Design And Development of Pyrazole-Substituted Chalcones: A Synthetic Perspective

Satvika Kollepara Phanisri Bangaru[1], Aditya Vaddi[2], Bhavana Vaddi[3], Naga Komal Kota[4], Devi Priya Gudupu[5], Sharmila M[6], Bhaskara Raju V[7]
[1,2,3,4,5] *Student, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, AP, India.*
[6]*Asso Professor, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, AP, India.*
[7]*Principal, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, AP, India.*

***Abstract*—Pyrazole & their derivatives wide range of biological activities, such as analgesic, anti-inflammatory, antibacterial, and anticancer effects, have attracted a lot of interest in synthetic and medicinal chemistry. One of the prominent methods for synthesizing pyrazoles involves the cyclization of chalcones with hydrazine or substituted hydrazine's. Chalcones, which are α, β-unsaturated ketones, serve as versatile intermediates in heterocyclic chemistry and facilitate the construction of the pyrazole ring system. This study focusses on the controlled reactivity of chalcones with hydrazine hydrate to produce a variety of pyrazole derivatives. Chalcone-based pyrazoles have the potential to be lead molecules in the creation of novel pharmacologically active substances, as this study demonstrates.**

***Index Terms*—α, β-unsaturated ketones, Chalcone, Pyrazoles.**

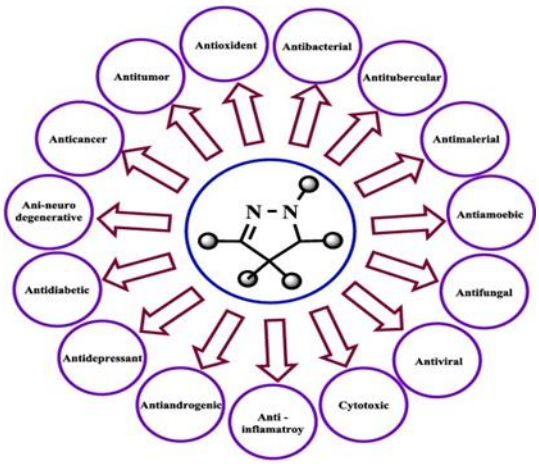
I. INTRODUCTION

Chalcone is a fundamental component of many different types of synthetic, semisynthetic, and naturally occurring compounds(Zhou B, 2015).Chalcone and its derivatives are found in abundance in a wide variety of foods and plants found in nature, including tea, vegetables, fruits, soy, and spices(Sahu N.K., 2012).Chalcones are phenolic chemicals that are members of the flavonoid class. They are among the biggest categories of naturally occurring bioactive compounds. The potential anticancer(Lopez S.N., 2001), antimicrobial(Nowakowska Z., 2008), antioxidant, anti-inflammatory(z, 2007), antiparasitic ,antibacterial properties of naturally occurring chalcones, and their unique chemical structural features inspired the synthesis of numerous chalcone derivatives. Chalcones are flavonoid-type phenolic phytochemicals, often referred to as 'open-chain flavonoids', and biosynthesized via the shikimate pathway(Nahar L., 2019).

In terms of chemistry, chalcones are typically α, β-unsaturated ketones made up of two aromatic rings (rings A and B) connected by a three-carbon alkenone unit.

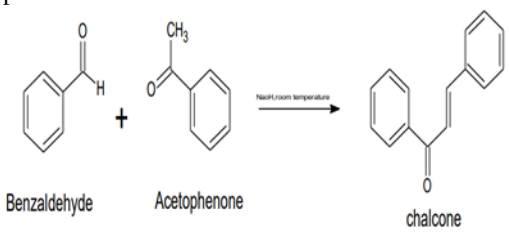
Chalcone synthesis was initially attempted in the 1800s and continued in the centuries(Gupta D, 2010). From as early as the 19th century,many researchers have developed synthetic chalcones , with Kostanecki and Tambor being acknowledged as the first to successfully prepare synthetic chalcones using a method involving treatment of o-acetoxychalcone dibromides with alcoholic alkali(Mahapatra D.K., 2015) (Hutchins W.A.). However, the current methods of chalcone synthesis utilize an alkaline base and a polar solvent to couple two coumpounds with an aromatic ring each , e.g.,acetophenone and benzaldehyde, and to produce the core chalcone nucleus(B.A, 1989)(Cazarolli L.H., 2013)(R.R, 2017)

The tissues that contain chalcones, one type of anthochlor pigments, typically have yellow to orange shade. The most yellow-colored blossoms attract insects due to their pigmentation, and they aid in pollination, even though these compounds are not the reason.(Brouillard, 1994)

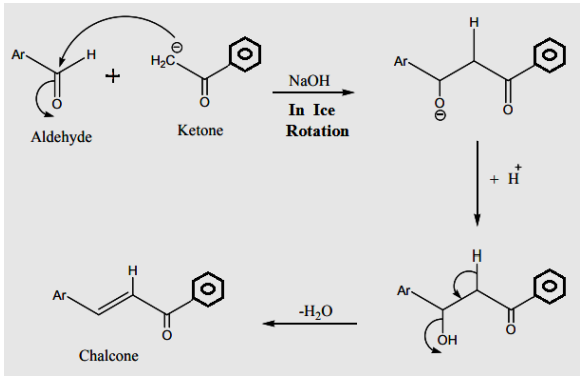


I. General synthesis of chalcones: -

An aromatic ketone (such as acetophenone) and an aromatic aldehyde (such as benzaldehyde) undergo a base-catalyzed Claisen-Schmidt condensation to produce chalcones



Mechanism: -

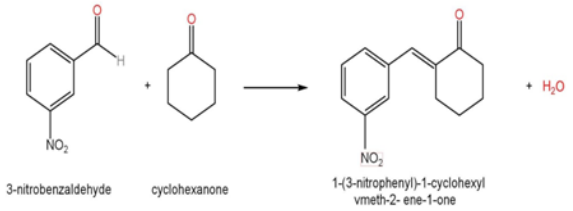


II. EXPERIMENTAL WORK

SYNTHESIS:-

1. Synthesis of 1-(3-nitrophenyl)-1-cyclohexyl meth-2-ene-1-one.

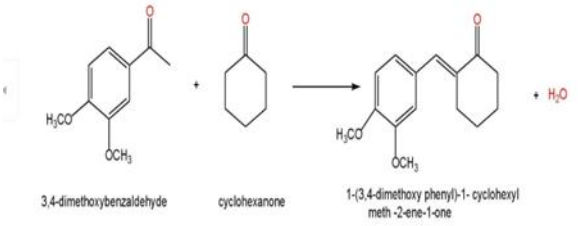
Cyclohexanone (10.36ml, 0.1M) add 30 ml of 10%NaOH was added and 50ml of ethanol in 250ml beaker with magnetic stirrer and the temp is maintained at 10C. 3-nitrobenzaldehyde (15.112gm, 0.1M) was added by drop wise and stirred vigoursly until the mixture was soo viscous till stirring is no longer effective(2-3 hrs).Reaction mixture was kept in freezer for 16hrs obtained product(compound1) was filtered, dried and recrystallized from ethanol and dried



(1a)

2.Synthesis of 1-(3,4 dimethoxy phenyl)-1-cyclohexyl meth-2-ene-1-one.

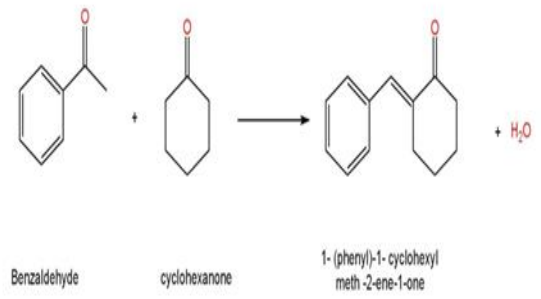
Cyclohexanone (10.36ml,0.1M) add 30 ml of 10%NaOH was added and 50ml of ethanol in 250ml beaker with magnetic stirrer and the temp is maintained at $10^{C.}$ 3,4 dimethoxy benzaldehyde(11.7gm,0.1M) was added by drop wise and stirred vigoursly until the mixture was soo viscous till stirring is no longer effective(2-3 hrs).Reaction mixture was kept in freezer for 16hrs obtained product(compound1) was filtered, dried and recrystallized from ethanol and dried.



(2a)

3.Synthesis of 1-(phenyl)-1-cyclohexyl meth-2-ene-1-one.

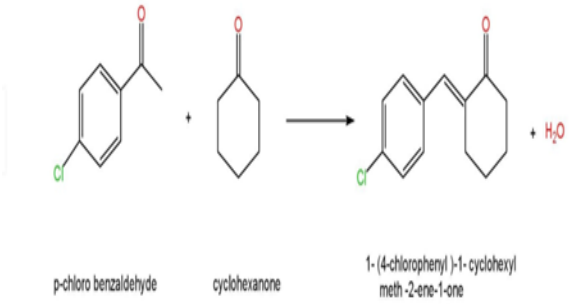
Cyclohexanone (10.36ml,0.1M) add 30 ml of 10%NaOH was added and 50ml of ethanol in 250ml beaker with magnetic stirrer and the temp is maintained at $10^{C.}$ benzaldehyde(10.20gm,0.1M) was added by drop wise and stirred vigoursly until the mixture was soo viscous till stirring is no longer effective(2-3 hrs).Reaction mixture was kept in freezer for 16hrs obtained product(compound1) was filtered, dried and recrystallized from ethanol and dried.



(3a)

4.Synthesis of 1-(4-chlorophenyl)-1-cyclohexyl meth-2-ene-1-one

Cyclohexanone (10.36ml,0.1M) add 30 ml of 10%NaOH was added and 50ml of ethanol in 250ml beaker with magnetic stirrer and the temp is maintained at $10^{C.}$ p-chloro benzaldehyde (14.0gm ,0.1M) was added by drop wise and stirred vigoursly until the mixture was soo viscous till stirring is no longer effective(2-3 hrs).Reaction mixture was kept in freezer for 16hrs obtained product(compound1) was filtered, dried and recrystallized from ethanol and dried.

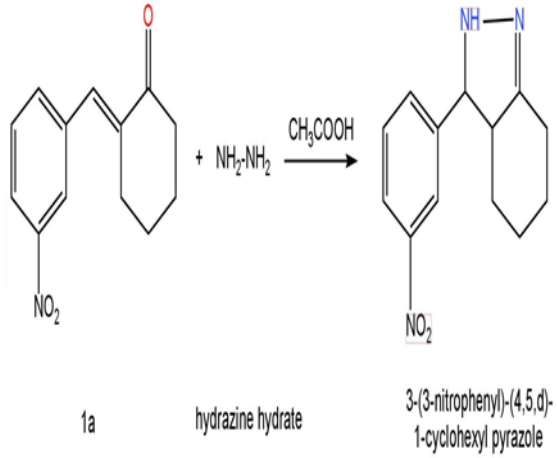


(4a)

STEP-2: -

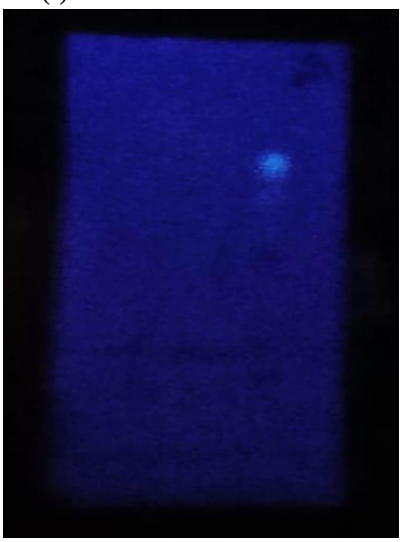
a) Synthesis of pyrazole derivative from 1a: -

1a (1.0413g) react with hydrazine hydrate (0.6409g) in presence of 10ml of Acetic acid followed by reflux for 6-8 hrs. The progress of the reaction was monitored by TLC (thin layer chromatography) using ethyl acetate: n-hexane(2:8) as an eluent and after completion the reaction mixture was cooled at room temperature. The remaining solid was filtered, washed and dried and recrystallized by using suitable solvent.



1b(I)

TLC for 1b (I): -



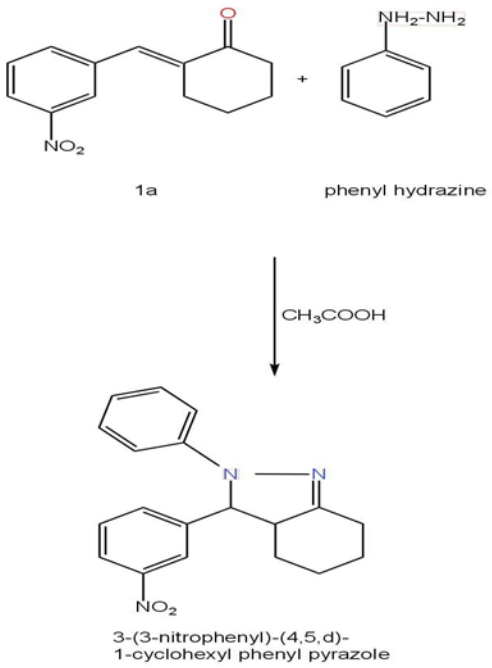
Molecular formula: -$C_{13}H_{15}N_2(NO_2)$

Molecular weight: - 245.28gm/mol

Recrystallization solvent: Ethanol

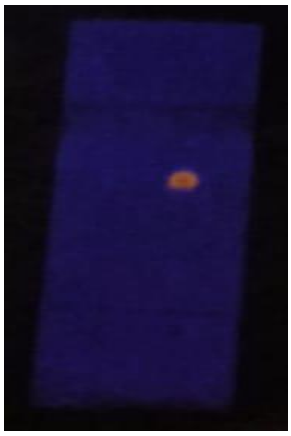
b) Synthesis of pyrazole derivative from 1a: -

1a (0.208g) react with phenylhydrazine (0.3ml) in presence of minimum amount of glacial acetic acid followed by reflux for 6-8 hrs. The progress of the reaction was monitored by TLC (thin layer chromatography) using ethyl acetate: n-hexane(2:8) as an eluent and after completion the reaction mixture was cooled at room temperature. The remaining solid was filtered, washed and dried and recrystallized by using suitable solvent



1a phenyl hydrazine

3-(3-nitrophenyl)-(4,5,d)-
1-cyclohexyl phenyl pyrazole

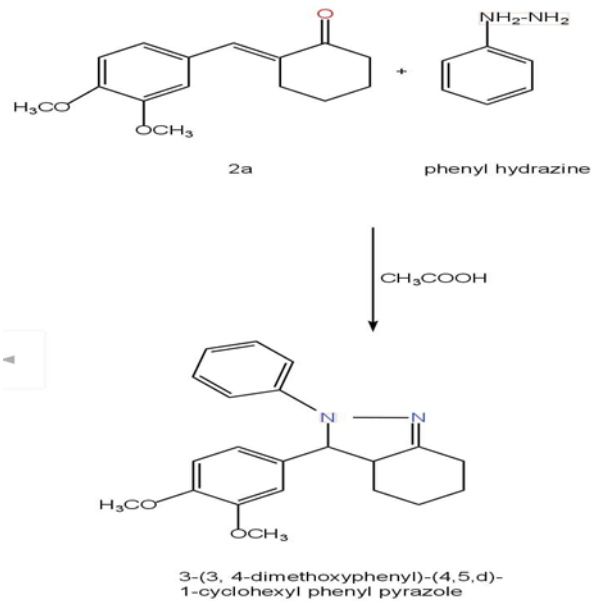


1b(II)

Molecular formula: -$C_{19}H_{19}N_2(NO_2)$
Molecular weight: - 321.37gm/mol
Recrystallization solvent:-Ethanol

c)Synthesis of pyrazole derivatives from 2a: -

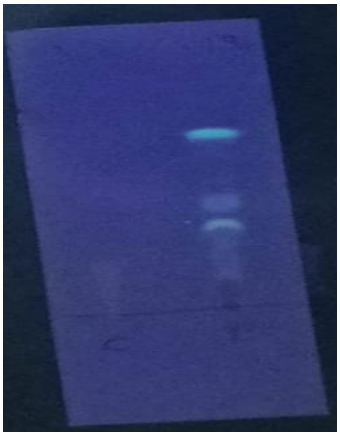
2a (0.208g) react with phenylhydrazine (0.3ml) in presence of minimum amount of glacial acetic acid followed by reflux for 6-8 hrs. The progress of the reaction was monitored by TLC (thin layer chromatography) using ethyl acetate: n-hexane (2:8) as an eluent and after completion the reaction mixture was cooled at room temperature. The remaining solid was filtered, washed and dried and recrystallized by using suitable solvent.



2a phenyl hydrazine

3-(3, 4-dimethoxyphenyl)-(4,5,d)-
1-cyclohexyl phenyl pyrazole

2b

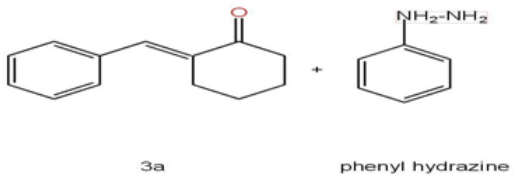


2b

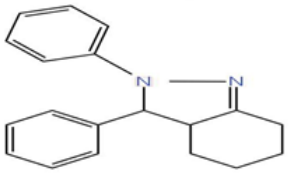
Molecular formula: -$C_{19}H_{18}N_2(OCH_3)_2$
Molecular weight: - 336.43gm/mol
Recrystallization solvent: -Ethanol

d)Synthesis of pyrazole derivatives from 3a:-

3a (0.208g) react with phenylhydrazine (0.3ml) in presence of minimum amount of glacial acetic acid followed by reflux for 6-8 hrs. The progress of the reaction was monitored by TLC (thin layer chromatography) using ethyl acetate: n-hexane (2:8) as an eluent and after completion the reaction mixture was cooled at room temperature. The remaining solid was filtered, washed and dried and recrystallized by using suitable solvent.



3a phenyl hydrazine



3-phenyl-(4,5,d)-1-cyclohexyl phenyl pyrazole

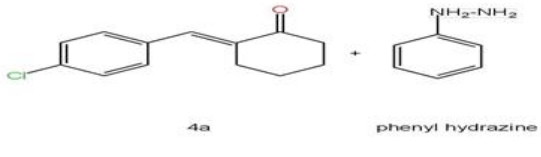
3b

3b

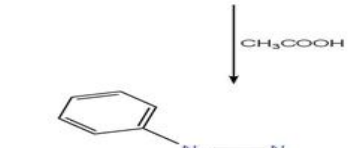
Molecular formula: - $C_{19}H_{19}N_2Cl$
Molecular weight: -310.82gm/mol
Recrystallization solvent: -Ethanol

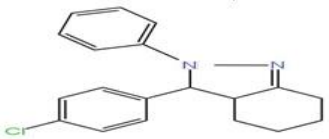
e) Synthesis of pyrazole derivatives from 4a: -

4a (0.208g) react with phenylhydrazine (0.3ml) in presence of minimum amount of glacial acetic acid followed by reflux for 6-8 hrs. The progress of the reaction was monitored by TLC (thin layer chromatography) using ethyl acetate: n-hexane (2:8) as an eluent and after completion the reaction mixture was cooled at room temperature. The remaining solid was filtered, washed and dried and recrystallized by using suitable solvent.



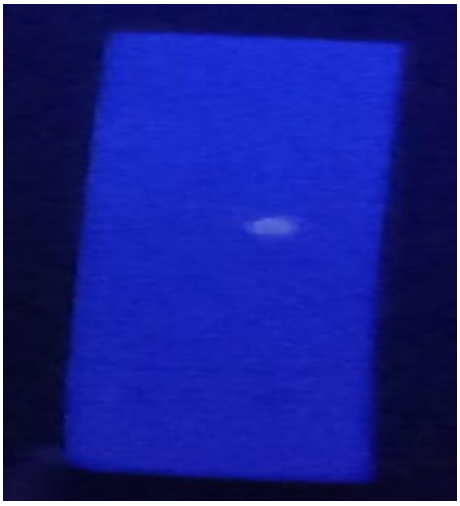
4a phenyl hydrazine





3-(4-chlorophenyl)-(4,5,d)-1-cyclohexyl phenyl pyrazole

4b



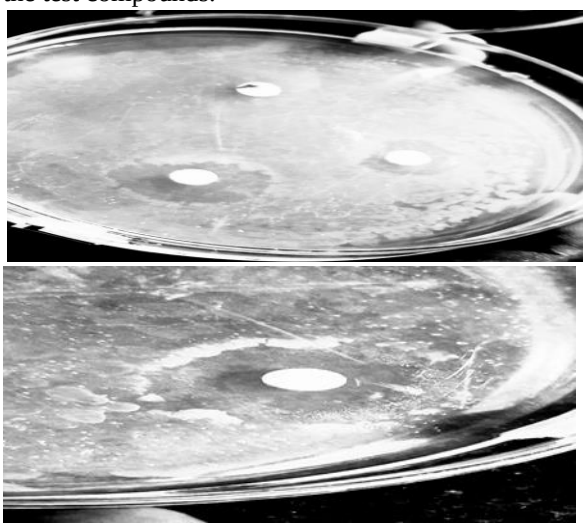
4b

Molecular formula: - $C_{19}H_{19}N_2Cl$
Molecular weight: -310.82gm/mol
Recrystallization solvent: -Ethanol

III. ANTI BACTERIAL ACTIVITY

The synthesized compounds were screened for anti-bacterial activity for determination of bacterial susceptibility test, both gram positive and gram-negative organisms are used. All the bacterial strains were obtained from the National Collection of Industrial Microorganisms. The stock solution amikacin was prepared and dilutions are prepared .All the strains were maintained by weekly subculturing on nutrient agar slant , stored at 4^0C after previous 24 hours incubation at 37^0C. Before each experiment, the organism was activated by successive subculturing and incubation. The activity is studied by using agar diffusion method.

Gram negative organism:-Escherichia coli All the compounds to be tested were dissolved in DMSO to obtain a stock concentration of 1 mg/ml .The required final concentrations (10 pg./mL, 20 µg/ml, 40 µg/ml, and 50 'ml.) were made from the stock solution, by using the same solvent. Amikacin was dissolved in water and a stock concentration of 1 mg/ml was prepared. The dilution was prepared similar to the test compounds. Inoculum of 100 milli liters solution from the standardized bacterial suspension was added to the molten agar (20 mL). The mixture was poured into sterile petri dishes, shaken slowly the uniform distribution and allowed to solidify. The plates were divided into three sections and cups were made in the agar plates, which were filled with the specific concentration of the prepared drug solution. The plates were incubated for 24 h at 35 °C in an ambient air incubator. Solvents and growth controls were kept and the zones of inhibition were measured with millimeter ruler across the cup. The zone of inhibition obtained was compared to the interpretive standard (Amikacin). The petri dishes which were needed with microorganism alone were regarded as negative controls and those dishes with bores containing reference drug solution were regarded as positive controls. The cups for each test compound were made in 3 Petri dishes so as to make (8), and the results were reported as mean. The same procedure was repeated for all the organisms with respect to all the test compounds.



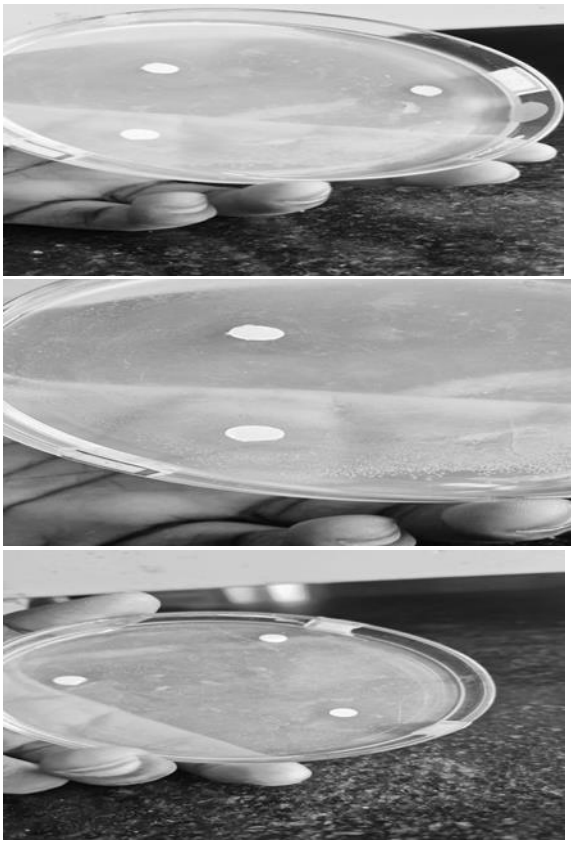


Fig-Anti bacterial activity results of compounds 1b(I),1b(II),2b,3b,4b are shown respectively in above pictures.

Observation-

Compound taken	Escheria coli
Standard	2.575
Control	0.525
Compound 1b(I)	0.725
Compound 1b(II)	0.654
Compound 2b	0.885
Compound 3b	0.6
Compound 4b	1.1

Table – Zone of inhibition average in millimeters

CONCLUSION

In conclusion, a useful and effective tactic in heterocyclic and medicinal chemistry is the synthesis of pyrazole derivatives from chalcones. A large variety of pyrazole compounds with substantial therapeutic potential can be created thanks to the structural flexibility of chalcones and their ease of production. The biological activity of the resultant pyrazoles is modified and enhanced by the addition of different substituents to the aromatic rings of chalcones. These compounds have shown

encouraging results in early biological screens, especially in tests that measure their anti-inflammatory, antibacterial, and anticancer properties. The biological evaluation of chalcones indicates tremendous potential, particularly when certain substituents are introduced, and their structural plasticity allows for the synthesis of different pyrazole frameworks. The compounds synthesized were characterized by physical (molecular weight, molecular formula). The pyrazole derivatives from chalcones were screened for anti-bacterial activity by agar diffusion method. These results encourage additional research into chalcone-based pyrazoles as lead compounds for medication development and discovery.

BIBLIOGRAPHY

[1] B.A, B. (1989). Chalcones and aurones-7. Methods Plant. Biochem, 1, 237–282.

[2] Brouillard, R. (1994). O. Dangles in The Flavonoids—Advances in Research Since 1986.

[3] Cazarolli L.H., K. V. (2013). Natural and synthetic chalcones: Tools for the study of targets of action—Insulin secretagogue or insulin mimetic. studies in natural products chemistry, 39, 47-89.

[4] Gupta D, J. D. (2010). Recent advances in chalcones as anti-infective agents. Int. J. Chem. Sci, 8, 649–654.

[5] Hutchins W.A., W. T. (n.d.). Chalkones: A new synthesis of chrysin, apigenin and luteolin. Chem. Soc, 91-94.

[6] Lopez S.N., C. M.-C. (2001). In vitro antifungal evaluation and structure–activity relationships of a new series of chalcone derivatives and synthetic analogues, with inhibitory properties against polymers of the fungal cell wall. Bioorg.Med.Chem , 9, 1999-2013.

[7] Mahapatra D.K., B. S. (2015). Chalcone scaffolds as anti-infective agents: Structural and molecular target perspectives. J. Med. Chem. Eur , 101, 496-524.

[8] Nahar L., S. S. (2019). Chemistry for Pharmacy Students: General, Organic and Natural Product Chemistry. (2, Ed.) wiley and sons.

[9] Nowakowska Z., K. B. (2008). Synthesis, physicochemical properties and antimicrobial evaluation of new (E)-chalcone. Eur. J. Med. Chem, 43, 707-713.

[10] R.R, W. (2017). Nutrition and Functional Foods for Healthy Aging. Elsevier Science, 1-386.

[11] Sahu N.K., B. S. (2012). Exploring pharmacological significance of chalcone scaffold: a review. Curr. Med. Chem, 19, 209–225.

[12] z, N. (2007). A review of anti-infective and anti-inflamatory chalcones. Eur. J. Med. Chem, 42, 125-137.

[13] Zhou B, x. c. (2015). Diverse molecular targets for chalcones with varied bio availability. Med Chem, 5, 388-404.