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Synthesis and antimicrobial activity of novel compounds containing pyrazolones and 1,3,4 oxadiazoles

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ABSTRACT

The mixture of hydrazide 4(a-f) and with appropriate ketone namely acetophenone, p-methyl acetophenone, p-chloro acetophenone, p-bromo acetophenone, p-nitro acetophenone was refluxed in methanol containing catalytic amount of glacial acetic acid to get the hydrazones (5 a-f). Cyclisation of hydrazones with excess of acetic anhydride to give corresponding 2-(4-acetyl -5-methyl-5-phenyl-4,5-dihydro-[1,3,4]oxadiazol-2-methyl)-5-methyl-4-(4'-substituted aryl hydrazono)-2,4-dihydro-pyrozole-3-one 6 a-j. The structures of these newly synthesized compounds were characterized by ^{1}H-NMR, Mass, IR and elemental analysis.

Key words: Synthesis and antimicrobial activity pyrazolones and oxadiazoles.

INTRODUCTION

1,3,4-Oxadiazoles belong to the group of heterocycles that have been attracting attention for last two decades due to their wide range of biological interactions. Many of them exhibit antibacterial, anticonvulsant, anticancer activities and are used to fight infections involving AIDS. They are also applied in agriculture as herbicides, fungicides or insecticides. Some1,3,4-oxadiazoles substituted with aryl groups at positions 2 and 5 are of significant interest of polymer and material science because of their electrochemical properties (phosphorescence).

Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical and material interest, which is documented by a steadily increasing number of publications and patents. For instance, 2-amino-1,3,4-oxadiazoles act as muscle relaxants[1] and show antimitotic activity [2] Analgesic, anti-inflammatory, anticonvulsive, diuretic and antiemetic properties are exhibited by 5-aryl-2-hydroxymethyl-1,3,4-oxadiazole derivatives,[3] and 2-hydroxyphenyl-1,3,4-oxadiazole acts as a hypnotic and as a sedative [4] Some material applications of 1,3,4-oxadiazole derivatives lie in the fields of photo sensitizers [5] and liquid crystals[6].

It was reported that 1, 3, 4-oxadiazole derivatives, suitably substituted at the 2 and 5 positions, exhibited considerable antibacterial and antifungal activity[7-10]. These heterocycles are of great interest to medicinal chemists for molecular manipulation and to biologists for further pharmacological evaluation. Pyrazolines and their derivatives are important biological agents and a significant amount of research activity has been directed towards this class of compounds. In particular, they are used as antitumor, antibacterial, antifungal, antiviral, antiparasitic, antitubercular and insecticidal agents[11-21]. Some of these compounds also have anti-inflammatory, antidiabetic, anesthetic and analgesic properties[21-24].

EXPERIMENTAL

All the chemicals were used as received without further purification. Melting points were determined in open capillary tubes in Buchi 530 circulating oil apparatus and are not corrected. Reactions monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. ^{1}H NMR spectra were determined either in $CDCl_3$ and DMSO-d_6 solution on 200 MHz AMX Spectrometers. Proton chemical shifts (d) are relative to tetramethylsilane as internal standard and expressed in ppm.

Biological screening antimicrobial activity test

The test was performed according to the disk diffusion method [25] adopted with some modifications for the prepared compounds using amoxicillin, and cefaclor as a references. The prepared compounds were tested against one strain of Gram +ve bacteria (*Staphylococcus aureus* NCCS 2079 and *Bacillus cereus* NCCS 2106), Gram –ve bacteria (*Escherichia coli* NCCS 265 and *Pseudomonas aeruginosa* NCCS2200).

The sysnthesized compounds were used at the concentration of 250 µg/ml and 500 µg/ml using DMSO as a solvent. The amoxicillin 10 µg/ disc and cefaclor 30 µg/disc were used as a standard (Himedia laboratories limited, Mumbai).

Whatman No. 1 filter paper disk of 5mm diameter were sterile nutrient agar at 45°C, the sterile disks were impregnated with different compounds synthesized compounds (250 µg/ml). The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 25 °C for 1 h. to permit good diffusion and then transferred to an incubator at 37 °C for 48 h. for bacteria, and at 28 °C for 72h. For yeast and fungi. The inhibition zones caused by the various compounds on the microorganisms were examined.

A similar procedure was adopted for studying the antibacterial activity against the other organisms.

The results of the preliminary screening test are listed in Table 1

Synthesis of compounds

4-substituted aryl hydrazono acetoacetic ester (1) was prepared by the procedure described by H.M.W.alborsky, M.E.Baum[26]

Hydrazine hydrate (0.01M) was added to suspension of compounds 1a-f (0.01M) in 20ml ethanol .the reaction mixture was heated under reflux for 8-10h. The excess solvent was removed under vacuum; the residue was purified by crystallization.

A mixture of [3-methyl-5-oxo-4-(4-substituted aryl hydrazono)-4,5-pyrazoline-5-one (2) (0.02M) anhydrous K_2CO_3 (0.03M) Chloro ethyl acetate (0.02M) and DMF was stirred at room temperature for 8 hours, the reaction mixture was diluted with ice-cold water. The separated solid was identified as (3). This was collected by filtration and recrystallized from ethanol.

A solution of 3 (0.01M) and hydrazine hydrate (0.015M) in ethanol 20 ml was refluxed for 5 hours. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford (4).

[3- methyl- 5- oxo- 4-(phenyl hydrazono) - 4, 5-dihydro-pyrazol-1-yl]-acetic acid (1-phenyl-ethylidene)-hydrazide 5(a-g)

To solution of 4a-f (0.01 mole) in hot methanol (25ml), Acetophenone (0.01 mole) and a drop of glacial acetic acid was added. The solid that separated on refluxing for 3 hours was filtered wash with cold methanol and recrystallized from methanol to give the title compound, the physical and analytical data of the synthesized title compounds are given as follows.

[3- methyl- 5- oxo- 4-(phenyl hydrazono) - 4, 5-dihydro-pyrazol-1-yl]-acetic acid (1-phenyl-ethylidene)-hydrazide 5a

yield 84%, m. p.236°C; IR ν_{max} in cm^{-1} 3185,1665,1660; ^{1}HNMR (DMSO-d_6, δ ppm): 1.52 (s,3H, CH_3), 2.35 (s,3H, N - CH_3), 7.25 (s,2H,

NCH_2CO), 10.92 (s, H, NH), 7.48 (s, H, Ar-NH), 7.58 (d, 2H, Ar - H), 7.4 -7.6 (m, 5H, Ar -H); ^{13}C-NMR: (DMSO-d_6, δ ppm):18.6, 19.5, 54.5, 116.3, 118.8, 128.6, 128.9, 129.2, 129.6, 131.1, 134, 143.1, 148.0, 168.5, and 172.8; EI ms: m/z: 376.16; Anal.Calcd.for $C_{20}H_{20}N_6O_2$ (376.41) Cal.C:63.90; H: 5.39; N: 22.40; Found C: 63.82; H: 5.36; N: 22.33.

[3- methyl- 5- oxo- 4-(p-tolyl- hydrazono) - 4, 5-dihydro-pyrazol-1-yl]-acetic acid (1-phenyl-ethylidene)-hydrazide 5b

yield 60%, m. p.220°C; IR ν_{max} in cm^{-1} 3175, 1670 1602; EI ms: m/z: 390.18; Anal.Calcd.for $C_{21}H_{22}N_6O_2$ (390.44) C:64.71; H: 5.77; N: 21.58; Found C: 64.60; H: 5.69; N: 21.52.

{4-[(4-methoxy-phenyl)-hydrazono]-3-methyl-5-oxo- 4, 5-dihydro-pyrazol-1-yl}-acetic acid (1-phenyl-ethylidene)-hydrazide 5c

yield 75%, m. p.215°C; IR ν_{max} in cm^{-1} 3200, 1665, 1605; EI ms: m/z: 406.18; Anal. Calcd. for $C_{21}H_{22}N_6O_3$ (406.44) C: 64.71; H: 5.77; N: 21.58; Found C: 64.60; H: 5.69; N: 21.52.

{4-[(4-ethoxy - phenyl)-hydrazono]-3-methyl-5-oxo-4, 5-dihydro-pyrazol-1-yl}-acetic acid (1-phenyl-ethylidene)-hydrazide 5d

yield 65%, m. p.200°C; IR ν_{max} in cm^{-1} 3190, 1670, 1604; EI ms: m/z: 420.19; Anal. Calcd. for $C_{22}H_{24}N_6O_3$ (420.46) C: 62.92; H: 5.83; N: 20.05; Found C: 62.84; H: 5.75; N:19.99.

{4-[(4-chloro - phenyl)-hydrazono]-3-methyl-5-oxo-4, 5-dihydro-pyrazol-1-yl}-acetic acid (1-phenyl-ethylidene)-hydrazide 5e

yield 63%, m. p.195°C; IR ν_{max} in cm^{-1} 3210, 1650, 1605; EI ms: m/z: 410.13; Anal. Calcd.for $C_{20}H_{19}N_6O_2Cl$ (410.86) C: 58.55; H: 4.73; N: 20.53; Found C: 58.47; H: 4.66; N: 20.45.

{4-[(4-bromo - phenyl)-hydrazono]-3-methyl-5-oxo-4, 5-dihydro-pyrazol-1-yl}-acetic acid (1-phenyl-ethylidene)-hydrazide 5f

yield 68%, m. p.210°C; IR ν_{max} in cm^{-1} 3215, 1660, 1602; EI ms: m/z: 454.08; Anal.Calcd.for $C_{20}H_{19}N_6O_2Br$ (455.31) C: 52.82; H: 4.27; N: 18.54; Found C: 52.76; H:4.21; N:18.46.

[3- methyl- 5- oxo- 4-(phenyl - hydrazono) - 4, 5-dihydro-pyrazol-1-yl]-acetic acid (1-m-tolyl-ethylidene)-hydrazide 5g

yield 70%, m. p.220°C; IR $^{0}_{max}$ in cm^{-1} 3195, 1670, 1605; ^{1}HNMR (DMSO-d_6, δ ppm): 1.50 (s,3H, CH_3), 2.26 (s, 3H, CH_3), 2.33 (s,3H, N -CH_3), 7.23 (s,2H, NCH_2CO), 10.90 (s, H, NH), 7.45 (s, H, Ar-NH), 7.56 (d, 2H, Ar - H), 7.72 (d, 2H, Ar - H), 7.3 -7.5 (m, 5H,Ar -H); EI ms: m/z: 390.18; Anal.Calcd.for $C_{21}H_{22}N_6O_2$ (390.44) C:64.71; H:5.77; N:21.58; Found C:64.60; H:5.68; N:21.52.

[3- methyl- 5- oxo- 4-(phenyl hydrazono) - 4, 5-dihydro-pyrazol-1-yl]-acetic acid [1-(3-chloro-phenyl)-ethylidene]-hydrazide 5h

yield 65%, m. p.215°C IR ν_{max} in cm^{-1}3190, 1675, 1604; ^{1}HNMR (DMSO-d_6, δ ppm): 1.58 (s,3H, CH_3), 2.39 (s,3H, N -CH_3), 7.27 (s,2H, NCH_2CO), 10.94 (s, H, NH), 7.9 (s, H, Ar-NH), 7.62 (d, 2H, Ar - H), 7.74 (d, 2H, Ar - H), 7.5 -7.7 (m, 5H, Ar - H); EI ms: m/z: 410.13; Anal.Calcd.for $C_{20}H_{19}N_6O_2Cl$ (410.86) C:68.54; H:4.72; N:20.51; Found C:68.47; H:4.66; N:20.45.

[3- methyl- 5- oxo- 4-(phenyl hydrazono) - 4, 5-dihydro-pyrazol-1-yl]-acetic acid [1-(3-methoxy-phenyl)-ethylidene]-hydrazide 5i

yield 70%, m. p.235°C; IR ν_{max} in cm^{-1}3205, 1660 , 1605; ^{1}HNMR (DMSO-d_6, δ ppm): 1.53 (s,3H, CH_3), 2.37 (s,3H, N -CH_3), 7.26 (s,2H, NCH_2CO), 10.93 (s, H, NH), 7.50 (s, H, Ar-NH), 7.60 (d, 2H, Ar - H), 7.76 (d, 2H, Ar - H), 7.5 - 7.6 (m, 5H, Ar - H) EI ms: m/z: 406.18; Anal.Calcd.for $C_{21}H_{22}N_6O_3$ (406.44) C:62.12; H:5.54; N:20.71; Found C:62.06; H:5.46; N:20.68.

[3- methyl- 5- oxo- 4-(phenyl hydrazono) - 4, 5-dihydro-pyrazol-1-yl]-acetic acid [1-(3-nitro-phenyl)-ethylidene]-hydrazide 5j

yield 67%, m. p.210°C; IR ν_{max} in cm^{-1}3180, 1660, 1604; ^{1}HNMR (DMSO-d_6, δ ppm): 1.48 (s,3H, CH_3), 2.30 (s,3H, N -CH_3), 7.20 (s,2H, NCH_2CO), 10.89 (s, H, NH), 7.43 (s, H, Ar-NH), 7.54 (d, 2H, Ar - H), 7.70 (d, 2H, Ar - H), 7.4 - 7.4 (m, 5H, Ar -H); EI ms: m/z: 421.15; Anal.Calcd.for $C_{20}H_{19}N_7O_4$ (421.41) C:57.09; H:4.62; N:23.66; Found C:57.00; H:4.54; N:23.57.

2-(4-acetyl -5-methyl-5-phenyl-4,5-dihydro-[1,3,4]oxadiazol-2-methyl)-5-methyl-4-(4'-substituted aryl hydrazono)-2,4-dihydro-pyrozole-3-one 6(a-j)

A mixture of 5a (0.01 mole) and excessive acetic anhydride (10 ml) was refluxed for 2 hours. The excessive acetic anhydride was distilled off and the residue was poured on to crushed ice. The title compound was filtered, washed, dried and re-crystallized from aqueous methanol to give title compounds (6a-j). The physical and analytical data of the synthesized title compounds are given as follows.

2-(4-acetyl-5-methyl-5-phenyl-4, 5-dihydro-[1,3,4] oxadiazole-2-yl (methyl)-5-methyl-4(phenyl hydrazono)-2,4-dihydrazono-pyrazol-3-one 6a

yield 67%, m. p.210^{0}C IR ν_{max} in cm^{-1} 3206,1685,1620; ^{1}HNMR ($CDCl_3$, δ ppm): 2.22(s, 3H CH_3), 2.40 (s, 3H, CH_3), 2.46 (s, 3H, $COCH_3$), 5.26 (s, 2H, NCH_2), 7.9 (s, H, Ar - NH), 7.28 (d, 2H, Ar - H), 7.85(d, 2H, Ar-H), 7.45 -7.6 (m, 5H, Ar-H); ^{13}C-NMR: ($CDCl_3$ d ppm):18.6, 23.7, 34.4, 49.7, 77.2, 116.3, 118.8, 126.8, 127, 128.6, 129.6, 142.6, 143.1, 163; EI ms: m/z: 418.18; Anal.Calcd.for $C_{22}H_{22}N_6O_3$ (418.45) C:63.29; H:5.47; N:20.27; Found C:63.15; H:5.30; N:20.08.

2-(4-acetyl -5-methyl-5-phenyl-4,5-dihydro-[1,3,4]oxadiazol-2-methyl)-5-methyl-4-(p-tolyl-hydrzono)-2,4-dihydro-pyrozole-3-one one 6b

yield 67%, m. p.210°C; IR ν_{max} in cm^{-1} 3195, 1690, 1622; EI ms: m/z: 432.19; Anal. Calcd. for $C_{23}H_{24}N_6O_3$ (432.48) C:64.03; H: 5.75; N: 19.60; Found C: 63.88; H: 5.59; N: 19.43.

2-(4-acetyl -5-methyl-5-phenyl-4,5-dihydro-[1,3,4]oxadiazol-2-methyl)-5-methyl-4-[(4-methoxy-phenyl)-hydrazono]-5methyl-2,4-dihydro-pyrozole-3-one 6c

yield 67%, m. p.210°C ; IR ν_{max} in cm^{-1} 3230, 1685, 1625; EI ms: m/z: 448.19 Anal.Calcd.for $C_{23}H_{24}N_6O_4$ (448.47) C:61.79; H: 5.56; N: 18.90; Found C: 61.60; H: 5.39; N: 18.74.

2-(4-acetyl -5-methyl-5-phenyl-4,5-dihydro-[1,3,4]oxadiazol-2-methyl)-5-methyl-4-[(4-ethoxy-phenyl)-hydrazono]-5methyl-2,4-dihydro-pyrozole-3-one 6d

yield 67%, m. p.210°C ; IR ν_{max} in cm^{-1} 3215, 1695, 1624; EI ms: m/z: 462.2; Anal.Calcd.for $C_{24}H_{26}N_6O_4$ (462.50) C:64.71; H: 5.77; N: 21.58; Found C: 62.33; H: 5.67; N: 18.17.

Table 1:

S. No.	Comp	R	R_1	R_2	Zone of inhibition (mm)			
					Staphylococcus aureus NCCS 2079	*Bacillus Cereus* NCCS 2106	*Escherichia coli* NCCS 2065	*Pseudomonas aeruginos* NCCS 2200
1	Amoxcycillin				21	27	24	22
2	Cefaclor				19	22	19	20
3	6a	H	CH_3	C_6H_5	6	5	5	7
4	6b	CH_3	CH_3	C_6H_5	6	5	4	6
5	6c	OCH_3	CH_3	C_6H_5	4	5	4	5
6	6d	OC_2H_5	CH_3	C_6H_5	8	6	4	7
7	6e	Cl	CH_3	C_6H_5	8	9	6	8
8	6f	Br	CH_3	C_6H_5	7	8	6	5
9	6g	H	CH_3	$CH_6C_6H_5$	4	5	4	5
10	6h	H	CH_3	ClC_6H_4	8	8	6	7
11	6i	H	CH_3	$OCH_3C_6H_4$	4	6	6	5
12	6j	H	CH_3	$NO_2C_6H_4$	7	8	6	7

2-(4-acetyl -5-methyl-5-phenyl-4,5-dihydro-[1,3,4]oxadiazol-2-methyl)-5-methyl-4-[(4-chloro-phenyl)-hydrazono]-5methyl-2,4-dihydro-pyrozole-3-one 6e

yield 67%, m. p.210°C ; IR ν_{max} in cm^{-1} 3230, 1675, 1630; EI ms: m/z: 452.14 ; Anal. Calcd. for $C_{22}H_{21}N_6O_3Cl$: (452.89) C:58.49; H: 4.90; N: 18.76; Found C: 58.34; H: 4.67; N: 18.56.

2-(4-acetyl -5-methyl-5-phenyl-4,5-dihydro-[1,3,4]oxadiazol-2-methyl)-5-methyl-4-[(4-bromo-phenyl)-hydrazono]-5methyl-2,4-dihydro-pyrozole-3-one 6f

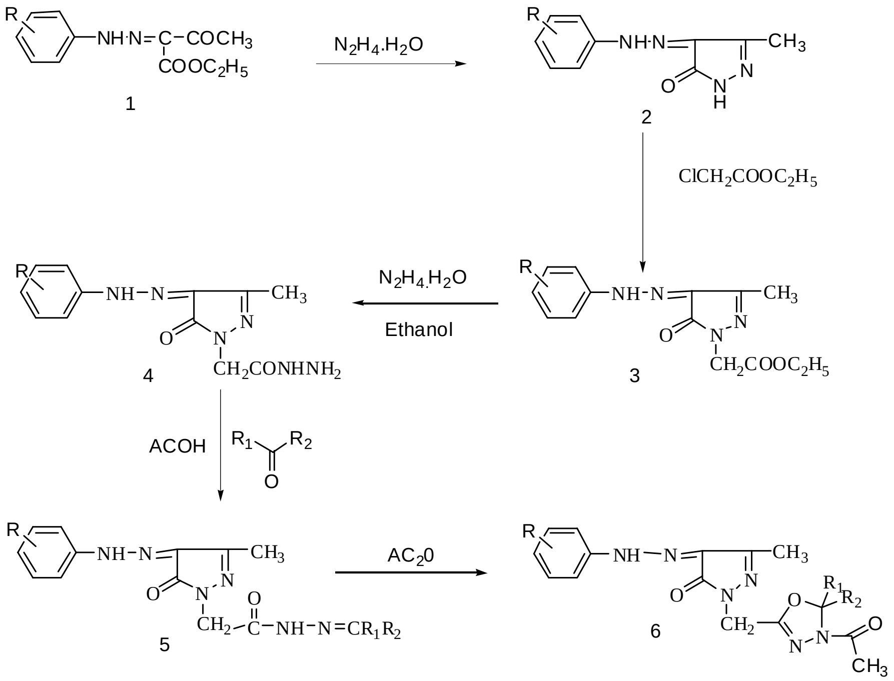
yield 67%. m.p.210°C; IR ν_{max} in cm^{-1} 3210, 1685, 1627; EI ms: m/z: 496.09; Anal.Calcd.for $C_{22}H_{21}N_6O_3Br$ (497.34) C: 53.29; H: 4.40; N: 17.08; Found C: 53.13; H: 4.26; N: 16.90.

2-(4-acetyl-5-methyl-5-m-tolyl-4, 5-dihydro-[1,3,4] oxadiazole-2-yl (methyl)-5-methyl-4(phenyl hydrazono)-2,4-dihydrazono-pyrazol-3-one 6g

yield 67%, m. p.210°C; IR ν_{max} in cm^{-1} 3180, 1695, 1627; ^{1}HNMR ($CDCl_3$, d ppm): 2.20(s, 3H CH_3), 2.26 (s,3H, CH_3), 2.39 (s, 3H, CH_3), 2.44 (s, 3H, $COCH_3$), 5.24 (s, 2H, NCH_2), 7.8 (s, H, Ar - NH), 7.26 (d, 2H, Ar - H), 7.83 (d, 2H, Ar-H), 7.4 - 7.6 9(m, 5H, Ar - H); EI ms: m/z: 432.19; Anal.Calcd.for $C_{23}H_{24}N_6O_3$ (432.48) C:64.02; H: 5.75; N: 19.66; Found C: 63.88; H: 5.59; N: 19.43.

2-(4-acetyl-5-(3- chloro -phenyl)-5-methyl-4, 5-dihydro-[1,3,4] oxadiazole-2-yl (methyl)-5-methyl-4(phenyl hydrazono)-2,4-dihydrazono-pyrazol-3-one 6h

yield 67%, m. p.210°C; IR ν_{max} in cm^{-1}



1a,2a,3a,4a,5a,6a R = H
1b,2b,3b,4b,5b,6b R = CH_3
1c,2c,3c,4c,5c,6c R = OCH_3
1d,2d,3d,4d,5d,6d R = OC_2H_5
1e,2e,3e,4e,5e,6e R = Cl
1f, 2f, 3f, 4f, 5f, 6f R = Br

5a, 6a R = H,R_1= CH_3,R_2=C_6H_5
5g, 6g R = H,R_1= CH_3,R_2=$CH_3C_6H_4$
5h, 6h R = H,R_1= CH_3,R_2=ClC_6H_4
5i, 6i R = H,R_1= CH_3,R_2=$OCH_3C_6H_4$
5j, 6j R = H,R_1= CH_3,R_2=$NO_2C_6H_4$

Scheme 1

3195, 1700, 1629 ; [1]HNMR ($CDCl_3$, d ppm): 2.19 (s, 3H CH_3), 2.37 (s, 3H, $COCH_3$), 2.24 (s, 2H, CH_3), 4.92 (s, 2H, NCH_2), 7.7 (s, H, Ar - NH), 7.42 (d, 2H, Ar - H), 7.78 (d, 2H, Ar-H), 7.4 - 7.6 (m, 5H, Ar -H); EI ms: m/z: 452.14; Anal.Calcd.for $C_{22}H_{21}N_6O_3Cl$ (452.89) C:58.50; H: 4.80; N: 18.74; Found C: 58.34; H: 4.67; N: 18.56.

2-(4-acetyl-5-(3-methoxy-phenyl)-5-methyl-4, 5-dihydro-[1,3,4] oxadiazole-2-yl (methyl)-5-methyl-4(phenyl hydrazono)-2,4-dihydrazono-pyrazol-3-one 6i

yield 67%, m. p.210°C; IR ν_{max} in cm^{-1} 3245, 1705, 1630 ; [1]HNMR ($CDCl_3$, δ ppm): 2.18 (s, 3H CH_3), 2.39 (s,3H, CH_3), 2.43 (s, 3H, $COCH_3$), 3.89 (s, 3H, OCH_3), 5.24 (s, 2H, NCH_2), 7.91 (s, H, Ar - NH), 7.91 (s, H, Ar-NH), 6.97 (d, 2H, Ar - H), 7.89 (d, 2H, Ar - H), 7.27 - 7.62 (m, 5H, Ar-H); EI ms: m/z: 448.19; Anal.Calcd.for $C_{23}H_{24}N_6O_4$ (448.47) C:61.75; H: 5.55; N: 18.90; Found C: 61.60; H: 5.39; N: 18.74.

2-(4-acetyl-5-(3-nitro-phenyl)-5-methyl-4, 5-dihydro-[1,3,4] oxadiazole-2-yl (methyl)-5-methyl-4(phenyl hydrazono)-2,4-dihydrazono-pyrazol-3-one 6j

yield 71%, m. p.215°C ; IR ν_{max} in cm^{-1} 3240, 1685, 1630; [1]HNMR ($CDCl_3$, δ ppm): 2.16 (s, 3H CH_3), 2.35 (s, 3H, CH_3), 2.40 (s, 3H, $COCH_3$), 5.22 (s, 2H, NCH_2), 7.6 (s, H, Ar - NH), 7.24 (d, 2H, Ar - H), 7.80 (d, 2H, Ar - H), 7.2 -7.6 (m, 5H, Ar-H); EI ms: m/z: 463.16 ; Anal.Calcd.for $C_{22}H_{21}N_7O_5$ (463.45) C:57.19; H: 4.7; N: 21.32; Found C: 57.02; H: 4.57; N: 21.16.

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