

# Synthesis and Characterization of New 2-amino-5-chlorobenzothiazole Derivatives Containing Different Types of Heterocyclic as Antifungal Activity

Shaima Ibraheem Chyad AL-Khazraji <sup>1</sup>  , Wafa Mohammad Sadik <sup>1</sup>  , Luma S. Ahamed <sup>2</sup>  

<sup>1</sup>Department of Chemistry, College of Education for Pure Sciences, University of Kirkuk, Kirkuk, Iraq.

<sup>2</sup>Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq.

\*Corresponding Author.

Received 03/01/2023, Revised 17/03/2023, Accepted 19/03/2023, Published Online First 20/08/2023,  
Published 01/03/2024



© 2022 The Author(s). Published by College of Science for Women, University of Baghdad. This is an Open Access article distributed under the terms of the [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

## Abstract

Nine new compounds of 2-amino-5-chlorobenzothiazole derivatives were synthesized. These new compounds were formed through the reaction of 2-amino-5-chlorobenzothiazole **1** with ethyl chloroacetate and KOH, which gave an ester derivative **2**, followed by refluxing compound **2** with hydrazine hydrate to afford hydrazide derivative **3**. The reaction of compound **3** with CS<sub>2</sub> and KOH gave 1,3,4-oxadiazole-2-thiol derivative **4**, and then the reaction of compound **2** with thiosemicarbazide to produce compound **5** then treated it with 4% NaOH led to ring closure to provide 1,2,4-triazole-3-thiol derivative **6**. The reaction of 2-amino-5-chlorobenzothiazole **1** with chloroacetic acid gave **7** followed by refluxing the latter compound with ortho amino aniline giving benzimidazole derivative **8**. Azomethine **9** was synthesized over 2-amino-6-chloro-benzothiazole with bromobenzaldehyde, the last compound **9** was converted to a thiazolidinone derivative **10** through the reaction of compound **9** with 2-mercaptoacetic acid. The prepared derivatives were established by using FT-IR, <sup>1</sup>H-NMR spectroscopy, elemental analysis C.H.N. and physical properties. Entirely compounds were examined for their anti-fungal action against *Candida glabrata* and *Aspergillus niger*, and the results revealed that some compounds showed a good measurable activity comparing with fluconazole as stander drug.

**Keywords:** 2-amino-5-chlorobenzothiazol, anti-fungal, benzimidazole, oxadiazole, thiazolidine-4-one, triazole.

## Introduction

Benzothiazole is a privileged bicyclic ring structure involving a 5-membered 1,3-thiazole bonded with a benzene molecule. The atoms and associated substituents of the two rings are coplanar. Benzothiazole is an illustration class of sulfur-involving, Fig. 1.

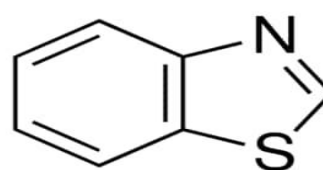
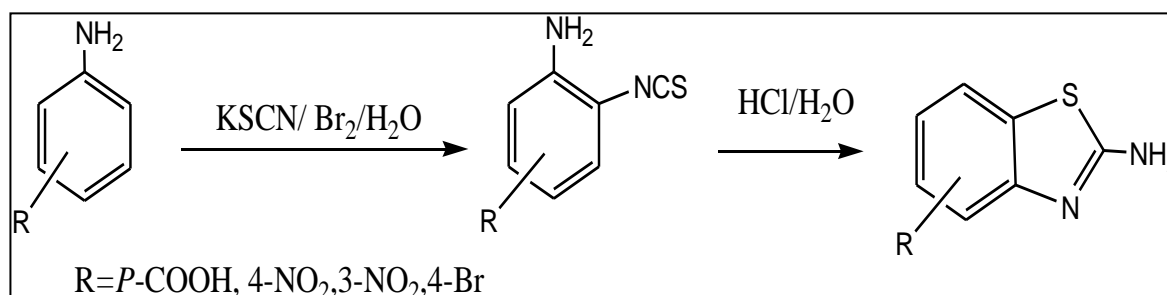


Figure 1. Benzothiazole structure

2-Aminobenzothiazole is commonly used as a portent in synthesizing drugs of medical significance. Benzothiazole plays a crucial role in medicinal chemistry and exhibits a wide variety of biological activities<sup>1</sup> such as those that are: “anti-cancer<sup>2</sup>, anti-bacterial<sup>3</sup>, anti-diabetic<sup>4</sup>, anthelmintic<sup>5</sup>, antitumour<sup>6</sup>, anti-viral<sup>7</sup>, anti-inflammatory<sup>8-9</sup>, anti-parkinsonism<sup>10</sup>, anticonvulsant<sup>11</sup>, muscle relaxant

activities, neuroprotective, inhibitors of several enzymes<sup>12</sup>, antioxidant<sup>13</sup>. The reported process by Matsui et al. is a single-step reaction carried out between a substituted aniline and potassium thiocyanate followed by bromination in acidic conditions at low temperatures of 0-5°C as shown in Scheme 1<sup>14</sup>.



**Scheme 1. Synthesis of 2-Aminobenzothiazole**

Moreover, many researchers found that the ortho-halogenated aniline could also synthesize benzothiazoles with “isothiocyanates, carbon disulfide and piperidine, aldehydes and sulfur, carbon disulfide and thiol, acid chloride and Lawesson's reagent”<sup>15-17</sup>. Here, the synthesis of nine

new derivatives of 2-amino-6-chlorobenzothiazol was described, and the structures of the prepared derivatives were established via FT-IR and <sup>1</sup>H-NMR spectroscopy. The final compounds were tested for their anti-fungal action.

## Materials and Methods

The melting points were calculated using a “Büchi (B-545) melting point apparatus” and have not been adjusted. The <sup>1</sup>H NMR spectroscopy was acquired using the “Bruker DRX-400 operating at 400 MHz and the Varian Mercury-300”, with a chemical shift in parts per million (ppm, δ) downfield from TMS as an internal standard. On a “Heraeus C.H.N./O Rapid microanalyser, elemental analyses” were done.

### Experiment:

#### Synthesis of ethyl (5-chlorobenzo[d]thiazol-2-yl) glycinate (2)<sup>18</sup>

An amount of ethyl chloroacetate (0.06 mol, 7.25 mL) was added gradually to a stirred mixture of 2-amino-5-chloro benzothiazole **1** (0.06 mol, 11.04g) and KOH (0.06 mol, 3.75 g) in ethanol absolute (20 mL.). The reaction mixture was heated for 7 hrs. The precipitate was filtered, washed with water and recrystallized from ethanol.

#### Synthesis of 2-((5-chlorobenzo[d]thiazol-2-yl) amino) acetohydrazide (3).

Compound **2** (0.01mol, 2.67g) and hydrazine hydrate 0.5 mL were added and heated in ethanol (15 mL.) absolute was refluxed for 4 hrs. The separated precipitate was filtered, washed with cold water, and recrystallized from ethanol.

#### Synthesis of 5-(((5-chlorobenzo[d]thiazol-2-yl) amino) methyl)-1,3,4-oxadiazol-2-thiol (4).

Compound **3** (0.01 mol, 2.5 g) in ethanol absolute (15 mL.) and carbon disulfide was added and refluxed for 7 hrs. The separated precipitate was filtered, washed with cold water, and recrystallized from ethanol.

#### Synthesis of 2-(((5-chlorobenzo[d]thiazol-2-yl) glycy)l) hydrazine-1-carbothioamide (5).

Compound **2** (0.01 mol, 2.6 g) in ethanol absolute (20 mL.) was added to a stirred solution of thiosemicarbazide (0.01 mol, 0.91g); the mixture was heated for 5 hrs and cooled to room

temperature. The cold was filtered and recrystallized from ethanol.

#### **Synthesis of 5-(((5-chlorobenzo[d]thiazol-2-yl)amino)methyl)-4H-1,2,4-triazole-3-thiol (6).**

Compound **5** (0.01mol, 2.69 g) and 4% NaOH, 10 mL was heated for 3 hrs, the reaction mixture was acidified with dil. HCl and the result were collected and recrystallized from ethanol.

#### **Synthesis of 5-chlorobenzo[d]thiazol-2-ylglycine (7)<sup>18</sup>.**

A mixture of potassium hydroxide (0.013 mol, 0.56 g) and compound 2-amino-5-chloro-benzothiazole **1** (0.013mol, 2.3 g) was dissolved in absolute ethanol (25 mL.). Then chloro acetic acid (0.013mol, 1.22 g) was added, and the mixture was heated for 6 hrs. The solvent was removed, and the formed solid was recrystallized from ethanol.

#### **Synthesis of N-((1H-benzo[d]imidazol-2-yl)methyl)-5-chlorobenzo[d]thiazol-2-amine (8).**

Compound **7**(0.007mol, 1.69 g) was refluxed with *o*-phenylene diamine (0.007 mol., 0.75 g) for 5 hrs, in absolute ethanol (20 mL.). The mixture was heated for 5 hrs. The formed solid was recrystallized from ethanol.

#### **Synthesis of 1-(4-bromophenyl)-N-(5-chlorobenzo[d]thiazol-2-yl)methanimine (9).**

To a stirring solution of compound 2-amino -6-chlorobenzothiazole**1**(0.01mol, 1.84 g) in ethanol absolute (15mL)., the appropriate bromobenzaldehyde (0.01 mol, 1.48 g) was added, and then the reaction mixture was heated for 6 hrs, and cooled to room temperature. The precipitate was filtered and recrystallized from ethanol.

## **Results and Discussion**

New benzothiazole compounds involving fused heterocyclic parts were synthesized according to the chemical reactions as shown in Scheme 2. The compound 2- amino-5-chlorobenzothiazole **1** was

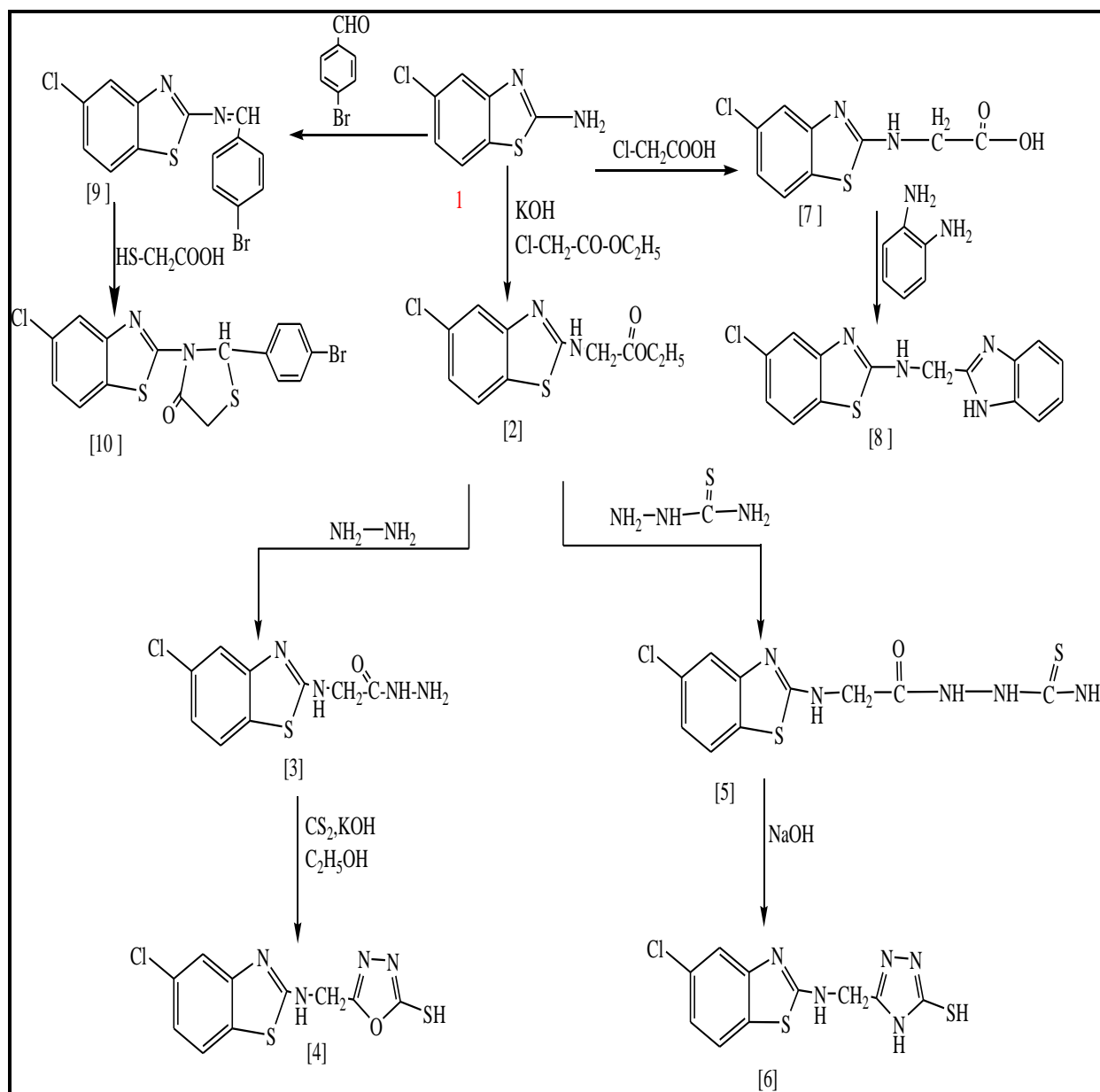
#### **Synthesis of 2-(4-bromophenyl)-3-(5-chlorobenzo[d]thiazol-2-yl) thiazolidin-4-one (10).**

A mixture of Schiff base (0.01mol, 3.41 g) and mercaptoacetic acid (0.02 mol, 0.13 mL) in dry benzene 25 mL was heated for 10 hrs, the reaction mixture was concentrated and recrystallized from methanol.

#### **Biological activity<sup>19</sup>:**

First, colonies of *A. niger* kept on Sabouraud Dextrose Agar (SDA) slant were subcultured on the SDA plate and incubated for three days at 35°C. *Candida –glabrata* and *Aspergillus Niger* colonies isolated from a 3-day-old fresh culture were combined with 1mL of sterile physiological saline solution and a drop of fluconazole to form a *Candida –glabrata* and *Aspergillus Niger* inoculum. After completing the dissolution, the supernatant of the inoculum was compared to the 0.5 McFarland standard and corrected using the physiological solution. The supernatant was used for anti-fungal evaluations. The anti-fungal properties of the prepared compound of *Candida –glabrata* and *Aspergillus Niger* were evaluated using SDA plates. The surface of the hardened SDA plate was infected evenly with sterile swabs containing test organisms. After inoculation, four 6mm diameter holes were drilled using a sterile cork borer. The holes were filled with 0.1mL of 150, 100, and 50 mg/mL concentrations of the prepared compounds, DMSO as a solvent and Fluconazole as stander drug. The plates were left at room temperature for 1hr for diffusion. After 48 hrs of incubation at 30°C, the zone of inhibition caused by *Candida –glabrata* and *Aspergillus Niger* were measured in four directions and recorded<sup>19</sup>. Each test was performed three times.

reacted successfully with ethyl chloroacetate and KOH. Treatment of **1** with hydrazine hydrate gave compound **3**.



**Scheme 2. Synthesis path for 2-amino-5-chlorobenzothiazol derivatives 2-10.**

The structure of compounds **2-10** was established by changing the physical properties and

spectrometric techniques in Table 1 and elemental analysis in Table 2.

**Table 1. Physical and IR data for the prepared derivatives 2-10**

Compound No.	Colour	MP °C	Yield	IR Data (v, cm <sup>-1</sup> ) KBr disc
2	yellow	208-210	77	3434 (v N-H), 2925 (v as, CH <sub>2</sub> ), 2854(v s, CH <sub>2</sub> ), 1739 (v C=O, ester), 1639(v C=N),1300(v C-N),1250(v C-O),1040(v C-S),820(v C-Cl)
3	nutty	204-206	73	3398 asy. and 3329sy. (v NH <sub>2</sub> ), 3280 (v NH), 2928and2835 (v CHalph. ), 1653(v C=O), 1629(v C=N),1023(v C-S),890(v C-Cl)
4	Brown	198-200	78	3361(v NH),3041(v CHarom.), 2978 and 2899 (vCHalph) ,2555(v SH),1631(v C=N), 1320(v C-N)
5	white	183-185	90	3327(v as NH),3322(v s NH),3320 (v NH), 1655 (v C=O, amide), 1200(v C=S).
6	red	190-192	84	3332 (v NH), 2918 and 2899(v CHalph.), 2550 (vSH), 1550 (vC=N).
7	White	222-224	91	3417(v OH), 3195(v NH), 2915 and, 2877(v s CHalph.), , 1710 (vC=O) carboxyl, 1607(v C=N).
8	Brown	235-237	89	3277and 3174(v NH), 2926 (v as CHalph), 3014 (v CHarom.), 1683-1614(v C=N).
9	white	212-214	75	1660 (vC=N), 1620 ( vC=N) ,585 (vC-Br).
10	yellow	131-133	71	2964(v CHalph.), 1615(v C=O lactam ring),1588(v C=N) .

**Table 2 Elemental analysis for the prepared compounds 2-10**

Compound No.	Formula	Calculated				Found			
		%C	%H	%N	%O	%C	%H	%N	%O
2	C <sub>11</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub> S	48.80	4.10	13.09	11.82	48.72	4.00	12.97	11.72
3	C <sub>9</sub> H <sub>10</sub> ClN <sub>4</sub> OS	41.95	3.91	21.74	6.21	41.85	3.84	21.62	6.12
4	C <sub>10</sub> H <sub>7</sub> ClN <sub>4</sub> OS <sub>2</sub>	40.20	2.36	18.75	5.36	40.10	2.22	18.62	5.25
5	C <sub>10</sub> H <sub>11</sub> ClN <sub>5</sub> OS <sub>2</sub>	37.91	3.50	22.11	5.05	37.85	3.42	22.09	5.00
6	C <sub>10</sub> H <sub>8</sub> ClN <sub>5</sub> S <sub>2</sub>	40.34	2.71	23.52	-	40.22	2.63	23.45	-
7	C <sub>9</sub> H <sub>7</sub> ClN <sub>2</sub> O <sub>2</sub> S	44.54	2.91	11.54	13.19	44.48	2.85	11.47	13.08
8	C <sub>15</sub> H <sub>11</sub> ClN <sub>4</sub> S	57.23	3.52	17.80	-	57.19	3.46	17.72	-
9	C <sub>14</sub> H <sub>8</sub> BrClN <sub>2</sub> S	47.82	2.29	7.97	-	47.75	2.18	7.82	-
10	C <sub>16</sub> H <sub>10</sub> BrClN <sub>2</sub> OS <sub>2</sub>	45.14	2.37	6.58	3.76	45.09	2.28	6.46	3.68

FT-IR spectrum, of ethyl chloroacetate Fig. 2, showed a sharp band at 1748.9 cm<sup>-1</sup> attributed to the stretching vibration of the carbonyl group (C=O). FT-IR spectrum of compound 2, Fig. 3 showed absorption (C=O) at 1739.6 cm<sup>-1</sup>. The spectrum also

showed the band at 3434.7 cm<sup>-1</sup> corresponding to the stretching vibration of the NH group, and the appearance of sharp strong at 2925.4 cm<sup>-1</sup>, and 2854.4 cm<sup>-1</sup> attributed to the asymmetric and symmetric stretching vibration of the CH<sub>2</sub> group.

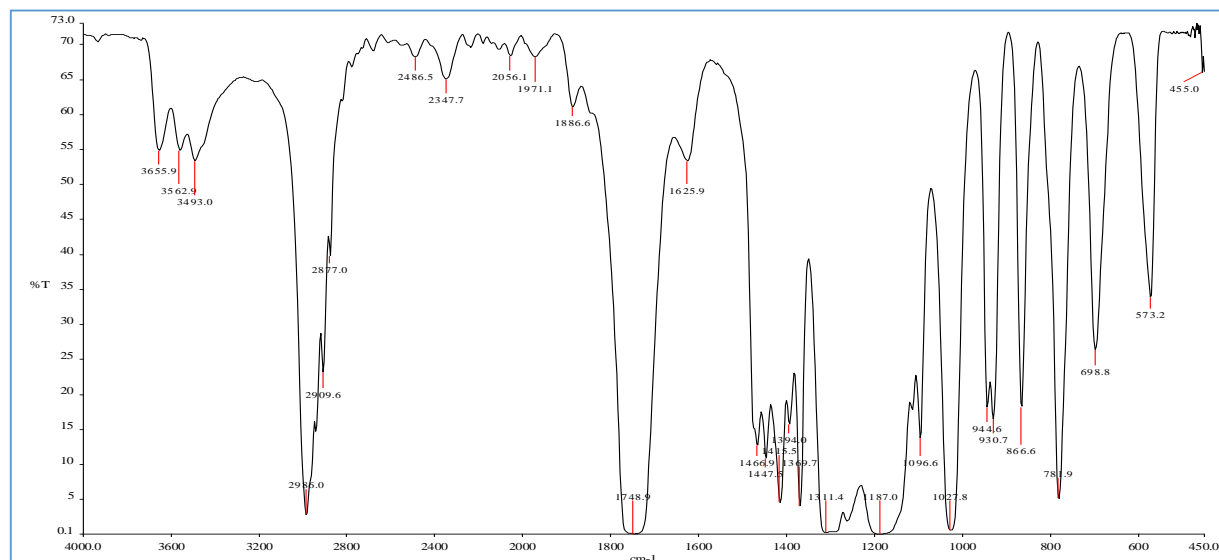


Figure 2. FT-IR spectrum of ethyl chloroacetate.

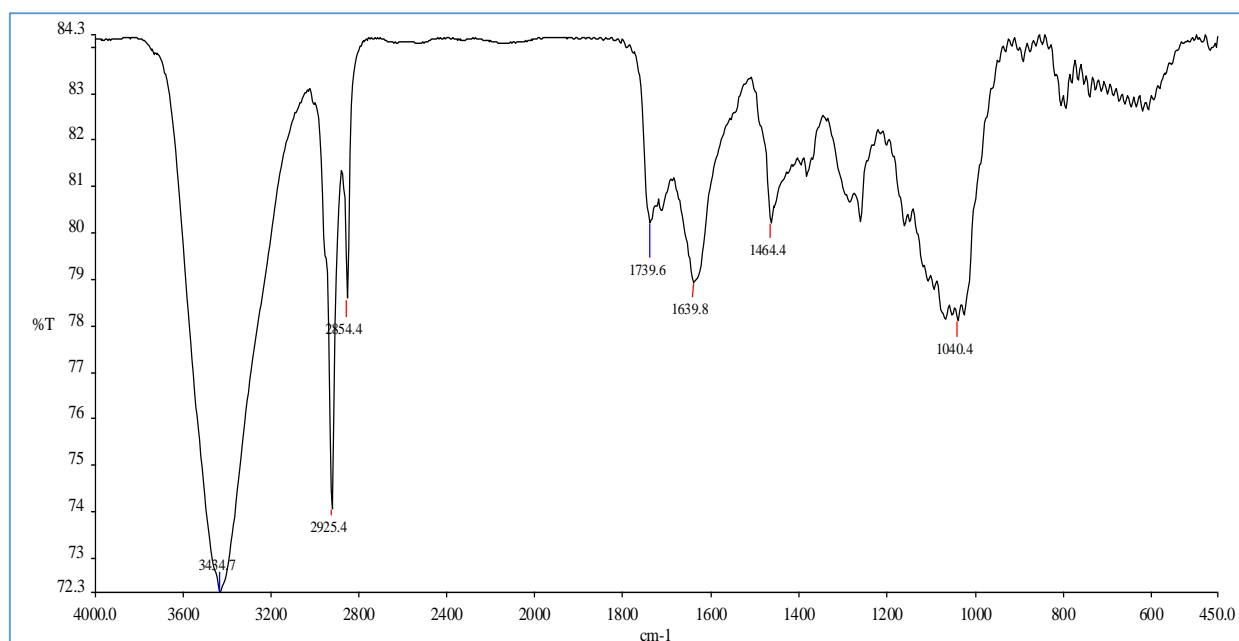


Figure 3. FT-IR spectrum of compound 2.

FT-IR spectrum of compound **8** showed the band at 3277 and 31740 cm<sup>-1</sup> which were assigned to (NH) and (CH) aromatic, respectively. Band at 1614-1683 cm<sup>-1</sup> due to  $\nu$  (C=N)<sup>20</sup> Fig. 4. The FT-IR spectrum of compound **10** showed the band at 2964-2931 cm<sup>-1</sup> attributed to the asymmetric and symmetric stretching vibration of the CH<sub>2</sub> group

and the appearance of a sharp and strong group (C=O) band at 1615 cm<sup>-1</sup> due to the stretching vibration of the carbonyl group and appearing strong band at the lower frequency at the 1588 cm<sup>-1</sup> attributed to the stretching vibration of imine group (C=N), Fig. 5.

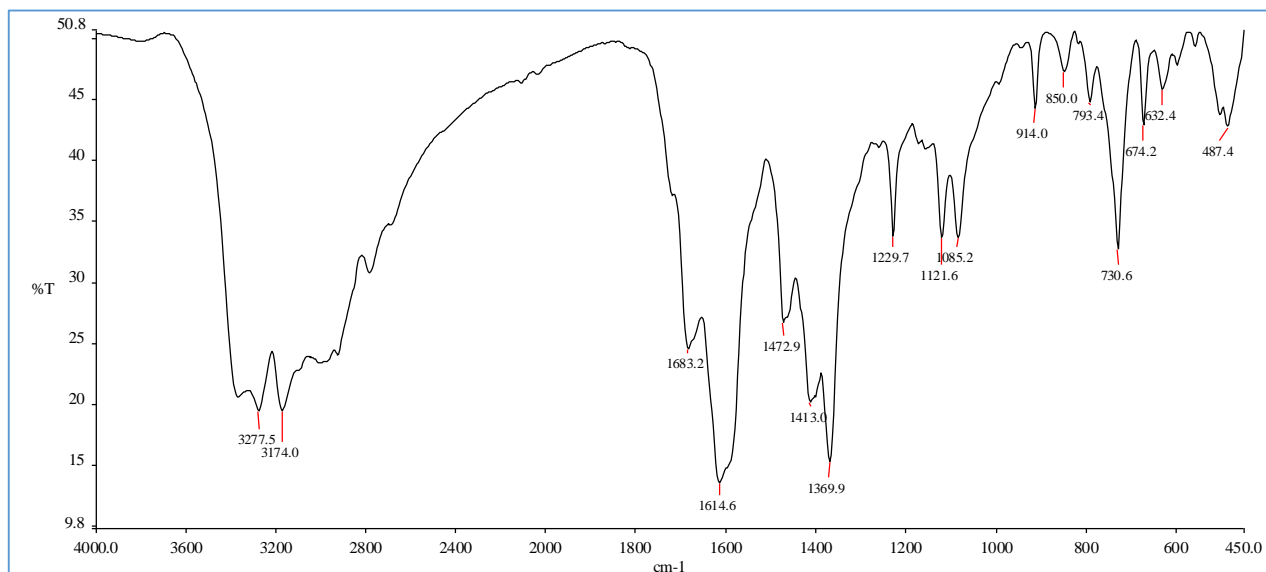


Figure 4. FT-IR spectrum of compound 8.

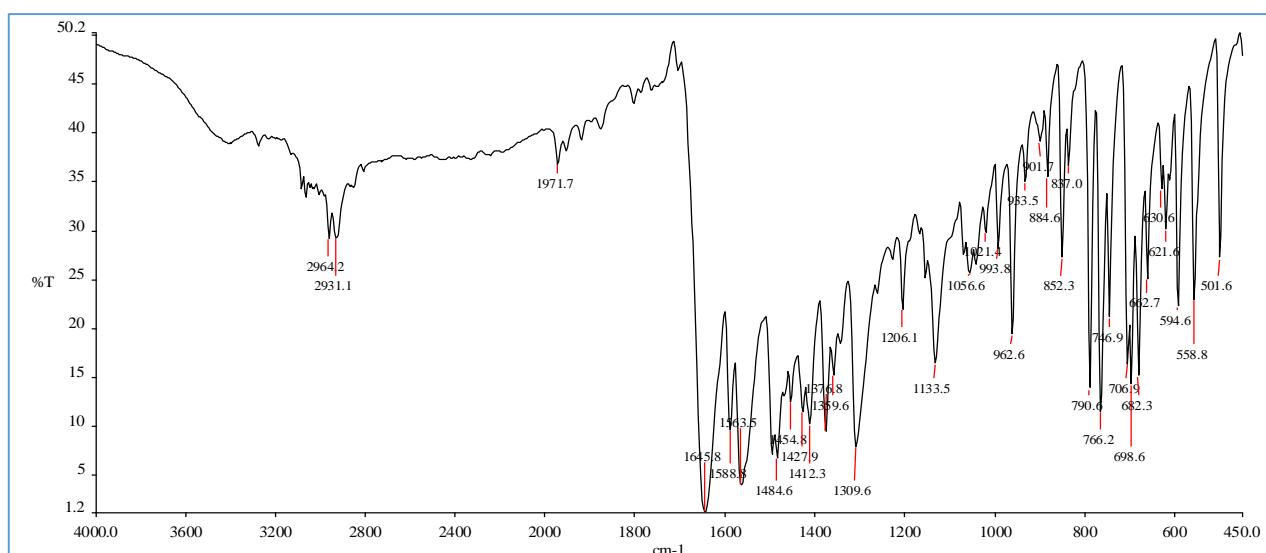


Figure 5. FT-IR spectrum of compound 10.

Figure 6 shows the <sup>1</sup>H-NMR spectrum for compound 4, which showed the following signals at  $\delta$  (ppm): Singlet signal at 4.3 ppm attributed to the CH<sub>2</sub> group, the signal at 6.6 ppm assigned to NH

group, the signals of aromatic protons appeared at the range 7.5- 8.0 ppm, the singlet at 13.1 ppm assigned to the proton of SH group.

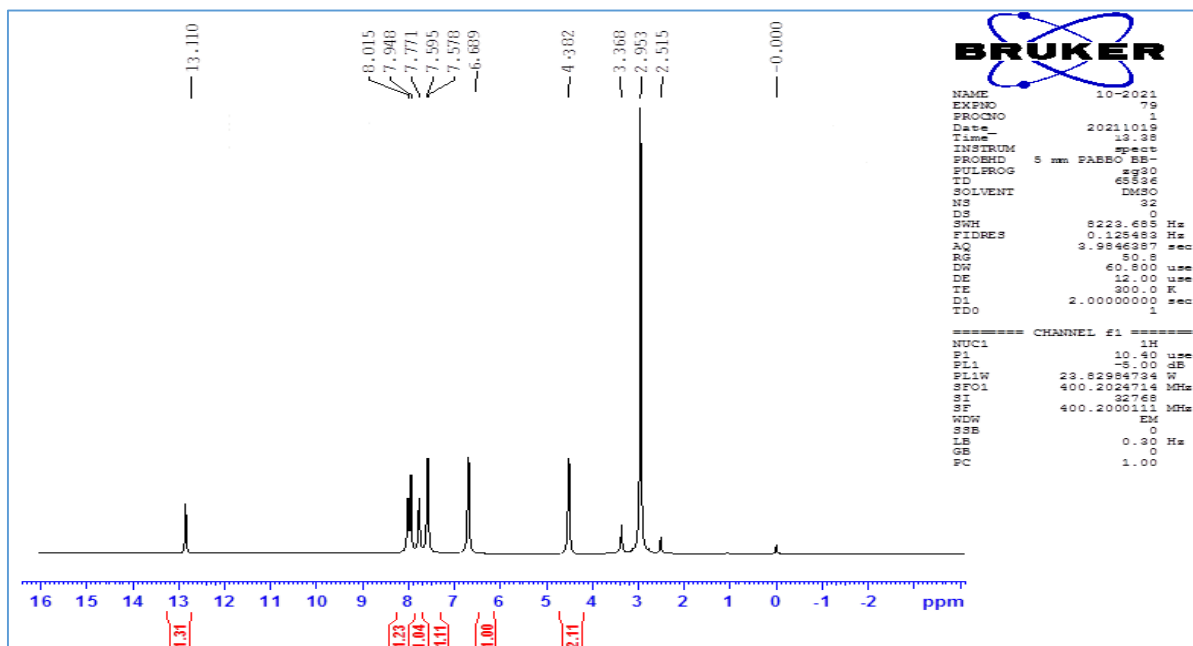


Figure 6. <sup>1</sup>H-NMR spectrum for compound 4.

The <sup>1</sup>H-NMR spectrum of compound 6 illustrated in Fig. 7, which indicated the following signals: 4.2(s, 2H, CH<sub>2</sub>); 6.8 (s,1H, NH); 7.5-8.0 (m, 3H, Ar-H); 11.1 (s,1H, NH); 13.0(s, 1H,SH).

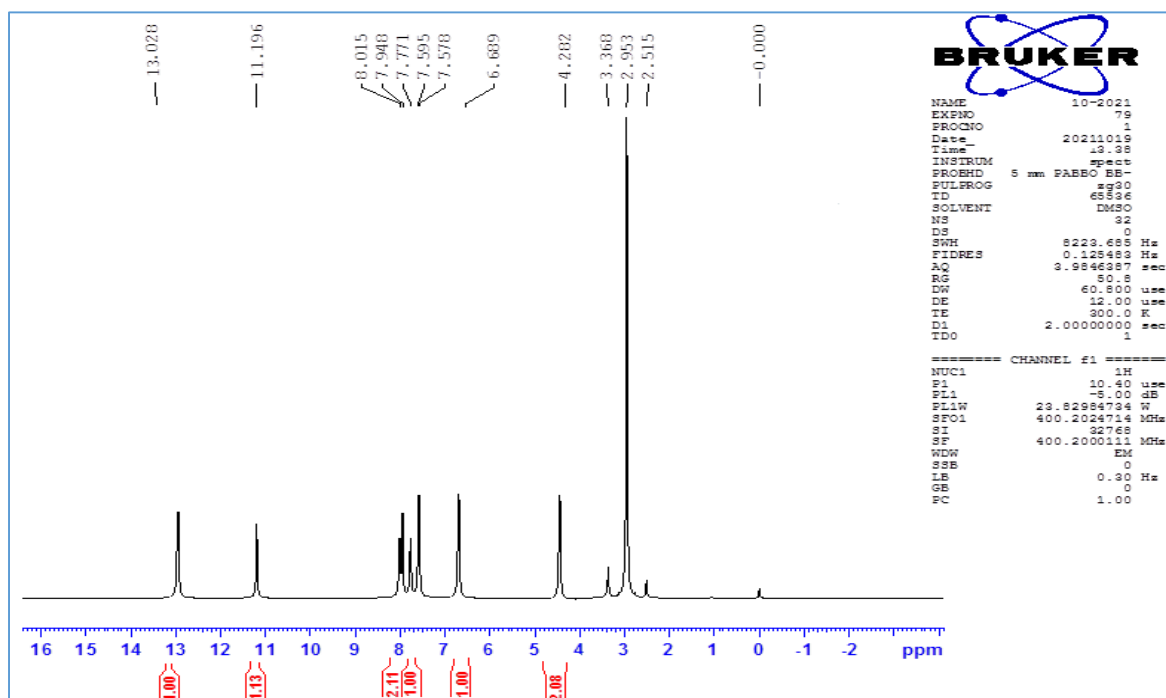


Figure 7. <sup>1</sup>H-NMR spectrum for compound 6.

The <sup>1</sup>H-NMR spectrum of compound 8 Fig. 8, shows the following signal at 4.3 ppm assignable for CH<sub>2</sub>, the singlet signal at 6.7 ppm assigned to the NH group, and multiple peaks at (7.5-8.0) ppm due to aromatic protons, the signal at 11.1 ppm attributed to the proton of SH group.



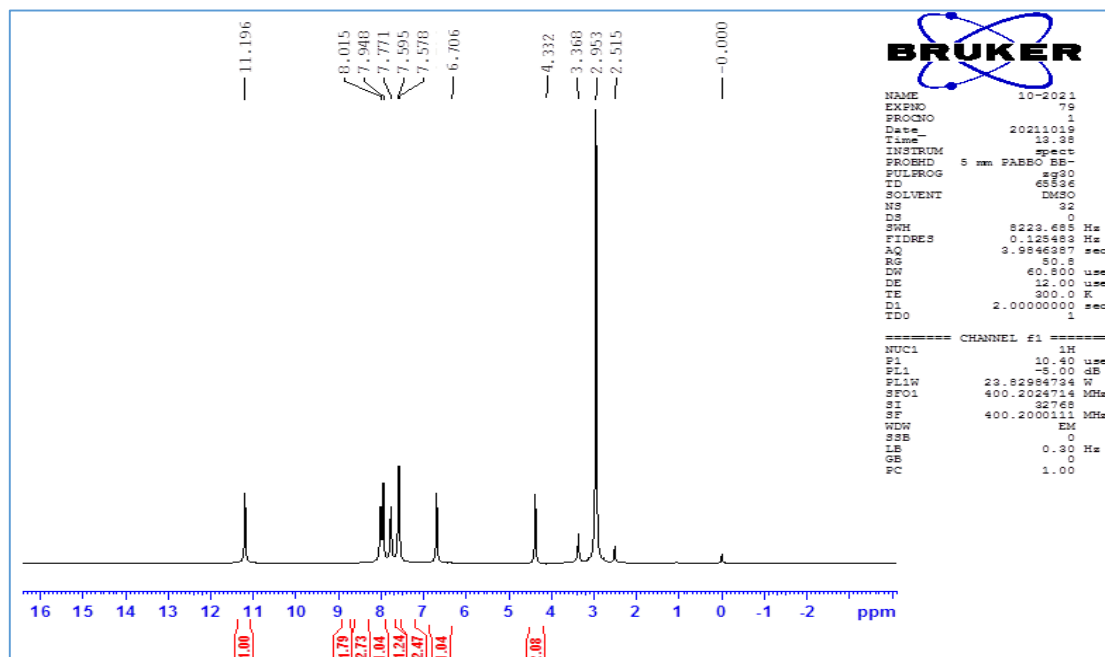


Figure 8. <sup>1</sup>H-NMR spectrum for compound 8.

The <sup>1</sup>H-NMR spectrum Fig. 9 for compound 10 (s,1H, CH); 7.14-7.19 (m,7H, Ar-H). Table 3 shows the chemical shift for the prepared compounds.

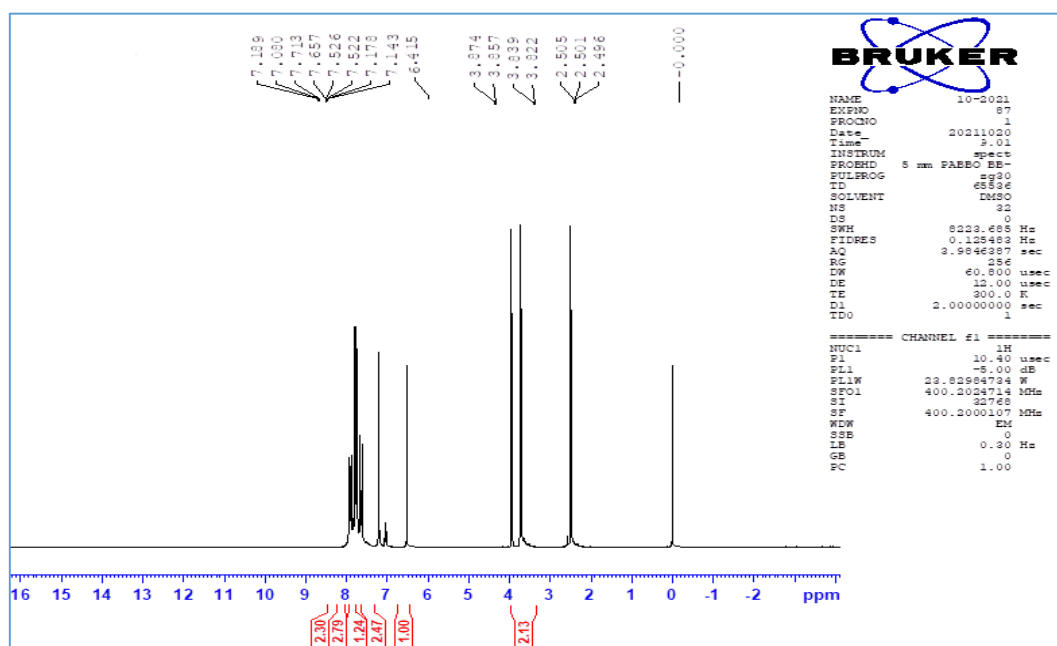


Figure 9. <sup>1</sup>H-NMR spectrum for compound 10.

Table 3. Chemical shifts of <sup>1</sup>H-NMR spectra for the prepared compounds

Comp. No	<sup>1</sup> H-NMR (DMSO- <i>d</i> <sub>6</sub> ) δ ppm
4	4.3 (s,2H, CH <sub>2</sub> ); 6.6 (s,1H, NH); 7.5-8.0 (m,3H, Ar-H); 13.1 (s,1H, SH)
6	4.2 (s,2H, CH <sub>2</sub> ); 6.6 (s,1H, NH); 7.5-8.0 (m,3H, Ar-H); 11.1 (s,1H, NH); 13.0 (s,1H, NH)
8	4.3 (s,2H, CH <sub>2</sub> ); 6.7 (s,1H, NH); 7.5-8.0 (m,7H, Ar-H); 11.1 (s,1H, NH)
10	3.82 (d, j=15.9Hz, 1H); 3.87 (d, j=15.9Hz, 1H); 6.4 (s,1H, CH); 7.1-9.9 (m,7H, Ar-H)

### Biological Evaluation (Anti-fungal Activity):<sup>21-24</sup>

The results are presented in Table 4 for the prepared compounds **2-10** which were tested for their anti-fungal action against *Candida –glabrata* and *Aspergillus Niger*; the agar-well diffusion technique was utilized to assess the anti-fungal properties<sup>25-26</sup>. All the prepared compounds showed significant results as anti-fungal action. Compound 9 showed a

good anti-fungal activity against *Candida –glabrata* may be due to thiazolidin-4-one ring while compound 5 showed a good anti-fungal activity against *Aspergillus Niger* may be due to imine group which, indicating that they potentially serve as a source of novel anti-fungal medications for the treatment of fungal disorders and most of them showed a good activity than fluconazole as the stander drug especially.

**Table 4 Anti-fungal activities for prepared compounds 2-10.**

Comp. Code	<i>Candida –glabrata</i>			<i>Aspergillus Niger</i>		
	Zone of Inhibition (mm)					
	Conc. (mg/ml)	Conc. (mg/ml)	Conc. (mg/ml)	Conc. (mg/ml)	Conc. (mg/ml)	Conc. (mg/ml)
	50	100	150	50	100	150
<b>2</b>	<b>4</b>	<b>7</b>	<b>16</b>	<b>6</b>	<b>12</b>	<b>12</b>
<b>3</b>	<b>3</b>	<b>8</b>	<b>8</b>	<b>NR.</b>	<b>15</b>	<b>19</b>
<b>4</b>	<b>9</b>	<b>14</b>	<b>28</b>	<b>4</b>	<b>16</b>	<b>18</b>
<b>5</b>	<b>NR.</b>	<b>5</b>	<b>12</b>	<b>21</b>	<b>23</b>	<b>27</b>
<b>6</b>	<b>6</b>	<b>9</b>	<b>15</b>	<b>41</b>	<b>64</b>	<b>82</b>
<b>7</b>	<b>NR.</b>	<b>16</b>	<b>18</b>	<b>5</b>	<b>15</b>	<b>42</b>
<b>8</b>	<b>5</b>	<b>25</b>	<b>27</b>	<b>NR.</b>	<b>16</b>	<b>25</b>
<b>9</b>	<b>3</b>	<b>31</b>	<b>52</b>	<b>31</b>	<b>42</b>	<b>72</b>
<b>10</b>	<b>13</b>	<b>42</b>	<b>64</b>	<b>20</b>	<b>31</b>	<b>44</b>
<b>DMSO</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>NR</b>	<b>NR</b>	<b>NR</b>
<b>Fluconazole</b>	<b>13</b>	<b>17</b>	<b>20</b>	<b>6</b>	<b>7</b>	<b>9</b>

NR: No response

### Conclusion

New heterocyclic derivatives were successfully synthesized by treating 2-amino-5-chloro benzothiazole with different organic reagents; the elemental and spectroscopy analysis by FT-IR, <sup>1</sup>H-NMR and elemental analysis C.H.N agreed well with the proposed structure. All of the prepared compounds exhibited varying degrees of anti-fungal activity against fungal strains. Compound 9 showed a good anti-fungal activity against *Candida –*

*glabrata* may be due to thiazolidin-4-one ring while compound 5 showed a good anti-fungal activity against *Aspergillus Niger* may be due to imine group which, indicating that they potentially serve as a source of novel anti-fungal medications for the treatment of fungal disorders and most of them showed a good activity than the stander drug especially. Future research will focus on the toxicity and fractionation of candidate chemicals.

### Acknowledgment

The authors express their appreciation to North Oil Company in Iraq for measuring IR spectra and

Baqubah General Hospital for measuring anti-fungal activity.

### Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore,

any Figures and images, that are not ours, have been included with the necessary permission for

re-publication, which is attached to the manuscript.

- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

### Authors' Contribution Statement

This work was carried out in collaboration between all authors S.I., contributed to the conception, design, and acquisition of data, W.M. contributed to the revision and proofreading L.S.

contributed to analysis, interpretation and drafting the manuscript. All the Authors read and approved the final manuscript.

### References

1. Yang Hu, Cui-Yun Li, Xiao-Ming Wang, Yong-Hua Yang, Hai-Liang Zhu. 1,3,4-Thiadiazole: Synthesis, Reactions, and Applications in Medicinal, Agricultural, and Materials Chemistry. *Chem Rev.* 2014 ; 114 (10): 5572-5610. <https://doi.org/10.1021/cr400131u>.
2. Irfan A, Batool F, Zahra Naqvi SA, Islam A, Osman SM, Nocentini A, et al. Benzothiazole derivatives as anticancer agents. *J Enzyme Inhib Med Chem.* 2020 ; Dec; 35(1): 265-279. <https://doi.org/10.1080/14756366.2019.1698036>
3. Ismail MMF, Abdulwahab HG, Nossier ES, El Menofy NG, Abdelkhalek BA. Synthesis of novel 2-aminobenzothiazole derivatives as potential antimicrobial agents with dual DNA gyrase/topoisomerase IV inhibition. *Bioorg Chem.* 2020 May; 98: 103716. <https://doi.org/10.1016/j.bioorg.2019.103437>
4. Zhilitskaya LV, Yarosh NO. Synthesis of biologically active derivatives of 2-aminobenzothiazole. *Chem Heterocycl Comp.* 2021; 57: 369–373. <https://doi.org/10.1007/s10593-021-02914-6>
5. Nikhil D, Amnerkar Kishore P. Bhusari. Synthesis of some thiazolyl aminobenzothiazole derivatives as potential antibacterial, antifungal and anthelmintic agents. *J Enzyme Inhib Med Chem.* 2011; 26(1): 22-28. <https://doi.org/10.3109/14756360903555258>
6. Alminderej F, Lotfi A. Design, Synthesis, Characterization and Anticancer Evaluation of Novel Mixed Complexes Derived from 2-(1H-Benzimidazol-2-yl)aniline Schiff base and 2-Mercaptobenzimidazole or 2-Aminobenzothiazole. *Egypt J Chem.* 2021; 64(7): 3351-3364. <https://doi.org/10.21608/ejchem.2021.60640.3305>.
7. Montalvão S, Leino TO, Kiuru PS, Lillsunde KE, Yli-Kauhaluoma J, Tammela P. Synthesis and Biological Evaluation of 2-Aminobenzothiazole and Benzimidazole Analogs Based on the Clathrocin Structure. *Arch Pharm (Weinheim).* 2016; 349(2): 137-149. <https://doi.org/10.1002/ardp.201500365>
8. Haroun M, Petrou A, Trairat C, Kositsi K, Gavalas A, Geronikaki A, et al. Discovery of benzothiazole-based thiazolidinones as potential anti-inflammatory agents: anti-inflammatory activity, soybean lipoxygenase inhibition effect and molecular docking studies. *SAR QSAR Environ Res.* 2022; 33(6): 485-497. <https://doi.org/10.1080/1062936X.2022.2084772>
9. Mahmood WAR, Aldabbagh AKA, Mahmoud MA. Synthesis and Characterization of New Benzothiazole-derived Schiff Bases Metal Complexes. *Baghdad Sci J.* 2022 Apr. 1 [cited 2023 Mar. 17]; 19(2): 0378. <https://doi.org/10.21123/bsj.2022.19.2.0378>
10. Nam MH, Park M, Park H, Kim Y, Yoon S, Sawant V S, et al. Indole-Substituted Benzothiazoles and Benzoxazoles as Selective and Reversible MAO-B Inhibitors for Treatment of Parkinson's Disease. *ACS Chem Neurosci.* 2017; 8(7): 1519-1529. <https://doi.org/10.1021/acscchemneuro.7b00050>
11. Abdulfatai U, Uzairu A, Uba S. Molecular docking and quantitative structure-activity relationship study of anticonvulsant activity of aminobenzothiazole derivatives. *Beni Suef Univ J Basic Appl Sci.* 2018; 7, (2): 204-214. <https://doi.org/10.1016/j.bjbas.2017.11.002>.
12. Gao X, Liu J, Zuo X, Feng X, Gao Y. Recent Advances in Synthesis of Benzothiazole Compounds Related to Green Chemistry. *Molecules.* 2020 Apr 5; 25(7): 1675. DOI: 10.3390/molecules25071675. PMID: 32260500; PMCID: PMC7181030.
13. Djuidje EN, Barbari R, Baldisserotto A, Durini E, Sciabica S, Balzarini J, et al. Benzothiazole Derivatives as Multifunctional Antioxidant Agents for Skin Damage: Structure-Activity Relationship of a Scaffold Bearing a Five-Membered Ring System. *Antioxidants (Basel).* 2022 Feb 17; 11(2): 407.

- <https://doi.org/10.3390/antiox11020407>. PMID: 35204288; PMCID: PMC8869097.
14. Gill RK, Rawal RK, Bariwal J. Recent Advances in the Chemistry and Biology of Benzothiazoles. *Arch. Pharm. Chem. Life Sci.* 2015; 348(3): 155-178. <https://doi.org/10.1002/ardp.201400340>
15. Nguyen T B. Recent Advances in the Synthesis of Heterocycles via Reactions Involving Elemental Sulfur. *Monatsh Chem.* 2020; 362 (17) :3448-3484. <https://doi.org/10.1002/adsc.202000535>
16. Hacıoğlu N, Güngör T, Tokay E, Önder, Ferah Cömert, Ay, Mehmet, Köçkar, Feray. Synthesis and biological evaluation of 2,4,6-trinitroaniline derivatives as potent antitumor agents. *Monatshefte für Chemie.* 2020; 151: 1629–1641. <https://doi.org/10.1007/s00706-020-02690-7>
17. Alzubaidy SN, Yasin MA, lateef OA, Thamer HF. Synthesis, Characterization and study biological activity of several 1-cyclopentene-1,2-dicarboxylimidyl Containing oxadiazole and Benzothiazole. *Baghdad Sci J.* 2014 Jun. 1; 11(2): 429-37. <https://doi.org/10.21123/bsj.2014.11.2.429-437>
18. Mohammed MH, chyad SI, Jabbar S. Abdul-Satar. Preparation, diagnostics, and biological evaluation of new 1,3,4-thiadiazol derivatives. *Mater Today Proc.* 2022; 61(3): 710–716. <https://doi.org/10.1016/j.matpr.2021.08.278>. <https://www.sciencedirect.com/science/article/pii/S2214785321057229>
19. Quiroga EN, Sampietro AR, Vattuone MA. Screening anti-fungal activities of selected medicinal plants. *J Ethnopharmacol.* 2001; 74: 89–96. [https://doi.org/10.1016/S0378-8741\(00\)00350-0](https://doi.org/10.1016/S0378-8741(00)00350-0)
20. Zheng X, Ma Z, Zhang D. Synthesis of Imidazole-Based Medicinal Molecules Utilizing the van Leusen Imidazole Synthesis. *Pharmaceuticals (Basel).* 2020; 13(3): 37. Published 2020 Mar 3. <https://doi.org/10.3390/ph13030037>
21. AlTamiemi EO, Khammas SJ, AlKaissi SS. Synthesis, Characterization and Study the Biological Activity of New Morpholine Derivative. *Baghdad Sci J.* 2015 Dec. 6; 12(4): 761-73. <https://doi.org/10.21123/bsj.2015.12.4.761-773>
22. Maged A, Ahamed LS. Synthesis of new heterocyclic derivatives from 2-furyl methanethiol and study their applications. *Eurasian Chem Commun.* 2021; 3(7): 461-476. <https://doi.org/10.22034/ecc.2021.279489.1158>
23. AL-Joubory AKJ, Abdullah LW, Mohammed AJ. Synthesis, Characterization and Biological Activity Evaluation of Some Pyrazoles, Thiazoles and Oxazoles Derived from 2-Mercaptoaniline. *Baghdad Sci J.* 2021 Mar. 30; 18(1(Suppl.): 0764. [https://doi.org/10.21123/bsj.2021.18.1\(Suppl.\).0764](https://doi.org/10.21123/bsj.2021.18.1(Suppl.).0764)
24. Ahamed LS, Ali RA, Ahmed RS. Solvent-free synthesis of new chalcone derivatives from 3-nitro phthalic acid and evaluation of their biological activities. *Egypt J Chem.* 2021; 64(6): 2963-2968. <https://doi.org/10.21608/ejchem.2021.55742.3176>
25. Hamzah MA, Jebur IK, Ahmed AK. Synthesis, Characterization and Biological Activity Evaluation of Some New Azo Derivatives from 2- Amino Benzothiazole and Their Derivatives. *KUJSS.* 2018; 13(1):219-224. [https://kujss.uokirkuk.edu.iq/article\\_143033.html](https://kujss.uokirkuk.edu.iq/article_143033.html)
26. Al-hitti NF, Jebur Ikh. Synthesis and characterization of some new 2-mercapto benzimidazole derivative from ortho phenylenediamine. *KUJSS.* 2015; 10 (4):229-230. [https://kujss.uokirkuk.edu.iq/article\\_124183.html](https://kujss.uokirkuk.edu.iq/article_124183.html)

## تحضير وتشخيص مشتقات 2-امينو-5-كلوروبنزوثيازول جديدة تحوي على انواع مختلفة من حلقات غير المتجانسة كمضادات للفطريات

شيماء ابراهيم جيا، وفاء محمد صادق<sup>1</sup>، لمى سامي احمد<sup>2</sup>

<sup>1</sup>قسم الكيمياء، كلية التربية للعلوم الصرفة، جامعة كركوك، كركوك، العراق.  
<sup>2</sup>قسم الكيمياء، كلية العلوم، جامعة بغداد، بغداد، العراق.

### الخلاصة

تم في هذا البحث تحضير تسع مركبات جديدة من مشتقات 2-امينو-5-كلوروبنزوثيازول من خلال تفاعل 2-امينو-5-كلوروبنزوثيازول مع اثيل كلورواسيتيت بوجود KOH ليعطي مشتق 2-امينو-5-كلوروبنزوثيازول استر 2 ادخل الاخير بعدة مسارات ، تفاعل مشتق الاستر مع هيدرازين هيدريت لتعطي مشتق الهيدرازايدي 3 ومفاعلة المركب الاخير مع CS<sub>2</sub> بوجود KOH ليعطي مشتق 1,3,4 اكساديزول-2-ثايول (4) بعدها تم مفاعله مركب الاستر المحضر مع ثايو سيمكاريزايد ليعطي مركب 5 ثم الغلق الحلقي بواسطه 4% من هيدروكسيد الصوديوم ليعطي مشتق 1,2,4-ثيازول-3-ثايول 6 في مسار اخر تم مفاعله 2-امينو-5-كلوروبنزوثيازول مع حامض كلورو اسيتك اسد ليعطي مركب 7 الذي تم مفاعله مع ارثو امينو انلين ليعطي بنزيميدازول 8. تم الحصول على مشتق ازوميثين 9 من خلال تفاعل 2-امينو-6-كلوروبنزوثيازول مع بروموبنزالديهايد. المركب الاخير 9 حول الى مشتق ثايوزولدينون 10 من خلال تفاعله مع 2-مركبتواسيتك اسد. المركبات المحضرة تم تشخيصها من خلال استعمال طيف الأشعة تحت الحمراء وطيف بروتون النووي المغناطيسي وتحليل العناصر C.H.N وتعيين الصفات الفيزيائية لكل المركبات المحضرة. كما تم فحص الفعالية البايولوجية للمركبات المحضرة تجاه نوعين من الفطريات وأظهرت النتائج لبعض فعاليات قياسية جيدة بالمقارنة مع العقار القياسي فلوكينازول.

**الكلمات المفتاحية:** 2-امينو-5-كلوروبنزوثيازول ، مضاد للفطريات، بنزيميدازول ، اكساديزول ، ثيازوليدين-4-اون ، تريازول.