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Synthesis and *in vitro* Assay of New Triazole Linked Decursinol Derivatives Showing Inhibitory Activity against Cholinesterase for Alzheimer's Disease Therapeutics

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ABSTRACT. With the goal of developing Alzheimer's disease therapeutics, we have designed and synthesized new triazole linked decursinol derivatives having potency inhibitory activities against cholinesterase [acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE)]. Since inhibition of cholinesterase (ChE) is still considered to be one of the most effective targets to treat AD patients, many new classes of ChE inhibitors have been synthesized. In an effort of identifying new type of cholinergic drug, decursinol derivatives **11**-**17** have been synthesized between decursinol and other biological interesting compounds such as lipoic acid, polyphenols, etc by using the click reaction and then evaluated their biological activities. Compound **12** (IC_{50} = 5.89 ± 0.31 mM against BuChE) showed more effective inhibitory activity against BuChE than galantamine (IC_{50} = 9.4 ± 2.5 mM). Decursinol derivatives can be considered a new class inhibitor for BuChE and can be applied to be a novel drug candidate to treat AD patients.

Key words: Triazole linked decursinol derivatives, Alzheimer's disease (AD), Acetylcholinesterase (AChE), Butyrylcholinesterase (BuChE)

INTRODUCTION

Alzheimer's disease (AD), the most common dementia in elderly people, is a complex neurodegenerative disorder of central nervous system. It is associated with a selective loss of cholinergic neurons and reduced levels of acetylcholine neurotransmitter. A wide range of evidence shows that acetylcholinesterase (AChE) inhibitors can interfere with the progression of AD.[1-4] The pathological abnormalities in AD are amyloid plaques, neurofibrillary tangles, and neuronal death.[5] In the past two decades, many efforts have been made to understand the molecular pathogenesis of AD, and to carry out its early diagnosis and therapeutic control. The cholinergic hypothesis is still the most successful approach for the symptomatic treatment of AD. Thus, the AChE inhibitors such as tacrine,[6] donepezil,[7] rivastigmine,[8] and galantamine[9] have been launched on the market for the symptomatic treatment of AD (*Fig.* 1).

There are growing evidences that BuChE may be one of the important enzymes involved in AD because AChE activity is decreased but BuChE activity is increased by 40–90% in case of AD.[10] Also, BuChE activity predominates in cognition and behavior regions of the brain.[11] Selective BuChE inhibition by cymserine analogs resulted in increased ACh levels in the brains of rodents,[12] but BuChE knocked out mice and silent mutants in humans have not exhibited any physiological disadvantage.[13] The active site of ChEs contains the binding site for the cationic choline moiety. Therefore, we have tried to design the target molecules to efficiently bind the cationic choline binding site. In our previous paper, the hybrid molecules between α-lipoic acid (ALA) and polyphenols (PPs) connected with the cationic linker demonstrated inhibitory activity against ChEs.[14] We also reported that α-lipoic acid (ALA)-benzyl piperazine hybrid molecules[15] and α-lipoic amide molecules with benzyl piperidin-4-yl[16] showed effective inhibitory activity against ChEs.

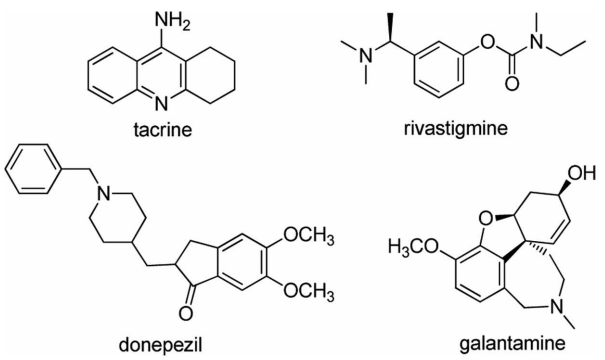


***Figure* 1.** Structure of the acetylcholinesterase inhibitors as FDA approved Alzheimer's disease therapeutics.

[†]These authors contributed equally to this work.

Since we have demonstrated inhibitory activity against ChEs using polyphenol-polyphenol hybrid molecules in previous report,[17] we have interested in investigating the inhibitory effects on ChEs of polyphenol compounds containing coumarin moiety. Decursinol contained the benzopyrone coumarin moiety and has been shown as interesting biological activities, such as analgesic effect,[18] antifungal activity,[19] antiandrogen receptor signaling activity,[20] etc. We report here the synthesis of new triazole linked decursinol derivatives and the evaluation of their *in vitro* inhibitory activities against ChEs.

EXPERIMENTAL

Materials

The chemicals used in this work were obtained from Fluka, Merck, or Sigma and were used without purification.

Apparatus

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 (400 MHz). Melting points were determined on SMP3. Mass spectrum was taken by using in Agilent G1956B. Biotage® microwave synthesizer was used for microwave synthesis reactions. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.040−0.063 mm). Analytical thin layer chromatography (TLC) was performed using pre-coated TLC plates with silica Gel 60 F254 (E. Merck). All of the synthetic reactions were carried out under argon atmosphere with dry solvent, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use and dichloromethane (DCM) was dried from calcium hydride. All chemicals were reagent grade unless otherwise specified. α-Lipoic acid, NHS, EDC, DIPEA, TEA, thionyl chloride, Cs_2CO_3, $Cu(PPh_3)_3Br$, cholinesterases [acetylcholinesterase (electric eel, cat. (C2888) and butyrylcholinesterase (from horse serum, cat. (C-7512)] were purchased from Sigma-Aldrich Chemical Co. or Acros Organics and they were used without purification. Decursinol was prepared from the hydrolysis of decursin and decursinol angelate which were isolated from the roots of Cham dang-gui (*Angelica gigas Nakai*).

Cholinesterase Assay

ChE-catalyzed hydrolysis of the thiocholine esters was monitored by following production of the anion of thiocholine at 412 nm by the Ellman's coupled assay.[21] Assays were conducted on HP8452A or HP8453A diode array UV-visible spectrophotometers and the cell compartments were thermostated by circulating water or Peltier temperature controller. Acetylthiocholine (ATCh) and butyrylthiocholine (BuTCh) were used as substrates for AChE and BuChE, respectively.

Synthesis

General procedure (A): The following procedure is a representative synthetic procedure for the synthesis of triazole linked decursinol derivatives by Click reaction without using microwave reactor. To a solution of decursinol-azide acid **10** in acetone, a corresponding propagyl derivative (1.1 eq) (**11~13,17**) and $Cu(PPh_3)_3Br$ (1.1 eq) were added at rt. The reaction mixture was stirring for 12 h at rt. The reaction was completed and then was concentrated under vacuum. After the solvent was removed under vacuum, the crude product was purified by silica gel column chromatography to give the corresponding triazole linked compound as a solid product.

General procedure (B): The following procedure is a representative synthetic procedure for the synthesis of triazole linked decursinol derivatives by Click reaction using microwave reactor. To a solution of decursinol-azide acid **10** in acetone, a corresponding propagyl derivative (1.1eq) (**14~16**) and $Cu(PPh_3)_3Br$ (1.1 eq) were added at room temperature. The reaction mixture was stirring for 30 min (**15**, **16**) or 2 h (**14**) at 65 °C (**15**, **16**) or 125 °C (**14**) in microwave reactor. The reaction was completed and then was concentrated under vacuum. After the solvent was removed under vacuum, the crude product was purified by silica gel column chromatography to give the corresponding triazole linked compound as a solid product.

2,2-Dimethyl-8-oxo-2,3,4,8-tetrahydropyrano[3,2g]chromen-3-yl 2-(4-((4-(6-fluorobenzo[d]isoxazol-3-yl)piperidi-n-1-yl)methyl)-1*H*-1,2,3-triazole-1-yl)acetate (11)

Compound **11** was obtained as a white solid in 73% yield by general procedure (A). mp 102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 6H), 2.03 (m, 4H), 2.23 (m, 2H), 2.86 (dd, J = 4.4, J = 17 Hz, 1H), 3.03 (m, 2H), 3.18 (dd, J = 4.4, J = 16 Hz, 1H), 3.69 (s, 2H), 5.10 (t , J = 4.4 Hz, 1H), 5.12 (s, 2H), 6.21 (d, J = 9.2 Hz, 1H), 6.75 (s, 1H), 7.01 (t, J = 8.8 Hz, 1H), 7.12 (s, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23(2C), 24(2C), 27(2C), 72, 76(2C), 97.2, 97.4, 104, 112.2, 112.4, 113, 113.5, 117, 122.4, 122.5, 128(2C), 142, 154, 155, 160, 162, 163.7, 163.8, 165; ESI-MS: *m/z* $[M+H]^+$ 588.3 (calcd. 587.6).

2,2-Dimethyl-8-oxo-2,3,4,8-tetrahydropyrano[3,2-g]chromen-3-yl 2-(4-((5-(1,2-dithiolan-3-yl)pentanamido)methyl)-1*H*-1,2,3-triazole-1-yl)acetate (12)

Compound **12** was obtained as a white solid in 75% yield by general procedure (A). mp 89 °C; ^{1}H NMR (400

MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.32 (s, 3H), 1.39 (m, 2H), 1.63 (m, 4H), 1.85 (m, 1H), 2.15 (t, *J* = 7.2 Hz, 2H), 2.40 (m, 1H), 2.86 (dd, *J* = 4.8 and 17.6 Hz, 1H), 3.09 (m, 2H), 3.18 (dd, *J* = 4.4, and 17.2 Hz, 2H), 3.50 (m, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 5.09 (m, 3H), 6.08 (br s, 1H), 6.17 (s, 1H), 7.12 (s, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23, 24, 25, 27, 28, 34.5, 34.7, 36, 38, 40, 50, 56, 72, 76, 104, 112, 113, 114, 123, 128, 143, 144, 154, 156, 160, 165, 172; ESI-MS: *m/z* $[M+H]^-$ 573.2 (calcd. 572.7).

2,2-Dimethyl-8-oxo-2,3,4,8-tetrahydropyrano[3,2-g] chromen-3-yl 2-(4-((2-acetyl-5-methoxyphenoxy)methyl)-1*H*-1,2,3-triazole-1-yl)acetate (13)

Compound **13** was obtained as a white solid in 63% yield by general procedure (A). mp 92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 6H), 2.48 (s, 3H), 2.86 (dd, *J* = 4.4 and 17.1 Hz, 1H), 3.18 (dd, *J* = 4.4 and 16 Hz, 1H), 3.82 (s, 3H), 5.10 (t, *J* = 4.4 Hz, 1H), 5.15 (s, 2H), 5.24 (s, 2H), 6.19 (d, *J* = 9.2 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 6.56 (s, 1H), 6.75 (s, 1H), 7.11 (s, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 7.70 (s, 1H), 7.70 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23, 24, 27, 31, 50, 55, 62, 72, 76, 99.3, 104, 106, 112, 113, 114, 121, 124, 128, 142(2C), 154, 155, 159, 160, 164, 165, 197; ESI-MS: *m/z* $[M+H]^-$ 543.3 (calcd. 542.5).

(*E*)-2,2-Dimethyl-8-oxo-2,3,4,8-tetrahydropyrano[3,2-g] chromen-3-yl 2-(4-((3-(3,4-dimethoxyphenyl)acryl amido) methyl)-1*H*-1,2,3-triazole-1-yl)acetate (14)

Compound **14** was obtained as a pale brown solid in 91.7% yield by general procedure (B). mp 155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.35 (s, 3H), 2.89 (dd, *J* = 4.8 and 17.2 Hz, 1H), 3.21 (dd, *J* = 4.8, 17.2 Hz, 1H), 3.90 (s, 6H), 4.63 (d, *J* = 6.0 Hz, 2H), 5.13 (t, *J* = 4.8 Hz, 1H), 5.14 (d, *J* = 3.6 Hz, 2H), 6.25 (d, *J* = 9.6 Hz, 1H), 6.25 (br s, 1H), 6.27 (d, *J* = 15.2 Hz, 1H), 6.79 (S, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 1.6 Hz, 1H), 7.07 (dd, *J* =1.6 and 8.4 Hz, 1H), 7.16 (S, 1H), 7.56 (d, *J* = 15.2 Hz, 1H), 7.58 (d, *J* = 15.2 Hz, 1H), 7.68 (S, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23, 24, 27, 29, 34, 50, 55, 72, 75, 104, 109, 110, 112, 113, 114, 118, 121, 123, 127, 128, 141, 142, 145, 148, 150, 154, 155, 160, 165, 166; ESI-MS: *m/z* $[M+H]^-$ 575.2 (calcd. 574.5).

2,2-Dimethyl-8-oxo-2,3,4,8-tetrahydropyrano[3,2-g] chromen-3-yl 2-(4-((4-acetoxy-3-ethyl-5-methoxybenzamido)methyl)-1*H*-1,2,3-triazole-1-yl)acetate (15)

Compound **15** was obtained as a pale brown solid in 95.3% yield by general procedure (B). mp 174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 6H), 2.30 (s, 3H), 2.85 (dd, *J* = 4.4 and 17.2 Hz, 1H), 3.17 (dd, *J* = 4.4 and 17.2 Hz, 1H), 3.81 (s, 6H), 4.65 (d, *J* = 5.2 Hz, 2H), 5.10 (m, 3H), 6.21 (d, *J* = 9.6 Hz, 1H), 6.75 (s, 1H), 6.81 (br s, 1H), 6.98 (S, 2H), 7.11 (s, 1H), 7.54 (d, *J* = 9.6 Hz, 1H), 7.66 (S, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20, 23, 24, 27, 35, 50, 56 (2C), 72, 76, 103 (2C), 104, 113.5, 113.5, 114, 124, 128, 131, 132, 143, 145, 152 (2C), 154, 155, 161, 165, 166, 168; ESI-MS: *m/z* $[M+H]^-$ 607.2 (calcd. 606.5).

(*E*)-2,2-Dimethyl-8-oxo-2,3,4,8-tetrahydropyrano[3,2-g] chromen-3-yl 2-(4-((3-(4-acetoxy-3-methoxyphenyl)acryl-amido)methyl)-1*H*-1,2,3-triazole-1-yl)acetate (16)

Compound **16** was obtained as a pale brown solid in 69.3% yield by general procedure (B). mp 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 6H), 2.03 (m, 4H), 2.31 (s, 3H), 2.89 (dd, *J* = 4.4 and 17.2 Hz, 1H), 3.21 (dd, *J* = 4.4 and 17.2 Hz, 1H), 3.85 (s, 3H), 4.63 (d, *J* = 5.6 Hz, 2H), 5.13 (m, 3H), 7.57 (d, *J* = 9.6 Hz, 1H), 6.24 (d, *J* = 9.6 Hz, 1H), 6.34 (d, *J* = 15.6 Hz, 1H), 6.38 (br s, 1H), 6.78 (s, 6H), 7.02 (d, *J* = 8.8 Hz, 1H), 7.06 (s, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.15 (s, 1H), 7.57 (d, *J* = 9.6 Hz, 1H), 7.58 (d, *J* = 15.6 Hz, 1H), 7.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20, 23, 24, 27, 29, 34, 50, 55, 72, 104, 111, 113.0, 113.5 (2C), 114, 120 (2C), 123 (2C), 128, 133, 140.5, 140.9, 143, 151, 154, 155, 161, 165 (2C), 168; ESI-MS: *m/z* $[M+H]^-$ 603.2 (calcd. 602.5).

(*E*)-4-(3-(((1-(2-((2,2-dimethyl-8-oxo-2,3,4,8-tetrahydropyrano[3,2-g]chromen-3-yl)oxy)-2-oxoethyl)-1*H*-1,2,3-triazole-4-yl)methyl)amino)-3-oxoprop-1-en-1-yl)-1,2-phenylene diacetate (17)

Compound **17** was obtained as a pale brown solid in 69% yield by general procedure (A). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.32 (s, 3H), 2.28 (d, *J* = 2.8 Hz, 6H), 2.87 (dd, *J* = 4.4 and 17.6 Hz, 1H), 3.17 (dd, *J* = 4.4 and 17.6 Hz, 1H), 4.57 (d, *J* = 6.0 Hz, 2H), 5.10 (t, *J* = 4.4 Hz, 1H), 5.16 (d, *J* = 8.4 Hz, 2H), 6.21 (d, *J* = 9.6 Hz, 1H), 6.39 (d, *J* = 15.6 Hz, 1H), 6.73 (s, 1H), 7.11 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.41 (br s, 1H), 7.48 (d, *J* = 15.6 Hz, 1H), 7.55 (d, *J* = 9.6 Hz, 1H), 7.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20, 23, 24, 27, 29 (2C), 72, 76, 104, 113, 113.5 (2C), 114, 122, 123 (2C), 126, 128 (2C), 133, 139, 142.3, 142.9, 143 (2C), 154, 155, 161, 165 (2C), 168 (2C); ESI-MS: *m/z* $[M+H]^-$ 631.2 (calcd. 630.6).

7-Hydroxy-8, 8-dimethyl-7, 8-dihydropyrano[3,2-g] chromen-2(6*H*)-one (decursinol (9))

To a solution of decursin **8** (3 g, 9.13 mmol) in 15 mL methylene chloride, NaOH (2.1 g, 52.5 mmol) dissolved in MeOH (15 mL) was added at rt slowly. The reaction mixture was stirring for 12 h at rt. The reaction was completed and then was concentrated under vacuum. After the solvent was removed under vacuum, the sticky crude compound was dissolved in water (200 mL) and then titrated in pH 5~6 by adding 2 N HCl solution. The result solution

was warmed to 75 °C and then cooled down to rt naturally to re-crystalize decursinol **9** as a solid product (1.5 g, 66% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.39 (s, 3H), 2.84 (dd, J =4.0 and 16.4 Hz, 1H), 3.11 (dd, J = 4.4 and 16.4 Hz, 1H), 3.87 (m, 1H), 6.22 (d, J = 9.2 Hz, 1H), 6.78 (s, 1H), 7.18 (s, 1H), 7.58 (d, J = 9.6 Hz, 1H).

2,2-Dimethyl-8-oxo-2,3,4,8-tetrahydropyrano[3,2-g]-chromen-3-yl 2-azidoacetate (decursinol-azide (10))

To a solution of 2-azido acetic acid (1.26 g, 12.5 mmol) in 20 mL methylene chloride, DMAP (0.35 g, 2.84 mmol) and EDC (2.39 g, 12.5 mmol) were added at rt. After stirring 5 min, decursinol **9** (1.5 g, 6.09 mmol) was added. The reaction mixture was stirring for 12 h at rt. The reaction was completed and then was quenched with 1N HCl solution, and was extracted with methylene chloride. The combined organic extract was dried over anhydrous $MgSO_4$. After the organic solvent was removed under vacuum, the crude product was re-crystalized in methylene chloride/hexane system to give decursinol-azide **10** as a white solid product (1.3 g, 65% yield) ^{1}H NMR (400 MHz, $CDCl_3$) d 1.34 (s, 3H), 1.35 (s, 3H), 2.15 (s, 2H), 2.86 (dd, J = 4.4 and 17.0 Hz, 1H), 3.18 (dd, J = 4.4 and 16.0 Hz, 1H), 3.83 (m, 2H), 5.10 (t, J = 4.4 Hz, 1H), 6.19 (d, J = 9.2 Hz, 1H), 6.75 (s, 1H), 7.11 (s, 1H), 7.54 (d, J = 6.8 Hz, 1H).

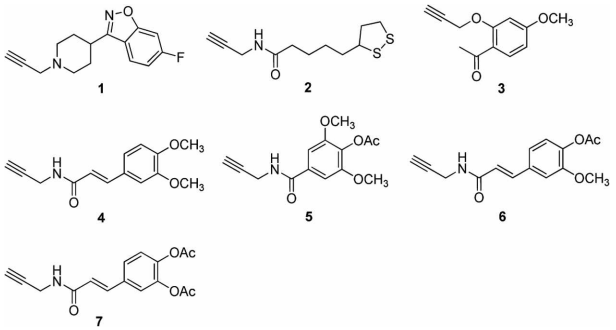
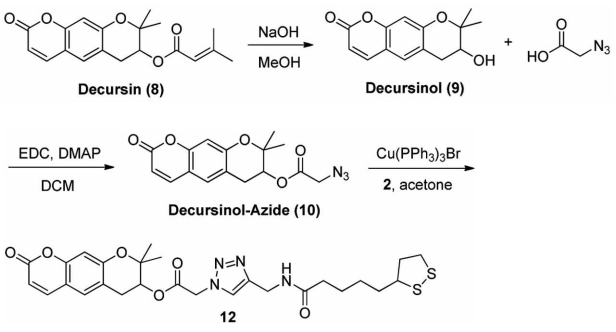


***Figure* 2.** The structures of propagyl compounds using in click reaction utilized in this work.



***Scheme* 1.** Synthesis of 2,2-dimethyl-8-oxo-2,3,4,8-tetrahydropyrano[3,2-g]chromen-3-yl 2-(4-((5-(1,2-dithiolan-3-yl)pentanamido)methyl)-1*H*-1,2,3-triazole-1-yl)acetate (**12**).

RESULTS AND DISCUSSION

The structures of propagyl compounds utilized in this work for the click reaction are shown in *Fig.* 2. The functional group selection of phenol type (**3**–**7**) was based on our previous report[17] showing as an effective inhibition against cholinesterase. Compound **2** was also selected in a same viewpoint from α-lipoic acid (ALA) derivatives.[16] Compound **1** was considered in benzothiazole moiety of Risperidone,[22] an antipsychotic drug mainly used to treat schizophrenia (including adolescent schizophrenia), schizoaffective disorder, the mixed and manic states of bipolar disorder, and irritability in people with autism.

Compounds (**1** and **3**) have been synthesized through S_N2 substitution reaction between propagyl chloride and piperidine involved benzothiazole moiety or a corresponding phenol moiety in the presence of Cs_2CO_3 and TEA, respectively. Compound **2** was synthesized by a coupling reaction between propagyl amine and NHS-activated α-lipoic acid (ALA)[15] in the presence of TEA. Compounds (**4** and **5**) have been synthesized by a coupling reaction between propagyl amine and a corresponding carboxylic acid moiety in the condition of EDC and DIPEA (or DMAP). Compounds (**6** and **7**) have been synthesized by a coupling reaction between propagyl amine and a corresponding acyl chloride moiety made by treatment of thionyl chloride to carboxylic acid moiety at reflux, respectively.

The decursinol-azide **10** was synthesized by a esterification reaction between 2-azido acetic acid and decursinol **9** (*Scheme* 1).

The triazole linked decursinol derivatives **12** was synthesized by Click reaction between decursinol-azide **10** and propagyl compound **2**. The decursinol derivatives synthesized in this work are listed in *Fig.* 3.

The inhibitory results (IC_{50} value) against AChE and BuChE with decursinol, α-lipoic acid (ALA), triazole linked decursinol derivatives are shown in *Table* 1 and *Fig.* 4. The issued decursinol **9** by itself showed inhibitory activity against AChE (IC_{50} = 93.4 ± 18.2 mM) but did not demonstrate any inhibitory activity against BuChE (IC_{50} value > 810 mM). Compound **11** having a benzothiazole moiety of Risperidone exhibited inhibitory activity for both ChEs. Even though α-lipoic acid (ALA) showed no inhibitory activity for both ChEs, ALA-decursinol hybrid **12** showed the best inhibitory activity against BuChE (IC_{50} = 5.89 ± 0.31 mM) among the triazole linked decursinol derivatives and its inhibitory activity is more effective than

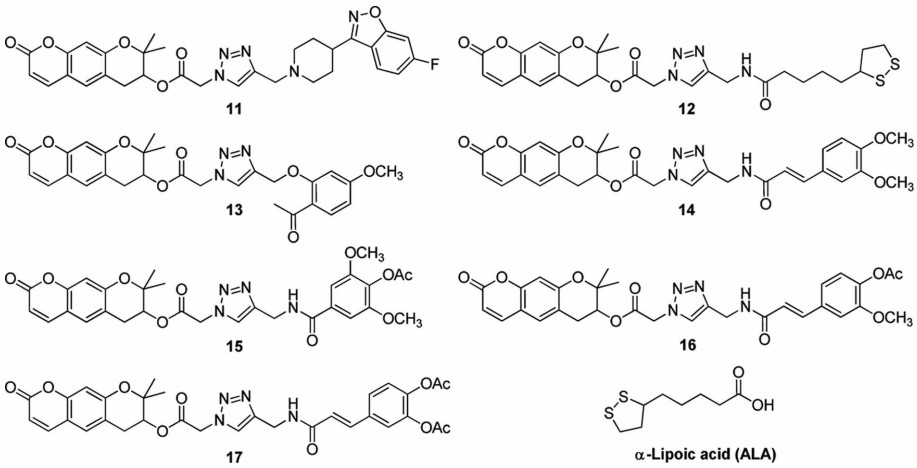


***Figure* 3.** The structures of triazole linked decursinol derivatives synthesized.

***Table* 1.** IC_{50} values for triazole linked decursinol derivatives for ChE inhibition[a]

Sample	AChE inh. IC_{50} (μM)	BuChE inh. IC_{50} (μM)
Gal.	1.7 ± 0.9	9.4 ± 2.5
Dec. (9)	93.4 ± 18.2	>810
ALA	>200	>200
11	61.91 ± 1.4	14.64 ± 0.18
12	>350	5.89 ± 0.31
13	>370	23.87 ± 0.04
14	>350	>350
15	84.74 ± 2.09	>330
16	>330	>330
17	>320	>320

[a]AChE (from electric eel) and BuChE (from horse serum) were used. IC_{50} values represent the concentration of inhibitors that is required to decrease enzyme activity by 50% and are calculated by using the mean of triplicate measurements.

those of galantamine (IC_{50} = 9.4 + 2.5 mM against BuChE). However, it showed no inhibitory activity against AChE (IC_{50} value > 350 mM). In our previous report,[15] the α-lipoic acid (ALA) derivatives usually exhibited better inhibitory effect against BuChE than AChE. Compound **13** also showed only BuChE inhibitory activity (IC_{50} = 23.87 + 0.04 mM). Interestingly, compound **15** consisted of short carbon chain with electron rich group (methoxy group) comparatively exhibited inhibitory activity against AChE (IC_{50} = 84.74 ± 2.09 mM) but no inhibitory activity against BuChE. Compounds (**14**, **16**, and **17**) exhibited no inhibitory activity for both ChEs. Although decursinol itself didn't show inhibitory activity against BuChE, hybridization with proper compounds resulted in effective inhibitory activity against BuChE.

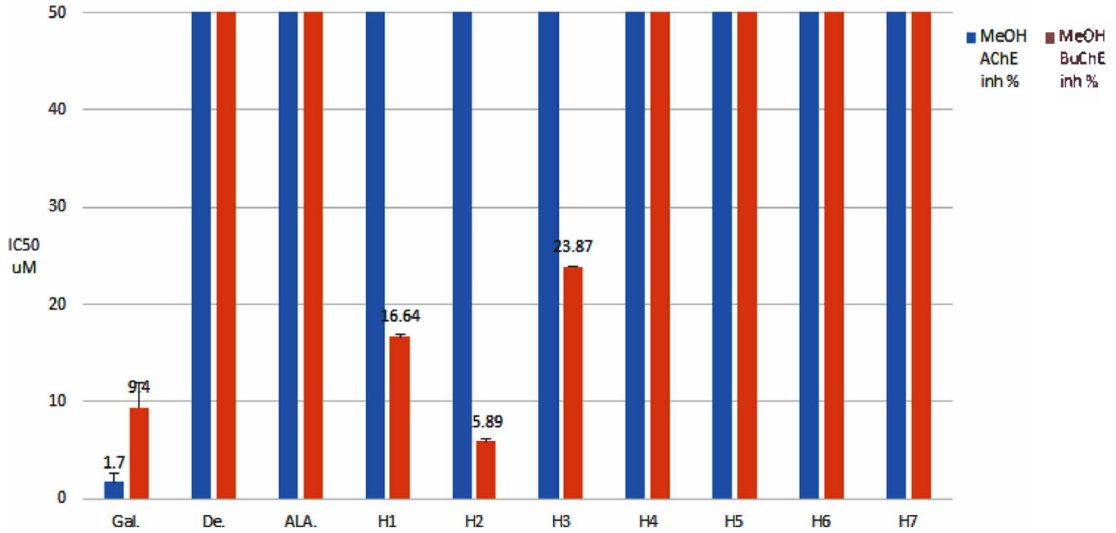


***Figure* 4.** IC_{50} values against BuChE using triazole linked decursinol derivatives (**11**–**17**), decursinol, α-lipoic acid (ALA) and galantamine (Gal).

CONCLUSION

Seven triazole linked decursinol derivatives (**11**–**17**) were synthesized to investigate the effectiveness of decursinol moiety for ChE inhibitory activity. Compounds (**11**–**13**) acted as an effective inhibitor against BuChE and compounds (decursinol **9**, **11**, and **15**) demonstrated inhibitory activity against AChE. Especially, compound **12** showed more effective inhibitory activity against BuChE than galantamine. Inhibitory activity and selectivity (AchE/BuChE) of triazole linked decursinol derivatives may result from not decursinol or triazolee moiety but hybrid compounds. Since decursinol[23] itself is an interesting bioactive pharmacological compound, the new biological activity of decursinol derivatives against BuChE will result in beneficial effects for treating AD patients. Also, selective inhibition of BuChE over AChE may have another beneficial effect compared with exclusive use of AChE inhibitors. Since decursinol derivatives can be a new type of inhibitor against ChEs, further investigations will be carried out to evaluate their activity against AD.

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