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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.

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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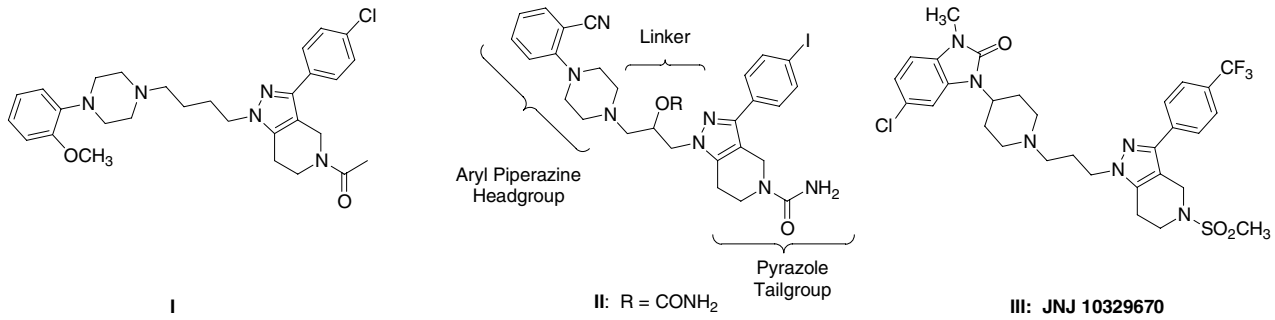


I II: R = $CONH_2$ III: JNJ 10329670

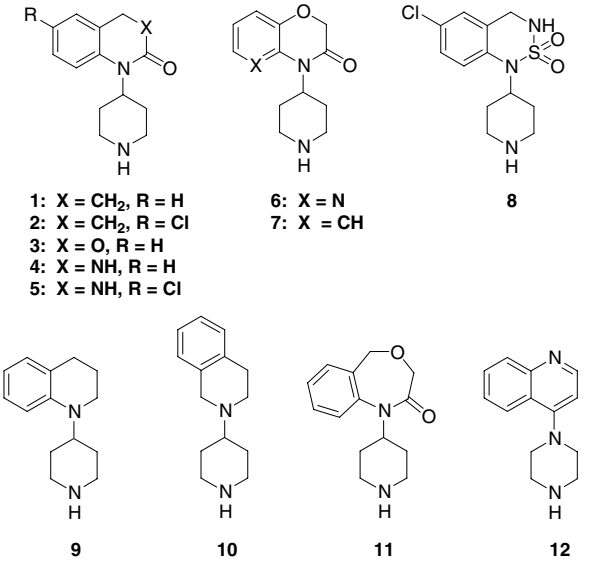
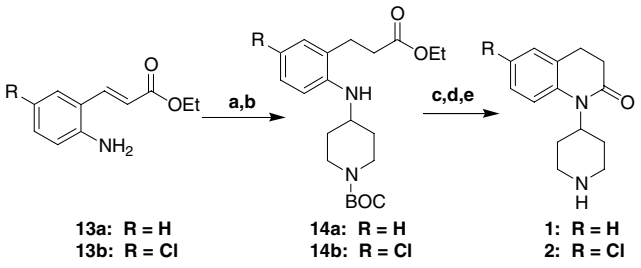
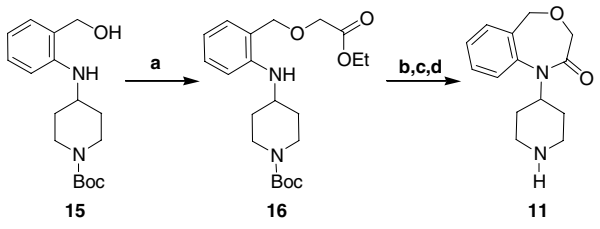


Figure 1. Aryl piperazine replacements.



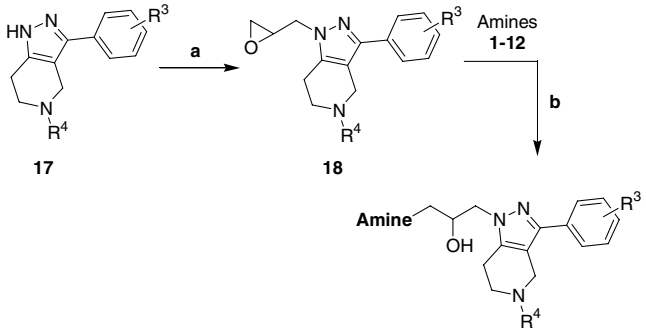
Scheme 1. Synthesis of compounds **1** and **2**. Reagents and conditions: (a) Boc-piperidone, $NaBH(OAc)_3$, CH_2Cl_2, AcOH, rt, R = H, 71%, R = Cl, 66%; (b) R = H: H_2, 10% Pd/C, EtOAc, rt, 95%; R = Cl: PtO_2, H_2, EtOAc, rt, 46%; (c) 1.0 M NaOH, 4:1 MeOH/H_2O, rt, R = H, 93%, R = Cl, 74%; (d) EDCI,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

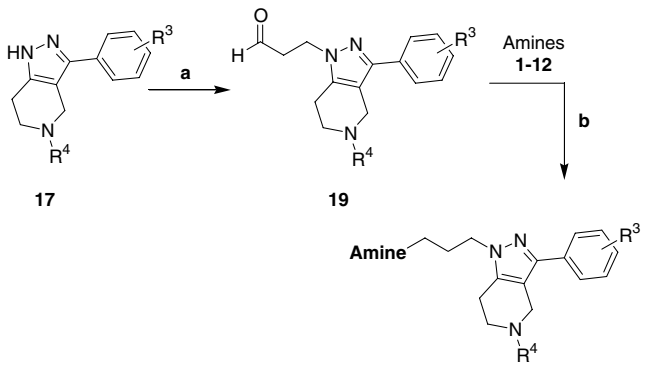


Scheme 2. Preparation of compound **11**. Reagents and conditions: (a) NaH, ethyl bromoacetate, DMF, 0 °C, 33%; (b) LiOH, H_2O, THF, rt, 93%; (c) HATU, DMF, rt, 33%; (d) 1:1 TFA/CH_2Cl_2, rt, 45 min, 49%.

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.

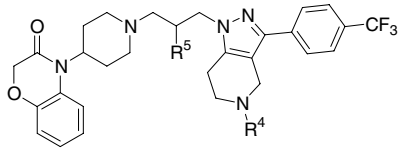
formation of a secondary alcohol in the linker region as depicted by structure **II** above. These analogs were prepared according to Scheme 3. The pyrazole **17** was converted to racemic epoxide intermediate **18** using epichlorohydrin. Epoxide ring opening was accomplished using the amines shown in Figure 1 in refluxing EtOH to afford the desired compounds in 50–90% yield.

The second method, Scheme 4, provides access to the unsubstituted linker analogs as depicted by structure **III** above.[5] Common intermediate **17**, was regioselectively alkylated with 3-bromopropanol. The alcohol was oxidized to the corresponding aldehyde using Dess–Martin periodinane. The amines from Figure 1 were coupled to the aldehyde under reductive amination conditions to afford the desired deshydroxy analogs in 40–80% yield.

Variation of R^4 (SO_2Me, Ac, Boc, and H), as shown in Table 1, indicates a preference for methyl sulfonamide. A notable loss of in vitro enzymatic activity is seen with R^4 = Boc and H. Substitution of H for OH at R^5 has a minimal effect on in vitro enzymatic activity or invariant chain degradation, with comparable analogs being equipotent (**22** vs **26** and **23** vs **27**). Both Tables 1 and 2 list the affinity for the alpha-1 ($\alpha 1_a$) adrenergic receptor as percent inhibition at 1 μM for select compounds. Several analogs described below, offer insight into substitutions that can be incorporated to decrease alpha-1 cross-reactivity. As previously reported in the literature, substitution at R^2 with a chloro substituent is expected to reduce potentially unwanted cross reactivity with the $\alpha 1_a$ receptor.[5] The data obtained for entries **38** and **42** support this trend.

As shown in Table 2, modifications of the C3-aryl moiety of the pyrazole confirmed both 4-trifluoromethyl and 4-bromo substituents as optimal for in vitro enzymatic activity. Comparison of compounds containing R^5 = OH and R^5 = H, again, demonstrates that this change has no effect on in vitro enzymatic activity. The data suggest a modest preference with respect to cellular potency for the C3 4-trifluoromethyl substitution as measured by the invariant chain degradation assay.

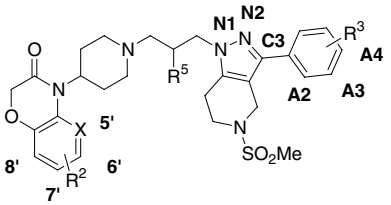
Table 1. Effect of N-substitution on cathepsin S activity



Entry	R^4	R^5	CatS IC_{50}[a] (nM)	Ii IC_{50} (μM)	$\alpha 1_a$[b]
20	H	OH	1925	—	—
21	Boc	OH	826	—	—
22	Ac	OH	120	1.1	—
23	$MeSO_2$	OH	28	0.41	60%
24	H	H	1800	—	—
25	Boc	H	900	—	—
26	Ac	H	100	0.81	—
27	$MeSO_2$	H	23	0.95	72%

[a] Average of 4–6 determinations.
[b] $\alpha 1_a$ % inhibition values at 1 μM were determined by Cerep, SA.

Table 2. Effect of aryl substitution on CatS activity



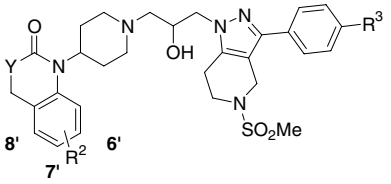
Entry	X	R^2	R^3	R^5	CatS IC_{50}[a] (nM)	Ii IC_{50} (μM)	$\alpha 1_a$[b]
23	C	H	A4-CF_3	OH	16	0.41	60%
27	C	H	A4-CF_3	H	23	0.95	72%
28	C	6′-Cl	A4-CF_3	OH	16	1.3	
29	C	6′-Cl	A4-CF_3	H	130	—	
30	C	5′-Me	A4-CF_3	H	145	2.0	
31	N	H	A4-CF_3	OH	80	1.3	
32	C	H	A4-Br	OH	32	1.8	
33	C	H	A4-Br	H	60	1.6	
34	C	6′-Cl	A4-Br	OH	48	4.4	
35	C	6′-Cl	A4-Br	H	130	2.6	
36	C	5′-Me	A4-Br	H	170	1.6	
37	N	H	A4-Br	OH	68	0.9	

[a] Average of 4–6 determinations.
[b] $\alpha 1_a$ % inhibition values at 1 μM were determined by Cerep, SA.

The data in Table 3 indicate that structural changes to Y, R^2, and R^3 failed to confer improved cellular activity but were well tolerated in terms of enzyme inhibition.

Additional molecules incorporating modifications to the left-hand side utilizing amines **8**, **9**, **10**, **11**, and **12** are included in Table 4. Substitution at the anilinic position (tetrahydroquinoline, **48**) versus the homolog (tetrahydroisoquinoline, **49**) is preferred for CatS enzymatic inhibition. However, the potency of **48** is an order of magnitude lower than **41**, suggesting that the presence of a second basic nitrogen in this position is unfavorable. Analogs **50** and **51** also substituted in the anilinic

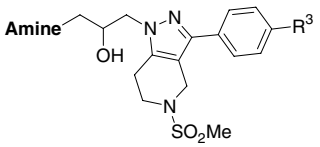
Table 3. Effect of varying the headgroup on cathepsin S activity



Entry	Y	R^2	R^3	CatS IC_{50}[a] (nM)	Ii IC_{50} (μM)	$\alpha 1_a$[b]
38	CH_2	7′-Cl	CF_3	13	0.98	<10%
39	CH_2	7′-Cl	Br	18	0.75	—
40	CH_2	H	CF_3	23	1.8	—
41	CH_2	H	Br	33	2.0	—
42	NH	7′-Cl	CF_3	18	1.9	40%
43	NH	7′-Cl	Br	33	1.5	—
44	NH	H	CF_3	48	1.4[c]	—
45	NH	H	Br	65	1.1[c]	—
46	O	H	CF_3	88	1.4[c]	—
47	O	H	Br	133	—	—

[a] Average of 4–6 determinations.
[b] $\alpha 1_a$ % inhibition values at 1 μM were determined by Cerep, SA.
[c] Single determination.

Table 4. Effect of varying the headgroup on cathepsin S activity



Entry	Amines (Fig. 1)	R^3	CatS IC_{50}[a] (nM)	Ii IC_{50} (μM)
48	9	Br	322	—
49	10	Br	1775	—
50	8	CF_3	30	1.3
51	8	Br	75	2.7[b]
52	11	CF_3	163	0.93[b]
53	12	CF_3	1700	—

[a] Average of four determinations.
[b] Single determination.

position are equipotent to analogs **42** and **43**, further supporting this hypothesis. Ring expansion of the oxazine ring, as illustrated by compound **52**, resulted in a 10-fold loss in enzymatic activity over compound **23**. Interestingly, these compounds show similar potency in the cellular assay. Maintaining the benzylic substitution but increasing the aromaticity of the pendant group with concomitant incorporation of a piperazine ring resulted in a significant drop in enzymatic activity as illustrated by compound **53**.

In conclusion, replacement of the *N*-arylpiperazine in our original series of inhibitors with 4-(6,6-bicyclic) piperidines resulted in the identification of several potent, noncovalent CatS inhibitors. The incorporation of substituents on the remote aryl ring of the bicyclic headgroups provided improved selectivity over the $\alpha 1_a$ adrenergic receptor while maintaining CatS activity. Several of these analogs have been selected for further evaluation.

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