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A NEW CLASS OF DIACIDIC NONPEPTIDE ANGIOTENSIN II RECEPTOR ANTAGONISTS

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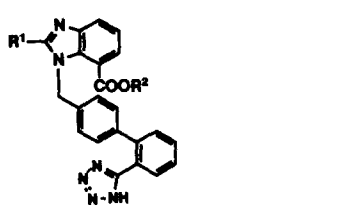
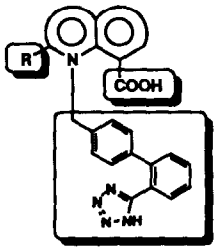
Abstract: A novel series of heterocyclic compounds I bearing two acidic functionalities, a carboxyl group and a tetrazole ring, was prepared and evaluated for *in vitro* and *in vivo* angiotensin II (AII) antagonistic activity. These compounds showed significantly more potent AII antagonistic activities than the parent compounds without the carboxyl groups. This structure-activity relationship (SAR) study revealed the importance of the carboxyl group attached to the heterocyclic moieties especially for insurmountable antagonism and enhancement of *in vivo* (po) activity.



CV-11194 (R^1=Bu, R^2=H)
CV-11974 (R^1=EtO, R^2=H)
TCV-116 (R^1=EtO, R^2=CH(Me)OCOO-⬡)



I

Blockade of the action of angiotensin II (AII) is a target for development of novel antihypertensive agents. A variety of heterocyclic compounds[1] were synthesized and evaluated as AII receptor antagonists. We recently discovered novel and potent nonpeptide AT_1 selective AII receptor antagonists, benzimidazole-7-carboxylic acid derivatives (CV-11194[2] and CV-11974[3]), which are much more potent than DuP 753 (losartan)[4]. The prodrug of CV-11974, TCV- 116, is an orally active, highly potent and long-acting AII receptor antagonist[5] and it is currently undergoing clinical evaluation as an antihypertensive agent.

The structure-activity relationship (SAR) studies on various benzimidazole derivatives related to CV-11974 revealed that the adjacent arrangement of a 1-tetrazolylbiphenylmethyl group, a 2-lipophilic substituent and a 7-carboxyl group was the common and important structural requirement for potent AII antagonistic activity. The presence of the 7-carboxyl

group was also very important for insurmountable AII antagonism.

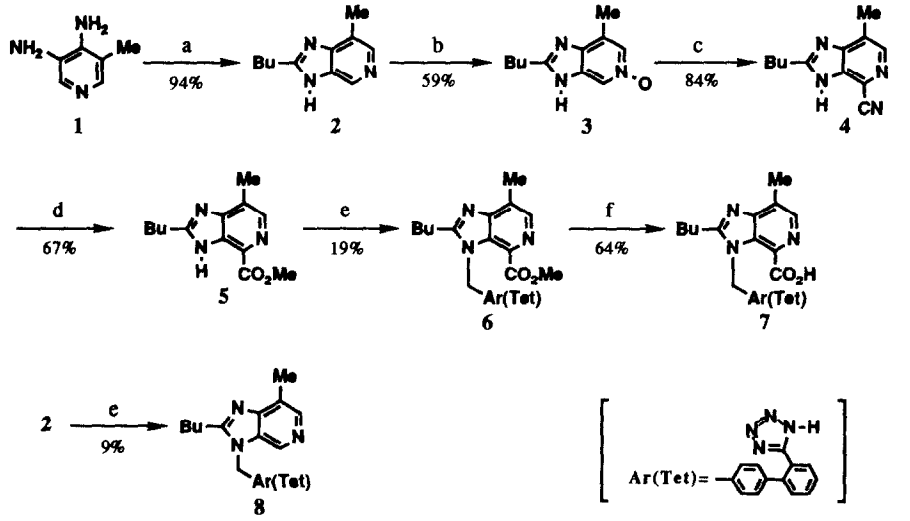
In order to investigate extensive SAR, a variety of heterocyclic compounds **I** bearing the key structural features mentioned above were prepared and evaluated for *in vitro* and *in vivo* AII antagonistic activities.

CHEMISTRY

Imidazo[4,5-c]pyridine, thieno[3,4-d]imidazole and imidazo[1,2-b]pyrazole derivatives were synthesized as target heterocyclic compounds by the routes outlined in Scheme I-III.

Diaminopyridine **1**[6] was cyclized to imidazo[4,5-c]pyridine **2**[7] by heating with valeric acid in polyphosphoric acid (PPA). Oxidation with hydrogen peroxide followed by Reissert reaction with trimethylsilyl cyanide[8] gave the nitrile **4**, which was treated with methanolic hydrogen chloride to afford the ester **5**. Alkylation of **5** with bromomethylbiphenyl derivative **9**[9] and subsequent deprotection yielded the tetrazole **6**, which was hydrolyzed to the carboxylic acid **7**. The parent compound without the carboxyl group **8** was prepared by alkylation of **2** with **9** followed by deprotection.

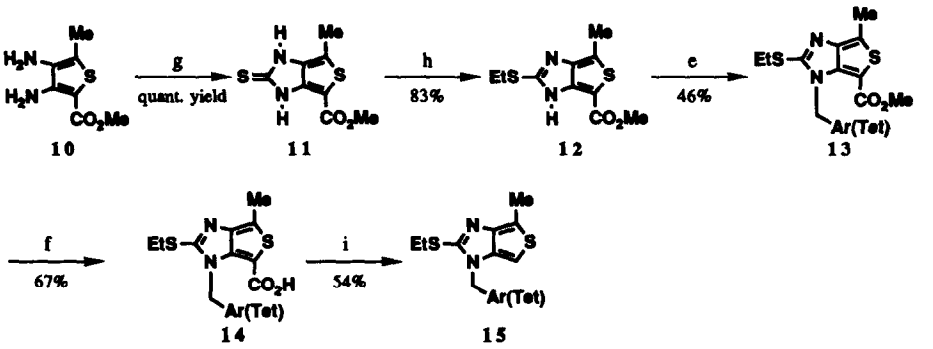
Scheme I



(a) $BuCO_2H$, PPA; (b) H_2O_2, AcOH; (c) TMS-CN, NEt_3; (d) HCl-MeOH;
(e) 1) NaH, $BrCH_2Ar(Tet\text{-}CPh_3)$ **9**, 2) 1N HCl; (f) 2N LiOH.

Diaminothiophene **10**[10] was reacted with 1,1'-thiocarbonyldiimidazole to give the 2-thione derivative **11**. S-Alkylation of **11** provided thieno[3,4-d]imidazole **12**, which was converted to the carboxylic acid **14**, as shown in Scheme II. The parent compound **15** was prepared by decarboxylation of **14** by heating with trifluoroacetic acid.

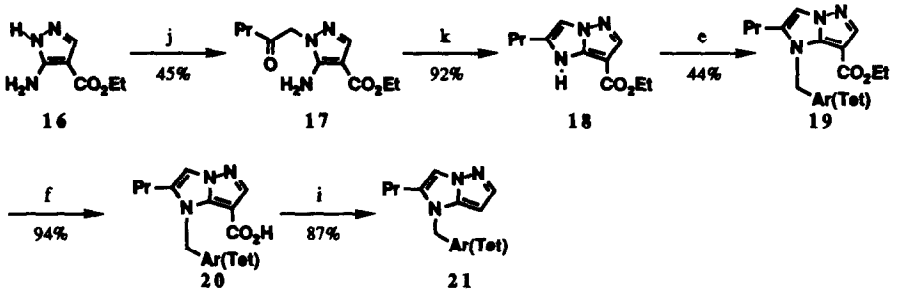
Scheme II



(g) 1,1'-thiocarbonyldiimidazole; (h) EtI, aq.NaOH; (e) 1) NaH, **9**, 2) 1N HCl; (f) 2N LiOH; (i) CF_3CO_2H.

Alkylation of aminopyrazole **16** with 1-bromo-2-pentanone[11] followed by acid-catalyzed cyclization furnished imidazo[1,2-b]pyrazole **18**, which was converted to the target compounds **20** and **21**, as shown in Scheme III.

Scheme III



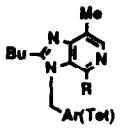
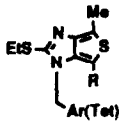
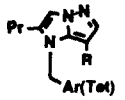
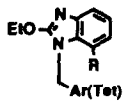
(j) NaH, 1-bromo-2-pentanone; (k) p-TsOH, toluene; (e) 1) NaH, **9**, 2) 1N HCl; (f) 2N LiOH; (i) CF_3CO_2H.

BIOLOGICAL RESULTS AND DISCUSSION

The AII antagonistic activities of these compounds were examined in *in vitro* assay systems, including AII receptor binding assay using membrane fractions of bovine adrenal cortex[12] and AII-induced contraction assay using rabbit aorta strips. These data are presented in Table I. In the binding assay, incorporation of the carboxyl group to the heterocyclic ring led to compounds **7,14,20,22** with improved binding affinity relative to their parent compounds **8,15,21,23.**

In the functional assay using rabbit aorta, the carboxylic acids **7,14,20,22** were 10 to 100-fold more potent than their parent compounds **8,15,21,23** regardless of the chemical structures of the heterocyclic moieties. It is noted that the carboxylic acids showed insurmountable antagonism, whereas their parent compounds showed surmountable

Table I Influence of the carboxyl group attached to various heterocycles on *in vitro* AII antagonistic activity

Compound			Inhibition of AII receptor binding $IC_{50}(M)^a$	Inhibition of contraction of rabbit aorta $pD_2'^b$	pA_2^b
	R=CO_2H	7	3.6×10^{-8}	9.16 ± 0.17	
	R=H	8	5.4×10^{-8}		7.92 ± 0.18
	R=CO_2H	14	5.0×10^{-7}	9.65 ± 0.08	
	R=H	15	1.2×10^{-6}		8.26 ± 0.09
	R=CO_2H	20	4.8×10^{-8}	9.58 ± 0.06	
	R=H	21	3.3×10^{-6}		7.24 ± 0.06
	R=CO_2H	22	1.1×10^{-7}	9.97 ± 0.10	
	R=H	23	3.9×10^{-7}		7.93 ± 0.21

[a] The IC_{50} value is the concentration of compound which inhibits [^{125}I]AII binding by 50%. Intraassay and interassay IC_{50} values for a given compound may vary less than 3% and less than 10%, respectively. For 22 the $IC_{50}(\times 10^{-7}M) \pm$ S.E.M. is 1.1±0.1 (n=3). [b] The pD_2' and pA_2 values were calculated by the method of Van Rossum[13]. The value is the mean ± S.E.M. of three to five experiments.

antagonism. Figure I shows the concentration-contractile response induced by AII in rabbit aorta strips. The carboxylic acid **14** at 10^{-9}M caused a nonparallel shift to the right of the dose-response curve for AII and reduced the maximal response. By contrast, the parent compound **15** at 10^{-8}M shifted the dose-response curve for AII to the right in a parallel manner and did not alter the maximal response.

The *in vivo* AII antagonistic activities of these compounds were evaluated for inhibition of AII-induced pressor response in conscious normotensive rats[14]. The inhibitory effects of the carboxylic acid **14** and its parent compound **15** at 1mg/kg, po are compared in Figure II. The carboxylic acid **14** was much more effective than its parent compound **15**. This result was consistent with the one in *in vitro* functional assay.

CONCLUSION

This study demonstrated that the adjacent arrangement of a tetrazolylbiphenylmethyl group, a lipophilic side chain and a carboxyl group, not only in benzimidazole but also

other heterocycles, was the key structural feature for the potent AII antagonistic activity *in vitro* and *in vivo*. In all cases, the presence of the carboxyl group is crucial for high potency, insurmountable antagonism and long duration of action.

These heterocyclic compounds bearing two acidic functionalities provide a new class of AII receptor antagonists[15].

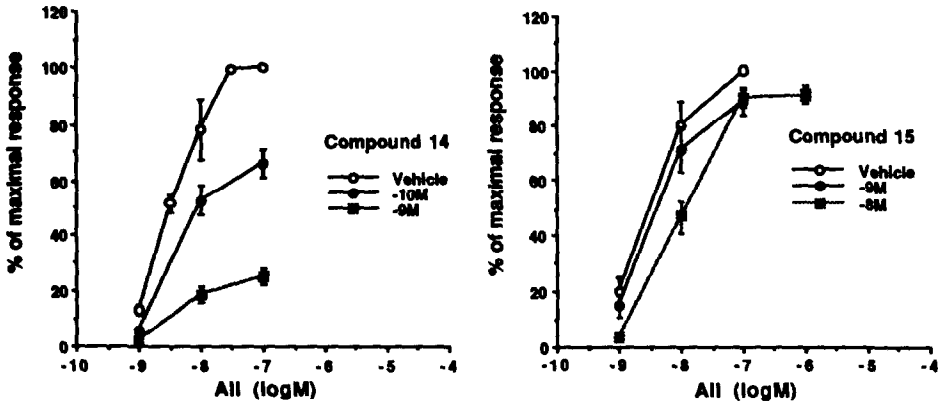


Figure I Concentration-response curves of thieno[3,4-d]imidazole-6-carboxylic acid 14 and its parent compound 15 on the AII (10nM) induced contraction in isolated rabbit aorta. Each point is the mean ± S.E.M. of three to five experiments.

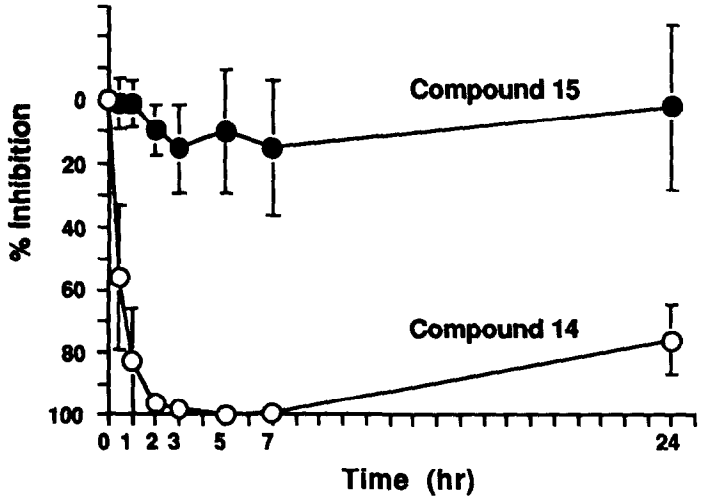


Figure II Comparison of inhibitory effects of thieno[3,4-d]imidazole-6-carboxylic acid 14 and its parent compound 15 (1mg/kg, po) on the AII (100ng/kg, iv) induced pressor response in conscious normotensive rats. Each point is the mean ± S.E.M. of four experiments.

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