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Tricyclic sulfones as orally active γ-secretase inhibitors: Synthesis and structure–activity relationship studies

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ABSTRACT

Tricyclic sulfones were designed as γ-secretase inhibitors and found to have excellent potency. Extensive SAR shows that a large number of sulfonamides at position 7 of the tricycle are very well tolerated. Compounds such as **15a** and **15c** showed remarkable in vivo potency.

Alzheimer's disease (AD) is a progressive neurodegenerative disease. The Aβ peptide (40–42 amino acids) is the major constituent of plaques found in AD patients brain. Inhibition of γ-secretase, one of the enzymes responsible for the cleavage of the amyloid precursor protein (APP) to produce the pathogenic Aβ-peptides, is an attractive approach to the treatment of AD. Because inhibition of γ-secretase blocks the production of Aβ, the identification of compounds that block the activity of this enzyme has become a major focus of AD research.[1–5]

A large number of simple sulfonamide based γ-secretase inhibitors (**1**, **2**)[6–9] have appeared in recent literature. The carbon analog of a sulfonamide, a sulfone (**3**), was designed and reported to have excellent γ-secretase activity.[10] The conformationally restricted compound **4** was also discovered (Fig. 1).[11] Based on the literature, together with our in house data, we designed and synthesized first generation bicyclic sulfones (**5**), that lead to the second generation tricyclic sulfone (**6**) as shown in Figure 2.[12a] A series of SAR studies on the cyclohexyl ring of compound **6** lead us to a number of sulfonamide compounds (at position 8) as illustrated by structure **7** with an improved affinity and pharmacokinetic properties.[12a] Further SAR development in this tricyclic series shown that position 7 is also very well tolerated and we have generated a number of γ-secretase inhibitors with excellent in vitro potency and in vivo efficacy. This paper describes the synthesis and SAR development at position 7 of the tricyclic core structure (**8**) as well as some SAR on the sulfone aryl ring.

The preparation of tricyclic compounds described in this letter is illustrated in Scheme 1. The enolate derived from valerolactone was added to vinyl sulfone (**9**) to obtain compound **10** in 86% yield. The lactone ring was opened with $Mg(OMe)_2$ in methanol followed by mesylation and cyclization under KO^tBu conditions to give the tricyclic compound **12**. Only one diastereoisomer was observed in this reaction.[12b] The ester group was reduced to the alcohol **13** in excellent yield. At this stage, the enantiomers were separated on a Chiralcel OD column. The (−) enantiomer (**13a**) was used for further SAR studies since the (+) enantiomer showed decrease

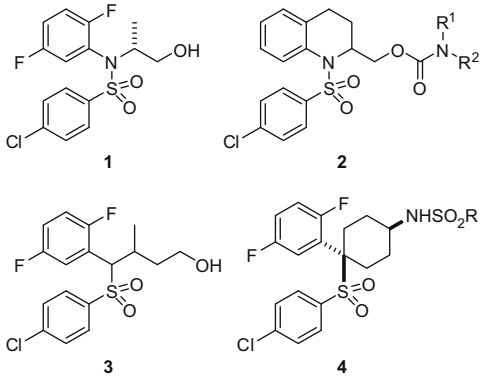

Figure 1. Early γ-secretase inhibitors.

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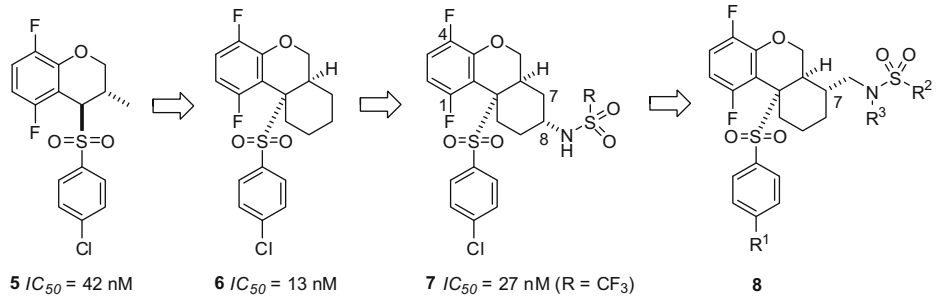
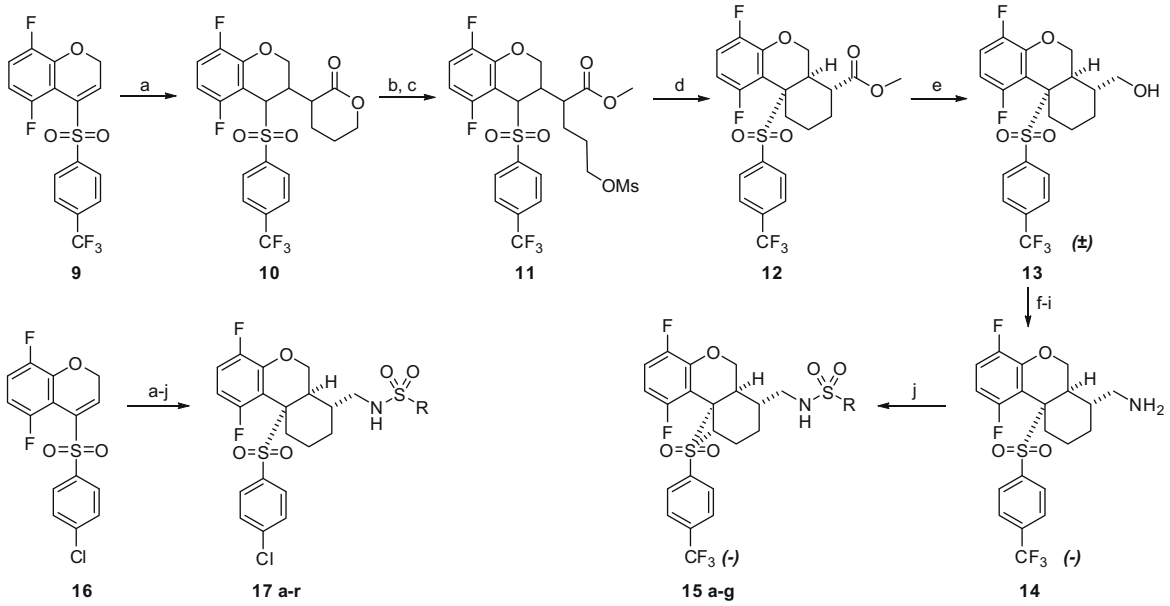
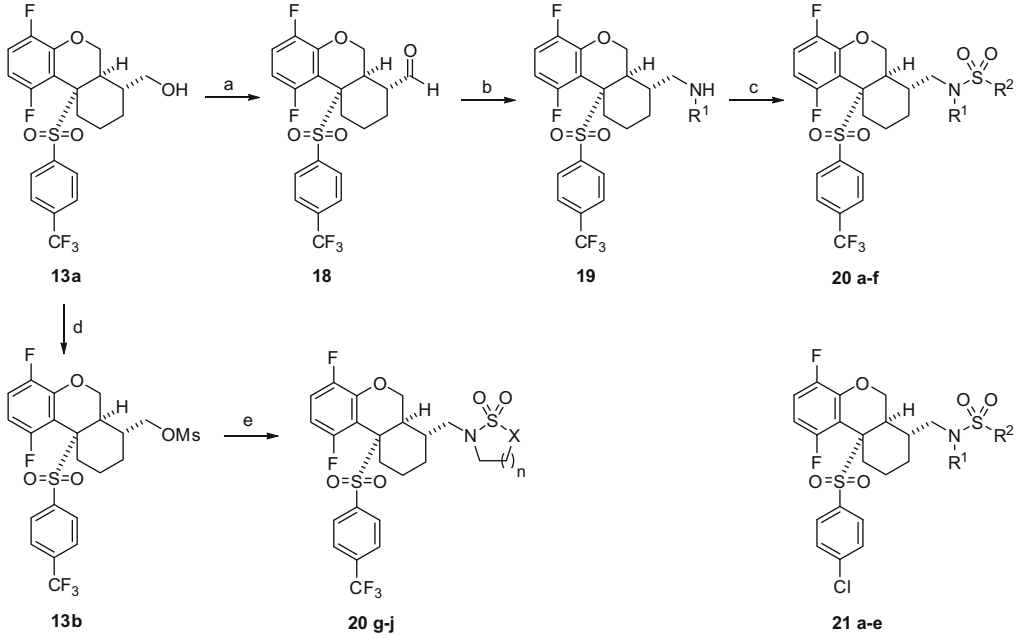


Figure 2. Design of tricyclic γ-secretase inhibitors.

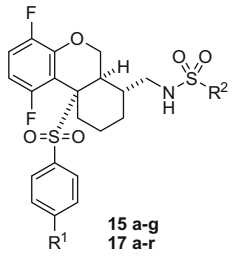


Scheme 1. Reagents and conditions: (a) LHMDS, valerolactone, THF, −78 °C, 86%; (b) $Mg(OMe)_2$, MeOH, 71%; (c) MsCl, TEA, DCM; (d) KO^tBu, THF, 74% (two steps); (e) $LiBH_4$, THF, 91%; (f) Chiral separation on Chiralcel OD Column, 45%; (g) MsCl/TEA, DCM; (h) NaN_3, DMF; (i) Ph_3P, H_2O, THF, 94% (three steps); (j) RSO_2Cl, TEA, DCM (for R = Me, 97%).



Scheme 2. Reagents and conditions: (a) Dess–Martin Periodinane, DCM, 90%; (b) R_1NH_2, $Na(OAc)_3BH$, DCM, 80–85%; (c) R_2SO_2Cl, TEA, DCM, 80–90%; (d) MsCl, TEA, DCM, 98%; (e) five or six-membered sultam, NaH, THF; cyclic sulfamide, NaH, THF, 50–60%.

Table 1
γ-Secretase membrane and cell IC_{50}'s



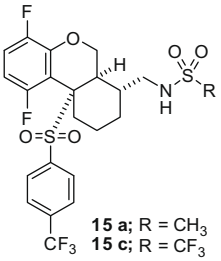
Compd	R^1	R^2	Membrane[a] IC_{50} (nM)	Cell Aβ40 IC_{50} (nM)	Cell Aβ42 IC_{50} (nM)
15a	CF_3	CH_3	13	12	3.6
15b	CF_3	CH_2CH_3	20	5.5	1.6
15c	CF_3	CF_3	41.7	40.6	1.6
15d	CF_3	CH_2CF_3	25	22.7	8
15e	CF_3	*c*Pr	19.7	17.5	6.3
15f	CF_3	NH_2	18.7	6	4
15g	CF_3	NMe_2	6.8	12.7	5.4
17a	Cl	CH_3	2.5	2	2
17b	Cl	CF_3	12	18	9
17c	Cl	CH_2CH_3	1.6	4	2
17d	Cl	CH_2CF_3	7.8	16	4
17e	Cl	$CH_2CH_2CH_3$	5.5	12	6
17f	Cl	$CH_2CH_2CH_2CH_3$	13	29	13
17g	Cl	CH_2CH_2COOEt	2	4	3
17h	Cl	*i*Pr	5.2	12	5
17i	Cl	*c*Pr	3.1	4	4
17j	Cl	Cyclohexyl	55	60	20
17k	Cl	NH_2	2	1	1
17l	Cl	NMe_2	2.7	2	1
17m	Cl	NEt_2	9	6	3
17n	Cl	Pyrrolidinyl	3.3	5	3
17o	Cl	Piperidinyl	6	19	11
17p	Cl	Morpholinyl	3.4	6	3
17q	Cl	Ph	61	128	46
17r	Cl	2-Thienyl	16.7	45	18
17s	Cl	2,6-diF-Ph	13	32	17

[a] Mean values ($n = 2$) ± SEM.

in potency in the γ-secretase assay.[13] The (−) alcohol obtained was mesylated and treated with NaN_3 followed by reduction afforded the tricyclic amine **14** in 94% overall yield. Sulfonamide compounds **15a–g** were prepared by standard sulfonylation methods. Similarly compounds **17a–r** were prepared starting from the chlorophenyl vinyl sulfone **16** as shown in Scheme 1.

Enantiomerically pure tricyclic alcohol **13a** was oxidized to the aldehyde **18** followed by reductive amination using various amines to afford **19**. Amines **19** were then sulfonylated under standard reac-

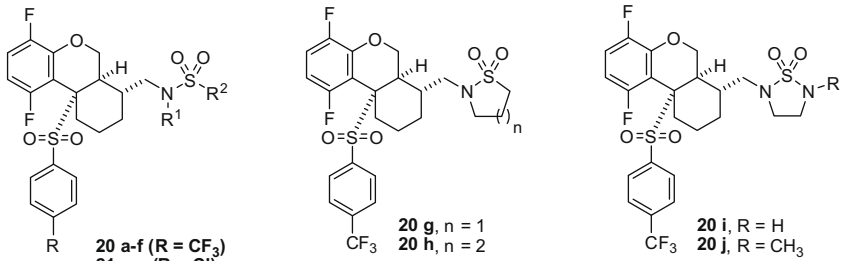
Table 3
Profile of **15a** and **15c**



Parameters	R = CH_3 (**15a**)	R = CF_3 (**15c**)
Membrane IC_{50} (nM)	13	41.7
Cell IC_{50} (nM) Aβ40, Aβ42	12, 3.6	40.6, 18.7
Caco-2 permeability	421 nm/s	230 nm/s
Efflux substrate	No	No
CYP 3A4 (μM)[a]	>30	>30
Rat PK (10 mg/kg PO) AUC (ng h/mL)[15]	2006	702[b]
Brain concn @ 6 h (ng/g)	80	91
Brain/plasma ratio	0.73	1.01
h-Plasma protein binding	98.1	99.9
Non TG % inhibition at 3 h (10 mg/kg po)	96 (pl), 69 (br)	101 (pl), 71 (br)

[a] Values determined after 30 min pre-incubation with compound.
[b] A slight increase in AUC was observed when sodium salt of **15c** was prepared. Free base AUC was 400 ng h/mL.

Table 2
γ-Secretase membrane and cell IC_{50}'s



Compd	R^1	R^2	Membrane[a] IC_{50} (nM)	Cell Aβ40 IC_{50} (nM)	Cell Aβ42 IC_{50} (nM)
20a	CH_2CH_3	CH_3	34	18.5	7.4
20b	CH_2CH_3	CF_3	97	42	21
20c	CH_2CH_3	*c*Pr	83	46.7	21
20d	*c*Pr	CH_3	5.8	9	6
20e	*c*Pr	CH_2CH_3	28	29.5	14.2
20f	*c*Pr	CF_3	35.3	15.3	14.2
20g	—	—	90	72	25
20h	—	—	122	na	na
20i	—	—	37.7	na	na
20j	—	—	68	23	13
21a	CH_2CH_3	CH_3	5.5	12	5
21b	CH_2CH_3	CH_2CH_3	16	15	7
21c	CH_2CH_3	*c*Pr	20.5	25	9
21d	*c*Pr	CH_3	3.3	6	4
21e	*c*Pr	CF_3	15	21	9

[a] Mean values ($n = 2$) ± SEM. na = not available.

tion conditions to give compounds **20a–f** as shown in Scheme 2. Alcohol **13a** was mesylated and displaced with sultam or cyclic sulfonamide to produce compounds **20g–j** as shown in Scheme 2. Similar chemistry was utilized for the preparation of compounds **21a–e**.

The SAR derived from the tricyclic scaffold is described in Table 1. Alkyl sulfonamides such as methyl (**15a**), ethyl (**15b**), trifluoromethyl (**15c**), trifluoroethyl (**15d**), and cyclopropyl (**15e**) derivatives showed excellent potency in the membrane as well as cellular assays. Simple sulfamides such as **15f** and **15g** were also very well tolerated. The sulfonamide SAR in the chlorophenyl sulfone series showed excellent potency; usually several fold enhancement relative to the trifluoromethylphenyl sulfone series. However, that difference in potency did not really translate into in vivo efficacy. Both series generally produce very similar in vivo numbers.[14] In the chlorophenyl sulfone series, a wide range of alkyl sulfonamides are tolerated as shown in Table 1. Long alkyl chains (**17a–h**) as well as small cyclic alkyls (**17i**) are very well tolerated. Cyclohexyl (**17j**) and phenyl (**17q**) sulfonamides showed a decrease in potency, however, 2,6-difluorophenyl (**17r**) and 2-thienyl (**17s**) sulfonamides showed very good in vitro affinity. The sulfamide analogs **17k–p** are also very well tolerated.

Next, we turned our attention to *N*-alkyl substituted sulfonamides as shown in Table 2. We have introduced ethyl and cyclopropyl substitutions on the nitrogen atom. Simple methane sulfonamide (**20a**) in this series showed 34 nM activity whereas trifluoromethyl (**20b**) and cyclopropyl (**20c**) sulfonamides showed diminished γ-secretase affinity. Sultam derivatives **20g** and **20h** showed less potency than the corresponding acyclic version and the cyclic sulfamide derivatives **20i** and **20j** were also showed diminished γ-secretase activity. As expected, the chlorophenyl sulfone derivatives **21a–e** exhibited better γ-secretase activity than their trifluoromethyl phenylsulfone analogs.

As described in Tables 1 and 2, SAR studies on the sulfonamide series led to the identification of a large number of potent γ-secretase inhibitors. Mouse efficacy and pharmacokinetic studies were carried out on numerous compounds and used as a key assay to discriminate better analogs. Data for two of the best compounds **15a** and **15c** are shown in Table 3. These compounds are orally bioavailable and showed excellent in vivo efficacy in a non-transgenic mouse model as shown in Table 3. Compound **15a** showed 96% inhibition of Aβ40 in the plasma and 69% inhibition in the brain at 10 mg/kg po. Compound **15c** also showed excellent inhibition both in plasma (101%) and brain (71%). It has been found that compounds **15a** and **15c** are inactive @ 30 μM in the P450 assay as well as in the hERG channel. The triflimide compound **15c** is highly protein bound. Both compounds are well absorbed and are not PGP efflux substrates.

In summary, we have identified a large number of highly potent, small molecule inhibitors that display excellent in vivo efficacy in rodents. Compounds **15a** and **15c** have excellent profile and are potent in vivo. Further biological characterization of these compounds will be presented in due course.

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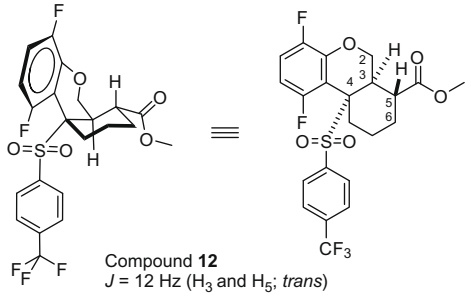

Compound **12**
J = 12 Hz (H_3 and H_5; *trans*)

13. Efficacy of γ-secretase inhibitors in intact cells was measured using HEK293 cells expressing human APP with both Swedish and London mutations. The cells were grown in 96-well plate with 100 μL media per well, and were changed to fresh media and incubated with γ-secretase inhibitor for 4 h. Ten microliters of conditioned media was used to measure Aβ40 using ECL technology as described in the following reference. Zhang, L.; Song, L.; Terracina, G.; Liu, Y.; Pramanik, B.; Parker, E. *Biochemistry* **2001**, *40*, 5049.
14. For example, Compound **17b** showed 86% inhibition of Aβ40 in plasma and 48% in brain at 10 mg/kg po and compound **15c** showed 101% inhibition of Aβ40 in plasma and 71% in brain at 10 mg/kg po.
15. Following the oral dosing at 10 mpk in 20% HPBCD, AUC in rats was measured over a period of 6 h, using cassette-accelerated rapid rat screen (CARRS): Korfmacher, W. A.; Cox, K. A.; Ng, K. J.; Veals, J.; Hsieh, Y.; Wainhaus, S.; Broske, L.; Prelusky, D.; Nomeir, A.; White, R. E. *Rapid Commun. Mass Spectrom.* **2001**, *15*, 335.