Synthesis and Characterization of Some New heterocyclic derivatives and Study Their antibacterial activity.

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Key words : hydrazide**,** pyrazol**,** phthalazin**,** pyridazin**,** oxazole**,** thiazol
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Abstract:

This work includes preparation of different types of heterocyclic compounds. These compounds including pyrazol**,** phthalazin**,** pyridazin**,** oxazole**,** thiazol. Thestructures of these compounds were identified by FT-IR,H-NMR,Uv spectroscopy and checked by TLC and study the anti-bacterial activities for some of the synthesized compounds. These activities were determined in vitro using well diffusion method against three types pathogenic strains bacteria staphylococcus aureus(G+), E.coli and proteus vulgaris(G-). The results revealed that some of these compounds showed measurable activity.

تحضير وتشخيص مشتقات حلقية غير متجانسة جديدة ودراسة فعاليتها المضادة للبكتريا.

ابتسام خليفه جاسم*وغزوان حسن عبد الوهاب الصميدعي** وسارة سلام خليل الشجيري**
*قسم الكيمياء كلية التربية للعلوم الصرفة \ ابن الهيثم \ جامعة بغداد \ بغداد \ العراق.
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مفتاح الكلمات : هيدرازايد,بيرازول ، فثالازين ، بيردازين ، أوكسازول و ثايوزول.

الملخص:

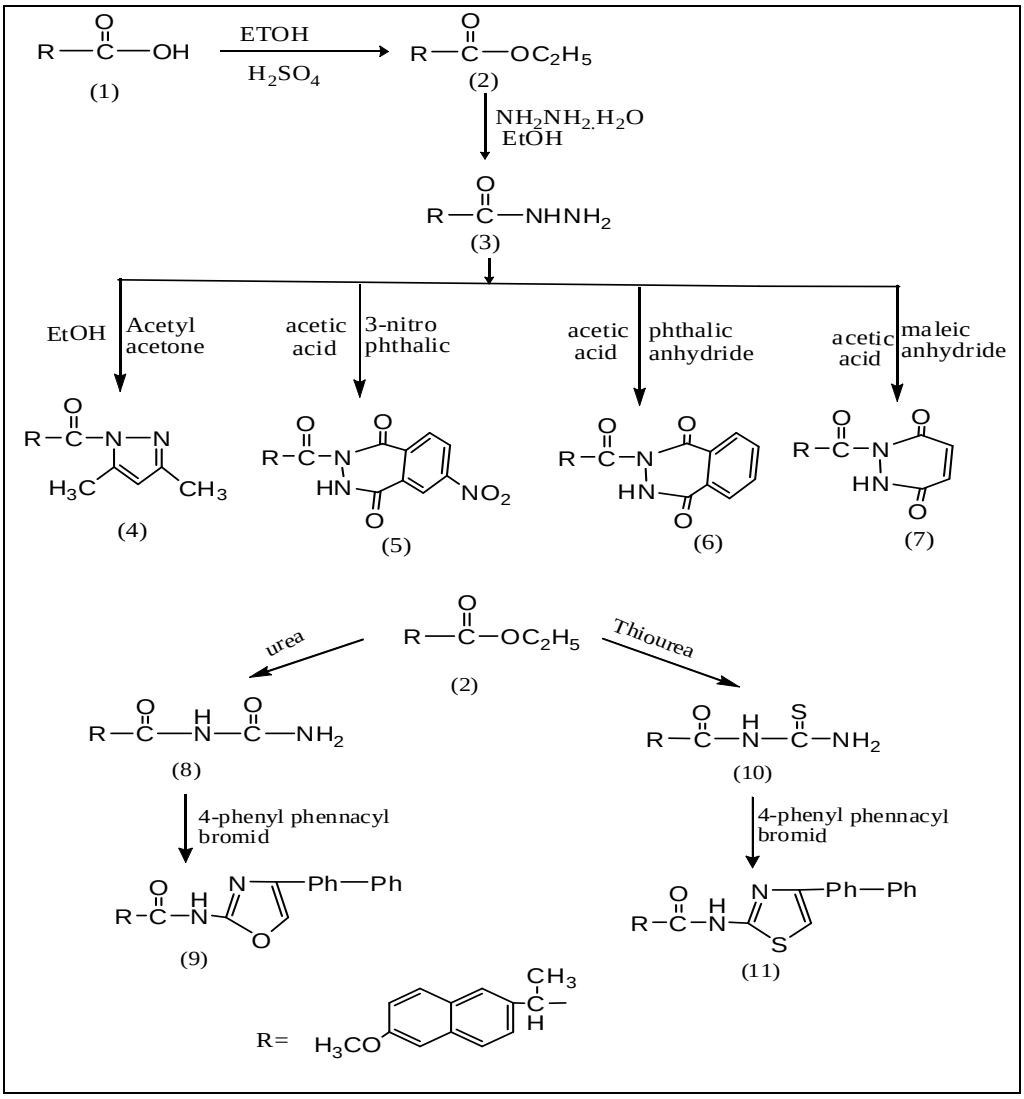
يتضمن هذا البحث تحضير أنواع مختلفة من المركبات الحلقية غير المتجانسة وهذه المركبات تتضمن بايروزول ، فثالازين ، بايرادازين ، أكسوزول و ثايوزول وتم تشخيص تراكيب المركبات المحضرة عن طريق أطياف الأشعة تحت الحمراء والرنين النووي المغناطيسي للبروتون والأشعة فوق البنفسجية، ودراسة الفعالية المضادة للبكتريا لبعض المركبات المحضرة ، تم تحديد هذه الأنشطة في المختبر بأستخدام طريقة الأنتشار بشكل جيد ضد ثلاث أنواع سلالات مرضية بكتريا االمكورات العنقودية الذهبية (G+)، القولونية والمتقلبة الأعتيادية (G-). اوضحت النتائج بان بعض هذه المركبات قد أظهرت فعالية جيدة ضد هذه البكتريا.

Introduction:

A heterocyclic compound is one which possesses a cyclic structure with at least two different of hetero atoms in the ring. Nitrogen , Oxygen and Sulphur are the most common heteroatoms. Heterocyclic compounds are very widely distributed in nature and essential to life in various ways. Most of the sugars and their derivatives, including vitamin C, for instance, exist in the form of five-membered (Furan) or six-membered (Pyran) rings containing one oxygen atom . Most members of vitamin B group possess heterocyclic ring containing nitrogen. One example is vitamin B6 (Pyridoxine), which is a derivative of Pyridine, essential in amino acid metabolism[(1)].

Pyridazine ring is a part of the structures of a number of drugs available in the market[(2)] like hydralazine, minaprine, cefozopran, pipofezine, etc. Pyridazine derivatives have been reported to possess various pharmacological activities including antibacterial [(3-6)] ntifungal [(4-6)] anti-tubercular [(7-9)] anticonvulsant [(9-11)] anhiypertensive[(12)] , analgesic and anti-inflammatory [(13,14)].

Similarly, pyrazole (five-membered nitrogen containing heterocyclic ring) derivatives also show potential biological activities including antimicrobial actions [15,16].



Experimental part:

1- Melting points are recorded using hot stage Gallen Kamp melting point apparatus and were uncorrected.

2- Infrared spectra are recorded using Fourier Transform infrared *SHIMADZU* (8300) (F.T.IR) infrared spectrophotometer, KBr disc or thin film was performed by Chemistry Department, Baghdad University and using Fourier Transform infrared *SHIMADZU* (8400) (F.T.IR) infrared spectrophotometer, KBr disc was performed by Al-Mustansryia Univrsity.

3- Thin layer chromatography (TLC) was carried out using Fertigfollen precoated sheets type polygram Silg, and the plates were developed with iodine vapour.

4- UV/vis spectra were recorded on Foruier Transform Varian spectrometer in Bahgdad University college of Education Ibn-Al-Haitham of pure science .

5- ^{1}H-NMR spectra were recorded on Foruier Transform Varian spectrometer, operating at 300 MHz with tetramethylsilane as internal standard in DMSO-d6; Measurements were made at Chemistry Department, in Iran.

7- Biological activity was studied at Biology department, Baghdad University.

8- Mass spectroscopy GC/Ms. These measurements were recorded by using GC/Ms – Qp 2010 Ulta shimadzu 24 in Al- Mustansyria University.

Some of the chemicals used are from (Fluka ,BDHm Aldrich ,Merck) and used directly without purification .

Synthesis:

1- Synthesis of Ethyl-2-(6-methoxy naphthalen-2-yl) propanoate [2] [17]:

For Compound [2]: treating (0.0092 mole, 15.248g) of 2-(6-methoxy naphthalen-2-yl) propanoic acid [1] with (20 ml) absolute ethanol, (3ml) sulfuric acid then refluxing the mixture for 3 hours . The mixture was cold and recrystallized from ethanol.

2- Synthesis of 2-(6-methoxy naphthalen-2 yl) propanehydrazide [3] [18][19] :

Compound [3] was synthesized by the addition of the hydrazine hydrate (10ml) to (0.01 mole, 3g) from compound [2] in (15ml) of absolute ethanol then the mixture was refluxed for 4 hours. After cooling, the product was filtered off and recrystallized by using ethanol .

3- Synthesis of 1-(3,5-dimethyl-1H-pyrazol-1-yl)-2-(6-methoxy naphthalen-2-yl) propan-1-one [4] [20]:

A mixture of compound [3] (0.00123mol, 0.3g) and acetylacetone (0.002 mol, 0.23 ml) in absolute ethanol (20) ml was heated at reflux temperature for 10 hours. The reaction mixture was cooled and the formed precipitate was filtered off to give the titled compound [4].

4- Synthesis of 2-(2-(6-methoxy naphthalen -2-yl)propanoyl)-6-nitro-2,3-dihydrophthalazine-1,4-dione [5] [21]:

Compound [3] (0.003 mole, 0.8g) was mixed with 3-nitro phthalic anhydride (0.003 mole, 0.63g) in acetic acid (15ml), the mixture was refluxed for 3 hours then cooled and added to crushed ice. The precipitate was filtered off, washed with water to give the final product.

5- **Synthesis of 2-(2-(6-methoxy naphthalen -2-yl)propanoyl)-2,3dihydrophthalazine-1,4-dione [6] [21]:**

Compound [3] (0.0004 mole, 0.2g) was mixed with phthalic anhydride (0.0008 mole, 0.12g) in acetic acid (20ml), the mixture was refluxed for 10 hours then cooled and added to crushed ice. The precipitate was filtered off, washed with water to give the final product.

6- Synthesis of 1-(2-(6-methoxy naphthalen -2-yl)propanoyl) -1-2-dihydropyridazine-3,6-dione [7] [21]:

Compound [3] (0.003mole, 0.7g) was mixed with maleic anhydride (0.0009 mole, 0.3 g) in acetic acid (15ml), the mixture was refluxed for 10 hours then cooled and added to crushed ice. The precipitate was filtered off, washed with water to give the final product.

7- Synthesis of N-(carbamoyl-2-(6-methoxy naphthalen -2-yl) propanamide [8], N-(thiocarbamoyl-2-(6-methoxy naphthalen -2-yl) propanamide [10] [22]:

A mixture of ester [2] (0.0009mol,0.24g) in absolute ethanol (20ml), urea (0.009mol, 0.56g) was added. The mixture was refluxed for 6hours. After cooling and filtering the product was re crystallized.

8- Synthesis of N-[4-(biphenyl-4yl) oxazole -2-yl)-2-(6-methoxy naphthalen -2-yl)propanamide[9], N-[4-(biphenyl-4yl)thiazol-2-yl)-2-(6-methoxy naphthalen -2-yl)propanamide[11] [22]:

A mixture of compound [8] (0.0037mol, 0.1g) or compound (10) was treated respectively with absolute ethanol (20ml) then ***p***-phenyl phenacyl bromide (0.0036mol, 0.1g) was added. The mixture was refluxed for 7 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water, and petroleum ether (80-100) was used for recrystallization.

Results and Discussion:

1- Characterization of ethyl 2-(6-methoxy naphthalen-2-yl) propanoate [2]:

Ethyl 2-(6-methoxynaphalen-2-yl) propanoate [2] prepared by reacting of 2-(6-methoxy naphthalene -2-yl) propanoic acid with absolute ethanol in presence of conc.,H_2SO_4.

The FTIR spectrum in figure (1), shows the disappearance of the (O-H) hydroxyl band group, yaeid of 2-(6-methoxy naphthalene-2-yl) catalyst con acid at (3000) cm^{-1} and appearance of bands at (1633) cm^{-1} due to carbonyl ester group.

The Uv/Vis Spectrum, figure (2) gave absorption bands at different wave lengths (332, 286) nm due to ($n\rightarrow\pi^*$) and ($\pi\rightarrow\pi^*$) transitions.

^{1}H-NMR spectrum of compound (2), figure (3), shows the following characteristic chemical shifts (DMSO-d6, ppm): the aromatic ring protons appeared as multiples signals at δ (7.12 - 7.79) ppm, signals at δ (4.04) ppm due to the (-CH_2-) group, Singlet signal at (3.88) ppm due to the (OCH_3) group, signals at δ1.45,and δ1.10ppm (6H) that could be assigned to two (CH_3) protons and δ(2.48) ppm for DMSO.

2- Characterization of 2-(6-methoxy naphthalene-2-yl) propane hydrazide [3]:

The acid hydrazide was synthesized by the reaction of ester [2] with hydrazine hydrate in absolute ethanol. The reaction of hydrazine hydrate with ester is one of the most common reactions to synthesize the acid hydrazide derivatives; it is a tetrahedral nucleophilic substitution reaction[23] .

The FTIR spectrum in figure (4) for hydrazide derivatives [3] shows the appearance of the characteristic absorption bands in the regions (3207-3304) cm^{-1} due to asymmetric and symmetric stretching vibration of the (NH-NH_2) group, the FT-IR spectrum also shows the appearance of absorption band in the region (1633) cm^{-1} due to the stretching vibration of the amide carbonyl group, while a new band appeared at (1606) cm^{-1}due to the stretching vibration of amide bending vibration band at (1460-1523) respectively.

^{1}H-NMR spectrum (in DMSO as a solvent) of acid hydrazide [3], figure (5), showed a signal at δ (9.22) ppm(1H) due to NH proton, many signals at δ (7.10 - 7.76) ppm that could be attributed to the six aromatic protons and exhibited a sharp singlet at δ (3.83) ppm for three protons of OCH_3 group.

3- Characterization of 1-(3,5-dimethyl-1H-pyrazol-1-yl)-2-(6-methoxy naphthalene -2-yl) propan-1-one [4] :

The pyrazol derivative was prepared through the reaction of hydrazide derivative [3] with acetyl acetone.

The FTIR spectrum of compound [4] in figure (6), shows the disappearance of υ NH_2 and υ NH bands in the region (3331-3230) cm^{-1}, aromatic υC-H band at (3095) cm^{-1} and υC=O band at (1627) $cm^{-1}$of the keto form in addition to the ring υ C=N at (1604) cm^{-1}.

4- Characterization of phthalazine and pyridazine [5,6,7] :

Compounds [5,6,7] were synthesized from the reaction of compound [3] with 3-nitro phthalic anhydride, phthalic anhydride and maleic anhydride respectively in the presence of acetic acid as a solvent and catalyst.

The FT-IR spectrum of compound [5] indicated the appearance of υN-H band at (3390) cm^{-1} and the (m-NO_2) substituted out of plane at (856) cm^{-1}, figure (7) shows the FTIR spectrum of compound [5].

The FT-IR spectrum of compound [6] in figure (10) shows the appearance of the two bands of NH group in the region (3151) cm^{-1} and appearance of a band due to aromatic υ(C-H) group at the range (3009) cm^{-1}. Two carbonyl groups of compound [6] appeared at (1656) cm^{-1} and at (1599) cm^{-1} for the amide carbonyl.

The FT-IR spectrum of compound [7] showed in figure (11) indicated the disappearance of N-H band at (3228) cm^{-1} and carbonyl group at (1728) cm^{-1}.

^{1}H-NMR spectrum of compound [7] many signals at δ (7.12-7.80) to the aromatic protons. A sharp singlet at δ 3.97 ppm due to three protons of (O-CH_3) group. a singlet at δ 3.35 ppm (1H) that could be attributed to one proton of (C-H) group. in figures (3-12).

5- Characterization of N-(carbamoyl-2-(6-methoxynaphalen-2-yl)propanamide [8] :

The refluxing ester with urea in absolute ethanol gave compound [8], The FT-IR spectrum showed a band at (3341) cm^{-1} due to υ(NH) group, other band at (1728) cm^{-1} for the υcarbonyl group and (1417-1502) cm^{-1} due to υ(C=C) stretching of aromatic system, figure (13).

6- Characterization of N-[4-(biphenyl-4yl)oxazol-2-yl)-2-(6-methoxy naphthalen-2-yl) propanamide [9] :

The reaction of compound [8] with ***p***-phenyl phenacyl bromide under refluxing condition affected on intermolecular cyclization through S_N2 mechanism giving the desired oxazole derivative [9].

The structure of oxazole derivative was confirmed by FT-IR spectrum showed a broad band of υ(N-H) at (3356-3443) cm^{-1}, carbonyl group at (1728) cm^{-1}, sharp absorption band at (1600) cm^{-1} due to υ (C=N) group , the aromatic (C=C) at (1454-1502) cm^{-1}, stretching band of (C-O-C) at (1176) cm^{-1}, and at (1502) cm^{-1} for δ (-NH). figure (15).

^{1}HNMR spectrum showed the following signals (in DMSO as a solvent) showed many signals in the region δ7.11-8.10 ppm due to ten aromatic protons and NH proton a singlet signal at δ5.01ppm (1H) due to (C-H) oxazole ring ,figure (16).

7- Characterization of N-(thiocarbamoyl-2-(6-methoxy naphthalen-2-yl) propanamide [10]:

The FT-IR spectrum showed a band at (3441) cm^{-1} which was assigned to the asymmetric and symmetric bands of (NH_2) and (NH) groups, at (1728) cm^{-1} for υ (C=O), at (1024) cm^{-1} for υ (C=S) and band at (3061) cm^{-1} which was due to υ (C-H) and band at (1419-1500) cm^{-1} due to υ (C=C) stretching of aromatic system, respectively, figure (17).

The Uv/vis. Spectrum of compound [10] Figure (18) showed the absorption bands at (280 nm and 332 nm) due to (π→π*) and (n→π*) transitions.

^{1}HNMR spectrum (in DMSO as a solvent) showed many signals at δ(7.11-7.78) belong to the aromatic protons figure (19B)

8- Characterization of N-[4-(biphenyl-4yl) thiazol-2-yl)-2-(6-methoxy naphthalen-2-yl) propanamide [11]:

The reaction of compound [10] with *p*-phenyl phenacyl bromide under refluxing condition affected on intermolecular cyclization through S_N2 mechanism giving the desired thiazole derivative [11].

The F.T.IR spectrum of compound [11] showed the appearance of carbonyl group (1728) cm^{-1} , Sharp absorption band at (1600)cm^{-1} due to υ(C=N), (3150) cm^{-1} due to υ(N-

H) cm^{-1} and the aromatic (C=C) at (1450) cm^{-1}, stretching band of υ (C-S-C) at (761) cm^{-1}, and band of δ (NH) at (1685) cm^{-1}as shown in figure (20).

9- Discussion of the biological activity:

The biological activity of compounds was determined by measuring the diameter of the empty region around the well (Inhibition zone).

1- Compounds [2,3,4,7,8,10 and 11] are moderately active against *E*.coli .
2- Compounds [2,3,7,8 and 10] are moderately active against *P*seudomonas.
3- compounds [4 and 11] are slightly active against *Pseudomonas*.
4- Compounds [3,7,10 and 11] are high effect against *Staphylococcus*.
5- Compounds [2,4 and 8] are moderately active against *Staphylococcus* .

The results of preliminary screening tests are listed in table (3)

Table (2-2): Physical properties of the synthesized compounds.

Comp. No.	Molecular formula	Molecular Weight (g/mole)	Yield (%)	M.P (ºC)	colour	Rf
1	$C_{14}H_{14}O_3$	230	-	-	white	-
2	$C_{16}H_{18}O_3$	258.31	75	81-82	white	0.93
3	$C_{14}H_{16}N_2O_2$	244.29	96	122-123	brown	o.90
4	$C_{19}H_{20}N_2O_2$	308.37	68	124-126	white	0.89
5	$C_{22}H_{17}N_3O_6$	419.11	79	68-69	yellow	0.94
6	$C_{22}H_{18}N_2O_4$	374.39	65	85-86	Pale brown	o.82
7	$C_{18}H_{16}N2O4$	324.33	67	91-92	white	0.90
8	$C_{15}H_{16}N_2O_3$	272.30	90	75-76	white	0.87
9	$C_{29}H_{24}N_2O_3$	448.51	93	71-73	Pale yellow	0.89
10	$C_{15}H_{16}N_2O_2S$	288.36	96	81-82	white	0.86
11	$C_{29}H_{24}N_2O_2S$	464.58	95	76-78	Pale yellow	0.87

Table (2) :The characteristic bands of compounds (2-11).

Comp. No.	UV, λmax ,nm, EtOH		IR, KBr, υ, cm^{-1}					
	(π →π*)	(n →π*)	(N-H) cm^-	(C-H) aromatic	(C-H) aliphatic	(C=O)	(C=C)	Others Bands
2	286	332	-	3061	2831-2982	1633	1450-1523	υ(C-O) 1033-1283

3	-	-	3207-3304	3059	2831-2955	1633	1460-1523	υ(C-N) 1365
4	-	-	3230-3331	3095	2837-2982	1627	1458-1504	υ(C=N) 1558
5	-	-	3390	3061	2841-2980	1728	1458-1502	-
6	-	-	3151	3009	2885-2958	1656	1440-1491	-
7	210-260	332	3228	3072	2885-2958	1728	1458-1502	-
8	-	-	3341	3061	2845-2982	1728	1417-1502	-
9	-	-	3356-3443	3057	2845-2982	1728	1454-1502	υ(C-O-C) 1176
10	280	332	3441	3061	2841-2982	1728	1419-1500	υ(C=S) 1024
11	-	-	3355	3055	2845-2982	1728	1450-1502	υ(C-S-C) 671

Table (3): Antibacterial activities for some of the prepared compounds.

Comp. No	Sample No. (In image)	E.coli (G-)	Pseudomonas (G-)	Staphylococcus (G+)
2	18	+ +	+ +	+ +
3	20	+ +	+ +	+ + +
4	22	+ +	+	+ +
7	26	+ +	+ +	+ + +
8	27	+ +	+ +	+ +
10	25	+ +	+ +	+ + +
11	28	+ +	+	+ + +

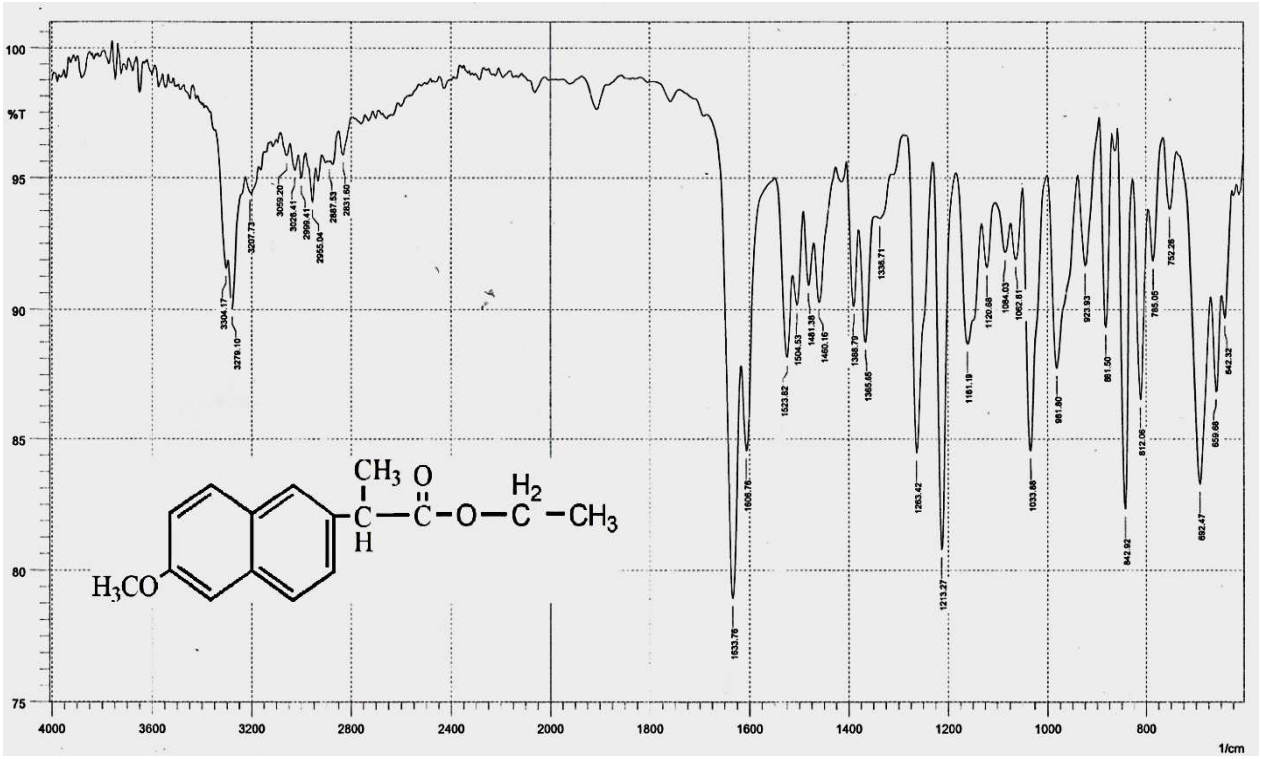


Figure (1): FT-IR spectrum of compound (2).

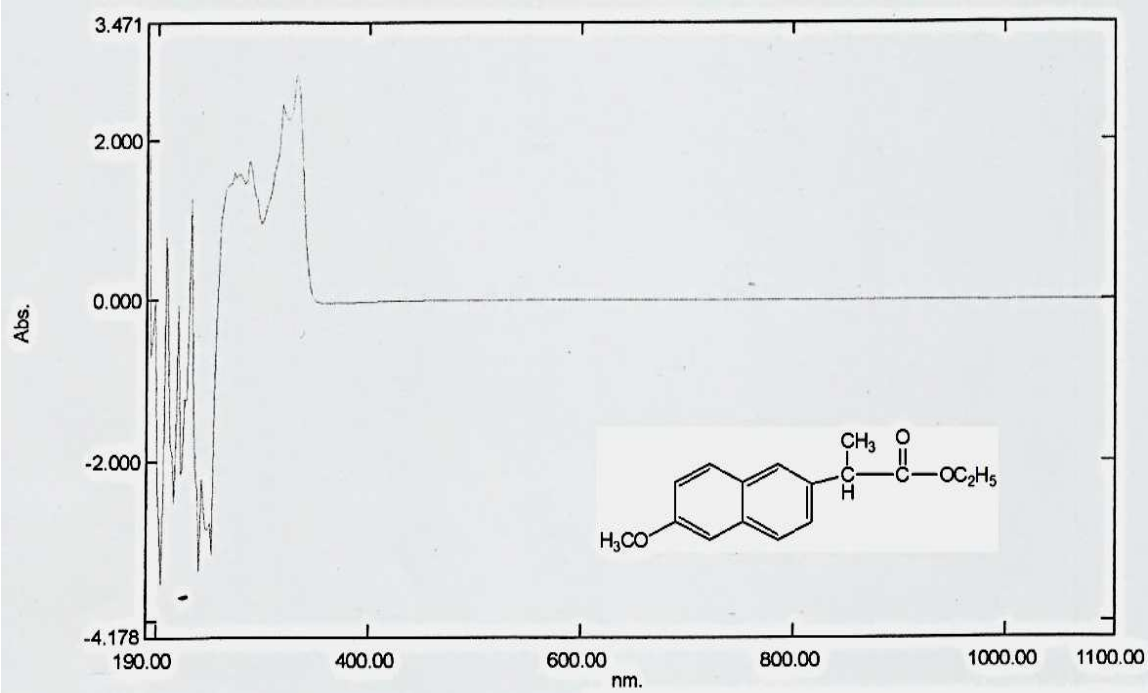


Figure (2): UV spectrum of compound (2).

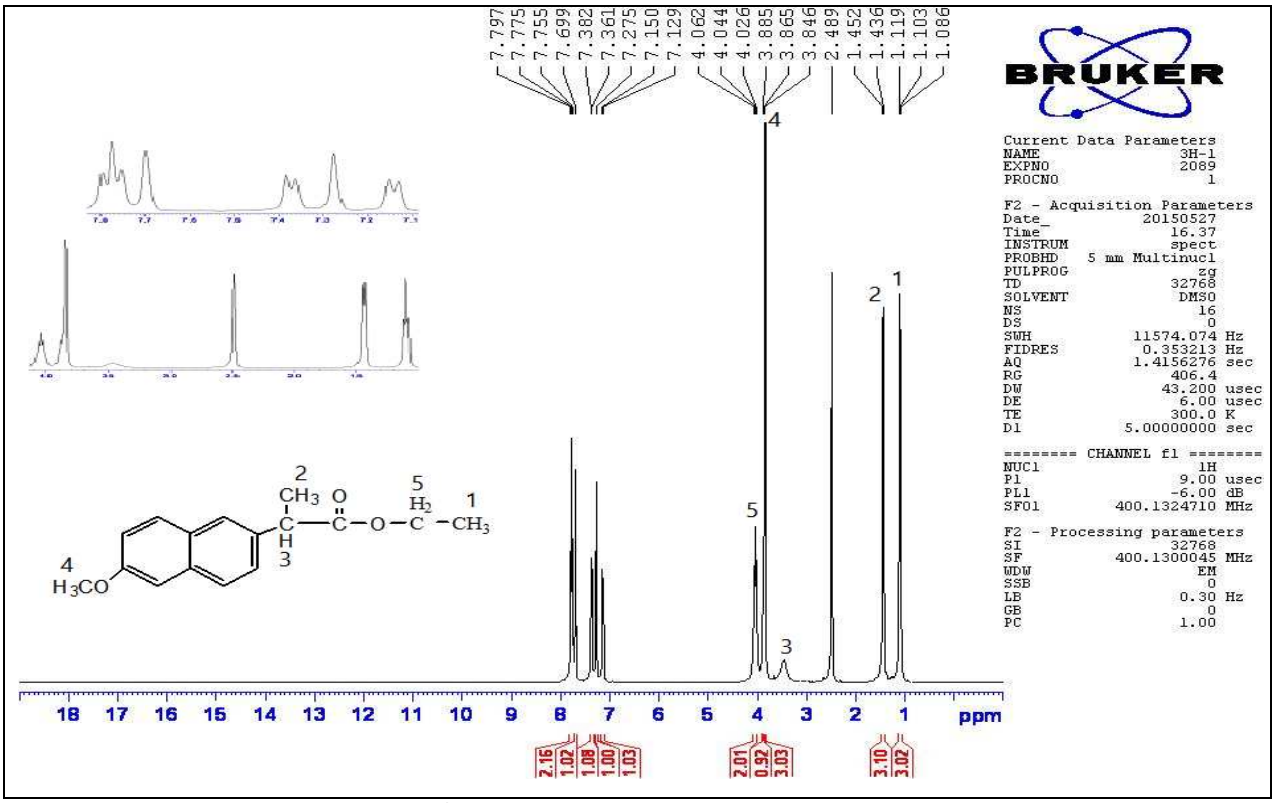


Figure (3) ^{1}H-NMR spectrum of compound (2).

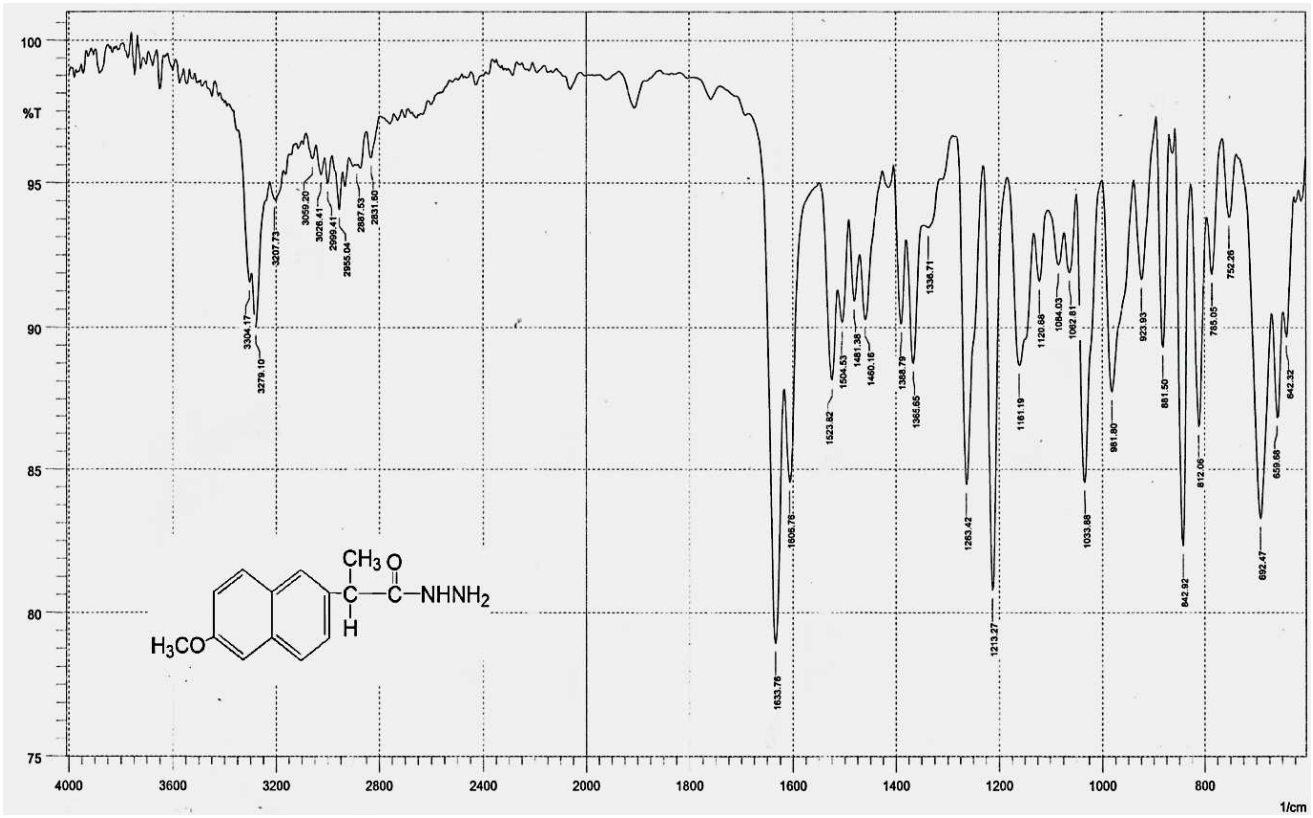


Figure (3-4): FT-IR spectrum of compound (3).

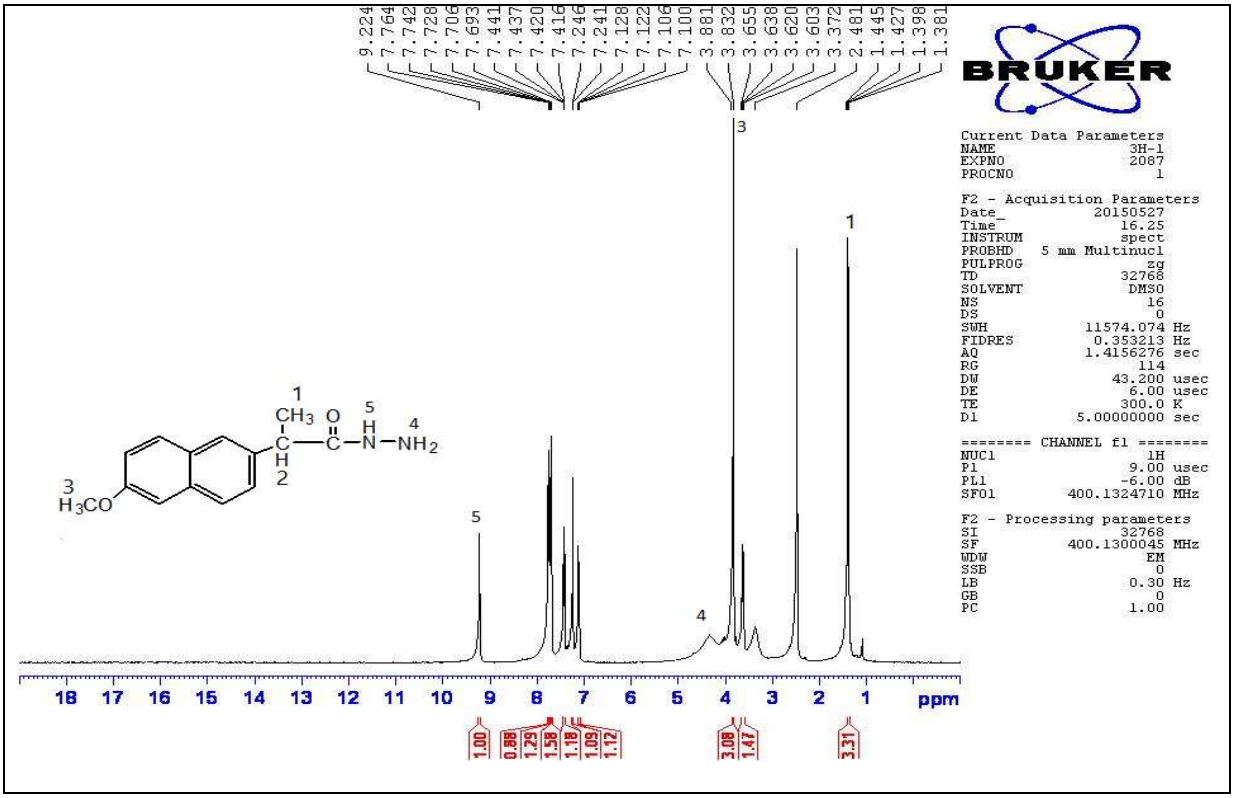


Figure (5): ^{1}H-NMR spectrum of compound (3).

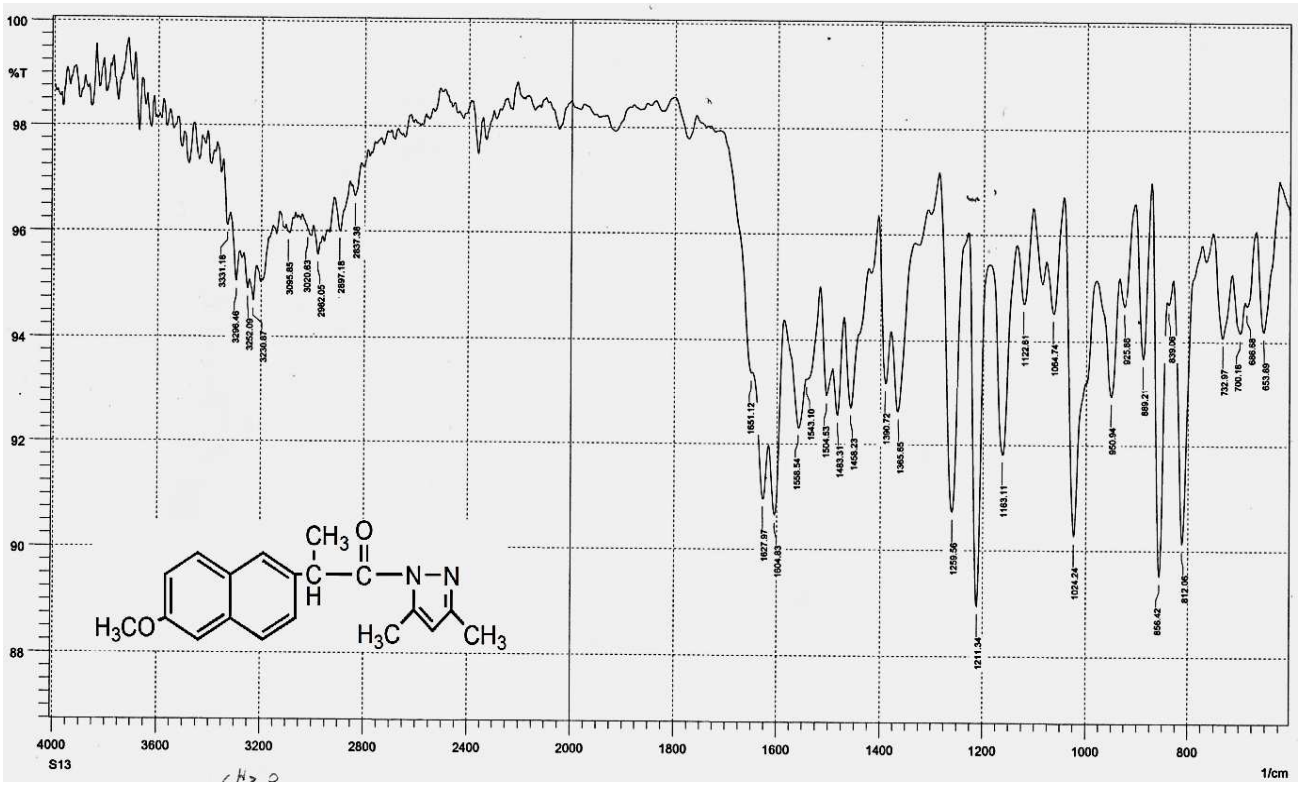


Figure (6): FT-IR spectrum of compound (4).

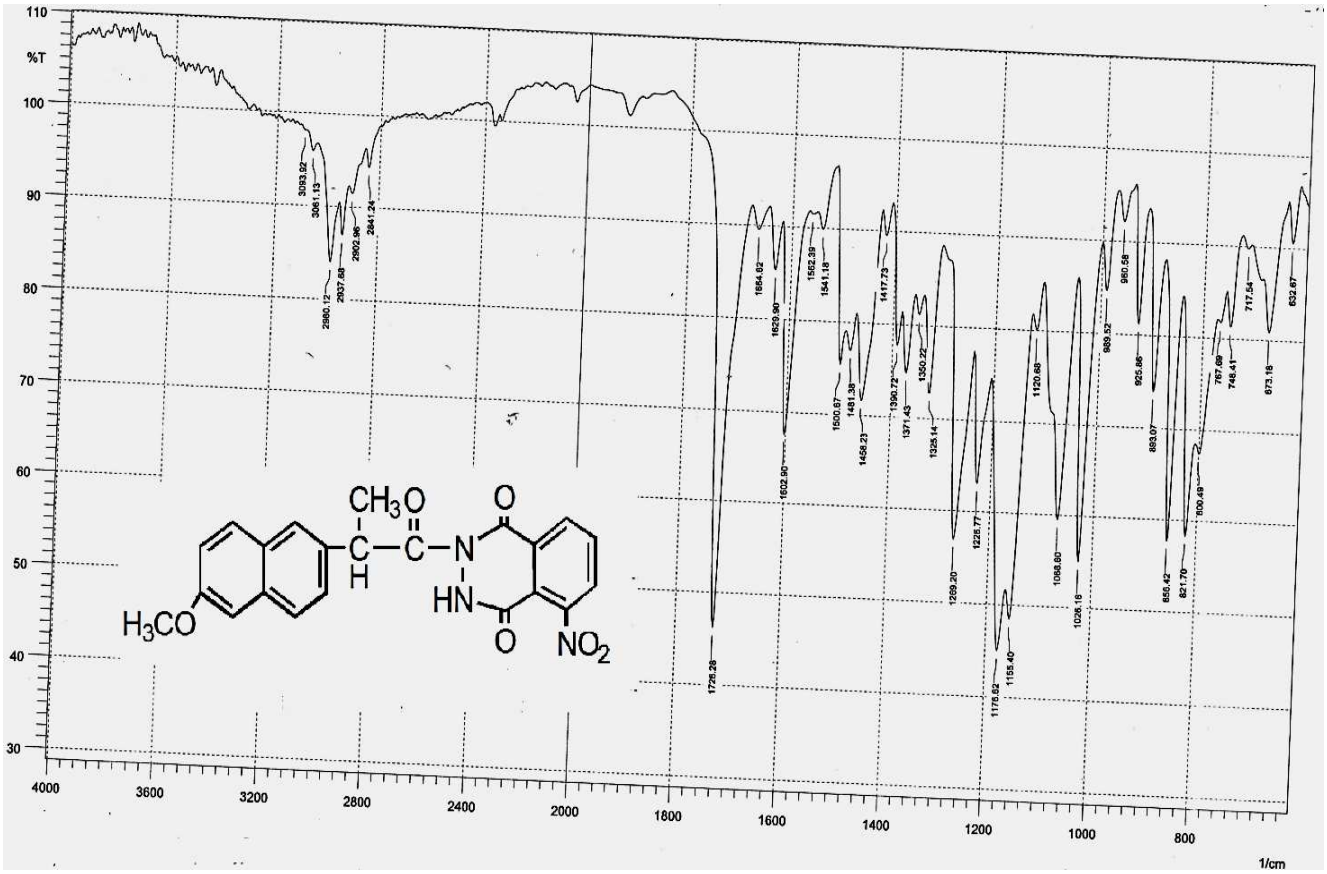


Figure (7): FT-IR spectrum of compound (5).

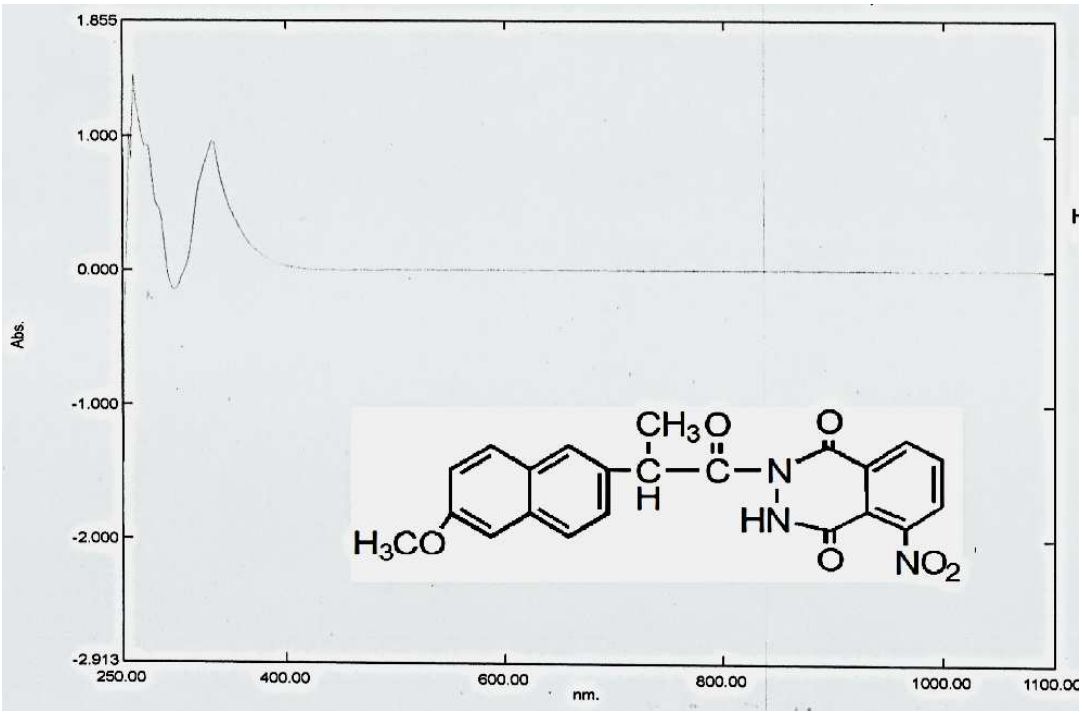


Figure (8): UV spectrum of compound (5).

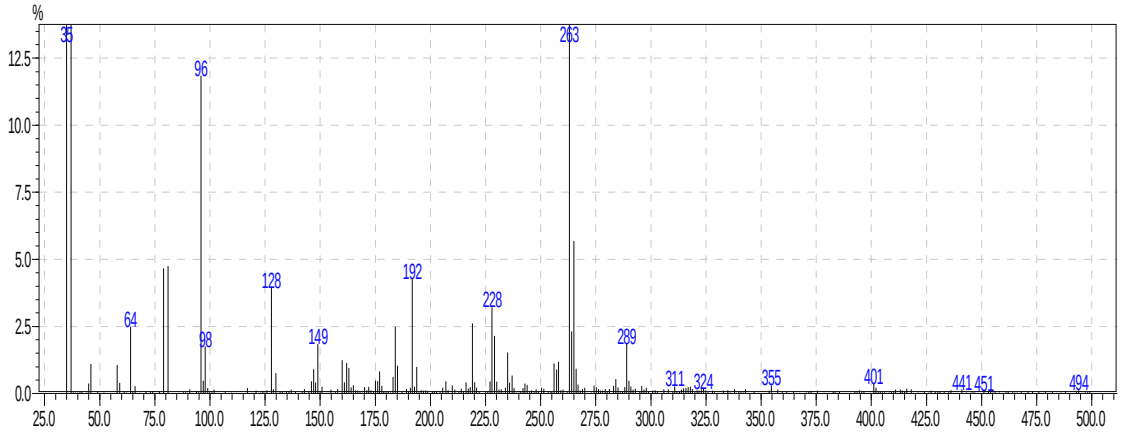


Figure (9): Mass spectrum of compound (5).

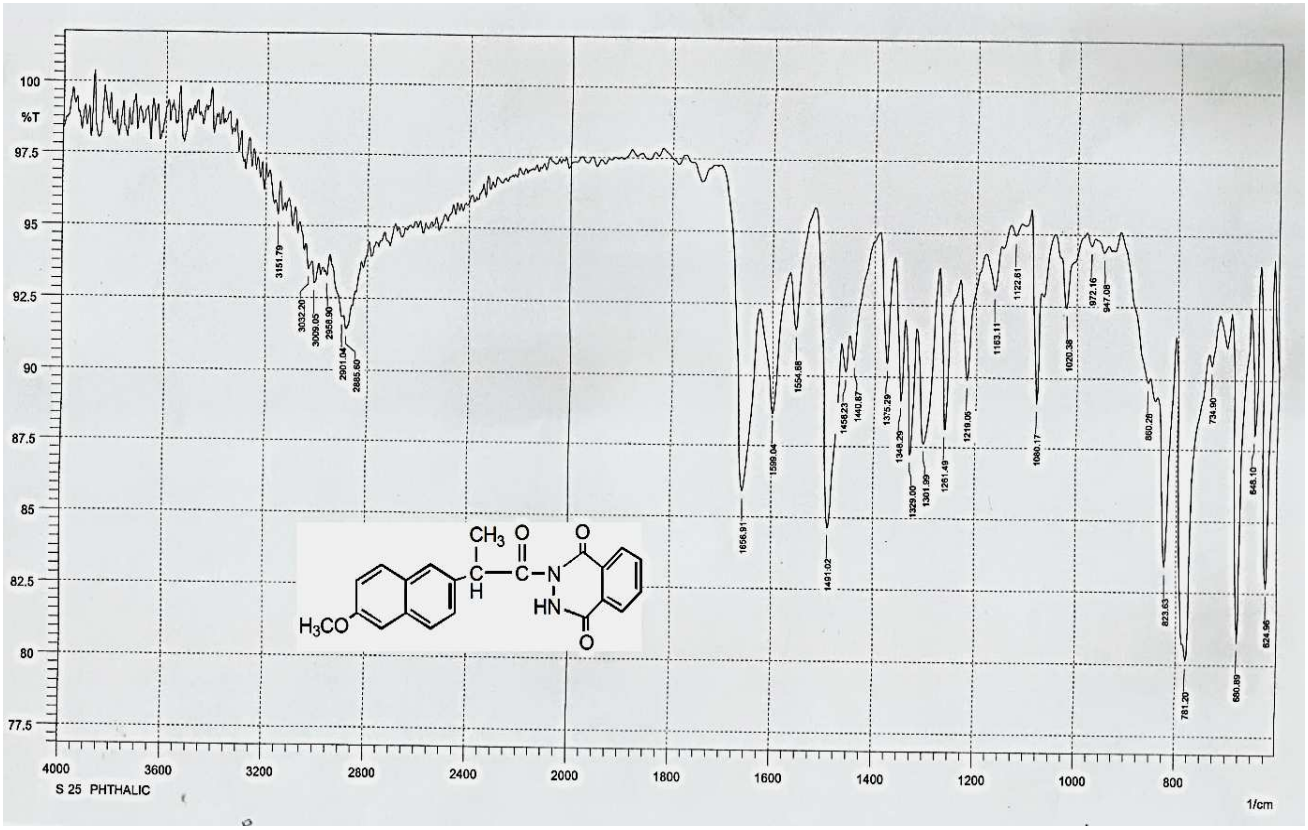


Figure (10): FT-IR spectrum of compound (6).

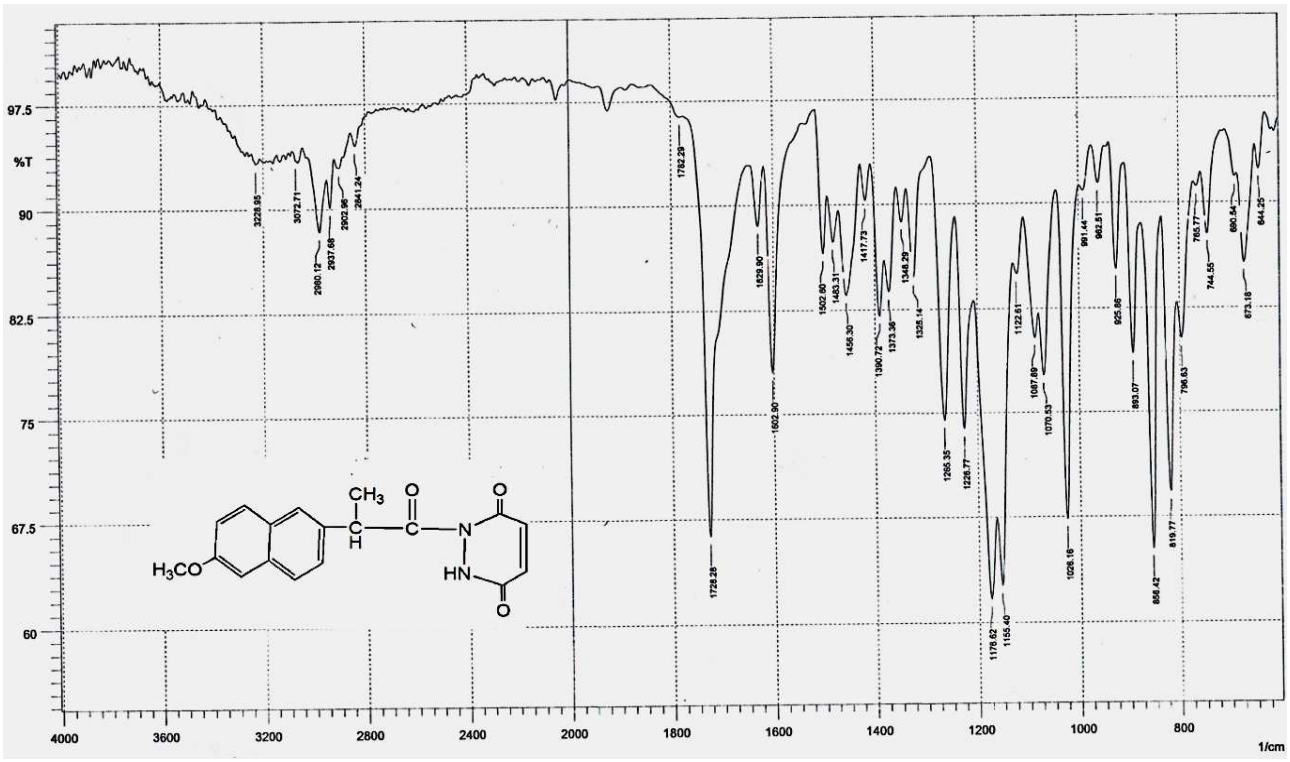


Figure (11): FT-IR spectrum of compound (7).

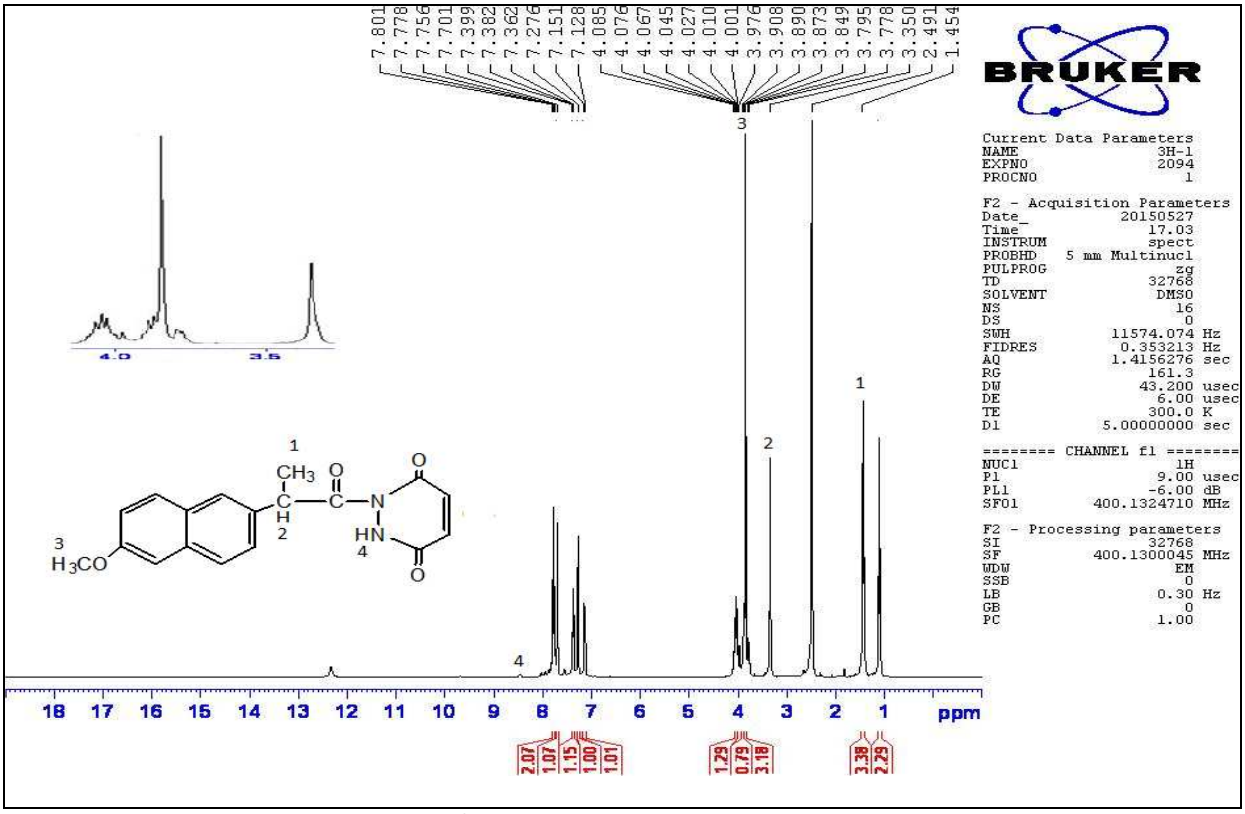


Figure (12): ^{1}H-NMR spectrum of compound (7).

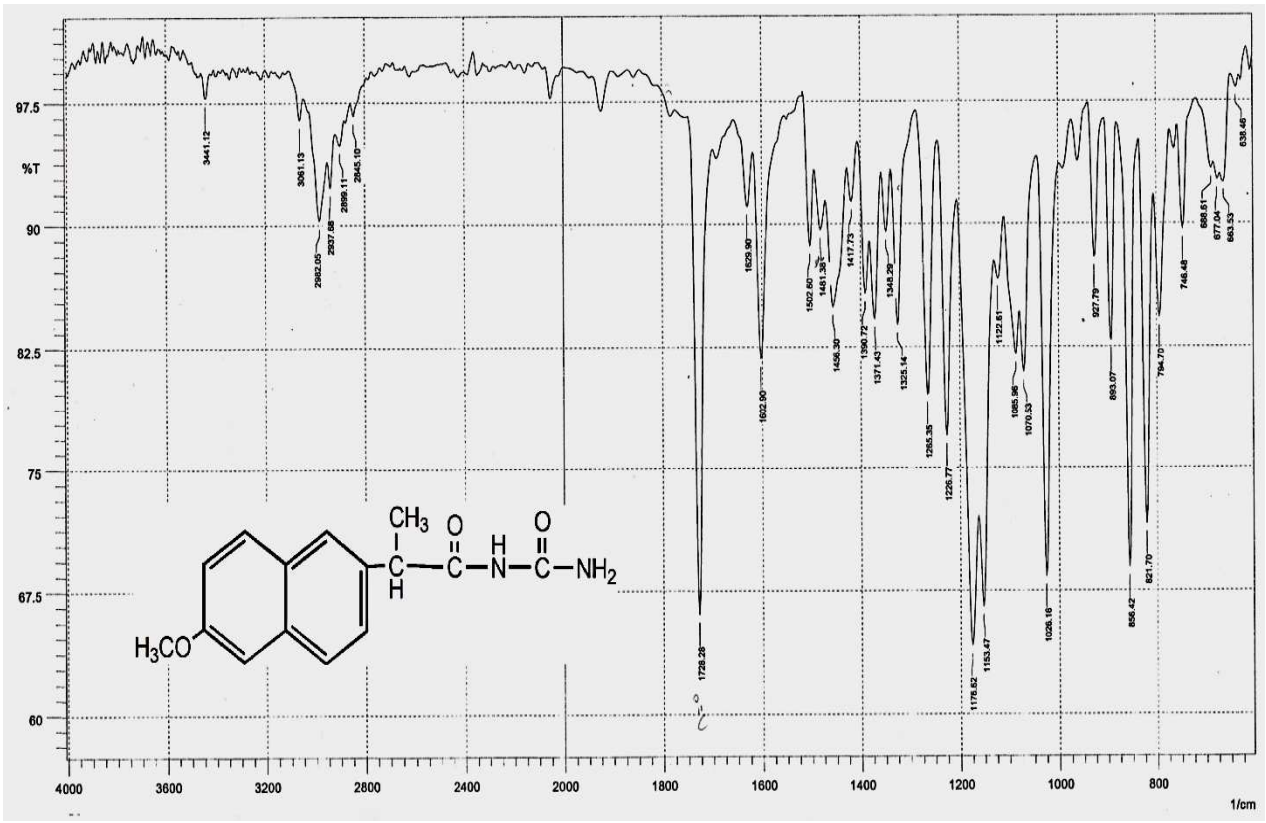


Figure (13): FT-IR spectrum of compound (8).

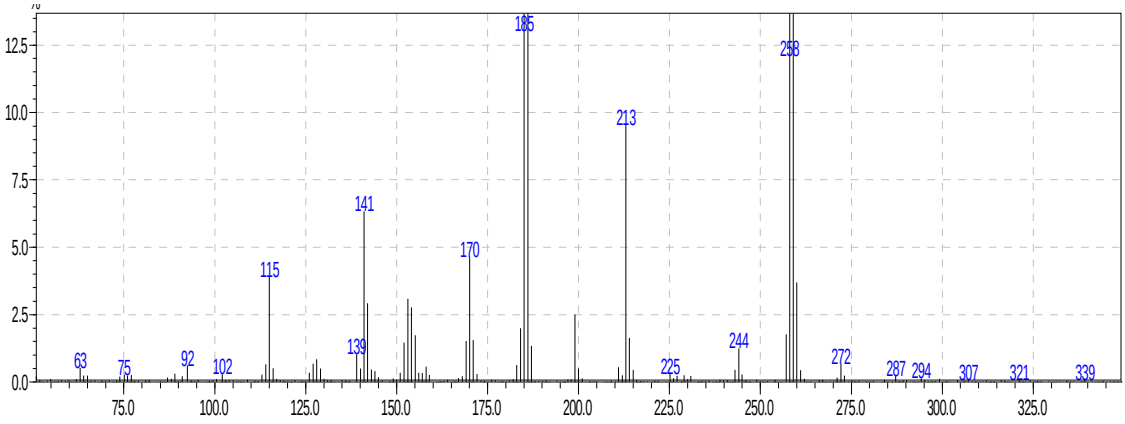


Figure (14): Mass spectrum of compound (8).

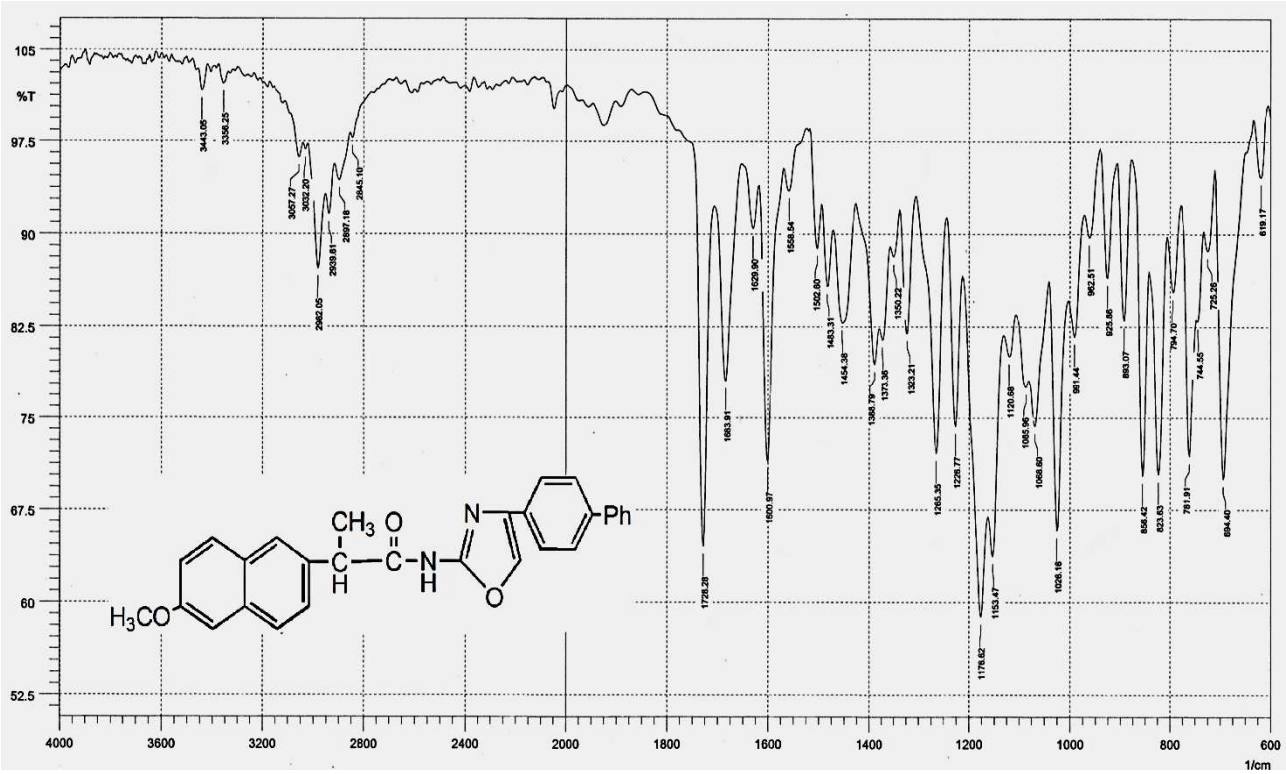


Figure (15): FT-IR spectrum of compound (9).

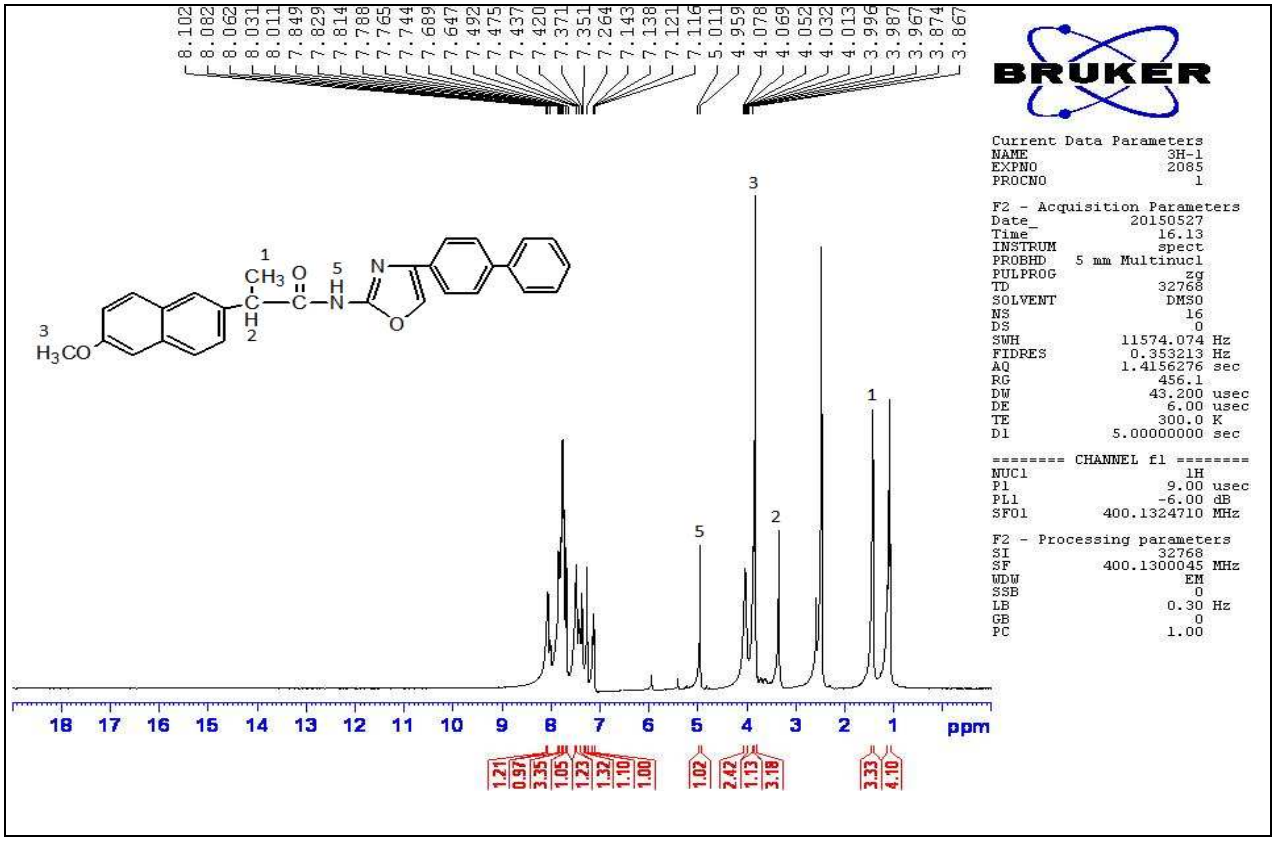


Figure (16) : ^{1}H-NMR spectrum of compound (9).

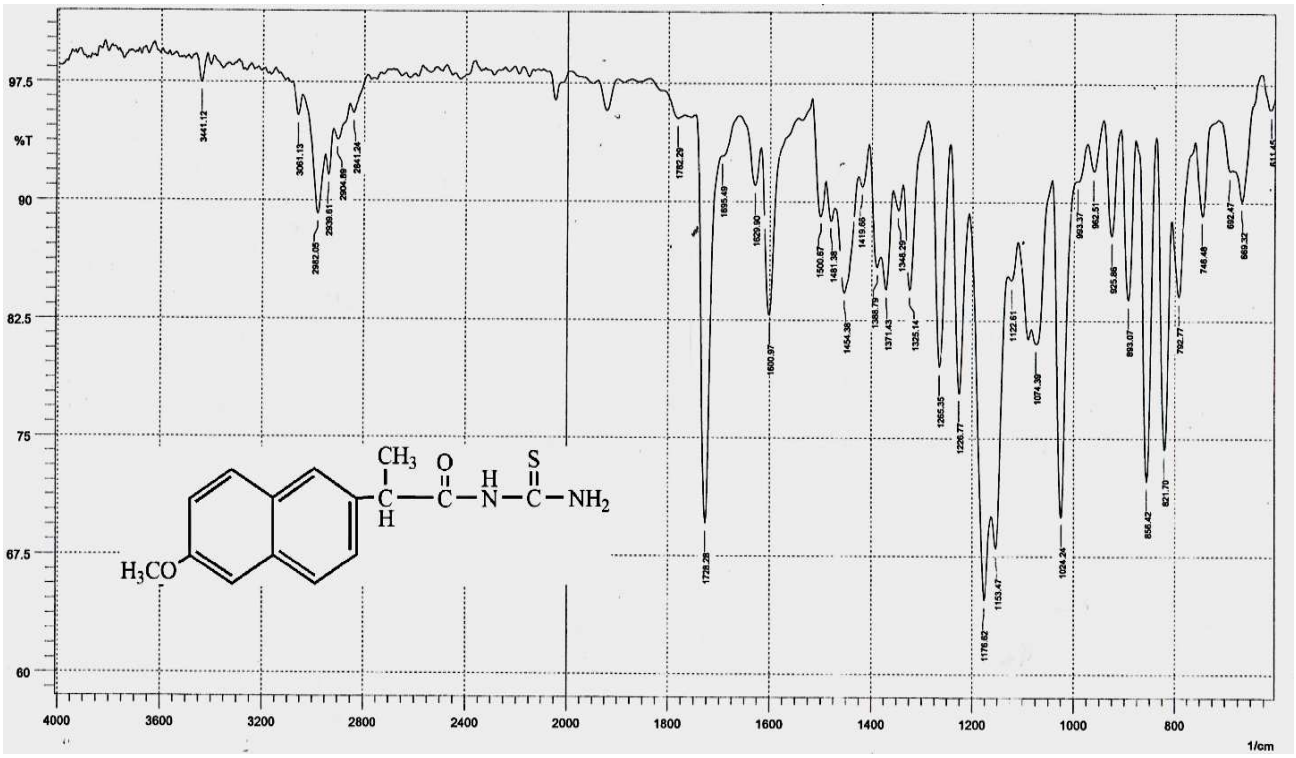


Figure (17): FT-IR spectrum of compound (10).

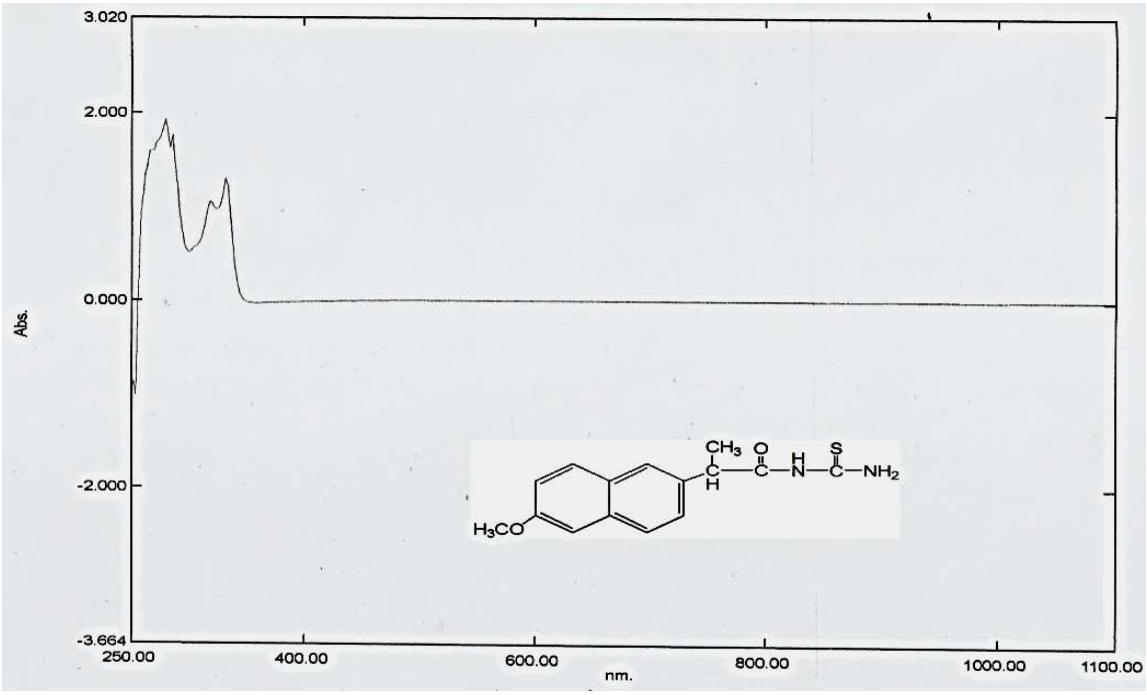


Figure (18) : UV spectrum of compound (10)

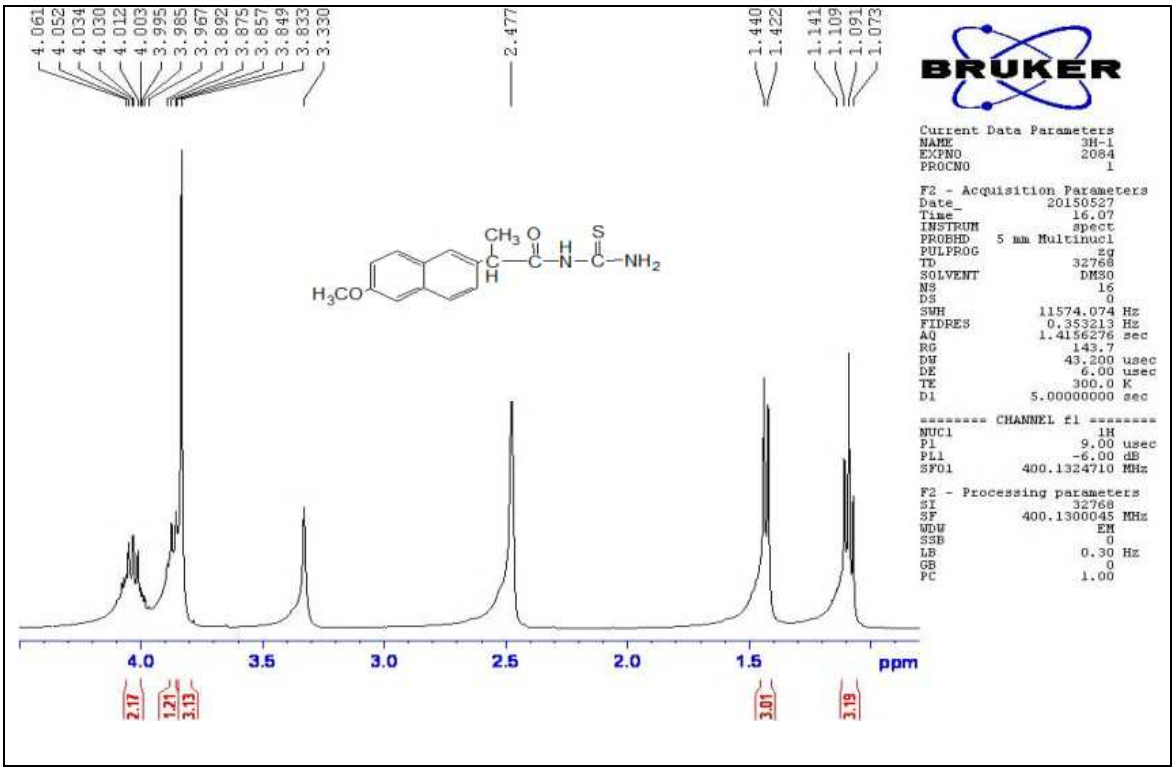


Figure (19A): ^{1}H-NMR spectrum of compound (10).

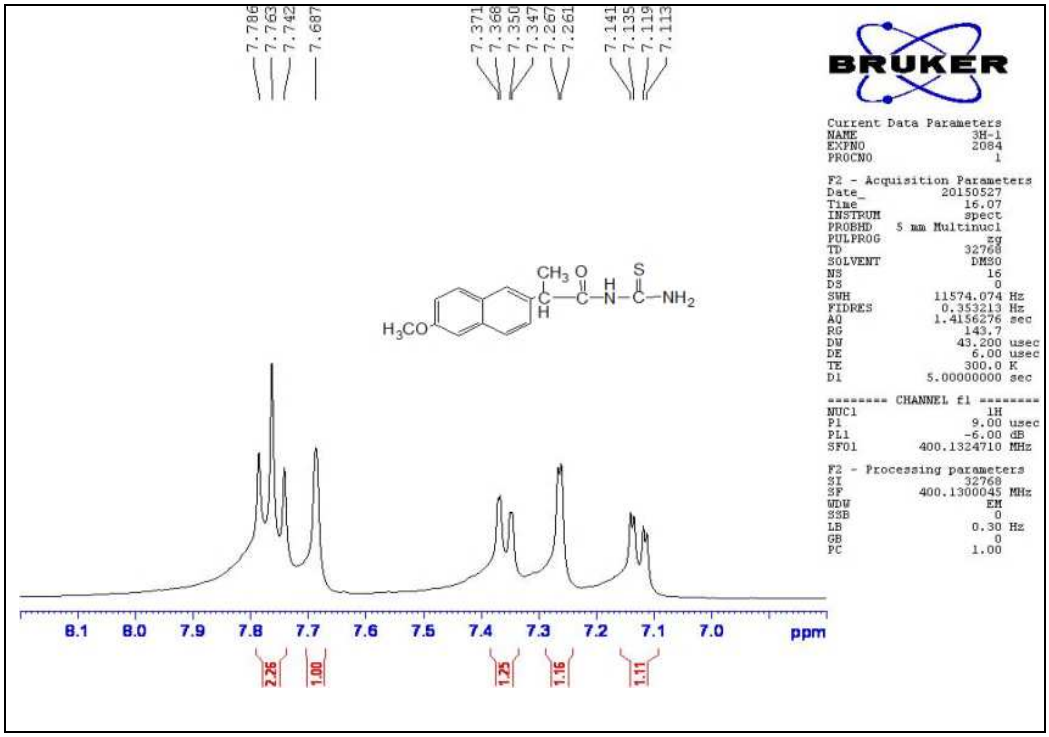


Figure (19B): ^{1}H-NMR spectrum of compound (10).

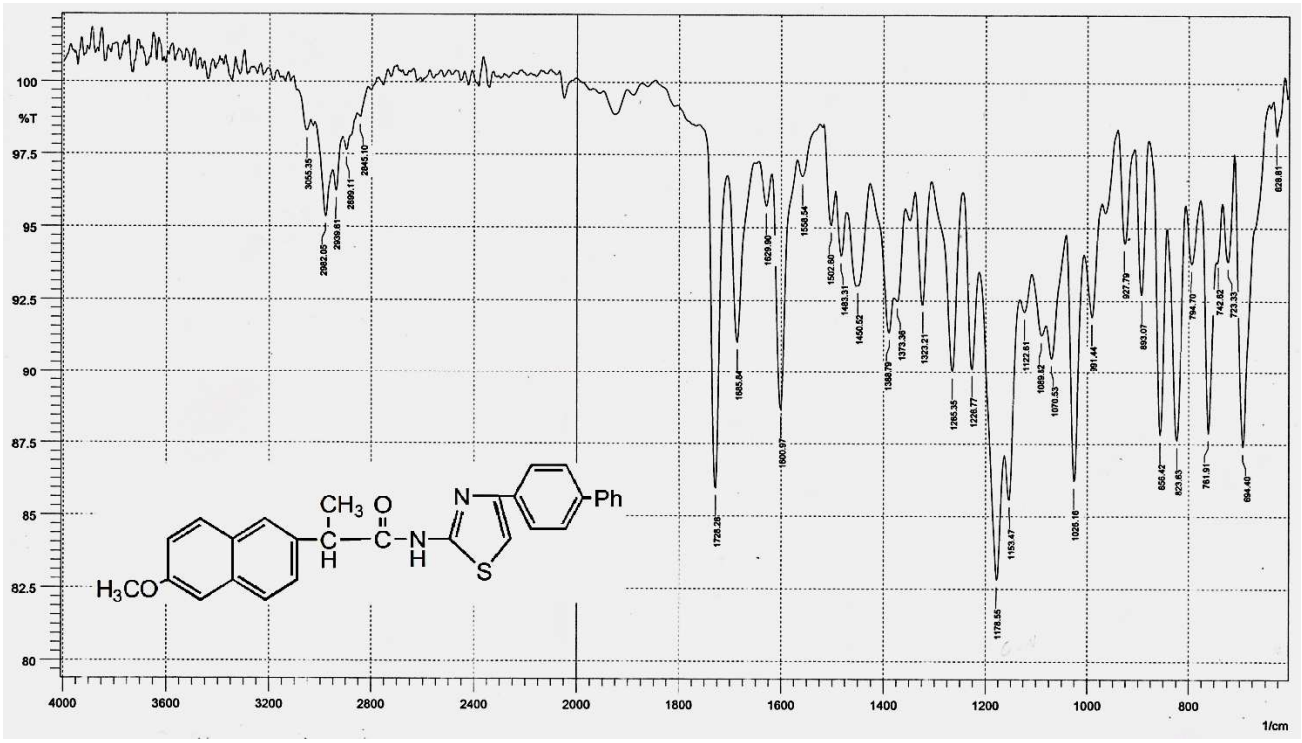


Figure (20): FT-IR spectrum of compound (11).

A	B

Figure (21): effect of compounds A(18 = 2,20 = 3), B(25 =10,26 =7,27 =8,28=11) against E.coli.

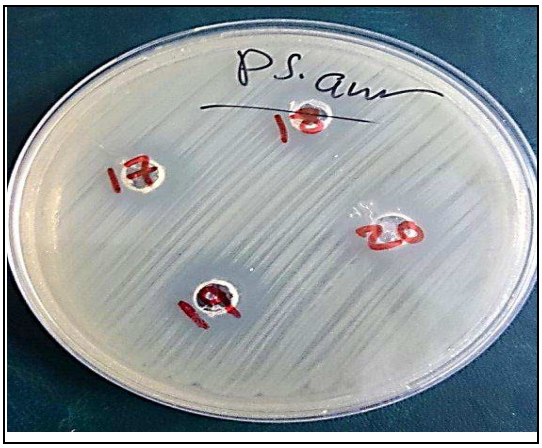


Figure (22): effect of compounds (18 = 2,20 = 3) against Pseudomonas.

A	B

Figure (23): effect of compounds A(18 =2 ,20 = 3), B(25 =10,26 = 7,27 = 8,28 = 11) against Staphylococcus.

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