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Synthesis and biological evaluation of some imidazoline derivatives

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Synthesis and biological evaluation of some imidazoline derivatives

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Abstract

The group of imidazoline derivatives is an important class of compounds that possess broad biological activity. Many derivatives that have been efficiently synthesized from 4,5-dihydro-1H-imidazole starting material to Synthesis of some new Schiff bases, 2-azetidinone and 4-thiazolidinone derivatives. The structures were characterized by FTIR and ¹H-NMR spectra. All the synthesized compounds were evaluated for their antimicrobial activities against two kinds of bacteria (gram +ve) [*S. aureus*, *S. epidermidis*] and (gram -ve) [*E. coli*, *Klebsiella spp*] as well as fungi [*C. albicans*] using the micro dilution procedure and compared with amoxicillin activity.

Keywords: imidazoline, 2-Azetidinone, 4-thiazolidinone, antimicrobial activity.

1: Introduction

Imidazoline is the most abundant and most important heterogeneous compound. They are extremely important in many medicinal formulations found in a wide range of medications and most vitamins and other natural products. In addition to the biological activity, these compounds are used as anticancer^{1,2}, antifungal^{3,4}, anti-inflammatory⁵, antimicrobial^{6,7}, Antioxidants⁸, Cytotoxic activity⁹ and antiviral¹⁰. Schiff base derivatives have attracted researchers' interest in bioorganic and medicinal chemistry fields to their significance for antibacterial and insecticidal properties¹¹. The 2-Azetidinones (nitrogen-containing four-membered heterocyclic) have the most significant range of research in medicinal chemistry field and were considered as a substantial contribution of science to humanity. Recently several studies have shown that PPAR γ / thiazolidinedione decrease IGF-1 levels and, thus, reduce cancer growth in carcinomas such as the pancreas, colon, liver, and prostate¹². In this study, we aimed to synthesize new heterocyclic derivatives (Schiff base, 2-Azetidinones, 4-thiazolidinone) from 4,5-dihydro-1H-imidazole with predictable biological activities.

2: Experimental Materials and Physical Measurements

All the chemicals that applied in our study are obtainable from [Fluka and Sigma Aldrich companies]; The Melting points (m.p) have been specified by Electro thermal capillary apparatus. Completing of the reaction was monitored by thin layer chromatography (TLC) using Merck silica coated plates and as mobile phase a mixture of hexane and ethyl acetate. Infrared spectra were obtained using ATR technique Shimadzu 8400S, Fourier Transforms Infrared spectroscopy SHIMADZU in the range (500-4000) cm⁻¹, made in Japan, at chemistry department, College of Science, Mustansiriyah University. The ¹H-NMR spectra were obtained on a Bruker, model ultra-shield 300MHz in University, Amman, Jordan. Using tetramethylsilane (TMS) as internal reference and DMSO-d₆, CDCl₃ as solvents.

3: Synthesis of compounds

2-(2-bromophenyl)-4,5-dihydro-1H-imidazole (1)

A mixture of 2-bromobenzaldehyde (0.05mole, 9.25g), ethylenediamine (0.05mole, 3g), (0.05mol, 5.20g NaHSO₃) and (50ml) N,N-dimethyl formamide (DMF) as solvent. The mixture was refluxed for 20 hr., the completion of the reaction was observed by (TLC) using ethylacetate : hexane system (3:7). The mixture was poured in (50 ml) cold water, The result product was filtered, washed with cold water, dried and recrystallized from ethanol to obtain (81%) yield of compound (1), colour: light yellow and melting point (221-223 °C); F-TIR (ATR. Cm⁻¹), ν max.[figure1]: 3142(NH), 3067(C-H arom.), 2850-2928(C-H aliph.), 1668(C=N), 1510-1585(C=C arom.); ¹H-NMR (DMSO-d₆), δ , ppm.[figure2], 7.36-7.73 (m, 4H, Ar-H), 3.77-3.81 (t, 4H, 2CH₂), 6.51 (s, 1H, NH).

Ethyl 2-(2-(2-bromophenyl)-4,5-dihydro-1H-imidazole-1-yl) acetate (2).

A mixture of compound (1) (0.03mol, 6.75g), K₂CO₃ (0.07mole, 10g) ethyl chloro acetate



(0.035 mol, 6g) in (50 mL) dry acetone as solvent. The mixture was refluxed for 6 hrs. The solvent was removed under reduced pressure, the products were collected by filtration and washed with water and recrystallization from 95% ethanol to give Yield: 87% of compound (2) colour: yellow and m.p : 117- 119°C; F-TIR (ATR. cm^{-1}), ν max. [figure2]: (3059, arom. C-H), (2933-2976, C-H aliph.), 1739 (C=O, ester); $^1\text{H-NMR}$ (DMSO- d_6), δ , ppm. [figure3]: 7.13-7.83 (m, 4H, Ar-H), 6.12-6.16 (t, 2H, CH_2), 5.13 (s, 2H, CH_2), 4.51-4.61-1.15 (q, 2H, CH_2), 3.61-3.66 (t, 2H, CH_2), 1.32-1.37 (t, 3H, CH_3).

2-(2-(2-bromophenyl) -4,5dihydro -1H-benzo[d]imidazol-1-yl)acetohydrazide (3).

Compound (2) (0.01 mol, 3.11g) and hydrazine hydrate 80% (16 mL) were mixed and refluxed for 10 hrs. With (20 mL) of absolute ethanol as solvent, the precipitate was formed in the mixture filtered and washed with cold water, dried and purification from ethanol 95%. Yield: 78%; colour: Light yellow m.p: 298-302°C; FT-IR (ATR, cm^{-1}), ν max. [figure4]: 3342, 3294 (NH_2), 3167 (NH), 1689 (C=O, amide), 1600 (C=N); $^1\text{H-NMR}$ (DMSO- d_6) δ , ppm. [figure5]: 9.12 (s, 1H, NH), 7.41-7.93 (m, 4H, Ar-H), 4.45-4.59 (t, 2H, CH_2), 4.51 (s, 2H, CH_2), 4.31 (s, 2H, NH_2), 4.12-4.17 (t, 2H, CH_2).

General procedure for the Schiff bases synthesized (4-6):

Compound (3) (0.0043 mol, 1.28 g), (0.0042 mole) of the various aldehyde and few drops of glacial acetic acid in (50 mL) methanol was refluxed for 8 hrs. The formed precipitate was filtered, dried and recrystallization from ethanol.

2-(2-(2-bromophenyl) - 4, 5 dihydro-1H-imidazole-1-yl)-N'-(4-(chlorobenzylidene) acetohydrazide (4).

Yield: 78%; colour: Off white m.p: 212-214°C; F-TIR (ATR, cm^{-1}), ν max. [figure6]: 3131 (NH), 1673 (C=O amid), 1596 (C=N), $^1\text{H-NMR}$ (DMSO- d_6) δ , ppm: 11.12 (s, 1H, NH), 8.55 (s, 1H, HC=N), 7.41-7.84 (m, 8H, Ar-H), 5.82-5.86 (t, 2H, CH_2), 4.03 (s, 2H, CH_2), 3.72-3.77 (t, 2H, CH_2).

2-(2-(2-bromophenyl) - 4, 5 dihydro-1H-imidazole-1-yl)-N'-(4-(pyridine-2-ylmethylene) acetohydrazide (5).

Yield: 73%; colour: light yellow, m.p: 189-191°C; F-TIR (ATR, cm^{-1}), ν max. [figure7]: 3145 (NH), 1686 (C=O), 1616 (C=N); $^1\text{H-NMR}$ (DMSO- d_6) δ , ppm: 10.62 (s, 1H, NH), 7.41-7.92 (m, 8H, Ar-H), 7.49 (s, 1H, HC=N), 5.82-5.86 (t, 2H, CH_2), 4.03 (s, 2H, CH_2), 3.72-3.77 (t, 2H, CH_2).

2-(2-(2-bromophenyl) - 4, 5 dihydro-1H-imidazole-1-yl)-N'-(4-(thiophen-2-ylmethylene) acetohydrazide (6).

Yield: 69%; colour: Light yellow m.p: 133-135°C; F-TIR (ATR, cm^{-1}), ν max. [figure8]: 3133 (NH), 1692 (C=O), 1622 (C=N); $^1\text{H-NMR}$ (DMSO- d_6) δ , ppm: 10.62 (s, 1H, NH), 7.49 (s, 1H, HC=N), 7.41-7.75 (m, 7H, Ar-H), 5.82-5.86 (t, 2H, CH_2), 4.03 (s, 2H, CH_2), 3.72-3.77 (t, 2H, CH_2).

General procedure for the synthesis of 2-azetidinones (7, 8):

Compounds (4, 5) (0.001 mol), triethylamine (0.025 mol) in dry 1, 4-dioxane (10 mL) was stirred in ice water bath (0-5°C). chloroacetyl chloride (0.01 mol, 1.17 mL) was added drop wise to mixture, then stirred for 3 hrs. The mixture was refluxed for 6 hrs. Mixture was filtrated and the solvent was removed under reduced pressure, the product was collected by filtration and washed with water, dried and recrystallization from chloroform.

2-(2-(2-bromophenyl) - 4, 5 dihydro-1H-imidazole-1-yl) - N-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl) acetamide (7).

Yield: 62%; colour black m.p: 93-95°C; F-TIR (ATR, cm^{-1}), ν max. [figure9]: 3172 (NH), 1720 (C=O, B-Lactam), 1627 (C=O, amide), $^1\text{H-NMR}$ (DMSO- d_6) δ , ppm: 8.72 (s, 1H, NH), 7.71-7.51 (m, 8H, Ar-H), 5.73-5.72 (d, 1H, CH-Cl), 5.45-5.42 (d, 1H, N-CH).

2-(2-(2-bromophenyl) - 4, 5 dihydro-1H-imidazole-1-yl) - N-(3-chloro-2-oxo-4-(pyridine-2-yl) azetidin-1-yl) acetamide (8).

Yield: 58%; colour: black m.p: 102-105°C; F-TIR (ATR, cm^{-1}), ν max. [figure10]: 3168 (NH), 1724 (C=O, B-Lactam), 1697 (C=O amide); $^1\text{H-NMR}$ (DMSO- d_6) δ , ppm. [figure11]: 8.72 (s, 1H, NH), 8.30-7.51 (m, 8H, Ar-H), 5.73-5.72 (d, 1H, CH-Cl), 5.49-5.46 (d, 1H, N-CH).

General procedure for the synthesis of 4-thiazolidinone (9-11):

A mixture of Compounds (4-6) (0.001mol) was solved in 25mL chloroform with ZnCl₂ (0.01g) and (0.005 mol, 0.35 mL) of thioglycolic acid was added to the mixture, the mixture was refluxed for 10hrs. The reaction completion was monitored by thin layer chromatography (TLC) using ethylacetate: hexane system (3:7). The solvent was removed under reduced pressure, residue treated by 10% NaHCO₃ solution to remove excess of mercaptoacetic acid, washed with water, dried and recrystallization from suitable solvent.

2-(2-(2-bromophenyl) - 4, 5dihydro-1H-imidazol-1-yl)-N-(4-(4-chlorophenyl)-2-oxothiazolidin-3-yl) acetamide (9).

Yield: 53%; colour: White, M. p: 155-157°C; F-TIR(ATR, cm⁻¹), ν max.[figure12]: 3122 (NH), 1733(C=O thiazolidinone), 1696 (C=O of amide); ¹H-NMR (DMSO-d₆) δ , ppm.[figure13]: 11.00 (s, 1H, NH), 7.89-7.34 (m, 8H, Ar-H), 6.02 (s, 1H, N-CH), 4.25 (s, 2H, CH₂), 4.10-3.90 (s, 2H, S-CH₂-C=O thiazolidin, geminal proton).

2-(2-(2-bromophenyl)- 4,5dihydro-1H-imidazol-1-yl)-N-(2-oxo-4-(pyridine-2-yl) thiazolidin-3-yl)acetamide (10)

Yield: 59%; colour: Off white, m.p: 125-127°C; F-TIR(ATR, cm⁻¹), ν max.[figure14]: 3136 (NH), 1723 (C=O), 1682 (C=O of amide); ¹H-NMR (300 MHz, DMSO- d₆, δ , ppm).[figure15]: 11.70 (s, 1H, NH), 8.09-7.35 (m, 8 H, Ar-H), 6.08 (s, 1H, N-CH), 4.25 (s, 2H, CH₂), 3.92-3.90 (s 2H, S-CH₂-C=O thiazolidin, geminal proton).

2-(2-(2-bromophenyl)- 4,5dihydro-1H-imidazol-1-yl)-N-(2-oxo-4-(thiophen-2-yl)- thiazolidin-3-yl)acetamide (11).

Yield: 57%; colour: Light yellow, m. p: 112-114°C; F-TIR (ATR, cm⁻¹), ν max.[figure15]: 3152(NH), 1736 (C=O), 1682 (C=O of amide); ¹H-NMR (300 MHz, DMSO- d₆, δ , ppm).[figure16]: 11.12 (s, 1H, NH), 7.85-7.34 (m, 7 H, Ar-H), 6.05 (s, 1H, N-CH), 4.25 (s, 2H, CH₂), 3.94, 3.92 (s, 2H, S-CH₂-C=O thiazolidin, geminal proton).

4: Biological activities

In vitro antimicrobial testing effects of imidazoline derivatives were estimated against four bacterial strains namely (*S. aureus*, *S. epidermidis*, *E. coli*, *Klebsiella spp* and fungi *C. albicans*). The antimicrobial activity was determined using the agar well diffusion method. Dimethyl sulfoxide worked as a control and the test was outright at 100mg/mL concentration using (DMSO) as solvent and ampicillin was taken as the standard compound. The fungi and 4 bacteria was sub cultured in agar. The plates were incubated at 37°C and checking after 24 hrs. For bacteria and 48 hrs. For fungi (Table1).

5: Results and Discussion

The structures formal of imidazoline derivatives were synthesized following outlined in [scheme 1]

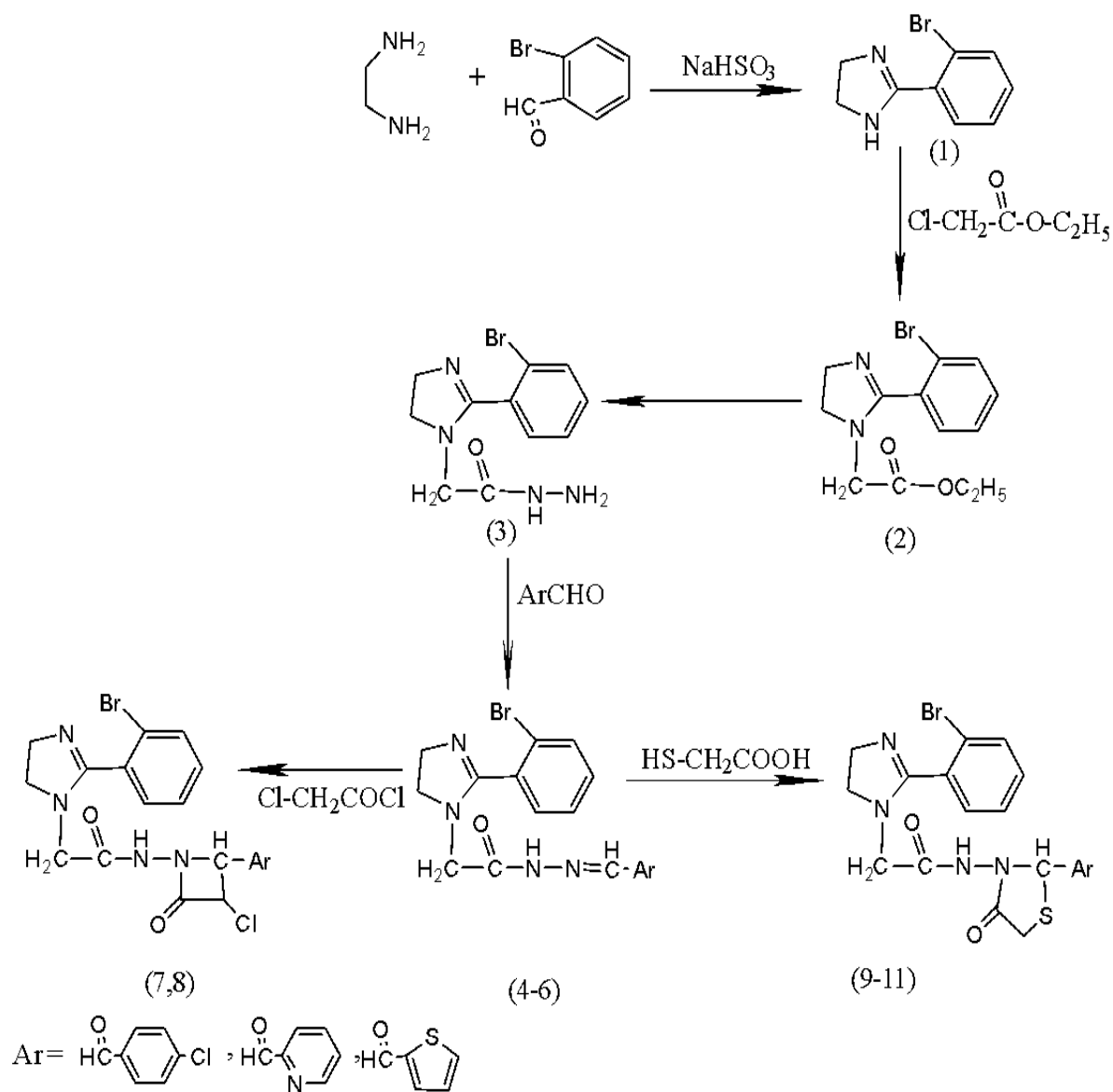
All the structures of compounds have been characterized on the base of their (TLC) thin layer chromatography, and spectral data. 2-(2-bromophenyl)-4,5dihydro-1H-imidazole (1) was prepared via the condensation of o-bromobenzaldehyde with ethylenediamine in DMF solvent and NaHSO₃. Compound (1) is identified by physical properties, FT-IR and ¹H-NMR spectroscopy. FT-IR spectrum of compound (1) show clear absorption bands at ν (3142 (NH) cm⁻¹, and ν (1668 (C=N) cm⁻¹ respectively. ¹H-NMR spectrum the same compound in DMSO-d₆ as solvent was the following data: 7.36-7.73 (m, 4H, Ar-H), 3.77-3.81 (t, 4H, 2CH₂), 6.51 (s, 1H, NH).

Compound (2) was synthesized by condensation of compound (1) with ethyl chloroacetate in dry acetone as solvent. Compound (2) is identified by physical properties, FT-IR and ¹H-NMR spectroscopy. The FT-IR spectrum of compound (2) showed disappearance of absorption bands at ν (3142 cm⁻¹ which belonging to (-NH) group and presence of new absorption bands at ν (1739) cm⁻¹ due to carbonyl ester (C=O) group. ¹H-NMR spectrum of this compound in DMSO-d₆ as solvent was the following data: 7.13-7.83 (m, 4H, Ar-H), 6.12-6.16 (t, 2H, CH₂), 5.13 (s, 2H, CH₂), 4.51-4.61-1.15 (q, 2H, CH₂), 3.61-3.66 (t, 2H, CH₂), 1.32-1.37 (t, 3H, CH₃).

The reaction between ester compound and hydrazine hydrate (80%) afforded the acid hydrazide derivatives (3) in typical yield. Compound (3) is identified by physical properties, FT-IR and ^1H -NMR spectroscopy. The spectrum showed the appearance of the NH_2 stretching absorption near $3325, 3232\text{ cm}^{-1}$ and C=O amide at 1660 cm^{-1} with disappearance the carbonyl of ester Figure 2. Spectrum of ^1H -NMR for compound (3) showed singlet signals 4.31 ppm due to (NH_2) and 4.51 ppm was attributed protons of CH_2 and 9.12 ppm belonged to NH , aromatic protons were appeared at $7.93\text{--}7.41\text{ ppm}$ figure 3.

Schiff base (4-6) was obtained by the reaction of compound (3) with various benzaldehyde in methanol. The formation of Schiff base has been indicated by the presence in their FT-IR spectra of imine (N=CH) stretching band at $1627\text{--}1596\text{ cm}^{-1}$ combined with the disappearance of (NH_2) stretching band of amine of compounds (3) and carbonyl of benzaldehyde Figure (4). Treatment of compounds (4,5) with Et_3N and chloroacetyl chloride ($\text{C}_2\text{H}_2\text{OCl}_2$) obtained azetidiny derivatives (7,8) The F-TIR spectrum indicated the appearance of $1768\text{--}1724\text{ cm}^{-1}$ band due to (C=O) β -lactam with disappearance of imine (N=CH) in the region $1627\text{--}1596\text{ cm}^{-1}$ figure (6). In the ^1H -NMR doublet signals at $5.49\text{--}5.46\text{ ppm}$ integrating for protons ring of azetidiny, protons of aromatic resonate at $8.30\text{--}7.51\text{ ppm}$ (Figure 7).

Cyclization of Schiff bases (4-6) with mercaptoacetic acid in chloroforme afforded thiazolidenone derivatives (9-11). Thiazolidenone compounds (9-11) are identified by physical properties, FT-IR and ^1H -NMR spectroscopy, FT-IR spectra of thiazolidenone compounds showed the appearance carbonyl stretching band at $1736\text{--}1723\text{ cm}^{-1}$ due to thiazolidinone ring was the characteristic evidence for success of cyclization step. ^1H -NMR spectrum of compound (9) in DMSO-d_6 as solvent was the following data: 11.00 (s, 1H, NH) , $7.89\text{--}7.34\text{ (m, 8H, Ar-H)}$, $6.02\text{ (s, 1H, N-CH)}$, $4.25\text{ (s, 2H, CH}_2\text{)}$, $4.10\text{--}3.90\text{ (s, 2H, S-CH}_2\text{ C=O thiazolidin, geminal proton)}$.



schem 1

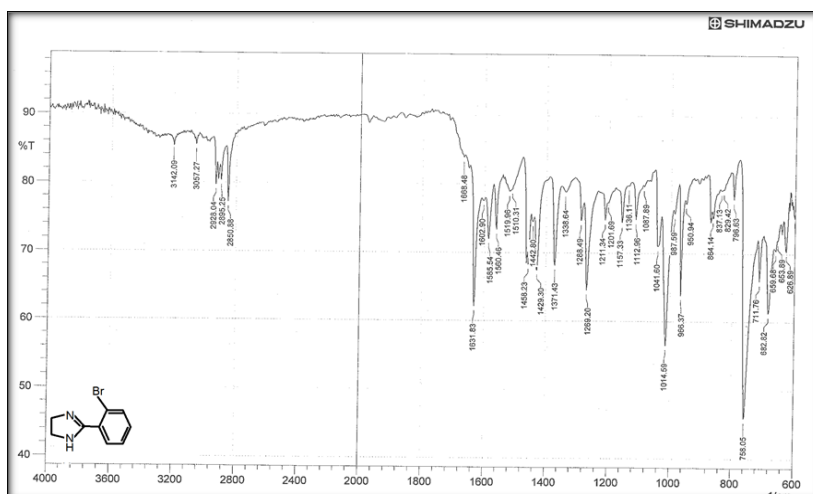


Figure 1. The FT-IR spectrum of compound [1]

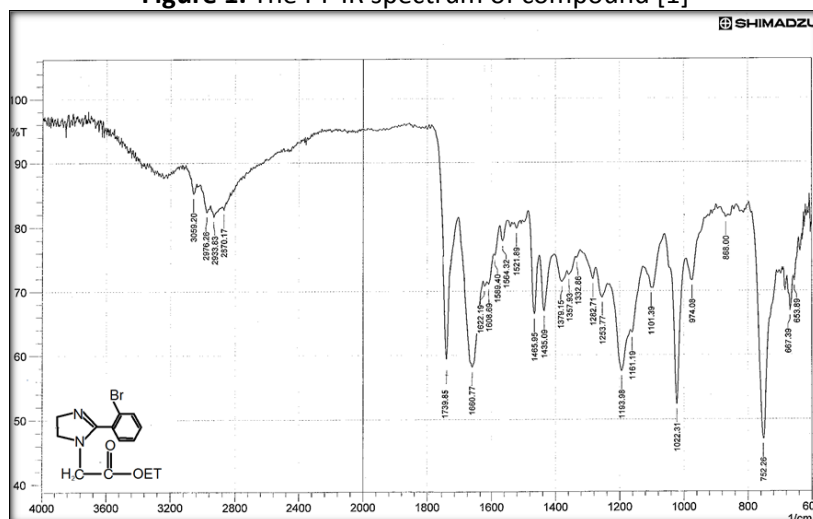
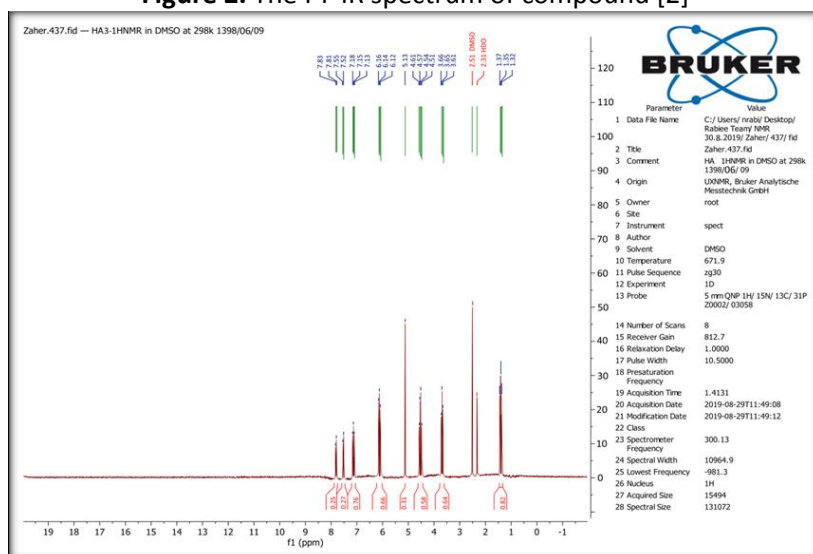


Figure 2. The FT-IR spectrum of compound [2]

Figure 3. The ^1H -NMR spectrum of compound [2]

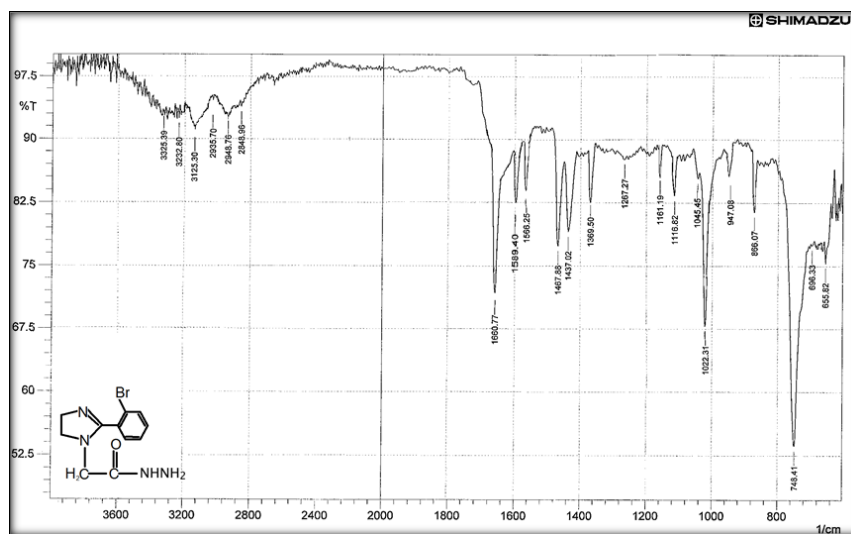


Figure 4. The FT-IR spectrum of compound [3]

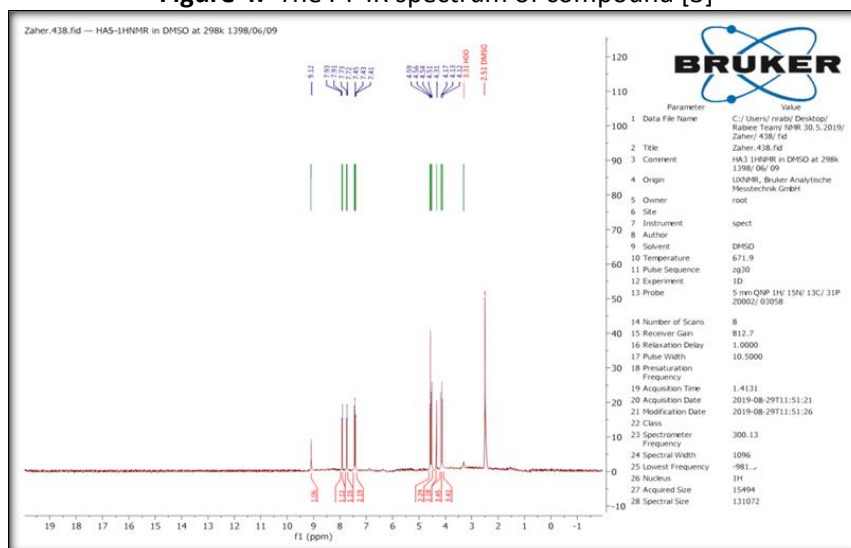
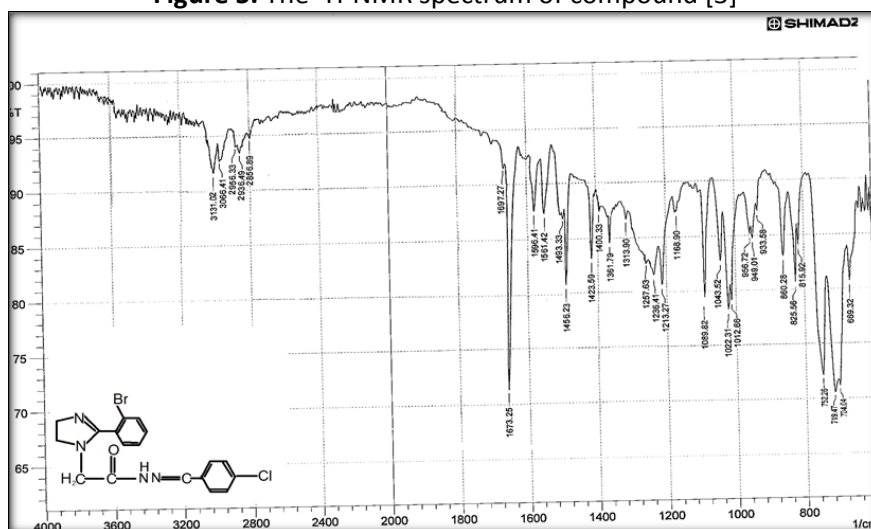
Figure 5. The ¹H-NMR spectrum of compound [3]

Figure 6. The FT-IR spectrum of compound [4]

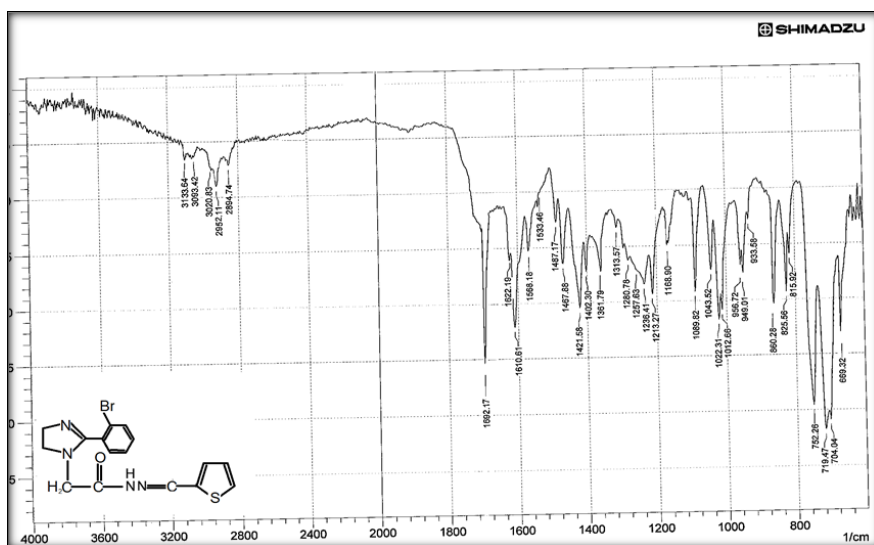


Figure 7. The FT-IR spectrum of compound [5]

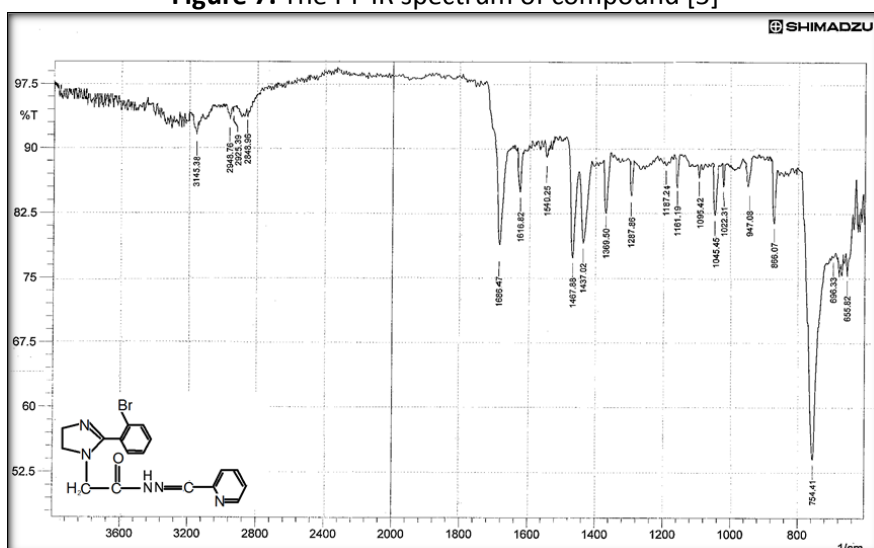


Figure 8. The FT-IR spectrum of compound [6]

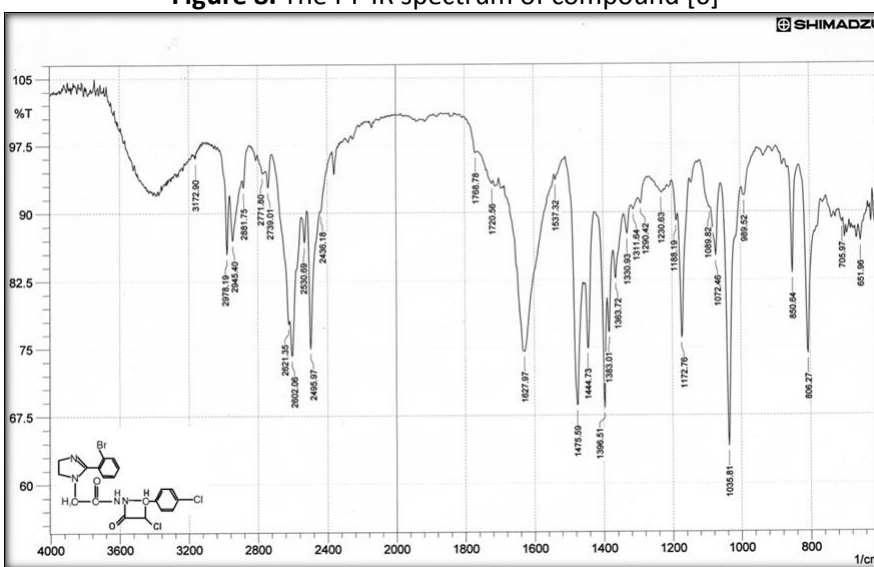


Figure 9. The FT-IR spectrum of compound [7]

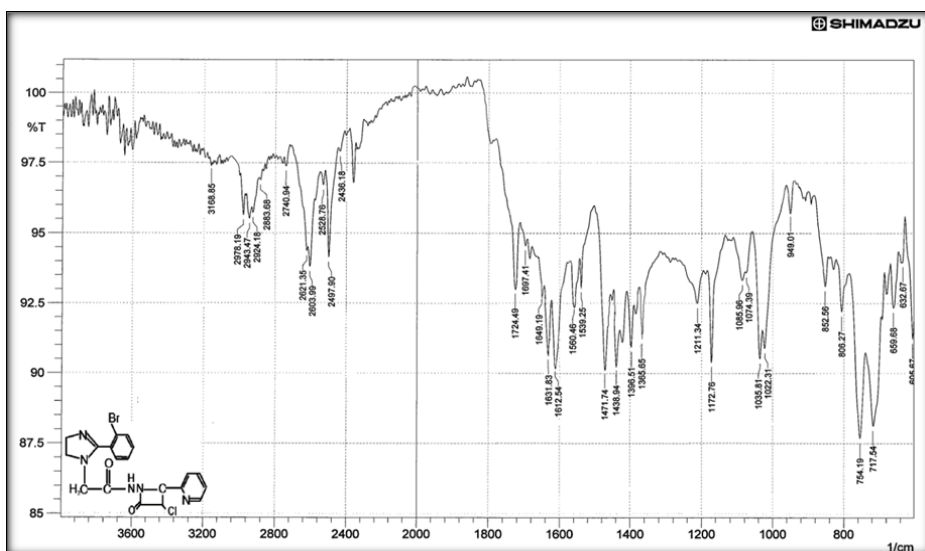


Figure 10. The FTIR spectrum of compound [8]

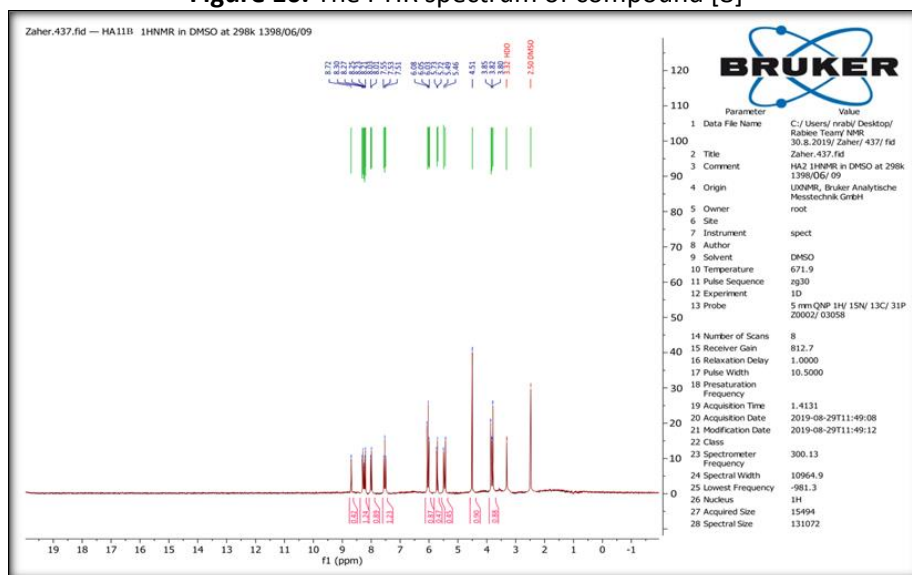
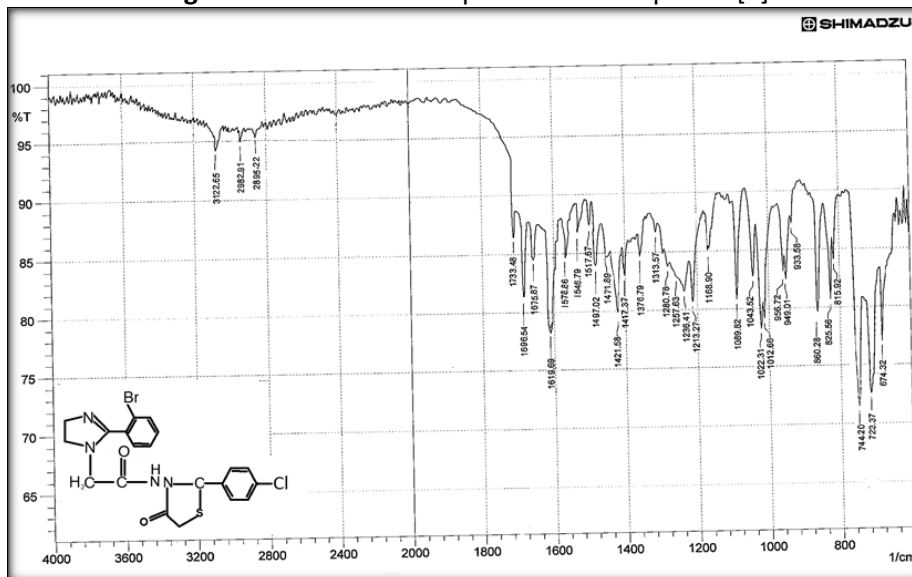
Figure 11. The ^1H -NMR spectrum of compound [8]

Figure 12. The FT-IR spectrum of compound [9]

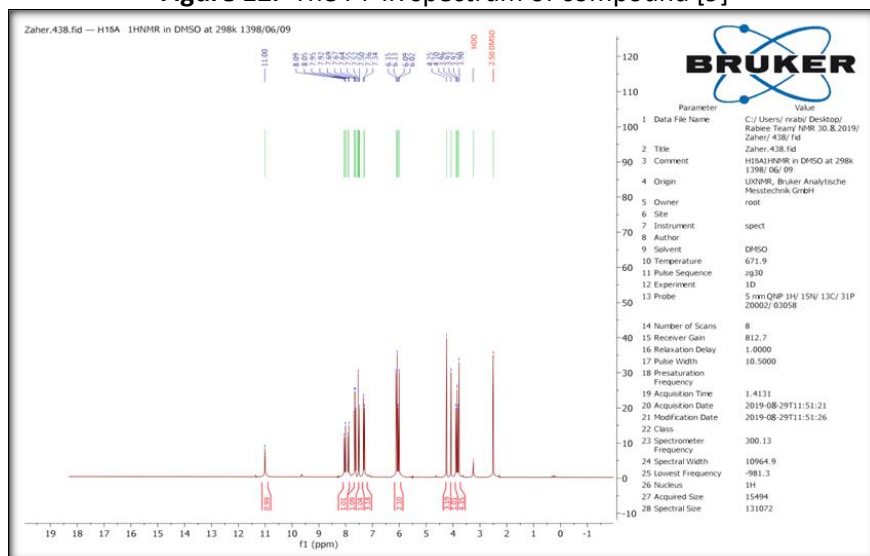


Figure 13. The ^1H -NMR spectrum of compound [9]

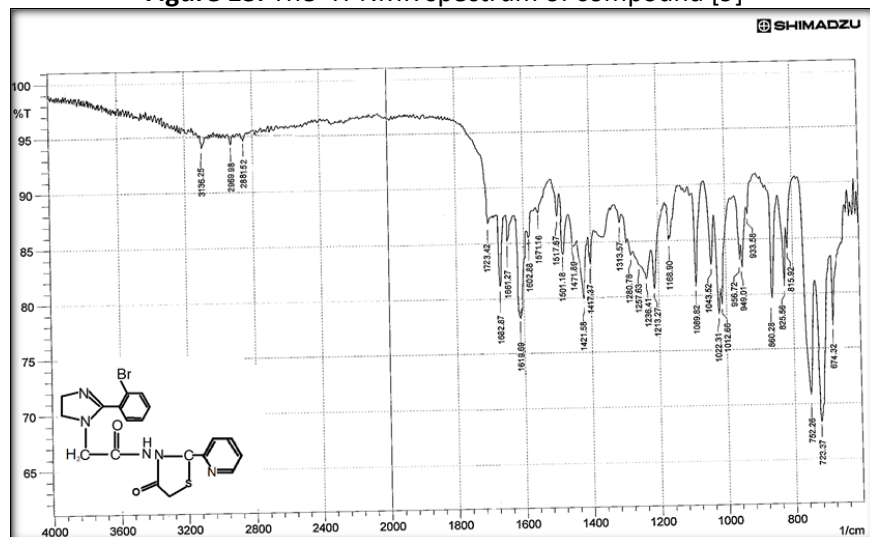


Figure 14. The FT-IR spectrum of compound [10]

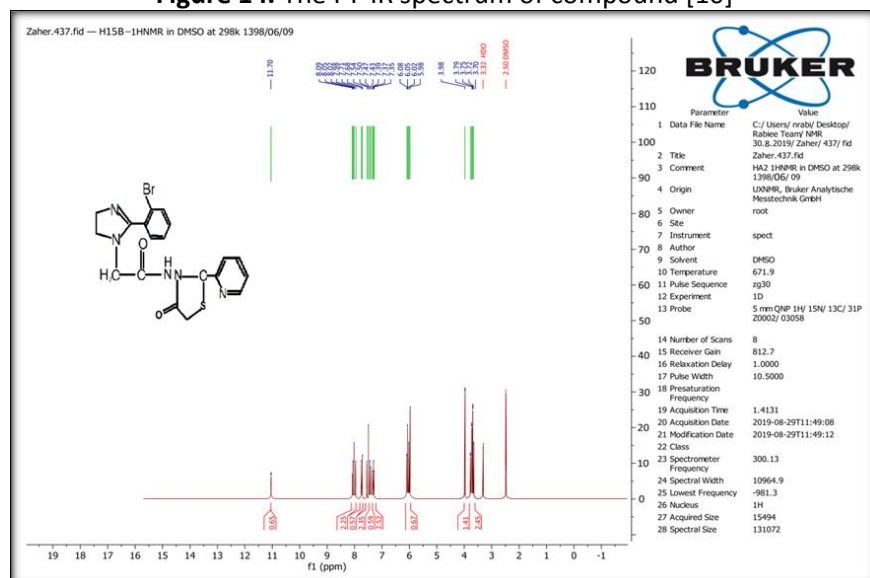
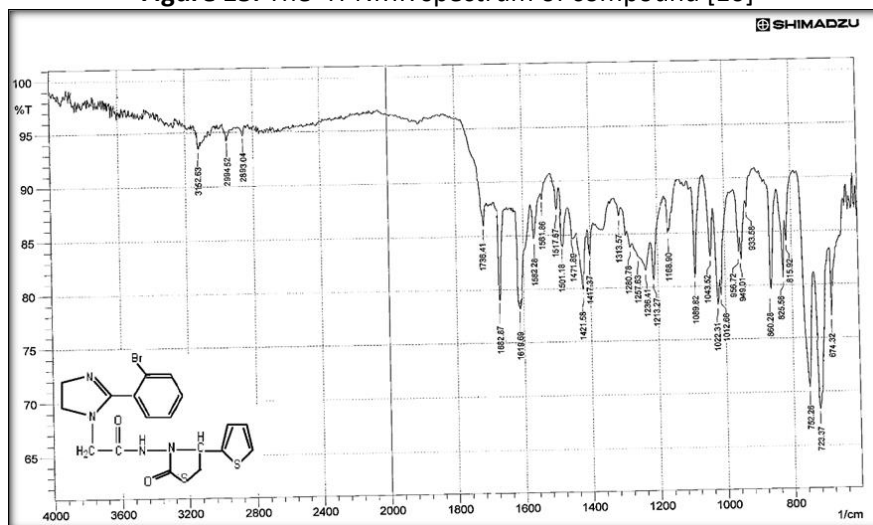


Figure 15. The ^1H -NMR spectrum of compound [10]**Figure 16.** The FT-IR spectrum of compound [11]**Biological activity**

A comparative zone of inhibition (mm) for Schiff bases, 2-azetidinones, 4-thiazolidinone and standard drugs are reported in Table (1). The test results presented in Table (1) from which it is clear that showed Schiff bases have moderate antibacterial activity in comparison with standard drugs. compounds showed highly active against *E. coli* as compared to Schiff bases.

Table1. Antimicrobial evaluation of compounds.

Hetero- cyclic deriva- tives derivatives	inhibition zone (mm) at 100 mg/mL				
	Gram positive		Gram negative		Fungi
	<i>S. aureus</i> <i>reus</i>	<i>S. epidermi dis</i>	<i>E. coli</i>	<i>Klebsiella spp</i>	<i>C. albicans</i>
1	6	-	-	8	9
2	8	-	8	9	-
3	17	17	13	10	17
4	12	-	11	10	8
5	10	13	10	8	14
6	14	13	12	9	7
7	10	11	12	12	11
8	8	14	10	13	11
9	14	13	13	13	13
10	16	15	10	6	16
11	15	8	12	13	14
Amoxicillin	10	17	16	17	21

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