RESEARCH ARTICLE

Synthesis, Characterization, and Study the Biological Activity for Shiff Base and β-lactam Derivatives from 2-amino-4-hydroxy-6-methyl pyrimidine

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ABSTRACT

This study includes synthesis and characterization of some shiff base and β-lactam derivatives) by three steps. The first reaction is done on 2-amino-4-hydroxy-6- methyl pyrimidine with 4-amino acetophenone in acid medume to get shiff base derivative 2-(4-amino-benzylidene amino)-6-methylpyrimidin-4-ol) (1). Further to that, (1) reacts with (3, 4-dimethoxybenzal dehyde, 4-methyl benzaldehyde, 4- di methyl ameno benzaldehyde, 4-bromo benzaldehyde, 4-hydroxy benzaldehyde, 4-Nitro benzaldehyde) to get shiff base derivatives (2-7).

In the last step (2-7), derivatives react with Chloro acetyl chloride to get β-lactam derivatives (8-13). All these compounds are characterization by fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (^{1}HNMR), carbon-13 nuclear magnetic resonance (^{13}CNMR). After that, study was done on the biological activity for all these derivatives with two kinds of bacteria.

Keywords: β-lactam, Bacteria, Biological activity, Schiff base.

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INTRODUCTION

Shiff bases are Compounds with an azomethine group (-CH=N-) can be prepared from react a carbonyl compound with a primary amine[1,2] Schiff bases have several applications. Lt is used as an intermediate compound to prepare many heterocyclic derivatives such as β-lactam.[3] They represent an important class of membered cyclic amides.[4] The first synthesis of a β-lactam was accomplished in 1907 when Staudinger discovered that ketenes and imines could undergo [2+2] cycloadditions to yield the β-lactam ring.[5] In 1940s, β-lactam antibiotics have been used to cure bacterial infection, several of the lactam derivatives are also a chemical reaction such as cephalosporins.[6] Also noted several other biological activities like anti-cancer activity, and the activity of blood sugar, and antitubercular activity and anti-leishmaniasis activity in a compound containing β-lactam ring[7] Hence, penicillins, cephalosporins, cephalexin, Ampicillin[8] β-lactamases are family of bacterial enzymes that cleave penicillins and cephalosporins with high catalytic efficiency and render these bacteria resistant to β-lactam antibiotics.[9]

MATERIALS AND METHODS

2-Amino-4-Hydroxy-6-Methyl Pyrimidine, 4-amino acetophenone, glacial Acetic acid, ethanol, 3, 4-DiMethoxy Benzaldehyde, 4-Methyl Benzeldehyde, 4- di Methyl amino benzaldehyde, 4-Bromo benzaldehyde, 4-Hydroxy benzaldehyde, 4-nitro benzaldehyde, Chloro acetyl Chloride, Tri ethyl amine, 1-4 Dioxan were used.

The Materials and all solvents used from (BDR, FLHC, Aldrich. GCC, CDH) (FT-IR) were recorded on the FIMIR SHIMADZU FTIR-8400S. ^{13}C-NMR and ^{1}HNMR were recorded on the Fourier Transformer spectrometer (500MHZ) with measurements (DMSO-ds) in the Chemistry Department, University of Tehran in Iran

Synthesis Schiff bases (1)E-2-((1-4-amino phenyl) ethylidene amino)-6-methyl pyrimidin-4-ol

The number of equal moles is mixed of the amino compound of (2-amino-4-hydroxyl-6- methyl pyrimidine) (1 g, 0.007 mol) and (4-amino acetophenone (1.08 g, 0.007 mol)) was added with ethanol (25 mL). Mix was heated with refluxed and added drop from glacial acetic acid and for (4 hours) at (78°C) the Mixture is then cooled and left for 24 hours. Then we precipitated, filtered and then re-crystallized with ethanol. Then we and then calculates the weight of the output and prove the physical properties.[10]

Synthesis Derivatives Schiff bases (2, 3, 4, 5, 6, 7)

The number of equal moles is mixed from a compound:

- (1 g, 0.0041 mol) with benzaldehyde derivatives (3, 4-Di Methoxy benzaldehyde (0.68 g, 0.0041 mol)

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- (4-methyl benzaldehyde (0.48 mL, 0.49 g)
- (4- Dimethyl amino benzaldehyde (0.61 g, 0.0041 mol)
- (4-Bromo benzaldehyde (0.76 g, 0.0041 mol)
- (4-Hydroxybenzaldehyde (0.50 g, 0.0041 mol))
- (4-nitro benzaldehyde (0.62 g, 0.0041 mol))
- were added with ethanol (25 mL)

and heated Mix with refluxed and added drop of glacial acetic acid for (5–6 hours) at (78°C). The Mixture is then cooled and left for 24 hours, then we precipitated the filtered and re-crystallized with ethanol. We calculated the weight of the output and proved the physical properties.[11]

Synthesis Derivatives β–lactama (8, 9, 10, 11, 12, 13)

The mixed of compounds (2, 3, 4, 5, 6, 7) (0.01 mol) with (0.006 mol) from triethylamine (0.21 mL) of (25 mL 1–4 Dioxan) added to Mixed cooled with stirring (0.0024 mol) in the from of Solution drops Chloro acetyl Chloride (0.05 mL) at (10°C) for 9 hours. precipitates the filtered and then re-crystallized with ethanol and then calculates the weight of the output and proves the physical properties.[12]

Preparation of Microbiology Culture Media

(38 g) of nutrient agar is dissolved in (1 L)of distillation water, then put in an autoclave for 15 minutes at (121°C) for sterilization pouring the media after becoming at (37°C) in Petri dishes, made ready for streaking by bacteria.It was getting (*Escherichia coli*) and (*Staphylococcus aurous*) isolated bacteria from hospital. It was cultured and plates were incubated at (37°C) for 24 hours for both bacterias. DMSO solvent was used to prepare solutions of various compounds in (5 mL) DMSO. The inhibition zones were examined for all compounds under test.[13]

RESULTS AND DISCUSSION

Compound 1: (E)- 2-((1-(4-amino phenyl) ethylidene) amino)-6- methyl pyrimidin -4- ol.

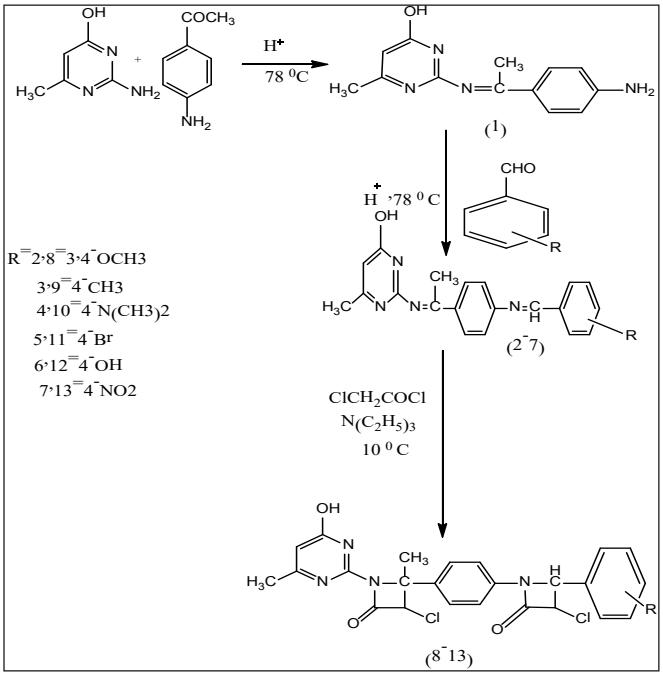
The FT-IR data of compound (1) showed band at (3332) cm^{-1} for (OH), (3070) cm^{-1} for (Ar-H), (1589) cm^{-1} (C=N) inside Pyrimidin ring, (1658) cm^{-1} for (C=N)Shiff base, (2947) cm^{-1} for (C-H) for (CH_3), (3224) cm^{-1} for (N-H) for (NH_2) and (1558) cm^{-1} due to aromatic (C=C), as in Figure 1.

Compound 2: 2-(((1E) -1-(4-((3, 4-di methoxy benzylidene) amino) phenyl) ethylidene) amino) -6- methyl pyrimidin-4-ol

The FT-IR data of comp. (2) Showed band at 3340 cm^{-1} for (OH), 3077 Cm^{-1} for (Ar-H), 1589 cm^{-1} (C=N) inside Pyrimidin ring, 1674 cm^{-1} for (C=N) Shiff base, 2939 cm^{-1} for (C-H) for (CH3), 1558 cm^{-1} due to aromatic (C=C), 1272 cm^{-1} for (C-O). The ^{1}H NMR (DMSO) spectrum data of compound (2) show δ: 9.8 (S, 1H, OH), 1.9 (S, 3H, N=C-CH_3), 2 (S, 3H, CH_3 pyrimidine), 3.7-3.8 (S, 6H, OCH3), 6.5-7.9 (M, 8H, Ar-H), 8.5 (S, 1H, CH). The C^{13}-NMR (DMSO) spectrum data of compound (2) show δ: 21(C_{20}), 25(C_{19}), 55(C_{21}, C_{22}) 172 (C_2), 163(C_5), 161(C_{12}), 155(C_1), 154(C_9), 153(C_{16}), 152(C_{17}), 100-149 (C- arom) as presented in Figures 2, 3, and 4.

Compound (3): 6-Methyl -2- (((1E) -1- (4-((4-methyl benzylidene) amino) phenyl) ethylidene)amino)pyrimidin -4-ol

The FT-IR data of compound (3) showed band at 3332 cm^{-1} for (OH), 3070 cm^{-1} for (Ar-H), 1589 cm^{-1} (C=N) inside pyrimidin ring, 1658 cm^{-1} for (C=N) Shiff base, 2947cm^{-1} for (C-H) for (CH3) str, 1550 cm^{-1} due to aromatic (C=C), 1357 cm^{-1} for (C-H) Ben. The ^{1}H-NMR (DMSO) spectrum data of compound (3) show δ: 8.6 (S, 1H, OH), 2 (S, 3H, CH3phenyl ring), 2.2



Scheme 1: Synthesis of Some heterocyclic compounds derivatives.

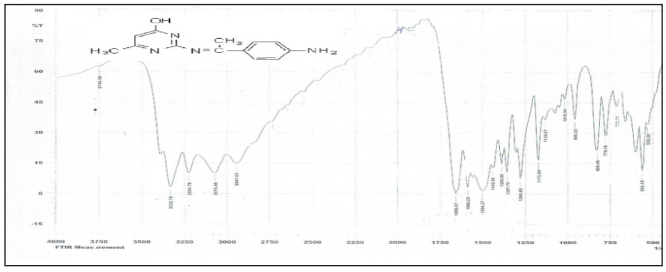


Figure 1: FT-IR Spectra of compound (1)

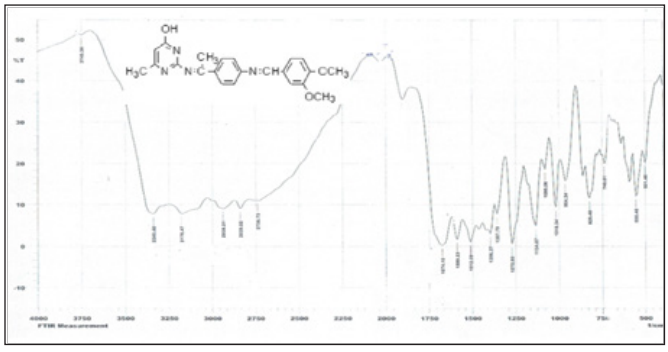


Figure 2: FT-IR Spectra of compound (2)

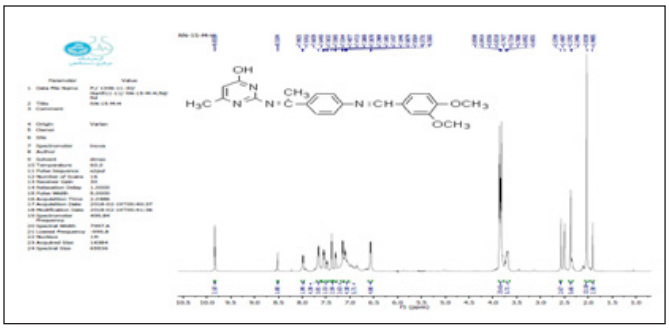


Figure 3: ^{1}H NMR spectrum of compound (2)

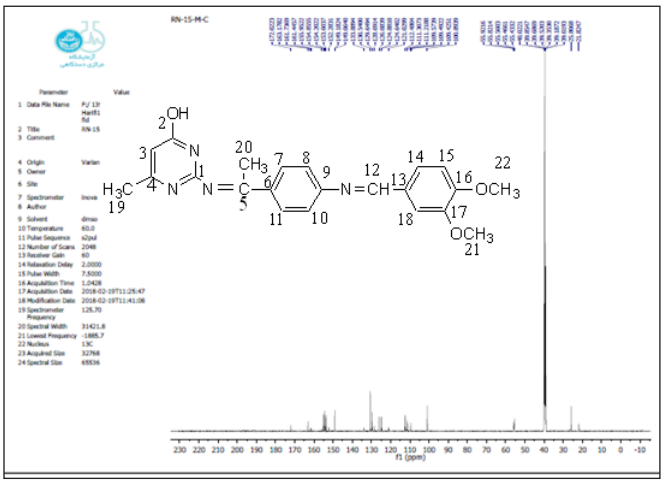


Figure 4: C^{13}- NMR spectrum of compound (2)

(S, 3H, N=C-CH_3), 2.3 (S, 3H, CH_3 pyrimidine), 7.7(S, 1H, N=CH), 6.5-7.6 (M, 9H, Ar-H). The C^{13}-NMR (DMSO) spectrum data of compound (3) Show δ: 20(C_{19}), 21(C_{18}), 25(C_{20}), 154(C_2), 153(C_5), 152(C_{12}), 145(C_1), 138(C_{16}.C_{17}), 101.130 (C_{Arom}).

Compound (4): 2-(((1E)-1-((4-(di methyl amino) benzylidene) amino) phenyl) ethylidene) amino) -6- methyl pyrimidin.

The FT-IR data of comp. (4) showed band at 3332 cm^{-1} for (OH), 3070 cm^{-1} for (Ar-H), 1542 cm^{-1} (C=N) inside pyrimidin ring, 1666 cm^{-1} for (C=N) shiff base, 2916 cm^{-1} for (C-H) for (CH_3), 1540 cm^{-1} due to aromatic (C=C). The ^{1}H-NMR (DMSO) spectrum data of compound (4) show δ: 9.6 (S, 1H, OH), 1.9(S, 3H, CH_3), 2.0(S, 3H, CH_3 in pyrimidin ring), 3, 0 (S, 6H, N-$(CH_3)_2$), 8.4 (S, 1H, CH), 6.5-7.9 (m, 9H, Ar-H). The C^{13}-NMR (DMSO) spectrum data of compound (4) show δ: 189.8(C_2), 189.7(C_4), 172(C_1), 154(C_9), 153(C_{16}), 131(C_{12}), 21(C_{21}), 25(C_{22}), 40(C_{19}, C_{20}).

Compound (5): 2- (((1E) -1-(4-((4-bromo benzylidene) amino) phenyl) ethylidene) amino) -6- methyl pyrimidin -4-ol

The FT-IR data of comp. (5) showed band at 3332 cm^{-1} for (OH), 3070 cm^{-1} for (Ar-H), 1589 cm^{-1} (C=N) inside pyrimidin ring, 1666 cm^{-1} for(C=N)Shiff base, 2939 cm^{-1} for (C-H) for (CH3), 1496 cm^{-1} due to aromatic (C=C), 462 cm^{-1} for(C-Br). The ^{1}H NMR (DMSO) spectrum data of compound (5) show δ: 2.0(S, 3H, CH_3), 2.3(S, 3H, CH_3 pyrimidine ring), 9.9(S, 1H, OH), 8.6(S, 1H, N=CH), 6.5-7.9(m, 9H, Ar-H). The C^{13}-NMR(DMSO) spectrum data of compound (5) show δ:21.9(C_{20}), 25(C_{19}), 163(C_2), 161.7(C_5), 161.3(C_{12}), 155(C_1), 153-163(C_9), 100-135(C –Arom).

Compound (6): 2-(((1E)-1- (4-((4-hydroxy benzylidene) amino) phenyl) ethylidene) amino) -6- methyl pyrimidin -4-ol.

The FT-IR data of comp. (6) showed band at 3332 cm^{-1} for (OH), 3070 cm^{-1} for (Ar-H), 1573 cm^{-1} (C=N) inside pyrimidin ring, 1666 cm^{-1} for (C=N) Shiff base, 2931 cm^{-1} for (C-H) for (CH_3), 1520 cm^{-1} due to aromatic (C=C). The ^{1}H-NMR (DMSO) spectrum data of compound (6) show δ: 9.77 (S, 1H, OH)in pyrimidin. 5.4 (S, 1H, OH)phenol. 1.9 (S, 3H, CH_3). 2.0(S, 3H, CH_3). 8.4(S, 1H, CH). 6.5-7.9 (m, 9H, Ar-H). The ^{13}C-NMR (DMSO) spectrum data of compound (6) δ: 22(C_{19}), 25(C_{20}), 26(C_{12}), 93 (C_5), 163.8(C_2), 163.4 (C_{16}), 162(C_1), 161 (C_9), 100-156 (C arom).

Compound (7): 6-methyl -2- (((1E) -1- (4-((4- nitro benzylidene) amino)phenyl)ethylidene amino) pyrimidin -4-ol.

The FT-IR data of comp. (7) showed band at 3332 cm^{-1} for (OH), 3078 cm^{-1} for (Ar-H), 1596 cm^{-1} (C=N) inside pyrimidin ring, 1658 cm^{-1} for (C=N) shiff base, 2939 cm^{-1} for (C-H) for (CH_3), 1542 cm^{-1} due to aromatic (C=C), (1500 – 1350) cm^{-1} for (NO2). The ^{1}H NMR (DMSO) spectrum data of compound (7) show δ: 9.5 (S, 1H, OH), 1.1 (S, 3H, N=C-CH3), 3.5 (S, 3H, CH3 pyrimidine ring), 8.2 (S, 1H, CH), 6-8.1 (m, 9H, Ar-H). The C^{13}-NMR (DMSO) spectrum data of compound (7) show δ: 15(C_{19}), 25(C_{20}), 52 (C_{12}), 61(C_5), 163 (C_2), 154(C_1), 153(C_9), 150 (C_{16}), 100-147(C- $_{Arom}$)

Compound (8): 3- Chloro -4- (4-(3-Chloro -2- (3, 4 dimethoxy phenyl) -4-oxoazetidin -1-yl) phenyl) -1-(4-hydroxy-6- methyl pyrimidin -2- yl) -4-methylazetidin -2- one.

The FT-IR data of comp. (8) showed band at 3332 cm^{-1} for (OH), 3078 cm^{-1} for (Ar-H), 2939 cm^{-1} for (C-H) for (CH_3), 1658 cm^{-1} for (C=O), 1589 cm^{-1} (C=N) inside pyrimidin ring, 1504 cm^{-1} due to aromatic (C=C), 1272 cm^{-1} for (C-O), 725 cm^{-1} for (C-Cl).The ^{1}H-NMR (DMSO) spectrum data of compound (8) show δ: 9.83 (S, 1H, OH), 1.8 (S, 3H, CH3 β-lactam), 1.9(S, 3H, CH3 pyrimidine), 3.05 (S, 6H, OCH3), 3.8 (d, 1H, CH), 5.3 (d, 1H, CH-Cl), 6.5 (S, 1H, CH-Cl), 7.1-7.5 (m, 8H, Ar-H). The C^{13}-NMR (DMSO) spectrum data of compound (8) show δ: 8.5 (C_{24}), 23(C_{23}), 25(C_{25}, C_{26}), 45 (C_{14}), 55.4 (C_5), 55.7 (C_{15}), 55.9 (C_6), 191.3 (C_6, C_7), 149 (C_{20}, C_{21}), 155 (C_2), 154(C_1), 100-130 (C_{Arom}).

Compound (9): 3-Chloro-4-(4-(3-Chloro-2-oxo-4-(p-tolyl) azetidin-1-yl) phenyl)-1-(4-hydroxy-6-methyl pyrimidin -2-yl)-4-methyl azetidin-2-one.

The FT-IR data of comp. (9) showed band at 3332 cm^{-1} for (OH), 3070 cm^{-1} for (Ar-H), 2923 cm^{-1} for (C-H) for (CH_3)str, 1689 cm^{-1} for (C=O), 1658 cm^{-1} (C=N) inside pyrimidin ring, 1496 cm^{-1} due to aromatic (C=C), 1357 cm^{-1} for (C-H) Band,

717 cm^{-1} for (C-Cl) The ^{1}H-NMR (DMSO) spectrum data of compound (9) show δ: 9.9 (S, 1H, OH), 1.9 (S, 3H, CH_3), 2.3 (S, 3H, CH_3 β-lactam), 2.3 (S, 3H, CH3 pyrimidine), 5.4 (d, 1H, CH), 6.01(S, 1H, CH-Cl), 6.5(d, 1H, CH-Cl), 6.7-8.5 (m, 9H, Ar-H). The C^{13}-NMR (DMSO) spectrum data of compound (9) show δ: 21(C_{25}), 21 (C_{24}), 22 (C_{23}), 25(C_{25}), 39 (C_5), 100.4 (C_{15}, C_6), 164 (C_2), 162 (C_1), 196-192 (C_{16}, C_{17}), 112-155(C-Arom).

Compound (10): 3-Chloro -4- (4-(3-Chloro -2-(4-(dimethyl amino) phenyl) -4- oxoazetidin -1- yl) phenyl) -1- (4-hydroxy -6- methyl pyrimidin -2- yl)-4- methyl azetidin -2- one.

The FT-IR data of comp. (10) showed band at 3332 cm^{-1} for (OH), 3070 cm^{-1} for (Ar-H), 2939 cm^{-1} for (C-H) for (CH_3), 1666 cm^{-1} for (C=O), 1650 cm^{-1} (C=N) inside pyrimidin ring, 1510 cm^{-1} due to aromatic (C=C), 717 cm^{-1} for (C-Cl). The ^{1}H-NMR (DMSO) spectrum data of compound (10) show δ: 9.5 (S, 1H, OH), 1.8 (S, 3H, CH_3), 1.9 (S, 3H, CH_3 β-lactam), 2.9 (S, 3H, CH_3 pyrimidine), 3.02 (d, 1H, CH), 3.32 (d, 1H, CH-Cl), 5.3 (S, H, CH-Cl), 6.5-8.4 (m, 9H, Ar-H). The C^{13}-NMR (DMSO) spectrum data of compound (10) show δ: 8.3 (C_{23}, C_{24}), 22.4 (C_{25}), 25 (C_{26}), 26(C_{14}), 39.02 (C_5), 45 (C_6, C_{15}), 189-196 (C_7, C_{16}), 163 (C_2), 161(C_1), 156 (C_4), 154(C_{20}), 153 (C_{11}), 100-133 (C_{Arom}).

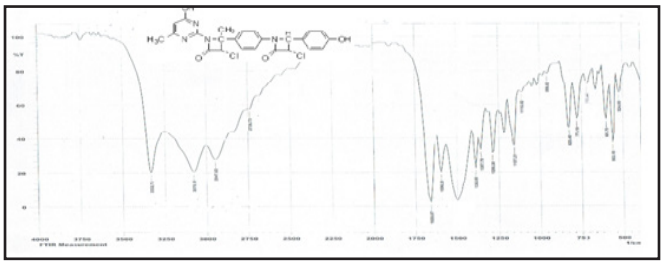


Figure 5: FT-IR spectra of compound (12)

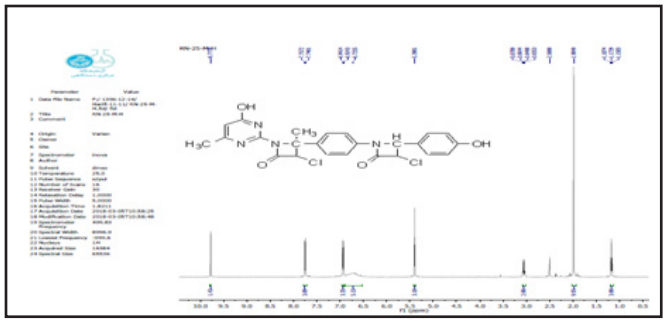


Figure 6: 1H- NMR spectrum of compound (12)

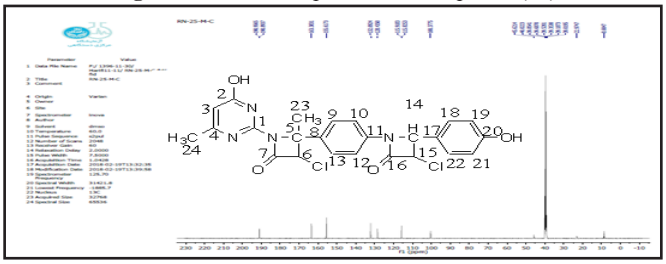


Figure 7: 13C- NMR spectrum of compound (12)

Compound (11): 4-(4-(2-(4-bromo phenyl) -3- Chloro -4-oxoazetidine -1- yl) phenyl) -3- Chloro -1- (4-hydroxy -6-methyl pyrimidin -2-yl)-4- methyl azetidin -2- one.

The FT-IR data of comp. (11) showed band at 3332 cm^{-1} for (OH), 3070 cm^{-1} for (Ar-H), 2939 cm^{-1} for (C-H) for (CH_3), 1658 cm^{-1} for (C=O), 1589 cm^{-1} (C=N) inside pyrimidin ring, 1512 cm^{-1} due to aromatic (C=C), 709 cm^{-1} for (C-Cl), 462 cm^{-1} for (C-Br). The ^{1}H-NMR (DMSO) spectrum data of compound (11) show δ: 10.5 (S, 1H, OH), 1.1 (S, 3H, CH_3 pyrimidine ring), 1.9(S, 3H, CH_3 β-lactam), 2.0(d, 1H, CH), 3.03(d, 1H, Cl-CH), 3.08 (S, 1H, Cl-CH), 6.5-7.7(m, 9H, Ar-H). The C^{13}-NMR(DMSO) spectrum data of compound (11) show δ: 8(C_{24}), 22(C_{23}), 25(C_{14}), 39(C_5), 45(C_6, C_{15}), 194-195 (C_{16}, C_{17}), 163.8 (C_2), 163.6 (C_1), 155(C_{11}), 153 (C_{20}), 100- 151 (C_{Arom}).

Compound (12): 3-Chloro-4-(4-(3-Chloro -2-(4-hydroxy phenyl)-4-oxoazetidin-1-yl) phenyl) -1-(4-hydroxy-6-methyl pyrimidin-2-yl) -4-methyl azetidin -2-one.

The FT-IR data of comp. (12) showed band at 3332 cm^{-1} for (OH), 3078cm^{-1} for (Ar-H), 2947 cm^{-1} for (C-H) for (CH_3), 1658 cm^{-1} for (C=O), 1596 cm^{-1} (C=N) inside pyrimidin ring, 1510 cm^{-1} due to aromatic (C=C), 717 cm^{-1} for (C-Cl). The ^{1}H-NMR (DMSO) spectrum data of compound (12) show δ: 9.7 (S, 1H, OH), 5.3 (S, H, OH), 1.15(S, 3H, CH_3 pyrimidine), 1.18 (S, 3H, CH_3 β-lactam), 1.9 (d, 1H, CH), 3.05 (d, 1H, Cl-CH), 3.07 (S,

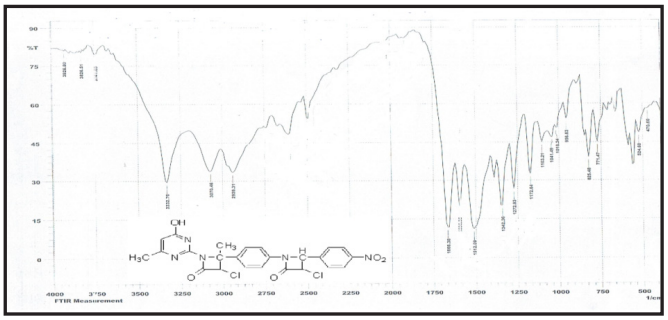


Figure 8: FT-IR spectra of compound (13)

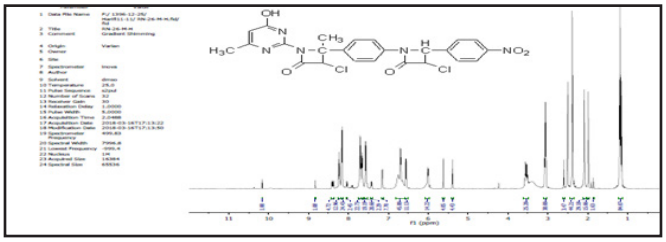


Figure 9: ^{1}H-NMR spectrum of compound (13)

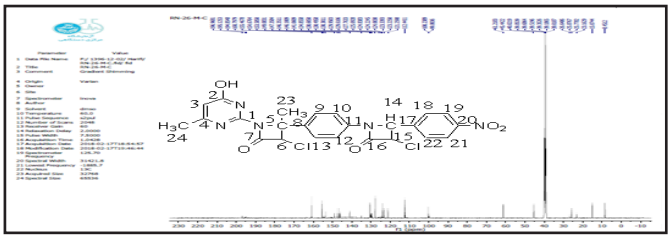


Figure 10: 13C- NMR spectrum of compound (13)

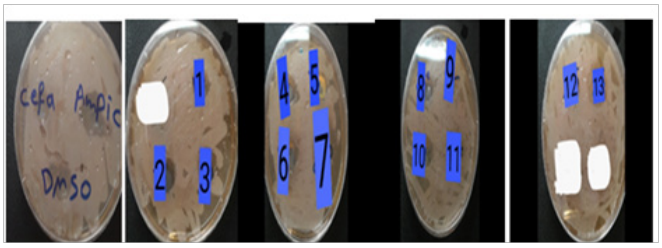


Figure 11: Biological activity of compound prepared against *S. aureus* bacteria

1H, Cl-CH), 6.7-7.7 (m, 9H, Ar-H). The C^{13}-NMR (DMSO) spectrum of compound (12) show δ: 190.8-190.9 (C_7, C_{16}), 8.6(C_{23}), 22.9(C_{24}), 39(C_{14}), 45(C_6, C_{15}), 163(C_2), 155(C_{20}), 100-132 (C_{Arom}). as in Figures 5, 6 and 7

Compound (13): 3-Chloro -4- (4-(3-Chloro -2-(4-nitro phenyl)-4- oxoazetidin -1-yl) phenyl) -1- (4-hydroxy -6-methyl pyrimidin -2-yl) -4- methyl azetidin -2- one.

The FT-IR data of compound (13) showed band at 3332 cm^{-1} for (OH), 3070 cm^{-1} for (Ar-H), 2939 cm^{-1} for (C-H) for (CH_3), 1666 cm^{-1} for (C=O), 1512 cm^{-1} due to aromatic (C=C), 1596 cm^{-1} (C=N) inside pyrimidin ring, 1500C–1342 cm^{-1} for (NO_2), 717 cm^{-1} for (C-Cl) The ^{1}H-NMR (DMSO) spectrum data of compound (13) shows δ: 10.1 (S, 1H, OH), 1.1 (S, 3H, CH_3 pyrimidin ring), 1.9 (S, 3H, CH_3 β-lactam), 3.4 (d, 1H, N-CH), 3.50 (d, 1H, CH-Cl), 5, 3 (S, 1H, CH-Cl), 6, 0 -8, 8 (m, 9H, Ar-H). The C^{13}-NMR (DMSO) spectrum data of compound (13) show δ: 194-196(C_{16}, C_7), 160 (C_2), 154(C_1), 153(C_4), 149(C_{11}), 147(C_{20}), 8(C_{23}), 15(C_{24}), 25(C_{14}), 45(C_5), 61(C_{15}), 99.8 (C_6)[14] as in Figures 8, 9 and 10

CONCLUSIONS

From the above studies, it can be concluded that the synthesized compounds exhibit significant antibacterial activity against bacteria *S. aureus* and *E. coli*. The compounds that appeared good activity are (7, 13) against (*S. aurous*). On the other hand, compound (3) shows good activity against (*E. coli*). The results of the antibacterial activity are shown in Figure 11.

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