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Green synthesis and investigation of antioxidant ability of new phosphonate derivatives

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Abstract: A novel and efficient procedure for the generation of phosphonate derivatives employing catalyst free the reaction of 2-hydroxyacetophenone, isatin or its derivatives, primary amines, dialkyl acetylenedicarboxylates, trimethyl phosphite or triphenyl phosphite and acidic solution of hydrogen peroxide in aqueous media at ambient temperature under ultrasonic irradiation was investigated. Without ultrasonic irradiation the reaction isn't performed and mixture of reaction is very busy. In addition, the power of some prepared compounds as antioxidant was studied using trapping of radical by DPPH (diphenyl-2-picrylhydrazyl) and ferric reduction activity potential (FRAP) experiment. Some advantages of this procedure are: short time of reaction, high yields of product, easy separation of products.

Keywords: Aminohydroxy acethophenone, Malononitrile, Ethyl cyanoacetate, Phosphonate derivatives, Multi component reaction.

Introduction

Recently a diversity of procedures and mechanisms has been developed based on green chemistry or sonochemistry [1]. Sonochemistry as an original and valuable method has attracted increasing interest in accelerating organic reactions [2-5]. This procedure can be very efficient and is applicable to a broad variety of practical synthesis. Luche and coworkers have carried out a number of investigations which provided the basis for using sonochemistry in organic synthesis [6-9]. The significant features of the ultrasound approach in organic reactions are improvement of reaction rates, formation of pure products with high yields and easier process. This method is also considered as an help in terms of energy protection and waste decreasing when compared with traditional methods [10, 11]. In recent year one of the important subjects is carrying out organic reaction in water that focused on economic features with the environmental concerns. Basis of this point, doing organic reaction in aqueous media as a green, economical, safe and eco-favorable solvent have some advantages such as saving time, money, energy and crude materials by performing reaction in one stage without separation of intermediate [12, 13]. Optically active phosphonates derivatives are valuable compounds [14, 15], which show biological activities related to antitumor [16], HIV transcriptase inhibition, and immunomodulation, [17] antibiotic activity [18], antibacterial activity [19], enzyme inhibitors, [20] and herbicides [21-23]. Many procedures for the novel synthesis of organophosphorus compounds are described in the published articles [24-31]. Another moiety in synthesized compounds is quinazolinone that are important compounds with pharmacological and biological activities such as antifungal [32],

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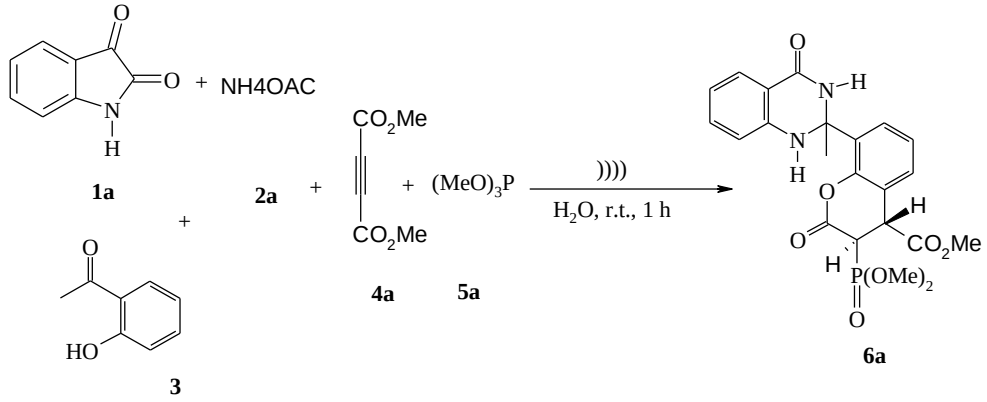
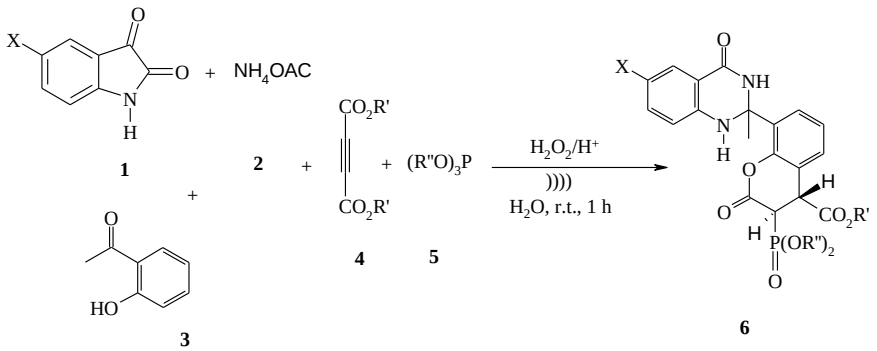
antibacterial [33], and antitumor [34] are s. Because of these important properties of quinazolinones, different procedures were reported for producing of some derivatives of quinazolinones in literature [35-42]. Another subject in this research is investigation of antioxidant activity in synthesized compounds. Because of reductive properties and chemical structure of compounds with antioxidant activity, these compounds use as transitional metals chelators and negative effect of free radicals eliminated by these compounds. These compounds along with it antioxidant activity could be avoid or decrease many illnesses such as Alzheimer, inflammatory bowel syndrome, cardiovascular, cancer and ageing [43-45]; In recent times, biologists, medicinal and food chemist test and discover new and efficient synthetic antioxidant compounds for protective of humans against these diseases. Herein, in continuation of previous works [46-47] and our studies for discovering new procedure for synthesis of important organic compounds,48-57 in this research a series of novel phosphonate derivatives containing quinazolinone were synthesized in excellent yields and short time using catalyst free the reaction of isatin or its derivatives **1**, ammonium acetate**2**, 2-hydroxyacetophenone **3**, dialkyl acetylenedicarboxylates **4**, trimethyl phosphite or triphenyl phosphite **5** in the presence of acidic solution of hydrogen peroxide in aqueous media at ambient temperature under ultrasonic irradiation (Scheme **1**).



Scheme 1. Synthesis of **6a.**

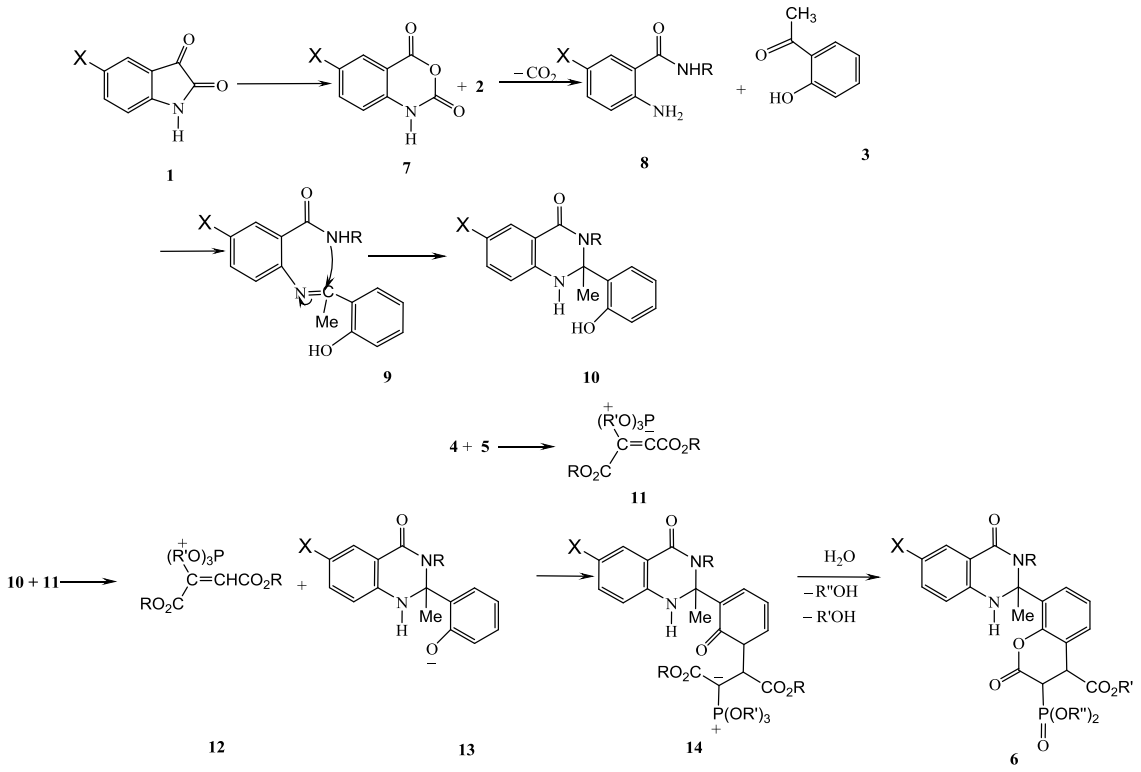
Initially, for determination the best conditions for generation of **6a**, the catalyst free reaction of isatin or its derivatives **1**, methyl amine **2a**, 2-hydroxyacetophenone **3**, dimethyl acetylenedicarboxylate **4a** and trimethylphosphite **5a** in the presence of acidic solution of H_2O_2 was selected as a model reaction. Optimum condition for generation of the product **6a** was achieved by changing of the solvent, temperature and condition of performing reaction including ordinary conditions or ultrasonic irradiation conditions. For selecting the best solvent, CH_2Cl_2, CH_3CN, $CHCl_3$, H_2O, Toluene, DMF, and solvent-free conditions were experimented in two conditions. The results of optimum conditions were showed in the Table **1**. Ultrasonic irradiation in water as solvent and room temperature was selected as best conditions because of excellent yields of compound **6a.**



6	R	R'	R"	X	Yield (%) of **6**
a	Me	Me	Me	H	92
b	Et	Me	Me	H	87
c	^{t}Bu	Me	Me	H	85
d	*iso*-Pr	Me	Me	H	82
e	Me	Et	Me	H	87
f	Me	Me	Ph	H	80
g	Me	Me	Et	H	85
h	Et	Me	Et	H	87

Scheme 2. Green synthesis of phosphonate quinazolinone derivatives **6** under ultrasonic irradiation

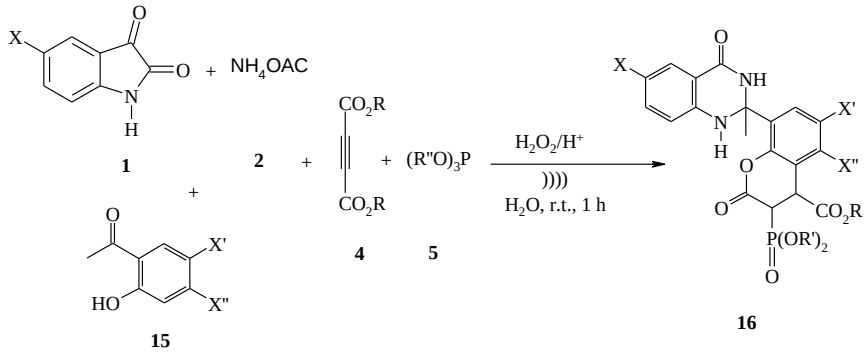
This work has been experimented under two different conditions including ultrasonic irradiation and ordinary conditions. The results of this process were exhibited in Table **1**. As shown in the Table **1**, the time of reaction under ultrasonic irradiation is shorter than the ordinary conditions. Also, the yield of compound **6a** under ultrasonic conditions is excellent and mixture of reaction is cleaner than to ordinary conditions. For this reason, these reactions are carried out in water under ultrasonic irradiation at room temperature. The structures of compounds **6** are confirmed by taking IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For instance, the ^{1}H NMR spectrum of compound **6a** display three singlets at 1.75, 2.15 and 2.56 ppm for methyl protons and one singlet at 3.69 for methoxy protons. The methoxy groups of the phosphoranyl moiety are diastereotopic and display two doublets at 3.85 (3 H, d, $^3J_{HP}$ = 11.5 Hz, MeO), 3.92 (3 H, d, $^3J_{HP}$ = 11.5 Hz, MeO) ppm and two doublet doublets for vicinal methine protons at 3.78 (1 H, dd, $^2J_{HP}$ = 19.8 Hz, $^3J_{HH}$ = 11.6 Hz, CH) and 4.68 (1 H, dd, $^3J_{HP}$ = 9.5 Hz, $^3J_{HH}$ 11.6 Hz, CH) ppm. The NH group was appeared at 6.23 (1 H, s, NH) along with signals for aromatic moiety. In the ^{13}C NMR spectrum, the resonances related to three carbonyl group of **6a** was appeared at δ 160.3 (C=O), 161.3 (d, $^2J_{PC}$ = 6.8 Hz, C=O), 167.5 (d, $^3J_{PC}$ = 22.5 Hz, C=O) ppm. Observation of $^3J_{HH}$ = 11.6 Hz for the vicinal methine protons in **6a** indicates the dominance of *anti* arrangement. Since compound **6a** possesses two stereogenic centers, two diastereomers with *anti* HCCH arrangements are possible (Figure **1**). Also, the observation of $^3J_{CP}$ of 22.5 Hz for the *C*O$_2$Me group and $^3J_{CP}$ of zero for *C* of benzene moiety is in agreement with the (2*R*,3*S*) or (2*S*,3*R*) diastereoisomer.[27f, 59, 60] Not with standing there is no details about the mechanism of these reactions, we have proposed the mechanism of reaction in Scheme **3**.



Scheme 3. Proposed mechanism for the formation of **6**.

According to proposed mechanism, the first isatin or its derivatives **1** react with acidic solution of H_2O_2 under ultrasonic irradiation and produce isatoic anhydride **7** according to Baeyer-Villiger oxidation. Isatoic anhydride **7** and ammonium acetate**2** reacted and generated intermediate **8** by elimination of CO_2. The euparin **3** [58] reacted with intermediate **8** and produced imine **9** that intramolecular cyclization of imine **9** under ultrasonic irradiation produce compound **10**. It should be noted intramolecular cyclyzation aren't perform without ultrasonic irradiation. According to chemistry of phosphorus nucleophiles, [60, 61] it is noteworthy to suppose that initial addition of the phosphite **5** to the activated acetylenic compounds **4** produce compound **11** that are protonated in the presence of compound **10** to generate intermediate **12** and **13**. By attack of carbon atom of intermediate **13** to cation **12**, intermediate **14** was generated. By hydrolysis and cyclization of intermediate **14**, phosphonate derivative **6** was produced.

Under similar conditions a series of novel phosphonate derivatives containing quinazolinone were synthesized in excellent yields and short time employing catalyst free the reaction of isatin or its derivatives **1**, ammonium acetate**2**, 2-hydroxy acetophenone or its derivatives **15**, dialkyl acetylenedicarboxylates **4**, trimethyl phosphite or triphenyl phosphite **5** in the presence of acidic solution of hydrogen peroxide in aqueous media at ambient temperature under ultrasonic irradiation (Scheme **4**).



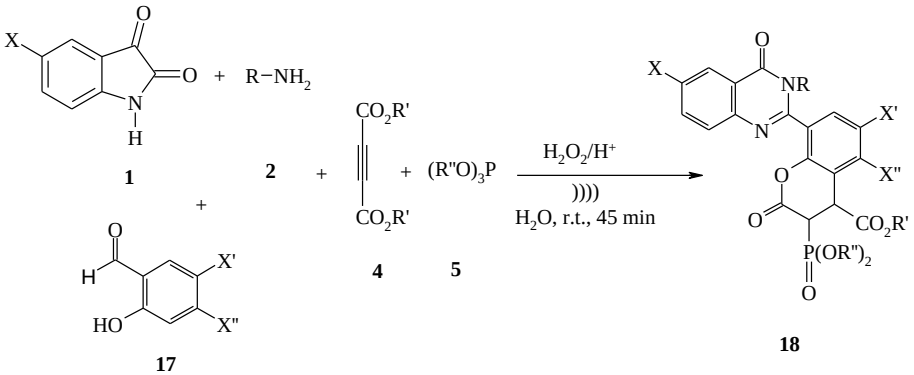
16	R	R'	R'	X	X'	X"	Yield (%) of **16**
a	Me	Me	Me	H	H	H	97
b	Et	Me	Me	H	MeO	H	95
c	*t*Bu	Me	Me	Me	MeO	H	95
d	*iso*-Pr	Me	Me	NO_2	H	Me	90

Scheme 4. Green synthesis of phosphonate quinazolinone derivatives **16** under ultrasonic irradiation

The structures of compounds **16** are confirmed by giving IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For example, the ^{1}H NMR spectrum of compound **16a** show two singlets at 1.65 and 2.58 ppm for methyl protons and one singlet at 3.75 ppm for methoxy proton. Two methoxy groups of the phosphoranyl moiety are diastereotopic and show two doublets at 3.87 and 3.93 ppm and two doublet doublets for vicinal methine protons at 3.83 (1 H, dd, $^2J_{HP}$ = 18.7 Hz, $^3J_{HH}$ = 10.6 Hz, CH) and 4.72 (1 H, dd, $^3J_{HP}$ = 9.2 Hz, $^3J_{HH}$ 11.5 Hz, CH) ppm. The NH group was appeared at 6.18 ppm along with signals for aromatic moiety. In the ^{13}C NMR spectrum, the resonances related to three carbonyl group of **16a** was appeared at δ 160.3 (C=O), 161.3 (d, $^2J_{PC}$ = 6.8 Hz, C=O), 167.5 (d, $^3J_{PC}$ = 22.5 Hz, C=O) ppm.

In continuous of my research, the catalyst free reaction of isatin or its derivatives **1**, ammonium acetate**2**, 2-hydroxy benzaldehyde or its derivatives **17**, dialkyl acetylenedicarboxylates **4**, trimethyl phosphite or triphenyl phosphite **5** was performed in the presence of acidic solution of hydrogen peroxide in aqueous media at ambient temperature under ultrasonic irradiation and produced a series of novel phosphonate derivatives containing quinazoline **18** in excellent yields and short time (Scheme **5**).

The structures of compounds **18** are confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For instance, the ^{1}H NMR spectrum of compound **18a** exhibited two singlets at 3.48 and 3.75 ppm for NMe and methoxy protons respectively. Tthe methoxy groups of the phosphoranyl moiety are diastereotopic because of stereogenic center and display two doublets at 3.89 (3 H, d, $^3J_{HP}$ = 11.6 Hz, MeO) and 3.95 (3 H, d, $^3J_{HP}$ = 11.6 Hz, MeO) ppm and two doublet doublets for vicinal methine protons at 3.83 (1 H, dd, $^2J_{HP}$ = 18.7 Hz, $^3J_{HH}$ = 11.4 Hz, CH) and 4.74 (1 H, dd, $^3J_{HP}$ = 8.9 Hz, $^3J_{HH}$ 11.2 Hz, CH) ppm along with signals for aromatic moiety. In the ^{13}C NMR spectrum, the resonances related to three carbonyl group of **18a** was appeared at δ 160.5 (C=O), 161.6 (d, $^2J_{PC}$ = 6.7 Hz, C=O), 168.2 (d, $^3J_{PC}$ = 22.5 Hz, C=O) ppm.



18	R	R'	R'	X	X'	X"	Yield (%) of **18**
a	Me	Me	Me	H	H	H	97
b	Et	Me	Me	H	MeO	H	95
c	^{t}Bu	Me	Me	Me	MeO	H	95
d	*iso*-Pr	Me	Me	NO_2	H	MeO	90

Scheme 5. Green synthesis of phosphonate quinazoline derivatives 1**8** under ultrasonic irradiation

Study of antioxidant activity employing Diphenyl-2-picrylhydrazyl (DPPH)

For the determination of antioxidant activity of some synthezied compounds and their antioxidant property in foods and biological systems [62,63] as well as power of compounds to take free radicals, diphenyl-2-picrylhydrazyl (DPPH) radical trapping experiment is widely used. In these experiment, the DPPH radical takes the hydrogen atom (or one electron) of synthezied compounds and gives an evaluation of antioxidant activity basis of free radical trapping. The antioxidant activity of **6a**, **6b**, **6e** and **6f** was investigated basis of their electron or hydrogen donating power to the DPPH radical. The absorption of DPPH radical was observed area 517 nm but when DPPH radical is reduced by an antioxidant or a radical species its absorption decreases. In this research, the antioxidant activity or power of compounds **6a**, **6b**, **6e** and **6f** to take free radicals was compared to BHT and TBHQ at different concentrations (Figure **1**).

As shown in Figure **1**, at all concentrations (200-1000 ppm), the new synthesized compounds have good differences compared to BHT and TBHQ but have excellent free radical trapping power compared to BHT and TBHQ at 1000 ppm concentration. Among selected synthezied compounds, **6f** was shown a noteworthy radical trapping activity relative to standards (BHT and TBHQ).

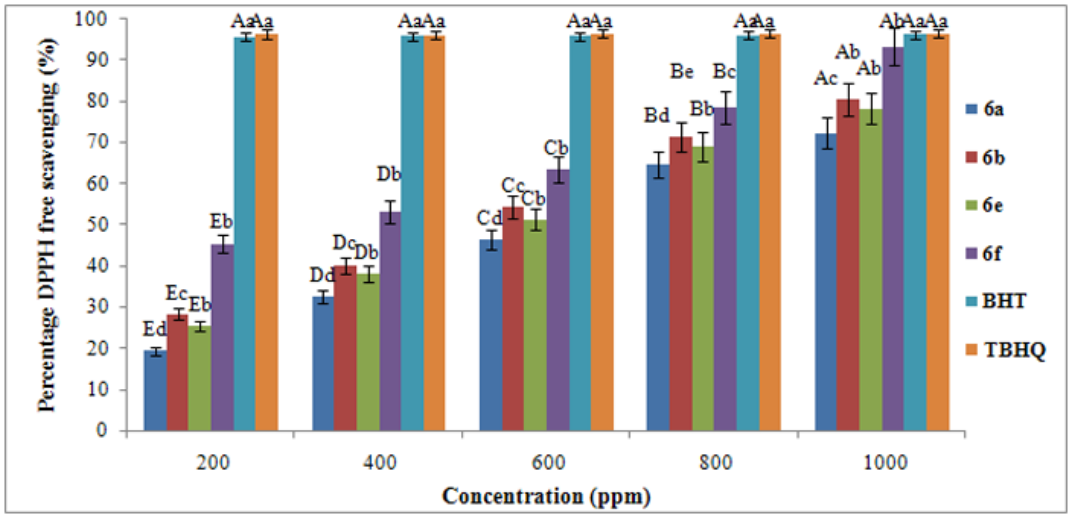


Figure 1. Radical scavenging activity of **6a**, **6b**, **6e** and **6f**

Ferric ions (Fe^{3+}) reducing potential (FRAP)

The power of reducing ferric ions (Fe^{3+}) by some Phosphonate quinazolinone derivatives such as **6a**, **6b**, **6e** and **6f** are calculated by the amount of conversion of Fe^{3+}/ferricyanide complex to the Fe^{2+}/ ferrous form at 700 nm. [64] As shown in Figure **2**, in this test, compound **6b** was shown very good reducing activity compared to standards (BHT and TBHQ).

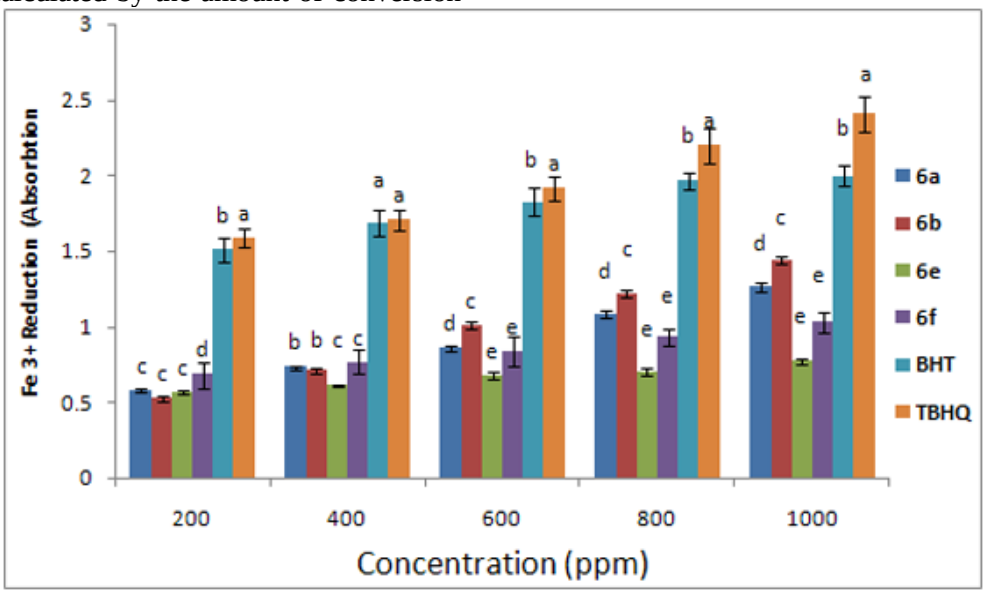


Figure 2. Ferric ions (Fe^{3+}) reducing antioxidant power (FRAP) of compounds **6a, 6b, 6e** and **6f**.

Conclusion

In conclusion, in this research we described an useful, green, and eco-friendly procedure for synthesis of novel phosphonate derivatives containing quinazolinone from the reaction of isatin or its derivatives, primary amine, 2-hydroxyacetophenon or its derivatives, 2-hydroxy benzaldehyde or its derivatives, activated acetylenic compounds and trimethyl phosphite or triphenyl phosphite in the presence of acidic solution of H_2O_2 in water at room temperature under ultrasonic irradiation. These reactions weren't performed under common conditions without catalyst but under ultrasonic irradiation these reaction have excellent yields and short time of reaction. This method has many advantages such as short time, high atom economy and yield, mild and clean reaction condition. As a result, the compound **6b** exhibit excellent DPPH radical trapping activity and compound **6b** showed good FRAP compared to synthetic antioxidants BHT and TBHQ.

Experimental

General procedure for preparation of compounds 6a–n:

A mixture of isatin **1** (2 mmol) in water (3 mL) and acidic solution of hydrogen peroxide (H_2O_2) (20 mol%) was sonicated at room temperature for 10 min in a beaker equipped with ultrasonic probe under the power of 60 W. After 10 min primary amine **2** (2 mmol) was added. After 5 min 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone (euparin) **3** (2mmol) was added under ultrasonic irradiation. The dialkyl acetylenedicarboxylate **4** (2 mmol) and trimethyl phosphite or triphenyl phosphate (2 mmol) **5** (2mmol) was added after 10 min. completion of all stages are monitored by TLC employing 5:1 ethyl acetate/n-hexane as an eluent. After completion the reaction, solid phase was separated by filtration and washed with Et_2O to afforded pure title compound **6**.

(8R,9S)-Methyl8-(dimethoxyphosphoryl)-5-(2,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl)-2-isopropenyl-7-oxo-8,9-dihydro-7H-furo[2,3-f]chromene-9-carboxylate (6a):

Yellow powder, mp 193-195˚C, Yield: 1.04 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 1742, 1738, 1695, 1625, 1585, 1468, 1375, 1294 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.75 (3 H, s, Me), 2.15 (3 H, s, Me), 2.56 (3 H, s, Me), 3.69 (3 H, s, MeO), 3.78 (1 H, dd, $^2J_{HP}$ = 19.8 Hz, $^3J_{HH}$ = 11.6 Hz, CH), 3.85 (3 H, d, $^3J_{HP}$ = 11.5 Hz, MeO), 3.92 (3 H, d, $^3J_{HP}$ = 11.5 Hz, MeO), 4.68 (1 H, dd, $^3J_{HP}$ = 9.5

Hz, $^3J_{HH}$ 11.6 Hz, CH), 4.75 (1 H, d, ^2J = 4.2 Hz, CH), 5.12 (1 H, d, ^2J = 4.2 Hz, CH), 6.23 (1 H, s, NH), 6.95 (1 H, d, $^3J_{HH}$ = 7.8 Hz, CH), 7.15 (1 H , t, $^3J_{HH}$ = 7.8 Hz, CH), 7.23 (1 H, t, $^3J_{HH}$ = 7.8 Hz, CH), 7.43 (1 H, s, CH), 7.52 (1 H, s, CH), 7.93 (1 H, d, $^3J_{HH}$ = 7.8 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 18.5 (Me), 25.3 (Me), 34.2 (NMe), 42.3 (d, $^2J_{PC}$ = 9.3Hz, CH), 46.3 (d, $^1J_{PC}$ = 143.2 Hz, CH), 51.2 (d, $^2J_{PC}$, 8.7 Hz, MeO), 52.4 (d, $^2J_{PC}$ = 8.7 Hz, MeO), 52.8 (MeO), 76.4 (C), 105.2 (C), 113.2 (CH_2), 114.2 (C), 114.8 (CH), 121.6 (C), 122.4 (C), 122.3 (CH), 124.3 (CH), 125.2 (CH), 127.4 (CH), 133.6 (CH), 137.6 (C), 142.3 (C), 151.8 (C), 152.3 (C), 154.3 (C), 160.3 (C=O), 161.3 (d, $^2J_{PC}$ = 6.8 Hz, C=O), 167.5 (d, $^3J_{PC}$ = 22.5 Hz, C=O) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ 19.6. Anal. Calcd for $C_{28}H_{29}N_2O_9P$ (568.52): C, 59.16; H, 5.14; N 4.93. Found: C, 59.34; H, 5.28; N, 5.14. MS, *m/z* (%): 568 (M^+, 10), 537 (92), 31 (100).

Methyl8-(dimethoxyphosphoryl)-5-(3-ethyl-2methyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl)-2-isopropenyl-7-oxo-8,9-dihydro-7H-furo[2,3-f]chromene-9-carboxylate (6b):

Yellow powder, mp 201-203˚C, Yield: 1.01 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1739, 1735, 1697, 1635, 1587, 1475, 1382, 1293 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (3 H, t, $^3J_{HH}$ = 7.3 Hz, Me), 1.73 (3 H, s, Me), 2.16 (3 H, s, Me), 2.75-2.83 (1 H, m, CH), 3.12-3.22 (1 H, m, CH), 3.75 (3 H, s, MeO), 3.82 (1 H, dd, $^2J_{HP}$ = 19.5 Hz, $^3J_{HH}$ = 11.5 Hz, CH), 3.89 (3 H, d, $^3J_{HP}$ = 11.7 Hz, MeO), 3.95 (3 H, d, $^3J_{HP}$ = 11.7 Hz, MeO), 4.74 (1 H, dd, $^3J_{HP}$ = 10.2 Hz, $^3J_{HH}$ 11.5 Hz, CH), 4.83 (1 H, d, ^2J = 4.5 Hz, CH), 5.23 (1 H, d, ^2J = 4.5 Hz, CH), 6.18 (1 H, s, NH), 7.02 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.18 (1 H , t, $^3J_{HH}$ = 7.6 Hz, CH), 7.28 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.47 (1 H, s, CH), 7.54 (1 H, s, CH), 7.87 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.2 (Me), 18.7 (Me), 25.4 (Me), 40.2 (NCH_2), 42.5 (d, $^2J_{PC}$ = 9.7Hz, CH), 45.8 (d, $^1J_{PC}$ = 145.2 Hz, CH), 51.2 (d, $^2J_{PC}$, 9.2 Hz, MeO), 52.5 (d, $^2J_{PC}$ = 9.2 Hz, MeO), 53.4 (MeO), 76.5 (C), 106.2 (C), 113.5 (CH_2), 114.3 (C), 114.5 (CH), 121.7 (C), 122.5 (CH), 122.9 (C), 124.2 (CH), 125.3 (CH), 127.6 (CH), 132.8 (CH), 137.5 (C), 142.4 (C), 151.6 (C), 152.6 (C), 154.5 (C), 160.5 (C=O), 161.7 (d, $^2J_{PC}$ = 7.3 Hz, C=O), 168.2 (d, $^3J_{PC}$ = 22.4 Hz, C=O) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ 20.3. Anal. Calcd for $C_{29}H_{31}N_2O_9P$ (582.54): C, 59.79; H, 5.36; N 4.81. Found: C, 59.93; H, 5.52; N, 4.96. MS, *m/z* (%): 582 (M^+, 15), 551 (86), 31 (100).

Methyl5-[3-(tert-butyl)-2-methyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl]-8-(dimethoxyphosphoryl)-2-isopropenyl-7-oxo-8,9-dihydro-7H-furo[2,3-f]chromene-9-carboxylate (6c):

Yellow powder, mp 215-217˚C, Yield: 1.04 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1740, 1737, 1698, 1642, 1576, 1478, 1376, 1284 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (9 H, s, *Me*$_3$C),1.68 (3 H, s, Me), 2.18 (3 H, s, Me), 3.72 (3 H, s, MeO), 3.83 (1 H, dd, $^2J_{HP}$ = 20.4 Hz, $^3J_{HH}$ = 12.2 Hz, CH), 3.87 (3 H, d, $^3J_{HP}$ = 11.8 Hz, MeO), 3.95 (3 H, d, $^3J_{HP}$ = 11.8 Hz, MeO), 4.73 (1 H, d, ^2J = 4.7 Hz, CH), 4.86 (1 H, dd, $^3J_{HP}$ = 9.8 Hz, $^3J_{HH}$ 12.2 Hz, CH), 5.15 (1 H, d, ^2J = 4.7 Hz, CH), 6.25 (1 H, s, NH), 7.04 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.18 (1 H , t, $^3J_{HH}$ = 7.6 Hz, CH), 7.25 (1 H, t, $^3J_{HH}$ = 7.7 Hz, CH), 7.45 (1 H, s, CH), 7.56 (1 H, s, CH), 8.02 (1 H, d, $^3J_{HH}$ = 7.7 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 18.6 (Me), 27.5 (Me), 31.4 (*Me*$_3$C), 42.7 (d, $^2J_{PC}$ = 10.2 Hz, CH), 47.4 (d, $^1J_{PC}$ = 147.3 Hz, CH), 51.5 (d, $^2J_{PC}$ = 9.5 Hz, MeO), 52.3 (d, $^2J_{PC}$ = 9.5 Hz, MeO), 52.8 (MeO), 62.3 (Me$_3$*C*), 77.4 (C), 113.3 (C), 114.2 (CH_2), 114.5 (CH), 115.3 (C), 116.3 (CH), 123.2 (C), 123.6 (C), 124.5 (CH), 125.8 (CH), 127.6 (CH), 134.3 (CH), 137.2 (C), 142.5 (C), 152.3 (C), 152.8 (C), 154.8 (C), 160.8 (C=O), 161.6 (d, $^2J_{PC}$ = 6.5 Hz, C=O), 169.4 (d, $^3J_{PC}$ = 21.8 Hz, C=O) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ 21.6. Anal. Calcd for $C_{31}H_{35}N_2O_9P$ (610.59): C, 60.98; H, 5.78; N 4.59. Found: C, 61.16; H, 5.89; N, 4.78. MS, *m/z* (%): 610 (M^+, 10), 553 (86), 57 (100), 31 (100).

Methyl5-(3-isopropyl-2-methyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl]-8-(dimethoxyphosphoryl)-2-isopropenyl-7-oxo-8,9-dihydro-7H-furo[2,3-f]chromene-9-carboxylate (6d):

Yellow powder, mp 209-211˚C, Yield: 0.98 g (82%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1736, 1695, 1658, 1586, 1484, 1375, 1293 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (6 H, d, $^3J_{HH}$ = 6.7 Hz, 2 CH_3), 1.76 (3 H, s, Me), 2.16 (3 H, s, Me), 3.68 (3 H, s, MeO), 3.74-3.85 (2 H, m, 2 CH), 3.89 (3 H, d, $^3J_{HP}$ = 12.2 Hz, MeO), 3.96 (3 H, d, $^3J_{HP}$ = 12.2 Hz, MeO), 4.75 (1 H, d, ^2J = 4.8 Hz, CH), 4.87 (1 H, dd, $^3J_{HP}$ = 10.3 Hz, $^3J_{HH}$ = 12.0 Hz, CH), 5.09 (1 H, d, ^2J = 4.8 Hz, CH), 6.22 (1 H, s, NH), 7.08 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 7.23 (1 H, t, $^3J_{HH}$ = 7.5 Hz, CH), 7.32 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.48 (1 H, s, CH), 7.62 (1 H, s, CH), 8.04 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 18.5 (Me), 22.4 (2 CH_3), 26.4 (Me), 42.3 (d, $^2J_{PC}$ = 10.5 Hz, CH), 43.5 (NCH), 47.6 (d, $^1J_{PC}$ = 148.6 Hz, CH), 51.7 (d, $^2J_{PC}$ = 10.2 Hz, MeO), 52.5 (d, $^2J_{PC}$ = 10.2 Hz, MeO), 53.2 (MeO), 76.2 (C), 105.3 (C), 113.3 (C), 114.3 (CH_2), 114.7 (CH), 121.4 (C), 122.2 (C), 122.5 (CH), 125.4 (CH), 125.8 (CH), 127.4 (CH), 133.6 (CH), 137.2 (C),

142.2 (C), 151.8 (C), 153.2 (C), 154.4 (C), 161.2 (C=O), 162.3 (d, $^2J_{PC}$ = 6.7 Hz, C=O), 170.3 (d, $^3J_{PC}$ = 22.3 Hz, C=O) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ 22.3. Anal. Calcd for $C_{30}H_{33}N_2O_9P$ (596.56): C, 60.40; H, 5.58; N 4.70. Found: C, 60.58; H, 5.74; N, 4.86. MS, *m/z* (%): 596 (M^+, 15), 565 (84), 31(100).

Ethyl8-(dimethoxyphosphoryl)-5-(2,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl)-2-isopropenyl-7-oxo-8,9-dihydro-7H-furo[2,3-f]chromene-9-carboxylate (6e):

Yellow powder, mp 186-188˚C, Yield: 1.01 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1740, 1737, 1698, 1634, 1587, 1476, 1378, 1297 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (3 H, t, $^3J_{HH}$ = 7.4 Hz, CH_3), 1.72 (3 H, s, Me), 2.18 (3 H, s, Me), 2.48 (3 H, s, Me), 3.75 (1 H, dd, $^2J_{HP}$ = 19.5 Hz, $^3J_{HH}$ = 11.6 Hz, CH), 3.83 (3 H, d, $^3J_{HP}$ = 11.3 Hz, MeO), 3.87 (3 H, d, $^3J_{HP}$ = 11.3 Hz, MeO), 4.12 (2 H, q, $^3J_{HH}$ = 7.4 Hz, CH_2O), 4.65 (1 H, dd, $^3J_{HP}$ = 9.8 Hz, $^3J_{HH}$ 11.6 Hz, CH), 4.78 (1 H, d, ^2J = 3.8 Hz, CH), 5.16 (1 H, d, ^2J = 3.8 Hz, CH), 6.16 (1 H, s, NH), 6.92 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.12 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.24 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.38 (1 H, s, CH), 7.43 (1 H, s, CH), 7.87 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.2 (Me), 18.3 (Me), 24.8 (Me), 34.5 (NMe), 42.5 (d, $^2J_{PC}$ = 9.7 Hz, CH), 46.8 (d, $^1J_{PC}$ = 147.4 Hz, CH), 51.3 (d, $^2J_{PC}$ = 9.2 Hz, MeO), 52.3 (d, $^2J_{PC}$ = 9.2 Hz, MeO), 61.2 (CH_2O), 78.3 (C), 105.4 (C), 112.8 (CH_2), 113.6 (C), 114.2 (CH), 121.3 (C), 122.5 (C), 122.5 (CH), 125.3 (CH), 125.8 (CH), 127.3 (CH), 133.2 (CH), 137.2 (C), 142.5 (C), 151.6 (C), 153.4 (C), 154.4 (C), 160.5 (C=O), 161.8 (d, $^2J_{PC}$ = 7.3 Hz, C=O), 168.4 (d, $^3J_{PC}$ = 21.8 Hz, C=O) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ 19.8. Anal. Calcd for $C_{29}H_{31}N_2O_9P$ (582.54): C, 59.79; H, 5.36; N 4.81. Found: C, 59.93; H, 5.52; N, 4.96. MS, *m/z* (%): 582 (M^+, 15), 537 (76), 45 (100).

Methyl8-(diphenoxyphosphoryl)-5-(2,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl)-2-isopropenyl-7-oxo-8,9-dihydro-7H-furo[2,3-f]chromene-9-carboxylate (6f):

Pale yellow powder, mp 216-218˚C, Yield: 1.01g (80%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1742, 1698, 1667, 1589, 1486, 1385, 1297 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.65 (3 H, s, Me), 2.14 (3 H, s, Me), 2.48 (3 H, s, Me), 3.68 (3 H, s, MeO), 4.25 (1 H, dd, $^2J_{HP}$ = 19.5 Hz, $^3J_{HH}$ = 11.8 Hz, CH), 4.86 (1 H, dd, $^3J_{HP}$ = 10.4 Hz, $^3J_{HH}$ = 11.8 Hz, CH), 4.93 (1 H, d, ^2J = 4.8 Hz, CH), 5.23 (1 H, d, ^2J = 4.8 Hz, CH), 6.32 (1 H, s, NH), 6.86 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.12 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH), 7.16 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH), 7.22 (1 H , t, $^3J_{HH}$ = 7.6 Hz, CH), 7.28 (1 H, t, $^3J_{HH}$ = 7.5 Hz, CH), 7.32 (1 H, t, $^3J_{HH}$ = 7.5 Hz, CH), 7.37 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.42 (2 H, t, $^3J_{HH}$ = 7.5 Hz, 2 CH), 7.48 (2 H, t, $^3J_{HH}$ = 7.5 Hz, CH), 7.52 (1 H, s, CH), 7.58 (1 H, s, CH), 7.96 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 18.7 (Me), 24.6 (Me), 34.5(NMe), 37.8 (d, $^2J_{PC}$ = 9.6 Hz, CH), 40.2 (d, $^1J_{PC}$ = 158.3 Hz, CH), 51.6 (MeO), 77.8 (C), 107.2 (C), 113.4 (CH_2), 114.2 (CH), 115.3 (C), 120.5 (d, $^3J_{PC}$ = 23.4 Hz, 2 CH), 121.6 (d, $^3J_{PC}$ = 23.4 Hz, 2 CH), 122.5 (C), 123.2 (CH), 123.5 (C), 125.3 (2 CH), 125.8 (CH), 126.3 (CH), 127.4 (CH), 128.3 (2 CH), 128.8 (2 CH), 133.5 (CH), 137.5 (C), 142.6 (C), 151.3 (d, $^2J_{PC}$ = 10.4 Hz, C), 151.8 (d, $^2J_{PC}$ = 10.4 Hz, C), 152.2 (C), 153.6 (C), 154.5 (C), 159.4 (C=O), 160.8 (d, $^2J_{PC}$ = 7.3 Hz, C=O), 165.6 (d, $^3J_{PC}$ = 22.8 Hz, C=O) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ 19.6. Anal. Calcd for $C_{38}H_{33}N_2O_9P$ (692.65): C, 65.89; H, 4.80; N 4.04. Found: C, 66.04; H, 4.95; N, 4.22. MS, *m/z* (%): 692 (M^+, 10), 661 (68), 31 (100).

Methyl8-(diethoxyphosphoryl)-5-(2,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl)-2-isopropenyl-7-oxo-8,9-dihydro-7H-furo[2,3-f]chromene-9-carboxylate (6g):

Yellow powder, mp 198-200˚C, Yield: 1.01 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1739, 1737, 1696, 1647, 1587, 1465, 1376, 1297 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (3 H, t, $^3J_{HH}$ = 7.4 Hz, CH_3), 1.23 (3 H, t, $^3J_{HH}$ = 7.4 Hz, CH_3), 1.72 (3 H, s, Me), 2.16 (3 H, s, Me), 2.47 (3 H, s, Me), 3.68 (3 H, s, MeO), 3.82 (1 H, dd, $^2J_{HP}$ = 20.4 Hz, $^3J_{HH}$ = 12.3 Hz, CH), 3.92-4.05 (2 H, m, CH_2O), 4.12-4.22 (2 H, m, CH_2O), 4.87 (1 H, dd, $^3J_{HP}$ = 10.3 Hz, $^3J_{HH}$ = 12.3 Hz, CH), 4.93 (1 H, d, ^2J = 5.4 Hz, CH), 5.16 (1 H, d, ^2J = 5.4 Hz, CH), 6.28 (1 H, s, NH), 7.08 (1 H, d, $^3J_{HH}$ = 7.7 Hz, CH), 7.16 (1 H , t, $^3J_{HH}$ = 7.6 Hz, CH), 7.26 (1 H, t, $^3J_{HH}$ = 7.5 Hz, CH), 7.52 (1 H, s, CH), 7.63 (1 H, s, CH), 8.04 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 15.2 (d, $^3J_{PC}$ = 8.2 Hz, Me), 16.4 (d, $^3J_{PC}$ = 8.2 Hz, Me), 18.7 (Me), 24.8 (Me), 34.7 (NMe), 42.5 (d, $^2J_{PC}$ = 9.8 Hz, CH), 47.2 (d, $^1J_{PC}$ = 156.4 Hz, CH), 51.4 (MeO), 62.4 (d, $^2J_{PC}$ = 9.3 Hz, CH_2O), 63.2 (d, $^2J_{PC}$ = 9.3 Hz, CH_2O), 77.3 (C), 105.6 (C), 113.4 (CH_2), 113.8 (C), 114.2 (CH), 122.3 (C), 123.4 (C), 123.8 (CH), 124.8 (CH), 125.6 (CH), 127.6 (CH), 133.8 (CH), 137.2 (C), 142.6 (C), 152.3 (C), 153.4 (C), 154.5 (C), 161.2 (C=O), 162.4 (d, $^2J_{PC}$ = 6.5 Hz, C=O), 168.2 (d, $^3J_{PC}$ = 21.8 Hz, C=O) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ 20.3. Anal. Calcd for $C_{30}H_{33}N_2O_9P$ (596.56): C, 60.40; H, 5.58; N 4.70. Found: C, 60.58; H, 5.76; N, 4.87. MS, *m/z* (%): 596 (M^+, 15), 551 (68), 45 (100), 31 (100).

Ethyl8-(diethoxyphosphoryl)-5-(2,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl)-2-isopropenyl-7-oxo-8,9-dihydro-7H-furo[2,3-f]chromene-9-carboxylate (6h):

Yellow powder, mp 203-205˚C, Yield: 1.06 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1739, 1698, 1652, 1583, 1468, 1386, 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (3 H, t, $^3J_{HH}$ = 7.4 Hz, CH_3), 1.25 (3 H, t, $^3J_{HH}$ = 7.4 Hz, CH_3), 1.34 (3 H, t, $^3J_{HH}$ = 7.5 Hz, CH_3), 1.78 (3 H, s, Me), 2.14 (3 H, s, Me), 2.45-2.58 (2 H, m, NCH_2), 3.72 (3 H, s, MeO), 3.84 (1 H, dd, $^2J_{HP}$ = 19.4 Hz, $^3J_{HH}$ = 11.2 Hz, CH), 3.95-4.09 (2 H, m, CH_2O), 4.15-4.26 (2 H, m, CH_2O), 4.65 (1 H, dd, $^3J_{HP}$ = 10.5 Hz, $^3J_{HH}$ = 11.2 Hz, CH), 4.84 (1 H, d, ^2J = 5.8 Hz, CH), 5.03 (1 H, d, ^2J = 5.8 Hz, CH), 6.32 (1 H, s, NH), 7.02 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.15 (1 H , t, $^3J_{HH}$ = 7.6 Hz, CH), 7.32 (1 H, t, $^3J_{HH}$ = 7.5 Hz, CH), 7.46 (1 H, s, CH), 7.58 (1 H, s, CH), 7.89 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.2 (Me), 14.8 (d, $^3J_{PC}$ = 9.4 Hz, Me), 15.6 (d, $^3J_{PC}$ = 9.4 Hz, Me), 18.6 (Me), 25.4 (Me), 40.2 (NCH_2), 41.6 (d, $^2J_{PC}$ = 11.2 Hz, CH), 47.5 (d, $^1J_{PC}$ = 155.8 Hz, CH), 51.6 (MeO), 61.8 (d, $^2J_{PC}$ = 9.8 Hz, CH_2O), 62.6 (d, $^2J_{PC}$ = 9.8 Hz, CH_2O), 76.3 (C), 106.4 (C), 113.6 (CH_2), 114.3 (C), 114.8 (CH), 121.4 (C), 122.3 (CH), 123.2 (C), 124.8 (CH), 125.8 (CH), 128.2 (CH), 133.4 (CH), 137.6 (C), 143.2 (C), 151.6 (C), 152.8 (C), 154.3 (C), 160.8 (C=O), 161.6 (d, $^2J_{PC}$ = 8.3 Hz, C=O), 169.4 (d, $^3J_{PC}$ = 22.3 Hz, C=O) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ 23.4. Anal. Calcd for $C_{31}H_{35}N_2O_9P$ (610.59): C, 60.48; H, 5.78; N 4.59. Found: C, 60.63; H, 5.92; N, 4.76. MS, *m/z* (%): 610 (M^+, 10), 565 (54), 45 (100), 31 (100).

1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical trapping test:

Radical trapping activity of **6a**, **6b**, **6e** and **6f** was calculated by DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical trapping experiment according to the reported method by Shimada et al. [63] Different concentrations of **6a**, **6b**, **6e** and **6f** (200–1000 ppm) were added to an equal volume of methanolic solution of DPPH (1 mmol/L). The mixtures were well shaken and then placed in a dark room. After 30 min at room temperature, the absorbance was recorded at 517 nm. In the control sample, **6a**, **6b**, **6e** and **6f** was exchanged with 3 mL methanol. Butylated hydroxytoluene (BHT) and 2-tertbutylhydroquinone (TBHQ) were employed as standard controls. The percentage inhibition of the DPPH radical was calculated according to the formula of Yen and Duh. [64]

Reducing power experiment:

The ability of compounds **6a**, **6b**, **6e** and **6f** to reduce iron (III) was evaluated by the method of Yildirim et al.[65] Samples (1 mL) were mixed with 2.5 mL of phosphate buffer (0.2 mol/L, pH 6.6) and 2.5 mL of potassium ferricyanide ($K_3Fe(CN)_6$; 10g/L) and display for 30 min at 50 ^{o}C. Then, 2.5 mL of trichloroacetic acid (10% w/v) were added to the solution and centrifuged for 10 min. In the end, 2.5 mL of supernatant was mixed with 2.5 mL of distilled water and 0.5 mL $FeCl_3$ (1 g/L). The absorbance of samples was measured at 700 nm. Higher absorbance means higher reducing power. Each measurement was performed in triplicate. The data were analyzed by running one way analysis of variance (ANOVA) using SPSS software version 18.0. A one way ANOVA was used to estimate dissimilarity in the mean value of samples and control. All mean separations were carried out by Duncan multiple range test employing the importance level of 95% ($P < 0.05$).

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