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Review Article

ADVANCES IN THE STUDIES OF BIOLOGICAL ACTIVITIES AND NOVEL GREEN SYNTHETIC ROUTES FOR PYRAZOLE SCAFFOLDS

Chandrashekhar P. Pandhurnekar*[1], Arvind J. Mungole[2], Himani C. Pandhurnekar[3], Babita G. Yadao[3]

[1]*Department of Chemistry, Shri Ramdeobaba College of Engineering and Management, Nagpur, Maharashtra, India*
[2]*Department of Botany, Nevjabai Hitkarini College, Bramhapuri, Maharashtra, India*
[3]*Department of Chemistry, Dada Ramchand Bakhru Sindhu Mahavidyalaya, Nagpur, Maharashtra, India*
Corresponding author: pandhurnekarcp@rknec.edu

ABSTRACT

In the class of heterocyclic compounds, pyrazole is one of the important classes which structure consists shows a ring (5-membered ring) which have the presence of carbon and nitrogen (mainly three carbon (C) atoms and also shows two neighboring nitrogen (N) atoms which has great importance. Pyrazole is very versatile which brings this compound for designing several potent bioactive agents. There are several applications of organic compounds which has pyrazole as a nucleus molecule in different areas which includes the pharmacy and agro-chemical industries. Due to its versatility, there is an increase in the synthesis, analysis of different properties, and also study of various applications of pyrazole and its derivatives. Pyrazole derivatives have exhibited a broad spectrum of biological activities which has created a huge interest in designing new pharmacological agents having pyrazole as a nucleus molecule. This review paper of pyrazole includes the discussion of various methods of its synthesis and applications of pyrazole and its analogues.

Keywords: Pyrazole, Heterocyclic compounds, Green synthetic methods, Biological activities, Microwave Synthesis.

1. INTRODUCTION

Heterocyclic compounds and their derivatives are considered as the class of compounds which have the presence of heteroatoms in its ring which can form numbers of derivatives thus gained enormous attention [1-2]. Heterocyclic compounds are highly valued and considered as one of the very important as well as a very unique class of the compounds. This class of compounds exhibited a wide range of characteristics such as physical, chemical, and biological [3-4]. In nature, these classes of compounds i. e. heterocyclic compounds are extensively available [5-7]. The heterocyclic ring systems have gained a great deal of attraction due to their occurrence in various biologically active molecules. A brief investigation of most of the active pharmacophores reveals that the nitrogen-based heterocycles molecules are the most predominant form of biologically related small molecules [8]. Amongst all the types of heterocyclic compounds, one of the very important compounds is nitrogen-containing heterocycles which are extensively observed as a core framework in enormous bioactive compounds [9].

The branch of chemistry which offers the Nitrogen-primarily based heterocyclic compounds is a vital and particular elegance amongst all of the carried-out branches of natural chemistry, with a considerable quantity of studies committed to the improvement of diverse novel molecules having bioactivities. They had been concerned withinside the improvement of various natural synthesis protocols and exhibited considerable programs withinside the subject of chemical sciences [10]. In this review article, we discuss one of the very important nitrogen-containing heterocyclic molecules i. e. pyrazole. Pyrazoles are a very important class of compounds that are five-membered heterocycles and are particularly very beneficial in the class of compounds which belong to organic synthesis. These compounds are measured as those classes of compounds that were studied many times among the family of azole compounds. Certainly, various varieties of synthetic approaches and synthetic correspondents informed from so many years [11]. Pyrazole **(1)** can be defined as those heterocycles which are an aromatic class of compounds that belongs to the azole family class of organic

compounds. They are those heterocycles ring compounds which having a five-membered system with the presence of two and three atoms like nitrogen atoms which are attached and carbon atoms respectively [12]. The nitrogen atom which is on position number 1 (N1) is just like ''pyrrole" because it shows an unshared electron that is coupled with an aromatic system. Whereas the Nitrogen atom which is present in position number 2 (N_2) is just like ''pyridine". After all, the unshared electrons have not cooperated with the resonance, which is just shown by the pyridine systems. Because of these differences shown by both the nitrogen atoms, the pyrazoles molecule responds like acids molecules as well as base molecules (Fig. 1) [13]. The other structural characteristics feature which is very important shown by pyrazole molecules as they show the tautomerism such as prototrophic. As they exhibit three tautomer in the unsubstituted pyrazoles which are shown in Fig. 2, whereas they also show the number of tautomers such as five tautomers in the monosubstituted pyrazoles molecules which are also shown in Fig. 3. The structures of pyrazole which are shown below i.e. 1a, 2a, and 2b are also very much related to each other as they show aromaticity [14-15].

Nowadays, pyrazole-containing compounds, as bio-molecules, have been reported as they fascinated much additional consideration because of their attractive pharmacological properties. Hence, such type of class of heterocycles is sketched in various well-developed drugs which belong a various class of the drugs which exhibited very wide beneficial activities such as Anti-inflammatory, Anti-psychotic, Anti-obesity, Analgesic, H2-receptor agonist, Anti-depressant, etc. (Fig. 4) [16].

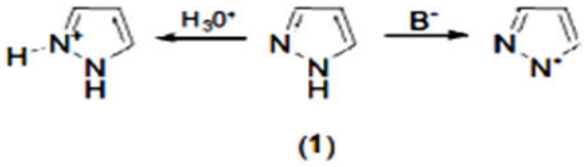

Fig. 1: Pyrazole molecule showing cations and anions.

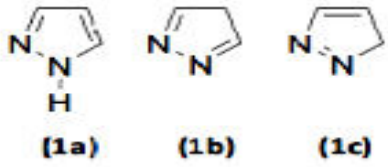

Fig. 2: Unsubstituted pyrazole moiety shows its tautomers.

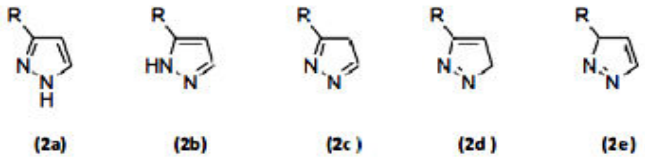

Fig. 3: 3 (5)-monosubstituted pyrazoles show it's tautomers.

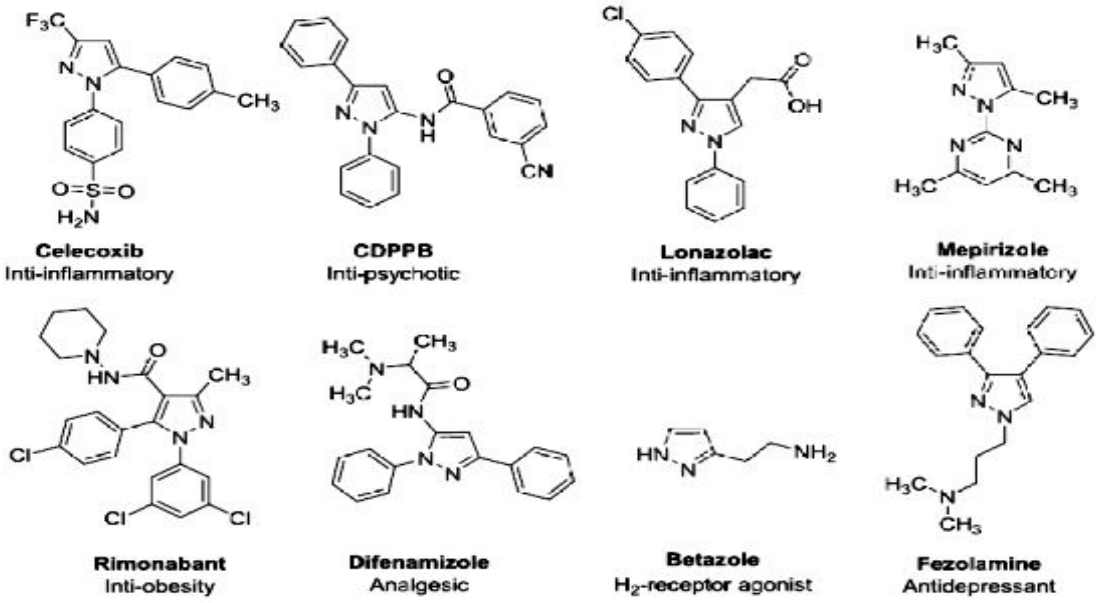

Fig. 4: Example of various pharmaceutical drugs having pyrazole.

These heterocyclic compounds can be synthesized by using the various methods by researchers but the advanced methods which come under the green tool have much more comfortable as compared to the classical method because green chemistry fascinates various considerations in the direction of sustainable growth [17]. These classes of chemistry such as green chemistry deal with the development of chemical processes which can support to minimize the usage, production of various harmful materials. Nowadays Green, sustainable chemistry has been a topic of very intensive research and the studies done in this area have been contributing towards the development of cleaner and comparatively benign chemical methods [18-19]. When any chemical reaction which can be followed by the green chemistry methods involves the use of three green components like catalyst, solvent, and energy consumption source then it is considered as a green reaction [20]. Green chemistry aims to protect environmental and economic profit which can be accomplished with a green technique like microwave irradiation (MW), ultra-sonication method, mortar and pestle method, biocatalysts method [21-22].

This review paper gives the details of various non-classical (green) methods which is used to design for the preparation of pyrazole and its derivatives, which gives information that how the researcher progress in the direction of development of more greener protocol which can help to minimizes the usage of poisonous chemicals, drastic reaction state, more usage of energy, less time for reaction and also minimize the cost that produces a huge quantity of pyrazole and its derivatives which exhibited additional properties in several areas like technology, medicine, and agriculture industry.

2. DIFFERENT GREEN CHEMICAL METHODS FOR THE PREPARATION OF PYRAZOLE MOLECULES AND THEIR ANALOGUES

R. Konakanchi *et al.,* [23] has reported the method which is used to prepare a compound dihydropyran pyrazoles by using the three (multi) constituent condensation of 3-Methyl-1-phenyl-2-pyrazoline-5-one, with different aromatic aldehydes and in the presence of malononitrile in aqueous methanol at ambient temperature using the green method like ultrasonication.

K. Longhi *et al.,* [24] explained the method of preparation of several derivatives of NH-pyrazoles by carrying out the reaction of β-dimethyl aminovinyl ketones and hydrazine sulfate (Fig. 6). The reaction takes place in solid-state by using grinding method through the p-toluenesulfonic acid (PTSA) which act as a catalyst in the absence of solvent, after grinding there is a formation of liquid and then eutectic mixture forms which dispense the reactants uniformly and finally afford the compound within a time of 6-12 min. The number of the reactions were carried out smoothly at room temperature and in the presence of solvent-free conditions. As compared to classical reaction conditions, in which solvent such as ethanol is used, this new synthetic method shows many advantages such as less time for completion of the reaction, higher yields of product, mild reaction conditions, and most importantly they are environmentally friendly.

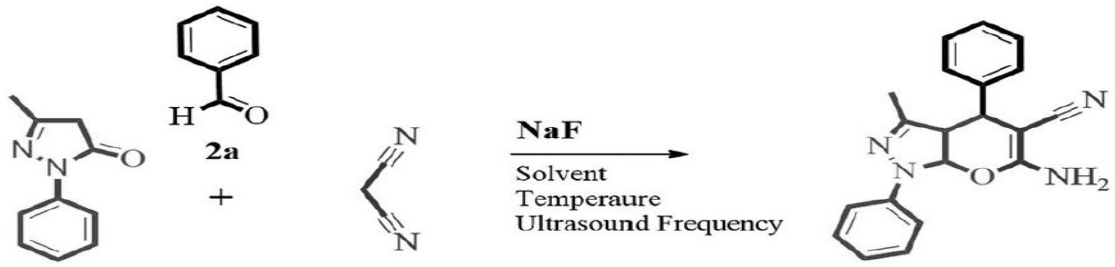

Fig. 5: Synthesis of pyrazole derivatives

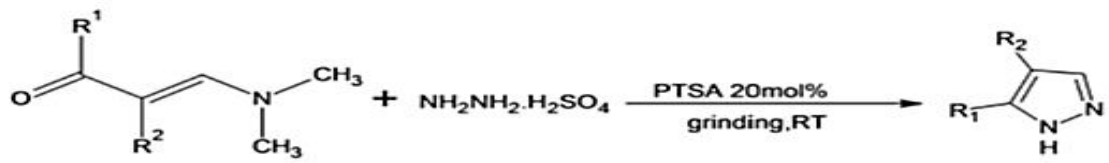

Fig. 6: Preparations of NH-pyrazoles by using a grinding method in Solvent-free conditions

G. N. Yallappa and co-authors have described the preparation of substituted pyrazoles (Fig. 7). Firstly, the different derivatives of Cinnamaldehydes were synthesized by using Claisen-Schmidt condensation reaction (by using a strong basic reagent). In the second step, the synthesized cinnamaldehydes were treated with Hydrazine hydrate, the reaction took place in the occurrence of ZnO Nano-catalyst by using green chemistry method microwave-assisted solvent-free conditions to obtain the various substituted pyrazoles. The newly obtained compounds were tested for in vitro tests in contrast to EAC cell lines. It has been observed that maximum compounds displayed good inhibitor effectiveness with IC_{50} values [25].

J. Trilleras *et al.,* have reported the synthesis of newly 1,3-diaryl-5-(1-phenyl-3-methyl-5-chloropyrazol-4-yl)-4,5-dihydropyrazole analogue (Fig. 8). The synthesis was carried out through green methods like sonication in the presence of a solvent such as an ethyl alcohol or methyl alcohol/glacial acetic acid present in mixture form with the proportion of 5:1 ratio with the two equivalents of hydrazines with several types of chalcone which obtained from 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde. This method having good applications as compared to the existing reaction procedures which include a simple process, less reaction time, and a good amount of obtained product [26].

P. Kumar *et al.,* have reported a calm, very benign, without solvent as well as one of the very effective methods for the preparation of chalcones derivatives which having substituted pyrazole which is carried out by the grinding process involves pyrazole, aldehydes, and acetophenones (Fig. 9). The reaction took place along with activated barium hydroxide (C-200). The product is obtained in a very good amount and reaction time is also reduced [27].

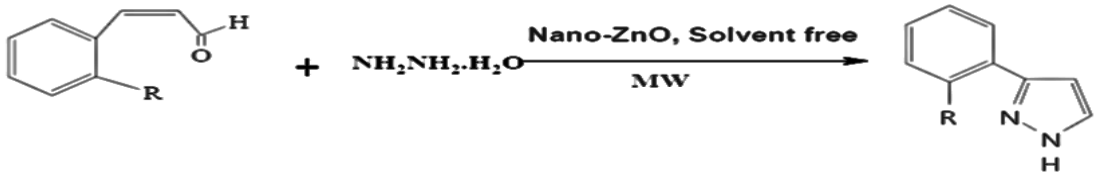

Fig. 7: synthesis of substituted pyrazoles by using ZnO Nano-catalyst

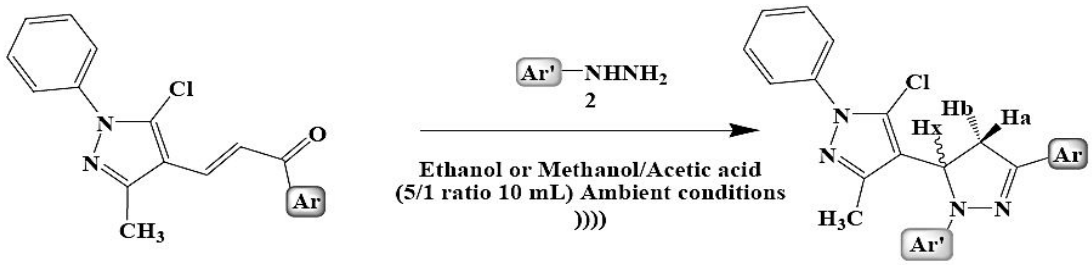

Fig. 8: Preparation of 5-(pyrazol-4-yl)-4,5-dihydropyrazole analogue of pyrazole

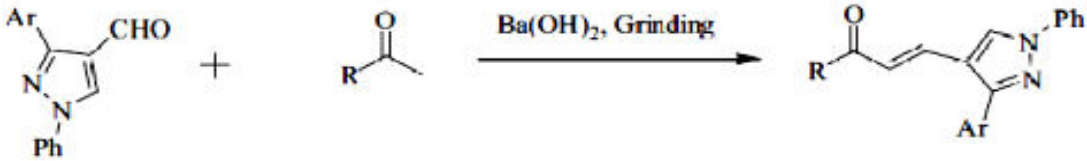

Fig. 9: Synthesis of pyrazole-substituted chalcones derivatives

N. Everson *et al.,* have reported the preparation of *N*-aryl substituted 1*H*-pyrazole-5-amines from 3-aminocrotonitrile and also the preparation of 1*H*-pyrazole-5-amines from α-cyanoketones (Fig. 10). The microwave reaction is carried out in between arylhydrazines and 3-aminocrotonitrile at the temperature of 150°C to afford 1*H*-pyrazole-5-amines and the reaction time is 10-15 minutes. The product

obtained moderate to excellent yields. The use of α-cyanoketones with phenylhydrazine and the reaction carried out under the same conditions also yields several 1*H*-pyrazole-5-amines in a short period (Fig. 11). This reaction process is suggestively quicker as compared to other methods, and during the reaction, some of the compounds need aqueous solutions [28].

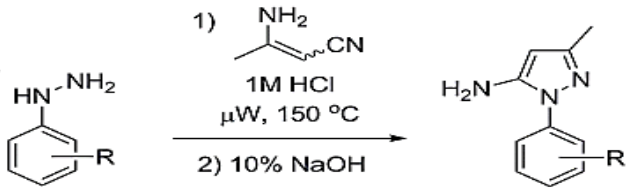

Fig. 10: Preparation of pyrazole analogue i.e. *N*-aryl substituted 1*H*-pyrazole-5-amines from a 3-aminocrotonitrile molecule.

D. S. Dodd and co-authors conveyed a well-organized scheme here for the solid-supported type of preparation of 5-*N*-alkylamino and 5-*N*-arylamino pyrazoles (Fig. 12). In this process, a very general, mild, and readily available resin-immobilized *â*-ketoamides is used as starting resources required for synthesis [29].

N. D. Argade *et al.,* have reported the green method such as microwave-assisted better-quality process required for preparation of pyrazole analogue containing 2,4-disubstituted oxazole-5-one (Fig. 13). The newly prepared compounds were tested for *in vitro* antibacterial and antifungal activities and they show good activity [30].

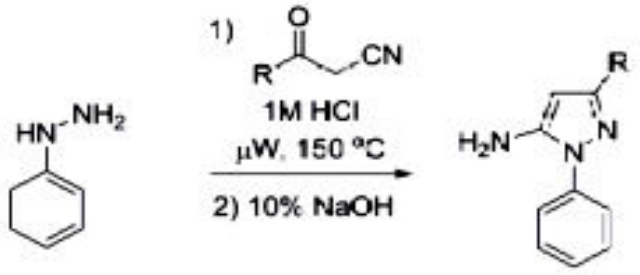

Fig. 11: Preparation of 1*H*-pyrazole-5-amines from α-cyanoketones.

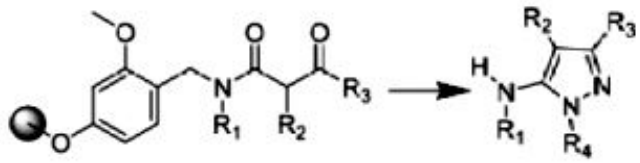

Fig. 12: Preparation of 5-aminopyrazoles by solid-phase process

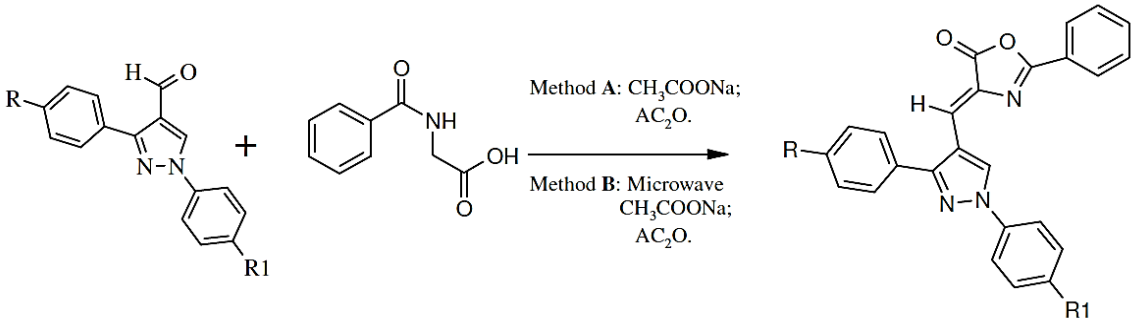

Fig. 13: Preparation of pyrazole analogue containing 2,4-disubstituted oxazole-5-one

3. BIOACTIVITIES OF PYRAZOLE AND ITS DERIVATIVES

Pyrazoles are recognized as one of the very important types of N-containing heterocycles which exhibits a broad range of various biological potencies like anti-inflammatory, anti-bacterial, anti-analgesic, anti-helmintic, antifungal, etc.

V. H. Bhaskar *et al.,* [31] synthesized various pyrazole derivatives of 5-phenyl-4-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4H-1,2,3-triazoles by conducting the reaction between hydrazine monohydrate with the chalcones, the reaction carried out when there is the presence of AcOH. The novel synthesized analogues were screened for anti-inflammatory activity.

N. C. Desai *et al.,* have done the in vitro study of about pyrazole analogue surrounding 2-pyridine represented effective antibacterial activity against the bacterial strains like Staphylococcus aureus at the non-cytotoxic concentrations [32].

G. M. Sreenivara and co-authors have reported the pre-

paration of a sequence of pyrazole derivatives and they screened the newly synthesized pyrazole derivative for their anthelmintic activity. These newly prepared compounds of pyrazole derivative were tested for anthelmintic activity against earthworms, Perituma Posthuma, and were compared to std. Albendazole [33].

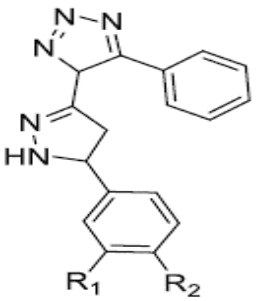

Fig. 14: Pyrazole derivatives showing anti-inflammatory activities

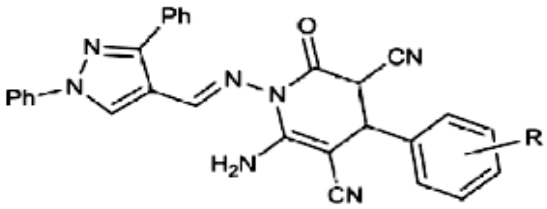

Fig. 15: Pyrazole derivatives having anti-bacterial activities

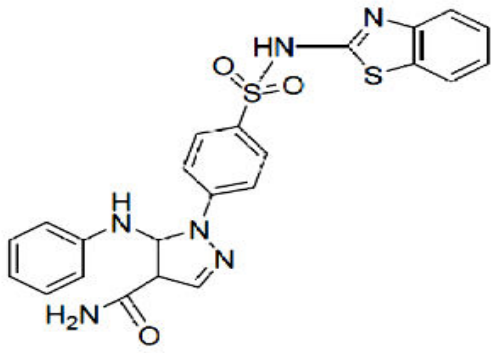

Fig. 16: Pyrazole derivative showing anti-helminthic activities

R. Nagamallu *et al.,* have reported the synthesized several coumarins appended bis(formylpyrazole) derivatives. The newly synthesized coumarin containing pyrazole derivatives presented respectable activity against the three different fungal species such as aspergillus niger, aspergillus flavus, and Candida Albicans [34].

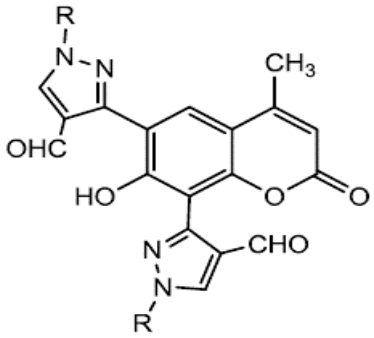

Fig. 17: Pyrazole derivative showing anti-fungal activities

A. K. Verma and co-authors have reported a novel pyrazole analogue of novel 1-(4-chlorobenzoyl)-3-(4-substituted phenyl)-1H-pyrazole-4-carbaldehyde. These derivatives of pyrazole were tested for anti-inflammatory, and analgesic activities. The pyrazole analogue shows important anti-inflammatory and analgesic activities [35].

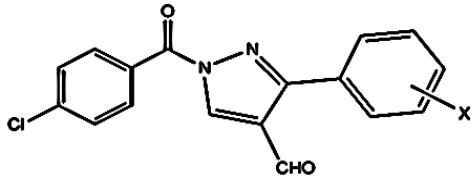

Fig. 18: Pyrazole derivative showing anti-inflammatory and analgesic activities

4. CONCLUSION

Various biological activities and synthetic protocols of pyrazoles and their derivatives discussed and emphasized in this analysis depict in the review article. Various research work has been done which is required for the development of pyrazole frameworks. The different green approaches for the preparation of pyrazole and its analogue having good advantages over the classical reaction methodologies which include a simple procedure, shorter reaction times, and a good yield of product and also proved as an environmentally benign method. This review paper will likely be accommodating in the future for research and also for new and novel ideas in the search of balanced designs

which includes new green approaches for the preparation of more promising pyrazoles and it's derivatives.

Conflict of Interest

In this review article, the authors confirm that there are no conflicts about the contents of this paper.

5. ACKNOWLEDGEMENTS

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6. REFERENCES

1. Kucukguzel SG, Senkardes S, *Eur J Med Chem*, 2015; **97**:786-815.
2. Kumar V, Kaur K, Gupta GK, Sharma AK, *Eur J Med Chem*, 2013; **69:**735-753.
3. Eftekhari-Sis B, Zirak M, Akbari A, *Chem Rev,* 2013; **113:** 2958-3043.
4. Ansari A, Ali A, Asif M, *New J Chem,* 2017;**41:**16-41.
5. Ju Y, Varma RS, *J Org Chem,* 2006; **71:**135-141.
6. Zárate-Zárate D, Aguilar R, Hernández-Benitez RI, Labarrios EM, Delgado F, Tamariz J, *Tetrahedron,* 2015; **71:** 6961-6978.
7. Gordon EM, Barrett RW, Dower WJ, Fodor SPA, Gallop MA, *J Med Chem,* 1994; **37:** 1385-1401.
8. Henary M, Kananda C, Rotolo L, Savino B, Owens EA, Cravotto G, *RSC Adv,* 2020; **10**:14170-14197.
9. Faisal M, Saeed A, Hussain S, Dar P, Larik FA, *J Chem Sci,* 2019; **131**:70-99.
10. Kerru N, Gummidi L, Maddila S, Gangu KK and Jonnalagadda SB, *Molecules,* 2020; **25**: 1909-1950.
11. Karrouchi K, Radi S, Ramli Y, Taoufik J, Mabkhot YN, Al-aizari FA, et al., *Molecules,* 2018; **23**:134.
12. Faria JV, Vegi PF, Miguita AGC, Santos MSD, Boechat N, Bernardino AMR, *Bioorg Med Chem,* 2017; **25**:5891-5903.
13. Netto AVG, Frem RCG, Mauro AE, *Quim Nova*, 2008; **31**:1208-1217.
14. Behr LC, Fusco R, Jarboe CH. The chemistry of heterocyclic compounds pyrazoles, pyrazolines, pyrazolidines, indazoles, and condensed rings. (NY): Interscience Publisher; 1967.
15. Gilchrist TL. Heterocyclic chemistry. (NY): Longman Scientific & Technical; 1992.
16. Karrouchi K, Radi S, Ramli Y, Taoufik J, Mabkhot YN, Al-aizari FA, et al., *Molecules,* 2018; **23**:134.
17. Sapkal A, Kamble S, *Chemistry Select,* 2020; **5**: 12971-13026.
18. Varma RS, *Green Chem*, 1999; **1**:43-55.
19. Varma RS, Rastogi N, Singh A, *Ind J Hetero Chem,* 2000; **12:**159.
20. Tucker JL, *Org Process Res Dev,* 2006; **10**:315-319.
21. Jukic M, Djakovic S, Filipovic-Kovacevic Z, Kovac V, Vorkapic-Furac J, *Kem Ind,* 2005; **54**:255-272.
22. Margetić D, *Kem Ind,* 2005; **54**:351-358.
23. Konakanchi R, Gondru R, Nishtala VB, Kotha LR, *Synth Commun*, 2018, **48(15):** 1994-2001.
24. Longhi K, Moreira DN, Marzari MRB, Floss VM, Bonacorso HG, Zanatta N, et al., *Tetrahedron Lettrs,* 2010; **51**:3193-3196.
25. Yallappa GN, Nagaraja D, Chandrashekhar U, *Pharmacophore*, 2019; **10(3)**:28-32.
26. Trilleras J, Polo E, Quiroga J, Cobo J, Nogueras M, *Appl Sci,* 2013; **3**:457-468.
27. Kumar P, Kumar S, Husain K, Kumar A, *Chin Chem Lett,* 2011; **22**:37-40.
28. Everson N, Yniguez K, Loop L, Lazaro H, Belanger B, Koch G, et al., *Tetrahedron Lett,* 2019; **60(1)**:72-74.
29. Dodd DS, Martinez RL, Kamau M, Ruan Z, Kirk KV, Cooper CB, et al., *J Comb Chem,* 2005; **7:**584-588.
30. Argade ND, Kalrale BK, Gill CH, *E-J. Chem*, 2008; **5(1):**120-129.
31. Bhaskar VH, Mohite PB, *J Optoelectron Biomed Mat,* 2011; **3:** 7-16.
32. Desai NC, Rajpara KM, Joshi VV, *Bioorg Med Chem Lett,* 2013; **23:** 2714-2717.
33. Sreenivasa GM, Jaychandran E, Shivkumar B, Kumar KJ, Vijay Kumar V, *Arch Pharm Sci Res,* 2009; **1**:150-157.
34. Nagamallu R, Srinivasan B, Ningappa MB, Kariyappa AK, *Bioorg Med Chem Lett,* 2016; **26**:690-694.
35. Verma AK, Martin A, Singh AK, *Asian J Biomed Pharm Sci,* 2014; **4(37):**21-25.