IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

"Synthesis And Characterization Of Heterocyclyl Substituted Pyrazoles And Antibacterial Activity"

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Abstract: The present research has systematic approach to synthesized a series of benzothiazolyl and benzimidazolyl substituted derivatives and to study their antimicrobial activity. The compounds were synthesized by green chemistry technique. i.e. 2-(2-(5-methyl-2,4-dihydro-3H-pyrazol-3-ylidene) hydrazinyl)benzothiazole. , 5-methyl-N-(2-phenylthiazol-5-yl)-2,4-dihydro-3H-pyrazol-3-imine. , 5-methyl-N-Phenyl-2,4-dihydro-3H-pyrazol-3-imine. , N'-(5-methyl-2,4-dihydro-3H-pyrazol-3-ylidene)isonictinohydrazide., N'-(5-methyl-2,4-dihydro-3H-pyrazol-3-ylidene)benzohrdrazide., and 2-hydroxy-N'-(5-methyl-2,4-dihydro-3Hpyrazol-3-ylidene)benzohydrazide. Antimicrobial study of these series of compounds was implemented with respect to *Klebsiella pneumoniae, Escherichia coli and Staphylococcus aureus*. Structures of all the newly synthesized compounds were confirmed by their IR, ^{1}H-NMR analysis. The selected compounds may be used to design more potent biologically active compounds.

Index Terms - Heterocyclyl Compounds, Substituted Pyrazoles, Pharmaceuticals, Applicability study

I. INTRODUCTION

Diverse Methods for Synthesis of novel heterocylyl derivatives of pyrazoles. The reaction of 1,3-diketones with hydrazine derivatives is the most widely used synthesis method for pyrazole derivatives [1-4]. Showing straightforward methods for the synthesis of pyrazole derivatives is one of the main issues [5]. In Green chemistry reactions was carried out at room temperature [6-10] without the need for organic solvents and without producing waste, is another crucial area of research in synthetic organic chemistry [11-15]. For instance, microwave and ultrasonic irradiation are used in solvent-free heterocyclic compound production. In the past few decades, microwave (MW) irradiation has been extensively [16] used to operate a variety of chemical synthesis processes. Dielectric heating produced by a microwave source can typically be combined with three different solvent-free processes [17] Phase transfer catalysis reactions, reactions between plain reagents, and reactions between supported reagents on mineral solid supports [18]. One of the three solventless methods, the pure reagent is routinely used because of the ease of preparation and the use of little solvent [19]. In particular, the application of microwave-assisted organic synthesis (MAOS) is becoming increasingly common in heterocyclic chemistry and especially in the synthesis of pyrazole derivatives [20]. Another way to promote green chemistry is the synthesis of pyrazole derivatives in aqueous media. There are many advantages to using water because water is cheap, readily available and environmentally friendly [21]. Water is a favourable solvent both economically and environmentally [22].

The unique structure and physicochemical properties of water, in addition to the trans phase interaction, also create special interactions between polarity [23], hydrogen bonds and hydrophobic effects that can influence the course of the reaction. In general, pyrazole derivatives are synthesized as a series of molecules [24-27]. Therefore, combinatorial synthesis is also mentioned in the current literature. In addition to combinatorial synthetic approaches in green chemistry, metal-assisted synthetic methods have been developed to produce new pyrazole derivatives [28-29].

In present work, we have synthesized the multi derivatives, this research articles existing a extremely skilled method for the synthesis of N-heterocyclic compounds with keto and thiazoles using alkaline medium in ethanol as a solvent under mild reaction conditions. (the product separation was done by extraction method, as extracting solvent is ethyl acetate and water. As the excess mineral acid were removed while extraction with extracting solvent (ethyl acetate) and water.

MATERIALS AND METHODS

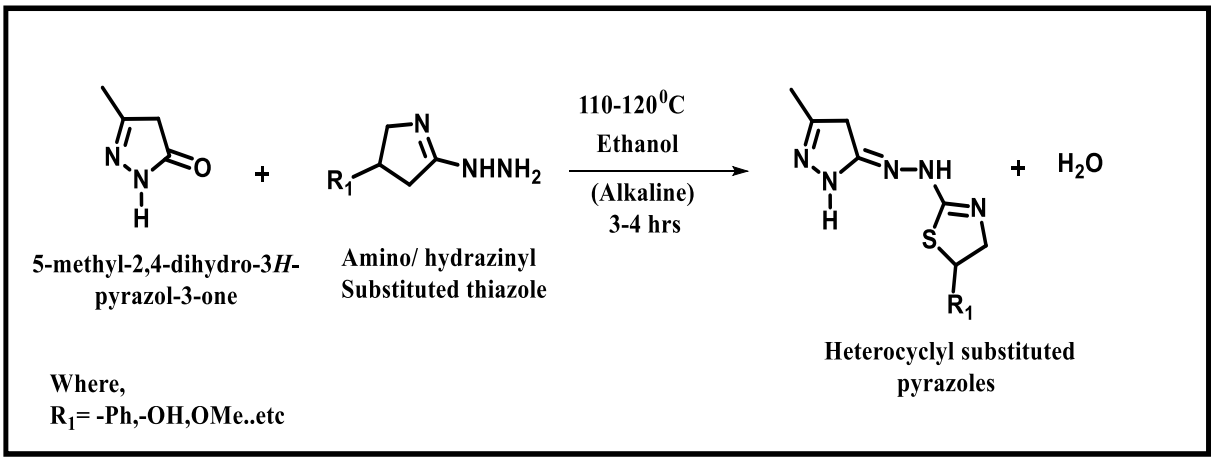
Methanol (99.5 %), Ethanol (99.9%), Aniline (98%), (97%), Sodium hydroxide (98%), substituted pyrazoles and substituted hydrazine thiazoles were purchased from SD Fine-Chem Ltd. Ethyl acetate (98%) were procured from Avra Chemical Pvt. Ltd. Sodium chloride were acquired from Sisco Research Laboratories Pvt. Ltd.

CHARACTERIZATION TECHNIQUE

The Chemical structure of synthesized compounds was confirmed by spectral data. ^{1}H-NMR spectra were recorded on BRUKER AVANCE NEO 500 MHz spectrometer using DMSO and $CDCl_3$ solvent and TMS as internal standards at SAIF, Punjab University, Chandigarh (India). Chemical shifts are expressed in ppm.

MODEL REACTION FOR SYNTHESIS OF PYRAZOLES DERIVATIVES

The synthesis of various N-heterocyclic substituted pyrazoles was developed by adapting from the literature. To a 50 mL round bottom flask substituted thiadiazol was added with alkaline medium and stirred for 3-5 minutes and addition of ethanol as a solvent and refluxed for 3-4 hr. Then after completion of reaction, the reaction mixture was taken in separating funnel and added the equimolar quantity of extracting solvent (ethyl acetate) and water with brine solution. and shake the separating funnel with 2-3 times properly for which the products can be easily separable. And then allow to stand the separating funnel for few minutes. We can saw the two layers one is organic layer (the product with ethyl acetate) and other layer with water. Drained out the water layer and collect the organic layer and kept it with 12 hr. with sodium sulphate for the absorption of excess moisture or water in organic layer. Lastly evaporate the organic layer by rotatory evaporator to get desired product via recrystallization with ethanol with water. And its structural analysis was confirmed by ^{1}H NMR



Scheme 1. Synthesis of Heterocyclic substituted pyrazole

Table 1. Schemes of Derivatives

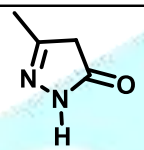
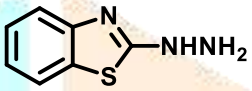
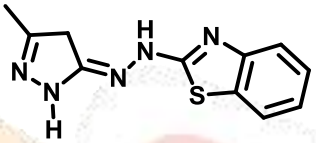
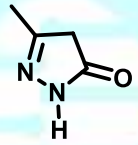
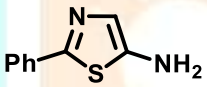
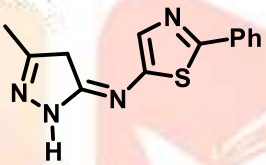
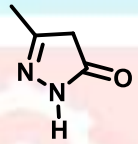
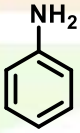
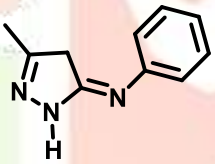
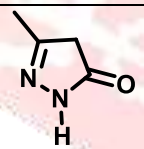
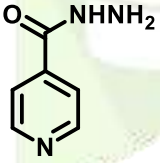
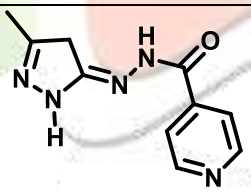
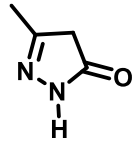
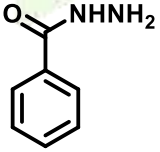
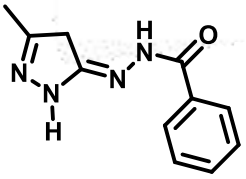
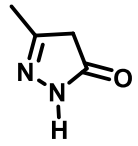
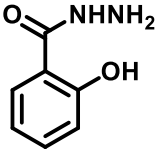
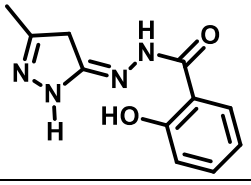
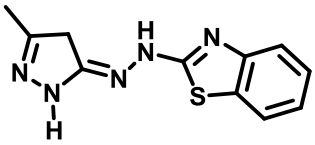
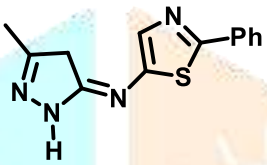
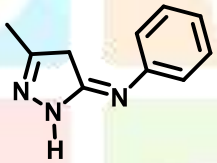
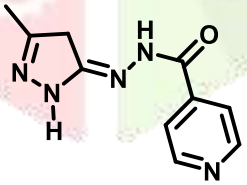
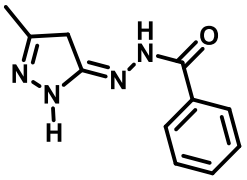
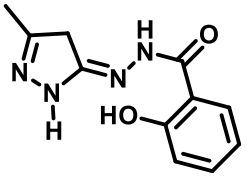
Sr. No	R1	R2	Product	Time In Hrs	Yield %
1				4	71
2				3	79
3				4	76
4				4	81
5				3.5	84
6				2	74

Table 2. Structural analysis of derivatives by^{1}HNMR

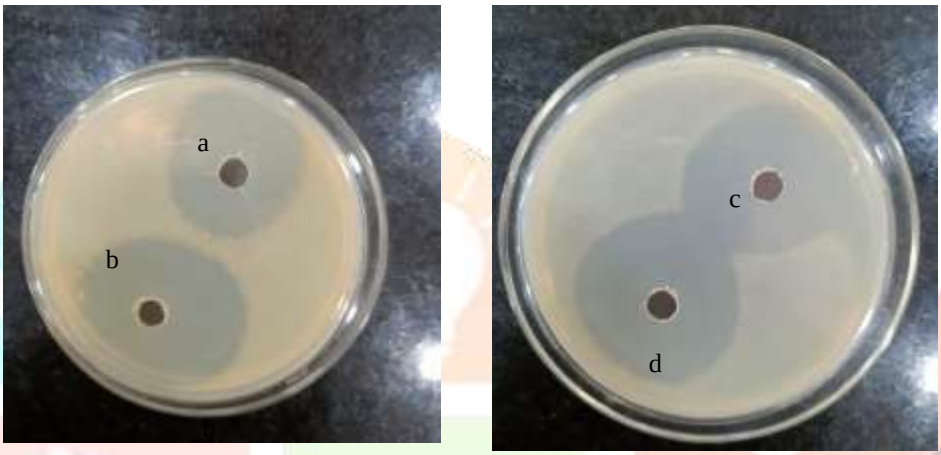
Structural Analysis

Sr .No.	Name of Compound	^{1}H NMR Analysis
1	(E)-2-(2-(5-methyl-2,4-dihydro-3H-pyrazol-3-ylidene)hydrazinyl)benzo[d]thiazole. 	^{1}H NMR (500MHz,DMSO): δ11.9(s,1H),7.58.1(m,4H),6.74(s,1H), 3.12(d,2H), 1.94(s,3H),
2	(E)-5-methyl-N-(2-phenylthiazol-5-yl)-2,4-dihydro-3H-pyrazol-3-imine. 	^{1}H NMR (500MHz,DMSO): δ 8.03 (m,3H),7.517.53(m,3H), 6.74(s,1H), 3.12(s, 2H), 1.94(s,3H)
3	(E)-5-methyl-N-Phenyl-2,4-dihydro-3H-pyrazol-3-imine. 	^{1}HNMR(500MHz,DMSO): δ 7.34(t,2H), 7.07(d,2H), 6.93(d,3H)6.74(s, 1H), 3. 12(s, 2H), 1.94 (s,3H)
4	(E)-N'-(5-methyl-2,4-dihydro-3H-pyrazol-3-ylidene)isonictinohydrazide. 	^{1}HNMR(500MHz,DMSO): δ 10.8(s, 1H), 8.78(d,2H), 7.82(d,2H),6.74(s, 1H), 3. 12(s, 2H), 1.94(s,3H),
5	(E)-N'-(5-methyl-2,4-dihydro-3H-pyrazol-3-ylidene)benzohrdrazide. 	^{1}HNMR(500MHz,DMSO): δ 10.8(s,1H)7.95(d,2H), 7.547.62(m,3H), 6.74(s,1H), 3.12(s, 2H), 1.94(s,3H)
6	(E)-2-hydroxy-N'-(5-methyl-2,4-dihydro-3Hpyrazol-3-ylidene)benzohydrazide. 	^{1}HNMR(500MHz,DMSO): δ 11.57(s,1H), 10.8(s,1H), 7.9(d,1H), 7.4(d,1H),6.94(d,2H),6.74(s,1H), 3.12(d,2H), 1.94(s,3H)

ANTIMICROBIAL AND ANTIBACTERIAL STUDY

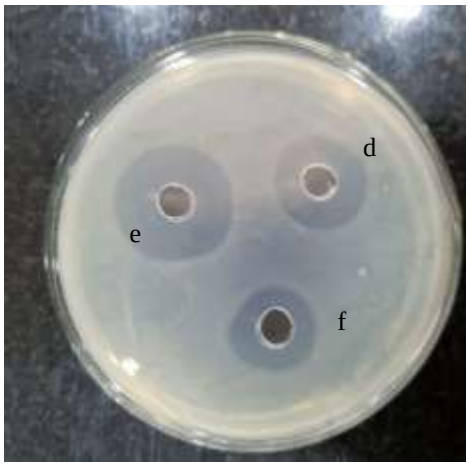
Using the agar well technique, some compounds were tested for their antibacterial properties against test organisms, including K. pneumoniae, S. aureus, and E. coli, at concentrations of 1000 mg/ml and 100 mg/ml, respectively. The medium was prepared by dissolving 28 g of ingredients in one litre of distilled water and then sterilized at 121°C temperature 151bs/ inch pressure in an auto clave for 15-20 minutes. After sterilization the medium was cooled to about 50°C and poured into sterile Petri plates and allow to solidify. The media plates then seeded with 24 hr. Old active nutrient broth cultures of the test organisms in order to get lawn culture. The standard 6 mm size wells (cups), which were then prepared in the solidified medium by using standard size borers. In aseptic conditions the operations were carried out under ultraclean air laminar flow system.[30-32]

Results of K. pneumoniae



Results of S. aureus

Results of E.coli



CONCLUSION

The synthesis of pyrazole derivatives and even their various functional group substitutions is well established. In most cases, the bioactivity of pyrazole derivatives has been studied in detail. Recently, efforts have been made to understand the various properties of pyrazole derivatives. In addition, there are some challenges to overcome. These challenges include the efficiency of high-yield synthesis, the creation of new pyrazole derivatives with bioactivity in the sub micromolar range, and the precise characterization of the properties of the derivatives. Therefore, we believe that it is necessary to explore new synthetic routes, explore different properties and find new applications for new derivatives, especially in mixtures with polymers. Therefore, the new trend of pyrazole derivatives is towards new applications in various fields. Among the tested compounds a, b, c showed potent activity against both bacteria such as Escherichia. coli and Staphylococcus. aureus and b, c showed moderate activity against E. coli and d, e, f showed inhibition against K. pneumoniae Staphylococcus. aureus Escherichia.coli bacterial species. It can be concluded that a, b, c as a template for further development through modification or derivatization to design more potent biologically active compounds. For future research the synthesized compounds will be implemented for physical parameter determination in binary solvent mixtures.

ACKNOWLEDGMENT

The authors would like to thanks authorities of Shri Shivaji Science College, Amravati for providing necessary facilities.

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