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Baghdad Science Journal **Vol.14(3)2017**

DOI: http://dx.doi.org/10.21123/bsj.2017.14.3.0564

Preparation and Characterization some New of Naproxen Drug Derivatives

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Received 8/1 /2017
Accepted 12/4 /2017

Abstract:

In this research four steps of the new derivatives of Naproxen drug have been made which are known as a high medicinal effectiveness; the first step involved converting Naproxen into the corresponding ester (A) by reaction Naproxen with methanol absolute in presence H_2SO_4. While the second step involved treatment methyl Naproxen ester (A) with hydrazine hydrate 80% in presence of ethanol .The third reaction requires synthesis of Schiff bases (C_1-C_{10}) by condensation of Naproxen hydrazide (B) with many substituted aromatic aldehydes . Finally, the fourth step synthesized new tetrazole derivatives (D_1- D_{10}) by the reaction of the prepared Schiff bases (in the third step) with Sodium azide in THF as a solvent .The prepared compounds were characterized by physical properties ,(FT-IR) ,UV, and somewhat of them by ^{1}H-NMR, ^{13}C-NMR spectroscopy.

Key words: Naproxen drug, Schiff base, Tetrazol compounds**.**

Introduction:

The Chemistry of heterocyclic compounds has been a fascinating scope of schooling of long time. The synthesis of piece Ttrazole derivatives and inquiry of their biological and chemical conduct has gained more momentousness in modern decades for all biologic and pharmaceutical reasons [1]. Tetrazole is a hetero cyclic compound which containing carbon atom and four nitrogen atoms in a five member ring[2]. Tetrazole compounds are used broadly in biochemistry, medicine pharmacology, explosives, and other scopes. Its derivatives have signification implementation in major scopes, like agriculture, imaging technology, and medicine and they are very stimulating hetero cycles from an academic view point [2-3]. Tetrazole and its derivatives have attracted much attention because of their individual form and implementation as anti-allergic,anti-hyper tensive nti-consultant agents anti, and biotic. Synthesis of tetrazole derivatives is obviously an important task in recent medicinal chemistry. [4] The development of the tetrazole chemistry has been imported, in the main as upshot result of the center roles played by tetrazoles in coordination chemistry as nitrogen containing heterocyclic legends[5-6] Naproxen is one of the most uniform used as a

propanoic acid derivative for the treatment of pain, joint swelling and symptoms of arthritis[7] is believed to work by blocking the action of cyclooxygenase (Cox) in evolved in the production of prostaglandins or prostaglandins straight after they have already been formed there by relieving pain and inflammation [8]. It is among the most commonly prescribed non-steroidal anti-inflammatory drugs (NSAIDs)for the management of inflammation and pain.[9]. They display biological activities that contain antibacterial, antifungal [9-10] anticancer [11], and herbicidal activities [12].

Materials and Methods: [13]

Chemicals employed were of analytical grade and used without further purification . Melting points were specified in Gallen Kamp melting point appliance and ethanol were not corrected. UV- visible spectra were recorded on T60u shimadzu spectrophotometer used as a solvent. FT-IR 8400 Fourier transform infrared spectrophotometer as KBr disc.^{1}H-NMR and ^{13}C-NMR spectra were written down on Bruker spectra spin Ultra shield magnets 300 MHz device using tetra methyl silane (TMS) as an inner standard .and DMSOd6 as a result in – Al bait University in the country of Jordan .

Procedure for the composition of methyl Naproxen [14]

Naproxen drug (1 gm, 0.004 mole) was taken in round bttom flask (250 ml) fitting tightly with a reflux condenser and calcium. Chloride guard tube add 25 ml methyl alcohol 99% add one or two drops of intense sulfuric acid and the mixture was refluxed for pouring in to 250ml of water incoming in a separating funnel add 20ml from di chloromethane to the separating funnel and the blend were jolted strenuously. The mixture was stopped and methyl Naproxen in dichloromethane detached and retained at the down of the separating funnel. The tower layer was cautiously split and the higher aqueous solution stratum was refused methyl Naproxen was returned to the funnel. and shaken with a powerful bicarbonate solution up to all the free aid was outside mthyl Naproxen was washed one time with solution water and dried by gushing to a mini dry conical flask be comprised two gm of anhydrous magnesium sulphate .This solution was shaken for 5 min and permit it to stand for 60 minutes. The methyl Naproxen solution was filtrated through a filter paper futed filter paper into a filtration flask. The flask was shaped with 360 $^{\circ}$C concenter and receiver flask .Dichloride methane was distilled of at 40°C and precipitate methyl Naproxen was acquired from flask. Ethanol was used dissolvent for purification of the ester is listed in Table (1).

Procedure of the preparation of naproxen hydroxide (B). [14]

A mixture of compound (A)(0.5g,0.004mole), Hydrazine hydrate 80% (0. 7ml and 0.004mole, ethanol (10ml) were put in round bottom flask and refluxed for 6 hrs. The mixture was contracted, cooled ,and the white crystal filtered derided and recrystallized from ethano1.The physical properties of compound (B) is listed in Table (1) .

Preparation of Schiff bases (C_1 -C_{10}) [6]

A chain of Schiff bases (C_1-C_{10}) were ready from the reaction of (0.01 mole)with different aromatic aldehydes (0.01 mole) in 25 ml ethanol absolute and one or two drops of glacial acetic acid .This blend was refluxed for 6 hrs The precipitate was recrystallized from ethanol. Melting points and yield % data are listed in Table (2).

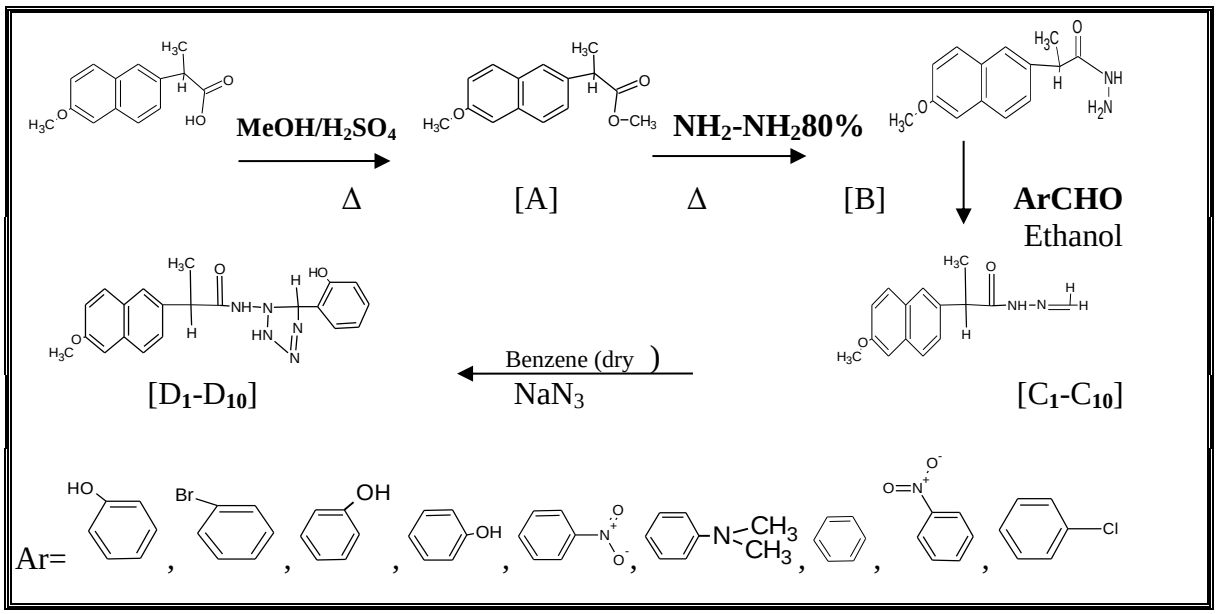
Preparation of Tetrazole derivatives (D_1 -D_{10}) [15].

Compounds of (C_1 -C_{10}) (0. 16gm, 0.01 mole) was dissolved in(20ml) tetra

hydro furan and mixed with (0.01ml) sodium azide. Those mixtures were heated in water bath at 75°C for 6 hrs. The precipitate was filtered and recrystallized from ethanol. The limit of reaction was checkup by TLC in methanol [16]. Melting points and yield % data are listed in Table(3).

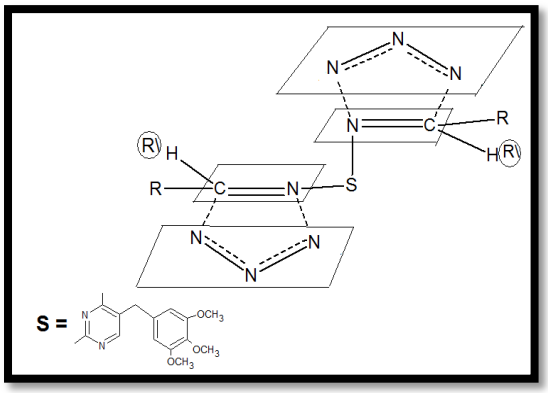
Results and Discussion:

Schiff bases can be prepared from condensing hydrazine with varies aromatic aldehydes; they have been prepared in the ratio 1:1 of to aromatic carbonyl compounds. The present investigation describes synthesis that is isolated and characterized by physical properties, spectroscopic data (Tables 1,2) .The FT-IR spectral data of Schiff bases compounds show the bands of the stretching vibrations due to the fact that (C-H) aromatic , (C-H) aliphatic , (C=N) imine group in the regions (3005-3180) cm^{-1}, (2852-2999) cm^{-1} and (1654-1739)cm^{-1} straight [14]. Schiff bases FT-IR spectrum of compound (C_6) show absence at (4) $cm^{-1}$for (NH_2) group in the starting material and appearance of the imine group (C=N)at (1654) cm^{-1}which is a good indication of successful condensation . Compound (C_6) shows absorption band at (2974) cm^{-1}due to (C-H) aliphatic ,(3001-3180) $cm^{-1}$for (C-H) aromatic , (1654) cm^{-1} (C=N) and (1471) cm^{-1} (C-N) listed in Table (4), Figure(7). The UV. Spectrum of (C_3) Figure (1) shows the absorption λ max of (235) nm due to the (π-π*) transition, whereas compound (C_5) Figure (2) shows the absorption λ max at (232) nm and (299)nm due to the (π-π*) and (n-π) transition^{1}H –NMR spectrum of compound (A) shows the signals (1.67) ppm is attributed to (CH_3) proton, multiple signals at (6.85-7.81) due to aromatic protons and singlet signal at (3.59) ppm due to (CO-CH) proton as shown in Figure (9) . ^{13}C-NMR spectrum of the same compound shows the signal at (147) for (C=O) amide and absorption at (119-136) for aromatic carbons as shown in Figure (10). The other route, reaction of Schiff bases with sodium azide [17] in dioxan with water bath produces tetrazol compound dispossess wide spectrum of biological activities, the overall steps of synthesized compounds are shown in Scheme(1)



Scheme (1) The mechanism of reacting

The mechanism of reacting systematically investigation as [3-2] cycloaddition which is called as 1,3 – dipolar cycloaddition reaction. It involves the addition of unsaturated systems, dipolarphiles, to 1,3 – dipoles a molecule possessing resonance contributors in which appositive and negative charge are placed in 1,3-position relative to each other .The accession results in five member rings, azides are a prominent class of 1,3-dipoles and azide1,3-dipolar cyclo addition [18] .



Scheme (2) Structure of tetrazol

The formula structure for tetrazol compound (D_1-D_{10}) is confirmed by spectroscopic data and physical properties in Table (3) and (2) . FT-IR spectra of the products show the absorption of the starching vibrations due to (C-H) aliphatic , (C-H) aromatic and (N=N) tetrazol group in the region (2937-2833)cm^{-1}, (3122-3008) cm^{-1} and (1653-1593)cm^{-1} respectively.

Moreover, the FT-IR spectra of these compounds are devoid of starches band at (2160 -2120) cm^{-1}attributed to starching frequency of azide group[19]. The above data agrees with the proposed structures assigned to these compounds. Compound [D_6] shows absorption band at (2848-2999) cm^{-1} for (C-H) aliphatic (3043-3182) cm^{-1} for (C-H) aromatic, (1654) cm^{-1} for (N=N)cm^{-1},and (2144) cm-1 for (=N-N=C-) ,tetrazol ring listed in Table (3) Figure (8). The UV. Spectrum of compound ($D_5$and D_8) Figure (3 and 4) show the absorption λ max at (233,299) nm due to the (π-π*).^{1}H-NMR Spectrum of compound (D_8) show the signals (1. 46ppm) due to (CH_3) proton, multiple signals at (7.14-7.89) due to aromatic protons and singlet signal at(3.86) due to (N-H) proton as shown in Figure (15), ^{13}C-NMR spectrum of the same compound showes the signal at (160-176) for (C=N) and absorption at(105-135) for (aromatic carbons as shown in Figure(16).

Table (1) The physical properties for Compounds (A, B)

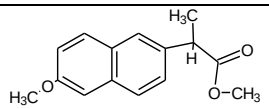
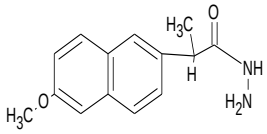
Comp. No.	Compound structure	Color	Melting Point/ ° C	Percentage %	Solvent used In recrystallization
A.	 $C_{15}H_{16}O_3$	Off White	82-84	83	Methanol
B.	 $C_{14}H_{16}N_2O_2$	Brown	119-121	44	Ethanol

Table (2) The Physical properties for Schiff base C (1-10)

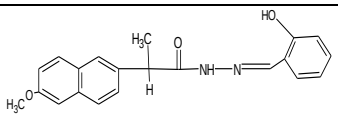
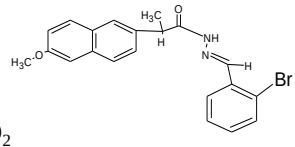
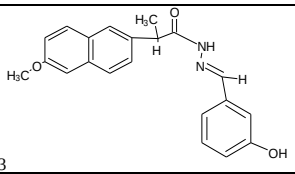
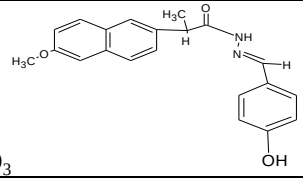
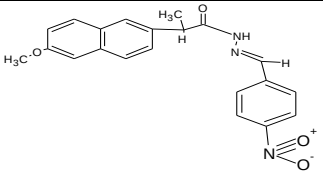
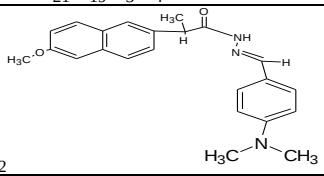
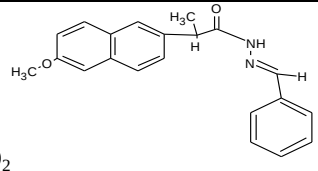
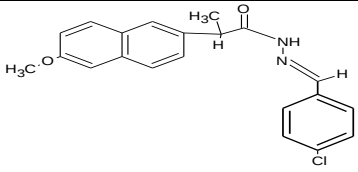
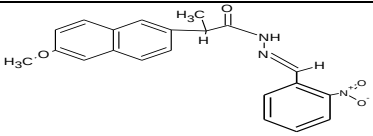
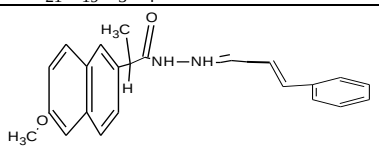
Comp. No.	Compound structure	Color	Melting Point/ ° C	Percentage%
C1	 $C_{21}H_{20}N_2O_3$	Light Yellow	88-90	51
C2	 $C_{21}H_{19}BrN_2O_2$	Yellowish brown	94-96	67
C3	 $C_{21}H_{20}N_2O_3$	Light brown	96-98	72
C4	 $C_{21}H_{20}N_2O_3$	brown	89-91	63
C5	 $C_{21}H_{19}N_3O_4$	Dark yellow	165-167	52
C6	 $C_{23}H_{25}N_3O_2$	yellow	160-163	56
C7	 $C_{21}H_{20}N_2O_2$	Light yellow	80-82	66
C8	 $C_{21}H_{19}ClN_2O_2$	Light yellow	90-92	77
C9	 $C_{21}H_{19}N_3O_4$	Brown	84-86	56
C10	 $C_{25}H_{26}N_2O_2$	Brown	86-88	51

Table (4) The FT-IR spectral data for all compounds

Comp. **No**	V(C=N)	V(C-H) aromatic	V(C-H) aliphatic	V(N-H)	V(C-N)	V(=N-N=C-)	(C=O)	Others
A	-	3080	2939	-	-	-	-	V(C-O)1193
B	-	3040	2979	3244	-	-	1700	-
C	-	3059	2978-2935	3294	1385	-	1635	-
C1	1678	3055	2954-2854	3213	1346	-	1635	V(O-H)3394
C2	1716	3070	2974-2830	3366	1336-1394	-	1639	-
C3	1660	3050	2976-2941	3350	1330	-	1637	V(C-OH)3566
C4	1639	3005	2848-2976	3246	1336	-	1620	V(C-OH)3587
C5	1700	3080	2925-2860	3300	1350	-	1605	V(C-NO_2) 1365-1506
C6	1654	3001	2974-2840	3292	1371	-	1635	-
C7	1680	3053	2935-2870	3238	1348	-	1683	-
C8	1675	3050	2999-2810	3223	1300	-	1625	V(C-Cl)825-1174
C9					-			
C10	1662	3014	2852-2962	3250	1350	-	1629	-
D1	-							
D2	-	3088	2929-2890	3290	1392	2127	1630	V(C-Br)640
D3	-	3080	2930-2810	3190	1356	2125	1670	V(C-OH) 3500
D4	-	3070	2850-2933	3298	1350	2129	1630	V(C-OH) 3388
D5	-	3113	2914-2981	3390	1360	2137	1620	V(C-NO_2) 1367-1550
D6	-	3043-3082	2848-2999	3296	1385	2144	1670	
D7	-	3070	2976-2850	3290	1385	2142	1668	
D8	-	3070	2933-2855	3390	1350	2123	1639	V(C-Cl) 1159-856
D9	-	3061	2825-2976	3296	1344	2108	1660	
D10	-	3100	2940-2820	3390	1392	2127	1631	-

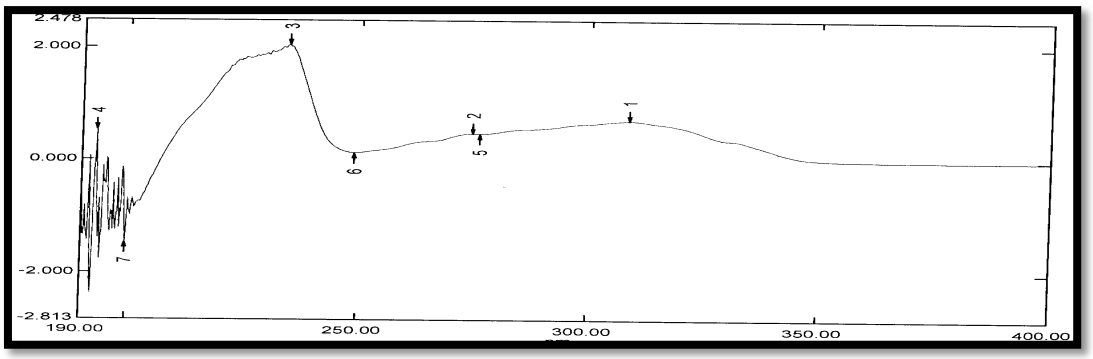


Fig. (1) UV spectrum for compoundC3

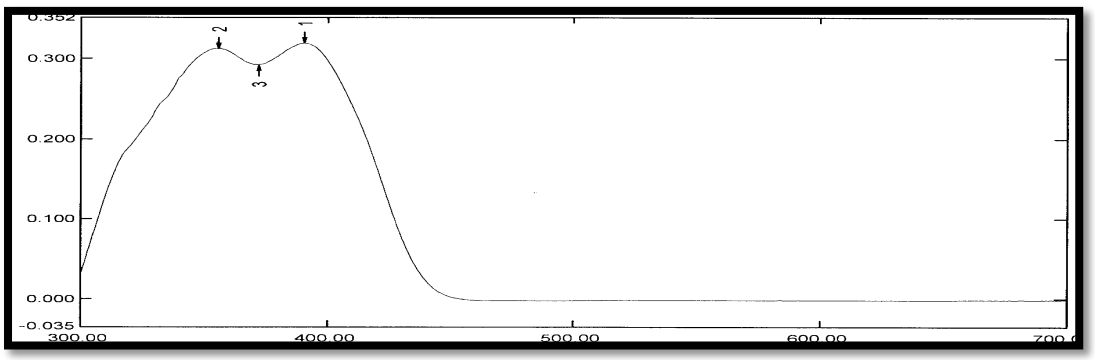


Fig.(2) UV spectrum for compoundC5

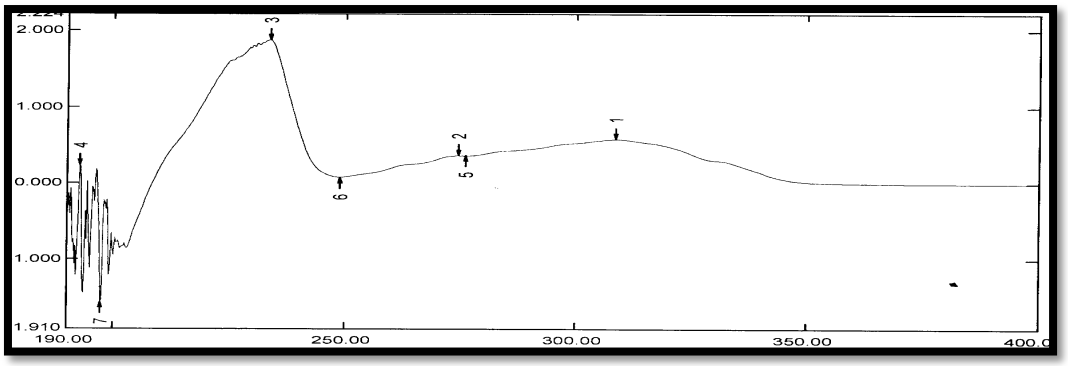


Fig. (3) UV spectrum for compo und D5

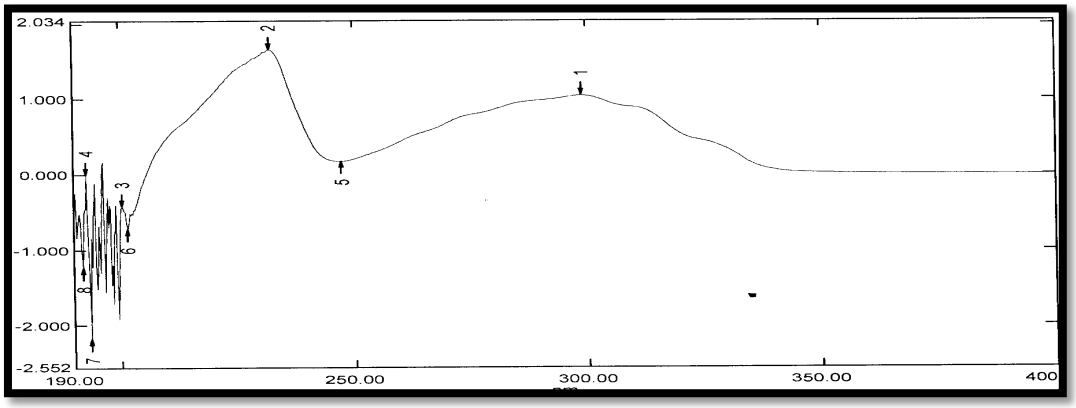


Fig. (4) UV spectrum for compound D8

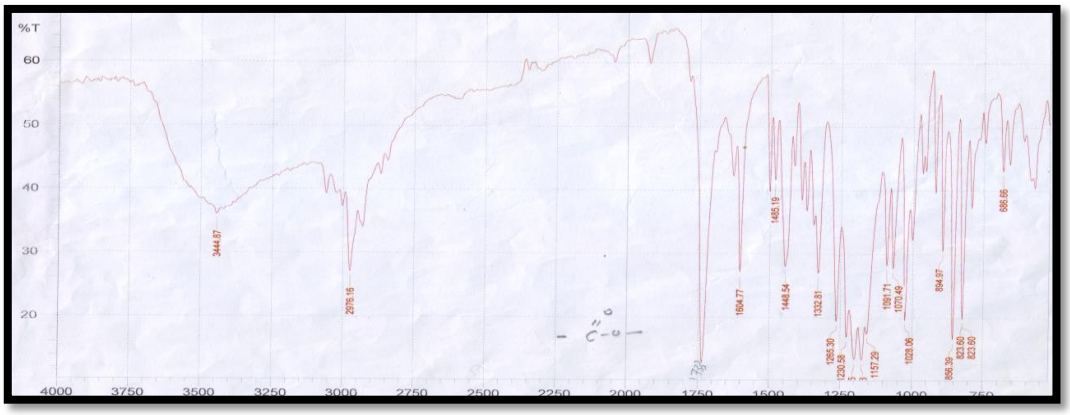


Fig. (5) FT-IR spectrum for compound(Ester) (A)

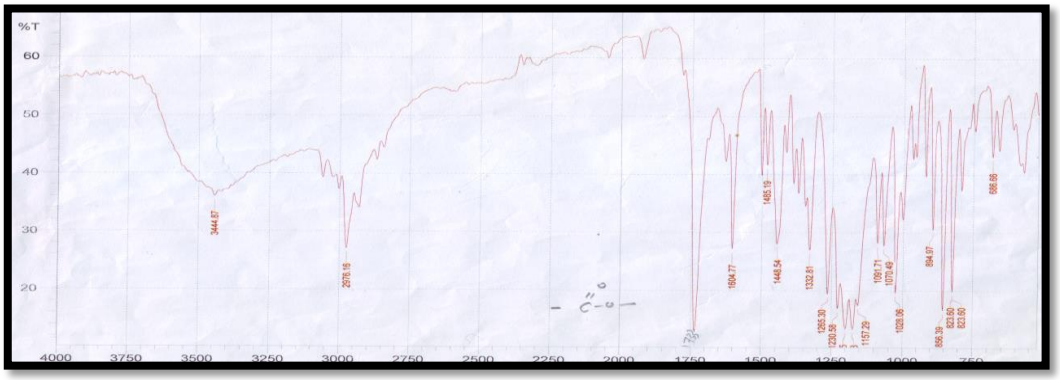


Fig. (6) FT-IR spectrum for compound (Hydrazid) (B)

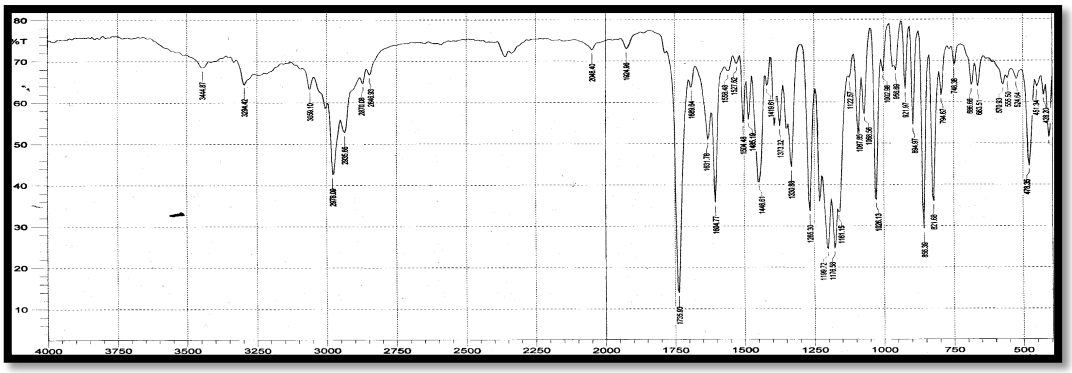


Fig. (7) FT-IR spectrum for compound (Schiff base) (C6)

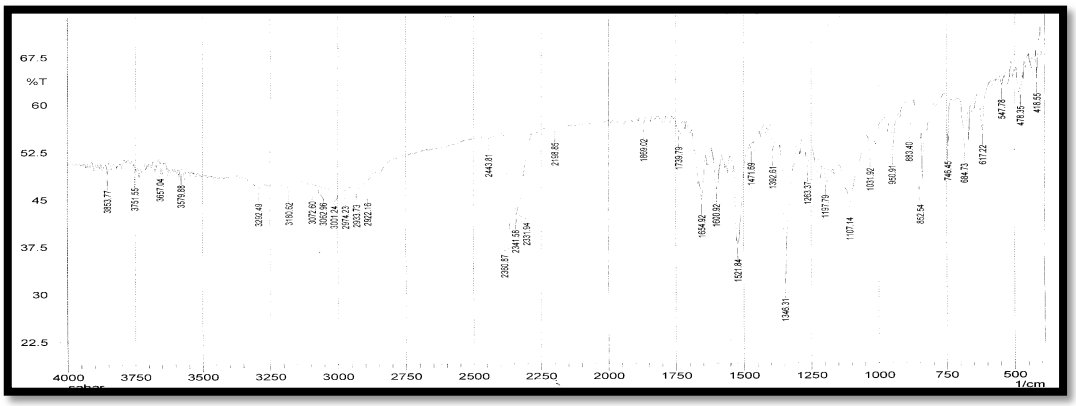


Fig. (8) FT-IR spectrum for compound (Titrazole) (D6)

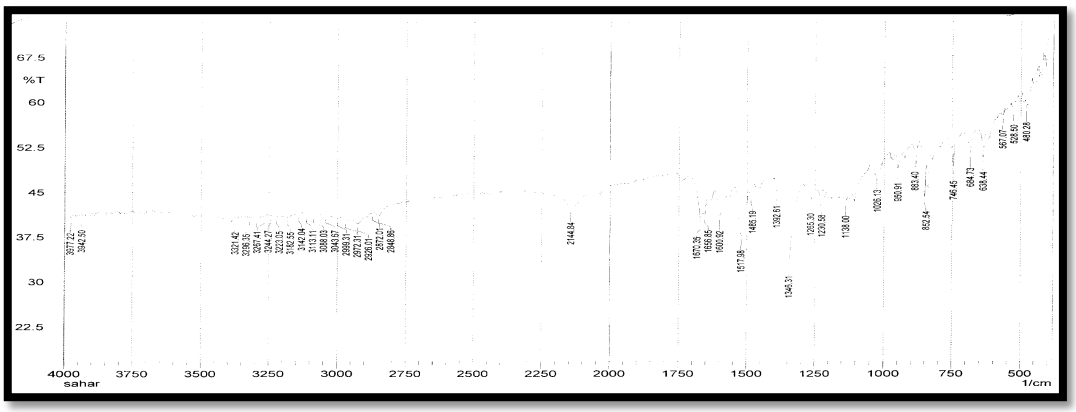


Fig. (9) [1] H-NMR spectrum for compound(Ester) (A)

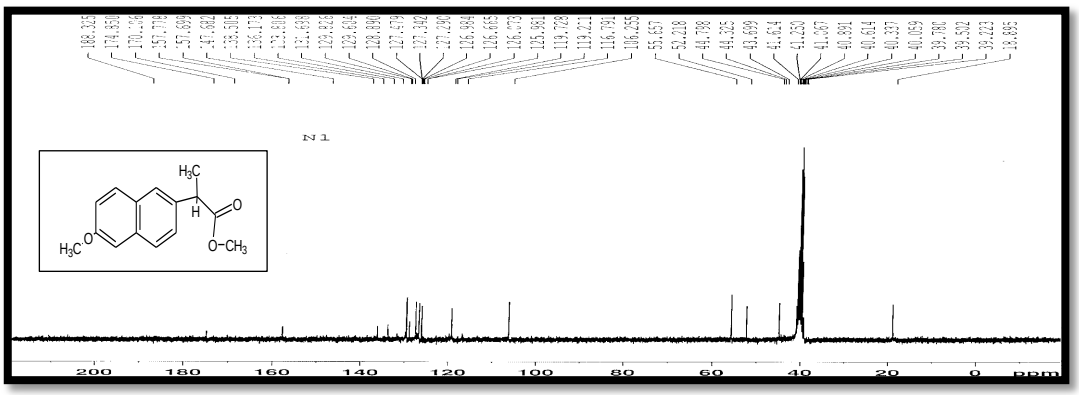


Fig. (10) [13]C-NMR spectrum for compound(Ester) (A)

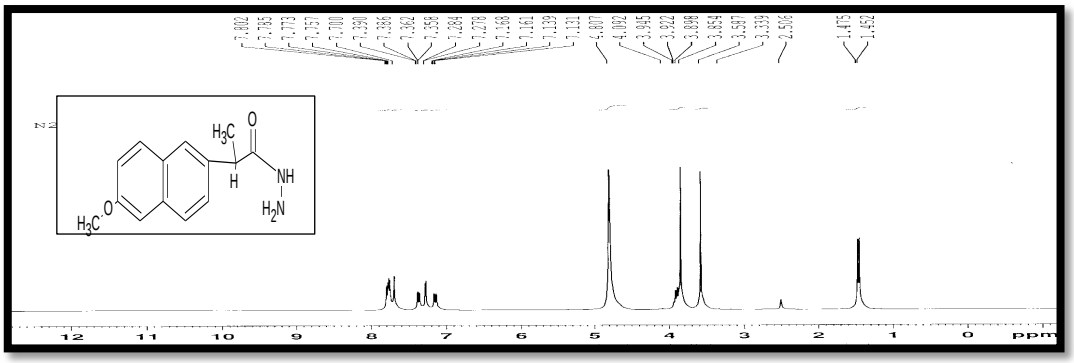


Fig. (11) ^{1}H-NMR spectrum for compound (Hydrazed) (B)

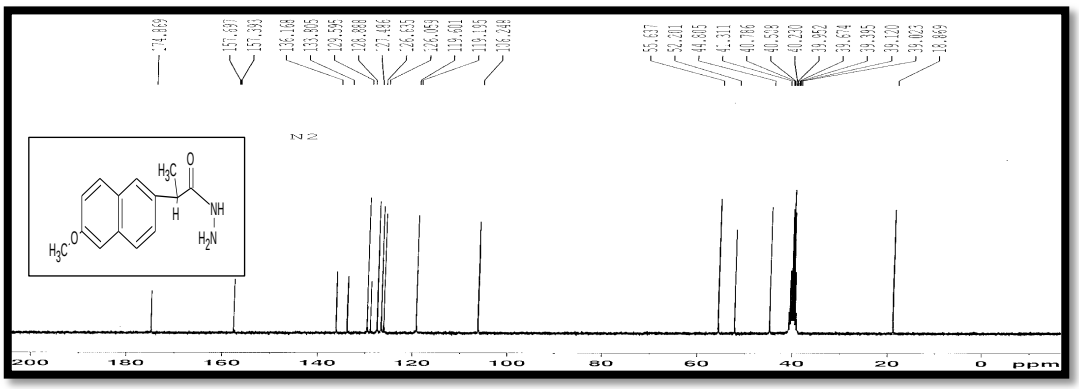


Fig.(12) ^{13}C-NMR spectrum for compound (Hydrazed)(B)

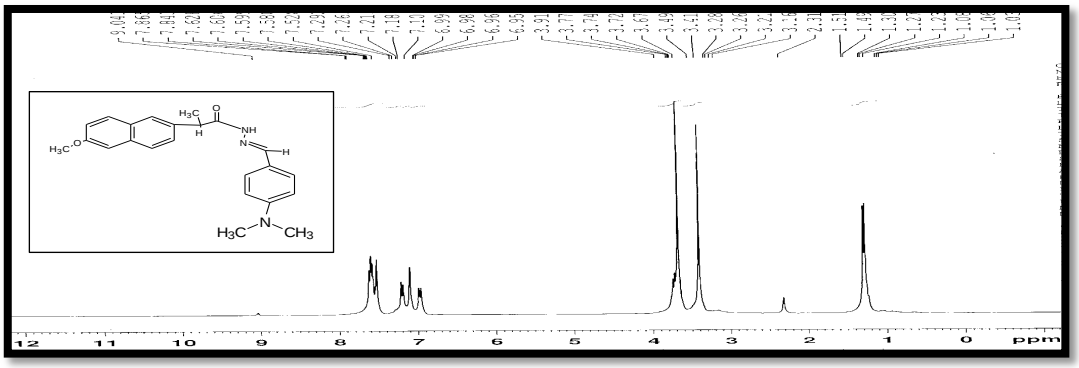


Fig. (13) ^{1}H-NMR spectrum for compound(Schiff base) (C_6)

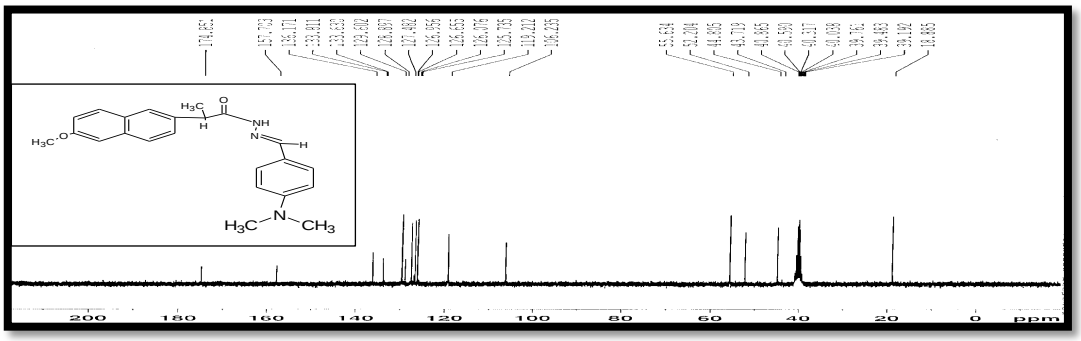


Fig. (14) ^{13}C-NMR spectrum for compound (Schiff base) (C_6)

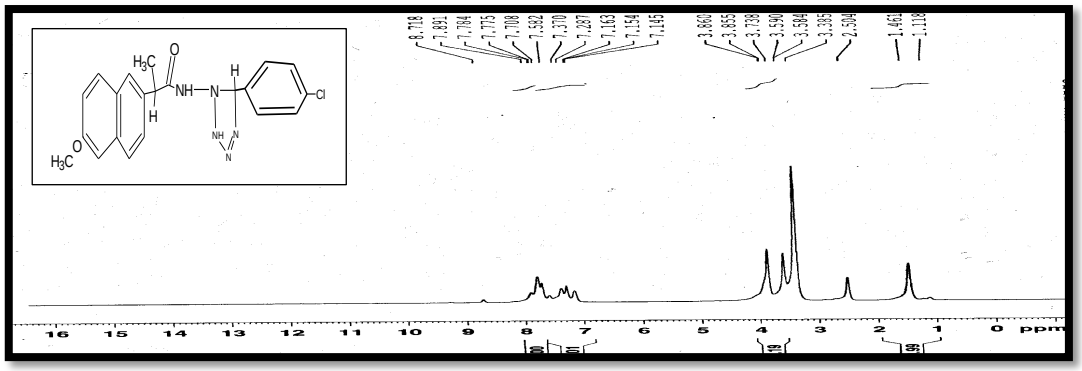


Fig. (15) ^{1}H-NMR spectrum for compound (Titrazol) (D8)

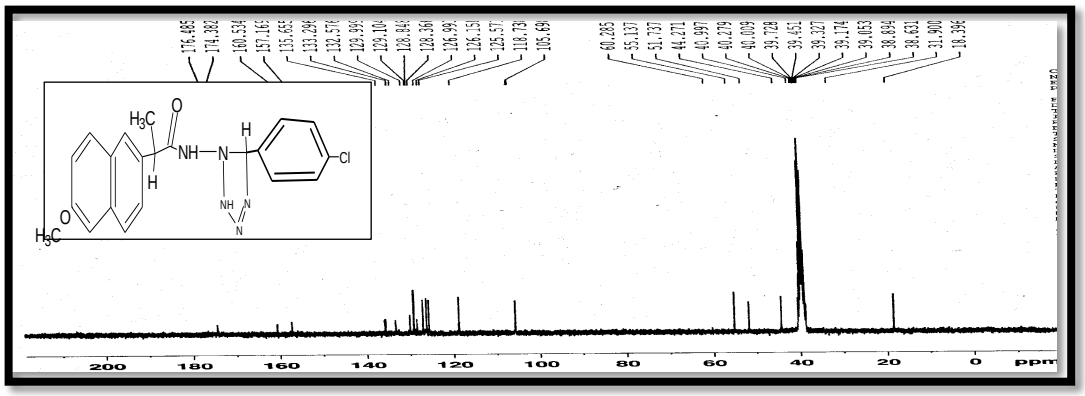


Fig.(16) ^{13}C-NMR spectrum for compound (Titrazol) (D8)

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تحضير وتشخيص بعض المشتقات الجديدة لدواء النبر وكسين

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الخلاصة:

حضرت مشتقات دواء النبروكسين ذو التأثيرات الدوائية بأربع خطوات تضمنت الخطوة الأولى تحويله إلى استر(A) عن طريق تفاعل النبروكسين مع الميثانول المطلق بوجود الوسط الحامضي . ثم الخطوة الثانية التي تضمنت تفاعل الاستر المحضر في الخطوة الاولى مع الهيدرازين المائي لإنتاج المركب (B) بوجود مذيب الايثانول المطلق، في حين الخطوة الثالثة من البحث تضمنت تفاعل المركب (B) مع بعض الالديهايدات الاروماتية المختلفة التعويض لإنتاج المشتقات (C_1-C_{10}) وأخيراً في الخطوة الرابعة يتم مفاعله قواعد شيف (C_1-C_{10}) (في الخطوة الثالثة) مع أزايد الصوديوم في مذيب THF كمذيب لإنتاج (D_1-D_{10}) . تم تشخيص المركبات فيزيائياً وطيفياًوذلك عن طريق قياس الخصائص الفيزيائية وباستخدام التقنيات الطيفيةUV,FTIR - ^{13}C NMR, - ^{1}H- NMR

الكلمات المفتاحية: دواء نبروكسين، قواعد شف، مركبات تترازول.