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Synthesis, Characterization and Antimicrobial Activity of Some Novel Quinoline Derivatives Bearing Pyrazole and Pyridine Moieties

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IN continuation of our interest in synthesis of novel quinoline derivatives with anticipated biological activity, we have synthesized new quinoline derivatives bearing pyrazole and pyridine moieties by formylation of quinoline hydrazones through the Vilsmeier-Haack reaction which is a common method for the synthesis of 4-formyl pyrazoles. Condensation of 2-hydrazinylquinoline **1** with 4-substituted acetophenone gave the corresponding hydrazones **2a–c** which in turn underwent the Vilsmeier-Haack reaction in $POCl_3$/DMF to furnish the corresponding 4-formyl pyrazole derivatives **3a–c**. One-pot reaction of compounds **3a–c** with malononitrile and thiophenol or ethyl mercaptan gave the 3,5-pyridine dicarbonitrile derivatives **11a–f**. The synthesized derivatives were screened for their antimicrobial activities against Gram negative bacteria, Gram positive bacteria and Fungi. Most of compounds showed excellent antimicrobial activities compared to the reference drugs. All the newly synthesized compounds have been characterized by means of elemental analyses, IR, ^{1}H NMR and MS.

Keywords: Quinoline, Vilsmeier-Haack reaction, 4-Formylpyrazole, 3,5-Pyridinedicarbonitrile, Antimicrobial activity.

Introduction

Quinoline derivatives have attracted considerable interest for many years due to their chemical reactivity and biological activity [1–4]. Literature surveys revealed that these derivatives possesses anti-inflammatory [5, 6] antimicrobial [7, 8], antimalarial [9, 10], antioxidant [11, 12], antitumor [13, 14], antiprotozoal [15], antituberculosis [16, 17] and antiulcer activity [18], as well as, A3 adenosine receptor antagonists [19]. On the other hand, pyrazole derivatives are known to exhibit diverse biological activities including anti-inflammatory [20], anticancer [21] and antimicrobial [22, 23] activity. Also, many pyridine dicarbonitrile derivatives were reported to have significant biological activity such as anti-inflammatory and analgesic activities [24]. In the light of these mentioned facts and our interest in designing new biologically active molecules, our efforts were directed towards the synthesis of new heterocyclic compounds containing quinoline ring bearing pyrazole and pyridine moieties with anticipated biological activities.

Experimental

General

All melting points were determined in open-glass capillaries and are uncorrected. IR spectra were recorded on a Bruker Vector 22 Germany spectrometer (KBr). ^{1}HNMR spectra were recorded on Bruker 400 MHz spectrometer using TMS as an internal reference. The Electron Impact mass spectrometry was obtained at 70 eV using Shimadzu QP-2010 Plus mass spectrometer. The reactions were monitored by thin-layer chromatography (TLC) on silica gel F254 aluminum sheets (Merck), and the spots were visualized by UV lamp at 254–365 nm.

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Preparation of 2-hydrazinylquinoline **1**

2-Chloroquinoline (1.0 g, 6.1 mmol) and hydrazine monohydrate (3 mL) in n-butanol (10 mL) were refluxed for 6 h. The solvent was removed under reduced pressure giving a brownish orange residue, the residue was triturated with ethanol then filtered to give compound **1**, orange crystals, yield 86.5 %; mp 140–142 °C; IR (KBr, cm^{-1}): 3282, 3188 (NH), 3042 (CH_{arom}), 1621(C=N).

General procedure for the synthesis of (E)-2-(2-(1-(4-substituted)ethylidene)hydrazineyl) quinoline derivatives **2a–c**

A mixture of compound **1** (1.0 g, 6.3 mmol) and substituted acetophenone (6.3 mmol), was refluxed in ethanol (20 mL) containing (1 mL) of hydrochloric acid for 6 h. The solvent was reduced to its half, and allowed to cool. The separated solid was filtered, dried, and recrystallized from ethanol.

(E)-2-(2-(1-phenylethylidene)hydrazineyl) quinoline **2a**

Yellow solid; yield 86 %; mp 160–162 °C; IR (KBr, cm^{-1}): 3431 (NH), 3106 ($NH_{stretch}$), 2966 (CH_{aliph}), 1599 (C=N); MS (m/z): 261 [M^+, 0.06 %], Anal. Calcd for $C_{17}H_{15}N_3$ (261.33): C, 78.13; H, 5.79; N, 16.08. Found: C, 77.98; H, 5.64; N, 15.93.

(E)-2-(2-(1-(p-tolyl)ethylidene) hydrazineyl)quinoline **2b**

Yellow solid; yield 83 %; mp 230–232 °C; IR (KBr, cm^{-1}): 3406 (NH), 3032 ($CH_{aromatic}$), 2919, 2854 (CH_{aliph}), 1582 (C=N); MS (m/z): 275 [M^+, 1.10 %], Anal. Calcd for $C_{18}H_{17}N_3$ (275.36): C, 78.52; H, 6.22; N, 15.26. Found: C, 78.38; H, 6.08; N, 15.12.

(E)-2-(2-(1-(4-chlorophenyl)ethylidene) hydrazineyl) quinoline **2c**

Grey solid; yield 82 %; mp 228–230 °C; IR (KBr, cm^{-1}): 3433 (NH), 3104 ($NH_{stretch}$), 2968 (CH_{aliph}), 1599 (C=N), MS (m/z): 295 [M^+, 0.43 %], Anal. Calcd for $C_{17}H_{14}ClN_3$ (295.77): C, 69.04; H, 4.77; N, 14.21. Found: C, 68.91; H, 4.64; N, 14.08.

General procedure for the synthesis of 3-(4-aryl)-1-(quinolin-2-yl)-1H-pyrazole-4-carbaldehyde **3a–c**

A cold solution of hydrazone derivatives **2a–c** (1.0 g) in dry DMF (10 mL) was added drop wise to the Vilsmeier-Haack reagent prepared from DMF (15 mL) and $POCl_3$ (3 mL) at 0^0C. The reaction mixture was stirred at 70^0C for 5 hrs and poured into ice cold water. The solid separated was filtered, washed with water and recrystallized from ethanol to give compounds **3a–c**.

3-Phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carbaldehyde **3a**

White solid; yield 80 %; mp 158–160 °C; IR (KBr, cm^{-1}): 3041 (CH_{arom}), 2924, 2827 ($CH_{stretching}$), 1680 (C=O), 1595, 1508 (C=N); MS (m/z): 299 [M^+, 0.23];^{1}H NMR (DMSO-d6): δ (ppm) = 10.11 (s, 1H, CHO), 9.6 (s, 1H, =CH pyrazole), 8.69 (d, 1H, H4 quinoline), 8.30–7.59 (m, 10H, Ar-H).Anal. Calcd for $C_{19}H_{13}N_3O$ (299.33): C, 76.24; H, 4.38; N, 14.04. Found: C, 76.10; H, 4.24; N, 13.90.

1-(Quinolin-2-yl)-3-(p-tolyl)-1H-pyrazole-4-carbaldehyde **3b**

White solid; yield 79 %; mp 189–191 °C; IR (KBr, cm^{-1}): 3038 (CH_{arom}), 2963 (CH_{aliph}), 2914, 2858 ($CH_{stretching}$), 1678 (C=O), 1597, 1508 (C=N); MS (m/z): 313 [M^+, 0.03 %]; ^{1}H NMR (DMSO-d6): δ (ppm) = 10.11 (s, 1H, CHO), 9.6 (s, 1H, =CH pyrazole), 8.69 (d, 1H, H4 quinoline), 8.30–7.59 (m, 9H, Ar-H), 2.25 (s, 3H, CH_3). Anal. Calcd for $C_{20}H1_5N_3O$ (313.36): C, 76.66; H, 4.83; N, 13.41. Found: C, 76.51; H, 4.68; N, 13.26.

3-(4-Chlorophenyl)-1-(quinolin-2-yl)-1H-pyrazole-4-carbaldehyde **3c**

Yellow solid; yield 89 %; mp 180–182 °C; IR (KBr, cm^{-1}): 3046 (CH_{arom}),2920, 2823 ($CH_{stretching}$),1648 (C=O), 1538 (C=N); MS (m/z): 333 [M^+, 0.98%], 144[Base peak, 100%];^{1}H NMR (DMSO-d6): δ (ppm) = 10.11 (s, 1H,CHO), 9.6 (s, 1H, =CHpyrazole), 8.69 (d, 1H, H4quinoline), 8.30–7.59 (m, 9H, Ar-H).Anal. Calcd for $C_{19}H_{12}ClN_3O$ (333.78): C, 68.37; H, 3.62; N, 12.59. Found: C, 68.24; H, 3.46; N, 12.43.

General procedure for the synthesis of 2-amino-4-(3-(4-aryl)-1-(quinolin-2-yl)-1H-pyrazol-4-yl)-6-(alkylthio)pyridine-3,5-dicarbonitrile **11a–f**

Aldehyde derivatives **3a–c** (1 mmol), malononitrile (2 mmol), thiophenol or mercapto ethanol (1 mmol) and few drops of piperidine were mixed in ethanol and refluxed for 1 h. to the completion of reaction (monitored by TLC). The reaction mixture was cooled and precipitate formed was filtered and recrystallized from ethanol to yield the pure product.

2-Amino-4-(3-phenyl-1-(quinolin-2-yl)-1H-pyrazol-4-yl)-6-(phenylthio)pyridine-3,5-dicarbonitrile **11a**

Yellow solid; yield 76 %; mp 160–162 °C;

IR (KBr, cm^{-1}): 3423, 3211 (NH_2), 3057 (CH_{arom}), 2924, 2849 ($CH_{stretching}$), 2359, 2202 (C≡N), 1623, 1557 (C=N); MS (m/z): 521 [M^+, 1.06 %]; ^{1}H-NMR (DMSO-d6): δ (ppm) = 9.23 (s, 1H, =CH pyrazole), 8.69 (d, 1H, H4 quinoline), 8.34–7.39 (m, 15H, Ar-H), 4.36 (s, 2H, NH_2).Anal. Calcd for $C_{31}H_{19}N_7S$ (521.60): C, 71.38; H, 3.67; N, 18.80. Found: C, 71.23; H, 3.52; N, 18.65.

2-Amino-6-(ethylthio)-4-(3-phenyl-1-(quinolin-2-yl)-1H-pyrazol-4-yl)pyridine-3,5-dicarbonitrile **11b**

Yellow solid; yield 73 %; mp 278–280 °C; IR (KBr, cm^{-1}): 3346, 3178 (NH_2), 3058 (CH_{arom}), 2966, (CH_{aliph})2926, 2881 (CH stretching), 2360, 2218 (CN), 1607, 1590 (C=N);^{1}H-NMR (DMSO-d6): δ (ppm) = 9.23 (s, 1H, =CH pyrazole), 8.69 (d, 1H, H4 quinoline), 8.34–7.45 (m, 10H, Ar-H), 4.36 (s, 2H, NH_2), 3.43 (q, 2H, CH_2), 1.35 (t, 3H, CH_3). MS (m/z): 473 [M^+, 0.07 %], Anal. Calcd for $C_{27}H_{19}N_7S$ (473.56): C, 68.48; H, 4.04; N, 20.70. Found: C, 68.32; H, 3.88; N, 20.54.

2-Amino-6-(phenylthio)-4-(1-(quinolin-2-yl)-3-(p-tolyl)-1H-pyrazol-4-yl)pyridine-3,5-dicarbonitrile **11c**

Yellow solid; yield 77 %; mp 210–212 °C; IR (KBr, cm^{-1}): 3441, 3306 (NH_2), 3062 (CH_{arom}), 2209, 2135 (CN), 1544, 1509 (C=N); MS (m/z): 535 [M^+, 0.62 %];^{1}H-NMR (DMSO-d6): δ (ppm) = 9.23 (s, 1H, =CH pyrazole), 8.69 (d, 1H, H4 quinoline), 8.34–7.45 (m, 14H, Ar-H), 4.36 (s, 2H, NH_2), 2.35 (s,3H, CH_3). Anal. Calcd for $C_{32}H_{21}N_7S$ (535.63): C, 71.76; H, 3.95; N, 18.31. Found: C, 71.60; H, 3.79; N, 18.15.

2-Amino-6-(ethylthio)-4-(1-(quinolin-2-yl)-3-(p-tolyl)-1H-pyrazol-4-yl)pyridine-3,5-dicarbonitrile **11d**

Yellow solid; yield 80 %; mp 260–262 °C; IR (KBr, cm^{-1}): 3385, 3166 (NH_2), 3052 (CH_{arom}), 2965 (CH_{aliph}), 2925, 2848 (CH stretching), 2210, 2150 (CN), 1551, 1508 (C=N); MS (m/z): 487 [M^+, 1.00 %];^{1}H-NMR (DMSO-d6): δ (ppm) = 9.23 (s, 1H, =CH pyrazole), 8.69 (d, 1H, H4 quinoline), 8.34–7.45 (m, 9H, Ar-H), 4.36 (s, 2H, NH_2), 3.43 (q, 2H, CH_2), 2.3 (s,3H, CH_3) 1.35 (t, 3H, CH_3).Anal. Calcd for $C_{28}H_{21}N_7S$ (487.59): C, 68.97; H, 4.34; N, 20.11. Found: C, 68.82; H, 4.19; N, 19.96.

2-Amino-4-(3-(4-chlorophenyl)-1-(quinolin-2-yl)-1H-pyrazol-4-yl)-6-(phenylthio)pyridine-3,5-dicarbonitrile **11e**

Yellow solid; yield 81 %; mp 210–212 °C; IR (KBr, cm^{-1}): 3396, 3216 (NH_2), 3059 (CH_{arom}),2929, 2849 (CH stretching), 2206, 2159 (CN), 1607, 1558 (C=N); MS (m/z): 556 [M^+, 2.16 %]; ^{1}H-NMR (DMSO-d6): δ (ppm) = 9.23 (s, 1H, =CH pyrazole), 8.69 (d, 1H, H4 quinoline), 8.34–7.45 (m, 14H, Ar-H). Anal. Calcd for $C_{31}H_{18}ClN_7S$ (556.04): C, 66.96; H, 3.26; N, 17.63. Found: C, 66.82; H, 3.12; N, 17.49.

2-Amino-4-(3-(4-chlorophenyl)-1-(quinolin-2-yl)-1H-pyrazol-4-yl)-6-(ethylthio)pyridine-3,5-dicarbonitrile **11f**

Yellow solid; yield 97 %; mp260–262 °C; IR (KBr, cm^{-1}): 3343, 3193 (NH_2), 3059 (CH_{arom}), 2923, 2843 (CH stretching), 2215, 2153(CN), 1597 (C=N); MS (m/z): 508 [M^+, 0.56 %]; ^{1}H-NMR (DMSO-d6): δ (ppm) = 9.23 (s, 1H, =CH pyrazole), 8.69 (d, 1H, H4 quinoline), 8.34–7.45 (m, 9H, Ar-H), 4.36 (s, 2H, NH_2), 3.43 (q, 2H, CH_2), 1.35 (t, 3H, CH_3).Anal. Calcd for $C_{27}H_{18}ClN_7S$ (508.00): C, 63.84; H, 3.57; N, 19.30. Found: C, 63.68; H, 3.41; N, 19.14.

Antimicrobial activity

The new compounds were evaluated for their antibacterial activities against two Gram positive bacteria (*Staphelococcus aureus* ATCC 6538 and *B. subtilis* ATCC6633), two Gram negative bacteria (*Salmonellatyphimurium* ATCC14028 and *E. coli* ATCC 8739) at a concentration 100 µg/ml. Also, the derivatives were tested for their antifungal activities against *(Candida albicans* ATCC10231). Dimethylsulfoxide was used as a solvent for tested compounds and was used as a negative control. Ciprofloxacin and Ketoconazole at concentration of 100 µg/mL in dimethylsulfoxide were used as positive control. After incubation period, the growth inhibition zones diameters were carefully measured in mm.

Results and Discussion

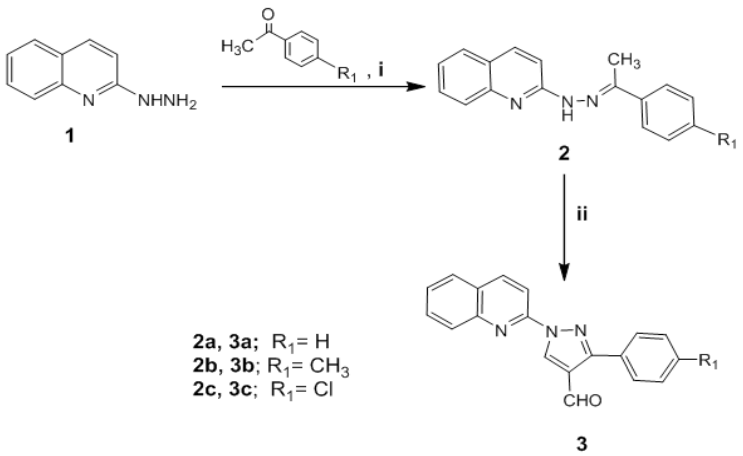
Synthesis of target compounds (**11a**–**f**) was achieved as outlined in (Schemes 1 and 3). The starting material 2-hydrazinylquinoline **1** was synthesized in a high yield from the reaction of hydrazine hydrate with 2-chloroquinoline in refluxing n-butanol, through procedures similar to the previously reported method [25] and its modification [26]. Structure of compound **1** was confirmed by its IR spectrum that revealed presence of two bands at 3282, 3188 cm^{-1} corresponding to NH groups and two bands at 3042, 1621 cm^{-1} corresponding aromatic CH and C=N, respectively. The melting point of the compound was close to the reported values (140–142° C). Reaction of

compound **1** with 4-substituted acetophenone in (1:1) molar ratio afforded the corresponding 2-(2-(1-arylethylidene-hydrazineyl- quinoline derivatives **2a–c** in a good yield. Structures of compounds **2a–c** were supported by their elemental analysis and spectral data. IR spectra of compounds **2a–c** showed peaks at 3431–3435, 3104–3108 cm^{-1}corresponding to NH groups and absorption peaks at 2966–2968 cm^{-1} due to aliphatic CH as well as other peaks at 1599–1601 cm^{-1} corresponding to C=N groups. Mass spectra of all derivatives showed the molecular ion peaks which were in agreement with their molecular formula.

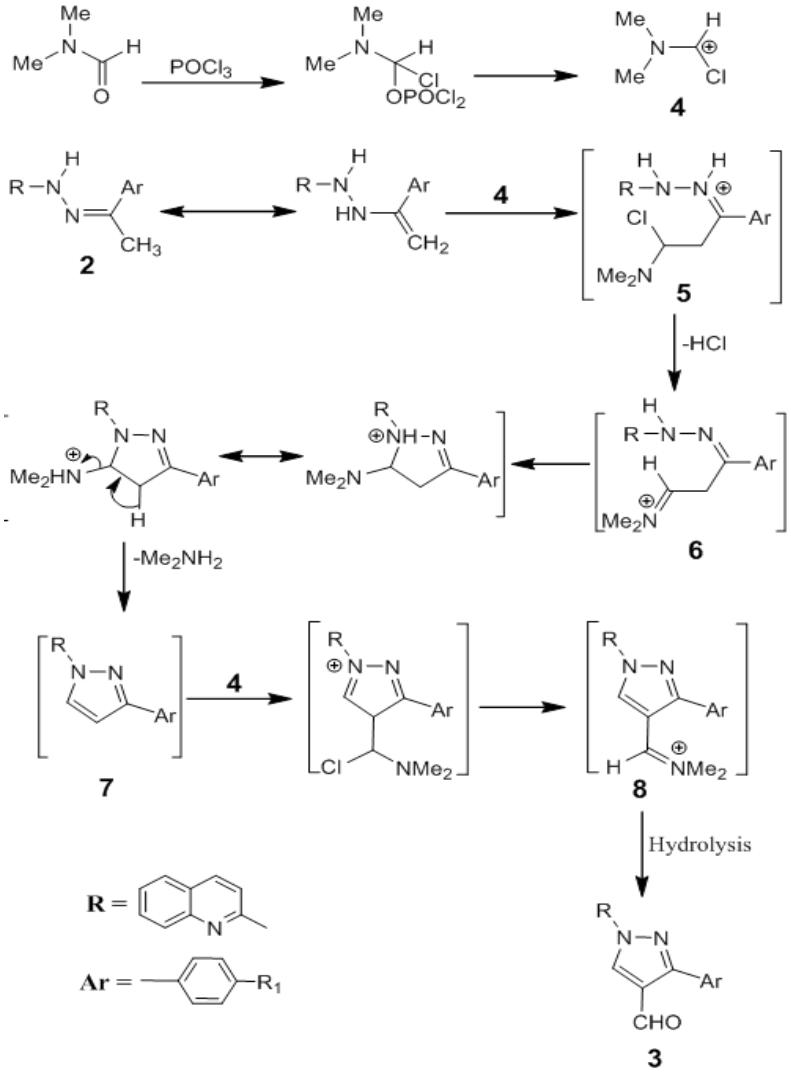
Solution of derivatives **2a–c** in DMF was added to a mixture of Vilsmeier-Haack reagent and the solution was stirred towards the completion of reaction, leading to formation of 3-(4-aryl)-1-(quinolin-2-yl)-1*H*-pyrazole-4-carbaldehyde derivatives **3a–c**. A proposed mechanism for the formation of 4-formylyrazoles is outlined in (Scheme 2) [27]. Initial electrophilic attack of Vilsmeier–Haack reagent **4** on hydrazone **2** yielded the intermediate **5** which subsequently loses a molecule of HCl to provide intermediate **6**. Then the nucleophilic attack by NH group initiates the cyclisation and the resulting pyrazoline immediately, loses Me_2NH to give the more stable pyrazole derivatives **7**. The pyrazole **7** reacts with another mole of Vilsmeier–Haack reagent **4** in an electrophilic substitution process giving an iminium salt **8**, which is hydrolyzed to the corresponding 4-formylpyrazoles **3a–c**. Formation of compounds **3a–c** was supported by their IR spectra that showed peaks at 2920–2823 and 1648–1680 cm^{-1} corresponding to CH and C=O stretching respectively and there was no absorption bands at the NH region. Also, their ^1H NMR spectra showed two sharp singlet signals at δ 10.11 ppm due to aldehydic proton of –CHO group and at δ 9.6 ppm due to =C–H of the pyrazole ring. On the other hand, the molecular ion peaks shown in the Mass spectra of all derivatives were in agreement with their molecular formula.

Derivatives **3a–c** in turn react in one-pot with malononitrile and thiophenol or ethyl mercaptan in absolute ethanol added to it a few drops of piperidine to give 2-amino-4-(3-(4-aryl)-1-(quinolin-2-yl)-1*H*-pyrazol-4-yl)-6-(alkylthio) pyridine-3,5-dicarbonitrile derivatives **11a–f** (Scheme 3).

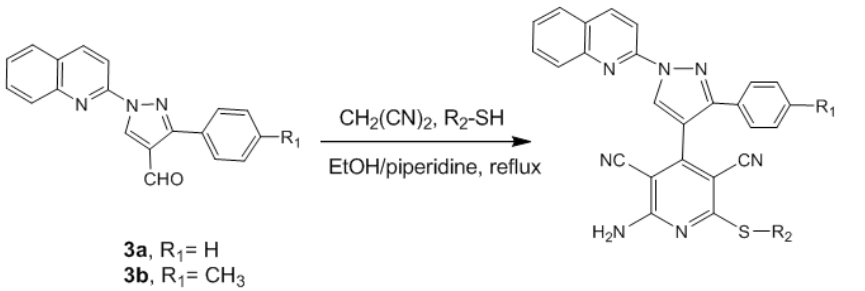
The mechanism of this reaction has been discussed in accordance with the mechanism suggested in literature [28], the first step of this process involves the Knoevenagel condensation of formylpyrazole derivative with malononitrile to form the corresponding 2-(1,3-substituted-l*H*-pyrazol-4-yl)methylene)malononitrile **9**; The second molecule of malononitrile then undergoes Michael addition to compound **9** followed by simultaneous thiolate addition to -C≡N of the adduct and cyclization to dihydropyridine **10** which on aromatization and oxidation under the reaction conditions leads to pyridine derivatives **11a-f**.



Scheme 1 Synthesis of derivatives **3a-c**.
Reagents and conditions:**i** EtOH/HCl/reflux, **ii** DMF/$POCl_3$/70°C



Scheme 2 Mechanism for the formation of 4-formylpyrazoles **3a-c**



3a, R_1= H
3b, R_1= CH_3
3c, R_1= Cl

11a, R_1= H, R_2 = Ph
11b, R_1= H, R_2 = CH_2CH_3
11c, R_1= CH_3, R_2 = Ph
11d, R_1= CH_3, R_2 = CH_2CH_3
11e, R_1= Cl, R_2 = Ph
11f, R_1= Cl, R_2 = CH_2CH_3

Scheme 3 Synthesis of derivatives **11a-f**.

Structures of compounds **11a–f** were supported by their elemental analysis and spectral data too. Mass spectrometry of all derivatives showed the molecular ion peaks close to their expected values. Also, ^{1}H NMR spectra showed characteristic singlet signals at δ 9.23 due to =C–H of the pyrazole ring, besides other singlet signals at δ 4.36 ppm which was assigned to NH_2 group. IR spectra of compounds **11a–f** have characteristic peaks at 3421–3396, 3216–3178 cm^{-1} due to $–NH_2$ groups, and peaks at 2360–2159 cm^{-1}due to -C≡N groups which in turn confirm the structure of target compounds.

Antimicrobial activity

New compounds were screened *in vitro* for their antibacterial activities against two Gram positive bacteria (*Staphelococcus aureus* ATCC 6538 and *B. subtilis* ATCC6633), two Gram negative bacteria (*Salmonellatyphimurium* ATCC14028 and *E. coli* ATCC 8739) at a concentration 100 µg/ml. Also, the derivatives were tested for their antifungal activities against *(Candida albicans* ATCC10231). Dimethylsulfoxide was used as a solvent for tested compounds and was used as a negative control showing no activity against tested microorganisms. Ciprofloxacin and Ketoconazole at concentration of 100 µg/mL in dimethylsulfoxide were used as positive control. Antimicrobial tests were carried out by the agar diffusion technique [29]. Table 1 summarizes the results of antimicrobial studies, in which compounds **3a–c** and **11a–f** exhibited excellent activity against *Candida albicans* compared to ketoconazole drug. On the other, hand compounds **3c** and **11a–f** possesses considerably broader antimicrobial activity compared to Ciprofloxacin. Rest of derivatives showed good to moderate activity against the tested microorganisms.

TABLE 1. In vitro anti-microbial activity of synthesized compounds expressed as inhibition zones (I.Z) diameter *

Compound	Gram +ve				Gram -ve				Fungus	
	S. aureus ATCC6538		*B. subtilis* ATCC6633		*E. coli* ATCC8739		S.*typhimurium* ATCC14028		*C. albicans* ATCC10231	
	I.Z	%A.I**	I.Z	%A.I	I.Z	%A.I	I.Z	%A.I	I.Z	%A.I
3a	N/A***	0	10	29%	11	34%	13	28%	12	48%
3b	N/A	0	10	29%	11	34%	11	24%	12	48%
3c	N/A	0	9	26%	12	38%	12	26%	10	40%
11a	11	28%	12	34%	13	41%	11	24%	14	56%
11b	11	28%	13	37%	14	44%	11	24%	13	52%
11c	11	28%	13	37%	14	44%	11	24%	13	52%
11d	10	25%	11	32%	12	38%	15	33%	13	52%
11e	10	25%	11	32%	12	38%	15	33%	13	52%
11f	10	25%	11	32%	12	38%	14	31%	12	48%
Ciprofloxacin	40	100%	35	100%	32	100%	46	100%	12	48%
Ketoconazole	18	45%	13	37%	20	62.5%	14	31%	25	100%

*Values are mean inhibition zone diameter (mm) of three replicates.
** A.I activity index.
*** N/A no activity.

Conclusion

Nine derivatives were synthesized and *in vitro* evaluated for antibacterial activity against five pathogenic microorganisms. In conclusion these compounds possess a broad spectrum of activity against a group of bacteria, responsible for causing most common bacterial diseases. This paper opens the possibility of finding new effective bactericidal compounds.

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تحضير وتوصيف وتقييم النشاط المضاد للميكروبات لبعض مشتقات الكينولين المحتوية على أنوية البيرازول والبيريدين

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تأكيداً على اهتمامنا المستمر بتحضير مشتقات الكينولين ذات النشاط البيولوجي، تم تحضير بعض مشتقات الكينولين الجديدة المحتوية على نواتي البيرازول والبيريدين من خلال تفاعل "فيلزماير- هاك"، (الذي يُعد إحدى الطرق الشائعة لتحضير مشتقات 4- فورميل بيرازول)، على مركبات الكينولين هيدرازون. عند تفاعل 2-هيدرازينيل كينولين **1** مع الأسيتوفينون المستبدل على الموضع 4، أعطى مشتقات الهيدرازون **2 أ–جـ** والتي بدورها خضعت لتفاعل "فيلزماير - هاك" لتعطي مشتقات 4- فورميل بيرازول **3 أ–جـ**.وعند مفاعلة المشتقات **3 أ–جـ** مع مالونونيتريل وثيوفينول أو إيثيل ميركابتان في إناء واحد فإنه يعطي مشتقات 3 و5- بيريدين داي كاربونيتريل **11 أ - و** . تم إجراء مسح بيولوجي للمركبات الجديدة كمضادات للبكتريا والفطريات، وأظهرت معظم المركبات نشاطاً ملحوظاً مقارنةً بالأدوية المرجعية. تم توصيف وإثبات التركيب الكيميائي لجميع المركبات الجديدة عن طريق التحليل العنصري للكربون والهيدروجين والنيتروجين وطيف الأشعة تحت الحمراء وكذلك الرنين النووي المغناطيسي لنواة ذرة الهيدروجين إضافةً إلى تحليل طيف الكتلة لجميع المركبات.