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 POCl₃/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, ¹H 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 possess 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). ¹H NMR 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.
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 aro), 1621 (C=N).

General procedure for the synthesis of (E)-2-(2-(1-(4-substituted)ethylidene)hydrazineyl) quinoline 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 strech), 2966 (CH aliph), 1599 (C=N); MS (m/z): 295 [M⁺, 0.43 %]; ¹H 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 C₃₀H₁₆N₄O (295.33): C, 76.66; H, 4.83; N, 13.14. Found: C, 76.68; H, 4.68; N, 13.26.

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

Yellow solid; yield 79%; mp 189–191 °C; IR (KBr, cm⁻¹): 3038 (CH aro), 2963 (CH aliph), 2914, 2858 (CH strech), 1678 (C=O), 1597, 1508 (C=N); MS (m/z): 313 [M⁺, 0.03 %]; ¹H 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). Anal. Calcd for C₂₇H₂₁N₄O (313.36): C, 76.66; H, 4.83; N, 13.41. Found: C, 76.51; H, 4.68; N, 13.26.

(E)-2-(2-(1-(3-chlorophenyl)ethylidene)hydrazineyl) quinoline 2c

Grey solid; yield 82%; mp 228–232 °C; IR (KBr, cm⁻¹): 3433 (NH), 3104 (NH strech), 2968 (CH aliph), 1599 (C=N); MS (m/z): 295 [M⁺, 0.43 %], Anal. Calcd for C₁₃H₁₁ClN₅ (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)-1H-pyrazol-4-yl)pyridine-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 POCl₃ (3 mL) at 0°C. The reaction mixture was stirred at 70°C 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 aro), 2924, 2827 (CH strech), 1680 (C=O), 1595, 1508 (C=N); MS (m/z): 299 [M⁺, 0.23 %]; ¹H 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 C₂₇H₂₁N₄O (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 aro), 2963 (CH aliph), 2914, 2858 (CH strech), 1678 (C=O), 1597, 1508 (C=N); MS (m/z): 313 [M⁺, 0.03 %]; ¹H 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). Anal. Calcd for C₂₇H₂₁N₄O (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 aro), 2920, 2823 (CH strech), 1648 (C=O), 1538 (C=N); MS (m/z): 333 [M⁺, 0.98 %], [144 Base peak, 100%]; ¹H 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). Anal. Calcd for C₂₇H₂₁ClN₄O (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 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;...
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IR (KBr, cm\(^{-1}\)): 3423, 3211 (NH\(_3\)), 3057 (CH\(_{=CH}\)), 2924, 2849 (CH stretching), 2359, 2202 (C=O), 1623, 1557 (C=C=N); MS (m/z): 521 [M\(^+\), 1.06 %]; \(^1\)H-NMR (DMSO-d\(_6\)): \(\delta\) (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). Anal. Caled for C\(_{41}\)H\(_{36}\)N\(_2\): C, 71.73; H, 3.65; N, 18.65. Found: C, 71.23; H, 3.52; N, 18.15.

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

Yellow solid; yield 77 %; mp 210–212 °C; IR (KBr, cm\(^{-1}\)): 3341, 3306 (NH\(_3\)), 3062 (CH\(_{=CH}\)), 2209, 2135 (CN), 1544, 1509 (C=C=N); MS (m/z): 535 [M\(^+\), 0.62 %]; \(^1\)H-NMR (DMSO-d\(_6\)): \(\delta\) (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), 1.35 (t, 3H, CH\(_3\))). Anal. Caled for C\(_{41}\)H\(_{36}\)N\(_2\): C, 71.76; H, 3.95; N, 18.31. Found: C, 71.60; H, 3.79; N, 18.15.

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\(^{-1}\)): 3341, 3306 (NH\(_3\)), 3062 (CH\(_{=CH}\)), 2209, 2135 (CN), 1544, 1509 (C=C=N); MS (m/z): 556 [M\(^+\), 0.62 %]; \(^1\)H-NMR (DMSO-d\(_6\)): \(\delta\) (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), 1.35 (t, 3H, CH\(_3\))). Anal. Caled for C\(_{41}\)H\(_{36}\)N\(_2\): 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\(_3\)), 3057 (CH\(_{=CH}\)), 2923, 2843 (CH stretching), 2215, 2153(CN), 1597 (C=C=N); MS (m/z): 508 [M\(^+\), 0.56 %]; \(^1\)H-NMR (DMSO-d\(_6\)): \(\delta\) (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), 3.43 (q, 2H, CH\(_2\)), 1.35 (t, 3H, CH\(_3\))). Anal. Caled for C\(_{41}\)H\(_{36}\)ClN\(_2\): 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 \(\mu\)g/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 \(\mu\)g/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 \(\mu\)g/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 I 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 I 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-formylpyrazoles 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$_2$NH 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 3-diarylamino-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 $^1$H NMR spectra showed two sharp singlet signals at $\delta$ 10.11 ppm due to aldehydic proton of –CHO group and at $\delta$ 9.6 ppm due to $\equiv$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-$lH$-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](image_url)  
**Scheme 1** Synthesis of derivatives 3a–c.  
Reagents and conditions: i EtOH/HCl/reflux, ii DMF/POCl$_3$/70°C
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Scheme 2 Mechanism for the formation of 4-formylpyrazoles 3a-c

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, $^1H$ NMR spectra showed characteristic singlet signals at $\delta$ 9.23 due to $=\text{C}–\text{H}$ of the pyrazole ring, besides other singlet signals at $\delta$ 4.36 ppm which was assigned to $\text{NH}_2$ group. IR spectra of compounds $11a$–$f$ have characteristic peaks at 3421–3396, 3216–3178 cm$^{-1}$ due to $\text{–NH}_2$ groups, and peaks at 2360–2159 cm$^{-1}$ due to $-\text{C≡N}$ 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 ($\text{Staphelococcus aureus ATCC 6538}$ and $\text{B. subtilis ATCC6633}$), two Gram negative bacteria ($\text{Salmonellatyphimurium ATCC14028}$ and $\text{E. coli ATCC 8739}$) at a concentration 100 µg/ml. Also, the derivatives were tested for their antifungal activities against ($\text{Candida albicans ATCC10231}$). 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 $\text{Candida albicans}$ 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>
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<th>Compound</th>
<th>Gram +ve</th>
<th>Gram -ve</th>
<th>Fungus</th>
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<tr>
<td>$S. aureus$ ATCC6538</td>
<td>$R. subtilis$ ATCC6633</td>
<td>$E. coli$ ATCC8739</td>
<td>$S. typhimurium$ ATCC14028</td>
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<tr>
<td>$3a$</td>
<td>0</td>
<td>3%</td>
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<tr>
<td>$3b$</td>
<td>0</td>
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<td>$3c$</td>
<td>0</td>
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<td>$11a$</td>
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<td>$11b$</td>
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<td>$11c$</td>
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<td>$11d$</td>
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<td>$11e$</td>
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<td>$11f$</td>
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<tr>
<td>Ciprofloxacin</td>
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<td>3%</td>
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<tr>
<td>Ketoconazole</td>
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*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 وتحقيق النشاط العضلي لبعض مشتقات الكينولين المحتوية على ألوية البيراميد والبيرازول والبيريدين

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تاكيدا، على اعتماد المستخدم لتحضير مشتقات الكينولين ذات النشاط البيولوجي، تم تحضير بعض مشتقات الكينولين الجديدة المحتوية على نوافذ البيراميد والبيرازول والبيريدين من خلال تفاعل "فيزامير - هايك"، والذي يعد إحدى الطرق الشائعة لتحضير مشتقات فيرميل بيرازول، على مركبات الكينولين هيدرازون. عند تفاعل 2-هيدرازون الكينولين مع الأسيتوفين المستخدم على الموضوع 4، أعطى مركبات الهيدرازون أنتج مشتق فيزامير - هايك. تفاعل مشتقات 4، فيرميل بيرازول 3، مع مادة المشتقات 2، بأجهز من مايكل زافلي وثيوفيتيون أو إيثيل مركبات على إيضاح واحد فقط. أعطى مركبات 3، و 5- نتائج كاربونليتريد 11. تم إجراء سح بيوجي للكيميائيات الجديدة كمضادات للكزيرويا والالتهابات، وأظهرت معظم المركبات نشاطًا ملحوظًا مقارنة بالدواء المرجعية. تم تحضير وإثبات التركيب الكيميائي لجميع المركبات الجديدة عن طريق التحليل العنصري للكبرين وendirودين والتانديرنج وطق الأشعة تحت الحمراء وكذلك الرنين النووي المغناطيسي لذوا نى الرمزوجين إضافة إلى تحليل طيف الكثافة لجميع المركبات.


