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N-Bridged bicyclic sulfonamides as inhibitors of γ-secretase

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ABSTRACT

The structural modification of a series of [3.3.1] bicyclic sulfonamide based γ-secretase inhibitors is described. Appropriate substitution on the bicyclic scaffold provides a significant increase in the metabolic stability of the compounds resulting in an improved in vivo metabolic profile.

Alzheimer's disease (AD) is the most prevalent form of dementia and affects approximately 24 million people worldwide.[1] Although the origin of the disease is not fully understood compelling evidence suggests that the accumulation of β-amyloid (Aβ) peptide and the subsequent formation of amyloid plaques in the cortex is responsible for neurodegeneration.[2] Aβ peptides are generated by cleavage of the β-amyloid precursor protein (β-APP) by two proteases, referred to as β-secretase and γ-secretase and thus inhibition of these enzymes is currently an important approach towards the development of disease modifying treatments for AD.[3]

A number of structurally diverse γ-secretase inhibitors have been reported[4] with several entering into clinical trials.[5] In this Letter we describe the structure–activity relationships of a series of *N*-bridged bicyclic sulfonamides as inhibitors of γ-secretase. Compound **1**[6], (Fig. 1) a representative member of the class, was developed during hit expansion from micromolar hits identified from high throughput screening of approximately 500 K small molecules. Compound **1** is a potent inhibitor of γ-secretase (IC_{50} = 2 nM) in an in vitro assay against recombinant APP substrate that measures potency of compound for inhibition of Aβ40 site cleavage in a partially enriched enzyme extract from IMR-32 cells, but suffers from poor metabolic stability and rapid glucuronide formation with only 15% of the compound remaining after a 30 min incubation with mouse liver microsomes (Table 1). This poor stability results in a short in vivo half-life (24 min), rapid clearance, and low oral bioavailability (F = 2.6%) in rat. In an attempt to improve the in vivo pharmacokinetic profile of this scaffold, we designed a series of analogs bearing substitution on the non-pyrazole fused side of the [3.3.1] ring system. It was reasoned that the highly lipophilic non-pyrazole fused side of the [3.3.1] ring system would be susceptible to oxidative metabolism and thus these modifications were designed to both block potential sites of metabolism and to further reduce the lipophilicity of the scaffold.

Due to the accessibility of intermediate **3** the first series of compounds that were synthesized involved adding substituents to the C-10 carbon on the back of the [3.3.1] bicycle. These analogs were all derived from a key intermediate, ester **6**, which was prepared from the known dialdehyde **2** as outlined in Scheme 1.[7]

The initial modifications of ester **6** are shown in Scheme 2. Reduction of the ester provided alcohol **7** and basic ester hydrolysis gave carboxylic acid **8**. In order to present more hydrophobic substituents methyl and ethyl ethers **10** and **11** were prepared. Protection of the pyrazole NH of ester **6** with SEM-Cl followed by reduction of the ester to the alcohol and subsequent O-alkylation and final removal of the SEM protecting group gave the ethers **10** and **11**. Ester **5** was also converted into cyclopropyl ether **14**. Protection of the ketone of **5** followed by conversion of the ester to a cyclopropyl alcohol under Kulinkovich conditions[8] and subsequent methylation gave compound **13** which was further elaborated into pyrazole **14**.

The influence of these substitutions on γ-secretase inhibition and in vitro metabolic stability is shown in Table 1. Ester **6** retains the single digit nanomolar potency of its parent **1** but alcohol **7** and

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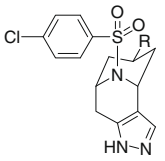
Table 1
γ-Secretase inhibition, and metabolic stability for compounds **1–22**



Compds[a]	R	GammaAPP IC_{50}[b] (nM)	OxMet% remaining[c] (m, h)	GlucMet% remaining[d] (m, h)
1[e]	H	2	15, 48	5, 0
6	CO_2Et	8	0, 0	0, 0
7	CH_2OH	678	na	89, 38
8	CO_2H	8813	na	na
10	CH_2OMe	9	16, 40	71, 28
11	CH_2OEt	20	4, 25	85, 35
14	Cyclopropyl methoxyl	194	4, 12	na
18	CN	32	74, 70	81, 45
18entA	CN	5957	80, 72	na
18entB	CN	13	86, 68	na
20	CF_2H	4	35, 40	24, 2
22	CCH	0.75	27, 63	33, 2
23	CCMe	0.52	2, 42	na
24	*cis*-CH=CHCl	2	3, 14	na
25	*trans*-CH=CHCl	1	7, 6	37, 1
26	*cis*-CH=CHCF3	26	17, 38	na
27	*trans*-CH=CHCF3	1	36, 6	39, 2

[a] Compounds are racemic unless stated otherwise.
[b] See Ref. 11.
[c] See Ref. 12.
[d] See Ref. 13.
[e] More active enantiomer.

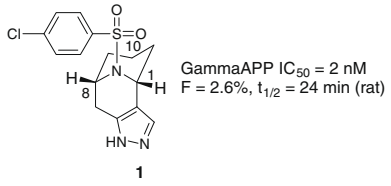


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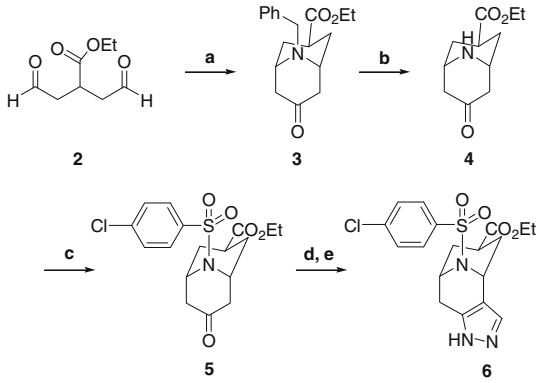
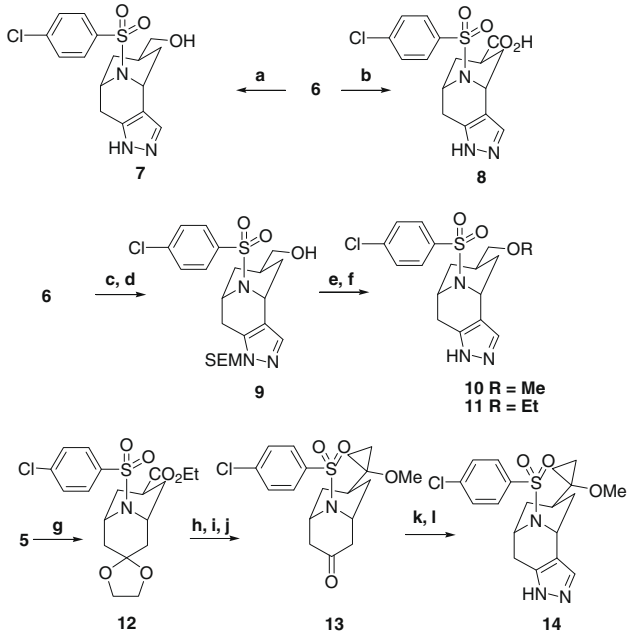
Figure 1. Representative *N*-bicyclic sulfonamide γ-secretase inhibitor.



Scheme 1. Reagents and conditions: (a) acetone-1,3-dicarboxylic acid, $BnNH_2$ NaOAc, HCl (aq), 3 days, rt, 40%; (b) $Pd(OH)_2/C$, H_2 (30 psi), CH_3OH, 12 h, rt, quant.; (c) 4-chlorobenzenesulfonyl chloride, Et_3N, CH_2Cl_2, 2 h, rt, 88%; (d) ethyl formate, NaOEt, THF/EtOH, 0.5 h, 60 °C, 94%; (e) hydrazine monohydrate, AcOH, EtOH, 1 h, rt, 97%.



Scheme 2. Reagents and conditions: (a) $LiBH_4$, THF, 60 °C, 2 h; (b) NaOH, H_2O/THF, rt, 4 h; (c) SEMCl, NaH, THF, 3 h, rt, 95%; (d) $LiBH_4$, THF, 6 h, rt, quant.; (e) RI, NaH, THF, 2 h, rt; (f) HCl, dioxane/H_2O, 18 h, rt; (g) ethylene glycol, TMSCl, CH_2Cl_2, 50 °C, 2 days, 90%; (h) EtMgBr, $Ti(OiPr)_4$, Et_2O, rt, 18 h, 84%; (i) MeI, NaH, THF, rt, 18 h; (j) HCl/dioxane, rt, 2 h, 96% (2 steps); (k) ethyl formate, NaOEt, THF/EtOH, 2 h, 40 °C; (l) hydrazine monohydrate, AcOH, EtOH, 1 h, rt.

acid **8** showed a significant loss of activity suggesting that polar hydrogen bond donors in this region are not well tolerated. The methyl and ethyl ethers (**10** and **11**, respectively) gain back the potency and interestingly, these two ethers provide a significant increase in the stability of the compounds towards glucuronide formation. Cyclopropyl ether **14** lost potency compared to methyl ether **10** suggesting that steric bulk in this region is not well tolerated.

Encouraged by this data further analogs were prepared. Ester **6** was converted into nitrile **18** via dehydration of an oxime derived from aldehyde **16** (Scheme 3 and Scheme 4). Nitrile **18** demonstrated reasonable γ-secretase inhibitory activity but also displayed a favorable improvement in oxidative and glucuronidation stability across species. Separation of the enantiomers gave **18entB** which has good potency (13 nM) and improved in vitro oxidative stability.

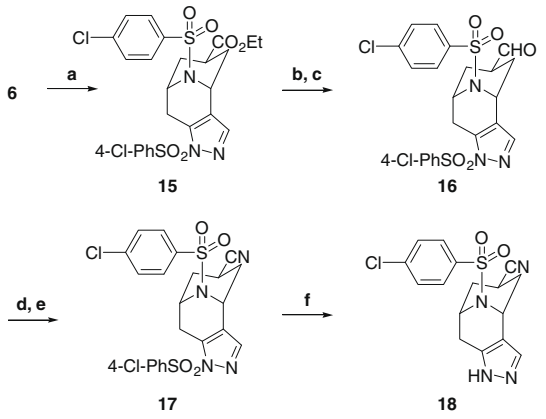
Aldehyde **16** was also converted into difluoromethyl analog **20** upon treatment with DAST. Compound **20** retained the potency of **1** with a modest improvement in oxidative and glucuronidation stability.

Further exploration of the structure activity relationships of this region was made with alkynyl analogs **22** and **23** (Scheme 5). The terminal alkyne **22** was derived from aldehyde **21** upon treatment with the Ohira–Bestmann reagent[9] and propyne **23** was obtained upon deprotonation of the terminal alkyne with LiHMDS followed by quenching with methyl iodide. These analogs showed a significant increase in potency over the parent compound **1** (**23** IC_{50} = 0.52 nM) but offered no advantages in terms of metabolic stability.

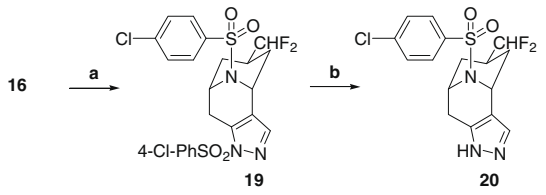
Since the alkynyl analogs **22** and **23** provided a significant increase in gamma secretase inhibition, a number of alkenes were prepared. Aldehyde **21** was converted into the *cis*- and *trans*-vinyl chlorides and trifluoromethyl[10] analogs as illustrated in Scheme 6. In both cases the *trans*-isomers were more potent than the *cis*-isomers. Interestingly, both *trans*-analogs **25** and **27** have similar potency (IC_{50} = 1 nM) but the *cis*-analogs **24** and **26**, possess an order of magnitude difference in gamma secretase inhibition (**24** IC_{50} = 2 nM and **26** IC_{50} = 26 nM). The trifluoromethyl analogs had improved metabolic stability compared to the vinyl chlorides although the stability was no improvement over the unsubstituted parent compound **1**.

Interestingly, the effect of substitution at the 10-position has a profound effect upon the amount of the glucuronide formed in the in vitro assay (Table 1). It is presumed that the pyrazole NH is the site of conjugation and it is intriguing that modification of the remote 10-position would have such an effect. Although no clear trend exists, the addition of substituents containing heteroatoms, such as ethers **10** and **11** and nitrile **18**, appear to substantially reduce the formation of glucuronides while the addition of hydrocarbon and halides seems to have a lesser effect (compounds **20**, **22**, **25** and **27**). Although it appears that the addition of electron withdrawing groups to the 10-position reduces the electron density and nucleophilicity of the pyrazole nitrogen, electronic effects alone cannot explain the observed SAR and the combination of steric and electronic effects may determine the ability of the glucuronosyltransferases to recognize the compounds.

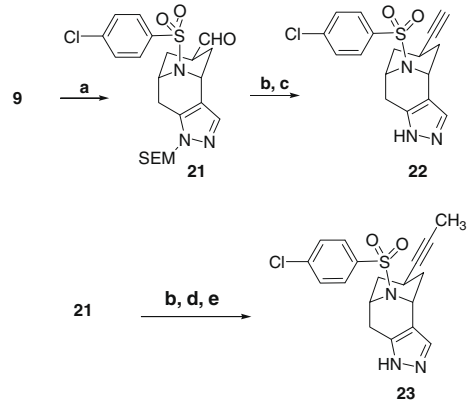
Since analogs bearing substitution on the carbon at the 10-position of the bicyclic scaffold demonstrated that it is possible to increase the in vitro metabolic stability of the inhibitors, it was decided to expand the series by replacing this carbon atom with a heteroatom. This replacement would both further lower the lipophilicity of the compounds and possibly provide further increases in the potency of the inhibitors. The general route for the preparation of these compounds is depicted in Scheme 7. Ozonolysis of furan **28** provided dialdehyde **30** which was elaborated to the morpholine analog **32**. Alternatively, the piperazine analog **34** was prepared via dihydroxylation of pyrrolidine **29** followed by oxidative cleavage to give dialdehyde **27** which was subsequently converted into compound **34**.



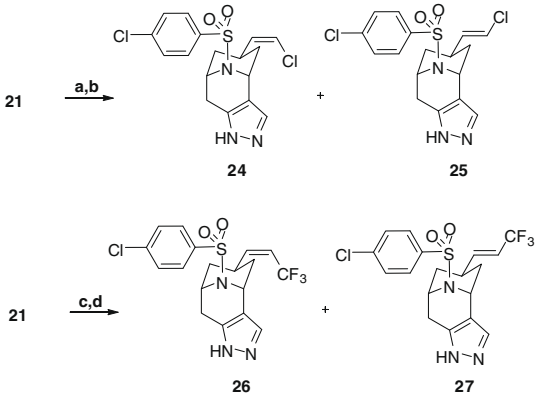
Scheme 3. Reagents and conditions: (a) 4-chlorobenzenesulfonyl chloride, pyridine, rt, 1 h, quant.; (b) $LiBH_4$, THF, rt, 2 h, 86%; (c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 2 h, 87%; (d) $NH_2OH{\cdot}HCl$, pyridine/EtOH, rt, 2 h; (e) MsCl, Et_3N, CH_2Cl_2, rt, 0.5 h; (f) NaOH, THF/H_2O, rt, 5 h.



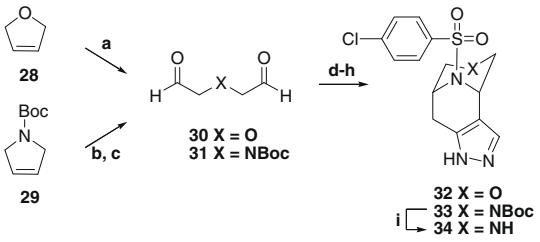
Scheme 4. Reagents and conditions: (a) DAST, CH_2Cl_2, 0 °C, 1 h; (b) NaOH, THF/H_2O, 60 °C, 3 h 31% (2 steps).



Scheme 5. Reagents and conditions: (a) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 2 h, 64%; (b) Ohira–Bestmann reagent, K_2CO_3, CH_3OH, rt, 18 h 70%; (c) HCl, dioxane/CH_3OH, 1 h, 60 °C, 90%; (d) LiHMDS, CH_3I, THF, −78 °C to rt, 4 h, 95%; (e) HCl, dioxane/CH_3OH, 4 h, 60 °C, quant.



Scheme 6. Reagents and conditions: (a) $ClCH_2PPh_3Cl$, ^nBuLi, THF, 0 °C, 1 h, 53%; (b) HCl/dioxane, CH_3OH, 2 h, 60 °C,; (c) $Ph_2P(O)CH_2CF_3$, TBAF, THF, −40 °C, 4 h, 12%; (d) HCl/dioxane, CH_3OH, 60 °C, 2 h.



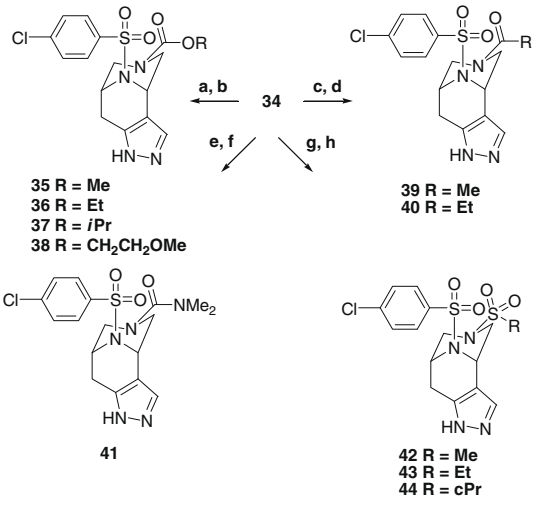
Scheme 7. Reagents and conditions: (a) O_3, CH_2Cl_2/CH_3OH, 10/1, v/v, Ph_3P, rt, 2 h; (b) OsO_4, NMO, acetone, rt, 18 h; (c) $NaIO_4$, THF/H_2O, rt, 3 h; (d) acetone-1,3-dicarboxylic acid, $BnNH_2$ NaOAc HCl (aq), 3 days, rt; (e) Pearlman's catalyst, H_2 (30 psi), CH_3OH, 12 h, rt; (f) 4-chlorobenzenesulfonyl chloride, Et_3N, CH_2Cl_2, 2 h, rt; (g) ethyl formate, NaOEt, THF/EtOH, 0.5 h, 60 °C; (h) hydrazine monohydrate, AcOH, EtOH, 1 h, rt; (i) HCl/dioxane, 2 h, rt.

In the nitrogen substituted series, piperazine **34** was converted into a series of carbamates, ureas, amides and sulfonamides upon treatment of **34** with the corresponding chloroformates, anhydrides, carbamoyl chlorides or sulfonamides as shown in Scheme 8. The γ-secretase inhibition and metabolic stability for these analogs are depicted in Table 2 and indicates that these piperazine analogs are generally less potent than the piperidine analogs described in Table 1. As with the previous series, the γ-secretase inhibitory activity is dependent upon the size of the substituents attached to the bicyclic ring system. This point is illustrated by comparing the loss of activity in the series of carbamates as the series moves from methyl (**35**) to ethyl (**36**), to isopropyl (**37**) and to the *tert*-butyl carbamate **33**. Interestingly, the carbamates are much more potent than the amides, and the sulfonamides possess only weak activity. In the absence of structural data the poor activity of the amides is difficult to rationalize. Generally, a heteroatom β to the 10-position results in favorable potency as is seen with carbamate **35**, ether **10** and nitrile **18** although this trend does not hold for the most potent compounds reported in this series, alkynes **22** and **23**. In general, all of the piperazine analogs have much improved oxidative and glucuronidation stability compared to the carbon analogs described in Table 1 which may be attributed to their overall lower lipophilicity.

Morpholine analog **32** demonstrated excellent in vitro metabolic properties both in terms of oxidative and glucuronidation stability (Table 3). Separation of the enantiomers provided the active enantiomer with an IC_{50} of 70 nM.

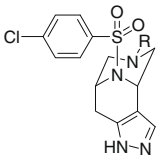
Thiomorpholine analog **48** was also synthesized starting from the known ketone **45** (Scheme 9).[14] N-Demethylation followed by sulfonamide formation and conversion of the ketone into a fused pyrazole gave compound **48** which demonstrates improved γ-secretase activity over morpholine **32**.

A select group of racemic compounds that displayed the most favorable combination of γ-secretase activity and metabolic stability were separated by chiral HPLC. The more active enantiomer for each compound was evaluated in rat to determine their in vivo pharmacokinetic parameters, the results of which are summarized in Table 4. It can be clearly seen that the improvements that were made in the in vitro metabolic stability of nitrile **18** and morpholine **32** compared to the parent compound **1** resulted in an improved in vivo pharmacokinetic profile with longer half-lives, lower clearance and improved oral bioavailability.



Scheme 8. Reagents and conditions: (a) ROC(O)Cl, Et_3N, CH_2Cl_2, rt, 2 h; (b) NaOH, THF/H_2O, 3 h, 70 °C (c) $(RCO)_2O$, pyridine, rt, 5 h; (d) NaOH, THF/H_2O, 2 h, rt; (e) *N,N*-dimethylcarbamyl chloride, Et_3N, CH_2Cl_2, 2 days, rt; (f) NaOH, THF/H_2O, 40 h, 70 °C; (g) RSO_2Cl, Et_3N, CH_2Cl_2, 1 h, rt; (h) NaOH, THF/H_2O, 2 h, 60 °C.

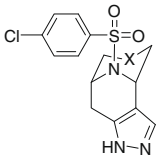
Table 2
γ-Secretase inhibition, and metabolic stability for compounds **34–44**



Compds[a]	R	GammaAPP IC_{50}[b] (nM)	OxMet% remaining[c] (m, h)	GlucMet% remaining[d] (m, h)
34	H	6443	29, 37	89, 76
33	CO_2tBu	5722	19, 21	na
35	CO_2Me	66	65, 83	89, 72
36	CO_2Et	202	39, 76	99, 86
37	CO_2iPr	1109	27, 53	90, 48
38	$CO_2CH_2CH_2OMe$	989	na	na
39	$C(O)CH_3$	1066	85, 82	94, 90
40	C(O)Et	826	85, 86	100, 98
41	$C(O)NMe_2$	175	56, 86	na
42	SO_2Me	5654	80, 84	96, 55
43	SO_2Et	2510	77, 89	na
44	SO_2cPr	4889	70, 98	95, 34

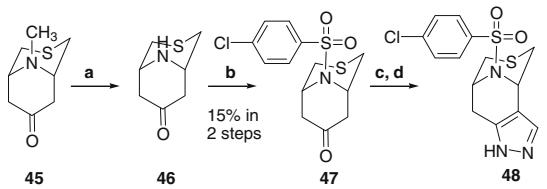
[a] Compounds are racemic unless stated otherwise.
[b] See Ref. 11.
[c] See Ref. 12.
[d] See Ref. 13.

Table 3
γ-Secretase inhibition, and metabolic stability for compounds **32** and **48**



Compds[a]	X	GammaAPP IC_{50}[b] (nM)	OxMet% remaining[c] (m, h)	GlucMet% remaining[d] (m, h)
32	O	151	80, 78	100, 86
32entA	O	70	78, 81	94, 71
32entB	O	6277	75, 100	93, 71
48	S	26	17, 47	57, 0

[a] Compounds are racemic unless stated otherwise.
[b] See Ref. 11.
[c] See Ref. 12.
[d] See Ref. 13.



Scheme 9. Reagents and conditions: (a) ACE, CH_2Cl_2, reflux, 6 h; (b) 4-chlorobenzenesulfonyl chloride, Et_3N, CH_2Cl_2, 2 h, rt, 15% (2 steps); (c) ethyl formate, NaOEt, THF/EtOH, 0.5 h, 60 °C; (d) hydrazine monohydrate, AcOH, EtOH, 1 h, rt, 25% (2 steps).

Table 4
Selected pharmacokinetic properties for compounds **1**, **18** and **32**

Compds	$t_{1/2}$ (min)	Clearance (mL/h/kg)	AUC (nmol h/mL)	*F*%
1	24	2335	0.16	2
18	61	1707	3.4	21
32	69	1873	2.9	19

In summary, we have expanded the structure–activity relationships of a series of *N*-bicyclic sulfonamide based γ-secretase inhibitors. The introduction of substituents in one region of the bicyclic scaffold resulted in improvements in the compounds' metabolic stabilities. These metabolic improvements were reflected in an improved in vivo pharmacokinetic profile. The advances reported here will allow further development of this series of compounds as disease modifying agents in the treatment of Alzheimer's Disease.

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12. 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 (m = mouse, h = human).
13. 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 50 μg/mL alamethacin at 37 °C in phosphate buffer (m = mouse, h = human).
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