"LITERATURE REVIEW ON NOVEL ANTIFUNGAL AGENTS BY MICROWAVE ASSISTED SYNTHESIS"

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ABSTRACT

An antifungal agents are the classes of drug that selectively eliminates fungal pathogens from a host with minimal toxicity to the host. The development of antifungal agents has lagged behind that of antibacterial agents. This is a predictable consequence of the cellular structure of the organisms involved. Bacteria are prokaryotic and hence offer numerous structural and metabolic targets that differ from those of the human host. Fungi, in contrast, are eukaryotes, and consequently most agents toxic to fungi are also toxic to the host. Furthermore, because fungi generally grow slowly and often in multicellular forms, they are more difficult to quantify than bacteria. This difficulty complicates experiments designed to evaluate the in vitro or in vivo properties of a potential antifungal agent. In 1958, the first antifungal drug was introduced is Amphotericin-B-deoxycholate. It has a broad spectrum of antifungal activity but it had some toxicities i.e. renal toxicity. In 1973 flucystein a pyrimidine derivative was introduced which is active against the species of candida and Cryptococcus. There are currently only three types of the drugs derivatives are used in the treatment of the fungal infections [1]

Keywords:- *Antifungal ,Microwave Assisted Synthesis ,Osthole derivative ,Oxazine derivative ,Benzimidazole derivative etc.*

1.INTRODUCTION

These are azole derivatives, polyenes, and echinocandis. The azole derivatives are classified into two generation –First generation azole derivatives fluconazole and Itraconazole these are the first generation drugs were introduced in 1990's. These drugs have very good antifungal activity against candida spp.second generation azole derivatives [2]. In the beginning of the 2000's voriconazole, posconazole, isavuconazole these drugs were introduced. They have the activity against the filamentous fungi. Azoles are the most widely used antifungals. In 2001, the newest class of antifungals was introduced i.e. echinocandins. This class of drugs have the potency against candida spp. as well as against other azole resistant organism or fungi. Nowadays the resistance is a major problems regarding the antibiotics and antifungal as well. The current drugs used to treat fungal infection may be limited by serious adverse effect or their interaction with the other drugs because of the long term use of the drug [3]. Currently there are three classes of the antifungal drugs were used for the treatment of the invasive fungal infection are – azoles, polyenes, echinocandins. Recently in antifungal resistance increased azole resistance among the candida albicans, aspergillus fungitus and echinocandins resistance in candida glabrata. As compared to the antibacterials, antifungals have the challenges that fungal pathogens are more closely related to the host. Scientific challenges are to identify the new key or lead compound for the development of new compound. Unfortunately as the above challenges there are some regulatory challenges regarding their clinical trials, permissions [4] . MW-assisted synthesis fulfills the promise of being a fast synthesis practice. Since the first reports in 1986. The microwave synthesizer works on the principle of 'dipoles of material in external field via excitation produced by microwave electromagnetic radiations. Lately, it has been postulated that the synthesis of nanomaterial's, metal nanoparticles, and nanostructures, whose growth is highly sensitive to the

reaction conditions, could benefit a great deal from the efficient and controlled heating provided by MW irradiation[5] . The use of nanomaterial's and magnetically recyclable catalysts in organic synthesis under benign aqueous reaction conditions is becoming increasingly popular. The microwave synthesizer operates or works at high temperature or at high pressure (310oC/60 bar) under microwave radiation. Higher pressure and temperature attained rapidly in MW-assisted processes may help increase the rate of reactions via enhanced homogeneous mixing of the reactants (inwater) and decreasing the hydrophobic effects (on-water). Despite these perceived limitations of reactions in water, it has great promise in MW-assisted organic synthesis (MAOS) and in MW-assisted nanomaterial synthesis (MANS) [6] . Microwave-assisted technique is a green method in current organic synthesis .It is attractive, offering reduced pollution, low cost, and high yields[5][6] . The green technique can often shorten the reaction time. In this we study about the following classes.

1. Osthole derivatives
2. Oxazine derivatives
3. Benzimidazole derivatives
4. Triazolinone derivatives
5. Triazole derivatives
6. Carboxylates derivatives
7. Pyridine derivatives
8. Quinoline derivatives
9. Oxadiazole derivatives
10. Cyanochromene derivatives
11. Dihydropyrimidinone derivatives
12. Hydrazone derivatives
13. Triazole Derivatives Containing Pyridine Moiety
14. Dihydropyridines and tetrahydropyrimidine-2-one
15. Azetidine derivatives

2. LITERATURE REVIEW

The term literature survey or review means the overview of previously published works on specific topic. In this we study or review the work done on the novel antifungal agents.in this we study the various antifungal agents

Sr.no	Author	Activity	Description
1	Ming-Zhi Zhang et al	Antifungal activity	Microwave assisted synthesis, structural activity relationship, antifungal activity of osthole derivatives; European Journal of Medicinal Chemistry 2016; 124:10-16;doi:10.1016
2	Ming-Zhi Zhang et al	Antifungal activity	Microwave assisted synthesis, structural activity relationship, antifungal activity of coumarin [8,7-e][1,3]oxazine derivatives; Springer International Publishing Switzerland, 2016;611-8;doi: 10.1007
3	Yanpeng Shi et al	Antifungal activity , antimicrobial activity	Microwave assisted synthesis, structural activity relationship, in vitro antifungal activity of2,5-disubstituted benzimidazole derivatives; Chem Biodivers. 2019 Mar 16 (3):e1800510. doi: 10.1002
4	Na-Bo Sun et al	Antifungal activity	Microwave assisted synthesis, structural activity relationship, antifungal activity ofnovel Triazolinone derivatives; Biomed Res Int. 2015;2015:916059. doi: 10.1155/2015/916059

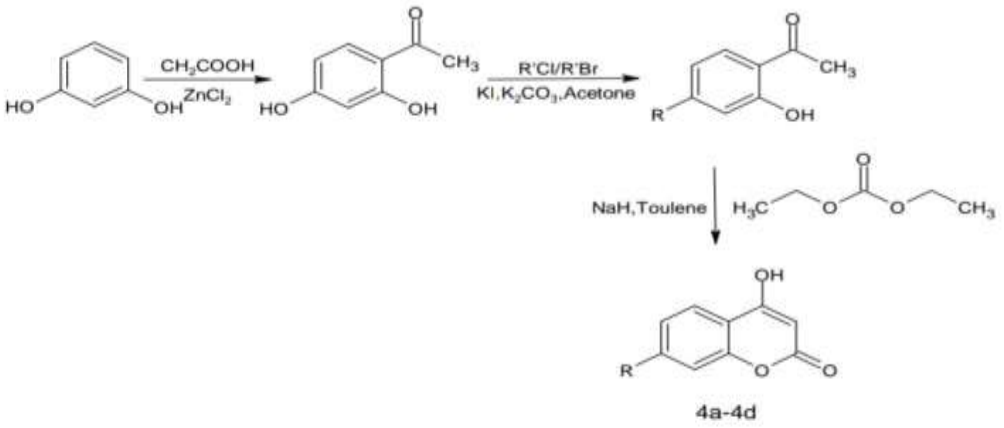
5	Aravind R. Nesaragi et al	Antifungal activity ,Antitubercular activity	Microwave assisted synthesis, structural activity relationship, antifungal activity of quinoline appended triazoles as potent anti-tubercular and antifungal agents via copper (I) catalyzed cycloaddition derivatives; Bioorganic & Medicinal Chemistry Letters,2021,3-9; doi:10.1016/j.bmcl.2021.127 984.
6	Ajmal R. Bhat et al	Antifungal activity	Microwave assisted synthesis, structural activity relationship, antifungal activity of new methyl-7-amino-4-oxo-5-phenyl-2- thioxo-2, 3, 4, 5-tetrahydo1H-pyrano [2, 3-d]-pyrimidine-6-carboxylates as potent antifungal agents; J Adv Res. 2015 Nov;6(6):941-8. doi: 10.1016/j.jare.2014.10.007
7	Jin-Xia Mu et al	Antifungal activity	Microwave assisted synthesis, structural activity relationship, antifungal activity of1,2,4-triazolo[4,3- a]pyridine derivatives containing hydrazone moieties; Chem Cent J. 2016 Aug 4;10:50. doi: 10.1186/s13065-016-0196-6.
8	Natália Aparecida Liberto et al	Antifungal activity, **Anticancer activity**	Microwave assisted synthesis, structural activity relationship, and antifungal activity of quinolines; Bioorganic & Medicinal Chemistry,2017 Feb 1;25(3):1153-1162. doi:10.1016/j.bmc.2016.12.023
9	Jaiprakash N. Sangshetti et al	Antifungal activity	Microwave assisted synthesis, structural activity relationship, antifungal activity of novel 2,5-disubstituted-1,3,4- oxadiazoles derivatives; Bioorganic Medicinal Chemistry. Letters. 2011 Jan 1;21(1):444-8. doi:10.1016/j.bmcl.2010.10. 120.
10	Muhammad Nawaz et al	Antifungal activity antibacterial activity, nematicidal activites.	Microwave assisted synthesis, structural activity relationship, antifungal activity of 2-amino-3-cyanochromenes; J Photochem Photobiol B. 2016 Nov;164:160-163. doi:10.1016/j.jphotobiol.2016.09.032.

3. EXPERIMENTAL WORK

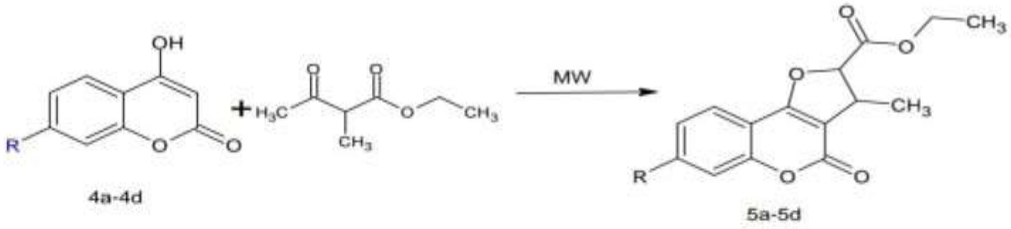
I)Osthole derivatives:-

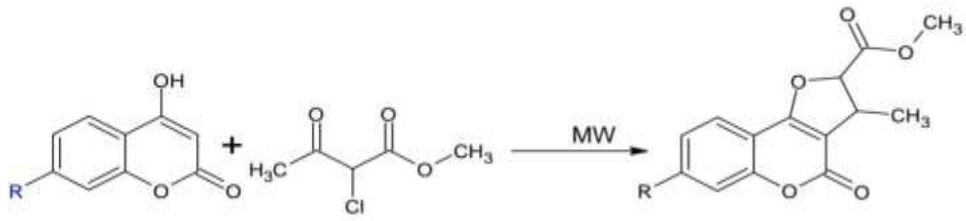
Microwave assisted synthesis of Osthole derivatives and their antifungal activity along with their structural activity relationship.

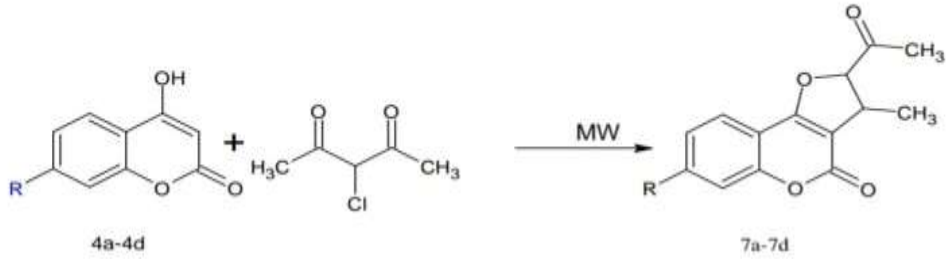
Synthesis :-

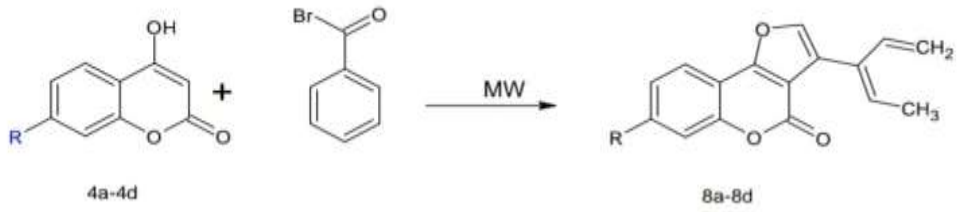


Scheme1.1 Synthetic routes for 4-hydroxycoumarine (4a-4d)









Compounds 5-8 could be prepared in moderate yields with toluene as the solvent, using 640W microwave irradiation, and DMAP as the catalyst. The yields vary from 61% to 77% considerably depending upon the

irradiative time, which determined by the TLC monitor. After the reaction was complete, toluene was removed by rotavapor, and the resulting residue was recrystallized from ethanol and water (10:1 in volume) or purified by column chromatography [7] .

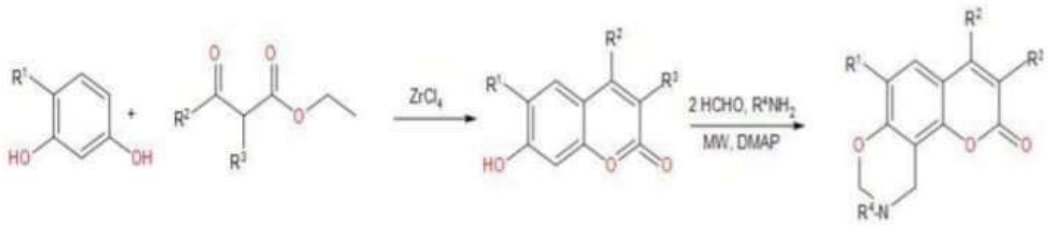
Antifungal activity:-

The antifungal activity of the targeted compounds done by carried out the biological assay. The activity of these compounds were compared with the positive control Azoxystrobin (azoxystrobin – broad spectrum of fungicide used for protecting the crops and plants from the fungal diseases) All of these derivatives shows antifungal activity after the screening against Botrytis cinerea, Rhizobacter solani, Collectrichum capsica. The EC50 value of the compound 6c, 7b, 8b, 8c were tested together with the Azoxystrobin. The EC50 value of compound 6c was low as 0.110 and 0.040 µM against the Botrytis cinerea and Collectrichum capsica. Compound 7b has exhibit better activity than the control Azoxystrobin (0.053 µM) against Rhizobacter solani.

II) Oxazine derivatives:-

Microwave-assisted Synthesis and antifungal activity of coumarin[8,7- e][1,3]oxazine derivatives and their antifungal activity along with their structural activity relationship.

Synthesis:-



5a-5t

The synthesis of novel coumarin [8, 7-e] [1, 3] oxazine derivatives through a microwave-assisted three component one-pot Mannich reaction is described in this study. The coumarin ring was prepared via a Pechmann condensation using ZrCl4 as catalyst, and the 1, 3-oxazine ring was introduced through a microwave-assisted Mannich reaction. Reaction times can be reduced from about 6 hours to 30 min, and isolated yields increased up to 65 %. Primary amine (5mmol) in dioxane (15ml) was treated with formalin solution (35%, 10mmol) at room temperature with stirring continuously for 1 hour. Then it is treated with the 7-hydroxycoumarin analogue 3a3e (5mmol) and irradiated at 400 W for 30 min. in microwave synthesizer [8]

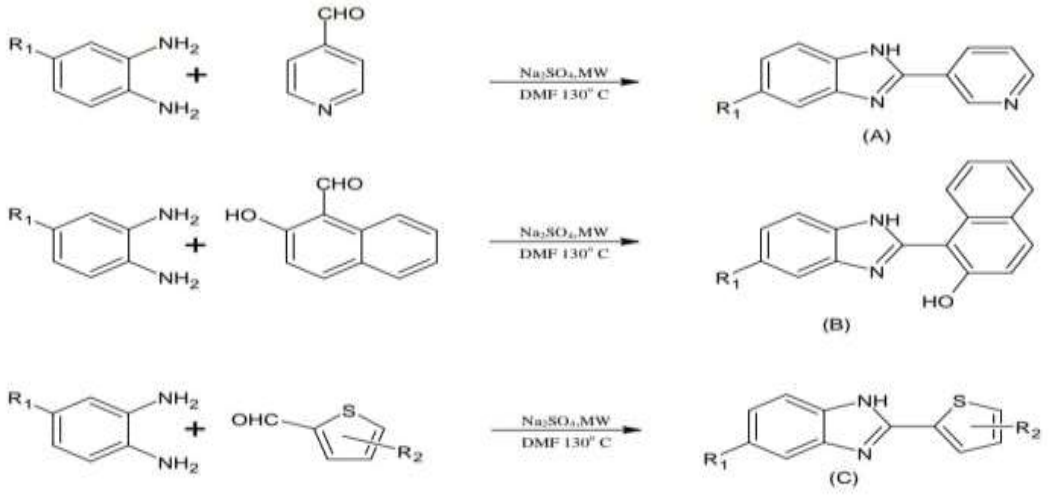
Antifungal activity:-

These targeted compounds have different growth inhibition rate against the fungi and shows the strong activity against the Rhizobacter solani and Botrytis cinerea. Compounds 5e, 5m, 5s has the greater inhibition rate than other compounds. Most of the coumarin derivatives have the poor antifungal activity and it is hard to study the structural activity of these compounds. The activity of these synthesized compounds were assessed using concentration of 50 ppm and osthole as the positive control. The EC50 values (i.e. potency) of these compounds are compared against the six pathogenic fungi botrytis cinerea, collectrichum capisci, aternaria solani, gibberella zeac, rhizoctoma solani, alternaria mali.

III) Benzimidazole derivatives :-

Microwavsse-assisted synthesis and in vitro antibacterial and antifungal activity of 2,5-disubstituted benzimidazole and their structural activity relationship.

Synthesis:-



A mixture of 4-substituted o-phenylenediamine (1.0 mmol), 3- pyridinecarboxaldehyde (1.1 mmol)2 32 or 2-hydroxy-1-naphthaldehyde (1.1 mmol) or substituted thiophene-2-carbaldehyde(1.1 mmol), Na2S2O5 (1.0 mmol) were dissolved in DMF (15 mL) or EtOH (15 mL) and fully transferred to a 250 mL microwave reaction bottle equipped with a magnetic stir bar, reflux condenser and thermocouple thermo element, then heated with microwave irradiation at 130oC for 10-15 min. [9]

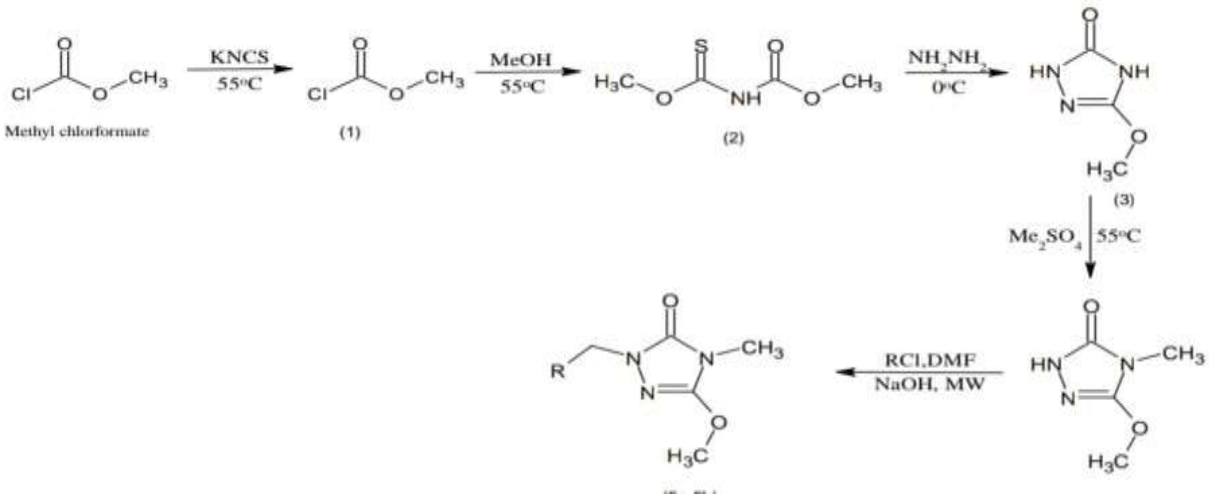
Antifungal activity:-

It is reported that benzimidazole analogues have good biological and pharmaceutical activities and drug-resistant properties including antifungal, antimicrobial, anticancer, etc. because they have a similar structure with a purine which play pivotal role in the synthesis of protein and nucleic acid in the bacteria.

IV) Triazolinone Derivatives:-

Microwave Assisted Synthesis Some Novel of triazolinone derivatives and their antifungal activity along with their structural activity relationship.

Synthesis:-



When the methyl carbonochloridate was reacted with potassium thiocyanate, the potassium thiocyanate was excess, while the drop speed must be slow, as fast speed decreased the yield of product. The potassium thiocyanate (10.69g, 0.11mol) and pyridine (0.40g) were dissolved in methyl isobutyl ketone (50mL); methyl chloroformate (9.45g, 0.10mol) was added drop wise at 55∘C, and the mixture was stirred for 4h. Then MeOH (20mL) was added to the mixture and stirred for 16h. The mixture was washed with concentrated hydrochloric

acid (3mL) and H2O. The intermediate 2 was easily prepared by the reaction of methoxycarbonyl isothiocyanate and methanol. In the synthesis process of intermediate3, the intermediate2 cyclized with hydrazine hydrate. The intermediate 3 exhibits two NH groups, which may be both methylated with (CH3)2SO4. We found that the pH values of two NH groups are different. The target compounds 5a∼5o were synthesized using microwave irradiation method. The signal of NCH 2 proton appeared around δ 3.66–5.04ppm. [10]

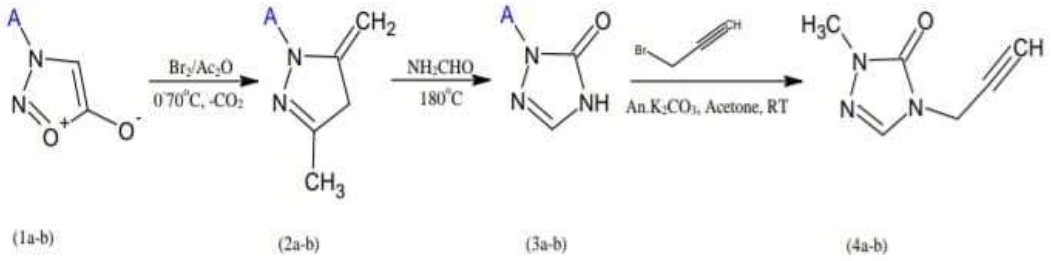
Antifungal Activity: -

The in vivo antifungal activity of 1, 2, 4-triazol-5(4H)-ones against Phytopthora infestans, Botrytis cinerea, Corynespora cassiicola, Rhizoctonia solani and Pythium ultimum were studied and dimethomorph, fludioxonil, chlorothalonil, validamycin and zhongshemycin were used as controls. It is shown thatcompounds5c, 5f and5h exhibited good control efficacy against Pythium ultimum at 500ppm. Compounds 5a, 5g, 5i, 5m, and5n showed moderate control efficacy against Pythium ultimum. Here we get some unexpected results that most of the synthesized compounds were promoting the growth of the Botrytis cinerea. Compound 5b and 5c showed good antifungal activity against the Corynespora cassiicola

V) Triazole derivatives :-

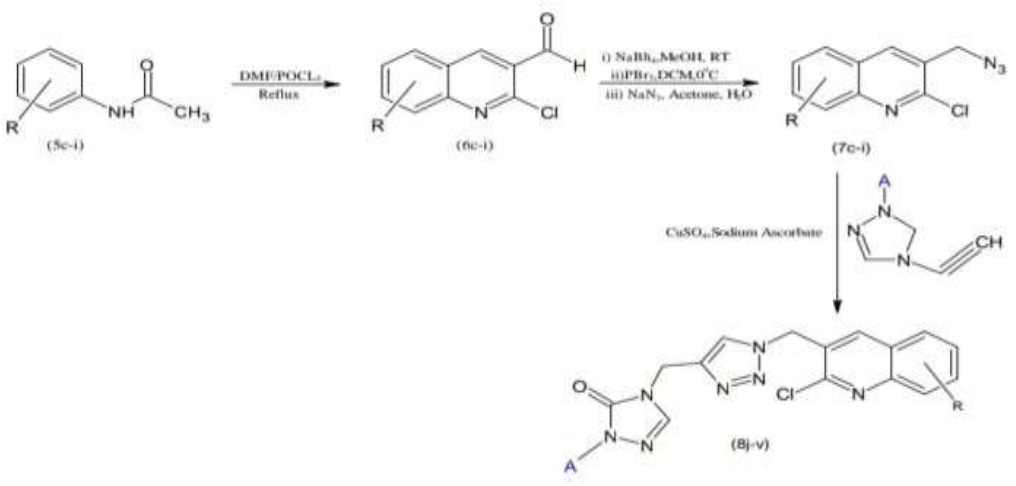
Microwave assisted synthesis of quinoline appended triazoles as antifungal & antitubercular via Cu-II catalyzed clycloaddition and their structural activity relationship.

Synthesis: -



(1a-b) (2a-b) (3a-b) (4a-b)

The synthesis of regioselective quinolinyl-1, 2, 3-triazolyl-1, 2, 4-triazol-3 (4H)-one 8j-v in a shorter amount of time with high yields and purity (Scheme 2). 2-Chloro6/7/8-substituted-quinoline Vilsmeier-Haack reaction was used to create 3- carbaldehyde 6c-i, which was then reduced to the equivalent alcohol using NaBH4 to produce 3-(bromomethyl) quinoline when it is treated with phosphorous tribromide in DCM. -2-Chloro-6/7/8-substituted Treatment of 3- with the equivalent dipolar azide 7c-i was achieved (bromomethyl) sodium azide in aqueous acetone at room temperature and 2-chloro-6/7/8-substituted quinoline. This was followed by the azidealkyne cycloaddition of the acetylenic dipolarophiles 4a-b (Scheme 1) and the 3- azidomethyl quinolines 7c-i, for



(5c-i) (6c-i) (7c-i)

which we adjusted the reaction conditions using a variety of CuSO45H2O in different solvents as a catalytic quantity.

PEG-400 has been tested in a variety of catalyst-to-solvent ratios and solvent systems, including dimethyl sulfoxide (DMSO), THF/H2O (2:1), THF/H2O (1:2), tbutanol/water (1:1), t-butanol/water (1:2), t-butanol/water (1:2), t-butanol/water (1:2). With previously disclosed reaction conditions and a variety of solvents, a product with modest yields was produced over an extended period of time. Only 15 mol% CuSO45H2O is used, which is generous to encourage the reaction to advance further. Adding more catalyst did not increase yields to any discernible extent .[11]

Antifungal activity:-

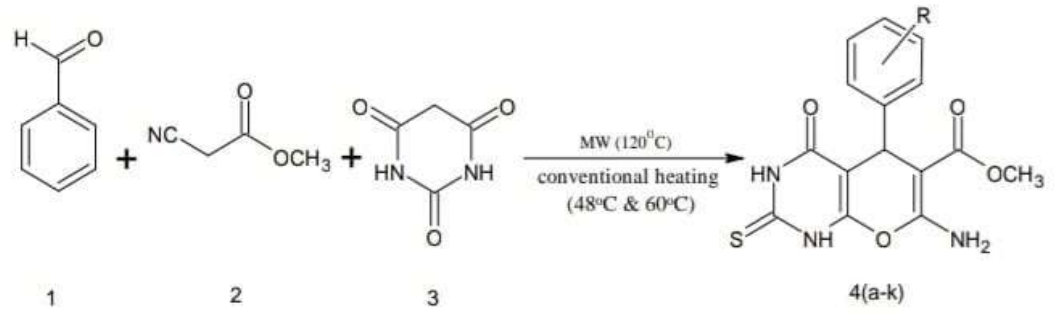
The antifungal activity of these targeted compounds were tested against the four different pathogenic fungi species these are Aspergillus niger, candida albicans ,aspergillus flavus and aspergillus fumigates .The MIC (minimum inhibitory concentrations) are summarized to get the comparison of the activity shown by the compounds against the fungi. Flucanazole is an antifungal drug which is used as the reference. Aspergillus niger with MIC values ranging from 0.20 to 6.25 µg/ml, candida albicans with MIC values ranging from 0.20 to 6.25 µg/ml, A. flavus with MIC values ranging from 0.20 to 12.50 µg/ml and Aspergillus fumigates with MIC values ranging from 3.12 to 50 µg/ml in comparison with fluconazole

VI) Carboxylate derivatives: -

Microwave assisted synthesis of new methyl-7-amino-4-oxo-5-phenyl-2-thioxo-2, 3, 4, 5-tetrahydo-1H-pyrano [2, 3-d]-pyrimidine-6-carboxylates as potent antifungal agents and their antifungal activity along with their structural activity relationship.

Synthesis:-

Synthesis: -



A mixture of benzaldehyde derivatives (1mmol), methyl cyanoacetate (1.2mmol), thiobarbituric acid (1mmol) and water was placed in teflon vessel and kept in microwave synthesizer for the irradiation under the catalyst free condition at 250W and 1200C. After cooling the above mixture at room temperature the product get precipitated. The precipitated product was filtered under vaccum and recrystallized by washing it with water and 95% ethanol to get the excellent yield of product. The reaction performed id completely free from catalyst. The reaction is monitored by thin layer chromatography .[12]

Antifungal activity: -

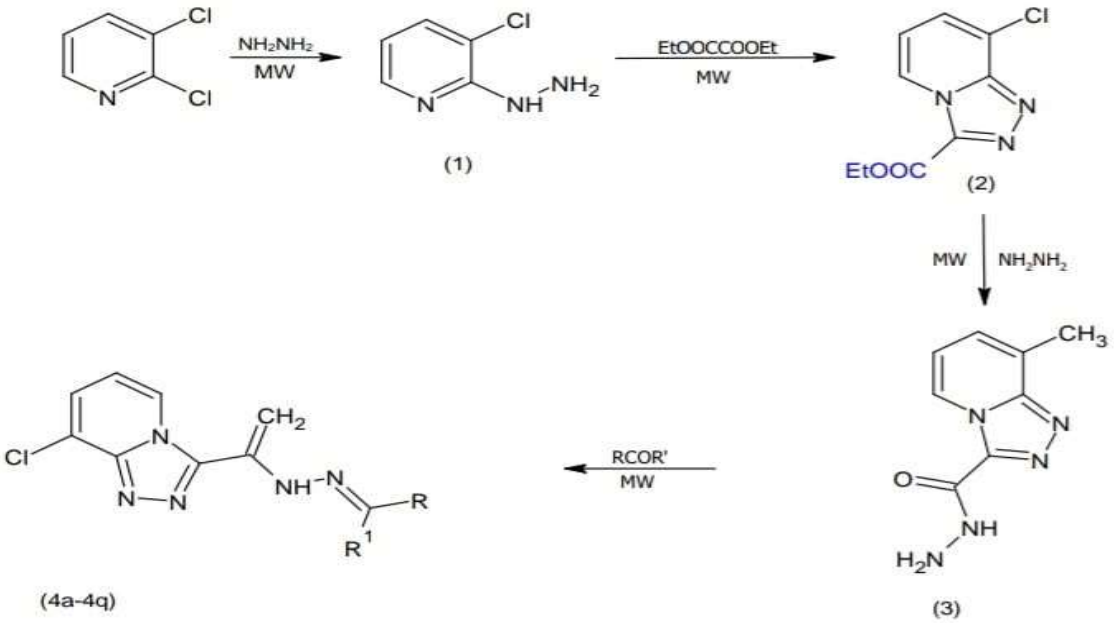
The targeted compounds have the more antibacterial activity than the antifungal but the targeted derivatives having the electron donating groups had more activity. In this study they had compared the MIC values of the targeted compound with the standard ones like streptomycin. The synthesized compound (4a-k) was screened in vitro antifungal activity against the aspergillus niger, penicillium chrysogenum strains as well it is also done for

the in vitro antibacterial actitvity. The screening showed that compounds 4d and 4d has the maximum effect than others.

VII) Pyridine derivatives –

Microwave assisted synthesis of 1, 2, 4-triazolo [4, 3-a] pyridine derivatives containing hydrazone moieties and their antifungal activity along with their structural activity relationship.

Synthesis:-



Microwave technology is the technology which is used to shorten the reaction duration and increases the yield. The synthesized compound 4a-4q from 8-chloro-[1,2,4]- triazolo-[4,3,a]-pyridine -3-carbohydrazide and substituted aldehyde under the microwave irradiation condition. The title compound (4a-4q) was synthesized from intermediate 3 and different aldehyde/ketone in solution of ethanol under the condition of 150W, 78oC at pressure of 200psi for 10 minute. [13]

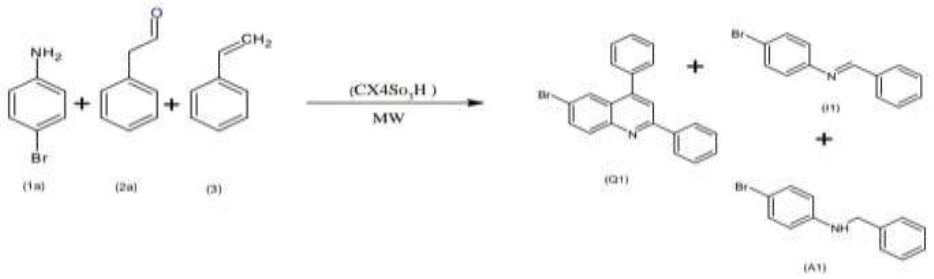
Antifungal activity:-

The antifungal activity of synthesized compound 4a-4q are seen against botrytis cinerea, stemphylium lycospersici, fusarium oxysporum spp. Compounds 4a,4b,4e,4l,4m,4n,4o,4p and 4q shows the moderate effect against fusarium oxysporum spp. But unfortunately most of the synthesized compounds have the low antifungal activities against botrytis cinerea. The zone of inhibition and the activity of the compound was compared to the activity as the control zhongshemycin.

VIII) Quinoline derivatives

Microwave-assisted Synthesis of quinolines derivatives and their antifungal activity along with their structural activity relationship.

Synthesis:-



In this reaction constituted of 4-bromoaniline (1a), benzaldehyde (2a) and styrene (3) was chosen and carried out in the presence of p-sulfonic acid calix [4] arene (CX4SO3H) as catalyst (1 mol %) under microwave irradiation. The use of ethanol or water as protic solvents yielded the quinoline Q1 in only 8% and 5%, respectively, in which the imine [I1] was isolated as the major product (up to 27% yield) and the amine [A1] in up to 15% yield, respectively. We can also use the aprotic solvents for the synthesis of Q1 compound but the yield we get is low as compared to the protic solvent. The Q1 yield of up to 35% was verified from incubation of reactions at 200 to 250 °C for 15 minute. For longer periods of reaction incubation 20 to 25 minutes the maximum temperature of 200 °C provided the best yields for compound Q1[14] .

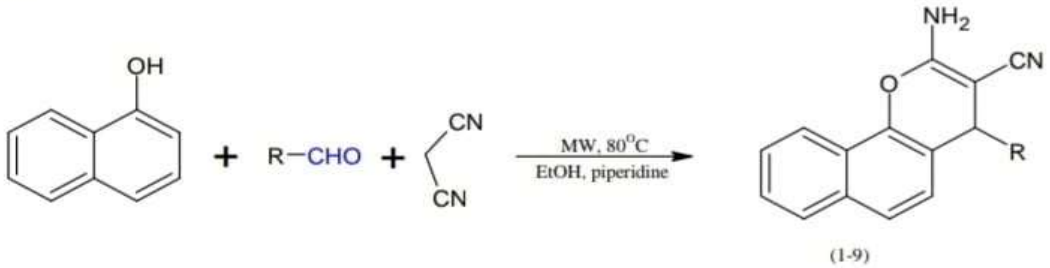
Antifungal activity: -

The MIC value (minimum inhibition concentration) of the synthesized compound is compared against the candida albicans and Cryptococcus neoformans had been studied with the different substituents at R1,R2,R3,R4,R5,R6these positions (majorly at R2,R3and R5). The MIC values i.e. MIC80 and MIC50 are compared with the reference (amphotericin-B) drug. MIC80 and MIC50 values correspond to the concentration of compound tested necessary to inhibit fungus growth by 80% and 50%, respectively. The most active compounds had the MIC50 values lower than 16 µg mL-1 .Overall Cryptococcus neoformans was more susceptible than candida albicans to 2, 4- disubstituted quinolines and their derivatives. The Q13 was the most active among the 2-substituted compounds (bearing –2-phenyl, 2-cyclohexyl or 2-furan) containing bromine at 6-position (R2).

IX) Cyanochromenes derivatives

Microwave assisted synthesis of 2-amino-3-cyanochromenes derivatives and their antifungal activity along with their structural activity relationship.

Synthesis: -



(1-9)

A mixture of 1-napthol (1.44g, 10mmol), aldehyde (10mmol), malonitrile (0.660g, 10mmol) and two drops of piperidine is added in ethanol (10ml) was refluxed in microwave reactor for 5-15 minutes at 80oC at the power 25-30 W. then the solid product is obtained is filtered and washed several times with the with the cold ethanol and dried under the vaccum [15] .

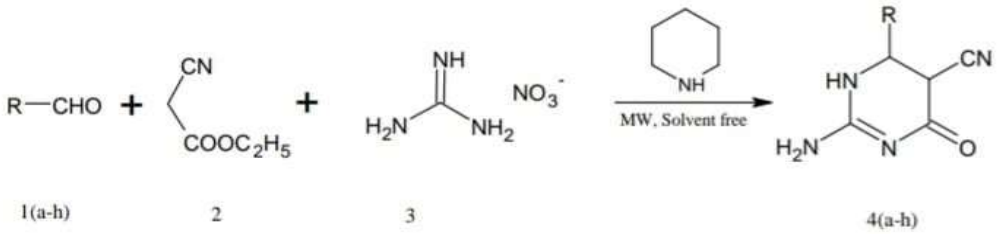
Antifungal activity: -

The all synthesized compounds 1-9 were screened for the antifungal activity were tested against the bacillus cereus, fusarium species and aspergillus niger by disc diffusion method. Standard agar method is used. 6 mm of the culture media disc of fungi placed at the center of agar plate. Each disc was impregnate with 50 µL of the compound and inoculated on the agar. Two concentrations of each compounds (1-9) were used are 1000 ppm and 500 ppm. For the control DMSO treated disc was used in each agar plate. Plates were incubated for 5 days at 37oC in dark and the zone of inhibition was measured

X) Dihydropyrimidinones derivatives

Microwave assisted synthesis of Dihydropyrimidinone Derivatives as antifungal agents along with their structural activity relationship.

Synthesis: -



1(a-h) 2 3 4(a-h)

In a 600W microwave oven, a mixture of aldehyde1 (1 mmol), ethylcyanoacetate2 (1.2mmol), guanidine nitrate3 (1.5 mmol), and a few drops of piperidine was microwave irradiated at 60% power for five minutes. (Successive irradiation lasting 30–40 seconds with cooling breaks; the temperature is 90–100 °C.) The mixture was cooled and quenched with water (3 10mL) when the reaction was complete, as shown by TLC. To obtain pure products4 (a-h) in good yields, the solid product was separated and recrystallized from ethanol [16] .

Antifungal activity: -

The all synthesized compounds 4(a-h) were screened for the antifungal activity were tested against the fungi Candida albicans, Aspergillus flavus, and Aspergillus niger. The disc diffusion method [20] was used to investigate the antifungal susceptibility of Sabouraud's dextrose agar. After sterilization, Candida albicans, Aspergillus flavus and Aspergillus niger were injected into the medium. Following that, a sterile micropipette was used to add the freshly synthesized compounds 4d, 4e, 4f, 4g, and 4h at a concentration of 100g/mL, along with solvent control (0.5 percent v/v Tween 80). After that, the plates were kept at 37°C for 24 h

4. CONCLUSION: -

In this study we report the synthesis, biological activity & structure activity relationship of various novel antifungal agents of various classes like osthole derivatives, oxazine derivatives, benzimidazole derivatives, Triazolinone derivatives, Triazole derivatives, Carboxylates derivatives, Pyridine derivatives, Quinoline derivatives, Hydrazone derivatives, Azetidine derivatives etc. via microwave assisted synthesis. The compounds 4-Hydroxycoumarins, coumarin[8,7-e][1,3]oxazine, 3- hydrazinoquinoxalin-2(1H)-one, like etc. and their derivatives are evaluated for their antifungal activity like fungicidal and fungi-static and has shown the very good kind of antiviral activity. These reported compounds further optimization and biological evaluation for different biological activity may show some potent pharmacological activity.

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