Synthesis, characterization & evaluation of anti-microbial activity of 2,4,5-triphenyl-1h-imidazole-1-yl derivatives

Ajay Kumar[1], Somesh verma[1], Jaswant Kumar[1], Imran Khan[2], Ashok Kumar Yadav[3*], Samiksha Srivastava

1. Department of Chemistry, Hygia Institute Of Pharmaceutical Education And Research, Lucknow,Lucknow Ghaila Road, Gazipur Balram Rd, near IIM Road, Prabandh Nagar, Lucknow, Uttar Pradesh 226020

2. Department of Chemistry, J .S Singh Institute of Pharmacy, Para Sarai Dhondhi Laharpur, Road, Sitapur, Uttar Pradesh 261207

3. Department of Chemistry, Ankerite College of Pharmacy, Vill-Sausheer Khera, Parvar Purab, Post, Mohanlalganj, Uttar Pradesh 226301.

E-mail:- ajayhp6393@gmail.com

Abstract

*In this experiment work, the synthesis of title compounds was planned in one step. Aim of the present study is synthesis of 2,4,5-triphenyl-1H-imidazole-1-yl derivatives starting from benzil, substituted benzaldehyde and ammonium acetate. Equimolar amount of Benzil (1mol) and substituted benzaldehydes (1 mol) were taken in ammonia solution (5 ml) then mixed with 30 ml of glacial CH_3COOH in a 100 ml of RBF and refluxed for 4-5 hours on oil bath. Reaction completion was monitored by TLC. When the reaction was completed, 300 ml of cold water was added to it, and it was then neutralized with a 5% ammonium hydroxide solution. After that, the mixture was then kept in fridge overnight. To get a yellow crystalline solid. The precipitated product was filtered and recrystallized with ethanol. Compound **(AJ-1)** was discovered to have good efficacy against the fungal strains, compounds **(AJ-1, AJ-3, AJ-4** and **AJ-6)** have the strongest antibacterial activity. The most effective compound with Minimum Inhibitory Concentration (MIC) was calculated using the well diffusion technique. The compound **(AJ-1)** had the strongest effects on the majority of the strains with MICs between 25 and 200 ug/ml. Studies on the relationship between structure and activity revealed the significance of electron withdrawing groups at the distant phenyl rings in the ortho and para positions, as these compounds tend to be most active than those with electron releasing groups, such as methoxy groups. Pharmacological studies have shown that synthesized compounds **(AJ-1, AJ-3, AJ-4** and **AJ-6)** exhibited statically significant antimicrobial activity when compared to the control and are comparable with the standard drug like tetracycline and fluconazole. The agar well diffusion method was used to evaluate all the produced compounds for their antibacterial activity against gram (+ve) (Staphylococcus aureus and Klebsiella pneumoniae), gram (-ve) (Pseudomonas aureginosa), and fungal strains (Candida albicans, Beauveria bassiana). Other bacterias used for antimicrobial activity are E.coli, B. subtilis.*

Keywords: *imidazole, ammonium hydroxide and antibacterial activity.*

Introduction

One of the major health concerns, according to the World Health Organization (WHO), is anti-microbial resistance (AMR). As per WHO, 12.7 million deaths in 2019 were directly attributable to antimicrobial resistance (AMR). Lesser respiratory infections posed the biggest health risk in 2019, and they were connected to more than 1 million deaths due to resistance. *E. coli, Staphylococcus aureus, Klebsiella pneumonia, Streptococcus pneumonia, Acinetobacter baumannii, and Pseudomonas aeruginosa* were the pathogens most often associated with resistance-related death

Heinrich Debus was first synthesized imidazole compounds in 1858, and different imidazole derivatives were identified as early on the 1840s, the pharmacological and physiological importance of imidazole has attracked the interest of many investigators. Singh et al. **[18]**

The five-member ring structure of imidazole (1,3-diyaza-2,4-cyclopentadiene) has 2 nitrogen atoms and 3 carbon atoms in the third position. The molecule formula $C_3H_4N_2$ is the most basic imidazole member. Ahmed et al. **[23]**

The fundamental name of a compounds is 1,3-diazole; an N-type pyrrole is formed as one of the nitrogen atoms with in ring combines with a hydrogen atom. The hydrogen atom is found in two separate tautomeric structures that can both include nitrogen atoms. EI- Sharief et al. **[25]**

Two s*p*2 hybridized nitrogen atoms may be found in imidazole, a five-member heterocyclic aromatic molecule. Both nitrogen atoms have distinct *p*Ka values due to the delocalization of the lone pair of electron on the nitrogen atom of imidazole ring while lone pair electron of the other nitrogen atom are not delocalized.

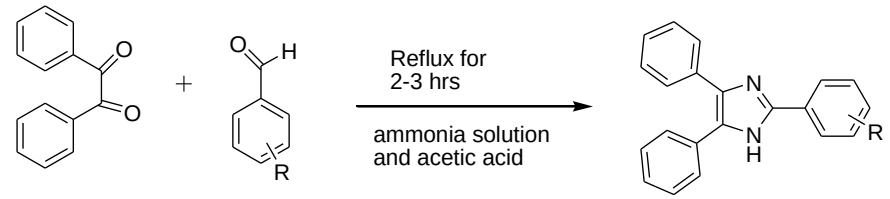
The delocalized lone-pair electron of the nitrogen atom has a *p*ka value is 7.0; as the extra nitrogen atom has a non-delocalized lone-pair of nitrogen atoms *p*ka value is 14.9. The imidazole molecule is amphoteric in nature, acting as both an acid and a base and being vulnerable to electrophilic and nucleophilic assault. Imidazole typically has an amine-like odor and is a white or light yellow solid. It is a diazole and an aromatic heterocyclic molecule. Polar solvents like water are soluble in imidazole. It may be dissolved in water and the other than polar solvents. Any of the two corresponding tautomeric forms of the two nitrogen atoms contains the hydrogen atom. Kumar et al. **[30]**

Imidazole analogues are a significant family of heterocyclic chemicals that are included in several medications, including antifungal and antibacterial medicines. Their biological action depends heavily on the imidazole moiety; an example of this is the azole class (Clotrimazole). Zala et al. **[43]**

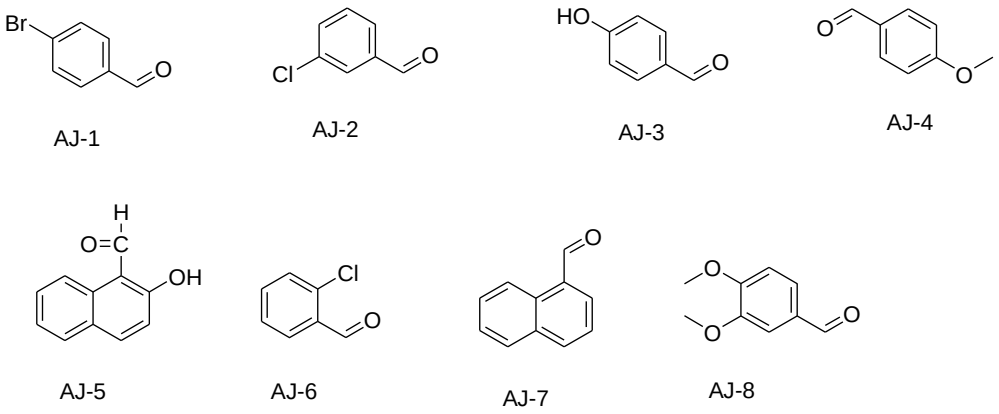
Through decades of historical development of organic synthesis, Researchers' interest in sulphur and nitrogen-containing heterocyclic compounds has mostly not changed, although other heteroatom’s such as phosphorus, oxygen, and selenium also emerge.

According to reports, imidazole compounds have pharmacological and physiological activity and are used to treat a number of diseases. Periyasamy Ramnathan **[33]**

Scheme



Where, R=



Synthesis

General procedure for Synthesis of 2-(4-bromophenyl)-4,5-diphenyl-1H-imidazole **[AJ-1]**

Equimolar amount of Benzil (1mol) and 4-bromo benzaldehyde (1 mol) were taken in ammonia solution (5 ml) then mixed with 30 ml of glacial CH_3COOH in a 100 ml of RBF and refluxed for 4-5 hours on oil bath. Reaction completion was monitored by TLC. When the reaction was completed, 300 ml of cold water was added to it, and it was then neutralized with a 5% ammonium hydroxide solution. After that, the mixture was then kept in fridge overnight. To get a colorless or light yellow crystalline solid, the precipitated product was filtered and recrystallized with ethanol.

Wavelength of Maximum Absorbance (λmax) = 322 Mass Spectrum of Compound, Observed molecular ion $[M]^+$ peak; MS-ESI *(m/z)*: 374.04 (78%) C=N (Imine) stretching 1663.76, N-H (Imine) stretching 3576.93, C=C (Aromatic) 1591.96, C-N (Imine) stretching 1320.27, C-H (Aromatic) 3064.92, Br (Aromatic) 688.41; ^{1}H-NMR Spectrum [(MHz 300, MeOD): δ 7.688-7.682(s, 2H bromobenzene); δ 7. 59-7.54 (m, 3H, benzene); δ7.96-7.95 (m, 1H imidazole)].

General procedure for Synthesis of 2-(3-chlorophenyl)-4,5-diphenyl-1H-imidazole **[AJ-2]**

Equimolar amount of Benzil (1mol) and 3-chloro benzaldehydes (1 mol) were taken in ammonia solution (5 ml) then mixed with 30 ml of glacial CH_3COOH in a 100 ml of RBF and refluxed for 4-5 hours on oil bath. Reaction completion was monitored by TLC. When the reaction was completed, 300 ml of cold water was added to it, and it was then neutralized with a 5% ammonium hydroxide solution. After that, the mixture was then kept in fridge overnight. To get a milky white crystalline solid, the precipitated product was filtered and recrystallized with ethanol.

[Wavelength of Maximum Absorbance (λmax) = 304]; Mass spectrum, Observed molecular ion $[M]^+$ peak; MS-ESI *(m/z)*: 330.81 (75%); IR Spectrum C=N (Imine) stretching 1663.76, N-H (Imine) stretching 3576.93, C=C (Aromatic) 1591.96, C-N (Imine) stretching 1320.27, C-H (Aromatic) 3064.92, Cl (Aromatic) 794.51; ^{1}H NMR Spectrum [(MHz 300, MeOD): δ 7.29-7.25 (s, chlorobenzene); δ 7. 59-7.54 (m, 3H, benzene); δ7.96-7.95 (m, 1H imidazole)].

General procedure for Synthesis of 4-(4,5-diphenyl-1H-imidazole-2-yl)phenol **[AJ-3]**

Equimolar amount of Benzil (1mol) and p-hydroxy benzaldehydes (1 mol) were taken in ammonia solution (5 ml) then mixed with 30 ml of glacial CH_3COOH in a 100 ml of RBF and refluxed for 4-5 hours on oil bath. Reaction completion was monitored by TLC. When the reaction was completed, 300 ml of cold water was added to it, and it was then neutralized with a 5% ammonium hydroxide solution. After that, the mixture was then kept in fridge overnight. To get a brown crystalline solid, the precipitated product was filtered and recrystallized with ethanol.

General procedure for Synthesis of 2-(4-methoxyphenyl)-4,5-diphenyl-1H-midazole **[AJ-4]**

Equimolar amount of Benzil (1mol) and 4-methoxy benzaldehydes (1 mol) were taken in ammonia solution (5 ml) then mixed with 30 ml of glacial CH_3COOH in a 100 ml of RBF and refluxed for 4-5 hours on oil bath. Reaction completion was monitored by TLC. When the reaction was completed, 300 ml of cold water was added to it, and it was then neutralized with a 5% ammonium hydroxide solution. After that, the mixture was then kept in fridge overnight. To get a colorless or light yellow crystalline solid, the precipitated product was filtered and recrystallized with ethanol.

General procedure for Synthesis of 1-(4,5-diphenyl-1H-imidazole-2yl)naphthalene-2-ol **[AJ-5]**

Equimolar amount of Benzil (1mol) and 2-hydroxy1-napthaldehydes (1 mol) were taken in ammonia solution (5 ml) then mixed with 30 ml of glacial CH_3COOH in a 100 ml of RBF and refluxed for 4-5 hours on oil bath. Reaction completion was monitored by TLC. When the reaction was completed, 300 ml of cold water was added to it, and it was then neutralized with a 5% ammonium hydroxide solution. After that, the mixture was then kept in fridge overnight. To get a dark brown crystalline solid, the precipitated product was filtered and recrystallized with ethanol.

General procedure for Synthesis of 2-(2-chlorophenyl)-4,5-diphenyl-1H-imidazole **[AJ-6]**

Equimolar amount of Benzil (1mol) and O-chloro benzaldehydes (1 mol were taken in ammonia solution (5 ml) then mixed with 30 ml of glacial CH_3COOH in a 100 ml of RBF and refluxed for 4-5 hours on oil bath. Reaction completion was monitored by TLC. When the reaction was completed, 300 ml of cold water was added to it, and it was then neutralized with a 5% ammonium hydroxide solution. After that, the mixture was then kept in fridge overnight. To get a milky white crystalline solid, the precipitated product was filtered and recrystallized with ethanol.

General procedure for Synthesis of 2-naphthalen-1-yl)-4,5-diphenyl-1H-imidazole **[AJ-7]**

Equimolar amount of Benzil (1mol) and 1-napthaldehydes (1 mol) were taken in ammonia solution (5 ml) then mixed with 30 ml of glacial CH_3COOH in a 100 ml of RBF and refluxed for 4-5 hours on oil bath. Reaction completion was monitored by TLC.

When the reaction was completed, 300 ml of cold water was added to it, and it was then neutralized with a 5% ammonium hydroxide solution. After that, the mixture was then kept in fridge overnight. To get a brown crystalline solid, the precipitated product was filtered and recrystallized with ethanol.

***General procedure for Synthesis of 2-(3,4-dimethoxyphenyl)-4,5-diphenyl-1H-imidazole* [AJ-8]**

Equimolar amount of Benzil (1mol) and 3,4-dimethoxy benzaldehydes (1 mol) were taken in ammonia solution (5 ml) then mixed with 30 ml of glacial CH_3COOH in a 100 ml of RBF and refluxed for 4-5 hours on oil bath. Reaction completion was monitored by TLC. When the reaction was completed, 300 ml of cold water was added to it, and it was then neutralized with a 5% ammonium hydroxide solution. After that, the mixture was then kept in fridge overnight. To get a white crystalline solid, the precipitated product was filtered and recrystallized with ethanol.

Spectral characterization of all synthesized compounds

The synthesized derivatives **(AJ-1 to AJ-8)** were characterized by various spectral methods such as UV-Visible, IR, Mass, and ^{1}H-NMR spectroscopy using standard procedures and the values were interpreted as corresponding peaks/signals.

AJ-1

AJ-AJ-3 UV Spectrum [Wavelength of Maximum Absorbance (λmax) = 329]; Mass spectrum, Observed molecular ion $[M]^+$ peak; MS-ESI *(m/z)*: 312.36 (77%); IR Spectrum, C=N (Imine) stretching 1663.76, N-H (Imine) stretching 3576.93, C=C (Aromatic) 1591.96, C-N (Imine) stretching 1320.27, C-H (Aromatic) 3064.92, OH (Aromatic) 3658.72; ^{1}H NMR Spectrum [(MHz 300, MeOD): δ7.994 -7.962(s, hydroxybenzene); δ 7. 59-7.54 (m, 3H, benzene); δ7.96-7.95 (m, 1H imidazole)].

AJ-4 UV Spectrum [Wavelength of Maximum Absorbance (λmax) = 326]; Mass spectrum $[M]^+$ peak; MS-ESI *(m/z)*: 326.39 (76%) IR Spectrum C=N (Imine) stretching 1663.76, N-H (Imine) stretching 3576.93, C=C (Aromatic) 1591.96, C-N (Imine) stretching 1320.27, C-H (Aromatic) 3064.92, C-OH (Aromatic) 3658.72; ^{1}H-NMR Spectrum [(MHz 300, MeOD): δ 3.92(s, methoxy); δ 7. 59-7.54 (m, 3H, benzene); δ7.96-7.95 (m, 1H imidazole)].

AJ-5 UV Spectrum (λmax) = 304; Mass spectrum $[M]^+$ peak; MS-ESI *(m/z)*: 362.42 (70%); IR C=N (Imine) stretching 1663.76, N-H (Imine) stretching3576.93, C=C (Aromatic) 1591.96, C-N (Imine) stretching1320.27, C-H (Aromatic) 3064.92, OH (Aromatic) 3658.72; ^{1}H-NMR (MHz 300, MeOD): δ 3.29-3.34 (m, OH); δ 7.74-7.69 (m, 6H naphthalene); δ 7. 59-7.54 (m, 3H, benzene); δ7.96.7.95 (m, 1H imidazole).

AJ-6 UV Spectrum (λmax) = 307; Mass $[M]^+$ peak; MS-ESI *(m/z)*: 330.81 (77%); IR C=N (Imine) stretching1663.76, N-H (Imine) stretching3576.93, C=C (Aromatic) 1591.96, C-N (Imine) stretching1320.27, C-H (Aromatic) 3064.92, Cl (Aromatic) 765.60; ^{1}H-NMR (MHz 300, MeOD): δ 7.631(s, chlorobenzene); δ 7. 59-7.54 (m, 3H, benzene); δ7.96-7.95 (m, 1H imidazole).

AJ-7 UV Spectrum λmax) = 305; Mass [M] $^{+}$ peak; MS-ESI *(m/z)*: 346.42 (79%); IR C=N (Imine) stretching1663.76, N-H (Imine) stretching3576.93, C=C (Aromatic) 1591.96, C-N (Imine) stretching1320.27, C-H (Aromatic) 3064.92; ^{1}H-NMR (MHz 300, MeOD): δ 7.74-7.69 (m, 6H naphthalene); δ 7. 59-7.54 (m, 3H, benzene); δ7.96-7.95 (m, 1H imidazole).
AJ-8 UV λmax) = 314; Mass [M] $^{+}$ peak; MS-ESI *(m/z)*: 356.15 (74%); C=N (Imine) stretching1663.76, N-H (Imine) stretching3576.93, C=C (Aromatic) 1591.96, C-N (Imine) stretching1320.27, C-H (Aromatic) 3064.92, C-OH (Aromatic) 3658.72 ^{1}H-NMR (MHz 300, MeOD): δ 3.310-3.315 (m, methoxy); δ 7.59-7.54 (m, 3H, benzene); δ7.96-7.95 (m, 1H imidazole).

Biological activity (*in-vitro)*

Antimicrobial drugs are the greatest contribution of the 20th century to therapeutics and their advent changed the outlook of the physician about the power the drugs can have on diseases. Selman Waksman used the term 'antibiotic' in 1941 to describe a tiny substance produced by a bacteria that have the ability to inhibit the development of other organisms or even kill them. Medicines that kill bacteria are referred to as "bactericidal," while, medicines that inhibit bacterial development are referred to as "bacteriostatic." They might be created chemically or, more likely, by naturally existing or genetically produced bacteria.

Well diffusion method:

The Kirby-Bauer method, also known as the agar well diffusion method, is commonly used to test for antibiotic susceptibility. Body fluids containing infectious bacteria are collected and disseminated on agar medium for antibiotic sensitivity testing. A gel puncher or pipette tip is used to make wells in the agar layer, and tiny wafers containing antibiotics are put into them.

Test organisms:

1. For Antibacterial test:

Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus

2. For Antifungal test:

Candida albicans, Beauveria bassiana

Requirements:

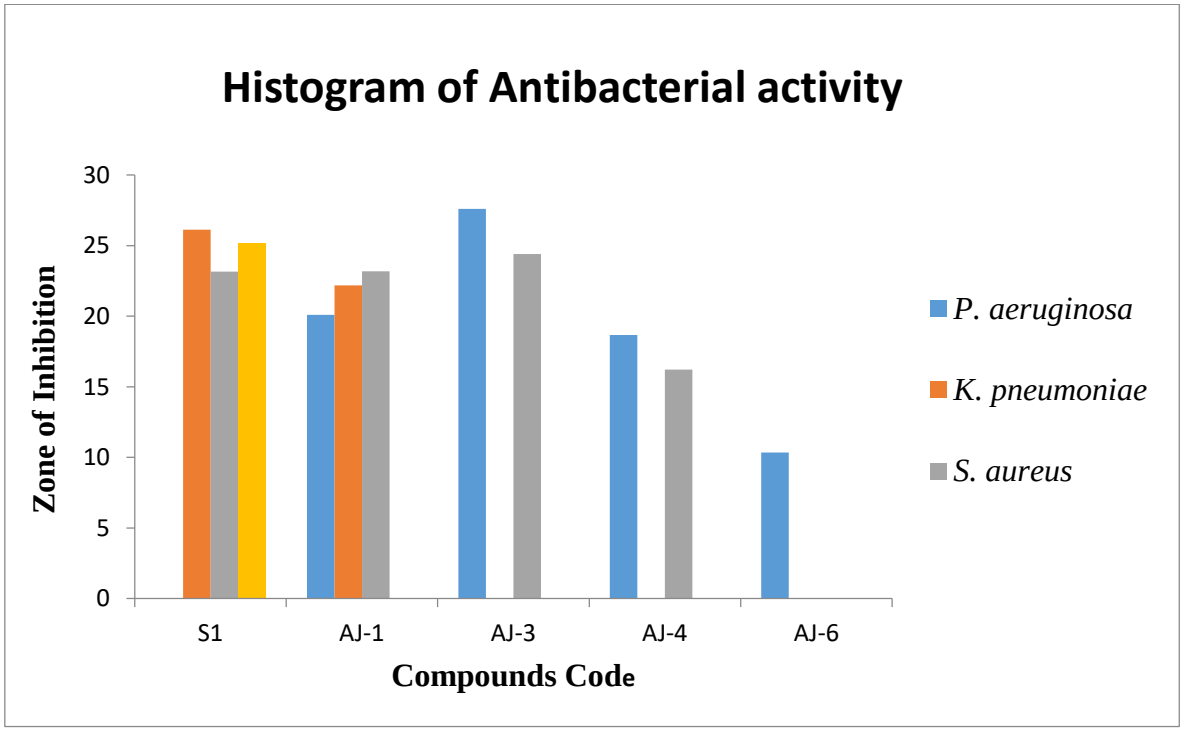
Nutrient agar media, 20µl of each of the pathogens, antibiotics: 10 mg/ml concentration of each of the tetracycline and fluconazole, forceps, pipette, and pipette tips, glass Spreader, spirit lamp.

Study protocol:

- 60 ml nutrient agar media and 3 Petri plates were prepared and autoclaved at 121 °C for 15 min at 15 psi.
- Media was poured to the plates and left for solidification.
- 20µl of each of the pathogen were spread separately.
- Were punctured and removed through forceps.
- The 40µl antimicrobial were loaded in each well on plates.
- Incubated at 37°C for overnight.
- After 24 hour of incubation, ZOI around the wells were measured.

Table 1 Antibacterial analysis of drugs

Pathogens	**Sample zone (zone of inhibition)**				
	AJ-1	**AJ-3**	**AJ-4**	**AJ-6**	**Tetracycline**
Pseudomonas aeruginosa	20.09 mm	27.60	10.34	18.68	26.12
Klebsiella pneumoniae	22.18 mm	0	0	0	23.16
Staphylococcus aureus	23.41 mm	24.22	0	16.22	25.19



S1= Tetracycline

Fig. 1. Histogram of Antibacterial activity

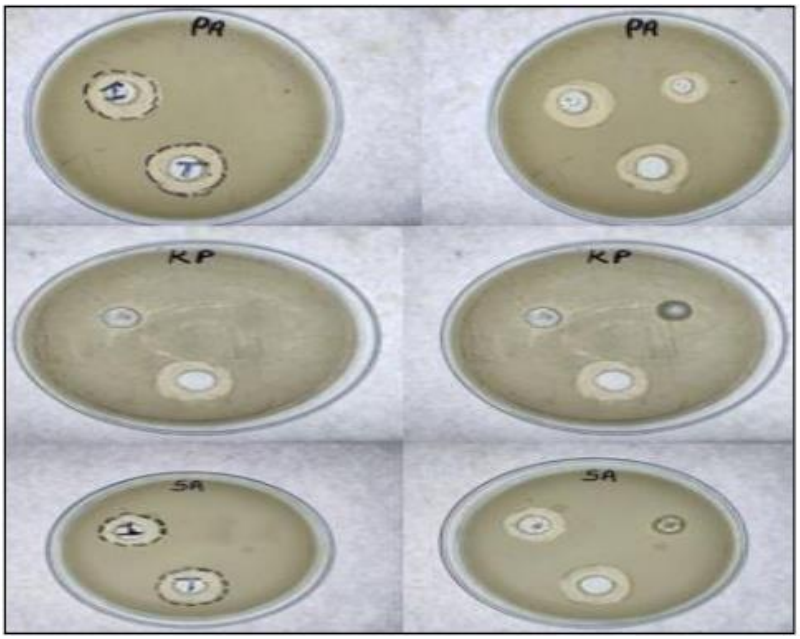
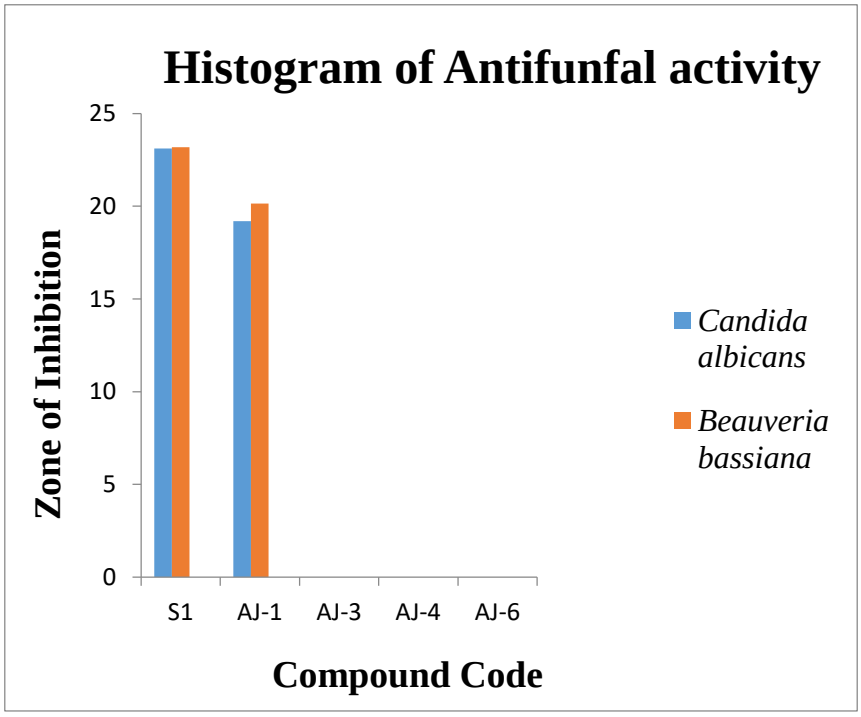


Fig. 2. Antibacterial analysis of drugs

Table 2. Antifungal analysis of drugs

Pathogens	**Sample zone (zone of inhibition)**				
	AJ-1	**AJ-3**	**AJ-4**	**AJ-6**	**Fluconazole**
Candida albicans	19.20 mm	0	0	0	23.12
Beauveria bassiana	20.15mm	0	0	0	23.18



S1= Fluconazole

Fig. 3. Histogram of Antifungal activity

Fig. 4. Antifungal analysis of drugs

Table 3. MIC analysis

Blank	**0.00**
62500 ug	0.09
3900 ug	0.10
243 ug	0.11
15 ug	0.27
Control	0.30

AJ-1: Mic = ≥ 243 ug

Blank	**0.00**
62500 ug	0.08
3900 ug	0.12
243 ug	0.32
15 ug	0.32
Control	0.32

AJ-3: Mic = ≥ 3900 ug

Blank	**0.00**
62500 ug	0.08
3900 ug	0.09
243 ug	0.15
15 ug	0.23
Control	0.23

AJ-4: Mic = > 243 ug

Blank	**0.00**
62500 ug	0.05
3900 ug	0.06
243 ug	0.10
15 ug	0.15
Control	0.30

AJ-6: Mic = > 15 ug

Result

Imidazole derivatives were synthesized by the reaction of benzil and substituted benzaldehydes. Synthetic way to the titled compound is shown as Scheme. Physical characterization of all the synthesized compound were done by using Thin layer chromatography (TLC), melting point (m.p.), percentage yield (%) and solubility.

The structures of all the synthesized compounds were supported by their physiochemical characteristics and spectral characterization, which were performed using FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopic techniques. FT-IR spectra showed the characteristic bonds for Ar-Cl str, OH str, OCH_3 str, C=N str, N-H str, C=C str, C-N str, C-H str, to be in the range of wave number 785-540, 3600-3650, 1690-1640, 3500-3100, 1500-1600, 1350-1000, 3000-3100 cm^{-1}, respectively.

The ^{1}H NMR spectral was recorded in Deuterated methanol (MeOD) is a common solvent used in MNR spectroscopy as the internal standard at 300 MHz on a Bruker spectrophotometer.

Antimicrobial activity

Using the well diffusion method, all the synthesized compounds derivatives **(AJ-1, AJ-3, AJ-4, and AJ-6)** were tested for their antibacterial activity against the (gram +ve) (*Staphylococcus aureus, Klebsiella pneumoniae*), (gram –ve) (*Pseudomonas aureginosa*), and fungal strains (*Candida albicans* and *Beauveria bassiana*). Concentration of the 10 mg/ml of the synthesized compounds was used for evaluation. It was discovered that the chemicals **(AJ-1)** were equivalent to the common medications fluconazole and tetracycline. Tetracycline and Fluconazole, two common antimicrobial medications, served as the controls in the comparison of the data for antibacterial and antifungal activity, respectively. When compared to their antifungal efficacy, the synthesized substance demonstrated antibacterial activity. Antibacterial > antifungal are the deduced patterns of the substituted imidazoles' antimicrobial activity. Significant in vitro antibacterial activity was displayed by each of the synthesized substituted imidazole derivatives.

CONCLUSION

In the current research work, novel triphenyl-imidazole derivatives **(AJ-1, AJ-3, AJ-4, and AJ-6)** were created and examined using the well diffusion method for their antibacterial efficacy against bacteria, fungi, and fungal strains. IR, ^{1}H NMR, and mass spectroscopy were used to characterize every molecule that was produced. According to the results of the antimicrobial activity tests, compounds **(AJ-1, AJ-3, AJ-4 and AJ-6)** with electron withdrawing groups at Ortho and Para positions (4-Br, 4-OH, 4-OCH_3, 2-Cl) substituted at distant phenyl rings exhibited the highest activities against Gram (+ve) and Gram (–ve) bacterial strains. It was discovered that a compound having the electron-withdrawing group chloro at the para position to the phenyl ring was considerably efficient against the fungi (*Candida albicans* and *Beauveria bassiana*). The current work would provide as the foundation for additional preclinical and clinical research to create derivatives of never imidazole as possible antibacterial medicines.

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