Synthesis, diagnosis and biological activity study of some heterocyclic compounds derived from 2-aminobenzothiazole

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Abstract

This study includes synthesis of some benzothiazole derivatives from treatment 2-aminothiazole with chloroacetyl chloride to form 1-hydrogen-benzothiazole-2yl-2-chloroastiamide (1). the last one was reacted with urea, thiourea, thiosymigarizaide, 2-amibenzenothiazole and parma-aminoaniline, respectively to form the compounds (2,6). Some shiff bases for 2-aminobenzothiazole (7,8) were prepared from the reacting with aromatic aldehydes and it was cycled by reaction with glycine to form two derivatives of amidazolidine (9,10). The prepared compounds were diagnosed by IR spectra and H NMR for proton, then, the bacterial susceptibility towards some prepared compounds (1,2,5,6,7) were estimated against E.coli and Proteus mirabilis.

1- Introduction

Thiazole derivatives occupy an important position among heterocycles that are containing N and S atoms [1,2], several of thiazole derivatives are characterized by their biological and pharmacological activity [3,4], therefore, it was studied at a wide range including several fields. thiazole cycle plays an important role in medicine [5] due to using it as antibiotic drugs against microbes [6], tuberculosis [7], viruses [8], malaria [9] and HIV[10] also in development of allergy [11] and in synthesis of sulfonlamide[12]. Benzothiazoles are used as anticancer [13] with mixture of amino acids complexes that introduced into the transference and replacement mechanisms of trace elements ions in human body [14]. The nucleus of benzothiazole are linked with various activities of antihistamine[15], some of chloride-cobalt complexes which contain benzothiazole were also showed high activity in increasing of agriculture production[16], the functional benzothiazole was reported to show the reverse applications as light stabilizer and complexity factors with metal [17].

2- Experiment & Methods

2-1 Methods

General procedure for Synthesis of benzothiazole-2yl-2chloroastiamide[18] (1)

(0.01 mol) (1.5 gm) 2-aminobenzothiazole, that dissolved in 15 ml of dry benzene, and was mixed with (0.01 mol) (1ml) chloroacetyl chloride, that dissolved in (5ml) from the same solvent. drops from triethyleamine were added to mixture then, refluxed in water bath for 3 hr., left the mixture to cool then filtered and using distill water to wash the precipitant, finally, it was recrystallized from ethanol.


(0.01mol)(2.19gm) from compound (1) was dissolved in (60ml) ethanol, then (0.01mol) (1.6gm) urea and (0.76gm) thiourea were added gradually. the mixture was refluxed in water bath for 24 hr. and left to cool, after that, drops of 10%NaOH were added to it, then, the precipitant was filtered and recrystallized from ethanol.

General procedure for Synthesis of benzothiazole-2yl(3-thiosymicarbizide) acetamide [19] (4)

(0.01mol) (2.91gm) from compound (1) was dissolved in (30ml) ethanol, then (0.01mol) (0.91gm) thiosinicarcabizide was added gradually, and after addition some drops of pyridine, the mixture was refluxed for 24 hr., then the precipitant was cooled, filtered and recrystallized from ethanol.

General procedure for Synthesis of 2-(benzothiazole-2yl) amino(benzothiazole-2yl) acetamide [20] (5)

(0.01mol)(2.19gm) from compound (1) was dissolved in (20ml) ethanol, then, (0.01mol) (1.5gm) from 2-
aminobenzothiazole was added gradually. The mixture was refluxed for 6 hr. and cooled. And it was neutralized with 10% sodium bicarbonate, then, the precipitant was filtered and washed by distilled water, finally, it was recrystallized from ethanol.

**General procedure for Synthesis of 2-(4-anilino)(benzothiazole-2-yl) acetamide** [20] (6) (0.01 mol) (2.19 gm) from compound (1) was dissolved in (20 ml) ethanol, then (0.01 mol) (1.08 gm) p-phenylene diamine was added gradually. The mixture was refluxed for 6 hr. then, it was concentrated to one-third the volume, and calibrated by 10% sodium bicarbonate. The precipitant was filtered and washed with distilled water, and recrystallized from ethanol.

**General procedure for Synthesis of (4-chloro/4-hydroxy) benzylidine-2-aminobenzothiazole** [21] (7-8) (0.01 mol) (2.19 gm) from 2-aminobenzothiazole was mixed with (0.01 mol) aromatic aldehyde in (30 ml) ethanol. The mixture was refluxed for 6 hr., then, the solution was cooled for 24 hr. at 0°C. The precipitant was filtered and recrystallized from ethanol.

**General procedure for Synthesis of [3-(benzothiazole-2-yl)-2-(4-chloro/4-hydroxy)phenyl] amidazolidine-on** [21] (9-10) (0.01 mol) from compound (7,8), that dissolved in THF, was mixed with (0.01 mol) glycine, which dissolved in (15 ml) THF. The mixture was refluxed for 24 hr., the precipitant was cooled, filtered and recrystallized from ethanol.

### 2-2 Bacterial susceptibility test for some prepared compounds (1-2-5-6-7)

Two species of pathogenic bacteria, that resistance to antibiotics, were used, which were *E.coli* and *Proteus Mirabilis*. The bacterial isolates were taken ready and diagnosed from laboratory of biology department in education collage of pure science / Tikrit university.

**2-2-1 culture media**

**a-** Nutrient broth: it was prepared and used according to the company’s instructions, it sterilized by autoclave at 121°C for 15 min. under 15 bar/inch², then, poured in petri dishes or special tubes and left to cool [22]

**b-** Muller Hinton agar: this medium is used to measure the biological activity for antibiotics and pharmacological, also is used to measure the diameter of inhibition zone [23].

### 2-2-2 Chemical solutions

The chemical solutions for some prepared compounds were prepared at concentration (0.01-0.1 gm/5 ml) and sterilized by autoclave at 121°C for 15 min under 15 bar/inch², then left to cool before used.

### 2-2-3 Estimation of biological activity by diffusion method

The biological activity was estimated by followed a Kirby Bauer method; it has been spread (0.1 ml) from bacterial suspension on the petri dishes that containing muller hinton agar and left for 5 min. to diffuse into medium. after that, 4 pores in each dishes were done using sterilize cort porer (5 mm diameter). (0.1 ml) from prepared solutions were added to each pores while the fourth pore filled by DMSO as control sample. All dishes were incubated for 24 hr. at 37°C [24-25]. The inhibition diameter was measured around each pore in mm according to Preslott method [26].

### Results and discussion:

The amino group in 2-aminobenzothiazole reacted with chloroacetyl chloride to form the compound (1) as shown in table (1) and figure(5). The IR spectra for this compound showed absorption band at 3506 cm⁻¹ for stretch of (NH) bond and the absorption band at 1693 cm⁻¹ for stretch of (C=O) bond, and also at 715 cm⁻¹ for (C=C) bond. The H-NMR spectra of this compound was showed a dual signal at frequency (4.46-4.51 δ ppm) attributed to (2H CH₂) protons, and a signal at (8δ ppm) to (H, NH) proton, as well as, a signal showed at range (7.24-7.98 δ ppm) attributed to (4H, phenyl group) as shown in figure (1).

The compound (1) was reacted with urea and thiourea to form oxazole and thiazole (2-3) respectively. IR spectra for these compounds showed absorption band at (3465 cm⁻¹) attributed to stretch (NH₂) bond, and at (1155 cm⁻¹) to stretch (C=O) bond, as shown in table (1).

The compound (1) was reacted with thiocymicambarzide and 2-amino benzothiazole and para aminoaoline to form compounds (4-5-6). IR spectra for these compounds showed absorption band at range (3506-3382 cm⁻¹) attributed to stretch of (N-H) bond, and at (1666-1616 cm⁻¹) to stretch of (C=O) bond, and at (1242 cm⁻¹) to (C=S) bond, as shown in table (2). H-NMR spectra of this compound showed a dual signal for compound (5) at range (3.59-3.66 δ ppm) attributed to (2H CH₂) proton, and a single signal at (4.15 δ ppm) to (H, CH₂ –NH) proton, and at (7.96 δ ppm) to (H, NH-CO) proton, also H-NMR showed a signal at (6.99-7.68 δ ppm) attributed to (8H phenyl group), as shown in figure (2).

The compound 2-aminobenzothiazole was also reacted with aromatic aldehydes to form shiff bases of compounds (7-8), IR spectra showed absorption band for these compounds at range (1631-1643 cm⁻¹) attributed to stretch (C=O) bond, and also at (744 cm⁻¹) to stretch (C-Cl) bond and (3392 cm⁻¹) to stretch (C-OH) bond as shown in table (3) and figure (6). H-NMR spectra for compound (7) showed a signal at (106 ppm) attributed to (H-CH) proton, as well as, a signal at range (6.95-7.95 δ ppm) to (8H-phenyl group), as shown in figure (3), while compound (8) showed a signal at (3.39 δ ppm) attributed to (H,OH) proton and a signal at range (7.64 δ ppm) to (H-CH) proton, as well as, a signal showed at range (6.62-6.97 δ ppm) attributed to (8H phenyl group) proton, as shown in figure (4).

The compound (7-8) were cycled using glycine and THF as solvent to formation amidazolidine-4-on
compounds that represent by compounds (9-10). IR spectra for these compounds was showed absorption band at range (1633-1683 cm\(^{-1}\)) attributed to stretch of (C=O) bond, also at (3332-3402 cm\(^{-1}\)) to stretch of (N=H) bond as shown in table (4).

**Biological activity for some compounds (1-2-5-6-7)**

The biological activity of some compounds (1-2-5-6-7) was measured, where compounds (1-2) showed a high efficiency towards *Proteus mirabilis* (susceptibility), also compound (6) showed an efficiency towards *E.coli*, while the rest compounds were ineffective towards these species of bacteria but compound (5) was had a low efficiency towards *E.coli* as shown in table (5).

<table>
<thead>
<tr>
<th>No.</th>
<th>Comp</th>
<th>Ar – H</th>
<th>N – H</th>
<th>C = O</th>
<th>C - S</th>
<th>C-Cl</th>
<th>NH(_2)</th>
<th>C – O</th>
</tr>
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<tbody>
<tr>
<td>(1)</td>
<td>3047</td>
<td>3506</td>
<td>1693</td>
<td></td>
<td>755</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(2)</td>
<td>3050</td>
<td></td>
<td></td>
<td>3465</td>
<td>1155</td>
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</table>

Reference

Table (1) The results of IR spectra for (1-2-3) compounds

![Chemical structures and reactions](image-url)
Table (2) The results of IR spectra for (4-5-6)compounds

<table>
<thead>
<tr>
<th>No. Comp</th>
<th>Ar – H Orma</th>
<th>N – H</th>
<th>CH₂ Aleph</th>
<th>C = O</th>
<th>C = S</th>
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<tr>
<td>(4)</td>
<td>3070</td>
<td>3360</td>
<td>2929</td>
<td>1641</td>
<td>1242</td>
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<tr>
<td>(5)</td>
<td>3035</td>
<td>3382</td>
<td>2925</td>
<td>1622</td>
<td>1200</td>
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<tr>
<td>(6)</td>
<td>3052</td>
<td>3313</td>
<td>2889</td>
<td>1616</td>
<td>1276</td>
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Table (3) The results of IR spectra for (7-8)compounds

<table>
<thead>
<tr>
<th>No. of comp</th>
<th>vA – H arom</th>
<th>vC = N</th>
<th>N=C – H Aleph</th>
<th>C – Cl</th>
<th>C-OH</th>
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</thead>
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<tr>
<td>(7)</td>
<td>3077</td>
<td>1637</td>
<td>2935</td>
<td>1744</td>
<td>3392</td>
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<tr>
<td>(8)</td>
<td>3053</td>
<td>1643</td>
<td>2927</td>
<td></td>
<td>3392</td>
</tr>
</tbody>
</table>

Table (4) The results of IR spectra for (9-10)compounds

<table>
<thead>
<tr>
<th>No. of comp</th>
<th>vAr – h arom</th>
<th>v N – H</th>
<th>C – N</th>
<th>C=O</th>
</tr>
</thead>
<tbody>
<tr>
<td>(9)</td>
<td>3063</td>
<td>3332</td>
<td>1591</td>
<td>1683</td>
</tr>
<tr>
<td>(10)</td>
<td>3037</td>
<td>3402</td>
<td>1541</td>
<td>1633</td>
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Table (5) The results of biological activity for (1-2-5-6-7) compounds

<table>
<thead>
<tr>
<th>No.comp</th>
<th>E.coil</th>
<th>Proteus</th>
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<tbody>
<tr>
<td>(1)</td>
<td>M</td>
<td>S</td>
</tr>
<tr>
<td>(2)</td>
<td>M</td>
<td>D</td>
</tr>
<tr>
<td>(5)</td>
<td>R</td>
<td>M</td>
</tr>
<tr>
<td>(6)</td>
<td>S</td>
<td>M</td>
</tr>
<tr>
<td>(7)</td>
<td>M</td>
<td>M</td>
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Comparative with ciprofloxacin
Sensitive intermediate Resistant
≥ 21 MM 15 – 20 ≤ 14

Table (6) The physical properties for (1-10) compounds

<table>
<thead>
<tr>
<th>No. of comp</th>
<th>Format</th>
<th>Colour</th>
<th>Yield %</th>
<th>Mp</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
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<td>(1)</td>
<td>C₅H₂N₂SOCl</td>
<td>Off-yellow</td>
<td>90 %</td>
<td>187 – 190</td>
<td>Benzene</td>
</tr>
<tr>
<td>(2)</td>
<td>C₁₀H₉N₂SO</td>
<td>White</td>
<td>93 %</td>
<td>228 – 230</td>
<td>Ethanol</td>
</tr>
<tr>
<td>(3)</td>
<td>C₁₀H₉N₂S₂</td>
<td>White</td>
<td>34 - %</td>
<td>238 – 340</td>
<td>Ethanol</td>
</tr>
<tr>
<td>(4)</td>
<td>C₁₀H₉N₃O</td>
<td>White</td>
<td>62 %</td>
<td>250 – 252</td>
<td>Ethanol</td>
</tr>
<tr>
<td>(5)</td>
<td>C₁₆H₁₂N₄S₂O</td>
<td>White</td>
<td>72 %</td>
<td>243 – 245</td>
<td>Ethanol</td>
</tr>
<tr>
<td>(6)</td>
<td>C₁₆H₁₂N₄SO</td>
<td>Grey</td>
<td>19 %</td>
<td>110-112</td>
<td>Ethanol</td>
</tr>
<tr>
<td>(7)</td>
<td>C₁₆H₁₃N₃SCl</td>
<td>Off.-green</td>
<td>59 %</td>
<td>115 – 118</td>
<td>Ethanol</td>
</tr>
<tr>
<td>(8)</td>
<td>C₁₆H₁₃N₃SO</td>
<td>Orange</td>
<td>35 %</td>
<td>105 – 107</td>
<td>Ethanol</td>
</tr>
<tr>
<td>(9)</td>
<td>C₁₆H₁₃N₃SCl</td>
<td>Yellow</td>
<td>40%</td>
<td>185 – 188</td>
<td>THF</td>
</tr>
<tr>
<td>(10)</td>
<td>C₁₆H₁₃N₃SO₂</td>
<td>Yellow</td>
<td></td>
<td>Oily</td>
<td>THF</td>
</tr>
</tbody>
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Figure (1) H¹ NMR for compound (1)
Figure (2) H\textsuperscript{1} NMR for compound (5)

Figure (3) H\textsuperscript{1} NMR for compound (7)

Figure (4) H\textsuperscript{1} NMR for compound (8)

Figure (5) FTIR for compound (1)
Figure (6) FTIR for compound (8)

References
تحضير وتشخيص ودراسة الفعالة البايولوجية لبعض المركبات الحلقية غير المتجانسة المشتقة من 2- أمينوبنزوثيازول

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الملخص