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Keto-1,3,4-oxadiazoles as cathepsin K inhibitors

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Abstract—We have prepared a series of cathepsin K inhibitors bearing the keto-1,3,4-oxadiazole warhead capable of forming a hemithioketal complex with the target enzyme. By modifying binding moieties at the P_1, P_2, and prime side positions of the inhibitors, we have achieved selectivity over cathepsins B, L, and S, and have achieved sub-nanomolar potency against cathepsin K. This series thus represents a promising chemotype that could be used in diseases implicated by imbalances in cathepsin K activity such as osteoporosis.

Osteoporosis can be described as brittle bone disease, manifested by loss of bone mass and an increased tendency to fracture. The condition can be brought on by an imbalance of the functions of osteoblasts, responsible for bone formation, and osteoclasts, which are responsible for bone resorption.[1] The major structural components of extracellular bone are hydroxyapatite and protein, of which the latter is 90% type I collagen. During bone resorption, multinucleated osteoclasts form lacunae on the surface of the bone, into which protons and proteases are secreted. This acidic environment is suitable for the proteolytic degradation of the collagen component.

Cathepsin K, a member of the papain superfamily of cysteine proteases, is the major cysteine protease expressed in osteoclasts.[2] Type I collagen is readily degraded by cathepsin K over a pH range of approximately 4–7, suggesting its potential as a target for osteoporosis therapeutics.

Recent reports on the inhibition of cathepsin K have focused on aldehydes,[3] aminomethyl ketones,[4] hydroxymethyl ketones,[5] ketobenzoxazoles,[6] and most recently nitriles.[7] In a recent article, the use of α-ketothiazoles was reported. By comparison, the lone example of a keto-1,3,4-oxadiazole displayed only micromolar potency.[8] While this ketoheterocycle has been described for inhibition of serine proteases,[9] there are no reports of sub-nanomolar potencies against cysteine proteases. We chose this oxadiazole functionality both for its ease of synthesis via commercially available methyl esters and also for the opportunity to explore prime side binding moieties (R′ in Scheme 1), wherein the inhibitors span the active site histidinium-thiolate-containing catalytic triad, anchored by a reversible hemithioketal bond.

We synthesized amino acid-derived 1,3,4-oxadiazole building blocks as illustrated in Scheme 1. Conversion of commercially available Boc-protected amino acids **1** to the aldehydes **2** (via Weinreb amides) proceeded smoothly. These were used without further purification. We prepared oxadiazoles **3** and subjected them to subsequent coupling with **2** using procedures outlined in Ref. 9. Conversion of the adducts **4** to the free amino alcohols **5** proceeded either through deprotection with HCl in dioxane, or, for more easily handled salts, with anhydrous tosic acid.

To probe the inhibitory effect of inhibitors targeting only the active site cysteine, the P_1 pocket, and the prime side of cathepsin K, we oxidized small samples of protected amino alcohols **4** with Dess–Martin periodinane (Scheme 2) to give the keto-1,3,4-oxadiazoles **6a–d**. We chose the norvaline (Nva) P_1 residue as a hydrophobic chain but without the branching that might favor serine

Keywords: Osteoporosis; Cathepsin; Cysteine protease; Inhibitor; Ketoheterocycle; Reversible; Selective; Potent.
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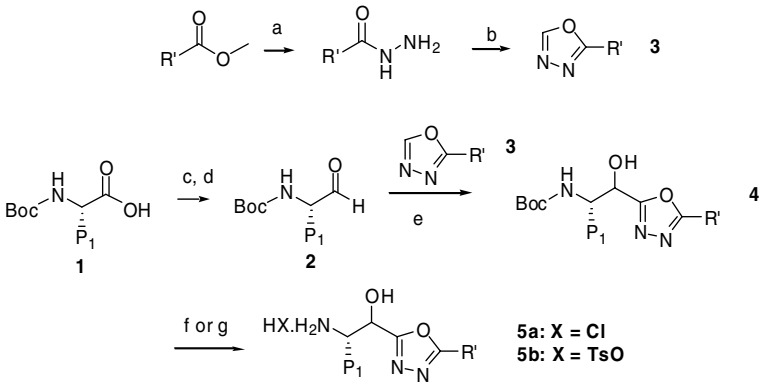
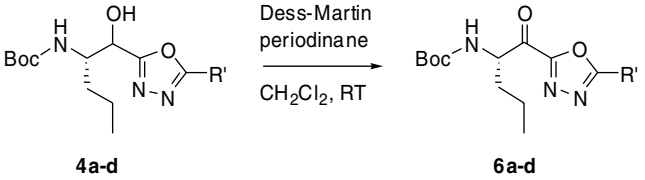


Scheme 1. Reagents and condition: (a) $NH_2NH_2{\cdot}H_2O$; (b) $HC(OCH_3)_3$ (Ref. 9); (c) $CH_3NHOCH_3{\cdot}HCl$, DCC, CH_2Cl_2; (d) $LiAlH_4$, THF, 0 °C; (e) BuLi, then $MgBr_2{\cdot}O(CH_2CH_3)_2$, THF; (f) 4 M HCl/dioxane, CH_2Cl_2; (g) anhydrous TsOH, Et_2O.

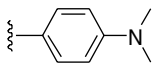
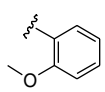
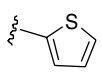


Scheme 2. Preparation of keto-1,3,4-oxadiazoles.

protease inhibition such as elastase or chymotrypsin.[10] Prior work in our laboratories has indicated that the Nva residue occupies similar geometry to the homophenylalanine residue (phenethyl) but without the additional molecular weight encumbrance that can hamper oral bioavailability.[11]

The inhibitory potencies (K_i(app.))[12] of these derivatives are shown in Table 1, reflecting the greatest potency for cathepsin K, with modest potencies for cathepsin S, and little or no inhibition of cathepsins B and L. The lack of P_2 binding moieties in this series suggests that significant potency can be achieved through fine tuning of the prime side moiety, the most potent compound (**6d**) bearing a thiophene residue. It does appear that electron-donating groups on the aromatic ring may have an adverse effect on inhibitory potency (entries **6a** and **6b**), whereas relatively small substituents afford good selectivity for cathepsin K.

Table 1. Inhibition of cathepsins K, B, L, and S by Boc-Nva-1,3,4-keto-oxadiazoles

Compound	R′ =	Cat K	Cat B	Cat L	Cat S
6a		33	>150	130	28
6b		17	>150	>150	19
6c		5.6	>150	>150	130
6d		0.81	120	63	12

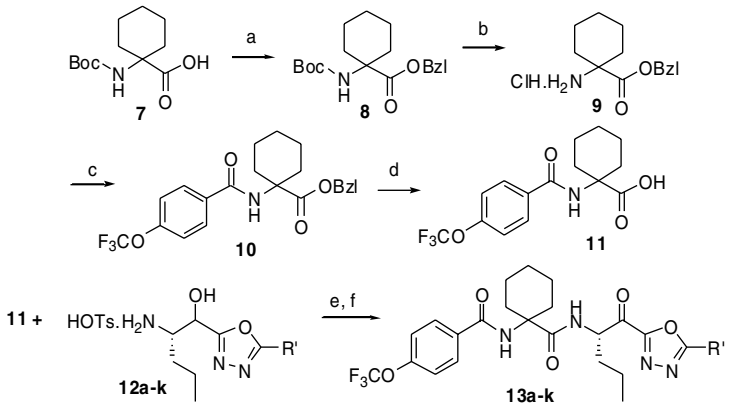
Inhibition constants (K_i(app.)) are given in μM units. Assay methods are described in Ref. 12.

We next prepared a series of inhibitors incorporating a P_2 residue known to be selective for cathepsin K, namely the aminocyclohexylcarboxyl group (Ac6) derivatized as the *p*-trifluoromethoxybenzamide, chosen based on cathepsin K's known preference for 4-substituted benzamides.[7a] Synthesis of the elaborated inhibitors is shown in Scheme 3. Transformation of the commercially available Boc-Ac6OH, **7**, proceeded via benzyl ester formation to give **8**, acidic cleavage of the Boc group to yield **9**, and coupling with 4-trifluoromethoxybenzoic acid in the presence of HATU to give **10**. Conversion to the free acid **11** took place via hydrogenolysis. Coupling with Nva-based amino alcohols **12a**–**h** (synthesized as described in Scheme 1) followed by oxidation to the ketone gave the final products **13a**–**h**, purified by flash chromatography.

This series was then tested as before against the panel of cathepsins K, B, L, and S. Table 2 shows the results of the enzymology.

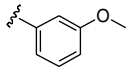
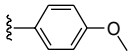
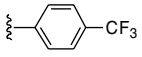
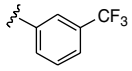
Several patterns emerged from this study. First, the selectivity of the inhibitors for cathepsin K largely paralleled our published observations in the nitrile warhead series. Potency was consistently submicromolar, as expected for benzamide derivatives of P_2-Ac6 containing cathepsin K inhibitors. The most telling observation, however, was the effect of the ketooxazole substituent in the prime side, wherein both size and electronic factors played a part in determining potency.

Unsubstituted or electron-donating groups in the para position of phenyloxadiazoles (**13a**, **13c**) showed consistent double digit nanomolar potency versus cathepsin K, with several 100-fold selectivity over cathepsins B, L, and S. While potency was similar for the *meta*-substituted examples, regardless of electronic push/pull (**13b**, **13e**) the selectivity was reduced. The most remarkable loss of potency was observed in the *p*-substituted electron-withdrawing example **13d**, perhaps as a result of greater



Scheme 3. Reagents: (a) benzyl alcohol, DCC, DMAP, CH_2Cl_2; (b) 4.0 M HCl/dioxane; (c) *p*-$F_3COC_6H_4CO_2H$, HATU, *i*-$PrNEt_2$, DMF; (d) H_2/Pd, EtOH; (e) HATU, *i*-Pr_2NEt, DMF; (f) Dess–Martin periodinane, CH_2Cl_2.

Table 2. Inhibition of cathepsins K, B, L, and S by 4-CF_3OPh-Ac6-Nva-1,3,4-keto-oxadiazoles

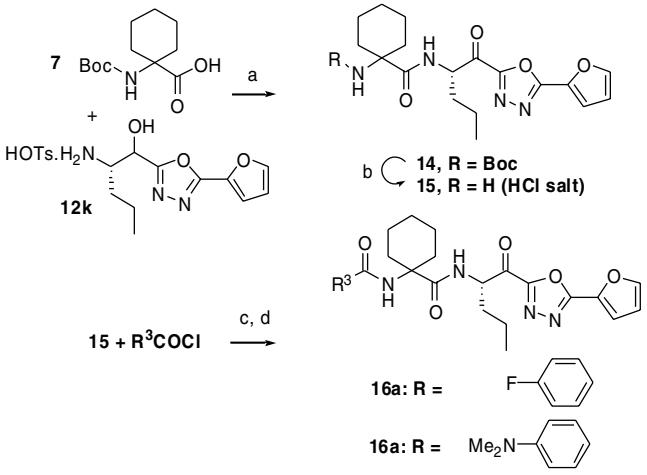
Compound	R′ =	Cat K	Cat B	Cat L	Cat S
13a		0.029	73	19	45
13b		0.037	2.1	7.5	10
13c		0.022	57	37	20
13d		0.55	23	11	13
13e		0.054	1.1	1.4	3.3
13f		1.3	10	10	17
13g		0.035	0.43	4.6	0.8
13h		0.0079	0.098	0.3	0.47
13i		0.0033	0.093	0.16	0.32
13j		0.0052	0.27	2.9	0.76
13k		0.0017	0.22	1.0	0.35

Inhibition constants (K_i(app.)) are given in μM units.

hydration of the active ketone and therefore less electrophilicity. The loss of potency created by the bulky substituent **13f** suggests that this accommodation of hindered groups in the prime side is limited to isopropyl (**13g**) and smaller.

The most potent compounds contained small ketooxadiazole substituents (**13h** and **13i**) but with increased potency across all enzymes, particularly cathepsin B. Nevertheless, at least 30-fold selectivity was achieved in the case of the most potent example, **13i**, whose electronics would also suggest favoring the ketone versus hydrate.

Finally, the thiophene and furan derivatives **13j**, **13k**, respectively, displayed the best balance of potency and



Scheme 4. Reagents: (a) HATU, *i*-Pr_2NEt, DMF; (b) 4.0 M HCl/dioxane; (c) Et_3N, THF; (d) Dess–Martin periodinane, CH_2Cl_2.

selectivity within the series, setting the stage for subsequent improvements.

In an attempt to improve potency to the sub-nanomolar level for cathepsin K inhibitors, mindful of potential shifts between enzyme potency and potency in cellular systems,we explored variations at the P_3 position. Because of the potential for reduced functional selectivity and/or lysosomotropism in cysteine protease inhibitors bearing both positive charges and lipophilic moieties,[13] our goal was to increase potency without resorting to aliphatic amine groups at P_3. Synthesis of this series (Scheme 4) proceeded in a similar manner to that previously described, except that the P_3 moiety was introduced at the penultimate step. Coupling of **7** with **12k** to give **14**, followed by HCl deprotection to yield **15**, coupling with the appropriate P_3 benzoyl chloride, and oxidation gave derivatives **16a** and **16b**.

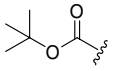
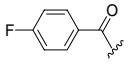
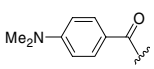
Assay results for the modified P_3 derivatives are shown in Table 3. Interestingly, the simple carbamate **14** retained good potency, but to increase potency to sub-nanomolar levels, the introduction of an amine function para to the carboxamide group served well.

Encouraged by the potency and selectivity of **16b**, we tested this compound in a bone resorption assay measuring the inhibition of resorption of bovine bone mediated by rabbit osteoclasts as a functional measure of cellular potency.[14] At the same time, we tested **16b** in a pharmacokinetic assay (cassette dosing in rats, intravenous route) to establish its suitability for in vivo efficacy studies. Table 4 indicates the results obtained. While the potency of the compound in the bone resorption assay was still reasonably high, this represented a significant shift between enzyme inhibition and functional potency, quite possibly due to membrane permeability.

In addition, while the low clearance value of 18 mL/min/kg was in line with our target, the relatively short mean residence time (MRT, calculated as Vss/CL) indicated that improvements would need to be made to consider the series for evaluation in efficacy models. (Table 5).

To this end, we chose to lengthen the P_1 residue by an additional carbon atom, so as to 'fine tune' hydrophobic interactions in the S_1 pocket without adding too much molecular weight. We prepared the norleucine series (Nle) in a similar manner to the Nva series described above, starting with commercially available materials. We consistently found an increase in potency over the shorter chain by using the four carbon substituent, suggesting a subtle but significant binding effect of this residue as compared to the three carbon chain. We continued to use the furoyl group on the oxadiazole portion of the inhibitor series and explored additional P_2 and P_3 residues to enhance potency and selectivity.

Table 3. Modifications at P_3 for P_3-Ac6-Nva-1,3,4-ketooxadiazoles

Compound	P_3 residue	Cat K	Cat B	Cat L	Cat S
14		0.043	7.3	18	0.96
16a		0.019	0.95	2.9	0.14
16b		0.00095	0.73	0.96	0.70

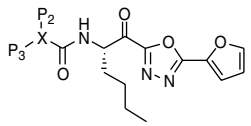
Inhibition constants (K_i(app.)) are given in μM units.

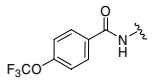
Table 4. In vitro, biology, rat PK analysis of **16b**

Bone res. IC_{50} (μM)	C_{max} (μM)	CL (min/mL/kg)	Vss (mL/kg)	MRT (min)
0.132	2.86 ± 0.55	18 ± 3.2	658 ± 68	37 ± 5.2

PK conditions: formulation: 0.5 mg/mL/compound in DMSO/Cremophor EL/PEG 400/Water 15/5/20/60, pH 4.7. WinNonlin PK Analyses: 2 compartmental. 1/y weighting.

Table 5. P_3-P_2-Nle-1,3,4-ketooxadiazoles, inhibition of cathepsins K, B, L, and S



Compound	P_3	P_2	X	K	B	L	S
17	None		CH_2	52	110	150	9.2
18	None		CH_2	9.6	25	100	2.6
19	None		O	3	34	28	2
20	None		O	0.5	16	14	0.38
21			(*S*)-CH	0.12	48	2.1	0.24
22	CBZ		(*S*)-CH	<0.00025	0.002	0.001	<0.00025
23		Ac6	C	<0.00025	0.075	1.3	0.3

Inhibition constants (K_i(app.)) are given in μM units.

While able to achieve sub-micromolar potency with the simple isobutyl carbamate **20**, we realized the necessity of a designed P_3 unit for sub-nanomolar potency, preferably with a hydrogen bond acceptor in the form of a carbamate or amide carbonyl; the simple trifluoroethylamine P_3 (**21**) was not beneficial in this series. The CBZ-Leu derivative **22** proved to be relatively non-selective against cathepsins S and L, in line with published series cited earlier. We were gratified, however, to see that our optimal P_2 residue and P_3 trifluoromethoxybenzamide group (**23**) yielded an even more potent and selective compound than we had seen in the case of the Nva series (**13k**), We thus illustrated that in this series, tuning of P_3, P_2, P_1, and prime side binding moieties, coupled with an activating electrophile, the 1,3,4-ketooxadiazole, yields potent and selective cathepsin K inhibitors that may be useful in treating osteoporosis and other diseases involving collagen breakdown.

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12. *Enzyme assays.* All enzymes used in these studies, with the exception of human cathepsin B, were produced by Celera Genomics. Cathepsin B was from human liver and was purchased from Athens Research and Technology (Athens, GA, USA). The substrates used in these studies were purchased from the following vendors: Z-Phe-Arg-AMC, Boc-Leu-Lys-Arg-AMC, and Z-Val-Val-Arg-AMC were from Bachem (Torrance, CA, USA) and Z-Leu-Arg-AMC was from Calbiochem-Novabiochem (San Diego, CA, USA). Bovine serum albumin was purchased from the Sigma Chemical Company (St. Louis, MO, USA). Routine buffer components and all other chemicals used in these experiments were of the highest available quality. Enzyme inhibition studies were performed under several sets of conditions; each set was tailored to provide the optimal activity of the given cathepsin being assayed. Each cathepsin was incubated with the inhibitor, present at variable concentrations, under the conditions specified below. Enzyme and inhibitor were incubated together for 30 min at room temperature (21–24 °C) in 96-well U-bottomed, microtiter plates (Falcon, from Becton–Dickinson, Franklin Lakes, NJ, USA). After the preincubation phase, reactions were initiated with the addition of the 7-amino-4-methylcoumarin (AMC) substrate specified below. The hydrolysis of these substrates yields 7-amino-4-methylcoumarin which was monitored fluorometrically (excitation at 355 nm and emission at 460 nm) using an FMAX 96-well plate reader from Molecular Devices (Sunnyvale, CA, USA) interfaced with a Macintosh computer. Under these experimental conditions 1 μM of product produces a fluorescence signal of approximately 125 U. The velocity of the enzyme-catalyzed reaction was obtained from the linear portion of the progress curves (usually the first 5 min after addition of substrate). Apparent inhibition constants, K_i(app.)'s, were calculated from the velocity data generated at the various inhibitor concentrations using the software package, BatchKi (obtained from Dr. Petr Kuzmic, Biokin Ltd., Pullman, WA, USA). BatchKi provides a parametric method for the determination of inhibitor potency using a transformation of the tight binding inhibition model described by Morrison[15] and further refines the appK_i values by nonlinear least-squares regression. The apparent inhibition constant is related to the true thermodynamic binding constant, K_i, by the following relationship: $K_i = \text{app}\,K_i/(1 + [\text{substrate}]/K_m)$ (2). Since substrates are typically supplied in the assays at their K_m, $K_i = \text{app}\,K_i/2$. Specific assay conditions for each cathepsin tested are as follows: cathepsin K: The buffer used to assay this enzyme consisted of: 50 mM MES (pH 5.5), 2.5 mM D,L-dithiothreitol (DTT), 2.5 mM ethylenediaminetetraacetic acid (EDTA), and 10% dimethylsulfoxide (DMSO). Recombinant cathepsin K was supplied at 1 nM. Substrate, Z-Phe-Arg-AMC, was supplied at 40 μM. Human cathepsin B: the buffer used to assay this enzyme consisted of: 50 mM MES (pH 6.0), 2.5 mM DTT, 2.5 mM EDTA, 0.001 Tween 20, and 10% DMSO. Human liver cathepsin B was supplied at 1 nM. Substrate, Boc-Leu-Lys-Arg-AMC, was supplied at 190 μM. Human cathepsin L: the buffer used to assay this enzyme consisted of: 50 mM MES (pH 5.5), 2.5 mM DTT, 2.5 mM EDTA, and 10% DMSO. Recombinant human cathepsin L was supplied at 500 pM. Substrate, Z-Phe-Arg-AMC, was supplied at 10 μM. Human cathepsin S: the buffer used to assay this enzyme consisted of: 50 mM MES (pH 6.5), 2.5 mM β-mercaptoethanol (BME), 2.5 mM EDTA, 100 mM NaCl, 0.001% bovine serum albumin (BSA), and 10% DMSO. Recombinant human cathepsin S was supplied at 500 pM. Substrate, Z-Val-Val-Arg-AMC, was supplied at 60 μM.
13. Falgueyret, J.-P.; Desmarais, S.; Oballa, R.; Black, W. C.; Cromlish, W.; Khougaz, K.; Lamontagne, S.; Masse, F.; Riendeau, D.; Toulmond, S.; Percival, M. D. *J. Med. Chem.* **2005**, *48*, 7535.
14. Falgueyret, J. P.; Oballa, R. M.; Okamoto, O.; Wesolowski, G.; Aubin, Y.; Rydzewski, R. M.; Prasit, P.; Riendeau, D.; Rodan, S. B.; Percival, M. D. *J. Med. Chem.* **2001**, *44*, 94.
15. Morrison, J. F. *Biochim. Biophys. Acta* **1969**, *185*, 269.