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Effect of the Chemical Structure of *m* and *p* N-vinylbenzylidene of 5-methyl-thiazole and 1,2,4-triazole on Antimicrobial Activity

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ABSTRACT

New Schiff bases heterocyclic structures have been synthesized and evaluated for their antibacterial and antifungal properties. They were prepared by a condensation reaction of 2-amino-5-methylthiazole, 4-amino-4H-1,2,4-triazole and 3-amino-1H-1,2,4-triazole with *p*-vinylbenzaldehyde 1p and *m*-vinylbenzaldehyde 1m. The synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, FT-IR and UV–Vis. The compounds were examined for antibacterial and antifungal activities *in vitro* using the disc diffusion method. Activity against two bacterial strains (gram positive bacteria and gram negative bacteria) and two fungal strains is discussed. These compounds are active against assayed bacteria (*Pseudomonas aeruginosa* ATCC 26883 and *Staphylococcus aureus* ATCC4330,) and fungal strain (*Candida albicans* ATTC 10231) with minimal inhibitory concentration (MIC) value of 10 µg/mL.

Keywords: 1,2,4-triazole; thiazole; Schiff bases; antibacterial and antifungal activity.

INTRODUCTION

The world health organization defines the antimicrobial resistance (AMR) as the ability of microbes to resist the effects of drugs aimed at destroying them[1]. Indeed, the micro-organisms including bacteria, fungus, viruses and certain parasites are not affected by the drugs used to eliminate them. The treatment becomes inefficient and the infections they cause persist[2-4]. Although the microbial resistance development of any organism is a natural phenomenon, human actions could substantially accelerate it. Actually the research in pharmaceutical chemistry has mainly targeted the

synthesis of new chemical compounds. The ultimate objective of which is to have hydrolysable therapeutic supports that offer versatile physico-chemical properties that exhibit high liberation efficiency[5].

Recently, we have synthesized the isomers via the grafting of *p*-vinylbenzaldehyde and *m*-vinylbenzaldehyde on the active ingredient. Note that the currently used isomers in the field of drug research are either the *para* or the *meta* as requested by the *in vitro* and *in vivo* pharmacological tests on the starting molecule. In this investigation we have chosen the imine function as the labile linkage for the grafting of the 1,2,4-triazole and thiazole heterocyclic. The literature reveals that Schiff bases are important intermediates for the synthesis of some bioactive compounds[6]. They have demonstrated a versatile interesting biological actions including antibacterial, antifungal and anticancer[7-9]. The Schiff bases derivatives of 1,2,4-triazole and thiazole are also associated with a variety of applications in biology, clinical and pharmacological domains[10-12].

In this paper we describe the synthesis of Schiff bases derived from 1,2,4-triazole and thiazole. The influence of the *para* and the *meta* substitution on the antibacterial and antifungal activity of the prepared Schiff bases is carried out.

MATERIALS AND METHODS

2-amino-5-methylthiazole, 4-amino-4H-1,2,4-triazole, 3-amino-1H-1,2,4-triazole, 4-chloromethylstyrene (CMS 60%) and *m*-vinylbenzaldehyde were purchased from Sigma Aldrich. Melting points were determined by REICHERT (N°184321) apparatus and are uncorrected. IR spectra were recorded on KBr discs using a JASCON FT/IR4200 spectrophotometer. ^{1}H-RMN and ^{13}C-RMN spectra were recorded (in $CDCl_3$/DMSO-d_6) as a solvent on a Bruker AC spectrometer at (200, 400, 75.5) MHz using TMS as an internal standard. UV spectra in ethanol solvent were taken on a SpectroScan 80DV UV spectrophotometer.

RESULTS

Synthesis of p-vinylbenzaldehyde (1p)

p-vinylbenzaldehyde was synthesized by using a mixture of 4-chloromethylstyrene (CMS 60%) and hexamethylenetetramine (HMTA) according to the method described by Sommelet[13]. The final product was distilled under reduced pressure using a vacuum pump. This compound was obtained as a yellow oil; (Yield: 79%), IR (KBr) cm^{-1}: 2825.20 and 2735.53 (OC-H), 1701.87 (C=O), 1604.48, 989.30 and 919.87 (CH_2=CH), 840.31 (C-H). ^{1}H-RMN ($CDCl_3$) δ ppm 5.43 (d, 1H, *J* =10.88 Hz, CH_2=CH), 5.90 (d, 1H, *J* =17.60 Hz, CH_2=CH), 6.78 (dd, 1H, *J* =10.88 Hz, *J* = 17.60 Hz, CH_2=CH), 7.54 (d, 2H, *J* =8.35 Hz, H-arom), 7.84 (d, 2H, *J* =8.27 Hz, H-arom), 9.98(s, 1H, CH=O). ^{13}C-RMN ($CDCl_3$) δ ppm 117.54, 126.80, 130.16, 135.72, 135.94, 143.51 (C Vinyl, Arom), 191.80 (CH=O ald). UV (Ethanol C = 10^{-4} mol L^{-1}) λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) 306 (33865), 224 (13979), 204 (13970) nm.

General procedure for the preparation of Schiff bases compounds

A mixture of equal volumes of heterocyclic amine (0.02 mol), and vinylbenzaldehyde (**1p** and **1m**) (0.02 mol) in the presence of some traces of 2,6-di-t-butyl catechol as the polymerization inhibitor, and 4–5 drops of glacial acetic acid used as reaction catalyst in 30 mL of absolute ethanol was refluxed for 3 h in water bath as shown in the Scheme 1. The resulting solution was concentrated in vacuum and cooled down in a freezer for 24 h. The precipitated product was filtered, washed with cold absolute ethanol and then dried.

N-(4-vinylbenzylidene)-5-methyl-thiazol-2-amine (2p)

yellow crystals, [Yield: 73%]; M.p. 88-90 °C; IR (KBr) cm^{-1}: 3078.80 (C-H arom), 1609.31 (CH=N imin), 1525.42 (CH=N thiaz), 997.01, 923.73 (C=C vinyl). ^{1}H NMR ($CDCl_3$) δ ppm 2.49 (d, 3H, *J* = 1.15 Hz, CH_3 thiaz), 7.35 (d, 1H, *J* = 1.17 Hz CH thiaz), 5.40 (d, 1H, *J* = 11.10 Hz, CH_2=CH), 5.90 (d, 1H, *J* = 17.59 Hz, CH_2=CH), 6.79 (dd, 1H, *J*= 10.91 Hz, *J* = 17.60 Hz, CH_2=CH), 7.52 (d, 2H, *J* = 8.29 Hz, H-arom), 7.93 (d, 2H, *J* = 8.29 Hz, H-arom), 8.92 (s, 1H, CH=N imin). ^{13}C-RMN ($CDCl_3$) δ ppm 12.67 (-CH_3 thiaz), 116.31, 126.63, 129.98, 133.14, 134.51, 136.13, 138.95 141.51 (C Vinyl, Arom, thiaz), 161.54 (C=N thiaz), 171.14 (CH=N imin). UV (Ethanol C = 10^{-4} mol L^{-1}) λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) 361 (14580), 239 (9260) nm, 213 (9680).

N-(3-vinylbenzylidene)-5-methyl-thiazol-2-amine (2m)

yellow crystals, [Yield: 72%]; M.p. 74-76 °C; IR (KBr) cm^{-1}: 3079.76 (C-H arom), 1613.16 (CH=N), 1576.25 (CH=N thiaz), 997.89, 924.70 (C=C vinyl). ^{1}H NMR ($CDCl_3$) δ ppm 2.40 (d, 3H, *J* = 1.09 Hz, CH_3 thiaz), 7.26 (d, 1H, *J* = 1.15 Hz CH thiaz), 5.26 (d, 1H, *J* = 10.95 Hz, CH_2=CH), 5.77 (d, 1H, *J* = 17.56 Hz, CH_2=CH), 6.71 (dd, 1H, *J*=10.90 Hz, *J* = 17.61 Hz, CH_2=CH), 7.34-7.94 (m, 4H, H-arom), 8.86 (s, 1H, CH=N imin). ^{13}C-RMN ($CDCl_3$) δ ppm 12.69 (-CH_3 thiaz), 115.26, 127.08, 129.09, 129.29, 130.13, 133.28, 135.39; 136.96, 138.29, 138.99 (C Vinyl, Arom, thiaz), 162.05 (C=N thiaz), 170.98 (CH=N imin). UV (Ethanol C = 10^{-4} mol L^{-1}) λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) 351 (11260), 244 (16880) nm, 214 (9580).

N-(4-vinylbenzylidene)-2H-1,2,4-triazol-2-amine (3p)

white crystals, (Yield: 81%); M.p. 156-158 °C; IR (KBr) cm^{-1}: 1603.52 (CH=N imin), 1557.24 (CH=N triaz), 850.45 (C-H arom). ^{1}H NMR ($CDCl_3$) δ ppm 5.42 (d, 1H, *J* =10.90 Hz, CH_2=CH), 5.90 (d, 1H, *J*=17.6 Hz, CH_2=CH), 6.77 (dd, 1H, *J* =10.90 Hz, *J* = 17.60 Hz, CH_2=CH), 7.53 (d, 2H, *J*=8.35 Hz, H-arom), 7.81 (d, 2H, *J*= 8.37 Hz, H-arom), 8.57 (s, 1H, CH=N imin), 8.62 (s, 2H, CH=N triaz). ^{13}C-RMN ($CDCl_3$) δ ppm 116.95, 127.02, 129.09, 130.81, 135.86, 142.10 (C vinyl, arom), 138.16 (2CH=N triaz); 156.37 (CH=N imin). UV (Ethanol C = 10^{-4}mol L^{-1}) λmax (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) 306 (33865), 224 (12979), 204 (13970) nm.

N-(3-vinylbenzylidene)-2H-1,2,4-triazol-2-amine (3m)

white powder, (Yield: 95%); M.p. 134-136 °C; IR (KBr) cm^{-1}: 1595 (CH=N), 1621,84 (CH=N triaz), 890, 808.99, 712.56 (C-H arom). ^{1}H NMR ($CDCl_3$) δ ppm 5.40 (d, 1H, *J*=10.90 Hz, CH_2=CH), 5.80 (d, 1H, *J*= 17.60 Hz, CH_2=CH), 6.70 (dd, 1H, *J*= 10.90 Hz, *J*= 17.60 Hz, CH_2=CH), 7.43-7.89 (m, 4H, H-arom), 8.61 (s, 1H, CH=N imin), 8.65 (s, 2H, CH=N triaz); ^{13}C-RMN ($CDCl_3$) δ ppm 115.81, 126.27, 128.09, 129.43, 130.49, 131.82, 135.59, 138.20 (C Vinyl, Arom), 138.63 (2CH=N triaz), 156.68 (CH=N imin), UV (Ethanol C = 10^{-4} mol L^{-1}) λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) 279 (20773), 245 (30761), 209 (24372) nm.

N-(4-vinylbenzylidene)-1H-1,2,4-triazol-3-amine (4p)

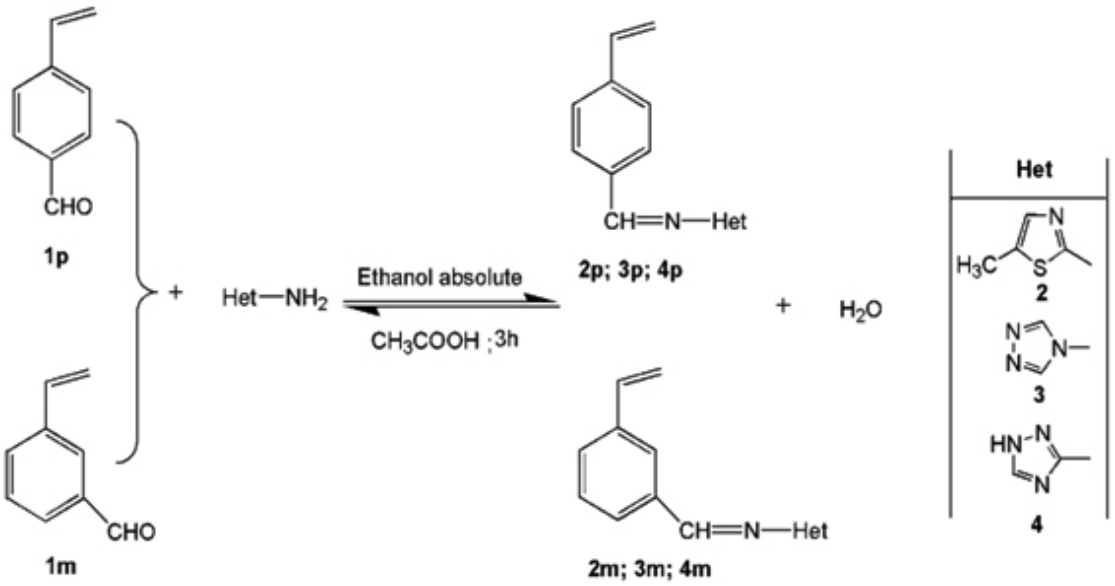
white crystals, (Yield: 86%); M.p. 180-182°C; IR (KBr) cm^{-1}: 3146.29 (NH triaz) 1599.66 (CH=N imin), 1522.25 (CH=N triaz), 986.41, 908.30 (C=C vinyl). ^{1}H NMR (DMSO-d_6) δ ppm 5.40 (d, 1H, *J* =11.49 Hz, CH_2=CH), 5.99 (d, 1H, *J* =17.68 Hz, CH_2=CH), 6.79 (dd, 1H, *J* =10.99 Hz, *J* = 17.68 Hz, CH_2=CH), 7.64 (d, 2H, *J* =8.31 Hz, H-arom), 7.99 (d, 2H, *J* =8.30 Hz, H-arom), 8.34 (d, 1H, *J* = 0.56 Hz, CH=N triaz), 9.32 (s, 1H, CH=N imin); 14.07 (d, 1H, *J* = 1.27 Hz, NH triaz). ^{13}C-RMN (DMSO-d_6) δ ppm 117.18, 127.15, 130.01, 135.17, 136.46, (C vinyl, arom), 141.35 (C=N triaz); 163.89 (CH=N imin). UV (Ethanol C = 10^{-4} mol L^{-1}) λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) 317 (18460), 230 (16500), 215 (13260) nm.

N-(3-vinylbenzylidene)-1H-1,2,4-triazol-3-amine (4m)

white powder, (Yield: 91%); M.p. 186-188 °C; IR (KBr) cm^{-1}: 3240.79 (NH triaz) 1589.06 (CH=N), 1482.03 (CH=N triaz), 910.23, 786.81, 710.46 (C-H, arom). ^{1}H NMR (DMSO-d_6) δ ppm 5.48 (d, 1H, *J* =10.83 Hz, CH_2=CH), 5.96 (d, 1H, *J* =17.64 Hz, CH_2=CH), 6.86 (dd, 1H, *J* =10.84 Hz, *J* =17.39 Hz, CH_2=CH), 7.36-8.11 (m, 4H, H-arom), 8.36 (d, 1H, *J* = 0.73 Hz, CH=N triaz), 9.25 (s, 1H, CH=N imin); 14.09 (d, 1H, *J* = 0.97 Hz, NH triaz). ^{13}C-RMN (DMSO-d_6) δ ppm 116.04, 127.28, 129.05, 129.78, 130.34, 136.12, 136.41, 138.28 (C vinyl, arom), 148.03 (C=N triaz); 163.91(CH=N imin). UV (Ethanol C = 10^{-4} mol L^{-1}) λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$) 393 (2080), 243 (4830), 214 (3790) nm.

Antimicrobial activities

The newly synthesized compounds were screened in vitro for their antimicrobial activity using disc diffusion method[14,15]. The following strains of bacteria and fungi were used as test microorganisms: *Pseudomonas aeruginosa* ATTC 26883 (*Gram-positive*), *Staphylococcus aureus* ATTC 4330 (*Gram-negative*), *Candida albicans* ATTC 10231 and *Aspergillus niger* ATTC 10404. The synthesized compounds were dissolved in sterile dimethylsulfoxide (DMSO) at different concentrations of 10, 50 and 500 µg/mL for bacteria and *Candida albicans* ATTC 10231 and 6.6 x 10^7 spores /mL for *Aspergillus niger* ATTC 10404. The antimicrobial activity of the compound that penetrates into the



Scheme 1: Synthesis of heterocyclic Schiff bases in *para*- and *meta*-substituted

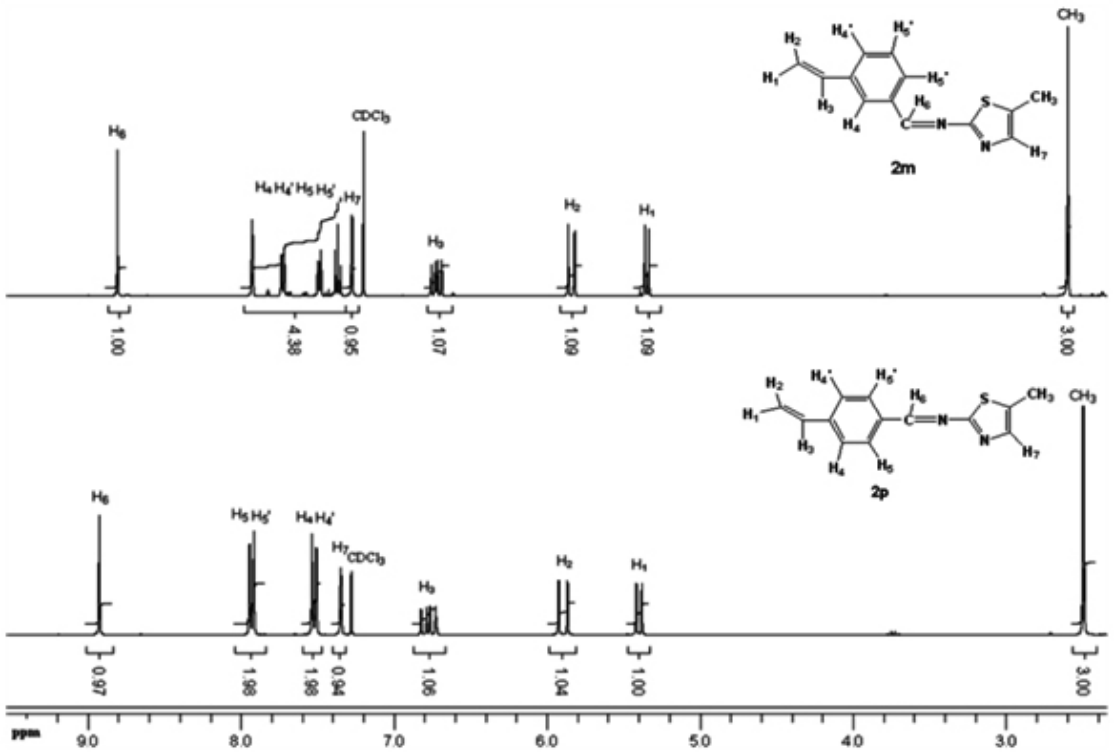


Fig. 1: ^{1}H-NMR spectrum of both isomers 2m and 2p

agar medium by diffusion is measured. The assays are based on the use of sterile discs filter paper (6 mm diameter) impregnated with 20 µL of the compound solution to be examined and allowed to dry at room temperature. A sterile disc impregnated with DMSO is used as negative control. After incubation for 24 h at 37°C for bacteria plates, while fungi plates are incubated for 3 days at 25°C, all the plates were controlled for zone of growth inhibition and a diameter of these zones was measured in millimeters. All experiments were performed in triplicates.

RESULTS AND DISCUSSION

Chemistry

The Schiff bases were synthesized by a condensation reaction of heterocyclic amine and vinylbenzaldehyde *para*- and *meta*-substituted as shown in the Scheme 1.

^{1}H NMR spectra

The products were identified using ^{1}H NMR spectroscopy in chloroform and DMSO. The signals spectra were divided into four categories of protons, namely those of the vinyl, the benzene ring, the imine function and the heterocyclic groups. All the protons of the imine function CH=N of the synthesized products appear as a singlet with near signals having a slight difference between 8.57 and 9.32 ppm for **3p** and **4p**. The protons of the aromatic ring represent a system of AA'XX' for the Schiff bases *para*-substituted but those of the *meta*-substituted ones form a multiplet of four protons. The chemical shifts of the vinyl groups are almost constant for all the products. A doublet at 5.42 ppm, a doublet

Table 1: Results of antibacterial evaluation of the compounds

Compound	Zone of inhibition at different concentrations after 24h (mm)					
	P. aeruginosa(ATTC 26883)			*S. aureus* (ATTC 4330)		
	10 µg/mL	50 µg/mL	500 µg/mL	10 µg/mL	50 µg/mL	500 µg/mL
2p	13.5	15.1	14.1	14.8	13.8	10
2m	14.3	15.2	15	12.5	12	11.5
3p	12.3	10.8	12.7	8	9	8
3m	15.3	15.2	15.5	9.3	9.8	8.8
4p	12.7	14.5	16	9.1	10	8.8
4m	14.7	15.3	13.7	10	10.5	9.8
DMSO	-	-	-	-	-	-

Table 2: Results of antifungal evaluation of the compounds

Compound	Zone of inhibition at different concentrations after 24h (mm)			Zone of inhibition at different concentration after 3 days (mm)		
	C. alibicans (ATTC 10231)			*A. niger* (ATTC 10404)		
	10 µg/mL	50 µg/mL	500 µg/mL	10 µg/mL	50 µg/mL	500 µg/mL
2p	10	11.5	10	9	-	-
2m	8.1	13	12.3	-	-	-
3p	11.8	12.2	12.2	-	-	-
3m	11	10.2	11.3	-	-	-
4p	9.5	10.7	10.2	-	-	-
4m	9	11	10.2	-	-	-
DMSO	-	-	-	-	-	-

(-) : not active.

at 5.90 ppm and a double of doublets at 6.77 ppm. However, different signals appear for the substituents of the heterocyclic rings depending on the type of their structure for example a singlet of three protons located at 2.49-2.40 ppm for the methyl group of **2m** and **2p** respectively as shown in the fig 1. Another singlet at 14.09-14.07ppm is assigned to (NH) of **4m** and **4p**.

^{13}C NMR spectra

The ^{13}C NMR spectra clearly confirm the presence of the azomethine function. It has almost the same chemical shift for the isomers containing the same heterocyclic ring. The values of 170.98-171.14 ppm are assigned to 2m and 2p structures, respectively.

FT-IR spectra

The FT-IR spectra of the Schiff bases synthesized revealed the absence of carbonyl (C=O) stretching vibrations expected at 1701.87 cm^{-1}. In contrast, a strong new band ranging from 1613.16 to 1599.66 cm^{-1} is present which is due to the azomethine (-CH=N-) linkage. The bands at 890, 808.99 and 712.56 cm^{-1} are assigned to (C-H) out of plane bending of the *meta*-substituted benzene ring. Whereas, the strong band appearing at 850.45 cm^{-1}, is assigned to the *para*-substituted benzene ring. The (NH) stretching vibration of the **4p** and **4m** is visible at 3240.79 - 3146.29 cm^{-1}.

UV/vis spectra

The UV/vis spectra of the products **2**, **3** and **4** were carried out in absolute ethanol at a concentration of 10^{-4} mol L^{-1} at room temperature. All heterocyclic compounds present strong bands at λ_{max} 361 and 279 nm. They are assigned to the electronic transition $\pi \rightarrow \pi^*$ of azomethine. The *para*-substituted isomers exhibit a higher intensity than their respective isomers. This is due to the higher degree of molecular planarity. Shifts of the absorption bands of medium intensity between λ_{max} 245 and 224 nm are assigned to a locally excited state of the benzal part of the molecule. These results agree with the UV spectra of aromatic and aliphatic Schiff bases reported in literature[16-18].

Antimicrobial activities

The newly synthesized compounds were screened *in vitro* for their antibacterial activity against gram positive bacteria *Staphylococcus aureus* (ATTC 26883) and gram negative bacteria *pseudomonas aeruginosa* (ATTC 4330). Their antifungal activity against *Candida albicans* (ATTC 10231) and *Aspergillus niger* (ATTC 10404). The results obtained are presented in tables 1 and 2.

The majority of the synthesized products exhibit an antibacterial activity as revealed by the values of the inhibition diameters zones.

All the products tested at the three indicated concentrations are very active against Gram negative bacteria *Pseudomonas aeruginosa*). Generally, the products activity as tested against *Staphylococcus aureus* is moderate and is dependent on the type and concentration of product used. Exception to this tendency is noticed for the products **2p** and **2m** which showed a relatively good effect on the bacteria. The heterocyclic compounds tested *in vitro* against both fungal strains prove moderately active on the growth of the yeast *Candida albicans.* In contrast, they do not show any activity against filamentous fungi *Aspergillus niger* except the product N-(4-vinylbenzylidene)-5-methyl-thiazol-2-amine **2p.** The microbial inhibition was due to the nature of the heterocyclic thiazole which contains electron donating methyl group -CH_3 present in the cycle. It has been demonstrated that the electron donating groups increase the electron density which renders the product efficient against the microorganisms[19]. In addition, the presence of the sulfur atom enhances the antimicrobial efficiency of the molecule[20].

The heterocyclic thiazoles are considered as interesting biocides[21]. The minimum inhibitory concentration (MIC) the growth of bacterial strains and that of the yeast *Candida albicans* is 10 µg/mL whatever the product under test. This concentration seems sufficient to inhibit the majority of the microbial strains.

The low antifungal activity and sometimes its absence is probably due to the resistance of fungal strains[22]. The results of the present investigation show that the heterocyclic compounds oriented to the *para* of the phenyl ring are more efficient than those oriented to the *meta*. This difference might originate from the fast release of the imine link CH=N

of the active ingredients when the phenyl ring is *para* oriented.

CONCLUSIONS

In this work the new heterocyclic Schiff bases derived from 5-methyl-thiazole and 1,2,4-triazole were successfully synthesized with a high yield. The spectroscopic analysis including ^{1}H-NMR, ^{13}C-NMR, FT-IR and UV-Vis confirmed perfectly the expected chemical structures of these compounds. The study *in vitro* of antimicrobial activities showed that they exhibit antibacterial and anticandidal properties except with the fungal strains of *Aspergillus niger*.

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