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P3 cap modified Phe*-Ala series BACE inhibitors

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Abstract—With the aim of reducing molecular weight and adjusting log D value of BACE inhibitors to more favorable range for BBB penetration and better bioavailability, we synthesized and evaluated several series of P3 cap modified BACE inhibitors obtained via replacement of the P3 NHBoc moiety as seen in **3** with other polar functional groups such as amino, hydroxyl and fluorine. Several promising inhibitors emerging from this P3 cap SAR study (e.g., **15** and **19**) demonstrated good enzyme inhibitory potencies (BACE-1 IC_{50} <50 nM) and whole cell activities (IC_{50} ~ 1 μM).

Almost a century after its initial description, Alzheimer's disease (AD) has been recognized as an emerging healthcare problem.[1] Although the actual cause of the disease has not been identified with certainty, numerous theories have been formulated to explain the pathology of AD with amyloid cascade hypothesis being the most popular one.[2] According to this β-amyloid hypothesis, $A\beta_{42}$ produced in excessive quantities, or cleared too slowly, or in the presence of aggregation factors, would form aggregates that lead to senile plaques, which may then initiate an immunologic and neurotoxic cascade resulting in the pathology of AD.[3] Since Aβ (40/42) peptides are produced by two consecutive protease cleavage events (by β- and γ-secretases)[4,5] of the β-amyloid precursor protein (APP), thus inhibition of the enzyme activity of either secretase involved could in theory slow down Aβ formation and thereby progression of Alzheimer's disease. Furthermore, a recent report from Vassar showed that BACE KO mice are healthy, fertile, and appear normal in gross anatomy, tissue histology, hematology, and clinical chemistry.[6] When taken together as a whole, the information presented herewith suggests that β-secretase is a prime drug target for the treatment of AD disease. Prompted by the mounting evidences supporting β-amyloid hypothesis,[7] we[8] and others[9] embarked on the design and evaluation of peptidyl mimetic BACE inhibitors. To build upon the Leu*-Ala series inhibitors reported recently by Tang's group,[10] we focused on both C- and N-termini SAR modifications surrounding Phe*-Ala based inhibitors. As a result of our effort, many inhibitors bearing *C*-termini Val-Pyridine moieties (as P2′–P2′cap) demonstrated excellent whole cell activities with IC_{50} values less than 1 uM.[8a]

During the course of our crystal structure based inhibitor design effort, we discovered that the N-termini Boc group such as that seen in **1** or **2** was not involved in the intimate contact with the BACE enzyme, suggesting that this functional group may be modified without significant loss of enzyme inhibitory activity.[8a] To take advantage of this observation, we decided to synthesize several novel P3 cap bearing inhibitors **4** through **7** endowed with reduced MW and possibly altered physical chemical properties (e.g., Log D, aqueous solubility, and tissue distribution) in comparison to compound **3** (Fig. 1).

The synthetic routes utilized for the preparation of inhibitors **5** and **7** are outlined in Scheme 1. PyBOP mediated coupling[11] reaction between AA and alanine methylester CC afforded the expected adduct EE (55%), which was then subjected to NaOH mediated ester hydrolysis to give the desired hydroxyacid GG (60%). Final coupling of GG with the known building block II[8a] was promoted by HOAt/EDCI,[12] providing the desired diol 5 in 30% yield after reverse-phase HPLC purification. Following essentially identical sequence as

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described for inhibitor **5**, the P3 NHBoc truncated inhibitor **7** was synthesized in three steps with 32% overall yield (see Scheme 1).

The synthetic route employed for the preparation of the P3 fluorinated inhibitor **6** is shown in Scheme 2. *N*-Acylation of (s)-4-benzyl-2-oxazolidinone **JJ** with isovaleryl chloride provided the adduct **LL** (93%). Treatment of **LL** with LiHMDS, followed by *N*-fluorodibenzenesulfonamide thus afforded the fluorinated intermediate **MM** (91%), which was then converted to the desired acid **NN** (71%) according to a published procedure.[13]

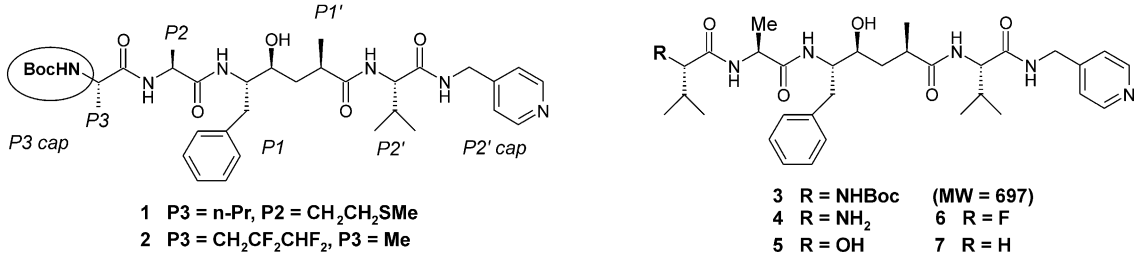
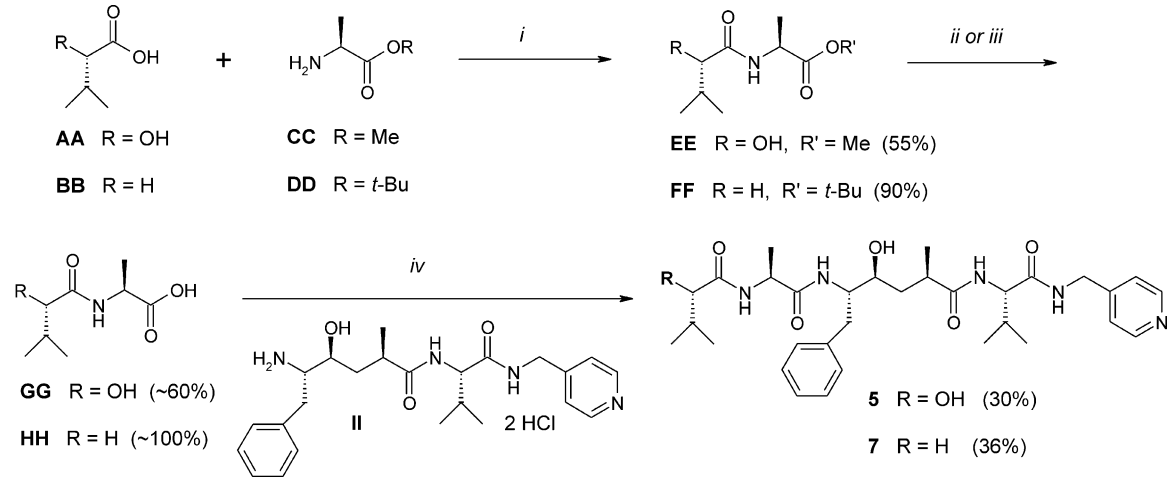
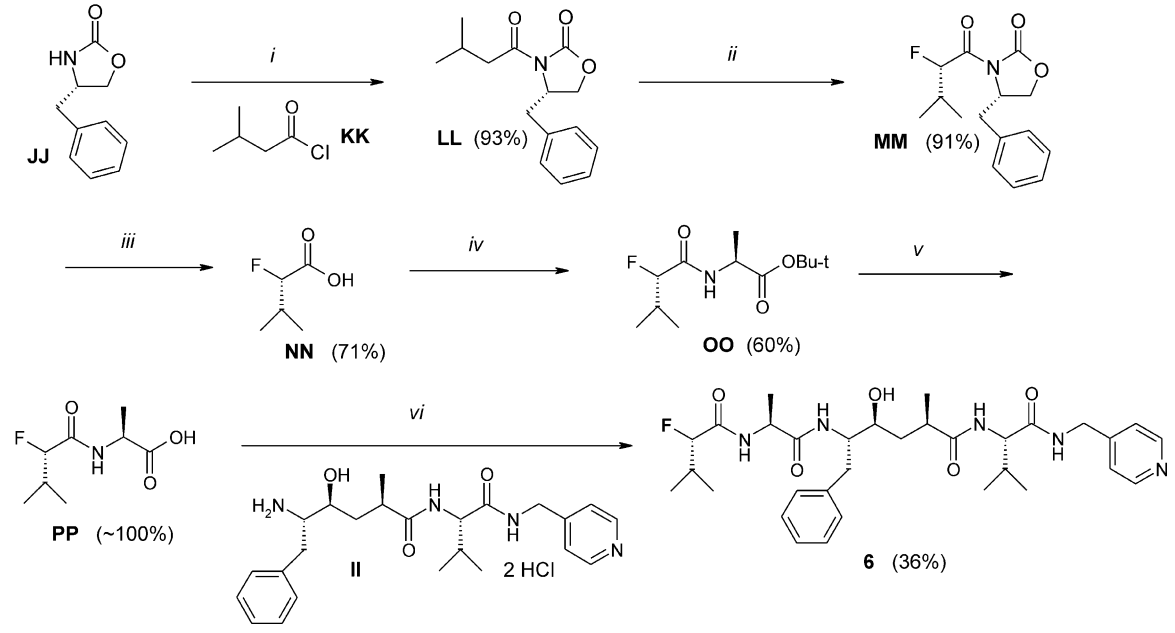


Figure 1. P3 cap modified BACE inhibitors.



Scheme 1. Syntheses of BACE inhibitors **5** and **7**. Reagents and conditions: (i) PyBOP/CH_2Cl_2/THF/*i*-Pr_2EtN; (ii) 1 N NaOH/MeOH, then 1 N HCl; (iii) 4 N HCl in dioxane/CH_2Cl_2; (iv) HOAt/EDCI/*i*-Pr_2EtN/THF + DMF.



Scheme 2. Synthesis of BACE inhibitor **6**. Reagents and conditions: (i) LiHMDS/THF/KK; (ii) LiHMDS/THF/F-N($SO_2Ph)_2$; (iii) LiOH/30% H_2O_2/THF/H_2O; (iv) HOAt/EDCI/CH_2Cl_2 + DMF, then L-Ala-OBu(*t*) and *i*-Pr_2EtN; (v) 4 N HCl in dioxane + CH_2Cl_2; (vi) HOAt/EDCI/THF + DMF, then **II**/*i*-Pr_2EtN.

HOAt/EDCI mediated coupling[12] of **NN** with alanine *t*-butylester provided the expected adduct **OO** (60%), which was further converted to its corresponding acid **PP** (100%) via saponification. Finally, coupling of the fluorinated acid **PP** with the requisite amine **II** provided the final product **6** in 36% yield.

It should be mentioned that the synthesis of the P3-amino moiety bearing inhibitor **4** was accomplished by treatment of the known inhibitor **3**[8a] with 4N HCl in dioxane at 0 °C. We noticed that prolonged acid treatment of **3** resulted in expected *N*-deprotection along with undesirable dehydration.

Four P3 cap modified BACE inhibitors **4**–**7** along with the P3 NHBoc containing derivative **3** were evaluated in the following assays: (1) in vitro homogenous BACE FRET (fluorescent resonance energy transfer) enzyme assay;[14] and (2) whole cell Aβ lowering assay in HEK293/APP751swe cells.[15] In addition, inhibitors **3**–**7** were also evaluated for BACE-2 selectivity[16] and Log D determination at neutral pH.[17] The results of these testing are summarized in Table 1.

As shown in Table 1, when compared with the NHBoc bearing inhibitor **3**, the P3 amino analogue **4** displayed slightly reduced enzyme activity (2-fold) along with rather significant reduction in whole cell activity (~20-fold). The poor cellular activity observed with **4** was likely attributed to its high hydrophilicity. On the other hand, the P3 hydroxyl bearing inhibitor **5** exhibited comparable enzyme inhibitory potency and slightly reduced whole cell activity (2–3-fold) relative to the P3 NHBoc containing counterpart **3**. Replacement of the P3 NHBoc in **3** with a fluorine or a hydrogen led to **6** or **7**, respectively. Judging from the data shown in Table 1, it is evident that neither **6** nor **7** showed significant biological activity with whole cell IC_{50} value ranging from 49 to >100 uM. When evaluated in the enzyme assay, inhibitors **6** and **7** were found to be at least 13-fold less potent than the P3 NHBoc bearing inhibitor **3**. Thus, in view of the data presented in Table 1, it is clear that replacing the P3 NHBoc moiety in **3** with a hydroxyl group resulted in only minimal loss of inhibitory activity (for **5**) in both the enzyme and whole cell assays. In addition, inhibitor **5** was found to be most selective against BACE-2 within the BACE inhibitors included in Table 1. Furthermore, when compared with the P3-NHBoc inhibitor **3**, the newly synthesized P3 hydroxylated inhibitor **5** had lower M_r (~100 mass units) as well as more favorable Log D value of 2.88 for brain penetration.[18] To build upon these results, we decided to pursue additional inhibitor **5** based SAR investigation to further optimize this novel series inhibitors. The syntheses and evaluation of these new inhibitors (**8**–**22**) are discussed in Tables 2–5.

1. Second round inhibitor evaluation

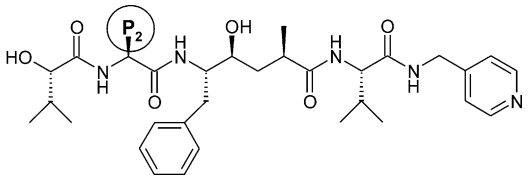
Following the same synthetic route described for **5**, five additional P2 modified inhibitors **8**–**12** were prepared starting with their corresponding P2–P3 hydroxyacids (**EE′**). As can be seen in Table 2, replacement of the P2 Ala. in **5** with either Met., Nva., or Ser. led to three new inhibitors **8**, **9**, and **10** exhibiting 3- to 5-fold reduced enzyme inhibitory activity and whole cell activity relative to inhibitor **5**. Furthermore, inhibitors containing either bulky (e.g., **11**) or branched alkyl (e.g., **12**) at the P2 pocket were much less potent than **5** in the enzyme assay.

Upon completion of our limited P2 SAR effort, we then embarked on P3 and C-termini optimizations. The P3

Table 1. P3 cap modified BACE inhibitors

Compd	M_r	BACE-1 IC_{50} (nM)	BACE-2 selectivity	Abeta (sw) IC_{50} (μM)	Log D @ pH = 7
3	697	82	0.4	2.1	4.36
4	597	190	0.52	38.4	Not tested
5 (2070103)	598	130	2.8	4.8–7.5	2.88
6	600	1130	1.35	49	3.45
7	582	1740	0.72	>100	3.2

Table 2. LY2070103 (**5**) based P2 modifications

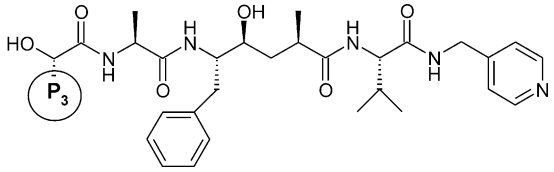


Compd	P_2	BACE-1 IC_{50} (μM)	Abeta (sw) IC_{50} (μM)	Log D (pH = 7)
5	Me (Ala)	0.13	4.8	2.88
8	CH_2CH_2SMe (Met)	0.35	25.2	3.64
9	CH_2CH_2Me (Nva)	0.55	30.4	3.46
10	CH_2OH (Ser)	0.35	20	2.73
11	CH_2OBu-*t*	4.49	Not tested	Not tested
12	$CHMe_2$ (Val)	4.64	Not tested	3.69

modified inhibitors **13**–**15** were synthesized according to the procedure outlined in Scheme 1 using either (s)-3-trifluromethyl lactic acid[19] or commercial available (s)-2-hydroxyl-3,3-dimethylbutyric acid, or (s)-2-hydroxyl-(s)-3-methyl pentanoic acid as their respective P3 residue. When evaluated in the BACE FRET and whole cell assays, whilst the P3 trifluoromethyl bearing inhibitor **13** showed similar activity to that of **5**, the P3 *i*-Bu bearing inhibitor **14** was found to be ~3-fold less potent than compound **5** in the cellular assay. To our satisfaction, the P3 Ile mimetic **15** demonstrated 4-fold enhanced enzyme and cellular potency in comparison to inhibitor **5**. It is worthwhile to mention that the SAR trend observed with **15** is in good agreement with that found with its corresponding P3-NHBoc bearing inhibitor.[8a]

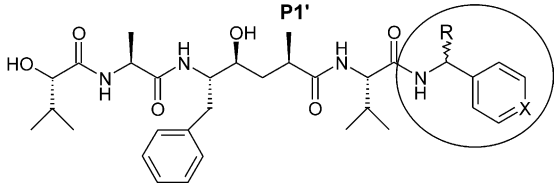
Parallel with the P3 optimization, we also modify the C-termini via either benzyl moiety incorporation or stereospecific installation of a methyl group at the benzylic position (see Table 4). All of the C-termini modified inhibitors **16**–**18** were prepared via coupling of the P2–P3 hydroxyacid **EE** with the appropriate **II**-like P1–P2′ units. On the basis of the biological activities determined for these new analogues, it is clear that (1) no stereochemistry preference was observed at the benzylic position (P2′ cap); (2) the C-termini Bn bearing inhibitor **16** displayed 4-fold better enzyme potency than **5**.

Table 3. LY2070103 (**5**) based P3 modifications



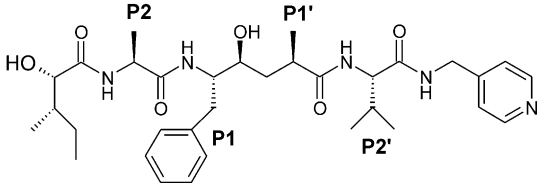
Compd	P_3	BACE-1 IC_{50} (μM)	Abeta (sw) IC_{50} (μM)	Log D (pH = 7)
5	$-CHMe_2$ (Val)	0.13	4.8	2.88
13	$-CH_2CF_3$	0.22	3.9	Not tested
14	$-CH_2CHMe_2$ (Leu)	0.23	16.9	3.36
15	–(s)-CHMeEt (i-Leu)	0.035	1.23	3.21

Table 4. LY2070103 (**5**) based P1′ and P2′ cap modifications



Compound	P1′	R	X	BACE-1 IC_{50} (μM)	Abeta (sw) IC_{50} (μM)	Log D (pH = 7)
5	Me	H	N	0.13	4.8	2.88
16	Me	H	CH	0.037	6.3	3.91
17	Et	*(R)*-Me	CH	0.06	19.8	Not tested
18	Et	*(S)*-Me	CH	0.10	13.6	4.46

Table 5. LY2090089 (**13**) based modifications



Compd	Structural modification	BACE-1 IC_{50} (μM)	Abeta (sw) IC_{50} (μM)	Log D (pH = 7)
15	None	0.035	1.23	3.21
19	CH_2CHF_2 as P2	0.045	1.08	3.71
20	Leu as P1	0.176	3.7	Not tested
21	$CH_2CH_2CH_2F$ as P1′	0.067	0.97–1.35	3.56
22	CH_2CHF_2 as P2′	3.18	>37.5	3.69

However, this enhanced enzyme potency did not translate into any improvement in cellular assay. The lack of correlation between enzyme and whole cell assays observed for **16**–**18** (>100 fold) is likely due to high lipophilicity of these inhibitors.[8a] This is due at least in part to the absence of the polar *C*-termini pyridyl moiety as seen in inhibitor **5**.

With the aim of further improving upon the potent inhibitor **15** (BACE $IC_{50}=35$ nM) identified via P3 SAR optimization, we decided to incorporate fluorinated amino acids into various position such as P2, P1′ and P2′. The syntheses of **19** and **22** were accomplished in accordance with the reaction sequence outlined in Scheme 1 using the appropriate P2 or P2′ residue. On the other hand, inhibitor **21** was prepared via incorporation of the fluorinated *n*-Pr moiety into the P1′ position.[8c] In order to synthesize compound **20**, we utilized the Leu. P1 bearing version of **II** as the building block, which was in turn prepared following a published procedure.[10a] With the new inhibitors in hand, we carried out comparative evaluation against inhibitor **15**. Careful inspection of the testing result shown in Table 5 reveals the following SAR trends: (1) fluorine incorporation at either P2 or P1′ position did not impact BACE inhibitory activity; (2) replacing the P1 Phe with Leu resulted in 3–4-fold drop in both the enzyme and cellular potency; and (3) introduction of the difluoroaminobutyric acid at the P2′ site resulted in significant loss of enzyme inhibitory activity and cellular potency (~100×).

2. Enzyme–inhibitor interaction

The co-crystal of the P3 hydroxylated inhibitor **5** with human BACE enzyme was solved using standard protocol.[20,21] Inspection of the structure shown in Figure 2 reveals that the P3 isopropyl group was indeed positioned at the P3 binding pocket. We also notice that the types of interactions made by the backbone and other side chains of **5** overlapped very well with that found with inhibitor **2**.[8a] It is also evident that the *N*-Boc moiety in **2** pointed away from the enzyme surface. Consistent with this finding, the enzyme inhibitory potency detected with **5** is very similar to that observed with **3** (see Table 1).

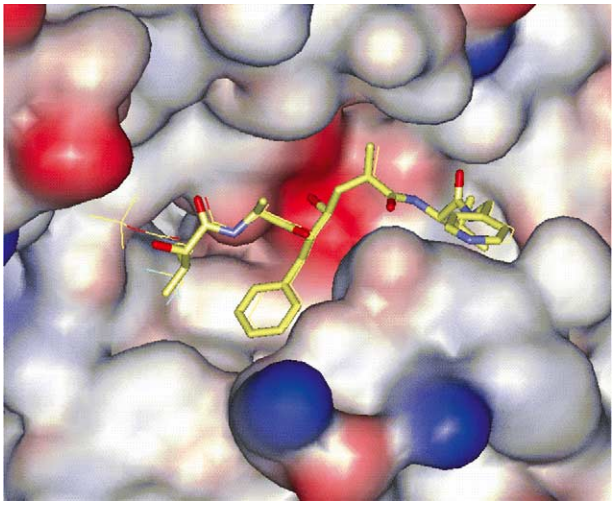


Figure 2. Crystal structures of inhibitors **2** and **5** binding to BACE-1.

Guided by the insights gained through detailed analysis of the co-crystal structures of **1** and **2** with human BACE enzyme, we designed and synthesized several novel series P3 cap modified inhibitors including the P3 hydroxylated inhibitor **5**. Compared with the P3 NHBoc bearing compound **3**, inhibitor **5** had lower molecular weight (~100 mass units) and more favorable Log D value for BBB penetration,[18] albeit with slightly reduced biological activity. Subsequently, we carried out compound **5** based systematic SAR modifications in hopes of identifying inhibitors with enhanced activity. As a result of this effort, we discovered several P3 hydroxylated inhibitors (e.g., **15**, **19**, and **21**) showing impressive enzyme (IC_{50} range: 35–67 nM) and cellular activities (IC_{50}~1 uM).

Acknowledgements

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14. BACE FRET assay uses 20 nM purified recombinant human BACE/Fc. The standard assay format contains 100 M ELGY-9 (an aminobenzoate based FRET peptide containing Swedish mutation) in 50 mM ammonium acetate, pH 4.6, 1 mg/mL BSA and 1 mM Triton X-100 at room temperature for 4 h. The enzyme activity is determined by an increase in the relative fluorescent of reaction mixture, with umbilliferone excitation/emission filter set.
15. Whole cell Aβ lowering assay measures intracellular inhibition of endogenous BACE expression in HEK293 (Human Embryonic Kidney) cells by BACE inhibitors. This cell line stably overexpresses APP751swe substrate. Testing subjects are incubated with cells for 4 h at 37 °C and 5% CO_2. The conditioned media are removed from the culture wells. The Aβ ELISA is used to measure amount of Aβ(total) peptide produced during the incubation time.
16. (a) The detailed assay conditions for BACE2 FRET is similar to that of BACE FRET assay. Purified recombinant BACE2/Fc (20 nM) is used in the assay. (b) For BACE subsite specificity, see: Turner, R. T., III; Koelsch, G.; Hong, L.; Castanheira, P.; Ghosh, A.; Tang, J. *Biochemistry* **2001**, *40*, 10001. (c) For BACE-2 subsite specificity, see: Turner, R. T., III; Loy, J. A.; Nguyen, C.; Devasamudram, T.; Ghosh, A. K.; Koelsch, G.; Tang, J. *Biochemistry* **2002**, *41*, 8742.
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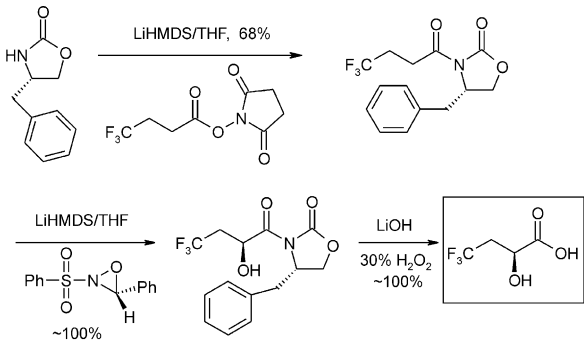
18. Literature survey shows that log D values determined for the majority of the FDA approved drugs for the treatment of various neuronal disorders range from 2.5 to 3.5.
19. Synthetic route used for preparation of the α-hydroxyl acid needed for **13** is shown below:



20. Co-crystal of **5** with BACE: Crystals of the BACE catalytic domain were grown in the presence of a 5-fold molar excess of LY2070103 (**5**) using minor modifications of previously described methods cited in ref 21. Diffraction data were collected at 100 K using a synchrotron source on beamline 17ID at the Advanced Photon Source. The LY2070103 (**5**) model was built into active site electron density using QUANTA (Accelrys, Inc) and O (*Acta Crystallogr.* **1991**, *A47*, 110). The structure of BACE bound to 2070103 has been determined at 2.05 Ang. resolution and refined to a crystallographic *R*-factor of 0.201 (R_{free} = 0.227). The figure shows a superposition of the 2070103 structure with the OM99-2 inhibitor structure (see ref 21).
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