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Synthesis, Antibacterial, and Antifungal Activities of 3-(4,5-Diphenyl-1*H*-Imidazol-2-yl)-1*H*-Indole Derivatives

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Abstract

Indolylimidazole ring-containing natural and synthesized compounds have shown vast biological activities. These indolylimidazole compounds contain both indole and imidazole rings. The indolylimidazole structure resembling compounds **1a-1d** and **2a-2d** were synthesized by a green and efficient one-pot four components condensation of indole-3-carbaldehyde, benzil, ammonium-acetate, and substituted amines under microwave irradiation using Amberlyst A-15 as a recyclable catalyst. The structures of synthesized compounds were characterized by FTIR, ^{1}H NMR, and Mass spectrometric studies. These compounds' antibacterial and antifungal activities were screened and compared with the standard drug. The compound **1c** was found to be the most active derivative in these compounds, with a minimum inhibitory concentration in the range of 09.9 to 12.5 µg/mL. Compound **1d** also showed potent activity against *Candida albicans*. The sensitivity order of compounds was found **1a**<**1b**<**1c**>**1d** against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Escherichia coli* and **1a**<**1b**<**1c**<**1d** for *C. albicans*. Compound **2a** showed good antimicrobial activity against *E. coli* and *C. albicans*.

Keywords: *E. coli*; Indolylimidazole; Microwave irradiation; Recyclable catalyst.

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1. Introduction

Indolylimidazoles are an imperative class of heterocycles. The imidazole and indole are the most noteworthy rings in heterocycles because these ring-containing natural and synthesized compounds have shown significant biological activities [1]. Due to the presence of both indole and imidazole rings in the same compound, indolylimidazole, the biological importance of this indolylimidazole compound has been enhanced. Indolylimidazole skeleton containing natural Rhopaladins A-D compounds have been isolated from *Okinawan tunicate Rhopalaea sp*. and reported as an antibacterial agent against *Sarcinalutea*, *Corynebacterium xerosis* [2]. Topsentin derivatives showed

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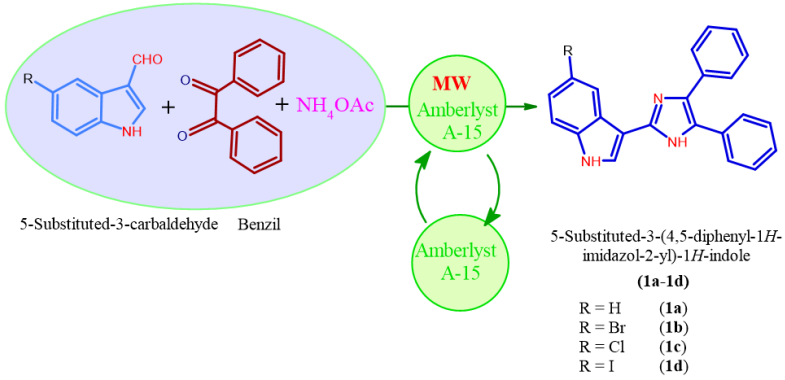
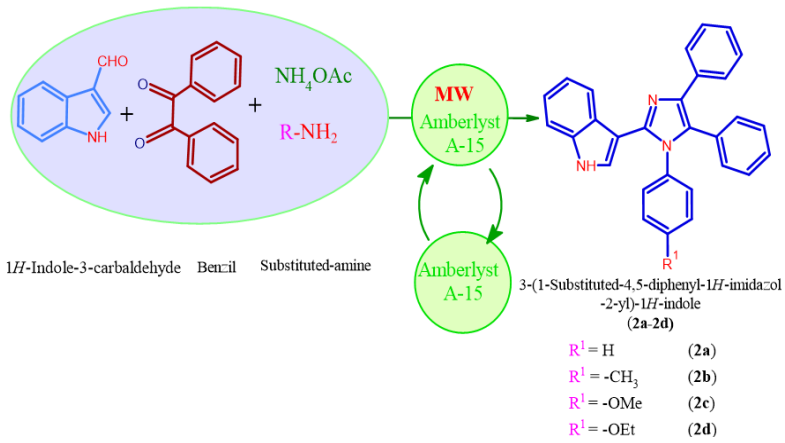
different biological activities such as antibacterial [3], antiviral [4], antitumor [4-6], and anti-inflammatory [7,8]. Nortopsentins A-C, topentin, and bromotopsentin showed in vitro cytotoxicity against P388 cells and antifungal activity against *Candida Albicans* [9]. Due to the most bioactivity and usefulness in various applications, the synthesis of indolylimidazoles has attracted growing interest in the last decade.

From the literature survey, it was monitored that indolylimidazole structure resembling synthesized compounds also showed various biological and pharmacological activities such as antibacterial [10, 11], antimicrobial [12,13], antifungal [13], anti-urease [13,14], antioxidant [14,15], MRSA PK inhibitor [16], radio-sensitizing against HT-29 cell line [17], anticancer, cytotoxicity against murine tumor cells and P388 cells [18]. Due to the great importance of indolylimidazole derivatives, there is a strong demand for a highly efficient and versatile method for synthesizing indolylimidazoles and their antibacterial and antifungal screening.

In the present work, we synthesized some compounds containing both imidazole and indole motifs (Scheme 1 and Scheme 2) and measured their antibacterial and antifungal activities *in vitro* by standard and newly developed tube dilution methods. Microwave irradiation (MW) was used for the synthesis of 2,4,5-triphenyl-1*H*-imidazole derivatives by condensation of substituted-benzaldehyde, benzil, ammonium acetate, and substituted amine in the presence of Amberlyst A-15 catalyst [19,20]. This method has been employed for preparing simple imidazoles without an indole ring. After some modifications, this green and efficient one-pot three components condensation method was utilized to synthesize indolylimidazole derivatives by substituted-indole-3-carbaldehyde, benzil, and ammonium-acetate under MW treatment using Amberlyst A-15 as a recyclable catalyst. The microwave radiation technique has gained attention due to its unique advantages, such as shorter reaction times, cleaner reaction products, higher yields, cost-effectiveness, high purity of the product, energy savings process, better selectivity, and rapid and uniform heating method [21]. These indolylimidazole compounds have been obtained in excellent yields with shorter reaction times. The Results of antibacterial and antifungal activities were compared with standard antibiotics Ampicillin and Amikacin for antibacterial and Fluconazole for antifungal activity.



Scheme 1. Synthesis of 5-substituted-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives.



Scheme 2. Synthesis of 3-(1-substituted-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives.

2. Materials and Methods

2.1. *Chemicals*

All the chemicals and reagents used for the synthesis of substituted-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives (**1a-1d** and **2a-2c**) were purchased from MERCK and Ranbaxy and used as received.

2.2. *Instrumentation*

A microwave oven (IFB, 23BC4, 1400 W) was used for synthesis. The products' melting point was measured by using an open capillary method. IR spectra were obtained in KBr by Jasco - FTIR-4100 spectrometer. ^{1}HNMR spectra were recorded in DMSO with TMS as the internal reference on JEOL - 400 MHz NMR spectrometer with a multiple probe facility (AL-400). The mass spectra were recorded on LCMS SQD-2 with the H Class UPLC instrument.

2.3. *General procedure*

The novel class of multi-substituted indolylimidazole derivatives series of substituted-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole was synthesized by utilizing a green and efficient one-pot condensation of indole-3-carbaldehyde, benzil, ammonium acetate and various amines under microwave irradiation using Amberlyst A-15 as a recyclable catalyst.

2.4. *One-pot synthesis of 5-substituted-3-(4,5-diphenyl-1H-imidazol-2-yl)-1H-indole derivatives (1a-1d)*

A mixture of 1*H*-indole-3-carbaldehyde (1 mmol), benzil (1 mmol), NH_4OAc (2 mmol), and Amberlyst A-15 (0.12 g) was taken into a 50 mL borosil beaker and irradiated with microwave for 8-15 minutes at almost constant temperature 80°C. Thin-layer chromatography (ethyl acetate: petroleum ether 1: 9) technique was used to monitor the headway of the reaction where Silica gel G-60 was a stationary phase. After completion, the reaction mixture was brought to room temperature and added dichloromethane. The solid Amberlyst A-15 was filtered and washed several times with dichloromethane. Pure Amberlyst A-15 was dried at 80 °C and reused again for the Na_2SO_4 swirls freely in the flask. The filtrate was then purposive by vacuum. The prepared products were washed first with dichloromethane, then recrystallized with cold ethanol, and dried. The purity of the obtained compound (**1a-1d**) was checked by TLC, besides microanalysis (Scheme 1).

2.4.1. *Physical and spectral data (Key diagnostic signals in bold text)*

***5-Chloro-3-(4,5-diphenyl-1H-imidazol-2-yl)-1H-indole (1c)*:** Colorless solid, m. p. 231–233 °C. Anal.: (Calcd): C (74.69 %), H (4.36 %), N (11.36 %), Cl (9.61 %), (Found): C (74.67 %), H (4.35 %), N (11.34 %), Cl (9.65 %). FTIR (KBr, cm^{-1}): *V*max: **3472**, 3445, 3220, 3187, 3110, 3085, 1680, 1635, 1600, 1535, **1462, 1456**, 1381, 1278, **1245**, 1082, 805, **769**, **693**; ^{1}H NMR (400 MHz, DMSO-d6): 14.953 (s, 1H, imidazole), 13.651 (s, 1H, indole), 8.912 (d, 1H, J = 2.9 Hz), 8.438 (d, 1H. J = 1.46 Hz), 8.258 (d, 1H, J = 7.424, 7.353), 7.953 (s, 1H, J = 2.441), 7.857–7.691 (m, 10H, Ar-H) ppm. HRMS ((+)-ESI): m/z = 369.8399 (calculated: 369.8462).

***5-Iodo-3-(4,5-diphenyl-1H-imidazol-2-yl)-1H-indole (1d)*:** Colorless solid, m. p. 273–275 °C. Anal.: (Calcd): C (59.88 %), H (3.50 %), N (9.11 %), I (27.51 %), (Found): C (59.89 %), H (3.48 %), N (9.10 %), I (27.53 %). FTIR (KBr, cm^{-1}): *V*max: **3458**, 3436, 3190, 3165, 3060, 3018, 1640, 1600, 1580, 1500, **1450, 1447**, 1361, **1268**, 1237, 1065, 800, **764**, **690**. ^{1}H NMR (400 MHz, DMSO-d6): 14.000 (s, 1H, imidazole), 12.125 (s, 1H, indole), 8.426 (s, 1H, J = 2.8 Hz), 8.295 (d, 1H. J = 1.45 Hz), 7.728 (d, 1H, J = 7.301, 7.811) 7.601 (s, 1H, J = 2.435), 7.512–7.221 (m, 10H, Ar-H) ppm. HRMS ((+)-ESI): m/z = 461.288 (calculated: 461.298).

2.5. *One-pot synthesis of synthesis of 3-(1-substituted-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole derivatives (2a-2d)*

A mixture of 1*H*-indole-3-carbaldehyde (1 mmol), benzil (1 mmol), NH_4OAc (1 mmol), substituted-amine (1 mmol), and Amberlyst A-15 (0.12 g) was taken into a 50 mL borosil beaker and irradiated with microwave for 8-15 minutes at almost constant temperature 80 °C. Thin-layer chromatography (ethyl acetate: petroleum ether 1:9) technique was used to monitor the headway of the reaction where Silica gel G-60 was a stationary phase. After completion, the reaction mixture was brought to room temperature and added

dichloromethane. The solid Amberlyst A-15 was filtered and washed several times with dichloromethane. Pure Amberlyst A-15 was dried at 80 °C and reused again for the Na_2SO_4 swirls freely in the flask. The filtrate was then purposive by vacuum. The prepared products were washed first with dichloromethane, then recrystallized with cold ethanol, and dried. The purity of the obtained compound (**2a-2d**) was checked by TLC, besides microanalysis (Scheme 2).

2.5.1. *Physical and spectral data (Key diagnostic signals in bold text)*

***3-[1-(4-Methylphenyl)-4,5-diphenyl-1H-imidazol-2-yl]-1H-indole (2b)*:** Colorless solid, m.p. 238-239 °C. Anal.: (Calcd): C (84.68 %), H (5.45 %), N (9.87 %), (Found): C (84.70 %), H (5.43%), N (9.85 %). FTIR (KBr, cm^{-1}): *V*max: **3418**, 3125, 1625, 1600, 1595, 1570, **1495, 1440, 1420**, 1394, 1242, 1050, 774, 760, 692. ^{1}H NMR (400 MHz, DMSO-d6): 11.754 (s, 1H, indole); 8.512 (s, 1H); 8.420 (d, 1H, J = 7.4 Hz); 7.807 (t, 1H. J = 7.4 Hz); 7.651 (d, 1H, J = 3.6 Hz); 7.579 (t, 1H, J = 3.7 Hz); 6.652 (d, 2H, J = 2.6 Hz); 6.199 (d, 2H, J = 2.6 Hz); 7.589–7.148 (m, 14H, Ar-H) 3.126 (s, 3H) ppm. HRMS ((+)-ESI): m/z = 425.515 (calculated: 425.524).

2.6. *Strains and media*

Two gram-positive *Staphylococcus aureus* (ATCC 25213), *Staphylococcus epidermidis* (ATCC 35984), and two gram-negative *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853) strains were used to measure antibacterial activity. *Candida albicans* (ATCC 10231) strain was used to measure antifungal activity. Mueller Hinton agar (MHA) media was used to culture and study antibacterial activity, whereas Sabouraud Dextrose agar (SDA) was used to culture and study antifungal activity. The strains and media used in this study were collected from the Department of Microbiology, J.L.N. Medical College Ajmer. The Organisms were cultured and maintained by subculturing periodically on a nutrient medium and preserved at 4^{o}C before use.

2.7. *Preliminary screening for antimicrobial activity*

Bauer-Kirby disk diffusion technique [22-26] was used to study the antibacterial and antifungal activities of compounds. The samples **1a-1d** dissolved in DMSO (250 µg/mL concentration for bacteria and 250 µg/mL for fungal strains). 6 mm diameter Whatman Number 1 filter paper impregnated discs of strains were prepared and placed aseptically on sensitivity plates with appropriate controls. The Mueller Hinton nutrient Agar plates containing an inoculum size of 106 CFU/mL and Sabouraud Dextrose Agar containing 2×105 spores for fungi were used. Ampicillin, Amikacin, and Fluconazole were used as standard antibacterial and antifungal antibiotics. Plates were incubated at 35 °C for 24 h for bacteria and 30 °C for 2-3 days for fungal spores. Sensitivity was recorded by measuring the clean zone of inhabitation in millimeters on an agar surface around the disc.

2.8. *Minimum inhibitory concentration*

The minimum inhibitory concentration (MIC) [27] assay is a technique used to determine the lowest concentration of antibiotics that inhibits the growth of an organism. The tube dilution method [28] was used to determine the MIC of compounds for the test organisms. The synthesized compound was dissolved in DMSO to prepare a stock dilution solution of 1000 μg/mL for MIC, minimum bactericidal concentration **(**MBC), and minimum fungicidal concentration (MFC) assays. All test tubes were sterilized. 2 mL of serial concentrations of the sample (0-250 μg/mL for bacterial strains and fungal strains) was added to a 2 mL of nutrient medium in separate test tubes. These tubes were then inoculated with the test organisms previously diluted to 0.5 McFarland [29] turbidity standard for bacterial strains and 106 cfu/mL for fungal strains.

The procedures were repeated on the test organisms by using standard antibiotics. A tube containing only the test organisms in the nutrient medium was served as control, and another one-test tub was labeled as growth control which contained only nutrient medium. Tubes containing bacterial cultures were then incubated at 35 °C for 24 h for bacterial growth, and fungal cultures were incubated at 30 °C for 2-3 days for fungal spores. After incubation, the tubes were examined for microbial growth by observing the turbidity. The tubes with turbidity indicated microbial growth, while tubes without turbidity and remained clear indicated no growth of microbial. The MIC of the sample was the lowest concentration that did NOT show microbial growth.

2.9. *Minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC)*

MBC [27,30] and MFC [31] were obtained by subculturing the contents of selective test tubes into the MIC series of determination. Subculture all tubes which do not show any growth (visible tube) in the same manner as the control tube described above and inoculate on sterile nutrient agar (for bacteria) and SDA media (for fungi) by streaking. Nutrient agar and SDA media plates were inoculated with bacteria and fungi and incubated at 37 °C for 24 h for bacteria and 30 °C for 2-3 days for fungi, respectively. After incubation, tests were examined for microbial growth and determined the concentration at which no visible growth was seen, and it was noted as MBC for bacteria and MFC for fungi.

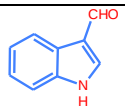
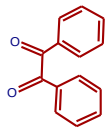
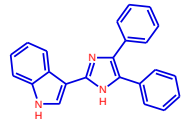
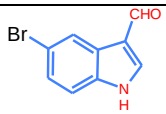
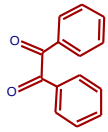
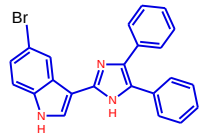
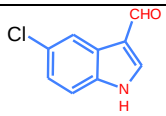
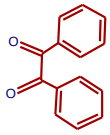
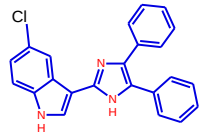
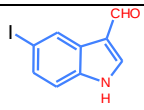
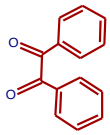
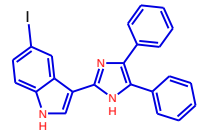
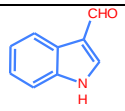
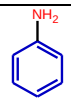
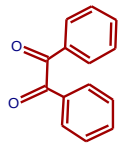
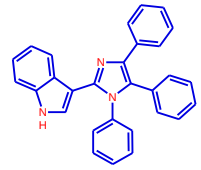
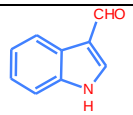
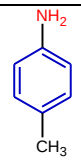
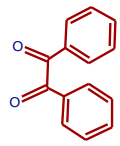
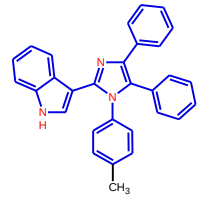
3. Result and Discussion

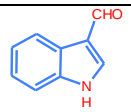
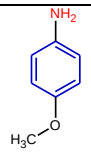
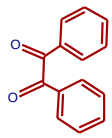
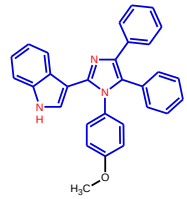
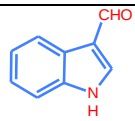
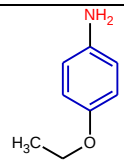
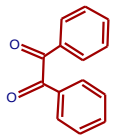
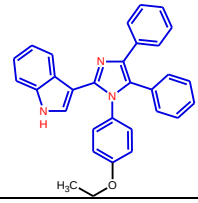
3.1. *Synthesis of substituted-3-(4,5-diphenyl-1H-imidazol-2-yl)-1H-indole derivatives*

An efficient, green, and eco-friendly one-pot multi-component condensation method has been used for the synthesis of indolylimidazole derivatives (**1a-1d**) and (**2a-2d**) by using Amberlyst A-15 as an effective, reusable catalyst under microwave irradiation. The 5-substituted-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives (**1a-1d**) were

synthesized by one-pot three components condensation of 5-substituted-indole-3-carbaldehyde, benzil, NH_4OAc under microwave irradiation using Amberlyst A-15 as a recyclable catalyst (Scheme 1).

Table 1. Physical properties of 4,5-diphenyl-2-(5-substituted indolyl) imidazole and 1-substituted-4,5-diphenyl-2-indolylimidazole derivatives.

Entry	Carbaldehyde	NH_4OAc/ amine	Benzil	Products	Reactn. (min)	Yield (%)	M.P. (°C)
1a		NH_4OAc			8	97	158-160
1b		NH_4OAc			14	92	237-239
1c		NH_4OAc			11	89	231-233
1d		NH_4OAc			13	90	273-275
2a					12	94	235-236
2b					12	93	238-239

2c					10	96	242-243
2d					9	97	207-209

The 3-(1-substituted-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives (**2a-2d**) were synthesized by one-pot four components condensation of 1*H*-indole-3-carbaldehyde, benzil, NH_4OAc and substituted-amine under microwave irradiation using Amberlyst A-15 as a recyclable (Scheme 2). The key advantage of this process involves being eco-friendly, very short reaction time, cost-effectiveness with the reusability of catalyst, easy workup, and purification of the product with excellent yields. The structures of all synthesized molecules (**1a-1d**) and (**2a–2d**) were identified by using FTIR, ^{1}H NMR, and Mass spectrometric studies. These indolylimidazole compounds have been obtained in excellent yields with shorter reaction times (Table 1).

All the compounds (**1a-1d**) and (**2a-2d**) give an absorption in 3472-3418 cm^{-1} due to N-H starching indole in FT-IR spectra. The compounds (**1a-1d**) give an additional absorption in 3445-3436 cm^{-1} due to N-H starching of imidazole in FT-IR spectra. The absorption of 1680-1640 cm^{-1} due to aromatic C=N function. The compounds (**2c-2d**) give two absorption in 1409 cm^{-1} and 1195 cm^{-1} due to =C-O starching and in 1250 cm^{-1} due to -O-C starching. The non-appearance of absorption of amine and carbonyl groups in the FT-IR range supported the synthesis of the new compounds.

The ^{1}H NMR spectra of all the compounds give a singlet in δ = 12.463 to 11.135 ppm region due to N-H of indole. All compounds' aromatic protons of the benzene ring give multiple at δ = 7.627 to 7.159 ppm. The mass spectra showed molecular ion peaks concurred with the molecular formula.

3.2. *Antibacterial and antifungal activity*

3.2.1. *Zone of inhibition (ZOI)*

The preliminary antimicrobial activities for all the products have shown in Table 1. In terms of zone of inhibition (ZOI), the maximum ZOI was shown by compound **1a** against *P. aeruginosa*, **1c** against *S. aureus*, *S. epidermidis* and *E. coli*, and compound **1d** against *S. aureus.* Compound **1c** showed significant activity against *S. aureus*, *S. epidermidis*, and *E. coli* when compared with standard antibiotics Ampicillin (AMP) and Amikacin.

Compound **1a** also exhibited a significant ZOI against *P. aeruginosa*, whereas compounds **1b** and **1d** exhibited moderate inhibition against *S. aureus*, *P. aeruginosa*, and *S. aureus*, respectively. Compound **2a** showed significant ZOI against *E. coli*, and **2c** exhibited moderate inhibition against *P. aeruginosa* when compared with standard antibiotic Ampicillin (Table 2).

The priority order for antibacterial activity in term of ZOI of compounds are as follows:

1c>**1b**>**1d**>**1a**>**2c**>**2a**>**2b**>**2d** against *S. aureus*

1c>**1b**>**1d**>**2a**>**2d**>**1a**>**2c**>>**2b** against *S. epidermidis*

1c>**1b**>**2a**>**1a**>**1d**>**2c**>**2d**>**2b** against *E. coli*

1a>1b>1c>2c>1d>2d>**2a**>**2b** against *P. aeruginosa*

1d>**1c**>**2a**>**1b**>**2c**>**1a**>**2d**>**2b** against *C. albicans.*

Table 2. Zone of inhibition in mm against test microorganisms.

Compound	Antimicrobial activity Zone of inhibition in mm (250 µg/mL)*				
	S. aureus ATCC 29213	*S. epidermidis* ATCC 35984	*E. Coli* ATCC 25922	*P. aeruginosa* ATCC 27853	*C. albicans* ATCC10231
1a	13.32±12	07.62±51	10.66±21	18. 96±21	08.14±11
1b	16.12±22	14.33±05	14.06±62	17.66±37	09.59±03
1c	20.68±31	18.68±30	18.54±31	13.54±08	10.24±07
1d	15.68±68	11.82±02	08.98±11	10.44±32	11.55±41
2a	08.20±38	09.38±09	12.22±06	09.24±64	09.74±03
2b	07.57±41	05.62±16	05.52±45	08.49±.09	06.30±03
2c	08.98±82	06.38±15	08.44±27	12.87±61	08.37±83
2d	05.64±76	08.58±55	07.57±87	09.68±69	06.82±.05
Ref.	15.03±38[a] 19.03±6[b]	15.00±53[a] 17.69±08[b]	07.53±08[a] 18.13±64[b]	12.09±09[a] 18.82±62[b]	21.23±06[c]
DMSO	-	-	-	-	-

[a] – Ampicillin (10 µg); [b] – Amikacin (30 µg); [c] – Fluconazole (10 µg); * –sample/DMSO

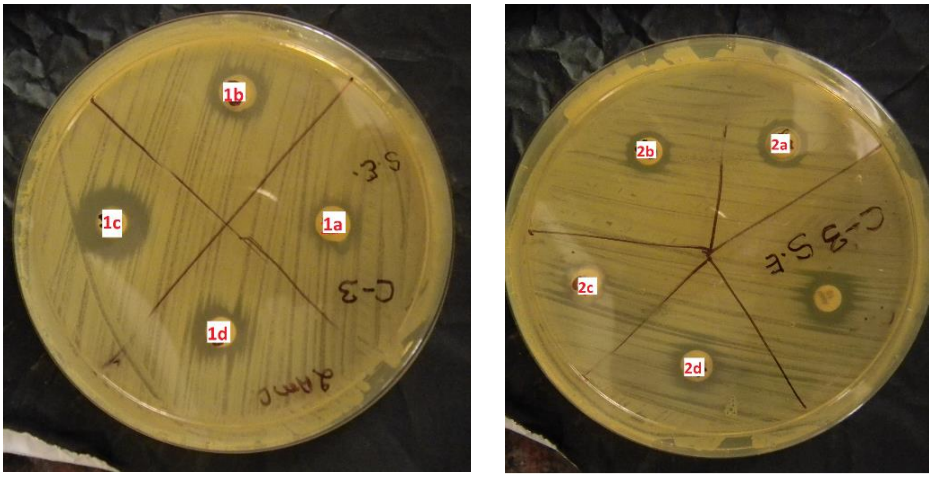


Fig. 1. Zone of inhibition study of compounds [1a-1d & 2a-2d] for *S. aureus.*

3.2.2. *Minimum inhibitory concentration, minimum bactericidal concentration and minimum fungicidal concentration*

The result of MIC, MBC, and MFC summarized in Table 3. The compound **1c** was highly sensitive against *S. aureus* with *a* MIC value 12.5, *S. epidermidis* with an MIC value 10.3, and moderate sensitive against *E. coli* with a MIC value 09.9. Compound **1a** also showed sensitivity against *P. aeruginosa* and almost similar moderate sensitivity shown by compound **1b** against *P. aeruginosa* and *S. epidermidis*. In this case, the most active compounds were found to be the halogenated derivatives **1c** and **1a**. It is also found that compound **1c** with Cl is most sensitive for all Strains.

Table 3. Results of MIC, MBC, and MFC.

Compound	Antimicrobial activity (μg/mL)									
	S. aureus ATCC 29213		*S. epidermidis* ATCC 35984		*E. Coli* ATCC 25922		*P. aeruginosa* ATCC 27853		*C. albicans* ATCC10231	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MFC
1a	54.2	51.8	>100	>100	30.5	27.5	19.2**	16.3	>100	>100
1b	15.6*	18.9	15.3*	13.9	20.9	17.8	21.5*	17.9	>100	>100
1c	12.5**	11.2	10.3**	07.2	09.9**	06.4	31.2	30.3	20.9	18.1
1d	21.3	23.7	18.5	16.3	>36.7	>34.1	>100	>100	17.8	14.9
2a	>100	>100	>100	>100	22.3	19.3	>100	>100	>100	>100
2b	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
2c	>100	>100	>100	>100	37.4	35.4	51.3	47.5	>100	>100
2d	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Ref.	22.1[a]	19.8[a]	12.5[a]	10.2[a]	10.8[b]	08.6[b]	20.3[b]	17.8[b]	4.2[c]	<0.5[c]
DMSO	-	-	-	-	-	-	-	-	-	-

[a] – Ampicillin (10 μg); [b] – Amikacin (30 μg); [c] – Fluconazole (10 μg)
MIC- Minimum Inhibitory Concentration; MBC-Minimum Bactericidal Concentration; MFC-Minimum Fungicidal Concentration
**- Significant activity; *- Moderate activity.

This result represents that the presence of Cl in the newly synthesized compound **1c** becomes a significant antimicrobial activity of compound **1c** and moderate activity of compounds **1b** and **1d** due to the presence of Br and I in compounds **1b** and **1d,** respectively.

4. Conclusion

This study aimed to the green synthesis of substituted-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole derivatives and determine the biological activities of these synthesized compounds against different microorganisms. We have used an efficient, mild, and rapid method for the synthesis of multi-substituted indolylimidazole derivatives by one-pot condensation of 1*H*-indole-3-carbaldehyde, benzil, ammonium acetate and using Amberlyst A-15 as a new and highly effective catalyst under solvent-free and microwave conditions. Most of the synthesized compounds were inactive, but compound **1c** has

shown significant antimicrobial activity against *S. aureus*, *S. epidermidis*, and *E. coli*. The compounds **1b** and **1d** have shown moderate antimicrobial activity against *S. aureus*, *P. aeruginosa*, and *S. aureus*, respectively. In summary, the sensitivity order of compounds was found **2d**<**2b**<**2a**<**2c**<**1a**<**1b**<**1c**>**1d** against *S. aureus*, *S. epidermidis*, and *E. coli* and **1a**<**1b**<**1c**<**1d** for *C. albicans*. This result represents that the presence of Cl in the newly synthesized compound **1c** becomes a significant antimicrobial activity of compound **1c** and moderate activity of compounds **1b** and **1d** due to the presence of Br and I in compounds **1b** and **1d,** respectively. Compound **2a** also has some antimicrobial activity against *E. coli* and *C. albicans*. Therefore, on behalf of the above conclusions, it can be stipulated that the compounds **1c** and **1d** can be a good advantage as antibacterial agents for the manufacture of novel medicines after clinical trials.

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