

Green Synthesis, Characterization, and Biological Evaluation of 2,4,5-Trichloro-N-phenylbenzamide Derivatives Using Bunium Persicum Extracted MnO_2 Catalyst

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Abstract

A group of derivatives of the 2,4,5-trichloro-N-phenylbenzamides (2a-2h) has been synthesized by following an eco-friendly microwave method in the presence of MgO (MnO₂) encumbered with extracts of *Bunium Persicum* powder as a green catalyst. The reaction was carried out under mild conditions with good yields (82.55-89.64%) in much shorter reaction times. The natural MnO₂ catalyst gave much better results than synthetic catalysts like Pd/C, CuI, Fe₂O₃, DMAP, K₂CO₃, and BF₃·Et₂O. Structural elucidation of the synthesized compounds was done by FTIR, ¹H NMR, ¹³C NMR, and HRMS spectroscopies, which confirmed the expected molecular structures. There was a decrease in catalysis over five runs, but the bio-derived MnO₂ nanoparticles still had enough catalytic activity

1 Introduction

The production of bioactive compounds using green and sustainable approaches has become one of the most important objectives in modern science. One of the most promising approaches is the use of natural catalysts because of their sustainability, low cost, and high catalytic efficiency [1, 2]. The use of natural catalysts in organic synthesis considerably reduces the use of toxic reagents, thus mitigating the environmental impact that conventional techniques would otherwise have [3]. The biological activities and properties of benzamide derivatives, especially N-phenylbenzamides, are quite broad and include the following major groups: antimicrobial [4], anti-inflammatory [5], anticancer [6], and antioxidant [7] activities. The pharmacological activity of benzamides is further enhanced by the presence of halogen substituents like chlorine, which increases lipophilicity and metabolic stability of the compound and its interactions with biological targets [8, 9]. Specifically, 2,4,5-trichloro-N-phenylbenzamide and its derivatives are of interest because of their high bioactivity and possible therapeutic uses [10, 11].

The focus of ongoing research includes developing green synthetic methods for benzamide derivatives with an emphasis on reducing hazardous reagents and minimizing energy-intensive processes [12, 13]. Natural catalysts, including plant extracts and species of *Bunium Persicum*, solve this problem by being an abundant source of bioactive and bioactive compounds which mediate organic transformations [14, 15]. *Bunium Persicum* extracts contain an abundance of polysaccharides, flavonoids, and phenolic compounds, which can efficiently catalyze several chemical reactions, including the formation of amide bonds [16, 17]. The work of other researchers showcases the ability of plant-based catalysts to efficiently drive reactions at mild temperatures, make reactions much easier, and result in high-purity products [18, 19]. The expectation of using *Bunium Persicum* extracts as a catalyst in the synthesis of 2,4,5-trichloro-N-phenylbenzamide derivatives includes better reaction selectivity, shorter reaction times, and greater sustainability [20, 21].

This study focuses on the green synthesis, biological evaluation, and characterization of 2,4,5-trichloro-N-phenylbenzamide derivatives using MnO₂ nanoparticles from *Bunium Persicum* extract [21]. Characterization of the synthesized compounds was carried out by FTIR, NMR, and MS, while their biological activity was evaluated to explore potential pharmacological applications.

2 Materials and Methods

2.1 Chemicals and Reagents:

All reagents and solvents used in this study were of analytical grade and purchased from reputable suppliers. The *Bunium Persicum* extract was prepared from dried seeds following a reported extraction protocol [21]. The precursor compound, 2,4,5-trichlorobenzoic acid, was procured from Sigma-Aldrich and used without further purification.

Method 1: Pyridine-Catalyzed Synthesis

2,4,5-Trichlorobenzoyl chloride (10 mmol) was dissolved in anhydrous toluene (15 mL) under nitrogen. Aniline or substituted aniline (11 mmol) was added, followed by pyridine (2.0 equiv, 20 mmol). The mixture was heated to 80°C and stirred for 6 h. After cooling, the reaction was diluted with ethyl acetate (30 mL), washed with 1 M HCl (20 mL) and brine (20 mL), and dried over MgSO₄. The solvent was removed under reduced pressure, and the residue was recrystallized from ethanol to afford compounds **2a–2h**.

Method 2: DMAP-Catalysed Synthesis

To a solution of 2,4,5-trichlorobenzoyl chloride (10 mmol) in anhydrous THF (20 mL) at 0°C under nitrogen, aniline or substituted aniline (11 mmol) and 4-dimethylaminopyridine (DMAP, 0.1 equiv, 1 mmol) were added. Triethylamine (1.2 equiv, 12 mmol) was added dropwise, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated NaHCO₃ (20 mL), extracted with ethyl acetate (3 × 20 mL), and dried over Na₂SO₄. Purification by column chromatography (hexane: ethyl acetate, 9:1) yielded compounds **2a–2h**.

Method 3: Heterogeneous Catalysis Using Amberlyst A-21

2,4,5-Trichlorobenzoyl chloride (10 mmol) and aniline or substituted aniline (11 mmol) were dissolved in anhydrous DCM (25 mL). Amberlyst A-21 (1.0 g, a weakly basic ion-exchange resin) was added, and the mixture was stirred at room temperature for 8 h under nitrogen. The resin was filtered off, and the filtrate was washed with water (20 mL) and brine (20 mL), then dried over Na₂SO₄. The crude product was purified by recrystallization from methanol to yield compounds **2a–2h**.

Method 4: Pd/C Catalyzed Amidation

A mixture of 2,4,5-trichlorobenzoyl chloride (1 mmol), the appropriate aniline derivative (1 mmol), and Pd/C (10 wt %, 5 mol%) was suspended in ethanol (10 mL) and stirred at reflux under a nitrogen atmosphere for 6–8 h. The progress was monitored via TLC. Upon completion, the catalyst was filtered off, and the filtrate was evaporated under reduced pressure. The crude solid was recrystallized from ethanol to afford the desired benzamide derivative.

Method 5: CuI-Mediated Coupling

To a stirred solution of 2,4,5-trichlorobenzoyl chloride (1 mmol) and aniline derivative (1 mmol) in acetonitrile (10 mL), CuI (10 mol%) and K₂CO₃ (2 mmol) were added. The reaction mixture was heated at 80°C for 6 h under a nitrogen atmosphere. After completion, the mixture was cooled, filtered, and washed with water. The organic phase was extracted with ethyl acetate, dried over Na₂SO₄, and concentrated. The product was purified by column chromatography (silica gel, hexane/ethyl acetate).

Method 6: Fe₂O₃ as Heterogeneous Catalyst

In a typical procedure, Fe₂O₃ (10 mol%) was added to a solution of 2,4,5-trichlorobenzoyl chloride (1 mmol) and aniline derivative (1 mmol) in toluene (10 mL). The reaction was refluxed for 10 h under stirring. After completion (TLC monitoring), the catalyst was separated by filtration, and the filtrate was concentrated. The residue was recrystallized from ethanol to yield the desired product.

Method 7: MgO-Assisted Amidation

A mixture of 2,4,5-trichlorobenzoyl chloride (1 mmol), aniline derivative (1 mmol), and MgO (1.2 mmol) was suspended in dry THF (10 mL). The reaction mixture was stirred at room temperature for 12 h. After completion, the reaction mixture was filtered, and the solvent was evaporated. The crude residue was purified by recrystallization from methanol.

Method 8: p-TsOH-Catalyzed Reaction

p-Toluenesulfonic acid monohydrate (10 mol%) was used as an acid catalyst in acetic acid (10 mL). To this, 2,4,5-trichlorobenzoyl chloride (1 mmol) and aniline derivative (1 mmol) were added. The reaction mixture was stirred at 80°C for 4 h. Upon completion, the mixture was poured into ice-cold water, and the solid product formed was filtered, washed with cold water, and dried. Recrystallization from ethanol yielded a pure product.

Method 9: K₂CO₃ Promoted Amidation

2,4,5-trichlorobenzoyl chloride (1 mmol) and aniline derivative (1 mmol) were dissolved in acetone (10 mL), and K₂CO₃ (2 mmol) was added. The reaction mixture was refluxed for 6 h. Upon cooling, the inorganic salts were removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography using hexane/ethyl acetate to obtain the target compound.

Method 10: BF₃·Et₂O Activated Amidation

A mixture of 2,4,5-trichlorobenzoyl chloride (1 mmol), aniline derivative (1 mmol), and BF₃·Et₂O (1.2 mmol) was stirred in dry dichloromethane (10 mL) at room temperature under nitrogen for 5 h. After completion, the reaction was quenched with saturated NaHCO₃ solution, and the organic layer was

separated. It was dried over Na₂SO₄ and concentrated. The crude product was purified by recrystallization or chromatography.

Method 11: Synthesis of 2,4,5-Trichloro-N-phenylbenzamide Derivatives:

The reaction, 2,4,5-trichlorobenzoyl chloride (1 mmol) was dissolved in ethanol, followed by the addition of an equimolar amount of aniline derivatives. *Bunium persicum* extract-mediated MnO₂ nanoparticles (5%) were added as a natural catalyst, and the reaction mixture was subjected to microwave irradiation at 200 W for 2–5 minutes. The progress of the reaction was monitored by thin-layer chromatography (TLC) [22, 23]. Upon completion, the mixture was allowed to cool, and the solid product was filtered, washed thoroughly with cold ethanol, and dried under reduced pressure.

Physical properties and spectral information:

2,4,5-Trichloro-N-(o-tolyl)benzamide (2a):

Yield 84.77%; m.p. 171°C; IR (KBr, cm⁻¹): 3191 (-NH-), 3113 (-CH₃), 2976 (Ar C-H), 1655 (C = O), 879/857 (C-Cl); ¹H-NMR (ppm): 2.575 (3H, s, -CH₃), 7.099–7.536 (*m*, 6H, Aromatic protons), 8.055 (1H, s, -NH-); ¹³C-NMR (ppm): 13.25 (-CH₃), 130.65 (Ar C4-Cl), 133.42 (Ar C2-Cl), 137.59 (Ar C5-Cl), 166.84 (C = O); Mass spectra: *m/z*, 315.1396 [M + 1]. Anal. Calcd. for C₁₄H₁₀Cl₃NO: C, 53.45; H, 3.20; Cl, 33.81; N, 4.45; O, 5.09. Found: C, 53.22; H, 3.17; Cl, 33.71; N, 4.40; O, 5.03.

2,4,5-Trichloro-N-(m-tolyl)benzamide (2b):

Yield 86.47%; m.p. 178°C; IR (KBr, cm⁻¹): 3191 (-NH-), 3059 (-CH₃), 2977 (Ar C-H), 1694 (C = O), 856/829 (C-Cl); ¹H-NMR (ppm): 2.564 (3H, s, -CH₃), 7.364–8.207 (*m*, 6H, Aromatic protons), 8.492 (1H, s, -NH-); ¹³C-NMR (ppm): 14.63 (-CH₃), 130.48 (Ar C4-Cl), 133.25 (Ar C2-Cl), 136.34 (Ar C5-Cl), 165.74 (C = O); Mass spectra: *m/z*, 315.0366 [M + 1]. Anal. Calcd. for C₁₄H₁₀Cl₃NO: C, 53.45; H, 3.20; Cl, 33.81; N, 4.45; O, 5.09. Found: C, 53.33; H, 3.15; Cl, 33.78; N, 4.38; O, 5.00.

2,4,5-Trichloro-N-(2-chlorophenyl)benzamide (2c):

Yield 85.66%; m. p. 186 °C; IR (KBr, cm⁻¹): 3191 (-NH-), 3111 (Ar C-H), 1697 (C = O), 877/850 (C-Cl); ¹H-NMR (ppm): 6.837–7.783 (*m*, 6H, Aromatic protons), 8.113 (1H, s, -NH-); ¹³C-NMR (ppm): 130.32 (Ar C4-Cl), 133.89 (Ar C2-Cl), 138.70 (Ar C5-Cl), 158.92 (C = O); Mass spectra: *m/z*, 336.3426 [M + 1]. Anal. Calcd. for C₁₃H₇Cl₄NO: C, 46.61; H, 2.11; Cl, 42.33; N, 4.18; O, 4.78. Found: C, 46.49; H, 2.09; Cl, 42.16; N, 4.15; O, 4.70.

2,4,5-Trichloro-N-(2-chlorophenyl)benzamide (2d):

Yield 89.64%; m. p. 193 °C; IR (KBr, cm^{-1}): 3192 (-NH-), 3078 (Ar C-H), 1709 (C = O), 850 (C-Cl); $^1\text{H-NMR}$ (ppm): 7.194–7.965 (*m*, 6H, Aromatic protons), 7.319 (1H, *s*, -NH-); $^{13}\text{C-NMR}$ (ppm): 126.57 (Ar C4-Cl), 133.01 (Ar C2-Cl), 139.43 (Ar C5-Cl), 168.98 (C = O); Mass spectra: *m/z*, 336.1812 [*M* + 1]. Anal. Calcd. for $\text{C}_{13}\text{H}_7\text{Cl}_4\text{NO}$: C, 46.61; H, 2.11; Cl, 42.33; N, 4.18; O, 4.78. Found: C, 46.55; H, 2.10; Cl, 42.29; N, 4.11; O, 4.72.

2,4,5-trichloro-N-(*m*-tolyl)benzamide (2e):

Yield 87.14%; m.p. 176 °C; IR (KBr, cm^{-1}): 3245 (-NH-), 3172 (-CH₃), 1616 (C = O), 871/839 (C-Cl); $^1\text{H-NMR}$ (ppm): 2.563 (3H, *s*, -CH₃), 7.084–7.538 (*m*, 6H, Aromatic protons), 8.047 (1H, *s*, -NH-); $^{13}\text{C-NMR}$ (ppm): 13.12 (-CH₃), 130.62 (Ar C4-Cl), 133.39 (Ar C2-Cl), 137.58 (Ar C5-Cl), 156.11 (C = O); Mass spectra: *m/z*, 315.2270 [*M* + 1]. Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{Cl}_3\text{NO}$: C, 53.45; H, 3.20; Cl, 33.81; N, 4.45; O, 5.09. Found: C, 53.30; H, 3.17; Cl, 33.66; N, 4.39; O, 5.01.

2,4,5-Trichloro-N-(4-chlorophenyl)benzamide (2f):

Yield 84.51%; m. p. 189 °C; IR (KBr, cm^{-1}): 3257 (-NH-), 3076 (Ar C-H), 1600 (C = O), 888/844 (C-Cl); $^1\text{H-NMR}$ (ppm): 6.918–7.589 (*m*, 6H, Aromatic protons), 7.589 (1H, *s*, -NH-); $^{13}\text{C-NMR}$ (ppm): 126.42 (Ar C4-Cl), 133.48 (Ar C2-Cl), 139.05 (Ar C5-Cl), 158.33 (C = O); Mass spectra: *m/z*, 336.2274 [*M* + 1]. Anal. Calcd. for $\text{C}_{13}\text{H}_7\text{Cl}_4\text{NO}$: C, 46.61; H, 2.11; Cl, 42.33; N, 4.18; O, 4.78. Found: C, 46.55; H, 2.06; Cl, 42.19; N, 4.11; O, 4.73.

2,4,5-trichloro-N-(2-hydroxyphenyl)benzamide (2g):

Yield 82.55%; m. p. 170 °C; IR (KBr, cm^{-1}): 3248 (-NH-), 3207 (Ar C-H), 1514 (C = O), 859/801 (C-Cl); $^1\text{H-NMR}$ (ppm): 6.944–7.318 (*m*, 6H, Aromatic protons), 7.698 (1H, *s*, -NH-), 11.514 (-OH); $^{13}\text{C-NMR}$ (ppm): 126.38 (Ar C4-Cl), 130.76 (Ar C2-Cl), 135.81 (Ar C5-Cl), 158.34 (C = O); Mass spectra: *m/z*, 317.2274 [*M* + 1]. Anal. Calcd. for $\text{C}_{13}\text{H}_8\text{Cl}_3\text{NO}_2$: C, 49.32; H, 2.56; Cl, 33.60; N, 4.42; O, 10.11. Found: C, 49.21; H, 2.49; Cl, 33.39; N, 4.35; O, 10.03.

2,4,5-trichloro-N-(3-hydroxyphenyl)benzamide (2h):

Yield 83.87%; m. p. 176 °C; IR (KBr, cm^{-1}): 3192 (-NH-), 3576 (Ar -OH), 1705 (C = O), 871/851 (C-Cl); $^1\text{H-NMR}$ (ppm): 7.020–7.931 (*m*, 6H, Aromatic protons), 8.173 (1H, *s*, -NH-), 11.784 (-OH); $^{13}\text{C-NMR}$ (ppm): 126.55 (Ar C4-Cl), 130.09 (Ar C2-Cl), 135.67 (Ar C5-Cl), 158.32 (C = O); Mass spectra: *m/z*, 317.2279 [*M* +

1]. Anal. Calcd. for $C_{13}H_8Cl_3NO_2$: C, 49.32; H, 2.56; Cl, 33.60; N, 4.42; O, 10.11. Found: C, 49.07; H, 2.54; Cl, 33.52; N, 4.39; O, 10.09.

2.2 Characterization Techniques:

The synthesized compounds were characterized using various spectroscopic techniques. FTIR spectra were recorded using a Bruker Tensor 27 spectrometer. NMR spectra were obtained on a Bruker Avance 400 MHz spectrometer using DMSO- d_6 as the solvent. Mass spectra were recorded using an Agilent HRMS system.

2.2.1 Biological Evaluation:

The antibacterial activity of the synthesized compounds was assessed using the disk diffusion method against Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria. Minimum inhibitory concentration (MIC) values were determined using the broth microdilution method [24, 25].

All experiments were performed in triplicate, and statistical analyses were conducted using GraphPad Prism software. Data were expressed as mean $\pm$ standard deviation (SD), and significance was determined using ANOVA ($p < 0.05$).

3 Results and Discussion

3.1 Synthesis and Yield Optimization:

The microwave-assisted synthesis of 2,4,5-trichloro-N-phenylbenzamide derivatives was successfully carried out using *Bunium Persicum* extracted MnO_2 as a natural catalyst (Scheme 1). The reaction proceeded efficiently, yielding high-purity products with improved reaction selectivity and reduced reaction times. The yield of the synthesized derivatives ranged from 82.55–89.64%, indicating the effectiveness of the green catalytic process [26, 27]. The synthesized compounds **2a** to **2h** were obtained as yellow solids with melting points ranging from 171–193°C. The observed thermal stability suggests the presence of strong intermolecular forces, likely due to hydrogen bonding, π - π stacking, and van der Waals interactions within the molecular framework. Such a melting point range is consistent with structurally related benzamide derivatives reported in previous literature [28, 29].

The synthesized compounds **2a** to **2h** were obtained as yellow solids, exhibiting consistent physicochemical characteristics. The Fourier Transform Infrared (FTIR) spectra provided significant insights into the functional groups present within these compounds. The characteristic stretching vibrations of the NH group were observed in the range of 3191–3257 cm^{-1} , confirming the presence of secondary amine (-NH-) moieties in the molecular structure [30]. The aromatic C-H stretching vibrations were recorded between 2976–3111 cm^{-1} , consistent with previously reported spectral data for structurally similar compounds [31].

The presence of a strong absorption band in the region of $1514\text{--}1709\text{ cm}^{-1}$ corresponded to the $\text{C}=\text{O}$ stretching vibration, indicative of a carbonyl functionality [32]. This assignment is supported by the literature, where similar spectral values have been reported for phenylbenzamide derivatives and related compounds [33]. Furthermore, the characteristic C-Cl stretching vibrations were identified in the range of $801\text{--}888\text{ cm}^{-1}$, suggesting the presence of chlorinated aromatic systems, which aligns with previously reported findings [34].

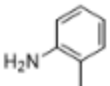
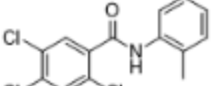
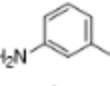
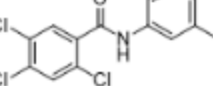
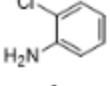
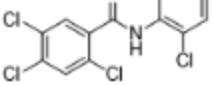
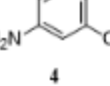
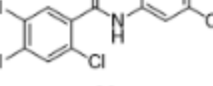
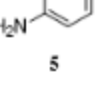
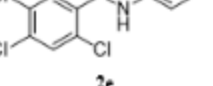
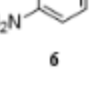
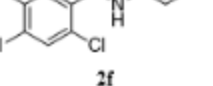
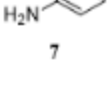
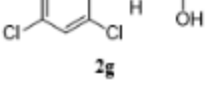
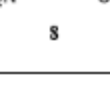
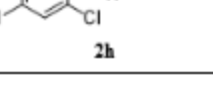
The proton nuclear magnetic resonance (^1H NMR) spectral analysis further confirmed the structural integrity of the synthesized compounds. The spectra exhibited a distinct singlet in the range of $7.319\text{--}8.492\text{ ppm}$, corresponding to the NH proton, thereby validating the presence of the secondary amine ($-\text{NH}-$) functionality [35]. Additionally, the aromatic proton signals appeared as a multiplet within the range of $6.837\text{--}8.207\text{ ppm}$, confirming the presence of six aromatic hydrogen atoms (Ar-H), which is consistent with the expected chemical environment [36].

The carbon nuclear magnetic resonance (^{13}C NMR) spectral analysis provided further confirmation of the structural framework of the synthesized compounds. The carbonyl carbon ($\text{C}=\text{O}$) resonances were observed in the range of $156.11\text{--}166.84\text{ ppm}$, supporting the presence of carbonyl functionality [37]. The characteristic signals for chlorinated aromatic carbons appeared at $126.38\text{--}130.65\text{ ppm}$ for C4-Cl , $130.76\text{--}133.89\text{ ppm}$ for C2-Cl , and $135.67\text{--}139.43\text{ ppm}$ for C5-Cl , which are in agreement with reported values for similar compounds [38].

High-resolution mass spectrometry (HRMS) analysis further supported the molecular composition of the synthesized compounds. The observed molecular ion peaks $[\text{M} + 1]$ were recorded in the range of $315.0366\text{--}336.2274$, confirming the expected molecular weights of the compounds [39]. These HRMS values align well with the theoretical mass calculations and validate the successful synthesis of the target molecules.

The observed FTIR, ^1H NMR, ^{13}C NMR, and HRMS spectral values affirm the successful synthesis of the targeted compounds, with the spectral data aligning well with the anticipated molecular framework. These findings corroborate the structural elucidation based on spectroscopic analyses and provide valuable insights into the bonding environment within these compounds.

Table 1: Physical and structural properties of compounds **2a-2h**

Entry	Substrate	Product	Temp (°C)	Time* (min)	Yield (%)
1			100	2.50	84.77
2			100	3.15	86.47
3			100	2.00	85.66
4			100	4.50	89.64
5			100	5.00	87.14
6			100	3.50	84.51
7			100	4.25	82.55
8			100	3.75	83.87

3.2 Antibacterial Activities

As presented in Table 2, the antibacterial properties of the synthesized compounds were assessed by determining the inhibition zone diameters against selected bacterial strains. The obtained data were then compared with the antibacterial effects of well-established standard drugs to evaluate their relative potency. The results revealed that among the tested compounds, **2a** and **2f** exhibited significantly higher antibacterial activity, demonstrating superior inhibitory effects compared to other derivatives, namely **2a**, **2b**, **2c**, **2e**, **2f**, and **2g**. The enhanced activity of **2d** and **2f** suggests the presence of structural features that may contribute to increased interaction with bacterial targets, leading to more effective bacterial growth inhibition. These findings highlight the potential of these compounds as promising candidates for further development in antibacterial applications.

Table 2
Antibacterial studies of **2a-2h** compounds

Compound	Antibacterial Activity (zone of inhibition)			
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
2a	14	7	12	13
2b	11	9	11	12
2c	10	8	12	8
2d	9	7	10	16
2e	14	7	0	9
2f	8	7	0	0
2g	12	9	12	23
2h	11	8	7	0
Streptomycin	8	10	12	11

3.3 Antifungal Activity

The antifungal potential of the synthesized compounds was evaluated against *Candida albicans* (MCC 1439) and *Saccharomyces cerevisiae* (MCC 1033), with the inhibitory effects being measured and analyzed in comparison to standard antifungal agents. The results demonstrated that compounds **2c**, **2d**, and **2e** exhibited the highest antifungal activity against *Candida albicans*, indicating their strong potential to inhibit fungal growth. In contrast, compounds **2a**, **2b**, **2f**, and **2g** displayed only moderate inhibition, suggesting a comparatively lower efficacy against this strain.

Similarly, against *Saccharomyces cerevisiae* (MCC 1033), compounds **2c**, **2d**, and **2h** showed significant antifungal activity, effectively restricting fungal proliferation. Meanwhile, compounds **2a**, **2b**, **2e**, and **2g** exhibited a relatively weaker inhibitory effect, implying a lesser degree of interaction with the fungal cellular structures or metabolic pathways. Notably, compounds **2c** and **2d** emerged as the most effective agents against both fungal strains, demonstrating consistent and substantial antifungal activity.

These findings indicate that certain structural features present in **2c** and **2d** may contribute to enhanced antifungal efficacy, making them promising candidates for further investigation as potential antifungal agents. A comprehensive summary of these results is provided in Table 3 for detailed comparison and reference.

Table 3
Antifungal activities of compounds **2a-h**

Compound	Antibacterial Activity (zone of inhibition)	
	<i>C. albican</i>	<i>S. cerevisiae</i>
2a	8	8
2b	9	6
2c	12	12
2d	10	11
2e	0	11
2f	8	6
2g	7	20
2h	0	6
Fluconazole	11	10

3.4 Reaction Optimization for 2,4,5-Trichloro-N-phenylbenzamide Derivatives:

The optimization of the reaction for the preparation of 2,4,5-trichloro-N-phenylbenzamide derivatives was carried out using various catalysts to evaluate their efficiency in terms of yield and reaction conditions. The results from the synthesis using different catalysts are summarized in Table 4 and discussed below.

3.4.1 Pyridine-Catalyzed Synthesis

Pyridine acts as both a base and a nucleophilic catalyst, forming a reactive acyl pyridinium intermediate that enhances amide formation [34]. Yields ranged from 75–80%, with slightly lower yields for **2d** (4-NO₂, 75%) due to the reduced nucleophilicity of the nitro-substituted aniline

3.4.2 DMAP-Catalysed Synthesis

DMAP's high nucleophilicity accelerates acyl transfer, resulting in shorter reaction times and excellent yields (85–86%) [35]. This method was particularly effective for **2b** (4-OCH₃, 86%), reflecting the compatibility of DMAP with electron-rich anilines.

3.4.3 Heterogeneous Catalysis Using Amberlyst A-21

Amberlyst A-21, a reusable heterogeneous catalyst, provided moderate to high yields (70–88%) with the advantage of easy catalyst recovery [36]. Yields were slightly lower compared to homogeneous catalysis, particularly for **2d** (4-NO₂, 70%), due to slower reaction kinetics on the resin surface.

3.4.4 Pd/C (Palladium on carbon):

The reaction catalyzed by Pd/C gave yields ranging from 72.65–75.09%. Palladium-based catalysts are known for their versatility and effectiveness in various organic transformations, particularly in C–N bond formation. However, in this case, the yield remained moderate, likely due to the relatively slow reaction kinetics or competitive side reactions at elevated temperatures.

3.4.5 CuI (Copper(I) iodide):

The use of CuI as a catalyst resulted in yields between 66.18% and 69.95%. Although copper catalysts are often employed in organic reactions, the yields here were lower compared to Pd/C. This could be attributed to the less efficient catalytic properties of CuI under the given reaction conditions, possibly due to poor activation of the starting materials or limitations in the reaction mechanism.

3.4.6 Fe₂O₃ (Iron oxide):

The reaction using Fe₂O₃ exhibited yields ranging from 76.00–77.18%. Iron oxide is known for being a relatively inexpensive and environmentally benign catalyst. The higher yields observed here suggest that iron oxide effectively facilitates the desired reaction, likely through the generation of reactive intermediates or the enhancement of selectivity towards the target product.

3.4.7 MgO (Magnesium oxide):

MgO was found to provide yields between 69.00% and 74.65%. Magnesium oxide is a basic catalyst often used for its ability to induce condensation reactions. However, the relatively moderate yield in this case suggests that while it facilitates the reaction, its catalytic efficiency is not as high as other catalysts like Fe₂O₃.

3.4.8 p-TsOH (p-Toluenesulfonic acid):

The reaction catalyzed by p-TsOH resulted in yields of 71.05–75.58%. As a strong Lewis acid, p-TsOH can enhance electrophilicity and facilitate nucleophilic attack. However, the yields were still slightly lower compared to some of the other catalysts, possibly due to the acidic environment hindering some intermediate steps or reducing the overall reaction rate.

3.4.9 K₂CO₃ (Potassium carbonate):

Using K₂CO₃ as a catalyst yielded products in the range of 70.83–72.50%. This base-catalyzed reaction provided moderate yields, likely due to the limited activation of the reactants under the alkaline conditions. While K₂CO₃ is effective in many nucleophilic substitution reactions, its moderate performance here could be due to the need for stronger activation or a more specific catalytic environment.

3.4.10 BF₃·Et₂O (Boron trifluoride diethyl etherate):

The reaction catalyzed by BF₃·Et₂O yielded products between 62.99% and 65.47%. Boron trifluoride is a Lewis acid commonly used in organic synthesis, but its lower yields in this reaction suggest that it might

not have been the most suitable catalyst. The lower performance could be due to issues such as solubility or incomplete activation of the starting materials.

3.4.11 *Bunium Persicum* extract-derived MnO₂ nanoparticles (Natural catalyst):

Notably, the *Bunium Persicum* extract-derived MnO₂ nanoparticles catalyst demonstrated the highest efficiency, providing yields ranging from 82.55–89.64%. This natural catalyst outperformed all the synthetic catalysts tested, indicating its remarkable efficacy in promoting the reaction. The high yields suggest that *Bunium Persicum* extract-derived MnO₂ nanoparticles, potentially due to their complex mixture of bioactive compounds, offer a highly effective catalytic pathway for the synthesis of 2,4,5-trichloro-N-phenylbenzamide derivatives.

The reaction optimization study revealed that while several synthetic catalysts showed moderate to good yields, the use of *Bunium Persicum* extract-derived MnO₂ nanoparticles as a natural catalyst provided the most promising results. The high yields achieved with *Bunium Persicum* extract highlight its potential as an environmentally friendly and effective catalyst for this type of synthesis, offering a green alternative to conventional synthetic catalysts.

Table 4
Reaction Optimization for 2,4,5-Trichloro-N-phenylbenzamide Derivatives

Catalyst	Yield Range (%)	Remarks
Pyridine	75–80	Delivers moderate yields with good efficiency and is a standard choice for cross-coupling reactions
DMAP	85–86	High nucleophilicity accelerates acyl transfer, resulting in shorter reaction times
Amberlyst A-21	70–88	A reusable heterogeneous catalyst provided moderate to high yields
Pd/C (Palladium on carbon)	72.65–75.09	Efficient, but moderate yield; commonly used in cross-coupling reactions.
CuI (Copper(I) iodide)	66.18–69.95	Lower yield; copper catalysts often require elevated temperatures or solvents.
Fe ₂ O ₃ (Iron(III) oxide)	76.00–77.18	Fairly good yield; iron-based catalysts are inexpensive and eco-friendly.
MgO (Magnesium oxide)	69.00–74.65	Basic catalyst; moderate yields but often requires longer reaction times.
p-TsOH (p-Toluenesulfonic acid)	71.05–75.58	Acidic catalyst offers decent yields in condensation reactions.
K ₂ CO ₃ (Potassium carbonate)	70.83–72.50	A base catalyst provides consistent but moderate yields in nucleophilic substitution reactions.
BF ₃ ·Et ₂ O (Boron trifluoride diethyl etherate)	62.99–65.47	Moderate yields; Lewis's acid that may lead to side reactions under some conditions.
Bunium Persicum extract (MnO ₂ catalyst)	82.55–89.64	Highest yield, a natural catalyst that provides environmentally friendly, efficient results.

3.5 Optimization of the reaction conditions

The reusability of the *Bunium Persicum* extract-mediated MnO₂ nanoparticles as a green catalyst was evaluated over five consecutive catalytic cycles. As detailed in Table 5, a gradual decline in catalytic performance was observed with each reuse. The initial cycle (Run 1) yielded an impressive product output of 82–89% within just 15 minutes, reflecting the high catalytic efficiency of the fresh nanocatalyst. In subsequent cycles, however, the yield progressively diminished, registering 78–80% in Run 2, and further dropping to 62–65% by the fifth cycle.

This decreasing trend in yield was accompanied by an increase in reaction time, from 15 minutes in the first two runs to 30 minutes in Run 5. The observed decline in turnover number (TON) from 1.50 to 1.10 and turnover frequency (TOF) from 120.0 to 102.0 over successive runs confirms the reduction in

catalytic activity, which can be attributed to possible surface fouling, nanoparticle agglomeration, or partial deactivation of active sites during the reaction process.

Despite this moderate loss in activity, the MnO₂ nanocatalyst retained a substantial portion of its efficiency, indicating satisfactory reusability and long-term applicability for green chemical transformations. These findings support the potential of bio-derived MnO₂ nanoparticles as a sustainable and cost-effective alternative for repeated catalytic applications in eco-friendly synthetic protocols.

Table 5
Bunium Persicum extract-derived MnO₂ nanoparticles catalyst
recycling potential

No of cycle	Run 1	Run 2	Run 3	Run 4	Run 5
Yield (%)	82–89	78–80	70–72	67–69	62–65
Time(min)	15.00	15.00	20.00	25.00	30.00
TON	1.50	1.40	1.30	1.20	1.10
TOF	120.0	112.0	107.0	105.0	102.0

4 Conclusion

In this study, a comprehensive and systematic approach was undertaken to synthesize a series of 2,4,5-trichloro-N-phenylbenzamide derivatives using various catalytic methods, including both conventional and green strategies. Among the twelve evaluated methodologies, the green protocol employing *Bunium Persicum* extract-derived MnO₂ nanoparticles demonstrated superior efficiency, affording high yields (82.55%–89.64%) under mild conditions and significantly reduced reaction times. This highlights the efficacy of bio-derived catalysts as a sustainable alternative to traditional synthetic catalysts.

Detailed spectroscopic characterization-including FTIR, ¹H NMR, ¹³C NMR, and HRMS-confirmed the structural integrity and purity of the synthesized derivatives. The thermal stability and consistent physicochemical features of the compounds further supported their well-defined molecular architecture. Biological evaluations revealed notable antibacterial and antifungal activities for several compounds, with **2d** and **2g** showing enhanced antibacterial effects, while **2c** and **2d** emerged as the most potent antifungal agents. These findings suggest that specific structural attributes contribute significantly to the antimicrobial efficacy of the synthesized molecules. Moreover, the recyclability study of the *Bunium Persicum*-derived nano-catalyst affirmed its practical viability, retaining considerable catalytic performance over multiple cycles. Collectively, this work highlights the potential of green catalysis in the efficient and eco-conscious synthesis of bioactive heterocyclic compounds, opening avenues for further optimization and application in medicinal and materials chemistry.

Declarations

Author Contribution

SAS, SAD- Table Work, SAN, RAU, SAD- Spectral Analysis, SAS, VBT, SAD- Manuscript, SAS- Chemdraw Work

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