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3,4-Fused cyclohexyl sulfones as γ-secretase inhibitors

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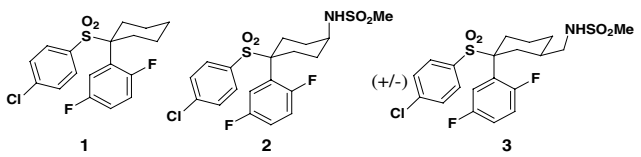
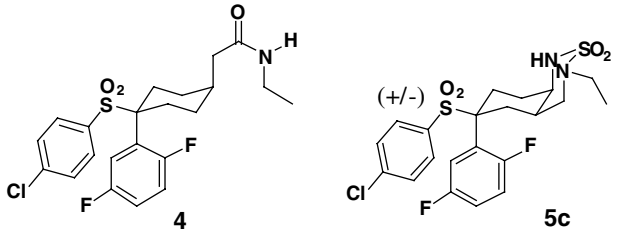
Abstract—The 3,4-fused sulfamides, sulfonamides and sulfone have been identified as highly potent γ-secretase inhibitors. Evaluation of the SAR of substitution within these series has allowed the identification of a range of compounds which significantly reduce brain Aβ in transgenic mouse models and thus have potential as possible treatments for Alzheimer's disease.

Alzheimer's disease (AD) is characterized by progressive cognitive decline accompanied by the deposition of plaques composed of the neurotoxic 40–42 amino acid peptide amyloid-β (Aβ) and by increased levels of soluble Aβ. One of the major hypotheses for the progression of AD is that the extracellular accumulation of Aβ is the primary pathological event leading to neurodegeneration, dementia and ultimately death. In order to test this hypothesis and potentially to provide pharmacological agents to arrest the progress of the disease, the inhibition of Aβ production is of particular interest. The release of Aβ is the result of cleavage of β-amyloid precursor protein (β-APP) by two proteases. The first cleavage of β-APP by β-secretase produces a β-APP C-terminal fragment which is cleaved within the cell membrane by the aspartyl protease γ-secretase to release Aβ. The identification of a selective orally active γ-secretase inhibitor has been targeted as an attractive way to test the amyloid hypothesis.[1]



As part of our ongoing medicinal chemistry programme the cyclohexane **1**[2] (3 nM) and the sulfonamides **2**[3] (4.2 nM) and (±)-**3**[3] (1.8 nM) were identified as potent γ-secretase inhibitors and previously disclosed.[4–7]

The tolerance for substitution of the cyclohexyl ring was significant in that it allowed improved absorption properties to be achieved. The compounds did, however, show a relatively short half-life in rodent (e.g., **2**: F 31%, $t_{1/2}$ 1.1 h in rat) and high turnover in rat liver microsomes (**2** 33%; **3** 78%).[8] We set out to synthesise stable analogs of these sulfonamides which should also take advantage of the known lipophilic binding pocket identified from the X-ray crystal structure of the potent inhibitor **4**.[9]



The relatively high potency of **2** and **3** compared to many of the substituted cyclohexanes which we had examined[3] led us to believe that a single sulfonamide binding site existed that could be accessed from either

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the 3 or 4 positions of the cyclohexane ring. A 3,4-fused cyclic sulfamide was postulated to take full advantage of this binding site, introduction of an N-substituent would then potentially allow us to access the lipophilic binding site. It was hypothesised (Fig. 1) that the ethyl substituted 3,4-fused cyclic sulfamide (±)-**5c** (orange carbons) would overlay both the hydrogen bond acceptor (SO_2) and the lipophilic group with the same groups in the X-ray crystal structure of **4** (grey carbons).[10]

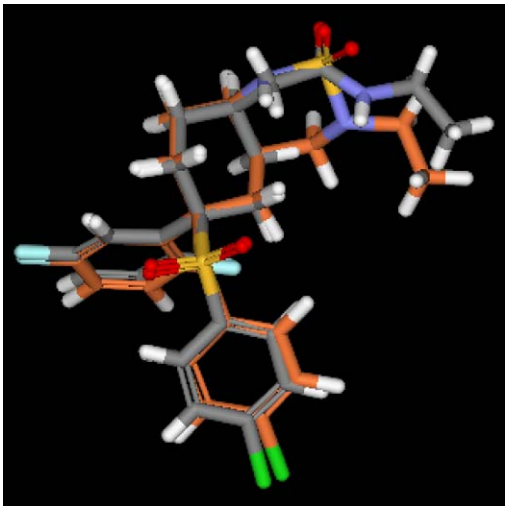
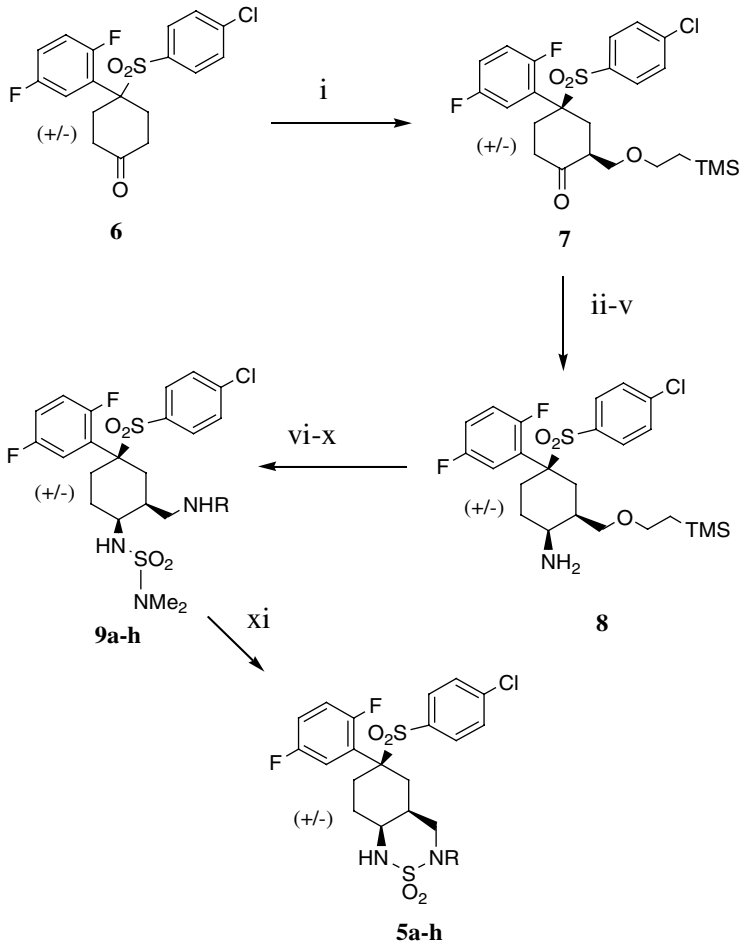


Figure 1. Overlay of the X-ray structure of **4** (grey carbons) with the minimised structure of the **5c** (orange carbons).

A versatile cyclic sulfamide synthesis was developed (Scheme 1) which allowed exploration of the lipophilic binding pocket by variation of the nitrogen substituent at the final stage (see Tables 1–3).

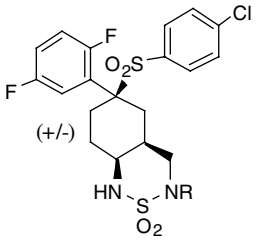
The cyclohexanone **6**[2] was alkylated with SEM–Cl to give, as a single isomer,[11] the protected α-hydroxymethyl ketone (±)-**7**.[12] Stereoselective reduction with sodium borohydride gave the *anti*-alcohol which underwent smooth azide displacement (via the mesylate) and subsequent reduction to give the *syn*-amine (±)-**8**.

Deprotection of the alcohol was followed by selective sulfonylation of the amine to afford the *N*,*N*-dimethylsulfamide. Oxidation of the primary alcohol to the aldehyde facilitated the introduction of an alkyl substituted amine (±)-**9**. This aminosulfamide underwent a facile cyclisation to the cyclic sulfamide (±)-**5**



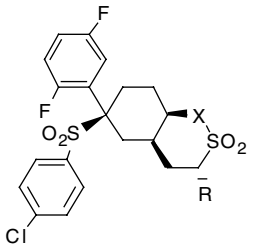
Scheme 1. Reagents and conditions: (i) LHMDS, THF, SEM–Cl, −78 °C; 60%; (ii) $NaBH_4$, −20 °C, IPA, 80%; (iii) MsCl, NEt_3, DCM, 97%; (iv) NaN_3, DMF, 90 °C, 75%; (v) PPh_3, THF, H_2O, 95%; (vi) $BF_3{\cdot}OEt_2$, DCM, 95%; (vii) Me_2NSO_2Cl, NEt_3, DMA, DCM, 80%; (vii) Dess–Martin periodinane, DCM, 80%; (ix) RNH_2, EtOH; (x) $NaBH_4$; (xi) THF, reflux, 70% (3 steps).

Table 1. Variation of properties with the introduction of N-substituents



R	Compound	IC_{50} (nM)[14]	Microsomal turnover (%)[8]
H	**5a**	6.18 (±2.0)	9
Me	**5b**	0.90 (±0.3)	17
Et	**5c**	0.40 (±0.1)	46
^{n}Pr	**5d**	1.17 (±0.7)	63
^{i}Pr	**5e**	0.41 (±0.1)	0
^{c}Pr	**5f**	0.19 (±0.2)	14
^{c}Bu	**5g**	0.26 (±0.04)	68
^{t}Bu	**5h**	1.39 (±0.5)	15

Table 2. Variation of biological properties with the cyclic sulfonamides and sulfones



X	R	Compound	IC_{50} (nM)[14]	Microsomal turnover (%)[8]
NH	Me	**12a**	0.08 (±0.02)	20
NH	Et	**12b**	0.06 (±0.05)	7
NH	^{n}Pr	**12c**	0.24 (±0.05)	32
CH_2	Et	**13**	0.76 (±0.06)	15

with extrusion of dimethylamine by heating in tetrahydrofuran.

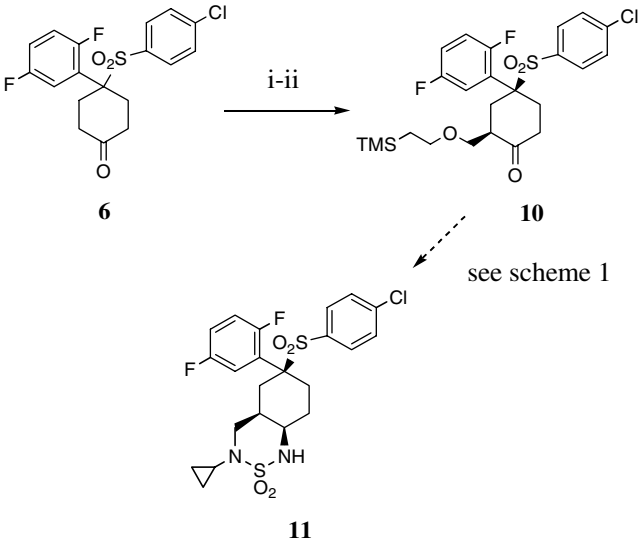
The resultant racemic cyclic sulfamides exhibited potent γ-secretase inhibition, indicating that the lipophilic binding pocket had been accessed. For unbranched alkyl groups optimal activity was seen with (±)-**5c** (R = Et), while small branched alkyl groups, for example, (±)-**5f** (R = ^{c}Pr) were of greatest potency. The larger alkyl-substituted analogues showed an increased turnover in rat liver microsomes (R = ^{c}Bu (±)-**5g**) as did the straight chain analogues (R = Et (±)-**5c** and R = ^{n}Pr (±)-**5d**).

An asymmetric synthesis was developed based on the chiral deprotonation[13] of the ketone **6** and trapping as a trimethylsilyl enol ether followed by a Tin (IV) chloride catalysed alkylation with SEM–Cl to give **10** (Scheme 2). This chemistry facilitated identification of the enantiomerically pure cyclopropyl cyclic sulfamide **11** (IC_{50} 0.04 ± 0.01 nM) for in vivo evaluation.

The stability of the unsubstituted ring system **5a** and the strong relationship between turnover and the N-substituent of the cyclic sulfamide led us to believe this was a major site of metabolism. We therefore targeted the carbon-linked derivatives, the cyclic sulfonamides **12a–c** (Scheme 3) and the cyclic sulfone **13** (Scheme 4).

The enantiomerically pure amine **14** obtained as outlined in Schemes 1 and 2 was N-sulfonylated and then allylated on nitrogen under forcing conditions to give the allyl sulfonamide **15**. Deprotection and activation as the tosylate gave the cyclisation precursor **16**. Treatment with butyl lithium achieved a clean cyclisation to the sultam. The sultam was deprotonated at low temperature before treating with alkyl iodide and allowing to warm to room temperature overnight. This gave very good selectivity (>19:1) for the *anti*-alkyl product. Nickel catalysed deprotection gave the desired cyclic sulfamide containing an equatorial alkyl group.

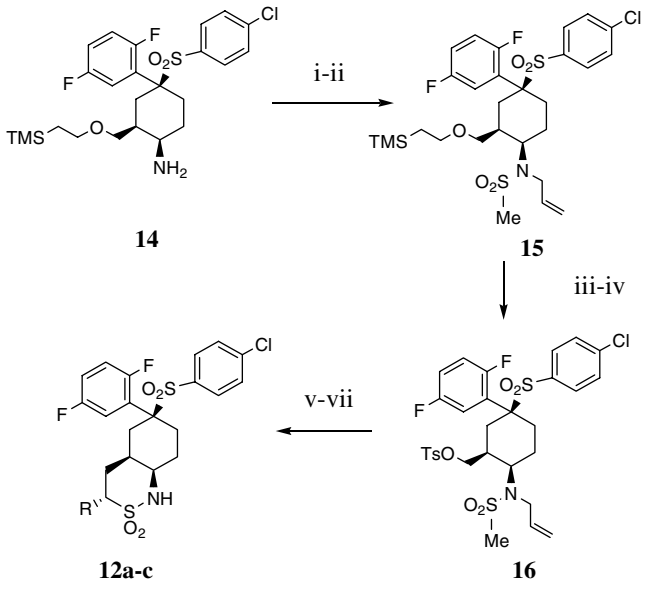
The enantiomerically pure ketone **10**[15] was homologated using a Horner–Emmons reaction to give the vinyl sulfone which could be stereospecifically reduced using



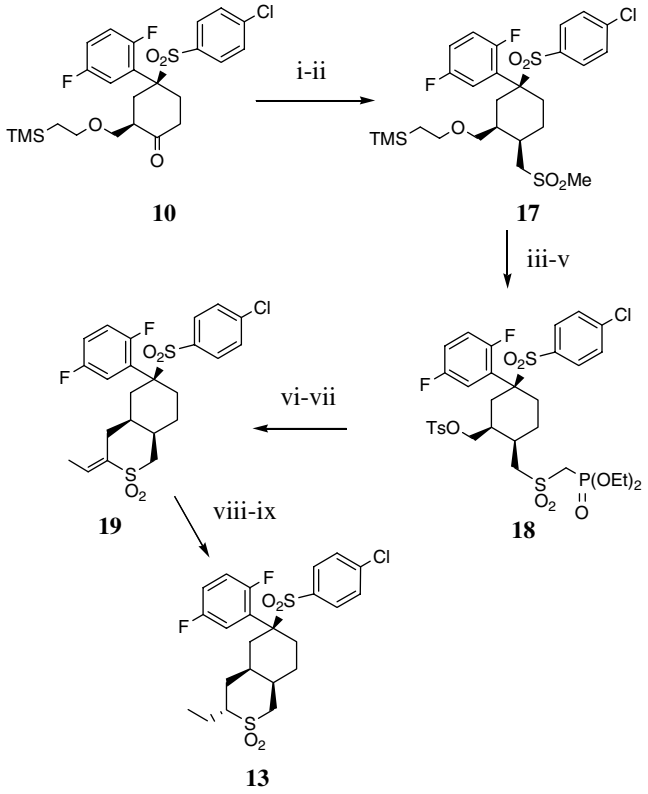
Scheme 2. Reagents and conditions: (i) BuLi, LiCl, [S-(R*,R*)]-(−)-bis-α-methylbenzylamine, −100 °C, TMS–Cl, THF; (ii) 1 mol% $SnCl_4$, −40 °C, SEM–Cl, DCM 75%.

Table 3. Variation of in vivo efficacy properties

Compound	In vitro IC_{50} (nM)[14]	[Plasma] EC_{50} (nM)[18]	[Brain] EC_{50} (nM)[18]	Brain/plasma ratio	ED_{50} at 4 h (mg/kg)[18]
11	0.04 (±0.01)	104 (±42)	20 (±4)	0.16	11.4 (±1.2)
12b	0.06 (±0.05)	380 (±89)	88 (±16)	0.18	2.8 (±1.2)
13	0.76 (±0.06)	761 (±216)	327 (±90)	0.41	3.9 (±1.2)



Scheme 3. Reagents and conditions: (i) MsCl, TEA, DCM, 95%; (ii) allyl bromide, NaH, DMF, 70 °C, 70%; (iii) $BF_3{\cdot}OEt_2$, DCM, 95%; (iv) TsCl, pyridine, DMAP, 80%; (v) ^{n}BuLi, THF, −30 °C to rt, 85%; (vi) LiHMDS, RI, −78 °C to rt, 90%. (vii) DIBAL-H, $(dppp)NiCl_2$, toluene, 70%.



Scheme 4. Reagents and conditions: (i) ^{n}BuLi, $MeSO_2CH_2P(O)(OEt)_2$, THF −78 °C, 78%; (ii) L-Selectride™, THF −40 °C, 90%; (iii) LiHMDS, diethyl chlorophosphonate, 68%; (iv) $BF_3{\cdot}OEt_2$, DCM, 85%; (v) TsCl, pyridine, DMAP, 90%; (vi) BuLi, −78 °C, THF 76%; (vii) LiHMDS, acetaldehyde 90%; (viii) 10% Pd/C EtOH, H_2 (1 atm), 95%; (ix) KO^{t}Bu, THF, 89%.

L-Selectride™ to give the *syn*-sulfone **17**. At this stage the methyl sulfone was activated as the phosphonate and then O-deprotection and activation were carried out as in Scheme 3. A cyclisation to the phosphonyl-3,4 fused cyclic sulfone was achieved in good yield.

A second Horner–Emmons reaction was carried out to provide the unsaturated sulfone **19**. Reduction of the double bond by hydrogenation gave the undesired *syn*-alkyl ring substituent (>19:1 ratio), this compound showing no inhibition of γ-secretase at concentrations up to 9 μM. The desired *anti*-alkyl compound **13** could be isolated cleanly after a base catalysed epimerisation.

The sulfonamides were highly potent inhibitors of γ-secretase and showed a similar SAR of straight chain alkyl substitution to that seen with the sulfamides (i.e., ethyl was optimal). There was, however, no further benefit seen from the introduction of branched alkyl groups (data not shown). The ethyl substituted cyclic sulfonamide **12b** was also optimal in terms of rat microsomal stability and showed reduced turnover relative to the corresponding sulfamides and the acyclic sulfonamides **2** and **3**.

The ethyl substituted sulfone **13** showed somewhat reduced in vitro inhibition of γ-secretase compared to the sulfonamide **12b** but was stable in rat liver microsomes.

With these data in hand we set about evaluating the in vivo properties of the compounds using the APP-YAC mouse model.[16] The brain levels of DEA-extractable Aβ[17] at 4 h post-oral dosing, relative to vehicle and a positive control γ-secretase inhibitor together with the plasma and brain drug concentrations were determined for the key compounds **11**, **12b** and **13**. The sulfone **13** was considered an interesting molecule to investigate in vivo because the absence of the sulfonamide NH was postulated to offer an improvement in terms of brain penetration.

In assessing the relative merits of the compounds we noted that the in vitro IC_{50} and brain level required for efficacy tracked well with each other. The highly potent cyclic sulfamide **11** had efficacy at very low brain concentrations, but relatively poor plasma levels were obtained after oral dosing leading to an ED_{50} of 11.4 mg/kg. The cyclic sulfonamide **12b** was shown to be efficacious at lower doses due to the improved pharmacokinetics observed. The cyclic sulfone **13** required higher brain levels to show efficacy but the expected improvement in brain penetration and the good pharmacokinetics meant that this compound compared well with the cyclic sulfonamide **12b** in terms of dose required for efficacy.

Separate evaluation showed that the compounds detailed in this communication inhibit notch cleavage at concentrations comparable to those required to inhibit Aβ production, consistent with data from several existing series of γ-secretase inhibitors.[19]

In conclusion, we have shown that by a combination of conformational restriction and exploitation of a well-defined lipophilic binding pocket, we can reliably achieve excellent in vitro γ-secretase inhibition. In addi-

tion, we have been able to reduce microsomal turnover and achieve good plasma levels after oral dosing. We have identified three different stable core structures with complementary in vivo properties. In the case of the cyclic sulfamides we achieved in vivo potency at low brain levels. With the cyclic sulfonamides we were able to add to this good pharmacokinetics after oral dosing. The cyclic sulfones offer an alternative series where improved brain–plasma ratio could lead to a more desirable profile for our target central inhibition of γ-secretase.

Acknowledgment

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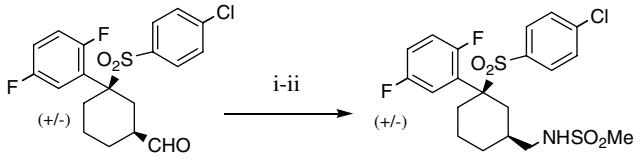

20 **3**

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