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

Amjad G. Eliwi*, Sahar Abdulla, Zeina Kedaer, Abdul Jabar Kh., Mudeer Mubarak, Marwah Abbas

Department of Chemistry, Mustansiriyah University, Baghdad, IRAQ.

*Correspondent email: a_amjadd@uomustansiriyah.edu.iq

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 Schiff's bases (1a,b) which suffering from intermolecular cyclization when treating with ethylchloroacetate to give compound (2a, b), reaction of compound (2a, b) with 4-bromobenzaldehyde produce compounds (3a, b), which is award six member ring product (compound 4a, b) when react with ethylacetocetate. 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 1H-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.

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] antitumor[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 apiivotalposition in modern medicinal chemistry because of their high potential biological activities[16]. The synthesis of beta lactame derivatives is important for their wide

79
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, using KBr discs. 1HNMR Spectra of some prepared derivatives were recorded in DMSO with TMS as internal standard on a Varian-Mercury 300 MHz Spectrometer the reaction were followed:

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

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

1a: 2-(4-bromo benzylidene) hydrazine carbothioamide: yield 65% mp. (°C ) 175-177 (FTIR v (Cm⁻¹) : 3437, 3290 (NH₂ amino group), 3167(NH), 3059 (CH aliph.), 2993 (CH aliph.), 1554–1524 (C=Car.), 1600 (C=N azomethene), 863(C-Br) H-NMR (ppm, ) 11.87 (NH), 8.43– 7.77 (m, 4H, ArH), 3.58 (s, aminos), 8.75 (s=CH)

1b: 2-(2-chlorobenzylidene)hydrazine carbothioamide: yield 60% mp (°C ) 154-156 FTIR v (Cm⁻¹) 3417, 3250 (NH₂), 2982 (CH aliph.), 3066(3157(NH),1621(C=N),159 3-1529 (C=Carom.), H-NMR (ppm, ) : 8.77 (=CH),11.6(NH) 3.4 (s, NH₂) 8.2- 7.6(m, 4H, ArH).

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

A mixture of compounds (1a or 1b) (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 recrystallized from ethanol.

2a: 3-[4-bromobenzylidene]amino]-2-thiooximidazolidine-4-one: yield 70% mp. (°C ) 220 – 222, FTIR v (Cm⁻¹) 3128 (NH), 3045(CH aliph.), 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=CH₂).

2b: 3-[2-chlorobenzylidene]amino]-2-thiooximidazolidine-4-one yield 75% mp. (°C ) 205 – 207, FTIR v (Cm⁻¹) : 3175 (NH), 1714 (C=O ), 1595-1513 (C=Car.), 3053 (Car.), 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. (°C ) 232 – 234 (benzene), , FTIR v (Cm⁻¹) : 3254 (NH imidazole) 3121 (=CH), 3028 (Car.), 1626 (Car.), 2926-2873 (CH aliph.), 1728 (C=O), 1599-1512 (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, NH₂),4.1(s,CH₂Hexa hydro benzimidazol).

3b: (5)-(5)-(4-bromobenzylidene)-3-[2-nitrobenzylidene]amino]-2-thioxo-3,5-dihydro-4H-imidazol-4-one yield 75% mp.(°C ) 221- 223 (ethanol), FTIR v (Cm⁻¹) : 3117 (NH), 1632(C= C=alkene), 3041 (Car.), 2923 (CH aliph.), 1718 (C=O ), 1530-1485 (C=Car.), 1653 (C=N) 1518-1512 (N02), H-NMR (ppm)3.51 (s, NH₂),11.14 (NH), 8.15(N=CH), 8.22– 7.6 (m, 8H, ArH), 4.2(s,CH₂Hexa hydro benzimidazol), 7.4 (s, C=CH).

**Synthesis of Ethyl 4-(4-bromo phenyl)-1-[(Arylidene)amino]-6-oxo-2thioxo octahydro-1H-benzo[d]imidazole-5-carboxylate(4a, b) [13]**

80

Eliwi et al. Synthesis and Biological Evaluation of some new 2-Thioimidazolidin-4-one Derivatives (part II) 2018
Ethyl acetoacetate (0.01 mole) was added 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-bromobenzylidine]amino]-6-oxo-2-thioxo octa-hydro-1H-benzo[d]imidazole-5-carboxylate: yield 60% mp.(°C ) 230 – 232(methanol), FTIR ν (Cm⁻¹) :3440(NH), 3054 (CH aliph.), 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- [[(Arylidene)amino]-6-oxo-2-thioxo octa hydro -1H-benzo[d]imidazole-5-carboxhydrazide (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-carboxhydrazide: yield 60% mp.(°C ) 224 – 226 FTIR ν (Cm⁻¹): 3186 (NH), 3431, 3320(NH₂),3075 (CH aliph.), 2954 (CH aliph.), 1687 (C=O amide), 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,NH₂),4.1(s,2H,CH₂Hexahydrobenzimid azol).

5b:4-(4-bromophenyl)-1-[[2-nitrobenzyliden] amino]-6-oxo-2-thioxo octa hydro -1H-benzo[d]imidazole-5-carboxhydrazide : yield 75% mp.(°C ) 208 – 210, FTIR ν (Cm⁻¹) 3453, 3318 (NH₂), 3119 (NH), 3073 (CH aliph.), 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, NH₂),11.14 (NH), 8.15(N=CH), 8.2 7.6 (m, 8H, ArH). 4.2(s,2H,CH₂Hexa hydro benzimidazol), 7.4 (s, C=CH)

Synthesis of 4-(4-bromophenyl)-N’-4-bromo benzyldiene-1-[[(2nitrobenzyliden) amino]-6-oxo-2-thioxo octa hydro-1H-benzo[d]imidazole-5-carboxhydrazide (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 benzyldiene-1-[[4-bromobenzylidine] amino]-6-oxo-2-thioxoctahydro-1H-benzo[d]imidazole-5-carboxhydrazide: yield 70% mp.(°C ) 234 – 236, FTIR ν (Cm⁻¹): 3428(NH amide), 3221 (NH, imidazole), 3054 (CH ar.), 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 benzyldiene -1-[[2-nitrobenzyliden)amino]-6-oxo-2-thioxo octahydro-1H-benzo[d]imidazole-5-carboxhydrazide: 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 (CH ar.), 2935 (CH aliph.), 1610-1511 (C=Car.)

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

Chloro acetyl chloride (0.02 mole) was added dropwise at 0-5°C 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...
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 NH2 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, NH2 group) table(2), in the same method synthesized compound (1b) by treatment of thiosemicarbazide with 2-chloro benzaldehyde
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 \text{ cm}^{-1}) and another 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 (3431 Asym., 3320 Sym. \text{ cm}^{-1}) for (NH$_2$) group, the $^1$H NMR 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 3.5 for (s, NH$_2$) and at 4.1 due to (s,2H,CH2 Hexa hydro benzimidazol).

Mechanism of this reaction is including: attacked carbon of carbonyl group with the lone pair of electron of amino group and then loss 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 \text{ 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 benzimidazol).

Antibacterial activity

The antibacterial activity of the some target derivatives (13) was tested by the agar disc-diffusion method against 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 except compounds 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 anter compounds showed have high inhibition toward E. coli while compounds2a and 4a have effect and have high inhibition on this kind of bacteria. The results of these studies given for antibacterial screening are mentioned in following Table 1.
Table 1: Antibacterial activity of the compounds 1-9a.

<table>
<thead>
<tr>
<th>compound</th>
<th>E. coli</th>
<th>proteus mirabilis</th>
<th>Staphylococcus</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>1a</td>
<td>8</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>1b</td>
<td>09</td>
<td>12</td>
<td>08</td>
</tr>
<tr>
<td>2a</td>
<td>16</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>2b</td>
<td>08</td>
<td>--</td>
<td>12</td>
</tr>
<tr>
<td>3a</td>
<td>--</td>
<td>07</td>
<td>--</td>
</tr>
<tr>
<td>3b</td>
<td>10</td>
<td>--</td>
<td>14</td>
</tr>
<tr>
<td>4a</td>
<td>14</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>4b</td>
<td>10</td>
<td>12</td>
<td>09</td>
</tr>
<tr>
<td>5a</td>
<td>-</td>
<td>10</td>
<td>--</td>
</tr>
<tr>
<td>5b</td>
<td>10</td>
<td>--</td>
<td>13</td>
</tr>
<tr>
<td>6a</td>
<td>09</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>7a</td>
<td>11</td>
<td>08</td>
<td>11</td>
</tr>
<tr>
<td>Clotirmazole</td>
<td>30</td>
<td>25</td>
<td>23</td>
</tr>
</tbody>
</table>

The minimum inhibitory concentration value mg/ml and corresponding zone of inhibition. Comparison with Clotirmazole.

**Conclusions**

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

**References**

1,2,4triazolederivtives


