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Synthesis of Some New 1,3,4-Thiadiazole Derivatives Derived from Cholic Acid and Evaluation of their Biological Activity

Intisar Q. Mahmood Al-araj[1]*, Rana A. Saeed[2], Linda R. Abdul-Raheem[1], Amena A. Ahmed[1]

[1] Chemistry Dept, College of Education for Pure Science, University of Mosul, Mosul, Iraq.
[2]Pharmacy Dept, Mosul Technical Institute, Mosul, Iraq.

Abstract: In this work, several oxadiazole, thiadiazole, and triazole derivatives, as well as new Schiff bases, were prepared. Cholic acid was used as a starting material to prepare the five-membered heterocyclic compounds. The synthesized compounds were identified by FTIR and ^{1}H,^{13}C-NMR spectroscopy, which elucidated and confirmed the structure of the target molecules. Estimation of the biological activity of the newly produced compounds has been conducted against two types of Gram-positive and Gram-negative pathogenic bacteria.

Keywords: Cholic acid, heterocyclic, Schiff bases, thiadiazoles, oxadiazoles, pathogenic bacteria

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*Corresponding author E-mail: mahmood_intisar@uomosul.edu.iq

1. INTRODUCTION

Cholic acid is an essential biliary acid and has a chemical name 4-(3,7,12-trihydroxy-10,13-dimethylhexa-decahydro-1H-cyclopenta[a] phenan-thren-17-yl) pentanoic acid (1). It is a kind of endogenous steroid that naturally occurs in many animals, including humans (2). It is being studied increasingly as a structural element in supramolecular chemistry. It has been discovered that the liver is where this acid is typically generated (3). Additionally, they function as surfactants to make vitamins and lipids soluble, so they may be absorbed in the colon (4). This occurs by combining with taurine or glycine to create water-soluble salt, and then micelles are formed around molecules that are attracted to lipophilicity (5). Cholic acid with chenodeoxycholic acid, known as an important primary bile acid, is synthesized by cholesterol, and it is also produced in the liver. The concentration of these two acids is equal in humans, and they are converted to amino biliary acids (6). Figure (1) gives An illustration of intestinal bacteria further transforming deoxycholic acid and lithocholic acid, respectively, into biliary acid (7,8).

1,3,4-Oxadiazoles are interesting compounds (10-12). The unique structure of these compounds has attracted researchers' interest in finding new therapeutic molecules (13). It has been found that these compounds have a great range of biological applications, which include antiviral (14), anticonvulsant (15), anti-inflammatory (16), anti-tubercular (17), antimicrobial, anti-allergic, antineoplastic, analgesic, antiproliferative, monoa-mine oxidase and tyrosine kinase inhibitory effects (18). Thiadiazols are also heterocyclic moieties consisting of one sulfur atom with two nitrogen atoms (19). Thiadiazols and their analogs are interesting chemical compounds due to their bioactivity effect, such as anti-tubercular and antimicrobial activity (20,21). Recently, it was found that 1,3,4-thiadiazole sulfonamide derivatives work as a modulator of anticancer treatment when joined with some cytotoxic substances. It can also be a lead molecule in treating new diseases, for instance, COVID-19 and black fungus infection (22).

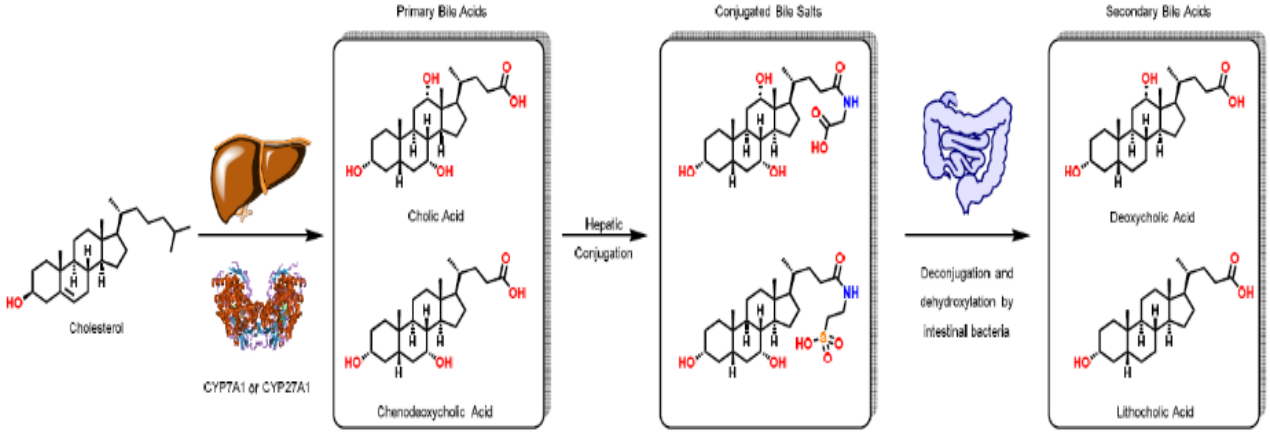


Figure 1: The Production of Bile Acids from Cholesterol (9)

Nowadays, compounds based on 1,3,4-thiadiazoles have been shown to have activity against various cancers by focusing on unchecked DNA replication and cell division, and malignancies in vitro and in vivo can be reduced (23). Furthermore, heteroatoms in thiadiazoles can form interactions with biological targets, including key kinases involved in tumorigenesis (24). Triazoles are good examples of heterocyclic compounds due to the exhibition of high aromatic stability compared to other organic compounds (25,26). Triazoles can form hydrogen bonds suitable for many biologically active molecules (27). Medicinal chemists emphasize the anticancer activity of such compounds (28) due to their crucial roles in the design of anticancer drugs (29). Biological studies have shown that the five-membered triazole heterocycles have a broad and potent biological activity (30), notably in antiviral activities such as those against the human immunodeficiency virus (HIV)(31), the hepatitis C virus (HCV), the hepatitis B virus (HBV)(32), the influenza virus (IV), the herpes simplex virus (HSV), the hepatitis A virus (HAV), the varicella-zoster virus (VZV), and the human cytomegalovirus (HCMV) (33). Currently, other molecules, such as Schiff bases derived from heterocycles, are the subject of many investigations because of their diverse range of biological functions (34). They are very important in various biological systems and have found applications in different industries (35). Schiff bases derived from various sources exhibit the ability to fight against several biological problems, including cancer, inflammation, and allergies. These can be treated using antibacterial, antifungal, antitumor, and antiviral substances containing Schiff bases. (36,37). In addition, the field of research dealing with Schiff-base chemistry has expanded greatly nowadays(38).

2. EXPERIMENTAL SECTION

2.1 General

Sigma Aldrich provided the cholic acid, while BDH and Fluka companies supplied the other reagents. All chemicals were used without further purification. Melting points (MP) were determined on the Electro Thermal IA1900. IR spectrometer with a 4000-400 cm^{-1} range was utilized using KBr disks on a Shimadzu FT-IR-8400. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Agilent USA 400 MHz spectrometer at Laboret Center, University of Tehran. Thin layer chromatography (TLC) was performed on TLC aluminum sheets to verify the purity of the compounds.

*2.1.1 Synthesis of compound (**1**)*

A mixture of cholic acid (0.01 mol) and conc. sulfuric acid (10 mL) was stirred in an ice bath. Then, the solution was heated in a steam bath 10 hrs) until one distinct spot-on TLC. This hot mixture was poured onto crushed ice, and ammonium hydroxide was concentrated to precipitate the free base. It recrystallized from ethanol to give a brown solid, m.p: 116-118 °C and 78% yield. ν_{max}: 3560, 3380, 2929, 2852, 1665, 1107,1050 cm^{-1}.

*2.1.2 Synthesis of compound (**2**)*

0.01 mol of compound (**1**), ethyl alcohol (50 mL), and 4-aminoacetophenone (0.01 mol) were refluxed together for 5 hrs and then cooled down to room temperature when TLC showed the end of the reaction. The resulting precipitate was filtered and then dried. Ethyl alcohol was used to recrystallize the product to produce a bright yellow solid m.p.: 107-109 °C and 70% yield. ν_{max}: 3541, 3376, 3050-3117, 1686-1661 cm^{-1}.

*2.1.3 Synthesis of compound (**3**)*

0.01 mol of compound (**2**) was dissolved in absolute EtOH (50 mL), bromoethyl acetate (0.01 mol) and sodium bicarbonate (3 g) were added. The mixture of reaction was refluxed for 8 hrs, and the mixture was monitored via TLC. Crushed ice was added to the residue after the solvent was evaporated, and the solution was extracted with dry ether (2x30 mL). The

mixture was then filtered, concentrated, and given a dark brown solid with m.p: 112 °C and 71% of yield. v_{max}: 3310, 2927, 2855, 1741, 1411, 1372 cm^{-1}.

*2.1.4 Synthesis of compound (**4**)*

A mixture of 10 mL of hydrazine hydrate (85%) and 0.01 mol of compound (3) in 50 mL abs. ethyl alcohol was refluxed for 3.5 hrs. TLC was used to follow the reaction, and then evaporation was done to obtain acid hydrazide (**4**); it produced a white solid after recrystallization from ethanol m.p: 200–201 °C and 92% yield. v_{max}: 3360, 2957, 2862, 1669, 1531, 1581, 1462 cm^{-1}.

*2.1.5 Synthesis of compound (**5**)*

0.01 mol of acid hydrazide (**4**) and ammonium thiocyanate (0.01 mol) were combined and dissolved in absolute ethanol (50 mL). Hydrochloric acid (8 mL) was added to the reaction mixture and then re-condensed for 2 hrs. Product formation was monitored using TLC. After the primary compounds disappeared from TLC, the crude product was combined with silica gel after the solvent had been evaporated under decreased pressure, and it was then purified using column chromatography, eluting with petroleum ether/EtOAc (1:1) gave pale brown solid, m.p: 145-147°C and 77% of yield v_{max}: 3314, 3012, 1667, 1583, 1549, 1420, 1210 cm^{-1}.

*2.1.6. Synthesis of compound (**6**)*

Refluxing of substituted thiosemicarbazide (**5**) (0.01 mol) with $NH_2NH_2.H_2O$ 85% (12 mL, 0.2 mol) for 2 hrs gave a solid that was isolated, dried, and recrystallized from ethyl alcohol to give yellow solid, m.p: 143-145 °C and 52% of yield. v_{max}: 3419, 3320, 3054, 2923, 1620 cm^{-1}.

*2.1.7. Synthesis of compound (**7**)*

A solution containing ten drops of glacial acetic acid and 0.01 mol of chlorobenzaldehyde in 15 mL of ethanol was added to a mixture containing 0.01 mol of compound (**6**) in ethanol (30 mL) and refluxed for 3 hrs when TLC revealed no starting material, the resultant solution is concentrated to half, the residue was then added to crushed ice. The product is filtered and washed with water to give a white solid, m.p.: 165–167 °C and 79% yield; recrystallization from methanol gave the desired compound. v_{max}: 3035,1706, 1430-1544, 688 cm^{-1}.

*2.1.8. Synthesis of compound (**8**)*

A mixture of 0.01 mol thiosemicarbazide (**5**) and 0.01 mol HgO in 25 mL of methanol was refluxed for 6 hrs, the reaction was observed using TLC, and the mixture was filtered while still hot. The solvent was evaporated and purified via column chromatography using petroleum ether/EtOAc (5:2) as eluent gave a deep yellow solid, m.p: 210-211 °C and 64% of yield. v_{max}: 3424, 3162, 3055, 2926, 2850, 1612, 1164, 1033 cm-^{1}.

*2.1.9. Synthesis of compound (**9**)*

The mixture of five drops of glacial acetic acid and 0.01 mol chlorobenzaldehyde was combined with compound (**8**) (0.01 mol) in 30 mL of ethanol. The same procedure of compound (**7**) was followed to prepare compound (**9**), column chromatography with CH_2CH_2/MeOH (5:1) as eluent was used for purification to give a white solid, m.p: 222-224 °C and 69% of yield. v_{max}: 3032, 1663, 1544, 1433, 687 cm^{-1}.

*2.1.10. Synthesis of compound (**10**)*

A substituted thiosemicarbazide (**5**) (0.01 mol) was added to a round-bottomed flask along with 10 mL of concentrated H_2SO_4 and refluxed in a water bath at 90 °C for (2 hrs), then the mixture was neutralized using a solution of concentrated NH_4OH with cooling. The resulting precipitation was filtered, washed, dried, and recrystallized from benzene to offer a white solid, m.p.: 214–215 °C and 71% of yield, v_{max}: (3421-3370), 1623, 3053, and 1034 cm^{-1}.

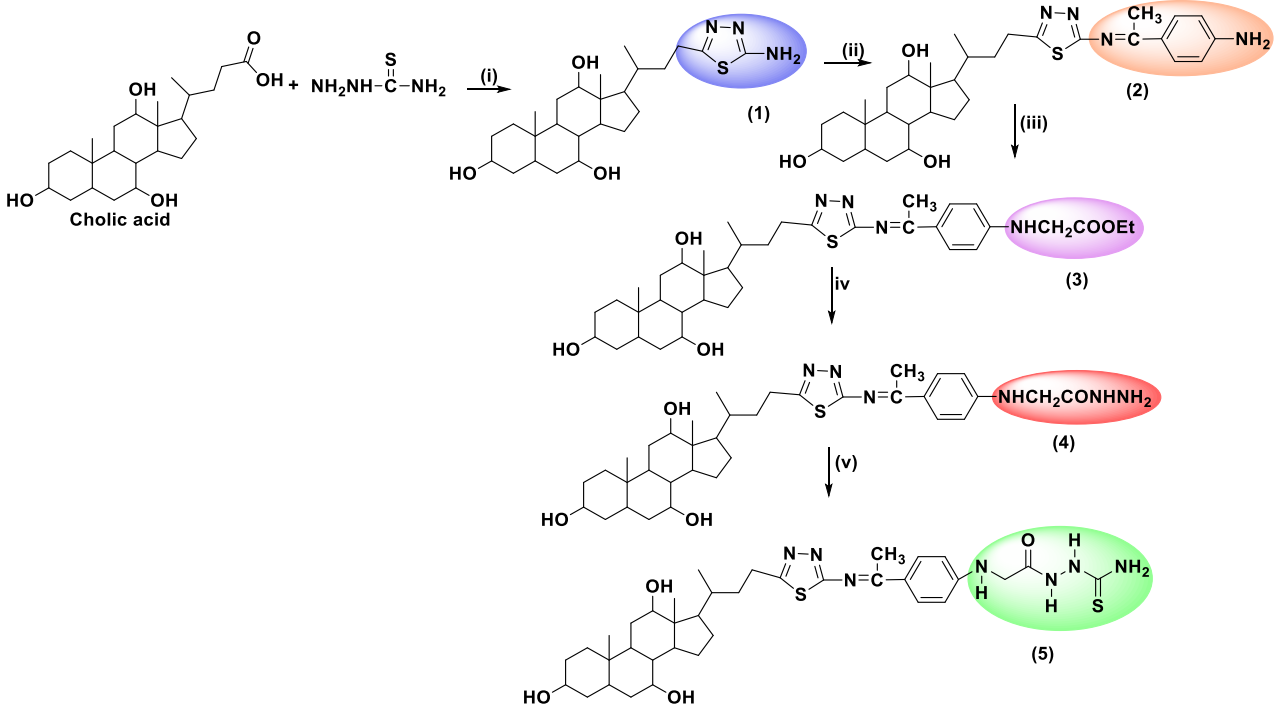
*2.1.11. Synthesis of compound (**11**)*

Compound (**10**) (0.01 mol) was dissolved in ethyl alcohol (30 mL) and then added to a solution comprising five drops of glacial acetic acid with chlorobenzaldehyde (0.01 mol). The synthesis conditions of compound (**7**) were employed to obtain the title compound (**10**), which gave a pale green solid, m.p: 230-231°C, and 74% yield. v_{max} 3025, 2922, 2850, 1670, 1544, 1433, 687 cm^{1}

3. RESULT AND DISCUSSION

The preparation of new substituted oxadiazoles, thiadiazols, triazoles, and Schiff bases starting from cholic acid, hydrazide, and substituted thiosemicarbazide, as well as their antibacterial evaluation, have been carried out according to a known protocol. Firstly, treating cholic acid with thiosemicarbazide gave 2-choly-5-amino-1,3,4-thiadiazol (**1**). The structure was confirmed by IR, which gave absorption at 3380, 1665, 1107,1050 cm^{-1} related to N-H, C=N, and C-S-C, respectively. Compound (**1**) was then treated with 4-aminoacetophenone and conc. HCl in ethyl alcohol to produce hydrazone (**2**), F.T-IR spectrum for compound (**2**) showed absorption for the C=N group at 1686–1661 cm^{-1} and for the aromatic C–H at 3050–3117 cm^{-1}. The ^{1}H-NMR spectrum showed two doublets at 7.41 and 6.68 ppm, which belong to aromatic protons of para-substitution, a singlet at 5.49 for the NH_2 group and a singlet at 2.42 for (3H) corresponding to methyl (CH_3) group of hydrazone. The ester compound (**3**) was then synthesized through the reaction between hydrazone (**2**) with ethyl 2-bromoacetate. The structure of the product was elucidated and confirmed by IR spectrum, which gave an absorption band at 1741 cm^{-1} for the carbonyl group; also ^{1}H-NMR recognized the structure by demonstrating a quartet at 4.15 ppm for methylene group (CH_2) and a triplet at 1.36 ppm for methyl group (CH_3).^{13}C-NMR gave two

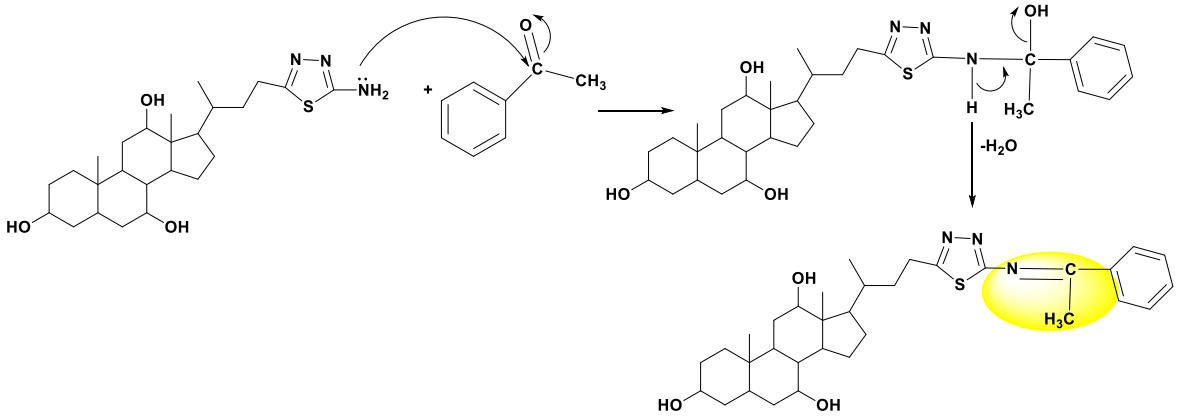
distinguished peaks belong to carbonyl at 170.2 ppm and 60.6 ppm for the carbon of methylene group. The conversion of ester (**3**) to acid hydrazide (**4**) was completed via the reaction with $N_2H_4.H_2O$ \ EtOH. The structure of (**4**) presented bands in IR spectroscopy at 3360 and 1669 cm^{-1} for (N-H) and (C=O) groups, respectively. ^{1}HNMR gave two peaks at 7.10 and 2.63 ppm for NH and NH_2. The substituted thiosemicarbazide (**5**) was prepared via the reaction of acid hydrazide and ammonium thiocyanate, which clearly showed IR absorbance at 3314 (N-H), 1667 (C=O) and 1210 (C=S) cm^{-1}. The ^{1}H-NMR exhibited a signal at 6.18 ppm for NH_2 next to the (C=S) group, and ^{13}C-NMR appeared peaks at 181.3 and 169.6 ppm for (C=S) and (C=O), respectively. All spectral data confirmed the structure formation of the compound (**5**).



Scheme 1: Preparation of substituted thiosemicarbazide (**5**).

Reagents and conditions:(i) Cholic acid, conc. H_2SO_4, steam bath (ii) EtOH, 4-aminoacetophenone, refl. (iii) abs. EtOH, bromo ethyl acetate, $NaHCO_3$, refl (iv) $N_2H_4.H_2O$ 85% abs.EtOH, refl (v) ammonium thiocyanate abs. EtOH. HCl, refl.

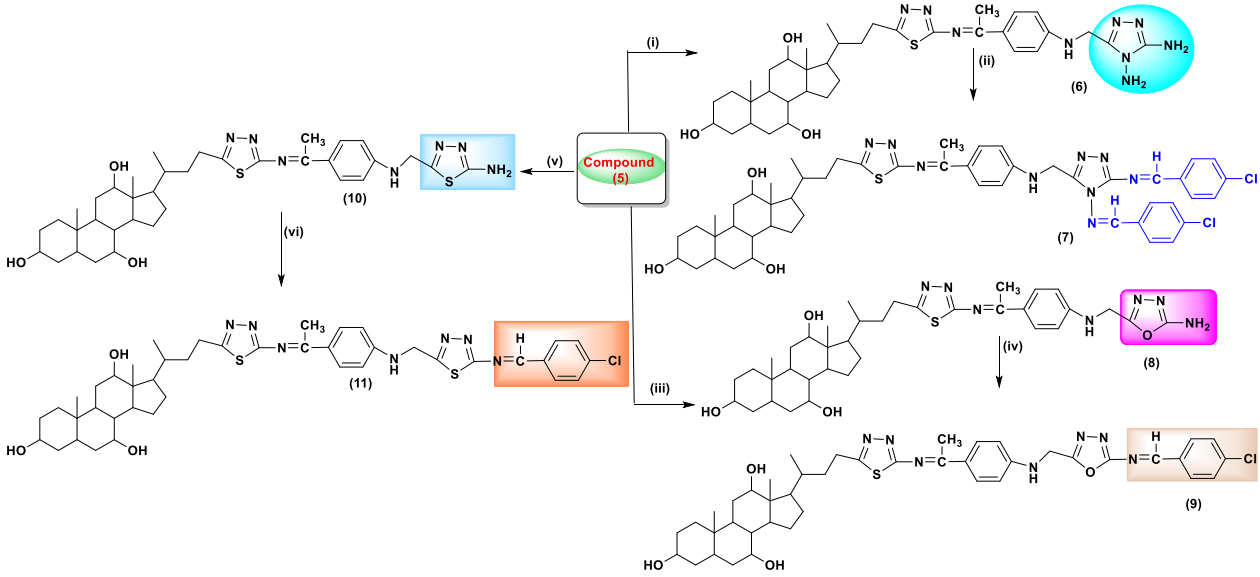
The following steps showed the suggested mechanism for the Schiff base formation reaction (39).



The substituted thiosemicarbazide (**5**) was then divided into three portions, which were converted to substituted 1,2,4-triazole (**6**), 1,3,4-oxadiazole (**8**), and 1,3,4-thiadiazole (**10**) via the reaction with hydrazine hydrate, mercuric oxide, and concentrated sulfuric acid, respectively. The IR spectral data of substituted 1,2,4-triazole (**6**) presented absorption at 3419,3320 cm^{-1} due to (NH) and 1620 cm^1 belonging to the (C=N) group. The ^{1}HNMR gave signals for two NH_2 groups at 5.42 and 4.56 ppm, respectively. The

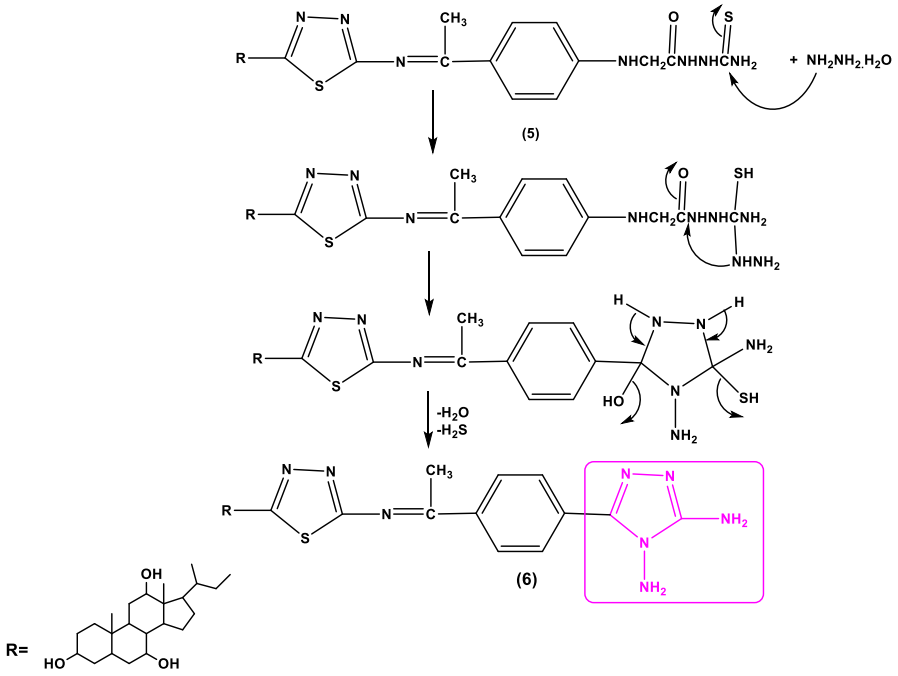
cyclization of (**5**) was successfully accomplished to offer the corresponding compounds [substituted 1,3,4-oxadiazole (**8**) and substituted 1,3,4-thiadiazole (**10**)]. Infrared spectrum gave absorbance in cm^{-1} at 3382, 3289 (NH_2), 1620 (C=N), 1110 (C-O-C) for compound (**8**) while compound (**10**) offered 3385,3278 (NH_2),1635 (C=N), 1096 (C-S-C). Finally, a series of Schiff bases (**7**, **9**, and **11**) were synthesized successfully via the reaction of substituted 1,2,4-triazole (**6**), 1,3,4-oxadiazole (**8**), and 1,3,4-thiadiazole (**10**) with 4-chlorobenzaldehyde and concentrated hydrochloric acid in ethanol. Again, the structure of the prepared Schiff bases was characterized by IR, compound (**7**) showed bands at 3035 cm^{-1} related to aromatic C-H, 1706 cm^{-1} for C=N and 688 cm^{-1} due to C-Cl, the ^{1}H- NMR confirmed the structure of the desired product by presenting two singlets at 8.83 (1H) and 8.66 (1H) ppm related to protons in two azo-methane CH=N groups, in addition,^{13}C-NMR gave peaks at 167.7 and 160.7 ppm for carbon atoms in two CH=N groups, peaks at 138.6, 138.5 ppm were also obtained for C-Cl. The IR spectrum proved the structure of compounds **8** and **10** by the disappearance of the stretching bands belonging to the carbonyl and thione groups. However, it was demonstrated absorption in cm^{-1} at (3424-3162), (3421-3370),1612,1623, 3055,3053, (1164-1033), and 1034 corresponding to the following groups NH, C=N, aromatic C-H, C-O-C, and C-S-C respectively. For compounds (**8** and **10**), the structures were also verified by NMR data. Also, characteristic peaks that are required to approve the chemical structure of compounds (**9** and **11**) were shown by ^{1}H-NMR spectrum, which exhibited multiple in the range of 7.02-8.28 ppm related to aromatic protons, singlet of CH = N proton at (8.34 ppm/ comp. 9), (876 ppm/ comp 11) respectively.

The proposed mechanism below shows the steps for the cyclization of substituted thiosemicarbazides (**5**) to substituted 1,2,4-triazole (**6**).



Scheme 2: Preparation of compounds (6-11).

Reagents and conditions:(i) $N_2H_4.H_2O$ 85% refl., (ii) EtOH, glacial acetic acid,chlorobenzaldehyde, refl.;(iii) HgO, MeOH, refl (iv) EtOH, glacial acetic acid,chlorobenzaldehyde, refl; (v) conc. H_2SO_4,90 °C (vi) EtOH, glacial acetic acid, chlorobenzaldehyde, refl.



4. THE BIOLOGICAL STUDY

In the current work, the two bacteria *S. aureus* and *P. aeruginosa* have been used in sensitivity tests by the disc diffusion method for the synthesized compounds (**2**, **5**, **7**, **8**, and **11**), with the results shown in Table 1. These different compounds have shown antibacterial activities against the bacteria mentioned above and can inhibit the growth of these two types. The species *S. aureus* was inhibited at a concentration of 200 mg/mL for compound **11** (23 mm) and (21 mm) for compound **8**, while compounds **2**, **5**, and **7** have inhibition zones (15, 20, and 19 mm), respectively. The species *P. aeruginosa* was inhibited at a 200 mg/mL concentration for compounds **5**, **8**, and **11** (21, 20, and 18 mm), respectively. Compounds **7** and **2** at 200 mg/mL have (16 and 14 mm), respectively.

Table 1: Biological activity of some prepared compounds.

Compound No.	Concentration mg/mL	Bacteria	
		S. aureus	***P.aeruginosa***
2	200	15	14
	100	12	11
	50	7	8
	25	7	5
	12.5	0	0
5	200	20	21
	100	17	14
	50	15	13
	25	13	8
	12.5	8	0
7	200	19	16
	100	16	12
	50	9	9
	25	0	5
	12.5	9	0
8	200	21	20
	100	17	17
	50	9	17
	25	0	8
	12.5	0	0
11	200	23	18
	100	19	14
	50	15	11
	25	12	8
	12.5	6	0
Amikacin (amk)	20 mg/dick	21	20

5. CONCLUSION

The target compounds, including 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, 1,2,4-triazoles, and Schiff bases, were successfully synthesized utilizing cholic acid as the initial substance. The chemical structures developed have been elucidated and confirmed using FTIR and 1H,13C-NMR spectroscopy. A preliminary assessment of bio-activity has indicated that several chemicals (refer to Table 1) exhibit noteworthy action against specific pathogenic organisms. In addition, the synthesized chemicals could be examined for a range of further bio-applications.

6. CONFLICT OF INTEREST

In relation to this study, the authors declare that they have no competing interests.

7. ACKNOWLEDGMENTS

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