SYNTHESIS OF SOME NEW N-SUBSTITUTED-1,2,3,4-TETRAHYDRO CARBAZOLE DERIVATIVES AND STUDY THEIR BIOLOGICAL ACTIVITY

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Abstract

The aim of this research synthesis compounds different heterocyclic new rings, sulfur and nitrogen containing in structures, substituted-N-(1,2,3,4-tetrahydrocarbazol) [THCz], through the prepared α-chloro-N-tetrahydocarbazol acetamide [2] which was prepared two ways. The first method by condensation [THCz] with chloro acetyl chloride in the presence of triethylamine and dry benzene as solvent. The second method the prepared $[THCz]_2Hg$ [1], then condensation with chloroacety chloride in DMSO. Which was treated hydrazinehydrate to give α-hydrazine-N-tetrahydrocabazol acetamide [3]. The hydrazine derivative [3] with five acid anhydrids [Maleic, Phthalic, Succinic, Glutaric and Citraconic] to produce novel diazine which contain the acid refered above on substituted-N-tetrahydrocarbazol acetamide [4a-e] respectively.

The compound [2] was treated with each of urea and thiourea to give compounds [5,6] respectively. Followed the cyclization of compounds [5,6] by used p-phenylphencylbromide gave oxazol [7] and thiazol [8] on substituted-N-tetrahydrocarbazol acetamide, furthermore, new Schiff base [9a-e] were prepared through the reaction of the hydrazine derivative [3] with aromatic aldehydes. The prepared compounds identified by spectral methods [UV, FTIR, H-NMR, ^{13}C-NMR] and measurement some of its physical properties and some specific reaction, furthermore we were studied the effects of the preparing on some strains of bacteria.

Introduction

1,2,3,4-Tetrahydrocarbazole [THCz] derivatives are well known for their pharmacological activities several search for newer physiologically active compounds. They are used in the synthesis of (antibacterial and antifungal[1,2]), cytotoxic against cancer cell lines[3-5], Screend for antinociceptive activity[6], antiobesitic[7], antidiabetic[8] (type II dibetes), antipsychotic activity[9], and anti-emetic medicine[10].

Furthermor five and six memberds heterocyclic like Diazine, Thiazole and Oxazole constitute apotetial class of compounds which posses abroad field of biological activity[11-13]. Consideration of all these factors lead to condense tetrahydrocarbazol with five and six membered heterocyclic mentioned above to synthesis new derivatives, that have biological activities. From the afore said facts it was concluded that the Schiff base formation was taking place by amino group of hydrazine-[THCz] with aromatic aldehyde.

Experimental

- Instruments

Melting points were determined on Gallenkamp melting point apparatus and are uncorrected.

FTIR spectra were recorded on Shimadzu FTIR 8400 spectrophotometer as KBr disc. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a make Bruker model ultrashield 300MHz NMR at the university of Jordan DMSO-d^6 was used as solvent and TMS as internal reference. U.V. spectra were recorded on Shimadzu UV-Vis recorder.

- Chemical

Starting chemical compounds were obtained from Fluka or Aldrich.

Preparation of 1,2,3,4-Tetrahydrocarbazole [THCz]

Standard Literature procedure was followed for preparing the 1,2,3,4-tetrahydro carbazole[14]. Physical properties of the product are Listed in Table (1-2).

Preparation of Bis(1,2,3,4-Tetrahydro carbazole) Mercury(II) [1][(15)]

1,2,3,4-Tetrahydrocarbazole (1 gm,5.78 m.mol) was added to a boiling mixture of 1N NaOH (30 mL.) and ethanol(30 mL.). To the stirred clear solution, (5 mL.) of hot ethanol containing (0.78 gm., 2.89 m.mol.) of mercuric chloride was added. A voluminous yellow precipitate began to separate immediately and terned gradually to fine white precipitate after 10 minutes of boiling. After cooling for overnight at (5-10 °C), the fine precipitate was collected on a filter paper and washed repatedly with distal water until the filtrate was free from chloride ion. The solid was washed once with ethanol and ether and dried at 110°C for 3hrs. physical properties are Listed in Tables (1-2).

Preparation of α-Chloro-N-(1,2,3,4-Tetrahydrocarbazole) acetamid [2]

This compound [2] was prepared by two ways.

Method(I)

To a solution of Bis(1,2,3,4-Tetrahydro carbazole) Mercuric [1] (1 gm., 0.001 mol) in dry dimethyl solfoxide (20 mL.) chloroacetyl chloride (0.2 mL., 0.001 mol) in dry DMSO (10 mL) was added with continuous stirring. The mixture was refluxed for 2 hrs., at (80-90 °C). The solvent was distilled to give residue which was washed with 5% $NaHCO_3$ to remove the acid impurities. Physical properties of the product is Listed in Tables (1-2).

Method(II)[(13)]

Treating (2gm., 0.01mol) of 1,2,3,4-Tetrahydrocarbazole with (40mL.) dry benzene, (1 mL., 0.01 mol) chloroacetyl chloride in dry benzene (10 mL), containing triethylamine (1mL) was added with continuous stirring. The mixture was refluxed on a water bath for 9 hrs. the solvent was distilled to give residue which was washed with 5% $NaHCO_3$. physical properties of the product is Listed in Tables (1-2).

Preparation of α-hydrazino-N-(1,2,3,4-tetrahydro carbazol) acetamide [3]

To a solution of compound [1] (6 gm., 0.025 mol.) in absolute ethanol 50 mL., hydrazine hydrate (3 mL., 0.04 mol.) was added with continuous stirring and the resulting mixture was refluxed on a water bath for 3 hrs. after cooling the mixture, yellow precipitate was formed. The precipitate was filtered. Physical properties of the product is listed in Tables (1-2).

Diazen Derivatives of α-hydrazino-N-(1,2,3,4-tetrahydro carbazol) acetamide [4a-e] General

A mixture of hydrazine [3] (0.5gm, 0.002 mol.) and acid anhydride(0.002 mol) in 30mL. of glacial acetic acid was heated under reflux for (7-9) hrs. then cooling the mixture by adding it to ice bath produceds the precipitates which was filtereds. Physical properties of the products are Listed in Tables (1-2).

α-(Urea-N-yl)-N-(1,2,3,4-tetrahydro carbazol) acetamide or α-(Thiourea-N-yl)-N-(1,2,3,4-tetrahydro carbazol) acetamide [5,6]

To a solution of compound [2] (0.5 gm., 0.002) in absolute ethanol 30 mL., urea (0.12 gm, 0.002 mol.) or Thiourea (0.15 gm., 0.002 mol) was added respectively the mixture was refluxed for (3-4) hrs., after cooling, the precipitate was filtered and dried. Physical properties of the product are Listed in Tables (1-2).

α-[4-p-Phenylphenyl-1,3-Oxazol-2-yl-amino]-N-(1,2,3,4-tetrahydrocarbazol) acetamide or α-[4-P-Phenylphenyl-1,3-Thiazol-2-yl-amino]-N-(1,2,3,4-tetrahydro carbazol) acetamide [7, 8][(17)]

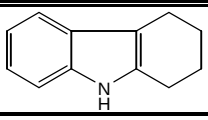
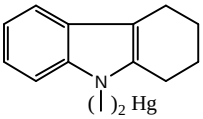
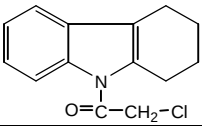
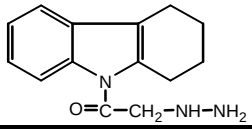
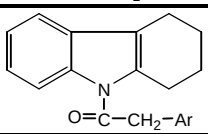
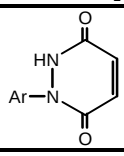
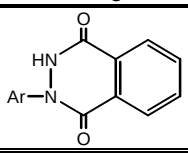
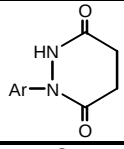
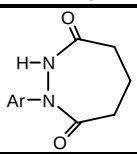
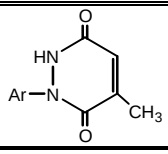
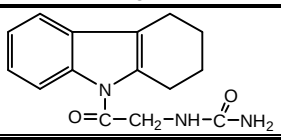
A mixture of compound [7 or 8] (0.80 mg. 0.003 mol) or (0.86 gm, 0.003 mol) respectively and was treated with absolute ethanol 20 mL., p-phenylphenacylbromide (0.83 gm, 0.003 mol.) was added. The mixture was refluxed for (7-8) hrs. cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water, and petroleum ether was used recrystallization. Physical properties of the products are Listed in Tables (1-2).

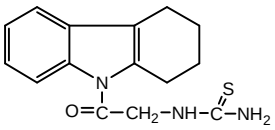
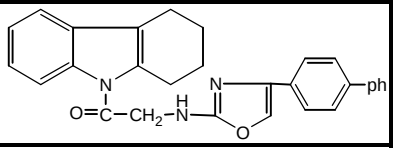
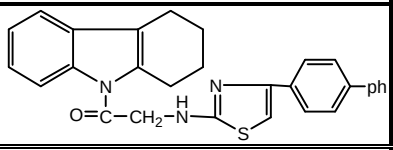
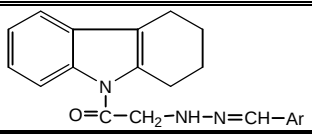
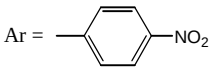
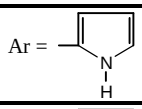
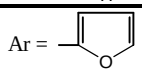
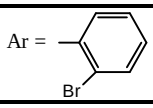
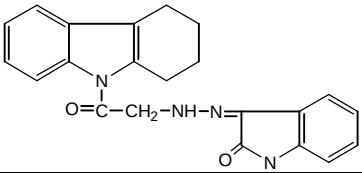
Schiff Base Derivatives of α-hydrazino-N-(1,2,3,4-Tetrahydro Carbazol) acetamide [9a-e]

General:

To a hot stirred solution of the hydrazide [3] (0.25 gm., 0.001 mol) in methanol 5 ml., approiate aromatic aldehyde (0.001 mol) was added. The reaction mixture was heated to (70-80) °C for (1-3) hrs. the separated solid was filtered. Physical properties of the products are Listed in Tables (1-2).

Table (2)
FTIR absorption spectra data $(cm)^{-1}$ of the prepared compounds.

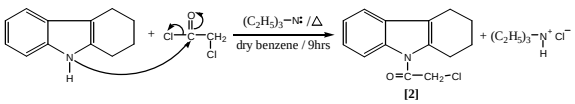
Comp. No.	Comp. Structure	νN-H	νC-H arom.	νC-H alph.	νC=O	νC=C	Other band
		3394	3055	2923 2846		1630	νC-N 1450
1			3040	2923		1615	νC-N 1450 νN-Hg 435
2			3045	2923 2850	1697	1605	νC-Cl 655
3		3195	3050	2924 2855	1693	1610	ν-NH_2 3407asym. and 3235 sym.
4							
4a		3220	3045	2925 2850	1720 sholder 1693 imide	1610	
4b		3215	3050	2920 2855	1705 sholder 1690 imide	1608	
4c		3205	3045	2924 2855	1700	1612	
4d		3230	3050	2950 2920 2850	1690	1610	
4e		3195	3035	2945 2880	1725 sholder 1690 imide	1625	
5		3255	3030	2940 2850	1676	1604	$νNH_2$ 3425asym. and 3310sym.

Comp. No.	Comp. Structure	νN-H	νC-H arom.	νC-H alph.	νC=O	νC=C	Other band
6		3186	3055	2923	1680	1620	νNH_2 3363asym. 3278 sym. νC=S 1234 weak
7		3240	3050	2923 2885	1690	1608	νC=N 1580 νC-O-C 1211
8		3213	3060	2923 2882	1690	1604	νC=N 1590
9							
9a		3195	3065	2923 2875	1710	1615	$\nu N=O_2$ 1525asym. 1334 sym.
9b		3198	3055	2923 2878	1695	1605	
9c		3185	3050	2925 2885	1685	1620	νC-O-C 1234
9d		3210	3050	2923 2885	1690	1618	νC-Br 601
9e		3205	3060	2940 2880	1735	1620	νN-H lacton 3420

Results and Discussion

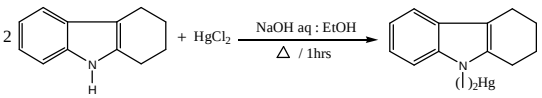
In this work we aimed to synthesize some different heterocyclic systems on substituted-N-tetrahydrocarbazol Scheme (I).

α-chloro-N-(1,2,3,4-Tetrahydrocarbazol) acetamide [2] was prepared by two ways, in the first method condensing (THCz) with chloroacetyl chloride in dry benzene according to the following equation[18].

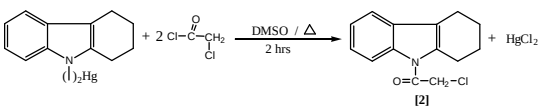


[2]

The second method react THCz with mercuric chloride in mixture of (1N.NaOH) aqueous and ethanol (1:1)[15].



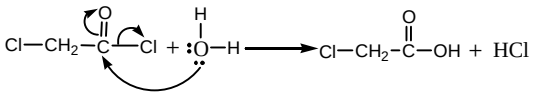
Then the compound [1] react with chloroacetyl chloride in dry Dimehyl solfoxide (DMSO) according to the following equation



[2]

The preparation compound [2] in the second method better yield and purity than first method.

The reaction should be carried in dry condition due to that the existence of water caused to water to react with $Cl-\overset{O}{\overset{\|}{C}}-CH_2Cl$ according to the following equation:

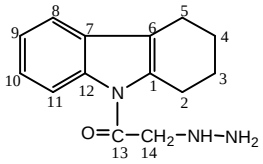


The structure of [1] was confirmed by physical properties which are Listed in Tabled (1). FTIR spectra showing the absorption at 3040 cm^{-1} for (νC-H Aromatic), 2923cm^{-1} for (νC-H alph.) 1615cm^{-1} for (νC=C), 435 cm^{-1} for ($\nu_{}^{}N-Hg$) and disappearance the absorption of ($\nu_{}^{}N-H$) group. While the U.V. spectra appearance the absorption at higher (λ_{max} = 338 nm) red shift, because of the chromophore group (Hg).

The compound [2] was confirmed by physical properties which are Listed in Table (1). FTIR spectra showing the absorption at (3045 and 2923, 2850) cm^{-1} for (νC-H Aromatic and νC-H alp.) respectively; 1697cm^{-1} for (νC=O amid) 1605 cm^{-1} for (νC=C), 655cm^{-1} for (C-Cl) and disappearance the absorption of ($\nu_{}^{}N-H$) group. Other chemical test was carried out to characterize the prepared [2] such as sliver natrate alcoholic test that confirmed the presence of chloren group[19].

The compound [2] through reaction with hydrazine hydrate gave α-hydrazno-N-(1,2,3,4-tetrahydrocarbazol) acetamid [3]. FITR spectrum data showed absorption at (3407, 3235 and 3195) cm^{-1} could be attributed to νasym.-NH_2, νsym.-NH_2 and ν-NH respectively. And disappearance the absorption of νC-Cl group. While the H-NMR spectra data of compound [3][20] δppm in DMSO-d6 solvent.

1.7-1.9 (m, 4H, 2CH_2 cyclic); 2.4-2.6 (m, 4H, 2CH_2 cyclic) 3.35(s, 2H, -CH_2-); 6.0-6.8 (broad, 3H, -NH-NH_2); 7.1-8.0 (m, 4H, Ar-H).^{13}C-NMR spectra for compound. Figure(1).



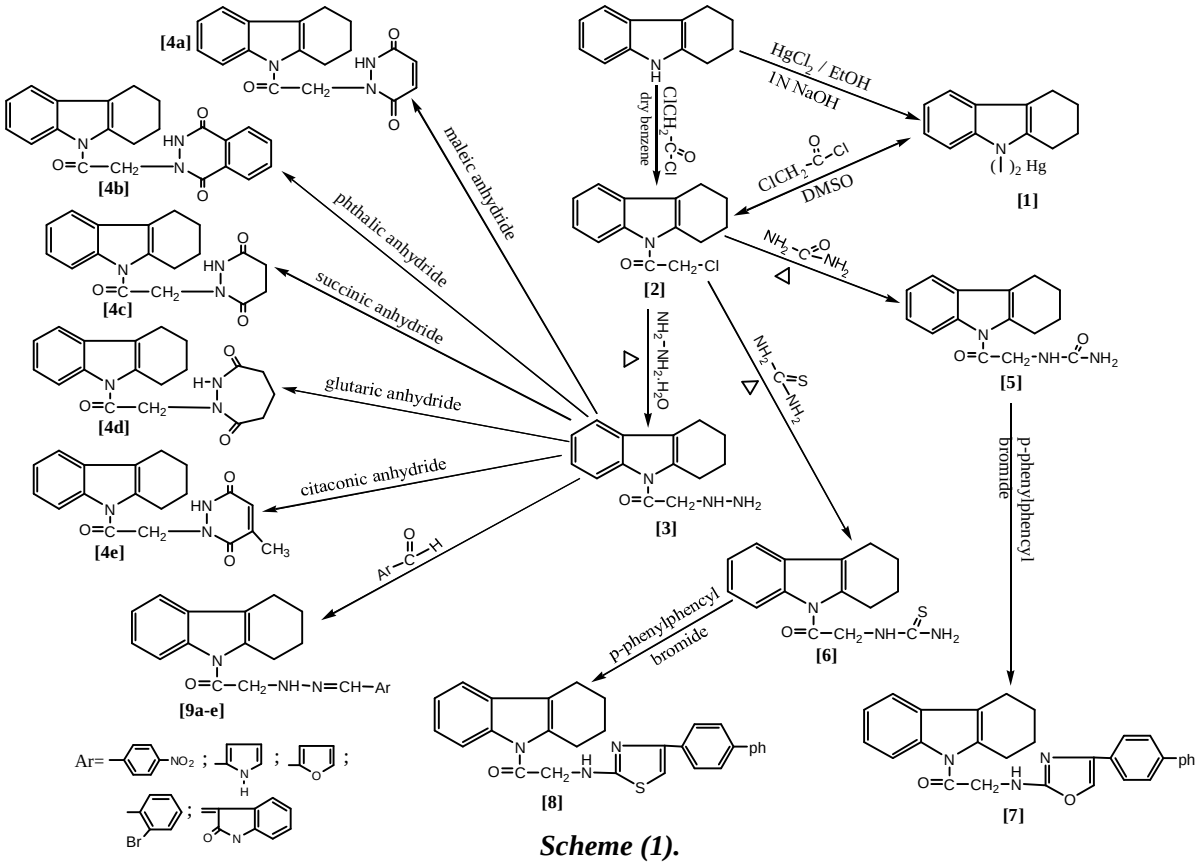
^{1}C:154.77; ^{2}C:48.47; ^{3}C:26.88; ^{4}C:23.66; ^{5}C:36.74; ^{6}C and ^{12}C:142.85; ^{7}C:142.85; ^{8}C:120.85; ^{9}C and ^{10}C:118.91; ^{11}C:122.48; ^{13}C:170.18; ^{14}C:80.41. Figure (2).

Six and seven hetero cyclic ring [4a-e] were synthesized by the reaction of hydrazide derivative [3] with five acid anhydrides, (Maleic, Phthalic, Succinic, Glutaric and citraconic) respectively. FTIR spectrum of compounds [4a-e] showed a shift in the (νN-H) band from (3195-3220) cm^{-1}, other absorptions at (1725-1690) cm^{-1} for (νC=O) imide and amide respectively, and disappearance of the two band of (ν-NH_2) group.

The Schiff bases [9a-e] were obtained in good yield through the reaction of hydrazine [3] with different aromatic aldehydes (scheme I). The FTIR spectrum of compounds [9a-e] are Listed in Table (2).

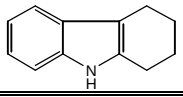
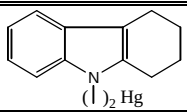
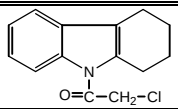
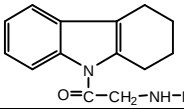
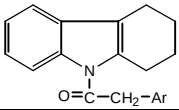
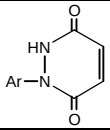
The compound [2] were converted to urea derivative [5] and thiourea derivative [6] by the reaction with urea or thiourea in abs. ethanol (scheme I). FTIR spectral data showed absorption at (3255-3186) cm^{-1} for (νN-H); (3425-3278) cm^{-1} asym. and sym. for (ν-NH_2) and (1234)cm^{-1} weak for (νC=S) group for the compound [6].

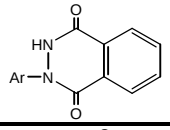
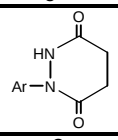
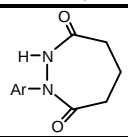
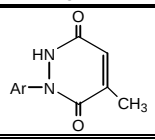
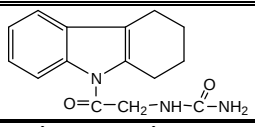
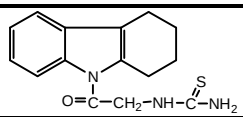
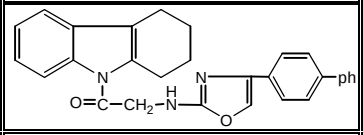
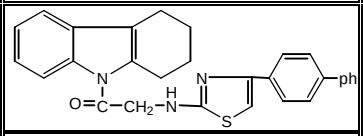
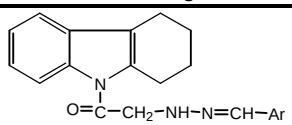
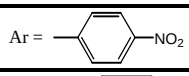
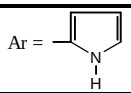
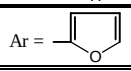
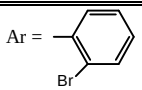
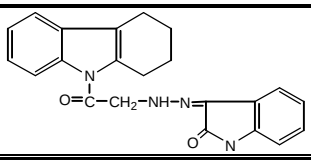
Treatment of compound [5] or [6] with p-phenylphencylbromide afford intramolecular cyclization to give the oxazol and thiazol on substituted-N-tetrahydrocarbazol acetamide [5 and 6] respective. The FTIR spectrum of compound [5] showed absorption at (3240) cm^{-1} for ν-NH-; (1690) cm^{-1} for νC=O; (1580) cm^{-1} for (νC=N); (1211) cm^{-1} for νC-O-C and disappearance the absorption (νNH_2) group. FTIR spectrum of compound [6] showed absorption at (3213) cm^{-1} for ν-NH-; (1690) cm^{-1} for νC=O; (1590) cm^{-1} for νC=N; and disappearance the absorption (ν-NH_2 and νC=S) group.



Scheme (1).

Table (1)
Physical Properties of the Prepared Compounds.

Comp. No.	Molecular Formula	Comp. Structure	m.p. °C	Yield %	Colour	Recryst. Solvents
	$C_{12}H_{14}N$		118-120	78	Pale yellow	Ethanol/water
1	$C_{12}H_{13}NHg$		196-197	85	White	Ethanol
2	$C_{14}H_{15}ClNO$		68-70	75	Deep violet	Ethanol/water
3	$C_{14}H_{18}N_3O$		150-151	80	Yellow	Ethanol
4	$C_{14}H_{15}NOAr$					
4a	$C_{18}H_{18}N_3O_3$		209-212	82	Deep yellow	Benzene

Comp. No.	Molecular Formula	Comp. Structure	m.p. °C	Yield %	Colour	Recryst. Solvents
4b	$C_{22}H_{20}N_3O_3$		230-233	72	Off white	Chloroform
4c	$C_{18}H_{20}N_3O_3$		190-193		Deep yellow	Ethanol/water
4d	$C_{19}H_{22}N_3O_3$		176-178	76	Green	Ethanol/water
4e	$C_{19}H_{20}N_3O_3$		220-223	65	Off white	Ethanol/water
5	$C_{15}H_{18}N_3O_2$		250-251	75	Pale Brown	Chloroform
6	$C_{15}H_{18}N_3OS$		250d	60	Brown	Chloroform
7	$C_{29}H_{26}N_3O_2$		120-122	70	Brown	Petroleum ether
8	$C_{29}H_{26}N_3OS$		114-115	65	Deep Brown	Petroleum ether
9	$C_{15}H_{17}N_3OAr$					
9a	$C_{21}H_{21}N_4O_3$		90-92	85	Red	Petroleum ether
9b	$C_{19}H_{21}N_4O$		220d	65	violet	Petroleum ether
9c	$C_{19}H_{20}N_3O_2$		240d	60	Brown	Methanol
9d	$C_{21}H_{21}N_3OBr$		230-234	60	Brown	Ether
9e	$C_{22}H_{21}N_4O_2$		176-178	70	orange	ethanol

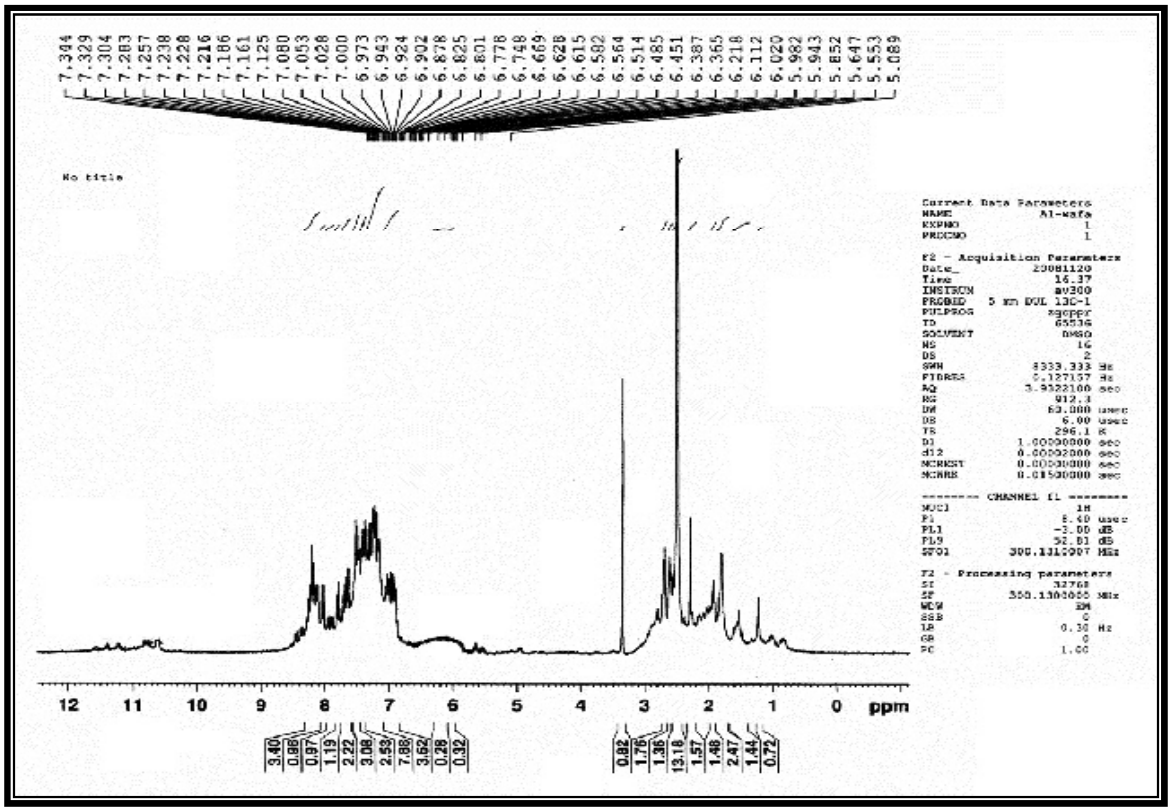


Fig.(1) : ^{1}H-NMR for compound No.[2].

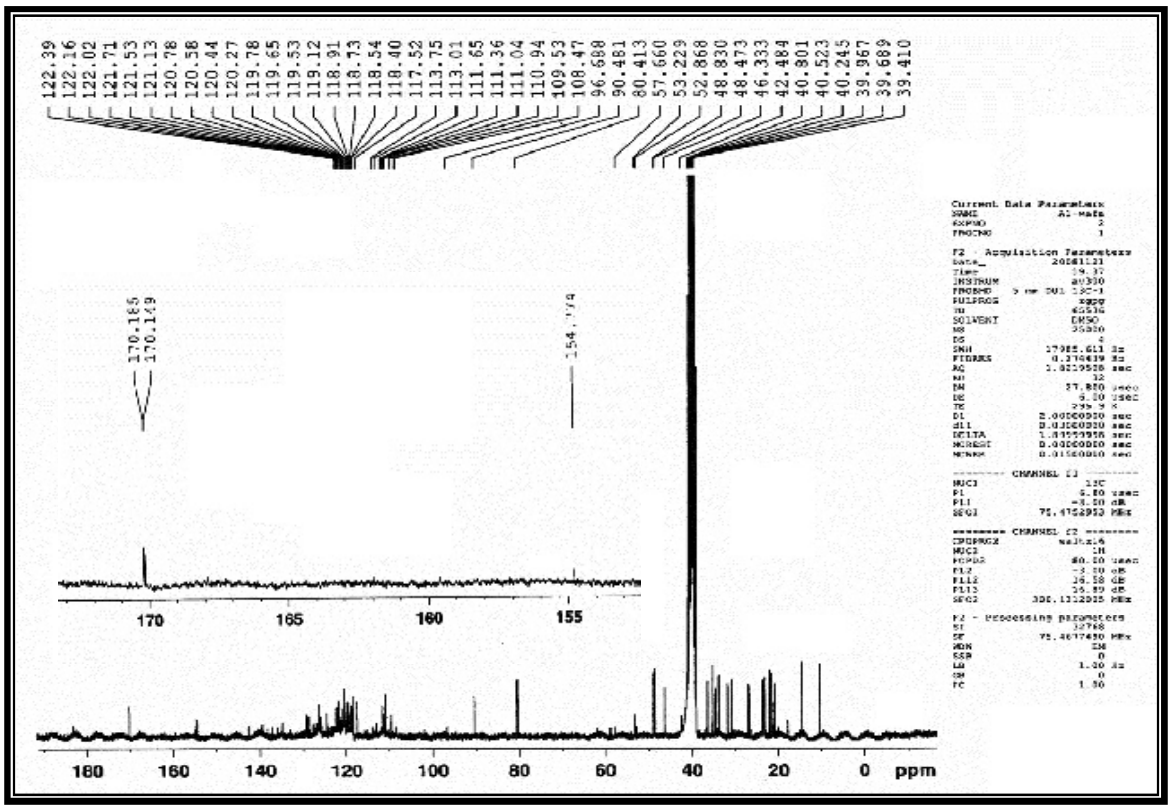


Fig.(2) : ^{13}C-NMR for compound No.[2].

Antimicrobial Activity Test

The test was performed according the disk diffusion method[21]. The some of the prepared compounds were tested against two strain of Gram $^{+}$ve (Bacilluscereus, S.aureus) and two strain of Gram $^{+}$ve bacteria (Escherichia Coli, Pseudomonas). What man No.1 filter paper disk of 5 mm diameter were sterilized by autoclaving for 15 min. at 121 °C the sterile disk were impregnated with different compounds (500 μg/disk). Agar plates were surface inoculated uniformly with 100 ML from the broth culture of the tested micro organisms. The impregnated disks were placed on the medium suitably spaced a part and plates incubated at 5°C for 1hr. to premit good diffattion and then transferred to an incubator at 37 °C for 24 hrs. the in hibition zones caused by the various compounds on the microorganisms were examined. The results are Listed in Table (3). From the data it is clear that compound [8] posses between moderate and Less activity against four types of bacteria and compounds [7 and 9a] possess Less activity against types of bacteria. While compounds [4a and 4c] possess Less activity against for one types of bacteria. As far as compound [9a] possess moderate specific activity against for (S. aureus) and have no effect on other strains.

Table (3)
Results of antimicrobial activity of the tested prepared compounds.

comp. No.	*B.cereus*	*S.aureus*	*E.Coli*	*Pseudomonas*
4a	-	+	-	-
4c	-	+	-	-
7	+	+	+	-
8	+	+	++	++
9a	-	++	-	-
9e	+	+	-	-

****Solvent: DMSO, [C]=500μg/ML.***
Key to symbols:
Highly active = +++ (inhibition zone 15-20 mm)
Moderately active = ++ (inhibition zone 10-14 mm)
Slightly active = + (inhibition zone 6-9 mm)
Inactive = - (inhibition zone <6 mm)

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الخلاصة

هدف البحث تحضير مركبات حلقية مختلفة غير متجانسة جديدة حاوية على الكبريت والنتروجين في تركيبها معوضة بذرة نتروجين [1، 2، 3، 4-تتراهيدروكاربزول] [THCz] وذلك من خلال تحضير الفا-كلورو-N-تتراهيدروكاربزول است امايد [2] الذي حصلنا عليه بطريقتين، الطريقة الاولى بتكاثف [THCz] مع كلورو اسيتال-كلوريد-، وتراي اثيل امين وبوجود-البنزين الجاف كمذيب. والطريقة الثانية بتحضير $(THCz)_2Hg$ ومن ثم تكاثفه مع كلورو اسيتال كلورايد وبوجود DMSO كمذيب. وعند معاملته مع الهايدرازين المائي ليعطي هايدرازين-N-هيدروكاربزول است امايد [3]. وبتفاعل مشتق الهايدرازين [3] مع خمسة من انهيدريدات الحوامض [المالينك، الفثاليك، السكسنيك، الكلوتاريك والستراكونك] مكوناً دايازينات جديدة من انهيدريدات الحوامض اعلاه المعوضة-N-تتراهيدروكاربزول است امايد [4a-e] بالتتابع. وعند معاملة المركب [2] مع كل من اليوريا والثايويوريا حصلنا على المركبين [5، 6] بالتتابع. حولق المركبين [5، 6] باستخدام بارا-فنيل فيناسيل بروماید نتج الاوكسازول [7] والثايزول [8] المعوضة-N-تتراهايدرو-كاربزول است امايد، بالاضافة الى ذلك تفاعل مشتق الهايدرازين [3] مع الالديهايدات الاروماتية حصلنا على قواعد شفت [9a-e].

شخصت المركبات المحضرة بالطرق الطيفية [UV، FTIR، H-NMR، ^{13}C-NMR] وتعين بعض خواصها الفيزياوية واجراء بعض الكشوفات النوعية. كما تم دراسة تاثير هذه المركبات على بعض انواع من البكتريا.

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