Chapter - I
Introduction
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The quinoline was discovered in coal tar distillate by Runge in 1834 and named "Leukol". The base was also obtained by Gerhardt in 1842 by alkaline distillation of quinine, cinchonine, strychnine and was named by him "Chinolein" or "Chinolin". Not until 1882 was the identity of leukol and Chinolin firmly established, when Hoogewerff and Van Drop showed that the samples from coal tar and from alkaloid distillation had the same boiling point, formed the same hydrate (3H₂O), platinichloride, bichromate, and argentonitrate. Both specimens were also converted by oxidation into quinolinic acid, which was decarboxylated to nicotinic acid. Körner was cited as the first to propose the structural formula for quinoline (in Die Chemie von Pyridins and Seiner Derivate by A. Calm) but Dewar in 1871 suggested that quinoline bore the same relationship to pyridine that naphthalene bore to benzene. The structure (1) was confirmed by the synthesis in which allylaniline was passed over glowing lead oxide, or from o-nitrocinnamaldehyde as shown in reaction.

Quinoline and their derivatives occur in numerous natural products. Many quinolines display interesting physiological activities and have found attractive applications as pharmaceuticals and agrochemicals as well as being general synthetic building blocks. Many synthetic methods have been developed for the preparation of quinolines. But, due to their great importance, the development of novel synthetic methods remains an active research area.
The synthesis of quinoline and their derivatives has been of considerable interest to organic and medicinal chemists for many years as large number of natural products and drugs contain this heterocyclic nucleus. The synthesis of the quinoline ring has been the subject of continued interest as several derivatives of this heterocyclic unit have been found to possess useful biological activities such as bacterial, antimalarial, antiinflammatory etc. Quinoline derivatives are very important in medicinal chemistry, because of their wide occurrence in natural products and drugs. It is well known that replacement of hydrogen with fluorine frequently confers bioactivity to organic molecules.

Literature survey shows that, there is an evidence that, antitumour activity is due to intercalation between the base pairs of DNA and interferences with normal functioning of enzyme topoisomerase-II, which is involved in the breaking, and releasing of DNA strands. The antitumour drugs that intercalate DNA are of growing interest in the field of anticancer derivatives. Generally, they are characterized by planar chromophore, often constituted by three or four condensed rings, which can intercalate into base pairs. The results of these various binding studies have been useful in designing new and promising anticancer agent for clinical use. The DNA binding studies of pyrimidothienoquinolines have been recently reported in literature. It has been proved that highly substituted thiophenes have attracted a great deal of interest, due to their presence in natural products as novel conducting polymers, isosteric replacement of phenyl groups in medicinal chemistry and as a optical chromophores.
Quinoline derivatives form an important class of N-heterocycles in that they display alternative application as pharmacological (e.g. antimalarial drugs) as well as being general synthetic building blocks due to their chemical and biological relevance\textsuperscript{26,27}. Among the natural products containing quinoline system, the most important ones are the antimalarial alkaloids cinchonine (5) and quinine (6) are present in the cinchona bark. Among the synthetic compounds of therapeutic properties, the most important ones are antimalarial drugs plasmoquine (7), pentaquine (8) and chloroquine (9).
**Tricyclic Condensed Quinolines**

Quinoline ring fused with five or six membered heterocyclic ring containing one or two heteroatoms in linear fashion is also found in natural products as well as in the synthetic compounds of biological interest. Quinoline condensed with furan in a linear fashion is present in the alkaloids isolated from Rutaceae. Dictamine (10), Skimmianine (11) and v-Fagarine (12) are the most important among them. Though plants containing furoquinoline alkaloids have been used medicinally, the alkaloids themselves have found no significant place in medicine. However, dictamine (10) is found to strongly contract the smooth muscle and to stop the isolated frog heart in diastole. Skimmianine (11) is known to relax intestinal muscle.

Interest in nitrogen analogue of the nucleus of dictamnine, i.e.; pyrrolo[2,3-b]quinoline (13) system, started during the investigations of constituents of harmala alkaloids. In connection with the constitution of harmine and harmaline, Perkin and Robinson attempted the synthesis of 1H-pyrrolo[2,3-b]quinoline (13), naming it as norisoharman and its methyl derivative (14) as isoharman. Tanaka et al. reported the synthesis of all aromatic 1H-pyrrolo[2,3-b]quinoline system both by dehydrohalogenation and by oxidation of reduced 1H-pyrrolo[2,3-b]quinolines, while Shanmugam et al. have reported stating from 2-chloro-3-vinylquinolines or 2-chloro-3(2-chloroethyl)quinolines. A number of reduced pyrrolo[2,3-b]quinolines are known to exhibit anti-inflammatory, analgesic, anticonvulsant, antibacterial, antipyretic, antihypertensive and interferon inducing activity.
Synthesis of thienoquinolines (15) and tetrahydrothienoquinoline (16) has also been reported in the literature and are found to display antibacterial and antimicrobial activity \(^{36-37}\).

Japanese workers \(^{38}\) have reported that thienoquinolone (17) exhibit antitumour activity in mice inoculated with P388 cells in addition to antibacterial activity. Quinolines condensed with pyrazole and imidazole systems are also known in the literature. Alfred Brack \(^{39}\) reported the synthesis of pyrazoloquinolines (18) starting from azomethines of 5-chloropyrazole-4-carboxaldehydes. In 1973 Siminoff et al. \(^{40}\) reported the interferon inducing activity of a different structural type, viz., pyrazolo[3,4-b]quinoline (19) [BL-20803]. Encouraged by this, Censhaw et al. \(^{41}\) in a later paper reported the synthesis and interferon inducing activity of 1,3-dimethyl-4-[3-dimethylaminopropylamine]-4(1H)-pyrazolo[3,4-b] quinoline (20).
In general, all the compounds tested are found to be active and some members of the series are among the most potent low molecular weight interferon inducers. Pyrazoloquinolines are also reported to exhibit hypocholesterolemic, hypolemic\(^1\), antifungal\(^2\), antibacterial\(^3\) and antiviral activity\(^4\).

With a view to exploring imidazo[4,5-b]quinolin-2-one system (21), Meanwell and collaborators\(^5\) have synthesized a series of 1,3-dihydro-(2H)-imidazo[4,5-b] quinolin-2-one derivatives and evaluated as inhibitors of human blood platelet cAMP phosphodiesterase (PDE), as well as ADP and collagen induced platelet aggregation, \textit{in vitro}. The parent heterocycle (22) displayed potent activity that was enhanced by the introduction of substituents like alkyl, alkoxy or halogen, at -6, -7, -8 positions, while methylation at N\(_1\) and N\(_3\) was unfavourable. Particularly interesting was, substitution at position -7 by groups like piperazinamide (22) and alkoxy alkanoic piperazinamide derivative (23). Structural modification in these compounds by variation of the side chain terminus, side chain length, and side chain connecting atoms resulted in the identification of compound (24) by Bristol-Myers laboratory under the name BMY 43351, as a new drug for inhibitors of blood platelet cAMP phosphodiesterase\(^5\).
The pyrimido[4,5-6]quinoline ring system is of interest, because of its structural similarity to the pyrimido[4,5-6]quinoxaline system of naturally occurring flavins. Synthesis of several pyrimido[4,5-6]quinolines (25, 26) have been reported in the literature, with a view to develop new chemotherapeutic agents.\(^{52-54}\). Recently, Althuis \textit{et al.},\(^ {55}\) have synthesized and tested a number of pyrimido[4,5-6]quinolines for their antiallergic property. Among the compounds tested, (27) were found to possess high oral activity. Pyrimido[5,4-b]quinolines (28), which are regarded as 10-deazaflavins have been synthesized and are found to be inhibitors of riboflavin synthesis.\(^ {56-58}\)
U.S. Patent^29 describes the preparation of polyfluorinated mono and dioxo tricyclic quinoline (29). These compounds are reported to display antifungal activity against *Trichophyton rubrum* and *Epidermophyton floccosum* at 1.6 and 0.39 mg / mL. Tilakraj and Ambekar^60-61 have reported the synthesis of 2H-pyran[2,3-b]quinolin-2-one (30), which may be considered as benzazacoumarin. Biological testing of these compounds reveal that relatively these compounds are more promising as antifungal than as antibacterial agents.

![Chemical structures of compounds 29 and 30](image)

**Tetracyclic Condensed Quinolines**

Quinoline condensed with indole ring system in linear fashion, i.e.; indolo[3,2-b] quinoline system, is present in the alkaloids cryptolepine (31) and norcryptolepine (32) isolated from the West African medicinal plant *Cryptolepis sanguinolenta* Sch^62-65_. Cryptolepine (31) is known to produce lowering of the body temperature and has marked vasodialator property.

![Chemical structures of compounds 31 and 32](image)

Mastoshi *et al.*,^66-68_ have reported the synthesis and antitumour activity of several anilinoindolo[3,2-b]quinolines (33-36) and found majority of them to possess potent antileukemic property. Particularly compounds (34) and (35) showed remarkable activity
against P388 in mice. Optimal dose = 25 mg / kg, the median survival time of treated group / control group is greater than 333 %.

German Patent\(^6^9\) describes the synthesis of the indolo[2,3-b]quinolines of the type (37) and their usefulness as CNS active pharmaceuticals and antibiotics. Very recently Kaczmarek and collaborators\(^7^0\)-\(^7^2\) have reported the synthesis of number of indolo[2,3-b]quinoline (38) and tested them for their bacteriostatic, cytostatic, antifungal and anticancer activities.

The compounds of the type (39) showed significant antitumour activity against P388 and L1210 leukemias, melanoma B16 in mice. It improved the survival rate by 150 % of control at 20 mg / kg administered in mice implanted with leukemia cells. Goerlitzer \textit{et al.},\(^7^3\) have synthesized indoloquinolines, benzofuranquinolines and benzothienoquinolines with N,N-dimethylaminopropylmercapto substituent (40) and tested them for their blood platelet aggregation inhibiting activity in platelet enriched human plasma \textit{in vitro}. Among the compounds tested, (40) (X = NCH\(_3\)) was found to be the most active one. Its inhibitory action was comparable to that of aspirin in collagen induced platelet aggregation\(^7^4\).
Tilakraj and Ambekar\textsuperscript{75-76} have reported the synthesis of a new tetracyclic heterocyclic system, pyrimido[4',5':4,5]thieno[2,3-b]quinolin-4(3H)-ones and 4-aminopyrimido[4',5':4,5]thieno[2,3-b]quinolines. They tested them for their blood platelet disaggregation activity in human blood platelet aggregation induced by ADP and collagen. Among the compounds tested, compounds (41,42) showed equipotent inhibition at the dose level 7.2 \textmu m. Mastoshi \textit{et al.}\textsuperscript{77} have reported the synthesis of several fused tetracyclic condensed quinolines and their DNA intercalative properties, KB cytotoxicity, antitumour activity (P388 leukemia) and ability to induce \textit{topoisomerase-II} dependent DNA cleavage. The benzofuro (43) and benzothieno (44) quinoline derivatives exhibited potent antitumour activities \textit{in vitro} and \textit{in vivo}, comparable to those of m-AMSA. They also intercalate DNA induced \textit{topoisomerase-II} dependent DNA cleavage.
Pentacyclic Condensed Quinolines

Camptothecin (45) an alkaloid with a condensed quinoline ring system, exhibiting potent antileukemic and antitumour activity in animals, has been isolated from the stem wood of Chinese tree *Camptotheca acuminata Decne Nyssacea*. Against leukemia L1210 in mice, camptothecin gives life prolongation as high as 100 % on a daily dose of 0.25-1.0 mg / kg against Walker 256 (intramuscular) tumour (rats); concentration as low as 1.25 mg / kg gives significant inhibition of growth. It also shows moderate toxicity against KB cell culture \( ED_{50}=0.07 \) mg / mL.

In 1991, Sawada and coworkers were prepared a series of A-ring modified 7,10-disubstituted camptothecins. The cytotoxicity of A-ring modified camptothecin was evaluated against KB cells *in vitro* and leukemia L1210 in mice. Significant cytotoxicity was observed in the derivatives having electron withdrawing chloro and bromo substituents at the 9 position and electron donating hydroxyl and amino group at the 10 position. All the 7,10-disubstituted camptothecins tested exhibited antitumour activity with higher activity being observed in suspension administration. Among these, 7-ethyl-
10-hydroxycamptothecin (46) was identified as a potential derivative for further modification.

In the recent years, lots of efforts are in track in order to synthesize and evaluate the biological application of quinoline derivatives. Alka Mital\textsuperscript{81} and coworker studied the antimycobacterial activities of certain trifluoromethyl-aminoquinoline (47) derivatives. Gopal\textsuperscript{82} and others were studied the biological properties of 8-methoxypyrimido [41,51:4,5]thieno(2,3-b)quinolin-4(3H)-one (48), as a new class of DNA intercalating drugs. Mehdi Adib and Mohammad Sayahi were reported an efficient synthesis of 4H-pyrrolo[3,2,1-ij]quinoline (48). Novel synthesis of 3-pyrrolylquinolines (49) were reported by Menasra\textsuperscript{83}. Very recent report of the synthesis and crystal structure of (S)-2-(2-chloroquinolin-3-yl)-2-[(S)-\(\alpha\)-methylbenzylamino]acetonitrile (50) is from Ali Belfaiah\textsuperscript{84} and his group.
Meth-Cohn et al.,\textsuperscript{85-87} have reported an elegant method of synthesizing 3-formyl-2-chloro-quinolines (52) in one step, starting from acetanilides (51).

![Diagram of reaction]

From our laboratory, we have reported an efficient and inexpensive method\textsuperscript{82} for the convention of 3-formyl-2-chloroquinolines (52) into 3-formyl-2-mercaptoquinolines (53). We have proved that this procedure provides a better and more practical alternative to the existing methodologies for the synthesis of 3-formyl-2-mercaptoquinoline derivatives. 3-Formyl-2-chloroquinolines and 3-formyl-2-mercaptoquinolines (52,53) carries two functional groups in adjacent carbon atoms. If these two substituents are properly functionalised, then they could serve as an excellent starting material for the synthesis of linearly fused condensed quinolines.

![Diagram of reaction]

The present work is aimed at exploring the synthetic utility of 2-chloro-3-cyanoquinolines, 3-formyl-2-mercaptoquinolines, 2-hydroxy-3-cyanoquinolines and 2-amino-3-cyanoquinolines for the synthesis of hitherto unknown condensed quinolines.
and investigation of biological activity of the some compounds. The work carried out in the present investigation is conveniently divided into seven chapters and are as follows...

Chapter II: *A simple and convenient synthesis of novel functionalised quinolines*

Chapter III: *Synthesis & reactions of furo[2,3-b]quinolines: An approach towards tetracyclic heterocyclic ring system*

Chapter IV: *Synthesis of benzo[b]-1-8-naphthyridines & pyrimido[4,5-b]quinolines*

Chapter V: *Chemistry of substituted quinolines: Thieno[2,3-b] & Thiopyrano [2,3-b]quinolines*

Chapter VI: *Synthesis of new seleno substituted quinolines*

Chapter VII: *Biological evaluation*
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