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Design and Bioevaluation of Novel Hydrazide-Hydrazones Derived from 4-Acetyl-*N*-Substituted Benzenesulfonamide

E. Bozkurt[a], Y. Sıcak[b], E. E. Oruç-Emre[a, 1], A. Karaküçük Iyidoğan[a], and M. Öztürk[c]

[a] *Department of Chemistry, Faculty of Arts and Sciences, Gaziantep University, Gaziantep, 27410 Turkey*

[b] *Department of Medicinal and Aromatic Plants, Köyceğiz Vocational School, Muğla Sıtkı Koçman University, Muğla, 48800 Turkey*

[c] *Department of Chemistry, Faculty of Sciences, Muğla Sıtkı Koçman University, Muğla, 48800 Turkey*

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Abstract—In this research, a series of hydrazine-hydrazone derivatives (**Ia–g**), (**IIa–h**) were synthesized to discover new antioxidant and anticholinesterase agents. The structures of synthesized compounds were characterized by spectroscopic data using UV, IR, ^{1}H, ^{13}C NMR, mass spectroscopy, and elemental analysis. The bio-evaluation of the synthesized compounds (**Ia–g**), (**IIa–h**) were evaluated according to in vitro activity assays. The results of β-carotene/linoleic acid assay showed that among the synthesized compounds, the (**Ib**), (**Ie**), (**IIb–IIe**), and (**IIh**) compound exhibited higher activity for the lipid peroxidation inhibitory activity. In the DPPH free scavenging activity and the cation radical scavenging activity in $ABTS^{\bullet+}$ activity, compound (**IIb**) was found to be more active. In the CUPRAC reduced power assay, the $A_{0.5}$ values of all synthesized compounds were better than α-TOC. In AChE assay, compound (**IIb**) exhibited the most activity with $IC_{50} = 11.12 \pm 0.74$ μM, while the compounds (**Ib–g**) and (**IIb–h**), exhibited excellent activity than the positive standard galantamine ($IC_{50} = 46.06 \pm 0.10$ μM) in the BChE assay.

Keywords: sulfonamide, hydrazone, antioxidant activity, anticholinesterase inhibitory activity, Lipinski's rules

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INTRODUCTION

Sulfonamides (sulfa drugs) are significant bioactive synthetic medicines. Over the last decades, many sulfa drugs have been developed and began using in the treatment. [1]. The brinzolamide, which is a carbonic anhydrase inhibitor, has been used to reduce intraocular pressure in patients with open-angle glaucoma or ocular hypertension [2]. An anti-glaucoma agent, dorzolamide, is used to decrease the production of aqueous humor [3]. Another sulfonamide drug sultiame having anticonvulsant activity is reported for the cure of West syndrome and epilepsy [4]. Besides, studies have shown that sulfonamides exhibit antioxidant and anticholinesterase activities [5–9].

Another essential organic compound class, hydrazones (–CONHN=CH–) are formed by the reaction of hydrazine and ketones/aldehydes [10]. Hydrazones can be used as intermediates to synthesize coupling products using the active hydrogen of the azomethine group. Besides, they are very effective organic compounds and used as drugs in the treatment such as isoniazid (antimicrobial), nifuroxazide (intestinal antiseptic), nitrofurantoin, and nifuratel (urine antiseptic), iproniazid and isocarboxazid (antidepressants) [11]. In the literature, it has been reported that hydrazide-hydrazone derivatives exhibit antioxidant and anticholinesterase activity [12–15].

In protecting the organism's health status, the balance between the antioxidant systems of the body with free radicals is essential [16]. Extreme reactive oxygen species (ROS) production eventuate oxidative stress that may be the reason for fatal damage to living cell structures [17]. Oxidative stress has also related some of the common diseases such as cancer, neurodegenerative, cardiovascular, inflammatory, and autoimmune. It is associated with the pathology of Alzheimer's disease, as well [18].

Alzheimer's disease is degeneration of the central nervous system, also is known as the most common form of dementia. As a progressive neurologic disorder, it is characterized mainly by premature senile mental deterioration that results in behavioral abnormalities in the patient [19]. The acetylcholinesterase (AChE) inhibitory compounds were used to treat Alzheimer's disease due to the deficiency of the insuffi-

[1] Corresponding author: phone: + (903) 423-17-29-98; fax: + (903) 423-60-10-32; e-mail: oruc@gantep.edu.tr.

cient amount of acetylcholine (ACh). However, these drugs have undesired side effects. Therefore, the improvement of novel effective antioxidants and AChE inhibitory compounds having fewer side effects are desired. According to some literature, using antioxidants may decrease the progression of Alzheimer's disease and reduce neuronal degeneration [20].

In our body, which is under oxidative stress, oxygen is divided into two atoms that do not have a paired electron. These atoms that travel alone and have missing electrons are called free radicals. However, electrons like to go around in pairs. That's why free radicals in our bodies travel our entire body to find another electron. During this circulation, cells, proteins, and DNA are damaged. Free radicals can cause many diseases. It can lead to diseases such as diabetes, Alzheimer's, and Parkinson's disease, vascular occlusion. In recent years, free radicals formed in our body have become a severe health problem with the increase of oxidation-related diseases. It is an advantage for an antioxidant compound if it inhibits or minimizes several diseases related to oxidative stress. Thus, the novel hydrazide-hydrazones, combined with the sulfonamide group to increase the pharmacological activities, were designed herein. These compounds (**Ia**–**g**), (**IIa**–**h**), derived from 4-acetyl-*N*-substituted benzenesulfonamide, were synthesized and evaluated for their in vitro antioxidant and anticholinesterase activities.

RESULTS AND DISCUSSION

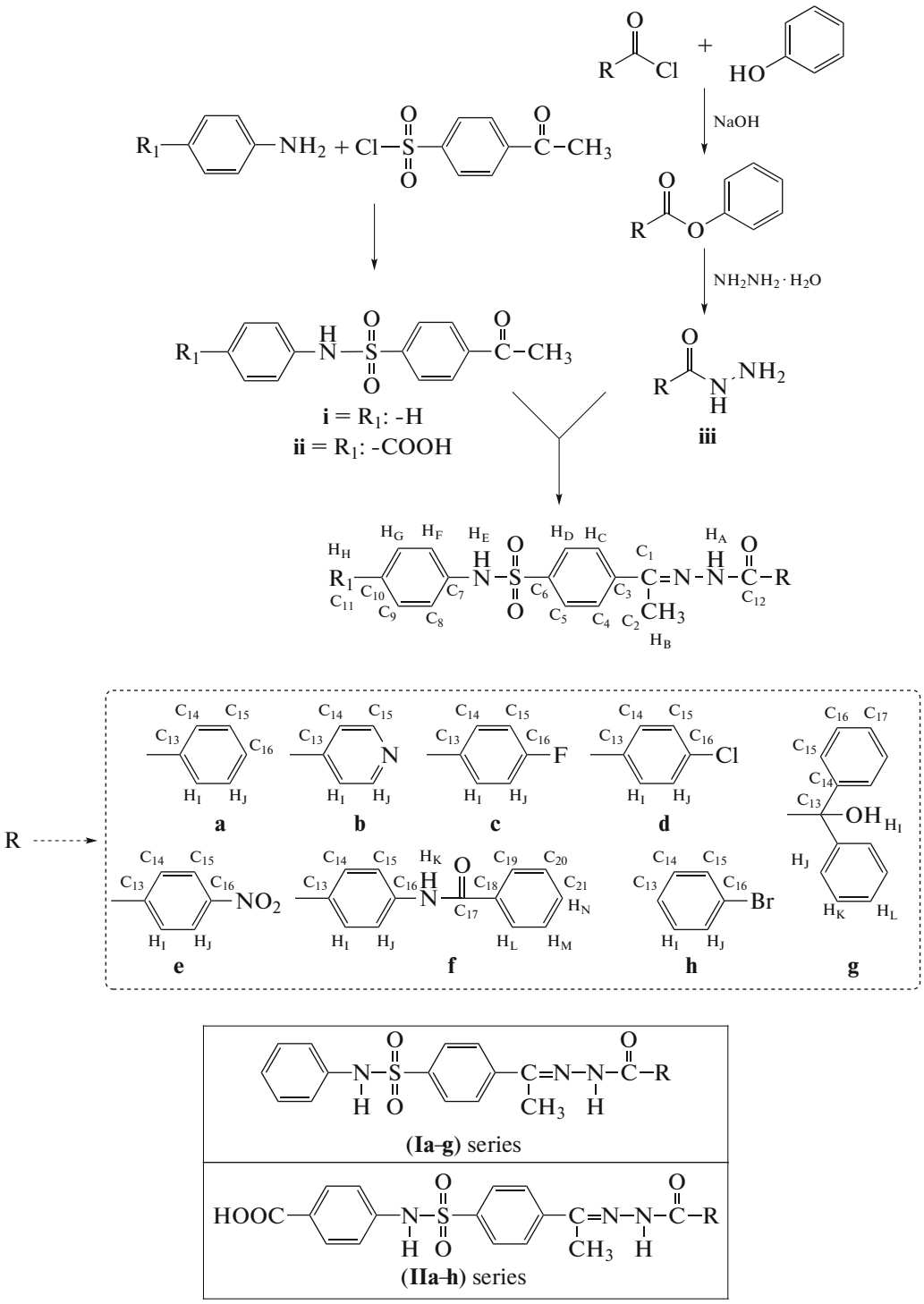
In this work, the new hydrazide-hydrazones (**Ia**–**g**), (**IIa**–**h**) derivated from 4-acetyl-*N*-substituted benzenesulfonamide were synthesized. In the first step, the substituted benzoylhydrazine derivatives were prepared by the treatment of substituted benzoylchloride with hydrazine hydrate. In the second step, sulfonamide compounds were synthesized via the treatment of 4-acetylbenzenesulfonylchloride with substituted aromatic amines. In the last step, substituted hydrazide-hydrazone derivatives were obtained by interacting substituted benzoylhydrazine with sulfonamide compounds in methanolic solution. The synthetic route followed for the preparation of the target molecules was shown outlined in Scheme 1.

In this research, the ultraviolet and visible (UV-Vis) spectra of all hydrazide-hydrazones derivatives were carried out (dissolved) in DMSO. In the UV-Vis spectra of hydrazone groups (**Ia**–**g**), (**IIa**–**h**), the K bands caused by transitions of $n \rightarrow \sigma^*$ and $\pi \rightarrow \pi^*$ of nitrogen in –C=N– group were detected at 274–285 nm. Also, characteristic R bands originating from the $n \rightarrow \pi^*$ transition, containing the carbonyl moiety of the hydrazide group (C=O), were at 295–315 nm.

The IR spectra of hydrazide-hydrazones (**Ia**–**g**), (**IIa**–**h**) provided the 3137–3354 cm^{-1} absorption as the weak NH band. Both weak NH and C–H bending absorption bands accompanied by the C=N absorption band between the 1591–1607 cm^{-1} region that was good evidence for the presence of an azomethine linkage. An additional strong band in the 1637–1671 cm^{-1} region, attributed to a carbonyl stretching, confirmed the hydrazone feature of all the compounds [21–24]. The asymmetric and symmetric stretching bands of the SO_2NH group of the synthesized molecules were in the range of 1335–1347 cm^{-1} and 1144–1166 cm^{-1}, respectively [25–28]. The absorption bands associated with substituents connected to the hydrazide-hydrazone skeleton appeared in the expected regions [29].

In the ^1H NMR spectra of the hydrazide-hydrazone derivatives, the proton of –CONHN= group resonated as a singlet at 10.49–11.19 ppm. The disappearance of the proton peaks of the free amino group is evidence of hydrazide-hydrazone synthesis. These data were compatible with the literature records [30–33]. Moreover, resonating of the proton of $-SO_2NH$ group as a singlet at the range of 10.32–10.92 ppm was another proof of the hydrazide-hydrazone group formation. In the structure of compounds **i** and **ii**, the protons of $-CH_3$ had resonance at 2.59 ppm as the electron density, after the formation of imine (–N=C–) resonated at 2.28–2.38 ppm. In the structure of compounds (**Ia**–**h**), the protons in *ortho* and *meta* positions relative to the sulfonamide group in the A ring resonated in the range of 7.03–7.24 ppm. In the structure of compounds (**IIa**–**h**), however, they displayed a peak at 7.83 ppm due to the electron-withdrawing property of the carboxylic acid. Chemical shifts of the protons belonging to the rings C and D of the compounds (**If**), (**IIf**) were observed in the range of 7.56–8.00 ppm, and the amide proton was observed in the range of 10.80–10.81 ppm [34]. The protons of the C and D rings of the compounds (**Ig**), (**IIg**) resonated in the range of 7.29–7.44 ppm, and the tertiary hydroxyl proton was detected in the range of 7.23–7.24 ppm [35, 36].

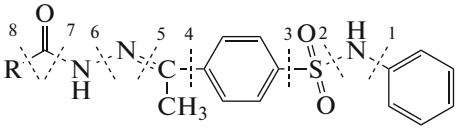
In the ^{13}C NMR spectrum of the compound **i** and **ii**, it was found that the $-CH_3$ carbon in the acetyl group resonated at 27.44–27.45 ppm, the aromatic carbons resonated in the range 118.86–143.58 ppm, the carbonyl carbons in the acetyl group were detected at 197.63–197.68 ppm, carbonyl carbon of COOH in the structure of compound **ii** was at 167.15 ppm, and the values herein were consistent with the literature data [27]. The resonance of the imine bond (–C=N) carbon in the range of 152.72–154.94 ppm was compatible with the literature data [37]. The methyl ($-CH_3$) carbon of hydrazones was a resonance in the range of 13.80–15.47 ppm, and the aromatic carbons were resonance in the range of 115.58–133.10 ppm, the carboxylic acid carbonyl carbon was a resonance in the range of 167.18–167.74 ppm, the carbonyl (–C=O) carbon bound to the hydrazone group was found to have resonance in the range of 163.23–169.37 ppm.



Scheme 1. Synthetic pathway of substituted hydrazide-hydrazones (**Ia**–**g**), (**IIa**–**h**).

The mass spectra of the synthesized compounds **(I, II, Ia**–**g**, **IIa**–**h)** were run using ESI (+) and (–) technique. According to the results, the compounds (**Ib**, **Ic**, **Id**, **Ig**, **IIa**–**d**, **IIf**, and **IIh**) exhibited [M^{+1}] molecular ion peaks while compounds (**II**, **Ie**, **IIe**) [M^{-1}], and the compounds (**I**, **Ia**) [M^{+2}], and the compounds (**If** and **IIg**) [M^{-2}]. The compounds (**I**, **Ia**–**g**, **IIa**, **IIf**, **IIg**) bearing the nonsubstituted phenyl ring in the structure, the ions formed as a result of the fragmentation of the phenyl ring and the cleavage ions of the phenyl ring were detected. Compounds (**IIa**–**h**) bearing acid groups have been generally found to form ions resulting from the cleavage of the α-cleavage relative to the acid carbonyl, –COOH (*m*/*z* 45). Formed ions

with cleavage of the pyridine ring (*m/z* 78) in compounds (**Ib**) and (**IIb**) and the cleavage products of this ring were detected. In general, when the mass spectra of all synthesized compounds were examined, it, unlike the molecular ion, has been found that the degradation proceeds from 8 points. In Scheme 2, fragmentation points on the skeletal structure of the synthesized compounds were indicated.



Scheme 2. Fragmentation points on the skeletal structure of the synthesized compounds.

Biological Activity

Antioxidant activity evaluation. The synthesized compounds (**Ia**–**g**, **IIa**–**h**) were screened for their antioxidant activity using four different assays (Table 1). The α-tocopherol and BHT (butylated hydroxyl toluene) were used as positive standards to compare the activity. In general, among the synthesized molecules (**Ia**–**g**), (**IIa**–**h**) series, the antioxidant activity of compounds (**IIa**–**h**) series were founded to be active than compounds (**Ia**–**g**) derivatives. β-carotene-linoleic acid assay is based on the discoloration of the yellowish color of a β-carotene having an absorption band at 470 nm. The singlet oxygen oxidizes the double bonds of linoleic acid added to the oxygenated media, which resulted in the lipid peroxyl radicals (L$^{\bullet}$ or LOO$^{\bullet}$). The produced radicals attach the β-carotene to degrade it. The antioxidant in the media neutralizes the radicals or stops the radicalic degradation radicals by transferring Hydrogen radical or scavenge the singlet oxygen, which accelerates the radicalic degradation [38–42]. Therefore, the higher absorbance at 470 nm indicates the higher antioxidant activity. According to the β-carotene/linoleic acid assay results, the compounds (**IIb**) (IC_{50} = 10.21 ± 0.12 μM), (**Ib**) (IC_{50} = 12.83 ± 0.19 μM), (**IIc**) (IC_{50} = 14.75 ± 0.44 μM), (**IIe**) (IC_{50} = 16.20 ± 0.48 μM), (**IId**) (IC_{50} = 18.83 ± 0.19 μM), (**Ie**) (IC_{50} = 20.16 ± 0.35 μM), and (**IIh**) (IC_{50} = 20.16 ± 0.37 μM) exhibited higher lipid peroxidation inhibitory activity among the synthesized compounds. The compounds (**IIb**), (**Ib**), (**IIc**), (**IIe**), (**IId**), (**Ie**), and (**IIh**) exhibiting high lipid peroxidation inhibitory activity sadi that they have the abilities of radical hydrogen transfer.

DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) free radical scavenging activity method is based on the neutralizes of DPPH radical by an antioxidant. The DPPH is a stable free radical absorbing at 517 nm wavelength. When the DPPH radical get an electron from an antioxidant, the absorption at 517 nm decreases [43]. This free radical is stable at room temperature. Therefore, it can be said that the antioxidant, if approaches DPPH molecule, transfers electrons to the DPPH, which resulted in the decrease of absorption at 517 nm [39–42, 44]. The lower absorbance at 517 nm indicates higher DPPH free radical scavenging activity. In the DPPH free scavenging activity, compounds (**IIb**) (IC_{50} = 26.77 ± 0.31 μM) demonstrated the best activity. Moreover, all series (**Ia**–**g**), (**IIa**–**h**) exhibited more activity than BHT (IC_{50} = 53.80 ± 0.92 μM).

ABTS (2,2'-azino-di-[3-ethylbenzthiazoline sulfonate) cation radical scavenging activity method is based on the neutralizes of ABTS cation radical by an antioxidant. The ABTS cation radical is produced by the oxidation of ABTS molecule with strong oxidizing agents, such as $K_2S_2O_7$ in water. The produced greenish radical absorbs at 734 nm. The advantage of this radical is the solubility in inorganic and organic solvents. Therefore, using this assay, both hydrophilic and hydrophobic compounds can be tested [45]. Another advantage of the ABTS assay is that the bulky compounds can approach this molecule to transfer electrons easily when compared with the DPPH molecule. In this assay, lower absorbance exhibits the higher ABTS cation radical scavenging activity [39–42, 46]. In ABTS assay, compound (**IIb**) (IC_{50} = 4.13 ± 0.54 μM) was the most active compound among the tested compounds (**Ia**–**g**), (**IIa**–**h**). Compounds (**Ib**) (IC_{50} = 7.08 ± 0.45 μM), (**IIe**) (IC_{50} = 7.45 ± 0.50 μM), (**Ie**) (IC_{50} = 9.69 ± 0.28 μM), (**IIc**) (IC_{50} = 10.88 ± 0.63 μM), (**Ic**) (IC_{50} = 11.85 ± 0.18 μM), (**IId**) (IC_{50} = 13.51 ± 0.49 μM), and (**Id**) (IC_{50} = 14.41 ± 1.13 μM) indicated good ABTS$^{\bullet+}$ cation radical scavenging activity.

The CUPRAC (Cupric Reducing Antioxidant Capacity) assay tests the electron giving power of the antioxidant. The antioxidant reduces the Cupric to Cuprous. The reduction potential is monitored by using the neocuproine ligand. The neocuproine ligand and cuprous can occur complex molecule which absorbs at 450 nm. Therefore, the amount of reduction of Cupric to cuprous indicates the power of antioxidants. Accordingly, the higher absorbance at 450 nm suggests the higher Cupric reducing antioxidant capacity [40–42, 47, 48]. In the CUPRAC assay, compound (**IIb**) ($A_{0.5}$ = 8.88 ± 0.01 μM) possessed the highest activity. The cupric reducing the antioxidant capacities of synthesized compounds (**Ia**–**g**), (**IIa**–**h**) were better than α-TOC ($A_{0.5}$ = 40.41 ± 0.03 μM).

In this study, according to the antioxidant activity assay results of the synthesized compounds, they exhibit better antioxidant activity than other compounds with the potential of forming free radicals by weakening the NH bond in the hydrazone group of the compounds (**Ib**) and (**IIb**) containing the heteroatom in the ring and compound (**Ic**), (**Id**), (**IIc**) and (**IId**) containing the halogen group bound to the ring.

Acetyl- and butyryl-cholinesterase inhibitory activities evaluation. The only known hypothesis to treat Alzheimer's disease is to inhibit the acetylcholinester-

Table 1. Antioxidant activity results of synthesized compounds[a]

Sample code	β-Carotene/linoleic acid assay IC_{50}, μM	$DPPH^{\bullet}$ assay IC_{50}, μM	$ABTS^{\bullet+}$ assay IC_{50}, μM	CUPRAC $A_{0.50}$, μM
(I)	44.18 ± 0.42	58.19 ± 0.54	40.11 ± 0.22	42.08 ± 0.00
(II)	39.56 ± 0.90	54.93 ± 0.71	36.77 ± 0.34	38.45 ± 0.01
(Ia)	35.47 ± 0.54	52.06 ± 0.18	34.17 ± 0.03	33.66 ± 0.03
(Ib)	12.83 ± 0.19	30.36 ± 0.85	7.08 ± 0.45	8.88 ± 0.00
(Ic)	22.77 ± 0.33	33.99 ± 1.14	11.85 ± 0.18	18.77 ± 0.04
(Id)	27.14 ± 0.60	36.76 ± 0.53	14.41 ± 1.13	21.64 ± 0.01
(Ie)	20.16 ± 0.35	32.01 ± 0.17	9.69 ± 0.28	16.47 ± 0.02
(If)	33.82 ± 0.66	49.40 ± 0.44	29.16 ± 0.40	28.30 ± 0.02
(Ig)	30.49 ± 0.76	44.26 ± 0.68	30.49 ± 0.07	24.11 ± 0.00
(IIa)	29.14 ± 0.88	50.65 ± 0.94	33.41 ± 0.89	20.35 ± 0.01
(IIb)	10.21 ± 0.12	26.77 ± 0.31	4.13 ± 0.54	8.40 ± 0.01
(IIc)	14.75 ± 0.44	33.24 ± 0.55	10.88 ± 0.63	9.73 ± 0.01
(IId)	18.36 ± 0.61	35.73 ± 0.26	13.51 ± 0.49	10.04 ± 0.00
(IIe)	16.20 ± 0.48	30.29 ± 0.75	7.45 ± 0.50	14.26 ± 0.00
(IIf)	25.88 ± 0.68	45.74 ± 0.59	25.37 ± 1.08	16.27 ± 0.00
(IIg)	22.84 ± 0.52	43.52 ± 0.36	29.70 ± 0.44	13.90 ± 0.04
(IIh)	20.16 ± 0.37	39.44 ± 0.58	17.30 ± 0.67	13.15 ± 0.03
BHT[b]	2.44 ± 0.07	53.80 ± 0.92	2.81 ± 0.43	3.84 ± 0.00
α-TOC[b]	4.63 ± 0.11	12.16 ± 0.16	4.93 ± 0.39	40.41 ± 0.03

[a] Values expressed are means ± SD of three parallel measurements. $p < 0.05$, significantly different with student's *t*-test. [b] Reference compounds.

ase (AChE) and butyrylcholinesterase (BChE), which are the chief enzymes of Alzheimer's disease. Therefore, acetylcholinesterase inhibitory drugs are used for the treatment of patients. The inhibition of both enzymes lessens the symptoms of Alzheimer's disease by increasing the communication between nerve endings and the activities in cholinergic pathways in the brain [49]. Accordingly, the anticholinesterase activity method is based on the inhibition of AChE and BChE enzymes. In a control test, where there is no testing compound, the enzyme hydrolyzes the acetylthiocholine or butyrylthiocholine to give thiocholine. The latter reacts with the DTNB to give a yellow color which can be measured at 412 nm. When any inhibitory compound added to the medium to be tested for its activity, the compound inhibits the enzymes; thus, thiocholine occurs a lesser amount, which resulted in lower absorbances. Therefore, the lower absorbance indicates higher activity. In other words, lower absorbance indicates higher acetylcholinesterase and butyrylcholinesterase inhibitory activity of the compound.

The in vitro anticholinesterase activity of synthesized compounds **(Ia–g)**, **(IIa–h)** against AChE and BChE were given in Table 2. In AChE inhibitory assay, the IC_{50} values of compounds **(IIb)**, **(Ib)**, **(IIe)**, **(IIc)**, and **(IId)** were 11.12 ± 0.74, 15.28 ± 0.33, 18.23 ± 0.64, 20.42 ± 0.71, and 23.19 ± 0.56 μM, respectively, which were lower than 25 μM. The said compounds they were exhibited better activity among synthesized compounds **(Ia–g)**, **(IIa–h)**. In the BChE assay, however, the IC_{50} of all compounds **(Ia–g)**, **(IIa–h)** except compounds **(Ia)** and **(IIa)**, were lower than galantamine used as a drug in mild Alzheimer patients. The compounds **(IIb)**, **(Ib)**, **(IIe)**, **(IIc)**, **(IId)**, **(Ie)**, **(Ic)**, **(Id)**, **(IIh)**, **(IIg)**, **(Ig)**, **(IIf)**, and **(If)** from synthesis series exhibited excellent activity with IC_{50} values of 14.26 ± 0.68, 17.25 ± 0.37, 20.74 ± 0.62, 21.88 ± 0.82, 26.65 ± 0.49, 26.65 ± 0.54, 31.19 ± 0.84, 35.20 ± 0.68, 36.35 ± 0.40, 40.72 ± 0.43, 43.34 ± 0.60, and 45.51 ± 0.61 μM, respectively. The galantamine possessed 46.06 ± 0.10 μM IC_{50} value in the same conditions. As a result, the compounds **(IIb)** and **(Ib)** the AChE and BChE against show better activity at low absorbance by inhibiting both enzymes better than other compounds.

Druglikeness Properties

According to Lipinski's rules of five, our results showed that the molecular weights of compounds except for **(If)**, **(IIf–g)** were not greater than 500 at the range of 393.47–499.59 Da. The logP values of all hydrazones were smaller than 5 at the range of 2.49–4.67. The number of groups that accepted hydrogen

Table 2. Acetyl-, and butyryl-cholinesterase inhibitory activities of synthesized compounds[a]

Sample	Anticholinesterase inhibitory activity	
	AChE assay IC_{50}, μM	BChE assay IC_{50}, μM
(I)	49.30 ± 0.67	54.47 ± 0.06
(II)	47.79 ± 0.44	51.73 ± 0.19
(Ia)	45.05 ± 0.26	48.76 ± 0.49
(Ib)	15.28 ± 0.33	17.25 ± 0.37
(Ic)	28.09 ± 0.33	31.19 ± 0.84
(Id)	33.70 ± 0.56	35.20 ± 0.68
(Ie)	25.07 ± 0.85	26.65 ± 0.54
(If)	41.23 ± 0.82	45.51 ± 0.61
(Ig)	38.04 ± 0.55	40.72 ± 0.43
(IIa)	44.52 ± 0.28	48.36 ± 0.79
(IIb)	11.12 ± 0.74	14.26 ± 0.68
(IIc)	20.42 ± 0.71	21.88 ± 0.82
(IId)	23.19 ± 0.56	26.65 ± 0.49
(IIe)	18.23 ± 0.64	20.74 ± 0.62
(IIf)	40.14 ± 0.40	43.34 ± 0.60
(IIg)	36.18 ± 0.83	40.52 ± 0.78
(IIh)	30.49 ± 0.50	36.35 ± 0.40
Galantamine[b]	4.50 ± 0.09	46.06 ± 0.10

[a] Values expressed are means ± SD of three parallel measurements. $p < 0.05$, significantly different with student's *t*-test. [b] Reference compounds.

atoms (*n*-ON) was less than 10 except compounds **(IIe)** and **(IIf)**, and the number of groups that donated hydrogen atoms (*n*-OHNH) was less than 5, which were within the Lipinski's rules. All data for the calculation of absorption (%ABS), according to Zhao et al. [50] and TPSA values were shown in Table 3**.**

CONCLUSIONS

Novel hydrazide-hydrazones **(Ia–g)**, **(IIa–h)** derivatized from 4-acetyl-*N*-substituted benzenesulfonamide were synthesized. The structures of synthesized compounds were confirmed by spectroscopy methods as UV-Vis, IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy, and elemental analysis (C, H, N, S). Antioxidant and anticholinesterase activities of the synthesized compounds **(Ia–g)**, **(IIa–h)** were reported for the first time in this study. The **(Ia–g)** and **(IIa–h)** hydrazone series in both activity assays were found to be more active than the starting materials. Fifteen different hydrazone derivatives tested for their antioxidant potency by in vitro antioxidant and anticholinesterase activities. Compound **(IIb)** and **(Ib)**, bearing heteroatom on the aromatic ring, were found to be the most potent antioxidant agents among all tested compounds. According to the antioxidant activity results, these two compounds may have a significant impact on the prevention of radical-induced oxidative stress. In anticholinesterase activity, compounds **(IIb)**, **(Ib)**, **(IIe)**, **(IIc)**, **(IId)**, **(Ic)**, and **(Id)** showed considerable activity against both AChE and BChE enzymes. Notably, the BChE activity of the compounds containing the heteroatom in the ring, the halogen, and nitro groups in the phenyl ring were was found to be more excellent from the galantamine used as standard. According to the data in Table 3, suggested that compounds **(IIb)** and **(Ib)** from novel synthesized hydrazide-hydrazone derivatives with tertiary amine groups can be evaluated as both AChE and BChE enzyme inhibitors, which may have promising features for the treatment of Alzheimer's disease.

EXPERIMENTAL

All chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA), Alfa Aesar, Fluka, and Merck. The reactions and the purities of the compounds were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 aluminum sheets purchased from Merck (Darmstadt, Germany). Melting points were recorded by open capillaries on the Stuart melting point SMP30 apparatus and are uncorrected. C, H, N, S percent of the compounds were detected by Thermo Scientific Flash 2000 (Finnegan MAT, USA) elemental analyzer. UV spectra, PG Instruments brand T80 + UV/Vis Spectrometer spectrometry was in the range of 190 to 1100 nm wavelengths. FTIR spectra were recorded on Perkin Elmer Frontier spectrometer by attenuated total reflectance (ATR) apparatus (Waltham, Massachusetts, USA). Mass spectra were recorded on Ab-SciEx 3200 Q-Trap MSMS detector with an electrospray ionization probe (Framingham, MA, USA). NMR spectra were recorded on Brucker Avance-400 MHz spectrometer (Billerica, MA, USA) by using DMSO-d_6 as a solvent and TMS as an internal standard. Bioactivity measurements were carried out on a 96-well microplate reader, SpectraMax 340PC^{384}, Molecular Devices (USA), at the Department of Chemistry, Mugla Sıtkı Kocman University.

Synthesis of 4-acetyl-*N*-phenyl benzenesulfonamide (i or I). To a solution of 4-acetylbenzenesulfonyl chloride (1 mmol) in acetone, 5 g of silicagel was added. 2 mmol of aniline was added dropwise to the stirred mixture at room temperature. After the reaction has been completed (as indicated by TLC), methanol was added and the silica gel was removed by filtration. The methanol solution was taken in a beaker and then purified water was added dropwise to crystallize the product by precipitation. The crystalline product was washed with water and filtered and dried [51]. This compound was previously synthesized by Gioiello [52]. Yield: 83%; orange solid, mp 99–101°C; IR (ν, cm^{-1}): 3273 (N–H); 3092, 3042 (aromatic C–H);

2962, 2885 (aliphatic C–H); 1687 (C=O); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.59 (s, 3H, H_B); 7.04 (t, 1H, J_1 = 6.8 Hz, J_2 = 6.8 Hz, H_H); 7.10 (d, 2H, J = 8.4 Hz, H_F); 7.24 (t, 2H, J_1 = 8.0 Hz, J_2 = 8.0 Hz, H_G); 7.88 (d, 2H, J = 8.4 Hz, H_D); 8.08 (d, 2H, J = 8.4 Hz, H_C); 10.47 (s, 1H, H_E); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 27.44 (C_2); 120.74, 124.87, 127.50, 129.48, 129.72 (C_4, C_5, C_8, C_9, C_{10}); 137.75, 140.20, 143.58 (C_3, C_6, C_7); 197.68 (C_1); MS (*m/z*) (%): 277 [M^{+2}]; UV-*Vis* (DMSO, λ_{max}, nm): 296, 280; Anal. calc. for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09; S, 11.65%; found: C, 61.09; H, 4.85; N, 5.00; S, 11.09%.

Synthesis of 4-(4-acetylphenylsulfonamido)benzoic acid (ii or II). 7.3 mmol of 4-aminobenzoic acid was added to 10 mL of purified water and the pH of the reaction mixture was maintained to 9 with aqueous $NaHCO_3$ solution. 7.3 mmol of 4-acetylbenzenesulfonyl chloride was then added in small portions to the reaction mixture and the reaction was stirred at room temperature. After the reaction has been completed (as indicated by TLC), the pH of the reaction mixture was changed to 2 with 1M HCl. The resulting precipitate was filtered off with water and dried. The crude product was purified by crystallization from methanol [53], this compounds was previously synthesized by Deng and Mani [27]. Yield: 84%; cream solid, mp 251–253°C; IR (ν, cm^{-1}): 3259 (N–H); 3110 (aromatic C–H); 2836 (aliphatic C–H); 1677 (C=O); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.60 (s, 3H, H_B); 7.22 (d, 2H, J = 8.4 Hz, H_F); 7.82 (d, 2H, J = 8.8 Hz, H_G); 7.95 (d, 2H, J = 8.4 Hz, H_D); 8.11 (d, 2H, J = 8.4 Hz, H_C); 10.99 (s, 1H, H_E); 12.81 (s, 1H, H_H); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 27.45 (C_2); 118.86, 126.42, 127.54, 129.64, 131.28 (C_4, C_5, C_8, C_9, C_{10}); 140.42, 142.02, 143.24 (C_3, C_6, C_7); 167.15 (C_{11}); 197.68 (C_1); MS (*m/z*): 317.7 [M^{-1}]; UV-Vis (DMSO, λ_{max}, nm): 293, 275; Anal. calc. for $C_{15}H_{13}NO_5S$: C, 56.42; H, 4.10; N, 4.39; S, 10.04%; found: C, 55.96; H, 3.87; N, 4.36; S, 9.91%.

Synthesis of the substituted hydrazide derivatives (iii). Firstly 4-substituted aroyl chloride (10 mmol) was reacted with phenol (10 mmol in 100 mL of 10% sodium hydroxide solution) to form 4-substituted phenyl benzoate. The crude product was washed with water and recrystallized from ethanol. Then the 4-substituted phenyl benzoate (5 mmol) was reacted with hydrazine hydrate (10 mmol) in methanol. The mixture was refluxed and monitored by TLC. The crude product was washed with water and recrystallized from ethanol [54].

Synthesis of substituted hydrazide-hydrazone derivatives (Ia–g), (IIa–h). To a solution of 1 mmol hydrazide derivatives (iii) in 10 mL, methanol was added a solution of 1 mmol acetylbenzenesulfonamide derivatives (i or ii) in 10 mL methanol. A few drops of glacial acetic acid was added to the reaction mixture. The mixture was refluxed on a water bath for 2 h. After cooling the mixture, the precipitate was filtered, dried, and recrystallized from ethanol [55].

Table 3. Druglikenees properties of hydrazones (**Ia–g**, **IIa–h**)*

Compound	Log P	TPSA	MW	*n*OH	*n*OHNH
(Ia)	3.78	87.63	393.47	6	2
(Ib)	2.49	100.52	394.46	7	2
(Ic)	3.94	87.63	411.46	6	2
(Id)	4.46	87.63	427.91	6	2
(Ie)	3.74	133.46	438.46	9	2
(If)	4.67	116.73	512.59	8	3
(Ih)	4.59	87.63	472.36	6	2
(Ig)	4.06	107.86	499.59	7	3
(IIa)	3.69	124.93	437.48	8	3
(IIb)	2.40	137.82	438.46	9	3
(IIc)	3.85	124.93	455.47	8	3
(IId)	4.37	124.93	471.92	8	3
(IIe)	3.65	170.75	482.47	11	3
(IIf)	4.58	154.03	556.60	10	4
(IIh)	4.50	124.93	516.37	8	3
(IIg)	3.97	145.16	543.60	9	4

* These parameters were determined with Molinspiration calculation software and Molsoft software.

4-(1-(2-Benzoylhydrazinylidene)ethyl)-*N*-phenylbenzenesulfonamide (Ia). Yield: 47%; white solid, mp 222–225°C; IR (ν, cm^{-1}): 3378, 3137 (N–H); 3024 (aromatic C–H); 2953, 2882 (aliphatic C–H); 1687 (C=O); 1600 (C=N); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.36 (s, 3H, H_B); 7.04 (t, 1H, J_1 = 8.0 Hz, J_2 = 6.8 Hz, H_H); 7.10 (d, 2H, J = 7.2 Hz, H_F); 7.24 (t, 2H, J_1 = 7.6 Hz, J_2 = 8.0 Hz, HG); 7.52 (t, 2H, J_1 = 6.8 Hz, J_2 = 6.8 Hz, H_J); 7.59 (d, 1H, J = 6.4 Hz, H_K); 7.80–7.97 (m, 6H, H_C, H_D, H_I); 10.33 (s, 1H, H_E); 10.89 (s, 1H, H_A); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 14.86 (C_2); 120.72, 124.69, 127.28, 127.47, 128.72, 129.65, 132.07, 134.37 (C_4, C_5, C_8, C_9, C_{10}, C_{14}, C_{15}, C_{16}); 137.40, 138.02, 140.20, 142.59 (C_3, C_6, C_7, C_{13}); 147.7 (C_1), 163.2 (C_{12}); MS (*m/z*) (%): 394.7 [M^{+2}]; UV-Vis (DMSO, λ_{max}, nm): 305, 279; Anal. calc. for $C_{21}H_{19}N_3O_3S$: C 64.10; H 4.87; N 10.68; S 8.15%; found: C 63.42; H 4.72; N 10.77; S 8.23%.

***N*-Phenyl-4-[1-[2-(pyridine-4-carbonyl)hydrazinylidene]ethyl]benzenesulfonamide (Ib).** Yield 46%; white solid, mp 232–235°C; IR (ν, cm^{-1}): 3284 (N–H); 3067 (aromatic C–H); 2870, 2815 (aliphatic C–H); 1671 (C=O); 1598 (C=N); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.38 (s, 3H, H_B); 7.04–

7.24 (m, 5H, H_F, H_G, H_H); 7.81–7.82 (m, 4H, H_D, H_I); 8.00 (d, 2H, J = 7.6 Hz, H_C), 8.78 (d, 2H, J = 7.6 Hz, H_J); 10.36 (s, 1H, H_E); 11.13 (s, 1H, H_A); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 15.17 (C_2); 120.75, 122.41, 124.72, 127.31, 127.69, 129.67, 150.59 (C_4, C_5, C_8, C_9, C_{14}, C_{15}); 133.58 (C_{10}); 137.99 (C_7); 140.49 (C_3); 141.41 (C_{13}); 142.31 (C_6); 154.94 (C_1); 163.28 (C_{12}); MS (*m/z*) (%): 395.1 [M^{+2}]; UV-Vis (DMSO, λ_{max}, nm): 305, 279; Anal. calc. for $C_{20}H_{18}N_4O_3S$: C 60.90; H 4.60; N 14.20; S 8.13%; found: C 60.30; H 4.46; N 14.37; S 8.27%.

4-(1-(2-(4-Fluorobenzoyl)hydrazono)ethyl)-*N*-phenylbenzenesulfonamide (Ic). Yield 56%; cream solid, mp 225–227°C; IR (ν, cm^{-1}): 3317 (N–H); 3073 (aromatic C–H); 2944, 2876, 2811 (aliphatic C–H); 1666 (C=O); 1603 (C=N); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.36 (s, 3H, H_B); 7.03 (t, 1H, J_1 = 7.6 Hz, J_2 = 7.2 Hz, H_H); 7.11 (d, 2H, J = 7.2 Hz, H_F); 7.24 (t, 2H, J_1 = 7.6 Hz, J_2 = 7.2 Hz, H_G); 7.35 (t, 2H, J_1 = 8.8 Hz, J_2 = 8.8 Hz, H_J); 7.80 (d, 2H, J = 8.0 Hz, H_C); 7.96 (m, 4H, H_D, H_I); 10.33 (s, 1H, H_E); 10.91 (s, 1H, H_A); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 14.78 (C_2); 115.67, 120.71, 124.73, 127.40, 129.67, 131.29 (C_4, C_5, C_8, C_9, C_{14}, C_{15}); 130.75, 135.82, 137.97, 140.21, 142.53 (C_3, C_6, C_7, C_{10}, C_{13}); 153.53 (C_1); 164.27 (C16), 166.35 (C_{12}); MS (*m/z*) (%): 411.9 [M^{+1}]; UV-Vis (DMSO, λ_{max}, nm): 305, 282; Anal. calc. for $C_{21}H_{18}FN_3O_3S$: C 61.30; H 4.41; N 10.21; S 7.79%; found: C 60.25; H 4.25; N 10.12; S 7.65%.

4-(1-(2-(4-Chlorobenzoyl)hydrazono)ethyl)-*N*-phenylbenzenslfonamide (Id). Yield 47%; white solid, mp 210–213°C; IR (ν, cm^{-1}): 3313, 3156 (N–H); 3078, 3029 (aromatic C–H); 2944, 2968, 2898 (aliphatic C–H); 1637 (C=O); 1598 (C=N); 1347 (SO_2 asymmetric stretching band); 1156 (SO_2 symmetric stretching band); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.36 (s, 3H, H_B); 7.03 (t, 1H, J_1 = 7.2 Hz, J_2 = 7.2 Hz, H_H); 7.11 (d, 2H, J = 8.0 Hz, H_F); 7.24 (t, 2H, J_1 = 7.6 Hz, J_2 = 8.0 Hz, H_G); 7.59 (d, 2H, J = 8.0 Hz, H_J); 7.80 (d, 2H, J = 7.6 Hz, H_C); 7.92–7.98 (m, 4H, H_D and H_I); 10.34 (s, 1H, H_E); 10.96 (s, 1H, H_A); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 14.97 (C_2); 120.71, 124.69, 127.40, 128.00, 129.66, 133.10 (C_4, C_5, C_8, C_9, C_{14}, C_{15}); 130.55, 136.95, 138.01, 139.04, 140.36, 142.47 (C_3, C_6, C_7, C_{10}, C_{13}, C_{16}); 149.63 (C_1); 162.27 (C_{12}); MS (*m/z*) (%): 429 [M^{+2}]; UV-Vis (DMSO, λ_{max}, nm): 305, 274; Anal. calc. for $C_{21}H_{18}ClN_3O_3S$: C, 58.94; H, 4.24; N, 9.82; S, 7.49%; found: C, 58.24; H, 4.11; N, 9.88; S, 7.22%.

4-(1-(2-(4-Nitrobenzoyl)hydrazono)ethyl)-*N*-phenylbenzensulfonamide (Ie). Yield 70%; yellow solid, mp 239–241°C; IR (ν, cm^{-1}): 3311 (N–H); 3083 (aromatic C–H); 2962, 2891 (aliphatic C–H); 1665 (C=O); 1600 (C=N); 1521 (NO_2 asymmetric stretching band); 1341 (SO_2 asymmetric stretching band); 1158 (SO_2 symmetric stretching band); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.39 (s, 3H, H_B); 7.04 (t, 1H, J_1 = 6.8 Hz, J_2 = 6.8 Hz, H_H); 7.11 (d, 2H, J = 8.0 Hz, H_F); 7.24 (t, 2H, J_1 = 7.6 Hz, J_2 = 8.0 Hz, H_G); 7.82–8.13 (m, 6H, H_C, H_D and H_I); 8.35 (d, 2H, J = 6.8 Hz, H_J); 10.34 (s, 1H, H_E); 11.19 (s, 1H, H_A); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 15.19 (C_2); 120.73, 123.90, 124.71, 127.31, 129.66, 130.04, 130.98 (C_4, C_5, C_8, C_9, C_{14}, C_{15}); 135.11, 137.97, 140.08, 140.44, 142.32 (C_3, C_6, C_7, C_{10}, C_{13}); 151.38 (C_{16}); 154.83 (C_1); 163.23 (C_{12}); MS (*m/z*) (%): 436.6 [M^{-1}]; UV-Vis (DMSO, λ_{max}, nm): 300; Anal. calc. for $C_{21}H_{18}N_4O_5S$: C, 57.53; H, 4.14; N, 12.78; S, 7.31%; found: C 56.99; H, 4.01; N, 12.79; S, 7.42%.

***N*-(4-(2-(1-(4-(*N*-Phenylsulfamoyl)phenyl)-ethyliden)-hydrazinocarbonyl)phenyl)benzamide (If).** Yield 77%; white solid, mp 259–261°C; IR (ν, cm^{-1}): 3345, 3280 (N–H); 3029 (aromatic C–H); 2918, 2846 (aliphatic C–H); 1654 (C=O); 1591 (C=N); 1339 (SO_2 asymmetric stretching band); 1161 (SO_2 symmetric stretching band); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.38 (s, 3H, H_B); 7.04 (t, 1H, J_1 = 7.2 Hz, J_2 = 7.6 Hz, H_H); 7.11 (d, 2H, J = 8.4 Hz, H_F); 7.24 (t, 2H, J_1 = 8.4 Hz, J_2 = 7.2 Hz, H_G); 7.56 (t, 2H, J_1 = 6.8 Hz, J_2 = 7.6 Hz, H_M); 7.63 (t, 1H, J_1 = 7.6, J_2 = 7.2 Hz, H_N); 7.80 (d, 2H, H_C); 7.93–8.00 (m, 8H, H_D, H_I, H_J and H_L); 10.33 (s, 1H, H_E); 10.51 (s, 1H, H_K); 10.80 (s, 1H, H_A); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 14.73 (C_2); 119.83, 120.72, 121.35, 124.70, 127.29, 127.45, 128.06, 128.78, 129.66 (C_4, C_5, C_{19}, C_8, C_9, C_{14}, C_{21}, C_{20}, C_{15}); 132.31, 134.56, 135.11, 136.60, 138.03, 140.14, 140.71 (C_3, C_6, C_7, C_{10}, C_{13}, C_{16}, C_{18}); 142.67 (C_1); 164.22 (C_{12}); 165.84 (C_{17}); MS (*m/z*) (%): 510.7 [M^{-2}]; UV-Vis (DMSO, λ_{max}, nm): 315, 278; Anal. calc. for $C_{28}H_{24}N_4O_4S$: C, 65.61; H, 4.72; N, 10.93; S, 6.26%; found: C, 64.76; H, 4.59; N, 11.04; S, 6.10%.

4-(1-(2-(2-Hydroxy-2,2-diphenylacetyl)hydrazono)-ethyl)-*N*-phenylbenzensulfon-amide (Ig). Yield 85%; orange solid, mp 228–231°C; IR (ν, cm^{-1}): 3268 (N–H); 3082, 3020 (aromatic C-H); 2972 (aliphatic C–H); 1650 (C=O); 1600 (C=N); 1342 (SO_2 asymmetric stretching band); 1166 (SO_2 symmetric stretching band); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.38 (s, 3H, H_B); 7.04 (t, 1H, J_1 = 7.6 Hz, J_2 = 7.6 Hz, H_H); 7.09 (d, 2H, J = 8.0 Hz, H_F); 7.23 (t, 2H, J_1 = 7.2 Hz, J_2 = 7.2 Hz, H_G); 7.29–7.38 (m, 10H, H_L, $H_{L'}$, H_K, $H_{K'}$, H_J and $H_{J'}$); 7.80 (d, 2H, J = 8.0 Hz, H_C); 7.94 (d, 2H, J = 8.0 Hz, H_D); 10.32 (s, 1H, H_E); 10.49 (s, 1H, H_A); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 13.83 (C_2); 81.16 (C_{13}); 120.83,

124.75, 127.30, 127.53, 127.85, 127.99, 128.23, 129,64 (C_4, C_5, C_8, C_9, C_{15}, C_{16}, C_{17}); 135.83, 137.97, 140.32, 142.40, 143.87 (C_3, C_6, C_7, C_{10}, C_{14}); 152.85 (C_1); 169.36 (C_{12}); MS (*m/z*) (%): 500.6 [M^{+1}]; UV-Vis (DMSO, λ_{max}, nm): 295; Anal. calc. for $C_{28}H_{25}N_3O_4S$: C, 67.32; H, 5.04; N, 8.41; S, 6.42%; found: C, 66.36; H, 5.00; N, 8.48; S, 6.12%.

4-(4-(1-(2-Benzoylhydrazono)ethyl)phenylsulfonamido)benzoic acid (IIa). Yield 48%; white solid, mp 244–246°C; IR (ν, cm^{-1}): 3327 (N–H); 3042 (aromatic C–H); 2931, 2864 (aliphatic C–H); 1688, 1652 (C=O); 1606 (C=N); 1335 (SO_2 asymmetric stretching band); 1158 (SO_2 symmetric stretching band); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.36 (s, 3H, H_B); 7.21 (d, 2H, J = 8.4 Hz, H_F); 7.52 (t, 2H, J_1 = 7.2 Hz, J_2 = 8.0 Hz, H_J); 7.59 (t, 1H, J_1 = 7.6 Hz, J_2 = 7.6 Hz, H_K); 7.81 (d, 2H, J = 8.4 Hz, H_G); 7.88–8.11 (m, 6H, H_C, H_D and H_I); 10.90 (s, 2H, H_A and H_E); 12.77 (s, 1H, H_H); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 14.75 (C_2); 118.76, 127.31, 127.64, 128.71, 129.6, 131.23, 132.05 (C_4, C_5, C_8, C_9, C_{14}, C_{15}, C_{16}); 126.23, 134.40, 139.90, 142.31, 142.91 (C_3, C_6, C_7, C_{10}, C_{13}); 146.78 (C_1); 1623.44 (C_{12}); 167.18 (C_{11}); MS (*m/z*) (%): 438.0 [M^{+1}]; UV-Vis (DMSO, λ_{max}, nm): 305, 279; Anal. calc. for $C_{22}H_{19}N_3O_5S$: C, 60.40; H, 4.38; N, 9.61; S, 7.33%; found: C, 60.15; H, 4.37; N, 9.18; S, 7.39%.

4-(4-(1-(2-Isonicotinoylhydrazono)ethyl)phenylsulfonamido)benzoic acid (IIb). Yield 41%; white solid, mp 288–290°C; IR (ν, cm^{-1}): 3364 (N–H); 3075 (aromatic C–H); 2966 (aliphatic C–H); 1687, 1656 (C=O); 1606 (C=N); 1338 (SO_2 asymmetric stretching band); 1161 (SO_2 symmetric stretching band); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.38 (s, 3H, H_B); 7.22 (d, 2H, J = 7.6 Hz, H_F); 7.81–7.83 (m, 4H, H_G and H_C); 7.89 (d, 2H, J = 8.0 Hz, H_D); 8.03 (d, 2H, J = 8.0 Hz, H_I); 8.78 (d, 2H, J = 8.0 Hz, H_J); 10.90 (s, 1H, H_E); 11.14 (s, 1H, H_A); 12.79 (s, 1H, H_H); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 15.11 (C_2); 118.79, 122.43, 123.39, 126.24, 127.35, 127.87, 131.25, (C_4, C_5, C_8, C_9, C_{10}, C_{14}); 140.20, 141.42, 142.62, 142.94 (C_3, C_6, C_7, C_{13}); 147.68 (C_1); 150.57 (C_{15}); 163.37 (C_{12}); 167.20 (C_{11}); MS (*m/z*) (%): 439.0 [M^{+1}]; UV-Vis (DMSO, λ_{max}, nm): 305, 279; Anal. calc. for $C_{21}H_{18}N_4O_5S$: C, 57.53; H, 4.14; N, 12.78; S, 7.31%; found: C, 56.85; H, 3.94; N, 12.71; S, 7.25%.

4-(4-(1-(2-(4-Fluorobenzoyl)hydrazono)ethyl)phenylsulfonamido)benzoic acid (IIc). Yield 69%; white solid, mp 239–241°C; IR (ν, cm^{-1}): 3264 (N–H); 3073 (aromatic C–H); 2824 (aliphatic C–H); 1675, 1657 (C=O); 1604 (C=N); 1336 (SO_2 asymmetric stretching band); 1160 (SO_2 symmetric stretching band); 1H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.36 (s, 3H, H_B); 7.22 (d, 2H, J = 8.4 Hz, H_F); 7.34 (t, 2H, J_1 = 8.8 Hz, J_2 = 8.8 Hz, H_J); 7.82 (d, 2H, J = 8.4 Hz, H_G); 7.87 (d, 2H, J = 8.4 Hz, H_C); 7.94–7.96 (m, 4H, H_D and H_I); 10.84 (s, 2H, H_A and H_E); 12.73 (s, 1H, H_H); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 14.78 (C_2); 115.58, 118.75, 118.88, 126.23, 127.33, 127.65, 129.64, 131.24 (C_4, C_5, C_8, C_9, C_{10}, C_{14}, C_{15}); 130.90, 139.91, 142.39, 142.86 (C_3, C_6, C_7, C_{13}); 145.52 (C_1); 164.17 (C_{16}); 166.50 (C_{12}); 167.18 (C_{11}); MS (*m/z*) (%): 457.1 [M^{+2}]; UV-Vis (DMSO, λ_{max}, nm): 305, 279; Anal. calc. for $C_{22}H_{18}FN_3O_5S$: C, 58.02; H, 3.98; N, 9.23; S, 7.04%; found: C, 57.81; H, 3.91; N, 8.51; S, 6.92%.

4-(4-(1-(2-(4-Chlorobenzoyl)hydrazono)ethyl)phenylsulfonamido)benzoic acid (IId). Yield 45%; white solid, mp 276–278°C; IR (ν, cm^{-1}): 3260 (N–H); 3080 (aromatic C–H); 2953, 2829 (aliphatic C–H); 1674, 1663 (C=O); 1607 (C=N); 1336 (SO_2 asymmetric stretching band); 1160 (SO_2 symmetric stretching band); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.36 (s, 3H, H_B); 7.22 (d, 2H, J = 8.4 Hz, H_F); 7.59 (d, 2H, J = 8.4 Hz, H_J); 7.81 (d, 2H, J = 8.8 Hz, H_G); 7.88–8.09 (m, 6H, H_C, H_D and H_I); 10.92 (s, 2H, H_A and H_E); 12.78 (s, 1H, H_H); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 15.47 (C_2); 119.31, 126.77, 127.90, 128.23, 129.35, 131.07 (C_4, C_5, C_8, C_9, C_{10}, C_{14}, C_{15}); 131.79, 140.60, 142.81, 143.34 (C_3, C_6, C_7, C_{13}); 146.09 (C_1); 167.74 (C_{11}); MS (*m/z*) (%): 473.0 [M^{+1}]; UV-*Vis* (DMSO, λ_{max}, nm): 305, 284; Anal. calc. for $C_{22}H_{18}ClN_3O_5S$: C, 55.99; H, 3.84; N, 8.90; S, 6.79%; found: C, 55.43; H, 3.71; N, 8.87; S, 6.87%.

4-(4-(1-(2-(4-Nitrobenzoyl)hydrazono)ethyl)phenylsulfonamido)benzoic acid (IIe). Yield 49%; yellow solid, mp 281–283°C; IR (ν, cm^{-1}): 3325 (N–H); 3108, 3047 (aromatic C–H); 2935, 2869 (aliphatic C–H); 1682, 1665 (C=O); 1603 (C=N); 1336 (SO_2 asymmetric stretching band); 1157 (SO_2 symmetric stretching band); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.38 (s, 3H, H_B); 7.22 (d, 2H, J = 7.6 Hz, H_F); 7.81 (d, 2H, J = 7.6 Hz, H_G); 7.89–8.13 (m, 6H, H_C, H_D and H_I); 8.35 (d, 2H, J = 8.4 Hz, H_J); 10.87 (s, 1H, H_E); 11.19 (s, 1H, H_A); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 15.15 (C_2); 118.78, 123.89, 126.23, 127.35, 127.53, 127.82, 129.63, 130.05, 131.23 (C_4, C_5, C_8, C_9, C_{10}, C_{14}, C_{15}); 140.20, 142.29, 142.62 (C_3, C_6, C_7); 149.66 (C_{16}); 154.66 (C_1); 163.26 (C_{12}); 167.17 (C_{11}); MS (*m/z*) (%): 480.6 [M^{-1}]; UV-Vis (DMSO, λ_{max}, nm): 354, 319, 285; Anal. calc. for $C_{22}H_{18}N_4O_7S$: C, 54.77; H, 3.76; N, 11.61; S, 6.65%; found: C, 54.12; H, 3.81; N, 11.27; S, 6.55%.

4-(4-(1-(2-(4-Benzamidobenzoyl)hydrazono)-ethyl)phenylsulfonamido)benzoic acid (IIf). Yield 78%; white solid, mp 291–293°C; IR (ν, cm^{-1}): 3354,

3308 (N–H); 3029 (aromatic C–H); 2918 (aliphatic C–H); 1680, 1656 (C=O); 1607 (C=N); 1347 (SO_2 asymmetric stretching band); 1163 (SO_2 symmetric stretching band); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.38 (s, 3H, H_B); 7.22 (d, 2H, J = 8.8 Hz, H_F); 7.56 (t, 2H, J_1 = 7.6 Hz, J_2 = 7.2 Hz, H_M); 7.63 (t, 1H, J_1 = 7.2 Hz, J_2 = 7.2 Hz, H_N); 7.82 (d, 2H, J = 8.4 Hz, H_J); 7.88 (d, 2H, J = 8.0 Hz, H_G); 7.93–8.00 (m, 8H, H_C, H_D, H_I and H_L); 10.52 (s, 1H, H_E); 10.81 (s, 1H, H_A); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 14.73 (C_2); 118.74, 119.82, 120.72, 126.21, 127.33, 127.61, 128.24, 128.92, 131.25 (C_4, C_5, C_8, C_9, C_{10}, C_{14}, C_{15}, C_{19}, C_{20}); 132.31, 133.14, 135.10, 135.17, 139.95, 142.32, 142.97 (C_3, C_6, C_7, C_{13}, C_{16}, C_{18}, C_{21}); 145.99 (C_1); 164.33 (C_{17}); 166.34 (C_{12}); 167.19 (C_{11}); MS (*m/z*) (%): 556.8 [M^{+1}]; UV-Vis (DMSO, λ_{max}, nm): 315, 279; Anal. calc. for $C_{29}H_{24}N_4O_6S$: C, 62.58; H, 4.35; N, 10.07; S, 5.76%; found: C, 61.75; H, 4.27; N, 10.16; S, 5.88%.

4-(4-(1-(2-(2-Hydroxy-2,2-diphenylacetyl)hydrazono)ethyl)phenylsulfonamido)benzoic acid (IIg). Yield 78%; orange solid, mp 111–113°C; IR (ν, cm^{-1}): 3345 (N–H); 3057 (aromatic C–H); 2952 (aliphatic C–H); 1682, 1606 (C=O); 1606 (C=N); 1335 (SO_2 asymmetric stretching band); 1156 (SO_2 symmetric stretching band); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.38 (s, 3H, H_B); 7.19–7.24 (m, 3H, H_F and H_I); 7.29–7.44 (m, 10H, H_L, $H_{L'}$, H_K, $H_{K'}$, H_J and $H_{J'}$); 7.80 (d, 2H, J = 8.4 Hz, H_G); 7.86 (d, 2H, J = 8.4 Hz, H_C); 7.97 (d, 2H, J = 8.4 Hz, H_D); 10.49 (s, 1H, H_E); 10.86 (s, 1H, H_A); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 13.80 (C_2); 118.84, 126.27, 127.33, 127.71, 127.84, 127.99, 128.23, 131.22 (C_4, C_5, C_8, C_9, C_{10}, C_{15}, C_{16}, C_{17}); 140.10, 142.25, 142.49, 143.86 (C_3, C_6, C_7, C_{13}); 152.72 (C_1); 167.17 (C_{12}); 169.37 (C_{11}); MS (*m/z*) (%): 541.8 [M^{-2}]; UV-Vis (DMSO, λ_{max}, nm): 295, 278; Anal. calc. for $C_{29}H_{25}N_3O_5S$: C, 64.08; H, 4.64; N, 7.73; S, 5.90%; found: C, 61.46; H, 4.59; N, 7.58; S, 5.81%.

4-(4-(1-(2-(4-Bromobenzoyl)hydrazono)ethyl)phenylsulfonamido)benzoic acid (IIh). Yield 70%; white solid, mp 287–289°C; IR (ν, cm^{-1}): 3262 (N–H); 3073 (aromatic C–H); 2951, 2829 (aliphatic C–H); 1674, 1662 (C=O); 1607 (C=N); 1336 (SO_2 asymmetric stretching band); 1160 (SO_2 symmetric stretching band); ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) δ (ppm): 2.36 (s, 3H, H_B); 7.22 (d, 2H, J = 7.6 Hz, H_F); 7.73 (d, 2H, J = 6.8 Hz, H_J); 7.81–8.01 (m, 8H, H_C, H_D, H_I and H_G); 10.92 (s, 2H, H_A and H_E); 12.77 (s, 1H, H_H); ^{13}C NMR (100 MHz) (DMSO-d_6/TMS) δ (ppm): 14.90 (C_2); 118.77, 126.25, 126.54, 127.34, 127.66, 130.68, 131.24 (C4, C_{16}, C_5, C_8, C_9, C_{10}, C_{14}, C_{15}); 131.7, 139.99, 142.29, 142.80 (C_3, C_6, C_7, C_{13}); 148.02 (C_1); 164.01 (C_{12}); 167.18 (C_{11}); MS (*m/z*) (%): 516.6 [M^{+1}]; UV-*Vis* (DMSO, λ_{max}, nm): 305, 279; Anal. calc. for $C_{22}H_{18}BrN_3O_5S$: C, 51.17; H, 3.51; N, 8.14; S, 6.21%; found: C, 50.63; H, 3.39; N, 8.20; S, 6.12%.

Biological Activity

Determination of antioxidant activity. The antioxidant activity was measured using four complementary assays. The β-carotene-linoleic acid assay differs from the others in that the antioxidant gives to media the hydrogen radical. In this assay, the antioxidant compound also scavenges the singlet oxygen and also transfers electrons to stop the radicalic degradation. Therefore, β-carotene-linoleic acid assay, lipid peroxidation inhibitory activity, is called total antioxidant activity. In the DPPH, ABTS, and CUPRAC assays, however, the antioxidant can transfer only electrons to neutralize the radical.

The lipid peroxidation inhibitory activity of the compounds was evaluated using the β-carotene-linoleic acid assay [56]. For this test, 25 L of linoleic acid, and 200 mg of Tween 40 emulsifier were added to 1 mL of chloroform containing 0.5 mg β-carotene. The chloroform solvent was evaporated under vacuum, and 100 mL of distilled water saturated with oxygen was added by vigorous shaking. One hundred and sixty microliters of this mixture were delivered into each well containing 40 μL of different concentrations of the compounds dissolved in DMSO. The zero-time absorbance was measured at 470 nm after the said emulsion was added to each well in a microplate reader. The emulsion system was kept at 50°C in an oven. The absorbance was read until the color disappeared in control wells by controlling in every 30 minutes. A blank, devoid of β-carotene, was prepared for background subtraction. BHT and α-tocopherol were used as positive standards to compare the activity.

The bleaching rate (R) of β-carotene was calculated according to the following equation:

$$\text{Bleaching rate (R): } \ln(a/b)/t,$$

where, ln = natural log, a = absorbance at time zero, b = absorbance at time t (120 min). The antioxidant activity (AA) was calculated in terms of percent inhibition relative to the control, using the following equation:

$$\text{Antioxidant activity (AA)}:$$
$$[(A_{control} - A_{compound})/A_{control}] \times 100.$$

Then results were given as IC_{50} μg/mL corresponding the concentration which protects 50% of β-carotene amount [39–42, 57].

The ABTS cation radical scavenging activity was determined spectrophotometrically [46] with slight modifications [39–42, 57]. The $ABTS^{\bullet+}$ was obtained by the reaction of 7 mM ABTS dissolved in H_2O with 2.45 mM potassium persulfate. The mixture was

stored in the dark at room temperature for 12 h. The radical cation was stable in this form for more than 2 days if stored in the dark at room temperature. To test the activity of the compounds, the prepared radical solution was diluted to get an absorbance of 0.700 ± 0.025 at 734 nm with ethanol for one cm cell length. Then, 160μL of the radical solution was added to 40 μL of compound solution dissolved in DMSO at different concentrations (5–50 μg/mL). After 10 min, the percentage inhibition at 734 nm was calculated for each concentration relative to a blank absorbance (methanol). Lower absorbance of the reaction mixture indicated higher free radical-scavenging activity. A blank, devoid of ABTS solution was prepared for background subtraction. BHT and α-tocopherol were used as positive standards to compare the activity.

The ability to scavenge the ABTS cation radical was calculated by using the following equation:

$$\text{ABTS cation radical scavenging activity (AA)}: \left[\left(A_{control} - A_{compound}\right)/A_{control}\right] \times 100.$$

Then results ABTS assay was given as IC_{50} μg/mL corresponding to the concentration, which scavenges 50% of ABTS cation radical.

DPPH free radical-scavenging activity of the extracts of compounds was determined using the DPPH radical [39, 44]. DPPH absorbs at 517 nm in its radical form. However, if reduced by an antioxidant transfer electron, its absorption at 517 nm decreases. To test the compounds in this assay, 0.1 mM DPPH solution was prepared in ethanol. 160 μL of this solution was added to 40 μL of compound solutions dissolved in DMSO at different concentrations. The 96 well plates were kept in the dark place. Thirty minutes later, the absorbance was measured at 517 nm. Lower absorbance of the reaction mixture indicated higher free radical-scavenging activity. A blank, devoid of DPPH solution was prepared for background subtraction. BHT and α-tocopherol were used as positive standards to compare the activity.

The ability to scavenge the DPPH radical was calculated by using the following equation:

$$\text{DPPH free radical scavenging activity (AA)}: \left[\left(A_{control} - A_{compound}\right)/A_{control}\right] \times 100.$$

Then results of DPPH assay were given as IC_{50} μg/mL corresponding to the concentration, which scavenges 50% of DPPH free radical.

The cupric reducing antioxidant capacity of the compounds was determined to see the reduction potential of the compounds. This method is based on the measurement of absorbance at 450 nm by the formation of a stable complex between neocuproine and copper (**I**), which is formed by the reduction of copper (**II**) in the presence of antioxidant [39, 48]. To test the cupric reducing antioxidant capacity of the compounds, 40 μL each of 10 mM Cu (II), 7.5 mM neocuprine, and NH_4Ac buffer (1 M, pH 7.0) solutions were added to 40 μL ml of compound solutions dissolved in DMSO at different concentrations. The 96 well plates were kept at room temperature for one hour. Then the absorbance at 450 nm was recorded against a blank. BHT and α-tocopherol were used as positive standards to compare the activity.

Then results of CUPRAC assay were given as $A_{0.50}$ μg/mL corresponding to the concentration of 0.500 absorbances at graph drawn absorbance versus concentration.

Determination of anticholinesterase activity. The Ellman method was used to measure acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activity [57, 58]. The commercial AChE from electric eel and BChE from horse serum were employed. As substrates of the enzymes, acetylthiocholine iodide and butyrylthiocholine chloride were utilized. 5,5'-dithio-bis(2-nitrobenzoic)acid (DTNB) was made use of for measurement of activity as a coloring reagent. To dissolve the compounds, ethanol solvent was used. To test the activity, 10 μL of sample solution dissolved in ethanol at different concentrations and 20 μL AChE (5.32×10^{-3} U) or BChE (6.85×10^{-3} U) enzyme dissolved in buffer were added to 150 μL of 100 mM sodium phosphate buffer (pH 8.0). Then incubated for 15 min at 25°C. After incubation, 10 μL of 0.5 mM DTNB were added, and the reaction was started by addition of 10 μL of acetylthiocholine iodide (0.71 mM) or butyryl-thiocholine chloride (0.2 mM). The measurement was monitored spectrophotometrically by the formation of yellow 5-thio-2-nitrobenzoate anion, as the result of the reaction of DTNB with thiocholine at 412 nm wavelength using a 96-well microplate reader (SpectraMax PC340, Molecular Devices, USA). Percentage of inhibition of AChE or BChE was determined by comparison of reaction rates of samples relative to blank sample (ethanol in phosphate buffer, pH 8) using the formula $(E - S)/E \times 100$, where E is the activity of enzyme without test compound, and S is the activity of the enzyme with a test compound. Galantamine was used as a reference compound [58].

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving human participants performed by any of the authors and does not contain any studies involving animals performed by any of the authors.

Conflict of Interests

The authors declare that they have no conflicts of interests.

SUPPLEMENTARY MATERIALS

Supplementary materials are available for this article at https://doi.org/10.1134/S1068162020050052 and are accessible for authorized users.

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