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Synthesis and Characterization of some new heterocyclic derivatives from Aromatic Carbonyl Compounds and Carboxylic Acids with Evaluation Some of Them for Biological Activity

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Abstract

In this research investigation, a total of eighteen diverse tetra- and penta-lateral cyclic compounds were synthesized. These included 1,3,4-thiadiazole, thiazolidin-4-one (via an alternative method), 1,2,4-triazole, carbothioamide, thiazole-4-one, azetidin-2-one, and oxazole. The synthesis procedure entailed a sequence of reactions. The thiazolidine-4-one 1 was obtained by reaction p-aminobenzoic acid with thiosemicarbazide, followed by treatment with p-tolualdehyde to produce Schiff base 2. Reaction Schiff base 2 with mercaptoacetic acid in dry benzene was carried out to produce thiazolidine-4-one 3. In another synthesis pathway, the esterification of p-nitro benzoic acid with ethanol in the presence of sulfuric acid was obtained to formation of compound 4. Compound 4 was subsequently reacted with thiosemicarbazide, yielding compound 5. Cyclization of compound 5 was then achieved using 4% sodium hydroxide solution. This formed the 1,2,4-triazole heterocycle, designated compound 6. Thiosemicarbazone 7-9 were prepared by reaction of thiosemicarbazide with different aldehydes. Additionally, 2-substituted-1,3-thiazolidine-4-one derivatives 10-12 were synthesized through the reaction of thiosemicarbazone with chloroacetic acid in the presence of anhydrous sodium acetate. The Oxazole derivative 15 was obtained through a series of reactions starting with the reaction of p-amino benzoic acid with ethyl chloroacetate, resulting in compound 13. Compound 13 was then treated with urea to obtain compound 14, followed by a reaction with 4-phenyl phenacyl bromide to yield the final product, the Oxazole derivative 15. The 2-aminooxadiazole derivative 16 was synthesized by reaction urea with 4-bromoacetophenone which was reacted with 4-bromobenzaldehyde to produce Schiff base derivative 17. Finally, β-lactam 18 is obtained through reaction Schiff base with chloroacetyl chloride in the presence of triethyl amine. FT-IR, 1H-NMR, and 13C-NMR spectroscopy were used to confirm their proposed structures. Moreover, the antibacterial and antifungal activities of certain synthesized compounds, specifically 2,3,6,11,13,15,17, and 18, were assessed against Staphylococcus aureus, Escherichia coli, and Candida albicans, demonstrating encouraging outcomes.Keywords: Antibacterial, antifungal activity, oxadaizole, heterocyclic derivatives, Oxazole.

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تخليق وتشخيص بعض المشتقات الحلقية غير المتجانسة الجديدة من مركبات الكاربونيل الاروماتية والحوامض الكاربوكسيلية مع تقييم بعضها للفعالية البايولوجية

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الخلاصة

في هذا البحث تم تخليق ثمانية عشر من المركبات الحلقية المتنوعة الرباعية والخماسية. شملت ذه المركبات 1و3و4-ثاياديازول، ثايازوليدين-4-ون (باستخدام طريقة بديلة)، 1و2و4-ترايازول، كاربوثايامايد، ثايازول-4-اون ، ازيتيدين-2-اون و اوكسادايازول. تضمنت عملية التحضير سلسلة من التفاعلات. تم الحصول على ثايازوليدين-4-اون **1** عن طريق مفاعلته حامض بارا امينوبنزويك مع ثايوسيميكاربازيد متبوعا بمعاملته مع بارا تولوالديهايد للحصول على قاعدة شيف **2**. انتج تصعيد قاعدة شيف **2** مع مركبتو حامض الخليك بوجود البنزين الجاف ثايازوليدين-4-اون **3**. مسار تخليقي اخر، استرة حامض بارا نايتروبنزويك مع الايثانول بوجود حامض الكبريتيك ادى الى تكوين المركب **4**. تم تفاعل المركب **4** لاحقا مع ثايوسيميكاربازيد، مما ادى الى انتاج المركب **5**. تم الغلق الحلقي للمركب **5** باستخدام 4% من محلول هيدروكسيد الصوديوم. انتج ذلك 1و2و4- ترايازول المركب الحلقي غير امتجانس المعين **6**. تم تحضير ثايوسيميكاربازون **7-9** عن طريق تفاعل ثايوسيميكاربازيد مع الديهايدات مختلفة. بالإضافة الى ذلك، تم الحصول على مشتقات 2-معوض-1و3-ثايازوليدين-4-اون **10-12** من تفاعل ثايوسيميكاربازون مع حامض كلورواستيك بوجود خلات الصوديوم اللامائية .تم الحصول عى مشتق اوكسازول **15**من خلال سلسلة من التفاعلات تبدا بتفاعل حامض بارا امينوبنزويك مع اثيل كلورواسيتات لانتاج المركب **13**. ثم تم معاملة المركب **13** مع اليوريا للحصول على المركب **14**. يليه تفاعل 4-فنيل بروميد الفيناسيل لانتاج المركب، مشت اوكسازول **15**. تم تخليق مشتق 2-ازيتيدينون بعدة خطوات بدأت بالغلق الحلقي لبارا بروموانيتوفينون مع اليوريا لانتاج المركب **16** والذي تفاعل بعد ذلك مع بارابروموبنزالديهايد لانتاج المركب **17**. تمت معاملة قاعدة شيف **2** بكلوريد كلورواسيتيل بوجود ثلاثي اثيل امين لانتاج المركب **18**. تم تشخيص المركبات المحضرة طيفيا باستخدام FTIR , ^{1}HNMR و ^{13}CNMR مما يؤكد تراكيبها المقترحة. علاوة على ذلك، تم تقييم النشاط المضاد للبكتريا والفطريات لبعض المركبات المحضرة ، وتحديدا **2**، **3**،**6**،**11**،**13**،15،**17** و **18** ضد *Escherichia coli*،*Staphylococcus aureus* و *Candida albicans* مما اظهر نتائج داعمة.

1. Introduction

Heterocyclic compounds differ substantially from homocyclic compounds due to their incorporation of diverse elemental constituents beyond just carbon into cyclic structures. Whereas homocyclic rings contain only a single element, heterocycles feature carbon atoms together with other elements like oxygen, nitrogen, and sulfur [1]. As a result, heterocyclic compounds exhibit vastly greater diversity and structural complexity compared to their homocyclic counterparts. Within the heterocyclic family, several key members stand out exhibiting their essential properties as building blocks. Through heterocyclic modification, solubility, lipophilicity, polarity, and hydrogen bonding ability have proven to be important for optimal biologically active agents' Heterocyclic rings can incorporate elements other than just carbon into molecular architectures. These are in contrast to homocyclic compounds, which are stable in only one elemental structure. The ability of heterocycles to incorporate oxygen, nitrogen, and sulfur greatly expands their flexibility with respect to simple homocyclic structures. Because of the drug's inherent flexibility, medicines as attractive drug

candidates can have their basic ADME/Tox features optimized, leading to improved safety profiles and increased therapeutic efficacy. Pharmaceutical scientists and researchers are certainly on a remarkable path as a result of the integration of chemistry principles with the discovery and use of heterocyclic compounds. They are working continuous to bring chemical synthesis and environmental stewardship into harmony and to create a more environmentally conscious and sustainable drug development landscape [2–5]. The molecular structure of a compound profoundly influences its biological activity, and herein lies the allure of heterocyclic compounds, many of which feature the inclusion of sulfur [6-7] and nitrogen [8-10] atoms. Such compounds bear the potential to wield substantial pharmaceutical activity and manifest in diverse medical applications, thus underscoring their significance and multifaceted nature [11]. Extensive studies have elucidated the therapeutic effects of compounds harboring the 1,3,4-thiadiazole ring [12-13], shedding light on their prowess in combating a myriad of pathological states encompassing antibacterial, antimycotic, antitubercular, anti-Parkinson, cancer-fighting, anti-inflammatory, and anticonvulsant activities. [14-18].

The 1,2,4-triazole ring has been shown to have a wide range of pharmacological properties, including antibacterial and antifungal properties [19]. Meanwhile, thiazolidine-4-one heterocycles exhibit various effects on health such as antimicrobial, antifungal, antitumor, antidiabetic, anti-inflammatory, gastrointestinal issues and several different methods of producing heterocycles through cyclization reactions have been discussed in the medical literature [20-25]. For example, thiazoles have been synthesized by cyclization of thiourea with acetic acid under alkaline conditions. Alternatively, the thiazole is formed by the reaction of a Schiff base with glycolic acid. Tetrazole synthesis requires the cyclization of thiosemicarbazide under strong initial conditions. Furthermore, oxadiazole and β-lactam can be synthesized via different literature methods [26-31].

In this paper, eighteen diverse heterocyclic derivatives were successfully synthesized from aromatic carbonyl compounds and carboxylic acids. These synthesized derivatives were subjected to thorough evaluation for their biological effects, specifically targeting two types of bacteria (Staphylococcus aureus and Escherichia coli) and assessing their antifungal activity against Candida albicans. The characteristics of each individual derivative were meticulously examined, including FTIR spectra, melting point analysis, and for some compounds, ^{1}H-NMR and ^{13}C-NMR spectra at 500 MHz were also utilized.

2. Experimental part

2.1. Materials and Methods

All chemicals were obtained from Sigma-Aldrich and without further purification. The SHIMADZU FTIR-8400 Fourier transform infrared spectrophotometer was used with KBr disc in the Department of Chemistry, University of Tikrit. ^{1}H-NMR and 500 MHz spectrometer spectra were recorded using Varian ^{13}C-NMR in Iran.

2.2. Methods of the synthesis of compounds

*Protocol for synthesis of compound **1** [32]*

Thiosemicarbazide (0.001 mol, 0.091g) was stirred with 0.001 mol of benzoic acid derivatives in 10 mL absolute ethanol, in the presence of 2 drops of glacial acetic acid, for a duration of 3 hours, then the solution was cooled and the white precipitate was filtered and recrystallized from ethanol in 81% yield, which was characterized by m.p.177-179^{0}C. IR: 3432,3326(υNH_2), 3063($\upsilon CH_{aromatic}$),1678,1631(υC=N),1318 (υC-N) $_{aromatic}$.

*Protocol for synthesis of compound **2** [33]*

Compound 1 (0.001 mol, 0.178g) was dissolved in 10 mL of absolute ethanol, and to this solution, p-tolualdehyde (0.001 mol, 0.12g) was added in the presence of glacial acetic acid. The reaction mixture was refluxed for 4 hr. The formed solid product was filtered and recrystallized from ethanol to precipitate as yellow color in 90% yield, which was characterized by m.p.131-133°C. IR: 3323, 3155 (υ NH_2), 2915& 2830 (υCH $_{alphatic}$) 1622 (υ C=N), 3029 (υ CH $_{aromatic}$).

*Protocol for synthesis of compound **3** [34]*

A quantity of 0.001 mol of compound 2 and 0.004 mol (0.026 mL) of mercaptoacetic acid was refluxed in 15 mL of benzene for 12 hours. The mixture was concentrated and recrystallized by absolute methanol, the precipitate product was filtered off and washed with ethanol, dried to give compound **3** as yellow color in 73 %yield, which was characterized by m.p.212-214°C .IR: 3432, 3269(υNH_2), 2918, 2833(υ CH $_{alphatic}$),1610(υ C=O), 3042(υ CH $_{aromatic}$), 1644 (υ C=N).

*Protocol for synthesis of compound **4** [35]*

A blend comprising 0.002 mol (0.334g) of p-nitrobenzoic acid in 10 mL of absolute ethanol and 2 mL of sulfuric acid underwent reflux for 5 hours. The resulting residue was recrystallized in ethanol, yielding compound 4 in white colour with a 54% yield., which was characterized by m.p. 165-167 °C. IR: 2965(υasCH, CH_3), 2869(υCH, CH_3),1513 (υasC-NO_2),1330 (υsC-NO_2),1726 (υC=O),1610 (υC=C).

*Protocol for synthesis of compound **5** [36]*

A quantity of 0.001 mol (0.183 g) of compound 4 was stirred in 10 mL of absolute ethanol, following which 0.001 mol (0.091 g) of thiosemicarbazide was introduced into the mixture. The mixture was refluxed for 4 hrs., then the obtained precipitate was washed and recrystallized with ethanol to afford compound **5** as yellow in 69% yield, which was characterized by m.p.179-182 °C. IR: 3275 (υNH_2), 3173 (υNH), 3030 (υCH, $_{aromatic}$), 1681(υC=O),1411(υasC-NO_2),1366(υs C-NO_2),1226 (υC=S).

*Protocol for synthesis of compound **6** [37]*

A mixture of compound **5** (0.001 mol,0.24g) with (10 mL) of 4% sodium hydroxide was refluxed with continuous stirring for 4 hrs., then the solution was cooled and filtered and the precipitate was then recrystallized to afford compound **6** as yellow color in 81% yield, which was characterized by m.p.163-165°C. IR: 3443(υNH),2255 (υ SH),3066 (υ CH,$_{aromatic}$),1611 (υ C=N) , 1451, 1329 (υ C-NO_2).

*Protocol synthesis of compounds **7-9** [38]*

A mixture containing aromatic aldehydes (0.001 mol) in 15 mL of ethanol and thiosemicarbazide (0.001 mol), along with two drops of glacial acetic acid, was subjected to heating for 4 hours. Subsequently, the resulting precipitate underwent recrystallization in ethanol.

Compound **7**: Off White in 62% yield, m.p.233-235°C. IR: 3415,3260 (υNH), υ3265 (υNH),3444 (υOH),1327(υ C=S), 1631(υC=N),3039 (υ$CH_{aromatic}$).
Compound **8**: Brown precipitate in 93% yield, m.p.119 -121 °C. IR: 3445 (υOH), 3411, 3261(υNH), 3169 (υNH),1249 (υC=S), 3032(υCH $_{aromatic}$).

Compound **9**: Brown in 74%, m.p .179-181 °C. IR: 3331, 3160 (υNH_2), 3268 (υNH), 2917 (υCH $_{alphatic}$), 1229 (υC=S), 3013(υCH $_{aromatic}$).

*Protocol for synthesis of compounds **10-12** [39].*

A mixture of (0.001 mol) from thiosemicarbazone derivatives **7-9** compounds in 10 mL ethanol, (0.001 mol) chloroacetic acid and (0.001 mol) anhydrous sodium acetate was refluxed for 5 hrs., and separated solid was filtered off dried and crystallized to afford compounds **10**-**12**.

Compound **10:** yellow color in 85%, which was characterized by m.p.256-259 ºC. IR: 3465(OH), 3291(υNH), 1627(υCH=N) ,1571(υC=C).

Compound **11**: yellow color in 75%, which was characterized by m.p.240-242 ºC. IR: 3302(OH), 1683(υC=O), 1559(υCH=N), 3017 (υCH $_{aromatic}$)

Compound **12**: brown color in 63%, m.p.229-231 ºC. IR: 3397 (CH), 2975, 2889 (υCH $_{alphatic}$), 1629 (υC=N),1647(υC=O).

*Protocol for synthesis of compound **13** [40]*

A (0.002 mol, 0.246g) ethyl chloroacetate was added to a mixture of (0.002 mol,0.27g) p-amino benzoic acid and (0.002 mol, 0.112 g) triethyl amine in 10 mL absolute ethanol, refluxed for 4 hrs., which as recrystallized and produced compound **13** as brown color in 70 % yield, which was characterized by m.p.139-141°C. IR: 3304 (υOH), 2913, 2871, (υ $CH_{aliphatic}$),1089 (υ C-O),1712 (υC=O).

*Protocol synthesis of compound **14** [41]*

A mixture of (0.002 mol, 0.44g) from compound **13** was refluxed with (0.002 mol, 0.12 g) from urea dissolved in 15 mL absolute ethanol, refluxed for 13hrs., then the dried to give compound **13** as Cream in 65 % yield, which was characterized by m.p.229-231°C. IR: 3309 (υ OH), 3415, 3265 (υNH), 1622 (υC=O), 3033(υCH $_{benzene\ ring}$).

*Protocol for synthesis of compound **15** [42]*

Compound **14** (0.002 mol, 0.46g) was refluxed with 4- phenyl phenacyl bromide (0.002 mol, 0.46g) in 10 mL of ethanol and the reaction mixture was refluxed for 10 hrs. the formed solid was recrystallized using ethanol to produce compound **15** as Brown ppt.in 65 % yield, which was characterized by m.p 174-176 °C. IR: 3444 (υOH), 3189 (υ NH), 2811(υCH_2),1725 (υC=O),1613 (υC=N).

*Protocol for synthesis of compound **16** [43]*

A mixture of iodine (0.003 mol, 0.761g), urea (0.012 mol, 0.72 g) and (0.003 mol ,0.56 g) p-bromoacetophenone, the mixture was heated for 9 h. on water bath, cooled, washed by diethyl ether and solution of sodium thiosulfate to obtain compound **16** as brown color in 85 % yield, which was characterized by m.p.219-222 °C. IR: 3309, 3110(υ NH_2) ,1609(υ C=N), 3006 (υ CH $_{aromatic}$).

*Protocol for synthesis of compound **17** [44]*

A mixture of compound **16** (0.001 mol, 0.341g) and p-bromobenzaldehyde was dissolved in 10 mL ethanol then refluxed for 4 hrs. and cooled at room temperature. The solid product was filtered and recrystallized by ethanol to give compound **17** as yellow color in 89 % yield,

which was characterized by m.p.181-183ºC. IR: 3021 (υ $CH_{alphilic}$),1623 (υ CH=N), 1069 (υ C-Br),1601 (υ C=N).

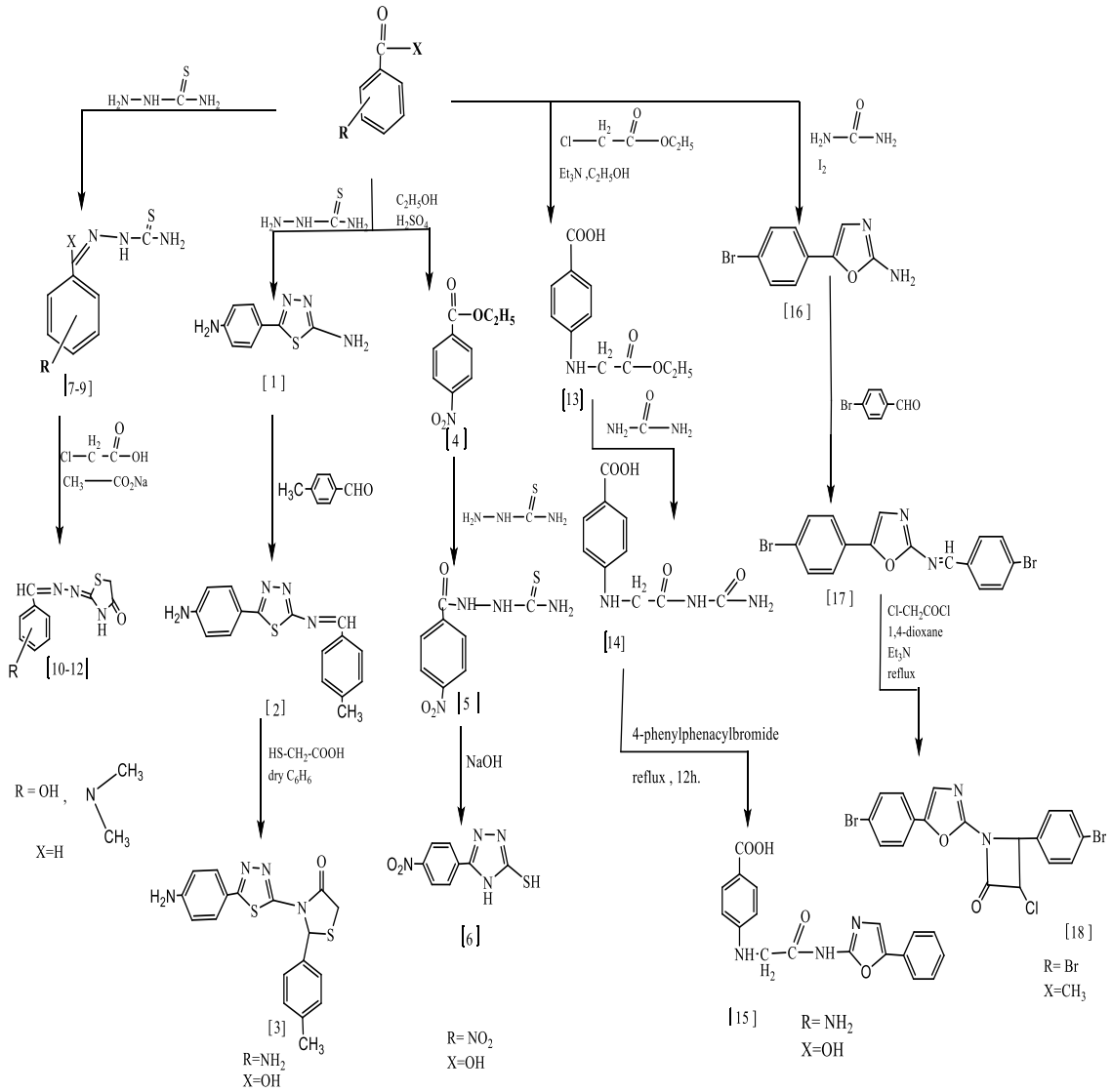
*Protocol for synthesis of compound **18** [45]*

A solution of compound **17** (0.001mol, 0.39g) and (0.002 mol, 0.2mL) triethyl amine in 15 mL of 1,4-dioxane was stirred and cooled then chloroacetyl chloride (0.002mol,0.22mL) was added drop wise at 10 ^{0}C. The reaction mixture was then stirred for an additional 4 h. and left at room temperature for 48 h. to give compound **18** as green-yellow color precipitate in 71 % yield, which was characterized by m.p.209-211ºC. IR: 3001(υ $CH_{aromatic}$),1666(υ C=O), 1611(υ C=N), 1031(υ C-Br),1001(υ C-Cl).

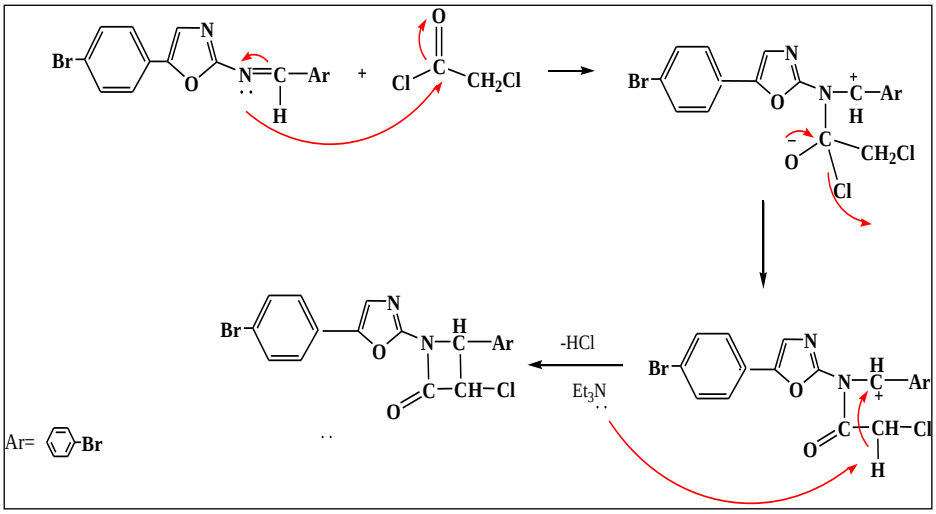
3. Results and discussion

This paper focuses on the synthesis and characterization of cyclic compounds by reacting derivatives of aromatic carbonyl with thiosemicarbazide, ethylchloroacetate, and urea

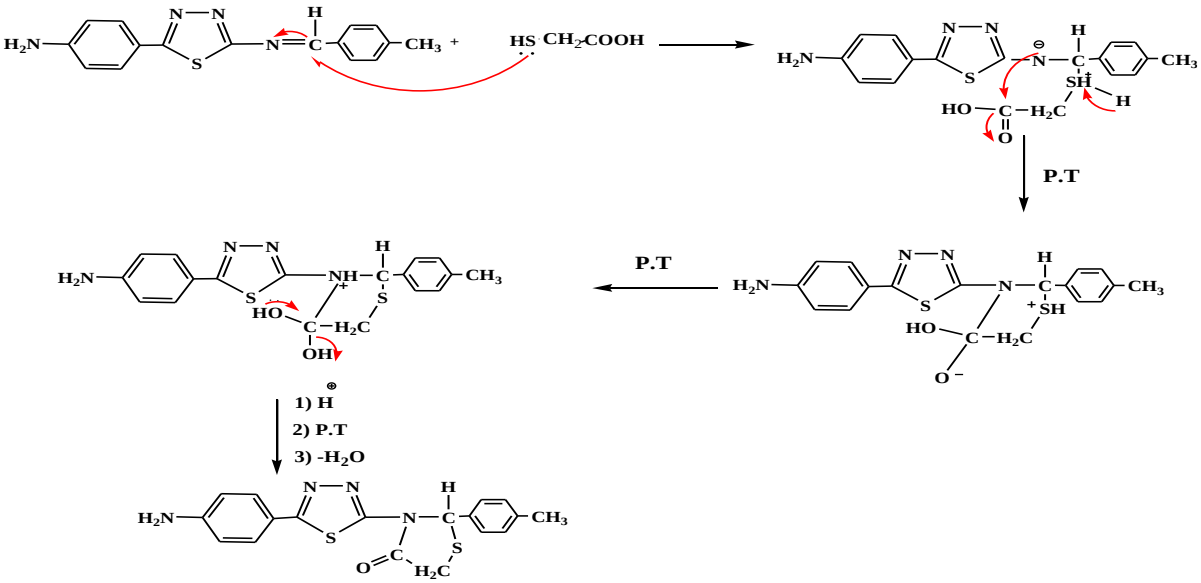
through cyclization reactions to produce (4,5)-membered rings (Scheme 1). Schemes 2 and 3 illustrate the ring-closure mechanisms for β-lactam and thiazolidine-4-one derivatives, respectively [46, 47].



Scheme 1: Schematic diagram of synthesized compounds **1-18**



Scheme 2: The mechanism of reaction for the synthesis of β-lactam derivative **18**



Scheme 3: The mechanism of reaction for the synthesis of thiazolidine-4-one derivative **3**

The structural confirmation of all the newly synthesized derivatives was conducted through spectroscopic methods, including IR, ^{1}H-NMR, and C^{13}-NMR. The spectra revealed signals and peaks corresponding to the functional groups present in some of the synthesized compounds listed in Tables 1 and 2.

Table 1: ^{1}H-NMR spectral data (δ, ppm) of the compounds **3**,**6**, **15**, and **18**

Compound No.	H^{1}-NMR (DMSO-d6) δ ppm
3	2.1(s,3H,CH_3), 3.8-3.9(d,2H,CH_2), 6.4(s,1H,CH), 6.5-7.7(m,8H,ArH), 5.2(s,2H,NH_2)
6	5.8(s,1H,NH), 8.1-8.3(m,4H,Ar-H), 10.9(s,1H,SH)
15	3.6(s,2H,$_{CH2}$), 6.1-7.9(m,13H,Ar-H), 10.5(s,1H,NH), 12.5(s,1H,OH)
18	5.0-5.4(m,1H,CH($_{B\text{-}Lactam}$)), 7.0-7.8(m,8H,Ar-H)

Table 2: ^{13}H-NMR spectral data (δ, ppm) of the compounds **3**,**6**, **15**, and **18**

Compound No.	C^{13}-NMR (DMSO-d6) δ ppm
3	$21.1(CH_3)_{group}$, $33.2(CH_2)_{group}$, $72(CH)_{thiazolidine\text{-}4\text{-}one}$, $115.1\text{-}145.3(CH)_{aromatic\ carbons}$,$173.8(C{=}O)_{thiazolring}$.
6	$124\text{-}155(CH)_{aromatic\ carbons}$, $180(SH)_{group}$.
15	$55.1(CH_2NH)_{group}$, $111.1(CH)_{aromatic\ carbons}$,$168(C{=}O)_{amide}$,$169(C{=}O)_{carboxylic\ acid.}$
18	$66.8(CH\text{-}Cl)_{B\text{-}Lactam}$, $62.3(CH_2)_{B\text{-}Lactam}$, $150\text{-}151\ (CH)_{oxazolring}$, $123.1(CH)_{carbon\ aromatic\ ring}$, $162\ (C{=}O)_{\ B\text{-}Lactam}$.

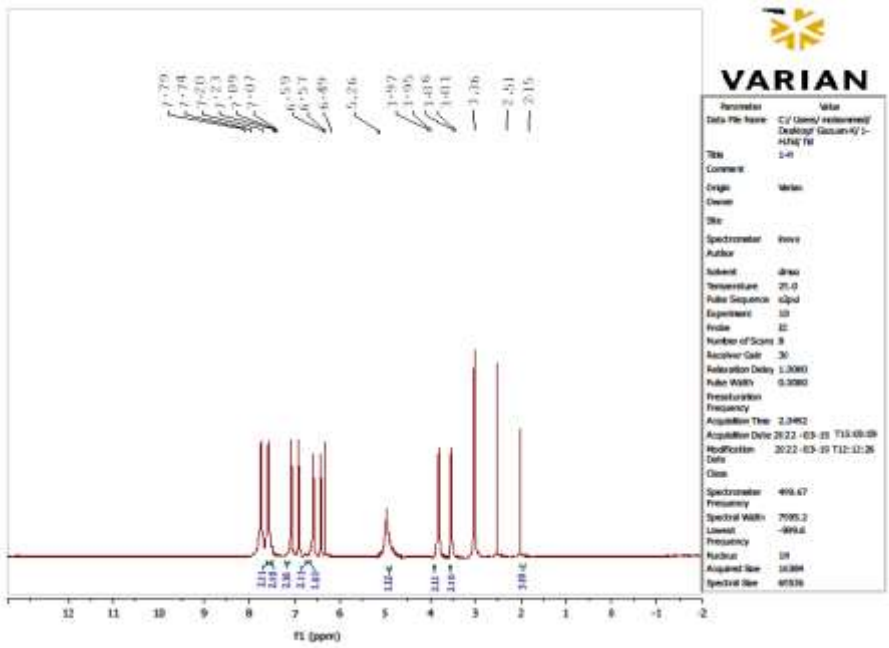


Figure 1: The ^{1}H NMR spectrum of compound **3**

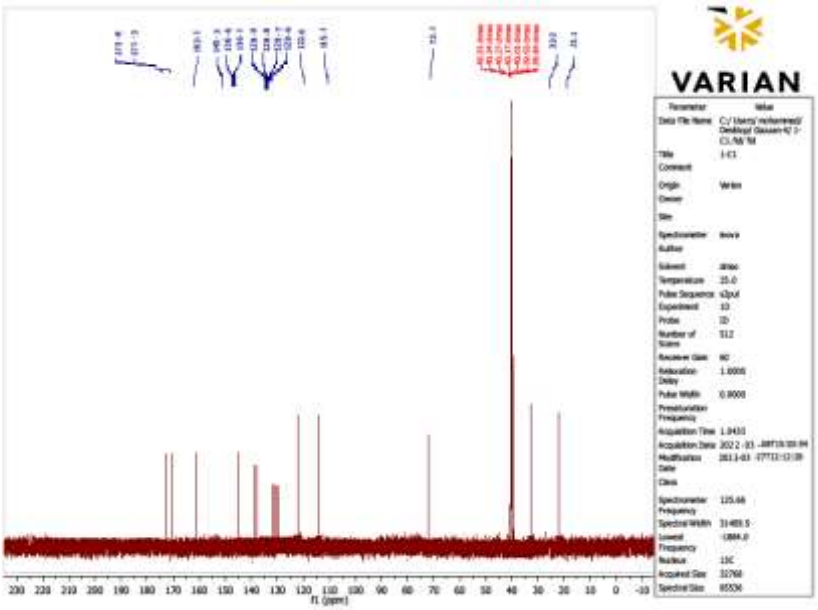


Figure 2: The ^{13}C NMR spectrum of compound **3**

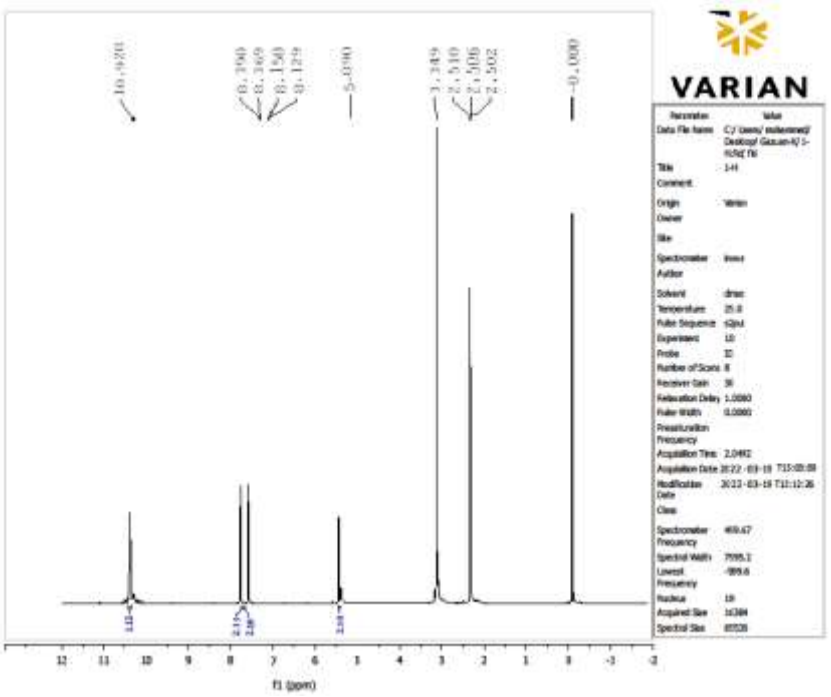


Figure 3: The ^{1}H NMR spectrum for compound **6**

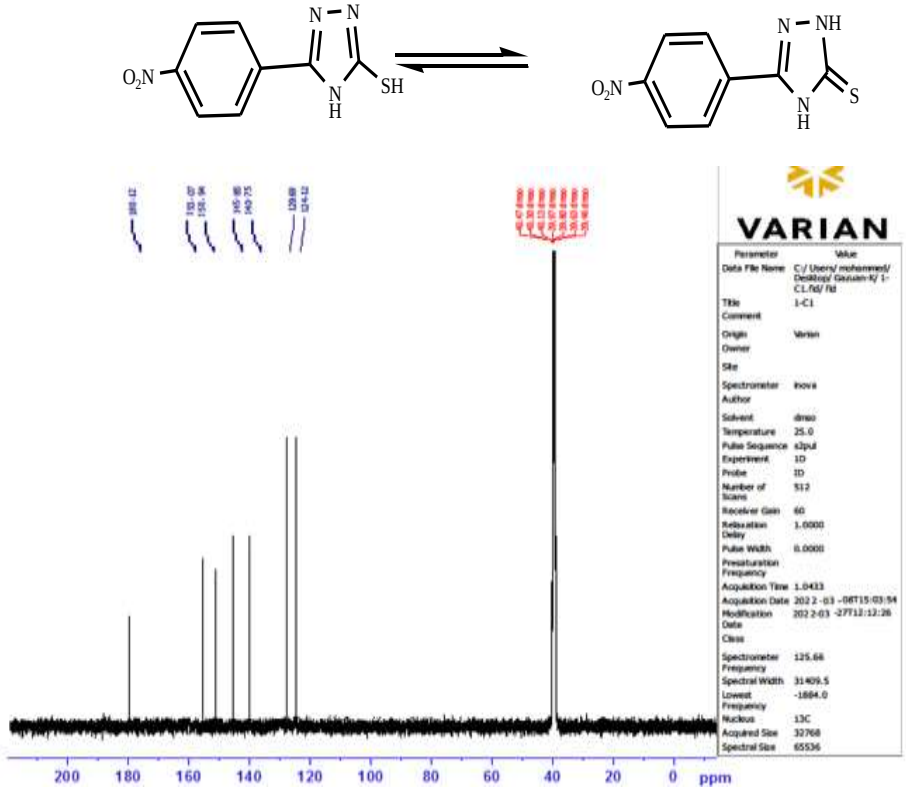


Figure 4: Thione - thiol tautomerism for compound **6**

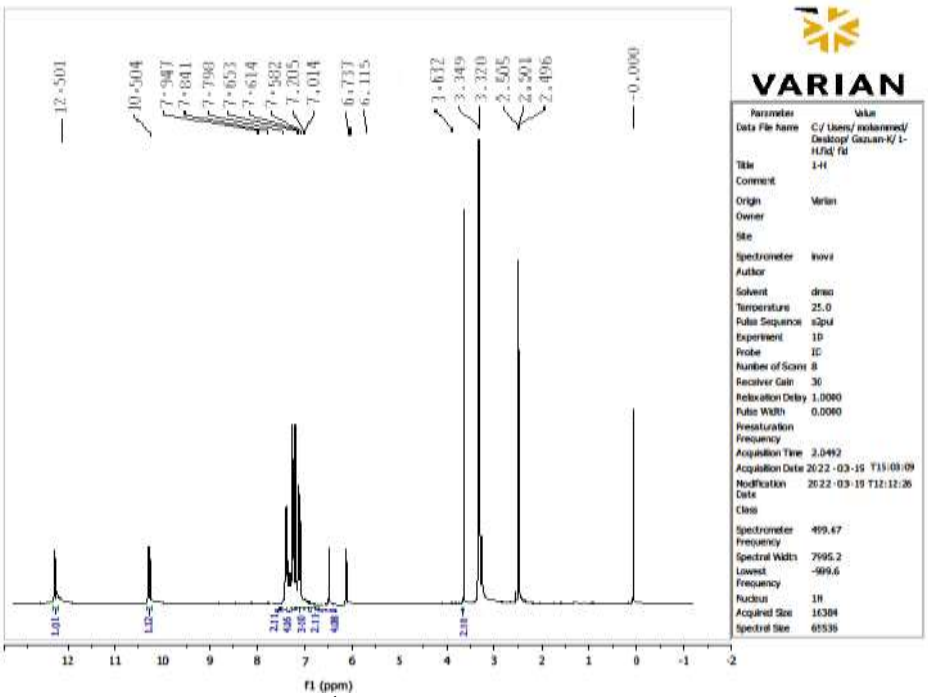


Figure 5: The ^{1}H NMR spectrum of compound **15**

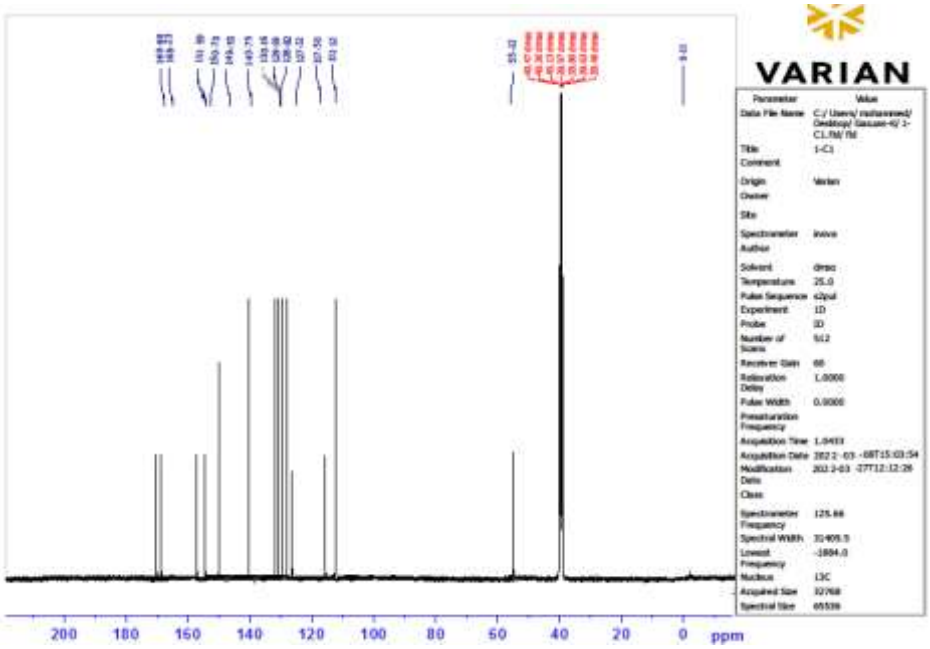


Figure 6: The ^{13}C NMR spectrum of compound **15**

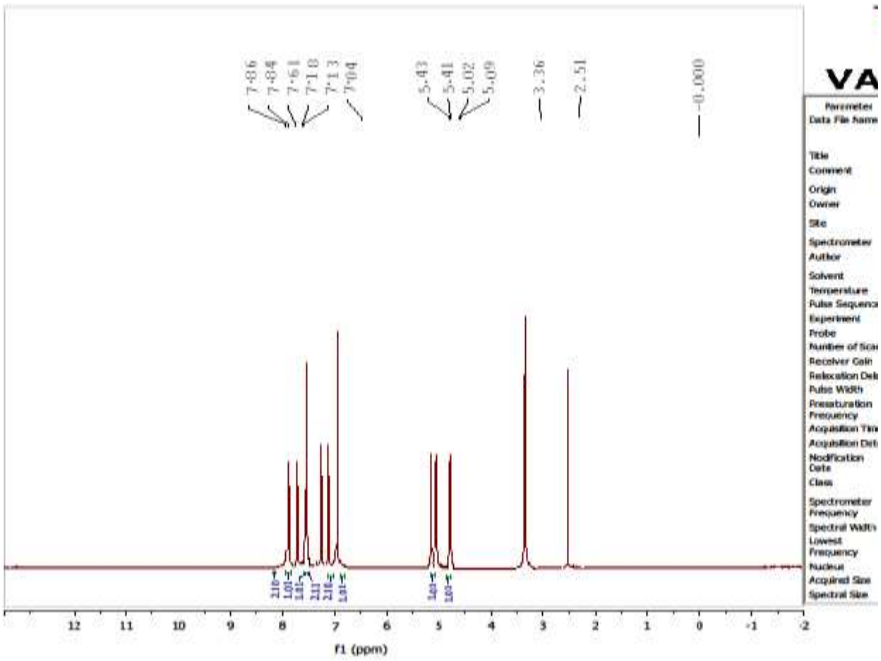


Figure 7: ^{1}H NMR spectrum of compound **18**

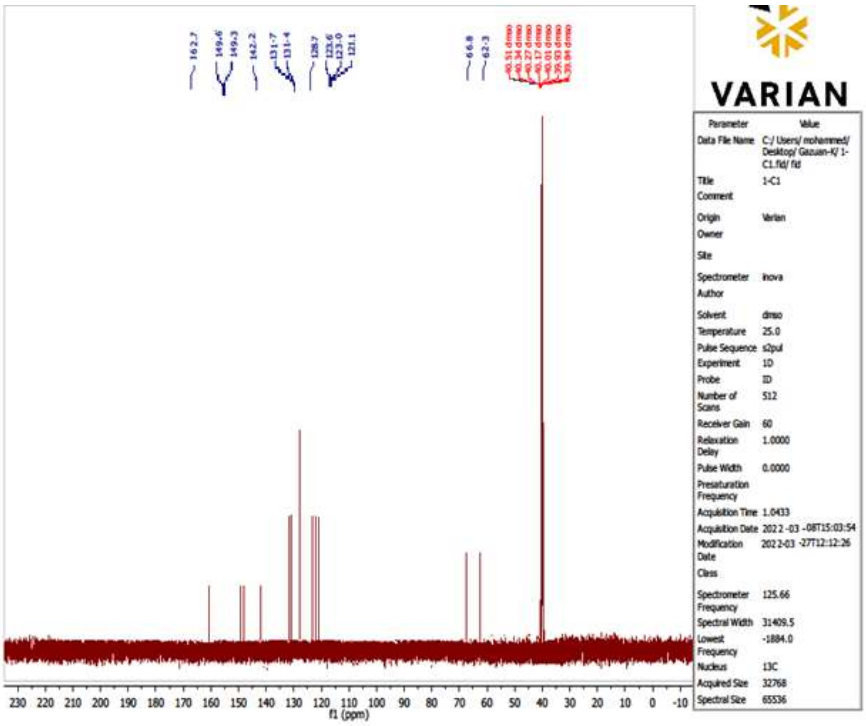


Figure 8: ^{13}C NMR spectrum of compound **18**

3.2. Biological Activity of some synthesized Compounds [48-50]

Some of the synthesized compounds were screened for their biological activities against both different type of bacteria ***E. Coli and Staphylococcus aureus*** and against fungal *Candida albicans* using their three concentrations in DMSO as solvent, the inhibition zones for these compounds are inserted in Tables 3 and Tables 4.

Table 3: Inhibiting activity of some synthesized compounds

Antifungal	Compounds	Zone of Inhibition (mm)		
		Concentrations (mg/mL)		
		50	**100**	**150**
Candida albicans	2	4	6	13
	3	5	8	17
	6	3	15	25
	11	13	17	21
	13	7	11	14
	15	17	22	27
	17	10	19	26
	18	22	29	33

Table 4: Effect of compounds on inhibition of gram-positive (*staphylococcus*) and gram-negative (*E.coli*) in mm unit.

Compounds		Bacteria (-) *E. Coli*			Bacteria (+) *Staphylococcus aureus*		
		Zone of Inhibition (mm)					
		Concentrations (mg/mL)					
		50	100	150	50	100	150
2		____	2	5	10	12	15
3		____	5	9	12	15	17
6		4	9	13	3	9	11
11		5	____	6	5	7	10
13		____	4	9	2	5	6
15		5	5	7	10	12	25
17		2	7	9	5	11	15
18		10	12	25	7	12	18
Chloramphenicol (30 mg/disc)	**Control**	18			15		
Gentamycin (10 mg/disc)		13			15		

Conclusion

The chemical structures of thiadiazole derivatives, thiazole, triazole, azetidin-2-one, and oxazole were confirmed through IR, H1-NMR, and C13-NMR spectra. These newly synthesized compounds exhibited promising capabilities in combating bacteria and fungi. Such compounds serve as crucial building blocks in diverse bioactive substances within medical, agricultural, and materials chemistry fields. In particular, the β-lactam **18** and oxadiazole **15** display a broad spectrum of biological activities including antibacterial and antifungal activity, compound18 showed a very good activity against antifungal and Escherichia coli whereas compound 15 showed a very good activity against *Candida albicans* and *Staphylococcus aureus*, and. The other prepared compounds showed different activities against the same previous types of bacteria and fungi showed different. Hence, it may be the better pharmacophore to explore the development of new bioactive moieties

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