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A novel series of potent γ-secretase inhibitors based on a benzobicyclo[4.2.1]nonane core

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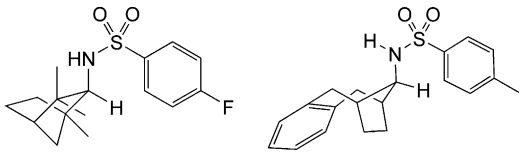
Abstract—A new series of γ-secretase inhibitors was developed from an in-house screening hit based on a benzobicyclo[4.2.1]nonane core. Lead optimisation studies led to the development of a series of potent inhibitors and in vivo efficacy was demonstrated.

Alzheimer's Disease (AD) is a progressive, neurodegenerative disorder and is currently the most common form of dementia worldwide. There is no effective treatment available with current therapies mainly reliant on improving cognitive function without really addressing the underlying cause of AD.[1] The opportunity, therefore, exists for the introduction of a novel therapeutic agent that could slow or even reverse the progression of AD.

One strategy involves modulating the production of amyloid-β peptide (Aβ), a 40–42 amino acid peptide, which is the major component of the neuritic plaques found in the brain tissue of patients suffering from AD. Inhibition of the proteases that cleave Amyloid-β Precursor Protein (APP)[2] leading to the formation of Aβ is central to such an approach. The first step in the pathway to Aβ formation is the cleavage of APP by β-secretase to generate a membrane-associated C-terminal fragment (C99) which is subsequently cleaved by γ-secretase to form Aβ (1–40) and Aβ (1–42). The work below describes the development of a series of nonpeptidic γ-secretase inhibitors.

A number of small molecule inhibitors of γ-secretase have been identified.[3a] Previously, a series of bicyclic aryl sulfonamides (e.g., **1**) has been disclosed.[3b] Screening of the Merck sample collection, using a whole cell γ-secretase inhibition assay using SHSY5Y cells,[4] identified the sulfonamide **2** with an IC_{50} = 651 nM. The compound showed potential as a nonpeptidic small molecule inhibitor of γ-secretase and a lead optimisation program was initiated to improve its potency.



1 **2**

In the first instance, structure–activity relationships of the sulfonamide substituent were investigated. The bicyclic amine **3**[5] was sulfonylated, in a modular fashion,

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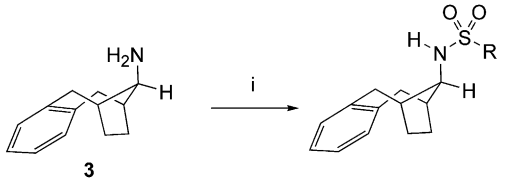


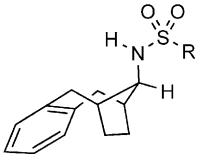
Scheme 1. (i) (a) RSO_2Cl, Py, DCM; (b) polyamine scavenger resin; (c) HPLC purification.

with a set of sulfonyl chlorides as outlined in Scheme 1. A range of commercially available aliphatic, aromatic and heteroaromatic (mainly thienyl) sulfonyl chlorides were utilised in the RAS run.

The structure–activity relationships of the sulfonamide substituent are summarised in Table 1. Variation of the substituents on the phenyl ring of the sulfonamide led to a modest improvement in potency. Thus, whilst replacement of the methyl group with chlorine (**11**) maintained inhibitory activity, deletion of the methyl substituent (**4**) or replacement with an *ortho*-, *meta*- or *para*-fluorine atom (**5**–**7**) resulted in a 2- to 5-fold improvement in potency. On the other hand, moving the methyl group to the 3-position of the phenyl ring (**8**), or replacing it with larger alkyl groups at the 4-position (**9**, **12**) proved to be detrimental. Introduction of electron-withdrawing substituents at the 4-position of the phenyl ring also resulted in a loss in potency (**10**, **13**). A number of straight chain alkyl sulfonamides were investigated with *n*-propyl and *n*-butyl (**15**, **16**) being equipotent with the tolylsulfonamide (**2**) whilst shorter or longer alkyl chains proved to be less effective (**14**, **17**). 2-Thienyl or 5-chloro-2-thienylsulfonamides (**18**, **19**) were found to be optimal in this study. Introduction of a second chlorine substituent on the thiophene ring (**20**) resulted, however, in a substantial loss in potency.

The effect of introducing substituents on the phenyl ring of the benzofused bicycle was investigated as outlined in Table 2.[6] The compounds were prepared either as the benzenesulfonamide or the optimised 5-chloro-2-thienylsulfonamide. Introduction of a fluorine substituent resulted in a small increase in inhibitory activity (**21**–**23**) but chlorine substitution proved to be detrimental (**24**, **25**). Incorporation of polar functionality (**26**, **28**) or an electron donating group (**27**) also caused a

Table 1. Structure–activity relationships of sulfonamides



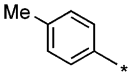
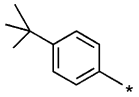
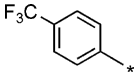
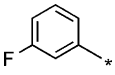
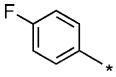
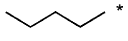
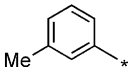
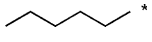
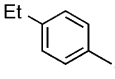
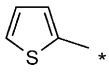
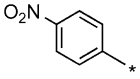
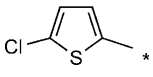
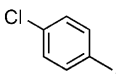
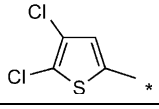
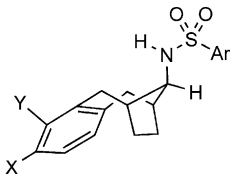
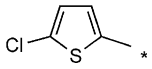
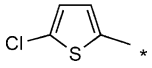
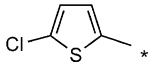
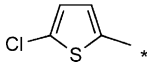
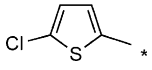
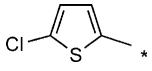
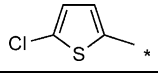
Entry	R	IC_{50}/nM (n)	Entry	R	IC_{50}/nM (n)
2		651 (2)	**12**		>1000 (2)
4		190 (3)	**13**		>1000 (2)
5		239 (2)	**14**		>1000 (2)
6		324 (3)	**15**		721 (2)
7		129 (2)	**16**		610 (2)
8		>1000 (2)	**17**		>1000 (2)
9		>1000 (2)	**18**		50 (7)
10		>1000 (2)	**19**		62 (10)
11		467 (2)	**20**		>1000 (2)

Table 2. Structure–activity relationships of substituents on aromatic ring on the benzofused bicycle

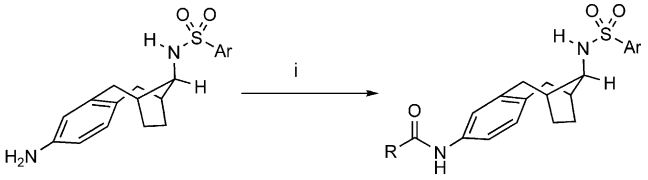


Entry	X	Y	Ar	IC_{50}/nM (n)
4	H	H		190 (3)
19	H	H		62 (10)
21	F	H		29 (3)
22	F	H		70 (3)
23	H	F		34 (3)
24	Cl	H		146 (2)
25	H	Cl		175 (2)
26	NH_2	H		6000 (2)
27	MeO	H		490 (2)
28	OH	H		269 (3)

decrease in potency. Although the introduction of an NH_2 group on the aromatic ring of the benzofused bicycle (**26**) resulted in a large reduction in potency, it did serve as a useful functionality for synthetic elaboration in order to probe space for a further binding interaction.

A series of carboxamides derived from the aniline **26** were prepared, in modular fashion, as outlined in Scheme 2.

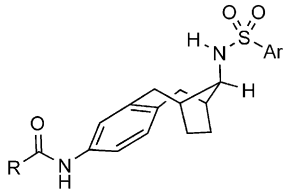
Initial SAR studies were carried out in the benzenesulfonamide series and analogues of interest were subsequently synthesised in the 5-chloro-2-thienyl-

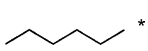
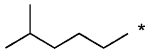
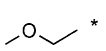
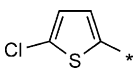
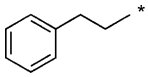
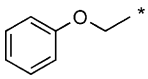
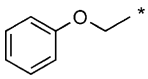
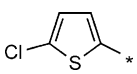
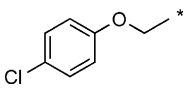
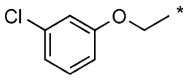


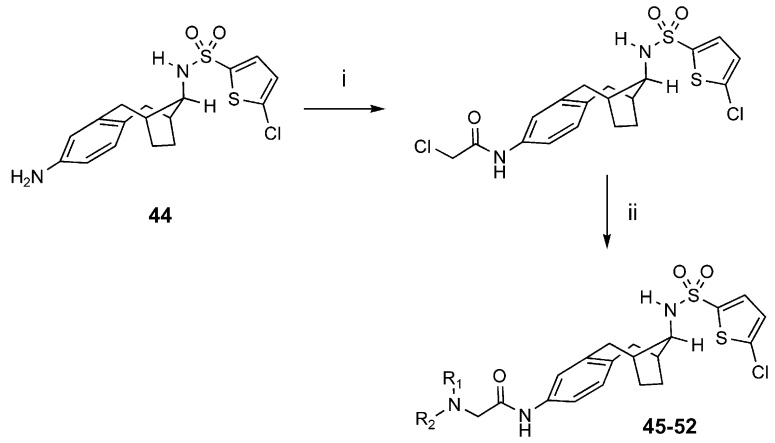
Scheme 2. (i) (a) RCO_2H, CDI, THF, 60 °C; (b) HPLC purification.

sulfonamide series (Table 3). The data shows that simple aliphatic and aromatic amides (**29–31**, **33**) are not well tolerated. However, inhibition of γ-secretase can be significantly enhanced by the incorporation of a heteroatom such as in picolinamides (**36, 37**) or in phenoxyacetamides (**39–41**). The position (**34**, **35**) and the

Table 3. Structure–activity relationships of amides



Entry	R	Ar	IC_{50}/nM (n)
29			>1000 (3)
30			>1000 (2)
31			535 (2)
32			>1000 (2)
33			>1000 (2)
34			>1000 (2)
35			>1000 (2)
36			75 (2)
37			12 (6)
38			>1000 (2)
39			74 (2)
40			23 (3)
41			16 (2)
42			412 (2)
43			153 (2)



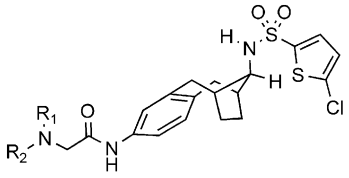
Scheme 3. (i) Chloroacetyl chloride, NMM, DCM; (ii) R_1R_2NH, NMM, DCM.

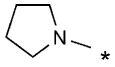
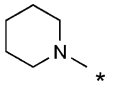
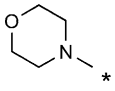
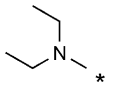
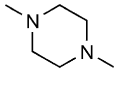
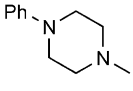
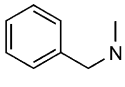
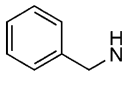
environment (**32**, **42**, **43**) of the heteroatom are important in order to achieve good potency. Replacement of the heteroatom in potent side chains with a carbon atom results in a large loss of activity (**33**, **38**). Having identified potent inhibitors, attention was directed towards the synthesis of analogues where the substituent at the terminus of the side chain was further diversified.

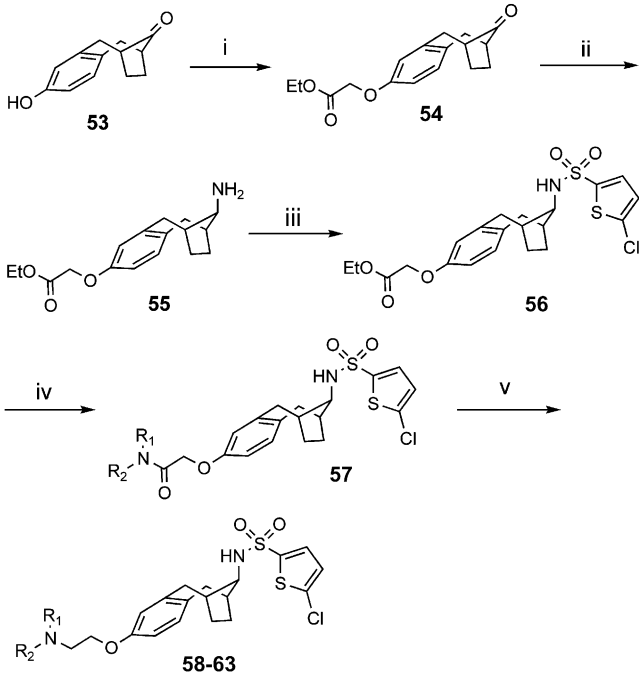
A series of amides was investigated which contained amines in the side chain. These compounds were prepared from the aniline **44**. Reaction with chloroacetyl chloride gave the chloromethyl amide which was treated with various amines to give the desired glycinamides (**45**–**52**) (Scheme 3).

The data (Table 4) shows that a variety of glycinamides containing cyclic amines (**45**–**47**, **50**) have high potency whilst acyclic amines (**48**, **51**–**52**) tend to show a decrease in potency relative to the pyridyl derivative **37**. Selected glycinamides displayed poor pharmacokinetic properties and further work was carried out to investigate alternative linkages from the benzofused bicycle to the amine terminus. Both ether and olefinic linkages were evaluated.

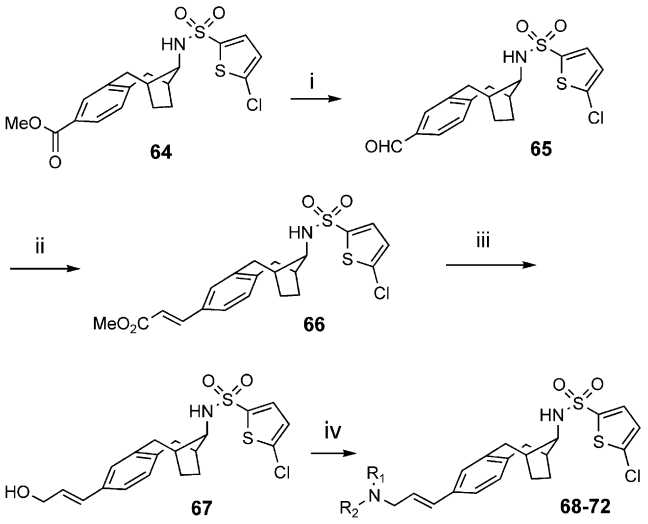
Table 4. Structure–activity relationships of glycinamides



Entry	R_1R_2	IC_{50}/nM (n)
45		7 (4)
46		6 (2)
47		7 (2)
48		41 (2)
49		69 (2)
50		5 (2)
51		226 (2)
52		3490 (3)



Scheme 4. (i) Ethyl bromoacetate, K_2CO_3, DMF; (ii) (a) $H_2NOH{\cdot}HCl$, NaOAc, EtOH, (b) H_2, PtO_2, AcOH; (iii) 5-chlorothiophene-2-sulfonyl chloride, NMM, DMAP, DCM; (iv) (a) $LiOH{\cdot}H_2O$, THF, H_2O, (b) R_1R_2NH, HBTU, DIPEA, MeCN; (v) $BH_3{\cdot}THF$.



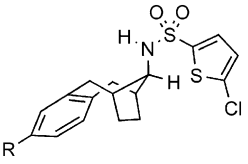
Scheme 5. (i) (a) DIBAH, PhMe, (b) PDC, DCM; (ii) methyl diethylphosphonoacetate, $LiOH{\cdot}H_2O$, THF; (iii) DIBAH, PhMe; (iv) (a) 1-bromo-*N*,*N*-trimethyl-propenylamine, DCM, (b) R_1R_2NH, DCM.

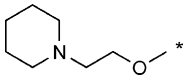
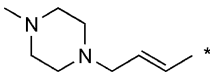
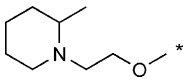
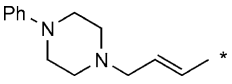
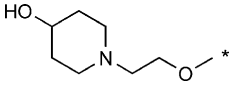
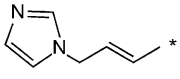
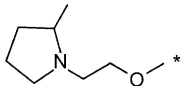
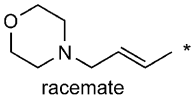
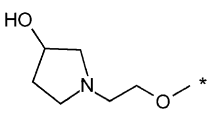
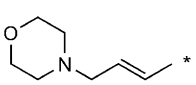
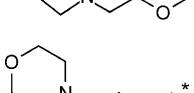
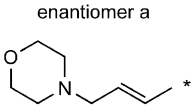
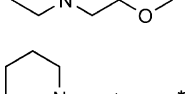
Phenol **53**[5] was alkylated with ethyl bromoacetate and the sulfonamide was then introduced by amination of the ketone **54** followed by sulfonylation of the subsequent amine **55** to give **56**. Saponification of the ethyl ester followed by HBTU mediated amide coupling of the carboxylic acid with a variety of amines afforded amides of the general structure **57**. Finally, borane reduction of the amides gave the desired amino ethers **58–63** (Scheme 4).

Compounds containing an olefinic linkage were prepared from the ester **64**. The ester was converted in to the aldehyde **65**, in two steps, by a DIBAH reduction to the alcohol and subsequent oxidation with PDC. The aldehyde **65** underwent Horner–Wadsworth–Emmons olefination to give exclusively the *trans*-alkene **66**. The ester was reduced to the cinnamyl alcohol **67** using DIBAH. A one-pot conversion of the alcohol to the desired cinnamylamines **68–72** was carried out by activation of the alcohol as the bromide using 1-bromo-*N*,*N*-trimethylpropenylamine[7] followed by subsequent displacement with various amines (Scheme 5).

The results for the compounds listed in Table 5 demonstrate that the amide linker can be replaced with either an ether or an olefin linkage. In particular, a terminal N-morpholino substituent in all three side chains gave rise to very potent compounds (**47**, **63**, **72**). Compound **72** was selected for further evaluation and was separated into its enantiomers using supercritical fluid chromatography.[8] The relative potencies of the two enantiomers (**73** and **74**) indicate enantiospecificity with respect to γ-secretase inhibition.

Table 5. Structure–activity relationships of aminoethers and cinnamylamines



Entry	R	IC_{50}/nM (n)	Entry	R	IC_{50}/nM (n)
58		73 (4)	**69**		39 (4)
59		227 (2)	**70**		21 (3)
60		623 (2)	**71**		15 (6)
61		335 (2)	**72**	 racemate	5 (4)
62		209 (2)	**73**	 enantiomer a	1 (11)
63		5 (4)	**74**	 enantiomer b	315 (3)
68		152 (2)			

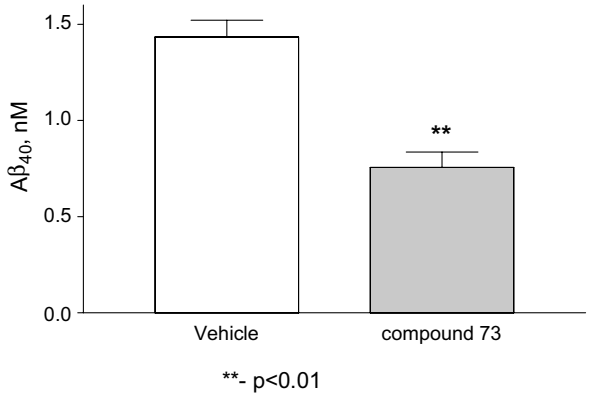


Figure 1. Reduction of brain Aβ40 by compound **73**, 4 h after dosing 100 mg/kg to APP-YAC mice.

The in vivo efficacy of compound **73**[9] was evaluated in transgenic APP-YAC mice (Fig. 1).[10] A 50% reduction of Aβ40 was obtained 4 h after a single 100 mg/kg po dose of **73** (drug levels: plasma > 7.91 μM; brain 16.70 μM).

In conclusion, a novel series of sulfonamides that inhibit γ-secretase has been developed. It was found that potency of the screening hit **2** could be enhanced firstly by modification of the sulfonamide substituent to a 5-chloro-2-thienylsulfonamide and subsequently by the introduction of an appropriate side chain on the aromatic ring of the benzobicyclo[4.2.1]nonane leading to compound **73** which reduced brain Aβ40 at a dose of 100 mg/kg po in APP-YAC mice.

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6. The compounds contained in Table 2 were prepared in analogous fashion to the compounds listed in Table 1. All compounds in Table 2 that contain a substituent on the phenyl ring of the benzofused bicycle and all subsequent compounds in Tables 3–5 are racemic unless otherwise stated.
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8. Conditions for the chromatography were: a 1 in. diameter OD column in SFC mode, 40% MeOH containing 25 mM isobutylamine; 50 mL/min; 100 bar; 320 nm.
9. For **73** (TFA salt): ^{1}H NMR (400 MHz, $CDCl_3$) 1.16 (m, 2H), 1.67 (m, 2H), 2.41 (m, 2H), 2.56–2.62 (m, 2H), 2.86 (m, 2H), 3.04 (dd, J = 3.1 Hz, J = 16.2 Hz, 2H), 3.56 (d, J = 11.7 Hz, 2H), 3.70–3.78 (m, 3H), 4.00 (m, 4H), 5.16 (d, J = 7.2 Hz, 1H), 6.13–6.21 (m, 1H), 6.67 (d, J = 15.9 Hz, 1H), 6.95 (d, J = 4 Hz, 1H), 7.04–7.12 (m, 3H), 7.45 (d, J = 3.9 Hz, 1H). *m/z* (ES^+) 494 ($M + H^+$).
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