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A-ring modification of SCH 900229 and related chromene sulfone γ-secretase inhibitors

Wen-Lian Wu *, Thavalakulamgara K. Sasikumar, Martin S. Domalski, Li Qiang, Duane A. Burnett, John Clader, William J. Greenlee, Tze-Ming Chan, Julie Lee, Lili Zhang

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

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ABSTRACT

Attempts to block metabolism by incorporating a 9-fluoro substituent at the A-ring of compound **1** (SCH 900229) using electrophilic Selectfluor™ led to an unexpected oxidation of the A-ring to give difluoroquinone analog **1a**. Oxidation of other related chromene γ-secretase inhibitors **2**–**8** resulted in similar difluoroquinone analogs **2a**–**8a**, respectively. These quinone products exhibited comparable in vitro potency in a γ-scretase membrane assay, but were several fold less potent in a cell-based assay in lowering Aβ40–42, compared to their parent compounds.

Alzheimer's disease (AD) is a progressive and devastating neurodegenerative disorder affecting millions of people. AD is the most severe form of dementia and the fourth major cause of death in the developed world. Currently there are no disease-modifying medications to slow down the progression of AD; the only therapies are palliative treatments of modest efficacy.[1] Amyloid plaques consisting of 40–42 amino acid β-amyloid peptides (Aβ) and neurofibrillary tangles are the two pathological hallmarks observed in AD patients brains. Accumulation of Aβ has been proposed to be responsible for neuronal toxicity that is associated with AD.[2,3] Aβ peptides are generated from a larger amyloid precursor protein (APP) by two sequential cleavages, first by β-site APP cleaving enzyme (BACE1) and then by γ-secretase.[4] Thus, reduction of Aβ levels by inhibition of BACE1 or γ-secretase should, in theory, represent a promising approach to develop disease-modifying treatments for AD. Indeed, many small molecule BACE1 and γ-secretase inhibitors have been pursued as potential treatments for AD in the last decade.[5]

Towards this end, we have successfully identified and developed a novel series of bis-pyran sulfone γ-secretase inhibitors. In previous communications, we have disclosed the discovery of our clinical compound SCH 900229 (**1**, Fig. 1)[6] and also described a detailed SAR study of the two sulfone side chains of that molecule.[7] Herein, SAR investigation on the A-ring of compound **1** and structurally related analogs **2–8** (Fig. 1) are reported.[8–11]

As part of our program to continue SAR investigations around the γ-secretase inhibitor **1**, we were interested in the incorporation of small groups at the 9-position of the A-ring, preferably fluorine, to potentially reduce metabolism of this relatively electron-rich site. In a rat pharmacokinetic and metabolism study (data not shown), an A-ring oxidation metabolite (M+16), presumably the C9-hydroxylated analog of **1**, was indeed observed. Owing to the linear synthesis of compound **1**,[7] the option of functionalization of the A-ring at a late stage was limited. Initially, as illustrated in Scheme 1, when compound **1** was treated with *N*-iodosuccinimide in the presence of trifluoroacetic acid, as expected compound **9** was obtained in good yield.[12] However, its potency dropped dramatically (Aβ40 membrane IC_{50} of 1276 nM) compared to compound **1**. This result indicated limited tolerance for steric bulk at this position.

Fluorine has been used widely in medicinal chemistry as an isosteric replacement for hydrogen, based on their similar sizes. Selectfluor™ is a well-known reagent for electrophilic fluorination of organic compounds, and thus was chosen for the introduction of 9-fluoro on the A-ring of compound **1**.[13] Thus, a solution of compound **1** and an excess amount of Selectfluor™ in acetonitrile was stirred at room temperature for 3 h. No reaction was detected by TLC and LC–MS. The solution was then heated at 80 °C overnight (20 h), and under those conditions, starting material **1** was completely consumed as judged by LC–MS, although no desired 9-fluoro-substituted product was detected. Instead, compound **1a** was isolated as the major product (Scheme 1). When compound **2** was subjected to the same reaction conditions, a similar analog **2a** was obtained (Scheme 2). Extensive analysis of **2a** employing various NMR techniques, including HSQC, COSY, and HMBC, confirmed its structure to be the oxidation product.[14] This result came as a surprise to us, considering the two electron-poor sites (with F-attached) were oxidized further while the electron-rich 9-position remained intact.

* Corresponding author. Tel.: +1 732 594 2987; fax: +1 732 594 3007.
E-mail address: wen-lian.wu@merck.com (W.-L. Wu).

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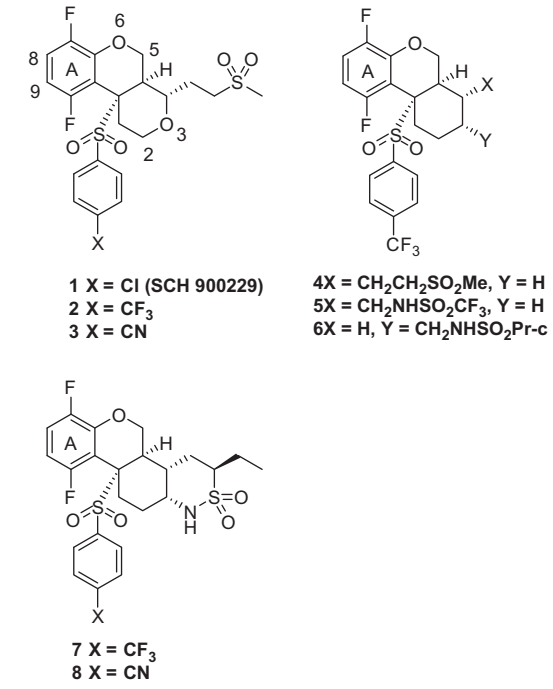
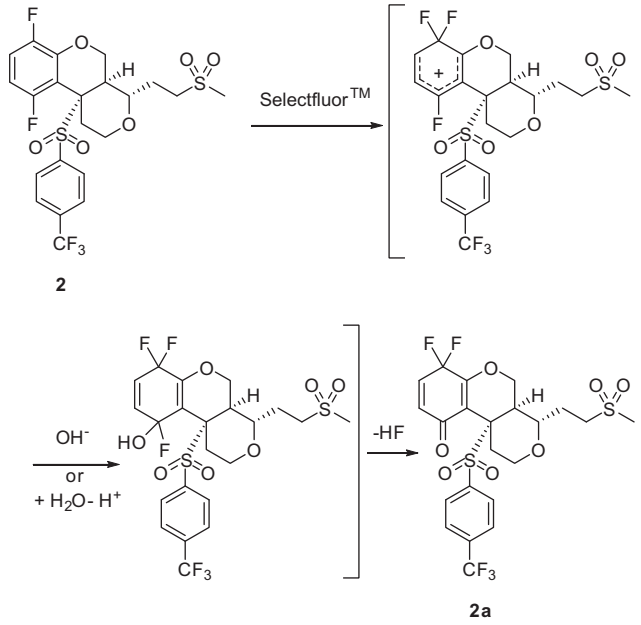
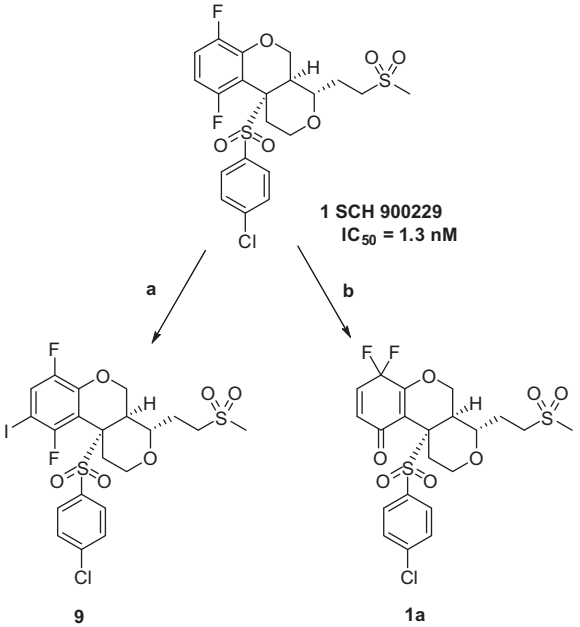


Figure 1. γ-Secretase inhibitors.



Scheme 2. Plausible reaction mechanism.



Scheme 1. Reagents and conditions. (a) NIS, CF_3COOH, room temperature; (b) Selectfluor™, MeCN, 80 °C.

A survey of the literature provided several precedents regarding this unusual type of reaction. For example, pentafluorophenyliodine tetrafluoride was oxidized by XeF_2–H_2O to give oxygen-containing perfluorocyclohexadiene-1-yliodine tetrafluorides;[15] treatment of 2-methoxynaphthalene and 2,5-diarylfurans with Selectfluor™ gave 1,1-difluo-2-oxo-1,2-dihydronaphthalene and the ring-opening product *cis*-enediones, respectively.[16,17] One plausible mechanism is illustrated in Scheme 2. This so-called electrophilic hydroxyfluorination likely involves a 1,4-addition of HOF to the A-ring to generate an unstable intermediate that decomposes to the stable difluoroquinone **2a**. The required HOF species is known to be formed from Selectfluor™ in combination with water present in the reaction system.[17]

A series of other related tricyclic and tetracyclic γ-secretase inhibitors **3–8** were subsequently treated with Selecfluor™ under the same conditions. Not surprisingly, all gave the corresponding difluoroquinone structures **3a–8a**. The yields for this transformation were modest, and no efforts were made to optimize the reaction conditions to achieve higher yields.

Interestingly, when compound **1a** was tested in the membrane assay for Aβ40 lowering, it displayed potency similar to that of parent compound **1**.[18] As revealed in Table 1, similar trends existed with other pairs, such as **5**/**5a**, **7**/**7a**, and **8**/**8a**. Compounds **2a**, **3a**, **4a** and **6a** were even several-fold more potent than their corresponding parents **2**, **3**, **4**, and **6**. However, in the cell-based assay,[19] all the difluoroquinone analogs **1a**–**8a** exhibited much less potency in lowering both Aβ40 and Aβ42 than their parent compounds **1**–**8**. The reason for the shift between the membrane and cell potency for these difluoroquinone analogs remains unclear; the cell shift could be related to the reduced *C*log*P* values of the difluoroquinone structures. For example, *C*log*P* for compound **1** is 2.58 whereas *C*log*P* for compound **1a** is 1.35, which may fall outside the optimal range for cell activity.

In summary, treatment of γ-secretase inhibitor SCH 900229 (**1**) with SelectfluorTM led to identification of an unusual modification of the A-ring. These difluoroquinone analogs have similar in vitro potency in Aβ reduction as their precursor difluorophenyl compounds but are less potent in the cell based assay. This result suggests other possibilities for A-ring replacement of compound **1**, such as non-polar, non-aromatic moieties.

Acknowledgment

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Table 1
Biological data for modified A-ring analogs[a]

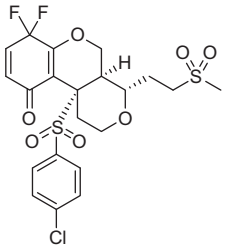
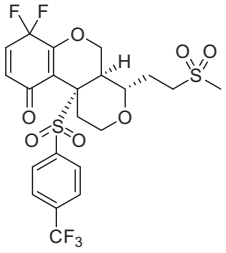
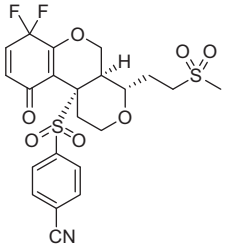
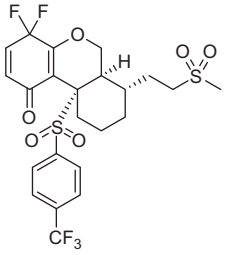
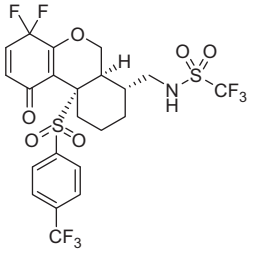
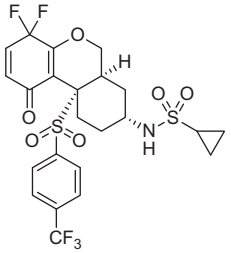
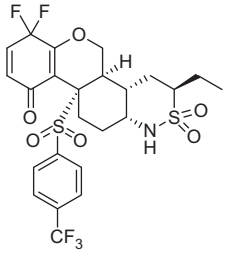
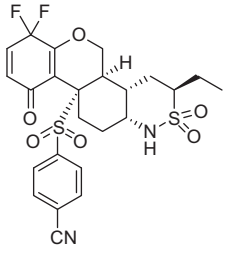
Compound	Structure	Aβ40 IC_{50}[b,c] (nM)		Aβ42 IC_{50}[b,c] (nM)
		Membrane	Cell	Cell
1		1.3	4.0	1.0
1a		1.2	26	11
2		15	11	4.0
2a		1.8	56	27
3		66	25	9.0
3a		21	1600	410
4		43	63	21
4a		1.9	130	49
5		54	73	32
5a		78	330	200
6		92	87	19
6a		6.8	280	110

Table 1 (*continued*)

Compound	Structure	Aβ40 IC_{50}[b,c] (nM)		Aβ42 IC_{50}[b,c] (nM)
7		1.9	5.0	2.0
7a		3.9	46	25
8		4.7	4.0	2.0
8a		3.5	110	31

[a] For compounds **1**–**8**, see Refs. 6–11.
[b] The IC_{50} data are an average of at least two measurements; the standard deviation was 20%.
[c] Determined in $HEK^{Awe\text{-}Lon}$ 293 cells.

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10. Compound **4** was prepared through a tricyclic core (**13b**) reported in Ref. 8 with installation of the sulfone side chain.
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14. *Typical procedure*: A mixture of 0.119 g (0.22 mmol) of compound **2** and 0.39 g (1.1 mmol) of Selectfluor™ (air products) in 6 mL of acetonitrile was heated at 80 °C for 20 h. The solvent was evaporated; the residue was diluted with 40 mL of water and extracted with two 50 mL portions of dichloromethane. The combined organic extracts were concentrated, and the residue was purified by reverse-phase HPLC (C18 column, 5–95% MeCN in water plus 1% HCOOH, over 20 min) to give 0.048 g (39%) of compound **2a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (d, J = 8.4 Hz, 1H), 7.8 (d, J = 8.4 Hz, 1H), 6.73 (dt, J = 10.3, 5.3 Hz, 1H), 6.14 (d, J = 10.3 Hz, 1H), 5.12 (dd, J = 12.8, 2.8 Hz, 1H), 4.64 (d, J = 12.8 Hz, 1H), 3.81 (ddd, J = 12.2, 4.2, 2.2 Hz, 1H), 3.30 (m, 1H), 3.29 (m, 1H), 3.07 (m, 1H), 3.02 (dt, J = 1.6, 12.2 Hz, 1H), 2.93 (s, 3H), 2.88 (d, J = 13.2 Hz, 1H), 2.67 (dd, J = 10.4, 2.8 Hz, 1H), 2.44 (m, 1H), 2.07 (ddd, J = 13.2, 12.2, 4.2 Hz, 1H), 2.05 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6 (s, $^4J_{CF}$ = 3.0, 3.0 Hz), 163.3 (s, $^2J_{CF}$ = 24.4, 24.4 Hz), 140.3 (s), 135.9 (s, $^2J_{CF}$ = 33.1,33.1,33.1 Hz), 133.0 (d, $^2J_{CF}$ = 27.5, 27.5 Hz), 132.3 (d, $^3J_{CF}$ = 8.8, 8.8 Hz), 131.4 (d), 125.7 (d, $^3J_{CF}$ = 3.6, 3.6, 3.6 Hz), 123.1 (s, $^1J_{CF}$ = 273.0, 273.0, 273.0 Hz), 107.2 (s, $^1J_{CF}$ = 234.8, 237.7 Hz), 105.6 (s, $^3J_{CF}$ = 3.8, 3.8 Hz), 72.2 (d), 66.4 (t), 65.3 (s), 63.7 (t), 50.8 (t), 40.9 (q), 37.3 (d), 29.5 (t), 25.8 (t). ^{19}F NMR (407 MHz, $CDCl_3$) δ −63.6 (s), −103.2 (dd, $^3J_{HF}$ = 5.3 Hz, $^2J_{FF}$ = 335 Hz), −104.1 (dd, $^3J_{HF}$ = 5.3 Hz, $^2J_{FF}$ = 335 Hz). LC–MS: calcd for $C_{22}H_{22}F_5O_7S_2$(MH+), *m/z* 557.1; found 557.3.
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