Executive Summary on Major Research Project

Title: Microwave Assisted Synthesis and Biological Studies of Novel Pyrimidin-2-thiones and Thiazolopyrimidines

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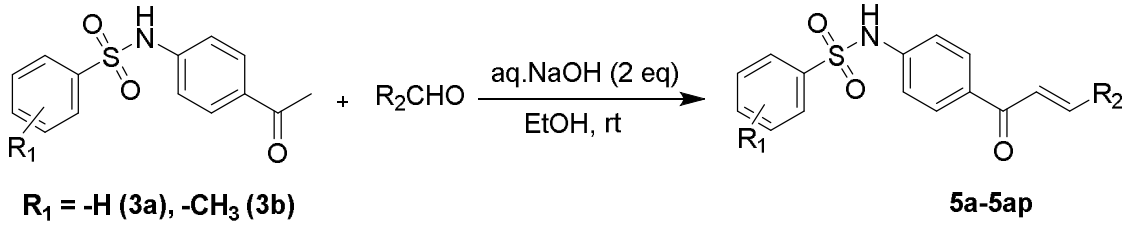
This project reports the utility of microwave irradiation in the synthesis of some diverse libraries of chalcones, pyrimidine-2-thiones and thiazolopyrimidines. The project reports the synthesis of aforesaid scaffolds which are somehow linked to sulphonamidophenyl group and all the synthesized compounds were evaluated for anti-filarial efficacy. In addition, the project also reports a green protocol for the synthesis of 3,4-dihydropyrimidin-2-(*1H*)-thiones. Report has been divided into four chapters.

Chapter 1 deals with the brief introduction of the importance of sulfonamide scaffolds in medicinal chemistry. It also summarizes the brief introduvtion about lymphatic filariasis. Lymphatic filariasis is one of the six most neglected tropical diseases. Moreover it is endemic in over 72 countries in Africa, Asia, South and Central America and the Pacific Islands. World Health Organization (WHO) notified that 120 million+ people are currently infected with about 40 million people worldwide suffers from nasty physical manifestations of lymphatic filariasis. This chapter discusses an overview of established anti-filarial agents.

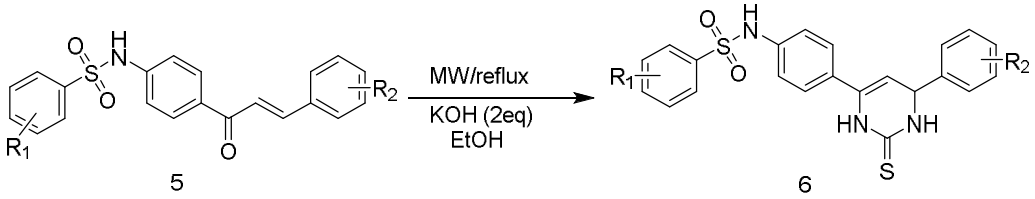
Chapter 2 deals with the synthesis and antifilarial evaluation of sulfonamide chalcones. Synthesis and characterization of various chalcones is described. Thirty seven different chalcones from two different ketones have been synthesized by Claisen-Schimdt condensation using aq. NaOH in ethanol medium (Scheme 1). Synthesized chalcones were characterized by IR, ^{1}H and mass spectral data.



Scheme1. Synthesis of *N*-(4-cinnamoylphenyl)arylsulfonamide derivatives

30 synthesized chalcones were screened for anti-filarial activity against *Brugia malayi* microfilariae. Out of these, 13 molecules showed 100% efficacy in terms of complete loss of motility of all the parasites. After initial screening selected chalcones were processed for IC_{50} (50% inhibitory concentration) and LD_{50} (50% lethal dose) by *in vitro* filarial motility and cytotoxicity assay against peripheral blood mononuclear cells respectively.

Chapter 3 has been divided into two sections. Section 1 deals with synthesis of pyrimidine-2-thiones by the cyclo-condensation of chalcones with thiourea under conventional and MW heating. A library of 28 different pyrimidin-2-thiones has been successfully synthesized in good yields. Rapid and efficient protocol for the synthesis of pyrimidine-2-thiones using MW irradiation has been developed. Using microwave irradiation (100W) in ethanol medium, the reaction proceeds to completion within 30 min whereas conventional method requires 6-8 hrs (Scheme 2).

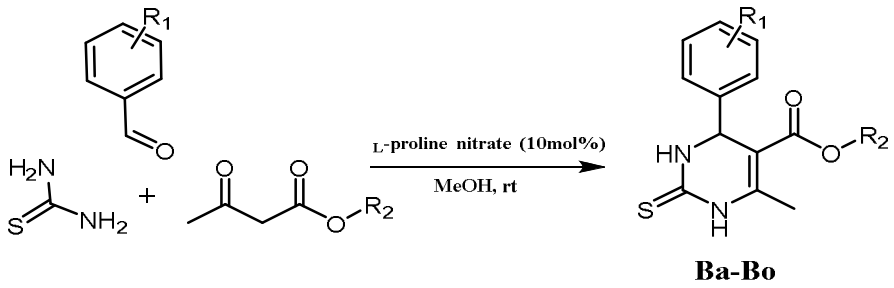


Scheme 2. Synthesis of series of N-(4-aryl 6-aryl-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-phenyl)arylsulfonamide

Among the pyrimidine-2-thiones, four compounds showed significant anti-filarial activity and have been screened further to determine IC_{50} and LD_{50} values.

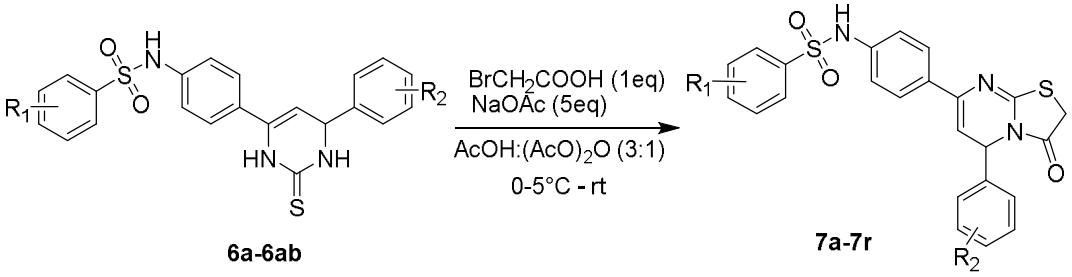
Section 2 deals with development of simple and efficient method for the synthesis of 3,4-dihydropyrimidin-2(*1H*)-thiones. This section describes the utility of $_L$-proline nitrate, which is an amino acid ionic liquid as proficient, recyclable and eco-friendly catalyst.

Synthesis of library of fifteen different Biginelli scaffolds have been described. Details about reusability of the catalyst has been described.



Scheme 3. $_{L}$-Proline nitrate mediated synthesis of 3,4-dihydropyrimidin-2-(1*H*)–thiones

Chapter 4 deals with the development of efficient and rapid protocol for the synthesis of fused thiazolo-pyrimidines. We have developed a more accessible method consisting of addition of solution of bromoacetic acid in acetic acid slowly in the preformed solution of *N*-(4-aryl-6-aryl-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)phenyl)arylsulfonamide compounds in the buffer system of acetic acid: acetic anhydride (3:1) with pH around 4 in the presence of excess anhydrous sodium acetate maintained at temperature 0-5°C and further heating of the reaction mixture at 60°C for about 1.30-2.30 hrs. Using this optimized protocol we synthesized 18 different derivatives of fused thiazolo-pyrimidines under solvent-free conditions. All the synthesized compounds are characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.



Scheme 1. Synthesis of 2,3-dihydro-5*H*-thiazolo[3,2-a]pyrimidin-7-yl) phenyl)benzene sulfonamide derivatives

In the microscopic observation of the motility of the mf worms pre-incubated with synthesized compounds belonging to the thiazolopyrimidine derivatives, out of all these compounds only *N*-(4-(5-(4-chlorophenyl)-3-oxo-2,3-dihydro-5*H*-thiazolo[3,2-a]pyrimidin-7-

yl)phenyl)-4-methylbenzenesulfonamide showed 100% efficacy in terms of complete loss of motility of all the parasites.

In summary greener protocol for the synthesis of some novel pyrimidin-2-thiones using microwave irradiation has been developed. Synthesized chalcones, pyrimidin-2-thiones and thiazolopyrimidines showed prospects as potential anti-filarial agents. Filaria is one of the most widespread diseases in the sub-tropical region like India. This project illustrates environmentally benign synthesis of some novel bio-active molecule which could be used as drugs in future.