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BACE1 inhibitors: A head group scan on a series of amides

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ABSTRACT

A series of amides bearing a variety of amidine head groups was investigated as BACE1 inhibitors with respect to inhibitory activity in a BACE1 enzyme as well as a cell-based assay. Determination of their basicity as well as their properties as substrates of P-glycoprotein revealed that a 2-amino-1,3-oxazine head group would be a suitable starting point for further development of brain penetrating compounds for potential Alzheimer's disease treatment.

The β-site amyloid precursor protein cleaving enzyme 1 (BACE1) plays a major role in the processing of the amyloid precursor protein (APP). Sequential cleavage of APP by BACE1 and γ-secretase leads to the formation of 40 or 42 amino acid-long amyloid β-peptides (Aβ) which aggregate in the brain of Alzheimer's disease (AD) patients. It is suggested that inhibition of BACE1 would prevent the build-up of Aβ and therefore slow down or stop AD.[1–3]

A high throughput screen (HTS) revealed the thiazine fragment **1** as a hit (BACE1 enzyme assay: IC_{50} = 41.2 μM; p$K_a \sim 9$) with an appealing ligand efficiency (LE) of 0.37 (LE = $(\Delta G)/N$, where $\Delta G = -RT\ln IC_{50}$ and N the number of non-hydrogen atoms) and co-crystallization with BACE1 showed ample opportunities for optimization. This aminothiazine heterocycle was initially synthesized at Roche[4] in the late 1970's and many examples of this compound class exhibit analgesic activity. It was recently explored by Shionogi and other research groups as a head group (HG) targeting the active site of BACE1.[5,6] X-ray analysis of **1** co-crystallized with BACE1 shows that both nitrogens of the protonated amidine moiety form tight hydrogen bonds to the catalytic aspartates D289 and D93 (Fig. 2).

We believed that altering the amidine head group to improve physicochemical properties, such as pK_a, log$D$, solubility and permeability, together with an extension reaching deep into the S3 pocket would result in highly potent and drug-like BACE1 inhibitors.[1] The comparison with other BACE1 X-ray structures, which had been soaked with inhibitors containing S1 and S3 substituents, had shown that the orientation of the amidine-containing head groups and the 3D shapes of the binding cavities were quite similar. Thus, 4bek was considered as a suitable template for interactive 3D modeling[7] in order to explore various options for optimizing the affinity of the thiazine headgroup. Modeling also revealed that the S3 pocket could be best reached by meta-substitution on the S1 phenyl ring. In order to displace bound water molecules in the S3 pocket, the S1 phenyl ring was meta substituted via an amide linker (Fig. 2: modeled compound in green). This enables the additional formation of a hydrogen bond to the backbone carbonyl of G291 indicated by a dotted line. X-ray analysis of selected compounds out of the series of amides **2–25** revealed that the NH of the amide bond indeed forms a hydrogen bond to the backbone carbonyl oxygen of G291 and also leads to a conformationally favorable fixation of the two aromatic rings in an almost planar arrangement. For the meta-substitution on the phenyl we used an aromatic amide and for the aromatic residue in S3 it was found that especially 2-pyridyl carboxylic acid derivatives are most preferred.[5] The 2-pyridyl moiety ensures a planar orientation at the amide linker mediated by a favorable electrostatic interaction between the

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amide NH and the pyridyl N. As depicted in Figure 1 the substitution at the pyridyl residue was found by many research groups to be most favorable in positions marked $R^{3'}$ and $R^{5'}$ where small substituents in $R^{3'}$ (e.g., Me and Cl) were preferred.[5,12–20] The deep S3 channel suggests a para substitution of the S3 pyridyl ring ($R^{5'}$) with halogens or small linear substituents such as cyano. To evaluate the various effects of the different head groups the $R^{5'}$ substituent was kept to Cl in this study (exception: compound **3**; Table 1). The BACE1 inhibitory activities of the compounds were determined in a human BACE1 enzyme as well as in a cell-based assay. The pK_a was examined by capillary electrophoresis (cEpK_a); exceedingly basic compounds often suffer from undesired potential liabilities of phospholipidosis[8] and polypharmacology.[9,10] The compounds' properties as a substrate of human P-glycoprotein (P-gp) expressed as the efflux ratio (ER) were determined. Further in vivo characterization of selected compounds for the AD indication was performed by measuring the reduction of Aβ40 in the brain 4 h after administration of 30 mg/kg p.o. in our *wild type* mice model.[11] For some compounds the plasma and brain exposure was also determined at this time point.

The 2-aminooxazoline HG in compound **2** showed a decent activity (IC_{50} = 2.02 μM); the corresponding thiazoline **3** was less active also because of the missing Cl in $R^{5'}$ and therefore lacking the deep penetration into the S3 pocket. Annelation by ring closure of the methyl group to the central phenyl ring (**6** and **7**) did not result in an improvement of activities (both pK_a = 8.3).

The less basic aminohydantoin HG in compound **4** (pK_a = 7.3) has been described as a part of a potent BACE1 inhibitor[12] but when decorated as in **4**, it proved to be only moderately active.

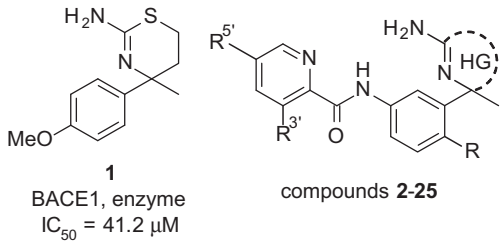


Figure 1. HTS hit **1** and general structure of compounds described in this study.

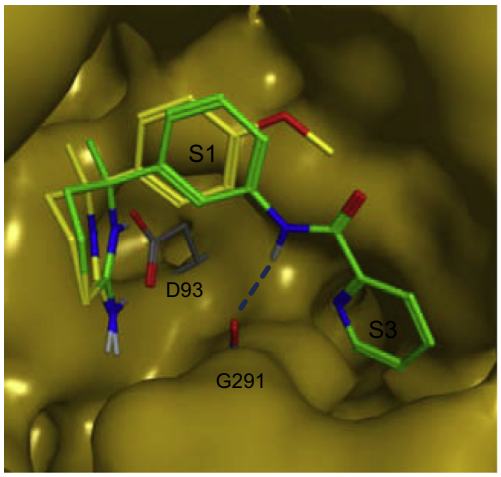


Figure 2. HTS hit **1** (yellow) bound to the BACE1 binding site, some flap residues have been removed for the sake of clarity (PDB code: 4bek). The protonated amidine motif in the thiazine head group forms tight hydrogen bonds to the catalytic aspartates D289 (not shown) and D93 (modeled amide compound in green).

Benzoannelation of the HG as in amidine **5** also produced a moderately active compound, but with much higher basicity though (pK_a = 9.7).

Enlarging the ring size from the aminohydantoin **4** by one CH_2 group to the 2-aminodihydropyrimidinone **8**[13] resulted in a very active compound (BACE1 enzyme IC_{50} = 0.015 μM, cellular assay IC_{50} = 0.001 μM), but the basic compound (pK_a = 8.4) was also found to be a very good P-gp substrate (hER 18.6) which led to in vivo inactivity (<10% reduction of Aβ40 at 30 mg/kg p.o.; exposure 4 h after 50 mg/kg p.o.: plasma: 2506 ± 426 ng/ml, brain: 586 ± 164 ng/g, brain/plasma ratio: 0.19). Removing the carbonyl group gave the almost equally potent cyclic guanidine **9**, but its basicity even exceeded the measurable range (pK_a >11) and it was due to very low exposure also inactive in vivo (<15% reduction of Aβ40 at 30 mg/kg p.o.; exposure 4 h after 30 mg/kg p.o.: plasma: <3 ng/ml, brain: <13 ng/g).

The aminopiperazinone **10**[14] was much less active than its position isomer **8** whereas removal of the carbonyl group from HG in **10** led to the corresponding aminopiperidine **11**[15] with improved in vitro activity but it is highly basic (pK_a = 10.2), a good P-gp substrate (hER 9.6) and therefore was not tested in vivo.

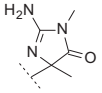
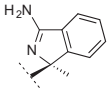
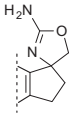
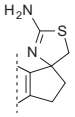
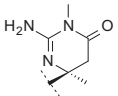
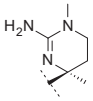
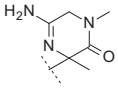
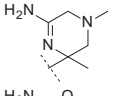
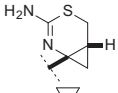
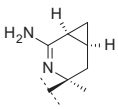
Enlarging the ring size from the 2-aminooxazoline **2** by one CH_2 group to the 2-amino-1,3-oxazine **12**[16,17] resulted in moderate activity in the enzyme assay (IC_{50} = 0.137 μM) but high activity in the cellular assay (IC_{50} = 0.010 μM). Surprisingly, the quite basic compound (pK_a = 9.8) showed at least marginal activity of 29% reduction of Aβ40 at 30 mg/kg p.o. despite being a very good P-gp substrate (hER 10.7). The same experiment in mice revealed a weak brain penetration with high variability (exposure 4 h after 30 mg/kg p.o.: plasma: 2702 ± 3987 ng/ml, brain: 363 ± 494 ng/g, brain/plasma ratio 0.13). Although **12** and **13** have quite similar permeability (PAMPA assay: **12**: p_{eff} = 6.12; **13**: p_{eff} = 6.77) and solubility (LYSA assay: **12**: 360 mg/l; **13**: 370 mg/l) the more lipophilic 2-amino-1,3-oxazine **13** (log*D*: **13**: 0.68; **12**: 0.26) bearing an extra chlorine substituent in position $R^{3'}$ was found to be even more potent in vitro (BACE1 enzyme IC_{50} = 0.039 μM, cellular assay IC_{50} = 0.001 μM) and also in vivo (38% reduction of Aβ40 at 30 mg/kg p.o.; exposure 4 h after 30 mg/kg p.o.: plasma: 190 ± 54 ng/ml, brain: 306 ± 44 ng/g, brain/plasma ratio: 0.99) – again despite being a very good P-gp substrate (hER 14.5). A single dose PK in mice for compound **13** (9.76 mg/kg p.o.) showed the following profile: t_{max} = 0.5 h, C_{max} = 1835 ng/ml, $t_{½}$ = 1.32 h, AUC = 4582 h ng/ml, *F* = 111%, brain/plasma ratio 0.14. Determination of the protein binding in mice revealed an 11% fraction of unbound compound. This quite promising profile was accompanied by undesired activities, like, example, cytochrome P450 2D6 isoenzyme inhibition (IC_{50} = 0.9 μM) and hERG inhibition (IC_{20} = 0.9 μM); both effects were largely attributed to the high basicity of **13**.

Another way of enlarging the ring size of the 2-aminooxazoline **2** by one CH_2 group led to 3-amino-1,4-oxazine **14**[18] which was highly active in vitro (BACE1 enzyme IC_{50} = 0.031 μM, cellular assay IC_{50} = 0.003 μM) but its extremely good P-gp substrate properties (hER 37.2) together with low exposure led to in vivo inactivity (<10% reduction of Aβ40 at 30 mg/kg p.o.; exposure 4 h after 30 mg/kg p.o.: plasma: 106 ± 41 ng/ml, brain: 51 ± 4 ng/g, brain/plasma ratio: 0.76). Addition of an extra chlorine substituent in $R^{3'}$ gave compound **15**, but no improvement of neither in vitro nor in vivo activity was observed.

A variation of the thiazine fragment by annelation of a cyclopropyl ring led to compound **16** which was not a P-gp substrate (hER 1.1), but only showed moderate in vitro activity.

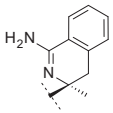
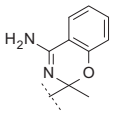
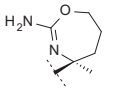
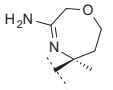
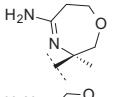
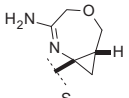
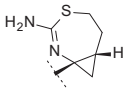
We also prepared plain 6-ring amidines, but with attached cyclopropyl groups to hopefully lower the pK_a, which resulted in spiro-compound **17** and bicycle **18** (both pK_a >11). Both compounds showed good in vitro activity but neither of them displayed any in vivo effect (**17**: <5% reduction of Aβ40 at 30 mg/kg p.o.;

Table 1
In vitro data of amides **2–25** described in this study

Compounds	R	$R^{3'}$	$R^{5'}$	Head group(HG)	IC_{50} (μM)[a]		P-gp hER[c]	pK_a[d]
					hBACE1 enzyme	Aβ40 cell-based[b]		
2	H	H	Cl		2.02	0.2	Nt	8.3
3	H	H	H		8.98	1.72	Nt	8.3
4	H	H	Cl		1.02	0.34	Nt	7.3
5	H	H	Cl		0.55	0.21	Nt	9.7
6	CH_2(to Me group)	H	Cl		10.78	1.3	Nt	8.3
7	CH_2(to Me group)	H	Cl		4.00	0.38	Nt	8.3
8	H	H	Cl		0.015	0.001	18.6	8.4
9	F	H	Cl		0.012	0.012	Nt	>11
10	H	H	Cl		0.348	1.04	Nt	Nt
11	H	H	Cl		0.032	0.037	9.6	10.2
12	F	H	Cl		0.137	0.010	10.7	9.8
13	F	Cl	Cl		0.039	0.001	14.5	9.7
14	F	H	Cl		0.031	0.003	37.2	9.2
15	F	Cl	Cl		0.045	0.004	Nt	Nt
16	H	H	Cl		0.76	0.14	1.1	Nt
17	F	H	Cl		0.031	0.015	Nt	>11
18	F	H	Cl		0.096	0.031	14.8	>11

(*continued on next page*)

Table 1 (*continued*)

Compounds	R	$R^{3'}$	$R^{5'}$	Head group(HG)	IC_{50} (μM)[a]		P-gp hER[c]	pK_a[d]
					hBACE1 enzyme	Aβ40 cell-based[b]		
19	F	H	Cl		0.061	0.025	21.2[e]	10.8
20	F	H	Cl		0.12	0.067	1.8	7.3
21	F	H	Cl		0.014	0.011	Nt	10.4
22	F	H	Cl		0.023	0.001	13.2	10.9
23	F	H	Cl		0.046	0.011	5.9	>10
24	F	H	Cl		0.37	0.073	16.6 (R = H)[e]	Nt
25	H	H	Cl		0.027	0.002	5.5[e]	8.9

R, $R^{3'}$ and $R^{5'}$ refer to the positions of R's in Figure 1. Nt, not tested.
[a] IC_{50} values are means of at least two independent experiments.
[b] HEK293 cells transfected with wild-type human APP.
[c] ER = efflux ratio in LLCPK1 cells stably expressing human MDR1.
[d] Measured by capillary electrophoresis (pK_a Analyzer ProTM by Advanced Analytical).
[e] Racemic compound tested.

exposure 4 h after 30 mg/kg p.o.: plasma: 81 ± 78 ng/ml, brain: 8 ± 2 ng/g, brain/plasma ratio: 0.1. **18**: <20% reduction of Aβ40 at 30 mg/kg p.o.; exposure 4 h after 30 mg/kg p.o.: plasma: 48 ± 69 ng/ml, brain: 32 ± 9 ng/g, brain/plasma ratio: 0.67).

Modifying the benzoannelated amidine **5** by ring enlargement with one CH_2 group gave compound **19**[19] which exhibited high basicity (pK_a = 10.8) and due to its P-gp substrate properties (hER 21.2) was not tested in our mice model. Exchanging the newly introduced CH_2 group by oxygen as in compound **20**[19] lowered the pK_a to the more desirable value of 7.3, almost retained the in vitro activity and finally reduced the P-gp substrate abilities (hER 1.8), but compound **20** was despite its good exposure still inactive in the in vivo model (<20% reduction of Aβ40 at 30 mg/kg p.o.; exposure 4 h after 30 mg/kg p.o.: plasma: 629 ± 70 ng/ml, brain: 1569 ± 89 ng/g, brain/plasma ratio: 2.49). When trying to isolate the pure enantiomers of **20** after separation on chiral HPLC we discovered a quick racemization due to the chemical instability of the aminal group which unfortunately made this head group unattractive for deeper exploration.

Further enlargement of the promising 2-amino-1,3-oxazine **12** to a 7-membered 2-aminooxazepine gave the in vitro potent compound **21** (BACE1 enzyme IC_{50} = 0.140 μM, cellular assay IC_{50} = 0.011 μM) but it also unfavorably increased the pK_a from 9.8 to 10.4. Shifting the oxygen in more remote positions from the amidine moiety as in **22**[18b,20] and **23**[20a] also gave in vitro highly potent compounds, but did not result in a decrease of the basicity.

Again annelation of a cyclopropyl group to oxazepine **22** gave the derivative **24**[20a] which substantially lost in vitro activity and still was a good P-gp substrate.

Enlarging the ring size of the annelated thiazine **16** by one CH_2 group to the corresponding thiazepine **25** (pK_a = 8.9) resulted in an in vitro highly active compound (BACE1 enzyme IC_{50} = 0.027 μM, cellular assay IC_{50} = 0.002 μM) but it also increased its P-gp substrate abilities (hER 5.5) (<10% reduction of Aβ40 at 30 mg/kg p.o.; exposure 4 h after 30 mg/kg p.o.: plasma: <9 ng/ml, brain: <26 ng/g).

In summary: exceedingly basic compounds like **9**, **17** and **18** resulted in very low exposure and in vivo inactivity. Together with the high exposure of the less basic, P-gp free and more lipophilic **20** (log*D* 2.51) this demonstrates the importance of a lower pK_a to achieve a more CNS-drug like profile. The 2-amino-1,3-oxazines **12** and **13**[21] show despite their basicity and P-gp substrate abilities because of compensation through high and long-lasting exposure some in vivo activity. They appear also from their chemical structure of the HG to be good starting points for further modifications and concomitant favorable profile changes (physicochemical properties, P-gp and especially pK_a) and therefore are positioned well for further drug development. Efforts in this direction were rewarded with the development of BACE1 inhibitors with high in vivo efficacy suitable for clinical evaluation in AD.[22]

Acknowledgments

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Supplementary data

Supplementary data (supplementary material with experimental details for the preparation of compounds **12**, **13**, **16**, **17** and **18**

as well as for the in vitro and in vivo assays is available) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.05.003.

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