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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL SCREENING OF SOME SUBTITUTED 1, 2, 4-TRIAZOLE DERIVATIVES

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ABSTRACT

A new series of substituted 1, 2, 4- triazoles were synthesized by oxidative cyclization method. The synthesized compounds were scaled for their spectral studies and the structures of the synthesized compounds were confirmed by IR, ^{1}H-NMR, Mass and elemental analysis. The newly synthesized compounds were subjected to antimicrobial activity by known standard method. Some of these compounds show promising antibacterial and antifungal activity as compared to standard drug Levofloxacin and Amphotericin-B.

KEYWORDS: 1, 2, 4-triazole, oxidative cyclization, antibacterial, antifungal activities.

INTRODUCTION

The ring formation reactions from acid hydrazides have been extensively studied. Mostly these reactions results in to the formation of five membered heterocycles with heteroatoms. The representative heterocycles are1,3,4-oxadiazoles,1,3,4-thiadiazoles and 1,2,4-triazoles. are1,3,4-oxadiazole,1,3,4-thiadiazole and 1,2,4-triazole ring

systems are typical planar six-p-electron partially aromatic systems and are used along with their derivatives as starting materials for the synthesis of many heterocycles. The 1,2,4-triazole and its derivatives were reported to exhibit various pharmacological activities likes antimicrobial activity[1], anti-inflammatory activity[2], anti cancer activity[3], anticonvulsant activity[4], Methionine aminopeptidase type II inhibitors[5], Anti-tubercular activity[6], anti viral activity[7], anti hypertensive activity [8], Tubulin inhibitors[9], etc. There are many marketed drugs containing the 1,2,4-triazole group e.g. Triazolam, Alprazolam, Etizolam and Furacyclin, Ribavarin (antiviral agents), Rizatriptan (antimigraine agents), Fluconazole and Itraconazole (antifungal agents) etc. In view of these findings we report on the synthesis, characterization and antibacterial activities of some substituted 1,2,4-triazole derivatives. The synthesis of 1,2,4-triazole derivatives from Schiff's bases of acid azides were prepared by using oxidative cyclization process using ferric chloride as an oxidative cyclising agent. All the synthesized compounds were prepared in water phase without expenditure of energy hence it is a green synthesis of 1,2,4-triazoles.

MATERIALS AND METHODS

Material

All the chemicals required for the synthesis were purchased from Modern Science, Nashik and are of AR grade.

Methods

ANTIBACTERIAL ACTIVITY

Anti bacterial study was carried out by using Cup-plate Agar diffusion method. The synthesized derivatives were tested in vitro for their anti bacterial activity against *E.coli* (NCTC 10418), *S. Aureus* (NCTC 6571) and *B. subtilis* which are pathogenic to human beings. Leavofloxacin had been used as a standard drug.

ANTI FUNGAL ACTIVITY

Anti-fungal activity was carried out by using Cup-Plate Agar diffusion method using nutrient agar as a culture media. The synthesized compounds were tested against *Candida albicans* (ATCC 10231) and *Aspergilus niger* (ATCC 16404). Amphotericin B had been used as a standard drug.

The synthesized compounds were dissolved in DMF and activities were carried out at a concentration of 200µg/ml.

EXPERIMENTAL

Melting points were determined in open capillary method and are uncorrected. Purity of the compound was checked on Silica gel TLC plates. IR spectra were recorded on Thermo Nicolate IR 200 spectrophotometer using KBr disc method. ^{1}H NMR spectra were recorded on Bruker AMX-400, DMSO δ6 as solvent and TMS as internal standard. Combustion analyses were found to be within the limits of permissible errors.

Synthesis of Schiff's bases from acid hydrazide and aromatic aldehyde[10]

0.01 mole of an acid hydrazide was dissolved in 10 ml of water along with little ammonia and stirred continuously with drop wise addition of 0.01 moles an aromatic aldehyde until a solid mass is obtained. Filter the precipitate and recrystallized from methanol.

Synthesis of 1,2,4-Triazoles from Schiff's bases[11]

0.01 mole of Schiff's base and 0.01 mole of acid hydrazide were triturated in a mortar and pestle in presence of oxidative cyclising agent ferric chloride. The completion of reaction was checked using TLC and then mass is digested in 20 ml of water. Filter the precipitate and recrystallized from ethanol to offer title compounds. Mobile phase: GAA: Methanol: Ethyl acetate-3:2:1.

SPECTRAL DATA

B_1: IR (cm^{-1}) KBr disc

3420.15 –NH str.; 3022.58 Ar-CH str.; 2865.36 –CH_3 str.; 1686.69 –CONH str.; 1575.24 -C=N str.; 1070.36 –C-O-C str.; **^{1}H-NMR (ppm):** 8.4-8.8 4H of pyridine, 6.8-7.6 11 H of phenyl, 5.0 2H of –NH, 1.2-2.6 9H of –CH_3; **m/e (100%):**490.

B_2: IR (cm^{-1}) KBr disc

3415.27 –NH str.; 3258.68 –OH str.; 3028.47 Ar-CH str.;2856.47 –CH_3 str.; 1686.69 –CONH str.; 1585.32 -C=N str.; **^{1}H-NMR (ppm):** 8.2-8.6 4H of pyridine, 6.2-7.4 11 H of phenyl, 5.0 2H of –NH, 4.0 1H of –OH, 1.0-1.8 6H of –CH3; **m/e (100%):**476.

B_3: IR (cm^{-1}) KBr disc

3420.86 –NH str.; 3030.14 Ar-CH str.; 2870.37–CH_3 str.; 1685.23 –CONH str.; 1585.24 -C=N str.; 985.26 –C-Cl bend; **^{1}H-NMR (ppm):** 8.4-8.8 4H of pyridine, 6.1-7.6 11 H of phenyl, 5.0 2H of –NH, 0.8-1.6 6H of –CH3; **m/e (100%):**494.

B_4: IR (cm^{-1}) KBr disc

3445.20 –NH str.; 3025.14 Ar-CH str.; 2836.39 –CH_3 str.; 1684.24 –CONH str.; 1586.29 -C=N str.; 1060.68 –C-O-C str.; **^{1}H-NMR (ppm):** 8.8-9.2 3H of pyrazine, 6.4-7.2 11 H of phenyl, 5.0 1H of –NH, 1.4-2.6 9H of –CH3; **m/e (100%):**476.

B_5: IR (cm^{-1}) KBr disc

3440.27 –NH str.; 3220.28 –OH str.; 3014.36 Ar-CH str.; 2855.34–CH_3 str.; 1687.24 –CONH str.; 1595.69 -C=N str.; **^{1}H-NMR (ppm):** 8.6-9.0 3H of pyrazine, 6.2-7.6 11 H of phenyl, 5.0 1H of –NH, 4.0 1H of –OH, 0.8-1.4 6H of –CH_3; **m/e (100%):**462.

B_6: IR (cm^{-1}) KBr disc

3450.48 –NH str.; 3065.38 Ar-CH str.; 2876.38–CH_3 str.; 1690.27 –CONH str.; 1588.34 -C=N str.;987.25 –C-Cl bend; **^{1}H-NMR (ppm):** 8.4-9.0 3H of pyrazine, 6.4-7.2 11 H of phenyl, 5.0 1H of –NH, 1.0-1.6 6H of –CH_3; **m/e (100%):**480.

B_7: IR (cm^{-1}) KBr disc

3486.84 –NH str.; 3068.48 Ar-CH str.; 2876.37 –CH_3 str.; 1694.25 –CONH str.; 1586.32-C=N str.; 1025.39 –C-O-C str.; 965.38 –C-Cl bend; **^{1}H-NMR (ppm):** 7.6-8.4 4H of pyridine, 6.6-7.4 11 H of phenyl, 5.0 2H of –NH, 1.2-1.6 5H of –CH_3; **m/e (100%):**490.

B_8: IR (cm^{-1}) KBr disc

3465.28 –NH str.; 3228.56 –OH str.; 3012.35 Ar-CH str.; 2865.36–CH_3 str.; 1686.26–CONH str.; 1590.39 -C=N str.;960.35 –C-Cl bend; **^{1}H-NMR (ppm):** 7.8-8.4 4H of pyridine, 6.4-7.4 11 H of phenyl, 5.0 2H of –NH, 4.0 1H of –OH, 0.8-1.2 2H of –CH_2; **m/e (100%):**476.

B_9: IR (cm^{-1}) KBr disc

3435.24 –NH str.; 3086.37 Ar-CH str.; 2860.35–CH_3 str.; 1684.38 –CONH str.; 1592.35 -C=N str.;968.35 –C-Cl bend; **^{1}H-NMR (ppm):** 7.6-8.2 4H of pyridine, 6.8-7.2 11 H of phenyl, 5.0 2H of –NH, 0.8-1.2 2H of –CH_2; **m/e (100%):**494.

B_{10}: IR (cm^{-1}) KBr disc

3445.68 –NH str.; 3025.69 Ar-CH str.; 2876.38 –CH_3 str.; 1684.37 –CONH str.; 1586.34 -C=N str.;1065.48 –C-O-C str.; 967.28 –C-Cl bend; **^{1}H-NMR (ppm):** 8.8-9.2 3H of pyrazine, 6.6-7.4 11 H of phenyl, 5.0 1H of –NH, 1.2-1.6 5H of –CH_3; **m/e (100%):**531.

B_{11}: IR (cm^{-1}) KBr disc

3446.85 –NH str.; 3235.36 –OH str.; 3025.61 Ar-CH str.; 2856.30 $–CH_3$ str.; 1685.64 –CONH str.; 1595.32 -C=N str.;986.25 –C-Cl bend; **^{1}H-NMR (ppm):** 8.4-9.0 3H of pyrazine, 6.8-7.6 11 H of phenyl, 5.0 1H of –NH, 4.0 1H of –OH, 0.8-1.2 2H of $–CH_2$; **m/e (100%):**517.

B_{12}: IR (cm^{-1}) KBr disc

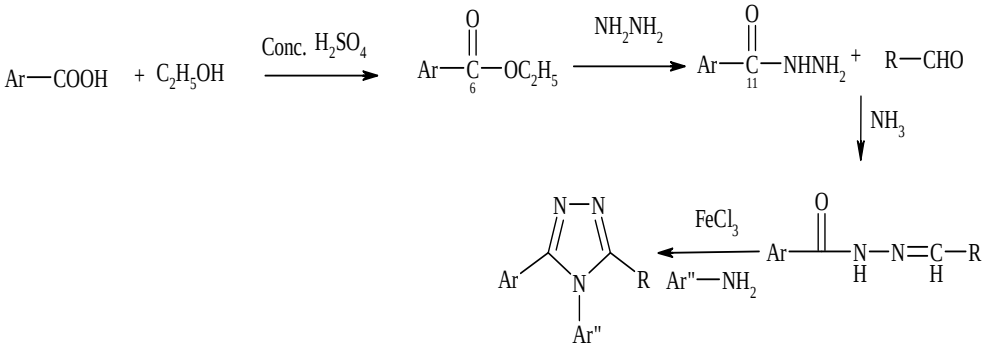
3455.68 –NH str.; 3025.64 Ar-CH str.; 2860.34 $–CH_3$ str.; 1687.32 –CONH str.; 1586.24 -C=N str.;976.38 –C-Cl bend; **^{1}H-NMR (ppm):** 8.8-9.2 3H of pyrazine, 6.8-7.2 11 H of phenyl, 5.0 1H of –NH, 1.0-1.4 2H of $–CH_2$; **m/e (100%):**535.

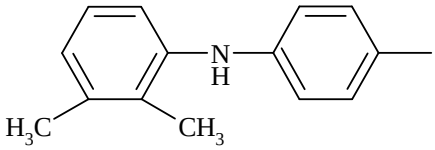
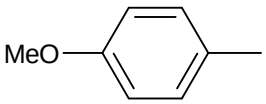
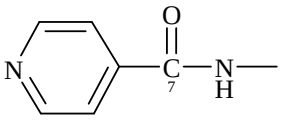
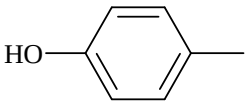
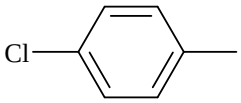
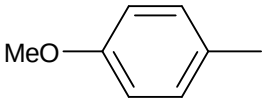
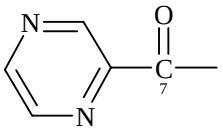
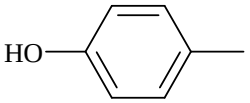
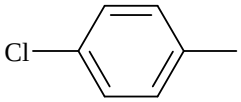
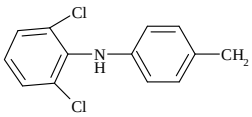
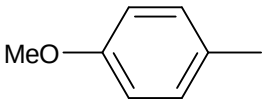
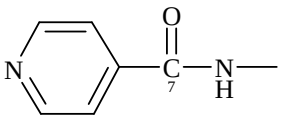
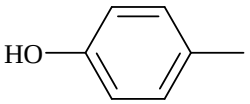
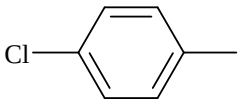
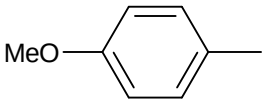
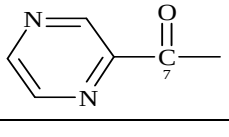
RESULTS AND DISCUSSION

The structures of the synthesized derivatives of 1,2,4-triazole (B_1-B_{12}) were established by IR, ^{1}H-NMR, Mass spectra and elemental analysis. The purity of synthesized compounds had been checked on TLC plates using GAA: Methanol: Ethyl acetate-3:2:1 as a mobile phase. The IR, ^{1}H-NMR and mass data reported in manuscript under section of spectral data. The IR spectra shows absorption bands like 3450-3480 cm^{-1} (-NH str.), 3220-3250 cm-1 (-OH str.), 3010-3050 cm-1 (aromatic –CH str.), 2840-2880 cm^{-1} (aliphatic –CH str.), 1685-1695 cm-1 (-CONH str.), 1570-1595 cm^{-1} (-C=N str.), 1030-1080 (-C-O-C str.), which are characteristic feature of 1,2,4-triazoles. ^{1}H-NMR shows peaks in 7.4-8.2 (H of pyridine), 8.4-9.2 (H of pyrazine), 6.4-7.8 (aromatic H), 5.0 (H of –NH), 4.0 (H of –OH), 1.2-2.6 (H of –CH3).

The synthesized compounds were subjected for anti bacterial activity. Out of twelve compounds the compounds B_3,B_4,B_5 and B_{10} had shown significant antibacterial activity. The structural features of the compounds like presence of electron donating group likes –CH3, -OCH3 along with hydroxyl group was thought to increase the biological activity. While other compounds which possess electron withdrawing substituents like –Cl, might be responsible for decrease in activity. In case of anti fungal compounds B_1,B_2,B_6 and B_{11} shows significant activity as they posses higher percentage of electron donating groups like CH_3, -OCH_3 which might increase the antifungal activity of these derivatives beside this these derivatives also contains a chloride linkage which increases the binding of drugs to the receptors this also responsible for increase in biological activities. Mostly Diclofenac derivatives shows significant antimicrobial activity as it brings inhibition of bacterial DNA synthesis.

Scheme



Comp. Code	Ar	R	Ar”
B_1			
B_2			
B_3			
B_4			
B_5			
B_6			
B_7			
B_8			
B_9			
B_{10}			

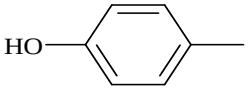
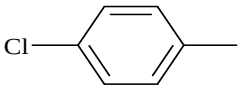
B_{11}			
B_{12}			

Table no. 01: Analytical data of synthesized compounds (B1-B12).

Comp. Code	Molecular Formula	Mole wt.	M.P. (0C)	Elemental analysis Found (cald.)			Rf Value	% Yield
				C	H	N		
B_1	$C_{29}H_{26}N_6O_2$	490.57	268-274	71.00 (69.68)	5.34 (5.02)	17.13 (16.95)	0.56	63
B_2	$C_{28}H_{24}N_6O_2$	476.54	264-278	70.57 (70.23)	5.08 (4.89)	17.64 (17.28)	0.51	60
B_3	$C_{28}H_{23}ClN_6O$	494.99	263-269	67.94 (67.59)	4.68 (4.37)	16.98 (16.74)	0.53	59
B_4	$C_{28}H_{24}N_6O_2$	476.54	257-262	70.57 (70.24)	5.08 (4.88)	17.64 (17.25)	0.47	49
B_5	$C_{27}H_{22}N_6O_2$	462.52	256-261	70.12 (69.85)	4.79 (4.42)	18.17 (17.88)	0.49	57
B_6	$C_{27}H_{21}ClN_6O$	480.96	248-253	67.43 (67.05)	4.40 (4.08)	17.47 (17.14)	0.53	59
B_7	$C_{29}H_{26}N_6O_2$	490.57	231-237	71.00 (69.78)	5.34 (4.98)	17.13 (16.98)	0.59	61
B_8	$C_{28}H_{24}N_6O_2$	476.54	239-243	70.57 (70.18)	5.08 (4.89)	17.64 (17.41)	0.57	63
B_9	$C_{28}H_{23}ClN_6O$	494.99	251-256	67.94 (67.59)	4.68 (4.35)	16.98 (16.67)	0.53	65
B_{10}	$C_{27}H_{20}Cl_2N_6O_2$	531.41	312-318	61.03 (60.85)	3.79 (3.48)	15.81 (15.48)	0.59	67
B_{11}	$C_{26}H_{18}Cl_2N_6O_2$	517.38	342-346	60.36 (60.03)	3.51 (3.14)	16.24 (15.98)	0.51	58
B_{12}	$C_{26}H_{17}Cl_3N_6O$	535.82	289-294	58.28 (57.89)	3.20 (2.98)	15.68 (15.39)	0.58	60

Table no. 02: Antibacterial and antifungal activity of synthesized compounds (B1-B12).

Compd. code	Zone of inhibition at 200 g/ml (in mm)				
	E.coli	*B.Subtilis*	*S.aureus*	*A. niger*	*C.albicans*
B_1	24	25	26	21	23
B_2	23	25	26	20	22
B_3	26	23	26	20	21
B_4	26	23	25	19	21
B_5	25	24	26	20	21
B_6	25	26	26	21	20
B_7	24	25	26	15	22
B_8	20	23	25	16	21
B_9	20	24	25	19	22

B_{10}	25	26	23	20	21
B_{11}	24	23	26	21	22
B_{12}	20	22	24	18	23
Levofloxacin	**26**	**25**	**26**	**-**	**-**
Amphotericin-B	**-**	**-**	**-**	**22**	**23**

CONCLUSION

The present study is innovative and novel total twelve new compounds were synthesized and structures of these compounds are confirmed by IR, ^{1}H-NMR, Mass and elemental analysis. These compounds were screened for antibacterial and antifungal activity by using Cup-Plate Agar Diffusion Method. Some of these compounds shows promising biological activity. These compounds with suitable molecular modification and manipulations. These compounds will prove as potent antimicrobial compounds in future.

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