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Investigation of ketone warheads as alternatives to the nitrile for preparation of potent and selective cathepsin K inhibitors

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ABSTRACT

Amino ketone warheads were explored as alternatives to the nitrile group of a potent and selective cathepsin K inhibitor. The resulting compounds were potent and selective inhibitors of cathepsin K and these nitrile replacements had a significant effect on metabolism and pharmacokinetics.

Osteoporosis is a condition where bone becomes weak and brittle. Consequently, osteoporosis significantly increases the risk of bone fractures. The condition is caused by an imbalance between bone formation and bone resorption, and it is believed that the lysosomal cysteine protease cathepsin K (Cat K) plays a key role in the degradation of the bone matrix.[1] More specifically, Cat K is involved in the degradation of type I collagen, which is the major organic component of the bone matrix.

In fact, several studies have shown that Cat K deficiency leads to an increase in bone mineral density (BMD).[2] As a consequence, it has been hypothesized that Cat K inhibitors could be used for the treatment of osteoporosis, and there has been considerable effort directed towards the development of potent and selective Cat K inhibitors over the last decade.[3] Recently, two Cat K inhibitors[4] have demonstrated reduction in bone resorption biomarkers and an increase in BMD in the clinic.

Most reported inhibitors of Cat K contain electrophilic 'warheads' which covalently bind to the catalytic Cys 25 residue of the enzyme. Several of these warheads, such as nitriles[5] and ketones,[6] bind reversibly to this active site cysteine and thus have the potential to be safer than earlier, irreversible inhibitors such as vinyl sulfones and epoxides.[7] Recently, we have reported the development of the reversible, non-basic, potent and selective Cat K inhibitor, odanacatib **1** (MK-0822) (Fig. 1).[8]

Selective and potent inhibition of cathepsin K is achieved by taking advantage of interactions with the six main subsites in the active site, which are designated S1, S2, S3 in the C-terminal direction and S1′, S2′, S3′ in the N-terminal direction of the scissile bond (prime side). The X-ray crystal structure of an odanacatib-like inhibitor bound to Cat K reveals several important inhibitor/protein interactions.[5f] The nitrile forms a hydrogen bond-stabilized thioimidate intermediate with Cys 25. The leucine moiety interacts with the hydrophobic S2 subsite and the biphenyl moiety with the S3 subsite. Also of importance, are the hydrogen bond interactions of the trifluroethylamine amide isostere with Gly 66. Furthermore, odanacatib does not interact with the prime side of Cat K.

After the discovery of odanacatib, we decided to direct effort towards the development of a structurally distinct series of reversible inhibitors. Since ketones have been extensively used as reversible Cat K inhibitors,[4] we decided to investigate replacement of the nitrile with previously reported cyclic ketone warheads.[6c,d,9] Substitution on the α-aminoketone nitrogen could conceivably allow interactions on the prime side of the scissile bond (Fig. 2). For example, carbonyl/sulfonyl substitutions could lead to hydrogen bond interactions with Trp 184 in S3′, as well as hydrophobic interactions with S2′. These interactions are of particular interest,

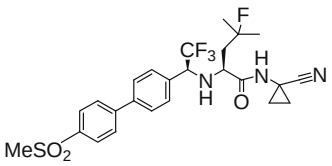

Figure 1. Odanacatib, **1**.

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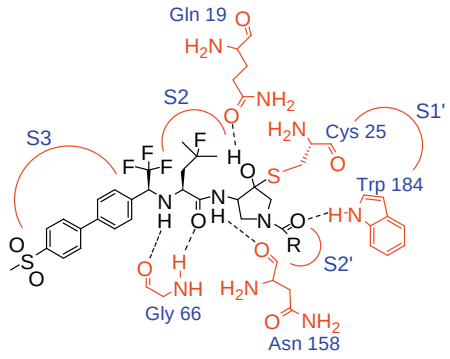
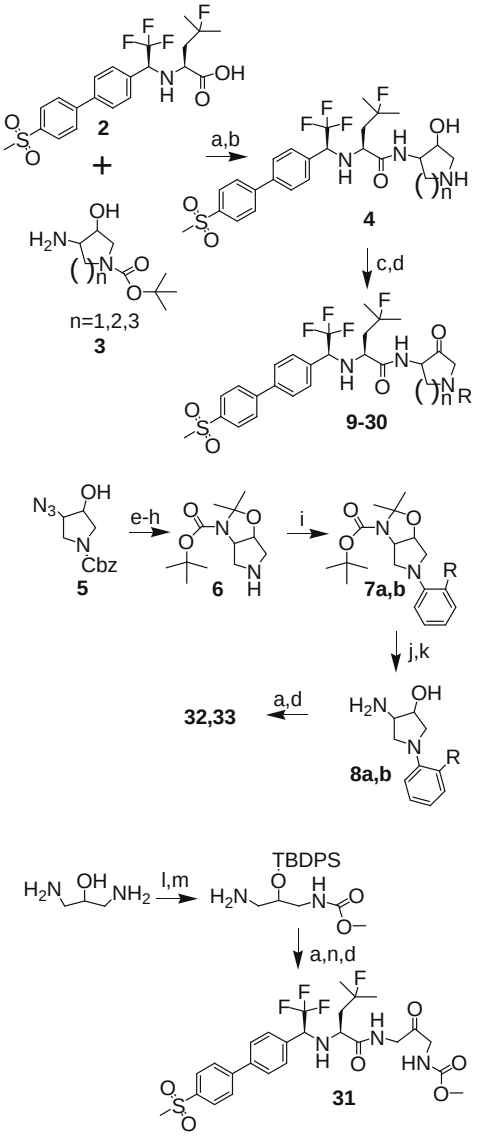


Figure 2. Hypothetical representation of ketone inhibitors in the Cat K active site.



Scheme 1. Synthesis of aminoketones. Reagents and conditions: (a) (**2**), HATU, DIEA, DMF; (b) TFA, DCM; (c) isocyanate, chloroformate or sulfonyl chloride, (TEA or pyridine), DCM; (d) $(ClCO)_2$, DMSO, DCM, −78 to −20 °C; (e) TPP, H_2O, THF, Δ; (f) Boc_2O, TEA, MeOH; (g) 2,2-dimethoxypropane, CSA, acetone; (h) H_2, Pd/C, MeOH; (i) *t*-BuONa, CTC-Q-Phos, $Pd(OAc)_2$, toluene, Δ (for **7a**, R = H), 2-fluorophenyl methyl sulfone, Cs_2CO_3, DMF, Δ (for **7b**, R = SO_2Me); (j) AcOH, H_2O; (k) HCl, dioxane (**8a**, R = H and **8b**, R = SO_2Me); (l) TBDPS-Cl, TEA, DMAP, DCM; (m) $ClCO_2Me$,TEA, DCM; (n) TBAF, AcOH, THF.

because the nitrile essentially end caps the inhibitor rendering the aforementioned interactions difficult to achieve with nitrile-based inhibitors. Moreover, replacement of the nitrile would also likely lead to inhibitors with distinct metabolic profiles.

Sulfonamides, carbamates, amides and ureas were prepared by condensation of acid **2**[10] (Scheme 1) with the appropriate Boc protected amino alcohol **3**.[6c,d] The amine was then deprotected, capped with an isocyanate, chloroformate or sulfonyl chloride, and the alcohol was oxidized to the ketone under Swern conditions. In cases where the Swern oxidation was sluggish, the reaction was performed at −20 °C (instead of −78 °C).

N-Aryl compounds (**32** and **33**) could not be prepared by direct arylation of intermediate **4**. Attempts to arylate the nitrogen of **4** via palladium coupling or nucleophilic substitution failed under various conditions. These conditions also failed with various protected intermediates of **3**. Fortunately, fully protected intermediate **6** (prepared from **5**[11] as shown in Scheme 1) was successfully arylated under Hartwig arylation conditions[12] to afford **8a**. Compound **8b** was prepared by aromatic nucleophilic substitution of **6** with 2-fluorophenyl methyl sulfone. Acyclic amino ketone **31** was also prepared in order to evaluate the importance of the restricted conformation of the cyclic amino ketones.

Our goal was to establish the structure–activity relationship between cyclic aminoketone ring size and nitrogen substitution (R group). The SAR of the ketones prepared is shown in Table 1. Activity against Cat K was determined by measurement of the IC_{50} values against humanized rabbit cathepsin K[5a] and selectivity of the inhibitors against human Cat L, B and S is also shown.

In previously reported work by Marquis et al.,[6c] the pyridine-2-sulfonamide group substitution on an azepanone produced a potent inhibitor (**34**) (Table 1). The replacement of the nitrile of odanacatib with this moiety led to some loss of potency regardless of the amino ketone ring size (**9**, **17**, **19** vs odanacatib), with the azepanone inhibitor the most potent. Separation of the diastereoisomers of compound **9** was performed by chiral HPLC and the potency and selectivity profiles of separated isomers **10** and **11** are shown in Table 1. Replacement of the pyridyl ring with a methyl group (**14**), or replacement of the pyridine sulfonamide group with a carbamate (**15**) led to loss of potency (8- and 27-fold, respectively). Also noteworthy, compound **9** shows superior selectivity against Cat L and S, when compared to compound **34**.

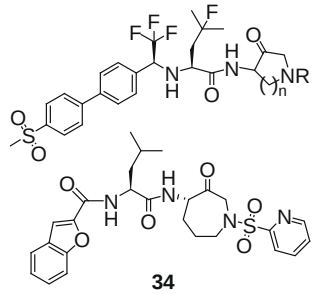
The pyridine sulfonamide substitution in the pyrrolidinone series (**19**) was 43 times less potent than its azepanone counterpart (**9**). However, potency could be improved by replacement of the pyridine sulfonamide group with short carbamates (**22**–**24**), amides (**25**, **26**) and ureas (**27**, **28**). These compounds were of comparable potency to azepanone **9**, with superior selectivity on Cat S, especially with smaller R groups (**22**, **23**, **26** and **27**).

Piperidinones were also examined. In this case, both the pyridine-2-sulfonamide (**17**) and ethyl carbamate (**18**) were tolerated, although with a loss of potency (relative to **9** and **23**). These compounds were also less selective on Cat S, especially when compared to the pyrrolidinone series (**18** vs **23**). Cyclic arylamines have also been reported.[11] Arylamines **32** and **33** were prepared, and had comparable potency to other piperidinones, but selectivity was essentially lost on Cat S and Cat B.

Consistent with the work by Marquis et al.[6c] the acyclic version **31** (Scheme 1) led to a loss of potency, suggesting that the restricted conformation is important.

Pharmacokinetic experiments of selected compounds were performed in rats.[5g] Animals were dosed at 2–5 mg/kg IV in 60% PEG 200. The measured half-lives ($t_{1/2}$) and clearance rates (Cl) are shown in Table 2. The half-lives and clearance rates of odanacatib and **34**[6c] are also shown for comparison. Rat hepatocyte incubations were also performed and results are expressed as % inhibitor remaining (by HPLC analysis) after a 2 h incubation.[5g]

Table 1
Potency and selectivity profiles of ketone Cat K inhibitors



34

Compound	N	R	Hrab Cat K IC_{50} (nM)	Cat L/K	Cat S/K	Cat B/K
Odanacatib			0.2	>1000	300	>1000
9	3	SO_2-2-Pyr	2.0	939	45	>1000
10[a]	3	SO_2-2-Pyr	10	>1000	54	>1000
11[a]	3	SO_2-2-Pyr	1.8	681	35	>1000
12	3	SO_2-2-Pyr-NO	2.6	984	33	>1000
13	3	SO_2CH_2Ph	159	>63	8	50
14	3	SO_2Me	16	617	114	>1000
15	3	COOEt	54	>185	46	>185
16	3	H	33	236	179	303
17	2	SO_2-2-Pyr	5.7	621	22	232
18	2	COOEt	9	>1000	10	364
19	1	SO_2-2-Pyr	85	118	27	118
20	1	SO_2Me	27	158	313	370
21	1	H	9.8	16	159	485
22	1	COOMe	4.3	604	304	637
23	1	COOEt	1.6	861	185	215
24	1	COO-*t*-Bu	3.9	403	29	27
25	1	COPh	2.9	197	14	188
26	1	COMe	4.2	>1000	604	>1000
27	1	$CONH_2$	7.3	40	104	355
28	1	CONHPh	7.3	40	104	355
29	1	$CONHCH_2Ph$	15	667	36	53
30	1	$CONHSO_2Ph$	68	>147	>6	9
31			45	152	38	148
32	2	Ph	8.3	101	8	2
33	2	Ph-2-SO_2Me	6.9	91	3.9	1
34			0.16	14	25	>1000

[a] Separated diastereoisomers of **9**. Separation accomplished on an ADRH HPLC column with acetonitrile/0.1% formic acid (10 was the first eluting diastereoisomer).

Odanacatib has been shown to be metabolically robust.[8] In rats this compound has a $t_{1/2}$ of 6 h, is cleared at a rate of 2 mL/min/kg and is very stable in rat hepatocyte incubation experiments (Table 2). In contrast, azepanone **9** has a very short $t_{1/2}\alpha$. Although the terminal $t_{1/2}\beta$, was much longer (11 h), the clearance rate was high (46 mL/min/kg). Previously reported **34**, with the same warhead, was also cleared quickly ($t_{1/2}$ = 0.5 h, Cl = 50 mL/min/kg).[6c]

Pharmacokinetic experiments on separated diastereoisomers **10** and **11** were performed, and it was found that these compounds rapidly re-equilibrated (<5 min) back to **9** in rat, indicating that the α-keto stereocenter is not stable in vivo, even though compounds with the same azepanone warhead had been reported to be stable under neutral and acidic pH.[6c] It is also evident that **9** is significantly more metabolized in rat hepatocytes than odanacatib (Table 2). In the hepatocyte incubations of **9**, many small unidentified metabolites were observed, none of which corresponded to pyridine *N*-oxide **12** (Table 1), this despite the observation that compound **34** undergoes metabolism through pyridine oxidation.[13]

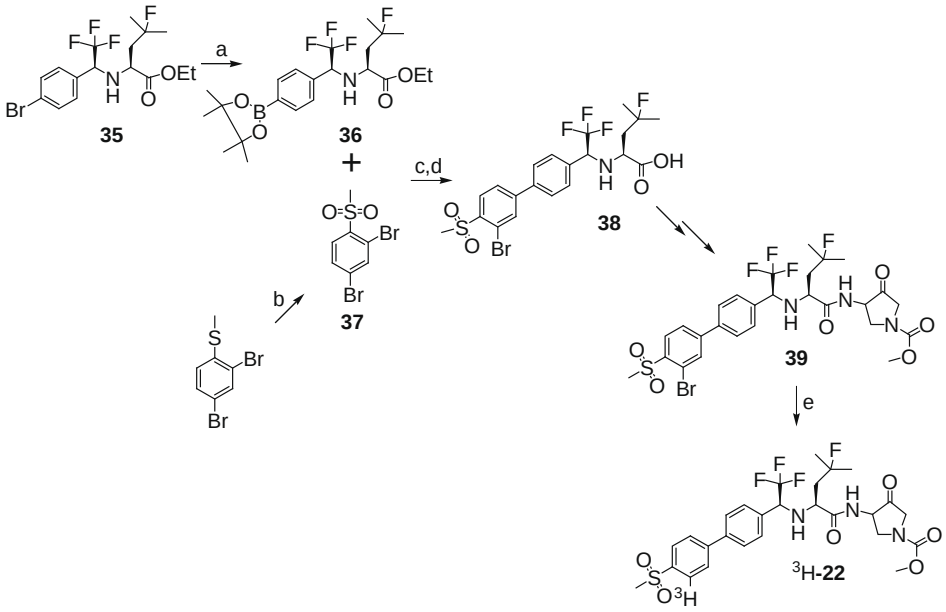
Considering the metabolically robust nature of odanacatib, it was proposed that heavy metabolism on the azepanone ring could account for the metabolic liability of **9**. On this basis, the smaller ring versions **17** and **19** were prepared with the hope that they would potentially have decreased metabolism. However, as shown in Table 2, the smaller ring versions were also cleared rapidly and showed decreased stability in hepatocytes. Acyclic compound **31**, carbamates (**22**, **23**) and amides (**26**) all showed similar pharmacokinetics to **9**.

Table 2
Metabolism and pharmacokinetics

Compound	$t_{1/2}$ (h)	% Inhibitor remaining in rat hepatocytes[a]	Cl (mL/min/kg)
34	0.54[b]	—	50[b]
Odanacatib[8]	6	96	2.0
9	0.6; 11[c]	56	46
17	0.6	—	24
19	1.3	15	43
22	2.8	11	40
23	2.1	20	53
26	1.2	—	67
31	1.1	—	17

[a] After 2 h incubation.
[b] Ref. 6c.
[c] Two half-lives were calculated since **9** clearly showed two long and distinct phases, indicated here as $t_{1/2}\alpha$ and $t_{1/2}\beta$, respectively.

In order to better understand the clearance of the ketones, a radiolabelled version of **22** was prepared from **35**[8] as shown in



Scheme 2. ^{3}H-**22**. Reagents and conditions: (a) bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, DMF, Δ; (b) H_2O_2, $Na_2WO_4{\cdot}2H_2O$, NBu_4HSO_4, EtOAc; (c) $PdCl_2$(dppf), $NaHCO_3$, DMF, Δ; (d) LiOH, MeOH, THF, Δ; (e) $^{3}H_2$, TEA, Pd/C, THF.

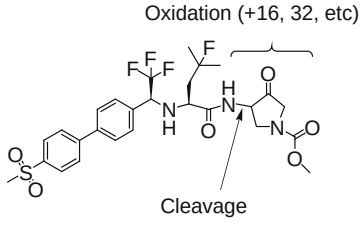


Figure 3. Metabolism of **22**.

Scheme 2. A rat bile cannulation study was performed with ^{3}H-**22**, and LC/MS analysis of the bile indicated the presence of many metabolites. Some of the more prominent metabolites were the result of cleavage between the amide nitrogen and the α-keto stereocenter, as well as oxidation on the pyrrolidinone (Fig. 3). Parent was detected in low amounts (<5%), indicating that excretion occurs mainly through metabolism.

In conclusion, ketone replacement of the nitrile of odanacatib led to potent and selective inhibitors of cathepsin K (compounds **22** and **26**). However, these inhibitors are rapidly cleared in rats, presumably due to metabolism on the ketone moiety. Substitutions on this cyclic ketone template could be explored to potentially stabilize the inhibitors.

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