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Amino Acid Derived Sulfonamide Hydroxamates as Inhibitors of Procollagen C-Proteinase: Solid-Phase Synthesis of Ornithine Analogues

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Abstract—A discussion of the solid-phase synthesis of ornithine derived sulfonamide hydroxamic acids is illustrated. These analogues are shown to be potent, non-peptide inhibitors of procollagen C-proteinase (PCP).

Procollagen C-proteinase has been determined to cleave the C-propeptide from procollagen, resulting in the formation of collagen fibrils. Overproduction of collagen can be problematic and lead to, for example, arthritis, adult respiratory distress syndrome, and surgical adhesions. However, if the undesired formation of excess collagen could be eliminated through inhibition of PCP, this would aid in treatment of these various inflammatory or fibrotic conditions.[1]

Our initial studies focused on di- and tri-peptidic hydroxamates.[2] Potent analogues were found, but it was desired to have non-peptide, small molecule inhibitors of PCP. High-throughput screening of our in-house library of probable zinc ligands (hydroxamates, carboxylates, thiols, etc.), revealed that the Ciba-Geigy compound, CGS 27023A,[3] was a weak inhibitor of PCP (3 μM) (Fig. 1).

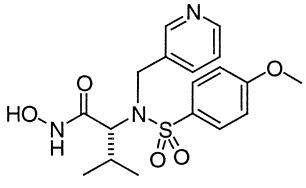

Figure 1. CGS 27023A first sulfonamide lead from screening.

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Related work in the quest for PCP inhibitors includes a Fibrogen patent[4] that discloses some related sulfonamides as inhibitors of PCP, however their most potent analogue disclosed is 50 μM. Researchers at the University of Manchester have also recently revealed dipeptide (succinate) type hydroxamic acids as inhibitors of PCP with potencies in the 0.1–10 μM range.[5]

A large number of libraries were prepared both in solution and on solid phase surrounding this lead compound, and variation at three positions and the zinc ligand (see Fig. 2) was investigated. This paper will focus on various substituted ornithine derivatives, with and without a substituent on the nitrogen of the sulfonamide (R^1).

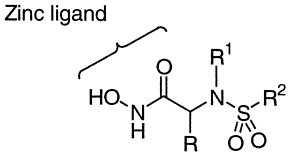

Figure 2. Points of variation on sulfonamide lead.

In a related structural class, $R^1 = 4\text{-}MeO_2CBn$ had shown to provide an improvement in inhibition of PCP, therefore a number of compounds were prepared in the ornithine series. However, none of these compounds were more potent than the original Ciba-Geigy lead.

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However, when R^1 = piperonyl, the activity increased dramatically leading to the discovery of the benzamide shown in Figure 3. Keeping this in mind, a number of compounds were prepared varying the terminal substituent on the ornithine and keeping the piperonyl and sulfonamide intact.

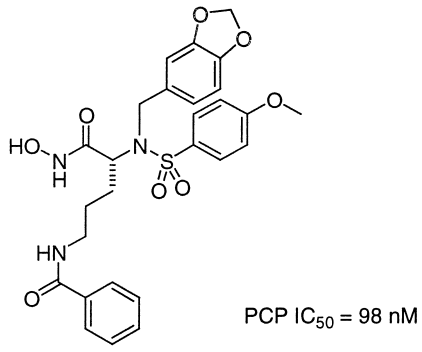
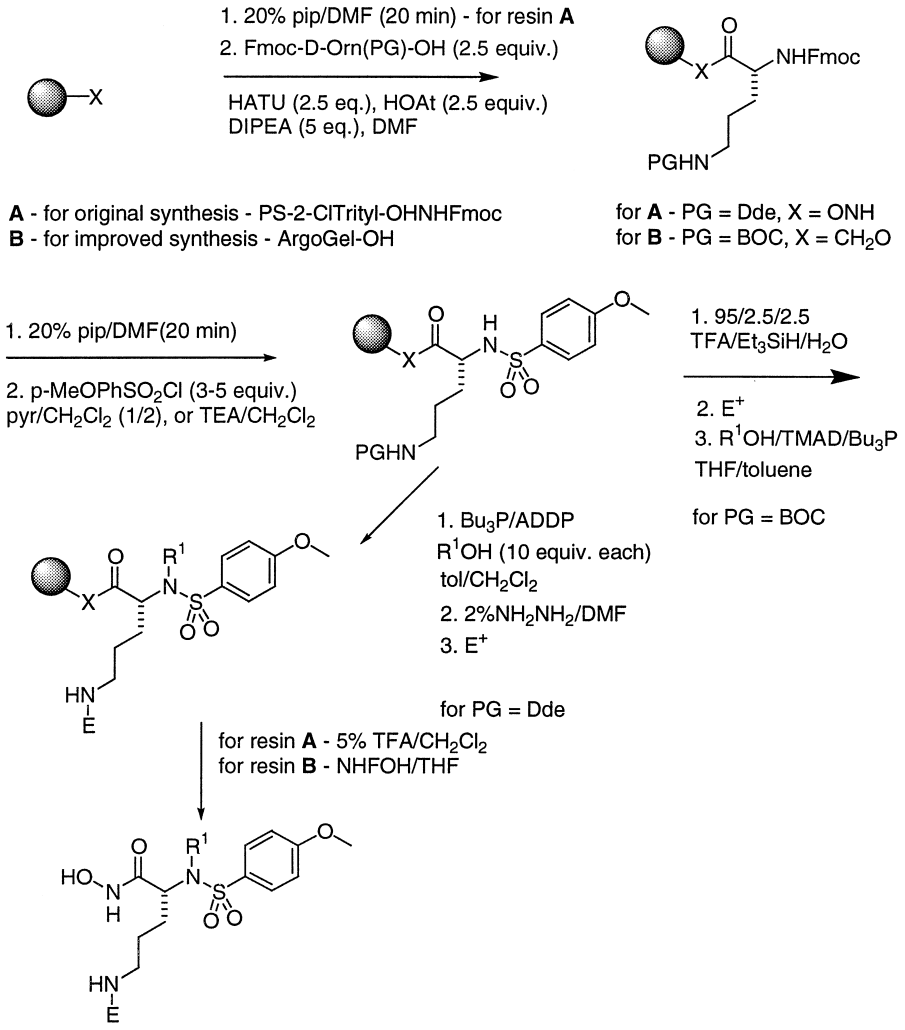


Figure 3. First ornithine compound that was superior to the original lead.

Scheme 1 illustrates the synthesis of the hydroxamic acids.[6] Some were prepared using 2-ClTritylNHOH resin (resin **A**),[7] but the majority were prepared using ArgoGel-OH® (resin **B**) as illustrated previously,[8] followed by cleavage with hydroxylamine.[9]

For R^1 = piperonyl, a library of carbamates and ureas was prepared (Table 1, Fig. 4). Substituted benzyl carbamates were shown to be the most potent compounds. Alkyl carbamates were somewhat less potent (*i*-Bu = 45 nM, Et = 220 nM).

During this study, it was very interesting to note that compounds lacking the R^1 group were showing potency, where this had not been seen with other amino acids studied previously. This was first observed with the protecting group left intact from Scheme 1 [D-Orn(Dde) *p*-methoxybenzene sulfonamide hydroxamic acid]. The compound with the Dde group remaining and R^1OH as piperonyl alcohol had an IC_{50} of 0.75 μM whereas that lacking an R^1 group on the sulfonamide nitrogen had an IC_{50} of 0.56 μM for PCP.



Scheme 1. For resin **A**: Conditions for: E^+ = RCOOH, HATU/HOAt/DIPEA/DMF/CH_2Cl_2, E^+ = ROCOOSu, pyr/CH_2Cl_2. Abbreviations: Dde = 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl; ADDP = 1,1′-(azodicarbonyl)dipiperidine. For resin **B**: Conditions for E^+ = ROCOOSu/ROCOCl/RNCO/RNCS: Et_3N/DMAP/THF, for RCOCl/RSO_2Cl: pyr/CH_2Cl_2. TMAD, azodicarboxylic acid bis(dimethylamide).

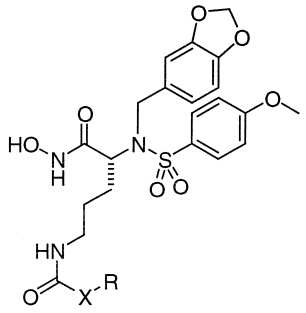


Figure 4.

Table 1. Most potent ureas (X = NH) and carbamates (X = O) prepared in library

Ureas R	PCP IC_{50} (nM)	Carbamates R	PCP IC_{50} (nM)
$Ph(CH_2)_2$	50	2-ClBn	3.9
3-MeBn	50	Bn	9
Bn	58	2-BrBn	24
Pr	97	3-NO_2Bn	38
(*S*)-1-NaphthylCH_2	120	4-NO_2Bn	45

Due to the increase in potency and the desirable decrease in molecular weight, a library of compounds was prepared lacking the R^1 group on the sulfonamide. The chemistry was performed as shown in Scheme 1, omitting the Mitsunobu reaction prior to the hydroxylamine cleavage step. The most potent analogues in this case were ureas. Some analogues were also prepared varying the sulfonamide and the stereochemistry of the amino acid. These are illustrated in Tables 2–4 (Figs 5 and 6).

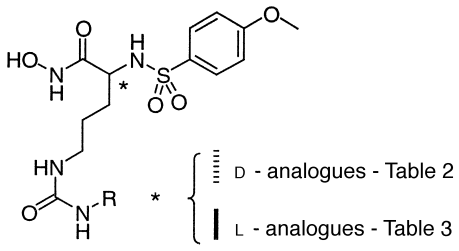


Figure 5.

Table 2. D-Ornithine analogues: most potent ureas (E^+ = RNCO) prepared in library

R	PCP IC_{50} (nM)	R	PCP IC_{50} (nM)
Ph	55	(*R*)-1-NaphthylCH(Me)	160
2-Thiophene$(CH_2)_2$	78	3-FPh	160
2-ClPh	92	*trans*-Ph-Cyclopropyl	170
(*R*)-α-MeBn	110	Cyclohexyl	230
(L)-Phe(OMe)	140	2-MePh	260

As can been seen in Tables 3 and 4, switching from D- to L-ornithine decreases the activity dramatically as does replacing *p*-MeOPh sulfonamide with other sulfonamides. Other functional groups were also incorporated on the ornithine nitrogen tail, but they also gave less potent compounds [Table 5 (upper), Fig. 7].

Lastly, it was determined that an unsubstituted sulfonamide was better than a small alkyl substituent by replacing the piperonyl with a methyl group. This was incorporated by alkylation of the sulfonamide with dimethyl sulfate in the presence of 7-methyl-1,5,7-triazobicyclo[4.4.0]dec-5-ene (MTBD) in DMF.[10] These analogues were consistently less potent that the corresponding NH analogues [Table 5 (lower), Fig. 7].

Table 3. L-Ornithine analogues: most potent ureas prepared in library

R	PCP IC_{50} (μM)	R	PCP IC_{50} (μM)
trans-Ph-Cyclopropyl	0.29	2-Thiophene$(CH_2)_2$	5.5
(*R*)-1-NaphthylCH(Me)	1.6	(L)-Phe(OMe)	5.9
(*R*)-α-MeBn	2.1	Ph	6.9
Cyclohexyl	3.6	2-ClPh	7.8
3-FPh	4		

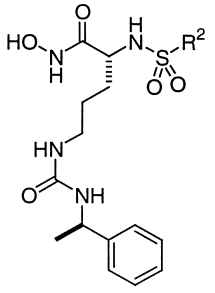


Figure 6.

Table 4. Variation of sulfonamide on D-ornithine analogues with (*R*)-α-MeBn urea

R^2	PCP IC_{50} (μM)	R^2	PCP IC_{50} (μM)
p-MeOPh	0.11	5-Cl-2-Thiophene	9.6
p-ClPh	0.91	2,6-Me_2-4-MeOPh	23
2-ClPh	2.3	2-Cl,4-FPh	61
4-$PhSO_2$-2-Thiophene	5		

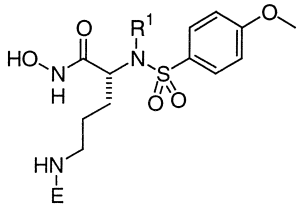


Figure 7.

Table 5. Variation of electrophilic-substituent (E) in the D-ornithine series (not included in other tables)

E R^1 = H	PCP IC_{50} (μM)	E R^1 = H	PCP IC_{50} (μM)
CyclopropylCO	0.77	CyclohexylCO	1.6
$Ph(CH_2)_2CO$	0.97	CyclohexylNHCS	1.7
BnNHCS	0.99	$PhSO_2$	3.4
i-PrCO	1.4	*t*-BuOCO	4.5
E R^1 = Me	**PCP IC_{50} (μM)**	**E R^1 = Me**	**PCP IC_{50} (μM)**
PhNHCO	1.6	2-ClPhNHCO	7.2
(*R*)-α-MeBnNHCO	2.3		

Nearly 200 compounds were prepared for these libraries on solid phase and represent an improvement of 1000-fold over the original screening lead. Also a novel lead lacking the nitrogen substituent was investigated and improved upon 10-fold. This compound is equipotent to the most active urea analogues with piperonyl group substitution on the sulfonamide. This work illustrates the power of solid-phase combinatorial chemistry in the drug discovery effort.

References and Notes

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