6484 J. Med. Chem. 2009, 52, 6484–6488
DOI: 10.1021/jm9008482

Journal of Medicinal Chemistry
Brief Article

Rational Design and Synthesis of Potent Dibenzazepine Motifs as β-Secretase Inhibitors

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Received June 2, 2009

We have identified small-molecule dibenzazepine inhibitors of β-secretase (BACE1). These BACE1 inhibitors possess two key salient features. The first is a seven-membered heterocyclic ring fused to two aromatic rings representing the P3−P2 residues. The second is an amide and/or amide bioisostere representing the P1′ residue. Rational optimization led to the identification of potent analogues, such as **10** (K_I = 211 nM).

Introduction

Alzheimer's disease (AD[a]) is a progressive, neurodegenerative disorder with no current cure and is the leading cause of dementia and death in elderly people.[1−3] A key hallmark of AD is deposition of aggregated β-amyloid peptides (Aβ-40, -42) as plaques in the brain.[4] Two proteases, β- and γ-secretase, have been identified to be involved in the sequential proteolysis of membrane-anchored amyloid precursor protein (APP).[5]

β-Secretase (BACE1) has been shown to be a membrane-bound aspartyl protease and is considered to be involved in the rate-limiting step in the processing of APP to Aβ peptide responsible for the production of the membrane-bound β-C-terminal fragment, which is then further cleaved to Aβ by γ-secretase (Figure 1).[6] BACE1 knockout homozygote mice show a complete absence of the plaques resulting from the production of Aβ in the brain, and the lack of BACE1 has been reported to have no side effects.[7] Thus, BACE1, which is highly expressed in the CNS, is deemed to be an attractive target for drug discovery through inhibition of Aβ production.[8]

Different classes of nonpeptidic potent BACE1 inhibitors, including acylguanidines, isophthalic acid derivatives, amino aromatic heterocyclic motifs, and arylpiperazines, have been reported.[8] In particular, the isophthalic acid derivatives were shown to demonstrate potent inhibitory activity in the subnanomolar range.[8c,d]

Results and Discussion

In the present study, it was anticipated that the isophthalic acid motifs reported by many groups could be envisioned to be superimposed on the more rigid dibenzazepine motifs (Figure 2).[8] Specifically, we hypothesized that the incorporation of a seven-membered diazepine ring system (representing P3 residue) fused to a phthalic acid derivative (representing P2 residue) might retain the pharmacodynamic properties and improve the pharmacokinetic characteristics found in isophthalic acid derivatives against BACE1 (Figure 2).[8] Furthermore, P1′-residue could be manipulated to include amides and/or amide bioisosters that might fit the S1′ pocket of the enzyme active site.

To verify this hypothesis, we have designed low molecular weight nonpeptidic BACE1 inhibitors that incorporate a dibenzazepine core. Although the hydroxyethylamine (HEA) derivatives of isophthalic acid published earlier are highly potent inhibitors of BACE1, these compounds suffered from poor pharmacokinetic stability.[8] Hence, we replaced both of the amides in isophthalic acid derivatives, represented in compound **1**, with dibenzazepine and imidazole isosters to fit in the S3 and S1′ subpockets (**I**, **II**), respectively. The synthetic route used to prepare these motifs to connect in tandem the probable blocks corresponding to P3−P1′ residues is outlined in Scheme 1.

Synthesis. Compound **4** was prepared in 85% yield (Scheme 2) through the nucleophilic aromatic substitution carried out between **2** and **3**. The nitro group in the diphenylamine **4** was subjected to Pd/C reduction using $HCONH_4$ as a source of H_2 to deliver the amine **5** in 75% yields after column chromatography. Amide formation using ethylformyl chloride followed by electrophilic aromatic substitution catalyzed by $POCl_3$ furnished the dibenzazepine framework **7**. Saponification of **7** produced acid **8**. At this stage, we took advantage of the flexibility present in the carboxylic acid appendage and the possibility of functionalizing this group with various residues.

Therefore, three different classes in relation to P1′ residue were synthesized. These included simple amides, substituted imidazole and benzimidazole derivatives as outlined in Schemes 3 and 4. The acid **8** was converted to the amides **9** and **10** through standard coupling protocol using TBTU/DIPEA (Scheme 3) in 85% and 87% yields, respectively. For the synthesis of the second class, conventional synthetic

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[a] Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; BACE1, β-site amyloid precursor protein cleaving enzyme 1.

 Published on Web 09/29/2009

procedures were followed to achieve our scaffolds. Therefore, the imidazole isosters **11** and **12** were synthesized through coupling between acid **8** with the desired α-bromo ketone followed by refluxing the produced esters in $AcONH_4$/AcOH (Scheme 3). The third types of motifs were benzimidazole analogues **13** and **14** (Scheme 4) and were made from acid **8** utilizing standard coupling with the desired diamine using TBTU/DIPEA followed by refluxing the amide products in AcOH.

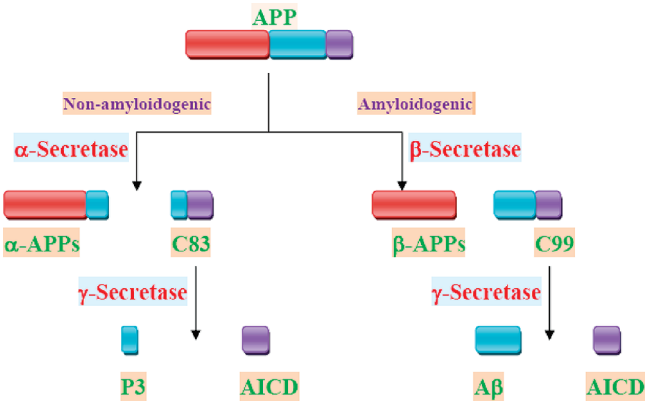


Figure 1. Schematic of the APP and its metabolites (not drawn to scale). APP can be processed along two major pathways, the α-secretase pathway and the amyloid forming *β*-secretase pathway. In the nonamyloidogenic pathway, α-secretase cleaves in the middle of the A*β* region to release a large soluble APP fragment, α-APPs. The C-terminal C83 peptide is metabolized to p3 and AICD (APP intracellular domain) by *γ*-secretase. In the amyloid forming *β*-secretase pathway, *β*-secretase releases a large soluble fragment, *β*-APPs. The C-terminal C99 peptide is then metabolized to A*β* and AICD by *γ*-secretase. *β*-Secretase inhibitors block the formation of *β*-APPs and C99.

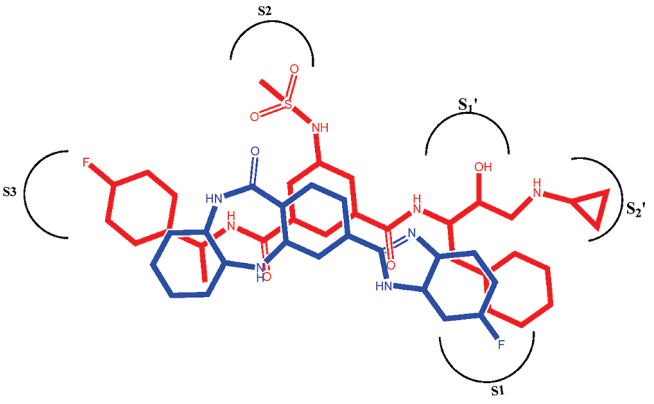
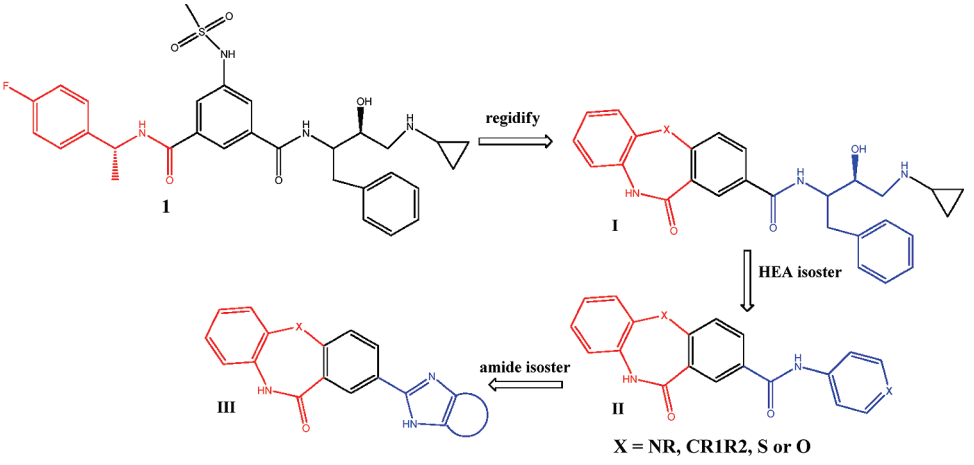


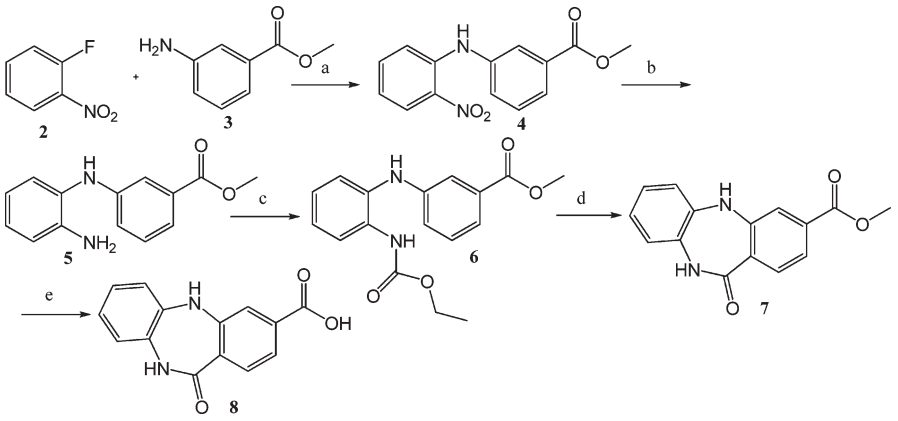
Figure 2. Two dimensional overlay of compound **14** (blue) and **1** (red) indicating the possible interaction modes with the BACE1 pockets.

Biology. BACE1 inhibitory activity of the synthesized motifs was determined using a fluorescence resonance energy transfer assay (FRET).[9] Analogues of **9** were then synthesized and allowed for optimization of the P1′ substituent. The activity of these novel derivatives is summarized in Table 1. In general, the fluorophenylamide motif **10** led to a compound that is a relatively more potent BACE1 inhibitor (K_I = 211 nM) than the corresponding pyridylamide analogue **9** (K_I = 295 nM). On the other hand, the aryl-fused imidazole derivatives (e.g., **14**, K_I = 244 nM) are more potent than the substituted imidazole systems (e.g., **12**, K_I = 293 nM). The fluorophenyl analog (**10**) was consistently the most potent in the BACE inhibition assay. Successively rigidifying P1′ substituents (**11** and **13**) eroded activity of the pyridyl motifs in a systematic fashion. The lack of a potency difference between amide **10** and its imidazole isoster **14** (Table 1) was striking, especially considering the small conformational difference observed in both analogues. In conclusion, these SAR findings suggested that the fluorophenyl analogues in the three derivatives (**10**, **12**, and **14**) are more active than their pyridyl analogues (**9**, **11**, and **13**), perhaps because of the similarity in the nature of interaction forces between these motifs and BACE1 active site. The absolute inhibition constants and the ligand efficiency indexes of our new diabenzazepine analogues are summarized in Table 1 and were found to be consistent with K_I values. Furthermore, in comparison with the known BACE1 inhibitors **1** and the peptide-based inhibitor OM99-2 (H-Glu-Val-Asn-*ψ*-Leu-Ala-Glu-Phe-OH; *ψ* denotes replacement of CONH by (*S*)-CH(OH)CH_2) (Figure 3), our designed scaffolds indicated their potential inhibition properties toward BACE1. At this junction it is worthwhile mentioning that **1** and the known peptide inhibitor OM99-2 showed obviously a 100-fold better activity than our developed compounds. But both are not applicable for clinical use because of their poor pharmacokinetic.[8] On the other hand, benzazepine derivatives are known to have appreciable pharmacokinetic profile and able to cross the blood−brain barrier.[10] Second, by calculation of the ligand efficiency (Δ*g* = free binding energy/number of non-hydrogen atoms), it could also be

Scheme 1. Rational Design of Dibenzazepine BACE1 Inhibitors Based on Isophthalic Acid Derivatives

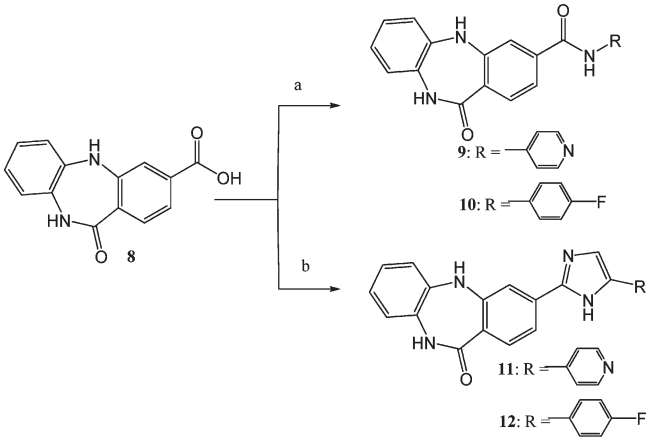


Scheme 2. Synthesis of the Benzodiazepam Starting Material[a]



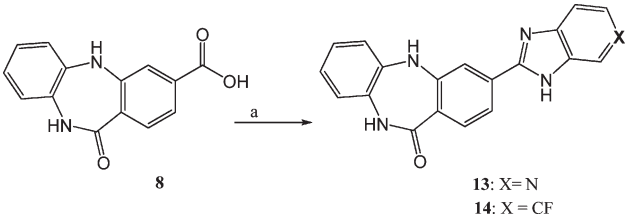
[a] (a) K_2CO_2, CuI, DMF, 60 °C, 12 h (85%); (b) 10 mol % of 10% Pd/C, methanol, $HCONH_4$, 50 °C, 5 h (75%); (c) ethyl carbonochloridate, pyridine, 0 °C, 6 h (93%); (d) $POCl_3$, P_2O_5, reflux, 6 h (62%); (e) NaOH, methanol, H_2O, 25 °C, 12 h (95%).

Scheme 3. Synthesis of BACE1 Inhibitors[a]



[a] Reagents and conditions. (a) **9**: 4-aminopyridine, TBTU, DIPEA, DMF, 0 °C, 6 h (85%). **10**: *p*-fluoroaniline, TBTU, DIPEA, DMF, 0 °C, 6 h (87%). (b) **11**: α-bromomethyl pyridyl ketone, DMF, DIPEA, 0 °C to room temp, 6 h (95%); then AcOH, $AcONH_4$, reflux, 8 h (55%). **12**: α-bromomethyl (4- fluorophenyl) ketone, DMF, DIPEA, 0 °C, 6 h (95%); then AcOH/$AcONH_4$, reflux, 8 h (60%).

Scheme 4. Synthesis of BACE1 Inhibitors[a]



[a] (a) **13**: 3,4-diaminopyridine, TBTU, DIPEA, DMF, 0 °C, 6 h (82%); then AcOH, reflux, 6 h (64%). **14**: 1,2-diamino-4-fluorobenezene, TBTU, DIPEA, DMF, 0 °C, 6 h (86%); then AcOH, reflux, 6 h (58%).

shown that our low molecular weight derivatives bind more efficiently to the target compared to the peptidic inhibitor OM99-2 ($\Delta g \approx 1.4$ kJ/mol for our described dibenzazepine inhibitors vs $\Delta g = 0.79$ kJ/mol for OM99-2; see Table 1). These findings support our assumption that the described concept of dibenzazepine ligands as BACE1 inhibitors might be the starting point of a new generation of anti-AD drugs.

In summary, the combination of dibenzazepine motif with optimized replacements for the P2/P3 residues and P1′ appendage resulted in compounds, **10** and **14**, that represent promising new series of BACE-1 inhibitors. These new compounds displayed good enzymatic inhibitory potency and a molecular weight below 350. Further improvement of these parameters and the incorporation of other druglike properties into these inhibitors are the subjects of ongoing efforts.

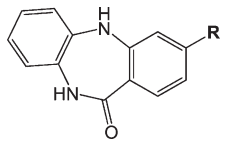
Experimental Section

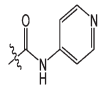
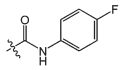
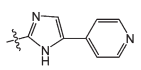
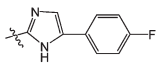
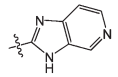
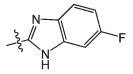
Chemistry. Materials and General Methods. Reagents and solvents were purchased from commercial sources and were used as received. Reaction progress was monitored by thin-layer chromatography on Merck silica gel 60 F-254 with detection by UV. Silica gel 60 (Merck 40−63 μm) was used for flash column chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker 500 and Bruker AMX-400 spectrometers using $CDCl_3$. Data are presented as follows: chemical shift (parts per million, ppm), multiplicity ((s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br) broad), coupling constant *J* (in hertz), and integration. Carbon magnetic resonance (^{13}C NMR) spectra were recorded at 75 or 125 MHz. Data for ^{13}C NMR are reported in terms of chemical shifts (ppm). The EI and FD mass spectra were recorded on a Finnigan MAT 312 mass spectrometer connected to a PDO 11/34 (DEC) computer system. Elemental analysis was performed on a Perkin-Elmer elemental analyzer, model 240.

All compounds were determined to be >95% pure by high-performance liquid chromatography (HPLC). Purity of compounds were determined on a Phenomenex Luna C18-(2), 3 mm column, 4.6 mm i.d. × 30 mm length, with 30−75% acetonitrile/water/0.1% trifluoroacetic acid, 1.0 mL/min elution at room temperature using 210, 254, or 280 nm wavelength.

BACE1 Enzyme Assay. BACE1 assay was carried out according to the manufacturer prescribed protocol available from Invitrogen (http://tools.invitrogen.com/content/sfs/manuals/L0724.pdf). Briefly, the in vitro assay was carried out by fluorescence resonance energy transfer (FRET). An APP-based peptide substrate (rhodamine-EVNLDAEFK-DABCYL, $K_M = 20$ μM) carrying the Swedish mutation and containing a rhodamine as a fluorescence donor and a quencher acceptor at each end was used. The intact substrate is weakly fluorescent and becomes highly fluorescent upon enzymatic cleavage. The assay was conducted in 50 mM sodium acetate buffer, pH 4.5, in a final enzyme reaction mixture of enzyme (1 U/mL), inhibitor (10, 3, 1, and 0.3 μM) and substrate (750 nM). Inhibitor compounds were diluted from stock solutions to result in 3.3% DMSO final concentration. The reaction was incubated for 60 min at 25 °C under dark conditions and then stopped with 2.5 M sodium acetate. Fluorescence was monitored with a

Table 1. SAR of BACE1 Inhibitors



Compound	R	K_I (nM)	ΔG (kJ/mol)	Δg (kJ/mol)
9		295 ± 12	-37.25	1.49
10		211 ± 27	-38.09	1.46
11		348 ± 36	-36.84	1.36
12		293 ± 44	-37.27	1.33
13		309 ± 15	-37.14	1.49
14		244 ± 28	-37.72	1.45

spectrofluorometer at 545 nm excitation and 585 nm emission. The assay kit was validated by manufacturer. The obtained values are the mean values of three different experiments. IC_{50} values were calculated by plotting the obtained relative fluorescence unit per hour (RFU/h) against the logarithm of inhibitor concentration. The measured inhibition data were analyzed in GraphPad Prism 4 for Windows (GraphPad Software Inc., La Jolla, CA) by nonlinear regression (curve fitting). Based on obtained IC_{50} values, K_I values were calculated (detailed description is in the Supporting Information).

Methyl 11-Oxo-*N*-(pyridin-4-yl)-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepine-3-carboxamide (9) and *N*-(4-Fluorophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepine-3-carboxamide (10). To a solution of methyl 11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepine-3-carboxylic acid (**8**) (254 mg, 1.0 mmol, 1 equiv) in DMF (8 mL) at 0 °C was added DIPEA (0.21 mL, 1.2 mmol, 1.2 equiv). After 10 min TBTU (551 mg, 1.2 mmol, 1.2 equiv) was added and the resulting mixture stirred at the same temperature for 30 min. Then 4-aminopyridine or 4-flouroaniline (1.1 mmol, 1.1 equiv) was added. The resulting mixture was stirred at 0 °C for 6 h and then quenched with ice−water. The precipitated solid was filtered, washed with water, and dissolved in EtOAc. The organic phase was washed with a 1 N HCl aqueous solution, then with a saturated $NaHCO_3$ aqueous solution, and finally with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/AcOEt, 9/1 to 7/3) to give methyl 11-oxo-*N*-(pyridin-4-yl)-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepine-3-carboxamide (**9**) (85%) or *N*-(4-fluorophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*]-[1,4]diazepine-3-carboxamide (**10**) (87%).

11-Oxo-*N*-(pyridin-4-yl)-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]-diazepine-3-carboxamide (9). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.34 (1H, bs), 7.24−7.02 (3H, m), 7.54 (1H, bs), 7.80 (2H, m), 7.92 (1H, bs), 8.00 (1H, d, J = 2.3 Hz), 8.63 (1H, dd, J = 2.1, 8.2 Hz), 9.13 (1H, bs), 9.51 (1H, bs). ^{13}C NMR: δ = 114.2, 114.8, 115.0, 115.9, 119.9, 122.3, 123.9, 125.8, 127.9, 129.2, 132.0, 137.5, 145.3, 146.7, 147.9, 148.1, 148.4, 163.2, 165.1. FD-MS (M + 1) = 331. Anal. Calcd for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 69.05; H, 4.21; N, 16.89.

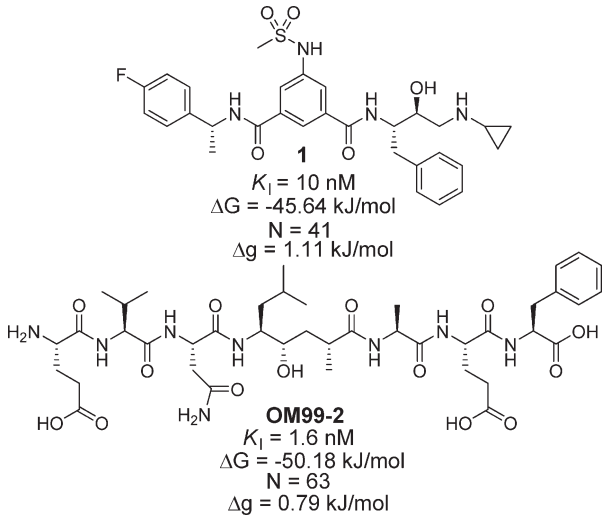


Figure 3. Structures of compounds **1** and OM99-2, their inhibition constants, and ligand efficiency indexes.

***N*-(4-Fluorophenyl)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*]-[1,4]diazepine-3-carboxamide (10).** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.52 (1H, bs), 7.26−7.01 (5H, m), 7.90−7.58 (3H, m), 8.00 (3H, m), 8.34 (1H, s), 9.01 (1H, bs). ^{13}C NMR: δ = 114.9, 115.1, 117.8, 119.5, 120.6, 121.9, 123.7, 123.8, 124.3, 127.3, 129.4, 133.6, 135.9, 137.0, 142.7, 151.3, 158.2, 163.4, 165.1. FD-MS (M + 1) = 348. Anal. Calcd for $C_{20}H_{14}FN_3O_2$: C, 69.16; H, 4.06; F, 5.47; N, 12.10. Found: C, 69.09; H, 4.13; F, 5.51; N, 12.09.

3-(5-(Pyridin-4-yl)-1*H*-imidazol-2-yl)-5*H* dibenzo[*b*,*e*][1,4]-diazepin-11(10*H*)-one (11) and 3-(5-(4-Fluorophenyl)-1*H*-imidazol-2-yl)-5*H* dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one (12). To a solution of methyl 11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]-diazepine-3-carboxylic acid (**8**) (254 mg, 1.0 mmol, 1 equiv) in DMF (10 mL) at 0 °C was added DIPEA (0.21 mL, 1.2 mmol, 1.2 equiv). The resulting mixture was stirred at 0 °C for 30 min followed by dropwise addition of the appropriate addition of the α-bromoketone (1.1 mmol, 1.1 equiv) in DMF. The resulting mixture was stirred at 0 °C for 6 h, then quenched with ice−water. The precipitated solid was filtered, washed with water, and dissolved in EtOAc. The organic phase was washed with a 1 N HCl aqueous solution and then a saturated $NaHCO_3$ aqueous solution, then H_2O, dried over $MgSO_4$, and concentrated in vacuo, which was used in the next stage without further purification. To the appropriate α-keto ester were added AcOH (25 mL) and $AcONH_4$ (924 mg, 12 mmol, 12 equiv), and the resulting suspension was refluxed for 8 h, cooled to room temperature, concentrated in vacuo, and diluted with crushed ice. The brown solid was filtered, washed thoroughly with water. The crude cake was dissolved in EtOAc washed with a saturated $NaHCO_3$ aqueous solution and with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/AcOEt, 8/2 to 7/3) to give 3-(5-(pyridin-4-yl)-1*H*-imidazol-2-yl)-5*H* dibenzo[*b*,*e*]-[1,4]diazepin-11(10*H*)-one (**11**) (55%) or 3-(5-(4-fluorophenyl)-1*H*-imidazol-2-yl)-5*H* dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one (**12**) (60%).

3-(5-(Pyridin-4-yl)-1*H*-imidazol-2-yl)-5*H*-dibenzo[*b*,*e*][1,4]-diazepin-11(10*H*)-one (11). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.34 (1H, s), 7.20−7.03 (2H, m), 7.28 (1 h, dd, J = 2.4, 8.3 Hz), 7.37 (1H, s), 7.53 (1H, m), 7.73−7.70 (2H, m), 9.92 (1 h, s), 7.99 (1 h, d, J = 1.82 Hz), 8.42 (2H, m), 8.49 (1H, dd, J = 2.3, 8.2 Hz), 9.21 (1H, s), 9.84 (1H, bs). ^{13}C NMR: δ = 117.8, 117.9, 118.4, 120.9, 121.5, 122.7, 124.0, 125.6, 127.6, 129.1, 129.3, 131.0,

133.1, 135.3, 136.5, 141.8, 142.8, 149.7, 151.0, 163.4. FD-MS (M + 1) = 354. Anal. Calcd for $C_{21}H_{15}N_5O$: C, 71.38; H, 4.28; N, 19.82. Found: C, 71.44; H, 4.32; N, 19.78.

3-(5-(4-Fluorophenyl)-1*H*-imidazol-2-yl)-5*H*-dibenzo[*b*,*e*][1,4]-diazepin-11(10*H*)-one (12). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.31 (1H, bs), 7.20−7.01 (5H, m), 7.29 (1H, dd, J = 2.2, 8.3 Hz), 7.55 (1H, m), 8.09−7.91 (4H, m), 8.61 (1H, dd, J = 2.2, 8.2 Hz), 9.24 (1H, bs), 10.1 (1H, s). ^{13}C NMR: δ = 115.9, 116.9, 117.5, 117.8, 122.3, 124.5, 124.5, 125.7, 125.4, 126.7, 127.5, 128.9, 129.8, 130.7, 130.9, 131.3, 131.6, 138.1, 153.4, 151.1, 161.8, 164.0. FD-MS (M + 1) = 371. Anal. Calcd for $C_{22}H_{15}FN_4O$: C, 71.34; H, 4.08; F, 5.13; N, 15.13. Found: C, 71.36; H, 4.11; F, 5.17; N, 15.20.

3-(3*H*-Imidazo[4,5-*c*]pyridin-2-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one (13) and 3-(6-Fluoro-1*H*-benzo[*d*]imidazol-2-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one (14). To a solution of methyl 11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepine-3-carboxylic acid (**8**) (254 mg, 1.0 mmol, 1 equiv) in DMF (8 mL) at 0 °C was added DIPEA (0.21 mL, 1.2 mmol, 1.2 equiv). After 10 min, TBTU (551 mg, 1.2 mmol, 1.2 equiv) was added and the resulting mixture stirred at the same temperature for 30 min. Then diaminopyridine or diaminobenzene (1.1 mmol, 1.1 equiv) was added. The resulting mixture was stirred at 0 °C for 6 h and then quenched with ice−water. The precipitated solid was filtered, washed with water, and dissolved in EtOAc. The organic phase was washed with a 1 N HCl aqueous solution, then with a saturated $NaHCO_3$ aqueous solution, and finally with H_2O, dried over $MgSO_4$, concentrated in vacuo, and then used in the next stage without further purification. To the appropriate amide was added AcOH (30 mL), and the resulting suspension was refluxed for 6 h, cooled to room temperature, concentrated in vacuo, and diluted with crushed ice. The brown solid was filtered and washed thoroughly with water. The crude was dissolved in EtOAc, washed with a saturated $NaHCO_3$ aqueous solution and with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/AcOEt, 8/2 to 7/3) to give 3-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-5*H*-dibenzo[*b*,*e*][1,4]-diazepin-11(10*H*)-one (**13**) (64%) or 3-(6-fluoro-1*H*-benzo-[*d*]imidazol-2-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one (**14**) (58%).

3-(3*H*-Imidazo[4,5-*c*]pyridin-2-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one (13). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.84 (1H, bs), 7.1−7.01 (2H, m), 7.29 (1H, bd, J = 2.5 Hz), 7.55 (2H, m), 7.90 (1H, bs), 8.00 (1H, dd, J = 2.2, 8.3 Hz), 8.30 (1H, d, J = 1.9 Hz), 8.60 (1H, dd, J = 2.4, 8.3 Hz), 8.90 (1H, s), 9.42 (1H, s), 9.81 (1H, s). ^{13}C NMR: δ = 105.5, 108.6, 117.8, 119.5, 120.9, 124.1, 125.3, 129.0, 130.1, 131.8, 133.4, 138.8, 139.1, 140.2, 140.7, 141.0, 145.7, 153.5, 164.0. FD-MS (M + 1) = 328. Anal. Calcd for $C_{19}H_{13}N_5O$: C, 69.71; H, 4.00; N, 21.39. Found: C, 69.68; H, 4.07; N, 21.43.

3-(6-Fluoro-1*H*-benzo[*d*]imidazol-2-yl)-5*H*-dibenzo[*b*,*e*][1,4]-diazepin-11(10*H*)-one (14). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.85 (1H, s), 7.20−7.05 (3H, m), 7.29 (1H, dd, J = 2.4, 8.3 Hz), 7.48−7.39 (2H, m), 7.84 (1H, s), 7.95 (1H, s), 8.12 (1H, dd, J = 2.2, 8.1 Hz), 8.50 (1H, d, J = 8.4 Hz), 9.30 (1H, bs), 9.88 (1H, s). ^{13}C NMR: δ = 105.1, 106.1, 116.4, 117.8, 118.6, 120.9, 121.7, 122.3, 125.7, 129.1, 130.2, 131.3, 136.5, 137.0, 137.2, 140.7, 148.1, 152.2, 1157.2, 167.5. FD-MS (M + 1) = 345. Anal. Calcd for $C_{20}H_{13}FN_4O$: C, 69.76; H, 3.81; F, 5.52; N, 16.27. Found: C, 69.71; H, 3.78; F, 5.59; N, 16.200.

Acknowledgment. We thank Dr. Thomas Nittoli (Wyeth Research, NY) for fruitful discussions and suggestions. The authors are also grateful to DAAD and the College of Graduate Studies and Research, University of Sharjah—UAE for supporting this project.

Supporting Information Available: Experimental procedures for the synthesis of **9**−**14**, in vitro assays and protocols for the determination of K_I. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Cummings, J. L. Alzheimer's Disease. *N. Engl. J. Med.* **2004**, *351*, 56–67. (b) Nguyen, J.; Yamani, A.; Kiso, Y. Views on Amyloid Hypothesis and Secretase Inhibitors for Treating Alzheimer's Disease: Progress and Problems. *Curr. Pharm. Des.* **2006**, *12*, 4295–4312. (c) For online resources and figures about AD, see www.alz.org and www.ahaf.org.

(2) Celsis, P. Age-related cognitive decline, mild cognitive impairment or pre-clinical Alzheimer's disease. *Ann. Med.* **2000**, *32*, 6–14.

(3) (a) Stavrovskaya, I. G.; Kristal, B. S. The Powerhouse Takes Control of the Cell: Is the Mitochondrial Permeability Transition a Viable Therapeutic Target against Neuronal Dysfunction and Death? *Free Radical Biol. Med.* **2005**, *38*, 687–697. (b) Milligan, C. Caspase Cleavage of APP Results in a Cytotoxic Proteolytic Peptide. *Nat. Med.* **2000**, *6*, 385–386.

(4) Yan, R.; Bienkowski, M. J.; Shuck, M. E.; Miao, H.; Tory, M. C.; Pauley, A. M.; Brashier, J. R.; Stratman, N. C.; Mathews, R. W.; Buhl, A. E.; Carter, D. B.; Tomasselli, A. G.; Parodi, L. A.; Heinrikson, R. L.; Gurney, M. Membrane-Anchored Aspartyl Protease with Alzheimer's Disease Beta-Secretase Activity. *Nature* **1999**, *402*, 533–537.

(5) (a) Iwatsubo, T.; Odaka, A.; Suzuki, N.; Mizusawa, H.; Nukina, N.; Ihara, Y. Visualization of Aβ42(43) and Aβ40 in Senile Plaques with End-Specific Aβ Monoclonals: Evidence That an Initially Deposited Species Is Aβ42(43). *Neuron* **1994**, *13*, 45–53. (b) St George-Hyslop, P. H.; Morris, J. C. Will Anti-Amyloid Therapies Work for Alzheimer's Disease? *Lancet* **2008**, *372*, 180–182. (c) Ghosh, A. K.; Bilcer, G.; Hong, L.; Koelsch, G.; Tang, J. Memapsin 2 (Beta-Secretase) Inhibitor Drug, between Fantasy and Reality. *Curr. Alzheimer Res.* **2007**, *4*, 418–422. (d) Durham, T. B.; Shepherd, T. A. Progress toward the Discovery and Development of Efficacious BACE Inhibitors. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 776–791.

(6) Wolfe, M. S. Secretase Targets for Alzheimer's Disease: Identification and Therapeutic Potential. *J. Med. Chem.* **2001**, *44*, 2039–2060.

(7) (a) Willem, M.; Garratt, A. N.; Novak, B.; Citron, M.; Kaufmann, S.; Rittger, A.; DeStrooper, B.; Saftig, P.; Birchmeier, C.; Haass, C. Control of Peripheral Nerve Myelination by the β-Secretase BACE1. *Science* **2006**, *314*, 664–666.

(8) (a) Stanton, M. G.; Stauffer, S. R.; Gregro, A. R.; Selnick, H. Discovery of Isonicotinamide Derived β-Secretase Inhibitors: In Vivo Reduction of β-Amyloid. *J. Med. Chem.* **2007**, *50*, 3431–3433. (b) Charrier, N.; Clarke, B.; Cutler, L.; Demont, E.; Dingwall, C.; Dunsdon, R.; East, P.; Hawkins, J.; Howes, C.; Hussain, I.; Jeffrey, P.; Maile, G.; Matico, R.; Mosley, J.; Naylor, A.; O'Brien, A.; Redshaw, S.; Rowland, P.; Soleil, V.; Smith, K. J.; Sweitzer, S.; Theobald, P.; Vesey, D.; Walter, D. S.; Wayne, G. Second Generation of Hydroxyethylamine BACE-1 Inhibitors: Optimizing Potency and Oral Bioavailability. *J. Med. Chem.* **2008**, *51*, 3313–3317. (c) Cumming, J. N.; Le, T. X.; Babu, S.; Carroll, C.; Chen, X.; Favreau, L.; Gaspari, P.; Guo, T.; Hobbs, D. W.; Huang, Y.; Iserloh, U.; Kennedy, M. E.; Kuvelkar, R.; Li, G.; Lowrie, J.; McHugh, N. A.; Ozgur, L.; Pan, J.; Parker, E. M.; Saionz, K.; Stamford, A. W.; Strickland, C.; Tadesse, D.; Voigt, J.; Wang, L.; Wu, Y.; Zhang, L.; Zhang, Q. Rational Design of Novel, Potent Piperazinone and Imidazolidinone BACE1 Inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3236–3241. (d) Kortum, S. W.; Benson, T. E.; Bielnkowski, M. J.; Emmons, T. L.; Prince, D. B.; Paddock, D. J.; Tomasselli, A. J.; Moon, J. B.; LaBorde, A.; TenBrink, R. E. Potent and Selective Isophthalamide S2 Hydroxyethylamine Inhibitors of BACE1. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3378–3383. (e) Iserloh, U.; Pan, J.; Samford, A. W.; Kennedy, M. E.; Zhang, Q.; Zhang, L.; Parker, E. M.; McHugh, N. A.; Favreu, L.; Strickland, C.; Voigt, J. Discovery of an Orally Efficacious 4-Phenoxypyrrolidine-Based BACE-1 Inhibitor. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 418–422.

(9) Choi, S.-H; Hur, J.-M.; Yang, E.-J.; Jun, M.; Park, H.-J.; Lee, K.-B.; Moon, E.; Song, K.-S. β-Secretase (BACE1) Inhibitors from *Perilla frutescens* var *acuta*. *Arch Pharm Res.* **2008**, *31*, 183–187. (b) http://tools.invitrogen.com/content/sfs/manuals/L0724.pdf.

(10) Albert, U.; Aguglia, E.; Maina, G.; Bogetto, F. Venlafaxine versus Clomipramine in the Treatment of Obsessive-Compulsive Disorder: A Preliminary Single-Blind, 12-Week, Controlled Study. *J. Clin. Psychiatry* **2002**, *63*, 1004–1009.