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DIOL SULFONAMIDES: A POTENT AND NOVEL CLASS OF INHIBITORS OF HUMAN RENIN

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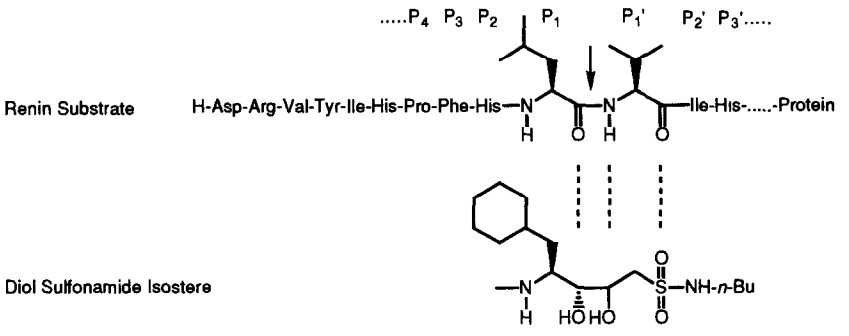
Abstract: *The syntheses and pharmacological activity of a series of diol sulfonamides which function as inhibitors of human renin are described. The most potent compound in this series, compound* ***20*** *(**SQ 33,800**), is a subnanomolar inhibitor of human renin (IC_{50} = 0.35 X 10^{-9} M).*

Regulation of the renin-angiotensin system (RAS) as a means of treating hypertension and congestive heart failure continues to be an area of active interest. Work directed at suppression of the RAS by reducing angiotensin II (Ang II) production has led to the development of various angiotensin converting enzyme (ACE) inhibitors[1] and renin inhibitors.[2] Recently, a great deal of effort has also been focused on the preparation of nonpeptidic Ang II receptor antagonists as a means of regulating the RAS.[3]

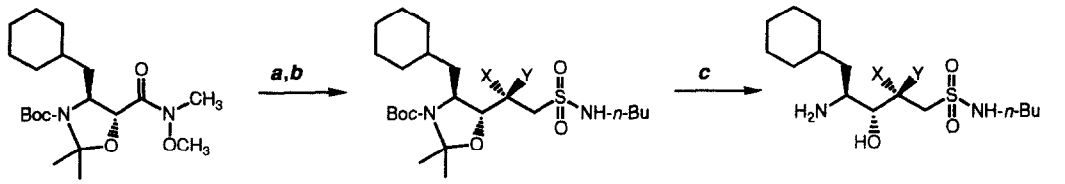
We wish to report a new class of inhibitors of human renin which utilize a novel diol sulfonamide moiety as a dipeptide isostere of the scissile Leu-Val portion of the renin substrate (**Figure 1**). The design of the diol sulfonamide moiety places the cyclohexyl ring in the hydrophobic P_1 pocket and uses the diol residue to function as a transition state mimic of the amide bond undergoing hydrolysis.[4] The sulfonamide is spaced to be positionally equivalent to the amide of valine present at the site of proteolysis, and the *n*-butyl sidechain of the sulfonamide is incorporated to fill the hydrophobic P_2' pocket occupied by the Ile side chain in the renin substrate.

Figure 1.



The synthesis of the diol sulfonamide moiety is presented in **Scheme 1** which outlines the preparation of the amino derivatives **1A** and **1B**. The synthesis starts with amide **2**.[5] Using sulfonamide dianion chemistry,[6] amide **2** was converted to *beta*-ketosulfonamide **3** which was then reduced to give *beta*-hydroxysulfonamides **4A** and **4B**.[7] Sulfonamides **4A** and **4B** were separated by chromatography and each was hydrolyzed independently to furnish **1A** and **1B**.

Scheme 1.



2

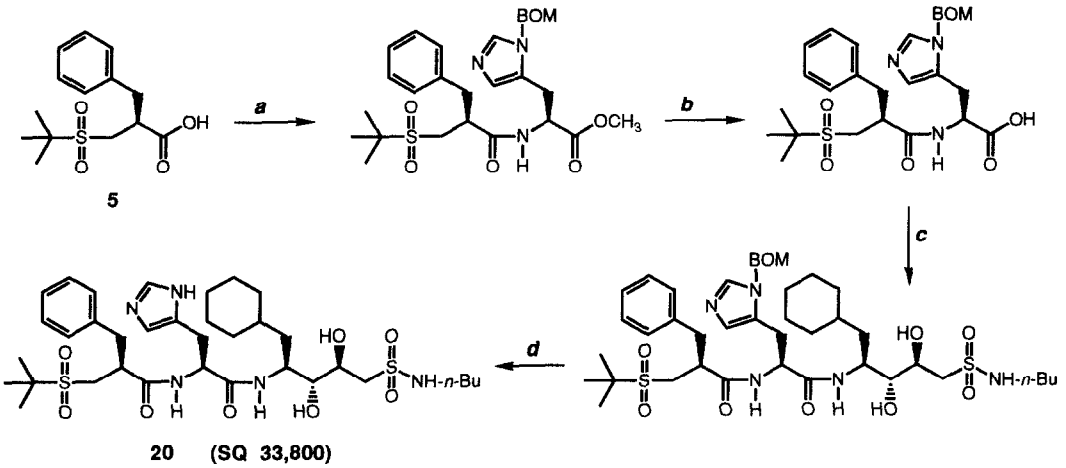
3 X = Y = O
4A X = H; Y = OH
4B X = OH; Y = H

1A X = H; Y = OH
1B X = OH; Y = H

a. CH_3SO_2NH-*n*-Bu/*n*-BuLi/THF (86%); *b*. *t*-$BuNH_2$-BH_3/Et_2O (4A 67% and 4B 25%); *c*. 10% aqueous HCl/ THF/CH_3CO_2H (1A 92%; 1B 95%)

The focus of our program was to identify a small molecule lead and attempt to incrementally build in additional potency. This effort began with the amino diol sulfonamides **1A** (IC_{50} = 470,000 nM) and **1B** (IC_{50} = 14,000 nM) which were weak inhibitors of human renin.[8] To enhance the activity of **1A** and **1B**, analogs containing additional functionality designed to mimic the P_2 and P_3 residues of the renin substrate were prepared (**Table**). The compounds in the **Table** were synthesized using standard peptide solution procedures. The synthesis of compound **20** (**SQ 33,800**), which began with sulfone acid **5**[9], is representative and is outlined in **Scheme 2.**

Scheme 2.

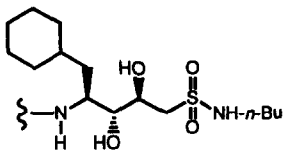


5

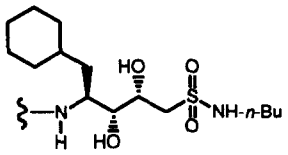
20 (SQ 33,800)

a. His(BOM)-OCH_3/WSC/HOBT/DMF (91%); *b*. NaOH/CH_3OH/H_2O (95%); *c*. 1A/DCC/HOBT/4-Methyl morpholine/THF (62%); *d*. H_2/Pearlman's catalyst/H_2O/HCl/CH_3OH (71%)

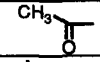
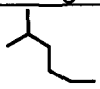
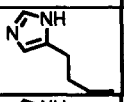
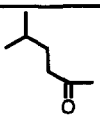
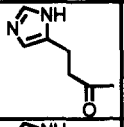
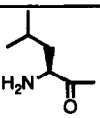
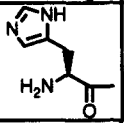
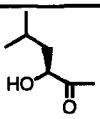
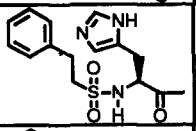
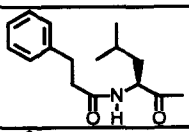
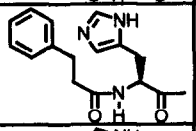
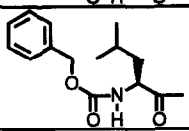
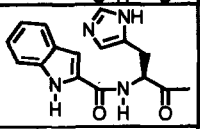
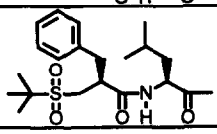
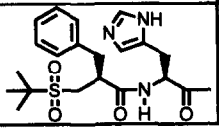
Table.



Isomer A



Isomer B

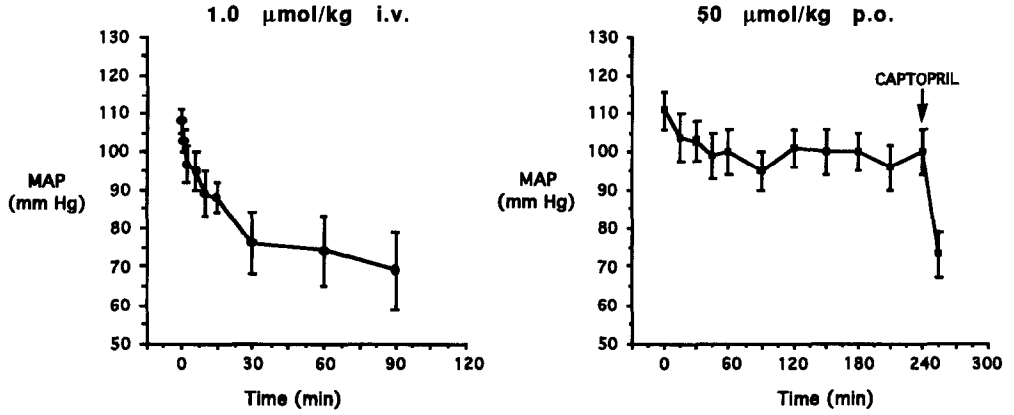
Compound		IC_{50} (nM) Isomer A	IC_{50} (nM) Isomer B	Compound		IC_{50} (nM) Isomer A	IC_{50} (nM) Isomer B
1	H	470,000	14,000				
6		>1,000,000	>1,000,000				
7		680,000	14,000	8		310,000	
9		>1,000,000	>1,000,000	10		>1,000,000	>1,000,000
11		>1,000,000		12		>1,000,000	
13		>1,000,000	>1,000,000	14		240	140,000
15		3,500		16		64	21,000
17		52,000		18		11	
19		1.7		20		0.35	

The compounds in the **Table** were evaluated as inhibitors of human renal renin at pH 7.0. The concentration of compound that inhibited renin activity by 50% (IC_{50}) was determined.[10] From the data, the following structure-activity relationships were identified: (1) Alkylation of the *N*-terminus of the diol sulfonamide moiety with residues which are isosteric with histidine and leucine side chains and designed to fill the P_2 binding pocket did not improve the activity (**1** vs. **7** or **8**). (2) Simple acylation of the *N*-terminus of **1A** or **1B** completely eliminated inhibitor potency (**1** vs. **6**). This result was indicative of the requirement for an amino group in smaller analogs. Furthermore, *N*-acylation with functionality designed to occupy only the P_2 binding site also completely eliminated inhibitor potency (**1** vs. **9-13**). The potency was enhanced, however, by acylation of the *N*-terminus with functionality that could occupy both the P_2 and P_3 binding sites (**14A-20A**). Histidine and leucine substitutions were explored at P_2, and aryl fragments were incorporated at P_3. (3) Replacement of histidine with leucine at P_2 reduced inhibitor potency (**15A** vs. **16A** and **19A** vs. **20A**) and demonstrated the enzyme's preference for histidine, the amino acid found at this position in the renin substrate. (4) *N*-acylation of the less potent dipeptide isostere **1A**, in which the hydroxyls are *anti*, provided derivatives with more potency than *N*-acylation of the more potent dipeptide isostere **1B**, in which the hydroxyls are *syn*. This result was dramatically demonstrated by the data for compounds **14** and **16**. Whereas, elaboration of **1A** to **14A** and **16A** improved the potency by 2000 and 7000 fold, respectively, similar elaboration of **1B** to **14B** and **16B** did not improve the potency at all and in the case of **14B** actually reduced potency ten fold. Workers at Abbott[4b] who have prepared similar diol containing renin inhibitors have also observed the enzyme's preference for diol derivatives having an *anti* relationship between the hydroxyls.

The most potent analog prepared in the series was compound **20** (**SQ 33,800**) which was a subnanomolar inhibitor of human renin ($IC_{50} = 0.35 \times 10^{-9}$ M).[11] To assess the efficacy of **20** (**SQ 33,800**) *in vivo*, it was administered by i.v. bolus to conscious, sodium depleted[12] cynomolgus monkeys (**Figure 2**). After administration of a dose of 1.0 μmol/kg to four monkeys, mean arterial pressure (MAP) attained a maximum reduction of approximately 35 mm Hg at 30 to 90 minutes. Following an oral dose of 50 μmol/kg to four monkeys, MAP was lowered by 16 mm Hg. Administration of the potent ACE inhibitor captopril (15 μmol/kg, i.v.) four hours after the initial oral dose, lowered MAP an additional 27 mm Hg. From these results, it was concluded that **20** (**SQ 33,800**) had not produced maximum renin inhibition. The poor response following oral administration was attributed to low oral bioavailability of the test compound.[13]

In summary, the diol sulfonamides represent a novel class of potent inhibitors of human renin. The most potent compounds in this series, as exemplified by compound **20** (**SQ 33, 800**) are subnanomolar inhibitors of human renin.

Figure 2. Intravenous and Oral *In Vivo* Effects of Compound **20** (**SQ 33,800**) on Mean Arterial Pressure (MAP) in Conscious, Sodium Depleted[12] Cynomolgus Monkeys (n = 4).



Acknowledgments: *We thank the Bristol-Myers Squibb Department of Analytical Chemistry for microanalysis and mass spectra.*

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1. (a) Petrillo, E. W.; Ondetti, M. A. *Med. Res. Rev.* **1982**, *2*, 1. (b) Wyvratt, M. J.; Patchett, A. A. *Med.Res. Rev.* **1985**, *5*, 483. (c) Greenlee, W. J. *Med. Res. Rev.* **1990**, *10*, 174. (d) Opie, L. H. *Angiotensin-Converting Enzyme Inhibitors: Scientific Basis for Clinical Use*; John Wiley & Sons: New York, 1992.

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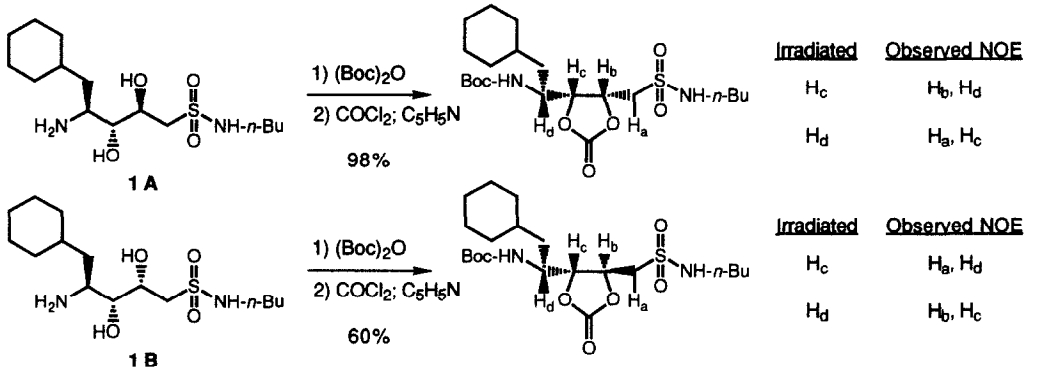
5. For the preparation of amide **2**, see: Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 1411.

6. Thompson, M. E. *J. Org. Chem.* **1984**, *49*, 1700.

7. The stereochemistry of the hydroxyl *beta* to the sulfonamide was determined by NOE studies on the corresponding cyclic carbonates prepared from **1A** and **1B**.



8. Replacement of the *n*-butyl sulfonamide residue in **1A** and **1B** with an *n*-butyl carboxamide gave two diastereomeric amides which were both completely inactive as inhibitors of human renin (IC_{50}'s > 1,000,000 nM).

9. For the preparation of sulfone acid **5**, see: Buhlmayer, P.; Caselli, A.; Fuhrer, W.; Goschke, R.; Rasetti, V.; Rueger, H.; Stanton, J. L.; Criscione, L.; Wood, J. M. *J. Med. Chem.* **1988**, *31*, 1839.

10. Inhibitor potency was determined using a partially purified preparation (No. 216, 2.4 μg Ang I/hr/mg) of human kidney renin kindly provided by Dr. E. Haas (Mt. Sinai Medical Center, Cleveland, OH). Human plasma (Mercer Regional Blood Center, Trenton, NJ) was used as the source of angiotensinogen substrate in the renin incubation mixtures. Incubation mixtures of 0.5 ml containing 0.10 mM EDTA, 0.10 mM sodium tetrathionate and 0.04 mM phenylmethylsulfonyl fluoride were buffered with 0.2 M TES to pH 7.0. Renin concentrations in the mixtures were adjusted to generate Ang I at rates, constant with time, of 20-80 ng Ang I/ml/hr. Human plasma was added at concentrations (10 to 50%) sufficient to provide a final angiotensinogen concentration of 0.5 μM. Test compounds were dissolved in DMSO, serially diluted, and added to the incubation mixtures. The final concentration of DMSO was fixed at either 0.5 or 1.0 %. Incubations were conducted for 30 minutes at 37 °C. The reactions were terminated by reduction of the temperature to 0 °C and Ang I concentrations were measured by radioimmunoassay.

11. Renin inhibitors containing the *N*-[(2S)-2-[(*tert*-butylsulfonyl)methyl]-3-phenylpropionyl]-His fragment were first reported by workers at Ciba-Geigy; see reference 9.

12. Sodium depletion was accomplished by administration of furosemide and a salt-restricted diet prior to experimentation.

13. The discovery of a peptide-based renin inhibitor with good oral bioavailability and efficacy is described in reference 2e.