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Synthesis, Characterization and Biological Evaluation Of 1h-Substituted 2,4,5-Triphenyl Imidazole Derivative

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Abstract

On the basis of various literature survey, imidazole derivatives show various activity such as anti microbial, 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. The present study focused on synthesis of various 1h-substituted 2,4,5-triphenyl imidazole derivatives. The synthesized compounds were also screened for their antimicrobial and antioxidant properties.

➢ INTRODUCTION :

Imidazoles are probably the most well known heterocycle which is common and important feature of a variety of natural products and medicinal agents. The compound $C_{21}H_{16}N_2$, has been known since 1877. Although the crystal structure of 36 derivatives of lophine are known, the structure of parent compound has remained unknown until now. On the basis of various literature surveys Imidazole derivatives shows variouspharmacological activities

- ❖ Antifungal and Anti-bacterial activity
- ❖ Anti-inflammatory activity and analgesic activity
- ❖ Anti tubercular activity
- ❖ Antidepressant activity
- ❖ Anticancer activity
- ❖ Antiviral activity
- ❖ Antileishmanial activity
- ❖ Anti arthritic activity
- ❖ Antiangiogenics

Biological significance and applications

Imidazole is incorporated into many important biological compounds. The most pervasive is the amino acid histidine, which has an imidazole side-chain. Histidine is present in many proteins and enzymes, e.g. by binding metal cofactors, as seen in hemoglobin. Imidazole-based histidine compounds play a very important role in intracellular buffering. Histidine can be decarboxylated to histamine. Histamine can cause urticaria (hives) when it is produced during allergic reaction. Imidazole substituents are found in many pharmaceuticals. Synthetic imidazoles are present in many fungicides and antifungal, antiprotozoal, and antihypertensive medications. Imidazole is part of the theophylline molecule, found in tea leaves and coffee beans, that stimulates the central nervous system. It is present in the anticancer medication mercaptopurine, which combats leukemia by interfering with DNA activities.

A number of substituted imidazoles, including clotrimazole, are selective inhibitors of nitric oxide synthase, which makes them interesting drug targets in inflammation, neurodegenerative diseases and tumors of the nervous system. Other biological activities of the imidazole pharmacophore relate to the downregulation of intracellular Ca2+ and K+ fluxes, and interference with translation initiation.

Pharmaceutical derivatives:

The substituted imidazole derivatives are valuable in treatment of many systemic fungal infections. Imidazoles belong to the class of azole antifungals, which includes ketoconazole, miconazole, and clotrimazole.

Industrial applications:

Imidazole itself has few direct applications. It is instead a precursor to a variety of agrichemicals, including enilconazole, climbazole, clotrimazole, prochloraz, and bifonazole.

Use in biological research:

Imidazole is a suitable buffer for pH 6.2 to 7.8. Pure imidazole has essentially no absorbance at protein relevant wavelengths (280 nm), however lower purities of imidazole can give notable absorbance at 280 nm. Imidazole can interfere with the Lowry protein assay.

➢ 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. ^{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.

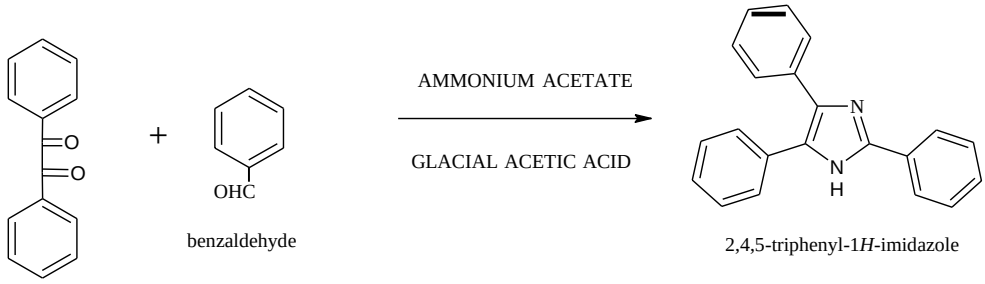
A). Experimental Method:

❖ **Step I:**

Compound A: Preparation of 2,4,5-Triphenyl Imidazole-

Benzil (1gm), Ammonium acetate (1gm), Benzaldehyde(2ml), Glacial acetic acid (2ml) are reflux for 3 hours. The reaction mixture was allowed to stand to attain room temperature. To that add 150 ml of water, the solid thus obtained was filtered. The filtrate is neutralized with ammonium hydroxide or sodium carbonate to give solid pasty mass and filtered. Then the solid mass was washed with

toluene and recrystallized from methanol.



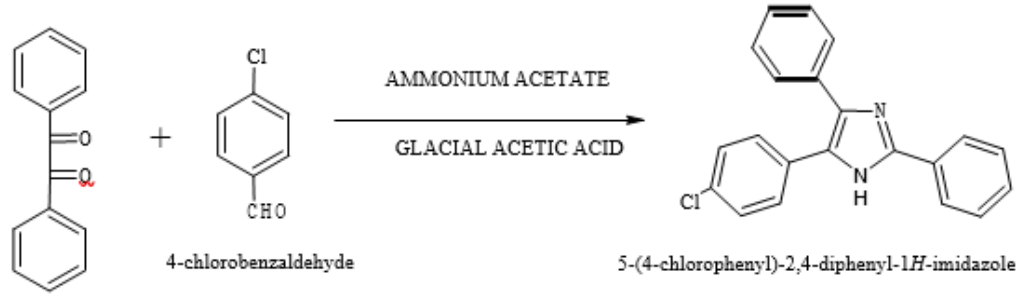
1,2-diphenylethane-1,2-dione

benzaldehyde

2,4,5-triphenyl-1*H*-imidazole

Compound B: Preparation of 5-(4-chlorophenyl)-2,4-diphenyl-1H- Imidazole-

Benzyl (1gm), Ammonium acetate (1gm)P-Chloro Benzaldehyde(2ml), Glacial acetic acid(2ml) are reflux for 3 hours. The reaction mixture was allowed to stand to attain room temperature. To that add 150 ml of water, the solid thus obtained was filtered. The filtrate is neutralized with ammonium hydroxide or sodium carbonate to give solid pasty mass and filtered. Then the solid mass was washed with toluene and recrystallized from methanol.



BENZIL

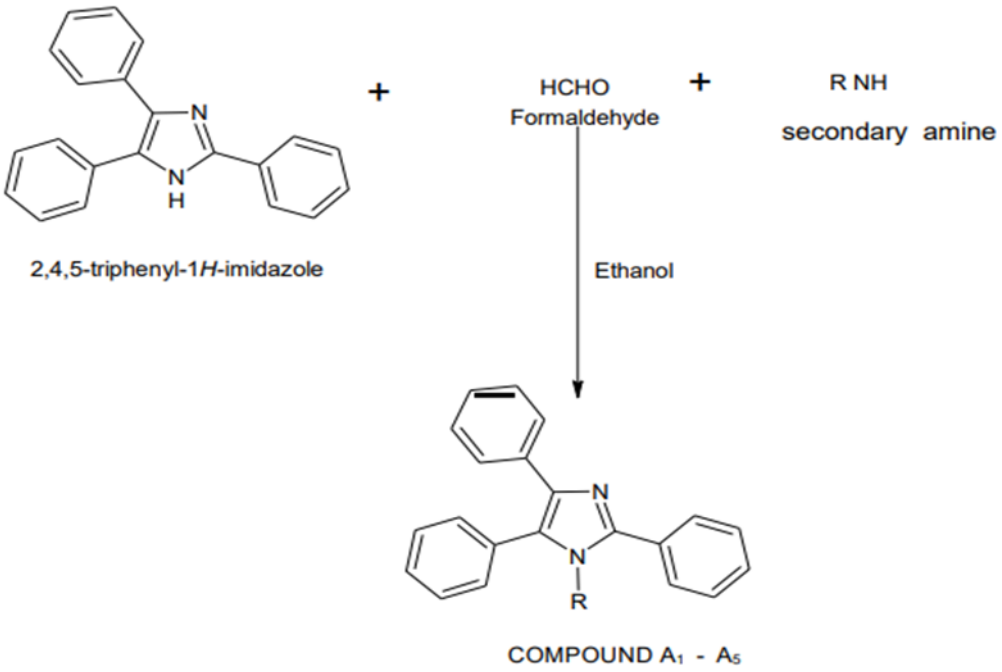
4-chlorobenzaldehyde

5-(4-chlorophenyl)-2,4-diphenyl-1*H*-imidazole

❖ **Step II:**

The mixture of ethanolic solution of 0.01M compound and formaldehyde 3gm was added slowly to ethanolic solution. The reaction mixture is stirred more than one hour at room temperature and kept it overnight in a refrigerator the solid form is filtered and is washed with ethanol.

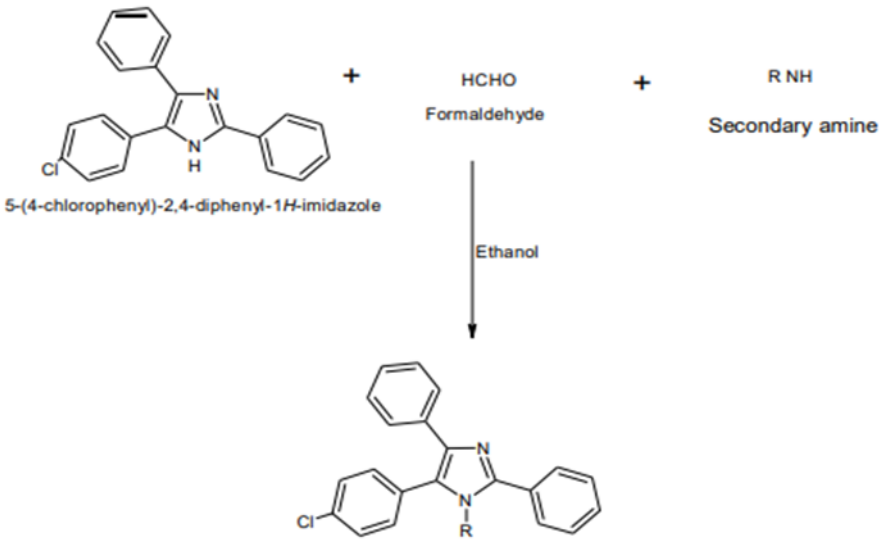
Compound A Derivatives: (A1 - A5)



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

Compound B: (A6 –A10)

The mixture of ethanolic solution of 0.01M compound and formaldehyde 3gm was added slowly to ethanolic solution. The reaction mixture is stirred more than one hour at room temperature and kept it overnight in a refrigerator the solid form is filtered and is washed with ethanol.



5-(4-chlorophenyl)-2,4-diphenyl-1*H*-imidazole

COMPOUND A6 - A10

COMPOUND	R
A6	Pyrrole
A7	Piperzine
A8	Diphenyl amine
A9	Pyrrolidine
A10	Dimethyl amine

Table 1 : Physical data of Synthesized compounds						
Comp.	**Molecular Formula**	**Appearance**	**Mol. Wt.**	**I.U.P.A.C Name**	**%YIELD**	**MELTING POINT -°C**
A1	$C_{25}H_{19}N_3$	Brown solid	361.438	2,4,5-triphenyl-1-(1H-pyrrole-1-yl) -1H-imidazole	78	130
A2	$C_{25}H_{24}N_4$	Sandal solid	380.484	2,4,5 triphenyl-1-(1H piperzine-1-yl) -1H-imidazole	72	110
A3	$C_{25}H_{19}N_3$	White solid	463.57	N,N diphenyl-2,4,5-triphenyl -1H-imidazol-1-amine	75	125
A4	$C_{25}H_{23}N_3$	White solid	365.47	2,4,5-Triphenyl-1-(pyrrolidin-1-yl) -1H-imidazole	77	140
A5	$C_{23}H_{21}N_3$	Pale white solid	339.43	N,N-dimethyl-2,4,5,triphenyl -1H-imidazol-1-amine	74	120
A6	$C_{25}H_{18}C_lN_3$	Dark brown solid	395.88	5-(4-Chlorophenyl)-2,4-diphenyl-1-(1H-pyrrole-1-yl)-1H-imidazole	79	135
A7	$C_{25}H_{23}C_lN_4$	Pale orange solid	414.92	5-(4-Chlorophenyl)-2,4-diphenyl-1H imidazole-1-yl piperzine	70	120
A8	$C_{33}H_{24}C_lN_3$	Pale yellow solid	498.016	5-(4-chlorophenyl)N,N-diphenyl-2,4 diphenyl-1H-imidazol amine	68	100
A9	$C_{25}H_{22}C_lN_3$	White solid	399.91	5-(4-chlorophenyl)-2,4-diphenyl-1-(pyrrolidin-1-yl)-1H-imidazole	71	130
A10	$C_{23}H_{20}C_lN_3$	Pale white solid	373.87	5-(4-chlorophenyl)-N,N-methyl-2,4diphenyl-1H-imidazol-1-amine	76	105

Table : 2 Spectral data of Synthesized compounds

Compounds	NMR Data		TLC Data	IR Data	
	Types of Proton	Observed Value in Ppm	Rf Value	Types Of Vibration	Observed Value (cm^{-1})
A1	S,15H ArH M,2H CH	8.8 7.7	0.64	C=C str,in benzene CH str aromatic C – C str C – N str C = N str N – H str N – N str	1598 2960 1174 1325 1649 3028 3444
A2	S,15H ArH S, 1H,NH	8.1 2.1	0.72	C=C str,in benzene CH str aromatic C – C str C – N str C = N str N – H str N – N str	1597 2939 1174 1323 1658 3037 3444
A3	S, 15H ArH S, 10H ArH	7.1 7.7	0.85	C=C str,in benzene CH str aromatic C – C str C – N str C = N str N – H str N – N str	1597 2920 1197 1244 1504 3010 3074
A4	S,15H ArH S,2H CH	7.0 7.5	0.61	C=C str,in benzene CH str aromatic C – C str C – N str C = N str N – H str N – N str	1597 2941 1174 1209 1658 3030 3471
A5	S, 10H ArH S,N-CH3	7.6 4.3	0.78	C=C str,in benzene CH str aromatic C – C str C – N str C = N str N – H str N – N str	1597 2879 1174 1323 1658 3037 3446
A6	S,15H ArH M,2H CH	7.4 8.0	0.61	C=C str,in benzene CH str aromatic C – C str C – N str C = N str N – H str N – N str C – Cl str	1597 2960 1174 1203 1658 3132 3273 767
A7	S,15H CH S, 1H ,NH	7.1 2.1	0.75	C=C str,in benzene CH str aromatic C – C str C – N str	1597 2958 1172 1346

				C = N str N – H str C – Cl str	1577 3028 794
A8	S, 15H ArH S,10H ArH	7.3 7.9	0.83	C=C str,in benzene CH str aromatic C – C str C – N str C = N str N – H str N – N str C – Cl str	1591 2962 1174 1325 1668 3026 3059 767
A9	S,15H ArH S, 2H CH	7.8 9.1	0.66	C=C str,in benzene CH str aromatic C – C str C – N str C = N str N – H str N – N str C – Cl str	1598 2960 1174 1325 1658 3026 3446 767
A10	S,15H ArH S,N-CH3	8.9 6.9	0.80	C=C str,in benzene CH str aromatic C – C str C – N str C = N str N – H str N – N str C – Clstr	1597 2960 1174 1211 1674 3026 3444 767

B). Biological Evaluation:

The synthesized compounds were screened for invitro antimicrobial and antioxidant activity.

♦ ***In vitro* Antimicrobial activity**:

Test Concentration: 100µg/ml, 200µg/ml

Organism Used: Bacillus subtilis, Klebsiella pneumonia

Solvent Used: DMSO

Standard Drug: Amikacin

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.

Table 3 : Zone of maximum inhibition of synthesized compound against 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	-
A6	9	-	9	-
A7	21	17	7	9
A8	12	9	9	-
A9	14	-	12	6
A10	16	6	12	8
STD	20	17	21	18

Zone of inhibition in mm

STD: BACTERIA – AMIKACIN, FUNGI - KETAKONAZOLE

♦ ***In vitro* Antioxidant activity**:

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 mixedwith 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 1.5mlof distilled water. Then added 0.1ml of 0.1%ferric chloride solution and the absorbance wasmeasured at 700nm in UV – Visible spectrophotometry. Higher the absorbance observed in test mixture indicates the strongerreducing power of the test solution. Ascorbic acid was used as standard and phosphate buffer used as blanksolution. The absorbance of the final reaction mixture of three parallel experimentswas expressed as mean ± standard error of the mean.

Table 4 : 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
A6	0.096±o.0008	0.145±0.002	0.285±0.003
A7	0.196±0.0017	0.285±0.0023	0.305±0.005
A8	0.102±0.0014	0.160±0.002	0.247±0.0011
A9	0.161±0.0024	0.257±0.0024	0.326±0.0017
A10	0.207±0.00024	0.274±0.0011	0.348±0.0015
STD	0.165±0.0014	0.368±0.0025	0.565±0.0026

STD: ASCORBIC ACID

***Mean 3value±SEM**

➢ RESULT AND DISCUSSION :

Total ten derivatives of 2,4,5-triphenyl imidazole has been synthesized. The synthesized compounds were found to be identified by **TLC** and purified and characterized by the **IR, NMR and MASS** spectral data. The physical and spectral data of synthesized compounds were presented in **Table 1.** The physical and spectral data of synthesized compounds were presented in **Table 2.**

All synthesized compounds were screened for their invitro antimicrobial and antioxidant activity.

The compound **A7** shows potent antibacterial activity against bacillus subtilis and Klebsiella pneumonia compared to standard Amikacin. The compound **A9** & **A10** shows moderate antifungal activity against candida albicans compared to standard ketokonazole. The compound **A7** minimum inhibition of antifungal activity against aspergillus niger compared to standard Ketokonazole. The maximum zone of inhibition of synthesized compound against antimicrobial activity is shown in **Table 3.**

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 **Table 4.** The following compounds **A7**, **A9**, **A10** are reducing the free radicals and prevent the tissue damage and producing best anti-oxidant properties which is evaluated by reducing power assay. When it is compared to standard like Ascorbic acid these are shows lesser activity.

CONCLUSION:

The study suggests that the imidazole ring is an important pharmacophore in modern drug discovery and the tested derivatives of imidazole have excellent scope for further development as commercial antimicrobial and anti-oxidant agents. All the synthesized compounds were screened for antimicrobial and antioxidant activities. The compound **A7 [5-(4-chlorophenyl)2,4, Diphenyl -1H imidazole 1-yl piperzine]** is the best compound compare than other than nine compounds having good *in vitro* Antimicrobial and Antioxidant activity.

➢ ACKNOWLEDGMENT:

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