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Review

A novel trifluoromethanesulfonamidophenyl-substituted quinoline derivative, GA 0113: synthesis and pharmacological profiles

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Abstract

The trifluoromethanesulfonamidophenyl-substituted quinoline GA 0113 have been synthesized from *o*-nitrobenzoyl chloride via a multi-step process. GA 0113 displaced specific binding of [^{125}I]-Sar1, Ile^{8}-Ang II to AT_1 receptors in membrane from Sf9 cells. In concious normotensive dogs, GA 0113 inhibited the Ang II-induced pressor response with ID_{50} of 0.032 mg/kg and dose-dependently increased plasma renin activity for 48 h. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: (Trifluoromethylsulfonamidophenyl)quinoline; Angiotensin-II receptor antagonist; Antihypertensive drug; MOPAC™

1. Introduction

The renin–angiotensin system (RAS) is well known to play an important role in blood pressure regulation and electrolyte homeostasis, and has the octapeptide angiotensin II (AII) as its principal active hormone [1]. The prevention of the formation of AII from angiotensin I (AI) by angiotensin-converting enzyme (ACE) inhibitors induces blockade of the RAS in antihypertensive therapy. However, the lack of specificity of ACE inhibitors, having the adverse effects, such as dry cough and angioedema, provided a major reason for developing alternative therapy.

Although saralasin (Sar^{1}-Ala^{8}-Ang II) was the first specific peptide antagonist of AII and used as pharmacological tools, the peptide has limited therapeutic value of the poor oral bioavailability and short duration of action. Many pharmaceutical industries have focused on finding a more specific way to block the RAS. Among them, nonpeptide AII antagonists were an attractive means, lacking the disadvantages of the peptide AII receptor antagonists. Most of them contain a nitrogen heterocycle linked to a biphenyltetrazole by a methylene spacer, as in losartan (Dup-753) [2] and candesartan cilexetil (TCV-116) [3].

There are some reports on the introduction of perfluoroalkyl substituents in nonpeptide AII receptor antagonists capitalizing on the enhanced binding affinity [4,5]. On the other hand, much attention has been paid to the replacement of aryltetrazole group as a means for improving the relatively low oral bioavailability. AII antagonists incorporating squaric acid, acylsulfonamides, trifluoromethansulfonamide (triflamide) [6,7], and acidic heterocycle moieties have recently been reported. Our strategy was to find a novel biphenyltetrazole replacement, and we describe herein the synthesis and pharmacological activity of the new potent nonpeptide nontetrazole AII receptor antagonist, designated GA 0113, which carries a triflamide group as a more lipophilic acidic group and a quinoline moiety.

2. Synthesis of GA 0113

The key intermediate carboxyphenyl substituted quinoline (**3**) was synthesized by the reaction of 5-methylisatin (**1**) with 2-acetylbenzoic acid followed by selective decarboxylation of the dicarboxylic acid thus produced (**2**) in the presence of catalytic amount of H_2SO_4 in quinoline (Scheme 1). After methyl esterification and benzylic bromination, an *N*-alkylation reaction with imidazopyridine derivative (**4**) followed by hydrolysis gave the carboxyphenyl-substituted quinoline GA 0056, which possessed antihypertensive activity. Curtius rearrangement methodology was then employed [using $(PhO)_2P(O)N_3$-Et_3N-*t*-BuOH] to convert the carboxyl group to amino ($CO_2H \rightarrow CON_3 \rightarrow$

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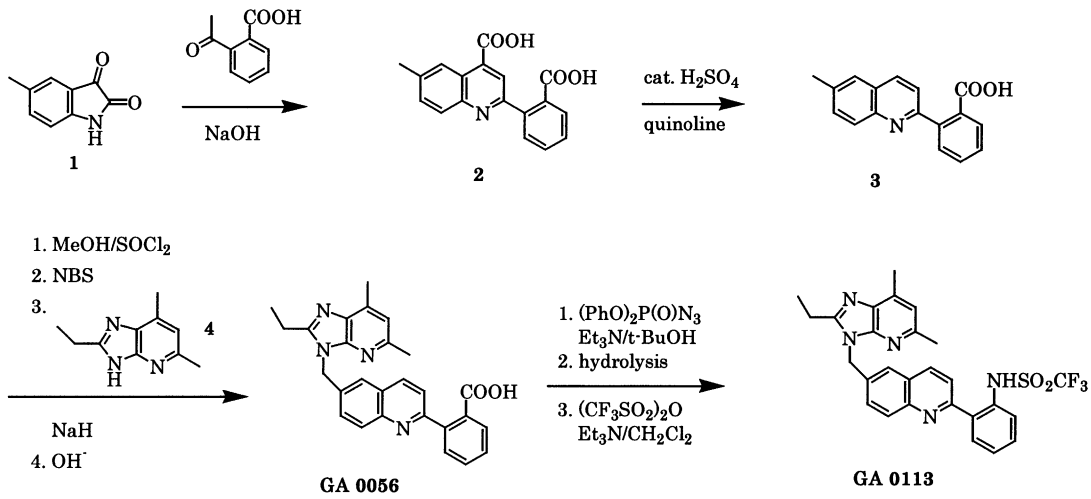


Scheme 1.

$N{=}C{=}O \rightarrow NHCO_2Bu^t \rightarrow NH_2$); however, the aniline derivative was obtained only in low yield (2% based on **1**), even after improving the reaction conditions. Finally, the quinolinylaniline was transformed into the desired triflamide GA 0113, 6-{(2-ethyl-5,7-dimethyl-3*H*-imidazo [4,5-*b*]pyridin-3-yl)methyl}-2-[2-trifluoromethanesulfonamido)phenyl]quinoline, by treatment with $(CF_3SO_2)_2O$.

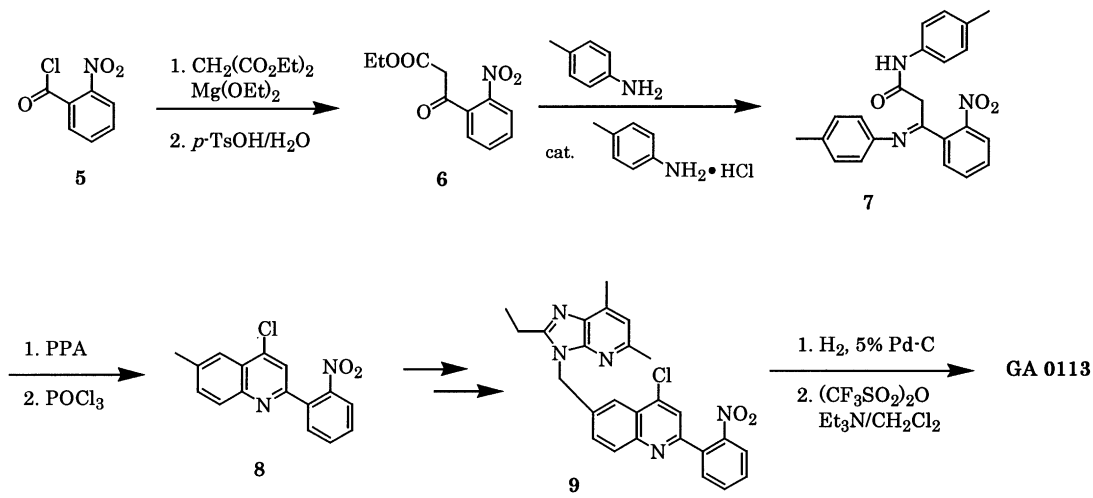
After several attempts to develop a satisfactory synthetic method for producing bulk quantities of the quinolinylaniline precursor of GA 0113, for example, unsuccessful decarboxylation of the nitrophenyl analogue of compound **2** or a modified Skraup reaction with 4-methylaniline and 3-(2-nitrophenyl)acrolein, we have found a practical process through the application of Conrad–Limpach's method (Scheme 2).

The key 2-nitrophenyl ketone (**6**) was synthesized from 2-nitrobenzoyl chloride (**5**) and diethyl malonate in the presence of magnesium ethoxide, and successive decarboxylation. Ring construction was accomplished by the reaction of **6** with *p*-toluidine, followed by treatment of **7** with polyphosphoric acid, then phosphorous oxychloride to give nitrophenylquinoline **8** in a fairly good yield. After *N*-alkylation according to the transformation of **3** to GA 0056 (Scheme 1), chloro-nitro compound **9** was reduced and the resulting aniline converted to GA 0113. The overall yield of GA 0113 from **5** was 10%.

3. Results and discussion

3.1. Biological data

Pharmacological profiles of GA 0113 are as follows [8]: a binding assay for AT_1 and AT_2 receptors was performed using commercially-available membrane fractions expressing either human AT_1 or AT_2. GA 0113 and CV-11974



Scheme 2.

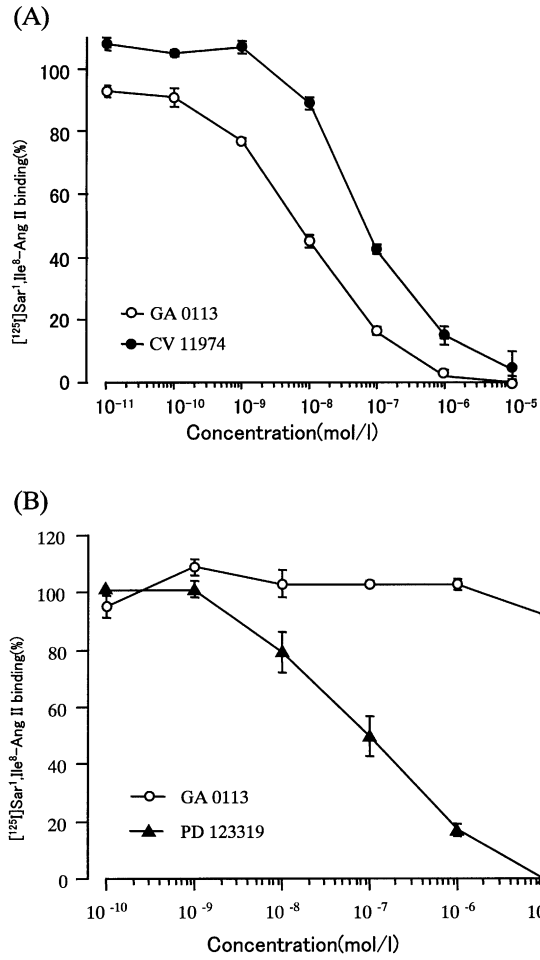


Fig. 1. Effects of GA 0113, CV-11974, and PD 123319 on specific binding of [^{125}I]-Sar1, Ile^8-Ang II to human AT_1 receptors (A) and AT_2 receptors (B).

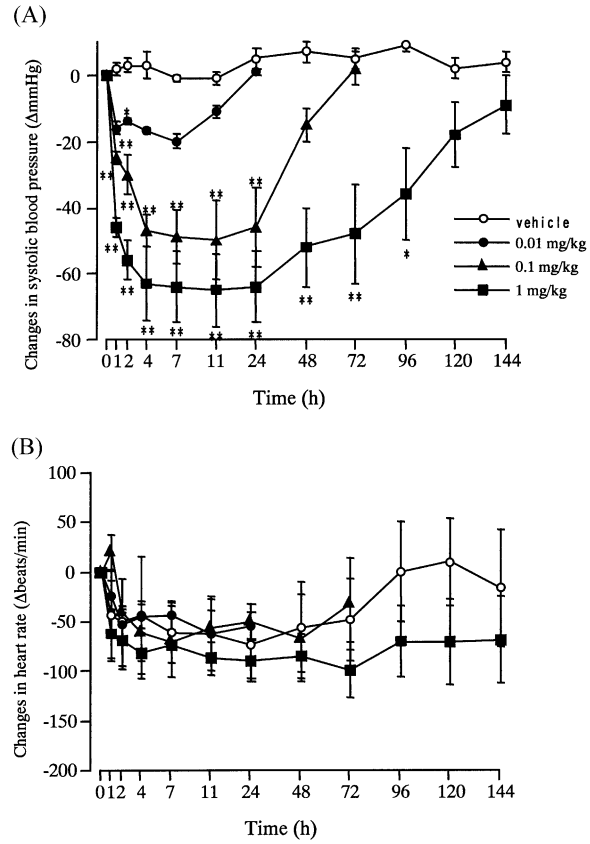


Fig. 2. Effect of oral administration of GA 0113 on systolic blood pressure (A) and heart rate (B) in renal artery ligated hypertensive rats.

(an AT_1 antagonist and a metabolite of TCV-116) displaced the specific binding of [^{125}I]-Sar^1, Ile^8-Ang II to binding sites in AT_1 in a concentration-dependent manner (Fig. 1), and the IC_{50} values were 1.1×10^{-8} and 1.3×10^{-7} mol/l, respectively. In contrast, specific binding of [^{125}I]-Sar^1, Ile^8-Ang II to binding sites in AT_2 was displaced by PD 123319, a selective AT_2 antagonist, but not by GA 0113.

Antihypertensive effects in renal artery ligated hypertensive rats (RALHR) was examined with male Wister rats. Administration of GA 0113 (0.01–1 mg/kg) reduced systolic blood pressure (SBP) in a dose-related manner with ED_{25} of 0.015 mg/kg, and at dose 0.1 mg/kg or more, SBP was reduced for more than 24 h without affecting heart rate (HR) significantly (Fig. 2). Pharmacokinetic examination revealed that GA 0113 has longer $T_{1/2}$ (12.2 h) and much better bioavailability (BA) (94%), whereas the $T_{1/2}$ and BA of TCV-116 have been reported to be 3.8 h and 19–28%, respectively [9]. The high BA might attribute to the replacement of the tetrazole group with the more lipophilic and metabolically more stable acidic isostere, triflamide group, taking into consideration that the p*K*a (5 to 6) of aryltetrazole is similar to that (4.45) of $PhNHSO_2CF_3$ [10], and a unique quinolinyl group.

3.2. MOPAC calculation

MOPAC™ PM3 calculation of anions $PhNSO_2R$ (R=CH_3, CH_2F, CHF_2, CF_3) in water ($\varepsilon = 78.4$) using COSMO method optimized by EF indicated that the bond-lengths of N–S increase gradually from 1.75 (CH_3) to 2.02 Å (CF_3) and the dipole moments of their anion are dramatically decreased from 14.3 (CH_3) to 9.7 D (CF_3). Moreover, we have found that AM1 Hamiltonian is not suitable for such anions because the C–N–S bond angle increased from 154.2°(CH_3) to 176.0°(CF_3).

4. Conclusion

Although GA 0113 is not structurally related to TCV-116 and other AT_1 receptor antagonists bearing a biphenyltetrazole moiety, it may become a potent agent for the treatment of hypertension and other Angiotensin II-related cardiovascular diseases.

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