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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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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]

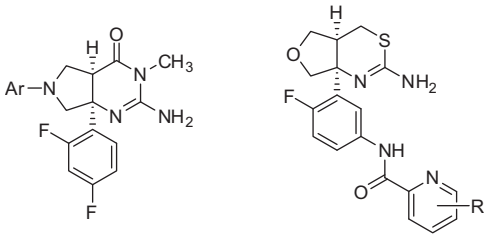

Figure 1. Literature bicyclic aminoheterocycle BACE-1 inhibitors.

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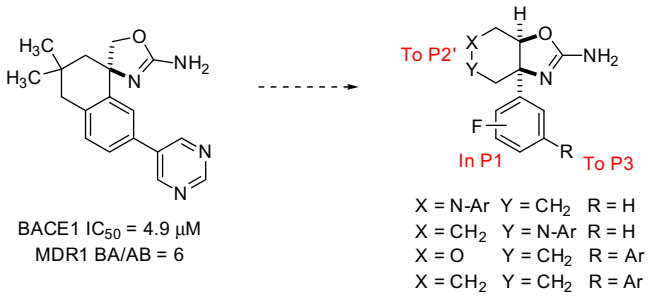


Figure 2. Bicyclic aminooxazoline targets.

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-

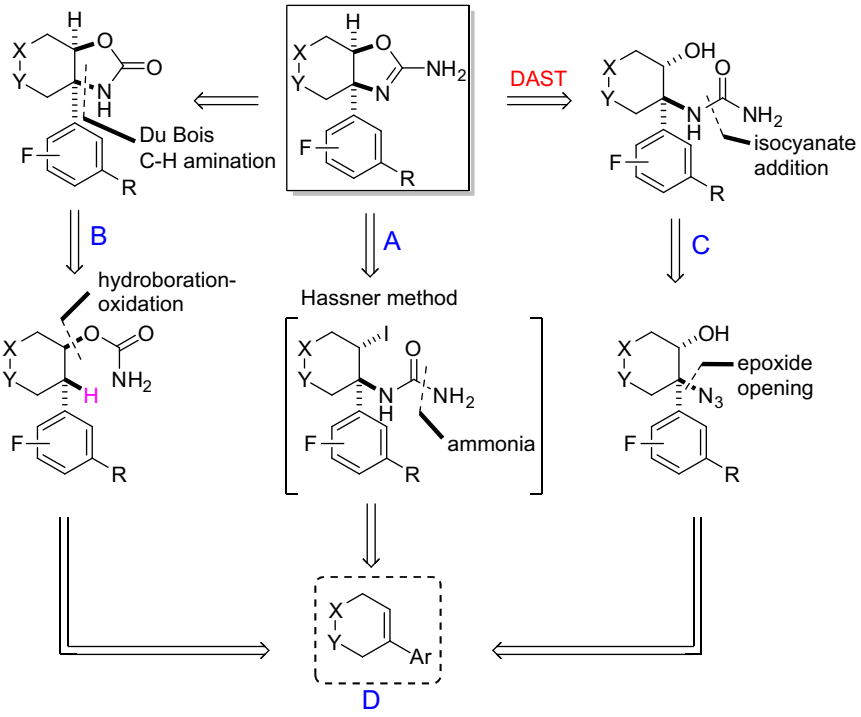
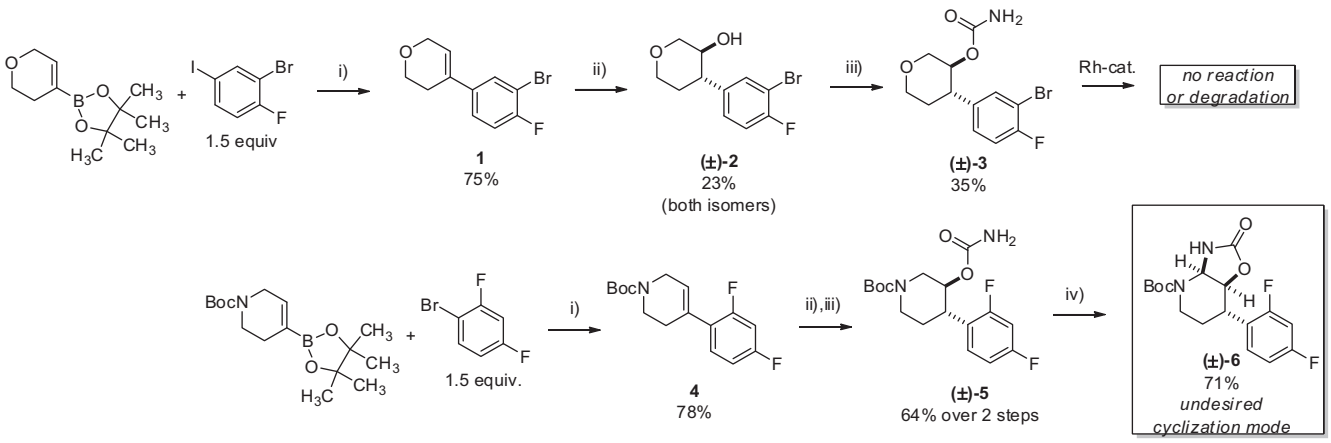
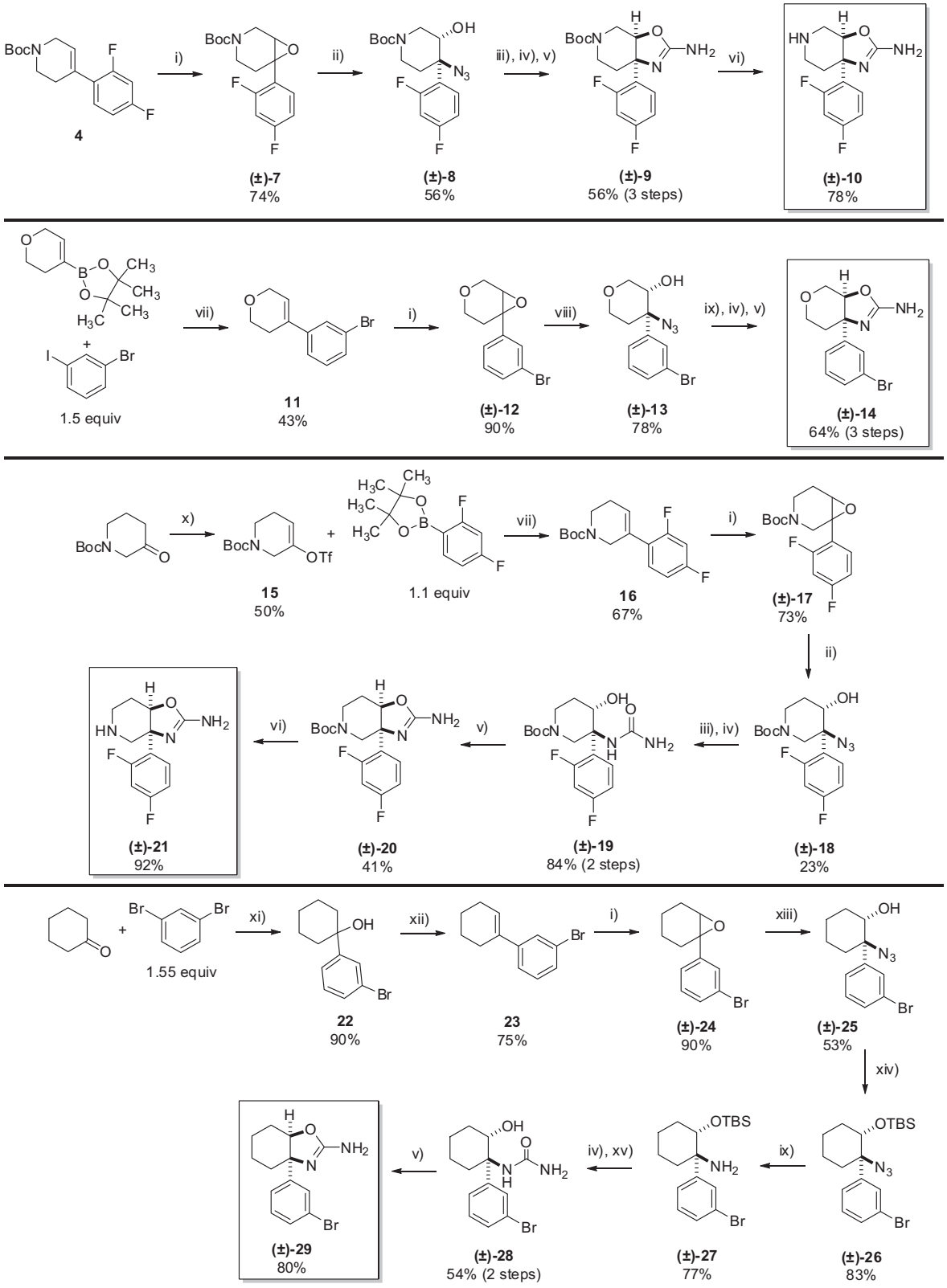


Figure 3. Retrosynthetic analysis of bicyclic aminooxazolines.



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.



Scheme 2. Reagents and conditions: (i) 2 equiv *m*-CPBA, CH_2Cl_2; (ii) 10 equiv NaN_3, 10 equiv NH_4Cl, TFE, 100 °C; (iii) 1 atm H_2, 20 mol % PtO_2, MeOH; (iv) (a) 40 equiv TMSNCO, 10–20 mol % H_2O, CH_2Cl_2 or *i*-PrOH, (b) 5 equiv K_2CO_3, MeOH; (v) 1.5–5 equiv DAST, CH_2Cl_2; (vi) 1:1 TFA/CH_2Cl_2, 0 °C to rt; (vii) 5 mol % $Pd(dppf)Cl_2$, 3 equiv K_2CO_3, 5:1 dioxane/H_2O, 80 °C; (viii) 10 equiv NaN_3, 5 equiv NH_4Cl, 8:1 MeOH/H_2O, 100 °C; (ix) 5 wt equiv Raney Ni, 20 equiv hydrazine hydrate, 20 equiv formic acid, MeOH, 0 °C to rt; (x) 1.2 equiv LiHMDS, 1.2 equiv $PhNTf_2$, THF, −78 °C to rt; (xi) 1.5 equiv *n*-BuLi, THF, −78 °C; (xii) 10 mol % *p*-TsOH·H_2O, toluene, 110 °C; (xiii) 4 equiv NaN_3, 4 equiv NH_4Cl, 6:1 TFE/H_2O, 80 °C; (xiv) 3 equiv TBSOTf, 5 equiv NEt_3, DMF; (xv) 20 equiv HCl in dioxane, 70 °C.

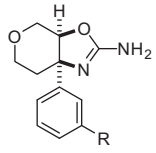
ically, the two isomeric piperidyl aminooxazolines (X = N, Y = CH_2 and X = CH_2, Y = N) provide alternate vectors toward P2′. The 2,4-difluorophenyl group was chosen to occupy P1 for these targets without a P3 substituent based on existing literature SAR for this region. The tetrahydropyranyl aminooxazoline (X = O, Y = CH_2) and cyclohexyl aminooxazoline (X = Y = CH_2) targets (without a practical vector to P2′) incorporate a substituent toward P3. These multiple points of diversity mandated that our synthetic route enable P2′ or P3 diversification at the last step.

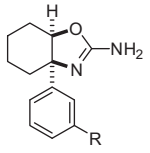
Our retrosynthetic analysis is presented in Figure 3. The most obvious disconnection (Fig. 3A) was to forge the aminooxazoline from an aryl alkene **D** in a single pot by the action of silver(I) cyanate and iodine, followed by introduction of ammonia—a method introduced by Hassner over forty years ago.[13] Alternatively (Fig. 3B), we envisioned the penultimate preparation of a bicyclic oxazolidinone via Rh-catalyzed C–H functionalization chemistry developed by Du Bois.[14] Finally (Fig. 3C), the target compound class could potentially arise from the diethylaminosulfur trifluoride (DAST)-mediated ring closure technique pioneered by Lellouche, Wipf and Williams.[9]

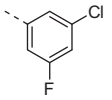
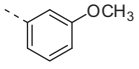
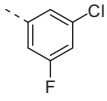
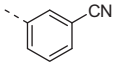
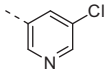
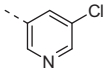
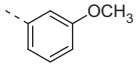
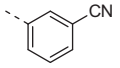
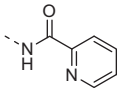
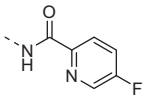
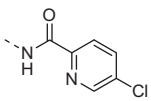
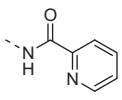
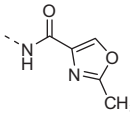
Scheme 1 depicts our results from the initial approaches **A** and **B**. The aryl alkenes **1** and **4** were easily obtained via Suzuki–Miyaura cross-couplings of commercially available starting materials.[15] Numerous attempts to invoke the Hassner method (Fig. 3A) and obtain aminooxazolines directly were unsuccessful (not shown). Iodoisocyanate was recalcitrant to engage either alkene **1** or **4** under a variety of conditions. Furthermore, we were not able to perform a direct attack of isocyanate nucleophiles onto in situ generated iodonium or bromonium ions. Although we hypothesized that there might be a prerequisite for an electron rich alkene, a variant of **1** possessing 4-methoxyphenyl instead of 3-bromo-4-fluorophenyl was also unreactive.[16]

In examining the C–H amination route (Fig. 3B), aryl alkene **1** underwent hydroboration–oxidation to provide a mixture of regioisomers (±)-**2** (Scheme 1, 23% yield). The choice of borane-dimethylsulfide complex was crucial since neither the tetrahydrofuran complex, catecholborane, nor 9-borabicyclo[3.3.1]nonane reacted with alkene **1**, even at elevated temperature. With (±)-**2** in hand, the primary carbamate (±)-**3** was secured through one-pot treatment with trichloroacetyl isocyanate and methanolysis of the resultant trichloroacetate (35% yield of (±)-**3**, plus 46% of the regioisomer).[17] In the piperidine series, the hydroboration–oxidation adduct of aryl alkene **4** was transformed directly to the carbamate (±)-**5** before purification (64% over two steps, plus 13% regioisomer). For the C–H amination step, tetrahydropyranyl carbamate (±)–**3** proved completely unreactive under a variety of con-

Table 1
BACE-1 SAR exploration for compounds based on tetrahydropyranyl aminooxazoline (±)-**14** and cyclohexyl aminooxazoline (±)-**29**





Compd	R	BACE1 IC_{50} (μM)	HLM CLhep (mL/min/kg)	Compd	R	BACE1 IC_{50} (μM)	HLM CLhep (mL/min/kg)
30		13.1	11	**29**		>200	4
31		37.1	14	**39**		26.6	–
32		46.4	5	**40**		11.8	7
33		45.8	6	**41**		38	18
34		99.3	2	**42**		34	6
35		>200	8	**43**		46.7	11
36		27.3	6	**44**		35.3	2
37		3.3	7	**45**		>200	–
38		38.2	6				

ditions. Interestingly, the piperidine carbamate (±)-**5** reacted smoothly under the original conditions reported by Du Bois to afford oxazolidinone (±)-**6** (71% yield), but with no evidence of the desired benzylic substitution event.[18]

The successful preparation of bicyclic aminooxazoline scaffolds using approach **C** (Fig. 3) is presented in Scheme 2. Commencing with aryl alkene **4**, epoxidation to (±)-**7** proceeded smoothly with *meta*-chloroperbenzoic acid (74% yield). Subsequent ring opening of epoxide (±)-**7** with sodium azide provided azidoalcohol (±)-**8** (56% yield, plus 11% recovered starting material). In initial studies on epoxide opening, we obtained mixtures of regioisomers which were separated and independently characterized spectroscopically.[19] For the major isomer in this case, a $^{1}H–^{15}N$ HMBC NMR correlation indicated that the azide was benzylic. Furthermore, oxidation of (±)-**8** to the corresponding ketone, along with the lack of reactivity of the constitutional tertiary alcohol with Dess–Martin Periodinane provided additional structural proof. Carrying forward, the amine resulting from azide reduction of (±)-**8** was treated with excess trimethylsilylisocyanate[20] in the presence of water to deliver a urea which, when treated with diethylaminosulfur trifluoride, produced bicyclic aminoxazoline (±)-**9** in 56% yield over three steps. Deprotection of (±)-**9** was accomplished with trifluoroacetic acid to produce 7a-(2,4-difluorophenyl)-3a,4,5,6,7,7a-hexahydrooxazolo[5,4-*c*]pyridin-2-amine (±)-**10** (78% yield).[21]

Tetrahydropyranyl bicyclic aminooxazoline (±)-**14** was obtained in a similar manner from aryl alkene **11** (Scheme 2). Following epoxidation to (±)-**12** (90% yield), ring opening with sodium azide was carried out in a mixture of methanol and water to afford (±)-**13** (78% yield, plus 9% of the regioisomer). This solvent mixture was necessary as trifluoroethanol solvent (used in the synthesis of compound (±)-**8**) afforded exclusively the undesired regioisomer as confirmed by X-ray crystallography of the final aminooxazoline products. Reduction of azide (±)-**13** in this case was performed with Raney nickel, hydrazine, and formic acid in methanol. The use of Raney nickel in the absence of hydrazine, formic acid, or both, resulted in hydrodebromination. The intermediate amine was then subjected to urea formation and DAST-mediated ring closure to produce bicycle (±)-**14** in 64% yield over three steps.[22]

The synthesis of bicycle (±)-**21** began with trifluoromethanesulfonation of the enolate derived from *N*-(*tert*-butoxycarbonyl)-piperidone (50% yield of **15**, plus 49% regioisomer).[23] Subsequent Suzuki cross-coupling of **15** afforded **16** (67% yield). Epoxidation ((±)-**17**, 73% yield), azide introduction ((±)-**18**, 23% yield, plus 47% recovered starting material), azide reduction and urea generation provided compound (±)-**19** in 84% yield over two steps. Reaction of (±)-**19** with DAST ((±)-**20**, 41% yield) and *N*-*tert*-butoxycarbonyl deprotection afforded 3a-(2,4-difluorophenyl)-3a,4,5,6,7,7a-hexahydrooxazolo[4,5-*c*]pyridin-2-amine (±)-**21** in 92% yield.[24]

Finally, cyclohexane-fused aminooxazoline (±)-**29** was constructed in nine steps from cyclohexanone (Scheme 2). The requisite aryl alkene **23** was produced by lithium–halogen exchange of 1,3-dibromobenzene and carbonyl addition onto cyclohexanone (**22**, 90% yield) followed by acid-catalyzed dehydration (75% yield). Thereafter, epoxidation ((±)-**24**, 90% yield), azide introduction ((±)-**25**, 53% yield), and *tert*-butyldimethylsilyl protection afforded (±)-**26** (83% yield). Azide reduction ((±)-**27**, 77% yield) was followed by acidic rupture of the silyl blocking group and urea formation to afford compound (±)-**28** (54% yield over two steps). When compound (±)-**28** was submitted to the action of DAST, bicycle (±)-**29** was produced in 80% yield.[25]

The final analogs were synthesized from aminooxazolines (±)-**10**, (±)-**14**, (±)-**21**, and (±)-**29** through Suzuki–Miyaura cross-couplings, Cu-mediated amidations, nucleophilic aromatic substitutions, or alkylations. The piperidyl aminooxazoline analogs based on compounds (±)-**10** and (±)-**21** with a variety of P2′ substituents such as carbamates, alkyls, 2-pyridyls, 2-pyrazinyl, and 2-pyrimidyls failed to provide IC_{50} <50 μM (Table S1). Despite poor binding affinity, X-ray structures in BACE-1 provided some insight into their binding mode and confirmed that the aminooxazoline functional group could interact with the catalytic aspartic acids in the active site (Fig. S1).

Accordingly, the bicyclic scaffolds without P2′ substituents were subsequently explored. Extending into the P3 pocket with the cyclohexyl and tetrahydropyranyl fused ring systems improved binding affinity for BACE-1 (Table 1). P3 aryl ((±)-**30** – (±)-**32**, (±)-**39**, (±)-**41**, (±)-**42**) and heteroaryl ((±)-**33**, (±)-**34**, (±)-**40**, (±)-**43**, (±)-**44**) substituents on the tetrahydropyranyl aminooxazoline

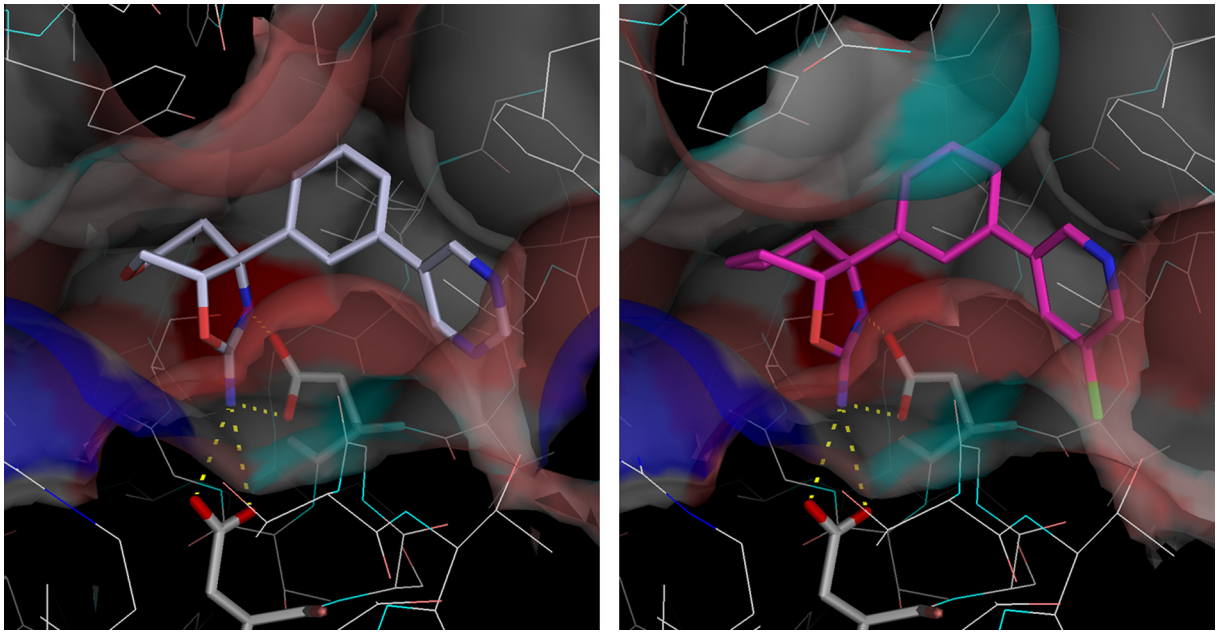


Figure 4. X-ray structures of compound (±)-**34** (left, 1.38 Å resolution) and compound (±)-**40** (right, 1.7 Å resolution) in BACE-1.

and cyclohexyl aminooxazoline scaffolds provided high micromolar activity against BACE-1. The 5-fluoropicolinamido and 5-chloropicolinamido substituents on the tetrahydropyranyl aminooxazoline afforded BACE-1 IC_{50} = 27.3 and 3.3 μM, respectively. In the cyclohexyl aminooxazoline scaffold, the 3-chloropyridyl (±)-**40**, which had an efflux ratio of 2.5 (MDR1-LLC–PK1 @ 1 μM),[26] was the most potent analog examined (BACE-1 IC_{50} = 11.8 μM). The analogs shown in Table 1 generally exhibited good to moderate human liver microsome stability. The X-ray structures of inhibitors (±)-**34** and (±)-**40** show the bicyclic aminooxazolines engaging the catalytic aspartic acids while occupying the P1 and P3 pockets (Fig. 4).[27] Interestingly, boat conformations of the tetrahydropyran- and cyclohexane-based inhibitors (±)-**34** and (±)-**40** were observed in the X-ray cocrystal structures and may indicate the ligands adopt a potentially unfavorable conformation to accommodate the flap region over the active site.

In summary, rescaffolding of a spiro-aminooxazoline to a bicyclic aminooxazoline provided new chemical matter. The synthesis of these bicyclic aminooxazoline compounds was enabled by the intramolecular diethylaminosulfur trifluoride (DAST)-mediated ring closure of a benzylic urea onto a secondary alcohol. Ultimately, these bicyclic aminooxazoline analogs did not provide an ideal vector to access the P2′ pocket; however, occupation of the P3 pocket afforded micromolar biochemical activity against BACE-1.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.136.

References and notes

1. (a) Querfurth, H. W.; LaFerla, F. M. *N. Engl. J. Med.* **2010**, *362*, 329–344; (b) Citron, M. *Nat. Rev. Drug Disc.* **2010**, *9*, 387–398; (c) Karran, E.; Mercken, M.; De Strooper, B. *Nat. Rev. Drug Disc.* **2011**, *10*, 698–712.
2. Brody, H. *Nature* **2011**, *475*, S1–S22.
3. Hargreaves, R. J. *ACS Med. Chem. Lett.* **2013**, *3*, 862–866.
4. (a) Vassar, R.; Bennett, B. D.; Babu-Khan, S.; Kahn, S.; Mendiaz, E. A.; Denis, P.; Teplow, D. B.; Ross, S.; Amarante, P.; Loeloff, R.; Luo, Y.; Fisher, S.; Fuller, J.; Edenson, S.; Lile, J.; Jarosinski, M. A.; Biere, A. L.; Curran, E.; Burgess, T.; Louis, J.-C.; Collins, F.; Treanor, J.; Rogers, G.; Citron, M. *Science* **1999**, *286*, 735–741; (b) Yan, R.; Bienkowski, M. J.; Shuck, M. E.; Miao, H.; Tory, M. C.; Pauley, A. M.; Brashler, J. R.; Stratman, N. C.; Mathews, W. R.; Buhl, A. E.; Carter, D. B.; Tomasselli, A. G.; Parodi, L. A.; Heinrikson, R. L.; Gurney, M. E. *Nature* **1999**, *402*, 533–537; (c) Sinha, S.; Anderson, J. P.; Barbour, R.; Basi, G. S.; Caccavello, R.; Davis, D.; Doan, M.; Dovey, H. F.; Frigon, N.; Hong, J.; Jacobson-Croak, K.; Jewett, N.; Keim, P.; Knops, J.; Lieberburg, I.; Power, M.; Tan, H.; Tatsuno, G.; Tung, J.; Schenk, D.; Seubert, P.; Suomensaari, S. M.; Wang, S.; Walker, D.; Zhao, J.; McConlogue, L.; John, V. *Nature* **1999**, *402*, 537–540.
5. (a) Ghosh, A. K.; Shin, D.; Downs, D.; Koelsch, G.; Lin, X.; Ermolieff, J.; Tang, J. *J. Am. Chem. Soc.* **2000**, *122*, 3522–3523; (b) Tung, J. S.; Davis, D. L.; Anderson, J. P.; Walker, D. E.; Mamo, S.; Jewett, N.; Hom, R. K.; Sinha, S.; Thorsett, E. D.; John, V. *J. Med. Chem.* **2002**, *45*, 259–262.
6. (a) Gerald, Z.; Ockert, W. *Nat. Rev. Drug Disc.* **2013**, *12*, 19–20; (b) May, P. C.; Dean, R. A.; Lowe, S. L.; Martenyi, F.; Sheehan, S. M.; Boggs, L. N.; Monk, S. A.; Mathes, B. M.; Mergott, D. J.; Watson, B. M.; Stout, S. L.; Timm, D. E.; LaBell, E. S.; Gonzales, C. R.; Nakano, M.; Jhee, S. S.; Yen, M.; Ereshefsky, L.; Lindstrom, T. D.; Calligaro, D. O.; Cocke, P. J.; Hall, D. G.; Friedrich, S.; Citron, M.; Audia, J. E. *J. Neurosci.* **2011**, *31*, 16507–16516; (c) Jeppsson, F.; Eketjäll, S.; Janson, J.; Karlström, S.; Gustavsson, S.; Olsson, L.-L.; Radesäter, A.-C.; Ploeger, B.; Cebers, G.; Kolmodin, K.; Swahn, B.-M.; von Berg, S.; Bueters, T.; Fälting, J. *J. Biol. Chem.* **2012**, *287*, 41245–41257.
7. Early work in these structural classes: (a) Barrow, J. C.; Stauffer, S. R.; Rittle, K. E.; Ngo, P. L.; Yang, Z.; Selnick, H. G.; Graham, S. L.; Munshi, S.; McGaughey, G. B.; Holloway, M. K.; Simon, A. J.; Price, E. A.; Sankaranarayanan, S.; Colussi, D.; Tugusheva, K.; Lai, M.-T.; Espeseth, A. S.; Xu, M.; Huang, Q.; Wolfe, A.; Pietrak, B.; Zuck, P.; Levorse, D. A.; Hazuda, D.; Vacca, J. P. *J. Med. Chem.* **2008**, *51*, 6259–6262; (b) Zhu, Z.; Sun, Z.-Y.; Ye, Y.; Voigt, J.; Strickland, C.; Smith, E. M.; Cumming, J.; Wang, L.; Wong, J.; Wang, Y.-S.; Wyss, D. F.; Chen, X.; Kuvelkar, R.; Kennedy, M. E.; Favreau, L.; Parker, E.; McKittrick, B. A.; Stamford, A.; Czarniecki, M.; Greenlee, W.; Hunter, J. C. *J. Med. Chem.* **2010**, *53*, 951–965; (c) Malamas, M. S.; Erdei, J.; Gunawan, I.; Turner, J.; Hu, Y.; Wagner, E.; Fan, K.; Chopra, R.; Olland, A.; Bard, J.; Jacobsen, S.; Magolda, R. L.; Pangalos, M.; Robichaud, A. J. *J. Med. Chem.* **2010**, *53*, 1146–1158.
8. Hunt, K. W.; Cook, A. W.; Watts, R. J.; Clark, C. T.; Vigers, G.; Smith, D.; Metcalf, A. T.; Gunawardana, I. W.; Burkard, M.; Cox, A. A.; Geck Do, M. K.; Dutcher, D.; Thomas, A. A.; Rana, S.; Kallan, N. C.; DeLisle, R. K.; Rizzi, J. P.; Regal, K.; Sammond, D.; Groneberg, R.; Siu, M.; Purkey, H.; Lyssikatos, J. P.; Marlow, A.; Liu, X.; Tang, T. P. *J. Med. Chem.* **2013**, *56*, 3379–3403.
9. (a) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168; (b) Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Heterocycles* **1995**, *41*, 947–958; (c) Burrell, G.; Evans, J. M.; Jones, G. E.; Stemp, G. *Tetrahedron Lett.* **1990**, *31*, 3649–3652.
10. (a) Audia, J. E.; Mergott, D. J.; Shi, C. E.; Vaught, G. M.; Watson, B. M.; Winneroski, Jr., L. L. *PCT Int. Appl.* (**2011**), WO 2011005738.; (b) Suzuki, Y.; Motoki, T.; Kaneko, T.; Takaishi, M.; Ishida, T.; Takeda, K.; Kita, Y.; Yamamoto, N.; Khan, A.; Dimopoulos, P. *PCT Int. Appl.* (**2009**), WO 2009091016.
11. Stamford, A. W.; Zhu, Z.; Mandal, M.; Wu, Y.; Cumming, J. N.; Liu, X.; Li, G.; Iserloh, U. *PCT Int. Appl.* (**2011**), WO 2009131975.
12. A single example of a related design that features a bicyclic aminothiazoline has appeared: See Ref. [10b].
13. Hassner, A.; Lorber, M. E.; Heathcock, C. *J. Org. Chem.* **1967**, *32*, 540–549.
14. (a) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598–600; (b) Du Bois, J. *Org. Process Res. Dev.* **2011**, *15*, 758–762.
15. These aryl alkenes were only stable for a few days, even when stored under inert atmosphere at 4 °C.
16. Obtained in the dihydropyranyl series through Suzuki–Miyaura coupling under otherwise identical conditions (46% yield).
17. Kočovský, P. *Tetrahedron Lett.* **1986**, *27*, 5521–5524.
18. *Data for (±)-**6**:* ^{1}H NMR (1.4:1 rotamer ratio, * denotes minor rotamer peaks, 500 MHz, $CDCl_3$) δ 7.14 (m, 1H), 6.81–6.88 (m, 2H), 5.93 (m, 1H), 5.45 (m, 1H), 5.19* (m, 1H), 4.77 (m, 1H), 4.06* (m, 1H), 3.77 (m, 1H), 3.29 (m, 1H), 3.20 (m, 1H), 1.86–2.00 (m, 2H), 1.49 (br s, 9H).
19. The use of trifluoroethanol (TFE) was crucial in favoring the desired isomer. We thank Professor Scott E. Denmark for this suggestion.
20. Neville, R. G. *J. Org. Chem.* **1958**, *23*, 937–938.
21. *Data for (±)-**9**:* ^{1}H NMR (1.4:1 rotamer ratio, * denotes minor rotamer peaks, 400 MHz, $CDCl_3$) δ 7.77–7.59 (m, 1H), 6.94–6.68 (m, 2H), 4.88–4.77 (m, 1H), 4.77–4.62* (m, 1H), 4.27 (d, *J* = 14.7 Hz, 1H), 4.10* (d, *J* = 14.7 Hz, 1H), 3.64–3.39 (m, 3H), 2.44–2.26 (m, 1H), 1.86–1.71 (m, 1H), 1.48 (s, 9H).
22. *Data for (±)-**14**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.29 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.77 (m, 1H), 4.05 (dd, *J* = 13.4, 3.1 Hz, 1H), 3.96–3.83 (m, 3H), 2.34–2.27 (m, 1H), 2.18–2.10 (m, 1H)
23. Mc Murry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979–982.
24. *Data for (±)-**20**:* ^{1}H NMR (1.1:1 rotamer ratio, * denotes minor rotamer peaks, 400 MHz, DMSO-d_6) δ 7.71 (q, *J* = 8.4 Hz, 1H), 7.22 (ddd, *J* = 11.7, 9.1, 2.6 Hz, 1H), 7.07 (ddd, *J* = 10.1, 5.6, 1.9 Hz, 1H), 6.15 (s, 2H), 4.69 (m, 1H), 3.59 (d, *J* = 13.4 Hz, 1H), 3.48* (d, *J* = 13.5 Hz, 1H), 3.41–3.31 (m, 2H), 3.26–3.06 (m, 1H), 2.21 (t, *J* = 8.6 Hz, 1H), 2.04–1.91 (m, 1H), 1.40 (s, 9H), 1.34* (s, 9H).
25. *Representative procedure for DAST-mediated cyclization:* To an ice-cooled solution of racemic 1-((1*R*,2*S*)-1-(3-bromophenyl)-2-hydroxycyclohexyl)urea (0.400 g, 1.28 mmol) in dichloromethane (10 mL) under nitrogen was added diethylaminosulfur trifluoride (0.95 mL, 7.2 mmol). The reaction mixture was allowed to warm to 24 °C. After 2.5 h, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution, and the resulting mixture was extracted with dichloromethane. The collected organics were dried over anhydrous sodium sulfate, filtered, and concentrated to afford racemic (3a*R*,7a*R*)-3a-(3-bromophenyl)-3a,4,5,6,7,7a-hexahydrobenzo[*d*]oxazol-2-amine as a yellow solid (370 mg, 80%); ^{1}H NMR (500 MHz, CD_3OD) δ 7.62 (s, 1H), 7.38 (m, 2H), 7.24 (m, 1H), 4.58 (m, 1H), 2.00–1.52 (m, 8H).
26. In vitro MDR1-transfected LLC–PK1 assay run at 1 μM concentration of test compound.
27. PDB codes: 4L7G and 4LC7.