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Synthesis, Characterization and Antimicrobial Activity of Some Schiff's Bases of 1, 2, 4-Triazole

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Abstract

Schiff bases are aldehyde- or ketone-like compounds in which the carbonyl group is replaced by an imine or azomethine group. They are widely used for industrial purposes and also exhibit a broad range of Antimicrobial Activity. The extreme efforts have been developed to design novel series of Schiff 's bases with triazole ring (8a and 8b) have been synthesized from 4-Amino-5-((4-amino-5-phenyl-4H-1,2,4-Triazol-3-ylthio)methyl)-4H-1,2,4-Triazole-3-thiol (7), which is built by multiple consecutive cyclization reactions starting from benzoic acid hydrazide (1). Infrared spectroscopy and melting points were used to characterize the synthesized compounds. The biological activity of compounds (7) and (8a and 8b) were evaluated toward gram negative bacteria (Escherichia coli) and gram positive bacteria (staphylococcus aureus).

Key words : Schiff's Base, 1,2,4-Trizole, Antimicrobial Activity.

Introduction

Heterocyclic compounds containing nitrogen, oxygen and sulphur have considerably a lot of attention due to wide application of pharmacological activity. Nitrogen, oxygen and sulfur are considered the most hetero atoms known[1]. 1,2,4-Triazoles are very objective for medicinal and pharmaceutical applications. 1,2,4-triazole derivatives investigated due to their wide range of biological activities such as antifungal, antibacterial[2-5], ant tubercular[6], anticonvulsants[7,8], antiviral[9], anti-inflammatory[10-12], antioxidant[5, 13,and 14], urease inhibitors[5,15], lipase inhibitors[15], and anticancer agents[16-20]. Also they used

as anticorrosion[21], and acid-based indicator[22]. The compounds carrying azomethine functional group (–C=N–) which are known as Schiff bases have gained importance in medicinal and pharmaceutical fields due to the most versatile organic synthetic intermediates and also showing a broad range of Antimicrobial Activity[23]. All of these remarkable observations opened horizon to prepare a new Schiff bases of 1, 2, 4-triazole, which expected to have Antimicrobial potency.

Experimental

All the chemicals and solvents were purchased from Fluka, BDH and Thomas Baker companies, used without further purification. FT-IR measurements were recorded on Shimadzu model FTIR-8400S. The melting points were determined on Electro thermal capillary apparatus (Chachan, MLP-01) and are uncorrected;

Synthesis of benzoic acid hydrazide (1) :

A mixture of methyl benzoate (0.01 mol, 1.36 g) and hydrazine hydrate (0.015 mol, 0.73 ml) was refluxed in existence of absolute ethanol for 4 hours. The product was isolated and recrystallized from ethanol[24].

Synthesis of potassium 2-benzoyl hydrazine carbodithioate (2) :

A mixture of benzoic acid hydrazide (0.01 mol, 1.36 g), potassium hydroxide (0.015 mol, 0.84 g) and (0.025 mol, 1.8 ml) carbon disulfide in (12.5 ml) of absolute ethanol was stirred for 16 hours and product was isolated from diethyl ether [24]. The potassium salt thus obtained was used in the next step without further purification.

Synthesis of 4-amino-5-phenyl-4H-1, 2, 4-triazole-3-thiol (3) :

A suspension of potassium salt dithiocarbazinate (0.01 mol, 2.5 g), hydrazine hydrate (0.02 mol, 0.97 ml) and water (40 ml) was refluxed for 8 hours. The color of the reaction mixture changed to green, hydrogen sulphide was liberated and a homogenous solution resulted. A white solid was precipitated by dilution with cold water (50 ml) and acidification with concentrated hydrochloric acid. The product was filtered, washed with cold water and recrystallized from ethanol[25].

Synthesis of ethyl 2-(4-amino-5-phenyl-4H-1, 2, 4-triazol-3-ylthio) acetate (4) :

To a solution of compound (3) (0.01 mol, 1.92 g) in absolute ethanol (20 ml), ethyl chloroacetate (0.02 mol, 2.13 ml) was added. The mixture was refluxed under stirring for 30 minutes in the presence of potassium hydroxide (0.01 mol, 0.56 g). Then, the solvent was evaporated to give the solid product. The crude product was recrystallized from H_2O:C_2H_5OH (1:1)[26].

Synthesis of 2-(4-amino-5-phenyl-4H-1,2,4-triazol-3-ylthio)acetohydrazide (5) :

A mixture of ester (4) (0.05 mol, 13.9 g) and hydrazine hydrate (0.075 mol, 3.64 ml) were refluxed in (10 ml) absolute ethanol for 2 hours. The solvent evaporated and the precipitate recrystallized from tetra chloromethane[26].

Synthesis of potassium 2-(2-(4-amino-5-phenyl-4H-1,2,4-triazol-3-ylthio) acetyl)hydrazine carbodithioate (6) :

A mixture of compound (5) (0.01 mol, 2.64 g), potassium hydroxide (0.015 mol, 0.84 g) and (0.025 mol, 1.8 ml) carbon disulfide in 12.5 ml of absolute ethanol was stirred for 16 hours and product was isolated from diethyl ether. The potassium salt thus obtained was used in the next step without further purification.

Synthesis of 4-amino-5-((4-amino-5-phenyl-4H-1,2,4-triazol-3-ylthio)methyl)-4H-1,2,4-triazole-3-thiol (7):

A suspension of salt (6) (0.01 mol, 3.78 g), hydrazine hydrate (0.02 mol, 0.1 ml) and water (40 ml) was refluxed for 8 hours. The color of the reaction mixture changed to green, hydrogen sulphide was librated and a homogenous solution resulted. A white solid was precipitated by dilution with cold water (50 ml) and acidification with concentrated hydrochloric acid. The product was filtered, washed with cold water and recrystallized from ethanol.

General procedure for the synthesis of 4-arylideneamino-5-((4-(arylideneamino)-5-phenyl-

4H-1, 2, 4-triazol-3-ylthio) methyl)-4H-1, 2, 4-triazole-3-thiol (8a) and (8b):

A mixture of (7) (0.01 mol, 3.2 g) and various aromatic aldehydes (0.02 mol) in (50 ml) absolute ethanol and two drops of glacial acetic acid, then refluxed for about 3 hours. Precipitate was filtered, dried and recrystallized from ethanol[27].

Biological activity :

The Antimicrobial test was performed according to the disc diffusion method[28]. Compounds (1-7), (8a) and (8b) were assayed for their antibacterial activity in vitro against two strains of bacteria was gram negative (Escherichia coli) and the other was gram positive (staphylococcus aureus). Prepared agar and Petri dishes were sterilized by autoclaving for 45 minutes at 121^0 C. The agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably spaced apart holes were made all 6 mm in diameter. These holes were filled with 0.1 ml of the prepared compounds with a concentration of (25 µg/ml) for each compound. Amoxicillin and Ceftriaxone were used as references antibiotic drugs with concentration of (25 µg/ml)[2], DMSO was used as a solvent[2]. One of these holes were filled with DMSO as control, to see the effect of solvent, these plates were incubated at 37 ^{0}C for 24 hours.

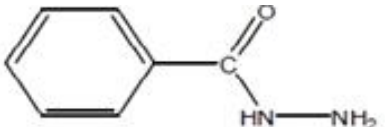
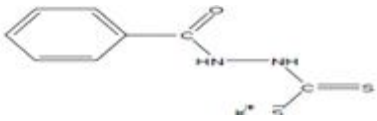
Results

Compounds (1), 8(a) and 8(b) were synthesized as shown in scheme (1). Some physical properties for these synthesized compounds were listed in table (1).

Table 1. Physical Properties for synthesized Compounds [1-8 (a and b)]

S.No.	Chemical Formula	Molecular Weight(g/mol)	Color	Melting Point (C°)	Yield (%)
1	$C_7H_8N_2O$	136.15	White	111-113	75.4
2	$C_8H_7KN_2OS_2$	250.38	Yellow	187-189	85
3	$C_8H_8N_4S$	192.24	White	199-201	60
4	$C_{12}H_{14}N_4O_2S$	278.33	White	175-177	57
5	$C_{10}H_{12}N_6OS$	264.30	White	215-217	68
6	$C_{11}H_{11}KN_6OS_3$	378.53	Yellow	270-272	80
7	$C_{11}H_{12}N_8S_2$	320.39	Yellowish White	209-211	55
8a	$C_{25}H_{20}N_8S_2$	496.60	Pale Yellow	180-182	87
8b	$C_{25}H_{18}Br_2N_8S_2$	654.40	Pale Yellow	120-122	61

Table 2. Spectroscopic Properties of synthesized Compounds [1-7]

	Structure of Compound	FTIR Spectra (cm^{-1})
1		3414cm^{-1} for N-H,(3298,3197)cm^{-1} for NH_2 group, 3024cm^{-1} for H- aromatic, and1658cm^{-1} duetocarbonylgroup.
2		(3383,3201) cm^{-1} for two N-Hgroups, 3028cm^{-1} dueto Haromatic, 702cm^{-1} which referto the appearances of C-Sband, and 1141 cm^{-1} for C=Sband.

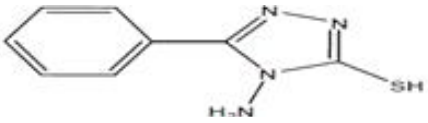
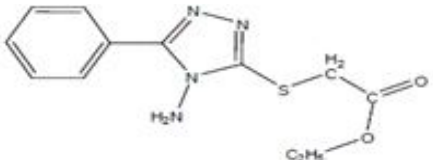
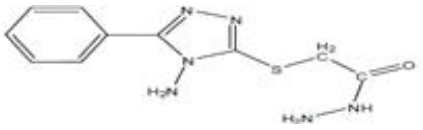
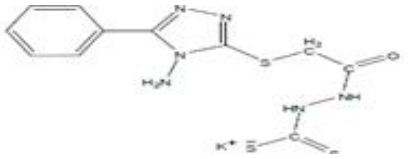
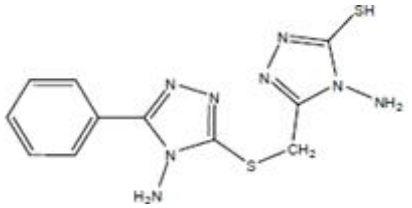
3		(3298,3198) cm^{-1} dueto NH_2 group, 3116cm^{-1}dueto H-aromatic, 1635cm^{-1} dueto C=Ngroup, 686cm-1dueto C-Sgroup, and 2754 cm^{-1} belongstoS-H group.
4		2954 cm^{-1} due to C-H aliphatic, 1651 cm^{-1} due to C=O, 1631 cm^{-1} due to C=N group, 1369 cm^{-1} due to C-H bend of (CH_3), and 1138 cm-1 due to C-O group.
5		(3410,3325) cm^{-1} dueto NH 2,3194 cm^{-1} belongsto NH group, 3062 cm^{-1}due to C-Haromatic,1620cm^{-1}dueto C=N group.
6		(3433,3311) cm^{-1}dueto NH 2,3039 cm^{-1} dueto C-Haromatic, 1635 cm^{-1} due to C=N group, 671 cm^{-1} which refer to the appearances of C-S band, and 1138cm^{-1} for C=S band.
7		(3452,3278) cm^{-1} due to NH2 group, 3059 cm^{-1} dueto H-aromatic, 1612cm^{-1} dueto C=N group, (1500,1446) cm^{-1} dueto C=C aromatic, 686cm^{-1} dueto C-S group, and 2758 cm^{-1} belongs to S-H group.

Table 3. Spectroscopic Properties of synthesized Schiff Bases [8a] and [8b]

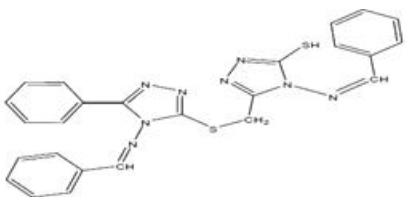
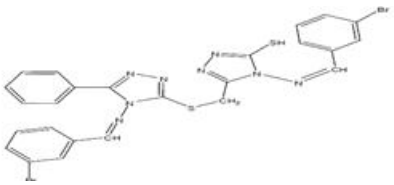
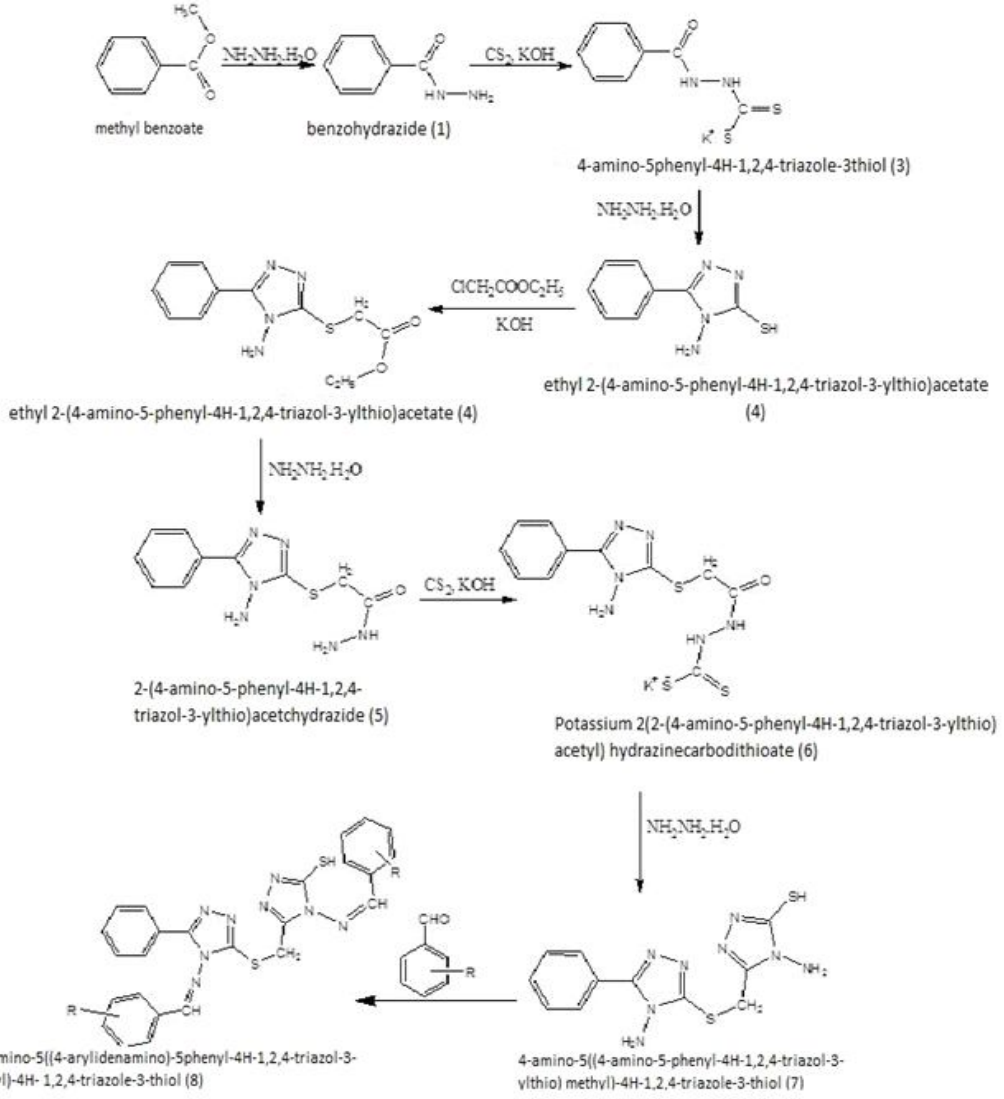
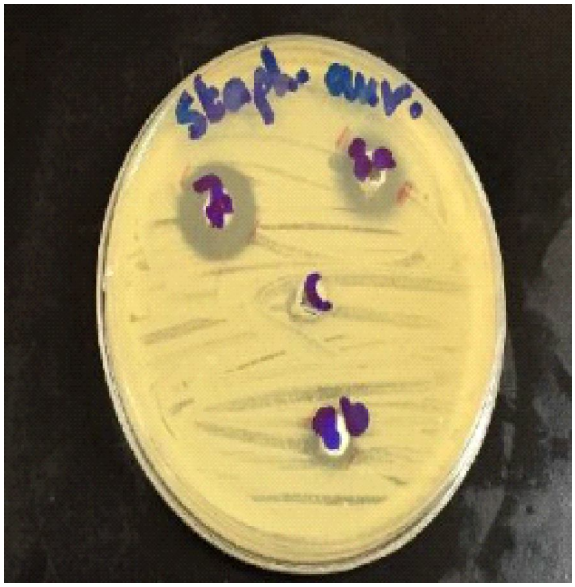
No.	Name of Compounds	Structures of Compounds	FTIR Spectra (cm^{-1})
8a	4-(benzylideneamin o)-5-((4- (benzylideneamino)-5-phenyl-4 H-1,2,4-triazol-3-yl thio)methyl)-4H-1,2, 4-triazole-3-thiol		3059 cm^{-1} due to H-aromatic, 2808 cm^{-1} belongs to C-H aliphatic, 1612 cm^{-1} due to C=N group, (1500, 1446) cm^{-1} due to C=C aromatic, 686 cm^{-1} due to C-S group, and 2762 cm^{-1} belongs to S-H group.
8b	4-(3-bromobenzylid eneamino)-5-((4-(3-bromobenzylideneamino)-5- phenyl-4H-1,2,4-triazol-3-ylthi o)methyl)-4H-1,2,4-triazole-3- thiol		3028 cm^{-1} due to H-aromatic, 1612 cm^{-1} due to C=N group, (1523, 1446) cm^{-1} due to C=C aromatic, 682 cm^{-1} due to C-S group, (790, 945) cm^{-1} due to meta-disubstitutedphenyl ring and 540 cm-1 due to C-Br.

Table 4. Inhibition Zones of synthesized Compounds [7], [8a] and [8b] compared with reference Antibiotics

Compound	Concentration(ìg/ml)	InhibitionZonein(mm)	
		Gram Positive (*S.aureus*)	Gram Negative (*E.coli*)
7	25	13	-
8a	25	12	7
8b	25	-	-
Ceftriaxone(2)	25	21	20
Amoxicillin(2)	25	13	15
DMSO		-	-

Scheme (1): Steps for Synthesis of Compounds [1-8(a-j)] R= H (a), m-Br (b)





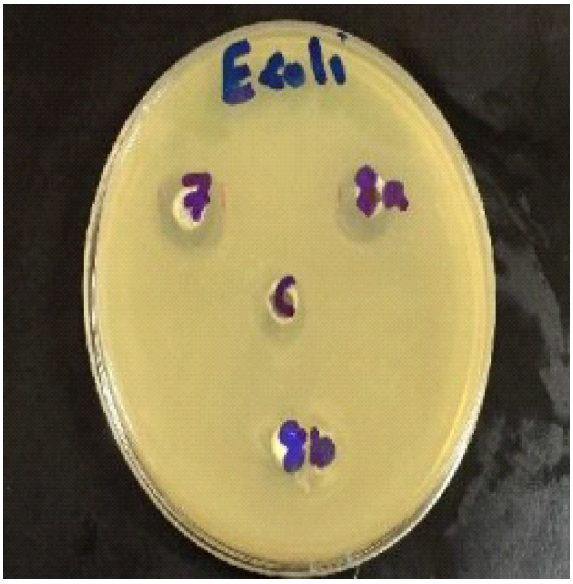
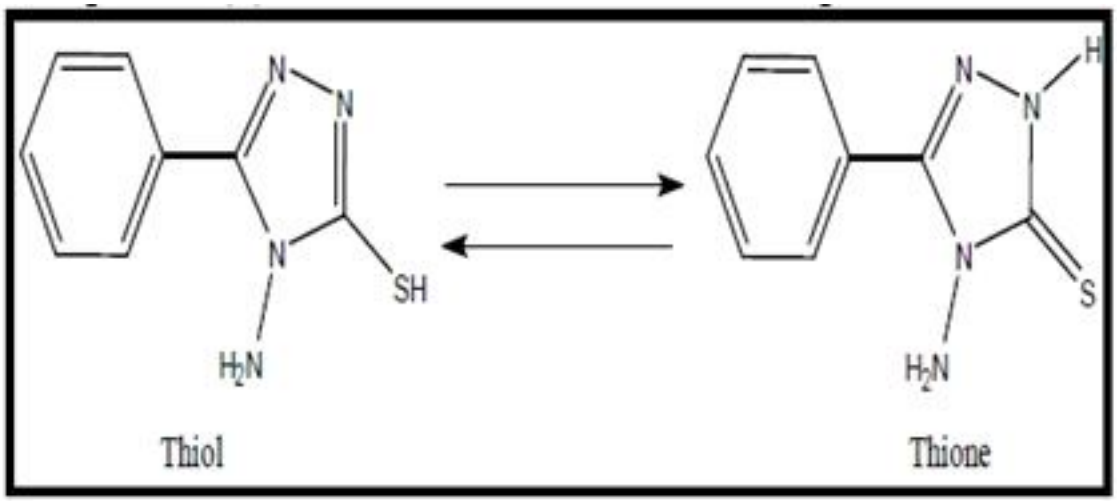


Fig 1. Inhibition zones of compounds [7], Fig 2. Inhibition zones of compounds [7], [8a][8a] and [8b] against *staphylococcus* and [8b] against *Escherichia coli*. C = control (DMSO) *aureus.* Where C = control (DMSO)

Discussion

Compound (1) has been synthesized from methyl benzoate and hydrazine hydrate using absolute alcohol. Appearance of a double bands at (3298 and 3197) cm^{-1} of (N-H) belongs to (NH_2) group, and shifting of intense peak at 1685 cm^{-1} for (C=O) of amide group were confirmed the formation of compound (1). Compound (2) is characterized by the presence of (C=S) absorption band at 1141 cm^{-1}. The formation of compound (3) was confirmed through appearance of two bands at 945 cm^{-1} and 1292 cm^{-1} which referring to N-C-S and N-N-C, respectively. In addition of two other characteristic bands at 2943cm^{-1} and 2754 cm^{-1} due to (N-H, thion form) and (S-H) stretching vibration, respectively. That means compound (3) can exist in the thiol-thion equilibrium.



Conversion of compound (3) to the ester (4) was distinguished by presence of (C-O) at 1138 cm^{-1} and (C=O) at 1651 cm^{-1}. Substitution of compound (4) with hydrazine hydrate could be revealed by appearance of (3410, 3325) cm^{-1} due to NH_2 group and 3194 cm^{-1} belongs to NH group. Reaction of carbon disulfide with compound (5) gave compound (6) which has a characteristic band at 1138 cm^{-1} belongs to (C=S). Compound (6) was cyclized by reacting with hydrazine hydrate to form compound (7) which identified by (S-H) band at 2785 cm^{-1}. The FTIR spectra of compounds (1-7) were listed in table 2 and figures 3-9.The nucleus 4-Amino-5-((4-amino-5-phenyl-4H-1,2,4-triazol-3-ylthio) methyl)-4H-1,2,4-triazole-3-thiol (7) was used to synthesize Schiff bases (8a) and (8b), FTIR spectra of prepared Schiff bases have general changes such as disappearance of (N-H) stretching band of primary amine at (3300-3500) cm^{-1} and appearance of stretching band at (1597-1634) cm^{-1} which belong to the formation of imino group (HC=N). Names and FTIR spectra of compounds (8a) and (8b) were listed in table 3.

Biological activity :

The inhibition zones brought about by the different compounds were analyzed (25µg/ml concentration for compounds (1-7), (8a) and (8b). The outcomes are recorded in Table 4. The compounds ((1-7) and (8a) have comparable bioactivity against S. aureus of Amoxicillin while compound (8b) has no bioactivity, as appeared in figure 1. Against E. coli, compounds (1-7), (8a) and (8b) have no biological activity in interestingly with Amoxicillin and Ceftriaxone, as shown in figure 2? In spite of the of presence of two triazole rings which has an extensive variety of bioactivity, but in our case it is invert and this point requirement for more reviews on the component of the work of these compound on bacteria.

Conclusion

The outcomes of current review offering ascend to the capacity of concluding that compounds (1-7), (8a) and (8b) were recognized to be biological inactive compounds against S. aureus and E. coli with concentration of (25 µg/ml), that both of reference drugs have higher Antimicrobial Activity than prepared compounds. Further study with other Schiff's bases with different ring substituents is recommended.

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