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An efficient Iodine Catalyzed Microwave Assisted One-Pot Multicomponent Synthesis of 5-amino-1, 3-diphenyl-1H-pyrazole-4-carbonitrile and its derivatives.

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ABSTRACT
The development of eco-friendly, time-efficient, and high-yielding synthetic methodologies for heterocyclic scaffolds remains a central focus in modern organic chemistry. In this study, we report an efficient iodine-catalyzed, microwave-assisted one-pot multicomponent protocol for the synthesis of amino pyrazoles and their derivatives. The synergistic effect of iodine catalysis and microwave irradiation significantly enhances reaction rates, minimizes by-product formation, and affords the desired amino pyrazoles in excellent yields within short reaction times. The operational simplicity, environmental benignity, and atom-economy of the method highlight its superiority over conventional protocols. Structural elucidation of the synthesized derivatives was achieved through spectral (FT-IR, ^{1}H NMR, ^{13}C NMR, and Mass) analyses. Furthermore, the synthesized compounds, bearing diverse functional substitutions, demonstrate promising potential for **biological applications**, as pyrazole-based frameworks are well-documented for their antioxidant activity.

Keywords: Iodine catalyst; Microwave irradiation; One-pot synthesis; Multicomponent reaction (MCR); Amino pyrazoles; Heterocyclic compounds; Green chemistry.

I. INTRODUCTION

Nitrogen-containing heterocycles represent one of the most important classes of organic compounds due to their widespread occurrence in natural products, pharmaceuticals, agrochemicals, and materials science [1,2]. Among them, pyrazole and its derivatives have attracted considerable attention in medicinal chemistry because of their remarkable pharmacological activities such as antimicrobial, anticancer, anti-inflammatory, antiviral, analgesic, and antidiabetic properties [3–6]. Functionalized pyrazoles, especially those bearing amino and cyano substituents, are recognized as privileged scaffolds in drug discovery programs owing to their strong hydrogen-bonding potential and ability to interact with diverse biological targets [7].

In this context, 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile and its derivatives have emerged as versatile bioactive molecules with diverse applications. They not only display promising biological activities including antimicrobial, antioxidant, anticancer, and enzyme inhibitory effects [8,9] but also serve as useful synthetic intermediates in the preparation of dyes, agrochemicals, and heteroaryl-based pharmaceuticals [10]. Therefore, the development of efficient and environmentally benign methodologies for their synthesis remains an important area of research.

Multicomponent reactions (MCRs**)** provide a powerful platform for the rapid construction of such heterocyclic frameworks in a one-pot manner, starting from simple and readily available precursors [11,12]. Compared to traditional stepwise synthesis, MCRs offer significant advantages such as operational simplicity, atom economy, reduced reaction time, and the ability to generate structurally diverse libraries of compounds [13]. Despite these advantages, many reported methods for pyrazole-4-carbonitrile synthesis still rely on prolonged heating, use of organic solvents, expensive catalysts, or harsh conditions, which limit their sustainability and industrial applicability [14].

The principles of green chemistry demand the development of cost-effective, eco-friendly, and efficient catalytic systems [15]. In this regard, molecular iodine (I_2) has emerged as a highly attractive catalyst owing to its low cost, ready availability, non-toxicity, and versatile Lewis acid character [16,17]. Iodine catalysis has been successfully employed in a variety of organic transformations, offering mild reaction conditions, high selectivity, and avoiding the drawbacks of

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transition-metal catalysts such as toxicity and complicated work-up procedures [18].

Another important advancement in sustainable synthesis is the application of microwave-assisted organic synthesis (MAOS), which has revolutionized heterocyclic chemistry by drastically reducing reaction times, improving yields, and enabling cleaner processes compared to conventional thermal methods [19,20]. The synergy of microwave irradiation with iodine catalysis provides an excellent opportunity to accelerate multicomponent reactions, minimize side products, and enhance overall efficiency under solvent-free conditions [21].

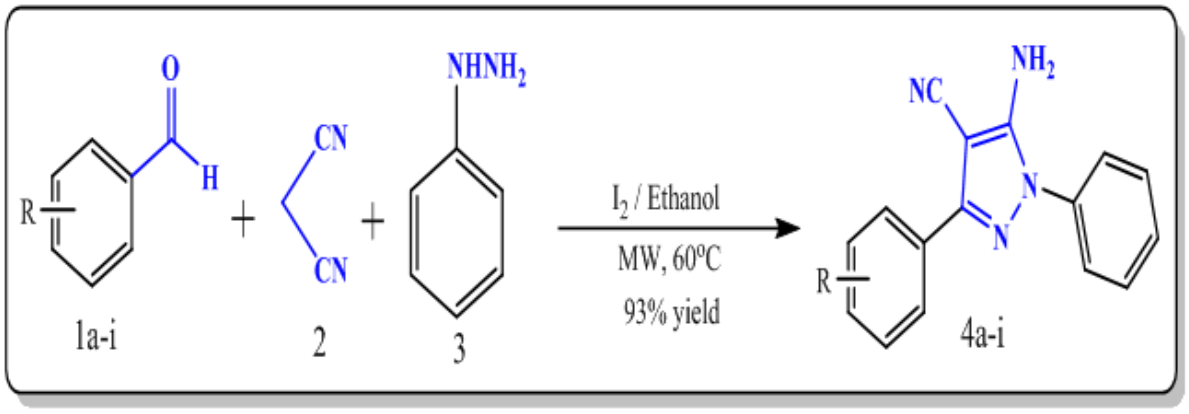
Considering these aspects, the present study focuses on an iodine-catalyzed, microwave-assisted one-pot multicomponent approach for the efficient synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile derivatives. This method integrates the benefits of green catalysis and microwave technology to achieve high yields, shorter reaction times, and environmentally benign conditions. The synthesized compounds were fully characterized using spectroscopic techniques (FT-IR, 1H NMR, 13C NMR, and mass spectrometry). Furthermore, due to the recognized pharmacological potential of pyrazole-based scaffolds, the obtained derivatives were evaluated for their antioxidant properties, highlighting their potential as lead candidates in drug discovery and development.

II. METHODS AND MATERIALS

All of the synthetic grade reagents and chemicals were obtained from Merck Chemicals and Sigma Aldrich India. As received, they were put to use. Using a Buchi melting point B-540 device, melting points were measured in open capillaries. Thin layer chromatography on silica plates seen with an iodine chamber was used to track the reaction.Chromatogen instruments were used to obtain 1H NMR spectra, with a reported chemical shift of δppm observed at 400 MHz. High-resolution ESI-MS (DFS) Thermo spectrometers (70 eV) were used to measure the mass spectra. Microwave irradiation was done in an MS2051DB DB1QILN microwave oven (2450 MHz, 1050 W) that had an Erlenmeyer flask attached.The primary instrument for the DPPH antioxidant assay is a UV-Vis spectrophotometer or microplate reader.

General procedure for the synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile and their derivatives

A mixture of substituted aldehyde (0.01 mol), phenyl hydrazine (0.01 mol), malononitrile (0.01 mol) and catalytic amount of Iodine in ethanol, were irradiate in microwave oven in an Erlenmeyer flask and irradiate until completion of the reaction. The reaction was monitored by TLC (ethyl acetate: n-hexane 8:2). The reaction mixture was poured in crushed ice and filtered it. Then crude product was collected and recrystallized in ethanol and dried. The entire product was characterized by physical constant and spectroscopic technique and compared with the standard method. The antioxidant potential of the synthesized compounds was evaluated using the DPPH assay at a concentration of 1 mg.



Scheme- 1

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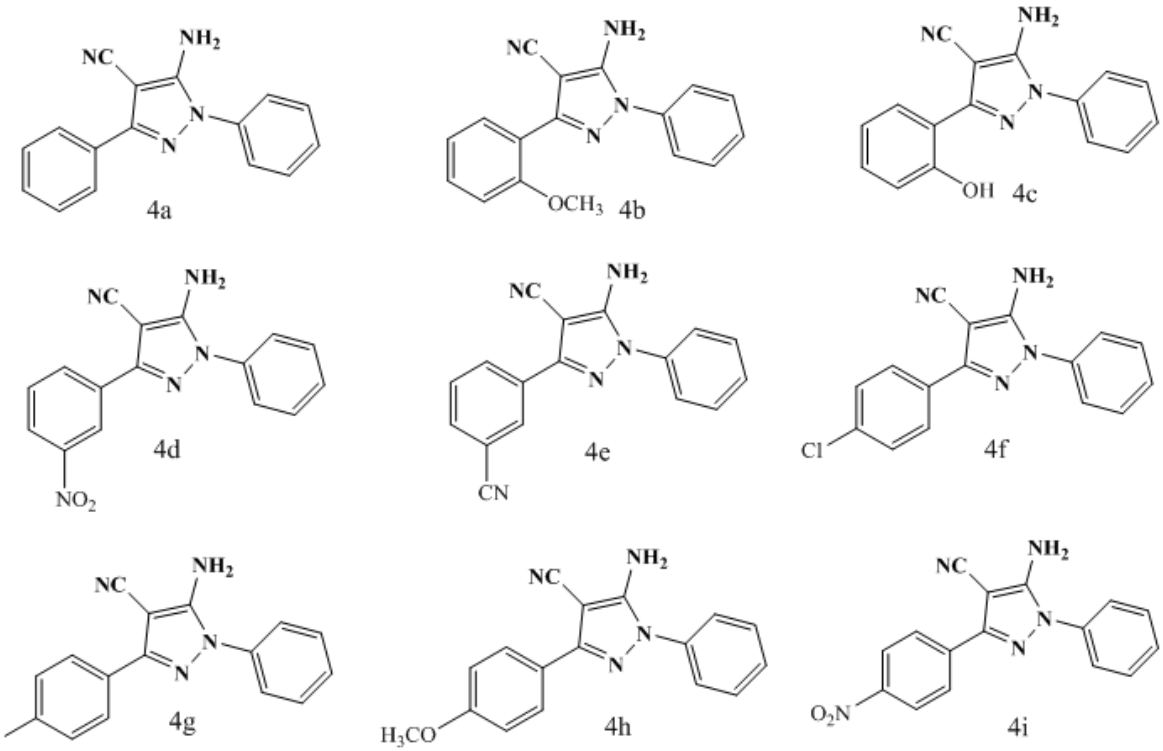

Fig.1 Synthesized derivatives of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile

Table1: Optimize the solvent for the synthesis of5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrileand its derivatives.

Entry	Solvent	Time(Min.)	%Yields
1	n-hexane	18	61
2	Toluene	15	67
3	DMF	13	73
4	DMSO	8.00	75
5	PEG-400	3.00	87
6	**Ethanol**	**1.00**	**93**

[a]Reaction condition: Substituted Arylaldehyde ,Malononitrile, and Phenylhydrizine in Iodine in Ethanol under Microwave irradiation.

III. RESULTS AND DISCUSSION:

Using substituted aryl aldehyde (1a-i), malononitrile (2), and phenyl hydrazine (3) in a catalytic amount of Iodine, we have attempted to establish a new synthetic methodology and one-pot synthesis for selectively 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile and their derivatives. Under microwave irradiation at 60^{o}C (Scheme-1), investigate this green technique and the reaction that yields the desired product (Table 3, 4a-i). n-hexane, Toluene, DMF, DMSO, PEG-400, and Ethanol are some examples of solvents that can be used to optimize reaction conditions. We looked at the reaction process in n-hexane and toluene, and after a longer period of time, the product was obtained with a lesser yield (Table 1, entry 1-2).The next solvent we tried was DMF and DMSO, which took longer to produce and had a lower yield (Table 1, entry 3-4). However, the yield product only slightly increased (to 73% and 75%, respectively), when we looked at the solvent with (Table 1, entry 5). At last, we looked at the outstanding Ethanol product, whose yield is 93% in a short amount of time (Table 1, entry 6). Iodine in ethanol is a green media for our model reaction since it is a less expensive, safe, and non-hazardous solvent when used as a medium for clean synthesis.

Here, we optimize the solvent that we

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choose for the Iodine in ethanol. The yield of the product is significantly impacted by this green technique. We found that the ethanol solvent is optimal for the sample reaction after experimenting with different solvent. With the help of this green protocol we has been developed a new strategy for the synthesis of amino pyrazole and their derivatives show in (Table 2, entry 4a-i).

Table2: Synthesized derivatives in Iodine and ethanol as a solvent under microwave irradiation(60°C/300W)

Entry	R	Time (Min. Sec)	% of yield	Melting point found(°C)	Melting Point [ref] Lit.
4a	-C6H5	7.30	83	160	159-160 [22]
4b	2-OCH3C6H4	5.30	86	131	130-132 [22]
4c	2-OHC6H5	8.00	90	161	160-162 [22]
4d	3-NO2C6H4	6.20	84	131	128-130 [22]
4e	3-CNC6H4	5.25	81	155	158-160 [22]
4f	4-ClC6H4	4.30	95	130	128-130 [22]
4g	4-CH3C6H4	6.00	87	120	117-118 [24]
4h	4-OCH3C6H4	7.15	89	105	106-108 [23]
4i	4-NO2C6H4	3.00	90	163	164-166 [23]

[a]Reaction condition: Substituted aryl aldehyde, Malononitrile, and phenylhydrazine Iodine under the Microwave irradiation.

The synthesized compounds 4a-i (Table 3) show the antioxidant potential was evaluated using the DPPH assay at a concentration of 1 mg. Among the tested samples, compound 4g exhibited the highest radical scavenging activity (66.4%), followed by compounds 4c (52.9%), 4h (46.77%), and 4i (45.85%). Moderate activity was observed for compounds 4a (27.6%) and 4b (32.1%), whereas compounds 4d, 4e, and 4f displayed poor to negligible antioxidant activity.

In comparison, the standard control ascorbic acid demonstrated the strongest activity (89.78%), confirming the reliability of the assay.

The structure–activity relationship (SAR) analysis indicates that substitution patterns play a significant role in modulating antioxidant potential. Electron-donating substituents and extended conjugation appear to enhance radical scavenging efficiency, as seen in compounds 4c, 4g, 4h, and 4i. On the other hand, the absence of such groups or steric hindrance may lead to reduced activity, explaining the weak antioxidant performance of 4d, 4e, and 4f. Thus, structural modifications favoring conjugation and electron donation are beneficial for improving antioxidant activity.

Table 3: % Antioxidant Potential Using DPPH Assay Method (Concentration: 1 mg)

No.	Sample	Antioxidant Potential (% Mean ± SD)
1	4a	27.6 ± 2.2
2	4b	32.1 ± 1.8
3	4c	52.9 ± 2.3
4	4d	28.6 ± 0.39
5	4e	0
6	4f	7.5 ± 0.52
7	4g	66.4 ± 2.6
8	4h	46.77 ± 2.65
9	4i	45.85 ± 2.63
10	+Ve Control (Ascorbic acid)	89.78 ± 3.23

All the data statistically analyzed and expressed as Mean ± SD (n = 3)

The entire derivatives was characterized by physical constant and spectral data.

4a.5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrileand:

(Molecular Formula: $C_{16}H_{12}N_4$)
Orange crystalline powder (85%) M.P. 161 °C.
IR (KBr, Cm-1): 3309.80, 2161.41, 2970.62, 1591.36, 1287.85.1HNMR (DMSO, 400MHz)

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δppm: 5.86 (s, Exch. D_2O, 2H), 7.21 (t, J=7.3 Hz, 1H (p-Ar-H)), 7.23 (t, J=7.3 Hz, 1H (p-Ar-H)), 7.31 (t, J=7.4, 2H (m-Ar-H)), 7.37 (t, J=7.4, 2H(m-Ar-H)), 7.39 (d, J=7.8, 2H(o-Ar-H), 7.41 (d, J=7.8, 2H(o-Ar-H)^{13}C NMR (DMSO,100.68 MHz): δppm: 113.20, 113.18, 120.39, 123.93, 126.40,128.71, 129.70, 131.92, 134.96, 142.08, 146.44, and 153.41. MS (m/z): 260.11 (M+)

4c.5-amino-3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbonitrile
(Molecular Formula: $C_{16}H_{12}N_4O$)
Pale yellow(89%) M.P. 160 ^oC.
IR (KBr, Cm-1): 3590, 3471,3346,3101,2356,2191,1606,1414,1225, 1191, 1109,1051.1HNMR (DMSO, 400MHz) δppm: 5.84 (s, Exch. D_2O, 2H)7.38 (d,J=7.8 2H (o-Ar-H)-N-phenyl ring), 7.30 (t, J=7.4 2H (m-Ar-H)-N-phenyl ring), 7.22 (t, J=7.31H (p-Ar-H)-N-phenyl ring),7.45 (d, J=7.9 1H (o-Ar-H)-OH-Phenyl ring)7.10 (dd, J=8.2, J=2.2 1H (m-Ar-H)-OH-Phenyl ring)6.95 (td, J=7.6, J=1.6 1H (p-Ar-H)-OH-Phenyl ring) 6.85 (dd, J=8.2, J=1.2 1H (m-Ar-H)-OH-Phenyl ring) 11-12 (s, 1H, (phenolic OH). ^{13}C NMR DMSO,100.68 MHz): δppm: 113.65, 115.70, 121.01, 122.35,126.40,130.05, 130.10, 131.25, 137.14, 146.65, 151.55, 154.05, and 157.55MS (m/z): 276.11 (M+)

4f.5-amino-3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile
(Molecular Formula: $C_{16}H_{12}ClN_4$)
White powder (88%) M.P. 161 ^oC
IR (KBr, Cm-1): 3445, 3319, 3068, 2361, 1593, 1421, 1292, 1253, 1132, and 1086. 1HNMR (DMSO, 400MHz) δppm: 5.89 (s, Exch. D_2O, 2H),7.45 (d, J=7.8 2H (o-Ar-H)-N-phenyl ring), 7.35 (t, J=7.4 2H (m-Ar-H)-N-phenyl ring), 7.27 (t, J=7.3 1H (p-Ar-H)-N-phenyl ring),7.36 (d, J=8.6 2H (o-Ar-H)-Cl-Phenyl ring)7.12 (d, J=8.6, 2H (m-Ar-H)-Cl-Phenyl ring). ^{13}C NMR (DMSO,100.68 MHz):: δppm:112.12, 113.34, 120.99, 129.11, 129.13, 129.77, 134.41, ,136.39, 144.37,150.28,155.22. MS (m/z): 294 (M+).

IV. CONCLUSION:

The present study demonstrates an efficient and sustainable protocol for the iodine-catalyzed microwave-assisted one-pot multicomponent synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile and its derivatives. The methodology offers several advantages, including shorter reaction times, high atom economy, excellent yields, and operational simplicity, highlighting the utility of iodine as an eco-friendly and cost-effective catalyst. The application of microwave irradiation further enhanced the reaction efficiency by providing uniform heating, reducing energy consumption, and eliminating the need for harsh reaction conditions.

The synthesized amino pyrazoles derivatives were evaluated for their antioxidant potential**,** and the results indicated significant free radical scavenging activity, suggesting that the structural features of the compounds play a vital role in their bioactivity. This emphasizes the relevance of the developed protocol not only in the field of green chemistry and heterocyclic synthesis but also in the design of biologically active molecules with therapeutic potential

Thus, the present work provides a practical, sustainable, and biologically relevant synthetic strategy, paving the way for the development of novel pyrazoles-based antioxidant agents. Future investigations may focus on exploring the pharmacological profiles of these derivatives to establish their potential as promising candidates in medicinal chemistry and drug discovery**.**

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