International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 734-743 www.ijprajournal.com ISSN: 2456-4494

Synthesis and Evalution of Pyrazole Derivatives by Different Method

Mahesh P Bhakare*, Md. Rayeesahmad, Syed A.A, Dinesh Gujrathi, Vaishnavi Siral, Sonaldoltade.

Address: 1. Department of pharmaceutical chemistry shivlingeshwar college of pharmacy, Almala. tq. Ausa, Dist. Latur-413520, Maharashtra (MH), India.

Date of Submission: 15-03-2025 Date of Acceptance: 25-03-2025

ABSTRACTS: -
Pyrazoline compounds are extensively used in organic synthesis because of their stable nature and ability to synthesize new compounds with various biological activities. Different methods can be employed to synthesize pyrazole derivatives, including ultrasonic irradiation, microwave irradiation, ionic liquids, and grinding techniques. In traditional heating methods, an oil bath or hot plate is used as a source of heat for a chemical reaction. In microwave-assisted synthesis, dipolar polarization and conduction are the basic mechanisms observed. Microwave-assisted synthesis provides numerous benefits, such as enhanced reaction rates, higher yields, greater selectivity, and economic advantages for the synthesis of a large number of organic molecules, making it the preferred method in modern chemical synthesis and drug discovery. This article emphasizes the importance of optimizing the synthesis reaction conditions and characterizes the synthesized compounds using various techniques. All the synthesized compounds were characterized by running TLC, elemental analysis, IR, NMR, and MS spectra. The results indicate that microwave irradiation is a more efficient method than the conventional method due to shorter reaction time and energy savings.

Keywords: -pyrazoline, microwave irradiation, ultrasonic irradiation, grinding method, ionic liquids

I. INTRODUCTION: -

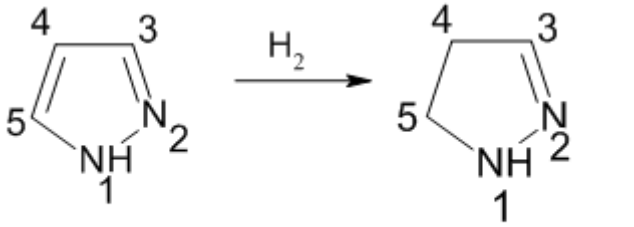
Pyrazolines are heterocyclic ring molecules that contain two adjacent nitrogen atoms, making them basic in nature. They also have only one endocyclic double bond and are derivatives of dihydropyrazole. There are three types of pyrazoline possible depending on the position of the double bonds [1]1-pyrazoline, 2-pyrazoline, and 1,3-pyrazoline. Pyrazoline, which is a derivative of chalcone, has been reported to have a broad spectrum of potential pharmacological activities, including antibacterial, antifungal, anti-inflammatory, analgesic, antipyretic, insecticidal, diuretic, cardiovascular, and antidepressant [2]. It is present in a number of pharmacologically active compounds.Recent trends in organic synthesis use nonconventional green techniques such as ultrasound (sonochemistry), microwave irradiation, grinding, and using ionic liquids, which have many advantages. Numerous solvent-assisted and solvent-free methods have been reported for the preparation of pyrazoline derivatives [3]. This article elaborates on various green techniques previously reported for synthesizing pyrazoline derivatives, which will be useful for researchers in producing pyrazoline derivatives in less time, with higher yields and safety.In the last few years, microwave-assisted organic reaction enhancement chemistry has gained popularity as a non-conventional technique for rapid organic synthesis[4]. Many researchers have described accelerated organic reactions, and a large number of research articles have proven the importance of microwave synthesis as a synthetic utility for routine organic synthesis. It can be termed as "e-chemistry" because it is easy, effective, economical, and eco-friendly and is believed to be a step towards green chemistry[5].

There are various green techniques available in the literature for the synthesis of pyrazoline derivatives. Some green methods for the organic synthesis of pyrazolines:

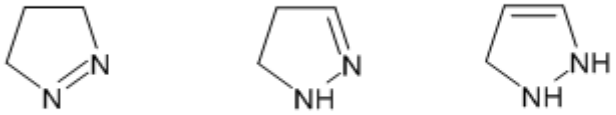
- Microwave Irradiation
- Conventional Method
- Ultrasonic Irradiation
- Ionic liquids
- Grinding Technique

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 734-743 www.ijprajournal.com ISSN: 2456-4494

Chemical structure and their derivatives: -



Pyrazole Pyrazoline



1-pyrazoline 2-pyrazoline 1,3-pyrazoline

Physical Properties (As shown in table no.1)**: -**

(Table No.1)

Molecular formula	$C_3H_6N_2$
Molar mass	70.095 $g.mol^{-1}$
Density	0.9±0.1 g/cm^3
Boiling point	10.4±23.0 °C at 760 mmHg
Flash Point	-58.1±17.7 °C

Comparison of synthesis methods(As shown in Table No. 2) [6,7]**: -**

(Table No.2)

METHODS → / **PARAMETERS** ↓	**Conventional Method**	**Microwave Assisted Synthesis**	**Ultrasonic Technique Synthesis**	**Grinding Technique**	**Synthesis by using Ionic Liquid**
Temperature	Reflux 110°C	The vessels are done by heating from afar 20-150 °C	25-50 °C	Room temperature (RT)	Mixed 100
Reaction Rate	The reaction rate is less.	The reaction rate is several-fold high.	The reaction rate is lower than Microwave.	The reaction rate is lower than the ultrasonic technique.	The reaction rate is slightly higher than the conventional synthesis
Reaction Time	3-7h	1-4 min	10-20 min	8-12 min	2-6 h
Source of energy	Electricity	Electromagnetic	Sound	Human	Heat/electricity

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 734-743 www.ijprajournal.com ISSN: 2456-4494

	and heat	waves are fired	waves (ultrasonic frequency >20 KHz)	energy/ tools	
Product Yield	55-75%	79-89%	72-89%	78-94%	87-96%

1. Microwave Irradiation: -

Green chemistry employs benign synthetic procedures that are highly efficient and eco-friendly to synthesize various bioactive heterocyclic frameworks. These frameworks are used in the production of drugs, plastics, petrochemicals, agricultural chemicals, cosmetics, and other products on a daily basis. In this particular methodology, pyrazolines are synthesized using microwave irradiation as shown in figure no 1.[8] The compound's structure is established by analyzing its elemental and spectral data. This method has several advantages over conventional synthesis procedures, including clean reaction procedures, easy inspection, and short reaction times, producing excellent results for the product. [9]

A sensitive and fast method was developed for these samples, and a pyrazoline derivative was obtained, which provided better results than conventional methods. Microwave energy is currently widely used because it is more environmentally friendly, safer, more selective, and does not require catalysts. It is faster, cleaner, and can produce more products than conventional methods. [9,10]It is often used as an alternative in more efficient synthesis due to its ease of operation and mild reaction conditions when mixed with free solvents. Previous studies have shown that microwave irradiation in dry media is energetically beneficial and saves more reaction time.[8,11]

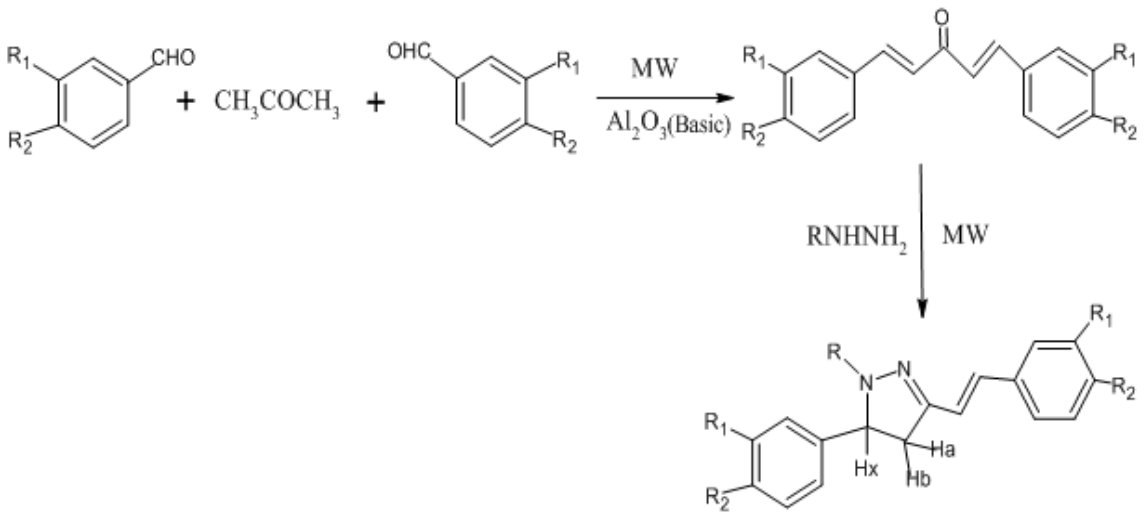


Figure No.1: Synthesis of pyrazoline derivatives using microwave irradiation

2. Conventional Methods: -

One of the simplest methods of synthesis is the conventional method, which is carried out using equipment such as reflux with the reaction as shown in figure no 2.[12] However, this method has some drawbacks. The heating reaction is slow and creates hot surfaces at certain reaction sites, leading to the decomposition of the substrate, reagents, and products over time. [11]In contrast, green chemistry techniques assisted by microwave energy facilitate more uniform heating of the vessels over a long distance, resulting in fewer decomposition products.[13]

Conventional heating uses an oil well that is heated first, followed by the solvent. This process results in an uneven distribution of decomposed products due to temperature differences in the solvent and bath wall.[14,15]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 734-743 www.ijprajournal.com ISSN: 2456-4494

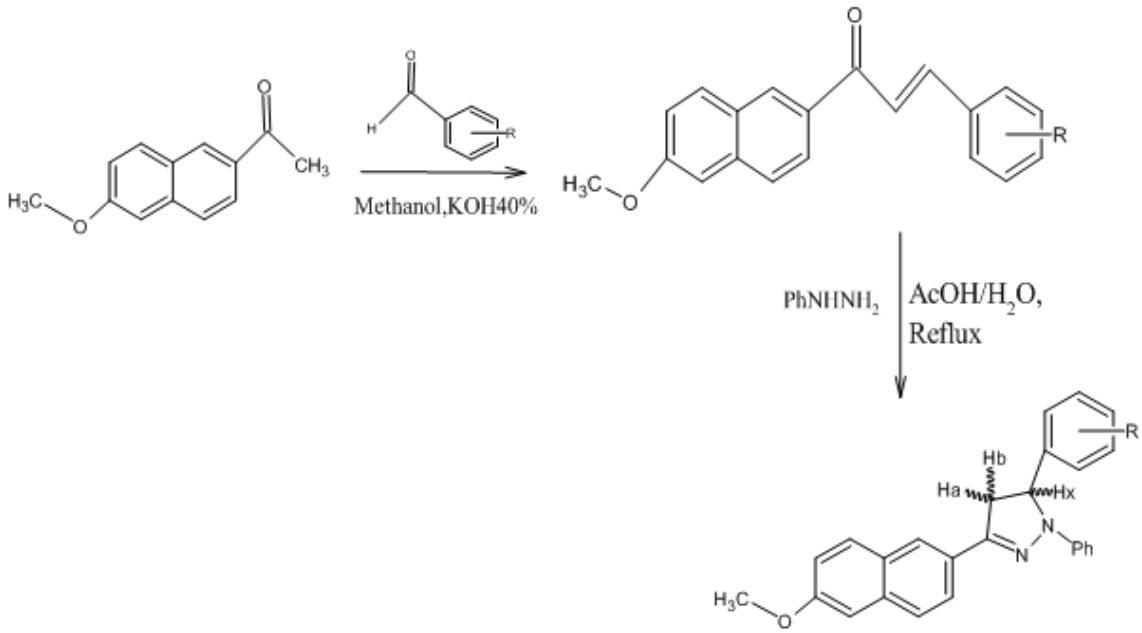


Figure No.2: Synthesis of pyrazoline derivatives using conventional methods

3. Ultrasonic irradiation: -

Ultrasonic irradiation has been employed as a promising technique in the fields of green chemistry and pharmacy. This technique utilizes the cavitation effect produced by sonication in the reaction media, as shown in figure no 3 which promotes faster and more efficient synthesis of pyrazoline derivatives. The localized effect of cavitation results in a rapid resolution of the reaction, producing a high yield of products in a short period. This method is known to efficiently synthesize pyrazoline derivatives with excellent results, providing a significant boost to the green chemistry and pharmacy industries. [16-18]

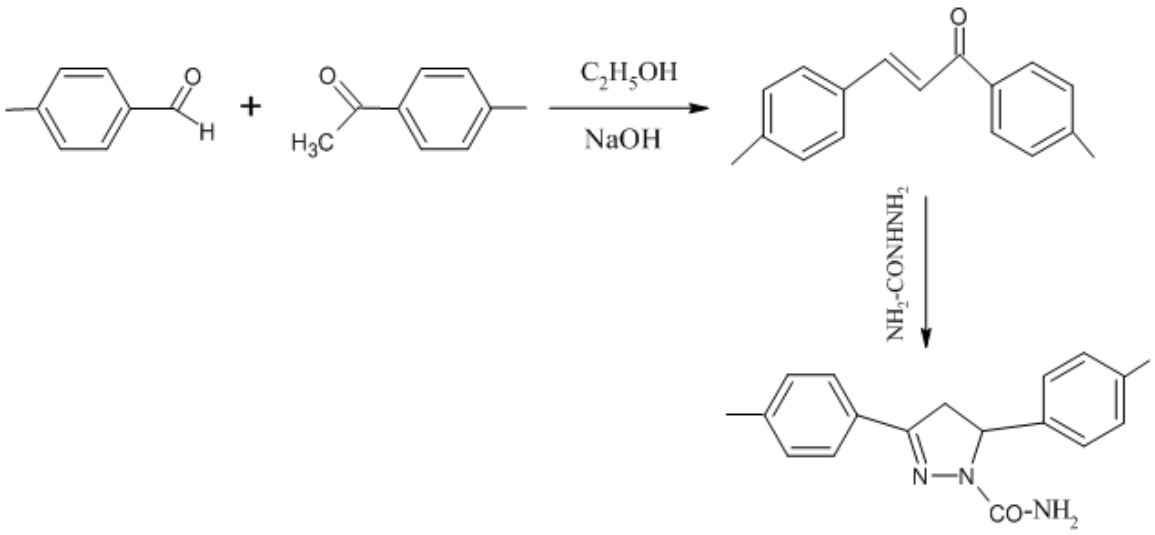


Figure No.3: Synthesis of pyrazoline derivatives using ultrasonic irradiation

4. Ionic liquid: -

The ionic liquid is a form of salt that exists in a liquid state at a temperature of 100°C. Liquid salt is different from regular liquid because it requires higher temperatures to melt. In 1948, the first ionic liquid and chloroaluminate were discovered, and since then, many studies have identified various ionic liquids that can be used in

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 734-743 www.ijprajournal.com ISSN: 2456-4494

synthesis. The use of 1- n- butyl- 3- methylimidazolium and 1- ethyl3- methylimidazolium (EMIM) has led to the development of a green route for synthesizing compounds such as 1,3,5- pyrazoline derivatives, which are substituted in liquid media with EMIM hydrogen ionic sulfate liquid. The EMIM acts as a catalyst in reflux conditions, resulting in better yields as shown in figure no 4. [19] 1,3,5- tri- substitute- 2- pyrazoline compounds are also used in this process, which involves a one-pot cyclo condensation between arylhydrazines and chalcones to obtain even better results.[20] The catalyst can be recycled without losing much of its catalytic activity, making it a cost-effective and sustainable process. [19]

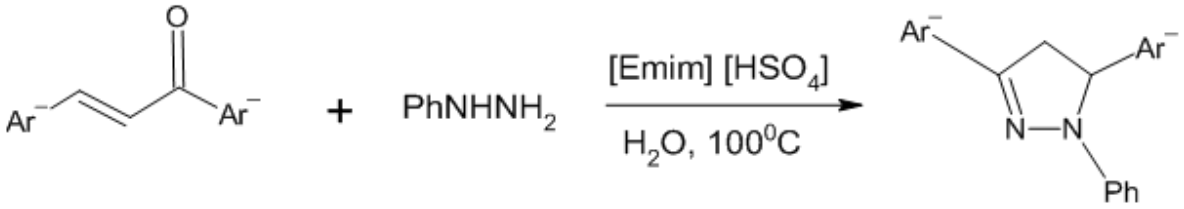


Figure No.4: Synthesis of pyrazoline derivatives using ionic liquid

5. Grinding technique: -

Milling is an effective technique for mixing substrates efficiently under solvent-free reaction conditions. The method involves using a simple apparatus such as pestles and mortars, through mixing and triturating mills. The grinding technique was developed as a new method for synthesizing organic heterocycles using mechanical techniques from ball milling as shown in Figure no 5. [21,22]This method requires mechanical engineering to grind the powder into finer particles. Unlike the classical method where reactants are broken down with solvent molecules, ball milling breaks down reactants using mechanical forces, resulting in an amorphous mixture of all reagents, and the reaction takes place on a larger surface. Despite being a rare technique in organic synthesis, ball milling is becoming popular due to its low cost, simplicity, and ability to produce pure forms without the need for further purification. This technique is also environmentally friendly, eliminating or minimizing toxic waste and reducing waste treatment costs[21,23] Therefore, this ball grinding technique is superior to conventional methods in terms of high selectivity, efficiency, purification, easy separation, mild reaction conditions, and safety for the surrounding environment.[22]

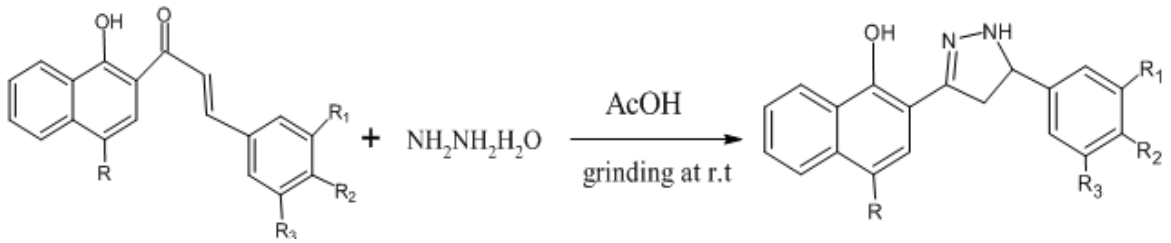


Figure No.5: Synthesis of pyrazoline derivatives using grinding technique under solvent-free conditions

Experimental Methods: -

Synthesis of 1- Isonicotinoylpyrazolidine-3, 5-dione:

Conventional method:

Two different methods were used to synthesize compound 1 using isonicotinohydrazide and diethyl malonate as starting materials. In the first method, isonicotinohydrazide (0.01 mole), diethyl malonate (0.01 mole), acetic acid (0.05 mole), and absolute ethanol (20.0 mL) were mixed in a round bottom flask and refluxed in a water-bath for approximately 11-12 hours.

Microwave method:

In the second method, isonicotinohydrazide (0.01 mole), diethyl malonate (0.01 mole), and a few drops of glacial acetic acid were mixed in an Erlenmeyer flask. The mixture was then stirred and irradiated in a microwave oven for 3 minutes at 40% power (i.e., 480 W). The

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 734-743 www.ijprajournal.com ISSN: 2456-4494

reaction was monitored using TLC. After cooling, the brownish oily product was recrystallized from ethanol to obtain compound 1. The spectral and analytical data of the obtained compound were similar for both the conventional and microwave methods.Isonicotinohydrazide (0.01 mole), diethyl malonate (0.01 mole), acetic acid (0.05 mole), and absolute ethanol (20.0 mL) were taken in a round bottom flask. The mixture was well stirred and refluxed in a water bath for about 11-12 hr.

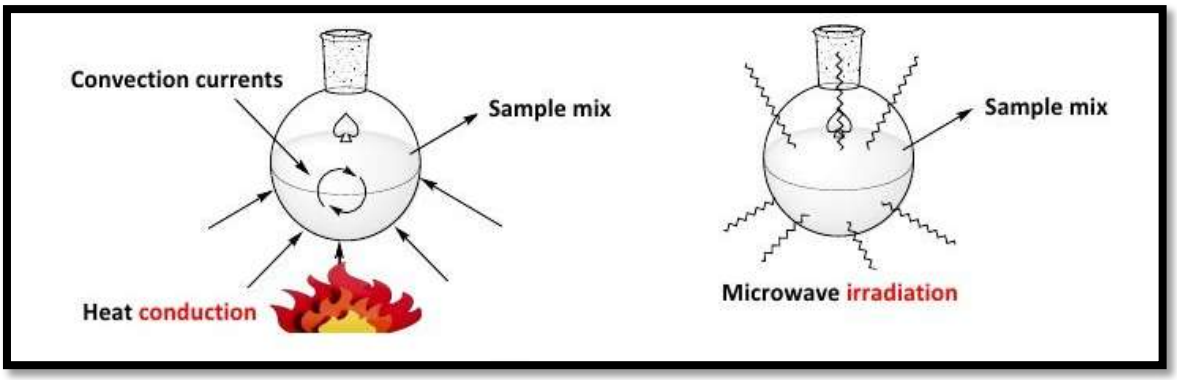


Figure No.6: Microwave vs Conventional Heating

Pharmacological activities: -

1. Antidiabetic activity: -

Diabetes is characterized by insulin deficiency in the body, which results in impaired lipid, carbohydrate, and protein metabolism. This causes hyperglycemia and glycosuria. Pyrazolines with B-amino acyl group[24]developed by were found to be inhibitors of DPP-IV at submicromolarconcentrations. The activity was attributed to the inhibition of the CYP3A4 enzyme. reported the blood glucose-lowering property of benzene sulphonamide-bearing pyrazoline.

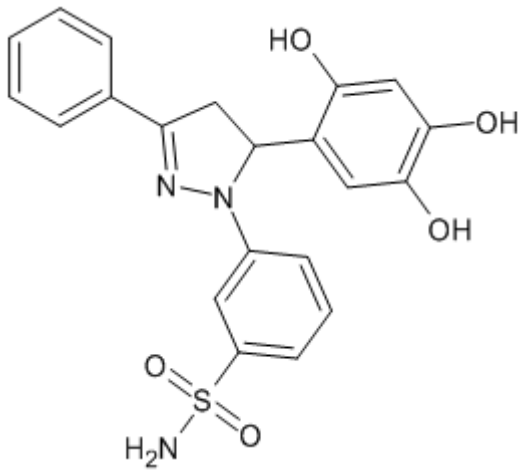


Figure No.7: Benzene sulphonamide

2. Cardiovascular activity: -

Cardiovascular diseases have undergone significant changes in therapy due to a better understanding of the disease's pathology. However, they continue to be the primary cause of mortality worldwide. Nonsteroidal pyrazolines [25] have been synthesized to treat hypertension and nephropathy. The compound acts as a mineralocorticoid receptor antagonist and is more potent than eplerenone. Therefore, it is currently under clinical trials. Additionally, novel Acyl CoA cholesterol acyltransferase inhibitors have been synthesized and found to have promising values.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 734-743 www.ijprajournal.com ISSN: 2456-4494

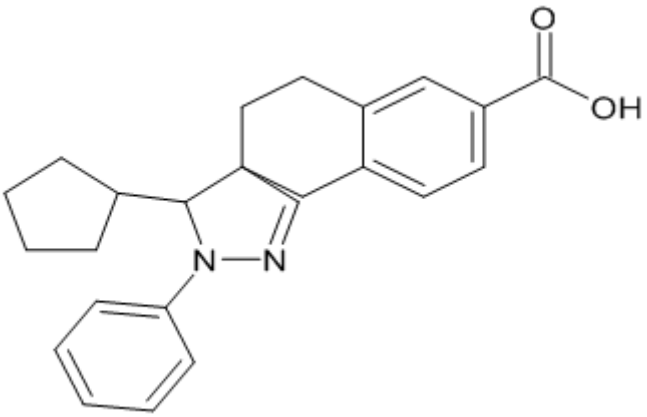


Figure No.8: Nonsteroidal pyrazoline

3. CNS activity: -

Central nervous system (CNS) disorders are a major concern, and a lot of research is being conducted in this field. Agents that act on the CNS are meant to either stimulate or suppress CNS activity depending on the patient's needs. Certain stiripentol[26]analogs were developed and evaluated for their anticonvulsant activity through the MES and PTZ methods. The compound's EDs were found to be 110mg/kg. Additionally, novel substituted diphenyl pyrazolines were synthesized to screen for anticonvulsant activity, which was evaluated by maximal electroshock seizure.

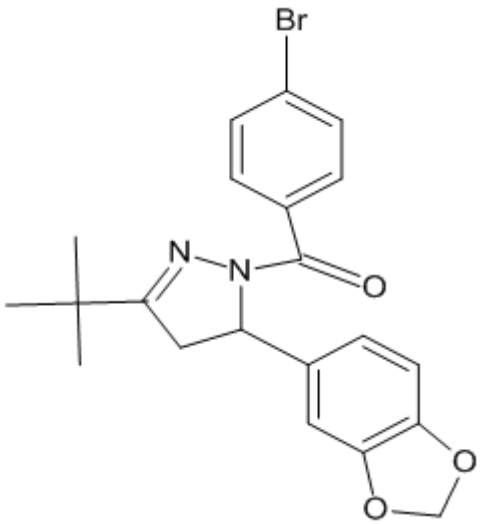


Figure No.9: Stiripentol

4. Antiviral activity: -

Viruses are obligate cellular parasites that require the host's cellular machinery for multiplication. The most common viral infections include the common cold, influenza, hepatitis, chickenpox, measles, mumps, and AIDS. Pyrazolines were synthesized and demonstrated anti-HIV activity with appreciable MIC value. Through high throughput screening, pyrazolines were identified as effective against West Nile Virus. The protease inhibition of SARS virus by pyrazolines was also reported. The compounds showed promising results with no cytotoxicity.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 734-743 www.ijprajournal.com ISSN: 2456-4494

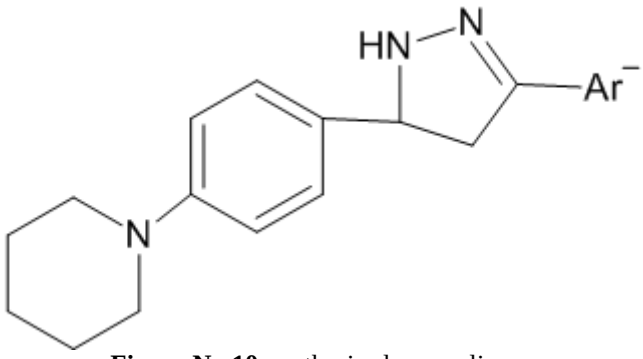


Figure No.10:synthesised pyrazoline

5. Antitubercular activity: -

Tuberculosis is a chronic infection caused by different strains of Mycobacterium tuberculosis. Over the decades, it has become a global health concern primarily due to the rise of resistant strains of bacteria. This emphasizes the need for the discovery of novel therapeutic agents against the disease. Certain pyrazoline-derivatizedcarbazoles[28] were synthesized as antitubercular agents, with a MIC of 3.5 µg/mL, and compared against the standards streptomycin and pyrazinamide. Substituted pyrazolines were also synthesized and tested for antitubercular activity. The best compound had a MIC of 0.0034 µM. Pyrazolines with antitubercular activity against INH-resistant strains were also developed, with a MIC of 0.26 um. 3-pyrazolines were also developed with good antitubercular activity, although the observed activity was less than the standard isoniazid.

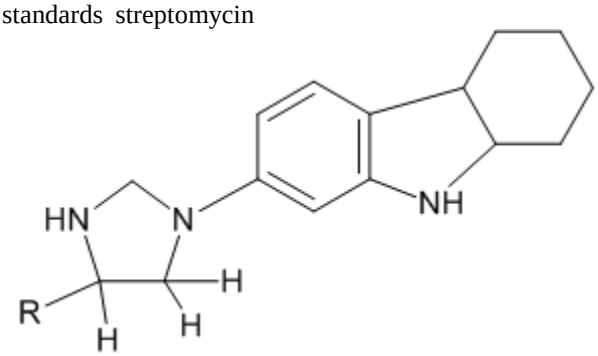


Figure No.11: Carbazole

II. CONCLUSION: -

Pyrazoline derivatives are synthesized using various methods. However, the conventional method has limitations in achieving high product yield. Researchers explore alternative methods to produce better-quality products by modifying solvent concentration, temperature, and catalyst. Microwave-assisted synthesis is a convenient and efficient method that uses microwaves to reduce reaction time, resulting in high-quality products. This method has several advantages over conventional methods, reducing energy consumption and increasing product yields. It is used in multistep total synthesis, medicinal chemistry, drug discovery, polymer synthesis, material sciences, nanotechnology, and biochemical processes.

REFERENCES: -

[1]. Thirunarayanan G, Mayavel P, Thirumurthy K, Kumar SD, Sasikala R, Nisha P, Nithyaranjani A. Eco-friendly synthesis and spectral correlations in some 1-phenyl-3- (5-bromothiophen-2-yl)-5-(substituted phenyl)-2- pyrazolines. European Chemical Bulletin. 2013 Apr 18; 2(9):598-605.

[2]. Khan SA, Asiri AM, Kumar S, Sharma K. Green synthesis, antibacterial activity and computational study of pyrazoline and pyrimidine derivatives from 3- (3, 4-dimethoxy-phenyl-1-(2, 5-dimethyl-thiophen-3- yl)-propenone. European

Journal of Chemistry. 2014 Mar 31; 5(1):85-90.

[3]. Al-Bogami AS, Alkhathlan HZ, Saleh TS. Microwave Enhanced Green Synthesis of 2-Pyrazolines, Isoxazolines and Cyclohexenones. Asian Journal of Chemistry. 2013 Jul 21; 25(11):6427.

[4]. Santhi N, Emayavaramban M, Gopi C, Manivannan C, Raguraman A. Green synthesis and antibacterial evaluation of some 2-pyrazoline derivatives. International Journal of Advanced Chemistry. 2014 Mar 9; 2(2):53-8.

[5]. ElShora AI. Crystal and molecular structure of 3- hydrazino-1-hydrazinothio-carbonyl pyrazoline (TNT3). Egypt J Sol. 2000; 23:251-4.

[6]. MeilindaSetyaPraceka, Sandra Megantara, Rani Maharani, MuchtaridiMuchtaridi, Comparison of various synthesis methods and synthesis parameters of pyrazoline derivates,2021, Journal of Advanced Pharmaceutical Technology & Research, 321-326.

[7]. Mahesh G Kharatmol, Deepali M Jagdale, Eco-Friendly Synthesis of Pyrazoline Derivatives, International Journal of Pharmaceutical and Clinical Research 2017; 9(4): 302-308.

[8]. Sharma BK, Ameta SC, Dwivedi VK. Ecofriendly Synthesis of Chalcones and Their 2-Pyrazoline andIsoxazolines Derivatives as Potential Microbial Agents. Int J Chem Sci. 2014; 12:1121-34.

[9]. Prajapati J, Dulawat M, Prajapat P, Rathore R, Dulawat SS. Microwave Induced Synthesis of Pyrazoline Compounds Containing Substituted Benzyloxy Phenyl Ring System. IRAInternational J Appl Sci. 2016; 04:145-51.

[10]. Jasril, Yuda HT, Aisyah, Nurlaili, Hendra R. Microwave Assisted Synthesis and Evaluation of Toxicity and Antioxidant Activity of Pyrazoline Derivatives. Indones J Chem. 2019; 19:583-91.

[11]. Akhtar W, Khan MF, Verma G, Akhter M. Coumarin-Pyrazoline Derivatives: Their One-Pot Microwave Assisted Synthesis and Antimalarial Activity Coumarin-Pyrazoline Derivatives: Their One-Pot Microwave Assisted Synthesis and Antimalarial Activity. J Pharm Med Chem. 2017; 3 Number 1:5-9.

[12]. Trilleras J, González-López E, León-Jaramillo J, Pérez-Gamboa A, Puello-Polo E, Romo P, et al. Syntheses, experimental and theoretical studies on absorption/emission properties of pyrazoline-containing aryl/methoxy naphthyl substituents. J Braz Chem Soc. 2018; 29:1210-17.

[13]. Patil PO, Belsare DP, Kosalge SB, Fursule RA. Microwave-assisted Synthesis and antidepressant activity of some. Int J Chem Sci 2008; 6:717-25.

[14]. Nayak J, Devi C, Vidyapeeth L. Microwave-assisted synthesis: Agreen chemistry approach. Int Res J Pharm Appl Sci 2016; 3:278-85.

[15]. Nain S, Singh R, Ravichandran S. Importance of microwave heating in organic synthesis. Adv J Chem A 2019; 2:94-104.

[16]. Emayavaramban M, Santhi N, Gopi C, Manivannan C, Raguraman A. Synthesis, characterization and anti-diabetic activity of 1,3,5-triaryl-2-pyrazolines in acetic acid solution under ultrasound irradiation. Int Lett Chem Phys Astron 2013; 14:172-85.

[17]. de Albuquerque DY, Damim AC, Faoro E, Casagrande GA, Back DF, Moura S, et al. Ultrasound-Promoted Synthesis, Structural Characterization and. 2019;00:1-10.

[18]. Ashok SP, Sunil DJ, Arvind SB, Santosh S, Ramesh BG. Ultrasound-Assisted Synthesis of 1,5-Diaryl and 1,3,5-Triaryl-2-pyrazolines by Using KOH/EtOH System with Cu(I) Catalyst. Asian J Chem. 2018; 32:894-96.

[19]. Kagne DR, Kalalawe VG, Niwadange SJ. A novel assent for the synthesis of pyrazoline derivatives by adopting graphene oxide nanosheets as carbon catalysts at reflux conditions. Int J Green Herb Chem 2018; 7:469-76.

[20]. Peter W, Wilhelm K. Ionic Liquids New Solutions for Transition Metal Catalysis. Angew Chem Int. 2000; 39:3772-89.

[21]. Zangade SB, Mokle SS, Shinde AT, Vibhute YB. An atom-efficient, green synthesis of 2-pyrazoline derivatives under solvent-free conditions using a grinding technique. Green Chem Lett Rev 2013; 6:123-7.

[22]. Safaei-Ghomi J, Masoomi R. Grinding-induced synthesis of

heterocyclic fullerene derivatives under solvent-free conditions. Chem Heterocyclic Compound 2015; 51:39-43.

[23]. M'Hamed MO. Ball milling for heterocyclic compounds synthesis in green chemistry: A review. Synth Commun 2015; 45:2511-28.

[24]. Jun, M.A.; Park, W.S.; Kang, S.K.; Kim, K.Y.; Kim, K.R.; Rhee, S.D.; Bac, M.A.; Kang, N.S.; Sohn, S.K., Kim, S.G.; Lee, J.O.. Lee, D.H.; Cheon, H.G.; Kim, S.S.; Ahn, J.H. Synthesis and biological evaluation of pyrazoline analogues with B-amino acyl group as dipeptidyl peptidase IV inhibitors. Eur. J. Med. Chem., 2008, 43, 1889-1902.

[25]. Meyers. M.J.; Arhancet, G.B.: Hockerman, S.L.: Chen, X.; Long, S.A. Maloney, M.W., Rico, J.R.: Garland. DJ: Blinn, J.R.; Collins, J.T. Yang, S. Huang, H.C. McGee. K.F. Wendling, J.M.: Dietz, J.D., Payne, M.A. Homer, B.L.: Heron, M.J.: Reitz, D.B.. Hu, X, Discovery of (38.3R)-2-(3-Chloro-4-cyanophenyl)- 3-cyclopentyl-3,3a 4.5-tetrahydro-2H-benzol glindazole-7- carboxylic acid (PF-38828451. orally efficacious mineralocorticoid receptor (MR) antagonist for hypertension and nephropathy. J. Med. Chem., 2010, 53.5979-6002.

[26]. Engin, M.N.A., El-Azzouny, A.A.: Att. M.I.: Makhad, Y.A.: Amin, K.M.: Rehim, MA; El-Behairy, M.F. Design and synthesis of novel stirpentol analogues as potential anticonvulsants. Eur. J Med. Chem. 2012, 47, 360-369.

[27]. Rizvi, S.U.F.; Siddiqui, H.L; Johns, M.; Detorio, M.; Schirazi R.F. Anti-HIV-1 and cytotoxicity studies of piperidyl-thienyl chalcones and their 2-pyrazolines derivatives. Med. Chem. Res. 2011, 21, 3741-3749.

[28]. Taj. T.: Kamble, R.R. Gireesh, T.M.; Hunnur, R.K.: Margankop, S.B. One-pot synthesis of pyrazoline derivatives carbazoles as antitubercular, anticancer agents, their DNA cleavage and antioxidant activities. Eur. J. Med. Chem, 2011, 46, 4366-4373.