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Design, Synthesis of Sulfadiazine Derivatives bearing Some New Heterocyclic Compounds with study Antimicrobial and Antioxidant Activity

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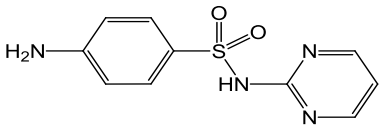
Abstract

In this work new heterocyclic derivatives were prepared. The most available (Sulfadiazine) compound treated with different aromatic aldehydes to synthesis (F1-F5) imine derivatives then cycloaddition reaction of imines with phenylthioacetic acid to produced azetidin-2-one derivatives(F6,F7). compound F1 treated ethylene glycol and hydrazine to get (F8) . (F9,F10) compounds has been synthesis by reacting (F1) compound with maleic anhydride and phthalic anhydride in dry benzene . compound F8 treated p-hydroxy benzaldehyde to get (F11) compound. Reaction (F11) with benzoyl chloride gave (F12) compound. Also, (F12) compound treated with urea to get urease derivative .These synthesized compounds (F1-F13) evaluated for their antimicrobial activity and antioxidant activity.

Keywords: Sulfadiazine , imines, azetidin-2-one , benzaldehyde, antioxidant activity.

1. Introduction

Sulfadiazine (SDZ), is (4-amino-N-pyrimidin-2-yl)benzenesulfonamide, and the common designation is sulfadiazine a heterocyclic organic compound, pyrimidinyl sulfonamide derivatives belongs to the stellate group of stars. Odorless or nearly opaque when exposed to light. [1].Figure(1) It shows the structural formula:



Figure(1): structural of Sulfadiazine

Where sulfadiazine and its derivatives were used in the treatment of many diseases [2]., where it was used to prevent infection with nocordia bacteria [3]., It is a topical antibiotic that is used to cover the places of burns in the form of a thick layer to prevent infection. [4]. Sulfathiazole derivative, which is an organic sulfur compound with molecular formula ($C_9H_9N_3O_2S_2$), has been prepared, containing in its composition the thiadiazole ring that is used in short-acting sulfa drugs.Sulfadiazine and its derivatives were used as an antibiotic used for the treatment of toxoplasmosis [5]., and for the treatment of otitis media, and for the prevention of rheumatic fever, for children with toxoplasmosis [6]., and the sulfathiazole derivative was used as an antibacterial and antifungal substance [7]. Sulfadiazine (SSD) cream was used in the treatment of superficial second degree burns in humans [8]. Anti-bacterial for use in wound healing [9].From the compounds of the Schiff's bases, it is possible to perform cyclic closure reactions and prepare different rings [10,11], as in the reaction of preparing quaternary ring derivatives (azetidine). 2-Azetidinone, is β-lactams contian a four membered cyclic amide and syntesis from imine of aniline and benzaldehyde by [2+2] cycloaddition [12]posses biological activities[13].

2.Experimental

Materials

All the used materials and solvents were obtained from Sigma/Aldrich, BDH and Merck chemicals and purchased from CDH and Reagent world companies respectively

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3.Synthetic methods

1. Synthesis of Imines Derivatives from (F1-F5) [14]

(0.01mmol) of compound F and substituted aldehydes (1 mmol) by (10-15mL) absolute ethanol with (2-3) drops of H_2SO_4 and heated in a water bath at (70- 80) ^{0}C for (2-4) h. The process of the reaction completion was followed by (TLC) using [ethanol/ethylacetate (1:1)], then the products were recrystalized from ethanol solvent.. Table 1.

2.Synthesis of azetidin-2-one (F6,F7) [15]

(0.5 g, 3 mmol) of (phenylthio)acetic acid, Imine, (1 mmol) and triethylamine (6 mmol, 1.5 mL) in 80 mL dry DCM was added drop wise(30-60)min at 0ºC, ($POCl_3$) (0.48 mL, 3 mmol) in 20 mL of DCM with stirring overnight at room temperature, The reaction was followed by TLC technique, washed with 1*N*HCl (30 mL), water (3x30 mL) ,5% $NaHCO_3$ (30 mL) and dried over anhydrous Na_2SO_4. Table 1.

3. Synthesis of 4,4'-(4-amino-3,5-diphenyl-1,2,4-triazolidine-1,2-diyl)bis(N-(pyrimidin-2-yl)benzenesulfonamide) (F8) [16]

(0.01mol, 1.63 gm) of the compound (F1) have been mixed with (80%) hydrazine hydrate with (10 mL) of ethylene glycol. The mixture reflexed for 10h, then 10ml from hydrochloric acid conc was added and reflex the mixture for 4h,then poured to 200ml of water and formation yellow crystal. The reaction was keep track of by TLC technique, cooled until the precipitation was formed. It was recrystallized from the appropriate solvent (absolute ethyl alcohol).Table 1.

4. Synthesis of 4,4'-(4-(1,3-dioxoisoindolin-2-yl)-3,5-diphenyl-1,2,4-triazolidine-1,2-diyl)bis(N-(pyrimidin-2-yl) benzene sulfonamide) (F9) , 4,4'-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3,5-diphenyl-1,2,4-triazolidine-1,2-diyl)bis(N-(pyrimidin-2-yl)benzene sulfonamide) (F10) [17]

F8 (0.01mol,3.56gm) was fused for 30 min in an oil bath with malic anhydride (1mmol,0.98gm,1.47gm) and phthalic anhydride (1mmol,0.98gm,1.47gm) then cooled ethanol was added with stiring.TLC was used to monitor the reaction, and the product was collected.The precipitate was recrystallized using 100% ethyl alcohol. Table 1.

5.Synthesis of 4,4'-(4-((4-hydroxy benzylidene) amino)-3,5-diphenyl-1,2,4-triazolidine-1,2-diyl) bis(N-(pyrimidin-2-yl)benzenesulfonamide) (F11) [18]

(4-chlorobenzyldyde) (1mmol,1.85gm) mixed with(1mmol,3.56gm)of F8 then 20 ml of ethanol was added to mixture,then two drop of glycial acetic acid was added, after that the mixture was reflexed for 4-5h then the mixture was filtered and the precipitation collected. TLC technique was applied.The precipitate recrystallized from (absolute ethyl alcohol).Table 1.

6.Synthesis of N-(chloro(4-hydroxy phenyl) methyl)-N-(3,5-diphenyl-1,2-bis(4-(N-(pyrimidin-2-yl)sulfamoyl) phenyl)-1,2,4-triazolidin-4-yl)benzamide (F12) [19]

To stirring solution of compound F11(0.01mol,4.44gm) in dry benzene(20ml) ,benzoyl chloride(0.01mol, 1.4gm) was added. The mixture was refluxed for 1h,then the excess of benzene was removed under vacuum. Precipitate was recrystallized by appropriate solvent.Table 1.

7.Synthesis of (N-(3,5-diphenyl-1,2-bis(4-(N-(pyrimidin-2-yl)sulfamoyl) phenyl)-1,2,4-triazolidin-4-yl)benzamido)(4-hydroxyphenyl)methyl carbamimidate (F13) [20,21]

Urea was added to a stirring solution of compound F12 (0.01mol,5.84gm) and Na2CO3 (0.01mol,1.06gm) in 100% ethanol (20ml), the mixture was refluxed for 5 hours, then filtered and water (200ml) was added.The precipitate recrystallized with ethanol.. Table 1.

4.Results and Discussion

Identification of compound (F1-F5)

The imine derivatives (F1-F5) were prepared by condensation reactions of Sulfadiazine with different aromatic aldehydes (benzaldehyde , ,*p*-chloro , *p*-methoxy ,, *p*-hydroxy benzaldehyde and Vanillin) .These materials dissolved in absolute ethanol under refluxing temperature in acidic medium as a catalyst to afford the imines derivatives as shown in (Scheme 1). The yields were monitored by (TLC) and characterized via m.p. , FT-IR, ^{1}H NMR.

The FT-IR spectra showed azomethane (C=N) group generation observed at strong absorption at $\bar{\upsilon}$= (1633-1654) cm^{-1} and the disappearance of NH_2 bands (asymmetric and symmetric) at $\bar{\upsilon}$=(3455 -3250) cm^{-1}.

Table 1 .The physical properrties of compounds (F1-F13).

Com No.	Molecular Formula	M.Wt	Color	m.p. °C	Yield %	Rf	(TLC)
F1	$C_{17}H_{14}N_4O_2S$	388	Brown reddish	Oily	85	-	ethanol/ethylacetate (1:1)-
F2	$C_{17}H_{13}ClN_4O_2S$	372	Light brown	122-124	93	0.77	ethanol/ethylacetate (1:1)
F3	$C_{18}H_{16}N_4O_3S$	368	Yellow-green	99-102	65	0.85	ethanol/ethylacetate (1:1)
F4	$C_{17}H_{14}N_4O_3S$	354	Yellow	88-92	75	0.68	ethanol/ethylacetate (1:1)
F5	$C_{17}H_{14}N_4O_3S$	354	White	98-102	86	0.7	ethanol/ethylacetate (1:1)
F6	$C_{19}H_{15}N_4O_3S_2$	411	Light yellow	169-170	64	0.71	hexane:ethyl acetate 7:3
F7	$C_{20}H_{17}N_4O_5S_2$	457	Dark orange	153-154	86	0.76	hexane :ethyl acetate 9:1
F8	$C_{34}H_{30}N_{10}O_4S_2$	706	yellow	88-89	75	0.85	hexane :acetone 1:1
F9	$C_{38}H_{30}N_{10}O_6S_2$	836	Light Orange	192-195	77	0.57	n-hexane:DCM 1: 1
F10	$C_{38}H_{30}N_{10}O_6S_2$	786	Orange	165-166	75	0.85	n-hexane:DCM 1: 1
F11	$C_{41}H_{43}N_{10}O_5S_2$	810	Yellow	96-98	78	0.72	n-hexane:acetone2:1
F12	$C_{48}H_{39}ClN_{10}O_6S_2$	950	Beige	150-154	88	0.78	n-hexane:CHCl3 1:1
F13	$C_{49}H_{42}N_{12}O_7S_2$	974	White	298-302	70	0.6	n-hexane:acetone1:1

In addition to stretching absorption bands of aromatic groups (C=C) showed two peaks of the stretching vibration at ῡ= (1525-1572) cm^{-1} beside small absorption bands in the range of ῡ=(3039- 3063) cm^{-1} of (C-H)ar. ῡ=(2926-2968) cm^{-1} of (C-H) aliphatic, ῡ=(1360)cm-1 of (C-N) group.Fig.(1-5)

^{1}H NMR spectra in DMSO-d_6 gives a strong evidence about the formation of imines derivatives throughout the presence of an individual peak at about δ=(8.94-8.50) ppm as (s,H,CH=N), and multiple peaks in the range of δ= (6.56- 7.94) ppm which was referring to the aromatic protons .

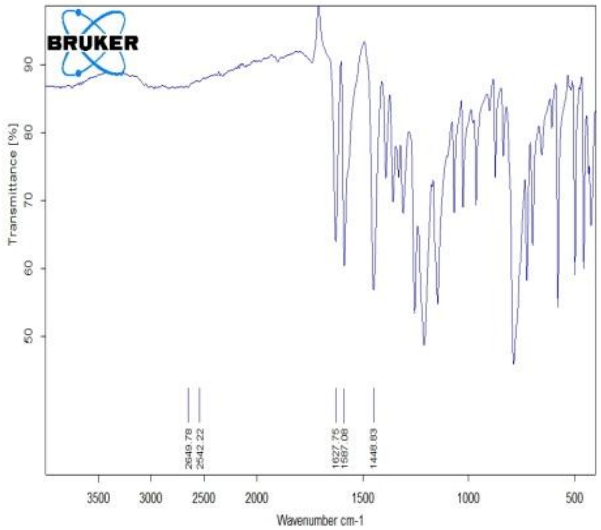


Fig.3: FT-IRspectrum of(F2) .

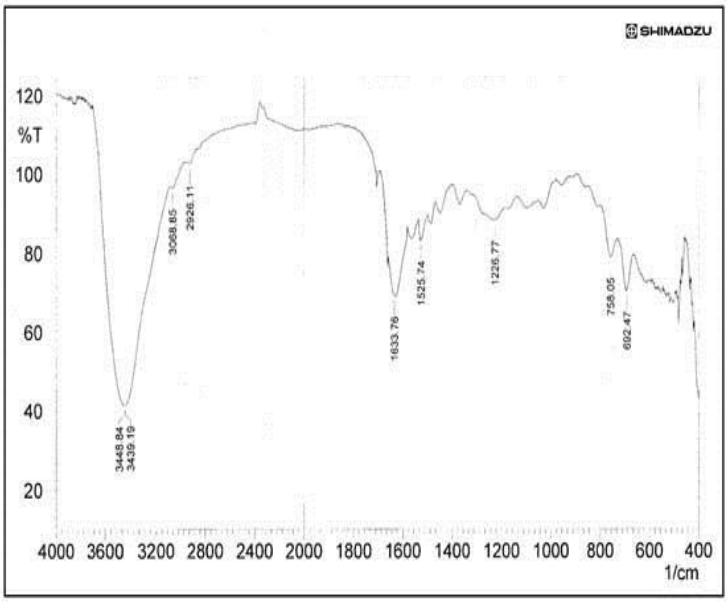


Fig.2: FT-IRspectrum of (F1) .

Identification of compounds (F6,F7)

Compounds azetidin-2-one (F6,F7) were prepared from appropriate Schiff bases of Sulfadiazine derivatives, using (phenylthio)acetic acid via [2+2] cycloaddition using $POCl_3$ as acondensation reagent . schemes (1). The FT-IR spectra of the different azetidin-2-ones were characterized by [22-24], (C=O) of amide carbonyl at ῡ= (1745) cm-1 of β-lactam ring and disappearance of (C=N) in ῡ=(1621)cm-1 of imines. The 1H NMR of β-lactams at the (4.37) ppm,

at δ=(5.2-5.7) ppm of (2C4-H) and disappearance the protons of imines (CH=N) in δ= (8.93) ppm, (6.71-8.11)ppm of $(CH)_{ar.}$ The 13C NMR of F6, at the δ=(49-54) of (C3-H) , at δ=(59-65) ppm of carbon (C4-H) and at δ=(165-170) ppm of (C=O) β-lactam ring [25,26].

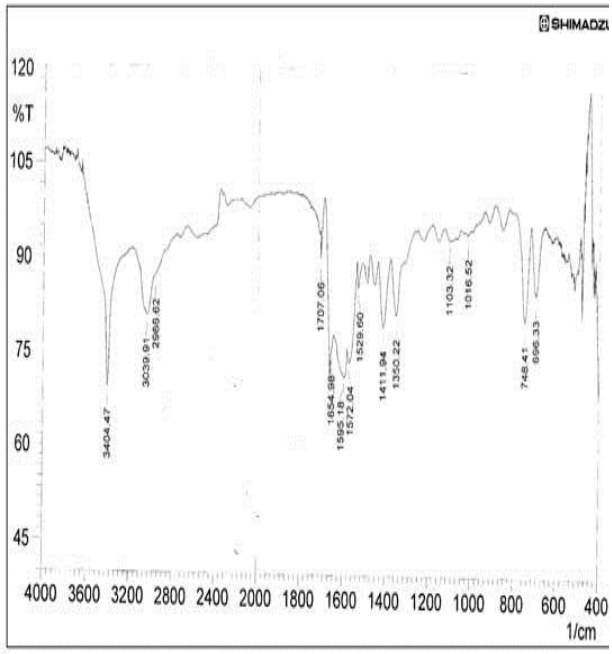


Fig.4: FT-IRspectrum of (F5) .

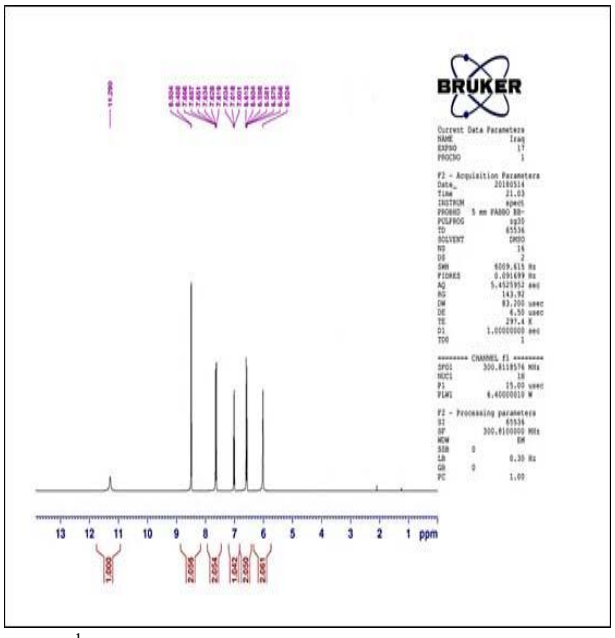


Fig.5: ^{1}H-NMR spectrum of (F1) .

Identification of compounds (F8)

Compound F8 was prepared by cyclic reactions between F1 compound (Schiff base) with hydrazine hydrate , ethylene glycol and presence of hydrochloric acid. The FT-IR spectrum showed the figure (12). The appearance band of NH_2 at(3312-3432)cm-1) , (3047cm-1) of (C-H) ar., (2947cm-1) of the aliphatic (C-H) , (1652cm-1) of C=N group ,(1353cm-1) of C-N group and (1577)cm^{-1} of(C=Car), (1263 -1021)cm^{-1} to (C-O). 1H-NMR spectra in Figure (13) included disappearance signal(CH=N) group at 8.58ppm and 4.32ppm of triazolidin ring , 7.08ppm-8.14 ppm for protons of aromatic.

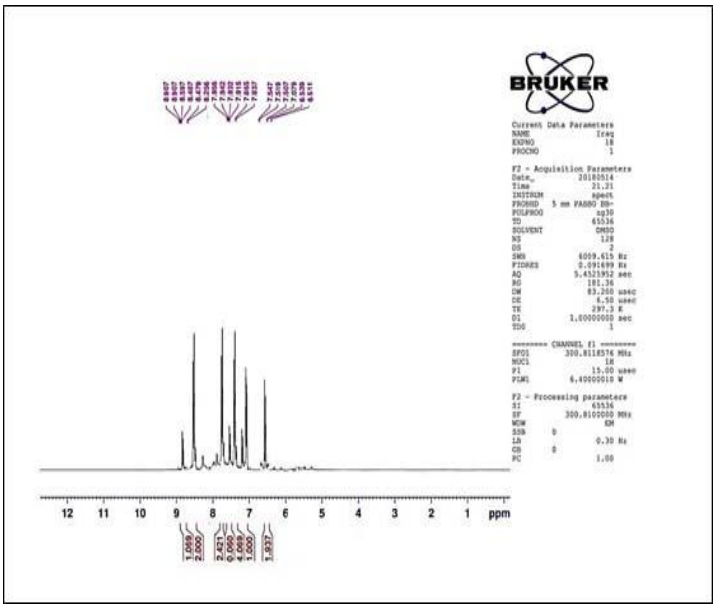


Fig.6: 1H-NMR spectrum of (F2) .

Identification of compounds (F9,F10)

Compounds F9,F10 was prepared by reaction F1 with phathalic and maleic anhydride in ethanol. The FT-IR spectrum showed the figure (14).: (3079cm-1) of (CH)ar., (3126cm-1) of NH , (2860cm-1-2969cm-1) for C-H aliphatic, 1625cm-1 to (C=N) ,C=C group at (1562cm-1-1513cm-1) and (1367cm-1) of C-N group, 1707cm-1 to (C=O) ,1492cm-1 of(C-H bend) and (1110cm-1 -1262cm-1) to(C-O) .

1H-NMR spectra in Figure (15) (F9) : 8.51ppm of NH group, 5.40ppm of triazolidin ring and 7.14ppm-7.91 ppm for protons of aromatic: 13C-NMR spectra in (Figure 16) of F10 showed signal 97.24ppm to triazolidin ring, and signal at 128.81ppm-144.24ppm (Car), 161.91ppm to(O=C-N).

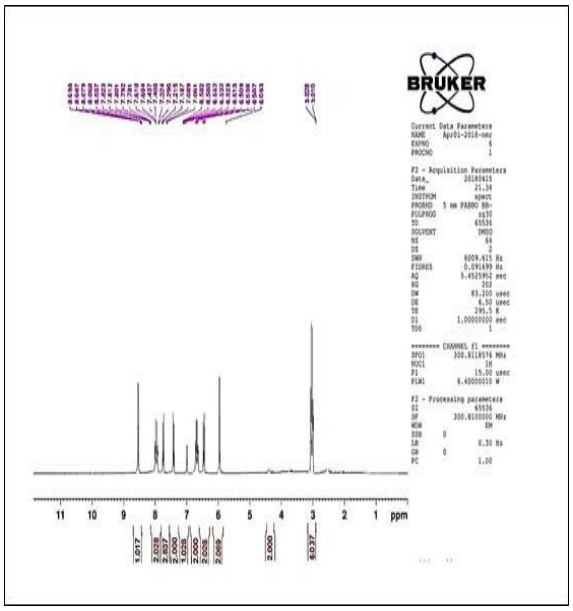


Fig.7: 1H-NMR spectrum of (F5) .

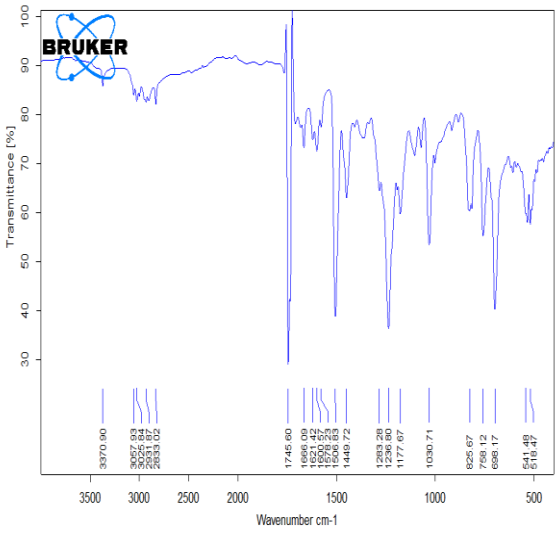


Fig.8: FT-IR spectrum of (F6)

Fig.9: FT-IR spectrum of (F7)

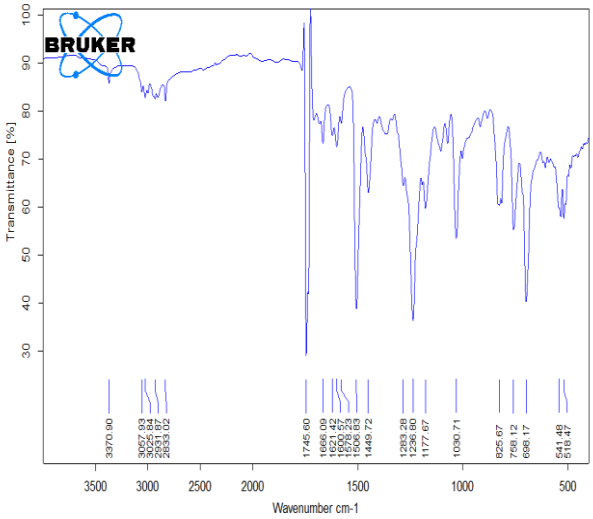


Fig.10: FT-IR spectrum of (F7)

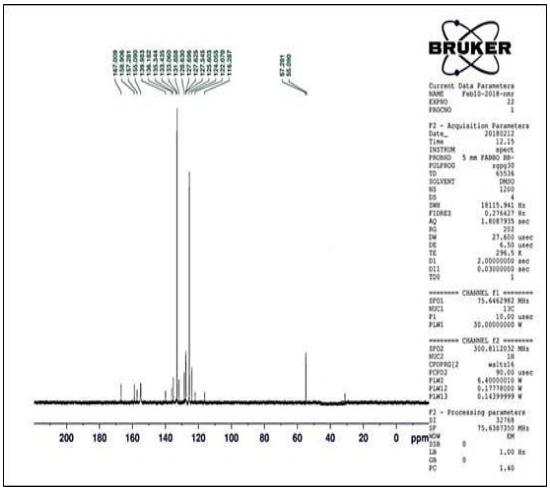


Fig.11: 13CNMR spectrum of (F6).

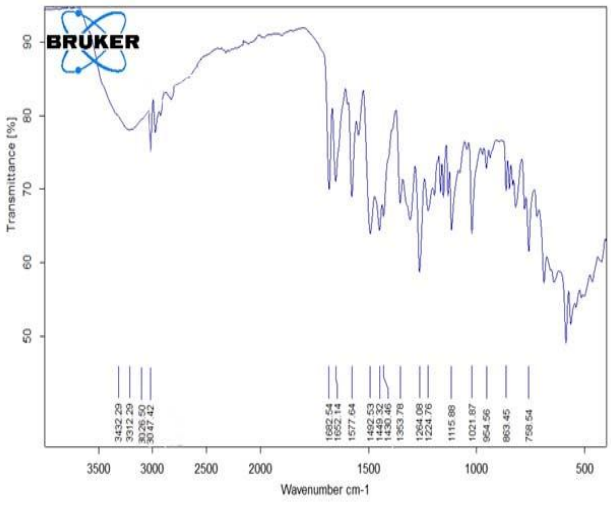


Fig.12: FT-IR spectrum of compound(F8)

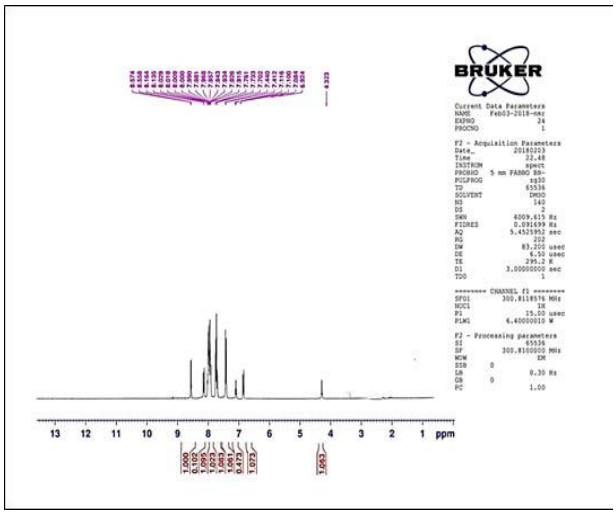


Fig.13: 1HNMRspectrum of (F8) .

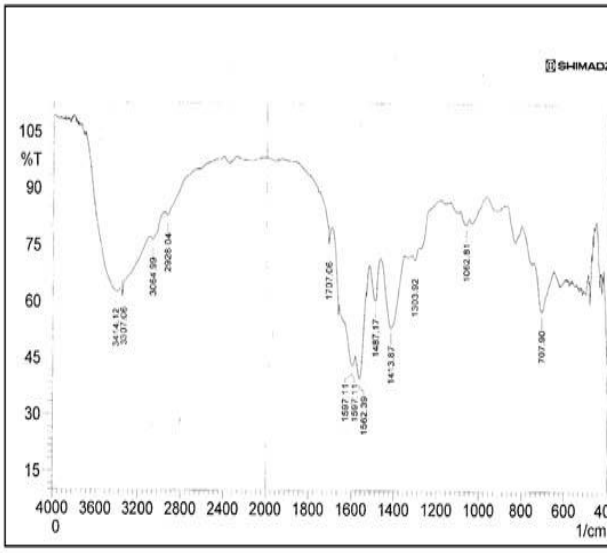


Fig.14: FT-IR spectrum of compound(F9) .

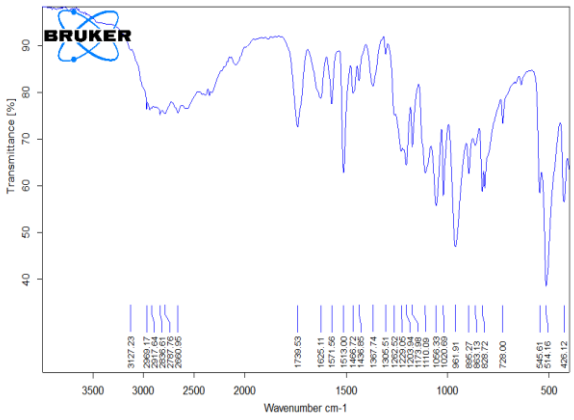


Fig.14: FT-IR spectrum ofcompound(F10) .

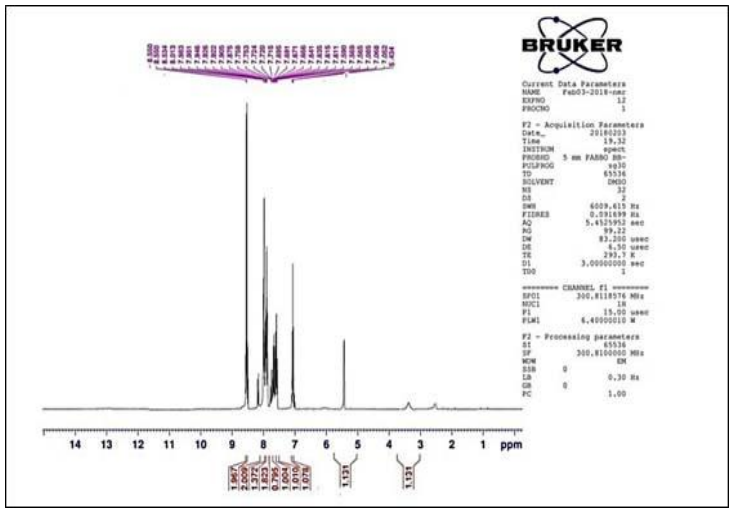


Fig.15:1HNMR spectrum of compound (F9) .

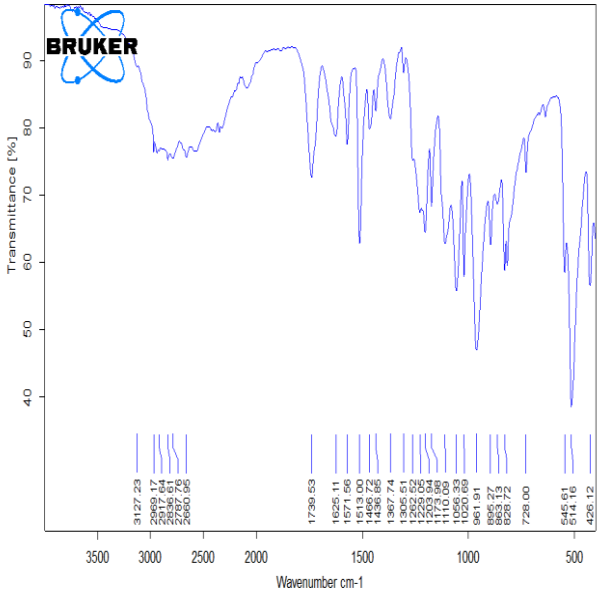


Fig.14: FT-IR spectrum ofcompound(F10) .

Identification of compounds (F13)

Cyclic closure reactions were prepared through the reaction of (F12) with urea using absolute ethanol solvent to give F13 compound.The FT-IR spectrum of compound (F13) , figures (19), includes appearance of (OH) band at (3506) cm-1,NH2 group at,(3429-3329)cm-1.,NH band at (3233 cm-1). C=O band at (1639cm-1),(C=C) at (1593cm-1-1519cm-1,), (CHalph) at (2985 cm-1), (CHar) at (3051 cm-1,). C-N band at(1388.75cm-1,). (C-O)at(1184cm-1-1072cm-1).1H-NMR spectra in Figures (19) of compound (F13) showed appearance protons OH at 9.4ppm, protons of triazolidin ring at 4.44ppm , CHar. at 7.08ppm-7.94 ppm and NH proton at 9.54ppm .

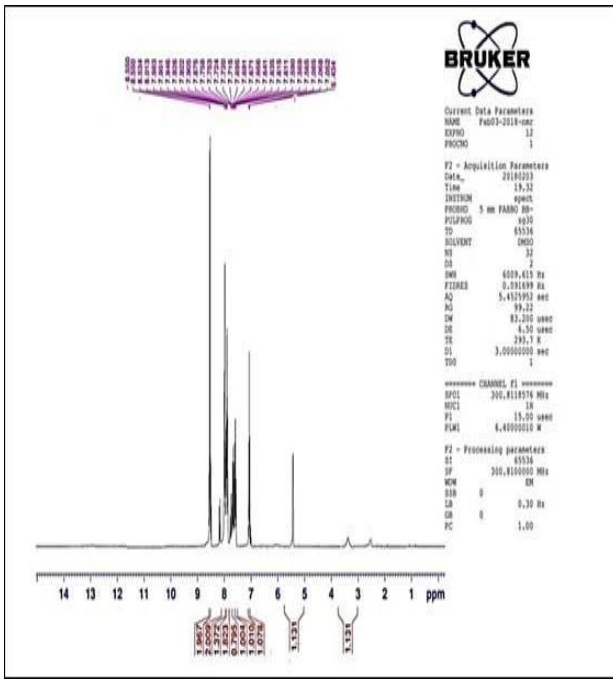


Fig.15:1HNMR spectrum of compound (F9) .

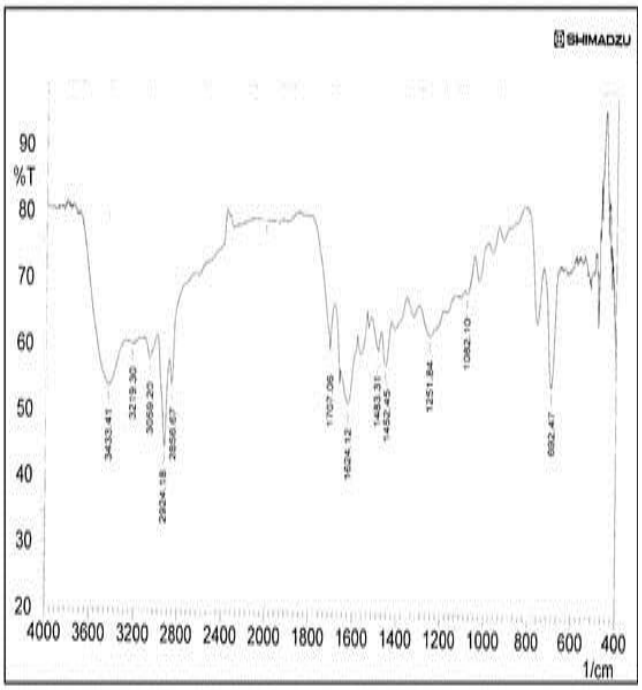


Fig.17: FT-IR spectrum of compound(F12) .

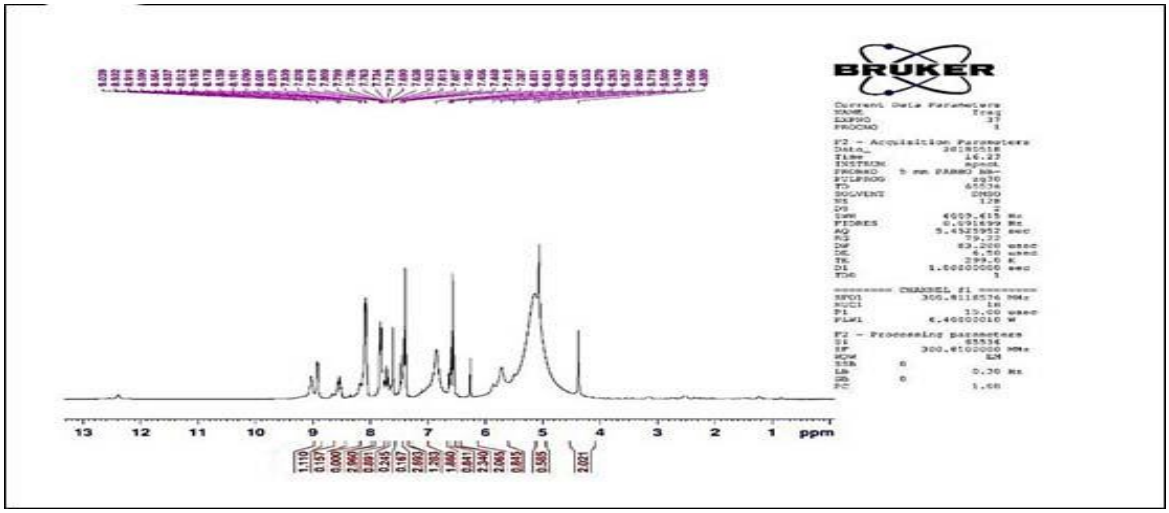


Fig.18: 1HNMR spectrum of compound(F12) .

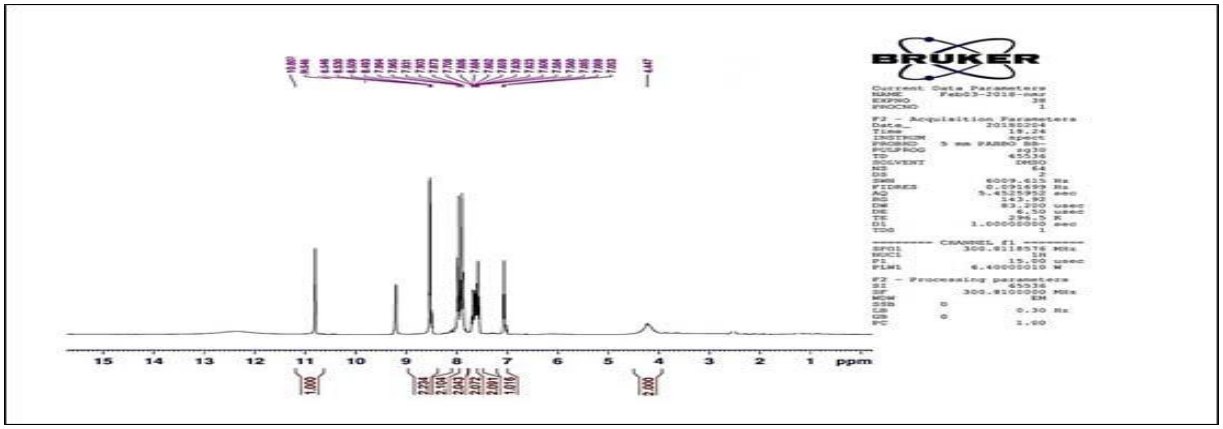
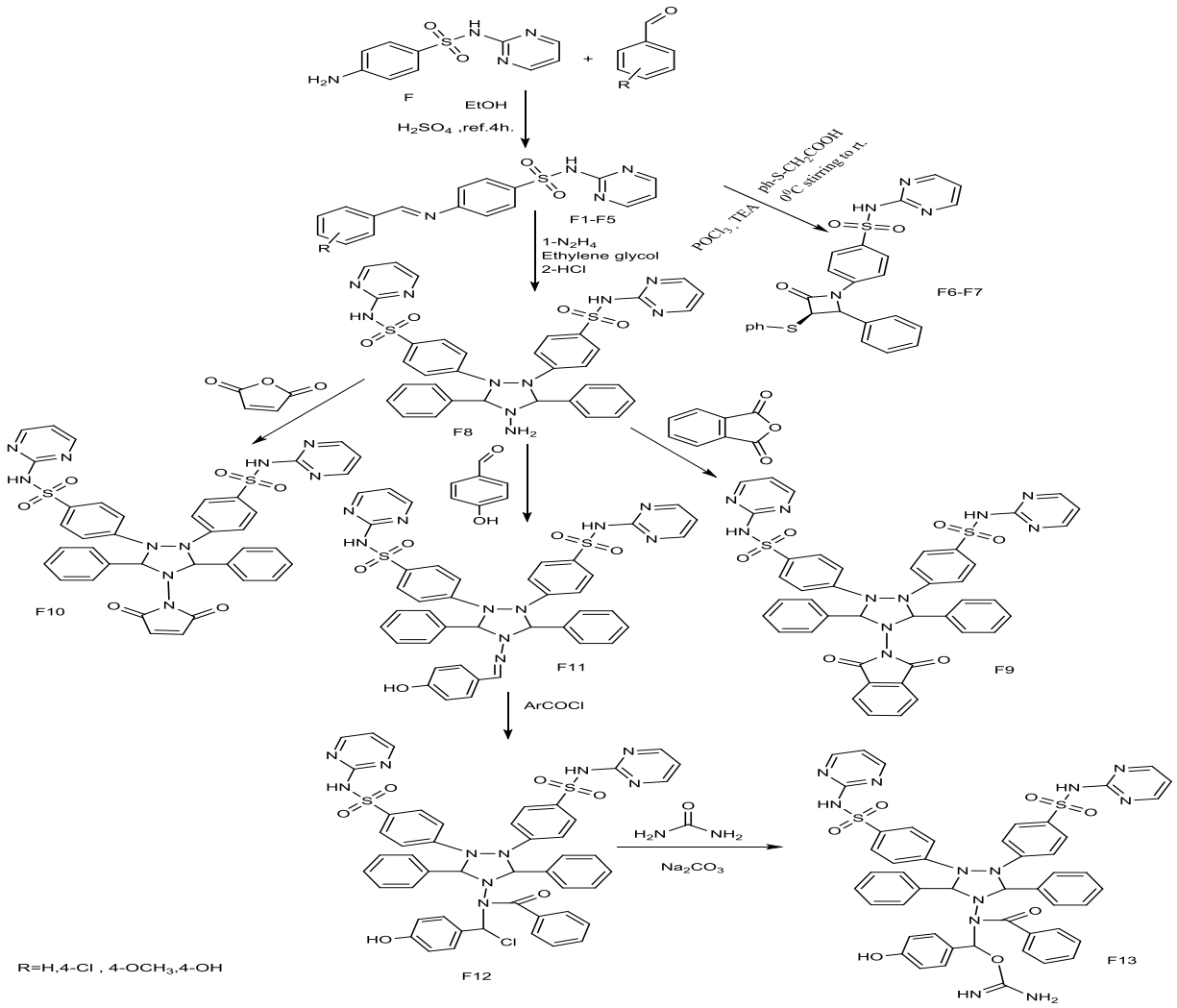


Fig.19: 1HNMR spectrum of compound(F13) .



Scheme 1:synthesis of compounds(F1-F13).

6.Biological efficiency

The majority of the chemicals examined had good antibacterial action, according to the data.These bacteria was chosen for their clinical value, as they cause a wide range of diseases and are resistant to a number of antibiotics and chemical drugs. Antibacterial activity of synthesized compounds(F1-F13) been studies towards G+ Staphylococcus and G-Escherichia coli compared to Cefotaxim at (100mg\ ml) concentrations, it was found that the compounds (F1,F3-F13) has a high effectiveness in inhibiting bacteria (G-) ,It was also found that the compounds (F1,F3-F8,F11-F13) have a high effectiveness in inhibiting bacteria (G+) .When compared the product to (Cefotaxim). Table (2) and Fig (20).

Table2.applications of anti-microbial for compounds

Comp. No.	***Escherichia coli***	***Staphylococcus aureus***
Cefotaxime (Antibiotic) Standard	12	**14**
F1	14	**17**

F2	9	**8**
F3	12	**15**
F4	14	**15**
F5	15	**12**
F6	18	**20**
F7	12	**17**
F8	17	**19**
F9	16	**11**
F10	19	**13**
F11	13	**15**
F12	13	**14**
F13	18	**20**

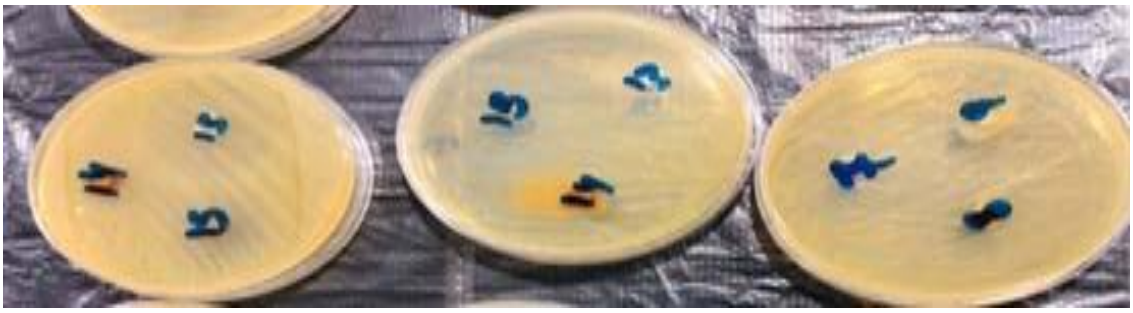


Figure (20) Biological Effect of compounds

6.Ant-oxidant activity

Compounds antiradical operation was carried out using the standard DPPH method [27,28].

DPPH (1.3 mg/ml) was produced as a standard solution in MeOH .The concentrations of the various compounds (25, 50, 75, and 100 g / ml) were prepared.1ml of the sample was diluted to 3 ml and 100 µl of DPPH was added, measure absorbance at 517 nmof each test tube after 30min. The antioxidant activity in table (3) indicates that the maximum of compounds displayed moderate to strong antioxidant activity in comparison (ascorbic acid) (IC50=31.95 µg / mL). The free radical scavenging operation of all synthesized compounds was achieved using ascorbic acid in the presence of stable free radical DPPH, After reviewing the readings, it was found that the following compounds (F1,F4,F9 and F13) are the best results due to contain NH and OH groups . Fig.(21).

Table .3.Observation of synthesized compounds antioxidant properties in vitro .

conc. µg\ml	**F1**	**F2**	**F4**	**F6**	**F8**	**F9**	**F13**	**STD** (Ascorbic acid)
25	48.41	47.76	50.34	49.41	45.35	47.76	50.34	46.12
50	57.42	49.83	57.21	57.42	58.22	49.83	57.21	60.14
75	60.26	53.77	66.23	62.26	62.16	53.77	66.23	65.01
100	69.44	65.21	72.11	67.44	68.18	65.21	72.11	78.3
IC50 µg\ml	28.82	44.09	24.01	32.27	33.24	25.26	23.91	31.95

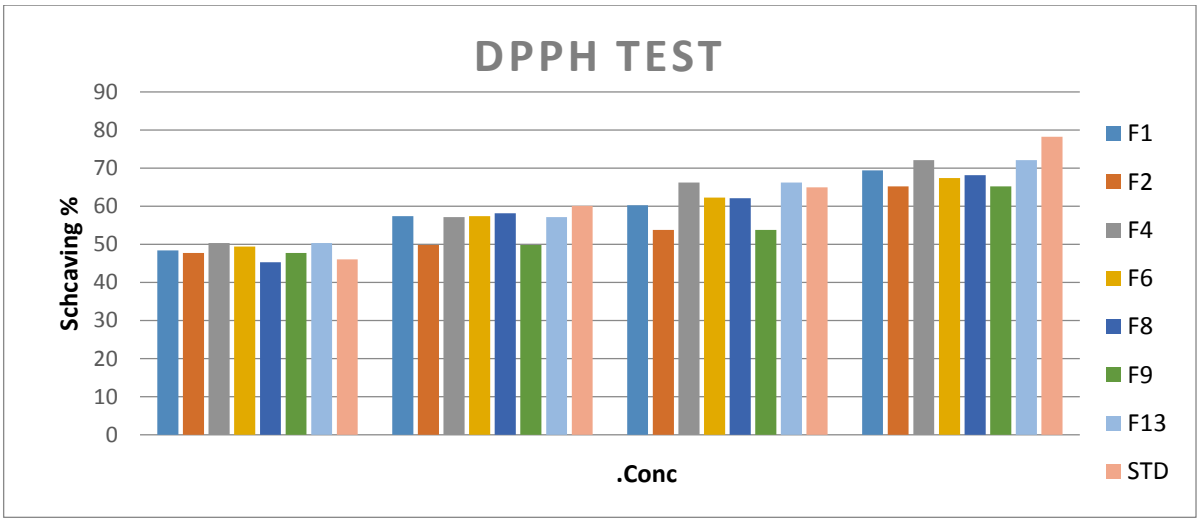


Fig. 21: DPPH scavenging activity of compounds (F1-F13).

7.CONCLUSION:

In present study New derivatives prepared from the sulfadiazine with benzaldehyde may be used to synthesis other derivatives as a result of having effective aggregates as well as the proportion of the productions were good and useful for continuation of subsequent step. From the antioxidant activity it has been interesting to note that the compounds were strong antioxidant activity and antibiotic.

8. Conflicts of Interest

There are no conflicts to declare.

9. Acknowledgments

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10.References

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