Tetrahedron Letters 54 (2013) 5802–5807

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Diethylaminosulfur trifluoride-mediated intramolecular cyclization of 2-hydroxycycloalkylureas to fused bicyclic aminooxazoline compounds and evaluation of their biochemical activity against β-secretase-1 (BACE-1)

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ARTICLE INFO

Article history:
Received 9 July 2013
Revised 19 July 2013
Accepted 25 July 2013
Available online 6 August 2013

Keywords:
Alzheimer's disease
BACE
Aminooxazolines
β-Secretase
Oxazolines

ABSTRACT

A series of unique bicyclic aminooxazolines were synthesized and found to exhibit micromolar inhibition of β-secretase-1 (BACE-1). The aminooxazolines were procured by an intramolecular diethylaminosulfur trifluoride (DAST)-mediated ring closure of a benzylic urea onto a secondary alcohol.

Alzheimer's disease is one of the most serious neurodegenerative diseases afflicting modern society.[1] The slow transition of patients from loss of memory to dementia and death not only incurs a great emotional cost to families, but also carries severe financial burdens, primarily due to long-term healthcare requirements.[2] Decades of research in the pharmaceutical sector has yielded no disease modifying drugs that halt the progression of the disease, and so the quest for new protein targets and a deeper biological understanding of the disease state continues.[3]

Currently, one of the lead protein targets for the treatment of Alzheimer's disease is β-secretase-1 (BACE-1).[4] Over the last decade, considerable resources within the drug discovery industry have been devoted to uncovering small molecule inhibitors of BACE-1. The initial wave of highly potent peptidomimetic BACE-1 inhibitors suffered from poor brain penetration and permeability due to high topological polar surface area (tPSA), molecular weight (MW), and rotatable bond count.[5] Although many recent efforts have still been confounded by poor blood–brain barrier permeability, as well as off-target effects with Cathepsin D, promising chemical matter is currently in human trials.[6] Advances in identifying potent amino-heterocyclic functional groups that interact with the catalytic aspartic acid residues of BACE-1 have allowed for the reduction of tPSA, MW, and rotatable bonds of inhibitors, resulting in compounds with good blood–brain barrier penetration (Fig. 1). In addition to the aspartic acid binding groups, additional potency can be achieved by aromatic side chains that extend into the P2′ and P3 pockets of the active site.[7]

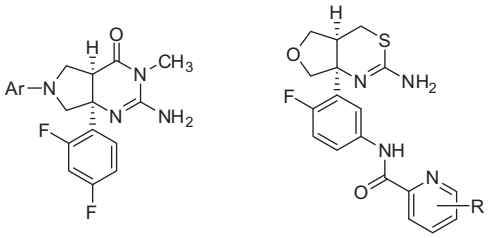

Figure 1. Literature bicyclic aminoheterocycle BACE-1 inhibitors.

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0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.07.136

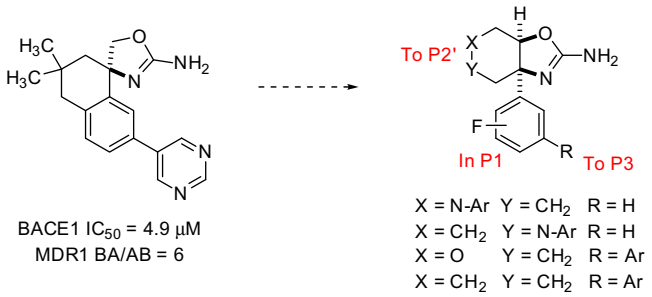


Figure 2. Bicyclic aminooxazoline targets.

While our BACE-1 program has focused primarily on the development of compounds possessing spirocyclic headgroups (Fig. 2),[8] we briefly investigated the fused heterocyclic headgroup strategy, which resulted in the synthesis of compounds possessing micromolar inhibition of BACE-1. These synthetic efforts are detailed here and represent a useful extension of the Lellouche–Wipf–Williams synthesis of oxazolines to fused systems possessing aryl functionality at the ring junction.[9]

Given the dihydrothiazine[10] and dihydropyrimidinone[11] structural classes of BACE-1 inhibitors in the literature (Fig. 1), we designed a novel bicyclic aminooxazoline scaffold type (Fig. 2).[12] The choice of an aminooxazoline headgroup was based on previously reported results for tetrahydronaphthalene-based spirocyclic compounds (Fig. 2) in which this headgroup displayed the best combination of moderate efflux properties and potency.[8] These bicyclic aminooxazoline targets allow for extension into the P3 pocket (R = Ar), and also provide a vector for aryl or aliphatic substituents toward P2′ (X or Y = *N*-Ar, *N*-aliphatic). In order to maintain reasonable physical properties, we initially aimed to occupy either P3 or P2′, but not both pockets simultaneously. Specif-

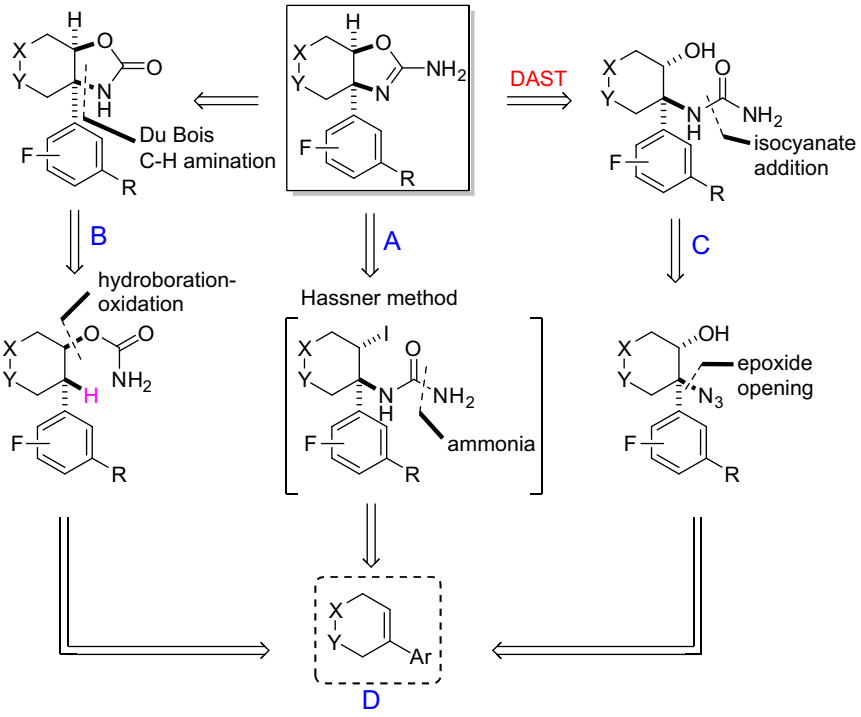
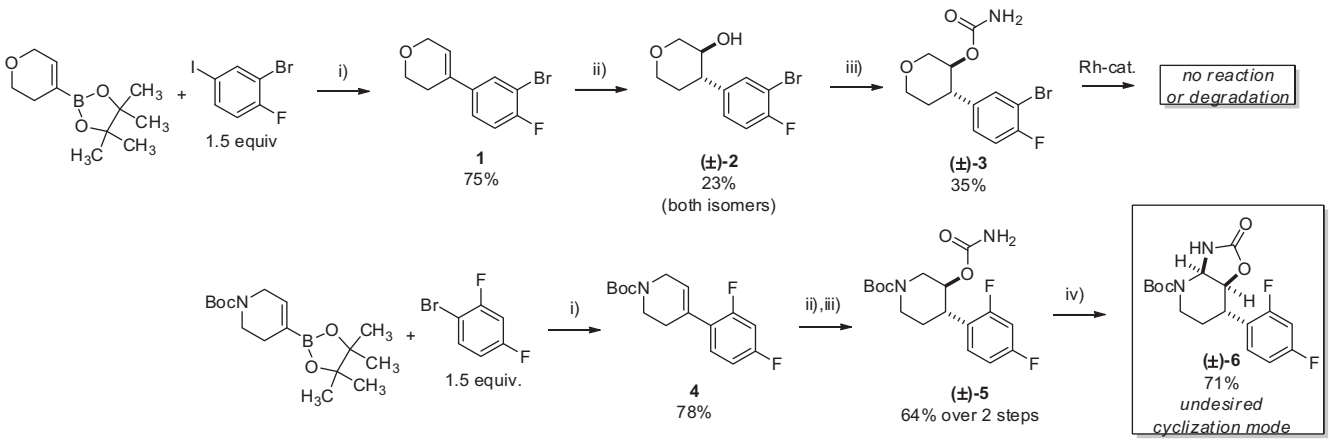


Figure 3. Retrosynthetic analysis of bicyclic aminooxazolines.



Scheme 1. Reagents and conditions: (i) 5 mol % $Pd(dppf)Cl_2$, 3 equiv K_2CO_3, 4:1 dioxane/H_2O, 80 °C; (ii) (a) 2 equiv BH_3·DMS, THF, 0 °C to rt, (b) aq NaOH, H_2O_2, 0–45 °C; (iii) (a) 5 equiv $Cl_3C(CO)NCO$, CH_2Cl_2, (b) 6 equiv K_2CO_3, MeOH; (iv) 10 mol % $Rh_2(OAc)_4$, 1.4 equiv $PhI(OAc)_2$, 2.3 equiv MgO, CH_2Cl_2, 40 °C.