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Piperidine-derived γ-secretase modulators

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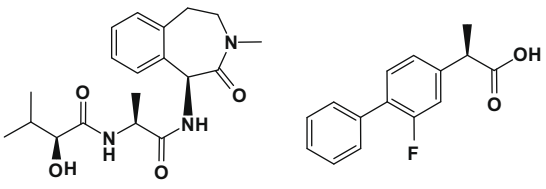
ABSTRACT

This Letter details the SAR of a novel series of piperidine-derived γ-secretase modulators. Compound **10h** was found to be a potent modulator in vitro, which on further profiling, was found to decrease Aβ42, increase Aβ38 and have no effect on Aβ40 levels. Furthermore, **10h** demonstrated excellent pharmacokinetic parameters in the mouse, rat and dog in addition to good CNS penetration in the mouse.

Alzheimer's disease (AD) is a devastating neurological disorder with bleak prognosis that results in cognitive impairment and loss of brain mass.[1] At present only the cognitive aspects of AD can be treated, thus novel treatments that slow or halt disease progression are highly desirable. AD was first characterised in 1906 by Alois Alzheimer following pathological examination of brain tissue.[2] This analysis revealed two underlying disease components, neurofibiliary tangles, composed of hyperphosphorylated tau protein, and amyloid plaques.[3] The latter are thought to be causative of the disease and consist of amyloid-beta (Aβ) peptides of 40–42 amino acids (Aβ40 and Aβ42, respectively).[4] Literature suggests that Aβ42 is the major pathogen, is less soluble than Aβ40 and seeds plaque formation, whereas Aβ40 does not initiate plaque formation itself but is a constituent of plaques.[4] These peptides are produced from amyloid precursor protein (APP) by the sequential action of β-secretase and γ-secretase, thus a significant effort has been invested to identify inhibitors of either enzyme to reduce Aβ production.[5] Several inhibitors of γ-secretase have been identified, such as LY-450139[6] (**1**, Fig. 1) and progressed through toxicological and clinical studies. Studies with γ-secretase inhibitors have uncovered several toxicological issues as it has been discovered that γ-secretase processes a number of substrates and in particular, inhibition of Notch processing has been found to manifest in toxicity of the gastrointestinal (GI) and immune system.[7]

Epidemiological analysis has shown that certain non-steroidal anti-inflammatory drugs (NSAIDs) lower the risk of developing AD.[8] Further analysis has shown this effect is independent of cyclooxygenase (COX) inhibition. NSAID derivatives devoid of COX inhibition,[9] such as tarenflurbil (MPC-7869, Flurizan™), **2** (Fig. 1) have been evaluated in phase 3 clinical trials for AD.[10] These derivatives have been shown to modulate, rather than inhibit, the action of γ-secretase.[11] Thus they shift the cleavage of γ-secretase to produce shorter, less pathogenic peptides such as Aβ40 and Aβ38.[12] In so doing, modulators do not alter the rate of enzyme processing or cause a build up of substrate.[13] Thus, substrates such as Notch are still processed and can effect their downstream signaling which should result in modulators having a better toxicological profile. However, one drawback has been that these compounds generally have weak in vitro activity and thus achieving sustained levels of compound in the brain to modulate γ-secretase is challenging.[10,14] Thus, new more potent γ-secretase modulators offer the potential of slowing or halting AD progression without the side effects associated with inhibitors.

We were interested in identifying novel, potent, γ-secretase modulators for the treatment of AD. Literature analysis revealed several carboxylic acid-derived templates, a selection of which is depicted in Figure 2. We were particularly interested in piperidine derivatives such as **5** and **6**.[15] Although still extremely lipophilic these compounds appeared less lipophilic than compounds such as **3**[16] and **4**.[17] Thus, we sought to synthesise and test novel com-



1, LY-450139 2, flurbiprofen

Figure 1. Structures of γ-secreatase inhibitor LY-450139 (1) and a γ-secretase modulator tarenflurbil (2).

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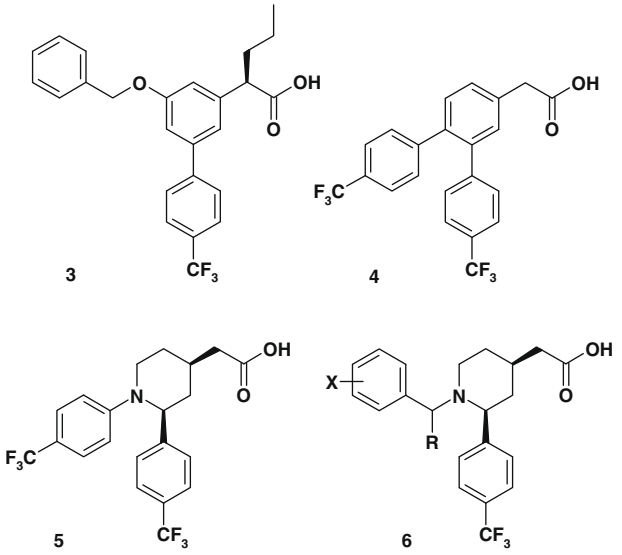


Figure 2. Selection of acetic acid γ-secretase modulators from patent application the literature.

pounds with heterocyclic aromatic groups on the 1-position of the piperidine to further lower lipophilicity.

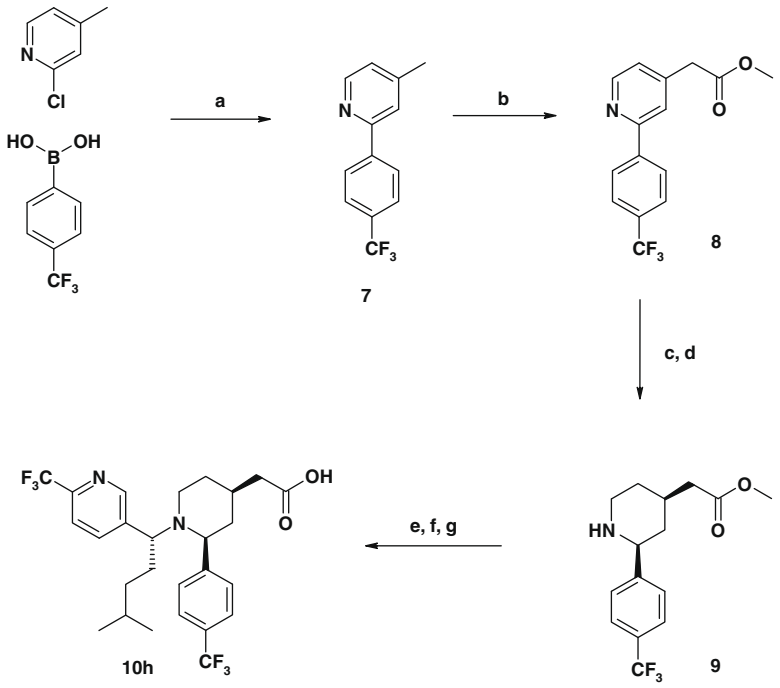
The synthesis of compounds is shown in Scheme 1, as exemplified by compound **10h**.[18] 2-Chloro-4-methylpyridine underwent Suzuki reaction with 4-trifluoromethylbenzene boronic acid to give **7**. Deprotonation of **7** and trapping with dimethylcarbonate gave ester **8**. Reduction of pyridine **8** gave the corresponding racemic cis-piperidine which underwent crystallization first with (L)-(+)-mandelic acid then (D)-(−)-mandelic acid to give enantiomerically pure piperidine **9**. The absolute configuration of **9** was confirmed by X-ray crystallographic analysis of the (D)-(−)-mandelic acid salt.

Piperidine **9** was then subjected to reaction with various aldehydes to give the corresponding imine which was subsequently trapped with benzotriazole followed by addition of organozinc reagents (which were either commercially available or could be prepared from the corresponding organomagnesium derivatives) to give compounds such as **10h**, upon ester saponification (Scheme 1).[18]

Compounds were incubated with SHSY5Y[19] cells overexpressing human APP Swedish variant for 48 h. The levels of Aβ42 and Aβ40 were determined by enzyme-linked immunosorbent assay (either Meso Scale Discovery [MSD] or AlphaLISA).[20] Compounds were also cross-screened for their ability to inhibit Notch processing.[20]

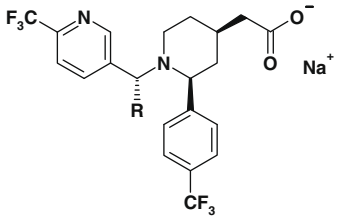
In the first round of structure–activity relationship (SAR) investigation we chose the trifluoromethylpyridyl unit as a starting point as 6-trifluoromethylpyridine-3-carbaldehyde was commercially available (Table 1). We were pleased to find that derivatives such as **10a** were moderately active at reducing Aβ42 secretion in our whole cell assay. Furthermore, we found that increasing the size of the R-group led to increased in vitro potency (**10b**–**i**) with maximal potency achieved with a 4–6 carbon unit. Introduction of an oxygen atom significantly reduced activity (compare **10g** to **10j**). Cyclic hydrocarbons were also active (**10k**) but aromatic substituents such as substituted phenyl (**10l**) and benzyl (**10m**) or phenethyl (**10n**) were slightly less active (Table 1).

Having identified several R-groups which provided good levels of in vitro potency, we selected the *iso*-amyl group and fixed this whilst we varied the pyridine with alternative aromatic heterocycles (Table 2). Initially we maintained the trifluoromethyl group in the 4-position relative to the connection point. Thus isomeric pyridine **11a**, containing a more basic nitrogen atom, was well tolerated. Addition of a second *N*-atom to give pyridazine **11b**



Scheme 1. Conditions and reagents: (a) $PdCl_2$(dppf)·CH_2Cl_2 (cat.), 1,2-dimethoxyethane, reflux, 20 h; 81%; (b) LDA, THF, −70 °C, 1 h, then dimethyl carbonate, −70 °C 10 min. then warm to rt, 89%; (c) PtO_2 (cat.), 4 N HCl in dioxane, MeOH, H_2, 50 °C, 50 psi, 3 h, 99%; (d) (L)-(+)-mandelic acid, *i*-PrOH, filtration and evaporation, (D)-(−)-mandelic acid, *i*-PrOH then CH_2Cl_2–2M Na_2CO_3, 38%; (e) 6-(trifluoromethyl)-3-pyridinecarbaldehyde, benzotriazole, PhMe, reflux (Dean–Stark), 5 h then evaporation; (f) DCM, 1-ZnX-3-methylbutane in Et_2O (X = Cl or Br, see Supplementary data for full details), 0 °C then rt 16 h; (g) 2 M NaOH, MeOH, 60 °C, 10 h.

Table 1
In vitro SAR for compounds **1**, **3** and **4** and **10a–n**



10a-n

Compds	R	Aβ42 pIC_{50}[a]	Aβ40 pIC_{50}[a] (%inhibition)[b]	Notch pIC_{50}[a] (%inhibition)[b]
1	n/a	7.4 ± 0.13	7.4 ± 0.13	6.5 ± 0.18
3	n/a	5.4 ± 0.26[c]	⩽4.8 (32)[d]	<4.7 (20)
4	n/a	5.7[e]	<4.7 (13)	<4.7 (23)
10a	Et	5.0 ± 0.14	<4.7 (20)	<4.7 (10)
10b	*i*-Pr	5.4 ± 0.17	<4.7 (24)	<4.7 (21)
10c	*c*-Pr	5.1 ± 0.14	4.3 ± 0.10	<4.7 (23)
10d	*n*-Bu	6.2 ± 0.15	4.8 ± 0.11	<4.7 (33)
10e	*i*-Bu	6.2 ± 0.09	4.5 ± 0.07	<4.7 (25)
10f	CH_2-*c*-Bu	6.6 ± 0.07	5.5 ± 0.01	<4.7 (17)[e, f]
10g	*n*-Pentyl	5.9 ± 0.16	5.1 ± 0.48	4.8 ± 0.03
10h	*i*-Amyl	6.5 ± 0.33	5.2 ± 0.72	<4.7 (24)[e, f]
10i	*n*-Hex	6.3 ± 0.12	4.8 ± 0.06	5.3 ± 0.45
10j	$-(CH_2)_3$–OMe	5.0 ± 0.15	4.5 ± 0.07	<4.7 (10)
10k	Cyhex	5.4 ± 0.22	4.6 ± 0.02	nt[g]
10l	*p*-CF_3phenyl	5.9 ± 0.21	⩽4.8 (33)[d]	5.1 ± 0.03
10m	CH_2Ph	5.8 ± 0.18	5.0 ± 0.18	<4.7 (34)
10n	CH_2CH_2Ph	5.7 ± 0.24	<4.7 (40)[h]	<4.7 (32)

[a] Values are means of at least two experiments ± standard deviation.
[b] %Inhibition at 20 μM.
[c] IC_{50} = 3.98 μM, lit. IC_{50} 1–10 μM.
[d] Single experiment giving pIC_{50} 4.8, all other experiments gave pIC_{50} <4.7.
[e] Single experiment.
[f] Single experiment giving pIC_{50} excluded as max asymtote <40%.
[g] nt = not tested.
[h] Two pIC_{50} values excluded as the asymptote maximums were very partial (~50%).

resulted in a slight decrease in potency. However, pyrimidine **11c** restored activity whereas pyrimidine isomer **11d** showed activity intermediate between **11b** and **11c**. The pyrazine derivative **11e** also displayed activity. Compounds **11f–i** demonstrated that the trifluoromethyl group could be moved around the ring or could be replaced by small alkyl groups. Although the majority of compounds had no effect on Notch processing (pIC_{50} <4.7), some compounds such as **11a** and **11i** did exhibit weak activity against Notch processing. However, these compounds were significantly more potent at inhibiting Aβ42 production.

Further profiling of a selection of compounds in a cell based assay (24 h incubation)[20] demonstrated a modulatory profile. Levels of Aβ42 were decreased in a concentration-dependent manner, whilst levels of Aβ38 were increased in a concentration-dependent manner and Aβ40 levels were unaffected (Table 3). Compounds also had no effect on total Aβ levels indicating the rise in Aβ38 compensates for the decrease in Aβ42. This is in contrast to the profile of inhibitors such as **1** (LY-450139) which decreases levels of all Aβ species (and therefore total Aβ). Furthermore, the compounds described in Table 3 were found not to be cytotoxic. Compound **10h** had a weak effect on cellular viability at high concentrations (30 and 100 μM). However, no cytoxicity was observed with this compound at the concentrations at which it lowered Aβ42.

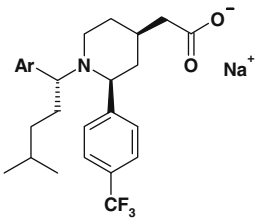
Following in vitro potency assessment compounds with a pIC_{50} value ⩾6 were assessed in terms of in vitro metabolic stability in rat and human liver microsomes and for inhibition of five human CYP isoforms (CYP1A2, 2C9, 2C19, 2D6 and 3A4). Selected analogues were profiled to assess their potential as time-dependent CYP inhibitors. Based on these data, compounds **10h** and **11d** emerged as the most interesting compounds, their in vivo pharmacokinetic profiles are listed in Table 4. Compounds **10h** and **11d** demonstrated low clearance and excellent bioavailability in the rat and dog. Compound **10h** was also profiled in the mouse where the pharmacokinetic parameters were found to be similar to the rat and dog, thus demonstrating consistent pharmacokinetics across species.

One of the issues with NSAID-derived γ-secretase modulators, such as **2** and **3** is that they have poor penetration of the central nervous system.[10,14] Thus, it is desirable to identify γ-secretase modulators with good CNS penetration (high brain-to-blood ratios, Br:Bl). In order to assess the potential of compounds from this series to access the CNS, compound **10h** was dosed orally at 5 mg/kg to mice and blood and brain samples were collected 2 h post-dose (Table 5).

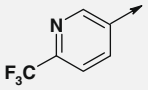
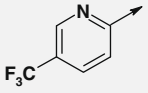
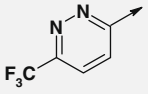
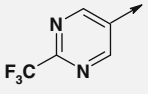
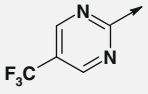
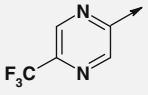
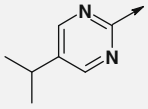
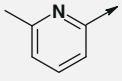
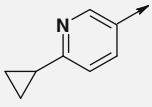
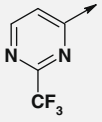
Thus compound **10h** demonstrated good penetration of the CNS and showed that a 5 mg/kg oral dose could deliver concentrations in excess of 4 μM which is significantly higher than the in vitro IC_{50} (0.3 μM) value indicating that compound **10h** has the potential to deliver in vivo efficacy at low doses.

In summary, we have identified a potent and selective γ-secretase modulator {(2*S*,4*R*)-1-{(1*R*)-4-methyl-1-[6-(trifluoromethyl)-3-pyridinyl]pentyl}-2-[4-(trifluoromethyl)phenyl]-4-piperidinyl}-acetic acid, **10h**, which has good pharmacokinetic properties in the mouse, rat and dog. Furthermore, this compound achieved good brain exposure in the mouse and is thus suitable to explore the efficacy of γ-secretase modulator in this species. Data from in vivo efficacy studies will be reported in due course.

Table 2
In vitro SAR for heterocyclic derivatives **10h** and **11a–i**



11a-i

Compd	Ar	Aβ42 pIC_{50}[a]	Aβ40 pIC_{50}[a] (%inhibition)[b]	Notch pIC_{50}[a] (%inhibition)[b]
1	n/a	7.4 ± 0.13	7.4 ± 0.13	6.5 ± 0.18
3	n/a	5.4 ± 0.26[c]	⩽4.8 (32) [d]	<4.7 (20)
10h		6.5 ± 0.33	5.2 ± 0.72	<4.7 (24)[e]
11a		6.5 ± 0.25	4.9 ± 0.16	4.9 ± 0.06
11b		5.9 ± 0.23	4.6 ± 0.08	<4.7 (17)
11c		6.4 ± 0.07	4.7 ± 0.01	4.7 ± 0.01
11d		6.1 ± 0.09	<4.7 (17)	4.6 ± 0.01
11e		6.4 ± 0.13	4.7 ± 0.21	<4.7 (21)
11f		6.1 ± 0.04	<4.7 (22)	<4.7 (27)
11g		5.9 ± 0.16	4.8 ± 0.28	<4.7 (4)
11h		6.2 ± 0.27	<4.7 (31)	<4.7 (15)
11i		6.4 ± 0.14	4.9 ± 0.09	5.4 ± 0.78

[a,b,c,d] See footnotes in Table 1.
[e] Single experiment giving pIC_{50} excluded as max asymtote <40%.

Table 3
In vitro SAR for compounds **1**, **3** and **4** and **10b–d**, **h** and **i** showing that the piperidine derivatives are γ-secretase modulators

Compd	Aβ42 pIC_{50}[a]	Aβ40 pIC_{50}[a]	Aβ38 pEC_{50}[a]	Aβtotal pIC_{50}[a]	Cytotox pIC_{50}[b]
1	6.9	6.7	6.9[c]	7.0	<4.0
3	5.8	<4.0	5.9	<4.0	<4.0
4	5.7	<4.0	5.1	<4.0	<4.0
10b	6.0	<4.0	5.0	<4.0	<4.0
10c	6.0	<4.0	5.0	<4.0	<4.0
10d	6.0	4.4	5.5	<4.0	<4.0
10h	6.0	4.4	6.3	4.0	4.0
10i	6.0	4.6	6.3	4.0	<4.0

[a] Values are single experiments.
[b] WST-1 cytotoxicity assay.
[c] Value is pIC_{50} as inhibitors cause a decrease in Aβ38 production.

Table 4
In vivo DMPK for compounds **10h** and **11d**

Species	Parameter	**10h**[b]	**11d**[c]
Mouse[d]	CLb (mL/min/kg)	4 ± 1	n.t.[a]
	V_{dss} (L/kg)	1.4 ± 0.1	n.t.[a]
	$t½$ (h)	4.3 ± 0.9	n.t.[a]
	F_{po}[g] (%)	>100	n.t.[a]
Rat[e]	CLb (mL/min/kg)	4 ± 1	9 ± 2
	V_{dss} (L/kg)	2.3 ± 0.3	3.0 ± 1
	$t½$(h)	6.6 ± 0.8	3.0 ± 0.3
	F_{po} (%)	>100	95 ± 4
Dog[f]	CLb (mL/min/kg)	3 ± 0.3	5.0
	V_{dss} (L/kg)	1.1 ± 0.1	1.2
	$t½$ (h)	5.2 ± 0.5	3.1
	F_{po} (%)	72 ± 5	>100

[a] nt = not tested.
[b] Data are the mean from three animals for all species.
[c] Data from rat studies are the mean from three animals, data from dog studies are from a single animal.
[d] Compound **10h** dosed at 3 mg/kg (iv) and 10 mg/kg (po).
[e] Compound **10h** dosed at 1 mg/kg (iv) and 3 mg/kg (po), compound **11d** dosed at 1 mg/kg (iv) and 2 mg/kg (po).
[f] Both compounds dosed at 1 mg/kg (iv and po).
[g] Oral bioavailability as sodium salt, vehicle = 1% methylcellulose.

Table 5
Mouse CNS penetration data for compounds **10h**

Compd	Blood concn (μM)	Brain concn (μM)	Br:Bl
10h[a]	5.601 ± 1.029	4.199 ± 1.021	0.74 ± 0.06

[a] Compound dosed orally in (5 mg/kg) 1% (w/v) methylcellulose aq. Values are the mean from three mice. Samples taken 2 h post-dose.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.08.072.

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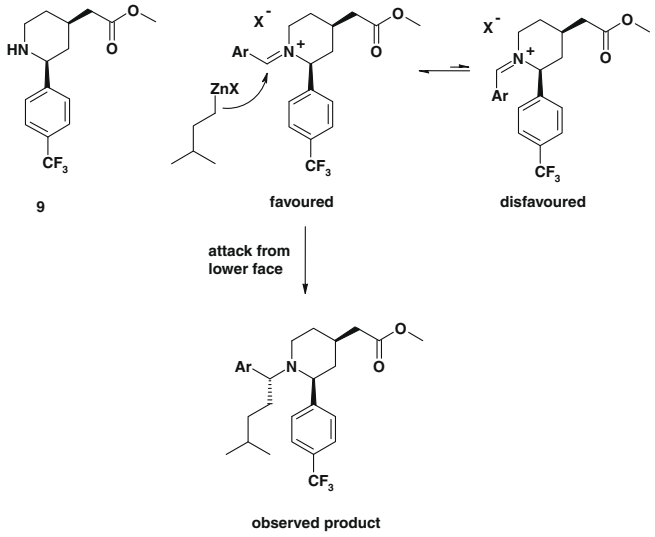
with attack from the least hindered *Re*-face. The (*Z*)-iminium ion is presumably disfavoured due to the steric clash between the Ar group and the substituted phenyl ring in the 2-position of the piperidine.



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