilst they also stimulate gastric acid secretion by release of somatostatin from D cells of the

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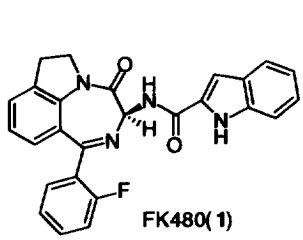
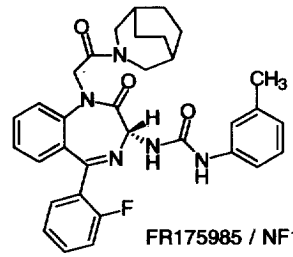
Figure 1 Chemical structures of FK480 (1) and FR175985 / NF127 (2)



FK480(1)



FR175985 / NF127(2)

gastric mucosa, which stimulates pancreatic exocrine secretion.[3] Therefore, the efficacy of a selective CCK-A receptor antagonist as an inhibitor of pancreatic exocrine secretion in the treatment of pancreatitis can be considered to be reduced by this stimulatory activity of gastric acid secretion. It is additionally well known that lowering of pH in the duodenum by gastric acid is one of the important factors in accelerating pancreatic exocrine secretion, which is considered to be an exacerbating factor of pancreatitis. Accordingly, gastric acid secretion inhibitors such as histamine H_2 blockers and proton pump inhibitors are often prescribed for the treatment of pancreatitis. A dual CCK-A and -B receptor antagonist can be expected to block the gastric acid secretion by the CCK-B antagonistic component in a similar manner as gastrin antagonists, since the molecular sequence of the CCK-B receptor is identical with that of the gastrin receptor.[4,5] In support of this hypothesis, casein-stimulated pancreatic exocrine secretion was more profoundly inhibited by joint administration of FK480, a CCK-A selective antagonist, and YM022, a CCK-B selective antagonist, than in separate treatment.[6]

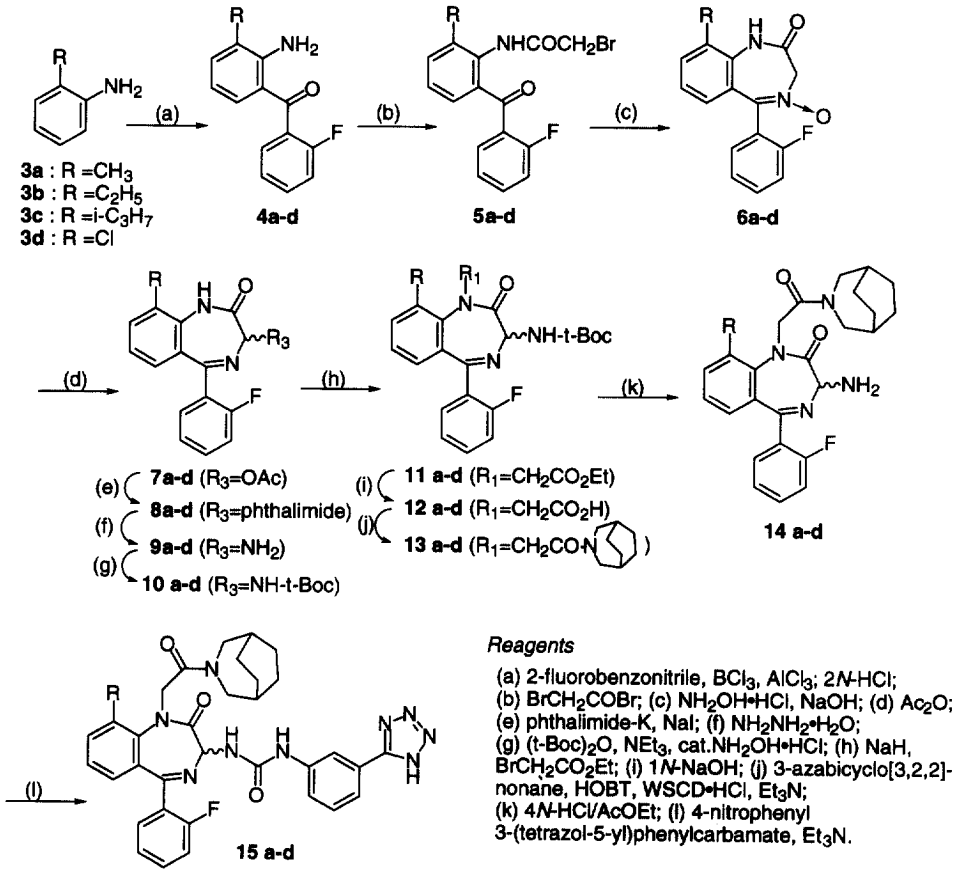
In order to obtain more potent dual CCK-A and -B receptor antagonists, we initiated structural comparisons of the CCK-A selective antagonist **1** and CCK-B selective antagonist **2** regarding configuration at the C3 position, the difference of the C3 substituents, and the relationship between the N1 and C9 substituents whose repulsion induces strain in the 1,4-diazepine ring. As a result, we expected that a dual CCK-A and CCK-B receptor antagonist could be obtained by making the total structure of **2** resemble that of **1**. The introduction of a methyl substituent to the C9 position of **2**, (**15a**), validated our hypothesis, and has already been reported.[7] In further studies, we examined other substituents such as ethyl, isopropyl and chloro groups at the C9 position in order to search for more suitable substituents than a methyl moiety. As a result of this examination we discovered a relationship between bulkiness of the substituents and the dual antagonistic activities.

In this paper we describes the preparation of novel C9 substituted 1,4-benzodiazepine derivatives and the relationship of the dihedral angles between the N1 and C9 substituents and their dual CCK-A and -B antagonistic activities.

Chemistry

The target compounds, **15b-d**, were prepared by similar procedures to those employed in the synthesis of **15a** described previously,[7] as illustrated in Scheme 1. Sugasawa reaction[8] of aniline derivatives, **3b-d**, with 2-fluorobenzonitrile gave 2-amino-2'-fluorobenzophenone derivatives, **4b-d**, respectively, which were acylated with bromoacetyl bromide to afford **5b-d**, followed by cyclization to 1,4-benzodiazepine 4-oxide, **6b-d**, with hydroxylamine in moderate yields. Treatment the oxides with acetic anhydride gave the rearranged 3-acetoxy derivatives, **7b-d**, whose acetoxy moiety was easily substituted with potassium phthalimide in the presence of a large excess of sodium iodide in dimethylformamide (DMF) to afford **8b-d**. Removal of the phthalimide moiety led to amines, **9b-d**, by the usual hydrazinolysis method and the amino group was reprotected with a t-butoxycarbonyl group to give **10b-d**.

Scheme 1



Reagents

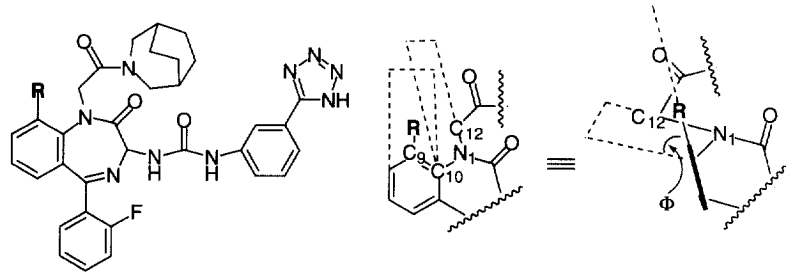
(a) 2-fluorobenzonitrile, BCl_3, $AlCl_3$; 2*N*-HCl;
(b) $BrCH_2COBr$; (c) NH_2OH•HCl, NaOH; (d) Ac_2O;
(e) phthalimide-K, NaI; (f) NH_2NH_2•H_2O;
(g) $(t\text{-}Boc)_2O$, NEt_3, cat.NH_2OH•HCl; (h) NaH, $BrCH_2CO_2Et$; (i) 1*N*-NaOH; (j) 3-azabicyclo[3,2,2]-nonane, HOBT, WSCD•HCl, Et_3N;
(k) 4*N*-HCl/AcOEt; (l) 4-nitrophenyl 3-(tetrazol-5-yl)phenylcarbamate, Et_3N.

The 3-protected amino-1,4-benzodiazepines, **10**, were alkylated with ethyl bromoacetate in the presence of sodium hydride to give **11b-d**, which were hydrolyzed and amidated with 3-azabicyclo[3,2,2]nonane using hydroxybenzotriazole (HOBT) and *N*-dimethylaminopropyl-*N'*-ethylcarbodiimide (WSCD•HCl) as condensing reagents, to afford **13b-d**. The protecing group was removed with 4*N*-HCl in ethyl acetate to afford **14b-d**, which were converted to the target compounds, **15b-d**, by treatment with 4-nitrophenyl 3-(tetrazol-5-yl)phenyl-carbamate in the presence of triethylamine in DMF at ambient temperature.

Biological Evaluation

Biological evaluation was performed as described previously,[9] (i) inhibition of ^{125}I-CCK-8 binding to guinea-pig cerebral cortical membranes, (ii) inhibition of ^{125}I-CCK-8 binding to rat pancreatic membranes, and (iii) the ratio of the IC_{50} values on racemic derivatives **15a-d**, because one enantiomer (FR193108) was superior in affinities for both CCK-A and -B receptors to the other and the values were found to be nearly equal to those of the racemate **15a** as already reported previously.[7] The results are summarized in Table I along with the calculated dihedral angles.

Table I Biological Evaluation Results and Dihedral Angles (Φ) of Compounds **15 a-d** and **2**



Compound No.	R	IC_{50}(nM) for CCK-B[1]	IC_{50}(nM) for CCK-A[2]	Selectivity (A/B)[3]	Dihedral Angles (Φ)
15a	CH_3	0.68	14	21	57.2°
15b	C_2H_5	0.81	18	22	58.2°
15c	i-C_3H_7	87.0 % (at 10^{-8}M)	12.2 % (at 10^{-8}M)	----	60.8°
15d	Cl	0.66	13	20	50.6°
2	H	0.087	62	710	40.2°

1) Inhibition of ^{125}I-CCK-8 binding to guinea-pig cerebral cortical membranes
2) Inhibition of ^{125}I-CCK-8 binding to rat pancreatic membranes
3) Ratio of IC50 values obtained by CCK-A and CCK-B receptor binding assays

Calculation of Dihedral Angles between N1 and C9 Substituents

Molecular structures were optimized by AM1 (MOPAC93)[10] and the dihedral angles between the N1 and C9 substituents were defined by two planes: one consists of the phenyl ring with the C9 substituent and the other the C10-N1-C12 substituents, as shown in Table I. All calculations were carried out using a SGI Indigo (R4400) workstation running on an IRIX 5.3 operation system. The calculation results are summarized in Table I along with those of compound **2** (FR175985 / NF127).

Discussion

We have succeeded in discovery of compound **15a**[7] (a racemate of FR193108) as a dual CCK-A and -B receptor antagonist according to our assumption that the introduction of a methyl group to the C9 position of our CCK-B selective antagonist **2** and the resulting repulsion between the C9 and N1 substituents made the total molecular structure of **2** resemble that of our CCK-A selective antagonist **1**.

In order to search for substituents than a methyl moiety, we calculated the dihedral angles (Φ) between imaginary C9 and N1 substituents. When comparing the results of the calculation and the biological evaluations in the receptor binding assays, it was found that suitable dihedral angles for compounds seem to be exist for possessing potent dual antagonistic activities against both CCK-A and -B receptors. The dihedral angles (Φ) of the compounds substituted at the C9 position with methyl and ethyl groups (**15a** and **15b**) were found to be almost equal, but the chlorine-substituted compound (**15d**) was smaller than that of **15a**, contrary to expectation based on steric size. However, they were found to be almost equally potent in their biological evaluations. The optimum dihedral angle (Φ) between N1 and C9 substituents appears to be between 50° and 60°, since the isopropyl moiety substituted compound **15c**, Φ is >60°, was found to be dramatically diminished in potency in both receptor binding assays.

Conclusion

It was found that a methyl, an ethyl and a chloro moieties were suitable C9 substituents in this series for dual CCK-A and -B receptor antagonistic properties. However, we selected a methyl group because of the smallness of the molecular weight when regarding with bioavailability. We are now involved in optimization research for substituents at other positions, keeping the substituent at the C9 position to be methyl.

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References

(1) Satoh Y, Matsuo T, Sogabe H, Ito H, Tada T, Kinoshita T, Yoshida K, Takaya T. Chem. Pharm. Bull. 1994; 42: 2071-2083.

(2) Katsumi I, Satoh Y, Mitsui H, Satoh Y, Tabuchi S, Ito H, Sogabe H, Kuno M, Tanaka H. 16th Med Chem Symp (Toyama, Japan 1996; Nov 27-29) Abst. 155.

(3) Lloyd K C, Raybould H E, Walsh J H. Am. J. Physiol. 1992; 263: G287-G292.

(4) Pisegna J R, DeWeerth A, Huppi K, Wank S A. Biochem. Biophys. Res. Commun. 1992; 189: 296-303.

(5) Lee Y M, Beinborn M, McBride E W, Lu M, Kolakowski Jr L F, Kopin A S. J. Biol. Chem. 1993; 268: 8164-8169.

(6) Kuno M, Ito H, Sogabe H, Satoh Y, Matsuo T, Motoyama Y, Tanaka H. Pancreas 1997; accepted.

(7) Tabuchi S, Ito H, Sogabe H, Kuno M, Katsumi I, Yamamoto N, Mitsui H, Satoh Y. Bioorg. Med. Chem. Lett. 1997; 7: 169-174.

(8) Sugasawa T, Toyoda T, Adachi M, Sasakura K. J. Am. Chem. Soc. 1978; 100: 4842-4852.

(9) Ito H, Sogabe H, Nakarai T, Satoh Y, Tomoi M, Kadowaki M, Matsuo M, Tokoro K, Yoshida K. J. Pharmacol. Exp. Ther. 1994; 268: 571-575.

(10) Stewart J J P. Fujitsu Limited, Tokyo, Japan 1993.