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ORIGINAL RESEARCH ARTICLE

Synthesis and biological evaluation of some new tetrazole derivatives by using oxazine and thiazine compounds

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ABSTRACT

This research included, in its first part, the preparation of the chalcone compound (M) from the reaction of para-nitroacetophenone with benzaldehyde in a basic medium of 40% aqueous sodium hydroxide solution. The second part of the research included the conversion of the compound (M) into the two compounds derived from 2-amino Thiazine (MS) and 2-aminooxazine (MO) by reacting the compound (M) with thiourea or urea, respectively, in a medium of alcoholic sodium hydroxide. In the third part of the research, the amine group in the two compounds (MS) and (MO) was exploited to prepare Schiff bases (MS_{1-4}) and (MO_{1-4}) through the reaction of the two compounds (MS) and ((MO) with some benzaldehyde derivatives. In the last part of the research, the tetrazole compounds (MST_{1-4}) and (MOT_{1-4}) were prepared From the reaction of the prepared Schiff bases (MS_{1-4}) and (MO_{1-4}) with sodium azide in a medium of 1,4-dioxane, a test was conducted for the biological effectiveness of the prepared tetrazole compounds against Gram-positive and Gram-negative bacteria. In addition, some spectroscopic and physical measurements were performed of the prepared compounds.

Keywords: chalcone; thiazine; oxazine; tetrazole; biological activity

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1. Introduction

Chalcone compounds are organic compounds that are classified as unsaturated alpha-beta ketone compounds. They are among the well-known and widespread compounds in nature in some types of plants such as (*Glycyrrihza, piper, anglica*)[1], which some peoples have used in some treatments[2] Perhaps the most prominent type of natural chalcone is (Echintatin), extracted from the licorice plant, which has been proven to have good therapeutic and biological efficacy[3]. Chalcone compounds were prepared laboratory-based for the first time at the end of the eighteenth century[4], and with the development of modern laboratory methods and techniques A large number of chalcone compounds have been manufactured, and a number of them have been proven to have high biological and Effective as a treatment for various diseases. Research has revealed that certain chalcone derivatives, such as those containing morphine, piperidine, and diamine ethanol groups, exhibit significant antimalarial activity[5]. Additionally, Another study demonstrated that aryloxypropanolamine chalcones are effective in managing diabetes[6]. Furthermore, it was found that some indole-based compounds primarily composed of

chalcones are effective against certain skin infections by inhibiting the enzymes COX-1 and COX-2[7].

Thiazine compounds: six membered heterocyclic organic compounds consisting of sulfur and nitrogen. Thiazine compounds exist in several forms according to the arrangement of the sulfur and nitrogen atoms: (1,2), (1,3) and (1,4)"thiazine"[8] Studies have proven that Research has shown that thiazine compounds are of great importance in the field of pharmacy and medicine, as cephalosporin drugs are among the most prominent well-known drugs widely used as antibiotics, which contain a thiazine ring in their composition[9]. Some research has also indicated that some thiazine compounds have shown high effectiveness as anti-tuberculosis agents[10] Fungi[11]. In the agricultural field, they were used as herbicides and insecticides[12], in addition to their use in organic chemistry as intermediate compounds used to manufacture other compounds[13].

Oxazine compounds: Heterocyclic organic compounds with a six membered ring consisting of oxygen and nitrogen. They exist in forms similar to the previously mentioned thiazine compounds in terms of the arrangement of heterogeneous atoms.1,3- oxazine derivatives are among the compounds known for their biological effectiveness.especially as antibiotics. Examples include Oxazine mycin[14] and indole mycin[15]. Oxazine compounds are also found naturally. They have been extracted from some types of plants, which are known as antibiotics and treat leukemia, the most important of which are (Maytansine, Maytanprine), extracted from (*Matanusbuchanani*), (*Maytanusovatus*) plants[16,17], as some have proven.

Tetrazole compounds: Heterocyclic organic compounds consisting of four nitrogen atoms and one carbon atom. They were prepared for the first time by Blyden in(1889) by the reaction of dicyanophenyl hydrazine with nitrous acid[18]. The proton attached to the nitrogen atom within the tetrazole ring is characterized by a high acidity close to the acidity of some Carboxylic acids. Therefore, some tetrazole compounds have been used as medications in treating and regulating blood pressure, the most famous of which are (Losartan and Valsartan)[19]. Other compounds have also shown effectiveness against microbes[20], viruses[21] and tuberculosis[22].

2. Experimental

All raw materials used in the research were subjected to physical and chemical tests and their purity and suitability were verified before being used in the research. Some spectroscopic measurements (I.R., ^{1}H-NMR) of the prepared materials were also carried out using a(**Bruker optics (FT – IR) Spectrophotometer CO. Alpha-P**) using a KBr disk, while the magnetic resonance spectrometer was of the type (**Bruker Avance 300MHz**) and using the deuterated solvent (DMSO-d6) and TMS as an internal reference, as well as a melting point measuring device of the type (**Stuart SMP10.Melting point**).

Measurement of the biological activity of some prepared materials against Gram-negative and Gram-positive bacteria was carried out.

Synthesis of compound (M)[23]: In around flask of (250 ml), (0.1 mole) of 4-Nitroacetophenone was dissolved with (0.1 mole) Benzaldehyde in (25 ml) of ethanol then a solution of (40% NaOH) was added to the mixture slowly, stirring for awhile. (15min) A "precipitate" of compound (M1) is gradually formed, which is washed, filtered, and recrystallized using ethanol. **Figure (2)** shows the nuclear magnetic resonance spectrum of compound (M).

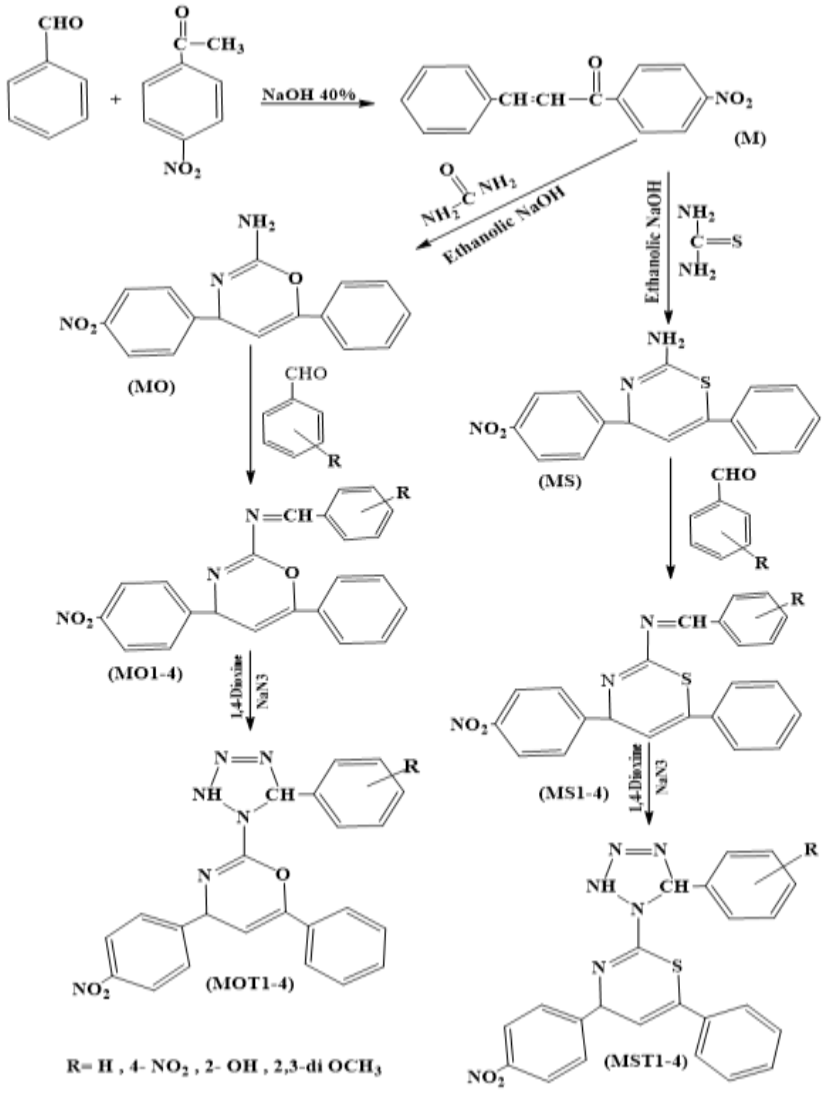
Synthesis of compound (MS)[24]: Place (0.01 mole) of compound (M) with (0.01 mole) of thiourea in around flask of (100 ml) and add (50 ml) of the newly prepared alcoholic sodium hydroxide solution. Bring the mixture to a boil while stirring for (8 h). Then add the mixture to ice water and continue stirring for an hour, then leave the mixture for (24 h) in a cold place, after which the sold is washed, filtered, and recrystallized with ethanol. **Figure (3)** shows the nuclear magnetic resonance spectrum of compound (MS).

Synthesis of the compound(MO)[25]: Equal moles (0.01mole) of both the compounds (M) and urea were placed in a around flask of (100ml), and after adding (50ml) of alcoholic sodium hydroxide solution, the mixture was risen with continuous stirring for a period of (8 h), after completing reflux: Pour the mixture into ice water while stirring for an hour, then leave it for (24 h). After washing and filtering, the sediment was recrystallized using ethanol. **Figure (4&5)** shows the nuclear magnetic resonance spectrum of compound (MO&MO2).

Synthsis of Schiff bases (MS_{1-4}) and (MO_{1-4})[26]: In a round flask with a capacity of (50 ml), dissolve (0.001 mole) of the compound (MS) or (MO) with (0.001 mole) of benzaldehyde derivatives in (25 ml of ethanol). After adding a few drops of glacial acetic acid, the mixture was heated with stirring for (3 h) and after the completion of the reflux, the mixture was added to ice water. After washing and dissecting the resulting precipitate, it was recrystallized with ethanol and water. **Figure (6&7)** shows the nuclear magnetic resonance spectrum of compound (MS&MST2).

Synthesis of tetrazole compounds(MST_{1-4})and(MOT_{1-4})[27]: Place (0.001mole) of the previously prepared Schiff bases (MST_{1-4}) or (MOT_{1-4}) with (0.001mole of sodium azide) in a 50ml round flask and add They have 20 ml of 1,4-dioxane and the mixture is heated for (4 h) in a water bath, after which the sediment is washed and filtered and recrystallized with methanol. **Figure (8)** shows the nuclear magnetic resonance spectrum of compound (MOT).

The following scheme shows the reaction flow of the prepared compounds:



3. Results and discussion

The prepared chalcone compound (M) showed in the infrared spectrum a vibration at (1661) cm^{-1} to the carbonyl group (C=O), where this group appeared at a low frequency and this is due to the presence of the sequence with the (C=C) group. As for The two compounds (MO) and (MS) are observed in the spectrum ((I.R). They have the appearance of two distinct bands at approximately (3200-3500)cm^{-1} that belong to the (NH_2) group and the disappearance of the band (1661) cm^{-1}that belonged to the (C=O) group. In the compound (M), a new band also appeared in both compounds at approximately (1595) cm^{-1} and belongs to the (C=N) group within the heterogeneous ring. As for the Schiff's bases (MS_{1-4}) and (MO_{1-4}), it showed these compounds have new frequencies at about (1680-1693) cm^{-1} that belong to the acyclic (C=N) group, and the disappearance of the (NH_2) group that was within the compounds (MS) and (MO). The prepared tetrazole compounds (MST_{1-4}) showed, (MOT_{1-4}) Characteristic frequencies of the (NH) group within the tetrazole ring between (3242-3280) cm^{-1}. In the 1H-NMR spectrum of some of the prepared compounds, it is noted that in the two compounds (MS) and (MO) there is a distinct signal for both compounds at (3.86) and (3.89) ppm respectively, which belongs to a proton. (NH_2) group in both compounds. While in the compounds ($M0_2$) and (MS_2), it is noted that there is a single signal for each of them at (8.61), (9.13) ppm respectively which belongs to the proton of the (CH=N) group. As for the tetrazole compounds ($MST_{2)}$, (MOT_2) the proton signal of the (NH) group within the tetrazole ring was distinct at ppm (4.26), (5.01)ppm respectively. As for the protons of the aromatic rings, they were for the prepared compounds between the range (6.93-7.93) ppm. **Tables 1, 2 and 3** show the physical and spectral properties of the prepared compounds. The measured spectral values were compared with the known literature and were consistent with it[28].

Table 1. Some physical properties of the prepared compounds.

crystallization solvent	Yield %	M.P C°	Color	Ar	Comp.NO.
Ethanol	95	137-139	Light Orange	------	M
Ethanol	88	169-171	Brownish yellow	------	MS
Ethanol	72	129-132	Reddish brown	4-NO_2	MS_1
Ethanol	64	156-158	Brown	H	MS_2
Ethanol	68	182-184	Yellow	2,3-di-OMe	MS_3
Ethanol	57	196-198	Yellow	2-OH	MS_4
Ethanol	82	272-274	Dark brown	------	MO
Ethanol	61	201-203	Brown	4-NO2	MO_1
Ethanol	52	214-216	Brown	H	MO_2
Ethanol	77	233-235	Brown	2,3-di-OMe	MO_3
Ethanol	47	247-249	Brown	2-OH	MO_4
Methanol	51	152-153	Brown	4-NO_2	MST_1
Methanol	62	144-146	Light brown	H	MST_2
Methanol	69	168-170	Yellowish brown	2,3-di-OMe	MST_3
Methanol	43	211-213	Brown	2-OH	MST_4
Methanol	60	184-186	Brown	4-NO_2	MOT_1
Methanol	67	180-182	Brown	H	MOT_2
Methanol	41	201-203	Reddish brown	2,3-di-OMe	MOT_3
Methanol	59	222-224	Reddish brown	2-OH	MOT_4

Table 2. Infrared spectrum of the prepared compounds.

I.R (vcm^{-1} , KBr)						
Others	**NH**	**C=N (cyclic)**	**(C=C)**	**Ar(C=C)**	**Ar(C-H)**	**Comp.NO.**
(C=O)1661 (NO_2)1513asym 1307sym	---	----	1588	1572	3051	M
(C-S) 615 (NO_2) 512asym,1311sym	3217-3349 (sym ,asym)	1594	----	1566	3058	MS
(C=N) acyclic 1680 (NO_2) 1515asym,1316sym	-----	1597	----	1566	3060	MS_1
(C=N) acyclic 1687 (NO_2) 1511asym,1309 sym	-----	1597	----	1567	3059	MS_2
(C=N) acyclic 1689 (NO_2) 1514asym,1310 sym (OCH_3) 2979,2893 (C-O) 1279asym ,1071sym	-----	1595	----	1567	3026	MS_3
(C=N)acyclic 1686 (NO_2) 1514asym,1309 sym (OH) 3357	-----	1594	----	1568	3060	MS_4
(NO_2) 1511asym,1311 sym (C-O) 1236 asym,1071sym	3208-3353 (sym-asym)	1595	-----	1567	3060	MO
(C=N) acyclic 1661 (NO_2) 1511asym,1312 sym	----	1596	----	1566	3060	MO_1
(C=N) acyclic 1693 (NO_2) 1516asym,1311 sym	----	1595	---	1565	3028	MO_2
(C=N)acyclic 1689 (NO_2) 1518asym,1310 sym (OCH_3) 2977 , 2938 (C-O) 1266 asym , 1069sym	----	1595	----	1566	3060	MO_3
(C=N)acyclic 1683 (NO_2) 1514asym,1309 sym (OH) 3367	----	1595	----	1567	3060	MO_4
(NO_2) asym 1512 ,1307_{sym} (N=N) 1472	3255	1601	----	1570	3067	MST_1
(NO_2) asym 1522 ,1352_{sym} (N=N) 1487	3274	1613		1571	3061	MST_2
(NO_2) 1524asym,1319 sym (OCH_3) 2932 (C-O) 1262asym ,1086sym (N=N) 1479	3249	1606	----	1568	3062	MST_3
(NO_2) 1508asym,1306 sym (OH) 3304 (N=N) 1485	3242	1610	----	1564	3066	MST_4
(NO_2) 1516 asym,1311 sym (N=N) 1472	3264	1609	----	1572	3062	MOT_1
(NO_2) 1511 asym,1305 sym (1479)	3280	1611	----	1571	3063	MOT_2
(NO_2) 1518asym,1329 sym (OCH_3) 2909 (C-O) 1288asym ,1031sym (N=N) 1468	3269	1605	----	1569	3069	MOT_3
(NO_2) 1521asym,1314 sym (OH) 3298 (N=N) 1476	3277	1621	----	1561	3073	MOT_4

Table 3. ^{1}H-NMR spectrum of compounds (M, MS, MO, MS_2, MO_2, MST_2, MOT_2).

Solvent	^{1}H-NMR δ (ppm)	Comp.No.
DMSO-d_6	7.09-7.15(d ,2H, CH=CH), 7.20-7.93(m , 9H, ArH+ sub.phenyl)	M
DMSO-d_6	3.86(s,2H,NH_2) , 7.28-7.62(m,5H, ArH + CH=C) , 7.75-7.78 (m,4H, ArH sub. phenyl)	MS
DMSO-d_6	3.89(s,2H,NH_2), 7.14-7.28 (m,5H,ArH + CH=C) ,7.29-7.85 (m,4H, ArH sub. phenyl)	MO
DMSO-d_6	7.11-7.48(m,10H, ArH + CH=C) , 7.50-7.81 (m,4H, ArH sub. phenyl) , 8.61(s, 1H, N=CH)	MS_2
DMSO-d_6	7.29-7.53(m,10H, ArH+ CH=C), 7.55-7.7 (m,4H, ArH sub. phenyl) , 9.13(s, 1H, N=CH)	MO_2
DMSO-d_6	6.93-7.30(m,10H,ArH+CH=C), 7.31-7.65 (m,4H, Ar sub. phenyl) , 4.26 (s,1H, NH)	MST_2
DMSO-d_6	7.11-7.29(m,10H,ArH+CH=C), 7.30-7.53 (m,4H, Ar sub. phenyl) , 5.01 (s,1H, NH)	MOT_2

Testing the biological effectiveness of the synthesis compounds[29-30]: The antibacterial activity was tested using (the disk diffusion method) known as the Kirby method for the prepared compounds. Gram-positive bacteria (*staphylococcus aureus*) and gram-negative bacteria (*Escherichia Coli*) were selected, and the results showed resistance of gram-negative bacteria to the prepared compounds. While the compounds (MS_1)(MST_1), (MOT_3) showed good biological activity against Gram-positive bacteria(*Staphylococcus aureus*) and the compounds (MS_4), (MST_4) and (MOT_1) showed acceptable activity against the same bacteria[31-32], as shown in the **Table 4**.

Table 4. Biological activity of compounds against bacteria.

Escherichia coli	*Staphylococos aures*	Comp. No.
−	-	M
−	6mm	MS
−	-	MO
−	14mm	MS_1
6mm	-	MS_2
−	−	MS_3
−	10mm	MS_4
−	-	MO_1
−	8mm	MO_2
−	-	MO_3
8mm	14mm	MST_1
−	-	MST_2
6mm	-	MST_3
−	10mm	MST_4
−	12mm	MOT_1
−	−	MOT_2
−	16mm	MOT_3
−	−	MOT_4
6mm	13mm	AMOXILLINE
Inferences	**Diameter Zone of inhibition(mm)**	
inactive	10 mm>	
Partially active	10-13 mm	
Active	14-19 mm	
Very active	19mm<	

4. Molecular docking study

A molecular docking study was conducted to evaluate the interaction of newly designed tetrazole derivatives incorporating oxazine and thiazine moieties with cyclooxygenase-1 (COX-1)[33]. The crystal structure of COX-1 was obtained from the Protein Data Bank (PDB ID: 1W07) and used as the target for docking analysis. The docking results revealed that the oxazine–tetrazole derivative exhibited the most favorable binding profile[34]. Specifically, the compound showed a binding energy of –12.4 kcal/mol, indicating a stable and energetically favorable interaction with COX-1. Strong hydrogen bonds were formed with Ser530, and π–π stacking interactions were observed with Phe381, which are critical for effective inhibition.The calculated docking parameters were: X = 5.05, Y = 51.34, and Z = 30.31, supporting the stable binding orientation of the oxazine–tetrazole derivative compared to the thiazine analog. The superior steric fit and electronic distribution of the oxazine scaffold enhanced its binding affinity within the COX-1 active pocket, suggesting a mechanism of inhibition similar to that of aspirin.These findings highlight the oxazine–tetrazole compound as a promising anti-inflammatory candidate with potential selectivity for COX-1. Further synthesis and biological evaluation are recommended to validate these in silico results and to assess selectivity against COX-2. We note that **Figure (1)** shows the details of the reaction.

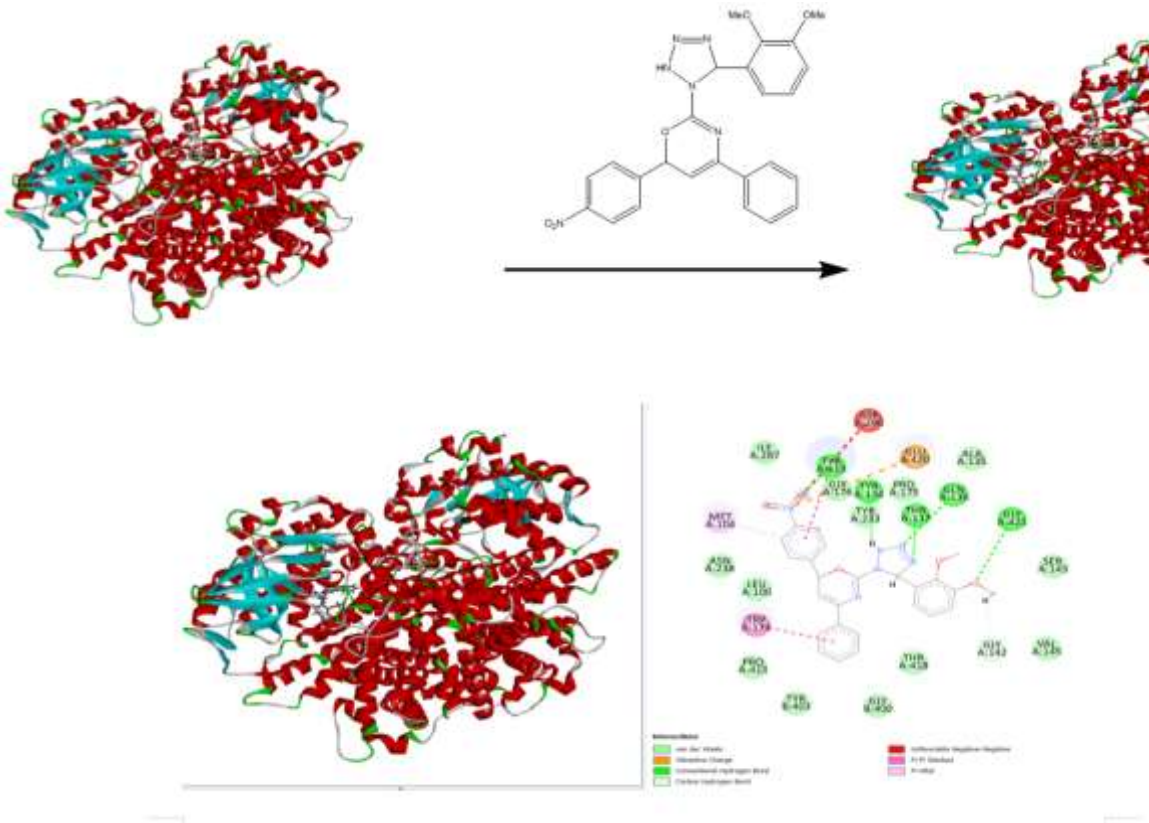


Figure 1. The interaction of (MOT_3) with cyclooxygenase-1 (COX-1).

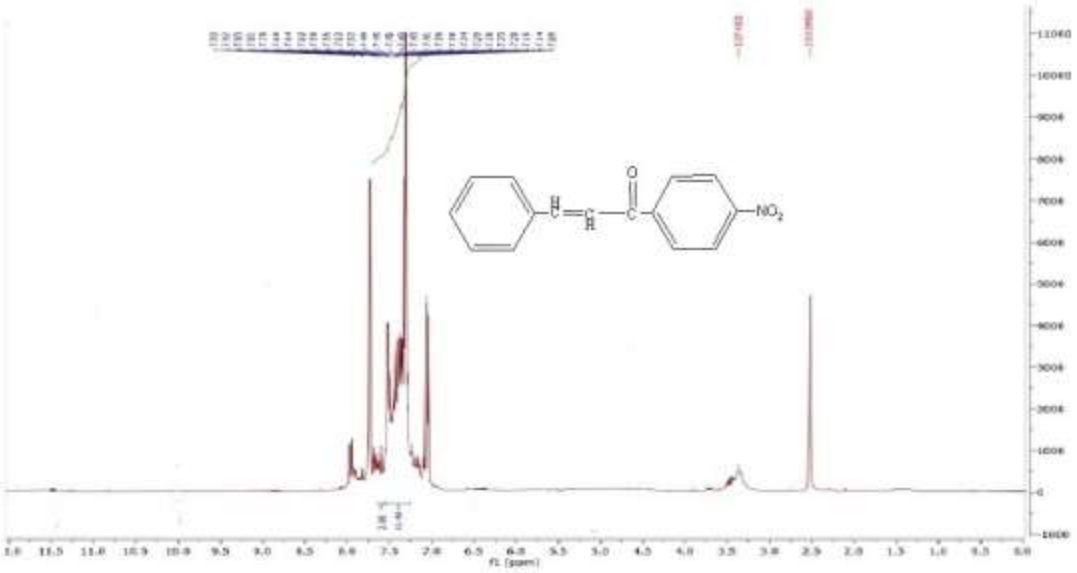


Figure 2. [1]H-NMR of compound (M).

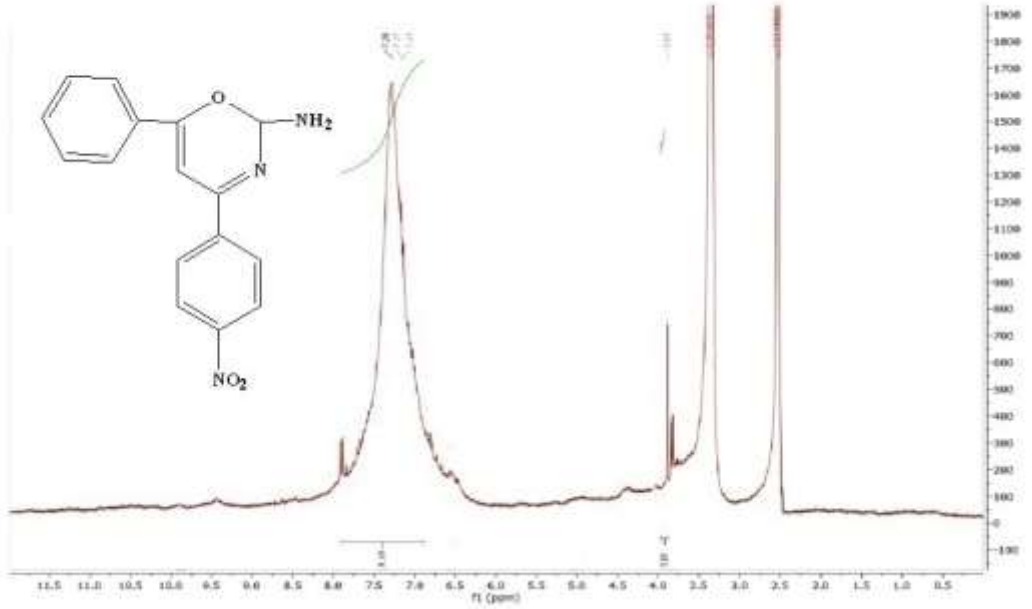


Figure 3. [1]H-NMR of compound (MO).

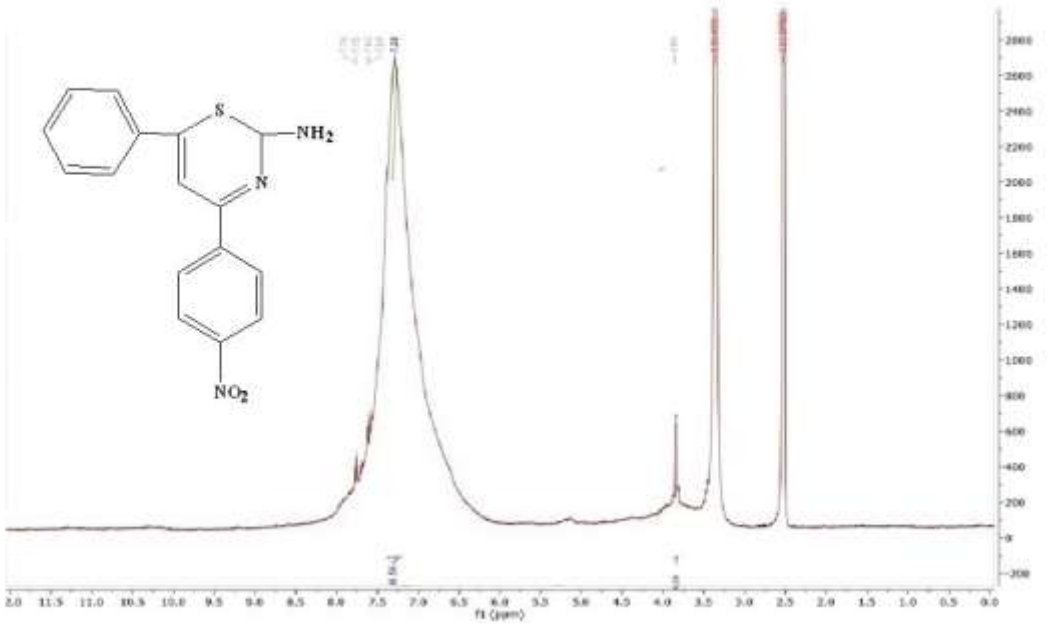


Figure 4. [1]H-NMR of compound (MS).

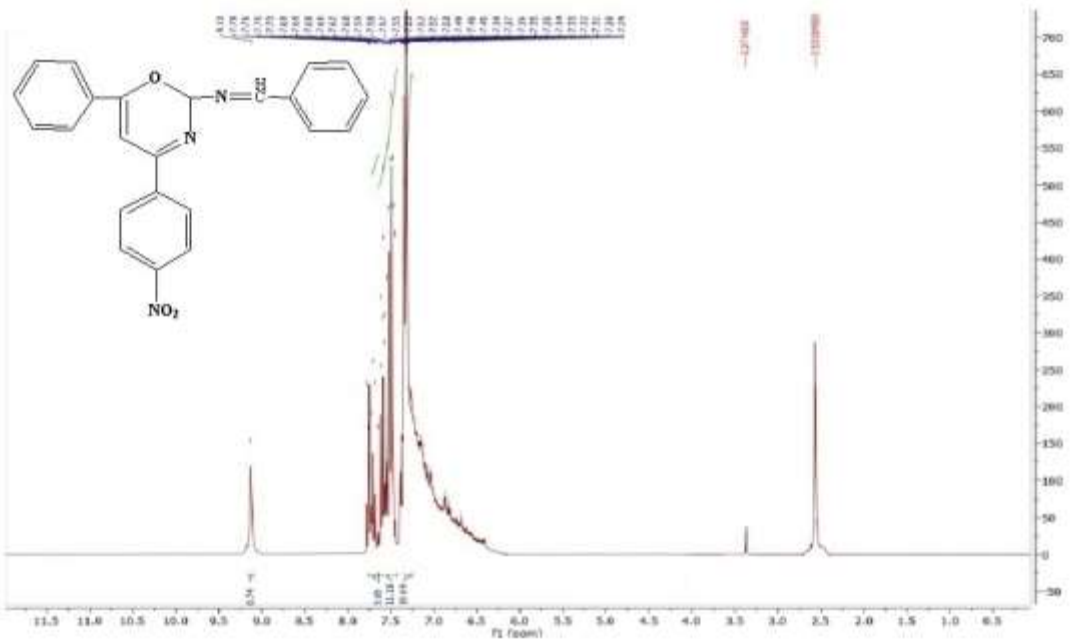


Figure 5. [1]H-NMR of compound (MO_2).

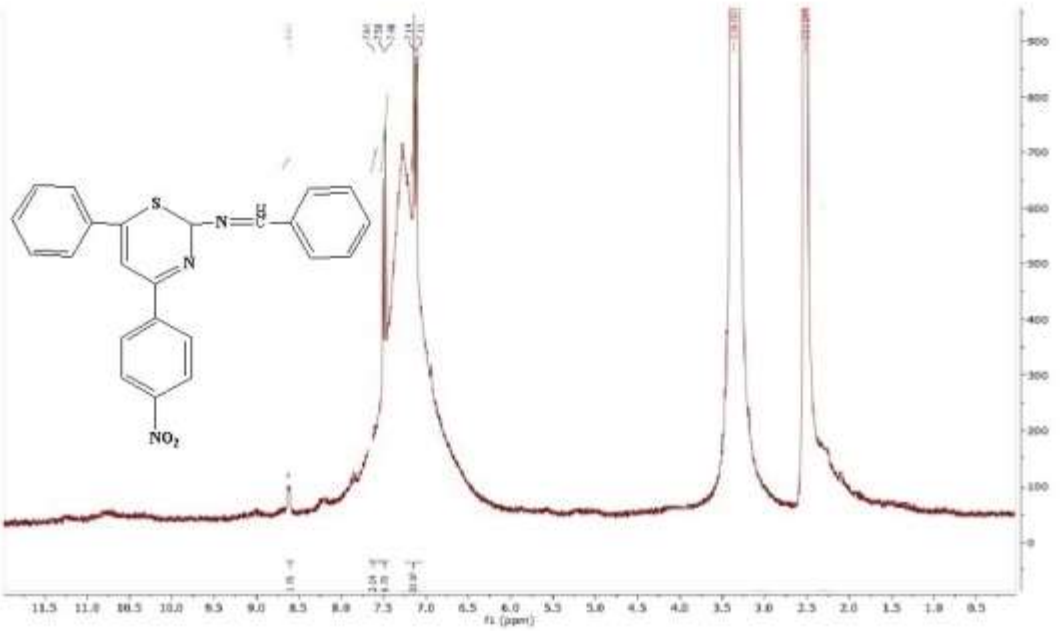


Figure 6. ^{1}H-NMR of compound (MS_2).

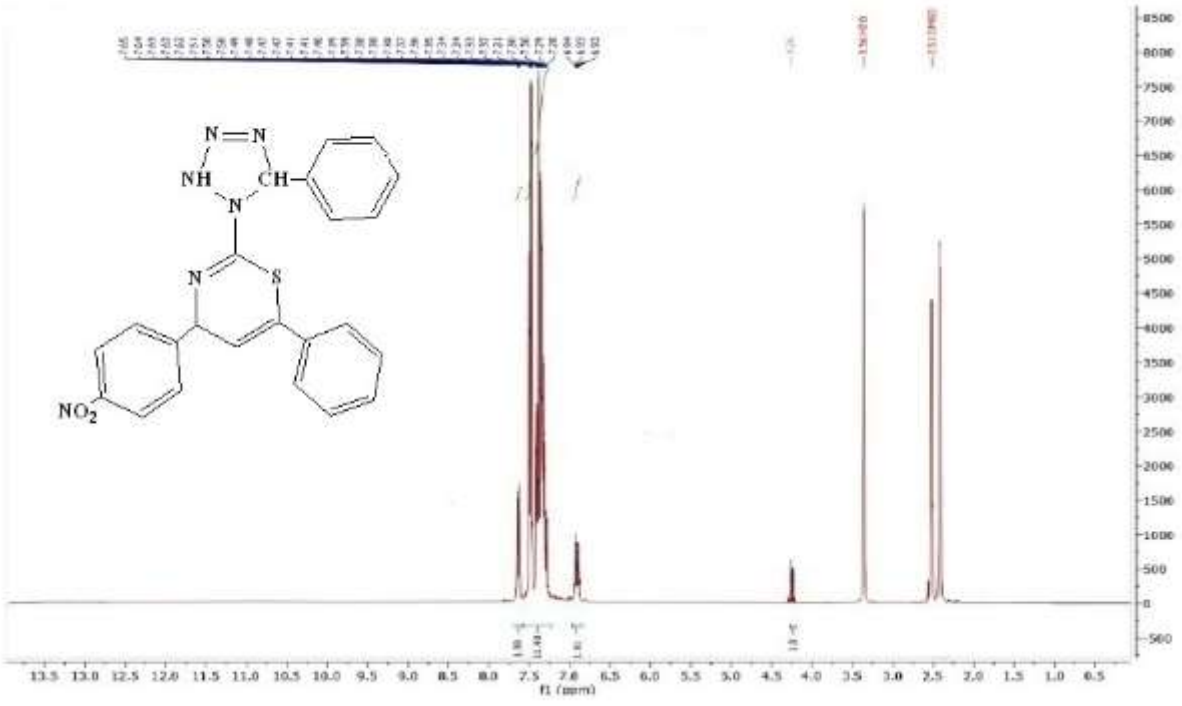


Figure 7. H-NMR of compound (MST2).

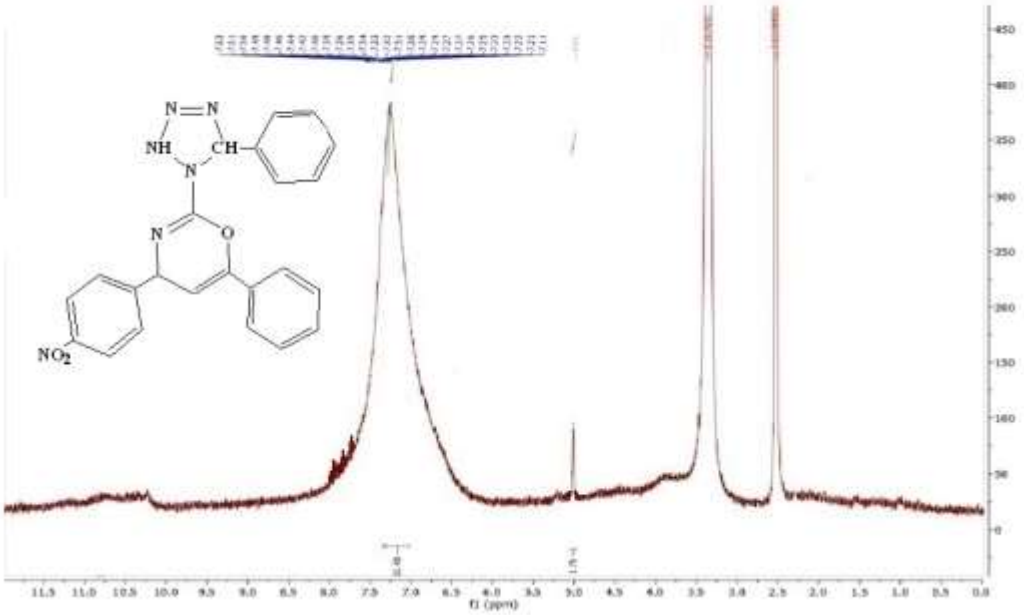


Figure 8. ^{1}H-NMR of compound (MOT_2).

5. Conclusion

In this manuscript, heterocyclic compounds containing a primary amine group of the chalcone were synthesized. The amine group was converted to Schiff bases. Then, Synthesis the tetrazine ring, which is considered one of the known drug nuclei. The identity of the synthetic compounds was determined using spectroscopic tests such as proton magnetic resonance and infrared to determine the synthetic compounds. The inhibitory effectiveness of the synthetic compounds was also examined with positive and negative types of gram stain bacteria to give excellent results compared to Amoxilline.

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Conflict of interest

The authors declare no conflict of interest.

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