Synthesis and Characterization of Some New Thiazine , Azetidine and Thiazolidine Compounds Containing 1,3,4-Thiadiazole Moiety And Their Antibacterial Study.

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Abstract

2-amino-5-mercapto-1,3,4-thiadiazole [I] were prepared by the cyclization of thiosemecarbazide with carbon disulphide and anhydrous sodium carbonate in ethanol as a solvent. The reaction of compound [I] with alkyl halides yielded 2- amino-5-thioalkyl-1,3,4-thiadiazole [II] and [III] . Compound [II] and [III] were reacted with different aromatic aldehydes to yieled 2-[(substituted benzyliden) amino] -5- thioalkyl-1,3,4- thiadiazole $[IV]_{a-c}$, $[V]_{a-d}$ and $[VI]_{a-d}$. Schiff 's bases $[IV]_{a-c}$, $[V]_{a-d}$ and $[VI]_{a-d}$ were found to react with 2-mercapto benzoic acid in the triethyl amine to give 3-[5-(alkylthio) -1,3,4- thiadiazol-2-yl] -2,3- dihydro- 2- (aryl) benzo [e] [1,3] thiazine -4-one $[VII]_{a-c}$ and $[VIII]_a$. The Schiff 's bases reacted with chloro acetyl chloride in the triethyl amine to give 3-chloro-1-(5-alkylthio)-1,3,4-thiadiazole-2-yl)-4-(aryl)azetidine-2-one$[IX]_{a,b}$, $[X]_c$ and $[XI]_{c,d}$ .Also Schiff 's bases reacted with 2-mercapto acetic acid in dry benzene to give 3-(5-mercapto-1,3,4-thiadiazole-2-yl)-2-(aryl)thiazolidine-4-one$[XII]_{a,c}$,$[XIII]_d$ and $[XIV]]_{c,d}$.

The structures of the newly synthesized compounds were confirmed by physical properties and spectral (UV-Vis , FT-IR and ^{1}H-NMR) analysis.

Key Words: 1,3,4-Thiadiazole , Thiazine-4-one, Azetidine-2-one , Thiazolidine-4-one .

*This paper is part of master thesis of the third author .

Introducation

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 the 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 B_6 (Pyridoxine) , which is a derivative of Pyridine , essential in amino acid metabolism[1].

Thiadiazoles have occupied an important place in drug industry ; 1,3,4-thiadiazoles have wide applications in many fields . The earliest uses were in the pharmaceutical area some of the later uses are as antitumor and anti-inflammatory agents . Pesticides , dyes , lubricants and analytical reagents [2].

Azetidine is a hydrolytically sensitive , four membered cyclic amide , which is present in clinically useful penicillins and cephalosporin . The N-CO distance of 1.38 A^o this has been attributed to ring strain and to inhibition of normal amide interaction. They are commonly known as β-lactams , are well known heterocyclic compounds among the organic and medicinal chemists . Azetidine is an important four-membered heterocyclic β-lactam compound because it is a part of penicillin group compounds which fused with thiazolidine compound[3].

Thiazolidinones are an importartant group of heterocyclic compounds , having diverse biological uses as antibacterial[4] anticonvulsant[5] , anti-inflammatory[6,7] , FSH receptor agonist[8] , anticancer[9] , antiviral[10] , antifungal [11] and antihistaminic activities [12,13] .

Materials and Methods

Experimental

All the chemicals used in the synthesis were of analytical grade . The melting points were determined in open capillary on Digimelt MPA 161 (MSRS) electronic apparatus and are uncorrected. The IR spectra of synthesized compounds were recorded on Shimadzu FT-IR 8400 spectrophotometer using potassium bromide. To monitor the reactions , as well as , to establish the identity and purity of reactants and products , thin layer chromatography was performed on microscopic glass slides coated with silica gel , using toluene-acetone , benzene-ether and chloroform-methanol , as the solvent systems and spots were visualized under UVradiation. Nuclear magnetic resonance spectra were recorded on Bruke, model:Ultra shield 300 MHz , model spectrometer using DMSO as a solvent and TMS as internal reference (chemical shifts in δ ppm) .

General Procedure for the Synthesis of Compounds.

Preparation of 2-amino-5-mercapto-1,3,4-thiadiazole[I][14].

A mixture of (2g, 0.02 mol.) of thiosemicarbazide and (2.33g, 0.02 mol.) of anhydrous sodium carbonate was dissolved in 25ml. abs. ethanol. To this solution (3.2g, 0.04 mol.) of carbon disulphide was added.

The resulting mixture was heated under reflux for 10 hrs. , the reaction mixture was then allowed to cool down to room temperature. Most of solvent was removed under reduced pressure and the residue was dissolved in 20ml. distilled water and then acidified with cold concentration hydrochloric acid to give pale yellow precipitate .The crude product was filtered and washed with cold water, recrystallized from water to give yellow product,yield (75%) , m.p (230-232)C^o .

Preparation of 2- amino-5 - thioalkyl-1,3,4-thiadiazole [II] , [III][15].

Compound [1] containing(-SH) group (0.001mol.) was dissolved in 10ml. dioxan , which contained (0.001mol.) potassium hydroxide. Ethyl iodide and isopropyl bromide(0.001mol.) were added using separating funnel dropwise with stirring . The reactants were refluxed for 3 hrs. The solvent was evaporated under reduced pressure ,water was added , and the crude product was extracted with ethyl acetate and dried with anhydrous magnesium sulphate .

Evaporation of the organic layer gave solid products , recrystallized from dioxan to give 2-amino-5-thioethyl-1,3,4-thiadiazole[II] , yield (68%) , m.p (120-121)C^{o} and 2-amino-5-thioisopropyl-1,3,4-thiadiazole[III] yield(80.5%) m.p (139-140)C^{o} .

Preparation of Schiff bases [IV]$_{a-c}$, [V]$_{a-d}$, [VI]$_{a-d}$ from the 2-amino-5-lthioalky-1,3,4-thiadiazole[16].

A mixture of compound [II]and compound [III] (0.01mol.) of appropriate aromatic aldehyde (0.01) in 15ml absolute ethanol . Three drops of glacial acetic acid were added and refluxed in water bath for 8hrs. The reaction mixture was then allowed to cool at room temperature, and the precipitate was filtered and dried , recrystallized from ethanol to give colored crystals.

Table (1) shows the m.p. , yield and synthesized compounds [IV]$_{a-c}$, [V]$_{a-d}$, [VI]$_{a-d}$.

Preparationof 3 - (5-(substitutedthio)-1,3,4-thiadiazole-2-yl)-2,3-dihydro-2-(Aryl)benzo[e] [1,3] thiazine-4-one[VII]$_{a,c}$, [VIII]$_{a}$ [17].

A mixture of Schiff base (0.01mol.) and 2-mercaptobenzoic acid (0.01mol.) were mixed with 30ml. dry benzene and 3drops of triethylamine were added . The mixture was refluxed for 6 hrs. Then the solvent was removed under reduced pressure . The residue was washed with 10% of sodium bicarbonate then filtered and recrystallized with dioxan.

Table (2) shows the m.p. , yield and synthesized compounds [VII]$_{a,c}$, [VIII]$_{a}$.

Preparation of 3- chloro -1- (5-mercapto-1,3,4-thiadiazole-2-yl) - 4 -(aryl) azetidine-2-one [X]$_{c}$, [IX]$_{a,b}$, [XI]$_{c,d}$ [18].

Chloro acetyl chloride (0.01mol.) in 10ml of dioxan cooled at (0-5) C^{o} , to this , triethylamine (0.01mol.) in(10ml.) dioxane was added , and Schiff bases (0.01mol.) in 10ml of dioxane was slowly added and refluxed in water bath for (12hrs) . After the reaction had been completed- (detectad by TLC) , the reaction mixture poured into ice-cold water to give solid precipitate , which was filtered and dried , recrystallized by benzene-ether(50-50).

Table (3) shows the m.p. , yield and synthesized compounds [X]$_{c}$ [IX]$_{a,b}$, , [XI]$_{c,d}$.

Preparation of 3- (5-mercapto-1,3,4-thiadiazole-2-yl) - 2 -(aryl) thiazolidin-4-one [XII]$_{a,c}$, [XIII]$_{d}$, [XIV]$_{c,d}$ [19].

To mercapto acetic acid (0.001mol. , 0.09g) in dry benzene (30ml) `was added slowly to (0.001mol.) of Schiff bases .The addition continued about(5min) with continous stirring then for about 3 hrs. Followed by refluxing on a steam bath for about 18 hrs. Excess solvent was evaporated and the residue was treated with sodium bicarbonate , filtered and recrystallized with dioxan.

Table (4) shows the m.p. , yield and synthesized compounds[XII]$_{a,c}$, [XIII]$_{d}$, [XIV]$_{c,d}$.

Biological evaluation[20]

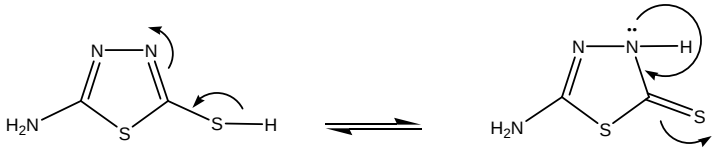
Some of synthesized compounds have been screend for antibacterial activities using cup-plate agar diffusion method.

Pencilin and azthromycin (50µg /ml) were used as a standard drug for antibacterial activity. The compounds were screened for antibacterial activity against (Staphylococcus and Escherichia coli) in nutrient agar medium. These sterilized agar media were poured into petri-dishes and allowed to solidify. On the surface of the media microbial suspensions were spread with the help of sterilized triangular loop. A stainless steel cylinder of 8mm diameter (pre-sterilized) was used to bore cavities. All the synthesized compounds (50µg /ml) were placed serially in the cavities with the help of micropipette and allowed to diffuse for 1 hr. DMSO was used as a solvent for all the compounds , and as a control. These plates were incubated at

37C° for 24 hr for antibacterial activities. The zone of inhibition observed around the cups after respective incubation was measured in mm .

Result and Discussion

The structure of compound [I] was identified by its melting point and FT-IR spectroscopy . The FT-IR spectrum of compound [I] , figure(1) , shows the following characteristic bands , two bands at 3396 cm^{-1} and 3278 cm^{-1} were due to asymmetric and symmetric stretching vibration of ($-NH_2$) group respectively , an absorption band at 3091 cm^{-1} was due to the (N-H) stretching (tautomeric form).The (-SH) stretching band found as very weak shoulder at 2331cm^{-1} , a band at 1604cm^{-1} was due to (C=N) stretching of the thiadiazole ring moiety .The sharp band at 1533cm^{-1} and 1330cm^{-1} are due to the (N-H) bending and (C-N) stretching vibration respectively . Also , the absorption band at 1055cm^{-1} for the (C=S) group which gives an evidence that compound [I] can exist in two tautomeric forms , thiol (A) and thione form (B) [14] .



(A) (B)

The compounds [II] and [III] were identified by m.p , T.L.C. , FT-IR and UV spectroscopy.

The FT-IR for compound [II] and [III] respectively showed disappearance of band at 2358 cm^{-1} which due to (S-H). Also disappearance of the very weak band at 1055 cm^{-1} of (C=S) group , and remaining the two functional group due to (C=N) exocyclic , (C=N)[21] endocyclic , at(1622,1633) cm^{-1} , (1525,1554) cm^{-1} respectively , and appearance band at(1321,1421) cm^{-1} due to ($S-CH_2CH_3$) , and appearance band at (1328,1411) cm^{-1} due to ($S-CH(CH_3)_2$)[22] . The UV-Vis spectrum of [II] shows the absorption peaks at (343-286) nm may attributed to (n- π*) and(π-π*) transitions.

FT-IR spectrum of compound $[IV]_{a-c}$, $[V]_{a-d}$, $[VI]_{a-d}$, showed the disappearance of two absorption band at (3396 ,3278)cm^{-1} due to the ($-NH_2$) stretching of amino group .

On the other hand, the FT-IR spectra showed bands for (C-H) olefinic, (C=C) aromatic,(C=N) endocyclic and exocyclic imine (C=N) group stretching vibration[14] . FT-IR absorption for these compounds are shown in table (1) .

Thiazine derivatives were prepared by the reaction of Schiff bases and 2-mercaptobenzoic acid in dry benzene . The products were identified by FT-IR ,UV-Vis spectroscopy , their melting points and checked by T.L.C. for compounds appearance of carbonyl group of the thiazines at (1662-1683) cm^{-1} and disappearance of the (C=N) group in (1610-1620) cm^{-1} and the disappearance of (O-H) broad band stretching vibration at 3450 cm^{-1} of 2-mercapto benzoic acid. Also all the spectral data for these compounds are listed in table (2).

The Schiff bases compounds were treated with chloroacetyl chloride followed by the addition of triethyl amine The FT-IR spectra of compounds $[XI]_c$, Figure (2) showed the appearance of the characteristic absorption band in region (1683-1707) cm^{-1} due to stretching vibration of carbonyl group of azetidine ring. Also the FT-IR spectrum showed the suggested band for olefinic (C-H) , (C=C) aromatic . All the spectral data for these compounds are listed in table (3).

The ^{1}H-NMR spectrum for compounds $[XI]_c$ [23] , Figure (3) showed the following characteristic chemical shifts , (DMSO)ppm , (CH) proton in azetidione ring for compound$[XI]_c$ appeared as two signals (doublet) at δ (3.77-3.79) ppm and (CH) proton fused

with chloro (doublet) at δ (4.27-4.46) ppm and δ (8.1-8.4) ppm for aromatic ring proton , multiplet signal at δ (3.02-3.5)ppm for proton of (C-H) in ($CH(CH_3)_2$) group. The doublet signal at δ (1.2) ppm for proton of methyl group.The (UV-Vis) spectrum of $[XI]_c$, shows the absorption peaks at (332-285) may attributed to(n - π*) and (π-π*) transition.

The thiazolidine-4-one derivatives $[XII]_{a,c}$, $[XIII]_d$, $[XIV]_{c,d}$ were synthesized by refluxing equimolar amounts from the imine compounds with thioglycolic acid in dry benzene .

The FT-IR spectra for compounds$[XII]_a$, Figure (4) showed the appearance of the characteristic absorption bands in the region (1689-1707) cm^{-1} due to stretching vibration of carbonyl group of thiazolidinone ring [24] .Also the FT-IR spectrum showed the suggested band for olefinic (C-H) , (C=C) aromatic. All the spectral datd for these compounds in table (4).

The ^{1}H-NMR spectrum for compound$[XII]_a$ Figure(5) showed the following characteristic chemical shifts , (DMSO)ppm: the aromatic ring protons of compound$[XII]_a$ appeared as multiplet at δ (6.8-7.8)ppm , singlet signal at δ (2.9) ppm due to (S-H) proton , signal at δ (8.4) ppm due to the (C-H) proton in thiazolidinone as singlet and protons of (CH_2) of thiazolidinone appeared at δ (3.35) ppm . The singlet signal at δ (3.07) ppm is for proton of (($CH_3)_2N$) group .

The (UV-vis) spectrum of compound $[XII]_a$, Figure(6) shows the absorption peaks at(340-264) nm which may attributed to (n- π*) and (π-π*) transition

Biological Activity

The results revealed that compounds showed varying degrees of inhibition against the tested microorganism.In general,the compounds [I,II,III] thiadiazole and thioalkyl compounds exhibited potent activity against E.coli and S. aureus bacteria. The compound [I] showed high activity among these compounds against E. coli more than standard drugs , while compound [III] showed high activity against S. aureus more than standard drugs .The results also showed that some of

schiff base compounds exhibited good activity against S. aureus (+ Gr) such as $[(IV)_b$, $(IV)_c$, $(V)_a$,$(V)_b$,$(VI)_a$,$(VI)_d]$,while compounds $[(IV)_a$, $(IV)_b$,$(VI)_a$, ,$(VI)_d]$ did not show any activity against E. coli (-Gr) when compared with the two standard drugs. The other Schiff base compounds showed moderate inhibitory against S. aureus and E.coli .

The compounds $[(IX)_a$,$(XII)_a$,$(VII)_a]$ showed good activity against gram positive than gram negative bacteria. Also the results showed that the compounds $[(XI)_c$, $(XI)_d$,$(XIV)_c$, $(XIV)_d]$ showed good activity against the two microorganisms , when the –SH group substituted by alkyl group. In comparsion , azetidine compounds exhibited the highest biological activity than thiazolidine and thiazine compounds , respectively. Thus , it is concluded from the screening results that the most of azetidine compounds and its derivatives have higher antibacterial activity more than the standard drugs against S. aureus than E.coli in a concentration of 50μg/ml[25].

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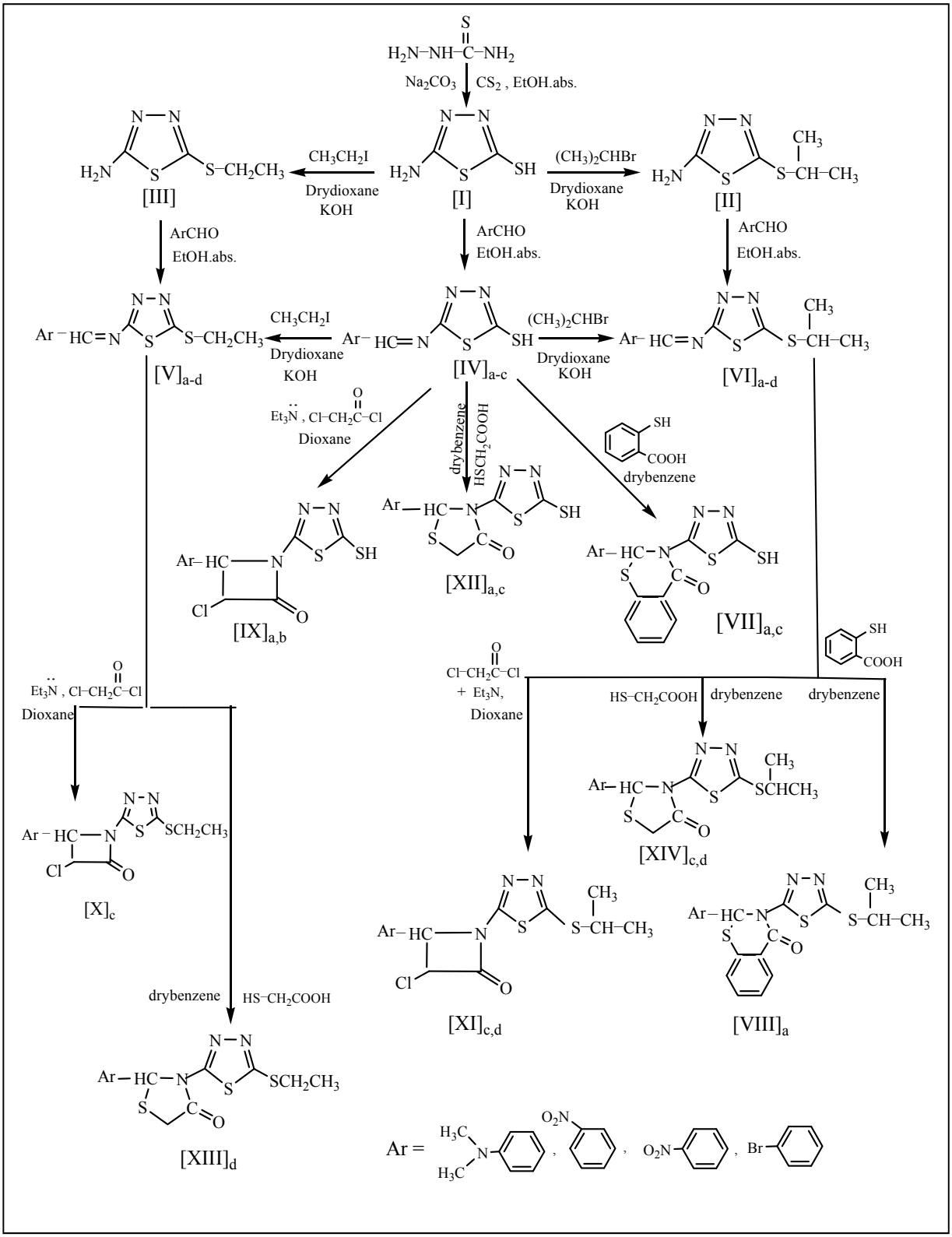

H2N–NH–C(=S)–NH2
Na2CO3
CS2 , EtOH.abs.
[III]
[I]
[II]
CH3CH2I
Drydioxane
KOH
(CH3)2CHBr
Drydioxane
KOH
ArCHO
EtOH.abs.
[V]a-d
[IV]a-c
[VI]a-d
Et3N , Cl–CH2C(=O)–Cl
Dioxane
drybenzene
HSCH2COOH
[IX]a,b
[XII]a,c
[VII]a,c
[X]c
[XI]c,d
[VIII]a
HS–CH2COOH
[XIII]d
[XIV]c,d
Ar =

Scheme No. (1)

Table No.(1) :Physical properties and FT-IR spectral data of compounds $[IV]_{a-c}$, $[V]_{a-d}$,

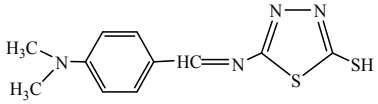
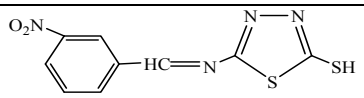
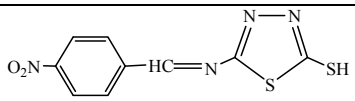
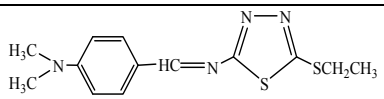
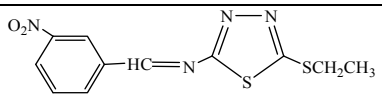
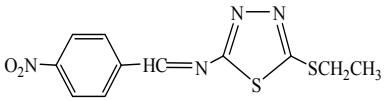
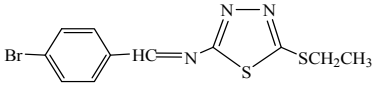
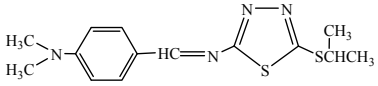
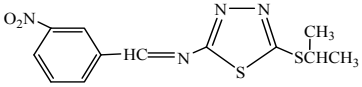
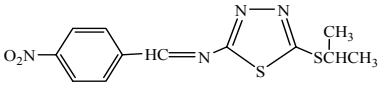
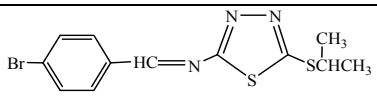
Com. No	Structral Formula	M.P	υ(C-H) arom.cm^{-1}	υ(C-H) aliph.cm^{-1}	υ(C=N) exo cm^{-1}	Others cm^{-1}
[IV]a		220-222	3089	2953	1614	υ (S-H) 2349
[IV]b		216-218	3128	2976	1612	υ (NO_2)1348-1531
[IV]c		195-197	3134	2978	1610	υ (NO_2)1348-1521
[V]a		160-161	3084	2962	1616	υ (N-Me)1367
[V]b		130-132	3086	2970	1614	υ (NO_2)1354-1527
[V]c		136-138	3138	2987	1612	υ (NO_2)1367-1523
[V]d		169-170	3147	2966	1614	υ (C-Br)821
[VI] a		180-181	3088	2960	1616	υ (N-Me)1371
[VI] b		116-118	3151	2972	1616	υ (NO_2)1340-1523
[VI] c		150-151	3109	2972	1616	υ (NO_2)1340-1525
[VI] d		113-114	3086	2964	1614	υ (C-Br)821

Table No. (2): Physical properties and FT-IR spectral data of compounds $[VII]_{a,c}$, $[VIII]_a$ $[VI]_{a-d}$.

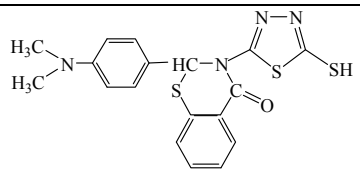
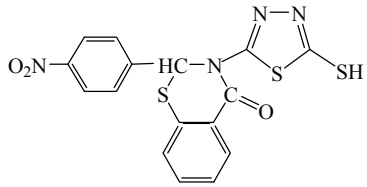
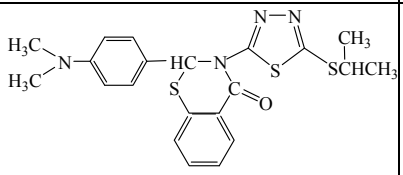
Comp.No	Structral Formula	M.P	υ(C-H) arom. cm^{-1}	υ(C-H) aliph.cm^{-1}	υ (C=O) cm^{-1}	Others bands cm^{-1}
[VII]a		240-242	3159	2978	1662	υ(S-H) 2376
[VII]c		211-212	3105-3007	2866	1678	υ(S-H) 2358
[VIII]a		142-144	3050	2960	1681	υ(C-S-C) 680

Table No. (3) : Physical properties and FT-IR spectral data of compounds$[X]_c$ $[IX]_{a,b}$, , $[XI]_{c,d}$

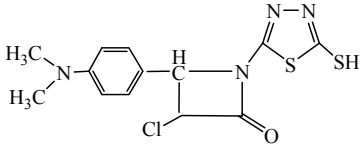
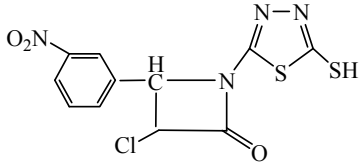
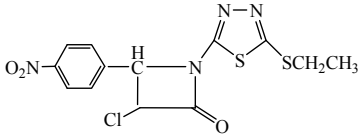
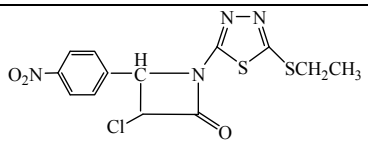
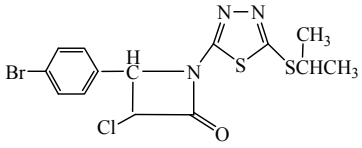
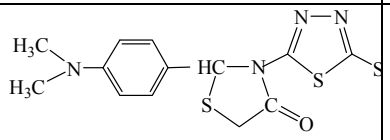
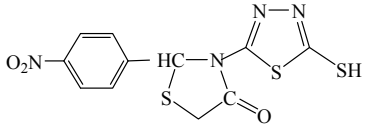
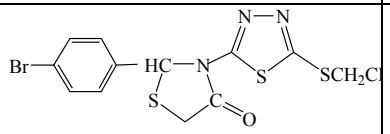
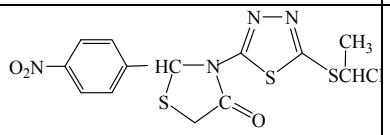
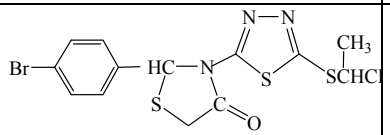
Comp.No	Structral Formula	M.P	υ(C-H) aliph. cm^{-1}	υ (C-H) arom.cm^{-1}	υ(C=O) cyclic cm^{-1}	Others Bands cm^{-1}
[IX]a		200-202	2978	3099	1683	υ(C-Cl)850, υ(C-N)1257
[IX]b		240 dec.	2949	3049	1687	υ(S-H)2351
[X]c		187-189	2966	3045	1705	υ(C-Cl)850 υ(C-N)1232
[XI]c		110-112	2964	3045	1707	υ(C-Cl)825
[XI]d		185-187	2914	3167	1685	υ(C-Cl)845

Table No. (4) : Physical properties and FT-IR spectral data of compounds $[XII]_{a,c}$, $[XIII]_{d}$, $[XIV]_{c,d}$

Comp.No	Structral Formula	M.P	υ(C-H) aliph. cm^{-1}	υ(C-H) arom. cm^{-1}	υ(C=O) Cyclic cm^{-1}	Others Bands cm^{-1}
[XII]a		210-212	2978	3140	1693	υ(C-N) 1172
[XII]c		182-184	2978	3105	1691	υ(S-H) 2360
[XIII]d		189-190	2978	3093	1689	υ(C-S-C) 682
[XIV]c		122-124	2920	3107	1707	υ(NO_2)1346-1521
[XIV]d		105-107	2968	3151	1697	υ(C-Br) 831

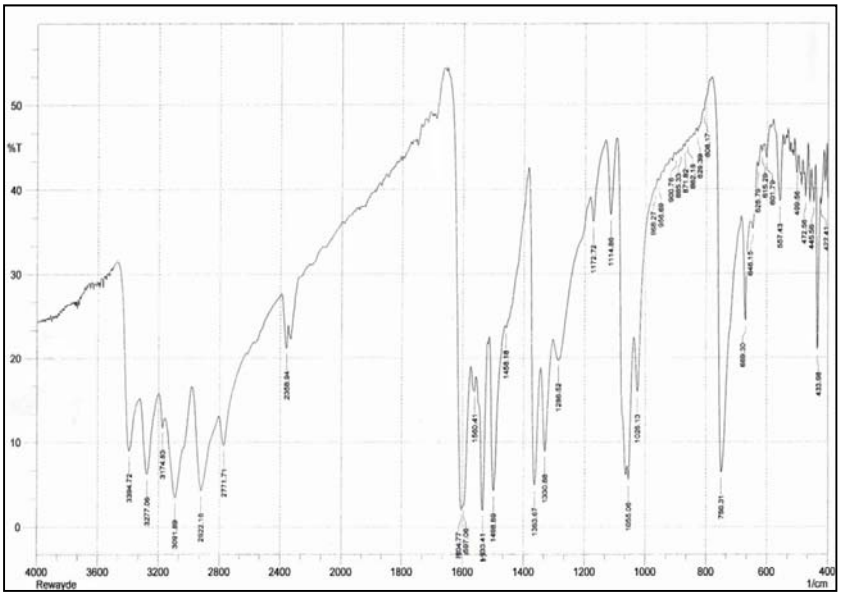


Figure No. (1): FTIR-Spectrum of compound [I]

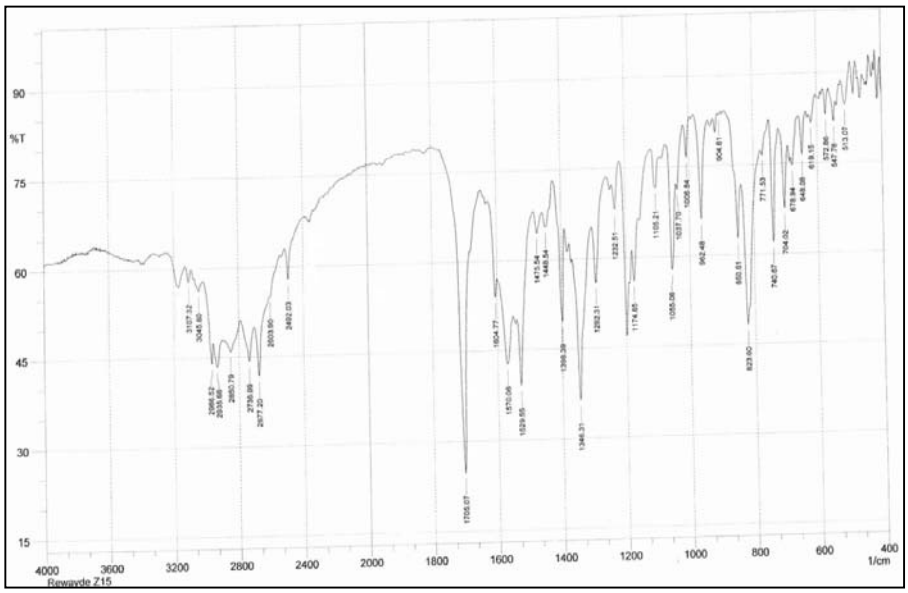


Figure No. (2): FTIR-Spectrum of compound [XI]c

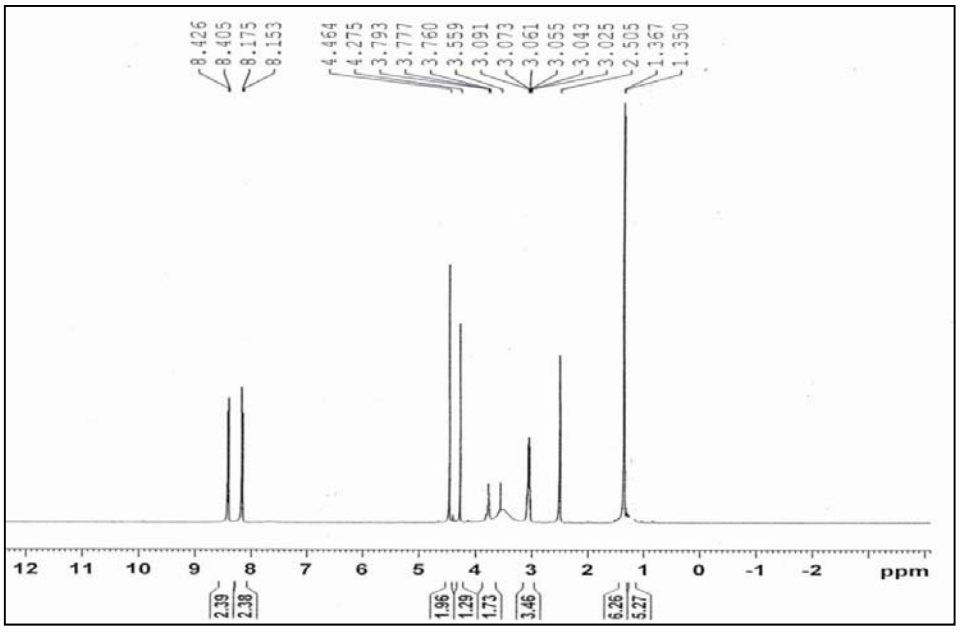


Figure No.(3): ^{1}H-NMR Spectrum of compound [XI]c

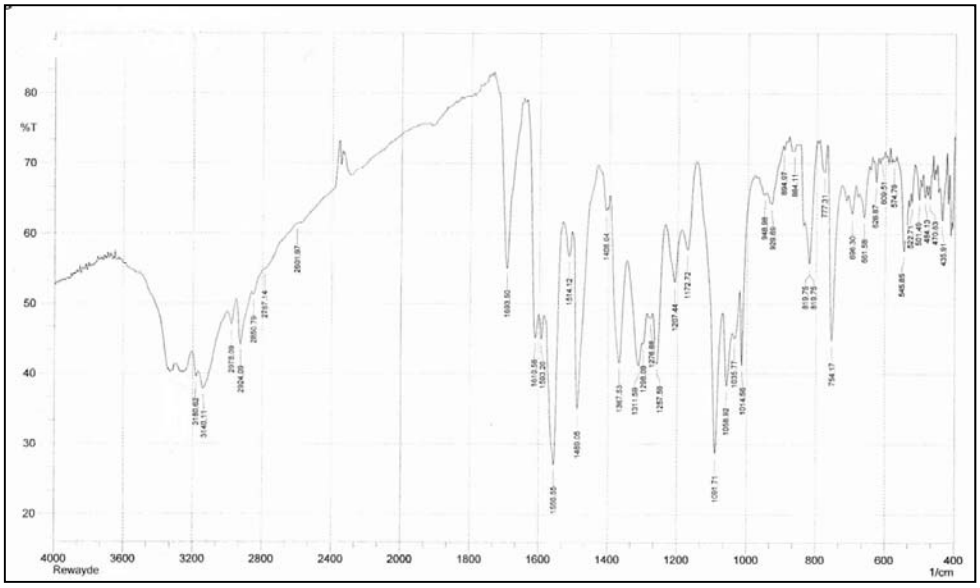


Figure No. (4): FTIR-Spectrum of compound [XII]a

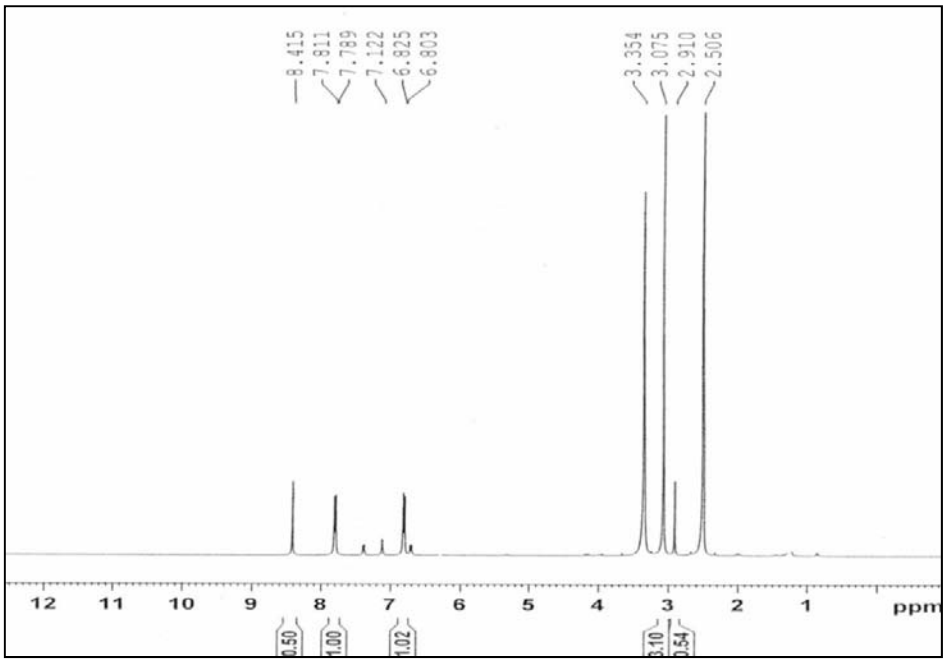


Figure No.(5): ^{1}H-NMR Spectrum of compound [XII]a

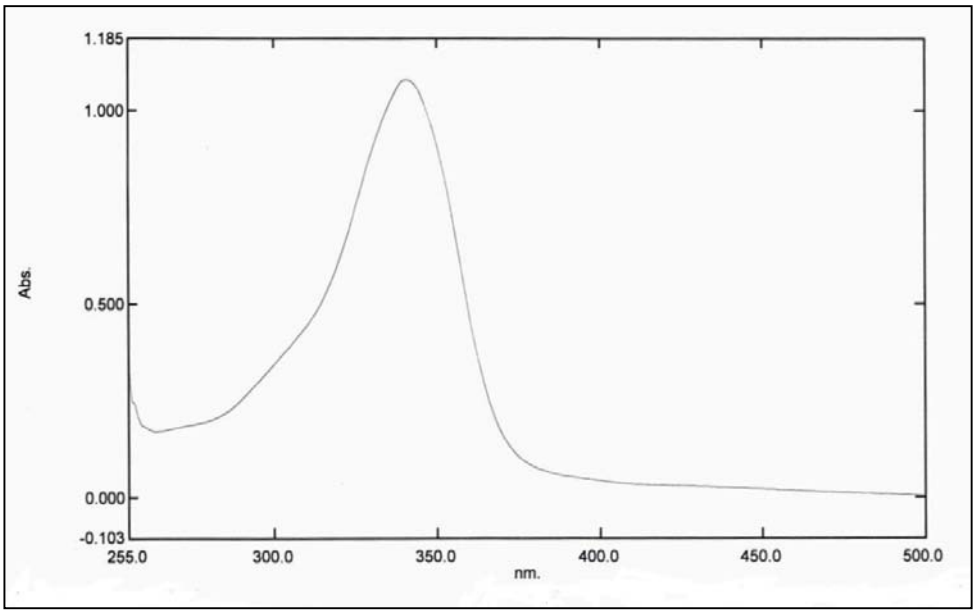


Figure No. (6): UV-Vis Spectrum of compound [XII]a

تحضير و تشخيص بعض مركبات الثيازين و الازيتيدين والثيازولدين الجديدة الحاوية على الوحدة 1و3و4- ثياديازول ودراسة الفعالية البايولوجية لها

علي حمادي سمير
خالد فهد علي
رويدة سمير سعيد
قسم الكيمياء/كلية التربية للعلوم الصرفة (ابن الهيثم)/ جامعة بغداد

استلم البحث في:17 اذار2014 ,قبل في:22 حزيران2014

الخلاصة

حضرالمركب 2- امينو-5- مركبتو-4,3,1- ثياديازول [I] بتحولق الثايوسميكاربازايد مع ثنائي كبريتيد الكاربون بوجود كاربونات الصوديوم اللامائية وفي مذيب كحولي. تفاعل المركب [I] مع هاليدات الالكيل ليعطي المركب 2- امينو -5- ثايوالكايل-4,3,1-ثياديازول [II] , [III] . تفاعل المركب [II] , [III] مع الديهايدات اروماتية مختلفة اعطى المركب 2- [(بنزلدين معوض) امينو]-5-ثايو الكايل-4,3,1- ثياديازول [VI]a-d , [V]a-d , [IV]a-c .وجد ان قواعد شف [VI]a-d , [[V]a-d , [IV]a-c . تتفاعل مع 2-مركبتو حامض البنزويك بوجود ثلاثي اثيل امين لتعطي المركب 3- [5– (ثايوالكايل)–4,3,1–ثياديازول -2- يل] -3,2- داي هايدرو-2-(اريل) بنزو][3,1] [e] [ثيازين -4- ون a [VII] a,c [VII]. وتفاعلت قواعد شف مع كلورو اسيتايل كلورايد بوجود ثلاثي اثيل امين لتعطي 3-كلورو-1-(5- ثايوالكايل)-4,3,1 -ثياديازول -2-يل)-4 -(اريل) ازيتيدين -2-ون [XI]c,d , [X]c , [IX]a,b .
كذلك تتفاعل قواعد شف مع 2-مركبتو حامض الخليك في البنزين الجاف لتعطي 3-(5- مركبتو-4,3,1-ثياديازول-2-يل)-2 -(اريل) ثيازولدين-4- ون [XIV]c,d , [XIII]d , [XII]a,c كما هو موضح في المخطط (1).
شخصت المركبات الجديدة المحضرة من خلال القياسات الفيزيائية واطياف الاشعة فوق البنفسجية و الاشعة تحت الحمراء وطيف الرنين النووي المغناطيسي.

الكلمات المفتاحية :4,3,1-ثياديازول , الثيازين , ازيتيدين , ثيازولدين .