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Tetrahedron Letters 48 (2007) 7990–7993
Tetrahedron Letters

Aspartic protease inhibitors via C_1-homologation of peptidic aldehydes and studies on reduced amide isosteres

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Received 29 June 2007; revised 29 August 2007; accepted 7 September 2007
Available online 12 September 2007

Abstract—(*R*)-Configured isophthalic hydroxyethylamines play an important role in the inhibition of β-secretase (BACE1). We present the synthesis of a number of (*S*)-configured hydroxyethylamine derivatives via 2-iodoethanol intermediates and the comparison with the (*R*)-analogues. An *N*-substituted indole was investigated as a substitute for the isophthalamide moiety.

Extracellular amyloid-β plaques are suspected to cause Alzheimer's disease.[1,2] These plaques consist mainly of amyloid-β peptides (Aβ) which are generated from the membrane bound APP (amyloid precursor protein) via the consecutive cleavages by β-secretase (BACE1, β-site amyloid precursor protein cleaving enzyme) and γ-secretase.[3] Thus, the inhibition of BACE1 constitutes a promising approach to block the onset of plaque formation by decreasing the Aβ levels in the brain.

A number of highly potent, but peptidic BACE1 inhibitors have been available for several years.[4,5] Inhibitors **1**–**3** have derived from the progressive elimination of peptidic features from the original heptapeptidic hydroxyethylenes (Fig. 1). The introduction of an isophthalic moiety in **1** was regarded as a milestone in the development of small BACE1 inhibitors.[6] The peptidic character of compound **1** was further reduced by the replacement of the hydroxyethylene with a hydroxyethylamine. Remarkably, the hydroxyethylamine in **2** is the only transition state isostere in BACE1 inhibitors that displays an (*R*)-configured secondary alcohol.[7] Compound **3** comprises a reduced amide transition state isostere with an additional sulfonamide

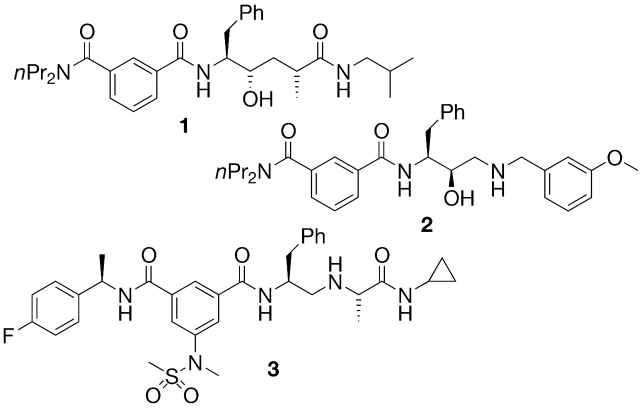

Figure 1. BACE1 inhibitors by Elan pharmaceuticals and MSD.

substituent in the P2 position and a modified P3 amide residue.[8] Compounds **1**–**3** are active at nanomolar concentrations in cell free assays and yet display different cellular activities. They are good substrates for the p-glycoprotein transporter, this was partially assigned to the isophthalic amide moiety.[9]

Here, we present an approach to isophthalamide based hydroxyethylamines and potential replacements thereof. We compared a linear to a convergent access to this class of compounds. The synthesis led to the (*S*)-configured secondary alcohols which were compared to the known (*R*)-analogue **2**. Furthermore, we investigated

Keywords: β-Secretase; Transition state isostere; Hydroxyethylamine; Reduced amide; Grignard reagent; Indole synthesis.
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doi:10.1016/j.tetlet.2007.09.047

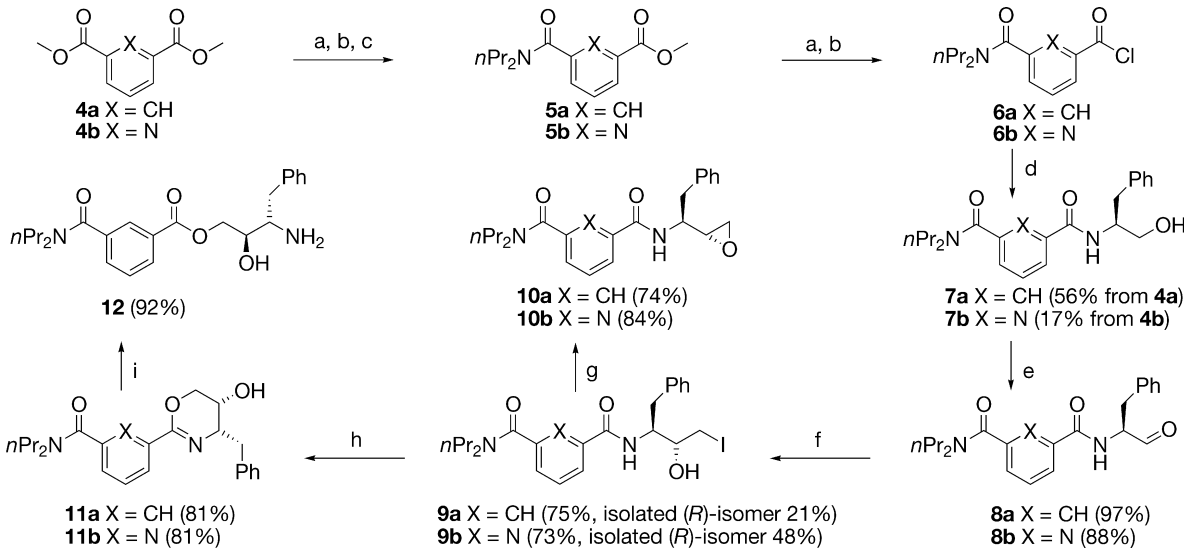

Figure 2. Synthesis of epoxides **10a** and **10b** and ester **12**. Reagents and conditions: (a) KOH, MeOH, rt; (b) $SOCl_2$, $CHCl_3$, reflux, (overnight); (c) *n*-Pr_2NH, CH_2Cl_2, 0 °C to rt; (d) L-phenylalaninol, CH_2Cl_2, 0 °C to rt; (e) IBX, DMSO, rt, 15 h; (f) *i*-PrMgCl, CH_2I_2, THF, −78 °C (15 min), 0 °C (2 h); (g) K_2CO_3, MeCN, rt (4 h); (h) 4-bromobenzylamine, MeCN, reflux (4 h); (i) water, THF, trifluoroacetic acid, 80 °C (1 h), rt (15 h).

an indole as a replacement for the isophthalamide portion, combined it with a reduced amide isostere and compared it to the isophthalamide analogue.

A reaction sequence starting from diester **4a** was employed for the generation of **5a**, **6a** and finally the isophthalamide **7a** comprising two different amide substituents on either carboxyl functionality (Fig. 2).[10] Alcohol **7a** was oxidized by IBX (2-iodooxybenzoic acid) furnishing aldehyde **8a** in a high yield and free of racemisation. The aldehyde was converted to a 2-iodoethanol using a moderately stereoselective C_1-homologation.[11] The reaction occurs upon treatment with *i*-PrMgCl/CH_2I_2 forming a mild Grignard reagent that undergoes addition to peptidic aldehydes in a high chemoselectivity leaving the α-chiral position unchanged. Product **9a** (crude ds = 3:1) was obtained in 75% yield as a diastereomeric mixture and further purification delivered pure **9a**. Treatment of **9a** with K_2CO_3 yielded epoxide **10a**. Surprisingly, **9a** was converted to oxazine **11a** upon treatment with any benzylamine in MeCN under reflux. **11a** could be opened to ester **12** by treatment with trifluoroacetic acid in a water/THF mixture. A small amount of the diastereomer of **11a** was generated likewise, and the cyclic structures of both diastereomers of **11a** served to assign the configuration of compounds **9**–**12**. The reactions to the analogous compounds **5b**–**11b** starting from dimethyl 2,6-pyridinedicarboxylate **4b** were conducted in a similar manner. The higher yield of **9b** (de = 100%) compared to **9a** is explained by the higher diastereoselectivity of the C_1-homologation (crude ds = 9:1). Even though the generation of **9a** or **9b** seemed to be a promising approach for a variety of benzylic hydroxyethylamines, the iodo compounds reacted under a variety of conditions to the undesired oxazines. This undesired reaction was circumvented in previous synthetic approaches:[12] (a) by the protection of the amide nitrogen or (b) by the conversion of an *N*-Boc-protected amino acid derivative (e.g., **15**) or its respective epoxide, which does not undergo cyclization. This difference in carbamate versus amide reactivity was applied to the synthesis of the desired hydroxyethylamines. Boc-phenylalaninol **13** was oxidized to **14** with IBX and converted to β-iodoethanols **15a** and **15b** (de >99%, crude ds = 3:2, Fig. 3).

Either diastereomer was obtained in high purity from the crude diastereomeric mixture (53%). Substitution of the iodide by various benzylamines provided hydroxyethylamines **16**. Deprotection and reaction with chloride **6a** led to the desired (*S*)-configured alcohols **17**–**20** and (*R*)-alcohol **2**. The configuration was assigned by single crystal X-ray analysis of **15a** and subsequent conversions of **15b** to known compounds and comparison of the NMR data.[11]

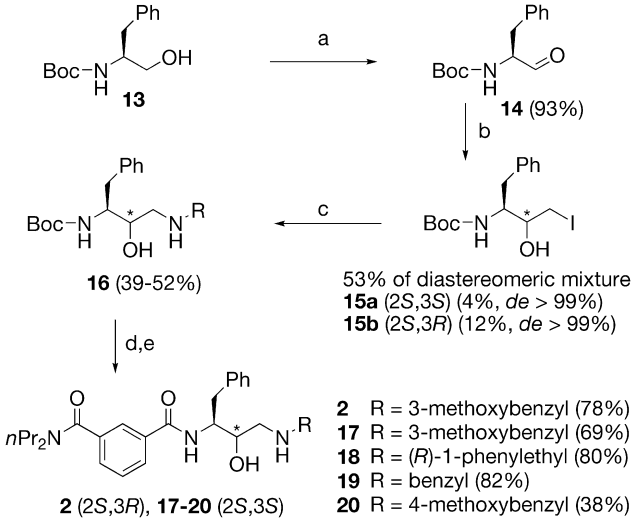

Figure 3. Reagents and conditions: (a) IBX, DMSO, rt (15 h); (b) *i*-PrMgCl, CH_2I_2, THF, −78 °C (15 min), 0 °C (2 h); (c) amine, MeCN, reflux (4 h); (d) trifluoroacetic acid, CH_2Cl_2; (e) **6a**, HOBt, CH_2Cl_2 (overnight).