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ARYL KETONES AS NOVEL REPLACEMENTS FOR THE C-TERMINAL AMIDE BOND OF SUCCINYL HYDROXAMATE MMP INHIBITORS

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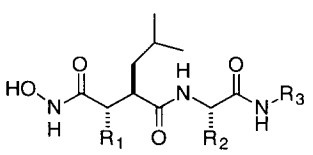
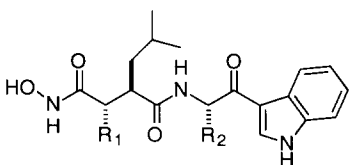
Abstract: A series of succinyl hydroxamate MMP inhibitors were prepared incorporating an aryl amino ketone moiety in place of the more typical C-terminal amino acid amides. Compounds of the C-terminal ketone series displayed potent inhibition of MMPs. Several compounds of the series were shown to be orally bioavailable.

The matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases involved in the remodeling and degradation of extracellular matrix proteins.[1] While the MMPs play a role in many physiological processes, unregulated MMP activity has been implicated in the pathology of a number of disease states, including arthritis and cancer.[2] Compounds inhibiting the spectrum of MMP activity, as well as some with limited subtype selectivity, are currently undergoing clinical investigation.[3]

The design of MMP inhibitors has typically been approached by combining a zinc ligating functionality with structural elements designed to mimic the binding scheme of a peptide substrate,[4] although more recently potent nonpeptide structures capable of achieving key interactions with the enzyme active site have been identified.[3–5] Probably the best studied class of inhibitors are the succinyl hydroxamate inhibitors of general structure **1**.



1



2

During the course of our work on antagonists of platelet-activating factor (PAF), we had found that a 3-acyl indole served as a suitable replacement for an aryl amide moiety.[6] It was believed to represent an isosteric aryl amide equivalent capable of accepting a hydrogen bond from the PAF-receptor. This modification not only enhanced the binding energy of the series, but also stabilized a hydrolysis-prone amide bond and gave rise to many compounds with good oral bioavailability. Since C-terminal aryl amides of general structure **1** (R_3 = phenyl) were reported to be potent MMP inhibitors, we undertook an investigation to see if the corresponding 3-acyl indoles **2** would inhibit the MMPs as well.

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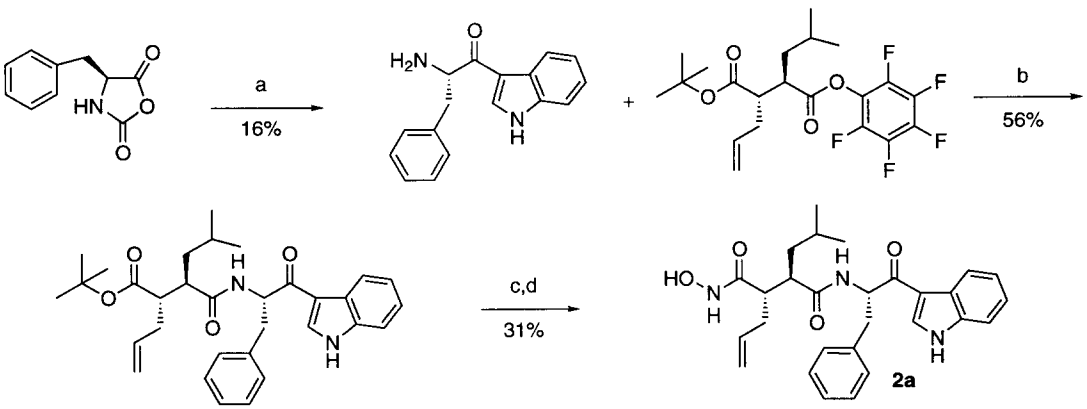
Rapid access to the desired structures was achieved through Friedel–Crafts acylation of indole with suitable amino acid *N*-carboxyanhydrides, providing the desired amino ketones in substantially stereochemically pure form.[7] Coupling with known succinate building blocks and subsequent hydroxamate introduction provided compounds **2**, as illustrated for compound **2a** in Scheme 1.

Scheme 1.

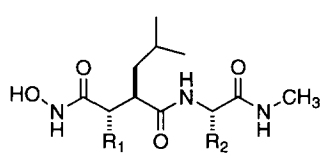


Reagents and conditions: (a) 5 equiv indole, 3 equiv $AlCl_3$, CH_2Cl_2; (b) DMF, 45 °C; (c) TFA; (d) $TBDMSONH_2$, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (EDCI), 1-hydroxybenzotriazole (HOBT), 1-methylmorpholine (NMM), DMF.

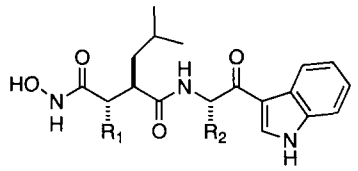
The compounds were tested for MMP inhibition using a fluorometric assay system.[8] As can be seen in Table 1, introduction of the 3-acyl indole moiety provided compounds with comparable MMP inhibitory activity to the corresponding amides **1**. As would be expected by analogy with structures related to **1**, compounds **2** bearing an isobutyl sidechain on the succinate moiety were found to be broad-spectrum MMP inhibitors.

The finding that indole ketones were accepted in place of the amide moiety led us to examine a number of other heteroaryl, aryl and alkyl ketones to determine their suitability as P2′ amide replacements. The heteroaryl amino ketones were typically prepared by addition of metalated heterocycles to BOC-protected phenylalanine methyl ester, with substantial racemization observed in most cases (Scheme 2). The phenyl and alkyl amino ketones were prepared by addition of a fourfold excess of the appropriate organolithium species to BOC-protected phenylalanine, followed by deprotection and isolation as the amine hydrochloride salt. Amino ketones prepared by this route were found to be substantially enantiopure.[9] The amino ketone fragments were converted to compounds **3** in a manner analogous to that shown in Scheme 1.

Table 1. MMP inhibitory activity of amides **1** and indole ketones **2**



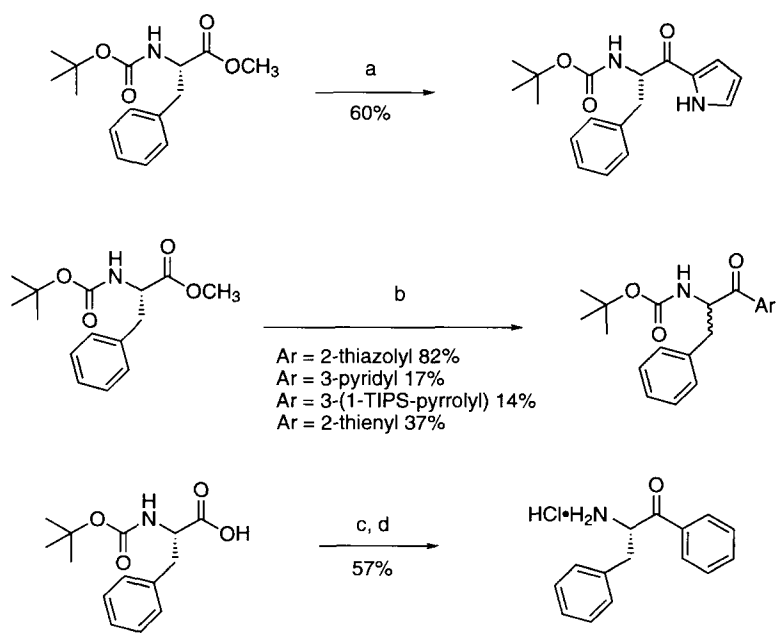
1



2

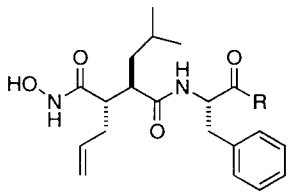
Compound	R_1	R_2	Enzyme Inhibition (IC_{50}, nM) MMP-1	MMP-2	MMP-3	MMP-7
1a	allyl	CH_2Ph	2.2	1.8	12	11
1b (BB-2516)	OH	*t*-Bu	1.1	0.85	10	11
1c (BB-94)	CH_2-S-(2-thienyl)	CH_2Ph	1.2	2.1	0.75	2.4
2a	allyl	CH_2Ph	1.1	1.1	2.3	2.2
2b	allyl	*t*-Bu	1.2	1.6	1.2	0.78
2c	OH	CH_2Ph	5.0	0.60	7.8	1.1
2d	OH	*t*-Bu	0.26	0.38	1.2	0.30
2e	H	CH_2Ph	5.1	1.0	5.6	4.3

Scheme 2



Reagents and conditions: (a) MeMgBr, pyrrole, toluene, -40 to -10 °C; (b) 2.5 equiv ArLi, THF, -78 to 0 °C; (c) 4 equiv PhLi, Et_2O, -78 to 0 °C; (d) 4 M HCl, dioxane.

Table 2. C-Terminal ketone modifications



3

Compound	R	Enzyme Inhibition (IC_{50}, nM) MMP-1	MMP-2	MMP-3	MMP-7
3a (RS)	3-(1-Me-indolyl)	4.7	23	36	29
3b (RS)	3-pyrrolyl	6.2	2.7	6.6	8.0
3c	2-pyrrolyl	2.6	1.1	1.7	1.2
3d (RS)	2-thiazolyl	NT	1100	360	220
3e (RS)	2-oxazolyl	2.7	7.2	1.8	4.2
3f (RS)	2-benzimidazolyl	180	110	54	68
3g	3-pyridyl	14	8.6	10	8.6
3h	phenyl	10	3.4	4.5	3.6
3i (RS)	2-thienyl	NT	6.5	3.2	13
3j	methyl	NT	22	16	45
3k	ethyl	40	33	82	39

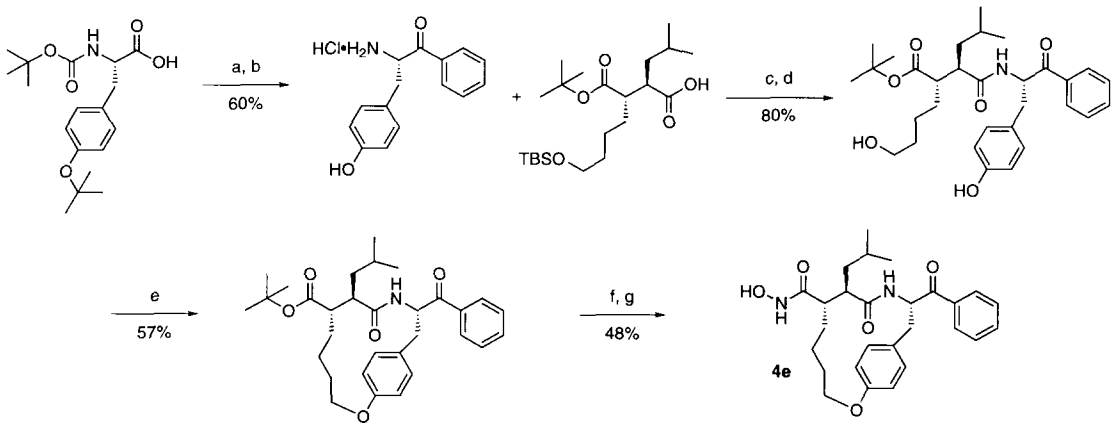
NT = not tested

In cases where racemization occurred during synthesis of the aminoketone, the final inhibitors were tested as a mixture of diastereomers, denoted as (RS) in Table 2. It was found that a number of heteroaryl and aryl ketones were accepted as P2′ amide replacements in terms of maintaining MMP inhibitory activity. In particular, the 2-pyrrolyl- (**3c**) and 2-oxazolyl- (**3e**) ketones gave inhibitors of equal potency to the 3-acyl indole **2a**. No meaningful levels of selectivity were noted among the MMPs assayed.

Recent reports from our laboratories[10] and others[11] have indicated that incorporation of a macrocyclic constraint linking the P2′ side chain of structures **1** to the succinate carbon adjacent to the hydroxamate gives rise to MMP inhibitors with good activity. As incorporation of an amide bond into a macrolactam has been reported to reduce enzymatic hydrolysis,[12] we chose to examine the effect of C-terminal amide replacement in combination with this strategy in the hopes that stabilization of both amide bonds of prototype structure **1** would give compounds with improved pharmaceutical properties. Incorporation of the aminoketones derived from tyrosine into the previously reported[10] synthetic sequence provided macrocyclic inhibitors **4**, as illustrated for the synthesis of **4e** in Scheme 3.

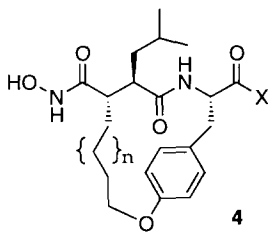
The results shown in Table 3 are consistent with those observed in the acyclic series. Replacement of the exocyclic amide bond (**4a**, **4b**) with a 3-acyl indole (**4c**) or 2-acyl pyrrole (**4f**) provided compounds of comparable in vitro activity, while replacement with a phenyl ketone (**4d**, **4e**) led to a small loss of activity. Small substituents on the phenyl ring were accommodated (**4h**, **4i**), while a bulky *t*-butyl group (**4g**) was not. As in the acyclic series, no meaningful levels of selectivity among the MMPs tested were observed.

Scheme 3



Reagents and conditions: (a) 4 equiv PhLi, Et_2O, -78 to 0 °C; (b) 4 M HCl, dioxane; (c) EDCI, HOBT, NMM, DMF; (d) TBAF, THF; (e) 1,1'-(azodicarbonyl)dipiperidine, Bu_3P, C_6H_6; (f) TFA; (g) $TBDMSONH_2$, EDCI, HOBT, NMM, DMF .

Table 3. Macrocyclic Inhibitors



Compound	X	n	Enzyme Inhibition (IC_{50}, nM) MMP-1	MMP-2	MMP-3	MMP-7
4a	NHMe	1	1.8	5.6	4.0	1.6
4b	NHMe	2	2.1	2.3	2.6	6.1
4c	3-indolyl	2	4.8	6.1	5.1	3.1
4d	Phenyl	2	9.1	3.9	2.7	2.2
4e	Phenyl	1	13	9.5	8.9	3.3
4f	2-pyrrolyl	1	1.9	7.2	7.2	4.2
4g	4-(*t*Bu)-Ph	1	270	91	110	40
4h	4-(SO_2Me)-Ph	1	60	8.5	9.8	5.7
4i	4-($HOCH_2$)Ph	1	5.0	5.1	3.4	1.5

In addition to the excellent in vitro MMP inhibition obtained with these compounds, we were excited to observe that in contrast to compound **1a**, compound **2a** displayed modest oral bioavailability in the rat (Table 4). In addition, compounds **2a**, **2d**, and **4e** displayed bioavailability in monkeys comparable to marimastat (**1b**), a broad spectrum MMP inhibitor currently in clinical trials.

Table 4. Pharmacokinetics

Compound	Species	Dose	t 1/2	F
1a	rat	30 mg/kg po	0.35 h (iv)	0%
1b	monkey	10 mg/kg po	27 h	15%
2a	rat	30 mg/kg po	1.45 h	7%
2a	monkey	10 mg/kg po	20 h	12%
2d	monkey	10 mg/kg po	12 h	10%
4e	monkey	10 mg/kg po	15 h	33%

In summary, a novel series of MMP inhibitors was obtained by replacement of the C-terminal amide moiety of known succinyl hydroxamate inhibitors with heteroaryl and aryl ketones. This transformation provided potent MMP inhibitors on both the cyclic and acyclic succinyl hydroxamate templates. Compounds from both series displayed oral bioavailability in primates.

References and Notes

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