Name Of Scholar : **Neha Singh**
Name Of Supervisor : **Dr. Amir Azam**
Name Of Co-Supervisor : **Prof. Kishwar Saleem**
Department : **Chemistry Department**
Title Of Thesis : **Designing, Synthesis and Biological Evaluation of some Heterocyclic Compounds.**

Abstract

In drug designing programs an essential component of the search for new leadings is the synthesis of molecules, which is novel yet resembles known biologically active molecules by virtue of the presence of critical structural features. Certain small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules. Numerous heterocyclic derivatives have received considerable attention because of their diverse biological activity. Pyrazoles and their reduced forms pyrazolines are well known nitrogen containing heterocyclic compounds and various procedures have been developed for their synthesis. The interest of scientists in such compounds has been stimulated by their various promising pharmacological properties. Pyrazolines, bicyclic pyrazolines and quinoxalines are also well known for their pronounced anti- inflammatory activity. These compounds have been developed as non-steroidal anti-inflammatory drugs. They block the formation of prostaglandins and have analgesic, antipyretic and anti- inflammatory activity. Investigations carried out to determine the structural requirements of heterocyclic anti-protozoan compounds have so far indicated that activity can be found preferentially in nitroimidazoles and nitro furans. Among these, nifuroxime, 5-nitro-2-furaldoxime, exhibited antitrychomonal activity and showed in vivo a systemic effect against *Entamoeba histolytica*. Thiosemicarbazones are a small class of molecules that have been evaluated over the last 50 years as antiviral and anticancer therapeutics, as well as for their parasitic avtion against a number of protozoa. The diverse parasitic protozoa such as *E. histolytica* has significant impact on the mucosal health of humans. Infection with *E. histolytica* may result in massive destruction of host tissue and life threatening disease. The protozoan parasite *E. histolytica* causes amoebic colitis and amoebic liver abscess, diseases that afflict millions of individuals in developing countries. More than 50 million people worldwide are infected and up to 110,000 of these die every year. Metronidazole is one of the most widely used medications against amoebiasis. More importantly, the drug is known to have common side effects include nausea. It is mutagenic in bacteria and higher doses may cause cancer rodents and also due to toxic effects on DNA, metronidazole is considered a potential carcinogenic chemical by the International Agency for Research on Cancer. Till date, the ideal treatment for amoebiasis does not exist. We have synthesized forty-six compounds of variegated nature such as thiosemicarbazone, oximes, oxime-ethers and pyrazolines derivatives.

Eighteen compounds have been screened for their antiamoebic activity against *HM1:IMSS* strain of *Entamoeba histolytica* by using microdilution method.

Out of these eighteen compounds, eleven compounds were found to be more active than metronidazole in vitro.

CHAPTER- 1

The First Chapter deals with the synthesis and characterization of Ferrocene carboxaldehyde thiosemicarbazones. Thiosemicarbazones of ferrocene carboxaldehyde were synthesized commencing with appropriate amines. The intermediate thiocarbomylthioglycolic acids were obtained involving initial treatment of amines with carbon disulphide in presence of potassium hydroxide followed by condensation with sodium chloroacetate and finally acidification of the reaction mixture with hydrochloric acid (pH~1). Condensation of thiocarbamylthioglycolic acids with hydrazine hydrate in alkaline medium afforded the corresponding aminothiocarbonylhydrazines in 55% to 70% yields. Treatment of aminothiocarbonylhydrazines with ferrocene carboxaldehyde under refluxing condition in argon atmosphere using ethanol as a solvent yielded the desired formylferrocene thiosemicarbazones (1-17) in 50 to 75% yields. This chapter contains seventeen

thiosemicarbazones. The structures of the synthesized compounds were confirmed by elemental analysis, UV, IR, ^{1}H and ^{13}C NMR and ESI-MS spectral data.

CHAPTER – 2

The Second Chapter describes the synthesis and characterization of 4-Acetyl Pyridine and Indole-3-Carboxaldehyde Oxime and their Oxime-Ethers. The synthesis of oxime was done by oximation using hydroxylamine hydrochloride in a mixture of ethanol and pyridine (2:1) under reflux. The reaction mixture was processed to obtain the oximes, which was condensed with hydrochlorides of 2-chloroethylamine, 2-(Dimethyl amino)ethyl chloride, 2-(Diisopropyl amino) ethyl chloride, 1-(2-Chloroethyl) pyrrolidine, 1-(2-Chloroethyl) piperidine, 4-(2-Chloroethyl) morpholine, 1-(2-Chlorophenyl) piperizine and 1-(3-Chlorophenyl) piperizine in anhydrous methanol containing freshly prepared sodium methoxide solution at refluxing temperature to give the desired oximino derivatives 1-16 respectively.

CHAPTER – 3

This chapter deals with the synthesis and characterization of **1-(N-substituted) thiocarbamoyl -3-(pyridine)-5-phenyl-2- pyrazoline.** Eleven pyrazoline derivatives were synthesized by cyclization of 4-acetyl pyridine chalcone with N-4 substituted thiosemicarbazides of variegated nature. The structures of the synthesized compounds were confirmed by elemental analysis, UV, IR, ^{1}H and ^{13}C NMR and ESI-MS spectral data.

CHAPTER – 4

This chapter deals with biological evaluation of some of the compounds against *E. histolytica*. The antiamoebic activities of the compounds were evaluated by microdilution method against *HM1:IMSS* strain of *Entamoeba histolytica* and the result were compared with the standard drug, metronidazole. Out of 46 compounds synthesized, a total of 18 compounds were screened and 11 of them were found having less IC_{50} value and more active than reference drug metronidazole.

CONCLUSION

Nitroimidazole antibiotics such as metronidazole, is the drug, most widely used in the treatment of anaerobic protozoan parasitic infections caused by *E. histolytica.* However, it is mutagenic and has been associated with serious side effects and some *E. histolytica* strain resistant to this drug have also begun to appear. Therefore it is desirable to search for new amoebicidal. Forty-six compounds of various classes of heterocyclic compounds such as thiosemicarbazones, oxime, oxime-ether and pyrazolines derivatives were synthesized and screened for their antiamoebic activity against *HM1:IMSS* strain of *E. histolytica*. Out of 46 compounds synthesized, 18 compounds were screened for their antiamoebic activity. 11compounds were found more active than metronidazole. On the basis of the results of in vivo studies, It was concluded that thiosemicarbazones were found having better antiamoebic activity those have bulkier groups at N^4 position. The presence of bulky groups at N^4 position of thiosemicarbazide greatly enhanced antiamoebic activity. 4-acetyl pyridine oxime did not show better activity as compared to metronidazole. The conversion of oxime (IC_{50} = 10.12) into oxime ether (IC_{50} = 1.90) reduces the IC_{50} value of the compounds thus enhancing their antiamoebic activity. The compounds which were found more active than the reference drug, their in vivo and cytotoxicity may lead to the development of new and urgently needed drugs for the treatment of amoebiasis.