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Synthesis, Characterization of Derivatives Tetrazoles for Trimethoprim Drug

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Abstract:

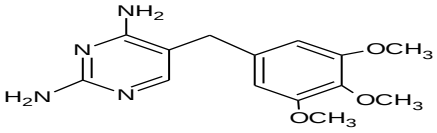
The present work involved synthesis of serval new substituted tetrazole via Schiff bases for trimethoprim drug by two steps. The first step involved direct reaction of different ketones and aldehydes with trimethoprim producing the corresponding Schiff bases (1-10), whereas the second step, involved preparation new tetrazoles derivatives (11-20) through reaction of the ready Schiff bases (in the first step) with sodium azidein in dioxin. The prepared compounds were characterized by UV, FT-IR, and some of them by ^{13}C-NMR, ^{1}H-NMR spectroscopy and physical properties.

Key words: trimethoprim drug, derivatives, tetrazoles, Schiff bases

Introduction:

Heterocyclic compounds have been a good field of study long time, the synthesis of novel tetrazole compounds and search of their biological and chemical behavior have gained more significance in the recent decades for pharmaceutical and biological reasons [1]. Tetrazole is a heterocyclic compound containing a carbon atom and four nitrogen atoms in a five membered ring [2]. Since 1950, when tetrazole compounds become widely used in agriculture, biochemistry, medicine, pharmacology, explosives, and other aspects, research began to develop rapidly .Tetrazole and its derivatives have attracted a lot of, attention because of their applications as antihypertensive and their unique structure ,anticonvulsant agents, antibiotic, and anti-allergic. Structure of tetrazole derivatives is obviously an important task in modern medicinal chemistry [3-5]. The evolution of the tetrazole chemistry has been significant, fundamentally as an outcome of central roles played by tetrazole in coordination chemistry as nitrogen – containing heterocyclic ligands [6-7].The N=CH (imine) group is fundamentally for Schiff bases. The are important compounds in pharmaceutical and medicinal field [8], they show biological activities including antifungal, antibacterial, anticancer [9], and herbicidal activities [10-11]. Furthermore, Schiff bases have been widely used as protective group of amino group in organic synthesis [12]. The

chemical designation of trimethoprim is 2,4- diamine-5-(3,4,5- trimethoxypenzyl) pyrimidine($C_{14}H_{18}N_4O_3$) was first describe by Roth and coworkers. It is a white to yellowish compound with better last the trade names of the combined product are bacterium and spectra[13].It was reacted with selected ketone to give new Schiff bases.



Materials and Methods:

Chemicals employed were of analytical grade and used without further purification. Melting points were determined in gallerkamp melting points apparatus and were uncorrected. UV – visible spectra were recorded on shimadzuT60u spectrophotometer using ethanol as a solvent, FT-IR 8400 Fourier transform infrared spectrophotometer as KBr disc. ^{1}H-NMR and ^{13}C- NMR spectra were recorded on Bruker specrosp in Ultra shield magnets 300MHz instrument using tetra methylsilane(TMS) as an internal standard and DMSO.d6 as a solvent in Al-Albate University in Jordan.

Preparation of Schiff Bases (1-10) [9]:

A series of Schiff bases (1-10) were prepared from the reaction of trimethoprim (0.01mol) with different aromatic aldehydes or ketones (0.01mol) in 25 ml DMF or absolute ethanol and few drops of glacial acetic acid. This mixture was refluxed for 5hrs. The precipitate was filtered and recrystallized from ethanol. Melting points, yield% data are listed in Table (1).

Preparation of Tetrazol Derivatives (11-20)[8]:

Compounds of (1-10) (0.01mol) were dissolved (20 ml) dioxan and mixed with (0.01 mol) sodium azide. The mixture was heated in water bath at 75 ºC for 7hrs. The precipitate was filtered and recrystallized from ethanol. The end of reaction was checked by TLC in methanol .Melting points, yield% data are listed in Table (2).

Table (1): Physical properties for Schiff bases compounds.

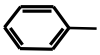
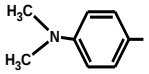
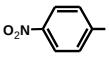
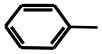
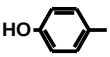
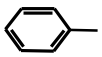
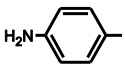
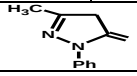
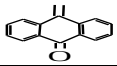
Sr.No.	R	R\	Molecule formal/ Molecule weight	M.P.	Yield%	Colour	Solvent
1.		-	$C_{28}H_{26}N_4O_3$ 466.53	201-205	69	Light Yellow	DMF
2.		-	$C_{32}H_{36}N_6O_3$ 552.66	150-152	70	Greenish yellow	DMF
3.		-	$C_{28}H_{24}N_6O_7$ 556.52	80-83	65	Light Yellow	DMF
4.			$C_{40}H_{34}N_4O_3$618.72	180-185	49	white	DMF
5.		-CH_3	$C_{30}H_{30}N_4O_3$ 494.58	197-200	55	Off white	Ethanol
6.			$C_{40}H_{34}N_4O_5$ 650.72	170-175	58	white	Ethanol
7.		-CH_3	$C_{30}H_{32}N_6O_3$ 524.61	98-100	71	Brown	Ethanol
8.		-CH_3	$C_{30}H_{32}N_6O_3$ 524.61	164-168	65	Brown	Ethanol
9.			$C_{34}H_{34}N_8O_3$ 602.68	112-114	50	Grey	Ethanol
10.			$C_{42}H_{34}N_4O_3$ 642.74	204-206	43	Light yellow	Ethanol

Table (2): Physical properties for tetrazol compounds

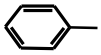
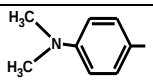
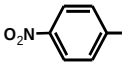
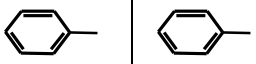
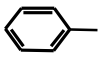
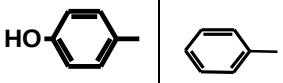
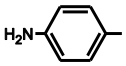
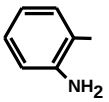
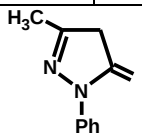
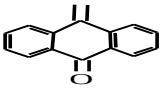
Sr.No.	R	R\	Molecule formal/ Molecule weight	M.P.	Yield%	Colour	Solvent
11.		-	$C_{28}H_{28}N_{10}O_3$ 552.58	198-200	70	White	Dioxan
12.		-	$C_{32}H_{38}N_{12}O_3$ 638.72	160-163	50	Off white	Dioxan
13.		-	$C_{28}H_{26}N_{12}O_7$ 642.85	169-171	44	Yellow	Dioxan
14.			$C_{40}H_{36}N_{10}O_3$ 704.77	156-158	62	Light Yellow	Dioxan
15.		$-CH_3$	$C_{30}H_{32}N_{10}O_3$ 580.64	192-194	70	Off white	Dioxan
16.			$C_{40}H_{36}N_{10}O_5$ 736.77	179-180	54	Off white	Dioxan
17.		$-CH_3$	$C_{30}H_{34}N_{12}O_3$ 610.66	153-155	64	Brown	Dioxan
18.		$-CH_3$	$C_{30}H_{34}N_{12}O_3$ 610.66	188-191	52	Yellow	Dioxan
19.			$C_{34}H_{36}N_{14}O_3$ 688.74	128-130	48	Brown	Dioxan
20.			[$C_{42}H_{36}N_{10}O_3$ 728.80	181-184	62	Yellow	Dioxan

Table (3): FT-IR spectral data for some functional group for all product compounds

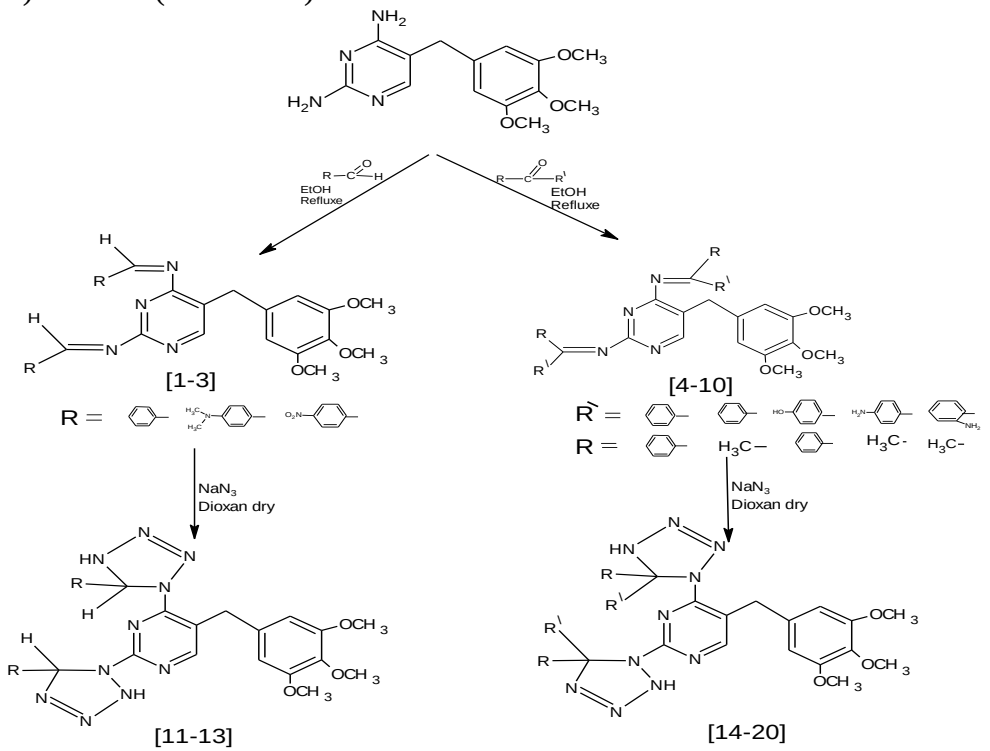
Sr.No	(C=N) In out ring	υ (C-H) Aliphatic cm^{-1}	υ (C-H) Aromatic cm^{-1}	υ (N-H)	υ (C-N)	υ (N=N)	=N-N=C-	Others
1.	1590	2835-2929	3012-3120	_	1410	_	_	_
2.	1662	2831	3134	_	1460	_	_	_
3.	1707	2841-2939	3078-3107	_	1421	_	_	υ($-NO_2$) 1364,1521
4.	1635	2850	3116	_	1421	_	_	_
5.	1635	2833-2929	3118	_	1508	_	_	_
6.	1635	2833-2929	3014-3120	_	1458	_	_	υ(-OH) 3469
7.	1591	2999	3100	_	1425	_	_	υ ($-NH_2$) 3448-3396
8.	1653	2833-2929	3014-3147	_	1458	_	_	υ($-NH_2$) 3448-3431
9.	1654	2833	3128	_	1498	_	_	_
10.	1630	2835-2931	3008-3122	_	1458	_	_	υ (C=O) 1645
11.	_	2854-2926	3116-3155	3390	1458	1597	2139	_
12.	_	2937-2833	3122	3429	1458	1593	2090	_
13.	_	2841-2935	3049-3080	3365	1456	1593	2119	υ ($-NO_2$) 1349,1506
14.	_	2835-2929	3012-3118	3469	1463	1640	2125	_
15.	_	2835-2931	3014-3122	3319	1458	1597	2125	_
16.	_	2927	3014-3118	3317	1412	1635	2133	υ (-OH) 3455
17.	_	2935-2931	3120	3224	1508	1653	2129	υ($-NH_2$) 3469-3332
18.	_	2835-2931	3120	3224	1508	1653	2129	υ($-NH_2$) 3469-3388
19.	_	2837-2929	3014-3120	3469	1458	1635	2125	_
20.	_	2835-2931	3014-3122	3390	1463	1597	21	υ (C=O) 1635

Results and Discussion:

Trimethoprim Schiff bases can be prepared from condensing trimethoprim with varies aromatic aldehydes and ketones. They were prepared in the ratio 1:2 of trimethoprim to aromatic carbonyl compounds. The present investigation describes synthesis, isolated, and characterized by physical properties, spectroscopic data (table1, table 3). The FT-IR spectral data of Schiff base compound showed the bands of the stretching vibrations due to (C-H) aromatic,(C-H) aliphatic,(C=N) imine group in the regions (3008-3147)cm^{-1}, (2831-2999)cm^{-1} and (1590- 1707) cm^{-1} respectively[14].

Schiff bases [1-10] FTIR spectrum show the absence at **υ**(3260,3370) cm^{-1}, for NH_2 group in the starting material and appearance of the imine group (C=N) band at (1590-1707) cm^{-1} which is a good indication of successful condensation. Compound [6] showing absorption band at (2833-2929) cm^{-1} (C-H) aliphatic, (3014-3120) cm^{-1} for **(**C-H) aromatic, (1635) cm^{-1} (C=N) and (1458) cm^{-1}(C-N) listed in table (3) Figure (1).The UV spectrum of compound[8] Figure (3) showed the absorption λ max at (290) nm due to the (π –π*) transitions, whereas compound [10] Figure (4) showed the absorption λ max at (364-306) nm due to the (π –π*) and (n –π*) transitions.

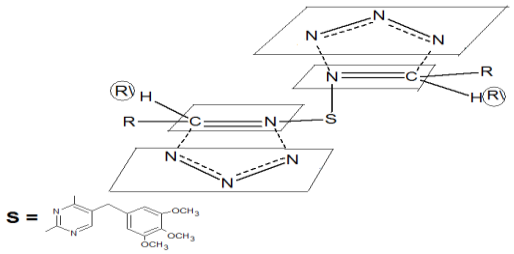
The other route, reaction of Schiff base with sodium azide in dioxin with water bath, produced tetrazol compounds that possess wide spectrum of biological activities, the overall steps of synthesized compounds are shown in scheme 1 and the mechanism of reaction shown in scheme (2).



Scheme 1: Overall reaction steps

The mechanism of reacting systematically investigation as [3-2] cycloadditions which christened as 1, 3-dipolar cycloaddition reaction[15].It involved the addition of unsaturated systems, dipolarphiles, to 1,3-dipoles a

molecule possessing resonance contributors in which a positive and negative charge are located in 1,3-position relative to each other. The addition results in a five member ring, azides are a prominent class of 1,3-dipoles and azide 1,3-dipolar cycloaddition[16].



Scheme 2: mechanism of reaction

The formula structure for tetrazol compound (11-20) was confirmed by spectroscopic data and physical properties in Table (3) and (2). FT-IR spectra of the products showed 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. Beside this, the FT-IR spectra of these compounds were devoid of starches band at (2160-2120) cm^{-1}attributed to stretching frequency of azide group. The above data agree with the proposed structures assigned to these compounds. Compound [16] showed absorption band at (2927) cm^{-1} for (C-H) aliphatic, (3014-3114) cm^{-1} for (C-H) aromatic, (1635) cm^{-1} for (N=N) cm^{-1} , and (2133) $cm^{-1}$for (=N-N=C-) tetrazole ring listed in Table (3) Figure (2).The UV spectrum of compound [18]F (5) showed the absorption λ max at (353 ,458) nm due to the (π –π*) and (n –π*)transitions, whereas compound [20] Figure (6) showed the absorption λ max at (264,324) nm due to the (π –π*)and (n –π*)transitions.

H^1-NMR spectrum of compound [12] showed the signals (1.9) due to (CH_3) proton, multiple signals at (7.1-7.6) due to aromatic protons and singlet signal at (5.2-6.2) due to(N-H) proton as shown in Figure (7) Compound[18]showed the signals(1.7) due to(CH_3) proton, multiple signals at (7.02-7.98) due to aromatic proton and singlet signal at (5.07-6.64) due to(N-H) proton as show in in Figure(8). The ^{13}C-NMR spectrum of compound (12) showed the signal at (18.9) for (C=N) and absorption at (122-135) for aromatic carbons as shown in Figure (9), whereas compound (18) showed the signal at (174) for (C=N) and absorption at (114-135) for aromatic carbons as shown in Figure (10).

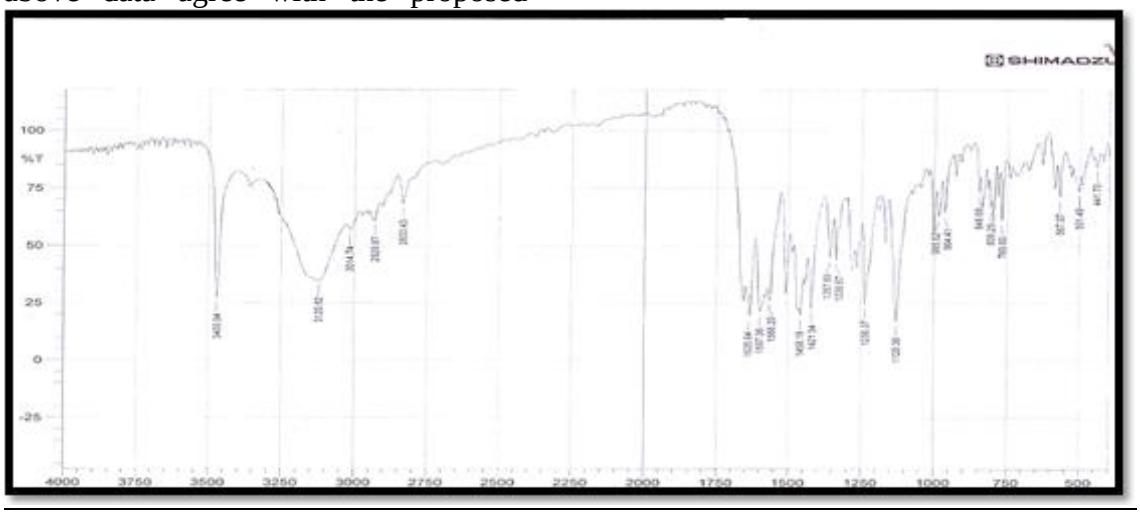


Fig. (1): FT-IR of compound 6

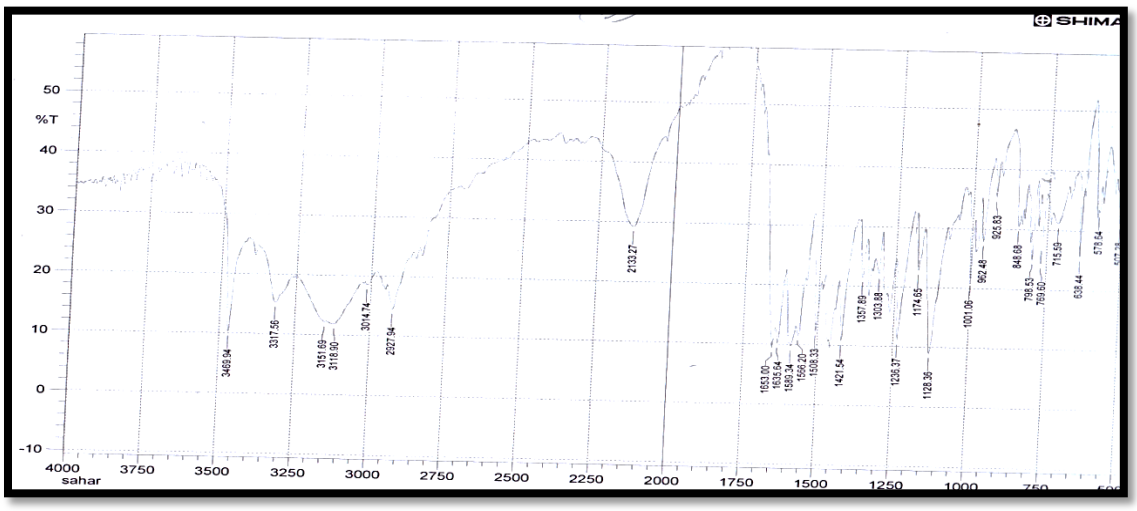


Fig. (2): FT-IR of compound 16

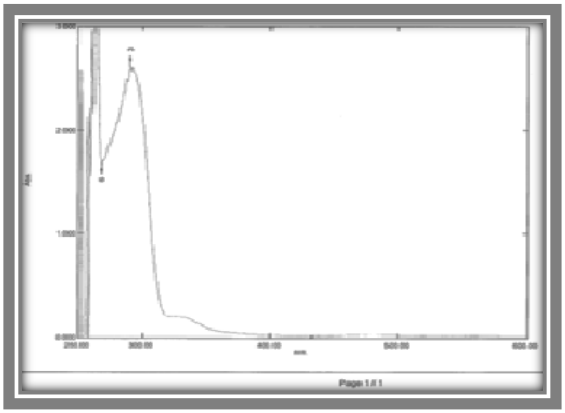


Fig.(3): UV for compound 8

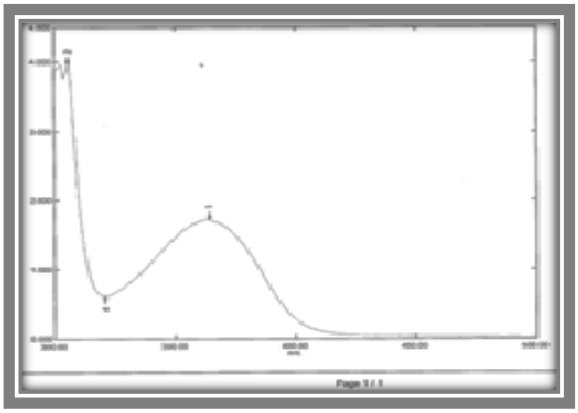


Fig.(4) UV of compound 10

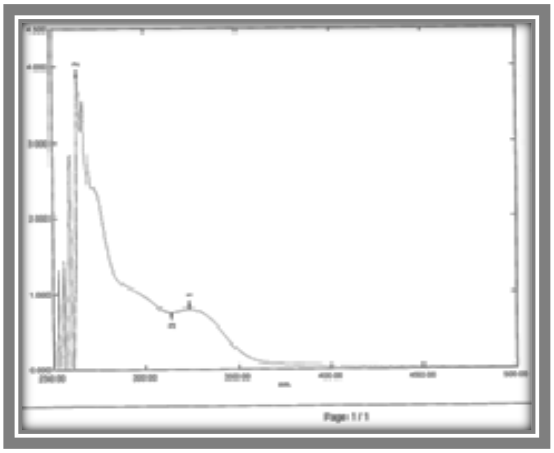


Fig. (5): UV of compound 18

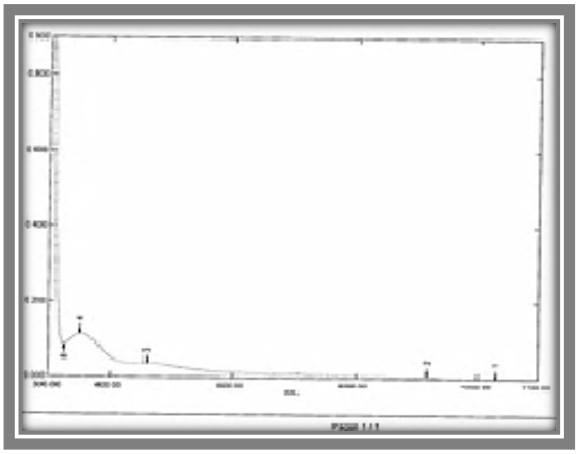


Fig. (6) UV of compound 20

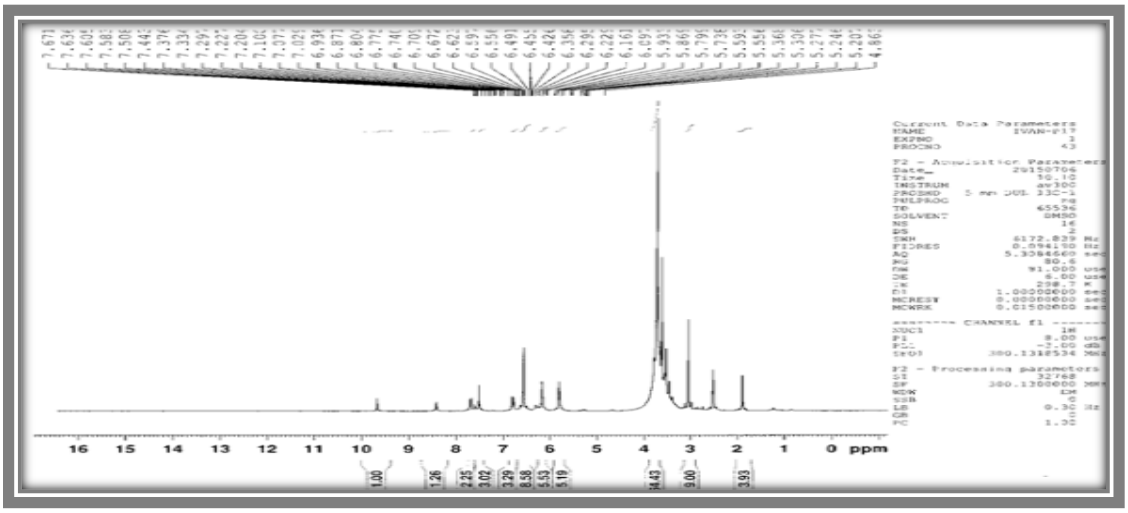


Fig. (7)^{1}H-NMRof compound 12

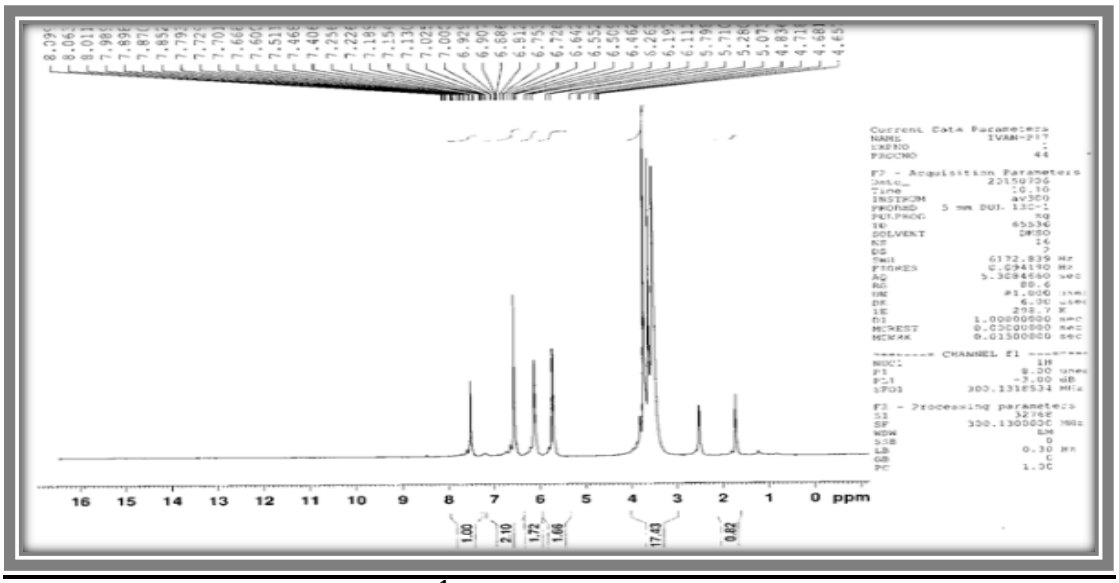


Fig. (8) ^{1}H-NMRof compound 18

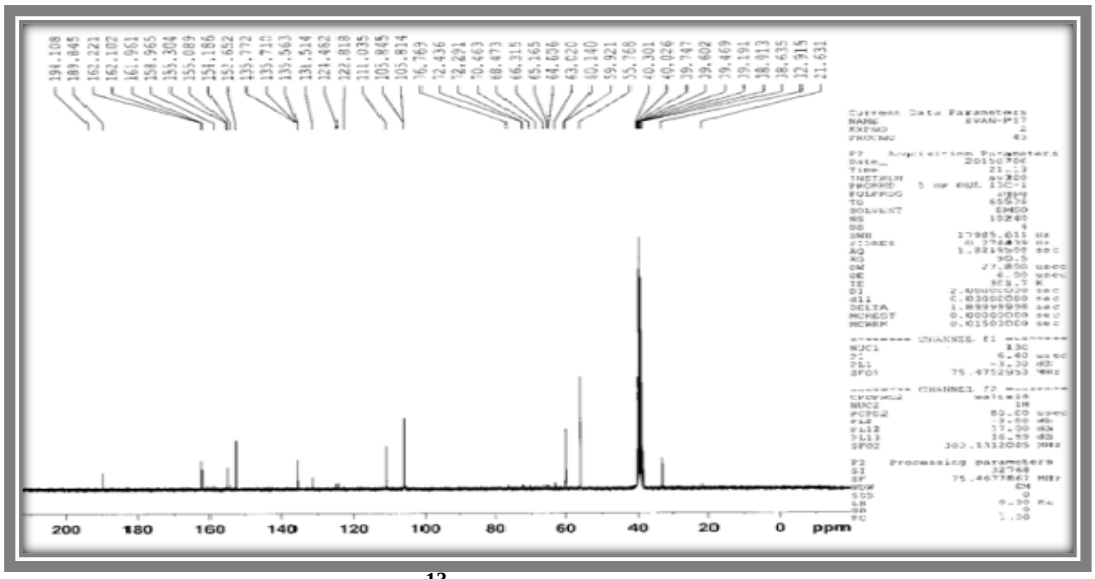


Fig. (9): ^{13}C-NMR of compound 12

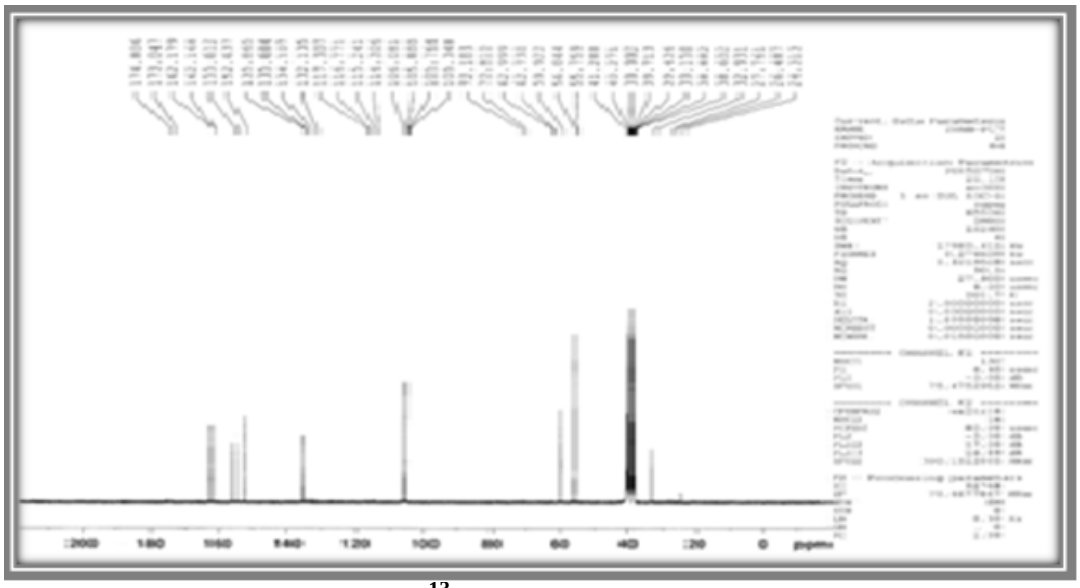


Fig. (10): ^{13}C-NMR of compound 18

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تحضير وتشخيص (مشتقات التترازول لدواء التراي مثبريم)

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الخلاصة:
يتضمن هذا البحث تحضير بعض المعوضات الجديدة للتترازول عن طريق قواعد شف لدواء التراي مثبريم وذلك من خلال اجراء خطوتين ، حيث تضمنت الخطوة الاولى تحضير قواعد شف (1-10) وذلك بتكاثف الديهايدات وكيتونات مختلفة مع دواء التراي مثيبريم، بينما تضمنت الخطوة الثانية تحضير عشرة مشتقات جديدة للتترازول(11 -20) من خلال تفاعل قواعد شف المحضرة في الخطوة الاولى مع ازايد الصوديوم بوجود الدايوكسان كمذيب.تم تشخيص المركبات المحضرة من خلال طيف,FT-IR وطيف UV وبعض منها عن طريق ^{1}H-NMR و ^{13}C-NMR بالاضافة الى دراسة الخواص الفيزيائية.

الكلمات المفتاحية: دواء التراي مثبريم، مشتقات، تترازول، قواعد شف