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Synthesis and SAR study of tricyclic sulfones as γ-secretase inhibitors: C-6 and C-8 positions

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ABSTRACT

SAR exploration at C-6 and C-8 positions of the tricyclic sulfone series was carried out. Several functional groups were found to be well tolerated at C-6 and C-8 positions. Selective combination of C-6 and C-8 modification resulted in new tricyclic sulfone analogs with efficacy in in vivo mouse $A\beta_{40}$ lowering model.

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is estimated to affect more than 5 million Americans and 15 million people worldwide.[1] These figures will likely continue to rise in the future and there is an urgent need for a treatment of the disease. One hallmark of AD pathology is the presence of extracellular plaques composed of β-amyloid peptides (Aβ), a 38–42 amino acid fragment generated by the sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases. The accumulation of $A\beta_{42}$, the longer form Aβ, is believed to lead to aggregation, plaque deposition and neurotoxicity.[2] In a recent paper from Merck, a series of tricyclic sulfones were discovered as potent γ-secretase inhibitors.[3] A SAR study was carried out at the C-8 position in the C ring and compounds **1a** and **1b** (Fig. 1) were identified with excellent overall profiles. In this Letter, we wish to report the synthesis and SAR studies at both C-6 and C-8 positions of such a tricyclic core.

The synthesis of C-6 analogs is outlined in Scheme 1. The β-keto ester **3** was converted to the vinyl triflate **4** in 90% yield.[4,5] The Suzuki coupling of **4** afforded the desired product **5** in 65–70% yield. After the conversion of this ester to the alcohol **6**, an intramolecular cyclization[6] went smoothly to afford the desired tricyclic core **7** in 50% yield in two steps, which was then quantitatively converted to the epoxide **8** by MCPBA oxidation. Following a literature procedure,[7] the regioselective epoxide ring opening by 4-chlorothiophenol gave rise to a 5:2 mixture of the *cis* and *trans* adducts and the desired *cis* alcohol **9** was isolated in 63% yield.[8] After O-alkylation with ethyl bromoacetate and ester reduction, the primary alcohol was converted to the corresponding mesylate **11**. This intermediate was treated with alkyl mercaptans to afford sulfides such as **12** which could be further oxidized to sulfones such as **13** and **15**. The mesylate could also be treated with potassium thioacetate followed by hydrolysis, oxidation[9] and amine quenching sequentially to provide the sulfonamides **17** and **18**. Alternatively, the mesylate could be easily converted to amines **19**–**21** or reverse sulfonamides **22** and **23** using standard conditions

The C-8 modification was carried out as shown in Scheme 2. Once the tetrasubstituted epoxide **24** was synthesized according to Scheme 1,[10] the *cis* and *trans* adducts **25a**/**b** were separated and subsequently converted to the ketone analogs **27a**/**b**. Further reduction of the ketone **27a** provided diols **28** and **29**.

Compounds with both C-6 and C-8 modification were prepared according to Scheme 3. Following the same route shown in Scheme

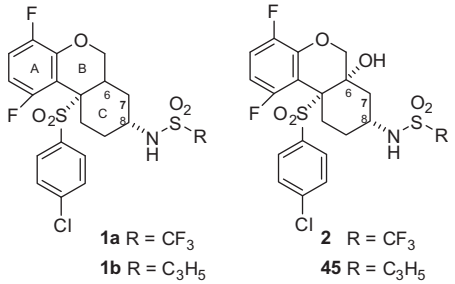

Figure 1. Tricyclic sulfones as γ-secretase inhibitors.

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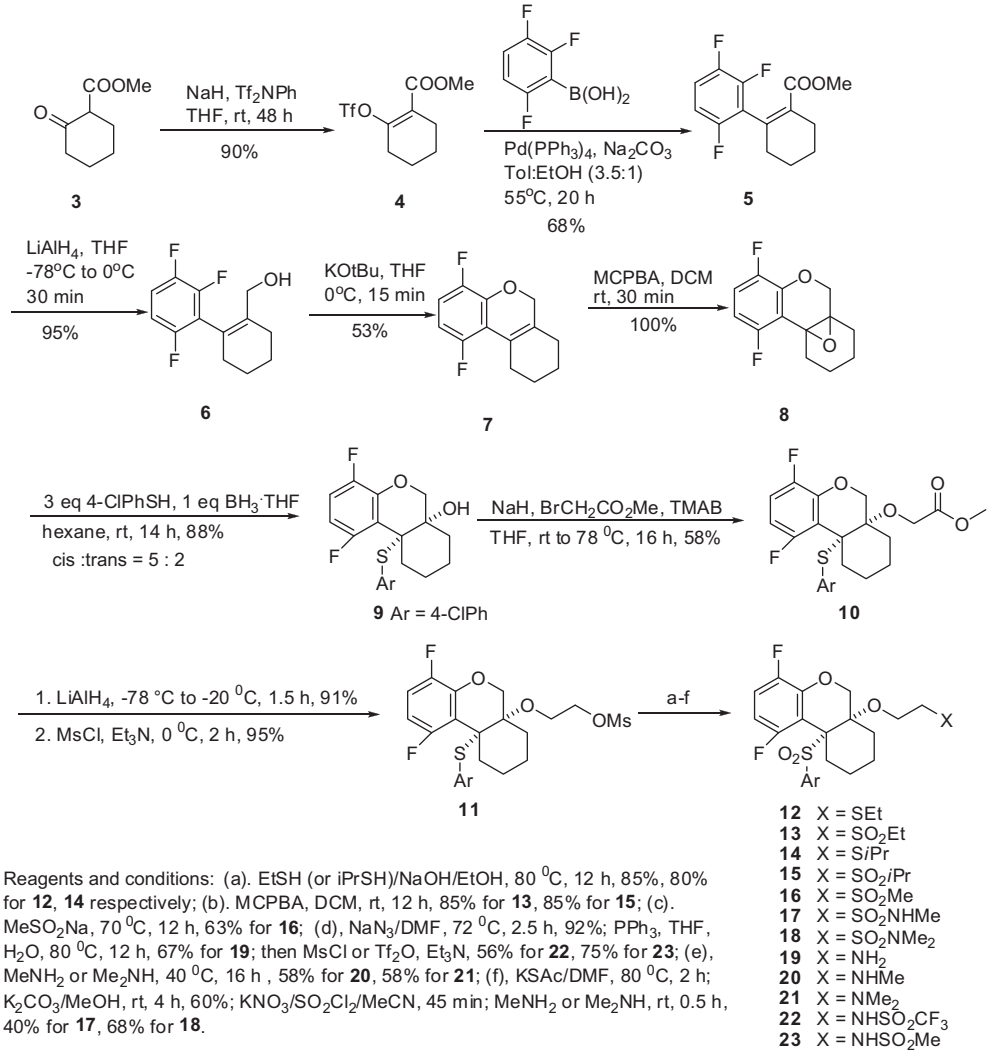


Scheme 1. Synthesis of C-6 analogs.

1, the C-6 side chain was installed and the sulfone group was introduced. Deprotection of the ketal group provided the ketone analogs **36** and **39**, which, could be further reduced to the alcohol analogs **37** and **40**. A sulfonamide analog **41** was also synthesized using the synthetic route for compound **22** (Scheme 1). To synthesize C-8 sulfonamide analogs **43**–**46**, the C-8 alcohol **28** was first converted to the azide via the mesylate intermediate, followed by reduction to afford the primary amine **42**. Compound **42** was then converted to the corresponding targets **43** to **46**.

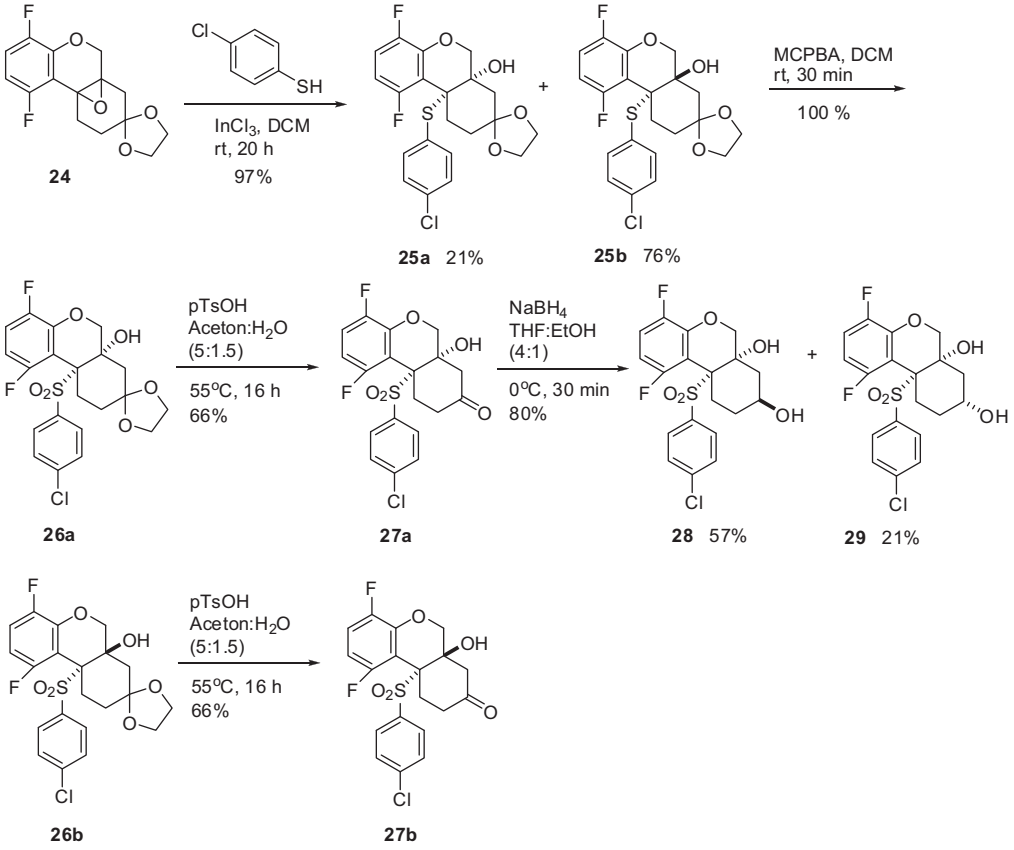
Other similar targets synthesized according to Schemes 1–3 are listed in Figure 2 except for compounds **32** and **33** which were reported earlier.[3]

All compounds were tested in the in vitro membrane $A\beta_{40}$ inhibition assay[11] and the biological data are shown in Table 1.[12] While analogs **12** and **14** with a C-6 alkyl sulfide group showed moderate activities (IC_{50} ~170–180 nM, Table 1), their corresponding sulfone analogs **13**, **15** and **16** were 10- to 20-fold more active (e.g., **15** had IC_{50} = 8 nM). The sulfonamide analogs **17** and **18** were about 5-fold less active than the sulfone analogs. Interestingly, the reversed methanesulfonamide analog **23** retained the strong inhibition (IC_{50} = 26 nM) whereas another analog –NHTf **22** was 11-fold less active. The side chain at the C-6 position also tolerated a basic amine group. For example, the primary amine **19** had IC_{50} = 12 nM while the secondary amine **20** and the tertiary amine **21** were 3-fold less active.

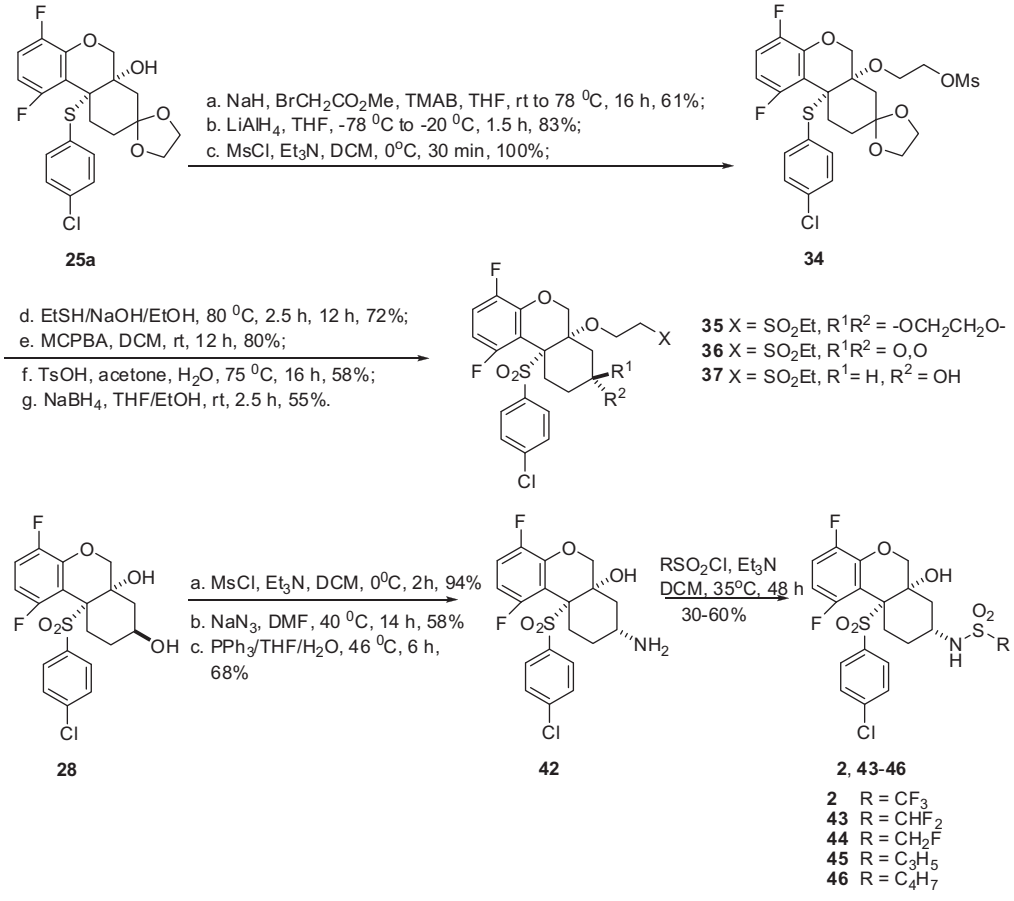
Comparison of compounds **27a** and **27b** demonstrated the importance of the relative stereochemistry at C-5 and C-6. While the *trans* isomer **27b** was completely inactive (IC_{50} = 3000 nM), the *cis* isomer **27a** had a IC_{50} of 21 nM, comparable to its C-6 des hydroxy analog **32** (IC_{50} = 13 nM). The IC_{50} values could be also influenced by substituents at the C-8 position: while installing a ketone group did not change the IC_{50} values (compounds **27a** and **32** vs **33**), the bulky ketal group was not tolerated at all (compounds **26a** vs **33**). The stereochemistry at the C-8 position could also make a difference: the *cis* diol **29** (IC_{50} = 29 nM) retained the binding activity while the *trans* diol **28** had an IC_{50} of 363 nM, a 12-fold decrease.

The combination of the C-6 side chain and C-8 substituents did not have a synergistic effect on the $A\beta_{40}$ inhibition. For example, with an alkylsulfone group on the C-6 side chain, the presence of a ketone or hydroxyl group led to a 10-, 6-fold decrease, respectively (compounds **36**/**37** vs **13**, **39**/**40** vs **15**). The presence of –NHTf on the C-6 side chain along with the C-8 hydroxy group led to the loss of activity for **41** (>13-fold drop compared with **22**).

On the other hand, the combination of just a C-6 hydroxy group and a C-8 sulfonamide group was well tolerated. Among them, The NHTf **2** and the cyclopropylsulfonamide **45** had IC_{50} <30 nM. Increasing the pK_a of the sulfonamide N*H* resulted in higher IC_{50} values (compounds **43**, **44** vs **2**).[13] Replacing the cyclopropylsulfonamide with cyclobutylsulfonamide led to a 7-fold decrease in



Scheme 2. Synthesis of C-6 hydoxy analogs with C-8 modification.



Scheme 3. Synthesis of tricyclic sulfones with C-6 and C-8 modification.

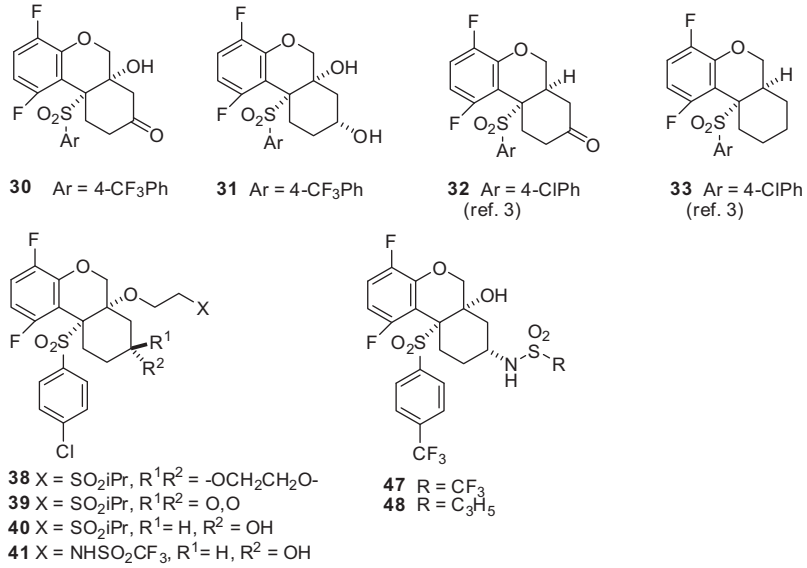
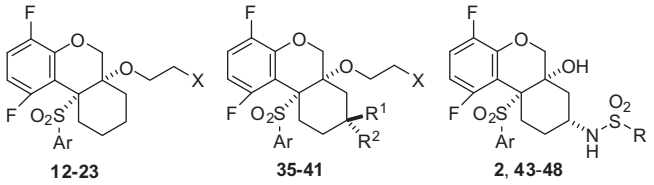


Figure 2. Other targets synthesized using the same synthetic route.

Table 1
Membrane $A\beta_{40}$ IC_{50} data



Compound	Ar	X	R^1, R^2	R	IC_{50}[a] (nM)
12	4-ClPh	SEt			170
13	4-ClPh	SO_2Et			15
14	4-ClPh	S*i*Pr			180
15	4-ClPh	SO_2*i*Pr			8
16	4-ClPh	SO_2Me			9
17	4-ClPh	SO_2NHMe			37
18	4-ClPh	SO_2NMe_2			50
19	4-ClPh	NH_2			12
20	4-ClPh	NHMe			40
21	4-ClPh	NMe_2			31
22	4-ClPh	$NHSO_2CF_3$			295
23	4-ClPh	$NHSO_2Me$			26
26a	4-ClPh				2900
27a	4-ClPh				21
27b	4-ClPh				3000
28	4-ClPh				363
29	4-ClPh				28
30	4-CF_3Ph				53
31	4-CF_3Ph				136
32	4-ClPh				13
33	4-ClPh				22
35	4-ClPh	SO_2Et	–OCH_2CH_2O–		1300
36	4-ClPh	SO_2Et	O, O		160
37	4-ClPh	SO_2Et	H, OH		87
38	4-ClPh	SO_2*i*Pr	–OCH_2CH_2O–		940
39	4-ClPh	SO_2*i*Pr	O, O		130
40	4-ClPh	SO_2*i*Pr	H, OH		52
41	4-ClPh	$NHSO_2CF_3$	H, OH		4100
1a (chiral)	4-ClPh				27
2	4-ClPh			CF_3	21
43	4-ClPh			CHF_2	68
44	4-ClPh			CH_2F	164
45	4-ClPh			C_3H_5	29
46	4-ClPh			C_4H_7	212
47	4-CF_3Ph			CF_3	23
48	4-CF_3Ph			C_3H_5	173

[a] Values are means of two experiments.

Table 2
In vivo efficacy study in CRND8 mouse model

Compound	IC_{50}[b] (nM) membrane	IC_{50}[b] (nM) cell $A\beta_{40}$, $A\beta_{42}$	CRND8 $A\beta_{40}$ inh. at 3 h[c] plasma, cortex (%)
1a (chiral)[a]	27	108, 46	90, 42
1b (chiral)[a]	8	9, 4	80, 58
2	21	11, 33	58, 33
45	29	3, 9	77, 71
47	23	80, 51	59, 48

[a] Data from Ref. 3.
[b] Values are means of two experiments.
[c] Dosed orally at 30 mg/kg.

IC_{50} values (**46** vs **45**). While switching 4-chlorophelsulfone at C-5 to 4-triflurometylphenylsulfone essentially did not change the IC_{50} when the C-8 position had the NHTf group (**47** vs **2**), it did lead to a 6-fold drop when the C-8 position had the cyclopropylsulfonamide group (**48** vs **45**).

Three compounds were selected for in vivo efficacy test in the CRND8 mouse model[14] and the results are shown in Table 2 along with data for **1a**/**b**.[3] The limited data indicated that, in general, the C-6 hydroxy analogs had similar efficacy as their C-6 dehydroxy analogs. Compound **45** inhibited plasma and cortex $A\beta_{40}$ by 77%, 71%, respectively, at 3 h after an oral dosing of 30 mg/kg.

In summary, we have synthesized a series of tricyclic sulfones to study SAR at C-6 and C-8 positions. While substituents at the C-6 position were well tolerated, the biological activity was more sensitive to those at the C-8 position. Selective combination of C-6 and C-8 modification led to compounds such as **2** and **45** that demonstrated in vivo efficacy comparable to that of our previously reported compounds **1a**/**b**.

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