Synthesis, Structure Activity Relationship and Biological Screening of Some Heterocyclic Compounds

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Much efforts in modern chemistry and its application in industry and other academic disciplines such as medicinal chemistry, biophysics, material science and chemical engineering involves manipulating of molecules which are for larger and perhaps better define in terms of thin architecture than was the case even the decade ago. More then ever, chemists are now in a unique position to tackle problems in biology. Heterocyclic chemistry is the basic of life and society. The present research is designed to rationalize organic reactivity of heterocyclic in terms of thin chemical structures and biological activities. This enables to develop novel improved synthetic molecules for a wide variety of biological applications.

The main aim of the research is to mimic the biological system through the basic organic molecules synthesized under this research project and the development of new antiprotozoal drugs. It was decided to exploit this interest led by ascertaining the molecular features essential for activity and utilizing them to develop a new class of antiprotozoal agents. Four libraries of sixty-seven compounds of variegated nature were prepared by multi-step synthesis belonging to meso-substituted porphyrins thiosemicarbazones, core-modified ferrocinyl porphyrins, 1, 2, 4-dioxazole derivatives and Bis-pyrazolines. These compounds were subjected for screening against parasitic disease i.e. amoebiasis and few against malaria.

Porphyrins attracted our attention because they process a broad spectrum of potentially useful chemotherapeutic properties. Two libraries of porphyrins were prepared. The **first library,** a series of 14 novel compounds, meso-substituted "5-(4-phenyl-N^4 $^-$substituted thiosemicarbazone)-10, 15, 20-(trisphenyl) porphyrin" were synthesized, characterized and evaluated for their in ***vitro*** antiamoebic activity. Some of these compounds were also screened for in ***vitro*** anti malarial activity.

These novels porphyrin thiosemicarbazones showed variable antiprotozoal activity against both ***P.falciparum*** and ***E. histolytica***. The compounds "5-(4-phenyl-N^4-m-toluidinethiosemicarbazone)-10,15, 20-(trisphenyl)porphyrin, 5-(4-phenyl-N^4-2-chlorobenzylthiosemicarbazone)- 10,15, 20-(trisphenyl)porphyrin, 5-(4-phenyl-N4-cyclohexylthiosemicarbazone))-10,15, 20-(trisphenyl)porphyrin, 5-(4-phenyl-N^4-p-toluidinethiosemicarbazone))-10,15, 20-(trisphenyl)porphyrin, 5-(4-phenyl-N^4-o-

toluidinethiosemicarbazone))-10,15, 20-(trisphenyl)porphyrin corresponds to 2.57 to 4.7 fold increase in activity than metronidazole (1.8μM), thus indicate better inhibitors of ***E.histolytica*** growth. In addition 5-(4-phenyl-N^4-m-toluidinethiosemicarbazone)-10,15, 20-(trisphenyl)porphyrin with meta toulidine as subtituent is approximately **5** times more potent than metronidazole in inhibiting ***E. histolytica*** growth and warrants further investigation. Six compounds were screened against ***P. falciparum*** and 5-(4-phenyl-N^4-m-toluidinethiosemicarbazone)-10, 15, 20-(trisphe-nyl) porphyrin showed better activity than chloroquine and quinine. All of these compounds show negative toxic effects to humane kidney epithelial cell line.

The social library, a series of 10 ferrocenyl derivatives of core-modified 5, 10-bis-2{(N-substituted amino) methylene} ferroocenyl-15, 20-diphenyl-21,23 dithiaporphyrin derivatives were synthesized, characterized by different spectroscopic techniques and were screened for antiamoebic activity. Porphyrins from the base of widely used Photodynamic therapy (PDT), which has gained acceptance as a front line cancer therapy for a variety of malignancies. In recent years a considerable amount of research has been devoted by the synthesis of various substituted ferrocenes. Such compounds can effectively be used in asymmetric catalysis and enantioselective synthesis. Enhanced antibiotic activity of penicillin & cephalosporin has been noted by replacing aromatic groups with the ferrocenyl moiety. The synthesis of core-modified ferrocenyl porphyrins involves multi steps and was carried through acid catalyzed 3+1 condensation of 2,5-Bis[{(2-secondaryamino)methylene}ferrocenyl)hydroxymethy]thiophene with 2,5-Bis-(1-phenyl-1-pyrrolomethylene)thiophene and subsequent oxidation with **DDQ**.
It is observed that out of ten compounds, six compounds were found with less IC_{50} values that metronidazole. The IC_{50}values for compounds 5, 10-bis-2{(N-ethylbenzylamino)-methylene} ferrocenyl-15,20-diphenyl-21,23-dithiaporphyrin (0.59 μM), 5,10-bis-2{(4-methylpiperidinyl)methylene}ferrocenyl-15,20-dipheny-21,23-dithia-porphyrin (1.41 μM), 5,10-bis-2{(hexamethyleneamino)methylene}ferrocenyl-15,20-diph-enyl-21, 23-dithiaporphyrin (0.72 μM), 5,10-bis-2{(diethyl amino)methylene}-ferrocenyl-15,20-diphenyl-21,23-dithiaporphyrin (1.57 μM), 5,10-bis-2{(Pyrollidinyl)methylene}ferro-cenyl-15,20-diphenyl-21,23-dithiaporphyrin (1.71 μM) and 5,10-bis-2{(2-ethyl-piperidinyl)methylene}ferrocenyl-15,20-diphenyl-21,23-dithiaporphyrin (1.56 μM) were considerably lower than that of metronidazole (IC_{50} = 1.8 μM), corresponding to 1.05 to 3.05 fold increase in activity.
A novel series of 33 compounds of dioxazoles comprises the **third library.** Azoles have long been targets of synthetic investigation because of their known biological properties like cognitive-enhancing and anxiolytic-like activity. Oxazoles an important number of the azoles family contains a number of biologically active modules, which play an important role in the drug chemistry. A number of compounds had been screened for antituberculosis activity.
These compounds were synthesized, characterized and were screened for ***in vitro*** antiamoebic activity against ***E.histolytica***. The activity of the dioxazole compounds was found structure dependent. Out of the thirty-three compounds, nine showed best activity, with 2.09 to 4.39 times more active than metronidazole. The IC_{50} values for these compounds are 3,5 bis-[2-chlorophenyl]-1,2,4-dioxazole (0.14 μM), 3-[2-chlorophenyl],5-[4-chlorophenyl]-1,2,4-dioxazole (0.48 μM), 3-[4-chlorophenyl]-5-[3-

chlorophenyl]- 1,2,4-dioxazole (0.51 µM), 3,5bis[4-chlorophenyl]-1,2,4-dioxazole (0.53 µM), 3-[2-chlorophenyl],5-[3-chlorophenyl]-1,2,4-dioxazole (0.62 µM), 3-[4-chlorophenyl]-5-[3-chlorophenyl]-1,2,4-dioxazole (0.71 µM), 3-[3-chlorophenyl]-5-[2-chlorophenyl]-1,2,4-dioxazole (0.72 µM), 1(0.81 µM), and 3-[3-chlorophenyl]-5-[4-chlorophenyl]-1,2,4-dioxazole (0.8 µM) compared with metronidazole (IC_{50} = 1.8 µM). six compounds were found moderately active, with 1.04- 1.97 times better than metronidazole.

Another series of compounds, Bis-pyrazolines comprises the **fourth liberary** of the biologically active synthesized molecules. Pyrazoles with their reduced form pyrazolines, are well known nitrogen containing heterocyclic compounds showing promising pharmacological activities. Compounds were pyrazole ring are interest because of their broad-spectrum biological activities against monoamine oxidase inhibitor, bacterial, depression, hypotensive, pyretic and inflammatory disease. A series of Bis-pyrazolines derivative has been synthesized and screened for antiamoebic activity.

These compounds were screened for ***in vitro*** antiamoebic activity and the **IC_{50}** values for compounds (4-nitrophenylamino)[5-(4-{1-[(4-nitrophenylamino)thioxomethyl] -3-phenyl(2-pyrazoline-5yl}phenyl)-3-phenyl(2-pyrazolinyl)methane-1-thione (0.42µM),[2,4-difluorophenyl)amino[5-(4-{1-{[(2,4-difluorophenyl)amino] thioxomethyl} -3-phenyl(2-pyrazoline-5yl}phenyl)-3-phenyl(2-pyrazolinyl)]meth-ane-1-thione (0.62 µM), and (cyclooctylamino)[5-(4-{1-[(cycloctylamino)thioxomethyl]-3-phenyl(2-pyrazoline-5yl}phenyl)-3-phenyl(2-pyrazolinyl)]methane-1-thione (0.920 µM), found to 1.95 to 4.28 fold increase in activity than the standard drug metronidazole. The most active compound is (4-nitrophenylamino)[5-(4-{1-[(4-nitrophenylamino)thioxomethyl] -3-phenyl(2-pyrazoline-5yl}phenyl)-3-phenyl(2-pyrazolinyl)]methane-1-thione and shown to be better inhibitor of growth of ***E. histolytica.***

Conclusion: Sixty-seven compounds were synthesized and subjected for screening against **HM1: IMSS** strain of ***E. histolytica***. Out of these compounds, thirty six compounds were found active. The compounds demonstrated approximately 1-4 times more activity than metronidazole against ***E. histolytica***. Six compounds were also screened for antimalarial activity and one compound was found active against the growth of ***P. falciparum*** some of the compounds were also tested for **MTT** essay. The results showed that the compounds are non-toxic to human kidney epithelial cell line.