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**Research Article**

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# Synthesis, characterization and preliminary biological activity of some new pyrazole carbohydrazide derivatives

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**ABSTRACT**

*A series of novel N'-[(aryl)methylene]-5-substituted-1H-pyrazole-3-carbohydrazide derivatives were synthesized by the reaction of substituted pyrazole carbohydrazide with functionalized aromatic aldehydes. The compounds were characterised using IR, $^1H$ NMR and mass spectral. All the newly synthesized compounds were tested for antimicrobial (Staphylococcus aureus CIP 4.83, Pseudomonas aeruginosa CIP 82-118, Bacillus subtilis CIP 52-62) and antifungal (Candida albicas CIP 48.72) activity.*

**Keywords:** Pyrazole, Carbohydrazide, Synthesis, Biological activity.

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## INTRODUCTION

Antibacterial and antifungal activities of the azoles are most widely studied and some of them are in clinical practice as antimicrobial agents. However, the azole resistant strains led to develop a new antimicrobial compounds. In particular pyrazole derivatives are extensively studied and used as antimicrobial agents [1-7]. Pyrazole is an important class of heterocyclic compound and many pyrazole derivatives are reported to have the broad spectrum of biological activities, such as anti-inflammatory [8-9], antifungal [10], herbicidal [11], insecticidal [12], antitumor, anti-HCV [13], and antiviral activities [14]. Pyrazole derivatives also acting as antiangiogenic agents [15], A3 adenosine receptor antogonists [16], neuropeptide YY5 receptor antagonists [17], kinase inhibitor for treatment of type 2 diabetes, hyperlipidemia, obesity [18], and thrombopiotinmimetics [19]. Recentely urea derivatives of pyrazole have been reported as potent inhibitors of p38 kinase [20].

Hydrazides, carbohydrazides and similar compounds are well known as useful building blocks for the synthesis of a variety of heterocyclic rings. A large number of heterocyclic carbohydrazides and their derivatives are reported to exhibit significant biological activites [21,22] and the carbohydrazide function represents an important pharmacophoric group in several classes of therapeutically useful substances [23-26].

Based on the above mentioned research results, the goal of this study is to synthesize some novel pyrazoles derivatives carrying aryl ring system, by condensing 5-substituted-1H-pyrazole-3-carbohydrazide with different functionalized aromatic aldehydes. The synthesis of the compounds was illustrated in Scheme 1.

## EXPERIMENTAL SECTION

Thin-layer chromatography (TLC) was carried out on Silica Gel 60 F254 plates (Merck KGaA). 1H NMR spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer, using DMSO as solvent and tetramethylsilane (TMS) as internal standard. Melting points were determined on a Büchi Melting Point B-545 capillary apparatus and are uncorrected. IR spectra were recorded with an IR spectrophotometer VERTEX 70 FT-IR (Bruker Optics). The mass spectrum were obtained on a API 3200 LC/MS/MS system.

## RESULTS AND DISCUSSTION

### 1. Chemistry

Synthesis of N'-[(aryl)methylene]-5-substituted-1H-pyrazole-3-carbohydrazide (**3**) is outlined in Scheme 1. Starting compounds, ethyl 3-substituted-1H-pyrazole-5-carboxylate (**1**) were readily prepared by the reaction of ehtyl-2,4-dioxo-4-substituted-butanoate (**5**), which can be obtained from commercially available acetone or acetephenone (**4**) and diethyl oxalate, with hydrazine in the presence of sulfiric acid at room temperature [27]. The reaction of ethyl 3-substituted-1H-pyrazole-5-carboxylate (**1**) with hydrazine hydrate in ethanol affordded 3-substituted-1H-pyrazole-5-carbohydrazide (**2**), compounds (**3**) were obtained by condensing of (**2**) with functionaliezd aromatic aldehydes at reflux in ethanol to produce the desired of N'-[(aryl)methylene]-5-substituted-1H-pyrazole-3-carbohydrazide (**3**) in good yields . The structure of these stable and cristalline compounds was fully characterized by usual methods (IR, $^1$H-NMR and mass spectroscopy). Thus, for example **3c** (R=$CH_3$, Ar= p-$N(CH_3)_2$-$C_6H_5$), obtained as yellow crystal, gave a [M+H]-ion peak at *m/z* 272.3 in the ESI-MS, in the accord with the molecular formula $C_{14}H_{17}N_5O$. The carbonyl group absorptions in hydrazide moiety were observed in the 1648 $cm^{-1}$ in IR spectra and NH and $NH_2$ bands in $CONHNH_2$ were observed in the 3233 $cm^{-1}$ and 3300-3230 $cm^{-1}$ regions, respectively. The $^1$H NMR spectra indicated the chemical shift of the NH in the pyrazole at δ = 12.999 ppm in the form of singlet peak. another NH proton in the CONH appeared at δ = 11.236 ppm in the form of singlet peack. The chemical shift of the N=CH appeared at δ = 8.306 ppm in the form of singlet peack. Two *ortho*-aromatic protons signals in 4-dimethylaminophenyl moiety appeared at the range of δ = 7.450 and 7.477 ppm, two *meta*-aromatic protons signals appeared at the range of δ = 6.65 and 6.83 ppm. The singlet appeared at δ = 6.445 ppm are constitent with the proton in pyrazole moiety. The singlet appeared at δ = 2.937 ppm are constitent with the protons in $N(CH_3)_2$. A singlet signal appeared at δ = 2.258 ppm are consistent with the protons in $CH_3$.

**General procedure for the preparation of 3-substituted-1H-pyrazole-4-carbohydrazides (2) :**

To a stirred solution of 1 mmol of the 3-substituted-1H-pyrazole-4-carboxylate (**1**) in ethanol (10 ml), 2 ml of 80% hydrazine monohydrate was added. The reaction mixture was maintained under reflux for 5–8 hours, until TLC indicated the end of reaction. After this time, the reaction mixture was poured on ice and the solid formed was collected by filtration, washed with cold water and recrystallized from ethanol.

***5-methyl-1H-pyrazole-3-carbohydrazide (2a) :***

Yield 51% (solid) ; M.p. 157-159°C; IR (KBr, ν(cm-1)) : 3269 – 3461 (NH, $NH_2$), 1634 (C=O); 1H-NMR (300 MHz, DMSO-$d_6$, δ(ppm)): δ = 2.206 (s,3H, –CH3), 4.321 (s, 2H, –$NH_2$), 6.344 (s, 1H, Pz-H), 9.169 (s, 1H, CO-NH), 12.823 (s, Pz-NH). MS: m/z = 141.4 ($M-H^+$).

***5-phenyl-1H-pyrazole-3-carbohydrazide (2b):***

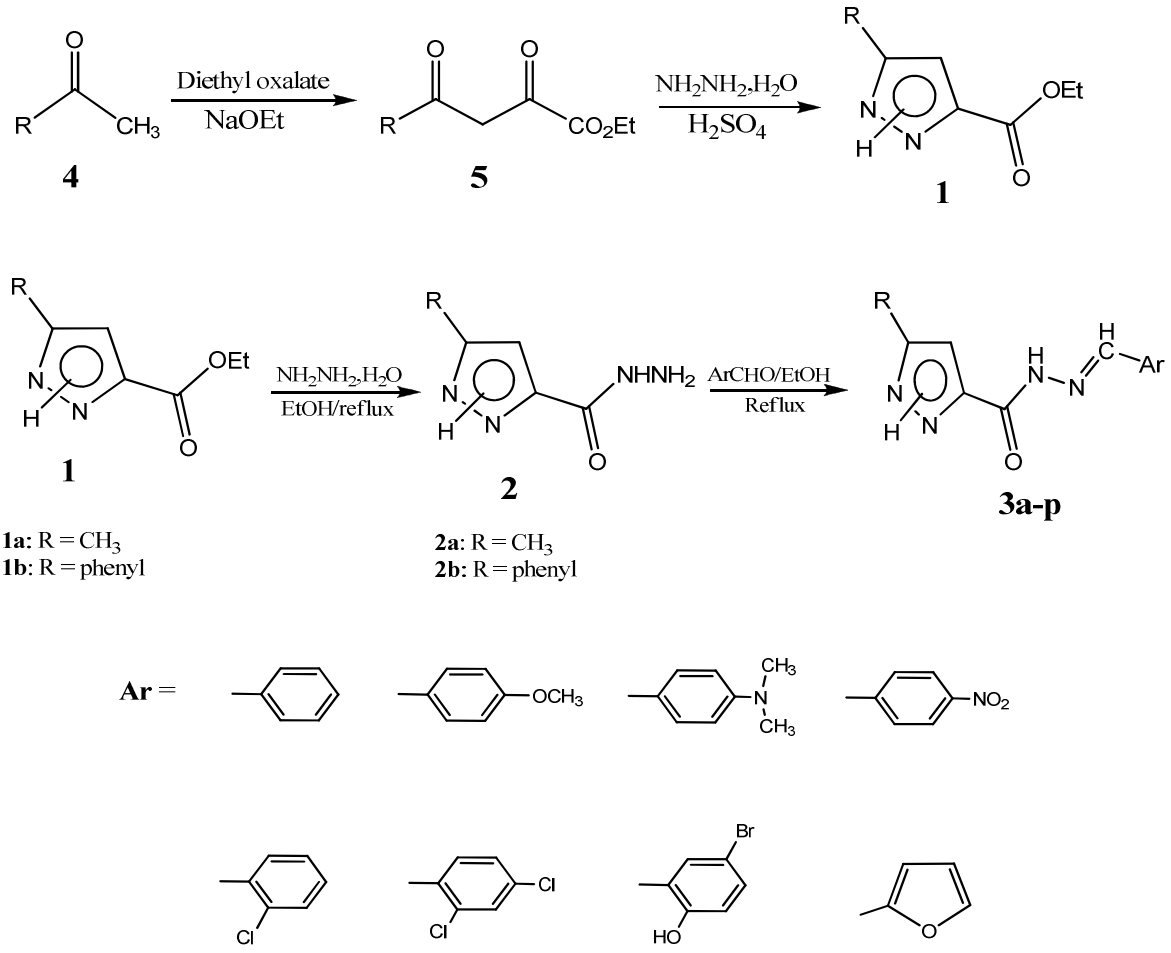
Yield 66% (solid), M.p. 157-159°C; IR (KBr, ν(cm-1)) : 3331 – 3207 (NH, $NH_2$), 1631 (C=O) ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 4.445 (s, 2H, NH2), 7.106 (s, 1H, Pz-H), 7.325 - 7.455 (m, 3H, ArH), 7.733, 7.757 (d, 2H, ArH), 9.492 (s, 1H, CO-NH), 13.586 (s, 1H, Pz-NH).1565, 955,745 ; MS: m/z = 203.3 ($M-H^+$)

**General procedure for the preparation of N′-[(aryl)methylene]-1H-pyrazole-4-carbohydrazides (3) :**

To a solution of derivatives (**2**) (1 mmol) in 10 ml of ethanol, it was added an equimolar amount of the appropriate benzaldehyde derivative in the presence of acetic acid. The mixture was maintained under reflux for 2 h, until TLC indicated the end of reaction. Then, the reaction mixture was poured in cold water, and the precipitate formed was filtered out washed with ethanol and recrystallized from Methanol/DMF.

***N'-benzylidene-5-methyl-1H-pyrazole-3-carbohydrazide (3a) :***

Yield 62% (solid), M.p. 243-245°C; IR (KBr, ν(cm-1)) : 3229 (NH), 1656 (C=O), 1608, 1407, 1368, 1023, 839 ; 1H-NMR (300 MHz, DMSO-$d_6$, δ(ppm)): δ = 2.274 (s,3H, –CH3), 6.488 (s, 1H, Pz-H), 7.410 - 7.673 (m, 5H, ArH), 8.478 (s, 1H, CO-NH), 11.588 (s, 1H, N=C-H) 13.076 (s, 1H, Pz-NH) ; MS: m/z = 229.3 ($M-H^+$).




**Scheme 1: General procedure for the synthesis of pyrazole derivatives**

***N'-(4-methoxybenzylidene)-5-methyl-1H-pyrazole-3-carbohydrazide (3b)*** *:*
Yield 78 % (solid), M.p. 260-262°C; IR (KBr, ν(cm-1)) : 3214 (NH), 1651(C=O), 1605, 1552, 1407, 1372, 1036, 834 ; 1H-NMR (300 MHz, DMSO-$d_6$, δ(ppm)): δ = 2.268 (s,3H, –CH3), 3.780 (s, 3H, –$OCH_3$), 6.470 (s, 1H, Pz-H), 6.972, 7.002 (d, 2H, ArH), 7.585, 7.617 (d, 2H, ArH), 8.405 (s, 1H, -NH), 11.434 (s, 1H, N=C-H) 13.046 (s, 1H, Pz-NH) ; MS: m/z = 259.2 ($M-H^+$).

***N'-(4-(dimethylamino) benzylidene)-5-methyl-1H-pyrazole-3-carbohydrazide (3c) :***
Yield 81% (solid), M.p. 259-261°C; IR (KBr, ν(cm-1)) : 3233 (NH), 1648 (C=O), 1602, 1525, 1445, 1408, 1063, 845 ; 1H-NMR (300 MHz, DMSO-$d_6$, δ(ppm)): δ = 2.258 (s,3H, –CH3), 2.937 (s, 6H, –$N(CH_3)_2$, 6.445 (s, 1H, Pz-H), 6.705, 6.731 (d, ArH), 7.450, 7.477 (d, 2H, ArH), 8.306 (s, 1H, CO-NH), 11.236 (s, 1H, N=C-H), 12.999 (s, 1H, Pz-NH) ; MS: m/z = 272.3 ($M-H^+$).

***N'-(4-nitrobenzylidene)-5-methyl-1H-pyrazole-3-carbohydrazide (3d):***
Yield 84% (solid), M.p. 283-285°C; IR (KBr, ν(cm-1)) : 3320 (NH), 1681 (C=O), 1512, 1406, 1022, 827 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 2.282 (s,3H, –CH3), 6.445 (s, 1H, Pz-H), 7.899, 7.928 (d, 2H, ArH), 8.260, 8.290 (d, 2H, ArH), 8.585 (s, 1H, -N=CH), 11. 923 (s, 1H, -CO-NH), 13.133 (s, 1H, Pz-NH) ; MS: m/z = 274.1 ($M-H^+$).

***N'-(2-chlorobenzylidene)-5-methyl-1H-pyrazole-3-carbohydrazide (3e):***
Yield 78% (solid), M.p. 273-275°C; IR (KBr, ν(cm-1)) : 3182 (NH), 1665 (C=O), 1552, 1441, 1358, 1024, 825 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 2.278 (s,3H, –CH3), 6.498 (s, 1H, Pz-H), 7.391 - 7.510 (m, 3H, ArH), 7.961, 7.992 (d, 2H, ArH), 8.907 (s, 1H, -N=CH), 11. 924 (s, 1H, -CO-NH), 13.094 (s, 1H, Pz-NH) ; MS: m/z = 263.1 ($M-H^+$).

***N'-(2,4-dichlorobenzylidene)-5-methyl-1H-pyrazole-3-carbohydrazide (3f):***
Yield 95% (solid), M.p. 258-260°C; IR (KBr, ν(cm-1)) : 3326 (NH), 11684 (C=O), 1584, 1529, 1464, 1407, 1023, 820 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 2.277 (s, 3H, –CH3), 6.498 (s, 1H, Pz-H), 7.475 - 7.509 (dd, 1H, ArH), 7.678, 7.685 (d, 1H, ArH), 7.963, 7.991 (d, 1H, ArH), 8.866 (s, 1H, -N=CH), 11. 986 (s, 1H, -CO-NH), 13.106 (s, 1H, Pz-NH) ; MS: m/z = 297.1 ($M-H^+$).

***N'-(5-bromo-2-hydroxybenzylidene)-5-methyl-1H-pyrazole-3-carbohydrazide (3g) :***
Yield 63% (solid), M.p. 254-256°C; IR (KBr, ν(cm-1)) : 3314 (NH), 1692 (C=O), 1533, 1476, 1341, 1211, 819 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 2.278 (s,3H, –CH3), 6.503 (s, 1H, OH), 6.506 (s, 1H, Pz-H), 6.856, 6.886 (d, 1H, ArH), 7.374 - 7.412 (dd, 1H, ArH), 7.657, 7.665 (d, 1H, ArH), 8.614 (s, 1H, -N=CH), 11. 379 (s, 1H, -CO-NH), 13.128 (s, 1H, Pz-NH) ; MS: m/z = 323,2 ($M-H^+$).

***N'-[(furan-2-yl) methylene]-5-methyl-1H-pyrazole-3-carbohydrazide (3h):***
Yield 73% (solid), M.p. 272-274°C; IR (KBr, ν(cm-1)) : 3224 (NH), 1652 (C=O), 1545, 1480, 1419, 1021, 802 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 2.269 (s,3H, –CH3), 6.467 (s, 1H, Pz-H), 6.591 – 6.608 (m, 1H, FurH), 6.826 – 6.837 (d, 1H, FurH 7.800 – 7.803 (d, 1H, FurH) 8.367 (s, 1H, -N=CH), 11.592 (s, 1H, -CO-NH), 13.059 (s, 1H, Pz-NH) ; MS: m/z = 219.3 ($M-H^+$).

***N'-benzylidene-5-phenyl-1H-pyrazole-3-carbohydrazide (3i) :***
Yield 70% (solid), M.p. 202-204°C; IR (KBr, ν(cm-1)) : 3250 (NH), 1644 (C=O), 1557, 1254, 954, 837 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 7.125 (s, 1H, Pz-H), 7.515 – 8.426 (m, 10H, ArH), 8.478 (s, 1H, N=CH), 10.847 (s, 1H, -CON-H), 13.016 (s, 1H, Pz-NH) ; MS: m/z = 291.1 ($M-H^+$).

***N'-(4-methoxybenzylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide* (3j):**
Yield 82% (solid), M.p. 276-278°C; IR (KBr, ν(cm-1)) : 3214 (NH), 1656 (C=O), 1603, 1564, 1511, 1406 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 3.794 (s,3H, –OCH3), 6.996, 7.025 (d, 2H, ArH), 7.199 (s, 1H, Pz-H), 7.364 - 7.465 (m, 3H, ArH), 7.631, 7.658 (d, 2H, ArH), 7.803, 7.827 (d, 2H, ArH), 8.439 (s, 1H, -CON-H), 11.570, 11.741 (d, 1H, N=C-H), 13.778 (s, 1H, Pz-NH), 827 ; MS: m/z = 259.2 ($M-H^+$).

***N'-(4-dimethylaminobenzylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (3k):***
Yield 78% (solid), M.p. 262-264°C; IR (KBr, ν(cm-1)) : 3219 (NH), 1648 (C=O), 1596, 1525, 1259, 847 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 2.958 (s,3H, -$N(CH3)_2$), 6.728 (s, 1H, Pz-H), 7.162 – 8.356 (m, 9H, ArH), 8.356 (s, 1H, N=CH), 11.357 (s, 1H, -CON-H), 13.722 (s, 1H, -N-H) ; MS: m/z = 334.5 ($M-H^+$).

***N'-(4-nitrobenzylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (3l):***
Yield 72% (solid), M.p. 288-290°C; IR (KBr, ν(cm-1)) : 3225 (NH), 1669(C=O) 1510, 1468, 1240, 828 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 7.237 (s, 1H, Pz-H), 7.386 – 8.306 (m, 9H, ArH), 8.636 (s, 1H, N=CH), 12.047 (s, 1H, -CON-H), 13.839 (s, 1H, Pz-NH) ;MS: m/z = 336.2 ($M-H^+$).

***N'-(2-chlorobenzylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (3m):***
Yield 89% (solid), M.p. 230-232°C; IR (KBr, ν(cm-1)) : 3145 (NH), 1643 (C=O), 1556, 1468, 1438,1251, 829 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 7.219 (s, 1H, Pz-H), 7.382 – 8.027 (m, 9H, ArH), 8.955 (s, 1H, N=CH), 12.052 (s, 1H, -CON-H), 13.809 (s, 1H, Pz-NH) ; MS: m/z = 325.3 ($M-H^+$).

***N'-(2,4-dichlorobenzylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (3n):***
Yield 62% (solid), M.p. 234-236°C; IR (KBr, ν(cm-1)) : 3182 (NH), 1657 (C=O), 1586, 1543, 1469, 1249, 833 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 7.218 (s, 1H, Pz-H), 7.383 – 8.041 (m, 8H, ArH), 8.913 (s, 1H, N=CH), 12.110 (s, 1H, -CON-H), 13.813 (s, 1H, Pz-NH) ; MS: m/z = 360.9 ($M-H^+$).

***N'-(5-bromo-2-hydroxybenzylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (3o) :***
Yield 91% (solid), M.p. 287-289°C; IR (KBr, ν(cm-1)) : 3205 (NH), 1664 (C=O), 1615, 1447, 1230, 821, 628 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 6.872 (s, 1H, OH), 7.223 (s, 1H, PzH),7.381 – 7.840 (m, 8H, ArH), 8.674 (s, 1H, N=CH), 12.144 (s, 1H, -CON-H), 13.838 (s, 1H, Pz-NH) ; MS: m/z = 386.2 ($M-H^+$).

***N'-(furan-2-ylmethylene)-5-phenyl-1H-pyrazole-3-carbohydrazide (3p):***
Yield 85% (solid), M.p. 207-209°C; IR (KBr, ν(cm-1)) : 3276 (NH), 1681 (C=O), 1611, 1580, 1531, 1262, 1024, 811 ; 1H-NMR (300 MHz, $d_6$-DMSO, δ(ppm)): δ = 6.609 - 6.654 (m, 1H, FurH), 6.871 (s, 1H, PzH) 7.186 – 7.825 (m, 7H, ArH, FurH), 8.417 (s, 1H, N=CH), 11.717 (s, 1H, -CON-H), 13.767 (s, 1H, Pz-NH) ; MS: m/z = 281.3 ($M-H^+$).

**2. Biological Activity**

The compounds described in this manuscript **3a-p** were first tested *in vitro* for their activity against three bacterial strains (*Sataphylococcus aureus CIP 4.83, Pseudomonas aeruginosa CIP 82-118 and Bacillus subtilis CIP 52-62*) and against fungal strains (*Candida albicans CIP 48.72*). Tetracyclin and Fluconazole were used as control drugs. The activities were determined by the agar diffusion technique as previously described [28]. 18 mL of Muller-Hinton agar medium were poured into petri dishes as a first layer, a suspension of each test bacterium was diluted with an appropriate volume of Muller-Hinton agar medium to contain about $10^5$ CFU/ml and 8 mL of it was poured on of the first layer of each petri dish. The petri dishes were kept 15 min at room temperature and then at 4°C. Cylindrical cavities were punched in the agar with a suitable device. 60 µl volume with concentration 2 mg/ml of each compound reconstituted in the DMSO was loaded into the cavities prepared in the agar. All the plates were incubated at 37 °C for 24h in case of bateria and after 48h in case of fungi at 25 °C.

In pharmacological term, all these products, with different ring system, were found to be inactive when compared with the CMI of the standard. We can thus conclude that introduction of different aryl ring system in N' position of 5-substituted-1H-pyrazole-3-carbohydrazide has not any impact on the antibacterial activity. Extension antiviral and antitumour activities are under study and will be reported in due course.

## CONCLUSION

The Main focus of this research work was to synthesize, characterize of the newly synthesized pyrazole carbohydrazide derivatives, structures of synthesized compounds were confirmed by means of their IR, $^1$H NMR and mass spectral. The preliminary *in vitro* test results of these compounds were negatives against the three studied microorganisms such as *Staphylococcus aureus CIP 4.83, Pseudomonas aeruginosa CIP 82-118, Bacillus subtilis CIP 52-62 and Candida albicas CIP 48.72.*

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