SYNTHESIS AND ANTIMICROBIAL STUDIES OF HETEROCYCLE TETHERED ACRIDINEDIONE ANALOGUES

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INTRODUCTION

Synthesis of acridinedione analogues by condensation of dimedione with 4-hydroxy aromatic monoaldehyde in environmentally green solvent system. Then the heterocyclic analogues was Acridinedione based molecules are highly significant due to their emerged biological properties including antibacterial, antimalarial, anticancer and mutagenic properties. The core unit in acridinedione is 1,4-dihydropyridine, which falls under special category of compounds because of the similarities in structure of biologically significant NADH and NADPH.[1] Acridinedione molecules are also interesting for their physical properties, immense utility in dye industries, chemical biology, and biomedical applications.[2] Utilizing "click chemistry" methodology to tether heterocyclic azide molecules with high regioselectivity with O-propargyl acridinedione will support us to achieve the target molecules.[3]

Chemicals that control microorganisms on body tissues are called antiseptics. Many chemicals kill or prevent growth of microorganisms. Such chemicals have been called antimicrobial agents. Particularly, heterocyclic compounds, having five- and six-membered rings, occupied an important place among organic compounds for their great pharmaceutical importance.[4] The synthesized compounds will be evaluated by *in vitro* antimicrobial studies against multidrug resistant pathogens such as *Pseudomonas aeruginosa, Vibrio cholerae, Salmonella typhi, E. coli, Klebsiella pneumonia, Staphylococcus aureus, Aspergillus niger, Aspergillus flavus* and *Candida albicans* by various analysis methods including diffusion and dilution methods and also further the bacterial and fungal effects will be determined by the time-kill test.

The heterocyclic azide is tethered with acridinedione unit through click chemistry methodology. The synthesized compounds will be evaluated by in vitro antimicrobial studies again multidrug resistant pathogens.

OBJECTIVES

The main objective of the presenting work is,

(a) To understand the basic concept in organic synthesis and safely handling all kind of chemical while doing synthesis.

(b) To carry out organic synthesis in environmentally benign solvents to reduce chemical pollution, particularly from traditionally used organic solvents in organic synthesis.

(c) To control and increase the product selectivity by using click chemistry methodology.

(d) Synthesized compounds were used to do antimicrobial studies against gram positive and gram negative bacteria.

MATERIALS AND METHODS

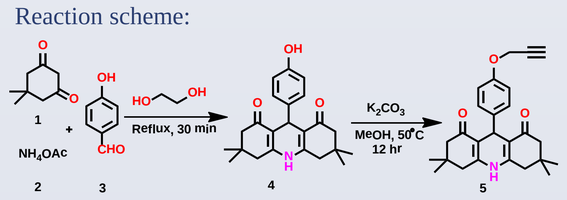
Chemistry

Materials:

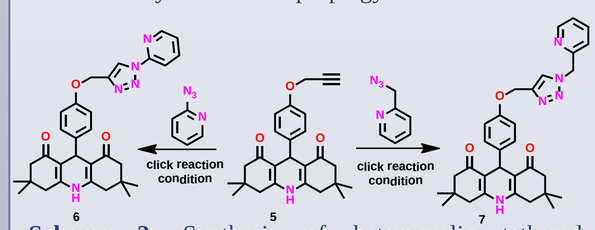
All the starting materials and solvents were purchased as reagents grade from Sigma chemicals and used without further purification. All chemical conversions were carried out as per their procedures, mostly in environmentally benign solvents like, EtOH, Ethylene glycol. FTIR, NMR, and Mass Spectra were recorded on SHIMADZU-FTIR, JEOL instruments respectively. Deuterated solvents were used for recording NMR spectra.

Acridinediones were synthesized through Hantzsch protocol by reacting active methylene group with *para* substituted aromatic carboxaldehyde and ammonium acetate in high polar solvent, as per our object we used a green solvent, ethylene glycol under thermal condition. Further, the synthesized acridinedione underwent O-propargylation by reaction with propargyl bromide in the presence of potassium carbonate base. Then click chemistry methodology supported to tether heterocyclic azide into the acridinedione alkyne.

Reaction scheme:



Scheme 1. Synthesis of O-propargyl acridinedione



Scheme 2. Synthesis of heterocyclic tethered acridinedione

Biology

Antimicrobial studies:

Our aim to use agar diffusion and agar dilution methods to determine the minimal inhibitory concentration (MIC) growth of pathogens. Microorganisms namely *Proteus vulgaris; Proteus mirabilis; Staphylococcus aureus; Salmonella typhi* can be used for their antimicrobial studies against our synthesized compounds.

Agar diffusion method: The agar diffusion method was used for the determination of antibacterial activity of acridinedione molecules against microorganisms. About 9 mL of nutrient agar media were poured into petri plates (9 cm in diameter) and inoculated with respective test organism. Wells are made with cork borer on the solid agar and loaded with 25, 50, 75 and 100 µg/mL of the test compound with tetracycline as control. Petri dishes were incubated at 37 °C for 24 h and the average diameter of the inhibition zone surrounding the wells was measured after specified incubation period.

Agar Dilution method: The MIC values are used to determine susceptibilities of bacteria for drugs and also to evaluate the activity of new antimicrobial agents. In this method, incorporation of different concentrations of the antimicrobial substance into a nutrient agar medium followed by loading standardized our newly synthesized compounds to the surface of the agar plate.

RESULTS

All the synthesized compounds were thoroughly analyzed and their structural elucidations were made on the basis of their spectroscopic data including FT-IR spectroscopy for their functional groups, 1H-NMR and 13C-NMR studies for their structure and the Mass spectra for their molecular weight determination. The recrystallized products were collected for antimicrobial studies.

The antibacterial activity of the acridinedione derived compounds against gram positive and gram negative bacteria with tetracycline as reference control will be done in the near future.

CONCLUSIONS

Synthesis of heterocyclic compounds tethered acridinedione analogues had been completed and their structures are determined by using various spectroscopic methods. Antimicrobial studies of the synthesized compounds is in under progress.

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