Effect of Cathepsin K Inhibitors on Bone Resorption

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On the basis of the pyrrolopyrimidine core structure that was previously discovered, cathepsin K inhibitors having a spiro amine at the P3 have been explored to enhance the target, bone marrow, tissue distribution. Several spiro structures were identified with improved distribution toward bone marrow. The representative inhibitor **7** of this series revealed in vivo reduction in C-terminal telopeptide of type I collagen in rats and monkeys.

Introduction

The human cysteine cathepsin family comprises 11 genes (cathepsins B, C, H, F, K, L, O, S, V, W, and X/Z). They are crucially important for terminal protein degradation in the acidic environment of lysosomes.[1] Among these cathepsins, cathepsin K including its isoforms X and O are thought to be critical in bone collagen degradation. Mice with cathepsin K deficiency exhibit retarded bone resorption, osteosclerosis, and osteopetrosis due to impaired osteoclastic resorption of bone matrix.[2] Most of the histological abnormalities observed in cathepsin-K-deficient mice closely resemble those described for pyknodysostotic humans.[3] In the osteoclastic pit formation assay in vitro, cathepsin K antisense treatment significantly reduces pit volume.[4] Additionally, cathepsin K is specifically and abundantly expressed in the osteoclasts compared with other tissues. The enzymatic analysis with recombinant cathepsins K, L, S, and B suggests that cathepsin K is the only cathepsin that can degrade native type-I collagen in a triple-helix structure.[5] Hence, the development of cathepsin K inhibitors was initiated as a novel approach for bone diseases with enhanced bone resorption.[6]

Starting from the identification of a potent cathepsin K inhibitor with a purine scaffold,[7] we have reported five scaffolds for nonpeptidic cathepsin K inhibitors.[8] The derivatives based on the scaffolds of purine nitrile are potent inhibitors for cathepsin K, but they exhibit only moderate specificity toward the highly homologous cathepsins L and S.[7] The heteroaromatic core of cyano pyrimidine amide has been explored in a series of cathepsin K inhibitors,[9] and also the pyrrolopyrimidine scaffold, derived from the pyrimidine derivatives, contributed to the discovery of new and specific cathepsin K inhibitors.[10] Additionally, we have recently reported two new chemotypes, cyano pryrimidine acetylene and cyano pryrimidine *t*-amine.[8]

Early in the research process, the pyrrolopyrimidine derivatives were found to show higher activity for the target enzymes than other scaffolds.[10] The parallel synthesis approach was taken to seek the structure activity relationship on the P3 moiety of pyrrolopyrimidine derivatives (Figure 1, left). By this approach, structurally diverse P3 moieties can be incorporated using the common intermediate, **1**[10,11] (Figure 1).

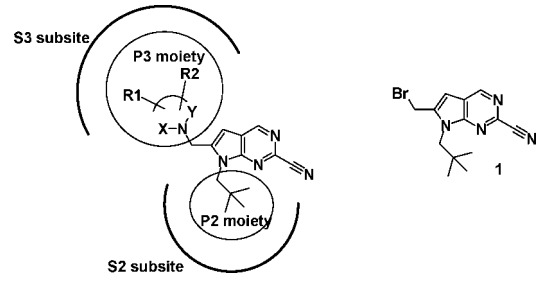

Figure 1. P2/S2 and P3/S3 interaction of cathepsin K inhibitors with pyrrolopyrimidine scaffold and structure of common intermediate **1**.

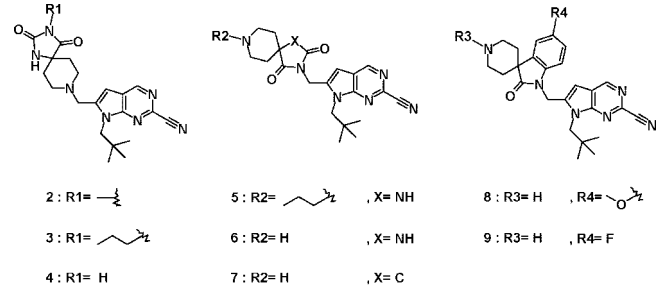

Figure 2. Structures of nonpeptidic cathepsin K inhibitors, **2**−**9**.

While examining the diversity of the P3 moiety, it has become evident that the piperazine analogues had a significant effect on cathepsin K inhibition but not on cathepsins S and L inhibition.[10] However, the early spiro-piperizine analogues (e.g., compounds **2** and **3** (Figure 2)) derived from piperazine analogues did not show a significant in vivo activity and it turned out to have low tissue distribution toward the target tissue, the bone marrow (BM[a]) of rat tibiae. In the search for the P3 moiety that contributes to the BM distribution, we prepared a series of cathepsin K inhibitors having spiro-piperizine analogues as the P3 moiety and tested the concentration of the inhibitors in the BM and the inhibition of C-terminal telopepides of type I collagen (CTx). Here we report on the relation between the BM distribution and in vivo activity with the cathepsin K inhibitors

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[a] Abbreviations: BM, bone marrow; CTx, C-terminal telopeptide of type I collagen.

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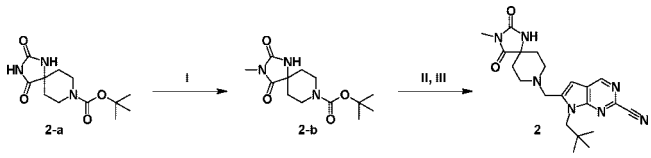
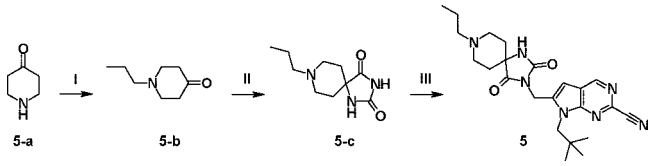
Scheme 1[a]



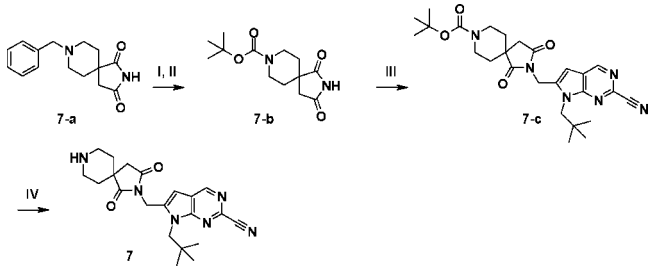
[a] Reagents and conditions: (I) MeI, K_2CO_3, DMSO, rt, 18 h; (II) TFA, CH_2Cl_2, rt, 1 h; (III) **1**, diisopropyl ethylamine, DMSO, rt, 4 h.

Scheme 2[a]



[a] Reagents and conditions: (I) 1-bromopropane, K_2CO_3, DMF, 0 °C to rt, 18 h; (II) NaCN, $(NH_4)_2CO_3$, H_2O, MeOH, rt, 48 h; (III) **1**, K_2CO_3, DMF, rt, 5 h.

Scheme 3[a]



[a] Reagents and conditions: (I) $Pd(OH)_2$, EtOH, acetic acid, H_2, rt, 15 h; (II) di-*t*-butylcarbonate, CH_2Cl_2, 1N NaOH, rt, 15 h; (III) **1**, K_2CO_3, DMF, rt, 15 h; (IV) TFA, CH_2Cl_2, 0 °C to rt, 2 h.

2−**9** (Figure 2) having three different spiro-piperizine groups as the P3 moiety.

Results and Discussion

Chemistry. The syntheses of the representative derivatives are illustrated in Schemes 1, 2, and 3. Compound **2-a**[12] was alkylated by iodomethane in the presence of K_2CO_3 in DMSO. The *t*-butoxycarbonyl (Boc) group of **2-b** was removed by TFA, followed by the coupling with **1** to give **2**. The derivative **3** (Figure 2) was prepared in the same way as for **2** shown in Scheme 1. The nonalkylated **4** was prepared from the deprotected **2-a** and **1** in the presence of K_2CO_3 in DMSO.

The synthesis of **5** is outlined in Scheme 2. 1-Bromopropane was coupled with **5-a** to afford **5-b**. The cyclization followed by a ring closure afforded 8-propyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (**5-c**). The coupling of **1** and **5-c** was performed in DMF to yield **5**. The protected **6** was prepared from **1** and **2-a** and the Boc group was removed by TFA to give the desired product **6**.[11] The protection group of **7-a**[13] was exchanged with the Boc group. The intermediate **7-b** was coupled with **1** and the acid labile group of **7-c** was removed to give **7** (Scheme 3).

The preparation of **8** and **9** was performed by the synthetic methods reported previously.[14]

Biology. All of the compounds **2**−**9** listed in Table 1 were found to be significantly active for human cathepsin K and less active for human cathepsins S and L. Rat cathepsin K has 88% identity compared to the human enzyme. The IC_{50} value for rat cathepsin K was higher than that of human cathepsin K. This would be due to the differences in two S2 residues at the positions 134 and 160. Species differences between human and rat in the substrate specificity of cathepsin K will be covered in a future publication.

The pharmacokinetic profiles of all compounds discussed here were evaluated by cassette dosing with a LC-MS/MS detection as depicted in Table 1. The compounds were administered intravenously and orally to male Sprague−Dawley rats. The half-lifes of **5**−**9** were over 2 h and their volume of distribution was relatively larger than that of **2**−**4**. The pharmacokinetics parameters indicated that inhibitor **9** had the longest elimination half-life ($t_{1/2}$ = 6.6 h) among the compounds listed in Table 1. The dealkylated inhibitor **6** exhibited a higher clearance and a larger volume of distribution than **2**−**5** and showed no oral bioavailability. The largest volume of distribution and the highest plasma clearance and bioavailability were observed for **7**, which differs from **6** only by the replacement of NH with carbon.

Bone resorption is measured in rats and monkeys in vivo by measuring serum and urinary level of CTx as a collagen degradation product with the RatLaps and CrossLaps ELISA, respectively.[15,16]

The effect of the cathepsin K inhibitors **2**−**9** on CTx was evaluated in intact rats following oral administration once a day for 11 days at the dose of 100 mg/kg (Table 2). Inhibitor **2** displayed a fairly weak inhibition in vivo against cathepsin K mediated collagen degradation even though it had sufficient in vitro potency against rat cathepsin K (IC_{50} = 12 nM). Similarly, treatment with **3** or **4** did not result in a significant reduction in the CTx. In contrast, compound **5**, which was a weaker rat cathepsin K inhibitor (IC_{50} = 27 nM) compared to **2**, significantly inhibited collagen degradation by 89.9%.

The serum concentration of **2**−**9** at 25 h after the final administration was examined as shown in Table 2. Although compounds **3** and **4** showed about a 9-fold higher serum concentration than **2**, they displayed almost no activity. In contrast, treatment with **5** did not give a higher concentration in the serum than that of **3** and **4**, but it showed the strongest CTx inhibition among the derivatives listed in Table 2. Inhibitors **7** and **8** prevented collagen degradation by 73.2% and 68.0% while producing a higher concentration in serum than **5**. The highest concentration in the serum was observed for **9**, however it only displayed moderate CTx inhibition. Considering the results described above, it is unlikely that the two factors, the IC_{50} value against rat cathepsin K and the concentration of the compounds in serum at 25 h after administration, can sufficiently explain the in vivo activity differences between the compounds.

Bone is actively resorbed by osteoclasts that reside on the bone surfaces and secrete protons to dissolve bone minerals, followed by bone matrix degradation by proteases. Cathepsin K inhibitors exposed to the bone surface is thought to mainly contribute to the antibone resorptive effect. Therefore, the distribution of the inhibitors to the target tissue was evaluated by measuring the concentration of the compounds in the BM of rat tibiae.

As shown in Table 2, the concentration of the inhibitors in the BM was measured to compare to that in serum at 25 h after administration. The concentration in the BM for **2** and **3**[17] was 1.5- to 4.7-fold higher, respectively, than their serum concentrations, while **4** revealed the countertrend. In contrast to **2**−**4**, efficacious **5**−**9** on the CTx inhibition gave more than 30-fold higher concentration in the BM than in the serum. Additionally, their BM/serum ratios were much higher than **2**−**4**. Compound **9** achieved the highest concentration in the BM, whereas the concentration of **9** in the BM was not closely linked to the

Table 1. Inhibitory Activity of Compounds **2**−**9** against Cathepsins K, S, and L and Rat Pharmacokinetics Data

	IC_{50} (nM)				PK profile in rat[e]			
compd	Cat K[a]	Cat S[a]	Cat L[a]	RCat K[c]	(iv) $t_{1/2}$ (h)[f]	(iv) CLp (L/h/Kg)[g]	(iv) V_{dss} (L/Kg)[h]	F (%)[i]
2	<1.0[b]	>1000[b]	>1000[b]	12	1.4	2.1	4.3	144
3	<1.0	>1000	>1000	ND[d]	1.9	2.7	6.7	58
4	<1.0	>1000	>1000	ND[d]	1.6	4.7	5.9	42
5	<1.0[b]	770[b]	>1000[b]	27	2.8	5.1	17.3	49
6	<1.0	>1000	>1000	76	3.3	14.7	59.2	*j*
7	<1.0[b]	>1000[b]	>1000[b]	30	4.7	14.3	97.2	98
8	<1.0	>1000	>1000	44	4.9	10.9	73.6	29
9	1.7[b]	>1000[b]	930[b]	78	6.6	7.9	78.4	36

[a] Inhibition of recombinant human cathepsins K, L, and S in a fluorescence assay.[9] [b] The IC_{50} values were quoted from the previous literature.[10] [c] Recombinant rat cathepsin K. [d] Not determined. [e] Dosage was mentioned in Supporting Information. [f] Terminal elimination half-life (noncompartmental estimate). [g] Plasma clearance. [h] Volume of distribution at steady state. [i] Bioavailability. [j] Incapable of measurement due to no absorption in rats.

Table 2. Concentration of **2**−**5** and **7**−**9** in Serum and Bone Marrow and Inhibition % of C-Terminal Telopeptides of Type I Collagen with **2**−**5** and **7**−**9**[a]

		conc of inhibitor in		
compd	inhibition of CTx[b](%)	serum (nM)	BM (nM)[c]	ratio of BM/serum
2	6.8	64	302	4.7
3	11.3	545	832	1.5
4	−7.9	557	381	0.7
5	89.9	133	17620	132.5
7	73.2	960	33496	34.9
8	68.0	288	45777	159.0
9	36.2	1200	118752	99.0

[a] The compounds were administered orally at a dose of 100 mg/kg daily one a day for 11 days. [b] CTx secreted into urine for 24 h after the final compound administration on day 11 in rats. Values are expressed as percentages of vehicle-treated controls. [c] Compound concentrations in the BM and serum were measured 25 h after the final treatment on day 11.

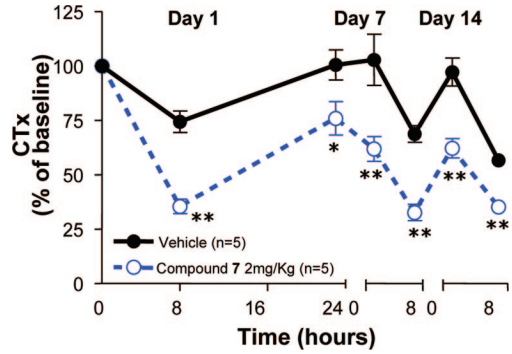


Figure 3. Effect of compound **7** on bone resorption in cynomologus monkeys. Compound **7** was administrated orally to the monkeys at a dose of 2 mg/kg daily one a day for 14 days. Data are means and SEM, $n = 4, 5$. Significant difference from vehicle control group (*: $p < 0.05$, **$p < 0.01$ by t- test).

outcome of the CTx inhibition. These findings suggest that the inhibition of CTx is accompanied by a high concentration in the BM and a high BM/serum ratio.

The data given in Table 2 underscore the importance of a high concentration in the target tissue for the in vivo activity in rats. The efficacious cathepsin K inhibitors **7**−**9** would be those that distribute themselves to the BM, and the capacity of the distribution is affected by the spiro structure in the P3 moiety. Interestingly, a preferential distribution of statins to the BM has also been found to increase cancelous bone volume in rats[18,19] even though the statins bear no structural similarity to **7**−**9**.

Finally, efficacy of compound **7**, which strongly reduced rat CTx with a high concentration even 25 h after administration in the target tissue (Table 2) and showed no signs of toxicity on prolonged administration (data not shown), was tested in vivo in cynomologus monkeys as shown in Figure 3. In vehicle-treated monkeys, CTx showed daily fluctuations, with 25−50% reduction in late afternoon. Compound **7** at 2 mg/kg/day significantly reduced CTx degradation at 8 h after the first oral administration. The CTx reduction continued for 24 h. The efficacy persisted on days 7 and 14 of continuing treatment. CTx reduction was observed before and 8 h after the administration on those days, and no signs of tolerance were observed.

Conclusion

The concentration of cathepsin K inhibitors in the target tissue and the BM/serum ratio were good, predictive parameters for antibone resorptive efficacy in vivo in rats. This characteristic of the distribution to the BM was shared by compounds that had pyrrolopyrimidines with 2,8-diazaspiro[4.5]decane-1,3-dione or the spiro[indole-3,4′-piperidin]-2(1*H*)-one analogue as the P3 moiety. In the monkey study with the representative inhibitor **7** of this series, the antibone resorptive efficacy was detected within 8 h after the compound administration. The efficacy continued without tolerance through the repeated treatment period of 14 days. From the data available in the present study, **7** may be a promising cathepsin K specific inhibitor, which can be used as an antiresorptive drug for the treatment of bone diseases with enhanced bone resorption such as osteoporosis and tumor-induced osteolysis.

Experimental Section

General Method. All starting materials were obtained from commercial sources unless otherwise specified. ^{1}H- NMR spectra (δ, ppm) were recorded using a Bruker DRX400 digital spectrometer (400 MHz). The high resolution mass spectrum was obtained with a Bruker-Daltonics-APEX III ca. 9.4 Tesla.

1,3-Dioxo-2,8-diaza-spiro[4.5]decane-8-carboxylic Acid *tert*-Butyl Ester (7-b). To 8-benzyl-2,8-diaza-spiro[4.5]decane-1,3-dione (**7-a**)[13] (28.3 g, 0.11 mol) and $Pd(OH)_2$ (8.5 g) in a 2 L flask, EtOH (438 mL) and acetic acid (5.5 mL) were added at ambient temperature. The reaction mixture was stirred under H_2 at room temperature for 15 h. The catalysts were removed by filtration, and EtOH was evaporated down to give 2,8-diaza-spiro[4.5]decane-1,3-dione in quantitative yield.

To a suspension of 2,8-diaza-spiro[4.5]decane-1,3-dione (4.2 g, 25.2 mmol) in CH_2Cl_2 (60 mL), 1N NaOH (26 mL, 26 mmol) and di-*t*-butyldicarbonate (6.1 g, 27.7 mmol) in CH_2Cl_2 (20 mL) were added at ambient temperature. The reaction mixture was stirred for 15 h. Then 10% citric acid was added to the reaction mixture, and the pH of the mixture was adjusted to 5. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated under vacuum to give a solid product, which filtrated with diethyl ether. Yield: 51%; $R_f = 0.25$ (*n*-hexane:ethyl acetate = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (brs, 1H), 4.04−4.01 (m, 2H), 3.02−2.97 (m, 2H), 2.63 (s, 2H), 2.02−1.95 (m, 2H), 1.57−1.53 (m, 2H), 1.47 (s, 9H).

2-[2-Cyano-7-(2,2-dimethyl-propyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-ylmethyl]-1,3-dioxo-2,8-diaza-spiro[4.5]decane-8-carboxylic acid *tert*-butyl ester (7-c). **1** (1.0 g, 3.25 mmol) and **7-b** (0.82 g, 3.42 mmol) were dissolved in DMF (15 mL), and potassium carbonate (0.58 g, 4.23 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 15 h and quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with water and brine and dried over magnesium sulfate. Chromatography on silica gel (eluent; *n*-hexane:ethyl acetate = 2:1) gave 1.56 g of desired **7-c** in 97% yield. R_f = 0.30 (*n*-hexane:ethyl acetate = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 6.62 (s, 1H), 4.91 (s, 2H), 4.25 (s, 2H), 3.88−3.85 (m, 2H), 2.93−2.89 (m, 2H), 1.68−1.67 (m, 4H), 1.40 (s, 9H), 0.99 (s, 9H).

7-(2,2-Dimethyl-propyl)-6-(1,3-dioxo-2,8-diaza-spiro[4.5]dec-2-ylmethyl)-7*H*-pyrrolo[2,3-*d*] pyrimidine-2-carbonitrile (7). To a solution of **7-c** (1.5 g, 3.1 mmol) in CH_2Cl_2 (20 mL), TFA (5 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After removal of the solvent, saturated sodium bicarbonate was added to the residue and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with water and brine and dried over magnesium sulfate and concentrated under vacuum to give desired product **7**. Yield: 91%; R_f = 0.15 (CH_2Cl_2:MeOH = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 6.59 (s, 1H), 4.91 (s, 2H), 4.34 (s, 2H), 3.16−3.13 (m, 2H), 2.72−2.69 (m, 2H), 2.66 (s, 2H), 2.02−1.95 (m, 2H), 1.69 (brs, 1H), 1.48−1.45 (m, 2H), 1.03 (s, 9H). HRMS: 395.2190 $[M + H]^+$ (calcd 395.2195).

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Supporting Information Available: Experimental procedures for the synthesis of compounds **2** and **5** and characterization (^{1}H NMR and HRMS) of compounds **3**, **4**, **6**, **8**, and **9**. Description of pharmacokinetics analysis, urinary CTx assay in rats and monkeys. This material is available free of charge via the Internet at http://pubs.acs.org.

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