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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF 1H-SUBSTITUTED 2, 4, 5- TRIPHENYL IMIDAZOLE DERIVATIVES

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Abstract:
On the basis of various literature survey, imidazole derivatives show various activity such as antimicrobial, anti-inflammatory, analgesic, antitubercular, anticancer etc. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazole nucleus. Thus imidazole offers better pharmacodynamic characteristics. Furthermore, some imidazole drugs, at high concentrations, could exert direct inhibitory effects on membranes, without interference with sterols and sterol esters. Various recent new drugs developments in imidazole derivatives show better effect and less toxicity. Prompted by the broad spectrum activities of 2, 4, 5- triphenylimidazole derivatives, it was decided to synthesize various 2, 4, 5-triphenyl-1-substituted imidazoles and to evaluate them for their biological activities.
Keywords:*Triphenyl imidazole,formaldehyde, secondary amine.*

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INTRODUCTION:

Triphenyl imdazole is a best nucleus and biologically active molecule. Now days this is a interesting research nucleus of s The compound $C_{21}H_{16}N_2$, has been known since 1877. Although the crystal structures of 36 derivatives of lophine are known, the structure of parent compound has remained unknown until now. The three phenyl rings bonded to the imidazole core are not coplanar with the latter, with dihedral angles of 21.4 (3), 24.7 (3), and 39.0 (3)°, respectively, between the phenyl ring planes in the 2-, 4- and 5-positions of the imidazole ring.There are acceptor and donor atoms for hydrogen bonds. The synthesis of novel 2,4,5-triphenylimidazole derivatives seems to be main focus of the medicinal research because compounds containing triphenyl imidazole moiety. Provides a number of needful biological activities such as analgesic and anti inflammatory activities. The substitution at C-2 benzene nucleus with benzyl, benzoyl, para amino benzoyl antifungal activity. The 2,4,5-triphenyl nucleus had been synthesized by microwave technique as well. The tri methoxybenzene nucleus at the 2 position of imidazole ring in antiinflammatory and antifungal activities.Addition of thiol group in 2,4,5-triphenylimidazole in increased activity. Azole ring in place of abstractable hydrogen in 2,4,5-triphenylimidazole ring potent antibacterial and antiinflammatory activity. The aim of the present study was to obtain triphenyl imidazole as biologically effective agent with good therapeutic values and minimum toxic levels.Past few years most of the research fellowship has done the project in triphenyl imidazole by the substitution of primary amine in the position of 1H group in imidazole. But I like to alter the simple modification in the synthesis for evaluate the anti arthritic and anti microbial activities.

MATERIAL AND METHOD:

Melting points of the synthesized compound was determined on melting point apparatus and are uncorrected. IR spectra of synthesized compound were determined on FTIR at Bombay College of Pharmacy, Mumbai.

^{1}HNMR were taken on progress and purity of the reaction and the intermediate were analyzed using precoated TLC plates and spots were detected by UV light.

EXPERIMENTAL METHOD:

STEP 1:

Synthesis of 2, 4, 5- triphenyl imidazole: It was synthesized by refluxing benzil, benzaldehyde with ammonium acetate in glacial acetic acid medium at 100°C for 3 hrs.

STEP 2:

Synthesis of 1-substituted 2, 4, 5 triphenyl imidazoles: The mixture of ethanolic solution of 0.01M compound and formaldehyde 3gm was added slowly to ethanolic solution of secondary amine the reaction mixture is stirred more than one hour at room temperature and kept it over night in a refrigerator the solid form is filtered and is washed with ethanol.

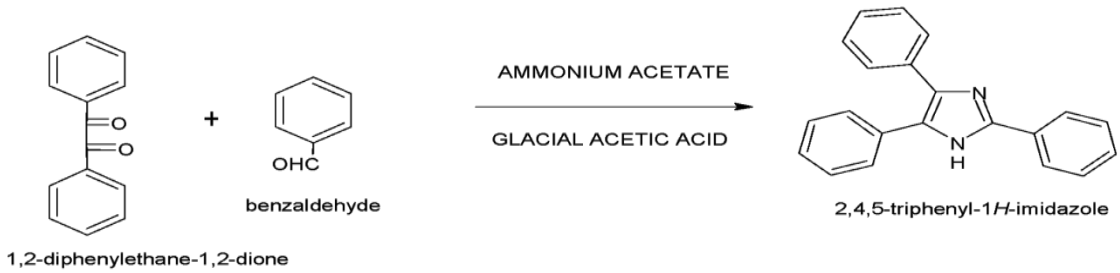
Qualitative analysis of the synthesized compounds was done by using

1. TLC
2. Melting point
3. IR spectroscopy
4. NMR spectroscopy

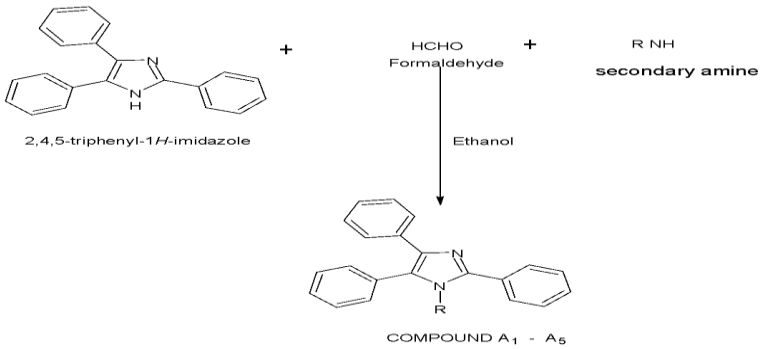
Biological evaluation of synthesized compounds was done by performing antimicrobial, analgesic and anti-inflammatory activity.

SCHEME OF REACTION

STEP –I PREPARATION F2,4,5 TRIPHENYL -1H-IMIDAZOLE



STEP – II PREPARATION OF 1H- SUBSTITUTED TRIPHENYL IMIDAZOLE DERIVATIVES



COMPOUND	R
A1	Pyrrole
A2	Piperzine
A3	Diphenyl amine
A4	Pyrrolidine
A5	Dimethyl amine

BIOLOGICAL EVALUATION: IN VITRO-ANTIBACTERIAL ACTIVITY
TEST CONCENTRATION: 100µg/ml, 200µg/ml,
ORGANISM USED: Bacillus subtilis, Klebsiella pneumonia
SOLVENT USED: DMSO,
STANDARDDRUG: Amikacin,
MEDIA PREPARATION: MULLER- HINTON AGAR MEDIUM:
INGREDIENTS: Beef infusion - 300ml, Casein Hydrolysate - 17.5g, Starch - 1.5g, Agar - 10g,
Distilled water - 1litr
PROCEDURE: Emulsify the starch in a small amount of cold water, pour into the beef infusion and add the casein hydrolysate and the agar. Make up the volume to 1litre with distilled water. Dissolve the constituents by heating gently at 100°C with agitation. Filter if necessary. Adjust the pH to 7.4.Dispense in screw-capped bottles and sterilized by autoclaving at 121°C for 20minutes and pour plates.

PREPARATION OF ANTIBACTERIAL SOLUTION: All the test compound were dissolved in dimethyl sulfoxide and taken at two concentration for testing antibacterial activity. The compounds were diffuse into the medium produced a concentration gradient. After the incubation period, the zone of inhibition were measured in mm.

EXPERIMENTAL PROCEDURE: The plates were inoculated by dipping a sterile swab into inoculums. The inoculation was dried at room temperature in aseptic condition. Ditch the bore in plate, to this bore add prepared antibacterial solution. These plates were placed in an incubator at 37°C within a few minutes of preparation. After 48 hours of incubation the diameter of zone of inhibition was measured and reading observed in millimeter.
ANTIFUNGAL ACTIVITY:
TEST CONCENTRATION: 100µg/ml, 200µg/ml,
ORGANISM USED: Candida Albicans, Aspergillus Niger
SOLVENT USED: DMSO
STANDARD DRUG: Ketokonazole
MEDIA PREPARATION: POTATO DEXTROSE AGAR MEDIUM
INGREDIENTS: Potato - 200g, Dextrose - 20g, Agar - 20g, Water - 1litre

PROCEDURE: Scrub but do not peel the potatoes and cut into 12mm cubes. Boil 200g potato in 1litre of water for 60 minutes. Squeeze as much of the pulp as possible through a fine sieve. Add agar and boil till dissolved. Add dextrose and make up to 1litre. Dispense in required amounts taking care to keep solids in suspension. Autoclave at 115°C and pour approximately 20ml amounts into petri dishes.

PREPARATION OF ANTI FUNGAL SOLUTION: All the test compound were dissolved in dimethyl sulfoxide and taken at two concentration for testing antibacterial activity. The compounds were diffuse into the medium produced a concentration gradient. After the incubation period, the zone of inhibition were measured in mm.
EXPERIMENTAL PROCEDURE: The plates were inoculated by dipping a sterile swab into inoculums.

The inoculation was dried at room temperature in aseptic condition. Ditch the bore in plate, to this bore add prepared antibacterial solution. These plates were placed in an incubator at 22°C within a few minutes of preparation. After 7 days of incubation the diameter of zone of inhibition was measured and reading observed in millimeter.

IN VITRO-ANTIOXIDANT ACTIVITY:
PRINCIPLE: This is spectrophotometric method and is based on the principle that increases in absorbance of the reaction mixture as concentration increase showing an increased antioxidant activity. The assay is based on the reduction of ferric in potassium ferric cyanide to potassium ferrocyanide by the sample and the subsequent formation of Prussian blue colour with ferric chloride. The absorbance of the blue complex is measured at 700nm.

INSTRUMENTS: Shimadzu UV Visible spectroscopy Model 1800
REAGENTS: 1%Potassium ferric cyanide 10% Trichloro acetic acid 0.2M, pH 6.6 phosphate buffer 0.1% ferric chloride
PROCEDURE: About 0.5ml of various concentration of synthesized compound was mixed with 0.75ml phosphate buffer and 0.75ml of 1% potassium ferricyanide then mixture was incubated at 50°C for 20 minutes. 0.75ml of 1% trichloro acetic acid was added to the mixture, allowed to stand for 10 minutes. The whole mixture was then centrifuged at 3000ppm for 10 minutes. Finally 1.5ml of supernatant solution was removed and mixed with 1.5ml of distilled water Then added 0.1ml of 0.1%ferric chloride solution and the absorbance was measured at 700nm in UV – Visible spectrophotometry. Higher the absorbance observed in test mixture indicates the stronger reducing power of the test solution. Ascorbic acid was used as standard and phosphate buffer used as blank solution. The absorbance of the final reaction mixture of three parallel experiments was expressed as mean ± standard error of the mean

IN VITRO - ANTI ARTHRITIC ACTIVITY:
Phosphate buffer saline pH 6.3: Dissolve 8gm of sodium chloride 0.2gm of potassium chloride 1.44gm of disodium hydrogen phosphate 0.24 gm in potassium dihydrogen phosphate in 800 ml of distilled water. The pH was adjusted to 6.3 using 1N HCl make up the volume to 1000ml with distilled water. METHOD: 1) Test solution (0.5ml) consists of 0.45ml of bovine serum (5% w/v aqueous solution)and 0.05ml of test solution various concentration. 2) Test control solution0.5ml consists of 0.45ml of bovine serum albumin and 0.05ml of water. 3) Product control 0.5ml consists of 0.45ml of water and 0.05ml of test solution. 4) Standard solution 0.5ml consists of 0.45ml of bovine serum albumin and 0.05ml of diclofenac sodium of various concentrations. 5) Various concentration (100,250,500µg/ml) of test drug and standard drug diclofenac sodium (100,250,500µg/ml)were taken respectively. 6) All the above solution were adjusted to pH 6.3 using 1N HCl. 7) The sample were incubated at 37°C for 20 minutes. Temperature was increased to keep the samples at 57°C for 3 minutes. 8) After cooling, add 2.5ml of phosphate buffer to the above solution. 9) The absorbance was measured using UV visible spectrophotometer at 416nm.

Percentage inhibition= 100 – {optical density of test control – optical Density of product control} x100
Optical density of test solution

RESULTS AND DISCUSSION:

The pecentage yield, melting point, solubility and appearance of the compound are determined. The purity of the compounds were checked by TLC and Rf value was calculated. The structure of the synthesized compounds were confirmed by IR spectraNMR spectra¬ and Mass spectra. ¬ All synthesized compounds were screened for their invitro antimicrobial, antioxidant, anti¬ arthritic activity. The antibacterial activity was performed against bacillus subtilis, klebsiella pneumonia.¬ The zone of inhibition was performed by cup-plate method and results are obtained were measured in milimeter. The antifungal activity was performed against candida albicans,aspegillus niger. The¬ zone of inhibition was performed by cup-plate method and results are obtained were measured in millimeter.. The maximum zone of inhibition of synthesized compound against antimicrobial activity. All synthesized compound were tested for invitro anti oxidant activity by reducing power¬ assay method in different concentration and compared with the standard Ascorbic acid. The result are shown in Table3.NoAll of the newly obtained compound were tested for invitro anti arthritic activity by¬ protein denaturated method in different concentration and compared with the standard Diclofenac.the result are showon in table 4.

TABLE 1: PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

CODE	MOLECULAR FORMULA	MOLECULAR WEIGHT	I.U.P.A.C NAME
A1	C25H19N3	361.438	2,4,5 triphenyl-1-(1H-pyrrole-1-yl)-1H-imidazole
A2	C25H24 N4	380.484	2,4,5 triphenyl-1-(1H piperzine-1-yl) -1H-imidazole
A3	C33H25N3	463.57	N,N diphenyl-2,4,5triphenyl -1H-imidazol-1-amine
A4	C25H23N3	365.47	2,4,5 Triphenyl-1-(pyrrolidin-1-yl)-1H-imidazdazole
A5	C23H21N3	339.43	N,N dimethyl-2,4,5,triphenyl -1H-imidazol-1-amine

TABLE 2: ZONE OF MAXIMUM INHIBITION OF SYNTHESIZED COMPOUND A1- A5AGAINST MICROBIAL AGENTS

ORGANISM	BACTERIA		FUNGI	
COMPOUNDS	BACILLUS	KLEBSIELLA	CANDIDA	ASPERGILLUS
A1	9	-	7	-
A2	17	12	6	-
A3	15	10	10	-
A4	14	8	8	-
A5	16	12	11	-
STD	20	17	21	18

Zone of inhibition in mm
STD: BACTERIA – AMIKACIN,
FUNGI - KETAKONAZOLE

TABLE 3: IN VITRO - REDUCING POWER ASSAY

COMPOUNDS/ CONCENTRATION	ABSORBANCE*		
	100µg/ml	200µg/ml	300µg/ml
A1	0.075±0.0032	0.12±0.0011	0.145±0.0011
A2	0.172±0.0030	0.238±0.0037	0.269±0.0055
A3	0.076±0.0020	0.111±0.0011	0.140±0.0026
A4	0.146±0.0011	0.207±0.002	0.231±0.0017
A5	0.163±0.0038	0.203±0.002	0.267±0.0024
STD	0.165±0.0014	0.368±0.0025	0.565±0.0026

STD: DICLOFENAC
STD: ASCORBIC ACID
*Mean 3value ±SEM
*Mean 3value±SEM

TABLE 4: IN VITRO – ANTIARTHRITIC ACTIVITY

COMPOUNDS/ CONCENTRATION	% INHIBITION*		
	100µg/ml	250µg/ml	500µg/ml
A1	41±0.54	62.9±0.52	72.8±0.46
A2	55±0.0.46	61.3±0.53	70.1±0.40
A3	58.8±0.61	60.9±0.52	70.7±0.25
A4	56.5±0.28	72.9±0.31	81±0.23
A5	57.3±0.35	67.2±0.43	78.3±0.35
STD	60.7±0.53	72.3±0.40	86.2±0.43

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