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

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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_2 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-chlorobenzothiazole1 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-mercaptoaceticacid. The prepared derivatives were established by using FT-IR, ^{1}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.

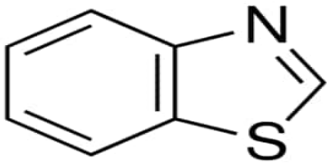

Figure 1. Benzothiazole structure

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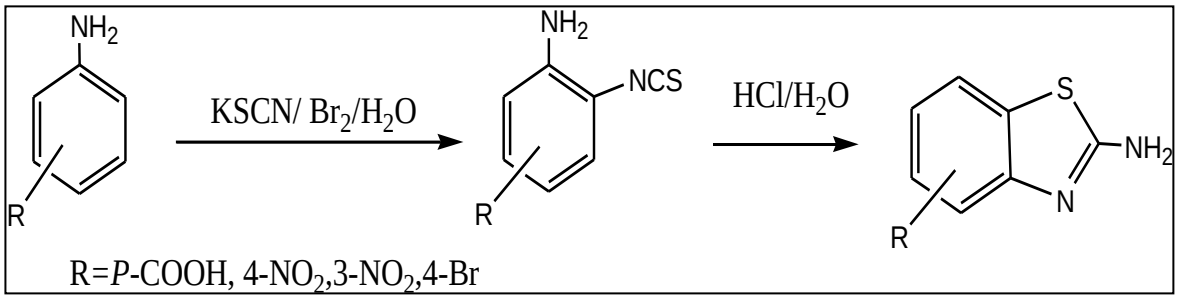
2-Aminobenzothiazole is commonly used as a portent in synthesizing drugs of medical significance. Benzothiazole plays a crucial role in medicinal chemistry and exhibits a wide variety of biological activities[1] such as those that are: "anti-cancer[2], anti-bacterial[3], anti-diabetic[4], anthelmintic[5], antitumour[6], anti-viral[7], anti-inflammatory[8-9], anti-parkinsonism[10], anticonvulsant[11], muscle relaxant activities, neuroprotective, inhibitors of several enzymes[12], antioxidant[13]. 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 [14].



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" [15-17]. 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 ^{1}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 ^{1}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) [18]

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) glycyl) 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

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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-yl) glycine (7) [18].
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.

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 [19]:
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[19]. Each test was performed three times.

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

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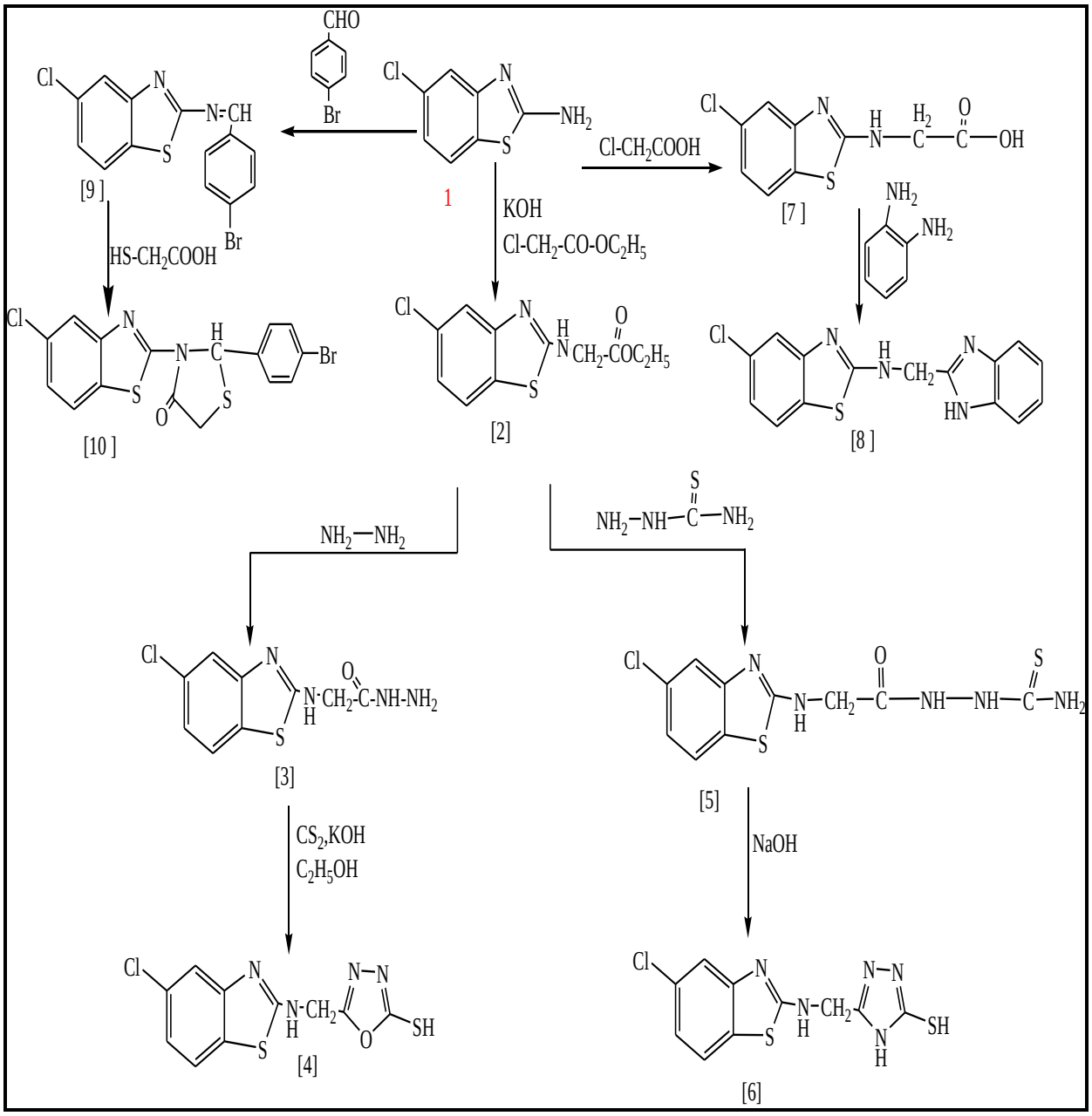

Scheme 2. Synthesis path for 2-amino-5-chlorobenzothiazol derivatives 2-10.

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.

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

Compound . No.	Colour	MP ˚C	Yield	IR Data (ν, cm^{-1}) KBr disc
2	yellow	208-210	77	3434 (ν N-H), 2925 (ν as, CH_2), 2854(ν s, CH_2), 1739 (ν C=O, ester), 1639(ν C=N),1300(ν C-N),1250(ν C-O),1040(ν C-S),820(ν C-Cl)
3	nutty	204-206	73	3398 asy. and 3329sy. (ν NH_2), 3280 (ν NH), 2928and2835 (ν CHalph.), 1653(ν C=O), 1629(ν C=N)),1023(ν C-S),890(ν C-Cl)
4	Brown	198-200	78	3361(ν NH),3041(ν CHarom.), 2978 and 2899 (νCHalph) ,2555(ν SH),1631(ν C=N), 1320(ν C-N)
5	white	183-185	90	3327(ν as NH),3322(ν s NH),3320 (ν NH), 1655 (ν C=O, amide), 1200(ν C=S).
6	red	190-192	84	3332 (ν NH), 2918 and 2899(ν CHalph.), 2550 (νSH), 1550 (νC=N).
7	White	222-224	91	3417(ν OH), 3195(ν NH), 2915 and, 2877(ν s CHalph.), , 1710 (νC=O) carboxyl, 1607(ν C=N).
8	Brown	235-237	89	3277and 3174(ν NH), 2926 (ν as CHalph), 3014 (ν CHarom.), 1683-1614(ν C=N).
9	white	212-214	75	1660 (νC=N), 1620 (νC=N) ,585 (νC-Br).
10	yellow	131-133	71	2964(ν CHalph.), 1615(ν C=O lactam ring),1588(ν 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	$C_{11}H_{11}ClN_2O_2S$	48.80	4.10	13.09	11.82	48.72	4.00	12.97	11.72
3	$C_9H_{10}ClN_4OS$	41.95	3.91	21.74	6.21	41.85	3.84	21.62	6.12
4	$C_{10}H_7ClN_4OS_2$	40.20	2.36	18.75	5.36	40.10	2.22	18.62	5.25
5	$C_{10}H_{11}ClN_5OS_2$	37.91	3.50	22.11	5.05	37.85	3.42	22.09	5.00
6	$C_{10}H_8ClN_5S_2$	40.34	2.71	23.52	-	40.22	2.63	23.45	-
7	$C_9H_7ClN_2O_2S$	44.54	2.91	11.54	13.19	44.48	2.85	11.47	13.08
8	$C_{15}H_{11}ClN_4S$	57.23	3.52	17.80	-	57.19	3.46	17.72	-
9	$C_{14}H_8BrClN_2S$	47.82	2.29	7.97	-	47.75	2.18	7.82	-
10	$C_{16}H_{10}BrClN_2OS_2$	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^{-1} 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^{-1}. The spectrum also showed the band at 3434.7 cm^{-1} corresponding to the stretching vibration of the NH group, and the appearance of sharp strong at 2925.4 cm^{-1}, and 2854.4 cm^{-1} attributed to the asymmetric and symmetric stretching vibration of the CH_2 group.

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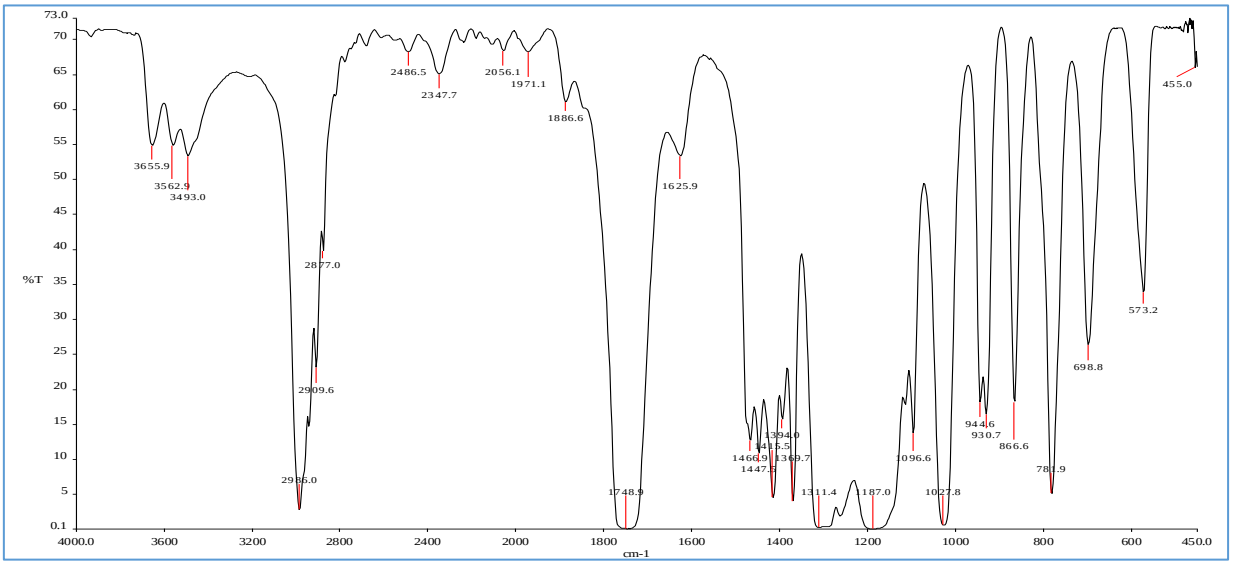

Figure 2. FT-IR spectrum of ethyl chloroacetate.

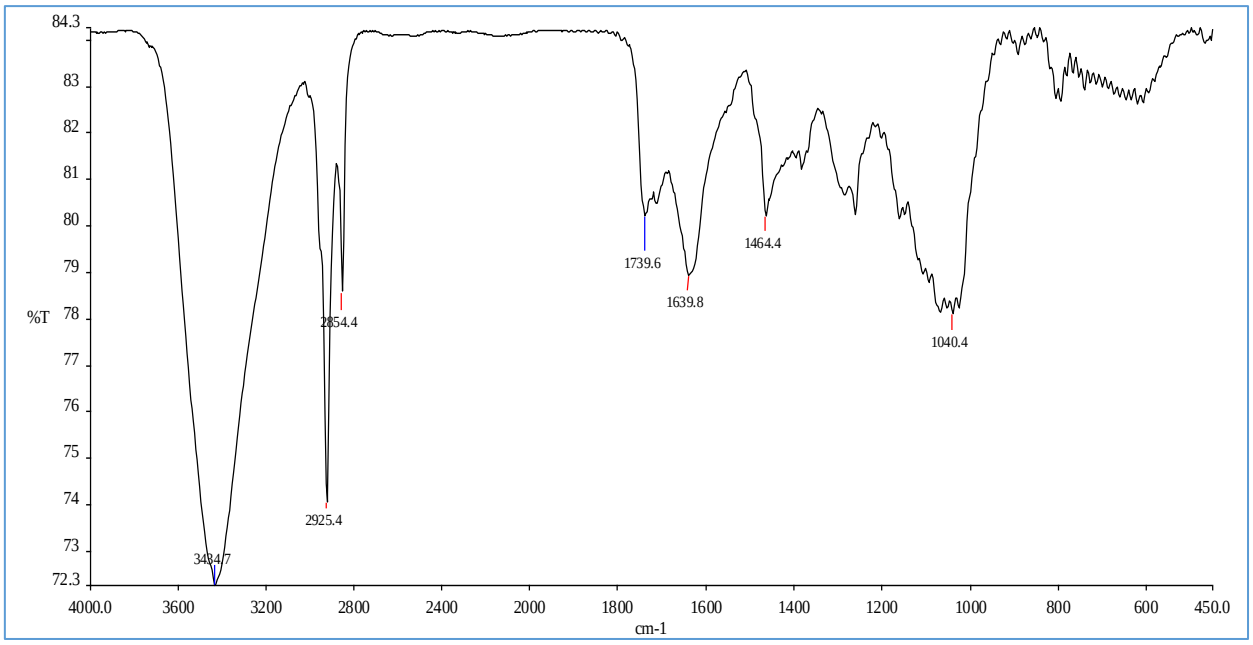

Figure 3. FT-IR spectrum of compound 2.

FT-IR spectrum of compound **8** showed the band at 3277 and 31740 cm^{-1} which were assigned to (NH) and (CH) aromatic, respectively. Band at 1614-1683 cm^{-1}due to ν (C=N)[20] Fig. 4.The FT-IR spectrum of compound **10** showed the band at 2964-2931 cm^{-1} attributed to the asymmetric and symmetric stretching vibration of the CH_2 group and the appearance of a sharp and strong group (C=O) band at 1615 cm^{-1} due to the stretching vibration of the carbonyl group and appearing strong band at the lower frequency at the 1588 cm^{-1} attributed to the stretching vibration of imine group (C=N), Fig. 5.

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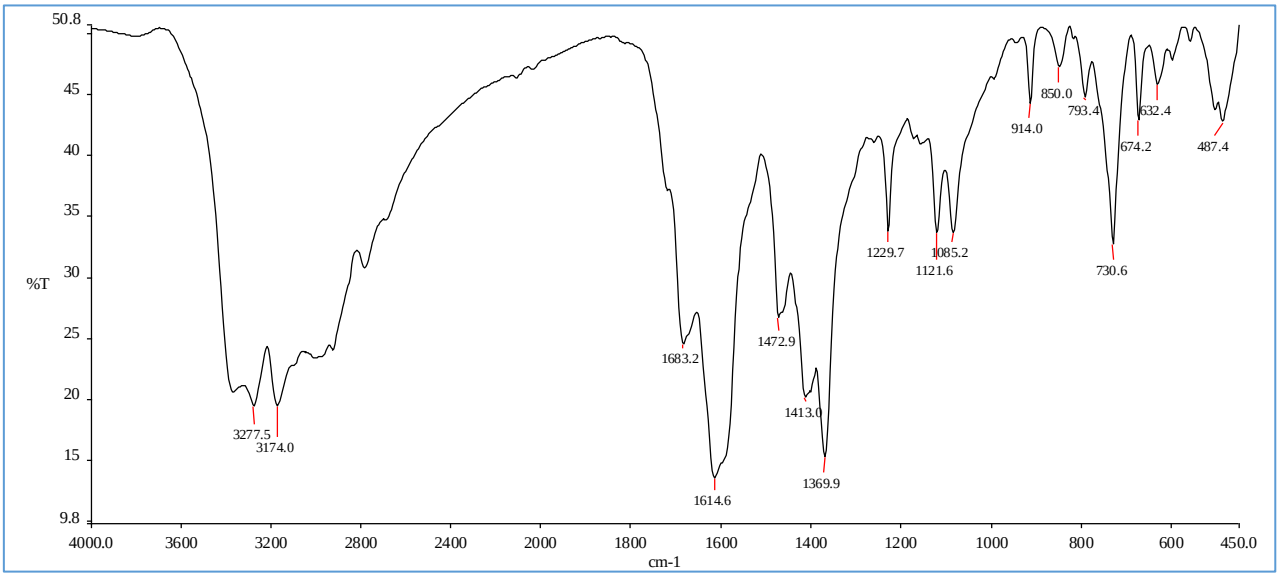

Figure 4. FT-IR spectrum of compound 8.

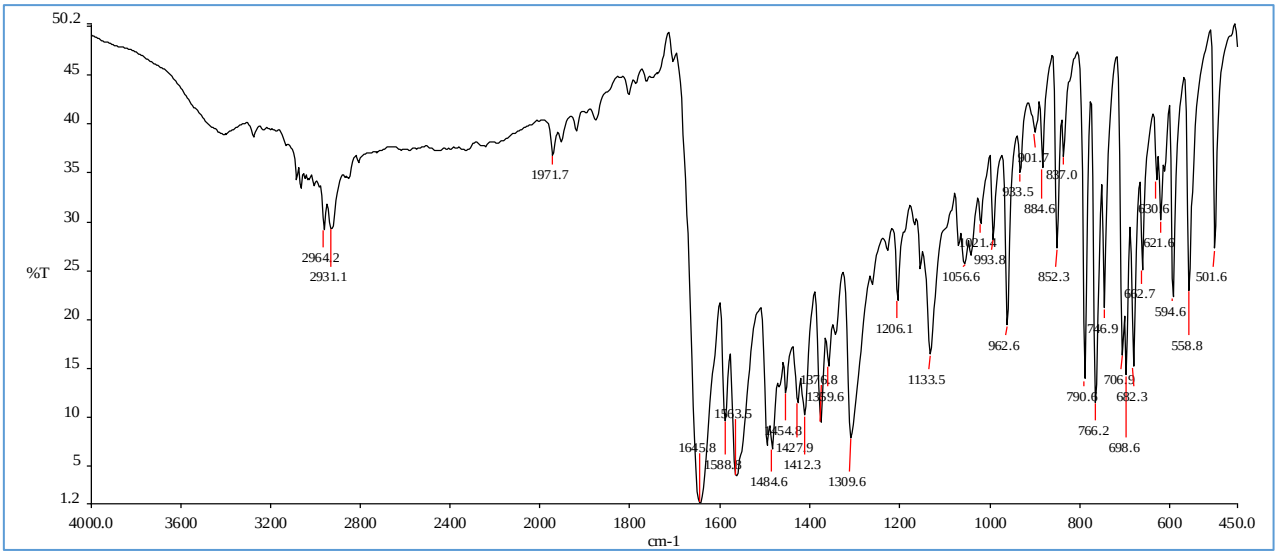

Figure 5. FT-IR spectrum of compound 10.

Figure 6 shows the ^{1}H-NMR spectrum for compound **4**, which showed the following signals at δ (ppm): Singlet signal at 4.3 ppm attributed to the CH_2 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.

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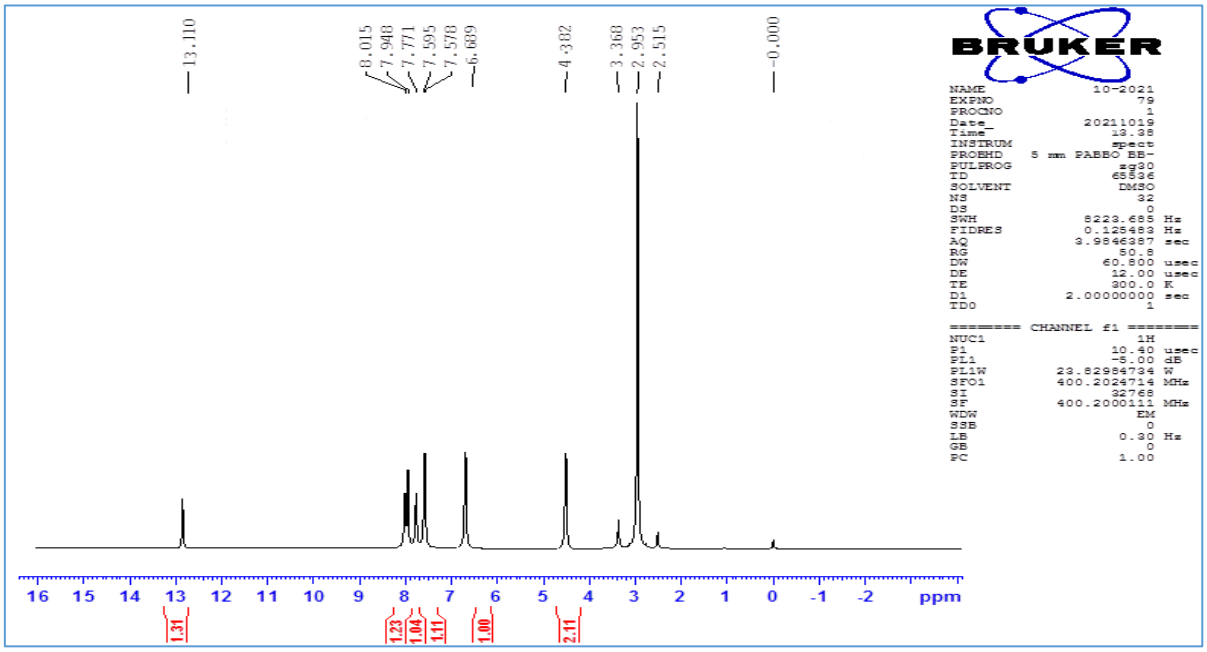

Figure 6. **^{1}H-NMR spectrum for compound 4**.

The ^{1}H-NMR spectrum of compound **6** illustrated in Fig. 7, which indicated the following signals: 4.2(s, 2H, CH_2); 6.8 (s,1H, NH); 7.5-8.0 (m, 3H, Ar-H); 11.1 (s,1H, NH); 13.0(s, 1H,SH).

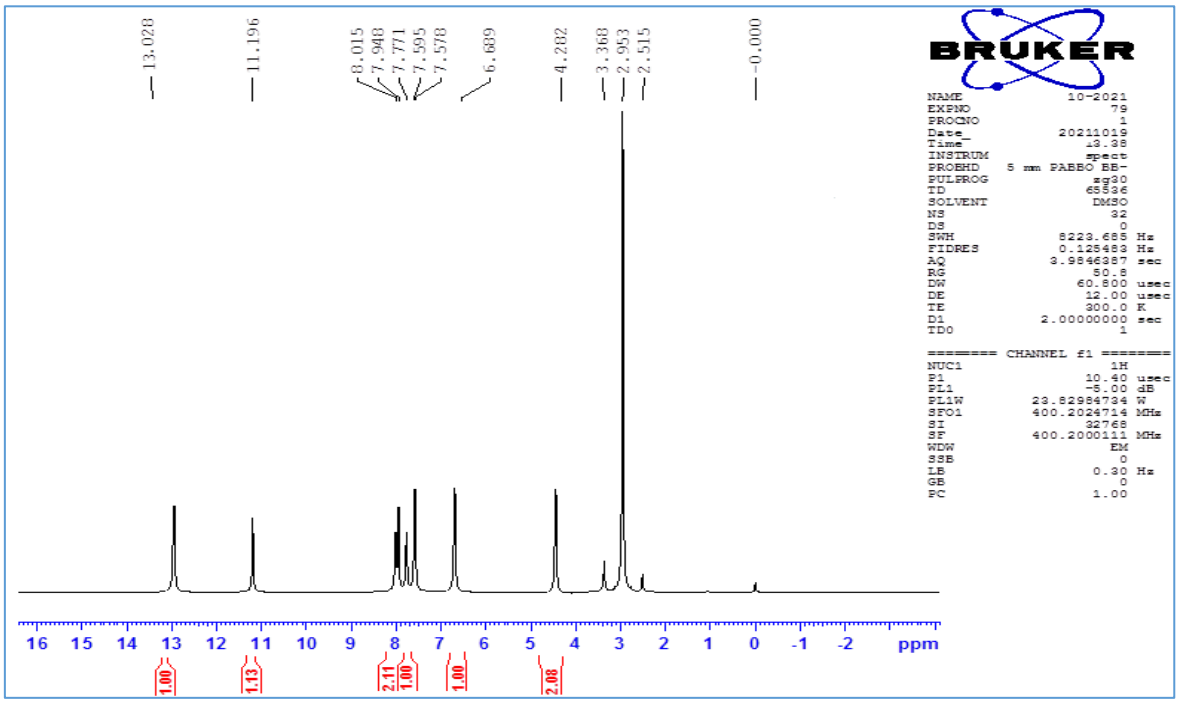

Figure 7. **^{1}H-NMR spectrum for compound 6.**

The ^{1}H-NMR spectrum of compound **8** Fig. 8, shows the following signal at 4.3 ppm assignable for CH_2, 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.

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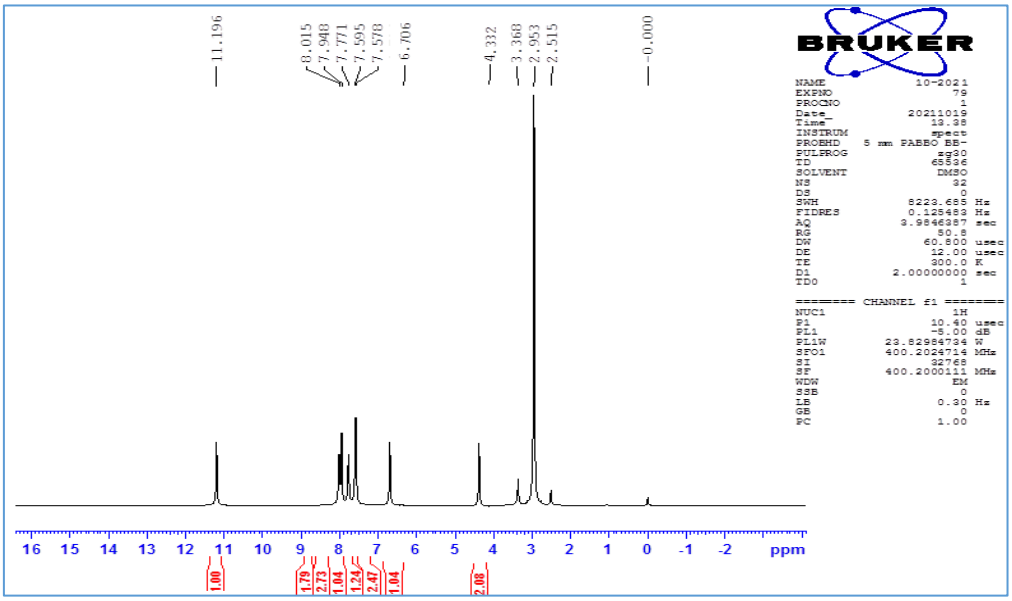

Figure 8. ^{1}H-NMR spectrum for compound 8.

The ^{1}H-NMR spectrum Fig. 9 for compound **10** showed a signal at 3.82-3.87) ppm (d,2H, CH_2); 6.4 (s,1H, CH); 7.14-7.19 (m,7H, Ar-H). Table 3 shows the chemical shift for the prepared compounds.

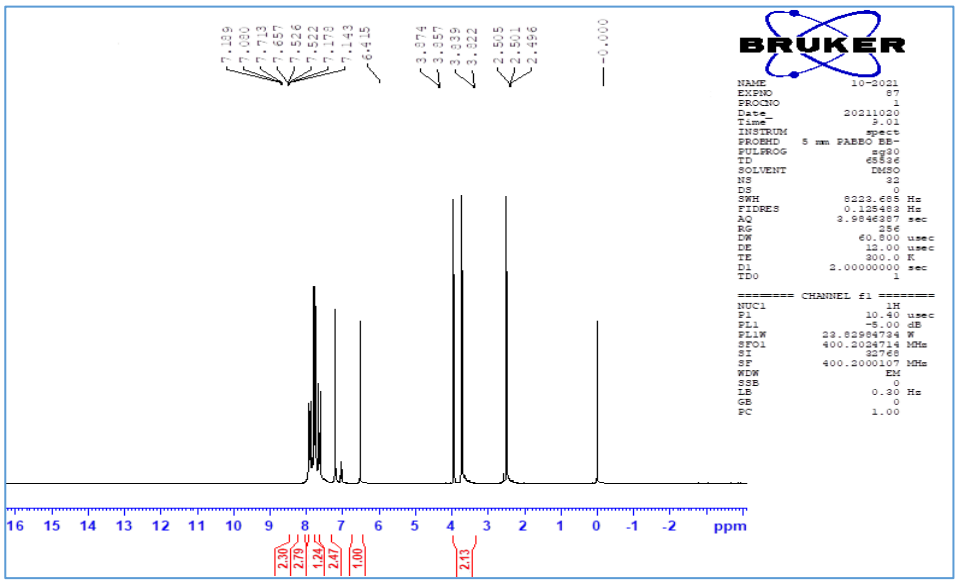

Figure 9. ^{1}H-NMR spectrum for compound 10.

Table 3. Chemical shifts of ^{1}H-NMR spectra for the prepared compounds

Comp. No	H^{1}-NMR (DMSO– d_6) δ ppm
4	4.3 (s,2H, CH_2); 6.6 (s,1H, NH) ;7.5-8.0 (m,3H, Ar-H);13.1(s,1H, SH)
6	4.2 (s,2H, CH_2); 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_2); 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**)**

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Biological Evaluation (Anti-fungal Activity):[21-24]

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[25-26]. All the prepared compounds showed significant results as anti- fungi 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.

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

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, ^{1}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.

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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.

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

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الخلاصة

تم في هذا البحث تحضير تسع مركبات جديدة من مشتقات 2-امينو-5-كلورو بنزوثايزول من خلال تفاعل2-امينو -5-كلوروبنزوثايزول **1**مع اثيل كلورواسيتيت بوجود KOH ليعطي مشتق2-امينو -5-كلوروبنزوثايزول استر**2** ادخل الاخير بعدة مسارات ، تفاعل مشتق الاستر مع هيدرازين هيدريت لتعطي مشتق الهيدرازايد**3** ومفاعلة المركب الاخير مع CS_2 بوجود KOH ليعطي مشتق 1,3,4اكساديزول-2-ثايول (**4**) بعدها تم مفاعله مركب الاستر المحضر مع ثايو سيمكاربزايد ليعطي مركب **5** ثم الغلق الحلقي بواسطه4%من هيدروكسيد الصوديوم ليعطي مشتق 1,2,4-ثايزول -3-ثايول **6** في مسار اخر تم مفاعله 2-امينو-5-كلورو بنزوثايزول مع حامض كلورو اسيتك اسد ليعطي مركب **7** الذي تم مفاعلته مع ارثو امينو انلين ليعطي بنزيميدازول **8**.تم الحصول على مشتق ازوميثين **9** من خلال تفاعل2-امينو6-كلوروبنزثايزول 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 الفيزياوية لكل المركبات المحضرة. كما تم فحص الفعالية البايولوجيه للمركبات المحضرة تجاه نوعين من الفطريات وأظهرت النتائج لبعض فعاليات قياسية جيدة بالمقارنة مع العقار القياسي فلوكينازول.

الكلمات المفتاحية: 2-امينو-5-كلوروبنزوثايزول ، مضاد للفطريات، بنزيميدازول ، اكسادايزول ، ثيازوليدين-4-اون ، تريازول.