Center Probe Report

Probe reports are generated for each compound that meets or surpasses the MLSCN requirements for a new probe.

Please provide the following specific information:

Project Title: Multiplexed HTS of Serine and Cysteine Proteases
Grant Number: MH076406-01

Screening Center Name: Penn Center for Molecular Discovery
Principal Investigator of Screening Center: Scott L. Diamond, Ph.D.

Assay Submitter & Institution: Scott L. Diamond, University of Pennsylvania

PubChem Bioassay Identifier (AID): 460

Probe PubChem Identifier: CID 16725315; SID 26681509

Please provide the following descriptions:

Specific Aim:

To perform a high throughput screen of the NIH Molecular Libraries Small Molecule Repository (MLSMR) to identify novel, potent, and selective inhibitors of human cathepsin L.

Significance/Rationale [1]:

"Cathepsins are a family of ubiquitous lysosomal proteases that have demonstrated important physiopathological roles in inflammation, osteo- and rheumatoid arthritis, osteoporosis, Alzheimer's disease, multiple sclerosis, pancreatitis, apoptosis, liver disorders, lung disorders, myocardial disorders, diabetes, muscular dystrophy, tumor invasion and metastasis [2-5]. Cathepsin L is an endopeptidase that is catalytically the most active known lysosomal cysteine protease [6]. It is a papain-like cysteine protease of interest due to involvement in many biological processes including epidermal homeostasis, hair follicle morphogenesis and cycling, extracellular matrix degradation, and viral entry of Severe Acute Respiratory Syndrome (SARS) coronavirus, Ebola virus, and Hendra virus [5, 7-10]. Due to the roles of many cathepsin L-like proteases in diseases such as malaria (falcipain), leishmaniasis (*Leishmania major* cathepsin L), Chagas disease (cruzipain), African trypanosomiasis (congopain), toxoplasmosis (*Toxoplasma gondii* cathepsin L), amoebiasis (histolysain), and sleeping sickness (rhodesain), inhibitors of human cathepsin L may be highly valuable as therapeutic treatments against these infectious diseases." [1]

Assay Implementation and Screening

PubChem Bioassay Name: Cathepsin L

PubChem Primary Assay Description [11]:

"Human liver cathepsin L (EC 3.4.22.15) is a lysosomal cysteine protease. Recent interest in cathepsin L has been generated by research showing that proteolysis by this enzyme is required for the entry and replication of the SARS and Ebola viruses in human cells. Thus cathepsin L inhibitors have potential as novel anti-viral agents.

Cathepsin L inhibitors may also be active against Plasmodium falciparum, the parasite responsible for human malaria. Plasmodium contains cathepsin L-like cysteine proteases known as falcipains that appear to promote virulence of the parasite through haemoglobin digestion and erythrocyte invasion.

The high-throughput screen for cathepsin L inhibitors reported here consisted of an end-point assay monitoring the release of the fluorophore aminomethyl coumarin (AMC) upon enzymatic hydrolysis of an AMC-labeled dipeptide.

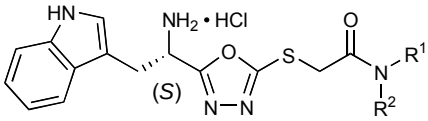
This assay is a part of the Molecular Libraries Screening Center Network." [11]

Center Summary of the Primary Screen:

57,821 compounds from the NIH Molecular Libraries Small Molecule Repository (MLSMR) were screened against human liver cathepsin L. This screen was performed in 384-well Corning 3676 black, low-volume, non-binding surface (NBS)-coated polystyrene plates using a total reaction volume of 10 µL per well. Final well concentrations were: 10 µM compound (2% DMSO), 300 pM (8.7 ng/mL) human liver cathepsin L, 1 µM Z-FR-AMC substrate, and 20 mM sodium acetate buffer containing 1 mM EDTA and 5 mM DTT, pH 5.5. Cathepsin L was activated in the assay buffer for 30 minutes prior to dispensing into wells. Assay plates were incubated at room temperature for one hour and the fluorescence intensity of each well was read with a PerkinElmer Envision plate reader (Ex: 355 nm, Em: 460 nm) to measure hydrolysis of the AMC substrate. The screen correctly identified E-64 and E-64c members of the library as potent inhibitors of cathepsin L. A Z' factor of 0.73 was calculated for this screen, indicating good plate uniformity throughout the run.

From the 57,821 compound primary HTS, 102 compounds (0.18%) showed >45% inhibition against human cathepsin L. Upon a confirmatory dose response assay, 49 (48%) of these small molecules inhibited human cathepsin L activity with an IC_{50}<50 µM. "Library samples containing 2,5-disubstituted oxadiazoles were identified as potent hits in a high throughput screen of the NIH Molecular Libraries Small Molecule Repository directed at discovering inhibitors of cathepsin L (**Table I**). However, when synthesized in pure form, the putative actives were found to be devoid of biological activity. Analyses by LC-MS of original library samples indicated the presence of a number of impurities, in addition to the oxadiazoles. Synthesis and bioassay of the probable impurities led to the identification of a thiocarbazate that likely originated via ring opening of the oxadiazole (**Figure 1**). Previously unknown, thiocarbazates were independently synthesized as single enantiomers and found to inhibit cathepsin L in the low nanomolar range." [12]

Table I. Cathepsin L inhibitory activity of oxadiazole-containing library samples[a].



+ ***Impurities***

PubChem SID	R^1	R^2	IC_{50} (μM)[b]
861540 (**1**)	2-ethylbenzene	H	0.13 ± 0.01
861087 (**2**)	2,4-dimethylbenzene	H	0.16 ± 0.05
861840 (**3**)	Me	Me	0.17 ± 0.02
861542 (**4**)	2,3-dimethylbenzene	H	0.30 ± 0.04
861992 (**5**)	Et	Et	0.51 ± 0.02

[a]Library samples containing the parent oxadiazole with impurities. [b]IC_{50} values are reported as mean ± standard deviation (number of determinations = 3).

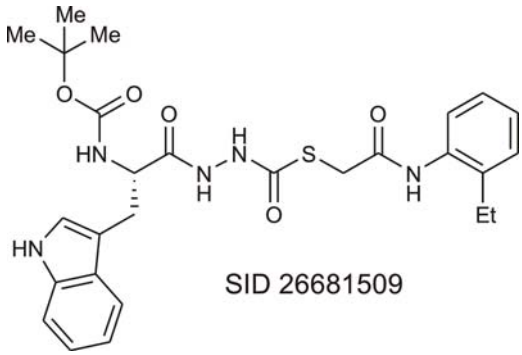


Figure 1. Thiocarbazate probe SID 26681509.

Probe Optimization

Center comments on chemistry strategy leading to probe identification [12]:

"The most potent well, cataloged in the MLSMR as disubstituted oxadiazole **1**, exhibited an IC_{50} of 0.13 μM [11]. Wells containing related analogs (**2-5**), differing only in the amide nitrogen substitution, displayed a range of activities (IC_{50} = 0.16-0.51 μM), suggesting a nascent structure activity relationship. As is our practice, library samples containing the putative active oxadiazoles were evaluated for both purity and integrity by LC-MS analysis. This analysis indicated that the primary constituent of each sample was indeed the expected oxadiazole, in up to 60% purity, however numerous impurities were also present. To confirm the biological activity attributed to **1**, a synthetic sequence was developed to generate the oxadiazoles in pure form [12]."

"To our surprise, the free base of **1** was found to be completely devoid of activity when assayed against cathepsin L. This result suggested that an impurity present in the original library sample was responsible for the observed activity. Based on LC-MS analyses of the biologically active samples, we hypothesized that the active component

was likely the ring-opened product **10**, formed via acid-promoted addition of H_2O to (+)-**8** (**Figure 2**).

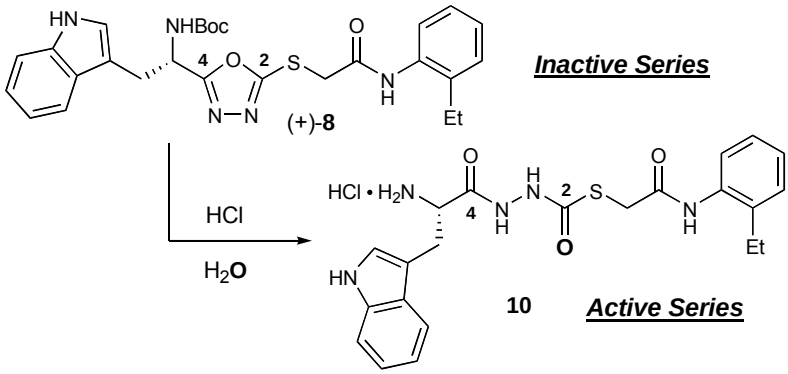
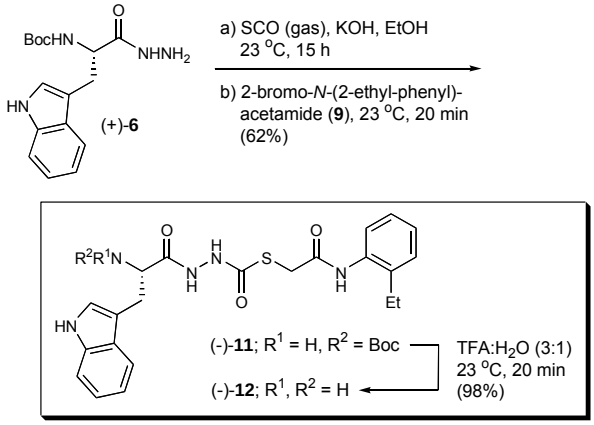


Figure 2. Conversion of oxadiazole (+)-**8** to thiocarbazate **10**.

The presence of a molecular [M+1] ion equal to 440 amu in the LC-MS analysis of impure samples was consistent with the presence of **10**, thereby providing strong support for the hypothesis.

To test the hypothesis that **10** was indeed the active species, we devised an expedient synthesis of this structural class. We envisioned that introduction of the C2 carbonyl unit of **10** could be achieved via chemistry in parallel to that used to prepare **1**, beginning with hydrazide (+)-**6**. We began the synthesis by converting tryptophan hydrazide (+)-**6** to an intermediate thiosemicarbazide (not shown) employing carbonyl sulfide (S=C=O) gas dissolved in ethanol (**Scheme 1**) [13].



Scheme 1. Synthetic procedure to prepare thiocarbazates.

The intermediate thiosemicarbazide did not precipitate from solution, therefore 2-bromo-*N*-(2-ethyl-phenyl)-acetamide (**9**) [14] was added to the reaction flask to generate thiocarbazate (-)-**11** [15]. Pleasingly, the yield for the two-step, one flask operation was 62%. Deprotection of (-)-**11**, employing our previously developed conditions (25% water in TFA), generated the free base (-)-**12** in 98% yield with >95% purity. This 3-step

sequence permitted construction of (-)-**12** on gram scale, starting from L-Boc-Trp-OH; the overall yield was 58%.

As anticipated, both (-)-**11**(*S*) and (-)-**12**(*S*) exhibited potent inhibitory activity against cathepsin L with IC_{50} values of 56 nM and 133 nM, respectively [16]. The *R*-enantiomer, (+)-**11**(*R*) [17], was only modestly active against cathepsin L (IC_{50} = 34 μM). Some variability in IC_{50} values determined for (-)-**12** prompted us to explore the stability of both (-)-**11** and (-)-**12** in solvents relevant to the bioassay. While (-)-**11** was found to be completely stable in DMSO, as well as in the buffer employed in the cathepsin L assay [e.g., NaOAc (20 mM), pH 5.5; EDTA (1 mM); cysteine (5 mM)], the free-base (-)-**12** proved unstable in DMSO, generating decomposition products **13**, **14**, and **15** after only 1 hour at room temperature (**Figure 3**).

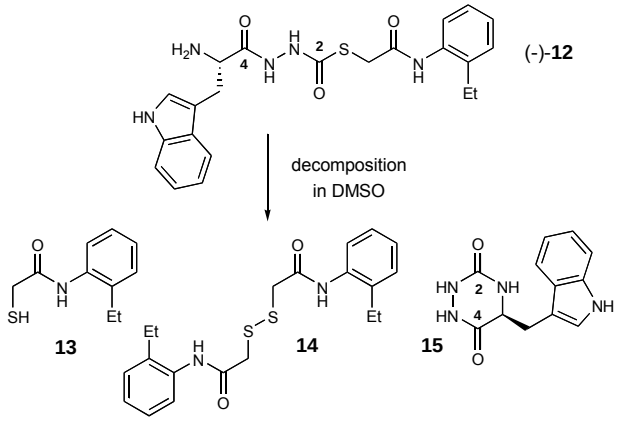


Figure 3. Decomposition products of (-)-**12** in DMSO.

Presumably **13-15** are formed from **(-)-12** via intramolecular attack of the primary amine on the C2 thiocarbazate moiety, and release of **13**. These products, prepared either via synthesis (**13** and **14**) or by HPLC purification of decomposed material (**15**), were assayed for cathepsin L activity and found to be inactive. Due to the instability of (-)-**12** under the assay conditions, IC_{50} values vary somewhat, rendering interpretation of the bioassay data difficult. We are however, confident in the accuracy of the bioassay results for (-)-**11**, as this compound is stable under all conditions evaluated. Thus, future efforts will be focused on the more stable thiocarbazate (-)-**11** and related congeners.

As most cysteine protease inhibitors contain an electrophilic "warhead," and work through a mechanism involving reaction with the active site cysteine [6, 18], we strongly believe these novel thiocarbazates behave similarly, and are active by virtue of their electrophilic carbonyl moiety. The formation of **15** supports this mechanism, and is indicative of the electrophilicity of the C2 carbonyl moiety. Reactivity at the anilide carbonyl is also a possibility, and cannot be ruled out. However, we observe no evidence of side-products resulting from reaction at this position (cf. **Figure 2**). A complete biochemical characterization of this novel chemotype is underway [1]." [12]

Center summary of probe properties and recommendations for the scientific use of probe as research tool [1]:

"A novel small molecule thiocarbazate (SID 26681509; (-)-**11**), a potent inhibitor of human cathepsin L with an IC_{50} of 56 nM, was developed following a 57,821 compound screen of the NIH Molecular Libraries Small Molecule Repository. After a 4 hr preincubation with cathepsin L, this compound became even more potent, demonstrating an IC_{50} of 1 nM. The thiocarbazate was determined to be a slow-binding and slowly reversible competitive inhibitor. Through a transient kinetic analysis for single-step reversibility, inhibition rate constants were k_{on} = 24,000 $M^{-1}s^{-1}$ and k_{off} = 2.2 x 10^{-5} s^{-1} (K_i = 0.89 nM). Molecular docking studies were undertaken using the experimentally-derived X-ray crystal structure of papain/CLIK-148 (1cvz.pdb). These studies revealed critical H-bonding patterns of the thiocarbazate with key active site residues in papain. The thiocarbazate displayed 11- to 150-fold greater selectivity toward cathepsin L than papain and cathepsins B, K, V, and S with no activity against cathepsin G." [1]

"Our kinetic analyses demonstrate that SID 26681509 is a highly potent and selective competitive inhibitor of human cathepsin L with slow binding and slow reversibility kinetics. Molecular docking of SID 26681509 into papain revealed hydrophobic interactions within the S2 and S1′ subsites and H-bonding interactions with Gln19, Cys25, Gly66, Asp158, and Trp177. These interactions share a high degree of similarity with the papain/CLIK-148 complex (**Figure 4**) [19, 20].

SID 26681509 is non-toxic to bovine aortic endothelial cells at 16.7 μM. It is also non-toxic at 100 μM to zebrafish in a live organism assay. The fact that SID 26681509 inhibits both malaria and leishmaniasis suggests that it acts in a cellular system requiring transit across lipid membranes. However, the micromolar potency, as opposed to sub-nanomolar potency against purified human cathepsin L, was not surprising since i) we have no measure of the internal concentration of inhibitor achieved in these organisms and ii) the active site geometries of their cathepsin L-like cysteine proteases might differ from that of the human enzyme. Further investigations of SID 26681509 and related analogs against purified cathepsin L-like enzymes such as falcipain, cruzipain, *T. gondii* cathepsin L, and rhodesain are warranted based on the findings of this study. The thiocarbazate scaffold can be readily derivatized, introducing functional groups to occupy specific binding sites in a variety of cysteine proteases, and thus holds promise as a general scaffold for the design of specific cysteine protease inhibitors." [1]

Table II. Summary of properties of SID 26681509.

IC_{50} (no preincubation)	56 nM
IC_{50} (4 hr preincubation)	1.0 nM
k_{on}	24,000 $M^{-1}s^{-1}$
k_{off}	2.2 x 10^{-5} s^{-1}
K_i	0.89 nM
(IC_{50} Cat B) / (IC_{50} Cat L)	45.1
Malaria assay	Toxic towards *Plasmodium falciparum* with an IC_{50} of 15.4 μM.
Leishmaniasis assay	Toxic towards *Leishmania major* with an IC_{50} of 12.5 μM.
Toxicity	Non-toxic to zebrafish at 100 μM. Non-toxic to bovine aortic endothelial cells at 16.7 μM.

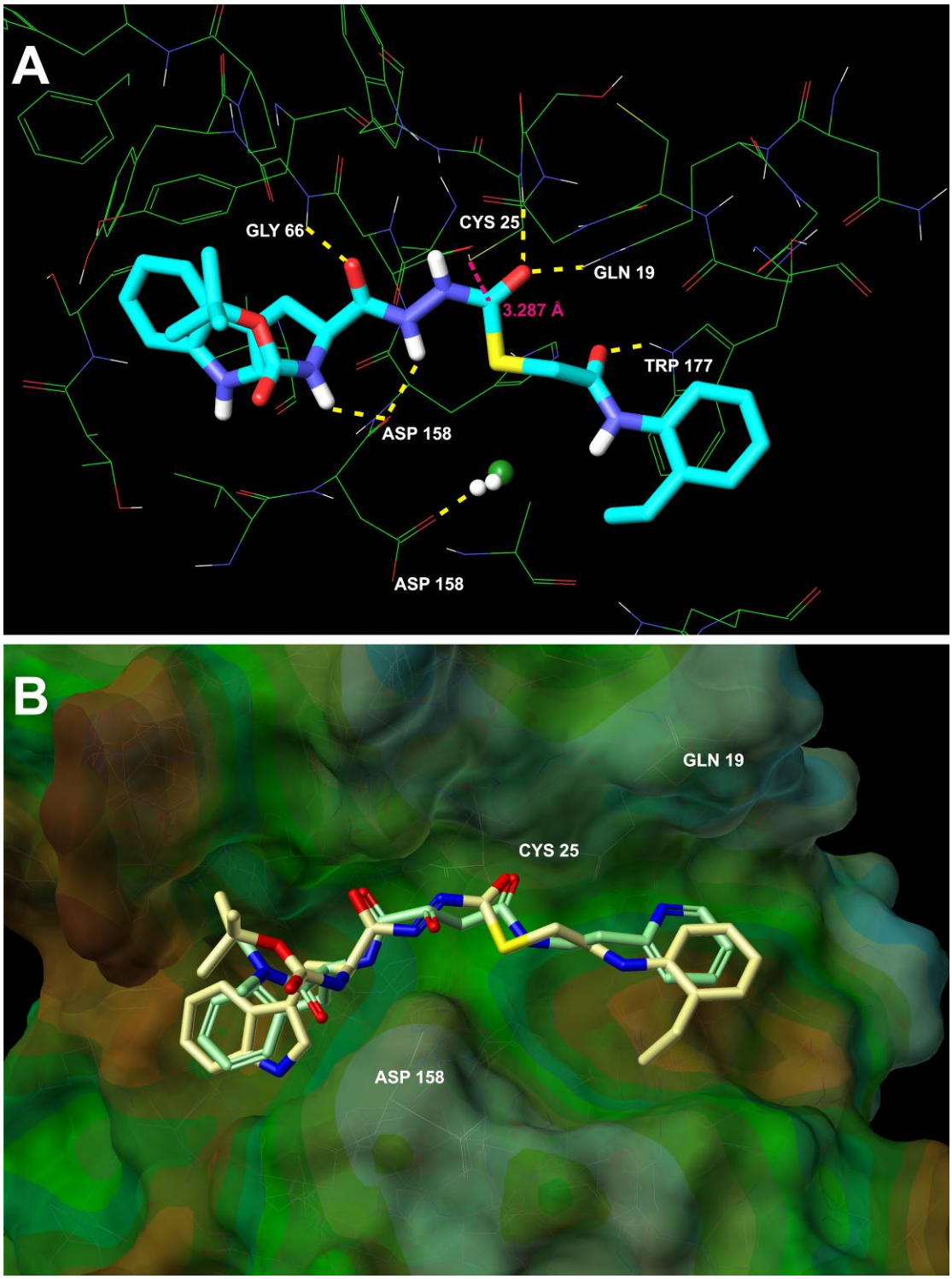


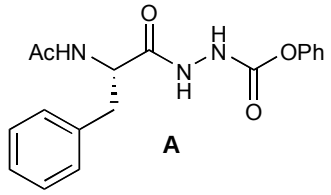
Figure 4. ***A.*** H-bonding interactions between SID 26681509 and papain involve catalytic residues Gln19, Cys25, Gly66, Asp158 and Trp177. The distance between the Cys25 sulfur atom and the thiocarbazate carbonyl carbon is 3.287 Å. This is the carbon likely to undergo nucleophilic attack by the sulfur. ***B.*** Overlay of papain/CLIK-148 (light green) with computational model of SID 26681509 in papain (tan). There are striking similarities between the binding interactions of the two inhibitors.

Appendices

Comparative data on probe, similar compound structures and prior probes [12]:

"Previously reported inhibitors of cathepsin L include the peptides, leupeptin and aprotinin, and the fluoromethyl ketone, Z-LLL-FMK [21, 22]. The few known, potent small molecule inhibitors are either peptidic and therefore likely to suffer from physiological instability and poor permeability, or are non-selective for cathepsin L [3, 21, 23]. The identification of potent, selective, stable, and cell permeable small molecule inhibitors would therefore be a valuable tool to interrogate cathepsin L and cathepsin L-like function, as well as to provide potential starting points for drug discovery and development [22, 24-28].

Thiocarbazates such as **10** have not been described previously in the literature. However, these compounds do bear structural resemblance to aza-peptides [29-31] (e.g. **A**; **Figure 5** [32]), examples of which have been reported to exhibit cysteine protease inhibitory activity through a mechanism involving attack by the active site cysteine on the carbamate carbonyl [18]." [12]



k_{on} = >11000 $M^{-1}s^{-1}$, papain
Abeles and Magrath (1992)

Figure 5. Known aza-peptide cathepsin inhibitor **A**.

Comparative data showing probe specificity for target [1]:

"SID 26681509 was tested for selectivity against papain and human cathepsins B, G, K, S, and V (**Table III**) with no preincubation of enzyme and inhibitor. The selectivity index of SID 26681509, a ratio of the IC_{50} against the assayed protease divided by the IC_{50} against cathepsin L, ranged from 11.0 to 150.8. SID 26681509 inhibited papain-like cysteine proteases including cathepsins B, K, S, and V with IC_{50} values ranging from 618 nM to 8.442 μM. As expected, SID 26681509 showed no inhibitory activity against the serine protease cathepsin G." [1]

Table III. Selectivity of SID 26681509 against papain and human cathepsins B, G, K, S, and V.

Enzyme	IC50 (μM)	Selectivity Index	% Identity to Cat L
Cathepsin L, human liver	0.056 ± 0.004	1.0	100
Cathepsin V, human, recombinant, NSO cells	0.618 ± 0.035	11.0	78
Cathepsin S, human spleen	0.724 ± 0.011	12.9	55
Cathepsin B, human liver	2.527 ± 0.073	45.1	26
Papain, *Carica papaya*	2.600 ± 0.208	46.4	48
Cathepsin K, human, recombinant, *E. coli*	8.442 ± 0.140	150.8	58
Cathepsin G, human neutrophil	>50	--	--

References

1. Shah, P.P., Myers, M. C., Beavers, M. P., Purvis, J. E., Jing, H., Grieser, H. J., Sharlow, E. R., Napper, A. D., Huryn, D. M., Cooperman, B. S., Smith, A. B, III, and Diamond, S. L., *Kinetic Characterization and Molecular Docking of a Novel, Potent, and Selective Slow-binding Inhibitor of Human Cathepsin L.* 2007. Submitted.
2. Turk, D. and G. Guncar, *Lysosomal cysteine proteases (cathepsins): promising drug targets.* Acta Crystallogr D Biol Crystallogr, 2003. **59**(Pt 2): p. 203-13.
3. Fujishima, A., et al., *The crystal structure of human cathepsin L complexed with E-64.* FEBS Lett, 1997. **407**(1): p. 47-50.
4. Leist, M. and M. Jaattela, *Triggering of apoptosis by cathepsins.* Cell Death Differ, 2001. **8**(4): p. 324-6.
5. Nomura, T. and N. Katunuma, *Involvement of cathepsins in the invasion, metastasis and proliferation of cancer cells.* J Med Invest, 2005. **52**(1-2): p. 1-9.
6. Otto, H.H. and T. Schirmeister, *Cysteine Proteases and Their Inhibitors.* Chem Rev, 1997. **97**(1): p. 133-172.
7. Turk, V., B. Turk, and D. Turk, *Lysosomal cysteine proteases: facts and opportunities.* Embo J, 2001. **20**(17): p. 4629-33.
8. Chandran, K., et al., *Endosomal proteolysis of the Ebola virus glycoprotein is necessary for infection.* Science, 2005. **308**(5728): p. 1643-5.
9. Pager, C.T. and R.E. Dutch, *Cathepsin L is involved in proteolytic processing of the Hendra virus fusion protein.* J Virol, 2005. **79**(20): p. 12714-20.
10. Simmons, G., et al., *Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry.* Proc Natl Acad Sci U S A, 2005. **102**(33): p. 11876-81.
11. PubChem web address for PCMD cathepsin L hits: http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=460.
12. Myers, M.C., Shah, P. P, Diamond, S. L., Huryn, D. M., and Smith, A. B, III., *Identification and Synthesis of a Unique Thiocarbazate Cathepsin L Inhibitor.* Bioorg Med Chem Lett, 2007. In press.
13. Chande, M.S. and K. Singh-Jathar, *Carbon Oxysulphide: A Novel Reagent for the Synthesis of 4-aminoanilino-3-aryl/aryloxymethyl/thiophenoxymethyl-1 ,2,4-triazolin-5-ones and 5-arylamino-2-mercapto-1,3,4-oxadiazoles.* Indian Journal of Chemistry B, 1998. **37B**: p. 352.
14. von Geldern, T.W., et al., *Pyrrolidine-3-carboxylic acids as endothelin antagonists. 4. Side chain conformational restriction leads to ET(B) selectivity.* J Med Chem, 1999. **42**(18): p. 3668-78.
15. Characterization data for (-)-**11** (PubChem SID 26681509) mp = 131 ^{o}C; $[\alpha]_D^{23}$ = -14.8 (*c* 0.5, AcOH); IR (KBr) 3412, 3343, 2971, 1680, 1529, 1167 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$, VT-350K) δ 10.61 (br s, 1H), 10.04, (br s, 1H), 9.88 (br s, 1H), 9.14 (br s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.16-7.11 (m, 3H), 7.05 (t, *J* = 7.1 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.47 (br s, 1H), 4.31 (br s, 1H), 3.73 (br s, 2H), 3.17 (dd, *J* = 14.7, 4.1 Hz, 2H), 2.96 (m, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 1.29 (br s, 9H), 1.13 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d$_6$, major rotamer) δ 172.7, 171.6, 166.9, 155.2, 137.3, 136.0, 135.4, 128.5, 127.1, 125.7, 125.5, 125.2, 124.0, 120.9, 118.5, 118.1, 111.3, 109.9, 78.0, 53.6, 33.1, 28.1, 27.7, 23.6, 14.2; high resolution mass spectrum (ES+) *m/z* 562.2126 [(M+Na)$^+$; calcd for $C_{27}H_{33}N_5O_5SNa$: 562.2100]. $[\alpha]_D^{23}$= -14.8
16. IC_{50} values and mean ± standard deviations: (-)-**11**(*S*) 56 nM ± 4 nM; (-)-**12**(*S*) 133 nM ± 3 nM; (+)-**11**(*R*) 34 μM ± 2 μM.
17. Optical rotation for (+)-**11**: $[\alpha]_D^{23}$= +12.8. The enantiomeric purity of both (-)-**11** and (+)-**11** were assayed using an OD-RH chiral column with the following LC parameters: 1.0 mL / min with a linear gradient of 90% water in acetonitrile to 10% water in acetonitrile over 15 min. Using this method, baseline separation was obtained for the enantiomers and retention times for (-)-**11** and (+)-**11** were 14.01 min and 13.02 min, respectively. The synthesis, outlined in Scheme 1, produced both enantiomers in >99% enantiomeric purity.
18. Powers, J.C., et al., Ir*reversible inhibitors of serine, cysteine, and threonine proteases. C*hem Rev, 2002. 102(12): p. 4639-750.

19. Katunuma, N., et al., St*ructure based development of novel specific inhibitors for cathepsin L and cathepsin S in vitro and in vivo. F*EBS Lett, 1999. 45**8(1**): p. 6-10.
20. Tsuge, H., et al., In*hibition mechanism of cathepsin L-specific inhibitors based on the crystal structure of papain-CLIK148 complex. B*iochem Biophys Res Commun, 1999. 26**6(2**): p. 411-6.
21. Esser, R.E., et al., Cy*steine proteinase inhibitors decrease articular cartilage and bone destruction in chronic inflammatory arthritis. A*rthritis Rheum, 1994. 37**(2**): p. 236-47.
22. Marquis, R.W., et al., A*zepanone-based inhibitors of human cathepsin L. J* Med Chem, 2005. 48**(2**2): p. 6870-8.
23. Montaser, M., G. Lalmanach, and L. Mach, CA-*074, but not its methyl ester CA-074Me, is a selective inhibitor of cathepsin B within living cells. B*iol Chem, 2002. 38**3(7**-8): p. 1305-8.
24. Schirmeister, T. and U. Kaeppler, No*n-peptidic inhibitors of cysteine proteases. M*ini Rev Med Chem, 2003. 3(**4**): p. 361-73.
25. Hernandez, A.A. and W.R. Roush, Re*cent advances in the synthesis, design and selection of cysteine protease inhibitors. C*urr Opin Chem Biol, 2002. 6(**4**): p. 459-65.
26. Zhou, N.E., et al., 3-*Acylamino-azetidin-2-one as a novel class of cysteine proteases inhibitors. B*ioorg Med Chem Lett, 2003. 13**(1**): p. 139-41.
27. Huang, L. and J.A. Ellman, Ge*neral solid-phase method to prepare novel cyclic ketone inhibitors of the cysteine protease cruzain. B*ioorg Med Chem Lett, 2002. 12**(2**0): p. 2993-6.
28. Chiva, C., et al., Sy*nthesis and NMR structure of p41icf, a potent inhibitor of human cathepsin L. J* Am Chem Soc, 2003. 12**5(6**): p. 1508-17.
29. Baggio, R., et al., Fro*m good substrates to good inhibitors: design of inhibitors for serine and thiol proteases. B*iochemistry, 1996. 35**(1**1): p. 3351-3.
30. Thompson, S.K., et al., De*sign of potent and selective human cathepsin K inhibitors that span the active site. P*roc Natl Acad Sci U S A, 1997. 94**(2**6): p. 14249-54.
31. Xing, R. and R.P. Hanzlik, A*zapeptides as inhibitors and active site titrants for cysteine proteinases. J* Med Chem, 1998. 41**(8**): p. 1344-51.
32. Magrath, J. and R.H. Abeles, Cy*steine protease inhibition by azapeptide esters. J* Med Chem, 1992. 35**(2**3): p. 4279-83.