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The SAR of 4-substituted (6,6-bicyclic) piperidine cathepsin S inhibitors

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Abstract—A series of competitive, reversible cathepsin S (CatS) inhibitors was investigated. An earlier disclosure detailed the discovery of the 4-(2-keto-1-benzimidazolinyl)-piperidin-1-yl moiety as an effective replacement for the 4-arylpiperazin-1-yl group found in our screening hit. Continued investigation into replacements for the 4-aryl piperazine resulted in the identification of potentially useful CatS inhibitors with enzymatic and cellular activity similar to that of JNJ 10329670 as disclosed in a previous publication.
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Cathepsin S (CatS), a cysteine protease found in the lysosome of hematopoietic cells, is integrally involved in antigen presentation of major histocompatibility complex class II (MHC-II) molecules. These molecules bind antigens and transport them to the cell surface for display to various cells of the immune system. The invariant chain (Ii), a component of MHC-II complex, prevents premature binding of non-antigenic peptides by acting as a chaperone. CatS mediates the cleavage of the Ii p10 fragment, prior to cell surface antigen presentation to $CD4^+$ T cells.[1–3] Inhibition of CatS would block the necessary degradation of the Ii, preventing antigen presentation, resulting in immunosuppression with specificity for $CD4^+$ T cells. In CatS −/− mice, the flow of MHC-II molecules to the cell surface is significantly reduced.[3] It is anticipated that selective inhibition of CatS would be therapeutically useful in diseases that are characterized by hyperimmune responses.

Recently, we reported on our efforts to identify novel noncovalent inhibitors of CatS.[4,5] Our initial lead compound **I**, as previously disclosed, was identified through virtual screening of a subset of the J&J PRD library using DOCK.[4] Subsequent development of the SAR led to the identification of compounds **II** and **III** (JNJ 10329670).[4,5] Compounds in the latter series have improved selectivity profiles, cellular activity, and pharmacokinetics, with suitable physicochemical properties for further development. Both series share several common structural motifs; the aryl substituted pyrazole group, a saturated linker three carbons in length, and a 1,4-substituted basic nitrogen containing ring. Increasing the lipophilicity of the tetrahydropyrazolopyridine aryl, substituent was previously noted to improve enzymatic CatS activity.[5,6]

In this report, we wish to detail our continued investigation into replacements for the aryl piperazine portion of compound **II**. The analogs included here maintain the structural commonality detailed above for both series **II** and **III**. The headgroup replacements of interest are shown in Figure 1.

Amines **1** and **2** were prepared according to Scheme 1 starting with readily available intermediates, **13a** and **13b**.[7] Reductive amination[8] of the anilines with *tert*-butyl-4-oxo-1-piperidinecarboxylate followed by reduction of the double bond using H_2 in the presence of Pd/C or PtO_2 afforded the desired amines **14a** and **14b**. Subsequent hydrolysis, cyclization, and deprotection using standard conditions resulted in the preparation of the desired amines.[9]

Keywords: Cathepsin S; Cysteine protease inhibitor.
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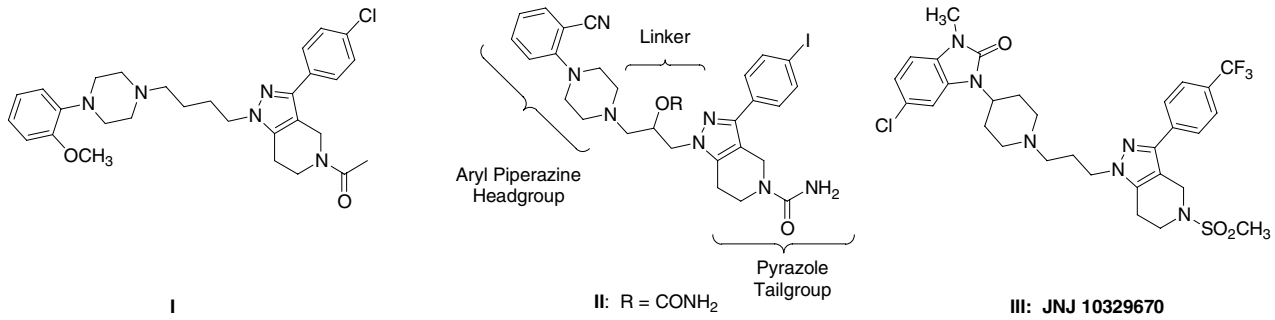


I II: R = $CONH_2$ III: JNJ 10329670

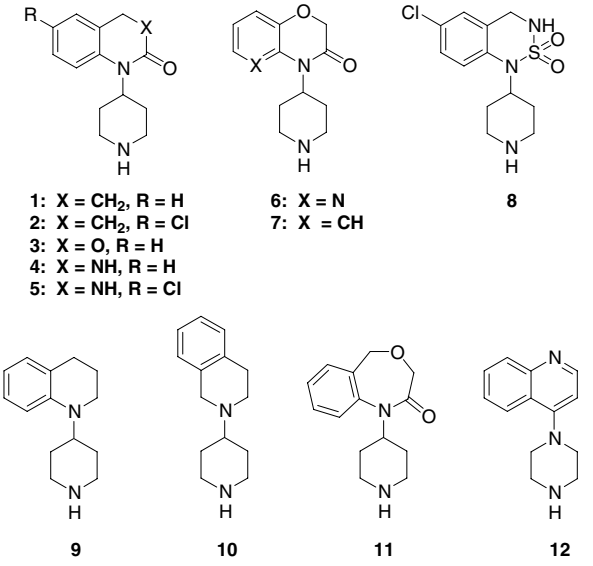
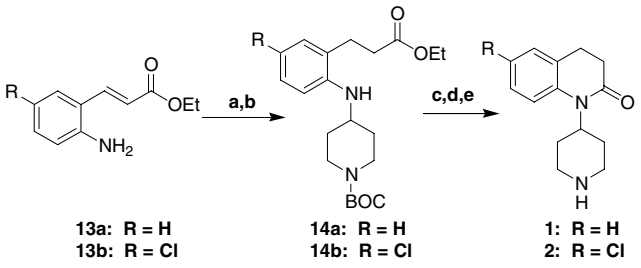
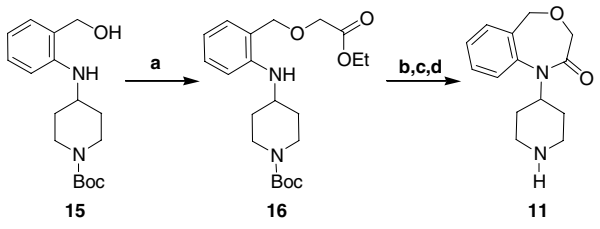


Figure 1. Aryl piperazine replacements.



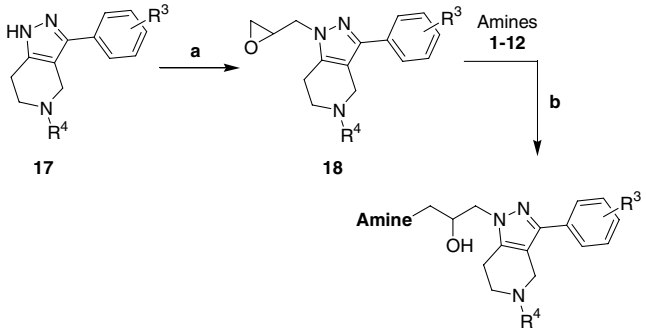
Scheme 1. Synthesis of compounds **1** and **2**. Reagents and conditions: (a) Boc-piperidone, $NaBH(OAc)_3$, CH_2Cl_2, AcOH, rt, R = H, 71%, R = Cl, 66%; (b) R = H: H_2, 10% Pd/C, EtOAc, rt, 95%; R = Cl: PtO_2, H_2, EtOAc, rt, 46%; (c) 1.0 M NaOH, 4:1 MeOH/H_2O, rt, R = H, 93%, R = Cl, 74%; (d) EDCI, CH_2Cl_2, rt, R = H, 95%, R = Cl, 52%; (e) 1:1 TFA/CH_2Cl_2, rt, R = H, 95%, R = Cl, 93%.

Piperidines **3**–**8** and piperazine **12** were prepared according to literature procedures.[10–12] Amines **9** and **10** were prepared via reductive amination using readily available starting materials.[8] Amine **11** was prepared according to Scheme 2. The hydroxyl group of compound **15**, prepared according to a literature procedure,[13] was alkylated with ethyl bromoacetate to yield ester **16**. Hydrolysis of the ester to the acid, followed by cyclization and deprotection, gave piperidine **11**.

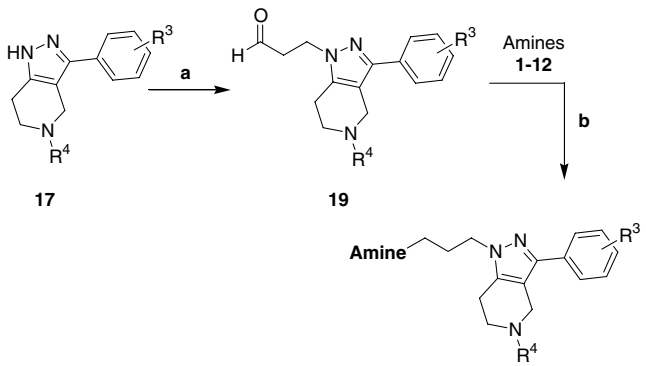


Scheme 2. Preparation of compound **11**. Reagents and conditions: (a) NaH, ethyl bromoacetate, DMF, 0 °C, 33%; (b) LiOH, H_2O, THF, rt, 93%; (c) HATU, DMF, rt, 33%; (d) 1:1 TFA/CH_2Cl_2, rt, 45 min, 49%.

The targeted CatS inhibitors were prepared using one of two methods as depicted by Schemes 3 and 4. Both procedures require the preparation of pyrazole **17**, as described previously.[4] The first method results in the



Scheme 3. Preparation of compounds **20**–**23**, **28**, **31**, **32**, **34**, and **37**–**57**. Reagents and conditions: (a) epichlorohydrin (4–6 equiv), Cs_2CO_3 (2 equiv), DMF, rt; (b) amine, EtOH, reflux.



Scheme 4. Preparation of compounds **24**–**27**, **29**, **30**, **33**, **35**, and **36**. Reagents and conditions: (a) 3-bromopropanol, Cs_2CO_3, DMF, rt; (b) amine, $NaBH(OAc)_3$, AcOH, CH_2Cl_2.

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