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Anilinotriazoles as potent gamma secretase modulators

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ABSTRACT

The design and synthesis of a novel series of potent gamma secretase modulators is described. Exploration of various spacer groups between the triazole ring and the aromatic appendix in **2** has led to anilinotriazole **28**, which combined high in vitro and in vivo potency with an acceptable drug-like profile.
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Dementia affects nearly 36 million people worldwide, a number which is expected to triple by 2050.[1] The most common form of dementia is Alzheimer's disease (AD),[2] a progressive, neurodegenerative illness described in 1906 by the German physician Alois Alzheimer. No treatment exists yet for this condition, the marketed drugs targeting only the amelioration of the symptoms.[3] Characteristic for AD is the deposition of extraneuronal amyloid plaques and intraneuronal neurofibrillary tangles of hyperphosphorylated tau protein in the limbic and cortical regions of the brain, which eventually leads to neurodegeneration. Based on genetic evidence, Hardy and Higgins formulated the amyloid hypothesis, according to which accumulation of amyloid peptides in the brain is the primary driver of the AD.[4,5]

Formation of the amyloid beta peptides in the brain is the result of a sequence of proteolytic cleavages of amyloid precursor protein, APP. This is first cleaved by β-secretase (BACE-1) to form a membrane bound C-terminal fragment (C99), which is further cleaved by gamma secretase (GS) to produce Aβ peptides of lengths varying from 37 to 43 aminoacids. Of these, Aβ42 and Aβ43 are most prone to aggregate and generate the neurotoxic amyloid plaques. The amyloid cascade theory opened the door to anti Aβ therapeutics as strategies for developing anti Alzheimer disease modifying drugs,[6] among which suppression of the Aβ42 production via BACE-1 inhibition and GS inhibition or modulation is intensively pursued.[7] In this regard, GS, the intra-membrane protease complex responsible for the final cleavage step in the amyloid cascade, represents an attractive yet challenging target.[8] Recently, GS inhibitors (GSIs) semagacestat and avagacestat were discontinued in clinical trials due to side effects such as toxicity related to inhibition of other GS substrates and decline in cognition.[8,9] GS modulators (GSMs),[10,11] a class of compounds which are able to reduce the level of longer, neurotoxic Aβ peptides by shifting the APP processing of γ-secretase towards shorter isoforms (such as Aβ37, Aβ38), represent a viable alternative to GS inhibition.[12] Several classes of GSMs are known to date: carboxylic acids derived from non-steroidal anti-inflammatory drugs (NSAIDs), such as tarenflurbil, non-NSAID GSMs such as aryl imidazole-derived GSMs and more recently, triterpene-derived modulators.[7]

Our own search towards aryl-imidazole derived GSMs led to the discovery of the benzimidazole derivative **1** (Fig. 1).[13] It is one of the most potent GSMs to date, suffering however from sub-optimal drug-like properties. More recently, we have described the design and synthesis of bicyclic triazolo-derivatives, such as triazolopiperidine **4** (Scheme 1),[14] as potent in vitro and in vivo GSMs with an improved drug-like profile. These compounds resulted from a conformational restriction of benzyltriazoles **3**, which in turn derived from the introduction of a methylene spacer in **2** between the central triazole ring (C) and the aromatic appendix D, in this case the 4-F-phenyl group. While this work was in progress, an

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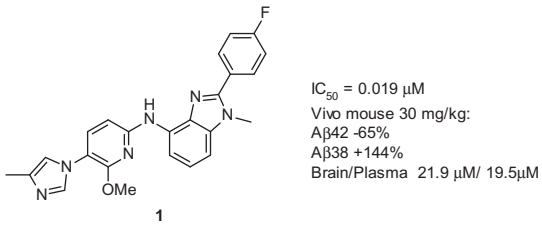


Figure 1. Benzimidazole derived GSM.
Note: IC_{50} represents the concentration of a compound that is required for reducing the Aβ42 level by 50%. IC_{50} values are a mean of at least 3 determinations. Mouse in vivo at 30 mg/kg p.o. after 4 h ($n = 6$) expressed as a percentage of Aβ42 lowering in brain compared with untreated animals. Plasma and brain samples were analyzed for the tested compound using a qualified research LC–MS/MS method.

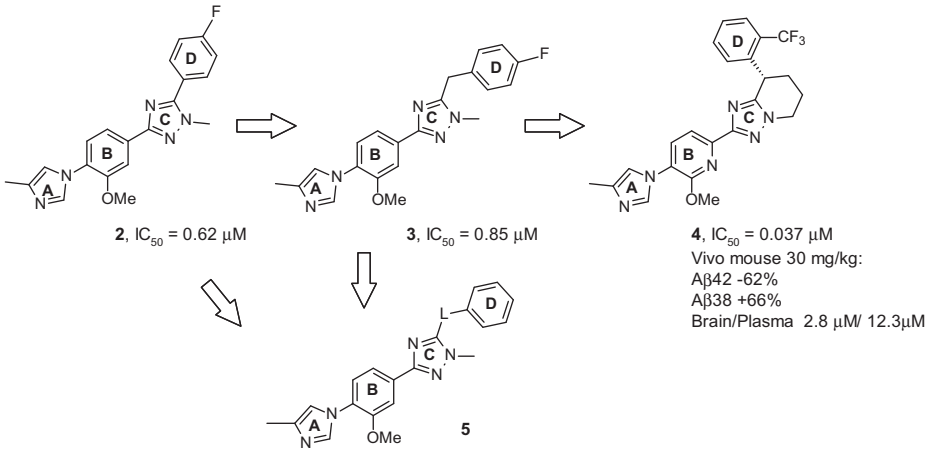
alternative approach to improve the potency of **2**, while maintaining its physicochemical properties (MW < 400, *c*log*P* < 4), was investigated.[15] Considering the influence of torsion between the C and D rings on potency,[14,15] other spacers in **2** that would disrupt the planarity between these rings were also evaluated (Table 1).

Starting from derivative **3**, small substituents were added on the benzylic position with the intent of pointing the D ring towards an active conformation, for instance by hindering free rotation, as in **6** (Table 1). This modification had no effect on potency. Replacement of the linker with a carbonyl function, as in ketone **7** or amide **8**, led to a significant decrease in activity. An extended sp^2-carbon linker on the other hand, such as the *E*-alkene in **9**, led to a 10-fold increase in potency. A saturated 2-atom spacer, such as in aniline **10** and benzylamine **11** was probably too flexible and did not manage to bring the IC_{50} under 100 nM. Changing the C linker in **3** to a heteroatom (**12**–**14**) led to the discovery of the highly potent aniline **14**, significantly more active than its phenol- and sulfide-analogs (**14** vs **12** and **13**). This result would indicate that the H-bond donor capability of **14** may contribute to the increase in potency (vide infra). Furthermore, the trifluoromethyl substituent on the 3-position of the aromatic D ring brought a 13-fold increase in potency versus the non-substituted analog **15**. Restriction of the free rotation of **15**, by cyclizing the aniline into the aromatic ring (**16**), did not improve the IC_{50}. Swapping the position of the aromatic and the methyl substituents on the triazole ring in **15** (compound **17**, Fig. 2) also had a detrimental effect on potency.

Aniline **14** (MW = 428, *c*log*P* = 4.9) was selected for further evaluation. When **14** was tested orally in mice at 30 mg/kg it showed no significant effect (−17%) on Aβ peptides levels 4 h after dosing, despite high compound brain levels (5.7 μM, B/P = 0.42). This compound was however highly bound to brain proteins, with the fraction of unbound compound in brain ($f_{u,b}$) under the detection limit ($f_{u,b} < 0.05\%$).[16] It can be hypothesized that the free brain concentration of **14** was not high enough for in vivo activity. Nevertheless, in the benzimidazole series of **1** many derivatives with $f_{u,b} < 0.1\%$ demonstrated robust in vivo activity.[13] Further exploration around this hit was aimed at identifying similarly potent analogs that would also demonstrate in vivo efficacy.

It was found that modifications on the aniline ring (Table 2) resulted in modulation of both in vitro and in vivo activity. Thus, substitution at 3- and 3,5-positions (compounds **18**–**19** in Table 2) with both electron withdrawing and electron donating substituents maintained the in vitro potency of the hit, compound **18** being one of the most potent GSMs in this series. As for **14**, this potency again did not translate in vivo in mice, as Aβ42 levels were not significantly reduced 4 h after administration. Compounds **18** and **19** were also highly bound to brain tissue and thus, despite the high compound brain levels, in both cases the free brain concentration ($C_{u,b}$) was probably not high enough for in vivo activity (estimated as less than 2 nM and 4 nM, respectively).[17] In mouse, the free brain concentration of **18** and **19** was at least 20 fold less than the IC_{50} in vitro as indicated by the coverage ratio ($CR = C_{u,b}/mIC_{50}$, <0.05, see Table 2). Substituents at the 4-position of the aniline ring did not bring an improvement in potency (**20**, not tested in vivo). A substituent present at the 2-position of the aniline (**21**–**28**) turned out to be essential for in vivo potency. Mono 2-substituted anilines, either with electron withdrawing (**21**) or lipophilic electron donating groups (**22**), had moderate in vitro activity, but showed good modulation of Aβ peptides levels in vivo. For **21** and **22**, the free brain concentrations were higher than their respective IC_{50} in vitro (CR = 1.7 and 2.7, respectively). A polar methoxy substituent was weakly active (**23**) and it was not tested in vivo. Additional substitution at the 5-position (compounds **24** and **25**) increased the in vitro potency and maintained the in vivo activity. Compound **24** had high brain and plasma levels and improved B/P ratio (close to 1).

More polar substituents introduced on the 5-position of the aniline ring (e.g., dimethyl amine in **25**) decreased the lipophilicity of the compounds (4.3 for **25** vs 5.1 for **24**), but did not affect their potency. For instance, **25** was highly potent in vitro and demonstrated a surprising 51% lowering of Aβ42 in mice at 30 mg/kg, 4 h from administration, despite a poor brain penetration (B/P = 0.2) and low mouse free brain concentrations ($C_{u,b}$ = 4 nM,



Scheme 1.
Note: IC_{50} represents the concentration of a compound that is required for reducing the Aβ42 level by 50%. The IC_{50} values are a mean of at least 3 determinations. Mouse in vivo at 30 mg/kg p.o. after 4 h (n = 6) expressed as a percentage of Aβ42 lowering in brain compared with untreated animals. Plasma and brain samples were analyzed for the tested compound using a qualified research LC-MS/MS method.

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