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Synthesis and evaluation of tricyclic pyrrolopyrimidinones as dipeptide mimetics: Inhibition of interleukin-1β-converting enzyme

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Abstract—The application of a tricyclic pyrrolopyrimidinone scaffold for the synthesis of peptidomimetic inhibitors of interleukin-1β-converting enzyme (ICE) is reported. The synthesis of the tricyclic scaffold and conversion of it to a variety of target ICE inhibitors were accomplished in 4–5 steps. In vitro biological evaluation of the tricyclic pyrrolopyrimidinones revealed fair to good ICE inhibitors, with the most active compound exhibiting an IC_{50} of 14 nM in a caspase-1 enzyme binding assay.

Interleukin-1β (IL-1β) has been implicated in a number of disease states, including rheumatoid arthritis, osteoarthritis (OA), and sepsis.[1] In recent years, significant attention has been given to IL-1β, as it is widely believed to contribute significantly to the cartilage degradation, joint inflammation and pain associated with OA.[2,3] Interleukin-1β-converting enzyme (ICE) is known to be responsible for processing pro-IL-1β to its active form (IL-1β) and then releasing it extracellularly.[4,5] Therefore, inhibition of ICE should provide a means of controlling IL-1β levels therapeutically, providing disease modification and symptomatic relief for OA patients.

ICE, or caspase-1, is a member of the Caspase family of enzymes, a class of cysteine proteases sharing sequence homology and a preference for an aspartate residue at the P1 position of their substrates.[6] As a result of this preference, most ICE inhibitors reported to date possess an aspartic acid derived cysteine trap that is essential for inhibition. Additionally, it is well known that a hydrophobic P4 residue in the substrate is essential for selective inhibition of caspase-1 over other caspases.[6]

Since Merck's first report of a potent reversible tetrapeptide ICE inhibitor, **1**[7] (Fig. 1), there have been several potent inhibitors described.[8] While most of the focus for inhibitor design has been on constrained dipeptide mimics such as **2**[9], there have been reports of non-peptidic pyrimidinone and pyridone-based inhibitors of ICE, such as **3**–**5**.[10–13] These heteroaryl-based inhibitors are reported to exhibit modest potency for ICE inhibition, demonstrating that constraining the P3 region of the inhibitor in the form of a planar amino pyrimidinone/pyridone ring maintains activity. Tricyclic pyrimidinone **5** effectively constrains the P2 region as well as the P3, but sacrifices a key hydrogen bond donor in the P3 residue.

The key binding elements for ICE inhibition are well known based on the reported crystal structure of tetrapeptide **1** bound to the active site of ICE.[14] A successful scaffold for inhibition of ICE must properly orient the aspartate-derived trap and the P4 hydrophobic group, while maintaining certain hydrogen bonds with the peptide backbone in the S1 and S3 residues (Fig. 2). The P3 carbonyl and NH both participate in critical hydrogen bonds that help to orient the inhibitor in the active site. It was our belief that an appropriately substituted heteroaryl-fused pyrimidinone could effectively mimic

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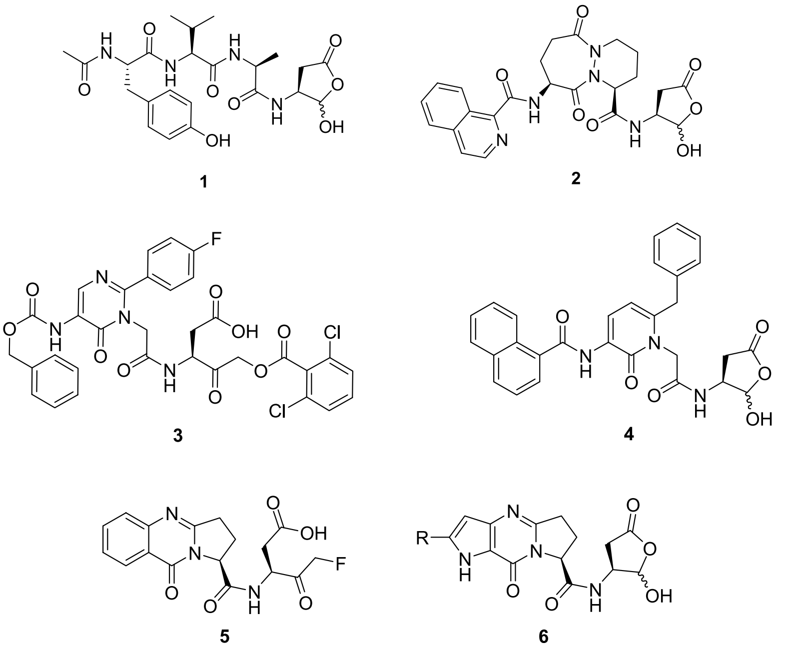


Figure 1. Selected inhibitors of ICE.

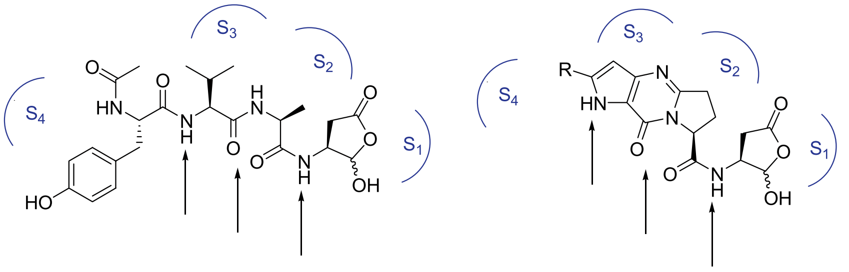
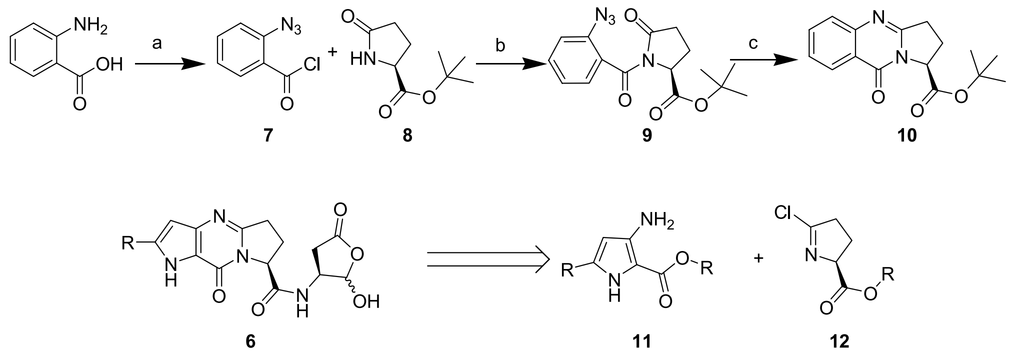


Figure 2. ICE inhibitor binding elements.

the preferred conformation for the P3–P4 region of the tetrapeptide while retaining the key hydrogen-bonding residues, thereby giving a potentially potent, non-peptide ICE inhibitor such as **6**. The R substituent of **6** may additionally provide the hydrophobic interactions essential for selectivity of caspase-1 over other caspases.

Though the proposed inhibitor **6** shares some structural similarity with compound **5**, we felt that incorporation of a pyrrole ring into our inhibitors would necessitate designing a new synthetic pathway. The reported synthesis of the related tricyclic core of **5** involved the diazotization of anthranilic acid, followed by acid chloride formation to yield **7**. Coupling of **7** with the lithium anion of *t*-butyl pyroglutamate gave compound **9**. The central ring was closed with an intramolecular aza-Wittig reaction to yield the tricyclic core **10** in four total steps.[13] (Scheme 1).

We believed that the tricyclic core of **6** could be prepared in a single step from the readily available amino esters **11** and chloroimine **12**. To test the validity of this



Scheme 1. Reagents and conditions: (a) 1: $NaNO_2/HCl/NaN_3/NaOAc$, 2: $SOCl_2$; (b) LDA; (c) PPh_3, xylene, reflux.