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Discovery and SAR of novel pyrazole-based thioethers as cathepsin S inhibitors: Part 1

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ABSTRACT

A series of pyrazole-based thioethers were prepared and found to be potent cathepsin S inhibitors. A crystal structure of **13** suggests that the thioether moiety may bind to the S3 pocket of the enzyme. Additional optimization led to the discovery of aminoethylthioethers with improved enzymatic activity and submicromolar cellular potency.

Cathepsin S (CatS) is a cysteine protease of the papain family that is involved in the presentation of antigens to the cell surface of certain antigen-presenting cells (APCs) for recognition by $CD4^+$ T-cells. The main target of the proteolytic activity of CatS is the invariant chain (Ii), a chaperone molecule for major histocompatibility complex class II molecules (MHC II).[1] Inhibition of CatS activity slows the removal of Ii and attenuates antigen presentation to $CD4^+$ T-cells, resulting in immunosuppression with specificity for these T-cells.

We have previously reported our efforts to identify novel noncovalent inhibitors of CatS based on a tetrahydropyrido-pyrazole heterocycle (Fig. 1).[2] Much of this work focused on the SAR of substituent variations of the 'headgroup' as well as the P4 group, as exemplified by compounds **1** and **2**. More recently, we became interested in exploring substitution that would access S1 binding, ultimately discovering novel arylalkynes, such as compound **3**, that bind to this region of the enzyme.[2f] Concurrent efforts to explore alternative binding elements led to the preparation of analogs containing aryl thioethers as a replacement for these arylalkynes.

Preliminary investigation of such thioethers was conducted using aryl iodide intermediates **4** and **5**, which were synthesized as previously reported.[2f] Metal-mediated coupling with commercially available thiols afforded the desired thioether products (Scheme 1).[3]

As seen in Table 1, these initial compounds exhibited promising activity. Compounds **6** and **7** share similarly moderate enzymatic activity, indicating that the elongation of the methylene tether is not detrimental to activity. Replacement of the phenyl group with a methyl group (**8**) appears to decrease activity, whereas the incorporation of a phenyl ether (**9**) leads to submicromolar inhibition. Exchanging the *para*-chloro moiety with a trifluoromethyl group maintains activity (**9** vs **10**). However, substituting the morpholine headgroup with 1-piperidin-4-yl-pyrrolidin-2-one led to threefold improved activity for compound **11**.

Re-design of the synthesis route enabled more facile access to thioether variations through aromatic substitution rather than palladium-mediated coupling (Scheme 2). In this instance, initial reaction with mercaptoethanol was followed by alkylation with 2-(2-bromoethyl)-1,3-dioxolane. Unmasking the aldehyde under acidic conditions and subsequent reductive amination provided hydroxyethylthioether **12**, which was found to be equipotent to ether analog **11**.

A crystal structure was obtained for a close analog of alcohol **12** (compound **13**, Fig. 2).[4] Notably, the hydroxyethylthioether of **13** points toward the S3 region of the active site rather than toward

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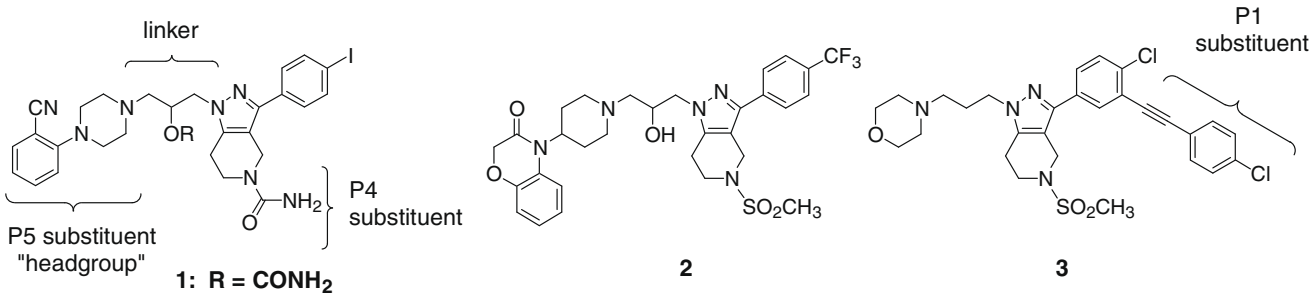
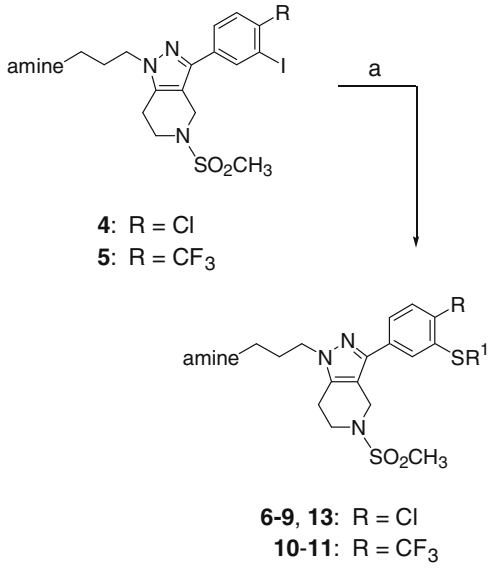
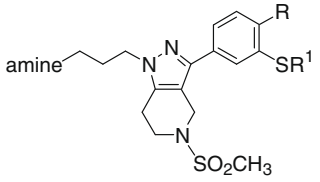


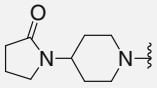
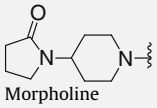
Figure 1. Previous CatS inhibitors with tetrahydropyrido-pyrazole core.



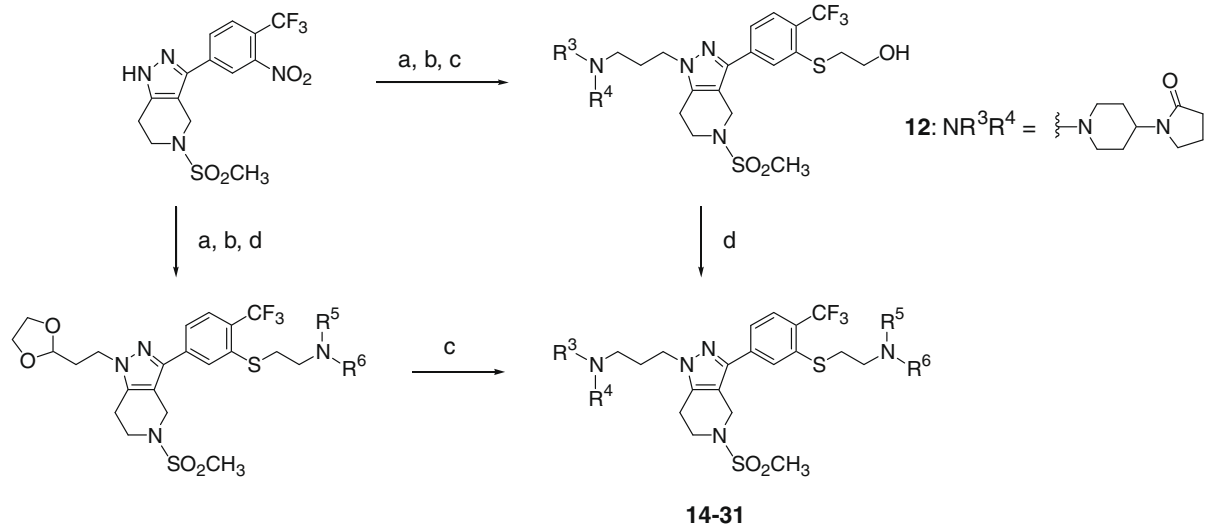
Scheme 1. Reagents and conditions: (a) HSR^1, $Pd_2(dba)_3$, dppf, Et_3N, DMF or NMP, 70–80 °C (36–95%). For $HSCH_2CH_2OH$: CuI, neocuproine, NaO*t*-Bu, toluene, 110 °C (43%). R^1 is defined in Table 1.

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



Compd	Amine	R	R^1	CatS IC_{50} (μM)
6	Morpholine	Cl	CH_2Ph	1.65
7	Morpholine	Cl	CH_2CH_2Ph	1.47
8	Morpholine	Cl	$CH_2CH_2CH_3$	3.60
9	Morpholine	Cl	CH_2CH_2OPh	0.60
10	Morpholine	CF_3	CH_2CH_2OPh	0.74
11		CF_3	CH_2CH_2OPh	0.22
12		CF_3	CH_2CH_2OH	0.20
13	Morpholine	Cl	CH_2CH_2OH	0.96

[a] CatS IC_{50} values are the mean of $n \geqslant 2$ runs and determined as described previously.[2b]



Scheme 2. Reagents and conditions: (a) $HSCH_2CH_2OH$, K_2CO_3, DMF, 90 °C (75–89%); (b) 2-(2-bromoethyl)-1,3-dioxolane, Cs_2CO_3, DMF (95%); (c) (i) 1 N HCl (aq), acetone, 55 °C; (ii) HNR^3R^4, acetic acid, $NaBH(OAc)_3$, CH_2Cl_2 (6–51%, two steps); (d) (i) CH_3SO_2Cl, Et_3N, CH_2Cl_2; (ii) HNR^5R^6, EtOH/DCE, 60 °C (33–65%, two steps). NR^3R^4 and NR^5R^6 are defined in Tables 2 and 3.