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Diamide amino-imidazoles: A novel series of γ-secretase inhibitors for the treatment of Alzheimer's disease

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ABSTRACT

The synthesis and structure–activity relationship (SAR) of a novel series of di-substituted imidazoles, derived from modification of DAPT, are described. Subsequent optimization led to identification of a highly potent series of inhibitors that contain a β-amine in the imidazole side-chain resulting in a robust in vivo reduction of plasma and brain Aβ in guinea pigs. The therapeutic index between Aβ reductions and changes in B-cell populations were studied for compound **10h**.

Dementia results from a wide variety of distinctive pathological processes. Alzheimer's disease (AD) is the most common cause of dementia, affecting nearly half of all people past the age of 85, the most rapidly growing portion of the population. The number of AD patients in the United States is expected to increase from 5 million to about 15 million by the middle of the next century.[1] Two hallmark pathologies of the AD brain are the accumulation of extracellular insoluble deposits known as amyloid plaques and abnormal lesions within neurons called neurofibrillary tangles.[2] Definitive diagnosis of AD is currently dependent upon observation of both of these pathological events in post-mortem brain tissue. The primary component of amyloid plaques are aggregated Aβ (such as $A\beta_{1-40}$ and $A\beta_{1-42}$) which result from sequential enzymatic processing of the APP (amyloid protein precursor) by β-secretase (BACE) and γ-secretase.[3] The causes of sporadic AD are unclear, however several familial forms of AD stem either from APP variants or PSI mutations. Furthermore, both soluble and insoluble Aβ assemblies demonstrate neurotoxicity.[4] As such, γ-secretase is a compelling target for the treatment of AD by inhibiting the production of toxic Aβ-peptides. To date, numerous γ-secretase inhibitors (GSI) such as LY-4501391, BMS-299897, GSI-953, and BMS-708163 have advanced into human clinical trials for the treatment of AD (Fig. 1).[5]

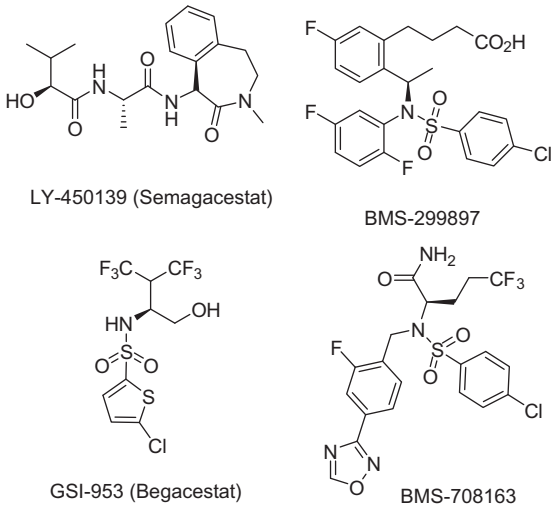

Figure 1. γ-Secretase inhibitors that have advanced to human clinical trials.

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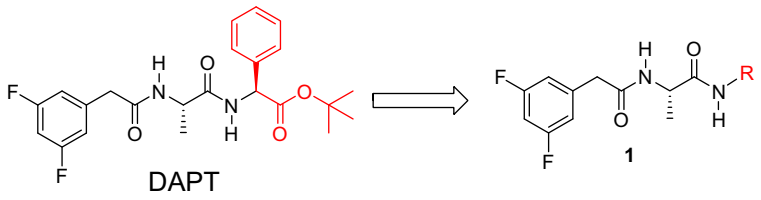
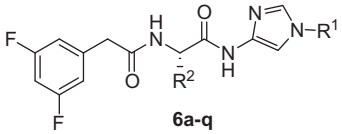


Figure 2. N-Terminal replacements of DAPT.

In 2001, coworkers at Eli Lilly and Elan reported on DAPT, the first report of a centrally active γ-secretase inhibitor with an MED = 30 mg/kg in the PDAPP mouse (Fig. 2).[6] While whole cell potency (0.02 μM) and low molecular weight (MW = 432.5) made this a compelling lead, further pharmacokinetic (PK) profiling revealed potential acid instability of the *t*-butyl ester group. In light of this result, our medicinal chemistry efforts focused on developing novel C-terminal heterocycles (*R*) as replacements for the ester functionality in DAPT. Initial efforts in this area led to a potent series of amino-thiazoles[7] and this manuscript describes the in vitro and in vivo characterization of a novel series of diamide amino imidazoles (**1**).

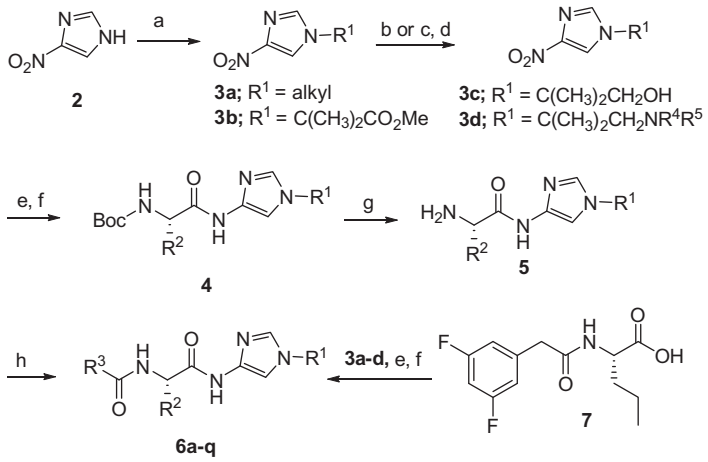
A general synthetic strategy for the preparation of 4-substituted amino imidazoles is illustrated in Scheme 1.[8] Starting from 4-nitroimidazole **2**, regioselective *N*-alkylation with an appropriate alkyl halide provides 3-substituted imidazoles **3a–b**. Subsequent reduction of the ester **3b** to the alcohol **3c** was accomplished with standard conditions. Alternatively, reduction of ester **3b** with DIBAL afforded the intermediate aldehyde that underwent reductive amination to furnish nitro imidazoles **3d**. Reduction of the

Table 1
In vitro potency of representative GSI



Compound	R^1	R^2	CFA IC_{50}[a,b] (nM)	WCA IC_{50}[b,c] (nM)	Total Aβ in h[d] (brain @ 3 h)
6a	CO_2Me		57.7	263	
6b	OH		82.8	306	
6c	N		52.7	114	
6d			0.39	2.4	<10%
6e	CO_2Me		2.7	5.1	
6f	CO_2Me		1.2	1.2	32%
6g	OH		2.5	14.6	
6h	OH		3.6	20.3	
6i	N		9.1	226	
6j	N		0.9	0.8	43%

[a] IC_{50} values in the cell free assay (CFA) were obtained from human HeLa cells by measuring $Aβ_{1-40}$ by DELFIA-based immunoassay.[10]
[b] Values are geometric mean of at least two experiments; compounds were typically dosed at log intervals from 0.1 nM to 10 μM.
[c] IC_{50} values in the whole cell assay (WCA) were obtained from H4 APP_{Sw} cells by measuring $Aβ_{1-X}$.[10]
[d] In vivo activity was determined by measuring $Aβ_{1-X}$, $Aβ_{1-40}$, and $Aβ_{1-42}$ in guinea pig brain and plasma by Delfia ELISA. Extracts were analyzed for changes in $Aβ_{1-X}$ using an IGEN assay.[11] A significant difference between groups was detected by one-way ANOVA followed by Dunnett's post-hoc in GraphPad Prism v5. Treatment effects were considered statistically significant following p <0.05 at the level of the ANOVA and post-hoc versus vehicle.

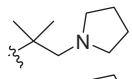
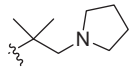
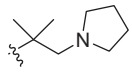
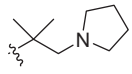
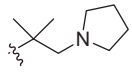
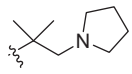
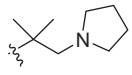


Scheme 1. Reagents and conditions: (a) R^1-Br, K_2CO_3, Et_3BnNCl, CH_3CN, 80 °C, 30–65%; (b) $LiAlH_4$, THF, reflux; (c) DIBAL, CH_2Cl_2, −30 °C; (d) R^4R^5-NH_2, 4AºMS, CH_2Cl_2, then $Na(OAc)_3BH$, 60% over 2 steps; (e) Pd/C (10%), H_2 (40 psi), MeOH, rt; (f) $BocNCHR^2CO_2H$, TPTU, iPr_2EtN, DMF, 40–80% for 2 steps; (g) TFA, CH_2Cl_2; (h) R^3CO_2H, EDC, HOBt, iPr_2EtN, rt, 70–95%.

nitroimidazole was accomplished via hydrogenation with Pd/C.[9] Due to the instability of the resultant aminoimidazole, coupling with an *N*-Boc protected amino acid was immediately carried forward to amide **4**. Removal of the Boc protecting group provided amine **5**, which was acylated to provide **6** bearing structural variations in the R_1, R_2, and R_3 positions. Alternatively, amino-acid **7** is coupled to the intermediate amino-imidazoles derived from nitroimidazoles **3a–d** to provide the desired analogs.

Preliminary SAR at the R_1 position of compounds **6a–j** (Table 1) revealed a range of substituents (esters, alcohols, and β-amines) were well tolerated on the imidazole side chain with respect to cell free assay (CFA) and whole cell assay (WCA) potencies.[10] The synthesis and evaluation of a wide range of straight chain and branched alkyls off the imidazole ring demonstrated the importance of α-branching for whole cell potency. From this early SAR, the 3-pentyl analog **6d** provided excellent in vitro potency in cell-free and whole assays. Analogous to the alkyl side chains, incorporation of α-branching on the R_1 side chain resulted in a significant improvement in whole cell potency for esters (**6a** vs **6e**), alcohols (**6b** vs **6g**) and β-amines (**6c** vs **6j**). The tether length off the imidazole side chain was investigated to understand the impact of spacing on potency. For esters **6e**/**6f** and alcohols **6g**/**6h**, a modest preference based upon whole cell potency was identified for the longer tethered substituents. Interestingly, the β-amine **6j** and the γ-amine **6i** gave comparable cell free potency but **6j** was ~100-fold more potent than **6i** in the whole cell assay. To assess the efficacy of inhibitors **6d**, **6f**, **6j**, guinea pigs were dosed acutely with subcutaneous (sc) injection and $Aβ_{1-X}$ was measured in brain and plasma by Delfia ELISA at the 3 h time point. While **6d** failed to reduce total brain $Aβ_{1-X}$ after a 10 mg/kg, sc screening dose due to poor central exposure, inhibitors **6f** and **6j** significantly reduced brain $Aβ_{1-X}$ (32% and 43%, respectively) after a 10 mg/kg, sc screening dose in guinea pig.[11]

Table 2
SAR of central amino amide R_2 substituent

Compound	R^1	R^2	CFA IC_{50}[a,b] (nM)	WCA IC_{50}[b,c] (nM)
6k			12.6	7.8
6l			7.0	4.3
6m			11.9	2.5
6n			55.0	21.6
6o			51.1	9.4
6p			39.7	8.2
6q			>10,000	>10,000

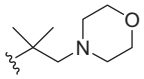
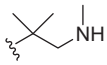
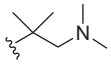
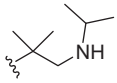
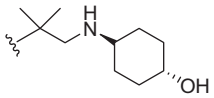
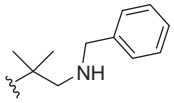
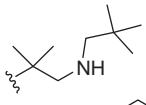
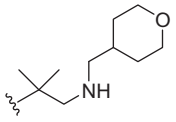
[a] IC_{50} values obtained from human HeLa cells and were used to test compounds in a cell free assay, and $Aβ_{1-40}$ was detected using a DELFIA-based immunoassay.[10]
[b] Values are geometric mean of at least two experiments; compounds were typically dosed at log intervals from 0.1 nM to 10 μM.
[c] IC_{50} values obtained from H4 APP_{Sw} cells were used to test compounds in a whole cell assay, and $Aβ_{1-X}$ was measured.[10]

With a desirable R_1 substituent, the central amino acid (R_2) of compound **6j** was varied (Table 2). A range of alkyl (**6k–m**), cycloalkyl (**6n**), and aryl (**6o**) groups were tolerated at this position but the propyl analog (**6j**) derived from (*S*)-norvaline proved superior with respect to in vitro potency. Attempts to incorporate polarity into the R_2 group such as ether **6p** resulted in a 10-fold lose in potency while the dimethylamide analog **6q** was inactive. Additional in vivo characterization of **6k** and **6l** in the guinea pig after an acute dose of 10 mg/kg, sc failed to show a reduction of total brain $Aβ_{1-X}$ at a 3 h time point. We speculated that the lack of robust efficacy was due to poor central exposure.

In order to further investigate cellular potency in the β-amine SAR on the imidazole side chain, a more versatile route was utilized to prepare a set of secondary and tertiary amines (Scheme 2). Amide coupling of an amino imidazole derived from nitroimidazole **8** with acid **7** utilizing the standard coupling procedure afforded diamide **9**. Subsequent reduction of the ester and reductive amination afforded the desired analogs **10a–i**.

In comparison to the pyrrolidine analog **6j** (Table 1), morpholine **10a** showed comparable whole cell potency while smaller alkyl amines such as monomethyl amine **10b** and dimethyl amine **10c** resulted in a ~90-fold and ~5-fold lose in potency,

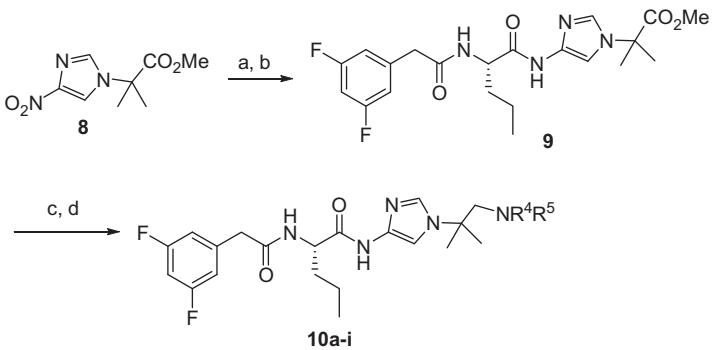
Table 3
Cell free potency (CFA), whole cell potency (WCA), and notch effects (FTOC) of GSI's with β-amino side chains

Compound	R^1	CFA IC_{50}[a,b] (nM)	WCA IC_{50}[b,c] (nM)	FTOC EC_{50}[d] (μM)
10a		0.6	0.4	0.1
10b		45.7	89.5	NT
10c		3.8	4.8	0.7
10e		29.0	7.9	>10.0
10f		64.6	72.7	>10.0
10g		1.7	3.1	4.3
10h		1.1	0.4	1.2
10i		0.5	0.4	4.0

NT = not tested.
[a] IC_{50} values obtained from human HeLa cells and were used to test compounds in a cell free assay, and $Aβ_{1-40}$ was detected using a DELFIA-based immunoassay.[10]
[b] Values are geometric mean of at least two experiments; compounds were typically dosed at log intervals from 0.1 nM to 10 μM.
[c] IC_{50} values obtained from H4 APP_{Sw} cells were used to test compounds in a whole cell assay, and $Aβ_{1-X}$ was measured.[10]
[d] Fetal thymic organ cultures (FTOC) were prepared for assessment of compound effects on notch processing.[13]

respectively (Table 3). A range of amines were tolerated at this position but secondary amines **10g–i** resulted in robust whole cell potency. To evaluate the potential effects on notch processing, compounds **10a–i** were evaluated in fetal thymic organ culture (FTOC) B- and T-cell populations. Interestingly, a range of selectivity was observed for reductions in Aβ as measured in the whole cell assay versus reductions in B- and T-cell populations. This selectivity in vitro suggested the potential for a therapeutic index (TI) in vivo.

To further characterize the in vivo performance of this series of compounds, guinea pigs were treated with compound **10h** from 1 to 32 mg/kg and total $Aβ_{1-X}$ was evaluated in brain and plasma at 3 h post treatment (Fig. 3A).[11,12] The reduction of brain Aβ was dose dependent from 1 to 32 mg/kg, sc resulting in a brain ED_{50} = 7.3 mpk. The reductions in plasma Aβ were sustained at ~60% and appeared to be a maximal reduction for this analog despite the increasing drug concentration in plasma. The corresponding drug exposures measured at 3.2 mg/kg, sc (3 h post dose) showed good coverage of the in vitro IC_{50} in brain (12 ng/g, 24 nM). To obtain an understanding of the Aβ changes over time in brain, CSF and plasma, guinea pigs were dosed acutely with **10h** and tissues were collected at 2 h intervals from 1 to 7 h post dose (Fig. 3B). At 1 h after dose, a significant reduction in plasma and brain Aβ could be detected while CSF was not significantly different than



Scheme 2. Reagents and conditions: (a) Pd/C (10%), H_2 (40 psi), MeOH, rt; (b) compound **7**, TPTU, iPr_2EtN, DMF, 75% for 2 steps; (c) DIBAL, CH_2Cl_2, −30 °C; (d) R^4R^5-NH_2, 4AºMS, CH_2Cl_2, then $Na(OAc)_3BH$, 60% over 2 steps.

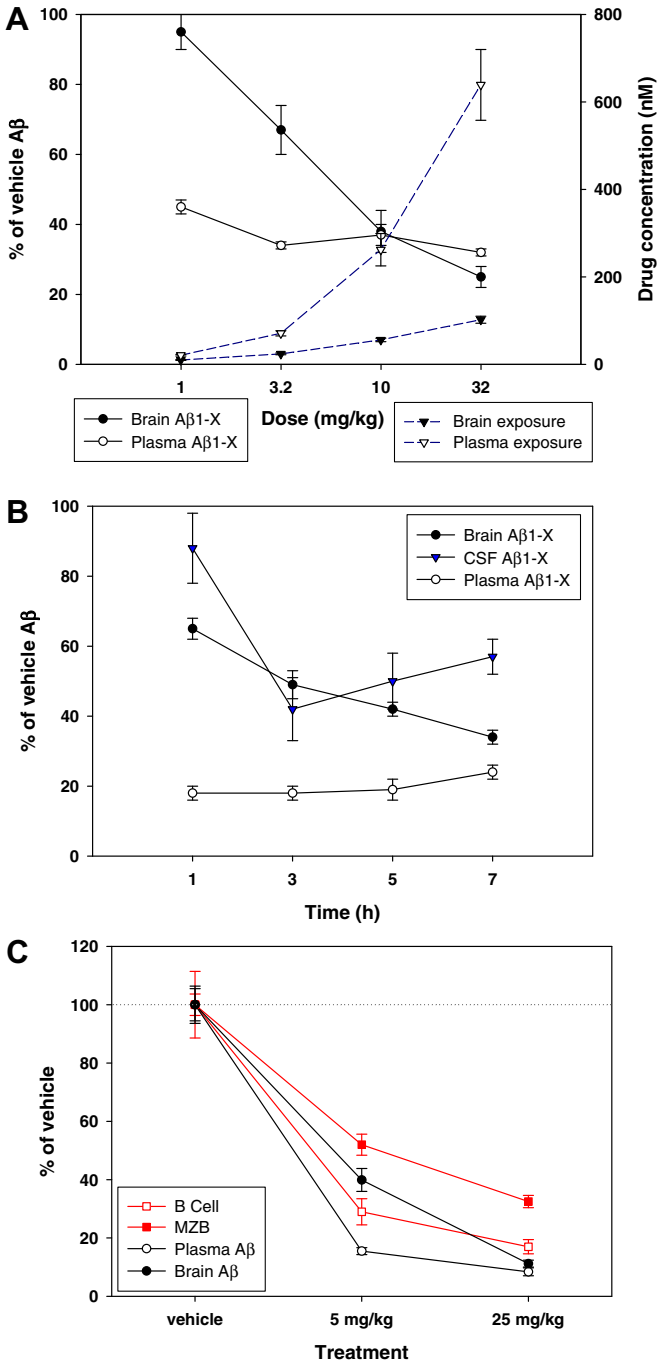


Figure 3. In vivo characterization of GSI **10h**: (A) dose responsive of brain and plasma Aβ; (B) time course of brain, plasma, CSF Aβ; (C) reduction of marginal and blood B-cell populations. (A and B) In vivo activity was determined by measuring $Aβ_{1-X}$, $Aβ_{1-40}$, and $Aβ_{1-42}$ were measured in guinea pig brain and plasma by Delfia ELISA. Extracts were analyzed for changes in $Aβ_{1-X}$ using an IGEN assay.[11,13] Mean ± S.E.M. exposure or percentage of vehicle Aβ are represented. (C) Spleen and whole blood B-cells (relative numbers or percentage) were evaluated by flow cytometry.[11,13]

controls (Fig. 3B). From 3 to 7 h, Aβ was significantly reduced in all compartments. A potential liability associated with inhibiting the γ-secretase complex is substrate specificity.[15] Cleavage of Notch by γ-secretase is necessary for differentiation of certain cell types within the intestine and blood cell populations. To evaluate the potential for Notch related toxicity in relationship to efficacy over time for this class of GSI, B-cell populations were analyzed by fluorescence activated cell sorting (FACS) of whole blood and spleen preparations after multiple doses in a 24 h time period (Fig. 3C).[13,14] Guinea pigs were treated with 5 and 25 mg/kg, sc of compound **10h** with three doses over a 24 h period (time 0, 12, and 24 h) and tissues were collected at 3 h after the final dose. A dose responsive relationship was observed for brain and plasma Aβ with compound **10h** and the 5 mg/kg, sc dose closely estimated a 50% reduction of brain $Aβ_{(1-X)}$. Despite the significant separation between APP processing in the whole cell assay and Notch inhibition in the FTOC assay, analysis of blood B cell and marginal zone B-cells (MZB) from the spleen suggested no therapeutic index (TI) was achieved for this GSI (Fig. 3C).

In conclusion, a series of amino imidazoles were synthesized based on DAPT. Efforts varying the N-terminal substituent on the imidazole ring lead to compound **10h** with robust cellular potency in the γ-secretase inhibition assay and significant reductions of brain, plasma, and CSF Aβ in guinea pigs after an acute dose. Despite in vitro selectivity between APP processing in the whole cell assay and B-cell reductions in FTOC, in vivo studies examining Aβ reductions and B cell changes within the same animals suggested that further optimization of the selectivity profile or distribution properties of these inhibitors will be required to obtain a therapeutic index. Future publications will focus on more detailed in vivo characterization and Notch related safety of this series of γ-secretase inhibitors.

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12. *Representative synthesis of compound* **10h**: To a solution of (*S*)-2-(2-(3,5-difluorophenyl)acetamido)-*N*-(1-(2-methyl-1-oxopropan-2-yl)-1*H*-imidazol-4-yl)pentanamide in DCM is added 2,2-dimethylpropan-1-amine (4.4 equiv), *p*TSOH (0.2 equiv), 4AºMS, and the solution is stirred for 4 h and then $Na(OAc)_3BH$ (3.3 equiv) is added. The reaction is stirred for 12 h, quenched

with sodium bicarbonate, extracted with DCM, concentrated and purified by flash chromatography to provide **10h**; ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 0.81 (t, *J* = 7.32 Hz, 3H) 1.20–1.34 (m, 2H) 1.51 (s, 6H) 1.56–1.70 (m, 5H) 1.71–1.88 (m, 1H) 2.25–2.40 (m, 4H) 2.67 (s, 2H) 3.49 (s, 2H) 4.76 (q, *J* = 7.35 Hz, 1H) 6.62–6.70 (m, 1H) 6.73–6.85 (m, 2 H) 7.41 (s, 1H) 7.59 (s, 1 H) 11.26 (s, 1H).

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