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Cyclic sulfamide γ-secretase inhibitors

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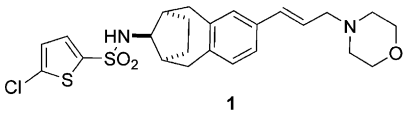
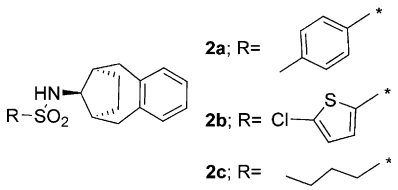
Abstract—A novel series of *N*-alkyl-substituted cyclic sulfamides were developed from a screening hit. Chemistries were developed which allowed surveys of *N*-alkyl groups and amines resulting in the identification of *N*-trifluoroethyl-substituted cyclic sulfamides with good in vitro and in vivo γ-secretase activity. One compound with subnanomolar activity elicited a reduction in brain Aβ40 after oral dosing in APP-YAC mice.

Alzheimer's disease (AD), the main form of dementia found in the elderly population, is the fourth leading cause of death and is predicted to affect 20 million people worldwide within 20 years.[1] Current therapies are palliative, and include the acetylcholinesterase inhibitors Aricept, Reminyl, and Exelon. One approach to identify a therapy capable of preventing the progression of AD is the inhibition of β-amyloid (Aβ) production, specifically Aβ42.[2] This peptide constitutes the major component of extracellular plaques and is a metabolite of β-amyloid precursor protein (β-APP), formed through sequential cleavage by β-secretase and then γ-secretase.

Recently, we described sulfonamide derivatives of substituted bicyclo [4.2.1]nonanes such as **1**, which are potent γ-secretase inhibitors.[3] Compound **1** was identified by optimization of screening hit **2a**. In parallel with the optimization of the sulfonamide substituent in **1**, alternative motifs to the sulfonamide were investigated. Here, we describe the evolution of a series of novel sulfamides with potent γ-secretase inhibitory activity and present data illustrating the in vivo efficacy of this new class of compounds. As previously reported, the first iteration from screening hit **2a** produced a number of potent compounds, including 5-chlorothiophene sulfonamide **2b** and *n*-butyl sulfonamide **2c**.[3] Initially, we investigated the incorporation of heteroatoms into the alkyl side chain of **2c**, in particular the replacement of a methylene with a nitrogen atom. Thus, reacting amine **3** with the appropriate sulfamoyl chloride **4** gave acyclic sulfamides **6** in one step (Scheme 1). Alternatively, to explore a wider range of amines more quickly, reaction with intermediate catechol sulfamate **5** produced sulfamides **6** in good yield. The endo stereochemistry of the NH_2 group in **3** was already established[4] but was confirmed through the observation of NOEs between the endo NH and pseudo axial protons on the benzylic carbons of **6b**.



1



Keywords: Alzheimer's disease; γ-Secretase inhibitor; Cyclic sulfamide.
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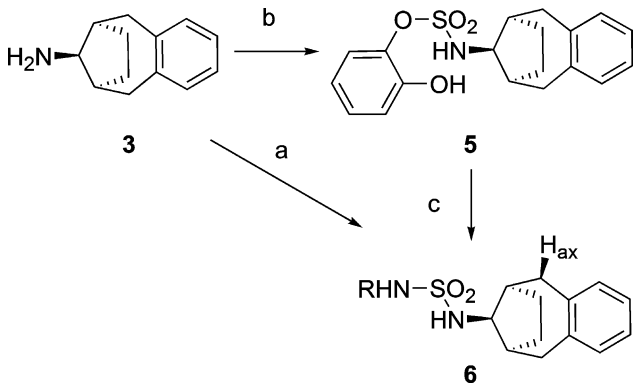
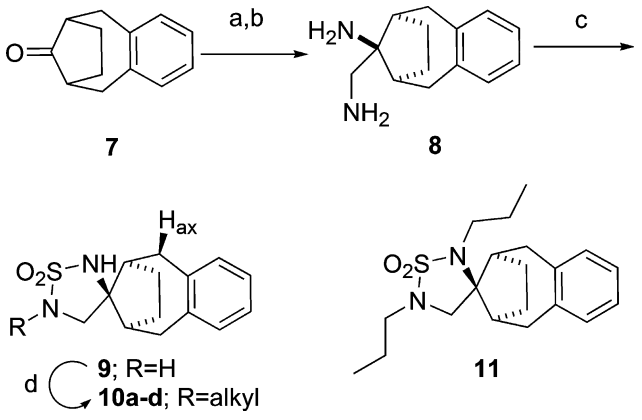


Scheme 1. Reagents and conditions: (a) $RNHSO_2Cl$ **4**, Et_3N, MeCN, reflux, 35–81%; (b) catechol sulfate, THF, 0 °C to rt, 81%; (c) amine, dioxane, 80 °C, 66–80%.

To restrict the freedom of rotation of the sulfamide group, conformationally constrained cyclic sulfamides **10** were synthesized. This was accomplished through a Strecker reaction and LAH reduction sequence on ketone **7**, followed by cyclization of diamine **8** with sulfamide in pyridine (Scheme 2). Subsequent alkylation of unsubstituted cyclic sulfamide **9**, using sodium hydride in DMF as base and the appropriate alkyl halide, furnished substituted cyclic sulfamides **10a**–**d**. Good regioselectivity was observed during the reaction, with no monoalkylation observed on the endo nitrogen. However, alkylation on both nitrogens gave rise to a small quantity of **11** (with *n*-propyl bromide as electrophile). The regiochemistry and stereochemistry of **10b** were confirmed by the observation of NOEs between the N–H and the pseudo axial protons on the 7-membered ring.

In an attempt to improve the potency of these compounds, substituents appended to the benzene ring were introduced following precedent from the sulfonamide series.[3] This was achieved regioselectively using the known lead tetraacetate-mediated oxidation of ketone **7** (Scheme 3), and the phenol converted to benzyl ether



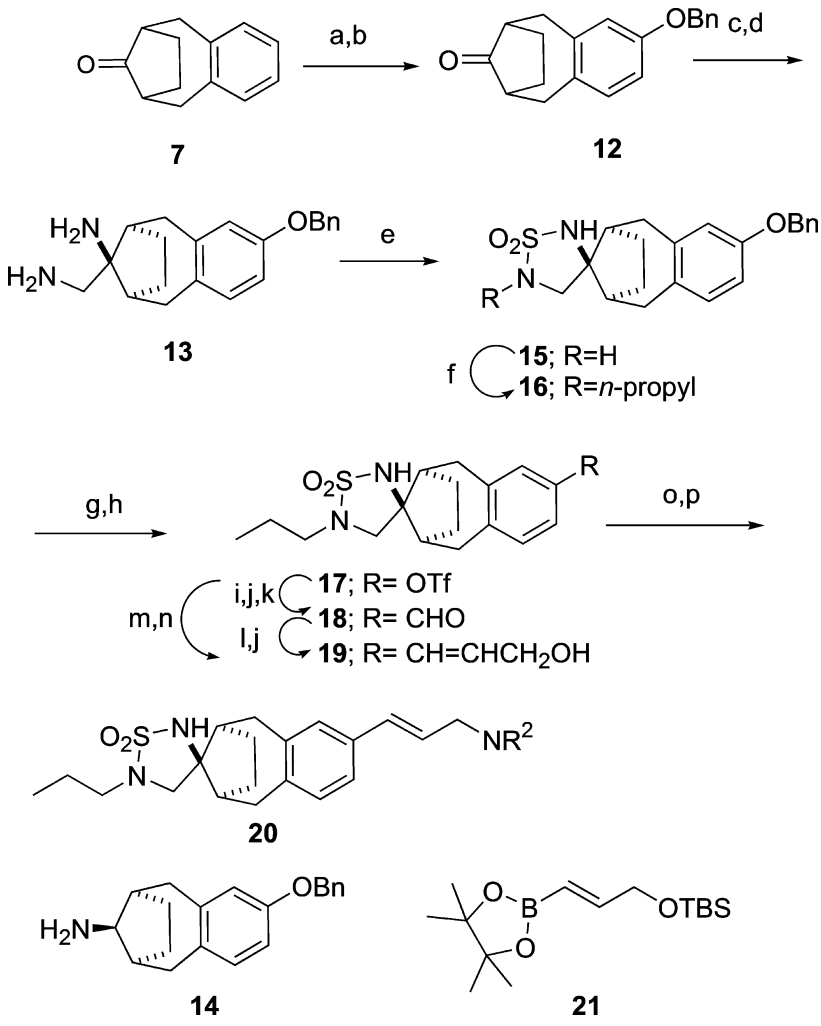
Scheme 2. Reagents and conditions: (a) NaCN, NH_4OH, ammonia, NH_4Cl MeOH, 0 °C, 70%; (b) LAH, THF, rt, 77%; (c) sulfamide, pyridine, reflux, 24 h, 85%; (d) NaH, alkyl halide, DMF, rt, 24 h, 10–71%.

12 in good overall yield.[4] Utilizing the same Strecker/LAH sequence as described previously, diamine **13** was prepared. A byproduct was observed during the reduction with LAH, identified as amine **14** (presumably derived from loss of cyanide and reduction of the imine). Amine **14** was removed by chromatography on silica. Diamine **13** was then cyclized to cyclic sulfamide **15** using sulfamide and then functionalized by alkylation with *n*-propyl bromide with high regioselectivity (>95% by crude NMR). Benzyl ether **16** was deprotected and converted to triflate **17**, which was carbonylated, reduced and oxidized to give aldehyde **18**. A Horner–Emmons reaction followed by reduction gave allylic alcohol **19**, which was activated with PBr_3 and reacted with an appropriate amine. Subsequently, a shorter synthetic sequence was developed, whereby triflate **17** was reacted with vinyl boronate **21**[5] and the resultant silyl ether deprotected with TBAF.

In the synthesis of cyclic sulfamides **10**, the direct alkylation route to the *N*-trifluoroethyl analogue **10d** was low yielding (10%). An improved route was required to facilitate the evaluation of more functionalized compounds. This was achieved by installation of the trifluoroethyl group prior to cyclic sulfamide formation. Thus, trifluoroacetylation of diamine **13** using trifluoroacetic anhydride followed by reduction with borane gave trifluoroethyl amine **22** (Scheme 4). The observed regioselectivity was attributed to preferential reactivity of the less-hindered primary amine. Cyclization gave sulfamide **23** in good yield. Side chains containing allylic amines could be introduced from triflate **24** as described above, allowing a range of amines to be incorporated efficiently. In a further evolution of this route, boronate **25a** was synthesized[6] and reacted with 4-(trifluoromethyl)piperidine to provide boronate **25b**, which was then coupled with triflate **24** to furnish **26f** in improved yield.

Some interesting structure–activity relationships were observed for the compounds described above. We found that the replacement of a methylene in compound **2c** (IC_{50} 610 nM)[7] with NH gave the more potent acyclic sulfamide **6b** (IC_{50} 106 nM; Table 1). However, shortening (**6a**) or increasing (**6c**) the length of the sulfamide alkyl group was detrimental to potency, whereas replacing the propyl group with a trifluoroethyl group resulted in an equipotent compound (**6d**). A different trend was observed for cyclic sulfamides, notably for the *n*-propyl (**10b**) and *n*-butyl (**10c**) analogues which were equipotent, but more interestingly **10d** that displayed an order of magnitude increase in potency. This may be attributable to the conformational restriction imposed by the cyclic sulfamide ring better orientating the lipophilic trifluoroethyl group for binding (**6d** vs **10d**). Compounds **9** and **11** were both found to be inactive (IC_{50}s > 10,000 nM).

Compound **2b** was found to have poor systemic exposure in rat after oral dosing (Table 2). In comparison, **6b** and **10b** showed improved exposure. Given the pharmacokinetic advantage of **10b** over **6b**, presumably due to the removal of one sulfamide N–H, further efforts focused on optimizing the cyclic sulfamide series.



Scheme 3. Reagents and conditions: (a) $Pb(OAc)_4$, TFA, 75%; (b) BnBr, NaH, DMF, rt, 48 h, 83%; (c) NaCN, NH_4OH, ammonia, NH_4Cl, MeOH, 0 °C, 74%; (d) LAH, THF, 53%; (e) sulfamide, pyridine, reflux, 24 h, 89%; (f) NaH, *n*-propyl bromide, DMF, rt, 24 h, 59%; (g) 10% Pd on C, H_2, EtOAc, MeOH, 4 h, 99%; (h) Tf_2O, pyridine, 0 °C to rt, 30 min, 89%; (i) CO, $Pd(OAc)_2$, dppb, Et_3N, MeOH, DMF, 56%; (j) DIBAL, THF, 95%; (k) PDC, DCM, 89%; (l) methyl diethylphosphono acetate, $LiOH{\cdot}H_2O$, THF, 79%; (m) **21**, $Pd(OAc)_2$, dppp, K_2CO_3, DMF, 80 °C, 14 h, 51%; (*n*) TBAF, THF, rt, 79%; (o) PBr_3, DCM, −5 °C, 1 h; (p) amine, DCM, rt, 63%.

To assess these improvements in more functionalized sulfamides, **20a** was synthesized and resolved[8] for direct comparison with **1**. While the inhibitory activity was reduced 7-fold, an order of magnitude increase in exposure was observed after oral dosing (Table 3).

N-Trifluoroethyl cyclic sulfamides containing allylic amine side chains were synthesized to improve potency. A 6-fold improvement in potency was observed by replacing the *n*-propyl (**20a**) with a trifluoroethyl group (**26a**; Table 4). To assess the effects on potency of replacing the morpholine with amines of different basicity and functionality, a range of amines was incorporated. The data suggested that a substituent in the 4-position of the piperidine improved activity (**26b** vs **26c**).

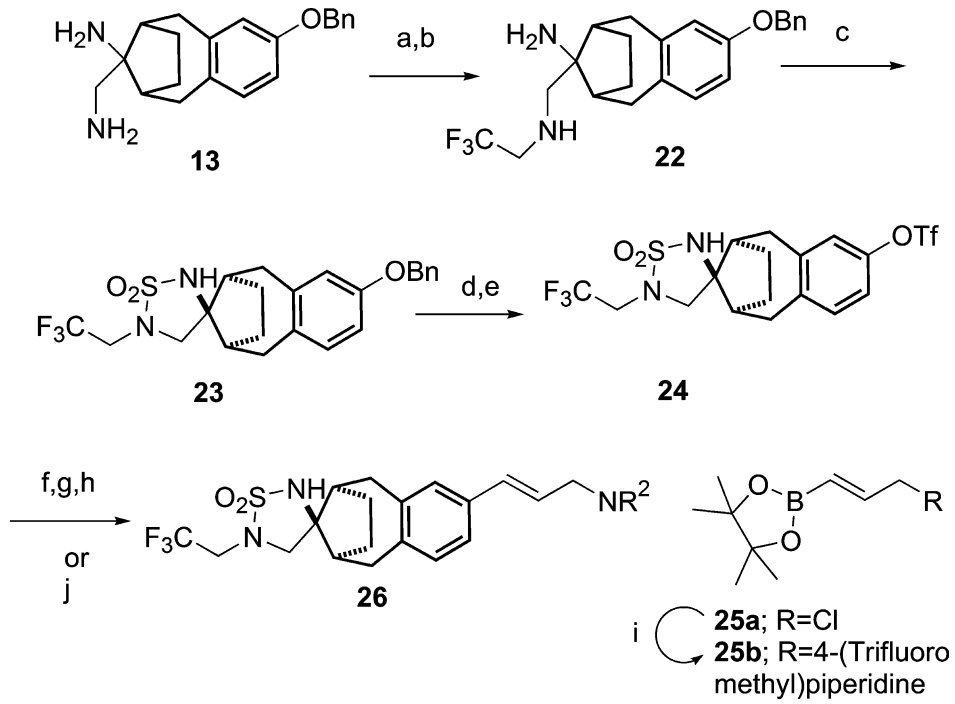
Good potency was observed for compounds with heteroatoms and/or substituents at the 4-position of the nitrogen heterocycle contributing to a pK_a value within the 6–7 range (**26a**, **e**, **f**, and **20b**).

From this study, the optimum amine was identified as 4-trifluoromethylpiperidine, which, when combined with an *N*-trifluoroethyl cyclic sulfamide, produced a compound with subnanomolar potency (**26f**). Further variations to the allylic side chain portion of these compounds will be reported shortly.

To assess the efficacy of **26f**, the racemate was resolved[8] and the (−)-enantiomer[10] (IC_{50} 0.24 nM ($n = 3$), 99% ee[8]; (+)-enantiomer IC_{50} 111 nM, 99% ee[8]) dosed orally to APP-YAC mice[11] (Chart 1). In a dose–response experiment, (−)-**26f** demonstrated a significantly improved efficacy profile compared to **1** with an ID_{50} of 17 mg/kg p.o.

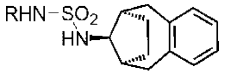
Summary

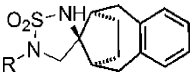
A novel series of cyclic sulfamides has been developed from screening hit **2a**. An improved pharmacokinetic profile was demonstrated for simple sulfamides **6b** and



Scheme 4. Reagents and conditions: (a) Trifluoroacetic anhydride, THF, −78 °C to rt, 24 h, 90%; (b) borane, THF, reflux, 2 h, 60–82%; (c) sulfamide, pyridine, reflux, 24 h, 91%; (d) H_2, Pd on C, EtOAc/MeOH, 6 h, 93%; (e) Tf_2O, pyridine, 0 °C to rt, 1 h, 88%; (f) **21**, $Pd(OAc)_2$, dppp, K_2CO_3, DMF, 80 °C, 14 h, 50%; (g) TBAF, THF, rt, 3 h, 79%; (h) i—PBr_3, DCM, −5 °C, 1 h, ii—amine, DCM, rt, 4 h, 45–83%; (i) 4-(triflouromethyl)piperidine, K_2CO_3, MeCN, rt, 95%; (j) **25b**, $Pd(OAc)_2$, dppp, K_2CO_3, DMF, 80 °C, 70%.

Table 1. Inhibitory activities of sulfamides **6** and **10**


6


10

Compound	IC_{50}, nM (*n*)	R	Compound	IC_{50}, nM (*n*)
6a	394(2)	Ethyl	**10a**	429(2)
6b	132(3)	*n*-Propyl	**10b**	138(2)
6c	766(2)	*n*-Butyl	**10c**	122(2)
6d	134(3)	Trifluorethyl	**10d**	17(5)

10b compared with sulfonamide **2b**. Functionalization of these sulfamides by appendage of allylic amines to the aromatic ring produced more potent inhibitors (**20** and **26**) in which improved pharmacokinetic properties were maintained. In a dose–response experiment, (−)-**26f** showed a significantly improved efficacy profile in APP-YAC mice compared with sulfonamide **1** and elicited a dose-dependent reduction in brain Aβ40 with an ID_{50} of 17 mg/kg p.o.

Table 2. Rat systemic exposures for **2b**, **6b**, and **10b**

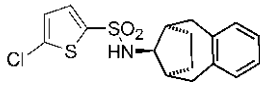
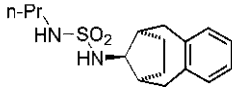
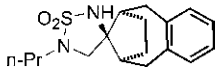
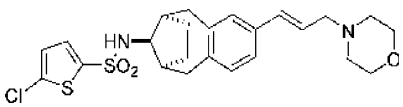
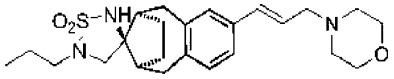
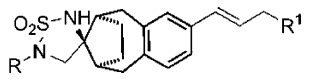
Compound		Dose (mpk)	AUC (systemic) (μM h)
2b		30	0.01
6b		30	0.6
10b		1	0.1

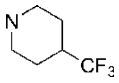
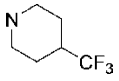
Table 3. Profiles of **1** and **20a**

Compound		IC_{50}, nM (*n*)	Dose (mpk)	AUC (systemic) (μM h)
1[a]		1(4)	4	0.38
20a[a]		7(2)	1	1.19

[a] Data shown for single enantiomers (absolute stereochemistry is unknown).

Table 4. Inhibitory activities of cyclic sulfamides **20** and **26**



Compound[a]	R	R^1	IC_{50}, nM (*n*)	pK_a[9]
20a	*n*-Propyl		19(5)	7.1
20b	*n*-Propyl		2.0(2)	6.7
26a	Trifluoroethyl		3.4(2)	6.8
26b	Trifluoroethyl		250(2)	7.9
26c	Trifluoroethyl		18(2)	7.5
26d	Trifluoroethyl		21(2)	5.2
26e	Trifluoroethyl		4(2)	6.1
26f	Trifluoroethyl		0.5(4)	6.4

[a] For comparison purposes, data shown for racemates.

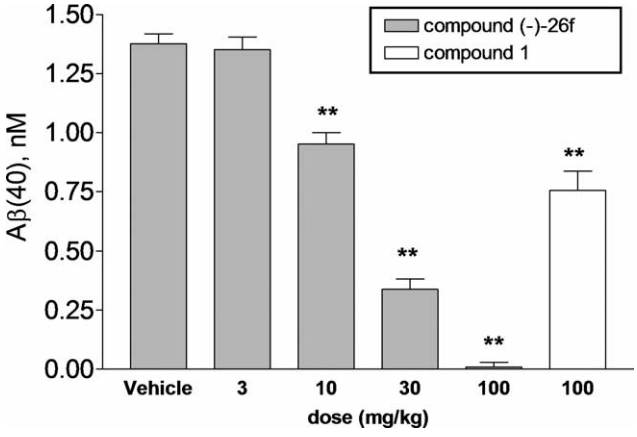


Chart 1. In vivo efficacy of **1** and (−)-**26f** in YAC mice.

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7. Compounds were screened using a whole cell γ-secretase inhibition assay in SHSY5Y cells: Clarke, E.; Shearman, M. S. *J. Neurosci. Methods* **2000**, *102*, 61.
8. Compounds were resolved using supercritical fluid chromatography: OD column eluting with 30–50% MeOH containing 25 mM *i*-$BuNH_2$ at 50 ml/min.
9. Determined by titration using a Sirius GLpKa autotitrator.
10. Crystallographic data (excluding structure factors) for (−)-**26f** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 263202. The absolute stereochemistry is as drawn in Table 4.
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