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Sulfonamide derivatives of bridgehead substituted bicyclo[4.2.1]nonanes as γ-secretase inhibitors

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Abstract—Bridgehead substituted derivatives of bicyclo[4.2.1]nonanes were synthesized and shown to be potent inhibitors of γ-secretase. Two related series were synthesized to explore the SARs. More potent compounds were found in the non-benzofused series compared with the benzofused series. One compound from each series showed good exposure in the hepatic portal vein (HPV) following oral dosing to rats.

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, and with life expectancy increasing, more patients than ever before will suffer progressive memory impairment, cognitive deficits and behavioural problems as a result of AD. Current therapies are palliative. Approaches towards a disease modifying therapy include reducing the production of amyloid-β42 (Aβ42) through inhibition of β-secretase or γ-secretase. Such approaches have been of interest to the pharmaceutical industry, and as a result, a number of γ-secretase inhibitors/modulators are in clinical development.[1]

Recently we described the use of sulfonamide derivatives of substituted bicyclo[4.2.1]nonanes and substituted cyclic sulfamides represented by **A** and **B** as γ-secretase inhibitors with potential for the treatment of Alzheimer's disease.[2,3]

Here we present new γ-secretase inhibitors, represented by **C** and **D** which, given the substitution pattern on the respective cores, represent synthetically challenging types of compounds for which pharmacological properties are unknown. However, related compounds have been proposed for use as analgesics and anti-inflammatories.[4] Furthermore, analogues of such bicyclo[4.2.1]nonanes were prepared to aid in the re-definition of Bredt's rule.[5]

The preparation of bridgehead substituted bicyclo[4.2.1]nonanes possessing a quaternary carbon inherent within this structural motif has attracted two main synthetic strategies (Scheme 1). One involves alkylating the carbon bearing the most acidic proton prior to cyclisation onto the methylene adjacent to the carbonyl (method A)[5a] and the second, generation of the bicyclic [4.2.1]nonane skeleton through reduction of an enol lactone (method B).[5b]

We planned to utilize the bridgehead position as a site from which a range of groups (R in **C** and **D**) could be installed to build upon the SAR of previously disclosed compounds[2] by exploring the effects of introducing polar, basic and lipophilic groups on the potency and pharmacokinetic properties of these molecules. Herein we describe the synthesis of bridgehead substituted benzofused and non-benzofused bicyclo[4,2,1]nonanes, and derivatisation to sulfonamides as γ-secretase inhibitors.

Keywords: Alzheimer's disease; γ-Secretase inhibitor.
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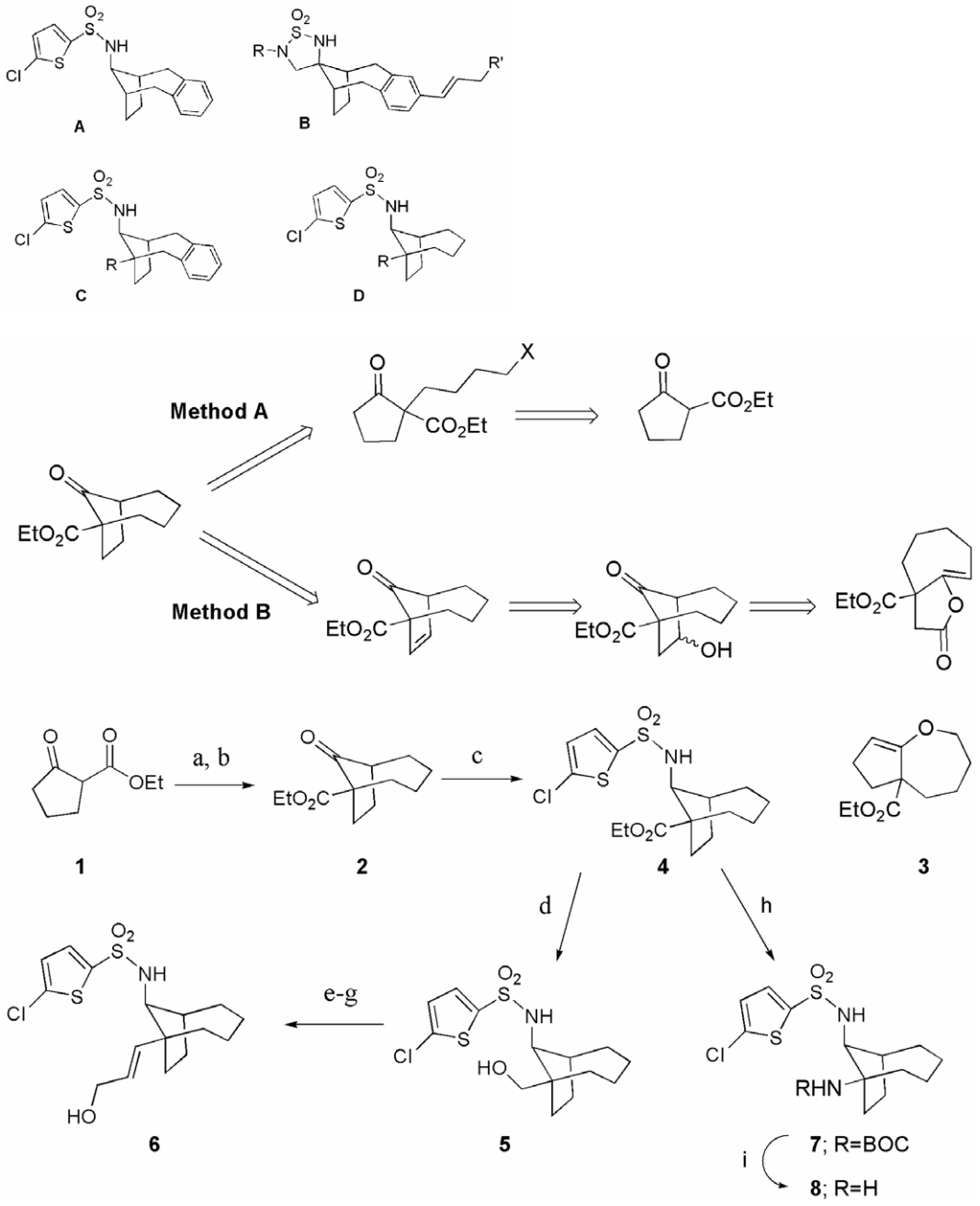


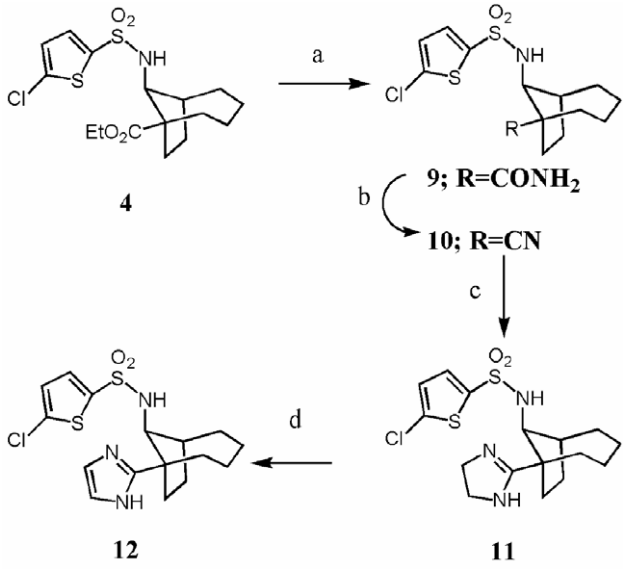
Scheme 1. Reagents and conditions: (a) 1,4-dibromobutane, K_2CO_3, acetone, reflux, o/n; (b) NaH, DMF, toluene, rt, 3 h (32% over 2 steps); (c) i—$TiCl_4$, Et_3N, 5-chlorothiophene-2-sulfonamide, THF; ii—$NaBH_4$, THF (67% over 2 steps); (d) lithium aluminium hydride, ether (99%); (e) SO_3·pyridine, DMSO (92%); (f) methyl diethylphosphonoacetate, $LiOH·H_2O$, THF (95%); (g) DIBAL, toluene (79%); (h) i—NaOH, THF (99%); ii—diphenylphosphoryl azide, Et_3N, toluene; iii—*t*-BuOH (49% over 2 steps); (i) HCl, ether (99%).

For the preparation of non-benzofused bicyclo[4.2.1] nonanes we used method A (Scheme 1). Thus, a combination of 1,4-dibromobutane as bis-electrophile, potassium carbonate as base and **1** followed by cyclisation with NaH as base in a mixture of DMF and toluene gave ketone **2** in modest overall yield. Attempts to improve the yield such as using different bases (e.g., LDA) and solvents (e.g., ether) failed. One by-product previously reported was the *O*-alkylated compound **3**,[5a] although no attempt was made to isolate it here. Though low yielding, sufficient quantities of ketone **2** were isolated which was converted to sulfonamide **4** using a one-pot imine formation/reduction protocol. The stereochemistry of the C–N bond in **4** was axial as proven by ^{1}H NMR nOe experiments. Subsequently, reduction with lithium aluminium hydride produced alcohol **5** which was oxidised to the aldehyde, then a Horner–Emmons reaction to the α,β-unsaturated ester followed by further reduction with DIBAL furnished allylic alcohol **6**. For the introduction of a bridgehead amine, ester **4** was converted to the acid then BOC-amine **7** via a Curtius reaction, and deprotected with acid to provide amine **8**.

Heterocyclic groups were appended from the core by converting ester **4** to the amide **9** via saponification,

followed by generation of the acid chloride and reaction with ammonia (Scheme 2). Subsequently, the amide was dehydrated to nitrile **10** and imidazoline **11** formed by reaction with ethylenediamine. Oxidation with barium manganate gave the imidazole **12**.

Benzofused analogues were prepared by analogy with method A. Thus, xylidene dibromide was reacted with ethyl 2-carboxycyclopentanone **1** and sodium ethoxide as base to give bromide **13** in low yield (Scheme 3). Simple attempts to improve the yield (stronger base, e.g., LDA) failed. The cyclisation again proved low yielding, in our hands using LDA as base gave 37% of ketone **14**. Subsequently, **14** was converted to amine **15** using a two-step procedure via the oxime and reduction with zinc in acetic acid. The reduction was highly stereoselective giving >95% of a single diastereoisomer (by NMR of the crude product).

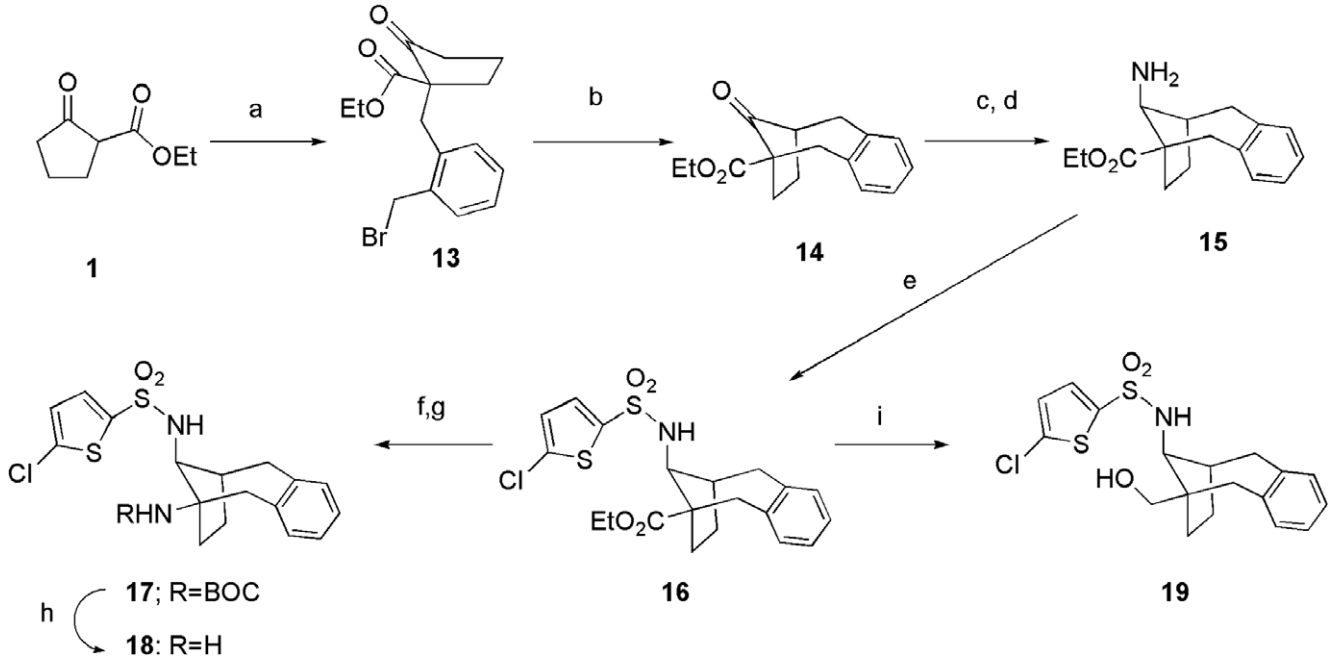


Scheme 2. Reagents and conditions: (a) i—NaOH, THF (93%); ii—oxalyl chloride, THF; iii—ammonia, THF (79% over 2 steps); (b) $POCl_3$, $NaHCO_3$ (81%); (c) i—gaseous HCl, MeOH, DCM; ii—ethylene diamine, THF (39% over 2 steps); (d) $BaMnO_4$, THF (51%).

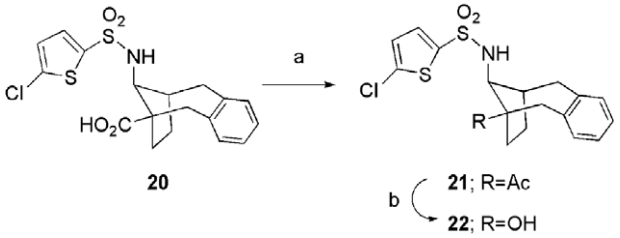
Capping of the amine with 5-chlorothiophene-2-sulfonyl chloride afforded sulfonamide **16**, which acted as the central intermediate for subsequent manipulations. Improved yields were found for the preparation of **16** using these conditions than those used for **4**. The stereochemistry of the C–N bond was again found to be axial as shown by nOe studies. For incorporating a bridgehead amine, intermediate **16** was saponified and the acid exposed to Curtius conditions to provide BOC-protected amine **17**, which was deprotected with acid to give **18**. Also, ester **16** was reduced with LAH to give primary alcohol **19**.

To further scope out the SAR, bridgehead hydroxyl compound **22** was synthesized via a Baeyer–Villiger oxidation of ketone **21**, produced from a Grignard reaction of the Weinreb amide of acid **20**, followed by hydrolysis (Scheme 4).

Compounds were assayed using a whole cell γ-secretase inhibition assay using SHSY5Y cells[6] (Table 1). Compounds **23** and **24**, as previously reported by our group, demonstrated reasonable potency. Overall, no



Scheme 3. Reagents and conditions: (a) xylidene dibromide, NaOEt, DMF, rt; (b) LDA, THF (37% over 2 steps); (c) hydroxylamine·HCl, NaOAc, THF; (d) zinc, AcOH; (e) 5-chlorothiophene-2-sulfonyl chloride, Et_3N, DCM (65% over 3 steps); (f) NaOH, THF (99%); (g) i—diphenyl phosphoryl azide, Et_3N, toluene; ii—*t*-BuOH (48% over 2 steps); (h) HCl, ether (99%); (i) lithium aluminium hydride, THF (90%).



Scheme 4. Reagents and conditions: (a) i—oxalyl chloride, *N*-*O*-dimethylhydroxylamine·HCl, pyridine, THF (46%); ii—MeMgBr, THF (73%); (b) i—*m*-CPBA, Na_2CO_3, DCM (32%); ii—lithium aluminium hydride, THF (76%).

significant improvement in potency was observed with the new compounds reported here. The non-benzofused series generally showed improved potency compared with benzofused compounds, notably for bridgehead ester (**4** and **16**) and primary alcohol substituents (**5** and **19**). This could be due to a size restriction in the active site, for which the presence of the benzofused moiety limits the space available to the bridgehead substituent. Additionally, basic groups were not tolerated in either series (**8**, **18**, **11** and **12**). Within both series, only hydroxyl containing groups **5** and **6** displayed comparable potency to the parent compound **23**, although other small groups were moderately well tolerated (**9** and **10**).

In the benzofused series, a hydroxyl group was well tolerated (**22**), showing improved potency compared to **24**, however introducing a methylene spacer (**19**) resulted in a significant loss in potency. In addition, analogue **18** was inactive.

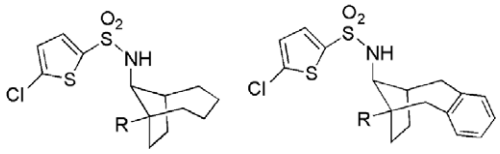
Table 2. Rat HPV levels for compounds **5**, **19** and **24**

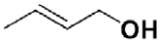
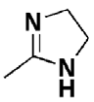
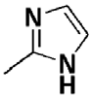
Compound	Dose (mg/kg)	HPV (ng h/ml)
24	30	8
5[7]	1	55
19[8]	5	425

Pharmacokinetic studies using oral dosing to rats showed that compound **24** was very poorly absorbed into the hepatic portal vein (HPV). To assess the effect on HPV levels of compounds containing polar bridgehead substituents, compounds **5** and **19** were dosed orally to rat. Gratifyingly, compound levels in the HPV were significantly improved (Table 2).

We have shown that the bridgehead position of compounds **23** and **24** could be substituted to produce two new classes of compounds. The non-benzofused compounds generally showed better γ-secretase potency than the benzofused series, in particular hydroxyl group containing substituents gave compounds equipotent (**5** and **6**) to parent (**23**). However, one compound from the benzofused series (**22**) showed potency comparable to parent (**24**). Furthermore, one compound from each series showed reasonable absorption into the HPV after oral dosing to rats (**5** and **19**). This represented an improvement compared with compound **24**.

Table 1. Inhibitory activity of sulfonamides **4**–**12** and **16**–**24**[6]



R	Compound	IC_{50} (nM) (*n*)	Compound	IC_{50} (nM) (*n*)
H	**23**	62 ± 23 (23)	**24**	63 ± 14 (4)
CO_2Et	**4**	212 ± 57 (4)	**16**	>10,000 (3)
CH_2OH	**5**	105 ± 22 (4)	**19**	491 ± 182 (3)
	**6**	81 ± 46 (4)	—	—
NHBOC	**7**	416 ± 183 (2)	**17**	>10,000 (2)
NH_2	**8**	>10,000 (2)	**18**	>10,000 (2)
$CONH_2$	**9**	685 ± 26 (3)	—	—
CN	**10**	257 ± 18 (3)	—	—
	**11**	>10,000 (2)	—	—
	**12**	>10,000 (2)	—	—
OH	—	—	**22**	23 (2)

Acknowledgments

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6. All new compounds were screened as racemates Clarke, E. E.; Shearman, M. S. *J. Neurosci. Methods* **2000**, *102*, 61.
7. For compound **5**: (360 MHz ^{1}H NMR, $CDCl_3$) 1.25–1.93 (12H, m), 2.19–2.27 (2H, m), 3.28 (1H, d, $J = 11.3$), 3.48 (1H, d, $J = 11.3$), 3.61–3.65 (1H, m), 4.90 (1H, d, $J = 8.6$), 6.92 (1H, d, $J = 4.0$), 7.42 (1H, d, $J = 4.0$); (^{13}C NMR, $CDCl_3$) 25.9, 27.3, 29.9, 31.6, 32.1, 35.6, 40.0, 50.3, 62.1, 69.5, 128.6, 133.5, 139.2, 141.0. *m/z* (ES+): 332 $[M-OH]^+$.
8. For compound **19**: (360 MHz ^{1}H NMR, $CDCl_3$) 1.13 (2H, m), 1.58 (2H, m), 2.20 (1H, d, $J = 15.7$), 2.35 (1H, m), 2.58 (1H, dd, $J = 7.7, 16.1$), 2.78 (1H, d, $J = 15.9$), 2.87 (1H, m), 3.04 (1H, d, $J = 16.2$), 3.42 (1H, d, $J = 11.2$), 3.63 (1H, d, $J = 11.2$), 3.70 (1H, dd, $J = 6.7, 6.8$), 5.47 (1H, d, $J = 7.6$), 6.95 (1H, d, $J = 3.7$), 7.07 (4H, m), 7.46 (1H, d, $J = 3.6$); *m/z* (ES+): 398 MH^+.