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Facile and Efficient Routes to New Pyrazolyl-imidazolone Analogues with Promising Antioxidant Activity.

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ABSTRACT

The readily obtainable pyrazolyl-oxazol-5(4H)-one **2** was realized and reacted with an equimolar amounts of p-phenylenediamine in glacial acetic acid containing freshly sodium acetate to yield 1-(4-aminophenyl)-4-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-2-phenyl-1,4-dihydro-5H-imidazol-5-one (**3**) in acceptable yield. The latter product **3** was served as synthon for the synthesis of polyfunctionally substituted pyrazolyl-imidazolone derivatives via its reactions with the convenient reagents. In another route, the behavior of the pyrazolyl-oxazol-5(4H)-one **2** towards some heterocyclic amines to attain pyrazolyl-imidazolone derivatives was also presented. The antioxidant activity has been examined using ABTS assay and pyrazolyl-imidazolone **14** has the most potent antioxidant activity with inhibition percentage at 66.4% while pyrazolyl-oxazolone **2** has the lowest activity with inhibition percentage at 18.2% compared to L-ascorbic acid.

Keywords: Oxazolone, Imidazolone, Pyrazole, *p*-Phenylenediamine, Antioxidant activity.

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INTRODUCTION

The pyrazole ring is an important structural motive found in diverse biologically active compounds because of the easiness preparation as well as its valuable biological and pharmacological effects [1-3]. The imidazolone moiety is the basic core of many synthetic and natural products [4] which have remarkable biological performance [5]. Imidazolones have been reported as potent analogues of V-RAF murine growth [6], phosphodiesterase inhibitors [7], antioxidant and cytotoxic agents [8]. These compounds were also antagonists of some receptors carrying neurokinin-1 [9] and the dopamine receptor [10]. Recently, the synthesis of products containing imidazolone scaffold [11] has been increased due to their valuable biological significance. Imidazolone is the nucleus of fluorescent probes associated with fluorescent proteins (**A**) [12] as well as structural fragments of active compounds against obesity-related disorders and hypertension (**B**) [13]. In addition, they are beneficial synthons for the preparation of natural alkaloids, for example, compounds **A** and **C** [14]. They have agrochemical applications such as herbicides, which are used to control weeds in pulses, grains and peanuts (**D**) [15] (Figure 1). Continuing our earlier work for the production of novel heterocyclic compounds with biological consequence [16], we report in this investigation a simple synthetic methods for the preparation of heterocyclic compounds that incorporate both two biolabile components (pyrazole and imidazolone) into a single molecule in order to assess their activities as antioxidant agents.

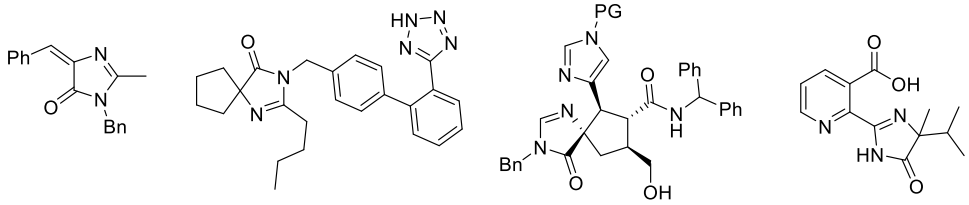
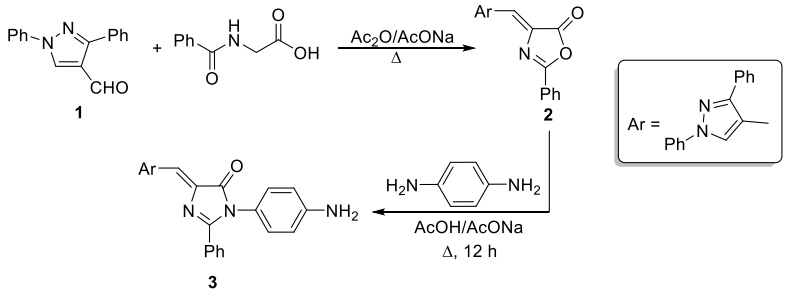


Figure 1. Structures of significant active imidazolones.

RESULTS AND DISCUSSION

Chemistry

The starting material pyrazolyl-oxazol-5(4*H*)-one derivative **2** was prepared in good yield as previously described [17] *via* heating 1,3-diphenyl-4-formyl-1*H*-pyrazole (**1**) [18] with *N*-benzoylglycine in acetic anhydride containing freshly fused sodium acetate. The reaction of **2** with an equimolar amount of *p*-phenylenediamine in glacial acetic acid in the presence of fused sodium acetate gave 1-(4-aminophenyl)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-1,4-dihydro-5*H*-imidazol-5-one (**3**) with an acceptable yield after purification by recrystallization (Scheme 1). The formation of pyrazolyl-imidazolone **3** is consistent with the announced results of lactone treatment with *p*-phenylenediamine [19-21]. Both IR and ^{1}H-NMR spectrum could support pyrazolyl-imidazolone **3** where the amino group showed two vibrational bands at 3300 and 3220 cm^{-1} in the IR spectrum and also appeared as a broad singlet signal at δ 6.50 ppm in the ^{1}H-NMR. The mass spectra of **3** evidenced the molecular ion peak at *m/z* = 481.54 (M$^+$, 74.48) which is in compact with the molecular formula of the proposed structure. Pyrazolyl-imidazolone **3** is also supported *via* its reactions with some convenient reagents. We have demonstrated the potential utility of **3** for achieving an easy and appropriate route to polyfunctionally substituted pyrazolyl-imidazolone derivatives of possible pharmaceutical importance.



Scheme 1. Synthesis of 1-(4-aminophenyl)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-1,4-dihydro-5*H*-imidazol-5-one (3)

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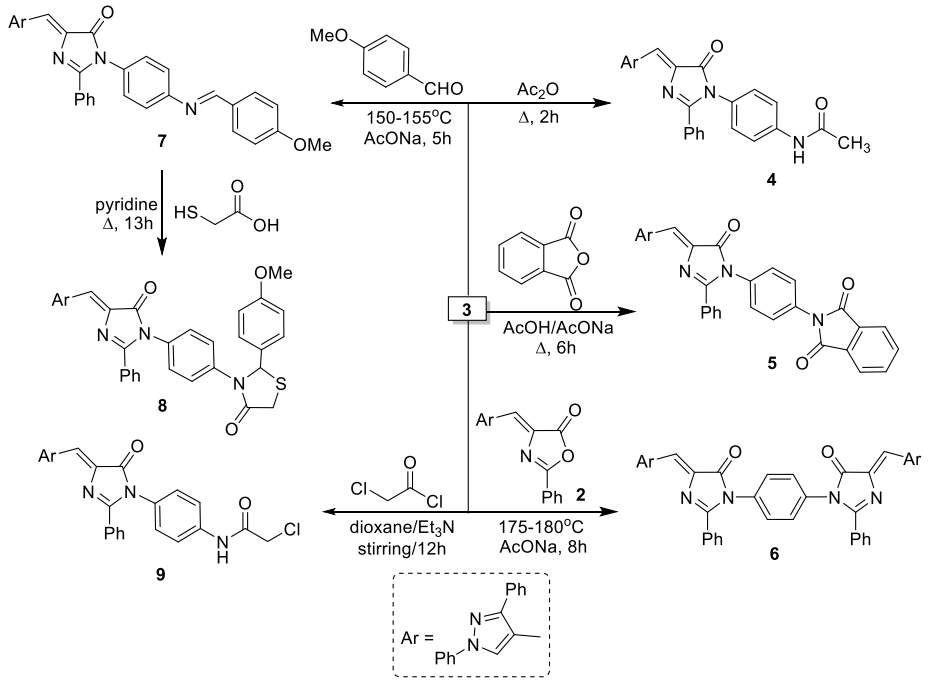
Thus, acetylation of pyrazolyl-imidazolone **3** by heating in acetic anhydride yielded the respective *N*-acetyl product **4** (Scheme 2) which was emphasized by ^{1}H NMR spectrum through the presence of two singlet signals at δ 2.35 and 9.95 ppm due to CH_3 and NH protons, respectively. Cyclocondensation of **3** with phthalic anhydride in refluxing glacial acetic acid and fused sodium acetate gave the phthalimide derivative **5**. Also, the neat reaction of **3** with pyrazolyl-oxazol-5(4*H*)-one **2** at 175–180 °C in the presence of sodium acetate yielded 1,1'-(1,4-phenylene)bis(4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-1,4-dihydro-5*H*-imidazol-5-one) (**6**). The mass spectra of **6** evidenced the molecular ion peak at *m/z* = 854.26 (M^+, 31.40), which is consistent with the molecular formula of the proposed structure. Moreover, the condensation of the respective aromatic amine **3** with *p*-anisaldehyde in equimolar amounts catalyzed by sodium acetate at 150–155 °C yielded the Schiff's base **7** which was proved by the presence of CH=N at δ 8.23 ppm and OCH_3 at δ 3.80 ppm in the ^{1}H NMR spectrum. Subsequently, cyclization of the Schiff's base **7** with 2-mercaptoacetic acid in pyridine under reflux produced successfully the anticipated thiazolidin-4-one derivative **8**. The appearance of signals due to thiazolidinone-H_2 and H_5 at δ 6.50 and 3.95 ppm, respectively in the ^{1}H NMR spectrum supported structure **8**. To additionally investigate the synthetic potential of pyrazolyl-imidazolone **3**, we have examined its reactivity towards chloroacetyl chloride. When a solution of **3** in dioxane containing three drops of triethylamine as a basic catalyst was stirred with chloroacetyl chloride at 25 °C, the 2-chloroacetamide derivative **9** was successfully isolated in a moderate yield. ^{1}H NMR spectrum revealed that 2-chloroacetamide derivative **9** was synthesized through two singlets at δ 4.29 and 10.37 ppm due to CH_2 and NH protons, respectively. The mass spectra of **9** evidenced the molecular ion peak at *m/z* = 559.60 (M^++1, 13.45), which is in agreement with the molecular formula of the proposed structure. The 2-chloroacetamide derivative **9** is a promising starting material for the preparation of other novel heterocyclic compounds *via* its reactions with some chemical reagents.



Scheme 2. Synthesis of imidazolone derivatives 4-9

Thiazolidin-4-one **10** was easily obtained by treatment **9** with ammonium thiocyanate in dioxane under reflux for 9 h and was proposed for this reaction product on the basis of spectral and analytical data (Scheme 3). Thiazolidin-4-one **10** was synthesized as mentioned by Vicini *et al* [22] *via* intramolecular cyclization and then by Dimroth-like rearrangements [23]. The chemical behavior of the 2-chloroacetamide derivative **9** has also been studied with respect to some sulfur nucleophiles. Thus, heating **9** with 2-benzo[d]thiazole-2-thiol or 5-amino-1,3,4-thiadiazole-2-thiol in dioxane and triethylamine afforded the corresponding sulfide derivatives **11** and **12**, respectively. The spectroscopic data of sulfide derivatives **11** and **12** were completely compact with the proposed structures.

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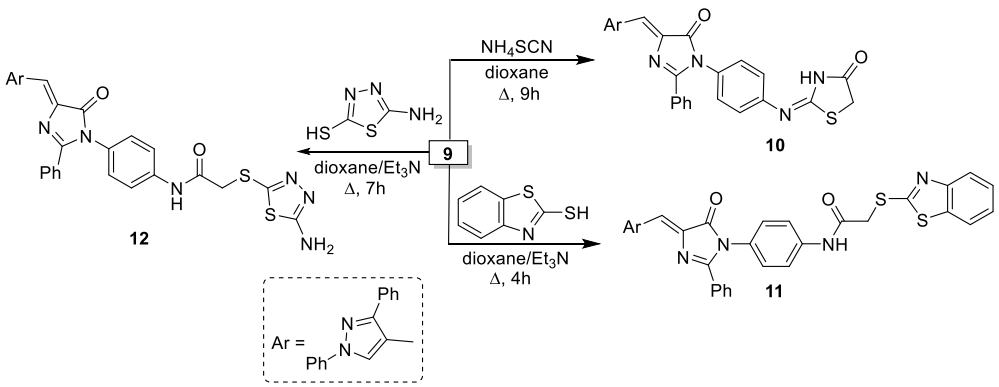
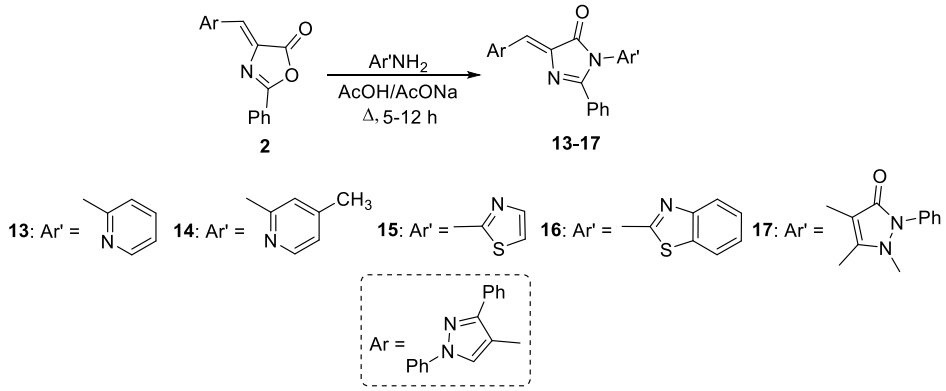


Scheme 3. **Synthesis of imidazolone derivatives 10-12**

Finally, the reaction of equimolar amounts of **2** with each of pyridin-2-amine, 4-methylpyridin-2-amine, thiazol-2-amine, benzo[d]thiazol-2-amine or antipyrine-4-amine in glacial acetic acid and sodium acetate yielded the expected 1-(hetaryl)-1,4-dihydro-5*H*-imidazol-5-ones **13-17**, respectively (Scheme 4).



Scheme 4. Reaction of pyrazolyl-oxazol-5(4*H*)-one 2 with some heterocyclic amines

Antioxidant activity

The antioxidant activity of imidazolones [8,24] and pyrazoles [25] were reported using several techniques. The effect of the synthesized compounds **2-17** on ABTS was assessed by means of the technique defined by Lissi *et al* [26]. *L*-Ascorbic acid (vitamin C) was used as an antibiotic standard. Table 1 presented that the tested compounds **2-17** exhibited variable degrees of inhibitory activity. The highest antioxidant activity was demonstrated by the pyrazolyl-imidazolones **8**, **13**, **14** and **17** with inhibition percentage at 61.4, 64.2, 66.4 and 61.0%, respectively. Remarkable inhibitory activity was also displayed by pyrazolyl-imidazolones **10**-**12**, **15** and **16**. The remaining pyrazolyl-imidazolones **3-7** and **9** appeared moderate activity with inhibition percentage range of 44.2-49.6%. Further interpretation of the results demonstrated that pyrazolyl-imidazolone **14** has the most potent antioxidant activity with inhibition percentage at 66.4% while pyrazolyl-oxazolone **2** has the lowest activity with inhibition percentage at 18.2%. The structure activity relationship of the prepared pyrazolyl-imidazolones in which the following results can be postulated: (1) Conversion of Pyrazolyl-oxazolone **2** to pyrazolyl-imidazolones **3-17** increase the activity. So, the presence of a basic skeleton imidazolone is indispensable for the wide spectrum of antioxidant efficiency. (2) Cyclization of the Schiff's base **7** to thiazolidin-4-one derivative **8** enhanced the antioxidant activity. (3) Unfortunately, activity did not change significantly when pyrazolyl-imidazolone **3** was transformed into bis-pyrazolyl-imidazolone **6**. High antioxidant activity can be correlated with low electron density of ring systems. (4) The incorporation of pyridine, thiazole, benzothiazole or antipyrine moieties to the imidazolone nucleus produced high antioxidant activity.

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

Entry	Compound No.	Absorbance	Inhibition %
1	**Control of ABTS**	0.500	0
2	***L*-Ascorbic acid**	0.058	88.4
3	**2**	0.409	18.2
4	**3**	0.260	48.0
5	**4**	0.255	49.0
6	**5**	0.279	44.2
7	**6**	0.252	49.6
8	**7**	0.264	47.2
9	**8**	0.193	61.4
10	**9**	0.258	48.4
11	**10**	0.242	51.6
12	**11**	0.239	52.2
13	**12**	0.243	51.4
14	**13**	0.179	64.2
15	**14**	0.168	66.4
16	**15**	0.216	56.8
17	**16**	0.209	58.2
18	**17**	0.195	61.0

MATERIALS AND METHODS

Melting points were determined on an electrothermal Gallenkamp apparatus (Germany) and are uncorrected. The IR spectra were measured on a Mattson 5000 FTIR Spectrometer (USA) in potassium bromide discs. ^{1}H NMR spectra were measured in DMSO-d_6 as solvent at 400 MHz on a Bruker Avance III spectrometer using TMS as internal standard and chemical shifts are expressed as δ_{ppm}. The mass spectra were recorded on Kratos MS (Kratos Analytical Instrument, Ramsey, NJ) apparatus (USA) and the ionizing voltage was 70 ev. Elemental analyses have been achieved by the Micro-analytical unit of Faculty of Science, Cairo University, Egypt. All reactions in the present consideration have been followed by TLC (silica gel, aluminum sheets 60 F254, Merck).

1-(4-Aminophenyl)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-1,4-dihydro-5*H*-imidazol-5-one (**3**)

A solution of **2** (1.95 g, 0.005 mol) in glacial acetic acid (10 ml) was added dropwise for 30 min to a stirred mixture of *p*-phenylenediamine (0.54 g, 0.005 mol) and freshly fused sodium acetate (0.42 g, 0.005 mol) in hot glacial acetic acid (10 ml), followed by stirring and heating for 12 hr. The reaction mixture was allowed to remain overnight at 25 ^{o}C. The precipitated solid product was filtered off, washed several times with acetic acid and recrystallized from EtOH/DMF mixture (1:1). Yield 0.99 g (41%); yellow crystals; mp 260-262 ºC; IR (KBr) ν_{max}/cm^{-1}: 3300-3220 (NH_2), 1640 (CO, amidic carbonyl), 1598 (C=N), 1565 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.59 (s, 1H, CH-pyrazole), 8.08 (s, 1H, CH=), 7.82-7.03 (m, 19H, Ar-H), 6.50 (br, s, 2H, NH_2); MS: (*m/z*, %): 481.54 (M^+, 74.48), 479.01 (30.17), 478.26 (24.94), 467.72 (25.56), 441.12 (35.40), 430.67 (47.82), 408.20 (53.43), 365.47 (47.48), 335.31 (53.05), 321.18 (83.69), 311.22 (80.34), 287.61 (47.48), 269.64 (66.81), 259.47 (85.42), 242.94 (44.94), 167.48 (43.07), 133.18 (100.0), 120.63 (94.0), 98.02 (71.61), 50.48 (41.25). Anal. Calcd for $C_{31}H_{23}N_5O$ (481.56): C 77.32; H 4.81; N 14.54%. Found: C 77.35; H 4.83; N 14.55%.

***N*-(4-(4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)-phenyl)acetamide** (**4**)

A solution of imidazolone **3** (1.44 g, 0.003 mol) in acetic anhydride (10 mL) was refluxed for 2 h, left to cool at room temperature and then poured onto crushed ice. The solid product obtained was filtered off, dried and ethyl alcohol was used for recrystallization. Yield 1.37 g (87%); yellow crystals; mp 288-290 ºC; IR (KBr) ν_{max}/cm^{-1}: 3219 (NH), 2920, 2871 (C-H, stretching), 1665 (2CO, amidic carbonyl), 1595 (C=N), 1534 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 9.95 (s, 1H, NH), 8.44 (s, 1H, CH-pyrazole), 7.89 (s, 1H, CH=), 7.71-7.02 (m, 19H, Ar-H), 2.35 (s, 3H, CH_3); MS: (*m/z*, %): 523.13 (M^+, 40.10), 522.39 (37.68), 515.88 (66.24), 509.65 (42.38), 502.28

(23.77), 491.46 (30.57), 483.51 (36.41), 458.61 (46.67), 452.49 (91.51), 448.58 (100.0), 427.94 (40.28), 409.90 (93.43), 396.15 (47.63), 334.60 (33.90), 275.94 (32.30), 242.25 (55.38), 189.56 (59.08), 140.88 (25.41), 107.67 (93.70), 88.63 (40.69). Anal. Calcd for $C_{33}H_{25}N_5O_2$ (523.60): C 75.70; H 4.81; N 13.38%. Found: C 75.72; H 4.82; N 13.40%.

2-(4-(4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)phenyl)isoindoline-1,3-dione (**5**)

To a mixture of imidazolone **3** (1.44 g, 0.003 mol) and phthalic anhydride (0.44 g, 0.003 mol) in glacial acetic acid (10 mL), freshly prepared sodium acetate (0.25 g, 0.003 mol) was added. The reaction mixture was refluxed for 6 h and then left to cool to room temperature. Product **5** was obtained as a crude product after being poured onto crushed ice and ethyl alcohol was used for recrystallization. Yield 1.23 g (67%); yellow crystals; mp 257-259 ºC; IR (KBr) ν_{max}/cm^{-1}: 1688, 1672 (3CO, amidic carbonyl), 1593 (C=N), 1589 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.32 (s, 1H, CH-pyrazole), 8.16 (s, 1H, CH=), 7.81-7.16 (m, 23H, Ar-H); MS: (*m/z*, %): 611.07 (M$^+$, 30.37), 610.39 (M$^+$ -1, 18.02), 598.79 (17.13), 587.21 (20.17), 559.46 (25.22), 550.21 (35.87), 548.53 (100.0), 487.06 (15.30), 440.47 (30.77), 393.42 (17.55), 342.33 (27.97), 319.49 (46.86), 270.38 (47.35), 218.35 (47.18), 193.35 (30.84), 169.56 (22.40), 94.75 (23.22), 75.40 (32.28), 55.44 (51.53). Anal. Calcd for $C_{39}H_{25}N_5O_3$ (611.66): C 76.58; H 4.12; N 11.45%. Found: C 76.60; H 4.14; N 11.47%.

1,1'-(1,4-Phenylene)bis(4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-1,4-dihydro-5*H*-imidazol-5-one) (**6**)

A mixture of imidazolone **3** (1.44 g, 0.003 mol) and pyrazolyl-oxazol-5(4*H*)-one **2** (1.17 g, 0.003 mol) catalyzed by fused sodium acetate (0.25 g, 0.003 mol) were heated in an oil bath at 175-180 ºC for 8 h. After accomplishment of the reaction by TLC, the solid bis-pyrazolyl-imidazolone formed was washed several times with diethyl ether, dried well, and ethyl alcohol was used for recrystallization. Yield 1.05 g (41%); brown crystals; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1}: 1678 (2CO, amidic carbonyl), 1599 (C=N), 1547 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 9.34 (s, 2H, 2CH-pyrazole), 8.31 (s, 2H, 2CH=), 8.02-7.13 (m, 34H, Ar-H); MS: (*m/z*, %): 854.26 (M$^+$, 31.40), 850.88 (11.31), 844.85 (21.46), 813.85 (33.58), 799.21 (31.66), 775.45 (71.12), 695.14 (33.19), 660.91 (100.0), 649.37 (45.02), 540.66 (17.59), 511.14 (24.32), 440.83 (30.59), 400.68 (59.87), 331.18 (59.67), 258.65 (26.54), 215.86 (33.47), 208.58 (37.28), 138.51 (37.57), 106.61 (21.62). Anal. Calcd for $C_{56}H_{38}N_8O_2$ (854.97): C 78.67; H 4.48; N 13.11%. Found: C 78.69; H 4.49; N 13.13%.

4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-1-(4-((4-methoxybenzylidene)amino)phenyl)-2-phenyl-1,4-dihydro-5*H*-imidazol-5-one (**7**)

A mixture of imidazolone **3** (1.44 g, 0.003 mol), *p*-anisaldehyde (0.41 g, 0.003 mol) and fused sodium acetate (0.25 g, 0.003 mol) were heated in an oil bath at 150-155 ºC for 5 h. After accomplishment of the reaction by TLC, the solid Schiff's base formed was washed several times with diethyl ether, dried well, and ethyl alcohol was used for recrystallization. Yield 1.31 g (73%); brown crystals; mp 251-253 °C; IR (KBr) ν_{max}/cm^{-1}: 2928, 2868 (CH-stretching), 1672 (CO, amidic carbonyl), 1643 (C=N), 1590 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.55 (s, 1H, CH-pyrazole), 8.23 (s, 1H, CH=N), 7.96 (s, 1H, CH=C), 7.95-7.17 (m, 23H, Ar-H), 3.80 (s, 3H, OCH_3); MS: (*m/z*, %): 599.54 (M$^+$, 10.76), 598.79 (19.64), 587.07 (14.09), 566.12 (16.55), 535.65 (15.65), 505.24 (12.99), 483.80 (17.24), 422.93 (16.97), 343.73 (25.17), 279.35 (20.52), 222.42 (23.51), 166.30 (40.74), 150.82 (45.37), 149.63 (100.0), 107.84 (40.94), 75.68 (17.77), 43.62 (12.02). Anal. Calcd for $C_{39}H_{29}N_5O_2$ (599.69): C 78.11; H 4.87; N 11.68%. Found: C 78.13; H 4.88; N 11.70%.

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

A mixture of Schiff's base **7** (1.79 g, 0.003 mol) and 2-mercaptoacetic acid (0.28 g, 0.003 mol) in pyridine (15 mL) were refluxed for 13 h and cooled to room temperature. The product was obtained as a crude product after being poured onto crushed ice-HCl and ethyl alcohol was used for recrystallization. Yield 1.07 g (53%); yellow crystals; mp 281-283 °C; IR (KBr) ν_{max}/cm^{-1}: 2923, 2864 (CH-stretching), 1666, 1641 (2CO, amidic carbonyl), 1597 (C=N), 1554 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.68 (s, 1H, CH-pyrazole), 8.27-7.15 (m, 23H, Ar-H), 8.23 (s, 1H, CH=), 6.50 (s, 1H, CH-thiazolidin-4-one), 3.95 (s, 2H, CH_2-thiazolidin-4-one), 3.76 (s, 3H, OCH_3); MS: (*m/z*, %): 674.91 (M$^+$ +1, 23.28), 673.47 (M$^+$, 19.20), 663.85 (56.13), 658.06 (47.17), 648.78 (52.50), 629.76

(55.54), 605.55 (54.62), 584.13 (40.47), 482.13 (31.23), 413.04 (46.50), 356.74 (27.02), 329.96 (47.03), 251.38 (47.78), 235.10 (100.0), 196.74 (28.24), 150.81 (47.92), 86.83 (22.89), 71.36 (35.11), 50.63 (22.86). Anal. Calcd for $C_{41}H_{31}N_5O_3S$ (673.79): C 73.09; H 4.64; N 10.39%. Found: C 73.11; H 4.66; N 10.40%.

2-Chloro-*N*-(4-(4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)phenyl)acetamide (**9**)

A mixture of imidazolone **3** (1.44 g, 0.003 mol) and chloroacetyl chloride (0.34 g, 0.003 mol) in dioxane (20 mL) and Et_3N (3 drops) were stirred for 12 h. The product was obtained after being poured onto crushed ice and ethyl alcohol was used for recrystallization. Yield 1.10 g (66%); yellow crystals; mp 231-233 °C; IR (KBr) ν_{max}/cm^{-1}: 2949, 2864 (C-H, stretching), 1670, 1652 (2CO, amidic carbonyl), 1607 (C=N), 1558 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 10.37 (s, 1H, NH), 8.62 (s, 1H, CH-pyrazole), 7.94 (s, 1H, CH=), 7.54-7.24 (m, 19H, Ar-H), 4.29 (s, 2H, CH_2); MS: (*m/z*, %): 559.60 (M^++1, 13.45), 558.39 (M^+, 20.31), 552.41 (23.73), 547.66 (35.57), 529.55 (47.0), 506.35 (26.81), 479.98 (45.89), 403.72 (39.37), 351.27 (29.91), 325.27 (54.19), 313.19 (100.0), 288.75 (32.35), 262.70 (58.72), 205.16 (46.91), 148.22 (35.28), 104.79 (45.58), 75.02 (54.08), 59.22 (22.77). Anal. Calcd for $C_{33}H_{24}ClN_5O_2$ (558.04): C 71.03; H 4.34; N 12.55%. Found: C 71.05; H 4.35; N 12.57%.

2-((4-(4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)phenyl)imino)thiazolidin-4-one (**10**)

To a solution of the 2-chloroacetamide derivative **9** (1.67 g, 0.003 mol) in dioxane (15 mL), ammonium thiocyanate (0.46 g, 0.006 mol) was added. The reaction mixture was refluxed for 9 h and then cooled at room temperature. The reaction mixture was poured onto crushed ice and the obtained solid was filtered off, dried and ethyl alcohol was used for recrystallization. Yield 1.06 g (61%); yellow crystals; mp 285-287 °C; IR (KBr) ν_{max}/cm^{-1}: 3139 (NH), 2923, 2854 (C-H, stretching), 1678, 1638 (CO, amidic carbonyl), 1600 (C=N), 1541 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 9.99 (s, 1H, NH), 8.65 (s, 1H, CH-pyrazole), 8.26 (s, 1H, CH=), 8.06-7.01 (m, 19H, Ar-H), 3.97 (s, 2H, CH_2-thiazolidin-4-one); MS: (*m/z*, %): 580.45 (M^+, 22.21), 564.67 (17.55), 538.33 (23.48), 516.74 (28.83), 486.67 (34.61), 467.39 (53.69), 458.36 (73.12), 437.58 (79.16), 412.09 (98.73), 384.20 (92.27), 381.46 (100.0), 313.81 (41.85), 263.99 (78.90), 225.77 (52.32), 157.55 (52.09), 137.59 (68.75), 105.42 (28.41), 84.15 (34.28). Anal. Calcd for $C_{34}H_{24}N_6O_2S$ (580.67): C 70.33; H 4.17; N 14.47%. Found: C 70.35; H 4.19; N 14.49%.

Synthesis of the sulfide derivatives 11 and 12

To a solution of the chloroacetamide derivative **9** (1.67 g, 0.003 mol) in 30 mL dioxane, benzo[d]thiazole-2-thiol, or 5-amino-1,3,4-thiadiazole-2-thiol (0.003 mol) in addition to Et_3N (3 drops) were added. The mixture was heated under reflux for 4-7 h and then left to cool at 25 °C. The precipitate which formed was isolated by filtration and ethyl alcohol was used for recrystallization.

2-(Benzo[*d*]thiazol-2-ylthio)-*N*-(4-(4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)phenyl) acetamide (**11**)

Yield 1.67 g (81%); yellow crystals; mp 264-266 °C; IR (KBr) ν_{max}/cm^{-1}: 3245 (NH), 2924, 2866 (C-H, stretching), 1673, 1638 (2CO, amidic carbonyl), 1596 (C=N), 1536 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 9.84 (s, 1H, NH), 8.44 (s, 1H, CH-pyrazole), 7.98-7.11 (m, 23H, Ar-H), 7.83 (s, 1H, CH=), 4.31 (s, 2H, CH_2); MS: (*m/z*, %): 688.58 (M^+, 6.13), 687.11 (12.35), 666.38 (21.99), 623.27 (19.27), 580.72 (16.04), 569.23 (40.90), 495.93 (19.53), 473.78 (37.95), 453.34 (100.0), 400.44 (37.95), 299.84 (45.66), 293.15 (55.04), 271.95 (90.62), 205.97 (27.58), 189.24 (34.04), 137.14 (57.53), 83.10 (47.13), 51.55 (17.47). Anal. Calcd for $C_{40}H_{28}N_6O_2S_2$ (688.82): C 69.75; H 4.10; N 12.20%. Found: C 69.77; H 4.13; N 12.22%.

2-((5-Amino-1,3,4-thiadiazol-2-yl)thio)-*N*-(4-(4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)phenyl)acetamide (**12**)

Yield 1.26 g (64%); yellow crystals; mp 255-257 °C; IR (KBr) ν_{max}/cm^{-1}: 3345-3270 (NH_2), 3166 (NH), 2924 (C-H, stretching), 1666, 1650 (2CO, amidic carbonyl), 1596 (C=N), 1542 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 10.28 (s, 1H, NH), 8.48 (s, 1H, CH-pyrazole), 7.93 (s, 1H, CH=), 7.90-7.11 (m, 21H, Ar-H, NH_2), 4.01 (s, 2H, CH_2); MS: (*m/z*, %): 654.44 (M^+, 12.22), 616.55 (67.11), 576.12 (10.81), 535.23 (3.54), 488.13 (17.87), 387.24 (100.0),

267.74 (15.04), 231.90 (67.88), 178.84 (45.54), 125.14 (57.53), 83.10 (55.12), 51.04 (17.47). Anal. Calcd for $C_{35}H_{26}N_8O_2S_2$ (654.77): C 64.20; H 4.00; N 17.11%. Found: C 64.22; H 4.03; N 17.12%.

General procedure for the preparation of 1-(hetaryl)-1,4-dihydro-5*H*-imidazol-5-ones (13-17)

To a mixture of pyrazolyl-oxazol-5(4*H*)-one **2** (1.95 g, 0.005 mol) and each of pyridin-2-amine, 4-methylpyridin-2-amine, thiazol-2-amine, benzo[d]thiazol-2-amine or antipyrine-4-amine (0.005 mol) in glacial acetic acid (15 mL), an equimolar amount of freshly fused sodium acetate (0.42 g, 0.005 mol) has been added. The reaction mixture was refluxed for 5-12 h and left to cool at room temperature. It was then poured on crushed ice and the solid product obtained was filtered off and ethyl alcohol was used for recrystallization.

4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-1-(pyridin-2-yl)-1,4-dihydro-5*H*-imidazol-5-one (13)

Yield 1.14 g (49%); yellow crystals; mp 266-268 °C; IR (KBr) ν_{max}/cm^{-1}: 1649 (CO, amidic carbonyl), 1597 (C=N), 1541 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.44 (s, 1H, CH-pyrazole), 8.17-7.13 (m, 19H, Ar-H), 7.90 (s, 1H, CH=); MS: (*m/z*, %): 467.93 (M^+, 37.51), 466.86 (M^+ -1, 40.60), 453.26 (39.21), 441.46 (59.94), 418.13 (38.45), 397.93 (38.50), 377.38 (100.0), 306.42 (32.09), 274.61 (40.29), 236.08 (76.90), 218.08 (91.45), 184.42 (41.27), 170.33 (65.58), 118.88 (47.94), 77.76 (48.79), 55.62 (37.20). Anal. Calcd for $C_{30}H_{21}N_5O$ (467.53): C 77.07; H 4.53; N 14.98%. Found: C 77.06; H 4.54; N 15.01%.

4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-1-(4-methylpyridin-2-yl)-2-phenyl-1,4-dihydro-5*H*-imidazol-5-one (14)

Yield 0.99 g (41%); yellow crystals; mp 254-256 °C; IR (KBr) ν_{max}/cm^{-1}: 2920, 2848 (C-H, stretching), 1659 (CO, amidic carbonyl), 1599 (C=N), 1533 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.39 (s, 1H, CH-pyrazole), 7.98-7.30 (m, 18H, Ar-H), 7.85 (s, 1H, CH=), 2.16 (s, 3H, CH_3); MS: (*m/z*, %): 481.22 (M^+, 28.36), 478.97 (16.80), 465.71 (27.65), 450.67 (33.41), 418.74 (43.63), 387.72 (41.08), 384.55 (100.0), 380.76 (69.66), 363.47 (52.29), 332.32 (43.0), 284.81 (54.78), 232.90 (48.51), 195.83 (66.43), 166.35 (47.22), 142.29 (35.76), 131.75 (87.75), 101.28 (38.94), 76.04 (55.28), 67.09 (30.31), 53.80 (40.78). Anal. Calcd for $C_{31}H_{23}N_5O$ (481.56): C 77.32; H 4.81; N 14.54%. Found: C 77.34; H 4.83; N 14.56%.

4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-1-(thiazol-2-yl)-1,4-dihydro-5*H*-imidazol-5-one (15)

Yield 1.21 g (51%); yellow crystals; mp 277-279 °C; IR (KBr) ν_{max}/cm^{-1}: 1644 (CO, amidic carbonyl), 1599 (C=N), 1534 (C=N); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.36 (s, 1H, CH-pyrazole), 7.86-7.16 (m, 16H, Ar-H, CH=), 7.66 (d, 1H, CH-thiazole), 7.30 (d, 1H, CH-thiazole); MS: (*m/z*, %): 473.66 (M^+, 25.86), 461.73 (20.40), 456.04 (57.35), 446.93 (22.11), 441.61 (34.11), 424.53 (36.95), 417.27 (43.60), 400.87 (44.44), 370.47 (43.35), 360.10 (49.62), 358.53 (30.55), 343.26 (59.66), 324.67 (41.85), 293.48 (39.75), 279.0 (54.86), 261.34 (48.81), 255.28 (94.05), 228.54 (47.73), 205.49 (39.57), 177.60 (38.17), 157.65 (54.83), 127.22 (31.39), 106.85 (74.42), 89.20 (100.0), 79.02 (23.93), 66.75 (52.13), 50.38 (92.44). Anal. Calcd for $C_{28}H_{19}N_5OS$ (473.55): C 71.02; H 4.04; N 14.79%. Found: C 71.04; H 4.05; N 14.82%.

1-(Benzo[*d*]thiazol-2-yl)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-1,4-dihydro-5*H*-imidazol-5-one (16)

Yield 1.13 g (43%); yellow crystals; mp 289-291 °C; IR (KBr) ν_{max}/cm^{-1}: 1655 (CO, amidic carbonyl), 1601 (C=N), 1542 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.39 (s, 1H, CH-pyrazole), 8.23-7.12 (m, 19H, Ar-H), 7.83 (s, 1H, CH=); MS: (*m/z*, %): 524.65 (M^++1, 4.11), 523.11 (M^+, 21.94), 496.41 (29.96), 475.07 (25.59), 466.08 (63.78), 394.53 (30.76), 380.43 (50.12), 373.19 (64.87), 300.94 (100.00), 266.69 (18.91), 182.12 (30.29), 126.08 (51.86), 82.43 (13.57). Anal. Calcd for $C_{32}H_{21}N_5OS$ (523.61): C 73.40; H 4.04; N 13.38%. Found: C 73.42; H 4.07; N 13.39%.

4-(4-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (17)

Yield 1.29 g (45%); yellow crystals; mp >300 °C; IR (KBr) ν_{max}/cm^{-1}: 2924 (C-H, stretching), 1669, 1644 (CO, amidic carbonyl), 1599 (C=N), 1539 (C=C); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.44 (s, 1H, CH-pyrazole), 7.81-7.27

(m, 20H, Ar-H), 7.83 (s, 1H, CH=), 3.27 (s, 3H, N-CH_3), 2.20 (s, 3H, CH_3); MS: (*m/z*, %): 576.32 (M^+, 23.08), 493.13 (11.32), 443.17 (41.11), 403.11 (12.43), 374.23 (16.12), 312.09 (100.0), 277.11 (43.48), 208.70 (48.77), 184.13 (45.63), 146.31 (47.10), 109.15 (24.05), 84.24 (43.09). Anal. Calcd for $C_{36}H_{28}N_6O_2$ (576.66): C 74.98; H 4.89; N 14.57%. Found: C 74.99; H 4.90; N 14.60%.

CONCLUSION

In summary, new pyrazolyl-imidazolone derivatives **3-17** have been synthesized starting from the readily accessible pyrazolyl-oxazol-5(4*H*)-one **2** and investigated their antioxidant efficiency using the ABTS assay. The results demonstrated that pyrazolyl-imidazolone **14** has the most potent activity with inhibition percentage at 66.4% while pyrazolyl-oxazolone **2** has the lowest activity with inhibition percentage at 18.2% compared to the results obtained with *L*-ascorbic acid.

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