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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF ETHYL 3-(N-ARYLIMINOMETHYL)-5-CHLORO-1H-INDOLE-2-CARBOXYLATE

Mohamed M. Said[(1)] Nagat Ghareb[(1)] Adel A. El-Gendy[(2)].

[(1)] Organic Chemistry Department, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt.

[(2)] Organic Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt.

ABSTRACT:

Condensation of 4-chlorophenylhydrazine (1) with ethyl pyruvate led to the formation of ethyl pyruvate 4-chlorophenylhydrazone (2). Fischer Indolization of (2) gave ethyl 5-chloro-1H-indole-2-carboxylate (3). Vilsmeier-Hacck formylation of (3) gave ethyl 5-chloro-3-formyl-1H-indole-2-carboxylate (4). The reaction of (4) with substituted anilines led to the formation of ethyl 3-(N-aryliminomethyl)-5-chloro-1H-indole-2-carboxylate (5-10). Structures of the new compounds were confirmed by both analytical and spectral data (IR, NMR and MS). Antimicrobial screening was also performed.

INTRODUCTION

Indole compounds were found to possess antibacterial[(1,2)], fungicidal[(3)], antifertility[(4)] and anticonvulsant activities[(5,6)]. In view of these findings, it was decided to synthesize a series of ethyl 3-(N-aryliminomethyl)-5-chloro-1H-indole-2-carboxylate to be screened for antimicrobial activity.

RESULTS AND DISCUSSION

In the present investigation, synthesis of 4-chlorophenylhydrazine **(1)** was carried out through reduction of diazonium salt of 4-chloroaniline with stannous chloride in acid medium[(7)]. Synthesis of ethyl 5-chloro-1H-indole-2-carboxylate **(3)** was achieved through improved Fischer indolization[(8)] of ethyl pyruvate 4-chloro phenylhydrazone **(2)**[(9-11)] using p-toluene sulphonic acid in dry benzene. The Vilsmeier-Hacck formylation of **3** led to the formation of ethyl 5-chloro-3-formyl-1H-indole-2-carboxylate **(4)**[(12,13)]. Ethyl 3-(N-aryliminomethyl)-5-chloro-1H-indole-2-carboxylate **(5-10)** were prepared[(14)] by refluxing(**4**) with substituted anilines in methanol in the presence of glacial acetic acid. Structures of these compounds were confirmed by IR, MS, NMR and elemental analysis. **(Scheme I)**

The activities of Schiff's bases **(5-10)** against representative Gram positive, Gram negative bacteria and fungi were tested by the disk diffusion method[(15)].

EXPERIMENTAL

Melting points were measured in open capillary tubes using Stuart melting point apparatus SMP10 and are uncorrected. Infrared (IR) spectra were measured on a Vector 22 Infrared spectrophotometer (υ_{max} in cm^{-1}). Proton Magnetic Resonance (^{1}H-NMR) spectra were recorded on Avenge AV 300 spectrometer (300 MHz). Chemical shifts are reported in δ values (parts per million, ppm) relative to tetramethylsilane (TMS) as internal standard and coupling constant values are given in Hz. Abbreviation used in NMR analysis are as follows: d=doublet, dd= doublet of doublets, m=multiplet, q=quartet, s=singlet, t= triplet. Electron impact mass spectra (EI-MS) were recorded on a Finnigan MAT 312 mass spectrometer connected with a MASPEC Data System. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel $60F_{254}$ and analyzed with UV light.

4-Chlorophenylhydrazine (1)

HCl (100 ml) was added with stirring to a solution of 4-chloro aniline (5.08 g, 40 mmol) in glacial acetic acid (20 ml) at room temperature. The reaction mixture was then cooled to 0°C and treated with sodium nitrite solution (2.76 g, 40 mmol in 8 ml water). The cold diazonium salt solution was rapidly filtered and treated drop wise with cold solution of stannous chloride dihydrate (20 g) in conc. HCl (20 ml). The insoluble salt was collected by filtration and washed with saturated sodium chloride solution (30 ml). 4-Chlorophenyl-hydrazine was liberated from the salt by treatment with aqueous sodium hydroxide (15%, 200 ml) the product was extracted twice with ether (200 ml). The combined extract was washed with water and then dried over anhydrous Na_2SO_4. The ethereal solution was evaporated then dried and recrystallized from ethanol.

4-Chlorophenyl hydrazine (1): mp 83°C, lit. mp 85-87°C [(7)], (yield 60%).

Ethyl pyruvate 4-chlorophenylhydrazone (2)

Ethyl pyruvate (1.3 g, 11 mmol) was poured dropwise with stirring into alcoholic solution of 4-chloro phenylhydrazine (1) (11 mmol) in presence of glacial acetic acid (0.5 ml). The resulting precipitate was further stirred for 15 min at room temperature. and then left for complete precipitation. The product was filtered, dried and recrystallized from ethanol.

Ethyl pyruvate 4-chlorophenylhydrazone (2): mp 136°C (lit. mp 138°C)[(10)], (yield 74%).

Ethyl 5-chloro -1H-indole-2-carboxylate (3)

A mixture of p-toluenesulfonic acid (3 g, 17.4 mmol) in dry benzene (50 ml) was heated under reflux using Dean-stark apparatus for 1.5 hour. A suspension of the hydrazone (2) (10 mmol) in dry benzene (30 ml) was added and the whole mixture was refluxed for 5 hours. The resulting solution was diluted with benzene, washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated to dryness. The resulting product was crystallized from ethanol.

Ethyl 5-chloro-1H-indole-2-carboxylate (3): mp 165°C (lit. mp 167-168°C) [(10)], (yield 82.77%). IR (cm^{-1}): 1699(C=O ester), 3317.8(NH indole). Mass spectrum: m/z: 223.1(M^+, 42.14%), 177.1(100%), 149(31.4%), 123(46.3%), 87(16.11%), 63.1(15.18%).

^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 1.32(t, 3H, CH_3 ethyl, J=7.0 Hz), 4.33(q, 2H, CH_2 ethyl, J=7.0 Hz), 7.11(s, 1H, H at C_3 indole), 7.23-7.26 (dd, 1H, J=8.8 Hz, J=2.0 Hz), 7.60 (d, 1H, J=8.8 Hz), 7.71 (d, 1H, J=1.5 Hz), 12.06(s, 1H, NH).

Ethyl 5-chloro-3-formyl-1H-indole-2-carboxylate(4)

In a 250 ml two necked round bottomed Flask, dry N, N-dimethylformamide (DMF 2 ml, 0.026mol) was cooled in an ice-bath for 30 minutes. Phosphorus oxychloride (0.7 ml, 0.004mol) was dropped into the reaction flask in about 5 minutes. The cooling bath was removed and the reaction mixture was then stirred at room temperature for 30 minutes. The mixture was cooled in an ice-bath and a solution 3 (4 mmol) in DMF (2 ml) was dropped in about 5 minutes into the reaction flask. The mixture was then stirred in aboiling water-bath for 2 h. The colored solution obtained was poured over crushed ice (20 g). The resulting orange precipitate was left overnight for complete precipitation. The collected product was filtered, washed first with warm H_2O and then with ethanol / water mixture and crystallized from ethanol.

mp 232°C (lit. mp 240-241°C)[16], (yield 81%). IR (cm^{-1}): 1639.7(C=O aldehyde), 1726.5(C=O ester), 3135.6(NH indole). Mass spectrum: m/z: 251.1 (M^+, 33.64%), 222 (100%), 204(82.47%), 177.1 (24.85%), 150 (23.23%), 114.1 (43.57%), 87 (16.27%), 63.1 (10.26%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 1.38 (t, 3H, CH_3 ethyl, J=7.1 Hz), 4.44(q, 2H, CH_2 ethyl, J=7.1 Hz), 7.39-7.42(dd, 1H, J=8.7 Hz, J=2.1 Hz), 7.57(d, 1H, J=8.7 Hz), 8.20(d, 1H, J=2.0 Hz), 10.54(s, 1H, CHO), 13.00(s, 1H, NH).

Ethyl 3-(*N*-aryliminomethyl)-5-chloro-1H-indole-2-carboxylate (5-10).

To a hot solution of (4) (0.232g, 1mmol) in methanol (10 ml) containing gl.acetic acid (0.5 ml) was added the appropriate aniline derivatives (1 mmol). Reflux was continued for 6 hours. and left to cool to R.T. the separated solid was filtered, dried and crystallized from ethanol.

Ethyl 5-chloro-3-((4-chlorophenylimino)methyl)-1H-indole-2-carboxylate (5): mp 192°C, (yield 75%).IR (cm^{-1}): 1611.3 (C=N imine), 1681.8 (C=O ester), 3301.9(NH indole). Mass spectrum: m/z: 360/362/364 (M^+/M+2/M+4, 61.3%/18.5%/7.8%), 331 (100%), 287 (13.8%), 252 (9.5%), 215 (8.7%), 188 (4.2%), 148 (11.5%), 111 (25.1%), 57 (14.1%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 1.37 (t, 3H, CH_3 ethyl, J=7.1 Hz), 4.44(q, 2H, CH_2 ethyl, J=7.1 Hz), 7.26-8.52 (m, 7H, Ar-H), 9.24(s, 1H, CH=N), 10.54 (s, 1H, NH). Anal.Calcd. for $C_{18}H_{14}Cl_2N_2O_2$: C, 60.00; H, 3.88; N, 7.77. Found: C, 59.77; H, 3.61; N, 7.45.

Ethyl 5-chloro-3-((4-fluorophenylimino)methyl)-1H-indole-2-carboxylate (6): mp 187°C, (yield 75%).IR (cm^{-1}): 1615.5 (C=N imine), 1689 (C=O ester), 3307.5 (NH indole). Mass spectrum: m/z: 344.2/346.2(M^+/M+2, 45.08%/15.04%), 315.1(100%), 297.1(40.46%), 234.1 (13.88%), 204 (19.69%), 148 (30.51%), 114.1(17.37%), 95(44.79%). ^{1}H-NMR (DMSO, 300 MHz):δ(ppm) = 1.40(t, 3H, CH_3 ethyl, J=7.0 Hz), 4.42 (q, 2H, CH_2 ethyl, J=7.1 Hz), 7.22-8.55 (m, 7H, Ar-H), 9.25(s, 1H, CH=N), 12.61(s, 1H, NH). Anal.Calcd. for $C_{18}H_{14}FN_2O_2$: C, 62.79; H, 4.06; N, 8.13. Found: C, 62.57; H, 3.88; N, 7.97.

Ethyl 5-chloro-3-((2-hydroxy-5-methylphenylimino)-methyl)-1H-indole-2-carboxylate (7): mp 170°C, (yield 60%).IR (cm^{-1}): 1615.2(C=N imine), 1685.7(C=O ester), 3286.5 (NH indole). Mass spectrum: m/z: 356/358 (M^+/M+2, 65%/20%), 327 (80%), 309 (100%), 283 (22.3%), 252 (22.7%), 222 (26.8%), 206 (48.2%), 177 (17.3%), 151 (19.5%), 114 (17.7%), 92 (19.1%), 51 (24.5%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 1.33(t, 3H, CH_3 ethyl, J=7.1 Hz), 2.32 (s, 3H, CH_3), 4.36(q, 2H, CH_2 ethyl, J=7.0 Hz), 7.23-7.26 (dd, 2H, J=8.7 Hz, J=1.8 Hz), 7.43(d, 2H, J=8.8 Hz), 7.96 (d, 2H, J=1.8 Hz), 8.30(s, 1H, CH=N), 10.02 (s, 1H, OH), 11.91(s, 1H, NH). Anal.Calcd. for $C_{19}H_{17}ClN_2O_3$: C, 63.90; H, 4.76; N, 7.85. Found: C, 63.77; H, 4.58; N, 7.49.

Ethyl 5-chloro-3-((2-hydroxyphenylimino)methyl)-1H-indole-2-carboxylate (8): mp 150°C, (yield 60%).IR (cm^{-1}): 1611.1 (C=N imine), 1726 (C=O ester), 3138(NH indole). Mass spectrum: m/z: 342/344 (M^+/M+2, 5.60%/1.25%), 295 (27.51%), 252.1 (27.85%), 222 (56.85%), 206 (77.33%), 177 (26.14%), 150(31.42%), 114(51.68%), 92(100%), 74(49.56%), 51(17.65%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 1.37(t, 3H, CH_3 ethyl, J=7.1 Hz), 4.42(q, 2H, CH_2 ethyl, J=7.0 Hz), 7.28-8.30(m, 7H, Ar-H), 9.29(s, 1H, CH=N), 10.45(s, 1H, OH), 12.96(s, 1H, NH). Anal.Calcd. for $C_{18}H_{15}ClN_2O_3$: C, 63.15; H, 4.38; N, 8.17. Found: C, 63.00; H, 4.02; N, 7.97.

Ethyl 5-chloro-3-((phenylimino)methyl)-1H-indole-2-carboxylate (9): IR (cm^{-1}): 1614 (C=N imine), 1684(C=O ester), 3296(NH indole). Mass spectrum: m/z: 326/328 (M^+/M+2, 29.29% /8.9%), 297 (88.1%), 253 (14.01%), 216.1 (16.58%), 190.1 (16.86%), 163.1 (4.39%), 114 (14.28%), 77 (100%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 1.37(t, 3H, CH_3 ethyl, J=7.0 Hz), 4.42(q, 2H, CH_2 ethyl, J=7.0 Hz), 7.24-8.56(m, 8H, Ar-H), 9.27 (s, 1H, CH=N), 12.65 (s, 1H, NH). Anal.Calcd. for $C_{18}H_{15}ClN_2O_2$: C, 66.25; H, 4.60; N, 8.58. Found: C, 66.02; H, 4.36; N, 8.34.

Ethyl 5-chloro-3-((4-methoxyphenylimino) methyl)-1H-indole-2-carboxylate (10): IR (cm^{-1}): 1614(C=N imine), 1687(C=O ester), 3311(NH indole). Mass spectrum: m/z: 356.2/358.2 (M^+/M+2, 78.41%/ 29.25%), 327.1 (100%), 309.1 (37.24%), 284.1 (10.04%), 239 (20.67%), 204 (18.77%), 177.1 (14.87%), 148 (9.36%), 114.1(5.85%), 92 (24.93%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 1.45(t, 3H, CH_3 ethyl, J=7.1 Hz), 3.83(s, 3H, OCH_3), 4.47(q, 2H, CH_2 ethyl, J=7.1 Hz), 6.92-8.81(m, 7H, Ar-H), 9.33(s, 1H, CH=N), 11.50(s, 1H, NH). Anal.Calcd. for $C_{19}H_{17}ClN_2O_3$: C, 63.90; H, 4.76; N, 7.85. Found: C, 63.66; H, 4.44; N, 7.52.

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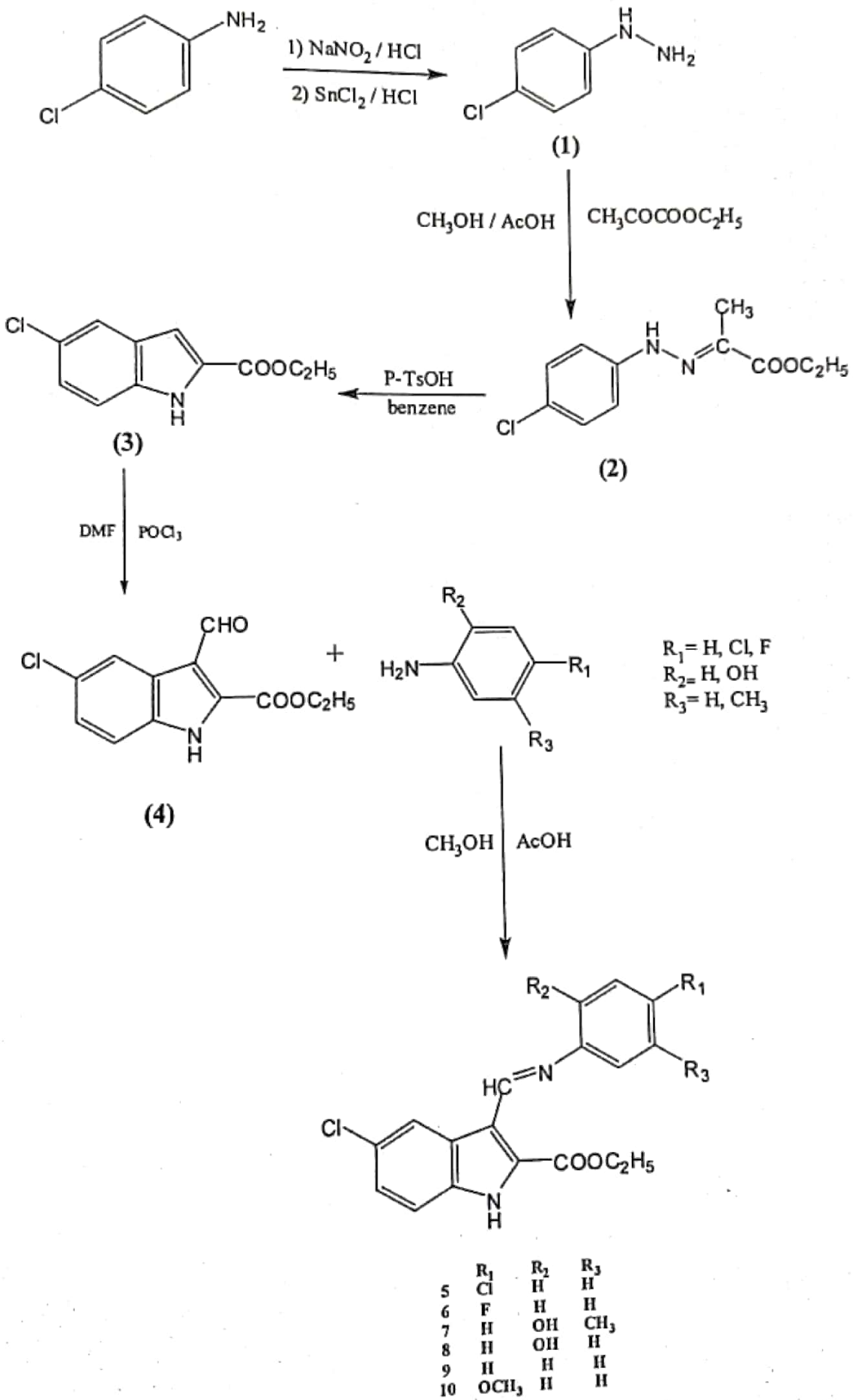
Scheme I



	R_1	R_2	R_3
5	Cl	H	H
6	F	H	H
7	H	OH	CH_3
8	H	OH	H
9	H	H	H
10	OCH_3	H	H

ANTIMICROBIAL ACTIVITY

Activities of Schiff's bases (5-10) against representative Gram positive and Gram negative bacteria as well as a fungus were tested by the disk diffusion method[15]. Results are listed in Table I. From the data it is clear that compounds 5-10 possess moderate activity against Gram negative bacteria and fungi.

Table I. Antimicrobial activity of tested compounds*

Comp. No	Gram negative bacteria	Gram positive bacteria		Fungi
	E. coli	*Staph. aureus*	*Bacillus subtilus*	*Candida albicans*
5	+	-	-	+
6	+	-	-	+
7	+	-	-	+
8	+	-	-	+
9	+	-	-	+
10	+	-	-	+

* Solvent: DMF, [c] = 20 µl ml^{-1}. Rating: + = moderately active (inhibition zone). reference substance for bacteria: Chloramphinicol and reference substance for fungi: Nystatine.

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تشييد بعض مشتقات الاندول-2-كربوكسيلات ودراسة فاعليتها ضد الميكروبات

محمد مختار آمن سعيد[1]،نجاة غريب عبادى[1] وعادل عباس الجندي[2]

[1] قسم الكيمياء العضوية- كلية الصيدلة- جامعة قناة السويس - الاسماعيلية- مصر

[2] قسم الكيمياء العضوية- كلية الصيدلة- جامعة القاهرة-القاهرة- مصر

تفاعل 4-كلورو فينيل هيدرازين(1) مع الايثيل بيروفات ادى الى تكوين ايثيل بيروفات 4-كلورو فينيل هيدرازون(2). استخدام طريقة فيشر لتحضير الاندول من مركب 2 نتج عنه ايثيل 5-كلورو-1-يد- اندول-2-كربوكسيلات (3). ادخال مجموعة الفورميل على مركب 3 باستخدام طريقة فلسميرادى الى تكوين ايثيل 3- فورميل- 5-كلورو-1-يد- اندول-2-كربوكسيلات(4). تفاعل ايثيل 3- فورميل-5-كلورو-1-يد- اندول-2-كربوكسيلات (4) مع مشتقات الانيلين نتج عنه مشتقات ايثيل 3- (ن - أريل ايمينوميثيل) 5-كلورو-1-يد- اندول-2-كربوكسيلات(5-10).

وقد تم التأكد من التركيب البنائى للمركبات عن طريق تحليل العناصر الدقيقة والأشعة تحت الحمراء والرنين المغناطيسى وطيف الكتلة