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Discovery of a novel sulfonamide-pyrazolopiperidine series as potent and efficacious γ-secretase inhibitors (Part II)

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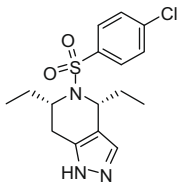
ABSTRACT

Significant improvement in metabolic stability on the pyrazolopiperidine scaffold over the original series were achieved and this stability improvement 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 Aβ42 in the brain of AD patients is thought to contribute to AD pathology.[1] Aβ, ranging from 37 to 42 amino acids in length, are 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]). Recently, we have reported on the discovery of novel GSIs as exemplified by **1**.[7] Herein, we report our progress to improve metabolic stability of this series while retain its excellent inhibitory activity (see Fig. 1).

Compound **1** demonstrated good potency and selectivity (18-fold selectivity over Notch in an enzymatic assay and 71-fold in a cellular assay) and was efficacious in a *wild type* FVB mouse model with 25% Aβ40 reduction in the brain at 5 mg/kg PO. This series, however, also suffers from poor oxidative metabolic stability, rapid glucuronide formation and glutathione conjugation. Therefore, we initiated efforts to overcome the above limitations.



1

IC_{50} (APP) = 0.3 nM
IC_{50} (Notch) = 6 nM
ED_{50} (APP) = 1 nM
ED_{50} (Notch) = 70 nM
F = 2.5%
$t_{1/2}$ = 3.8 h (rat)

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

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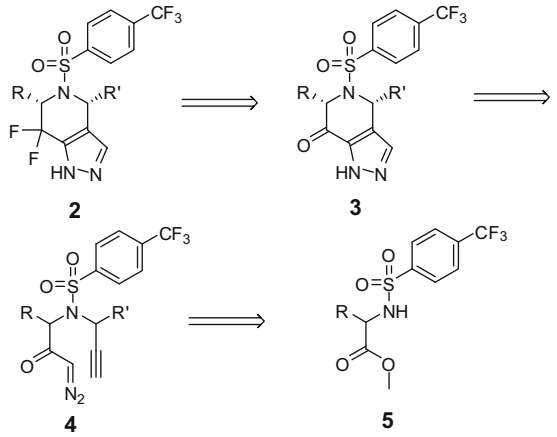
Metabolic identification studies revealed that the poor metabolic stability resulted from extensive oxidation on the ethyl groups and the methylene carbon adjacent to the pyrazole ring. Also, glutathione conjugation on the phenyl ring of the arylsulfonamide was detected. In our previous papers,[7,8] we reported that the cyclopropyl group was an effective replacement for the ethyl group to achieve better stability while maintaining its potency. To alleviate the glutathione conjugation, we needed to find substituents to replace the chloride on the phenyl ring, and trifluoromethyl turned out to be the choice as demonstrated by our previous papers.[7,8] Glucuronidation occurred on the pyrazole ring. Since our SAR indicates that the unsubstituted pyrazole was critical to the binding interaction,[9] we hoped we could minimize glucuronidation through an electronic effect. For the methylene carbon next to the pyrazole ring, we believed that the best strategy was to convert it to difluoromethylene, since it has been well established in the literatures that fluorine can enhance metabolic stability by lowering the susceptibility of nearby moieties to cytochrome P450 enzymatic oxidation.[10] By doing so, we hoped that this change could reduce glucuronidation due to the electron-withdrawing effect of the fluorine atoms adjacent to the pyrazole ring.

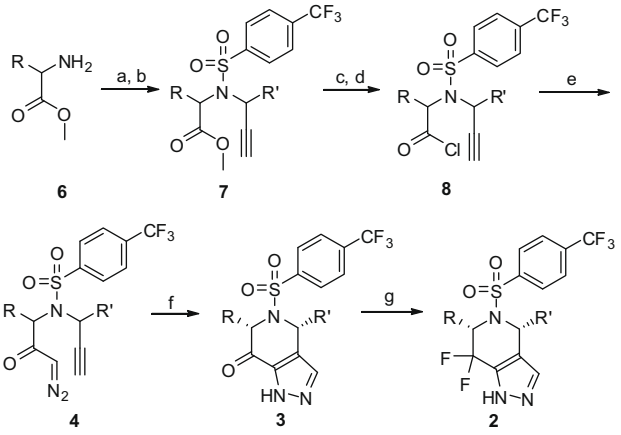
Retrosynthetic analysis illustrated in Scheme 1 led to compound **5** as the key intermediate that could be rapidly prepared from the readily available amino acid for this synthesis.

The synthesis is illustrated in Scheme 2. Starting with the commercially available amino acid **6**, sulfonylation followed by Mitsunobu reaction with the appropriate propargyl alcohol, either from a commercially available source or prepared from the corresponding aldehyde and ethynylmagnesium bromide, gave the intermediate **7**. Saponification of the ester, followed by treatment with oxalyl chloride, yielded acid chloride **8**. On treatment with diazomethane, generated from methylnitronitroso-guanidine (MNNG), acid chloride **8** was converted to diazoketone **4**. The [2+3] cyclization[11] was carried out in refluxing ethanol leading to key ketopyrazole **3**. After treatment with bis(2-methoxymethyl)aminosulfur trifluoride (BAST), various difluoro analogs (**2**) were obtained.

Initially we anticipated that we could control the stereochemistry outcome in this synthesis by starting a chirally pure amino acid, because we rationalized that only *syn* isomer of compound **4** would be able to cyclize to give the compound **3**, as only the *syn* isomer could bring the diazoketone and the alkyne groups in a close proximity to react. However, partial racemization was observed in Mitsunobu step (~10–15%). For [2+3] cyclization, the fact that both *syn* and *anti* compound **4** gave cyclized products further dampened hope to control the stereochemistry outcome in this synthesis, although in many cases the *trans* products were not stable and some of them decomposed during separation by flash chromatograph.



Scheme 1.



Scheme 2. Reagents and conditions: (a) 4-trifluoromethylbenzenesulfonyl chloride, DCM, TEA; (b) Ph_3P, DIAD, THF, corresponding propargyl alcohols; (c) LiOH, H_2O, THF; (d) oxalyl chloride, DCM, DMF (cat.); (e) MNNG, KOH, Et_2O; (f) EtOH, 80 °C, 1 h; (g) BAST.

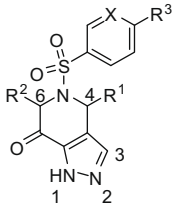
A number of compounds were synthesized using this scheme. The ketone compounds are listed in Table 1 while the fluoro compounds in Table 2. Both the ketones (compound **3**) and their difluoro analogs (compound **2**) have excellent potencies,[12] sometimes slightly higher than that of compound **1** (e.g., **3aa** and **2hh**).

As listed in Table 1, although both 4-trifluoromethy-lbenzenesulfonamide and the trifluoromethylpyridiyl-sulfonamide are slightly less potent than 4-chloro-benzenesulfonamide analog, metabolic identification studies on these compounds revealed that both are free of the glutathione conjugation. Furthermore, to our satisfaction, all ketones and all fluorine compounds give very good stabilities in the glucuronidation assay, suggesting the electronic effect of the carbonyl group or fluorine atoms adjacent to the pyrazole ring indeed works as anticipated. Oxidative stability was improved over compound **1**, especially when cyclopropyl groups were used for the side chains. However, one noticeable concern for the ketone compounds was a dramatic loss of the activity in the cellular assay[13] compared with its activity in the enzymatic assay. In the series of compounds with compound **1** as the prototype, we normally observed about 3–5-fold potency loss in the cellular assay over the enzymatic assay.[7] However, for some ketone compounds **3**, 50–1000-fold potency decrease was observed. Interestingly, this loss of cellular potency correlated well with the size of the substituent in C6 position. Indeed, when *tert*-butyl is used in C6 position (compounds **3t** and **3u**), the ratio fell back to the range of 3–5-fold reduction. Metabolic identification study established that this potency loss was due to the instability of compound **3** under the conditions of cellular assay, and decomposition occurred via elimination of the sulfinic acid and subsequent tautermization leading to a fully aromatic system as the driving force (Scheme 3).

Substitution at C4 position appears to have huge impact in its potency. Methyl group at this position is far less potent than cyclopropyl group (compounds **3f** and **3g**). Isopropyl and cyclopropyl group are almost identical (**3h** and **3i**) and ethyl group is slightly less potent than isopropyl and cyclopropyl groups (compounds **3p** and **3q**). On the other hand, substitution at C6 position generally has small effect on potency (compounds **3i** and **3n**).

The fluoro compounds, as expected, do not have this elimination–aromatization problem. As we can see from Table 2, the potency discrepancy between the cellular and enzymatic assays improved dramatically compared with the ketone compounds. More importantly, these compounds have very good metabolic stability almost across the board.

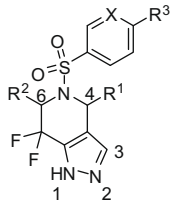
Table 1
In vitro activities of synthetic analogues of the ketone compounds



Compound	R1	R2	X	R3	Notes	γ APP (cell-free) IC_{50}[a] (nM)	γ Notch (cell-free) IC_{50}[a] (nM)	SNC Cellular ED_{50}[a] (nM)	SNC γ cellular Notch IC_{50}[a](nM)	Glucuron. Microsom. % remain (human)[c]	Oxidat. Metabol. % remain (human)[d]
3a	Et	Et	CH	Cl	cis, rac.	0.3	N/A	6 (1)[b]	546	77	6
3aa	Et	Et	CH	Cl	cis, ent of **3a**	0.1	5 (2)[b]	5	288	65	10
3b	*i*-Pr	H	CH	Cl	cis, rac.	3.7	91 (1)[b]	3999 (1)[b]	>40,000	71	12
3c	Et	H	CH	CF_3	Racemic	6.5	N/A	>10,000 (1)[b]	>40,000	N/A	19
3d	*c*-Pr	H	CH	CF_3	cis, rac.	9.1	354 (1)[b]	>10,000 (1)[b]	>40,000	N/A	N/A
3e	CF_3	H	CH	CF_3	Racemic	2.6	51 (1)[b]	>10,000 (1)[b]	>40,000	6	1
3f	Me	Me	CH	CF_3	Enantiomer A	6.8	89 (1)[b]	5106	>40,000	77	63
3g	*c*-Pr	Me	CH	CF_3	Enantiomer A	0.5	12 (1)[b]	2335 (1)[b]	>40,000	67	62
3h	*i*-Pr	*i*-Pr	CH	CF_3	cis, ent.	0.5	14 (1)[b]	33	2302	82	0
3i	*c*-Pr	*c*-Pr	CH	CF_3	Racemic	0.4	21 (2)[b]	21 (2)[b]	2792	76	67
3j	*c*-Pr	$MeOCH_2$	CH	CF_3	cis, rac.	3.2	126 (1)[b]	>10,000 (1)[b]	>40,000	N/A	14
3k	*c*-Pr	H	N	CF_3	Racemic	5.6	193 (2)[b]	5995 (1)[b]	>40,000	42	5
3l	Me	Me	N	CF_3	cis, ent. A	13.2	144 (1)[b]	1099 (1)[b]	18,334	91	67
3m	Me	Me	N	CF_3	cis, ent. B	91	2267 (1)[b]	>10,000 (1)[b]	>40,000	N/A	62
3n	*c*-Pr	Me	N	CF_3	cis, ent. A	0.6	21 (1)[b]	>10,000 (2)[b]	>40,000	59	72
3o	*c*-Pr	3,5-diF-Ph	N	CF_3	Racemic	0.7	17 (2)[b]	>1000 (1)[b]	>4000	N/A	9
3p	Et	Et	N	CF_3	cis, ent.	0.8	36 (1)[b]	21 (1)[b]	2361	83	57
3q	*c*-Pr	*c*-Pr	N	CF_3	cis, rac.	0.3	10 (1)[b]	130 (2)[b]	6704	75	77
3r	*c*-Pr	*c*-Pr	N	CF_3	trans, rac.	3	66	374 (2)[b]	25,072	87	21
3s	*c*-Pr	4-THP	N	CF_3	Racemic	1	19	1 (2)[b]	187	64	57
3t	*c*-Pr	*t*-Bu	N	CF_3	Unassigned	0.2	6	0.6	71	66	8
3u	*c*-Pr	*t*-Bu	N	CF_3	Unassigned	4.8	107 (1)[b]	16 (2)[b]	1636	N/A	12

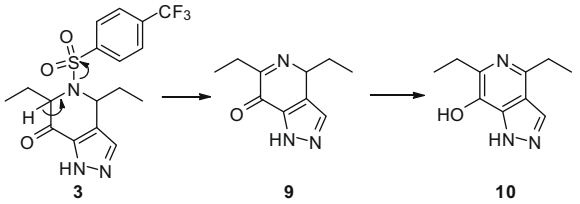
[a] Values are means of at least three experiments unless otherwise noted.
[b] Number in bracket indicates the number of experiments.
[c] Percentage of compound (2 μM) remaining after 30 min incubation in liver microsomes (0.5 mg protein) supplemented with 1 mM UDPGA, 100 mM $MgCl_2$ and 25 μg/mL alamethacin 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.

Table 2
In vitro activities of synthetic analogues of the fluoro compounds

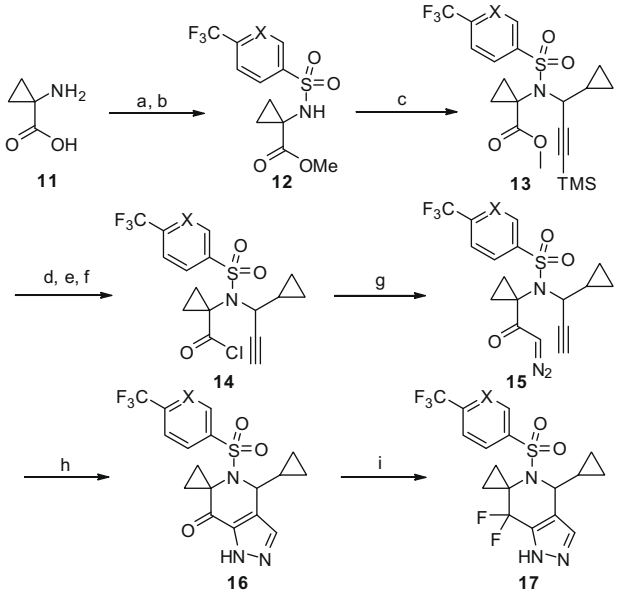


Compound	R1	R2	X	R3	Notes	γ APP cell-free IC_{50}[a] (nM)	γ Notch cell-free IC_{50}[a] (nM)	SNC Cellular ED_{50}[a] (nM)	SNC γ cellular Notch IC_{50}[a] (nM)	Glucuron. Microsom. % remain (human)[c]	Oxidat. Metabol. % remain (human)[d]
2a	*i*-Pr	H	CH	Cl	Racemic	0.7	12 (1)[b]	11 (2)[b]	574	42	2
2b	*c*-Pr	Me	CH	CF_3	cis, ent. A	1	18	7	418	46	75
2c	*c*-Pr	Me	N	CF_3	cis, ent. A	1.2	20	6	358	59	79
2d	*c*-Pr	*c*-Pr	CH	CF_3	Diaster. Mix	1.5	42 (1)[b]	6 (1)[b]	771	64	76
2e	Et	Et	N	CF_3	cis, rac.	1.8	50 (1)[b]	6 (1)[b]	304	66	22
2f	CF_3	H	CH	CF_3	Racemic	0.9	10 (2)[b]	4	403	35	84
2g	*c*-Pr	*c*-Pr	N	CF_3	cis, rac.	0.8	47 (2)[b]	3	304	67	71
2gg	*c*-Pr	*c*-Pr	N	CF_3	cis, ent. of **2g**	0.6	23	2	138	75	80
2h	*c*-Pr	*c*-Pr	N	CF_3	trans, rac.	0.3	3	0.5	34	61	53
2hh	*c*-Pr	*c*-Pr	N	CF_3	trans, ent of **2h**	0.1	3	0.2	13	41	43

[a] Values are means of at least three experiments unless otherwise noted.
[b] Number in bracket indicates the number of 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 3.



Scheme 4. Reagents and conditions: (a) HCl(g), MeOH; (b) TEA, DCM, the corresponding sulfonyl chloride (X = N or CH), 0 °C; (c) DIAP, TBP, PhMe, 1-cyclopropyl-3-(trimethylsilyl)prop-2-yn-1-ol; (d) LiOH, MeOH, rt; (e) LiI, pyridine, 115 °C; (f) oxalyl chloride, DCM, DMF (cat.); (g) CH_2N_2, Et_2O; (h) EtOH, 80 °C; (i) BAST.

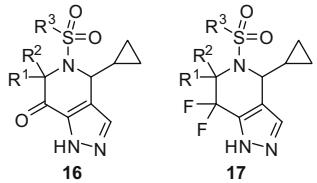
As mentioned above, there are huge potency discrepancies of the ketone compounds between the cellular assay and the enzymatic assay, which we assume is a result of decomposition of the ketone compounds via elimination–aromatization process. We also pointed out that the substituent at the C6 position does not contribute to compound's activity much. Based on these observations, we proposed to introduce gem-dialkyl substitution at the C6 position to ameliorate the elimination process, therefore, to solve this potency discrepancy.

Gem-dimethyl was obviously the easy choice. We also decided to have a spiro-cyclopropyl group at this position, in case we would observe oxidative liability for the gem-dimethyl compound, because cyclopropyl group has been proven to fare better in oxidative assay than methyl group. The synthetic route is illustrated in Scheme 4 with the same strategy as Scheme 2, except for a few modifications. One is that TMS protected propargyl alcohol was used to afford a better yield in the Mitsunobu reaction step. The other is basic hydrolysis condition failed to hydrolyze the methyl ester and allene formation was observed when temperature was raised. Fortunately, this problem was solved by LiI/pyridine condition via a dealkylation mechanism.

Using this synthesis, we made the gem-dimethyl, spiro-cyclopropyl and spiro-cyclobutyl compounds. Since the ketone will not be able to cause the elimination–aromatization any more, we just convert one ketone compound to its difluoro analog to check out its properties. All compounds are listed in Table 3.

As expected, the potency discrepancies between the cellular assay and enzymatic assay on these ketone compounds fall into the normal range of 3–5-fold. All compounds are very potent, suggesting that the original assumption of di-substitution tolerance in C6 position is valid. Interestingly, spiro-cyclobutyl group (compound **16d**) is significantly more potent than spiro-cyclopropyl group (compound **16b**). This is in contrast to the observed relative insensitivity when varying methyl to ethyl or isopropyl group at C6 position in compound **3**. We also observed significant potency increase in this spiro substituted system when converting the ketone to the difluoro compound (**16c** to **17a**), while a slight loss of

Table 3
In vitro activities of synthetic analogues of the di-substituted compounds



Compound	R1	R2	R3	Notes	γ APP cell-free IC_{50}[a] (nM)	γ Notch cell-free IC_{50}[a] (nM)	SNC Cellular ED_{50}[a] (nM)	SNC γ cellular Notch IC_{50}[a] (nM)	Glucuron. Microsom. % remain (human)[c]	Oxidat. Metabol. % remain (human)[d]
16a	Me	Me	4-CF_3-Ph	Racemic	7.3	268 (2)[b]	60	2656	67	68
16b	CH_2CH_2		4-CF_3-Ph	Racemic	1.9	69 (2)[b]	11 (2)[b]	995	84	85
16c	CH_2CH_2		6-CF_3-3-Py	Racemic	1.8	35 (2)[b]	7 (2)[b]	688	91	86
16d	$CH_2CH_2CH_2$		4-CF_3-Ph	Racemic	0.4	8 (1)[b]	2	235	N/A	3
16e	CH_2CH_2		6-CF_3-3-Py	ent. A of 16c	1071	N/A	2681 (1)[b]	>40,000	88	83
16f	CH_2CH_2		6-CF_3-3-Py	ent. B of **16c**	1.4	15 (1)[b]	4 (1)[b]	250	94	86
16g	CH_2CH_2		5-CF_3-2-Py	Racemic	24	502 (2)[b]	87 (1)[b]	6209	89	76
16h	CH_2CH_2		5-CF_3-2-Py	ent. A of **16g**	897	8276 (1)[b]	1854 (1)[b]	>40,000	N/A	80
16i	CH_2CH_2		5-CF_3-2-Py	ent. B of **16g**	9.6	223	26 (2)	2289	96	82
16j	CH_2CH_2		5-Cl-2-Thiophene	Racemic	2	18	7 (2)[b]	576	N/A	1
17a	CH_2CH_2		6-CF_3-3-Py	Racemic	0.2	2	0.5	50	89	61
17b	CH_2CH_2		6-CF_3-3-Py	ent. A of **17a**	0.2	1	0.3	25	85	85
17c	CH_2CH_2		6-CF_3-3-Py	ent. B of **17a**	56	221	86	9277	100	72

[a] Values are means of at least three experiments unless otherwise noted.
[b] Number in bracket indicates the number of 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.

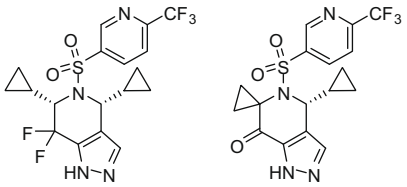


Figure 2. Representative in vivo compounds.

potency was observed from this conversion in the previous system (compounds **3q** to **2g**).

The in vivo activity of compounds **2gg** and **16f** (Fig. 2) were evaluated in our wild type FVB mouse model. Both compounds achieved significant Aβ40 reduction (20% and 27%, respectively) in the brain 3 h after a single 1 mg/kg oral dose of **2gg** and **16f**. Clearly, the improvement of the in vitro PK properties of these compounds has translated to improved in vivo activity when comparing with the result of compound **1**.[7]

In summary, by applying medicinal chemistry principals, we have dramatically improved the metabolic stability of the original series while still maintaining its favorable potency. These improved pharmacokinetic properties have resulted in better efficacy in an animal model.

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12. IC_{50}s determined as described in note 11 in Ref. 8.
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