Summary
Malaria can be considered as one of the deadliest diseases around the world which affects 500 million people causing 2.5 million deaths annually. It is estimated that there are some 300-500 million cases and between 1.5 to 2.7 million deaths from malaria each year. The existing chemotherapy is not satisfactory in terms of its lack of effectiveness and also due to the toxicity associated to long-term treatments with empirically discovered drugs. Drug resistance and different strain sensitivity to the available drugs are major drawbacks for the clinically accessible chemotherapy. Therefore, in the absence of vaccines, new chemotherapies are urgently needed to help in the prevention and control of this parasitic disease. Quinoline and its derivatives represent a very important class of antimalarial drugs that function by targeting the parasite specific hemoglobin breakdown pathway.

Our present work is an attempt to find new lead molecules exhibiting good antimalarial activity. A systematic study is needed to find effective leading compounds using 4-aminoquinoline as basic skeleton. These quinoline derivatives had previously shown promising antimalarial activity with lesser side effects. In literature it is quite well reported that aliphatic 2-3 carbon linker chain, planner quinoline ring and free amino group at position 4 exhibits encouraging antimalarial activity because of the complexion of free heme. There are several drugs like mefloquine or amodiaquine available which neither have aliphatic chain nor free amino group at position 4 of quinoline ring but are very effective against chloroquine resistant strains. Amodiaquine Fis still clinically useful due to the effectiveness but it has some serious side effects like heptatotoxicity and agranulocytosis. To prevent the formation of toxic metabolite, amodiaquine quinoneimine was developed having potent in vitro activity against CQ-resistant parasites. Unfortunately, the unacceptable high first pass metabolism of isoquine to dealkylated metabolites did not allow further drug development process. Modification of isoquine directed the discovery of drug candidate N-tert-butyl isoquine. In addition, 4-fluoro-N-tert-butylamodiaquine was also identified as a back-up compound for N-tertbutyl isoquine based on potent activity against CQ-sensitive and
resistant parasites. Thus, these findings manifest considerable scope for developing new antimalarial with quinoline nucleus. After analysing all the facts we have designed the analogs under scheme-I. In continuation of our research programme devoted to synthesis of various classes of heterocycles as antimalarial agents, we identified trisubstituted triazines, as potential antimalarials. The 4-anilinoquinoline moiety has been shown to be responsible for CQ-sensitive and CQ-resistant activity in *P. falciparum*. We predicted that combining two intrinsically active antimalarial moiety 4-anilinoquinoline and triazine would lead to develop more potent antimalarials. After surveying all these literature materials, we have used substituted triazines on series-I analogs to synthesize triazine-quinoline scaffolds under series-II. This study will be useful to understand the effect of triazine on antimalarial activity and crystallization pattern on the analogs of series-I.

Further, in scheme-III and IV, we liked 4-aminoquinoline and aromatic aldehydes together via flexible linear chained diaminoalkanes likers so that molecule has enough flexibility to fit in the binding site of the target, and as a result, this kind of hybrid molecules may show better antimalarial activity. Chauhan *et al.*, 2009 already reported the synthesis of 4-aminoquinolinepyrimidine conjugates in which 4-aminoquinoline and pyrimidine moieties were linked through an aromatic ring, and some of these compounds have shown moderate activity. These compounds are synthesised to study the structure-activity relationship of quinoline derivatives. Among all synthetic molecules 4-amino-7-chloroquinoline is kept constant as a basic scaffold.

Among these compounds, few compounds of series-I are crystallized in ethanol. These crystals were characterized by CrysAlisPro CCD Oxford Diffraction with X-ray generator 49.30 kV and 0.980 mA, using Mo Kα radiation (λ=0.7107 Å). Data reduction and cell refinement was carried out using CrysAlisPro. Structure was solved in the WinGX suite of programs by direct methods using SHELXL-97. Main purpose behind this investigation was to determine the role of hydrogen bonds in stabilizing crystal packing patterns of quinoline derivatives. Hydrogen bonding is universally acknowledged yet hydrogen bond formation to control intermolecular association has not been explored well as required. Nature of hydrogen bonding is important to predict the interaction and aggregation of molecules in solution or in liquid phases. These
bindings are also responsible to forecast the cumulative structures in the packing patterns. Chloroquine and some of its analogs are well-known medicinally acclaimed moiety especially as antimalarial agents. But, till date these compounds are not very explored in solid state. To explore behaviour of 4-aminoquinoline derivatives, we have characterised ten crystals of 4-aminoquinoline derivatives by several spectroscopic techniques and carried out crystallographic analysis. After examine all the data we concluded that there is a formation of N-H···Cl or N hydrogen bonds giving rise to different structural motifs, namely dimers, chains and ribbon. These hydrogen bonds are one of the basic factors for three dimensional nature of particular derivative. Apart from hydrogen bonds, there are many, much weaker, non-covalent interactions which are responsible for the 3-dimensional configuration of biological systems. These interactions play a very vital role in the flexibility of the macromolecules & their interactions with each other in the cell. Among these interactions, halogen bonding is also very important where halogen atoms make short contacts with lone pair possessing atoms such as oxygen or nitrogen, which analogous to hydrogen bonding. Along with H-bonds we also determined halogen···halogen interactions (both homo & hetero) in 4-aminoquinoline derivatives and compared differences between neutral molecule vs. salt. Two crystals viz., 7-(chloroquinolin-4-yl)-(3,4-difluorophenyl)-amine and 7-(chloroquinolin-4-yl)-(3,4-difluorophenyl)-amine hydrochloride exhibited different their packing features and halogen···halogen interactions. Since no such reports are available in literature which could highlight this bonding especially in such a medicinally important scaffold.

Interaction studies of drugs to serum albumin proteins are of great importance as absorption, distribution, metabolism and excretion properties of drugs can significantly alter after binding with albumin proteins. As a kind of serum albumin, bovine serum albumin (BSA) has the advantages of medical importance, low cost, ready availability and unusual ligand-binding properties. Bovine and human serum albumin tertiary structures are 76% similar and the results of all studies are consistent with the fact that human and bovine serum albumins are homologous proteins. In continuation to determine the properties of 4-aminoquinoline derivatives, performed binding studies with BSA and HSA. We initially characterized the compound (7-chloroquinolin-4-yl)-
(2,5-dimethoxyphenyl)-amine hydrochloride dihydrate (CQDPA) by single crystal X-ray crystallographic analysis. Crystal packing exhibited four molecules per unit cell (figure-3.4). X-ray crystal analysis reveals that the dimethoxy ring is twisted at an angle of 68.66° with respect to 7-chloroquinoline ring.

We have selected this compound because this compound exhibited antimalarial in vitro activity in nano molar range. So far, the specific mode of interaction of such type of 4-aminoquinoline derivatives with albumin proteins has seldom been studied at the molecular level. Keeping the promising antimalarial activity of compound in mind, we have studied the interaction of CQDPA with bovine and human serum albumin in detail using steady state fluorescence at three different temperatures. Thermodynamic parameters were calculated which suggested the mode of interaction between albumin proteins and small molecule. Conformational changes were described on the basis of circular dichroism results. In addition to this, distance between acceptor and donor was calculated using Foster energy transfer theory.

Literature survey revealed that five to six membered heterocyclic compounds containing one or two heteroatoms fused to a quinoline ring in linear fashion were found to possess antimalarial, antitumor and anticancer properties. Quinoline derivatives, such as chloroquine is also a potential drug as chemosensitizer in cancer in combination with some conventional antineoplastic agents. Chloroquine recently showed to inhibit the function of membrane-associated proteins belonging to the p-glycoprotein and multi-drug resistance (MDR) protein families. These proteins are at the forefront as mediators of chemotherapy resistance in a wide range of cancers. Generally, active compounds are required to possess an approximately planar structure, with a medium-sized planar area and some hydrophobic character. To investigate the mode of binding of quinoline derivatives to DNA, we carried out a series of spectroscopic studies including UV-visible, Tm and CD spectra. These studies are vital for the elucidation of the mechanisms of drug action and designing of more efficient and specifically targeted drugs with lesser side effects. We have selected three compounds viz. ligand-1, 2 & 3 from three different series of synthesised derivatives of 4-aminoquinoline scaffolds.
This study would be very useful to predict the interaction of small molecule to DNA in general. Since these compounds contain aromatic rings to facilitate the intercalating, thus the interaction may be intercalation. In addition to this, these compounds are small molecule with the low bonding size, therefore, the minor groove binding is preferable than the major one. From all the experiments it can be concluded that binding of quinoline derivatives to DNA resulted in significant changes in the structure and conformation of DNA and act as an intercalator via increasing the stability of DNA by increasing Tm, increase in absorbance and alteration of CD spectra. The absorption spectrum of DNA reveals higher degree of hyperchromism. Hyperchromism is a characteristic feature which develops due to the interaction between aromatic chromophores and base pairs.