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 (A1) was obtained by the reaction of glycine with benzoyl chloride , then was Schiff base (A16-A22) ,finally react with succinic anhydride to get (A23-A29) . The product compounds were characterized by FTIR and HNMR spectra.

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 (-pine) 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 have been synthesized and evaluated antimicrobial activity for some them.

MATERIALS AND METHODS

Synthesis of (4-X-benzoylamino)acetic acids (A1)

Glycine (10mmol) in 10ml of 1N sodium hydroxide was cooled at 0-5°C 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 (A1-Aa)

To a stirring mixture of compound (0.01 mol) acetic acid (5 ml) acetic anhydride (20 ml), aromatic chloride (0.01 mol) was added. Refluxed with temperature of reaction was reached to 80°C for 4 hr., 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.

Synthesis of (E)-3-[(Arylideneamino)-2-(Aryl)-5-(Arylidene)-3,5-dihydro-4H-imidazol-4-ones

Aryl aldehyde (0.01 mol) was added to a stirred solution of compound [A16-A22] (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.

RESULTS AND DISCUSSION

Synthesis of all compounds were shown in scheme (1) for synthesis of target compounds (A1) 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 (A1) (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 (nNH).frequency of (C=O)acid...
The treatment of compound (A1) with (3072, 3054) (C-H)α (2843-2981), C-O (1294) yields (88%) m.p (178-180), color (Light Yellow). FT-IR cm-1: C≡N (1657), C=O (1715), (C-H)ar (3074, 3103) (C-H)α (2897-2999), (C-O) (1299).  

A1: yield (90%), FT-IR cm-1: C≡N (1656), C=O (1708), (C-H)ar (3073, 3104), (C-H)α (2898-2999), (C-O) (1299).  

The compound from (A2-A8) react with ethylene diamine was obtained (A9-A15). The structure of compound [A1] was confirmed by FT-IR and 1H NMR spectrum.  

FT-IR spectrum of compound [A1], the following bands, two bands at (3169-3132) cm⁻¹ due to stretching vibrations (asymmetric and symmetric) for (NH₂) group, while new band at (1641) cm⁻¹ belongs to stretching vibration of aldehyde. Spectrum also shows other characteristic The 1H NMR of compound [A1], the following signals: Singlet at (2.50) ppm due to (NH₂) group. Multiple at (7.31-7.43) ppm due to aromatic protons.  

A1: yield (86%) m.p (162-164), color (White), FT-IR cm-1: C≡N (1656), C=O (1715), (C-H)ar (3105, 3043), (C-H)α (2898-3052), (C=O) (1294), (C-H)β (1377).  

A2: yield (85%), FT-IR cm-1: C≡N (1656), C=O (1715), (C-H)ar (3105, 3043), (C-H)α (2898-3052), (C-O) (1299), (C=O) (1299).  

The formation of the NH₂ stretching vibration band and appearance of new stretching vibration of (C=N). The structure of compound [A20] was confirmed by FT-IR, 1H NMR spectrum (Fig.5) of compound [A20], band at (1686) cm⁻¹ for stretching vibration of (C=N) group. The 1H NMR of compound [A1] shows the following signals: Multiply at (4.14-4.23) ppm due to (CH₂CH₂) aliphatic protons.  

The Compounds [A16-A22] undergo condensation reaction with a different aromatic aldehydes in absolute ethanol to give Schiff-bases [A16-A22]. Schiff's bases were indicated by the disappearance of the NH₂ stretching vibration band and appearance of new stretching vibration of (C=N). The structure of compound [A16] was confirmed by FT-IR, 1H NMR spectrum (Fig.5) of compound [A16], band at (1686) cm⁻¹ for stretching vibration of (C=N) group. The 1H NMR of compound [A16] shows the following signals: Multiply at (4.14-4.23) ppm due to (CH₂CH₂) aliphatic protons.
The structure of compound [A27] was indicated by the appearance the stretching vibration of (OH) of carboxylic acid and appearance of the two stretching vibration bands (1672-1734) to carboxyl group. The structure of compound [A27] was confirmed by FT-IR and 1H-NMR spectrum. FT-IR spectrum of compound [A27] 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 1H-NMR of compound [A27] the following signals: Singlet at (6.63) ppm due for (C=CH) group, Singlet at (2.32) ppm due for (CH\(_2\)) γ-lactam ring, Singlet at (3.12) ppm due for (CH\(_2\)) aliphatic proton, Doublet at (5.30) ppm due aliphatic (CH) γ-lactam ring near aromatic ring, Multiplet at (6.73-7.43) ppm due aromatic proton. Singlet at (11.10) ppm due to (COOH) group. A27: yield (75%) m.p (225-227), FT-IR cm\(^{-1}\) (C=O)acid(1732), (C=O)amide(1643), (C=C)ar(1599, 1579), (C-H)ar (3064, 3121), (C=CH)aliphatic proton of imidazole ring (11.375) for (s, COOH) group, (2.41) (COCH\(_2\)) (3.569) C-H, (7.460-8.775) (m, aromatic proton), A27: yield (69%) m.p (250, 3441), FT-IR cm\(^{-1}\) (C=O)acid(1734), (C=O)amide(1634), (C=C)ar(1570, 1593), (C-H)ar (3028, 3167), (C=CH)aliphatic proton (2916-2931), (m, aromatic proton), s(6.63) for (C=CH) aliphatic proton, s(2.32) for (CH\(_2\)) aliphatic proton, s(11.10) for (COOH) group, s(5.30) for (CH) γ-lactam ring, s(11.10) for (C=CH) aliphatic proton, s(7.460-8.775) for aromatic proton.

**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

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Pseudomonas aeruginosa</th>
<th>Acinetobacter baumanii</th>
<th>Staphylococcus aureus</th>
<th>Candida albicans</th>
</tr>
</thead>
<tbody>
<tr>
<td>A9</td>
<td>16</td>
<td>17</td>
<td>20</td>
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<tr>
<td>A10</td>
<td>17</td>
<td>13</td>
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<td>10</td>
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<td>A11</td>
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<td>A12</td>
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<td>A16</td>
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<td>A19</td>
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<td>11</td>
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<tr>
<td>A20</td>
<td>10</td>
<td>18</td>
<td>10</td>
<td>10</td>
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<td>A21</td>
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<td>A29</td>
<td>17</td>
<td>19</td>
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(-): 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 compund 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.
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REFERENCE
10- F. Mahle, T. Guimaraes, A. Meira, R. Correa, R. Cruz, R. Nunes, V. Cechinel-Filho, F. Campos-Buzzi, Med. Chem., 2012, 45, 4761-.
12- Swellmeen, L. I. 3-Oxazole derivatives: A review of biological activities as antipathogenic luoba swellmeen. Der Pharma Chemica, 2016, 8, 269-286.- 1-