Preparation and characterization of some new heterocyclic compounds with evaluating of its biological activity.

*Department of Chemistry, College of Education/IBN- Al –Haitham, University of Baghdad -Baghdad / IRAQ.
**Department of Chemistry, College of Science, University of Al-Nahrain -Baghdad / IRAQ.

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Abstract:

New compounds of 2-amino 6-bromo benzothiazole [2], 2-(substituted benzylidene)-6-bromobenzothiazole [3a-e], 2-(p-N,N-dimethylamino phenyl)-2-yl)tetrazolo)6-bromobenzothiazole[4], 2-(p-N,N-dimethylaminophenyl) - (4'-oxy-I,3-thiazolidin-2-yl)6-bromobenzothiazole[5], 2-(p-N,N-dimethylaminophenyl)-2-yl)2,3-dihydro-1,3-oxazine-4,7-dione)-6-bromobenzothiazole[6], 2-(p-N,N-dimethylamino phenyl)-2-yl)2,3-dihydro-1,3-oxazine-4,7-dione)-6-bromobenzothiazole[7], and 2-(p-N,N-dimethylamino phenyl)imidazolidine-4-one)-6-bromo benzothiazole[8] have been synthesized. The structures of these compounds were identified by FT-IR, H-NMR, Uv spectra and checked by TLC. Some of these compounds were tested against bacteria (Escherchia coli and Staphococcus aureus).

تحضير وتثبيطر بعض المركبات الغير متجانسة الحالة مع تقييم فاعليتها البايولوجية.

وسام خليفة جاسم* وسهاد خالد شير وسري رياض** وابتسام خليفة جاسم* 
قسم الكيمياء/كلية التربية – ابن الهيثم/جامعة بغداد- بغداد- العراق. 
قسم الكيمياء/كلية العلوم /جامعة التهرين –بغداد – العراق.

مفتاح الكلمات: بنزتايزول تترزازول ثيازولدين

الملخص:

تم في هذا البحث تحضير مركبات جديدة من 2- أمين-6-بروموبنزوزايزول (2) - (بنزالدين معوض)، 6- بروموبنزوزايزول (3a-e)، 2-(بارا-N،N-ثنائي أمينوفينيل)-2-يل) تترزازولو (6) - بروموبنزوزايزول (4) - (بارا-N،N-ثنائي أمينوفينيل) (4) - أوكسوسو-1،3-تايالوزولين-2-يل)، 6- بروموبنزوزايزول (5)، 2-(بارا-N،N-ثنائي أمينوفينيل) (3، 2-ثنائي هيدرو-1،3،7-إوكسازين-4،7-ثنائي اون)، 6- بروموبنزوزايزول (6)، 2-(بارا-N،N-ثنائي أمينوفينيل) (2، 3-ثنائي هيدرو-1،3،7-إوكسازين-4،7-ثنائي اون)، بروموبنزوزايزول (7)، وكذلك 2-(بارا-N،N-ثنائي أمينوفينيل) (6)، بروموبنزوزايزول (8). وتم تشخيص تراكيب المركبات المحضرية عن طريق الطرق الأشعة تحت الحمراء وأرنين النموي المغناطيسي للبروتون والاشعة فوق البنفسجية وكذلك من خلال تقنية الطيفية الدقيقة. كذلك تمت دراسة التأثير البايولوجي للبعض من المركبات المحضرية ضد بكتريا أشرشفيا كولي وستافيراوكوس ايريس.
Introduction:

The synthesis of these heterocycles compounds has received considerable attention in recent years. Triazoles and thiadiazoles and their derivatives countries an important class of organic compounds with divers agricultural, industrial and biological activities including anti-microbial, sedative, anti-convulsant-inflammatory\textsuperscript{(1-4)}. Benzothiazole and its derivatives are of great importance in medicinal chemistry because of their wide variety of biological and pharmacological applications \textsuperscript{(5,6)}. A large number of benzimidazole derivatives have been found to exhibit various biological activities such as anti-inflammatory, antifungal, antibacterial and anthelmintic activities\textsuperscript{(7-11)}. The ring system in which a benzene ring is fused to the 4,5-positions of imidaizole is designated as benzimidazole\textsuperscript{(9)}. Such as aminobenzothiazoles were recognized most effective structures as antimicrobial and antifungal\textsuperscript{(12)}.

Instruments:

Melting points were measured using hot stage \textit{Gallen Kamp} melting point apparatus and were uncorrected. The F.T.IR spectra in the range \((4000-400)\text{ cm}^{-1}\) were recorded using KBr disk on a \textit{SHIMADZU} F.T.IR 8300 spectrophotometer Japan. Uv/vis spectra were recorded on Uv-Cary-100 spectrophoto-meters in (ISSC). \textsuperscript{1}H-NMR spectra were recorded a BRUKER-400 MHz operating with tetra methyl silane as internal standard in CDCl\textsubscript{3} and DMSO-d\textsubscript{6} as a solvent, measurements were made at Chemistry Department, AL-Albaite University-Jordan. Thin Layer Chromatography (TLC) was carried out using Fertigfollen precoated sheets type PolyGram silg, and the plates were developed with iodine vapor. The biological activity was performed by biology department/ college of Science, Tikrit University.

Methods:

1-Synthesis of 2-amino 6-bromo benzothiazole \textsuperscript{[2]}\textsuperscript{(13)}.

\textit{p}-bromo aniline was dissolved in glacial acetic acid and added to ammonium thiocyanate solution. The reaction mixture was treated with bromine and stirred for four hours at lower temperature. The mixture was neutralized with NaOH. The product was filtered and washed with water and dried.

2-Synthesis of 2-( substituted benzylidene) 6-bromo benzothiazole \textsuperscript{[3a-e]}\textsuperscript{(14)}.

A solution of 2-amino -6-bromo benzothiazole(0.01mol) and appropriate substituted benzaldehyde (0.01mol) in absolute ethanol with few drops of glacial acetic acid was refluxed for 3 hours. The reaction mixture cooled to room temperature, table (1). Yield 80%.

3-Synthesis of 2-(\textit{p}-N,N-dimethylaminophenyl)- (6-bromo benzothiazole-2-yl)- tetrazolo-1-yl \textsuperscript{[4]}\textsuperscript{(15)}.

A mixture of (0.01mol) of Schiff bases \textsuperscript{3} tetrahydrofuran (THF) (15ml) and sodium azide (0.01mol) was heated on a water bath, the temperature of the water bath was controlled between \((50-55)\text{°C}. \) The end of the reaction was checked by (TLC) which showed the disappearance of the starting material.
4-Synthesis of 2-(p-N,N-dimethylaminophenyl)-(6-bromo benzothiazole-2-yl)-thiazolidine-4-one[5][16].

A (0.01) mole of 2-mercaptoacetic acid was added dropwise to (0.01) mole of Schiff base in (20 ml) of dry benzene, the mixture was refluxed for (24) hours then the solvent was evaporated and then the formed precipitate was re-crystallized from ethylacetate and benzene, yield (75%).

5- Synthesis of 2-(p,N,N-dimethylamino phenyl)-(6-bromo benzothiazole 2-yl)-2,3-dihydro-1,3-oxazpine-4,7-dione [6,7][17].

A mixture of Schiff base [3a] (0.01 mole) and (0.01) mole of maleic or phthaleic anhydride in (20 ml) of benzene was refluxed for (24) hours then the solvent evaporated and then the formed precipitate was re-crystallized from appropriate solvents, yield (70%).

6- Synthesis of 2-(p,N,N-dimethylamino phenyl)-(6-bromo benzothiazole-2-yl)-imidazolidine-4-one –[8][18].

A mixture of Schiff base (0.01 mole) and glycine (0.01 mole) in (20 ml) of THF was refluxed for (24) hours then it cooled to room temperature and the formed precipitate was filtered and re-crystallized from ethanol, yield (75%).

Results and discussion:

The FT-IR spectrum of 2-aminobenzothiazole showed the appearance of bands at 3250 cm\(^{-1}\) due to amino group. Besides, the appearance of band of NH\(_2\) group at 3430 cm\(^{-1}\). The second step refers to the Schiff bases (3). The reaction occurs according to method described in the literature [19], into absolute ethanol and in the catalytic amount of glacial acetic acid. The new band which appears at (1640 -1650)cm\(^{-1}\) in the IR spectrum of (3) which is attributed to the new azomethine (C=N) group.

The terazole [4] was characterized using FT-IR spectrum which showed the disappearance of band of azomethine (C=N) at the region (1640-1650) cm\(^{-1}\) and a band appeared in the region (3334)cm\(^{-1}\) due to v(N-H)) stretching vibration. The analytical and spectral data are in accordance with the structures assigned.

The thiazolidene [5] was characterized using FT-IR spectrum which showed the disappearance of band of azomethine (C=N) at the region (1640-1650) cm\(^{-1}\) and a band appeared in the region (2534) cm\(^{-1}\) due to v(C=S)) stretching vibration. The analytical and spectral data are in accordance with the structures assigned.

The FT-IR spectrum of compound [6] indicates the disappearance of azomethine band at (1640 cm\(^{-1}\)) and appearance of carbonyl bands of oxazepine ring. \(^1\)H-NMR spectrum of compound [6], shows the following characteristic chemical shifts (DMSO-d\(_6\)) ppm. (δ 9.25) due to protons of (N-H). Also, the (C-H) protons absorbed at (δ 4.4), (C-H) proton absorbed at(δ 3.4), four aromatic ring protons appear at the range (δ 7.3-7.8).

The titled compounds [7] and [8] were synthesized from the reaction between compound [3] and phthalic anhydride and glycine respectively.

These compounds [7,8] were characterized by their melting points and FT-IR spectra.
Table (2): FT-IR spectral data of compounds [4,5].

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>$\nu$(N-H) cm$^{-1}$</th>
<th>$\nu$(C-H) Aliphatic. cm$^{-1}$</th>
<th>$\nu$(C=O) cm$^{-1}$</th>
<th>$\nu$(C=N) cm$^{-1}$exo</th>
<th>$\nu$(C-H)ar cm$^{-1}$</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3440</td>
<td>2970</td>
<td>1675</td>
<td>1612</td>
<td>3089</td>
<td>N(CH$_3$)$_2$ N(H-Me) 1373</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>2920</td>
<td>1662</td>
<td>1660</td>
<td>3082</td>
<td>-</td>
</tr>
</tbody>
</table>

The compounds [1,3]oxazepine-4,7-dione [6,7] were synthesized from the reaction of compound [3] with maleic or phthalic anhydride in dry benzene.

The suggested mechanism of the reaction is shown in scheme (below):

Scheme, Mechanism steps for the prepared compounds [6,7].

The FT-IR spectrum of compound [7] as example was confirmed from the appearance of carbonyl group band at (1720 cm$^{-1}$) and (C-H) aliphatic band at (2924-2854 cm$^{-1}$), besides the (C=N) band of benzothiazole ring at (1610cm$^{-1}$) and bands at (1239 and 1118 cm$^{-1}$) belong to the asymmetric and symmetric (C-O-C) band,]. All the spectral data for other compounds are listed in table (3).

Table (3): FT-IR spectral data for (7,8) compounds.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>$\nu$(N-H) cm$^{-1}$</th>
<th>$\nu$(C-H) Aliphatic. cm$^{-1}$</th>
<th>$\nu$(C=O) cm$^{-1}$</th>
<th>$\nu$(C=N) cm$^{-1}$</th>
<th>$\nu$(C=C) cm$^{-1}$</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>3320</td>
<td>2950</td>
<td>1675</td>
<td>1650</td>
<td>1600</td>
<td></td>
</tr>
</tbody>
</table>
Thiazolidinones play a vital role due to their wide range of biological activity and industrial importance as stabilizer for polymeric material.

Table (4): Physical properties of the synthesized compounds.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Molecular formula</th>
<th>Molecular Weight</th>
<th>Yield (%)</th>
<th>M.P (°C)</th>
<th>Colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₄NBr</td>
<td>172</td>
<td>-</td>
<td>77-78</td>
<td>White</td>
</tr>
<tr>
<td>2</td>
<td>C₇H₅N₂SBr</td>
<td>229</td>
<td>75</td>
<td>229</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>3</td>
<td>C₁₀H₁₄N₂SBr</td>
<td>360</td>
<td>73</td>
<td>222-224</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>4</td>
<td>C₁₆H₁₅N₆SBr</td>
<td>403</td>
<td>70</td>
<td>160-163</td>
<td>Yellow</td>
</tr>
<tr>
<td>5</td>
<td>C₁₈H₁₆N₅OS₂Br</td>
<td>434</td>
<td>77</td>
<td>212-215</td>
<td>orange</td>
</tr>
<tr>
<td>6</td>
<td>C₂₀H₁₆N₃O₃SBr</td>
<td>458</td>
<td>72</td>
<td>203-205</td>
<td>Red</td>
</tr>
<tr>
<td>7</td>
<td>C₂₄H₁₈N₅O₃Br</td>
<td>476</td>
<td>60</td>
<td>164-166</td>
<td>orange</td>
</tr>
<tr>
<td>8</td>
<td>C₁₈H₁₇N₄OSBr</td>
<td>417</td>
<td>78</td>
<td>213-215</td>
<td>=</td>
</tr>
</tbody>
</table>

The synthesis and interesting pharmacological properties of tetrazole compounds were recently described. For synthesis of the target tetrazoles, the reaction sequence outlined in the scheme below. The compound [3] Schiff base was heated in water bath at (55-60°C) with sodium azide, to give the desired product. The titled compounds were characterized by their melting points, FT-IR spectra and checked by T.L.C.

Scheme: Regents and conditions of the preparation of tetrazole. [4]

The mechanism of the reaction systematically investigated as [3+2] cyclo additions which christened as a 1,3-dipolar cycloaddition. [20]. It involved the addition of unsaturated systems, dipolarphiles, to 1,3-dipoles, a molecule possessing resonance contributors in which a positive and negative charge are located in 1,3-position relative to each other. The addition results in a five-member ring. Azides are a prominent class of 1,3-dipoles and azide 1,3-dipolar...
cycloadditions. They are of great synthetic value and have been studied mechanistically in
great detail. The common features of this type of reactions is best accommodated by a T.S.
geometry in which the dipolaraphile and its ligands lies in one plane, and the azide lies in a
parallel plane above or below, so that the orbitals perpendicular to the planes interact to form
bonds, scheme below.

![Scheme: Approximate transition state geometry for azide addition.](image)

The FT-IR absorption bonds, was utilized to characterize the specific structure of the
synthesized compounds. The disappearance of band at (1605-1635 cm\(^{-1}\)), attributed to (C=N)
(imine group) stretching frequency is good evidence for the success of this step of reaction. It
also, the IR spectra for these compounds were devoid of a strong band at (2120–2160) cm\(^{-1}\)
attributed stretching frequency of a zide group. A band at (1531 cm\(^{-1}\)) was due to the cyclic
(N=N) stretching of tetrazole ring and a band at (3390 cm\(^{-1}\)) was due to (N-H) grou

Imidazolidine derivatives prepared by the heating of Schiff bases derivatives with glycine
(\(\alpha\)-amino acetic acid ) in THF the product were identified by the FT-IR spectrum which show the
appearance of NH vibration in (3230-3390 cm\(^{-1}\) ) and the disappearance of C=N band in
1612,or1662 cm\(^{-1}\).

**Microbiological tests:**

In this work, the antibacterial test was performed according to the disc diffusion method.
Compound (8) was assayed for its antimicrobial activity in vitro against Gram-negative bacteria
(*Escherichia coli*) and Gram-positive bacteria (*staphylococcus aureus*). Prepared agar and Petri
dishes were sterilized by autoclaving for 15min at 121°C. DMSO was used as a solvent. These
plates were incubated at 37°C for 24h for both bacteria. The inhibition zones caused by the
various compounds were examined. The results of the preliminary screening tests are listed in
table (8).
The biological activity test showed that compounds with free (-SH) groups and free (-NH\(_2\))
groups having a biological effect on each of *E.Coli* and *Staph.aureus*, these compounds are also
considered biologically active on *bacteria*.

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Table (5): Antimicrobial activity for some prepared compounds.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Staph. aureus</th>
<th>E. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Key the symbols: (-) = No inhibition, (±) = 6-9 mm, (+++) = 15-22 mm.

Conclusion:

1. Compounds [5,6] showed slight activity on *Escherichia coli*.

Compounds [5,6,7] showed no effect on *Staphylococcus aureus*.

References:

5. H. J. Zhu, B. T. Zhao, W. M. Dai, J. Zhou and X.
5-. H. J. Zhu, B. T. Zhao, W. M. Dai, J. Zhaau and X.


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1. \( 
\text{Br} - \text{NH}_2 \xrightarrow{\text{Br}_2 / \text{NH}_4 \text{SCN}} \text{CH}_3 \text{COOH} \)

2. \( \text{Br} - \text{N} \xrightarrow{\text{EtOH}} \text{CH}_3 \text{COOH} \)

3. \( \text{Br} - \text{N} = \text{CH} \xrightarrow{\text{THF}} \text{NaN}_3 \)

4. \( \text{Br} - \text{N} \xrightarrow{\text{O}} \text{O} \)

5. \( \text{Br} - \text{N} \xrightarrow{\text{O}} \text{O} \)

6. \( \text{Br} - \text{N} \xrightarrow{\text{O}} \text{O} \)

7. \( \text{Br} - \text{N} \xrightarrow{\text{O}} \text{O} \)

8. \( \text{Br} - \text{N} \xrightarrow{\text{O}} \text{O} \)

and

9. \( \text{Br} - \text{N} \xrightarrow{\text{O}} \text{O} \)

10. \( \text{Br} - \text{N} \xrightarrow{\text{O}} \text{O} \)

11. \( \text{Br} - \text{N} \xrightarrow{\text{O}} \text{O} \)

12. \( \text{Br} - \text{N} \xrightarrow{\text{O}} \text{O} \)