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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 °C, to get structural prerequisite indispensable for anticancer 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 pharmacological properties this heterocyclic can be traced in an enumerate of well-established medicate belonging to separate categories with drives curative activities [15,16].

Pyrazole and their analogues represent a class of important five-member aza-heterocycles occurring in many natural product and synthetic molecules along with a wild inhibitors, HIV-1 reverse transcriptase inhibitors and protein kinase inhibitors range of biological activity, such as cyclooxygenase-2 [17–19]. Synthesis of substituted pyrazole derivatives having one of the *N*-atom substituted with biologically active moieties such as acylamide, aryl/sulfonyl, benzene sulfonamide

etc. are reported [20]. A series of 1,3,5-trisubstituted pyrazoline(s) bearing *N*1-isonicotinoyl were synthesized from chalcones and hydrazides using catalytic glacial acetic acid [21] and pyridine [22]. Recently we notice that a rapid synthesis of similar pyrazoline derivatives from chalcones were reported with microwave radiations [23] as well as ultrasonification [24] method.

In continuation of our previous work, [25–33], we have developed the new protocol for the microwave-assisted as well as conventional facile synthesis, of new substituted-3-methyl-1-substituted phenyl-1H-pyrazole derivatives. The substituted 1-phenylbutane-1,3-dione was then subjected to a condensation with the phenylhydrazine which was synthesized to provide new series of target compounds **3a-h**. Target compounds were synthesized by microwave irradiation (MW) as well as conventional method at room temperature stirring with zinc oxide and water.

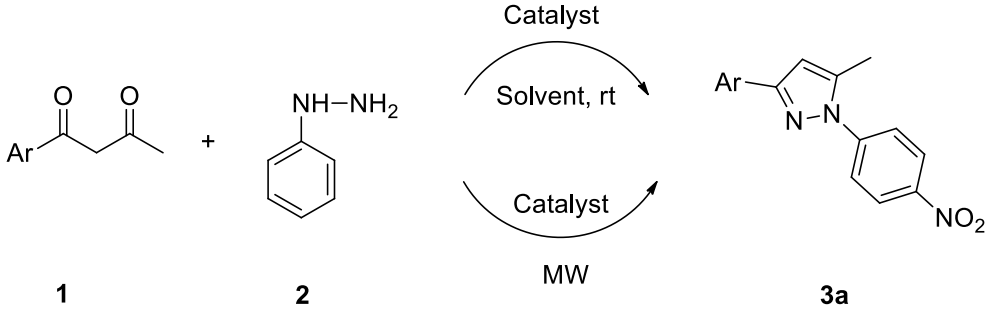
2. Result and Discussion

2.1. Chemistry

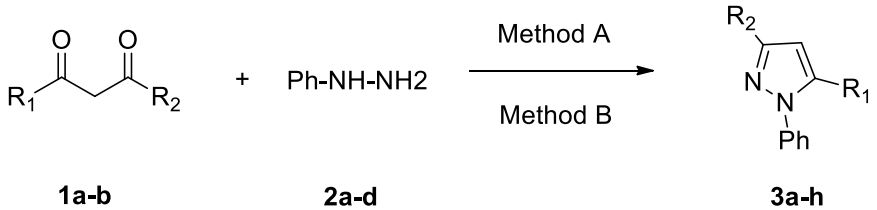
We have been synthesized and screening of model reaction of of 5-methyl-1-(4-nitrophenyl)-3-phenyl-1H-pyrazole **(3a)** (Scheme 1, Table 1) and synthesis of substituted-3-methyl-1- substituted phenyl-1H-pyrazole derivatives (Scheme 2, Table 2) under microwave irradiation as well as conventional method. 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.



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.

We synthesized and screening of model reaction under microwave irradiation and conventional method of the compound of 5-methyl-1-(4-nitrophenyl)-3-phenyl-1H-pyrazole **(3a)** (Scheme 1, Table 1). The reaction in which the compound **1** (1 mmol), compound **2** (1 mmol), various catalyst and various solvents were selected as a model reaction to optimize the reaction conditions. In terms of the effect of solvents and catalyst on the condensation reaction zinc oxide was found to be the better catalyst and water was found to be the best solvent for the reaction (Table 1, entry 3); other solvents, including ethanol, methanol, N,N- dimethylformamide (DMF) and toluene were less efficient (Table 1, entries 1–2, 4–7, 9–12 and 14-15). Rest all of these yields were generally was the best among these solvents (Table 1, entries 3, 8 and 13). To increase the efficiency of the condensation reaction, the effects of different catalyst were investigated (Table 1, entries 1–15). Zinc oxide exhibited the best performance with used solvents and gave better yield. Sodium acetate and potassium carbonate gave lower yields with other solvents, but gave better yield in water as a solvent (Table 1, entries 8 and 13). All the reactions were carried out in equimolar amounts of each compound in 1 mL of solvent. Among these reactions same amounts of the solvent, namely 1 mL of water turned out to be the best choice with yields of 98%, 94% and 92% (Table 1, entries 3, 8 and 13).

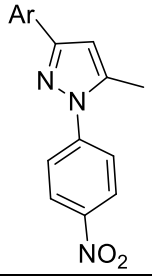
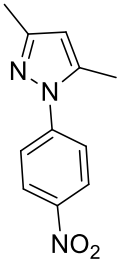
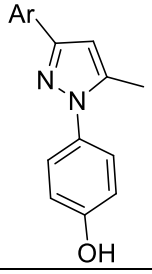
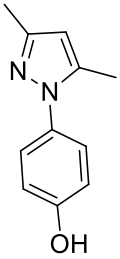
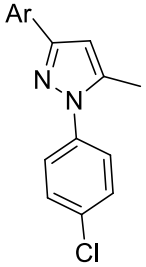
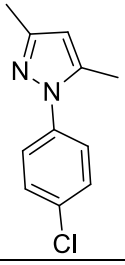
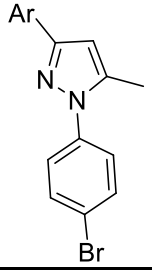
Table 1. Screening of base, solvents, reaction time, and yield for the synthesis (**3**) [a].

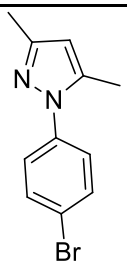
9	Base	Solvent	Conventional Method Time (h)	Microwave Method Time (Min.)	Yield [b] (%) Conventional Method	Yield [b] (%) Microwave Method
1	ZnO	Ethanol	4	4	80	94
2	ZnO	Methanol	4	3	85	95
3	ZnO	Water	2	2	90	98
4	ZnO	DMF	4	4	85	94
5	ZnO	Toluene	5	5	86	96
6	CH_3COONa	Ethanol	6	4	82	90
7	CH_3COONa	Methanol	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
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.

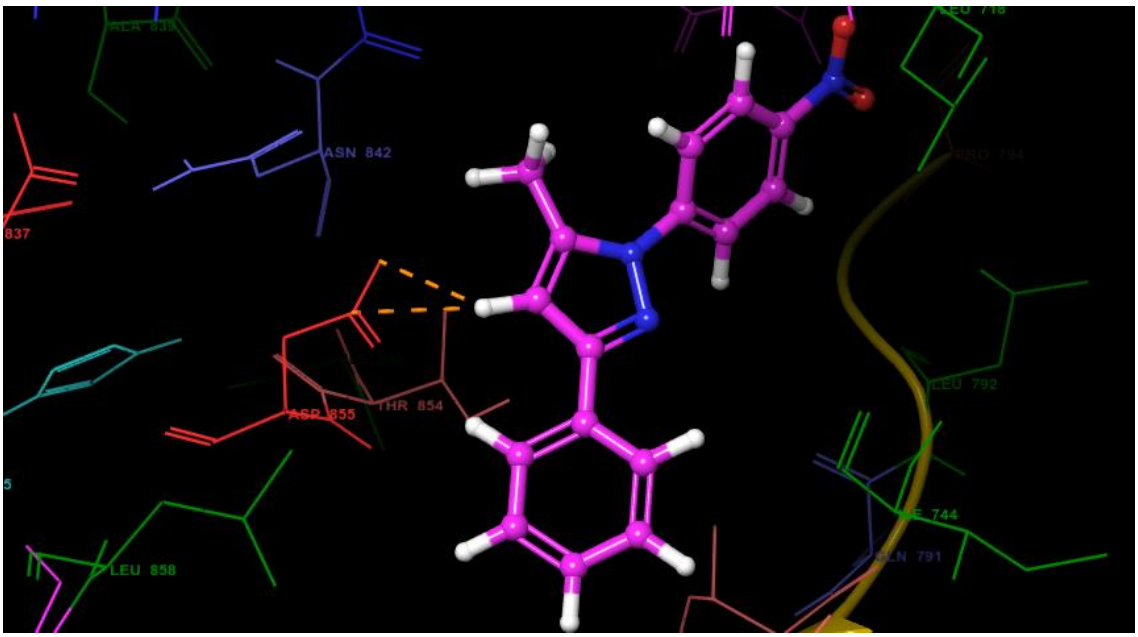


Figure 1. The compound docked was found to attach at the binding pocket of EGFR enzyme (PDB Id: 3w33). Compound showed hydrogen bonding interactions with amino acids ASP 855 and THR 854 shown in the Figure 1.

2.3. Molecular Docking Study

Molecular docking study was carried out using EGFR kinase enzyme of Human (PDB ID: 3W33). Molecular docking was performed using Autodock vina. The crystal structures of Human EGFR kinase in complex with compound 19b were picked up from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb/explore/explore.do?structureId=3W33) (PDB code: 3W33). The X-raycrystal structure of the EGFR enzyme (PDB code 3W33) was obtained from the protein data bank and prepared by removing water molecules and minimized usingAmber94 force field with Chimera modeler. The total number of loops was set to 1000 toensure maximum minimization of the protein. The minimization was terminated when the energy converged or the route mean square deviation (RMSD) reached a maximum cutoff of 0.30 Å. Ramachandran plot at was set to check the total number of disallowed residues. The minimized protein was converted to PDBQT format applicable for docking process. By means of targeted docking process, the minimized protein was then subjected to grid generation through Autodock by creating a configuration text file. All the ligands were drawn using Marvin sketch were converted to PDBQT format by using Babel. Finally, the configuration text file, ligands and the protein were collected in a singlefile with the vina extension and through the command prompt the docking procedure was processed. The results for each input ligand was saved as a text file consisting of docking scores and RMSD values of each ligand conformation which was used for analysis of data. The output file was then converted into Pymol readable extension of image saving.

We have also synthesized and screening of model reaction under conventional method and the results of these findings are presented in Table 1. The reaction in which the compound **1a** (1 mmol), compound **2** (1 mmol), various catalyst and various solvents were selected as a model reaction to optimize the reaction conditions. In terms of the effect of solvents and catalyst on the condensation reaction, zinc oxide was found to be the better catalyst and water was found to be the best solvent for the reaction (Table 1, entry 3); other solvents, including ethanol, methanol, DMF and toluene were less efficient (Table 1, entries 1–2, 4–7, 9–12 and 14–15). Nevertheless, all of these yields were generally low before further optimizations. Water gave the corresponding product in 80–90% yield, which was the best among these solvents (Table 1, entries 3, 8 and 13). To increase the efficiency of the condensation reaction, the effects of different catalyst were investigated. Zinc oxide exhibited the best performance with used solvents and gave better yield, (Table 1, entries 11–15). Sodium acetate and potassium carbonate gave lower yields with other solvents, but gave better yield in water as a solvent (Table 1, entries 8 and 13). All the reactions were carried out in equimolar amounts of each compound in 1 mL of solvent. Among these reactions same amounts of the solvent, namely 1 mL of water turned out to be the best choice with yields of 90%, 85% and 80% (Table 1, entries 3, 8 and 13).

We would like to mention here that water as a solvent with zinc oxide as catalyst was the best choice with a yield of 90% and less time required for the completion of the reaction (Table 1, entry 3). Thus we decided to carry out the further reactions in water as a solvent with zinc oxide a catalyst. As a result the reaction time was shortened; thermal decomposition was also minimized, at reflux temperature stirring, resulting in higher isolated yields. But in this synthesis, we compared to the reaction between MW and conventional method, the MW is the best method. Because the studies indicated that the use of MW irradiation made the reactions very fast, very less time required to complete the reaction, and recorded high product yields 90%, 85% and 80% (Table 1, entries 3, 8 and 13) and surprisingly, in the conventional method, the reactions sluggish and recorded low yields 90%, 85% and 80% (Table 1, entries 3, 8 and 13). After that we plane to synthesize another derivative. Physical data of the synthesized compounds (**3a-h**) are shown in Table 2.

3. Material and Methods

3.1. Experimental

3.1.1. 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%.

3.1.2. 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-(3,5-dimethyl-1H-pyrazol-1-yl)phenol (3d)

Yellow solid. Yield 98%, mp 235-237 °C; ES-MS m/z (%): 188.09, ^{1}H NMR (500 MHz, DMSO-*d6*): δ 8.63–7.58 (m, 2H), 7.58–6.93 (m, 2H), 6.00 (s, 1H), 2.30 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*): δ = 156.73, 149.43, 139.23, 132.50, 125.71, 115.85, 107.37, 13.69, 13.61.

1-(4-chlorophenyl)-5-methyl-3-phenyl-1H-pyrazole (3e)

Yellow solid. Yield 96%, mp 210-212 °C; ES-MS m/z (%): 268.08, ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.87–7.85 (m, 2H), 7.53–7.50 (m, 2H), 7.49–7.43 (m, 5H), 6.73 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*): δ = 150.45, 138.98, 138.86, 133.73, 132.60, 128.78, 128.76, 128.64, 125.93, 125.53, 105.65, 13.69.

1-(4-chlorophenyl)-3,5-dimethyl-1H-pyrazole (3f)

Yellow solid. Yield 96%, mp 145–147 °C; ES-MS m/z (%): 206.06, ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.46–7.44 (m, 2H), 7.42–7.40 (m, 2H), 6.00 (s, 1H), 2.29 (s, 3H), 2.13 (s, 3H).^{13}C NMR (125 MHz, DMSO-*d6*): δ = 149.43, 139.20, 138.12, 132.60, 128.76, 125.04, 107.37, 13.69, 13.61.

1-(4-bromophenyl)-5-methyl-3-phenyl-1H-pyrazole (3g)

Yellow solid. Yield 96%, mp 176-178 °C; ES-MS m/z (%): 312.03, ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.87–7.85 (m, 2H), 7.62–7.60 (m, 2H), 7.56–7.43 (m, 5H), 6.73 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*): δ = 150.45, 139.55, 138.86, 133.73, 132.22, 128.78, 128.64, 125.93, 125.32, 120.54, 105.65, 13.69.

1-(4-bromophenyl)-3,5-dimethyl-1H-pyrazole (3h)

Yellow solid. Yield 98%, mp 155-157 °C; ES-MS m/z (%): 250.01, ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.60–7.58 (m, 2H), 7.55–7.53 (m, 2H), 6.00 (s, 1H), 2.29 (s, 3H), 2.13 (s, 3H).^{13}C NMR (125 MHz, DMSO-*d6*): δ = 149.43, 139.24, 138.25, 132.22, 124.99, 120.54, 107.37, 13.69, 13.61.

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 anticancer activity of the synthesized compounds.

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Reference

1. Akbas, E.; Berber, I. Antibacterial and antifungal activities of new pyrazolo [3, 4-d] pyridazin derivatives. *Eur. J. Med. Chem.* **2005**, *40*, 401–405.
2. Akbas, E.; Berber, I.; Sener, A.; Hasanov, B. Synthesis and antibacterial activity of 4-benzoyl-1-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid and derivatives. *IL Farmaco* **2005**, *60*, 23–26.
3. Jamwal, A.; Javed, A.; Bhardwaj, V. A review on pyrazole derivatives of pharmacological potential. *Int. J. Pharma Biol. Sci.* **2013**, *3*, 114–123.
4. Kumari, S.; Paliwal, S.; Chauhan, R. Synthesis of pyrazole derivatives possessing anticancer activity: current Status. *Synth. Commun.* **2014**, *44*, 1521–1578.
5. Venkat Ragavan, R.; Vijaykumar, V.; Suchetha Kumari, N. Synthesis of some novel bioactive 4-oxy/thio substituted-1H-pyrazol-5 (4H)-ones via efficient cross-Claisen condensation. *Eur. J. Med. Chem*. **2009**, *44*, 3852–3857.
6. Gursoy, A.; Demirayak, S.; Capan, G.; Erol, K.; Vural, K. Synthesis and preliminary evaluation of new 5-pyrazolinone derivatives as analgesic agents. *Eur. J. Med. Chem*. **2000**, *35*, 359–364.
7. Castagnolo, D.; Manetti, F.; Radi, M.; Bechi, B.; Pagano, M.; Logu, A.D.; Meleddu, R.; Saddi, M.; Botta, M. Synthesis, biological evaluation, and SAR study of novel pyrazole analogues as inhibitors of Mycobacterium tuberculosis: part 2. Synthesis of rigid pyrazolones. *Bioorg. Med. Chem*. **2009**, *17*, 5716–5721.
8. Mariappan, G.; Saha, B.P.; Sutharson, L.; Haldar, A. Synthesis and bioactivity evaluation of pyrazolone derivatives. *Indian J. Chem*., **2010**, *49B*, 1671–1674. 398
9. Nikhil, P.; Kalpana, M.; Pratik, P.; Manoj, R. *Int. J. Pharm Tech Res.* **2011**, *3*, 540.
10. Murray, W.; Wachter, M.; Barton, D.; Forero-Kelly, Y. The regioselective synthesis of tepoxalin, 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] N-hydroxy-N-methylpropanamide and related 1, 5-diarylpyrazole anti-inflammatory agents. *Synthesis* **1991**, *1*, 18–20.
11. Luo, Y.; Potvin, P.G. Chelation-Controlled Regioselectivity in the Synthesis of Substituted Pyrazolylpyridine Ligands. 1. Bidentates. *J. Org. Chem.* **1994**, *59*, 1761–1765.
12. Katritzky, A.R.; Wang, M.; Zhang, S.; Voronkov, M.V. Regioselective synthesis of polysubstituted pyrazoles and isoxazoles. *J. Org. Chem.* **2001**, *66*, 6787–6791.
13. Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, A. From 200 to Mid 2010: A fruitful decade for the synthesis of pyrazoles. *Chem. Rev*. **2011**, *111*, 6984–7034.
14. Ansari, A.; Ali, A.; Asif, M. Biologically active pyrazole derivatives. *New J. Chem*. **2017**, *41*, 16–24.
15. Tewari, A.; Mishra, A. Synthesis and anti-inflammatory activities of N4, N5-disubstituted-3-methyl-1H-pyrazolo [3, 4-c] pyridazines. *Bioorg, Med. Chem*. **2001**, *9*, 715–718.
16. Michon, V.; du Penhoat, C.H.; Tombert, F.; Gillardin, J.; Lepage, F.; Berthon, L. Preparation, structural analysis and anticonvulsant activity of 3-and 5-aminopyrazole N-benzoyl derivatives. *Eur. J. Med. Chem.* **1995**, *30*, 147–201.
17. Elguero, J.; Katritzky, A.R.; Rees, C.W.; Scriven, E.F.V. *Comprehensive Heterocyclic Chemistry II*; Pergamon-Elsevier Science: Oxford, UK, 1996; Volume 6, pp. 1–75.
18. Fustero, S.; Anchez-Rosell, M.S.; Barrio, P.; Sim, A. From 2000 to mid-2010: A fruitful decade for the synthesis of pyrazoles. *Chem. Rev*. **2011**, *111*, 6984–7034.
19. Hornum, M.; Kumar, P.; Podsiadly, P.; Nielsen, P. Increasing the stability of DNA: RNA duplexes by introducing stacking phenyl-substituted pyrazole, furan, and triazole moieties in the major groove. *J. Org. Chem*. **2015**, *80*, 9592–9602.
20. Piotrowski, D.W.; Kamlet, A.S.; Dechert-Schmitt, A.R.; Yan, J.; Brandt, T.A.; Xiao, J.; Wei, L.; Barrila, M.T. Regio-and Enantioselective Synthesis of Azole Hemiaminal Esters by Lewis Base Catalyzed Dynamic Kinetic Resolution. *J. Am. Chem. Soc*. **2016**, *138*, 4818–4823.
21. Tanime, A.; Oyamada, Y.; Ofuji, K.; Fujimoto, M.; Suzuki, K.; Ueda, T.; Terauchi, H.; Kawasaki, M.; Nagai, K.; Wachie, M.; et al. Synthesis and antibacterial activity of novel and potent DNA gyrase inhibitors with azole ring. *Bioorg. Med. Chem.* **2004**, *12*, 5515–5524;

22. Paulis, T.; Hemstapat, K.; Chen, Y.; Zhang, Y.; Saleh, S.; Alagille, D.; Baldwin, R.M.; Tamagnan, G.D.; Conn, P.J. Substituent effects of N-(1, 3-diphenyl-1 H-pyrazol-5-yl) benzamides on positive allosteric modulation of the metabotropic glutamate-5 receptor in rat cortical astrocytes. *J. Med. Chem.* **2006**, *49*, 3332–3344.
23. Bekhita, A.A.; Abdel-Aziemb, T. Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory-antimicrobial agents. *Bioorg. Med. Chem.* **2004**, *12*, 1935–1945;
24. Genin, M.J.; Biles, C.; Keiser, B.J.; Poppe, S.M.; Swaney, S.M.; Tarpley, W.G.; Yagi, Y.; Romero, D.L. Novel 1, 5-diphenylpyrazole nonnucleoside HIV-1 reverse transcriptase inhibitors with enhanced activity versus the delavirdine-resistant P236L mutant: lead identification and SAR of 3-and 4-substituted derivatives. *J. Med. Chem.* **2000**, *43*, 1034–1040.
25. Shaik, A.; Bhandare, R.R.; Palleapati, K.; Nissankararao, S.; Kancharlapalli, V.; Shaik, S. Antimicrobial, antioxidant, and anticancer activities of some novel isoxazole ring containing chalcone and dihydropyrazole derivatives. *Molecules.* **2020**, *25*, 1047–1059.
26. Venkateswarlu, V.; Kour, J.; Aravinda, Kumar, K.A.; Verma, P.K., Reddy, G.L., Hussain, Y., Tabassum, A., Balgotra, S., Gupta, S., Hudwekar, A.D.; et al. Direct N-heterocyclization of hydrazines to access styrylated pyrazoles: Synthesis of 1, 3, 5-trisubstituted pyrazoles and dihydropyrazoles. *RSC Adv.* **2018**, *8*, 26523–26527.
27. Rathish, I.G.; Javed, K.; Ahmad, S.; Bano, S., Alam, M.S., Pillai, K.K., Singh, S.; Bagchi, V. Synthesis and antiinflammatory activity of some new 1, 3, 5-trisubstituted pyrazolines bearing benzene sulfonamide. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 255–258.
28. Ahmad, P.; Woo, H.; Jun, K.Y. Design, synthesis, topoisomerase I & II inhibitory activity, antiproliferative activity, and structure–activity relationship study of pyrazoline derivatives: An ATP-competitive human topoisomerase IIα catalytic inhibitor. *Bioorg. Med. Chem.* **2016**, *24*, 1898–1908.
29. Vidhya, K.R.; Syed Shafi, S. *Der Pharma Chemica.* **2014**, *6*, 283–287.
30. Swarnkar, D.; Ameta, R.; Vyas, R.J. *Pharm Innov*. **2014**, *3*, 5–9.
31. Dipankar, B.; Panneerselvam, P.; Asish, B. Synthesis, characterization and antimicrobial activities of some 2-pyrazoline derivatives. *Asian J. Pharm. Clin. Res.* **2012**, *5*, 42–46.
32. Prasad, Y.R.; Raja Sekhar, K.K.; Shankarananth, V.; Sireesha, G.; Swetha Harika, K.; Poroikov, V. Synthesis and Insilico biological activity evaluation of some 1, 3, 5-Trisubstituted-2-pyrazolines. *J. Pharm. Res.* **2011**, *4*, 558–560.
33. Chawala, R.; Sahoo, U.; Arora, A.; Sharma, P.C.; Radhakrishnan, V. Microwave-assisted synthesis, molecular docking study and in vitro evaluation of halogen substituted flavonols against P388 Murine leukemia cells. *Acta Pol. Pharm. -Drug Res.* **2010**, *67*, 55–61.
34. Kannan, D.; Naveen, S.; Jagadeesan, G.; Lokanath, N.K.; Thennarasu, S. Ultrasonic Cavitation Facilitates Rapid Synthesis of Trisubstituted Pyrazole Scaffolds through Michael Addition/Domino Cyclization. *Chem. Select.* **2019**, *4*, 9807–9810.
35. Pansare, D.N.; Shelke, R.N.; Pawar, C.D. Microwave Assisted and Efficient Synthesis of Substituted Thiazole Acid Derivatives. *Lett. Org. Chem*. **2017**, *14*, 517–524.
36. Pansare, D.N.; Shelke, R.N.; Shinde, D.B. A Facial Synthesis and Anticancer Activity of (Z)-2-((5-(4-nitrobenzylidene)-4-oxo-4, 5-dihydrothiazol-2-yl) amino)-substituted Acid. *J. Het. Chem.* **2017**, *54*, 3077–3086.
37. Pansare, D.N.; Shinde, D.B. A facile synthesis of novel series (Z)-2-((4-oxo-5-(thiophen-2-ylmethylene)-4, 5-dihydrothiazol-2-yl) amino) substituted acid. *J. Saudi. Chem. Soc*. **2017**, *21*, 434–440.
38. Pawar, C.D.; Chavan, S.L.; Pawar, U.D.; Pansare, D.N.; Deshmukh, S.V.; Shinde, D.B. Synthesis, anti-proliferative activity, SAR, and kinase inhibition studies of thiazol-2-yl-substituted sulfonamide derivatives. *J. Chin. Chem. Soc*. **2019**, *66*, 257–264.
39. Pawar, C.D.; Pansare, D.N.; Shinde, D.B. (Substituted)-benzo [b] thiophene-4-carboxamide Synthesis and Anti-proliferative Activity Study. *Lett. Drug. Des. Disc*. **2020**, *17*, 563–573**.**
40. Pansare, D.N.; Shinde, D.B. *Res. Rev. J. Chem.* **2015**, *4*, 8–14.
41. Shelke, R.N.; Pansare, D.N.; Pawar, C.D.; Khade, M.C.; Jadhav, V.N.; Deshmukh, S.U.; Sarkate, A.P.; Pawar, R.P.; Gore, N.S.; Shinde, D.B.; et al. THIONYL CHLORIDE INDUCED CONVENIENT SYNTHESIS OF BENZAMIDES FROM 3-BROMO-5-NITROBENZOIC ACID AND AMINES UNDER SOLVENT FREE CONDITIONS. *Eur. Chem. Bull*. **2019**, *8*, 63–70.

42. Pansare, D.N.; Shelke, R.N.; Khade, M.C.; Jadhav, V.N.; Pawar, C.D.; Jadhav, R.A.; Bembalkar. S. R. New thiazolone derivatives: Design, synthesis, anticancer and antimicrobial activity. *Eur. Chem. Bull*. **2019**, *8*, 7–14.
43. Shelke, R.N.; Pansare, D.N.; Pawar, C.D.; Khade, M.C.; Jadhav, V.N.; Deshmukh, S.U.; Dhas, A.K.; Chavan, P.N.; Sarkate, A.P.; Pawar, R.P.; et al. Synthesis and anticancer evaluation of new benzenesulfonamide derivatives. *Eur. Chem. Bull.* **2019**, *8*, 1–6.