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ACTIVATED KETONES AS POTENT REVERSIBLE INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME

Adnan M. M. Mjalli*[1], Kevin T. Chapman, Malcolm MacCoss, Nancy A. Thornberry[2], and Erin P. Peterson.[2]

Department of Medicinal Chemical Research, [2]Department of Biochemistry,
Merck Research Laboratories
Rahway, New Jersey 07065

[1] Current Address: Ontogen Corporation, 2325 Camino Vida Roble,
Carlsbad, California 92009

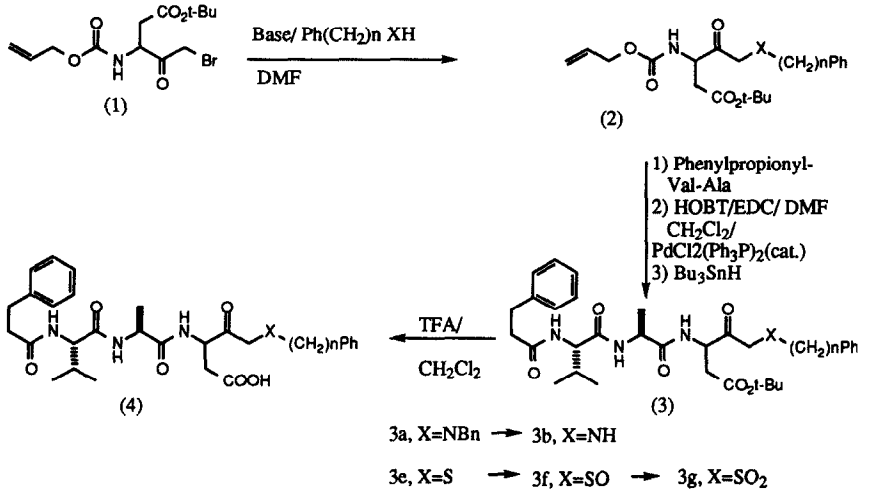
Abstract: Replacement of the β'-carbon of the side chain of the phenylalkyl ketones **4** with a heteroatom or electron-withdrawing group resulted in significant improvement in inhibitory activity against the cysteine proteinase Interleukin1-β Converting Enzyme(ICE).

Our laboratory has been actively involved in developing potent and novel inhibitors of the cysteine proteinase Interleukin1-β Converting Enzyme (ICE), an enzyme implicated in the formation of the cytokine IL-1β which is a potent mediator in the pathogenesis of chronic and acute inflammatory diseases.[1] It has been reported that ICE may play a major role in the inflammation caused by cowpox virus[2] and also in cell death induced by deprivation of nerve growth factor.[3] In both cases ICE was specifically inhibited by the gene product of cytokine reponse modifier gene (*crm*A).

Recently, we reported that phenylalkyl ketones are potent and competitive reversible inhibitors of ICE.[4] Substitution of two fluorine atoms at the α'-position of the carbonyl was also reported in an attempt to activate the carbonyl group towards reaction with the active site thiol of ICE.[5] Replacement of the β'-carbon atom of **5** ($X=CH_2$) with a heteroatom or an electron withdrawing group is an alternative approach to enhance the

potency of these inhibitors against ICE. We report herein the synthesis of a number of activated phenylalkyl ketones and their inhibition of ICE. The bromomethyl ketone **1** was prepared from the N-allyloxycarbonyl-β-t-butyl-aspartic acid following a reported procedure.[6] Reaction of compound **1** with a variety of nucleophiles in the presence of potassium carbonate in DMF afforded ketones of general structure **2** in excellent yield (>90%). Compounds **2** were coupled with 3-phenylpropionyl-Val-Ala using an *in situ* procedure[4] to afford the tripeptide ketones **3** in good yields (60-80%).

Hydrogenation of the N-benzyl compound **3a** using 10% $Pd(OH)_2/C$ in methanol afforded the compound **3b** in 92% yield. Oxidation of sulfide **3e** with one equivalent of *m*-CPBA in dichloromethane afforded sulfoxides **3f** as a 1:1 mixture of diastereomers in 80% yield. Further treatment of sulfoxide **3f** with another equivalent of *m*-CPBA gave the sulfone **3g** in 90% yield. Cleavege of the t-butyl group using a 1:1 mixture of trifluoroacetic acid and dichloromethane afforded the final compounds **4** in quantitative yield.



The compounds which were prepared by the methods described above and their inhibitory activity against ICE are shown in Table 1.

TABLE 1

The inhibition of ICE (K_i) by compounds **4a-4g**

Entry	X	n	K_I(nM)
4a	NBn	2	60
4b	NH	2	4.7
4c	OCO	2	2.7
4d	OCONH	1	120
4e	S	3	11
4f	SO	3	27
4g	SO_2	3	113
5	CH_2	2	100

The phenylethylbenzylaminomethyl ketone **4a** showed enhanced potency against ICE (K_i = 60nM) compared to the carba-analogue **5** (K_i = 100nM) in the phenylalkyl ketone series.[4] Removal of the benzyl group provided the phenylethylaminomethyl ketone **4b** (k_i =4.6nM) which represents 25-fold enhancement of potency compared to the carba-analogue **5**. Significant improvement of the activity was observed when the β-carbon was replaced with an ester (OCO) group **4c**(K_i =2.7nM). A 10-fold improvement in activity with repect to **5** was observed with the phenylpropylthiomethyl ketone **4e** (11.4nM). No further improvement was observed when the sulfide **4e** was oxidized to the sulfoxides **4f**. The sulfone **4g** was less active the sulfoxide possibly as a result of enolization of the carbonyl group as observed by 500MHz NMR.

No evidence of time dependent inhibition or irreversible inhibition was observed in these activated ketones. These results demonstrate that tetrapeptide phenylalkyl ketones **5** (X= CH_2) may be further activated towards probable enhanced reaction with

the active site thiol to provide more potent reversible inhibitors of the cysteinyl proteinase, ICE.

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