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PHARMACOLOGICAL SCREENING OF SOME CHALCONES SYNTHESIZED USING MICROWAVE INDUCED IRRADIATION TECHNIQUE

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ABSTRACT:

Chalcones are α, β unsaturated aromatic ketones characterized by the presence of an enone moiety, and they demonstrate a diverse range of pharmaceutical and biological activities. Nitrogen-containing heterocyclic compounds represent a highly significant category of organic compounds, exhibiting a wide array of pharmaceutical activities. Pyrazolines, which are N-heterocyclic compounds, display a broad spectrum of pharmaceutical activities and are synthesized from chalcones, resulting in enhanced biological efficacy.

Key Words: Chalcones, pharmaceutical activities, α, β unsaturated aromatic ketones, Pyrazolines.

Introduction

Chalcones containing an α,β-unsaturated carbonyl framework[1] are utilized in the synthesis of a diverse range of acyclic, cyclic, and heterocyclic compounds. Chalcones are known for their extensive biological activities, which include anticancer[2], antituberculosis, antidiabetic, antioxidant,[3] anti-inflammatory[4], antimicrobial, and antimalarial properties. In addition to their significance as the primary precursors of flavonoid systems, they also play a crucial role in the natural coloration of plants. The remarkable increase in publications in this domain is undoubtedly indicative of the global interest in chalcones. Their biological activity and synthetic applicability in the creation of various bioactive heterocycles render these compounds among the most versatile synthons for numerous transformations. Recently, microwave-assisted synthesis[5,6] of heterocyclic compounds has gained prominence due to its safety, speed, eco-friendliness, and cost-effectiveness. The recent integration of microwave technology with reactions on solid support media [7]and/or in the absence of solvents represents an environmentally friendly technique that eliminates the need for highly contaminating, toxic, and expensive organic solvents. Considering the significance of microwave-assisted solid-phase synthesis and the biological relevance of chalcones, it was deemed worthwhile to explore this field for the advancement of new bioactive heterocycles.

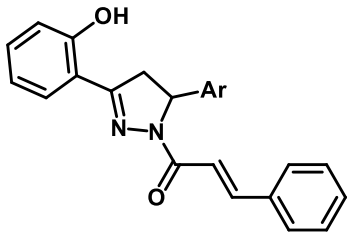
In the current investigation, we have conducted transformations of chalcones into various heterocyclic systems using microwave-assisted methods to develop new heterocyclic systems that may be beneficial in the design of potentially active molecules. Chalcones represent a significant class of natural products. Their application as natural pigments and biocides has consistently drawn the interest of chemists and biologists. The presence of an α, β-unsaturated carbonyl group within their structure

imparts antibiotic properties to them. Numerous chalcones and their derivatives, including heterocyclic analogues, have demonstrated notable biological activities that adversely affect the growth of microbes[8], tubercular bacilli[9-10], malarial parasites[11], Staphylococcus aureus[12], and intestinal worms[13]. Various 2-substituted benzimidazoles have been reported to possess wide variety of biological activities like antiinflammatory[14], analgesic[15], antihelmintic, antibacterial[16],antiviral[17], antifungal[18] and anticonvulsant[19] avtivities.

Experimental

(A)Synthesis of 1-[3-(2'-hydroxyphenyl)-5-aryl-2-pyrazolin-1-yl]-3-phenyl-prop-2-ene-1-one(1a-f):

N'-Acetyl pyrazolines(0.01mole),, benzaldehyde(0.012mole) and NaOH (4 gm) were heated under MWI for 3-5 minutes to give1-[3-(2-hydroxy phenyl)-5-aryl-2-pyrazolin-1-yl]-3-phenyl-prop-ene-1-one .After completion of reaction, the residue obtained was cooled, washed with water and dried. It was crystallized from suitable solvent to afford the title compounds in 80-86% yield. Following pyrazolinyl propenones (1a-f) have been prepared:



(1a-f)

1 a 1-[3-(2'-Hydroxy phenyl)-5-aryl-2-pyrazolin-1-yl]-3-phenyl-prop-2-ene-1-one.

1.b 1-[3-(2'-Hydroxy phenyl)-5-(4'-methoxy phenyl)-2-pyrazolin-1-yl]-3-phenyl-prop-2-ene-1-one.

1. c 1-[3-(2'-Hydroxy phenyl)-5-(3,4-dimethoxy phenyl)-3-phenyl-prop-2-ene-1-one.

1. d 1-[3-(2'-Hydroxyphenyl)-5-(3,4,5-trimethoxy phenyl)-3-phenyl-prop-2-ene-1-one.

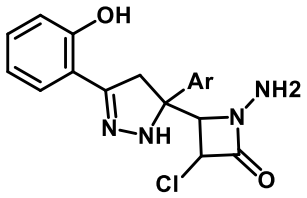
1. e 1-[3-(2'-Hydroxy phenyl)-5-(4'-chloro phenyl)-3-phenyl-prop-2-ene-1-one.

1. f 1-[3-(2'-Hydroxy phenyl)-5-(4-N,N'-dimethyl amino phenyl)-3- phenyl- prop-2 ene-1-one.

(B) Synthesis of 1-amino-3-chloro-4-[3,5-diaryl-2-pyrazolin-1-yl]-azetidinones(2a-f):

2-Azetidinones commonly known as β-lactum are the well known heterocyclic compounds among the organic and medicinal chemistry[20]. The β-lactum ring is a lactum with a heteroatomic ring structure consisting of three carbon atoms and one nitrogen atom. It serves as an important synthon for many biological important classes of organic compounds.

Due to our growing interest in the synthesis of organic compounds including heterocyclic system using non conventional, ecofriendly green chemical routes like microwave induced protocol. In the present investigation we have carried out the synthesis of some azetidine-2-ones containing pyrazoline moiety. 3,5-Diaryl-2-pyrazolin-1-carboxaldehyde hydrazones (0.01 mole) (2 a-f) were treated with chloroacetyl chloride(0.015 mole) under microwave irradiation for 2-3 minutes to give 1-amino-3-chloro-4-[3,5-diaryl-2-pyrazolin-1-yl]-azetidinones (2a-f) in 80-85% yield. After completion of the reaction as indicated by TLC the residue obtained was cooled to room temperature and poured into ice cold water .The separated solid was filtered off, dried and crystallized from alcohol as colourless crystals of 48 a- f in 80-85% yield. Following 2-azetidinones were prepared:



(2a-f)

2 a 1-Amino-3-chloro-4-[3-(2-hydroxy phenyl)-5-(phenyl)-2-pyrazolin-1-yl]-azetidin-2-one.

2 b 1-Amino-3-chloro-4-[3-(2-hydroxy phenyl)-5-(4'-methoxy phenyl)-2-pyrazolin-1-yl]-azetidin-2-one.

2 c 1-Amino-3-chloro-4-[3-(2-hydroxy phenyl)-5-(3',4'-dimethoxy phenyl)-2-pyrazolin-1-yl]-azetidin-2-one.

2d 1-Amino-3-chloro-4-[3-(2-hydroxy phenyl)-5-(3',4',5'-trimethoxy phenyl)-2-pyrazolin-1-yl]-azetidin-2-one.

2 e 1-Amino-3-chloro-4-[3-(2-hydroxy phenyl)-5-(4'-chloro phenyl)-2- pyrazolin-1-

yl]-azetidin-2-one. pyrazolin-1-yl]-azetidin-2-one.

2f 1-Amino-3-chloro-4-[3-(2-hydroxy phenyl)-5-(4-N,N'-dimethyl amino phenyl)

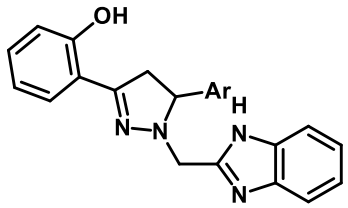
-2-pyrazolin-1-yl]-azetidin-2-one.

(C) Synthesis of some 2- [N'- methyleny l - 3,5-diaryl-2'-pyrazolin-1-yl] -benzimidazoles (3a-f):

Keeping in view the pharmacological utility of benzimidazoles and synthetic importance of pyrazoline derivatives as well as the present day need of using nonconventional energy source as green chemical route for synthesis of various classes of organic compounds, in the present investigation we have carried out the synthesis of

some new benzimidazole derivatives containing a pyrazoline constituent under microwave induced solid phase solvent less protocol

Benzimidazole constitutes on important class of bicyclic heterocycles which has been shown to possess a wide range of pharmacological activities. 2-[3,5-diaryl-2-pyrazoline-1-yl]-ethanoic acid o-phenylene were treated with DMF under MWI to give 2-[N'- methylenyl-3,5-diaryl-2-pyrazolin-1-yl]-benzimidazoles (3a-f) in 80-85% yield. Following 2-[N'-methylenyl-3,5-diaryl-2'-pyrazolin-1-yl]-benzimidazole have been synthesized:



(3a-f)

3.a 2-[N'-Methylenyl-3-(2'-hydroxy phenyl)-5-phenyl-2'-pyrazolin-1-yl]-benzimidazole.

3.b 2-[N'-Methylenyl-3-(2'-hydroxy phenyl)-5-(4'-methoxy phenyl)-2-pyrazolin-1-yl]-benzimidazole.

3.c 2-[N'-Methylenyl-3-(2'-hydroxy phenyl)-5-(3',4,-dimethoxy phenyl)-2'-pyrazolin-1-yl]-benzimidazole.

3.d 2-[N'-Methylenyl-3-(2'-hydroxy phenyl)-5-(3',4,5'-trimethoxy phenyl)-2'-pyrazolin-1-yl]-benzimidazole.

3e 2-[N'-Methylenyl-3-(2'-hydroxy phenyl)-5-(4'-chloro phenyl)-2'-pyrazolin-1-yl]-benzimidazole.

3.f. 2-[N'-Methylenyl-3-(2'-hydroxy phenyl)-5-(4'-N,N'-dimethyl amino phenyl)-2'-pyrazolin-1-yl]-benzimidazole.

All the synthesized compounds have been characterized by their melting point, elemental analysis and spectral data.

Material and Methods:-

Compounds (1 a-f), (2 a-f) and (3a-f) were screened for their antibacterial activity against gram positive and gram negative strains. The newly prepared compounds were screened for their bacterial activity in vitro.

1. Bacterial Activity:-

All the synthesized compounds were tested against following strains of various micro organisms for their bacterial activity.

Gram Negative:

Escherichia coli

Proteus vulgaris, P. aeroginosa

Klebsilla pneumoniae

Gram Positive:

B. typhii, B. subtilis

Chalcones containing an α,β-unsaturated carbonyl framework are utilized in the synthesis of a diverse range of acyclic, cyclic, and heterocyclic compounds. In addition to their significance as the primary precursors of flavonoid systems, they also play a crucial role in the natural coloration of plants. The remarkable increase in publications in this domain is undoubtedly indicative of the global interest in chalcones.

Growth Media:-

In assessing bacterial activity, peptone nutrient broths were utilized. For gram-negative organisms, the media was formulated by incorporating 2% Mecconey agar into the nutrient broths, while for gram-positive organisms, it was prepared by adding 10% sheep blood to 2% nutrient agar.

Procedure: Well Method[21]

The nutrient agar medium underwent sterilization through autoclaving at 15 psi and 121^0C for a duration of 20 minutes. The media was then poured into sterilized petri dishes and allowed to solidify. These petri dishes were inoculated with a 0.2 ml suspension of organisms using the spread plate method180. Utilizing a sterile borer, wells were created in the medium, which were subsequently filled with a solution of synthesized compounds (250 µg/ml in DMF). The petri dishes were incubated at 37^0C in an incubator. After 24 hours, the petri dishes were examined for zones of inhibition. The results were compared against standard drugs Amikacin, Ciprofloxacin, and Amoxiclav at a concentration of 30 µg/disc. The zones of inhibition were measured in millimeters and are presented in tables.

2. Antifungal Activity:-

The newly prepared compounds were evaluated for their antifungal activity against Aspergillus fumigatus and Candida albicans.

Growth Medium:-

Potato Dextrose Agar (PDA) was employed as the growth medium. It was prepared by combining 250 grams of peeled potato, 20 grams of dextrose, and 15 grams of agar in 1 liter of distilled water

Procedure:-

The efficacy of the newly prepared compounds was assessed in vitro using the poisoned food technique. The required quantity of compounds was measured and mixed with sterilized PDA medium, which was then aseptically poured into sterilized petri dishes. A medium without protectant served as the control. A 5 mm piece was excised from a 7-day-old culture and placed at the center of each petri dish. The petri dishes were incubated

at 25^0C for 5 days, with each treatment replicated. After 5 days of incubation, the percentage of growth inhibition was calculated using the following formula:

$$I = \frac{C-T}{C} \times 100$$

Where: I: Inhibition percentage
C: Control diameter (mm)
T: Colony diameter in treatment (mm)

The zone of inhibition measured has been listed in Table.

Results and Discussion:-

All the newly prepared chalcones were found to be active against both gram positive and gram negative strains of micro organisms. The activity of compounds was high for K.pneumoniae and P. vulgaris.

TABLE -1- BIOLOGICAL SCREENING OF COMPOUNDS (1 a-f), (2 a-f) and (3 a-f)

Compound	Antibacterial activity [Zone of inhibition(mm)]				Antifungal activity [Zone of inhibition(mm	
	E.coli	K.pneumoniae	B.typhii	P.vulgaris	C.albicans	A.Fumigatus
1a	3	9	1	10	4	4
1b	3	10	1	6	9	5
1c	2	7	1	9	6	8
1d	10	9	5	5	2	6
1e	8	11	5	8	4	2
1f	11	9	9	8	6	1
2a	1	1	1	2	13	12
2b	2	3	3	2	7	9
2c	2	2	3	3	4	18
2d	2	3	3	3	9	15
2e	1	3	4	1	2	5
2f	2	2	2	4	6	7
3a	1	9	1	2	1	12
3b	1	5	1	3	7	12
3c	1	8	1	1	7	15
3d	2	4	2	3	4	16
3e	2	6	2	4	10	17
3f	1	6	1	2	3	10
Ciprofloxacin	17	16	15	20	-	-
Furanysole (STG.DRUG)					10	-

Conclusion:

All the transformations were carried out in domestic microwave oven. The use of microwave irradiation technique leads to considerable saving in the reaction time, ecofriendly, easy with shorter time. The screening of biological activities of chalcone derivatives has been proved .

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