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Preparation and Charactrisation of 1,3-dipolar cycloaddition of nitrones with 4-amino antipyrene

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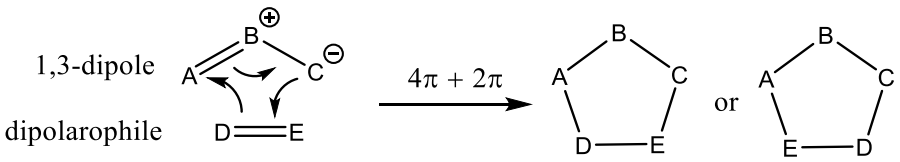
Abstract:
Some nitrones (1-5), derived from N–phenyl hydroxylamine with substituted benzaldehyde such as (3-chlorobenzaldehyde, 4-chlorobenzaldehyde, 3-nitrobenzaldehyde, 4-florobenzaldehyde, 2-nitrobenzaldehyde). In subsequent 1,3-dipolar cycloaddition reactions of nitrones with 4-amino antipyrene give isoxazolidines (6-10), They have been identified by ^{1}HNMR, ^{13}CNMR, IR and Mass spectra

keyword: nitrones, isoxazolidines, 1,3-dipolar cycloaddition, dipolarophile , heterocycles, benzaldehyde, N–phenyl hedroxyl amine, 4-amino antipyrene.

1. Introduction:

Nitrones were discovered by E.Becmann in the 1880s by N-alkylation of oximes[1]. In the 1960s the high-yielding synthesis of isoxazolidines were discovered by Cope, Lebel, Brown, Delpierre and Huisgen. The reactions of nitrones dipoles play an important role in the history of cycloaddition reaction. The 1,3-dipolar cycloaddition also known as the Huisgen cycloaddition[2] is a classic reaction in organic chemistry consisting of the reaction of dipolarophile with a 1,3-dipolar compound that allows the production of various five–membered heterocycles[3]. High specificity

stereoselectivity associated with these reactions make them synthetically important[4-6]. The 1,3-dipolar cycloaddition reaction was proposed to proceed through a concerted mechanism[7]. Figuer 1.



Fiuger 1: Generalized 1,3-dipolar cycloaddition reaction

For the concerted mechanism, the cycloaddition involves a reaction between a species containing four electrons in a three orbital array in the 1,3-dipole with the two electrons of the dipolarophile. The cycloaddition between these species is referred to as a [4π + 2π] cycloaddition. Most of dipolarophile are alkenes[8], alkynes[9] and molecules possessing related hetero atom functional groups (such as carbonyls[10,11] and nitriles[12,13]). Both inter and intra molecular nitrone and alkene cycloaddition reaction have received attention of heterocycles of biological interest [14-16].

The arguments for the alternative are based on Sustmann's molecular orbital perturbation theory[17] which can be simply illustrated by using the frontier π-MO's of the 1,3-dipole, the transition state of the cycloaddition, and the dipolarophile (Figure 2).

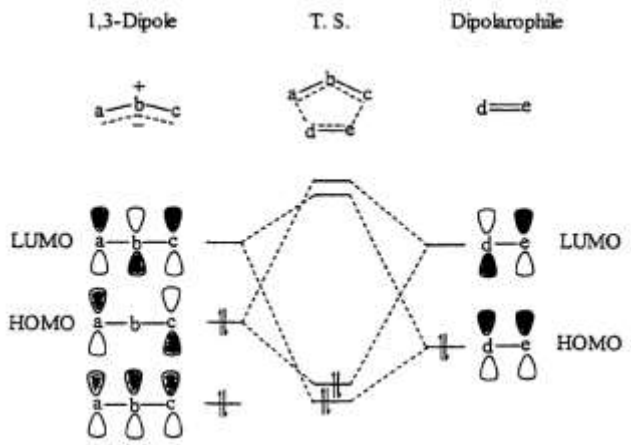
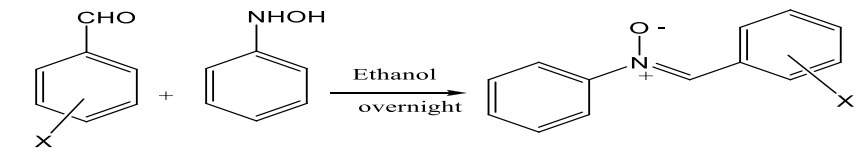


Figure 2: The frontier π-MO's 1,3-dipolar cycloaddition

There are two sets of HOMO-LUMO pairs. When the energy gap between one pair of the HOMO-LUMO is much smaller than the other pair, the electron flow would be unidirectional, in a concerted process. Otherwise the electron flow would be two directional: from HOMO (1,3-dipole) to LUMO (dipolarophile) and back from HOMO (dipolarophile) to LUMO (1,3-dipole) to from the two new σ-bonds. The two step cycloaddition process will take place only under one of the following conditions: either the atomic coefficient at one end of the 1,3-dipole is much smaller than at the other or a strong steric hindrance exists at one end of the 1,3-dipole.[18] The reactivity and regioselectivity in 1,3-dipolar cycloaddition reactions can also be approached by using Figure 2.

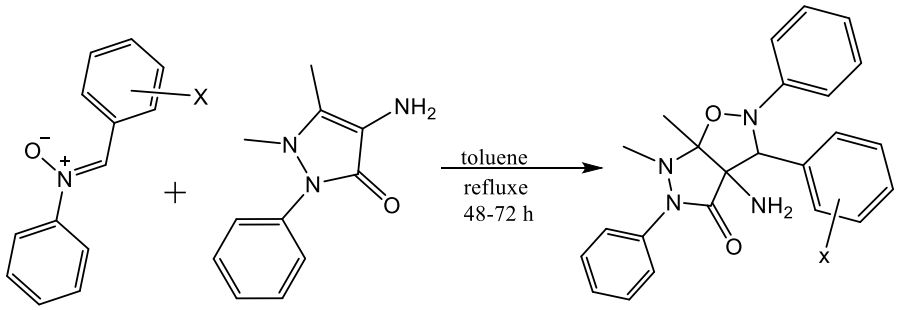
2. Results and Discussion

The nitrones (1-5) used in this study were easily prepared from the corresponding aldehyde with N–phenyl hedroxyl amine.[19,20] Scheme 1.



schem 1

The cycloaddition of nitrones (1-5) with 4-amino antipyrene were carried out by refluxing (48-72 h) in dry toluene at 110 ˚C to give isoxazolidines (6-10). In all cases, the compounds were purified by column chromatography[21] allowed the isolation of pure compounds. Scheme 2.



6: X = 3-Cl
7: X =3-NO_2
8: X =4-F
9: X =2-NO_2
10: X =4-Cl

schem 2

The obtained isoxazolidines were characterized spectroscopically. The formation of the cycloadducts was established by the ^{1}H NMR,^{13}C NMR, and IR spectroscopy. The ^{1}H NMR spectrum of isoxazolidines (6-10) showed a singlet at δ 9.49-10.02 ppm for (NH_2), a multiplet at δ 7.09-7.79 ppm for the aromatic protons, including a singlet at δ 7.36-7.39 ppm for ($^{H}_{N\text{-}C\text{-}ph}$), singlet at 2.99-3.19 ppm for (N-CH_3) and a singlet at δ 2.3-2.47 ppm for (C-CH_3). See figures (3-7), More detail of the ^{1}H NMR data analysis for compounds (6-10) can be seen in Table (1).

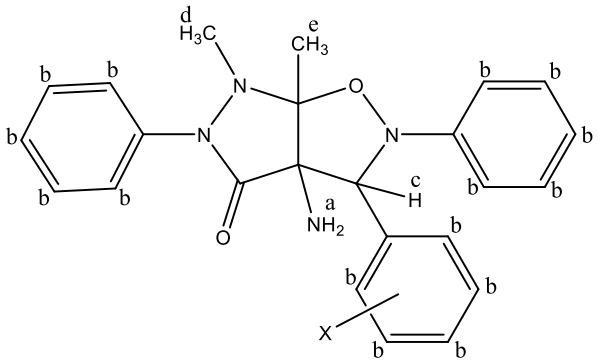


Table (1):^{1}H NMR data analysis of isoxazolidines (6-10)

Comp.	X	H_a	H_b	H_c	H_d	H_e
6	3-Cl	9.72(s, 2H)	7.37-7.79(m, 14H)	7.36(s, 1H)	3.16(s, 3H)	2.4(s, 3H)
7	3-NO_2	9.7(s,2H)	7.32-7.91(m, 14H)	7.38(s, 1H)	3.17(s, 3H)	2.4(s, 3H)
8	4-F	9.57(s, 2H)	7.16-8.48(m, 14H)	7.37(s, 1H)	3.02(s, 3H)	2.3(s, 3H)
9	2-NO_2	9.73(s, 2H)	7.099-7.85(m, 14H)	2.47(s, 3H)	3.14(s, 3H)	7.39(s, 1H)
10	4-Cl	10.02(s, 2H)	7.32-8.14(m, 14H)	2.46(s, 3H)	3.19(s, 3H)	7.39(s, 1H)

The ^{13}C NMR spectrum of isoxazolidines (6-10) included singlet at δ 160-180 ppm for the (C=O), at δ 125-160 ppm for aromatic carbons. See figures (8-11). More detail of the ^{13}C NMR data analysis for compounds (6-10) can be seen in Table (2).

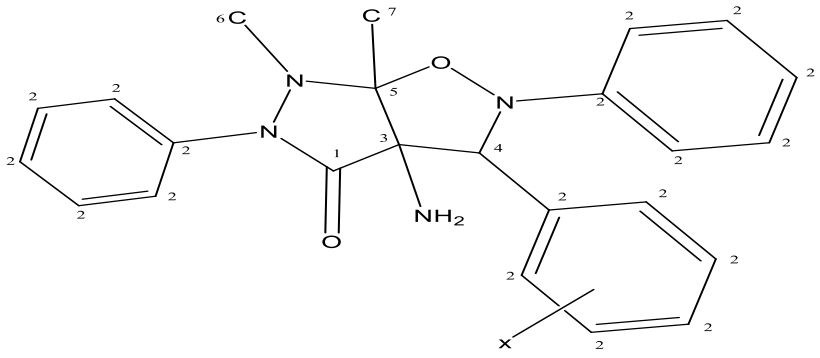


Table (2): ^{13}C NMR data analysis of isoxazolidines (6-10)

Comp.	X	C1	C2	C3	C4	C5	C6	C7
6	3-Cl	160 δ	130-155 δ	118.29 δ	124.75 δ	134 δ	35.98 δ	10.35 δ
7	3-NO_2	160 δ	124-157 δ	118.2 δ	124.77 δ	134.9 δ	35.9 δ	10.4 δ
8	4-F	160 δ	124-160 δ	117.65 δ	121.7 δ	134.68 δ	35.74 δ	10.37 δ
9	2-NO_2	160 δ	124.3-153.2δ	117.62 δ	121 69 δ	134.68 δ	35.73 δ	10.35 δ

The IR spectrum included a peak at 3059-3150 cm^{-1} for the NH_2 stretch and the sharp peak at 1647-1651 cm^{-1} for C=O stretch. See figures (16-20). The mass spectrum of compounds (6-10) gave the correct molecular ion. See figures (12-15).

The synthesis of isoxazolidines (6-10) were confirmed using ^{1}H NMR, ^{13}C NMR , Mass spectrometry and IR.

The results described above are in general agreement with the frontier orbital treatment of 1,3-dipolar cycloadditions.[22] This view suggests the formation of the carbon substituted isoxazolidines regioselectivity. As the ionization potential and the electron affinity of the alkene increase (i.e. as the HOMO-LUMO level decrease in energy) there is an increasing tendency towards the formation of a regioisomeric mixture of adducts. In this cycloaddition reaction, the carbon-carbon and carbon-oxygen bond formation in the transition state may not happen in a synchronous manner.

3. Conclusion:

In conclusion, 1,3-dipolar cycloaddition reaction of some nitrones (1-5) to 4-amino antipyrene to give new isoxazolidines (6-10).

4- Experimental

4.1 General methods:

Melting points were determined using a Gallenkamp melting point apparatus. Proton and carbon NMR spectra were recorded on a Bruker DRX 500 Advance spectrometer at 500 MHz and 125 MHz, respectively, using deuterated solvents and TMS as an internal standard

Chemical shifts are reported as δ values in ppm. Infrared spectra were obtained an FT-IR-1600 Perkin-Elmer spectrophotometer thin layer chromatography (TLC) was performed on aluminum sheets silica gel from merk. Column chromatography was carried out using Merck silica gel (230-400 mesh). The TLC spots were visualized in UV and I_2. Mass spectra recorded on High-resolution mass spectra were recorded on an ESI-TOF Mariner Spectrometer (Perspective Biosystem)

4.2 Preparation Methods

4.2.1 Preparation of the nitrones (1-5)

The N–phenyl hedroxyl amine was prepared from nitrobenzene according to ref [26] and α-aryl-N-phenyl nitrones (1-5) from the respective substituted benzaldehyde and N–phenyl hedroxyl amine according to ref [23-27].

4.2.2 Preparation of the isoxazolidines (6-10)

General procedure for cycloaddition of nitrones (1-5) to 4-amino antipyrene. To a stirred solution of the nitrones (1-5) (5 mmole) in dry toluene (50 ml) was added to 4-amino antipyrene (5 mmole) and the solution was heated at reflux (48-72 h). The resulting mixture was evaporated under reduced

pressure. The crude product was purified by column chromatography on silica gel eluting to give pure isoxazolidines (6-10).

4.2.2.1 3α-amino-3-(4-chlorophenyl)-6,6a-dimethyl-2,5- diphenyltetrahydro-2H-pyrazolo[4,3-d]isoxazol-4(5H)-one (6): the product (6) was isolated by column chromatography on silica gel eluting with benzene\ methanol(8:2) as a brown solid product in 60 % yield, m.p= 254-255C°.

IR: 1651 cm^{-1} (C=O), 3100 cm^{-1} (NH_2), 1455 cm^{-1} (C=C),1300 cm^{-1} (C-N); ^{1}H NMR : δ 9.75 ppm (s,2H), 7.32-7.79 ppm (m,15 H aromatic) including singlet at 7.36 ppm for (ph-CH), 3.16 ppm (s,3H), 2.4 ppm (s,3H); ^{13}C NMR: δ 160 ppm (C=O), 155-130 ppm (C aromatic), 134 ppm (C-O), 124.75 ppm (C-ph) , 35.98 ppm (N-CH_3), 10.35 ppm (C-CH_3); Mass: m\ z = 434$[M]^+$.

4.2.2.2 3α-amino-3-(3-chlorophenyl)-6,6a-dimethyl-2,5-diphenyltetrahydro-2H-pyrazolo[4,3-d]isoxazol-4(5H)-one(7): the product (7) was isolated by column chromatography on silica gel eluting with benzene \ methanol(8:2) as a brown solid product in 51 % yield, m.p= 186 C°.

IR: 1647 cm^{-1} (C=O), 3150 cm^{-1} (NH_2), 1423 cm^{-1} (C=C),1307 cm^{-1} (C-N);

^{1}H NMR: δ 9.7ppm (s,2H), 7.32- 7.91 ppm (m,15 H aromatic) including singlet at 7.3 ppm for ph-CH, 3.17 ppm (s,3H), 2.4 ppm (s,3H); ^{13}C NMR: δ 160 ppm (C=O), 157-124 ppm (C aromatic), 118.2 ppm (C-NH_2), 134.9 ppm (C-CH_3), 124.77 ppm (C-ph), 35.9 ppm (N-CH_3), 10.4ppm (C-CH3); Mass: m\ z = 434.3$[M]^+$.

4.2.2.3 3α-amino-6,6a-dimethyl-3-(3-nitrophenyl)2,5diphenyltetrahydro-2H-pyrazolo[4,3-d]isoxazol-4(5H)-one(8): the product (8) was isolated by column chromatography on silica gel eluting with benzene\ methanol(8:2) as a yellow solid product in 55 % yield, m.p= 210- 212 C°.

IR: 1647 cm^{-1} (C=O), 3100 cm^{-1} (NH_2), 1492 cm^{-1} (C=C),1311 cm^{-1} (C-N), 1023 cm^{-1} (NO_2 Asym), 1340 cm^{-1} (NO_2 , sym);

^{1}H NMR : δ 9.57 ppm (s,2H), 7.16- 8.48 ppm (m,15 H aromatic) including singlet at 7.37 ppm for ph-CH, 3.02 ppm (s,3H), 2.3 ppm (s,3H); ^{13}C NMR: δ 180 ppm (C=O), 160-124.3 ppm (C aromatic),117.65 ppm (C-NH_2), 134.68 (C-CH_3), 121.7 ppm (C-ph) , 35.7 ppm (N-CH_3), 10.37 ppm (C-CH_3); Mass: m\z = $[M]^+$.

4.2.2.4 3α-amino-3-(4-fluorophenyl)-6,6a-dimethyl-2,5-diphenyltetrahydro-2H-pyrazolo[4,3-d]isoxazol-4(5H)-one (9) yield 52 %, m.p= 230- 231 C°.

IR: 1651 cm^{-1} (C=O), 3100 cm^{-1} (NH_2), 1492 cm^{-1} (C=C),1303 cm^{-1}

^{1}H NMR : δ 9.73 ppm (s,2H), 7.9- 7.85 ppm (m,15H aromatic) including singlet at 7.39 ppm for (ph-CH), 3.14 ppm (s,3H), 2.47 ppm (s,3H); ^{13}C NMR: δ 160 ppm (C=O), 153.2-124.3 ppm (C aromatic),117.62 ppm (C-NH_2), 134.68 ppm (C-CH_3), 121.69 ppm (C-ph) , 35.73 ppm (N-CH_3), 10.37 ppm (C-CH_3); Mass: m\ z = 418 $[M]^+$.

4.2.2.5 3 α -amino-6,6a-dimethyl-3-(2-nitrophenyl)-2,5-diphenyltetrahydro-2H-pyrazolo[4,3-d]isoxazol-4(5H)-one(10): yield 60 %, m.p= 209- 210 C°.

IR: 1651 cm -1 (C=O), 3120 cm^{-1} (NH_2), 1485 cm^{-1} (C=C), 1303 cm^{-1} (C-N), 1519 cm^{-1} (NO_2 Asym.), 1357 cm^{-1} (NO_2 , sym.);

^{1}H NMR : δ 10.02 ppm (s,2H), 7.32- 8.14 ppm (m,15 H aromatic) including singlet at 7.39 ppm for (ph-CH), 3.19 ppm (s,3H), 2.46 ppm (s,3H); Mass: m\ z = 459 $[M]^+$.

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تحضير وتشخيص ودراسة الاضافة
الحلقية 3,1- ثنائية القطب للنايترونات مع

4-أمينوانتي بايرين

داخل زغير مطلق و رائد جميل علي
قسم الكيمياء كلية التربية للعلوم الصرفة جامعة البصرة

الملخص:
حضرت بعض مركبات النايترونات (1-5) مشتقة من تفاعل ن- فنيل هيدروكسيل امين مع معوضات البنزالدهايد . ضمن تفاعلات الاضافة الحلقية 3,1- ثنائية القطب للنايترونات مع 4-أمينو انتي بايرين ليعطي مركبات الازوكسازولدينات (6-10) وتم تعيينها باستخدام طيف بروتون وكاربون-13 للرنين النووي المغناطيسي وطيف الاشعة تحت الحمراء وكذلك طيف الكتلة.

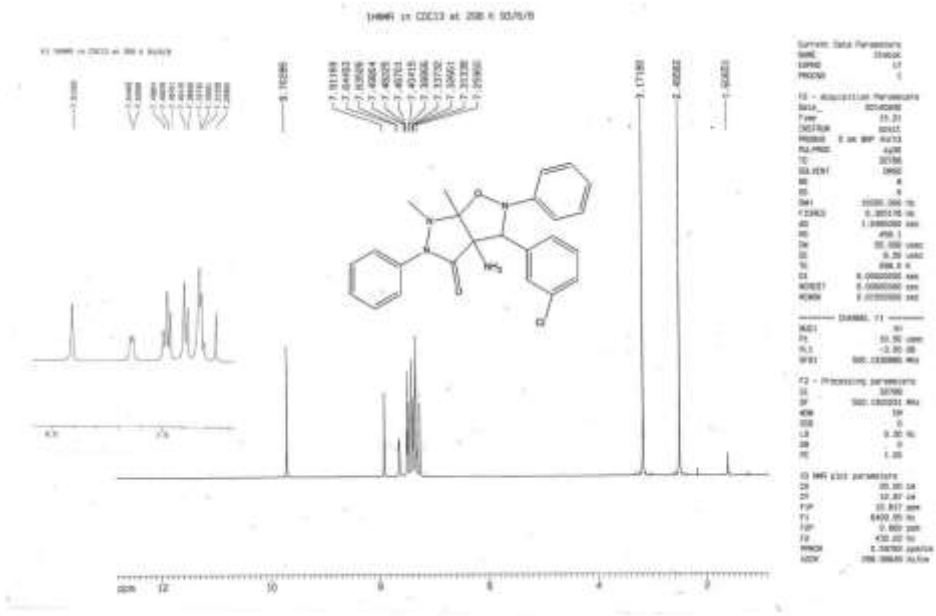

Fig. (3) ^{1}HNMR for compound (6)

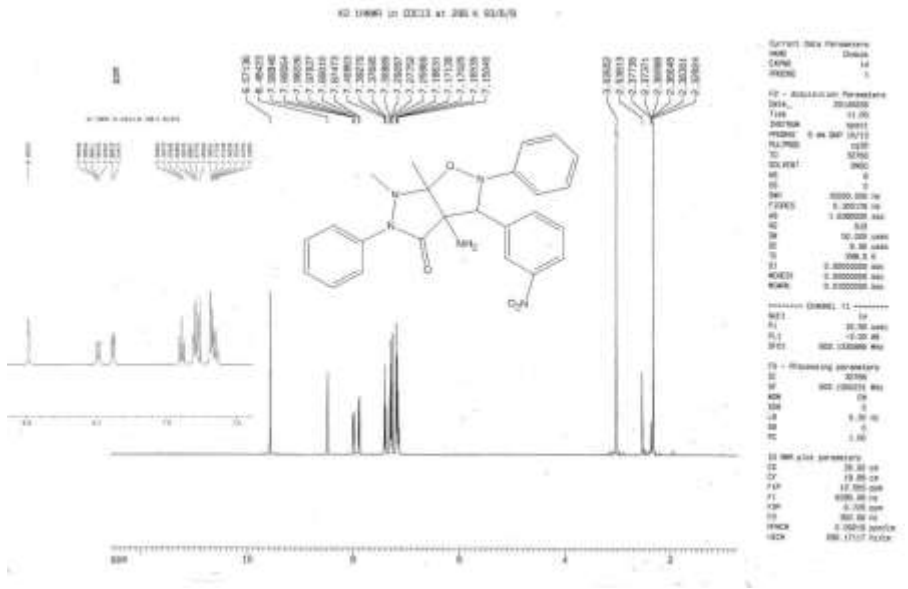

Fig. (4) ^{1}HNMR for compound (7)

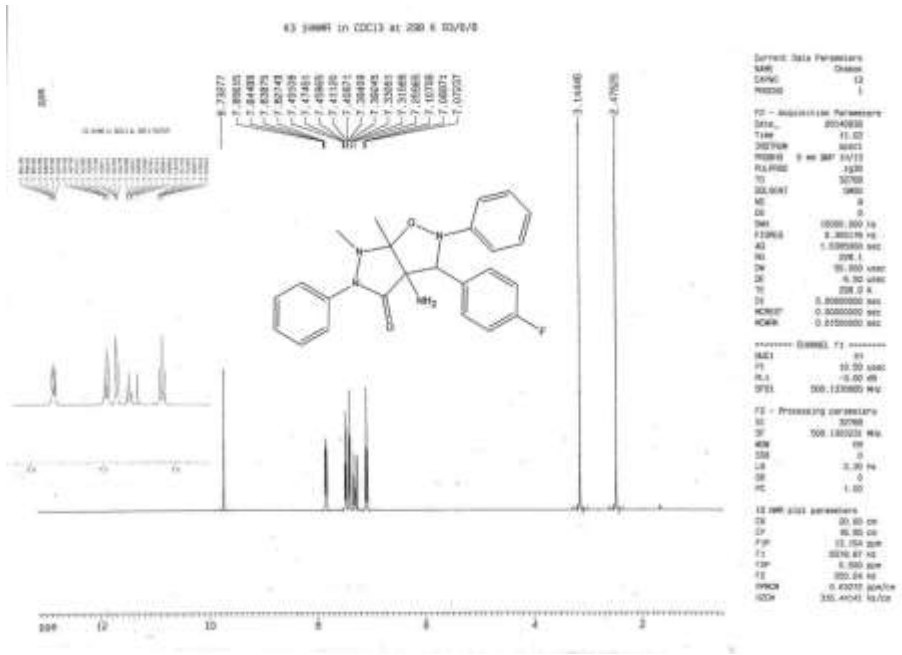

Fig. (5) ^{1}HNMR for compound (8)

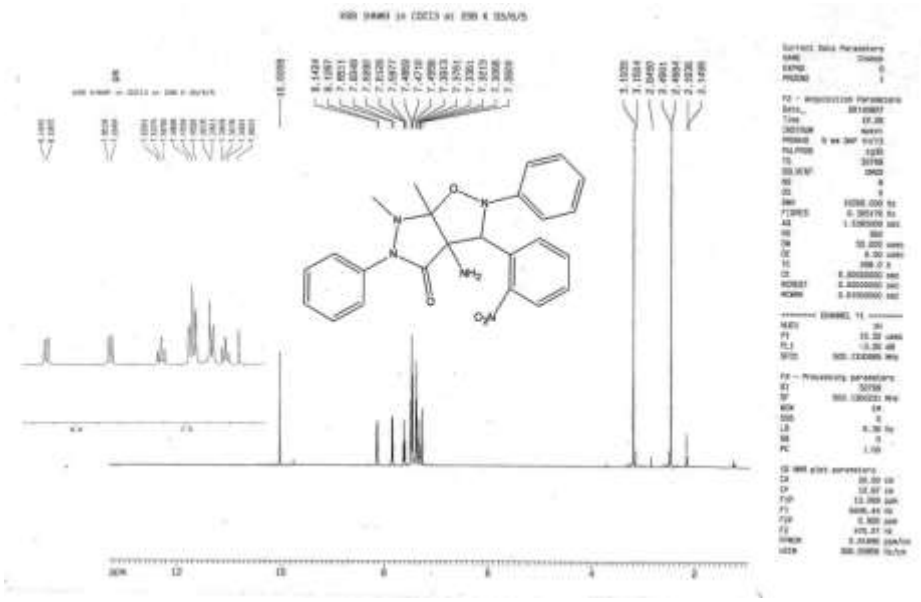

Fig. (6) ^{1}HNMR for compound (9)

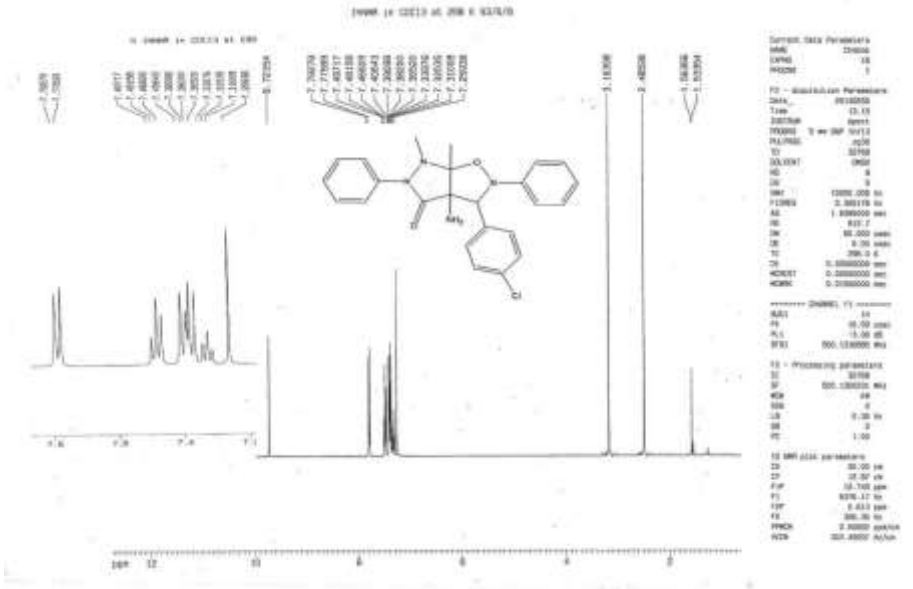

Fig. (7) ^{1}HNMR for compound (10)

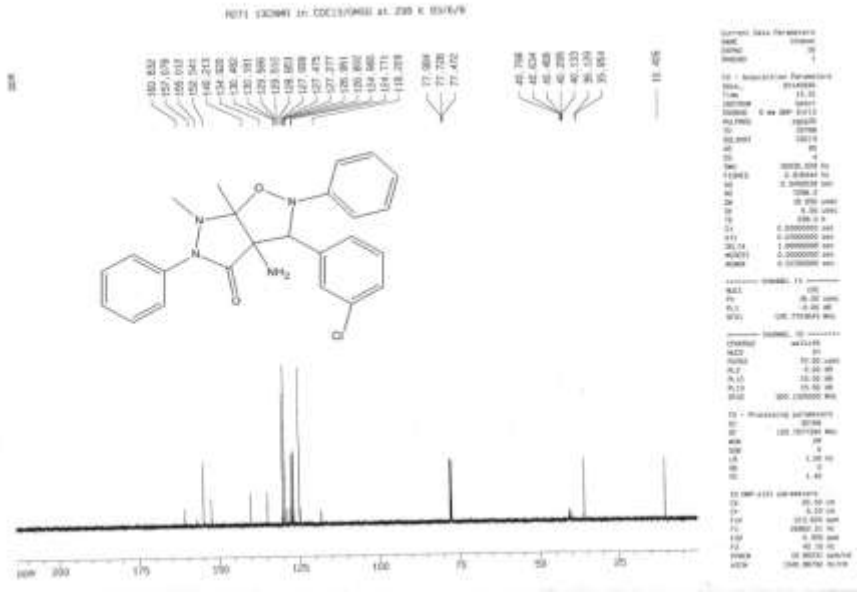

Fig. (8) ^{13}CNMR spectrum for compound (6)

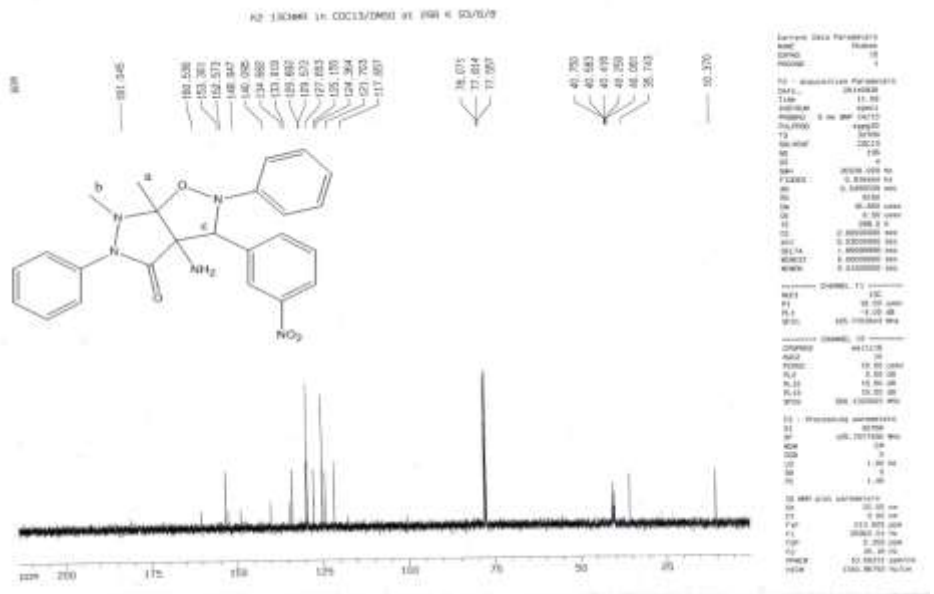

Fig.(9) ^{13}CNMR spectrum for compound (7)

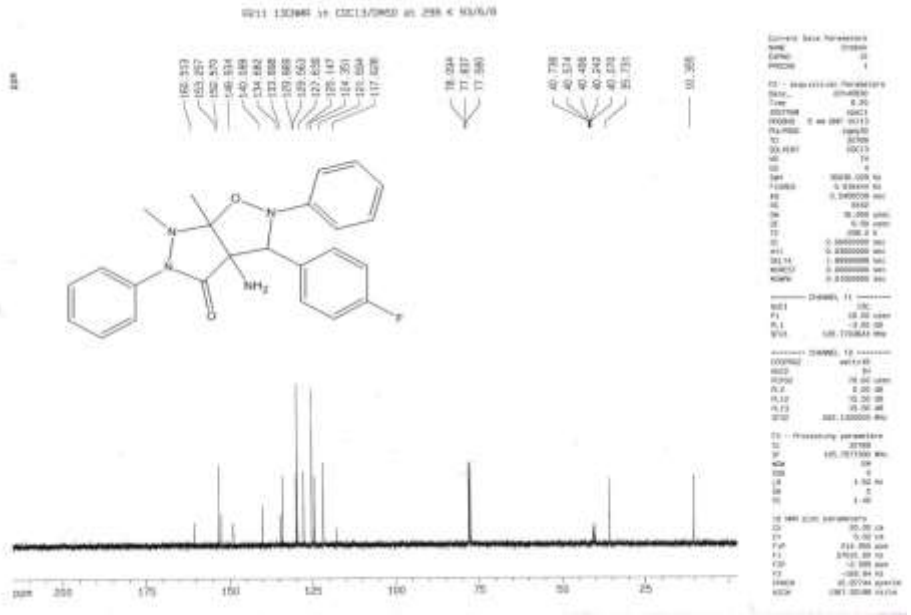

Fig. (10) ^{13}CNMR spectrum for compound (8)

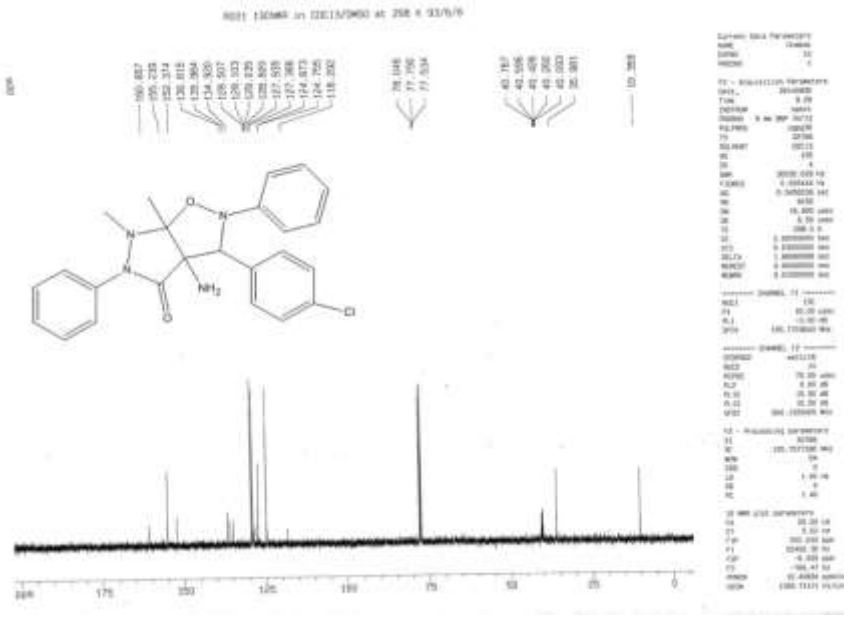

Fig. (11) ^{13}CNMR spectrum for compound (10)

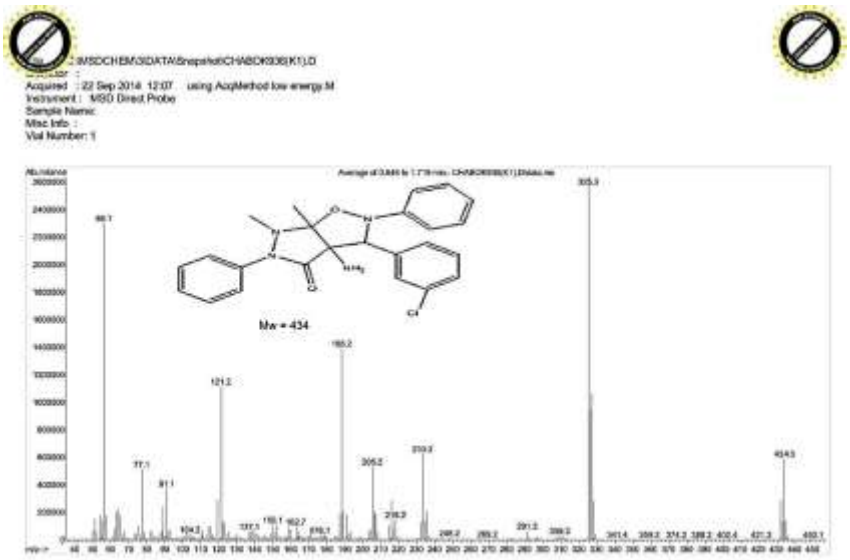

Fig. (12) Mass spectrum for compound (6)

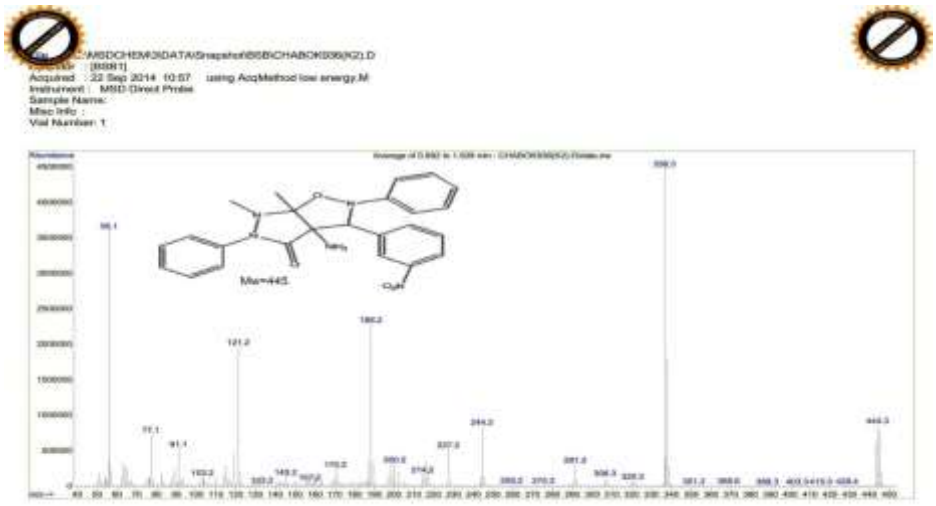

Fig. (13) Mass spectrum for compound (7)

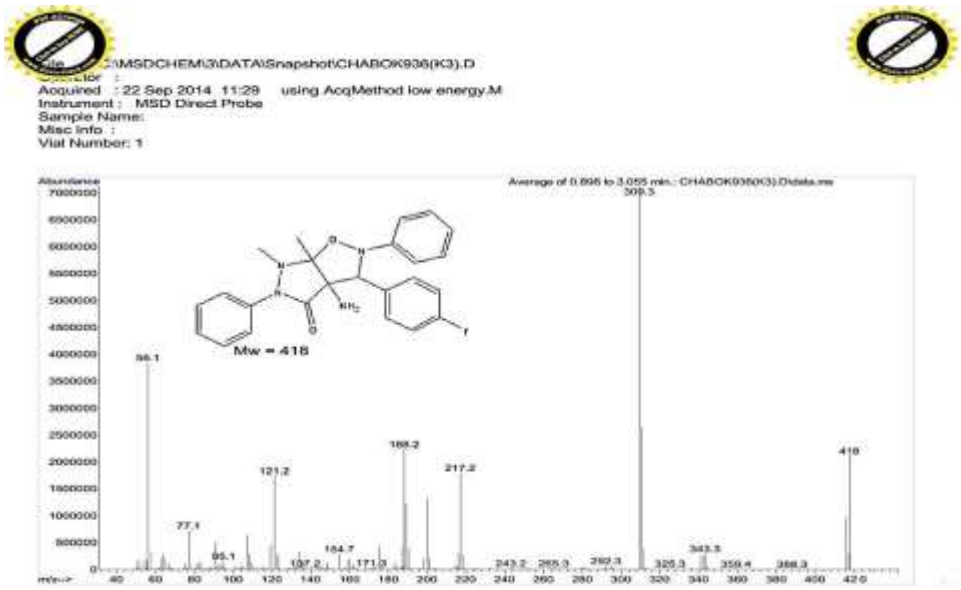

Fig. (14) Mass spectrum for compound (8)

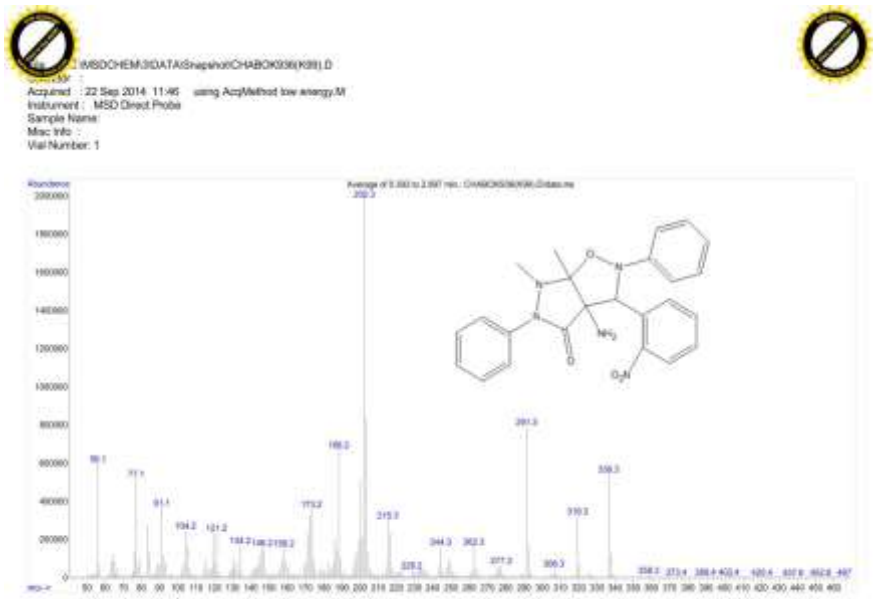

Fig. (15) Mass spectrum for compound (9)

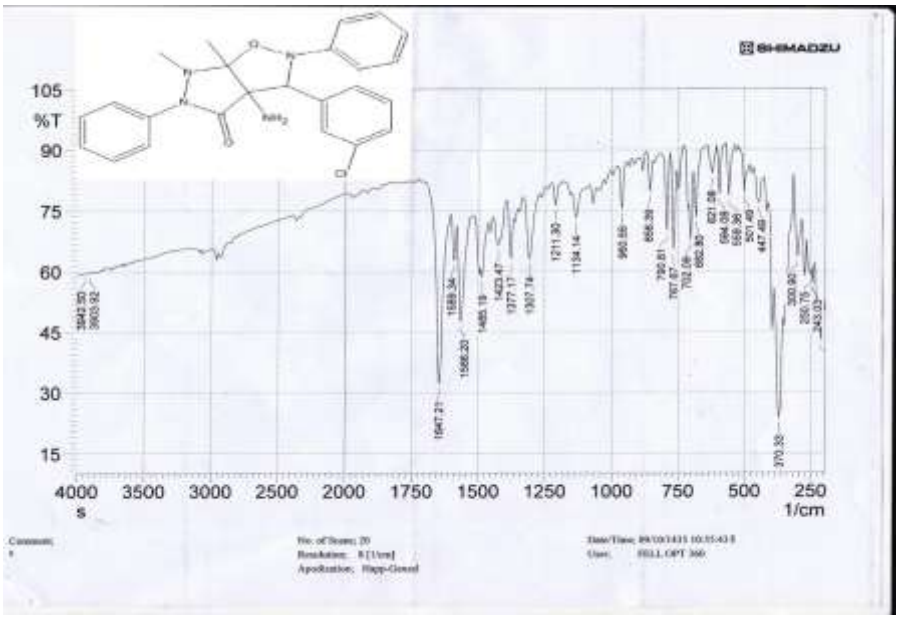

Fig. (16) IR spectrum for compound (6)

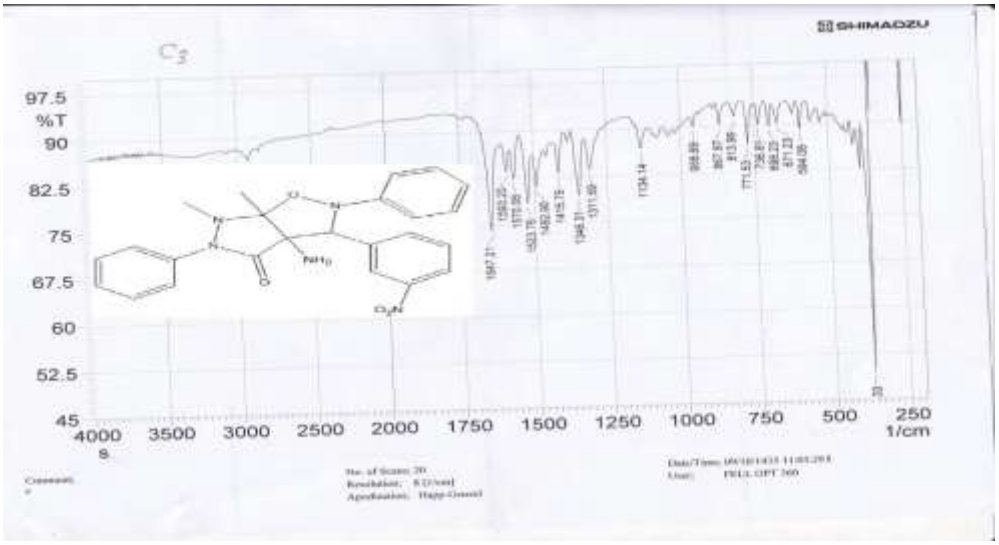

Fig. (17) IR spectrum for compound (7)

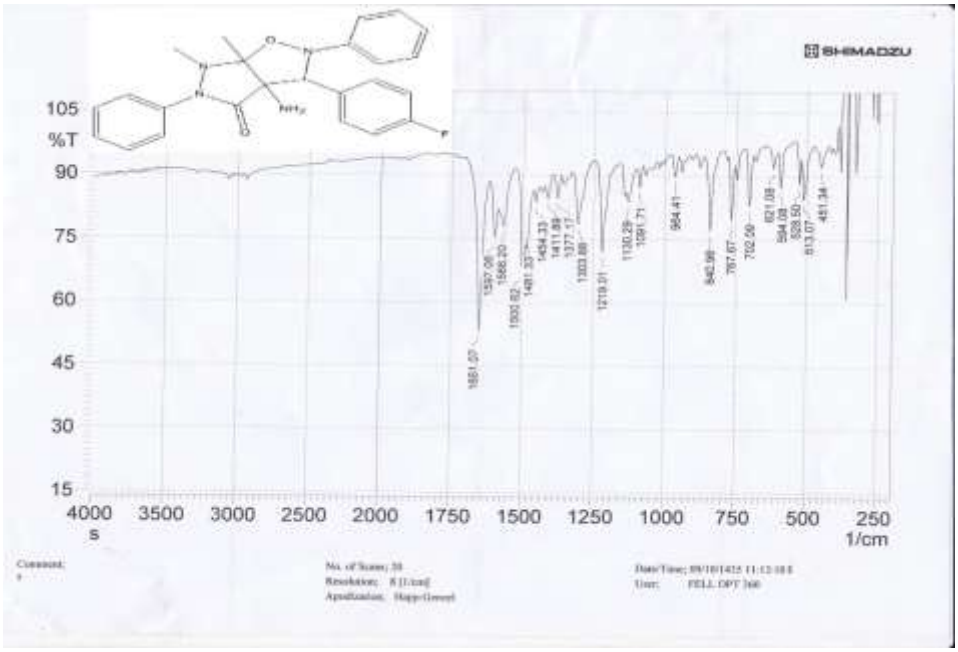

Fig. (18) IR spectrum for compound (8)

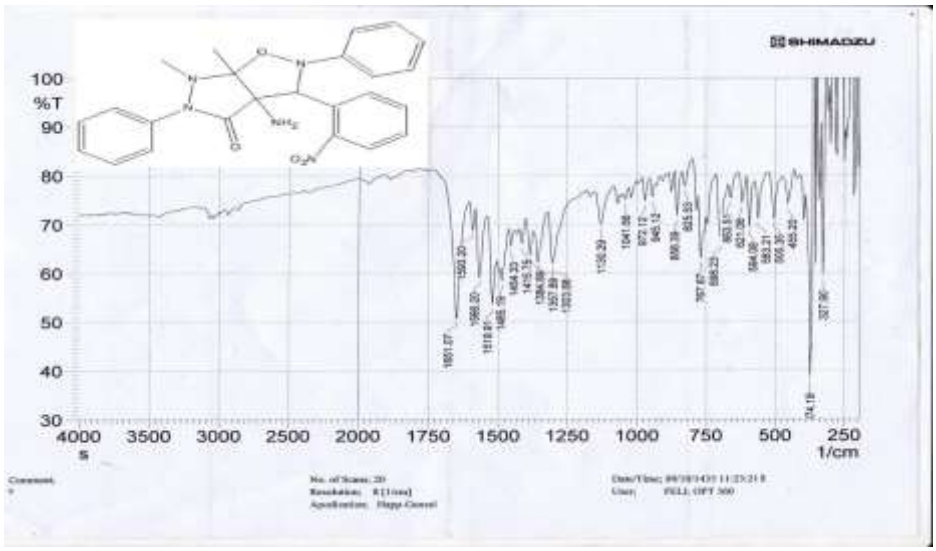

Fig. (19) IR spectrum for compound (9)

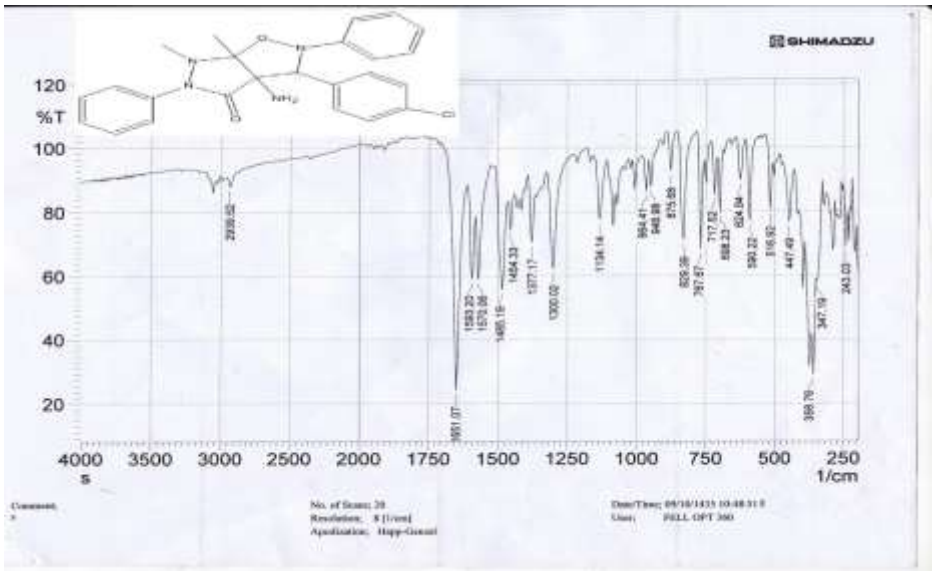

Fig. (20) IR spectrum for compound (10)