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Tetracyclic sulfones as potent γ-secretase inhibitors: Synthesis and structure–activity relationship studies

T. K. Sasikumar *, Duane A. Burnett, Theodros Asberom, Wen-Lian Wu, Chad Bennett, David Cole, Ruo Xu, William J. Greenlee, John Clader, Lili Zhang, Lynn Hyde

Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA

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ABSTRACT

Complex tetracyclic sulfones were designed as γ-secretase inhibitors and a stereoselective synthesis was achieved. γ-Secretase activity was seen predominately in the (−) enantiomeric series. Compounds such as **2a** and **2b** showed remarkable in vitro and in vivo potency.

Alzheimer's disease (AD) is a neurodegenerative disease affecting millions of people world wide. AD is the fourth major cause of death in the developed world. The number of Alzheimer's patients is reported to be over 35 million-globally. Currently there are no treatments to delay or halt the progression of the disease available. Numerous approaches have been taken towards the cure of this progressive disease. It is widely believed that the beta amyloid deposits made from oligomeric Aβ peptides of 40–42 amino acids are the fundamental cause of the disease.[1] Inhibition of the enzyme complex γ-secretase by small molecules has been shown to lower levels of plasma and cortical Aβ peptides.[2] Several small molecule γ-secretase inhibitors have been identified and some of them have been progressed to humans clinical studies.[3–5]

An aryl sulfone core was present in a number of recent publications on γ-secretase inhibitors from various pharmaceutical companies including Schering-Plough.[6–8] The bicyclic chromane sulfone **1a** from our laboratories showed excellent in vitro potency in the γ-secretase assay (membrane IC_{50} = 42 nM). The potent bicyclic chromanes prompted the design of conformationally restricted tricyclic analogs such as structure (**1b**) as shown in Figure 1.[6] To our delight, the newly designed tricyclic sulfone showed remarkable γ-secretase activity. A series of SAR studies on the cyclohexyl ring lead us to a number of sulfonamide compounds at position 8 as illustrated by structure **1b** with an improved γ-secretase affinity and pharmacokinetic properties. It was also found that small substitutions at position 7 of the tricyclic system was very well tolerated (see Fig. 1 for numbering).[6] Recent reports from Merck shows that a bicyclic sulfonamide bearing a trifluromethylphenyl sulfone moiety (**3**) is a very potent γ-secretase inhibitor.[9,10] The overlay of compounds **1b** and **3** suggested that the addition of a fourth ring might suitably dispose our pharmacophores for maximal potency. We, thus, decided to incorporate the cyclic sulfonamide moiety to our benzochromane structure previously discovered, leading to a conformationally rigid tetracyclic frame work (**2b**) as shown in Figure 1.

The synthesis of the tetracyclic compound starts from the known tricyclic ketone **4** which served as a versatile intermediate for a variety of other γ-secretase inhibitors.[6,11] An efficient route to our tetracycle from ketone **4** was inspired by the camphor sultam synthesis reported by Davis et al.[12] Accordingly, the vinyl sulfonamide (**5**) was prepared in three steps from commercially available starting materials.[13] The copper enolate derived from compound **4** upon 1,4-addition to vinyl sulfonamide **5** under Davis' reaction conditions gave us very low isolated yield. However we found that high dilution conditions omitting the copper salt gave us compound **6** in a reproducible 30–40% average yield. We also observed significant quantities of a side product whose structure was confirmed to be a 1:2 bisalkylated adduct based on the NMR data. Enolates at both positions 7 and 9 of ketone **4** reacted with vinyl sulfonamide **5** to form 1:2 adduct in this undesired pathway. Any attempts to reduce the formation of dimeric product were unsuccessful. The desired Michael product **6** could be purified by repeated precipitation from hexane–ethyl acetate solvent mixture. Treatment of compound **6** with 50% TFA/DCM gave the tetracyclic core structure in 74% isolated yield. It has been found that the imine double bond isomerized to the tetrasubstituted enamine position thus destroying the newly created stereocenter at C7.

* Corresponding author. Tel.: +1 908 740 4373; fax: +1 908 740 7164.
E-mail addresses: sasikumartk@yahoo.com, thavalakulamgar.sasikumar@merck.com (T.K. Sasikumar).

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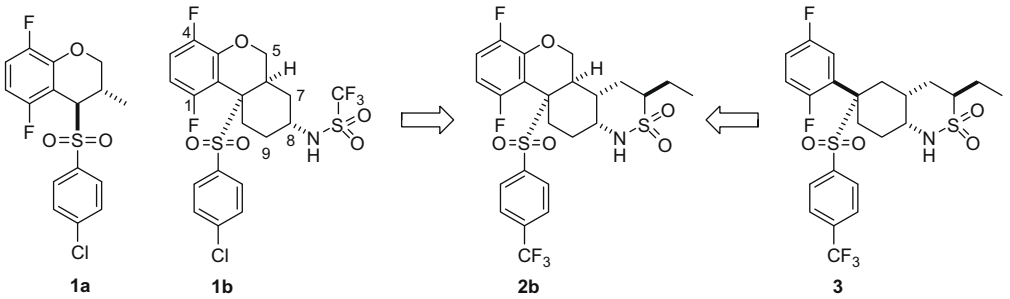


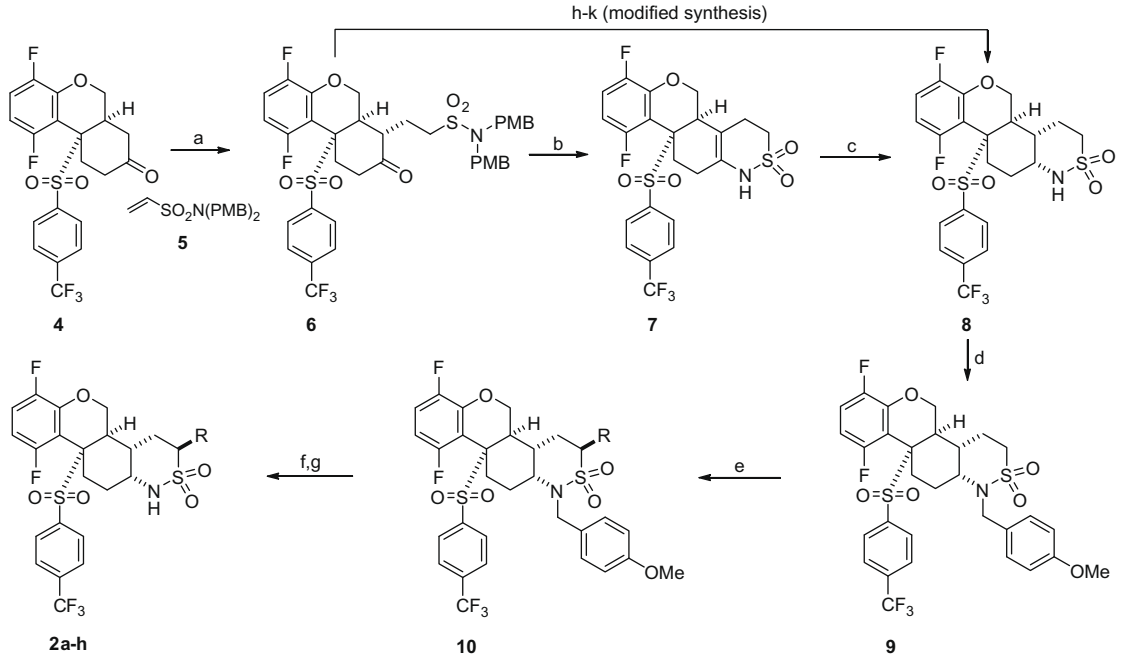
Figure 1. Tetracycle (**2b**) design.

The enamine **7** was reduced to compound **8** in 45% isolated yield. The relative stereochemistry was confirmed by NMR and X-ray studies of a closely related compound. It has been found that a small amount of the *trans* stereoisomer was also isolated from the reduction reaction. PMB protection of the sulfonamide nitrogen followed by stereoselective α-alkylation and deprotection afforded the final tetracyclic compounds **2a–h** as shown in Scheme 1.[14] The enantiomers were separated on a Chiralcel OD column using isopropanol/hexane as eluent. It has been found that the (−) enantiomers are significantly more potent at inhibiting γ-secretase than are the corresponding (+) enantiomers.[15]

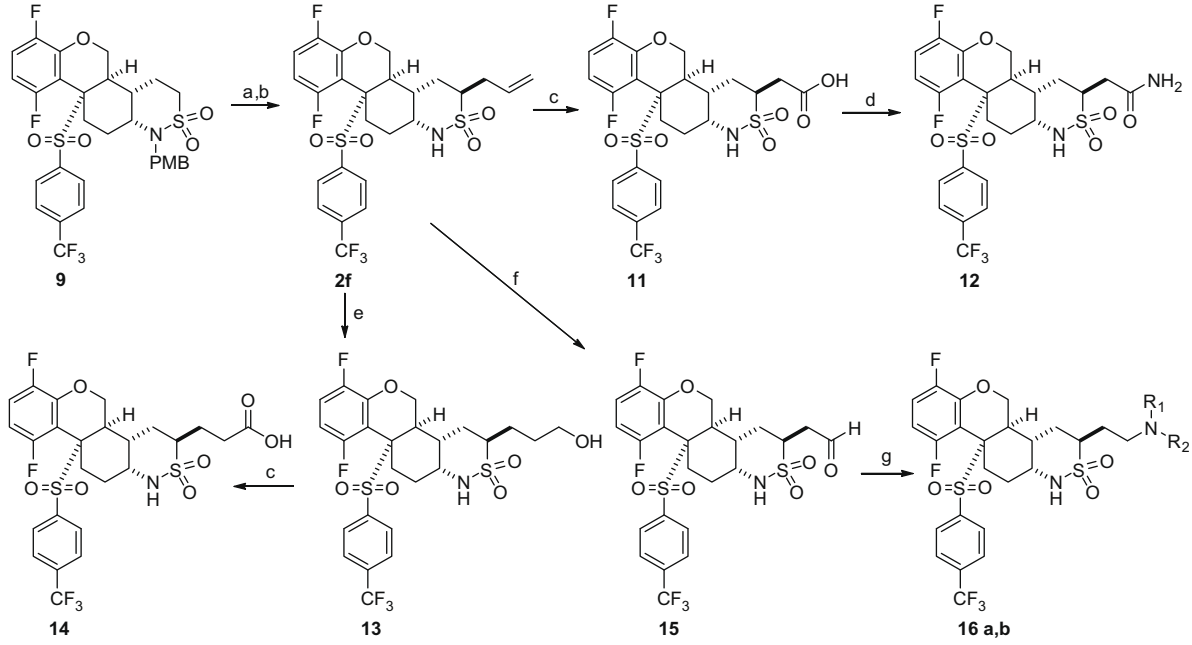
During scale up efforts directed to compound **2**, reduction of the double bond of compound **7** proved inconsistent and prompted us to develop alternate method for the construction of the fourth ring. To that end, compound **6** was stereoselectively reduced to the *trans* alcohol using $NaBH_4$ and the resulting alcohol was converted to the mesylate. Deprotection of the PMB group using TFA followed by NaH mediated cyclization afforded the tetracyclic compound **8** in 50–60% overall yield for the four step sequence. Alkylations were carried out as in Scheme 1 and the final deprotection was achieved in acidic medium to obtain the tetracyclic compounds.

Further SAR studies were initiated from the PMB protected tetracycle **9** as shown in Scheme 2. Stereoselective allylation with allyl iodide followed by deprotection afforded compound **2f** in good yield. Compound **2f** served as an excellent starting point for a number of modifications. Allyl derivative **2f** was directly converted to the acid **11** and further derivatised to the amide **12** under standard conditions.[16] Hydroboration of **2f** followed by base treatment afforded compound **13** and then converted to the acid **14** in good yields.[17] Ozonolysis of compound **2f** provided aldehyde **15** which upon reductive amination gave compounds **16a** and **16b**.

The data for the inhibition of Aβ40 production measured using membrane based preparations of γ-secretase is shown in Table 1. We also assessed the cell permeation properties utilizing whole cells.[15] Unadorned analog **8** showed good membrane IC_{50} (30 nM). Simple alkylation products (**2a**, **2b** and **2d**) enhanced the γ-secretase (both membrane and cellular) affinity by several fold. Allyl, crotyl and methoxymethyl derivatives (**2e**, **2g**, **2f**) showed single digit nanomolar affinity, however, the affinity of cinnamyl derivative **2h** dropped fourfold as compared to the crotyl derivative **2g**. Recently carboxylic acid derived γ-secretase inhibitors have been reported in the literature.[18] The tetracyclic carboxylic acid derivatives **11** and **14** showed good γ-secretase activity. The primary amide **12** derived from compound **11** showed excellent cellular Aβ42 IC_{50} value. Alcohol derivative **13** also showed single digit nanomolar potency. Tetracyclic compounds bearing a basic amine moiety (**16a** and **16b**) are also very well tolerated.

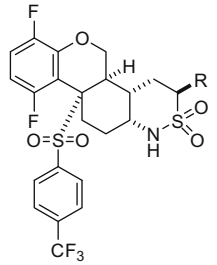


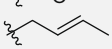
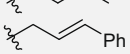
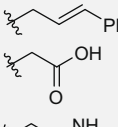
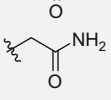
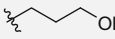
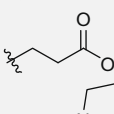
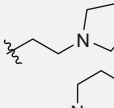
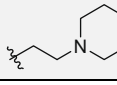
Scheme 1. Reagents and conditions: (a) LHMDS, THF, then **5**, 30–40%; (b) TFA, DCM, 74%; (c) H_2, PtO_2, EtOAc, 45%; (d) LHMDS, NaI, PMB-Cl, THF, 70%; (e) NaHMDS, RI, THF; (f) TFA, DCM, 60–70% for two steps; (g) chiral separation on OD column; (h) $NaBH_4$; (i) MsCl, TEA, DCM; (j) TFA, DCM; (k) NaH, DMF, 50–60% for four steps.



Scheme 2. Reagents and conditions: (a) NaHMDS, allyl iodide; (b) TFA/DCM, 57% for two steps; (c) $RuCl_3{\cdot}H_2O$, $NaIO_4$, EtOAc, CH_3CN, H_2O, 63%; (d) $SOCl_2$, $CHCl_3$, 50 °C, then NH_3, MeOH, 80%; (e) 9-BBN, H_2O_2, NaOH, THF, 49%; (f) O_3, DCM, then Ph_3P, 78%; (g) R_1R_2NH, $NaBH(OAc)_3$, DCM, 45%.

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

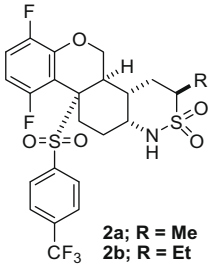


Compd[a]	R	Membrane[b] IC_{50} (nM)	Cell Aβ40 IC_{50} (nM)	Cell Aβ42 IC_{50} (nM)
8	–H	30	na	na
2a	$-CH_3$	1.6	1	0.5
2b		1.9	5	2
2d		5.5	3	1
2e		7.7	7	2
2f		9.0	7.8	8.0
2g		14.6	na	na
2h		60.9	na	na
11		48.3	930	1198
12		na	na	4
13		9.5	3.8	4.9
14		17	40.6	64
16a		45.5	na	na
16b		48.4	na	na

na = not available.
[a] Only compounds **8**, **2a** and **2b** are (−) enantiomers, all others are racemic.
[b] Mean values ($n = 2$) ± SEM.

Compounds **2a** and **2b** displayed excellent in vitro and cellular potency and were chosen for further evaluation in a rapid rat PK study.[19] The results of these studies and additional biological properties are shown in Table 2. The compounds were dosed orally (10 mg/kg) as a suspension in 20% HPBCD. These compounds showed moderate exposure with low brain concentration. Compounds **2a** and **2b** showed no CYP and hERG issues and human hepatocyte clearance was low. These compounds are also highly protein bound (plasma protein binding >97.3%). Compounds **2a** and **2b** were profiled in vivo in the non-transgenic mouse model and demonstrated a robust decrease of both plasma and brain Aβ levels with a dose of 10 mg/kg as shown in Table 2.[20]

Table 2
Profile of **2a** and **2b**



Parameters	R = CH_3 (**2a**)	R = C_2H_5 (**2b**)
Membrane IC_{50} (nM)	1.6	1.9
Whole cell Ab40 IC_{50} (nM)	1.0	5.0
Whole cell Ab42 IC_{50} (nM)	0.5	2.0
Rat PK, (10 mg/kg), AUC (ng h/mL)[19]	139	40
Brain concn @ 6 h (ng/g)	<10	<10
Brain/plasma	na	1
CYP (3A4, 2D6 and 2C9) mM	>30	>30
hERG (rubidium efflux) % @ 5 μg/mL	4	10
h-Hepatocyte clearance (μL/min/M cells)	0.4	0.3
Plasma protein binding	97.3	98.1
NonTG mouse % reduction of Aβ40[a] @ 10 mpk/po[20]	72 (pl); 57 (br)	84 (pl); 42 (br)

[a] Mean values ($n = 5$). Expressed as a percent relative to vehicle controls.

In conclusion, we have discovered potent tetracyclic sulfone γ-secretase inhibitors that are useful for reducing Aβ production in vivo. Compounds such as **2a** and **2b** showed excellent in vitro and in vivo properties. Details of further SAR studies of these tetracyclic γ-secretase inhibitors as well as broad biological testing will be reported in subsequent publications.

Acknowledgments

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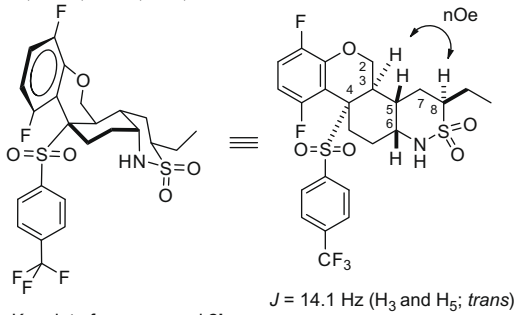
14. Data for compound **2b**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.85 (d, 2H), 7.82 (d, 2H), 7.12 (m, 1H), 6.48 (m, 1H), 5.25 (d, 1H), 4.49 (d, 1H), 4.44 (d, 1H), 3.72 (br s, 1H), 3.13 (d, 1H), 2.46 (d, 1H), 2.29 (m, 1H), 2.12 (m, 1H), 1.97 (m, 1H), 1.78 (m, 1H), 1.53 (m, 5H), 1.16 (t, 3H).



Key data for compound **2b**

J = 14.1 Hz (H_3 and H_5; *trans*)
J = 3.5 Hz (H_5 and H_6; *cis*)

15. 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 microlitres of conditioned media was used to measure Aβ40 using ECL technology as described in the following reference. Song, L.; Terracina, G.; Liu, Y.; Pramanik, B.; Parker, E. *Biochemistry* **2001**, *40*, 5049.
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19. 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.
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