

RESEARCH ARTICLE

 MICROWAVE ASSISTED SYNTHESIS OF SOME PYRAZOLINE DERIVATIVES AS POTENT
ANTICANCER AGENT: A REVIEW

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ABSTRACT

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Heterocycles have attracted considerable attention in the design of biologically active molecules. The class of pyrazolines possesses a broad spectrum of biological effectiveness including anticancer activities. pyrazoline derivatives is quite stable and has inspired chemists, to utilize pyrazoline fragment in bioactive moieties, to synthesize new pyrazoline derivatives. The past studies of pyrazoline derivative revealed that they are useful in pharmaceutical and agrochemical research. Pyrazoline derivatives display various biological activities such as antitumor, antitubercular, antimicrobial, antibacterial, anti-inflammatory and antioxidant etc

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INTRODUCTION

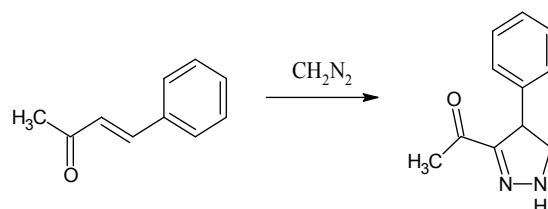
 The study of biological evaluation of pyrazoline derivatives has been an interesting field of medicinal chemistry. The synthesis of pyrazoline derivatives and investigation of their chemical and biological behavior has gained more important in recent decades for biological and pharmaceutical reasons. The synthesis of pyrazole derivatives has been well explored using the so-called [3+2] atom fragments, where β -diketones or α, β -unsaturated ketones are used as the 3-atom building block and hydrazines as the 2-atom fragment. Pyrazolines are a five membered heterocyclic having two adjacent nitrogen atoms within the ring with only one endocyclic double bond and is basic in nature. Pyrazoline exhibit biological activities such as anti-inflammatory, antimicrobial, antitumor, antitubercular etc.

GENERAL METHODS OF PREPARATION OF PYRAZOLINES

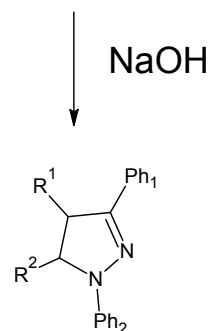
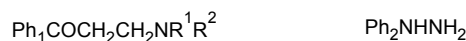
 1. Benzylideneacetone on reaction with diazomethane by 1,3-dipolar cycloaddition yield 2-pyrazolines. This is probably the first example of the synthesis of a pyrazoline from the reaction of an α, β -unsaturated ketone and diazomethane and was published by Azzarello (1906). Later, this reaction was reinvestigated by Smith and Howard (1943) and by Raju and Rao (1989) and the assumption made by Azzarello were corroborated.

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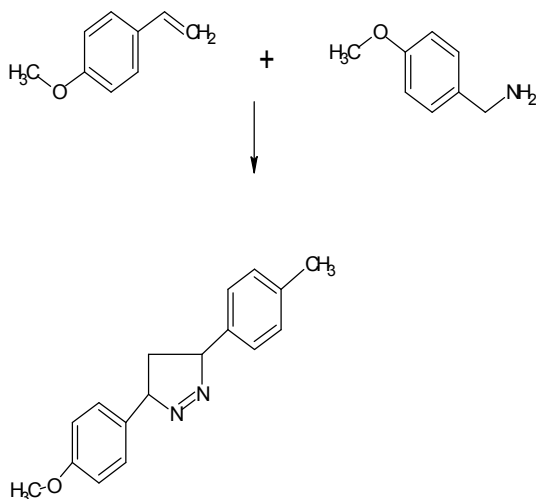
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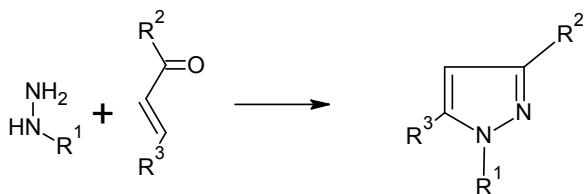
2. Mannich bases on reaction with phenylhydrazine and aqueous ethanolic NaOH at reflux temperature yield substituted 2-pyrazolines 4


 3. Cycloaddition reaction of substituted styrenes with *p*-anisyl diazomethane at

low temperature yield *trans*-3,5-bis-(*p*-anisyl)-1-pyrazoline(5)

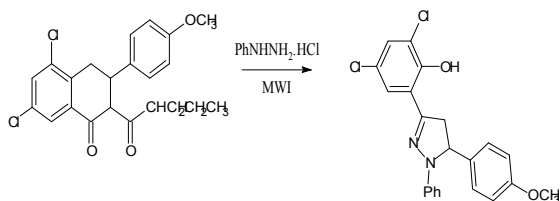


4. The reaction of chalcones with hydrazines is probably the most popular procedure for the synthesis of 2-pyrazolines. The most commonly used method is the reaction of hydrazine and the chalcones in acetic acid solution to prepare 2-pyrazolines in high yield (6-8). Synthesis of 2-pyrazolines can also be achieved under alkaline conditions by using pyridine as catalyst in ethanolic solution (9). In some cases the two reactants were refluxed in alcoholic solution without a catalyst to provide 2-pyrazolines (10,11)



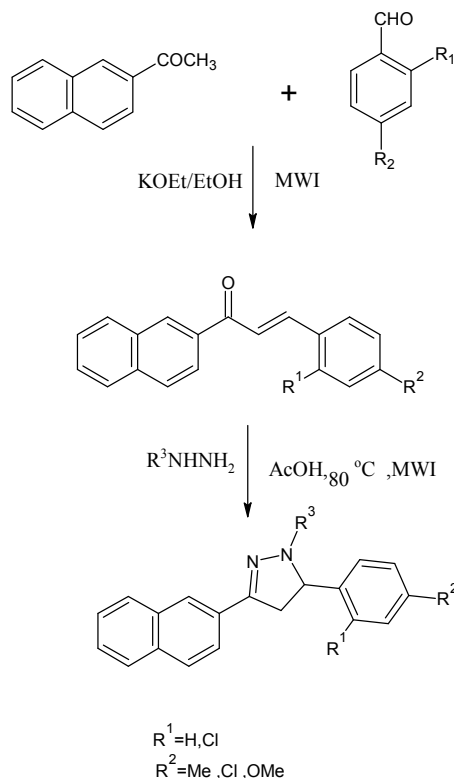
MICROWAVE ASSISTED REACTIONS

1. **Boob and Rajput** (12) synthesize pyrazoline by using a mixture of the 3-aryol/alkoylflavanone (0.01mole) and phenylhydrazine hydrochloride (0.02 mole) was dissolved in ethanol (5mL) then K₂CO₃ (4 gm) was added stirred vigorously. After 5 min. solvent was removed under vacuum and the dry powder to irradiated in the microwave oven for the appropriate time. After the completion of reaction chilled water was added to the reaction mixture. The solid product thus obtained, was filtered dried and crystallized from suitable solvent (Ethanol).



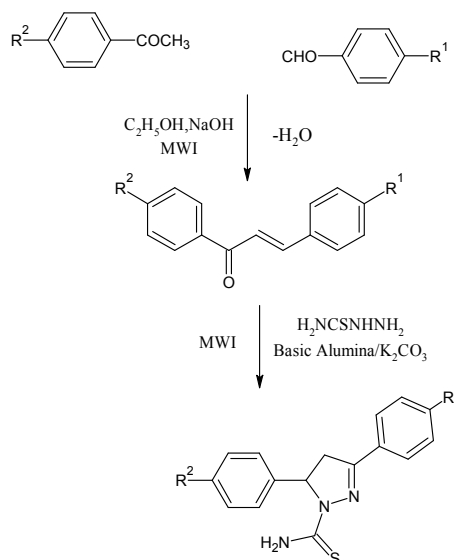
2. **Davood and Hassan** (13) synthesize pyrazolines by Condensation of 2-acetylnaphthalene with benzaldehydes under microwave irradiation affords chalcones which undergo facile and clean cyclizations with hydrazines

RNHNH₂ (R= H, Ph, Ac) to afford 3,5-arylated 2-pyrazolines in quantitative yields, also under microwave irradiation and in the presence of dry AcOH as cyclizing agent.

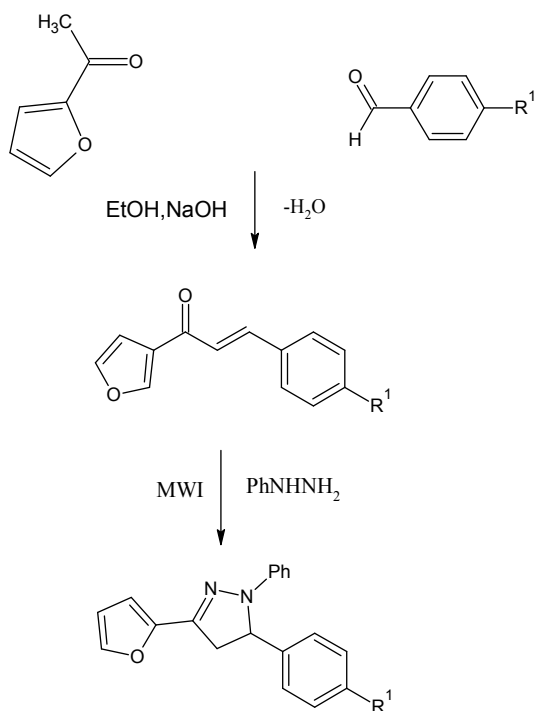


3. **Rakesh Chawla et al** (14) Synthesis of 3-substituted phenyl-5-substituted

phenyl-4,5-dihydro-pyrazole-1-carbothioamides using a mixture of the chalcone (0.022 mol) and thiosemicarbazide (0.02 mol) was dissolved in acetone (5 mL) and ethanol (5 mL), respectively. Basic alumina (4 g) was added and stirred vigorously. After 5 min, the solvent was removed under vacuum and the dry powder was irradiated in a microwave oven for the appropriate time, at 650 W. After completion of the reaction the product was eluted with acetone. Removal of the solvent under reduced pressure yielded the product which was recrystallized from acetone-ethanol mixture.



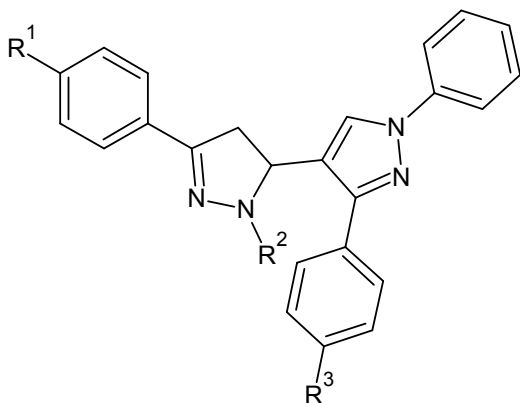
4. **Phirke and Meshram**(15) synthesize pyrazoline using a solution of 2-furyl acetone(0.05mole) and appropriately substituted benzaldehyde (0.05mole) in ethanol taken in conical flask. Sodium hydroxide was added into reaction mixture. Reaction mixture zapped in microwave oven for 30 sec to 1 min at 180 watt and then cooled in refrigerator overnight. The product obtained was filtered and washed with water and recrystallization from ethanol. Then these synthesized chalcones reacts with phenyl hydrazine in microwave oven at 180 watt gives different substituted pyrazolines.



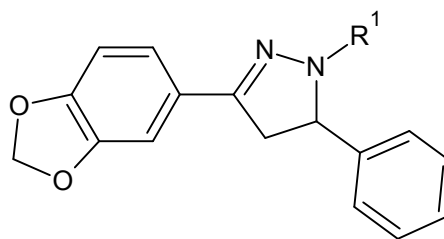
BIOLOGICAL ACTIVITY OF PYRAZOLINES

ANTITUMOR ACTIVITY

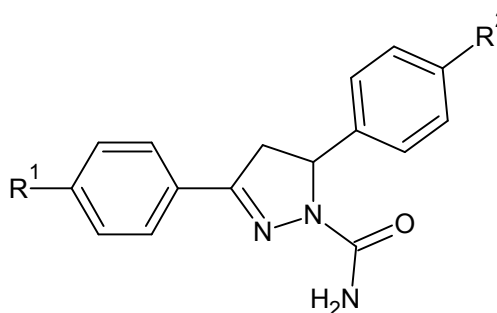
Braulio Insuasty et al (16) synthesized a series of novel 3-aryl-4-(3-aryl-4,5-dihydro-1H-pyrazol-5-yl)-1-phenyl-1H-pyrazoles and screened their antitumor activity.



Braulio Insuasty et al. (17) synthesized a series of 1-substituted 3-aryl-5-aryl(hetaryl)-2-pyrazolines and study of their antitumor activity.

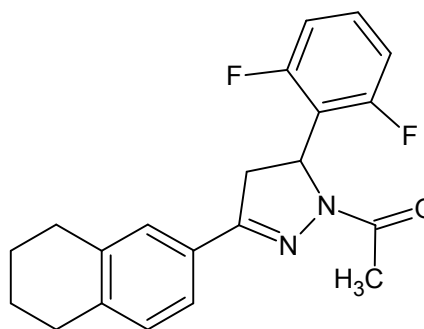


Hai-Liang Zhu et al.(18) Synthesized a series of 3-(substituted phenyl)-5-(substituted phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide and 1-(5-(substituted phenyl)-3-(substituted phenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone as anticancer agents



Anticancer Activity

Ebtehal S. Al-Abdullah (19) synthesized compounds and were tested for in vitro cytotoxic activity against cancer cell lines, newly synthesized compounds showed certain activity against tumor cell. The Compound below showed potent and broad antitumor activity against tumor cell lines compared to the potent anticancer drug 5-flourouracil (5-FU) used as a reference standard



Conclusions

Pyrazoline ring containing compounds with alkylating groups can act as antitumor agents, further alkoxy groups and halogen atoms as substituent groups on the aromatic ring of the molecules can show significant anticancerous activity. Microwave synthesis is rapid, efficient and environmentally friendly method for synthesis of pyrazolines, and the results obtained confirm the superiority of the microwave irradiation method over the classical heating one.

REFERENCES

- Azzarello, J., 1906. *Gazz. Chim. Ital.*, 36, 50.
- Smith, L.I. and Howard, K.L., 1943. *J. Am. Chem. Soc.*, 65, 165.
- Raju, G.V.S. and Rao, K.S., 1989. *Curr. Sci.*, 58, 1030.
- Sammour, A.E.A., 1967. *Tetrahedron*, 20, 1067.
- Overberger, C.G., Weinshenker, N. and Anselme, J.P., 1965. *J. Am. Chem. Soc.*, 87, 4119.
- Raiford, L. C. and Entrikin, J. B., 1933. *J. Am. Chem. Soc.*, 55, 1125.
- Auwers, K. V. and Voss, H., 1909. *Ber. Dtsch. Chem. Ges.*, 42, 441. 147.
- Auwers, K. V. and Lammerhirt, 1921. E., *Ber. Dtsch. Chem. Ges.*, 54, 1000.
- Anjaneyulu, A.S.R., Sudha Rani, G., Gowri Annapurna, K., Mallavadhani, U.V. and Murthy, Y.L.N., 1995. *Indian J. Chem.*, 34, 933.
- Auwers, K. V. and Heimke, P., 1927. *Ann. Chem.*, 458, 186.
- Habib, O.M.O., Khalil, A.M., Kandeel, E.M. and Abdalla, E.B., 1986. *Rev. Roum. Chim.*, 31, 629.
- Boob and Rajput, Orient. 2010. *J. Chem.*, Vol. 26(3), 879-889.
- Rakesh Chawla *et al*, 2010. *Acta Poloniae Pharmaceutica n Drug Research*, Vol. 67 No. 1, pp. 55- 61.
- Phikre and Meshram, 2014. *Indian J. Applied Res.*, Volume : 4 | Issue : 7 | July.
- Braulio Insuasty, Alexis Tigreros, Fabian Orozco, Jairo Quiroga, Rodrigo Abonia Manuel Noguerras, Adolfo Sanchez, and Justo Cobo. 2010. Synthesis of novel pyrazolic analogues of chalcones and their 3-aryl-4- (3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-1- phenyl-1*H*-pyrazole derivatives as potential antitumor agents, *Bioorg. Med. Chem.*, 18(14): 4965–4974.
- Braulio Insuasty, Leidy Chamizo, Jhon Munoz, Alexis Tigreros, Jairo Quiroga, Rodrigo Abonia, Manuel Noguerras, and Justo Cobo. 2012. Synthesis of 1-substituted 3- a yl-5-aryl (hetaryl)-2- pyrazolines and study of their antitumor activity, *Arch. Pharm. Chem. Life Sci.*, 345: 275–286.
- Peng-Cheng Lv, Huan-Qiu Li, Juan Sun, Yang Zhou, and Hai-Liang Zhu, 2010. Synthesis and biological evaluation of pyrazole derivatives containing thiourea skeleton as anticancer agents, *Bioorg. Med. Chem.*, 18(13): 4606–4614.
- Ebtehal S. Al-Abdullah, *Molecules* 2011, 16, 3410-3419.
