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RESEARCH ARTICLE

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Macrocyclic sulfone derivatives: Synthesis, characterization, in vitro biological evaluation and molecular docking

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Abstract

An artificial series of macrocycles based on 4,4′-sulfonyldiphenol intermediate was synthesized using a multistep procedure involving oxidation of bisphenol sulfide, etherification of phenolic hydroxyl groups, and final ring closure with different diamines. Different chemical species having aromatic, heteroaromatic, and aliphatic characters were incorporated into macrocyclic frameworks in the final step of ring closure. This simple and easily executable synthetic strategy was applied to synthesize 15 macrocycles (**5a**-**o**) in excellent yields. Characterization of the synthesized products was achieved through well-known modern spectroscopic techniques such as IR, NMR, and Mass. Macrocycles **5m** and **5n** were found to show significant AChE inhibition with IC_{50} values of 76.9 ± 0.24 and 71.2 ± 0.77 μM, respectively. Macrocycle **5n** was also found to be an active inhibitor of butyrylcholinesterase (BChE) with IC_{50} score of 55.3 ± 0.54 μM. Among others, macrocycle **5l** cyclized with *o*-phenylenediamine demonstrated moderate inhibition with IC_{50} value of 81.1 ± 0.54 μM. Increasing interest in studying interactions of macrocycles with different enzymatic targets compelled us to design and synthesize sulfone-based macrocycles that might prove as highly potent class of biologically active compounds.

KEYWORDS
4,4′-sulfonyldiphenol, anticholinesterase activity, etherification, macrocycles, molecular docking, oxidation, ring-closure

1 | INTRODUCTION

Alzheimer's disease (AD) has increased at an alarming rate and is now a worldwide health problem. It is a progressive neurodegenerative disorder, characterized initially by selective loss of cholinergic neurons in the basal forebrain, followed by cognitive and behavioral impairments that increasingly disrupt activities of daily life, resulting in impaired memory and behavior, as well as loss of intellectual, social abilities and eventually death (Zheng et al., 2009). Inhibitors of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) leading to inhibition of acetylcholine and butyrylcholine breakdown constitutes the main therapeutic strategy for AD. Currently, a very few therapeutic agents such as galantamine, donepezil, and rivastigmine are available as approved drugs for the treatment of AD. The problem with these drugs is that they have symptomatic effect only, and this makes it need of the day to discover and develop new and more effective inhibitors for the disease.

Macrocycles are considered important scaffolds in modern drug discovery. They bear properties such as good solubility, lipophilicity, metabolic stability, oral bioavailability and desirable pharmacokinetic as well as pharmacodynamic properties (Yu & Sun, 2013). These properties make this class of compounds ideal for pharmaceutical industry. Some

of the clinically available macrocyclic antibiotics are azithromycin, erythromycin, vancomycin, daptomycin, bacitracin, spiramycin, and rifampin (Alvarez-Elcoro & Enzler, 1999; Chopra, 2007; Gulhane et al., 2014; Jones & Barry, 1987; Rybak et al., 2009; Zuckerman et al., 2011). They are being used in medicines, as complexing agents in chelation therapy, in radionuclide therapy, energy storage molecules and as photochromes (Fernandes et al., 2011; Hirose et al., 2008; Karcz et al., 2014; Mallinson & Collins, 2012; Tanaka et al., 2010; Vlasceanu et al., 2016; Wilson et al., 2015; Yin et al., 2008). Despite the proven therapeutic potential, macrocycles are one of the most under-explored and poorly exploited drug class. The possible reason is that organic chemists consider macrocycle synthesis, a difficult and time-consuming task in terms of lack of versatile synthetic routes, work up procedures and low yields. Still, because of their widespread importance in the modern era, chemists are compelled to design new synthetic strategies for the synthesis of novel macrocyclic drugs.

Two important functional groups, a sulfone and an amide are of special interest to both organic and medicinal chemists. Biological studies on the recently synthesized sulfones have revealed their antifungal (Xu et al., 2011), antiparasitic (Kerr et al., 2009), antimicrobial (Patil et al., 2010), antiviral (La Regina et al., 2007), antimalarial (Bader et al., 1969), antileprotic (Dhar, 1975), insecticidal, ascarcidal, analgesic, and hypnotic (Buehler & Masters, 1939) activities. Similarly, amide group owes its importance due to its presence in many synthetic intermediates, biomolecules and active pharmaceutical products (Grbović et al., 2018). It is noteworthy that combining the two groups into the same molecule might render important biological properties to the molecule. In a hope to find new molecules that can target cholinesterases, we have designed and synthesized 15 macrocyclic compounds based on bisphenol sulfone and tested them for their inhibition potential against AChE and BChE enzymes. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) from equine serum were used to explore the enzymes inhibitory potential of the synthesized compounds using Ellman's assay (Chen et al., 2015; Ellman et al., 1961).

2 | METHODS

2.1 | Chemistry

2.1.1 | General

The solvents used were distilled before use. In some cases, dry solvents were also used. Thin Layer Chromatography was performed to monitor the progress of reactions and pre-coated Kieselgel-60 HF 254 cards were used for this purpose. Silica gel 60 (70–230 mesh) was used for column chromatography to separate and purify products of different reactions. Melting points were recorded on Gallenkamp digital melting point apparatus (MGB-595-010-M). The reactions were performed according to standard procedures using clean glassware and synthetic grade chemicals. Reagents were purchased from Sigma Aldrich, TCI, and Acros and were used without further purification. Characterization of pure compounds was done by spectroscopic techniques such as IR, ^{1}H- and ^{13}C-NMR and Mass spectrometry.

2.1.2 | Oxidation of 4,4′-thiodiphenol (1) into to 4,4′-sulfonyldiphenol (2)

To a stirred solution of 4,4′-thiodiphenol (**1**) 0.5 g (0.0023 mol, 1 eq) in AcOH:CH_3CN (1:1) was slowly added drop wise a solution of $NaIO_4$ 1.25 g (0.00575 mol, 2.5 eq) in a mixture of AcOH/H_2O. The reaction mixture was stirred until the formation of a residue. The completion of reaction was monitored through TLC using hexane/ethyl acetate solvent system. After completion, solvent was removed from the reaction mixture under reduced pressure and the residue was suspended in brine and neutralized with a saturated solution of K_2CO_3. The resulting suspension was filtered, and residue washed with water and dried in air. The filtrate was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried with anhyd. Na_2SO_4, filtered and evaporated in vacuo to give the corresponding 4,4′-sulfonyldiphenol (**2**) (white soapy).

2.1.3 | Synthesis of diethyl-2,2′-(4,4′-sulfonylbis (4,1-phenylene)bis(oxy))diacetate (4)

To a 1000 mg, (4 mmol) solution of 4,4′-sulfonyldiphenol (**2**) in DMF was added 1656 mg, (6 mmol) of K_2CO_3 and refluxed for 30 minutes. After 30 minutes 1468 mg (6 mmol) of ethyl-2-chloroacetate (**3**) was added and the reaction mixture was refluxed for 2–3 hours. The progress of reaction was monitored by TLC using hexane/ethyl acetate (6:4) as a solvent system. The reaction was worked up by pouring the hot mixture into an ice-cold water, thus forming a white precipitate, which was then filtered and air dried.

Yield: 97%; white solid.

HRMS: *m/z* $[M]^+$ calcd. For $C_{20}H_{22}O_8S$: 422.1035; found: 422.1550.

IR (KBr disc, ν cm^{-1}): 3010 (C—H Ar), 2930 (C—H aliphatic), 1740 (—OCOR), 1589 (C═C Ar), 1290 (Ar —SO_2—Ar).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 1.2 (t, *J* = 7.2 Hz, 6H, 2 —CH_3), 4.16 (q, *J* = 7.4 Hz, 4H, 2 —CH_2—), 4.90 s (4H, 2 —CH_2—), 7.1 (d, *J* = 8.0 Hz, 4H, Ar—H), 7.83 (d, *J* = 8.0 Hz, 4H, Ar—H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 169.11 (2 —C═O), 161.0 (2 Ar—C, Sulfone), 134.0 (2 Ar—C, Sulfone), 129.3 (4 Ar—C, Sulfone), 115.4 (4 Ar—C, Sulfone), 64.2 (2 —CH_2—), 60.0 (2 —CH_2—), 14.0 (2 —CH_3).

2.1.4 | General procedure for macrocyclization of diacetate (4) with diamines

To a stirred solution of diacetate (**4**) (0.1 g, 0.237 mmol) various diamines were dissolved in 50 mL of ethyl alcohol in a 100 mL round bottom flask. In each case, the reaction mixture was refluxed at 80°C for 4–7 hours. TLC was used to monitor the progress of reaction.

The solvent system used for TLC consisted of 40% ethyl acetate and 60% hexanes. At completion of reaction, the hot reaction mixture was poured into ice cold water, immediately obtaining a precipitate of macrocycle. In case of impure products, the precipitates were further purified through Silica gel 60 (70–230 mesh) column using suitable solvent systems.

*Synthesis of 8,20-dithioxo-4,12,16,24-tetraoxa-2,14-dithia-7,9,19,21-tetraaza-1,3,13,15 (1,4)-tetrabenzenacyclotetracosaphane-6,10,18,22-tetraone-2,2,14,14-tetraoxide (**5a**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (Thiourea) given above.

Yield: 95% (103.6 mg); white solid; m. p. 140-142°C.

HRMS: *m/z* $[M]^+$ calcd. For $C_{34}H_{28}N_4O_{12}S_4$: 812.0587; found: 812.2183.

IR (KBr disc, ν cm^{-1}): 3270 (—NH—), 3170 (—CSNH—), 3050 cm^{-1} (—CH_2—), 3010 cm^{-1} (=C—H Ar), 1690 cm^{-1} (—CONH—), 1589 cm^{-1} (C=C aromatic), 1336 (—CS—), 1249 cm^{-1} (Ar—O—R), 1140 cm^{-1} (Ar —SO_2—Ar).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.4 (s, 4H, —NH—), 4.90 (s, 8H, 4 —CH_2—), 7.1 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.84 (*J* = 8.0 Hz, 8H, Ar—H 8H, Ar—H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 182 (2 > C=S), 169.11 (4 —C=O), 161.66 (4 Ar—C, Sulfone), 134.54 (4 Ar—C, Sulfone), 129.80 (8 Ar—C, Sulfone), 115.95 (8 Ar—C, Sulfone), 65.19 (4 —CH_2—).

*Synthesis of 4,12,16,24-tetraoxa-2,14-dithia-7,9,19,21-tetraaza-1,3,13,15(1,4)-tetra benzenacyclotetracosaphane-6,8,10,18,20,22-hexaone-2,2,14,14-tetraoxide (**5b**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (Urea) given above.

Yield: 92% (98.4 mg); white solid; m. p. 158–160°C.

HRMS: *m/z* $[M]^+$ calcd. For $C_{34}H_{28}N_4O_{14}S_2$: 780.1043; found: 780.0964.

IR (KBr disc, ν cm^{-1}): 3050 cm^{-1} (—CH_2—), 3010 cm^{-1} (=C—H Ar), 1690 cm^{-1} (—CONH—), 1589 cm^{-1} (C=C aromatic), 1313 (Ar—NH—), 1249 cm^{-1} (Ar—O—R) 1140 cm^{-1} (Ar —SO_2—Ar).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.2 (s, 4H, —NH—), 4.90 (s, 8H, 4—CH_2—), 7.11 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d_6): δ (ppm) 169.11 (6—C=O), 161.66 (4 Ar—C, Sulfone), 134.54 (4 Ar—C, Sulfone), 129.80 (8 Ar—C, Sulfone), 115.95 (8 Ar—C, Sulfone), 65.19 (4—CH_2—).

*Synthesis of 4,14,18,28-tetraoxa-2,9,16,23-tetrathia-7,11,21,25-tetraaza-1,3,15,17(1,3),8,10,22,24(1,4)-octabenzenacyclooctacosaphane-6,12,20,26-tetraone-2,2,9,9,16,16,23,23-octaoxide (**5c**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (Bis-(3-Aminophenyl)sulfone) given above.

Yield: 90% (116.6 mg), white solid; m. p. 150–152°C.

HRMS: *m/z* $[M]^+$ calcd. For $C_{56}H_{44}N4O_{16}S_4$: 1156.1635; found: 1156.2242.

IR (KBr disc, ν cm^{-1}): 3050 (—CH_2—), 3010 (=C—H Ar), 1690 (—CONH—), 1589 (C=C aromatic), 1249 (Ar—O—R), 1140 (Ar —SO_2—Ar).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.3 (s, 4H, —NH—), 4.90 (s, 8H, 4—CH_2—), 7.16–7.20 (m, 4H, Ar—H), 6.73 (d, *J* = 7.6 Hz, 4H, Ar—H), 6.88 (d, *J* = 7.8 Hz, 4H, Ar—H), 7.1 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d_6): δ (ppm) 169.11 (4—C=O), 161.66 (4 Ar—C, Sulfone), 150 (2 Ar—C), 140 (4 Ar—C), 134.54 (4 Ar—C, Sulfone), 131 (12 Ar—C), 129.80 (8 Ar—C, Sulfone), 115.95 (8 Ar—C, Sulfone), 114 (4 Ar—C), 65.19 (4—CH_2—).

*Synthesis of 4,13,17,26-tetraoxa-2,15-dithia-7,8,10,20,22,23-hexaaza-1,3,14,16(1,4)-tetra benzenacyclohexacosaphane-6,9,11,19,21,24-hexaone 2,2,15,15-tetraoxide (**5d**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (semicarbazide/hydrazinecarboxamide) given above.

Yield: 95% (107.3 mg), white solid; m. p. 170–172°C.

HRMS: *m/z* $[M]^+$ calcd. For $C_{34}H_{30}N_6O_{14}S_2$: 810.1261; found: 810.1544.

I R (KBr disc, ν cm^{-1}): 3050 (—CH_2—), 3010 (=C—H Ar), 1690 (—CONH—), 1589 (C=C aromatic), 1313 (Ar—NH—), 1249 (Ar—O—R), 1140 (Ar —SO_2—Ar).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.4, 9.53, 9.3 (s, 6H, —NH—), 4.53 (s, 4H, 2—CH_2—), 4.90s (4H, 2—CH_2—), 7.1 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d_6): δ (ppm) 168.62 (6—C=O), 161.16 (4 Ar—C, Sulfone), 134.04 (4 Ar—C, Sulfone), 129.30 (8 Ar—C, Sulfone), 115.45 (8 Ar—C, Sulfone), 64.75 (4—CH_2—).

*Synthesis of 9,21-dithioxo-4,13,17,26-tetraoxa-2,15-dithia-7,8,10,20,22,23-hexaaza-1,3,14,16(1,4)-tetrabenzenacyclohexacosaphane-6,11,19,24-tetraone-2,2,15,15-tetraoxide (**5e**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (thiosemicarbazide/hydrazinecarbothioamide) given above.

Yield: 77% (85.5 mg), white solid; m. p. 162–164°C.

HRMS: *m/z* $[M]^+$ calcd. For $C_{34}H_{30}N_6O_{12}S_4$: 842.0805; found: 842.1550.

IR (KBr disc, ν cm^{-1}): 3050 (—CH_2—), 3010 (=C—H Ar), 1690 (—CONH—), 1589 (C=C aromatic), 1389 (—CS—), 1313 (Ar—NH—), 1249 (Ar—O—R), 1140 (Ar —SO_2—Ar).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.3, 9.53, 10.4, (s, 6H, —NH—), 4.86 (s, 4H, 2—CH_2—), 4.53 (s, 4H, 2—CH_2—), 7.06 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.8 (d, *J* = 8.0 Hz, 8H, Ar—H).

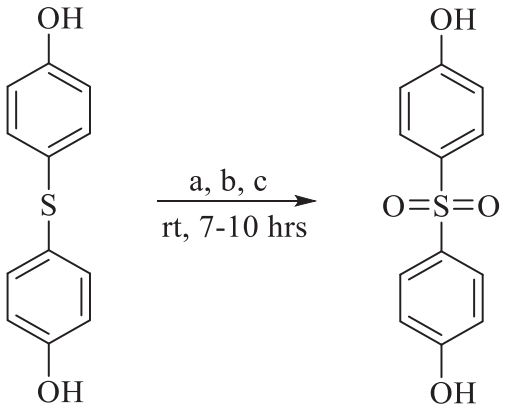
^{13}C NMR (100 Hz, DMSO-d_6): δ (ppm) 182 (2 > C=S), 169.11 (4—C=O), 161.66 (4 Ar—C, Sulfone), 134.54 (4 Ar—C, Sulfone), 129.80 (8 Ar—C, Sulfone), 115.95 (8 Ar—C, Sulfone), 65.19 (4—CH_2—).

*Synthesis of 2,4,9,13,18,20,25,29-octaoxa-11,27-dithia-6,16,22,32-tetraaza-1,3,5,17,19,21 (1,3),10,12,26,28(1,4)-decabenzenacyclodotriacontaphane-7,15,23,31-tetraone-11,11,27, 27-tetraoxide (**5f**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (1,3-Bis(3-Aminophenoxy)benzene) given above.

Yield: 90% (121.5 mg), white solid; m. p. 136–138°C.

HRMS: *m/z* $[M]^+$ calcd. For $C_{68}H_{52}N_4O_{16}S_2$: 1245.2802; found: 1245.2069.



1 2

SCHEME 1 (a) $NaIO_4$, CH_3COOH/H_2O (1:2.5), (b) *m*-CPBA, DCM (1:2.5), (c) CH_3COOH/H_2O_2 (1:3)

IR (KBr disc, ν cm^{-1}): 3050 (—CH2—), 3010 (=C—H Ar), 2920 (Ar—CH2—Ar), 1690 (—CONH—), 1589 (C=C aromatic), 1313 (Ar—NH—), 1249 (Ar—O—R), 1150 (Ar—O—Ar), 1140 (Ar —SO_2—Ar).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.23 (s, 4H, 4—NH—), 4.90 (s, 8H, 4—CH_2—), 6.17 (dd, *J* = 8.2 Hz, 6H, Ar—H), 6.32 (dd, *J* = 8.2 Hz, 6H, Ar—H), 6.67 (dd, *J* = 8.2 Hz, 6H, Ar—H), 6.19 (t, *J* = 7.8 Hz, 2H, Ar—H), 6.98 (t, *J* = 7.5 Hz, 2H, Ar—H), 7.30 (t, *J* = 8.3 Hz, 2H, Ar—H), 7.11 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d_6): δ (ppm) 168.62 (4—C=O), 161.71 (4 Ar—C, Sulfone), 157.0 (8 Ar—C), 150.52 (4 Ar—C), 134.04 (4 Ar—C, Sulfone), 130.07 (6 Ar—C), 129.30 (8 Ar—C, Sulfone), 115.45 (8 Ar—C, Sulfone), 112.62 (4 Ar—C), 109.60 (4 Ar—C), 108.34 (4 Ar—C), 106.02 (2 Ar—C), 64.68 (4—CH_2—).

*Synthesis of 4,13,17,26-tetraoxa-2,15-dithia-7,10,20,23-tetraaza-1,3,14,16(1,4)-tetra benzenacyclohexacosaphane-6,11,19,24-tetraone-2,2,15,15-tetraoxide (**5g**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (1,2-Ethylenediamine) given above.

Yield 80% (92.0 mg), white solid; m. p. 153–155°C.

HRMS: *m/z* $[M]^+$ calcd. For $C_{36}H_{36}N_4O_{12}S_2$: 780.1771; found: 780.1594.

IR (KBr disc, ν cm^{-1}): 3050 (—CH_2—), 3010 (=C—H Ar), 2920 (Ar—CH2—Ar), 1690 (—CONH—), 1589 (C=C aromatic), 1560 (—NH—CH_2—CH_2—NH—), 1313 (Ar—NH—), 1249 (Ar—O—R), 1140 (Ar —SO_2—Ar).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.2 (s, 4H, —NH—), 3.60 (s, 8H, 4—CH_2—), 4.56 s (8H, 4—CH_2—), 7.11 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d_6): δ (ppm) 167.02 (4—C=O), 161.34 (4 Ar—C, Sulfone), 133.89 (4 Ar—C, Sulfone), 129.25 (8 Ar—C, Sulfone), 115.56 (8 Ar—C, Sulfone), 66.92 (4—CH_2—), 41.21 (4—CH_2—).

*Synthesis of 4,14,18,28-tetraoxa-2,16-dithia-7,11,21,25-tetraaza-1,3,15,17(1,4)-tetra benzenacyclooctacosaphane-6,12,20,26-tetraone-2,2,16,16-tetraoxide (**5h**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (1,3-Propyle nediamine) given above.

Yield: 84% (100.8 mg), white solid; m.p. 122–124°C.

HRMS: *m/z* $[M]^+$ calcd. For $C_{38}H_{40}N_4O_{12}S_2$: 809.2118; found: 809.2183.

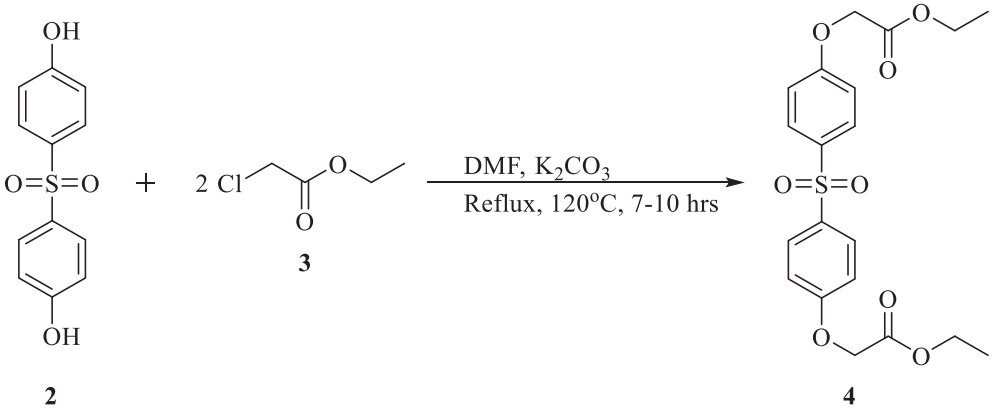
IR (KBr disc, ν cm^{-1}): 3050 (—CH_2—), 3010 (=C—H Ar), 2920 (Ar—CH_2—Ar), 1690 (—CONH—), 1589 (C=C aromatic), 1580 (—NH—CH_2—CH_2—NH—), 1313 (Ar—NH—), 1249 (Ar—O—R), 1140 (Ar —SO_2—Ar).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 1.75 (q, *J* = 4.9 Hz, 4H, 2—CH_2—), 8.22 s (4H, —NH—), 3.16 (t, *J* = 7.2 Hz, 8H, 4—CH_2—), 4.58 (s, 8H, 4—CH2—), 7.11 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.86 (d, *J* = 8.0 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d_6): δ (ppm) 166.78 (4—C=O), 161.32 (4 Ar—C, Sulfone), 133.92 (4 Ar—C, Sulfone), 129.25 (8 Ar—C, Sulfone), 115.56 (8 Ar—C, Sulfone), 66.97 (4—CH_2—), 40.10 (8—CH_2—), 36.00 (2 —CH_2—).

*Synthesis of 8^{9}H,20^{9}H-4,12,16,24-tetraoxa-2,14-dithia-7,9,19,21-tetraaza-8,20(2,6)-dipurina-1,3,13,15(1,4)-tetrabenzenacyclotetracosaphane-6,10,18,22-tetraone 2,2,14,14-tetraoxide (**5i**).*

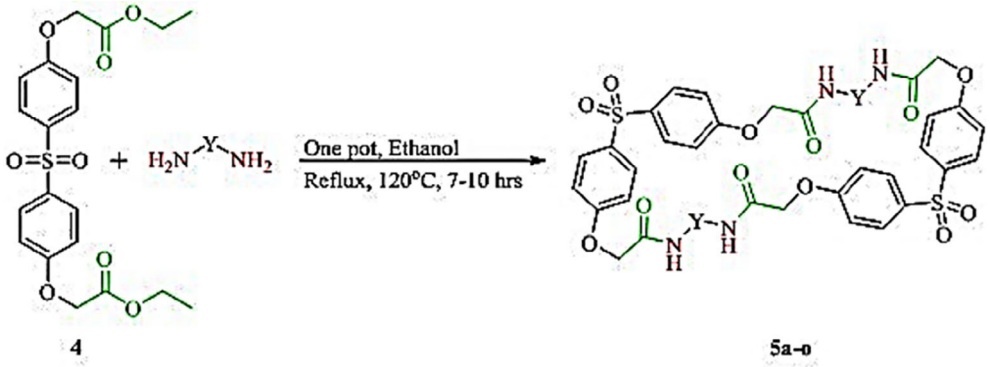
Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (9H-Purine-2,6-diamine) given above.



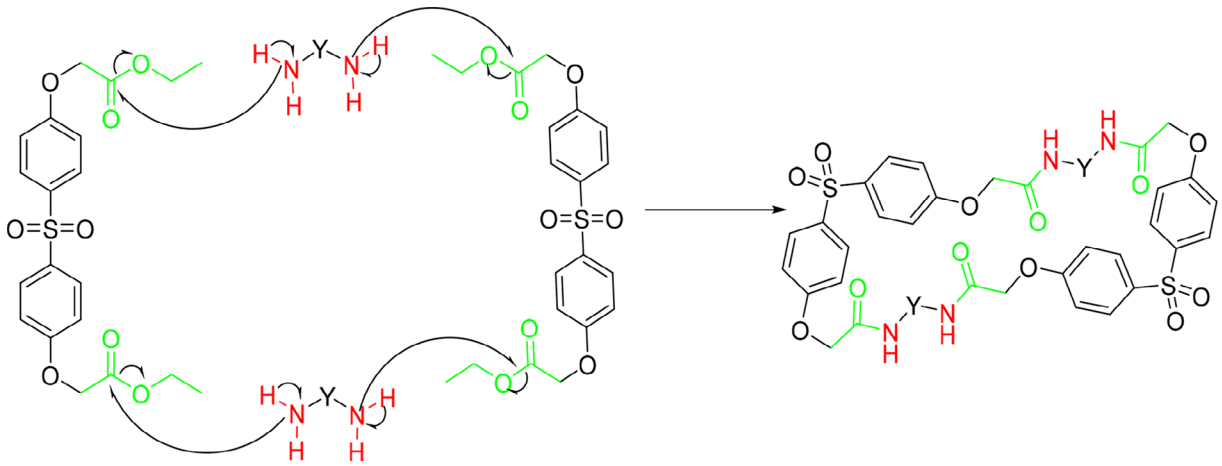
2 4

SCHEME 2 Etherification reaction of 4,4′-sylfonyldiphenol **2** into diethyl-2,2′-(4,4′-sulfonylbis(4,1-phenylene)bis (oxy))diacetate **4**

SCHEME 3 Steps for the synthesis of macrocycles (**5a-o**)



Macrocycle	Diamine (NH_2-Y-NH_2)
5a	Thiourea
5b	Urea
5c	Bis-(3-Aminophenyl)sulfone
5d	semicarbazide
5e	thiosemicarbazide
5f	1,3-Bis(3-Aminophenoxy)benzene
5g	1,2-Ethylenediamine
5h	1,3-Propylenediamine
5i	9H-Purine-2,6-diamine
5j	1,3-propanediyledibenzoate
5k	*p*-Phenylendiamine
5l	*m*-phenylenediamnie
5m	Hydrazine
5n	2,2'-((sulfonylbis(4,1-phenylene))bis(oxy))di(acetohydrazide)
5o	2,2'-((thiobis(4,1-phenylene))bis(oxy))di(acetohydrazide)



SCHEME 4 Proposed mechanistic approach to the synthesis of macrocycles (**5a-o**)

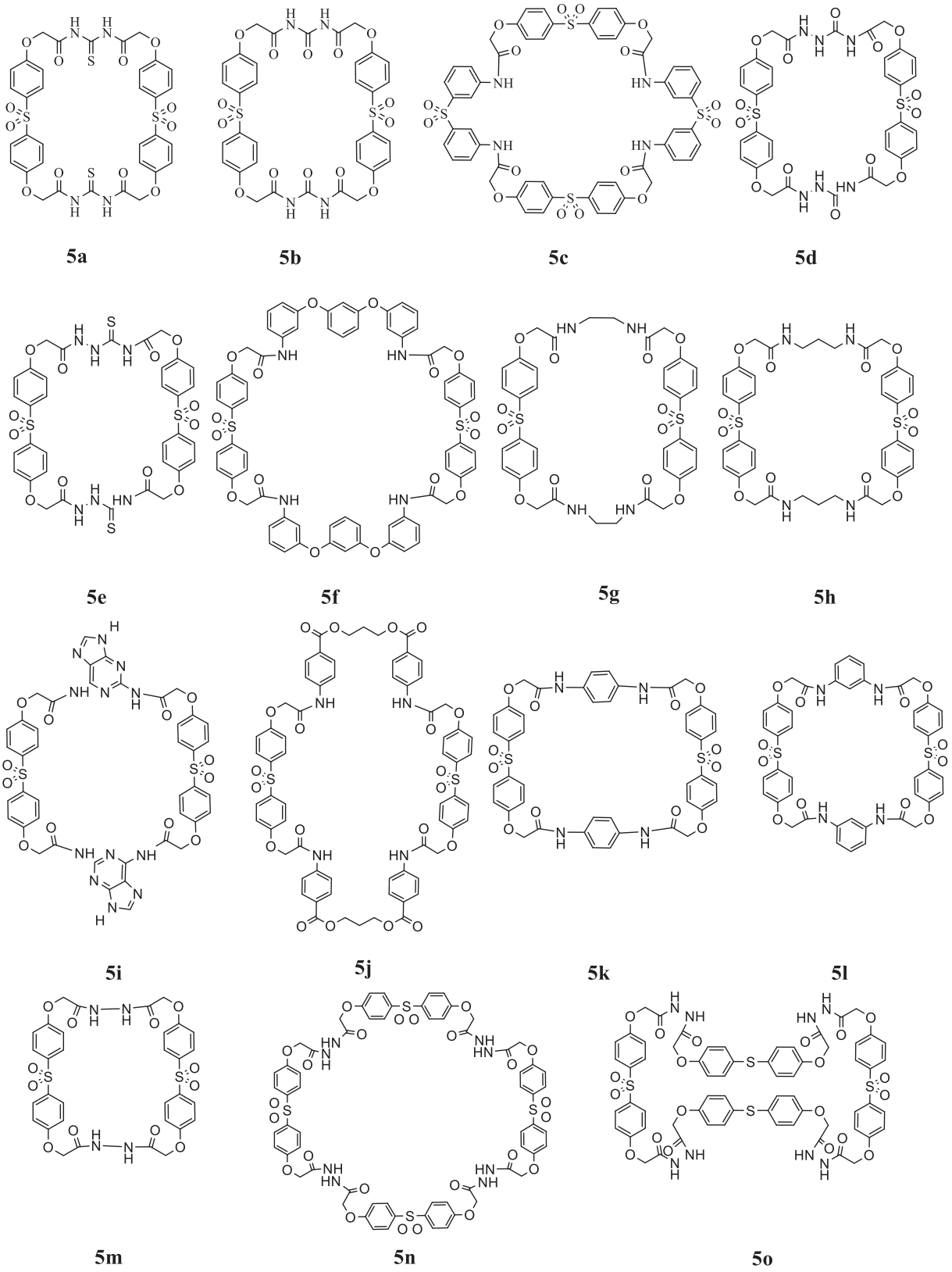


FIGURE 1 Structures of synthesized macrocycles (**5a-o**)

TABLE 1 Anticholinesterase activity of compounds **5a-o**

Compound	AChE[a] IC$_{50}$ (μM)	BChE[a] IC$_{50}$ (μM)
5a	246.3 ± 0.34	387.9 ± 0.55
5b	576.9 ± 0.54	576.9 ± 0.67
5c	Not active	Not active
5d	234.6 ± 0.44	296.3 ± 0.22
5e	Not active	Not active
5f	667.2 ± 0.55	691.3 ± 0.69
5g	Not active	Not active
5h	457.9 ± 0.66	569.3 ± 0.54
5i	430.2 ± 0.45	540.7 ± 0.69
5j	341.6 ± 0.66	528.0 ± 0.67
5k	422.4 ± 0.51	570.8 ± 0.15
5l	**81.1 ± 0.54**	234.0 ± 0.54
5m	**76.9 ± 0.24**	248.6 ± 0.34
5n	**71.2 ± 0.77**	**55.3 ± 0.54**
5o	245.7 ± 0.12	361.3 ± 0.58
Galantamine	69.7 ± 0.18	52.3 ± 0.53

[a]Inhibition of AChE and BChE expressed in mean ± *SD* (*n* = 3). Significant activity against each enzyme are shown in bold font.

Yield: 87% (118.0 mg), white solid; m. p. 145–147°C.

HRMS: *m/z* [M]$^+$ calcd. For $C_{42}H_{32}N_{12}O_{12}S_2$: 960.1704; found: 960.1776.

IR (KBr disc, ν cm^{-1}): 3050 (—CH$_2$—), 3010 (═C—H Ar), 1690 (—CONH—), 1589 (C═C aromatic), 1313 (Ar—NH—), 1249 (Ar—O—R), 1140 (Ar —SO$_2$—Ar).

^{1}H NMR (DMSO-d$_6$, 400 MHz, δ ppm): 9.6 (s, 4H, 4—NH—), 12.76 (s, 2H, 2—NH—), 7.80 (s, 2H, 2—C═CH—), 4.90 (s, 8H, 4—CH$_2$—), 7.1 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d$_6$): δ (ppm) 168.62 (4—C═O), 161.16 (4 Ar—C, Sulfone), 152.7, 152.3, 151.8 (6 Ar—C), 138.7, (2 Ar—C), 134.04 (4 Ar—C, Sulfone), 129.30 (8 Ar—C, Sulfone), 115.3 (2 Ar—C), 115.45 (8 Ar—C, Sulfone), 64.68 (4—CH$_2$—).

*Synthesis of 4,10,14,20,24,30,34,40-octaoxa-2,22-dithia-7,17,27,37-tetraaza-1,3,8,16,21, 23,28,36(1,4)-octabenzenacyclotetracontaphan-6,9,15,18,26,29,35,38-octaone-2,2,22,22-tetraoxide (**5j**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (1,3-propanediyledibenzoate) given above.

Yield: 90% (124.0 mg), white solid; m. p. 113–115°C.

HRMS: *m/z* [M]$^+$ calcd. For $C_{66}H_{56}N_4O_{20}S_2$: 1288.2929; found: 1288.1231.

IR (KBr disc, ν cm^{-1}): 3050 (—CH$_2$—), 3010 (═C—H Ar), 1725 (ArCOOR), 1690 (—CONH—), 1589 (C═C aromatic), 1313 (Ar—NH—), 1249 (Ar—O—R), 1140 (Ar —SO$_2$—Ar).

^{1}H NMR (DMSO-d$_6$, 400 MHz, δ ppm): 9.85 (s, 4H, 4—NH—), 4.90 (s, 8H, 4—CH$_2$—), 4.22 (t, *J* = 7.4 Hz, 8H, 4—CH$_2$—), 1.9 (q, *J* = 7.1 Hz, 4H, 2—CH$_2$—), 7.23 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.57 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.11 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d$_6$): δ (ppm) 169.11 (4—C═O), 161.66 (4 Ar—C, Sulfone), 142.8 (24 Ar—C), 134.52 (4 Ar—C, Sulfone), 130.10, (24 Ar—C), 129.81 (8 Ar—C, Sulfone), 125, (24 Ar—C), 118.10, (24 Ar—C), (8 Ar—C, Sulfone), 115.95, (24 Ar—C), 66.18 (4—CH$_2$—), 61.60 (4 —CH$_2$—), 30.53 (2 —CH$_2$—).

*Synthesis of 4,12,16,24-tetraoxa-2,14-dithia-7,9,19,21-tetraaza-1,3,8,13,15,20(1,4)-hexa benzenacyclotetracosaphane-6,10,18,22-tetraone-2,2,14,14-tetraoxide macrocycle (**5k**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (*p*-Phenylendiamine) given above.

Yield: 80% (90.4 mg), violet solid; m. p. 170–174°C.

HRMS: *m/z* [M]$^+$ calcd. For $C_{44}H_{36}N_4O_{12}S_2$: 876.1771; found: 876.1973.

IR (KBr disc, ν cm^{-1}): 3050 (—CH$_2$—), 3010 (═C—H Ar), 1690 (—CONH—), 1589 (C═C aromatic), 1313 (Ar—NH—), 1249 (Ar—O—R), 1140 (Ar —SO$_2$—Ar).

^{1}H NMR (DMSO-d$_6$, 400 MHz, δ ppm): 8.73 (s, 4H, 4—NH—), 7.52 (s, 8H, Ar—H), 4.90 (s, 8H, 4—CH$_2$—), 7.1 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d$_6$): δ (ppm) 169.62 (4—C═O), 161.16 (4 Ar—C, Sulfone), 134.04 (4 Ar—C, Sulfone), 134.04, (6 Ar—C), 129.30 (8 Ar—C, Sulfone), 121.8, (6 Ar—C), 115.45 (8 Ar—C, Sulfone), 64.68 (4—CH$_2$—).

*Synthesis of 4,12,16,24-tetraoxa-2,14-dithia-7,9,19,21-tetraaza-1,3,13,15(1,4),8,20(1,3)-hexabenzenacyclotetracosaphane-6,10,18,22-tetraone-2,2,14,14-tetraoxide (**5l**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (*m*-phenylenediamnie) given above.

Yield: 75% (84.5 mg), white solid; m. p. 178–180°C.

HRMS: *m/z* [M]$^+$ calcd. For $C_{44}H_{36}N_4O_{12}S_2$: 876.1771; found: 876.1973.

IR (KBr disc, ν cm^{-1}): 3050 (—CH2—), 3010 (═C—H Ar), 1690 (—CONH—), 1589 (C═C aromatic), 1313 (Ar—NH—), 1249 (Ar—O—R),1140 (Ar —SO$_2$—Ar).

^{1}H NMR (DMSO-d$_6$, 400 MHz, δ ppm): 9.30 (s, 4H, 4—NH—), 4.84 (s, 8H, 4—CH$_2$—), 7.15 (d, *J* = 8.4 Hz, 4H, Ar—H), 7.32 (t, *J* = 8.6 Hz, 2H, Ar—H), 7.56 (d, *J* = 8.2 Hz, 2H, Ar—H), 7.05 (d, *J* = 8.1 Hz, 8H, Ar—H), 7.78 (d, *J* = 8.1 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d$_6$): δ (ppm) 169.12 (4—C═O), 161.66 (4 Ar—C, Sulfone), 142.00, (3 Ar—C), 134.54 (4 Ar—C, Sulfone), 129.80 (8 Ar—C, Sulfone), 128.00, 118.00, (9 Ar—C), 115.95 (8 Ar—C, Sulfone), 113.00, (12 Ar—C), 65.18 (4—CH$_2$—).

*Synthesis of 4,11,15,22-tetraoxa-2,13-dithia-7,8,18,19-tetraaza-1,3,12,14(1,4)-tetra benzenacyclododecosaphane-6,9,17,20-tetraone-2,2,13,13-tetraoxide (**5m**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (Hydrazine hydrate) given above.

Yield: 90% (100.8 mg), white solid; m. p. 268-270°C.

HRMS: *m/z* [M]$^+$ calcd. For $C_{32}H_{28}N_4O_{12}S_2$: 724.1145; found: 724.0021.

IR (KBr disc, ν cm^{-1}): 3050 (—CH2—), 3010 (═C—H Ar), 1690 (—CONH—), 1589 (C═C aromatic), 1313 (Ar—NH—), 1249 (Ar—O—R), 1140 (Ar —SO$_2$—Ar).

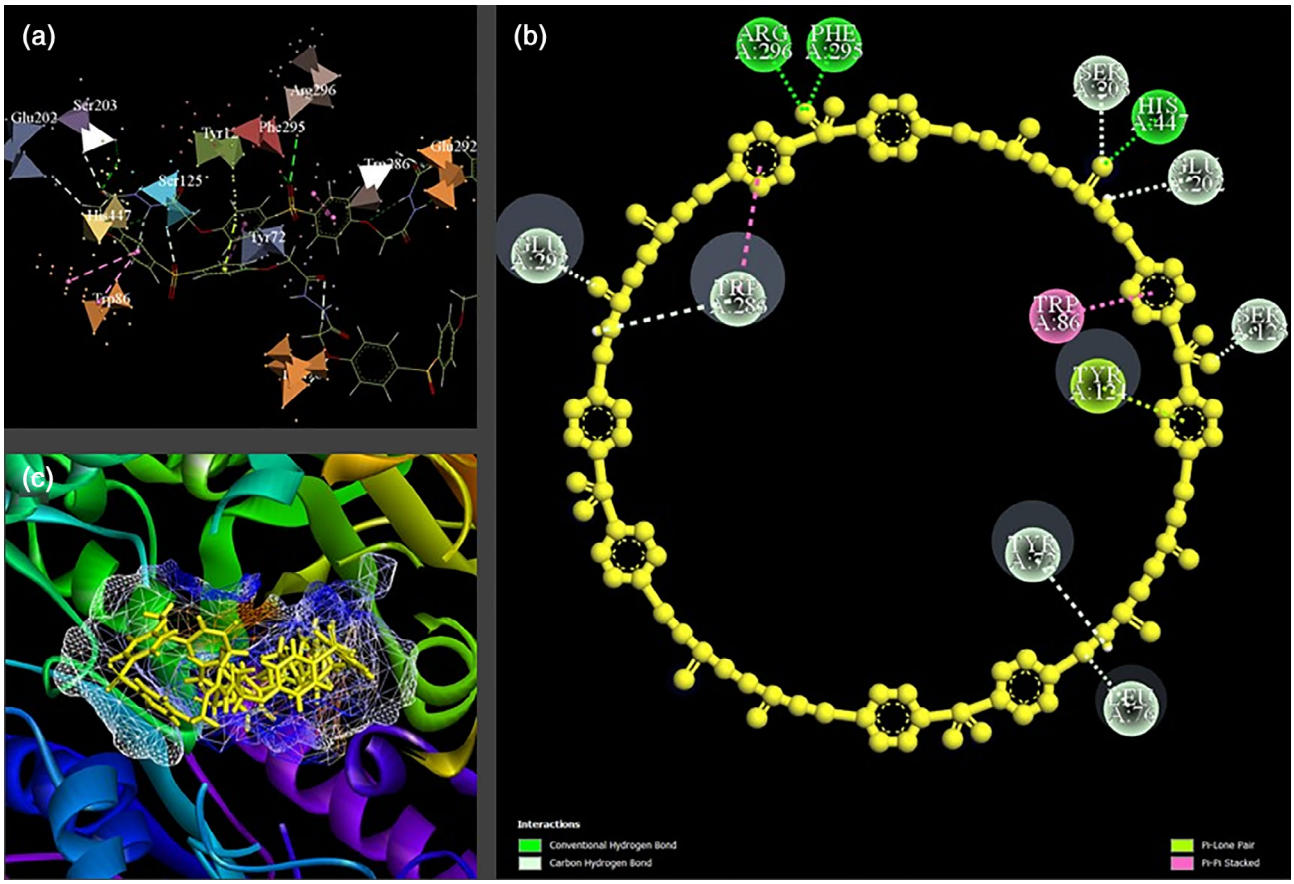


FIGURE 2 (a) 3D view of the docking pose of macrocycle **5n** (green colored line-view model) in the binding pocket of AChE (4EY6). (b) Two-dimensional (2D) interaction diagram for **5n**. (c) Ribbon diagram depicting docked pose of **5n** (yellow) in the binding cavity (mesh surface) of AChE (4EY6)

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.4 (s, 4H, 4—NH—), 4.90 (s, 8H, 4—CH_2—), 7.11 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d_6): δ (ppm) 169.18 (4—C═O), 161.16 (4 Ar—C, Sulfone), 134.02 (4 Ar—C, Sulfone), 129.30 (8 Ar—C, Sulfone), 115.45 (8 Ar—C, Sulfone), 65.19 (4—CH_2—).

*Synthesis of 4,11,15,22,26,33,37,44-octaoxa-2,13,24,35-tetrathia-7,8,18,19,29,30,40,41-octaaza-1,3,12,14,23,25,34,36(1,4)-octabenzenacyclotetratetracontaphan-6,9,17,20,28,31,39,42-octaone- 2,2,13,13,24,24,35,35-octaoxide (**5n**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (2,2′-((sulfonylbis(4,1-phenylene))bis(oxy))di (acetohydrazide)) given above.

Yield: 85% (164.4 mg), white solid; m.p. 226–228°C.

HRMS: *m/z* $[M]^+$ calcd. For $C_{64}H_{56}N_8O_{24}S_4$: 1448.2290; found: 1448.1878.

IR (KBr disc, ν cm^{-1}): 3050 (—CH2—), 3010 (═C—H Ar), 1690 (—CONH—), 1589 (C═C aromatic), 1313 (Ar—NH—), 1249 (Ar—O—R), 1140 (Ar —SO_2—Ar).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.55 s (8H, 8—NH—), 4.90s (16H, 8—CH_2—), 7.11 (d, *J* = 8.0 Hz, 16H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 16H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d_6): δ (ppm) 168.02 (8—C═O), 161.16 (8 Ar—C, Sulfone), 134.04 (8 Ar—C, Sulfone), 129.30 (16 Ar—C, Sulfone), 115.45 (16 Ar—C, Sulfone), 64.68 (8—CH_2—).

*Synthesis of 4,11,15,22,26,33,37,44-octaoxa-2,13,24,35-tetrathia-7,8,18,19,29,30,40,41-octaaza-1,3,12,14,23,25,34,36(1,4)-octabenzenacyclotetratetracontaphan-6,9,17,20,28,31, 39,42-octaone-2,2,24,24-tetraoxide (**5o**).*

Prepared according to general procedure for macrocyclization of diacetate (**4**) with diamine (2,2′-((thiobis(4,1-phenylene))bis(oxy))di (acetohydrazide)) given above.

Yield: 80% (148.8 mg), white solid; m. p. 235–240°C.

HRMS: *m/z* $[M]^+$ calcd. For $C_{64}H_{56}N_8O_{20}S_4$: 1384.2494; found: 1384.1652.

IR (KBr disc, ν cm^{-1}): 3050 (—CH2—), 3010 (═C—H Ar), 1589 (C═C aromatic), 1140 (Ar —SO_2—Ar), 1249 (Ar—O—R), 1690 (—CONH—), 1313 (Ar—NH—).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.50 (s, 8H, 8—NH—), 4.90 (s, 16H, 8—CH_2—), 7.63 (d, *J* = 8.0 Hz, 8H, Ar—H), 6.54 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.11 (d, *J* = 8.0 Hz, 8H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 8H, Ar—H).

^{13}C NMR (100 Hz, DMSO-d_6): δ (ppm) 168.62 (8—C═O), 161.16 (4 Ar—C, Sulfone), 153.52, (6 Ar—C) 134.04 (4 Ar—C, Sulfone), 129.30

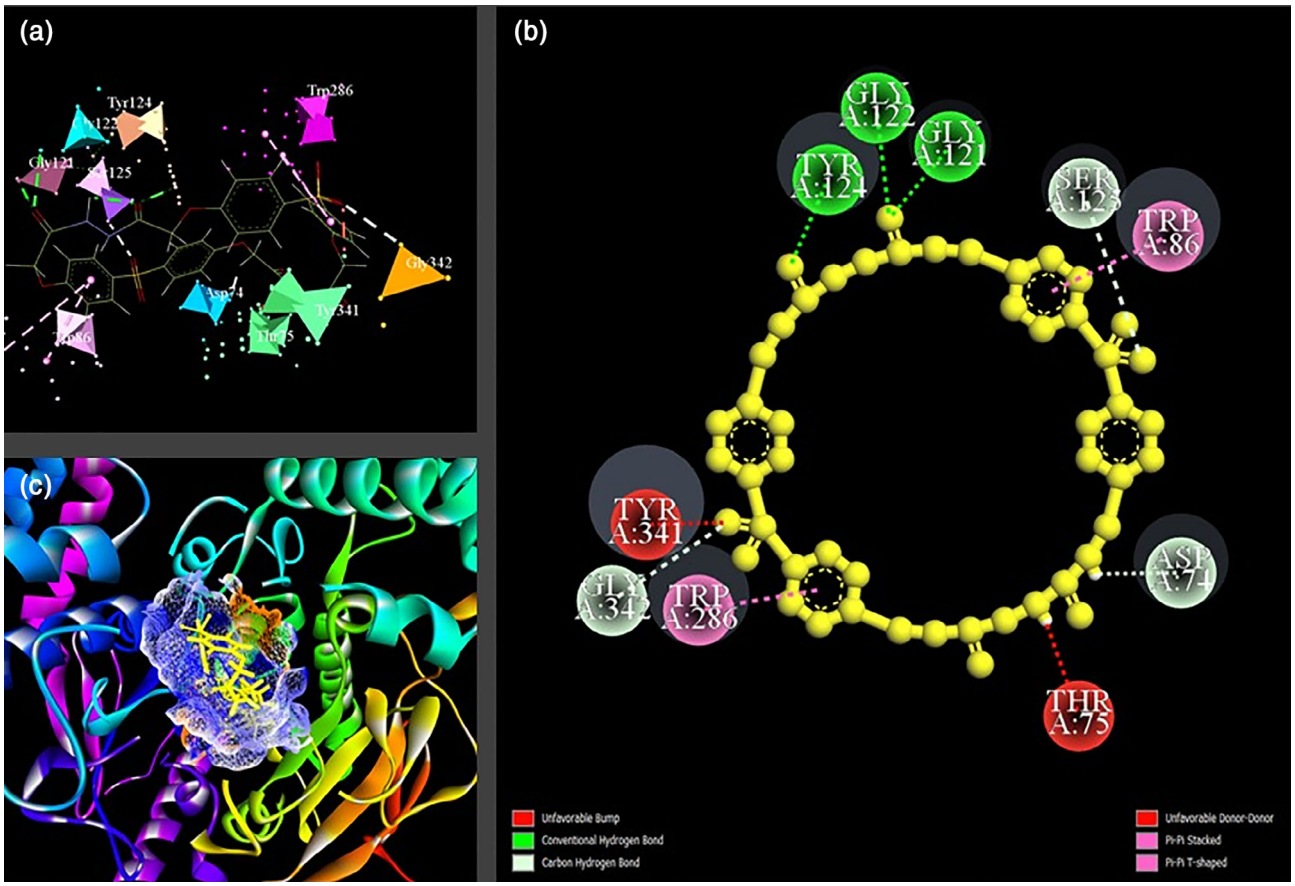


FIGURE 3 (a) 3D view of the docking pose of macrocycle **5m** (green colored line-view model) in the binding pocket of AChE (4EY6). (c) Two-dimensional (2D) interaction diagram for **5m**. (c) Ribbon diagram depicting docked pose of **5m** (yellow) in the binding cavity (mesh surface) of AChE (4EY6)

(8 Ar—C, Sulfone), 129.18, 128.00, (12 Ar—C), 115.74 (14 Ar—C, Sulfone), 64.68 (8—CH_2—).

2.1.5 | Pharmacology

Enzyme inhibition

Enzymes and reagents including acetylcholine iodide (AChI), butyrylcholine chloride (BChCl), 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) and galantamine were purchased from Sigma Aldrich. Reported protocol (Ahmad et al., 2018) employing a spectrophotometric method was used to determine enzyme inhibitions of the synthesized macrocycles (**5a-o**) in comparison to galantamine as reference standard.

Solutions consisting of DTNB (0.2 mM) in 62 mM sodium phosphate buffer (pH 8.0, 880 μL), solution of macrocycles (40 μL) and acetylcholinesterase or butyrylcholinesterase (40 μL) were mixed and incubated for 15 min (25°C). In each case, the initiation of activity took place by adding 40 μL acetylcholine (ACh) or butyrylcholine (BCh). The hydrolysis of acetylcholine or butyrylcholine was estimated at a wavelength of 412 nm. Each experiment was repeated thrice and concentrations of compounds and standard that caused 50% inhibition (IC_{50}) of the two cholinesterase enzymes were expressed as mean ± *SD*.

Molecular docking

The interactions of our synthesized macrocycles with amino acid residues in the active sites of two target cholinesterase enzymes namely acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) were studied through molecular docking approach as part of our computer aided drug design project. A highly efficient software package by the name Molecular Operating Environment (MOE) was used to dock the synthesized compounds. Two dimensional structures of macrocycles (**5a-5o**) obtained as files with .sdf extensions from ChemDraw Professional version 16.0 were opened as three dimensional sterostructures in the program. These structures were first 3D protonated and then energy minimized using default parameters of the software (gradient: 0.05, Force Field: MMFF94X). The three-dimensional structures of AChE and BChE were obtained from the protein databank with PDB IDs of 4EY6 and 4BDS, respectively. The structures of our target enzymes were prepared in MOE by sequential removal of water molecules, 3D protonation and energy minimization using default values in the MOE.

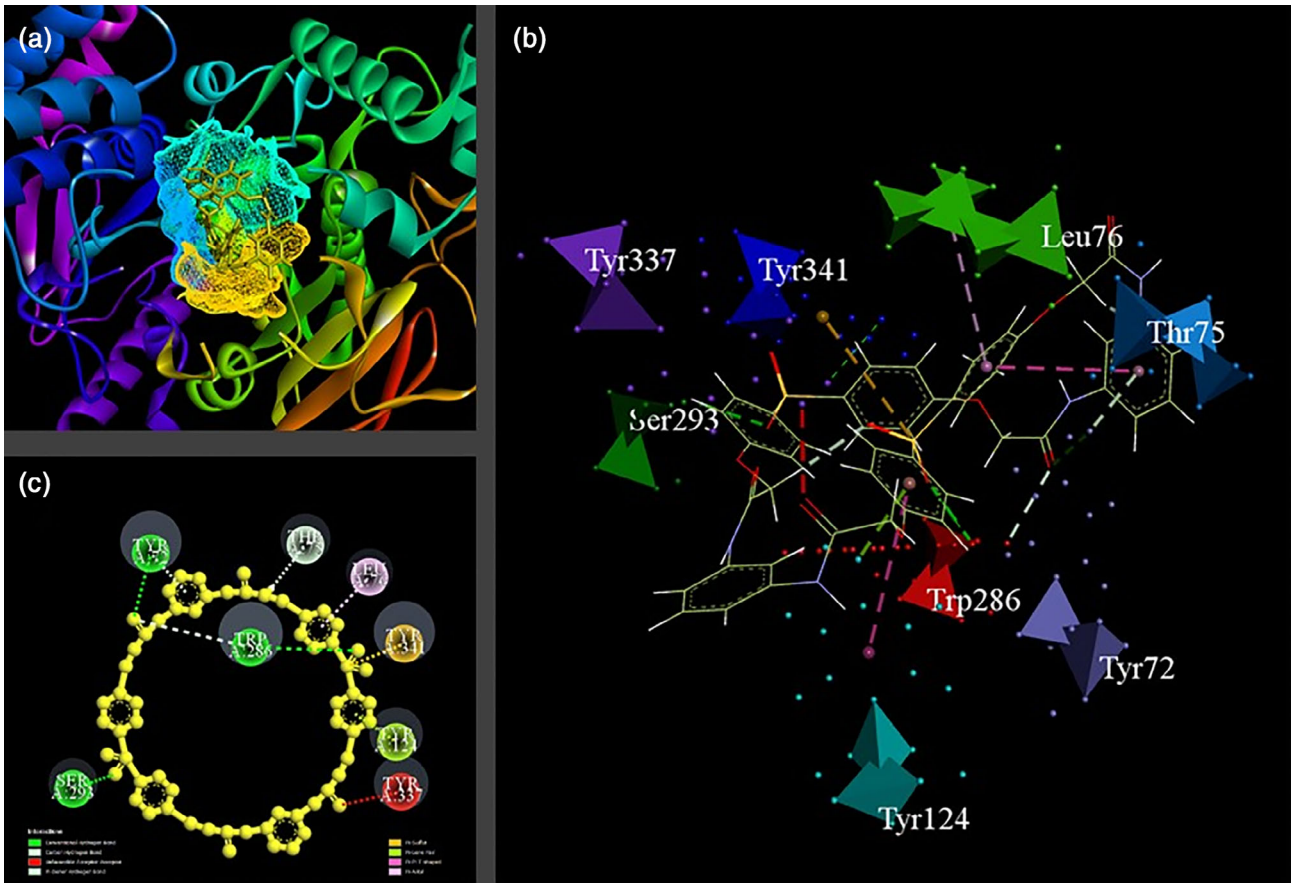


FIGURE 4 (a) Ribbon diagram depicting docked pose of **5l** (yellow) in the binding cavity (mesh surface) of AChE (4EY6). (b) 3D view of the docking pose of macrocycle **5l** (green colored line-view model) in the binding pocket of AChE (4EY6). (c) Two-dimensional (2D) interaction diagram for **5l**

3 | RESULTS AND DISCUSSION

3.1 | Synthesis and mechanistic rationalization of macrocycles 5a-o

In light of the importance of sulfonyl functional group, the idea of synthesizing macrocycles deploying this important moiety was developed. An effective strategy to synthesize sulfone-based macrocycles was adopted employing previously described methods of oxidation, etherification, and macrocyclization.

Our strategy was to optimize conditions for the three steps in our protocol. Different oxidizing agents and solvents were employed for oxidation of 4,4′-thiodiphenol (**1**). The synthesis of 4,4′-sylfonyldiphenol (**2**) by oxidation with different oxidizing agents like $NaIO_4$, H_2O_2 and *m*-chloroperbenzoic acid (*m*-CPBA) from 4,4′-thiodiphenol (**1**) at room temperature is shown below in **Scheme 1**.

The etherification of 4,4′-sylfonyldiphenol (**2**) into diethyl-2,2′-(4,4′-sulfonylbis(4,1-phenylene)bis(oxy))diacetate (**4**) was carried out with ethyl-2-chlororacetate (**3**) in DMF as a reaction medium under reflux conditions (**Scheme 2**).

The formation of diethyl-2,2′-(4,4′-sulfonylbis(4,1-phenylene)bis(oxy))diacetate (**4**) was subsequently followed by ring closure in a condensation reaction with various aromatic and aliphatic diamines using ethyl alcohol as a medium for the reaction under the same conditions (**Scheme 3**). Under diluted conditions, various diamines were dropped into solution of diethyl-2,2′-(4,4′-sulfonylbis(4,1-phenylene)bis(oxy))diacetate (**4**) and the desired macrocyclic products (**5a-o**) were obtained in very good yields. The optimized conditions for the synthesis of macrocycles consisted of stirring of 1 equivalent of the diacetate with 0.5 equivalent of diamines. Both DMF and EtOH were used as solvents, but good results in terms of product yield were obtained with EtOH as it could be very easily removed from reaction mixture. To investigate the substrate scope and limitations we have synthesized a total of **15** macrocycles (**5a-o**) according to **Scheme 3**.

A mechanistic rationalization for the cyclization reaction is provided in **Scheme 4**. It is conceivable that the initial step involves condensation of the carbonyl and a diamine group to form the desired products through nucleophilic addition reactions. Diamines added to the carbonyl groups lose protons which are taken up by ethoxide groups from the diacetates, thus

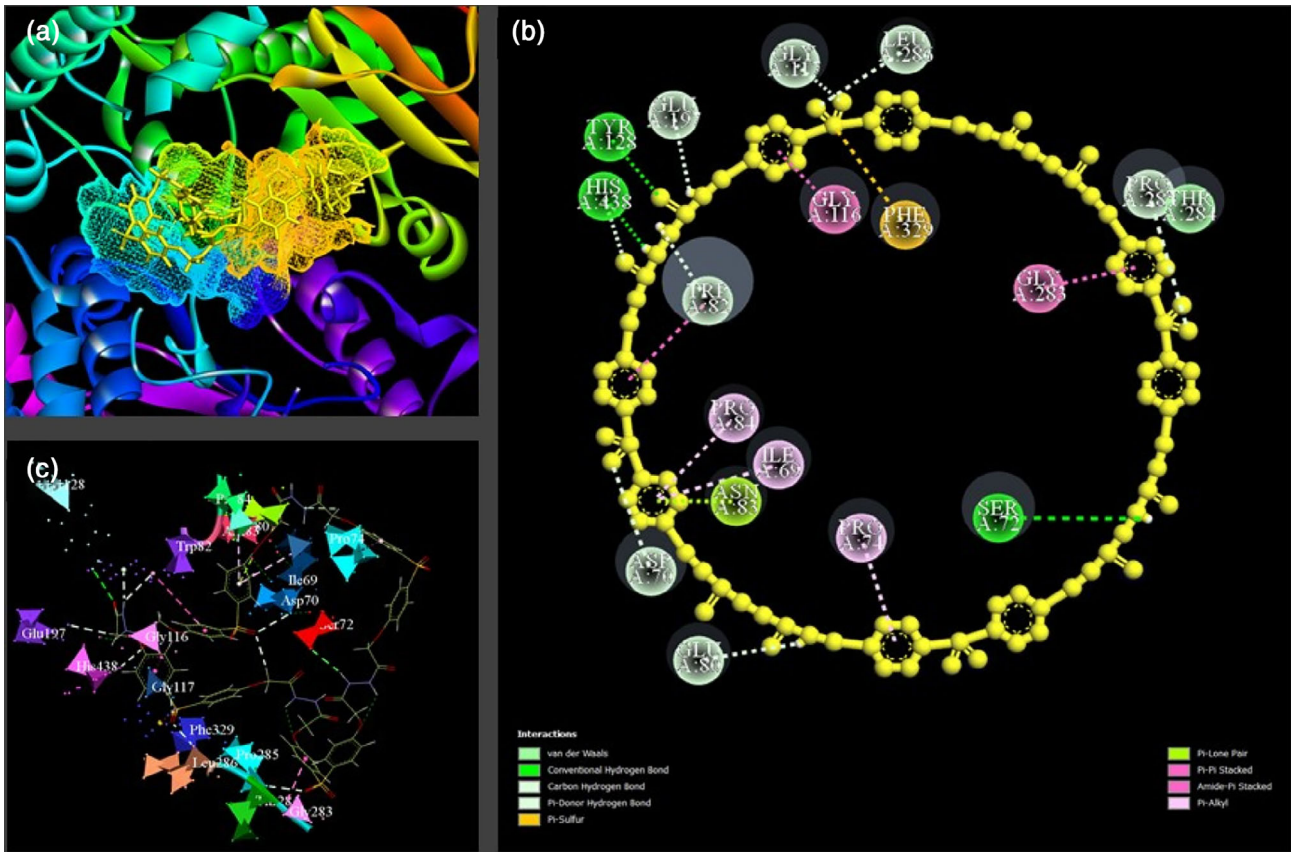


FIGURE 5 (a) Ribbon diagram depicting docked pose of **5n** (yellow) in the binding cavity (mesh surface) of BChE (4BDS) (b) two-dimensional (2D) interaction diagram for **5n**. (c) 3D view of the docking pose of macrocycle **5n** (green colored line-view model) in the binding pocket of BChE (4BDS)

forming ethyl alcohol and the desired macrocyclic products (Figure 1).

3.2 | Anticholinesterase activity

The synthesized macrocycles were initially tested against two important cholinesterase enzymes (AChE & BChE) involved in the neurological disorder called Alzheimer's. The final results of this assay were expressed as 50% inhibitory concentration (IC_{50}) values in micromole (μM) unit as displayed in Table 1. Galantamine was chosen as a dual reference inhibitor for the two enzymes. Low to moderate activity was recorded by the set of compounds (**5a-o**) as compared to galantamine. From a structural point of view (Figure 1), it can be hypothesized that hydrazine-closed macrocycles show significant inhibition against the selected enzymes and therefore, indicating importance of –NH – NH– linkage in the inhibition process. Two such macrocycles **5m** and **5n** which were symmetric around hydrazide linkage (–NH – NH–) were found to show significant AChE inhibition with IC_{50} values of 76.9 ± 0.24 and 71.2 ± 0.77 μM, respectively. Macrocycle **5n** was also found to be an active inhibitor of butyrylcholinesterase (BChE) with IC_{50} score of 55.3 ± 0.54 μM. Amongst others, macrocycle **5l** cyclized with *o*-phenylenediamine demonstrated moderate inhibition with IC_{50} value of 81.1 ± 0.54 μM. It is interesting to note that **5k**, a macrocyclic analogue of **5l** closed with *p*-phenylenediamine showed non-significant activity.

3.3 | Molecular docking interactions

Based on experimental observations, macrocycles showing significant cholinesterase inhibitions were further chosen for protein-ligand interaction studies. MOE docking software with default parameters was used for transporting ligand molecules (**5n**, **5m**, and **5l**) into the active gorges of both AChE and BChE crystal structures. A total of five conformations were generated for each ligand and the top ranked conformations were further subjected to analysis for their protein-ligand interactions. The most active macrocycle **5n** was found to fit into active site of AChE with a docking score of –11.7884 by establishing significant interactions with Glu 292, Trp 286, Arg 296, Phe 295, Ser 203, His 447, Glu 202, Trp 86, Ser 125, Tyr 124, Tyr 72, and Leu 76 as shown in the interaction diagram (Figure 2). Arg 296, Phe 295, and His 447 showed hydrogen bonding interactions with sulfonyl and carbonyl oxygen atoms of the ligand. Some pi-pi stacking interactions were also found between Trp 86 and Trp 286 and phenyl rings of the docked ligand.

Macrocyle **5m** was also active with MOE docking score of −9.4188 that can fit in the active gorge of AChE. Upon visual inspection **(**Figure 3**)**, different types of interactions between **5m** and amino acid residues of AChE such as Ser 203, Gly 122, Gly 121, Trp 86, Ser 125, Tyr 124, Asp 74, Tyr 72, and Trp 286 can be seen. Trp 86 showed π-π stacked interaction and Trp 286 showed π-π T-shaped interactions with phenyl ring. Hydrogen bonding interaction of Gly 122, Gly 121, Tyr 72 with docked ligand and some carbon-hydrogen bonding interactions can also be observed i.e. Ser 203, Ser 125 and Asp 74 with Carbonyl oxygen, sulphonyl oxygen and CH of the ligand.

Macrocycle **5l** also showed some acetylcholinesterase inhibition activity and was successfully docked into the active pocket of AChE (4EY6) with a docking score of −7.8816. Various types of interactions were identified upon visual inspection **(**Figure 4**)**. Amino acid residues Ser 293, Tyr 72 and Trp 286 displayed hydrogen bonding interactions with carbonyl and sulphonyl oxygen of the ligand (**5l**). Thr 75 revealed carbon hydrogen bonding interaction with CH and Leu 76 exhibited π-π T-shaped interaction with phenyl ring. Tyr 341 showed pi-sulfur interaction, Tyr 124 pi-lone pair interaction with the docked ligand.

The only macrocycle that showed significant activity against BChE is **5n**. It was well-placed in the active site of BChE (4BDS) with a docking score of −11.7884. Upon visual inspection, different interactions were seen **(**Figure 5**)** like π-π stacked interaction of Trp 82 and amide-pi stacked interaction of Gly 116, Gly 283 with phenyl ring. Ile 69, Pro 74 and Pro 84 showed pi-alkyl interaction. Various Hydrogen bonding interactions i.e. Ser 72, Tyr 128, His 438, carbon hydrogen bonding interactions such as Gly 117, Gly 197, Leu 286, Pro 285, Pi-donor hydrogen bonding interaction of Asp 70, Glu 80, Pi-sulfur interaction of Phe 329, pi-lone pair interaction of Asn 83 and various van dar waals interactions with docked ligand can also be displayed.

4 | CONCLUSIONS

In conclusion, we have introduced a very mild, straightforward, sequential, rapid and highly diverse synthetic pathway for the synthesis of macrocycles. These artificial macrocyclic scaffolds were formed by ring closure reactions via various diamines (aromatic and aliphatic). The overall sequence used here was to introduce different ring sizes using readily available starting materials in a three-step procedure. It is worthy to notice that amongst the synthesized compounds, hydrazine-based macrocycles (**5 m** and **5n**) can be developed as leads for drug development against cholinesterases and hence can be considered as alternate molecules for treating Alzheimer's.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this research work have been included in this article

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