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Research Article

NOVEL SYNTHESIS OF (*E*)-4-(BENZYLIDENEAMINO)-5-(3-METHOXY-2-METHYLPHENYL) -4H-1, 2, 4-TRIAZOLE-3-THIOL DERIVATIVES AND THEIR BIOLOGICAL SIGNIFICANCE

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ABSTRACT

This article describes the synthesis of a novel series of (*E*)-4-(benzylideneamino)-5-(3-methoxy-2-methylphenyl)-4H-1, 2, 4-triazole-3-thiol derivatives **(4b-4k)** and its biological application. All the synthesized compounds were elucidated based upon the spectral data of FT- IR, ^{1}H NMR, ^{13}C NMR, and LC-MS analysis. The antimicrobial features of the compounds were examined against Gram positive (*Staphylococcus aureus, Bacillus subtilis)* and Gram negative (*Escherichia coli)* bacteria, also with fungus of *Candida albicans* and *Aspergillus niger* via disc diffusion method. Most of the compounds showed good to moderate activity against the tested microbes.

Keywords: aromatic acid, aryl aldehyde, Schiff base, 1, 2, 4- triazole , antimicrobial activity.

1. INTRODUCTION

Heterocyclic chemistry is one of the greatest branches of organic chemistry which is still being emphasizing various applications explored with long standing literature evidence in numerous field. Amicably, they are very important pharmacore to the metabolism of all living cells which are widely distributed in nature everywhere. Basically, DNA and RNA structural units are of the main constituent of all living organism which are further keenly sub-divided into a type of hetero-cyclic compounds like purine and pyrimidine bases. In the recent decades, heterocyclic chemistry emboldened its potency to bring out so many reagents with several synthetic routes for synthesizing drugs [1] candidates like pesticides [2], and insecticides [3], as well as in material science [4], dyes [5], explosives [6], cytotoxicity [7], lipoxygenase inhibitors [8] etc.

However, among all other nitrogenous heterocyclic's, the 1,2,4- triazole motif is an abundant class of hetero-cyclic compound containing five membered ring which is extensively possessing various biological and pharma-ceutical activities [9, 10]. In addition, according to the literature perspective, 1, 2, 4-triazole systems are considered to be a basic unit, commonly involved in the commercially available pharmaceutical and agrochemical products [11] and also for pharmacological activities [12-16]. Very interestingly, the usefulness of 1, 2, 4-triazole derivatives were found to have a remarkable attention in day to day life owing to their pervasive application in the pharmaceuticals as therapeutic drugs like benzotriazole, uniconazole and paclobutrazol etc,. Furthermore, it is also been well reported that Schiff-bases containing of 1, 2, 4-triazole derivatives play a significant role in various field including antioxidant [17], analgesic [18], against corrosion [19] and also in anticancer activity [20]. Encouraged by the earlier reports, as a continuation of our research, the present study reveals that a novel series of 1, 2, 4 - triazole derivatives embedded with Schiff base were developed. All synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR and all these synthesized compounds were subjected to their anti-microbial activities against some bacteria and fungi strains.

2. EXPERIMENTAL

All reagents were purchased from commercial suppliers and were used without purification. Melting points were determined in Buchi B-545melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance-400 & 300 NMR MHZ spectrometer in DMSO-d_6 & $CDCl_3$ solution using TMS as an internal reference and ^{13}C NMR were recorded at 100 MHz. Mass spectra were recorded on LC-MS-Agilent.

2.1. General Procedure for the synthesis of Ethyl-3-methoxy-2methylbenzoate (4.2)

A mixture of compound **4.1** (1 mmol) and thionyl chloride (5mmol) in ethanol (20v) was heated at 50°C, for 4 h under nitrogen atmosphere. After completion of the reaction, the reaction mass was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 x 75 ml), washed with water, followed by brine. The organic layer was dried over sodium sulphate followed evaporation to dryness to give compound **4.2** as a yellow liquid (22 g, 70%).

2.2. General Procedure for the synthesis of 3-methoxy-2methylbenzohydrazide (4.3)

A mixture of compound **4.2** (1 mmol) and hydrazine hydrate (10 mmol) in ethanol (20 v) was heated at 100°C, for 12 h under nitrogen atm. After completion of the reaction, the reaction mass was evaporated to dryness and triturated with hexane at room temperature to afford **4.3** as off white solid (21g, 60%).

2.3. General Procedure for the synthesis of 4-amino-5-(3-methoxy-2-methylphenyl)-4H-1, 2, 4-triazole-3-thiol (4.4)

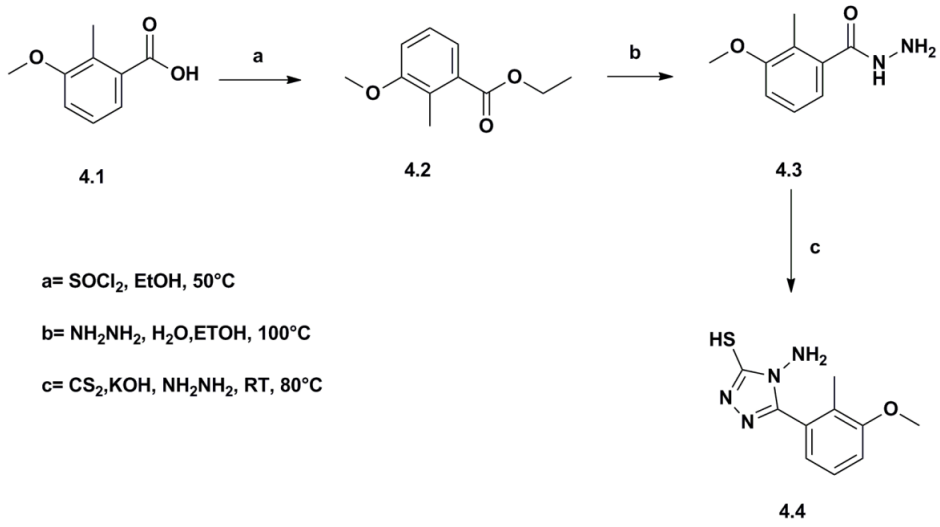
A mixture of compound **4.3** (1 mmol) and carbondisulphide (1.5 mmol), potassium hydroxide (1.5 mmol) in water (10 v) was stirred at 0°C to RT for 6 h. After completion of the reaction, the reaction mass was evaporated to dryness and the residue was heated under nitrogen atmosphere with hydrazine hydrate (15 mmol) in ethanol (5v) at 80°C, for 12 h. The reaction mass was evaporated to dryness to give compound **4.4** as white solid (crude), which was taken for the next step without purification.

2.4. General Procedure for the synthesis of *(E)*-4-(benzylideneamino)-5-(3-methoxy-2-methylphenyl)-4H-1,2,4-triazole-3-thiol derivatives (4b-4k)

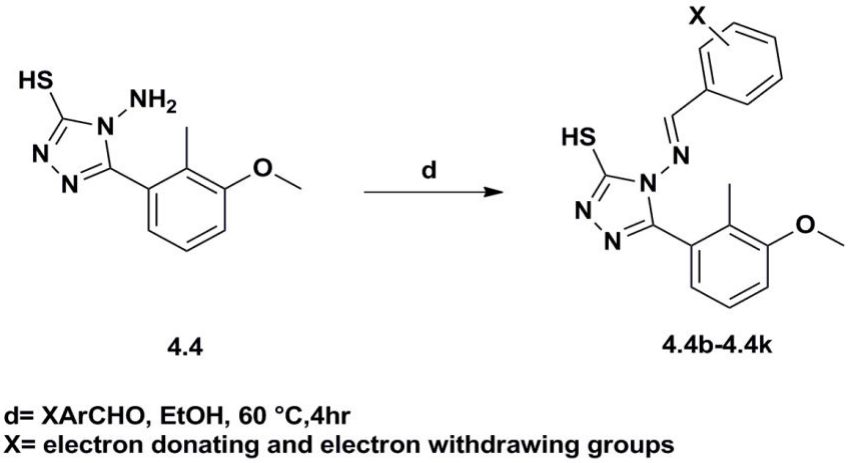
A mixture of compound **4.4** (1 mmol), aryl aldehyde (1.2 mmol) in ethanol (5 v) with catalytic amount of hydrochloric acid was heated under nitrogen atm at 60°C, for 4 hrs. After completion of the reaction, the reaction mass was cooled to 0-15°C to get solid and the solid was filtered to furnish 1, 2, 4-triazole-3-thiol derivatives (**4.4b-4.4k**) in good to moderate yield.

3. RESULTS AND DISCUSSION

In order to derive the scaffold **4.4**, the compound **4.1** was heated with thionyl chloride in ethanol at 50°C to furnish **4.2.** Reaction of hydrazine hydrate with compound **4.2** upon heating afforded **4.3** as an off white low melting solid. Subsequent treatment of **4.3** with the mixture of carbon-disulphide and hydrazine hydrate under heating gave scaffold **4.4** as a white solid in good to excellent yield. The compound **4.4** was heated with various aryl aldehydes bearing electron withdrawing and electron donating functional groups in the presence of catalytic amount of hydrochloric acid in ethanol successfully offered the corresponding 1, 2, 4-triazole derivatives containing schiff-base in good to moderate yield (Table 1).

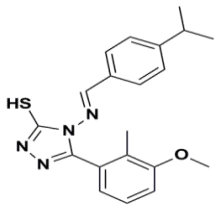
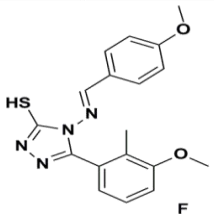
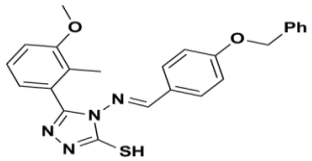
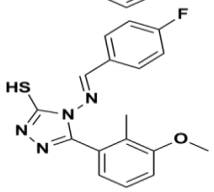
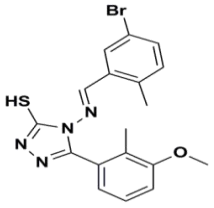
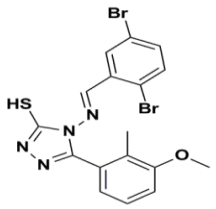
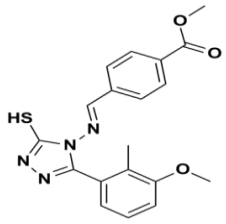
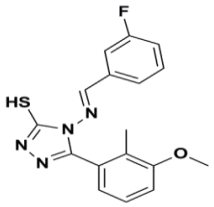
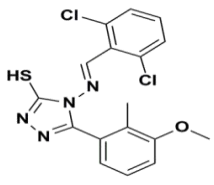
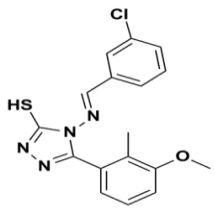


Scheme 1: 4-Amino-5-(3-methoxy-2-methylphenyl)-4H-1, 2, 4-triazole-3-thiol



Scheme 2: ***(E)*****-4-(benzylideneamino)-5-(3-methoxy-2-methylphenyl)-4H-1,2,4-triazole-3-thiol derivatives**

Table 1: ***(E)*****-4-(benzylideneamino)-5-(3-methoxy-2-methylphenyl)-4H-1, 2, 4-triazole-3-thiolderivatives**

Entry	Compound	Yield	Entry	Compound	Yield
4.4 b		87	4.4 g		80
4.4 c		88	4.4 h		82
4.4 d		80	4.4 i		80
4.4 e		78	4.4 j		78
4.4 f		83	4.4 k		78

3.1. Biological evaluation

All the synthesized compounds were evaluated for their in *vitro* antimicrobial activity based on the method of Nutrient Agar (NA-Himedia) Media for Bacteria and PDA-Himedi Media for Fungi. The microbial strains employed in the biological assays were Gram positive bacteria; *Staphylococcus aureus*, *Bacillus subtilis* and Gram negative bacteria; *Escherichia coli,* also with fungus of *Candida albicans* and *Aspergillus niger* via disc diffusion method. The test organism was inoculated on solidified agar plate with the help of micropipette and spread and allowed to dry for 10 mints. The surfaces of media were inoculated with bacteria/fungi from a broth culture. A sterile cotton swab is dipped into a standardized bacterial/fungi test suspension and used to evenly inoculate the entire surface of the Nutrient agar/PDA plate. Briefly, inoculums containing *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis* specie of bacteria were spread on Nutrient agar plates for bacteria and *Candida albicans* and *Aspergillus niger* specie were spread on potato dextrose agar for fungus strains. Using sterile forceps, the sterile filter papers (6 mm diameter) containing the crude extracts (50µl, 100µl and 150µl) were laid down on the surface of inoculated agar plate. The plates were incubated at 37°C for 24 h for the bacteria and at room temperature (30±1°C) for 24-48 hr. for yeasts strains. Standard solution as Chloramphenicol (Bacteria) and Fluconazole (Fungi) (25mg/ml distilled water- 30µl) used to compare the test solution. From the result of antimicrobial activity revealed that the derivatives of **4.4 b to 4.4 k** disclosed good to moderate activities.

At the outset, the efficient antibacterial activity may attributed for the compounds of **4.4d and 4.4g** on the basis of mean diameter of zone of inhibition around the disc in millimetres against Gram positive *S.aureus, B. subtilis* and Gram negative *E. coli* microorganism. Albeit, the antifungal activity of compounds **4.4 f** and **4.4 j** revealed excellent properties against the fungus of *Candida albicans* and *Aspergillus niger*. These antimicrobial screening results of 1, 2, 4- triazole derivatives were cleanly depicted in the Table 2.

Table 2: Anti-microbial activity of synthesized 1, 2, 4-triazole derivatives using disc diffusion method

Compound	Zone of Inhibition (mm)				
	Gram –ve bacteria	Gram +ve bacteria		Fungi	
	E. coli	*S.aureus*	*B. subtilis*	*C.albicans*	*A.niger*
4.4b	3.80	4.60	3.90	2.60	2.10
4.4c	4.30	3.70	4.20	3.10	4.20
4.4d	**7.50**	**6.80**	**7.10**	3.90	4.10
4.4e	4.10	3.80	4.50	3.40	2.80
4.4f	6.00	5.90	6.20	**7.00**	**6.30**
4.4g	**8.10**	**7.20**	**6.80**	4.00	3.30
44h	5.80	6.10	5.90	2.10	3.20
4.4i	4.50	5.00	4.30	5.60	5.20
4.4j	3.90	4.80	4.90	**7.40**	**6.10**
4.4k	4.60	3.80	4.70	2.90	3.80
Chloramphenicol	6.50	6.50	6.50	-	-
Fluconazole	-	-	-	6	6

3.2. Analytical data for synthesized compounds (E)-4((4-isopropylbenzylidene)amino)-5-(3-methoxy-2-methylphenyl) 4H-1, 2, 4-triazole-3-thiol (4.4b)

yield 87%; mp 152-165°C. IR (KBr cm^{-1}):3099 (Ar-CH), 2939(CH-aliphatic), 2757(SH), 1724(C=C), 1565(C=N), 1437(Ar-CH3), 1275(C-N), 1120(C-C), 1107(-OCH_3), 694(C-S). ^{1}H NMR (300 MHZ $CDCl_3$) δ: 1.23-1.29 (m, 6H,J=6.9Hz), 2.16 (s, 3H), 2.8-3.01 (m,1H, J=6.9), 3.8(s,3H), 7.02 (d,2H, J=9Hz), 7.39 (d,2H,J=8.1Hz), 7.65(s,1H), 7.80-7.83(m,2H), 9.9 (s,1H),11.08(s,1H). ^{13}C NMR (75 MHZ $CDCl_3$):δ13.6, 23.6, 34.5, 55.6, 112.5, 122.7, 126.02, 126.5, 126. 79, 127.04, 127.17, 127.6, 129.16, 129.94, 150.16, 154.12, 157.84. LCMS: 366 (m+1).

3.3. (E)-4-((4-benzyloxybenzylidene) amino)-5-(3-methoxy-2-methylphenyl)4H-1,2,4-triazole-3-thiol (4.4c)

yield 88%; mp 158-168°C. IR (KBr cm^{-1}):3098(Ar-CH),2936(CH-aliphatic), 2760(SH), 1603(C=C), 1565 (C=N),1437(Ar-CH_3), 1258(C-N), 1111(C-C), 1170(-

OCH_3), 695(C-S). ^{1}H NMR (300 MHZ $CDCl_3$) δ: 2.06(s,3H),3.82(s, 3H), 5.19((s, 2H), 7.02-7.14(m, 3H), 7.28 (d,2H ,J=7.8Hz),7.43(m,5H,J =4.8),7.69(d,2H,J=8.7Hz),9.49 (s,1H), 14.1(s,1H).^{13} C NMR (75 MHZ $CDCl_3$):δ 13.7, 56.3, 69.9, 113.01, 115.8, 122.9, 124.9, 126.6, 127.17, 128.3, 128.9, 130.46, 131.05, 136.9, 149.3, 157.7, 162.2, 162.48, 166.4. LCMS: 430 (m+1).

3.4. (E)-4((5-bromo-2-methylbenzylidene) amino)-5-(3-methoxy-2-methylphenyl) 4H-1, 2, 4-triazole-3-thiol (4.4d)

yield 80%; mp 164-176°C. IR (KBr cm^{-1}):3099(Ar-CH), 2938(CH-aliphatic), 2752(SH), 1590(C=C), 1562(C=N), 1481(Ar-CH_3), 1261(C-N), 1130(C-C), 1103(-OCH_3), 828, 715(C-S) .^{1}H NMR (300 MHZ $CDCl_3$) δ: 2.06 (m, 6H), 3.80 (s, 3H), 7.06 (d,1H, J=7.5 Hz), 7.196-7.155 (m, 3H), 7.32 (d,1H, J=8.1Hz),7.704(s,1H), 10.13 (s,1H), 14.23 (s,1H). ^{13}C NMR (75 MHZ $CDCl_3$) δ: 13.1, 20.09, 55.56, 111.7, 121.7, 122.5, 123.8, 126.8, 127.18, 129.4, 133.4, 135.5, 139.2, 145.6, 148.2 151.2, 155.2, 157.9 LCMS: 417 (m+1).

3.5. (E)-methyl 4-(((3-mercapto-5-(3-methoxy-2-methylphenyl)-4H-1,2, 4-triazol-4-yl)-imino) methyl) benzoate (4.4e)

yield 78%; mp 158-166°C. IR (KBr cm^{-1}):3096(Ar-CH), 2935(CH-aliphatic), 2750(SH), 1658(C=O), 1610 (C=C), 1568(C=N), 1483(Ar-CH_3), 1268(C-N), 1128(C-C), 1113(-OCH_3), 692(C-S). ^{1}H NMR (300 MHZ $CDCl_3$) δ: 2.16 (s, 3H), 3.8(s, 3H), 3.9 (s, 3H), 7.02(m, 2H, J=8.1), 7.29(s, 1H), 7.76(d, 2H, J=8.4), 8.06(d, 2H, J=8.1)10.44, (s, 1H), 10.8 (s, 1H). ^{13}C NMR (75 MHZ $CDCl_3$) δ: 13.6, 52.4, 55.69, 112.4, 122.6, 125.7, 126.5, 127.6, 128.4, 130, 133.1, 136.5, 151.2, 157.88, 160.06, 162.6, 166.3. LCMS: 382 (m+1).

3.6. (E)-4-((2, 6-dichlorobenzylidene) amino)-5-(3-methoxy-2-methylphenyl)-4H-1,2,4-tria-zole-3-thiol (4.4f)

yield 83%; mp 161-172°C. IR (KBr cm^{-1}): 3090(Ar-CH), 2939(CH-aliphatic), 2757(SH), 1570(C=C), 1504(C=N), 1465(Ar-CH_3), 1257(C-N), 1145(C-C), 1099(OCH_3), 835(C-Cl), 718(C-S). ^{1}H NMR (300 MHZ $CDCl_3$) δ: 2.04 (s, 3H), 3.8(s, 3H), 7.12-7.29 (m, 2H), 7.43 (s, 1H), 7.45-7.59 (m, 3H), 10.59 (s, 1H), 14.33(s, 1H). ^{13}C NMR (75 MHZ $CDCl_3$) δ: 13.6, 56.15, 113.09, 123.18, 129.5, 129.7, 130.03, 130.17, 130.46, 133.3, 135.09, 150.18, 157.67, 158.3, 161.9. LCMS: 392 (m+1).

3.7. (E)-5-(3-methoxy-2-methylphenyl)-4-((4-methoxybenzylidene) amino)-4H-1, 2, 4-triazole-3-thiol (4.4g)

yield 80%; mp 154-164°C. 3095(Ar-CH), 2925(CH-aliphatic), 2748(SH), 1627(C=C), 1605(C=N), 1464 (Ar-CH3), 1258(C-N), 1132(C-C), 1102(-OCH_3), 670 (C-S). ^{1}H NMR (300 MHZ $CDCl_3$) δ: 2.06(s, 3H), 3.8 (s, 6H), 7.022-7.069 (m, 3H), 7.13 (s, 1H), 7.29 (s, 1H), 7.68 - 7.71 (m, 2H), 9.48 (s, 1H), 14.17 (s, 1H). ^{13}C NMR (75 MHZ $CDCl_3$) δ: 13.7, 56.07, 113.01, 115.15, 122.19, 124.7, 126.5, 126.7, 127.16, 131.06, 149.38, 157.7, 162.2, 163.4, and 166.7: 354(+1)

3.8. (E)-4((4-fluorobenzylidene) amino)-5-(3-methoxy-2-methylphenyl)4H-1,2, 4-triazole -3-thiol (4.4h)

yield 82%; mp 156-166°C. 3097(Ar-CH), 2937(CH-aliphatic), 2750(SH), 1629(C=C), 1595(C=N), 1458 (Ar-CH3), 1257(C-N), 1130(C-C), 1102(-OCH_3), 698 (C-S). ^{1}H NMR (300 MHZ $CDCl_3$) δ: 2.07(s, 3H), 3.8 (s, 3H), 7.17(s, 1H), 7.3 (s, 1H), 7.8 (m, 2H, J=8.1Hz), 8.16 (m, 3H), 9.9(s, 1H), 14.3 (s, 1H). ^{13}C NMR (75 MHZ $CDCl_3$) δ: 13.68, 52.9, 56.1, 113.14, 123.03, 126.5, 126.60, 127.21, 129.2, 130.1, 130.32, 133.2, 136.5, 149.58, 157.82, 162.1, 164.78, 166.01, 193.44: 342(m+1)

3.9. (E)-4((2, 5-dibromobenzylidene) amino)-5-(3-methoxy-2-methylphenyl)4H-1,2,4-triazole-3-thiol (4.4i)

yield 80%; mp 160-170°C. 3098(Ar-CH), 2941(CH-aliphatic), 2756(SH), 1617(C=C), 1576(C=N), 1462 (Ar-CH3), 1258(C-N), 1151(C-C), 1105(-OCH_3), 695(C-S). ^{1}H NMR (300 MHZ $CDCl_3$) δ: 2.07(s, 3H), 3.77 (s, 3H), 7.02 - 7.14 (m, 3H), 7.25 (s, 1H), 7.32 (s, 1H), 7.69 (s, 1H) ,9.63 (s, 1H), 14.19 (s,1H). ^{13}C NMR (75 MHZ $CDCl_3$) δ: 13.66, 56.24, 113.2, 121.7, 123.2, 124.06, 124.6, 126.7 127.1, 130.1, 135.9, 136.8, 156.9, 157.8, 158.9, 162.07. LCMS: 482(m+1)

3.10. (E)-4-((3-fluorobenzylidene) amino)-5-(3-methoxy-2-methylphenyl) 4H-1, 2, 4-triazole-3-thiol (4.4 j)

yield 78%; mp 158-169°C. 3091(Ar-CH), 2934(CH-aliphatic), 2754(SH), 1598(C=C), 1608(C=N), 1467 (Ar-CH3), 1248(C-N), 1108(C-C), 1112(-OCH_3), 698(C-S). ^{1}H NMR (300 MHZ $CDCl_3$) δ: 2.06(s, 3H), 3.8 (s, 3H), 7.336- 7.339 (m, 2H), 7.632-7.828 (m,

5H), 10.13 (s, 1H), 14. 23 (s, 1H). ^{13}C NMR (75 MHZ $CDCl_3$) δ: 13.7, 56.2, 60.68, 106.3, 113,115.1, 123, 126.6, 127.5, 131, 141.7, 149.5, 153.7, 157.8, 162.1, 165.6. : 342m+1)

3.11. (E)-4((3-chlorobenzylidene) amino)-5-(3-methoxy-2-methylphenyl) 4H-1, 2, 4-triazole-3-thiol (4.4 k)

yield 78%; mp 154-165°C. 3169(Ar-CH), 2931(CH-aliphatic), 2820(SH), 1635(C=C), 1521(C=N), 1445 (Ar-CH3), 1243(C-N), 1128(C-C), 1083(-OCH_3), 640(C-S). ^{1}H NMR (300 MHZ $CDCl_3$) δ: 2.14(s, 3H), 3.8 (s, 3H), 7.3(s, 1H), 7.49 - 7.55 (m, 3H), 7.6 (s, 1H), 7.7 (s, 1H), 7.9(s, 1H), 8.56 (s, 1H), 10.33 (s, 1H). ^{13}C NMR (75 MHZ $CDCl_3$) δ: 13.58, 55.7, 112.4, 124.3, 126.5, 127.6, 130.1, 130.9, 132.4, 133.4, 133.8, 135.5, 136.5, 151.1, 157.9, 158.9, 160.3: 358(m+1)

4. CONCLUSION

A novel derivative of Schiff bases bearing 1, 2, 4-triazoles were synthesized and characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. All synthesized derivatives were evaluated for their anti-bacterial and anti-fungal activity using disc diffusion method. This result reveals that most of the compound exhibit good to moderate activity. Among all other compound, **4.4 d, 4.4 g** and **4.4 f, 4.4 j** posses promising bacterial and fungal activity against the tested microorganism.

5. REFERENCES

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