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Synthesis and anti-microbial activity of new 4-carboxylic imidazole derivatives

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Abstract

New γ -lactam was synthesized with good yields using simple methodology **.** 1,3 oxazole have been synthesized and evaluated antimicrobial activity for some them. All derivatives were synthesized from hippuric acid (A_1) was obtained by the reaction of glucine with benzoyl chloride . oxazole derivatives (A_2-A_8) was obtained by the reaction of acetic anhydride with acetic acid then to get (A_9-A_{15}) react with ethylene di amine, then was schiffe base (A_{16}-A_{22}) ,finally react with succinic anhydride to get (A_{23}-A_{29}) . The product compounds were characterized by FTIR and 1HNMR spectra

The synthesized derivatives were *In vitro* screened against several bacterial species *Staphylococcus aureus, Pseudomonas aeruginosa* and *Acinetobacter baumanii* as well as *Candida albicans* and revealed good antimicrobial activity.

Keywords: 1,3oxazole, Schiff's bases, imidazole derivatives

INTRODUCTION

Heterocyclic compounds are found as construction units through several biological molecules(1) and mostly are molecules which contain five, six and seven membered rings(2) For monocyclic rings, the proper nomenclature is derived from combining an appropriate prefix and suffix to a given stem, where the suffix (-ole), (-ine) and (-epine) are given for unsaturated five, six and seven membered rings containing nitrogen atom(3) , Five-membered ring lactams, which are known as γ-lactams or 2-oxopyrrolidines , are important structural motifs in biologically active natural products(4) which are also found in medicinal leads and approved drugs .1,3 imidazole is one of the most important compounds in heterocyclic chemistry and drug designing and detection (5) such as anti-microbial (6-7), antitumor(8) ,antiangiogenic (9), analgesic (10), Antioxidant activity(11) . 1,3Oxazole is a five membered ring consisting of three carbon atoms, one nitrogen atom, and one oxygen atom separated by one carbon(12) .Oxazoles play a fundamental role in the synthesis of numerous biologically active drugs such as anticancer(13), antimicrobial(14), Antihelmenthic(15), Antipathogenic(16), analgesics(17), antiinflammatory,(18) , Antifungal(19).

MATERIALS AND MWTHODS

Synthesis of(4-X-benzoylamino)acetic acids (A_1)

Glycine (10mmol) in 10ml of 1N sodium hydroxide was cooled at 0-5C and the cold solution was added drop wise to a solution of 10 mmol of appropriate benzoyl chlorides . The reaction mixture was continued under stirring for an additional one hour. The aqueous layer was separated and acidified with 2N hydrochloric acid. The products were collected by filtration and recrystallized from 80% ethanol as colorless needles

Synthesis of(Z)-4-benzylidene-2-phenyloxazol-5(4H)-ones (A_2-A_8)

To a stirring mixture of compound 8 (0.01 mol) acetic acid (5 ml) acetic anhydride (20 ml), aromatic aldehyde (0.01 mol) was added. Refluxed with temperature of reaction was reached to 80C° for 4hr., The mixture became almost solid, and then as the temperature rises, it gradually liquefied and turned appropriated in color. The reaction is allowed to cool. , then the mixture was poured into crushed ice and stirred for 30 min. the product was collected and recrystallized from ethanol.

Synthesis of (Z)-3-(2-aminoethyl)-5-benzylidene-2-phenyl-3,5-dihydro-4H-imidazol-4-one

To a mixture of compound (4) (0.01 mol) in (20ml) dry benzene , (0.01 mole) ethylene diamine was added. The reaction mixture was refluxed for 2 h. Then, the mixture was allowed to cool to room temperature. The product was recrystallized from ethanol to yield the desired compound.

Synthesisof (5E)-3-[(Arylidene)amino]-2-(Aryl)-5 (Arylidene)-3,5-dihydro-4H-imidazol-4-ones Aryl aldehyde (0.01 mol) was added to a stirred solution of compound [A_{16}-A_{22}] (0.01 mol) in absolute ethanol (30 ml) and the mixture was refluxed for 8 h. After cooling, the mixture was filtered and the solid recrystallized from ethanol to afford the desired compound.

Synthesis of (E) -1-(4-benzylidend-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)-2-(4-nitrophenyl)-5-oxoopyrrolidine-3-carboxylic acid (A23-A29)

A Mixture of imines (0.02 mole) ,(2g , 0.02 mole)succinic anhydride in 30 ml of chloroform was heated in water bath at (55-60 ^{0}C) ,for (18 hrs)with stirring the solvent evaporated, the solid recrystallized by appropriate solvent afford the desired compound .

Determination of antimicrobial activity :

The agar well diffusion method was used to detect antimicrobial activity for compound (A9-A29) against various bacterial species from Gram negative bacteria ,*Pseudomonas aeruginosa* and *Acinetobacter baumanii* was chosen while *Staphylococcus aureus* was used as Gram positive bacteria , and *Candida albicans* (yeast) .These isolates were obtained from department of Biology/College of Science /Mustansiryah University. The concentrations for each compound were 1000 µg/ml. Plates were prepared by spreading approximately 10^5 CFU/ml culture broth of each indicator bacterial isolates on Muller Hinton agar surface using sterile cotton swabs. The agar plates were left for about 10 min before aseptically dispensing the 50µl of each compound into the agar wells already bored in the agar plates. The plates were then incubated at 37°C for 24 h. inhibition zones were measured and recorded in millimeter diameter. The Dimethyl sulfoxide used as control**.**

RESULTS AND DISCUSSION

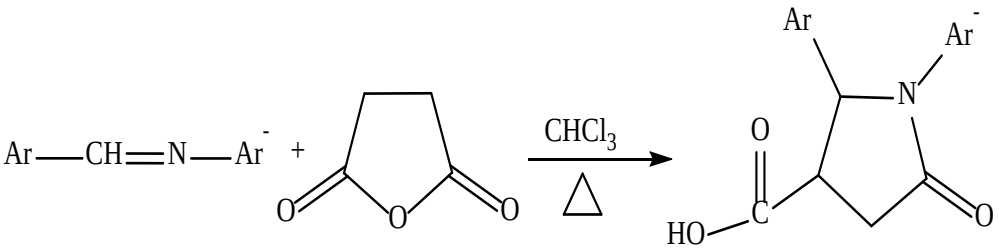
Synthesis of all compounds were shown in scheme (1)for Synthesis of targer compounds (A_1) synthesized by the reaction of glycine in the presence of sodium hydroxide(10%) with benzoyl chloride through nucleophilic displacement mechanism (SN2) The FT-IR spectrum of compound[A_1] (Fig. 1), appearing of stretching vibration of (OH) group of carboxylic acid at(2602-3400)cm^{-1} and appearance of new absorption band at (3344) cm^{-1} due to stretching vibration of (υNH).frequency of (C=O)acid

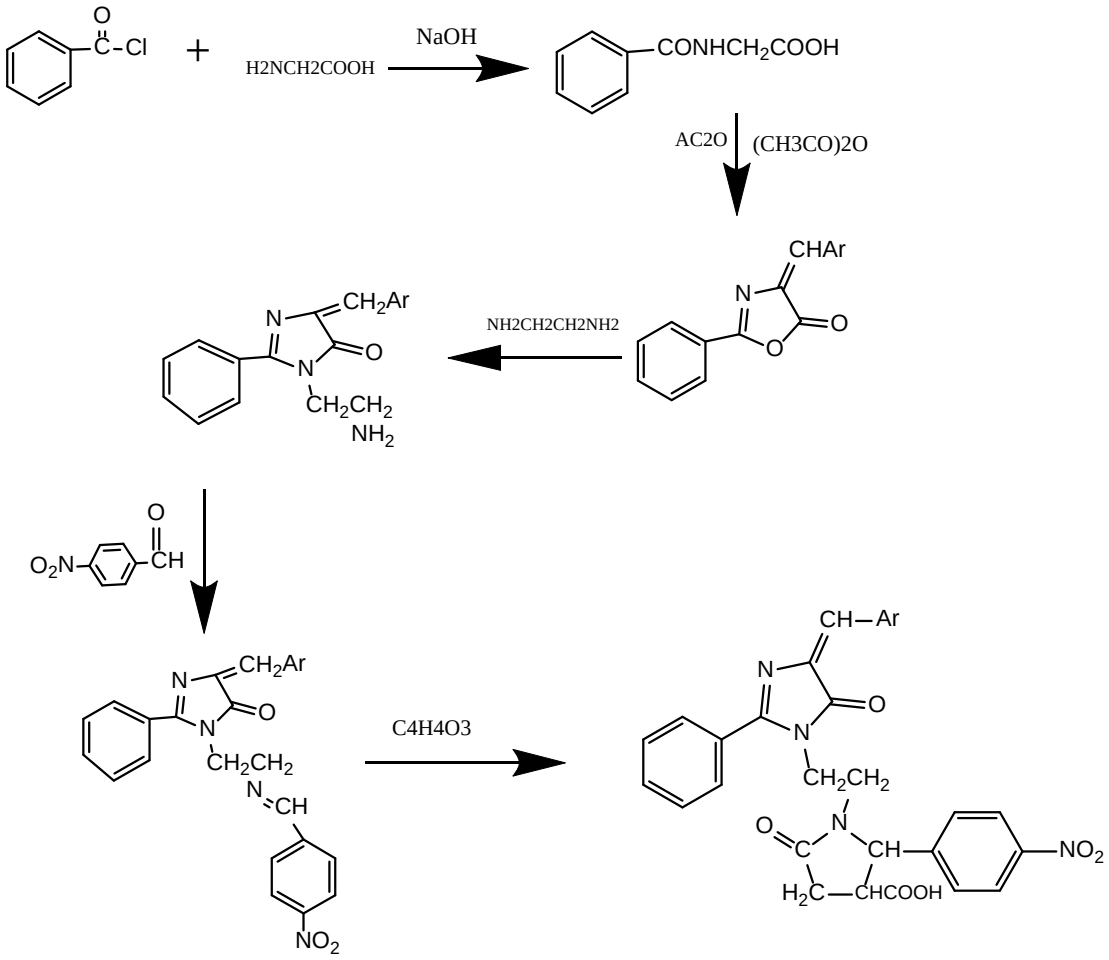
to(1745)cm^{-1} Other IR characteristics absorption bands were listed in Table (3-1), A_1:yield (93%).m.p (186-188),color (White), FT-IR cm-1, O-H (3335-2602), N-H(3315), (C=O)acid (1739),(C=O)amid (1600), (C=C)ar 3075, C=C aromatic (1553,1487), (C-H)alph,(2997-2883), The treatment of compound (A_1) with aryl aldehyde in presence of acetic acid and acetic anhydride lead to the formation of compounds(A_2 and A_8); A_2:yield (90%), FT-IR cm^{-1}C=N(1653), C=O(1795), (C=C)ar(1599,1554),(C-H)ar (3072,3054) ,(C-H)alph (2843-2981) , C-O(1294) . A_3:yield (91%) , FT-IR cm^{-1} C=N(1674) ,C=O(1798), (C=C)ar(1586,1524), (C-H)ar (3018,2974) ,(C-H)alph (2895-2874) , C-O(1296) . A_4:yield (88%) , FT-IR cm^{-1}C=N(1657) ,C=O(1792),(C=C)ar(1581,1556),(C-H)ar (3150,3038) ,(C-H)alph (2940-3052) , C-O(1287) ,(C-Br)775. A_5:yield (89%), FT-IR cm^{-1}C=N(1654) ,C=O(1797),(C=C)ar(1598,1558),(C-H)ar (3103,3043) ,(C-H)alph (2897-2999) , C-O(1299). A_6 : yield (90%), FT-IR cm^{-1} C=N(1653) ,C=O(1795),(C=C)ar(1590,1554),(C-H)ar (3088,3144) ,(C-H) (2926-2951) , C-O(1234) ,C-Cl(692) . A_7:yield (84%), FT-IR cm-1C=N(1645) ,C=O(1793),(C=C)ar(1599,1556),(C-H)ar (3080,3101) ,(C-H)alph (3012-2945) , C-O(1297). A_8:yield (89%), FT-IR cm^{-1} C=N(1649) ,C=O(1795), (C=C)ar(1583,1554),(C-H)ar (2983,3059) ,(C-H) (2820-2905) , C-O(1292). The compound from (A2-A8) react with ethylene diamine was obtained (A9-A15); The structure of compound [A_{13}] was confirmed by FT-IR and ^{1}HNMR spectrum. FT-IR spectrum of compound [A_{13}] the following bands, two bands at (3169-3132)cm^{-1} due to stretching vibrations (asymmetric and symmetric)for (NH_2)group ,while new band at (1641) cm^{-1}belongs to stretching vibration ofamide .Spectrum also shows other characteristic The ^{1}H-NMR of compound [A_{13}], the following signals:Singlet at (2.50) ppm due to (NH_2) group proton. Multiplate at (7.31-7.43) ppm due to aromatic protons.

A_9:yield (86%) m.p (162-164),color (wite)), FT-IR cm-NH2(3323,3269) , (C=C)ar(1595,1570), C=N(1643) ,C=O(1715),(C-H)ar (3082) ,(C-H)alph (2879-2916) . A10:yield (88%) m.p (256-258),color (Deep red)), FT-IR cm-NH2(3298 ,3302) , (C=C)ar(1556,1523), C=N(1600) ,C=O(1717),(C-H)ar (3084) ,(C-H)alph (2899-2929) ; 1H-NMR(PPM)(DMSO d), (4.217-4.309)(m, CH2CH2) , (2.832)(s,NH2), s(6.845) for(C=CH) aliphatic proton of imidazole ring , (7.231-7.500) (m ,aromatic proton) , Recy.solvent ethanol. A_{11}:yield (84%) m.p (195-197),color (Yellow)), FT-IR cm-NH2(3213 ,3157) , (C=C)ar(1597,1581), C=N(1647) ,C=O(1714),(C-H)ar (3074 ,2976) ,(C-H)alph (2895-2929) ,C-Br (7560). A_{12}:yield (85%) m.p (248-250),color (Dark Yellow) , FT-IR cm-NH2(3221 , 3207) , (C=C)ar(1599,1581), C=N(1649) ,C=O(1718),(C-H)ar (3057 , 3014) ,(C-H)alph (2893-2947) other , ParaNO2 (1518 ,1342) ; 1H-NMR(PPM)(DMSO d), (3.175-3.570)(m, CH2CH2) , (2.504)(s,NH2), s(6.516) for(C=CH) aliphatic proton of imidazole ring (7.167-7.832) (m ,aromatic proton) , Recy.solvent ethanol A_{13}:yield (88%) m.p (178-180),color (Light Yellow)), FT-IR cm-NH2(3252 ,3242) , (C=C)ar(1585,1523), C=N(1641 , 1604) ,C=O(1716),(C-H)ar (3107 , 3055) ,(C-H)alph (2999) C-Cl (746) ; 1H-NMR(PPM)(DMSO d), (4.189-4.259)(m, CH2CH2) , (2.504)(s,NH2), s(7.134) for(C=CH) aliphatic proton of imidazole ring , (7.317-7.388) (m ,aromatic proton) , Recy.solvent ethanol A_{14}:yield (62%) m .p (206-208),color (Brown)), FT-IR cm-NH2(3308,3227) , (C=C)ar(1599,1556), C=N(1633) ,C=O(1715),(C-H)ar (3107 , 3064) ,(C-H)alph (2955-2918) , other NO2 (1500) , A_{15}:yield (87%) m.p (180-18),color (Yelloew)), FT-IR cm-NH2(3321,3205) , (C=C)ar(1600,1581), C=N(1647) ,C=O(1714),(C-H)ar (3136 , 3030) ,(C-H)alph (2960-2997) ; 1H-NMR(PPM)(DMSO d), (4.060-4.125)(m, CH2CH2) , (3.249)(s,NH2), s(7.357) for(C=CH) aliphatic proton of imidazole ring , (7.662-7.948) (m ,aromatic proton) , Recy.solvent ethanol .

The Compounds [A_9,A_{15}] undergo condensation reaction with a different aromatic aldehydes in absolute ethanol to give Schiff-bases [A_{16}-A_{22}], Schiff's bases were indicated by the disappearance of the NH_2 stretching vibration band and appearance of new stretching vibration of (C=N).The structure of compound [A_{20}] was confirmed by FT-IR. FT-IR spectrum (fig:5) of compound [A_{20}], , band at(1686) cm^{-1} for stretching vibration of (C=N) group. The ^{1}H-NMR of compound [A_{18}] ,shows the following signals: Multiplate at (4.16-4.23) ppm due (CH_2CH_2) aliphatic protons.

- Multiplate at (7.40-7.87) ppm due to aromatic protons, Singlet at (8.97) ppm due to(N=CH) group.,Singlet at (7.35) ppm due to(C=CH) group . A_{16}:yield (79%) m.p (183-185), FT-IR cm-1 , C=O(1683) (C=C)ar(1600,1570), C=N(1643) ,(C-H)ar (3107 , 3074) ,(C-H)alph (2916-2931) ; 1H-NMR(PPM)(DMSO d), (3.878-3.995)(m, CH2CH2) , (8.677)(s,N=CH), s(7.353) for(C=CH) aliphatic proton of imidazole ring , (7.480-8.507) (m ,aromatic proton) , Recy.solvent ethanol . A_{17}:yield (86%) m.p (296-298), FT-IR cm-1 , C=O(1695) (C=C)ar(1591,1525), C=N(1651) ,(C-H)ar (3074) ,(C-H)alph (2872-2995) other (1267) C-N , Recy.solvent ethanol . A_{18}:yield (77%) m.p (220-222), FT-IR cm-1 , C=O(1697) (C=C)ar(1602,1583), C=N(1647) ,(C-H)ar (3095 , 3032) ,(C-H)alph (2823-2945) ,(707) C-Br ; 1H-NMR(PPM)(DMSO d), (4.162-4.232)(m, CH2CH2) , (8.979)(s,N=CH), s(7.352) for(C=CH) aliphatic proton of imidazole ring , (7.353-7.761) (m ,aromatic proton) , Recy.solvent ethanol A_{19}:yield (65%) m.p (270-272), FT-IR cm-1 , C=O(1699) (C=C)ar(1599,1579), C=N(1699) ,(C-H)ar (3074 , 3125) ,(C-H)alph (2929-2976) paraNO2(1516,1340) ; 1H-NMR(PPM)(DMSO d), (4.189-4.289)(m, CH2CH2) , (7.368)(s,N=CH), s(7.284) for(C=CH) aliphatic proton of imidazole ring , (7.485-8.017) (m ,aromatic proton) , Recy.solvent ethanol . A_{20}:yield (82%) m.p (208-210), FT-IR cm-1 , C=O(1686) (C=C)ar(1591,1552), C=N(1656) ,(C-H)ar (3066) ,(C-H)alph (2902-2999) , (727) C-Cl ;Recy.solvent ethanol . A_{21}:yield (75%) m.p (232-234), FT-IR cm-1 , C=O(1689) (C=C)ar(1595,1586), C=N(1678) ,(C-H)ar (3.25 , 3149) ,(C-H)alph (2913-2972) ,(1500) NO2 . A_{22}:yield (80%) m.p (225-227), FT-IR cm-1 , C=O(1699) (C=C)ar(1600,1577), C=N(1664) ,(C-H)ar (3072 , 3103) ,(C-H)alph (2906-2939) ,(746) C-Br ,The formation of γ-lactams (A_{36}-A_{42}) were done by reaction of succinic anhydride with imines (A_{29}-A_{35}) in the chloroform as solvent as shown in below equation.





Scheme 1: Synthesized of compounds

The structure of compound [A_{27}] was Formation of γ-lactam was indicated by the appearance the stretching vibration of (OH)of carboxylic acid and appearance of the two stretching vibration bands(1672-1734) to carbonyl group .the structure of compound [A_{27}] was confirmed by FT-IR and ^{1}H-NMR spectrum. FT-IR spectrum of compound [A_{27}] ,the following bands .band at(3064) cm^{-1} due to aromatic (C-H) ,band at(2928,2852) cm^{-1} due to (CH) aliphatic ,bands at (1734 due to C=O of γ-lactam and 1672 due to (C=O) amide ,band at (2552-3446)cm^{-1} due to (OH) of carboxylic acid ,The ^{1}H-NMR of compound [A_{27}] the following signals:Singlet at (6.63) ppm due for (C=CH)group ,Singlet at (2.32) ppm due for (CH2) γ-lactam ring ,Singlet at (3.12) ppm due for (CH) γ-lactam ring ,Multiplate at (4.02-4.08) ppm due to (CH_2andCH_2) aliphatic proton ,Doublet at (5.30) ppm due aliphatic (CH) γ-lactam ring near aromatic ring., Multiplate at (6.73-7.43) ppm due aromatic proton. Singlet at (11.10) ppm due to(COOH)group. A_{23}:yield (75%) m.p (225-227), FT-IR cm-1 , (C=O)acid(1734) , (C=O)amide(1672), (C=C)ar(1595,1554) ,(C-H)ar (3064 , 3146) ,(C-H)alph (2852-2928) , O-H (2552,3446) . A_{24}:yield (80%) m.p (334-336), FT-IR cm-1 , (C=O)acid(1731) , (C=O)amide(1656), (C=C)ar(1556,1539) ,(C-H)ar (3091 , 3109) ,(C-H)alph (2924-2949) , O-H (2663,3306),m,(3.82,4.11)for(CH2CH2) aliphatic proton, m(6.93-7.88) for aromatic proton, s(6.21)for(C=CH)aliphaticproton ,s(2.92)for(CH2),s(11.17)for (COOH)group ,d(3.21)(CH)for γ-lactam ring, s(4.77)(CH) for γ- . A_{25}:yield (70%) m.p (294-296), FT-IR cm-1 , (C=O)acid(1735) , (C=O)amide(1696), (C=C)ar(1579,1600) ,(C-H)ar (3013 , 3161) ,(C-H)alph (2928-2974) , O-H (2502,3441) . A_{26}:yield (65%) m.p (302-304), FT-IR cm-1 , (C=O)acid(1732) , (C=O)amide(1693), (C=C)ar(1599,1579) ,(C-H)ar (3064 , 3121) ,(C-H)alph (2829-2964) , O-H (2621,3361) ; 1H-NMR(PPM)(DMSO d), (4.015-4.088)(m, CH2CH2) , (5.399)(s,N=CH), s(7.041) for(C=CH) aliphatic proton of imidazole ring , (11.375)for (s,COOH) group, (2.419)(COCH2) ,(3.569)(C-H), (7.460-8.775) (m ,aromatic proton) . A_{27}:yield (69%) m.p (246-248), FT-IR cm-1 , (C=O)acid(1734) , (C=O)amide(1643), (C=C)ar(1570,1593) ,(C-H)ar (3028 , 3167) ,(C-H)alph (2916-2931) , O-H (2628,3424) m,(4.02,4.08) for (CH2CH2) aliphatic proton , m(7.43-6.73) for aromatic proton, s(6.63)for(C=CH)aliphaticproton ,s(2.32)for(CH2), s(11.10)for (COOH)group ,d(5.30)(CH)for γ-lactam ring, s(3.12)(CH) for γ-lactam ring . A_{28}:yield (69%) m.p (281-283), FT-IR cm-1 , (C=O)acid(1733) , (C=O)amide(1692), (C=C)ar(1568,1574) ,(C-H)ar (3045 , 3102) ,(C-H)alph (2805-2942) , O-H (257,3404) . A_{29}:yield (72%) m.p (267-269), FT-IR cm-1 , (C=O)acid(1732) , (C=O)amide(1689), (C=C)ar(1547,1582) ,(C-H)ar (3054 , 3092) ,(C-H)alph (2853-2938) , O-H (2628,3394) .

Antimicrobial activity

The *in vitro* assay of the synthesized Imidazol derivatives against different pathogenic bacteria and yeast were achieved using 1000 µg/ml concentration as illustrated by Table **1**. The effect of compounds **(A9-A29)** was evaluated against *Staphylococcus*

aureus (gram positive bacteria), *Pseudomonas aeruginosa* and *Acinetobacter baumanii* (gram negative bacteria), and *Candida albicans* (yeast). Most of prepared compounds revealed a good activity against *S. aureus*, *P.aeruginosa*, *A.baumanii* and *C. albicans*.

Table 1: Antimicrobial Activity of (A9-A29) compounds

Compounds	Inhibition Zone diameters (mm) against			
	Pseudomonas aeruginosa	*Acinetobacter baumanii*	*Staphylococcus aureus*	Candida albicans
A9	16	17	20	-
A10	17	13	10	10
A11	10	13	12	-
A12	14	12	16	-
A13	16	16	18	-
A14	12	14	13	-
A15	16	14	17	-
A16	12	14	15	-
A17	12	10	7	12
A18	7	6	6	12
A19	12	11	13	-
A20	10	18	10	10
A21	18	20	6	15
A22	10	12	6	12
A23	14	17	22	20
A24	15	17	17	-
A25	12	13	12	-
A26	14	12	12	20
A27	13	14	18	18
A28	11	15	16	20
A29	17	19	21	-

(-): not tested

Compound A21 and A29 shows highest inhibition activity against Gram –ve bacteria(*Pseudomonas aeruginosa* and *Acinetobacter baumanii*) ,A9 and A 23 had highest effect against Gram + ve bacteria (*Staphylococcus aureus*) . The compond A 23 evaluated as potent antifungal agent against yeast (*C.albicans*), with inhibition zone equal 20 mm.(Table 1)

Serious Pseudomonas infections usually occur in people in the hospital and/or with weakened immune systems. Infections of the blood, pneumonia, and infections following surgery can lead to severe illness and death in these people.The ability of P. aeruginosa to survive on minimal nutritional requirements and to tolerate a variety of physical conditions has allowed this organism to persist in both community and hospital settings. In the hospital, P. aeruginosa can be isolated from a variety of sources, including respiratory therapy equipment, antiseptics, soap, sinks, medicines, and physiotherapy and hydrotherapy pools.

Pseudomonas infections are generally treated with antibiotics. Unfortunately, in hospitalized patients, Pseudomonas infections, are becoming more difficult to treat because of increasing antibiotic resistance. Selecting the right antibiotic usually requires that a specimen from a patient be sent to a laboratory to test to see which antibiotics might still be effective for treating the infection.

Staphylococcus aureus infections range from mild to life threatening. The bacteria tend to infect the skin; often causing abscesses. However, the bacteria can travel through the bloodstream (causing bacteremia) and infect almost any site in the body, particularly heart valves ‘and bones (osteomyelitis). The bacteria also tend to accumulate on medical devices in the body, such as artificial heart valves or joints, heart pacemakers, and tubes (catheters) inserted through the skin into blood vessels.

Strains of bacteria that are resistant to beta-lactam antibiotics are called methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA strains are common if infection is acquired in a health care facility, and more infections acquired in the community, including mild abscesses and skin infections, are caused by MRSA strains

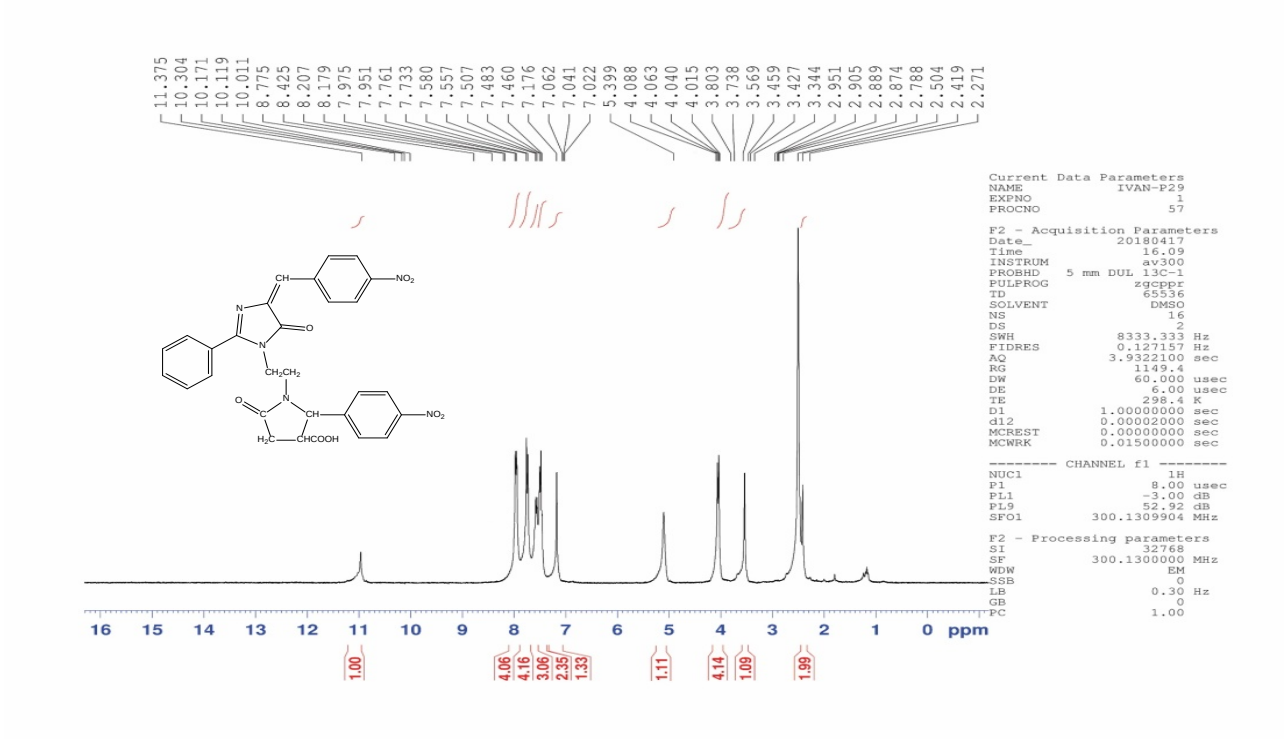


Figure 1: FT-IR spectrum of compound[A_1]

Acknowledgments

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