



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Sulfonamides as multifunctional agents for Alzheimer's disease

Seema Bag^{a,†}, Rekha Tulsan^{a,†}, Abha Sood^{a,†}, Hyejin Cho^{a,†}, Hana Redjeb^{a,†}, Weihong Zhou^{a,†}, Harry LeVine III^b, Béla Török^{a,*}, Marianna Török^{a,*}^a Department of Chemistry, University of Massachusetts Boston, 100 Morrissey Blvd., Boston, MA, USA^b Department of Molecular and Cellular Biochemistry, Chandler School of Medicine, and Center on Aging, University of Kentucky, Lexington, KY 40536, USA

ARTICLE INFO

Article history:

Received 29 October 2014

Accepted 3 December 2014

Available online xxxx

Keywords:

Alzheimer's disease

Amyloid- β

Cholinesterase inhibition

Antioxidant

Sulfonamides

ABSTRACT

Sulfonamide linker-based inhibitors with extended linear structure were designed and synthesized with the aim of producing multifunctional agents against several processes involved in the pathology of Alzheimer's disease (AD). The potency of the compounds were assessed in the inhibition of A β self-assembly (fibril and oligomer formation), in modulating cholinesterase (AChE, BuChE) activity, and scavenging free radicals. Several compounds exhibited promising A β self-assembly and cholinesterase inhibition and in parallel, showed good free radical scavenging properties. The investigation of the scaffold described in this study resulted in the identification of three compounds (**14**, **19** and **26**) as promising leads for the further design of multifunctional drug candidates for AD.

© 2014 Published by Elsevier Ltd.

Alzheimer's disease (AD) is a complex neurodegenerative disorder of the central nervous system.^{1,2} In response to the pressing need of an aging population several treatment strategies have been explored.^{3–7} The most common approaches are related to the cholinergic⁸ and amyloid cascade hypotheses.⁹ The formation of A β peptide self-assemblies (oligomers and fibrils) and their neurotoxic effects are believed to be major contributors to the development of AD.¹⁰ Due to the potent effect of multiple A β neurotoxic products on disease development, a broad range of A β self-assembly inhibitors have been identified.¹¹ In addition, a low level of certain neurotransmitters, such as acetylcholine (ACh), is also associated with the disease.¹² The first generation of AD drugs were acetylcholinesterase (AChE) inhibitors with the goal of reducing ACh breakdown and therefore increasing ACh concentration, to provide symptomatic treatment.¹³ In addition to AChE another cholinesterase enzyme, butyrylcholinesterase (BuChE), also appeared to negatively affect the level of neurotransmitters.¹⁴ Recent studies indicate that the peripheral binding site of AChE may contribute to the initiation of A β self-assembly, as well.¹⁵ In vivo studies also suggested elevated levels of both metals and oxidative stress are present in the AD affected brain.¹⁶ There is a growing sentiment that multitarget therapeutics may combat the complex pathogenesis of the disease more effectively than single-target approaches.¹⁷

Extending our recent efforts on the development of anti-amyloidogenic compounds^{18–24} we describe the synthesis, biochemical evaluation, and potential multifunctional application of sulfonamide-based small molecule agents, including saccharin, and other analogues. Sulfonamides exhibit a broad range of biological effects and are well-tolerated in biomedical applications. Their applications include use as early antibacterial agents²⁵ or saccharin, one of the most commonly sold artificial sweeteners.²⁶ Sulfonamides have also been found to be beneficial in AD. Kumar *et al.* proposed *N*-aryl sulfonamide substituted 3-morpholino arecoline derivatives for the symptomatic treatment of Alzheimer's dementia.²⁷ Other reports include the inhibition of amyloid- β formation from β -amyloid precursor protein (APP) or its self-assembly by a series of sulfonamide derivatives.^{28–31} The sulfonamide analogs reported in this study are either novel and their synthesis never reported, or although commercially available their testing as multifunctional anti-AD agents has not been reported. We tested these compounds in a series of assays, including the inhibition of A β self-assembly, modulation of cholinesterase activity, and assessment of potential antioxidant properties.

The above reports inspired the investigation of several small commercially available sulfonamides (Fig. 1 and 1–6).

The commercial compounds were evaluated in the inhibition A β self-assembly, including fibrillogenesis and oligomer formation inhibition, modulation of cholinesterase activity and free radical scavenging. Some compounds showed promising results in these assays and also pointed toward possible improvements. We decided to synthesize additional derivatives focusing on the extension of the length of the compounds.

* Corresponding authors. Tel.: +1 617 287 6159; fax: +1 617 287 6030.

E-mail addresses: bela.torok@umb.edu (B. Török), marianna.torok@umb.edu (M. Török).

† Tel.: +1 617 287 6159; fax: +1 617 287 6030.

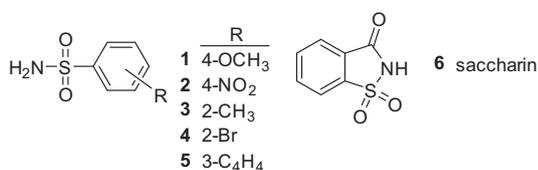


Figure 1. Structure of the tested commercial sulfonamides.

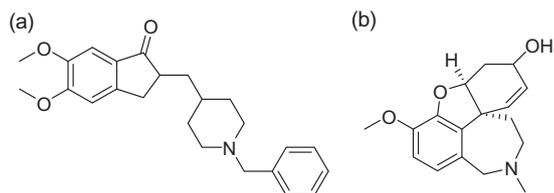


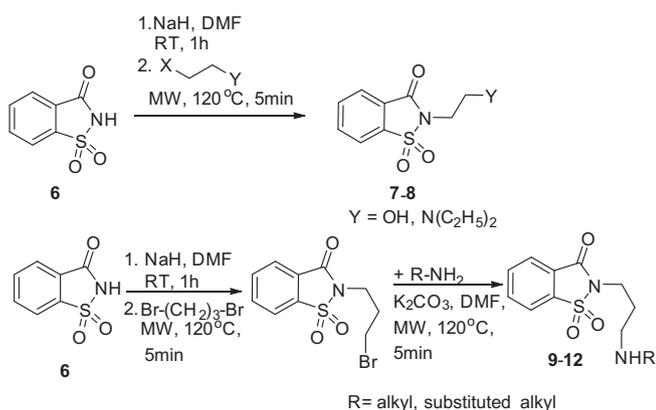
Figure 2. Structure of donepezil (a) and galanthamine (b).

We expected that compounds with longer alkyl chains might act as better cholinesterase inhibitors, mimicking the structural features of donepezil (Fig. 2a); a well-known AChE inhibitor without decreasing the efficiency of the compounds in other assays.³² Therefore, several saccharin derivatives (7–12) were synthesized as illustrated in Scheme 1.

After the preliminary assays further modifications were executed on the scaffold. Instead of having the sulfonamide moiety in a ring, a relatively long, linear chain was introduced to the scaffold, positioning the sulfonamide group in the chain. Aromatic head and tail groups were added as well. This design aims to provide more flexibility to the compounds and at the same time to continue to have large flat end-units. The synthesis of these second generation compounds (14–26) is summarized in Scheme 2a.

Two additional compounds; 27 and 28 were also prepared (Scheme 2b) to determine how the activity would be affected if the sulfonamide moiety was eliminated from the scaffold. Each product was characterized by ¹H and ¹³C NMR spectroscopy and by LC–MS. The spectroscopic characterization of the new compounds was in agreement with their structures (see Supporting information). The complete list of the compounds synthesized in this work, except 27 and 28 (Scheme 2b), is shown in Figure 3.

To determine the activity profile of the compounds they were first subjected to Aβ fibrillogenesis assays. The quantitative Thioflavin-T (THT) fluorescence assay was applied to determine the antifibrillogenic potency of the compounds.³³ All data were normalized to the fluorescence of the inhibitor-free control (*I*_{control}). The fibrillogenesis assay data are presented in Figure 4.



Scheme 1. Structure of the tested commercial sulfonamides.

The data indicate that the compounds overall belong to two different groups. The commercially available sulfonamides (1–6) and the rather compact saccharin derivatives (7–12) commonly promote fibril formation. In contrast, the long linear-shaped compounds (13–28) exhibited moderate to good fibrillogenesis inhibition. Compounds 14, 18, 19, 21 and 26 showed the most significant effect (87%, 60%, 43%, 64% and 45%, respectively). To confirm that inhibition was not due to THT displacement by compounds during the above assays, complementary Atomic Force Microscopy (AFM) experiments were performed.³⁴ For example, AFM images of the solvent treated control and the sample incubated in the presence of compound 14 (Fig. 3), which showed the best (87%) fibril inhibition are depicted in Figure 5.

The images confirm the interpretation of the THT results. The control sample showed the expected well-developed mature fibrils, while the image of the inhibitor-containing sample reflects the high, although not complete, inhibition. The small amount of remaining fibril-like assemblies were thinner and shorter in appearance indicating the profound effect of 14 on the Aβ fibrillogenesis.

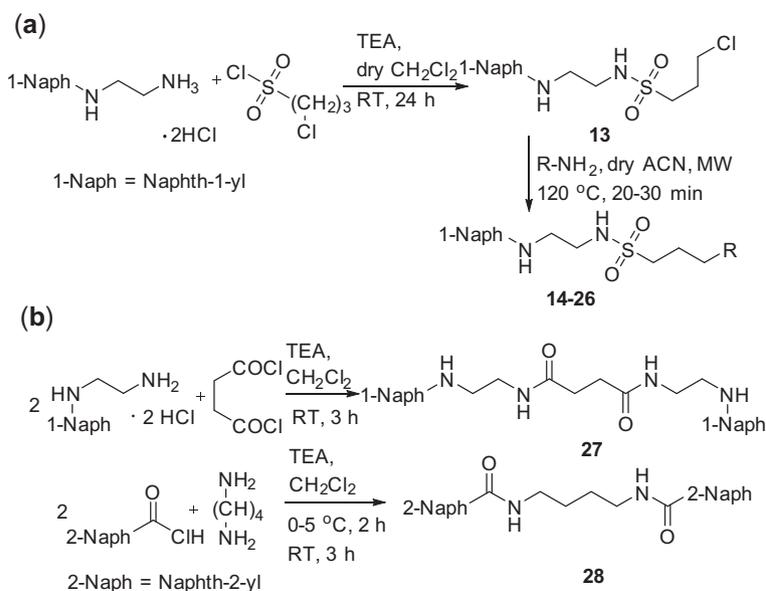
The compounds were also tested for their activity in the inhibition of oligomer formation by the biotinyl-Aβ(1–42) single-site streptavidin-based assay.³⁵ The samples were incubated for 30 min in the assays, using Aβ/inhibitor = 0.0002 ratio at 0.01 μM Aβ concentration. The intensity of the inhibited samples was normalized to the control sample containing Aβ and the solvent. The percentile values were calculated similarly to those of fibril inhibition as shown above. The data are illustrated in Figure 6.

Comparing Figure 6 to Figure 4, indicates that compounds active against oligomers were poorly active against fibrillogenesis and vice versa. The small commercial sulfonamides and saccharin derivatives (1–12) showed moderate inhibition (up to 54%, except 11) of oligomers while the long chain linker containing sulfonamides (13–26) were generally oligomer formation promoters. Interestingly, 27 and 28 showed 50–100% inhibition of oligomer formation. These compounds are similar to the long chain sulfonamides (13–26), however, they lack the sulfonamide moiety. Comparing the activity of the compounds in the two Aβ self-assembly inhibition assays one cannot fail to notice that the behaviour of the compounds in the two assays are the opposite; a compound is either a fibril inhibitor or an oligomer inhibitor. This observation is in agreement with our earlier findings^{21–24} and literature data.¹⁰

Oxidative stress caused by free radicals also plays an important role in development of AD. Thus, the potential antioxidant character of the compounds was also assessed. The scavenging of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical was measured by the decrease of its absorbance. The data are compared to those obtained with reference compounds ascorbic acid³⁶ and resveratrol,³⁷ both of which are well-known antioxidants. The data are illustrated in Figure 7.

Three of our synthetic sulfonamides (19, 23 and 24) showed higher free radical scavenging property than ascorbic acid, two molecules (23 and 24) were even better than resveratrol.

With an aim to have multi-target functionality each compound was assayed for the inhibition of cholinesterases. All of the synthesized molecules were subjected to Ellman assay of the hydrolysis of acetylthiocholine to determine their potency towards inhibition of AChE and BuChE (Figs. 8 and 9). For AChE inhibition, the molecules were assayed at 2 M; which is the IC₅₀ of galanthamine (Fig. 2b).³⁸ Molecule 19 (Fig. 3) produced 88% inhibition at 2 μM, while galanthamine at same concentration showed 54% inhibition. Molecules 18 and 26 (Fig. 3) showed greater than 40% inhibition at the same concentration. Due to solubility issues molecule 28 (Scheme 2) could not be tested in either assay. For BuChE inhibition, the molecules were assayed at 10 μM; which is the IC₅₀ of galanthamine against that enzyme.³⁹ Nine out of 15 synthesized



Scheme 2. Synthesis of second generation sulfonamides (a) and compounds **27** and **28** that lack the sulfonamide linker (b).

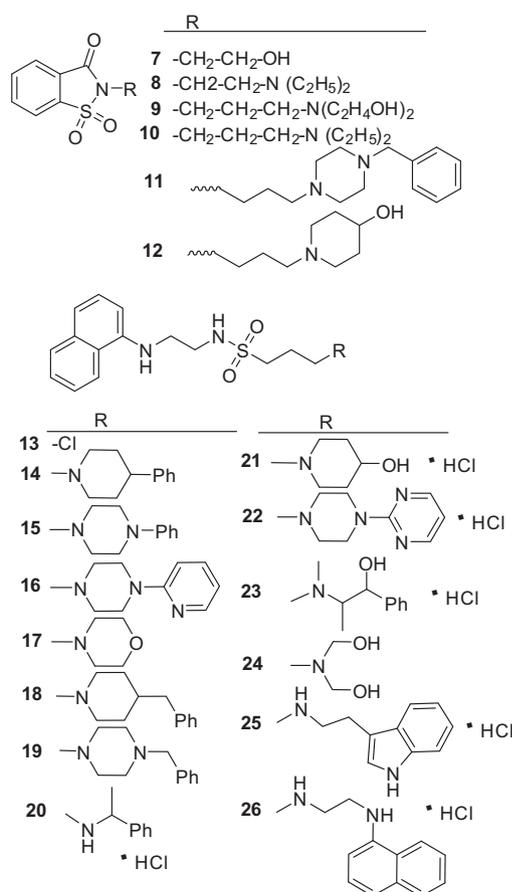


Figure 3. Structure of sulfonamides synthesized in this work.

molecules showed more than 40% inhibition at 10 μ M. Compounds **19**, **25**, and **26** (Fig. 3) exhibited more than 80% inhibition at this concentration.

Several of the compounds showed lower IC₅₀ values than the galanthamine standard. For compound **19** (Fig. 3), which showed

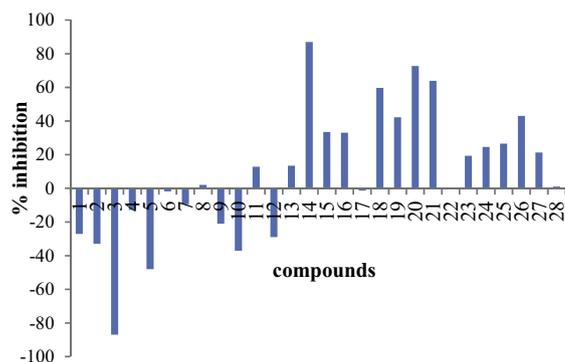


Figure 4. Inhibitory effect of sulfonamide derivatives on the A β fibrillogenesis. The assays were carried out at an A β /inhibitor = 1:10 ratio at 100 μ M A β concentration, except **26** where the ratio was 1:1.

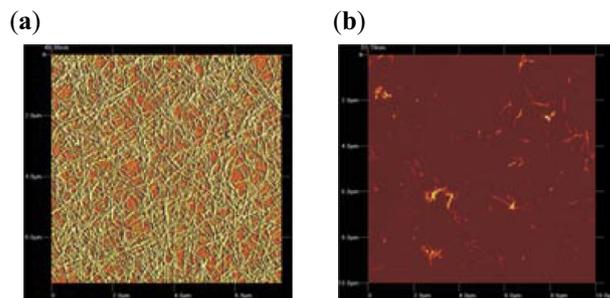


Figure 5. Atomic Force Microscopy images of A β (1–40) samples incubated (a) without sulfonamides (control) and (b) with compound **14** for 4 days.

88% AChE inhibition at 2 μ M concentration, the IC₅₀ was 160 nM. For compound **14** (Fig. 3), which showed 58% BuChE inhibition at 10 μ M concentration, the IC₅₀ was 5.08 μ M. In the case of molecule **6**, which showed 73% BuChE inhibition at 10 μ M concentration, the IC₅₀ was 3.60 μ M. For compounds **19** and **26** (Fig. 2) with 90% and 99% BuChE inhibition, respectively, at 10 μ M concentration, the IC₅₀'s were 2.00 μ M and 930 nM. Molecule **19** showed >85% inhibition for both enzymes. However, molecule **18** and **26** also exhibited

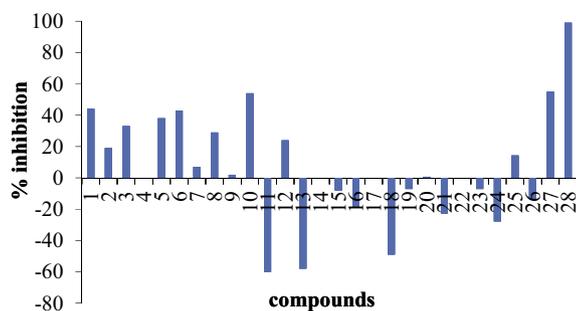


Figure 6. Inhibitory effect of sulfonamide derivatives on the A β oligomer formation. The assays were carried out at A β /inhibitor = 0.0002 ratio at 0.01 μ M A β concentration.

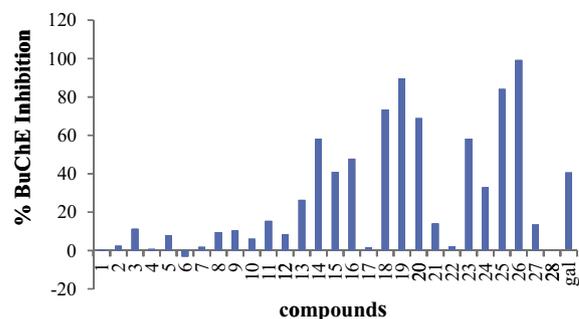


Figure 9. Inhibition of BuChE activity by commercial and synthetic sulfonamides tested at 10 μ M concentration.

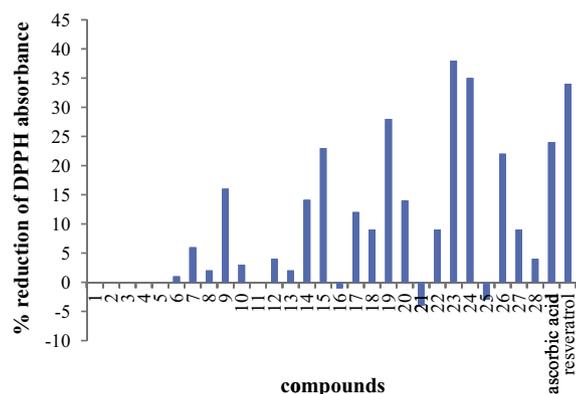


Figure 7. Radical scavenging activity of the sulfonamides (10 μ M) determined as the % decrease of the DPPH radical absorbance at λ = 519 nm after a 60 min incubation.

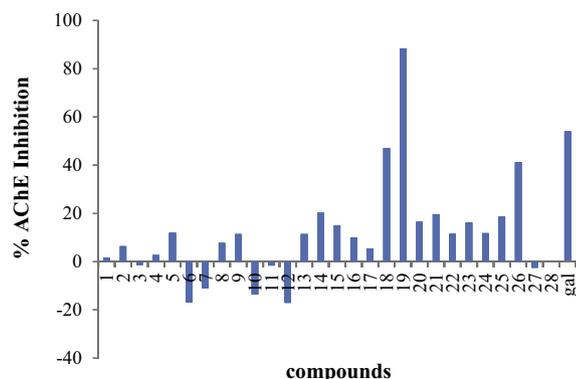


Figure 8. Inhibition of AChE activity by commercial and synthetic sulfonamides tested at 2 μ M concentration.

notable inhibition for AChE and nearly complete inhibition for BuChE at 10 μ M. This is significant, in view of the renewed interest in dual AChE and BuChE inhibitors as symptomatic therapeutics for AD.

With the aim of understanding the cholinesterase inhibition property of these new molecules, they were docked in the active site of AChE (PDB code: 1EVE). The superimposition of compound **19** with donepezil and galanthamine (known AChE inhibitors) in the active site of 1EVE is as shown in the Figure 10.

From the superimposition of molecule **19** (green) with donepezil (brown) in the active site of 1EVE (Fig. 10) it is evident that the **19** occupies the active site (magenta), and extends throughout the

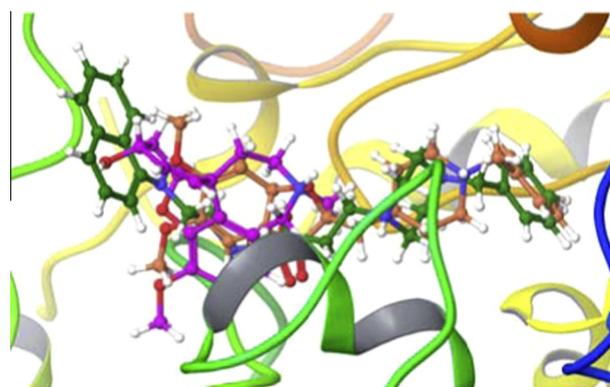


Figure 10. Superimposition of molecule **19** (green, ball and stick) with donepezil (brown, ball and stick) and galanthamine (magenta, ball and stick) in the active site of AChE (PDB code: 1EVE).

active site occupying both the catalytic site and the peripheral anionic site. Its position is similar to that of donepezil (brown) and significantly different from that of galanthamine (green). The interactions shown by the docked conformation of molecule **19** were studied in detail. Both nitrogens of the benzyl piperazine ring in **19** formed two cation– interactions with Phe330 residue (centroid: centroid = 4.67 Å and 4.48 Å) of the active site. One π – π interaction was seen between the benzyl ring of benzyl piperazine with Trp84 residue (centroid: centroid = 4.28 Å) of the active site. The aliphatic-N of benzyl piperazine formed a hydrogen bond with Phe330 of 1EVE. These interactions further stabilized the molecule in the active site accounting for the improved potency.

Most of the synthesized molecules (**13–26**, Fig. 3) have an extended linear structure with a sulfonamide moiety. In order to observe whether the sulfonamide plays any role in the activity measured in our different assays, two more compounds (**27**, **28**, Scheme 2b), which also have an extended linear structure but lack the sulfonamide moiety, were synthesized. These two new molecules had little or no effect on the inhibition of fibril formation, cholinesterase inhibition and free radical scavenging. In contrast, one of these compounds (**28**) exhibited 99% oligomer assembly inhibition. In all 26 sulfonamides have been synthesized and tested in a variety of assays related to AD pathology and neurochemical abnormalities of the disease. The compounds can be categorized into three groups: commercially available, sulfonamides with limited length and size (**1–5**); cyclic sulfonamides (**6–12**) and open-chain sulfonamides (**13–26**) with a head and tail group that was linked with a long chain in order to span the active center of the cholinesterases. The structure–activity relationship in the different assays reveals significant information for future design. The cyclic sulfonamides (saccharin derivatives), while promoting the fibril

formation, inhibit the formation of oligomers and practically are inactive in enzyme inhibition and radical scavenging. In contrast, the long chain sulfonamides performed more consistently in all of the assays. While largely inactive against oligomers, they performed well in the other assays indicating potential for multifunctionality. These observations provide further experimental evidence for the existence of multiple pathways that distinguish amyloid oligomer and fibril formation.⁴⁰

In conclusion, a variety of commercially available and newly synthesized novel cyclic and long chain aliphatic sulfonamides were tested with the aim of identifying multifunctional compounds with cholinesterase and A β self-assembly inhibitory and promising antioxidant properties for AD treatment. While the small and cyclic derivatives (saccharins) were largely inactive in the assays, the open chain sulfonamides showed potency and efficacy in four of the five assays. Sulfonamides containing extended linkers have potential as leads for development of new drug candidates for AD.

Acknowledgments

Financial support provided by the University of Massachusetts Boston through the 2013 Joseph P. Healey Research Grant and National Institute of Health (R21AG028816-01 to H.L.) is gratefully acknowledged.

Supplementary data

Supplementary data (the synthesis and characterization of the sulfonamides as well as the detailed description of the biochemical assays) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bmcl.2014.12.006>.

References and notes

- Kelley, B. J.; Petersen, R. C. *Neurol. Clin.* **2007**, *25*, 577.
- Ballard, C.; Gauthier, S.; Corbett, A.; Brayne, C.; Aarsland, D.; Jones, E. *Lancet* **2011**, *377*, 1019.
- Chen, X.; Tikhonova, I. G.; Decker, M. *Bioorg. Med. Chem.* **2011**, *19*, 1222.
- Jakob-Roetne, R.; Jacobsen, H. *Angew. Chem.* **2009**, *121*, 3074.
- Neugroschl, J.; Sano, M. *Curr. Neurol. Neurosci. Rep.* **2009**, *5*, 368; Bolognesi, M. L.; Matera, R.; Minarini, A.; Rosini, M.; Melchiorre, C. *Curr. Opin. Chem. Biol.* **2009**, *13*, 303; Relkin, N. R. *Expert Rev. Neurother.* **2007**, *7*, 735; Findeis, M. A. *Biochim. Biophys. Acta* **2000**, *1502*, 76.
- Ballard, C. G.; Greig, N. H.; Guillozet-Bongaarts, A. L.; Enz, A.; Darvesh, S. *Curr. Alzheimers Res.* **2005**, *2*, 307.
- Darvesh, S.; Hopkin, D. A.; Geula, C. *Nat. Rev. Neurosci.* **2003**, *4*, 131.
- Bartus, R. T.; Dean, R. L., III; Beer, B.; Lippa, A. S. *Science* **1982**, *217*, 408; Silman, I.; Sussman, J. L. *Curr. Opin. Pharmacol.* **2005**, *5*, 293.
- Belinson, H.; Kariv-Inbal, Z.; Kaye, R.; Masliah, E.; Michaelson, D. M. *J. Alzheimers Dis.* **2010**, *22*, 959; Liu, L.; Murphy, R. M. *Biochemistry* **2006**, *45*, 15702; Selkoe, D. J. *Nature* **2003**, *426*, 900; Murphy, R. M. *Annu. Rev. Biomed. Eng.* **2002**, *4*, 155.
- Kayed, R.; Cantó, I.; Breydo, L.; Rasool, S.; Lukacsovich, T.; Wu, J.; Albay, R., III; Pensalfini, A.; Yeung, S.; Head, E.; Marsh, J. L.; Glabe, C. G. *Mol. Neurodegener.* **2010**, *5*, 57; Zhao, W. Q.; Santini, F.; Breese, R.; Ross, D.; Zhang, X. D.; Stone, D. J.; Ferrer, M.; Townsend, M.; Wolfe, A. L.; Seager, M. A.; Kinney, G. G.; Shughrae, P. J.; Ray, W. J. *J. Biol. Chem.* **2010**, *285*, 7619; Shankar, G. M.; Leissring, M. A.; Adame, A.; Sun, X. Y.; Spooner, E.; Masliah, E.; Selkoe, D. J.; Lemere, C. A.; Walsh, D. M. *Neurobiol. Dis.* **2009**, *36*, 293; Kaye, R.; Head, E.; Thompson, J. L.; McIntire, T. M.; Milton, S. C.; Cotman, C. W.; Glabe, C. G. *Science* **2003**, *300*, 486.
- Török, B.; Dasgupta, S.; Török, M. *Curr. Bioact. Compd.* **2008**, *4*, 159; Török, B.; Bag, S.; Sarkar, M.; Dasgupta, S.; Török, M. *Curr. Bioact. Compd.* **2013**, *9*, 37.
- DeKosky, S. T.; Scheff, S. W. *Ann. Neurol.* **1990**, *27*, 457.
- Larner, A. J. *Expert Rev. Neurother.* **2010**, *10*, 1699; Wollen, K. A. *Alt. Med. Rev.* **2010**, *15*, 223; Francis, P. T.; Ramirez, M. J.; Lai, M. K. *Neuropharmacol.* **2010**, *59*, 221.
- Darvesh, H.; Hopkins, D. A.; Geula, C. *Nat. Rev. Neurosci.* **2003**, *4*, 131.
- Alvarez, A.; Alarcon, R.; Opazo, C.; Campos, E. O.; Munoz, F. J.; Calderon, F. H.; Dajas, F.; Gentry, M. K.; Doctor, B. P.; De Mello, F. G.; Inestrosa, N. C. *J. Neurosci.* **1998**, *18*, 3213; De Ferrari, G. V.; Canales, M. A.; Shin, I.; Weiner, L. M.; Silman, I.; Inestrosa, N. C. *Biochemistry* **2001**, *40*, 10447; Bartolini, M.; Bertucci, C.; Cavrini, V.; Andrisano, V. *Biochem. Pharmacol.* **2003**, *65*, 407.
- Huang, X.; Moir, R. D.; Tanzi, R. E.; Bush, A. I.; Rogers, J. T. *Ann. N.Y. Acad. Sci. U.S.A.* **2004**, *1012*, 153; Barnham, K. J.; Masters, C. L.; Bush, A. I. *Nat. Rev.* **2004**, *3*, 205.
- Bolognesi, M. L.; Simoni, E.; Rossini, M.; Minarini, A.; Tumiatti, V.; Melchiorre, C. *Curr. Top. Med. Chem.* **2011**, *11*, 2797.
- Török, B.; Milton, S.; Kaye, R.; Wu, P.; McIntire, T.; Glabe, C. G.; Langen, R. J. *Biol. Chem.* **2002**, *277*, 40810.
- Török, M.; Abid, M.; Mhadgut, S. C.; Török, B. *Biochemistry* **2006**, *45*, 5377.
- Sood, A.; Abid, M.; Hailemichael, S.; Foster, M.; Török, B. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6931.
- Sood, A.; Abid, M.; Sauer, C.; Hailemichael, S.; Foster, M.; Török, B.; Török, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2044.
- Borkin, D.; Morzhina, E.; Datta, S.; Rudnitskaya, A.; Sood, A.; Török, M.; Török, B. *Org. Biomol. Chem.* **2011**, *9*, 1394.
- Török, B.; Sood, A.; Bag, S.; Tulsan, R.; Ghosh, S.; Borkin, D.; Kennedy, A. R.; Melanson, M.; Madden, R.; Zhou, W.; LeVine, H., III; Török, M. *Biochemistry* **2013**, *52*, 1137.
- Bag, S.; Ghosh, S.; Tulsan, R.; Sood, A.; Zhou, W.; Schifone, C.; Foster, M.; LeVine, H., III; Török, B.; Török, M. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2614.
- Henry, R. J. *Bacteriol. Rev.* **1943**, *7*, 175.
- Moeker, J.; Peat, T. S.; Bornaghi, L. F.; Vullo, D.; Supuran, C. T.; Poulsen, S. A. *J. Med. Chem.* **2014**, *57*, 3522.
- Kumar, S. Y. C.; Malviya, M.; Chandra, N. S. J. N.; Sadashiva, C. T.; Kumar, A. C. S.; Prasad, B. S. B.; Prasanna, D. S.; Subhash, M. N.; Rangappa, K. S. *Bioorg. Med. Chem.* **2008**, *16*, 5157.
- Sterrette J. R. US2011/0071199 A1, 2011.
- Madin, A.; Redgill, M. P. US 7,144,910 B2, 2003.
- Kreft, A. F.; Resnick, L.; Mayer, S. C.; Diamantidis, G.; Cole, D. C.; Harrison, B. L.; Hoke, M.; Wang, T.; Galante, R. J. US 7,858,658 B2, 2010.
- Lin, S.-J.; Shiao, Y.-J.; Chi, C.-W.; Yang, L. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1173.
- Kawakami, Y.; Inoue, A.; Kawai, T.; Wakita, M.; Sugimoto, H.; Hopfinger, A. J. *Bioorg. Med. Chem. Lett.* **1996**, *4*, 1429; Kryger, G.; Silman, I.; Sussman, J. L. *Structure* **1999**, *7*, 297; Nightingale, L. *JAMA* **1997**, *277*, 10.
- Naiki, H.; Higuchi, K.; Hosokawa, M.; Takeda, T. *Anal. Biochem.* **1989**, *177*, 244; LeVine, H., III. *Protein Sci.* **1993**, *2*, 404; Nilsson, M. R. *Methods* **2004**, *34*, 151.
- Török, B.; Sood, A.; Bag, S.; Kulkarni, A.; Borkin, D.; Lawler, E.; Dasgupta, S.; Landge, S. M.; Abid, M.; Zhou, W.; Foster, M.; LeVine, H., III; Török, M. *ChemMedChem* **2012**, *7*, 910.
- LeVine, H., III. *Anal. Biochem.* **2006**, *356*, 265; LeVine, H., III; Ding, Q.; Walker, J. A.; Voss, R. S.; Augelli-Szafran, C. E. *Neurosci. Lett.* **2009**, *465*, 99.
- Balsano, C.; Alisi, A. *Curr. Pharm. Des.* **2009**, *15*, 3063.
- Ono, K.; Condrón, M. M.; Ho, L.; Wang, J.; Zhao, W.; Pasinetti, G. M.; Teplow, D. B. *J. Biol. Chem.* **2008**, *283*, 32176.
- Greenblatt, H.; Kryger, G.; Lewis, T.; Silman, I.; Sussman, J. L. *FEBS Lett.* **1999**, *463*, 321.
- Sussman, J. L.; Harel, M.; Frolow, F.; Oefner, C.; Goldman, A.; Toker, L.; Silman, I. *Science* **1999**, *253*, 872; Zhou, X.; Wang, X.; Wang, T.; Kong, L. *Bioorg. Med. Chem.* **2008**, *16*, 8011.
- Necula, M.; Kaye, R.; Milton, S.; Glabe, C. G. *J. Biol. Chem.* **2007**, *282*, 10311.