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Identification of potent type I MetAPs inhibitors by simple bioisosteric replacement. Part 2: SAR studies of 5-heteroalkyl substituted TCAT derivatives

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Abstract—Systematic SAR studies on the thiazole ring 5-substituent of TCAT derivatives revealed that the introduction of a β-alkoxy or an amino group enhanced the inhibitory activity significantly. The present compounds are representative of specific Co(II)-MetAP1 inhibitors. Before the physiologically relevant metal ions for MetAPs are established, these small molecular compounds could be used as tools for detailed biological studies.

The methionine aminopeptidases (MetAPs) are a novel class of dinuclear metalloprotease responsible for removal of the initiator N-terminal methionine residue of nascent proteins.[1] It is widely found in prokaryotic and eukaryotic cells and exists in two forms: type I (MetAP1) and type II (MetAP2).[2] The removal of methionine represents a critical step in the maturation of proteins for proper function, targeting, and eventual degradation.[3–6] MetAPs present good targets for new antibiotic drug discovery because of their important physiological functions.[7–9] Moreover, MetAPs have been shown, biochemically and structurally, to be the molecular target of the antiangiogenesis agent fumagillin and its derivatives.[10] And inhibitors of MetAPs offer hope as new treatments for bacterial and fungal infections and cancers.[11]

In the preceding paper, we obtained a new series of potent MetAP1 inhibitors through simple bioisosteric replacement from the PCAT series of compounds.[12] Preliminary systematic SAR studies of these TCAT series compounds demonstrated that the introduction of β-methoxy to the 5-alkyl-substituted compounds improved the inhibitory activity against the enzymes dramatically. These series of β-methoxy-containing compounds interested us particularly, because of their prominent potency against *Ec*MetAP1, as well as the structural feature of β-methoxy-containing alkyl substituents at the 5-position, which stimulated us to investigate the effect of the heteroalkyl group at the 5-position on the inhibition of MetAP1s. In this study, we report the synthesis and evaluation of a series of heteroalkyl-containing TCAT derivatives (Fig. 1).

Initially, we synthesized a series of β-alkoxy-containing compounds from the corresponding α,β-unsaturated aldehyde using a similar method with the syntheses of

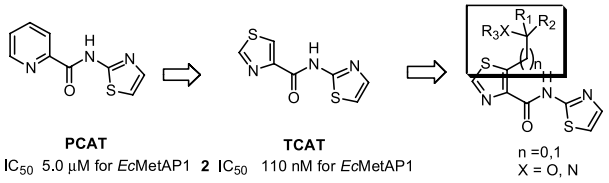

Figure 1.

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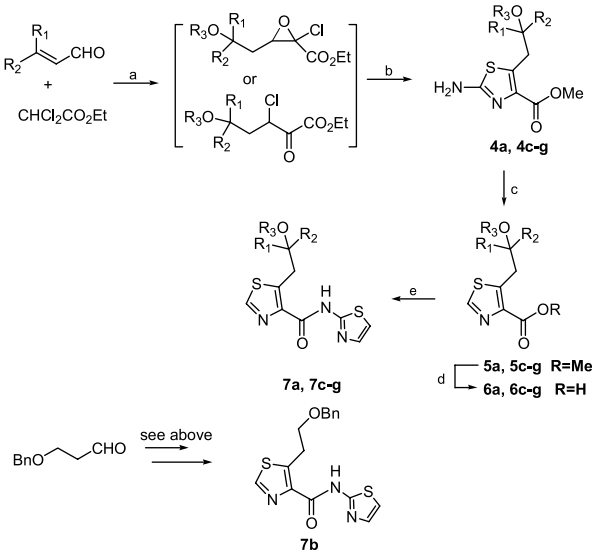
3a and **3b**. As shown in Scheme 1, the Michael addition reaction took place in the first Darzens reaction of ethyl dichloroacetate and the α,β-unsaturated aldehyde with NaOMe or NaOEt in Et_2O, and the resulted intermediates reacted with thiourea to form 2-aminothiazole-4-carboxylate **4a**, **4c**–**g**.[13] Replacement of the 2-amino-group with hydrogen and further basic hydrolysis gave **6a**, **6c**–**g**, followed by condensation with 2-aminothiazole in the presence of EDC in DMF afforded **7a**, **7c**–**g**. Similarly compound **7b** was synthesized from 3-benzyloxypropionaldehyde.

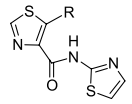
As shown in Table 1, all 7-alkoxy derivatives **7a**–**g** showed good inhibition of *Ec*MetAP1 with IC_{50} values less than 100 nM except **7a**. In particular, the ethoxy derivative **7e** exhibited potent inhibition activity for *Ec*MetAP1 (IC_{50} = 28 nM) and *Sc*MetAP1 (IC_{50} = 150 nM). Although the introduction of methoxy (**7a**) or benzyloxy (**7b**) to the β-position had little effect on the activity against the enzymes, the effect of adding a methyl group to the end of **7a** was striking (**3a** vs **7a**). However, an additional methyl group (**7c**) decreased the *Sc*MetAP1 activity and improved the *Ec*MetAP1 selectivity. Both straight chain and branched chain alkyl derivatives (**7d** and **3b**, respectively) showed good activity against two enzymes. In addition, changing the methoxy to ethoxy increased the activity (**7e** vs **3b**). The results may suggest that besides the importance of the oxygen of the alkoxy, these alkyl groups are reaching out to fill a hydrophobic pocket on the active site of the enzymes. This hydrophobic pocket was able to accommodate medium-sized alkyl groups such as isobutyl and cyclohexyl (**7f** and **g**, respectively).

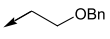
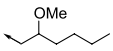
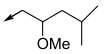
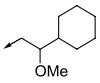
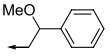
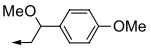
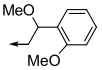
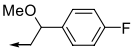
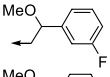
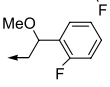
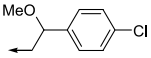
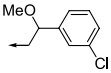
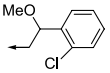
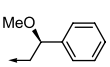
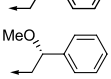
On the basis of the above analyses, we became interested in the syntheses of analogues containing β-methoxy and aryl groups at the 5-position of TCAT. However, attempts to prepare analogous compounds by the condensation of ethyl dichloroacetate with cinnamaldehyde



Scheme 1. Reagents: (a) NaOMe or NaOEt, Et_2O; (b) NH_2CSNH_2, MeOH, reflux; (c) $NaNO_2$, H_3PO_2; (d) LiOH, MeOH–H_2O; (e) 2-aminothiazole, DCC, HOBt, DMF.

Table 1. Inhibition of *Ec*MetAP1 and *Sc*MetAP1[a]



Compound	R	IC_{50} (μM)	
		*Ec*MetAP1	*Sc*MetAP1
1[b]	—	5.0 ± 0.8	7.0 ± 0.1
2	—	0.11 ± 0.02	2.26 ± 0.38
3a		0.074 ± 0.008	0.88 ± 0.08
3b		0.089 ± 0.006	0.50 ± 0.05
7a		0.15 ± 0.02	6.43 ± 0.57
7b		0.09 ± 0.02	4.25 ± 1.47
7c		0.069 ± 0.005	3.21 ± 0.47
7d		0.10 ± 0.01	0.45 ± 0.05
7e		0.028 ± 0.001	0.15 ± 0.02
7f		0.09 ± 0.01	0.50 ± 0.07
7g		0.054 ± 0.010	0.40 ± 0.01
7h		0.043 ± 0.002	0.44 ± 0.06
7i		0.023 ± 0.002	0.31 ± 0.07
7j		0.035 ± 0.006	0.57 ± 0.08
7k		0.057 ± 0.003	0.39 ± 0.08
7l		0.037 ± 0.008	0.34 ± 0.05
7m		0.034 ± 0.002	0.27 ± 0.01
7n		0.033 ± 0.002	0.57 ± 0.13
7o		0.09 ± 0	0.52 ± 0.08
7p		0.17 ± 0.01	0.23 ± 0.05
7q		0.097 ± 0.020	7.53 ± 1.22
7r		0.061 ± 0.008	0.75 ± 0.04
7h(R)		0.036 ± 0.004	0.45 ± 0.02
7h(S)		0.066 ± 0.004	0.45 ± 0.03

[a] Assays were performed as previously described.[12a]
[b] See Ref. 12a.