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SYNTHESIS AND BIOLOGICAL SCREENING OF (17E)-N-((2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDIN-3-YL]METHYLENE)-4-ARYLAMINES

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ABSTRACT

The constitution of newly synthesized compounds have been supported by using elemental analysis, infrared spectroscopy, ^{1}H NMR &^{13}C NMR spectroscopy and further supported by mass spectrometry. Purity of all the compounds has been checked by thin layer chromatography. Looking to the interesting properties of azo methines, with an intension to synthesize a better therapeutic agent Azomethine derivatives have been synthesized by the condensation of 2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridine-3-carbaldehyde with different aromatic amines in order to study their biodynamic behavior. All the compounds have been evaluated for their antibacterial activity against Gram Positive bacteria like *Staphylococcus aureus, Bacillus subtilis* and Gram Negative bacteria like *Escherichia coli, Salmonella peratyphi B* and they were also evaluated for antifungal activity against *Candida albicans* and *Aspergillus niger*.

Keywords: Antibacterial activity, Anti-inflammatory, Azomethine derivatives, Antifungal activity.

1. INTRODUCTION

The study of mannich reaction appealed a great deal of attention to the chemists because it plays a vital role due to their wide range of biological and industrial applications, furthermore mannich bases are also employed as an intermediate in chemical synthesis [1-3].

Today, much interest has been focused on the synthesis of mannich bases due to its varied range of pharmacological activities. Several therapeutic important molecules prepared through mannich reaction have received more attention in recent years [4-6].

The heterocycles fused with pyridine ring are important source of biologically relevant compounds and have been made through various methods, often involving building the fused ring by attaching functionality around pyridine, a compound that is difficult to functionalize in a rapid and flexible manner. Nitrogen-containing heterocycles are an important class of compounds which attract much attention as biologically active agents and play a significant role in material science and pharmaceutical industry. Amongst them, imidazo [1,2-a] pyridine derivatives possess especial structures that proved their numerous pharmaceutical importance [7].

Imidazo [1,2-a] pyridines are a class of N-bridged fused bicyclic compounds, which attracted significant attention in recent years due to the broad spectrum of pharmacological profiles displayed. Among the various imidazopyridine derivatives, imidazo [1,2-a] pyridine moiety is the most important in the area of natural products and pharmaceuticals. These derivatives show a wide range of biological activities such as antifungal [8], anti-inflammatory [9], antitumor [10], antiviral [11], antibacterial [12], antiprotozoal [13], antipyretic [14], analgesic [15], antiapoptotic [16], hypnoselective [17] and anxioselective [18] activities. Some other works were also done by our laboratory on different heterocyclic compounds and their biological activities [19-23].

Having wide range of activity of imidazo[1,2-a]pyridine it was thought to synthesize some new imidazo pyridines. All the synthesized compounds (12a-h) were characterized by elemental analysis, infrared spectroscopy, ^{1}H NMR &^{13}C NMR spectroscopy and further supported by mass spectrometry to find the efficiencies of imidazo pyridine derivatives.

2. MATERIAL AND METHODS

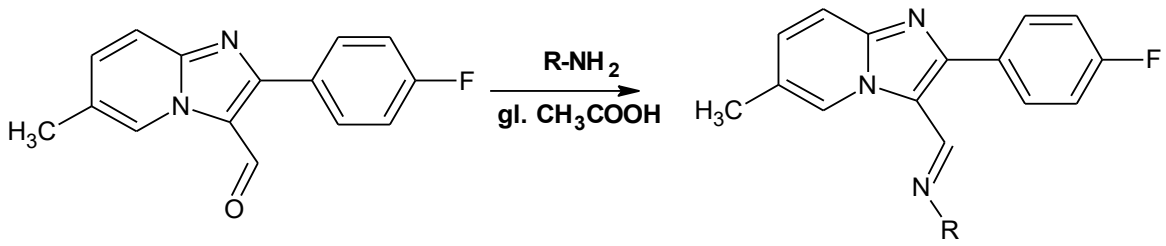
All the chemicals were acquired from Sigma-Aldrich Chemical Co (Sigma-Aldrich, Bangalore, India). The infrared spectra (KBr) were recorded using SHIMADZU-FT-IR 8400-Spectrophotometer operating on 4000-400 cm^{-1}. The proton NMR and Carbon NMR were recorded using BRUKER Spectrometer (300MHz) with $CDCl_3$ and the chemical shifts are expressed in ppm. The mass

spectra (EI) were recorded using Jeol JMS D-300 spectrometer

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mantle. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica gel-G as stationary phase. 40% Ethyl acetate in Hexane was used as a mobile phase.

All the compounds have been screened for them *in vitro* biological assay like antibacterial activity towards Gram positive bacterial strains like *Staphylococcus aureus, Bacillus subtilis* and Gram negative bacterial strains like *Escherichia coli* and *Salmonela typhi B* and antifungal activity towards *Aspergillus niger*, *Candida albicans* at a concentration of 2000/1000/500 µg/ml. To evaluate these new synthesized products for drug potential against different strains of bacteria and fungi antimicrobial screening to the level of minimum inhibitory concentration of each compound of the series, using Agar Dilution Method was performed. Primary screening at 2000 to 1000, Secondary screening at 1000 to 250 and tertiary screening at 250 to 3.9 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values was performed. The biological activities of the synthesized compounds have been compared with standard drugs like Ciprofloxacin.

Looking to the interesting properties of azomethines, with the aim to prepare better therapeutic agents, azomethine derivatives have been synthesized by the condensation of 2-(4-Fluorophenyl)-6-methyl *H*-imidazo [1,2-α] pyridine-3-carbaldehyde with different aromatic amines in order to study their biodynamic behavior.



Synthetic Scheme

2.1. General procedure for synthesis of (17E)-N-((2-(4-fluorophenyl)-6-methyl*H*-imidazo [1,2-α]pyridin-3-yl]methylene)-4-methy-lbenzenamines:

Initially, 2-(4-Fluorophenyl)-6-methyl *H*-imidazo[1,2-α] pyridine-3-carbaldehyde have been prepared by taking a well stirred solution of phosphorus oxychloride (11 ml), chloroform (32 ml) and DMF (8 ml) maintained at 0-10 °C were added slowly to the solution of 2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridine(4.52 gm, 0.02mol) in chloroform (140 ml). The mixture so obtained was refluxed for 8 hours, the solution was evaporated to dryness in vacuum. The residue was treated with cold water, filtered and crystallized from methanol. Then for Synthesis of (17E)-N-((2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl]methylene)-4-methyl -benzenamines in the laboratory the mixture of 2-(4-Fluorophenyl)-6-methyl *H*-imidazo [1,2-α]pyridine-3-carbaldehyde (2.54gm, 0.01 mole) and p-toludine(1.08 gm, 0.01 mole) in methanol (20 ml) in presence of catalytic amount of glacial acetic acid was refluxed for 6 hours. The contents were cooled and product isolated was crystallized from methanol and the yield is 52%.

2.2. Antibacterial Activity Study

Organic compounds may be bacteriostatic or bactericidal for microbial cultures. Mueller Hinton Agar plates (showing no visible growth of bacteria), sub culturing was carried out on Nutrient Agar plates (Collins, 1967). After streaking, Nutrient Agar plates were incubated for 24 h at 37°C. Then after statement was made to see the colonies formed. If colonies were found, the dilution was measured as bacteriostatic and if no colonies observed, it was measured as bactericidal. Bactericidal dilutions of the organic compounds were considered as exact Minimum inhibitory concentration (MIC) for a particular organic compound.

2.3. Antifungal Activity Study

For fungal cultures the fungal media Yeast Nitrogen base agar plate (YNBG) (Difco Make) 6.7 g and Glucose 10 g, dissolved in 100 ml of distilled water and filter sterilized was used. The inoculum was

prepared from 3-4 days old sabouraud's Dextrose agar slants. The growth was uniformly mixed with Distilled water. The Size of inoculum prepared for inoculating YNBG agar plates was 102-103 cfu/ml, adjusted with McFarland solution. After inoculation of properly diluted fungal solution, the plates were incubated at 37°C for 48 hours.

3. RESULTS AND DISCUSSION

3.1. Characterization of synthesized compounds.

3.1.1. (17E)-N-((2-(4-Flurophenyl)-6-MethylH-imidazo[1,2-α]pyridine-3yl)methylene) benzenamine (12A).

^{1}H NMR: ($CDCl_3$) δ 7.3 (s, 5H); 6.97 (d, 1H); 7.42 (d, 1H); 7.03 (d, 2H); 2.32 (d, 3H); 7.46 (d, 2H); 8.07 (s, 1H); 7.50 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 162.9, 151.8, 149.0, 145.7, 144.4, 134.4, 133.8, 130.1.129.1, 122.4, 122.3, 122.0, 116.0, 114.8, 24.7. Mass for ($C_{21}H_{16}FN_3$) 329.13. IR (nujal) cm^{-1}: C-H str. (asym.) 29 62, C-H str. (sym.) 2868, CH def. (asym.) 1448, C-H def. (sym.) 1373, C=C str. 1487, C=N 1602, C-F str. 711, C-N 1070.

3.1.2. (17E)-N-((2-(4-Flurophenyl)-6-MethylH-imidazo[1,2-α]pyridin-3-yl)methylene)-4 methylbenzenamine (12B)

^{1}H NMR: ($CDCl_3$) δ 2.35 (s, 3H); 6.97 (d, 1H); 7.42 (d, 1H); 7.03 (d, 2H); 2.32 (d, 3H); 7.46 (d, 2H); 8.07 (s, 1H); 7.50 (s, 1H); 7.1 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 162.9, 151.8, 146.0, 145.7, 144.4, 136.9, 134.4, 133.8, 130.4.129.1, 128.7, 122.4, 122.2, 122.0, 116.0, 114.8, 24.7, 24.3, Calculated mass for ($C_{22}H_{18}FN_3$) 343.15. IR (nujal) cm^{-1}: C-H str. (asym.) 2962, C-H str. (sym.) 2868, CH def. (asym.) 1448, C-H def. (sym.) 1373, C=C str. 1488, C=N 1601, C-F str. 713, C-N 1070.

3.1.3. (17E)-N-((2-(4-Flurophenyl)-6-MethylH-imidazo[1,2-α]pyridin-3-yl)methylene)-2 methylbenzenamine (12C)

^{1}H NMR: ($CDCl_3$) δ 2.35 (s, 3H); 6.97 (d, 1H); 7.42 (d, 1H); 7.03 (d, 2H); 2.32 (d, 3H); 7.46 (d, 2H); 8.07 (s, 1H); 7.50 (s, 1H); 7.1 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 162.9, 151.8, 147.0, 145.7, 144.4, 134.4, 133.8, 130.6, 130.4, 129.1, 128.7, 127.2, 127.1, 122.4, 122.2, 122, 116.0, 114.8, 24.7, 15.7. Calculated mass for ($C_{22}H_{18}FN_3$) 343.15. IR (nujal) cm–1: C-H str. (asym.) 2962, C-H str. (sym.) 2868, CH def. (asym.) 1448, C-H def. (sym.) 1373, C=C str. 1487, C=N 1602, C-F str. 711, C-N 1070.

3.1.4. (17E)-N-((2-(4-Flurophenyl)-6-MethylH-imidazo[1,2-α]pyridin-3-yl)methylene)-2,5-dimethylbenzenamine (12D)

^{1}H NMR: ($CDCl_3$) δ 2.35 (s, 6H); 6.97 (d, 1H); 7.42 (d, 1H); 7.03 (d, 2H); 2.32 (s, 3H); 7.46 (d, 2H); 8.07 (s, 1H); 7.50 (s, 1H); 6.9 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 162.9, 151.8, 146.9, 145.7, 144.4, 136.7, 134.4, 133.8, 130.3, 129.1, 128.7, 127.6, 127.5, 123.8, 122. 4, 122, 116.0, 114.8, 24.7, 15.7. Calculated mass for ($C_{23}H_{20}FN_3$) 357.16. IR (nujal) cm–1: C-H str. (asym.) 2962, C-H str. (sym.) 2868, CH def. (asym.) 1448, C-H def. (sym.) 1373, C=C str. 1487, C=N 1602, C-F str. 711, C-N 1070.

3.1.5. (17E)-N-((2-(4-Flurophenyl)-6-MethylH-imidazo[1,2-α]pyridin-3-yl)methylene)-4 methoxybenzenamine (12E)

^{1}H NMR: ($CDCl_3$) δ 3.73 (s, 3H); 6.97 (d, 1H); 7.42 (d, 1H); 7.03 (d, 2H); 2.32 (s, 3H); 7.46 (d, 2H); 8.07 (s, 1H); 7.50 (s, 1H); 6.8 (d, 2H); 7.2 (d, 2H). ^{13}C NMR ($CDCl_3$) δ 162.9, 151.8, 145.7, 144.4, 141.3, 134.4, 133.8, 129.1, 128.7, 123.3, 122.4, 122, 116.0, 115.6, 114.8, 55.9, 24.7. Calculated mass for ($C_{22}H_{18}FN_3O$) 359.14. IR (nujal) cm–1: C-H str. (asym.) 2962, C-H str. (sym.) 2868, CH def. (asym.) 1448, C-H def. (sym.) 1373, C=C str. 1487, C=N 1602, C-F str. 711, C-N 1070.

3.1.6. (17E)-2,5-dichloro-N-((2-(4-Flurophenyl)-6-MethylH-imidazo[1,2-α]pyridin-3-yl)methylene)benzenamine (12F)

^{1}H NMR: ($CDCl_3$) δ 6.97 (d, 1H); 7.42 (d, 1H); 7.03 (d, 2H); 2.32 (s, 3H); 7.46 (d, 2H); 8.07 (s, 1H); 7.50 (s, 1H); 7.2 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 162.9, 151.8, 145.7, 144.4, 140.5, 134.4, 133.8, 133.7, 131.6, 129.1, 128.8, 128.7, 125.9, 124.0, 122.4, 122, 116.0, 114.8, 24.7. Calculated mass for ($C_{21}H_{14}Cl_2FN_3$) 397.05. IR (nujal) cm–1: C-H str. (asym.) 2962, C-H str. (sym.) 2868, CH def. (asym.) 1448, C-H def. (sym.) 1373, C=C str. 1487, C=N 1602, C-F str. 711, C-N 1070.

3.1.7. (17E)4-chloro-N-((2-(4-Flurophenyl)-6-MethylH-imidazo[1,2-α]pyridin-3yl) methy-lene) benzenamine (12G)

^{1}H NMR: ($CDCl_3$) δ 6.97 (d, 1H); 7.42 (d, 1H); 7.03 (d, 2H); 2.32 (s, 3H); 7.46 (d, 2H); 8.07 (s, 1H); 7.50

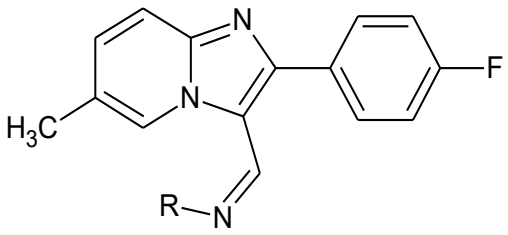
(s, 1H); 7.2 (d, 2H); 7.3 (d, 2H). ^{13}C NMR ($CDCl_3$) δ 162.9, 151.8, 147.1, 145.7, 144.4, 134.4, 133.8, 132.8, 130.2, 129.1, 128.7, 123.7, 122.4, 122, 116.0, 114.8, 24.7. Calculated mass for ($C_{21}H_{15}ClFN_3$) 363.09. IR (nujal) cm–1: C-H str. (asym.) 2962, C-H str. (sym.) 2868, CH def. (asym.) 1448, C-H def. (sym.) 1373, C=C str. 1487, C=N 1602, C-F str. 711, C-N 1070.

3.1.8. (17E)-4-fluoro-N-((2-(4-Flurophenyl)-6-MethylH-imidazo[1,2-α]pyridin-3-yl)methy-lene) benzenamine (12H)

^{1}H NMR: ($CDCl_3$) δ 6.97 (d, 1H); 7.42 (d, 1H); 7.03 (d, 2H); 2.32 (s, 3H); 7.46 (d, 2H); 8.07 (s, 1H); 7.50 (s, 1H); 7.2 (d, 2H); 7.0 (d, 2H). ^{13}C NMR ($CDCl_3$) δ 162.9, 151.8, 145.7, 144.6, 144.4, 134.4, 133.8, 129.1, 128.7, 123.9, 122.4, 122, 116.8, 116.0, 114.8, 24.7. Calculated mass for ($C_{21}H_{15}F_2N_3$) 347.12. IR (nujal) cm–1: C-H str. (asym.) 2962, C-H str. (sym.) 2868, CH def. (asym.) 1448, C-H def. (sym.) 1373, C=C str. 1487, C=N 1602, C-F str. 711, C-N 1070.

The synthesis of imidazopyridine (2a-g) involves two components one pot reaction of 2-(4-fluorophenyl)-6-methyl-H-imidazo[1,2-α]pyridine-3-carbaldehyde and different aromatic amine in methanol (20 mL) in presence of catalytic amount of glacial acetic acid for the synthesis and product yield in the range 66 to 86% has been achieved after the isolation. The structures of the synthesized compounds were established on the basis of FT-IR, 1 H NMR ^{13}C NMR and mass spectral data. All the title compounds showed a characteristic absorption bands in the range between 1590-1610 cm-1 for C=N, near of 1070 cm^{-1} for C-N frequencies of imidazopyridine ring. ^{1}H NMR spectrum supported the structures of imidazopyridine derivatives and exhibits a multiplet between 6.97-8.00 ppm for aromatic protons and singlet between 8.0 to 8.2 ppm for (CH=N). Further, the structures were confirmed from the mass analysis in which the calculated mass values were well correlated with the observed data.

Table 1: Physical constants of (17E)-N-((2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl]methylene)-4-arylamines.



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
12a	C_6H_5-	$C_{21}H_{16}FN_3$ 329.37	163	81	76.69 (76.58)	4.98 (4.90)	12.79 (12.76)
12b	4-CH_3-C_6H_4-	$C_{22}H_{18}FN_3$ 343.39	154	72	76.95 (76.80)	5.38 (5.28)	12.33 (12.24)
12c	2-CH_3-C_6H_4-	$C_{22}H_{18}FN_3$ 343.39	147	86	76.95 (76.84)	5.36 (5.28)	12.29 (12.24)
12d	2,5-$(CH_3)_2$-C_6H_3-	$C_{23}H_{20}FN_3$ 357.42	158	78	77.36 (77.29)	5.74 (5.64)	11.89 (11.76)
12e	4-OCH_3-C_6H_4-	$C_{22}H_{18}FN_3O$ 359.39	110	73	73.59 (73.52)	5.21 (5.05)	11.65 (11.69)
12f	2,5-$(Cl)_2$-C_6H_3-	$C_{21}H_{14}Cl_2FN_3$ 398.26	159	66	63.41 (63.33)	3.59 (3.54)	10.59 (10.55)
12g	4-Cl-C_6H_4-	$C_{21}H_{15}ClFN_3$ 363.81	168	70	69.38 (69.33)	4.29 (4.16)	11.64 (11.55)
12h	4-F-C_6H_4-	$C_{21}H_{15}F_2N_3$ 347.36	113	67	72.69 (72.61)	4.48 (4.35)	12.26 (12.10)

3.2. Antimicrobial activity of (17E)-N-((2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl]methylene)-4-arylamines

All the compounds have been evaluated for antimicrobial and antifungal activity as described. Appropriate dilutions were done by taking 1 ml quantity of antimicrobial solution to Mueller Hinton agar (19 ml quantity) that has been allowed to equilibrate in a water bath for 45 to 50 °C. One part of antimicrobial solution is added to nine parts of liquid agar. The agar and antimicrobial solution were mixed thoroughly and the mixture was poured into Borocil glass Petri dishes having 9 cm diameter on a level surface to result in an agar depth of 3 to 4 mm. In order to prevent cooling and partial solidification in the mixing container and to avoid bubbles the plates should be poured as quickly after mixing. Solidification of the Agar plate was allowed at room temperature, and the plates were either used immediately or stored in sealed plastic bags at 2 to 8°C for up to five days for reference work, or longer for routine tests. Before using the plates they were stored at 2-8°C to equilibrate at room temperature, assuring that the agar surface was dry before inoculating the plates. If required, plates were placed in an incubator or laminar flow hood for approximately 30 minutes with their lids which helps agar to accelerate drying of the agar surface.

Table 2: Antimicrobial activity of (17E)-N-((2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl]methylene)-4-arylamines

Code NO	Antibacterial activity												Antifungal activity					
	Gram +ve Bacteria						Gram -ve Bacteria						Uni/Multicellular Fungi					
	Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonela typhi B*			*Aspergillus niger*			*Candida albicans*		
	Conc. (µg/ml)			Conc. (µg/ml)			Conc. (µg/ml)			Conc. (µg/ml)			Conc. (µg/ml)			Conc. (µg/ml)		
	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
12a	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-
12b	+	+	-	+	+	+	-	-	-	+	+	-	+	+	+	-	-	-
12c	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
12d	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-
12e	-	-	-	+	+	-	+	+	-	+	+	-	-	-	-	-	-	-
12f	+	+	-	+	+	+	-	-	-	-	-	-	+	+	-	+	+	-
12g	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-
12h	+	+	+	+	+	+	-	-	-	-	-	-	+	+	-	+	+	-

Primary screening at 2000 to1000, Secondary screening at 1000 to 250 and tertiary screening at 250 to 3.9 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values were conducted. From the results of experiments using newly synthesized organic compounds' it is clear that all the compounds were moderately active at lower dilution *i.e.* high concentration like 2000 µg/ml and 1000 µg/ml conc. of compounds. In the series (12a-h), almost three compounds 12c, 12g and 12h were found active at 500 µg/ml conc. against *staphylococcus aureus*. *Bacillus Subtilis* was inhibited at 500 µg/ml conc. by six compounds 12a, 12b, 12c, 12f, 12g and 12h.

In this present work, valuable factors are focused. Antimicrobial & antifungal activities of product were recorded and synthesized compounds have been compared with standard drugs. The product (17E)-N-((2-(4-fluorophenyl)-6-methyl-*H*-imidazo[1,2-α]pyridin-3-yl]methylene)-4-arylamines is prepared by good method. This method gives good yields and simple work up. From which Compound **12a** which shows yield of 81% and it is reddish brown in color. The other compounds having good % yields are, **12c** has yield of 86%, **12d** has yield of 78%. The purified products are uncontaminated.

4. CONCLUSION

A heterocyclic systems namely imidazo[1,2-α]pyridine has enhanced the pharmacological effect and hence they are ideally suited for further modifications to obtain more efficacious antibacterial and antifungal compounds. The structures of all the compounds were confirmed by, 1H NMR & 13C NMR spectroscopy, mass and FT-IR. The manufactured compounds were

tested for potential biological activities. All the compounds were found to possess reasonably good antifungal and antimicrobial activities.

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