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The design and synthesis of sulfonamides as caspase-1 inhibitors

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Abstract—A series of sulfonamides (**1**) has been prepared as inhibitors of interleukin-1β converting enzyme (ICE), also known as caspase 1. These compounds were designed to improve potency by rigidifying the enzyme bound molecule through an intramolecular hydrogen bond. An X-ray crystal structure of a representative member of this series bound to the active site of ICE, confirms the presence of the hydrogen bonding interaction.

Interleukin-1β (IL-1β) is a cytokine involved in the pathogenesis of chronic and acute inflammatory disease.[1] IL-1β has been implicated in several disease states including arthritis[2] Alzheimer's disease,[3] and septic shock.[4] Modulating IL-1β levels may be valuable in the treatment of these and other diseases where inflammation is a contributing factor in the disease.[5] Since IL-1β is normally present in an inactive pro-form, and requires processing in order to provide the active cytokine, levels of IL-1β may be controlled by inhibiting the processing of the pro-IL1β.[6] This processing is performed by interleukin-1β converting enzyme (ICE), also known as caspase-1. As a result, inhibition of caspase-1 is one way to modulate the levels of IL-1β, and thus control inflammation.

Caspase-1, the first of a family of cysteine proteases, is highly specific for cleavage of aspartic acid residues. The unique structure and specificity of caspase-1 provides an interesting target for the design of inhibitors as potential drug candidates.[7] Early synthetic inhibitors of caspase-1 were based on the peptide scaffold of AcTyrValAlaAsp, and contained specific electrophilic groups on the Asp, usually an aldehyde, arylmethyl ketone, or a halomethylketone.[8] In some of these inhibitors, the AcTyr residue was replaced with a benzyloxycarbonyl[9] or a phenylpropionate[10] group and retained good binding.

To aid our rational design of new inhibitors of caspase-1, the known inhibitor (**2**) was prepared,[11] and the crystal structure of this compound bound into the active site of the enzyme was obtained.[12] This inhibitor was chosen because it spanned the enzyme from P4 and extended into the prime side of the enzyme. The key points of contact of the inhibitor with the active site of the enzyme were: the interactions of the Asp side chain carbonyl with Arg179, Arg341, and Gln283, forming the P1 pocket; the hydrogen bond of the Asp amide nitrogen with the carbonyl of Ser339; and the interaction of the ketone carbonyl with Cys285 and His237. On the P′-side, hydrophobic interactions of the phenyl group of the inhibitor with Pro177, Ile176, and Ile239 were observed.

Since **1** has many degrees of freedom, it was reasoned that additional potency could be obtained by increasing the rigidity of the molecule. Based on the crystal structure of **1** in the enzyme, and on additional modeling, one way to rigidify the molecule would be to include a hydrogen bond from an NH alpha to the Asp ketone carbonyl to the carbonyl of the Asp amide bond (Fig. 1). After considering several factors, including ease of synthesis and novelty in the literature, a sulfonamide moiety adjacent to the ketone was chosen as the hydrogen bond donor.

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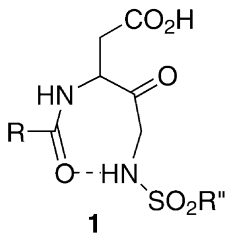
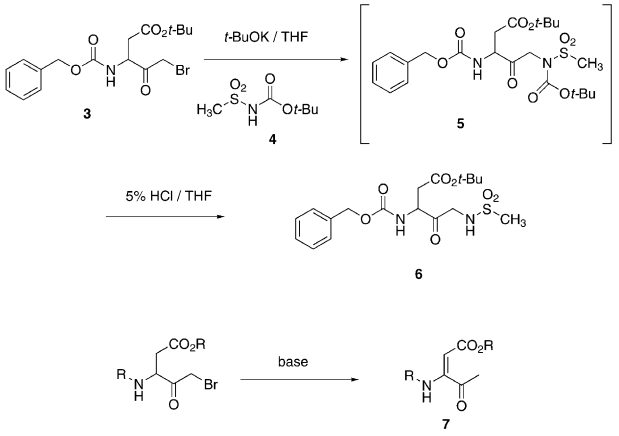


Figure 1.

Sulfamidomethyl ketones have been reported as inhibitors in a few enzyme systems, notably phosphdiesterase-4 (PDE4),[13] and the cysteine proteinases hepatitis A virus 3C proteinase (HAV 3C),[14] cathepsins B[15] and K,[16] calpains I and II,[17] and falcipain.[18] Of these, only the inhibitors of the calpains and cathepsins are secondary sulfonamides, which have the NH available for hydrogen bonding. For screening purposes, a benzyloxycarbonyl group (Cbz) was used on the nitrogen of the Asp moiety, to have a minimal binding contribution in the P2 pocket of the enzyme, with no contribution from P3 or P4, and to better differentiate the binding contributions of the various groups on the P′ side of the potential inhibitors.

As shown in Scheme 1, the sulfonamides were readily obtained by displacement of a bromomethyl ketone **3**, with the potassium salt of *N*-Boc sulfonamides. *N*-Boc sulfonamides are known to undergo fascile displacements of bromomethyl ketones[19] and participate in Mitsunobu reactions[20] under mild conditions. Early attempts at the displacement with the anions of unprotected sulfonamides were unsuccessful, and caused elimination of the bromide. Bromomethyl ketones similar to **3** are known to eliminate under basic conditions to form **7**.[21] Pre-forming the potassium salt of the Boc-sulfonamides, before addition of the bromomethyl-ketone, avoided the problem of elimination. The *N*-Boc intermediate may be deprotected in situ, using 5% aqueous HCl. Alternatively, the *N*-Boc intermediate may be chromatographed, followed by deprotection using 5% aqueous HCl in THF.[22]

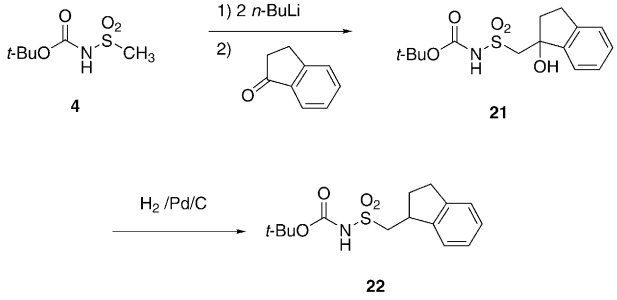
The *N*-Boc sulfonamides were made in two general ways. The first method is by treating primary sulfonamides with di-tertbutyl dicarbonate.[23] The second method, described in Scheme 2, involves generating the dianion of **4** with *n*-BuLi, followed by treatment with a ketone, followed by elaboration to the desired sulfonamides. The dianion reacts readily with these aromatic ketones, even those with enolizable protons. No attempts at optimizing the reaction conditions were made. Until now, the only known example of the elaboration of the dianion of **4** has been to generate the (trimethylsilyl) ethylsulfone protected carbamate.[19]



Scheme 1.

The results of the K_i and IC_{50} assays are shown in Tables 1 and 2.[24] Table 1 compares the activities of the P′ side chains, with Cbz as the common P side functionality. The compounds are compared to **8**, the Cbz analogue of **2**. The simplest methyl sulfonamide **6** had only minimal binding, and serves as a basis for comparing the binding abilities of groups on the P′ side of the inhibitors. It is significant that such a small molecule exhibits any measurable binding. Replacing the methyl with a phenyl **9**, and increasing the hydrophobicity of the substrate, improved the binding 3-fold. Likewise, a 1-naphthyl substitution **10** lowered the K_i 5-fold from **8**. Adding methylene groups between the aryl group and the sulfonamide kept improving the K_i until a maximum potency was achieved with two methylenes as spacers, with the phenyl compound **12** having a slightly lower K_i than the 1-naphthyl compound **14**. A crystal structure of **12** bound to the enzyme was obtained, and it showed that the bond angles and distances between the sulfonamide nitrogen and the Cbz carbonyl are consistant for a hydrogen bond between them. Replacing the phenyl **12** with a cyclohexyl **13** showed that an aromatic group is preferred over saturated ring systems in the binding site. Adding a third methylene as a spacer **15** also saw an increase in the K_i. Modeling indicated that the methylene chain of **15** had to adopt a non-ideal conformation in order to place the phenyl ring in its preferred position in the hydrophobic space between Pro177, Ile176, and Ile239.

As shown in Table 2, the 2-phenylethyl sulfonamide analogues of the peptide based inhibitors **2** and **17** showed significant improvement in K_i and IC_{50}, presumably due to the favorable intramolecular hydrogen bonding interactions of the sulfonamides. The Cbz groups in **2** and **20** serve as mimics of the tyrosine groups of **17** and **19**, with a loss of activity when removing the extra functionalities.



Scheme 2.

Table 1. Structure–activity relationship of caspase-1 inhibitors

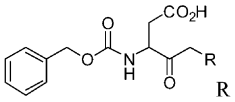
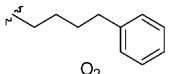
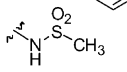
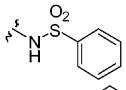
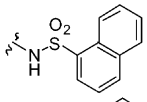
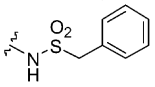
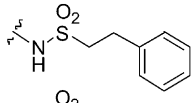
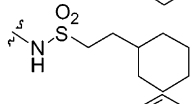
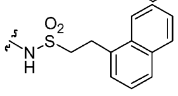
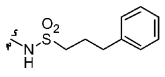
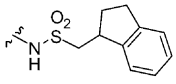
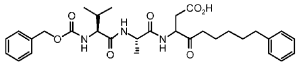
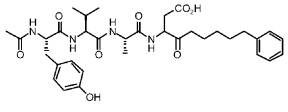
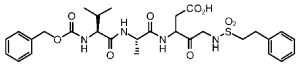
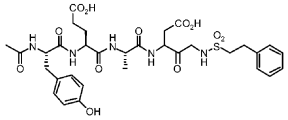
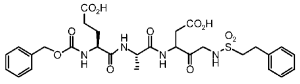
Compd	Structure	Caspase-1 K_i (μM)	Caspase-1 IC_{50} (μM)
			
8		119	1034
6		735	1833
9		37	291
10		22	174
11		18	168
12		11	73
13		33	136
14		16	55.6
15		34.5	245
16		65	194

Table 2. Structure–activity relationship of peptide based caspase-1 inhibitors

Compd	Structure	Caspase-1 K_i (μM)	Caspase-1 IC_{50} (μM)
2		0.1340	0.9760
17		0.0140	0.0710
18		0.0040	0.0720
19		0.0040	0.0034
20		0.0239	0.0253

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22. General experimental for synthesis of the sulfonamides: 3-benzyloxycarbonylamino-4-oxo-5-(2-phenyl-ethanesulfonylamino)-pentanoic acid (**12**): To a solution of 1,1-dimethylethyl [(2-phenylethyl)-sulfonyl]-carbamate (0.28 g) in dry DMF (dimethylformamide) (2 mL) was added potassium *tert*-butoxide (0.12 g) and the resulting solution was added dropwise to an ice-cooled solution of 3-benzyloxycarbonylamino-5-bromo-4-oxo-pentanoic acid 1,1-dimethylethyl ester (0.32 g) in DMF (2 mL). The reaction mixture was stirred at room temperature for 24 h, poured into water (100 mL), and the resulting solution was neutralized with dilute aqueous NH_4Cl. The mixture was extracted with diethyl ether (3×50 mL) and the combined organic layers were washed with water, dilute $Na_2S_2O_3$, and then brine. The solution was dried over sodium sulfate, filtered, and the solvent was evaporated to give the crude intermediate ester (0.49 g) as a yellow oil. The oil was dissolved in methylene chloride (10 mL) and trifluoroacetic acid (10 mL) and the resulting solution was stirred at room temperature for 6 h. The solvent was evaporated to give a yellow oil which was purified by column chromatography (silica; 1% acetone/1% formic acid/methylene chloride gradient to 20% acetone/1% formic acid/methylene chloride) and recrystallized from ether/hexane to give 3-benzyloxycarbonylamino-4-oxo-5-(2-phenyl-ethanesulfonylamino)-pentanoic acid (0.04 g), mp 100–101 °C. (NMR [CD_3OD], ppm) 7.4–7.1 (m, 10H), 5.1 (s, 2H), 4.5 (t, 1H), 4.35 (d, 1H), 4.15 (d, 1H), 3.3–3.0 (m, 4H), 2.9–2.7 (m, 2H).
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