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Design, Synthesis, Molecular Docking and Biological Evaluation of Donepezil Analogues as Effective Anti-Alzheimer Agents

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Abstract

Discovering a cure for Alzheimer's disease remains an intricate endeavor. Acetylcholinesterase enzyme (AChE) inhibitors, such as donepezil, hold a crucial position in Alzheimer's therapy. Our present study focused on the innovative design and synthesis of new analogues of donepezil, employing a click chemistry approach. We characterized the molecular structures of these synthesized compounds through a combination of elemental analysis and various spectroscopic techniques, including FT-IR, ^{1}H NMR, and ^{13}C NMR methods. These substances underwent assessment to determine their ability to inhibit AChE activity. Most of the tested compounds demonstrated the capacity to effectively inhibit AChE. The *in vitro* experiments were utilized to determine the IC50 values for the most promising candidates, which were subsequently validated using molecular docking techniques. Interestingly, compound **15** displayed the best profile with IC_{50} of about IC_{50} = 0.392 µg/mL, in addition to its high docking score (-8.86 kcal/mol) and good *in silico* pharmacokinetic prediction. Therefore, **15** could be a promising compound that can be used for further development of novel drugs for Alzheimer's disease.

Keywords: Donepezil; Click chemistry; Triazoles; Glycosides; Alzheimer's disease; Acetylcholine esterase

1. Introduction

Alzheimer's disease (AD) poses a significant challenge as a neurodegenerative disorder, primarily affecting individuals aged 65 and above. The intricate nature of the disease complicates the search for effective treatments. Currently, AD affects over 50 million people globally, and this number is expected to triple by the year 2050 [1-4]. Consequently, there is an urgent need for drug developers to discover effective anti-AD agents [5, 6]. Although the precise mechanism of AD remains uncertain, it is widely recognized that the disease is a complex syndrome resulting from various neurochemical factors [7]. Several molecular mechanisms have been proposed, including the β-amyloid cascade [8], cholinergic dysfunction [9], as well as various other mechanisms and hypotheses that have been suggested and documented [10-16]. These findings not only inspire

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the development of new anti-AD agents with diverse mechanisms but also shed light on the intricate nature of AD. The FDA has authorized five drugs for AD symptom relief, four of which are acetylcholinesterase (AChE) inhibitors: rivastigmine, galantamine, tacrine, and donepezil (Figure 1). Among these, donepezil stands out as the most favorable AChE inhibitor due to its unique benefits [17]. Numerous donepezil analogues have been developed and shown promise as effective anti-Alzheimer agents [18-27]. The 1,2,3-triazole and its derivatives play a critical role as essential heterocyclic compounds extensively employed as pharmacophores in pharmaceutical drugs and diverse fields. Their biological activities have been extensively explored and validated through various studies [28-40]. By incorporating donepezil-triazole with a sugar moiety, these compounds demonstrate the ability to effectively target and deliver drugs across the blood-brain barrier, allowing for potential therapeutic benefits in combating neurological conditions such as AD. Based on the insights from previously cited reports and our ongoing research in synthesizing biologically active compounds [41-47], we have successfully developed novel donepezil analogs by combining its precursor with a 1,2,3-triazole core and diverse sugar/non-sugar components through click chemistry. These compounds were evaluated, aiming to enhance the potential for treating Alzheimer's disease effectively.

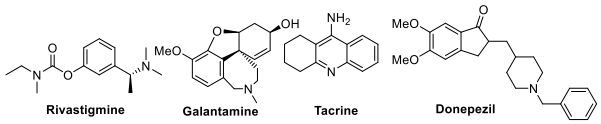


Fig. 1**:** Structures of five drugs approved by FDA in the treatment of Alzheimer's disease (AD).

2. Materials and methods

2.1 Experimental section

2.1.1 Synthesis methods

All melting points are uncorrected and were measured using an Electro thermal IA 9100 apparatus. The ^{1}H NMR and ^{13}C NMR spectra were measured on a BRUKER 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR at Faculty of Science, Zagazig University, Egypt. The coupling constants (J) were given in Hertz. The chemical shifts are expressed on the δ (ppm) scale using TMS as the standard reference. The FT-IR spectra were recorded on a Shimadzu IR 8400s spectrophotometer. The microanalytical data were carried out on a Vario El-Mentar instrument, at the Micro Analytical Laboratory, National Research Center, Cairo, Egypt. The reactions were monitored by thin layer chromatography (TLC). TLC was performed on Macherey-Nagel aluminum-backed plates, pre-coated with silica gel 60 (UV254). Column chromatography was carried out on silica gel 60 (0.040–0.063 mm) under flash conditions. All chemicals and solvents were purchased from Sigma-Aldrich, Alfa Aesar and ACROS Organics and used as provided. 2,3,4,6-Tetra-O-acetyl-α-D-gluco-or galactopyranosyl bromide, 2,3,4,6-tetra-O-acetyl-β-D- gluco-or galactopyranosyl azide, 2,3,4-tri-O-acetyl-β-D-xylopyranosyl azide [47], [48], 2-azidoethan-1-ol , 2-(2-azidoethoxy)ethan-1-ol [49] and 5,6-dimethoxy-2-(piperidin-4-yl)methylene-indan-1-one [50] were prepared according to the respective published methods.

5,6-Dimethoxy-2-((1-(prop-2-yn-1-yl)piperidin-4-yl)methyl)-2,3-dihydro-1H-inden-1-one (3).

A mixture of compound 2 (2.50 g, 8.65 mmol), K_2CO_3 (3.6 g, 26.0 mmol) and NaI (2.0 g, 13.3 mmol) in dry DMF (15 mL) was stirred at room temperature for 15 minutes, and then propargyl bromide (0.86 mL, 9.6 mmol) was added. After stirring overnight at room temperature under an argon atmosphere, the reaction mixture was treated with a saturated solution of NH_4Cl and extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain compound 3 as a yellow solid. Yield: 83 %, mp 65 - 67 °C. IR (KBr, υ, cm^{-1}): 3040, 3010, 2938, 2218, 1720. ^{1}H NMR (DMSO–d_6, δ ppm): 1.17-1.48 (m, 4H), 1.61-2.15 (m, 5H), 2.62-2.89 (m, 3H), 3.11 (s,1H, acetylenic proton), 3.20-3.22(m, 2H), 3.39 (dd, 2H, NCH_2), 3.78 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 7.04-7.07 (d, 2H, Ar). ^{13}C NMR (DMSO–d6, δ ppm): 31.2, 32.5, 32.6, 33.4, 38.2, 44.7, 46.4, 51.8, 55.6, 55.9, 64.9, 75.4, 79.7, 103.9, 108.1, 128.4, 148.7, 149.1, 155.2, 206.6. m/z: 327.18 (100.0%), 328.19 (22.0%), 329.19 (2.9%). Anal. Calcd for $C_{20}H_{25}NO_3$ (327.43): C, 73.37; H, 7.70; N; 4.28; O; 14.66 %. Found: C, 73.39; H, 7.72; N; 4.28; O; 14.67 %.

General procedure for synthesis of 1,2,3-triazole acetylated *N*-glycosides derivatives (10-12).

To a well-stirred solution of the terminal acetylenic compound **3** (0.654 g, 2.0 mmol) in a mixture of THF–H_2O (1:2, 15 mL) was added the azido-sugar (2,3,4,6-tetra-O-acetyl-D-glucopyranosyl or 2,3,4,6-tetra-O-acetyl-D-galactopyranosyl or 2,3,4-tri-O-acetyl-D-xylopyranosyl azide), (2.0 mmol) was added. Sodium ascorbate (0.08 g, 0.4 mmol) and a

few drops of diisopropylethylamine (DIPEA) followed by $CuSO_4.5H_2O$ (0.4 mmol, 0.11 g) were then added. The mixture was stirred at room temperature overnight (TLC, petroleum ether–ethyl acetate (4:1). After completion of the reaction (as monitored by TLC), the reaction mixture was extracted with AcOEt (5 x 5 mL), then the mixture was dried over $MgSO_4$ and was concentrated in vacuo. The crude residue was separated/purified using column Chromatography (hexane/ethyl acetate, 5:1, as the eluent) to give the title products.

(2S,3S,4R,5S,6S)-2-(Acetoxymethyl)-6-(4-((4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-methyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (10).

The product **10** was obtained as a white solid (70 % yield), mp = 70 –75 °C. IR (KBr, υ, cm^{-1}): 3040, 2946, 1751, 1728, 1701; ^{1}H NMR ($CDCl_3$, δ ppm): 1.22-1.78 (m, 7H, $3CH_2$ + CH); 1.85, 2.00, 2.05, 2.07 (all s, 3H each, 4 x CH_3CO); 2.68 (m, 2H), 2.95 (s, 1H), 3.22 (dd, 1H), 3.75 (m, 1H); 3.88 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3); 3.99 (dd, *J* = 12.6 Hz, *J* = 5.4 Hz, 1H, H6a′), 4.15 (dd, *J* = 12.6 Hz, *J* = 1.7 Hz, 1H, H6b′), 4.31 (ddd, *J* = 9.7 Hz, *J* = 5.4 Hz, *J* = 1.7 Hz, 1H, H5′), 5.24 (t, *J* = 9.3 Hz, *J* = 9.3 Hz, 1H, H3′), 5.41 (t, *J* = 9.3 Hz, *J* = 9.0 Hz, 1H, H2′), 5.85 (d, *J* = 9.0 Hz, 1H, H1′), 6.83 (s,1H; Ar), 7.13 (s, 1H, Ar); 7.76 (s, 1H, triazole-H); m/z:700.30 (100.0%), 701.30 (37.7%), 702.30 (9.8%). Anal. Calcd for $C_{34}H_{44}N_4O_{12}$ (700.74): C, 58.28; H, 6.33; N, 8.00; O, 27.40 %. Found: C, 58.26; H, 6.33; N, 8.02; O, 27.40 %.

(2S,3R,4R,5S,6S)-2-(Acetoxymethyl)-6-(4-((4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1H-iden-2-yl)-methyl)piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (11).

The product **11** was obtained as a white solid (69 % yield), mp = 118-120 °C. IR (KBr, υ, cm^{-1}): 3132, 3035, 2948, 1754, 1725. ^{1}H NMR (DMSO–d6, δ ppm): 1.21-1.69 (m, 7H, CH, CH_2); 1.81, 1.95, 2.00, 2.20 (all s, 3H each, 4 x CH_3CO); 2.61-2.64 (dd, 2H); 2.79 (bs, 1H); 3.17-3.24 (dd, *J* = 8.0 Hz, 1H); 3.35-3.37 (m, 2H); 3.55 (bs, 1H); 3.51-3.58 (bs, 2H); 3.78 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); 4.09 (dd, 1H, *J* = 4.8, *J* = 10.8 Hz, H-6'), 4.13 (dd, 1H, *J* = 3.2, *J* = 11.2 Hz, H-6"), 4.60 (t, 1H, *J* = 5.6 Hz, H-5‘); 5.43-5.48 (m, 2H, H-4‘+ H-3‘); 5.58 (t, 1H, *J* = 9.6 Hz, H-2‘); 6.24 (d, 1H, *J* = 9.2 Hz, H-1‘), 7.04-7.07 (d, 2H, Ar); 8.19 (s, 1H, triazole-H). ^{13}C NMR (DMSO–d6, δ ppm): 20.0, 20.3, 20.4, 20.5, 31.3, 32.6, 33.60, 38.2, 44.7, 52.7, 55.6, 55.9, 61.6, 67.3, 67.9, 70.4, 73.0, 84.3, 103.9, 108.2, 123.1, 128.4, 148.7, 149.1, 155.2, 168.5, 169.5, 169.9, 170.0, 206.6. m/z: 700.30 (100.0%), 701.30 (37.7%), 702.30 (9.8%). Anal. Calcd for $C_{34}H_{44}N_4O_{12}$ (700.74): C, 58.28; H, 6.33; N, 8.00; O, 27.40 %. Found: C, 58.26; H, 6.33; N, 8.02; O, 27.40 %.

(2S,3S,4R,5R)-2-(4-((4-((5,6-Dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl)-piperidin-1-yl)-methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (12).

To a well stirred solution of the terminal acetylenic derivative **3** (0.654 g, 2.0 mmol) in a mixture of THF–H_2O (1:2, 15 mL), 2,3,4-tri-O-acetyl-D-xylopyranosyl azide was added following the general procedure. The title compound was separated and purified by column chromatography (Petroleum ether/ethyl acetate 8/2). Yield: 68 %, as pale brown syrup. IR (KBr, υ, cm^{-1}): 3132, 2946, 1752, 1720, 1705; ^{1}H NMR (DMSO–d6, δ ppm): 1.23-1.91(m, 7H, CH, CH_2); 1.99, 2.02, 2.04 (all s, 3H each, 3 x CH_3CO); 2.61-2.64 (d, 2H); 2.86 (s, 1H); 3.17-3.24 (dd, *J* = 8.0 Hz, 1H); 3.21-3.69 (m, 2H); 3.55 (bs, 1H); 3.51-3.58 (bs, 2H); 3.78 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3); 4.09 (dt, 2H, H-5‘); 5.14 (m, 1H, H-4‘), 5.50 (t, 1 H, H-2‘), 5.60 (t, 1H, H-3’), 6.20 (d, 1 H, *J* = 8.0 Hz, H-1‘), 7.05-7.08 (d, 2H, Ar), 8.30 (s, 1H, triazole-H). ^{13}C NMR (DMSO–d6, δ ppm): 19.9, 20.3, 20.5, 32.6, 33.1, 33.2 38.1, 39.3, 44.7, 52.4, 55.6, 55.9, 64.1, 68.0, 70.2, 70.4, 71.8, 84.7, 103.9, 108.2, 128.4, 148.7, 149.1, 155.2, 168.5, 169.1, 169.6, 206.6. m/z: 628.27 (100.0 %), 629.28 (34.4 %), 630.28 (7.8 %), 629.27 (1.5 %), 631.28 (1.4 %). Anal. Calcd for $C_{31}H_{40}N_4O_{10}$ (628.68): C, 59.23; H, 6.41; N, 8.91; O, 25.45 %. Found: C, 59.24; H, 6.42; N, 8.91; O, 25.46 %.

2-((1-((1-(2-(2-Hydroxyethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-piperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one (14).

To a well stirred solution of the terminal acetylenic derivative **3** (0.654 g, 2.0 mmol) in a mixture of THF–H_2O (1:2, 15 mL), 2-(2-azidoethoxy)ethan-1-ol **13a** (0.262 g, 2.0 mmol) was added. Sodium ascorbate (0.08 g, 0.4 mmol) and few drops of diisopropylethylamine (DIPEA) followed by $CuSO_4.5H_2O$ (0.4 mmol, 0.11 g) were then added. The mixture was stirred at room temperature overnight (TLC, petroleum ether–ethyl acetate (4:1). Extraction of the organic compound layer was performed by shaking the mixture twice times for 5 min with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 and the solvent was evaporated. Purification by column chromatography (hexane/ethyl acetate, 5:1, as the eluent) gave the title product. Yield: 64 %, as pale yellow syrup. IR (KBr, υ, cm^{-1}): 3368, 2920, 2869, 1693, 1613, 1458, 1140, 1060. ^{1}H NMR ($CDCl_3$): 1.22-2.06 (m, 7H, CH_2, CH), 2.63-2.90 (m, 6H, CH_2), 3.21 (m, 1H, CH), 3.47-3.51(m, 6H, $3CH_2$); 3.60 (t, 2H, CH_2); 3.78 (s,

3H, OCH_3), 3.86 (s, 3H, OCH_3); 4.51 (t, 2H, CH_2); 7.04 (s, 1H; Ar), 7.08 (s, 1H, Ar); 8.00 (s, 1H, triazole-H). ^{13}C NMR (125 MHz, $CDCl_3$): 21.3, 29.0, 30.6, 30.9, 32.1, 32.6, 33.4, 34.23, 38.1, 44.71, 49.4, 50.1, 52.7, 55.6, 55.9, 60.2, 60.2, 68.7, 69.2, 72.1, 72.2, 103.9, 108.2, 124.5, 128.4, 148.7, 149.1, 155.2, 206.6. m/z: 458.25 (100.0%), 459.26 (26.5%), Anal. Calcd for $C_{24}H_{34}N_4O_5$ (458.25): C, 62.86; H, 7.47; N, 12.22; O, 17.44. Found: C, 62.87; H, 7.46; N, 12.22; O, 17.44.

2-((1-((1-(2-Hydroxyethyl)-1H-1,2,3-triazol-4-yl)methyl)piperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one (15).

To a well stirred solution of the terminal acetylenic derivative **3** (0.654 g, 2.0 mmol) in a mixture of THF–H_2O (1:2, 15 mL), 2-azidoethan-1-ol **13b** (0.174 g, 2.0 mmol) was added. Sodium ascorbate (0.08 g, 0.4 mmol) and a few drops of diisopropylethylamine (DIPEA) followed by $CuSO_4.5H_2O$ (0.4 mmol, 0.11 g) were then added. The mixture was stirred at room temperature overnight (TLC, petroleum ether–ethyl acetate (4:1). Extraction of the organic compound layer was performed by shaking the mixture twice times for 5 min with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 and the solvent was evaporated. Purification by column chromatography (hexane/ethyl acetate, 5:1, as the eluent) gave the title product. Yield: 71 %, brown syrup. (KBr, υ, cm^{-1}): 3388, 2925, 1722, 1460, 1123, 1062. ^1H NMR ($CDCl_3$): 1.19-2.10 (m, 7H, CH_2, CH), 2.61-3.00 (m, 6H, $3CH_2$), 3.21—3.63 (m, 5H, CH_2, CH), 3.78 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3); 4.38 (t, 2H, NCH_2CH_2); 5.75 (s, 1H, OH); 7.06-7.08 (d, 2H, Ar); 7.97 (s, 1H, triazole-H). m/z: 414.23 (100.0%). Anal. Calcd for $C_{22}H_{30}N_4O_4$ (414.51): C, 63.75; H, 7.30; N, 13.52; O, 15.44. Found: C, 63.78; H, 7.31; N, 13.52; O, 15.44.

General procedure for synthesis of acetylated *N*-glycosides derivatives (16, 17).

To a solution of compound **2** (1.447 g, 5 mmol) in aqueous potassium hydroxide (0.561 g, 10 mmol) in distilled water (16 ml), a solution of 2,3,4,6-tetra-O-acetyl-α-D-gluco-or galactopyranosyl bromide **4**, **5** (5 mmol) in acetone (20 mL) was added. The reaction mixture was stirred at room temperature for 10 h (TLC; pet. ether/ethyl acetate, 4:1). The solvent was evaporated under reduced pressure at 40 °C and the residue was extracted with ethyl acetate. The organic phase was washed by saturated NaCl (aq), dried over Na_2SO_4, concentrated, and directly purified by preparative thin-layer chromatography (Petroleum ether/ethyl acetate as the eluent) to afford the product.

(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-methyl)piperidin-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (16).

The product **16** was obtained as yellow syrup (66 % yield). IR (KBr, υ, cm^{-1}): 3015, 2990, 1735, 1699; ^1H NMR ($CDCl_3$, δ ppm): 1.11-1.34 (m, 4H), 1.61-1.77 (m, 2H), 1.86-1.93 (m, 1H), 1.96, 1.98, 2.00, 2.01 (4s, 12H, CH_3 acetate), 2.57-2.74 (m, 4H), 3.06-3.11 (m, 2H), 3.23 (dd, 1H), 3.58–3.62 (m, 1H), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.96 (m, 1H, H-5‘), 4.20 (m, 2H, H6‘, 6"), 5.20 (t, 1H, H-4'), ,5.37–5.44 (m, 2H, H-2‘, H-3‘), 5.96 (d, 1H, *J* = 10.5, H-1'), 7.05- 7.07 (d, 2H, Ar); ^{13}C NMR, δ (ppm): 20.0, 20.1, 20.2, 20.3, 31.6, 32.6, 33.4, 44.3, 38.7, 45.4, 46.8, 46.9, 56.1, 56.3, 61.8, 68.2, 68.3, 71.8, 72.9, 82.1, 104.4, 107.4, 129.5, 148.8, 149.5, 155.5, 169.8, 169.9, 170.0, 170.1, 207.8. m/z: 619.26 (100.0%), 620.27 (34.5%), 621.27 (8.2%), 622.27 (1.5%). Anal. Calcd for $C_{31}H_{41}NO_{12}$ (619.66): C, 60.09; H, 6.67; N, 2.26; O, 30.98 %. Found: Found: C, 60.10; H, 6.65; N, 2.26; O, 30.99 %.

2R,3S,4S,5R,6R)-2-(acetoxymethyl)-6-(4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-methyl)piperidin-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (17).

The product **17** was obtained as yellow syrup (74 % yield). IR (KBr, υ, cm^{-1}): 3040, 2986, 1751, 1705; ^1H NMR (DMSO–d6, δ ppm): 1.13-1.33 (m, 4H), 1.62-1.77 (m, 2H), 1.83-1.94 (m, 1H), 1.97, 1.98, 2.00, 2.02 (4s, 12H, CH_3 acetate), 2.56-2.74 (m, 4H), 3.04-3.12 (m, 2H), 3.23 (dd, 1H), 3.57–3.62 (m, 1H), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.96 (m, 1H, H-5‘), 4.20 (m, 2H, H6‘, 6"), 5.20 (t, 1H, H-4'), 5.37–5.44 (m, 2H, H-2‘, H-3‘), 5.96 (d, 1H, *J* = 10.4, H-1‘'), 7.05 (s,1H; Ar), 7.07 (s, 1H, Ar). Anal. Calcd for $C_{31}H_{41}NO_{12}$ (619.66): C, 60.09; H, 6.67; N, 2.26; O, 30.98 %. Found: C, 60.08; H, 6.66; N, 2.27; O, 30.99 %.

2.2 *In Vitro* Acetyl-Cholinesterase Enzyme Inhibition Assay

The acetylcholinesterase activity was assessed using QuantiChrom™ Screening Kit (IACE-100) obtained from BioAssay Systems. Three positive controls; Donezepil, Tacrine and Rivastagmine were tested alongside the **7** synthesized compounds, following the kit's instructions. A dose-response curve was generated by performing serial logarithmic dilutions (10 - 1000 nM) of all the tested compounds, and IC_{50} values were calculated from the curve.

2.3 Molecular docking

2.3.1 Receptor preparation

The protein sequence data of hAChE was obtained from the protein data bank (PDB) with the

ID 4EY7. The selected PDB file was prepared using MOE v.2019.01 with the AMBER10: EHT forcefield. The preparation steps included adding 3D protonation, deleting water molecules that were more than 4.5 Å away from the complex, and refining the structure to 0.1 kcal/mol/Å.

2.3.2 Ligand preparation

The 2D structures of the 7 designed compounds were drawn using ChemDraw 15.0 and saved in .cdx format. The ligand file was then opened in Open Babel, a software that converts chemical formats. Hydrogen atoms were added to the ligand using the Add hydrogen option and the pH was set to the standard physiological pH of 7.4. The ligand files were saved in Mol2 format, which is a common format for molecular modeling.

2.3.3 Docking

Docking is a molecular modeling technique that is used to predict how a protein interacts with ligands. MOE v.2019.01, a software for molecular modeling and simulation, was used to redock the co-crystallized ligand to validate the docking parameters. Then, the 7 synthesized compounds were docked on the ligand binding site using the triangle matcher for the placement and two rescoring functions: London dG and GBVI/WSA dG.

2.3.4 Pharmacokinetics and toxicity in silico prediction.

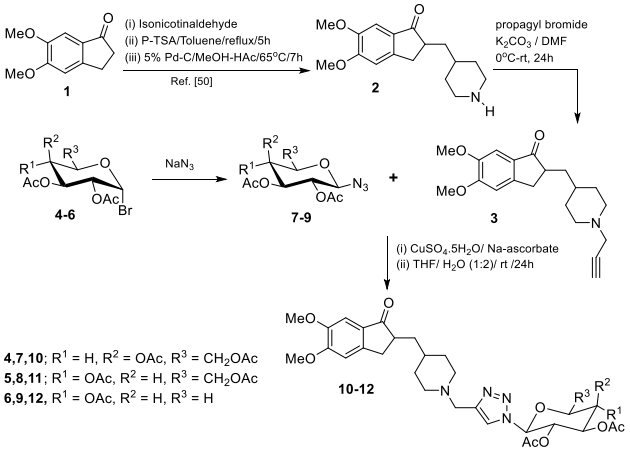
ADME studies are crucial for analyzing the pharmacodynamics properties of a ligand. two online tools were utilized to assess the drug-likeness profiles of the seven designed compounds in silico. The SWISS-ADME online web tool (http://www.swissadme.ch/index.php) was employed to predict various ADME features of the ligands, including solubility class, blood-brain barrier (BBB) permeability, bioavailability score, and detection of PAINS alerts. Additionally, the pkCSM online web tool (http://biosig.unimelb.edu.au/pkcsm/prediction) was used to predict other ADME and toxicity parameters such as human intestinal absorption, volume of distribution (VDss), AMES toxicity and hERG I inhibition.

3. Results and Discussion

In the search for AChE inhibitors, a small library of donepezil analogs was synthesized starting from 5,6-dimethoxy-2-(piperidin-4-yl)methylene-indan-1-one **2** as shown in schemes 1-3. Donepezil precursor **2** was prepared from the condensation of available 5,6-dimethoxy-indan-1-one **1** with 4-pyridinecarboxaldehyde followed by hydrogenation according to a reported procedure [50]. In the current investigation, two new types of donepezil analogues were designed. In the first type, new donepezil conjugates bearing a 1,2,3-triazoles core and different sugar/non sugar moieties have been prepared using click reactions. In the second new type, donepezil conjugates attached directly to sugar moieties without bearing a 1,2,3-triazoles core have been also synthesized.

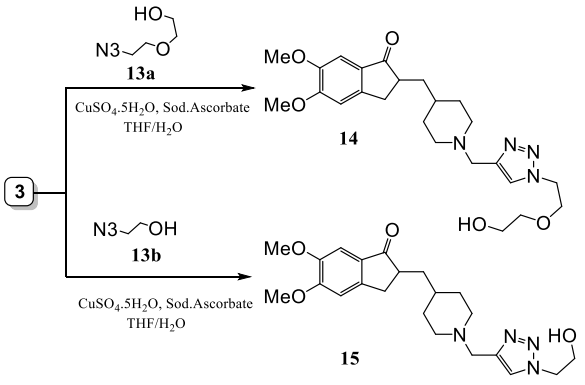
To achieve the first type, the piperidinyl derivative **2** was subsequently converted to its alkyne **3** in an acceptable yield by its propargylation at ambient temperature with propargyl bromide in the presence of anhydrous DMF and K_2CO_3. The resulting alkynyl derivative was identified through IR spectra, which revealed distinct absorption bands characteristic of acetylenic moieties at 2218 cm^{-1}. Moreover, the ^1H NMR spectra exhibited evident signals corresponding to the acetylene protons of the propargyl group and methylene protons at δ = 3.11, 3.20 ppm, respectively.

In a separate set of reactions, the terminal acetylenic compound **3** was allowed to react with three glycosyl azides: definitely tetra-O-acetyl-*β*-D-gluco-, tetra-O-acetyl-*β*-D-gluco- and tri-O-acetyl-*β*-D-xylopyranosyl azides **7-9** (Scheme 1), under click dipolar cycloaddition conditions, which led to the formation of the targeted 1,2,3-glycoside derivatives **10-12**, respectively, in 68-70 % yield. The proposed structures were validated through elemental analyses and verified by employing IR, ^1H NMR, ^{13}C NMR, and mass spectra.



Scheme 1: Synthesis route of compounds 2 and 10-12

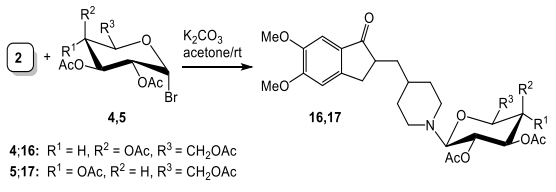
Analogously, under click reaction conditions, coupling of compound **3** with acyclic azides namely 2-(2-azidoethoxy) ethan-1-ol **13a** and 2-azidoethan-1-ol **13b**, afforded the products **14** and **15** in yields of 64 % and 71 %, respectively.



Scheme 2: Synthesis route of compounds 14 and 15

The procedure for synthesizing the click products involved dissolving the reagents in an equimolar ratio within a THF/H_2O solvent mixture. Subsequently, $CuSO_4.5H_2O$/NaAc aqueous catalyst was introduced to the reaction mixture, with $CuSO_4$ serving as the source of copper ions. To prevent the formation of oxidative byproducts, sodium ascorbate was added as a reducing agent. The reaction was conducted at room temperature for 24 hours, resulting in the attainment of high yields of pure products.

The structures of compounds **10, 11, 12, 14,** and **15** were confirmed through a combination of spectroscopic data and elemental analyses, which remained consistent with the expected structures. For instance, the IR analysis of donepezil analogs **10-12** revealed distinct stretching vibrations of the acetate carbonyl groups, observed at 1751, 1754, and 1752 cm^{-1}, respectively. Additionally, the presence of the CH-triazole proton signal in the ^{1}HNMR spectrum, along with the appearance of two distinct signals corresponding to C(4) and C(5) of the triazole ring in the ^{13}C NMR spectrum, provides compelling evidence confirming the successful formation of the desired product.



Scheme 3: Synthesis route of compounds 16 and 17

In the generation of the second group of metabolites, the piperidine derivative **2** reacted with acetylated bromosugars **4** and **5**, yielding *N*-glycosylated nucleosides **16** and **17** in yields of 66 % and 74 % respectively (shown in Scheme 3). The purity of the compounds was confirmed using thin-layer chromatography with a chloroform/methanol mixture (9:1 ratio). The identities of products **16** and **17** were verified through elemental analysis and various spectral techniques (MS, IR, 1H NMR, and ^{13}C NMR). As an example, compound **16**'s data showed a molecular formula of $C_{31}H_{41}NO_{12}$, with its mass spectrum indicating a molecular ion peak at m/z 619. In the ^{1}H NMR spectrum, the glucose moiety's anomeric proton appeared as a doublet at δ 5.96 ppm, suggesting a *β*-configuration. The acetoxy groups showed as singlets between δ 1.96 and 2.01 ppm, and other glucopyranose ring protons appeared at δ 3.96–5.44 ppm. The ^{13}C NMR displayed signals at δ 169.8, 169.9, 170.0, 170.1, and 207.8 ppm for acetoxy carbonyl carbons and one indanone ring carbonyl. Acetate methyl carbons appeared at δ 20.0–20.3 ppm. Sugar carbons were observed at δ 68.2, 68.3, 71.8, 72.9, and 82.1 ppm, while other signals matched expected values.

3.1. *In Vitro* Acetyl-Cholinesterase Enzyme Inhibition Assay and SAR

To evaluate the activity of the seven synthesized compounds as potent AD symptomatic candidates, an *in vitro* inhibition assay on the AChE was conducted and compared to three FDA-approved drugs as AChE inhibitors: donepezil, tacrine, and rivastigmine. Inhibitory concentration (IC_{50}) data, shown in **Fig. 2** and **Table 1**, reveals that compound **15** exhibits the most potent AChE inhibition activity (IC_{50} = 0.392 µg/mL) which is approximately 9 folds more active than rivastigmine (IC_{50} = 3.58 µg/mL) but one third to one half the activity of donepezil and tacrine, which demonstrated IC_{50} values of 0.134 and 0.19, respectively. The next best activities were shown by compounds **16** and **14,** with IC_{50} values of 0.988 and 2.107 µg/mL, respectively, which are still more potent than rivastigmine. Compounds **17** and **11** showed intermediate activity (IC_{50} = 7.077 and 9.277 µg/mL, respectively). The least potent derivatives were **10** and **12** (IC_{50} = 16.1 and 30.71 µg/mL, respectively).

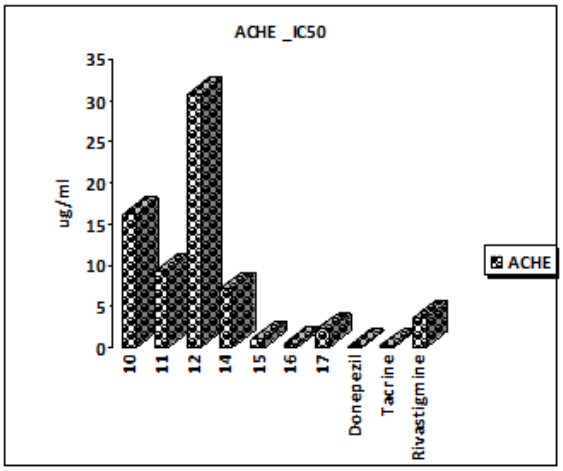


Figure 2: Statistical comparison of inhibitory concentration data (IC_{50} values) of 7 synthesized compounds, Donepezil, Tacrine, and Rivastigmine against acetylcholinesterase (AChE).

Table 1. IC_{50} values of compounds **10, 11, 12, 14, 15, 16, 17,** Donepezil, Tacrine, and Rivastigmine against acetylcholinesterase (AChE). * Experiments were run in triplicates and the data presented are the mean IC_{50} values ± standard deviation

Compound no	**AChE**	
	IC_{50} (µg/mL)	**± SD***
10	16.1	0.86
11	9.227	0.49
12	30.71	1.63
14	2.107	0.11
15	0.392	0.02
16	0.988	0.05
17	7.077	0.38
Donepezil	0.134	0.01
Tacrine	0.19	0.01
Rivastigmine	3.58	0.19

Accordingly, SAR studies show that conjugating 1,2,3-triazole with a glycosidic moiety to donepezil increases its inhibitory activity by more than 100-folds, as seen in compounds **10**, **11**, and **12** (Scheme 1). The tri-O-acetyl-β-D-xylopyranosyl azides derivative (compound **12**) shows nearly 2-fold greater activity than the tetra-O-acetyl-β-D-glucosyl azides derivatives (compounds **10** and **11**). However, replacing the glycosidic moiety with an aliphatic alcohol decreases their activity by more than 10-fold. Short aliphatic alcohols are less favorable, as compound **15** demonstrates approximately 5-fold less inhibitory concentration than compound **14**, which contains a longer aliphatic alcoholic moiety with an ether group. Similarly, conjugating donepezil to a glycosidic moiety without a triazole moiety (compounds **16** and **17**) shows better inhibitory activity (about 3-fold) compared to triazole alone but still much less than when combined with 1,2,3-triazole and a glycosidic moiety.

3.2. Molecular docking and *in silico* pharmacokinetics prediction

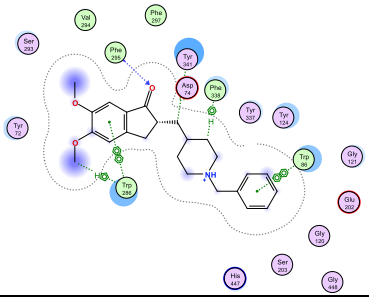
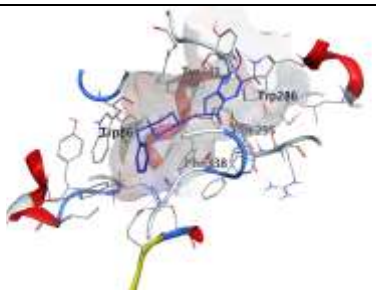
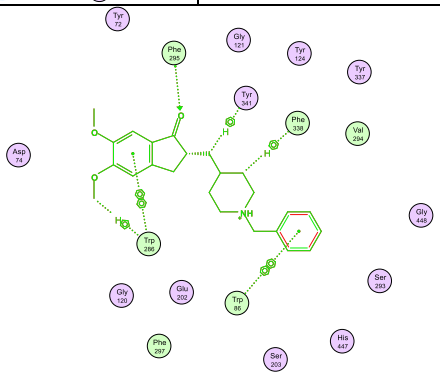
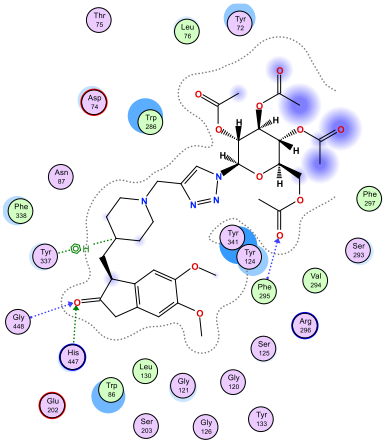
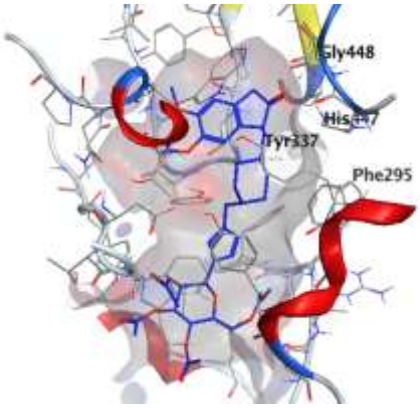
All the 7 synthesized derivatives showed better S-Scores on Acetyl-choline esterase (-8.8602 =< S-Score =< -11.5243 kcal/mol), which is much better than its native co-crystallized ligand (donepezil), showing docking scores of -8.7716 Kcal/mol **(Table 2)**.

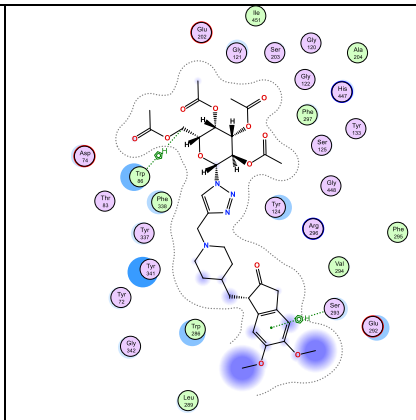
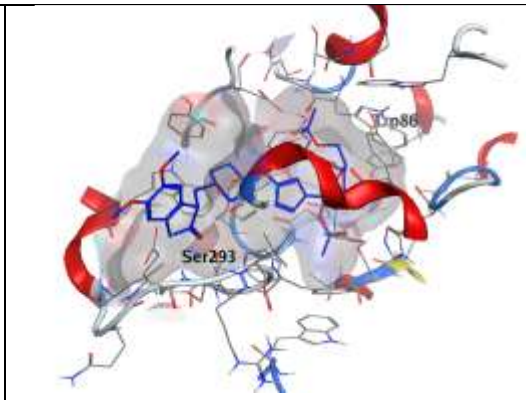
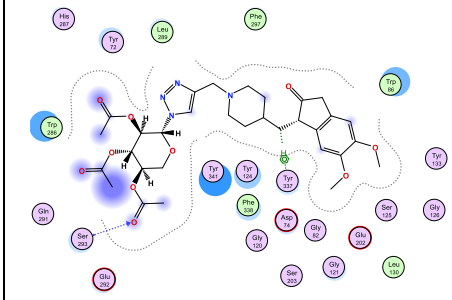
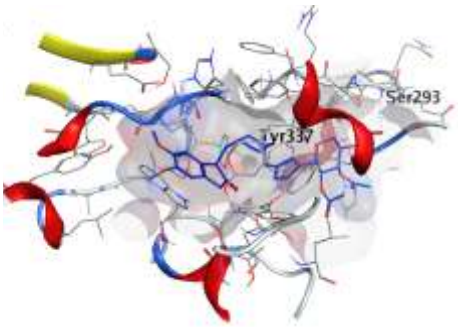
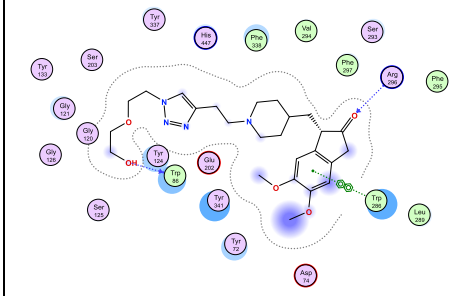
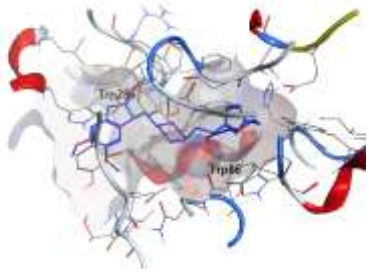
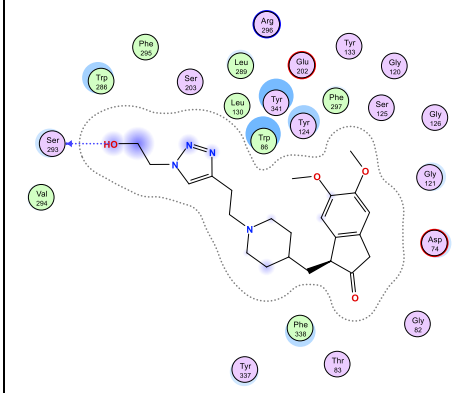
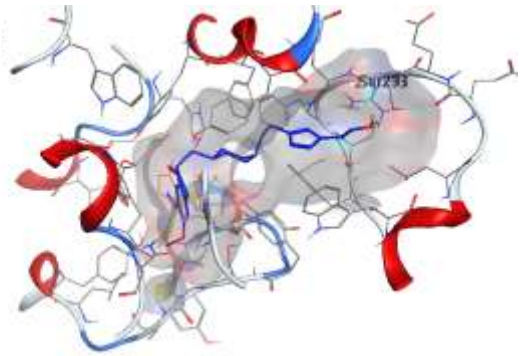
Table 2. Docking S-Score for compounds **10, 11, 12, 14, 15, 16, 17** and native co-crystallized ligand (Donepezil) against acetyl-cholinesterase (PDB ID. 4EY7).

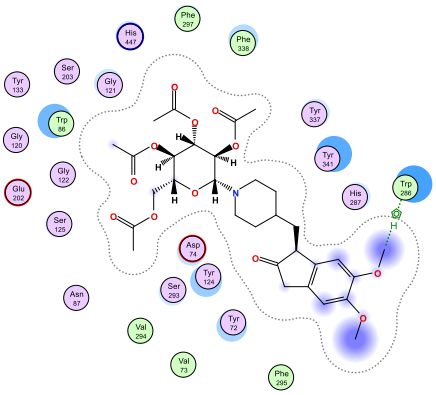
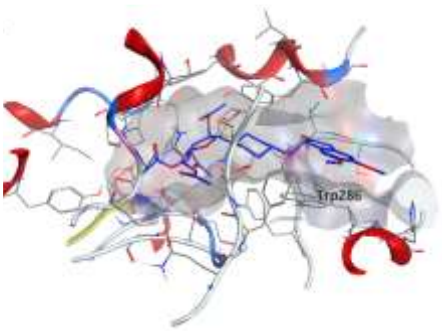
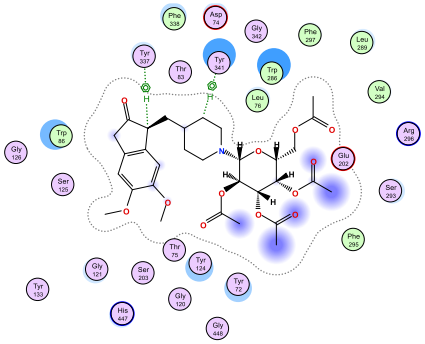
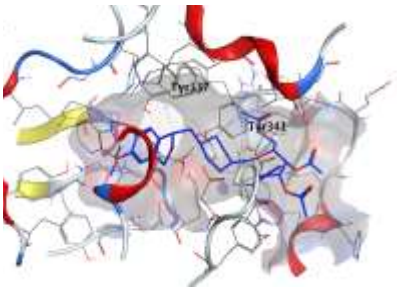
Compound number	S-Score (kcal/mol)
	AChE
10	-11.5243
11	-11.3859
12	-10.7498
14	-9.7283
15	-8.8602
16	-10.8546
17	-9.9943
Native (Donepezil)	-8.7716

Six main interactions are shown between AChE and its co-crystallized ligand (donepezil): 2 H-bonds with Phe295 and Tyr341, 2 pi-pi interactions with Trp86 and Trp286 and 2 H-pi interactions with Phe338 and Trp286. Docking results of the test set showed that all of them maintained at least one of these main interactions but with better binding affinity. where compound **10** showed 3 H-bonds with Phe295, Gly448 and His447 and a H-pi interaction with Tyr 337. 2 H-pi interactions with Trp86 and Ser293 are shown in compound **11,** and similarly, compounds **12** and **17** showed 2 interactions: a H-bond with Ser293 and a H-pi interaction with Tyr337 for compound **12**, and 2 H-pi interactions with Tyr337 and Tyr341 for compound **17**. Compounds **15** and **16** showed only 1 interaction with the pocket: an H-bond with Ser293 and an H-pi interaction with Trp286, respectively. 2 H-bonds with Trp86 and Arg296 and a pi-pi interaction with Trp286 are shown for compound **14 (Table 3)**. Compounds **15** and **16** showed only 1 interaction with the pocket: an H-bond with Ser293 and an H-pi interaction with Trp286, respectively. 2 H-bonds with Trp86 and Arg296 and a pi-pi interaction with Trp286 are shown for compound **14 (Table 3)**.

Table 3. 2D and 3D interaction of compounds **10, 11, 12, 14, 15, 16, 17** and native co-crystallized ligand (Donepezil) against acetylcholine-sterase (PDB ID. 4EY7).

Comp. no	2D-interaction	3D-interaction
	Acetyl-choline esterase	
Native (Donepezil)		
Native overlay	 RMSD=0.0947	
10		
11		

		
12		
14		
15		

16		
17		

According to the ADME prediction obtained from the SwissADME online tool, none of the ligands can pass the blood-brain barrier (BBB), and none exhibit PAINS alerts. Compounds **14** and 1**5** displayed the highest solubility, while the other compounds showed moderate solubility. Additionally, they all demonstrated good oral bioavailability, with a predicted score of 0.55, whereas the remaining six ligands exhibited lower bioavailability scores (0.17) **(Table 4)**.

Table 4. Pharmacokinetics prediction results using SwissADME for compounds **10, 11, 12, 14, 15, 16 and 17**

Compound no	Solubility Class	BBB permeant	Bioavailability Score	PAINS #alerts
10	Moderately soluble	No	0.17	0
11	Moderately soluble	No	0.17	0
12	Moderately soluble	No	0.17	0
14	Soluble	No	0.55	0
15	Soluble	No	0.55	0
16	Moderately soluble	No	0.17	0
17	Moderately soluble	No	0.17	0

The ADMET data predicted from PkCSM, shown in **Table 5**, confirmed the previous observations where compounds **14** and **15** showed the highest human intestinal absorption levels (78.5 and 94.5%, respectively) and accordingly showed the best human volume of distribution with values of 0.125 and 0.548, respectively. All 7 ligands show neither AMES toxicity nor hERG I inhibition ability. According to PK predictions from both online tools, compound **12** is expected to exhibit the best ADMET properties among the 7 ligands, in addition to showing a good binding affinity with good interaction and binding scores with both AChE and the highest inhibition concentration.

Table 5. Pharmacokinetics and toxicity prediction results using pkCSM for compounds **10, 11, 12, 14, 15, 16 and 17.**

Compound no	Solubility Class	BBB permeant	Bioavailability Score	PAINS #alerts
10	64.986	0.164	No	No
11	64.986	0.164	No	No
12	64.649	-0.011	No	No
14	78.525	0.125	No	No
15	Soluble	No	0.55	0
16	Moderately soluble	No	0.17	0
17	Moderately soluble	No	0.17	0

4. Conclusion

The current work focuses on the synthesis of new donepezil analogues using the click chemistry approach. Extensive studies were conducted to assess the inhibitory activities of these compounds against acetylcholinesterase (AChE), including molecular docking and SAR studies. The results of the screening revealed that most of the tested compounds exhibited inhibitory activity against AChE. Among them, compound **15** demonstrated the most promising profile, with an IC50 value of approximately 0.392 μg/mL, a high docking score of -8.86 kcal/mol, and favorable in silico pharmacokinetic predictions. Based on these findings, compound 15 emerges as a particularly potential candidate for further development as a novel drug for Alzheimer's disease. Its strong inhibitory activity against AChE and favorable molecular properties makes it a promising lead compound worth exploring in subsequent stages of drug development.

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Informed Consent Statement: Not applicable

Data Availability Statement: The data presented in this study are available.

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