Synthesis of Some 1 ,3 ,4- Oxadiazole and 1,2,4-Triazole Derivatives and Evaluation the Antibacterial Activity

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Keywords: Schiff Bases, 1,3,4- Oxadiazole , 1,2,4- Triazole, Antibacterial Activity.

(Received :October2011, Accepted :June2012)

Abstract:

Some of hydrazone derivatives[2a-e] were prepared from the reaction of 2-phenyl acetic acid hydrazide[1] with different substituted benzaldehydes, then cyclization of hydrazones in glacial acetic acid and lead dioxide resulted into the formation of new 1,3,4-Oxadiazole derivatives [3a-e], Symmetrical 4-amino Triazole derivatives [5a-e] were prepared from reaction of 3,5-dibenzyl-4-amino 1,2,4-Triazole[4] with different substituted benzaldehydes to product new series of different Schiff bases [5a-e]. The prepared compounds were characterized by FT-IR, and UV spectroscopy, the melting points were determined and the purity and reaction time was checked by TLC, the biological activity was evaluated against different types of bacteria.

تحضير بعض مشتقات 4, 3,1 - اوكسادايازول و4,2,1- ترايازول وتقييم فعاليتها البايولوجية

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الكلمات المفتاحية: قواعد شيف ,4,3,1- االوكسادايازول , 4,2,1- ترايازول ,الفعالية البايولوجية.

الخلاصة:

تم تحضير بعض مشتقات هيدرازون 2- فنيل حامض الخليك[2a-e] من تفاعل هيدرازيد 2- فنيل حامض الخليك [1] مع معوضات بنزلديهايدات مختلفة , ثم حولقة الهيدرازونات المتكونة بواسطة حامض الخليك الثلجي وثنائي اوكسيد الرصاص الى مشتقات جديدة من 4,3,1- اوكسادايازول [3a-e] كما تم مفاعله 4- امينو ترايازول المتناظر[4] والمحضر من صهر مركب هيدرازيد 2- فنيل حامض الخليك [1] مع معوضات مختلفة للبنزالديهايد للحصول على أنواع جديدة ومختلفة من قواعد شيف [5a-e] , شخصت المركبات المحضرة بطيف الأشعة تحت الحمراء (IR) والأشعة فوق البنفسجية (UV) وبقياس درجات الانصهار وتم متابعة التفاعلات بكروموتوغرافيا الطبقة الرقيقة (TLC) , درست الفعالية لبايولوجية ضد أنواع مختلفة من البكتريا.

Introduction:

Hydrazones and their derivatives have versatile applications in the biological fields as antimicrobial, anticonvulsant, analgesic, anti-inflammatory, ant platelet, antitubercular, antitumor and antibacterial activity[1-5].1,3,4-Oxadiazole derivatives are reported to show a broad spectrum of biological activities, which include antibacterial [6] anti-inflammatory[7] anticonvulsant [8, 9] CNS stimulant [10] and antihypertensive [11].

Over the last few decades, there has been considerable interest in the synthesis and characterization of 4-amino 1,2,4-triazoles because of the biological and pharmaceutical properties of this heterocyclic[12-14].

In addition 1,3,4-Oxadiazol is versatile lead molecule for designing potent bioactive agent[15]. This interesting group of compounds possess diverse biological activity such as anticonvulsant[16], antimicrobial[16,17], antitubercular[18], anticancer[19], anti-HIV[20], hypoglycemic[21] and genotoxic[22] activities.

Experimental:

Materials: different substituted benzaldehydes were BDH annular grade, solvents and other chemicals used of annular grade.

Uncorrected melting points were determined using Electrothermal melting point apparatus(Electrothermal Engineering LTD S.N 10853). The IR spectra were recorded by Shimadzu FT-IR spectrophotometer as KBr disc (400-4000 cm^{-1}) range , the UV absorption spectra were measured in ethanol(95%) as a solvent by Jascow 32 V-530, TLC- Merck Silica gel 60 F254 Plate was used.

A) Synthesis methods:

1) Synthesis of ethyl 2-phenyl acetate [23] .

A mixture of 2-phenyl acetic acid (0.1mol), excess of ethanol and concentrated sulphuric acid (5ml) was refluxed for 6 hrs. with stirring. After that the solvent was distilled under vacuum, the product washed by sodium bicarbonate solution then with diethyl ether (40ml) B.P= 225°C (Lit. 226°C) ,yield = 60% .

2) Synthesis of 2-phenyl acetic acid hydrazide [1] [23].

Ethyl 2-phenyl acetate (0.1mol) and hydrazine hydrate 98% (0.1mol) were dissolved in absolute ethanol (40ml) and refluxed for 6hrs., after cooling to room temperature , the precipitate was filtered ,washed , recrystallized. from ethanol and dried .The physical properties of this compound is given in Table (1).

3) Synthesis of [(substituted benzylidene)hydrazon-3-oyl] phenyl methane [2a-e][24]

A mixture of compound [1] (0.01 mole) and substituted benzaldehydes (0.01 mole) in ethanol (25 ml) was refluxed for 3 hrs., the precipitate was filtered and crystallized from ethanol .The physical properties of these derivatives are given in Table (2).

4) Synthesis of [2-(substituted phenyl)5-benzyl]-1,3,4-Oxadiazole [3a-e].[24]

(0.01 mole) of compounds [2a-e] were dissolved in (40 ml) of glacial acetic acid with stirring until the obtaining of a homogeneous solution. Lead dioxide (0.01 mole) was added with stirring at 25 °C for 1 hr., the product was poured on crushed ice. The crude material was filtered off and washed with cold water and recrystallized from ethanol. The physical properties of these derivatives are given in Table (3).

5) Synthesis of 3,5-dibenzyl-4-amino 1,2,4-Triazole[4] [25]

2-Phenyl acetic acid hydrazide (1.5gm) was melted at (200-220 ºC) for 2hrs.,then cooled and to the reaction mixture was added (50ml) of water and refluxed 1 hr., filtered hot, the white precipitate was recrystallized from ethanol and dried . The physical properties are given in Table (4).

6) Synthesis of 3,5-dibenzyl 4-arylmethylenimino-(4H) 1,2,4-Triazole [5a-e] [26]

A mixture of compound [4] (0.01 mole) and substituteds benzaldehyde (0.01 mole) in ethanol(25 ml) and add drops of glacial acetic acid was refluxed for 6 hrs., the precipitate was filtered and recrystallized from ethanol. The physical properties of these derivatives are given in Table (5).

B) The biological activity[27]

The bacteria species used are listed in Table (6). All strains were obtained from College of Medicine, Tikrit University. They were grown up to the stationary phase nutrient bath at 37 °C and a sample of (0.5 ml) of each bacteria was spread over a surface of a nutrient agar plate .

Antibacterial assay[27]

Disc of filter paper (6 mm diameter) were sterilized at 140 °C for 1 hrs. and impregnated with the germs, absolute ethanol was used as a solvent for compounds [2a-e], [3a-e],[4] and [5a-e] . The same solvent was used for antibiotics, blank paper discs of absolute ethanol was used as control. The inoculated plates were incubated at 37 °C for 24 hrs., and the inhibition zone (mm) were measured[28]. In all experiments, the mean of each triplicate was measured[29].

Results and Discussion:

1) Characterization of [(substituted benzylidene) hydrazon-3-oyl] phenyl methane [2a-e]

Hydrazone compounds [2a-e] were prepared by the condensation reaction of 2-phenyl acetic acid hydrazide[1] with substitutes benzaldehyde.The IR characteristic absorption bands of the hydrazone compounds were given appeared at (1650-1680) cm^{-1} and (1650-1660) cm^{-1} for (C=O) and (C=N) respectively. While single band at (3200-3300) cm^{-1} for (N-H). UV and IR absorbance spectra are given in Table(7). Minimize energy conformation of prepared compounds[2a-e] are given in fig.(1-5).

2) Characterization of[2-(substituted phenyl)5-benzyl] 1,3,4-Oxadiazole [3a-e].

1,3,4-Oxadiazoles [3a-e] were synthesized by the reaction of equimolar amounts of hydrazone compounds [2a-e] with lead dioxide in glacial acetic acid.

The FT-IR spectra of 1,3,4- Oxadiazole derivatives have exhibited the significant bond at about (1640-1681)cm^{-1} duet to cyclic (C=N) stretching. Also spectra has displayed an asymmetrical (C-O-C) aromatic stretching band at (1240-1267) cm^{-1}, with symmetrical near (1040-1087) cm^{-1}, in addition to a peak at (1054-1080) cm^{-1} duet to (N-N) group, beside UV spectra show the transitions $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ which confirmed the presence of the un-bonded pair electrons on Nitrogen, Oxygen atoms and aromatic system. (double bond). UV and IR absorbance spectra are given in Table(8). Minimize energy conformation of prepared compounds[3a-e] are given in fig.(6-10).

The U.V spectra gave absorption band at different wave lengths for the resulted hydrazones and 1,3,4-Oxadiazoles (in % 95 EtOH), due to $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ transition and all these transition are listed in Table (7,8).

3) Characterization of 3,5-dibenzyl-4-amino 1,2,4-Triazole [4].

1,2,4-Triazole compound was prepared by melting dry powder of 2-phenyl acetic acid hydrazide [1] at high temperature 200-225C.

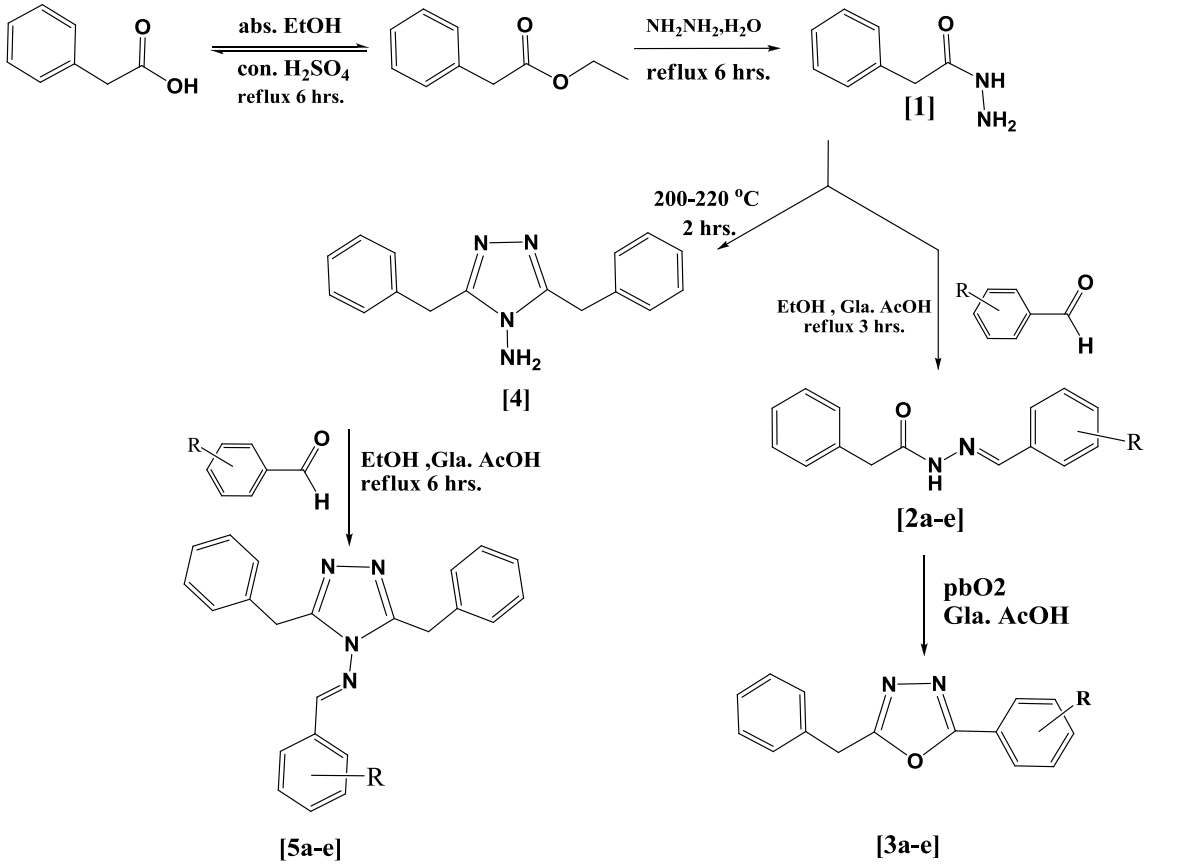
IR spectrum of compound[4] Fig.(17), exhibited significant two bands in the region (3199)cm^{-1} and (3411)cm^{-1} which could be attributed to symmetric and asymmetric stretching vibration of NH_2 group[30] besides a band at about (1649) cm^{-1} due to cyclic C=N, stretching is also observed. UV and IR absorbance spectra are given in Table(9). Minimize energy conformation of compound [4]is given in fig.(11).

4) Characterization of 3,5-dibenzyl 4-arylmethylenimino-(4H) 1,2,4-Triazole [5a-e].

Schiff bases compounds [5a-e] were synthesized from reaction of compound [4] with different substitutes benzaldehyde. The synthesis of these compounds were carried out according to the steps outlined in scheme(1).The reaction was followed by disappearance of NH_2 absorption bands at (3199)cm^{-1} and (3411)cm^{-1} while appearance of C=N absorption band in the IR spectra of the products at(1641-1650) cm^{-1} see fig.(18-20). Beside UV spectra show the transitions $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ which confirmed the presence of the un-bonded pair electrons on Nitrogen, Oxygen atoms and aromatic system. (double bond). UV and IR absorbance spectra are given in Table(10). Minimize energy conformation of prepared compounds[5a-e] are given in (12-16).

Biological activity:

In this work, antimicrobial activity of the compounds [2a-e],[3a-e],[4] and [5a-e] were examined by the agar diffusion method using four different bacterial species i.e. *Escherichia coli, Staphylococcus aureus, Salmonella typhi* and *Pseudomonas aeruginosa*. The results indicated that all the assayed compounds showed activity against the tested organism up to 3.2 mg/disc.The prepared compounds [2a-e], [3a-e],[4] and [5a-e] showed higher activity towards *Staph. aureus* and *E. coli* compared with the other germs. The hydrazones [2a-e] were more active than 1,3,4-Oxadiazoles[3a-e].The Antibacterial activity of synthesized compounds are given in Table (6).



Scheme (1)

Table(1) physical properties of 2-phenyl acetic acid hydrazide [1].

Compd. No.	Molecular Formula	Color	M.P °C	Yield%	Rf	Recr. Solvent
1	$C_8H_{10}N_2O$	White	182	72	0.78	Ethanol

Table(2) physical properties of hydrazone derivatives [2a-e].

Compd. No.	R	Molecular Formula	Color	M.P ^{o}C	Yield %	Rf	Recr. Solvent
2a	4-Cl	$C_{15}H_{13}N_2OCl$	White Yellow	210-212	74	0.62	Ethanol
2b	3-NO_2	$C_{15}H_{13}N_3O_3$	Yellow	280-282	72	o.56	Ethanol
2c	4-NO_2	$C_{15}H_{13}N_3O_3$	Yellow	264-266	70	o.60	Ethanol
2d	4-$N(CH_3)_2$	$C_{17}H_{19}N_3O$	Brown	192-194	68	o.65	Ethanol
2e	3-OH, 4-OCH_3	$C_{16}H_{16}N_2O_3$	Yellow	Gum	73	o.64	Ethanol

Table(3) physical properties of 1,3,4- Oxadiazole derivatives [3a-e]

Compd. No.	R	Molecular Formula	Color	M.P ^{o}C	Yield %	Rf	Recr. Solvent
3a	4-Cl	$C_{15}H_{11}N_2OCl$	Brown	132-134	75	0.82	Ethanol
3b	3-NO_2	$C_{15}H_{11}N_3O_3$	Brown	140-142	62	0.76	Ethanol
3c	4-NO_2	$C_{15}H_{11}N_3O_3$	Light Brown	225-227	85	0.73	Ethanol
3d	4-$N(CH_3)_2$	$C_{17}H_{17}N_3O$	Brown	150-152	60	0.70	Ethanol
3e	3-OH , 4-OCH3	$C_{16}H_{14}N_2O_3$	Light Brown	240-242	72	0.75	Ethanol

Table(4) physical properties of 3,5-dibenzyl 4-amino 1,2,4-Triazole[4].

Compd. No.	Molecular Formula	Color	M.P ^{o}C	Yield%	Rf	Recr. Solvent
4	$C_{16}H_{16}N_4$	Gray	220	75	0.82	Ethanol

Table(5) physical properties of 3,5-dibenzyl 4-arylmethelenimino -(4H)1,2,4-Triazole derivatives [5a-e]

Compd. No.	R	Molecular Formula	Color	M.P °C	Yield%	Rf	Recr. Solvent
5a	H	$C_{23}H_{20}N_4$	Dusty	265Dec.	72	0.75	Ethanol
5b	4-Br	$C_{23}H_{19}N_4Br$	Yellow	140-142	62	0.76	Ethanol
5c	4-OH	$C_{23}H_{20}N_4O$	White	144-146	75	0.73	Ethanol
5d	4-$N(CH_3)_2$	$C_{25}H_{25}N_5$	Yellow	240Dec.	60	0.70	Ethanol
5e	4-Cl	$C_{23}H_{19}N_4Cl$	Yellow	200-202	70	0.75	Ethanol

Table (6): Antibacterial activity of synthesized compounds[2a-e],[3a-e],[4],[5a-e] .

Comp. No.	*Staph. Aureus*	*E.Coli*	*Sal. Typhi*	*Ps .Aeruginosa*
2a	++	++	+	-
2b	+	+	+	+
2c	++	++	+	-
2d	±	+	±	-
2e	+	+	-	-
3a	+	+	-	+
3b	+	++	-	±
3c	±	-	-	+
3d	-	+	+	-
3e	+-	-	±	-
4	+	-	+	-
5a	++	+	+	-
5b	++	+	+	-
5c	±	-	+	±
5d	-	±	-	+
5e	±	±	-	±

Notes (-) = no inhibition, (+)=5-10 mm, (+ +) = 15-20 mm and (+ + +)= more than 20 mm

Table (7): UV-Vis (nm) and Infra-red absorption(cm^{-1}) of hydrazone derivatives [2a-e].

Comp. No.	R	UV(nm), EtOH, λmax1 λmax2	IR,(KBr)cm^{-1}			
			ν NH δ NH	ν C=N	ν C=O	Others
2a	4- Cl	225 292	3250 1530	1650	1670	δ C-H Ar., p-sub. 820, ν CCl 970
2b	3-NO_2	230 310	3240 1540	1655	1675	δ C-H Ar., p-sub. 804 , ν NO2(as., s.) 1520,1320
2c	4-NO_2	210 315	3300 1535	1650	1660	δ C-H Ar., p-sub. 806 ν NO2(as., s.) 1530,1310
2d	4-$N(CH_3)_2$	240 340	3200 1525	1656	1680	δ C-H Ar., p-sub. 806 , νCH_3(as.,s.) 2974,2896
2e	3-OH, 4-OCH_3	228 350	3210 1530	1660	1670	ν C-H Ar., p-sub. 829 ν OH, 3398 νCH_3(as.,s.) 2958,2878

Table (8): UV-Vis (nm) and Infra-red absorption (cm^{-1}) of 1,3,4- Oxadiazole derivatives [3a-e]

Comp. No.	R	UV (nm), EtOH , λmax_1 λmax_2	IR,(KBr)cm^{-1}			
			ν C=N ν C-N	ν COC as./s.	ν N-N	Others
3a	4- Cl	225 280	1640 1310	1240 1050	1080	δ C-H Ar., p-sub. 820, ν CCl 964
3b	3-NO_2	216 300	1681 1321	1250 1087	1060	δ C-H Ar., p-sub. 811 , ν NO2(as., s.) 1515,1301
3c	4-NO_2	205 305	1666 1323	1245 10 40	1070	δ C-H Ar., p-sub. 824 ν NO2(as., s.) 1540,1310
3d	4-$N(CH_3)_2$	215 300	1660 1320	1250 1070	1060	δ C-H Ar., p-sub. 840 , νCH_3(as.,s.) 2980,2890
3e	3-OH, 4-OCH_3	220 290	1672 1310	1267 1070	1054	ν C-H Ar., p-sub. 862, νOH3200νCH_3(as.,s.) 2940,2846

Table (9): UV/Vis (nm) and Infra-red absorption (cm^{-1}) of 3,5-dibenzyl 4-amino 1,2,4-Triazole [4].

Comp. No.	UV (nm), EtOH , λmax1 λmax2	/IR,(KBr)cm^{-1}			
		νNH_2 as./s.	νC-H arom.	νC=N	Others
4	230 270	3411 3199	3031	1649	νN-N 1157 ν CH_2(as.,s.) 2921, 2850

Table (10): UV-Vis (nm) and Infra-red absorption (cm^{-1}) of 3,5-dibenzyl 4-amino 1,2,4-Triazole derivatives [5a-e].

Comp. No.	R	UV (nm), EtOH , λmax1 λmax2	IR,(KBr)cm^{-1}		
			νC=N	νCH_2 as./s.	Others
5a	H	220 350	1641	2929 2854	δ C-H Ar., p-sub. 808
5b	4-Br	230 330	1646	2975 2840	δ C-H Ar., p-sub. 804 , ν CBr 1016
5c	4-OH	235 310	1643	2981 2848	δ C-H Ar., p-sub. 808 ν OH, 3431,
5d	4-$N(CH_3)_2$	224 340	1641	2929 2875	δ C-H Ar., p-sub. 810 , ν CH_3(as.,s.) 2993,2875
5e	4-Cl	225 260	1650	2935 2856	δ C-H Ar., p-sub. 811, ν CCl 970

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Appendix: Minimize energy conformation of some prepared compounds.

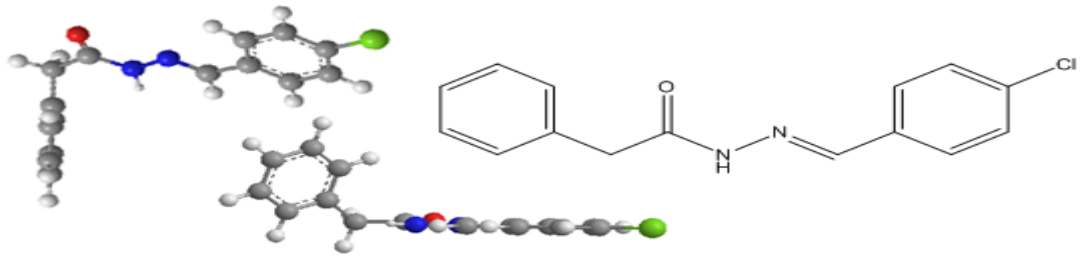

Fig. (1): Minimize energy conformation of compound [2a].

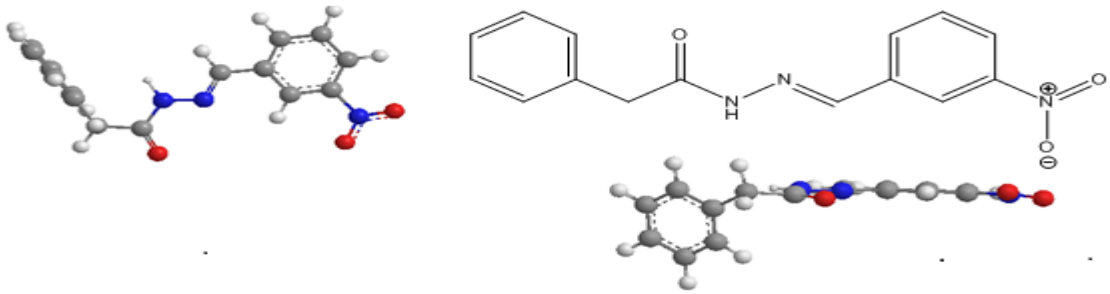

Fig. (2):Minimize energy conformation of compound [2b].

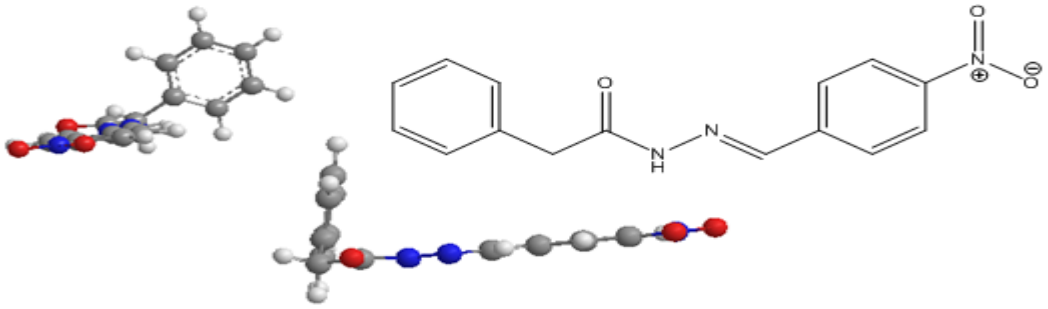

Fig. (3):Minimize energy conformation of compound [2c].

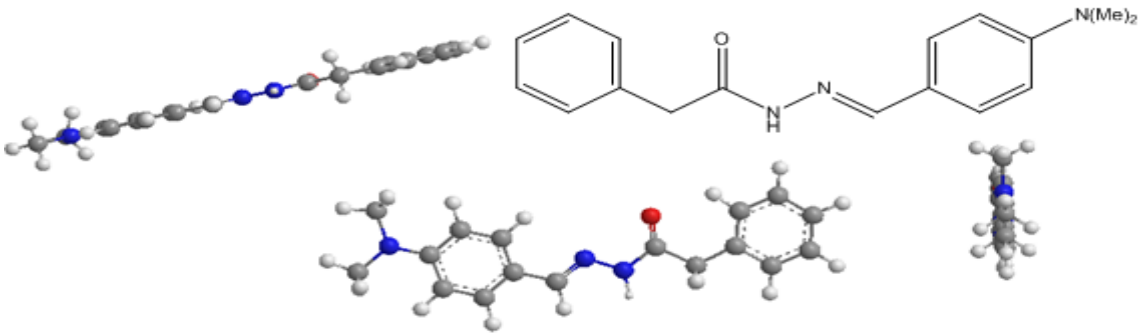

Fig. (4):Minimize energy conformation of compound [2d].

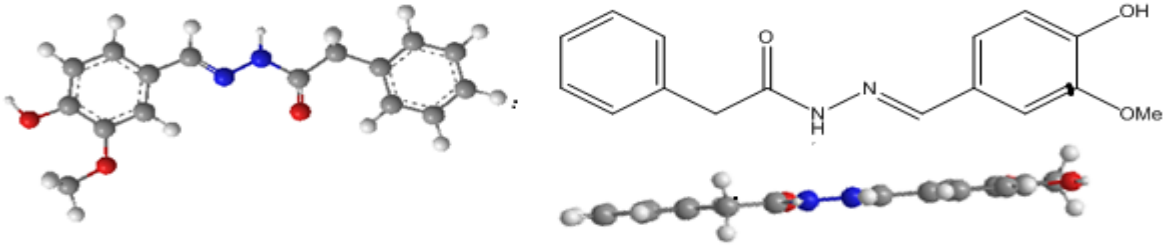

Fig. (5): Minimize energy conformation of compound [2e]

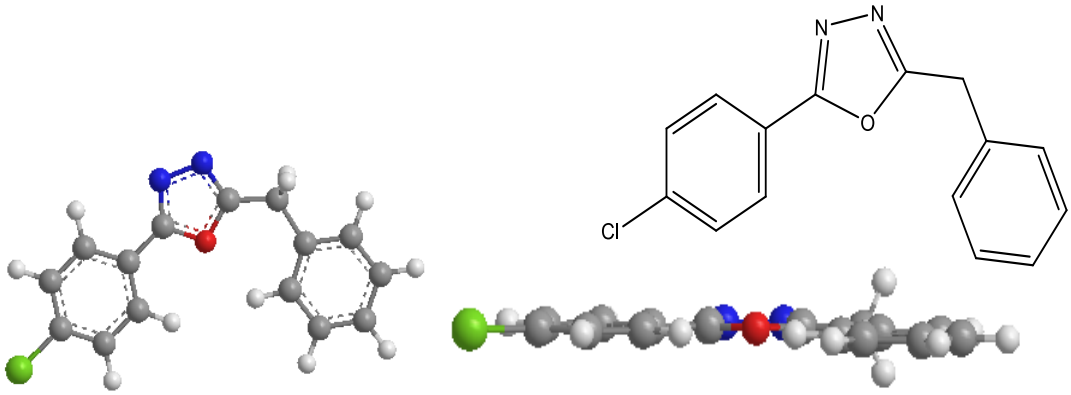

Fig. (6):Minimize energy conformation of compound [3a].

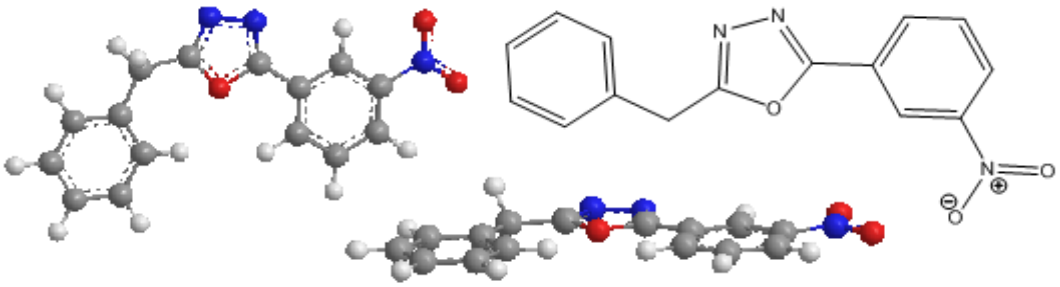

Fig. (7):Minimize energy conformation of compound [3b].

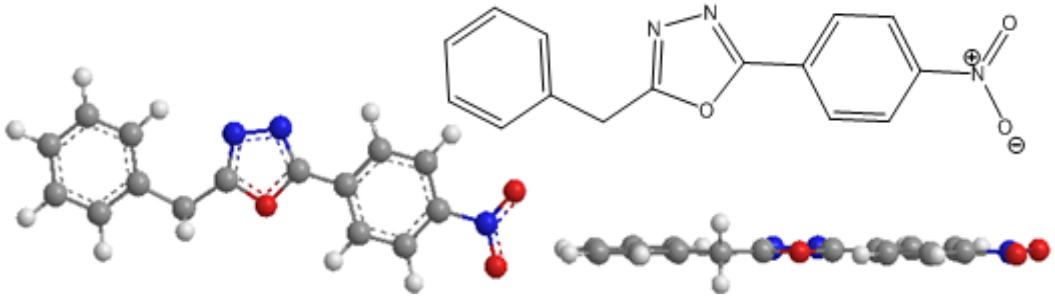

Fig. (8):Minimize energy conformation of compound [3c].

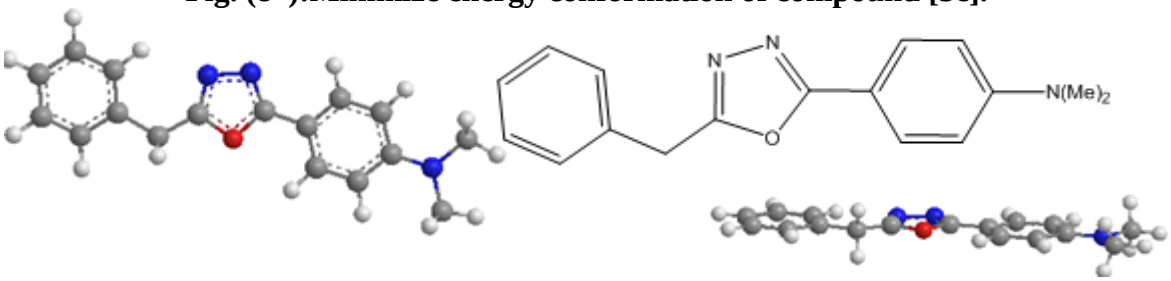

Fig. (9):Minimize energy conformation of compound [3d].

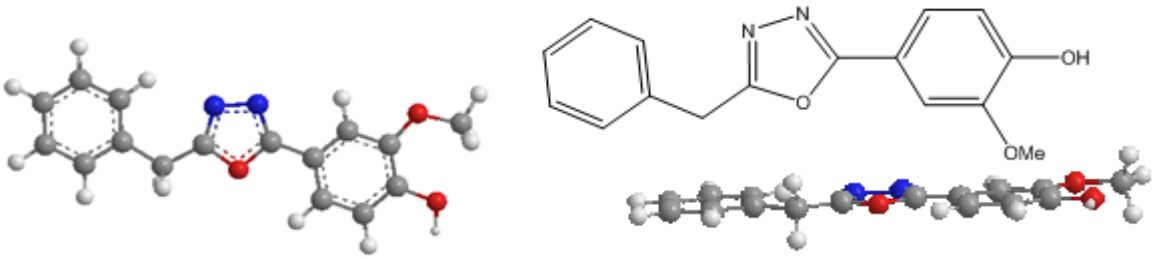

Fig. (10):Minimize energy conformation of compound [3e].

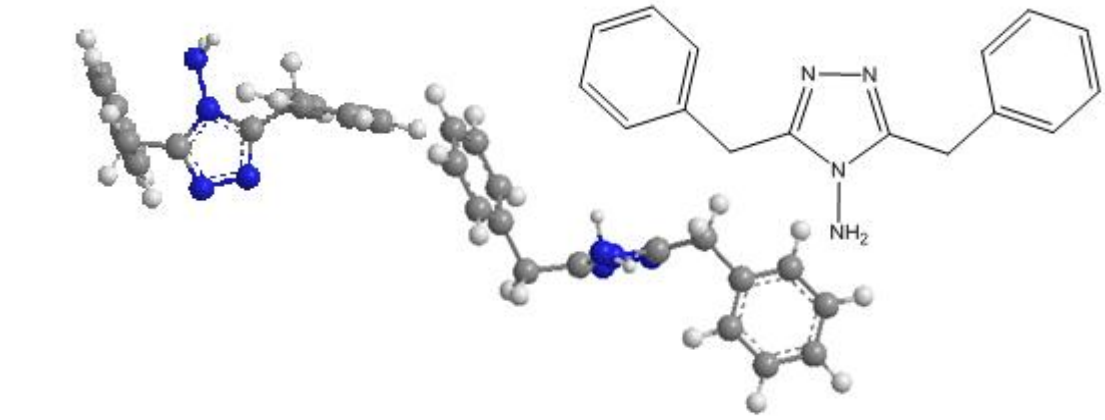

Fig. (11):Minimize energy conformation of compound [4].

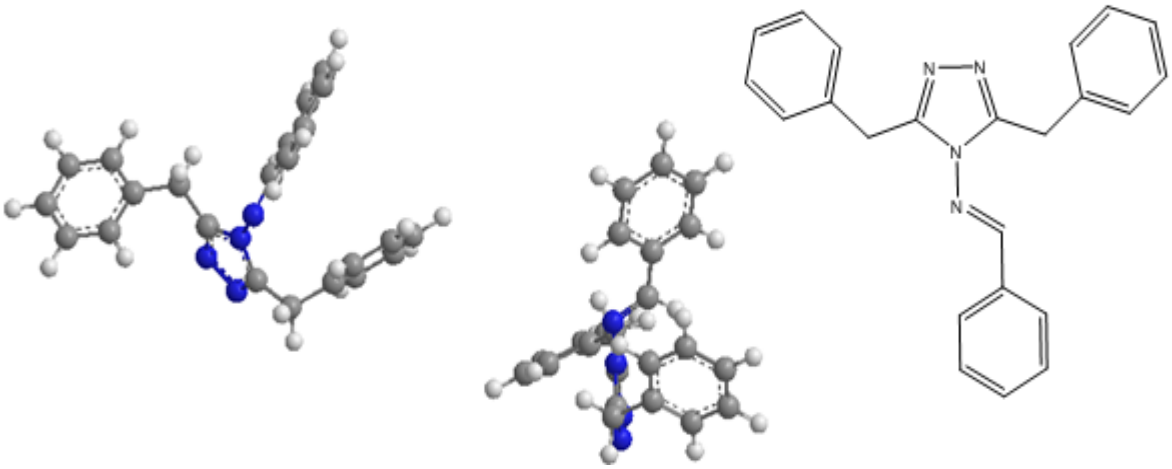

Fig. (12):Minimize energy conformation of compound [5a].

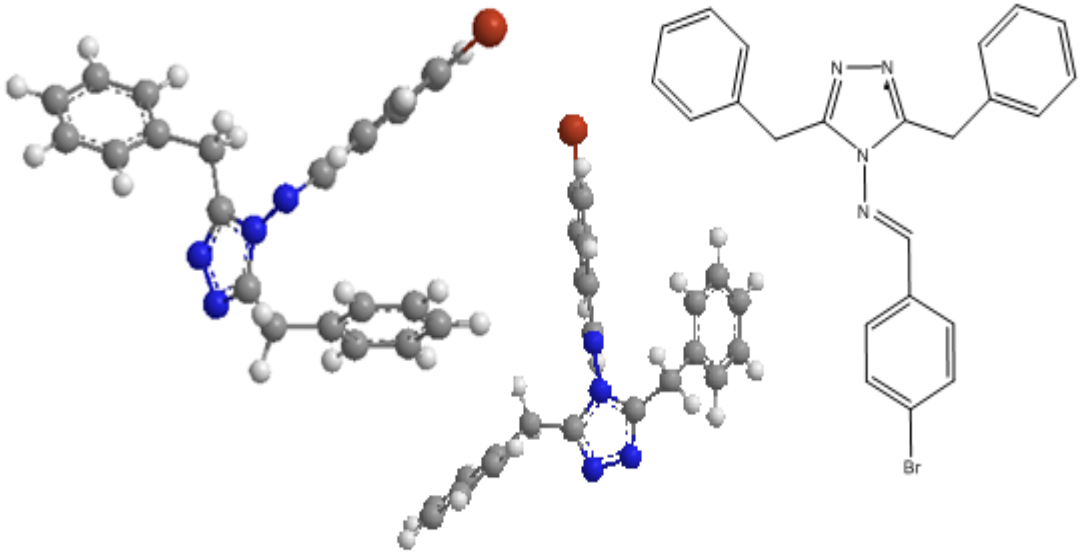

Fig. (13):Minimize energy conformation of compound [5b].

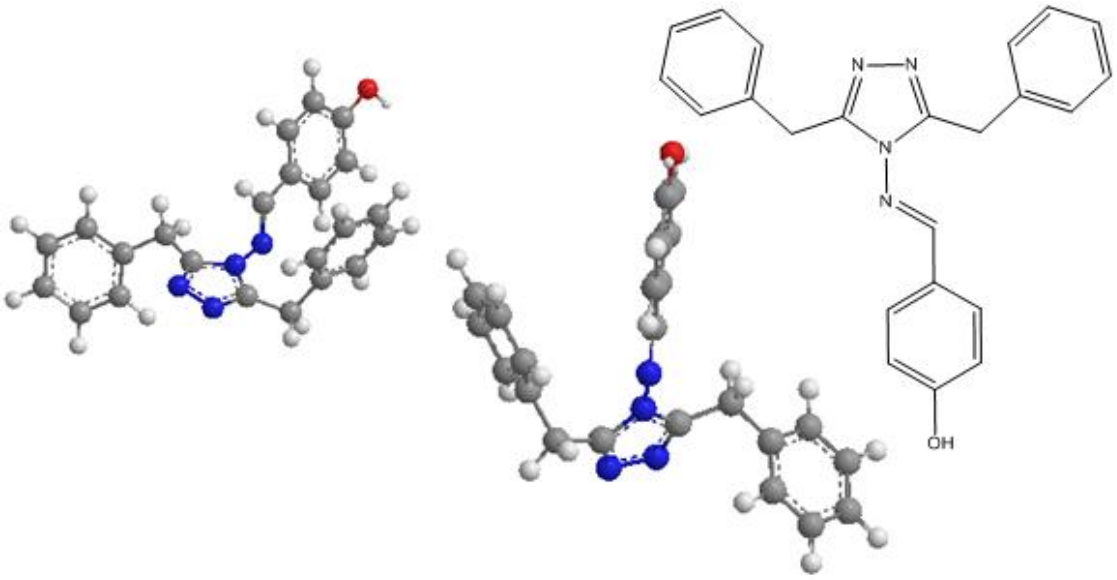

Fig. (14):Minimize energy conformation of compound [5c].

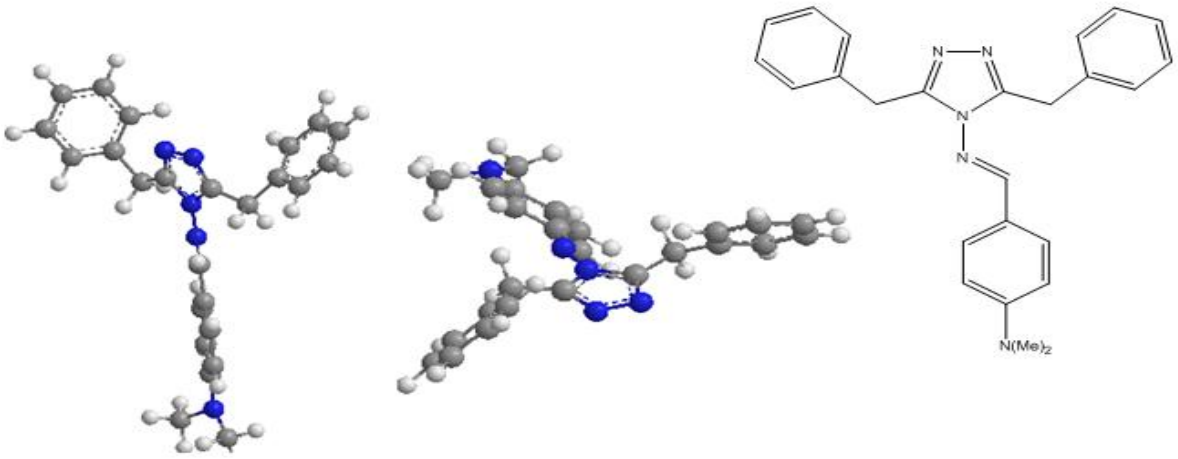

Fig. (15):Minimize energy conformation of compound [5d].

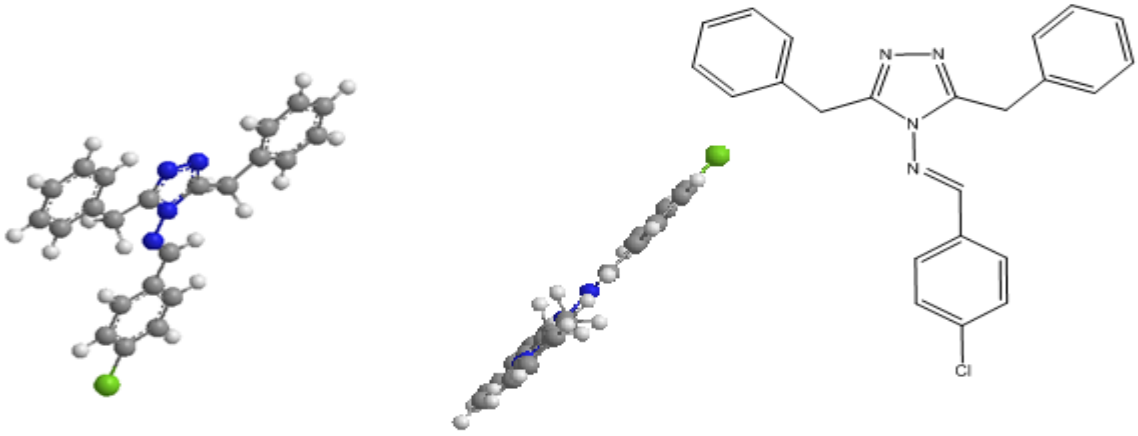

Fig. (16):Minimize energy conformation of compound [5e].

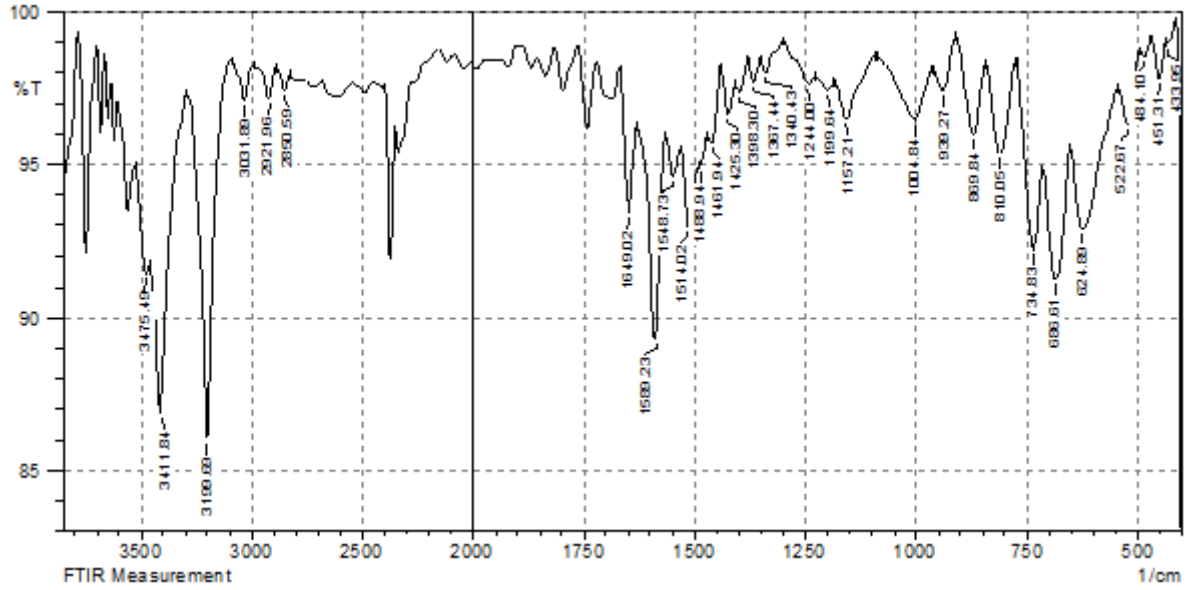

Fig.(1 7): IR spectrum of the compound [4].

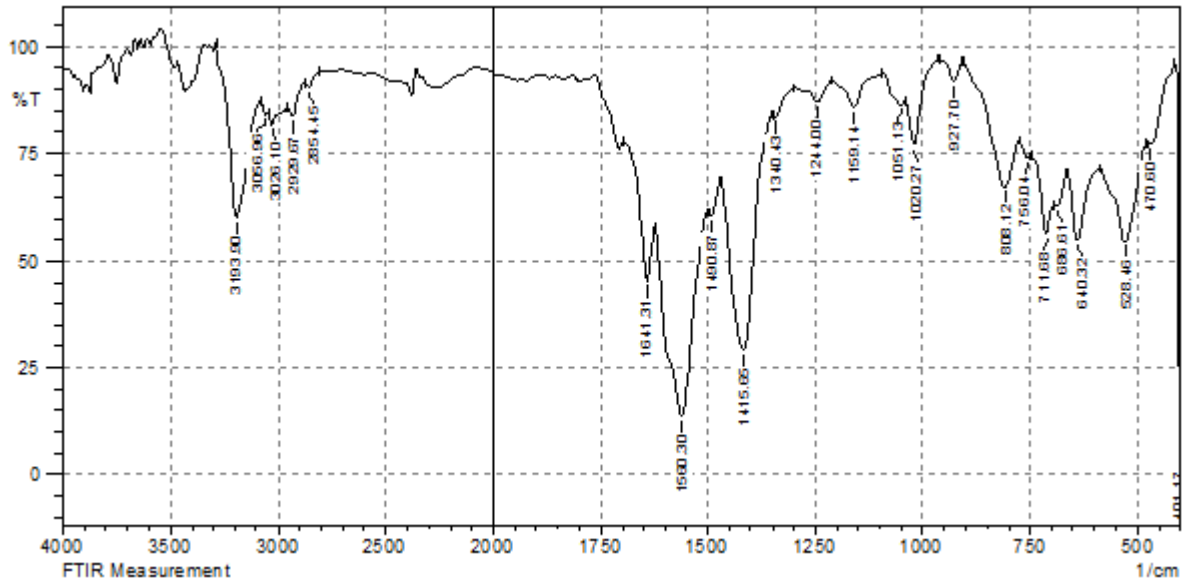

Fig.(18): IR spectrum of the compound [5a].

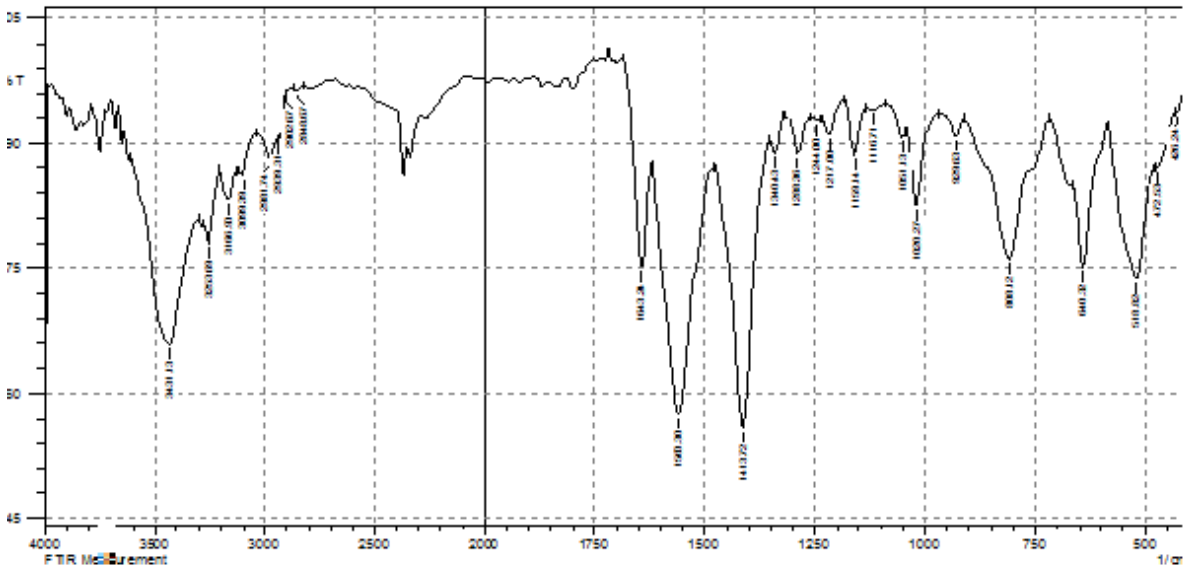

Fig.(19): IR spectrum of the compound [5c].

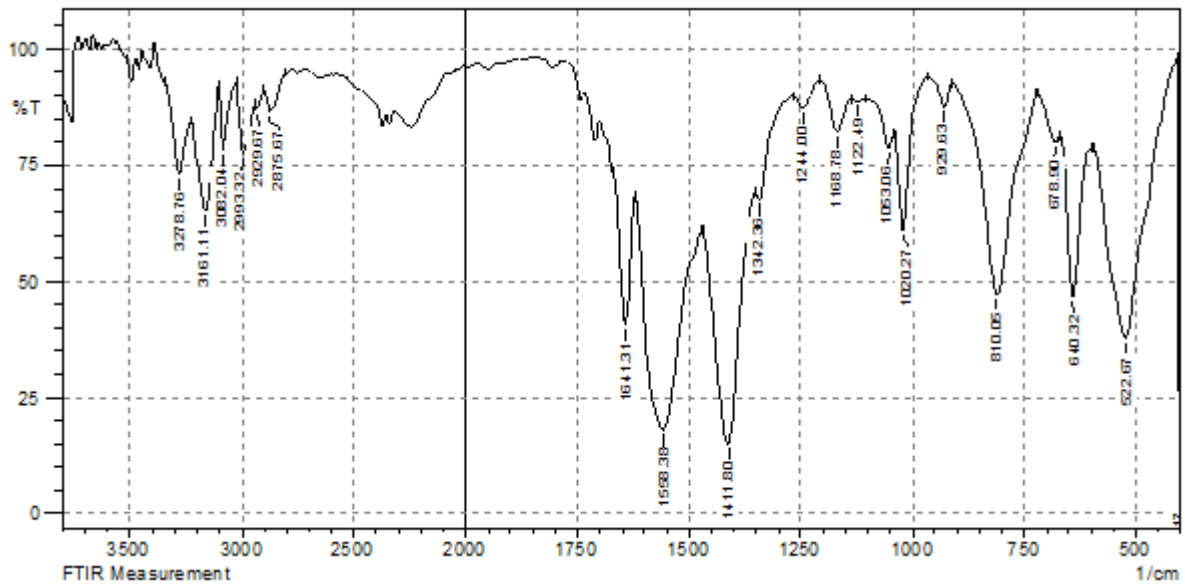

Fig.(20): IR spectrum of the compound [5d].