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STRUCTURE-BASED DESIGN OF NON-PEPTIDIC PYRIDONE ALDEHYDES AS INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME.

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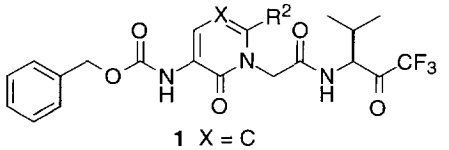
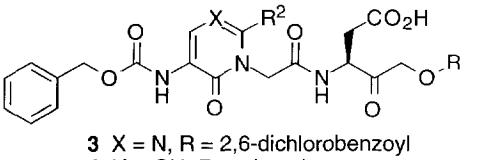
Abstract. Pyridone derivatives, especially with 6-aryl substituents, have been shown to be useful P_2-P_3 peptidomimetic scaffolds for the design of potent inhibitors of ICE. © 1997 Elsevier Science Ltd.

Interleukin-1β (IL-1β) is an important mediator in inflammatory and infectious diseases.[1] Interleukin-1β converting enzyme (ICE; caspase-1), which cleaves its substrates at aspartic acid, converts the inactive form of IL-1β to its mature form.[2,3] Thus, ICE offers an opportunity for the development of small molecules able to disrupt specifically the production of this cytokine as novel antiinflammatory agents. Prototype ICE inhibitors have been shown to block type II collagen induced arthritis in mice, acute inflammation and pyrexia.[4,5] ICE-deficient mice are resistant to endotoxic shock, showing reduced secretion of IL-1α as well as IL-1β.[6] Recently, ICE has been shown to activate IGIF, a potent inducer of interferon-γ (IFN-γ).[7] Mice lac
ng IFN-γ or its receptor are also resisitant to endotoxic shock indicating that ICE may have additional mechanisms by which it may exert proinflammatory effects.[7,8] Although, a number of peptide-based ICE inhibitors have been reported, these compounds are likely to suffer from poor oral bioavailability and rapid clearance.[9]

The results of N-methyl scans[10] and X-ray crystallography data of ICE complexed with inhibitors[11] revealed that ICE binds substrates and active site inhibitors through hydrogen bonds between the enzyme backbone and P_1-NH, P_3-NH, and P_3 C=O in a manner similar to serine proteases of the chymotrypsin superfamily. By substituting the P_3 amino acid with a pyridone or pyrimidone containing lipophilic groups at the 6-position to access the S_2 pocket, researchers at Zeneca converted a peptide-based inhibitor of elastase into a series of potent inhibitors with little peptidic character.[12] In direct analogy to the elastase inhibitors **1** and **2**, a series of pyrimidone and pyridone based ICE inhibitors **3** has been reported.[13] We report the results of our exploration of the S_2 pocket in ICE from the 6-position of the 3-aminopyrid-2-ones.



1 X = C
2 X = N



3 X = N, R = 2,6-dichlorobenzoyl
4 X = CH, R = phenyl

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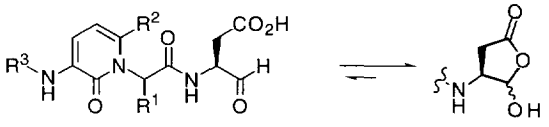
Our investigation of the peptidomimetic inhibitors was based on the tetrapeptide aldehyde ICE inhibitor **4** reported by scientists at Merck.[14] The sixfold loss in potency caused by replacement of the acetyl-tyrosine group at P_4 by dihydrocinnamate (DCA) to give **5**, was acceptable because it simplified the synthesis of new compounds. This group was adopted as our P_4 standard. In the case of pyridone-based elastase inhibitors replacement of P_3-Ala and P_2-Pro with the pyridone-glycine peptidomimetic resulted in only 13-fold loss of potency.[12] However, in ICE, replacement of the P_3-Val and P_2-Ala with pyridone-glycine peptidomimetic results in a dramatic 90-fold drop in enzyme potency (**5** to **8**). The resulting compound **8** has a K_i of 4.8 μM. Comparison of the peptides **6** and **7** suggested that replacement of the P_2-Gly in **8** with alanine should result in a significant improvement in enzyme potency. In fact, this change resulted in a 32-fold increase in potency (compound **9**; K_i = 150 nM).

Table 1. Inhibitory Activity of Pyridones and against Interleukin-1β Converting Enzyme.



Compound	R^1	R^2	R^3	K_i (nM) ICE[a]
8	H	H	DCA[b]	4800
9	(*S*)-CH_3	H	DCA	150
10	H	Ph	DCA	900
11	H	CH_2Ph	DCA	150
12	H	CH_2CH_2Ph	DCA	1200
13	H	CH_3	DCA	3500
14	H	*n*-Bu	DCA	1000
15	(*R,S*)-CH_3	CH_2Ph	DCA	970
16	H	CH_2Ph	Ac-Tyr	54
4	Ac-Tyr-Val-Ala-Asp-H			9
5	DCA-Val-Ala-Asp-H[c]			54
6	Cbz-Val-Ala-Asp-H			55
7	Cbz-Val-Gly-Asp-H			1300

[a]Method reported in ref 10a. [b]DCA = dihydrocinnamoyl. [c]Prepared in ref 10a.

To aid in the design of more potent compounds, we wished to determine the bound conformation of the pyridone-glycine scaffold. However, we were unable to obtain crystals of the complex of ICE and compound **9**. To circumvent this problem the irreversible compound **8a** (Scheme 1), a direct analog of aldehyde **8**, was prepared and formed diffraction-quality crystals with ICE.[15] The crystal structure confirmed the irreversible nature of **8a**, Figure 1. The sulfur of Cys^{285} of ICE displaces the dichlorobenzoate group and forms a covalent bond with the methyl ketone. The P_1 carbonyl oxygen of **8a** is bound in the oxyanion hole, formed by the backbone nitrogens of Cys^{285} and Gly^{238}. The position of the carbonyl oxygen is different from that observed for the thioacetal hydroxy group of the aldehyde structure of **4**. As a result of this interaction, **8a** is shifted ca. 1 Å toward the active site cysteine and P_1 Asp side chain enters the S_1 subsite from a different angle from that observed for **4**.[11a] However, the positioning of P_2-P_4 and the corresponding hydrogen bonds were relatively unaffected compared to the bound structure of compound **4**.[11] Examination of the bound structure **8a**

suggested it should be possible to access a lipophilic pocket near S_2 with a benzyl or phenethyl off of the 6-position of the pyridone ring. This pocket is defined by residues Trp^{340}, Val^{338}, and Pro^{290}. The 6-phenyl (**10**), 6-benzyl (**11**), and 6-phenethyl (**12**) compounds were prepared. The 6-benzyl compound **11** (K_i = 150 nM) is 32-fold more potent than the unsubstituted compound **8**. The 6-phenyl compound **10** and the 6-phenethyl compound **12** are only four- to fivefold more potent than the unsubstituted compound **8**. The 6-methyl (**13**) and 6-*n*-butyl (**14**) compounds were also prepared. The methyl compound **13** is essentially equipotent to **8**, whereas the 6-*n*-butyl compound **14** is 4 to 5-fold more active than **8**. The modest improvement in enzyme potency with the introduction of a 6-phenyl (**11**) compared to the 6-methyl (**13**) is also seen in a set of pyrimidone-based irreversible inhibitors.[13] The combination of the P_2 alanine of compound **9** with the 6-benzyl substituent of **12** to produce compound **15** resulted in a modest loss of enzyme potency. Molecular modeling studies indicate that steric interactions between the P2 alanine and 6-benzyl subsituent hinder compound **15** from adopting the necessary binding conformation. Recently, similar SAR was reported for pyridone-based inhibitors with phenoxymethylketone as the P' warhead.[13a]

To confirm the interaction of the benzyl substituent with the S_2 pocket we sought to solve the X-ray crystal structure of **11**. As seen with compound **9**, the aldehyde **11** would not crystallize with ICE. However, its irreversible analog **11a** (Scheme 1) readily crystallized, Figure 2. The bound conformation of the pyridone-glycine dipeptidomimetic of **11a** is identical to **8a** and the 6-benzyl substituent of **11a** interacts with the residues of the S_2 pocket as predicted.[16]

Figure 1. Crystal Structure of **8a** bound to ICE.[a]

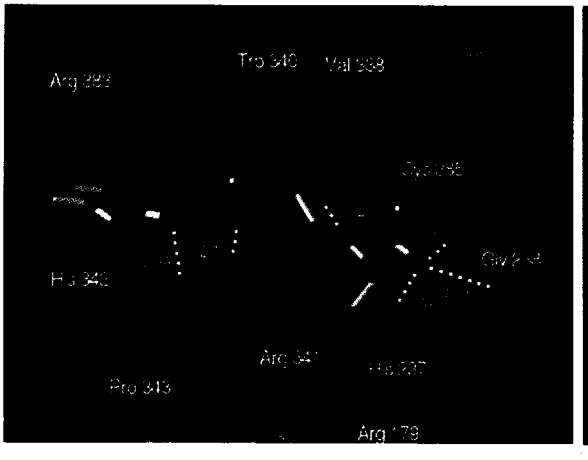
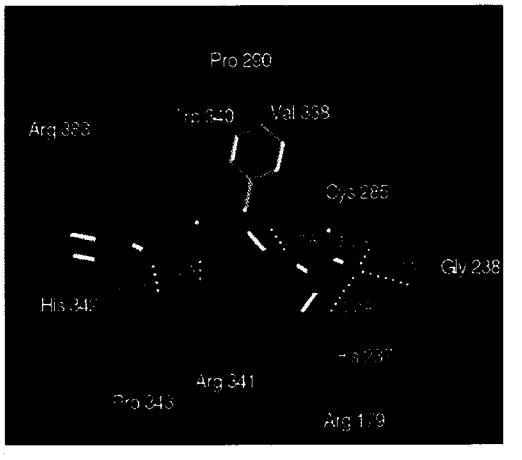


Figure 2. Crystal Structure of **11a** bound to ICE.[a]

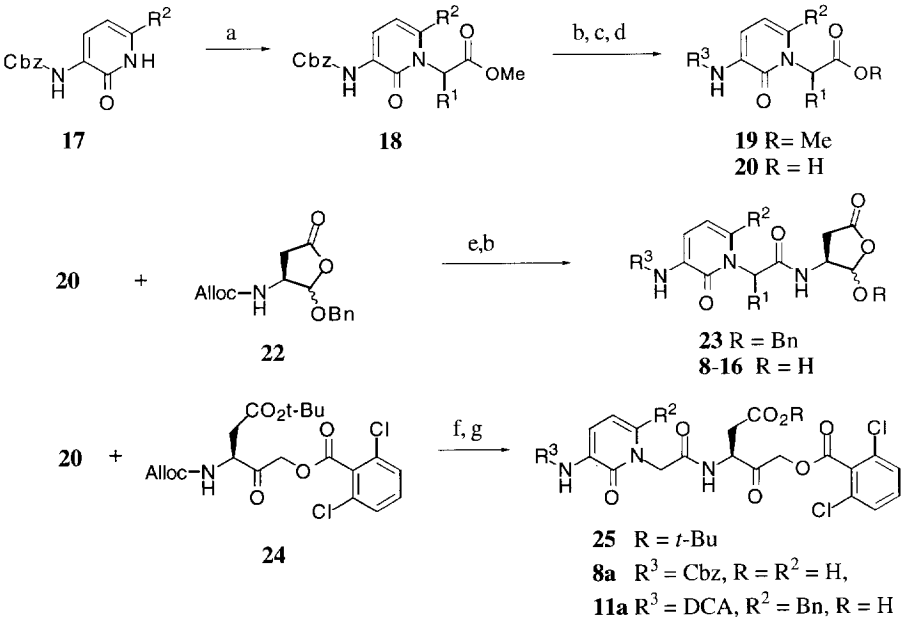


[a] The inhibitor **8a** and **11a** (liqourice bonds) are colored by atom type with oxygen red, nitrogen blue, carbon green, and sulphur yellow. Hydrogen bonds between compound **8a/11a** and the enzyme referred to in the text are shown as dashed lines.

Synthesis of Pyridone-Based ICE Inhibitors[17]

The pyridones **8–16** in Table 1 were prepared by the procedure in Scheme 1. Alkylation of **17** with methyl bromoacetate and NaH gave **18** in 67-97%.[18] Removal of the Cbz of **18** and coupling the resulting amine with dihydrocinnamyl chloride or with Ac-Tyr-(OBn)-OH gave **19**. Saponification of **19** gave the fully functionalized scaffold **20**. In situ removal of the Alloc group of **22** and coupling with **20** following the method of Chapman[19] gave the benzyl protected aspartic acid aldehydes **23**. Deprotection with H_2 and 10% Pd/C gave the desired products **8–16**. The irreversible inhibitors **8a** and **11a** were prepared in a similar manner by coupling **20** to **24** giving *t*-butyl ester **25**.[20] Deprotection of **25** with TFA/CH_2Cl_2 gave the **8a** and **11a**.

Scheme 1. Synthesis of Pyridone-Based ICE Inhibitors.[a]



[a] The generic groups R^1, R^2, and R^3 are defined in Table 1. Reagents: (a) 80% oil dispersion of NaH, $BrCH_2CO_2Me$ or (*R*) $CF_3SO_3CH(CH_3)CO_2Me$, THF; (b) 1 atm. H_2, 10% Pd/C, MeOH; (c) $PhCH_2CH_2COCl$, $NaHCO_3$, dioxane or Ac-Tyr(OBn)-OH, DIEA, HBTU, DMF ; (d) 1 N NaOH (aq), MeOH; (e) (i) Bu_3SnH, cat. $(Ph_3P)_2PdCl_2$, DMF, CH_2Cl_2, 5 min; (ii) HOBt, EDC, 0–20 °C, 18 h; (f) (i) **20**, HOBt, EDC, 25 min; (ii) cat. $(Ph_3P)_2PdCl_2$, **24**, Bu_3SnH, THF; (g) TFA, CH_2Cl_2.

Conclusions

A pyridone-based peptidomimetic was found to be a suitable replacement for P_2-P_3 found in peptide-based ICE inhibitors. X-ray crystallographic and molecular modeling studies were used to improve the potency of the pyridone-based ICE inhibitors. A prototype pyridone-based peptidomimetic **8** was found to be 90-fold less active than its corresponding peptide **5**. Rigidification of the inhibitor backbone of **8** by introduction of alanine at P_2 resulted in a 30-fold improvement in enzyme potency. The lipophilic S_2 pocket of ICE was

identified in the crystal structure of **8a** bound to ICE. Substituents on the 6-position of the pyridone ring of **8** increased potency by filling the S_2 pocket. A 6-benzyl substituent on the pyridone ring (compound **11**; K_i = 150 nM) gives the optimal interaction with S_2 of ICE, resulting in a 30-fold increase in enzyme inhibition. The pyridone **11** is only threefold less active than its corresponding peptide-based inhibitor **5** and is less peptidyl in nature (i.e., **11** has two fewer chiral centers and one less peptide bond than **11**).

Acknowledgement

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15. Crystals of compound **8a** inhibited ICE were grown by vapor diffusion. Protein complex (12 mg/mL in 50 mM citrate, 2.0 mM DTT, pH 6.5) was mixed (6 mL:3 mL) with reservoir (15% PEG 4K, 400 mM $LiSO_4$, 200 mM sodium HEPES, 5 mM sodium cacodylate, 0.5% beta-octyl glucoside, pH 7.0) and allowed to stand over the reservoir solution at 4 °C. A single crystal was mounted directly into a glass capillary from the crystallization droplet for X-ray data collection at 0 °C. X-ray data were collected on an Raxis IIC image plate and processed using software provided by the manufacturer (Molecular Structures Corp. Woodlands, Texas). The crystal had space group symmetry $P4_32_12$, with unit cell dimensions a = b = 64.4 Å, and c = 162.7 Å. R-merge for the data was 8.9%, with I/sig(I) = 2.3 at 2.6 Å resolution. The structure was solved by difference Fourier techniques using coordinates for a previous structure (Brookhaven entry 1ICE) solved in the same space group. The structure was refined against 7219 reflections (F>1sF) in the 7.0–2.6 Å resolution shell (85% completeness) to a R-factor of 18.1%, with deviations from ideal bond lengths and angles of 0.011 Å and 2.9°, respectively. Model refinement was carried out using the XPLOR suite of programs [Bruenger, A. T. (1992) X-PLOR version 3.1 Manual (Yale University Press, New Haven, CO).
16. A crystal of compound **11a** in complex with ICE was grown using similar conditions as compound **8a**, and X-ray data was collected and processed in the same manner. The crystal had unit cell dimensions a = b = 64.2 Å, and c = 162.8 Å. A total of 30790 observations of 13324 unique reflections were measured with an overall agreement (R_{sym}) of 8.1% on intensities and completeness of 89% to 2.7 Å. Data to 2.2 Å was included in the refinement, but the completeness in the shells beyond 2.7Å was limited to 40% due to anisotropy in the diffraction pattern. The structure was refined using X-PLOR to a R-factor of 20.2% versus 12597 reflections (F>1sF) between 7-2.2 Å , with deviations from ideal bond lengths and angles of 0.009 Å and 2.7°, respectively.
17. All new compounds were characterized by ^{1}H NMR and purity determined (>95%) by reverse-phase HPLC. Compound **8**: ^{1}H NMR (CD_3OD) δ 8.32 (1H, d, *J* = 7.5), 7.19 (6H, m), 6.34 (1H, t), 5.1–4.6 (3H, m), 4.32 (1H, m), 2.7 (6H, m). Compound **8a**: ^{1}H NMR (DMSO-d_6) δ 8.96 (1H, d, *J* = 7.3), 8.34 (1H, s), 7.85 (1H, dd, *J* = 7.3), 7.58 (3H, m), 7.35 (5H, m), 6.29 (1H, t, *J* = 7.3), 5.26 (2H, m), 5.15 (2H, s), 4.69 (3H, m), 2.75 (2H, m). Compound **9**: ^{1}H NMR (CD_3OD) δ 8.28 (1H, d), 7.35 (1H, d), 7.20 (5H, m), 6.36 (1H, t), 5.49 (1H, q), 4.59 (1H, t), 4.25 (1H, m), 2.98, 2.74 (2 x 2H, 2 x m), 2.59 (2H, m), 1.57 (3H, d). Compound **10**: ^{1}H NMR (CD_3OD) δ 8.36 (1H, d), 7.49–7.14 (10H, m), 6.27 (1H, dd), 4.54 (3H, m), 4.30 (1H, m), 3.0, 2.73 (2 x 2H, 2 x m), 2.7–2.29 (2H, m). Compound **11**: ^{1}H NMR (CD_3OD) δ 8.25 (1H, d, *J* =7.7), 7.25 (10H, m), 6.15 (1H, 2d, each *J* = 7.7), 4.73 (2H, 2q), 4.59 (1H, m), 4.30 (1H, m), 3.95 (2H, s), 2.98 (2H, m), 2.75 (2H, m), 2.8-2.42 (2H, m). Compound **11a**: ^{1}H NMR (DMSO-d_6) δ 9.24 (1H, s), 8.88 (1H, d, *J* = 7.6), 8.18 (1H, d, *J* = 7.7), 7.60 (3H, m), 7.26 (10H, m), 6.06 (1H, d, *J* = 7.7), 5.23 (2H, ABq), 4.69 (3H, m), 3.93 (2H, s), 2.78 (6H, m). Compound **12**: ^{1}H NMR (CD_3OD) δ 8.18 (1H, d, *J* = 7.8), 7.22 (10H, m), 6.15 (1H, d, *J* = 7.8), 4.75 (2H, s), 4.58 (1H, m), 4.30 (1H, m), 3.01-2.28 (10H, m). Compound **13:** ^{1}H NMR (CD_3OD) δ 8.19 (1H, d, *J* = 7.6), 7.19 (5H, m), 6.21 (1H, d, *J* = 7.6), 4.80 (2H, m), 4.59 (1H, m), 4.30 (1H, m), 2.98 (2H, m), 2.72 (2H, m), 2.80–2.40 (2H, m), 2.30 (3H, s). Compound **14**: ^{1}H NMR (CD_3OD) δ 8.22 (1H, d, *J* = 7.8), 7.24 (5H, m), 6.22 (1H, d, *J* = 7.8), 4.80 (2H, m), 4.60 (1H, s), 4.28 (1H, m), 2.98 (2H, m), 2.72 (2H, m), 2.58 (4H, m), 1.48 (4H, m), 0.97 (3H, t, *J* = 7.1). Compound **15**: ^{1}H NMR (CD_3OD) δ 8.23 (1H, m), 7.27 (10H, m), 6.28 (1H, m), 4.84 (1H, m), 4.53 (1H, m), 4.22 (1H, m), 4.10 (2H, m), 2.96 (2H, m), 2.72 (2H, m), 2.39 (2H, m), 1.21 (3H, m). Compound **16**: ^{1}H NMR (DMSO-d_6/$CDCl_3$) δ 8.16 (1H, d, *J* = 7.7), 7.26 (5H, m), 7.03 (2H, d, *J* = 8.4), 6.61 (2H, d, *J* = 8.4), 6.03 (1H, d, *J* = 7.7), 4.58 (3H, m), 4.44 (1H, m), 4.13 (1H, m), 3.84 (2H, s), 3.07-2.30 (4H, m).
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