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Novel biphenyl *bis*-sulfonamides as acetyl and butyrylcholinesterase inhibitors: Synthesis, biological evaluation and molecular modeling studies

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ABSTRACT

A series of new biphenyl *bis*-sulfonamide derivatives **2a**–**3p** were synthesized in good to excellent yield (76–98%). The inhibitory potential of the synthesized compounds on acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) was investigated. Most of the screened compounds showed modest *in vitro* inhibition for both AChE and BChE. Compared to the reference compound eserine (IC_{50} 0.04 ± 0.0001 μM for AChE) and (IC_{50} 0.85 ± 0.0001 μM for BChE), the IC_{50} values of these compounds were ranged from 2.27 ± 0.01 to 123.11 ± 0.04 μM for AChE and 7.74 ± 0.07 to <400 μM for BuChE. Among the tested compounds, **3p** was found to be the most potent against AChE (IC_{50} 2.27 ± 0.01 μM), whereas **3g** exhibited the highest inhibition for BChE (IC_{50} 7.74 ± 0.07 μM). Structure–activity relationship (SAR) of these compounds was developed and elaborated with the help of molecular docking studies.

1. Introduction

Alzheimer's disease (AD), a progressive neurodegenerative disease, associated with selective loss of cholinergic neurons and reduced level of acetylcholine neurotransmitter. The disorder is characterized by multiple cognitive impairments including gradual loss of memory, judgment and learning ability [1,2]. Reports have revealed that an estimated 35.6 million people worldwide suffer from this ailment [3]. The amyloid β-peptide (Aβ) plaques, intracellular neurofibrillary tangles, loss of central cholinergic function are the typical pathological hallmarks of AD [4,5]. The cholinergic hypothesis manifests that AChE plays a major role in functioning of cholinergic system and is associated with AD through involvement in the acetylcholine metabolism [6]. In addition, cholinergic neurotransmission is co-regulated by BChE, whose activity is increased in AD. The current therapeutic approach implies inhibition of AChE and BChE [7–9] to enhance central cholinergic function [10] which in turn increase acetylcholine level in the brain. Therefore the existing remedies that are used to alleviate the symptoms of AD such as donepezil, [11] rivastigmine, [12] and more recently galantamine [13] belong to the class of cholinesterase inhibitors (Fig. 1).

Unfortunately, the potential effectiveness of these inhibitors is often limited as they suffer from central and peripheral side effects. Clinical studies have indicated that tacrine has hepatotoxic liability [14,15] and due to adverse events, it was discontinued [16]. Studies have revealed that inhibition of AChE-induced Aβ aggregation [17] by cholinesterase inhibitors employ additional benefits for AD treatment [18,19]. In recent years, a significant number of studies have shown advancement in the development of dual cholinesterase inhibitors [20,21].

Sulfonamides, an important class of pharmacophores, constitute nearly 200 drugs currently in the market. Numerous sulfonamide-based medicines have been developed as diuretics, anti-migraine agents, cyclooxygenase-II (COX-2)-specific anti-inflammatory drugs recently as AChE [22,23]. In addition, aromatic/heterocyclic sulfonamides possessing free amino function have shown effective inhibition of three carbonic anhydrase isozymes [24]. Since biphenyl based sulfonamides are considered great pharmacophores in medicinal chemistry, and recently we

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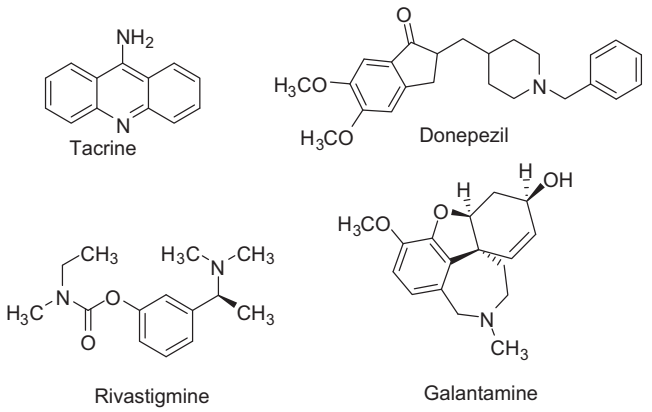


Fig. 1. Chemical structures of potent AChE inhibitors.

reported their LOX inhibition activity [25] and as part of our extensive efforts in the search of potent cholinesterase inhibitors [26]. Herein we report synthesis of a series of new biphenyl bis-sulfonamides analogues (**2a–3p**) (Scheme 1) and their AChE and BChE inhibition activities along with molecular modeling investigations.

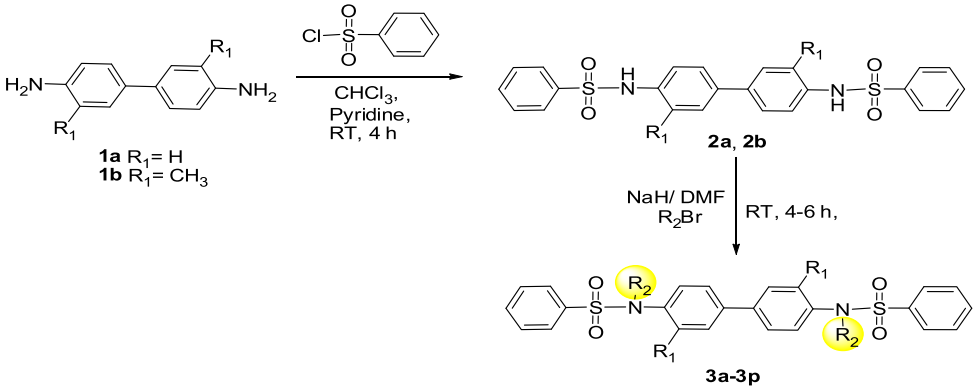
2. Results and discussion

2.1. Chemistry

A series of structurally related sulfonamides derivatives (**2a–3p**) were synthesized as outlined in Scheme 1. Condensation of appropriate benzidines (**1a** or **1b**) with benzenesulfonyl chloride yielded the corresponding sulfonamides **2a** and **2b**. N-alkylation or acylation of the intermediates **2a** and **2b** with appropriate alkyl or acyl halides in DMF at room temperature, using pyridine as a base, afforded the desired biphenyl bis(benzenesulfonamides) **3a–3p** in good to excellent yield (Scheme 1).

2.2. AChE and BChE inhibition

All synthesized compound (**2a–3p**) were screened for their *in vitro* inhibition against AChE and BChE using commercially



Entry	Comp	R_1	R_2	Yield (%)	Entry	Comp	R_1	R_2	Yield (%)
1	2a	H	H	98%	**10**	3h	H	$CH_2(C_6H_5)$	90%
2	2b	CH_3	H	98%	**11**	3i	CH_3	$COCH_3$	82%
3	3a	H	$COCH_3$	90%	**12**	3j	CH_3	$CH(CH_3)_2$	76%
4	3b	H	$CH(CH_3)_2$	76%	**13**	3k	CH_3	$CH_2(CH_2)_2CH_3$	85%
5	3c	H	$CH_2(CH_2)_2CH_3$	84%	**14**	3l	CH_3	$CH_2(CH_2)_3CH_3$	84%
6	3d	H	$CH_2(CH_2)_3CH_3$	89%	**15**	3m	CH_3	$CH_2(CH_2)_4CH_3$	81%
7	3e	H	$CH_2(CH_2)_4CH_3$	79%	**16**	3n	CH_3	$CH_2(CH_2)_5CH_3$	89%
8	3f	H	$CH_2(CH_2)_5CH_3$	82%	**17**	3o	CH_3	$CH_2(CH_2)_{14}CH_3$	83%
9	3g	H	$CH_2(CH_2)_{14}CH_3$	80%	**18**	3p	CH_3	$CH_2(C_6H_5)$	91%

Scheme 1. Synthesis of biphenyl bis-sulfonamides (**2a–3p**).

available eserine as control [27]. The results summarized in Table 1 indicated that compounds **3p**, **3o**, **3k**, **3g** and **3c** were found to be more potent AChE inhibitors as compared to others with moderate affinity. Compound **3a** possessing electron withdrawing acetyl moiety on nitrogens of sulfonamide, exhibited weak activity (IC_{50} 103.21 ± 0.11 μM), however replacement of acetyl moiety with isopropyl groups, yielding **3b**, moderately improved the activity (IC_{50} 73.21 ± 0.11 μM). Likewise, compound **3c** (IC_{50} 8.41 ± 0.07 μM) bearing n-butyl substituent at nitrogens, significantly enhanced the activity. This indicated that electronic releasing alkyl moieties on nitrogen are important for the higher activity of these compounds. This hypothesis was further supported by the observation of increase activity in the case of 3,3′-dimethylbiphenyl analogues. For instance when acetyl moieties on nitrogens in **3i** (IC_{50} 96.31 ± 0.14 μM) were replaced with n-butyl group, yielding **3k** (IC_{50} 3.72 ± 0.01 μM), significantly increased the activity. Interestingly, the activity started diminishing, both in the biphenyl and 3,3′-dimethylbiphenyl analogues (**3d**–**3f** and **3l**–**3n**) alike, when substituents on nitrogens of sulfonamide were changed from n-butyl group to the next higher homologues i.e. n-pentyl, n-hexyl and n-heptyl groups. This revealed that the bulkiness of the attached function on nitrogens cause diminishing activity. Surprisingly, the activity of compounds **3g** (IC_{50} 4.63 ± 0.05 μM) and **3o** (IC_{50} 2.45 ± 0.01 μM) increased enormously when substituents on nitrogens were replaced to n-hexadecanyl group. Whereas compound **3h** (IC_{50} 61.57 ± 0.05 μM), possessing benzyl group on nitrogens showed moderate activity, the 3,3′-dimethylbiphenyl analogue **3p** (IC_{50} 2.27 ± 0.01 μM), bearing benzyl moiety on nitrogens turned out to be the most potent among the compounds screened for AChE inhibition. This revealed that both the 3,3′-dimethylbiphenyl functionality as well as benzyl moiety on nitrogens are crucial for the higher activity of **3p**.

In case of BuChE inhibition studies, compound **3g** (IC_{50} 2.27 ± 0.01 μM) was turned out to be the most active. The higher activity of **3g**, bearing n-hexadecanyl moiety on nitrogens, is a similar trend as was the case in AChE inhibition and could be attributed to the hydrophobic bulkiness of the n-hexadecanyl group. Compounds **3k** (IC_{50} 20.27 ± 0.32 μM), **3o** (IC_{50} 24.74 ± 0.01 μM), **3p** (IC_{50} 31.31 ± 0.05 μM) and **3h** (IC_{50} 35.82 ± 0.05 μM) have shown good to moderate activity whereas the rest of the compounds have shown either low activity or were inactive against BChE.

Compound **3c** showed moderate activity for both AChE and BChE but possessed the highest selectivity toward AChE (14.8525). The most potent AChE inhibitor Compound **3p**, being in the series, has also shown good selectivity (13.792). Likewise compound **3o** also exhibited good and moderate inhibition for BChE and AChE, respectively, have also shown good selectivity (10.097).

2.3. Docking studies

All synthesized compounds were docked to the active site of both cholinesterases. The docking results showed that the whole group of the analyzed biphenyl derivatives except **3g** and **3o** displayed similar binding mode with AChE. Ligand binding within the active site of AChE was limited to hydrophobic interactions with Trp84, Phe330, and Phe331 from anionic sub-site, Phe290 from acyl pocket as well as Tyr121, Trp279 and Tyr334 from peripheral anionic site (PAS). Biphenyl fragment was engaged in more specific π–π and CH–π interactions with Trp279, Phe331 and Tyr334. Oxygen atoms in sulfonamide groups might create weak H-bonds with hydroxyl group of Tyr70 or unionized form of Asp72. The arrangement of the most active compound **3p** in the active gorge of AChE is shown in Fig. 2. In case of compounds **3g** and **3o** long aliphatic chain in R_2 position occupied the appreciable part of the active site, and this caused the shift of the biphenyl fragment toward the exit from the gorge of enzyme. Docking results did not show distinct differences between the compounds having a methyl group at the R_1 position and not-substituted derivatives.

Similar results were observed in case of docking to the active site of BChE. Most of the compounds revealed common binding mode, and hydrophobic interactions between the inhibitors and aromatic amino acids such as Trp82 and Tyr332 seemed to be crucial for binding. The pose adopted by compound **3k** which was the second compound in BChE inhibitory activity order is shown in Fig. 3. Compounds **3f**, **3n**, **3h** and **3p** could additionally bind with hydrophobic pocket consisting of Phe398, Trp231, Leu286 and Phe329. As in case of AChE, inhibitors **3g** and **3o** bound partially inside and partially beyond the enzyme active site due to the long alkyl substituents. Binding at the entry to the gorge could block the access of substrate to the catalytic site.

Summing up, it can be assumed that the binding of the tested compounds with AChE and BChE was mainly provided due to the presence of hydrophobic interactions. We did not observe any strong hydrogen bonds as well as salt bridges. However, the obtained compounds are interesting starting point for their further development and synthesis of potent cholinesterase inhibitors. Structural modifications leading to increase of number of hydrogen bond donors and acceptors should augment the strength and specificity of binding to enzymes.

3. Conclusions

In summary, 18 new biphenyl bis-sulfonamides analogues (**2a**–**3p**) have been successfully synthesized and were evaluated for their potentially *in vitro* AChE and BuChE inhibition. Among the series, compounds **3p** and **3o** have shown the highest activity for AChE. In case of BChE inhibition assay, compound **3g** turned out to be the most potent. Compounds **3p** and **3o** are quite promising in the sense that they have shown higher activity both for AChE and BChE as well as good selectivity for AChE. Molecular modeling studies further demonstrated the binding modes of this series into both cholinesterases. Based on these results we believe the present research would lead to the development of more potent AChE and BChE inhibitors to treat AD.

4. Experimental

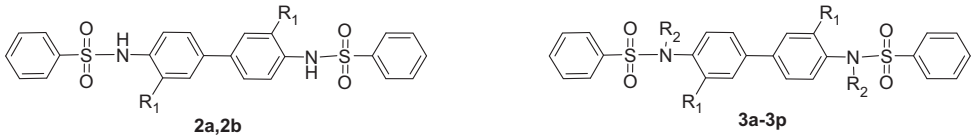
4.1. Material and methods

All chemicals and solvents used are of analytical grade and were purchased from Sigma, Aldrich and Merck Chemical Co. and were used without further purification. Melting points were taken in open capillary tubes and are uncorrected. TLC was performed on silica coated aluminum sheets (6F254, 0.2 mm) and visualized in low UV light. IR spectra in KBr pellets were recorded on FT-IR Perkin Elmer spectrum BX spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 using Bruker NMR 500 MHz. Splitting patterns were as follows s (singlet), d (doublet), dd (double doublets), t (triplet), and m (multiplet). Chemical shifts are reported in δ (ppm) and coupling constants are given in Hz.

4.2. General procedure for the precursor sulfonamides (*2a*, *2b*)

To a stirred solution of benzidine **1a** or *o*,*o*′-tolidine **1b** (0.01 mol) in dichloromethane (50 mL) pyridine (around 1 mL, to adjust pH 8) was added. Then benzenesulfonyl chloride (0.02 mol, 0.443 g) was added to the reaction and the mixture was stirred at room temperature while maintaining the pH of the

Table 1
In vitro AChE & BChE inhibitory activity of compounds **2a–3p** (inhibition percentage and IC_{50} values are means given with SEM).



Entry	Sample code	Conc. (mM)	AChE inhibition		BuChE inhibition		Selectivity
			Inhibition (% ± SEM)	IC_{50} (μM ± SEM)	Inhibition (% ± SEM)	IC_{50} (μM ± SEM)	AChE/BuChE
1	2a	0.5	96.54 ± 0.12	42.31 ± 0.11	60.26 ± 0.16	203.11 ± 0.31	4.8005
2	2b	0.5	76.08 ± 0.21	123.11 ± 0.04	28.15 ± 0.61	–	
3	3a	0.5	78.51 ± 0.34	103.21 ± 0.11	72.19 ± 0.45	156.21 ± 0.31	1.5135
4	3b	0.5	89.61 ± 0.25	73.21 ± 0.11	35.98 ± 0.64	–	
5	3c	0.5	98.74 ± 0.15	8.41 ± 0.07	92.72 ± 0.21	124.91 ± 0.08	14.8525
6	3d	0.5	88.47 ± 0.52	79.61 ± 0.21	40.95 ± 0.47	–	
7	3e	0.5	89.05 ± 0.33	78.61 ± 0.17	44.81 ± 0.61	–	
8	3f	0.5	95.61 ± 0.36	58.61 ± 0.12	33.61 ± 0.25	–	
9	3g	0.5	98.55 ± 0.13	4.63 ± 0.05	98.67 ± 0.13	7.74 ± 0.07	1.617
10	3h	0.5	92.91 ± 0.19	61.57 ± 0.05	97.72 ± 0.11	35.82 ± 0.05	0.5817
11	3i	0.5	85.61 ± 0.24	96.31 ± 0.14	34.11 ± 0.31	–	
12	3j	0.5	83.29 ± 0.51	101.21 ± 0.11	22.74 ± 0.61	–	
16	3k	0.5	97.82 ± 0.21	3.72 ± 0.01	93.21 ± 0.18	20.32 ± 0.08	5.4623
13	3l	0.5	92.51 ± 0.25	51.21 ± 0.08	40.62 ± 0.18	–	
14	3m	0.5	93.37 ± 0.32	49.61 ± 0.11	50.66 ± 0.62	<400	
15	3n	0.5	95.97 ± 0.38	43.21 ± 0.14	94.71 ± 0.14	48.71 ± 0.11	1.127
17	3o	0.5	97.37 ± 0.13	2.45 ± 0.02	94.35 ± 0.19	24.74 ± 0.09	10.097
18	3p	0.5	98.94 ± 0.12	2.27 ± 0.01	95.23 ± 0.14	31.31 ± 0.05	13.792
Control	Eserine[b]	0.25 mM	91.29 ± 1.17	0.04 ± 0.0001	82.82 ± 1.09	0.85 ± 0.0001	21.25

[a] All samples were tested in triplicates and averaged. SEM is standard mean error of the three experiments.
[b] Standard used for AChE and BChE inhibition.

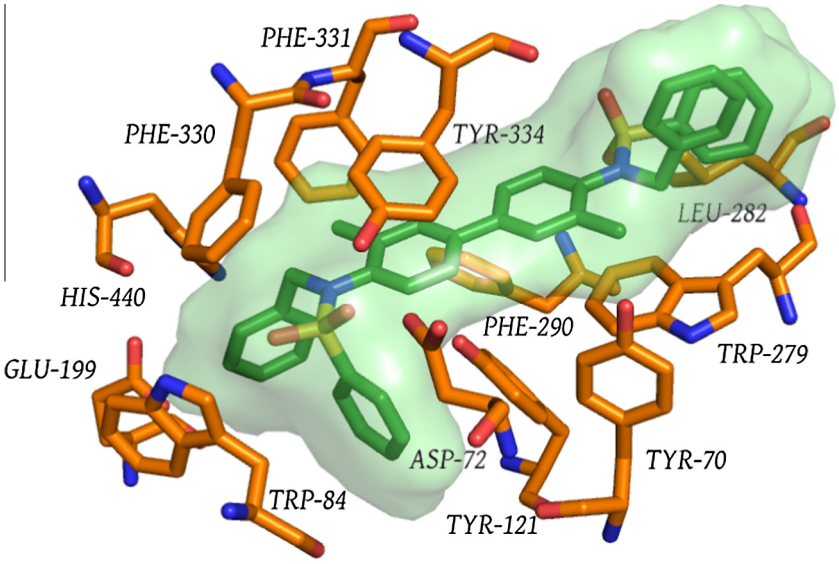


Fig. 2. Binding mode of compound **3p** within the active site of AChE.

mixture to ~8.0 with occasional addition of pyridine. After completion of reaction in 4 h (monitored by TLC), pH of the reaction mixture was adjusted to 2.0 by adding 1 M HCl where the desired product **2a** or **2b** was solidified which was filtered and washed with distilled water (50 mL). Recrystallization from methanol afforded the required product in essential pure form.

*4.2.1. N,N′-(biphenyl-4,4′-diyl)dibenzenesulfonamide **(2a)***

Violet solid; Yield: 98%; m.p.: 249 °C; IR (υ_{max}, KBr, cm^{-1}): 3350 (N—H *str*), 3029 (C—H *str* Ar), 1330 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 10.36 (2H,s,NH), 7.82 (4H,d, *J* = 10 Hz, ArH), 7.77–7.75 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (4H, d, *J* = 8.5 Hz),6.69 (4H, d, *J* = 9 Hz); ^{13}C NMR (500 MHz; DMSO-d_6): 140.6 (2C), 133.4 (2C), 131.3 (2C), 129.7 (4C), 128.8 (2C), 127.3 (4C), 127.20 (4C), 120.7 (4C); Anal. Calcd for $C_{24}H_{20}N_2O_4S_2$: C, 62.05; H, 4.34; N, 6.03; O, 13.78; S, 13.80. Found: C, 62.13; H, 4.38; N, 6.14 S, 13.34.

*4.2.2. N,N′-(3,3′-dimethylbiphenyl-4,4′-diyl) dibenzenesulfonamide (**2b**)*

White solid; Yield: 98%; m.p.:251 °C; IR (υ_{max}, KBr, cm^{-1}): 3376 (N—H str), 3027 (C—H str Ar), 1335 (S—O str); ^{1}H NMR (500 MHz,

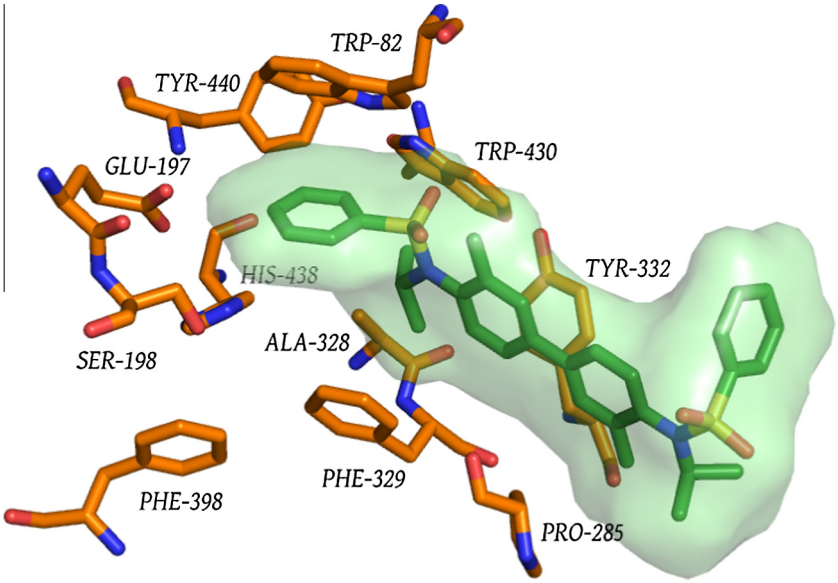


Fig. 3. Binding mode of compound **3k** within the active site of BuChE.

DMSO-d_6): 9.62 (2H, s, NH), 7.88 (4H, d, J = 10 Hz, ArH), 7.72–7.70 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (2H, s, ArH), 7.38 (2H, d, J = 8.5 Hz, ArH), 6.33 (2H, d, J = 8.2 Hz, ArH), 1.9 (6H, s, CH_3); ^{13}C NMR (500 MHz; DMSO-d_6): 140.6 (2C), 137.1 (2C), 134.5 (2C), 132.9 (4C), 129.3 (2C), 128.8 (4C), 126.7 (4C), 126.6 (2C), 124.4 (2C), 17.7 (2C); Anal. Calcd for: $C_{26}H_{24}N_2O_4S_2$: C, 63.39; H, 4.91; N, 5.69; O, 12.99; S, 13.02. Found: C, 63.45; H, 5.52; N, 5.56; S, 13.06.

4.3. General procedure A for the Synthesis of **3a–3p**

To a solution of compound **2a** or **2b** (10 mmol) in DMF (10 mL) n-hexane washed sodium hydride (2.5 mmol, 0.6 g) was added and after being stirred for 40 min at room temperature, the corresponding alkylating/acylating reagent (20 mmol) was added to the mixture. The mixture was stirred until the completion of reaction which was monitored by TLC. When the reaction was completed the reaction mixture was poured on the crushed ice. The pH of the mixture was adjusted to 4.0 with 1 N HCl and the precipitated product was filtered and washed twice with distilled water.

4.3.1. *N,N′-(biphenyl-4,4′-diyl)bis(N-(phenylsulfonyl)acetamide)* ***(3a)***

Pink solid; Yield: 90%; m.p.: 259 °C; IR (υ_{max}, KBr, cm^{-1}): 3029 (C—H *str* Ar), 1330 (S—O *str*), 1707 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6): 7.82–7.79 (12H, m, ArH), 7.75–7.73 (2H, m, ArH), 7.62–7.60 (4H, m, ArH); 2.04 (6H, s, CH_3); ^{13}C NMR (500 MHz; DMSO-d_6): 171.1 (2C), 140.6 (2C), 137.9 (2C), 133.8 (2C), 133.0 (2C), 129.0 (4C), 128.7 (4C), 127.3 (4C), 120.0 (4C), 28.3 (2C). Anal. Calcd for $C_{28}H_{24}N_2O_6S_2$: C, 61.30; H, 4.41; N, 5.11; S, 11.69. Found: C, 61.34; H, 4.35; N, 5.08; S, 11.71.

4.3.2. *N,N′-(biphenyl-4,4′-diyl)bis(N-isopropylbenzenesulfonamide)* ***(3b)***

Brown solid; Yield: 76%; m.p.: 235 °C; IR (υ_{max}, KBr, cm^{-1}): 3029 (CH *str* Ar), 2927 (CH *str*), 1332 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.82 (4H, d, J = 10 Hz, ArH), 7.77–7.75 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (4H, d, J = 8.5 Hz), 6.69 (4H, d, J = 9 Hz), 2.75–2.74 (2H, m, CH), 1.25 (12H, d, J = 6.2 Hz, CH_3); ^{13}C NMR (500 MHz; DMSOd_6): 140.6 (2C), 133.4 (2C), 131.3 (2C), 129.7 (4C), 128.8 (2C), 127.3 (4C), 127.20 (4C), 120.7 (4C), 43.0 (2C), 20.2 (4C). Anal. Calcd for $C_{30}H_{32}N_2O_4S_2$: C, 65.67; H, 5.88; N, 5.11; S, 11.69. Found: C, 65.99; H, 5.55; N, 5.13; S, 12.57.

4.3.3. *N,N′-(biphenyl-4,4′-diyl)bis(N-butylbenzenesulfonamide)* ***(3c)***

White solid; Yield: 84%; m.p.:224 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 2940 (CH_2 *str*), 1334 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.82 (4H, d, J = 10 Hz, ArH), 7.77–7.75 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (4H, d, J = 8.5 Hz), 6.69 (4H, d, J = 9 Hz), 3.50 (4H, t, J = 7.1 Hz, CH_2), 1.57 (4H, m, CH_2), 1.23 (4H, m, CH_2), 0.91 (6H, t, J = 7.1 Hz, CH_3); ^{13}C NMR (500 MHz; DMSOd_6): 140.6 (2C), 133.4 (2C), 131.3 (2C), 129.7 (4C), 128.8 (2C), 127.3 (4C), 127.2 (4C), 120.7 (4C), 48.7 (2C), 27.3 (2C), 24.1 (2C), 14.1 (2C). Anal. Calcd for $C_{31}H_{34}N_2O_4S_2$: C, 66.16; H, 6.09; N, 4.98; S, 11.40. Found: C, 66.97; H, 5.96; N, 5.9; S, 11.97.

4.3.4. *N,N′-(biphenyl-4,4′-diyl)bis(N-pentylbenzenesulfonamide)* ***(3d)***

Light pink solid; Yield: 89%; m.p.: 227 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 2938 (CH_2 *str*), 1334 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.82 (4H, d, J = 10 Hz, ArH), 7.77–7.75 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (4H, d, J = 8.5 Hz), 6.69 (4H, d, J = 9 Hz), 3.53 (4H, t, J = 7.1 Hz, CH_2), 1.50 (4H, m, CH_2), 1.30–1.29 (8H, m, CH_2), 0.85 (6H, t, J = 7.1 Hz, CH_3); ^{13}C NMR (500 MHz; DMSO-d_6): 140.6 (2C), 133.4 (2C), 131.3 (2C), 129.7 (4C), 128.8 (2C), 127.3 (4C), 127.2 (4C), 120.7 (4C), 49.0 (2C), 28.5 (2C), 27.7 (2C), 22.0 (2C), 13.6 (2C). Anal. Calcd for $C_{34}H_{40}N_2O_4S_2$: C, 67.52; H, 6.67; N, 4.63; S, 10.60. Found: C, 67.61; H, 6.42; N, 4.92; S, 11.06.

4.3.5. *N,N′-(biphenyl-4,4′-diyl)bis(N-hexylbenzenesulfonamide)* ***(3e)***

Pink solid; Yield: 79%; m.p.: 251 °C. IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 2932 (CH_2 *str*), 1334 (S—O *str*); ^{1}H NMR (500 MHz, $CDCl_3$): 7.82 (4H, d, J = 10 Hz, ArH), 7.77–7.75 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (4H, d, J = 8.5 Hz), 6.69 (4H, d, J = 9 Hz), 3.5 (4H, t, J = 7.1 Hz, CH_2), 1.5 (4H, m, CH_2), 1.27–1.25 (12H, m, CH_2), 0.85 (6H, t, J = 7.1 Hz, CH_3); ^{13}C NMR (500 MHz; DMSOd_6): 140.6 (2C), 133.4 (2C), 131.3 (2C), 129.7 (4C), 128.8 (2C), 127.3 (4C), 127.2 (4C), 120.7 (4C), 40.0 (2C), 31.4 (2C), 29.5 (2C), 27.3 (2C), 24.1 (2C), 14.1 (2C). Anal. Calcd for $C_{36}H_{44}N_2O_4S_2$: C, 68.32; H, 7.01; N, 4.43; S, 10.13. Found: C, 68.44; H, 7.77; N, 4.38; S, 10.94.

*4.3.6. N,N′-(biphenyl-4,4′-diyl)bis(N-heptylbenzenesulfonamide) (**3f**)*

Light yellow solid; Yield: 82%; m.p.: 252 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 1333 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.82 (4H, d, *J* = 10 Hz, ArH), 7.77–7.75 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (4H, d, *J* = 8.5 Hz), 6.69 (4H, d, *J* = 9 Hz), 3.51 (4H, t, *J* = 7.1 Hz, CH_2), 1.59–1.57 (4H, m, CH_2), 1.29–1.27 (16H, m, CH_2), 0.88 (6H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR; (500 MHz; DMSO-d_6): 140.6 (2C), 133.3 (4C), 132.2 (2C), 130.9 (2C), 129.7 (4C), 127.2 (2C), 126.9 (4C), 120.7 (4C), 40.0 (2C), 39.8 (2C), 39.7 (2C), 39.5 (2C), 39.3 (2C), 39.1 (2C), 14.1 (2C). Anal. Calcd for $C_{38}H_{48}N_2O_4S_2$: C, 69.06; H, 7.32; N, 4.24; S, 9.70. Found: C, 69.76; H, 4.38; N, 4.20; S, 9.97.

*4.3.7. N,N′-(biphenyl-4,4′-diyl)bis(N-hexadecylbenzenesulfonamide) (**3g**)*

Light Brown solid; Yield: 80%; m.p.: 257 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 1350 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.82 (4H, d, *J* = 10 Hz, ArH), 7.77–7.75 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (4H, d, *J* = 8.5 Hz, ArH), 6.69 (4H, d, *J* = 9 Hz, ArH), 3.51 (4H, t, *J* = 7.1 Hz, CH_2), 1.59–1.57 (4H, m, CH_2), 1.29–1.27 (52H, br s, CH_2), 0.88 (6H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (500 MHz; DMSO-d_6): 140.6 (2C), 133.4 (2C), 131.3 (2C), 129.7 (4C), 128.8 (2C), 127.3 (4C), 127.2 (4C), 120.7 (4C), 47.8 (2C), 31.8 (2C), 29.6 (16C), 29.3 (4C), 27.7 (2C), 26.5 (2C), 23.7 (2C), 17.71 (2C), 14.0 (2C). Anal. Calcd for $C_{56}H_{84}N_2O_4S_2$: C, 73.64; H, 9.27; N, 3.07; S, 7.02. Found: C, 73.66; H, 9.77; N, 3.18; S, 7.28.

*4.3.8. N,N′-(biphenyl-4,4′-diyl)bis(N-benzylbenzenesulfonamide) (**3h**)*

Brown solid; Yield: 90%; m.p.: 262 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 2940 (CH_2 *str*), 1345 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.82 (4H, d, *J* = 10 Hz, ArH), 7.77–7.75 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (4H, d, *J* = 8.5 Hz), 6.69 (4H, d, *J* = 9 Hz) 7.33–7.23 (10H, m, ArH), 4.41 (4H, s, CH_2); ^{13}C NMR (500 MHz; DMSO d_6): 145.1 (2C), 140.5 (2C), 142.0 (2C), 139.6 (2C), 132.74 (2C), 129.3 (4C), 129.3 (4C), 128.7 (4C), 127.4 (4C), 126.3 (4C), 126.0 (2C), 124.7 (4C), 47.2 (2C). Anal. Calcd for $C_{38}H_{32}N_2O_4S_2$: C, 70.78; H, 5.00; N, 4.34; S, 9.95. Found: C, 70.54; H, 4.68; N, 4.43; S, 9.96.

*4.3.9. N,N′-(3,3′-dimethylbiphenyl-4,4′-diyl)bis(N-(phenylsulfonyl) acetamide) (**3i**)*

White solid; Yield: 82%; m.p.: 257 °C. IR (υ_{max}, KBr, cm^{-1}): 3028 (CH *str* Ar), 1330 (S—O *str*), 1713 (C═O); ^{1}H NMR (500 MHz, DMSO-d_6): 7.88 (4H, d, *J* = 10 Hz, ArH), 7.77 (2H, d *J* = 5 Hz, ArH), 7.73 (2H, d, *J* = 8.2 Hz, ArH) 7.72–7.70 (2H, m, ArH), 7.64–7.62 (4H, m, ArH), 7.53 (2H, d, *J* = 10 Hz, ArH), 2.49 (6H, s, Ar—CH_3), 1.9 (6H, s, CH_3); ^{13}C NMR (500 MHz; DMSO-d_6): 171.1 (2C), 140.6 (2C), 137.1 (2C), 134.5 (2C), 132.9 (4C), 129.3 (2C), 128.8 (4C), 126.7 (4C), 126.6 (2C), 124.4 (2C), 18.9 (2C), 17.7 (2C). Anal. Calcd for $C_{30}H_{28}N_2O_6S_2$: C, 62.48; H, 4.89; N, 4.86; S, 11.12. Found: C, 62.56; H, 4.75; N, 5.07; S, 11.41.

*4.3.10. N,N′-(3,3′-dimethylbiphenyl-4,4′-diyl)bis(N-isoprpylbenzenesulfonamide) (**3j**)*

White solid; Yield: 76%; m.p.: 234 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 2940 (CH_2 *str*), 1332 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.88 (4H, d, *J* = 10 Hz, ArH), 7.72–7.70 (2H, m, ArH), 7.62 7.60 (4H, m, ArH), 7.54 (2H, s, ArH), 7.38 (2H, d, *J* = 8.5 Hz, ArH), 6.33 (2H, d, *J* = 8.2 Hz, ArH), 2.97–2.95 (2H, m, CH), 1.57 (6H, s, Ar—CH_3), 1.25 (12H, d, *J* = 6.2 Hz, CH_3); ^{13}C NMR (500 MHz; DMSO-d_6): 140.6 (2C), 137.1 (2C), 134.5 (2C), 132.9 (4C), 129.3 (2C), 128.8 (4C), 126.7 (4C), 126.6 (2C), 124.4 (2C), 44.0 (2C), 20.9 (4C), 17.9 (2C). Anal. Calcd for: $C_{32}H_{36}N_2O_4S_2$ C, 66.64; H, 6.29; N, 4.86; S, 11.12. Found: C, 66.59; H, 6.17; N, 4.72; S, 12.0.

*4.3.11. N,N′-(3,3′-dimethylbiphenyl-4,4′-diyl)bis(N-butylbenzenesulfonamide) (**3k**)*

Light Brown solid; Yield: 85%; m.p.: 215 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 2940 (CH_2 *str*), 1333 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.88 (4H, d, *J* = 10 Hz, ArH), 7.72–7.70 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (2H, s, ArH), 7.38 (2H, d, *J* = 8.5 Hz, ArH), 6.33 (2H, d, *J* = 8.2 Hz, ArH), 3.16 (4H, t, *J* = 7.1 Hz, CH_2), 2.01 (6H, s, Ar—CH_3), 1.49 (4H, m, CH_2), 1.32 (4H, m, CH_2), 0.90 (6H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (500 MHz; DMSO-d_6): 140.6 (2C), 137.1 (2C), 134.5 (2C), 132.9 (4C), 129.3 (2C), 128.8 (4C), 126.7 (4C), 126.6 (2C), 124.4 (2C), 44.0 (2C), 25.7 (2C), 18.9 (2C), 17.7 (2C), 13.8 (2C). Anal. Calcd for $C_{33}H_{38}N_2O_4S_2$: C, 67.09; H, 6.48; N, 4.74; S, 10.85. Found: C, 67.05; H, 6.57; N, 4.98; S, 10.73.

*4.3.12. N,N′-(3,3′-dimethylbiphenyl-4,4′-diyl)bis(N-pentylbenzenesulfonamide) (**3l**)*

Light yellow solid; Yield: 84%; m.p.: 224 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 2940 (CH_2 *str*), 1335 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.88 (4H, d, *J* = 10 Hz, ArH), 7.72–7.70 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (2H, s, ArH), 7.38 (2H, d, *J* = 8.5 Hz, ArH), 6.33 (2H, d, *J* = 8.2 Hz, ArH), 3.16 (4H, t, *J* = 7.1 Hz, CH_2), 2.31 (6H, s, Ar—CH_3), 1.39–1.38 (4H, m, CH_2), 1.2–1.18 (8H, m, CH_2), 0.77 (6H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (500 MHz; DMSO-d_6): 140.6 (2C), 137.1 (2C), 134.5 (2C), 132.9 (4C), 129.3 (2C), 128.8 (4C), 126.7 (4C), 126.6 (2C), 124.4 (2C) 51.2 (2C), 28.2 (2C), 27.5 (2C), 21.7 (2C), 17.7 (2C), 14.0 (2C). Anal. Calcd for $C_{36}H_{44}N_2O_4S_2$: C, 68.32; H, 7.01; N, 4.43; S, 10.13. Found: C, 68.60; H, 7.67; N, 4.41; S, 9.91.

*4.3.13. N,N′-(3,3′-dimethylbiphenyl-4,4′-diyl)bis(N-hexylbenzenesulfonamide) (**3m**)*

Light Brown solid; Yield: 81%; m.p.: 205 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 2940 (CH_2 *str*), 1335 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.88 (4H, d, *J* = 10 Hz, ArH), 7.72–7.70 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (2H, s, ArH), 7.38 (2H, d, *J* = 8.5 Hz, ArH), 6.33 (2H, d, *J* = 8.2 Hz, ArH), 3.16 (4H, t, *J* = 7.1 Hz, CH_2), 2.01 (6H, s, Ar—CH_3), 1.48–1.46 (4H, m, CH_2), 1.23 (12H, br s, CH_2), 0.79 (6H, t, *J* = 7.1 Hz CH_3); ^{13}C NMR (500 MHz, DMSO-d_6): 140.6 (2C), 137.1 (2C), 134.5 (2C), 132.9 (4C), 129.3 (2C), 128.8 (4C), 126.7 (4C), 126.6 (2C), 124.4 (2C) 48.0 (2C), 32.3 (2C), 27.2 (2C), 22.0 (2C), 17.7 (2C), 14.0 (2C). Anal. Calcd for $C_{38}H_{48}N_2O_4S_2$: C, 69.06; H, 7.32; N, 4.24; S, 9.70. Found: C, 69.41; H, 7.79; N, 4.56; S, 9.78.

*4.3.14. N,N′-(3,3′-dimethylbiphenyl-4,4′-diyl)bis(N-heptyl-benzenesulfonamide) (**3n**)*

Yellow solid; Yield: 89%; m.p.: 240 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 2940 (CH_2 *str*), 1335 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.88 (4H, d, *J* = 10 Hz, ArH), 7.72–7.70 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (2H, s, ArH), 7.38 (2H, d, *J* = 8.5 Hz, ArH), 6.33 (2H,d, *J* = 8.2 Hz, ArH), 3.16 (4H, t, *J* = 7.1 Hz, CH_2), 2.03 (6H, s, Ar—CH_3), 1.49–1.47 (4H, m, CH_2), 1.31–1.29 (16H, br s, CH_2), 0.88 (6H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (500 MHz; DMSO-d_6): 140.6 (2C), 137.1 (2C), 134.5 (2C), 132.9 (4C), 129.3 (2C), 128.8 (4C), 126.7 (4C), 126.6 (2C), 124.4 (2C), 50.1 (2C), 32.8 (2C), 30.1 (2C), 28.0 (2C), 26.5 (2C), 23.7 (2C), 17.7 (2C), 14.0 (2C). Anal. Calcd for $C_{40}H_{52}N_2O_4S_2$: C, 69.73; H, 7.61; N, 4.07; S, 9.31. Found: C, 69.53; H, 7.82; N, 4.27; S, 9.39.

*4.3.15. N,N′-(3,3′-dimethylbiphenyl-4,4′-diyl)bis(N-hexadecylbenzenesulfonamide) (**3o**)*

White solid; Yield: 83%; m.p.: 250 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 2940 (CH_2 *str*), 1350 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.88 (4H, d, *J* = 10 Hz, ArH), 7.72–7.70 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (2H, s, ArH), 7.38 (2H, d, *J* = 8.5 Hz, ArH), 6.33 (2H, d, *J* = 8.2 Hz, ArH), 3.16 (4H, t, *J* = 7.1 Hz, CH_2),

2.01 (6H,s, Ar CH_3), 1.50–1.49 (4H, m, CH_2), 1.31–1.29 (48H, br s, CH_2), 0.84 (6H, t, J = 7.1 Hz, CH_3); ^{13}C NMR (500 MHz; DMSO-d_6): 140.6 (2C), 137.1 (2C), 134.5 (2C), 132.9 (4C), 129.3 (2C), 128.8 (4C), 126.7 (4C), 126.6 (2C), 124.4 (2C), 50.0 (2C), 31.8 (2C), 29.6 (16C), 29.3 (4C), 27.72 (2C), 26.5 (2C), 23.7 (2C), 17.7 (2C), 14.0 (2C). Anal. Calcd for $C_{58}H_{88}N_2O_4S_2$: C, 73.99; H, 9.42; N, 2.98; S, 6.81. Found: C, 73.69; H, 9.74; N, 3.10; S, 7.54.

4.3.16. *N,N′-(3,3′-dimethylbiphenyl-4,4′-diyl)bis(N-benzylbenzenesulfonamide)* ***(3p)***

Brown solid; Yield: 91%; m.p.: 232 °C; IR (υ_{max}, KBr, cm^{-1}): 3021 (CH *str* Ar), 2940 (CH_2 *str*), 1332 (S—O *str*); ^{1}H NMR (500 MHz, DMSO-d_6): 7.88 (4H, d, J = 10 Hz, ArH), 7.72–7.70 (2H, m, ArH), 7.62–7.60 (4H, m, ArH), 7.54 (2H, s, ArH), 7.49–7.24 (12H, m, ArH), 6.33 (2H, d, J = 8.2 Hz, ArH), 4.33 (4H, s, CH_2), 2.14 (6H, s, CH_3); ^{13}C NMR (500 MHz; DMSO-d_6): 145.1 (2C), 142.0 (2C), 140.5 (2C), 139.6 (2C), 132.74 (2C), 131.2 (C), 129.3 (4C), 128.7 (4C), 127.4 (4C), 126.3 (4C), 126.0 (4C), 122.7 (2C), 47.8 (2C), 17.7 (2C). Anal. Calcd for $C_{40}H_{36}N_2O_4S_2$: C, 71.40; H, 5.39; N, 4.16; S, 9.53. Found: C, 71.50; H, 4.98; N, 4.31; S, 9.85.

4.4. Acetylcholinesterase assay

The AChE inhibition activity was determined according to the Ellman's method [28] with slight modifications. Total volume of the reaction mixture was 100 μL. It contained 60 μL Na_2HPO_4 buffer with concentration of 50 mM and pH 7.7. Ten μL test compound (0.5 mM well^{-1}) was added, followed by the addition of 10 μL (0.005 unit well^{-1}) enzyme. The contents were mixed and pre-read at 405 nm. Then contents were pre-incubated for 10 min at 37 °C. The reaction was initiated by the addition of 10 μL of 0.5 mM well^{-1} substrate (acetylthiocholine iodide), followed by the addition of 10 μL DTNB (0.5 mM well^{-1}). After 30 min of incubation at 37 °C, absorbance was measured at 405 nm. Synergy HT (BioTek, USA) 96-well plate reader was used in all experiments. All experiments were carried out with their respective controls in triplicate. Eserine (0.5 mM well^{-1}) was used as a positive control. The percent inhibition was calculated by the help of following equation.

$$\text{Inhibition } (\%) = \frac{\text{Control} - \text{Test} \times 100}{\text{Control}}$$

IC_{50} values (concentration at which there is 50% enzyme inhibition) of compounds were calculated using EZ–Fit Enzyme kinetics software (Perella Scientific Inc. Amherst, USA).

4.5. Butyrylcholinesterase assay

The butyrylcholinesterase (BChE) inhibition activity was determined according to the Ellman's method [28] with minor modifications. Total volume of the reaction mixture was 100 μL containing 60 μL, Na_2HPO_4 buffer, 50 mM and pH 7.7. Ten μL test compound 0.5 mM well^{-1}, followed by the addition of 10 μL (0.5 unit well^{-1}) BChE. The contents were mixed and pre-read at 405 nm and then pre-incubated for 10 min at 37 °C. The reaction was initiated by the addition of 10 μL of 0.5 mM well^{-1} substrate (butyrylthiocholine bromide) followed by the addition of 10 μL DTNB, 0.5 mM well^{-1}. After 30 min of incubation at 37 °C, absorbance was measured at 405 nm. Synergy HT (BioTek, USA) 96-well plate reader was used in all experiments. All experiments were carried out with their respective controls in triplicate. Eserine (0.5 mM well^{-1}) was used as positive control. The percent inhibition and IC_{50} values were determined as mentioned above for AChE.

4.6. Molecular modeling

The docking studies were performed according to the previously described method [29]. The three-dimensional structures of compounds were built with Corina on-line tool (Molecular Networks). Protonation states were predicted at neutral pH by Marvin (Chemaxon). The atom and bond types were checked and Gasteiger–Marsili charges were assigned by Sybyl-X 1.1 (Tripos). Ligand structures were saved in the mol2 format. The structures of AChE from *Torpedo californica* (resolution 2.5 Å, PDB code: 1EVE) and butyrylcholinesterase from *Homo sapiens* (resolution 2.0 Å, PDB code: 1P0I) were downloaded from Protein Data Bank. All histidine residues were protonated at Nε atom (HSE tautomer); ligand and needless water molecules were removed. Missing hydrogens were added using Hermes 1.5 (CCDC). The binding site was defined as all amino acid residues within 10 Å from donepezil molecule in AChE complex and 20 Å from glycerol in BChE complex. Dockings were performed with Gold 5.1 software (CCDC) using genetic algorithm with default settings. Chem Score function and analysis of binding mode were applied to find final ligand poses. Results were visualized by PyMOL 0.99rc2 (DeLano Scientific LLC).

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