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AMIDE SURROGATES OF MATRIX METALLOPROTEINASE INHIBITORS: UREA AND SULFONAMIDE MIMICS

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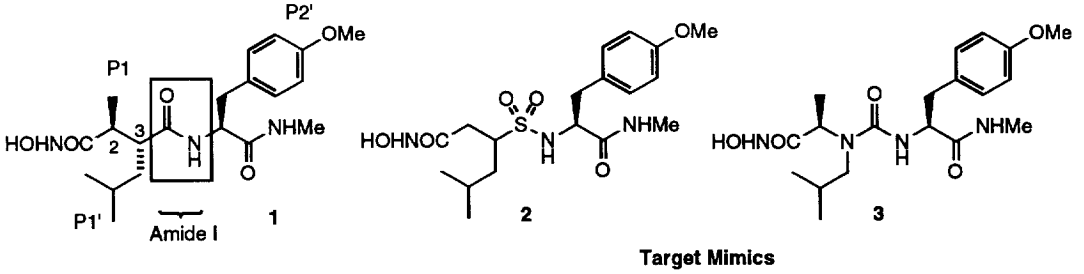
Abstract: A new method for the synthesis of succinyl sulfinyl chlorides was applied to the preparation of sulfonamide peptide mimics of MMP inhibitors. Sulfonamide mimics were determined to be active against MMPs and represent promising new leads for further optimization. Urea mimics were also prepared and found to be unstable and prone to hydantoin formation in protic media.

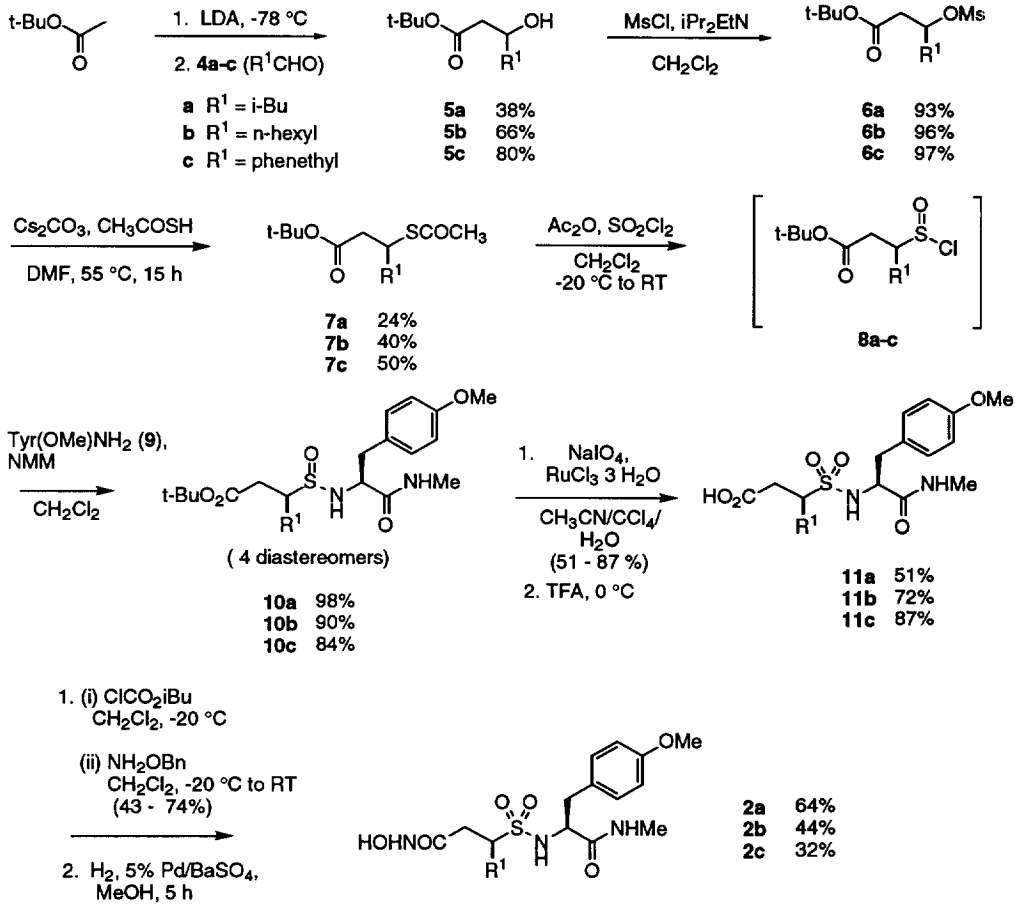
Matrix metalloproteinases[1] are a family of zinc containing enzymes that have been implicated in a number of diseases such as arthritis[2] and cancer.[3] A number of potent inhibitors for these enzymes have been developed in which a Zn liganding group such as thiol, carboxylate, or hydroxamic acid is incorporated into a "peptide" fragment containing recognition elements for the enzyme. Several inhibitors which bind with subnanomolar affinity, have been discovered and show considerable promise for development into therapeutics for the treatment of disease.[4]

Part of our drug discovery effort in this area was directed toward examination of the replacement of the amide bonds in what has come to be recognized as the standard carboxy terminus motif **1** for the matrix metalloproteinase inhibitors. This strategy was pursued to identify compounds that are less peptidic in nature and to also explore novel inhibitor binding modes that might be further optimized and exploited to find MMP selective inhibitors (selective within the class). In this paper we describe the synthesis and in vitro data determined on compounds containing amide I replacements with a sulfonamide **2** and urea **3** (Figure 1).

Figure 1



Scheme 1



Sulfonamide Mimics of Amide I

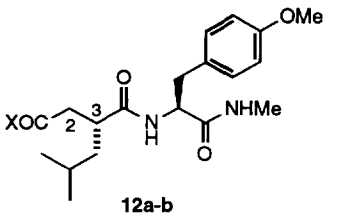
The sulfonamide mimics **2a–c** were prepared as described in Scheme 1. The nature of the P1' group is known to have a significant effect on inhibitor affinity for this class of compounds.[5] To facilitate the investigation of P1' (R^1) substitution, we desired a synthetic scheme amenable to changes in this position. To test this mimic, we simplified the target structure in which the P1 group becomes H. Our synthesis provides mixtures of C-3 diastereomers, however it is worth noting that the use of an asymmetric aldol reaction in step 1 could in principle give optically pure products.

The synthetic challenge in this target (**2**) was the preparation of the sulfinyl chloride succinate precursor **8**. Aldol reaction of *t*-butyl acetate with aldehydes **4a–c** gave the β-hydroxy esters **5a–c** in 38 to 80% yield. High yield conversion to the mesylates **6a–c** followed by nucleophilic displacement with the cesium salt of thioacetate

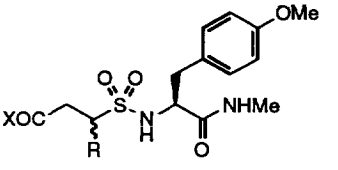
gave intermediates **7a–c**. Conversion to the sulfinyl chlorides **8a–c** was accomplished using the procedure recently disclosed by Liskamp.[6] The sulfinyl chloride succinate derivatives reacted smoothly with amino acid **9** to give diastereomeric mixtures of products **10a–c** in good yields. Mild oxidation with $RuCl_3/NaIO_4$ gave the desired sulfonamides which were then deprotected with acid to give carboxylates **11a–c**. Conversion to the hydroxamic acid was accomplished using the two step procedure described, to give the desired test compounds **2a–c.**

The in vitro enzyme data[7] for the target compounds is presented in Table 1. For comparison, the enzyme data for the carboxylates **11a–c** are also presented in the table. While both the carboxylate and hydroxamate sufonamides were active, in general these compounds were found to be >2 orders of magnitude less potent than the corresponding amide parent compounds (**12a–b**). The carboxylate **11b** was found to be selective for MMP-9 (4x vs MMP-2, 39x vs MMP-1 and >200x vs MMP-3). The n-hexyl P1' hydroxamate **2b** was also found to be more potent against the gelatinases MMP-2 and 9 vs MMP-1 (11x) and MMP-3 (19x). Modeling[8] the sulfonamides in the active site of MMP-3 revealed a less than optimal fit of the sulfonamide mimic replacement, based on an overlap of the hydroxamic acid binding interaction with Zn of compound **12b**. The H-bond normally observed from the carbonyl of amide I to the Leu NH 164 of MMP-3 appears to be energetically less accessible to the sulfonyl oxygen because of the pyramidal nature of the sulfonamide. From this analysis, the more planar arrangement of the amide bond appears to be preferred for maximum binding.

Table 1



12a-b



2a-c
11a-c

			K_i (uM)			
Example	**X**	**R'**	**MMP-1**	**MMP-2**	**MMP-3**	**MMP-9**
11a	OH	i-Bu	>50	3.0	19.1	19.2
11b	OH	n-hexyl	11.2	1.3	10%@50	0.29
11c	OH	phenethyl	22.4	5.3	10%@50	9.9
12a	OH	i-Bu	0.336	0.86	29.4	0.184
2a	NHOH	i-Bu	0.77	0.62	4.1	0.62
2b	NHOH	n-hexyl	2.3	0.43	4.0	0.21
2c	NHOH	phenethyl	0.64	0.55	2.2	1.5
12b	NHOH	i-Bu	<0.01	<0.01	<0.01	<0.01

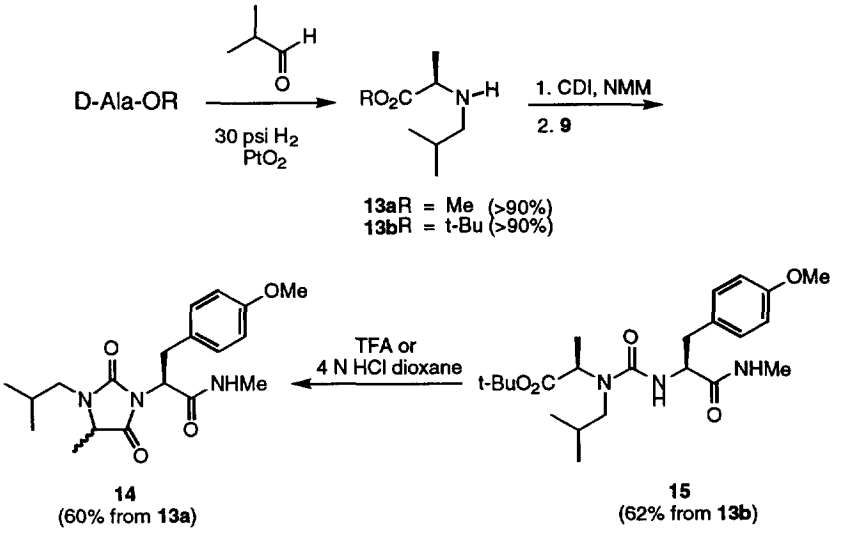
Urea Mimic of Amide I

Our target urea mimic **3** has the asymmetric C-3 replaced with a nitrogen. Although the **R** C-3 stereochemistry has been shown to be preferred, we reasoned that the effect of flattening out this bond might be tolerable, if the overall geometry (binding conformation) of the inhibitor was maintained. This hypothesis was confirmed by molecular modeling. While the overall conformation of the inhibitor was predicted to change from the corresponding amide, the availability of H-bond/acceptor to the enzyme is maintained with this mimic. Preparation of urea **3** is shown in Schemes 2 and 3.

The reaction of **13a** (prepared in 80% yield via reductive amination of D-alanine methyl ester with isobutyraldehyde in the presence of PtO_2) with CDI at 0 °C followed by treatment with **9** gave only hydantoin product **14** in 60% yield with none of the desired urea recovered. We reasoned that the propensity for hydantoin formation could be suppressed by using a more sterically hindered ester.

Reaction of **13b** (prepared in an analogous manner to **13a** starting from the *t*-butyl ester of D-alanine) with CDI and **9** as described above, did give the desired urea **15**, in 62% yield. Our synthetic plan required functional group conversion of the *t*-butyl ester to a hydroxamic acid. However, attempts to remove the *t*-butyl group under standard acidic conditions resulted in complete and rapid formation of **14**. Clearly, cyclization to give the hydantoin product is thermodynamically favored with this substrate. Utilizing neutral conditions did finally facilitate our desired transformation to **3**.

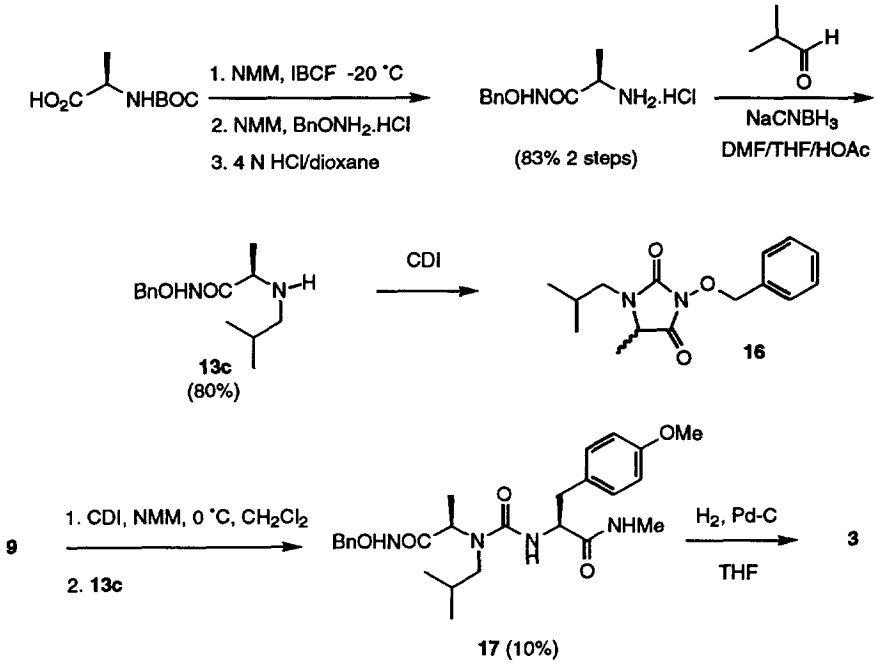
Scheme 2



Preparation of **13c** was accomplished as depicted in Scheme 3 from BOC-D-Ala and O-benzylhydroxylamine, followed by reductive amination with isobutyraldehyde and sodium cyanoborohydride.

Treatment of **13c** with CDI at 0 °C gave only the new hydantoin **16** in 90% yield. Coupling to give the desired urea **17** was realized through inverse addition of **9** to CDI at 0 °C followed by **13c**, albeit in a modest 10% yield. Hydrogenolysis of **17** with 10% Pd-C in THF gave the desired hydroxamic acid urea **3** in 95% yield (hydrogenation in methanol gave hydantoin product **14** exclusively).

Scheme 3



The hydroxamic acid **3** was found to be labile and prone to cyclize to the hydantoin **14**. Urea **3** displayed a T1/2 of 70 min. in methanol at 24 °C as determined by ^{1}HNMR kinetics study. After 15 min. of heating at 40 °C in methanol, **3** was completely converted to **14**. These findings made determining an affinity binding constant for the enzymes of interest difficult, since our normal assay conditions of pH 6.5 aqueous buffer also facilitates cyclization of **3** to **14**. We determined IC_{50}'s for this molecule to be greater than 10 uM, however tlc analysis of the final test mixture indicated a preponderance of **14** in solution.

In summary, sulfonamide and urea amide I mimic MMP inhibitors were prepared and studied. The ureas were found to be unstable and prone to hydantoin formation, making them unsuitable for further consideration as drug candidates. Sulfonamide mimics were prepared using the Liskamp procedure[6] proceeding through a sulfinyl chloride succinate derivative. In general, the amide I sulfonamides were discovered to be more potent against the gelatinases (low μM affinity) as compared to collagenase (MMP-1) and very weakly potent against stromelysin (MMP-3). The sulfonamides represent a novel structural class of MMP inhibitors that are being studied further to optimize for potency and selectivity against metalloproteinases in this class.

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