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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF SOME NEW SUBSTITUTED IMIDAZOLES

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ABSTRACT: In the present study, a new series of 2, 4, 5- trisubstituted imidazoles derivatives were synthesized taking different aldehydes as substitutions. The preliminary characterization of synthesized compounds identified by physical constants determination and TLC. The chemical structures were confirmed by means of IR, ^{1}H-NMR and Mass spectral data. The synthesized compounds were screened for their anti-microbial and antifungal activity using standard methods. Both gram positive and gram negative organisms such as *E.coli, B.subtilis, S.aureus, A. niger, C.albicans* were used. The compounds screened for their antibacterial and antifungal activities A_1, A_2, A_4 have shown promising antibacterial and antifungal activity against as compared to standard drugs Ciprofloxacin and Griseofulvin. The compounds were also screened for their antidepressant activities using forced swimming test in mice in which A_1, A_2 and A_6 are found to be most significant while compounds A_4 and A_5 showed moderate activity as compared to standard drug Fluoxetin. The compound A_4, 4-(4, 5-diphenyl-1H-imidazole-2-yl) phenol exhibited excellent activity.

INTRODUCTION: Imidazole is a planar 5-membered ring and is amphoteric. That is, it can function as both an acid and as a base. As an acid, the pK_a of Imidazole is 14.5, making it less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. The acidic proton is located on N-1. As a base, the pK_a of the conjugate acid (cited above as pK_{BH}^+ to avoid confusion between the two) is approximately 7, making imidazole approximately sixty times more basic than pyridine.

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The basic site is N-3, protonation gives the imidazolium cation, which is symmetrical. The compound is classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. Different drugs containing these basic moieties with good pharmacological activity have been reported earlier. They undergo different types of chemical reactions and are found useful in synthesis of variety of heterocyclic compounds. Imidazole and their derivatives were used for the synthesis of various types of medicinal compounds having a good therapeutic value.

Literature survey reveals that, imidazole derivatives exhibited diverse pharmacological activities. Such as, antimicrobial activity,[1-6] anti-HCV and anti

tumor activity,[7] antinociceptive activity, leishmanicidal activity,[8] anticonvulsant activity,[9] GABA uptake inhibitory activity,[12] cytotoxic,[13,14] anticancer activity,[15] antiproliferative activity,[16, 17] aromatase inhibitory activities,[18] antitubercular,[19] anti fungal agents [20] etc. Based on above observation it is worthwhile to synthesis newer compounds for their pharmacological activities. The aim of present study is to synthesize new potential 2, 4, 5-trisubstituted Imidazole derivatives (A_{1-6}) and to evaluate possible pharmacological activities like antifungal, antibacterial and antidepressant activities.

MATERIALS AND METHODS:

Melting points were determined by open capillary tubes and were found uncorrected. IR were recorded on FT-IR spectrometer (BRUKER) using KBr disc method. ^{1}HNMR spectra were recorded on NMR spectrometer (BRUKER AV-300MHz) in DMSO. The compounds were analysed for elemental analysis and their percentages were found to be very near that of the calculated values. Physical parameters data of compounds are recorded in **Table 1** and spectral data recorded in **Table 2**.

TABLE 1: PHYSICAL PARAMETERS AND ELEMENTAL ANALYSIS OF COMPOUNDS

Compound	Mol. Formula	Mol.wt	M.P [^{0}C]	% Yield	Rf	Elemental analysis (calculated)					
						%C	%H	%N	%O	%S	%Cl
A_1	$C_{21}H_{16}N_2$	296	280	86	0.62	84.55	6.51	8.94	-	-	-
A_2	$C_{21}H_{16}N_2O$	312	172	73	0.58	80.12	5.98	7.96	5.94	-	-
A_3	$C_{23}H_{22}N_2$	326	180	65	0.67	85.10	6.81	8.09	-	-	-
A_4	$C_{22}H_{18}N_2O$	326	194	67	0.72	81.07	8.06	4.53	6.34	-	-
A_5	$C_{19}H_{15}N_2O$	287	168	59	0.76	79.56	9.87	4.93	5.64	-	-
A_6	$C_{21}H_{16}N_2O$	312	187	68	0.69	78.39	8.55	6.81	6.25	-	-

TABLE 2: SPECTRAL ANALYSIS OF SYNTHESISED COMPOUNDS

Compound	IR (KBr) ν (cm-1)	^{1}H NMR (DMSO) δ in ppm
A_1	3037.96 (Ar-CH, st), 2840.85 (-NH,st), 1586.97 (-C=N, st), 1202.18 (-C-N,st)	6.8-8.2 (15 H of phenyl), 4.0 (1H of -NH)
A_2	3267.46 (-OH st), 3058.08 (Ar-CH,st), 2729.81 (-NH,st), 1536.00 (-C=N,st), 1257.27 (--N,st)	7.4-8.4 (14 H of phenyl), 2.5 (1H of –NH), 1.5 (1H of -OH)
A_3	3427.95 (CH=CH, st), 3211.91(–NH, st), 3060.83(Ar-CH, st), 1585.41 (-C=N, st), 1239.12(–C-N, st),	7.6-8.6 (15 H of phenyl), 5.4-5.6 (2H of –CH=CH), 2.5 (1H of –NH)
A_4	3267.77 (–NH, st), 3027.82 (Ar-CH,st), 2804.81 (-CH_3,st), 1600.32 (-C=N, st), 1258.00 (–C-N, st), 1028.38 (-C-O-C-,st)	7.6-8.6 (15 H of phenyl), 5.4-5.6 (2H of –CH=CH), 3.5-4.0 (3H of CH_3), 2.5 (1H of –NH)
A_5	3037.96 (–NH, st), 2988.92 (Ar-CH,st), 1586.97 (-C=N, st), 1202.18 (–C-N, st), 1028.71(-C-O-C-,st)	6.4-7.8 (13 H of phenyl), 2.2 (1H of –NH), 6.7-7.2 (furfuryl)
A_6	3267.46 (-OH, st), 3058.08 (ArCH, st), 2729.81 (–NH, st), 1602.33(–C=N, st), 1296.18 (–C-N, st)	7.1-7.9 (14 H of phenyl), 2.5 (1H of –NH), 1.8 (1H of -OH)

Synthesis of 2, 4, 5-triphenyl-1H-imidazole [A_1 to A_6]

0.01 mole of Benzil was refluxed with 0.01 mole of an aromatic aldehyde in presence of 5 ml of glacial acetic acid and 0.01 moles of ammonium acetate for 4 hours. After which the resulting reaction mixture was cooled to room temperature. The reaction mixture was then poured in 15 ml of water and kept for refrigeration overnight. The resulting precipitate was collected, dried and recrystallized from hot ethanol. Scheme was illustrated in **Figure1.** Physical data were given in the **Table 3.**

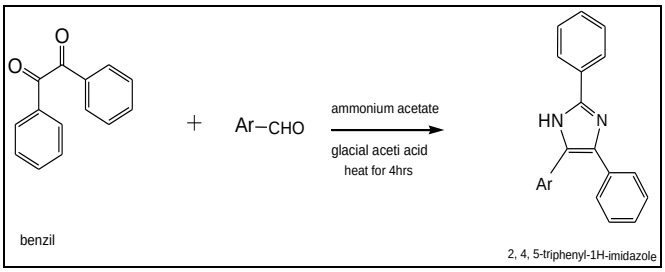
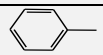
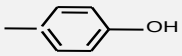
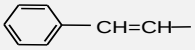
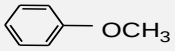
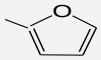
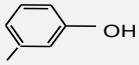


FIG 1: SCHEME FOR THE SYNTHESIS OF COMPOUNDS

TABLE 3: PHYSICAL DATA OF COMPOUNDS

S.NO	Compound code	-Ar	Name of compound
1	A_1		2,4,5-triphenyl-1H-imidazole
2	A_2		4-(2,4-diphenyl-1H-imidazole-5-yl)phenol
3	A_3		2,4-diphenyl-5-(4-prop-1-enyl)phenyl-1H-imidazole
4	A_4		5-(4-methoxyphenyl)-2,4-diphenyl-1H-imidazole
5	A_5		5-(furan-2-yl)-2,4-diphenyl-1H-imidazole
6	A_6		3-(2,4-diphenyl-1H-imidazole-5-yl)phenol

Antibacterial activity:

The compounds were tested *in-vitro* for their antibacterial activity against two microorganisms viz. Gram positive organisms: *Staphylococcus aureus* (ATCC 29737) and *Bacillus subtilis* (ATCC 6633), Gram negative organism: *Escherichia coli* (NCTC 10418) which are pathogenic in human beings using Cup-plate agar diffusion method using Nutrient agar.

Antifungal activity:

The compounds were tested *in-vitro* for their antifungal activity against *Aspergillus niger* (NCIM 596) and *Candida albicans* (NCIM 3102) using Cup-plate agar diffusion method using Sabouraud-Dextrose agar.

Antidepressant activity:

All the compounds were screened for antidepressant activity also. Behavioural despair was proposed as a model to test for antidepressant activity by Porsolt et al. (1977, 1978). It was suggested that mice or rats forced to swim in a restricted space from which they cannot escape are induced to a characteristic behaviour of immobility. This behaviour reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression.

RESULTS AND DISCUSSION:

All the synthesised compounds were characterized and identified by using different physico-chemical parameters. Such as, TLC, melting point, elemental analysis, IR and ^{1}HNMR. From the literature survey it reveals that, the substituted imidazoles have been reported for number of pharmacological activities. The prepared compounds were screened for their anti-bacterial activity by using cup-plate agar diffusion method against various gram positive, gram negative and fungal stains. Some of the compounds show comparable activity with that of the standard (Ciprofloxacin and Griseofulvin).

The compounds screened for their antibacterial and antifungal activities A_1, A_2, A_4 have shown promising antibacterial and antifungal activity against *E.coli* (NCTC 10418), *B. subtilis* (ATCC 6633)**,** *S. aureus* (ATCC 29737), *A.niger* (NCIM 596) *and C.albicans* (NCIM 3102) as compared to standard drug Ciprofloxacin and Griseofulvin. The results were shown in **Table 4** and **Fig 2** and **3**. The compounds were also screened for their antidepressant activity at 100 mg/kg dose level. However, the compounds A_1, A_2 and A_6 are found to be most significant while compounds A_4 and A_5 showed moderate activity as compared to standard drug Fluoxetin. Results were recorded in **Table 5** and the graphical representation given in **Fig 4**.

TABLE 4: ANTI-BACTERIAL AND ANTI-FUNGAL ACTIVITY OF SYNTHESIZED COMPOUNDS

Compound	Zone of inhibition at 200µcg/ml(in.mm)				
	Antibacterial			Antifungal	
	E.coli	***B.subtilis***	***S.aureus***	***A. niger***	***C.albicans***
A_1	23	17	16	22	24
A_2	22	23	22	18	19
A_3	19	20	19	18	17
A_4	26	22	23	23	24
A_5	16	14	18	15	16
A_6	14	18	20	19	16
Ciprofloxacin	28	24	26	-	-
Griseofulvin	-	-	-	28	26

-Not identified against organism

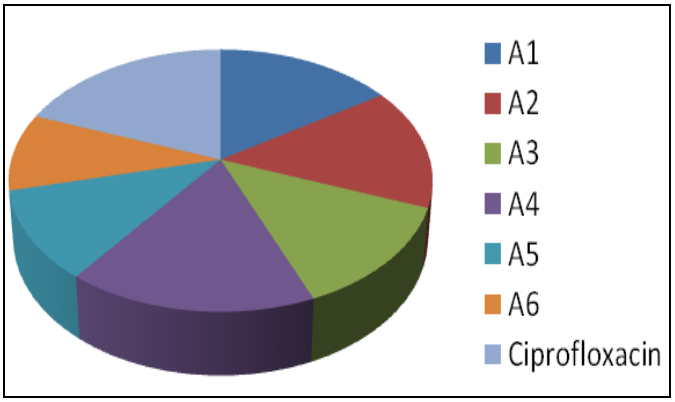


FIG 2: GRAPHICAL PRESENTATION OF ANTIBACTERIAL ACTIVITY

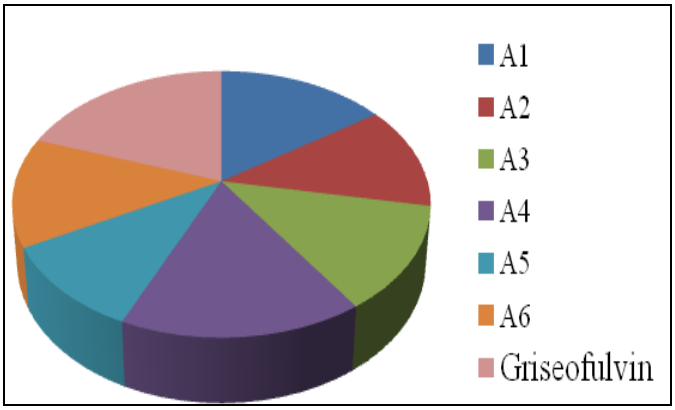


FIG 3: GRAPHICAL PRESENTATION OF ANTIFUNGAL ACTIVITY

TABLE 5: ANTIDEPRESSANT ACTIVITY OF THE SYNTHESIZED IMIDAZOLE DERIVATIVES

Compound	Duration of immobility(s)	% change from control
A_1	12.0±1.0488	75.10
A_2	11.4±0.5099	76.34
A_3	39.2±1.8814	18.67
A_4	25.6±4.6216	46.88
A_5	24.3±3.5341	49.58
A_6	11.8±1.1438	75.51
STD(fluoxetin)	63.6±3.385	31.95
Control(vehicle)	48.2±8.145	-

Compounds were tested at 100 mg kg^{-1} dose level, I.P.

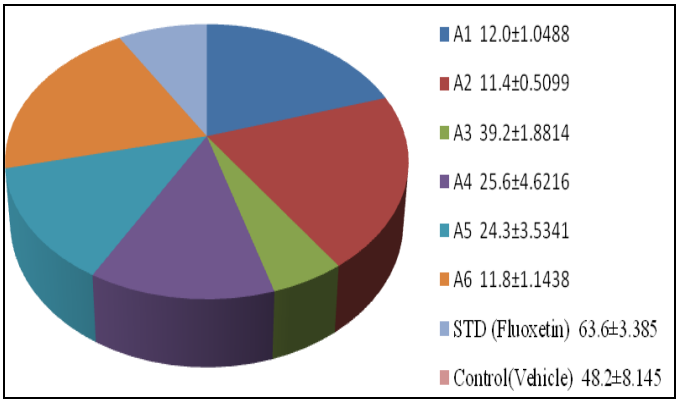


FIG 4: GRAPHICAL PRESENTATION OF ANTIDEPRESSANT ACTIVITY

CONCLUSION: The present work is a bonafide and novel for the synthesis of derivatives 2,4,5-trisubstituted imidazoles. In this view, we have made extensive review on substituted imidazole derivatives for their medicinal values with the help of chemical abstracts, journals, internet surfing and text books. Compounds A_1, A_2, A_4 have shown promising antibacterial and antifungal activity. The compounds A_1, A_2 and A_6 have shown promising antidepressant activity also.

The proposed work has given out many active antibacterial, antifungal and antidepressant agents. Some of the compounds have showed moderate activities. These compounds with suitable modification can be explored better for their therapeutic activities in the future. The promising biological activities may consider these compounds as a lead for drug development and drug discovery in future. The toxicity studies of these compounds will be carried out in future to find the effective therapeutic index.

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