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Synthesis of Some Novel Pyridine, Sulfonamide, Coumarin and Thiophene Derivatives

Ammar H. Al-Sabawi [a*], Shahla A. Younis [a] and Rana A. Saeed [b]

[a]*Department of Chemistry, College of Science, University of Mosul, Mosul, IRAQ.*

[b]*Department of Pharmaceutical, Mosul Technical Institute, Northern Technical University, Mosul, IRAQ.*

Abstract

A series of novel pyridine, sulfonamide, coumarin, thiophene, α,β-unsaturated carbonyl compounds, and pyrazole derivatives were synthesized from hydrazide-hydrazone derivatives with different reagents (substituted benzaldehydes, hydrazine hydrate, malononitrile, 2-hydroxy-1-naphthaldehyde, tetralone, cyclopentanone, and ethyl cyanoacetate). Hydrazide-hydrazone derivatives were prepared by reactions 2-cyanoacetohydrazide with 2-acetylpyridine or 4-acetyl-*N*-(p-tolyl)benzenesulfonamide. On the basis of their spectral information, the structures of the newly synthesized chemical derivatives were determined.

*Keyword***:** 2-cyanoacetohydrazide**,** 4-acetyl-N-(p-tolyl)benzenesulfonamide, pyridine, sulfonamide,coumarin,thiophene, and pyrazoles derivatives.

Introduction

Sulfonamides are biologically active in a variety of ways [1, 2]. Furthermore, according to the literature review, aryl/heteroaryl sulfonamides may serve as anticancer agents via a variety of pathways [3]. In previous literature, on the synthesis and biological activity of certain sulfonamides with various physiologically active moieties, and discovered that several of them have the anticancer potential [4]. Also, many heterocyclic compounds with thiophene and benzothiophene moieties also demonstrated anticancer potential [5, 6]

Hydrazines and their derivatives are a class of chemicals with a wide range of applications in organic synthesis [7, 8]. While hydrazines have traditionally been used to derivatize and characterize (C=O) compounds, In a number of pharmacological drugs, the nitrogen-nitrogen bond has recently been employed as a significant structural design. Rising number of the nitrogen-nitrogen bond containing peptidomimetics and heterocycles are being developed used in pharmacological and agricultural applications [9, 10]. Hydrazide-hydrazones have recently gained popularity because to their wide range of biological features, which include antitumoral [11, 12], vasodilator [13], antiviral activity [14], antiplatelet [15], antimalarial [16], antimicrobial [17], anticonvulsant [18], analgesic [19] and anti-inflammatory [20]. We disclose here the production of a number of hydrazide, as well as their employment in a number of heterocyclic processes, with the goal of creating novel hydrazide-hydrazones which are expected to have a wide range of medicinal uses.

Experimental:

The melting points were uncorrected determined by a Stuart melting point apparatus. ^{1}H- NMR and ^{13}C-NMR spectra (DMSO-d6, δ ppm) was recorded using Bruker advance 400 MHz (Germany). FT-IR spectra was recorded using FT-IR spectrometer (KBr, ν cm-1).

2-cyano-*N*′-(1-(pyridin-2-yl)ethylidene)acetohydrazide (1a)

In absolute ethanol (20 mL), a combination of 2-cyanoacetohydrazide (4.95 g, 50 mmol) and 2-acetylpyridine (6.05 g, 50 mmol) was refluxed for

*Corresponding author e-mail: ammar-alsabawi@uomosul.edu.iq

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45 min., Then leave to cool. The precipitate was collected, dried, and recrystallized from ethanol to obtain the required compound. Table 1,3

2-cyano-3-substitutedphenyl-*N'*-(1-(pyridin-2-yl)ethylidene)acrylohydrazide (2-6).

In absolute ethanol (20 mL) with a catalytic quantity of triethylamine (8 drops), a combination of compound **1a** (0.606 g, 3 mmol) with substituted benzaldehyde (1.5 mmol) was refluxed for 6 hours, then leave cool and pour onto cold water. From ethanol, the product was recrystallized. Table 1,3

5-amino-3-substitutedphenyl-*N'*-(1-(pyridin-2-yl)ethylidene)-1*H*-pyrazole-4-carbohydrazide (7-10)

In absolute ethanol (15 mL), a mixture of compounds (**2, 3, 5, 6**) (1.5 mmol) and hydrazine hydrate (0.1g, 2 mmol) was refluxed for 6 hours, then leave cool and pour onto cold water. From aqueous ethanol, the product was recrystallized. Table 1,4

3,5-diamino-4-cyano-*N'*-(1-(pyridin-2-yl)ethylidene)thiophene-2-carbohydrazide (11).

In absolute ethanol (20 mL) with elemental sulfur (0.048 g, 1.5 mmol), a combination compound **1a** (0.303 g, 1.5 mmol), triethylamine (4 drops), with malononitrile (0.01 g, 1.5 mmol) was refluxed for 4 hours, then leave cool and pour onto cold water. From ethanol, the product was recrystallized. Table 1,5,7,8

3-imino-*N'*-(1-(pyridin-2-yl)ethylidene)-3*H*-benzo[f]chromene-2-carbohydrazide (12).

In absolute ethanol (15 mL) with a catalytic quantity of triethylamine (3 drops), a combination of compound **1a** (0.303 g, 1.5 mmol) with 2-hydroxy-1-naphthaldehyde (0.258 g, 1.5 mmol) was refluxed for 4 hours, then leave cool. From ethanol, the product was recrystallized. Table 1,5,7

3-oxo-*N'*-(1-(pyridin-2-yl)ethylidene)-3*H*-benzo[f]chromene-2-carbohydrazide (13)

Dissolves the iminochromene derivative **12** (1 mmol) in HCl (4 mL) and absolute ethanol (15 mL) was refluxed for 3 h, leave to cool. The solid was filtered, rinsed by water. From ethanol, the solid was recrystallized. Table 1,5,7

Synthesis of *N*-(4-acetylphenyl)-4-methylbenzenesulfonamide (14).

The solution was made up of (5.72 g, 30 mmol) 4-toluenesulphonyl chloride dissolved in 10 mL dichloromethane and kept at 0°C.

Table 1: Physical Properties of Compounds (1a & 2-13).

Comp. No.	X	Colour	m.p °C	Yield %
1a	------	Onion	193 - 195	95
2	H	Brown	150 – 152	90
3	4-Br	Light Yellow	152 – 153	60
4	4-OCH_3	Dark Brown	94 – 96	50
5	2-Cl	Deep Yellow	161 – 162	88
6	3,4-O_2CH_2	Light Yellow	226 – 229	56
7	H	Yellow	93 – 95	
8	4-Br	Deep Orange	Decomposed	23
9	2-Cl	Yellow	85 – 86	26
10	3,4-O_2CH_2	Dark Burgundy	116 - 118	65
11	------	Brown	173 – 175	50
12	------	Green	224 – 226	98
13	------	Light Yellow	256 – 258	65

Drop-wise additions of 4-aminoacetophenone (4.05 g, 30 mmol), *N*-methylpiperdine (2.97 g, 30 mmol), and dichloromethane (10 mL) were made to this solution, and it was stirred for 3 hours. The extra solvent was under vacuum and placed in the refrigerator for the following day. Filtered, dried and from ethanol, the solid was recrystallized. Table 2, 6

***N*-(4-(1-(2-(2-cyanoacetyl)hydrazineylidene)ethyl)phenyl)-4-methyl benzenesulfonamide (1b).**

In absolute ethanol (20 mL), a combination of 2-cyanoacetohydrazide (1.19 g, 12 mmol) and *N*-(4-acetylphenyl)-4-methylbenzenesulfonamide (14) (3.47 g, 12 mmol) was refluxed for 3 h. Then leave to cool. To obtain the desired compound, the precipitate filtered. Table 2,6-8

***N*-(4-(1-(2-(3-amino-4,9-dihydronaphtho[2,3-b]thiophene-2-carbonyl) hydrazineylidene) ethyl)phenyl)-4-methylbenzenesulfonamide (15) and *N*-(4-(1-(2-(3-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-2-carbonyl)hydrazineylidene)ethyl)phenyl)-4-methyl benzenesulfonamide (16)**

In absolute ethanol (15 mL) with elemental sulfur (0.032 g, 1.0 mmol), a mixture compound **1b** (0.37 g, 1.0 mmol), triethylamine (5 drops), and tetralone or cyclopentanone (1.0 mmol). After 3 hours of heating under reflux, the reaction mixture was allowed to cool. The solid obtained was recrystallized from ethanol to give 19 & 20. Table 2,6,7

ethyl2,4-diamino-5-(2-(1-(4-((4-methylphenyl) sulfonamido) phenyl) ethylidene) hydrazine-1-carbonyl)thiophene-3-carboxylate (17)

In dioxane (15 mL) with elemental sulfur (0.032 g, 1.0 mmol), a mixture compound **1b** (0.37 g, 1.0 mmol), triethylamine (5 drops), and ethyl cyanoacetate (0.113 g, 1.0 mmol). After 5 hours of heating under reflux, then leave cool and pour onto cold water. From ethanol, the product was recrystallized. Table 2,6

Table 2: Physical Properties of Compounds (1b & 14-17).

Comp. No.	Colour	m.p ^{o}C	Yield %
1b	Light Yellow	177 – 180	90
14	Light Yellow	196 – 197	80
15	Deep Brown	193 – 195	37
16	Deep Brown	162 – 164	25
17	Brown	194 – 195	33

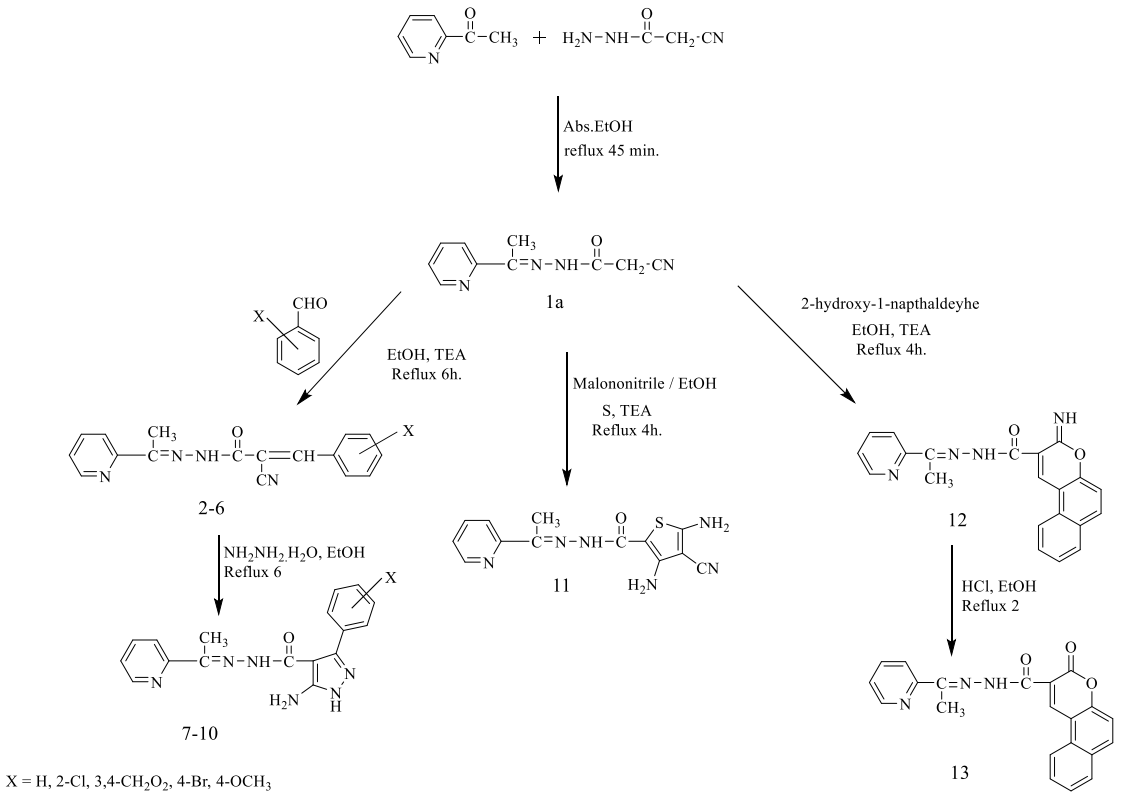
Result and Discussion

The reaction of cyanoacetohydrazide and 2-acetyl pyridine yielded 2-cyano-N'-(1-(pyridin-2-yl)ethylidene)acetohydrazide **1a** as before mention it in the literature [21]. The IR spectra of the compound **1a** exhibit (NH and CN) had strong intensity bands at 3199 & 2264 cm^{-1}, demonstrating the synthesis of cyanoacetyl hydrazono derivative. Reactions of various aromatic aldehydes with hydrazide **1a** were used to investigate the reactivity of the CH_2 group. This reaction was carried out at reflux temperature in ethanol with a catalytic quantity of triethylamine to produce the appropriate arylidene derivatives **2-6** in excellent yields. Spectral analysis were used to describe compounds **2-6**. The NH and CN functions occurred in the 3205–3140 cm^{-1} and 2208–2204 cm^{-1} regions in the IR spectra of **2-6**, respectively, and the C=O band appeared at 1697–1678 cm^{-1}, through the values of the frequency of the carbonyl group in the products, we notice a decrease in the frequency value of the carbonyl group than it was in the starting material and this is due to the conjugation that occurs between the carbonyl group and the double bond in the formed product, which indicates the occurrence of a reaction and the formation of arylidene derivatives **2-6**. The corresponding 1*H*-pyrazole-4-carbohydrazide derivatives **7-10** were obtained when hydrazine hydrate reacted with compounds **2-6** in refluxing ethanol yielded products **7-10**. The FT-IR spectrum revealed additional absorption bands at 3423-3302 and 3210 - 3205 cm^{-1} for NH_2, the appearance of a new frequency band belonging to the NH_2 group in the product is evidence of the formation of the pyrazole compound, (Scheme 1).

The reaction of hydrazide **1a** with malononitrile in absolute ethanol containing elemental sulfur and quantity of triethyl amine to get 3,5-diamino-4-cyano-N'-(1-(pyridin-2-yl) ethylidene) thiophene-2-carbohydrazide **11**, this reaction runs parallel to the reported Gewald's synthesis of thiophene [22], (Scheme 1). Because of the NH_2 group, the IR spectra of **11** revealed additional absorption bands at 3420 and 3360 cm^{-1}, the appearance of a new frequency band belonging to the NH_2 group in the product is evidence of the formation of the required compound. In addition, at δ 6.21 ppm, ^{1}H-NMR revealed a novel singlet signal for the NH_2 group. Also, ^{13}C-NMR at δ 82.00, 137.07, 155.24, and 160.00 ppm this values revealed a novel signals for the thiophene ring.

Similarly, in refluxing ethanol containing a catalytic quantity of triethylamine, the cyclocondensation reaction of 2-hydroxy-1-naphthaldehyde with cyanoacetohydrazide **1a** yielded 2-iminochromene **12**. When the above reaction was carried out in heating ethanol with HCl, however, coumarin derivatives were obtained **13**. Analytical and spectroscopic data were used to deduce the structures of compounds **12 & 13**. The IR spectrum of **12** exhibited of the disappearance of a significant band at 2264 cm^{-1} attributed to the (CN) function. The ^{1}H-NMR revealed an aromatic multiplet in the range of 7.50 – 8.65 ppm, as well as the disappearance of the singlet signal of (CH_2) protons at δ 3.36 ppm. The IR spectra of **13** exhibited a new strong absorption band at 1708 cm^{-1} for the C=O of the coumarin ring. ^{1}H-NMR of **13** revealed a signal at 11.87 ppm ascribed to the (NH) proton, as well as the disappearance of the singlet signal of the second (NH) proton at δ 9.4, (Scheme 1).

On the other hand, The synthetic techniques used to make the goal compounds are described in (Scheme 2), which can completely build the most wanted sulfonamide derivatives **1b & 14-17** from the starting materials *N*-(4-acetylphenyl)-4-methylbenzenesulfonamide **14**, by reacting the nitrogen nucleophilic of 2-cyanoacetohydrazide with compound **14** yielded N-(4-(1-(2-(2-cyanoacetyl) hydrazineylidene) ethyl)phenyl)-4-methyl benzene sulfonamide **1b** (Scheme 2).



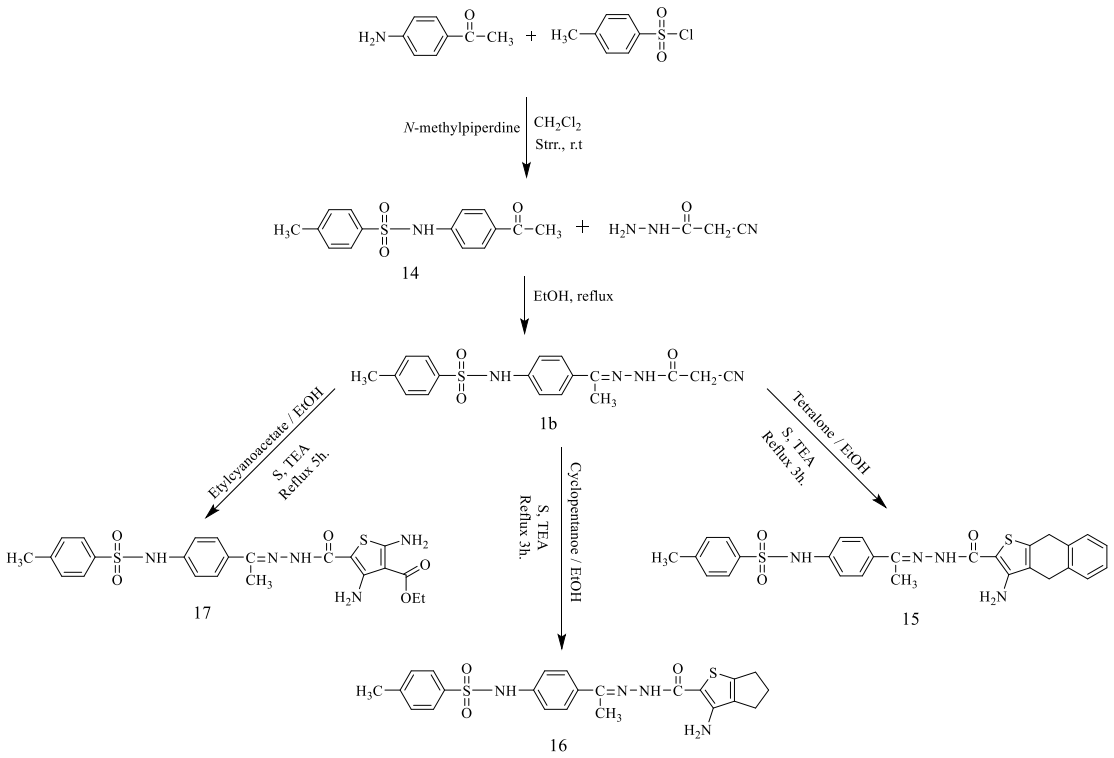
Scheme 1: Synthesis of the hydrazide-hydrazones (1a, 2-13)

Physical properties with spectroscopic (^{1}H-NMR, ^{13}C-NMR and IR spectrum) investigations were used to assign structural assignments to synthesized compounds. The IR spectra of the compound **1b**, the introduced (NH and CN) had strong intensity bands at 3209 & 2274 cm^{-1}, demonstrating the synthesis of cyanoacetyl hydrazono derivative. The inserted CH_2 group produced singlet at 4.18 ppm, while NH groups produced singlet at 7.83 and 10.62 ppm in the ^{1}H-NMR spectrum. ^{13}C-NMR revealed a new signal for CH_2 at 25.31 ppm & a new signal for CN at 127.72 ppm. The target compounds **15 & 16** are synthesized by reacting **1b** with tetralone or cyclopentanone in refluxing absolute ethanol with elemental sulfur and triethylamine to give thiophene derivatives **15 & 16**, respectively, the reaction runs based on to like reported reactions [23]. Their FT-IR spectrum inveterate the certain structures by the appeared of a new NH_2band and the disappearance of the CN band at their particular regions. ^{1}H-NMR spectrum appeared the disappearance of singlet at 4.18 ppm of the methylene function that was included in the cyclization transformation with a novel signal specific for the (NH_2) function displayed at 10.95 ppm.

In addition, compounds **1b** was reacted with ethyl cyanoacetate in the refluxing dioxane containing elemental sulfur with quality of triethylamine yielded the thiophene derivatives **17** (Scheme 2) this reaction runs parallel to the reported Gewald's synthesis of thiophene [22] and the spectroscopic information for compound **17**. The FT-IR spectrum confirmed the certain structures by the attendance of new bands for (C=O) ester with NH_2 and the disappearance of the CN band at their particular regions which was included in the cyclization transformation.

Table 3: FT-IR data of (1a) & 2-cyano-3-substitutedphenyl-*N'*-(1-(pyridin-2-yl)ethylidene)acrylohydrazide (2-6).

Compd. No.	X	FT-IR, ν (cm^{-1})				
		NH	CN	C=O	C=N	C=C
1a	-----	3199	2264	1705	1614	-----
2	H	3188	2206	1678	1597	1575
3	4-Br	3200	2204	1697	1624	1587
4	4-OCH_3	3203	2206	1683	1589	1580
5	2-Cl	3205	2208	1697	1620	1587
6	3,4-O_2CH_2	3140	2202	1689	1600	1579



Scheme (2): Synthesis of the hydrazide-hydrazones (1b, 14-17)

Table 4: FT-IR data of 5-amino-3-substitutedphenyl-*N'*-(1-(pyridin-2-yl)ethylidene)-1*H*-pyrazole-4-carbohydrazide (7-10)

Compd. No.	X	FT-IR, ν (cm^{-1})			
		NH_2	NH	C=O	C=N
7	H	3423, 3210	3167	1622	1573
8	4-Br	3319, 3309	3210	1635	1589
9	2-Cl	3309, 3209	3160	1624	1577
10	3,4-O_2CH_2	3302, 3205	3197	1629	1602

Table 5: FT-IR data of Compounds (11-13)

Compd. No.	FT-IR, ν (cm^{-1})					
	NH_2	NH	CN	C=O	C=N	C=C
11	3420,3360	3197	2264	1689	1610	1577
12	-----	3331	-----	1683	149	1600
13	-----	3174	-----	1670, 1708	1670	1640

Table 6: FT-IR data of Compounds (1b & 14-17)

Compd. No.	FT-IR, ν (cm^{-1})							
	NH_2	NH	CN	C=O	C=N	C=C	SO_2 asymt.	SO_2 symt.
1b	-----	3209	2274	1678	1599	-----	1338	1165
14	-----	3219	----	1670	-----	1598	1361	1161
15	3444, 3238	3140	-----	1674	1608	1599	1330	1159
16	3440, 3232	3160	-----	1683	1610	1599	1332	1159
17	3360, 3280	3219	-----	1750, 1670	1599	-----	1340	1159

Table 7: The ^{1}H-NMR spectral data of compounds (1b, 11-13, 15).

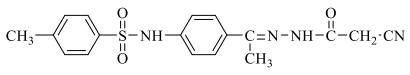
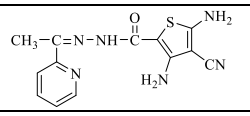
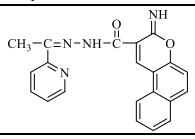
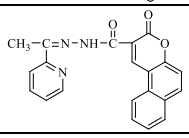
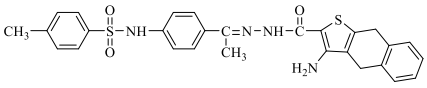
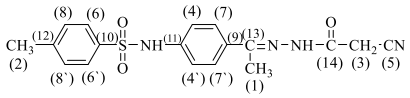
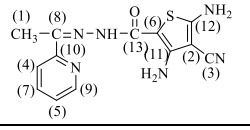
Compd. No.	Structure	^{1}H-NMR, (ppm), DMSO-d6
1b		2.18 [s, 3H, CH_3], 2.32 [s, 3H, CH_3 tolyl], 4.18 [s, 2H, CH_2],7.10-7.73 [m, 8H, Ar-H], 7.83 [s, 1H, SO_2NH], 10.62 [s, 1H, NH]
11		2.36 [s, 3H, CH_3], 6.21 [s, 4H, $2NH_2$], 7.39-8.61 [m, 4H, pyridine-H], 10.82 [s, 1H, NH]
12		2.47 [s, 3H, CH_3], 7.50-8.65 [m, 11H, pyridine-H & coumarin-H], 9.40 [s, 1H, NH], 13.7 [s, 1H, NH]
13		2.50 [s, 3H, CH_3], 7.13-8.72 [m, 11H, pyridine-H & coumarin-H], 11.87 [s, 1H, NH]
15		2.18 [s, 3H, CH_3], 2.46 [s, 3H, CH_3 tolyl], 3.10, 4.18 [s, 4H, $2CH_2$ cyclohexane],7.09-7.87 [m, 12H, Ar-H], 7.92 [s, 1H, SO_2NH], 10.60 [s, 2H, NH_2], 10.95 [s, 1H, NH]

Table 8: The ^{13}C-NMR spectral data of compounds (1b, 11).

Compd. No.	Structure	^{13}C-NMR, (ppm), DMSO-d6
1b		14.55, 21.46, 25.31, 119.36, 127.72, 127.88, 130.23, 133.49, 137.00, 139.35, 143.00, 148.92, 166.18, 196.89
11		12.66, 82.00, 116.66, 120.79, 124.60, 137.07, 149.02, 149.14, 150.27, 155.14, 155.24, 160.00, 166.48

Conclusion

The hydrazide-hydrazone derivatives **1a & 1b** were obtained by reacting 2-cyanoacetohydrazide with 2-acetyl pyridine or *N*-(4-acetylphenyl)-4-methyl benzene sulfone amide **14** in this study. The last was reacted with various reagents to produce thiophene, coumarin, α,β-unsaturated carbonyl compounds, and pyrazole derivatives, which are thought to have biological significance, hence this research focused on these compounds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

University of Mosul.

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