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Graphical Abstract

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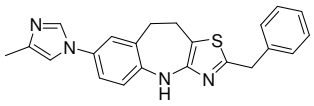

Compound **6**
Abeta1-42 IC_{50} = 35 nM

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ABSTRACT

Beginning with a diaminotriazine screening hit, several series of novel, tricyclic gamma-secretase modulators (GSMs) were designed. The SAR of several related series of GSMs is presented, and the in vivo profile of a lead molecule from the series is described.

1. Introduction

Alzheimer's disease (AD) is an age-related, chronically progressive neurodegenerative disorder affecting more than 35 million people worldwide and an estimated 5.5 million in the US.[1] Current marketed drugs such as acetylcholinesterase inhibitors and the NMDA antagonist memantine only treat disease symptoms and don't slow or reverse the underlying progression of the disease. Thus, the development of disease-modifying treatments remains a major interest in the pharmaceutical industry.

Pathological examination of AD brain tissue has revealed two underlying disease components, neurofibilliary tangles and amyloid plaques. Plaques are formed from the precipitation of the amyloid beta peptides (Aβ), which range from 37 to 42 amino acids in length and are produced from sequential cleavages of the amyloid precursor protein (APP) by β-secretase 1 (BACE 1) and γ-secretase.[1] While the exact cause of the disease is still an active area of research, a current prevailing hypothesis suggests that oligomers of the 42-amino acid form of the beta amyloid peptide (Aβ1-42) are central to the disease process.[2] Efforts to reduce Aβ1-42 production by interfering with the action of γ-secretase have led to the identification of full inhibitors of the enzyme complex (γ-secretase inhibitors, or GSIs), several of which have been advenced into clinical trials.[3] This approach, however, is complicated by issues including inhibition of Notch processing by unselective GSIs and the clinical failure of the GSIs semagacestat and avagacestat.[4] These issues have led to the continued development of additional treatment options. A recent additional approach is to target the γ-secretase complex with molecules that change the length of the Aβ peptides produced. This class of molecules, known as γ-secretase modulators (GSMs), are believed to change the processing of APP-CTFβ (the substrate for γ-secretase) so that shorter, more soluble peptides (such as Aβ1-38) are produced instead of the highly insoluble and neurotoxic Aβ1-42.[5] Because they do not block γ-secretase processing, GSMs do not interfere with Notch signaling,[6] and it is possible that they may avoid some of the issues of nonselective GSIs. The first generation of GSMs, including NSAID derivatives such as ibuprofen, indomethacin and tarenflurbil generally have weak in-vitro potency (Aβ1-42 IC_{50} = 25-200 μM) and were not effective in the clinic. Second generation GSMs have been disclosed by a number of companies and have demonstrated effacy in a number of preclinical AD animal models.[7]

Based on the interesting biological profile of the GSM class, we screened the BMS compound collection for compounds that inhibit Aβ1-42 production in a cellular assay.[8] Active compounds were then rescreened for their effect on total Aβ production to identify potential GSMs. To our delight, a class of diaminotriazines represented by compound **1** was identified as having modest potency for inhibition of Aβ1-42 production (IC_{50} = 180 nM) with no effect on total Aβ production (Figure 1).[9]

Our initial efforts to optimize the diaminotriazine scaffold have already been described, including the observation that

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lengthening the triazine aryl substituent to a benzyl substituent and changing the triazole group to a methyl imidazole as in

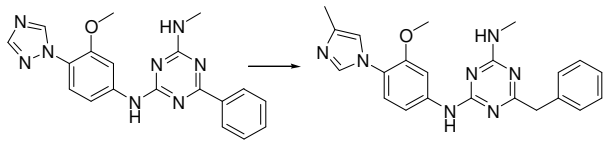


Figure 1. Triazine GSMs

compound **2** resulted in a nearly 10-fold increase in potency. We were also able to incorporate heterocycles other than triazine as the core of the molecule.[9] In an effort to increase potency by conformational restriction, we questioned whether an additional ring could be constructed linking the aniline ring back to the triazine or other heterocycle. The resulting compounds would be somewhat related to the well-known tricyclic antidepressants, and might be expected to have reasonable brain penetration (Figure 2).

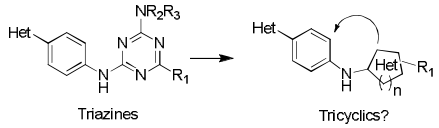
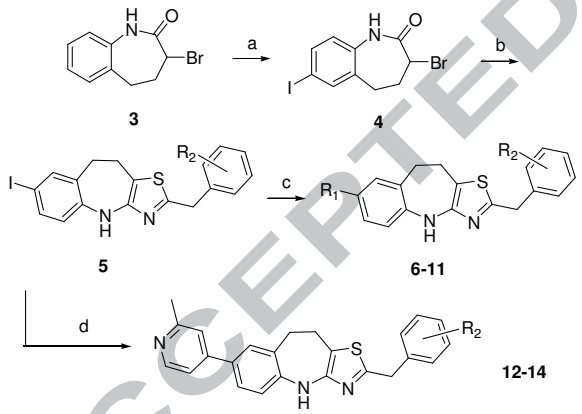


Figure 2. Tricyclic GSM concept

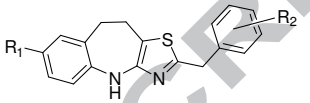
We selected a thiazole ring as the first heterocycle simply for the synthetic ease of using the well-established Hantszch cyclization to construct the ring. The synthesis of these initial analogs is outlined in Scheme 1.

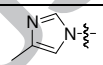
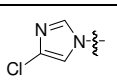
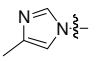
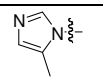
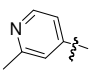
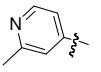
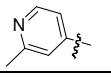


Scheme 1. Reagents and conditions: (a) excess ICl, AcOH, 100%, rt; (b) benzyl thioamides, EtOH, 25-40%, rt; (c) heterocycle or ZnCN, CuI, *N, N*-dimethylglycine, K_2CO_3, DMSO, 125 °C, 13-30%; (d) 2-methylpyridin-4-ylboronic acid, $Pd(dppf)Cl_2$, Na_2CO_3, DME/ H_2O, 80 °C, 31-42%.

Iodination of commercially available **3** with excess ICl in AcOH gave a quantitative yield of **4**, which was cyclized with benzyl thioamides to give the 2-benzyl-9,10-dihydro-4*H*-1-thia-3,4-diaza-benzo[*f*]azulenes **5**. Coupling of the iodides **5** with heterocycles including imidazoles, triazoles, or zinc cyanide using Ullman conditions provided the final molecules (**6-11**). Alternatively, coupling of **5** with 2-methylpyridin-4-ylboronic acid under standard Suzuki conditions provided examples **12-14**. The activity of compounds **6-14** is summarized in Table 1. We were immediately gratified to see compound **6** was a potent inhibitor of Aβ1-42 production (IC_{50} = 35 nM). Additional assays (data not shown) demonstrated that compound **6** had no effect on total Aβ production, confirming the GSM mechanism for this chemotype. We observed that 4-methylimidazole was the most potent heretocycle at the R_1 position in the thiazole series, with similar activity observed with the 3-methyl-4-pyridyl group (**12**, IC_{50} = 50 nM). There was an approximate 4-fold loss of potency for the related 3-methyl triazole (**7**, IC_{50} = 140 nM) or 4-chloroimidazole (**8**, IC_{50} = 140 nM). The nitrile (**9**) and 5-methylimidazole (**11**) groups were poorly tolerated. Adding a 4-fluoro substituent on the ring led to little change in potency (compare examples **6** and **10** or examples **12** and **13**), while 3,4-difluoro was slightly less well tolerated (**14**, IC_{50} = 120 nM).

Table 1. Activity of tricyclic thiazoles



Ex.	R_1	R_2	IC_{50} Aβ1-42 H4 (nM)[a]
6		H	35
7		H	140
8		H	140
9		H	1200
10		4-F	20
11		4-F	1800
12		H	50
13		4-F	80
14		3,4-di-F	120

[a]Activity assayed in H4 cells according to reference [7] with n >/= 2.

Having successfully designed compounds that showed potent GSM activity in cells, we further profiled compound **6**. The compound showed good metabolic stability when incubated with human liver microsomes (rate of metabolism 0.035 nmol/min/mg) and was not a hERG blocker in our high-throughput assay,[10] however it did show some broad μM inhibition of CYPs in fluorescence assays, including inhibition of CYP3A4 with an IC_{50} = 0.7 μM. The compound was also highly protein bound (> 99.8%) in both human and mouse plasma. We then tested compound **6** in 3xTg-AD mice.[11] These animals, which overproduce human Aβ1-42, are a convenient model because of the increased ability to detect the otherwise low brain Aβ1-42 concentration. Compound **6** was dosed orally in a vehicle consisting of 84% PEG-400/15% ethanol/1% Tween 80 at doses of 1, 3, 10, 30, and 100 mpk and Aβ1-42 levels were

collected 3 hours post dose. Plasma drug levels were determined at all doses, and brain drug levels were determined at 30 mpk. As is shown in Table 2, compound concentrations increased with dose

Table 2. Exposure and efficacy of compound **6** in 3xTg-AD mice

Dose	Plasma total (nM)	Brain total (nM)	Brain Aβ 1-42 (% Veh)	Brain/ Plasma
1 mpk	210	NT	110	NT
3 mpk	480	NT	100	NT
10 mpk	3800	NT	70	NT
30 mpk	8000	8900	60	1.1
100 mpk	25,000	NT	50	NT

NT = Not tested

and overall exposure was quite high. At 30 mpk, the brain/plasma ratio of the compound was 1.1, indicating significant brain penetration. As enumerated in Table 2 and shown graphically in Figure 3, compound **6** significantly reduced brain Aβ1-42 concentrations at doses of 10 mpk and higher, with an ED_{50} at the 100 mpk dose. No inhibition of total Aβ production was seen at any dose (data not shown).

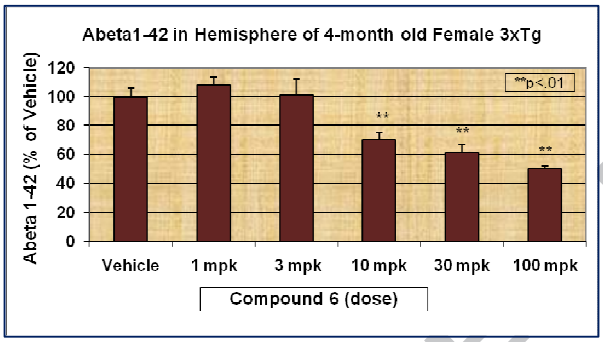
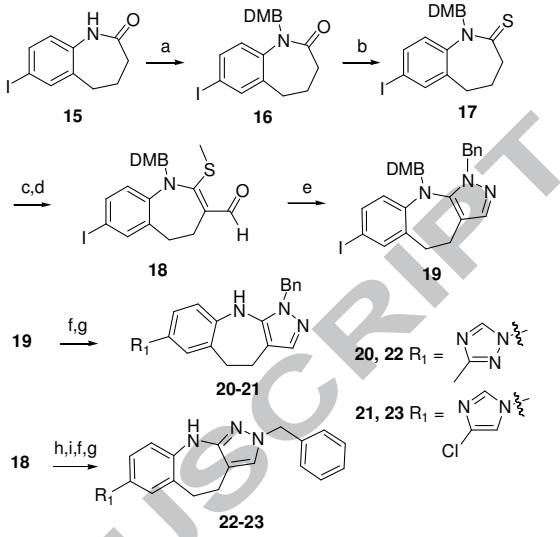


Figure 3. Activity of compound **6** in 3xTg-AD mouse brain

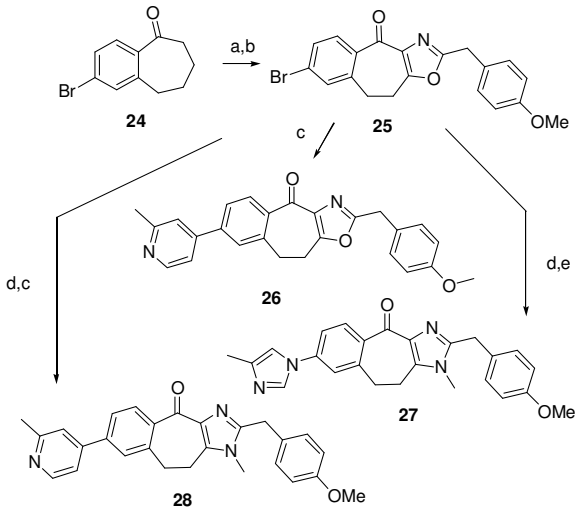
While these results represent a good starting point, it was clear that to move a molecule toward clinical development we must improve efficacy, achieve these results at a lower overall dose and exposure, and we must remove the CYP3A4 inhibition liability in compound **6**. In order to more broadly assess the potential of this new series of GSMs, we investigated synthesis of related compounds with different heterocycles in place of the thiazole ring.

First, we turned to pyrazoles. As shown in Scheme 2, the pyrazoles were constructed beginning with 7-iodo-4,5-dihydro-1*H*-benzo[b]azepin-2(3*H*)-one **15**.[12] Protection with a dimethoxybenzyl group followed by conversion of the amide to the thioamide produced intermediate **17**. Installation of an α-aldehyde using Bredereck's reagent (*tert*-butoxy-bis(dimethylamino)methane) followed by thione methylation gave cyclization precursor **18**. Direct cyclization with benzylhydrazine produced the 1-benzyl-7-methyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[4,3-f]azepine core intermediate **19**, which was coupled with heterocycles as before to produce compounds **20** and **21** after acidic deprotection. Alternatively, cyclization of **18** with hydrazine followed by benzylation produced the alternate 2-benzyl core, allowing production of compounds **22** and **23** where the position of the benzyl group is more analogous to the thiazole series. Indeed, compounds **20** and **21** were inactive, while compounds **22** and **23** had Aβ1-42 IC_{50}'s of 180 and 40 nM, respectively. Profiling of the pyrazoles, however, revealed that compounds **22** and **23** were both stronger inhibitors of CYP3A4 (IC50's = 0.3 μM), discouraging further work in this series.



Scheme 2. Reagents and conditions: (a) NaH, DMF, DMB-Br, rt 79%; (b) Lawesson's reagent, toluene, reflux, 69%; (c) neat Bredereck's reagent, 115 °C, 7 h, 58%; (d) MeI, K_2CO_3, AcCN, rt, 98%; (e) neat $BnNHNH_2$, 70 °C, 20 h, 84%; (f) 3-methyl-1,2,4-triazole or 4-chloro-imidazole, CuI, K_3PO4, trans-1,2-bis(methylamino)cyclohexane, DMF, 130 °C, 34-71%; (g) neat TFA, rt, 53-80%; (h) NH_2NH_2, THF, 81%; (i) BnBr, KHMDS, THF, rt, 88%.

In order to address the Cyp inhibition issue, we tested the possibility of further changes in the heterocycle combined with reducing the electron density in the ring system by swapping the central aniline nitrogen atom for a ketone. Scheme 3 details the synthesis of these analogs, which started with 7-bromobenzosuberone.[13] Oxime installation followed by

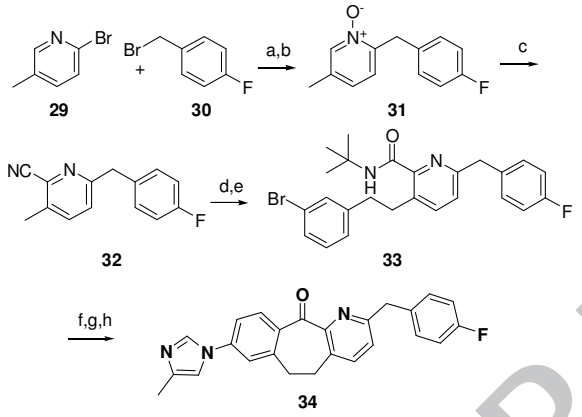


Scheme 3. Reagents and conditions: (a) isopentyl nitrite, 2.0 M HCl/Et_2O, rt, 73%; (b) 4-methoxyphenylacetic anhydride, 4-methoxyphenylacetic acid, 4-methoxyphenylacetyl chloride, 85 °C, 53%; (c) 2-methylpyridin-4-ylboronic acid, $Pd(dppf)Cl_2$, Na_2CO_3, DME/H_2O, 100 °C, 31-75%; (d) $MeNH_2$, THF, μwave, 100 °C, 6 h, 79%; (e) 4-methylimidiazole, CuI, *N*, *N*-dimethylglycine, K_2CO_3, DMSO, 125 °C, 12%.

cyclization with 4-methoxyphenylacetic acid produced the tricyclic 2-(4-methoxy-benzyl)-7-methyl-9,10-dihydro-1-oxa-3-aza-benzo[f]azulen-4-one core **25**. Suzuki coupling produced

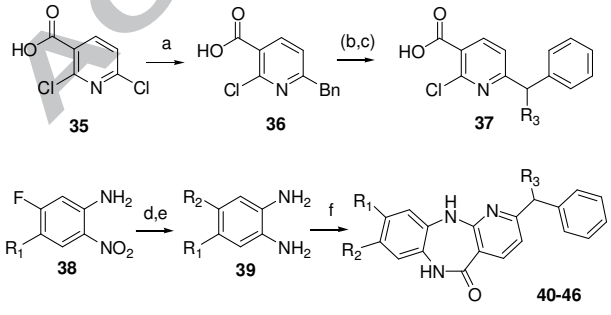
tricyclic **26** (IC_{50} = 0.30 μM) , while addition of methylamine into intermediate **25** produced the corresponding tricyclic imidazole core which allowed production of analogs **27** and **28** (IC50's = 1.1 μM and 0.38 μM respectively). All three analogs were modest GSMs with IC50's > 300 nM. Unfortunately, all three analogs remained potent CYP3A4 inhibitors (IC50's = 0.3 – 0.5 μM). While the 4-methoxybenzyl substituent did not allow direct comparison of activity to the thiazole series, we were encouraged that the first analogs containing the central ketone were modestly active and wanted to test expanding the heterocyclic ring to a 6-membered pyridyl ring.

A first pyridyl analog was synthesized using the suberone core using a slight variant of established chemistry (Scheme 4).[14] Negishi coupling of **29** and **30** was followed by *N*-oxidation and rearrangement to the pyridyl 2-nitrile **32**.[15] Formation of the *tert*-butyl amide followed by deprotonation and alkylation of the pyridyl methyl group gave **33**. Dehydration back to the nitrile followed by acid-catalyzed cyclization and Ullman coupling gave the desired compound **34**. This initial 6-membered ring analog had an Aβ1-42 IC_{50} = 1 μM and was still a CYP3A4 inhibitor (IC_{50} = 0.3 μM).



Scheme 4. Reagents and conditions: (a) Zn, $BrCH_2CH_2Br$, 4-fluorobenzylbromide, then $(Ph_3P)_4Pd$, THF, 0 °C to rt, 92%; (b) H_2O_2, AcOH, reflux; (c) TMS-CN, dimethylcarbamic chloride, DCM, rt, 34% for two steps; (d) H_2SO4, *t*-BuOH, 70 °C, 100%; (e) LDA, 1-bromo-3-(bromomethyl)benzene, THF, -70 °C to rt, 24%; (f) $POCl_3$, DMF, toluene, 115°C, 99%; (g) triflic acid, MeOH/H_2O, 65-85 °C, 62%; (h) 4-methylimidiazole, CuI, *N, N*-dimethylglycine, K_2CO_3, DMSO, 125 °C, 12%.

Hoping to both improve the potency of the analogs and further improve the Cyp inhibitor profile we next moved to the well-established 6,11-dihydro-5H-benzo[b]pyrido[2,3-e][1,4]diazepin-5-one core,[16] where existing chemistry would allow for additional modifications of both the steric and electronic environment of the inhibitor. Synthetically we

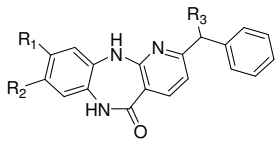


Scheme 5. Reagents and conditions: (a) 9-Bn-9-BNN, $(Ph_3P)_4Pd$, K_2CO_3, THF, 85 °C, 44%; (b) MeI, NaH, DMF, rt, 42%; (c) LiOH, THF/H_2O, rt, 93%; (d) 4-methylimidazole, 4-chloroimidazole, or 4-methyltriazole, K_2CO_3, DMSO, 65 °C, 28-96%; (e) H_2 balloon, Pd/C, MeOH, rt, 79-89%; (f) **36** or **37**, tetramethylenesulfone, 145-165 °C, 16 h, 3-53%.

accessed the desired analogs by selectively installing a 6-benzyl group on 2,6-dichloronicotinc acid **35** using a Negishi coupling protocol. In order to test steric blocking of the pyridyl group, **36** was bismethylated and then saponified to produce **37**. Separately, the left-hand heterocycle was installed on 4-fluoronitro intermediates **38**. Reduction to the diamine followed by thermal condensation with the preformed chloronicotinic acids produced the desired analogs **40-45**, albeit in modest chemical yield. The desired regioisomer was typically favored, but purification was necessary to produce pure material.

The Aβ1-42 activity and inhibition of CYP3A4 for compounds **40-45** is summarized in Table 3. The parent 4-methylimidazole analog **40** was the most potent inhibitor in the series (IC_{50} = 50 nM), with activity similar to that of the more potent compounds in the thiazine series **6-14** (IC_{50} = 35 nM). The inhibition of CYP3A4, however, was not improved by changing to this core (IC_{50} = 0.15 μM). In this particular series, the chloroimidazole **41** was 2-3 fold more active than the corresponding methyltriazole **42**. Somewhat surprisingly, fluorine was poorly tolerated at R_1, with over a 10-fold loss in Aβ1-42 potency and an increase in CYP3A4 inhibition. Interestingly, the chloroimidazoles **41** and **45** had a dramatically improved CYP3A4 profile (IC_{50} > 13 μM). This is not solely the result of a solubility change, as the assay is monitored for drug precipitation. The data suggest that in this series the CYP3A4 SAR closely tracks with heterocycle basicity, with the methyl imidazole being most potent, follwed by the triazole, while the weakly basic chloroimidazole is a poor binder. More analogs would be needed to confirm these observations, however the series overall suffered from modest potency at Aβ 1-42, so additional analogs were not prepared. As a benchmark, compound **40** was also examined at 30 mpk in the 3xTg-AD mouse model, but no activity was observed.

Table 3. Activity of tricyclic GSMs.



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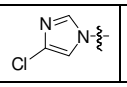
Ex.	R_1	R_2	R_3	IC_{50} Aβ1-42 H4 (nM)[a]	CYP3A4 IC_{50} (μM)
40	H		H	50	0.15
41	H		H	190	> 13
42	H		H	460	2.0
43	F		H	820	0.03
(+/-) 44	H		Me	100	0.2

(+/-) **45**	H		Me	200	> 13

[a]Activity assayed in H4 cells according to reference 7 with n >/= 2.
NT = not tested

In summary, starting from a class of aniline triazines GSMs, we designed multiple series of conformationally restriained, tricyclic GSMs. The 2-benzyl-9,10-dihydro-4*H*-1-thia-3,4-diaza-benzo[*f*]azulenes including compound **6** were effective in an animal model of Aβ1-42 production at high exposure. In an efffort to explore the SAR and separate efficacy from inhibition of CYP3A4 activity, a variety of additional tricyclic cores was explored. While we were able to construct additional scaffolds with moderate to good *in vitro* potency, the combination of high potency without inhibition of CYP3A4 remains an issue to be addressed.

Acknowledgements
The authors appreciate the contributions of Tracey Fiedler and Jason Corsa who conducted the rat and mouse *in vivo* experiments. Rudy Krause and Alan Lin executed the accompanying Aβ assays.

References and notes

All new compounds reported herein gave satisfactory analytical data including parent mass, proton NMR spectral integrity, and high purity by HPLC characterization.

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