FUSED QUINOLINES. RECENT SYNTHETIC APPROACHES TO AZOLOQUINOLINES. A REVIEW

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Abstract – Azoloquinoline derivatives such as pyrrolo-, furo-, thienoquinolines and their benzo or heterocyclic annelated derivatives have attracted interest for their important biological applications. This review highlights the recent synthetic approaches to various azoloquinolines.

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Introduction
The polynuclear heterocycles derived from quinolines showed wide spectrum of biological applications. The importance of these cyclic compounds arose from their natural origin of most of six-membered and five membered derivatives and their very important pharmaceutical applications. The literature survey indicated that an attention had been drawn to pyrano-, pyrido- and pyridazinoquinolines. Whereas the ring systems such as pyrrolo-, indolo- and furoquinolines were found in enormous plants and animals so that an increasing synthetic work has been recently directed to these targets. Similarly thienoquinolines attracted the interest of much research work in the last decade especially with discovery of their high activity in the medicinal application field. We have noticed that the literature lakes for a recent overview regarding monoazoloquinolines. The most recent revision on this subject was appeared by Milata in 2001
who reviewed only azoloquinolines have an azole ring fused to benzene ring of quinoline in which some diazoloquinolines and triazoloquinolines were described.\textsuperscript{1} This review did not cover monoazoloquinolines anyway. Majumdar and Das gave a brief review of the regioselective synthesis of some thieno- and furoquinolines in which they partially viewed certain method for the regioselective synthesis of quinolones with 3,4-fused furan ring systems by Claisen rearrangement.\textsuperscript{2}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Parent_Azoloquinolines.png}
\caption{Parent Azoloquinolines}
\end{figure}
Herein we will review the different syntheses of the trio monoazoloquinolines (Figure 1). We will focus on the last fifteen years to cover most recent advances regarding quinoline route of synthesis of monoazoloquinolines beside the other routes of building up quinoline moiety on a preliminarily prepared suitably substituted monoazole. Also the revision will exemplify for the reported biological activities attached with some azoloquinolines.

1. Synthesis of Pyrroloquinolines and Indoloquinolines

1.1. Pyrrolo[1,2-a]quinolines

Cycloaddition reaction of ethyl 6,7-difluoro-1,4-dihydro-1-ethoxycarbonylmethyl-4-oxoquinoline-3-carboxylates (1) with methyl methacrylates resulted in the [3+2]adducts diethyl 7,8-difluoro-1,2,3,3a,4,5-hexahydro-3-methoxycarbonyl-3-methyl-5-oxopyrrolo[1,2-a]quinoline-1,4-dicarboxylates (2) (R¹, R² = H; R¹ = H, R² = F; R¹ = R² = F) (Scheme 1).

Haldar et al. described a simple and high yielding general methodology for the synthesis of 3,3a-dihydro-2H,5H-pyrrolo[1,2-a]quinoline-1,4-dione derivatives (4) through a highly regioselective rhodium(II)-catalyzed carbenoid sp² C–H insertion reaction on suitably substituted γ-lactam diazoacetyl compounds (3) (Scheme 2).

2-(Pyrrolidin-1-yl)benzaldehyde (5) was reacted with cyclic active methylene compounds such as cyclohexane-1,3-dione and/or 2,2-dimethyl-1,3-dioxane-4,6-dione (6) under Knoevenagel condensation conditions to give spiro-coupled hexahydropyrrolo[1,2-a]quinolines (8) (R = H, X = CH₂; R = Me, X = O)
The intramolecular Heck cyclization of N-(2-iodophenyl)-5-allyl-2-pyrrolidinone (9) using palladium acetate catalyst afforded an inseparable 2:1 mixture of regioisomers pyrrolo[1,2-α]quinolin-1-ones (10a,b) in 74% yield. This mixture was hydrogenated to give the 2,3,3a,4,5-tetrahydro-1H-pyrrolo[1,2-α]quinolin-1-ones (11) (R1 = H, R2 = Me; R1 = Me, R2 = H) (Scheme 4).6

The synthesis of 3a-methyl-1,2,3,3a-tetrahydropyrrolo[1,2-α]quinoline (16) involved an acetylide addition to 5-chloro-2-pentanone (12) with ethynylmagnesium bromide. The produced alcohol (13) was then esterified to the corresponding acetate (14) with acetic anhydride and 4-dimethylaminopyridine in pyridine. A tandem propargylation/alkylation of aniline with this acetate derivative in the presence of copper(I) chloride and triethylamine afforded (R,S)-2-ethynyl-2-methyl-1-phenylpyrrolidine (15). Cyclization of this pyrrolidine derivative occurred in the presence of copper(I) chloride, to afford the (R,S)-3a-methylpyrrolidino[1,2-α]quinoline (16) (Scheme 5).7
An interesting ring rearrangement of the spiro[2-benzofuran-1,2'-quinoline]-3,5'-dione derivative (17) took place on treatment with p-toluenesulfonic acid in boiling xylene. This transformation led to the formation of 2,2-dimethyl-1,2,3,4,5,11-hexahydroisoindolo[2,1-a]quinoline-4,11-dione (18) (Scheme 6).8

On deprotonation of 2-phthalimidoacetophenone (19) using lithium bistrimethylsilylamide (LBTSA), 6,7a-dihydroxy-12H-isindolo[1,2-a]quinolin-12-one (20) was afforded in excellent yield. Thermal dehydration of compound (20), in absence of solvent, quantitatively yielded 6-hydroxy-6H,12H-isindolo[1,2-a]quinolin-12-one (21) (Scheme 7).9
1.2. Pyrrolo[2,3-b]quinolines

Palladium-catalyzed heteroannulation of 2-amino-3-iodoquinoline derivatives (22) with 1-trimethylsilyl-propynes provided 1H-pyrrolo[2,3-b]quinolines (23) (R\(^1\)= Me, Ph, PhCH\(_2\); R\(^2\)= Me, n-Bu, CH\(_2\)OH, (CH\(_2\))\(_2\)OH, Ph, 3-thienyl) (Scheme 8).\(^{10}\)

\[
\begin{array}{cccc}
\text{R}^1 & \text{R}^2 & \text{Yield (%)} \\
\text{PhCH}_2 & \text{Me} & 65 \\
\text{Ph} & \text{Me} & 67 \\
\text{Me} & \text{n-Bu} & 72 \\
\text{Me} & \text{CH}_2\text{OH} & 63 \\
\text{Me} & (\text{CH}_2)_2\text{OH} & 60 \\
\text{PhCH}_2 & \text{Ph} & 65 \\
\text{PhCH}_2 & \text{3-thienyl} & 57 \\
\end{array}
\]

Scheme 8

6-Methyl-6\(H\)-indolo[2,3-b]quinoline (cryptotackienine) (25) was smoothly obtained via an intramolecular aza-Wittig cyclocondensation of 1-methyl-3-(2-azidophenyl)quinolin-2(1\(H\))-one (24) using trimethylphosphine, in nitrobenzene (Scheme 9).\(^{11}\)

\[
\begin{array}{cccc}
\text{Me}_3\text{P} & \text{PhNO}_2 & \text{40\%} \\
\end{array}
\]

Scheme 9

1.3. Pyrrolo[3,4-b]quinolines

The illumination of 2-N,N-diethylcarbamoylquinolines (26), induced alkyl insertion to the (CO–NH) bond and five-membered cyclization, afforded 2-(2-ethylaminopropanoyl)quinolines (27) with small amounts of 1\(H\)-pyrrolo[3,4-b]quinolin-3(2\(H\))-ones (28). This rearrangement took place by photochemical induced hydrogen atom abstraction (Scheme 10).\(^{12}\)
The cyclocondensation reaction of ethyl 2-chloromethyl-4-phenylquinoline-3-carboxylate (29) with phenylhydrazine furnished a mixture of 2-anilino-2,3-dihydro-1H-phenylpyrrolo[3,4-b]quinolin-1-one (30) and ethyl 4-phenyl-2-[(Z)-(phenylhydrazono)methyl]quinoline-3-carboxylate (31) (Scheme 11).13

Methyl 1-methyl-4-methylslufanyl-2,5-dioxo-3-pyrrole-3-carboxylate (32) was subjected to react with substituted anisidine to give methyl 1-methyl-2,5-dioxo-4-(4-methoxyphenylamino)-3-pyrrole-3-carboxylate (33), which was thermally converted to 9-hydroxy-7-methoxy-2-methylpyrrolo[3,4-b]-quinoline-1,3(2H)-dione (34), in 94 % yields (Scheme 12).14

Treating a solution of N,2-diacetyl-6-methoxy-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (35) in DMF with sodium hydride under an oxygen atmosphere led to 2-acetyl-7-methoxy-3-methyl-9-oxo-
1,3,4,9-tetrahydropyrrolo[3,4-b]quinoline (36), a medicament has hypnotic and sedative effects (Scheme 13).\(^{15}\)

Aminolysis of 9-phenylfuro[3,4-b]quinolin-3(1H)-one (37) with benzylamine gave N-benzyl-3-hydroxymethyl-4-phenylquinoline-2-carboxamide (38). The compound (38) was chlorinated using thionyl chloride to give N-benzyl-3-chloromethyl-4-phenylquinoline-2-carboxamide (39) in good yield. Ring-closure of the latter quinolines derivative (39) was effected by action of sodium hydride under inert atmosphere to give the linear tricyclic 2-benzyl-2,3-dihydro-9-phenyl-1H-pyrrolo[3,4-b]quinolin-3-one (40) (Scheme 14).\(^{16}\)

Recently van Es et al. reported that nucleophilic reaction of 3,3,9-trichloro-3H-thieno[3,4-b]-quinolin-1-one (41) with propylamine resulted in a mixture of 2-propyl-9-propylamino-3-propylimino-2,3-dihydrothieno[3,4-b]quinolin-1-one (42) and 2-propyl-3-propylimino-9-thioxo-2,3,4,9-tetrahydrothieno[3,4-b]quinolin-1-one (43) (Scheme 15).\(^{17,18}\)
A linear pentacyclic hetero compound was prepared via a two-steps reaction between 2-bromo-3-bromomethylquinoline (44) and quinazolin-4(3\(H\))-one (45) using potassium tert-butoxide. The reaction involved base catalyzed substitution at the 3-bromomethyl group to give 3-(quinolin-3-ylmethyl)-4-quinazolinone (46) in excellent yield. This biheterocyclic methyl derivative was cyclized via a palladium catalyzed biaryl coupling reaction to give 11,13-dihydroquin[2',3':3,4]-pyrrolo[2,1-b]quinazolin-11-one (47) in 86 % yield (Scheme 16). \(^{19}\)

\[
\text{Condensation of 3-aminomethyl-2-bromoquinoline (48) with 4-ethyl-2-methylhepta-2,4-dienoic acid (49) yielded in the corresponding amide (50), which was then transformed to the acrylate derivative (50) via the palladium catalyzed intramolecular cycloaddition of the acrylate (51) resulted in the interesting tetracyclic indolizino[1,2-b]quinolinone (52) (Scheme 17).}^{20}\]

\[
\text{Scheme 16}
\]

\[
\text{Scheme 17}
\]
Also 3-aminomethyl-2-bromoquinoline (48) was used to synthesize the pentacyclic pyrano[3',4':6,7]-indolizino[1,2-b]quinolinone (58). Thus condensation with the pyran-3-carboxylic acid (53) afforded the corresponding amide (54), which underwent catalyzed coupling with 3,3,3-triethoxy-1-propyne providing the respective propyne orthoester (55). The latter compound was converted to the corresponding carboxylate ester (56), which underwent an intramolecular base catalyzed cycloaddition reaction giving the pyrrolo[3,4-b]quinoline (57). Photochemical iodine induced intramolecular cyclization of 57 followed by debenzylation resulted in the linear pentacyclic compound (58) (Scheme 18).21

![Scheme 18](image)

An improved preparation of indolizino[1,2-b]quinoline hydrochlorides (61), in 57-91% yields, using microwave-assisted synthesis was reported. The process involved Friedlander reaction of o-amino-benzaldehydes and/or imines (59) with tetrahydroindolizinediones (60) in the presence of acetic acid (Scheme 19).22
1.4. *Pyrrolo[3,2-b]quinolines*

The linear tricyclic 1-alkyl-3-(cyano/ethoxycarbonyl)-4*H*-pyrrolo[3,2-b]quinolin-2(1*H*-ones (63) (R¹= PhCH₂, n-Pr; R²= CN, CO₂Et) were obtained by intramolecular condensation 3-[N-alkyl-(cyano or ethoxycarbonyl)acetamido]quinoline-1-oxides (62) via treatment with acetic anhydride in chloroform (Scheme 20).²³

![Scheme 19](image)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>PE</td>
<td>CN</td>
<td>71</td>
</tr>
<tr>
<td>PE</td>
<td>H</td>
<td>CN</td>
<td>57</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>CN</td>
<td>59</td>
</tr>
<tr>
<td>H</td>
<td>PE</td>
<td>CONH₂</td>
<td>61</td>
</tr>
<tr>
<td>PE</td>
<td>H</td>
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<td>72</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>CONH₂</td>
<td>86</td>
</tr>
<tr>
<td>H</td>
<td>PE</td>
<td>AcNHCH₂</td>
<td>74</td>
</tr>
<tr>
<td>PE</td>
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<td>AcNHCH₂</td>
<td>60</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>AcNHCH₂</td>
<td>91</td>
</tr>
</tbody>
</table>

PE= 2-piperidinoethoxy

![Scheme 20](image)

The synthesis of 10*H*-indolo[3,2-b]quinoline (quindoline) (66) was accomplished by initial phenylation of 3-aminoquinoline (64), using triphenylbismuth diacetate in the presence of metallic copper. The product, 3-phenylaminoquinoline (65) was then cyclized via intramolecular aromatic coupling catalyzed by palladium(II) acetate (Scheme 21).²⁴

![Scheme 21](image)

1.5. *Pyrrolo[2,3-c]quinolines*
The synthesis of ethyl 4-aryl-3H-pyrrolo[2,3-c]quinoline-2-carboxylates (68) (R = Ph, 4-MeOC₆H₄, 4-ClC₆H₄, 4-pyridyl) was accomplished by Knoevenagel condensation of ethyl azidoacetate with 4-formylquinolines (67) in the presence of sodium ethoxide, followed by loss of N₂ (Scheme 22).²⁵

![Scheme 22](image)

1.6. Pyrrolo[3,4-c]quinolines

Bromination of ethyl 3-methylquinoline-4-carboxylates (69) was achieved via its reaction with N-bromosuccinimide (NBS) in the presence of benzoyl peroxide. Ethyl 3-bromomethylquinoline-4-carboxylates (70) were obtained and consequently subjected to cyclization reaction with 8-methyl-8-azabicyclo[3.2.1]octane (71) affording endo-2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-1-ones (72) (R = H, Cl, OPr). These compounds had been found to be potent and selective antagonists of the 5-HT3 serotonin-like receptor and can therefore be used in various pathological conditions of the central nervous system, and as antitussives (Scheme 23).²⁶

![Scheme 23](image)

A new synthetic route for obtaining 2H-pyrrolo[3,4-c]quinolin-4-ones (74) (R¹ = H, Me; R² = H, Me, Ph;
R³= H, Me; R⁴= H, Cl) had been developed via reductive cyclization of ethyl 4-(2-nitrophenyl)pyrrole-3-carboxylates (73) using iron powder and glacial acetic acid (Scheme 24).²⁷

![Scheme 24](image)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Reaction Time (h)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>0.75</td>
<td>74</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>2</td>
<td>60</td>
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<td>Cl</td>
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</tr>
<tr>
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<td>Ph</td>
<td>H</td>
<td>H</td>
<td>4</td>
<td>69</td>
</tr>
</tbody>
</table>

Ethyl cinnamates (75) as dipolarophiles were treated with paraformaldehyde and an excess of N-methyl- or N-benzylglycine to give the corresponding pyrrolidine cycloadducts (76). Hydrogenation of these cycloadducts in the presence of Pd-C yielded the respective anilines (77), which were subsequently cyclized in the presence of p-toluenesulfonic acid to give 1,2,3,3a,5,9b-hexahydro-4H-pyrrolo[3,4-c]-quinolin-4-ones (78) (R¹= H, Me, PhCH₂; R²= H, MeO; R³, R⁴= H, MeO, OCH₂O) (Scheme 25).²⁸

![Scheme 25](image)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>85</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>O-CH₂-O</td>
<td>56</td>
<td>96</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>74</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>58</td>
</tr>
<tr>
<td>PhCH₂</td>
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<td>H</td>
<td>H</td>
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</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>76</td>
</tr>
</tbody>
</table>
1.7. **Pyrrolo[3,2-c]quinolines**

The preparation of methyl 3-amino-4-chloro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (81) was performed, in 85 % yield. Thus, nucleophilic replacement of the chlorine atom at 4-position of 2,4-dichloroquinoline-3-carbonitrile (79) with methyl glycinate hydrochloride led to the N-quinolinyl-glycinate (80). Annelation of the compound (80) by action of sodium methoxide furnished the candidate tricyclic compound (81). Similarly, intramolecular cyclocondensation of ethyl N-(3-ethoxycarbonylquinolin-4-yl)glycinate (82), using potassium tert-butoxide led to ethyl 3-hydroxy-1H-pyrrolo[3,2-c]-quinoline-3-carboxylate (83) (Scheme 26).

![Scheme 26](image)

The hydrazones (85) were obtained from 4-hydrazinoquinolin-2(1H)-one (84) and phenylacetaldehyde or deoxybenzoinin acetic acid. Thermal cyclization of these hydrazones smoothly gave the corresponding 1H-pyrrolo[3,2-c]quinolin-4(5H)-ones (86) (R= H, Ph) (Scheme 27).

![Scheme 27](image)
6-Methoxy-3-methyl-1-(2-methylphenyl)-1\textit{H}-pyrrolo[3,2-\textit{c}]quinoline (88), a useful gastric acid secretion inhibitor especially against ethanol induced gastric ulcer, was prepared via palladium catalyzed cyclization of 4-allylamino-3-iodoquinoline (87) in 77 % yield (Scheme 28).\textsuperscript{32}

![Scheme 28]

The ethyl \{[(2-nitrophenyl)methylene]amino\}acetate (89) was reacted with ethyl acrylate as dipolarophile to give the \textit{syn-endo} pyrrolidine cycloadducts (90) stereoselectively. The reduction of these cycloadducts with sodium hydrosulfite or hydrogenation in the presence of 10\% Pd/C gave ethyl 4-oxo-2,3,3a,4,5,9b-hexahydro-1\textit{H}-pyrrolo[3,2-\textit{c}]quinoline-2-carboxylates (91) (R\textsuperscript{1}= H, MeO, Br; R\textsuperscript{2}= H, MeO; R\textsuperscript{1}-R\textsuperscript{2} = OCH\textsubscript{2}O) in 86-98 \% yields (Scheme 29).\textsuperscript{33}

![Scheme 29]

The preparation of 5-ethyl-2,3,3a,4,5,9b-hexahydro-1\textit{H}-pyrrolo[3,2-\textit{c}]quinolines (95) was realized in one step (90 \% yield) using a formal [4\pi+2\pi]cycloaddition involving the cationic azadiene (92) and the 1-benzylxycarbonyl-2-pyrroline (93) as dienophile and deprotection of the adduct (94) (Scheme 30).\textsuperscript{34}
Cyanation of 3-methylene-4-oxo-1,2,3,4-tetrahydroquinoline (96), using potassium cyanide, proceeded smoothly to provide the trans-3-cyanomethylquinolin-4-one (97) in good yield. Reductive cyclization of the compound (97) proceeded along with debenzylation to afford 2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-c]quinoline (98) (Scheme 31).\(^{35}\)

Reacting 6-substituted 2,3-dihydrofuro[3,2-c]quinolin-4(5H)-ones (99) with some aniline derivatives in diethylene glycol (DEG) under drastic conditions of elevated temperature and long heating time, resulted in the insertion of the nitrogen of these anilines into the position-1, replacing oxygen of furan ring to give 6-substituted 1-aryl-2,3-dihydropyrrolo[3,2-c]quinolin-4(5H)-ones (100), in 76-85 % yields (Scheme 32).\(^{36}\)
Intramolecular thermal cyclization of 1-methyl-3-(2-azidophenyl)quinolin-2(1H)-one (24) and subsequent reduction of the obtained 5-methyl-11H-indolo[2,3-c]quinolin-6(5H)-one (101), using sodium bis(methoxyethoxy)aluminum hydride (Red-Al), gave the known 5-methyl-5H-indolo[3,2-c]quinoline (isocryptolepine) (102).\(^{11}\) 3-Aryl-4-(chloro/tosyloxy)-7-methoxyquinolin-2(1H)-ones (103) underwent thermolytic ring closure upon reaction with sodium azide, in refluxing DMF, giving the corresponding 4-azidoquinolinone intermediates (104), which loses nitrogen to give 5-alkyl-3-methoxy-11H-indolo[3,2-c]quinolin-6(5H)-ones (105) (R\(^1\)= Me, Et; R\(^2\)= H, OMe) (Scheme 33).\(^{37}\)

\[\text{Scheme 32}\]

\[\text{Scheme 33}\]
A recent approach to the angular tetracyclic isocryptolepine (102) was achieved via first synthesis of 11H-indolo[3,2-ε]quinoline (108) in a two-step procedure. Thus selective Buchwald-Hartwig nucleophilic amination of 4-chloroquinoline (106), using 2-chloroaniline, gave 4-(2-chloroanilino)quinoline (107) which was then cyclized to give the indoloquinoline (108), in 95% yield. Methylation of the compound (108) by methyl iodide afforded the desired alkaloid (102) (Scheme 34).38

![Scheme 34]

11H-5-Methylin[3,2-ε]quinolin-6(5H)-one (101) was smoothly prepared in 62 % yield, via Fisher-Indole cyclization of 4-phenylhydrazinoquinolinone (110) in boiling glacial acetic acid. The compound (110) was preliminary obtained by nucleophilic substitution reaction via treating 4-chloro-1-methylquinolin- 2(1H)-one (109) with phenyl hydrazine in boiling DMF (Scheme 35).39

![Scheme 35]
The potential antitumoral 11-benzenesulfonyl-11H-indolo[3,2-c]quinolin-6(5H)-one (114) was synthesized by intramolecular Heck cyclization of the corresponding 1-benzenesulfonyl-3-(2-iodophenyl)aminocarbonyl-1H-indole (113). The indole-3-carboxylic acid (111) was used as starting material to obtain the amide (112), which was N-protected before cyclization process (Scheme 36).\(^{40}\)

1.8. Pyrrolo[2,3-f]quinolines

Treatment of 5-nitroquinoline (115) with 4-chlorophenoxyacetonitrile, in the presence of potassium tert-butoxide in tetrahydrofuran, gave 6-cyanomethyl-5-nitroquinoline (116). The compound (116) was used as precursor for obtaining 1H-pyrrolo[2,3-f]quinolines (117) by catalytic hydrogenation using 10% Pd/C in glacial acetic acid (Scheme 37).\(^{41}\)

1.9. Pyrrolo[3,2-f]quinolines

The formation of a number of 2-aryloxyethyl-3,6-dimethyl-1-methoxymethylpyrrolo[3,2-f]quinolinones (121) (Ar= Ph, 4-ClC\(_6\)H\(_4\), 4-MeC\(_6\)H\(_4\), 4-NO\(_2\)C\(_6\)H\(_4\), 2,4-Cl\(_2\)C\(_6\)H\(_3\), 2,4-Me\(_2\)C\(_6\)H\(_3\), 3,5-Me\(_2\)C\(_6\)H\(_3\)) was performed through butynylation of 1-methyl-6-methylaminoquinolin-2(1H)-one (118) with 1-aryloxy-4-chlorobut-2-ynes, in the presence of potassium carbonate and sodium iodide. Thence the treatment of the obtained 6-[4-aryloxybut-2-yn-1-ylamino]quinolinones (119) with
m-chloroperbenzoic acid. The obtained benzoates (120) were easily converted to the corresponding 1-methoxymethyl derivatives (121) by refluxing with methanol. The process is explicable by the initial formation of an N-oxide intermediate, which underwent a sigmatropic rearrangement giving an allenoxaymine intermediate that rearranged to a ketol and aromatized (Scheme 38).42

Scheme 38

2-Ethyl-1-methyl-9-trifluoromethyl-3H-pyrrolo[3,2-f]quinolin-7(6H)-one (123) was produced when 6-hydrazinoquinolinone (122) was heated with 3-pentanone in the presence of an acid catalyst (Scheme 39).43
The reaction of 6-nitroquinoline (124) with 4-chlorophenoxyacetonitrile in the presence of potassium tert-butoxide furnished 5-cyanomethyl-6-nitroquinoline (125), which was hydrogenated in the presence of 10% Pd-C to afford 3H-pyrrolo[3,2-f]quinoline (126) (Scheme 40).41

Ethyl 5-amino-7-methoxy-1H-indole-2-carboxylic acid (127) was treated with dimethyl trans-2-ketoglutaconate followed by dry hydrogen chloride gas at room temperature to give ethyl 7,9-dimethoxycarbonyl-4-methoxy-3H-pyrrolo[3,2-f]quinoline-2-carboxylate (128) (Scheme 41).44

7-Methylcyclopentano[4,5]pyrrolo[3,2-f]quinolin-10-one (132) was synthesized in 25% yield by irradiation of 6-[N-(1-oxo-cyclopent-2-en-3-yl)-N-methyl]aminoquinoline (131), which was prepared by condensation of 6-aminoquinoline (129) with cyclopentane-1,3-dione, in the presence of toluenesulfonic acid and methylation of the obtained 6-cyclopentenylaminoquinoline (130) (Scheme 42).45
5-Methoxy-7H-indolo[3,2-f]quinolines (137) \((R^1= \text{H, OMe, Br}, R^2= \text{H, OMe})\) were synthesized starting with 5-bromo-8-methoxyquinolines (133) by using cross-coupling reaction with (2-aminophenyl)boric acid, followed by deprotection, azidation and regioselective thermal cyclization of 5-(2-azidophenyl)-8-methoxyquinolines (136) in boiling 1,2-dichlorobenzene effected loss of molecular nitrogen with the formation of the compound (137) (Scheme 43).46
1.10. **Pyrrolo[3,2-g]quinolines**

The preparation of 1H-pyrrolo[3,2-g]quinolinediones (140) (R= Me, Et, n-Pr, iso-Pr, n-Bu, HOCH₂CH₂, MeOCH₂CH₂, cyclopropyl, cyclohexyl, PhCH₂, Ph) was achieved via an interesting two-step regioselective substitution. The reaction of the key start compound 6,7-dichloroquinoline-5,8-dione (138) with diethyl malonate, in the presence of sodium amide in boiling toluene, selectively afforded diethyl (7-chloro-5,8-dioxo-5,8-dihydroquinolin-6-yl)malonate (139). Treating the compound (139) with alkyl amines or unsubstituted aniline, in the presence of potassium carbonate or triethyl amine, furnished the corresponding pyrrolo[3,2-g]quinoline derivatives (140).⁴⁷ Also, the reaction of 6,7-dichloroquinoline-5,8-dione (138) with ethyl cyanoacetate furnished the corresponding quinolinylcyanoacetate derivative which in analogy to this synthesis of pyrrolo[3,2-g]quinoline (140) was cyclized by treating with the same alkyl amines to furnish its 2-amino isomer (Scheme 44).⁴⁸

![Scheme 44](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
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</thead>
<tbody>
<tr>
<td>Me</td>
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</tr>
<tr>
<td>Et</td>
<td>42</td>
</tr>
<tr>
<td>n-Pr</td>
<td>21</td>
</tr>
<tr>
<td>iso-Pr</td>
<td>11</td>
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<tr>
<td>n-Bu</td>
<td>27</td>
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<tr>
<td>HOCH₂CH₂</td>
<td>35</td>
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<tr>
<td>MeOCH₂CH₂</td>
<td>36</td>
</tr>
<tr>
<td>cyclopropyl</td>
<td>34</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>40</td>
</tr>
<tr>
<td>PhCH₂</td>
<td>32</td>
</tr>
<tr>
<td>Ph</td>
<td>32</td>
</tr>
</tbody>
</table>

In a study of hetero Diels–Alder reactions of (1E,2E)-but-2-enal dimethylhydrazone with 1H-indole-4,7-diones (141), it was reported that the regiochemistry of the reaction was governed by the nature of substituents R¹ on the nitrogen atom and R² on the carbon atom at position-2. The unsubstituted indoledione (141) afforded the 5-methyl-5,8-dihydro-1H-pyrrolo[3,2-g]quinoline-4,9-dione (142) as the major product while indolediones, substituted with electron-withdrawal groups, predominately gave 8-methyl-5,8-dihydro-1H-pyrrolo[2,3-g]quinoline-4,9-diones (143) (Scheme 45).⁴⁹
The synthesis of a novel tetracyclic structure, 1-benzyl-5-methyl-7-pivaloyl-8,9-dihydroimidazo-[4,5-c]pyrrolo[3,2-g]quinolin-4(5H)-one (148) had been achieved by a convergent pathway. Coupling of the weakly nucleophilic hindered aromatic amine; 6-amino-5-bromo-N-pivaloylindoline (144) with 1-benzylimidazole-5-carboxylic acid (145) afforded the N-(5-Bromo-1-pivaloylindolin-6-yl)-1-benzylimidazole-4-carboxamide (146) using a DCP-DMF complex. Then methylation of this amide, with methyl iodide in the presence of sodium hydride, gave N-(5-bromo-1-pivaloylindolin-6-yl)-N-methyl-(1-benzylimidazol-4-yl)carboxamide (147) and subsequent Heck-type arylation led to desired tetracyclic molecule imidazo[4,5-c]pyrrolo[3,2-g]quinolin-4(5H)-one (148) (Scheme 46).50

1.11. Pyrrolo[2,3-h]quinolines
Methyl 4,5,8-trioxo-1,4,5,8-tetrahydroquinoline-2-carboxylate (149) reacted with ethyl 3-benzylamino-but-2-enoate, in glacial acetic acid, to afford 3-benzyl-1-ethoxycarbonyl-5-hydroxy-8-methoxycarbonyl-2-methylpyrrolo[2,3-h]quinolin-6(9H)-one (150) (Scheme 47).51
Scheme 47

Doebner-von Miller reaction of the ethyl 4-amino-7-methoxy-1H-indole-2-carboxylate (151) with dimethyl trans-ketogluconate gave the pyrrolo[2,3-h]quinoline (152), in 77% yield (Scheme 48).44

Scheme 48

Cyclocondensation of benzenesulfonylacetonitrile with 5-E-diethylaminomethylidene-4-imino-2-methyl-1-phenyl-4,5,6,7-tetrahydro-1H-indole (153) proceeded smoothly, in boiling ethanol, to afford 3-benzenesulfonyl-8-methyl-7-phenyl-5,7-dihydro-1H,6H-pyrrolo[2,3-h]quinolin-2-one (154), in 80% yield (Scheme 49).52

Scheme 49

1.12. Pyrrolo[3,2-h]quinolines

Treatment of 8-nitroquinoline (155) with 4-chlorophenoxyacetonitrile in the presence of potassium tert-butoxide in tetrahydrofuran led to the formation of 7-cyanomethyl-8-nitroquinoline (156). Hydrogenation of the compound (156) using 10% Pd/C resulted in 1H-pyrrolo[3,2-h]quinoline (157) (Scheme 50).41
Conrad-Limpach reaction of ethyl 7-aminoindole-2-carboxylate (158) with benzoylacetone, dibenzoylmethane and/or β-ketoesters was catalyzed with toluene-4-sulfonic acid. The condensation was carried out at 160-220 °C to afford ethyl 1H-pyrrolo[3,2-h]quinoline-2-carboxylates (159) (Scheme 51).53

<table>
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<tr>
<th>R1</th>
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</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Ph</td>
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<td>Ph</td>
<td>OH</td>
<td>43</td>
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<tr>
<td>CF3</td>
<td>OH</td>
<td>46</td>
</tr>
</tbody>
</table>

Ethyl 7-amino-4-methoxy-1H-indole-2-carboxylate (160) underwent Doebner-von Miller condensation reaction, at room temperature, with dimethyl trans-ketoglutoconate to yield the angular tricyclic pyrrolo[2,3-h]quinoline (161) (Scheme 52).44

1.13. Pyrrolo[3,2,1-ij]quinolines

Treating 1-(4-phenoxybut-2-ynyl)quinoline (162) with m-chloroperbenzoic acid gave di[2-phenoxy-methyl-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl]methane (164). A trapping reaction with KCN, led to pyrrolo[3,2,1-ij]quinoline (165), supported a mechanism involving pyrroloquinolinol (163) (Scheme
Thermal cyclocondensation of 2-methylindolines (166) with diethyl malonate led to good yields of 8-hydroxy-5-methyl-4,5-dihydropyrrolo[3,2,1-ij]pyrano[3,2-c]quinoline-7,10-diones (167). Alkaline ring opening of the compounds (167) with sodium hydroxide in ethylene glycol and water resulted in 5-acetyl-6-hydroxy-2-methyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-ones (168) (R= H, Me). The thermal condensation reaction of indoline (169) with ethyl methanetricarboxylate yielded the tricyclic ethyl 1,2-dihydro-6-hydroxy-4H-pyrrolo[3,2,1-ij]quinoline-5-carboxylate (170), in 90 % yield (Scheme 54).
polyphosphoric acid (PPA), elimination of the substituent located at position 4 of the phenyl ring occurs and only one product was formed, viz. 3'-ethoxycarbonyl-4',7',7'-trimethyl-4-oxo-2',6',7',8'-tetrahydro-spiro(cyclohexa-2,5-diene-1,2'-pyrrolo[4',3',2'-de]quinolines) (172) \((R^2 = H, \text{Cl})\) and hydrogen halide was evolved from the reaction mixture (Scheme 55).^57

![Scheme 55](image)

2. Synthesis of Furoquinolines and Benzofuroquinolines

2.1. *Furo*[2,3-*b*]quinolines

The preparation of 4-cyanofuro[2,3-*b*]quinolines (175) \((R = H, \text{Me, Cl, Br})\) was achieved by addition of bromine to the 3-vinylquinoline derivatives (173) to produce the 3-dibromoethylquinoline (174), which was subjected to acid hydrolysis with annelation leading to this linear heterocyclic system.\(^58\) Bromination of the 3-allylquinolin-2(1*H*)-one (176) afforded 3-(2,3-dibromopropyl)quinolin-2(1*H*)-one (177). This dibromo derivative was treated with potassium hydroxide in ethanol to afford 2,4-dimethylfuro[2,3-*b*]quinolin-7-ol (178) (Scheme 56).\(^59\)

![Scheme 56](image)

Treatment of 3-prenylquinolin-2(1*H*)-ones (179) with iodine and mercuric oxide (Prevost reagent) in acetic acid effected the cyclization of which at the face (b) giving the linear 2-isopropyl-
furo[2,3-\(b\)]quinolines (180) (\(R^1, R^4= H, Me, OMe; R^2, R^3= H, Me\)) (Scheme 57).60-62

\[
\begin{array}{cccccc}
R^1 & R^2 & R^3 & R^4 & \text{Yield (\%)} \\
H & H & H & H & 70 \\
Me & H & H & H & 60 \\
H & H & Me & H & 54 \\
H & Me & H & Me & 59 \\
OMe & H & H & OMe & 66 \\
\end{array}
\]

Scheme 57

Treatment of 4-hydroxy-1-methyl-3-prenylquinolin-2(1\(H\))-ones (181) with \(m\)-chloroperbenzoic acid in chloroform furnished the intermediate epoxides (182), which were cyclized by action of 3 M hydrochloric acid or sodium hydroxide to give the isopropanol derivative (183). The linear immunosuppressive 2-isopropyl-2,3-dihydrofuro[2,3-\(b\)]quinolin-4-ones (184) (\(R= H, OMe\)) were obtained via dehydration of the compound (183) (Scheme 58).63

The palladium catalyzed alkynylation of 3-iodo-4,6,8-trimethoxyquinolin-2(1\(H\))-ones (185) with 2-methyl-3-butyn-2-ol smoothly furnished the corresponding 2-(4,6,8-trimethoxyfuro[2,3-\(b\)]quinolin-2-yl)propan-2-ol (186), in 81% yield (Scheme 59).64
Bar et al. reported that a mixture of linear and angular tricyclic furoquinolinones was obtained from the ultrasound assisted reaction of phenylacetylene with 4-hydroxy-1-methylquinolin-2(1\(H\))-one (187), in the presence of manganese(III) acetate. The reaction led to 9-methyl-2-phenylfuro[2,3-\(b\)]-quinolin-4(9\(H\))-one (188) and 5-methyl-2-phenylfuro[3,2-\(c\)]quinolin-4(5\(H\))-one (189) (Scheme 60).

\[ \text{Mn(OAc)}_3 \cdot 2\text{H}_2\text{O} \quad 4\text{ h}, \quad 60^\circ\text{C}, \quad \text{ultrasound} \]

\[ 60\% \]

\[ 188 \quad (43\%) \quad 189 \quad (17\%) \]

**Scheme 60**

2.2. Furo[3,4-\(b\)]quinolines

Reduction of methyl 2-methylquinoline-3-carboxylate (190) produced the 3-hydroxymethyl-2-methylquinoline (191). Selective oxidation of the latter alcohol using selenium dioxide in boiling ethanol furnished 3-ethoxy-1,3-dihydrofuro[4,3-\(b\)]quinoline (192). The ether (192) was then de-ethylated via heating in a mixed solvent of water, acetic acid and THF to afford 3-hydroxy-1,3-dihydrofuro[4,3-\(b\)]quinoline (193). Bromolactonization of the methyl 2,2,7,7-tetramethylquinoline-3-carboxylate (194) with NBS gave 6,6-dimethyl-1,3,4,5,6,7,8,9-octahydrofuro[3,4-\(b\)]quinoline-1,8-dione (195) (Scheme 61).

\[ \text{LiAlH}_4 \quad \text{THF} \quad \text{overnight, rt} \quad 48\% \]

\[ \text{SeO}_3 \quad \text{EtOH, cyclohexane} \quad \text{8 h, reflux} \quad 52\% \]

\[ 192 \quad 193 \quad 190 \quad 191 \quad 194 \quad 195 \]

**Scheme 61**
The tetracyclic benzofuro[3,2-b]quinolin-10(5H)-one (198) was synthesized in two steps from 2-(2-fluorophenacyloxy)benzonitrile (196). Thus treatment of the compound (196) with sodium ethoxide at room temperature provided the 3-amino-2-(2-fluorobenzoyl)-1-benzofuran (197), in 93% yield. Cyclization of the latter compound was performed by action of sodium hydride, at 100 °C, afforded the benzofuroquinolinone (198), in 91% yield (Scheme 62).

\[
\begin{align*}
\text{EtONa, EtOH} & \xrightarrow{2 \text{ h, rt}} 93\% \\
\text{50\% NaH} & \xrightarrow{\text{DMF}} \xrightarrow{2 \text{ h, 100 °C}} 91\%
\end{align*}
\]

Scheme 62

2.3. Furo[2,3-c]quinolines

2,5-Dimethylfuro[2,3-c]quinolin-4-ones (202) (R = H, Br) and (204) (R = H R¹ = H; R = Br R¹ = H; R = Br R¹ = Me) were synthesized starting by allylation of 3-hydroxy-1-methylquinolin-2(1H)-ones (199) followed by [3,3]sigmatropic rearrangement of the allyl ethers (200) to give the corresponding 4-allyl-3-hydroxyquinolinones (201). The compounds (201) were easily cyclized to the respective furo[2,3-c]quinolinones (202) and 1,2-dihydrofuro[2,3-c]quinolinones (203) when treated with concentrated sulfuric acid. The latter derivatives (203) were dehydrogenated, using (10 %) Pd/C in boiling diphenyl ether, affording 2,5-dimethylfuro[2,3-c]quinolin-4-ones (204) (Scheme 63).

3-(4-Aryloxybut-2-ynyloxy)-1-metylquinolin-2(1H)-ones (205) were obtained by butynylation of the appropriate 3-hydroxyquinolinones (199) in good yields. Thermal Claisen rearrangement of these ethers chlororbenzene provided mainly 1-aryloxymethyl-6-methyl-3H-pyran[2,3-c]quinolin-5(6H)-ones (206), which on heating in N,N-diethylaniline (DEA) underwent an unusual ring contraction to give 1-aryloxymethyl-2,5-dimethylfuro[2,3-c]quinolin-4(5H)-ones (207), in 66-79 % yields. Also the 3-butynlyoxyquinolinones (205) can be converted directly to the corresponding furo[2,3-c]quinolinones (207), in 65-80%, by heating in N,N-diethylaniline (Scheme 64).
Scheme 63

Scheme 64
The preparation of 2,3a,4,5-tetrahydrofuro[2,3-c]quinoline-2,4-diones (211) \( (R^1 = \text{H, Me, Ph}; R^2 = \text{n-Bu, Ph, PhCH}_2) \) proceeded smoothly via intramolecular Wittig reaction of the 3-phosphonioacetoxy-2,4-quinolinediones (210), using sodium hydroxide. The compound (210) was preliminarily prepared by bromoacetylation of the 3-hydroxy-2,4-quinolinediones (208) to give the 3-acetoxy-2,4-quinolinediones (209), followed by reaction with triphenylphosphine in refluxing benzene (Scheme 65).\(^{73}\)

![Scheme 65](image)

<table>
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<th>211</th>
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<td>71</td>
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</table>

Scheme 65

Sigmatropic thermal rearrangement of 3-(cyclohex-2-enyl)oxy-1-methylquinolin-2(1H)-one (212) in boiling chlorobenzene furnished 4-(cyclohex-2-enyl)-3-hydroxy-1-methylquinolin-2(1H)-one (213), which upon treatment with pyridinium tribromide produced 8-bromo-5-methyl-7a,8,9,10,11,11a-hexahydro[1]benzofuro[2,3-c]quinolin-6(5H)-one (214) (Scheme 66).\(^{74}\)

![Scheme 66](image)

2.4. Furo[3,2-c]quinolines

Meth-Cohn and Taylor reported that the reaction of \( N \)-methylformanilide (215) with 4-(4-hydroxybutyryl)morpholine (216) in the presence of phosphorus oxychloride resulted in 4-chloro-3-
(2-chloroethyl)quinolinium phosphorus hexafluoride (217) in 63 % yield. This salt when treated with methanolic sodium hydroxide afforded the 3,4-dihydrofuro[3,2-c]quinolinium salt (218).\textsuperscript{75} 5-Methyl-furo[3,2-c]quinolin-4(5H)-one (220) was provided, in 96 % yield, via treatment of 4-hydroxy-1-methylquinolin-2(1H)-one (187) with chloroacetaldehyde in the presence of potassium carbonate and dehydration of the resulting 3-hydroxy-5-methyl-2,3-dihydrofuro[3,2-c]quinolin-4(5H)-one (219) using 6 M hydrochloric acid (Scheme 67).\textsuperscript{76}

\[
\begin{align*}
\text{Me} & \text{CHO} + \text{O} & \text{POCl}_3 & \rightarrow & \text{N} & \text{O} & \text{Cl} & \text{Me} & \text{Cl} & \text{PF}_6^- \\
\text{215} & & & 2 \text{h}, 80 \text{oC} & & & 63\% & & & 217
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \text{CICH}_2\text{CHO} & \text{K}_2\text{CO}_3, \text{H}_2\text{O} & \rightarrow & \text{N} & \text{O} & \text{Me} & \text{O} & \text{O} & \text{OH} \\
\text{187} & & & 5 \text{h}, \text{rt} & & & 60\% & & & 219
\end{align*}
\]

\[
\begin{align*}
\text{NaOH, MeOH} & \rightarrow & \text{N} & \text{O} & \text{Me} & \text{PF}_6^- \\
\text{217} & & & & & & & & & 218
\end{align*}
\]

\[
\begin{align*}
\text{6 M HCl} & \rightarrow & \text{O} & \text{O} & \text{Me} \\
\text{219} & & & & & & & & & 220
\end{align*}
\]

**Scheme 67**

Condensation of the compound (187) with 2- or 4-nitrobenzaldehydes generated 2,4-dioxo-3-methylidene-quinolines (221), which underwent [4+1]cycloaddition with cyclohexyl isocyanide, followed by a [1,3]hydrogen shift to produce 3-aryl-2-cyclohexylamino-5-methylfuro[3,2-c]quinolin-4(5H)-ones (222) (Scheme 68).\textsuperscript{77}

\[
\begin{align*}
\text{OH} & \text{CHO} & \text{benzene} & \text{reflux} & 82-84\% \\
\text{187} & & & & 221
\end{align*}
\]

\[
\begin{array}{c|c|c}
\text{R}^1 & \text{R}^2 & \text{Yield (\%)} \\
\hline
\text{H} & \text{NO}_2 & 84 \\
\text{NO}_2 & \text{H} & 82 \\
\end{array}
\]

**Scheme 68**
An efficient synthesis of 5-methyl-2-phenylfuro[3,2-c]quinolin-4(5H)-one (223) was developed by ceric(IV) ammonium nitrate (CAN) mediated oxidative cycloaddition of 4-hydroxyquinolinone (187) with phenylacetylene (Scheme 69).

Reish and Iding reported that treating the 4-hydroxy-1-methylquinolin-2(1H)-one (187) with 1,4-dibromo-2-methyl-2-butene, under phase transfer catalysis conditions (PTC), afforded (±)-2,3-dihydro-5-methyl-2-(propen-2-yl)furo[3,2-c]quinolin-4(5H)-one (224) in 42 % yield. It was noticed that the product (224) was accompanied with three by-products; E-4-(4-bromo-3-methyl-2-buten-1-yl)-1-methylquinolin-2(1H)-one (225), 1-methylisatine (226), and bis(4-hydroxy-1-methyl-2-oxo1,2-dihydro-3-quinolinyl)methane (227) in 8, 11, and 1.2 % yields, respectively (Scheme 70).

The treatment of 3-acyl-4-hydroxy-1-methylquinolin-2(1H)-one (228) (R= Me, Ph, n-pentyl) with ethyl (triphenyl-phosphoranylidene)acetate led to 5,6-dihydro-2H-pyrano[3,2-c]quinoline-2,5-diones (229), which were brominated to furnish the 3-bromopyranoquinolines (230). Alkaline hydrolysis of (230)
afforded 2-substituted 4-oxo-4,5-dihydrofuro[3,2-c]quinoline-3-carboxylic acids (231), which underwent decarboxylation using copper dust to give the corresponding furo[3,2-c]quinolinones (232) (Scheme 71).\textsuperscript{80}

![Scheme 71](image)

<table>
<thead>
<tr>
<th>R</th>
<th>229</th>
<th>230</th>
<th>231</th>
<th>332</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>70</td>
<td>82</td>
<td>28</td>
<td>47</td>
</tr>
<tr>
<td>pentyl</td>
<td>65</td>
<td>79</td>
<td>26</td>
<td>58</td>
</tr>
<tr>
<td>Ph</td>
<td>71</td>
<td>77</td>
<td>34</td>
<td>43</td>
</tr>
</tbody>
</table>

It was reported that the reaction of 3-acetyl-4-hydroxy-1-methylquinolin-2(1H)-one (228) with ethyl chloro(triphenylphosphoranylidene)acetate proceeded not only at the acetyl group but also at the amide group to give a mixture of ethyl 3,5-dimethyl-4-oxo-4,5-dihydrofuro[3,2-c]quinoline-2-carboxylate (233) and ethyl chloro(3-chloro-4,6-dimethyl-2-oxo-2,6-dihydro-5H-pyrano[3,2-c]quinolin-5-ylidene)acetate (234) (Scheme 72).\textsuperscript{80}

![Scheme 72](image)

The preparation of 5-ethyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline (236) was achieved in one step (75 % yield) using a formal [4π+2π]cycloaddition involving the cationic azadiene (92) and the 2,3-dihydrofuran (235) as dienophile (Scheme 73).\textsuperscript{34}
Indium-mediated domino reaction of nitrobenzene derivatives with 2,3-dihydrofuran (235) in water was described as an efficient synthesis of cis- and trans-4-(3-hydroxypropyl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinolines (238) and (239), in 43-87 % overall yields. The mechanism involves first reduction of the nitro group, followed by formation of the imine intermediates (237), which in turn undergo [4+2]cycloaddition with another molecule of 2,3-dihydrofurn. Yadav et al. reported that [4+2]cycloaddition of 2,3-dihydrofuran (235) with the imine intermediates (237) can be carried out using scandium triflate immobilized in 1-butyl-3-methylimidazolium hexafluorophosphate under solvent-free conditions to give the cis- and trans-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinolines (238) and (239) in 85-91 % overall yields (Scheme 74).

Recently, a three-step liquid phase protocol for the synthesis of 4-aryl-2,3-dihydrofuro[3,2-c]quinolines (242) was described. The one-pot three-component aza-Diels-Alder reaction of polyethylene glycol-supported benzaldehydes, anilines and 1,2-dihydrofurn (235) gave the corresponding PEG-supported 2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinolines (240), which were assuredly oxidized using DDQ and then cleaved from the support to afford the compounds (241) with reasonable yields and purity. When the PEG-supported (240) was cleaved using sodium methoxide, cis- and trans-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinolines (242) were obtained in 80-93% overall yields (Scheme 75).
Srinivas and Das showed that Fe\(^{3+}\)-K-10 monomorillonite clay and HY-zeolite are two solid acids, which can be employed efficiently for single-step synthesis of cis- and trans-2,3,3a,4,5,9b-hexahydrofuro[3,2-c] quinolines (243), and (244), in high yields (76-89 %) and diastereoselectivity by coupling of benzaldehydes, anilines, and 1,2-dihydrofurn (235) (Scheme 76).\(^8^4\) Similar result was obtained using lithium tetrafluoroborate as the catalyst to give the furo[3,2-c]quinoline derivatives (243), and (244), in 87-93 % yields.\(^8^5\) Also potassium hydrogen sulfate was used to catalyze this one-pot reaction affording both stereoisomers (243) and (244) (R\(^1\)-R\(^4\)= H; R\(^1\)-R\(^3\)=H, R\(^4\)= Cl), in 60-67 % overall yields.\(^8^6\)
4-(Cyclohex-2-enyl)oxy-1-methylquinolin-2(1H)-one (245) underwent thermal sigmatropic Claisen rearrangement to give 3-(cyclohex-2-enyl)-4-hydroxy-1-methylquinolin-2(1H)-one (246). The cyclization of the compound (246) was effected, using pyridinium tribromide, to afford the tetracyclic [1]benzofuro[3,2-c]quinolinone (247), which was dehydrobrominated with ethanolic potassium hydroxide and aromatized to give the [1]benzofuro[3,2-c]quinolin-6(5H)-one (248) (R= Me, R¹= R²= H) in 90% yield. 87 Palladium catalyzed cyclization of 4-hydroxy-3-phenylquinolin-2(1H)-ones (249) proceeded in refluxing diphenyl ether, in 27-39% yields, to furnish [1]benzofuro[3,2-c]quinolin-6(5H)-ones (248) (R= H, R¹= H, OMe, F; R²= H, OMe,) (Scheme 77). 31

\[
\begin{array}{cccc}
R & R^1 & R^2 & \text{Yield (\%)} \\
\hline
\text{Me} & \text{H} & \text{H} & 90^a \\
\text{H} & \text{OMe} & \text{H} & 36^b \\
\text{H} & \text{H} & \text{OMe} & 32^b \\
\text{H} & \text{F} & \text{H} & 27^b \\
\end{array}
\]

\(^a\) Ref. 87  
\(^b\) Ref. 31

Scheme 77

2.5. Furo[2,3-f]quinolines

The reaction of the methyl 4,5,8-trioxo-1,4,5,8-tetrahydroquinoline-2-carboxylate (250) with the 3-dimethylamino-1-phenylprop-2-en-1-one and/or 4-dimethylaminobut-3-en-2-one, in glacial acetic acid, led exclusively to methyl 3-acetyl/benzoyl-2-methyl-5,9-dioxo-5,6,9,9b-tetrahydrofuro-[2,3-f]quinoline-7-carboxylates (251) (R = Me, Ph) (Scheme 78). 51

\[
\begin{array}{cccc}
\text{R} & \text{Yield (\%)} \\
\hline
\text{Me} & 59 \\
\text{Ph} & 37 \\
\end{array}
\]

Scheme 78
Alkylation of 5-hydroxyquinoline (252) with ethyl 2,3-dibromopropanoate was carried out in the presence of potassium carbonate to give a mixture of ethyl 2,3-dihydrofuro[2,3-f]quinoline-2-carboxylate (253) and spiro[2-carbethoxycyclopropane-1,8’-(5’-oxo-5’,8’-dihydroquinoline)] (254) (Scheme 79).88

\[ \text{OH} \quad \text{Br} \quad \text{CO}_2\text{Et} \]

\[ \text{Br} \quad \text{CO}_2\text{Et} \quad \text{K}_2\text{CO}_3, \text{acetone} \quad 24 \text{ h, reflux} \]

\[ \text{HO} \quad \text{N} \quad \text{O} \]

\[ \text{Me} \quad \text{N} \quad \text{O} \]

\[ \text{252} \quad \text{253 (23%)} \quad \text{254 (21%)} \]

Scheme 79

2.6. Furo[3,2-f]quinolines

Treatment of 6-hydroxy-1-methylquinolin-2(1H)-one (255) with allyl halides (X= Cl, Br; R1= H, Me; R2= H, Cl) gave the allyl ethers (256), which in turn were subjected to thermal [3,3]sigmatropic rearrangement in boiling N,N-diethylaniline affording the corresponding 5-allyl-6-hydroxyquinolin-2(1H)-ones (257). 1,6-Dimethylfuro[3,2-f]quinolin-2(1H)-one (258) was obtained via cyclization of the chloroallyl derivative (257) (R1= H, R2= Cl) with ethanolic potassium hydroxide while the 6,7-dihydro isomers (259) were obtained by cyclization of the allyl derivatives (257) (R1= H, Me; R2= H) by stirring in concentrated sulfuric acid (Scheme 80).89

\[ \text{HO} \quad \text{Me} \quad \text{N} \quad \text{O} \]

\[ \text{Me} \quad \text{N} \quad \text{O} \]

\[ \text{255} \quad \text{256} \]

\[ \text{R}^1 \quad \text{R}^2 \quad \text{X} \]

\[ \text{Yield (%)} \]

\[ \begin{array}{cccc}
\text{R}^1 & \text{R}^2 & \text{256} & \text{257} \\
\text{H} & \text{H} & 70 & 70 \\
\text{Me} & \text{H} & 75 & 65 \\
\text{H} & \text{Cl} & 75 & 65 \\
\end{array} \]

\[ \text{Scheme 80} \]

Similarly, thermal rearrangement of 6-(cyclohex-2-enyl)oxy-1-methylquinolin-2(1H)-one (260) in boiling chlorobenzene furnished 5-(cyclohex-2-enyl)-6-hydroxy-1-methylquinolin-2(1H)-one (261),
which upon treatment with pyridinium tribromide in methylene chloride resulted in the 8-bromo-4-methyl-7a,8,9,10,11,11a-hexahydro[1]benzofuro[3,2-f]quinolin-3(4H)-one (262), in 85% yield (Scheme 81).90

![Scheme 81]

2.7. Furo[3,2-g]quinolines
The reaction of 6-acetyl-7-hydroxy-4-methylquinolin-2(1H)-one (263) with 4-chlorophenacyl bromide in the presence of potassium carbonate in DMSO smoothly led to the linear 2-(4-chlorobenzoyl)-3,5-dimethylfuro[3,2-g]quinolin-7(8H)-one (264) (Scheme 82).91

![Scheme 82]

2.8. Furo[2,3-h]quinolines
Treating 8-acetyl-7-hydroxy-4-methylquinolin-2(1H)-one (265) with 4-chlorophenacyl bromide in the presence of potassium carbonate in DMSO resulted in the angular tricyclic 2-(4-chlorobenzoyl)-1,6-dimethylfuro[2,3-h]quinolin-8(9H)-one (266) (Scheme 83).91

![Scheme 83]

8-Allyl-7-hydroxy-4-methylquinolin-2(1H)-one (267) was submitted to cyclization in concentrated
sulfuric acid, yielding the corresponding 4,8-dimethyl-8,9-dihydrofuro[2,3-h]quinolin-2(1H)-one (268), which was methylated with dimethyl sulfate to give 1,4,8-trimethyl-8,9-dihydrofuro[2,3-h]quinolin-2(1H)-one (269) and 4,8-dimethyl-2-methoxy-8,9-dihydrofuro[2,3-h]quinoline (270). These methylated products were aromatized using DDQ to the corresponding furo[2,3-h]quinolinone (271) and furo[2,3-h]quinoline (272) (Scheme 84).

Condensation of 5-dimethylaminomethylene-6,7-dihydro[1]benzofuran-4(5H)-one (273) with alkyl cyanoacetates was carried out at room temperature to afford alkyl 2-oxo-1,2,5,6-tetrahydrofuro[2,3-h]quinoline-3-carboxylates (274) (R= Me, Et). These products were aromatized using DDQ to the corresponding furo[2,3-h]quinolinone (275) (Scheme 85).
2.9. *Furo[3,2-h]quinolines*

The reaction of ethyl 1-cyclopropyl-1,4-dihydro-6,7,8-trifluoro-4-oxoquinoline-3-carboxylate (276) with some acetoacetate esters (\(R^1= \text{H, MeO; } R^2= \text{Me, } t\text{-Bu}\)) in the presence of potassium \(t\text{-butoxide}\) afforded the corresponding ethyl 3-alkoxycarbonyl-9-cyclopropyl-6,8-dioxo-4-fluoro-6,7,8,9-tetrahydrofuro[3,2-\(h\)]quinoline-7-carboxylates (277) (\(R^1= \text{H, MeO; } R^2= \text{Me, } t\text{-Bu}\)) (Scheme 86).94

\[
\begin{array}{cccc}
R^1 & R^2 & \text{Yield(%)} \\
\text{H} & t\text{-Bu} & 66 \\
\text{OMe} & \text{Me} & 58 \\
\end{array}
\]

Scheme 86

3. Synthesis of Thienoquinolines and Benzothienoquinolines

3.1. *Thieno[2,3-b]quinolines*

Some 2-methylthieno[2,3-b]quinolin-4(9\(H\))-ones (280) (\(R^1= \text{Me, Et, Ph; } R^2= \text{H, Me}\)) were regioselectively obtained utilizing the 4-propynloxyquinoline-2(1\(H\))-thione derivatives (279) in a thermal sigmatropic rearrangement process. The latter quinoline-2-thiones were prepared in two steps from the 4-hydroxyquinolin-2(1\(H\))-ones (187) (\(R^1= \text{Me, Et, Ph}\)), which were propynylated with 3-chloropropyne derivatives (\(R^2= \text{H, Me}\)). Hence, the so obtained ethers (278) were thiated (Scheme 87).95

\[
\begin{array}{cccc}
R^1 & R^2 & \text{Yield(%)} \\
\text{Me} & \text{H} & 65 & 80 & 80 \\
\text{Me} & \text{Me} & 65 & 80 & 90 \\
\text{Et} & \text{H} & 64 & 75 & 88 \\
\text{Et} & \text{Me} & 65 & 80 & 80 \\
\text{Ph} & \text{H} & 60 & 78 & 85 \\
\text{Ph} & \text{Me} & 62 & 70 & 82 \\
\end{array}
\]

Scheme 87
Reaction of 2,4-dichloro-3-(3,3-dichloroallyl)quinoline (281) with thiourea in dry acetone produced S-(4-chloro-2-quinolinyl)isothiourea hydrochloride (282). Alkaline hydrolysis of this salt led to the formation of 4-chloro-2-dichloromethyl-2,3-dihydrothieno[2,3-b]quinoline (283) (Scheme 88).96

The literature showed that many thieno[2,3-b]quinolines were prepared based on utilizing 2-thioxoquinoline-3-carbonitriles as synthones. The synthesis may proceed by cascade S-alkylation under basic medium with a suitable α-activated alkyl halides and cyclization to thieno[2,3-b]quinolines by Michael-type intramolecular addition. In certain cases the open chain thioethers were separated and can be cyclized subsequently on using a more relevant base catalyst.

Thus, reaction of 5-oxo-2-thioxoquinoline-3-carbonitriles (284) with chloroacetamide and/or chloroacetonitrile afforded the intermediates 2-(substituted methyl)sulfanylquinoline-3-carbonitrile (285). In situ cycloaddition of the active methylene group to the ortho carbonitrile effected annelation to give
the corresponding thieno[2,3-b]quinolines (286) \((R^1 = \text{CONH}_2, \text{CN}; R^2 = \text{Me})\).\(^{97}\) Similarly the reaction of the compound (284) \((R^2 = \text{Ph})\) with phenacyl bromides gave the 2-aryltienoquinoline analogues (286) \((R^1 = \text{ArCO}; R^2 = \text{Ph})\) (Scheme 89).\(^{98}\) 2-Thioxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile (287) \((R^2 = \text{H, OMe, Cl, 4-ClC}_6\text{H}_4)\) was reacted with chloroacetone in the presence of sodium acetate as catalyst. Then the obtained 2-acetonylsulfanylquinolines (288) were cyclized to give the 5,6,7,8-tetrahydrothieno[2,3-b]quinolines (289) \((R^1 = \text{Me, OEt, NH}_2; R^2 = \text{H, OMe, Cl, 4-ClC}_6\text{H}_4)\) (Scheme 89).\(^{99,100}\)

Several 4-methyl-2-thioxo-1,2-dihydroquinoline-3-carbonitrile (290) were alkylated with certain activated halomethanes in the presence of sodium hydroxide to give 2-alkylsulfanylquinoline-3-carbonitriles (291), which were then cyclized by action of sodium ethoxide furnishing thieno[2,3-b]quinolin-3-amines (292) in quantitative yields. When the alkylation reaction of the compound (290) was carried out in the presence of sodium ethoxide, the thienoquinolines (292) were obtained directly in 23-87% yields. Similarly, compound (293) was obtained via reaction with chloroacetonitrile (Scheme 90).\(^{101-103}\)

\[
\begin{align*}
\text{Scheme 90}
\end{align*}
\]

2-Thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (295) was synthesized by treatment of sodium 2-oxocyclohexylidenemethanolate (294) with cyanothioacetamide. The alkylation of compound (295) was performed easily using \(\alpha\)-halocarbonyl compound derivatives and sodium acetate to give \(S\)-alkylated
derivatives (296), which were treated with sodium ethoxide to form the respective 5,6,7,8-tetrahydrothieno[2,3-b]quinolin-3-amines (297). Compounds (297) were directly obtained from compound (295) via treating with α-halocarbonyl compounds and potassium carbonate as the catalyst (Scheme 91).104

Treating 4-alkylamino-2-chloroquinoline-3-carbonitriles (298) with thioglycolic acid in the presence of sodium ethoxide afforded ethyl 4-alkylamino-3-aminothieno[2,3-b]quinoline-2-carboxylates (300) (R = Me, Et, i-Pr, i-Bu). The acetate intermediates (299) were cyclized in situ by action of the used base (Scheme 92).105

3.2. Thieno[3,4-b]quinolines
Treating 1-ethyl-2-methyl-4-oxoquinoline-3-carboxylic acid (301) with thionyl chloride led to the formation of 3,3,9-trichlorothieno[3,4-b]quinolin-1-one (41) (R = H, F) as a result of chloro-de-ethylation
during the course of cyclization reaction. However the 3,3-dichlorothieno[3,4-b]quinoline-1,9-dione (302) was separated when the reaction was carried out at room temperature and could be transformed to the trichloro derivative (41), on refluxing with excess reagent. This new interesting approach to annelation of quinoline with thiophene ring was earlier reported by Semenov et al. thus it was observed the formation of 3,3-dichlorothieno[3,4-b]quinolin-1(3H)-one (304) during reaction of 2-methylquinoline-3-carboxylic acid (303) with thionyl chloride (Scheme 93).

The readily available methyl 4-oxotetrahydrothiophene-3-carboxylate (305) was reacted with aniline to give methyl 4-(phenylimino)tetrahydrothiophene-3-carboxylate (306), which was cyclized to 1,4-dihydrothieno[3,4-b]quinolin-9(3H)-one (307) by heating in biphenyl (Scheme 94).

3.3. Thieno[3,2-b]quinolines
The low-temperature reaction between isatoic anhydride (308) and 4,5-dihydrothiophen-3(2H)-one (309), was base catalyzed by lithium diisopropylamide (LDA) to give 4-methyl-2,3-dihydrothieno[3,2-b]-quinolin-9(4H)-one (310) (Scheme 95).

![Scheme 93](image)

![Scheme 94](image)

![Scheme 95](image)
3.4. **Thieno[2,3-c]quinolines**

Palladium catalyzed reaction of methyl 3-iodothiophene-2-carboxylate (311) with 2-nitrophenylboronic acid (312) afforded methyl 3-(2-nitrophenyl)thiophene-2-carboxylate (313), which on reductive treatment with activated zinc in an acetate buffer yielded the 5-hydroxythieno[2,3-c]quinolin-4(5H)-one (314), while iron in acetic acid medium yielded the thieno[2,3-c]quinolin-4(5H)-one (316). With phosphoryl chloride and phosphorus pentachloride the lactam (316) was converted into the 4-chlorothieno[2,3-c]quinoline (317). This compound was the starting material for the preparation of the various compounds with activity against *Plasmodium falciparum*. Alternative to the approach via the Suzuki product (313) the lactam (316) was also prepared in a tandem reaction between the iodothiophene (311) and pinacol 2-aminophenyl- boronate (315) (Scheme 96).\(^\text{110}\)

\[\text{Scheme 96}\]

6-Methyl[1]benzothieno[2,3-c]quinoline (320) had been synthesized starting from the 2-acetyl-3-phenylbenzo[b]thiophene oxime (318). The cyclization was accomplished by activating oxime as O-(2,4-dinitrophenyl) derivative (319) via coupling with 2,4-dinitrochlorobenzene and subsequent cyclocondensation in the presence of sodium hydride (Scheme 97).\(^\text{111}\)

\[\text{Scheme 97}\]
Thieno[3′,2′:4,5]thieno[2,3-c]quinolinone (326) was synthesized in multistep synthesis starting from 3-formylthiophene (321) and malonic acid reacting in aldol condensation or from 3-bromothiophene (322) reacting in Heck reaction. The product 3-(3-thienyl)acrylic acid (323) was cyclized into thieno[2,3-c]-thiophene-2-carbonyl chloride (324) and converted into the carboxamide (325). The compound (325) was photochemically dehydrogenated to give thienothienoquinolinone (326), which was found to exert marked antitumor activity (Scheme 98).\textsuperscript{112}
Luo et al. showed that 3-chloro[1]benzothieno[2,3-b]thiophene-2-carbonyl chloride (327) and its isomer 3-chloro[1]benzothieno[3,2-b]thiophene-2-carbonyl chloride (328) reacted with aniline, in boiling benzene, affording the corresponding anilides (329) and (330). Photochemical cyclization of these anilides was carried out using mercury lamp in the presence of triethylamine provided the pentacyclic [1]benzothieno[3′,2′:4,5]thieno[2,3-c]quinolin-6(5H)-one (331), in 82 % yield, and [1]benzothieno-[2′,3′:4,5]thieno[2,3-c]quinolin-6(5H)-one (332), in 94 % yield, respectively (Scheme 98).

3.5. Thiено[3,4-c]quinolines

4-Methyl-2-oxo-1,2-dihydroquinoline-3-carbonitrile (334) was obtained via the cyclization reaction between 2-aminoacetophenone (333) and ethyl cyanoacetate in the presence of ammonium acetate. Treating the compound (334) with sulfur and piperidine in DMF led to the formation of 3-aminothieno[3,4-c]quinolin-4(5H)-one (335) in 83 % yield (Scheme 99).

Treatment of methyl 4-oxotetrahydrothiophene-3-carboxylate (305) with triflic anhydride gave methyl 4-[(trifluoromethylsulfonyl)oxy]-2,5-dihydrothiophene-3-carboxylate (336), which underwent Suzuki coupling with 2-t-butoxycarbonylaminobenzeneboronic acid (337) to afford 3,5-dihydro-1H-thieno[3,4-c]quinolin-4-one (338) (Scheme 100).

3.6. Thiено[3,2-c]quinolines

The reaction of 4-chloroquinolin-2(1H)-ones (109) with thioglycolic acid and/or 2-sulfanylpropionic acid in the presence of a base catalyst afforded the corresponding thio ethers (339), which were subjected to cyclodehydration using polyphosphoric acid (PPA) to yield 3-hydroxythieno[3,2-c]quinolin-4(5H)-ones (340) (R1= H, Me; R2= Me, Et, Ph) (Scheme 101).
Several 3-aryloxyacetyl-2,3-dihydro-5-methylthieno[3,2-c]quinolin-4(5H)-ones (343) (Ar= Ph, 2-ClC₆H₄, 4-ClC₆H₄, 2-MeC₆H₄, 4-MeC₆H₄, 2,5-Me₂C₆H₃) were regioselectively synthesized, in 80-90% yield, from the oxidative rearrangement of 4-[(4-aryloxybut-2-ynyl)sulfanyl]quinolin-2(1H)-ones (342). These thio-ethers were prepared by S-butynylation of the respective 4-sulfanylquinolin-2(1H)-ones (341) with 1-aryloxy-4-chloro-2-butynes under phase transfer catalysis conditions. Oxidation of the 2,3-dihydrothienoquinolinone (343) (Ar= 4-ClC₆H₄), using DDQ, afforded the corresponding aromatized thieno[3,2-c]quinolin-4(5H)-one (344) (Scheme 102).
3.7. *Thieno*[2,3-g]quinolines and *Thieno*[3,2-g]quinolines

Hetero Diels–Alder regioselective reaction of (1*E*,2*E*)-but-2-enal dimethylhydrazone with methyl 4,7-dioxo-4,7-dihydro-1-benzo[b][1,4]dithiophene-2-carboxylate (345) yielded the navy blue crystalline adduct methyl 5-methyl-4,9-dioxo-5,8-dihydrothieno[3,2-g]quinoline-2-carboxylate (346). The 2D-NMR spectral studies revealed that thieno[2,3-g]quinoline (347) is not affordable under the described reaction conditions. Oxidation of the compound (346) to the thieno[3,2-g]quinoline (348) proceeded smoothly using PCC on neutral alumina (Scheme 103).118

Cycloaddition reaction between quinoline-5,8-dione (349) ethyl 2(S,R)-phenylthiazolidine-4(S)-carboxylate (350) was carried out using silver carbonate and DBU as base catalyst. The reaction led to formation of a mixture of pyrido[3,4-g]quinoline (351), pyrido[4,3-g]quinoline (352), ethyl 3-amino-4,9-dioxo-2,3,4,9-tetrahydrothieno[2,3-g]quinoline-3-carboxylate (353), and ethyl 3-amino-4,9-dioxo-2,3,4,9-tetrahydrothieno[3,2-g]quinoline-3-carboxylate (354). The products (351) and (352) are inseparable while the two thienoquinolines (353) and (354) are obtainable as 2.2:1 regioisomeric mixture, which separated chromatographically (Scheme 104).119
3.8. Thieno[2,3-h]quinolines

The reaction of 3-formylpyridine (355) with diethyl 2-thienylphosphonate (356) was carried out in the presence of sodium hydride to yield trans-1-(3-pyridyl)-2-(2-thienyl)ethene (357). Photochemical cyclization of this ethene derivative resulted in thieno[2,3-h]quionline (358) and thieno[3,2-f]isoquionline (359) in 2:1 yield ratio (Scheme 105).120

\[
\begin{align*}
N\text{Me}_2O & \quad \xrightarrow{NC\text{CH}_2\text{CO}_2R} \quad N\text{Me}_2O \\
350 & \quad \xrightarrow{DDQ, \text{toluene}} \quad 360
\end{align*}
\]

\[
\begin{align*}
R & \quad \text{Yield(%) } \quad 361 \quad 362 \\
\text{Me} & \quad 57 \quad 61 \\
\text{Et} & \quad 76 \quad 49
\end{align*}
\]

Scheme 106

Condensation of 5-dimethylaminomethylene-6,7-dihydro[1]benzothiophen-4(5H)-one (360) with alkyl cyanoacetates was carried out at room temperature to give alkyl 2-oxo-1,2,5,6-tetrahydrothieno[2,3-h]quinoline-3-carboxylates (361) (R= Me, Et). These products were aromatized using DDQ to the corresponding thieno[2,3-h]quinolinone (362) (Scheme 106).93

3.9. Thieno[3,2-h]quinolines

The reaction of 3-formylpyridine (355) with diethyl 3-thienylphosphonate (363) was carried out in the presence of sodium hydride to yield trans-1-(3-pyridyl)-2-(2-thienyl)ethene (364). Photochemical cyclization of this ethene derivative resulted in thieno[3,2-h]quionline (365) and thieno[2,3-f]isoquionline (366) in 1:3 yield ratio (Scheme 107).120
4. BIOLOGICAL APPLICATIONS OF AZOLOQUINOLINES

Azoloquinolines showed a diverse and distinctive biological applications. The literature during the last decade revealed that pyrroloquinolines and indoloquinolines are an important pharmaco-core for many chemical treatments of several viral, bacterial, fungal infections. Indoloquinolines revealed significant efficiency in curing tumors. Interestingly a lot of pyrroloquinolines and furoquinolines are known alkaloids and their found activities in the field of cancer chemotherapy can be improved or enhanced with modification of their chemical structures. Similarly many dangerous diseases can be controlled by the well-known effect of quinolinone derivatives, especially the fused systems, such as malaria, bilharzias, ulcer, inflammations, etc. The following are some recent examples for the biological uses of azoloquinolines.

4.1. Pyrroloquinolines

A series of pyrrolo[2,3-\(h\)]quinoline-2-ones was synthesized and evaluated as photo-reagents toward cultured human tumor cells. Remarkable photo toxicity resulted for some derivatives, especially those bearing the phenyl group at the 7-position.\(^{52}\) Some 4\(H\)-pyrrolo[3,2,1-\(ij\)]quinolin-4-ones inhibited farnesyl protein transferase. These compounds are useful for the treatment of proliferative disorders, such as cancer.\(^{121}\)

Effects of 2-[2-(1-benzylpiperidin-4-yl)ethyl]-2,3-dihydro-9-methoxy-1\(H\)-pyrrolo[3,4-\(b\)]quinolin-1-one hemifumarate (T-82) on drug- and basal forebrain lesion-induced amnesia models were examined in rats. The results suggested that T-82 might ameliorate the impairment of memory induced by acetylcholinergic dysfunction.\(^{122}\) Denny \textit{et al.} disclosed the anti-cancer activity of certain less toxic 2,3-dihydro-1\(H\)-pyrrolo[3,2-\(f\)]quinolines and their complexes of cobalt and chromium.\(^{123}\) New pyrroloquinoline derivatives exhibited potent and selective growth inhibition activities in the NCI 60 human tumor cell line screen and could be suggested as potent small molecule drugs associated with
potential anticancer potency and therapeutic activities as either single, or as sensitizing agents to conventional radio- or chemotherapeutic strategies.\textsuperscript{124} Pyrrolo[2,3-\textit{b}]quinoline derivatives had low cytotoxicity for human MCF-7 human breast carcinoma cells. These compounds in pharmaceutical compositions with chemotherapeutic agents (Taxol, Vincristine) prevented efflux of said agents resulting in greater efficacy.\textsuperscript{125} The preparation of pyrroloquinolines and related tricyclic compounds was performed and these new derivatives were found useful for the treatment of acne, male-pattern baldness, impotence, sexual dysfunction, wasting disease, hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, cancer cachexia, and hormone-dependent cancers.\textsuperscript{30} A series of pyrrolo[3,2-\textit{c}]quinoline derivatives were synthesized and evaluated as inhibitors of selected enzymes of the kynurenine pathway. 7-Chloro-3-methyl-1\textit{H}-pyrrolo[3,2-\textit{c}]quinoline-4-carboxylic acid was found to be a relatively potent and selective inhibitor of kynurenine-3-hydroxylase (KYN-3-OHase). A molecular modeling study showed a good superimposition of I with PNU-156561 and kynurenine the natural substrate of KYN-3-OHase.\textsuperscript{126} Some \textit{N}-{4-[(3\textit{H}-pyrrolo[3,2-\textit{f}]quinolin-1-ylmethyl)amino]phenyl}methanesulfonamides had been synthesized and tested as antiproliferative agents. These compounds showed activity against a panel of liquid and solid tumor-derived cell lines (the \textit{in vitro} primary antitumor screen), in particular leukemias, with a mechanism different from that exhibited by amsacrine. Although the compounds were able to stimulate topoisomerase poisoning at high concentration, the cell growth inhibition properties did not appear to rest principally on this mechanism of action. Overall, the most active products proved to be the derivatives those having the \textit{m}-methoxy substituent typical of amsacrine, followed by the 7-methyl derivative and by the unsubstituted derivative. Comparison with previously investigated regioisomers shows modulation of activity dictated by the position and conformational freedom of side-chain groups.\textsuperscript{127} Also, the new compounds exhibited interesting cell growth inhibitory properties when tested against cell lines, in particular those obtained from solid tumors like CNS-, melanoma- and prostate-derived cells.\textsuperscript{128} Several pyrrolo[3,4-\textit{b}]quinolines were found as novel inhibitors for two members of the PI3-kinase related kinase (PIKK) family, Ataxia-Telangiectasia-mutated (ATM) protein and the mammalian Target of Rapamycin (mTOR). These compounds suggest novel leads for the discovery of potent small molecule inhibitors of PIKKs as potential anticancer drugs, with therapeutic activities as either single, or as sensitizing agents to conventional radio- or chemotherapeutic strategies.\textsuperscript{124}

4.2. \textit{Indoloquinolines}

Biological activity studies of 11\textit{H}-indolo[3,2-\textit{c}]quinoline derivatives revealed that several compounds were found to possess cytotoxic activity against the growth of human promyelocytic leukemia cells (HL-60) and against the small cell lung cancer.\textsuperscript{129} The bis(dimethylaminoethyl) derivative of quindoline
(10H-indolo[3,2-b]quinoline), an alkaloid from the West African shrub *Cryptolepis sanguinolenta*, was synthesized. This has been shown to have modest cytotoxicity, as well as inhibitory activity against the telomerase enzyme.\textsuperscript{130} A number of 2-substituted indoloquinolines had been synthesized and evaluated in antifungal screens and several had been shown to increase potency and expand the antifungal spectrum of cryptolepine. Comparison of MICs of a number of these analogues with standard antifungal agents showed them to be comparable to Amphotericin B and Ketoconazole. Substitution at the 2-position of the 5-alkylated quinoline \{indolo[3,2-b]quinoline\} ring had resulted in more potent and broader spectrum of antifungal activity.\textsuperscript{131}

4.3. Furoquinolines and Benzofuroquinolines

4-Anilinofuro[2,3-b]quinoline derivatives have potent antitumor activity.\textsuperscript{132} 4-Phenoxyfuro[2,3-b]quinoline derivatives exhibited potent anti-inflammatory activities.\textsuperscript{133} The neuroprotective effects of 2-(2-oxypyrrolidin-1-yl)-N-(2,3-dimethyl-5,6,7,8-tetrahydrofuro[2,3-b]quinolin-4-yl)acetamide against retinal injury were observed.\textsuperscript{134} 1,3,4,5,6,7,8,9-Octahydro-7,7-dimethyl-9-aryl[3,4-b]quinoline-1,8-dione derivatives were studied as calcium antagonists and showed high tissue selectivity compared with nicardipine.\textsuperscript{135} The design, synthesis and biological evaluation of new seco-cyclopropyltetrahydrofurano[2,3-f]quinoline (seco-CFQ) analogues of the duocarmycins were described. Secco-CFQ compounds were shown to preferentially alkylate the adenine-N3 position within the minor groove of long stretches of A-residues. The cytotoxicity of cyclopropyltetrahydrofuro[2,3-f]quinolines was determined against the growth of murine leukemia (L1210), mastocytoma (P815) and melanoma (B16) cell lines. The concentrations of compounds required to inhibit the growth of these tumor cells by 50% is in the range of \(10^{-8}\) M. These compounds were also tested against a panel of human cancer, demonstrating that the compounds exhibited a high level of activity against selected solid tumors. Secco-cyclopropyltetrahydrofuro[2,3-f]quinoline was significantly of low toxicity. Flow cytometric analysis of P815 cells that had been incubated for 24 h with secco-cyclopropyltetrahydrofuro[2,3-f]quinoline at its cytotoxic IC\textsubscript{50} concentration indicated the induction of apoptosis in a large percentage of cells.\textsuperscript{136}

4.4. Thienoquinolines and Benzothienoquinolines

It was found that a series of 4-amino-5,6,7,8-tetrahydro-2,3-diphenylthieno[2,3-b]quinolines and their furo[2,3-b]quinolines analogues strongly inhibited acetylcholinesterase, and showed excellent selectivity regarding butyrylcholinesterase.\textsuperscript{137} Some new pyrrolylthieno[2,3-b]quinoline derivatives exhibited antibacterial and antifungal activities.\textsuperscript{99} The anticancer efficacy against B16 melanoma, has provided evidence of major antitumour activity for 8-methyl-4-[3-diethylaminopropylamino]pyrimido[4′,5′:4,5]-
thieno[2,3-b]quinoline. Single or multiple intraperitoneal doses of drug proved high level activity against the subcutaneous grafted B16 melanoma, significantly increasing survival ($p<0.001$) and inhibiting tumor growth ($T/C$ of 4%).\textsuperscript{138} The antiproliferative activity of all the newly synthesized thienoquinolines was evaluated and compared to 8-methoxypsoralen (8-MOP), the drug widely used in PUVA-therapy. The 3-unsubstituted thienoquinolinones were generally the most potent derivatives, followed by the furo-analogues. In particular, the unsubstituted thieno[2,3-h]quinoline-2(1H)-one showed the highest activity in T2 bacteriophage, HeLa cells and Ehrlich cells tests. All the compounds, assayed on Escherichia coli WP2 TM9, showed a similar mutagenic activity, very close to that of 8-MOP. 2-Oxo-1,2-dihydrothieno[2,3-h]quinoline-3-carboxylic acid appeared to be very effective. The N-methyl analogues only induced moderate skin erythemas on albino guinea pigs. On the basis of these results, the unsubstituted thieno[2,3-h]quinoline-2(1H)-one seems to be the most interesting potential drug for PUVA photochemotherapy and photopheresis.\textsuperscript{93} Recently, Seck and Kirsch reported the synthesis of new 4-amino-5,6,7,8-tetrahydrothieno[3,2-b] and new 4-amino-5,6,7,8-tetrahydrothieno[2,3-b]quinolin-4-ols as pharmacomodulation of 5-amino-4-hydroxy-1,2,3,4-tetrahydroacridine (Velnacrine) which is the first drug authorized has the less hepatotoxic for Alzheimer’s disease therapy.\textsuperscript{139} Evaluation of new substituted [1]benzothieno[3,2-b]quinoline-4-carboxamides for cytotoxicity in a panel of cell lines showed that small lipophilic substituents in the non-carboxamide ring, in a pseudo-peri position to the side chain, significantly increased cytotoxic potency while retaining a pattern of cytotoxicity consistent with a non-topo II mode of action.\textsuperscript{140} The results presented that association of 8-methoxypyrimido[4′,5′:4,5]- thieno[2,3-b]quinolin-4(3H)one (MPTQ) with DNA can be explained by a mechanism of intercalation, which probably accounts for its reported antitumour activity. In many ways MPTQ behaved as an ideal intercalating agent on binding to DNA hydrodynamic changes consistent with extension and unwinding of the DNA helix were clearly seen. Binding to DNA showed some dependence on the nucleotide content and/or sequence, as evidenced by the increase in the association constant for M. lysodeikticus DNA, which has a higher GC content than calf thymus DNA.\textsuperscript{141}

5. Conclusions
The survey of literature about the recent advances in synthesis of azoloquinolines revealed that:

1. Different types of pyrroloquinolines can be obtained via Claisen rearrangements and on wide range application of sigmatropic rearrangement afforded several important azoloquinolines.

2. Fischer indolation of the arylhydrazinoquinolines and its analogous cyclization of ortho-arylazido-quinolines lead to formation of many naturally known and/or novel indoloquinolines.

3. Applications of Heck cyclization and palladium catalyzed alkenylation and arylation give interesting intermediates, which can be cyclized in tandem fashion leading to fused polyheterocyclic systems.
Oxyquinolines are good synthones for the preparation of furoquinolines.

4. Most of the reported thienoquinolines are limited to those thiophene rings fused at the face \([b]\) or \([c]\) of quinoline. Little derivatives of other fused types are observed, indicating that the chemistry of thienoquinolines, especially that is dealing with benzo-annelated thienoquinolines, is still of need to be explored.

5. Biological applications of the different azoloquinolines show their significant uses and the importance to increase the research work in this field.

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