Summary

In the past two decades, a dramatic rise in the incidence of life threatening systemic microbial infections have been observed as well as the emergence of multi-drug resistant organisms poses a challenge in the treatment of infectious diseases. One way to battle with this challenge is the conscious usage of the currently marketed antibiotics; the other is the development of novel antimicrobial agents. Hence, there will always be a vital need to discover new chemotherapeutic agents to avert the emergence of resistance and ideally shorten the duration of therapy. Furthermore, the ever-increasing drug resistance, toxicity and side effects of currently used antituberculosis drugs, and the absence of their bactericidal activity highlight the need for new, safer and more effective antimycobacterial compounds.

Quinoline moiety is of great importance to chemists as well as biologists as it is found in a large variety of naturally occurring compounds and also chemically useful molecules having diverse biological activities. Amongst the various activities of their derivatives, antimicrobial & antimalarial activity is noteworthy.

In the light of these facts, we have been particularly engaged with the synthesis of quinoline incorporating structures for antimicrobial evaluation. The library of 130 new compounds has been constructed keeping quinoline core as a common structural feature.

We specifically targeted heterocyclic derivatization to achieve $N$-arylamino biquinoline, $1H$-pyrazolo[1,2-b]phthalazine-5,10-dione, $N$-pyridyl biquinoline, 4-(heteryl) substituted benzo[g]chromene, 4-(heteryl)substituted pyrano[3,2-c]pyridine. The utmost diversity index has been pulled up to biquinoline synthesis on the premise of earlier work of our group. The reaction strategies involved are multicomponent reaction (MCR) approach, microwave irradiation (MWI), and conventional syntheses. The reactions engaged with that synthetic work are Knoevenagel condensation, heteroannulation, Michael addition, nucleophilic displacement and Vilsmeier-Haack reaction.

All the synthesized compounds were characterized by using $^1H$-NMR, $^{13}C$-NMR, FT-IR and elemental analysis as well as subjected to in vitro antimicrobial activity (MIC) by using Broth microdilution method & in vitro antimycobacterial activity by using Lowenstein-Jensen medium (conventional method). Also one series
of \(N\)-arylamino biquinoline derivatives have been screened \textit{in vitro} for antimalarial activity.

The work described in the thesis is briefly summarized chapter wise highlighting the most effective candidates in each series of compounds.

\textbf{Chapter-2: \textit{N}}-\textit{ARYLAMINO BIQUINOLINE DERIVATIVES}

Heteroaromatic rings containing nitrogen atoms often play an important role as the scaffolds of bioactive substances. Quinoline is one of the most popular \(N\)-heteroaromatic frameworks present in many pharmaceuticals and exhibits a wide spectrum of pharmacological effects. Of the pharmacologically active quinoline derivatives, \(N\)-aryl quinoline has attracted much interest in recent years because of their significant synthetic as well as medicinal utility like antimicrobial and anticancer. In the present chapter an effort has been made to synthesize and study the biological activity of \(N\)-aryl biquinoline derivatives.

\textbf{(Part-I)}:

\(N\)-arylamino biquinoline derivatives are obtained in good to excellent yields by one-pot multicomponent reaction of 2-chloro-3-formyl quinoline with malononitrile and enhydrazinoketones in ethanol. Of the compounds studied, 5h and 5s were found as the most effective antibacterial agents. Unfortunately, majority of compounds showed poor inhibition of \textit{M. tuberculosis} (MTB) growth.

The compounds were evaluated in \textit{vitro} for their activity against the growth of \textit{Plasmodium falciparum}, the malaria causing parasite. Some of them showed antimalarial activity with IC\(_{50}\) values as low as 0.005-0.009 µg/mL.
Summary

IC$_{50}$ = 0.015

IC$_{50}$ = 0.008

IC$_{50}$ = 0.009

IC$_{50}$ = 0.005

IC$_{50}$ = 0.014

IC$_{50}$ = 0.019

IC$_{50}$ = 0.012

IC$_{50}$ = 0.014
(Part-II):

An efficient one-pot, three-component method for the preparation of \(N\)-arylaminobiquinoline derivatives has been developed through the Michael addition to enhydrazoneketones, which was achieved by both microwave irradiation and conventional heating.

Reviewing the antimicrobial activity data, it has been concluded that the inhibitory effect was more pronounced for gram positive strains specially \textit{Clostridium tetani} and \textit{Bacillus subtilis} than for gram negative strains and indicative of the efficacy of the compounds to inhibit gram positive bacteria. It is interesting to note that these compounds preferentially inhibit pathogenic strains suggestive of their potential in antimicrobial chemotherapy. Compounds 5f and 5q exhibited excellent against \textit{Escherichia coli} while compounds 5k and 5u preferentially showed pronounced inhibition against \textit{Salmonella typhi}. Compound 5u also showed good activity towards \textit{Streptococcus pneumoniae}.
Comparing the biological evaluation of the entire series presented in part I with part II of this chapter, it has been observed that the compound found most active against particular species in part I are found less active or having poor activity against the same species in part II and vice versa i.e. replacement of CN group by COOEt in the quinoline ring shows pronounced change in activity. Compounds 5a, 5f and 5q which shows pronounced activity against \textit{E. coli} in part II are found to exhibit moderate to good activity in part I whereas compound 5h which shows pronounced activity against \textit{E. coli} in part I is found less active in part II. Same point is also noticeable for the antituberculosis results. The compound showing better inhibition in part I (Compounds 5c, 5h and 5x) are found poor in part II while the compounds 5b, 5q and 5r of part II series are less active in part I series i.e. replacement of CN with COOEt the activity is reversed.

\textbf{Chapter-3: 1H-PYRAZOLO[1,2-b]PHTHALAZINE-5,10-DIONE DERIVATIVES}

The development of new synthetic methods for the efficient preparation of heterocycles containing phthalazine ring fragment is an interesting challenge because they show some pharmacological and biological activities. Similarly, pyrazoles are important compounds that have many derivatives with a wide range of interesting properties. The diverse biological activities of quinoline, phthalazine and pyrazoles pharmacophores encouraged us to envisage the combination of three moieties in a compact system. The present chapter deals with an efficient synthesis and investigation of antimicrobial activity of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives.

The antimicrobial data revealed that majority of the compounds were found to be active against \textit{Clostridium tetani} and \textit{Bacillus subtilis}. In antifungal activity, majority of the compounds have shown excellent activity against \textit{Candida albicans} as
compared to griseofulvin. Out of all the synthesized compounds, 5b and 5n showed chief activity against *Escherichia coli* while compound 5l towards *Vibrio cholerae* and 5g towards *Bacillus subtilis* exhibited excellent activity.

![Chemical structures](image)

**Chapter-4: BIQUINOLINE PYRIDINE HYBRIDS**

The pyridine substructure is one of the most prevalent heterocycles found in natural products, pharmaceuticals, and functional materials. Biquinoline derivatives are often encountered in molecules of biologically active compounds. On the basis of all of these observations, we have designed some new biologically important agents containing both of these pharmacophores. This study reports the synthesis, characterization, and *in vitro* antimicrobial & antitycobacterial activities of these new biquinoline pyridine hybrids.

![Chemical structure](image)
The obtained antimicrobial data revealed that irrespective of substitution of $R_1$ compounds with $R_2 = \text{COOMe}$ (Compounds 4i-l) were found to be highly active against gram positive bacteria *Clostridium tetani* and *Bacillus subtilis*. Compound 4b and 4i showed chief activity against gram negative strain *Escherichia coli*, where as 4g exhibited good activity towards *Salmonella typhi*. Analogs 4d, 4e and 4i were found highly potent against *Candida albicans*. Compound 4g (MIC = 12.5 µg/mL) is found to be more potent than standard drug rifampicin with 96% inhibition in primary screen against *Mycobacterium tuberculosis* H37Rv.

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**Chapter-5: 4H-BENZO[g]CHROMENE DERIVATIVES**

Benzo[g]chromenes show a variety of biological activities, including anticancer, anti-inflammatory, antimalarial, and pesticides activities. This moiety also occurs in different natural products. Looking to the biological importance of these compounds, it is worthy of modifying this significant scaffold further. So the 2-aryloxyquinolines substituents were introduced at position 4, thus the ultimate structure 6a-r were obtained.
Reviewing the antibacterial activity of 4H-benzo[g]chromene derivatives 6a-r, assay indicated that compounds 6b and 6g exhibited potent activity against all the micro-organism tested. Substitution of methyl group on either 6-position of the quinoline ring or 4-position of phenoxy phenyl ring plays an important role in producing antimicrobial activity of whole molecule. Analogs 6d, 6f, 6h, 6j, 6m and 6o showed good % inhibition against Mycobacterium tuberculosis H37Rv. Of the entire 4H-benzo[g]chromenes derivatives, 6m was found more potent than standard drug rifampicin.

**Chapter-6: 4H-PYRANO[3,2-c]PYRIDINE DERIVATIVES**

4H-Pyran pharmacophore is an important kernel structure of many natural products. It plays an important role in the field of medicinal chemistry due to the various potential biological and pharmacological activities of its derivatives. A new series of 3,5-bis(2-chloro-6-substitutedquinoline-3-yl)-4-piperidones and and a series of 4H-pyran[3,2-c]pyridines, were designed to explore the scope and limitations of their antimicrobial and antituberculosis activities.
Examination of antimicrobial & antmycobacterial data reveal that compound 4k was found to be highly potent antibacterial and antmycobacterial agent. An examination of the antibacterial activity of pyrano[3,2-c]pyridine derivatives 6a-x, assay indicated that 6r was able to inhibit all the species tested including M. tuberculosis. Majority of 3,5-bis(2-chloro-6-substitutedquinoline-3-yl)-4-piperidones exhibited increase in antmycobacterial profile after cyclization with malononitrile/ethyl cyanoacetate. Analogs 6g, 6i, 6n, 6r, 6u, 6v and 6w were found more potent than standard drug rifampicin against M. tuberculosis. It has been observed that compounds having benzyl substituent on the 4-piperidone ring (R₂ = CH₂Ph) and either CN or COOEt on the pyran ring (R₃ = CN/COOEt) and R₁ be H/CH₃/OCH₃ are found to have good antmycobacterial profile.
Summary

MIC 6.25 against *M. tuberculosis*

MIC 12.5 against *M. tuberculosis*
MIC 25 aganist *M. tuberculosis*