Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 3839–3842

3-Substituted *gem*-cyclohexane sulfone based γ-secretase inhibitors for Alzheimer's disease: Conformational analysis and biological activity

Richard A. Jelley,[a,*] Jason Elliott,[a] Karl R. Gibson,[a] Timothy Harrison,[a] Dirk Beher,[b] Earl E. Clarke,[b] Huw D. Lewis,[b] Mark Shearman[b] and Jonathan D. J. Wrigley[b]

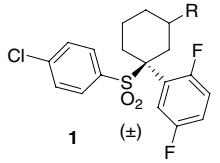
[a]*Department of Medicinal Chemistry, Merck Sharp and Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*
[b]*Department of Molecular and Cellular Neuroscience, Merck Sharp and Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*

Received 30 January 2006; revised 6 April 2006; accepted 8 April 2006
Available online 6 May 2006

Abstract—Previously, chemistry effort on the *gem*-cyclohexane series of γ-secretase inhibitors has focused on the 4-position of the cyclohexane ring. Recently chemistry has been directed towards the 3-position and substitution here has also provided compounds with high γ-secretase activity.

Alzheimer's disease (AD) is the major cause of dementia in the developed world. It is characterized clinically by a progressive decline in memory and cognitive function which ultimately leads to death. For more than a decade, it has been proposed that the neurodegeneration observed in AD is due to the accumulation and aggregation of amyloid β-peptide (Aβ) into extracellular proteinaceous plaques.[1] The potential consequence of plaque formation is the loss of synaptic and neuronal function. Aβ-peptides are formed from the sequential cleavage of amyloid precursor protein (APP) by two proteases (β- and γ-secretase). It is the subsequent aggregation and precipitation of Aβ-peptide that leads to the formation of amyloid plaques. One particularly compelling approach to the treatment of AD would be the inhibition of either of the two proteases involved in the formation of Aβ-peptide. Based on this hypothesis, a chemistry programme was initiated to develop a selective inhibitor of γ-secretase activity in order to reduce Aβ and delay the onset and progression of Alzheimer's disease.

In a previous publication from our laboratories we reported the identification of a novel series of γ-secretase inhibitors.[2] In the substituted *gem*-cyclohexane series of γ-secretase inhibitors, work had primarily focused on the 4-position of the cyclohexane ring. Recent chemistry has been directed towards substituted analogues at the 3-position, for example, **1**. This communication describes the synthesis of compounds which illustrate how the conformation of the substituents on the cyclohexane ring relates to in vitro γ-secretase activity.

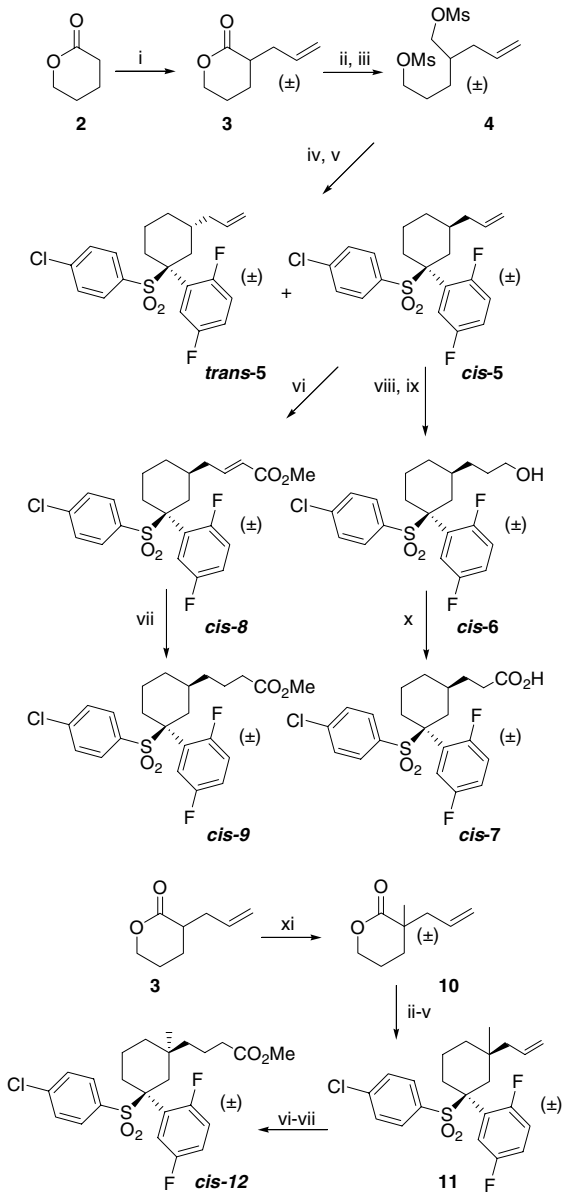


1 (±)

The *gem*-substituted cyclohexanes were initially prepared as outlined in Scheme 1. Reaction of δ-valerolactone **2** with lithium bis(trimethylsilyl)amide and allylbromide gave **3** in moderate yield. Facile reduction of the lactone ring with lithium borohydride and subsequent activation of the diol as the bis-mesylate **4** allowed double alkylation of **13**[2] to generate the *gem*-cyclohexane. The resulting mixture of diastereoisomers *cis*-**5** and *trans*-**5** was

Keywords: *gem*-Cyclohexane; Sulfone; γ-Secretase inhibitors; Alzheimer's disease; Conformational analysis; Biological activity.
* Corresponding author. Tel.: +44 1279 600767; fax: +44 7970 075142; e-mail: richard_jelley@yahoo.co.uk

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.04.019



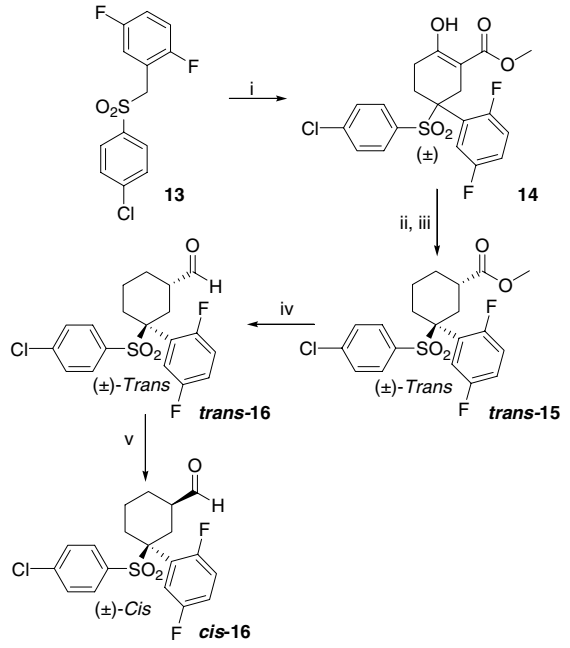
Scheme 1. Reagents and conditions: (i) LHMDS, allyl bromide, THF, −78 °C to rt, 35%; (ii) $LiBH_4$, THF, 0 °C to rt, 71%; (iii) MsCl, EtN^iPr_2, CH_2Cl_2, rt, 73%; (iv) **13**, NaH, KO^tBu, THF, rt; (v) separate diastereoisomers, (1:1) 40%; (vi) methylacrylatetricyclohexylphosphine[1,3-bis(2,4,6-trimethyl phenyl)-4,5-dihydroimidazol-2ylidene][benzylidine]ruthenium(IV) dichloride, CH_2Cl_2, rt, 90%; (vii) H_2, 35 psi, Rh/C, EtOAc/EtOH, 70%; (viii) BH_3·THF, THF, 0 °C, 4 h; (ix) NaOH, H_2O_2, 76%; (x) PDC, DMF, rt, 31%; (xi) NaH, MeI, DMF, 75%.

obtained as a (1:1) mixture and separated using flash chromatography. Each diastereoisomer was processed separately using the same chemistry, however, only *cis* structures are shown in Scheme 1. The terminal olefin was functionalized using a cross-metathesis reaction with methyl acrylate utilising Grubb's second generation catalyst.[3] The unsaturated ester *cis*-**8** was obtained. Hydrogenation using rhodium on carbon gave the desired saturated ester *cis*-**9** without any cleavage of the aromatic chlorine. Alternatively hydroboration of *cis*-**5** using borane–tetrahydrofuran complex at low temperature gave the truncated alcohol, *cis*-**6**. Subsequent conversion to the acid *cis*-**7** was achieved using pyridinum dichromate in DMF.

By starting with the methyl analogue **10** (where a methyl group was introduced at the 3-position of the cylohexane ring after the initial allylation step) a second quaternary centre was generated. This ultimately gave compound *cis*-**12** after employing identical chemistry to that described previously.

An alternative route to 3-substituted *gem*-cyclohexanes is illustrated in Scheme 2. Double addition of methyl acrylate to **13**[2] using sodium hydride and potassium *tert*-butoxide as base gave the β-keto ester **14** in moderate yield. The ketone was selectively reduced by conversion to the enol mesylate and treatment with sodium borohydride/nickel chloride to give a moderate yield of the ester *trans*-**15** as a 1:10 mixture of *cis*:*trans* diastereoisomers. This reaction was complicated by competing reduction of the arylchloride moiety; however this by-product was easily separated by chromatography. Attempts to epimerise the *trans*-ester to the *cis*-isomer failed. However, by reducing the ester to the aldehyde *trans*-**16** and treating with potassium carbonate in methanol, complete epimerisation to the *cis*-aldehyde *cis*-**16** (where both the aryl sulfone and the aldehyde occupy an equatorial position) was achieved.

Previous results with 4-substituted *gem*-cyclohexane sulfones[2] have demonstrated the importance of an axially disposed aryl and an equatorial sulfone for high enzyme inhibition. The large sulfone group dictates the



Scheme 2. Reagents and conditions: (i) methylacrylate, NaH, KO^tBu, THF, rt, 45%; (ii) MsCl, EtN^iPr_2, CH_2Cl_2, rt; (iii) $NaBH_4$, $NiCl_2·6H_2O$, CH_2Cl_2/MeOH, 0 °C, 40% (1:10 *cis*:*trans*); (iv) DIBAl-H, $PhCH_3$, −78 °C, 77% (1:10 *cis*:*trans*); (v) K_2CO_3, MeOH, rt, 2 h, 100%.

conformation; it adopts an equatorial position, even if this results in an axial 4-substituent (Fig. 1). As a result, both *cis* and *trans* diastereoisomers are potent γ-secretase inhibitors.

Analysis of the SAR (Table 1) shows a different pattern for 3-substituted *gem*-cyclohexane sulfones.

For most examples, the *cis*-isomer is more potent than the corresponding *trans*-isomers. Analysis of ^{1}H NMR data for the *cis* isomers, such as *cis*-**9** (Fig. 2),[5] shows unsurprisingly, that the molecules adopt a conformation (A) in which both the sulfone and the 3-substituent are equatorial. The alternate conformer (B) is extremely unfavourable as it would place both large substituents axial; unfavourable 1,3-diaxial interactions would further destabilise this conformer. The preferred conformation therefore fits the pharmacophore model; the 3-equatorial substituent is well tolerated and the molecules are good inhibitors of γ-secretase.

If the compound is di-substituted at the 3-position (*cis*-**12**) 1,3-diaxial interactions occur in both conformations A and B (Fig. 2) but the energetic benefit of placing the large sulfone group equatorial dominates and the active conformation A is again the only one present in solution.[5]

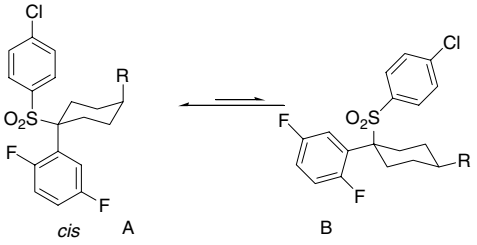
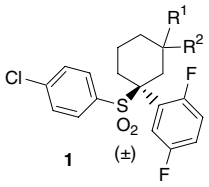


Figure 1.

Table 1. γ-Secretase inhibition for 3-substituted sulfones



Entry	R^1	R^2	IC_{50}[4] (nM)
cis-**5**		H	44
trans-**5**		H	85
cis-**6**	OH	H	8
trans-**6**		H	112
cis-**7**	CO_2H	H	24
trans-**7**		H	380
cis-**8**	CO_2Me	H	10
trans-**8**		H	210
cis-**9**	CO_2Me	H	3
trans-**9**		H	376
cis-**16**	CHO	H	77
trans-**16**		H	55
cis-**12**	CO_2Me	CH_3	10
trans-**12**			1628

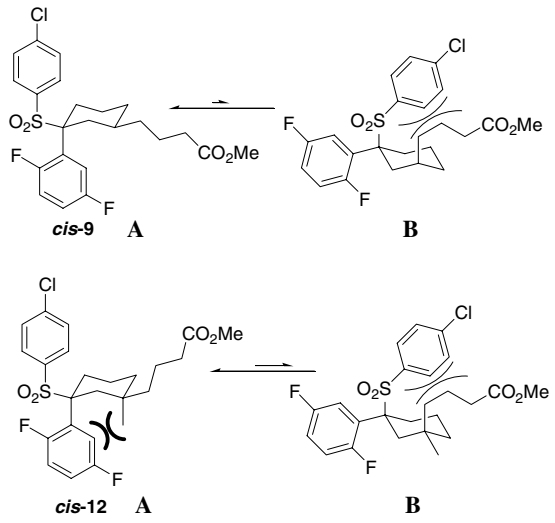


Figure 2.

In the case of *trans* isomers, such as *trans*-**9** (Fig. 3), ^{1}H NMR analysis shows that the sulfone no longer dominates the conformation;[5] it is forced into an axial position. This is in marked contrast to the 4-substituted cyclohexanes and can be attributed to the added presence of unfavourable 1,3-diaxial interactions (A). With the sulfone axial (B), the molecules no longer fit well into the pharmacophore and therefore show relatively poor enzyme inhibition.

There are some notable exceptions however. For smaller 3-substituents (e.g., allyl, *trans*-**5**), the *trans*-isomer shows improved inhibition. In the case of the smallest group (carboxaldehyde, *trans*-**16**) the difference in potency between *cis* and *trans* actually reverses. Again, this can be explained by analysis of ^{1}H NMR data

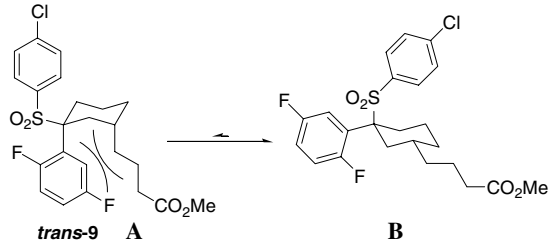


Figure 3.

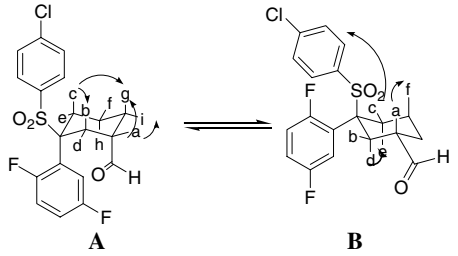


Figure 4.

(Fig. 4);[5] it is evident that both conformations A and B are in rapid equilibrium as the observed NOE's between H_b–H_c and H_d–H_e are not both possible within a single conformer. This reflects the decreasing importance of unfavourable 1,3-diaxial interactions as the 3-substituent is reduced in size. With the equatorial sulfone conformation (A) present in solution, enzyme inhibition is recovered.

In conclusion, we have further explored the effect of conformation on enzyme inhibition for the cyclohexyl sulfone γ-secretase inhibitors and demonstrated that substitution at the 3-position is well tolerated, provided that it does not destabilise the equatorial sulfone conformation through 1,3-interactions. This was a key discovery which allowed the further development of this series to useful compounds for the treatment of Alzheimer's disease. This work will be reported subsequently.

Acknowledgment

The authors thank Steve Thomas for his support in obtaining spectral data.

References and notes

1. Hardy, J.; Selkoe, D. J. *Science* **2002**, 356; Thorsett, E. D.; Latimer, L. H. *Curr. Opin. Chem. Biol.* **2000**, 377; Citron, M. *Mol. Med. Today* **2000**, 392; Vassar, R.; Citron, M. *Neuron* **2000**, 419.
2. Teall, M.; Oakley, P.; Harrison, T.; Shaw, D.; Kay, E.; Elliott, J.; Gerhard, U.; Castro, J. L.; Shearman, M.; Ball, R. G.; Tsou, N. N. *Bioorg. Med. Chem. Lett.* **2005**, 2685.
3. BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, 1451.
4. SH-SY5Y cells stably overexpressing the βAPP C-terminal fragment SPA4CT (Dyrks, T.; Dyrks, E.; Monning, U.; Urmoneit, B.; Turner, J.; Beyreuther, K. *FEBS Lett.* **1993** *335*, 89) are induced with sodium butyrate prior to plating. Compounds are added at a range of concentrations after 2 h and incubated overnight. Aliquots of conditioned media are removed for analysis by a homogeneous time resolved fluoresence (HTRF) assay (Clarke, E. E; Shearman, M. S. *J. Neurosci. Methods* **2000**, 61). All IC_{50} data shown are geometric means of a minimum of three independent results. Cell viability is measured by a colorimetric cell proliferation assay CellTitre 96™ AQ assay, Promega.
5. Samples were dissolved in chloroform-*d* (100% D). All experiments were acquired on a Bruker AV 500 MHz NMR instrument equipped with a 3 mm triple resonance probe ($^1H/^{19}F/^{13}C$) with Z gradients. A temperature of 300 K was maintained throughout the data acquisition.