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Synthesis and Biological Evaluation of some new 2-Thioxoimidazolidin- 4-one Derivatives (part II)

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Abstract

In the present work, a various new derivatives of 2-thioxoimidazolidin-4-one have been synthesized starting from reaction of thiosemicarbazide with two substituted aromatic aldehydes (4-bromobenzaldehyde, 4-chlorobenzaldehyde) to afford shiff's bases (1a,b) which suffering from intermolecular cyclization when treating with ethylchloroacetate to give compound (2a, b), reaction of compound (2a, b) with4-bromobenzaldehyde produce compounds (3a, b), which is award six member ring product (compound 4a, b) when react with ethylacetoacetate. After a series of reactions with different reagents compound (4a, b) converted to anther compounds by reaction with hydrazine, aldehyde and then with chloroacetylchloride bearing β-Lactam moiety. The structures of the newly synthesized compounds have been confirmed on the basis of FT-IR and some of them by ^{1}H-NMR. All of the prepared compounds were tested for their antibacterial activity against *E.coli*, *P. mirabilis*, and *Staphylococcus* and some of these compounds give good results.

Keywords: thiosemicarbazone, chalcone, beta lactone, imidazolidin-4-one, antibacterial Activity.

الخلاصة

في هذا البحث تم تحضير مشتقات جديدة لمركب 2-thioxoimidazolidin-4-one M بث الـ دء بتفاعل لركب M ربزايد لع اثنين لن على قواعد شيفيدراتية المعوضة M4 رولوبنزالديهايد M2 ديهايد) للحصول ثم اجري لها تفاعل (1a, b) M قي لها مع مركب روخلات الاثيل للحصول على M (2a, b) M تفاعل لمركب M (2a) M ديهايد دات اولاتية المعوضه M بعطى المركبات M (3a, b) M المركبات M (4a, b) M الحصول عليها من M لن تفاعل المركبات (3a, b) M ميتو خلات الاثيل , بقية المشتقات تم تحضيرها لن المركبات (4a, b) مع د للحصول على واعد شيف ثم لع رو اسيتيل كلوريد للحصول على بيتا لاكتام M. تركيب كبات المحضرة تم اثـ اتها باستخدام وبعضها باستخدام NMR M كل المركبات المحضرة تم اختبار عاليتها بكتريا *E.coli, P. mirabilis, and Staphylococcus* M بعضها M نتائج جـ دة جدا

Introduction

Derivatives of Imidazole-thione have long been known for their diverse pharmacological properties such as fungicides and herbicides[1,2] and (heterocyclic compounds) display a broad biological activities as well as therapeutics [3-5].which has been reported to possess including antibacterial [6,7] anti-tumor[8] anti-inflammatory[9], anti-fungal [10] and anti-mutagenic[11]. Moreover, Imidazole-thione derivatives have been reported as inhibitors of serine protease [12, 13] and liver glycogen phosphorylases [14], the thioimidazolone is an antimicrobial drug for the infections of urinary tract [15]. theimidazolidine or thiazolidine nucleus occupy apivotalposition in modern medicinal chemistry because of their high potential biological activities[16]. The synthesis of beta lactame derivatives is important for their wide

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range of pharmacological and biological properties like antibiotic,anti-inflammatory activities [17, 18].

Experimental

Instrument:

The melting point was determined in open capillary tubes on a Gallenkamp melting point apparatus and was left uncorrected. The IR Spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer,usingKBr discs. 1HNMR Spectra of some prepared derivatives were recorded in DMSO with TMS as internal standard on aVarian-Mercury 300 MH_Z Spectrometer the reaction were followed:

Synthesis of 2-(4- arylidine) hydrazine carbothioamide (1a, b)

To mixture of substituted of aromatic aldehyde (0.01 mole), and thiosemicarbazide (0.01 mole) in ethanol (30ml) were mix in round bottom flask and refluxed for 3 hrs according to literature procedure [19], resulting mixture was poured in to crash ice and stirred for 5 min,the solid filtered and recrystillaztion from ethanol

1a: **2-(4-bromo benzylidene) hydrazine carbothioamide**: yield 65% mp. .(℃) (175-177) FTIR ν (Cm^{-1}) : 3437, 3290 (NH_2 amino group), 3167(NH) ,3059 (CHar.), 2993 (CH aliph.), 1554-1524 (C=Car.), 1600 (C=N azomthene), 863(C-Br) H-NMR (ppm,) 11.87 (NH), 8.43- 7.77 (m, 4H, ArH), 3.58 (s, amino), 8.75 (=CH)

1b:2-(2-chlorobenzylidene)hydrazine carbothioamide : yield 60% mp (℃) 154-156 FTIR ν (Cm^{-1}) 3417, 3250 (NH_2), 2982 (CH aliph.),3066(CHar.),3157(NH),1621(C=N),1593-1529 (C=Carom.), H-NMR (ppm,) : 8.77 (=CH),11.6(NH) 3.4 (s, NH_2) 8.2- 7.6(m, 4H, ArH).

Synthesi of 3-[(4-bromobenzylidene)amino]-2- thioxoimidazolidine--4-one(2a)and 3-[(2-*chlorobenzylidene)amino]-2-*thioxoimidazolidine --4-one(2b) [13]

A mixture of compounds (1a or1b) (0.02 mole) and(0.02 mole) ethyl chloroacetate were dissolved in ethanol (50 ml) in present of anhydrous sodium acetate then refluxed for (20 hrs.), the mixture was cold and filtered to obtained the solid, the product was recrystillazed from ethanol .

2a: 3-[(4-bromobenzylidene)amino]-2-thioxoimidazolidine--4-one : yield 70% mp. .(℃) 220 – 222, FTIR ν (Cm^{-1}) 3128 (NH) ,3045(CHar.), 2939 (CH aliph.), 1710 (C=O carbonyl imidazole), 1605-1519 (C=Car.), 1637 (C=N),12.24(NH),, H-NMR (ppm,) : 8.4 (N=CH), 7.73- 7.66 (m, 4H, ArH), 3.37 (N-CH_2).

2b: 3-[(2-chlorobenzylidene)amino]-2-thioxoimidazolidine--4-one yield 75% mp. .(℃) 205 – 207, FTIR ν (Cm^{-1}) : 3175 (NH), 1714 (C=O), 1595-1513 (C=Car.), 3053 (CHar.), 2928 (CH aliph.), 1639(C=N), H-NMR (ppm,) : 8.52- 7.75 (m, 4H, ArH), 12.24(NH), 3.46 (N-CH2),8.74 (=CH),

Synthesis of (5)-5-(Arylidene)-3-[(4-bromobenzylidene)amino]-2-thioxo –3,5-dihydro-4H-imidazol-4-one(3a, 3b) [2]

To a reaction mixture of compound (2a) (0.01 mole) and (0.01 mole) aromatic aldehyde in mixture of acetic acid (5 ml) and acetic anhydride (20 ml), then refluxed for (4 hrs.) after the reaction was complete left to cool at room temperature. The precipitate was collected and recrystallized from ethanol.

3a:(5)-5-(4-bromobenzylidene)-3-[(4-bromobenzylidene)amino]-2-thioxo–3,5-dihydro-4H-imidazol-4-one: yield 50% mp. .(℃) 232 – 234 (benzene)**,** , FTIR ν (Cm^{-1}) **:** 3254 (NH imidazole) 3121 (=CH), 3028 (Car.), 1626 CHar.), 2926-2873 (CH aliph.), 1728 (C=O), 1599-1512 (C= (C=C alkene), 1645 (C=N), 873 (C-Br)**,** 11.6 (NH), H-NMR (ppm,) 8.3- 7.76 (m, 8H, ArH), 7.56 (s, C=CH), 8.35 (N=CH), 3.5 (s, NH_2),4.1(s,2H,CH2 Hexa hydro benzaimidazol).

3b: (5)-5-(4-bromobenzylidene)-3-[(2-nitrobenzylidene)amino]-2-thioxo -3,5-dihydro-4H-imidazol-4-one yield 75% mp.(℃) 221- 223 (ethanol),, FTIR ν (Cm^{-1}) : 3117 (NH), 1632(C=C alkene), 3041 (CHar.), 2923 (CH aliph.), 1718 (C=O), 1530-1485 (C=Car.), 1653 (C=N) 1518-1312(N02)., H-NMR (ppm)3.51 (s, NH_2),11.14 (NH), 8.15(N=CH), 8.2-- 7.6 (m, 8H, ArH), 4.2(s,2H,CH2Hexa hydro benzaimidazol), 7.4 (s, C=CH)

Synthesis of Ethyl 4-(4-bromo phenyl)-1-[(Arylidene)amino]-6-oxo-2thioxo octa-hydro-1H- benzo[d]imidazole-5-carboxylate(4a, b)

Ethyl acetoacetate (0.01 mole) was add dropwise to stirring solution of compound (3a or 3b) (0.01 mole) in ethanol (20 ml) and (0.02 mole) sodium hydroxide,the reaction mixture was refluxed for (6 hrs) [20], precipitate formed was filtered off and washed with water, and recrystallization was carried out with ethanol.

4a: Ethyl 4-(4-bromo phenyl)-1-[(4-bromobenzylidene)amino]-6-oxo-2-thioxo octa-hydro-1H-benzo[d]imidazole-5-carboxylate: yield 60% mp.(°C) 244-246(ethanol)**,** FTIR ν (Cm^{-1}) :3337(NH), 1726 (C=O ester), 3073(CHar.), 2937 (CH aliph.), 1706 (C=O ketone), 1642 (C=N), 1605-1512 (C=Car.), 864 (C-Br)

4b: Ethyl 4-(4-bromo phenyl)-1-[(2-nitrobenzylidene)amino]-6-oxo-2-thioxo octa-hydro-1H-benzo[d]imidazole-5-carboxylate: yield 55% mp.(°C)230 – 232(methanol)**,** FTIR ν (Cm^{-1}) : 3440(NH), 3054 (CHar.), 1728(C=O ester), 2967 (CH aliph.), 1711 (C=O ketone), 1650 (C=N), 1576-1510 (C=Car.) 1528 -1378(nitrogroup).

Synthesis of 4-(4-bromo phenyl) -1-[(Arylidine)amino]-6-oxo-2-thioxo octa hydro -1H-benzo[d]imidazole-5-carbohydrazide (5a, b)

A mixture of compound (4a, 4b) (0.01 mole) and(98%) hydrazine hydrate (10mL) was refluxed for (5 hrs), ethanol (30ml) was added and refluxed for (3 hrs) [21] ,After that the reaction mixture cooled to room temperature. Separated precipitate was filtered and washed with dilute ethanol, and recrystallized from ethanol.

5a:4-(4-bromophenyl)-1-[(2nitrobenzyliden) amino]-6-oxo-2-thioxo octa hydro -1H-benzo[d]imidazole-5-carbohydrazide: yield 60% mp.(°C)224 – 226 FTIR ν (Cm^{-1})**,** 3186 (NH), 3431, 3320(NH_2),3075 (CHar.), 2954 (CH aliph.), 1687 (C=O amide), 1723 (C=O ketone), 1615-1508 (C=Car.), 1654 (C=N), , 832 (C-Br) H-NMR (ppm) 11.6 (NH), 8.3- 7.76 (m, 8H, ArH), 7.56 (s, C=CH), 8.35 (N=CH), 3.5(s,NH_2),4.1(s,2H,CH2Hexahydrobenzaimidazol).

5b:4-(4-bromophenyl)-1-[(2-nitrobenzyliden)amino]-6-oxo-2-thioxo octa hydro -1H-benzo[d]imidazole-5-carbohydrazide : yield 75% mp.(°C)208 – 210**,** FTIR ν (Cm^{-1}) 3453, 3318 (NH_2), 3119 (NH), 3073 (CHar.), 2978 (CH aliph 1610-1512 (C=Car.) 1680(C=O amide), .), 1730 (C=O ketone), 1660(C=N) 1538-1341(N02) ,H-NMR (ppm), 3.51 (s, NH_2),11.14 (NH), 8.15(N=CH), 8.2 7.6 (m, 8H, ArH),) 4.2(s,2H,CH2Hexa hydro benzaimidazol), 7.4 (s, C=CH)

Synthesis of 4-(4-bromophenyl)-N'-4-bromo Arylidine -1-[(Arylidene)amino]-6-oxo-2-thioxo octa hydro-1H-benzo[d]imidazole-5-carbohydrazide (6a, b) [2]

A solution of compounds (5a or 5b) and (0.01 mole) 4-bromo benzaldehyde (0.01 mole) in ethanol (30ml) was refluxed for (9 hrs.) After cooling the produced precipitate was filtered and recrystallized from ethanol.

6a:4-(4-bromophenyl)-N'-4-bromo benzylidene-1-[(4-bromobenzylidene) amino]-6-oxo-2-thioxooctahydro-1H-benzo[d]imidazole-5-carbohydrazide: yield 70% mp.(°C)234 – 236**,** FTIR ν (Cm^{-1}): 3428(NH amide), 3221 (NH, imidazole), 3054 (CHar.), 2967 (CH aliph.), 1641(C=O amide), 1720 (C=O ketone), 1600-1503 (C=Car.), 1624(C=N), 821 (C-Br)

6b:4-(2-bromophenyl)-N'-4-bromo benzylidene -1-[(2-nitrobenzylidene)amino]-6-oxo-2-thioxooctahydro-1H-benzo[d]imidazole-5-carbohydrazide: yield 65% mp.(°C)221 – 223**,** FTIR ν (Cm^{-1})**:** 3255 (NH, imidazole), 3314(NH amide), 1643 (C=O amide), 1718 (C=O ketone),3064 (CHar.), 2935 (CH aliph.), 1610-1511 (C=Car.)

Synthesis of N-(3-chloro-2-(4-bromo phenyl)-4-oxoazetidin-1-yl)-1-(Arylideneamino)-4-(4-bromo phenyl)6-oxo-2-thioxooctahydro-1H- benzo[d]imidazole -5-carboxamide (7a, b)

Chloro acetyl chloride (0.02 mole) was added dropwise at 0-5C to a stirred solution of compounds (8a or 8b) (0.01 mole) and (0.01 mole) triethyl amine in dioxane (30ml).the reaction mixture was refluxed for (12hrs) [22], the filtrate cooling and concentrated under

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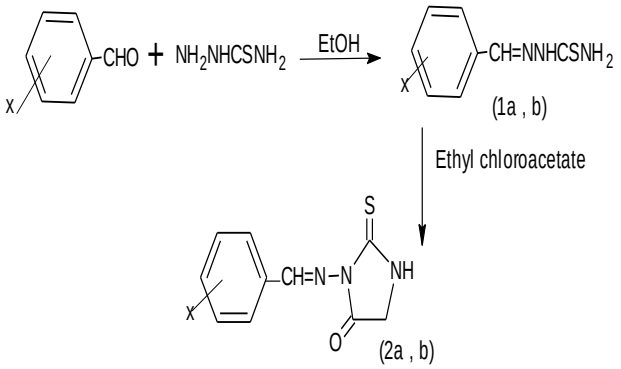
reduced pressur, the obtained solid product recrystallized from benzene.

7a: N-(3-chloro-2-(4-bromophenyl)-4-oxoazetidin-1-yl)-1-(4bromobenzylideneamino)-4-(4-bromophenyl)6-oxo-2-thioxooctahydro-1H-benzo[d]imidazole -5-carboxamide: yield 65% mp.(°C)253-255**,** FTIR (Cm^{-1})**:**3240(NH amide), 1730(C=O beta lactame), 3101 (NH, imidazole), 3067 (CHar.), 1600-1495 (C=Car.), 2937(CH aliph.), 1631(C=O amide), 846(C-Br), 781(C-Cl)**,** 4.2-4.4(d,d,2H aziditene ring), 1H-NMR (ppm) 11.12 (NH), 8.2 (N=CH), 7.6(s, C=CH) 3.4 (s, NH_2),4.5(s,2H,CH2 Hexa hydro benzaimidazol). 8.3- 7.77(m, 8H, ArH

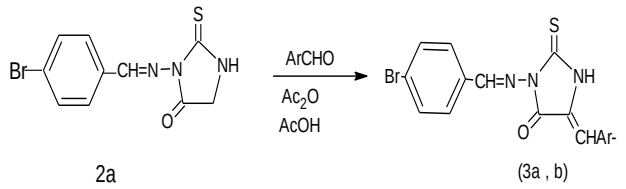
7b: N-(3-chloro-2-(4-bromo phenyl)-4-oxoazetidin-1-yl)-1-(2-nitrobenzylideneamino)-4-(4-bromo phenyl)6-oxo-2-thioxooctahydro-1H-benzo[d]imidazole -5-carboxamide yield 55% mp.(°C)242 – 244, FTIR ν (Cm^{-1}):1741 (C=O beta lactame),3321 (NH amide), 3237 (NH, imidazole), 3057 (CHar.), 2928 (CH aliph.), 1643(C=O amide), 1559-1508 (C=Car.), 1541,1329 (NO_2), 819(C-Br), 1H-NMR (ppm) : 11.10 (NH), 4.1-4.2(d,d,2H aziditene ring), 8.2 7.8 (m, 8H, ArH), 7.5(s, C=CH) 3.5 (s, NH_2),4.6(s,2H,CH2 Hexa hydro benzaimidazol

Results and Discussion

The synthesis of the desire new 2-thioxoimidazolidin-4-one derivatives containing various moieties was accomplished according to the reactions sequences represented in following steps.The structure of compound (1a, b) was confirmed by appearance of the new band at (1600 Cm^{-1}) for (C=N) and at (3290 Cm^{-1}) for NH anther band at (3437 Asym., 3290 Sym. Cm^{-1}) for stretching vibration of NH_2 group, disappearance of the (C=O) group of aldehyde and the Spectrum show anther bands, 1554-1524 (C=Car.), 3059(CHar.), 2993 (CH aliph.), 869 (C-Br) , the ^{1}HNMR spectrum shows signals at 11.87 (NH), 8.75 (=CH), 8.43-7.77 (m, 4H, ArH), 3.58 (s, NH_2 group) table(2), in the same method synthesized compound **(1b)** by treatment of thiosemicarbazide with 2-chloro benzaldehyde the FTIR Spectrum show (3417 Asym., 3250 Sym. Cm^{-1}) for NH_2 group and show anther bands, 3157(NH), 1593-1529 (C=Car.), 1621 (C=N), the ^{1}HNMR spectrum shows signals at 11.76 (NH), 8.86(=CH), 8.6- 7.81 (m, 4H, ArH.), 3.64 (s, NH_2 group), imidiazolidine **(2a,b)** were synthesis by the treatment of compounds (1a,b) with ethyl chloroacetate, the reaction happened by elimination of HCl and ethanol, FTIR spectrum of compound 2a shows new band at1710 Cm^{-1} for carbonyl group of Imidazoline -4-one , anther bands shown in Figure 2, the ^{1}HNMR spectrum shows signals (ppm) at 12.21 (NH), 8.43- 7.86(m, 4H,aromatic proton), 8.7 (=CH), new signal at 4.3due to (CH_2 methylene), G-Mass (M^{*+}) 298 Figure 5, FTIR Spectrum ofcompound **(2b)** shows (C=O) group at1714 Cm^{-1}, and at 3175 Cm^{-1} due to (NH) of Imidazoline, band at 3053 Cm^{-1} due to (CHar.), and at 2928 Cm^{-1} for (CH aliph.), bands at 1595-1513 for (C=Car.) and 1639 (C=N), the ^{1}HNMR spectrum shows signals (ppm) at 12.31(NH), 8.74 (=CH), 8.52-7.75 (m, 4H, ArH), 4.26(CH_2).

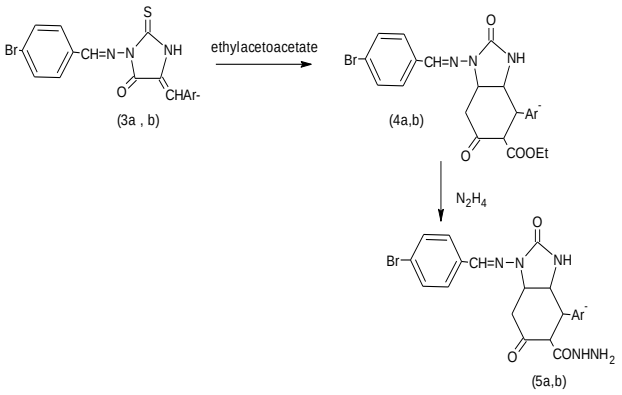


Reaction of compounds (2a) with aromatic aldehyde afforded the corresponding chalcone (3a, b) which take place by elimination of H_2O . The FTIR spectrum show new band (C=C alkene) at (1626 Cm^{-1}), the ^{1}HNMR(DMSO-d6)(ppm)of compound (3a) 11.86(NH), 8.31 (N=CH), 8.2- 7.87 (m, 8H, aromatic proton), 7.64 (s, C=CH) table (2).

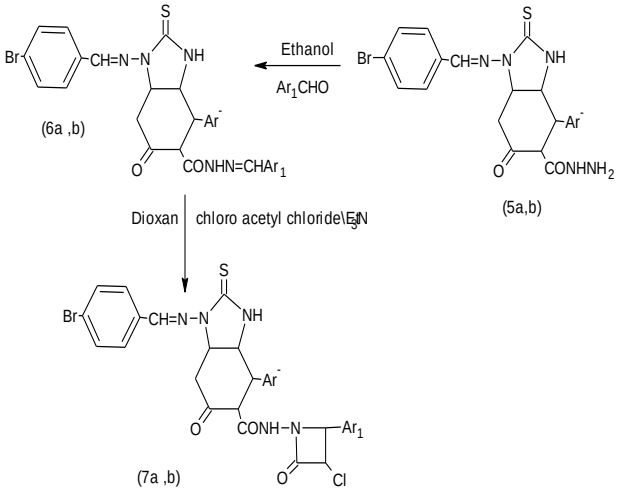


2a (3a , b)

Treatment of compounds (3a, 3b) with ethyl acetoacetate, derivatives (4a, 4b) were obtained in high yield. The FTIR spectrum of compound (4b) exhibited appearance band of (C=O ester) at (1725 Cm^{-1}) and anther bands as shown in experimental .Hydrazide derivative (5a, 5b) were synthesis by reaction of compounds (4a, 4b) with hydrazine hydrate the formation of compound (5a) was confirmed by the presence sharp absorption band at (3431Asym., 3320 Sym. Cm^{-1}) for (NH_2) group, the ^{1}HNMR spectrum for this compound shows signal at 11.6 due to (NH), at 8.35 for (N=CH) and at 8.3- 7.76 for (m, 8H, ArH), signals at 7.56 due to (s, C=CH), at 3.5for (s, NH_2) and at 4.1 due to (s,2H,CH2 Hexa hydro benzaimidazol). Mechanism of this reaction is including: attacked carbon of carbonyl group with the lone pair of electron of amino group and then loos ethanol.



Condensation compound (5a, 5b) with p-bromo benzaldehyde in ethanol gave the Schiff's bases (6a ,6b). The formation of this compounds was indicated by the presence in their FTIR spectrum of compound (8a) shows azomethine group (HC=N) at 1620 Cm^{-1} and disappearance bands of NH_2. The treatment of Schiff's bases (6a, 6b) with Chloro acetyl chloride produced beta lactam derivative (7a, 7b). The structure of these compounds were confirmed by FTIR and ^{1}HNMR, the FTIR spectrum shows stretching band at (1730) due to carbonyl of beta lactam for compound (7a), ^{1}HNMR spectrum (ppm) give signals at 11.10 due to (NH), at 8.18 for (N=CH), at 4.1-4.2(d,d,2H aziditene ring),at 8.2 7.8 due to (m, 8H, ArH), and at 7.5 for (s, C=CH) at 3.5 for (s, NH_2), and at 4.3 due to (s,2H,CH2 Hexa hydro benzaimidazol).



Antibacterial activity

The antibacterial activity of the some target derivatives (13) was tested by the agar disc-diffusion methodagainst *Staph. aureus, E. coli, and proteus mirabilis* bacteria,the concentration of tested compounds were (10^{-3}M) and The results of these compounds are summarized in Table 1. It could be observed that all the tested compounds were active toward *Staph. aureus* expectcompounds **3a and 5a** show no activity . All the tested compounds were active toward*proteus mirabilis*, except 2b, 3b and 5b while compound **4a,** show high activity, so only compounds **3a** and **5a**were no active toward *E. coli*. On the other hand, all anther compounds showed have highinhibition toward *E. coli* while compounds2a and 4a have effected and have high inhibition on this kind of bacteria. The results of these studies given for antibacterial screening are mentioned in following Table 1.

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Table 1: Antibacterial activity of the compounds 1-9a.

compound	***E.coli***	***proteus mirabilis***	***Staphylococcus***
DMSO	--	--	--
1a	8	10	11
1b	09	12	08
2a	16	11	17
2b	08	--	12
3a	--	07	-
3b	10	--	14
4a	14	13	16
4b	10	12	09
5a	-	10	--
5b	10	--	13
6a	09	12	11
7a	11	08	11
Clotirmazole	30	25	23

.the minimum inhibitory concentration value mg\ml and corresponding zone of inhibition
Compairsion with Clotrimazole

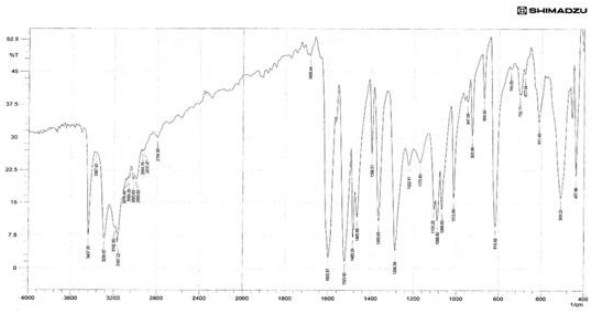

Figure 1: represent FTIR for compound (1a).

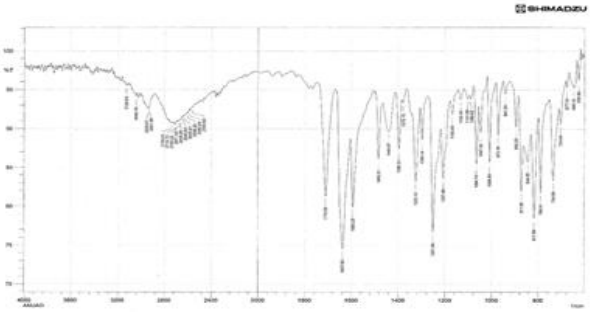

Figure 2: represent FTIR for compound (2a).

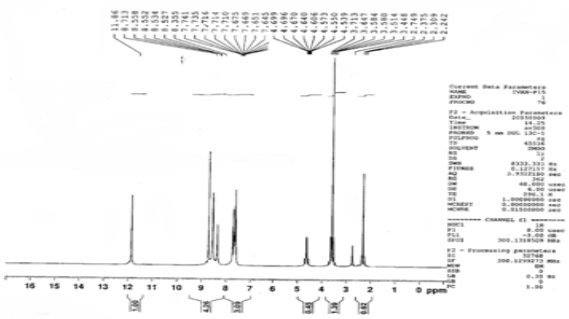

Figure 3: represent H-NMR for compound(3a).

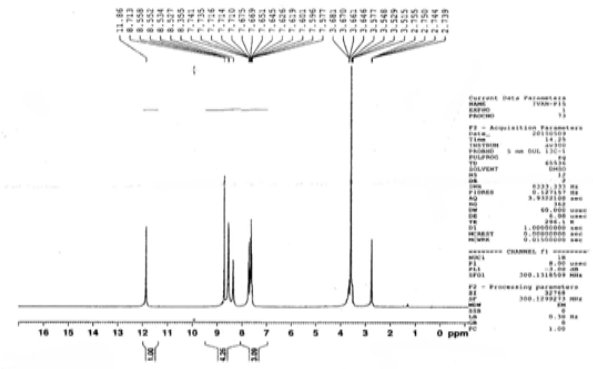

Figure **4**: represent H-NMR for compound(3a).

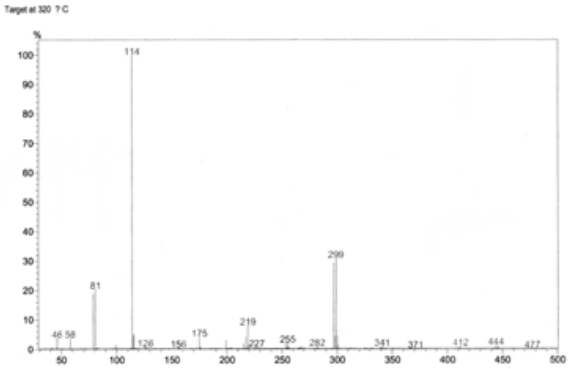

Figure 5: represent mass spectrum of compound (2a).

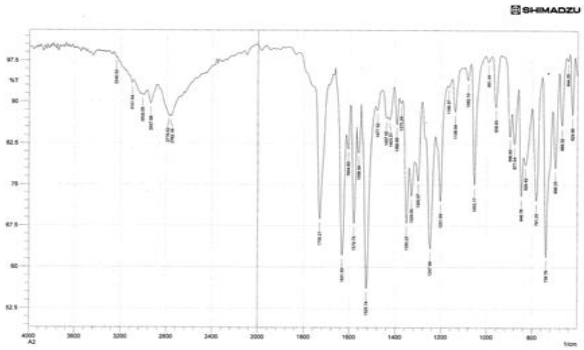

Figure 6: represent FTIR forcompound (7a).

Conclusions

In summary,Schiff bases derivatives were cyclized by chloro ethyl acetate to obtain thio oxoimidazolidine 4- one ,some of the derivatives were evaluated for antibacterial.All the synthesized compounds gave spectral and analytical data .the screeingof antibacterial data revealed that most of the synthesized compounds show good antibacterial activity.

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