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Improving the permeability of the hydroxyethylamine BACE-1 inhibitors: Structure–activity relationship of *P2′* substituents

Anh P. Truong [a], Gary D. Probst [a,*], Jose Aquino [a], Larry Fang [a], Louis Brogley [a], Jennifer M. Sealy [a], Roy K. Hom [a,*], John A. Tucker [a], Varghese John [a], Jay S. Tung [a], Michael A. Pleiss [a], Andrei W. Konradi [a], Hing L. Sham [a,b], Michael S. Dappen [b], Gergley Tóth [c], Nanhua Yao [c], Eric Brecht [c], Hu Pan [c], Dean R. Artis [c], Lany Ruslim [d], Michael P. Bova [d], Sukanto Sinha [d], Ted A. Yednock [a,b,c,d,e], Wes Zmolek [e], Kevin P. Quinn [e], John-Michael Sauer [e]

[a] *Department of Medicinal Chemistry, Elan Pharmaceuticals, 180 Oyster Point Boulevard, South San Francisco, CA 94080, United States*
[b] *Department of Process and Analytical Chemistry, Elan Pharmaceuticals, 180 Oyster Point Boulevard, South San Francisco, CA 94080, United States*
[c] *Department of Molecular Design, Elan Pharmaceuticals, 180 Oyster Point Boulevard, South San Francisco, CA 94080, United States*
[d] *Department of Biology, Elan Pharmaceuticals, 1000 Gateway Boulevard, South San Francisco, CA 94080, United States*
[e] *Department of Lead Finding, Drug Disposition, and Safety Evaluation, Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, CA 94080, United States*

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ABSTRACT

Herein we describe further evolution of hydroxyethylamine inhibitors of BACE-1 with enhanced permeability characteristics necessary for CNS penetration. Variation at the *P2′* position of the inhibitor with more polar substituents led to compounds **19** and **32**, which retained the potency of more lipophilic analog **1** but with much higher observed passive permeability in MDCK cellular assay.

Alzheimer's disease (AD) is a form of senile dementia, characterized by a progressive loss of memory and cognitive ability, affecting more than 35 million elderly people worldwide with skyrocketing healthcare costs far exceeding 100 billion dollars annually.[1] The pathology of this neurodegenerative disorder uniquely manifests itself with the presence of extraneuronal aggregation of plaques composed of β-amyloid peptides (Aβ).[2] Intracellular neurofibrillary tangles (NFTs), aggregates of aberrantly hyperphosphorylated tau proteins, are also a component of the pathology but not exclusive to AD.[3] Aβ-peptides are derived from the sequential proteolytic cleavage of the β-amyloid precursor protein (β-APP) by two aspartic acid proteases, referred to as β- and γ-secretase, respectively.[4] Inhibition of either protease has been demonstrated to result in reduction of brain Aβ-peptide in preclinical studies.[5] Inhibitors of either protease offer attractive candidates as potentially disease-modifying, rather than palliative, treatments for people afflicted with this debilitating malady.[6]

Between these two proteases, β-secretase (BACE-1)[7] is the more alluring therapeutic target based on the following distinctions. γ-Secretase processes a myriad of substrates,[8] such as Notch, raising concerns about mechanism-based side-effects due to a deficiency in selectivity.[9] Conversely, gene deletion of BACE-1 in mice produced no consistent phenotypic differences between their *wild type* counterparts.[10] These knockout mice are without compensatory activity, thus devoid of the ability to generate Aβ in the brain.[11] Modest reductions of BACE-1 activity resulted in significant reduction of plaque burden.[12] Furthermore, cleavage of β-APP by BACE-1 is the rate-limiting step in Aβ-peptide production[4] and releases the soluble N-terminal APP fragment which initiates a cascade event ultimately leading to apoptosis.[13] Additionally, soluble oligomeric Aβ42 indirectly signals for hyperphosphorylation of tau at AD-specific epitopes producing NFTs that lead to neurotoxicity.[14] Moderately abating the production of Aβ monomers results in a disproportionate reduction of synaptotoxic soluble Aβ oligomers leading to improved synaptic plasticity.[15] This validates BACE-1 and presents its clear advantages over γ-secretase as a therapeutic target, and buttresses the amyloid cascade hypothesis.

Previously, we reported our research in the *S1′* pocket with our hydroxyethylamine (HEA) peptidomimetics.[16] Although our HEA inhibitors were potent, they were deficient of the pharmacokinetic parameters, most notably high permeability and low Permeability-glycoprotein (P-gp) efflux, necessary for an efficacious central

* Corresponding authors. Tel.: +1 650 616 2684; fax: +1 650 877 7486. (R.K.H.)
E-mail addresses: gary.probst@elan.com (G.D. Probst), roy.hom@elan.com (R.K. Hom).

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Table 1
Classification of permeability and recovery

Class	P_{app} (nm/s)	% Recovery
Poor	$\leq$ 25 nm/s	$\leq$ 10%
Low	26 nm/s $\leq$ 50 nm/s	11% $\leq$ 30%
Moderate	51 nm/s $\leq$ 99 nm/s	31% $\leq$ 50%
Good	—	51% $\leq$ 70%
High	$\geq$ 100 nm/s	$\geq$ 71%

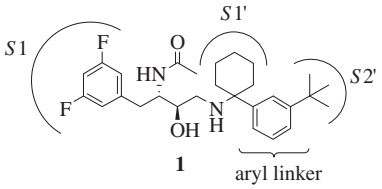


Figure 1. Binding mode of the HEAs.

nervous system drug. We opted to address these impediments in an incremental fashion by first focusing on improving the passive permeability of the inhibitors. Herein, we will describe the properties of the HEAs that generated our working hypothesis concerning the pharmacokinetic issues, and the strategy to design highly permeable and potent BACE-1 inhibitors. The terminology used to classify the permeability and recovery of the compounds is outlined in Table 1. The recovery is a measure of the inhibitors affinity to embed in the membrane, vide infra.

The crystal structure of BACE-1 complexed with compound **1**[16] illustrates the active site binding mode (Figs. 1 and 2). The difluoroaryl, cyclohexyl, and *tert*-butyl substituents occupy the *S*1, *S*1′, and *S*2′ pockets, respectively, as shown in Figures 1 and 2. The *S*2′ pocket is amphiphilic in nature. The "top" is composed of Ser35, Ile126, and Tyr198 which forms the border between the *S*1′ and *S*2′ (Fig. 3). Two hydrophilic residues Asn37 and Arg128 constitute the "rear" portion of the pocket. The "bottom" of the pocket consists of Val69 and Pro70, and Tyr71 on the "left side." The protonated amine and hydroxyl group binds at the scissile site to Asp32 and Asp228, respectively (not shown). The carbonyl of Gly34 also forms a hydrogen bond with the ionized amine and hydrogen on the aryl linker flanked by the two alkyl groups.[17] The acetamide functions as a bi-dentate ligand with the carbonyl forming a hydrogen bond with the flap residue Gln73 while the NH interacts with Gly230.

The synthetic route employed to synthesize the HEA inhibitors is outlined in Scheme 1. An aryl lithium generated from **3** was added to cyclohexanone to produce a tertiary alcohol which in turn was converted to the amine **4** via the azide. Epoxide ring opening of **5**[18] with the amine **4**, deprotection, and acetylation[19] of the primary amine afforded compound **6**. The aryl iodide **6** served as a versatile synthetic intermediate for transition metal catalyzed cross-coupling reactions such as Suzuki–Miyaura,[20] Stille,[21] Negishi,[22] Heck,[23] N-arylation,[24] and enolate arylation.[25] This approach was highly effective and versatile for the synthesis of compounds **9**–**12**, **19**–**26**, and **30**–**44**. Alternatively, **1** and **13**–**18** were prepared with the same chemistry in Scheme 1, but with the *P*2′ moiety already in place.[16]

Initially success in increasing the potency was achieved by the placement of alkyl substituents in the *S*2′ pocket (Table 2). The *tert*-butyl group was optimal for enzymatic potency while reduced branching resulted in a decrease in biochemical potency (**8**–**10**) as did extension deeper into the pocket (**11**–**13**). The permeability of these highly lipophilic inhibitors (**1** and **9**) was low, and in several cases (**11**–**13**) the recovery of the compound from the permeability assay was so poor ($\leq$10%) that the result was deemed to be unreliable, thus the compounds were considered un-testable.

The low recovery from the permeability assay indicated that the compounds embedded into the membrane of the Madin-Darby canine kidney (MDCK) cells. Highly lipophilic molecules that possess a basic amine exhibit a pronounced affinity towards membranes.[26] Since compound **1** has a measured log *P* of 4.8 and pK_a of 8.1, our working hypothesis involved the basic amine binding to the polar head and the greasy portion partitioning into the lipophilic tail of the membrane (Fig. 4). In order to overcome this liability, we envisioned replacing the *tert*-butyl group with a polar moiety which would lower the log *P* leading to reduced membrane affinity, thereby generating the high rate of permeability required to penetrate

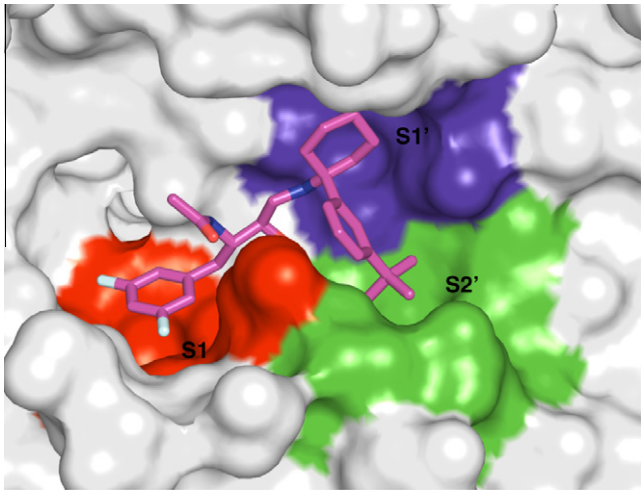


Figure 2. Crystal structure of **1** binding to truncated (56-455) human BACE-1 (1.8 Å resolution). The PDB deposition code is 3ivh.

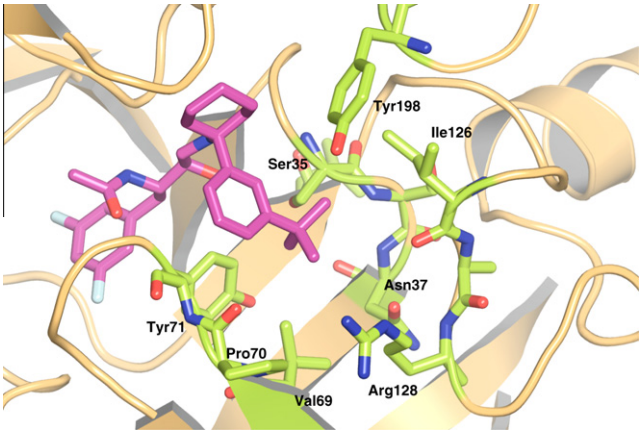
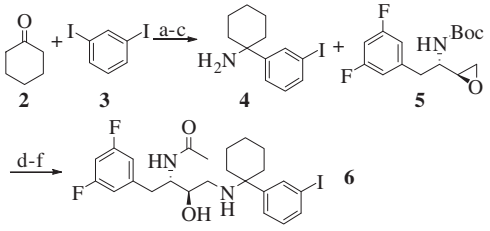
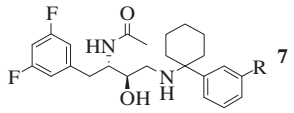


Figure 3. Crystal structure of **1** binding to BACE-1 with the *S*2′ residues highlighted.



Scheme 1. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 50–70%; (b) $TMSN_3$, BF_3-OEt_2, CH_2Cl_2, reflux or TFA, NaN_3, CH_2Cl_2, reflux, 30–50%; (c) PMe_3, H_2O, THF, 60 °C; (d) *N*,*N*-diisopropylethylamine, isopropanol, reflux, 60–70% over two steps; (e) 4 N HCl in dioxane; (f) Ac_2NOMe, triethylamine, CH_2Cl_2, 70–80% over two steps.

Table 2
SAR of alkyl groups[a]



#	R	BACE-1 IC_{50}, nM Cell ED_{50}, nM	P_{app}, nm/s %Recovery
1		47 17	7 11%
6	–I	460 85	 na
8	–H	>10,000 >1000	31 40%
9	–Et	690 120	11 na
10		100 13	Un-testable Low recovery
11		380 120	Un-testable Low recovery
12		130 200	Un-testable Low recovery
13		810 230	Un-testable Low recovery

[a] See Ref. 16 for experimental details.

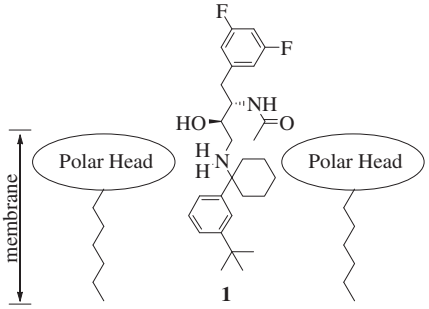
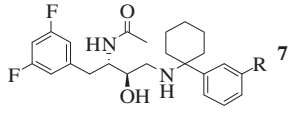


Figure 4. Schematic of proposed HEA anchoring into the cell membrane.

Table 3
SAR of polar groups[a]

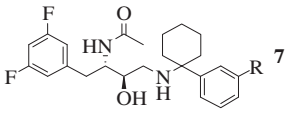


#	R	BACE-1 IC_{50}, nM Cell ED_{50}, nM	P_{app}, nm/s %Recovery
14		410 44	39 41%
15		166 ≤40	58 47%
16	–CN	6200 93	91 64%
17		260 42	20 69%
18	$-SO_2Me$	720 55	36 82%

[a] See Ref. 16 for experimental details.

the blood–brain barrier. Concurrently, the potency could be retained and/or improved with this newly introduced polar moiety

Table 4
SAR of aromatic rings[a]



#	R	BACE-1 IC_{50}, nM Cell ED_{50}, nM	P_{app}, nm/s %Recovery
19		59 4.0	72 54%
20		1100 110	Un-testable Low recovery
21		120 36	Un-testable Low recovery
22		44 34	Un-testable Low recovery
23		370 310	Un-testable Low recovery
24		110 13	8 31%
25		1600 26	19 69%
26		7700 110	45 36%

[a] See Ref. 16 for experimental details.

by forming a hydrogen bond with one of the side chains of Asn37, Arg128, or Tyr198 in the *S2′* pocket.

A select group of examples illustrated in Table 3 demonstrate that moieties more polar than *tert*-butyl afforded improved permeability, but the potency was diminished. The dimethylaniline **14** had a low rate of permeability (39 nm/s) with a moderate recovery (41%), while **15** and **16** had moderate rates of forward flux (58 and 91 nm/s) in conjunction with a further increase in recovery. The alcohol **17** and sulfone **18** exhibited poor (20 nm/s) and low (36 nm/s) rates permeability coupled with good (69%) and high (82%) levels of recovery, respectively, indicating that the compounds had become too polar, thus losing the membrane affinity necessary for the requisite passive permeability. While these results were certainly less than ideal from a potency perspective, they indicated that the direction of the research was on the correct path to improve the permeability of the inhibitors. Also, these results underscored the fact that a fine balance of physiochemical properties would be necessary to effectuate the requisite passive permeability.

Next, we examined aromatic rings as the *P2′* substituents with representative examples in Table 4. The N-linked pyrazole **19** (measured log $P = 4.0$ and $pK_a = 7.8$) is nearly equipotent to **1** in an enzymatic assay and 4.0 nM in the cellular assay, but exhibited a significant increase in both permeability and recovery. X-ray co-crystal structure of **19** with BACE-1 shows a hydrogen bond (2.7 Å) between the pyrazole in **19** and the phenolic hydrogen of Tyr198 (Fig. 5). Surprisingly, the 2-furan **20** lost nearly 20-fold in potency while the 3-furan **21** was only twofold less active relative to **19**, but neither gave measurable permeability. Similarly, the 3-thienyl moiety **22** has a comparable potency to **1** and **19**, but not the 2-thienyl compound **23**. Neither **22** nor **23** were testable in the permeability assay due to the low recovery. The thiazole **24** led to a twofold decrease in potency with a substantial decrease in permeability in comparison to **19**. Imidazoles and triazoles, such as **25** and **26**, were significantly less potent, and offered only marginal improvements to the permeability relative to **1**. A plethora of

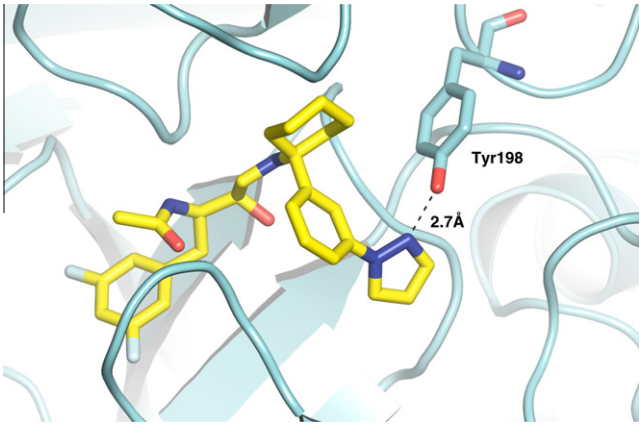
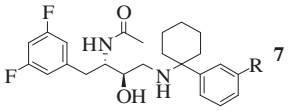


Figure 5. Crystal structure of **19** binding to truncated (57-453) human BACE-1 (2.7 Å resolution). The PBD deposition code is 3N4L. The pyrazole is depicted as hydrogen bonding to Tyr198 (2.7 Å).

six-membered aromatic rings were synthesized but none had sub-micromolar activity.

Cyclic non-aromatic moieties were synthesized to explore for potency and examine their effect on permeability (Table 5). Rings of different sizes and shapes combined with hydrogen bond donors and/or acceptors offered different presentations to hydrogen bond with one of the polar residues of BACE-1. In addition to cyclohexyl, cyclopropyl was another commonly used *P*1′ substituent (Table 6), but as a general rule they were three-to-four times less potent than their cyclohexyl counterparts (**31** vs **46**). An exemplary synthetic route to these cyclopropyl analogs is outlined in Scheme 2. Starting with the alkyne **27**, formation of a vinyl bromide,[27] removal of the THP protecting group, and a Suzuki coupling[20] with 3-cyanophenylboronic acid afforded compound **28**. Iodo-etherification of the olefin **28**, reduction of the iodide, and a Kulinkovich reaction[28] gave the cyclopropylamine **29** with which the standard chemistry (vide supra) was used to complete the synthesis. The tetrahydrofurans, **31** and **32** (measured log *P* = 4.0), were 5- and 10-times more potent than the cyclopentyl analog **30**, and highly permeable (⩾ 100 nm/s) with good recoveries (68% and 64%). Molecular modeling indicated that the oxygen formed a hydrogen bond with the Tyr198, and that both epimers of **31** and **32** had similar binding energies. The 2-methyltetrahydrofuran **47** was designed to fill space like the *tert*-butyl and hydrogen bond with the Tyr198 but the potency was disappointing. Molecular modeling indicates that the pyrans **48** and **49** form a hydrogen bond with Tyr198. Carbonyls at the 2-position of five-membered rings did not increase the binding affinity (**33**–**36** vs **30**) but did so for six-membered rings (**38**–**41** vs **37**) by forming a hydrogen bond with the Tyr198 as predicted by molecular modeling. The conformation of the *P*2′ ring appears to be an important factor for binding (**37** vs **51**). Seven-membered rings afforded sub-optimal potency (**42**–**44**). The carbonyl derivatives (**33**–**35** and **38**–**42**) consistently resulted in poor rates of permeability (⩽25 nm/s) (except **38** at 31 nm/s) in conjunction with high levels (⩾ 71%) of recovery (except **41** at 55%) indicating that the substrates had lost membrane affinity. The ketone **36** bucked this trend with a moderate permeability (51 nm/s). Ethers (**31**–**32**, **43**–**44**, and **46**–**50**) consistently generated high rates of permeability coupled with good to high levels of recovery indicating very good passive permeability. Reducing the basicity of the amine (pK_a = 6.5–6.7) and lipophilicity associated with the cyclopropyl *P*1′, compared to the cyclohexyl *P*1′, did not affect the permeability or recovery with a polar *P*2′ (**31** vs **46**), and an ether was still required to generate high rates of permeability (**50** vs **51**).

Table 5
SAR of non-aromatic cyclic moieties with P1' cyclohexyl[a]



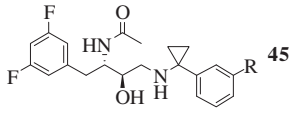
#	R	BACE-1 IC_{50}, nM Cell ED_{50}, nM	P_{app}, nm/s %Recovery
30		940 na	Un-testable Low recovery
31[b]		180 23	117 68%
32[b]		88 7.1	100 64%
33		820 66	24 90%
34		1300 170	22 81%
35		1400 97	7 77%
36[b]		800 75	51 90%
37		>10,000 >1000	Un-testable Low recovery
38[c]		340 25	31 93%
39		250 20	11 79%
40		1300 110	8 84%
41		1000 76	2 84%
42		750 63	5 55%
43[b]		560 43	138 77%
44		700 43	107 86%

[a] See Ref. 16 for experimental details.
[b] 1:1 mixture of epimers.
[c] 1:1 mixture of diastereomers at the bridgehead positions.

Despite the considerable improvements to the rate of passive permeability, the P-gp efflux of these inhibitors remained unacceptably high precluding efficacy in *wild type* animal models (Table 7). Reduced, but untenable, P-gp liability was a general phenomena observed with cyclopropyl as the *P*1′ (**46**) due to the lower pK_a of the amine.[5a,29]

In conclusion, via chemistry driven SAR with support from molecular design substantial improvements to the permeability, an important pharmacokinetic parameter, have been introduced into the BACE-1 inhibitors by incorporating a polar *P*2′ substituent in place of a lipophilic group. The *S*2′ pocket is highly selective since only three of newly introduced *P*2′ moieties maintained potency comparable to compound **1**. Ethers proved to be a functional group that consistently produced desirable rates of permeability and recoveries. The cell-to-enzyme ratios were excellent possibly due to compartmentalization,[30] which could result in higher local concentrations of the inhibitor relative to the BACE-1 enzymatic assay. Also, none of these *P*2′ perturbations enhanced

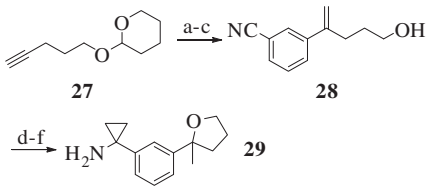
Table 6
SAR of non-aromatic cyclic moieties with P1' cyclopropyl[a]



45

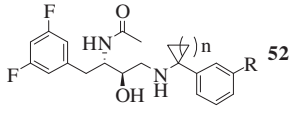
#	R	BACE-1 IC_{50}, nM Cell ED_{50}, nM	P_{app}, nm/s %Recovery
46[b]		580 700	114 69%
47[b]		580 66	90 57%
48[b]		1700 300	111 67%
49[b]		4000 750	100 78%
50[c]		2400 230	139 97%
51[c]		1900 410	Un-testable Low recovery

[a] See Ref. 16 for experimental details.
[b] 1:1 mixture of epimers.
[c] 1:1 mixture of diastereomers at the bridgehead positions.



Scheme 2. Reagents and conditions: (a) 9-BBN-Br, CH_2Cl_2, 0 °C, then glacial AcOH; (b) CSA, MeOH; (c) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DME, H_2O, 80 °C, 7% yield over three steps; (d) NIS, Et_2O, reflux; (e) 10% Pd/c, EtOAc, H_2, 24% over two steps; (f) $Ti(O\text{-}iPr)_4$, EtMgBr, Et_2O, 0 °C to ambient temperature then $BF_3\text{-}OEt_2$, 30%.

Table 7
P-gp efflux ratios of potent inhibitors[a]



52

#	*n*	R	BACE-1 IC_{50}, nM	P-gp efflux ratio	P_{app}, nm/s %Recovery
1	4		47	19	7 11%
19	4		59	22	72 54%
32[b]	4		88	31	100 64%
46[b]	1		580	12	114 69%

[a] See Ref. 16 for experimental details.
[b] 1:1 mixture of epimers.

the selectivity for BACE over cathepsin-D relative to **1**.[16] Unfortunately, the P-gp efflux was high prohibiting efficacy in *wild type* animal models that express P-gp at their blood–brain barrier for acute reductions of brain Aβ following oral dosing. Subsequent efforts to address the P-gp liability will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.112.

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