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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Microwave-assisted synthesis of new sulfonyl hydrazones, screening of biological activities and investigation of structure–activity relationship

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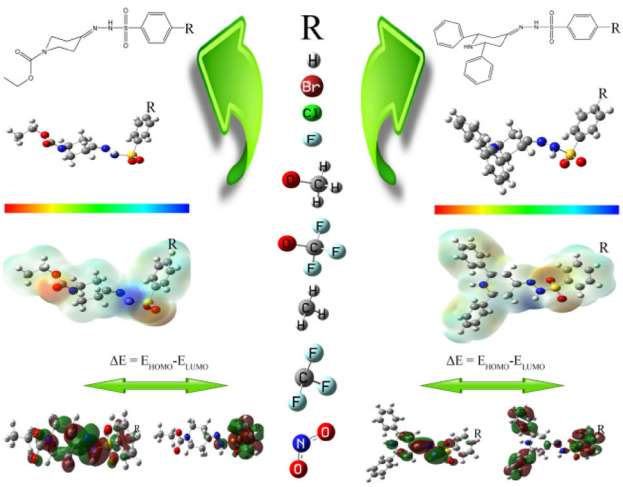
Abstract Sulfonyl hydrazone scaffold and the piperidine rings have important role in medicinal chemistry. This study shows the synthesis of two novel series of sulfonyl hydrazone having piperidine derivatives by condensing benzene sulfonyl hydrazides with ethyl 4-oxopiperidine-1-carboxylate and 2,6-diphenylpiperidin-4-one. Physical and chemical properties of compounds have been characterized and reported by utilizing their melting point, elemental analysis, IR, ^{1}H-NMR, ^{13}C NMR, 2D NMR and mass spectra results. Synthesized compounds were evaluated for antioxidant capacity and anticholinesterase activity. The antioxidant capacity of the compounds were screened through four complementary test, i.e., β-carotene–linoleic acid for lipid peroxidation, DPPH free radical (DPPH$^{\cdot}$), ABTS cation radical (ABTS$^{+\cdot}$) and CUPRAC assays. Assay results showed that *N*′-(2,6-diphenylpiperidin-4-ylidene)-4-bromobenzenesulfonohydrazide (**11**) has the highest lipid peroxidation inhibitory activity. Within the assay series, *N*′-(2,6-diphenylpiperidin-4-ylidene)-4-bromobenzenesulfonohydrazide (**11**) exhibited better activity than standard BHT in DPPH$^{\cdot}$ scavenging, while *N*′-(2,6-diphenylpiperidin-4-ylidene)benzenesulfonohydrazide (**10**) showed the best ABTS$^{+\cdot}$ scavenging assay. The CUPRAC assay revealed that ethyl 4-(2-(4-methoxyphenylsulfonyl)hydrazono)piperidine-1-carboxylate (**5**) indicated the best activity with $A_{0.50}$ value among the tested compounds than the antioxidant standard α-tocopherol. According to AChE assay, *N*′-(2,6-diphenylpiperidin-4-ylidene)-4-chlorobenzenesulfonohydrazide (**12**) had the best activity, while in BChE assay the highest activity was found for compound *N*′-(2,6-diphenylpiperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (**16**). Electronic and structural characteristics and density functional studies of the all newly synthesized compounds have been reported for better understanding in molecular-level. NMR, molecular electrostatic potential (MEP), $\Delta E_{\text{HOMO–LUMO}}$ band gap and the dipole moments of the molecules have been also analyzed and reported.

Graphical Abstract



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Introduction

Alzheimer disease (AD) has been known more than a century, but there is still no medical treatment to retard or stop this disease. In the "World Alzheimer Report 2013," it is reported that over 35 million people worldwide suffer from dementia including AD and this number is expected to be 70 million in 2030 (Prince *et al.*, 2013). Currently, acetylcholinesterase inhibitors (AChEIs) such as donepezil (Rao *et al.*, 2007), rivastigmine (Jann and Pharm, 2000) and galantamine (Michaelis, 2003) are used to decrease the effects of the disease (Fig. 1) and beneficiary effects of these drugs vary among patients. Therefore, new effective anti-Alzheimer's molecules are urgently needed.

The principal enzyme acetylcholinesterase (AChE) hydrolyzes acetylcholine to choline and acetate at cholinergic synapses. In the AD brain, the amount of acetylcholine is lower than the healthy brain as AChE is in excess. One of the main approaches to treat AD is to increase the concentration of acetylcholine. Accordingly, developing AChE inhibitors can be potential strategy in anti-Alzheimer's drug research. It has been shown that not only the inhibition of AChE but also the inhibition of butyrylcholinesterase (BChE) is necessary to restore the level of the acetylcholine and butyrylcholine to cure the disease. In addition, amyloid beta (Aβ) peptides, found in the brain of the Alzheimer's disease patients, are formed by the cleavage of the amyloid precursor protein by γ-secretase. Thus, inhibiting γ-secretase can be another approach in AD treatment. AChE, BChE and γ-secretase inhibitors which are derivatives of piperidine ring, ester and sulfonyl hydrazone groups were previously reported (Gundersen *et al.*, 2005; Viegas *et al.*, 2005; Josien *et al.*, 2007; Kwon *et al.*, 2007; Li *et al.*, 2007; Pissarnitski *et al.*, 2007; Girisha *et al.*, 2009; Prinz *et al.*, 2013).

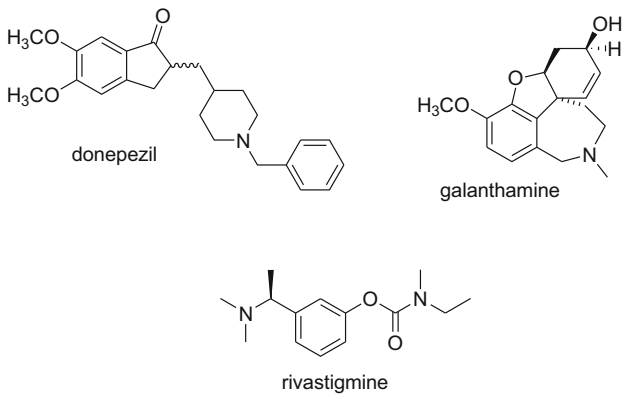

Fig. 1 Drugs as acetylcholinesterase inhibitors

Studies on the donepezil molecule and its applications prompted us to design series of compounds consisting of piperidine, sulfonyl and hydrazone groups. In addition to these groups, halogen, methyl, trifluoromethyl, methoxy, trifluoromethoxy and nitro-substituted phenyl groups were used in order to determine the effects of the substituents on activity. These types of molecules carrying piperidine ring and hydrazone also have been shown to exhibit significant antioxidant properties (Parthiban *et al.*, 2011; Bala *et al.*, 2012). The proper use of antioxidants can reduce AD progress, and accordingly, the neuronal degeneration can be minimized. Thus, in this work the *β*-carotene–linoleic acid for lipid peroxidation activity, DPPH free radical scavenging, ABTS cation radical scavenging and cupric reducing antioxidant capacity (CUPRAC) analysis of the synthesized compounds were also screened in addition to acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activities.

Theoretical studies on piperidine and sulfonyl hydrazone derivatives utilized B3LYP density functional method with 6-31G(d) basis set (Vayner and Ball, 2000; Alver *et al.*, 2007; Parlak, 2010; Shalaby *et al.*, 2014). In addition, GIAO/DFT (gauge-including atomic orbitals/density functional theory) approach is mostly used for the calculations of chemical shifts for a variety of heterocyclic compounds (Rauhut and Pulay, 1995). Studies related to electronic structure of the title compounds have not been previously reported and analyzed. In this study, investigation of molecular geometry optimization, ^{1}H and ^{13}C NMR chemical shifts, molecular electrostatic potential surface, frontier molecular orbital properties and dipole moment (μ) were determined with Gaussian 09 W software package (Frisch *et al.*, 2009).

Materials and methods

General

All chemicals used in the synthesis of the compounds and ethyl 4-oxo-piperidine-1-carboxylate were purchased from Sigma-Aldrich (St. Louis, MO, USA). The reactions and the purities of the compounds were monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254} aluminum sheets purchased from Merck (Darmstadt, Germany). Melting points were recorded by open capillaries on EzMelt melting point apparatus and were uncorrected. FTIR spectra were recorded on Perkin-Elmer Frontier spectrometer by attenuated total reflectance (ATR) apparatus (Waltham, Massachusetts, USA). C, H, N, S percent of the compounds were detected by Thermo Scientific

Flash 2000 (Finnegan MAT, USA) elemental analyzer. By direct injection in Ab-SciEx 3200 Q-Trap MSMS detector with electrospray ionization probe (Framingham, MA, USA), mass spectra were recorded. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker Avance −400 MHz spectrometer (Billerica, MA, USA) by using DMSO-d_6 or $CDCl_3$ as a solvent and TMS as an internal standard. The peaks of the DMSO-d_6 and $CDCl_3$ were observed at 2.5 and 7.2 ppm, respectively. The water peaks of the solvents were seen at 3.3 ppm with DMSO and 1.6 ppm with chloroform. The activity tests were done by using Molecular Devices Spectra Max PC340 microplate reader (Sunnyvale, CA, USA). The NMR spectra of the compounds **2–18** were given in the supporting information.

Synthesis of the compounds

Synthesis of 2,6-diphenylpiperidine-4-one

Acetone, benzaldehyde and ammonium acetate in 1:2:1 ratio in ethanol were reacted at room temperature using %30 L-proline as a catalyst according to the procedures presented in Baliah (1983) and Hemalatha *et al.* (2008).

Synthesis of 4-substituted phenylsulfonyl hydrazides

0.01 mol 4-substituted phenylsulfonyl chloride was added into 0.04 mol hydrazine monohydrate in dichloromethane dropwise, stirred at room temperature and monitored by TLC after dichloromethane was distilled off and the crude product was washed with water and hexane (Siemann *et al.*, 2002; Kummerle *et al.*, 2012).

*Synthesis of 4-substituted phenyl sulfonyl hydrazones (**2−18**)*

0.01 mol ketone, 0.01 mol 4-substituted phenylsulfonyl hydrazide and 30 mL ethanol were heated inside a microwave oven for 15 min at 400 W. After cooling to room temperature, the crude products were obtained by filtration and then dried. The crudes were purified by washing with diethyl ether or petroleum ether (Siemann *et al.*, 2002; Kummerle *et al.*, 2012).

*Ethyl 4-(2-(4-bromophenylsulfonyl)hydrazono)piperidine-1-carboxylate (**2**)* White powder (the compound was prepared by the reaction of 4-bromophenylsulfonyl hydrazide with ethyl 4-oxo-piperidine-1-carboxylate. It was obtained as white solid, yield 85 %); m.p. 176–178 °C; IR ν_{max} 3117 (N–H), 3090 (aromatic C–H), 2988, 2943, 2889, 2855 (aliphatic C–H), 1673 (C=O), 1643 (C=N), 1323 (asym S=O), 1171 (sym S=O), 1112 (C–Br) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.18 (3H, t, J = 6.8 Hz, H_G), 2.26 (2H, t, J = 5.6 Hz, H_E), 2.41 (2H, t, J_1 = 6.0 Hz, J_2 = 6.8 Hz, H_D), 4.05 (2H, q, J = 6.8 Hz, H_I), 8.01 (2H, d, J = 8.0 Hz, H_C), 8.06 (2H, d, J = 8.0 Hz, H_B), 10.63 (1H, s, H_A); ^{1}H-NMR ($CDCl_3$/TMS, 400 MHz): δ = 1.28 (3H, t, J_1 = 6.8 Hz, J_2 = 7.2 Hz, H_G), 2.37 (2H, t, J = 6.0 Hz, H_E), 2.43 (2H, t, J_1 = 6.0 Hz, J_2 = 6.4 Hz, H_D), 3.57–3.60 (4H, m, H_F), 4.16 (2H, q, J_1 = 6.8 Hz, J_2 = 7.2 Hz, H_I), 7.69 (2H, d, J = 6.8 Hz, H_C), 7.83 (2H, d, J = 6.8 Hz, H_B), 7.66 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 159.4 (C4), 155.0 (C7), 138.6 (C10), 132.6 (C12, C14), 130.0 (C11, C15), 127.2 (C13), 61.3 (C8), 43.6, 40.6 (C2, C6), 33.5, 28.1 (C3, C5), 15.0 (C9); MS *m/z* (%) 403.6 $[M-H]^-$ (9.33); 221.2 (100); 219.2 (1.16); 201.2 (1.08); 173.2 (2.93); 156.8 (19.97); 155.4 (1.47); 99.4 (3.55); 81.4 (58.06); 79.4 (4.93); 64.2 (1.23); Anal. calcd. for $C_{14}H_{18}BrN_3O_4S$: C, 41.59; H, 4.49; N, 10.39; S, 7.93 %. Found: C, 41.60; H, 4.49; N, 10.18; S, 7.45 %.

*Ethyl 4-(2-(4-chlorophenylsulfonyl)hydrazono)piperidine-1-carboxylate (**3**)* White powder (the compound was prepared by the reaction of 4-chlorophenylsulfonyl hydrazide with ethyl 4-oxo-piperidine-1-carboxylate. It was obtained as white solid, yield 80 %); m.p. 160–162 °C; IR ν_{max} 3113 (N–H), 3086, 3072 (aromatic C–H), 2989, 2972, 2885, 2836 (aliphatic C–H), 1645 (C=O, C=N), 1345 (asym S=O), 1170 (sym S=O), 1112 (C–Cl) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.18 (3H, t, J_1 = 6.8 Hz, J_2 = 7.2 Hz, H_G), 2.25 (2H, t, J = 6.0 Hz, H_E), 2.39 (2H, t, J = 6.0 Hz, H_D), 3.41–3.46 (4H, m, H_F), 4.04 (2H, q, J_1 = 6.8 Hz, J_2 = 7.2 Hz, H_I), 7.69 (2H, d, J = 8.8 Hz, H_C), 7.84 (2H, d, J = 8.4 Hz, H_B), 10.45 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 159.4 (C4), 155.0 (C7), 138.4 (C10), 138.3 (C13), 129.9 (C11, C15), 129.6 (C12, C14), 61.3 (C8), 43.6, 41.8 (C2, C6), 33.5, 28.1 (C3, C5), 15.0 (C9); MS *m/z* (%) 359.6 $[M-H]^-$ (14.16); 177.2 (100); 113.4 (43.36); 111.4 (6.34); 64.4 (2.07); 37.4 (3.10); Anal. calcd. for $C_{14}H_{18}ClN_3O_4S$: C, 46.73; H, 5.04; N, 11.68; S, 8.91 %. Found: C, 47.11; H, 5.06; N, 11.51; S, 8.53 %.

*Ethyl 4-(2-(4-fluorophenylsulfonyl)hydrazono)piperidine-1-carboxylate (**4**)* White powder (the compound was prepared by the reaction of 4-fluorophenylsulfonyl hydrazide with ethyl 4-oxo-piperidine-1-carboxylate. It was obtained as white solid, yield 87 %); m.p. 145–147 °C; IR ν_{max} 3187 (N–H), 3065, 3047 (aromatic C–H), 2976, 2326 (aliphatic C–H), 1658 (C=O, C=N), 1339 (asym S=O), 1295 (C–F), 1156 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.17 (3H, t, J_1 = 6.8 Hz, J_2 = 7.2 Hz, H_G), 2.25 (2H, t, J_1 = 5.6 Hz, J_2 = 6.0 Hz, H_E), 2.39 (2H, t, J = 6.0 Hz, H_D), 3.41–3.47 (4H, m, H_F), 4.04 (2H, q, J_1 = 6.8 Hz, J_2 = 7.2 Hz, H_I), 7.42–7.47 (2H, m, H_C), 7.89–7.93 (2H, m, H_B), 10,42 (1H, s, H_A); ^{13}C-

NMR (DMSO-d_6/TMS, 100 MHz): δ = 166.1, 163.6 (C13), 159.2 (C4), 155.0 (C7), 135.9, 135.9 (C10), 131.1, 130.9 (C11, C15), 116.8, 116.5 (C12, C14), 61.3 (C8), 43.7, 41.7 (C2, C6), 33.5, 28.1 (C3, C5), 15.0 (C9); MS *m/z* (%) 341.7 $[M-H]^-$ (11.97); 159.6 (100); 139.4 (2.16); 111.4 (3.01); 95.4 (68.65); 79.4 (1.03); 75.4 (1.08); 64.4 (7.15); Anal. calcd. for $C_{14}H_{18}FN_3O_4S$: C, 48.97; H, 5.28; N, 12.24; S, 9.34 %. Found: C, 48.55; H, 5.27; N, 12.09; S, 8.91 %.

*Ethyl 4-(2-(4-methoxyphenylsulfonyl)hydrazono)piperidine-1-carboxylate (**5**)* White powder (the compound was prepared by the reaction of 4-methoxyphenylsulfonyl hydrazide with ethyl 4-oxo-piperidine-1-carboxylate. It was obtained as white solid, yield 57 %); m.p. 132–134 °C; IR ν_{max} 3121 (N–H), 3098 (aromatic C–H), 2969, 2935, 2883, 2842 (aliphatic C–H), 1669 (C=O), 1643 (C=N), 1336 (asym S=O), 1162 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.18 (3H, t, J_1 = 6.8 Hz, J_2 = 7.2 Hz, H_G), 2.24 (2H, t, J = 6.0 Hz, H_E), 2.38 (2H, t, J_1 = 5.6 Hz, J_2 = 6.4 Hz, H_D), 3.41–3.46 (4H, m, H_F), 3.84 (3H, s, H_J), 4.04 (2H, q, J = 7.2 Hz, H_I), 7.11 (2H, d, J = 9.2 Hz, H_C), 7.77 (2H, d, J = 9.2 Hz, H_B), 10.21 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 162.2 (C4, C13), 155.1 (C7), 130.0 (C10, C11, C15), 113.9 (C12, C14), 61.3 (C8), 55.8 (C16), 44.0, 42.2, 40.6 (C2, C6), 34.1, 28.5 (C3, C5), 15.1 (C9); MS *m/z* (%) 353.7 $[M-H]^-$ (19.69); 171.4 (100); 108.4 (5.97); 107.4 (22.57); 92.4 (4.2); 64.4 (31.42); Anal. calcd. for $C_{15}H_{21}N_3O_5S$: C, 50.69; H, 5.96; N, 11.82; S, 9.02 %. Found: C, 50.17; H, 5.86; N, 11.46; S, 8.41 %.

*Ethyl 4-(2-(4-trifluoromethoxyphenylsulfonyl)hydrazono)-piperidine-1-carboxylate (**6**)* White powder (the compound was prepared by the reaction of 4-trifluoromethoxyphenylsulfonyl hydrazide with ethyl 4-oxo-piperidine-1-carboxylate. It was obtained as white solid, yield 75 %); m.p. 107–109 °C; IR ν_{max} 3239 (N–H), 3104 (aromatic C–H), 2986, 2965, 2878 (aliphatic C–H), 1698 (C=O), 1650 (C=N), 1344 (asym S=O), 1163 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.16 (3H, t, J_1 = 6.6 Hz, J_2 = 7.2 Hz, H_E), 2.24 (2H, t, J = 6.0 Hz, H_E), 2.38 (2H, t, J = 6.0 Hz, H_D), 3.41–3.44 (4H, m, H_F), 4.02 (2H, q, J_1 = 6.6 Hz, J_2 = 7.2 Hz, H_I), 7.58 (2H, d, J = 8.4 Hz, H_C), 7.95 (2H, d, J = 8.4 Hz, H_B), 10.46 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 159.7 (C4), 155.0 (C7), 151.6 (C13), 138.4 (C10), 130.6 (C11, C15), 128.1 (C12, C14), 120.7 (C16), 61.4 (C8), 43.6, 41.7 (C2, C6), 33.5, 28.1 (C3, C5), 15.0 (C9); MS *m/z* (%) 407.8 $[M-H]^-$ (12.06) 225.6 (73.35); 205.4 (1.63); 177.4 (2.05); 161.4 (24.92); 85.6 (100); 64.4 (1.20); Anal. calcd. for $C_{14}H_{18}BrN_3O_4S$: C, 44.01; H, 4.43; N, 10.26; S, 7.83 %. Found: C, 43.68; H, 4.88; N, 10.06; S, 7.63 %.

*Ethyl 4-(2-(4-methylphenylsulfonyl)hydrazono)piperidine-1-carboxylate (**7**)* (Imanishi *et al.*, 1982) White powder (the compound was prepared by the reaction of 4-methylphenylsulfonyl hydrazide with ethyl 4-oxo-piperidine-1-carboxylate. It was obtained as white solid, yield 76 %); m.p. 148–150 °C (lit 149–151 °C) (Imanishi *et al.*, 2006); IR ν_{max} 3259 (N–H), 3051 (aromatic C–H), 2986, 2954, 2924, 2869 (aliphatic C–H), 1694 (C=O), 1641 (C=N), 1329 (asym S=O), 1168 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.18 (3H, t, J_1 = 6.8 Hz, J_2 = 7.2 Hz, H_G), 2.24 (2H, t, J = 6.0 Hz, H_E), 2.37–2.40 (5H, m, $H_{D,\ J}$), 3.42–3.46 (4H, m, H_F), 4.04 (2H, q, J = 7.2 Hz, H_I), 7.39 (2H, d, J = 8.0 Hz, H_C), 7.73 (2H, d, J = 8.4 Hz, H_B), 10.28 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 158.5 (C4), 155.0 (C7), 143.6 (C10), 136.8 (C13), 129.8 (C11, C15), 128.0 (C12, C14), 61.3 (C8), 43.7, 40.6 (C2, C6), 33.5, 28.0 (C3, C5), 21.5 (C16), 15.0 (C9); MS *m/z* (%) 337.7 $[M-H]^-$ (7.78); 155.41 (100); 107.6 (5.26); 91.4 (12.82); 64.4 (43.36); Anal. calcd. for $C_{15}H_{21}N_3O_4S$: C, 53.08; H, 6.24; N, 12.38; S, 9.45 %. Found: C, 53.41; H, 6.27; N, 12.04; S, 9.32 %.

*Ethyl 4-(2-(4-trifluoromethylphenylsulfonyl)hydrazono)-piperidine-1-carboxylate (**8**)* Pale yellow powder (the compound was prepared by the reaction of 4-trifluoromethylphenylsulfonyl hydrazide with ethyl 4-oxo-piperidine-1-carboxylate. It was obtained as pale yellow solid, yield 50 %); m.p. 121–123 °C; IR ν_{max} 3155 (N–H), 2983 (aromatic C–H), 2930, 2867 (aliphatic C–H), 1669 (C=O), 1651 (C=N), 1320 (asym S=O), 1164 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.18 (3H, t, J = 7.2 Hz, H_G), 2.25 (2H, t, J_1 = 5. 6 Hz, J_2 = 6.4 Hz, H_E), 2.39 (2H, t, J = 6.0 Hz, H_D), 3.41–3.46 (4H, m, H_F), 4.04 (2H, q, J_1 = 6.8 Hz, J_2 = 7.2 Hz, H_I), 7.77 (2H, d, J = 8.8 Hz, H_C), 7.83 (2H, d, J = 8.8 Hz, H_B), 10.46 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 163.0 (C4), 155.0 (C7), 129.0 (C13), 126.8 (C10, C16), 125.4, 125.3 (C12, C14), 123.2 (C11, C15), 46.6, 40.6 (C2, C6), 15.0 (C9); MS *m/z* (%) 391.8 $[M-H]^-$ (15.00); 209.4 (100); 189.4 (5.47); 161.4 (32.85); 145.4 (93.29); 141.4 (1.00); 121.4 (1.54); 85.4 (1.16); 64.4 (1.54); Anal. calcd. for $C_{15}H_{18}F_3N_3O_4S$: C, 45.80; H, 4.61; N, 10.68; S, 8.15 %. Found: C, 45.02; H, 4.69; N, 10.34; S, 7.86 %.

*Ethyl 4-(2-(4-nitrophenylsulfonyl)hydrazono)piperidine-1-carboxylate (**9**)* Pale yellow powder (the compound was prepared by the reaction of 4-nitrophenylsulfonyl hydrazide with ethyl 4-oxo-piperidine-1-carboxylate. It was obtained as pale yellow solid, yield 97 %); m.p. 117–119 °C; IR ν_{max} 3117 (N–H), 3106, 3042 (aromatic C–H), 2985, 2910, 2874, 2834 (aliphatic C–H), 1652 (C=O, C=N), 1540, 1352 (NO_2), 1338 (asym S=O), 1162 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.17 (3H, t, J_1 = 6.8 Hz, J_2 = 7.2 Hz, H_G), 2.25 (2H,

t, $J_1 = 5.6$ Hz, $J_2 = 6.0$ Hz, H_E), 2.41 (2H, t, $J = 6.0$ Hz, H_D), 3.41–3.47 (4H, m, H_F), 4.03 (2H, q, $J_1 = 6.8$ Hz, $J_2 = 7.2$ Hz, H_I), 8.10 (2H, d, H_B), 8.42 (2H, d, H_C), 10.74 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 160.2 (C4), 155.0 (C7), 150.3 (C13), 144.8 (C10), 129.6 (C12, C14), 124.8 (C11, C15), 61.3 (C8), 43.6, 41.8 (C2, C6), 33.5, 28.2 (C3, C5), 15.0 (C9); MS *m/z* (%) 370.9 $[M + H]^+$ (25.00); 293.6 (100); 274.8 (5.00); 215.4 (7.5); 185.2 (7.5); 173.2 (5.00); 149.0 (6.25); 131.2 (6.25); 127.2 (5.0); 125.2 (5.00); 121.0 (5.00); 119.2 (6.25); 113.4 (15.0); 111.2 (7.5); 98.4 (11.25); 97.4 (8.75); 85.2 (7.5); 72.4 (61.25); 71.2 (11.25); 57.4 (27.5); 56.6 (10.00); Anal. calcd. for $C_{14}H_{18}N_4O_6S$: C, 45.40; H, 4.90; N, 15.13; S, 8.66 %. Found: C, 44.87; H, 5.04; N, 14.99; S, 8.27 %.

N'-(2,6-diphenylpiperidin-4-ylidene)benzenesulfonohydrazide ***(10)*** White powder (the compound was prepared by the reaction of phenylsulfonyl hydrazide with 2,6-diarylpiperidine-4-one. It was obtained as white solid, yield 52 %); m.p. 160–162 °C; IR ν_{max} 3290 (seconder amine N–H), 3194 (sulfonyl hydrazone N–H), 3086, 3060 (aromatic C-H), 2969, 2910, 2805, 2791 (aliphatic C–H), 1651 (C=N), 1340 (asym S=O), 1154 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.95 (1H, t, $J_1 = 12.0$ Hz, $J_2 = 14.0$ Hz, H_E), 2.23–2.35 (2H, m, $H_{D', E'}$), 2.76 (1H, s, H_G), 3.05 (1H, d, $J = 13.6$ Hz, H_D), 3.77 (2H, t, $J_1 = 11.6$ Hz, $J_2 = 12.0$ Hz, H_F), 7.23–7.28 (2H, m, $H_{K, K'}$), 7.30–7.38 (4H, m, $H_{I,I'}$), 7.45 (2H, d, $H_{J'}$), 7.50 (2H, d, H_C), 7.59–7.69 (2H, m, H_J), 7.87 (2H, d, H_B), 10.39 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 159.6 (C4), 144.4, 144.2 (C7, C7′), 139.7 (C13), 133.3 (C16), 129.5 (C14, C18), 127.9 (C15, C17), 128.7, 127.7, 127.6, 127.1, 127.1 (C8, C9, C10, C11, C12), 61.3, 60.0 (C2, C6), 43.3, 36.9 (C3, C5); MS *m/z* (%) 405.9 $[M + H]^+$ (12.51); 301.6 (9.78); 249.8 (7.69); 247.6 (7.58); 194.8 (20.5); 160.6 (8.93); 159.6 (11.84); 144.6 (4.74); 128.6 (5.19); 115.6 (8.18); 106.8 (100); 103.6 (5.94); 91.6 (8.81); 83.6 (7.46); 79.8 (33.64); 77.6 (13.07); 65.6 (2.39); Anal. calcd. for $C_{23}H_{23}N_3O_2S$: C, 68.12; H, 5.72; N, 10.36; S, 7.91 %. Found: C, 67.23; H, 5.33; N, 9.83; S, 7.63 %.

N′-(2,6-diphenylpiperidin-4-ylidene)-4-bromobenzenesulfonohydrazide ***(11)*** White powder (the compound was prepared by the reaction of 4-bromophenylsulfonyl hydrazide with 2,6-diarylpiperidine-4-one. It was obtained as white solid, yield 74 %); m.p. 162–164 °C; IR ν_{max} 3231 (sulfonyl hydrazone N–H), 3084, 3058 (aromatic C–H), 2841, 2822, 2804 (aliphatic C–H), 1321 (asym S=O), 1179 (sym S=O), 1106 (C–Br) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.97 (1H, t, $J_1 = 12$ Hz, $J_2 = 13.6$ Hz, H_E), 2.24–2.36 (2H, m, $H_{D', E'}$), 2.81 (1H, s, H_G), 3.03 (1H, d, $J = 13.6$ Hz, H_D), 3.75–3.82 (2H, m, H_F), 7.23–7.28 (2H, m, $H_{K, K'}$), 7.30–7.38 (4H, m, $H_{I,I'}$), 7.46 (2H, d, $J = 7.2$ Hz, $H_{J'}$), 7.51 (2H, d, $J = 7.2$ Hz, H_J), 7.80 (2H, d, $J = 8.8$ Hz, H_C), 7.84 (2H, d, $J = 8.8$ Hz, H_B), 10.46 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 160.2 (C4), 144.3 (C7, C7′), 138.9 (C13), 132.6 (C15, C17), 130.0 (C14, C18), 127.2 (C16), 128.7, 127.7, 127.6, 127.1, 127.1 (C8, C9, C10, C11, C12), 61.3, 60.0 (C2, C6), 43.2, 36.9 (C3, C5); MS *m/z* (%) 486.9 $[M + H]^+$ (6.74); 343.2 (10.11); 277.4 (6.74); 265.4 (33.71); 251.4 (8.99); 250.6 (5.62); 249.0 (7.86); 205.4 (14.61); 199.4 (16.85); 187.4 (87.64); 173.4 (39.33); 171.4 (15.73); 157.4 (37.08); 145.4 (26.97); 127.4 (100); 113.4 (67.42); 97.4 (60.67); 77.4 (3.37); Anal. calcd. for $C_{23}H_{22}BrN_3O_2S$: C, 57.03; H, 4.58; N, 8.67; S, 6.62 %. Found: C, 56.18; H, 4.37; N, 8.31; S, 6.06 %.

N′-(2,6-diphenylpiperidin-4-ylidene)-4-chlorobenzenesulfonohydrazide ***(12)*** White powder (the compound was prepared by the reaction of 4-chlorophenylsulfonyl hydrazide with 2,6-diarylpiperidine-4-one. It was obtained as white solid, yield 73 %); m.p. 158–160 °C; IR ν_{max} 3320 (seconder amine N–H), 3216 (sulfonyl hydrazone N–H), 3085, 3024 (aromatic C–H), 2974, 2918, 2836, 2792 (aliphatic C–H), 1645 (C=N), 1347 (asym S=O), 1165 (sym S=O), 1112 (C–Cl) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.96 (1H, t, $J_1 = 12$ Hz, $J_2 = 13.6$ Hz, H_E), 2.24–2.36 (2H, m, $H_{D', E'}$), 2.81 (1H, s, H_G), 3.03 (1H, d, $J = 13.6$ Hz, H_D), 3.78 (2H, t, $J = 12.8$ Hz, H_F), 7.23–7.28 (2H, m, $H_{K, K'}$), 7.30–7.38 (4H, m, $H_{I,I'}$), 7.46 (2H, d, $J = 7.6$ Hz, $H_{J'}$), 7.51 (2H, d, $J = 7.6$ Hz, H_J), 7.79 (2H, d, $J = 8.0$ Hz, H_C), 7.88 (2H, d, $J = 8.4$ Hz, H_B), 10.50 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 160.2 (C4), 144.3, 144.2 (C7, C7′), 138.4 (C13), 138.2 (C16), 129.9 (C14, C18), 129.7 (C15, C17), 128.7, 127.7, 127.6, 127.1, 127.1 (C8, C9, C10, C11, C12), 61.3, 60.0 (C2, C6), 43.2, 36.9 (C3, C5); MS *m/z* (%) 439.6 $[M-H]^-$ (8.00); 177.4 (100); 175.4 (10.60); 157.2 (2.60); 155.0 (1.00); 129.4 (4.20); 113.4 (46.00); 112.0 (3.00); 111.4 (13.6); 64.2 (2.6); 37.4 (1.80); Anal. calcd. for $C_{23}H_{22}ClN_3O_2S$: C, 62.79; H, 5.04; N, 9.55; S, 7.29 %. Found: C, 62.59; H, 5.00; N, 9.67; S, 6.98 %.

N′-(2,6-diphenylpiperidin-4-ylidene)-4-fluorobenzenesulfonohydrazide ***(13)*** Pale yellow powder (the compound was prepared by the reaction of 4-fluorophenylsulfonyl hydrazide with 2,6-diarylpiperidine-4-one. It was obtained as pale yellow solid, yield 63 %); m.p. 160–161 °C; IR ν_{max} 3212 (seconder amine N–H), 3103 (sulfonyl hydrazone N–H), 3073, 3044 (aromatic C–H), 2974, 2919, 2835, 2804 (aliphatic C–H), 1647 (C=N), 1333 (asym S=O), 1293 (aromatic C–F), 1154 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.96 (1H, t, $J_1 = 12.4$ Hz, $J_2 = 13.6$ Hz, H_E), 2.24–2.36 (2H, m, $H_{D', E'}$), 2.76 (1H, s, H_G), 3.03 (1H, d, $J = 13.6$ Hz, H_D), 3.77 (2H, t, $J_1 = 12.4$ Hz, $J_2 = 13.6$ Hz, H_F), 7.19–7.38 (6H, m, $H_{I,I',K,K'}$), 7.44–7.47 (4H, m, $H_{C, J'}$), 7.50 (2H, d,

$J = 7.2$ Hz, H_J), 7.92–7.95 (2H, m, H_B), 10.44 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 166.1, 163.6 (C16), 160.1 (C4), 144.3, 144.2 (C7, C7′), 135.9, 135.9 (C13), 131.1, 131.0 (C14, C18), 116.8, 116.6 (C15, C17), 128.7, 127.7, 127.6, 127.1, 127.1 (C8, C9, C10, C11, C12), 61.3, 60.0 (C2, C6), 43.2, 36.9 (C3, C5); MS *m/z* (%) 423.9 $[M + H]^+$ (9.97); 319.6 (5.72); 249.8 (5.81); 247.6 (7.60); 194.6 (11.31); 160.6 (5.14); 159.6 (6.66); 115.6 (7.29); 106.6 (100); 103.6 (6.21); 91.8 (7.02); 83.6 (5.28); 79.8 (37.06); 77.6 (7.73); 65.6 (1.70); 53.6 (1.30); Anal. calcd. for $C_{23}H_{22}FN_3O_2S$: C, 65.23; H, 5.24; N, 9.92; S, 7.57 %. Found: C, 64.93; H, 5.21; N, 9.99; S, 6.98 %.

*N′-(2,6-diphenylpiperidin-4-ylidene)-4-methoxybenzenesulfonohydrazide (**14**)* White powder (the compound was prepared by the reaction of 4-methoxyphenylsulfonyl hydrazide with 2,6-diarylpiperidine-4-one. It was obtained as white solid, yield 54 %); m.p. 146–148 °C; IR ν_{max} 3317 (seconder amine N–H), 3215 (sulfonyl hydrazone N–H), 3065, 3024 (aromatic C–H), 2971, 2843 (aliphatic C–H), 1641 (C=N), 1343 (asym S=O), 1157 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.96 (1H, t, $J_1 = 12.4$ Hz, $J_2 = 13.2$ Hz, H_E), 2.28–2.32 (2H, m, $H_{D', E'}$), 2.83 (1H, s, H_G), 3.03 (1H, d, $J = 13.2$ Hz, H_D), 3.75–3.80 (2H, m, $H_{F, F'}$), 3.84 (3H, s, H_L), 7.13 (2H, d, $J = 8.8$ Hz, H_C), 7.24–7.39 (6H, m, $H_{I,I',K,K'}$), 7.46 (2H, d, $J = 7.2$ Hz, $H_{J'}$), 7.51 (2H, d, $J = 7.6$ Hz, H_J), 7.80 (2H, d, $J = 8.8$ Hz, H_B), 10.30 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 162.9 (C16), 159.0 (C4), 144.1 (C7, C7′), 131.31, 130.3, 130.1 (C13, C14, C18), 128.7, 127.7, 127.7, 127.5, 127.2 (C8, C9, C10, C11, C12), 114.6 (C15, C17), 61.3, 60.0 (C2, C6), 56.1 (C19), 43.1, 36.6 (C3, C5); MS *m/z* (%) 436 $[M + H]^+$ (11.64); 331.6 (7.86); 247.6 (5.17); 194.6 (55.42); 171.4 (12.54); 167.6 (8.56); 160.6 (7.16); 159.6 (19.10); 152.4 (5.27); 128.4 (5.08); 123.4 (6.37); 116.6 (9.06); 115.6 (10.35); 106.6 (100); 103.6 (5.97); 92.6 (6.17); 91.6 (13.13); 83.6 (9.06); 79.6 (37.71); 77.6 (15.82); 64.4 (1.59); Anal. calcd. for $C_{14}H_{18}BrN_3O_4S$: C, 66.18; H, 5.79; N, 9.65; S, 7.36 %. Found: C, 65.63; H, 5.76; N, 9.59; S, 7.65 %.

*N′-(2,6-diphenylpiperidin-4-ylidene)-4-trifluoromethoxybenzenesulfonohydrazide (**15**)* White powder (the compound was prepared by the reaction of 4-trifluoromethoxyphenylsulfonyl hydrazide with 2,6-diarylpiperidine-4-one. It was obtained as white solid, yield 50 %); m.p. 108–110 °C; IR ν_{max} 3317 (seconder amine N–H), 3210 (sulfonyl hydrazone N–H), 3063, 3030 (aromatic C–H), 2969, 2899, 2834, 2814 (aliphatic C–H), 1636 (C=N), 1332 (asym S=O), 1156 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.97 (1H, t, $J = 12.8$ Hz, H_E), 2.25–2.37 (2H, m, $H_{D',E'}$), 2.82 (1H, s, H_G), 3.03 (1H, d, $J = 13.2$ Hz, H_D), 3.79 (2H, t, $H_{F,F'}$), 7.23–7.39 (6H, m, $H_{I,I',K,K'}$), 7.45 (2H, d, $J = 7.2$ Hz, $H_{J'}$), 7.51 (2H, d, $J = 7.2$ Hz, H_J), 7.62 (2H, d, $J = 8.4$ Hz, H_C), 7.99–8.02 (2H, m, H_B), 10.56 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 160.3 (C4), 151.6 (C16), 144.1 (C7, C7′), 138.5 (C13), 130.6 (C14, C18), 128.7, 127.7, 127.6, 127.1, 127.1 (C8, C9, C10, C11, C12, C19), 121.7 (C15, C17), 61.3, 60.0 (C2, C6), 40.6, 39.4 (C3, C5); MS *m/z* (%) 487.7 $[M-H]^-$ (9.23); 225.4 (84.93); 205.4 (1.58); 177.4 (2.07); 161.4 (24.66); 85.04 (100); Anal. calcd. for $C_{14}H_{18}BrN_3O_4S$: C, 58.89; H, 4.53; N, 8.58; S 6.55 %. Found: C, 58.93; H, 4.78; N, 8.54; S, 6.96 %.

*N′-(2,6-diphenylpiperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (**16**)* White powder (the compound was prepared by the reaction of 4-methylphenylsulfonyl hydrazide with 2,6-diarylpiperidine-4-one. It was obtained as white solid, yield 67 %); m.p. 145–147 °C; IR ν_{max} 3318 (seconder amine N–H), 3215 (sulfonyl hydrazone N–H), 3063, 3031 (aromatic C–H), 2973, 2957, 2836, 2816 (aliphatic C–H), 1644 (C=N), 1334 (asym S=O), 1155 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.95 (1H, t, $J_1 = 12$ Hz, $J_2 = 13.6$ Hz, H_E), 2.24–2.32 (2H, m, $H_{D', E'}$), 2.39 (3H, s, H_L), 3.05 (1H, d, $J = 13.6$ Hz, H_D), 3.75–3.82 (2H, m, H_F), 7.23–7.39 (6H, m, $H_{I, I', K, K'}$), 7.41 (2H, d, $J = 8.0$ Hz, H_C), 7.46 (2H, d, $J = 7.2$ Hz, $H_{J'}$), 7.51 (2H, d, $J = 7.2$ Hz, H_J), 7.76 (2H, d, $J = 8.0$ Hz, H_B), 10.37 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 159.2 (C4), 144.1, 144.0 (C7, C7′), 143.6 (C13), 136.8 (C16), 129.9 (C14, C18), 128.0 (C15, C17), 128.7, 127.7, 127.7, 127.2, 127.1 (C8, C9, C10, C11, C12), 61.3, 60.0 (C2, C6), 43.1, 36.7 (C3, C5), 21.5 (C19); MS *m/z* (%) 419.9 $[M + H]^+$ (12.27); 315.6 (8.94); 249.6 (5.61); 247.6 (5.76); 194.6 (45.61); 167.6 (5.91); 160.6 (13.18); 159.6 (19.09); 155.4 (1.36); 142.6 (5.30); 128.6 (5.00); 116.6 (8.49); 116.6 (9.55); 106.6 (100); 91.6 (17.58); 83.6 (11.82); 79.6 (36.67); 77.6 (11.50); 65.6 (8.33); Anal. calcd. for $C_{24}H_{25}N_3O_2S$: C, 68.71; H, 6.01; N, 10.02; S, 7.64 %. Found: C, 67.76; H, 6.01; N, 9.99; S, 7.24 %.

*N′-(2,6-diphenylpiperidin-4-ylidene)-4-trifluoromethylbenzenesulfonohydrazide (**17**)* White powder (the compound was prepared by the reaction of 4-trifluoromethylphenylsulfonyl hydrazide with 2,6-diarylpiperidine-4-one. It was obtained as white solid, yield 64 %); m.p. 137–138 °C; IR ν_{max} 3316 (seconder amine N–H), 3220 (sulfonyl hydrazone N–H), 3063, 3031 (aromatic C–H), 2968, 2899, 2813 (aliphatic C–H), 1640 (C=N), 1323 (asym S=O), 1160 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.98 (1H, t, $J = 12.8$ Hz, H_E), 2.25–2.36 (2H, m, $H_{D', E'}$), 2.84 (1H, s, H_G), 3.03 (1H, d, $J = 13.2$ Hz, H_D), 3.79 (2H, t, $J_1 = 9.6$ Hz, $J_2 = 11.2$ Hz, $H_{F, F'}$), 7.23–7.39 (6H, m, $H_{I, I', K, K'}$), 7.45 (2H, d, $J = 7.2$ Hz, $H_{J'}$), 7.51 (2H, d, $J = 7.2$ Hz, H_J), 8.02 (2H, d, $J = 8.4$ Hz, H_C), 8.09 (2H, d, $J = 8.4$ Hz, H_B), 10.7 (1H, s, H_A); ^{13}C-NMR

(DMSO-d_6/TMS, 100 MHz): δ = 160.6 (C4), 144.1, 143.4 (C7, C7′), 129.0 (C16), 128.7, 127.7, 127.6, 127.2, 127.1 (C8, C9, C10, C11, C12, C19), 126.8 (C13), 125.3 (C15, C17), 122.6 (C14, C18), 61.2, 60.0 (C2, C6), 43.1, 36.9 (C3, C5); MS *m/z* (%) 473.9 $[M + H]^+$ (6.76); 249.8 (7.41); 247.6 (7.53); 194.6 (6.61); 160.6 (3.95); 159.6 (5.18); 144.6 (5.13); 115.6 (6.88); 106.6 (100); 103.6 (5.03); 91.6 (6.73); 79.6 (31.38); 77.6 (6.61); Anal. calcd. for $C_{24}H_{22}FN_3O_2S$: C, 60.88; H, 4.68; N, 8.87; S, 6.77 %. Found: C, 60.37; H, 4.71; N, 8.70; S, 6.43 %.

N′-(2,6-diphenylpiperidin-4-ylidene)-4-nitrobenzenesulfonohydrazide (***18***) White powder (the compound was prepared by the reaction of 4-nitrophenylsulfonyl hydrazide with 2,6-diarylpiperidine-4-one. It was obtained as white solid, yield 61 %); m.p. 172–173 °C; IR ν_{max} 3322 (seconder amine N–H), 3223 (sulfonyl hydrazone N–H), 3108, 3085, 3028 (aromatic C–H), 2986, 2960, 2818 (aliphatic C–H), 1637 (C=N), 1530, 1348 (NO_2), 1341 (asym S=O), 1161 (sym S=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS, 400 MHz): δ = 1.99 (1H, t, J_1 = 12 Hz, J_2 = 13.6 Hz, H_E), 2.26–2.39 (2H, m, $H_{D',E'}$), 3.07 (1H, d, J = 13.6 Hz, H_D), 3.79 (2H, t, J_1 = 13.6 Hz, J_2 = 12.0 Hz, H_F), 7.23–7.39 (6H, m, $H_{I,\ I',\ K',\ K'}$), 7.45 (2H, d, J = 7.6 Hz, $H_{J'}$), 7.51 (2H, d, J = 7.6 Hz, H_J), 8.13 (2H, d, J = 8.8 Hz, H_B), 8.43 (2H, d, J = 8.8 Hz, H_C), 9.42 (1H, s, H_A); ^{13}C-NMR (DMSO-d_6/TMS, 100 MHz): δ = 160.5 (C4), 150.3 (C16), 145.0 (C13), 144.0 (C7, C7′), 129.6 (C15, C17), 128.8, 127.7, 127.7, 127.2, 127.1 (C8, C9, C10, C11, C12), 124.8 (C14, C18), 61.3, 60.0 (C2, C6), 43.1, 36.8 (C3, C5); MS *m/z* (%) 450.9 $[M + H]^+$ (8.35); 295.8 (6.94); 249.8 (6.50); 247.6 (10.57); 144.6 (5.67); 128.6 (5.05); 115.6 (6.35); 106.6 (100); 91.6 (6.06); 79.8 (29.34); 77.6 (7.15); 65.4 (1.16); Anal. calcd. for $C_{23}H_{22}N_4O_4S$: C, 61.32; H, 4.92; N, 12.44; S, 7.12 %. Found: C, 60.83; H, 4.63; N, 12.01; S, 6.81 %.

Biological studies

β-Carotene–linoleic acid assay

The total antioxidant activity was evaluated using the β-carotene–linoleic acid model test system (Marco, 1968; Öztürk *et al.*, 2011). Solutions of synthesized compounds were prepared at concentrations of 400, 200, 100, 50, 25, 12.5 and 6.25 μM. DMSO was used as a control, while BHT and α-tocopherol were used as reference standards. The results were given as 50 % concentration (IC_{50}). IC_{50} was determined from the graph of antioxidant activity percentage against sample concentration.

DPPH free radical scavenging assay

The free radical scavenging activity was determined spectrophotometrically by the DPPH assay (Öztürk *et al.*, 2007; Blois, 1958). Solutions of synthesized compounds were prepared at concentrations of 400, 200, 100, 50, 25, 12.5 and 6.25 μM. DMSO was used as a control, while BHT and α-tocopherol were used as reference standards. The results were given as 50 % concentration (IC_{50}).

ABTS cation radical scavenging assay

The spectrophotometric analysis of $ABTS^{+\cdot}$ scavenging activity was determined according to the previously described method (Re *et al.*, 1999) with slight modifications (Öztürk *et al.*, 2007). Solutions of synthesized compounds were prepared at concentrations of 400, 200, 100, 50, 25, 12.5 and 6.25 μM. The $ABTS^{+\cdot}$ was produced by the reaction between 7 mM ABTS in water and 2.45 mM potassium persulfate, stored in the dark at room temperature for 12 h. Before usage, the $ABTS^{+\cdot}$ solution was diluted to get an absorbance of 0.703, 0.025 at 734 nm with DMSO. DMSO was used as a control, while BHT and α-tocopherol were used as reference standards. The results were given as 50 % inhibition concentration (IC_{50}). The sample concentration providing 50 % $ABTS^{+\cdot}$ scavenging effect (IC_{50}) was calculated from the graph of $ABTS^{+\cdot}$ scavenging effect percentage against sample concentration.

Cupric reducing antioxidant capacity (CUPRAC)

The cupric reducing antioxidant capacity was determined according to the previous method (Apak *et al.*, 2004; Öztürk *et al.*, 2007). Solutions of synthesized compounds were prepared at concentrations of 400, 200, 100, 50, 25, 12.5 and 6.25 μM. Results were given as absorbance compared with the absorbances of BHT and α-tocopherol used as antioxidant standards.

Determination of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activity

AChE and BChE inhibitory activities were measured by the spectrophotometric method. AChE from electric eel and BChE from horse serum were used, while acetylthiocholine iodide and butyrylthiocholine chloride were employed as substrates. DTNB (5,50-dithiobis(2-nitrobenzoic)acid was used for the measurement of the anticholinesterase activity (Ellman *et al.*, 1961; Tel *et al.*, 2013).

Calculations

The geometry optimization of the compounds (**1–18**) was carried out by using DFT/cam-B3LYP/6-31G(d)(6D, 7F) level; in addition, ultrafine and tight convergence criteria (Lee *et al.*, 1988; Becke, 1993) were performed. Calculation of chemical shift was performed gauge-independent atomic orbital (GIAO) method, one of the most common approaches for calculating nuclear magnetic shielding tensor (Ditchfield, 1974). These calculations have been carried out by using b3lyp/6-311++G (2*d*, 2*p*) level in the DMSO solvent. Selected descriptors such as ionization potential ($I = -E_{\mathrm{HOMO}}$), electron affinity ($A = -E_{\mathrm{LUMO}}$), global hardness ($\eta = I - A/2$), electronegativity ($\chi = I + A/2$) chemical potential ($\mu = -\chi$), softness ($S = 1/\eta$) and global electrophilicity index ($\omega = \mu^2/2\eta$) were calculated with DFT/cam-b3lyp/6–31g(d) level from HOMO and LUMO energies (Koopmans, 1934). In order to understand and predict the reactive characteristic of numerous of chemical systems, the map of molecular electrostatic potential (MEP) surface was also visualized reactive sites of the molecules in both electrophilic and nucleophilic reactions (Truhlar, 1981). Molecular electrostatic potential $V(r)$ is defined by;

$$V(r) = \sum_A \frac{Z_A}{(R_A - r)} - \int \frac{\rho(r')}{(r' - r)} d(r')$$

Z_A is the charge of nucleus A, located R_A, and $\rho(r')$ is the electronic density function for the molecule (Truhlar, 1981; Politzer *et al.*, 1985). In the map of total electron density, surface with the electrostatic potential is defined by the negative and positive charge contribution. Different values of the electrostatic potential are demonstrated the range values of different color scales to figure out the negative (red) and the positive (blue) potential region. Potential increase red < orange < yellow < green < cyan < blue, respectively. Hence, while blue is showing the positive region, red side shows negative region of the surface and green appears over zero. To observe electrophilic or nucleophilic region of the molecule, map of molecular electrostatic potential for the ground state geometry has been obtained at cam-b3lyp/6-31G(d) level.

Results and discussion

Chemistry

In this study, we synthesized seventeen sulfonyl hydrazones bearing piperidine ring and evaluated their anticholinesterase and antioxidant activities. The general schematic representation describing the synthesis of target compounds is shown in Fig. 2. Previously, 2,6-diaryl piperidine 4-one was shown to be obtained with 20 % yield

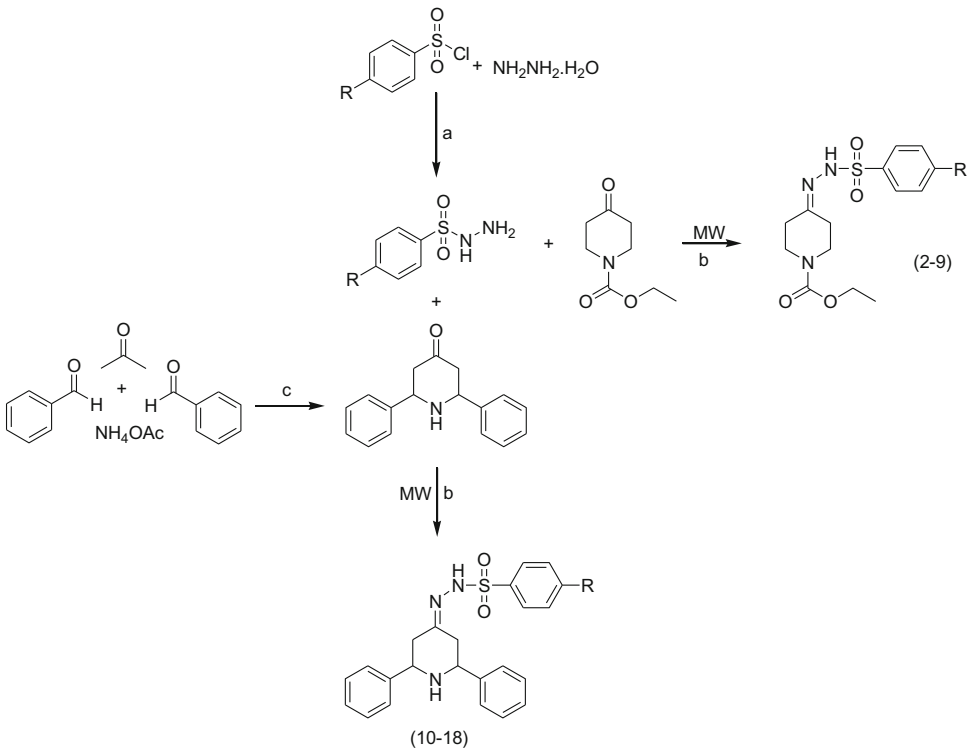

Fig. 2 Synthetic pathway of 4-substituted phenylsulfonyl hydrazones (**2–18**). Reagents and conditions: **a** DCM, rt.; **b** EtOH, reflux; and **c** EtOH, *L*-proline, rt

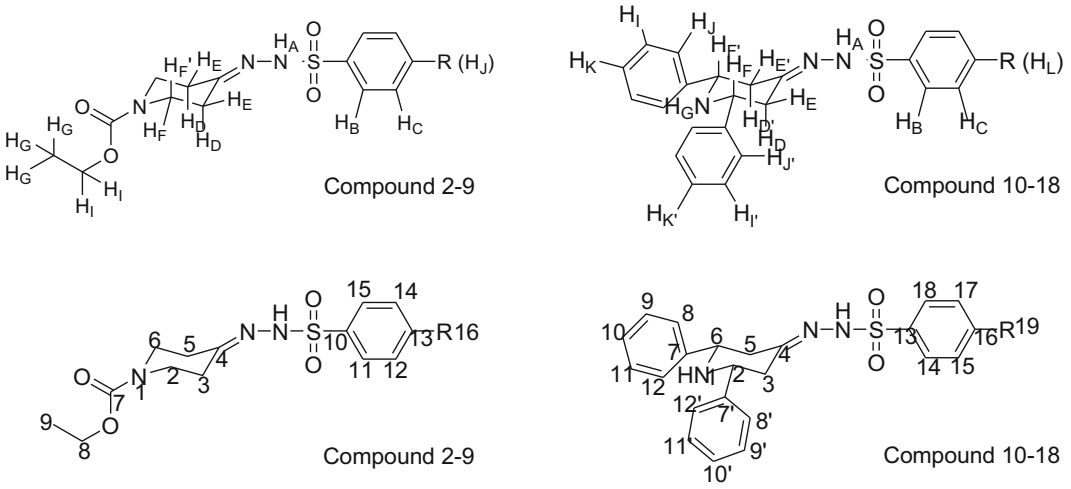

Fig. 3 Compound labeling for ^{1}H NMR and ^{13}C NMR

by the condensation of benzaldehyde, acetone and ammonium acetate in the ratio of 2:1:1 (Baliah, 1983; Hemalatha *et al.*, 2008). Several initial quantities, reaction times and temperatures were tested to increase the yield. When the reaction time and temperature were increased, the yield decreased due to the polymerization of intermediate imines (Vatsadze *et al.*, 2000); therefore, the reaction time and temperature should not exceed 30 min and 60 °C, respectively. It has been shown that the use of ketones in stoichiometric ratio can improve the yield. In such cases, the reaction requires 4 times more mole of acetone to obtain 35 % yield. After literature survey, we decided that L-proline could be useful catalyst as it was used for similar reactions (Aznar *et al.*, 2006). We performed some tests using 30 % L-proline as catalyst and improved the yield by 65 % (Supporting information—Table 1).

The sulfonyl hydrazides were obtained according to the previously reported procedures (Siemann *et al.*, 2002; Kummerle *et al.*, 2012) and then condensed with ethyl 4-oxo-piperidine-1-carboxylate and 2,6-diarylpiperidine-4-one. To determine the appropriate method for synthesizing the sulfonyl hydrazones, the conventional method was compared with the *MW*-assisted method. When 4-chlorosulfonyl hydrazide was condensed with ethyl 4-oxopiperidine-1-carboxylate, using the conventional method only the 35 % yield was reached, but with the *MW*-assisted method 80 % yield was obtained. Similarly, the yield was increased from 37 to 82 % by using the *MW* method for the condensation of same hydrazide with 2,6-diarylpiperidine-4-one. It was decided to use *MW* in the synthesis of all derivatives after getting similar results for other substituents. The compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis.

In the IR spectra, the C=N stretching vibration bands were observed at 1640 and 1651 cm^{-1}; N–H stretching vibrations of sulfonyl hydrazones were observed at 3103–3259 cm^{-1}; C=O stretching vibration bands at 1640–1698 cm^{-1}; asymmetric S=O stretching vibrations at 1320–1347 cm^{-1}; and symmetric S=O stretching vibrations at 1155–1179 cm^{-1}.

Piperidine molecules generally prefer chair conformation (Jayabharathi *et al.*, 2007; Aridoss *et al.*, 2009). In order to elicit the exact conformation, compounds **4** and **13** were chosen as a prototype and the spectra of other compounds were interpreted according to theirs. For that purpose COSY, HETCOR, NOESY and ROESY spectra were acquired in addition to ^{1}H and ^{13}C NMR spectra. All discussions were carried out according to the labeling of the compounds in Fig. 3.

In the ^{1}H NMR spectra, H_A protons of the compounds **4** and **13** had a chemical shift of 10.42 and 10.44 ppm, respectively, as a singlet. NOESY and ROESY spectra indicated far interactions between protons. In the NOESY spectrum of compound **13** (Fig. 4), there is two far interactions of H_A, that is, with H_G and H_D, but H_G interaction is smaller. According to the COSY spectrum (Fig. 5), $H_{D'}$ and $H_{E'}$ interacted with each other, where only the $H_{E'}$ was affected by $H_{F'}$, so the multiplet at 2.24–2.36 ppm was attributed to the $H_{D'}$ and $H_{E'}$ together. H_E proton split into triplet at 1.95 ppm by the H_D and H_F protons. H_D resonated as doublet at 3.01 ppm affected by only the H_E proton. $H_{F,F'}$ split into triplet at 3.76 ppm by H_E and $H_{E'}$. Because of the conformation of the molecule, H_J and $H_{J'}$ were not identical; the H_J shifted to the downfield where the $H_{J'}$ and H_C resonated together. The chemical shift of the aromatic field protons aligned as following $H_B > H_J > H_{J'+C} > H_{I+I'+K+K'}$ to the diamagnetic area (Muhlhausen *et al.*, 2010). The COSY spectrum results were supported by the HETCOR spectrum (Fig. 5) that H_D and H_E belonged to C3 and $H_{D'}$ and $H_{E'}$ belonged to C5. Compound **4** had more far

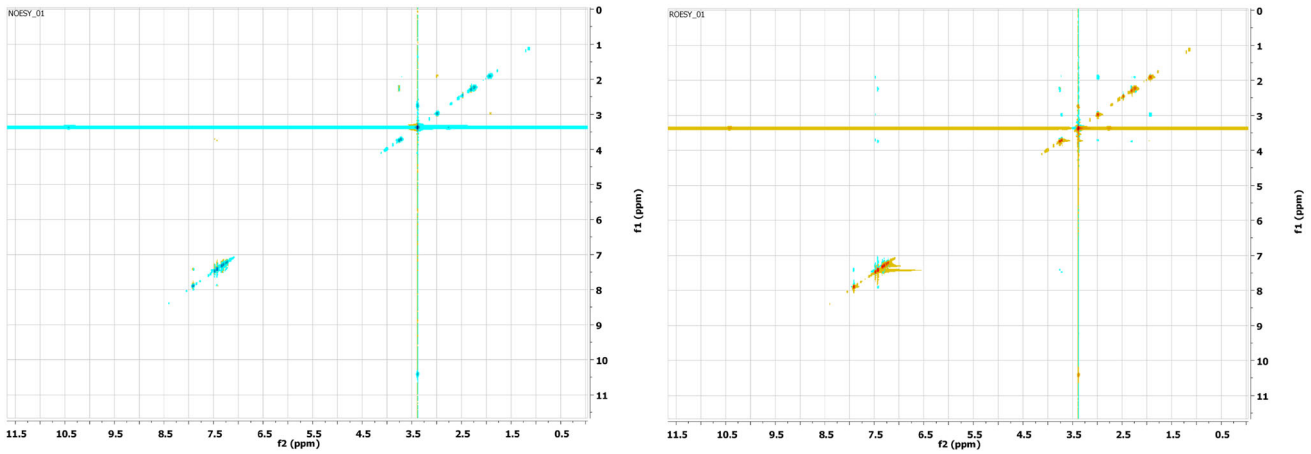

Fig. 4 NOESY and ROESY spectrum of compound **13**

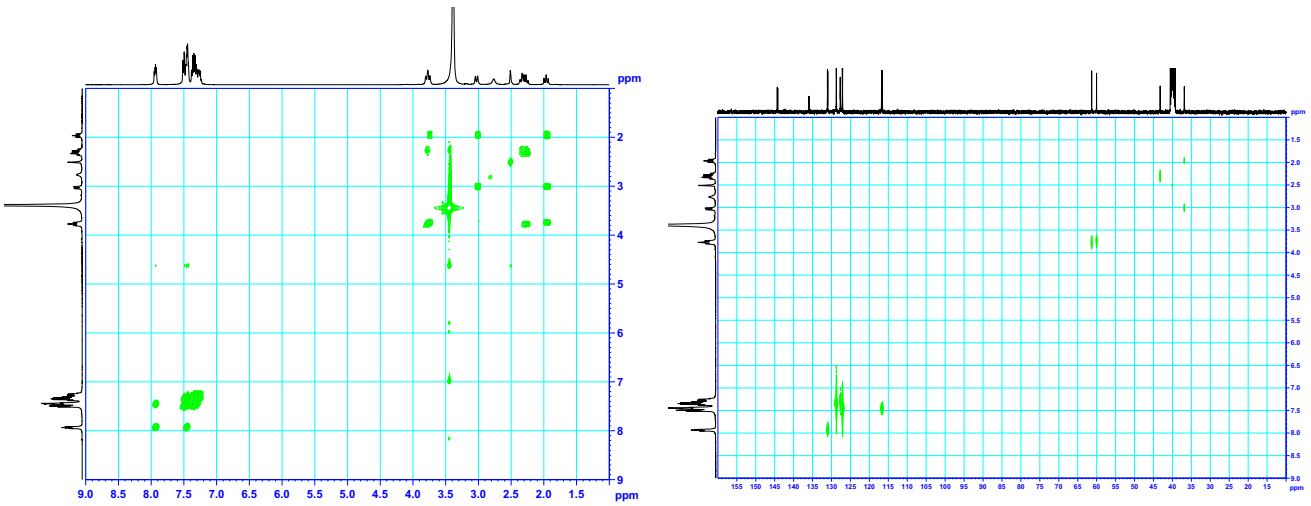

Fig. 5 COSY and HETCOR spectrum of compound **13**

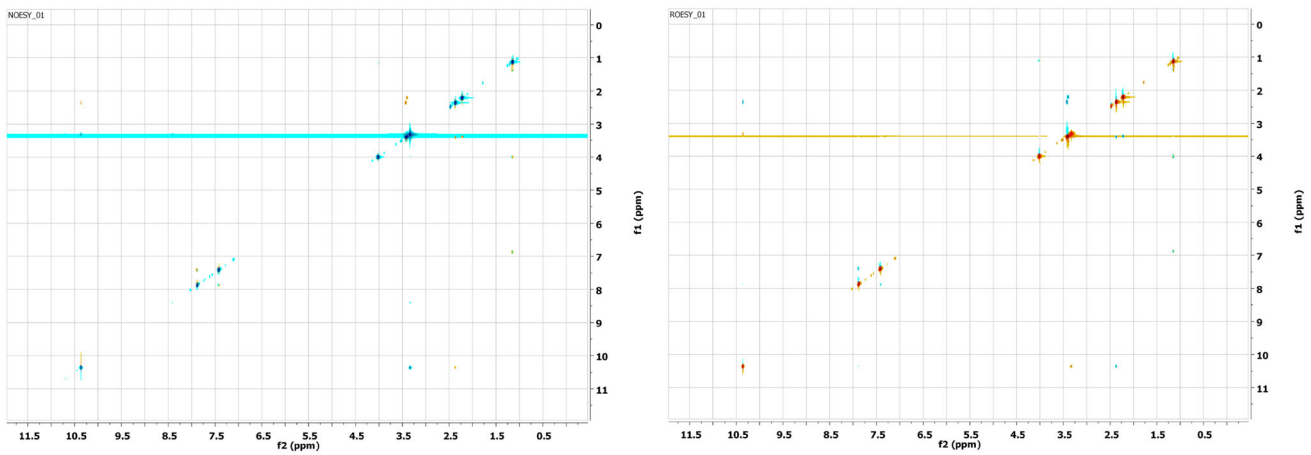

Fig. 6 NOESY and ROESY spectrum of compound **4**

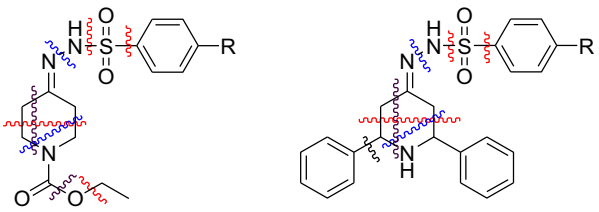

Fig. 7 Mass fragmentation pattern of the compounds

interactions than compound **13** according to the NOESY and ROESY spectra (Fig. 6) that H_A was coupled with H_D, where H_C correlates with the protons H_I, H_D, H_E, H_F and H_G. The H_I split into quartet at 4.04 ppm by H_G protons; quartet at 3.44 ppm was the correlation peaks between H_F and H_{D+E}. The H_D and H_E gave triplet by the interaction between each other and H_F at 2.39 and 2.25 ppm, respectively. Finally, H_G gives triplets at 1.18 ppm. In the aromatic field of these compounds, H_B and H_C were expected to resonate as doublets, but by the effect of the fluorine atom at *para* position, protons split again and gave multiplets.

^{13}C NMR spectra were analyzed, and C4 carbons were observed at 159.2–163.0 ppm. In the spectra of compounds **2–9**, the peak of 155.0 ppm was attributed to the C7. Analyzing the HETCOR spectrum, C7 and C7′ of compounds **10–18** were observed at 143.4–144.4 ppm. The other aromatic carbons of benzene rings attached to the piperidine ring were observed between 127.0 and 128.7 ppm. In the aliphatic range of compounds **2–9**, at 40.6–44.0 ppm C2 and C6 and at 28.0–33.5 ppm C3 and C5 were observed as two separate peaks. The peaks at 61.3–61.4 ppm were attributed to C8 and at 15.0–15.1 ppm to C9. In the aliphatic range of compounds **10–18**, at 60.0–61.3 ppm C2 and C6 and at 36.6–43.2 ppm C3 and C5 were detected as two separate peaks. Because of the high electronegativity of fluorine atoms, carbon of trifluoromethoxy appeared at 120.7 ppm (compound **6**) and 119.0 ppm (compound **15**) where the carbon of methoxy was observed at 55.8 ppm (compound **5**) and 56.1 ppm (compound **14**). Similarly, carbon of methyl group was observed at 21.5 ppm (compound **7**) and 21.49 ppm (compound **16**). As compounds **2–9** were considered, sulfonyl group withdraw the electrons so the peak of the C10 shifted to the downfield. According to the substituent, occasionally the peak of ipso carbon C13 shifted more than the ipso carbon C10 to the downfield. In the case of fluorine, methoxy and trifluoromethoxy groups attached to the benzene ring at para position, by the inductive effect of oxygen and fluorine atoms C13 resonated at 151.5–166.0 ppm, but by the resonance effect of these atoms C12 and C14 were shifted to the upfield. In this study, all C11 and C15 resonated at 129.9–131.0 ppm,

Table 1 Antioxidant activity results of compounds (**2–18**), BHT and α-tocopherol by the β-carotene/linoleic acid, $DPPH^{\cdot}$, $ABTS^{+\cdot}$ and CUPRAC assay

Compounds	R	β-carotene/linoleic acid assay IC_{50} (μM)[a]	$DPPH^{\cdot}$ assay IC_{50} (μM)[a]	$ABTS^{+\cdot}$ assay IC_{50} (μM)[a]	CUPRAC $A_{0.50}$ (μM)[a]
2	Br	–	75.76 ± 0.34	104.37 ± 0.97	36.01 ± 0.03
3	Cl	–	57.88 ± 0.81	55.31 ± 1.17	30.93 ± 0.03
4	F	–	57.20 ± 0.37	93.66 ± 1.72	23.49 ± 0.01
5	OCH_3	62.71 ± 0.70	52.23 ± 0.39	55.19 ± 1.90	17.72 ± 0.03
6	OCF_3	85.62 ± 1.80	63.92 ± 0.44	70.40 ± 2.46	83.11 ± 0.02
7	CH_3	–	78.99 ± 0.33	59.41 ± 1.42	19.95 ± 0.05
8	CF_3	89.55 ± 0.57	69.30 ± 1.60	71.59 ± 1.22	87.82 ± 0.01
9	**NO_2**	79.10 ± 0.70	35.17 ± 0.30	36.88 ± 0.61	34.63 ± 0.02
10	H	–	73.56 ± 0.65	7.26 ± 0.47	29.95 ± 0.02
11	**Br**	51.52 ± 0.91	30.56 ± 0.03	24.64 ± 1.18	41.93 ± 0.02
12	**Cl**	–	92.00 ± 0.49	11.06 ± 0.86	22.46 ± 0.01
13	**F**	–	38.38 ± 0.88	39.86 ± 0.79	30.11 ± 0.01
14	**OCH_3**	94.60 ± 0.12	70.19 ± 0.61	75.40 ± 2.58	52.41 ± 0.01
15	**OCF_3**	–	34.99 ± 0.61	45.66 ± 1.10	37.12 ± 0.01
16	**CH_3**	–	37.56 ± 0.39	35.23 ± 1.84	17.89 ± 0.03
17	**CF_3**	–	31.35 ± 1.07	40.92 ± 1.24	44.82 ± 0.02
18	**NO_2**	93.81 ± 1.15	52.45 ± 0.33	10.91 ± 0.68	57.42 ± 0.05
BHT[b]		2.34 ± 0.09	54.97 ± 0.99	2.91 ± 0.55	3.80 ± 0.02
α-Tocopherol[b]		4.50 ± 0.09	12.26 ± 0.07	4.87 ± 0.45	40.48 ± 1.87

[a] Values expressed are mean ± SEM of three parallel measurements. $p < 0.05$, significantly different with student's t test

[b] Reference compounds

Table 2 Acetyl- and butyrylcholinesterase inhibitory activities of compounds (**2–18**)

Compounds	Anticholinesterase assay		Compounds	Anticholinesterase assay	
	AChE assay IC_{50} (μM)[a]	BChE assay IC_{50} (μM)[a]		AChE assay IC_{50} (μM)[a]	BChE assay IC_{50} (μM)[a]
2	104.44 ± 0.56	94.03 ± 0.64	**11**	108.24 ± 0.38	120.72 ± 0.57
3	119.23 ± 0.34	89.05 ± 1.09	**12**	80.32 ± 0.69	112.15 ± 0.44
4	137.43 ± 0.36	99.31 ± 1.06	**13**	91.72 ± 0.42	83.94 ± 0.98
5	109.39 ± 0.8	136.38 ± 0.97	**14**	97.79 ± 0.05	83.42 ± 0.97
6	130.82 ± 0.36	116.42 ± 1.62	**15**	102.02 ± 0.36	82.85 ± 0.59
7	119.69 ± 1.52	119.06 ± 0.84	**16**	96.93 ± 0.16	76.39 ± 0.74
8	134.52 ± 0.09	112.14 ± 0.60	**17**	125.83 ± 0.05	93.52 ± 1.32
9	101.53 ± 0.58	80.63 ± 1.67	**18**	142.46 ± 0.17	124.68 ± 1.20
10	139.89 ± 0.58	90.75 ± 1.06	**Galantamine**[b]	4.48 ± 0.78	46.03 ± 0.14

[a] Values expressed are mean ± SEM of three parallel measurements. $p < 0.05$, significantly different with student's t test

[b] Reference compound

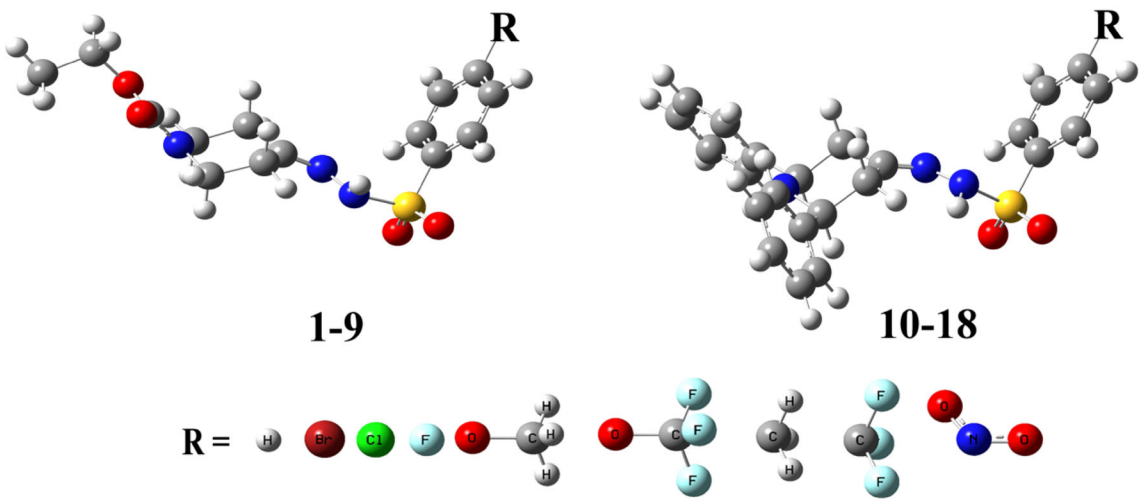

Fig. 8 Geometry-optimized molecular structures of the compounds **1–18** with the **R** substitutions

except the nitro and trifluoromethyl groups, which were most electron-withdrawing groups (DeBergh *et al.*, 2013; Backes *et al.*, 2014; Madabhushi *et al.*, 2014).

It was also confirmed by the presence of molecular ion peaks for the sulfonyl hydrazones in the mass spectra, the cleavage of N–N bond and the R group at *para* position of benzene, and benzene sulfonamide fragment was observed in all mass spectra. The other observed peaks were obtained by the fragmentation of piperidine ring according to the fragmentation pattern shown in Fig. 7. This confirmed the spectral analysis of the structure.

Pharmacology

Antioxidant activity of synthesized compounds

Compound **11** (IC_{50}: 51.52 ± 0.91 μM) exhibited the highest lipid peroxidation inhibitory activity, followed by compounds **5**, **9**, **6**, **8**, **18** and **14**, respectively. In DPPH assay, all the synthesized compounds were inhibited DPPH radical very well. The IC_{50} values of all compounds were calculated lower than 100 μM. Compounds **5, 9, 11, 13, 15, 16, 17** and **18** showed very good free radical scavenging activity, indicating IC_{50} values between 30.56 ± 0.03 and 52.23 ± 0.39 μM. At the conditions, the BHT exhibited less activity (IC_{50}: 54.97 ± 0.99 μM) than those of compounds. In the ABTS assay, among the tested compounds, **10**, **18** and **12** exhibited higher cation radical scavenging activity. The lower activity was observed for **4** and **2**. In the CUPRAC assay, most of the synthesized sulfonyl hydrazones exhibited good reducing effect. The $A_{0.50}$ values were calculated between 17.72 ± 0.03 and 37.12 ± 0.01 μM. $A_{0.50}$ value of α-tocopherol, however, was 40.48 ± 1.87 μM. The compounds **6, 8, 14** and **18** had lesser reducing effect capacity which are higher than 50 μM (Table 1).

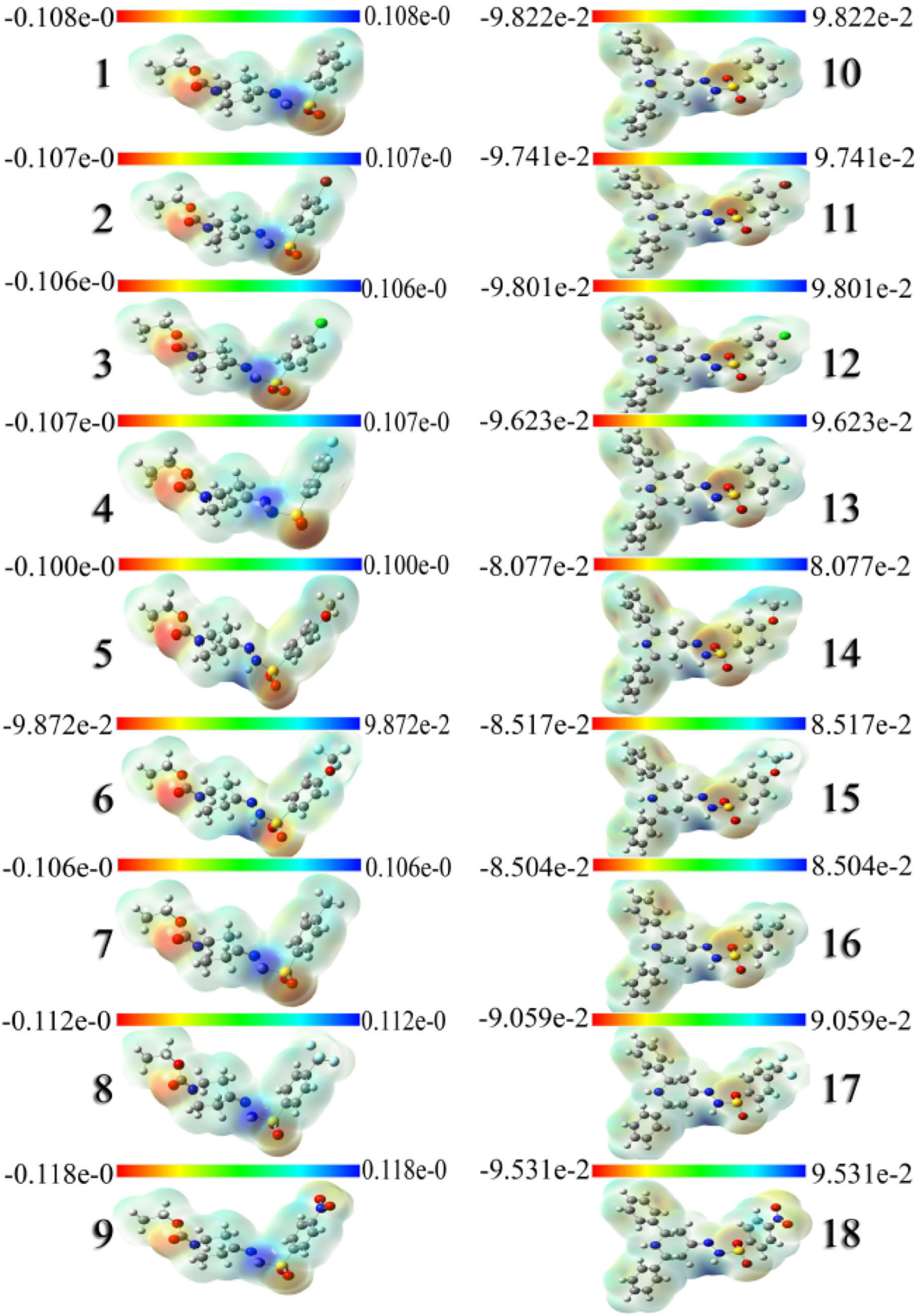

Fig. 9 Molecular electrostatic potential of the compounds **1–18**

Acetyl- and butyrylcholinesterase inhibitory activities of synthesized compounds

The synthesized seventeen compounds were tested for their in vitro inhibitory activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes at five different concentrations (200–100–50–25–12.5–6.25–3.125 μM) compared to that of galantamine. Galantamine is used to treat Alzheimer's disease and demonstrates good inhibition against AChE and BChE (IC_{50}: 4.48 ± 0.78 and 46.03 ± 0.14 μM, respectively). The synthesized compounds were unable to exhibit more activity against both enzymes. Nevertheless, since the IC_{50} values of compounds **12**, **13**, **16** and **14** were lower than 100 μM, it can be said that they have had good activity against AChE. Compounds **16** and **9** having methyl and nitro group at *para* position of phenyl ring, among all compounds against BChE, showed better IC_{50} values. Similarly, compounds **2**–**4**, **9**–**10** and **13**–**17** have had good potential against BChE (Table 2).

Structure activity relationship

In this study, the series of sulfonyl hydrazone were designed in order to discuss the structure–activity relationship that two derivatives of piperidine ring and 4-substituted benzene rings with both electron-withdrawing and electron-donating groups were preferred.

For the antioxidant activity, the DPPH assay results revealed that molecules (**10–18**) including 2,6-diphenyl substituted piperidine ring possessed better activity than the molecules (**2–9**) bearing non-substituted piperidine ring. In ABTS assay, non-substituted derivative (**10**) was most potent that the activity was decreased for the compounds having substituent at *para* position of the benzene ring. For CUPRAC assay, in the presence of the electron-

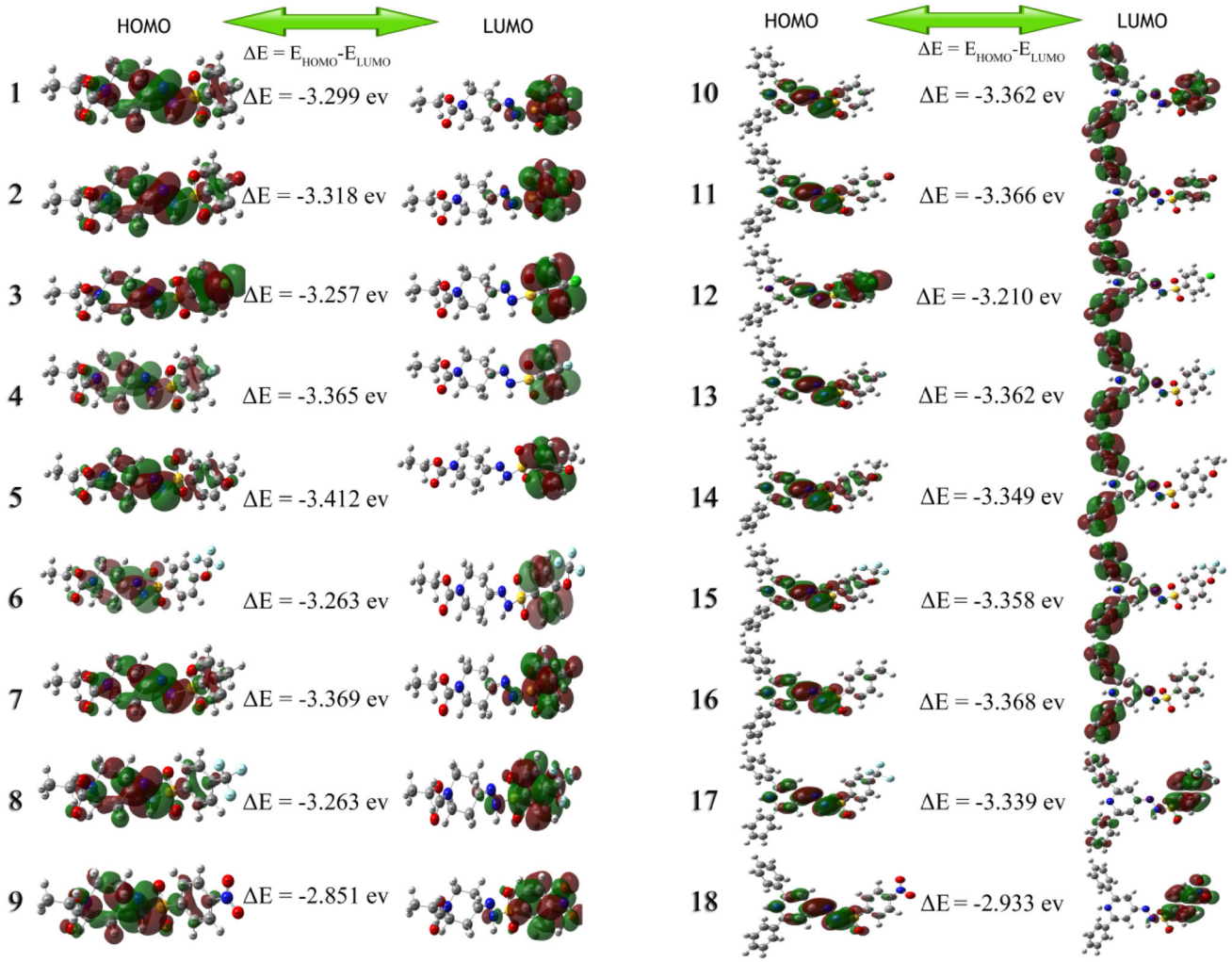

Fig. 10 HOMO–LUMO molecular orbital plots of optimized compounds **1–18**

Table 3 Calculated energy values of E_{LUMO} (eV), E_{HOMO} (eV), $\Delta E_{HOMO-LUMO}$ (eV), ionization potential (I, eV), electron affinity (A, eV), chemical hardness (η, eV), electronegativity (χ, eV), chemical potential (μ, eV), softness (S, 1/eV), electrophilicity index (ω, eV) and dipole moment (μ, Debye) by DFT calculations

Compounds	E_{LUMO}	E_{HOMO}	$\Delta E_{HOMO-LUMO}$	I	A	η	χ	μ	S	ω	μ
1	−5.103	−8.402	−3.299	8.402	5.103	1.649	6.753	−6.753	0.303	13.824	6.199
2	−5.078	−8.396	−3.318	8.396	5.078	1.659	6.737	−6.737	0.301	13.680	5.211
3	−5.003	−8.260	−3.257	8.260	5.003	1.629	6.631	−6.631	0.307	13.501	5.129
4	−5.020	−8.385	−3.365	8.385	5.020	1.682	6.702	−6.702	0.297	13.349	5.357
5	−5.003	−8.415	−3.412	8.415	5.003	1.706	6.709	−6.709	0.293	13.189	5.792
6	−5.136	−8.399	−3.263	8.399	5.136	1.631	6.768	−6.768	0.306	14.038	3.907
7	−5.030	−8.399	−3.369	8.399	5.030	1.684	6.715	−6.715	0.297	13.384	6.532
8	−5.136	−8.399	−3.263	8.399	5.136	1.631	6.768	−6.768	0.306	14.038	3.907
9	−5.546	−8.397	−2.851	8.397	5.546	1.425	6.972	−6.972	0.351	17.050	4.752
10	−5.116	−8.478	−3.362	8.478	5.116	1.681	6.797	−6.797	0.297	13.742	4.238
11	−5.110	−8.476	−3.366	8.476	5.110	1.683	6.793	−6.793	0.297	13.709	4.451
12	−5.106	−8.316	−3.210	8.316	5.106	1.605	6.711	−6.711	0.312	14.033	4.492
13	−5.106	−8.468	−3.362	8.468	5.106	1.681	6.787	−6.787	0.297	13.703	4.283
14	−5.105	−8.454	−3.349	8.454	5.105	1.674	6.779	−6.779	0.299	13.725	4.734
15	−5.108	−8.466	−3.358	8.466	5.108	1.679	6.787	−6.787	0.298	13.715	4.388
16	−5.106	−8.474	−3.368	8.474	5.106	1.684	6.790	−6.790	0.297	13.691	4.357
17	−5.141	−8.480	−3.339	8.480	5.141	1.670	6.811	−6.811	0.299	13.891	4.759
18	−5.548	−8.482	−2.933	8.482	5.548	1.467	7.015	−7.015	0.341	16.777	6.242

donating groups attached to the benzene ring (especially compounds having methyl group), activities were found better among the other compounds.

For the anti-Alzheimer activity, by the presence of the phenyl groups attached to the piperidine ring (**10–18**), the activities of the compounds were increased. As the electron donor groups, such as –F, $–OCH_3$ and $–CH_3$, were substituted at *para* position of the benzene ring, activities were observed better than the non-substituted derivatives. Among the all compounds, 4-methyl-substituted phenyl ring derivative (**16**) was found to be more active.

Computational studies

DFT calculation studies were carried out to support the chemical and pharmacological findings. The most stable conformer found in the DFT studies coincided with the conformer predicted by the NMR spectral studies. As seen from the lowest-energy conformer, molecules preferred chair conformation (Fig. 8) (Kassaee *et al.*, 2005). And also the calculations of the ^{1}H and ^{13}C NMR data were mostly correlated with the experimental values (Supporting information—Table 2 and Table 3).

To screen the electrophilic and nucleophilic region of the molecule, maps of MEP were prepared (Fig. 9). According to the maps, nitrogens of hydrazone group were observed as blue; oxygens of the sulfonyl and the ester groups were observed as red, as expected. As compounds **1–9** compared to compounds **10–18**, the electrophilicity of the hydrazo moiety was decreased because the benzene rings attached to the piperidine ring, donated electrons. Methoxy-substituted benzene ring (compounds **5** and **14**) was observed less positive because of the resonance effect of the oxygen, while the trifluoromethoxy-substituted benzene (compounds **6** and **15**) was more positive because of the high electronegativity of the fluorine atoms. Similar relationship was analyzed between the methyl- and trifluoromethyl-substituted derivatives (compounds **7, 8, 16** and **17**). Benzene ring of the methyl-substituted compound was less positive than the trifluoromethyl substituted. The sulfonyl group of compounds **11–13** was more negative than the other compounds by the resonance effect of the halogens.

The HOMO and LUMO are shown in Fig. 10. The HOMO showed that the charge density localized mainly on piperidine and hydrazo moiety. The LUMO showed that the charge density localized mainly on benzene groups.

The other calculated energy values including ionization potential (I), electron affinity (A), electronegativity (χ) and frontier orbital energy (HOMO and LUMO) were useful in predicting global chemical reactivity trends (Table 3).

The electron affinity (A) value of compound **18** was 5.548 eV which was the highest value among other

compounds. Compound **18** was also found among most active compounds according to the ABTS method. In addition, for compound **18** high electronegativity energy (χ) value was observed as 7.015 eV. Accordingly, the low electronegativity value of compound **4** as 6.702 eV belonged to low activity value according to ABTS method. Compound **18** having lowest E_{LUMO} energy value exerted activity value of 10.91 μM in ABTS and 52.45 μM in DPPH method which were good values. Also lowest $\Delta E_{HOMO-LUMO}$ energy gap values of compounds **5, 7** and **16** showed best antioxidant activities in CUPRAC test. These compounds have OCH_3 and CH_3 groups at 4-position of benzene ring. High ionization potential values of compounds **13–16** were concluded as good antiBChE activity and good antioxidant activity according to CUPRAC method. High dipole moment values of compounds **2–5** and **7** at a range of 5.129–6.532 Debye concluded good antioxidant effect according to the CUPRAC method (17.72–36.01 μM). In the same manner, compounds **6** and **8** show that lowest antioxidant values of 83.11 and 87.82 μM had a dipole moment value of 3.907 Debye.

Conclusions

In this report, we have synthesized seventeen sulfonyl hydrazone carrying piperidine rings to test for antioxidant and anticholinesterase effects. In the synthesis, 2,6-diaryl piperidine 4-one was obtained by using L-proline as catalyst and the target compounds were synthesized by MW-assisted method to increase the yield. According to the results, compounds **11** exhibited the highest lipid peroxidation inhibitory activity and the highest DPPH free radical scavenging activity. In the latter activity, compounds **17**, **15**, **9**, **16** and **13** having IC_{50} value less than 50 μM were also good antioxidants as free radical scavengers. All are competing with BHT which is a powerful antioxidant used in food and pharmaceutical industries. In addition to free radical scavengers, compounds **10**, **18** and **12** were also good cation radical scavengers as observed in ABTS assay. In CUPRAC assay, compound **5** was better reductant than that of α-tocopherol (vitamin E), indicating 17.72 ± 0.30 μM $A_{0.50}$ value. In addition, except **6, 8, 14** and **18** all compounds were also the good reductants that IC_{50} values were less than 50 μM. Briefly, except **6, 8** and **14** all compounds exhibited antioxidant activity in a good manner. A few compounds indicated IC_{50} value under 100 μM for anticholinesterase activity. In AChE assay, **12** had the best activity, while in BChE assay **16** had highest activity among the other compounds. The DFT calculations also support the experimental studies. As a future perspective, similar to sulfonyl hydrazones presented here, benzoyl hydrazones will be synthesized and evaluated for the changes of activity results.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest to disclose.

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