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A NEW CLASS OF ANGIOTENSIN II RECEPTOR ANTAGONISTS WITH A NOVEL ACIDIC BIOISOSTERE

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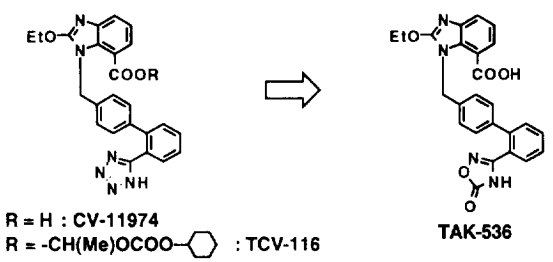
Abstract: The synthesis and angiotensin II (AII) antagonistic activity of 2-substituted benzimidazole-7-carboxylic acids (**8**) bearing a novel acidic bioisostere, a 5-oxo-1,2,4-oxadiazole ring, are described. These compounds had *in vitro* and *in vivo* AII receptor antagonistic activity comparable to that of tetrazole analogs. The representative compound, **TAK-536 (8e)** is a potent, orally active and specific AII receptor antagonist.



Angiotensin II (AII) is the primary effector hormone in the renin-angiotensin system (RAS), which plays an important role in the regulation of blood pressure and electrolyte balance.[1] AII receptor antagonists which specifically block the RAS at the final step is expected to be a novel and effective antihypertensive agent. We have already reported a novel and potent AT_1 selective AII receptor antagonist, the benzimidazole-7-carboxylic acid such as CV-11974.[2] The prodrug of CV-11974, TCV-116[3] is highly effective, orally active and long-acting AII receptor antagonist, which is currently under clinical evaluation as an antihypertensive agent.

As shown in Chart 1, our research efforts were so far mainly directed to modification of heterocycles (part A) of the compound (**1**) having the biphenyl tetrazole group.[2-5] To find a new class of AII antagonists, we turned our attention to chemical modification of the biphenyl tetrazole moiety (part B). The heterocycle (A) was fixed by the benzimidazole-7-carboxylic acid moiety, one of the most potent heterocycles possessing a biphenyltetrazole group,[2] and a series of 2-ethoxy (or 2-butyl) benzimidazole-7-carboxylic acids, in which one benzene ring (X and/or Y) of biphenyl group was replaced by other heterocycles (e.g., pyridine, pyrrole, quinoline and pyrimidine) was prepared and evaluated for AII antagonist activity. The results are not presented here, but these compounds were found to have the same or weaker activity compared with the biphenylmethyl derivatives.[6] Thus our next target was turned to search for a novel tetrazole replacement by other acidic heterocycles.[7] A variety of acidic five- or six-membered heterocycles including the known

acidic bioisosteres[8] were synthesized and evaluated for AII receptor antagonistic activity.[9] Some of them showed the AII antagonistic activity comparable to that of the tetrazole derivative. Herein we focus on a 5-oxo-1,2,4-oxadiazole ring, which is a novel class of the tetrazole replacement, and report the synthesis, AII antagonistic activity and structure-activity relationship (SAR) of 2-substituted benzimidazole-7-carboxylic acids possessing the 5-oxo-1,2,4-oxadiazole ring as a novel acidic bioisostere.

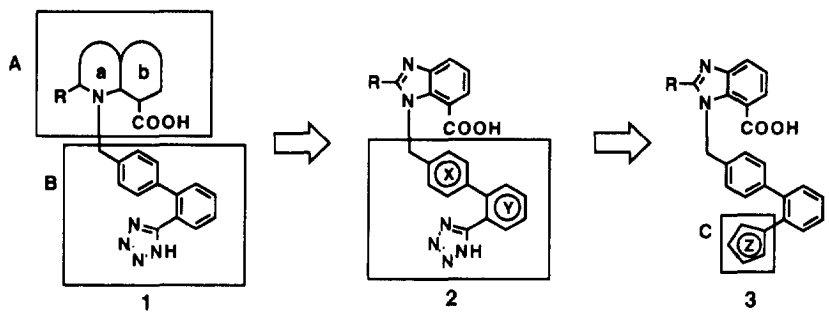
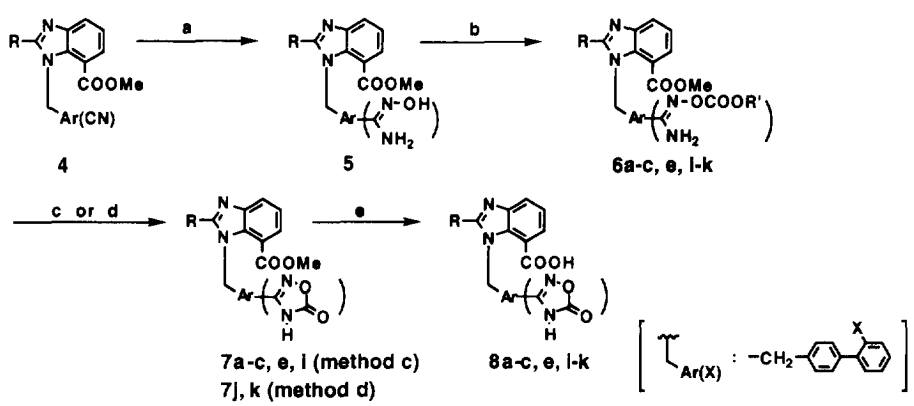


Chart 1

Chemistry

A series of 2-substituted benzimidazole-7-carboxylic acids (**8**) bearing the 5-oxo-1,2,4-oxadiazole ring was synthesized by two routes outlined in Scheme 1 and 2.

Scheme 1



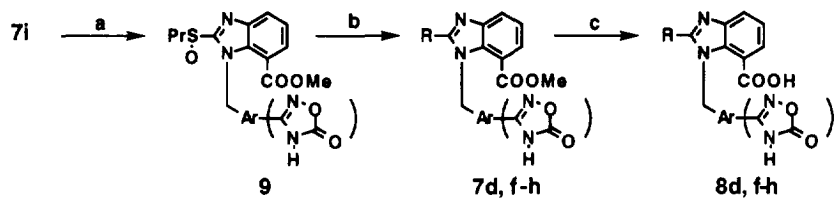
(a) Et_3N, NH_2OH-HCl; (b) pyridine or Et_3N, ClCOOR' (R'= Me or 3-heputyl); (c) xylene, reflux; (d) DBU; (e) aq.NaOH

As shown in Scheme 1, oxadiazolones **8a-c,e,i-k** were synthesized from the amidoximes **5** according to the general method.[10] The amidoximes **5**, which were prepared from nitriles **4**[2] with hydroxylamine, were reacted with chloroformate in the presence of triethylamine or pyridine to afford acylamidoximes **6**. Cyclization of **6** by heat or treatment with DBU provided the

5-oxo-1,2,4-oxadiazole derivatives **7**, which were hydrolyzed to the corresponding carboxylic acids **8a-c,e,i-k**.

8d,f-h were prepared from 2-propylthiobenzimidazole **7i** as shown in Scheme 2. Substitution reaction of **9**, which was synthesized by oxidation of **7i** with m-CPBA, with an appropriate nucleophile yielded oxadiazolones **7**, followed by alkaline hydrolysis to afford **8d, f-h**.

Scheme 2



(a) m-CPBA; (b) nucleophiles (NaOMe, NaOPr, MeSH, EtSH); (c) aq.NaOH

Biological Results and Discussion

The compounds were tested for the binding affinity to the AII receptor with respect to the inhibition of [^{125}I]-AII (0.2nM) binding to bovine adrenal cortical membranes (Table 1).[11]

Comparison of the IC_{50} values for the compounds demonstrated that the optimal length of R at the 2-position of benzimidazole ring seemed to be two or three atoms (C, N, O and S) regardless of the nature of R. 2-Alkylamino derivatives (**8j**, **8k**) had a slightly enhanced binding affinity than the others.

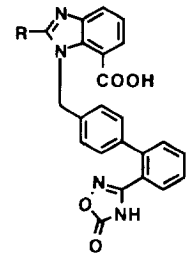
The compounds were further evaluated *in vivo* for inhibition of the pressor response induced by AII (100ng/kg, i.v.) in conscious rats[11] and the data are listed in Table 1. Varying R was found to cause effects on inhibitory activity similar to those on binding affinity. The optimum activity was found to be associated with a chain length of two or three atoms (C, N, O and S) regardless of the nature of R. An alkoxy group was more effective than other substituents at the 2-position of the benzimidazole ring on inhibitory activity. 2-Alkylamino derivatives (**8j**, **8k**) had weaker inhibitory activity than the others in spite of high binding affinity.

The structure-activity relationship (SAR) of the benzimidazole derivatives (**3**) possessing a 5-oxo-1,2,4-oxadiazole ring was similar to that of the tetrazole counterparts. 2-Ethoxy derivative **8e** (**TAK-536**) was selected for further pharmacological studies.

As shown in Figure 1, in isolated aorta helical strips,[11] **TAK-536** inhibited AII-induced contraction as potently as the tetrazole derivative, CV-11974 in a non-competitive manner. This inhibitory manner was the same as that of CV-11974. The pD_2' values of **TAK-536** and CV-11974 were 9.93 and 9.97 [12] respectively.

As shown in Figure 2, in conscious normotensive rats,[11] **TAK-536** at more than 0.01mg/kg,p.o. inhibited AII-induced pressor response dose-dependently and its ID_{50} value was 0.06mg/kg. This inhibitory activity of **TAK-536** was as strong as that of TCV-116 (ID_{50}, 0.06mg/kg).[12]

Table 1. Inhibitory effects on the specific binding of [^{125}I]AII and AII-induced pressor responses in rats



compound	R	Receptor affinity IC_{50}, 10^{-7}M	%Inhibition, 1mg / kg, p.o. 3h / 7h
8a	Et	3.1	88 / 67
8b	Pr	4.2	100 / 88
8c	Bu	6.2	68 / 64
8d	MeO	3.6	90 / 88
8e (TAK-536)	EtO	4.2	100 / 100
8f	PrO	7.9	100 / 100
8g	MeS	3.9	100 / 100
8h	EtS	4.8	83 / 100
8i	PrS	8.5	80 / 100
8j	MeNH	2.6	14 / 13
8k	EtNH	0.42	25 / 6
CV-11974		1.1	100 / 92
losartan		1.5	21 / 34

Figure 1. Mode of inhibitory effects of TAK-536 and CV-11974 on AII-induced rabbit aorta contraction

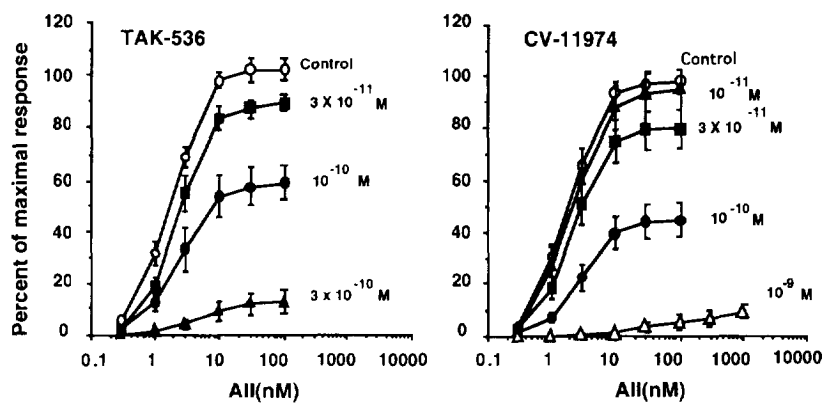
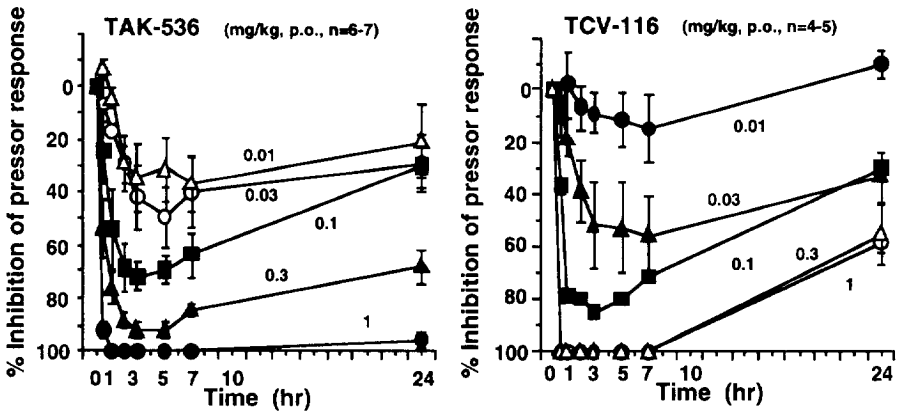
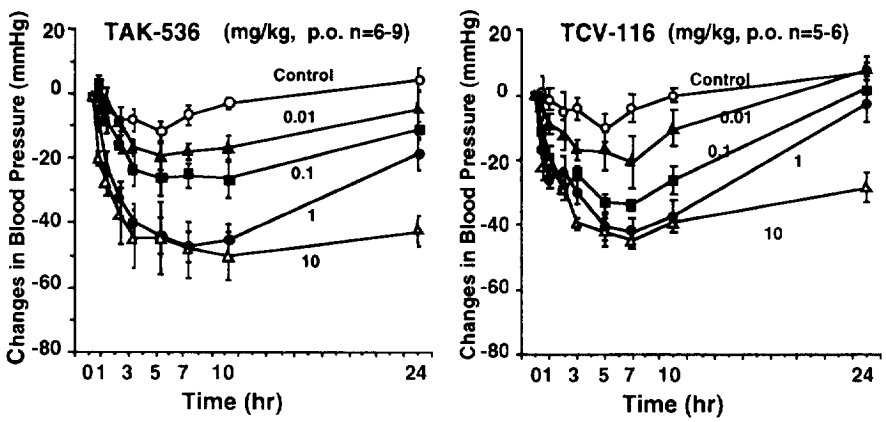


Figure 2. Inhibitory effects of TAK-536 and TCV-116 on AII-induced pressor response in conscious rats



As shown in Figure 3, in spontaneously hypertensive rats (SHR),[11] **TAK-536** at more than 0.1mg/kg,p.o. reduced blood pressure dose-dependently and its ED_{25} (p.o.) value was 0.40mg/kg. The antihypertensive effect of oral administration of **TAK-536** was comparable to that of TCV-116 (ED_{25}, 0.68mg/kg).[13]

Figure 3. Antihypertensive effects of TAK-536 and TCV-116 in spontaneously hypertensive rats (SHR)



These findings suggested that the oral bioavailability (BA) of **TAK-536** was improved compared with that of CV-11974.[3] Actually, the BA of **TAK-536** in rats was examined and found to be 20%[14] comparable to that of TCV-116.[3] Therefore this indicated that further chemical modification of **TAK-536** was not necessary any more for improvement of its oral BA. This difference of BA between **TAK-536** and CV-11974 may be explained by the difference of

physico-chemical properties between the 5-oxo-1,2,4-oxadiazole ring and the tetrazole ring. To examine the lipophilicity and acidity of **TAK-536** and CV-11974, the observed partition coefficients (log P) between 1-octanol and water and the pKa values of these compounds were measured. **TAK-536** (log P=0.90) was found to be more lipophilic than CV-11974 (log P= 0.32) and 5-oxo-1,2,4-oxadiazole ring (pKa=6.1)[15] showed somewhat higher pKa value in comparison to that of the tetrazole ring (pKa=5.3).[15] We think that the higher lipophilicity and pKa value of **TAK-536** may result in the improvement of the BA. **TAK-536** is undergoing clinical evaluation as an antihypertensive agent.

Conclusion

Herein, we demonstrated that the 5-oxo-1,2,4-oxadiazole ring was a novel class of acidic bioisostere of the tetrazole ring. The representative compound, **TAK-536** is a new class of potent, orally active and long-acting AII receptor antagonist, which has higher oral bioavailability than CV-11974. Consequently, further chemical modification of **TAK-536** was not necessary for improvement of the BA. We believe that a novel class of acidic bioisostere, the 5-oxo-1,2,4-oxadiazole ring can be applied to other drug design.

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14. The bioavailability (BA) was estimated as described previously, see reference 3.
15. The pKa values of the methylester of **TAK-536** and CV-11974 were measured in DMSO-H_2O (2:3) at 26°C by potentiometric titration with standardized 0.1N NaOH.

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