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SYNTHESIS, CHARACTERIZATION OF 2-[4-(4,5-DIPHENYL-1*H*-IMIDAZOL-2-YL)PHENYL]ISOINDOLINE-1,3-DIONE DERIVATIVES AND THEIR BIOLOGICAL ACTIVITY EVALUATION

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ABSTRACT

In the present study, derivatives of imidazole-isoindoline-1,3-dione were synthesized by cyclization of benzil, 4-nitrobenzaldehyde**,** and ammonium acetate in glacial acetic acid at reflux conditions followed by reduction and coupling with phthalic anhydride derivatives. All newly synthesized compounds were explicated by spectroscopic techniques and screened for their biological activities against Gram-positive, Gram-negative, and fungi strains. Antimicrobial screening results revealed that **7** was the most active compound.

Keywords: Phthalic anhydride, Imidazole, Isoindoline-1,3-dione, Biological Activity.

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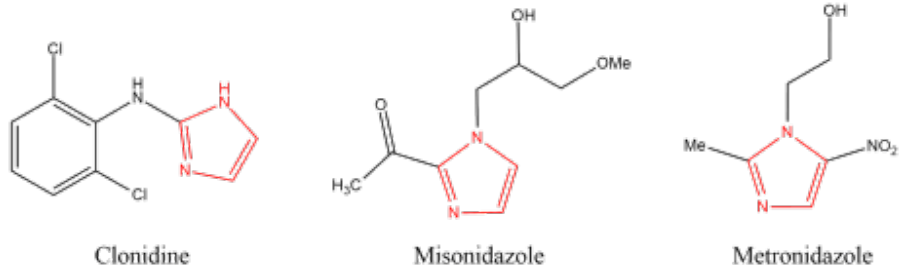
INTRODUCTION

Heterocycles containing imidazole gallows occupied a unique position in heterocyclic chemistry. The imidazole moiety is an important constituent in various biomolecules such as histidine, histamine, nucleic acid, purines, biotin, and pilocarpine alkaloids.[1,2] Imidazole analogs have attracted the attention of many chemists due to their wide range of biological and pharmaceutical properties such as analgesic,[3] anti-convulsant,[4] anti-inflammatory,[5] anticancer,[6,7] antimalarial,[8] and antimicrobial.[1,9] Selected examples[10] of marketed drugs containing imidazole skeleton are shown in Fig.-1.



Clonidine Misonidazole Metronidazole

Fig.-1: Selected Examples of Drugs containing Imidazole Skeleton

Also, isoindoline-1,3-dione nucleus is a vital drug candidate known to possess different biological properties such as antimycobacterial,[11] antimicrobial,[12-15] antimalarial,[16] antiviral,[17] antitumor,[18] and antitubercular.[19]

So, considering this reported distinct activity of imidazole and isoindoline-1,3-dione structural motifs, we synthesized new imidazole-isoindoline-1,3-dione derivatives and screened their antibacterial activity against Gram-positive, Gram-negative bacterial strains, and their antifungal activity against fungi strains.

EXPERIMENTAL

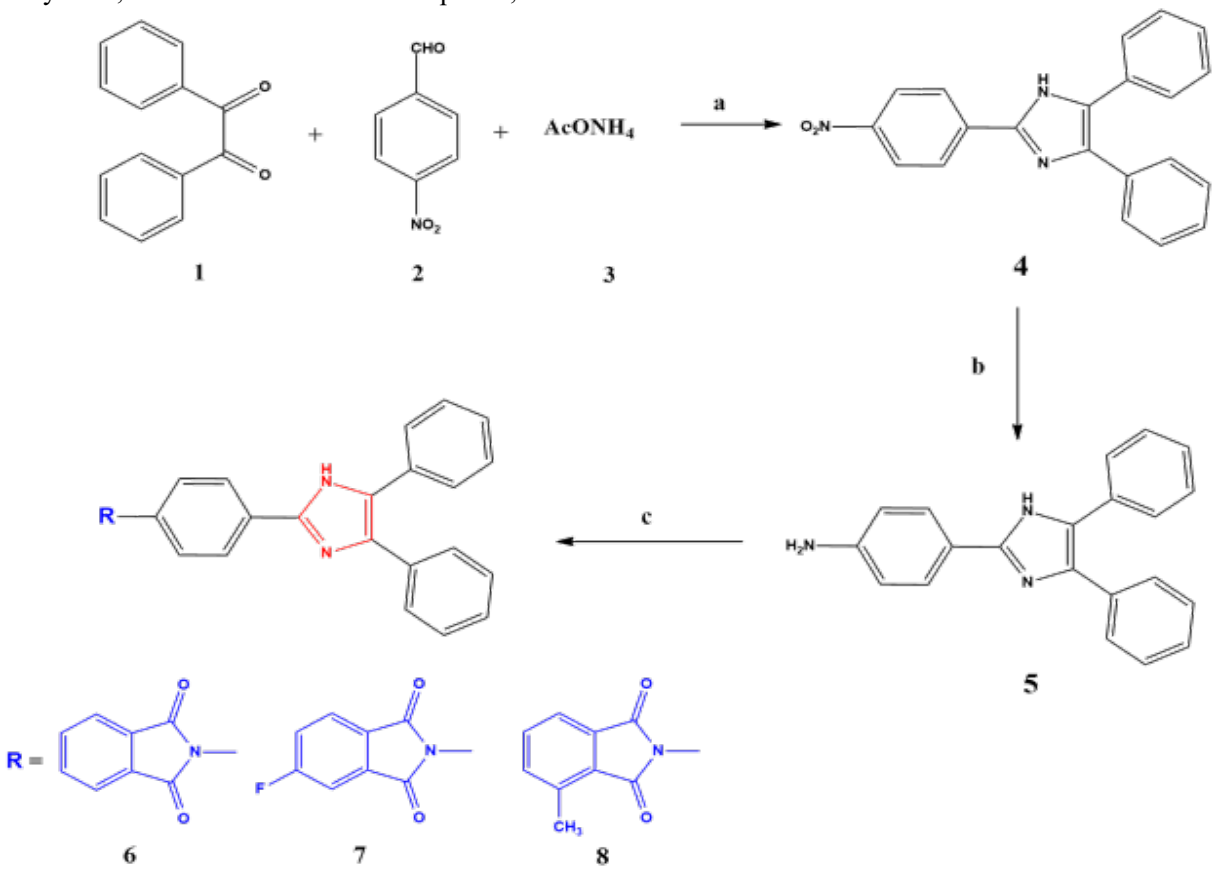
Material and Methods

All chemicals required for the synthesis were directly used without further purification. The purity of the compounds was checked by TLC on pre-coated silica gel aluminium sheets (Merck) (eluents petroleum ether -AcOEt in various proportions) and spots were visualized by UV lights. ^{1}H and ^{13}C-NMR spectra

were recorded on a JEOL spectrometer (600 MHz) and all chemical shifts were referred to in parts per million from TMS and deuterated solvent (chloroform-d or DMSO-d*6*) as an internal standard. All characterization was performed at Sophisticated Analytical Instrument Facility (SAIF), IIT Bombay, Mumbai.

Procedure

The synthesis of 2-[4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl]isoindoline-1,3-dione derivatives were obtained in a four-step synthesis (Scheme-1). The reaction step including three-component reaction (cyclization) of benzil **1**, 4-nitrobenzaldehyde **2,** and ammonium acetate **3** in glacial acetic acid at reflux conditions for 4 h to afford 2-(4-nitrophenyl)-4,5-diphenyl-1*H*-imidazole **4** in good yield. The reduction of **4** with Fe/HCl produced 2-(4-aminophenyl)-4,5-diphenyl-1*H*-imidazole **5** according to the previous study.[20] At the final step, **5** reacted with phthalic anhydride and its derivatives (4-fluoro and 3-methyl phthalic anhydride) to obtain 2-[4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl]isoindoline-1,3-dione derivatives **6-8** (Table-1). Furthermore, we have attempted reacting **5** with 3-nitro & 4-nitrophthalic anhydride, but reactions were not completed, even after 18 h of duration.



Scheme-1: Synthesis of 2-[4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl]isoindoline-1,3-dione derivatives **(6-8)**. Reagents and Conditions; **a**: Glacial AA, reflux, 4h, **b**: Fe/HCl, ethanol/water, reflux, 6h, **c**: Phthalic anhydride and its derivatives (4-fluoro and 3-methylphthalic anhydride), Glacial AA, reflux, 3h.

Table-1: Synthesis of Compounds 6-8

Entry	Name of the Compound	Yield (%)
1	2-[4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl]isoindoline-1,3-dione (6)	85
2	2-[4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl]-4-fluoroisoindoline-1,3-dione (7)	86
3	2-(4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl)-3-methylisoindoline-1,3-dione (8)	36

2-(4-nitrophenyl)-4,5-diphenyl-1*H*-imidazole (4)
Procedure (irrespective of weight of the reactants) followed according to the previous study,[20] 2.36 g of **4** was obtained as a dark yellow powder. ^{1}H-NMR (600 MHz, $CDCl_3$): δ-7.29-7.35 (m, 6H, Ph), δ-7.51-7.66 (m, 4H, Ph), δ-8.05 (d, J = 8.2 Hz, 2H, Ph), δ-8.24 (d, J = 8.5 Hz, 2H, Ph), δ-10.15 (s, 1H, NH). 13C-NMR (150 MHz, $CDCl_3$): δ-124.39, 125.51, 127.88, 128.01, 128.76, 135.48, 143.43, 147.53. Analysis for $C_{21}H_{15}N_3O_2$ (341.36): Calculated: C, 73.89; H, 4.43; N, 12.31; O, 9.37. Found: C, 73.78; H, 4.32; N, 12.11; O, 9.27.

2-(4- aminophenyl)4,5-diphenyl-1*H*-imidazole (5)
Procedure (irrespective of weight of the reactants) followed according to the previous study,[20] 0.41 g of **5** was obtained. ^{1}H-NMR (600 MHz, DMSO-d*6*): δ-5.36 (s, 2H, NH_2), δ-6.62 (d, J = 8.4 Hz, 2H, Ph), δ-7.26-7.57 (m, 10H, Ph), δ-7.75 (d, J = 8.5 Hz, 2H, Ph), δ-12.21 (s, 1H, NH)**.** 13C-NMR (150 MHz, DMSO-d*6*): δ-113.62, 118.19, 126.52, 126.82, 127.65, 128.35, 146.87, 149.17. 13C-NMR (150 MHz, $CDCl_3$): δ-17.74, 121.46, 126.54, 126.59, 127.82, 128.12, 128.19, 128.27, 128.43, 129.00, 129.73, 130.78, 130.96, 132.00, 132.48, 134.00, 136.87, 136.94, 138.62, 144.64, 167.10, 167.75. Analysis for $C_{21}H_{17}N_3$ (311.38): Calculated: C, 81.00; H, 5.50; N, 13.49. Found: C, 80.78; H, 5.32; N, 13.21.

2-(4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl)isoindoline-1,3-dione (6)
0.100 g (0.32 mmol) of 2-(4-aminophenyl)-4,5-diphenyl-1*H*-imidazole **(5)** and 0.048 g (0.32 mmol) of phthalic anhydride was taken in 10 ml of the single necked round bottom flask, which then refluxed in 5 ml glacial acetic acid for 3 h. The reaction mixture was then cooled and poured onto crushed ice. The crude product was filtered, washed several times with water and then dried. Yield: 0.120 g (85%). ^{1}H-NMR (600 MHz, DMSO-d*6*): δ-7.32-7.69 (m, 13H, Ph), δ-7.91-8.22 (m, 13H, Ph), δ-12.98 (s, 1H, NH)**.** 13C-NMR (150 MHz, DMSO-d*6*): δ-123.49, 125.61, 127.37, 127.49, 127.84, 128.50, 129.55, 130.75, 131.55, 131.78, 132.92, 134.81, 144.80, 166.96, 168.65. Analysis for $C_{29}H_{19}N_3O_2$ (441.48): Calculated: C, 78.90; H, 4.34; N, 9.52; O, 7.25. Found: C, 78.58; H, 4.22; N, 9.30; O, 7.07.

2-(4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl)-4-fluoroisoindoline-1,3-dione (7)
0.110 g (0.36 mmol) of 2-(4-aminophenyl)-4,5-diphenyl-1*H*-imidazole **(5)** and 0.059 g (0.36 mmol) of 4-fluoro-phthalic anhydride was taken in 10 ml of single necked round bottom flask, which then refluxed in 5 ml glacial acetic acid for 3 h. Yield: 0.140 g (86%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ-7.32-8.35 (m, 17H, Ph), δ-12.88 (s, 1H, NH)**.** 13C-NMR (150 MHz, $CDCl_3$): δ-111.22, 111.38, 117.22, 117.37, 121.55, 121.70, 125.63, 126.25, 126.31, 127.43, 127.78, 128.50, 129.68, 131.63, 134.58, 144.77, 165.11, 165.71, 166.02, 166.79. Analysis for $C_{29}H_{18}FN_3O_2$ (459.47): Calculated: C, 75.81; H, 3.95; F, 4.13; N, 9.15; O, 6.96. Found: C, 76.01; H, 4.10; F, 4.35; N, 9.30; O, 6.75.

2-(4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl)-3-methylisoindoline-1,3-dione (8)
0.115 g (0.37 mmol) of 2-(4-aminophenyl)-4,5-diphenyl-1*H*-imidazole **(5)** and 0.060 g (0.37 mmol) of 3-methyl-phthalic anhydride was taken in 10 ml of single necked round bottom flask, which then refluxed in 5 ml glacial acetic acid for 3 h. Yield 0.060 g (36%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ-2.72 (s, 3H, CH_3), δ-7.20-8.22 (m, 17H, Ph). 13C-NMR (150 MHz, $CDCl_3$): δ-17.74, 121.46, 126.54, 126.59, 127.82, 128.12, 128.19, 128.27, 128.43, 129.00, 129.73, 130.78, 130.96, 132.00, 132.48, 134.00, 136.87, 136.94, 138.62, 144.64, 167.10, 167.75. Analysis for $C_{30}H_{21}N_3O_2$ (455.51): Calculated: C, 79.10; H, 4.65; N, 9.22; O, 7.02. Found: C, 79.33; H, 4.89; N, 9.03; O, 7.17.

RESULTS AND DISCUSSION

The antimicrobial activity of the newly synthesized heterocyclic compounds **6-8** was performed on two Gram-positive bacterial strains (Staphylococcus aureus & Streptococcus pyogenes) and two Gram-negative bacterial strains (Escherichia coli & Pseudomonas aeruginosa). The antifungal activity was carried out on three fungal strains (Candida albicans, Aspergillus niger & Aspergillus clavatus). The determination of biological activities was examined using the agar-diffusion method (Broth Dilution

Method) in which the minimum inhibitory/fungicidal concentration (MIC) (µg/ml) of the investigated compounds were determined and compared with Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin as standard antibacterial drugs and Nystatin, Griseofulvin as standard antifungal drugs.

The results of the antibacterial and antifungal screening are summarized in Table-2. Results revealed that compounds **7** and **8** showed more efficacy against E. coli and compounds **6** and **7** were more effective against S. aureus than the standard Ampicillin as they have lower MIC values than the standard. All compounds showed lower fungal activity compared to the standard Nystatin. However, compound **7** had better antifungal activity (MIC=250 µg/mL) against C. albicans than the standard Griseofulvin (MIC=500 µg/mL), but less active against A. niger and A. clavatus compared with both the standards. The improved antibacterial and antifungal activity was observed in the presence of the EWG group (i.e. fluoro).

Table-2: Antimicrobial Activity of the newly synthesized Compounds against G+, G- and Fungal Strains

		Antibacterial Activity				Antifungal Activity		
		Minimum Inhibition Concentration				Minimum Fungicidal Concentration		
		microgram/mL				microgram/mL		
Compounds	Codes	*E.coli*	*P.aeruginosa*	*S.aureus*	*S.pyogenes*	*C.albicans*	*A.niger*	*A.clavatus*
		MTCC 443	MTCC 441	MTCC 96	MTCC 442	MTCC 227	MTCC 282	MTCC 1323
6	NR-16	125	125	100	250	500	500	500
7	NR-17	50	100	125	250	250	1000	1000
8	NR-23	12.5	250	250	500	500	500	500
Gentamycin		0.05	1	0.25	0.5	-	-	-
Ampicillin		100	-	250	100	-	-	-
Chloramphenicol		50	50	50	50	-	-	-
Ciprofloxacin		25	25	50	50	-	-	-
Norfloxacin		10	10	10	10	-	-	-
Nystatin		-	-	-	-	100	100	100
Griseofulvin		-	-	-	-	500	100	100

CONCLUSION

In this study, we have synthesized 2-[4-(4,5-diphenyl-1*H*-imidazole-2-yl)phenyl]isoindoline-1,3-dione derivatives **(6-8)** by the conventional method. The synthesized compounds were explicated by spectroscopic and analytical techniques. The antimicrobial activity of synthesized compounds revealed that the aromatic ring with the electron-withdrawing group had more efficacy in terms of antibacterial and antifungal activities.

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