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Part 2. Notch-sparing γ-secretase inhibitors: The study of novel γ-amino naphthyl alcohols

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ABSTRACT

One therapeutic approach for Alzheimer's disease is to inhibit the cleavage of the amyloid precursor protein (APP) by γ-secretase. At the beginning of a series of studies from our laboratories, a series of novel γ-amino alcohols (**1**) were found to possess γ-secretase inhibitory activity and Notch-sparing effects. A new one-pot synthesis of γ-amino alcohols and the structure–activity relationship (SAR) of these analogs will be discussed.

Oligomerization of the amyloid-β peptide (Aβ) is a key step in the pathogenesis of Alzheimer's disease (AD).[1] The production of Aβ is a result of sequential cleavages of the amyloid-β precursor protein (APP) by β- and γ-secretases.[2] Inhibitors targeting these two enzymes have been intensely pursued as potential disease-modifying therapeutics for AD.[3] γ-Secretase is a multifunctional protease. It degrades a number of substrates, including APP and the Notch receptors, the latter being essential cell signaling proteins.[4] One fundamental requirement for AD therapeutics that target γ-secretase is to selectively inhibit the proteolysis of APP without altering the γ-secretase-mediated cleavage of the Notch receptors, in particular Notch1.[5] Our research to identify novel 'Notch-sparing' γ-secretase modulators and inhibitors has led to several chemical series of small molecules that can modulate γ-secretase to decrease Aβ production without alternation of Notch receptor processing. The work presented here is a series of γ-amino alcohols (**1**) that possess this selective inhibitory profile.

In our early work, two known Janus tyrosine kinase 3 (JAK3) inhibitors, ZM39923 and ZM449829 (Fig. 1), were identified as γ-secretase inhibitors that showed Notch-sparing properties.[6] However, the *N*-benzyl isopropyl-amino fragment of ZM39923 undergoes a facile elimination to yield ZM449829, which contains a reactive vinyl ketone. The unstable and reactive liabilities of these two compounds prevented them from being potential lead molecules. A simple conversion of the carbonyl of ZM39923 into a hydroxyl group by standard reduction methodology retained the selective profile of ZM39923 in inhibiting γ-secretase and provided a novel lead compound, 3-(benzyl (isopropyl)amino)-1-(naphthalen-2-yl)propan-1-ol (**1**).

To synthesize analogs of compound **1**, a straightforward way would be to prepare the β-amino ketone precursor (e.g., ZM39923) followed by reduction of the ketone group to give the corresponding amino alcohols. The Mannich reaction is well suited procedure for synthesizing β-amino ketones in one pot. However, when formaldehyde, *N*-isopropyl benzylamine and phenyl methyl ketone were used to perform the one-pot reaction, very little desired product was obtained.

Thereafter, a Michael addition reaction was utilized, coupling benzylisopropyl amine and naphthalene-2-yl vinyl ketone in the presence of a stoichiometric amount of solid $LiClO_4$ under solvent-free conditions. The resultant β-amino ketone (ZM39923) was reduced with $NaBH_4$ to yield the desired β-amino alcohol (**1**) in high yield (Scheme 1). Alcohol **1** was evaluated for some drug-like properties (e.g., solubility, Log*D*, plasma protein binding, permeability, and human and rodent microsomal stability—see Supplemental data) and these results supported a reasonable profile to begin synthesizing analogs of **1**.

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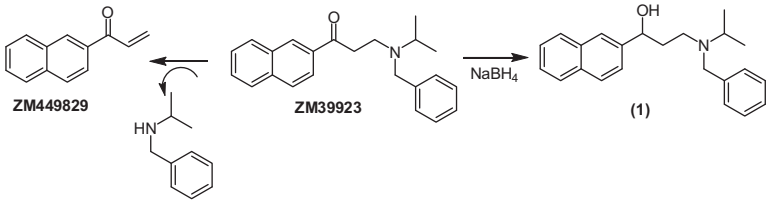
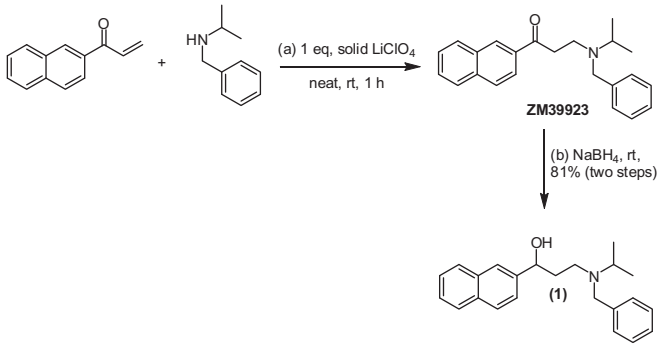
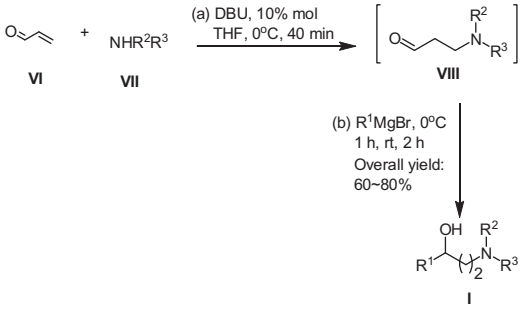


Figure 1. Conversion of ZM39923 to ZM449829 by elimination and to compound **1** by reduction using sodium borohydride.



Scheme 1. Preparation of **1** by Michael addition.

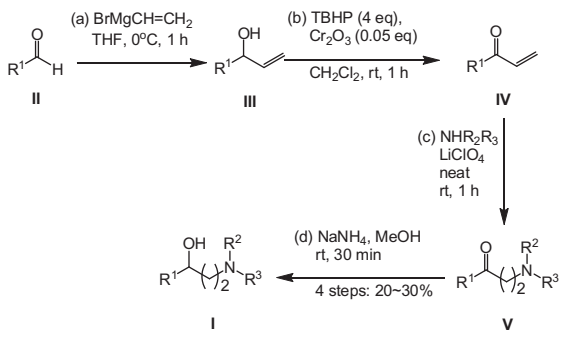


Scheme 3. Method B for synthesis of γ-amino alcohol **I**.

To facilitate structural modification of **1**, we developed a synthetic method toward substituted vinyl ketones (**IV**) from various aldehydes, which could be subsequently converted to β-amino alcohol analogs (**I**) as shown in Scheme 2.

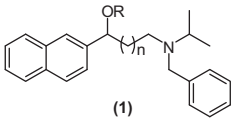
The addition of the readily available vinyl Grignard reagent to aryl aldehyde (**II**) gave the desired vinyl alcohol (**III**). The resulting crude vinyl alcohol was dissolved in dichloromethane and oxidized with *tert*-butylhydroperoxide (TBHP) in the presence of chromium (**III**) oxide as catalyst to give the α,β-unsaturated ketone (**IV**). Michael addition of disubstituted amines to aryl vinyl ketone (**IV**) in the presence of a stoichiometric amount of solid $LiClO_4$ led to β-amino ketone (**V**) in high yield. However, subsequent purification of the Michael reaction product (**V**) by silica gel chromatography resulted in its decomposition to vinyl ketone (**IV**). Hence, the crude adduct (**V**) was directly reduced with sodium borohydride to yield the desired β-amino alcohol (**I**) in good yield (Scheme 2). The syntheses of these β-amino alcohols and some selected amines have been reported previously by our laboratory.[7]

Alternatively, we prepared some of the desired product (**I**) from another synthetic route, which employed acrolein (**VI**) and secondary amines (**VII**) in a Michael addition catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give β-amino aldehydes (**VIII**). These aldehydes were then treated with Grignard reagents in situ to form the desired γ-amino alcohols (**I**) in good yield.



Scheme 2. Method A for synthesis of γ-amino alcohols **I**.

Table 1
Alkyl linker and methyl alcohol analog of **1**



Entry	R	*n*	Aβ40 (%) inhibition[a]	Notch1 processing[b]
1	H	1	81	No change
2	H	0	0	Inhibition
3	H	2	18	Inhibition
4	Me	1	51	No change

[a,b] See Refs. 12, 13 for assay description.

Notably, the Michael addition did not work well when primary amines were employed. However, this route (Method B, Scheme 3) consumed a shorter time and less purification steps in comparison with Method A (Scheme 2) to obtain product (**I**).

The compounds (**I**) reported in Tables 1–3 were synthesized either by Method A or Method B and then evaluated[8,9] for inhibitory effects on γ-secretase-mediated Aβ production using purified human γ-secretase complexes[10] and a commercial ELISA for human β amyloid 1-40 (Invitrogen).[11] The effects of the synthesized compounds on γ-secretase-mediated Notch processing were examined by Western Blot analysis using a method previously described.[6] Compounds with at least a 50% inhibition in the Aβ40 ELISA were evaluated for their effect on the Notch processing. Testing at a high concentration was implemented in the early stages of lead identification so that no compound with any significant activity and desired selectivity was overlooked. All amino alcohol analogs exemplified in Tables 1–5 are in racemic form. Selected amino alcohol analogs of this chemical series were evaluated for additional biological data, such as % inhibition of Abeta 42 and also inhibition of Abeta 42 and the Notch receptor in cells (see Supplemental data). Overall, Abeta 42 inhibition was similar to the Abeta 40 inhibition and in general, compounds tend to be less potent in cellular assays.

We first looked into the influence of the linker length between the amino and hydroxyl groups, and the importance of the free