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Discovery of a novel series of Notch-sparing γ-secretase inhibitors

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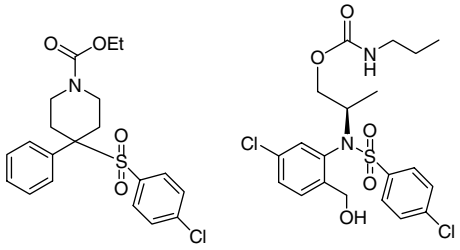
ABSTRACT

Using a cell-based assay, we have identified a new series of Notch-sparing γ-secretase inhibitors from HTS screening leads **2a** and **2e**. Lead optimization studies led to the discovery of analog **8e** with improved γ-secretase inhibitory potency and Notch-sparing selectivity.

Alzheimer's disease (AD), the most common form of dementia, is the biggest unmet medical need in neurology due to the lack of disease-modifying anti-Alzheimer's drugs (DMAADs).[1,2] Because the incidence of AD increases with age and our population is increasing in longevity, the levels of AD are already approaching epidemic levels.[3] Unless new therapies are found that block or delay the progression of AD, the anticipated burden on caregivers and society threatens to overwhelm available resources.[4]

One of the major hopes for a DMAAD is to target the putative AD pathogens Aβ40 and Aβ42 either by blocking their synthesis (from their precursor APP), their aggregation (required for toxicity), or alternatively accelerating their degradation or clearance.[5] An enormous effort is underway to discover inhibitors of the Aβ40 and Aβ42 biosynthetic enzymes BACE and γ-secretase.[6,7] However, the identification of γ-secretase inhibitors (GSIs) as potential DMAADs has been made more difficult not only by the lack of an X-ray structure of γ-secretase,[8,9] but also by the subsequent discovery of a multitude of other γ-secretase substrates such as Notch and the resulting concerns about selectivity and mechanism-based side effects such as Notch-related G.I. toxicity and effects on T-cell differentiation.[10]



1 (EC_{50}Aβ40 = 12,200 nM) **1a** (EC_{50}Aβ40 = 85 nM)

Recently, we have reported[11] on the discovery of novel GSIs as exemplified by **1** (EC_{50}Aβ40 = 12,200 nM) based on molecular modeling of the GSI **1a**.[12] Compound **1a** was of particular interest because it not only was a potent GSI (EC_{50} Aβ40 = 85 nM in CHO cells stably expressing a wild-type recombinant human APP),[11] but also exhibited promising Notch-sparing selectivity (EC_{50}Notch = 746 nM, Notch-sparing selectivity = 8.8).[13] As with any other novel drug class, one needs to define a therapeutic window, which allows some

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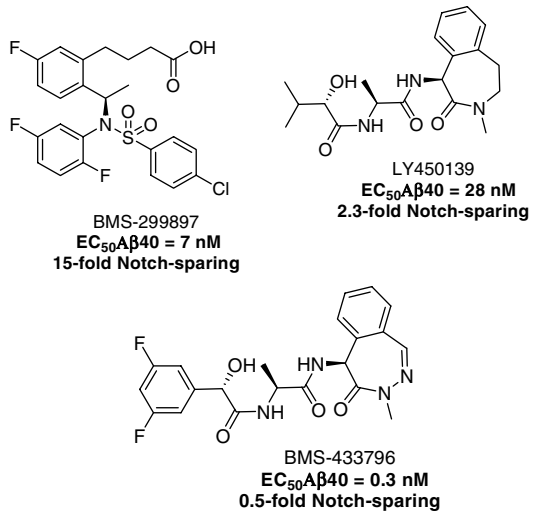
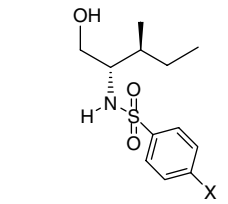
γ-secretase activity for Notch signaling but reduces Aβ40 and Aβ42 generation significantly enough to affect AD disease progression.[14] A successful example of this approach of partial enzyme inhibition is the use of statins for blocking cholesterol biosynthesis without mechanism-based side effects.[15] The fact that an increase as small as 30% in the levels of Aβ42 can cause familial AD suggests that lowering Aβ42 by a similar amount could have a disease-modifying effect.[16–18] It has been reported in several recent publications that the GSI BMS-299897 (EC_{50}Aβ40 = 7 nM) which has 15-fold Notch-sparing selectivity did not cause Notch-related G.I. toxicity and untoward effects on T-cell differentiation seen with nonselective GSIs such as the clinical compound LY450139[20] (EC_{50}Aβ40 = 28 nM, Notch-sparing selectivity = 2.3) and BMS-433796 (EC_{50} Aβ40 = 0.3 nM, Notch-sparing selectivity = 0.5).[21] This suggests that this degree of Notch-sparing selectivity may be sufficient to avoid mechanism-based toxicity.[19,22–24] Unfortunately, BMS-299897 itself has been shown to induce its own metabolism and subsequently loses in vivo efficacy over time.[19] However,the demonstration that BMS-299897 can lower brain Aβ40 and Aβ42 levels in animal models without Notch-related side effects encouraged us to continue to pursue novel GSIs that would possess this Notch-sparing selectivity profile.[18,25]



Because we were unable to significantly improve upon the in vitro Aβ-lowering potency of **1** (EC_{50}Aβ40 = 12,200 nM), we turned to HTS screening of the combined Wyeth and ArQule compound collections as an alternate approach to the discovery of novel Notch-sparing GSIs. This approach afforded the two related leads **2a**, X = Cl and **2e**, X = Br (EC_{50}Aβ40 = 5449 and 2214 nM, respectively) utilizing our cell-based assay.[11] These leads were established as GSIs by virtue of their ability to elevate β-CTF levels using a human APP reporter construct containing the Swedish KM to NL mutation.[11] Encouragingly, both **2a** and **2e** exhibited promising Notch-sparing selectivity Table 5 (EC_{50} Notch = 20,000 nM and 20,000 nM, Notch-sparing selectivity = 3.7 and 9.0, respectively).



In this letter, we will present the SAR of these initial leads with the goals of improving GSI inhibitory potency and Notch-sparing selectivity.

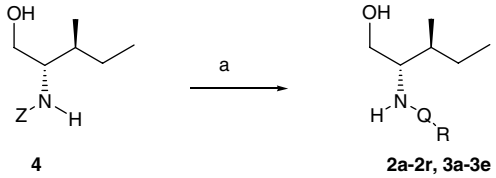
Our first attempts to improve the GSI potency of the initial leads **2a** and **2e** were to vary the substitution on the benzene ring and the sulfonamide linker. Compounds **2a**–**2r** and **3a**–**3e** were prepared by reaction of the β-amino alcohol **4** with the requisite acid chloride, isocyanate, or benzyl chloride (Scheme 1).

Variation of the para substituent on the phenyl ring revealed that potency was not retained when halogen was replaced by non-halogen substituents other than hydrogen or acetyl (compounds **2a**, **2r** vs **2d**–**2l**, Table 1). Exploration of the position of the halogen substituent revealed that para-substitution was preferred (compounds **2a**–**2c**, Table 1). Di-substituted halogen analogs were less potent in Aβ-lowering activity than the parent compound **2a** (compounds **2m**–**2q**, Table 1).

Replacement of the SO_2 in **2a** by other linkers afforded **3a**–**3e** (Table 2), which were weakly active, at best (EC_{50}Aβ > 100,000 nM).

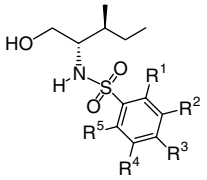
Alkylation of the sulfonamide nitrogen of **2a** with MeI/K_2CO_3 in DMF gave **5** (Scheme 2) which was almost an order of magnitude less potent (EC_{50}Aβ40 = 5449 and 46,710 nM, respectively).

The preferred chirality of the *s*-butyl side chain at the carbon bearing the sulfonamide nitrogen in **2a** was found to be the *S* absolute configuration since **6**, the enantiomer of **2a**, had significantly



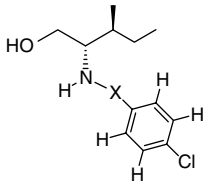
Scheme 1. Reagents: For Q = SO_2, CO, CH_2, $COCH_2$, CONH and Z = H. (a) RQCl or RNCO, Et_3N or EtN(*i*-Pr)$_2$, THF or DCM. For Q = SO_2NH_2 and Z = FMOC: (a) Trityl resin/AgOTf followed by subsequent reaction with piperidine; RNH_2, *p*NO_2PhOSO_2Cl, EtN(*i*-Pr)$_2$, TFA, DCM.

Table 1
SAR of the phenylsulfonamide substitution

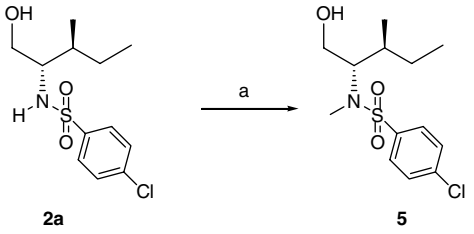


Compound	R^1	R^2	R^3	R^4	R^5	Aβ40EC_{50} (nM)
2a	H	H	Cl	H	H	5449
2b	H	Cl	H	H	H	18,304
2c	Cl	H	H	H	H	56,619
2d	H	H	F	H	H	4243
2e	H	H	Br	H	H	2214
2f	H	H	CN	H	H	>100,000
2g	H	H	CH_3	H	H	14,292
2h	H	H	CF_3	H	H	13,053
2i	H	H	$COCH_3$	H	H	6021
2j	H	H	SO_2CH_3	H	H	>100,000
2k	H	H	NO_2	H	H	20,903
2l	H	H	OCF_3	H	H	23,532
2m	H	Cl	Cl	H	H	37,002
2n	H	F	Cl	H	H	7840
2o	Cl	Cl	H	H	H	4274
2p	H	Cl	H	Cl	H	23,496
2q	Cl	H	H	Cl	H	54,808
2r	H	H	H	H	H	4145
LY450139						28

Table 2
SAR of the SO_2 replacement

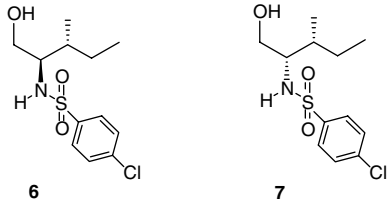


Compound	X	Aβ40EC_{50} (nM)
2a	SO_2	5449
3a	SO_2NH	>30,000
3b	CO	>100,000
3c	CH_2	>100,000
3d	$COCH_2$	>100,000
3e	CONH	47,313



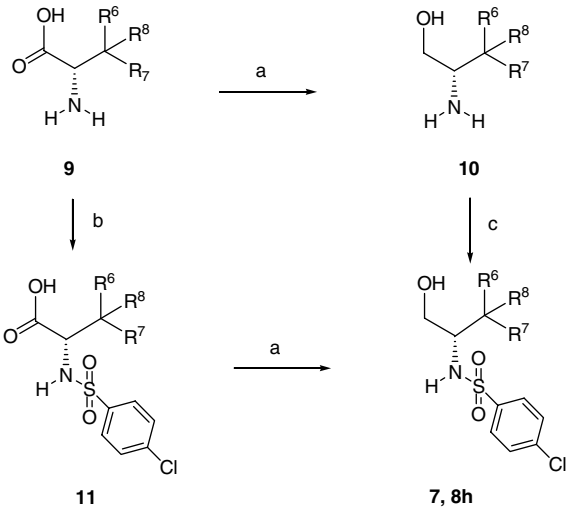
Scheme 2. Reagents: (a) MeI, K_2CO_3, DMF.

reduced activity in lowering Aβ40 production (EC_{50}Aβ > 100,000 nM). This is consistent with a stereospecific interaction with the γ-secretase complex.

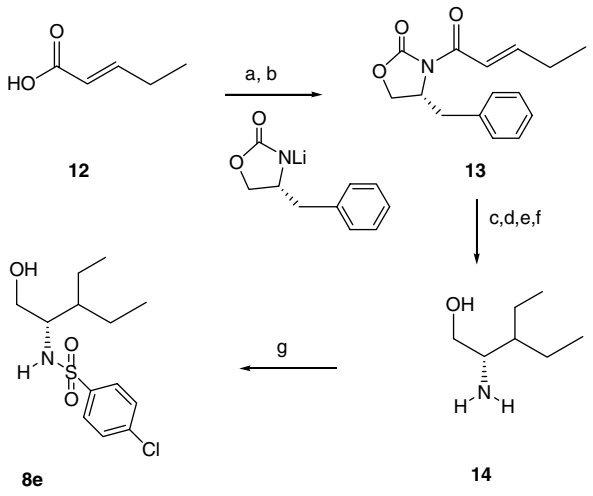


Interestingly, **7**, the analog with the 2-*S*, 3-*R* stereochemistry, was found to be somewhat more potent than **2a** which has the 2-*S*, 3-*S* stereochemistry (EC_{50}Aβ40 = 758 nM and 5449 nM, respectively). For preparation of side chain analogs **8a**–**d** and **8f**, the method of Scheme 1 was used substituting the requisite commercially available amino alcohol for *S*-isoleucinol (**4**, Z = H). For preparation of side chain analogs **7** and **8h**, we employed two routes when the requisite amino alcohol was not commercially available: (1) reduction of the α-amino acid **9** to the corresponding amino alcohol **10** followed by sulfonylation to yield **7** and **8h**, or (2) sulfonylation of the α-amino acid **9** (or its methyl ester) to afford **11** followed by reduction to provide **7** and **8h** (Scheme 3).

For preparation of the side chain analog **8e** derived from an unnatural α-amino acid whose related amino alcohol or acid was not commercially available we utilized chemistry first developed by Hruby[26] employing an Evans chiral auxiliary (Scheme 4). The unsaturated acid **12** was first converted to the imide **13**, which was subsequently reacted with the relevant Grignard reagent in the presence of cuprous ion. Trapping of the resultant enolate with NBS, displacement of the bromide with azide anion followed by reduction with $LiAlH_4$ gave the β-amino alcohol **14** which upon sulfonylation afforded the target compound **8e**.



Scheme 3. Reagents: (a) $LiAlH_4$, THF; (b) *p*-Cl-$PhSO_2Cl$, aq MeCN, Et_3N; (c) *p*-Cl-$PhSO_2Cl$, THF, Et_3N.



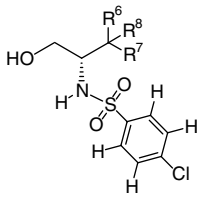
Scheme 4. Reagents: (a) *t*-BuCOCl, Et_3N, THF; (b) Li 4-(*R*)-4-benzyl-2-oxazolidinone; (c) EtMgBr, CuBr-DMS, THF; (d) NBS,THF; (e) $TMGN_3$, MeCN; (f) $LiAlH_4$, THF; (g) *p*-Cl-$PhSO_2Cl$, Et_3N, THF.

Replacement of the *s*-butyl group in **2a** by other side chains (Table 3, compounds **8a**–**8h**) improved GSI potency if the side chain was branched at the β position and the branches were longer than methyl (e.g. **8e**). Cyclization of the side chain led to the less active analog **8g**. Aromatizing the side chain led to **8h** which had a further loss in GSI potency.

Attachment of one or two methyl groups to the carbon bearing the hydroxyl group resulted in a significant loss of GSI potency (Table 4, compounds **15a**–**15b**). The secondary alcohol **15a** (as a mixture of diastereomers) was prepared by oxidation of **2a** with PCC to afford the aldehyde **16** followed by reaction with methylmagnesium bromide (Scheme 5). The tertiary alcohol **15b** was prepared by conversion of **17**, *S*-isoleucine methyl ester, to the intermediate **18** followed by reaction with methylmagnesium bromide (Scheme 5).

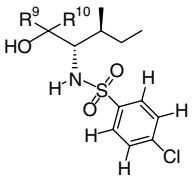
A free hydroxyl group was important for GSI activity. The methyl ether **19** prepared from **2a** (by sequential action of TsCl/pyr, followed by NaO *t*-Bu/MeOH/THF) had significantly reduced Aβ-lowering activity (EC_{50}Aβ40 > 100,000 nM). Interestingly, the aldehyde **16**[27] and methyl ester **18** (prepared as in Scheme 5) were active although weaker in potency compared to **2a** (EC_{50}Aβ40 =

Table 3
SAR of the side chain



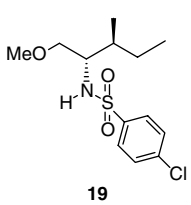
Compound	R^6	R^7	R^8	Aβ40EC_{50} (nM)
8a	H	H	H	>100,000
8b	CH_3	H	H	>100,000
8c	CH_3	CH_3	H	4575
8d	CH_3	CH_3	CH_3	29,108
2a	CH_3CH_2	CH_3 (*S*)	H	5449
7	CH_3CH_2	CH_3 (*R*)	H	758
8e	CH_3CH_2	CH_3CH_2	H	294
8f	$(CH_3)_2CH$	H	H	15,279
8g	$R^6 + R^7$ = cyclohexyl		H	1122
8h	$R^6 + R^7 + R^8$ = phenyl			68,843

Table 4
SAR of substitution on carbon bearing hydroxyl group

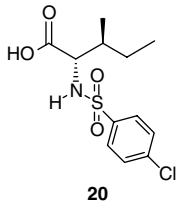


Compound	R^9	R^{10}	Aβ40EC_{50} (nM)
2a	H	H	5449
15a	CH_3	H	49,266
15b	CH_3	CH_3	>100,000

7859, 64,947 and 5449 nM, respectively). However, the related acid **20** (prepared as in Scheme 3) had significantly reduced Aβ-lowering activity (EC_{50}Aβ > 100,000 nM).



19



20

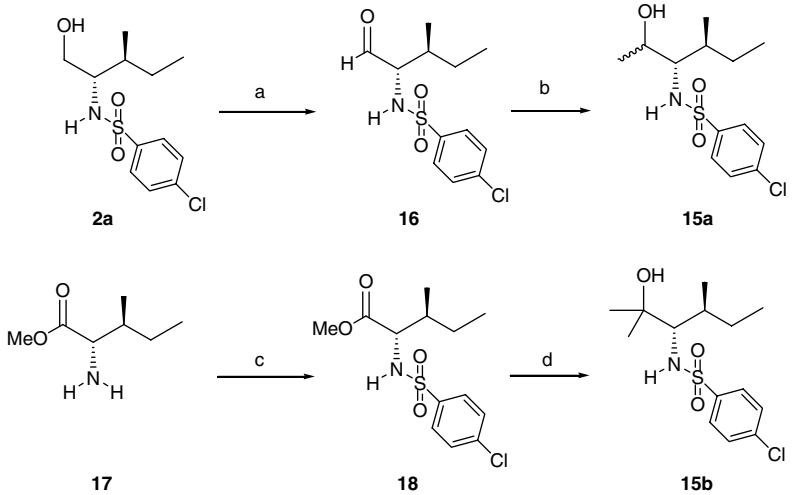
It is interesting to compare the results of our SAR on **2a** with the structural features present in **1a** and BMS-299897. In contrast to **1a** and BMS-299897 which have the *R* absolute configuration at the β-amino alcohol-derived chiral center, we have found that in our series, compounds with the *R* absolute configuration at the β-amino alcohol-derived chiral center are much less active than the corresponding *S* enantiomers with respect to GSI activity.

In contrast to **1a** which has a masked hydroxyl, we have found that in our series a free hydroxyl is important for GSI activity. In contrast to **1a** and BMS-299897 which have a small alkyl side chain, we have found that in our series a large β-branched side chain is important for potent GSI activity. In contrast to **1a** and BMS-299897, which have an alkylated sulfonamide nitrogen, we have found that in our series an unalkylated sulfonamide nitrogen is important for good GSI activity.

With the initial SAR to improve Aβ-lowering potency completed, we next turned to evaluation of the Notch-sparing selectivity of selected compounds (Table 5). We were gratified to find that **8e** not only had improved Aβ-lowering potency but also had increased Notch-sparing selectivity relative to our initial lead **2a**. The Notch-sparing selectivity of **8e** is comparable to the published[19] Notch-sparing selectivity of BMS-299897. This is in contrast to LY450139 that had very low Notch-sparing selectivity.

Table 5
Notch-sparing selectivity of selected GSIs

Compound	Aβ40EC_{50} (nM)	NotchEC_{50} (nM)[13]	Notch-sparing selectivity[13]
1	85	746	8.8
2a	5449	20,000	3.7
2e	2214	20,000	9
8e	294	4086	13.9
LY450139	28	63	2.3



Scheme 5. Reagents: (a) PCC, DCM; (b) MeMgBr, THF; (c) *p*-Cl-$PhSO_2Cl$, Et_3N, MeCN; (d) MeMgBr, THF.

In summary, we have improved the potency of HTS leads **2a** and **2e** by sequential modification of six regions of the molecule. Out of this SAR effort **8e** emerged which had ~14-fold selectivity for APP cleavage relative to Notch cleavage. This novel GSI scaffold with improved Notch-sparing selectivity represents an advance over clinical GSIs such as LY450139[20] that do not possess this degree of Notch-sparing selectivity. Further optimization of this new series to identify a clinical candidate is in progress.

Acknowledgments

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24. Note that the safety of a compound is also dependent on drug disposition in vivo (e.g. a GSI with Notch-sparing selectivity of 100 may be more peripherally toxic than a GSI of comparable potency and with Notch-sparing selectivity of 15 if the former compound has poor brain penetration and the latter compound has high brain penetration).
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