"Synthesis, Characterization & Evaluation of Biological Activity of Some Heterocyclic Compounds "

Scholar
Kakul Husain

Supervisor
Dr. Amir Azam
Department of Chemistry
Jamia Millia Islamia

The thesis comprises of four chapters. Eighty compounds of variegated nature were prepared by multi-step synthesis belonging to thiosemicarbazone, cyclised pyrazoline compounds, oxime ether derivatives and the modification of Metronidazole drug by introducing transition metals. These compounds were subjected for in vitro screening against amoebiasis.

FIRST CHAPTER

The **First Chapter** describes the synthesis, characterization of thiosemicarbazone derivatives and screening of these compounds for their antiamoebic activity. In the past few years, thiosemicarbazones derived from 2-formylpyridine and related aldehydes have been of great interest because of their reported antiparasitic and antitumor action. This chapter deals with the synthesis, characterization and antiamoebic activity of indole-3-carboxaldehyde thiosemicarbazones and modification of these compounds by the introduction of palladium to enhance the activity. Thiosemicarbazones were prepared by simple method in which N^4-thiosemicarbazone moiety was replaced by aliphatic, arylic and cyclic amines. Thiosemicarbazone metal complexes have raised considerable interest due to their pharmacological properties. In some cases highest activity is associated with a metal complex. All the thiosemicarbazone metal complexes were synthesized by refluxing the solution of thiosemicarbazone (TSC) with metal precursor.

It is observed that the presence of certain bulky groups at position N^4 of the thiosemicarbazone moiety greatly enhances biological activity. On screening against HM1: IMSS strain of *E. histolytica*, the most promising compound was Indole-3-carboxaldehyde-2-chlorobenzylamine thiosemicarbazone palladium(II) complex.

SECOND CHAPTER

The **Second Chapter** presents the synthesis, characterization of pyrazolines derivatives and in vitro evaluation of their antiprotozoal activity. The Chemistry of cyclised heterocyclic systems especially containing pyrazoline moiety has been largely investigated because they are effective in many pharmacological areas. Their derivatives posses a great number of biological activities such as antitumor, antiparasitic,

antifungal, antiviral and anti-inflammatory activities. The chemistry of pyrazole and pyrazolate metal complexes is described quite extensively in the literature and it has been suggested that introducing appropriate substituents at positions 3, 4 or 5 of the heterocyclic ring may modify the nucleophilicity of N2 (sp^2) and the acid character of pyrazole. Consequently, our investigations have been directed towards the preparation of cyclised pyrazoline thiosemicarbazone ligands and their metal complexes at random.

A series of pyrazoline derivatives has been synthesized by the reaction of Mannich Base of Propiophenone with substituted thiosemicarbazides. These compounds were screened in vitro and it was found that the most active compound was 3-phenyl-4-methyl-2-pyrazoline-1-(N-phenylpiperizenyl)thiocarboxamide palladium(II) chloride showed remarkable activity.

THIRD CHAPTER

The **Third Chapter** deals with the synthesis, characterization of oxime ether derivatives and evaluation of their antiprotozoal activity. The oxime ethers attracted our attention because they possess a broad spectrum of potentially useful chemotherapeutic properties.

In recent years a considerable amount of research has been devoted to the synthesis of various substituted oxime ether derivatives. Most medicinal compounds possess one or the other heterocyclic ring. Furans and their derivatives are widely present in nature and not only one of the most important heterocyclic compounds in organic chemistry, but also building blocks which are essential for the total synthesis of the complicated naturally occurring metabolites. Furthermore, polyfunctionalized furans are versatile and convenient synthetic starting materials for the preparation of a variety of heterocyclic and acyclic compounds. It was thought of interest to evolve a synthetic route for preparing compounds containing furan ring system.

These compounds were screened in vitro and it was found that compound Compounds **5** and **6** showed antiamoebic activity which is less compared to metronidazole while compound **6**showed exhibited most promising antiamoebic activity.

FOURTH CHAPTER

The **Fourth Chapter** describes the synthesis of metronidazole complexes analogues and evaluation of their antiprotozoal activity. Literature survey reveals that the metal complexes of active drugs as ligands can have important pharmaceutical properties. Complexation with metal can reinforce the activity of the compound by the combination of effects from the ligands and from the metal residue. To enhance the activity of metronidazole, transition metals {Au(I) and Ru(II)} were introduced into the molecular structure of metronidazole by the reaction of appropriate metal precursor. Their antiamoebic studies were carried out to ascertain their effectiveness in comparison to

metronidazole. The IC_{50} values for the complexes were found to be IC_{50} = 0.32 µ M for **1** and IC_{50} = 0.51 µ M for compound **2**, which was better than metronidazole (1.81 µ M). The complexes **1** and **2** were 6 and 4 folds more toxic than metronidazole.

CONCLUSION

Eighty compounds of variegated nature (thiosemicarbazone, pyrazoline analogs, oxime ether and metronidazole derivatives) were synthesized and screened against *E. histolytica* for their antiamoebic evaluation by using microdilution method. Out of these compounds, thirty-one compounds were found active. *In vitro* test against *E. histolytica* showed that the incorporation of the metal fragments in thiosemicarbazone and in pyrazoline derivatives generally produced an enhancement of their efficacy. These results illustrate well the potential of the novel metal-based approach for the development of chemotherapies against amoebiasis and other tropical diseases. Oxime ether derivatives of 2-acetyl furan were prepared which were studied for their antiamoebic evaluation. Three out of six compounds showed better antiamoebic activity as compared to metronidazole.

For the modification of metronidazole (Currently available antiamoebic drug), the novel Au(I) and Ru(II) metronidazole analogues also have been synthesized and screened for amoebiasis *in vitro*. It was found that incorporation of metal increase the activity of metronidazole. Due to lack of facilities, we have synthesized and screened these compounds only *in vitro*; it would be better it these compounds can be screened for *in vivo* and pharmacokinetic studies.

It is hoped that these studies will stimulate further efforts towards the development of new and urgently needed drugs for the treatment of amoebiasis.