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Synthesis and Antioxidant Activity of Some New 2-pyrazolin-5-one-1-carbothioamide Derivatives.

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ABSTRACT

A new series of 4-substituted-2-pyrazolin-5-one-1-carbothioamide derivatives **5**, **7**, **9**, **10**, **11** and **12** was synthesized through the reaction of 3-methyl-2-pyrazolin-5-one-1-carbothioamide **(2)** as a core compound with various electrophilic reagents. The structures of the newly synthesized compounds were confirmed by IR, ^{1}H NMR, MS and elemental analysis. They were evaluated for their potential antioxidant activity by using ABTS Radical Cation Decolorization Assay. Among the tested compounds, **2** and **9** displayed promising antioxidant activity against ABTS free radical.

Keywords: 2-Pyrazolin-5-one-1-carbothioamide, phenyl isothiocyanate, carbon disulfide, 2-aminophenol, *o*-phenylene diamine, antioxidant activity.

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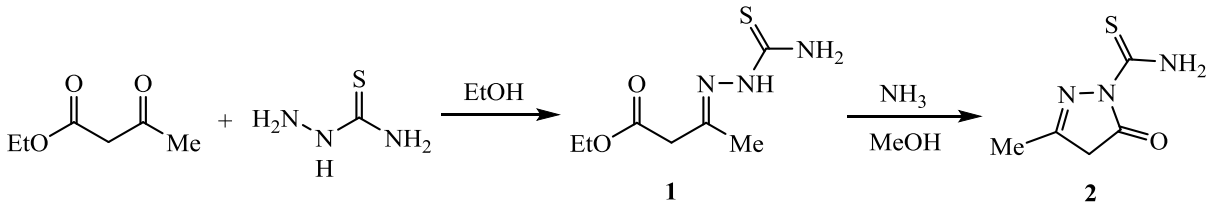
INTRODUCTION

Because of their pharmacological activities, heterocyclic compounds are acquiring more importance in recent years. Pyrazolones have a particular value due to their broad spectrum of biological activity and their wide-ranging utility as synthetic tools in the design of various bioactive molecules. Pyrazolones have gained importance as drug substances in pharmaceutical industry in view of their biological importance [1-11]. Synthesis of pyrazole-1-carbothioamide have been achieved by condensation of α,β-unsaturated carbonyl compounds, 1,3-diketone compounds or compounds containing activated double bond with thiosemicarbazide or its derivatives [12-16]. In the literature, pyrazole derivatives are of interest principally for antioxidant properties due to the presence of conjugated π-system, which delocalize after donation of hydrogen atom and stabilize the antioxidant molecule; activity is also related to the concentration and type of substituent present [17]. In the present study, we report on the synthesis of some new 2-pyrazolin-5-one-1-carbothioamide derivatives, their characterization by spectral data (IR, ^{1}H NMR and MS) and evaluation of their antioxidant properties by using (ABTS Radical Cation Decolorization Assay).

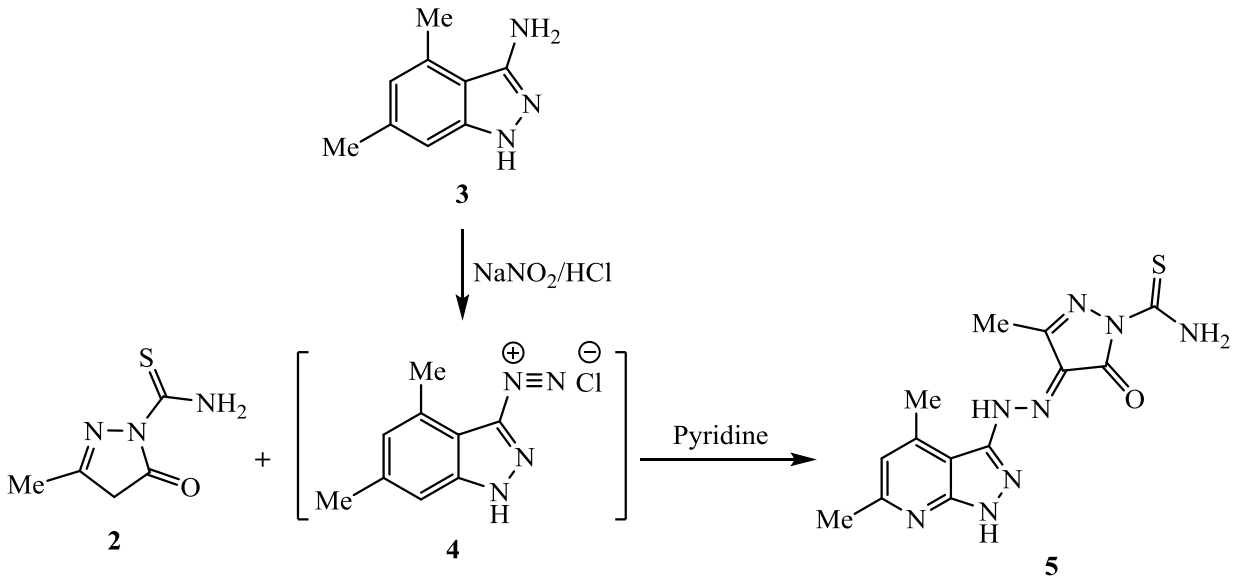
RESULTS AND DISCUTION

The key compound 3-methyl-2-pyrazolin-5-one-1-carbothioamide **(2)** was prepared using a known method [18,19] exploiting the reaction of thiosemicarbazide with ethyl acetoacetate followed by treatment of the resulting ethyl 3-thiosemicarbazidobutanoate **(1)** with ammonia in methanol (Scheme 1).



Scheme (1)

In order to explore the potential of compound **2** in heterocyclic synthesis, the diazocoupling reaction of 3-methyl-2-pyrazolin-5-one-1-carbothioamide **(2)** with 4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridine-3-diazonum chloride **(4)** (in situ prepared from diazotization of 3-amino-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridine **(3)** with $NaNO_2$ in the presence of concentrated HCl) was also investigated. The reaction can be accomplished at temperature 0-5^{o}C to afford 4-(2-(4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridine-3-yl)hydrazono)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-1carbothioamide **(5)** in good yield as shown in Scheme (2).



Scheme (2)

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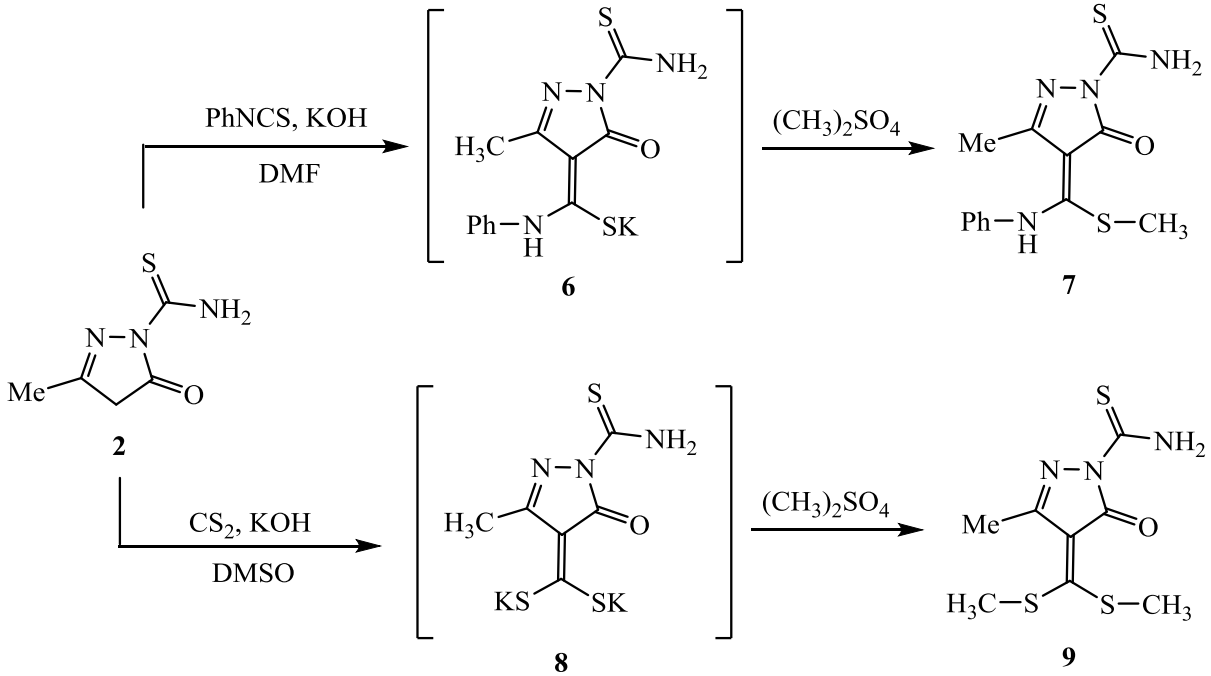
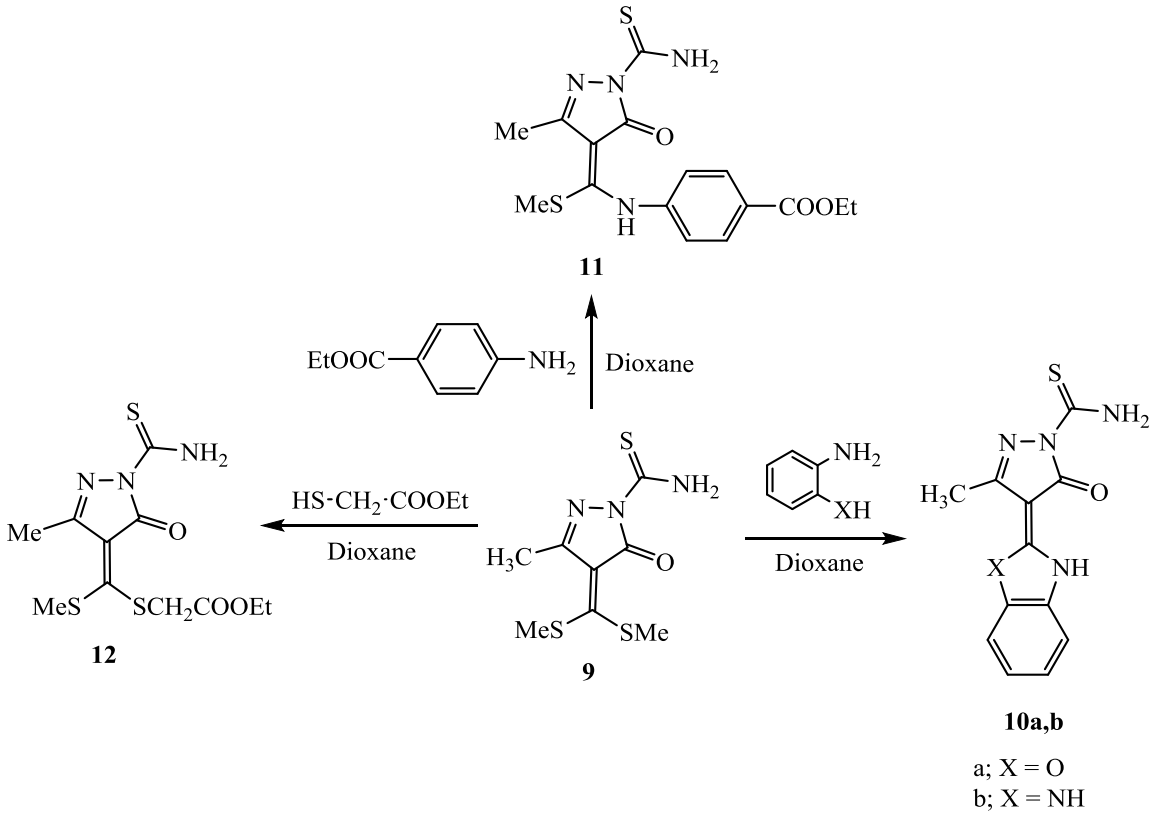
In continuing our interest to synthesis heterocyclic compounds, herein we wish to report synthesis of new pyrazole-1-carbothioamide derivatives and its 4-substituted derivatives. The base catalyzed reaction of 3-methyl-2-pyrazolin-5-one-1-carbothioamide **(2)** with phenyl isothiocyanate in DMF and in the presence of KOH followed by addition of dimethyl sulfate afforded the corresponding 3-methyl-4-(methylthio)(phenylamino)methylene)-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide **(7)**. The spectral data of the isolated product are in agreement with the assigned structure. For example, the ^{1}H NMR spectrum of the isolated compound revealed singlet signal at 10.10 ppm (NH), singlet signal at 9.60 ppm (NH_2), multiplet signal in the region 7.57-7.01 ppm for the aromatic protons, singlet signal at δ 2.43 ppm (CH_3-S) in addition to singlet signal at δ 2.34 ppm (pyrazole C_3-CH_3). When 3-methyl-2-pyrazolin-5-one-1-carbothioamide **(2)** was treated with carbon disulfide in presence of DMSO followed by addition of dimethyl sulfate, it afforded the corresponding 4-(bis(methylthio)methylene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide **(9)** in a good yield. Compound **(9)** was exploited to synthesize some new pyrazole derivatives by reaction with different reagents.



Scheme (3)

Compound **(9)** possess replaceable active methyl thio groups that can be replaced by reaction with various nucleophiles as shown in Scheme (4). When compound **(9)** was condensed independently with *o*-phenylenediamine or *o*-aminophenol afforded the expected, 4- (benzo[d]oxazol-2(3*H*)-ylidene)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **(10a)** or 4-(1,3-dihydro-2*H*-benzo[d]imidazol-2-ylidene))-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **(10b)** respectively. The chemical structure of **10a,b** was elucidated based on their spectral techniques. The IR spectrum of **10a** showed the characteristic absorption bands for NH_2 and NH stretching at 3461 and 3165 cm^{-1}. The ^{1}H NMR spectrum of **10b** displayed singlet signal at δ 12.48 ppm due to the protons of NH groups, singlet signal at 9.11 ppm for the protons of NH_2 function, multiplet signal at δ 7.42–7.12 ppm assigned to the aromatic protons in addition to singlet signal at δ 2.22 ppm due to the pyrazole C-5 methyl protons. The mass spectrum of **10a** showed a molecular ion peak at m/z = 274 corresponding to the molecular weight of the molecular formula $C_{12}H_{10}N_4O_2S$, in addition to other fragments at 256, 215, 192, 160, 128, 64. While treatment of **9** with ethyl 4-aminobenzoate, gave only the open ethyl -4-(((1-carbam -othioyl-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)-(methylthio)-methyl)amino)-benzoate **(11)**. The chemical structure of **11** was inferred based on spectral data. The IR spectrum showed two strong absorption bands at 1720 and 1669 cm^{-1} characteristic for the two carbonyl groups. The ^{1}H NMR spectrum displayed a new downfield singlet signal at 13.22 ppm assigned to the NH proton, singlet signal at 9.18 ppm for the protons of NH_2 group, two doublet signals at 8.05 and 7.94 ppm due to the aromatic protons, quartet and triplet signals at 4.34 and 1.34 for the protons of ethyl group, in addition to two singlet signals at 2.50 and 2.38 corresponding to the protons of methyl groups. Under similar conditions compound **9** was also treated with ethyl mercaptoacetate to yield the corresponding 3-methyl-4-(1,3-oxathiolan-2-ylidene)-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide **(12)**. The structure of the compound

12 was established on the basis of its spectroscopic data. The IR (KBr) spectrum of the target compound **12** showed characteristic NH_2, C=O (ester) and C=O absorptions at 3201-3124 cm^{-1}, 1721 cm^{-1} and 1648 cm^{-1} respectively. The ^1H NMR spectrum of this compound in DMSO exhibited the expected quartet at 4.62-4.55 ppm and triplet at 1.34-1.38 ppm due to the presence of ethyl protons ester group. The NH_2 protons appeared singlet at δ 9.44 ppm, whereas -S–CH_2-COO-, -S-CH_3, and pyrazolone methyl protons showed up at δ 3.29, 2.63 and 2.38 ppm respectively as singlet signals.



Scheme (4)

Antioxidant Activity

The newly synthesized 2-pyrazolin-5-one-1-carbothioamide derivatives **2, 5**, **7**, **9**, **10**, **11** and **12** were tested for their antioxidant activities by using ABTS Radical Cation Decolorization Assay [20,21]. The results (Table 1) indicated that most of the examined compounds exhibited moderate to good antioxidant activity. Among the tested compounds, **2** and **9** displayed excellent antioxidant property (90.4%) and (89.4%) respectively. They were even more active than the standard inhibitor (L-Ascorbic acid 88.20%).

Table 1: Antioxidant activity of the synthesized 4-substituted-2-pyrazolin-5-one-1-carbothioamide derivatives.

Method	ABTS Abs(control)-Abs(test)/Abs(control)×100	
Compounds	**Absorbance of samples**	**% Inhibition**
Control of ABTS	**0.520**	**0%**
Ascorbic acid	**0.056**	**88.20%**
2	0.050	90.4%
5	0.079	84.8%
7	0.062	88.1%
9	0.055	89.4%
10a	0.167	67.9%
10b	0.084	83.8%
11	0.067	87.1%
12	0.118	77.3%

In conclusion, we synthesized a variety of heterocyclic systems consolidating pyrazole-1-carbothioamide and its 4-substituted derivatives. It has active methylene group at 4-position which is ready to react with the suitable reagent. Hence, it has enough scope for further study in developing these as potent biologically active compounds. The elemental and spectroscopy analysis were good agreement with the proposed structures.

EXPERIMENTAL

All melting points were determined on Gallenkamp electric melting point apparatus and being incorrect. The IR spectra were recorded using FT-IR spectrometer (Thermo Scientific Nicolet iS 50) in KBr disks, microanalysis unit, Chemistry Department, Faculty of Science, Mansoura University. The ^{1}H NMR Spectra were measured on a Varian Spectrophotometer at 300 MHz, using TMS as an internal reference and DMSO-d_6 as solvent at the Chemistry Department, Faculty of Science, Cairo University. Elemental analyses were carried out at Microanalysis Center, Faculty of Science, Cairo University. All Reactions were monitored by thin layer chromatography (TLC) using silica gel (GF 254) coated plates with visualization by irradiation with ultraviolet lamp.

Synthesis of 4-(2-(4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridine-3-yl)hydrazono)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-1carbothioamide (5):

A cold solution of sodium nitrite (0.21 g in 10 mL water) was added drop by drop to a cold solution of 3-amino-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridine (0.48 g, 0.003 mol) in hydrochloric acid (1.0 mL) with continuous stirring at 0-5 °C. The freshly prepared diazonium salt solution was then added dropwise to a cooled and stirred solution of 3-methyl-2-pyrazolin-5-one-1-carbothiomide **2** (0.47 g, 0.003 mol) in 10 mL pyridine. The reaction mixture was stirred at 0-5 °C for 2 hours and the resulting precipitate was collected, washed with water, and recrystallized from ethanol to give **5**.

Orange powder; yield = 75 %; m.p. = 250-251°C. R_f = 0.68 using petroleum ether : ethyl acetate (2:1) as eluent system. IR ($\bar{\nu}$ /cm^{-1}): 3351, 3254 (NH_2), 3146 (NH), 1625 (C=O), 1591 (N=N). ^{1}H NMR (DMSO): δ/ppm = 9.48 (s, 2H, NH_2), 8.94 (s, 1H, NH), 6.96 (s, 1H, NH), 6.93 (s, 1H, C_5-pyridine), 2.66 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.14 (s, 3H, CH_3). MS (EI): m/z (%) = 330 (10.32), 271 (100.0), 243 (42.57), 187 (22.75), 161 (71.03), 147 (38.40), 132 (30.92), 106 (23.89). Anal. Calcd. for $C_{13}H_{14}N_8OS$ (330.37): C, 47.26; H, 4.27; N, 33.92%; found: C, 47.43; H, 4.20; N, 33.98%.

Synthesis of 3-methyl-4-[(methylthio)(phenylamino)methylene]-5-oxo-4,5-dihydro-1*H*- pyrazole-1-carbothioamide (7):

To a cold suspension solution of finely powdered KOH (0.56 g, 0.01 mol) in DMF (15 ml), compound **2** (0.78 g, 0.005 mol) and phenyl isothiocyanate (0.6 ml, 0.005 mol) were added. The reaction mixture was stirred at 0-5 ^{o}C for 7 h, and then treated with dimethyl sulfate (1.2 ml, 0.01 mol) was added drop by drop and the stirring was continued at 0-5 ºC for 4 h. The reaction mixture was poured onto ice-cold water, the solid product that separated was filtered, washed with water and recrystallized from EtOH to give compound **7**.

Yellow powder; yield = 77 %; m.p. = 172-174 °C, R_f = 0.65 using petroleum ether : ethyl acetate (2:1) as eluent system. IR ($\bar{\nu}$ /cm^{-1}): 3384, 3204 (NH_2), 3139 (NH), 1653 (C=O). ^{1}H NMR (DMSO): δ/ppm = 10.10 (s, 1H, NH), 9.60 (s, 2H, NH_2), 7.57-7.01 (m, 5H, Ar-H), 2.43 (s, 3H, CH_3), 2.34 (s, 3H, CH_3 pyrazole). MS (EI): m/z (%) = 306 (31.23), 292 (14.58), 233 (58.33), 200 (100.00), 93 (91.22). Anal. Calcd. for $C_{13}H_{14}N_4OS_2$ (306.40): C, 50.96; H, 4.61; N, 18.29%; found: C, 50.87; H, 4.57; N, 18.20%.

Synthesis of 4-(bis(methylthio)methylene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide (9):

To a stirred solution of compound **2** (0.78 g, 0.005 mol) in DMSO (15 ml), KOH (0.56 g, 0.01 mol) and carbon disulfide (1.4 ml, 0.02 mol) were added. The mixture was stirred at 0 - 5 ^{o}C for 4 h, dimethyl sulfate (0.95 ml, 0.01 mol) was added drop by drop and the stirring was continued at 0 - 5 ºC for 3 h. The reaction mixture was poured onto (150 ml) ice-cold water. The solid product that separated was filtered, washed with water and recrystallized from EtOH and drops DMF to give compound **9**.

Orange powder; yield = 68 %; m.p. = 225-226 °C. R_f = 0.44 using petroleum ether : ethyl acetate (2:1) as eluent system. IR ($\overline{\nu}$ /cm^{-1}): 3419, 3224 (NH_2), 1649 (C=O). ^{1}H NMR (DMSO): δ/ppm = 9.34 (s, 2H, NH_2), 2.50 (s, 6H, $2CH_3$), 2.33 (s, 3H, CH_3). MS (EI): m/z (%) = 261 (10.22), 256 (91.20%), 192 (32.76), 160 (67.71), 128 (72.12), 63 (100.0%). Anal. Calcd. for $C_8H_{11}N_3OS_3$ (261.38): C, 36.76; H, 4.24; N, 16.08%; found: C, 36.88; H, 4.31; N, 16.17%.

Synthesis of 4-substitutedylidene-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide 10, 11 and 12:

A mixture of compound **9** (0.522 g, 0.002 mol) and 2-aminophenol, *o*-phenylenediamine, ethyl 4-aminobenzoate or ethyl mercaptoacetate (0.002 mol) in dioxane (20 mL) was refluxed for 4 h. The reaction mixture was allowed to cool at room temperature, poured into crushed ice, the solid product was filtered, washed with water and recrystallized from EtOH.

4-(Benzo[d]oxazol-2(3*H*)-ylidene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide (10a):

Brown powder; yield = 44 %; m.p. = 260-261 °C. R_f = 0.44 using petroleum ether : ethyl acetate (2:1) as eluent system. IR ($\overline{\nu}$ /cm^{-1}): 3461 (NH_2), 3165 (NH), 1645 (C=O). ^{1}H NMR (DMSO): δ/ppm = 11.82 (s, 1H, 1NH), 9.23 (s, 2H. NH_2), 7.66-7.25 (m, 4H, Ar-H), 2.50 (s, 3H, CH_3). MS (EI): m/z (%) = 274 (12.31), 256 (78.39), 215 (82.13), 192 (28.01), 160 (69.50), 128 (72.85), 64 (100.00). Anal. Calcd. for $C_{12}H_{10}N_4O_2S$ (274.30): C, 52.55; H, 3.67; N, 20.43%; found: C, 52.43; H, 3.69; N, 20.34%.

4-(1,3-Dihydro-2H-benzo[d]imidazol-2-ylidene))-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide (10b):

Brown powder; yield = 61 %; m.p. = 268-269 °C. R_f = 0.49 using petroleum ether : ethyl acetate (2:1) as eluent system. IR ($\overline{\nu}$ /cm^{-1}): 3446 (broad, NH_2 and NH), 1648 (C=O). ^{1}H NMR (DMSO): δ/ppm = 12.48 (s, 2H, 2NH), 9.11 (s, 2H. NH_2), 7.42-7.12 (m, 4H, Ar-H), 2.22 (s, 3H, CH_3). MS (EI): m/z (%) = 273 (10.02), 206 (19.21), 150 (100.00), 118 (26.69), 106 (23.89). Anal. Calcd. for $C_{12}H_{11}N_5OS$ (273.31): C, 52.73; H, 4.06 ; N, 25.62 %; found: C, 52.61; H, 3.98; N, 25.52 %.

Ethyl 4-[((1-carbamothioyl-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)-(methylthio)methyl)amino]-benzoate (11):

Brown powder; yield = 68 %; m.p. = 157-159 °C. R_f = 0.44 using petroleum ether : ethyl acetate (2:1) as eluent system. IR ($\overline{\nu}$ /cm^{-1}): 3458, 3224 (NH_2 and NH), 1720 (C=O, ester), 1669 (C=O, pyrazole). ^{1}H NMR (DMSO): δ/ppm = 13.22 (s, 1H, $NH_)$, 9.18 (s, 2H, NH_2), 8.05 (d, 2H, Ar-H), 7.94 (d, 2H, Ar-H), 4.34-4.27 (q, 2H, CH_2, J = 7.15 Hz), 2.50 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 1.34-1.30 (t, 3H, CH_3, J = 7.15 Hz). MS (EI): m/z (%) = 378 (9.44), 256 (65.97), 192 (52.13), 165 (71.10), 159 (80.02), 140 (34.93), 120 (100.00). Anal. Calcd. for $C_{16}H_{18}N_4O_3S_2$ (378.47): C, 50.78; H, 4.79; N, 14.80%; found: C, 50.91; H, 4.73; N, 14.84%.

Ethyl 2-[((1-carbamothioyl-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)-(methylthio)methyl)thio)] acetate (12):

Yellow powder; yield = 55 %; m.p. = 180-182°C. R_f = 0.68 using petroleum ether : ethyl acetate (2:1) as eluent system. IR ($\overline{\nu}$ /cm^{-1}): 3201, 3124 (NH_2), 1721 (C=O, ester), 1648 (C=O, pyrazole). ^{1}H NMR (DMSO): δ/ppm = 9.44 (s, 2H, NH_2), 4.62-4.55 (q, 2H. CH_2), 3.29 (s, 2H, -$COCH_2$-S), 2.63 (s, 3H, CH_3-S-), 2.38 (s, 3H, CH_3), 1.43-1.38 (t, 3H, CH_3). MS (EI): m/z (%) = 333 (11.14), 242 (7.55), 206 (100.00), 189 (54.72), 149 (21.18), 109 (22.51). Anal. Calcd. for $C_{11}H_{15}N_5O_3S_3$ (333.44): C, 39.62; H, 4.53; N, 12.60 %; found: C, 39.56; H, 4.69; N, 12.44 %.

Antioxidant Activity Screening Assay by the ABTS Method

This assay employs the radical cation derived from 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) as stable free radical. The advantage of ABTS-derived free radical method over other methods is that the produced color remains stable for more than 1 h and the reaction is stoichiometric [20,21]. By screening our reported compounds in this work for antioxidant activity by the latter method. For each of the

investigated compounds (2 mL) of ABTS solution (60 µM) was added to 3 mL MnO_2 solution (25mg/mL), all prepared in (5 mL) aqueous phosphate buffer solution (pH 7, 0.1 M). The mixture was shaken, centrifuged, filtered and the absorbance of the resulting green blue solution (ABTS radical solution) at 734 nm was adjusted to approx. ca. 0.5. Then, 50 µl of (2 mM) solution of the tested compound in spectroscopic grade MeOH/phosphate buffer (1:1) was added. The absorbance was measured and the reduction in color intensity was expressed as inhibition percentage. L–Ascorbic acid was used as standard antioxidant (Positive control). Blank sample was run without ABTS and using MeOH/phosphate buffer (1:1) instead of tested compounds. Negative control was run with ABTS and MeOH/phosphate buffer (1:1) only [22,23].

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