Bioorganic & Medicinal Chemistry 16 (2008) 7177–7184

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Synthesis of *scyllo*-inositol derivatives and their effects on amyloid beta peptide aggregation

Yedi Sun [a], Guohua Zhang [a], Cheryl A. Hawkes [b,c], James E. Shaw [b,c], JoAnne McLaurin [b,c], Mark Nitz [a,*]

[a] Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ont., Canada M5S 3H6
[b] Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ont., Canada
[c] Department of Laboratory Medicine and Pathobiology, University of Toronto, Ont., Canada

ARTICLE INFO

Article history:
Received 12 May 2008
Revised 19 June 2008
Accepted 24 June 2008
Available online 26 June 2008

Keywords:
scyllo-Inositol
Alzheimer's
Amyloid
Inositol
Aβ peptide
Aggregation inhibitors

ABSTRACT

scyllo-Inositol has shown promise as a potential therapeutic for Alzheimer's disease, by directly interacting with the amyloid β (Aβ) peptide to inhibit Aβ42 fiber formation. To explore the molecular details of the inositol-Aβ42 interaction, a series of *scyllo*-inositol derivatives have been synthesized which contain deoxy, fluoro, chloro, and methoxy substitutions. The effects of these compounds on the aggregation cascade of Aβ42 have been investigated using electron microscopy (EM). EM analyses revealed that the 1-deoxy-1-fluoro- and 1,4-dimethyl-*scyllo*-inositols significantly inhibit the formation of Aβ42 fibers. The other derivatives showed some alterations in the morphology of the Aβ42 fibers produced. These findings indicate the importance of all of the hydroxyl groups of *scyllo*-inositol for complete inhibition of Aβ aggregation.

1. Introduction

Alzheimer's disease (AD), the most common cause of dementia in individuals over the age of 65, is a progressive neurodegenerative disorder characterized clinically by cognitive impairment and memory loss.[1] Many research groups have sought to design compounds which inhibit or disrupt Aβ peptide aggregation as a therapeutic strategy to treat AD.[2] These compounds have a range of structures including a large number of polyphenols, peptides, tetracyclines, copper, and zinc chelators as well as many aromatic heterocycles.[3–8]

Previous work from our laboratory has demonstrated that *scyllo*-inositol is able to directly interact with the Aβ42 peptide, the most neurotoxic component of the senile plaques that are deposited in Alzheimer's disease (AD).[9–11] Results from in vitro experiments have shown that incubation of randomly structured Aβ42 with *scyllo*-inositol induced an immediate change in the secondary structure of the peptide, stabilized small Aβ oligomers and completely blocked fibril formation.[10] Oral administration of *scyllo*-inositol in the TgCRND8 mouse model of AD, inhibited Aβ aggregation, attenuated Aβ-induced impairments in spatial memory, reduced the cerebral Aβ pathology, and decreased the rate of mortality.[12] These therapeutic effects occurred regardless of whether the compound was given before or well after the onset of the AD-like phenotype, suggesting that *scyllo*-inositol acts to both prevent plaque formation and disrupt pre-formed Aβ fibers.[12]

To date, the molecular details of the inositol binding site within the Aβ42 peptide remain unknown. Of the 12 stereochemically related inositols and inososes explored for their ability to inhibit Aβ42 fiber formation and Aβ42 cellular toxicity, *scyllo*-inositol remains the most potent compound.[10,11] Given the promise of *scyllo*-inositol as a potential therapeutic agent, and the specificity of the Aβ-*scyllo*-inositol interaction, we set out to explore the Aβ42-*scyllo*-inositol structure–function relationship by studying the effect of closely related *scyllo*-inositol derivatives on $A\beta_{42}$ fiber formation. A series of *scyllo*-inositol derivatives were synthesized in which one or two of the hydroxyl groups were replaced with fluoro, chloro, methoxy or hydrogen substituents (Fig. 1). The approach of replacing hydroxyl groups on carbohydrate ligands with these substituents has provided information about hydrogen bonding requirements, hydrophobicity, and steric interactions of a given hydroxyl group in the carbohydrate binding site of lectins and antibodies.[13–15] In this initial study, the effects of each *scyllo*-inositol derivative on Aβ42 aggregation were assessed by electron microscopy (EM). We report here that while all modifications alter the *scyllo*-inositol-Aβ42 interaction, a single fluoro substitution, and the 1,4-dimethylation, of *scyllo*-inositol provides compounds which remain effective in preventing Aβ42 fiber formation.

* Corresponding author.
E-mail address: mnitz@chem.utoronto.ca (M. Nitz).

0968-0896/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2008.06.045

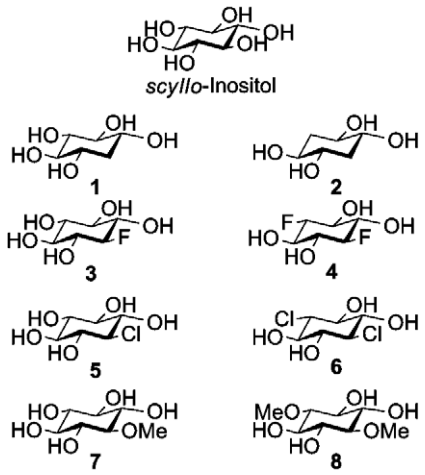
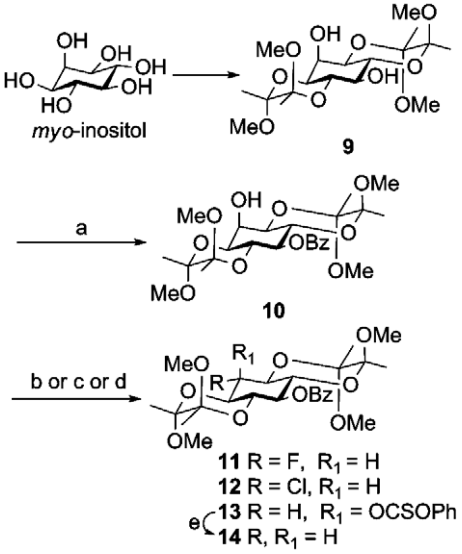


Figure 1. Structures of the synthesized *scyllo*-inositol derivatives; 1-deoxy-*scyllo*-inositol (**1**), 1,4-dideoxy-*scyllo*-inositol (**2**), 1-deoxy-1-fluoro-*scyllo*-inositol (**3**), 1, 4-dideoxy-1,4-difluoro-*scyllo*-inositol (**4**), 1-chloro-1-deoxy-*scyllo*-inositol (**5**), 1,4-dichloro-1,4-dideoxy-*scyllo*-inositol (**6**), 1-*O*-methyl-*scyllo*-inositol (**7**), and 1,4-di-*O*-methyl-*scyllo*-inositol (**8**).

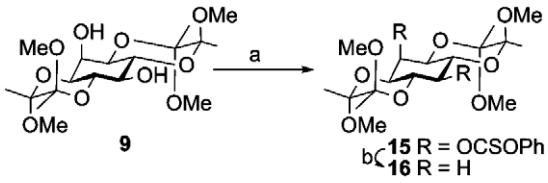
2. Results

2.1. Synthesis of *scyllo*-inositol derivatives

myo-Inositol was used as the starting material for the synthesis of all of the *scyllo*-inositol derivatives **1–8** (Fig. 1). The key bisacetal protected diol **9** was synthesized from *myo*-inositol using the previously reported condensation with 2,3-butanedione.[16,17] This persistent protecting group strategy allowed rapid access to the inositol derivatives **1**–**8**. Selective benzoylation of the equatorial alcohol of diol **9** gave the protected alcohol **10** in 64% yield. Orthogonal functionalization of the alcohol **10** gave access to the mono-substituted inositols **1**, **3**, and **5**. Direct fluorination or chlorination of **10** with diethylaminosulfur trifluoride (DAST), or phosphorus pentachloride gave compounds **11** and **12** in moderate yield. Formation of the phenyl thiocarbonate **13**, followed by radical promoted deoxygenation, gave the protected 1-deoxy-*scyllo*-inositol



Scheme 1. Reageants and conditions: (a) BzCl, Pyr/CH_2Cl_2, 64%; (b) Et_2NSF_3, toluene, **11**, 62%; (c) PCl_5, Pyr, 0 °C, **12**, 31%; (d) PhOCSCl, Pyr, **13**, 50%; (e) Bu_3SnH, AMBN, toluene, 91%.



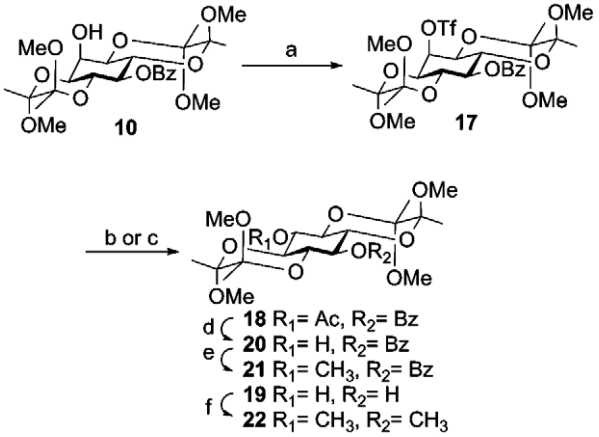
Scheme 2. Reageants: (a) PhOCSCl, pyridine, 84%, (b) Bu_3SnH, AMBN, toluene, 84%.

14 in high yield (Scheme 1). Debenzoylation of compounds **11**, **12**, and **14** with sodium methoxide in methanol followed by acetal cleavage with 95% trifluoroacetic acid yielded the desired *scyllo*-inositol derivatives **1**, **3**, and **5**.

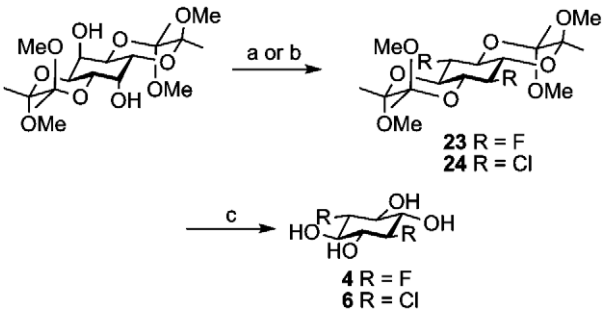
The 1,4-dideoxy-*scyllo*-inositol **2** was synthesized directly in high yield from the bisacetal protected *myo*-inositol derivative **9**. Formation of the bis-thiocarbonate **15** followed by reduction under radical conditions gave compound **16** (Scheme 2). After removal of the bisacetal protecting groups, compound **2** was isolated in high yield.

Methylated *scyllo*-inositol derivatives **7** and **8** were synthesized from the selectively protected *scyllo*-inositol **10**. Treatment of **10** with trifluoromethanesulfonic anhydride gave compound **17**. The selectively protected *scyllo*-inositol **18** was prepared in 91% yield by treatment of the triflate ester **17** with potassium acetate in dimethylacetamide. Selective removal of the sole acetyl protecting group of **18** by treatment with HCl in methanol produced compound **20** in 84% yield. Careful alkylation of compound **20** at 0 °C with methyl iodide gave the protected methyl-inositol derivative **21.** Treatment of the triflate ester **17** with potassium hydrogen carbonate in DMF and water gave triflate displacement and benzoate ester cleavage, yielding the diol **19**. Methylation of the diol **19** gave the protected dimethyl-inositol derivative **22** (Scheme 3). Compounds **7** and **8** were isolated after removal of the protecting groups from compounds **21** and **22** by sequential treatment with sodium methoxide in methanol followed by 95% TFA.

The synthetic route to produce the dichloro- and difluoro-*scyllo*-inositol derivatives **4** and **6** is illustrated in Scheme 4. Previously, a facile route to produce *neo*-inositol was developed by Riley et al., using the same protecting group strategy as employed here.[18] Direct fluorination of the selectively protected *neo*-inositol derivative with DAST proceeded with inversion of stereochemistry to give the protected 1,4-difluoro-*scyllo*-inositol derivative **23**. Chlorination of the acetal protected *neo*-inositol was achieved by treatment with sulfuryl chloride, yielding the protected dichloro *scyllo*-inositol



Scheme 3. Reageants and conditions: (a) Tf_2O, CH_2Cl_2/pyridine, 0 °C, 70%; (b) KOAc, DMA, 70 °C, **18,** 91%; (c) $KHCO_3$, H_2O/DMF, 80 °C, **19,** 86%; (d) AcCl, CH_2Cl_2/CH_3OH, rt, 84%; (e) CH_3I, NaH, DMF, 0 °C, 91%; (f) CH_3I, NaH, DMF, 91%.



Scheme 4. Reageants: (a) Et_2NSF_3, CH_2Cl_2, **23**; (b) SO_2Cl_2, pyridine, **24**; (c) 95% TFA.

mimic **24** in moderate yield. It was found that higher yields of the dichloro inositol derivative **24** could be obtained with sulfuryl chloride than with phosphorus pentachloride. Purification of compounds **23** and **24** could not be achieved with silica gel chromatography due to the low solubility of the compounds in low boiling point organic solvents. After removal of the bisacetal protecting groups with 95% TFA, compounds **4** and **6** could be crystallized from ethanol/water mixtures.

2.2. Effects of inositol derivatives on Aβ aggregation

To evaluate the effects of the inositol derivatives on the morphology of Aβ42 aggregates, the synthesized compounds were incubated with randomly structured (as determined by circular dichroism) Aβ42 for 7 days and the resulting aggregates were analyzed by negative-stain EM (Fig. 2). Although this simple assay does not provide a detailed picture of the action of these potential AD therapeutics, it does reveal which compounds have similar effects to *scyllo*-inositol on the formation of Aβ42 aggregates and fibers.

As previously reported, co-incubation of Aβ42 (5 μM) with *scyllo*-inositol (3 mM), completely prevented fiber formation (Fig. 2B). Platinum-carbon shadowing EM experiments have previously shown that *scyllo*-inositol stabilizes Aβ42 in small micellar aggregates as is most likely the case in the current experiment.[19]

A wide range of effects were observed on the morphology of the Aβ42 aggregates with the synthesized *scyllo*-inositol derivatives **1**–**8** (5 mM) (Fig. 2). The synthesized compounds were not as potent as *scyllo*-inositol at inhibiting fiber formation, and thus a higher concentration (5 mM) of inhibitor was used in the aggregation assays.

We first examined how reduction in the number of hydroxyl groups of *scyllo*-inositol affects its ability to prevent Aβ42 fiber formation. Incubation of Aβ42 with 1-deoxy-*scyllo*-inositol (**1**) produced fibers that were similar in length and width to those formed in samples containing only Aβ42 (Fig. 2C). A similar lack of effect on fiber morphology was also noted in Aβ42 preparations incubated with 1,4-dideoxy-*scyllo*-inositol (**2**) [Fig 2D]. These results suggest that the removal of substituents from *scyllo*-inositol results in compounds that are not effective in preventing fiber formation during the Aβ42 aggregation cascade.

Next we examined the effects of the fluorinated *scyllo*-inositol derivatives **3** and **4**. These were the most conservative of our substitutions considering the similar size and polarity of fluorine when compared to oxygen and in light of the ability of fluorine to act as a weak hydrogen bond acceptor. Incubation of Aβ42 and 1-deoxy-1-fluoro-*scyllo*-inositol (**3**) over a 7 day period produced a population of small amorphous aggregates. These aggregates were morphologically distinct from those observed with *scyllo*-inositol, but are of similar shape to those previously observed with platinum-carbon shadowing of the *scyllo*-inositol-Aβ42 aggregates[19] (Fig. 2E). When a second fluorine atom was introduced into the structure to give 1,4-dideoxy-1,4-difluoro-*scyllo*-inositol (**4**) Aβ42 fibers were produced during the aggregation which were mixed with amorphous aggregates (Fig. 2F).

The effect of the chlorine substitutions, which are less polar than the fluoro derivatives, on Aβ42 aggregation was also investigated. Incubation of random coil Aβ42 in the presence of 1-chloro-1-deoxy-*scyllo*-inositol (**5**) produced poorly formed fibers suggesting weak inhibition of fiber formation (Fig. 2G). The fibers formed during incubation with 1,4-dideoxy-1,4-dichloro-*scyllo*-inositol (**6**) were as robust as those formed with Aβ42 alone, however more small protofibrils were noted, suggesting a weaker interaction with Aβ42 than that observed with a single chlorine substitution (Fig 2H).

Methylation of the hydroxyl groups on *scyllo*-inositol introduces a larger hydrophobic group into the structure. The methyl substituent should probe the periphery of the Aβ42-inositol binding site for potential hydrophobic interactions. Methyl substituents have previously lead to higher affinity interactions between carbohydrates and their cognate binding proteins.[20] As seen in Fig. 2I, fibers produced after 7 days of incubation of Aβ42 with 1-*O*-methyl-*scyllo*-inositol (**7**) resembled those seen in control samples and included a heterogeneous mixture of intermediate and short fiber fragments. The related compound 1,4-di-*O*-methyl-*scyllo*-inositol (**8**) had a more pronounced effect on Aβ42 aggregation, in that it produced a more homogenous population of small amorphous aggregates and no fibers were detected (Fig. 2J). These results suggest that compound **8** dramatically altered the aggregation cascade of Aβ42 away from fiber formation.

3. Discussion

The synthesis of compounds **1**,[21] **2**,[22] **3**,[23] **5**,[24] and **7**[25] have been described previously by alternate synthetic routes. We developed the streamlined synthesis reported here to give the most direct route to a wide range of *scyllo*-inositol analogues including compounds **1**–**8** desired for our on-going investigations of the interaction between inositols and Aβ42.

We have previously demonstrated, and replicated in this report, that incubation of *scyllo*-inositol with randomly structured Aβ42 peptides inhibited fiber formation.[10] As a first step toward determining the structure–function relationship of this interaction, we synthesized eight *scyllo*-inositol derivatives, each bearing one or two hydroxyl group substitutions and evaluated the morphology of Aβ42 aggregates formed in their presence. Analyses using EM revealed minor or no change in the morphology of the Aβ42 fibers formed in the presence of the deoxy-, dideoxy-, difluoro-, dichloro-, and methyl-*scyllo*-inositol derivatives (**1**, **2**, **4**, **6, and 7**). 1-Deoxy-1-chloro-*scyllo*-inositol (**5**) had an intermediate effect on Aβ42 fibrillization and the fluoro- and dimethoxy-*scyllo*-inositol derivatives (**3** and **8**) had the strongest effects on the morphology of the Aβ42 aggregates produced.

The majority of interactions between highly hydroxylated compounds, such as the inositols or carbohydrates, and proteins are mediated through the directionality of hydrogen bonding and hydrophobic interactions with the faces of the rings. In polyol-protein interactions, if hydroxyl groups which do not form hydrogen bonds to the protein surface are replaced by less polar groups (i.e., methoxy or chloro substituents), similar or higher affinity interactions are often observed. If key hydroxyl groups that form direct hydrogen bonds to the protein are replaced, the affinity of the interaction is dramatically reduced. In this series of compounds (**1**–**8**) substitutions were chosen that would have minimal steric implications while still probing the hydrogen bonding and polarity of the surroundings of a given hydroxyl substituent. It was ex-

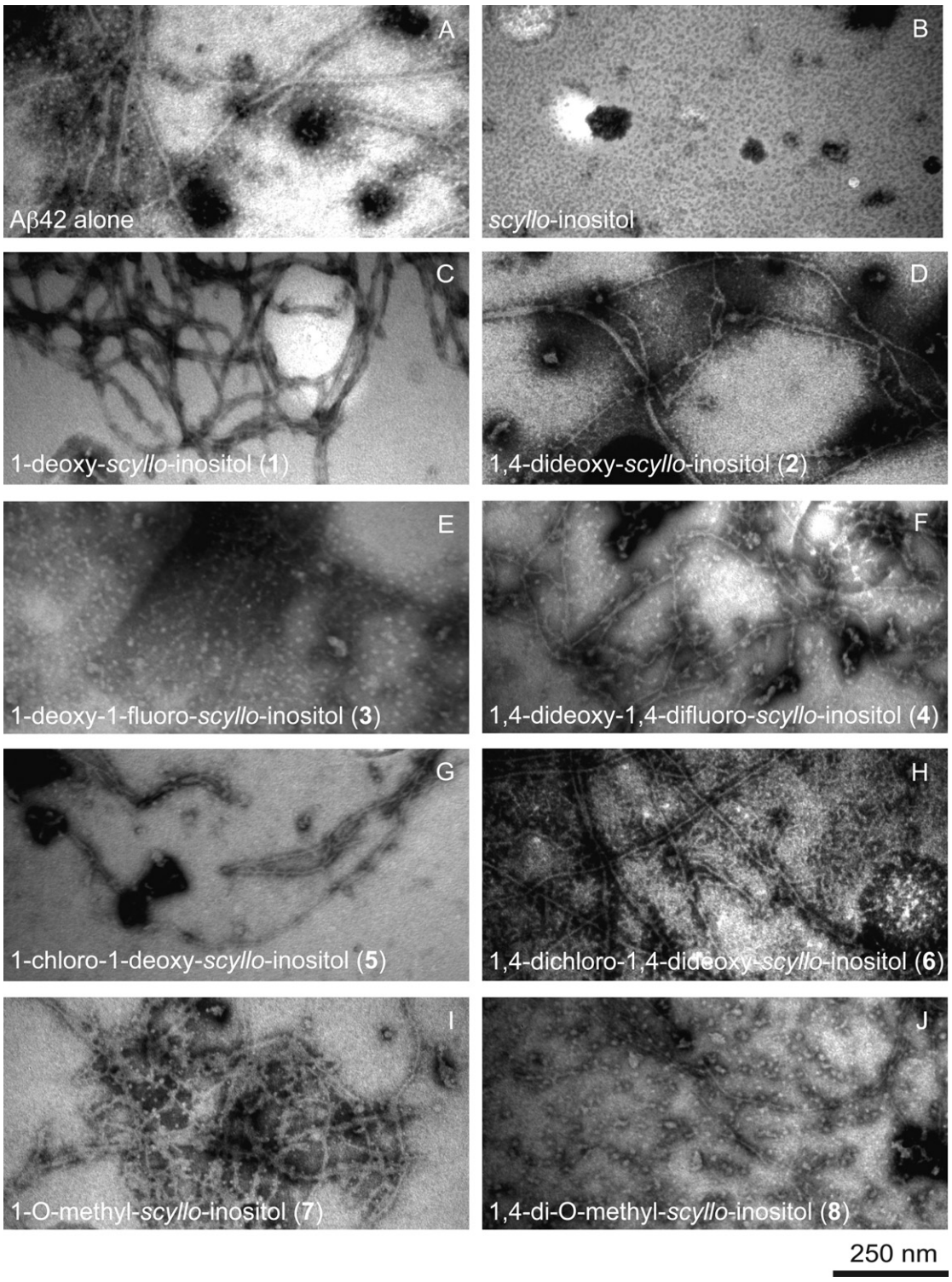


Figure 2. Negative-stain electron microscopy of Aβ42 (5 μM) in the presence and absence of inositol derivatives. A) $A\beta_{42}$ alone, (B) *scyllo*-inositol (3 mM); (C) 1-deoxy-*scyllo*-inositol (**1**) (5 mM); (D) 1,4-dideoxy-*scyllo*-inositol (**2**) (5 mM); (E) 1-deoxy-1-fluoro-*scyllo*-inositol (**3**) (5 mM); (F) 1,4-dideoxy-1,4-difluoro-*scyllo*-inositol (**4**) (5 mM); (G) 1-chloro-1-deoxy-*scyllo*-inositol (**5**) (5 mM); (H) 1,4-dichloro-1,4-dideoxy-*scyllo*-inositol (**6**) (5 mM); (I) 1-*O*-methyl-*scyllo*-inositol (**7**) (5 mM); (J) 1,4-di-*O*-methyl-*scyllo*-inositol (**8**) (5 mM).

pected that at least one of the hydroxyl groups of *scyllo*-inositol would not make hydrogen bond contacts to Aβ42, and thus the removal or methylation of a single hydroxyl group would lead to compounds with similar effects on Aβ42 aggregation to *scyllo*-inositol. Surprisingly, our data suggest that none of the hydroxyl groups of *scyllo*-inositol can be replaced with a smaller hydrogen atom or a larger more hydrophobic methoxy substituent without significantly reducing the compounds ability to block Aβ42 fiber formation. Substitution of a single hydroxyl group with a relatively conservative chloro or fluoro substituent leads to compounds that maintain moderate to strong effects on the morphology the Aβ42 aggregates, but the introduction of a second chloro or fluoro substituent is not tolerated. In contrast to the single methyl substituent in compound **7**, a dramatic effect was seen with the Aβ42 samples

incubated with 1,4-di-*O*-methyl-*scyllo*-inostiol (**8**). These data indicate that the second methyl group introduced additional favorable hydrophobic interactions not present with 1-*O*-methyl-*scyllo*-inositol. This result suggests further simultaneous elaborations at the 1 and 4 positions of *scyllo*-inositol with hydrophobic groups may lead to new aggregation inhibitors.

4. Conclusions

In conclusion, these studies provide a practical synthetic route to a series of *scyllo*-inositol derivatives. The preliminary data on the effects of these compounds on Aβ aggregation suggest that only the most conservative single hydroxyl substitutions are tolerated, thus 1-deoxy-1-fluoro-*scyllo*-inositol behaves similarly to the parent compound. But, the introduction of two hydrophobic substituents as in 1,4-dimethyl-*scyllo*-inostiol (**8**) also provides a potent compound for altering the Aβ42 aggregation cascade. This substitution pattern provides a useful lead in generating new inositol based Aβ peptide aggregation inhibitors.

5. Experimental

5.1. Generalities for organic synthesis

Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Varian Mercury 400 or Varian Mercury 300 NMR spectrometers. Chemical shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents ($CHCl_3$: δ 7.27, CD_2HOD: δ 3.31). Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvents ($CDCl_3$: δ 77.0, CD_3OD: δ 49.05). Data are represented as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), integration, coupling constant, and assignment. Silica column chromatography was performed using silica gel (230–400 mesh) from Silicycle.

5.2. Synthesis of compounds 1–8

5.2.1. 5-*O*-Benzoyl-1,6:3,4-bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-*myo*-inositol (10)

To a stirred suspension of diol **9** (1.00 g, 2.45 mmol, previously dried at 100 °C under vacuum for 2.5 h), in dry CH_2Cl_2 (20 mL) and dry pyridine (20 mL) was added benzoyl chloride (0.30 mL, 2.6 mmol) dropwise at 0 °C. The reaction mixture was allowed to stir for 14 h. The solution was diluted with CH_2Cl_2 (200 mL), washed with 1 M HCl (2× 150 mL) and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (pentane/ethyl acetate = 3:1) of the residue gave compound **10** as a white solid (0.80 g, 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.33 (s, 6H), 3.14 (s, 6H), 3.27 (s, 6H), 3.73 (dd, 2H, *J* = 2.8, 10 Hz), 4.10 (t, 1H, *J* = 2.8 Hz), 4.26 (dd, 2H, *J* = 10, 10 Hz), 5.40 (t, 1H, *J* = 10 Hz), 7.45 (dd, 2H, *J* = 7.2, 8.0 Hz), 7.56 (t, 1H, *J* = 7.2 Hz), 8.07 (d, 2H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 165.67, 133.29, 130.79, 130.07, 128.87, 100.58, 99.79, 71.36, 69.40, 69.06, 67.72, 48.51, 48.09, 18.13, 18.09; HRMS *m*/*z* (ESI) calculated for $C_{25}H_{36}O_{11}Na$ $(M+Na)^+$ 535.2149; found: 535.2151.

5.2.2. 2-*O*-Benzoyl-1,6:3,4-bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-5-fluoro-*scyllo*-inositol (11)

To a stirred solution of compound **10** (300 mg, 0.59 mmol) in dry toluene (30 mL), maintained under an atmosphere of dry nitrogen, was added 4-dimethylaminopyridine (147 mg, 1.20 mmol). The solution was cooled to −30 °C, and diethylaminosulfur trifluoride (0.16 mL, 1.2 mmol) was added dropwise. The mixture was warmed to room temperature and then heated for 2 h at 65 °C under nitrogen. The reaction was then cooled to −30 °C, saturated aqueous sodium bicarbonate (10 mL) was added, and the reaction was allowed to warm to room temperature. This mixture was then added into an ethyl acetate/water mixture (2:1, 60 mL), and the organic layer was separated and dried over $MgSO_4$. Evaporation of the solvent gave a yellow oil that was purified by column chromatography using pentane/ethyl acetate (6:1) to give **11** (149 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2H, *J* = 8.0 Hz), 7.57 (t, 1H, *J* = 7.5 Hz), 7.45 (dd, 2H, J = 7.5, 8.0 Hz) 5.45 (t, 1H, *J* = 9.9 Hz), 4.58 (dt, 1H, *J* = 9.2, 53.6 Hz), 3.96–3.87 (m, 3H), 3.82 (dd, 2H, *J* = 10.1, 10.1 Hz), 3.28 (s, 6H), 3.14 (s, 6H), 1.32 (s, 6H), 1.21 (s, 6H); ^{13}C NMR ($CDCl_3$ δ 164.90, 132.94, 129.51, 128.41, 99.50, 99.41, 89.72, 87.85 (*J* = 187.10 Hz), 69.52,69.20, 69.01, 67.83, 67.72, 47.91, 47.67, 17.44, 17.42; HRMS *m*/*z* (ESI) calculated for $C_{25}H_{35}$ FO_{10} $(M+Na)^+$ 537.2106; found: 537.2112.

5.2.3. 2-*O*-Benzoyl-1,6:3,4-bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-5-chloro-*scyllo*-inositol (12)

To a stirred solution of **10** (300 mg, 0.59 mmol) in pyridine (15 mL) at 0 °C was added PCl_5 (246 mg, 1.18 mmol) in three portions over 15 min. After stirring for 1 h at 0 °C followed by 3 h at 22 °C, the mixture was poured onto ice-water (50 g) containing $NaHCO_3$ (3 g). The mixture was allowed to stir overnight and then was extracted with CH_2Cl_2 (2× 60 mL). The organic layer was washed with 5% aqueous $NaHCO_3$, water, brine, and then dried using Na_2SO_4. The solvent was removed in vacuo to leave a yellow solid, which was purified on a silica gel column (pentane/ethyl acetate = 5:1) to give a white solid **12** (109 mg, 31%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 2 H, *J* = 7.5 Hz), 7.57 (t, 1H, *J* = 7.4 Hz,), 7.45 (dd, 2H, J = 7.4, 7.6 Hz), 5.44 (t, 1H, *J* = 9.3 Hz), 3.89–3.75 (m, 5H), 3.32 (s, 6H), 3.14 (s, 6H), 1.33 (s, 6H), 1.21 (s, 6H); ^{13}C NMR ($CDCl_3$ δ 169.68, 133.11, 130.29, 129.77, 128.63, 99.91, 99.44, 70.06, 69.70, 68.96, 47.97, 47.78, 17.45, 17.35; HRMS *m*/*z* (ESI) calculated for $C_{26}H_{38}O_{11}Na$ $(M+Na)^+$ 553.1810; found: 553.1819.

5.2.4. 1,6:3,4-Bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-2-*O*-phenylthionoformate-5-*O*-benzoyl-*myo*-inositol (13)

To a stirred suspension of **10** (2.0 g, 3.9 mmol) in dry CH_2Cl_2 (20 mL) and dry pyridine (20 mL) was added *O*-phenyl chlorothionoformate (0.79 mL, 5.8 mmol). The reaction mixture was allowed to stir for 2.5 h. The solution was diluted with CH_2Cl_2 (200 mL), washed with 1 M HCl (2× 150 mL) and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (pentane/ethyl acetate = 4.5:1) of the residue yielded compound **13** as white solid (1.29 g, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 6H), 1.28 (s, 6H), 3.10 (s, 6H), 3.27 (s, 6H), 3.90 (dd, 2H, *J* = 2.4, 10.4 Hz), 3.99 (dd, 2H, *J* = 10.4, 10.3 Hz), 5.38 (t, 1H, *J* = 10.3 Hz), 6.05 (t, 1H, *J* = 2.4 Hz), 7.22 (m, 2H), 7.35 (t, 1H, *J* = 9.6 Hz), 7.44–7.50 (m, 4H), 7.57 (t, 1H, *J* = 9.6 Hz), 8.04 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 194.19, 165.20, 153.71, 133.06, 130.29, 129.73, 129.65, 128.56, 126.39, 122.08, 100.22, 99.56, 79.49, 70.64, 67.98, 67.44, 48.33, 47.85, 17.74, 17.64; HRMS *m*/*z* (ESI) calculated for $C_{32}H_{40}O_{12}NaS$ $(M+Na)^+$ 671.2132; found: 671.2124.

5.2.5. 1,6:3,4-Bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-2-*O*-benzoyl-5-deoxy-*scyllo*-inositol (14)

To a stirred suspension of **13** (0.60 g, 0.93 mmol) in toluene (30 mL) was added tributyltin hydride (0.76 mL, 2.8 mmol), and 2,2′-*azobis*(2-methylbutyronitrile) (AMBN) (50 mg). The mixture was heated under reflux for 2.5 h and then allowed to cool to rt. The solution was concentrated under reduced pressure. Silica gel chromatography (pentane/ethyl acetate = 7:1) of the residue gave

compound **14** as white solid (0.42 g, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.29 (s, 6H), 1.67–1.75 (m, 1H), 1.98 (td, 1H, J = 12, 3.6 Hz), 3.14 (s, 6H), 3.27 (s, 6H), 3.75 (m, 4H), 5.35 (t, 1H, J = 5.6 Hz), 7.45 (dd, 2H, J = 8.0, 7.6 Hz), 7.56 (t, 1H, J = 7.6 Hz), 8.06 (d, 2H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 165.30, 132.98, 130.52, 129.76, 128.58, 99.73, 99.62, 72.35, 70.79, 65.75, 48.15, 47.80, 31.40, 17.87, 17.81; HRMS m/z (ESI) calculated for $C_{25}H_{36}O_{10}Na$ (M+Na)$^+$ 519.2200; found: 519.2224.

5.2.6. 1,6:3,4-Bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-2,5-*O*-phenylthionoformate-*myo*-inositol (15)

To a stirred suspension of diol **9** (1.00 g, 2.45 mmol) previously dried at 100 °C under vacuum, in dry CH_2Cl_2 (20 mL) and dry pyridine (20 mL) was added *O*-phenyl chlorothionoformate (0.99 mL, 7.3 mmol). The reaction mixture was allowed to stir for 14 h. The solution was diluted with CH_2Cl_2 (20 mL), washed with 1 M HCl (2× 150 mL) and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (pentane/ethyl acetate = 8:1) of the residue gave compound **15** as a white solid (1.4 g, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 6H), 1.31 (s, 6H), 3.26 (s, 6H), 3.28 (s, 6H), 3.89 (dd, 2H, J = 2.4, 10.2 Hz), 4.09 (dd, 2H, J = 10.1, 9.9 Hz), 5.63 (t, 1H, J = 9.9 Hz), 6.04 (t, 1H, J = 2.4 Hz), 7.10 (d, 2H, J = 8.1 Hz), 7.20 (d, 2H, J = 8.1 Hz), 7.31 (dd, 2H, J = 6, 2.1 Hz), 7.40–7.45 (m, 4H); ^{13}C NMR ($CDCl_3$) δ, 194.54, 194.41, 153.75, 153.66, 129.64, 129.65, 126.72, 126.56, 122.02, 121.94, 100.32, 99.68, 79.97, 79.05, 68.01, 67.26, 48.41, 48.12, 17.81, 17.68; HRMS m/z (ESI) calculated for $C_{32}H_{40}O_{12}NaS_2$ (M+Na)$^+$ 703.1853; found: 703.1873.

5.2.7. 1,6:3,4-Bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-2,5-dideoxy-*scyllo*-inositol (16)

To a stirred suspension of **15** (0.75 g, 1.1 mmol) in toluene (60 mL) was added tributyltin hydride (1.75 mL, 6.51 mmol) and 2,2′-*azobis*(2-methylbutyronitrile) (AMBN) (100 mg). The mixture was heated under reflux for 2.5 h and then allowed to cool to rt. The solution was then concentrated under reduced pressure. Silica gel chromatography (pentane/ethyl acetate = 8:1) of the residue gave compound **16** as white solid (0.40 g, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 12H), 1.56 (m, 2H), 1.91–1.94 (m, 2H), 3.27 (s, 12H), 3.56–3.57 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 100.10, 69.61, 48.59, 30.00, 18.45; HRMS m/z (ESI) calculated for $C_{18}H_{40}O_8Na$ (M+Na)$^+$ 399.1989. Found: 399.2010.

5.2.8. 1,6:3,4-Bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-2-*O*-trifluoromethanesulphonyl-5-*O*-benzoyl-*myo*-inositol (17)

To a stirred suspension of **10** (2.5 g, 4.9 mmol) in dry CH_2Cl_2 (30 mL) and dry pyridine (1.75 mL) was added trifluoromethanesulfonic anhydride (1.75 mL, 9.76 mmol) under nitrogen at −78 °C. The reaction mixture was then allowed to stir for 2.5 h at 0 °C. The solution was diluted with CH_2Cl_2 (250 mL), washed with water (3× 150 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (pentane/ethyl acetate = 3:1) of the residue gave compound **17** as a white solid (2.2 g, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 6H), 1.28 (s, 6H), 3.13 (s, 6H), 3.27 (s, 6H), 3.88 (dd, 2H, J = 2.4, 10 Hz), 4.15 (dd, 2H, J = 10, 10 Hz), 5.09 (t, 1H, J = 2.4 Hz), 5.43 (t, 1H, J = 10 Hz), 7.46 (dd, 2H, J = 7.8, 7.4 Hz), 7.58 (t, 1H, J = 7.4 Hz), 8.08 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, δ): 165.26, 133.23, 130.08, 129.83, 128.67, 100.52, 99.69, 84.06, 70.07, 67.33, 66.17, 48.48, 48.01, 17.70, 17.31; HRMS m/z (ESI) calculated for $C_{26}H_{35}O_{13}F_3NaS$ (M+Na)$^+$ 677.1642; found: 667.1646.

5.2.9. 2-*O*-Acetyl-5-*O*-benzoyl-1,6:3,4-bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-*scyllo*-inositol (18)

A mixture of compound **17** (500 mg, 0.78 mmol) and KOAc (100 mg, 1.0 mmol) in dimethylacetamide (30 mL) was stirred at 60 °C for 1 h and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (pentane/ethyl acetate = 4:1) of the residue gave the compound **18** (394 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2H, J = 7.3 Hz), 7.56 (t, 1H, J = 7.4 Hz), 7.44 (dd, 2H, J = 7.4, 7.8 Hz), 5.42 (t, 1H, J = 9.7 Hz), 5.20 (t, 1H, J = 9.7 Hz), 3.85 (dd, 2H, J = 10.0 Hz, 9.7 Hz), 3.77 (dd, 2H, J = 9.7 Hz, 10.0 Hz), 3.21 (s, 6H), 3.11 (s, 6H), 2.11 (s, 3H), 1.23 (s, 6H), 1.18 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 169.76, 155.40, 133.11, 130.29, 129.77, 128.63, 99.64, 99.61, 99.61, 70.06, 68.96, 47.76, 47.76, 21.00, 17.70, 17.68; HRMS m/z (ESI) calculated for $C_{27}H_{38}O_{12}Na$ (M+Na)$^+$ 577.2255; found: 577.2265.

5.2.10. 1,6:3,4-Bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-*scyllo*-inositol (19)

A mixture of compound **17** (500 mg, 0.78 mmol) and $KHCO_3$ (155 mg, 1.55 mmol) in DMF/H_2O = 2:1 (50 mL) was stirred at 80 °C for 1 h and then concentrated under reduced pressure. Recrystallization of the residue from a mixture of methanol/dichloromethane gave compound **19** (274 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (br, 2H), 4.04 (br, 4H), 3.27 (s, 12H), 1.34 (s 12H); ^{13}C NMR ($CDCl_3$ δ 99.83, 66.69, 48.04, 47.96, 17.74; HRMS m/z (ESI) calculated for $C_{18}H_{32}O_{10}Na$ (M+Na)$^+$ 431.1887; found: 431.1908.

5.2.11. 5-*O*-Benzoyl-1,6:3,4-bis-[*O*-(2,3-dimethoxybutane-2,3-diyl]-*scyllo*-inositol (20)

To a stirred solution of **18** (400 mg, 0.72 mmol) in CH_3OH (100 mL), acetyl chloride (1.0 mL, 14 mmol) was added dropwise, and the mixture was stirred at rt overnight. The solution was concentrated after neutralization with triethylamine and purified by column chromatography (pentane/ethyl acetate = 3:1) to yield compound **20** (310 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 2H, J = 7.8 Hz), 7.57 (t, 1H, J = 7.4 Hz), 7.43 (dd, 2H, J = 7.4, 7.8 Hz), 5.43 (t, 1H, J = 9.8 Hz), 3.83–3.77 (m, 3H), 3.69 (dd, 2H, J = 9.8, 9.7 Hz), 3.29 (s, 6H), 3.14 (s, 6H), 1.32 (s, 6H), 1.20 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.97, 132.87, 130.14, 129.55, 128.40, 99.48, 99.47, 70.36, 70.43, 69.35, 47.94, 47.67, 17.57, 17.53; HRMS m/z (ESI) calculated for $C_{25}H_{36}O_{11}Na$ (M+Na)$^+$ 535.2149; found: 535.2154.

5.2.12. 5-*O*-Benzoyl-1,6:3,4-bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-2-methoxy-*scyllo*-inositol (21)

To a solution of compound **20** (300 mg, 0.59 mmol) in DMF (15 mL) were added MeI (74 μL, 1.2 μmol) and NaH (60% dispersion in mineral oil) (25 mg) while stirring at 0 °C. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water. The combined aqueous layers were acidified with dilute HCl and extracted with CH_2Cl_2. The combined CH_2Cl_2 extract was washed successively with cold dilute HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained product was purified by column chromatography (pentane/ethyl acetate = 5:1) to get the corresponding compound **21** (187.0 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2H, J = 7.8 Hz), 7.56 (t, 1H, J = 7.4 Hz), 7.45 (dd, 2H, J = .4, 7.8 Hz), 5.37 (t, 1H, J = 9.7), 3.78 (dd, 2H, J = 10.1, 9.7 Hz), 3.71 (dd, 2H, J = 10.1, 9.2 Hz), 3.66 (s, 3H), 3.39(t, 1H, J = 9.2 Hz), 3.29 (s, 6H), 3.14 (s, 6 H), 1.31 (s, 6H), 1.20 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 169.62, 133.20, 130.43, 129.74, 128.57, 99.53, 99.49, 99.45, 78.59, 71.14, 70.17, 69.04, 48.05, 47.84, 17.90, 17.71; HRMS m/z (ESI) calculated for $C_{26}H_{38}O_{11}Na$ (M+Na)$^+$ 549.2306; found: 549.2311.

5.2.13. 2,5-Di-methoxy-1,6:3,4-bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-*scyllo*-inositol (22)

To a solution of compound **19** (300 mg, 0.73 mmol) in DMF (10 mL) were added MeI (180 μL, 2.9 μmol) and NaH (60% dispersion in mineral oil) (120 mg) while stirring at room temperature.

After 2 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with water. The combined aqueous layers were acidified with dilute HCl and extracted with CH_2Cl_2. The combined CH_2Cl_2 extract was washed successively with cold dilute HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained product was purified by column chromatography (pentane/ethyl acetate = 5:1) to give compound **22** (290 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (br, 4H), 3.58 (br, 2H), 3.56 (s, 6H), 3.24 (s, 12H), 1.27 (s, 12H); ^{13}C NMR ($CDCl_3$ δ 99.07, 78.24, 67.68, 60.80, 47.81, 17.83; HRMS *m*/*z* (ESI) calcd for $C_{20}H_{36}O_{10}Na$ $(M+Na)^+$ 459.2200; found: 459.2216.

5.2.14. 1-Deoxy-*scyllo*-inositol (1)

To a stirred solution of 95% aqueous trifluoroacetic acid (TFA) (4 mL) at 0 °C was added **14** (200 mg, 0.40 mmol). The solid dissolved to give a clear yellow solution. Stirring was continued at 0 °C for 2.5 h. The solution was then concentrated under reduced pressure. Co-evaporation with EtOH removed traces of TFA and butanedione, yielding 1-deoxy-4-*O*-benzoyl-*scyllo*-inositol as a white solid (100 mg, 0.37 mmol, 93%); ^{1}H NMR (300 MHz, D_2O) δ 1.59 (td, 1H, *J* = 12.3, 12.3 Hz), 2.32 (td, 1H, *J* = 4.8, 12.3 Hz), 3.76 (m, 4H), 5.04 (t, 1H, *J* = 9.3 Hz), 7.60 (dd, 2H, *J* = 8.2, 7.2 Hz), 7.75 (t, 1H, *J* = 7.2 Hz), 8.15 (d, 2H, *J* = 8.2 Hz). To a stirred suspension of 1-deoxy-4-*O*-benzoyl-*scyllo*-inositol (100 mg, 0.37 mmol) in MeOH (10 mL) was added Na metal (4 mg). The reaction mixture was allowed to stir for 14 h. The solution was neutralized by Dowex 50 cation-exchange resin and concentrated under reduced pressure to give **1** as white solid (56 mg, 84%). ^{1}H NMR (300 MHz, D_2O) δ 1.49 (td, 1H, *J* = 16, 16 Hz), 2.22 (td, 1H, *J* = 4.2, 16.4 Hz), 3.26–3.36 (m, 3H), 3.54–3.62(m, 2H); ^{13}C NMR (D_2O) δ 76.84, 73.93, 68.44, 36.28; HRMS *m*/*z* (ESI) calculated for $C_6H_{12}O_5Na$ $(M+Na)^+$ 187.0576; found: 187.0583.

5.2.15. 1,4-Dideoxy-*scyllo*-inositol (2)

To a stirred solution of 95% aqueous TFA (2 mL) at 0 °C was added **16** (100 mg, 0.26 mmol). The solid dissolved to give a clear yellow solution. Stirring was continued at 0 °C for 2.5 h. The solution was then concentrated under reduced pressure. Co-evaporation with EtOH removed traces of TFA and the butanedione to give a white solid, which was recrystallized from an ethanol/water mixture to give **2** (21 mg, 54%); ^{1}H NMR (300 MHz, D_2O) δ *1.37–1.41* (m, 2H), 2.17–2.21 (m, 2H), 3.51–3.54 (m, 2H); ^{13}C NMR (D_2O) δ 71.98, 37.10; HRMS *m*/*z* (ESI) calculated for $C_6H_{16}NO_4$ $(M+NH_4)^+$ 166.1073; found: 166.1086.

5.2.16. 1-Deoxy-1-fluoro-*scyllo*-inositol (3)

Compound **11** (100 mg, 0.19 mmol) was dissolved in trifluoroacetic acid (5 mL), and the mixture was stirred at rt overnight. Concentration of the mixture, followed by deacylation in a solution of CH_2Cl_2 (1 mL) and CH_3OH (10 mL) saturated with ammonia at rt for 24 h, gave compound **3** (32 mg, 90%) after concentration under vacuum; ^{1}H NMR (400 MHz, D_2O) δ 4.15 (dt, 1H, *J* = 9.2 Hz, 52.1 Hz), 3.57–3.46 (m, 2H), 3.30–3.19 (m, 3H); ^{13}C NMR ($CDCl_3$ δ 95.82, 93.55 (*J* = 177.90 Hz), 73.27, 72.47, 72.35, 72.71, 71.62; HRMS *m*/*z* (ESI) calculated for $C_6H_{11}O_5FNa$ $(M+Na)^+$ 205.0482; found: 205.0478.

5.2.17. 1,4-*Dideoxy*-1,4-difluoro-*scyllo*-inositol (4)

To a stirred suspension of 1,6:3,4-bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*neo*-inositol[18] (100 mg, 0.245 mmol) in dry dichloromethane (30 mL) was added diethylaminosulfur trifluoride (DAST) (0.32 mL, 2.5 mmol) dropwise under nitrogen at −78 °C. The reaction mixture was allowed to warm to room temperature, and was stirred for 6.5 h. The reaction mixture was then cooled to −78 °C again and water (5 mL) was added dropwise. The solution was diluted with CH_2Cl_2 (150 mL), washed with water (2× 100 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The yellow solid, 1,6:3,4-bis[*O*-(2,3-dimethoxybutane-2,3-diyl)]-2,5-difluoro-*scyllo*-inositol (**23**), was used in the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 12H), 3.28 (s, 12H), 3.75–3.80 (m, 4H), 4.53 (dt, *J* = 53.2, 7.2 Hz); MS *m*/*z* (ESI) found 379.2 $(M-H_2OMe)^+$. To a stirred solution of 95% aqueous TFA (4 mL) at 0 °C was added **23**. The mixture was stirred in an ice bath for 3 h. The solution was then concentrated under reduced pressure. Co-evaporation with EtOH removed traces of TFA and butanedione. Crystallization of the product in a mixture of ethanol/water gave compound **4** (13 mg, overall 28% yield over two steps). ^{1}H NMR (400 MHz, D_2O) δ *3.71–3.76* (m, 4H), 4.29–4.42 (m, 2H); ^{13}C NMR (D_2O) δ 94.31 (dd, 2C, *J* = 179, 1.5 Hz), 70.965–70.667 (m, 4C); HRMS *m*/*z* (ESI) calculated for $C_6H_{10}O_4F_2Na$ $(M+Na)^+$ 207.0439; found: 207.0431.

5.2.18. 1-Chloro-1-deoxy-*scyllo*-inositol (5)

Compound **5** (34 mg, 92%) was obtained from compound **12** (100 mg, 0.19 mmol) using the same procedure as for compound **1**; ^{1}H NMR (400 MHz, D_2O) δ 3.60 (t, 1H, *J* = 10.1 Hz), 3.44–3.40 (m, 2H), 3.27–3.24 (m, 3H); ^{13}C NMR (D_2O δ 128.00, 74.24, 73.89, 73.28; HRMS *m*/*z* (ESI) calculated for $C_6H_{11}O_5ClNa$ $(M+Na)^+$ 221.0187; found: 221.0182.

5.2.19. 1,4-Dichloro-1,4-dideoxy-*scyllo*-inositol (6)

To a stirred suspension of 1,6:3,4-bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*neo*-inositol[18] (100 mg, 0.245 mmol) in dry pyridine (30 mL) was added sulfuryl chloride (0.2 mL, 2.45 mmol) dropwise under nitrogen at 0 °C. The reaction mixture was allowed to stir for 6.5 h at rt. The reaction mixture was then cooled to 0 °C again and water (5 mL) was added dropwise. The solution was diluted with CH_2Cl_2 (150 mL), washed with 1 M HCl (3× 100 mL), saturated $NaHCO_3$ (2× 100 mL), water (2× 100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The yellow solid containing 1,6:3,4-bis[*O*-(2,3-dimethoxybutane-2,3-diyl)]-2,5-dichloro-*scyllo*-inositol **(24)** was used in the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 12H), 3.31 (s, 12H), 3.60–3.66 (m, 4H), 3.79–3.84 (m, 2H); MS *m*/*z* (ESI); found: 467.1 $(M+Na)^+$. To a stirred solution of 95% aqueous TFA (4 mL) at 0 °C was added **24**. The mixture was stirred in an ice bath for 3 h. The solution was then concentrated under reduced pressure. Co-evaporation with EtOH removed traces of TFA and butanedione. Crystallization of the product in a mixture of ethanol/water gave product **6** (16 mg, 30% yield over steps). ^{1}H NMR (400 MHz, D_2O) δ *3.57–3.63* (m, 4H), 3.77–3.81 (m, 2H); ^{13}C NMR (D_2O) δ 74.40, 64.28;

5.2.20. 1-*O*-Methyl-*scyllo*-inositol (7)

Compound **7** (33.9 mg, 92%) was obtained from compound **21** (100 mg, 0.19 mmol) using the same procedure as for compound **1**; lit[26] ^{1}H NMR (400 MHz, D_2O) δ 3.62 (s, 3H), 3.47–3.30 (m, 5H), 3.15 (t, 1H, *J* = 9.3 Hz); ^{13}C NMR (D_2O) δ 83.57, 73.66, 73.57, 73.10, 59.98; HRMS *m*/*z* (ESI) calculated for $C_7H_{14}O_6Na$ $(M+Na)^+$ 217.0682; found: 217.0693.

5.2.21. 1,4-Di-*O*-methyl-*scyllo*-inositol (8)

Compound **8** (43.0 mg, 90%) was obtained from compound **22** (100 mg, 0.23 mmol) using the same procedure as for compound **2**; ^{1}H NMR (400 MHz, D_2O) δ 3.46 (s, 6H), 3.30 (m, 4H), 2.69 (m, 2H); ^{13}C NMR (D_2O δ 83.41, 73.02; 60.00 HRMS *m*/*z* (ESI) calculated for $C_8H_{16}O_6Na$ $(M+Na)^+$ 231.0839; found: 231.0843.

5.3. Aβ42 Peptide

Aβ42 was synthesized by solid-phase Fmoc-chemistry by the Hospital for Sick Children's Biotechnology Centre (Toronto, Canada). To ensure that the peptide remained monomeric and free of

fibril seeds it was purified by RP-HPLC on a C18 μμbondapak column. Aβ was initially dissolved in 5 mL of 10% formic acid in distilled water at a concentration of 2 mg/mL. The peptide was recovered from the RP-HPLC in fractions, immediately frozen and lyophilized. Aβ was then dissolved in a solution of 40% 2,2,2-trifluoroethanol (Aldrich Chemicals) in distilled H_2O and stored at −20 °C until used. Only the HPLC purified fractions that were verified to be random coil by circular dichroism spectroscopy as previously described were used in the electron microscopy experiments.[10]

5.4. Electron microscopy

$A\beta_{42}$ (5 μM) was incubated in the presence and absence of inositol derivatives (5 mM). Aβ42 stock (~500 μM) was diluted into distilled water (~100-fold) containing the inositol derivatives and incubated in a temperature-controlled incubator with shaking at 37 °C for up to 7 days. For negative-stain electron microscopy, carbon-coated pioloform grids (Canemco-Marivac, Lakefield, Canada) were floated on aqueous solutions of peptides. After the grids were blotted and air-dried, the samples were stained with 1% (w/v) phosphotungstic acid (Aldrich Chemicals) and examined on a Hitachi 7000 electron microscope operated at 75 kV. The results presented are representative images from two separate experiments on different Aβ42 stocks.

Acknowledgments

The authors thank Dr. N.-C. Wang at the Hospital for Sick Children's Biotechnology Center for synthesis of the Aβ42 peptide. The authors acknowledge support from the Canadian Institutes of Health Research (J.M., M.N., C.H., and G.Z,), Natural Science and Engineering Research Council of Canada (J.M., M.N., and G.Z.), Ontario Alzheimer's Society (J.M.), and Alzheimer's Society of Canada (C.H, J.E.S., and M.N.).

Appendix A Supplementary data

^{1}H NMR data are available for compounds **1**–**8** and are available free of charge. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.06.045.

References

1. Hardy, J.; Selkoe, D. J. *Science* **2002**, *297*, 353.
2. Roberson, E. D.; Mucke, L. *Science* **2006**, *314*, 781.
3. Ono, K.; Yoshiike, Y.; Takashima, A.; Hasegawa, K.; Naiki, H.; Yamada, M. *J. Neurochem.* **2003**, *87*, 172.
4. Sciarretta, K. L.; Gordon, D. J.; Meredith, S. C. *Methods Enzymol.* **2006**, *413*, 273.
5. Choi, Y.; Kim, H. S.; Shin, K. Y.; Kim, E. M.; Kim, M.; Kim, H. S.; Park, C. H.; Jeong, Y. H.; Yoo, J.; Lee, J. P.; Chang, K. A.; Kim, S.; Suh, Y. H. *Neuropsychopharmacology* **2007**, *32*, 2393.
6. Cherny, R. A.; Atwood, C. S.; Xilinas, M. E.; Gray, D. N.; Jones, W. D.; McLean, C. A.; Barnham, K. J.; Volitakis, I.; Fraser, F. W.; Kim, Y. S.; Huang, X. D.; Goldstein, L. E.; Moir, R. D.; Lim, J. T.; Beyreuther, K.; Zheng, H.; Tanzi, R. E.; Masters, C. L.; Bush, A. I. *Neuron* **2001**, *30*, 665.
7. Cohen, T.; Frydman-Marom, A.; Rechter, M.; Gazit, E. *Biochemistry* **2006**, *45*, 4727.
8. Torok, M.; Abid, M.; Mhadgut, S. C.; Torok, B. *Biochemistry* **2006**, *45*, 5377.
9. McLaurin, J.; Franklin, T.; Chakrabartty, A.; Fraser, P. E. *J. Mol. Biol.* **1998**, *278*, 183.
10. McLaurin, J.; Golomb, R.; Jurewicz, A.; Antel, J. P.; Fraser, P. E. *J. Biol. Chem.* **2000**, *275*, 18495.
11. Nitz, M.; Fenili, D.; Darabie, A. A.; Wu, L.; Cousins, J. E.; McLaurin, J. *FEBS J.* **2008**, *275*, 1663.
12. McLaurin, J.; Kierstead, M. E.; Brown, M. E.; Hawkes, C. A.; Lambermon, M. H. L.; Phinney, A. L.; Darabie, A. A.; Cousins, J. E.; French, J. E.; Lan, M. F.; Chen, F. S.; Wong, S. S. N.; Mount, H. T. J.; Fraser, P. E.; Westaway, D.; St. George-Hyslop, P. *Nat. Med.* **2006**, *12*, 801.
13. Auzanneau, F. I.; Bundle, D. R. *Carbohydr. Res.* **1993**, *247*, 195.
14. Glaudemans, C. P. J. *Chem. Rev.* **1991**, *91*, 25.
15. Swaminathan, C. P.; Gupta, D.; Sharma, V.; Surolia, A. *Biochemistry* **1997**, *36*, 13428.
16. Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, J. F.; Warriner, S. L.; Wesson, K. E. *J. Chem. Soc. Perkin. Trans. 1* **1997**, 2023.
17. Montchamp, J. L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897.
18. Riley, A. M.; Jenkins, D. J.; Potter, B. V. L. *Carbohydr. Res.* **1998**, *314*, 277.
19. Kierstead, M.; McLaurin, J.; Brown, M. *Neurobiol. Aging* **2002**, *23*, S109.
20. Zhang, P.; Appleton, J.; Ling, C.-C.; Bundle, D. R. *Can. J. Chem.* **2002**, *80*, 1141.
21. Angyal, S. J.; Odier, L. *Carbohydr. Res.* **1982**, *101*, 209.
22. Mccasland, G. E.; Furuta, S.; Johnson, L. F.; Shoolery, J. N. *J. Org. Chem.* **1963**, *28*, 894.
23. Sawyer, D. A.; Potter, B. V. L. *J. Chem. Soc. Perkin Trans. 1* **1992**, 923.
24. Mccaslan, Ge; Naumann, M. O.; Durham, L. J. *J. Org. Chem.* **1969**, *34*, 1382.
25. Sarmah, M. P.; Shashidhar, M. S.; Sureshan, K. M.; Gonnade, R. G.; Bhadbhade, M. M. *Tetrahedron* **2005**, *61*, 4437.
26. Ueno, Y.; Hasegawa, A.; Tsuchiya, T. *Carbohydr. Res.* **1973**, *29*, 520.