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Structure based design, synthesis and SAR of cyclic hydroxyethylamine (HEA) BACE-1 inhibitors

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ABSTRACT

This Letter describes the de novo design of non-peptidic hydroxyethylamine (HEA) inhibitors of BACE-1 by elimination of P-gp contributing amide attachments. The predicted binding mode of the novel cyclic sulfone HEA core template was confirmed in a X-ray co-crystal structure. Inhibitors of sub-micromolar potency with an improved property profile over historic HEA inhibitors resulting in improved brain penetration are described.

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by a progressive decline in cognitive function. Amyloid-beta (Aβ) peptide deposits and neurofibrillary tangles are the two major pathologic hallmarks associated with AD.[1] The perturbation in rate of formation and/or clearance of the Aβ peptide initiates a cascade of events leading to the formation of neurotoxic oligomers, insoluble amyloid plaques that disrupt neuronal function and lead to neuroinflammation, cell death and memory loss.[2] Aβ is generated by the proteolytic processing of the membrane bound amyloid precursor protein (APP) via two consecutive cleavages, first by the β-site cleaving enzyme (BACE-1) followed by γ-secretase. APP is cleaved by BACE-1 to form a β-secretase-derived C-terminal fragment of APP (βCTF), which undergoes further cleavage by the γ-secretase to create Aβ isoforms ranging from 37 to 42 amino acid residues. $A\beta_{40}$ is the most abundant isoform, while the plaques linked with ADpathogenesis consist primarily of aggregated $A\beta_{42}$. Inhibition of BACE-1 has emerged as an attractive therapeutic target for AD, since BACE-1 knockout APP transgenic mice lacking $A\beta_{40/42}$, do not form amyloid plaques and are viable and fertile.[3,4] Recently, it has been demonstrated that inhibition of BACE-1 in primates lowers the production of $A\beta_{40}$ and $A\beta_{42}$ in cerebrospinal fluid.[5]

The identification of small molecule inhibitors of aspartyl proteases is challenging since the enzymes normally recognize 6–10 amino acids of their substrate for binding and selectivity. Inhibitors of most aspartyl proteases (renin, HIV) that have been reported in the literature contain a central transition state (TS) isostere as the key binding element flanked by N- and C-terminal fragments resembling the corresponding peptide sequence.[6] The highly peptide-like character of such inhibitors results in borderline drug-like physicochemical properties (MW, log P, polar surface area (PSA), Lipinski's number of oxygen and nitrogen H-acceptors (N_{HA}).[7] This in turn translates into poor pharmacokinetic properties and low blood–brain distribution and permeability glycoprotein (P-gp) mediated efflux.[8] To mediate brain Aβ lowering by inhibition of BACE-1, the synthesis of transition state based inhibitors able to cross the blood–brain barrier (BBB) presents a formidable challenge which requires the development of highly permeable inhibitors with as few as possible P-gp recognition sites.[9]

Recently, there have been reports surfacing in the literature describing inhibitors with novel core templates to evade the poor property space of traditional TS isostere based inhibitors.[10,11] Noticeably, a strong influence of the basicity of the HEA TS mimetics on P-gp mediated efflux and brain exposure has been demonstrated by different investigators.[12,13] The extent of the pK_a reduction however needs to be individually balanced against the decline of cellular activity, since compounds with a pK_a <6 do not inhibit amyloid secretion in cell based assays.[12]

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We decided to generate compounds within a more restrained chemical space (MW <450, *C* log *P* <4, PSA <90 Å^2, N_{HA} ⩽5, pK_a <7) to allow the identification of compounds with CNS penetration. With these constraints in mind, we initiated the structure based design of cyclic HEA templates containing suitable attachment points for direct extensions into the corresponding S2′- and S_1/S_3 sub-sites to gain potency and selectivity (Fig. 1). A reduction in conformational flexibility and number of sub-site interactions, compared to current published hydroxethyl- (like OM99-2, Fig. 2)[14] and HEA dipeptide isostere inhibitors,[10,11] will lead to an improvement of the ligand efficiency.[15] Comparison of X-ray crystallographic data on different HEA inhibitors revealed that the binding mode and cavity were highly conserved.[16] In an iterative process (Fig. 2) different 5–7 membered HEA ring templates tethered with P1 and P2′ substituent's were docked using QXP with the Flo modeling package[17] and conformational energy and the overall binding potential was assessed. The functional group (X) was selected based on its capability to interact with the flap and to lower the pK_a.[18] The modified templates were re-docked again until inhibitors with the desired property profile were identified. Candidate **1** and **2** from this design cycle (Fig. 3) were synthesized and the binding activity determined. Inhibitor **2** was co-crystallized with BACE-1 (Fig. 5) to compare the binding mode with the initial docking pose in Figure 4.

The co-crystal structure of BACE-1 in complex with **2** was determined at 2.4 Å resolution.[19] The crystallographic data confirmed that the designed binding interactions were fully formed, including H-bonding with Asp32 and Asp228, as well as the phenolic-OH with the backbone amide of Phe108. The embedded sulfone moiety in the cyclic HEA template considerably lowered the basicity of the amine (**2**, pK_a 5.7 vs **1** pK_a 7.1) and formed optimal H-bonds with the flap residues Thr72 and Gln73. **2** binds to a closed conformation of the flap, similar to acyclic or macro-cyclic HEA inhibitors.[20]

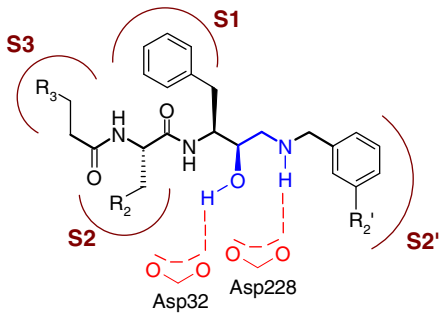


Figure 1. Binding mode of HEA dipeptide isosteres.

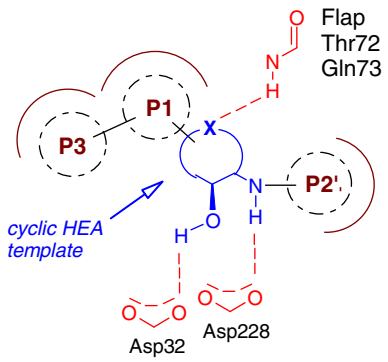


Figure 2. Design concept for sub-site linked cyclic HEA inhibitors.

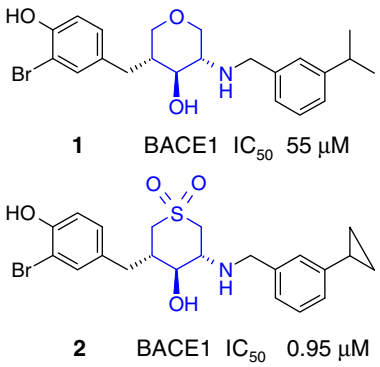


Figure 3. Amino-pyranol **1** and amino-dioxo-hexahydro-thiopyranol derivative **2**.

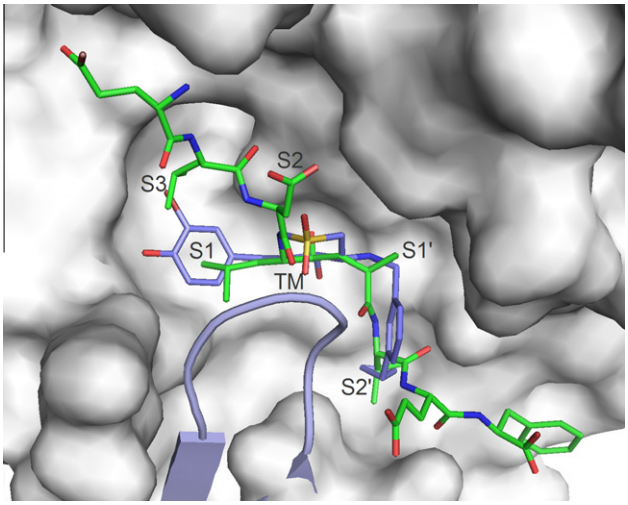


Figure 4. Overlay of **2** (blue sticks) with hydroxyethyl dipeptide isostere inhibitor OM99-2 (green sticks); the flap of BACE is omitted for clarity.

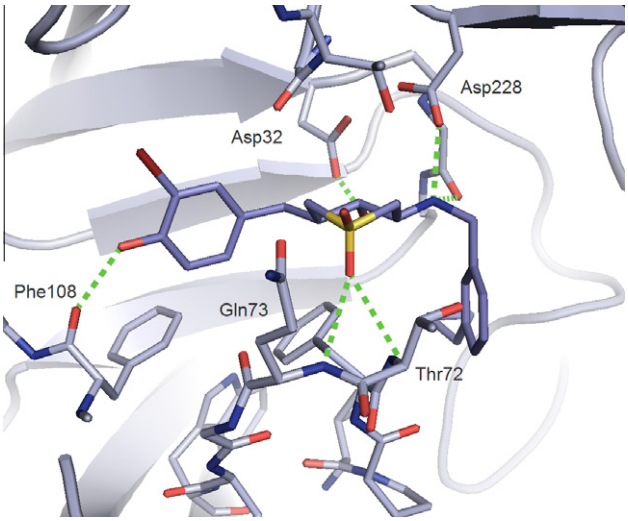


Figure 5. Co-crystal structure of **2** in complex with BACE-1.

In addition, excellent hydrophobic contacts were observed in the adjacent S1 and S2′ pockets resulting in micro molar activity (IC_{50} 0.95 μM).

The pyran based inhibitor **1,** not being able to form close interactions with the flap, resulted in a 50-fold weaker activity. This finding indicated that the optimal H-bonding interactions of the sulfone with the Thr72 and Gln73 amides of the flap resulted in a considerable binding contribution, whereas further docking experiments did not predict such interactions in similarly substituted larger and smaller rings. Based on the results of these two benchmark compounds, we selected the cyclic sulfone HEA as core template and started to probe the S3 pocket by extensions from the P1 phenyl ring (Table 1, **14**–**20**) with minimal N_{HA} and PSA contributing moieties to facilitate BBB penetration and minimize P-gp efflux. The same principles were applied for the optimization of the hydrophobic contacts in the S2′ pocket (Table 2, **22a**–**e**) to gain potency and selectivity.

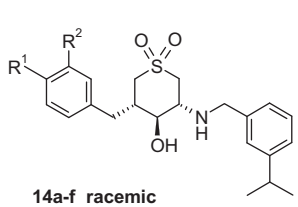
The stereoselective synthesis of this new class of cyclic sulfone HEA inhibitors[21] starting from dimethyl-3,3′-thio-dipropionate **3** is summarized in Scheme 1.

The methyl keto-ester formed by a Dieckmann condensation resisted direct γ-alkylation with benzyl halides. A Knoevenagel condensation, however limited to electron rich benzaldehyde derivatives, gave access to the unsaturated keto-ester. Quantitative oxidation of the thioether to the sulfone with mCPBA and subsequent hydrogenation over catalytic platinum provided the saturated sulfone keto-ester **4** in 60% overall yield. A stereoselective reduction of the keto-ester to the racemic hydroxyl-ester **5** with the desired (3S,4S,5S)-configuration could not be achieved. An alternative sequence via a stereoselective $NaBH_3CN$ reduction, hydrolysis of the (4R)-hydroxy-methyl ester followed by a Curtius rearrangement and *N*-Boc protection afforded crystalline **6**, without chromatographic purification at any intermediate step. O-deprotection in MeOH catalyzed by Cs_2CO_3 and Parikh–Doering oxidation of the alcohol provided the protected amino-ketone **7** with the desired relative (3R,5S)-configuration. From this intermediate a stereoselective reduction of the ketone could be achieved with $LiAlH_4$ and N-deprotection provided the racemic core cyclic sulfone HEA template **9**. After attachment of the P′ side fragment by reductive amination, the amino and hydroxyl group of **11** (Scheme 2) were transformed into the oxazolidinone **12a** or **12b**, to permit the exploration of the P3 pocket with a wide range of chemical transformations. The applied synthetic sequence to the differently substituted P1 derivatives (Table 1, **14a**–**f**) is illustrated in Scheme 2.

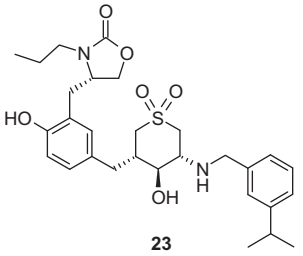
The synthesis of enantiopure inhibitors was achieved by simulated moving bed chromatography on ChiralPak-AD with the more soluble *N,O*-acetal **17** (Scheme 3) prepared from racemic *N*-Boc amino-alcohol **8**. The aryl bromide **17** was then converted into aldehyde **18** by a Suzuki cross-coupling with 2,4,6-trivinylcyclotriboroxane pyridine complex and subsequent ozonolysis of the styrene derivative. The different P3 extensions (R^2) were prepared from the aldehyde **18** by Wittig olefination and subsequent catalytic hydrogenation over Pd-*C* or by $NaBH_4$ reduction. Removal of the *N*-Boc protecting group with 4 N HCl in dioxane, hydrolysis of the *N,O*-acetal and cleavage of the MeO-group with BBr_3, gave access to the amino-alcohol **19** and **21**. After reductive amination with the corresponding P2′-aldehyde the final inhibitors **20a–f** (Table 1) and **22a–e** (Table 2) were obtained.

Our de novo design approach produced a moderately active lead (**2**, IC_{50} = 0.95 μM) with a slightly improved ligand efficiency (0.31 vs 0.29) compared to HEA inhibitor **24**[22] occupying a similar chemical space (PSA, N_{HA}). A crystal structure of **2** with BACE-1 (Fig. 3)

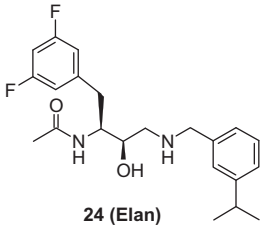
Table 1
SAR of P3 modifications for racemic **14a–f** and enantiopure compounds **20a–g** and **23** compared against an acyclic HEA BACE-1 inhibitor **24**



14a-f racemic
20a-g enantiopure



23



24 (Elan)

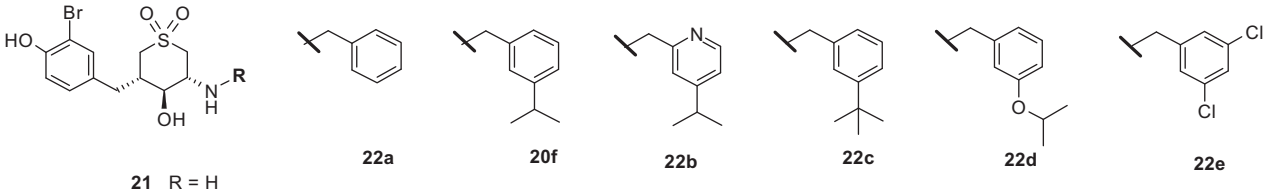
Compd	R_1	R_2	*C* log *P*	PSA (Å^2)	hBACE-1 IC_{50}[a] (μM)	hCath D IC_{50}[a] (μM)	MDR1-MDCK P^b_{AP-BL} (10^{-6} cm/s)	MDR1-MDCK P^b_{BL-AP} (10^{-6} cm/s)	Efflux ratio P_{BL-AP}/P_{AP-BL}
14b	H	H	3.0	66	1.1	1.9	19	24	1.2
14c	H	Br	3.9	66	0.76	2.3	5.4	7.7	1.4
14c	H	O*n*Pr	4.0	76	2.3	2.0	5.7	7.9	1.4
14d	H	CH_2O*n*Pr	3.7	76	1.1	0.9	7.0	13	1.8
11	OMe	Br	3.7	78	2.8	2.4	3.7	9.7	2.6
14e	OH	H	2.3	87	1.8	5.4	9.0	37	4.2
14f	OH	3-Me-Bn	4.4	87	6.2	7.1	––	––	––
20a	OH	CH_2OH	2.0	87	1.2	2.1	1.8	30	17
20b	OH	$(CH_2)_2OH$	1.5	107	0.99	1.7	0.9	28	32
20c	OH	*n*Bu	4.4	87	0.15	1.9	0.8	4.2	5.5
20d	OH	*n*Pr	3.9	87	0.19	1.8	4.2	18	4.4
20e	OH	Et	3.3	87	0.37	2.4	15	45	3.1
20f	OH	Br	3.2	87	0.30	1.2	11	33	3.0
20g	OCONHMe	Br	3.0	105	0.06	0.37	3.8	88	23
23[19,21]			3.3	116	0.15	6.4	1.4	26	19
24[22]			3.6	61	3.2	4.7	2.2	41	18

IC_{50} values for BACE-1 and cathepsin D inhibition, and inhibition of cellular release of $A\beta_{40}$ were determined as already described.[20]

[a] Values are means of at least three experiments.

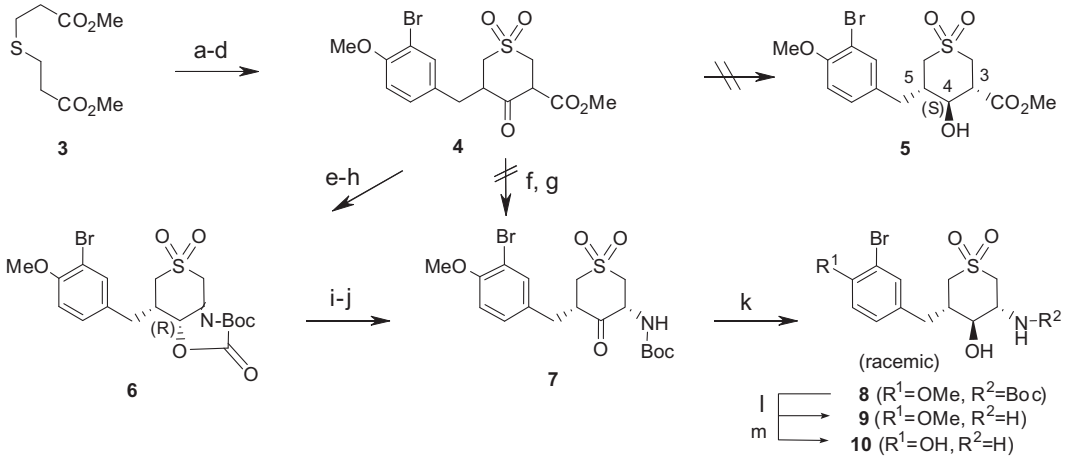
[b] P_{AP-BL} is the permeability across MDR1-MDCK cell monolayer in the apical-to-basolateral and P_{BL-AP} in the basolateral to the apical direction.[23]

Table 2
SAR of P2′ modifications



Compd	*C* log *P*	PSA (Å)	hBACE-1 IC_{50}[a] (μM)	hCath D IC_{50}[a] (μM)	$Aβ_{40}$ CHO IC_{50}[a] (μM)	MDR1-MDCK P_{AP-BL}[b] (10^{-6} cm/s)	MDR1-MDCK P_{BL-AP}[b] (10^{-6} cm/s)	Efflux ratio P_{BL-AP}/P_{AP-BL}
21	−0.4	101	>100					
22a	1.8	87	66					
20f	3.2	87	0.30	1.2	1.5	11	33	3.0
22b	1.7	100	4.3	––				
22c	3.6	87	0.055	0.42	0.55	7.7	16	2.1
22d	2.6	96	1.4	0.67	8.5			
22e	3.2	87	4.2					

IC_{50} values for BACE-1 and cathepsin D inhibition, and inhibition of cellular release of $Aβ_{40}$ were determined as already described.[20]
[a] Values are means of at least three experiments.
[b] P_{AP-BL} is the permeability across MDR1-MDCK cell monolayer in the apical-to-basolateral and P_{BL-AP} in the basolateral to the apical direction.[23]



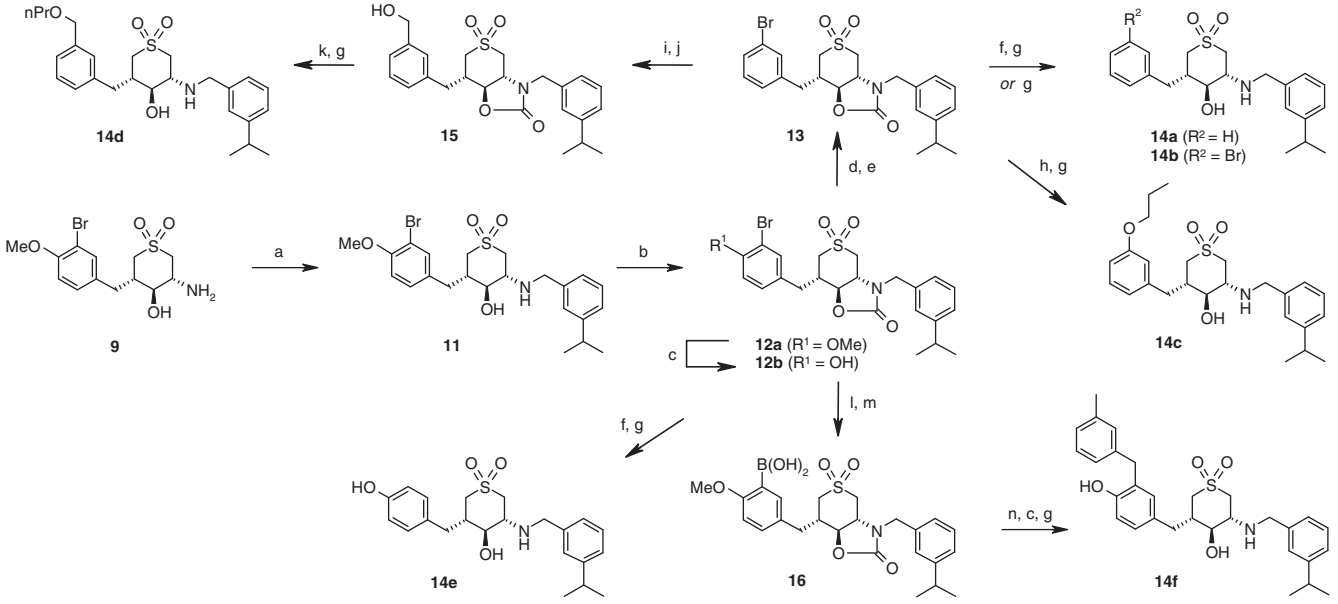
Scheme 1. Reagents and conditions: (a) NaOMe, Et_2O, 25 °C; (b) 3-bromo-4-hydroxy-benzaldehyde, AcOH, pyrrolidine, EtOH-H_2O 10:1, reflux; (c) mCPBA, CH_2Cl_2, 40 °C; (d) H_2, PtO_2, THF, 25 °C; (e) $NaBH_3CN$, iPrOH–AcOH 4:1, 40 °C; (f) 4 N NaOH–dioxane 1:1, 25 °C; (g) (i) DPPA, NEt_3, dioxane, (ii) *t*BuOH, reflux; (h) $(Boc)_2O$, NEt_3, DMAP, 50 °C; (i) Cs_2CO_3, MeOH, 25 °C; (j) Py-SO_3, DMSO, NEt_3, 25 °C; (k) $LiAlH_4$, THF, −70 °C; (l) 4 N HCl in dioxane, 25 °C; (m) BBr_3, CH_2Cl_2, 0 °C.

revealed an only partially occupied P3 pocket. We envisaged a substantial gain in activity with different P3 fragments through additional hydrophobic and H-bonding interactions. To our surprise only a 10-fold increase in potency could be achieved with hydrophobic extensions (Table 1, **20c**–**d**) compared to the P3 unsubstituted analog **14e,** accompanied by a three-fold increase in selectivity. Insertion of P3 residues containing a strong hydrogen bond donor (**20a**, **20b**) or acceptor functionality (**20g**, **23)** resulted in equally to slightly more potent analogs, however at the expense of a substantial increase in P-gp mediated efflux. The phenolic substituent on the P1 residue was originally selected to form an additional H-bond to Phe108 only possible in BACE-1 and not in cathepsin D. However, the observed effect on potency and selectivity was minimal deduced by comparison of **14b** and **20f**. In addition, the additional H-bond donor induced a three-fold increase in efflux (**14a** vs **14e**). The synthetic utility of the phenol is further offset by the low metabolic stability in rat liver microsomes (Table 3), as well as its potential to undergo phase II metabolism.

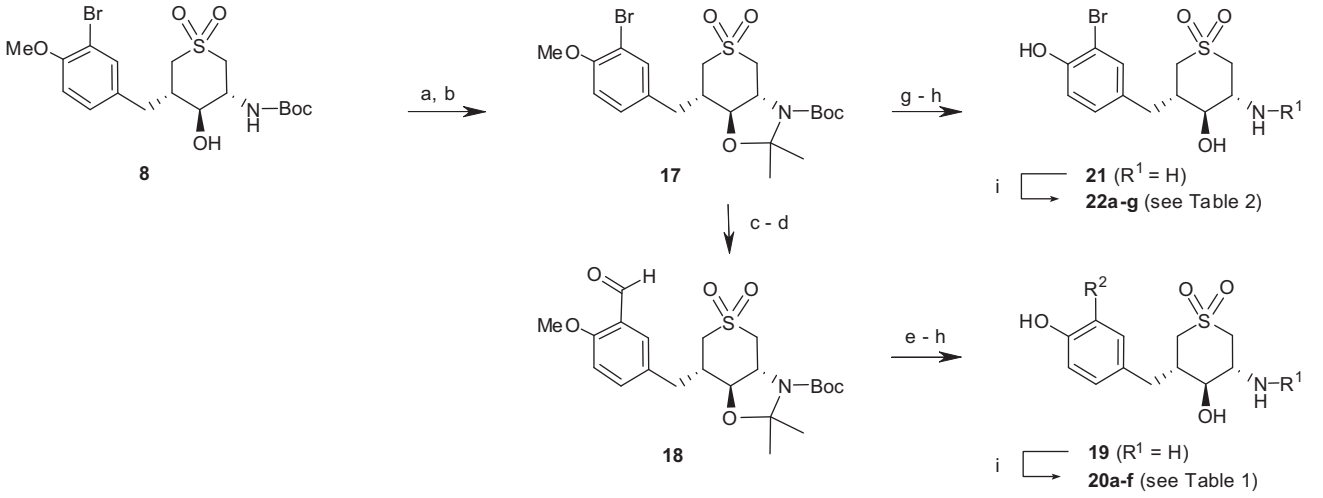
Of the extensive SAR work in P′ (>50 compds) of simple benzyl substituent's (a few representative examples are displayed in Table 2), a steep SAR was observed and only hydrophobic 3-aryl substituted P2′ fragments demonstrated activity in the micro-molar range. The most potency enhancing effect was observed with the bulky 3-*tert*-butyl-benzyl P2′ fragment, resulting in inhibitor **22c** with a five-fold increase in potency (IC_{50} = 0.055 μM) over the 3-*iso*-propyl analog **20f** (IC_{50} = 0.30 μM) and a ∼10-fold selectivity over cathepsin D.

When administered in mice, no brain exposure was observed as expected with the high efflux compound **23** (efflux ratio 19). Having a *C* log *P* of 3.3, N_{HA} of 8, and a PSA of 116 Å^2, compound **23** did not comply with Norinder's rule of thumbs for good blood–brain (BB) distribution (rule 1: PSA <75 Å^2 and $N_{HA} \leqslant 5$ and rule 2: if log $P-N_{HA}$ >0, then log *BB* is positive).[8b] On the other hand, substantial brain exposure was achieved with compound **20f** (*C* log *P* 3.3) and **22c** (*C* log *P* 3.6) having a 2- to 3-fold efflux ratio, a pK_a of 5.6, N_{HA} of 5 and a borderline PSA of 87 Å^2.

In summary, the de novo designed cyclic sulfone HEA inhibitors residing close to the desired CNS descriptor space showed a reduced P-gp liability compared to 'historic' HEA. Furthermore, we could demonstrate that potent and selective BACE inhibitors containing a low to medium P-gp efflux ratio could achieve



Scheme 2. Reagents and conditions: (a) 3-isopropyl-benzaldehyde, NaOAc, $NaBH_3CN$, CH_2Cl_2–MeOH 1:1, 25 °C; (b) $CO(Im)_2$, DIPEA, DMAP, 1,2-dichlorethane, reflux; (c) BBr_3, CH_2Cl_2, 0 °C; (d) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C; (e) HCOOH, nBu_3N, $(PPh_3)_2PdCl_2$, DPPP, DMF, 110 °C; (f) H_2, 10% Pd–C, MeOH–THF, 25 °C; (g) $KOSiMe_3$, THF, 50 °C; (h) *n*-PrOH, $Pd(OAc)_2$, 2-di-*t*-butylphosphino-1,1′-binaphthyl, Cs_2CO_3, toluene, microwave 130 °C; (i) 2,4,6-trivinylcyclotriboroxane–pyridine complex, $Pd_2(dba)_3$, tBu_3P, Cs_2CO_3, dioxane, microwave 160 °C; (j) (i) O_3, CH_2Cl_2–MeOH, −78 °C; (ii) $NaBH_4$, MeOH, 25 °C; (k) NaH, 1-iodo-propane, DMF, 25 °C; (l) 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, $PdCl_2$(dppf), NEt3, dioxane, microwave 200 °C; (m) 2 N HCl, $NaIO_4$, THF–H_2O, 25 °C; (n) 1-bromomethyl-3-methyl-benzene, $PdCl_2$(dppf), K_2CO_3, EtOH, microwave 120 °C.



Scheme 3. Reagents and conditions: (a) 2,2-dimethoxy-propane, pTsOH, CH_2Cl_2, reflux; (b) enantiomer separation on ChiralPak-AD (hexane-*t*BuOMe–THF 5:4:1); (c) 2,4,6-trivinylcyclotriboroxane–pyridine complex, $Pd_2(dba)_3$, tBu_3P, Cs_2CO_3, dioxane, microwave 170 °C; (d) (i) O_3, CH_2Cl_2–MeOH, −78 °C; (ii) PPh_3, MeOH, 25 °C; (e) wittig reagents, KHMDS, THF, 25 °C; (f) H_2, 10% Pd–C, MeOH–THF, 25 °C or $NaBH_4$, MeOH, 25 °C; (g) (i) 4 N HCl in dioxane, 25 °C; (ii) 2 N HCl–MeOH 1:4, 25 °C; (h) BBr_3, CH_2Cl_2, 0 °C; (i) aldehyde of the corresponding P2′ fragment, NaOAc, $NaBH_3CN$, CH_2Cl_2–MeOH 1:1, 25 °C.

Table 3
Plasma and brain concentration in mice (dose: 2 μmol/kg, iv)

Compd	Plasma[a] 0.25 h (μM)	Brain[a] 0.25 h (μM)	Efflux ratio	Microsomal stability rat ($t_{1/2}$ (min))
23	0.67	<0.05	19	4
20f	1.03	0.21	3.0	3
22c	0.32	0.18	2.1	6

[a] Values are means of four animals.

moderate brain exposure. Subsequent efforts to address the remaining issues such as inadequate potency, selectivity and metabolic stability of these new cyclic HEA inhibitors will be reported in due course.

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X-ray data collection of the BACE-1 complex with compound **23** was performed at the Swiss Light Source, Paul Scherrer Institut, Villigen, Switzerland. We are grateful to the machine and beamline groups whose outstanding efforts have made these experiments possible.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.02.038.

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