MANSOURA JOURNAL OF CHEMISTRY
Official Journal of Faculty of Science, Mansoura University, Egypt
E-mail: scimag@mans.edu.eg ISSN: 2974-4938

Synthesis and antioxidant evaluation of pyrazolyl-imidazolone analogues utilizing 4-((1,3-diphenyl-1*h*-pyrazol-4-yl)methylene)-2-phenyl-1,3-oxazol-5(4*h*)-one synthon

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Received:19/4/2019
Accepted: 29/4/2019

Abstract: A new series of pyrazolyl-imidazolone derivatives **3-6** were synthesized *via* the reaction of the readily obtainable pyrazolyl-oxazol-5(4*H*)-one **2** with various aromatic amines namely, 4-aminophenol, ethyl 4-aminobenzoate, 4-aminoacetophenone and 2-aminobenzoic acid in acetic acid including freshly melted sodium acetate. Furthermore, the pyrazolyl-imidazolone **3** on reaction with ethyl 2-chloroacetate, acetic anhydride, benzoyl chloride or benzenesulfonyl chloride afforded the corresponding pyrazolyl-imidazolone derivatives **7-10**. The novel compounds were characterized by spectral data and elemental analysis and measured as antioxidant agents using ABTS assay. The candidates showed moderate to good activity compared to ascorbic acid.

keywords: Oxazolones; imidazolones; pyrazole; 4-aminoacetophenone; antioxidant activity

1.Introduction

Imidazolone moiety is the basic core of many synthetic and natural products [1], which have remarkable biological performance [2]. Imidazolones have been reported as potent analogues of V-RAF murine [3] growth and phosphodiesterase inhibitors [4, 5]. These compounds were also antagonists of some receptors carrying neurokinin-1 [6] and the dopamine receptor [7]. Recently, the synthesis of products containing imidazolone [8-15] has been increased due to their valuable biological significance. Imidazolone is the nucleus of fluorescent probes associated with fluorescent proteins (**A**) [16-20] as well as structural fragments of active compounds against obesity-related disorders and hypertension (**B**) [21-24]. In addition, imidazolones are beneficial intermediates for the preparation of natural alkaloids, for example, compounds **A** and **C** [25]. They also found agrochemical applications such as herbicides, which are used to control weeds in pulses, grains and peanuts (**D**) [26, 27] (Fig. 1). The synthesis of azlactones by Erlenmayer has been found to be beneficial because these analogs can be suitably converted to imidazolones by an amidation/ring closure [16].

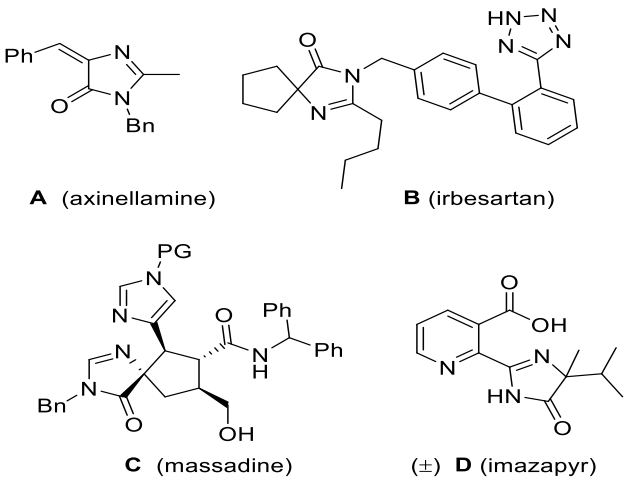


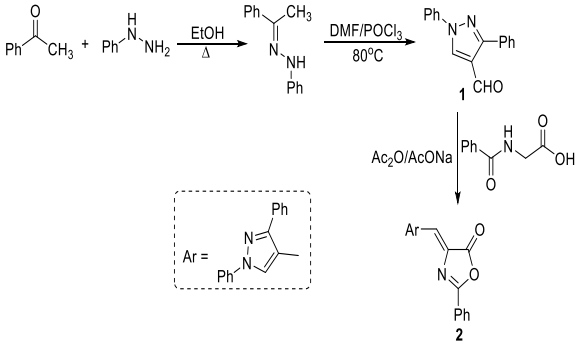
Figure 1. Structures of significant active imidazolones.

Continuing of our earlier work for the synthesis of novel biologically active heterocyclic compounds [28-30], we report in this paper a simple synthetic method for the preparation of a series of heterocyclic compounds containing pyrazolyl-imidazolone ring systems in order to assess their activity as antioxidant agents.

2. Results and Discussion

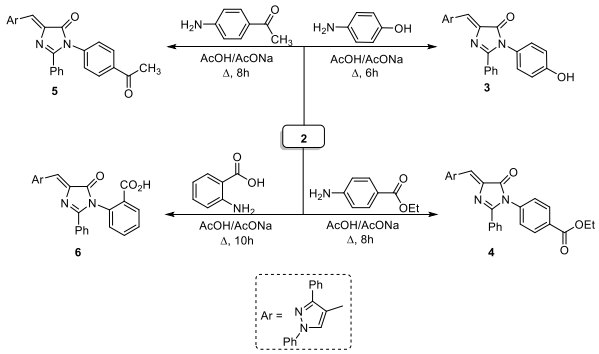
2.1. Synthetic Chemistry

The pyrazolyl-oxazol-5(4*H*)-one **2** was prepared in good yield as previously described [31, 32] in two steps *via* heating acetophenone with phenyl hydrazine in ethanol to yield 1-phenyl-2-(1-phenylethylidene)-hydrazine, which upon treatment with phosphorus oxychloride in dimethylformamide at 80°C produced the anticipated 1,3-diphenyl-4-formyl-1*H*-pyrazole **(1)** [33]. The latter product was converted to compound **2** upon heating with benzoylglycine in acetic anhydride having freshly melted sodium acetate (Scheme 1).



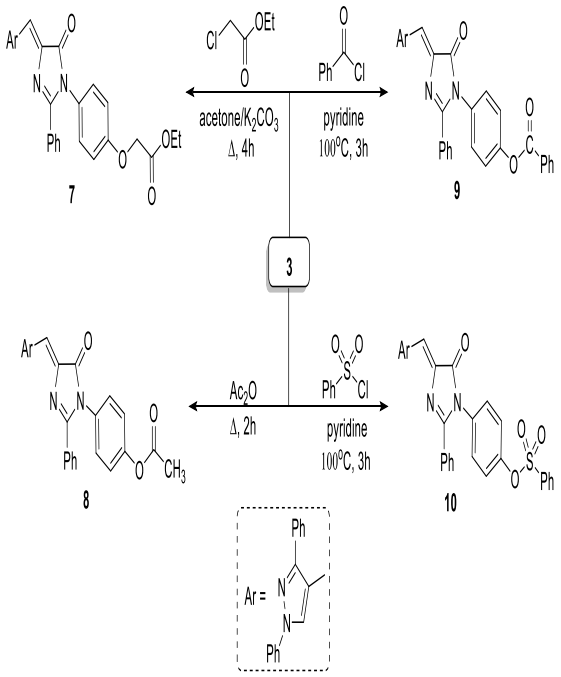
Scheme 1. Synthesis of pyrazolyl-oxazol-5(4*H*)-one **2**.

The pyrazolyl-oxazol-5(4*H*)-one **2** was utilized as a reactive precursor in reaction with various aromatic amines. Thus, heating **2** with 4-aminophenol, ethyl 4-aminobenzoate, 4-aminoacetophenone and 2-aminobenzoic acid in acetic acid having freshly melted sodium acetate afforded pyrazolyl-imidazol-5-ones **3-6**, respectively. The mechanism of formation of the pyrazolyl-imidazolones **3-6** was illustrated by aminolysis nucleophilic attack of amino group of aromatic amines at the carbonyl group of lactone ring involving ring opening followed by a cyclocondensation step with the elimination of water molecule. (Scheme 2).



Scheme 2. Reactions of the pyrazolyl-oxazol-5(4*H*)-one **2** with different aromatic amines.

Structures of the pyrazolyl-imidazolones **3-6** were established by both spectral data and elemental analysis. For example, compound **3** exhibited in the IR spectrum characteristic absorption bands at 3331 and 1641 cm^{-1} because of phenolic OH and amidic carbonyl groups, respectively. In addition, the carbonyl ester group of compound **4** appeared at 1712 cm^{-1}. Compound **3** revealed in the ^{1}H-NMR spectrum singlet signal at δ 9.44 ppm as a result of OH proton, whereas for compound **4**, it exhibited a triplet signals at δ 1.30 ppm for the methyl protons of $COOCH_2CH_3$ group and a quartet signals at δ 4.30 ppm because of CH_2 protons of $COOCH_2CH_3$ group. Furthermore, the ^{1}H-NMR spectrum of imidazolone **5** exhibited a singlet signal at δ 2.51 ppm as a result of CH_3 protons, beside the signals for the other expected protons. The mass spectra of compounds **3-6** appeared the molecular ion peaks at *m/z* = 482.85 (M^+, 59.83), 538.22 (M^+, 10.96), 508.89 (M^+, 14.59) and 510.0 (M^+, 8.81), respectively, which are in agreement with the molecular formula of the proposed structures. Heating the pyrazolyl-imidazolone **3** with ethyl 2-chloroacetate in acetone containing potassium carbonate to give the corresponding phenoxyethyl acetate **7**. In addition, acetylation of **3** by heating in acetic anhydride yielded the phenyl acetate **8**. Benzoylation of compound **3** using benzoyl chloride in pyridine gave the phenyl benzoate **9**. Sulfonylation of **3** with benzenesulfonyl chloride by heating in pyridine gave the phenyl benzenesulfonate **10** (Scheme 3). The IR spectra of imidazolones **7-10** lacked absorption band due to OH group. Imidazolone **7** disappeared a singlet signal due to OH proton in the ^{1}H-NMR spectrum and appeared a triplet signals at δ 1.19 ppm due to methyl protons of $COOCH_2CH_3$ group, a quartet signals at δ 4.15 ppm because of CH_2 protons of $COOCH_2CH_3$ group and a singlet signal at δ 4.84 ppm for -O-$\underline{CH_2}$ protons. Furthermore, imidazolone **8** appeared in the ^{1}H-NMR spectrum a singlet signal at δ 2.29 ppm as a result of CH_3 protons and lacked a singlet signal due to OH proton. The mass spectra of imidazolones **7-10** evidenced the molecular ion peaks at *m/z* = 568.99 (M^+, 15.11), 524.79 (M^+, 18.94), 586.78 (M^+, 28.14) and 622.20 (M^+, 38.23), respectively, which are in agreement with the molecular formula of the proposed structures.



Scheme 3. Synthesis of the pyrazolyl-imidazolone derivatives **7-10**.

2.2. Pharmacology

Antioxidant activity using ABTS method

The effect of the synthesized pyrazolylimidazolones **2-10** on ABTS was assessed by means of the technique defined by Lissi *et al* [34]. Table 1 presented that compounds **3-7** and **10** showed good to moderate antioxidant activities while compounds **2**, **8** and **9** showed low activities compared to the results of ascorbic acid. Between the results of the evaluated compound, it was found that compound **6** has the most potent antioxidant activity. Fig. 1 showed a comparison of the % inhibition of the investigated compounds related to the value of ascorbic acid. Fig. 1 also showed the structure activity relationship of the potent prepared compounds in which the following results can be explained: (1) compound **6** showed the potent antioxidant activity due to the presence of carboxylic acid moiety which can be enhance the antioxidant results. (2) The high results of compounds **4** and **10** are due to the presence of two and three oxygen atoms of ethyl benzoate and sulfonate functions, respectively which are electron rich centers that trap the free radical of ABTS. (3) The phenolic moiety of compound **3** enhance the antioxidant capacity due to the presence of stable free radical.

Table 1. Antioxidant activity for the synthesized compounds using ABTS assay.

Entry	Compound No.	Absorbance	%Inhibition
1	**Control ofABTS**	0.500	0
2	**Ascorbic acid**	0.058	88.4
3	2	0.409	18.2
4	3	0.386	22.8
5	4	0.372	25.6
6	5	0.393	21.4
7	6	0.334	33.2
8	7	0.395	21.0
9	8	0.425	15.0
10	9	0.424	15.2
11	10	0.375	25.0

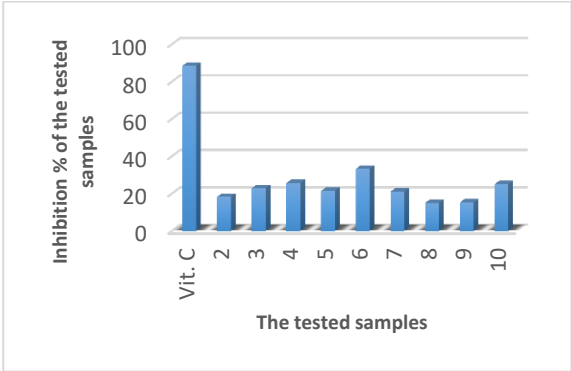


Fig. 1. Comparison of the % inhibition of the tested samples.

3. Materials and Methods

Melting points were determined in degree Celsius on an electrothermal Gallenkamp (Germany) apparatus. The infrared spectra υ cm^{-1} (KBr) were determined on a Mattson 5000 FTIR Spectrometer (USA). The ^{1}H-NMR spectra were run on a Bruker Avance III spectrophotometer at 400 MHz. The mass measurements were recorded on Kratos MS (Kratos Analytical Instrument, Ramsey, NJ) apparatus by EI mode with ionizing voltage 70 eV. Elemental (C, H, and N) analyses were measured on Perkin-Elmer 2400 (PerkinElmer Instruments, Shelton, CT).

General procedure for the preparation of pyrazolylimidazolones 3-6

To a mixture of the oxazol-5(4*H*)-one **2** (1.95 g, 0.005 mol) in acetic acid (20 mL) and sodium acetate (0.615 g, 0.0075 mol), 4-aminophenol, ethyl 4-aminobenzoate, 4-aminoacetophenone or 2-aminobenzoic acid (0.0055 mol) was added. Reflux the mixture for

6-10 h, stand at 25°C to cool and the precipitated solid pyrazolylimidazolone was separated by filtration and ethyl alcohol was used for recrystallization.

4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-1-(4-hydroxyphenyl)-2-phenyl-1,4-dihydro-5*H*-imidazol-5-one (**3**). Yellow crystals; yield 61%; mp 222-224°C. IR (ν_{max}, cm^{-1}): 3331 (OH), 1641 (CO, amidic), 1593 (C=N), 1519 (C=C). ^{1}H-NMR (DMSO-d_6) δ (ppm): 9.44 (s, 1H, OH), 8.44 (s, 1H, CH-pyrazole), 7.83 (s, 1H, CH=), 7.68-6.90 (m, 19H, Ar-H). MS: (ESI) (*m/z*, %): 484.12 (M^+ + 2, 40.25), 482.85 (M^+, 59.83), 469.72 (25.43), 458.30 (21.49), 394.40 (36.68), 341.75 (32.90), 313.18 (74.46), 253.94 (44.6), 213.96 (45.54), 184.49 (100.0), 178.16 (92.20), 157.10 (39.46), 119.83 (46.25), 92.06 (45.35). Calc. for $C_{31}H_{22}N_4O_2$ (482.54): C, 77.16; H, 4.60; N, 11.61%; Found: C, 77.18; H, 4.62; N, 11.65%.

Ethyl 4-(4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)-benzoate (**4**). Yellow crystals; yield 52%; mp 260-262°C. IR (ν_{max}, cm^{-1}): 1712 (CO, ester), 1646 (CO, amidic), 1598 (C=N), 1522 (C=C). ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.88 (s, 1H, CH-pyrazole), 8.38-7.17 (m, 19H, Ar-H), 7.79 (s, 1H, CH=), 4.30 (q, 2H, $\underline{CH_2}CH_3$), 1.30 (t, 3H, $CH_2\underline{CH_3}$). MS: (ESI) (*m/z*, %): 538.22 (M^+, 10.96), 513.10 (33.65), 488.79 (39.31), 450.46 (41.79), 420.35 (53.40), 392.95 (98.22), 303.69 (36.46), 283.97 (38.91), 270.47 (32.54), 220.01 (100.0), 197.09 (42.46), 145.06 (57.86), 97.95 (23.30), 69.09 (44.26). Calc. for $C_{34}H_{26}N_4O_3$ (538.61): C, 75.82; H, 4.87; N, 10.40%; Found: C, 75.83; H, 4.90; N, 10.42%.

1-(4-Acetylphenyl)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-1,4-dihydro-5*H*-imidazol-5-one (**5**). Yellow crystals; yield 66%; mp 233-235°C. IR (ν_{max}, cm^{-1}): 1680 (CO, amidic), 1646 (CO, ketonic), 1597 (C=N), 1530 (C=C). ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.44 (s, 1H, CH-pyrazole), 8.01-7.28 (m, 19H, Ar-H), 7.83 (s, 1H, CH=), 2.51 (s, 3H, $COCH_3$). MS: (ESI) (*m/z*, %): 508.34 (M^+, 46.69), 507.26 (M^+-1, 39.33), 500.06 (32.96), 493 (M^+-CH_3, 33.23), 472.93 (28.23), 422.08 (33.47), 373.86 (61.46), 347.74 (100.0), 293.97 (66.91), 270.95 (33.20), 258.68 (39.57), 236.55 (33.71), 228.17 (66.87), 201.37 (58.03), 120.87 (80.16), 93.67 (61.97), 74.29 (27.06), 56.81 (75.85). Calc. for $C_{33}H_{24}N_4O_2$ (508.58): C, 77.94; H, 4.76; N, 11.02%; Found: C, 77.96; H, 4.77; N, 11.04%.

2-(4-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)benzoic acid (**6**). Yellow crystals; yield 51%; mp 258-260°C. IR (ν_{max}, cm^{-1}): 3411 (OH, acid), 1690 (CO, acid), 1652 (CO, amidic), 1594 (C=N), 1556 (C=C). ^{1}H-NMR (DMSO-d_6) δ (ppm): 12.35 (s, 1H, OH), 8.61 (s, 1H, CH-pyrazole), 7.96-7.23 (m, 19H, Ar-H), 7.85 (s, 1H, CH=). MS: (ESI) (*m/z*, %): 510.0 (M^+, 8.81), 498.39 (39.22), 496.23 (28.32), 482.11 (M^+- CO, 26.04), 459.99 (16.56), 413.47 (28.54), 323.21 (25.45), 300.08 (34.05), 285.85 (24.16), 274.86 (100.0), 229.36 (46.33), 161.77 (21.51), 121.39 (23.66), 68.80 (87.22), 59.55 (13.70). Calc. for $C_{32}H_{22}N_4O_3$ (510.55): C, 75.28; H, 4.34; N, 10.97%; Found: C, 75.30; H, 4.34; N, 10.99%.

Ethyl 2-(4-(4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)phenoxy)acetate (**7**).

To a mixture of the pyrazolyl-imidazolone **3** (2.41 g, 0.005 mol) in acetone (20 mL) and K_2CO_3 (1.035 g, 0.0075 mol), ethyl 2-chloroacetate (0.61 g, 0.005 mol) was added. Heat the mixture for 4 h, stand at 25°C to cool. The precipitated solid phenoxyethyl acetate **7** was separated by filteration and ethyl alcohol was used for recrystallization. Orange needles; yield 75%; mp 266-268°C. IR (ν_{max}, cm^{-1}): 1726 (CO, ester), 1647 (CO, amidic), 1595 (C=N), 1555 (C=C). ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.37 (s, 1H, CH-pyrazole), 7.79-7.00 (m, 19H, Ar-H), 7.77 (s, 1H, CH=), 4.84 (s, 2H, -O-$\underline{CH_2}$), 4.15 (q, 2H, $\underline{CH_2}CH_3$), 1.19 (t, 3H, $CH_2\underline{CH_3}$). MS: (ESI) (*m/z*, %): 568.99 (M^+, 15.11), 468.11 (13.56), 376.23 (31.12), 292.91 (35.14), 255.23 (100.0), 219.22 (14.33), 151.21 (44.31), 111.33 (13.16), 68.80 (55.42), 59.55 (13.70). Calc. for $C_{35}H_{28}N_4O_4$ (568.63): C, 73.93; H, 4.96; N, 9.85%; Found: C, 73.95; H, 4.98; N, 9.87%.

4-(4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)phenyl acetate (**8**).

The pyrazolyl-imidazolone **3** (4.82 g, 0.01 mol) in Ac_2O (10 mL) on reflux for 2 h, then stand at 25°C to cool and cold water was used

for dilution. The formed solid phenyl acetate **8** has been separated by filteration and ethyl alcohol was used for recrystallization.

Yellow crystals; yield 88%; mp 278-280^{o}C. IR (ν_{max}, cm^{-1}): 1712 (CO, ester), 1666 (CO, amidic), 1596 (C=N), 1565 (C=C). ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.38 (s, 1H, CH-pyrazole), 7.79-7.17 (m, 19H, Ar-H), 7.77 (s, 1H, CH=), 2.29 (s, 3H, CO$\underline{CH_3}$). MS: (ESI) (*m/z*, %): 524.79 (M^+, 18.94), 482.23 (12.15), 390.01 (34.52), 354.34 (54.47), 335.31 (56.60), 319.80 (100.00), 282.39 (30.68), 191.76 (30.30), 167.63 (57.23), 53.69 (61.36). Calc. for $C_{33}H_{24}N_4O_3$ (524.58): C, 75.56; H, 4.61; N, 10.68%; Found: C, 75.58; H, 4.63; N, 10.69%.

General procedure for the synthesis of the pyrazolyl-imidazolones 9 and 10

To a mixture of the pyrazolyl-imidazolone **3** (2.41 g, 0.005 mol) in pyridine (15 mL), benzoyl chloride or benzenesulfonyl chloride (0.006 mol) was added. The products were heated on water bath for 3 h, then stand to cool at 25^{o}C and cold water was used for dilution. The formed solid pyrazolyl-imidazolone has been collected by filteration and ethyl alcohol was used for recrystallization.

4-(4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)phenyl benzoate (**9**). Yellow crystals; yield 64%; mp 270-272^{o}C. IR (ν_{max}, cm^{-1}): 1710 (CO, ester), 1650 (CO, amidic), 1599 (C=N), 1549 (C=C). ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.44 (s, 1H, CH-pyrazole), 8.07-7.06 (m, 24H, Ar-H), 7.98 (s, 1H, CH=). MS: (ESI) (*m/z*, %): 586.78 (M^+, 28.14), 524.79 (20.32), 470.82 (35.62), 466.30 (39.57), 390.40 (37.58), 312.69 (28.03), 281.75 (100.00), 197.71 (31.18), 150.16 (41.14), 103.81 (20.60), 41.53 (35.99). Calc. for $C_{38}H_{26}N_4O_3$ (586.65): C, 77.80; H, 4.47; N, 9.55%; Found: C, 77.83; H, 4.47; N, 9.57%.

4-(4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)phenyl benzenesulfonate (**10**). Yellow crystals; yield 67%; mp 288-290^{o}C. IR (ν_{max}, cm^{-1}): 1673 (CO, amidic), 1607 (C=N), 1572 (C=C), 1375 (SO_3). ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.38 (s, 1H, CH-pyrazole), 7.89-6.91 (m, 24H, Ar-H), 7.80 (s, 1H, CH=). MS: (ESI) (*m/z*, %): 622.20 (M^+, 38.23), 593.12 (45.66), 446.10 (51.14), 320.76 (51.81), 245.74 (34.60), 123.17 (100.00), 93.62 (38.75). Calc. for $C_{37}H_{26}N_4O_4S$ (622.70): C, 71.37; H, 4.21; N, 9.00%; Found: C, 71.39; H, 4.21; N, 9.03%.

In summary, A new series of pyrazolyl-imidazolone derivatives **3-10** were synthesized starting from the commercially accessible pyrazolyl-oxazol-5(4*H*)-one **2** and investigated their antioxidant efficiency using ABTS assay. The results demonstrated that imidazolones **3-7** and **10** showed good to moderate antioxidant activities. Particularly compound **6** demonstrated to be the best compound in this investigation with potent antioxidant activity

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