Microwave assisted facile synthesis and anticancer evaluation of new substituted-3-methyl-1- substituted phenyl-1H-pyrazole

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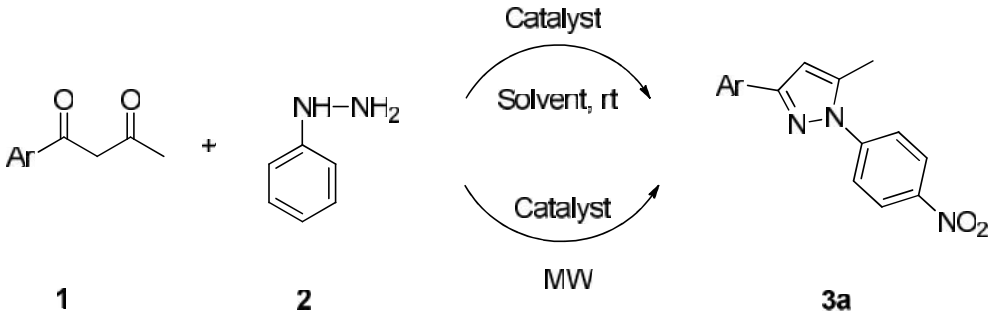
- **Abstract:**
- Herewith, we report the design and synthesis of a series of the cyclocondensation of the substituted hydrazine derivatives with the substituted 1,3-dicarbonyl compound is a simple and rapid approach to obtain substituted pyrazoles (**3a-h**). This compound was obtained by using catalyst and water as solvent under microwave irradiation for about 2-4 min (800 W) at 80^0C, to get structural prerequisite indispensable for anticonvulsant activity. The reaction was perform in mild reaction condition, good to excellent yields, easy workup and easily available starting material make the reaction attractive for the preparation of compounds **3a-h**.

- **Keywords:** Pyrazole, 1,3-dicarbonyl compound; Microwave irradiation;

- **1. INTRODUCTION**

The pyrazole and its derivatives are the important class of nitrogen containing heterocyclic compounds. Recently, substitute pyrazole derivatives are significant interest due to their role in the medicinal and agriculture industries [1-4]. Pyrazolones, which are close structure analogues of pyrazoles, are also associated with broad spectrum of biological activities [5-9]. The various methods have been developed in order to the synthesis of the substituted pyrazole derivatives. Hydrazines and 1,3-diketones are most commonly used in the synthesis of substituted pyrazole compounds [10-12]. The presence of the pyrazole nucleolus in separate construction directions to a diversified recourse in different areas such as technology, medicine, and farming inhibitors of protein glycation [13,14]. Nowadays pyrazole systems as biomolecules have attached more addition due to their exciting

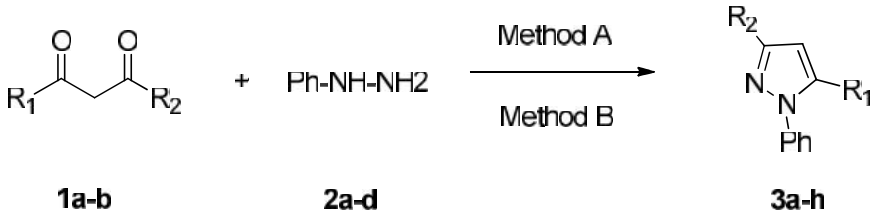
Scheme 1. Screening of model reaction of 5-methyl-1-(4-nitrophenyl)-3-phenyl-1H-pyrazole **(3a)**



Reaction condition (3a): 1-phenylbutane-1,3-dione (**1**) (1 mmol), phenylhydrazine (**2**) (1 mmol), Catalyst (10 mmol), Solvent, rt, 2-6 h**,** / Microwave 2-8 min.

[b]Isolated yield

Scheme 2. Synthesis of substituted-3-methyl-1- substituted phenyl-1H-pyrazole



Reaction condition (3a-h): Method A: Compound (**1a-b**) (1 mmol), Compound (**2a-d**) (1 mmol), Water, ZnO, Catalyst (10 mmol), Microwave, 2-4 min.

Method B: Compound (**1a-b**) (1 mmol), Compound (**2a-d**) (1 mmol), Water, Catalyst (10 mmol), ZnO, rt, 3-4 h**.**

[b]Isolated yield

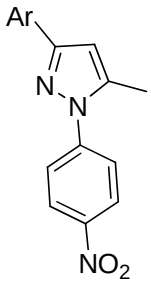
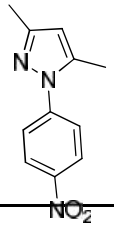
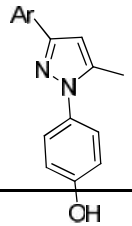
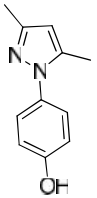
Table 1 Screening of base, solvents, reaction time, and yield for the synthesis (**3**)[a]

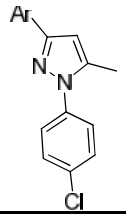
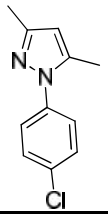
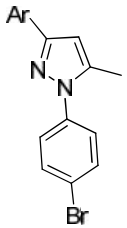
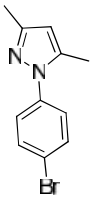
Entry	Base	Solvent	Conventional method Time (h)	Microwave method Time (Min.)	Yield[b] (%) Conventional method	Yield[b] (%) Microwave method
1	ZnO	Ethanol	4	4	80	94
2	ZnO	Methanol	4	3	85	95
3	ZnO	Water	2	2	90	98
4	ZnO	DMF	4	4	85	94
5	ZnO	Toluene	5	5	86	96
6	CH_3COONa	Ethanol	6	4	82	90
7	CH_3COONa	Methanol	6	5	82	92
8	CH_3COONa	Water	3	3	85	94
9	CH_3COONa	DMF	6	5	80	88
10	CH_3COONa	Toluene	6	6	80	90
11	K_2CO_3	Ethanol	5	6	74	86
12	K_2CO_3	Methanol	4	7	72	86
13	K_2CO_3	Water	3	4	80	92
14	K_2CO_3	DMF	5	8	70	84
15	K_2CO_3	Toluene	5	7	70	85

[a] All the reactions were carried out in equimolar amounts of each compounds in 1 mL of solvent

[b] Isolated yield.

Table 2 Physical data of the synthesized compounds (**3a-h**) [a]

Compounds	Product	Conventional method Time (h)	Microwave method Time (Min.)	Yield[b] (%) Conventional method	Yield[b] (%) Microwave method	Melting point (°C)
3a		2	3	88	96	160-162
3b		2	3	86	96	170-172
3c		3	3	88	96	253-255
3d		3	3	90	98	235-237

Compounds	Product	Conventional method Time (h)	Microwave method Time (Min.)	Yield[b] (%) Conventional method	Yield[b] (%) Microwave method	Melting point (°C)
3e		3	3	88	96	210-212
3f		3	2	90	96	145-147
3g		3	2	88	96	176-178
3h		4	4	90	98	155-157

Reaction condition (3a-h): Method A: Compound (**1a-b**) (1 mmol), Compound (**2a-d**) (1 mmol), Water, ZnO, Catalyst (10 mmol), Microwave, 3-4 min.

Method B: Compound (**1a-b**) (1 mmol), Compound (**2a-d**) (1 mmol), Water, ZnO (10 mmol), rt, 2-4 h**.**

[b]Isolated yield

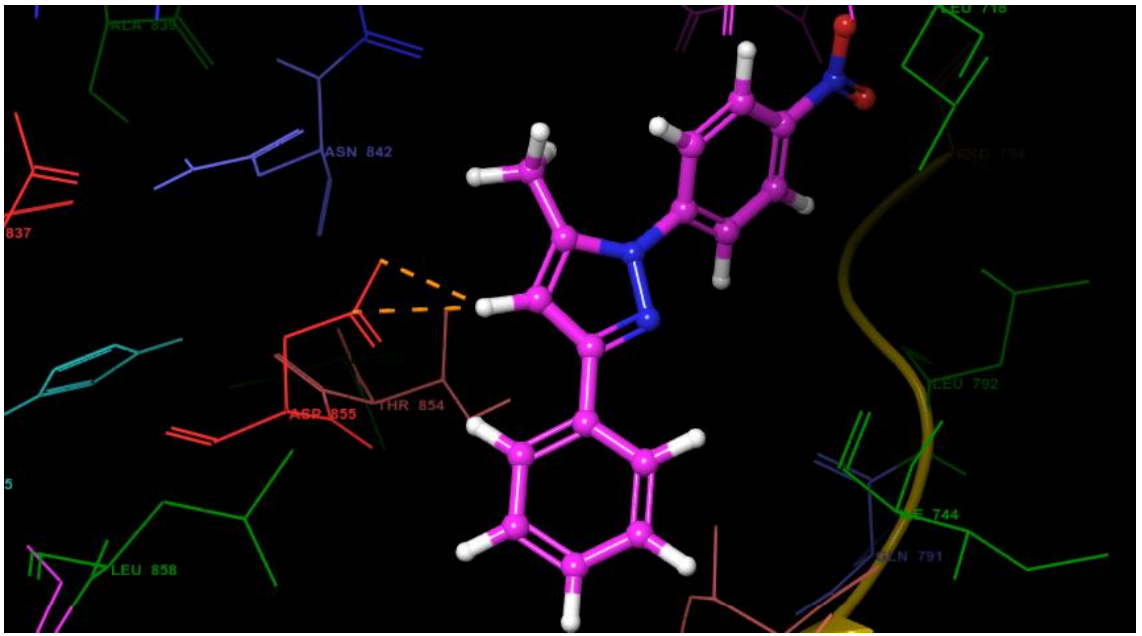


Figure 1.

The compound docked was found to attach at the binding pocket of EGFR enzyme (PDB Id: 3w33). Compound showed hydrogen bonding interactions with amino acids ASP 855 and THR 854 shown in the Figure 1.

2. RESULT AND DISCUSSION

2.1. Chemistry

- We have been synthesized and screening of model reaction of of 5-methyl-1-(4-nitrophenyl)-3-phenyl-1H-pyrazole **(3a)** (Scheme 1, Table 1) and synthesis of substituted-3-methyl-1-substituted phenyl-1H-pyrazole derivatives (Scheme 2, Table 2) under microwave irradiation as well as conventional method. We would like to mention here we find out best result as a zinc oxide (ZnO) good base and water good solvent. However, the MW reaction provided cleaner reaction, short reaction time, and the products were only required to be washed with ice-cold water. The yields were good to excellent.

2.2. Effect of catalyst and solvents

- A variety of catalysts were screened under microwave irradiation in order to validate the right choice and the results are shown in Table 1. We have justified the influence of the catalyst; the reaction was carried out in the presence of catalyst zinc oxide wherein a maximum yield of 98% could be obtained (Table 1, Entry 3). It was further observed that the yield of the reaction hardly improved in the presence of other like sodium acetate and potassium carbonate catalysts (Table 1, Entries 8 and 13) in presence of water, whereas the use of zinc oxide as catalyst significantly improved the yield to 98% (Table 1, Entry 3) by MW method. Hence zinc oxide under microwave irradiation was selected for our further studies.

3. MATERIAL AND METHODS

3.1. Experimental:

Method A: Microwave-assisted synthesis:

In a 100 ml round bottom flask, the compound substituted 1-phenylbutane-1,3-dione (1 mmol), phenylhydrazine (1 mmol), ZnO (10 mmol) with solvent was added and this mixture subjected to MW irradiation (800 W), for 2-4 min. The progress of the reaction was monitored by TLC (20% n-hexane: ethyl acetate). After completion of the reaction, the reaction mixture was concentrated *in vacuo*. The residue was washed with water (2×10 ml) to afford the crude product. The crude product was recrystallized using ethanol as solvent to give yield in the range 96-98 %.

Method B: Conventional synthesis:

In a 100 ml round bottom flask, the compound substituted 1-phenylbutane-1,3-dione (1 mmol), phenylhydrazine (1 mmol), ZnO (10 mmol), with solvent was added and this mixture subjected to stirred for 2-4 h at room temperature. The progress of the reaction was monitored by TLC (20% n-hexane: ethyl acetate). After completion of the reaction, the reaction mixture was concentrated *in vacuo*. The residue was washed with water (2×10 ml) to afford the crude product. The crude product was recrystallized using ethanol as solvent to give yield in the range 86-90 %.

5-methyl-1-(4-nitrophenyl)-3-phenyl-1H-pyrazole (3a)

Yellow solid. Yield 96%, mp 160-162 °C; ES-MS m/z (%): 279.10, ^{1}H NMR (500 MHz, DMSO-*d6*): δ 8.31 – 8.29 (m, 2H), 7.87 – 7.85 (m, 2H), 7.82 – 7.48 (m, 5H), 6.73 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*): δ=150.45, 146.74, 145.20, 138.76, 133.72, 128.78, 128.64, 125.93, 124.69, 123.81, 105.65, 13.69.

3,5-dimethyl-1-(4-nitrophenyl)-1H-pyrazole (3b)

Yellow solid. Yield 96%, mp 170-172 °C; ES-MS m/z (%): 217.09, ^{1}H NMR (500 MHz, DMSO-*d6*): δ 8.31 – 8.25 (m, 2H), 7.81 – 7.75 (m, 2H), 6.00 (s, 1H), 2.30 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*): δ=149.43, 146.74, 144.32, 139.13, 124.69, 123.73, 107.37, 13.69, 13.61.

4-(5-methyl-3-phenyl-1H-pyrazol-1-yl)phenol (3c)

Yellow solid. Yield 96%, mp 253-255 °C; ES-MS m/z (%): 250.11, ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.87–7.85 (m, 2H), 7.61–7.59 (m, 2H), 7.49–7.42 (m, 5H), 6.73 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*): δ=156.73, 150.45, 138.75, 133.89, 133.72, 128.78, 128.64, 126.01, 125.93, 115.85, 105.65, 13.69.

4. CONCLUSION

- In conclusion, we have successfully developed an easy access to a new series of substituted-3-methyl-1- substituted phenyl-1H-pyrazole derivatives by MW irradiation as well as conventional method. The mild reaction conditions, stirring at reflux temperature, good to excellent yields, easy workup, and easily available substrates make the reactions attractive for the preparation of compounds **3a-h**. Efforts towards the synthesis of other important drug molecules with substituted-3-methyl-1-substituted phenyl-1H-pyrazole derivative by MW irradiation as well as conventional method are ongoing in our laboratory. Also work is in progress to obtain biological activity such as antibacterial, antifungal and anticancer of these important compounds.

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Thank You