

# Synthesis of Schiff Bases of 4-Amino-5- (2-Hydroxyphenyl)-4H-1,2,4-Triazole-3-Thiol as Potent Antimicrobial Agents

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## Highlights

- Some new aryl substituted Schiff bases of 4-amino-1,2,4-triazole were synthesized
- Synthesized compounds were characterized by spectral techniques
- Evaluated for antimicrobial activities against some pathogenic bacteria and fungi
- Antimicrobial activities were mainly due to toxicophoric part (-N=C-N-) of triazole ring

## Abstract

In recent years, the emergence and rapid spread of multidrug-resistant microbes are increasingly becoming major concerns for public health because infections from such pathogens lead to higher mortality imposing huge healthcare costs. With the currently available drugs becoming ineffective due to the drug resistance developed by pathogens, the synthesis of more powerful antimicrobial agents with a broad spectrum of activity has become a crucial need for the treatment of microbial infections. Some new amino-substituted Schiff bases with triazole ring (4a-c) were prepared by cyclization of potassium 2-(2-hydroxybenzoyl) hydrazinecarbodithioate (2) with hydrazine hydrate followed by condensation with aromatic aldehydes. The newly synthesized compounds were characterized by spectral techniques like FTIR, <sup>1</sup>H-NMR, and <sup>13</sup>C-NMR. Antimicrobial screening of the synthesized compounds revealed that they possess good to moderate activities against a variety of microorganisms.

**Keywords:** Heterocycles, 1,2,4-Triazole, Schiff bases, Synthesis, Antimicrobial activities.

## Introduction

Heterocyclic chemistry is the continuously explored and more adequately rewarding field in organic chemistry with present society and prospects (Haddad, Yousif & Ahmed 2013). Heterocyclic compounds are of great significance to life because of their abundance in structural subunits of many natural products as well as in agrochemicals (Al-Harbi & Gad 2018), dyes (Zhao, Qian & Huang 2018), and many other compounds (Kumari 2018). The heterocyclic compounds with one or more hetero-atoms in ring positions have significant pharmacological activities (Chanda, Baravalia & Baluja 2010). Among the five-membered heterocycles, the nitrogenous compounds especially 1,2,4-triazoles are abundantly found in most of the medicinal compounds. The name 'Triazole' was given to the five-membered diunsaturated ring structure composed of three nitrogen atoms and two carbon atoms at non-adjacent positions having molecular formula C<sub>2</sub>H<sub>3</sub>N<sub>3</sub> (Bladin 1885). Out of the isomeric pair, 1,2,4-triazole has a wide range of biological targets (Kravchenko, Panasenko & Knysh 2018). 1,2,4-Triazole nucleus and its derivatives represent one of the most biologically active class of compounds that are associated with diverse pharmacological activities such

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as antimicrobial (Barbuceanu *et al.*, 2012), antibacterial (Hanif *et al.* 2012, Kapri & Shakya 2018), antifungal (Güzeldemirci & Küçükbasmaci 2010, Kapri & Shakya 2018), antiviral (Holla, Akberali & Shivananda 2001; He *et al.*, 2014), antitubercular (Küçükgüzel, Tatar, Küçükgüzel, Rollas & De Clerq 2008), anticancer (Holla, Poojary, Rao & Shivananda 2002, Bekircan, Kahveci & Kuçuk 2006; El-Sayed, Fiefel & Morsy, 2012), antioxidant (Sancak *et al.* 2012, Khan *et al.* 2010), antitumoral (Bhat, Poojary, Prasad, Naik & Holla 2009, Al-Soud & Al-Masoudi 2003), anti-inflammatory (Abuo-Rahma, Abdel-Aziz, Farag & Kaoud 2014, Mousa & Shaker 2012), anticonvulsant (Siddiqui & Ahsan 2010, Husain, Naseer & Sarafroz 2009), antidepressant (Demirci, Basoglu, Bozdereci & Demirbas 2013, Kane, Dudley, Sorensen & Miller 1988), and analgesic (Alam *et al.* 2012, Turan-Zitouni, Kaplancikli, Erol & Kilic 1999) properties. Besides these, a variety of biological properties have been reported for a large number of their derivatives, such as antiprotozoal (Dürüst, Karakuş, Kaiser & Tasdemir 2012), antimalarial (Boechat, Pinheiro, Santos-Filho & Silva 2011), hypoglycemic, anti-urease and anti-lipase (Bekircan, Mentese, Ulker & Kucuk 2014) etc.

Over the last few years, the synthesis of a large number of fused heterocycles from 1,2,4-triazole moiety has become an interesting task for heterocyclic chemists due to their synthetic flexibility, effective medicinal importance, safety profile and high therapeutic index. 1,2,4-triazole nucleus has been incorporated into a wide variety of therapeutically important agents that are commercially available in the markets such as Fluconazole, Itraconazole, Terconazole, Voriconazole, Ravuconazole, etc. (Richardson, Brammer, Marriott & Troke 1985, Turan-Zitouni, Kaplancikli, Yildiz, Chevallet & Kaya 2005). Some other commercially available and therapeutically important medicines like Alprazolam, Etizolam, Triazolam, Rizatriptan, and Furacylin, etc. also contain a 1,2,4-triazole nucleus (Street *et al.* 1995, Bektaş, Karaali, Şahin, Demirbaş, Karaoglu & Demirbaş 2013).

Schiff bases, the versatile nitrogen donor molecules, are the synthetic intermediates of heterocyclic compounds usually obtained as condensation products of carbonyl compounds with primary amines. These compounds contain azomethine ( $-\text{CR}=\text{N}-$ ) group which has been demonstrated to be critical to bioactivity. Several of Schiff bases have been extensively used in biology, medicine as well as industry. They have been used as active drugs against tumor (Tadele & Tsega 2019) and tuberculosis (Kratky *et al.* 2017, Sager *et al.* 2018), and also as insect repellents (Butler 2007) and fungicides (Shakdofa, Labib, Abdel-Hafez & Mousa 2018).

During the past decades, the problem caused by the increasing number of multidrug-resistant microbes has reached an alarming level around the world. Therefore, the synthesis of a new class of antimicrobial agents with novel mechanisms has become an urgent need for the treatment of microbial infections. All of these remarkable observations opened horizon and new efforts have been developed for the syntheses of new Schiff bases by the reaction of 4-Amino-5-(2-hydroxyphenyl)-4H-1,2,4-triazole-3-thiol with different aromatic aldehydes and were expected to exhibit a broad spectrum of antimicrobial activities.

## Materials and Methods

The reagents and solvents of analytical grade *viz.* methyl salicylate (Fischer Scientific), hydrazine hydrate (Qualigens), carbon disulphide (Merck), ethanol (Alpha Chemika), cinnamaldehyde (Loba Chemie), vanillin (Himedia), *p*-chlorobenzaldehyde (Himedia), potassium hydroxide (Fischer Scientific), etc. were purchased from chemicals suppliers and were used without further purification.

The Melting points of the compounds were determined in the optics technology melting point apparatus. The progress of the reaction was monitored by thin layer chromatography (TLC) on silica gel coated aluminum plates and spots were observed in UV light. Infrared spectra were measured from 4000 – 400  $\text{cm}^{-1}$  on IR Trace 100 FTIR-Spectrometer in KBr pellets.  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra were recorded at room temperature on Advanced III HD Fourier Transform 400 MHz from BRUKER using TMS as an internal standard. Chemical shifts are expressed in  $\delta$  ppm and signals are described as singlet (s), broad singlet (br s), doublet (d), triplet (t), and multiplet (m). Antimicrobial activities of the compounds were evaluated according to the cup-plate assay.

## Experimental

The synthetic route leading to the formation of Schiff bases is outlined in Scheme 1.



refluxed for 3h and the brownish yellow solid precipitated was collected, washed with cold ethanol and recrystallized with hot ethanol. Yield: 66%. mp 197-200 °C. IR  $\nu_{\max}$  in KBr (selected bands):  $\text{cm}^{-1}$  3085 (O-H str, aromatic), 2948 (C=CH str, aromatic), 2591 (S-H str), 1602 (C=N str), 1551-1488 (C=C str, aromatic), 1250 (O-H bend, aromatic), 1052 (N-N str), 750 (C-H bend, aromatic).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  ppm 14.07 (1H, br s, SH), 10.07 (1H, br s, OH), 9.35 (1H, d,  $J = 9.5$  Hz, H-13), 7.78-7.65 (2H, m, H-2'), 7.53-7.29 (6H, m, H-9, H-11, H-15, H-3', H-4'), 7.13 (1H, dd,  $J = 15.9$  Hz,  $J = 9.5$  Hz, H-14), 7.02-6.87 (2H, m, H-8, H-10).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  ppm 167.8 (C-3), 161.6 (C-13), 156.2 (C-7), 148.2 (C-5), 146.5 (C-1'), 134.9 (C-15), 132.3 (C-11), 131.1 (C-9), 130.2 (C-3'), 128.9 (C-2'), 128.0 (C-4'), 123.5 (C-10), 118.9 (C-14), 115.6 (C-6), 113.0 (C-8).

### Synthesis of 4-(4-Hydroxy-3-Methoxybenzylideneamino)-5-(2-Hydroxyphenyl)-4H-1,2,4-Triazole-3-Thiol (4b)

To a mixture of hot ethanolic solution of Vanillin (0.01 mol) and 4-5 drops of concentrated sulphuric acid, a hot ethanolic solution of compound (3) (0.01 mol) was added in small fractions with vigorous shaking. The content was refluxed for 3h and the off-white solid thus precipitated was collected, washed with cold ethanol and recrystallized with hot ethanol. Yield: 60%. mp 202-205 °C. IR  $\nu_{\max}$  in KBr (selected bands):  $\text{cm}^{-1}$  3297 (O-H str, aromatic), 2605 (S-H str), 1578 (C=N str), 1534-1466 (C=C str, aromatic), 1275 (O-CH<sub>3</sub>, str), 1252 (O-H bend), 1136 (N-N str), 730 (C-H bend, aromatic).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  ppm 14.04 (1H, br s, SH), 10.05 (1H, br s, OH), 9.98 (1H, br s, OH vanillin), 9.26 (1H, br s, H-13), 7.44-7.31 (3H, m, H-9, H-11, H-2'), 7.30-7.25 (1H, m, H-6'), 6.99-6.86 (3H, m, H-8, H-10, H-5'), 3.77 (3H, br s, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  ppm 166.6 (C-3), 161.9 (C-13), 156.2 (C-7), 151.3 (C-5), 148.2 (C-4'), 148.0 (C-3'), 132.3 (C-11), 131.2 (C-9), 124.1 (C-1'), 123.4 (C-6'), 118.9 (C-10), 116.0 (C-6), 115.7 (C-8), 113.0 (C-5'), 110.9 (C-2'), 55.6 (CH<sub>3</sub>).

### Synthesis of 4-(4-Chlorobenzylideneamino)-5-(2-Hydroxyphenyl)-4H-1,2,4-Triazole-3-Thiol (4c)

To a hot ethanolic solution (15 mL) of compound (3) (0.01 mol), a mixture of hot ethanolic solution (15 mL) of *p*-chlorobenzaldehyde (0.01 mol) and 4-5 drops of conc. sulphuric acid, was added fractionally with constant stirring. The resulting mixture was heated for 3h under reflux condition and the brown solid obtained was filtered, washed with cold ethanol and recrystallized with hot ethanol. Yield: 62%. mp 187-190 °C. IR  $\nu_{\max}$  in KBr (selected bands):  $\text{cm}^{-1}$  3100 (O-H str, aromatic), 2940 (C=CH str, aromatic), 2586 (S-H str), 1583 (C=N str), 1545 – 1496 (C=C str, aromatic), 1248 (O-H bend, aromatic), 1098 (N-N str), 747 (C-H bend, aromatic), 620 (C-Cl str).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  ppm 14.15 (1H, br s, SH), 10.07 (1H, s, OH), 9.70 (1H, s, H-13), 7.80 (2H, d,  $J=8.1$  Hz, H-2'), 7.58 (2H, d,  $J=8.1$  Hz), 7.47-7.22 (2H, m, H-9, H-11), 7.16-6.84 (2H, m, H-8, H-10).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  ppm 164.0 (C-3), 161.8 (C-13), 156.2 (C-7), 148.4 (C-5), 137.3 (C-4'), 132.4 (C-11), 131.1 (C-2'), 131.0 (C-1'), 130.2 (C-9), 129.3 (C-3'), 118.9 (C-10), 113.0 (C-6), 112.8 (C-8).

### Antimicrobial screening

The antimicrobial activities of triazole thiol derivatives (4a-c) in two different concentrations (1% and 5%) were evaluated against various microorganisms, representing Gram-positive bacteria (*Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli* and *Klebsiella pneumoniae*) and fungus (*Candida albicans*), according to the cup-plate assay. The overnight culture of bacterial and fungal species from nutrient agar and Sabouraud dextrose agar respectively were adjusted to 0.5 McFarland standards and was spread on the surfaces of Muller-Hinton agar plates using a sterile cotton swab to prepare microbial lawns. The suitably spaced apart wells of 6 mm diameter were made on each agar plate and the labeled wells were loaded with 50  $\mu\text{L}$  of each triazole solution. Ofloxacin (32  $\mu\text{g}/\text{mL}$ ) and Fluconazole (40  $\mu\text{g}/\text{mL}$ ) were used as reference antimicrobials and DMSO was used as a negative control. The Petri dishes were kept 30 minutes for diffusion and incubated at 37 °C for 24 h. After incubation, the diameters of the inhibition zones were measured in mm and the results of antimicrobial activities were interpreted.

## Results and Discussion

### Chemistry

Schiff bases of 4-Amino-5-(2-hydroxyphenyl)-4H-1,2,4-triazole-3-thiol bases (4a-c) were synthesized from methyl salicylate. Methyl salicylate was converted into corresponding acid hydrazide (1) by treating with hydrazine monohydrate. The acid hydrazide (1) was treated with carbon disulphide in presence of ethanolic potassium hydroxide to obtain potassium

dithiocarbazinate (**2**). The intermediate (**2**) was refluxed with hydrazine monohydrate and the resulting triazole thiol (**3**) was condensed with desired aldehyde to get the Schiff base (**4**). The Schiff bases (**4a-c**) were obtained in good yield. They were stable in air at room temperature, slightly soluble in  $\text{CHCl}_3$ , and readily soluble in polar solvents like MeOH and DMSO. The structures of the synthesized compounds were confirmed by IR,  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectroscopy.

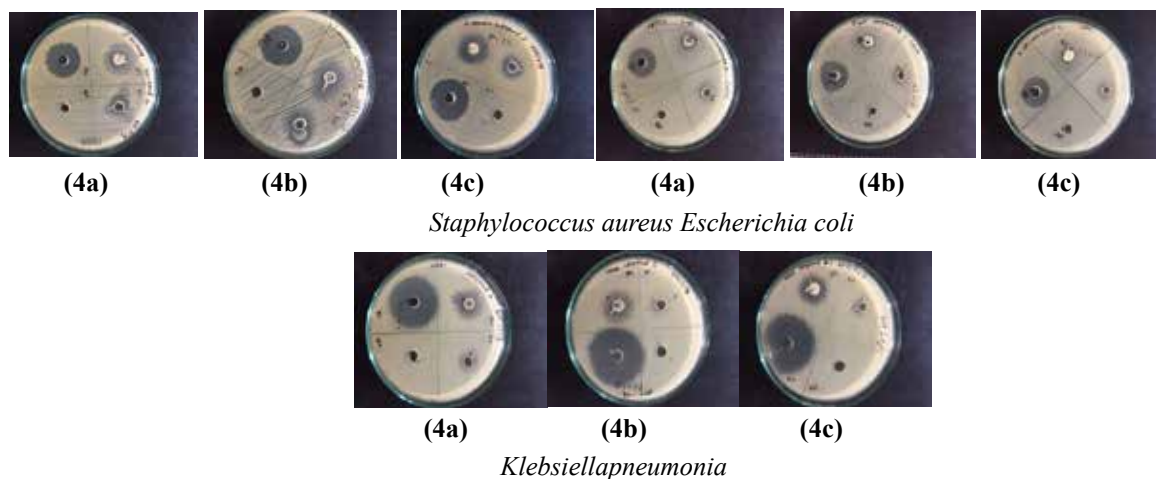
### Antimicrobial evaluation

The diameters of inhibition zones (Table 1) indicate that all three compounds (**4a-c**) exhibited various degrees of antimicrobial activity against the tested microbial species. Among the tested microorganisms, the inhibition of bacterial growth was more pronounced in Gram-positive bacteria *S. aureus*. A significant inhibitory effect was observed for all compounds against *K. pneumoniae*. Conversely, the compounds were found to be relatively less effective against *E. coli* as compared to the other two bacterial species. Moreover, the compounds were able to give a moderate inhibitory activity against a fungal species of *Candida albicans* where the compound **4c** displayed least activity against it.

The compounds **4a** and **4b** containing electron donating groups 3-phenylallyl and 4-Hydroxy-3-methoxybenzyl groups respectively were found to exhibit more potent activity compared to compound **4c** containing electron withdrawing 4-Chlorobenzyl group. This indicates that the electron density on N-4 position of 1,2,4-triazole nucleus can affect the antibacterial and antifungal activities. The slightly enhanced antibacterial and antifungal activity of **4a** and **4b** may be due to the electron donating ability of the substituents on N-4 position.

**Table 1.** Inhibition zones showing antimicrobial activities of Schiff bases and the references antibiotic

Sample Code	Concentration (%)	Diameter of Inhibition Zone (mm)			
		Bacterial Species			Fungal species
		Gram positive <i>S. aureus</i>	Gram negative <i>E. coli</i> <i>K. pneumoniae</i>		<i>C. albicans</i>
4a	1	7	5	4	4
	5	14	8	12	8
4b	1	9	4	2	3
	5	16	6	12	8
4c	1	5	4	2	3
	5	12	5	10	6
Ofloxacin	32 $\mu\text{g/mL}$	22	14	31	--
Fluconazole	40 $\mu\text{g/mL}$	--	--	--	26



**Fig. 2.** Antibacterial activity of synthesized compounds



Fig. 3. Antifungal activity of synthesized compounds on *Candida albicans*

## Conclusions

The present study highlighted the successful synthesis of three new Schiff bases of 1,2,4-triazole derivatives viz. 5-(2-Hydroxyphenyl)-4-(3-phenylallylideneamino)-4*H*-1,2,4-triazole-3-thiol, **4a**; 4-(4-Hydroxy-3-methoxybenzylideneamino)-5-(2-hydroxyphenyl)-4*H*-1,2,4-triazole-3-thiol, **4b** and 4-(4-Chlorobenzylideneamino)-5-(2-hydroxyphenyl)-4*H*-1,2,4-triazole-3-thiol, **4c** starting from methyl salicylate via 4 steps. The molecular structures of newly synthesized compounds were characterized by analytical and spectral techniques. All the Schiff bases exhibited good to moderate antimicrobial activities against the tested microbial species. The activity of all compounds against Gram-positive bacteria were found to be more as compared to Gram-negative bacteria probably due to highly polar substituents in the synthesized compounds. Compound **4c** with electron withdrawing 4-Cl-C<sub>6</sub>H<sub>4</sub> substituent exhibited comparatively lesser antibacterial and antifungal activities. Though the change in electron density on triazole ring due to difference in substituents at N-4 position affect the antimicrobial activity, the little difference in the activity of the synthesized compounds suggests that the antimicrobial activities were mainly due to the –N=C–N– toxicophoric part of the triazole ring.

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