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Discovery of a novel sulfonamide-pyrazolopiperidine series as potent and Efficacious γ-Secretase Inhibitors

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ABSTRACT

Discovery of a series of pyrazolopiperidine sulfonamide based γ-secretase inhibitors and its SAR evolution is described. Significant increases in APP potency on the pyrazolopiperidine scaffold over the original *N*-bicyclic sulfonamide scaffold were achieved and this potency increase translated in an improved in vivo efficacy.

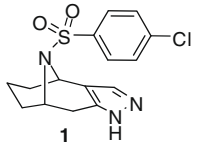
Alzheimer's disease (AD) is a progressive neurodegenerative disorder accompanied by cognitive impairment, memory deficit, and visual–spatial disorientation. Amyloid plaques and neurofibrillary tangles within the hippocampus and the cerebral cortex, containing aggregated amyloid beta peptide (Aβ) and hyperphosphorylated tau protein are the defining diagnostic feature of AD. Aggregation/deposition of Aβ in the brain of AD patients is thought to contribute to AD pathology.[1] Aβ is a 40–42 amino acid peptide, formed by sequential cleavage of amyloid precursor protein (APP) by two aspartyl proteases, β-secretase (BACE) and γ-secretase, respectively. In addition to APP, γ-secretase also cleaves a large number of other type 1 transmembrane proteins including Notch.[2] The inhibition of Notch proteolysis has been shown to result in undesirable side effects observed in the thymus, spleen and intestine.[3] Accordingly, while an inhibitor of γ-secretase may serve as a treatment for AD, nonselective inhibitors may find limited utility.

The first example of a γ-secretase inhibitor (GSI) that achieved in vivo inhibition of brain Aβ was the dipeptide, DAPT. This work was jointly reported by researchers from Elan and Eli Lilly.[4] Since then, several classes of nonpeptidic, orally bioavailable GSIs have been reported in the literature (for recent reviews, see Olson and Albright[5] and Garofalo[6]). Herein, we report our progress to discovery potent, selective and orally active, small molecule GSIs.

As reported in another Letter from Mattson et al.,[7] a novel series of potent and selective GSIs exemplified by **1** has been identified in our laboratories (Fig. 1).

Compound **1** demonstrated good potency and selectivity (15-fold selectivity over Notch in an enzymatic assay and 90-fold in a cellular assay) and was efficacious in a wild type FVB mouse model at 30 mg/kg PO. This series, however, suffers from metabolic instability. Further limitations include a challenging synthesis that does not allow for rapid analog development and relatively flat SAR. Therefore, we initiated efforts to derive a new series aimed at overcoming the aforementioned limitations.

Initial effort on the pyrazole region did not yield any single analog that compared with compound **1** in terms of potency[7],



IC_{50} (APP) = 2 nM
IC_{50} (Notch) = 29 nM
F = 2.6%
$t_{1/2}$ = 24 min (rat)

Figure 1. Representative *N*-bicyclic sulfonamide γ-secretase inhibitor.

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suggesting that the unsubstituted pyrazole is critical for activity. Analoging efforts in this series clearly demonstrated the need to maintain the arylsulfonamide. The importance of this pharmacophore to GSIs is further confirmed by its prevalence in a number of recently patented chemical series.[8–16] Therefore, we turned our attention to the backside hydrocarbon area. Our plan was to break up the bicyclic skeleton and replace those hydrocarbon atoms with suitable functional groups in the hope of gaining better inhibitor potency. Prior to the introduction of pyrazole in our inhibitors we found 2-alkyl piperidine sulfonamides to be low micromolar inhibitors (Scheme 1).

Clearly, the substituent scan of the piperidine sulfonamide scaffold revealed that phenyl (**4e**) was the best for this position (Table 1).[17] This result prompted us to initiate a transformation as depicted in Scheme 2.

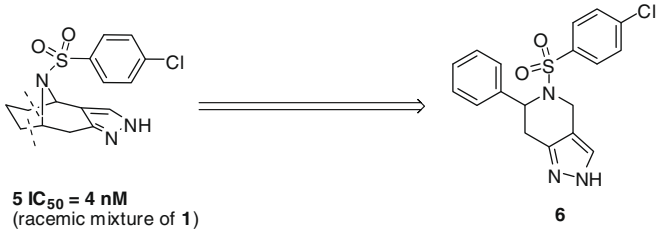
The synthesis of compound **6** is illustrated in Scheme 3. Starting with commercially available ketone **7**, a procedure reported by Trost et al.[18] was able to provide us the desired pyrazole **8** with excellent regiochemistry-control. After deprotection, sulfonylation occurred on both the piperidine and pyrazole nitrogens. Hydrolysis of the pyrazole sulfonamide with sodium hydroxide led to the racemate **6**.

As anticipated, compound **6** was quite potent in our γ APP assay and markedly more selective over Notch compared with compound **1** (Table 2). Encouraged by this result, further analogs were prepared as illustrated in Scheme 4. Using a two step procedure reported by Kozikowski and Park,[19] the commercially available Cbz protected 4-piperidinone was converted to enone **11**. Comins and co-workers[20] have reported that a copper-catalyzed conjugate addition by alkyl Grignard reagent worked very well on this enone system. Following his protocol, we found that it worked as well for aryl Grignard reagents to lead to compound **12**. Standard chemistry as described in Scheme 3 was used then to afford compound **15**.

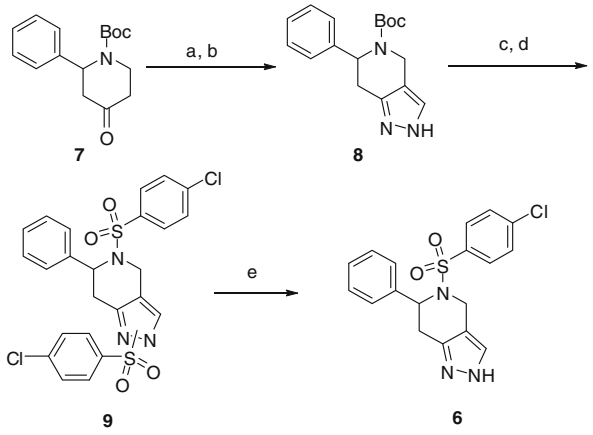
Unfortunately, the copper-catalyzed conjugate addition did not work for heteroaromatic Grignard reagents. Therefore, a Diels-Alder strategy[22] was employed to make key intermediate **19** (Scheme 5). Formylation of these analogs, however, did not afford single regioisomers. Instead, inseparable mixtures were obtained with 2-pyridylpiperidinones after pyrazole formation. 2-Pyrimidinylpiperidinones gave mixtures that were separable using chiral HPLC. The mixture of four isomers after pyrazole formation and the active enantiomer from each pair are listed in Table 2.

Similarly, compounds **20d** and **21d** were synthesized using ethyl glyoxylate as the starting aldehyde. Once again, chiral HPLC was applied to separate all four isomers. Accordingly, compounds **20e**, **21e** and **21f–g** were synthesized from the corresponding esters.

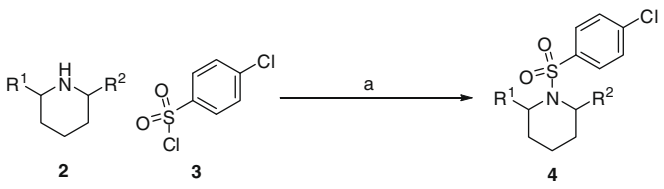
As shown in Table 2, although only a slight improvement in potency was achieved while changing halogens and their substitution pattern on the phenyl ring at the C-6 position, those compounds (**6** and **15a–d**) demonstrated significantly higher selectivity ratio in both enzymatic and cellular assays[23] over compound **1**. Interestingly, when the phenyl group was replaced by benzyl group, potency decreased 10-fold and selectivity also dropped. When a



Scheme 2.



Scheme 3. Reagents and conditions: (a) HCO_2Et, NaH, MeOH, PhH; (b) $N_2H_4{\cdot}H_2O$, MeOH, rt; (c) TFA, rt; (d) 4-chlorobenzenesulfonyl chloride, pyridine; (e) NaOH, THF, H_2O.

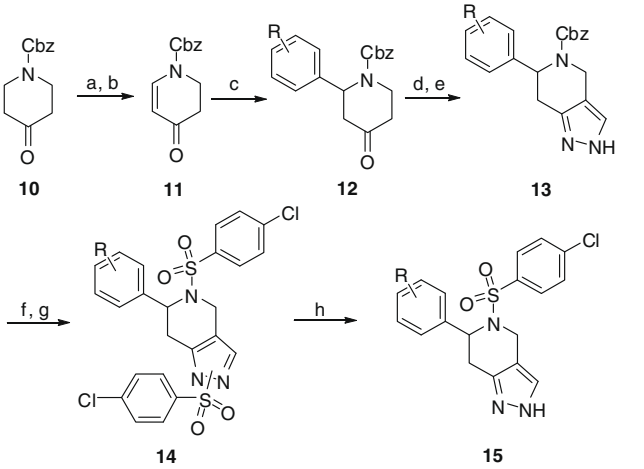


Scheme 1. Reagents: (a) pyridine, O/N.

Table 1
Structure–activity relationships of N-arylsulfonylated piperidine

Compound	R1	R2	γ APP IC_{50}[a] (nM)	Notes
4a	H	H	>30,000	
4b	Me	H	8278 ± 1964	Racemic
4c	Et	H	2002 ± 912	Racemic
4d	*n*-Pr	H	1698 ± 72	Racemic
4e	Ph	H	760 ± 82	Racemic
4f	Me	Me	1004 ± 227	*cis*, *rac*

[a] Values are means of at least three experiments with standard errors



Scheme 4. Reagents and conditions: (a) Br_2, ethylene glycol; (b) DBU, DMSO, 85 °C, then HCl; (c) $CuBr{\cdot}SMe_2$, $BF_3{\cdot}OEt_2$, THF, Grignard reagent; (d), HCO_2Et, NaOH, PhH, MeOH; (e) $N_2H_4{\cdot}H_2O$, MeOH, rt; (f) HBr, DCM or Pd/C, H_2, MeOH; (g) pyridine, 4-chlorobenzenesulfonyl chloride; (h) NaOH, THF, H_2O.