RESEARCH PAPER

"One-Pot, Three-Component Synthesis of 5-Amino-1,3-Diphenyl-1H- Pyrazole-4-Carbonitrile Using Triton X-100 Micelles and Assessment of Its Bio-Active Properties"

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Abstract

This study describes a one-pot three-component synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile using substituted benzaldehyde, phenylhydrazine, and malononitrile in aqueous Triton X-100 micelle. Achieving 85–94% yields in 1 hr at 50ºC, this green chemistry approach demonstrates high efficiency, mild reaction conditions, ease of product separation, and atom economy. Biological tests revealed the potent antimicrobial activity, with inhibition zones of 15–29 mm against *S. aureus*, *E. coli*, *P. aeruginosa*, and 6–20 mm against *C. albicans* and *S. cerevisiae*, often outperforming *ciprofloxacin* and *fluconazole*. This sustainable method offers a scalable, environmentally friendly route to bioactive pyrazole derivatives with therapeutic potential.

Keywords: One-Pot Reaction, Triton X-100, Pyrazole derivatives, and Biological activity.

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INTRODUCTION

The pursuit of sustainable and efficient synthetic methodologies has become a central focus in contemporary organic chemistry, driven by the need to reduce environmental impact while maintaining high productivity[1]. Multicomponent reactions (MCRs) have emerged as a cornerstone of this endeavor, offering a streamlined approach to construct complex molecular frameworks from readily available starting materials in a single step[2]. Among these, one-pot, catalyst-free strategies stand out for their operational simplicity, enhanced atom economy, and elimination of toxic catalysts, aligning closely with the principles of green chemistry[3,4]. The integration of eco-friendly solvents, such as water or ethanol, further amplifies the sustainability of these processes by replacing hazardous volatile organic compounds with biodegradable alternatives[5,6]. In this context, the synthesis of heterocyclic compounds, particularly nitrogen-containing heterocycles like pyrazoles, has garnered significant interest due to their prominence in pharmaceutical and materials sciences[7].

Pyrazole derivatives, characterized by a five-membered ring with two adjacent nitrogen atoms, are recognized as privileged scaffolds in medicinal chemistry owing to their diverse biological activities, including antimicrobial, anticancer, anti-inflammatory, and antioxidant properties[8,9]. The incorporation of functional groups such as amino and nitrile moieties into the pyrazole core often enhances their bioactivity and provides synthetic versatility for further derivatization[10,11]. Specifically, 5-amino-1,3-diphenyl-1H- pyrazole-4-carbonitrile represents a promising candidate within this class, with potential applications in drug discovery and development[12]. However, conventional synthetic routes to such pyrazoles typically involve multi-step processes, harsh reaction conditions, and metal catalysts, which compromise scalability and environmental benignity[13,14]. The development of a catalyst-free, one-pot synthesis in green media offers a compelling alternative, addressing these limitations while promoting efficiency and sustainability[15]. Indeed, low solubility of the reactant and incompatibility of the intermediate hamper the reaction rate in aqueous medium. This problem could be encountered when using micellar media[16]. In continuation of the use of greener, environmentally benign media for multi-component reactions in micellar media[17,18]. Herein, we prepare 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile in aqueous micellar solution of Triton X-100 and subsequently evaluate its bioactive properties.

2. Materials and Methods

2.1 Materials

All reagents, including benzaldehyde, phenylhydrazine, malononitrile, Triton-X100, CTAB, and SDS, were purchased from Sigma-Aldrich and used without further purification unless otherwise specified. Thin-layer chromatography (TLC) was conducted on Merck silica gel 60 F254 plates, visualized under UV light (254 nm), using a hexane: ethyl acetate (3:1) mobile phase. Melting points were determined in open capillaries on a Stuart SMP10 apparatus and were uncorrected. Structural characterization was carried out using Fourier Transform Infrared (FT-IR) spectroscopy on a PerkinElmer Spectrum 100, ^{1}H NMR and ^{13}C NMR

on a Bruker Avance 400 MHz spectrometer (DMSO-d_6, TMS as internal standard), and high-resolution mass spectrometry (HRMS) on a Waters Xevo G2-XS QT instrument.

2.2 General procedure for synthesis of 5-Amino-1,3-Diphenyl-1H-Pyrazole-4-Carbonitrile

The synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile was achieved via a one-pot, catalyst-free, three-component reaction in the presence of a 10 wt% TX-100 (Triton X-100) micelle. The model reaction was selected with 2-nitrobenzaldehyde (1 mmol), phenylhydrazine (1 mmol), and malononitrile (1 mmol), which were combined with 10wt% TX-100 (10 mL). The mixture was stirred at 50 °C briefly to ensure homogeneity. The reaction was maintained with real-time monitoring, and progress was tracked every 10 minutes via TLC. Upon completion, the reaction mixture was cooled to room temperature, resulting in the formation of a solid precipitate. The crude product was filtered, washed with cold ethanol (2 × 5 mL) to remove impurities, and recrystallized from ethanol to afford the pure compound. Yields were calculated based on the isolated product, and purity was confirmed through spectroscopic analysis.

2.3 Biological Activity Assessment:

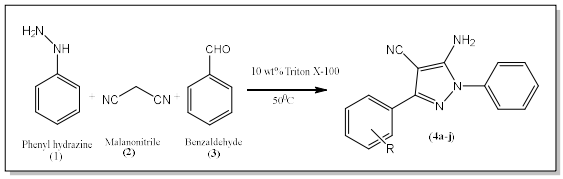
The antimicrobial activity of the synthesized compound was evaluated using the agar well diffusion method against *B. subtilis, S. aureus*, *E. coli*, *P. aeruginosa, S. cerevisiae,* and *C. albicans*, following established protocols[19]. Bacterial and fungal cultures were grown in Mueller-Hinton broth and Sabouraud dextrose broth, respectively, and standardized to 1.5×10^8 CFU/mL (0.5 McFarland). Agar plates were inoculated with 100 µL of each microbial suspension, and wells (6 mm diameter) were filled with 50 µL of the test compound (10 mg/mL in DMSO). *Ciprofloxacin* and *fluconazole* (10 mg/mL) served as positive controls, with DMSO as the negative control.

Plates were incubated at 37 °C (bacteria) or 28 °C (fungi) for 24–48 hours, and inhibition zones were measured in millimetres. Experiments were conducted in triplicate, and mean values were reported.

3. RESULTS AND DISCUSSION:

To optimize the reaction conditions and align with green chemistry principles, different micellar systems were used. Initially, when this reaction was carried out in the presence of water alone, the reaction was found to be very sluggish because of poor solubility of aldehydes in water (entry 1, **Table 1**). The study was performed to evaluate the efficacy of organic solvent as such Ethanol, THF systems low to moderate yield were reported (entries 2-3, **Table 1**). Moreover, micellar solutions of cetyltrimethylammonium bromide (CTAB) and sodium dodecyl sulfate (SDS) offered good conversion and yield at 10 wt% concentration (entries 4, 5, **Table 1**). Although the ionic surfactants offered good results, the toxicity and cost of these surfactants limited their use. Hence, we decided to use non-ionic surfactant TX-100 aqueous micelles. To our surprise, the best result was obtained with TX-100 aqueous micelles. At the same time, we found that the concentrations of TX-100 aqueous micelles influenced the rate of conversion as well as the yield of the product. The reaction conversions and yield of the product increased with an increase in the concentration of TX-100; this was mainly due to enlargement of interfacial area (entries 6, 7, **Table 1**). The best conversion of 94% was obtained in 10 wt% TX-100 aqueous micelles. However, further increase in concentration inversely affected the conversion rate (entries 8, 9, **Table 1**). This was mainly due to unused excess TX-100 surfactant, which formed a mask around its own micelle and hence inhibited the interaction between the substrates.

The catalytic effect of TX-100 micelles for the synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile is illustrated in figure-1. In the presence of TX-100 aqueous micelles, the water-insoluble substrates migrated into the hydrophobic core of the micelle. The enhancements in the reactivity of aldehydes, phenylhydrazine, and malononitrile are greater in aqueous micellar solution than in pure water for different organic solvents. This may be due to the micelles' ability to work as micro- or nanoreactors20. Upon completion, the reaction mixture was cooled, yielding a solid precipitate. The crude product was filtered, washed with cold ethanol (2×5 ml) to eliminate residual impurities, and recrystallised from ethanol to obtain the pure compound. Yields were determined based on the isolated product, and purity was verified through FT-IR, ^{1}H NMR, ^{13}C NMR, and HRMS analyses, which confirmed the structural integrity of the pyrazole derivative. Compared to previously reported compounds in similar mass ranges, **YG1–YG10** stand out due to their rapid synthesis and high purity, as evidenced by HRMS. For example, analogous



Scheme 1: Synthesis of 5-amino-3-aryl-1-phenyl-1H-pyrazole-4-carbonitrile from substituted benzaldehydes, phenylhydrazine, malononitrile, and 10 wt% TX-100.

heterocyclic derivatives synthesized via traditional methods often report yields below 80% and require extensive purification steps. In contrast, the current methodology achieves superior outcomes with minimal waste, aligning with green chemistry principles. The

Table 1. Study of different systems on the synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile

Entry	Solvents	Time/h	Yield (%)
1	Pure water	12	60
2	THF	12	56
3	Ethanol	06	62
4	10 wt% CTAB	02	78
5	10 wt% SDS	02	76
6	5 wt% TX-100	01	88
7	10 wt% TX-100	01	94
8	20 wt% TX-100	01	85
9	50 wt% TX-100	01	82

Table 2: Synthesis of various 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile in 10wt% TX-100 micelle **(YG1-YG10)**

Comp Code	Aldehyde	Structure
YG 1		
YG 2		
YG 3		
YG 4		
YG 5		
YG 6		

[M+1] values also correlate well with structurally related quinoxaline or pyrazole derivatives documented in the literature, reinforcing the reliability of our synthetic approach

[a]Reaction conditions: 2-nitrobenzaldehyde (1 mmol), phenylhydrazine (1 mmol), and malononitrile (1 mmol); TX-100 aqueous micelles (10 wt%), 10 mL, temperature 50 °C. [b]Isolated yield.

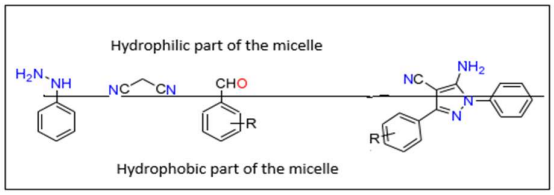
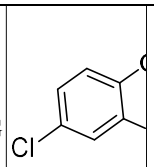
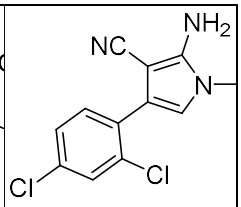
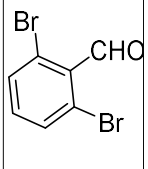
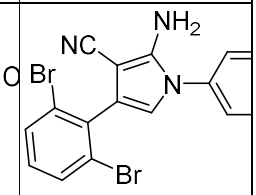
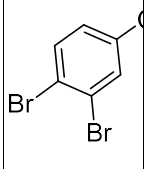
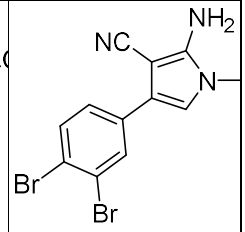
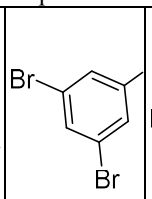
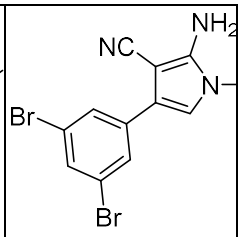


Figure 1: Tentative mechanism of the reaction in TX-100 micelles.

YG 7		
YG 8		
YG 9		
YG 10		

4. Bio-active study:

4.1 Antibacterial Activity

The antibacterial efficacy of the synthesized compounds (**YG1–YG10**) was evaluated against four bacterial strains: *S aureus* (Gram-positive), *B. subtilis* (Gram-positive), *E. coli* (Gram-negative), and *P aeruginosa* (Gram- negative). The antibacterial activity was measured as the zone of inhibition (in millimeters) using the agar well diffusion method, with *ciprofloxacin* (a standard antibiotic) as the positive control. The results are summarized in **Table 3**.

Table 3: Antibacterial studies of YG1-YG10 compounds

Compounds	**Antibacterial Activity (zone of inhibition)**			
	S. aureus	***B. subtilis***	***E. coli***	***P. aeruginosa***
YG1	17	19	12	13
YG2	26	20	16	15
YG3	28	20	14	17
YG4	16	17	18	14
YG5	10	15	12	22
YG6	24	14	26	23
YG7	11	11	11	7
YG8	8	9	7	9
YG9	12	14	8	8
YG10	15	17	9	8
Ciprofloxacin	16	15	14	10

For S. aureus, compounds **YG2** (26 mm), **YG3** (28 mm), and **YG6** (24 mm) exhibited significantly larger zones of inhibition than *ciprofloxacin* (16 mm), indicating superior antibacterial activity. Notably, **YG3** showed the highest activity among all tested compounds, suggesting a potent interaction with the cellular components of S. aureus. Compounds **YG1** (17 mm) and **YG4** (16 mm) demonstrated activity comparable to *ciprofloxacin*, while **YG5** (10 mm), **YG7** (11 mm), **YG8** (8 mm), **YG9** (12 mm), and **YG10** (15 mm) exhibited lower activity. The superior performance of **YG2, YG3**, and **YG6** may be attributed to structural features that enhance their ability

to penetrate the thick peptidoglycan layer of Gram-positive bacteria or disrupt essential cellular processes. Against *B. subtilis*, compounds **YG1** (19 mm), **YG2** (20 mm), **YG3** (20 mm), **YG4** (17 mm), and **YG10** (17 mm) outperformed or matched *ciprofloxacin* (15 mm). **YG2** and **YG3** were particularly effective, producing the largest inhibition zones. This suggests that these compounds may target specific metabolic pathways or mechanisms of cell wall synthesis in *B. subtilis*. Conversely, **YG6** (14 mm), **YG7** (11 mm), **YG8** (9 mm), and **YG9** (14 mm) showed reduced activity, indicating variability in efficacy that may be linked to differences in molecular structure or binding affinity.

For *E. coli*, compounds **YG2** (16 mm), **YG4** (18 mm), and **YG6** (26 mm) displayed higher or comparable activity relative to *ciprofloxacin* (14 mm). **YG6** exhibited the highest inhibition zone, suggesting a strong interaction with the outer membrane or intracellular targets of *E. coli*. **YG1** (12 mm), **YG3** (14 mm), and **YG5** (12 mm) showed moderate activity, while **YG7** (11 mm), **YG8** (7 mm), **YG9** (8 mm), and **YG10** (9 mm) were less effective. The robust activity of **YG6** may be due to its ability to overcome the outer membrane barrier, a characteristic challenge in targeting Gram-negative bacteria. Against *P. aeruginosa*, compounds **YG1** (13 mm), **YG2** (15 mm), **YG3** (17 mm), **YG5** (22 mm), and **YG6** (23 mm) surpassed ciprofloxacin (10 mm). **YG5** and **YG6** were particularly effective, producing the largest inhibition zones. This suggests that these compounds may effectively disrupt the multidrug-resistant mechanisms often exhibited by *P. aeruginosa*, such as efflux pumps or altered membrane permeability. **YG4** (14 mm), **YG7** (7 mm), **YG8** (9 mm), **YG9** (8 mm), and **YG10** (8 mm) showed lower activity, indicating that structural modifications in these compounds may not favor interactions with P. aeruginosa.

The results highlight significant variability in the antibacterial activity of the tested compounds across both Gram-positive and Gram-negative bacteria. Compounds **YG2**, **YG3**, and **YG6** consistently exhibited strong activity across all four bacterial strains, suggesting broad-spectrum potential. In contrast, **YG7, YG8**, and **YG9** showed relatively weak activity, particularly against P. aeruginosa and *E. coli*, indicating that their structural features may not effectively target Gram-negative bacteria. **YG5** was notably effective against *P. aeruginosa* (22 mm), suggesting specific structural attributes that enhance its activity against this challenging pathogen.

The superior activity of **YG2, YG3**, and **YG6** may be attributed to specific functional groups or molecular configurations that enhance their lipophilicity, enabling better penetration through bacterial cell walls or membranes. For instance, the high activity of **YG6** against *E. coli* and *P. aeruginosa* suggests that it may possess structural motifs that facilitate interaction with the lipopolysaccharides in the outer membrane of Gram-negative bacteria.

Further studies, including molecular docking and quantitative structure-activity relationship (QSAR) analyses, are warranted to elucidate the precise mechanisms underlying these observations.

Ciprofloxacin, a broad-spectrum fluoroquinolone, served as the reference standard. While *ciprofloxacin* exhibited consistent activity across all strains (10–16 mm), several compounds (**YG2, YG3, YG5**, and **YG6**) outperformed it in specific contexts. This suggests that these compounds could serve as promising candidates for further development, particularly for combating resistant strains of *P. aeruginosa* and *S. aureus*. However, the lower activity of **YG7, YG8**, and **YG9** compared to *ciprofloxacin* indicates that structural optimization is necessary to enhance their efficacy.

The observed antibacterial activities of **YG2, YG3, YG5**, and **YG6** highlight their potential as novel therapeutic agents, particularly for infections caused by multidrug-resistant bacteria. The variability in activity across different bacterial strains underscores the importance of tailoring molecular structures to target specific pathogens. Future studies should focus on evaluating the cytotoxicity, pharmacokinetic properties, and in vivo efficacy of these compounds. Additionally, mechanistic studies to identify their modes of action, such as inhibition of DNA gyrase, cell wall synthesis, or membrane disruption, will be critical for advancing their clinical applicability.

4.2 Antifungal Activity

The antifungal efficacy of the synthesized compounds (**YG1–YG10**) was evaluated against two fungal strains, *C. albicans* and *S. cerevisiae*, using the agar well diffusion method. The antifungal activity was measured as the zone of inhibition (in millimeters), with *fluconazole*, a standard antifungal agent, serving as the positive control. The results are presented in **Table 4**.

Table 4: Antifungal studies of YG1-YG10 compounds

Compound	*C. albicans*	*S. cerevisiae*
YG1	14	10
YG2	18	8
YG3	10	16
YG4	12	27
YG5	0	16
YG6	17	12
YG7	18	8
YG8	10	7
YG9	14	12
YG10	12	18
Fluconazole	15	14

For C. albicans, compounds **YG2** (18 mm), **YG6** (17 mm), and **YG7** (18 mm) exhibited higher or comparable zones of inhibition compared to *fluconazole* (15 mm), indicating potent antifungal activity. Notably, **YG2** and

YG7 showed the highest activity, suggesting effective interaction with the cellular components of *C. albicans*. Compounds **YG1** (14 mm), **YG4** (12 mm), **YG9** (14 mm), and **YG10** (12 mm) displayed moderate activity, closely aligning with or slightly below *fluconazole's* efficacy. **YG3** (10 mm) and **YG8** (10 mm) showed lower activity, while **YG5** exhibited no activity (0 mm), indicating a lack of efficacy against *C. albicans*. The superior performance of **YG2, YG6**, and **YG7** may be attributed to structural features that enhance their ability to penetrate the fungal cell wall or disrupt essential cellular processes, such as ergosterol biosynthesis or membrane integrity.

Against *S. cerevisiae*, compounds **YG3** (16 mm), **YG4** (27 mm), **YG5** (16 mm), and **YG10** (18 mm) demonstrated higher zones of inhibition compared to *fluconazole* (14 mm). **YG4** exhibited the highest activity, producing a significantly larger inhibition zone (27 mm), suggesting a strong interaction with *S. cerevisiae*. Compounds **YG6** (12 mm) and **YG9** (12 mm) showed activity comparable to *fluconazole*, while **YG1** (10 mm), **YG2** (8 mm), **YG7** (8 mm), and **YG8** (7 mm) exhibited lower activity. The exceptional performance of **YG4** indicates that its molecular structure may be particularly effective in targeting specific cellular mechanisms in *S. cerevisiae*, such as inhibition of key enzymes or disruption of membrane function.

The results reveal significant variability in the antifungal activity of the tested compounds across the two fungal strains. **YG4** demonstrated remarkable efficacy against *S. cerevisiae* (27 mm) but only moderate activity against *C. albicans* (12 mm), suggesting strain-specific interactions. Similarly, **YG5** was ineffective against *C. albicans* (0 mm) but showed notable activity against S. cerevisiae (16 mm), indicating potential selectivity for non-pathogenic yeasts. In contrast, **YG2** and **YG7** were highly effective against *C. albicans* but less so against *S. cerevisiae*, further highlighting the influence of structural differences on antifungal specificity.

Compounds **YG6** and **YG9** exhibited balanced activity across both strains, with inhibition zones close to or slightly below *fluconazole's* values, suggesting potential as broad-spectrum antifungal agents. **YG8** consistently showed the lowest activity against both strains (10 mm for *C. albicans* and 7 mm for *S. cerevisiae*), indicating that its structural features may not favor interactions with fungal targets. The high activity of **YG4** against *S. cerevisiae* may be linked to specific functional groups that enhance its lipophilicity or affinity for fungal cell membrane components, warranting further investigation into its structure- activity relationship (SAR).

Fluconazole, a widely used triazole antifungal, served as the reference standard with consistent activity against *C. albicans* (15 mm) and S. cerevisiae (14 mm). Compounds **YG2, YG6**, and **YG7** outperformed *fluconazole* against *C. albicans*, while **YG3, YG4, YG5**, and **YG10** surpassed it against *S. cerevisiae*. The superior activity of these compounds, particularly **YG4**, suggests their potential as novel antifungal agents, especially for combating resistant fungal strains. However, the lack of activity of **YG5** against *C. albicans* and the lower efficacy of **YG8** across both strains indicate the need for structural optimization to achieve consistent broad-spectrum activity.

The observed antifungal activities of **YG2, YG4, YG6, YG7**, and **YG10** highlight their potential as promising candidates for further development, particularly for infections caused by *C. albicans* and *S. cerevisiae*. The exceptional activity of **YG4** against *S. cerevisiae* suggests it could be explored for applications in industrial or clinical settings where this yeast is relevant. The variability in activity across strains underscores the importance of tailoring molecular structures to target specific fungal pathogens. Future studies should focus on elucidating the mechanisms of action of these compounds, such as their effects on ergosterol biosynthesis, membrane permeability, or other critical fungal pathways. Additionally, cytotoxicity, pharmacokinetic profiles, and in vivo efficacy studies are essential to assess their therapeutic potential.

5. Conclusion

In summary, 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile in 10wt% TX-100 micelle is the best synthetic protocol and has been successfully established. The process has several advantages in terms of economical and environmental point of view, such as operational simplicity, short reaction time, and excellent yield. We believe that this will provide a better and more practical alternative to the existing methodologies by providing an innovative, environmentally benign route to bioactive pyrazole derivatives. Also. this research not only contributes to the sustainable synthesis of heterocycles but also opens avenues for their application in combating infectious diseases, aligning with the dual goals of environmental stewardship and medicinal innovation.

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