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Synthesis of pyrimido[4,5-*c*]azepine- and pyrimido[4,5-*c*]oxepine-based γ-secretase modulators

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Ring-closing metathesis (RCM)

ABSTRACT

This Letter describes an efficient ring-closing metathesis approach to 2-chloro-4-amino-pyrimido[4,5-*c*]azepines and 2-chloro-4-amino-pyrimido[4,5-*c*]oxepines. These chlorides were applied to the synthesis of several potent γ-secretase modulators (GSMs).

There is substantial evidence to suggest that β-amyloid (Aβ) peptide, particularly the longer 42 amino acid form, Aβ42, plays a critical role in the progression of Alzheimer's disease (AD).[1–4] Aβ is derived from the β-amyloid precursor protein (APP) by proteolysis. Cleavage of APP by β-site APP cleaving enzyme-1 (BACE1) results in shedding of the APP ectodomain, and the remaining membrane bound C-terminal fragment, C99, is further processed by γ-secretase (GS) to produce Aβ peptides of lengths varying from 37 to 43 amino acids. Accumulation and aggregation of the toxic Aβ peptide, particularly the 42-amino acid form Aβ42, initiates neuronal dysfunction that eventually leads to brain atrophy, dementia, and death. Thus, inhibition of BACE1 or GS to reduce Aβ production is a plausible approach to test the amyloid hypothesis.[5–7] Recently, the GS inhibitors (GSIs) semagacestat and avagacestat were discontinued in clinical trials presumably due to side effects such as toxicity related to inhibition of other GS substrates and decline in cognition.[8,9] A viable alternative to direct GS inhibition is GS modulation. GS modulators (GSMs) reduce the level of longer, neurotoxic Aβ peptides (Aβ42 and Aβ43) by shifting the APP processing by γ-secretase towards shorter isoforms (such as Aβ37, Aβ38) without blocking GS processing. Because GS activity is not blocked, this modulating mechanism does not inhibit intracellular signaling resulting from GS activity, and should offer a differentiated safety profile versus GSIs. GSMs are distinguished in cell assays by combining lowering of secreted Aβ42 in specific ELISAs without lowering the total amount of Aβ secreted using ELISAs that detect all Aβ species.[10]

Our early efforts in the GSM area led to diaminotriazine **1** which exhibited good potency for inhibition of Aβ1–42 production (IC_{50}: 29 nM) and no effect on total Aβ production.[11] In an effort to increase potency through conformational restriction, we sought to prepare pyrimido[4,5-*c*]azepine analogs **2a**/**b** (Fig. 1). The fused bicyclic ring system is somewhat related to the well-known benzodiazepine drugs, and may contribute to desired brain penetration. In terms of a heterocyclic head group, we chose 4-chloroimidazole instead of 4-methylimidazole as present in lead compound **1** because the former results in an improved CYP 3A4 inhibition profile.[11]

The synthesis of **2a**/**b** required easy access to pyrimido[4,5-*c*]azepines **3a**/**b** (Fig. 1). Surprisingly, azepines of this type are unknown in the literature. In contrast, the corresponding benzo[*c*]azepines **4** are common intermediates that have been widely used in the synthesis of benzazepine agents for the treatment of central nervous system disorders.[12–15] In general, two methodologies exist for the preparation of benzo[*c*]azepines **4** (Scheme 1). The first one (Roche synthesis) involves palladium-catalyzed coupling of iodide **5** with propargylphthalimide **6** to give the acetylenic benzophenone **7**.[12,13] Removal of the phthaloyl protecting group leads to a free primary amine **8**, which undergoes partial hydrogenation followed by spontaneous ring closure to furnish benzazepine **10** (Scheme 1). The alternative procedure makes use of the unprotected (*Z*)-3-(tributylstannyl)allylamine (**12**).[14] The palladium-catalyzed cross-coupling reaction of **12** with bromide **11** affords the substituted *cis* allylic amine **13**, which cyclizes

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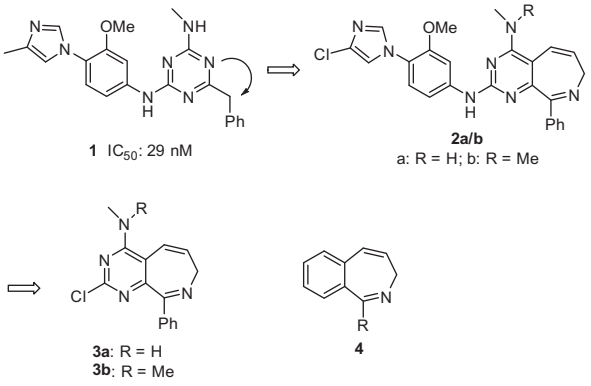
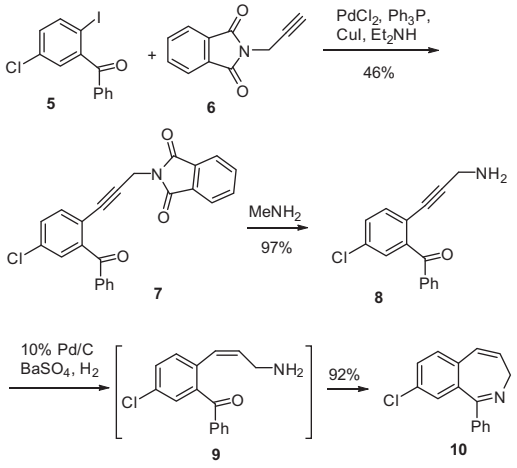
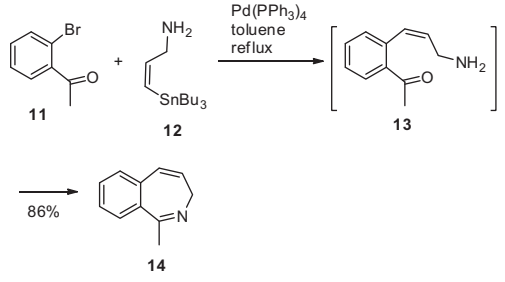


Figure 1. Retrosynthesis of bicyclic GSMs.



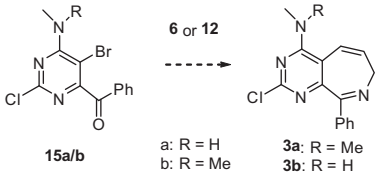
Scheme 1. Roche synthesis of benzo[*c*]azepines.



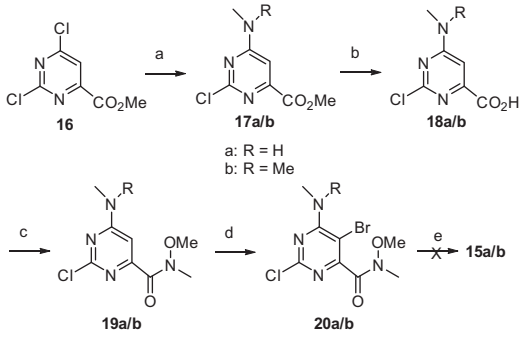
Scheme 2. Corriu synthesis of benzo[*c*]azepines.

spontaneously to give benzazepine **14** (Scheme 2). We started our work hoping to leverage this existing methodology for the synthesis of **3a**/**b**, and both methods required access to the bromopyrimidinyl phenyl ketones **15a**/**b** (Scheme 3) as starting materials.

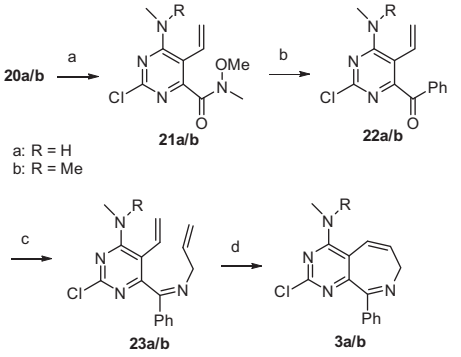
Scheme 4 describes our approach to phenyl ketones **15a**/**b**. Addition of methylamine and dimethylamine to the readily available methyl 2,6-dichloropyrimidine-4-carboxylate (**16**) gave 6-methylamino- and 6-dimethylamino-pyrimidines **17a** and **17b**, respectively. Both esters were hydrolyzed with aqueous lithium hydroxide to furnish free carboxylic acids **18a**/**b**, which were coupled with *N*,*O*-dimethylhydroxylamine hydrochloride to afford Weinreb amides **19a**/**b**. Bromination of **19a**/**b** with NBS was carried out smoothly in toluene at 80 °C to afford Weinreb amides **20a**/**b**. However, treatment of **20a**/**b** with phenylmagnesium bromide or



Scheme 3. Initial approach to pyrimido[4,5-*c*]azepines **3a**/**b**.



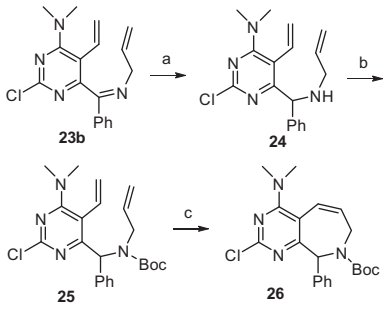
Scheme 4. Reagents and conditions: (a) dimethylamine or methylamine, 89–95%; (b) lithium hydroxide, THF, H_2O, rt, 79–85%; (c) *N*,*O*-dimethylhydroxylamine hydrochloride, HATU, Hünig's base, rt, 78–94%; (d) NBS, toluene, 80 °C, 3 h, 78–94%; (e) PhMgBr or PhLi, THF or ether, various temperatures.



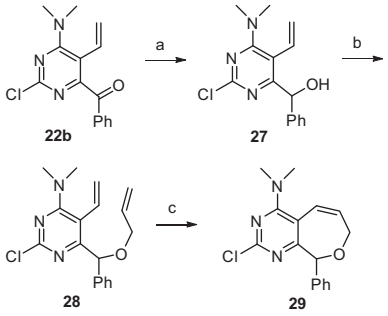
Scheme 5. Reagents and conditions: (a) tributylvinyltin, $Pd(PPh_3)_4$, toluene, 80 °C, sealed vial, 10 h, 74–79%; (b) PhMgBr, THF, rt, 92–97%; (c) allylamine, $TiCl_4$, rt, 48–84%; (d) Grubbs II (5 mol %), toluene, 80 °C, 15 min, 92–98%.

phenyllithium under numerous conditions failed to produce the desired phenyl ketones **15a**/**b** due to decomposition of the starting material.

Due to the difficulty in accessing intermediates **15a**/**b** we considered alternative approaches that could intercept our existing intermediates. Thus, we decided to investigate a ring-closing metathesis (RCM) approach which could leverage our existing intermediates **20a**/**b**.[16] Despite its simplicity, this approach has never been utilized to construct benzo[*c*]azepine compounds.[17] Scheme 5 describes our RCM approach to azepines **3a**/**b**. Weinreb amides **20a**/**b** underwent Stille coupling with tributyl(vinyl)stannane to give vinylpyrimidines **21a**/**b** in good yields. These compounds were also prepared via Suzuki coupling with 2,4,6-trivinyl-1,3,5,2,4,6-trioxatriborinane, but the yields were significantly lower (<30%). In contrast to our results with the bromo-substituted Weinreb amides **20a**/**b**, addition of phenylmagnesium bromide to the vinyl-substituted Weinreb amides **21a**/**b** proceeded cleanly to give phenyl ketones **22a**/**b**. Condensation of **22a**/**b** with allylamine was performed in the presence of titanium tetrachloride, and the resulting imines **23a**/**b** were sufficiently stable that



Scheme 6. Reagents and conditions: (a) $NaBH_3CN$, HOAc, MeOH; (b) Boc_2O, Hünig's base, CH_2Cl_2, 78% from **22b**; (c) Grubbs II (5 mol %), toluene, 80 °C, 15 min, 92%.



Scheme 7. Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 95%; (b) allyl bromide, sodium hydride, DMF, rt, 92%; (c) Grubbs II (5%), toluene, 80 °C, 15 min, 92%.

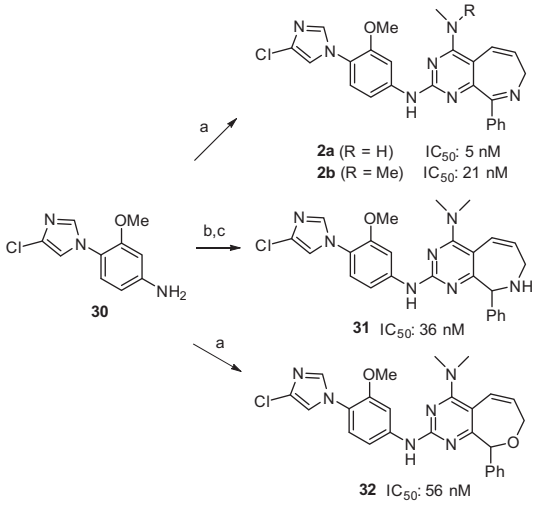
they could be purified using standard silica gel chromatography, and they showed no appreciable decomposition when exposed to air at room temperature for a few months. Treatment of either **23a**/**b** with the Grubbs II catalyst in toluene at 80 °C for 15 min brought about a clean RCM transformation to give **3a**/**b** in excellent yield.[18] In the case of RCM substrate **23a**, the free secondary amine functionality required no protection, thus leading to a direct synthesis of **3a**.

We also used imine **23b** in the synthesis of the related *N*-Boc protected azepine **26** (Scheme 6). The secondary amine in the GSMs derived from **26** (see **31**, Scheme 8) offered additional polarity and a potential avenue for substitution. Reduction of **23b** with sodium cyanoborohydride furnished secondary amine **24**, which was converted to the *N*-Boc derivative **25**. Exposure of **25** to the Grubbs II catalyst led to the azepine **26** in good yield.[19]

We also extended the RCM approach to the synthesis of pyrimido[4,5-*c*]oxepine **29** (Scheme 7).[20] Reduction of ketone **22b** with sodium borohydride afforded alcohol **27**, and subsequent O-allylation furnished allyl ether **28**. Metathesis of **28** using the Grubbs II catalyst gave oxepine **29** in excellent yield.[21]

The azepine and oxepine intermediates were utilized in the synthesis of GSMs similar to other analogs we have reported (Scheme 8).[11] Treatment of aniline **30** with **3a**/**b** or **29** with acetic acid in dioxane at 100 °C afforded **2a**/**b** and **32**, respectively, in moderate yields (not optimized). The palladium-catalyzed coupling of azepine **26** with **30** and subsequent removal of the *N*-Boc group gave **31** in good yield. We also attempted hydrogenation of the olefinic double bond in these analogs, but without success.

The monomethylamino-substituted pyrimido[4,5-*c*]azepine **2a** was shown to be a potent inhibitor of Aβ1-42 production (IC_{50}: 5 nM), and was approximately 6-fold more potent than the lead compound **1**. Since the 4-methylimidazole head group contributes to activity to the same extent as 4-chloroimidazole, the potency enhancement observed with azepine **2a** likely results from its rigid



Scheme 8. Reagents and conditions: (a) **3a** or **3b** or **29**, dioxane, acetic acid, 100 °C, 5 h, 16% (**2a**); 23% (**2b**); 21% (**29**); (b) **26**, $Pd_2(dba)_3$ (4 mol %), Xantphos (10 mol %), cesium carbonate, dioxane, 100 °C, 12 h, 40%; (c) TFA, CH_2Cl_2, rt, 71%.

pyrimido[4,5-*c*]azepine core structure. The dimethylamino-substituted analog **2b** (IC_{50}: 21 nM) was 4-fold less active than the monomethylamino-substituted counterpart **2a**. Accordingly, we speculate that the side chain nitrogen atom may serve as a hydrogen-bond donor instead of an acceptor to a residue on GS. Azepine **31** (IC_{50}: 36 nM) was comparable to its imine analog **2b** (IC_{50}: 21 nM), but about twice as active as oxepine **32** (IC_{50}: 56 nM).

Despite their potent cellular inhibitory activity, compounds **2a**/**b** demonstrated only marginal reduction in brain Aβ peptides in rodents relative to the vehicle treated control even at 30 mg/kg PO. The brain exposure data (not shown) indicated low exposure of the compounds in rat brain, explaining the lack of in vivo activity.

In summary, we have developed an efficient route to 2-chloropyrimido[4,5-*c*]azepines **3a**/**b** and **26** as well as 2-chloropyrimido[4,5-*c*]oxepine **29**. These chlorides were incorporated into several GSMs, and the activity of azepine **2a** (IC_{50}: 5 nM) suggested that this type of conformational constriction is a viable approach to the discovery of potent GSMs.

Acknowledgements

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18. **3a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ d 7.51–7.46 (m, 2H), 7.41–7.32 (m, 3H), 6.64 (d, J = 9.5 Hz, 1H), 6.32 (dt, J = 9.5, 6.7 Hz, 1H), 4.06–3.67 (m, 1H), 3.85–3.46 (br s, 1H), 3.27 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.3, 165.0, 159.5, 156.9, 139.2, 130.0, 129.6, 129.5, 127.9, 126.2, 118.1, 41.5 and 29.8. Exact mass calcd for $C_{16}H_{16}ClN_4$ (M+H): 299.1064; found: 299.1056. **3b**: ^{1}H NMR (500 MHz, CD_3OD) d 7.51–7.31 (m, 1H), 6.76 (d, J = 9.5 Hz, 1H), 6.47 (dt, J = 9.7, 6.4 Hz, 1H), 4.8–3.4 (2H, br S), 3.07 (s, 3H). ^{13}C NMR (CD_3OD, 125 MHz) δ 167.4, 162.1, 157.6, 157.5, 138.6, 133.6, 130.0, 129.5, 128.0, 122.8, 117.3, 49.0, and 27.6. Exact mass calcd for $C_{15}H_{14}ClN_4$ (M+H): 285.0907; found: 285.0900.
19. **26**: at room temperature, this compound appears as a ~5:2 mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 3H), 7.10–7.01 (m, 2H), 6.31 (s, 1H), 6.08–6.00 (m, 1H), 5.71 (dt, J = 12.3, 3.3 Hz, 1H), 4.78–4.65 (m, 1H), 3.37 (dt, J = 19.6, 2.4 Hz, 1H), 3.11 (6H, s), 1.39 (s, 9H). Peaks corresponding to the minor rotamer are present at: δ 6.49 (s, 1H), 6.13–6.05 (m, 1H), 5.71 (dt, J = 12.3, 3.3 Hz, 1H), 5.69 (dt, J = 12.3, 3.3 Hz, 1H), 4.56 (d, J = 19.9 Hz, 1H), 3.10 (6H, s), 1.47 (s, 9H). MS (M+H): 401.20.
20. For a RCM approach to 1,3-dihydrobenzo[*c*]oxepines, see: Pathak, R.; Panayides, J.; Jeftic, T. D.; de Koning, C. B.; van Otterlo, W. A. L. *Synlett* **1859**, 12.
21. **29**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.31 (m, 3H), 7.23–7.11 (m, 2H), 6.20 (dt, J = 12.4, 2.2 Hz, 1H), 5.89–5.82 (m, 2H), 4.46 (dt, J = 18.9, 2.6 Hz, 1H), 4.16 (dt, J = 18.9, 2.4 Hz, 1H), 3.15 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 166.3, 156.1, 135.4, 132.7, 129.2, 128.5, 122.4, 122.7, 84.4, 67.3, 41.4, 21.1. Exact mass calcd for $C_{16}H_{167}ClN_3O$ (M+H): 302.1060; found: 302.1054.