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Antimicrobial activity of few nitrogen heterocyclic compound synthesized under microwave irradiation

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Abstract: A series of few nitrogen heterocyclic compounds have been synthesized by using with or without sulphur under microwave irradiation. The synthesized compounds were screened for their antibacterial activity against *pseudomonas aeruginosa*, *Escherichia- coli, Klebsiella pneumonia, Proteus species and Bacillus subtilis* by disc diffusion method using ethanol as solvent. The same synthesized compounds were screened for their antifungal activity against *Aspergillus flavus, Mucor himealis, Rhizopus nigricans and candida albicans* by streak isolation method using ethanol as a solvent. The tested compounds have shown different activity in terms of growth inhibition of microorganism. Synthetic derivatives of heterocyclic compounds are an important group of medicines, characterized by varied pharmacological activity.

Keywords: Nitrogen heterocyclic compounds, microwave irradiation, antibacterial activity, anti-fungal activity

Introduction

Heterocyclic compounds occur widely in nature and in a variety of non-naturally occurring compounds. Heterocyclic compounds can be synthesized in a number of ways. The most conventional and common methods are refluxing the reactants. In most of the reactions, the process consumes lot of time .Several reactions end up in impure products. It is normally a tedious job for a research to purify a compound. Also many reactions require use of large amounts of solvents. Solvents like benzene, chloroform, acetonitrile, alylalcohol, diazomethane, DMF, dioxanes are toxic and harmful. Hence chemists, search for methods which require use of lesser amounts of solvents. Reviewing on the foresaid matter we made a search for a suitable methodology to adopt for synthesis of heterocyclic compounds. Our research narrowed to microwave synthesis owing to its user friendly nature.

Materials and Methods

Melting points were determined by

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using a (Joshibha) Model melting point approach and are uncorrected IR spectra were recorded on Perkin Elmer spectrometer. The reaction progress and purity of all prepared compounds was followed by TLC in the system benzene/ethyl acetate and benzene/pet ether visualizing spots with UV lamp and iodine vapour. All microwave reactions were carried out in a microwave oven (IFB Model 179 MIS).

Synthesis of heterocyclic compounds

Synthesis of 4-phenyl-3- vinyl quinoline-2-ones (A)

2-aminobenzophenone (4g) was mixed with pyridine (1.8) g in anhydrous benzene, the solution was cooled and to this was added a drop wise a solution of 3-butenoyl chloride in benzene. After the addition was complete the reaction mixture was aside for an hour under cooling and thereafter it was poured into ice water. The benzene layer was separated, sequentially washed with ice cold dilute hydrochloric acid. After during, the solvent was evaporated under pressure. The residue was dissolved in ethanol, cooled and mixed with ethanolic potassium hydroxide. This concentration of the alkali was found to be optimum. It was kept aside for one hour at room temperature, and poured into ice water the resulting solution was carefully neutralized with dilute hydrochloric acid. The precipitated solid was collected, washed with water and recrystallised from a suitable solvent.

Microwave enhanced synthesis of 2-chloro- 4- phenyl-3-vinyl quinolines.(B)

4-phenyl-3-vinyl quinoline-2 (1H (2.5g) was micro waved at 350W with phosphorous oxychloride in a domestic microwave. The completion of the reaction was monitored every 30 seconds by recording thin layer chromatography of the reaction mixture. After completion of the reaction as noted by the disappearance of the starting compound, the reaction mixture was cooled and poured into ice water. It was then macerated well, carefully neutralized with ammonia solution. The neutralized reaction mixture was extracted with chloroform and the extract was washed with water, dried and evaporated.

Microwave enhanced synthesis of 4-phenyl-3-vinyl quinoline-2-thiones.(C)

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A mixture of 2-chloro-4-phenyl-3-vinyl quinolines (1.33g,) thiourea (0.53g) and anhydrous ethanol were micro waved. The completion of the reaction was monitored every 30 seconds by recording thin layer chromatography of the reaction mixture. After completion of the reaction as noted by the disappearance of the starting compound, the reaction mixture was cooled and poured into ice water. It was then macerated well, carefully neutralized with ammonia solution. The neutralized reaction mixture was extracted with chloroform and the extract was washed with water, dried and evaporated.

Antimicrobial activity of compounds.

The synthesized compound 4- phenyl-3- vinyl quinoline-2-one, 2-chloro- 4-phenyl-3-vinyl quinolines, 4-phenyl-3-vinyl quinoline-2-thiones were tested for their antibacterial and antifungal activity. The compound synthesized will be designed as A, B, C for the purpose of easy reference.

Preparation of culture media for antibacterial antifungal studies.

Preparation of Nutrient agar medium

Three grams of beef extract, 50g of peptone of NaCl and 15g of agar were taken in a beaker and then distilled water (1000ml) was added. The mixture was boiled and mixed thoroughly with a glass rod. After complete dissolution of agar the medium it was dispensed into several conical flask of 250ml volume. The conical flasks were closed with cotton plug and rapped with aluminum foil. It was there auto claved for 15 minutes at 121°C and 15 psi.After autoclaving, the medicine was used for culturing different micro organism.

Preparation of Sabouard Dextrose Agar. (SDA medium)

65g of SDA were suspended in 100ml distilled water. It was heated to boiling to dissolve the medium completely and the sterilized by autoclaving at 15 ibs, pressure (121°C) for 15min.

Antimicrobial testing

Disc method for determination of zone of inhibition of antibacterial.

Paper discs of 4mm in diameter and glass Petri plates of 90mm in diameter were used throughout the experiment. Paper discs were sterilized in an autoclave and dried at 100°C in oven. Then the disc was soaked with test chemicals at the rate of 50g per disc for antibacterial analysis. One drop of bacterial suspension was taken in

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sterile Petri dish and then approximately 20ml of sterilized and melted NA (~45˚C) was poured into the plate, and then mixed thoroughly. The paper discs after soaking with test chemicals were placed at the center of the inoculated pour plate. A control plate was also maintained in each case with alcohol. Firstly, the plates were kept for 4hrs at low temperature (4˚C) the test chemicals diffused from disc to the surrounding medium by this time. The plates were then incubated at (35± 2) ˚C for growth of test organisms and were observed at 24 hours intervals for two days. The activity was expressed in terms of inhibition zone diameter in mm. Each experiment was repeated three times. The standard antibiotic, streptomycin and gentamycin was used as a positive control and compared with test chemicals under identical condition. The antimicrobial activities of the compounds were recorded.

Streak plate isolation method for determination of zone of inhibition of antifungal activity.

The required amount of SDA medium was taken in a conical flask separately and was sterilized in an autoclave (at120c and 15psi) for 15min.A tube of SDA was liquefied and poured into a petridish.The plate was rotated gently for uniform distribution of the medium. The inoculating loop was held at a 60˚C angle in the hottest part of the Bunsen burner flame. The entire tube was heated to redness. The loop was allowed to cool for 15 to 20 seconds before it touched the culture. A small amount of the culture was removed from the tube with the sterilized inoculating loop and the microorganisms were streaked in the plate. The stock solutions were prepared by dissolving the compounds in ethanol. Inoculation process was done under aspectic condition and the spores were inoculated in the medium and incubated for 5 days. A clear zone or ring was present on SDA plate .The diameters of the zone are measured.

Result

For the study of heterocyclic compounds have been prepared and characterized by their IR spectra. Their antimicrobial activities have been assessed.

Microwave enhanced synthesis show that, there is a considerable decrease in the time of synthesis ~11/2 hours reduction in time for compound B and ~ 21/2 hours reduction in time for compound C. one of the most useful, advantage of Microwave-Induced Organic Reaction Enhancement is the solvent free synthesis which will reduce the drastic solvent pollution

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and will be therefore eco friendly green approach.

The melting points of synthesized compounds A, B, C were taken in a melting point apparatus and compared with literature value. The IR spectral values of the compounds were recorded and compared with literature values. The spectral values and melting points are tabulated. (Table-1 and 2).

(i) Antibacterial activity of compounds A,B,C

The synthesized compounds A,B,C were screened for their antibacterial activity against *pseudomonas aeruginosa*, *Escherichia- coli, Klebsiella pneumonia, Proteus species and Bacillus subtilis* by disc diffusion method using ethanol as solvent.The solution of compounds 10 µg/ml were compared with standard drug gentamycin for antibacterial study.

Activity of compounds A,B,C against *pseudomonas aeruginosa*

From the screening result (table-3) it observed that compound A& C were highly sensitive and compound B to be resistant. Compounds A, B, C were found to inhibit equal, twelve and one time respectively when compared with the standard gentamycin which gave zone of inhibition 14mm.

Activity of compounds A, B, C against *Escherichia- coli*

It was observed from the table-3 that the inhibition of compounds A and C were highly sensitive and compound B resistant. Compounds A and B were found to inhibit ten times when compared with the standard gentamycin which gave zone of inhibition 17 mm.

Activity of compounds A,B,C against *Klebsiella pneumonia*

It was observed from the table-3 that compound A was highly sensitive, Compound C moderately sensitive and compound B to be resistant. Compound A and C were found to inhibit more or less equally and compound B was found to inhibit 15 times when compared with standard gentamycin.

Activity of compounds A,B,C against *Proteus species*

It was noted from zone of inhibition values in the table-3 ,that compound A and C showed excellent inhibition against this bacterium, and also the inhibitions were much highly sensitive than streptomycin. The inhibition of compound B was observed to be resistant. Compound A

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(14mm) and compound C (13mm) were found to inhibit more when compared with compound B (4mm).

Activity of compounds A,B,C against *Bacillus subtilis*

It was observed from the table-3 that compound A exhibited high sensitivity against this micro organism then compared B and C which were resistant. Compound A was found to inhibit equally and compound B and C found to inhibit three and five times respectively when compared with the standard streptomycin (11mm).

(ii). Antifungal activity of compound A, B and C.

The synthesized compounds A.B and C were screened for their antifungal activity against *Aspergillus flavus, Mucor himealis, Rhizopus nigricans and candida albicans* by streak isolation method using ethanol as a solvent. The solutions of compounds 10 µg/ml were compared with standard drug flucanozole for antifungal study.

Activity of compounds A, B, C against *Aspergillus flavus*

From the screening results table-4 it observed that compound A, B, C showed resistance to the fungi. Compound A, B, C were found to inhibit twice when compared with the standard flucanozole (10 mm).

Activity of compounds A,B,C against *Rhizopus nigricans*

It was observed from the table -4that compounds A,B,C showed resistance. Compound A, B and C were found to inhibit twice when compared with the standard flucanozole with zone of inhibition (10 mm).

Activity of compounds A,B,C against *Mucor himealis*

It was found from table-4 compound A, B, C showed resistance. Compounds A, B and C were found to inhibit twice when compared with the standard flucanozole.

Activity of compounds A, B, C against *candida albicans*

It was found from table-4 compound A, B, C showed resistance. Compounds A,B and C were found to inhibit twice when compared with the standard flucanozole.

Table-1

IR Spectra of synthesized compounds Band C

S.NO	*Reaction*	*Spectral values*
1	*2-chloro- 4-phenyl-3-vinyl quinolines*	*1540,990,935 cm^{-1} Peaks 990,935 are due to vinyl*

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		absorptions
2	*4-phenyl-3-vinyl quinoline-2-thiones*	*1190 cm^{-1} due to thio carbonyl absorption 930,985 are due to vinyl absorptions*

Table-2

S.NO	*Compounds*	*Melting point (°C)*
1	*A*	*229-230*
2	*B*	*78-79*
3	*C*	*189-190*

Table-3

Zone of inhibition observed against bacteria by the test compounds A, B, C.

Bacteria	*A (mm)*	*B (mm)*	*C (mm)*	*Control(mm) Gentamycin/Streptomycin*
pseudomonas aeruginosa	*14*	*0.6*	*13*	*14*
Escherichia-coli	*15*	*1.5*	*14*	*17*
Klebsiella pneumonia	*14*	*1*	*9*	*16*
Proteus species	*14*	*4*	*13*	*2*
Bacillus subtilis	*11*	*4*	*2*	*11*

Table-4

Zone of inhibition observed against fungus by the test compounds A, B, C.

Fungus	*A (mm)*	*B (mm)*	*C (mm)*	*Control(mm) Flucanozole*
Aspergillus flavus	*4*	*5*	*3*	*10*
Rhizopus nigricans	*4*	*5*	*2*	*10*
Mucor himealis	*4*	*2*	*2*	*10*
candida albicans	*1*	*2*	*1*	*10*

Conclusion

The pharmalogical significance of the synthesized compounds is well evident from the study. The graphic enhancements in the speed of

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reactions using microwave technology are striking. Less use of solvents, simplicity in processing and handling of microwave reaction is also quite obvious from the study.

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