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Original article

Synthesis and antimicrobial activity of some new 4-hetarylpyrazole and furo[2,3-*c*]pyrazole derivatives

Samir Bondock*, Wesam Khalifa, Ahmed A. Fadda

Department of Chemistry, Faculty of Science, Mansoura University, ET-35516 Mansoura, Egypt

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ABSTRACT

In continuation of our efforts to find a new class of antimicrobial agents, a series of 4-hetarylpyrazoles and furo[2,3-*c*]pyrazoles were prepared *via* the reaction of 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**1**) with an appropriate nucleophilic reagents. These compounds were screened for their antibacterial activity against Gram-positive bacteria (*Bacillus subtilis* and *Bacillus thuringiensis*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and antifungal activity against *Fusarium oxysporum* and *Botrytis fabae*. Among the synthesized compounds, 1-(5-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole-4-yl)-2-methylfuran-3-yl)ethanone (**12**) showed equal activity with chloramphenicol against *B. subtilis* (MIC 3.125 μg/mL), while its activity was 50% lower than of chloramphenicol against *B. thuringiensis*. *N*-[(4*Z*)-3-Methyl-1-phenyl-1*H*-furo[2,3-*c*]pyrazol-4(5*H*)-ylidene]-1*H*-benzimidazol-2-amine (**7**) and 2-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-furo[3,2-*c*]chromen-4-one (**13**) were found to exhibit the most potent in *vitro* antifungal activity with MICs (6.25 μg/mL) against *B. fabae* and *F. oxysporum*.

1. Introduction

The pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds. This is mainly due to the ease preparation and the important pharmacological activity. Therefore, the synthesis and selective functionalization of pyrazoles have been the focus of active research area over the years [1–5]. Pyrazoles have been reported to possess antibacterial activity and inhibitor activity against DNA gyrase and topoisomerase IV at their respective ATP-binding sites [6–8]. Moreover, pyrazole-containing compounds have received considerable attention owing to their diverse chemotherapeutic potentials including versatile antineoplastic activities. Literature survey revealed that some pyrazoles have been implemented as antileukemic [9–11], antitumor [12–16], antiproliferative agents [17,18], GABA receptor antagonists and insecticides [19], anti-inflammatory and antimicrobial agents [20–23].

In addition to, furans and their derivatives with substituent(s) at C-2 and/or C-3 have attracted strong interest due to their widespread in a large number of natural products and for their useful biological and pharmacological properties [24–28]. The antifungal agent *Cicerfuran*, obtained from the roots of wild species of chickpea, *Cicer bijugum*, reported to be a major factor in the defense system against *Fusarium* wilt [29]. In addition, Nitrofurantoin and Furazolidone are potent nitrofuran drugs. They have been reported to possess broad antimicrobial properties, including activity against trypanosomes [30,31].

Prompted by the above-mentioned results, it was planned to study structure variation by attaching some biologically active heterocycles such as quinoxaline, benzothiazine, benzoxazine, furan, benzofuran and furo[3,2-*c*]coumarin at position 4 of the main pyrazole moiety as well as construction of some furo[2,3-*c*]pyrazoles. These combinations were suggested in an attempt to investigate the possible synergistic influence of such structure hybridizations on the anticipated activity, hoping to discover a new lead structure that would have a significant antimicrobial activity at very small concentration.

In continuation of our recent work aiming at the synthesis of heterocyclic systems with remarkable biological importance [32–37], we report herein on the utility of 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone as building blocks for the synthesis of functionalized 4-hetarylpyrazoles and furo[2,3-*c*]pyrazoles, and study their antimicrobial activity in order to get a new compounds that could be optimized for potent antimicrobial agents.

* Corresponding author. Tel.: +20 502369267; fax: +20 502246781.
E-mail address: Bondock@mans.edu.eg (S. Bondock).

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2. Results and discussion

2.1. Chemistry

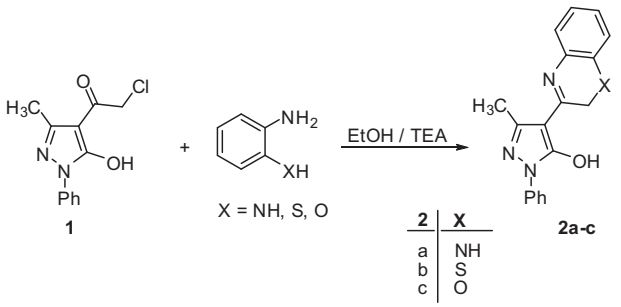
The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1–3. The starting material, 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**1**) was prepared by refluxing 5-pyrazolone with chloroacetyl chloride in a basic dioxane solution following a procedure described earlier by Jensen et al. [38]. Treatment of **1** with *o*-phenylenediamine in boiling ethanol gave a sole product that was identified as 4-(3,4-dihydroquinoxalin-2-yl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**2a**). In the same manner, compound **1** reacts with 2-aminothiophenol and 2-aminophenol to afford product that may be formulated as 1,4-benzothiazine **2b** and 1,4-benzoxazine **2c** derivatives based on both elemental analysis and spectral data (Scheme 1).

Next, we studied the reactivity of **1** toward some heterocyclic amines namely, 2-aminopyridine, 2-aminopyrazine, 3-amino-4*H*-1,2,4-triazole and 2-aminobenzimidazole as a possible synthetic route to get bridghead heterocyclic nitrogen compounds of potential pharmacological interest. Surprisingly, the reaction of **1** with either 2-aminopyridine or 2-aminopyrazine in refluxing ethanolic triethylamine afforded in each case a single product identified as furo[2,3-*c*]pyrazoles **3a**–**b** rather than the expected imidazo[1,2-*a*]pyridine **4a** and imidiazo[1,2-*a*]pyrazine **4b**. The chemical structures of compounds **3a**–**b** were elucidated on the basis of elemental analyses, spectral data and an alternative synthetic route. Thus, treatment of 3-methyl-1-phenyl-1*H*-furo [2,3-*c*]pyrazol-4(5*H*)-one (**5**), which was synthesized from **1** by boiling in ethanol containing a catalytic amount of triethylamine, with 2-aminopyridine or 2-aminopyrazine in boiling ethanol gave product identical in all aspects (mp., mixed mp., and spectra) with **3a**–**b** (Scheme 2).

It is worthwhile to mention that compounds **3a**–**b** can exist in two diastereomeric *E*- and *Z*-isomers. The preferential formation of *Z*-isomer was supported from molecular orbital calculation using Hyperchem 7, semi-empirical method (PM3), which revealed that the heat of formation of *Z*-isomer is lower than *E*-isomer by about 0.5 kcal/mol.

Analogously, the appropriate 3-amino-4*H*-1,2,4-triazole or 2-aminobenzimidazole was reacted with compound **1** under the same experimental conditions gave *N*-(3-methyl-1-phenyl-1*H*-furo [2,3-*c*]pyrazol-4(5*H*)-ylidene-4*H*-1,2,4-triazol-3-amine (**6**) and *N*-(3-methyl-1-phenyl-1*H*-furo[2,3-*c*]pyrazol-4(5*H*)-ylidene)-1*H*-benzimidazol-2-amine (**7**), respectively. The assigned structures **6** and **7** were confirmed on the basis of elemental analyses and spectral data (see experimental).

The plausible mechanism for the formation of compounds **3a**–**b**, **6**, and **7** may be attributed to the first nucleophilic displacement of the chloride by the hydroxyl group to form compound **5** that underwent *in situ* condensation with heterocyclic amines to afford the target molecules.



Scheme 1. Synthesis of pyrazolyl-quinoxaline, 1,4-benzothiazine, and 1,4-benzoxazine **2a**–**c**.

In contrast to the behavior of compound **1** toward heterocyclic primary amines, it has been found that refluxing of compound **1** with heterocyclic secondary amines such as piperidine and/or morpholine in absolute ethanol furnished the substitution products **9a**–**b** rather than the enamines **8a**–**b**. The structures of compounds **9a**–**b** were determined by elemental analyses, which give the molecular formula $C_{17}H_{21}N_3O_2$ for **9a** and $C_{16}H_{19}N_3O_3$ for **9b**, as well as spectral data (see experimental).

Moreover, we investigated the reactivity of **1** toward salicyaldehyde, 2-hydroxyacetophenone, acetylacetone and 4-hydroxycoumarin as a possible synthetic route to attain furan, benzofuran and furo[3,2-*c*]chromenone derivatives. Thus, treatment of **1** with salicylaldehyde and/or 2-hydroxyacetophenone in dimethylsulfoxide in the presence of anhydrous potassium carbonate furnished benzofuran derivatives **10** and **11**, respectively. Structure of the isolated products **10** and **11** was confirmed on the basis of their elemental analyses and spectral data. For example, the IR spectrum of compound **11** revealed an absorption bands at 3390 and 1635 cm^{-1} characteristic to OH and C=O groups. The lower frequency of a ketonic carbonyl group is attributed to the hydrogen bonding formation with hydroxyl group. Its ^1H NMR spectrum revealed three singlet signals at δ 2.31, 2.50 and 12.80 ppm assignable to CH_3 of pyrazole ring, CH_3 of furan ring and OH protons, respectively, besides a multiplet centered around 6.93–8.01 ppm due to aromatic protons. The ^{13}C NMR spectrum of compound **11** revealed eighteen carbon types. The carbonyl carbon is displayed at δ 165.5 ppm. Other important signals are displayed at δ 12.3 and 16.4 ppm characteristics for two methyl carbons, while C-5 pyrazole was displayed downfield at δ 154.2 ppm. Moreover, the mass spectrum of **11** showed a molecular ion peak at $m/z = 333$ (M^+) corresponding to a molecular formula $C_{20}H_{16}N_2O_3$.

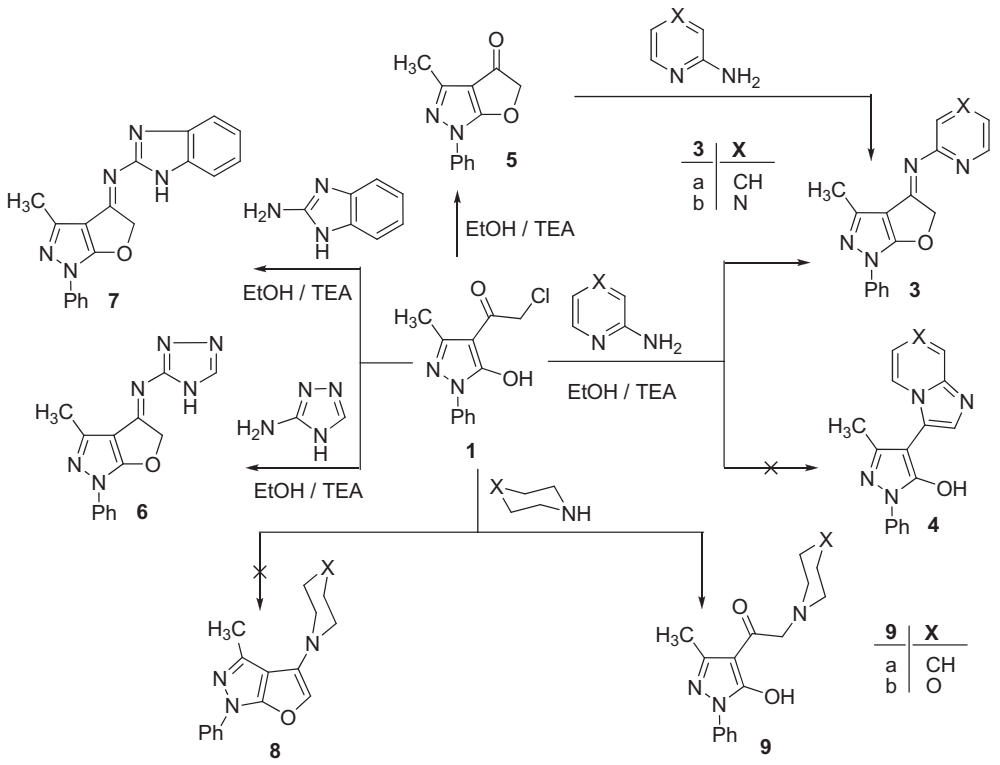
In a similar manner, 1-(5-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole-4-yl)-2-methylfuran-3-yl)ethanone (**12**) and 2-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole-4-yl)-4-*H*-furo[3,2-*c*]chromen-4-one (**13**) were obtained in a good yield upon treatment of compound **1** with acetylacetone and 4-hydroxycoumarin in ethanolic sodium ethoxide solution. Structures **12** and **13** were established on the basis of their elemental analyses and spectral data. For example, the IR spectrum of compound **12** revealed an absorption bands at 1695 (acetyl C=O) and 3440 (OH). The ^1H NMR spectrum of compound **12** displayed three singlet signals at δ 2.33, 2.43 and 2.61 ppm characteristic for three methyl groups and broad D_2O-exhangeable signal at 12.82 characteristic for OH, in addition to multiplets centered around 7.15–7.84 ppm due to aromatic protons and furan H-4. Its mass spectrum revealed a molecular ion peak at $m/z = 296$ (M^+) and the base peak at 173 (100%) due to the fragment [1-phenyl-3-methyl-5-hydroxypyrazole]$^+$.

The formation of compounds **10**–**13** may be rationalized by two step reactions, which involve the base promote alkylation of the hydroxyl group by the α-chloroketone followed by *in situ* intramolecular C–C bond formation of the initial O-alkyl adduct. It is worthwhile to mention that all trials to isolate the initially formed O-alkyl adduct was failed. The preference formation of angular furo [3,2-*c*]coumarin **13** is also in the line with similar report by Risitano and coworkers [39].

3. Pharmacology

3.1. Antimicrobial evaluation

The tested microorganisms were obtained from the culture collection at the Microbiology laboratory, National Organization for



Scheme 2. Synthesis of furo[2,3-*c*]pyrazole derivatives.

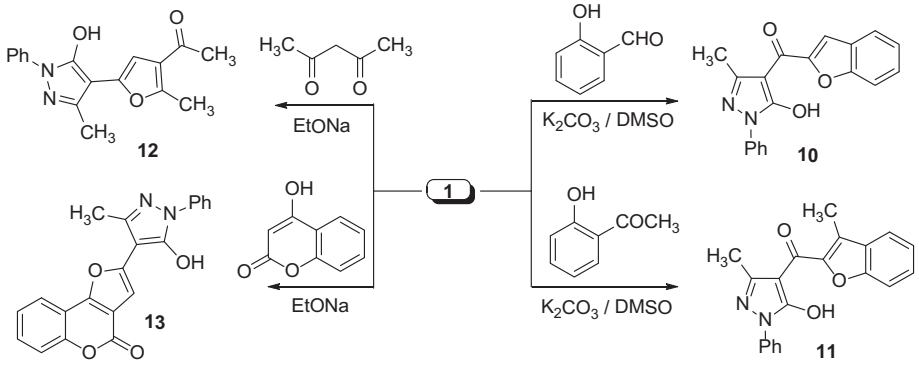
Drug Control and Research (NODCAR). Thirteen of the newly synthesized target compounds were evaluated for their in *vitro* antibacterial activity against *Bacillus subtilis* (ATCC 6633) and *Bacillus thuringiensis* (ATCC 6051) as examples of Gram-positive bacteria and *Escherichia coli* (ATCC 14169) and *Pseudomonas aeruginosa* (ATCC 27853) as examples of Gram-negative bacteria. They were also evaluated for their in *vitro* antifungal potential against *Fusarium oxysporum* (ATCC 16417) and *Botrytis fabae* (ATCC 14862) fungal strains.

Agar-diffusion method was used for the determination of the preliminary antibacterial and antifungal activity. Chloramphenicol, cephalothin and cycloheximide were used as reference drugs. The results were recorded for each tested compound as the average diameter of inhibition zones (IZ) of bacterial or fungal growth around the disks in mm. The minimum inhibitory concentration (MIC) measurement was determined for compounds showed significant growth inhibition zones (>14 mm) using twofold serial dilution method [40]. The MIC (μg/mL) and inhibition zone diameters values are recorded in Table 1.

The inhibition zone diameters values cited in Table 1 between brackets are attributed to the tested original concentration (1 mg/mL) as a preliminary test. The results depicted in Table 1 revealed that most of tested compounds displayed variable inhibitory effects on the growth of the tested Gram-positive and Gram-negative bacterial strains, and also against fungal strains.

In general, most of the tested compounds revealed better activity against the Gram-positive rather than the Gram-negative bacteria. It would be also noticed that compounds belonging to the furo[2,3-*c*]pyrazoles and furylpyrazole series (Schemes 2 and 3) exhibited better antibacterial potentials than members of the pyrazolyl-quinoxaline, pyrazolyl-1,4-benzothiazine and pyrazolyl-1,4-benzoxazine (Scheme 1).

Regarding the activity of the furylpyrazoles against Gram-positive bacteria, the results revealed that compounds **10**, **11**, and **12** exhibited divergent antibacterial activity against the tested organisms. In this view, compound **12** was equipotent to chloramphenicol in inhibiting the growth of *B. subtilis* (MIC 3.125 μg/mL), while its activity was 50% lower than of chloramphenicol against



Scheme 3. Synthesis of furan, benzofuran and furo[3,2-*c*]coumarin derivatives.

Table 1
Minimal inhibitory concentrations (MIC, μg/mL) and inhibition zone (mm) of some new synthesized compounds.

Compound no.	MIC[a] in μg/mL, and zone of inhibition (mm)					
	Bacteria				Fungi	
	Gram-positive bacteria		Gram-negative bacteria			
	B. subtilis	*B. thuringiensis*	*E. coli*	*P. aeruginosa*	*F. oxysporum*	*B. fabae*
2a	50 (19)	100 (15)	100 (15)	50 (19)	100 (15)	50 (20)
2b	100 (15)	100 (15)	100 (15)	100 (16)	100 (15)	50 (19)
2c	50 (20)	50 (19)	50 (19)	100 (15)	100 (15)	100 (15)
3a	25 (26)	25 (25)	6.25 (38)	100 (15)	100 (16)	50 (20)
3b	12.5 (32)	100 (15)	50 (20)	100 (16)	12.5 (31)	100 (16)
6	6.25 (38)	6.25 (38)	100 (15)	100 (16)	100 (15)	50 (19)
7	3.125 (44)	6.25 (37)	50 (19)	50 (20)	100 (14)	6.25 (37)
9a	3.125 (43)	6.25 (38)	50 (19)	100 (16)	100 (14)	12.5 (31)
9b	12.5 (32)	6.25 (38)	100 (16)	50 (20)	50 (19)	50 (19)
10	6.25 (38)	6.25 (37)	100 (15)	12.5 (33)	25 (26)	50 (19)
11	6.25(37)	6.25 (37)	25 (27)	50 (19)	100 (15)	100 (15)
12	3.125 (42)	6.25 (37)	100 (15)	50 (18)	50 (20)	25 (26)
13	12.5 (33)	100 (15)	100 (15)	6.25 (38)	6.25 (37)	100 (15)
Reference drugs						
Chloramphenicol	3.125 (42)	3.125 (44)	6.25 (37)	6.25 (38)	NT[b]	NT
Cephalothin	6.25 (36)	6.25 (37)	6.25 (38)	6.25 (37)	NT	NT
Cycloheximide	NT	NT	NT	NT	3.125 (43)	3.125 (42)

[a] MIC: Minimal inhibitory concentration values.
[b] NT: Not tested.

B. thuringiensis. Compounds **10** and **11** showed 50% of the activity of chloramphenicol (MIC 6.25 μg/mL) but they were equipotent to cephalothin in inhibiting the growth of *B. subtilis* and *B. thuringiensis* (MIC 6.25 μg/mL).

On the other hand, compounds **2a, 2b, 2c, 3a**, **3b**, **9b** and **13** exhibited weak to moderate growth inhibitory activity against Gram-positive bacteria as revealed from their MIC values (25–100 μg/mL). Among these compounds **3b** and **13** showed relatively good growth inhibitory profiles against *B. subtilis* (MIC 12.5 μg/mL) which were about 25% of the activity of chloramphenicol and 50% of cephalothin against the same organism. Moreover, distinctive anti-Gram-positive profile was displayed by compound **7** where it proved to be equipotent as chloramphenicol against *B. subtilis* (MIC 3.125 μg/mL) together with a significant activity against *B. thuringiensis* (MIC 6.25 μg/mL).

Concerning the antibacterial activity of the compounds **2c**, **3b**, **7**, and **9a** revealed weak growth inhibitory against the tested Gram-negative bacteria (MIC 50 μg/mL). On the other hand, compounds **3a** and **13** showed equipotent activity as chloramphenicol and cephalothin (MIC 6.25 μg/mL) against *E. coli* and *P. aeruginosa*.

Regarding the activity 4-hetarylpyrazoles and furo[2,3-*c*]pyrazoles, against fungal strains, the results revealed that compounds **7** and **13** were 50% lower than cycloheximide in inhibitory the growth of *B. fabae* and *F. oxysporum* (MIC 6.25 μg/mL), while the reactivity of compound **3b** was 25% lower than cycloheximide against *F. oxysporum* (MIC 12. 5 μg/mL).

The results of the antimicrobial screening demonstrated the following assumptions about the structural activity relationship (SAR):

- It is interesting to point out that furylpyrazoles **10**–**12** having electron withdrawing groups such as $COCH_3$ or ArCO (Ar = benzofuryl) recorded higher antibacterial activity.
- The incorporation of furan or benzofuran to pyrazole nucleus at position 4 directly (in case of furan) or *via* a carbonyl linker (in case of benzofuran) produced a high antimicrobial activity.
- Conversion of compound **1** to furo[2,3-*c*]pyrazoles **3a**–**b** enhanced also the antimicrobial activity. On the other hand, incorporation of quinoxaline, 1,4-benzothiazine and/or 1,4-benzoxazine to pyrazole nucleus at position 4 in compounds **2a**, **2b**, and **2c** unfortunately produced weak antimicrobial activity.
- High biological activity can be correlated with low electron density of ring systems.

In conclusion, the objective of the present study was to synthesize and investigate the antimicrobial activities of some new functionalized 4-hetarylpyrazoles and furo[2,3-*c*]pyrazoles with the hope of discovering new structure leads serving as potent antimicrobial agents. Our aim has been verified by the synthesis of three different groups of structure hybrids comprising basically the pyrazole moiety attached to either quinoxaline, 1,4-benzothiazine, 1,4-benzoxazine, polysubstituted furan, benzofuran, furo[3,2-*c*]chromenone, or fused to furan counter parts through various linkages of synthergistic purpose. The obtained results clearly revealed that compounds derived from furan, benzofuran and furo[2,3-*c*]pyrazoles exhibited better antimicrobial activity than their quinoxaline, 1,4-benzothiazine and 1,4-benzoxazine structure variants.

4. Experimental

All melting points were measured on a Gallenkamp electrothermal melting point apparatus. IR spectra were recorded for KBr disc on a Mattson 5000 FTIR spectrophotometer. ^{1}H NMR spectra were measured on a Bruker AC 300 (300 MHz) in $CDCl_3$ or DMSO-d_6 as solvent, using TMS as an internal standard, and chemical shifts are expressed as δ_{ppm}. Mass spectra were determined on Finnigan Incos 500 (70 ev). Elemental analyses were carried out in the Microanalytical Unit of the Faculty of Science, Cairo University. 2-Chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**1**) [38] was prepared according to literature procedure.

*4.1. General procedure for reaction of compound **1** with aromatic and heterocyclic amines*

To a solution of compound **1** (2.50 g, 10 mmol) in absolute ethanol (30 mL), an equimolar amount of the appropriate aromatic or heterocyclic amines and two drops of triethylamine was added and the mixture was heated under reflux for 8 h, then left to cool.

The solid products that obtained was collected by filtration, washed with ethanol, dried well and recrystallized from the appropriate solvent.

4.1.1. 4-(3,4-Dihydroquinoxalin-2-yl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**2a**)

This compound was prepared from *o*-phenylenediamine (1.08 g, 10 mmol) by heating for 8 h under reflux and recrystallized from DMF.

Red crystals; Yield 70%; mp 235–236 °C; IR (KBr) υ_{max}/cm^{-1} = 3430 (OH), 3260 (NH), 2924 (C–H aliph.), 1620 (C=N). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.44 (s, 3H, CH_3), 4.54 (s, 2H, *N*CH_2), 6.32 (s, 1H, NH), 7.0–8.10 (m, 9H, Ar–H), 12.75 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 12.2 (CH_3), 34.4 (CH_2N), 102.2 (pyrazole C-4), 116.5, 119.7, 122.5, 126.6, 130.1, 132.2, 136.6, 138.0 (Ar–C), 149.4 (pyrazole C-3), 157.2 (quinoxaline C-2), 164.4 (pyrazole C-5). MS *m*/*z* (%): 304 (M^+, 87.7) 210 (10.2), 119 (21.8), 169 (22), 91 (17.9), 77 (100). Anal.; For $C_{18}H_{16}N_4O$ (304.35) Calcd.: C 71.04; H 5.30; N 18.41%, Found: C 71.13; H 5.33; N 18.29%.

4.1.2. 4-(2H-1,4-benzothiazin-3-yl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**2b**)

This compound was prepared from *o*-aminothiophenol (1.25 g, 10 mmol) by heating for 8 h under reflux and recrystallized from DMF.

Yellow crystals; Yield 75%; mp 210–211 °C; IR (KBr) υ_{max}/cm^{-1} = 3433 (OH), 2920 (C–H aliph.), 1610 (C=N). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.44 (s, 3H, CH_3), 4.20 (s, 2H, SCH_2), 7.14–8.17 (m, 9H, Ar–H), 13.10 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 12.4 (CH_3), 23.9 (CH_2S), 99.1 (pyrazole C-4), 122.5, 122.8, 123.0, 124.2, 126.4, 127.6, 128.9, 130.2, 137.7, 141.9 (Ar–C), 145.3 (pyrazole C-3), 156.2 (benzothiazine C-3), 165.2 (pyrazole C-5). MS *m*/*z* (%): 321 (M^+, 29.8) 288 (24.1), 186 (9.2), 148 (3.6), 91 (14.7), 77 (100). Anal.; For $C_{18}H_{15}N_3OS$ (321.40) Calcd.: C 67.27; H 4.70; N 13.07%, Found: C 67.13; H 4.77; N 13.36%.

4.1.3. 4-(2H-1,4-benzoxazin-3-yl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**2c**)

This compound was prepared from *o*-aminophenol (1.09 g, 10 mmol) by heating for 10 h under reflux and recrystallized from DMF.

Yellow crystals; Yield 80%; mp 200–201 °C; IR (KBr) υ_{max}/cm^{-1} = 3431 (OH), 2945 (C–H aliph.), 1616 (C=N). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.22 (s, 3H, CH_3), 4.75 (s, 2H, OCH_2), 7.21–8.14 (m, 9H, Ar–H), 12.72 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 12.6 (CH_3), 65.5 (CH_2O), 102.0 (pyrazole C-4), 117.4, 122.3, 123.5, 124.2, 125.6, 126.4, 130.1, 136.4, 137.0, 148.0 (Ar–C), 147.2 (pyrazole C-3), 148.5 (benzoxazine C-3), 164.9 (pyrazole C-5). MS *m*/*z* (%): 305 (M^+, 35.8), 229 (20.9), 200 (15.4), 173 (8.6), 105 (18.3), 91 (12.3), 77 (100). Anal.; For $C_{18}H_{15}N_3O_2$ (305.33) Calcd.: C 70.81; H 4.95; N 13.76%, Found: C 70.72; H 4.99; N 13.91%.

4.1.4. N-[(4Z)-3-Methyl-1-phenyl-1H-furo [2,3-c]pyrazol-4(5H)-ylidene]pyridin-2-amine (**3a**)

This compound was prepared from 2-aminopyridine (0.94 g, 10 mmol) by heating for 6 h under reflux and recrystallized from DMF.

Brown crystals; Yield 76%; mp 245–246 °C; IR (KBr) υ_{max}/cm^{-1} = 2935 (C–H aliph.), 1635 (C=N). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.33 (s, 3H, CH_3), 5.04 (s, 2H, OCH_2), 7.13–7.82 (m, 9H, Ar–H). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 12.6 (CH_3), 69.9 (CH_2O), 104.7 (C-3a), 118.9 (pyridine C-5), 120.5, 126.6, 129.6, 136.6 (Ar–C), 123.4 (pyridine C-3), 136.0 (pyridine C-4), 146.3 (C-3), 146.9 (pyridine C-6), 153.2 (C-4), 159.4 (pyridine C-2), 161.2 (C-6a). MS *m*/*z* (%): 290 (M^+, 8.4), 251 (31.5), 198 (100), 105 (8.24), 91 (18.1), 77 (15). Anal.; For $C_{17}H_{14}N_4O$ (290.32) Calcd.: C 70.33; H 4.86; N 19.30%, Found: C 70.23; H 4.90; N 19.36%.

4.1.5. N-[(4Z)-3-Methyl-1-phenyl-1H-furo [2,3-c]pyrazol-4(5H)-ylidene]pyrazin-2-amine (**3b**)

This compound was prepared from 2-aminopyrazine (0.95 g, 10 mmol) by heating for 12 h under reflux and recrystallized from DMF.

Brown crystals; Yield 86%; mp 272–273 °C; IR (KBr) υ_{max}/cm^{-1} = 2926 (C–H aliph.), 1630 (C=N). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.36 (s, 3H, CH_3), 4.97 (s, 2H, OCH_2), 7.18–7.95 (m, 8H, Ar–H). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 12.6 (CH_3), 69.7 (CH_2O), 104.9 (C-3a), 120.5, 126.6, 129.6, 136.6 (Ar–C), 131.0 (pyrazine C-5), 142.9 (pyrazine C-6), 145.6 (pyrazine C-3), 146.3 (C-3), 150.0 (pyrazine C-2), 154.5 (C-4), 161.4 (C-6a). MS *m*/*z* (%): 291 (M^+, 11.8), 198 (15.4), 185 (15.8), 172 (74.2), 105 (9.3), 91 (53.2), 77 (100). Anal.; For $C_{16}H_{13}N_5O$ (291.31) Calcd.: C 65.97; H 4.50; N 24.04%, Found: C 65.37; H 4.90; N 24.16%.

4.1.6. N-[(4Z)-3-Methyl-1-phenyl-1H-furo [2,3-c]pyrazol-4(5H)-ylidene]-4H-1,2,4-triazol-3-amine (**6**)

This compound was prepared from 3-amino-4*H*-1,2,4-triazole (0.84 g, 10 mmol) by heating for 4 h under reflux and recrystallized from a mixture of EtOH/DMF (1:1).

Brown crystals; Yield 79%; mp 192–193 °C; IR (KBr) υ_{max}/cm^{-1} = 3380 (NH), 2928 (C–H aliph.), 1628 (C=N). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.38 (s, 3H, CH_3), 5.24 (s, 2H, OCH_2), 7.15–8.12 (m, 6H, Ar–H). MS *m*/*z* (%): 280 (M^+, 16.5), 252 (11.2), 212 (16.5), 198 (68.9), 174 (54.5), 105 (15,1), 91 (49.9), 77 (100). Anal.; For $C_{14}H_{12}N_6O$ (280.28) Calcd.: C 59.99; H 4.32; N 29.98%, Found: C 59.89; H 4.26; N 30.09%.

4.1.7. N-[(4Z)-3-Methyl-1-phenyl-1H-furo [2,3-c]pyrazol-4(5H)-ylidene]-1H-benzimidazol-2-amine (**7**)

This compound was prepared from 2-aminobenzimidazole (1.33 g, 10 mmol) by heating for 5 h under reflux and recrystallized from a mixture of EtOH/DMF (1:1).

Pale yellow crystals; Yield 82%; mp 180–181 °C; IR (KBr) υ_{max}/cm^{-1} = 3320 (NH), 2920 (C–H aliph.), 1627 (C=N). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.39 (s, 3H, CH_3), 5.33 (s, 2H, OCH_2), 7.21–8.18 (m, 9H, Ar–H), 9.15 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 12.6 (CH_3), 68.6 (CH_2O), 95.2 (C-3a), 114.6, 118.9, 121.3, 122.6, 123.2, 126.6, 129.8, 136.7, 137.9 (Ar–C), 135.5 (C-6a), 144.8 (C-3), 156.4 (C-4), 157.8 (C-6a), 167.1 (benzimidazole C-2). MS *m*/*z* (%): 329 (M^+, 19.2), 252 (10.6), 224 (10.2), 198 (58.8), 131 (43.8), 105 (16.6), 91 (49.9), 77 (100). Anal.; For $C_{19}H_{15}N_5O$ (329.36) Calcd.: C 69.29; H 4.59; N 21.26%, Found: C 69.24; H 4.63; N 21.27%.

4.2. Synthesis of 3-methyl-1-phenyl-1H-furo [2,3-c]pyrazol-4-(5H)-one (**5**)

A solution of compound **1** (1.25 g, 5 mmol) and triethylamine (1 mL) in absolute ethanol (25 mL) was heated to 50 °C for 3 h. After cooling the resultant precipitate was filtered and crystallized from ethanol.

Colorless crystals; Yield 78%; mp 152–153 °C; IR (KBr) υ_{max}/cm^{-1} = 2923 (C–H aliph.), 1631 (C=O). ^{1}H NMR ($CDCl_3$): δ_{ppm} = 2.52 (s, 3H, CH_3), 5.05 (s, 2H, OCH_2), 7.27–7.81 (m, 5H, Ar–H). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 15.4 (CH_3), 73.5 (CH_2O), 100.3 (C-3a), 122.5, 127.8, 128.5, 136.4 (Ar–C), 149.6 (C-3), 159.8 (C-6a), 191.5 (C=O). MS *m*/*z* (%): 214 (M^+, 40.1), 186 (22.2), 137 (19.3), 109 (18.5), 105 (53.2), 77 (100). Anal.; For $C_{12}H_{10}N_2O_2$ (214.22) Calcd.: C 67.28; H 4.71; N 13.08% Found: C 67.52; H 4.64; N 12.91%.

4.3. Alternative method for the synthesis of compounds **3a–b**

A mixture of 2-aminopyridine (0.47 g, 5 mmol) or 2-aminopyrazine (0.48 g, 5 mmol) and 3-methyl-1-phenyl-1*H*-furo[2,3-*c*]pyrazol-4(5*H*)-one (**5**) (1.07 g, 5 mmol) in ethanol (25 mL) was refluxed for 4 h. The solution was allowed to cool and poured on cold water (50 mL). The solid that obtained was collected, dried, and crystallized from DMF to give compounds **3a–b**.

4.4. General procedure for reaction of compound **1** with secondary amines

To a solution of compound **1** (1.25 g, 5 mmol) in absolute ethanol (20 mL) was added piperidine (0.6 g, 7 mmol) or morpholine (0.65 g, 7 mmol) at room temperature. Immediately a deep colored solution (usually red) was obtained and the temperature of the reaction mixture was rose to 60–65 °C. After standing for 30 min, the reaction mixture was run into cold water (100 mL). The precipitated solid was collected by filtration, washed with water, dried, and recrystallized from ethanol.

4.4.1. 1-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-(piperidin-1-yl)ethanone (**9a**)

Yellow crystals; Yield 76%; mp 165–166 °C; IR (KBr) υ_{max}/cm^{-1} = 3380 (OH), 2924 (C–H aliph.), 1660 (C=O). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.13–1.45 (m, 6H, $3CH_2$), 2.27 (t, J = 6.5 Hz, 4H, $2NCH_2$), 2.33 (s, 3H, CH_3), 3.43 (s, 2H, NCH_2CO), 7.12–7.65 (m, 5H, Ar–H), 12.92 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 15.0 (CH_3), 24.7 (piperidine C-4), 26.3 (piperidine C-3 and C-5), 55.6 (piperidine C-2 and C-6), 61.5 (CH_2N), 102.8 (pyrazole C-4), 121.3, 126.4, 128.9, 136.1 (Ar–C), 146.2 (pyrazole C-3), 158.6 (pyrazole C-5), 188.3 (C=O). MS *m*/*z* (%): 299 (M^+, 34.9), 284 (8.6), 201 (20.2), 187 (12.8), 174 (9.6), 125 (7.2), 98 (100), 84 (10.1). Anal.; For $C_{17}H_{21}N_3O_2$ (299.37) Calcd.: C 68.20; H 7.07; N 14.04%, Found: C 68.39; H 7.14; N 14.16%.

4.4.2. 1-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-(morpholin-4-yl)ethanone (**9b**)

Yellow crystals; Yield 80%; mp 145–146 °C; IR (KBr) υ_{max}/cm^{-1} = 3395 (OH), 2935 (C–H aliph.), 1665 (C=O). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.29 (t, J = 6.8 Hz, 4H, $2NCH_2$), 2.36 (s, 3H, CH_3), 3.47 (s, 2H, NCH_2CO), 3.75 (t, J = 6.8 Hz, 4H, $2CH_2O$), 7.16–7.75 (m, 5H, Ar–H), 12.85 (s, 1H, OH). MS *m*/*z* (%): 301 (M^+, 36.7), 284 (7.9), 201 (26.2), 173 (19.8), 128 (15.3), 100 (100), 86 (14.3). Anal.; For $C_{16}H_{19}N_3O_3$ (301.34) Calcd.: C 63.77; H 6.36; N 13.94%, Found: C 63.86; H 6.40; N 13.99%.

4.5. General procedure for reaction of compound **1** with salicyaldehyde and 2-hydroxyacetophenone

To a solution of compound **1** (0.71 g, 2.84 mmol) and anhydrous potassium carbonate (1.0 g) in 15 mL DMSO was added an equimolar amount of salicyaldehyde or 2-hydroxyacetophenone and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was then poured into water (25 mL) and the precipitate obtained was filtered, dried, and crystallized from an appropriate solvent.

4.5.1. 1-Benzofuran-2-yl(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methanone (**10**)

Yellow crystals (EtOH/DMF); Yield 85%; mp 185–186 °C; IR (KBr) ν_{max}/cm^{-1} = 3380 (OH), 2924 (C–H aliph.), 1635 (CO). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.31 (s, 3H, CH_3), 7.12–8.01 (m, 10H, Ar–H and benzofuran H-3), 12.92 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 15.6 (CH_3), 104.3 (pyrazole C-4), 108.2 (benzofuran C-3), 117.1, 119.8, 123.9, 125.7, 126.8, 128.0, 129.3, 138.6 (Ar–C), 143.7 (benzofuran C-2), 155.7 (pyrazole C-3), 157.5 (pyrazole C-5), 164.3 (C=O). MS *m*/*z* (%): 318 (M^+, 15), 278 (31.5), 261 (12.1), 201 (45), 174 (28.8), 118 (96.1), 91(89.6), 77 (100). Anal.; For $C_{19}H_{14}N_2O_3$ (318.33) Calcd.: C 71.69; H 4.43; N 8.80%, Found: C 71.62; H 4.32; N 8.69%.

4.5.2. (5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-(3-methyl-1-benzofuran-2-yl)methanone (**11**)

Pale yellow crystals (EtOH/DMF); Yield 88%; mp 195–196 °C, IR (KBr) ν_{max}/cm^{-1} = 3390 (OH), 2924 (C–H aliph.), 1635 (CO). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.31 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.93–8.01 (m, 9H, Ar–H), 12.80 (s, 1H, OH). MS *m*/*z* (%): 333 (M^+, 24.32), 201 (100), 134 (56.4), 91 (26.4), 77 (6.7). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 12.3 (CH_3), 16.4 (CH_3), 96.3 (benzofuran C-3), 114.0, 117.4, 118.1, 123.1, 123.8, 125.9, 128.6, 130.2, 136.7, 138.8 (Ar–C), 144.1 (benzofuran C-2),146.7 (pyrazole C-3), 154.2 (pyrazole C-5), 165.5 (C=O). Anal.; For $C_{20}H_{16}N_2O_3$ (332.35) Calcd.: C 72.28; H 4.85; N 8.43%, Found: C 72.32; H 4.77; N 8.51%.

4.6. General procedure for reaction of compound **1** with acetylacetone and 4-hydroxycoumarin

To an ethanolic solution of NaOEt (prepared from sodium metal (0.11 g, 5 mg atom) and 25 mL of absolute ethanol) was added (5 mmol) of the appropriate acetylacetone or 4-hydroxycoumarin. After stirring for 15 min at room temperature, compound **1** (1.25 g, 5 mmol) was added and stirring continued for 24 h. The solvent was evaporated under reduced pressure, and the remainder was poured onto ice-water (50 mL) and neutralized with diluted HCl. The solid products obtained were collected by filtration, washed with water, dried, and crystallized from an appropriate solvent.

4.6.1. 1-(5-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-methylfuran-3-yl)ethanone (**12**)

Pale yellow crystals (EtOH); Yield 82%; mp 220–221 °C; IR (KBr) υ_{max}/cm^{-1} = 3440 (OH), 2923 (C–H aliph.), 1695 (C=O). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.33 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.15–7.84 (m, 6H, Ar–H and furan H-4), 12.82 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 12.4 (CH_3), 14.3 (CH_3), 28.9 (CH_3), 100.5 (furan C-3), 103.2 (pyrazole C-4), 110.2 (furan C-4), 120.8, 126.7, 128.6, 137.2 (Ar–C), 144.4 (pyrazole C-3), 159.1 (pyrazole C-5), 161.8 (furan C-2), 166.2 (furan C-5), 195.4 (C=O). MS *m*/*z* (%): 296 (M^+, 15), 281 (16.9), 253 (17.9), 219 (19.8), 201 (13.8), 173 (100), 105 (39), 77 (56.2). Anal.; For $C_{17}H_{16}N_2O_3$ (296.12) Calcd.: C 68.91; H 5.44; N 9.45%, Found: C 68.79; H 5.29; N 9.53%.

4.6.2. 2-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4H-furo[3,2-c]chromen-4-one (**13**)

Yellow crystals (EtOH/$CHCl_3$); Yield 80%; mp 195–196 °C; IR (KBr) ν_{max}/cm^{-1} = 3380 (OH), 2925 (C–H aliph.), 1715 (CO). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.30 (s, 3H, CH_3), 7.12–7.94 (m, 10H, Ar–H and furan H-3), 12.98 (s, 1H, OH). MS *m*/*z* (%): 358 (M^+, 12.1), 282 (6.8), 253 (16), 214 (42), 198 (17), 173 (100), 144 (6.3), 105 (40), 91 (45), 77 (56.2). Anal.; For $C_{21}H_{14}N_2O_4$ (358.35) Calcd.: C 70.39; H 3.94; N 7.82% Found: C 70.24; H 3.90; N 7.88%.

5. Antimicrobial evaluation

The disks of Whatman filter paper were prepared with standard size (5.0 mm diameter) and kept into 1.0 Oz screw capped wide mouthed containers for sterilization. These bottles are kept into hot air oven at a temperature of 150 °C. Then, the standard sterilized filter paper disks impregnated with a solution of the test compound in DMF (1 mg/mL) were placed on nutrient agar plate seeded with the appropriate test organism in triplicates. Standard concentrations

of 10^6 CFU/mL (Colony Forming U/mL) and 10^4 CFU/mL were used for antibacterial and antifungal assay, respectively. Pyrex glass Petri dishes (9 cm in diameter) were used and two disks of filter paper were inoculated in each plates. The utilized test organisms were: *B. subtilis* and *B. thuringiensis* as examples of Gram-positive bacteria and *E. coli* and *P. aeruginosa* as examples of Gram-negative bacteria. They were also evaluated for their in *vitro* antifungal potential against *F. oxysporum* and *B. fabae* fungal strains. Chloramphenicol, cephalothin and cycloheximide were used as standard antibacterial and antifungal agents, respectively. DMF alone was used as control at the same above-mentioned concentration and due this there was no visible change in bacterial growth. The plates were incubated at 37 °C for 24 h for bacteria and for 48 h for fungi. Compounds that showed significant growth inhibition zones (>14 mm) using the twofold serial dilution technique, were further evaluated for their minimal inhibitory concentrations (MICs).

5.1. Minimal inhibitory concentration (MIC) measurement

The microdilution susceptibility test in Müller–Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) was used for the determination of antibacterial and antifungal activity, respectively. Stock solutions of the tested compounds, chloroamphenicol, cephalothin and cycloheximide were prepared in DMF at concentration of 1000 μg/mL. Each stock solution was diluted with standard method broth (Difco) to prepare serial twofold dilutions in the range of 500–3.125 μg/mL 10 mL of the broth containing about 10^6 CFU/mL of test bacteria was added to each well of 96-well microtiter plate. The sealed microplates were incubated at 37 °C for 24 h for antibacterial activity and at 37 °C for 48 h for antifungal activity in a humid chamber. At the end of the incubation period, the minimal inhibitory concentrations (MIC) values were recorded as the lowest concentrations of the substance that had no visible turbidity. Control experiments with DMF and uninoculated media were run parallel to the test compounds under the same conditions.

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