

Synthesis of New Heterocyclic compounds derived from Pyrazoline-5-one compound

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الخلاصة:

تناول هذا البحث تحضير مركب البايرازولين المشتق من ملح كلوريد الدايزونيوم للمركب 4-امينو حامض البنزويك، والخطوة الثانية تم تحضير مركب الازو عن طريق مفاعلة ملح كلوريد الدايزونيوم مع مركب حاوي على مجموعة المثليين الفعالة مثل (اثيل اسيتو اسيتيت) باستخدام الايثانول كمذيب بوجود خلاص الصوديوم للحصول على المشتق (1). ثم تضمن غلق حلقي للمركب (1) مع الهيدرازين لتكوين المشتق (2) في الايثانول المغلي. بعدها صُعد المركب (2) مع كلوريد الثايونيل للحصول على مشتق حامض الكلوريد (3)، تم تحويل المشتق حامض الكلوريد الى: ثايوسمي كاربازيد حامض الكاربوكسيل (4)، الاسترات (7-9)، استرات الثايول (10 و 11) والاميد (12-14) بالمفاعلة مع الكحولات، ثايولات الالكيل والاميدات على التوالي.

تضمن البحث تحضير مشتق لحلقة 1,2,4-الترايزول وحلقة 1,3,4-الثايدايوزول الغير المتجانسة والتي قد تستخدم كمادة فعالة بايولوجياً، تم تحضيرها عن طريق مفاعلة مشتق الثايوسيميكاربازيد (4) مع محلول هيدروكسيد الصوديوم (4%) ثم تحميص الناتج باستخدام حامض الهيدروليك (10%) للحصول على المشتق (5) ضمن نفس الاطار تم تحضير (6) من معاملة مشتق الثايوسيميكاربازيد مع حامض الكبريتيك المركز. وأخيراً تم تفاعل مشتق البايرازول مع بارا هيدروكسي بنزالديهايد للحصول على المشتق (15)، والخطوة الاخيرة تم تصعيد الناتج مع 5-امينو -1,3,4-ثايدايازول -2- ثايول لتحضير المشتق (16). شُخصت المركبات المحضرة من قياس درجات انصهارها وتحليل أطيايف الاشعة تحت الحمراء والاشعة فوق البنفسجية (IR,UV).

Abstract

In this work new heterocyclic pyrazolin derivatives have been synthesized from diazonium chloride salt of 4-aminobenzoic acid: firstly, Azo compounds were prepared from the reaction of an ethanolic solution of sodium acetate and calculated amount of active methylene compound namely, (ethyl acetoacetate) obtain the corresponding hydrazono derivative (1). Secondly, Cyclocondensation reaction of compound (1) with hydrazine hydrate (2) in

boiling ethanol affording the corresponding pyrazoline-5-one. Then compound (2) reacted with thionyl chloride to give the corresponding acid chloride derivative(3), followed by conversion into the corresponding carboxylic acid thiosemicarbazide (4), esters (7-9), thioesters (10), (11), and amides (12-14), when treated hydrazine hydrate, thiosemicarbazide, alcohols, alkylthiol and secondary amines in dry refluxing benzene; respectively. Furthermore, 1,2,4-triazole heterocyclic ring, which might result in biologically active agents, have been prepared by refluxing thiosemicarbazide derivative (4) with sodium hydroxide solution (4%) followed acidification of the result using (10%)HCl solution. Moreover, 1, 3, 4, - thiadiazole heterocyclic ring (6) has been prepared by treatment of thiosemicarbazide derivative with concentrated sulfuric acid as cyclization agent. Finally, derivative (15) has prepared by reflux (1) with p-hydroxybenzaldehyde then the product reflux with 5-amino-1, 3, 4-thiadiazol-2-thiol to product (16) derivative. All structures of newly synthesized compounds have been characterized and identified via of their physical properties and spectral data analysis (IR, UV.)

Introduction:

Heterocyclic compounds represent an important class of biologically active molecules. Specifically, those containing the pyrazole nucleus have been shown to possess high biological activities as herbicides, fungicides, analgesics, etc ^[1]. Some novel pyrazole derivatives containing sulfonamide moieties as anti microbial agents, Various sulfa drugs were coupled with active methylene compounds to give various hydrazones, then novel series of pyrazoles derivatives ^[2]. Past few years, biologically active pyrazoles comprising fused pyrimidine moiety into the 1-position of the pyrazole ring system ^[3]. Moreover; reaction of azo compounds with substituted acetoacetic ester derivatives using acetic acid as solvent ^[4].

Materials and Methods:

Apparatus and Chemicals:

Electrothermal 9100 melting point apparatus, Perkin-Elmer 1310 infrared spectrophotometer or a Shimadzu FTIR-800, as KBr discs or thin films, UV-Visible Varian UV-Cary-100 spectrophotometers were used in this work. All the chemicals used were supplied by Merck, Fluka and BDH chemicals. The solvents were purified by distillation and dried with calcium chloride.

Experimental:

4-{(1-(ethoxycarbonyl)-2-oxopropyl)diazenyl}benzoic acid (1) ^[4]

To an ice-cooled mixture of active methylene compound (ethyl acetoacetate) (0.01 mole) and sodium acetate (0.05 mole, 4.10 g) in ethanol (50 ml), was added dropwise with stirring to a cooled solution of the diazonium salt over 15 minute. The solid product was collected and recrystallized from ethanol .

4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)benzoic acid (2) ^[4]

A mixture of azo derivative (0.01 mole) and hydrazine hydrate (95 %) (0.012 mole, 0.35 g) in ethanol (30 ml) was heated under reflux for 4 hours. The reaction mixture was concentrated and the reaction product was allowed to cool. The separated product was filtered off, washed with water, and recrystallized from the appropriate solvent.

4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)benzoyl chloride (3) ^[5]

A mixture of compound (2) (0.01 mole, 2.46 g) and thionyl chloride (7 ml) was gently refluxed for 2 hours. After cooling, excess thionyl chloride was removed under reduced pressure. the product was recrystallized from benzene

2-{4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)benzoyl} hydrazinecarbothioamide (4)

To a solution of (3) (0.005 mole, 1.32 g) in dry benzene (25 ml), thiosemicarbazide (0.005 mole 0.45 g) was added. The mixture was refluxed for 3 hour, cooling, filtered and recrystallized from ethanol.

4-{(4-(5-mercapto-4H-1,2,4-triazol-3-yl) phenyl)diazenyl}-5-methyl-2,4-dihydro-3H-pyrazol-3-one (5)

A mixture of (4) (0.001 mole, 0.319 g) and (4%) sodium hydroxide solution (25 ml) was refluxed for 4 hours, cooled, poured into crushed ice and acidified with dilute hydrochloric acid (10 %). The resultant precipitate was filtered, washed with water and recrystallized from ethanol.

4-{(4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl)diazenyl}-5-methyl-2,4-dihydro-3H-pyrazol-3-one (6)

Compound (4) (0.001 mole, 0.32 g) was dissolved in cold concentrated sulfuric acid (10 ml) and stirred at room temperature for 24 hours, poured into crushed ice the product was diluted and filtered, recrystallized from ethanol

prop-2-ynyl 4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl) benzoate (7)

3-chloro-4-formylphenyl 4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)benzoate (8)

isobutyl 4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl) benzoate(9)

To a solution of compound (2) (0.005 mole, 1.23 g) in dry benzene (25 ml), alkyl, or phenyl alcohol (0.005 mole) was added, the mixture was refluxed for 6 hours.

S-benzyl 4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl) benzenecarbothioate(10) ^[6]

S-butyl 4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl) benzenecarbothioate (11) ^[6]

To a solution of compound (2) (0.005 mole, 1.23 g) in dry benzene (25 ml), alkylthiol (0.005 mole) was added, mixture was refluxed for 6 hours.

5-methyl-4-((4-(piperidin-1-ylcarbonyl)phenyl)diazenyl)-2,4-dihydro-3H-pyrazol-3-one (12) ^[7]

5-methyl-4-((4-(morpholin-4-ylcarbonyl)phenyl)diazenyl)-2,4-dihydro-3H-pyrazol-3-one (13) ^[7]

N,N-dimethyl-4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)benzamide (14) ^[7]

To a solution of compound (2) (0.005 mole, 1.23 g) in dry benzene (25 ml), secondary amine (0.005 mole) was added, and refluxed for 3 hours.

4-formylphenyl 4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)benzoate (15)

A mixture of compound (1) (0.01 mole, 2.46 g) was refluxed with 4-hydroxybenzaldehyde (0.01 mole, 1.22 g) on oil bath at 140–160 °C for 2 hours. The product was cooled recrystallized from the appropriate solvent.

4-((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl}phenyl 4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)benzoate (16)

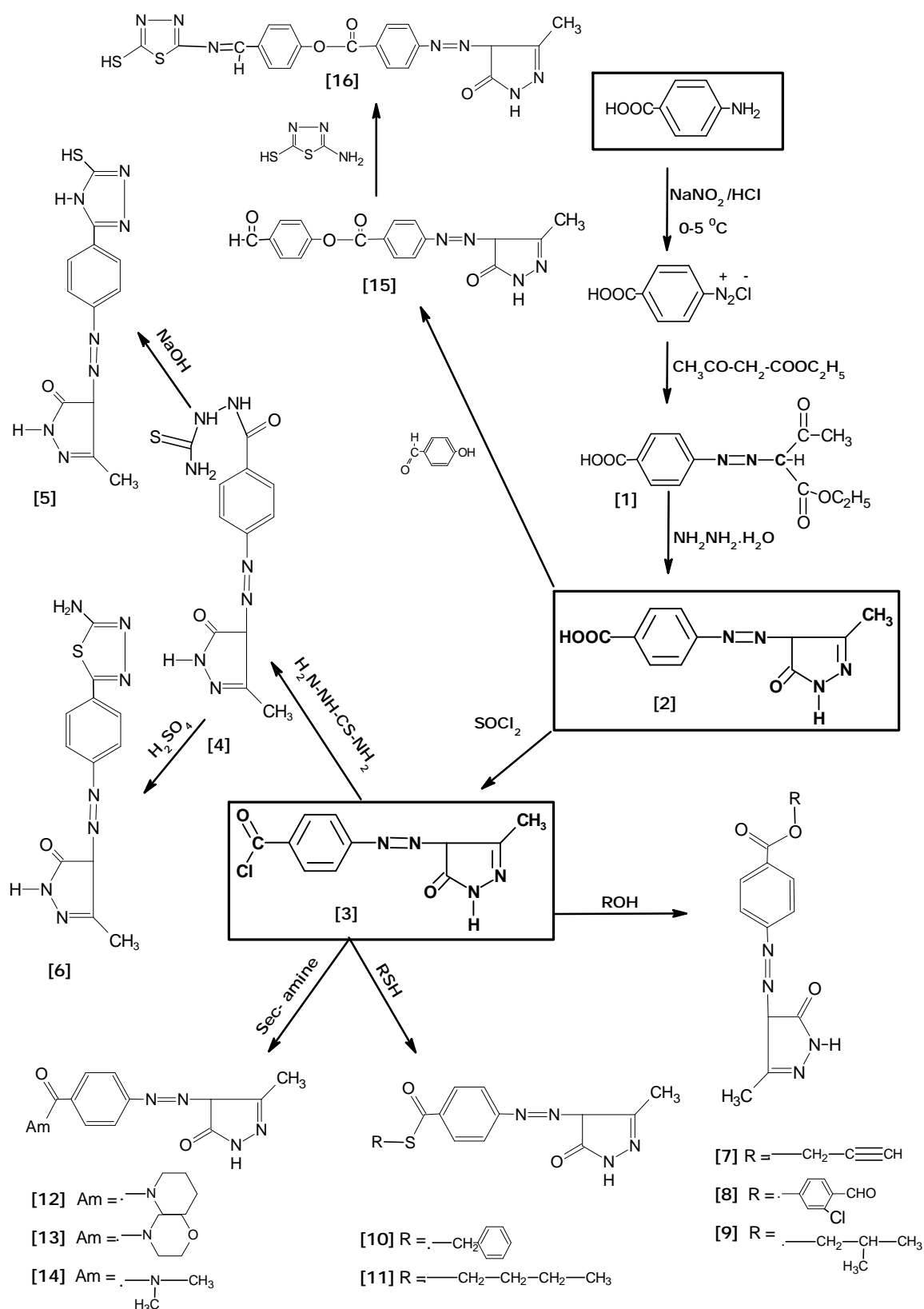
To a solution of 5-amino-1,3,4-thiadiazol-2-thiol (0.001 mole, 0.133 g) in (10 ml) of absolute ethanol, compound (15) (0.001 mole, 0.35 g) was added. The mixture was refluxed for (3 hours), cooled, filtered and recrystallized from ethanol.

Compound Number	Molecular Formula	M.P/ °C	Color	Purification Solvent	Yield (%)
1	C ₁₃ H ₁₄ N ₂ O ₅	201-203	Green	Ethanol	88
2	C ₁₁ H ₁₀ N ₄ O ₃	240-242	Orange-Yellow	Ethanol	68
3	C ₁₁ H ₉ ClN ₄ O ₂	217 dec.	Deep-Green	Benzene	82
4	C ₁₂ H ₁₃ N ₇ O ₂ S	287-289	Brown	Ethanol	70
5	C ₁₂ H ₁₁ N ₇ OS	230-232	Brownish red	Ethanol	43
6	C ₁₂ H ₁₁ N ₇ OS	295-297	Green	Ethanol	52
7	C ₁₄ H ₁₂ N ₄ O ₃	188-190	Yellow	Benzene	75
8	C ₁₈ H ₁₄ ClN ₄ O ₄	200dec.	Pale Brown	Benzene	42
9	C ₁₅ H ₁₈ N ₄ O ₃	166-168	Yellow	Chloroform	83
10	C ₁₈ H ₁₆ N ₄ O ₂ S	177 dec.	Brown	Benzene	32
11	C ₁₅ H ₁₈ N ₄ O ₂ S	158 dec.	Brown	Chloroform	59
12	C ₁₆ H ₁₉ N ₅ O ₂	201-203	Brown	Chloroform	72
13	C ₁₅ H ₁₇ N ₅ O ₃	207 dec.	Pale-brown	Chloroform	55
14	C ₁₃ H ₁₅ N ₅ O ₂	185 dec.	Yellow	Chloroform	70
15	C ₁₈ H ₁₄ O ₄ N ₄	320 dec.	Brown	Ethanol\water 1:1	56
16	C ₂₀ H ₁₅ N ₇ O ₃ S ₂	300 dec.	Pale-yellow	Ethanol	68

Table-1: The physical properties of compounds (1-16)

Results and Discussion

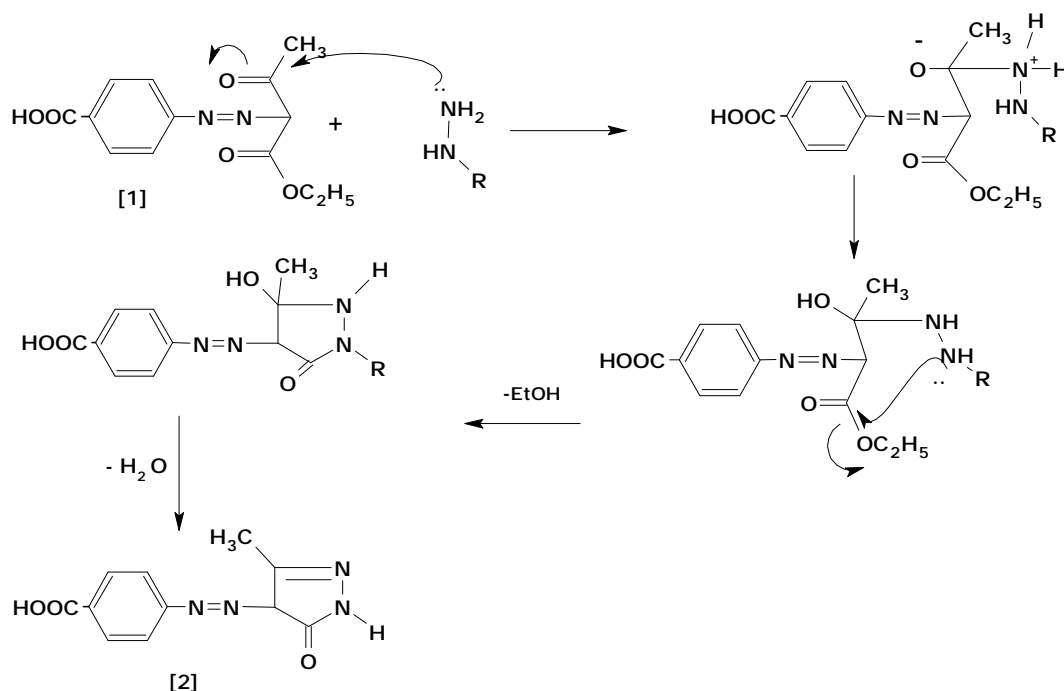
For the synthesis of the target 4-aminobenzoic acid derivatives in this work, the reaction sequences are outlined in scheme (1).



Scheme (1)

Hydrazons are easily undergoing cyclocondensation reaction with hydrazine hydrate in boiling ethanol afford to the corresponding pyrazoline-5-one derivatives of p-aminobenzoic acid. Thus cyclization of azo compound with hydrazine hydrate afford the corresponding derivative (2). The IR spectrum of compound (1) shows a characteristic bands at (1735 cm^{-1}) for the carboxylic ester moiety, while bands at (1715 cm^{-1}), (1685 cm^{-1}) corresponding to the characteristic (C=O) of acetyl and carboxylic acid, respectively. The band at (1530 cm^{-1}) corresponds to the stretching vibration of the azo group, and the broad band at (2600-3200 cm^{-1}) refers to stretching vibration of hydroxyl group.

The mechanism of this cyclocondensation reaction may be outlined as follow:



Scheme (2)

The IR spectrum of compound (2), shows the disappearance of the characteristic bands of the acetyl carbonyl group and carboxylic acid ester at (1735, 1715 cm^{-1}), and the appearance of strong bands in the (3450 cm^{-1}), attributed to (N-H) stretching vibration and the bands of (C=O) carboxylic acid appeared at (1680 cm^{-1}), pyrazolinone ring (C=O) stretching vibration appeared at (1650 cm^{-1}) and (OH)_{st} appear at (2600-3300 cm^{-1}).

The IR spectrum of compound (3) shows the disappearance of the hydroxyl group of the starting material and appearance of the new (C=O) band at (1780 cm^{-1}), for the acetyl chloride. The spectrum also shows an absorption band at (700 cm^{-1}) referring to (C-Cl) band [8]. The U.V. spectrum of this compound, has λ_{max} (MeOH) at (240 and 344 nm) responsible for (π - π^*).

The IR spectrum of compound (4), shows the main characteristic bands at (1220 cm^{-1}) refers to (C=S) stretching vibration, an absorption band at (1680

cm^{-1}) for (C=O) stretching vibration which appears at (1780 cm^{-1}) in the acid chloride derivatives and at (3350) for (N-H) and ($3300-3450 \text{ cm}^{-1}$) for (NH_2) stretching vibration. The success of the reaction has been confirmed by comparing the (C=O) absorption in the acid chloride and hydrazide derivatives.

The IR spectrum of compound (**5**), shows characteristic (S-H) stretching vibration as weak band at (2650 cm^{-1}) and (C=S) stretching vibration as weak band at (1233 cm^{-1}) which confirmed the tautomersim between thion and thiol^[9] form and an absorption band at (1640 cm^{-1}) due to (C=N) stretching vibration of triazole transition.

The IR spectrum of compound (**6**) shows absorption band at (1260 cm^{-1}) due to (N-N) stretching vibration and at ($3300-3450 \text{ cm}^{-1}$) due to (NH_2) stretching vibration. The IR spectrum of compound (**7**) shows the disappearance of (C-Cl) stretching band and appearance of absorption band at (1730 cm^{-1}) due to (C=O) stretching vibration, appearance of (C≡C-H) stretching band at (3200 cm^{-1}) and band at (2170 cm^{-1}) for (C≡C) assymetrical stretching vibration^[9].

The success of the reaction has been confirmed by the appearance of the triple bond of the acetylenic group the thioester compounds have been synthesized by the reaction of acid chloride and RSH in refluxing dry benzene with mechanism similar to that of alcoholic ester.

The IR spectrum of compound (**10**) shows band at (1690 cm^{-1}) due to (C=O) stretching vibration which had appeared at (1800 cm^{-1}) in acid chloride compound (**3**), band at (660 cm^{-1}) due to (C-S) stretching vibration. The IR spectrum of compound (**12**), shows the main characteristic bands at (1640 cm^{-1}) due to (C=O) of amide, and at (2970 cm^{-1} asy and 2880 cm^{-1} sym)^[10] for aliphatic (C-H) stretching vibration.

Compound (**15**) has been synthesized by treatment of compound (**2**) with p-hydroxybezaldehyde The IR spectrum of (**15**), shows the disappearance of the broad stretching band for (OH) of the carboxylic group of compound (**2**), and appearance of an absorption band at (1740 cm^{-1}) due to (C=O) stretching vibration of ester group, which interfered with the (C=O) stretching vibration of the aldehyde group (1725 cm^{-1}) and appearance of a weak band of (H-C=O) aldehyde in (2700 cm^{-1}).

Compound (**16**) was prepared by treatment of compound (**15**) with 5-amino-1,3,4-thiadiazol-2-thiol in absolute ethanol as a solvent. The IR spectrum of compound (**16**), shows absorption band at (1640 cm^{-1}) due to (C=N) stretching vibration. The U.V. spectrum of this compound, table (2) has λ_{max} (MeOH) at (293 and 275 nm) responsible for ($\pi-\pi^*$).

Compound Number	UV λ_{\max} (nm)	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{N})$	$\nu(\text{N}=\text{N})$	$\nu(\text{C-H})_{\text{al}}$ $\nu(\text{C-H})_{\text{ar}}$	Others
1	362 238	1735(ester) 1715(acetyl) 1685 (acid)	-----	1530	(2970) _{asy} (2850) _{sy} 3050	2600-3200 (OH) _{st}
	285 261	1650(ring) Interfere with 1680(acid)	1620 interfere with C=C	1580	(2920) _{asy} (2850) _{sy} 3090	2600-3300 (O-H) Interfere with 3450(NH) _{st}
	344 240	1780 1660(ring)	1610 interfere with C=C	1550	(2950) _{asy} (2800) _{sy} 3050	700 (C-Cl) _{st} 3350 (N-H) _{st}
	389	1680 Interfere with 1660 (ring)	1630 interfere with C=C	1540	(2960) _{asy} (2800) _{sy} 3050	1220 (C=S) _{st} 3350 (NH) _{st} Interfere with 3300-3450 (NH ₂) _{st}
	377 271	1665 (ring)	1640	1555	(2970) _{asy} (2850) _{sy} 3080	1233 (C=S) _{st} 2650(SH) _{st} 3300 (NH) _{st}
6	356	1655 (ring)	1630 interfere with C=C	1555	(2900) _{asy} (2800) _{sy} 3050	1260 (N-N) 3250 (NH) _{st} Interfere with 3300-3450 (NH ₂) _{st}
	395	1730 (ester) 1650 (ring)	-----	1555	2950 3080	3200 (C≡C) _{st} 2170 C≡C) _{st} 3350 (NH) _{st}
8	310	1730 (ester) 1660 (ring)	-----	1550	2970 3050	3320(NH) _{st}
9	298	1730 (ester) 1660 (ring) interfere with 1680 (aldehyde)	-----	1555	2900 3050	2690 (C-H) aldehyde 3350 (NH) _{st}
	416 292	1690 1670	-----	1550	2975 3100	3300(NH) _{st} 660(C-S) _{st}
11	398 285	1700 1650	-----	1558	2980 3050	3270 (NH) _{st} 675(C-S) _{st}
	328 217	1640 1650(ring)	1560	1540	(2970) asy (2880) sy 3050	3350(NH) _{st}
13	310	1630	1625 interfere with (C=O)	1550	2950 3080	1160(C-O-C) 3350 (NH) _{st}
14	337 288	1630	1625 interfere with (C=O)	1550	(2950) asy (2800) sy 3050	3300 (NH)
15	379 256	1740 (ester) 1725(amide) 1680 (ring)	1610	1550	(2950) asy (2800) sy 3080	weak 2700, 2800 (C- H) _{ald} 3350 (NH) _{st}
16	293 275	1730(ester) 1660 (ring)	1640	1540	(2900) asy (2820) sy 3050	weak 2550 (C-H) _{ald} 3400 (NH) _{st}

Table-2: Spectral data for compounds (1-16)

References:

- 1- Ren, X.; Wu, H. Li., C. and Yang, H. (2005). Synthesis of a small library containing substituted pyrazoles .*Arkivoc* (xv) pp.59-67.
- 2- El-Gaby, M. S. A.; Taha, N. M.; Micky J. A. and El-Sharief , M. A. (2002). Preperation of some new novel 3,5-diaminopyrazole, pyrazolo(1,5-a) (1,3,5)triazine derevatives containing sulfonamide moities as antimicrobial agents .*Acta, Chim, Slov.*, Vol.(49).pp.159-71.
- 3- Saleh,M. A.; Abdel-Mageed, M. F.; Abdo, M. A. and Shoker A. B. M. (2003) .Synthesis of Novel 3H-Quinazolin-4-ones Containing Pyrazolinone, Pyrazole and Pyrimidinone Moieties. *Molecules*,Vol.(8) . pp. 363-73.
- 4- El-Assiery, S. A.; Sayed, G. H. and Foude, A. (2004). Synthesis of some new annulated pyrazolo-pyrido (or pyrano) pyrimidine, pyrazolopyridine and pyranopyrazole derivatives. *Acta Pharm.* Vol. (54) pp. 143-50.
- 5- Mc, Murry. John. "Organic Chemistry", 5th Edition, Cornel University press, (2002).
- 6- Abdul-jabbar, K. A. (2003).Preparation of new compounds derived from 5-ethyl-5-phenyl barbituric acid. Ph. D. thesis Al-Mustansiriya University.pp.55.
- 7- Abo-Orabi; S. T. (2002). Review1, 3-Dipolar Cycloaddition Reactions of Substituted Benzyl Azides with Acetylenic Compounds .*Molecules*, Vol. (7) pp. 302-14.
- 8- March, J. "Advanced Organic Chemistry" Ed., Jhon Wiely and Sons, New York, (1985).
- 9- Katritzky, A. R. and Pozharskii, A. F. " HandBook of Heterocyclic Chemistry", 2nd ed. Pergamon, Amesterdam, 361-63 (2000).
- 10- Parikh, V. M. "Absorption Spectroscopic of Organic Molecules" Translated by A. H. Khuthier, J. M. A. Al-Rawi, M. A. Al-Iraqi, Mousul University (1985).