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Original Article

Synthesis of New 1,3-Oxazole and 1,3-Thiazole Derivatives with Expected Biological Activity

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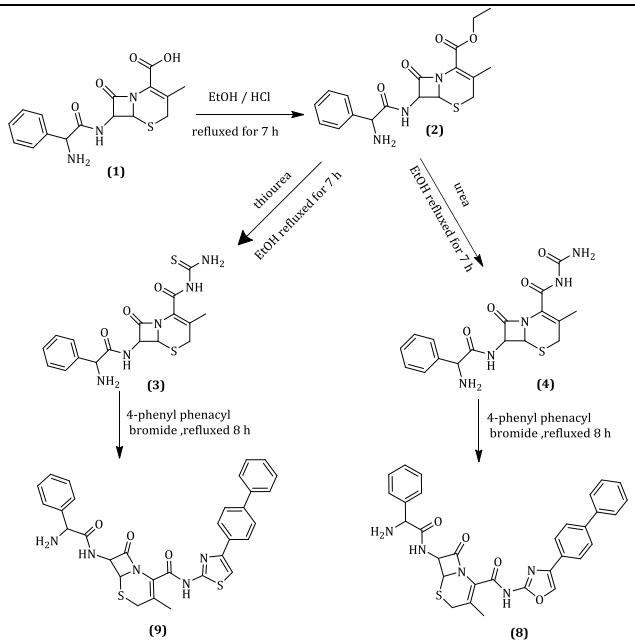
ABSTRACT

The novel compounds were prepared to start from cephalexin in this work. It was converted into five-membered rings (1,3-oxazole and 1,3-thiazole). The cephalexin was reacted with ethanol absolute and hydrochloride at first to obtain compound (**2**), and in the second step, compound (**2**) reacted with thiourea to obtain a compound (**3**), then compound (**2**) reacted with urea to obtain a compound (**4**); when compound (**4**) was reacted with 4-phenyl phenacyl bromide, we got 1,3-oxazole derivative from this reaction, also when compound (**3**) reacted with 4-phenyl phenacyl bromide in the presence of absolute ethanol, we got 1,3-thiazole derivative. The melting points of the synthesized compounds were recorded, the purity was checked by TLC, and the structures of the prepared compounds were identified by FT-IR and ^{1}H-NMR spectra. The biological activity of these compounds was tested.

GRAPHICAL ABSTRACT



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Introduction

1,3-Oxazole is distinctive five-membered nitrogen and oxygen-containing heterocyclic compound. The versatility of this heterocyclic ring system makes it an important class of heterocyclic compounds [1].

Oxazole, the utility of oxazole as intermediates for the synthesis of synthesizing new chemical entities in medicinal chemistry, have been has increased in the past few years. Oxazole is an essential heterocyclic nucleus having with a wide spectrum of biological activities which. It drew the attention of researchers around the globe to synthesize various oxazole derivatives and screen them for their various biological activities. The present review article aims to review the work reported on the therapeutic potentials of oxazole scaffolds which are valuable for medical applications during the new millennium. It was first made in 1947. Substitution patterns in oxazole derivatives are essential for determining biological activity, for example, antibacterial, anti-cancer, antitubercular, anti-inflammatory, antidiabetic, antiobesity, and antioxidant, among others [2].

Thiazole is a five-membered aromatic heterocyclic chemical molecule with the molecular ring formula C_3H_3NS. Hantzch and Weber were the first to describe thiazole in 1887. In 1889, Prop verified its structure. The sulfur atom is the starting point for thiazole numbering. Numerous publications have been published highlighting their chemistry and pharmacological applications. In thiazoles, the Pi-electron delocalization is more significant than in equivalent oxazole's [3]. Free thiazole is a light-yellow liquid with a pyridine-like smell**.** Thiazole derivatives are one of the most active groups of chemicals with a wide range of applications, such as antibacterial activity [4], antifungal properties [5], antimalarial properties [6], antitubercular action [7], antiviral action [8], anti-inflammatory activity [9], antidiabetic activity [10]. Anthelmintic action [11-17], anticonvulsant action [12,18], antioxidant activity [13-19] and as well as anti-cancer properties [14-20]. Many thiazole scaffolds, such as commercialized anti-cancer medicines, have been discovered to have solid antitumor efficacy [15].

Materials and Methods

The melting points (°C) of all the materials are unadjusted. A Perkin-Elmer spectrophotometer was used to measure the FT-IR spectra. On a 400 MHz device, the ^{1}H-NMR spectra were acquired. TMS was used as the internal reference while DMSO was used as the solvent. Melting points (°C) were determined using Gallen Kamp melting point equipment with a heated stage, and no adjustments were made. Infrared spectra were captured using a Fourier Transform infrared SHIMADZU (8300) (F.T.IR) infrared spectrophotometer, and KBr discs were examined using a SHIMADZU (8400) (F.T.IR) infrared spectrophotometer (Ibn -Sina company, Baghdad-Iraq). Fertigfollen precoated sheets type polygram Silk was used for thin-layer chromatography (TLC), and the plates were produced using iodine vapor. Thiourea, urea, and 4-phenyl phenacyl bromide were utilized in the experiment.

General synthetic procedures

*(A) Synthesis of ethyl 7-(2-amino-2-phenylacetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate (**2**)*

By dissolved 7 g from 7-(2-amino-2-phenyl acetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (**1**) in 25 mL pure ethanol with hydro chloride added. The mixture was then refluxed for 5 hours while being monitored using TLC. The compound (**2**) was then cooled, the surplus solvent was evaporated, and the product produced was collected. Darkorange, yield: 79%, mp 96-98 °C.

*(B) Synthesis of 7-(2-amino-2-phenyl acetamido)-N-carbamothioyl-3-methyl-8-oxo-5-thia-1-azabicycle [4.2.0] oct-2-ene-2-carboxamide (**3**)*

Combining thiourea (0.2 g) with 1 g ester (**2**) in pure ethanol (25 mL), after confirming through TLC, the mixture was refluxed for 7 hours to obtain the solid compound (**3**) as a result of

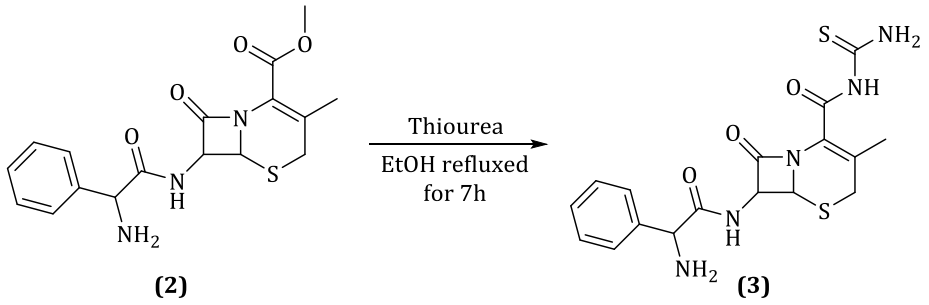
solvent evaporation (Scheme 1). Light brown, yield: 78%, mp 72-74 °C.

*(C) Synthesis of 7-(2-amino-2-phenylacetamido)-N-carbamoyl-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxamide (**4**)*

Through combining urea (0.168 g) with 1 g ester (**2**) in pure ethanol (25 mL). After confirming through TLC, the mixture was refluxed for 7 hours. To obtain the solid (**4**) as a result of solvent evaporation (Scheme 2). Brown, yield: 85%, mp 52-54 °C.

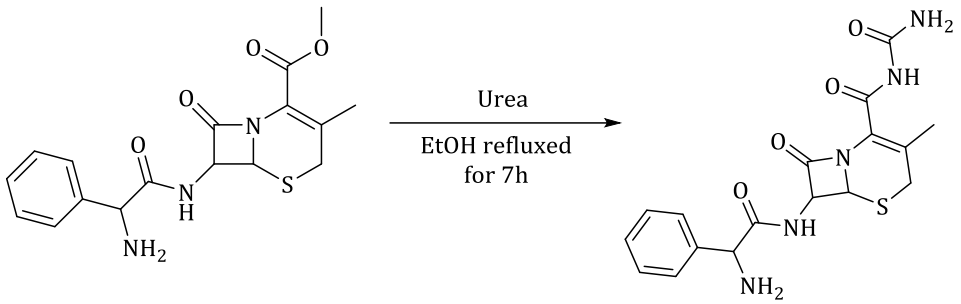
*(D) Synthesis of N-(4-([1,1'-biphenyl]-4-yl) oxazol-2-yl)-7-(2-amino-2-phenylacetamido)-3-methyl-8-oxo-5-thia-1-azabicycle [4.2.0] oct-2-ene-2-carboxamide (**8**)*

The chemical compound (**8**) was synthesized by dissolving compound **4** (0.5 g) in pure ethanol (25 mL) and then adding 4-phenyl phenacyl bromide (0.370 g). After that, the mixture was allowed to reflux for 8 hours [with TLC monitoring; ethanol]; The precipitate was then filtered before being recrystallized with ethanol absolute recrystallizing with absolute ethanol (Scheme 3). Light brown, yield: 81%, mp 58-60 °C.



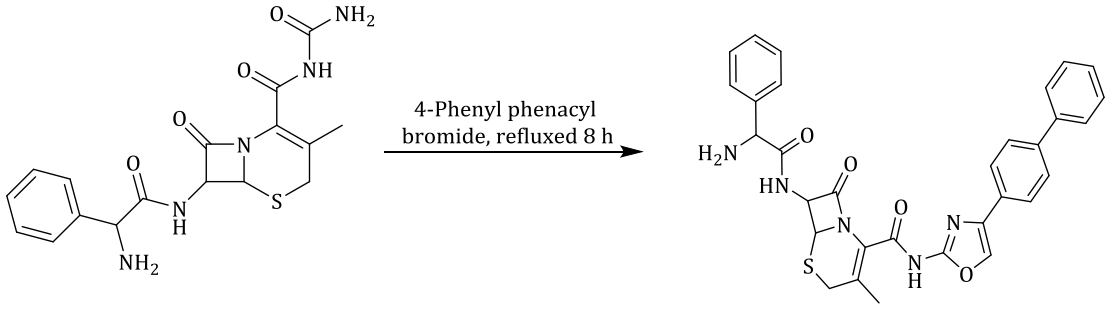
(2) **(3)**

Scheme 1: Synthesis of compound **3**



(2) **(4)**

Scheme 2: Synthesis of compound **4**

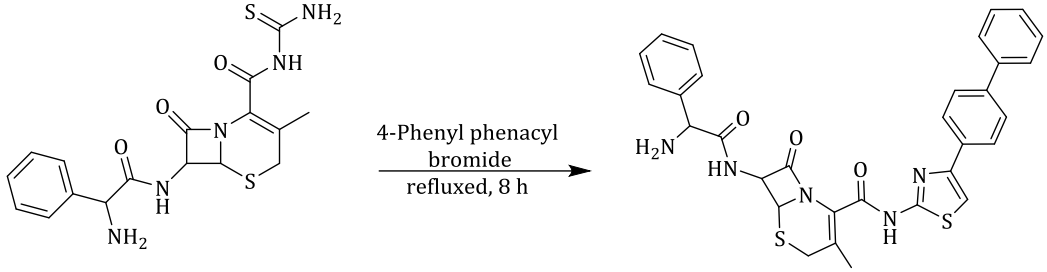


(4) **(8)**

Scheme 3: Synthesis of compound **8**

*(E) Synthesis of N-(4-([1,1'-biphenyl]-4-yl) thiazol-2-yl)-7-(2-amino-2-phenylacetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxamide (**9**)*

The chemical compound (**9**) was synthesized by dissolving compound **3** (0.5 g) in pure ethanol (25 mL) and then adding 4-phenyl phenacyl bromide (0.370 g). After that, the mixture was left to reflux for 8 hours [monitored by TLC; ethanol], The precipitate was then filtered before being recrystallized with absolute ethanol (Scheme 4). Pale golden, yield: 96%, mp 116-118 °C.



(3) **(9)**

Scheme 4: Synthesis of compound **9**

Results and Discussion

The melting temperatures of the synthesized compounds were recorded, and the purity was confirmed using FT-IR and ^{1}H-NMR spectra. The FT-IR spectrum reveals that the hydroxyl group (O-H) has disappeared at 3300 cm^{-1} and the band appeared at 1762 cm^{-1} due to the carbonyl ester group in the compound (**2**) and we can the results of infrared spectroscopy showed bands other as in Table 1, ^{1}H-NMR spectrum for compound **2** shows the following distinctive chemical shifts: At 7.54-7.31 ppm the aromatic ring protons emerged as numerous signals, a signal at 4.97 ppm as a result of the O-CH_2- group, at δ 1.96 ppm due to the -CH_3 group, the signal at δ 2.49 ppm for Me, δ 9.57 ppm NH_2, at δ 9.55 ppm for NH, at δ 4.98 ppm for Ar-CH-NH_2 at δ 5.05 ppm =N-CH- and at δ 4.98 ppm for -CH-S-. ^{1}H-NMR of compounds (**3**), (**4**), (**8**), and (**9**) are listed in Table 2. Compound (**3**) is prepared by reacting an ester compound (**2**) with thiourea in the presence of ethanol in its pure for; for 7 hours, the mixture was refluxed. The FT-IR spectrum of compound (**3**) in this reaction appears in a new band at 1091 cm^{-1} for the C=S group in thiourea added with a disappearing band at 1226 for C-O from compound **2**, and other bands found as in Table 1.

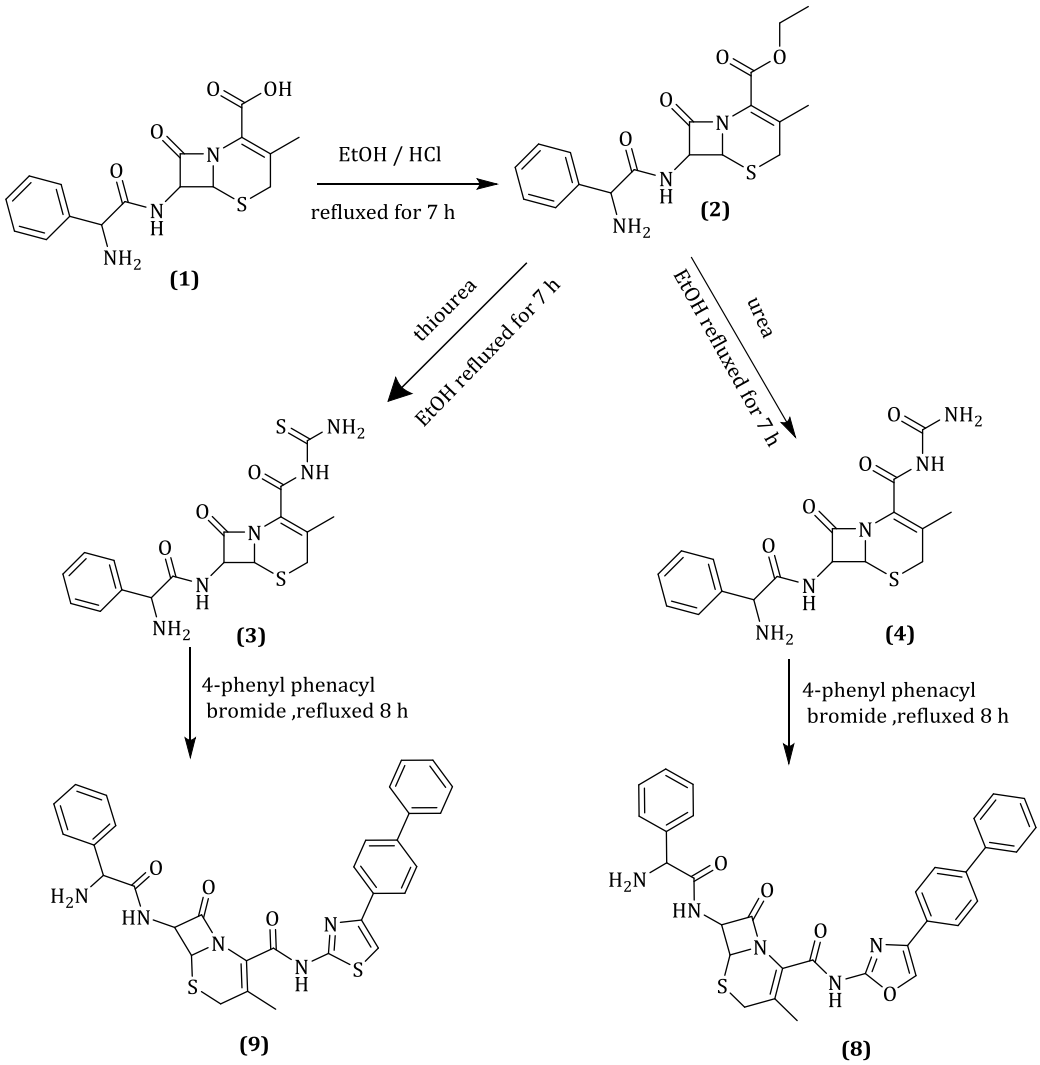
A plausible mechanism for the new synthesis of oxazole and thiazole derivatives are is shown in Schemes 5, 6 and 7.

Table 1: FT-IR of compounds

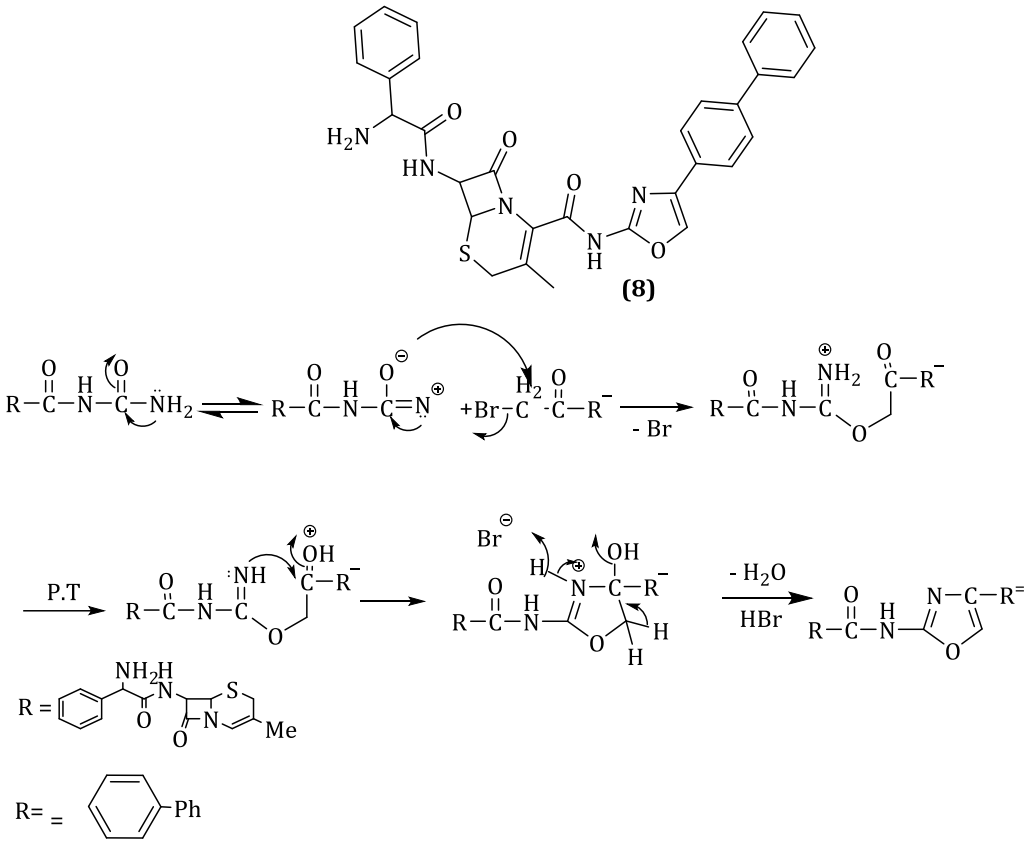
No.	NH	NH_2	C=O	C=C	(C-H) aromatic	(C-H) aliphatic	Others
1	3421	3271-3213	1759	1689	3043	2931-2885	OH (3300)
2	3400	3224	1762	1685	3062	2974-2939	C-O (1226)
3	3500	3464-3414	1732	1685	3217	2981-2931	C-S-C (1234-1215)
4	3460	3356	1732	1670	3062	2981-2935	C-S-C (1246-1215)
8	3400	3209	1732	1685	3032	2978-2935	C=N (1697)
9	3379	3263-3116	1690	1624	3035	2981-2862	C=N (1678)

Table 2: ^{1}H-NMR of compounds

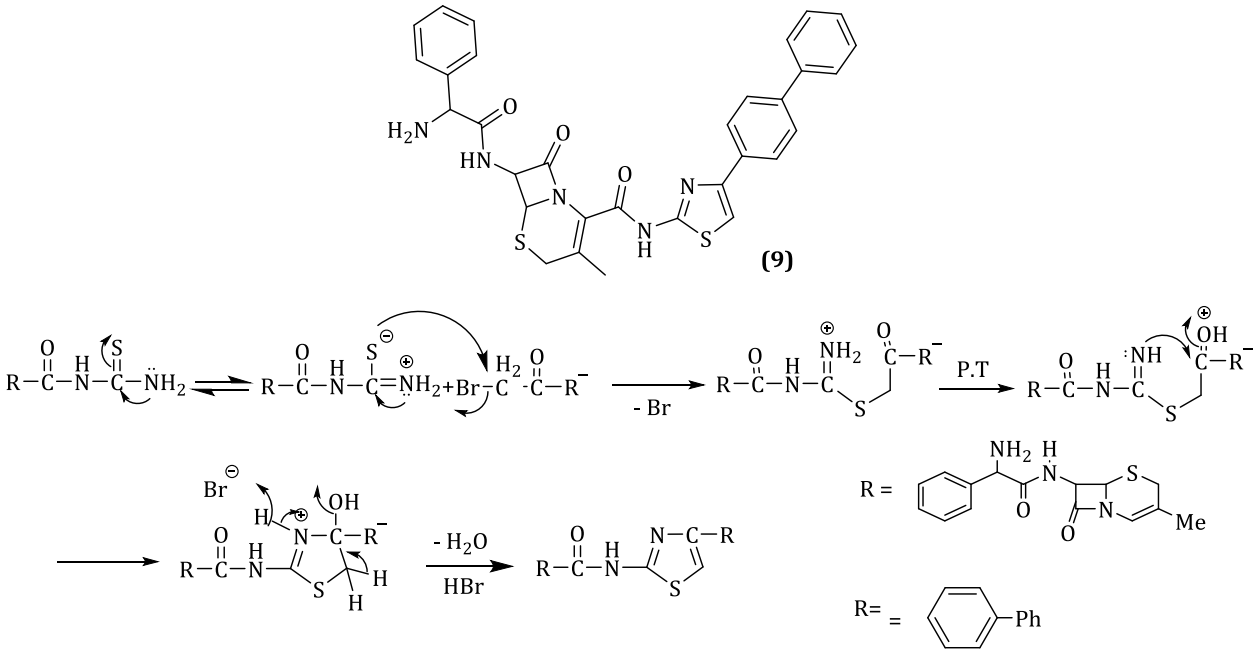
No .	NH_2 (ppm)	NH (ppm)	H-aromatic (ppm)	N-CH- (ppm)	-CH-S- (ppm)	S-CH_2- (ppm)	CH_3 (ppm)	Others peaks (ppm)
3	8.77	8.64	7.32 - 8.51	5.44	5.00	4.97	2.33	-N-CH- (4.97) (-NHCSNH_2) NH (8.97) NH_2 (8.84)
4	8.68	8.65	7.87 - 7.33	4.97	5.44	5.00	2.33	-N-CH- (4.97) (-NHCONH_2) NH (8.77) NH_2 (8.57)
8	8.08	8.06	7.39 - 8.03	5.43	5.26	4.85	2.50	-N-CH- (4.85) CO-NH (8.12)
9	7.83	7.81	7.02 - 7.79	5.44	5.27	4.82	2.50	-N-CH- (4.88) CO-NH (7.86)



Scheme 5: Synthesis of new oxazole and thiazole derivatives



Scheme 6: The mechanism of the reaction for compound **8**



Scheme 7: The mechanism of the reaction for compound **9**

Biological activity

Antibacterial activity of several of the generated compounds was examined in vitro against four pathogenic strains: Bactria *S.aureus* (G+), *Bacillus* (G+), *E.coli*, and *K.pneumoniae* using the appropriate diffusion method (G-). The

obtained data revealed that several of these substances had quantifiable activity, as shown in Table 3, and the imaging of the biological activity of bacteria (G + and G-) and activity of fungi are shown in Figure 1.

Table 3: Bacteria s.aureus (G+), Bacillus(G+), E.coli, and Klebsiella pneumonia (G-)

Number.	*sample code*	*Sample*	*E. coli (G -)*	*K.pneumonia (G -)*	*S. aurus(G+)*	*Bacillus(G+)*	*Cndidaalbicas (Fungl)*
1	A	**2**	+++	+++	+++	+++	++
2	C	**3**	+++	+++	+++	+++	++
3	F	**4**	++	++	++	++	++
4	B	**8**	-ve	-ve	-ve	++	+++
5	E	**9**	++	+++	++	+++	++
6	-	DMSO	-ve	-ve	-ve	-ve	-ve

Inactive: _ (inhibition Zone < 5 mm)
Highly active: +++ (Inhibition Zone > 20 mm)
Moderately active: ++ (Inhibition Zone 11-20 mm)

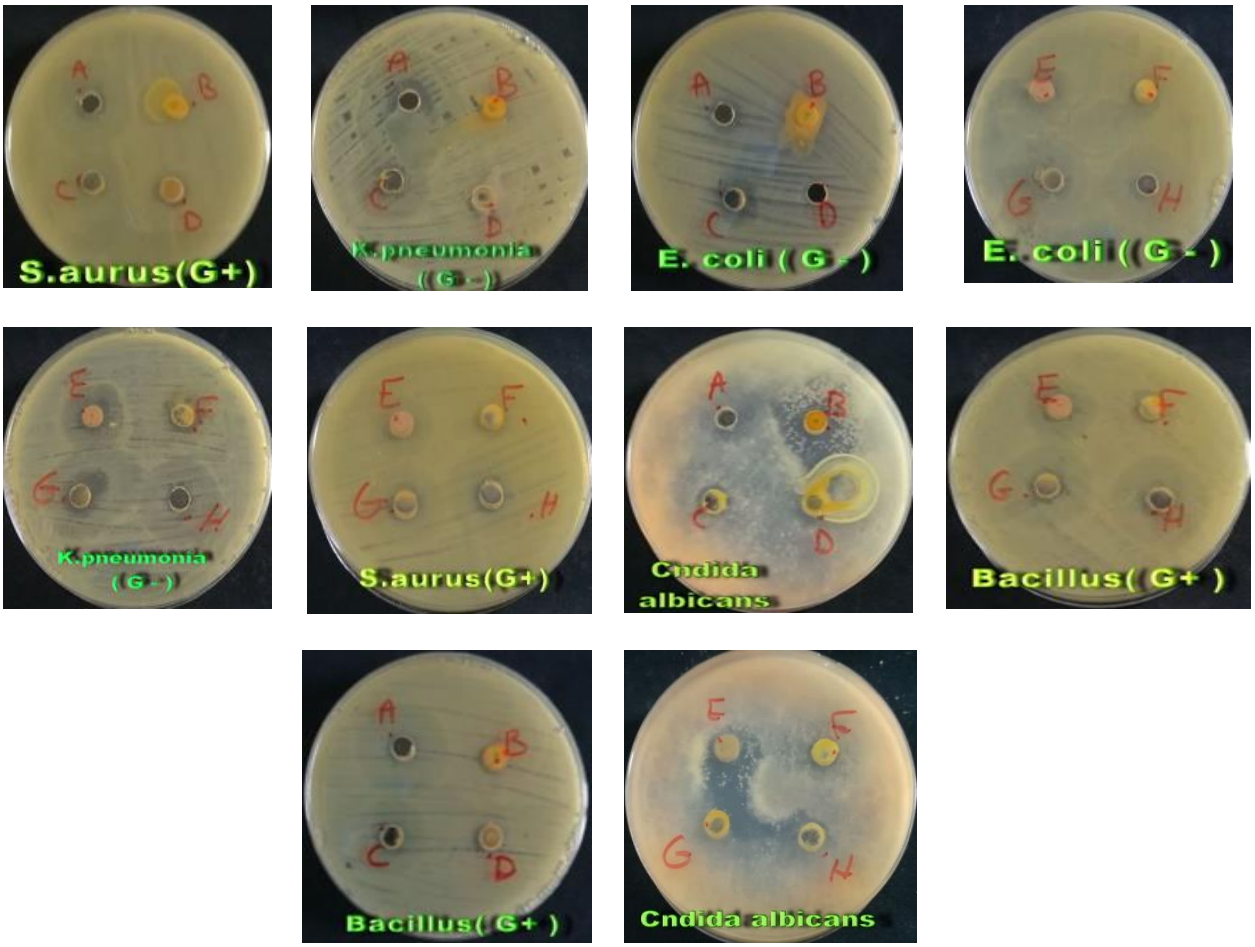


Figure 1: imaging the biological activity of bacteria (G + and G-) and activity of fungi

Conclusion

The synthesized compounds were confirmed using spectroscopic techniques (FT-IR and ^{1}H-NMR). Some of the prepared compounds gave excellent efficiency. The biochemical studies revealed that the newly synthesized compounds caused activators effects on four types of bacteria (Bactria S.aureus, Bacillus, E.coli, and

K.pneumoniae) and one type of fungal (Cndidaalbicas).

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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References

[1]. Shinde S.R., Girase P., Dhawan S., Inamdar S.N., Kumar V., Pawar C., Palkar M.B., Shinde M., Karpoormath R., A systematic appraisal on catalytic synthesis of 1, 3-oxazole derivatives: A mechanistic review on metal dependent synthesis. *Synthetic Communications*, 2022, **52**:1 [Crossref], [Google Scholar], [Publisher]

[2]. Narasimhan Kakkar S., B., A comprehensive review on biological activities of oxazole derivatives. *BMC Chemistry*, 2019, **13**:1 [Crossref], [Google Scholar], [Publisher]

[3]. Qureshi A., Pradhan A., Short review on thiazole derivative. *Journal of Drug Delivery and Therapeutics*, 2019, **9**:842 [Crossref], [Google Scholar], [Publisher]

[4]. Abdel-Latif E., Almatari A.S., Abd-ElGhani G.E., Synthesis and Antibacterial Evaluation of Some New Thiazole-Based Polyheterocyclic Ring Systems. *Journal of Heterocyclic Chemistry*, 2019, **56**:1978 [Crossref], [Google Scholar], [Publisher]

[5]. Lino C.I., de Souza I.G., Borelli B.M., Matos T.T.S., Teixeira I.N.S., Ramos J.P., de Souza Fagundes, E.M., de Oliveira Fernandes, P., Maltarollo, V.G., Johann, S. and de Oliveira, R.B., Synthesis, molecular modeling studies and evaluation of antifungal activity of a novel series of thiazole derivatives. *European Journal of Medicinal Chemistry*, 2018, **151**:248 [Crossref], [Google Scholar], [Publisher]

[6]. Bueno J.M., Carda M., Crespo B., Cuñat A.C., De Cozar, C., León, M.L., Marco, J.A., Roda, N., Sanz-Cervera, J.F., Design, synthesis and antimalarial evaluation of novel thiazole derivatives. *Bioorganic & Medicinal Chemistry Letters*, 2016, **26**:3938 [Crossref], [Google Scholar], [Publisher]

[7]. Andreani A., Granaiola M., Leoni A., Locatelli A., Morigi R., Rambaldi M., Synthesis and antitubercular activity of imidazo [2, 1-b] thiazoles. *European journal of Medicinal Chemistry*, 2001, **36**:743 [Crossref], [Google Scholar], [Publisher]

[8]. Dawood K.M., Eldebss T.M., El-Zahabi H.S., Yousef M.H., Synthesis and antiviral activity of some new bis-1, 3-thiazole derivatives. *European Journal of Medicinal Chemistry*, 2015, **102**:266 [Crossref], [Google Scholar], [Publisher]

[9]. Manju S.L., Identification and development of thiazole leads as COX-2/5-LOX inhibitors through in-vitro and in-vivo biological evaluation for anti-inflammatory activity. *Bioorganic Chemistry*, 2020, **100**:103882 [Crossref], [Google Scholar], [Publisher]

[10]. Resende M.F.D., Lino C.I., Souza-Fagundes E.M.D., Rettore J.V.P., Oliveira R.B.D., Labanca R.A., Assessment of anti-diabetic activity of a novel hydrazine-thiazole derivative: in vitro and in vivo method. *Brazilian Journal of Pharmaceutical Sciences*, 2019, **55**:1 [Crossref], [Google Scholar], [Publisher]

[11]. Amnerkar N.D., Bhusari K.P., Synthesis of some thiazolyl aminobenzothiazole derivatives as potential antibacterial, antifungal and anthelmintic agents. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 2011, **26**:22 [Crossref], [Google Scholar], [Publisher]

[12]. Siddiqui N., Ahsan W., Triazole incorporated thiazoles as a new class of anticonvulsants: Design, synthesis and in vivo screening. *European Journal of Medicinal Chemistry*, 2010, **45**:1536 [Crossref], [Google Scholar], [Publisher]

[13]. Kurt B.Z., Gazioglu I., Sonmez F., Kucukislamoglu, M., Synthesis, antioxidant and anticholinesterase activities of novel coumarylthiazole derivatives. *Bioorganic chemistry*, 2015, **59**:80 [Crossref], [Google Scholar], [Publisher]

[14]. Sharma P.C., Bansal K.K., Sharma A., Sharma D., Deep A., Thiazole-containing compounds as therapeutic targets for cancer therapy. *European Journal of Medicinal Chemistry*, 2020, **188**:112016 [Crossref], [Google Scholar], [Publisher]

[15]. Alqahtani A.M., Bayazeed A.A., Synthesis and antiproliferative activity studies of new functionalized pyridine linked thiazole derivatives. *Arabian Journal of Chemistry*, 2021, **14**:102914 [Crossref], [Google Scholar], [Publisher]

[16]. Ali S.H., Sayed A.R., Review of the synthesis and biological activity of thiazoles. *Synthetic Communications*, 2021, **51**:670 [Crossref], [Google Scholar], [Publisher]

[17]. Muhiebes R.M., Al-Tamimi E.O., Synthesis of derivatives of tetrazoline on Creatinine and study their biological activity. *Asian Journal of Green Chemistry*, 2021, **5**:404 [Crossref], [Google Scholar], [Publisher]

[18]. Pandya K.M., Dave B.P., Patel A.H., Patel R.J., Patel J.T., Desai P.S., 2020. Synthesis, pharmacological evaluation and structure-activity relationship study of hydrazones. *Asian Journal of Green Chemistry*, 2020, **4:**416 [Crossref], [Google Scholar], [Publisher]

[19]. Srikanta S.A., Parmeswara Naik P.N., Electrochemical behaviour of 5-methoxy-5, 6-bis (3-nitropheyl-4, 5-dihydro-1, 2, 4-triazine-3 (2H))-thione in presence of salicylaldehyde on zinc cathode with surface morphology and biological activity. *Asian Journal of Green Chemistry*, 2020, **4**:149 [Crossref], [Google Scholar], [Publisher]

[20]. Ibrahim H.M., Green synthesis and characterization of silver nanoparticles using banana peel extract and their antimicrobial activity against representative microorganisms. *Journal of Radiation Research and Applied Sciences*, 2015, **8**:265 [Crossref], [Google Scholar], [Publisher]

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