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Discovery of SCH 900229, a Potent Presenilin 1 Selective γ-Secretase Inhibitor for the Treatment of Alzheimer's Disease

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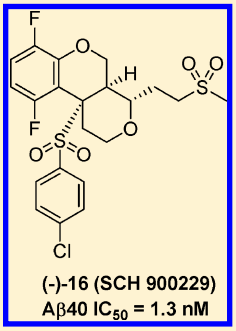
Supporting Information

ABSTRACT: An exploration of the SAR of the side chain of a novel tricyclic series of γ-secretase inhibitors led to the identification of compound (−)-**16** (SCH 900229), which is a potent and PS1 selective inhibitor of γ-secretase (Aβ40 IC_{50} = 1.3 nM). Compound (−)-**16** demonstrated excellent lowering of Aβ after oral administration in preclinical animal models and was advanced to human clinical trials for further development as a therapeutic agent for the treatment of Alzheimer's disease.



KEYWORDS: *γ-Secretase inhibitor, Alzheimer's disease, amyloid, notch, clinical candidate*

Alzheimer's disease (AD) was first described a century ago[1] and has since become increasingly prevalent in recent decades, presumably reflecting an aging population. Current standard treatments, chiefly cholinesterase inhibitors, are only palliative in nature and are insufficient to stop the progression of the disease.[2] Alzheimer's disease is a neurodegenerative disorder manifested by cognitive and memory deterioration, as well as impairment of language and other activities of daily life. Two pathological hallmarks are intracellular neurofibrillary tangles and extracellular amyloid plaques. The well-known amyloid hypothesis postulates that production and deposition of β-amyloid (Aβ) is the leading cause of damage and death of neurons and eventual onset of Alzheimer's disease.[3,4] Aβ is generated from the large transmembrane amyloid precursor protein (APP) by two proteolytic reactions. Following cleavage by β-secretase (BACE1) at the N-terminus, γ-secretase processes the C-terminus to produce Aβ fragments of 37−42 residues. Aβ40 is the major isoform; however, Aβ42 is more hydrophobic and thereby more prone to aggregate to form plaques.[5] In recent years, there has been much interest in developing γ-secretase inhibitors as disease-modifying treatments to slow the formation of amyloid and in theory have a positive impact on Alzheimer's disease, as reflected by reports that several structurally distinct inhibitors, such as **1** (Semagacestat),[6] **2** (Begacestat),[7] and **3** (Avagacestat)[8] have progressed into different stages of clinical trials (Figure 1).

One critical aspect of development of γ-secretase inhibitors for the treatment of Alzheimer's disease is the potential for mechanism-based side effects. In addition to APP, γ-secretase also processes many other natural substrates, with the most physiologically significant being the cell surface Notch receptor. Notch processing is involved in cell differentiation and development, and blocking the Notch pathway may have detrimental side effects.[9,10] A critical goal of this work was to achieve potent γ-secretase inhibition with high selectivity against Notch processing. A series of γ-secretase inhibitors bearing novel tricyclic cores, developed in our laboratories, has been previously reported.[11,12] In this communication, further structure−activity relationship (SAR) exploration of the side

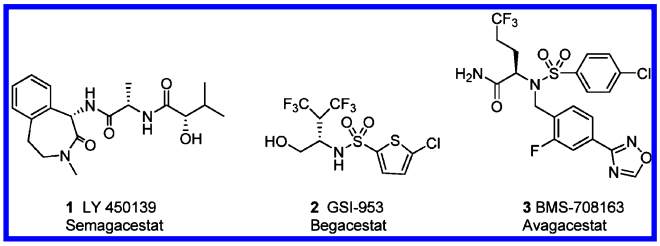


Figure 1. Representative γ-secretase inhibitors.

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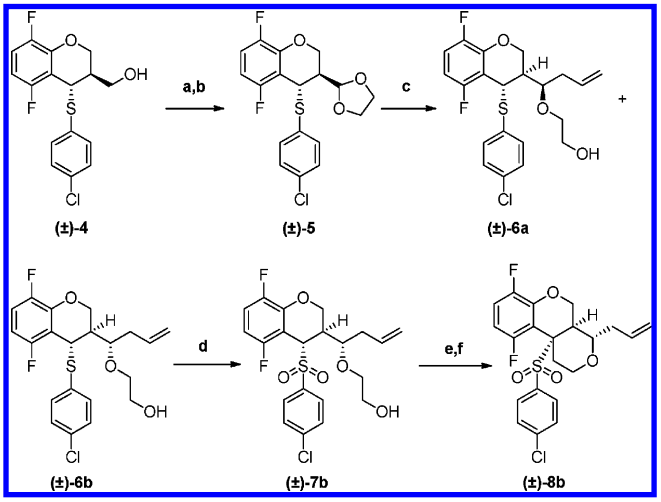
chain of the bispyran series and identification of a clinical candidate will be described.

To facilitate synthesis of analogues bearing the bispyran core, we designed and developed an efficient route to the allyl substituted intermediate **8b** starting from the readily available racemic alcohol **4**,[11] as depicted in Scheme 1. Dess−Martin

Scheme 1. Synthesis of Tricyclic Intermediate 8b[a]



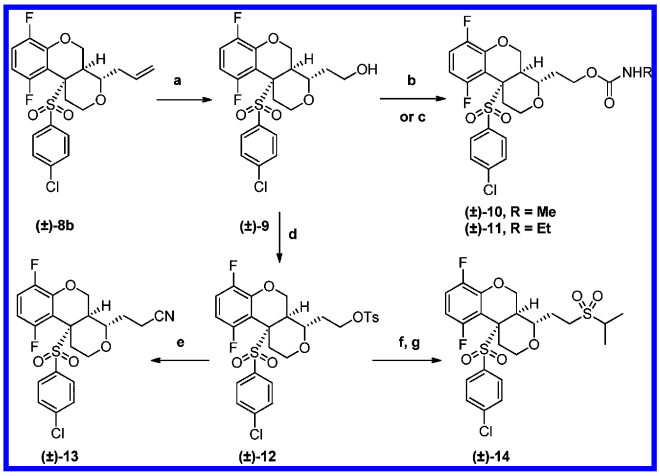
[a]Reagents and conditions: (a) Dess−Martin periodinane, CH_2Cl_2; (b) $(TMSOCH_2)_2$, TMSOTf; (c) allyltrimethylsilane, $BF_3{-}OEt_2$, CH_2Cl_2; (d) potassium peroxomonosulfate, MeCOMe−H_2O; (e) MsCl, Et_3N, CH_2Cl_2; (f) t-BuOK, THF.

oxidation of the alcohol **4** gave an aldehyde[13] which in turn was converted to the acetal **5**.[14] Unlike the aldehyde intermediate, which is prone to β-elimination under basic conditions, the acetal **5** is very stable under basic and even mild acidic conditions. Lewis acid catalyzed addition of allyltrimethylsilane gave a mixture of two diastereoisomers **6a** and **6b**[15] in a ratio of approximately 1:2 that was separated by chromatography. The desired isomer **6b** was then oxidized to the sulfone **7b**, whose mesylate derivative was subsequently treated with potassium *tert*-butoxide to effect a smooth ring closure, producing racemic **8b**. With this tricyclic scaffold in hand, we next turned to elaborate the allyl side chain to generate other polar functional groups, as shown in Scheme 2.

The allyl compound (±)-**8b** was subjected to ozonolysis and subsequent reductive workup to afford the racemic alcohol **9**. From this alcohol, several derivatives were prepared in straightforward fashion. Treatment of **9** with 4-nitrophenylchloroformate, followed by methylamine, gave carbamate **10**; reaction of compound **9** with ethyl isocyanate furnished carbamate **11**. Alternatively, the alcohol **9** was converted to its tosylate **12**, which was treated with sodium cyanide to give the nitrile **13**. In another avenue, compound **12** was reacted with isopropyl mercaptan to generate a thioether intermediate that was oxidized with *m*-chloroperbenzoic acid to afford the racemic sulfone **14**.

As revealed in Table 1, analogues **10**, **11**, **13**, and **14** were potent in inhibiting Aβ40 production in the membrane and cell-based assays,[16,17] suggesting that a variety of structural motifs are tolerated in this region. However, when compounds **13** and **14** were dosed orally in mice,[18] only the sulfone **14** demonstrated lowering of Aβ in the cortex. Having achieved preliminary success with an active series, we decided to pursue enantiomerically pure analogues. Thus, as illustrated in

Scheme 2. Elaboration of 8b to Various Side Chain Analogues[a]



[a]Reagents and conditions: (a) O_3, dichloromethane; Ph_3P, $NaBH_4$; (b) 4-nitrophenylchloroformate; $MeNH_2$; (c) ethyl isocyanate; (d) TsCl, Et_3N; (e) NaCN, DMF; (f) i-PrSH, KOH, EtOH, 70 °C; (g) mCPBA, CH_2Cl_2.

Scheme 3, the racemic alcohol **9** was first resolved by chiral HPLC to give two pure enantiomers (+)-**9** and (−)-**9**. The enantiomer (−)-**9** was more potent in Aβ40 inhibition than enantiomer (+)-**9**, as listed in Table 1. Assignment of absolute configuration to the enantiomer (−)-**9** was based on the close similarity of related active γ-secretase inhibitors and later confirmed by determining the X-ray structure of its derivative sulfone (−)-**16**.[19] As described above, enantiomer (−)-**9** was converted to its tosylate (−)-**12**, which was treated with isopropyl mercaptan followed by oxidation of the resultant sulfide to provide the sulfone (−)-**14**. The corresponding ethyl sulfone analogue (−)-**15** was also prepared accordingly. The methyl sulfone (−)-**16** was obtained by treatment of the tosylate (−)-**12** with *n*-tetrabutylammonium iodide and sodium methansulfinate in one-pot, although a small amount (5−10%) of the O-alkylation product **17** was also isolated.[20]

As shown in Table 1, all three enantiomerically pure sulfone analogues (−)-**14**, (−)-**15**, and (−)-**16** were very potent in reduction of Aβ40 and Aβ42, in both membrane and cell-based assays. More importantly, all of them also lowered Aβ *in vivo* at 3 h following a single oral dose in transgenic CRND8 or nontransgenic B6C3F1 mice.[18] Particularly, the methyl sulfone (−)-**16** exhibited excellent Aβ lowering *in vivo* in both plasma and cortex and was selected to be scaled up for further study.

In an effort to improve the overall yield of (−)-**16**, we designed a tactic to take advantage of the seemingly wasted diastereoisomer (±)-**6a**, as outlined in Scheme 4. Compound **6a** was converted to the tricyclic compound **8a** in three steps, as described for compound **8b**. The double bond of **8a** was then migrated using $RhCl_3{\cdot}3H_2O$ as a catalyst to give a mixture of olefins **18**, favoring the trans-isomer.[21] Cleavage by ozonolysis and reductive workup furnished the aldehyde **19**. Conformational analysis revealed that the carboxyaldehyde group is oriented axially, and also cis to the adjacent ring substituent. We envisioned that, under basic conditions, this β-oriented aldehyde would equilibrate to its more stable α-epimer (equatorial orientation) that could be used for the synthesis of the sulfone (−)-**16**. Indeed, treatment of **19** with potassium carbonate in methanol at room temperature proceeded smoothly to give the aldehyde **20**,[22] with complete inversion

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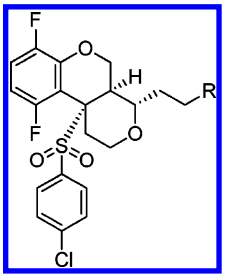
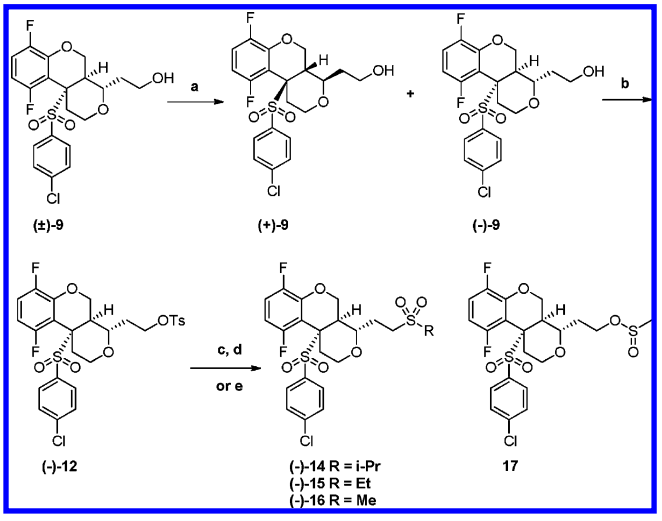
Table 1. In Vitro and in Vivo Biological Data



		Aβ40 IC_{50} (nM)[a,b]		Aβ42 IC_{50} (nM)[a,b]	PS2/PS1	in vivo Aβ40 (%)[c]	
compd	R	membrane	cell	cell	ratio	plasma	cortex
(−)-**9**	OH	20	18	8	ND		
(+)-**9**	OH	320	ND	ND	ND		
(±)-**10**	OCONHMe	8	8	6	3		
(±)-**11**	OCONHEt	24	48	20	ND		
(±)-**13**	CN	22	37	16	6	+18[d]	ND
(±)-**14**	SO_2i-Pr	24	26	10	6	−20[d]	−57[d]
(−)-**14**	SO_2i-Pr	6	8	3	ND	−2[e]	−58[e]
(−)-**15**	SO_2Et	3	5	2	26	−60[f]	−79[f]
(−)-**16**	SO_2Me	1.3	4	1	25	−89[f]	−78[f]
(+)-**16**	SO_2Me	377	ND	ND	ND		

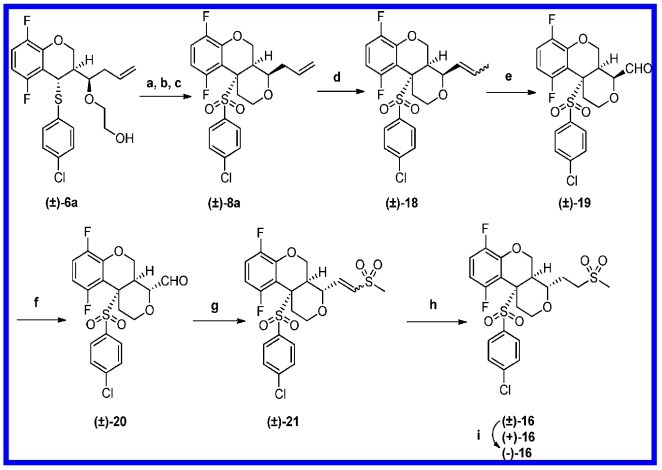
[a]The IC_{50} data are an average of at least two measurements; the standard deviation was 20%. [b]Determined in $HEK^{Awe\text{-}Lon}$ 293 cells. [c]Measured at 3 h after oral dosing, (−) indicates lowering, (+) indicates increase, see ref 18. [d]These data are from CRND8 mice dosed at 30 mg/kg. [e]These data are from B6C3F1 mice dosed at 10 mg/kg. [f]These data are from B6C3F1 mice dosed at 30 mg/kg.

Scheme 3. Synthesis of Enantiomerically Pure Sulfone Analogues[a]



[a]Reagents and conditions: (a) Chiralcel OJ column, i-PrOH-hexanes; (b) TsCl, Et_3N, CH_2Cl_2; (c) RSH, KOH, EtOH, 70 °C; (d) mCPBA, CH_2Cl_2; (e) n-Bu_4NI, $MeSO_2Na$, THF.

Scheme 4. Alternative Route to Compound (−)-16[a]



[a]Reagents and conditions: (a) Potassium peroxomonosulfate, MeCOMe−H_2O; (b) MsCl, Et_3N, CH_2Cl_2; (c) t-BuOK, THF; (d) $RhCl_3$−$3H_2O$, EtOH, reflux; (e) O_3, CH_2Cl_2, Ph_3P; (f) K_2CO_3, MeOH; (g) $(EtO)_2P(O)CH_2SO_2Me$, LiHMDS, THF; (h) $NaBH_4$, THF−MeOH; (i) Chiralcel OD column.

at the α-position. Horner−Wittig elongation of the aldehyde **20** with diethyl methylsulfonomethylphosphanate under basic conditions gave a mixture of α,β-unsaturated sulfones **21**, in favor of the trans-isomer.[23] Reduction of **21** with sodium borohydride furnished the racemic sulfone **16**,[24] which was resolved on a Chiralcel OD column to obtain the desired enantiomerically pure sulfone (−)-**16** and its enantiomer (+)-**16**. Not surprisingly, (+)-**16** is much less potent than (−)-**16**, as shown in Table 1. The spectroscopic characterization of enantiomer (−)-**16**, including proton NMR, LC-MS, and optical rotation, is in full agreement with that of (−)-**16** prepared according to Scheme 3.

The success of the synthetic route described in Scheme 4 not only augmented the overall yield of (−)-**16** from 4% to 6% but suggested immediately a unified pathway to (−)-**16**. As depicted in Scheme 5, starting from the acetal intermediate **5**, oxidation with mCPBA gave the sulfone **22**. Ring-opening of the ketal was carried out using cyanotrimethylsilane instead of allyltrimethylsilane,[25] to give a mixture of two diastereoisomeric alcohols **23** in a ratio of roughly 1:1. Without separation, the alcohols were transformed to their mesylates, and base-promoted

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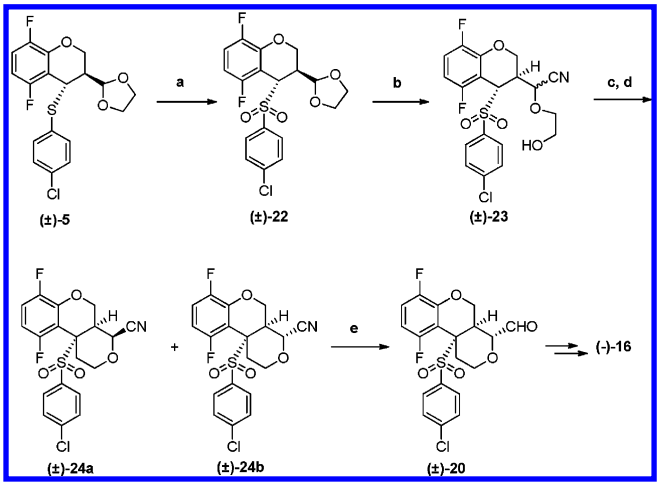
Scheme 5. Efficient Synthesis of Compound (−)-16[a]



[a]Reagents and conditions: (a) mCPBA, CH_2Cl_2; (b) Me_3SiCN, BF_3−OEt_2; (c) MsCl, Et_3N, CH_2Cl_2; (d) t-BuOK, THF; (e) DIBAL in toluene, CH_2Cl_2; t-BuOK, THF.

ring closure gave the tricyclic nitriles **24a** and **24b**, with the ratio of α- to β-epimer being enriched to ca. 8:1. DIBAL reduction of **24b** gave the desired α-epimer aldehyde **20**. Conversion of the aldehyde **20** to (−)-**16** was then achieved as described previously in Scheme 3. Alternatively, similar reduction of a mixture of **24a** and **24b** (1:4) followed by treatment of the crude aldehyde with t-BuOK also furnished **20** as the major isomer (95% purity), which was used directly in the next step. This streamlined synthesis of (−)-**16** delivered a higher overall yield (12%) than the combined yield from the routes shown in Schemes 3 and 4. It also featured two other advantages: no tedious separation of diastereoisomers **6a** and **6b** and no process-unfriendly ozonolysis operation.

Compound (−)-**16** was characterized in different preclinical species for its ability to reduce Aβ. When CRND8 mice were acutely dosed orally with (−)-**16**, Aβ40 in plasma and cortex were reduced significantly at the 3 h time point,[18] with ED_{50} values of 0.5 and 0.4 mg/kg, respectively. In a separate subchronic study, CRND8 mice were dosed with (−)-**16** BID orally for 6 days, and a similar lowering of Aβ in both plasma (ED_{50} 0.4 mg/kg) and cortex (ED_{50} 0.3 mg/kg) was observed. No evidence of Notch-related effects, such as a reduction in thymus size or intestinal goblet cell hyperplasia, was observed. Compound (−)-**16** showed an IC_{50} of 46 nM in an in vitro cell-based Notch cleavage assay.[17] This level of selectivity between Notch and Aβ40 processing was comparable to that of semagacestat. Compound (−)-**16** displayed a high PS2/PS1 ratio of 25 (see Table 1) when tested with reconstituted γ-secretase complexes, suggesting it is a PS1 selective inhibitor of γ-secretase.[26] This feature is distinct from those of many early GSI's, such as semagacestat (PS2/PS1 = 1) and Begacestat (PS2/PS1 = 1), and it may contribute to its high therapeutic window observed in rodents. Moreover, compound (−)-**16** was found to be excellent at lowering of $A\beta_{40}$ in all three compartments (plasma, CSF, and cortex) in rats (ED_{50} values of 1.1, 3.7, and 0.3 mg/kg, respectively) and dogs, and detailed data will be reported in due course. As shown in Table 2, the pharmacokinetic properties of (−)-**16** were determined in rat, monkey, and dog. Overall, it displayed good to excellent exposure with sufficient oral bioavailability in all species tested.

In summary, we have identified and developed a series of tricyclic analogues bearing two sulfone groups as potent and selective γ-secretase inhibitors. Among them, sulfone (−)-**16** exhibited significant selectivity against Notch processing and demonstrated robust lowering of Aβ after oral administration in rodents and large animals, as well as generally favorable pharmacokinetic profiles across species. On the basis of these promising results, (−)-**16** was advanced to human clinical trials for the treatment of AD.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details for synthetic procedures and compound characterization for compounds **5**−**24** and crystallographic data of compound (−)-**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

AD, Alzheimer's disease; Aβ, β-amyloid; CSF, cerebrospinal fluid; PS1, presenilin-1; PS2, presenilin-2; APP, amyloid precursor protein; BACE1, β-secretase 1, β-site APP cleaving enzyme; GSI, γ-secretase inhibitor; BID, twice daily; SAR, structure−activity relationship; mCPBA, *m*-chloroperbenzoic acid

Table 2. Pharmacokinetic Profiles of Compound (−)-16[a,b]

species (vehicle)	dose (mg/kg)	AUC (0−∞) (μM·h)	C_{max} (μM)	T_{max} (h)	$T_{1/2}$ (h)	*F* (%)	CL (mL/min/kg)	Vd(ss) (L/kg)
rat (20% HPβCD)	10	1.4	0.65	0.7	1.1	29	69	5.4
rat (0.4% HPMC)	10	1.0	0.24	0.3	1.0	6.4	20.8	3.4
monkey (0.4% HPMC)	5	8.9	1.39	1.7	4.6	45	8.2	1.9
dog (0.4% HPMC)	5	85.6	2.74	2.0	23.9	86	1.7	3.1

[a]Data are averages from three rats, monkeys, and dogs (n = 3; PO). [b]CL and Vd(ss) obtained with iv administration (5 mg/kg for rat, 2.5 mg/kg each for monkey and dog).

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