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Research Article

Synthesis, characterization, and antimicrobial evaluation of new Schiff bases derived from vanillic acid conjugated to heterocyclic 4*H*-1,2,4-triazole-3-thiol

Noor Ali Hussein Sabzi[1], May Mohammed Jawad Al-Mudhafar[1]

1 *College of Pharmacy, University of Baghdad, Baghdad, Iraq*

Corresponding author: Noor Hussein (noorsabzi1989@gmail.com)

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Abstract

A multistep synthesis was established for the preparation of a new vanillic acid-1, 2, 4- triazole-3-thiol conjugate (**4**). Finally, several aromatized aldehydes reacted with compound (**4**) to produce Schiff bases derivatives (**5–11**). The purpose of this research is to prepare new vanillic acid derivatives with 1, 2, 4-triazole-3-thiol heterocyclic ring structures and to evaluate their antimicrobial activity in a preliminary assessment. Fourier-transform infrared (FT-IR) and proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) were used to verify the structures of the newly synthesized compounds. all the final synthesized compounds **(5–11)** were tested for antimicrobial activity. The findings of this study demonstrate the viability of synthesizing vanillic acid combined with a 1, 2, 4-triazole-3-thiol ring derivative, which then reacted with various aldehydes to yield several new Schiff bases derivatives. Finally, the presence of an electron-withdrawing group at the fourth position (*p*- chloro group) of the aromatic ring improves the antibacterial activity of the derivative of the vanillic acid-triazole conjugate. Compound **8** with para chloro substituted Schiff base derivative showed potent activity when compared to other final derivatives but of no activity toward *K. pneumonia*.

Keywords

Vanillic acid, 4*H*-1, 2, 4- Triazole-3-thiol, Schiff's Bases, Antimicrobial Activity

Introduction

Heterocyclic compounds are the most significant complicated toroidal branches of organic compounds whose atomic structures contain one (mostly five or six-membered rings) with at least one heteroatom, the most prevalent heteroatoms are oxygen, nitrogen, and sulfur (Hossain and Nanda 2018). Heterocycles having Sulfur and nitrogen atoms are present in naturally occurring substances, commercially available medications, and substances with the potential to be active pharmaceutical constituents (Ardón-Muñoz and Bolliger 2022).

In general, the reaction that occurs between substances containing amino groups (NH_2, NH_2OH, NH_2–NH_2, etc.) and other carbonyl groups (aldehydes or specific ketones) is known as the Schiff base reaction, which was named after the German chemist Hugo Schiff (Schiff 1864). Schiff bases derived from 1, 2, 4- triazole exhibited powerful biological effects. In particular, they are antibacterial (Bader et al. 2020), antifungal (Sumangala et al.

2013), antitubercular (Mohan Krishna et al. 2014), antioxidant1(Aktas-Yokus et al. 2015), antitumor (Bekircan et al. 2006; Li et al. 2012), analgesic (Vijesh et al. 2013), anti-inflammatory (Karrouchi et al. 2016), and pesticide (Wang et al. 2011).

Vanillic acid (4-hydroxy-3-1methoxybenzoic acid, V+A1) is a benzoic acid derivative. It is a vanillin oxidized form that is produced when vanillin is converted into ferulic acid. It is used as a flavoring agent, food additive, and preservative in the food industry (Kaur et al. 2022). The pharmacological activities of vanillic Acid itself can be outlined; sedative activity (Ingole et al. 2021), antidepressant effects (Wang et al. 2019), antinociceptive effects (Khoshnam et al. 2017), antihypertensive (Ingole et al. 2021), anticancer effects (Gong et al. 2019), antifungal activities (Vishnu et al. 2018), antioxidant activity (Vinothiya and Ashokkumar 2017) and anti-diabetic activity (Gupta et al. 2021). Many vanillic acid derivatives were produced and evaluated for different biological activities; vanillic Acid- oxadiazole Schiff bases showed interesting antibacterial activity (Tawfeeq and Qassir 2020a), novel ester-hybrid derivatives of vanillic acid were examined for their antibacterial activity, the methyl vanillate derivative has significant anti-bacterial activity against tested Gram-positive and Gram-negative bacteria (Satpute et al. 2019) Other series of amides derivatives of vanillic acid exhibit promising selective inhibitory effects against α–amylase, and α–glucosidase enzymes (Gupta et al. 2021).

There is a great need for more effective antibacterial and antifungal medication today because of the high mortality rates connected to bacterial and fungal infections as well as the rising number of multidrug1-resistant strains. Therefore this study aimed to synthesize new derivatives of vanillic acid incorporating a 1, 2, 4-triazole-3-1thiol ring connecting imine moiety with expected antimicrobial activity.

Materials and methods

All of the analytical-grade reagents and solvents were supplied by (Sigma-Aldrich Germany, Riedel-de Haën Germany, and Merck Germany). Incorrect melting points were obtained using the Stuart SMP3 melting point apparatus in open capillary tubes. The retention factor (R*f*) values were estimated using two solvent systems: the first: toluene: methanol (8:2) and the second: chloroform: ethyl acetate (7:3) (Mahdi et al. 2017b). The infrared spectra were determined using a Fourier Transform Infrared (FT-IR) spectrophotometer, Shimadzu, Japan, and the Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectrum was recorded using an NMR ultra shield spectrophotometer 500 MHz, BRUKER (Switzerland).

General synthetic procedure

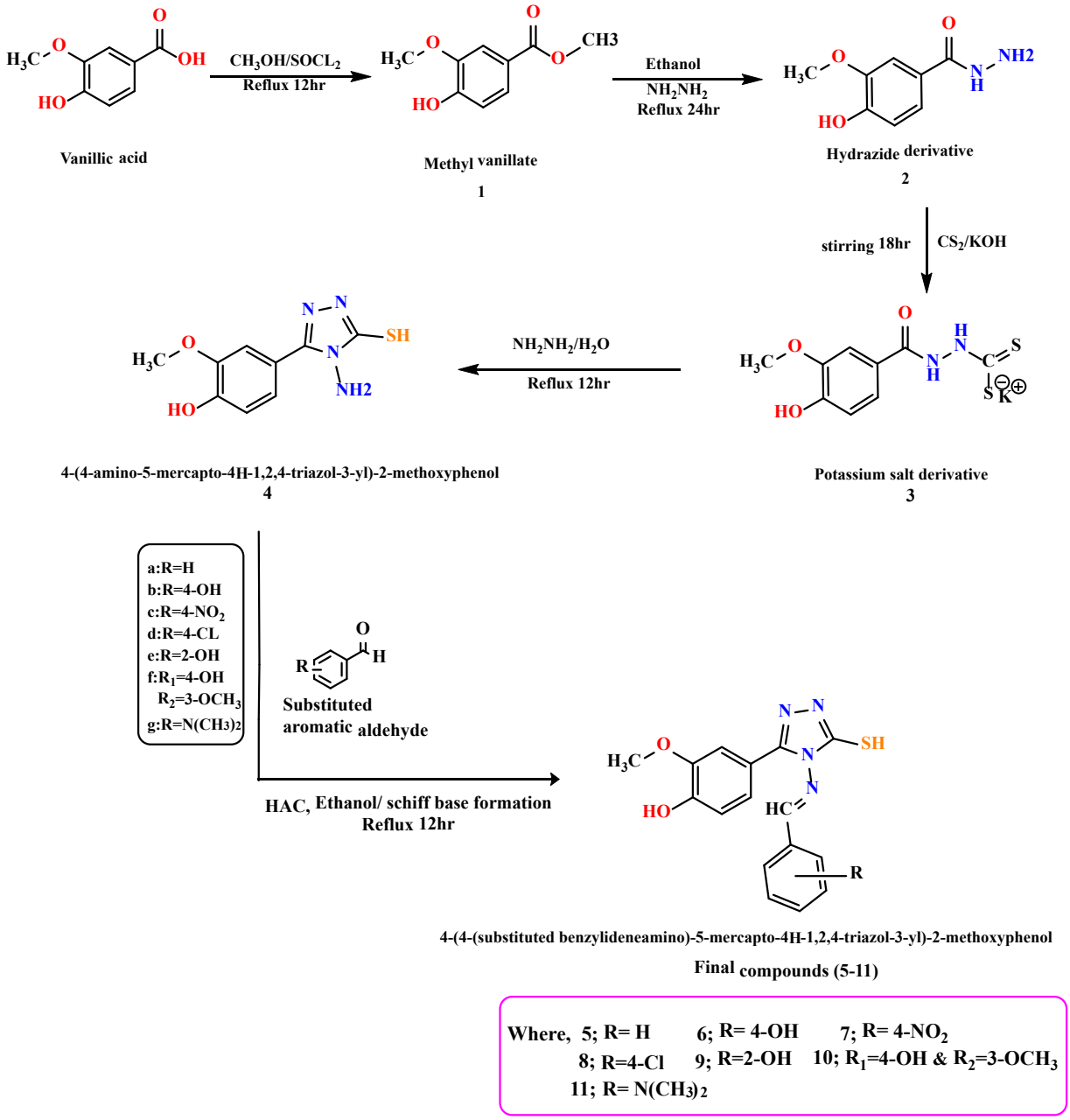
Scheme (1) provides a summary of the procedures for synthesizing the final compounds and their precursors. Methyl vanillate (compound **1**) was produced when the carboxy group of vanillic acid was esterified in the presence of thionyl chloride ($SOCl_2$) in cold MeOH. Then, methyl vanillate was combined with hydrazine hydrate to produce a hydrazide derivative (compound **2**), which was then involved in a reaction with carbon disulfide in presence of potassium hydroxide (KOH) to give potassium dithiocarbamate derivative (compound **3**), which then underwent cyclization with hydrazine hydrate to produce 1,2,4-1triazole-3-thiol heterocyclic ring derivative of vanillic acid (compound **4**). Several new azomethine derivatives, as final compounds (**5–11**), were produced by the reaction of the primary amine group of the 1, 2, 4-triazole ring with various aldehydes.

Synthesis of methyl 4-hydroxy-3-methoxybenzoate; methyl vanillate, Compound (1)

Vanillic acid (1.38 gm, 10 mmol) in methyl alcohol (50ml) was cooled to -20 °C, and then thionyl chloride ($SOCl_2$) (1.09ml, 15.5mmol) was added drop by drop. The obtained mixture was held for five hrs at 40 °C and another five hrs of refluxing, and then at room temperature for the remainder of the night. The Methyl alcohol was then evaporated to dryness, and the residue 1redissolved in absolute ethyl alcohol and evaporated. This operation was repeated many times until all of the unreacted thionyl chloride ($SOCl_2$) was removed. The residual was recrystallized from ether\methanol to give a compound (**1**). Chemical formula; ($C_9H_{10}O_4$), color, and appearance: the powder is white, yield 70%, and melting point: 60–62 °C (the previously observed m.p: 64 °C) (King 1939). **FT-IR** (υ, cm^{-1}): 3468 (OH str.), 3017 (C-H, aromatic str.), 2978 & 2839 (C-H, asymm. and symm. str. of -OCH_3 group), 1686 (C=O str. of carbonyl ester), 1597 & 1528 (aromatic, C=C, str.), 1227 (C-O-CH_3, asymm. str.).

Synthesis of 4-Hydroxy-3-methoxybenzohydrazid; compound (2)

Compound (**1**) (4.99g, 27mmol) was solubilized in a small quantity of 12ml of 99.8% ethanol, and 80% of hydrazine hydrate (13.5g, 270mmol) was added drop by drop. The mixture was refluxed for 24 hrs then monitored and checked by TLC. After cooling the reaction mixture, a precipitate began to form, it was filtered and dried in an oven set to 60 °C, yielding 2g of compound (**2**). The precipitate of the vanillic acid hydrazide was recrystallized from 70% ethanol to get the off-white crystals of the compound (**2**). Chemical formula; ($C_9H_{10}N_2O_3$), color and appearance: off-white colored powder, yield 60%, melting point: 208–210 °C (the previously reported melting point was 210–211 °C) (Kalb and Groß 1926). **FT-IR** (υ, cm^{-1}): 3306 (OH str. overlapped with N-H asymm. str. of primary amine), 3256 (N-H symm. str. of primary amine), 3209 (N-H symm. str. of sec. amide), 3051(Ar. C-H str.), 2939 & 2835 (C-H, asymm. and symm. str. of -CH_3 group), 1628 (C=O str. of amide), 1585 & 1504 (aromatic, C=C 1str.), 1273 (C-O-CH_3, asymm. str.).



Scheme 1. Synthesis of the target 1compounds and their intermediates.

Synthesis of potassium [(4-hydroxy-3-methoxyphenyl)formohydrazido] methanethioyl sulfanide, compound (3)

After mixing vanillic acid hydrazide (1.4 g, 10 mmol), potassium hydroxide (0.6 g, 15 mmol), and (2 ml, 25 mmol) carbon disulfide(CS_2) in 12 ml of absolute ethanol, followed by stirring for 18 hrs and then isolating the formed product diethyl ether (Husain et al. 2009). Compound (**3**), the potassium salt, was produced and used in the next step without needing to be purified. Chemical formula: ($C_9H_9KN_2O_3S_2$), color and appearance: off-white powder, yield 50%, m.p: 250 °C (decomp.). **FT-IR** (υ, cm^{-1}): 3333 (OH str. overlapped with (N-H) str. of NH-NH-CSS^- K^+), 3167(N-H str. of NH-NH-CSS^- K^+), 3059(Ar. C-H str.), 2973 & 2866 (C-H asymm. and symm. 1str. of CH_3 group), 1651 (C=O str. of amide), 1593 & 1508 (aromatic, C=C str.), 1277 (C=S str.).

Synthesis of 4-(4-amino-5-sulfanyl-4H-1, 2, 4-triazol-3-yl)-2-methoxyphenol; compound (4)

In a suspension, hydrazine hydrate 80% (1.1 ml, 22.1 mmol), compound (**3**) (4 g, 10.98 mmol), and 20 ml of distilled water were refluxed for 12 hours. A homogeneous solution was formed as a result of the evolution of hydrogen sulfide (H_2S) gas, which caused the reaction mixture to turn a greenish-brown color. After adding 100 ml of

cold water and then acidifying it with a few drops of diluted 35% HCl solution, a pale yellow solid precipitated (Husain et al. 2009). The solid product was filtered and washed with 50 ml of cold water twice, then recrystallized from 70% ethanol to form a faint yellow powder. Chemical formula :($C_9H_{10}O_2N_4S$), color and appearance: faint yellowish powder, yield 60%, melting point: (190–192 °C). **FT-IR** (υ, cm^{-1}): 3310 (OH str. overlapped with N-H asymm. str. of primary amine), 3229 (N-H symm. str. of primary amine), 3109 (Ar. C-H str.), 2935 & 2822 (C-H asymm. and symm. str. of CH_3 group), 2534 (S-H str. of thiol tautomer), 1604 (C=N 1str.), 1593 & 1504 (aromatic, C=C str.), 1207 (C=S str.). **^{1}H-1NMR** (δ ppm) 13.8 (s, 1H, SH), 9.66 (s, 1H, OH), 7.57–6.88 (m, 3H, Ar-H), 5.79 (s, 2H, N-NH_2), 3.81 (s, 3H, OCH_3).

Synthesis of Final compounds (5–11)

Compound (**4**) (1.1g, 3.29mmol) and (3.29 mmol) suitable aromatic aldehydes (benzaldehyde (**a**); 0.45ml, 4-hydroxybenzaldehyde (**b**); 0.42g, 4-nitrobenzaldehyde (**c**); 0.48g, 4-chlorobenzaldehyde (**d**); 0.48g, 2- hydroxybenzaldehyde (**e**); 0.48g, 4-hydroxy-3-methoxybenzaldehyde (**f**); 0.45g, 4-dimethylaminobenzaldehyde (**g**); 0.5g) were mixed, separately, with 25 ml absolute ethanol and heated to reflux on a water bath for 3–18 hours, then left stirring at room temperature for 24 hours, during the refluxing process 3 or 4 drops of glacial acetic acid were added. At the end of the reaction time, a rotary evaporator successfully evaporated the solvent, and the product was then generated by adding the residue to ice-cooled water. It underwent filtering, rinsing with cold water, and drying. The final product was purified and recrystallized from hot ethanol.

2-methoxy-4-{4- (phenylmethylidene) amino-5-sulfanyl-4*H-1*, 2, 4-triazol-3-yl} phenol, Compound (5):

Chemical formula: ($C_{16}H_{14}O_2N_4S$), color and appearance: a faint yellow powder, yield 60%, 1m.p: (210–212 °C). **FT-IR** (υ, cm^{-1}): 3210 (OH str. of phenol), 3400–2700 (hydrogen bonded O-H broadband), 3056 (aromatic, C-H str.), 2959 & 2854 (C-H str. of CH_3 group asymm. and symm.), 1601 (C=N str.), 1551 & 1508 (aromatic, C=C str.). **^{1}H-NMR** (δ 1ppm): 14.11 (s, 1H, SH), 9.71 (s, 1H, OH), 9.68 (s, 1H, N-N=CH)**,** 7.93–7.34 (m, 8H, Ar-H), 3.77 (s, 3H, OCH_3).

4-{4-[4-hydroxyphenyl) methylidene] amino]-5-sulfanyl-4*H*-1, 2, 4-triazol-3-yl}-2-methoxyphenol, Compound (6):

Chemical formula: ($C_{16}H_{14}O_3N_4S$), color and appearance: off-white powder, yield 60%, melting point: (230–232 °C). **FT-IR** (υ, cm^{-1}): 3483, 3248 (O-H str. of phenols), 2700–3300 (hydrogen bonded O-H broadband), 3086 (aromatic, C-H str.), 2931 & 2840 (C-H str. of CH_3 group asymm. and symm.), 1604 (C=N str.), 1562 & 1516 (aromatic, C=C str.). **^{1}H-NMR** (δ ppm): 14.02 (s, 1H, SH), 10.44 (s, 1H, OH), 9.73 (1s, 1H, OH), 9.32 (s, 1H, N-N=CH), 7.79–6.87 (m, 7H, Ar-H), 3.75 (s, 3H, OCH_3).

4-{4-[(4-nitrophenyl) methylidene] amino]-5-sulfanyl-4*H*-1, 2, 4-triazol-3-yl}-2-methoxy phenol, Compound (7):

Chemical formula: ($C_{16}H_{13}O_4N_5S$), color and appearance: faint orange powder, yield 70%, m.p:(248–250 °C). **FT-IR** (υ, cm^{-1}): 3244 (OH str. of phenol), 3124 (aromatic, C-H str.), 2966 & 2831 (C-H str. of CH_3 asymmetric and symmetric), 1604 (C=N str.), 1585 & 1512 (C=C str.), 1516 (NO_2 asymm. str.), 1346 (NO_2 symm. str.). **^{1}H-NMR** (1δ ppm): 14.19 (s, 1H, SH), 10.04 (1s, 1H, OH), 9.73 (s, 1H, N-N=CH), 8.19–6.92 (m, 7H, Ar-H), 3.83 (s, 3H, OCH_3).

4-{4-[(4-chlorophenyl)methylidene]amino]-5-sulfanyl-4*H*-1,2,4-triazol-3-yl}-2-methoxyphenol, Compound (8):

Chemical formula: ($C_{16}H_{13}O_2ClN_4S$), color and appearance: a yellow powder, yield 63%, is melting point: (210–212 °C). **FT-IR** (υ, cm^{-1}): 3117 (OH str.), 3300–2700 (hydrogen bonded O-H broadband) 3028 (aromatic, C-H str.), 2962 & 2831 (C-H str. of CH_3 group asymmetric and symmetric), 1604 (C=N str.), 1543 & 1512 (aromatic, C=C str.). **^{1}H-NMR** (δ ppm):, 14.12 (s, 1H, SH), 9.75 (1s, 1H, OH), 9.71 (s, 1H, N-N=CH), 7.66–6.92 (m, 7H, Ar-H), 3.77 (s, 3H, OCH_3)

4-{4-[(2-hydroxyphenyl)methylidene]amino]-5-sulfanyl-4*H*-1,2,4-triazol-3-yl}-2-methoxyphenol, Compound (9):

Chemical formula: ($C_{16}H_{14}O_3N_4S$), color and appearance: off-white powder, yield 60%, m.p:(224–225 °C).**FT-IR** (υ, cm^{-1}): 3248,3120 (O-H str. of phenols), 2700–3300 (hydrogen bonded O-H broadband), 3005(aromatic, C-H str.), 2954 & 2840 (C-H str. of CH_3 asymm. and symm.), 1601 (C=N str.), 1540 & 1519 (aromatic, C=C str.). **^{1}H-NMR** (1δ ppm): 14.09 (s, 1H, SH), 10.50 (s, 1H, OH), 9.89 (1s, 1H, OH), 9.75 (s, 1H, N-N=CH), 7.90–6.92 (m, 7H, Ar-H), 3.83 (s, 3H, OCH_3).

4-{4-[(4-hydroxy-3-methoxyphenyl)methylidene]amino]-5-sulfanyl-4*H*-1,2,4-triazol-3-yl}-2-methoxyphenol, Compound (10):

Chemical formula: ($C_{17}H_{16}O_4N_4S$), color and appearance: off-white fine powder, yield 60%, m.p: (177–178 °C). **FT-IR** (υ, cm^{-1}): 3383, 3240 (OH str.) of phenol group of vanillic acid and another phenol group of vanillin (aldehyde), 3300–2700 (hydrogen bonded O-H broadband) 3109 (aromatic, C-H str.), 2935 & 2871 (C-H str. of CH_3 group asymmetric and symmetric), 1604 (C=N str.), 1577 & 1512 (aromatic, C=C str.). 1^1**H-NMR** (δ ppm):, 14.03 (s, 1H, SH),9.72 (1s, 1H, OH), 9.65 (s, 1H, OH), 9.29 (s, 1H, N-N=CH), 7.58-6.88 (m, 6H, Ar-H), 3.85 & 3.83 (s, 3H, OCH_3).

4-{4-{[4-(dimethylamino)phenyl]methylidene}amino]-5-sulfanyl-4*H*-1,2,4-triazol-3-yl}-2-methoxyphenol, Compound (11):

Chemical formula: ($C_{18}H_{19}O_2N_5S$), color and appearance: faint-orange powder, yield 62%, m.p: (196–197 °C).

FT-IR (υ, cm^{-1}): 3375 (OH str.), 3300–2700 (hydrogen bonded O-H broadband) 3101 (aromatic, C-H str.), 2920 & 2854 (C-H str. of CH_3 group asymmetric and symmetric), 1612 (C=N str.), 1589 & 1512 (aromatic, C=C str.). **^{1}H-NMR** (δ ppm): 13.94 (s, 1H, SH), 9.67 (1s, 1H, OH), 9.16 (s, 1H, N-N=CH), 7.50–6.80 (m, 7H, Ar-H), 3.82 (s, 3H, OCH_3), 3.03 (s, 6H, NCH_3).

In vitro Antimicrobial screening

The newly synthesized compounds (1,2,4-triazole-3-thiol derivatives) were evaluated for antimicrobial activity as primary screening in one concentration against Gram-positive (*Staphylococcus aureus*, *B. subtilis*) and Gram−1negative (*Escherichia coli*, *Pseudomonas aeruginosa*, *P. mirabilis*, and *Klebsiella pneumonia*) bacteria and (*Candida albicans*) fungi by using well diffusion technique (Balouiri et al. 2016). The inhibition zone (IZ) was measured in mm. and compared with three different standards; Amoxicillin, Ciprofloxacin, and Fluconazole. All the examined and standard compounds were dissolved in dimethyl sulfoxide (DMSO.) to give a concentration of 200mg/ml. The *in vitro* antimicrobial activity was evaluated by the Aljazeera Company (J.P.I).

Results and discussion

Chemistry

The seven final derivatives of vanillic acid Schiff bases (**5–11**), as well as the four intermediates (1–4), were produced using the classical chemical processes, which are described in Scheme 1. In the first step, Vanillic acid was esterified using methyl alcohol in the presence of thionyl chloride to produce an intermediate termed acyl chloride, which then reacted with the initial alcohol (MeOH) to yield methyl ester of vanillic acid compound **(1)** and was distinguished by carbonyl moiety of aromatic ester at 1686 cm^{-1} in its **FT−IR** spectrum.

The process used to synthesize a compound (**2**) essentially occurred under basic conditions (hydrazinolysis of ester), with two hydrazine molecules acting as the rate-determining step. The next-1step involves steadily leaving one molecule of hydrazine with one alcohol molecule (Tawfeeq and Qassir 2020b). For compound (**2**), two stretching vibration bands for the primary amine of the hydrazide molecule were present in the FT-IR spectrum at 3306 cm^{-1} and 3256 cm^{-1}, respectively, a characteristic NH amide band at 3209 cm^{-1} stretching vibration, as well as a stretching vibration carbonyl amide band at 1628 cm^{-1}, and NH_2 bending vibration band at 1601 cm^{-1}.

The combination of acid hydrazide (compound **2**) with carbon disulfide (CS_2) in an ethanolic potassium hydroxide solution will give the potassium salt derivative; compound (**3**). The reaction is a nucleophilic addition process and the product was the potassium salt of the more stable dithiocarbamic acid than the free acid (Braverman et al. 2005; Rudorf 2007; Schroeder 1955). The **FT-IR** spectrum was distinguished by stretching vibration bands at 3333 cm^{-1} OH str. overlapped with (N-H) str. of NH-NH-CSS^-K^+, 3167cm^{-1} (N-H) str. of NH-NH-CSS^-K^+ and 1651cm^{-1} (C=O)str. of amide.

Then potassium salt intermediate was cyclized using hydrazine hydrate to give the 1, 2,4-triazole-3-thiol derivative of vanillic acid. The carbonyl group is attacked by the hydrazine with loss of water molecules, intra-molecular cyclization by adjacent moiety nucleophile amine attacking the carbon of carbon disulfide (CS_2) by nucleophilic substitution reaction, and the formation of the potassium salt occurred with a loss of H_2S gas. Acidification of the potassium salt with concentrated hydrochloric acid (35%) generated compound **4** (Mahdi et al. 2017a). The **FT-IR** spectrum of this compound was characterized by (N−H) asymmetric str. of primary amine overlapped with 3310 cm^{-1} OH str. and 3229 cm^{-1} (N−H) symmetric str. of primary amine and disappearance of 1651cm^{-1} carbonyl band of salt. **^{1}H-NMR** was distinguished by the appearance of a distinct signal at 5.79 ppm (s, 2H, N-NH_2).

The free amine of 1, 2, 4-triazole ring of compound **4** was reacted with various aldehydes (**a**-**g**) to produce a variety of Schiff bases derivatives of vanillic acid. In this reaction, Schiff bases (imines) (**5–11**) were produced as a result of the primary amine attacking the carbon of the carbonyl group in an acidic medium (Mahdi et al. 2017b). The absence of both vibration bands at 3310 cm^{-1} and 3229 cm^{-1} of NH_2 in **FT-IR** spectra indicates the formation of the imine group, as well as the new bands (1601–1604) cm^{-1}, indicating the (-C=N) formation in **FT-IR** spectra. **^{1}H-NMR** was distinguished by the appearance of new signals at 9.75 to 9.16 (s, 1H, N-N=CH) for compounds (**5–11**), and the disappearance of the signal at the 5.79 ppm for the NH_2 group.

Antimicrobial evaluation

According to the findings in Table 1; for the anti-bacterial assessment, all the prepared compounds exhibited moderate to potent anti-bacterial activity towards *E. coli* at 200 mg/mL, and less activity or inactive against *K. pneumonia*, *P. mirabilis*, *S. aureus*, and *B. subtilis* at the same concentration compared to the standard drugs (amoxicillin and ciprofloxacin).

Furthermore, compound **8** with *para* chloro substituted Schiff base derivatives at 200mg/ml concentration showed moderate activity against all tested bacteria comparable with amoxicillin drug and no activity toward *K. pneumonia*. The other targeting compounds were not effective against Gram-negative bacteria (*P. mirabilis*) even amoxicillin (standard drug), while only compound **8** showed moderate activity. Because compound **8** has a chlorine atom, which considerably improves the lipophilicity of the molecule and therefore its activity, then it has better activity, Salihović et al. hypothesize that the presence of chlorine in Schiff bases may lead to an increase in compound activity (Salihović et al. 2021).

Table 1. Antimicrobial activities of the target compounds **(5-11)**, in concentration (200 mg/ml).

Compound	(IZ) Inhibition zone in mm						
	Gram-positive		Gram-negative				Fungus
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumonia*	*P. mirabilis*	*P. aeruginosa*	*C. albicans*
5	_	_	**18**	**13**	_	**12**	**5**
6	_	_	**16**	**14**	_	_	_
7	**10**	**12**	**12**	_	_	**8**	_
8	**18**	**12**	**16**	_	**13**	**14**	_
9	_	_	**18**	**10**	_	_	_
10	_	_	**16**	**8**	_	_	_
11	**10**	_	**12**	_	_	_	_
Amoxicillin*	**30**	_	**15**	**10**	_	**35**	_
Ciprofloxacin*	**52**	**28**	**30**	**18**	**45**	**40**	-
Fluconazole**	_	_	_	_	_	_	**30**
DMSO***	_	_	_	_	_	_	–

* Standard drugs for antibacterial activity, ** Standard drug for antifungal activity, IZ = inhibition zone. Highly active (IZ = more than 15 mm), moderately active (IZ = 10–15 mm), slightly active (IZ = 5–10 mm), and no activity (IZ = (-))(Sahib and Mohammed 2020).

For antifungal activity against *C. albicans*; the tested compounds exhibited no activity, except compound **5** exhibited low activity compared to fluconazole (standard drug).

Finally, the results obtained in Table 1 proved that these vanillate-triazole Schiff base derivatives showed good antibacterial than antifungal effects.

Conclusion

Seven derivatives of 4-(4-(substituted benzylidene amino)-5-mercapto-4*H*-1, 2, 4-triazol-3-yl)-2-methoxy phenol are synthesized in good yields and characterized by FT-IR and NMR spectroscopies. 1, 2, 4-.Triazoles are found to have potential antibacterial activity, and conjugation of 1, 2, 4-triazole-3-thiol, with another natural antibacterial compound such as vanillic acid might provide new and more effective .antibacterial candidates.

The conjugation of the 1heterocyclic ring (4*H*-1, 2, 4-triazole) to vanillic acid molecule will improve the antimicrobial activity of vanillic acid, this depends on the type of aldehyde molecule that forms an imine base with that heterocyclic ring. The incorporation of substituted .aromatic aldehyde which possesses an electron-withdrawing group at the *para* position, named *p*-chlorobenzaldehyde, increases the antibacterial activity of vanillate-triazole Schiff base derivatives.

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