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Synthesis and SAR of hydroxyethylamine based phenylcarboxyamides as inhibitors of BACE

Yong-Jin Wu [a,*], Yunhui Zhang [a], Andrew C. Good [b], Catherine R. Burton [c], Jeremy H. Toyn [c], Charles F. Albright [c], John E. Macor [a], Lorin A. Thompson [a]

[a] Neuroscience Discovery Chemistry, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492, USA
[b] Computer-Aided Drug Design, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492, USA
[c] Neuroscience Discovery Biology, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492, USA

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ABSTRACT

A series of *N*-((2*S*,3*R*)-1-(3,5-difluorophenyl)-3-hydroxy-4-(3-methoxybenzylamino)-butan-2-yl)benzamides has been synthesized as BACE inhibitors. A variety of P2 and P3 substituents has been explored, and these efforts have culminated in the identification of several 1,3,5-trisubstituted phenylcarboxyamides with potent BACE inhibitory activity.

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Diverse lines of evidence suggest that β-amyloid (Aβ) peptide, particularly the longer 42 amino acid form, Aβ42, plays a critical role in the progression of Alzheimer's disease (AD).[1–3] Although Aβ is a major constituent of the neuritic plaques that are characteristic of the AD brain, recent studies suggest that soluble forms of Aβ, potentially including oligomeric, protofibrillar, and intracellular Aβ, may play a dominant role in the disease process.[4–8] Aβ is derived from the β-amyloid precursor protein (APP) by proteolysis. Cleavage of APP by β-site APP cleaving enzyme (BACE) results in the shedding of the APP ectodomain, and the remaining membrane bound C-terminal fragment, C99, is further processed by γ-secretase to produce Aβ and the APP intracellular domain (AICD), respectively.[9] BACE and γ-secretase are therefore attractive pharmaceutical targets because of their roles in Aβ generation. However, γ-secretase also cleaves other transmembrane proteins, including Notch, which is involved in cell differentiation. Thus, chronic high doses of γ-secretase inhibitors may disrupt Notch-mediated processes in the gastrointestinal tract, spleen, and thymus leading to potential mechanism-based toxicity. In contrast, Notch inhibition is not expected for BACE inhibitors, potentially making BACE a more attractive therapeutic target for AD.[10,11]

BACE is a type I membrane-associated aspartyl protease. The commonly utilized fragments that interact with the catalytic aspartates are transition state isosteres including the hydroxyethylamine dipeptide isosteres (HEA). In fact, the HEA fragment has been incorporated as part of the central core into a number of BACE inhibitors as exemplified by isophthalamide **1a** (Fig. 1), which was previously disclosed by Maillard et al.[12] This compound exhibited good enzyme (IC_{50} = 20 nM) and cellular activity (IC_{50} = 15 nM). In our own work, we have focused on HEA isostere-based inhibitors with substituted lactams as P2–P3 headgroups,[13] and we have noted increases in binding potency with appropriately placed P2 substituents. Compound **1a** seemed to offer a unique and possibly smaller molecular weight scaffold as a P2–P3 linking group, but with the P2 region of the inhibitor mostly unexplored. Examination of the published X-ray structure of the 3-iodophenyl analog **1b**[12] suggested a hydrogen bonding network was formed between a heteroatom of the C-3 substituent, residues in the P3 pocket, and an interstitial water molecule at the P2/P3 interface (see Fig. 2b, vide infra). In an attempt to improve the affinity in this series further, we introduced a series of C-3 substituents of the isophthalate bearing a heteroatom such as the carbonyl oxygen in an acetyl group in an attempt to both gain affinity in the P2 pocket and displace the water molecule with a substituent on the inhibitor. This Letter describes the synthesis and SAR of the resulting 3-substituted hydroxyethylamine based phenylcarboxyamides as inhibitors of BACE.

* Corresponding author. Tel.: +1 203 677 7485; fax: +1 203 677 7702.
E-mail address: yong-jin.wu@bms.com (Y.-J. Wu).

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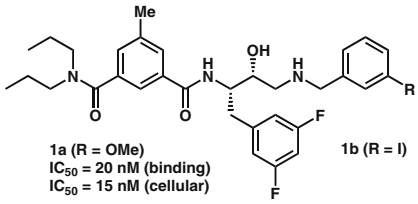
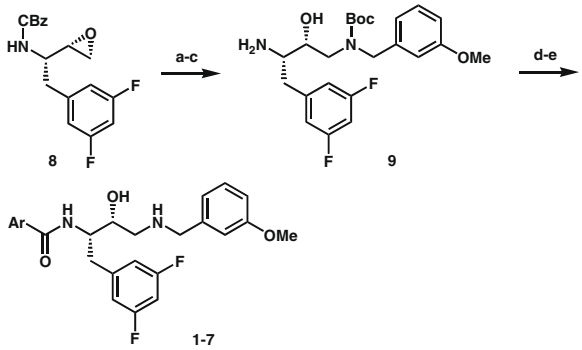


Figure 1.

Phenylcarboxyamides **1–7** for this study are shown in Tables 1–4. These compounds were prepared according to Scheme 1. The key primary amine intermediate **9** was obtained from the known epoxide **8**[12,14] in three steps: lithium perchloride-induced epoxide opening with (3-methoxyphenyl)methanamine;



Scheme 1. Reagents and conditions: (a) (3-methoxyphenyl)methanamine, $LiClO_4$, MeCN, 60 °C, 65%; (b) Boc_2O, Et_3N, CH_2Cl_2 78%; (c) 10% Pd/C, EtOH, H_2 (50 psi), 95%; (d) $ArCO_2H$, HATU, Et_3N, DMF, 60–95%; (e) TFA, CH_2Cl_2, 90–100%.

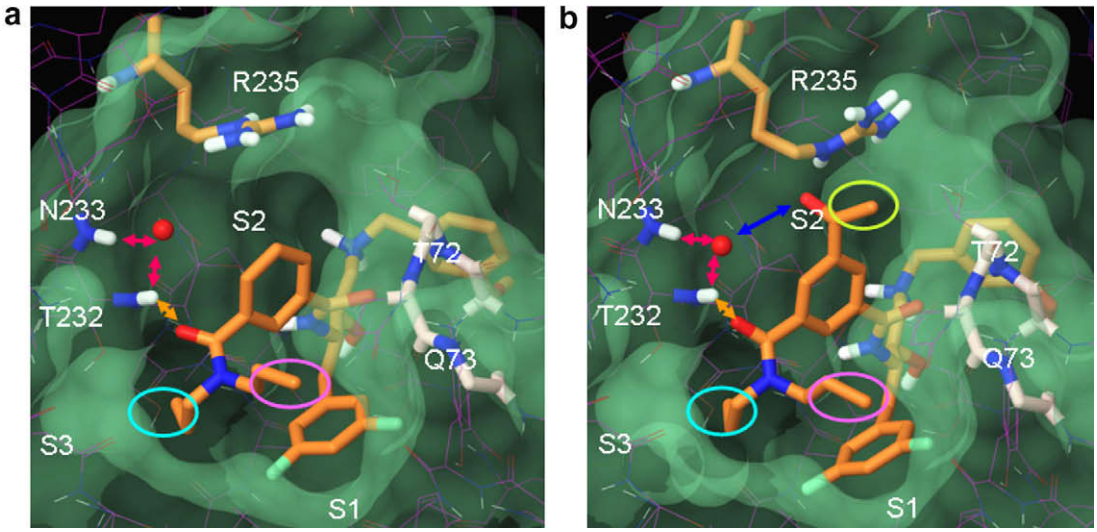
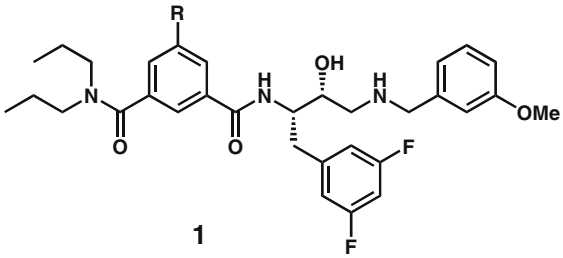


Figure 2. (a) (Left) Model of compound **1c** in human BACE-1. (b) (Right) Docked inhibitor **1d** in BACE-1 enzyme. Hydrophobic interaction with S3 pocket (light blue circle); H-bonds through interstitial water and N233/T232 (red arrow); H-bond to backbone of T232 (deep yellow arrow); metastable interaction to Q73 (pink circle); H-bond of the acetyl oxygen to interstitial H_2O (deep blue arrow); hydrophobic interaction of the acetyl methyl with T72 side chain (yellow circle).

Table 1
Binding and Cellular IC_{50} values of 3-substituted isophthalamides



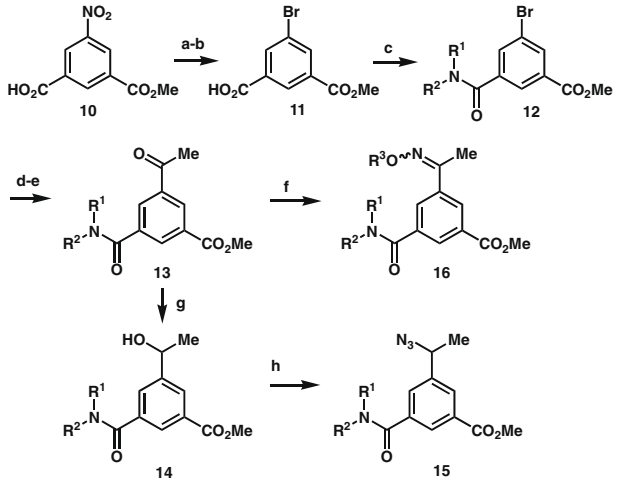
R	H												
Compd	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**	**1i**	**1j**	**1k**	**1m**	**1n**	**1p**	**1q**
IC_{50} (nM)[a,c]	31	4	3	1	10	55	67	2	16	10	>2000	123	20
IC_{50} (nM)[b,c]	80	19	27	42	120	367	534	12	34	53	NA	640	45

[a] Binding data.
[b] Cellular data.
[c] Average of 2–4 determinations.

protection of the secondary amine; and selective deprotection of the Cbz group to give primary amine **9**. Coupling of amine **9** with various arylcarboxylic acids using HATU and subsequent deprotection of the Boc group provided amides **1–7**.

The arylcarboxylic acids required for the synthesis of amides **1–7** were generally derived from the corresponding methyl benzoates. Scheme 2 describes the preparation of the 3-substituted methyl 5-(di-alkylcarbamoyl)benzoate **16** from the commercially available 3-(methoxycarbonyl)-5-nitrobenzoic acid (**10**). Catalytic hydrogenation of **10** followed by Sandmeyer reaction gave bromide **11**, which was coupled with various amines to provide bromophenylcarboxyamides **12**. These bromides underwent the palladium-catalyzed Heck vinylation reactions under microwave irradiation, and the resulting aryl vinyl ethers were hydrolyzed in situ with hydrochloric acid to give the methyl ketones **13**.[15] Reduction of the ketone moiety with sodium borohydride furnished alcohols **14**, which were converted to azides **15** using diphenyl phosphorazidate (DPPA). Oximation of **13** proceeded smoothly to give a mixture of two oxime isomers **16**. The methyl 3-(1-azidoethyl)-5-(di-propylcarbamoyl)benzoate **15** was converted to the final 3-(1-aminoethyl)-phenylcarboxyamide **1 m** (Table 1) in a 4 step sequence: hydrolysis of the methyl ester, coupling with amine **9**; catalytic hydrogenation of azide to amine (10% Pd/C, EtOAc, hydrogen balloon); and deprotection of the Boc group.

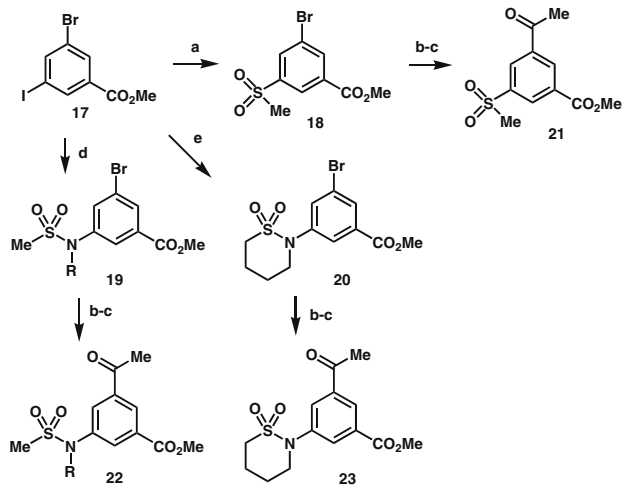
Scheme 3 describes the preparation of 3-acetyl-5-(sulfonamido)benzoates required for the synthesis of amides **4–6** shown in Table 3. The copper-catalyzed coupling of methyl



Scheme 2. Reagents and conditions: (a) 10% Pd/C, H_2, EtOH, 85%; (b) *t*-BuONO, $CuBr_2$, DMF, 55%; (c) R_1R_2NH, HATU, CH_2Cl_2, 75–95% (d) 1-(vinyloxy)butane, $Pd(OAc)_2$, DPPP, K_2CO_3, DMF, H_2O; (e) HCl, 35–55%; (f) $R_3ONH_2{\cdot}HCl$, EtOH, 80 °C, 85%; (g) $NaBH_4$, EtOH, 94%; (h) $(PhO)_2PON_3$, Hünig's base, toluene, 78%.

3-bromo-5-iodobenzoate (**17**) with sodium methanesulfinate provided methylsulfone **18**, and the palladium-catalyzed reaction of **17** with the N-substituted methanesulfonamide and 1,4-butanesultam furnished sulfonamide **19** and sultam **20**, respectively.[16] The introduction of the acetyl group onto **18**, **19** and **20** was carried out in the same fashion as **12** to **13** (Scheme 2) to give the corresponding ketone esters **21**, **22** and **23**.

Scheme 4 describes the synthesis of methyl 3-(di-propylcarbamoyl)-5-phenoxy, 5-phenylthio, and 5-phenylsulfonyl benzoates that were used for the synthesis of compounds with formula **7**

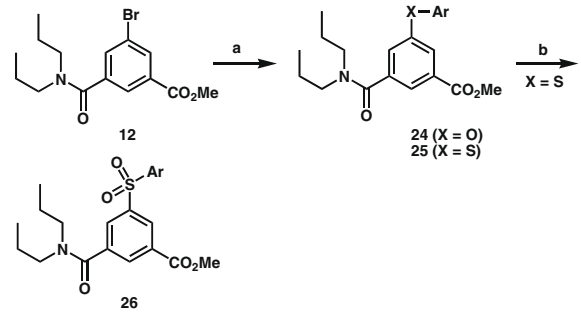


Scheme 3. Reagents and conditions: (a) $(CuOTf)_2{\cdot}PhH$ (5 mol %), *N,N'*-dimethylethylenediamine (10 mol %), MeS(O)ONa, toluene, 90 °C, 65%; (b) 1-(vinyloxy)butane, $Pd(OAc)_2$, DPPP, K_2CO_3, DMF, H_2O; (c) HCl, 35% over two steps; (d) $Pd_2(dba)_3$, xantphos, Cs_2CO_3, $RNHSO_2Me$, toluene, 90 °C, 56%; (e) $Pd_2(dba)_3$, xantphos, Cs_2CO_3, 1,4-butanesultam, toluene, 90 °C, 57%.

(Table 4). The copper-catalyzed arylation of phenols and arylthiols with bromide **12** under microwave irradiation generated aryl ethers **24** and aryl sulfides **25**, respectively.[17] Oxidation of sulfide **25** with *m*CPBA led to sulfones **26**.

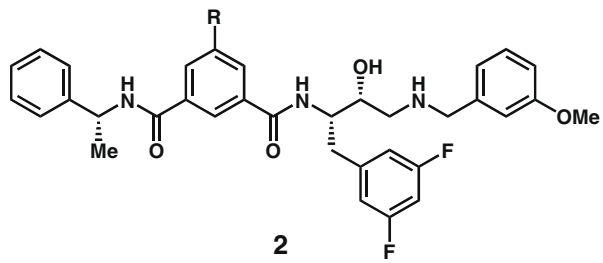
Primary inhibitor potency was measured in a standard radioligand displacement assay with the radiolabelled BACE inhibitor [^{3}H]BMS-599240.[18] The cell-based assay was used to measure the amount of inhibition of Aβ40 production by native BACE-1 enzyme in HEK cells overexpressing APP with the Swedish mutation.[19]

The binding and cellular IC_{50} values of the 3-substituted isophthalamides are shown in Table 1. Among the oxime series, methoxyoxime **1f**, hydroxyoxime **1e** and methylketone **1d** were the best in terms of both binding affinity and cellular activity (binding $IC_{50} < 5$ nM; cellular $IC_{50} < 50$ nM), and they were superior to the unsubstituted compound **1c** (binding $IC_{50} = 31$ nM; cellular $IC_{50} = 80$ nM). In general, the inhibitory activity (both binding and cellular) of the oxime analogs decreased as the alkyl group of the oxime moiety becomes bulkier. The 3-(1-hydroxyethyl) analog **1j** also exhibited potent inhibitory activity in both assays. In comparison with the α-hydroxyl analog **1j**, both β-hydroxyl derivatives **1k** and **1m** were several-fold less potent in terms of the binding affinity, but they still showed enhanced potency toward BACE-1 relative to the unsubstituted compound **1c**. The



Scheme 4. Reagents and conditions: (a) ArOH or ArSH, CuI, Cs_2CO_3, NMP, 195 °C, 35%; (b) *m*CPBA, CH_2Cl_2, 65%.

Table 2
IC_{50} values of (1-phenylethyl)isophthalamides



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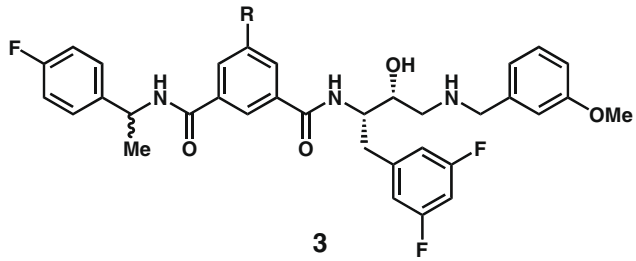

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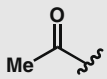
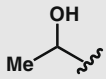
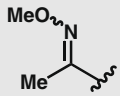
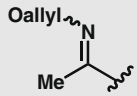
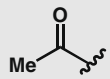
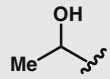
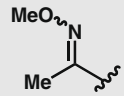
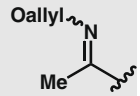
R	H					H				
Compd	**2a**	**2b**	**2c**	**2d**	**2e**	**3a**	**3b**	**3c**	**3d**	**3e**
IC_{50} (nM)[a,c]	89	20	29	32	86	166	51	37	24	168
IC_{50} (nM)[b,c]	198	73	92	82	500	266	91	164	276	530

[a] Binding data.
[b] Cellular data.
[c] Average of 2–4 determinations.

bis-methoxy analog **1n** was devoid of measurable inhibitory activity. Replacement of the hydroxyl in **1j** with primary amine (see **1p**) dramatically reduced inhibitory activity, but the activity was partially restored through acetylation of the primary amine in **1p** (see **1q**). The same set of substituents was also introduced onto the *N*-methyl-*N*-propylisophthalamide series, and the SAR was similar to that observed in the *N*,*N*-diisopropylisophthalamide series (data not shown).

Recently, Stachel et al. demonstrated that the *N*,*N*-diisopropyl group of the isophthalamide series can be effectively replaced with α-methylbenzyl amine moiety.[20,21] To this end, we sought to determine the impact of the 3-substituents onto the α-methylbenzamide class of inhibitors. The IC_{50} values of these analogs are summarized in Table 2. Again, acetyl (**2b** and **3b**), 1-hydroxyethyl (**2c** and **3c**) and 1-(methoxyimino)ethyl (**3d**) enhanced inhibitory activity by 2–4-fold in both assays. The *O*-allyl oxime analogs **2e** and **3e** were comparable to their respective unsubstituted compound **2a** and **3a**.

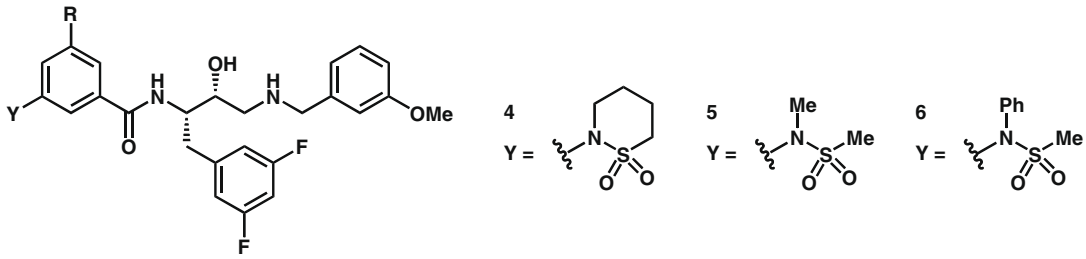
A series of 3-substituted sulfonamides **4–6** was also prepared, and the IC_{50} values of these compounds are summarized in Table 3. The impact of the 3-substituents such as acetyl and α-hydroxyethyl was less pronounced than that observed in the isophthalamide series. For example, the acetyl analogs **4b**, **5b** and **6b** were slightly less active than their respective unsubstituted compounds **4a**, **5a** and **6a** in the binding assay, as opposed to 2–8-fold enhancement observed in the isophthalamide series. Of particular interest is that the benzyloxime analogs **4i**, **5i** and **6i** were significantly more active than their respective *iso*-butyloxime counterparts **4h, 5h** and **6h** in the binding assay. In contrast, both benzyloxime (**1g**) and *iso*-butyloxime (**1f**) of the isophthalamide series (Table 1) exhibited similar inhibitory activity. Thus, this benzyl effect improving potency appeared to be unique to the sulfonamide series.

In addition to the acetyl, α-hydroxylethyl and oximes, we also investigated the impact of phenyloxy, phenylthio and phenylsulfonyl in the isophthalamide series as shown in Table 4. In general, these analogs showed slightly enhanced binding affinity with the exception of **7c**, but their cellular activity was significantly diminished, presumably due to the increased molecular weight and size.

In the isophthalamide series, the 3-acetyl group enhanced binding activity by up to eightfold. This enhancement can be rationalized by examining the binding model of compound **1d** in comparison with a model of the unsubstituted compound **1c**. All compounds were modeled starting from the reported crystal structure[12] of the 3-iodophenyl analog **1b** using Maestro 7.5.1 (Schrodinger Inc, 120 West 45th Street, 29th floor New York NY 10036.) According to this model, the acetyl group is engaged in a hydrogen bonding interaction with the interstitial water in the S2 pocket, leading to the observed modest increase in enzyme affinity. Like the acetyl group, the oxime and α-hydroxylethyl groups are expected to create similar hydrogen bonding networks. The α-aminoethyl at C-3 of **1p** (Table 1) should be protonated under physiological conditions and is unlikely to participate in hydrogen bonding to the interstitial water, and it also generates electrostatic repulsion with R235. In contrast, the α-acetamidoethyl group of **1q** can take part in the interaction with the enzyme through the interstitial water. As a result, the α-aminoethyl moiety of **1p** (Table 1) reduced binding activity of isophthalamides, while the α-acetamidoethyl in **1q** maintained good activity.

The impact of the C-3 acetyl and the α-hydroxyethyl, as well as the benzyloxime in the sulfonamide series (Table 3) differed from the trend observed in the isophthalamide series (Table 1) because they occupy different spaces in the active site. In the isophthalamide series, the acetyl group is located within the S2 pocket, while the diisopropyl moiety occupies the S3 pocket. However, in the sulfonamide series, the phenyl group rotates, placing the acetyl group in the S3 pocket, and the methylsulfonamido group in the S2 pocket. The sulfonamide of isophthalamides is known to occupy the S2 site.[22] Figure 3a displays a binding model for inhibitor **27**[19] in the BACE-1 active site based on its x-ray structure,[20] and Figure 3b shows a binding model of the *E*-isomer of sulfonamide **4i**. The sulfonamide moiety of both inhibitors fills the S2 pocket, and the hydrophobic interaction of the phenyl with the S3 pocket is also similar. Both compounds appear to bind with BACE1 enzyme in the same fashion, thereby resulting in comparable intrinsic inhibitory activity.

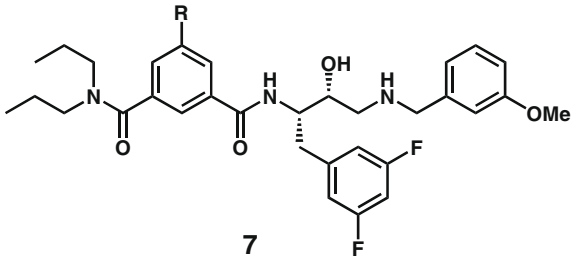
Table 3
IC_{50} values of sulfonamides



R	H								
Compd	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**
IC_{50} (nM)[a,c]	74	90	43	38	52	25	111	428	31
IC_{50} (nM)[b,c]	182	248	305	117	345	205	1232	2098	821
Compd	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**
IC_{50} (nM)[a,c]	75	124	43	76	60	59	151	173	9
IC_{50} (nM)[b,c]	80	559	122	429	52	217	363	>666	>333
Compd	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**	**6h**	**6i**
IC_{50} (nM)[a,c]	11	17	NA	9	10	6	27	242	12
IC_{50} (nM)[b,c]	137	>263	NA	91	86	184	162	NA	88

[a] Binding data.
[b] Cellular data.
[c] Average of 2–4 determinations.

Table 4
IC_{50} values of sulfonamides



R	H								
Compd	**1a**	**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	**7h**
IC_{50} (nM)[a,c]	31	10	10	54	22	13	27	11	12
IC_{50} (nM)[b,c]	80	>333	412	>666	94	>333	30	148	392

[a] Binding data.
[b] Cellular data.
[c] Average of 2–4 determinations.

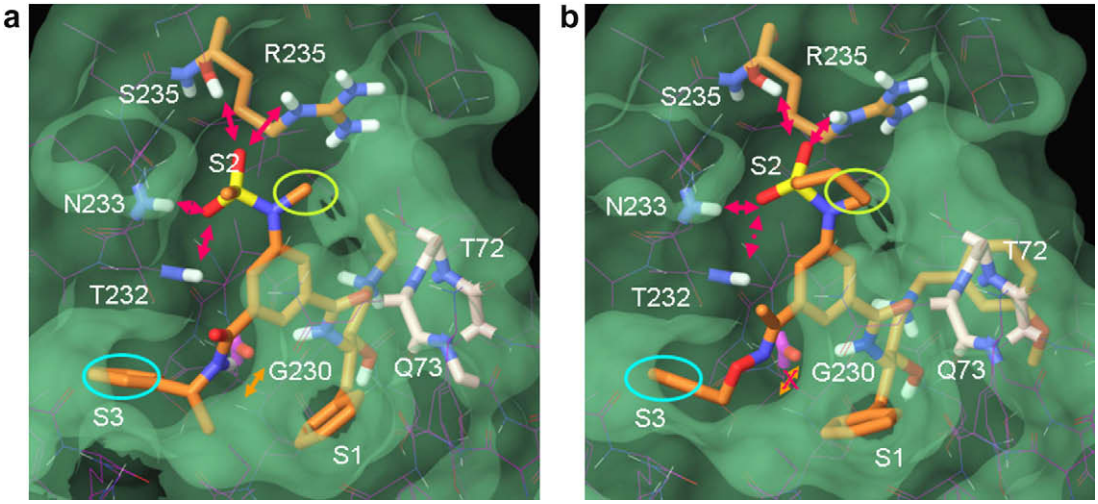
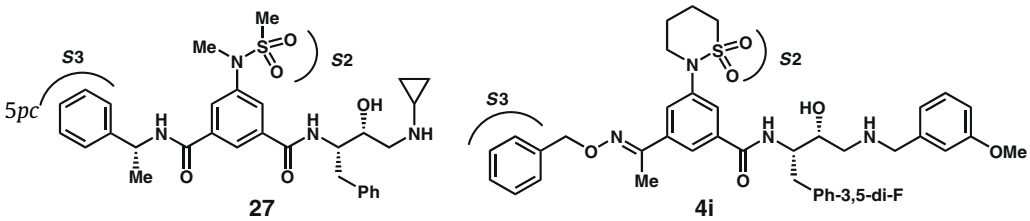


Figure 3. (a) (Left). Binding model of inhibitor **27** (Merck)[19] based on its X-ray crystal structure with human BACE-1. (b) (Right) Docked inhibitor **5i** (*E*-isomer) in BACE-1 enzyme. hydrophobic interaction with S3 pocket (light blue circle); H-bonds to SO_2 displacing interstitial H_2O (red); H-bond to backbone of G230 (yellow) (only in **27**); hydrophobic interaction with T72 side chain (light green circle).



The acetyl, α-hydroxyethyl and α-methoxyiminoethyl at C-3 generally enhanced binding affinity in the isophthalamide series presumably due to the hydrogen bonding network created through their positive interaction with interstitial water in the enzyme, as well as hydrophobic interaction with T72 side chain. The isophthalamides with acetyl or α-hydroxyethyl groups at C-3 also exhibited optimal cellular activity. However, these substituents show less pronounced effects in the sulfonamide series because they occupy the S3 pocket instead of the S2 pocket, as in the case of isophthalamides. The structure-based optimization for potency led to several 1,3,5-trisubstituted phenylcarboxyamides with potent cellular activity (IC_{50}s < 100 nM). However, these compounds were shown to be Pgp substrates and had poor pharmacokinetic properties.[22,23] Our efforts to address both of these liabilities will be reported in due course.

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