The thesis entitled ñ**Studies on synthesis of novel quinoline derivatives and their biological activity**ò has been divided into four chapters.

Chapter-I: Introduction

In ancient days to cure diseases, our ancestors used nature as the best remedy and compounds which are isolated from natural sources were used. The present modern lifestyle lead to deadly diseases like cancer, HIV, T.B., etc. and prompt innovative research is necessary to deal with resistance and side effects associated with current therapies. Natural compounds like alkaloids as well as synthetic drug candidates which have nitrogen atom at unique position exhibit various biological properties and among them quinoline ring system shown diverse application in pharmaceuticals. Aim of this work is to synthesize a new variety of quinoline analogues and screen against various diseases in order to find promising molecules. Fluoro or trifluoromethyl substituted compounds are of great interest due to strong electron-withdrawing effect which adds to high pharmacokinetic properties. Aim of this work is to synthesize a new variety of quinoline with substituted fluoro or trifluoromethyl analogues and screen against various diseases in order to find promising molecules. In this research program, efforts have been initiated towards the investigation of more potent molecules based on structural features. Thus, synthesized a number of new analogues of quinolin-2(1*H*)-one and its fused heterocycles like pyrazolo[3,4-*b*]quinolinyl acetamide and pyrazolo[3,4-b]quinolin-1-yl derivatives and subjected to activity screening. The research work is pursued in four chapters which include introduction and work of each chapter is briefly outlined below.

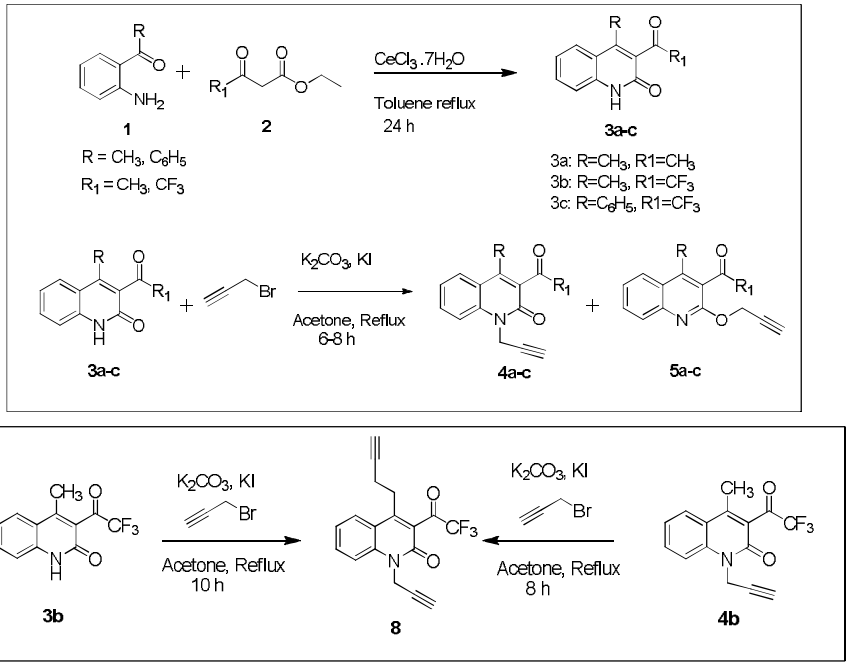
Chapter-II

Statement of the problem:

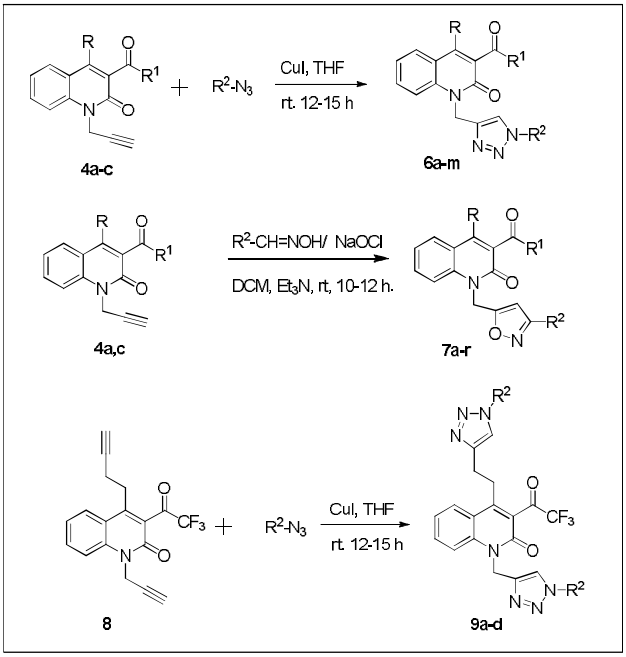
Functionalized quinolin-2(1*H*)-one derivatives are attractive compounds for drug discovery as many of them found to show promising biological activities. Some of them are considered as receptor antagonists for angiotensin II, glycine NMDA, endothelin , antiplatelet and antitumor agents. Ciprofloxacin and Oflaxacin, a large group of quinoline derivatives and 1,2,3-triazoles/isoxazole derivatives are considered as one of the most important scaffolds embedded in many biologically active compounds and attracted attention. These findings encouraged us and increasing interest in structural modification of the antitumor properties containing both quinolin-2(1*H*)-one and 1,2,3-triazole/isoxazole pharmacophores in a compact system.

Methodology: A series of novel *N*-triazole alkyl quinolin-2(1*H*)-one derivatives **6a-m** and **9a-d** were prepared starting from 2-amino aceto/benzophenone **1** via cyclization, propargylation to form compound **4** followed by reaction with different azides under Sharpless conditions obtained triazole alkyl tagged quinolin-2(1*H*)-one derivatives **6a-m** and **9a-d**. Compound **4** on reaction with aryl aldoximes through 1,3-dipolar cycloaddition resulted isoxazole alkyl quinolin-2(1*H*)-one derivatives **7a-r.**

Synthesis and Anticancer Activity of Novel *N*-triazole/isoxazole Alkyl Functionalized Quinolin-2(1*H*)-one Derivatives



Scheme 1: Synthetic pathways for compounds **4a-c**, **5a-c** and **8**



Scheme 2: Synthetic pathways of compounds **6a-m**, **7a-r** and **9a-d**

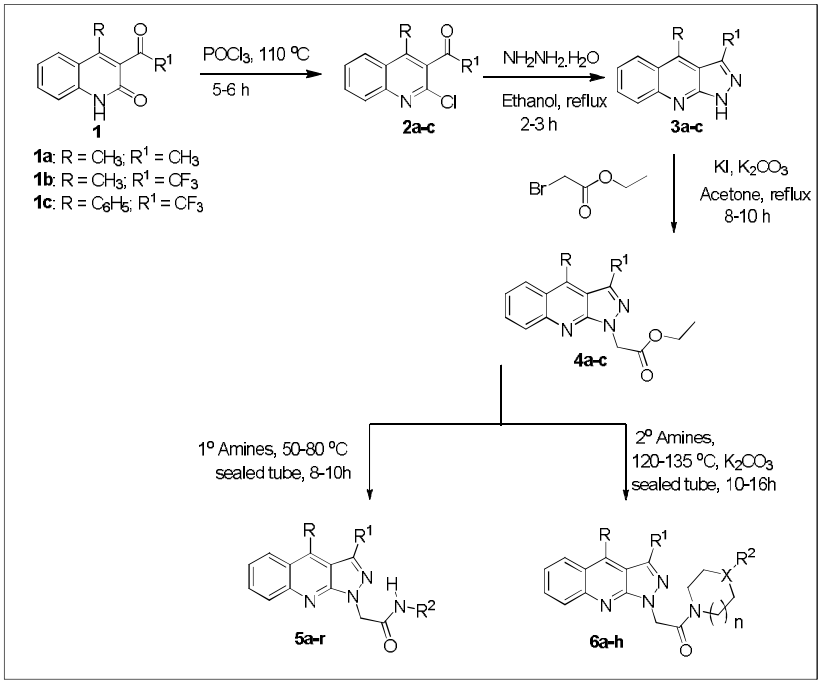
Result: A series of novel *N*-triazole/isoxazole alkyl quinolin-2(1*H*)-one derivatives **6a-m**, **7a-r** and **9a-d** were synthesized and all these analogs were screened for anticancer activity against four human cancer cell lines. Compounds **6d**, **6k** which showed promising activity at micro molar concentration have been identified.

Chapter III

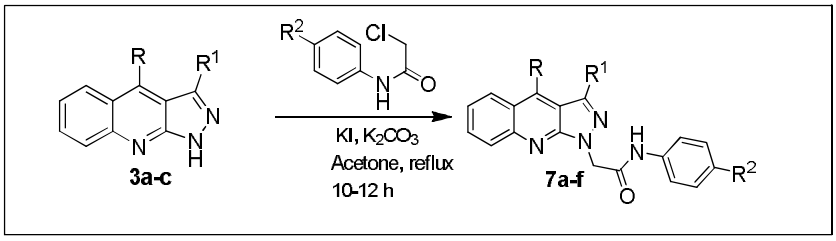
Statement of the problem: Bacterial and fungal infections became a threat and a major cause of deaths in immune compromised persons. Cancer is the second most leading and debilitating disease all over the world. Recently, substituted quinolines at 2 and 3 position exhibited excellent pharmacological properties such as antimicrobial, antifungal and antitumor activities. Similarly, some natural products like ellipticine and camptothecin type of core moieties with small alterations have resulted in promising quinoline fused pyrazole hybrids which showed good anxiolytic and neuroprotective activities. Pyrazolo fused quinoline analogs were used to kill microorganisms (as antimicrobial agents) and also inhibits uncontrolled cell division (as anticancer agents) both properties in a single molecule which drags us to develop a new series of analogs of these derivatives. Based on the importance of fused heterocyclic compounds, we have focused our attention to synthesis of novel trifluoromethyl substituted pyrazolo[3,4-*b*]quinolinyl acetamide derivatives, screened for antimicrobial, antifungal and anticancer activity.

Methodology: A series of novel pyrazolo[3,4-*b*]quinolinyl acetamide analogs **5a-r**, **6a-h** and **7a-f** were prepared starting from quinolin-2(1*H*)-ones **1a-c** on chlorination with $POCl_3$ resulted in 2-chloroquinolines **2a-c** followed by reaction with hydrazine hydrate resulted in 2,3-pyrazole fused quinoline derivatives **3a-c**. Compounds **3a-c** further reacted with 2-bromoethylacetate to form *N*-alkylated ester of 2,3-pyrazole fused quinoline derivatives **4a-c.** Compounds of series **4** were reacted with primary aliphatic amines, cyclic amines and secondary amines to obtain amide derivatives **5a-r** and **6a-h** respectively. Similarly, compounds of the series **4** on reaction with primary aromatic amines did not result in the products of series **7**. An alternate approach has been developed to obtain products **7a-f** by reaction of 2,3-pyrazole-fused quinoline derivatives **3** with chloroacetyl aniline derivatives under basic conditions as they are not easily accessible by reaction of **4** with aromatic primary amines due to their less nucleophilicity.

Synthesis of novel pyrazolo[3,4-*b*]quinolinyl acetamide analogs, their evaluation for antimicrobial and anticancer activities



Scheme 1: Synthesis of 1^{o} and 2^{o} alkyl amide tagged pyrazolo quinoline derivatives **5a-r** and **6a-h**.



Scheme 2: Synthesis of 1^{o} aryl amide tagged pyrazolo quinoline analogs **7a-f**.

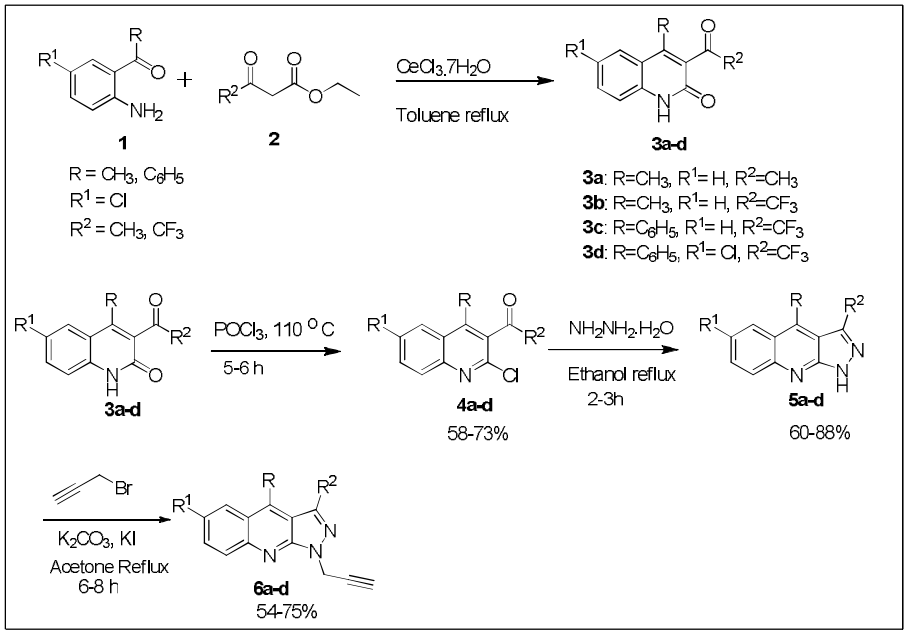
Result: A series of novel alkyl amide functionalized 2,3-pyrazole fused quinoline derivatives were prepared and screened for antibacterial activity and the promising compounds identified were further evaluated for antifungal and antibio-film activities. Compound **5r** exhibited MIC values ranging between 3.9-7.8 µg/mL against different bacterial strains and was identified as a promising lead. Compound **5r** also showed good antifungal and anti bio-film activities against various fungal and bacterial strains. Compound **5r** when treated on mature *S. aureus* MLS16 biofilms showed increased levels of intracellular ROS accumulation which may be contributing to the bactericidal activity. Further, the cytotoxicity evaluation against four human cancer cell lines revealed that the compounds **5c, 5d**, **5r** and **7f** exhibited promising cytotoxicity. Based on these assays, the lead compound **5r** was identified.

Chapter-IV

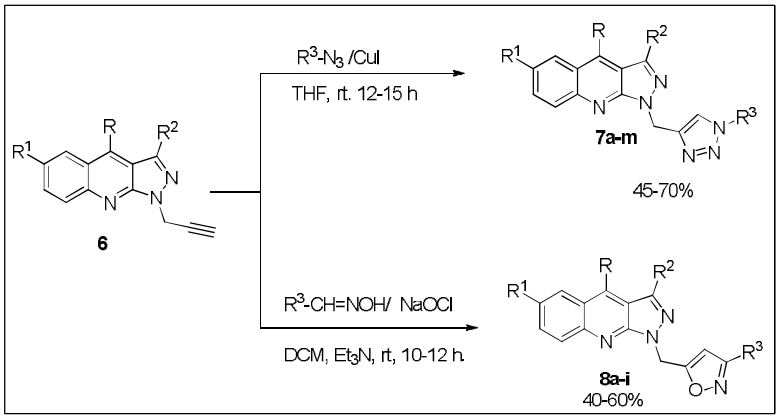
Statement of the problem: Triazole and isoxazole tagged pyrazoloquinoline which contain five membered ring systems, enough nitrogen and oxygen atoms they can contribute substantially in increasing pharmacological activity by participating in hydrogen bonding interactions with the receptors. 1,2,3-Triazoles are useful building blocks in organic synthesis because of their wide range of biological activity, and are stable to moisture, oxygen, light and also metabolism in the body. Moreover, these moieties can be tuned to form powerful pharmacophores and also plays an important role in bio-conjugation. Introduction of pyrazolo[3,4-*b*]quinoline moiety to the triazole core will increase the hydrophilicity of the molecule, which promotes biological activity. Recent literature reveals that, a pyrazoloquinoline scaffold identified to display significant role as various pharmaceutical agents, especially antitumor agent, antimicrobial agent, PDE10A inhibitory activity, etc. Based on the above findings, encouraged us to predict the combination of both pharmacophores in a compact system and synthesized new series of hybrids novel 3,4 substituted 1-*N*-alkyl tagged triazole/isoxazle and pyrazolo[3,4-*b*]quinoline derivatives.

Methodology: A series of novel pyrazolo[3,4-*b*]quinolinyl triazole and isoxazole analogs **7a-m** and **8a-i** were prepared starting from quinolin-2(1*H*)-ones **3a-d** on chlorination with $POCl_3$ resulted in 2-chloroquinoline derivatives **4a-d** followed by reaction with hydrazine hydrate resulted 2,3-pyrazole fused quinoline derivatives **5a-d**. Compounds **5a-d** further reacted with propargyl bromide to form *N*-alkylated 2,3-pyrazole fused quinoline derivatives **6a-d.** Compounds of series **6** were reacted with different azides under Sharpless conditions obtained 1,2,3-triazole alkyl tagged pyrazolo[3,4-*b*]quinoline derivatives **7a-m**. Similarly, compounds of the series **6** on reaction with aryl aldoximes through 1,3-dipolar cyclo addition resulted products of series **8a-i**.

Sec A: Synthesis of novel *N*-triazole/ isoxazole alkyl functonalized pyrazolo quinoline derivatives



Scheme 1: Synthetic pathways for *N*-alkylated pyrazoloquinoline derivatives **6a-d**.



Scheme 2. Synthetic pathways for formation of compounds **7a-m** and **8a-i** derivatives

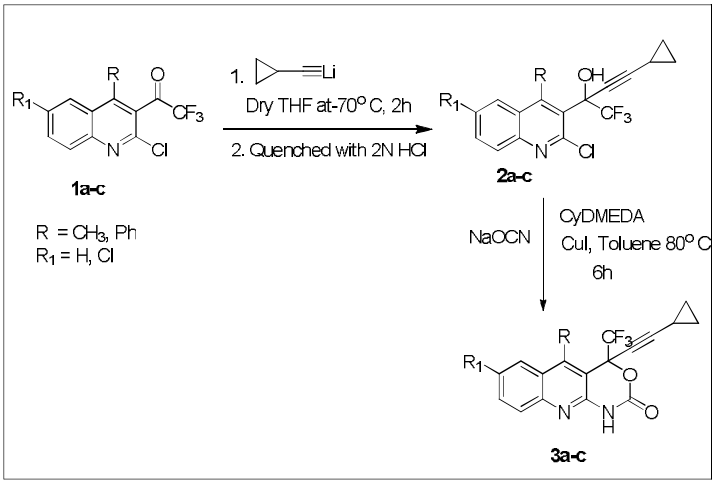
Results: A series of novel *N*-alkyl pyrazoloquinoline derivatives **6a-d** and 1,2,3-triazole/isoxazole functionalized pyrazoloquinoline derivatives **7a-m** and **8a-i** were prepared in series of steps. All the compounds were screened for anticancer activity against human cancer cell lines and potent compounds have been identified.

Sec B: Synthesis of novel 4,4-disubstituted-5-alkyl/aryl substituted 1*H*-[1,3]oxazino[4,5-b]quinolin-2(4*H*)-one derivatives

Statement of the problem: HIV is uncurable disease till now as no clearcut drug was invented, however there are some drugs sold in combo to treat patients adequately. Some of them are listed here as Abacavir, Efavirenz, Emtricitabine, Tenofovir disoproxil,

Zidovudine, etc. Among them, Efavirenz is considered as promising molecule and some structural modification may lead to an interesting result for synthetic as well as medicinal. We took this challenge and synthesized few analogs which structurally mimic with Efavirenz skeleton.

Methodology: A series of novel 4,4-disubstituted-5-alkyl/aryl substituted 1*H*-[1,3]oxazino[4,5-b]quinolin-2(4*H*)-one derivatives **3a-c** were prepared starting from substituted 2-chloroquinolinones **1a-c** on nucleophilic addition with *in-situ* generated lithium cyclopropylacetylide resulted 2-chloroalcohol **2a-c** followed by reaction with NaOCN resulted substituted 1*H*-[1,3]oxazino[4,5-b]quinolin-2(4*H*)-one derivatives **3a-c**.



Scheme 1. Synthesis of substituted 1*H*-[1,3]oxazino[4,5-b]quinolin-2(4*H*)-one derivatives (**3a-c**)

Result: A series of novel 4,4-disubstituted-5-alkyl/aryl substituted 1*H*-[1,3]oxazino[4,5-b]quinolin-2(4*H*)-one derivatives **3a-c** were synthesized starting from 2-chloro quinoline derivatives **1**.