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6-Phenyl-1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile as cathepsin S inhibitors

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ABSTRACT

6-Phenyl-1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile analogues were identified as potent and selective cathepsin S inhibitor against both purified enzyme and in human JY cell based cellular assays. This core has a very stable thio-trapping nitrile war-head in comparison with the well reported pyrimidine-2-carbonitrile cysteine cathepsin inhibitors. Compound **47** is also very potent in in vivo mouse spleenic Lip10 accumulation assays.

Eleven members of the cathepsin family cysteine proteases have been identified in the human genome (cathepsins B, C, H, F, K, L, O, S, V, W and X).[1] Two of these, cathepsins K and S have been the subject of extensive effort in the pharmaceutical industry.[1–3] Cathepsin S is highly expressed in antigen presenting cells and plays a major role in the degradation of the invariant peptide chain associated with the major histocompatibility complex and affects antigen presentation. Selective cathepsin S inhibitors should then be useful therapeutics for autoimmune disorders, for example, rheumatoid arthritis (RA) and multiple sclerosis (MS). More recently cathepsin S has also been indicated for neuropathic pain.[4] Several cathepsin K inhibitors have progressed into human clinical trials for osteoporosis[5] but as yet there are no reports of any cathepsin S inhibitors in advanced stages of human clinical trials. Several different cathepsin S inhibitor chemotypes have been reported in the literature, most of which contain some kind of peptide feature within the molecule and pose some challenges in terms of pharmacokinetic property optimization.[2]

Several groups have reported[6–17] heteroaryl nitrile based human cathepsin K and S inhibitors. Recently, we reported 2-phenyl-9*H*-purine-6-carbonitrile[18] and 6-phenyl-pyridine-2-carbonitrile[19] as selective human cathepsin S inhibitors (Fig. 1).

These compounds differ from other reported aryl nitrile cysteine protease inhibitors where the nitrile war-head is flanked between two electron-negative aromatic nitrogen atoms and has relatively high reactivity towards nucleophiles. These 2-phenyl-9*H*-purine-6-carbonitrile compounds however still suffer from a war-head reactivity issue in our glutathione based war-head stability NMR assay.[19] Although the pyridine-2-carbonitrile based compounds are stable towards nucleophiles, such as glutathione, we were unable to optimize their cathepsin S inhibitory activity to better than 10 nM.

In this Letter, we report a novel series of 6-phenyl-1*H*-*[4,5-c]*pyridine-4-carbonitrile based selective cathepsin S inhibitors **3**. These new inhibitors are equivalent to a hybrid between structures **1** and **2** and they combined both 'transition state stabilization' [18] (Fig. 2a) and 'in situ double activation'[19] (Fig. 2b) in the same molecule.

The initial 6-phenyl-1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile compounds were synthesized according to Scheme 1. N-Nitration of the commercially available 4-amino-2,6-dichloropyridine **4** followed by a sulfuric acid promoted rearrangement gives compound **5** in high yield. Treatment of compound **5** with copper(I) cyanide in NMP at 180 °C for 15–20 min selectively displaces the 2-position chloride to give 4-amino-6-chloro-3-nitropyridine-2-carbonitrile **6** in 80% yield. Suzuki coupling of **6** with boronic acids or esters gives compound **7**. Reduction of the nitro group by means of

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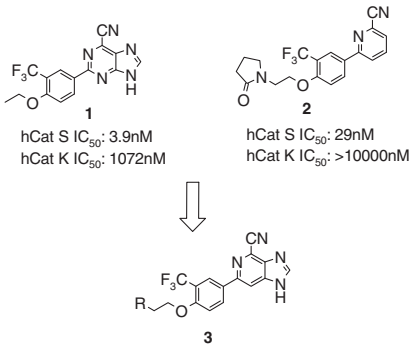


Figure 1. 9*H*-Purine-6-carbonitrile **1**, pyridine-2-carbonitrile **2** based selective cathepsin S inhibitors and their hybrid 1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile **3.**

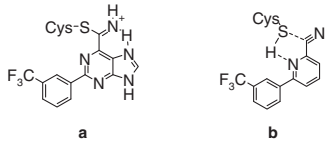
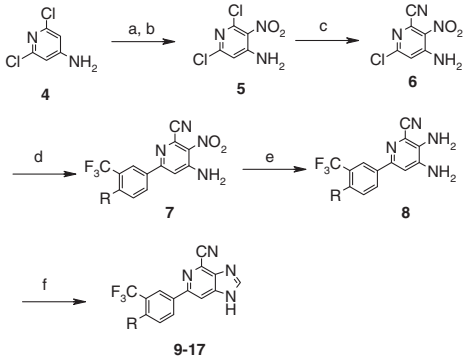


Figure 2. (**a**) Transition state stabilization through hydrogen bond between thioimidate NH and N7 purine nitrogen; (**b**) electrostatic interaction between SH proton and pyridine ring nitrogen makes nitrile war-head more electrophilic and cysteine thiol more nucleophilic.



Scheme 1. Reagents and conditions. (a) HNO_3/H_2SO_4, 0 °C, 3 h; (b) H_2SO_4, 100 °C, 1 h; (c) CuCN, NMP, 180 °C, 15–20 min; (d) $Pd_2(DBA)_3$, K_3PO_4, (c-Hex)$_3$P, dioxane–H_2O, 100 °C, 3 h; (e) $Pd/C/H_2$, EtOAc, 1 h; (f) $CH(OEt)_3$, Yt(OTf)$_3$ (cat), MeCN, 90 °C, 30 min.

hydrogenation gives the bisaniline product which is then ring-closed with triethyl orthoformate catalyzed by ytterbium triflate to give the desired final products **9–17**. Results of this study are shown in Table 1.

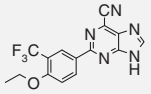
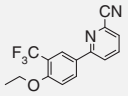
Although 6-phenyl-1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile appeared to be less potent than the corresponding purine analogues (compound **11** vs purine compound in Table 1), the imidazole ring of compound **11** contributed a 66-fold activity in comparison with the corresponding pyridine based compound (**11** vs pyridine compound in the Table 1). The reasons for this contribution can be explained by the binding to the S1 pocket, as shown later by an X-ray structure analysis, as well as an intramolecular H-bonding induced stabilization of the transition state.[18] Among the first nine compounds synthesized, the ethoxyl compound **11** appeared to be the most potent. Longer chain (**13**) or other non-oxygen based compounds (**16, 17**) have lower activity.

Having established the 6-phenyl-1*H*-[4,5-*c*]pyridine-4-carbonitrile as a scaffold for selective human cathepsin S inhibition, our next objective was to synthesize a water soluble compound to assess its nitrile war-head stability with the intention to further improve the activity. Computer aided docking studies suggest that N1 and C2 attachments should be exposed to the solvent and have little or no impact on activity. To validate this theory early in the project a series of N1- and C2- substituted analogues (data not shown) of compound **11** were synthesized. The selected N1 substituted compounds were synthesized according to Scheme 2. Mitsunobu coupling of 2-bromoethanol or 3-bromopropanol with compound **11** provided intermediates **18** which were then treated with primary or secondary amines to give the desired products **19–22**. It is worth noting that there are no war-head related side products detected when intermediate **18** was heated with 10 equiv of primary or secondary amines at temperature as high as 120 °C in DMF for 40 min. This indicates that the nitrile group of this 1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile core has good stability towards nucleophiles.

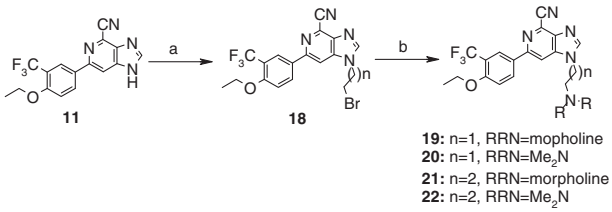
The biological results of compounds **19–22** are shown in Table 2. As expected all compounds exhibited cathepsin S inhibitory activity within half a log unit of compound **11**. It is noticeable however that all these weakly basic compounds are less selective towards cathepsin K. Unfortunately these compounds had only modest cellular activity against the degradation of invariant chain measured by accumulation of cathepsin S substrate Lip10 in the human JY cells.

In order to improve cellular activity, we then focused on increasing the interactions with the S2 pocket.[19] Compounds with the expanded P2 motif were synthesized according to Scheme 3 and 4.

Table 1
Cathepsin S and K inhibitory activity

Compd	R	IC_{50} (nM)[a,b]	
		Cat S	Cat K
		3.9	1072
		1660	>10,000
9	H	1047	1995
10	MeO	339	8511
11	EtO	25	8310
12	$HO(CH_2)_2O$	145	2818
13	*n*-PrO	200	7762
14	$HO(CH_2)_3O$	63	2691
15	BenzylO	676	>10,000
16	EtNH	105	>10,000
17	AcNH	3236	>10,000

[a] For assay conditions see Ref. 6.
[b] Compounds inactive against human cathepsin B and L.



Scheme 2. Reagents and conditions. (a) bromoethanol/bromopropanol, betaine, THF, 4 h; (b) amine, DMF, 120 °C, 5 min.

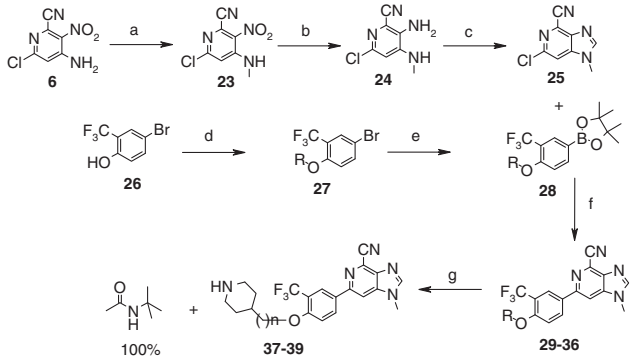
Table 2
Activity against human cathepsin S and K and cellular activity in human JY cells

Compd	IC_{50}[a] (k_i) (nM)		Lip10[b,20] IC_{50} (nM)
	Cat S	Cat K	
19	37 (9.1)	1660 (603)	>10,000
20	32 (13.8)	447 (302)	854
21	35	513	na
22	27 (14.5)	270 (339)	260

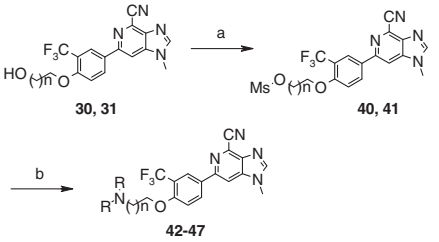
[a] For assay conditions see Ref. 6.
[b] Measured by western blot using human B lymphoblastoid cells, 500,000/ml, mouse anti-CD74 Pin. One monoclonal antibody, 50% of the maximum activity of LHVS in the same assay as IC_{50}; na = not available.

N-Methylation of compound **6** gives compound **23** in high yield. Reduction of the nitro group with stannous chloride provides the bisaniline intermediate **24**. Compound **25** was obtained in high yield by heating compound **24** in triethyl orthoformate at 90 °C for an hour using ytterbium triflate as a catalyst. Independently, alkylation of the phenol **26** gives the intermediate **27** which was then converted to boronic ester **28** by applying standard palladium chemistry. Suzuki coupling between the intermediates **25** and **28** afforded the final compounds **29–36**. Compounds **37–39** were synthesized using the above route where the secondary amine was protected by a Boc group. The Boc protecting group was then finally removed using trifluoroacetic acid in a mixed solvent of DCM and acetonitrile (v/v 10–30%) in nearly quantitative yield. The by-product *N*-*t*-butyl acetamide is easily removed by washing the final solid TFA salt product with 1:1 EtOAc: Et_2O. The use of acetonitrile as a co-solvent is essential to stop *t*-butyl cation related side reactions by the in situ 'Ritter' reaction. Only 25–50% yield of product can be obtained without acetonitrile as co-solvent in the cases of compounds **37**–**39**. The use of acetonitrile as a co-solvent could offer a generic solution for all Boc/*t*-butyl ester deprotections where *t*-butyl cation trapping is necessary to replace the widely used phenols or thiols. The alcohols **30** and **31** were further modified to give compounds **42–47** via the methanesulfonate intermediates **40** and **41**, respectively (Scheme 4). Biological results from this optimization are shown in Table 3.

In comparison with compound **11**, the *N*1-methyl derivative **29** is only slightly less active against human cathepsin S. Although selectivity against cathepsin K is reduced, it was selected as a new starting point for P2 optimization as this *N*1-methyl substituted imidazopyridine is potentially more permeable. As reported in our previous publication,[19] the extended P2 region is very accommodative for a variety of functional groups, e.g. hydroxyl

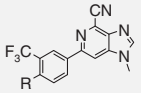
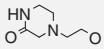
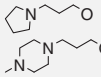


Scheme 3. Reagents and conditions. (a) MeI, K_2CO_3, MeCN, reflux, 4 h; (b) $SnCl_2$, EtOH, 40 min; (c) $CH(OEt)_3$, $Yt(OTf)_3$, 90 °C, 1 h; (d) 3-iodopropanol or 2-bromoethanol, K_2CO_3, MeCN, reflux, 4 h; (e) $PdCl_2$(DPPF), KOAc, dioxane, 100 °C; (f) $Pd_2(DBA)_3$, K_3PO_4, (c-Hex)$_3$P, dioxane–H_2O, 100 °C, 3 h; (g) TFA–DCM–MeCN, rt, 20 min.



Scheme 4. Reagents and conditions. (a) MsCl, DIPEA, NMP, rt, 1 h; (b) amine, DMF, 120 °C, 10–40 min.

Table 3
Activity against human cathepsin S and K and cellular activity in human JY cells

Compd	 R	IC_{50}[a,b] (k_i) (nM)		Lip10[c,20] (nM)
		Cat S	Cat K	
29	EtO	40	1259	na
30	$HO(CH_2)_2$	71	3162	na
31	$HO(CH_2)_3$	24	1071	na
32		20 (3)	2291	853
33		12.6	>10,000	na
34		10	>10,000	na
35		11	2042	267
36		7.8 (1.6)	2512	1420
37		316	891	na
38		14.1	240	na
39		8.3 (2)	178	9
42		209	5888	na
43		7.8	1175	na
44		41 (7.7)	776	84
45		28	871	89
46		9.5	468	106
47		7.2 (2.9)	331	63

[a] For assay conditions see Ref. 6.
[b] Compounds inactive against human cathepsin B and L.
[c] na = not available; measured by western blot using human B lymphoblastoid cells, 500,000/ml, mouse anti-CD74 Pin. One monoclonal antibody, 50% of the maximum activity of LHVS in the same assay as IC_{50}.

(**31**), pyridine residues (**32**–**35**), amides (**36**). The basic nitrogen is also well tolerated in this region as long as a minimum distance between this basic nitrogen and the imidazopyridine core is maintained, for example, compound **39** is more active than compound **37** and **44** better than **42**. However, when the pk_a of the basic nitrogen is reduced to lower than assay pH (5.5), such as compound **43** (pk_a <4), the cathepsin S inhibitory activity is unaffected. Although compound **44** has very similar cathepsin S inhibitory activity as compound **20**, its cellular activity against Lip10 degradation is increased by 10-fold. An x-ray structure of compound **46** bound to human cathepsin S was obtained (Fig. 3). The Cys25 thiol formed a covalent bond with the nitrile war-head with the formation of a flat thioimidate which is co-planar with the imidazopyridine ring. The imidazole ring binds to the shallow S1 pocket with the N3 nitrogen atom well setup for an intramolecular hydrogen bond

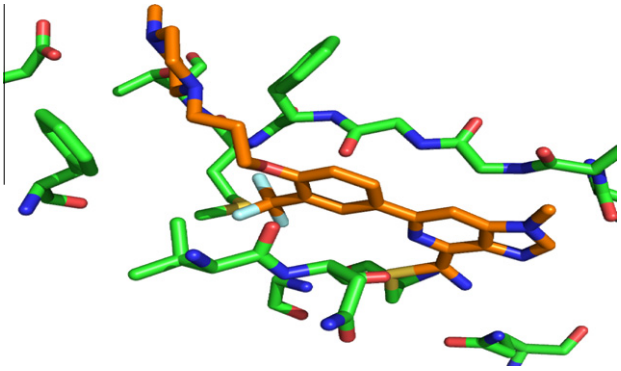
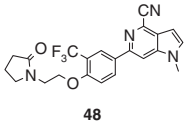


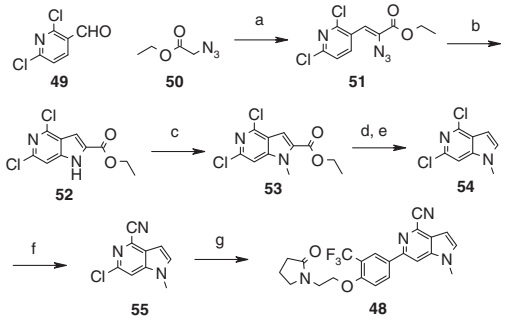
Figure 3. X-ray structure of compound **46** bound to human cathepsin s enzyme, solved at 2.1 Å resolution (PDB code: 3N4C).



48

hCat S IC_{50}: 661nM
hCat K IC_{50}: >10000nM

Figure 4.



Scheme 5. Reagents and conditions. (a) NaOMe, MeOH, rt, 24 h; (b) Mesitylene, 165 °C, 1 h; (c) MeI, DMF, K_2CO_3, rt, 2 h; (d) LiOH, THF–H_2O, rt, 2 h; (e) quinoline, Cu, 185 °C, 3 h; (f) CuCN, $Pd(DBA)_2$, DPPF, dioxane, 100 °C, 3 h; (g) boronic ester (**28**), $Pd_2(DBA)_3$, K_3PO_4, $(c\text{-Hex})_3P$, dioxane–H_2O, 100 °C, 3 h.

with the newly formed thioimidate NH group. The important CF_3 group is buried inside the S2 pocket interacting with methionine residue. The O-CH_2 has hydrophobic interactions with Val162 and the middle CH_2 with Phe70. The three CH_2 groups attached to the internal piperazine nitrogen atom are well positioned to interact with Phe211. The protonated external piperazine nitrogen may have ionic interactions with the glutamic acid residue Glu115 which is immediately outside the S2 pocket.

The N3 nitrogen of 1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile is important, although not critical, for its cathepsin S inhibitory activity. Compounds **48** (Fig. 4) was synthesized (Scheme 5) and it is 85 times less active than the corresponding analogue **36** of Table 3. An intramolecular hydrogen bond formation in the transition states probably best explains these results, although nitrile activation through the electron withdrawing of the N3 nitrogen may also contribute.

To further assess the nitrile war-head stability, compound **46** and a few other compounds from the pyrimidine-2-carbonitrile[19] and pyridine-carbonitrile[19] series were tested in a NMR based stability assay. The results are shown in Table 4. The nitrile group in

Table 4
Nitrile war-head reactivity with glutathione measured by ^1H NMR in 1:1 D_2O–CD_3OD at 20 °C at p*D* 7.5

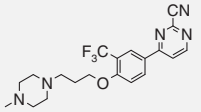
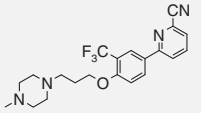
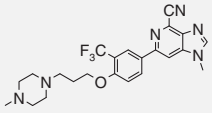
Compd	Concentration (mM)		$T_{1/2}$
	Inhibitor	GSH	
	1.15	7.22	<15 min
	1.24	7.06	>100 h
	1.25	7.06	>100 h

Table 5
Pharmacokinetic parameters (iv 2 mg/kg; po 10 mg/kg, gelatin mannitol) and mouse cathepsin S inhibitory activity

Compd	Cl (mL/min/kg)	V_{ss} (L/kg)	*F* (%)	Mouse Cat S (IC_{50}, nM)
32	10	0.7	54	2.6
44	327	58	58	2.6
47	28	2.0	9	2.5

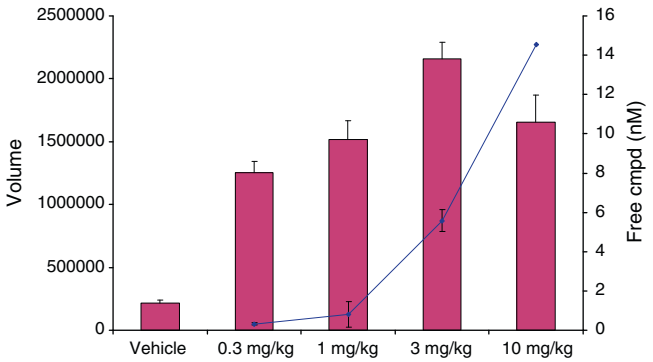


Figure 5. C57Bl/6 (18–25 g) mice were dosed by gavage with vehicle (0.5% gelatin, 5% mannitol in water) or 0.3–30 mg/kg compound **47**. Blood and spleen were collected at 4 h time point after dosing. Spleens were lysed in 1% Triton X-100, the supernatants collected and measured for protein concentration. Protein/lane (0.5 μg) of each sample was subjected to SDS–PAGE followed by Western blotting using 0.5 mg/ml rat anti-mouse CD74 mAb (clone In-1, Fitzgerald Industries); Liplo level: bar chart; free compound plasma level: line chart.

1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile appears to be very stable towards glutathione with a half life ($T_{1/2}$) well over 100 h in comparison with the corresponding pyrimidine-2-carbonitrile compound of less than 15 min. 1*H*-Imidazo[4,5-*c*]pyridine-4-carbonitrile should be chemically stable enough to pursue further.

Selected compounds **32**, **44** and **47** were evaluated for pharmacokinetic properties with male Wistar rats. The PK results together with their mouse cathepsin S inhibitory activity are listed in Table 5. These compounds possess modest to good oral bioavailability. The most basic compound, **44**, has a plasma clearance (327 mL/min/kg), much higher than the rat hepatic blood flow and a large distribution volume (58 L/kg). The high clearance and distribution volume suggest a rapid tissue distribution after dosing. All compounds have low nanomolar mouse cathepsin S inhibitory activity and compound **47** has an in vitro Lip10 IC_{50} of 6.5 nM using splenocytes isolated from mouse spleens (BD Falcon cell strainers).

In vivo pharmacodynamic effect of compound **47** was examined by measuring the accumulation of Lip10 in the spleen of C57Bl/6 mice by western blot after oral dosing. After 4 h compound **47** was shown to significantly induce Lip10 accumulation in the spleen at doses as low as 0.3 mg/kg (Fig. 5). The lower than Lip10 IC_{50} free compound level in plasma suggests that this compound might be sequestered in the lysosome. Further analysis showed that compound level is ~50-fold greater in spleen than in the plasma.

In summary, 6-phenyl-1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile core was identified as a good scaffold for cathepsin S inhibition. This core offers much improved nitrile war-head stability in comparison with other arylnitrile based cathepsin S and K inhibitors. The optimized compounds have good cellular activity in human JY cells measured by cathepsin S substrate Lip10 accumulation.

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