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Pyrazole-based cathepsin S inhibitors with arylalkynes as P1 binding elements

Michael K. Ameriks [a,*], Frank U. Axe [a], Scott D. Bembenek [a], James P. Edwards [a], Yin Gu [a], Lars Karlsson [a], Mike Randal [b], Siquan Sun [a], Robin L. Thurmond [a], Jian Zhu [a]

[a] Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 3210 Merryfield Row, San Diego, CA 92121, USA
[b] Sunesis Pharmaceuticals, 341 Oyster Point Boulevard, South San Francisco, CA 94080, USA

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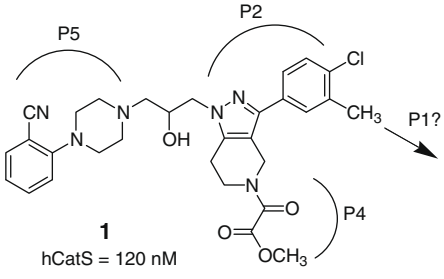
ABSTRACT

A crystal structure of **1** bound to a Cys25Ser mutant of cathepsin S helped to elucidate the binding mode of a previously disclosed series of pyrazole-based CatS inhibitors and facilitated the design of a new class of arylalkyne analogs. Optimization of the alkyne and tetrahydropyridine portions of the pharmacophore provided potent CatS inhibitors (IC_{50} = 40–300 nM), and an X-ray structure of **32** revealed that the arylalkyne moiety binds in the S1 pocket of the enzyme.

Cathepsin S (CatS), a cysteine protease of the papain family, is found in the lysosome of certain antigen-presenting cells. Through proteolytic degradation of the invariant chain (Ii), a chaperone protein for major histocompatibility complex class II molecules (MHCII), CatS plays a key role in facilitating antigen presentation to $CD4^+$ T-cells.[1] Inhibition of CatS activity impedes the removal of Ii from MHCII molecules, and may help to regulate immune hyperresponsiveness by attenuating antigen presentation. Other pharmacologically relevant activities have also been attributed to CatS.[2] Most CatS inhibitors have traditionally relied upon covalent modification of the active site cysteine to achieve good activity, but recently several noncovalent inhibitors have been disclosed as well.[3–6]

We have previously reported potent noncovalent inhibitors of human CatS characterized by a fused tetrahydropyrido-pyrazole heterocycle.[6] In order to elucidate the binding mode of this class of compounds, a crystal structure of **1** bound to a Cys25Ser mutant[7] of cathepsin S was obtained (Fig. 1).[8]



1
hCatS = 120 nM

Two hydrogen bonds are observed between the oxamide of **1** and the backbone amide of Val162 as well as the side chain amide of Asn161 in the S4 subsite of CatS.[9] These interactions anchor the

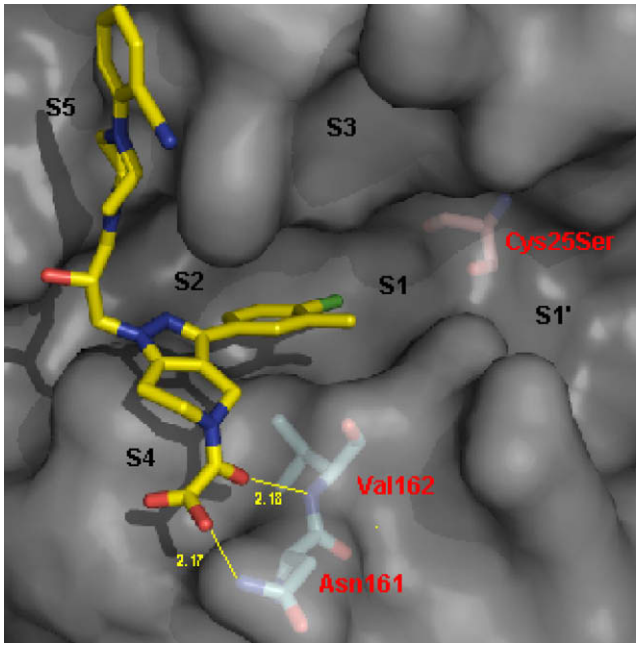


Figure 1. Crystal structure of **1** bound to a Cys25Ser mutant of cathepsin S. Compound conformation is shown as an average of two enantiomers.

* Corresponding author.
E-mail address: mameriks@its.jnj.com (M.K. Ameriks).

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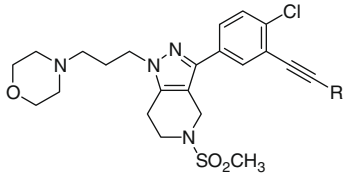
tetrahydropyrido-pyrazole core of **1** in the S2 region and the arylpiperazine moiety in S5. Notably, ligand **1** differs from previously reported CatS inhibitors in that it binds distal to the active site and does not access the S1, S1′, or S3 regions of the enzyme. However, further analysis reveals that the methyl group *ortho* to the arylchloride in **1** is oriented towards the S1 pocket, suggesting that a judicious choice of substituents at this position might provide access to the active site. In this Letter, we describe the successful implementation of this design strategy, and disclose a series of arylalkyne analogs of **1** that bind in S1.

At the onset, we targeted aryliodide **3** as a key synthetic intermediate for introducing potential P1 groups through Pd-catalyzed cross-couplings (Scheme 1). For ease of synthesis, a sulfonamide was selected as a P4 group, and following our previously described route, the tetrahydropyrido-pyrazole core **2** was assembled in three steps from *N*-methanesulfonyl piperidone. Subsequent regioselective pyrazole alkylation, acetal hydrolysis, and reductive amination afforded the desired intermediate **3** in moderate yield. This sequence allowed for removal of the chiral center in **1** and provided a potential late-stage opportunity to screen P5 binding elements. However, a morpholine ring was initially chosen as a solubilizing replacement for the bulky arylpiperazine moiety in **1**, and was held constant to facilitate identification of a suitable P1 group. Based on molecular modeling for a variety of scaffolds, we initially focused on alkyne linkers as it was anticipated that the rigidity imposed by sp-hybridization would direct substituents to the S1 pocket.

Using standard Sonogashira conditions, a small library of alkynes (**4–11**) was prepared from aryliodide **3** (Table 1). Preliminary results proved discouraging as terminal acetylene **11** demonstrated only micromolar inhibition of CatS. Appending a heteroatom onto the alkyne (**4**) failed to improve potency, as did the introduction of linear, branched, or cyclic alkyl groups (**5–7**). However, direct attachment of aromatic rings provided a dramatic improvement in potency, affording compounds (**8–9**) with submicromolar inhibition of CatS. In fact, the phenyl-substituted alkyne **8** demonstrated a 10-fold improvement in enzymatic activity (0.6 μM vs 7.4 μM) compared to the unsubstituted alkyne **11**.

In order to optimize the potency of phenylalkyne **8**, we explored the effect of substitution around the terminal aromatic ring. The

Table 1
Effect of alkyne substitution on cathepsin S activity[a]



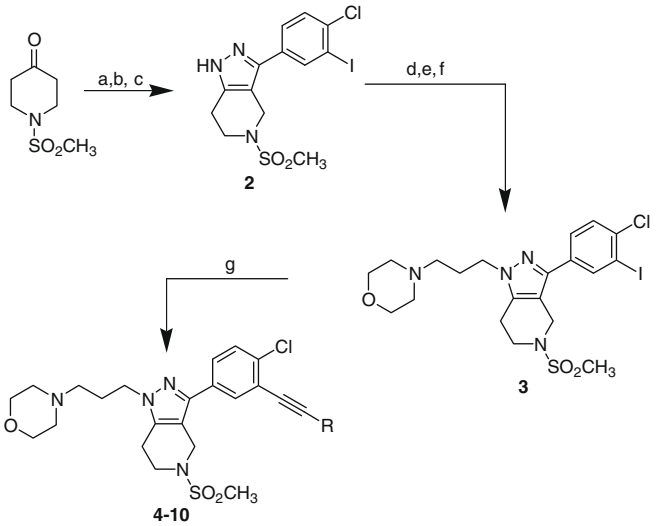
Compound	R	CatS IC_{50} (μM)
4	CH_2OH	7.9
5	*n*-Butyl	11
6	*i*-Butyl	8.3
7	Cyclohexyl	6.7
8	Phenyl	0.61
9	2-Thiophene	0.79
10	3-Thiophene	1.5
11	H	7.4

[a] CatS IC_{50} values are the mean of $n \geqslant 2$ runs and determined as described previously.[6a] All IC_{50}s were within a twofold range.

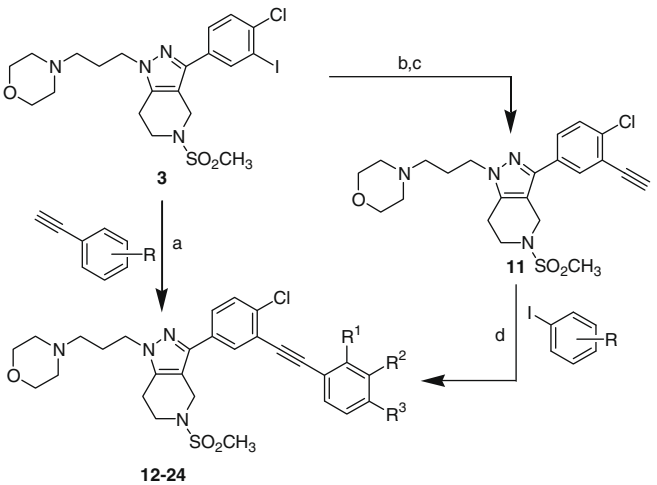
substituted arenes **12–20** could be prepared by either coupling the parent aryliodide **3** with commercially available arylacetylenes, or by introducing a terminal alkyne **11** through a standard two-step sequence, followed by a second Sonogashira coupling with a variety of aryliodides (Scheme 2).

CatS inhibition for a range of substituted arylalkynes is shown in Table 2. The SAR of *ortho*- and *meta*-substituted arenes is quite flat, as lipophilic (Cl, CH_3), electron-donating (OCH_3), and electron-withdrawing (CF_3) groups all failed to significantly enhance enzymatic potency relative to the unsubstituted arene **8**. The introduction of *para*-substituents, however, slightly improved activity. Both electron-donating (OCH_3, NH_2) and electron-withdrawing (CF_3, CO_2H) functionalities were tolerated, and the 4-chloro analog **18** consistently exhibited a threefold improvement in CatS inhibition (0.20 μM vs 0.61 μM for **8**).

Further profiling of compound **18** revealed several promising attributes (Fig. 2). In addition to inhibiting human CatS, **18** demonstrated sub-micromolar inhibition of mouse CatS activity (IC_{50} = 690 nM). This is encouraging because previous pyrazole-based inhibitors displayed markedly reduced affinity for murine CatS, making it difficult to test these compounds in in vivo disease models.[6a] Furthermore, alkyne **18** exhibited exquisite selectivity

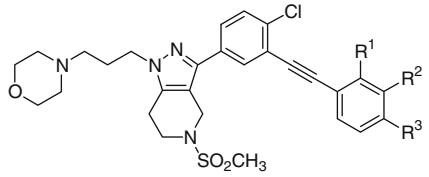


Scheme 1. Reagents and conditions: (a) Morpholine, *p*-TSA·H_2O (1–3%), benzene, 80 °C; (b) 4-Chloro-3-iodobenzoyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt; (c) H_2NNH_2, EtOH (36%, three steps); (d) 2-(2-Bromoethyl)1,3-dioxolane, Cs_2CO_3, DMF (85%); (e) 1 N HCl, acetone, 55 °C; (f) Morpholine, $Na(OAc)_3BH$, acetic acid, CH_2Cl_2 (60%, two steps); (g) H–≡–R, 10% $Pd(PPh_3)_2Cl_2$, 10% CuI, Et_3N, THF, rt (50–95%).



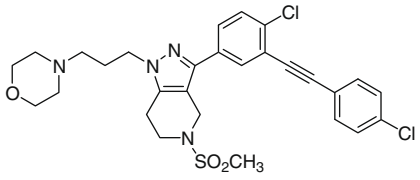
Scheme 2. Reagents and conditions: (a) 10% $Pd(PPh_3)_2Cl_2$, 10% CuI, Et_3N, THF (50–95%); (b) Trimethylsilylacetylene, 10% $Pd(PPh_3)_2Cl_2$, 10% CuI, Et_3N, THF (91%); (c) TBAF, THF (67%); (d) 10% $Pd(PPh_3)_2Cl_2$, 10% CuI, Et_3N, THF (50–70%).

Table 2
Effect of aryl substitution on cathepsin S activity[a]



Compound	R^1	R^2	R^3	CatS IC_{50} (μM)
8	H	H	H	0.61
12	Cl	H	H	0.72
13	CH_3	H	H	1.1
14	CF_3	H	H	0.87
15	OCH_3	H	H	0.55
16	H	Cl	H	0.70
17	H	CF_3	H	1.5
18	H	H	Cl	0.20
19	H	H	CH_3	0.28
20	H	H	CF_3	0.28
21	H	H	OCH_3	0.48
22	H	H	NH_2	0.43
23	H	H	CO_2H	0.51
24	H	Cl	Cl	0.32

[a] See Table 1 for details.



18

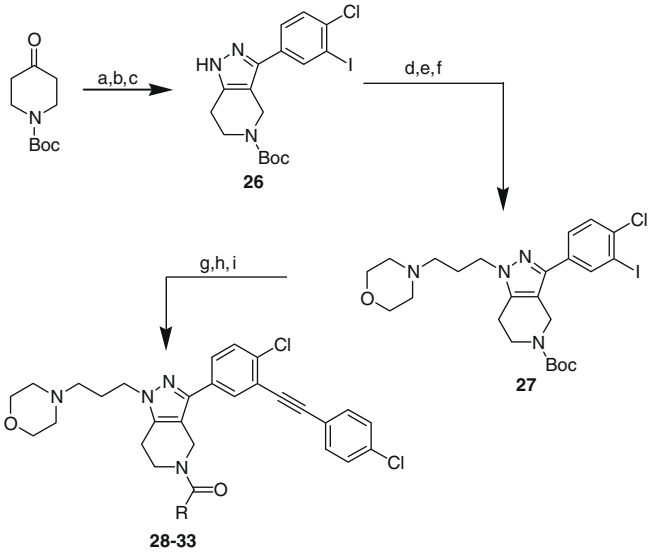
hCatS = 200 nM; mCatS = 690 nM; hCatB, hCatF, hCatL > 20 μM
Rat PK (male Sprague-Dawley, n = 3):
po, (10 mpk): C_{max} = 0.53 μM; AUC = 48 μmol*h/L
iv, (2 mpk): $t_{1/2}$ = 2h; Cl = 0.18 L/h; %F = 21

Figure 2. Profile of alkyne **18**.

for CatS over the closely related cathepsins B, F, and L (>100-fold), and also reached systemic circulation following oral dosing in rats (%*F* = 21). However, despite their encouraging enzymatic potency, all of the alkynes shown in Table 2 failed to demonstrate any activity in a secondary cellular assay measuring Ii degradation in human JY cells (data not shown).

In order to further optimize the enzymatic activity of the alkyne series, sulfonamide replacements on the tetrahydropyridine nitrogen were investigated (Scheme 3). The N-Boc tetrahydropyridine **26** could be prepared in an identical manner to the *N*-methanesulfonyl analog described earlier. Due to the poor stability of the Boc group under the acidic conditions used for the acetal hydrolysis, an alternate route to the P5 morpholine linker was developed. Conjugate addition of pyrazole **26** to acrylonitrile and subsequent nitrile reduction afforded an aldehyde, which was immediately subjected to a reductive amination with morpholine to yield iodide **27**. Introduction of 4-chloro-ethynylbenzene under Sonogashira conditions, followed by removal of the Boc group, provided the free tetrahydropyridine, which was acylated with commercially available carboxylic acids or acid chlorides to generate the targeted alkynes **28–33**.

Based on the crystal structure of **1** bound to CatS, it was anticipated that the incorporation of a P4 group with two hydrogen-bond acceptors would improve potency by interacting with both Asn161 and Val162. Although heterocyclic (**28–30**) and acyclic

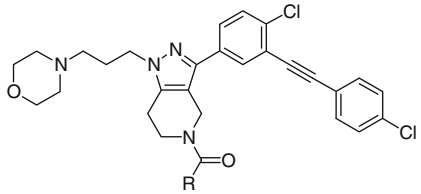


Scheme 3. Reagents and conditions: (a) morpholine, *p*-TSA·H_2O (1–3%), benzene, 80 °C; (b) 4-chloro-3-iodobenzoyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt; (c) H_2NNH_2, EtOH (62%, three steps); (d) acrylonitrile, 1% aq NaOH, THF (72%); (e) DIBAL, CH_2Cl_2, −78 °C to rt; (f) morpholine, $Na(OAc)_3BH$, acetic acid, CH_2Cl_2 (51%, two steps); (g) 4-Chloro-ethynylbenzene, 10% $Pd(PPh_3)_2Cl_2$, 10% CuI, Et_3N, THF (93%); (h) TFA, CH_2Cl_2 (92%); (i) RCOCl, pyridine, CH_2Cl_2 (75–95%), or RCO_2H, EDC (polymer-bound), CH_2Cl_2 (85%).

(**31–32**) hydrogen-bond acceptors failed to significantly enhance CatS inhibition relative to sulfonamide **18**, the introduction of an oxamide moiety **33** provided a fivefold improvement in enzymatic activity (IC_{50} = 40 nM, Table 3). Despite the modest enzymatic activity observed for many of these sulfonamide replacements, X-ray analysis of compound **32** bound to Cys25Ser CatS revealed the presence of two hydrogen bonds between the α-hydroxyamide and the targeted S4 residues (PDB ID: 3IEJ, Fig. 3).[7] Furthermore, the crystal structure confirmed that the 4-chlorophenylalkyne group in **32** resides in the S1 pocket, thus validating the molecular modeling predictions that inspired our design strategy.

In conclusion, a crystal structure of **1** bound to a Cys25Ser mutant of cathepsin S helped to elucidate the binding mode of a previously disclosed series of pyrazole-based CatS inhibitors and facilitated the design of a new class of arylalkyne analogs. Optimization of the alkyne and tetrahydropyridine portions of the pharmacophore provided potent CatS inhibitors (IC_{50} = 40–300 nM),

Table 3
Effect of N-substitution on cathepsin S activity[a]



Compound	R	CatS IC_{50} (μM)
28	2-Pyridyl	0.14
29	2-Furanyl	0.33
30	(±)-2-Tetrahydrofuranyl	0.31
31	CH_2OAc	0.28
32	CH_2OH	0.22
33	$C(O)OCH_3$	0.04

[a] See Table 1 for details.

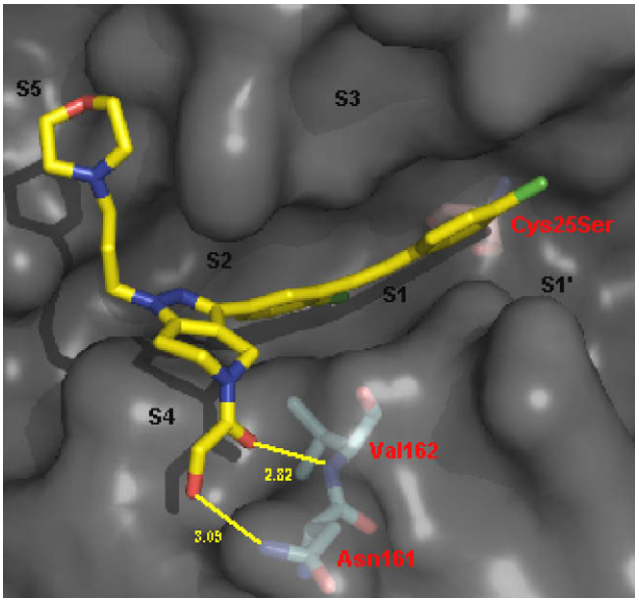


Figure 3. Crystal structure of **32** bound to a Cys25Ser mutant of CatS.

and an X-ray structure of **32** confirmed that the arylalkyne moiety binds in the S1 pocket of the enzyme.

Acknowledgment

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8. The crystal structure of compound **1** could not be uploaded into the PDB because structure factors were not provided by Sunesis Pharmaceuticals, presumably because they were note required for submission into the PDB at the time this structure was solved (2003).
9. The electron density for the methyl group in oxamide **1** could not be observed, so it is not clear which oxygen of the oxamide forms a H-bond with Asn161.