Bioorganic & Medicinal Chemistry Letters 20 (2010) 2195–2199

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

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

Xiaocong M. Ye [a,*], Andrei W. Konradi [a], Jenifer Smith [a], Ying-Zi Xu [a], Darren Dressen [a], Albert W. Garofalo [a], Jennifer Marugg [a], Hing L. Sham [a], Anh P. Truong [a], Jacek Jagodzinski [b], Michael Pleiss [a], Hongbin Zhang [c], Erich Goldbach [c], John-Michael Sauer [c], Elizabeth Brigham [d], Michael Bova [e], Guriqbal S. Basi [e]

[a] Department of Medicinal Chemistry, Élan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, CA 94080, United States
[b] Department of Process and Analytical Chemistry, Élan Pharmaceuticals, 1000 Gateway Boulevard, South San Francisco, CA 94080, United States
[c] Department of Lead, Discovery, and Optimization, Élan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, CA 94080, United States
[d] Department of In Vivo Pharmacology, Élan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, CA 94080, United States
[e] Department of Biology, Élan Pharmaceuticals, 1000 Gateway Boulevard, South San Francisco, CA 94080, United States

ARTICLE INFO

Article history:
Received 17 December 2009
Revised 5 February 2010
Accepted 8 February 2010
Available online 13 February 2010

Keywords:
Alzheimer's disease
Amyloid precursor protein
γ-Secretase
γ-Secretase inhibitor

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.

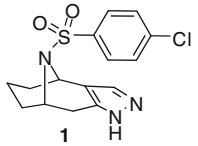
Alzheimer's disease (AD) is a progressive neurodegenerative disorder accompanied by cognitive impairment, memory deficit, and visual–spatial disorientation. Amyloid plaques and neurofibrillary tangles within the hippocampus and the cerebral cortex, containing aggregated amyloid beta peptide (Aβ) and 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.

* Corresponding author. Tel.: +1 650 616 2683; fax: +1 650 794 2387.
E-mail address: michael.ye@elan.com (X.M. Ye).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.02.039

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.

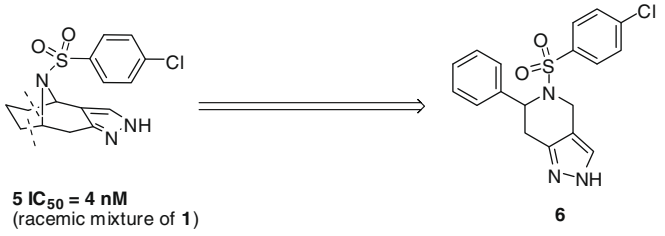
The synthesis of compound **6** is illustrated in Scheme 3. Starting with commercially available ketone **7**, a procedure reported by Trost et al.[18] was able to provide us the desired pyrazole **8** with excellent regiochemistry-control. After deprotection, sulfonylation occurred on both the piperidine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

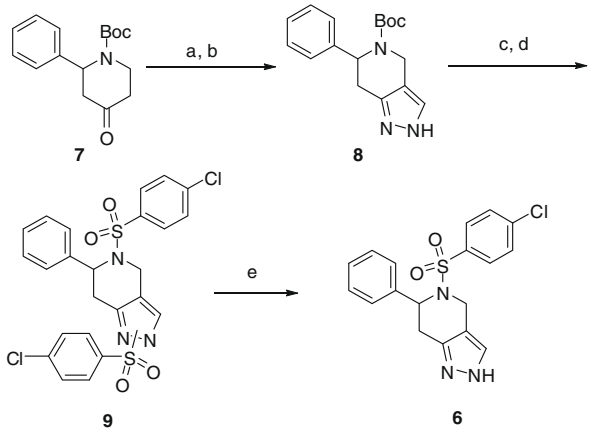
Unfortunately, the copper-catalyzed conjugate addition did not work for heteroaromatic Grignard reagents. Therefore, a Diels-Alder strategy[22] was employed to make key intermediate **19** (Scheme 5). Formylation of these analogs, however, did not afford single regioisomers. Instead, inseparable mixtures 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.

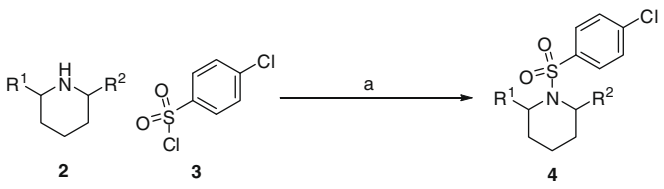
As shown in Table 2, although only a slight improvement in potency was achieved while changing halogens and their substitution pattern on the phenyl ring at the C-6 position, those compounds (**6** and **15a–d**) demonstrated significantly higher selectivity ratio in both enzymatic and cellular assays[23] 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.

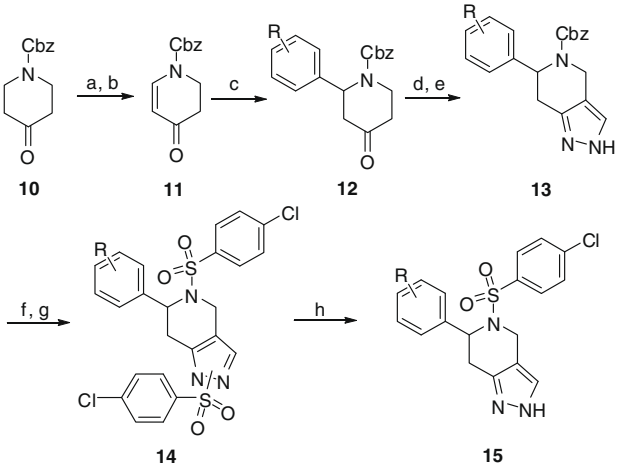


Scheme 1. Reagents: (a) pyridine, O/N.

Table 1
Structure–activity relationships of N-arylsulfonylated piperidine

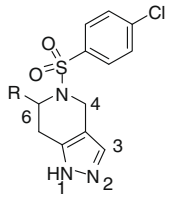
Compound	R1	R2	γ APP IC_{50}[a] (nM)	Notes
4a	H	H	>30,000	
4b	Me	H	8278 ± 1964	Racemic
4c	Et	H	2002 ± 912	Racemic
4d	*n*-Pr	H	1698 ± 72	Racemic
4e	Ph	H	760 ± 82	Racemic
4f	Me	Me	1004 ± 227	*cis*, *rac*

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

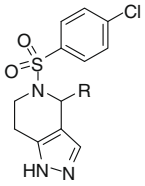


Scheme 4. Reagents and conditions: (a) Br_2, ethylene glycol; (b) DBU, DMSO, 85 °C, then HCl; (c) $CuBr{\cdot}SMe_2$, $BF_3{\cdot}OEt_2$, THF, Grignard reagent; (d), HCO_2Et, NaOH, PhH, MeOH; (e) $N_2H_4{\cdot}H_2O$, MeOH, rt; (f) HBr, DCM or Pd/C, H_2, MeOH; (g) pyridine, 4-chlorobenzenesulfonyl chloride;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

Table 2
In vitro activities of synthetic analogs of the pyrazolopiperidine series



20



21

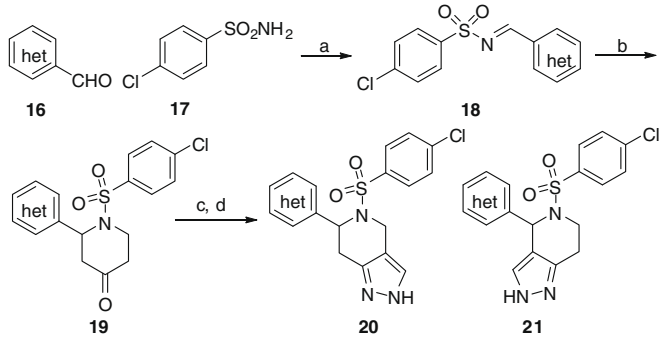
Compound	R	γ APP IC_{50}[a] (nM)	γ Notch IC_{50}[a] (nM)	SNC Cell ED_{50}[a] (nM)	SNC γ Notch IC_{50}[a] (nM)	Glucuron. microsom. % remain[c] (human)	Oxidat. metabol. % remain[d] (human)	Notes
6	Ph	7.7 ± 0.2	598 ± 41	55.3 ± 5.0	6514 ± 806	8	5	Racemic
15a	4-ClPh	3.4 ± 0.2	311 ± 41	17.5[b]	2586[b]	33	12	Racemic
15b	4-FPh	5.4 ± 0.1	481 ± 14	28.0 ± 4.4	5319 ± 645	N/A	12	Racemic
15c	3-FPh	8.3 ± 0.1	662 ± 54	47.1 ± 10	11,397 ± 1467	0	6	Racemic
15d	3,5-diFPh	9.7 ± 0.3	776 ± 61	60.1 ± 7.2	14,126 ± 1367	0	14	Racemic
15e	$PhCH_2$	80.9 ± 2.2	1554[b]	340 ± 67	16,625 ± 1528	N/A	3	Racemic
15f	*i*-Pr	16.1 ± 0.7	87[b]	86 ± 12	6759 ± 529	N/A	3	Racemic
20/21a	3-Pyridyl	96.7 ± 2.4	1109[b]	558[b]	14,770[b]	57	67	*rac*, regio mix. of 4
20/21b	4-Pyridyl	451 ± 6.2	5431[b]	1419[b]	>40,000	26	21	*rac*, regio mix. of 4
20c	5-Pyrimidyl	536 ± 19	10,375 ± 943	400[b]	>40,000	70	67	Active enant.
21c	5-Pyrimidyl	12.0 ± 0.6	120 ± 14	47.1 ± 11	2305 ± 145	85	50	Active enant.
20d	CO_2Et	431 ± 22	5851[b]	1423[b]	>40,000	0	8	Active enant.
21d	CO_2Et	10.2 ± 0.1	204[b]	137[b]	10263[b]	1	1	Active enant.
20e	2-Thiazolyl	244 ± 13	5750 ± 900	1271[b]	33565[b]	8	54	Racemic
21e	2-Thiazolyl	29.1 ± 2.7	858 ± 122	139[b]	6527[b]	59	57	Racemic
21f	CH_2OH	557 ± 46	8658[b]	3127[b]	>40,000	N/A	84	Active enant.
21g	$CH_2OC(O)NMe_2$	350 ± 6.2	8251[b]	5324[b]	>40,000	37	15	Racemic

[a] Values are means of three experiments with standard errors unless noted.
[b] Values are single experiment or means of two experiments.
[c] Percentage of compound (2 μM) remaining after 30 min incubation in liver microsomes (0.5 mg protein) supplemented with 1 mM UDPGA, 100 mM $MgCl_2$ and 25 μg/mL alamethacin at 37 °C in phosphate buffer.
[d] Percentage of compound (1 μM) remaining after 30 min incubation in liver microsomes (0.5 mg protein) supplemented with 1 mM NADPH at 37 °C in phosphate buffer.

simply alkyl group such as *iso*-propyl was used at this position (compound **15f**), potency decreased just twofold. Clearly, substitution at C-4 position achieves a better potency than it at C-6 position (compound **21c** vs **20c**, **21d** vs **20d**). When the ester group was converted to the alcohol and carbamate group, substantial loss in potency was observed. These results suggest the binding pocket in the right side of the molecule is very sensitive.

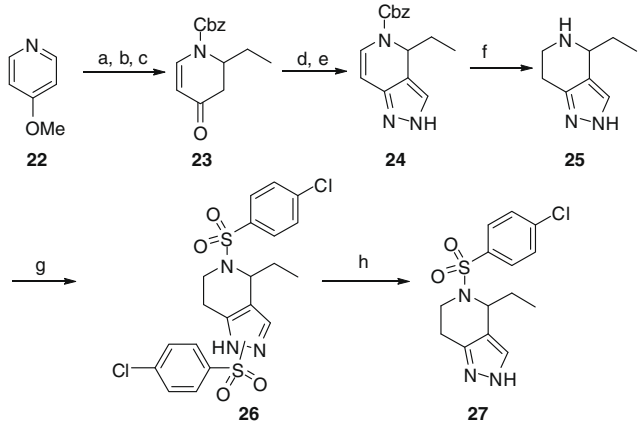
While it is clear that aryl group at C-6 position is better than alkyl group in terms of potency, we need to discover if this is the case for C-4 position. This is even more important if we consider that the SAR at C-4 position seems more sensitive than C-6. From Table 1, an ethyl group is clearly better than methyl group in terms of potency for that simple piperidine sulfonamide. Therefore, we decided to synthesize a compound with ethyl group at C-4 position.

The synthesis is illustrated in Scheme 6. Reaction of 4-methoxypyridine with benzyl chloroformate followed by Grignard addition with ethylmagnesium bromide gave the 2,3-dihydropyridinone **23**.[20] Treatment with DMF–DMA complex afforded the enamine intermediate, to which was then added hydrazine to form the pyrazole **24**. Hydrogenation with palladium on carbon as the catalyst cleaved the Cbz group and reduced the double bond simultaneously. Once again, the sulfonylation occurred at both nitrogen



16 **17** **18** **19** **20** **21**

Scheme 5. Reagents: (a) 4A MS, MP-TsOH, PhMe, reflux; (b) Danishefsky diene, THF, reflux; (c) HCO_2Et, NaOEt or DMF–DMA; (d) $N_2H_4{\cdot}H_2O$.



22 **23** **24** **25** **26** **27**

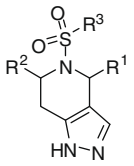
Scheme 6. Reagents: (a) CbzCl, PhMe; (b) EtMgBr, THF; (c) HCl; (d) DMF–DMA; (e) $N_2H_4{\cdot}H_2O$, HOAc; (f) Pd/C, H_2, MeOH; (g) pyridine, 4-chlorobenzenesulfonyl chloride; (h) NaOH, THF, H_2O.

atoms. After treatment with NaOH, the desired final product was obtained.

The γ APP assay (see Table 3) reveals that compound **27** is not only more potent than compound **15f** (1 nM vs 16 nM), but also surpasses compound **1**. At this point, it seems that the best substituent at the 6-position is 4-chlorophenyl and ethyl group at the 4-position. Therefore, we decided to synthesize compound **34** which combines the best substituents into one molecule. The synthesis is illustrated in Scheme 7 using similar strategy as scheme 6. It is noteworthy that the Grignard addition gave predominately *syn* adduct.[21] Formylation led to two regioisomers in a 2:5 ratio, which were then carried forward separately to the final products **32** and **34**.

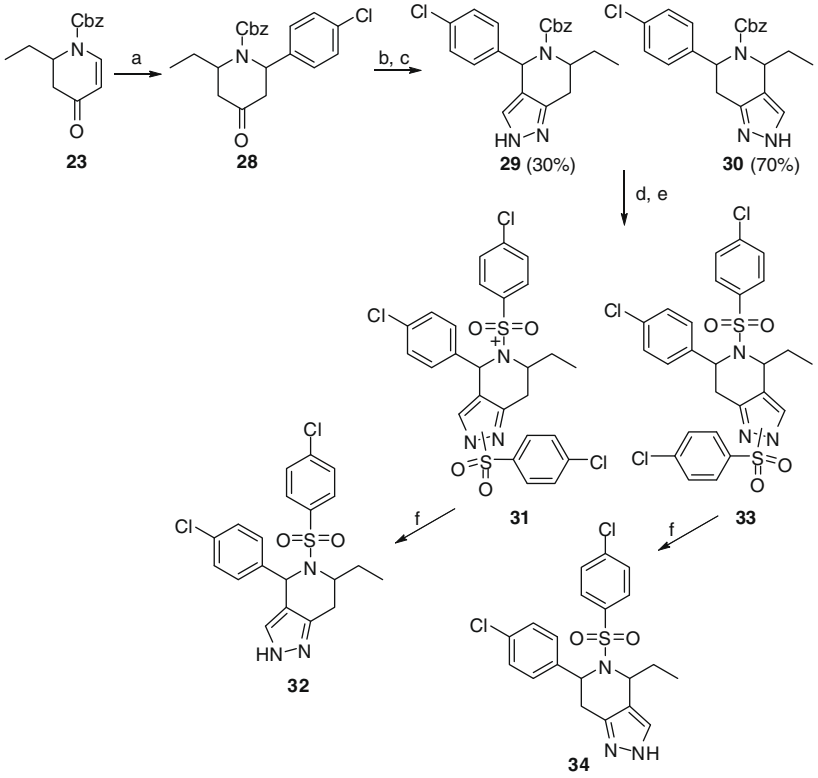
Surprisingly, the combination resulted in potency loss compared with compound **27**, as compound **32** is 20 nM and **34** is 3.3 nM.

Table 3
In vitro activities of synthetic analogs of the pyrazolopiperidine series

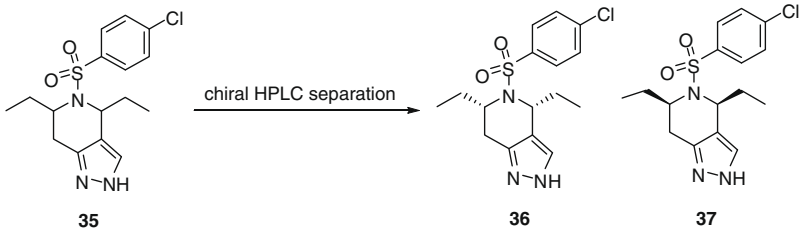


Compound	R1	R2	R3	γ APP IC_{50}[a] (nM)	γ Notch IC_{50}[a] (nM)	SNC Cell ED_{50}[a] (nM)	SNC γ Notch IC_{50}[a] (nM)	Glucuron. microsom. % remain[c] (human)	Oxidat. metabol. % remain[d] (human)	Notes
27	Et	H	4-ClPh	1.01 ± 0.03	15.3[b]	19.0 ± 4.4	736 ± 185	N/A	18	*rac*, *cis*
32	Et	4-ClPh	4-ClPh	3.7 ± 0.4	75.5[b]	16.7[b]	1568[b]	31	10	*rac*, *cis*
34	4-ClPh	Et	4-ClPh	22.4 ± 1.2	125.5[b]	182.3[b]	15455[b]	25	4	*rac*, *cis*
35	Et	Et	4-ClPh	0.48 ± 0.01	5.0 ± 0.2	1.27[b]	123[b]	2	1	*rac*, *cis*
36	Et	Et	4-ClPh	0.35 ± 0.03	5.8 ± 1.3	0.98 ± 0.2	70 ± 8	1	1	ent. A of 40
37	Et	Et	4-ClPh	62.6 ± 5.2	N/A	157[b]	6854[b]	1	0	ent. B of 40
38	*c*-Pr	*c*-Pr	4-CF_3-Ph	0.77 ± 0.02	23.4[b]	2.8[b]	295[b]	32	10	*rac*, *cis*

[a] Values are means of three experiments with standard errors unless noted.
[b] Values are single experiment or means of two experiments.
[c] Percentage of compound (2 μM) remaining after 30 min incubation in liver microsomes (0.5 mg protein) supplemented with 1 mM UDPGA, 100 mM $MgCl_2$ and 25 μg/mL alamethacin at 37 °C in phosphate buffer.
[d] Percentage of compound (1 μM) remaining after 30 min incubation in liver microsomes (0.5 mg protein) supplemented with 1 mM NADPH at 37 °C in phosphate buffer.



Scheme 7. Reagents and conditions: (a) 4-chlorophenylmagnesium bromide, CuBr·SMe_2, BF_3·OEt_2; (b) NaH, HCO_2Et, MeOH, PhH; (c) N_2H_4·H_2O; (d) TMSI, CH_3CN; (e) 4-chlorobenzenesulfonyl chloride.



Scheme 8.

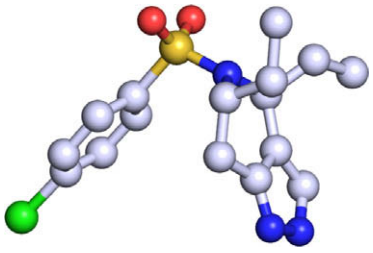


Figure 2. Compound **37** (inactive enantiomer).

Although we do not have a clear understanding of this result, we believe the potency loss may be due to steric effect that forces the molecule to twist its conformation. We then decided to make the simple diethyl substituted compound and to see if this less crowded molecule would be more potent.

The same chemistry illustrated in Scheme 7 was used to make this symmetrical di-substituted pyrazolopiperidine compounds such as **35**, just switching the 4-chlorophenylmagnesium bromide with ethylmagnesium bromide. Indeed, compound **35** is extremely potent demonstrating picomolar APP activity (see Table 3). Compound **35** was subjected to chiral HPLC separation using Chiralcel OD column, eluting with ethanol/hexane mixture, to afford both enantiomers, **36** and **37**, each in greater than 99% ee (Scheme 8). Absolute configuration of the compound **37** (the inactive enantiomer) was determined by analysis of anomalous X-ray scattering by the single crystal. The determination (CCDC 764934) indicates that the spatial configuration of the active isomer, **36**, is analogous to compound **1**[7] (see Fig. 2).

Although compound **36** is extremely potent, it still suffers from poor metabolic stability. Metabolic identification studies revealed that the poor metabolic stabilities arise from the ethyl groups and the methylene group adjacent to pyrazole ring. Also, the studies revealed that the *p*-chlorobenzenesulfonamide was oxidized to an epoxide followed by glutathione conjugation. The glutathione conjugation problem was alleviated when trifluoromethyl was used to replace the chlorine substituent. At the same time, the diethyl groups were replaced by dicyclopropyl groups and the subsequent molecule **38** (its synthesis will be disclosed in a separate Letter) afforded higher stability in an in vitro glucuronidation assay, although it still performed poorly in an in vitro oxidation assay. Table 3 lists the data of those compounds.

The in vivo efficacy of compound **36** was evaluated in the wild type FVB mouse model. A significant 25% Aβ40 reduction was observed 3 h after a single 5 mg/kg po dose of **36** (brain/plasma: 0.8).

In summary, we have identified a novel, potent and efficacious series of γ-secretase inhibitors. This series displays in vivo activity for reduction of brain Aβ. Although this series achieved a good efficacy result, it has suffered from poor metabolic stability. Our effort to improve its in vivo pharmacokinetic profile will be reported in another Letter.

Acknowledgements

We would like to thank Gary D. Probst, Daniel Ness, Lee Latimer, Michael Dappen, Jing Wu, David Quincy, Pam Keim, Lan Nguyen, William Wallace, David Nakamura, Karina Wong, Wes Zmolek, Michael Lee, Kang Hu, Anna Liao, Terence Hui, Tracy Cole, Cristian Cabrera, Ferdie Soriano, Bhushan Samant, Rose Lawler, Juri Fukada for their contributions to this work. We also would like to thank Wherly Hoffman for data statistics analysis and Hu Pan for X-ray structure display.

References and notes

1. (a) Selkoe, D. J.; Schenk, D. *Annu. Rev. Pharmacol. Toxicol.* **2003**, *43*, 545; (b) Wolfe, M. S. *J. Med. Chem.* **2001**, *44*, 2039.
2. Radtke, F.; Wilson, A.; Mancini, J. C.; MacDonal, H. R. *Nat. Immunol.* **2004**, *5*, 247.
3. Wong, G. T.; Manfra, D.; Poulet, F. M.; Zhang, Q.; Josien, H.; Bara, T.; Engstrom, L.; Pinzon-Ortiz, M.; Fine, J. S.; Lee, H. J.; Zhang, L.; Higgins, G. A.; Parker, E. M. *J. Biol. Chem.* **2004**, *279*, 12876.
4. Dovey, H. F.; John, V.; Anderson, J. P.; Chen, L. Z.; de Saint Andrieu, P.; Fang, L. Y.; Freedman, S. B.; Folmer, B.; Goldbach, E.; Holsztynska, E. J.; Hu, K. L.; Johnson-Wood, K. L.; Kennedy, S. L.; Kholodenko, D.; Knops, J. E.; Latimer, L. H.; Lee, M.; Liao, Z.; Lieberburg, I. M.; Motter, R. N.; Mutter, L. C.; Nietz, J.; Quinn, K. P.; Sacchi, K. L.; Seubert, P. A.; Shopp, G. M.; Thorsett, E. D.; Tung, J. S.; Wu, J.; Yang, S.; Yin, C. T.; Schenk, D. B.; May, P. C.; Altstiel, L. D.; Bender, M. H.; Boggs, L. N.; Britton, T. C.; Clemens, J. C.; Czilli, D. L.; Dieckman-McGinty, D. K.; Droste, J. J.; Fuson, K. S.; Gitter, B. D.; Hyslop, P. A.; Johnstone, E. M.; Li, W.-Y.; Little, S. P.; Mabry, T. E.; Miller, F. D.; Ni, B.; Nissen, J. S.; Porter, W. J.; Potts, B. D.; Reel, J. K.; Stephenson, D.; Su, Y.; Shipley, L. A.; Whitesitt, C. A.; Yin, T.; Audia, J. E. *J. Neurochem.* **2001**, *76*, 173.
5. Olson, R. E.; Albright, C. F. *Curr. Top. Med. Chem.* **2008**, *8*, 17.
6. Garofalo, A. W. *Expert Opin. Ther. Pat.* **2008**, *18*, 693.
7. Mattson, M. N.; Neitzel, M. L.; Quincy, D. A.; Semko, C. M.; Garofalo, A. W.; Keim, P. S.; Konradi, A. W.; Pleiss, M. A.; Sham, H. L.; Brigham, E. F.; Goldbach, E. G.; Zhang, H.; Sauer, J.-M.; Basi, G. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2148.
8. Schering Corp. WO05028440, 2005.
9. Schering Corp. WO04101562, 2004.
10. Schering Corp. WO07084595, 2007.
11. Wyeth-Arqule. WO03103660, 2007.
12. Wyeth. WO05073198, 2005.
13. Bristol-Myers Squibb CO. WO05054180, 2005.
14. F. Hoffmann-La Roche AG. WO07020190, 2007.
15. Elan Pharmaceuticals, Inc. WO05042489, 2005.
16. Elan Pharmaceuticals, Inc. WO06078753, 2006.
17. IC_{50}s determined as described in Ref. 11 in Truong, A. P.; Aubele, D. L.; Probst, G. D.; Neitzel, M. L.; Semko, C. M.; Bowers, S.; Dressen, D.; Hom, R. K.; Konradi, A. W.; Sham, H. L.; Garofalo, A. W.; Keim, P. S.; Wu, J.; Dappen, M. S.; Wong, K.; Goldbach, E.; Quinn, K. P.; Sauer, J.-M.; Brigham, E. F.; Wallace, W.; Nguyen, L.; Hemphill, S. S.; Bova, M. P.; Basi, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4920.
18. Trost, B. M.; Hiroi, K.; Jungheim, L. N. *J. Org. Chem.* **1980**, *45*, 1839.
19. Kozikowski, A. P.; Park, P.-U. *J. Org. Chem.* **1990**, *55*, 4668.
20. Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445.
21. Asberom, T.; Clader, J. W.; Josien, H. B.; Pissarnitski, D. A.; Zhao, Z.; Mcbriar, M. D. PCT/US2005/011456.
22. Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549.
23. Basi, G.S. et al. In preparation.