Bioorganic & Medicinal Chemistry Letters 26 (2016) 1554–1557

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

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

Yong-Jin Wu *, Yunhui Zhang, Jeremy H. Toyn, John E. Macor, Lorin A. Thompson

Research and Development, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, United States

ARTICLE INFO

Article history:
Received 17 January 2016
Revised 4 February 2016
Accepted 6 February 2016
Available online 8 February 2016

Keywords:
γ-Secretase modulator (GSM)
2-Chloro-pyrimido[4,5-*c*]azepin-4-amine
2-Chloro-pyrimido[4,5-*c*]oxepin-4-amine
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

* Corresponding author.
E-mail address: Yong-Jin.wu@bms.com (Y.-J. Wu).

http://dx.doi.org/10.1016/j.bmcl.2016.02.016
0960-894X/

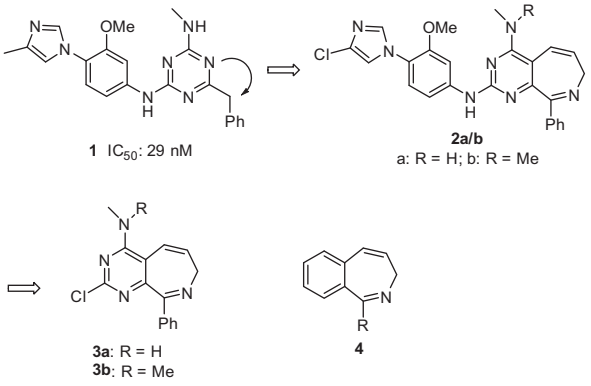
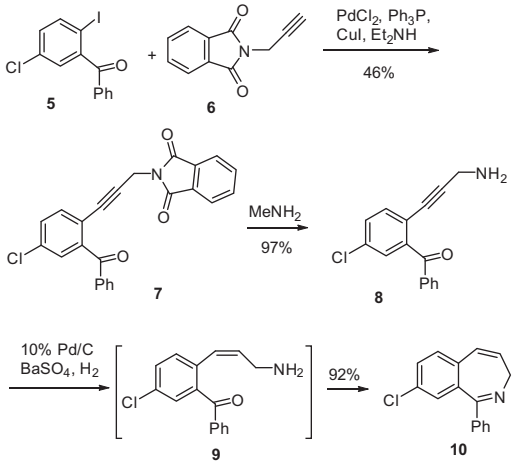
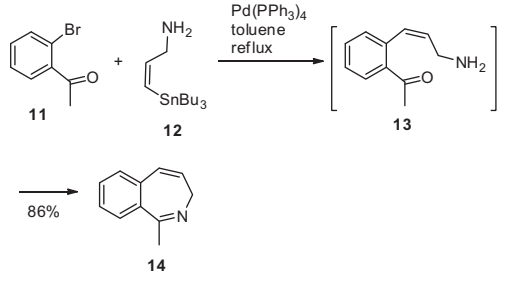


Figure 1. Retrosynthesis of bicyclic GSMs.



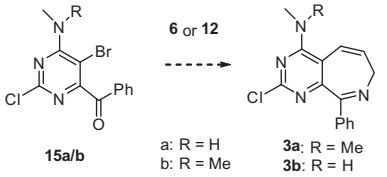
Scheme 1. Roche synthesis of benzo[*c*]azepines.



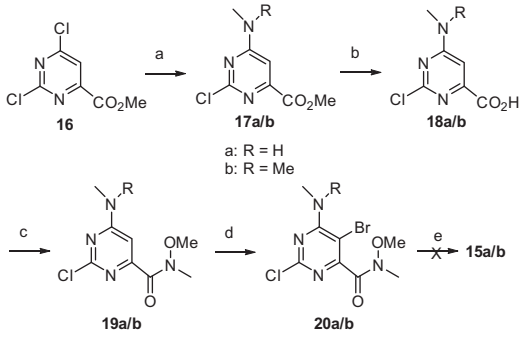
Scheme 2. Corriu synthesis of benzo[*c*]azepines.

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.

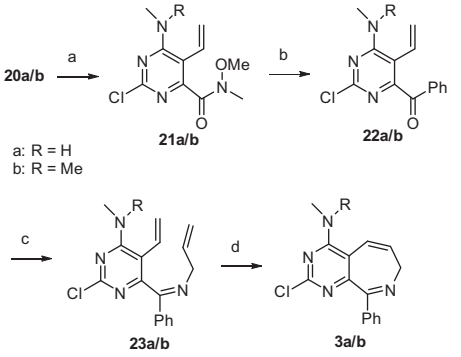
Scheme 4 describes our approach to phenyl ketones **15a**/**b**. Addition of methylamine and dimethylamine to the readily available methyl 2,6-dichloropyrimidine-4-carboxylate (**16**) gave 6-methylamino- and 6-dimethylamino-pyrimidines **17a** and **17b**, respectively. Both esters were hydrolyzed with 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