Synthesis of New Alkylene-Linked Donepezil-Aminothienoquinoline Hybrid Related Derivatives

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Alzheimer's disease (AD) is characterized by the deficits in the cholinergic system[1,2] and presence of neurofibrillary tangles and amyloid plaques.[3,4] Since the deficiency in cholinergic neurotransmission is believed to be one of the major causes of the decline in cognitive and mental functions associated with AD, cholinergic system became a target for the design of anti-Alzheimer drugs. Acetylcholinesterase (AChE) inhibitors by "cholinergic hypothesis" have been a useful and practical treatment for the treatment of AD.[5,6] Moreover, the interest for AChE inhibitors has been greatly renewed due to the recent evidences that AChE might function to accelerate β-amyloid peptide (Aβ) formation and could play a role during amyloid deposition in AD brain.[7,8] The dimers of tacrine (**1**) which was the first AChE inhibitor approved by FDA have been synthesized and studied to improve potency and selectivity of AChE inhibition as the dual binding site strategy. In this series of compounds, the heptamethylene-linked tacrine dimer (**2**), the so-called *bis*(7)-tacrine, turned out to be more potent and selective for AChE inhibition than the parent compound, **1**. This activity can be explained by the effective and simultaneous binding of the tacrine units to catalytic and peripheral sites of AChE.[9-12]

Therefore, the search for novel and potent tacrine-related homo- and heterodimer ligands as dual binding site AChE inhibitors has become an area of very active research.[13-16] Several classes of these inhibitors have been developed by connecting through a suitable linker the two interacting units, which are generally derived from known AChE inhibitors or their analogs. Compound **4**, for example, donepezil-tacrine hybrid which was combined different fragments of donepezil (**3**) with **1**, was recently synthesized and investigated for the inhibition of AChE and AChE-induced Aβ aggregation.[17,18] We have reported the synthesis of new 4-amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline and 4-amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-5-ol derivatives (**5**) as potential AChE inhibitors.[19]

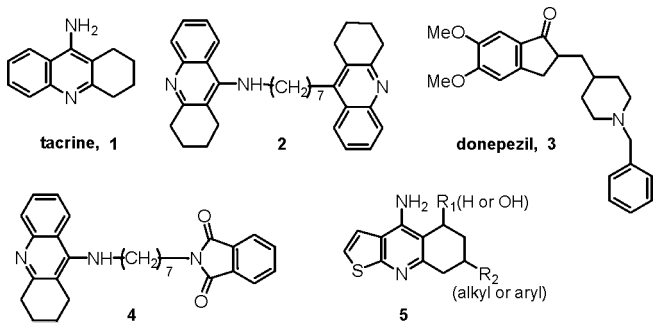
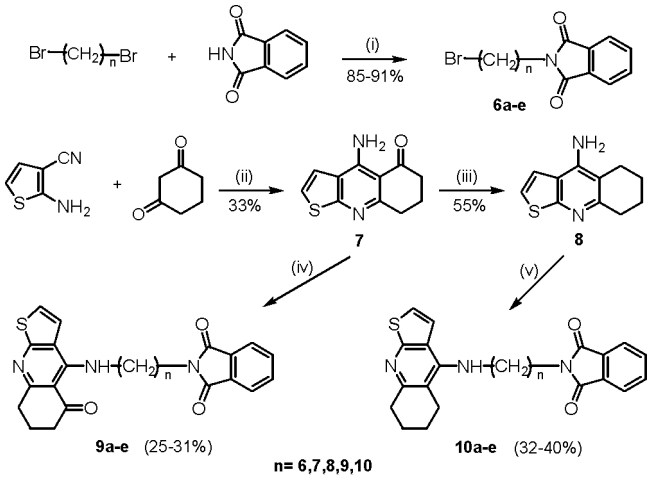


Figure 1

In view of the outstanding pharmacological profile of compound **4** and taking into account the tricyclic system of its tacrine units and a tether length of methylene groups for an optimal AChE inhibitory activity, we have designed new alkylene-linked donepezil-aminothienoquinoline hybrid related derivatives based on **3** and **5**. As a continuation of our previous works on thienopyridine and thienopyrimidine,[19-21] we now report the synthesis of a series of 2-[n-(5-oxo-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)alkyl]isoindole-1,3-dione (n = 6,7,8,9,10) (**9a-e**) and 2-[n-(5,6,7,8-tetrahydrothieno-[2,3-*b*]quinolin-4-ylamino)alkyl]isoindole-1,3-dione (n = 6, 7, 8, 9, 10) (**10a-e**).

The alkylation of phthalimide with different dibromoalkanes (n = 6,7,8,9,10) afforded intermediates **6a-e** in good yields.[17] The key intermediate **7** was also prepared by two-step reactions, starting from 2-aminothiophene-3-carbonitrile and cyclohexane-1,3-dione according to the procedure we have previously reported.[19] The carbonyl of **7** was transformed into methylene group by modified Wolff-Kishner reduction (hydrazine hydrate and KOH under hot ethylene glycol) to give **8** in 55% yield.[22]

The synthesis of alkylene-linked donepezil-aminothieno-



Scheme 1. Reagents and conditions; (i) NaH, DMF, rt; (ii) (a) cat. *p*-TsOH, toluene, reflux, (b) K_2CO_3/CuCl, THF, reflux; (iii) hydrazine hydrate, KOH/ethylene glycol, reflux; (iv) KOH, DMSO, **6a-e**, rt; (v) KOH, DMSO, **6a-e**, rt.

quinoline hybrid related derivatives **9a-e** and **10a-e** was carried out through direct alkylation of **6a-e** with **7** and **8**. The 2 equiv of powdered KOH was added to the solution of compound **7** or **8** (1 equiv) in DMSO and stirred vigorously at room temperature for 4 h. The each of compounds **6a-e** (n = 6,7,8,9,10) in DMSO was then added dropwise to the reaction solution. The resulting solution was stirred at room temperature for 12 h to give the desired hybrid derivatives **9a-e** or **10a-e** in moderate yields (25-40%). The side product that was alkylated at alpha carbon of carbonyl group in **6** was not obtained. Marked improvements in yield and reaction time could not be made when other solvents, bases or phase transfer catalysts were used. The alkylation of **7** with **6a** in the presence of KOH was also attempted by using the solvent-free microwave assisted methods,[23] but it was found to yield instead an inseparable mixture of compounds. The structure of compounds **9a-e** and **10a-e** was characterized by their spectral data and elemental analysis.

In conclusion, we reported the facile synthesis of new alkylene-linked donepezil-aminothienoquinoline hybrid related derivatives **9a-e** and **10a-e** as potential AChE inhibitors. The AChE inhibition study of these compounds is underway and will be reported elsewhere.

Experimental Section

General procedure for the preparation of 2-[n-(5-oxo-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)alkyl]isoindole-1,3-dione (n = 6,7,8,9,10) (9a-e) and 2-[n-(5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)alkyl]isoindole-1,3-dione (n = 6, 7, 8, 9, 10) (10a-e). The powered KOH (20 mmole) was added to a solution of **7** or **8** (10 mmole) in DMSO (20 mL) under nitrogen. The mixture was vigorously stirred for 4h at room temperature, and then each bromophthalimide derivatives **6a-e** (10 mmole, n = 6,7,8,9,10) was added dropwise to the reaction solution. After stirring at room temperature for 12h, it poured into water and extracted with chloroform. The solvent was evaporated to dryness and the residue was then purified by silica gel column chromatography eluting with a 50:50 v/v ethyl acetate/chloroform mixture.

2-[6-(5-Oxo-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)hexyl]isoindole-1,3-dione (9a): Yield 30%; brown oil; ^{1}H NMR ($CDCl_3$): δ 10.91 (s, 1H, NH), 7.84 (dd, 2H, phenyl), 7.71 (dd, 2H, phenyl), 7.54 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.12 (d, J = 5.9 Hz, 1H, thiophene H-3), 3.72-3.67 (m, 4H, 2 × N-CH_2), 3.06 (t, 2H, H-8), 2.70 (t, 2H, H-6), 2.06 (m, 2H, H-7), 1.77-1.67 (m, 4H), 1.34-1.25 (m, 4H). MS: (m/z) 447 (M^-), 245, 231, 218, 203, 160. *Anal.* Calcd. for $C_{25}H_{25}N_3O_3S$: C, 67.09; H, 5.63; N, 9.39. Found: C, 67.24; H, 5.56; N, 9.20.

2-[7-(5-Oxo-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)heptyl]isoindole-1,3-dione (9b): Yield 26%; brown oil; ^{1}H NMR ($CDCl_3$): δ 10.97 (s, 1H, NH), 7.84 (dd, 2H, phenyl), 7.70 (dd, 2H, phenyl), 7.53 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.12 (d, J = 5.9 Hz, 1H, thiophene H-3), 3.72-3.70 (m, 4H, 2 × N-CH_2), 3.06 (t, 2H, H-8), 2.69 (t, 2H, H-6), 2.05 (m, 2H, H-7), 1.77-1.67 (m, 4H), 1.37-1.25 (m, 6H). MS: (m/z) 461 (M^+), 245, 231, 160. *Anal.* Calcd. for $C_{26}H_{27}N_3O_3S$: C, 67.66; H, 5.90; N, 9.10. Found: C, 67.79; H, 6.12; N, 9.27.

2-[8-(5-Oxo-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)octyl]isoindole-1,3-dione (9c): Yield 29%; brown oil; ^{1}H NMR ($CDCl_3$): δ 10.92 (s, 1H, NH), 7.83 (dd, 2H, phenyl), 7.70 (dd, 2H, phenyl), 7.54 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.12 (d, J = 5.9 Hz, 1H, thiophene H-3), 3.73-3.70 (m, 4H, 2 × N-CH_2), 3.06 (t, 2H, H-8), 2.70 (t, 2H, H-6), 2.06 (m, 2H, H-7), 1.77-1.67 (m, 4H), 1.37-1.24 (m, 8H). MS: (m/z) 475 (M^-), 245, 231, 160. *Anal.* Calcd. for $C_{27}H_{29}N_3O_3S$: C, 68.19; H, 6.15; N, 8.84. Found: C, 68.32; H, 6.01; N, 9.01.

2-[9-(5-Oxo-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)nonyl]isoindole-1,3-dione (9d): Yield 31%; brown oil; ^{1}H NMR ($CDCl_3$): δ 10.90 (s, 1H, NH), 7.84 (dd, 2H, phenyl), 7.71 (dd, 2H, phenyl), 7.54 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.12 (d, J = 5.9 Hz, 1H, thiophene H-3), 3.72-3.68 (m, 4H, 2 × N-CH_2), 3.06 (t, 2H, H-8), 2.69 (t, 2H, H-6), 2.06 (m, 2H, H-7), 1.77-1.66 (m, 4H), 1.34-1.24 (m, 10H). MS: (m/z) 489 (M^+), 245, 231, 218, 160. *Anal.* Calcd. for $C_{28}H_{31}N_3O_3S$: C, 68.69; H, 6.38; N, 8.58. Found: C, 68.78; H, 6.54; N, 8.40.

2-[10-(5-Oxo-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)decyl]isoindole-1,3-dione (9e): Yield 25%; brown oil; ^{1}H NMR ($CDCl_3$): δ 10.84 (s, 1H, NH), 7.83 (dd, 2H, phenyl), 7.71 (dd, 2H, phenyl), 7.54 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.12 (d, J = 5.9 Hz, 1H, thiophene H-3), 3.72-3.69 (m, 4H, 2 × N-CH_2), 3.06 (t, 2H, H-8), 2.70 (t, 2H, H-6), 2.06 (m, 2H, H-7), 1.77-1.65 (m, 4H), 1.34-1.20 (m, 12H). MS: (m/z) 503 (M^+), 245, 231, 160. *Anal.* Calcd. for $C_{29}H_{33}N_3O_3S$: C, 69.16; H, 6.60; N, 8.34. Found: C, 68.98; H, 6.75; N, 8.46.

2-[6-(5,6,7,8-Tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)-hexyl]isoindole-1,3-dione (10a): Yield 35%; yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.84 (dd, 2H, phenyl), 7.72 (dd, 2H, phenyl), 7.42 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.10 (d, J = 5.9 Hz, 1H, thiophene H-3), 3.70-3.62 (m, 4H, 2 × N-CH_2), 2.96 (t, 2H, H-8), 2.50 (t, 2H, H-5), 1.91-1.88 (m, 4H, H-6 and H-7), 1.72-1.70 (m, 4H), 1.36-1.25 (m, 4H). MS: (m/z) 433 (M^-), 204, 188, 176, 160. *Anal.* Calcd. for $C_{25}H_{27}N_3O_2S$: C, 69.26; H, 6.28; N, 9.69. Found: C, 69.40; H, 6.36; N, 9.88.

2-[7-(5,6,7,8-Tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)-heptyl]isoindole-1,3-dione (10b): Yield 32%; yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.84 (dd, 2H, phenyl), 7.72 (dd, 2H, phenyl), 7.42 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.11 (d, J = 5.9 Hz, 1H, thiophene H-3), 3.70-3.61 (m, 4H, 2 × N-CH_2), 2.96 (t, 2H, H-8), 2.49 (t, 2H, H-5), 1.90-1.88 (m, 4H, H-6 and H-7), 1.72-1.70 (m, 4H), 1.36-1.23 (m, 6H). MS: (m/z) 447 (M^-), 204, 188, 174, 160, 148. *Anal.* Calcd. for $C_{26}H_{29}N_3O_2S$: C, 69.77; H, 6.53; N, 9.39. Found: C, 69.80; H, 6.39; N, 9.50.

2-[8-(5,6,7,8-Tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)-octyl]isoindole-1,3-dione (10c): Yield 40%; yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.84 (dd, 2H, phenyl), 7.73 (dd, 2H, phenyl), 7.42 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.11 (d, J = 5.9 Hz, 1H, thiophene H-3), 3.70-3.61 (m, 4H, 2 × N-CH_2), 2.97 (t, 2H, H-8), 2.50 (t, 2H, H-5), 1.91-1.88 (m, 4H, H-6 and H-7), 1.72-1.70 (m, 4H), 1.38-1.22 (m, 8H). MS: (m/z) 461 (M^-), 204, 188, 174, 160, 82. *Anal.* Calcd. for $C_{27}H_{31}N_3O_2S$: C,

70.25; H, 6.77; N, 9.10. Found: C, 70.38; H, 6.66; N, 9.27.

2-[9-(5,6,7,8-Tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)-nonyl]isoindole-1,3-dione (10d): Yield 36%; yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.84 (dd, 2H, phenyl), 7.73 (dd, 2H, phenyl), 7.42 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.12 (d, J = 5.9 Hz, 1H, thiophene H-3), 3.70-3.62 (m, 4H, 2 × N-CH_2), 2.96 (t, 2H, H-8), 2.50 (t, 2H, H-5), 1.92-1.88 (m, 4H, H-6 and H-7), 1.72-1.68 (m, 4H), 1.36-1.23 (m, 10H). MS: (m/z) 475 (M^+), 204, 188, 176, 160. *Anal.* Calcd. for $C_{28}H_{33}N_3O_2S$: C, 70.71; H, 6.99; N, 8.83. Found: C, 70.80; H, 6.81; N, 9.01.

2-[10-(5,6,7,8-Tetrahydrothieno[2,3-*b*]quinolin-4-ylamino)-decyl]isoindole-1,3-dione (10e): Yield 38%; yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.84 (dd, 2H, phenyl), 7.72 (dd, 2H, phenyl), 7.42 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.11 (d, J = 5.9 Hz, 1H, thiophene H-3), 3.70-3.61 (m, 4H, 2 × N-CH_2), 2.96 (t, 2H, H-8), 2.49 (t, 2H, H-5), 1.91-1.88 (m, 4H, H-6 and H-7), 1.72-1.70 (m, 4H), 1.36-1.25 (m, 12H). MS: (m/z) 489 (M^+), 204, 188, 176, 149, 67. *Anal.* Calcd. for $C_{29}H_{35}N_3O_2S$: C, 71.13; H, 7.20; N, 8.58. Found: C, 70.02; H, 7.01; N, 8.77.

References

1. Perry, E. K.; Perry, R. H.; Blessed, G.; Tomlinson, B. E. *Lancet* **1977**, *1*, 189.
2. Bartus, R. T.; Dean III, R. L.; Beer, B.; Lippa, A. S. *Science* **1982**, *217*, 408.
3. Crowther, R. A.; Goedert, M. *J. Struct. Biol.* **2000**, *130*, 271.
4. Reve, R. L.; McPhie, D. L.; Chen, Y. *Brain Res.* **2000**, *886*, 54.
5. Marco, J. L.; Carreiras, M. C. *Mini Rev. Med. Chem.* **2003**, *3*, 518.
6. Selkoe, D. J. *Nature* **1999**, *399*, A23.
7. Inestrosa, N. C.; Alvarez, A.; Pérez, C. A.; Moreno, R. D.; Vicente, M.; Linker, C.; Casanueva, O. I.; Soto, C.; Garrido, J. *Neuron* **1996**, *16*, 881.
8. Bartolini, M.; Bertucci, C.; Cavrini, V.; Andrisano, V. *Biochem. Pharmacol.* **2003**, *65*, 407.
9. Pang, Y.-P.; Quiram, P.; Jelacic, T.; Hong, F.; Brimijoin, S. *J. Biol. Chem.* **1996**, *271*, 23646.
10. Pang, Y.-P.; Hong, F.; Quiram, P.; Jelacic, T.; Brimijoin, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, *2*, 171.
11. Carlier, P. R.; Han, Y. F.; Chow, E. S.-H.; Li, C. P.-L.; Wang, H.; Lieu, T. X.; Wong, H. S.; Pang, Y.-P. *Bioorg. Med. Chem.* **1999**, *7*, 351.
12. Recanatini, M.; Cavalli, A.; Belluti, F.; Piazzi, L.; Rampa, A.; Bisi, A.; Gobbi, S.; Valenti, P.; Andrisano, V.; Bartolini, M.; Cavrini, V. *J. Med. Chem.* **2000**, *43*, 2007.
13. Savini, L.; Campiani, G.; Gaeta, A.; Pellerano, C.; Fattorusso, C.; Chiasserini, L.; Fedorko, J. M.; Saxena, A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1779.
14. Savini, L.; Gaeta, A.; Fattorusso, C.; Catalanotti, B.; Campiani, G.; Chiasserini, L.; Pellerano, C.; Novellino, E.; McKissic, D.; Saxena, A. *J. Med. Chem.* **2003**, *46*, 1.
15. Haviv, H.; Wong, D. M.; Grenblatt, H. M.; Carlier, P. R.; Pang, Y. P.; Silman, I.; Sussman, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 11029.
16. Elsinghorst, P. W.; Cieslik, J. S.; Mohr, K.; Tränkle, C.; Gütschow, M. *J. Med. Chem.* **2007**, *50*, 5685.
17. Alonso, D.; Dorronsoro, I.; Rubio, L.; Munoz, P.; Garcia-Palomero, E.; Del Monte, M.; Bidon-Chanal, A.; Orozco, M.; Luque, F. J.; Castro, A.; Medina, M.; Martinez, A. *Bioorg. Med. Chem.* **2005**, *13*, 6588.
18. Camps, P.; Formosa, X.; Galdeano, C.; Gómez, T.; Muñoz-Torrero, D.; Scarpellini, M.; Viayna, E.; Badia, A.; Clos, M. V.; Camins, A.; Pallàs, M.; Bartolini, M.; Mancini, F.; Andrisano, V.; Estelrich, J.; Lizondo, M.; Bidon-Chanal, A.; Luque, F. J. *J. Med. Chem.* **2008**, *51*, 3588.
19. Song, Y.-H.; Seo, J. *J. Heterocycl. Chem.* **2007**, *44*, 1439.
20. Joe, B. S.; Son, H. Y.; Song, Y.-H. *Heterocycles* **2008**, *75*, 4301.
21. Song, Y.-H. *Heterocycl. Commun.* **2007**, *13*, 33.
22. Huang-Minlon, *J. Am. Chem. Soc.*, **1946**, *68*, 2487.
23. *Microwave in Organic Synthesis*, revised ed.; Laupy, A., Ed.; Wiley-VCH: Weinheim, 2006.