Hindawi Publishing Corporation
Advances in Chemistry
Volume 2014, Article ID 961076, 5 pages
http://dx.doi.org/10.1155/2014/961076

Research Article

Heteroring Annulated Benzimidazolinone Condensed Azepinone Derivatives: A New Class of Highly Potent Antioxidants

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Received 22 April 2014; Revised 29 June 2014; Accepted 1 July 2014; Published 20 July 2014

Academic Editor: Bor-Sen Wang

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A new class of benzimidazolinone condensed azepinone derivatives annulated on its face "d" with pyrazole, isoxazole, pyrimidine, benzodiazepine, and benzothiazepine nucleus in **3–8**, respectively, have been evaluated for their antioxidant activity by DPPH method. Results indicate these to belong to a novel class of highly potent antioxidant agents.

1. Introduction

Azepinone template has emerged as a potent privileged structural fragment in synthesis, due to its broad pharmacological spectrum and its affinity to various biotargets [1]. On account of this feature, the combination of its nucleus with other heterocycles which have a proven record of biological potential has been a promising approach to the "drug like molecule build-up" in medicinal chemistry.

Recent synthetic endeavours directed towards the development of biologically important materials have stressed the need to identify certain building block set in synthesis and to explore their potential to provide access to the library of compounds of medicinal utility. We envisioned that this concept could be applied in our synthetic work by utilizing the potential of a novel building block developed from the benzimidazolinone condensed analogue of azepinone **2** which could be realized in two simple steps from benzimidazolinone nucleus involving first its reaction with succinic anhydride followed by its cyclocondensation with acid. We utilized the inherent potential of this building block in heteroannulation of its face "d" with such heterocyclic scaffolds as pyrazole, isoxazole [1–3], pyrimidine [4], benzodiazepine [5], and benzothiazepine [6] which had the previous history of being highly biologically active in the literature.

The synthesis of the heterocyclic materials **3–8** shown in Scheme 1, each having a benzimidazolinone pharmacophore fused on to one side of the azepinone framework and a wide range of biologically active heterocyclic scaffolds on to its other side, was conceived in the present work on this anticipation that their presence together, in the same molecular framework, could bring a favorable impact on to overall antioxidant activity in resulting materials.

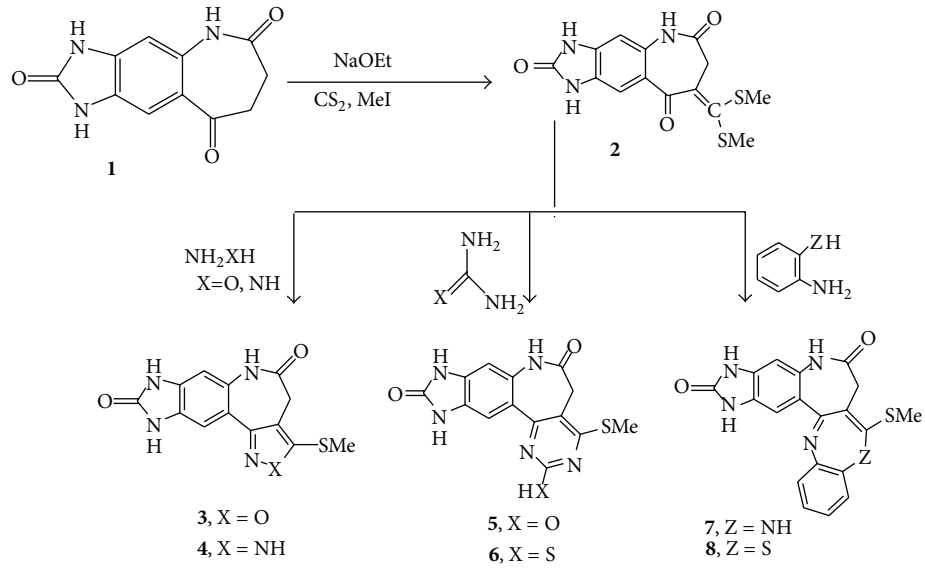
As per to this expectations, compounds **1–8** responded fairly well in showing a remarkably high level of antioxidant activity.

2. Results and Discussion

Results emanated from antioxidant studies of few selected compounds have been presented in Table 1. Perusal of results realized that the compounds analysed have exhibited moderate to good activity when compared with standard ascorbic acid. It has been observed that amongst the selected compounds, **1**, **3**, **4**, and **5** showed almost 90% inhibition at 50 μg/mL concentration level, and these results are almost comparable to the standard ascorbic acid which also showed 90.28% inhibition at the same concentration. The IC50 values of synthesized compounds were found in the range of 20.64 to 196.85 μg/mL.

The results revealed that compound **5** was the most potent (IC50 20 μg/mL) which reached more close to ascorbic acid value (16.45 μg/mL).

A positive impact which the pyrazole, isoxazole, and the privileged nucleus of pyrimidine, benzodiazepine, benzothiazepine, and so forth, have shown to inherit on the overall



Scheme 1

Table 1

Compound number	Concentration	Percent inhibition	IC50
1	5	78.85	196.85
	25	80.01	
	50	85.05	
2	5	19.03	125.50
	25	21.01	
	50	30.82	
3	5	77.06	88.63
	25	80.05	
	50	89.46	
4	5	77.88	169.06
	25	81.01	
	50	85.08	
5	5	65.94	20.64
	25	71.08	
	50	89.94	
6	5	74.51	92.88
	25	70.06	
	50	61.78	
7	5	71.46	131.38
	25	75.28	
	50	78.67	
8	5	71.46	137.75
	25	76.88	
	50	78.67	

activity of the molecules, in which these are present, provided an impetus to us in the present work, to append these pharmacophores on to the benzimidazolinone condensed azepinone nucleus **2** with the aim to develop a newer series of the heteroring annulated analogues **3**–**8**, respectively (Scheme 1). There has been considerable interest on the heterocyclic systems bearing such pharmacophoric scaffolds in their molecules, with regard to their chemistry and the pharmacological activity.

Literature is replete with a wide variety of examples of one pot synthesis of heterocyclic systems bearing five, six, and seven membered rings from the corresponding oxoketene dithioacetals derivatives [5, 7].

In view of the generality and versatility which the oxoketene dithioacetals show in synthesis, eversince to their discovery, the generality and versatility which the oxoketenedithioacetals have shown in synthesis, have caused them to remain in the mainstay as evergreen synthons in synthesis. Their application has been so mammoth and multidimensional that their importance in synthesis can never be overstated.

The oxoketene dithioacetals derivative **2** was realized by a simple base catalysed reaction of **1** with CS_2 and CH_3I. Treatment of **2** with hydroxylamine hydrochloride and hydrazine hydrate furnished the corresponding isoxazole and pyrazole annulated analogues **3** and **4**, respectively.

A similar reaction of **2** with urea and thiourea formed the corresponding pyrimido annulated analogues **5** and **6**, respectively. In view of the wide spectrum of biological activity of the privileged nucleus of benzodiazepines and benzothiazepines, we considered it of interest to append another nitrogen (and sulphur) containing seven membered on to the face "d" of the azepinone nucleus, by reacting **2** with O-phenylenediamine and O-aminothiophenol which afforded **7** and **8**, respectively. The analytical and spectral (IR, ^{1}HNMR, ^{13}CNMR, and MS) data were found to be consistent with the structures assigned to the compounds.

3. Antioxidant Activity

DPPH radical scavenging antioxidant [8, 9] activity was evaluated based on the percentage inhibition of DPPH which was employed as standard.

4. DPPH Radical Scavenging Assay

The radical in the 1,1-diphenyl-1-picrylhydrazyl (DPPH) gives a strong absorption maximum at 517 nm and is purple in color. The absorbance of DPPH reduces, when the radical of the DPPH becomes paired with an electron or acceptance of the hydrogen radical from the antioxidant. 1 mL solution of the various concentrations of the test compounds (5, 25, and 50 μg/mL) in methanol were used to make homogeneous solution. After making desired concentration, methanol added 2.5 mL solution of DPPH was applied on each test tube by using pipette. The room temperature was recorded and the test tube was incubated at 27°C for 30 min to complete the reaction. The absorbance was read against blank at 517 nm. Decrease in the absorbance of DPPH solution indicated an increase in the radical scavenging activity. The DPPH solution without sample was used as control. Ascorbic acid was used as standard. The experiments were carried out in triplicate. Percentage inhibition was calculated using following formula:

$$\% \text{ Inhibition} = \frac{\text{Control} - \text{Sample}}{\text{Control}} \times 100. \quad (1)$$

DPPH radical scavenging activities of compounds **1**–**8** tested in doses 5, 50, and 250 μg/mL and were expressed as percent of inhibition Table 1.

We have considered the concentration in the range of 5, 25, and 50 μg/mL to obtain a straight line to calculate the IC50 values of the test materials.

5. Conclusion

In summary, in a quest to develop a newer series of antioxidant agents from azepinone derivatives, we used its benzimidazolinone fused analogue as a building block, in the heteroannulation of this nucleus with such heterocyclic scaffolds as pyrazole, isoxazole, pyrimidine, benzodiazepine, and benzothiazepine which had the previous history of being highly biologically active. Interesting results emanated on the evaluation of the antioxidant activity of this new class of compounds.

6. Experimental

*6.1. Preparation of 8-(Bis(methylthio)methylene)-7,8-dihydroazepino[2,3-f]benzimidazole-2,6,9(1H,3H,5H)-trione **(2)**.* To a mixture of 7,8-dihydroazepino[2,3-f]benzimidazole-2,6,9(1H,3H,5H)-trione **(1)** (2.31 g, 0.01 mol) and CS_2 (1.0 mL, 0.006 mol) was added to a well stirred and cold suspension of t-BuOK (2.24 g, 0.02 mol) in dry benzene (5.0 mL) and DMF (5.0 mL). The reaction mixture was allowed to stand at room temperature for 4 h. Methyl iodide (2.82 mL, 0.02 mol) was gradually added with stirring and external cooling (exothermic reaction). The reaction mixture was allowed to stand for further 4 h. at room temperature with occasional shaking. It was, then, refluxed on a water bath for 3 h. The mixture was poured on to the crushed ice and the benzene layer was collected. The aqueous portion was extracted with benzene and the combined extracts were washed, with water dried over anhydrous sodium sulphate. The solvent was removed by distillation. The product **2** thus obtained was recrystallized from ethanol (1.52 g, yield 66%), m.p. 110–20°C. IR (KBr) cm^{-1}: 3230 (NH str.), 2949 (C–H str. ArH), 1731 (C=O str.), 1685 (C=O str.), 1670 (C=O str.), 1690 (C=C unsaturated), 1580 (C=C str. ArH), 1455 (C–H str. $-CH_3$), 1020 (C–N str.), 680 (C–S str.); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δppm: 8.30 (1H, s, CH), 8.09 (1H, s, CH), 8.0 (1H, s, NH), 6.0 (1H, s, NH), 2.90 (2H, s, CH_2), 2.80 (3H, s, CH_3); C^{13}NMR ($CDCl_3$ + DMSO-d_6) δppm: 13.5 (CH_3); 27.4 (CH_2, azepinone); 113, 121.3 (CH, arene); 124.1, 126.4, 135.4, 137.2 (C, arene); 146.8, 160.8 (C=C); 152.2 (C=O, imidazolone); 168.2, 179 (C=O, azepinone); MS m/z (percent abundance): (M^+): 335.04 (25%), 134 (100%), 294.04 (66%), 149 (56%), 204 (75%), 44 (88%) Analytical data Calcd./found for $C_{14}H_{13}N_3O_3S_2$: C, 50.12/50.43, H, 3.90/3.94, N, 12.51/12.33, S, 19.11/19.41.

*6.2. Preparation of 3-(Methylthio)-8,10-dihydro-2H-benzimidazolo [5,6-b]isoxazolo[3,4-d]azepine-5,9(4H,6H)-dione **(3)**.* To hydroxylamine hydrochloride (2.78 g, 0.04 mol) in absolute methanol (10.0 mL) was added to sodium methoxide (2.28 g, 0.04 mol) in absolute methanol (25.0 mL) and the mixture was stirred for 10 min. 8-(bis(methylthio)methylene)-7,8-dihydroazepino[2,3-f]benzimidazole-2,6,9(1H,3H,5H)-trione **(2)** (1.34 g, 0.004 mol) was added and the mixture was refluxed for 5 h. Most of the methanol was evaporated under reduced pressure and the mixture was poured into ice-cold water. The solid separated was filtered and recrystallized to give **3** from ethanol (0.84 g, yield 63%), m.p. 276–78°C. IR (KBr) cm^{-1}: 3310 (NH str.), 2965 (C–H str. ArH), 1700 (C=O str.), 1680 (C=O), 1590 (C=C str. ArH), 1540 (C=N), 1425 (C–H str. $-CH_3$), 1115 (C–N str.), 890 (C–O–N str.), 700 (C–S str.); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δppm: 8.17 (1H, s, CH), 8.03 (1H, s, CH), 8.0 (1H, s, NH), 6.0 (1H, s, NH), 3.49 (2H, s, CH_2), 2.53 (3H, s, CH_3); C^{13} NMR ($CDCl_3$ + DMSO-d_6) δppm: 18.9 (CH_3); 22 (CH_2, azepinone); 100, 150 (C, isoxazolo azepinone); 113, 119.3 (CH, arene); 124.1, 126.4, 130.4, 135.2 (C, arene); 152.2 (C=O, imidazolone); 158.9 (C, isoxazole); 168.2 (C=O, azepinone); MS m/z (percent abundance): (M^+): 302.31 (95%), (M^++2): 304.31 (4.5%), 256.22 (100%), 243 (80%), 215.21 (52%), 149.15 (70%), 68.08 (19%). Analytical data Calcd./found for $C_{13}H_{10}N_4O_3S$: C, 51.65/51.58, H, 3.33/3.38, N, 18.53/18.72, S, 10.61/10.56.

*6.3. Preparation of 3-(Methylthio)-8,10-dihydro-2H-benzimdazolo[5,6-b]pyrazolo[3,4-d]azepine-5,9(4H,6H)-dione **(4)**.* To a solution of 8-(bis(methylthio)methylene)-7,8-dihydroazepino[2,3-f]benzimidazole-2,6,9(1H,3H,5H)-trione **(2)** (1.34 g, 0.004 mol) in ethanol was added hydrazine hydrate (3.2 mL, 0.10 mol). The solution was heated under reflux for 3 h. The resulting mixture was poured in crushed ice and precipitate thus obtained was recrystallized with dichloromethane to give **4**. (1.04 g, yield 78%), m.p. 175–180°C. IR (KBr) cm^{-1}: 3320 (NH str.), 2920 (C–H str. ArH), 1705 (C=O str.), 1680 (C=O), 1590 (C=C str. ArH), 1530 (C=N), 1450 (C–H str. $-CH_3$), 1120 (C–N str.), 680 (C–S str.); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δppm: 12.62 (1H, s, NH),

8.17 (1H, s, CH), 8.03 (1H, s, CH), 8.0 (1H, s, NH), 6.0 (1H, s, NH), 3.49 (2H, s, CH_2), 2.53 (3H, s, CH_3); C^{13} NMR ($CDCl_3$ + DMSO-d_6) δppm: 18.7 (CH_3); 26.7 (CH_2, azepinone); 113, 119.3 (CH, arene); 115, 150 (C, pyrazolo azepinone); 124.1, 126.4, 130.4, 135.2 (C, arene); 134 (C, pyrazole); 152.2 (C=O, imidazolone); 168.2 (C=O, azepinone); MS m/z (percent abundance): (M^+): 301.32 (95%), (M^+ + 2): 303.32 (4.5%), 255.22 (100%), 243 (82%), 215.21 (52%), 149.15 (70%), 69.02 (19%). Analytical data Calcd./found for $C_{13}H_{11}N_5O_2S$: C 51.82/51.91, H, 3.68/3.60, N, 23.24/23.44, S, 10.64/10.82.

6.4. Preparation of 4-(Methylthio)-9,11-dihydrobenzimidazolo[5,6-b]pyrimido[4,5-d]azepine-2,6,10(3H,5H,7H)-trione ***(5)***. To a mixture of urea (0.12 g, 0.002 mol), sodium ethoxide (0.13 g, 0.002 mol) and ethanol (30 mL) were added **2** (0.67 g, 0.002 mol) and the reaction mixture was refluxed for 14 h. The solvent was removed by distillation and residue was treated with glacial acetic acid (7–10 mL just enough to dissolve sodium salt of the pyrimidine) and refluxed for 15 min. The reaction mixture was acidified with AcOH and precipitate obtained was collected and purified by crystallization with ethanol to give **5** (0.46 g, yield 70%), m.p. 190–192°C. IR (KBr) cm^{-1}: 3600 (OH str.), 3345 (NH str.), 2995 (C–H str. ArH), 1735 (C=O str.), 1695 (C=O str.), 1600 (C=C str. ArH), 1532 (C=N str.), 1050 (C–N str.); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δppm: 9.88 (1H, s, OH), 8.24 (1H, s, ArH), 8.17 (1H, s, ArH), 8.0 (1H, s, NH), 6.0 (2H, s, NH), 2.90 (2H, s, CH_2), 2.25 (3H, s, CH_3); C^{13} NMR ($CDCl_3$ + DMSO-d_6) δppm: 11.7 (CH_3); 27.5 (CH_2, azepinone); 89, 164 (C, pyrimidino azepinone); 112, 121.3 (CH, arene); 118.9, 125.8, 132, 137.1 (C, arene); 143 (C, pyrimidine); 152.2 (C=O, imidazolone); 160 (C=O, pyrimidine); 168.2 (C=O, azepinone); MS m/z (percent abundance): (M^+): 329.31 (96%), (M^+ + 2): 331.31 (4.0%), 283.24 (100%), 267.24 (82%), 177.05 (76%), 149.15 (70%), 80.04 (19%). Analytical data Calcd./found for $C_{14}H_{11}N_5O_3S$: C, 51.06/51.11, H, 3.37/3.39, N, 21.27/21.55, S, 9.74/9.89.

6.5. Preparation of 4-(Methylthio)-2-thioxo-2,3,9,11-tetrahydrobenzimidazolo[5,6-b]pyrimido[4,5-d]azepine-6,10(5H,7H)-dione ***(6)***. To a mixture a thiourea (0.152 g, 0.002 mol), sodium ethoxide (0.13 g, 0.002 mol) and ethanol (30.0 mL) were added **2** (0.67 g, 0.002 mol) and the reaction mixture was refluxed for 14 h. The solvent was removed by distillation and residue was treated with glacial acetic acid (7–10 mL just enough to dissolve sodium salt of the pyrimidine) and refluxed for 15 min. The reaction mixture was acidified with AcOH and precipitate obtained was collected and purified by crystallization with ethanol to give **6** (0.42 g, yield 63%), m.p. 210–212°C. IR (KBr) cm^{-1}: 3350 (NH str.), 2954 (C–H str. ArH), 2190 (S–H str.), 1712 (C=O str.), 1680 (C=O str.), 1604 (C=C str. ArH), 1458 (C=N str.), 1096 (C–N str.), 750 (C–S str.); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δppm: 12.15 (1H, s, SH), 8.24 (1H, s, ArH), 8.17 (1H, s, ArH), 8.0 (1H, s, NH), 6.0 (2H, s, NH), 2.90 (2H, s, CH_2), 2.25 (3H, s, CH_3); C^{13} NMR ($CDCl_3$ + DMSO-d_6) δppm: 19.2 (CH_3); 35.7 (CH_2, azepinone); 112, 119.3 (CH, arene); 126.8, 126.9, 130.1, 135 (C, arene); 127 (C, pyrimidino azepinone); 152.2 (C=O, imidazolone); 165, 168 (C, pyrimidine); 168.2 (C=O, azepinone); 175.5 (C, pyrimidine); MS m/z (percent abundance): (M^+): 345.40 (95.6%), (M^+ + 2): 347.41 (4.4%), 299.31 (100%), 267.24 (80%), 177.05 (76%), 149.15 (70%), 80.04 (19%). Analytical data Calcd./found for $C_{14}H_{11}N_5O_2S_2$: C, 48.68/48.80, H, 3.21/3.27, N, 20.28/20.44, S, 18.57/18.49.

6.6. Preparation of 7-(Methlythio)-12,14-dihdrobenzimidazolo[7,8-b]benzo[b][1,4]diazepino[4,3-d]azepine-9,13(6H,8H)-dione ***(7)***. A mixture of o-phenylenediamine (1.08 g, 0.01 mol), **2** (0.67 g, 0.002 mol), and ethanol (20–25 mL) was refluxed for 4-5 h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water, and dried over anhydrous sodium sulphate to give **7** (0.44 g, yield 66%), m.p. 275–76°C. IR (KBr) cm^{-1}: 3380 (NH str.), 2920 (C–H str. ArH), 1730 (C=O str.), 1690 (C=O str.), 1580 (C=N str.), 1375 (C–H str. CH_3), 1030 (C–N str.), 680 (C–S str.); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δppm: 8.03 (1H, s, ArH), 8.0 (1H, s, NH), 7.96 (1H, s, ArH), 7.00 (2H, d, ArH), 6.50 (2H, d, ArH), 6.0 (2H, s, NH), 4.0 (1H, s, NH), 2.90 (2H, s, CH_2), 2.25 (3H, s, CH_3); C^{13} NMR ($CDCl_3$ + DMSO-d_6) δppm: 12.0 (CH_3); 27.8 (CH_2, azepinone); 87, 151, 164.6 (C, diazepine); 112.6, 116.2, 118.9, 119.8, 122.8, 127.9 (CH, arene); 121.3, 125.8, 132.6, 137.2, 139.8, 140.3 (C, arene); 152.2 (C=O, imidazolone); 168.2 (C=O, azepinone); MS m/z (percent abundance): (M^+): 377.42 (96%), (M^+ + 2): 379.42 (4.0%), 331.33 (100%), 319.32 (82%), 144.17 (74%), 94 (35%), 77.04 (29%). Analytical data Calcd./found for $C_{19}H_{15}N_5O_2S$: C, 60.46/60.59, H, 4.01/4.06, N, 18.56/18.72, S, 8.50/8.79.

6.7. Preparation of 7-(Methlythio)-12,14-dihdrobenzimidazolo[7,8-b]benzo[b][1,4]dithiazepino [4,3-d]azepine-9,13(6H, 8H)-dione ***(8)***. A mixture of o-aminothiophenol (1.08 g, 0.01 mol), **2** (0.67 g, 0.002 mol), and ethanol (20–25 mL) was refluxed for 4-5 h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water, and dried over anhydrous sodium sulphate to give **8**. (0.48 g, yield 72%), m.p. 347–48°C. IR (KBr) cm^{-1}: 3320 (NH str.), 2923 (C–H str. ArH), 1704 (C=O str.), 1685 (C=O str.), 1596 (C=C str.), 1488 (C=N str.), 1380 (C–H str. CH_3), 1157 (C–N str.), 663 (C–S str.); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δppm: 8.03 (1H, s, ArH), 8.0 (1H, s, NH), 7.96 (1H, s, ArH), 7.10 (2H, d, ArH), 7.00 (2H, d, ArH), 6.0 (2H, s, NH), 2.90 (2H, s, CH_2), 2.25 (3H, s, CH_3); C^{13} NMR ($CDCl_3$ + DMSO-d_6) δppm: 12.0 (CH_3); 27.8 (CH_2, azepinone); 98, 151, 164.6 (C, diazepine); 112.6, 116.2, 118.9, 119.8, 122.8, 127.9 (CH, arene); 121.3, 125.8, 132.6, 137.2, 139.8, 140.3 (C, arene); 152.2 (C=O, imidazolone); 168.2 (C=O, azepinone); MS m/z (percent abundance): (M^+): 394.47 (95.4%), (M^+ + 2): 396.47 (4.6%), 348.24 (100%), 336.06 (78%), 111.16 (16%), 149.15 (70%). Analytical data Calcd./found for $C_{19}H_{14}N_4O_2S_2$: C, 57.85/57.71, H, 3.58/3.52, N, 14.20/14.35, S, 16.26/16.50.

7. DPPH Radical Scavenging Assay

The radical in the 1,1-diphenyl-1-picrylhydrazyl (DPPH) gives a strong absorption maximum at 517 nm and is purple in color. The absorbance of DPPH reduces, when the radical of

the DPPH becomes paired with an electron or acceptance of the hydrogen radical from the antioxidant. 1 mL of various concentrations of the test compounds (5, 25, and 50 μg/mL) in methanol to make homogeneous solution. After making desired concentration, methanol added 2.5 mL solution of DPPH was applied on each test tube by using pipette. The room temperature was recorded and the test tube was incubated at 27°C for 30 min. to complete the reaction. The absorbance was read against blank at 517 nm. Decrease in the absorbance of DPPH solution indicated an increase in the radical scavenging activity. The DPPH solution without sample was used as control. Ascorbic acid was used as standard. The experiments were carried out in triplicate.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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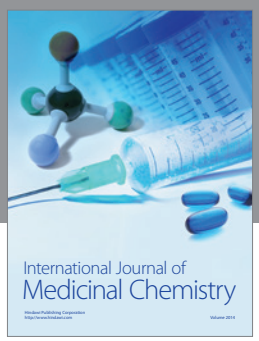

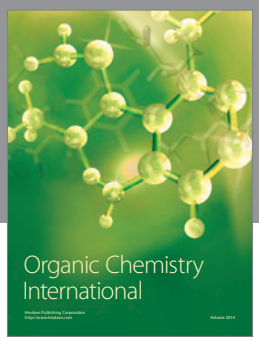

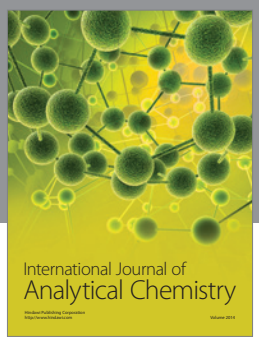

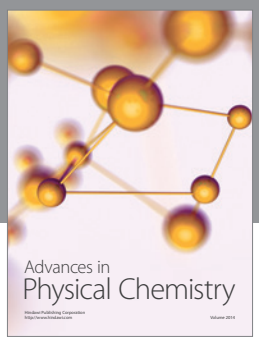

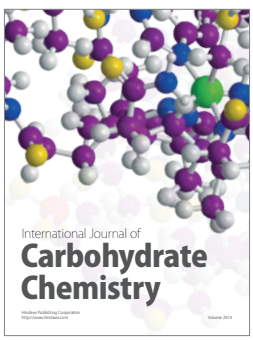

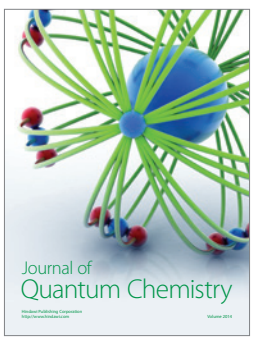

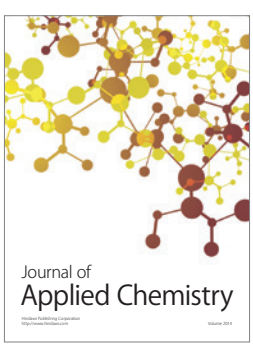

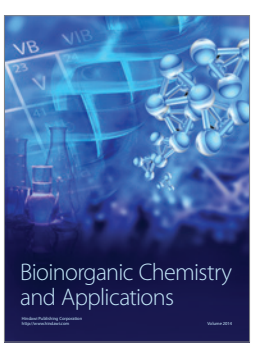

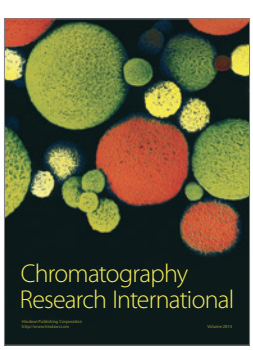

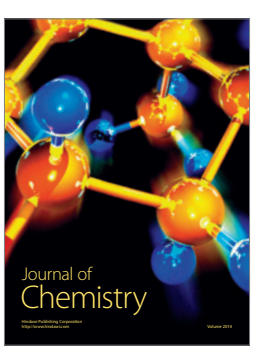

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