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Synthesis of Benzothiophenones and Naphthothiophenone as Anticholinesterases

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Since AChE and BuChE belong to the same serine hydrolazes, we designed and synthesized compounds **1-6** as anticholinesterases and measured their inhibition poteucies on ChEs. 7-Methoxy-3*H*-benzo[c]thiophen-1-one **4**, 4,6-dibromo-5,7-methoxy-3*H*-benzo[c]thiophe-1-one **5** and 9-methoxy-3*H*-naphtho-[2,3-c]thiophen-1-one **6** were synthesized by using ethyl 2-methoxy-6-methylbenzoate, ethyl 3,4-dibromo-2,4-dimethoxy-6-methylbenzoate and ethyl 1-methoxy-3-methyl-2-naphthoate.

Key Words: Cholinesterase, Inhibition, Benzothiophenone, Naphthothiophenone.

INTRODUCTION

The physiological role of AChE is hydrolysis of the neurotransmitter, acetylcholine (Ach) the acetate and choline. AChE inhibitors are used as chemical warfare agents, insecticides and drugs against Alzheimer's disease (AD). Numerous evidences suggest that the neurobiological basis of senile dementia in Alzheimer's disease and related dementias is a loss of cholinergic neurons and a resultant decline in acetylcholine (Ach) in brain regions which regulate behavioural and emotional responses[1-5]. Well known AChE inhibitors such as tacrine (THA, Cognex), E2020 (Donepezil, Aricept), rivastigmine (Exelon) and galantamine (Raminyl) are approved by FDA as drugs against Alzheimer's disease[6-14]. In the healthy brain AChE predominates (80 %) and BuChE is considered to play a minor role in regulating vrain Ach levels. In the Alzheimer's disease brain, BuChE activity rises while AChE acitivity remains unchanged or declines. Therefore, both enzymes are likely to have involvement in regulating Ach levels and represent legitimate therapeutic targets to ameliorate the cholinergic deficit. Powers *et al*., showed that serine protease such as elastase and chymotrypsin is inactivated by isobenzofuranone and benzopyrandiones[15-19]. If a compound has a functionality similar to the thioester of acetylthiocholine and hydrophobic region, it is expected that the compound would bind to the AChE active site. Most insecticides are irreversible inhibitors of AChE and thus specific irreversible inhibitors are also required to develop. The benzothiophenone compounds have hydrophobic group and the carbonyl group and expected to inhibit ChEs. Since AChE and BuChE belong to the same serine hydrolases, we designed and synthesized compounds **1-6** (Fig. 1) as anticholinestrases and measured their inhibition potencies on ChEs.

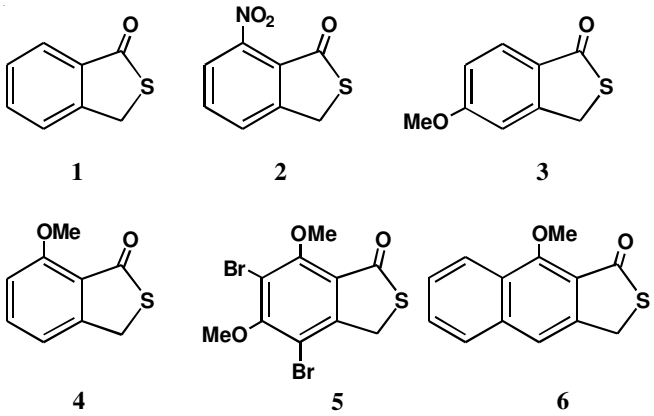

Fig. 1. Synthesized products

EXPERIMENTAL

Electic eel AChE, type V-S lyophilized powder and horse serum BuChE were purchased from Sigma Chemical Co and was used as received. Prior to use they were dissolved in 0.1 M, pH 7.3 sodium phosphate buffer, containing 0.1 M NaCl. Acetylthiocholine (ATCh), butyrylthiocholine (BuTCh), 5,5'-dithio-*bis*(2-nitrobenzoic acid) (DTNB) and buffer components were also purchased from Sigma Chemical Co. Water used in experiments was distilled and deionized by passage through a mixed bead ion-exchange column. NMR spectra were obtained with a Bruker AC200 spectometer (200 MHz) using tetramethylsilane or D_2O as internal standards.

Synthesis of 3*H*-benzo[c]thiophen-1-one (1): To a solution of ethyl *o*-methylbenzoate (8.21 g. 50 mmol) and benzoyl peroxide (10 mg, 41.3 mmol) in carbon tetrachloride (125 mL) was added N-bromosuccinimide (8.90 g, 50 mmol)

and refluxed for 6 h. After completion of the reaction the mixture was filtered and evaporated. The residue in acetone (50 mL) was mixed with thiourea (4.19 g, 55 mmol) and refluxed for 5.5 h. After removal of acetone by evaporation, the obtained thiouronium salt was warmed to 80-90 ºC in 20 % $NaHCO_3$ solution (50 mL) under nitrogen for 2 h. Then, the solution was acidified with 20 % HCl solution. The oily residue was subjected to silica gel column chromatography (eluent; hexane:ethyl acetate = 10:1, v/v) to give **1** (4.81 g, 64 %): m.p. 58-60 ºC (Ref.[17] m.p. 58-60 ºC): IR (KBr, n_{max}, cm^{-1}) 3030, 1686, 1595, 1237; ^1H NMR (200 MHz, $CDCl_3$) δ 4.45 (s, 2H), 7.38-7.97 (m, 4H); anal. calcd. (%) for C_8H_6OS: C, 63.97; H, 4.03; S, 21.35. Found (%): C, 63.84; H, 4.02; S, 21.30.

Synthesis of 4-nitro-3*H*-benzo[c]thiophen-1-one (2): To a solution of ethyl 2-methyl-3-nitrobenzoate (10.45 g, 50 mmol) and benzoyl peroxide (10 mg, 41.3 mmol) in carbon tetrachloride (125 mL) was added N-bromosuccinimide (8.90 g, 50 mmol) and refluxed fo 7 h. After completion of the reaction the mixture was filtered and evaporated. The residue in acetone (50 mL) was mixed with thiourea (4.19 g, 55 mmol) and refluxed for 5.5 h. After removal of acetone by evaporation, the obtained thiouronium salt was warmed to 80-90 ºC in 20 % $NaHCO_3$ solution (50 mL) under nitrogen for 2 h. Then, the solution was acidified with 20 % HCl solution. The oily residue was subjected to silica gel column chromatography (eluent; hexane:ethyl acetate = 10:1, v/v) to give **2** (4.39 g, 45 %): m.p. 105 ºC; IR (KBr, ν_{max}, cm^{-1}) 3030, 1685, 1595, 1530; ^1H NMR (200 MHz, $CDCl_3$): δ 4.40 (s, 2H), 7.04 (d, 1H), 7.29 (d, 1H), 7.72 (t, 1H); anal. calcd. (%) for $C_8H_5NO_3S$: C, 49.23; H, 2.58; N, 7.18; s, 16.43. Found (%): C, 49.28; H, 2.53; N, 7.19; s, 16.32.

Synthesis of 5-methoxy-3*H*-benzo[c]thiopen-1-one (3): To a solution of ethyl 2-methyl-3-nitrobenzoate (10.45 g, 50 mmol) and benzoyl peroxide (10 mg, 41.3 mmol) in carbon tetrachloride (125 mL) was added N-bromosuccinimide (8.90 g, 50 mmol) and refluxed fo 7 h. After completion of the reaction the mixture was filtered and evaporated. The residue in acetone (50 mL) was mixed with thiourea (4.19 g, 55 mmol) and refluxed for 5.5 h. After removal of acetone by evaporation, the obtained thiouronium salt was warmed to 80-90 ºC in 20 % $NaHCO_3$ solution (50 mL) under nitrogen for 2 h. Then, the solution was acidified with 20 % HCl solution. The oily residue was subjected to silica gel column chromatography (eluent; hexane:ethyl acetate = 10:1, v/v) to give **3** (4.09 g, 45 %): m.p. 103-104 ºC; IR (KBr, ν_{max}, cm^{-1}) 3030, 1660, 1592, 1247; ^1H NMR (200 MHz, $CDCl_3$): δ 3.96 (s, 3H), 4.40 (s, 2H), 7.0 (m, 2H), 7.72 (m, 1H); anal. calcd. (%) for $C_9H_8O_2S$: C, 59.98; H, 4.47; S, 17.79. Found (%): C, 59.97; H, 4.46; S, 17.80.

Similar method was adopted to synthesize, 7-methoxy-3*H*-benzo[c]thiophen-1-one (**4**), 4,6-dibromo-5,7-methoxy-3*H*-benzo[c]thiophen-1-one **5** and 9-methoxy-3*H*-naphtho-[2,3-c]thiophen-1-one (**6**) by using ethyl 2-methoxy-6-methylbenzoate, ethyl 3,4-dibromo-2,4-dimethoxy-6-methylbenzoate and ethyl 1-methoxy-3-methyl-2-naphthoate.

7-Methoxy-3*H*-benzo[c]thiophen-1-one (4): Yield: 61 %; m.p. 70-71 ºC; IR (KBr, ν_{max}, cm^{-1}) 3030, 1679, 1590, 1473; ^1H NMR (200 MHz, $CDCl_3$): δ 3.96 (s, 3H), 4.40 (s, 2H), 6.88 (d, *J* = 8 Hz, 1H), 7.08 (d, *J* = 8 Hz, 1H), 7.52 (t, *J* = 8 Hz, 1H); anal. calcd. (%) for $C_9H_8O_2S$: C, 59.98; H, 4.47; S, 17.79. Found (%): C, 59.97; H, 4.46; S, 17.80.

4,6-Dibromo-5,7-methoxy-3*H*-benzo[c]thiophen-1-one (5): yield: 65 %; m.p. 142-143 ºC; IR (KBr, ν_{max}, cm^{-1}) 3030, 1687, 1561, 1385; ^1H NMR (200 MHz, $CDCl_3$): δ 3.95 (s, 3H), 4.30 (s, 2H); anal. calcd. (%) for $C_{10}H_8O_3SBr_2$: C, 32.63; H, 2.19; S, 8.72. Found (%): C, 32.62; H, 2.19; S, 8.71.

9-Methoxy-3*H*-naphto[2,3-c]thiophen-1-one (6): Yield: 52 %; m.p. 129-130 ºC; IR (KBr, ν_{max}, cm^{-1}) 3035, 1690, 1054; ^1H NMR (200 MHz, $CDCl_3$): δ 4.10 (s, 3H), 4.50 (s, 2H), 7.63 (m, 4H), 8.30 (m, 1H); anal. calcd. (%) for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; S, 13.93. Found (%): C, 67.81; H, 4.37; S, 13.94.

RESULTS AND DISCUSSION

The designed compounds were synthesized and tested as anticholinesterases. They turned out to be ChE inhibitors with the inhibition constant shown in Table-1. The inhibition constant obtained by a replot of K_m/V_{max} *versu*s inhibitor concentration ranges from μM to nM. The boronic acid and its protected form are effective inhibitors of AChE and BuChE. The inhibition constant for AChE.

TABLE-1
ANTICHOLINESTREASE ACTIVITIES OF THE COMPONDS

Compound	K_i for AChE (μM)	K_i for BuChE (μM)	K_i(BuChE)/ K_i(AChE)
1	59.8 ± 3.1	4894 ± 358	82
2	11.8 ± 1.2	341 ± 30	29

78 nM is close to that of the most potent AChE inhibitors such as tacrine and huperzine A. Since the inhibitors increased the Michaelis constant while they have little effect on the maximal velocities, the inhibition mechanism is mixed (data not shown).

The benzothiophenone **1** and the nitro substituted one **2** inhibit ChE with much less potency. The nitro group in **2** increased the inhibition potency by **5** fold toward AChE compared to **1**. These compounds are not good inhibitors for BuChE, either. Compound **1** is the least potent BuChE inhibitor with the inhibition constant of 4.9 mM among the tested compounds. This may due to the increased hydrophobic site of BuChE and the absence of any electronic effect by the nitro group. As the inhibition potency decrease, the K_i(BuChE)/ K_i(AChE) also decreases, meaning the selectivity decreases.

7-Methosxy-3*H*-benzo[c]thiophen-1-one (**4**), 4,6-dibromo-5,7-methoxy-3*H*-benzo- [c]thiophen-1-one (**5**) and 9-methoxy-3*H*-naphtho[2,3-c]thiophen-1-one (**6**) were synthesized by using ethyl 2-methoxy-6-methylbenzoate, ethyl 3,5-dibromo-2,4-dimethoxy-6-methylbenzoate and ethyl 1-methoxy-3-methyl-2-naphthoate in same method.

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