2-Chloroquinoline-3-carbaldehydes: synthesis, reactions and applications

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Abstract
This review summarizes the synthetic methods, reactions and biological applications of 2-chloroquinoline-3-carbaldehydes during the period from 1999 to 2011. The reactions are subdivided in groups that cover reactions at the chloro or aldehyde substituent and reactions which involve both groups. Most reaction types have been successfully applied and used in the production of biological active compounds.

Keywords: Vilsmeier-Haack reaction, quinolines, aldehydes

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1. Introduction

Interesting pharmacological properties have been associated with 2-chloroquinoline-3-carbaldehydes and their derivatives.\(^1\)\(^2\) These compounds have shown antimicrobial,\(^1\)\(^2\)\(^3\) antimalarial,\(^4\)\(^5\) anti-inflammatory,\(^6\)\(^7\)\(^8\)\(^9\) antitumor,\(^10\)\(^11\) and anti-parasitic activity.\(^12\) Despite this versatile importance, and in connection to our previous review articles about biologically active heterocyclic systems,\(^13\) 2-chloroquinoline-3-carbaldehydes have not been previously reviewed. The main objective of the present survey is to provide the synthesis, reactions, and biological applications of 2-chloroquinoline-3-carbaldehydes from 1999 to the end of 2011 and provide useful and up-to-date data for organic and medicinal chemists.

2. Synthetic Methods

There have been a number of practically important routes to synthesise of 2-chloroquinoline-3-carbaldehydes, e.g. (i) Vilsmeier-Haack reaction of acetanilides, (ii) oxidation of the corresponding alcohols.

2.1. Vilsmeier-Haack reaction

2-Chloroquinoline-3-carbaldehydes 2 were synthesized from acetanilides 1 via a Vilsmeier-Haack reaction either by traditional methods\(^14\)\(^-\)\(^23\) or by microwave,\(^24\) or ultrasonic irradiation (Scheme 1).\(^25\)

\[
\text{Me}\quad \text{N} \quad \text{CHO} \quad \text{Cl} \\
\text{1} \quad \text{POCl}_3/\text{DMF}, \; 0 \; ^\circ \text{C} \quad \text{R} = \text{alkyl, alkoxy, halo} \\
i \quad \text{80-90} \; ^\circ \text{C}, \; 5 \; \text{h} \quad \text{or MWI} \\
\text{2}
\]

Scheme 1
2.2. Oxidation of the corresponding alcohols

(2-Chloroquinolin-3-yl)methanol 3 was oxidized to aldehyde 2 using a combination of diethyl diazene-1,2-dicarboxylate (DEAD) and catalytic ZnBr₂ in refluxing toluene (Scheme 2).²⁶

\[
\text{CH}_2\text{OH} \quad \text{EtO}_2\text{C}^{-} \quad \text{N}^- \quad \text{CO}_2\text{Et} \quad \text{ZnBr}_2, \text{PhMe, reflux, 2 h} \quad \text{CHO} 
\]

86%

Scheme 2

3 Chemical Reactions

3.1. Substitution reactions

Treatment of 2-chloroquinoline-3-carbaldehydes 2 with prenyl thiolate or prenyl alcohoilate 4 in the presence of sodium hydroxide or potassium t-butoxide, furnished S/O-prenyl aldehydes 5 in 72-84% yield, respectively. S/O-prenyl aldehyde 5, underwent imino Diels-Alder reactions with various substituted anilines in the presence of InCl₃ in acetonitrile resulting in the formation mixture of cis and trans products 7 and 8 in 55-71% yields by intramolecular cycloaddition reaction of the imine 6 generated in situ in the one pot-reaction (Scheme 3).¹⁴

\[
\begin{align*}
\text{R} & \quad \text{CHO} \\
\text{Cl} & \quad + \quad \text{NaX} \\
\text{EtOH} & \quad \text{reflux} \\
\text{R} & \quad \text{CHO} \\
\text{5} & \quad \text{X} \\
\text{R} & \quad \text{X} \\
\text{6} & \quad \text{X} \\
\end{align*}
\]

\[
\text{R} = \text{H}; \text{R}₁ = \text{H, Me, OMe, Cl, Br, NO₂; X = O, S}
\]

Scheme 3

Knoevenagel hetero Diels-Alder reaction of 5 (X = O) with N,N'-dimethylbarbituric acid in water was carried out in the presence of piperidine at room temperature. The intermediate
Knoevenagel adduct 9 was not isolated and allowed to cyclise at room temperature after 3 h stirring gave the *cis*-fused pentacyclic pyrano[2,3-*b*]quinoline derivatives 10 with high yield (80%) and diastereoselectivity (> 99%) (Scheme 4).27

**Scheme 4**

Recently, tetrahydrocyclopenta[c]acridines 14 were synthesized from reaction of substituted aldehyde 2 with alkyne 11 in DMF in the presence of Et₃N to afford alkynyl quinolines 12 which were reacted with allyl magnesium bromide followed by Pauson-Khand cyclization using Co₂(CO)₈ (Scheme 5). The synthesized compounds were used as kinase inhibitors in particular for treating cancer.11,12

**Scheme 5**
Similarly, a convenient and one-pot synthesis of 1-methoxy-3-phenyl-1H-pyrano[4,3-b]-quinoline 15 from reaction of aldehyde 2 with phenyl acetylene 11 (R₆ = Ph) in acetonitrile in the presence of Pd(OAc)₂ and triphenylphosphine was reported (Scheme 6).²⁸

![Scheme 6]

Reaction of aldehydes 2 with phenylacetylene 11 (R₆ = Ph) was carried out in the presence of PdCl₂, triphenylphosphine, and triethylamine in acetonitrile at 80 °C under an inert atmosphere to give 2-(phenylethynyl)quinoline-3-carbaldehydes 16 in 87% yield.²⁹-³¹ The later compounds were reacted with aqueous ammonia to afford 3-phenylbenzo[b][1,6]naphthyridine 17 in 88% yield (Scheme 7).³¹

![Scheme 7]

Reaction of one equivalent of S-(-)-BINOL with 2.1 equivalent of aldehyde 2 in DMF in the presence of K₂CO₃ gave the dialdehyde 18, which was reduced to diol 19 using NaBH₄ in methanol, followed by reaction with phosphorus tribromide (PBr₃) to give the dibromide 20 in 71% yield. Reaction of the dibromide 21 with 2.1 equivalent of benzimidazole in acetonitrile in the presence of aqueous NaOH for 2 days afforded the precyclophane 21 in 69% yields. Coupling of the precyclophane with one equivalent of 2,6-bis(bromomethyl)pyridine under reflux and under high dilution conditions for 5 days gave the quinolinophane 22 in 67% yield (Scheme 8).³²
3-(Quinolin-3-ylmethyl)quinazolin-4(3H)-one 27 (79%) was synthesized via reaction of 3-(bromomethyl)quinoline 25 with quinazolin-4(3H)-one 26 in DMF in the presence of NaH under ultrasound irradiation. 3-(Bromomethyl)quinoline 25 (77%) was prepared by reduction of aldehyde 23, which resulted from reaction of aldehyde 2 with p-cresol in DMF in the presence of K₂CO₃, in methanol in the presence of NaBH₄ followed by treated with PBr₃ in dichloromethane under ice cold condition (Scheme 9). The synthesized compound was screened in vitro for antimicrobial activity.⁴₃
The reaction of aldehyde 2 with ethanol in the presence of KOH, afforded 2-ethoxy-3-formylquinoline 28 which was reduced with NaBH₄ in methanol to give the alcohol which on further reaction with PPh₃ and I₂ in the presence of imidazole in dry CH₂Cl₂ gave 2-ethoxy-3-(iodomethyl)quinoline 29 in good yield. The later compound when reacted with sodium azide in DMF at 60 °C 3-(azidomethyl)-2-ethoxyquinoline 30 was obtained. Quinoline azide 30 was reacted with bis(propargyloxy)-(S)-BINOL 31 in the presence of CuSO₄·5H₂O and sodium ascorbate in a mixture of water and THF (1:3) at room temperature to give the bis-triazole chiral dendrimer 32 in excellent yield (Scheme 10). ⁴
Aldehyde 2 was treated with allyl alcohol in the presence of sodium hydroxide under phase transfer catalytic conditions to give allyl ether 33. Oxime 34 was prepared from reaction of allyl ether with hydroxylamine hydrochloride in the presence of aqueous sodium hydroxide. Compound 34 on treatment with NaOCl in the presence of Et₃N at 0-20 °C afforded dihydro-3H-[1,2]oxazolo[3',4':4,5]pyran[2,3-b]quinoline 36 in excellent yields via 1,3-dipolar cycloaddition of the nitrile oxides (Scheme 11).

Scheme 11

3-Formyl-2-mercaptoquinolines 37 were synthesized in good yields by one-pot reaction of aldehyde 2 with sodium sulfide and hydrochloric acid in hot ethanol. Isothiazolo[5,4-b]-quinolines 38 were obtained by reaction between 37 and hydroxylamine followed by cyclization with Ac₂O. Subsequently, compound 38 was oxidized with H₂O₂ in acetic acid to give 2H-isothiazolo[5,4-b]quinoline 1,1-dioxides 39 (Scheme 12).

Scheme 12
2-hydroselenoquinoline-3-carbaldehydes 40 were synthesized in a quantitative yield by reaction of aldehydes 2 with sodium hydrogen selenide in ethanol. 2-hydroselenoquinoline-3-carbaldehydes 40 were reacted with aniline in glacial acetic acid to give 3-[(phenylimino)methyl]quinoline-2-selenol 41. Subsequently, the later compound was refluxed with a stoichiometric and nonstoichiometric amount of chloroacetyl chloride in DMF to afford the corresponding 3-[(phenylimino)methyl]quinolin-2-yl chloroethaneselenates 42 and [3-(3-chloro-4-oxo-1-phenylazetidin-2-yl)quinolin-2-yl] chloroethaneselenates 43, respectively (Scheme 13).39

Selenopheno[2,3-b]quinoline-2-carboxamide 44 and phenyl(selenopheno[2,3-b]quinolin-2-yl)methanone 45 were prepared in good yields by treating 2-(hydroseleno)quinoline-3-carbaldehyde with 2-chloroacetamide and phenacyl bromide, respectively under solvent free microwave irradiation in one pot reaction (Scheme 14).40

Scheme 13
Scheme 14

2-(Naphthalen-2-ylthio)quinoline-3-carbaldehyde 47 was prepared from reaction between aldehyde 2 and naphthalene-2-thiol 46 in K₂CO₃/DMF (Scheme 15).⁴¹

Scheme 15

2-(5-Aryl-4H-1,2,4-triazol-3-ylthio)quinoline-3-carbaldehydes 49 were prepared by reaction of aldehyde 2 with 5-aryl-4H-1,2,4-triazole-3-thiol 48 in refluxing ethanol in the presence of pyridine. The later compound on reaction with substituted acetophenone gave 1-aryl-2-(2-aryl-9H-[1,2,4]triazolo[3,2-b][1,3]thiazino[6,5-b]quinolin-9-yl)ethanones 50 (Scheme 16).⁴²
It has been reported that the amination of aldehyde 2 occurs either by microwave-enhanced reaction using ammonium acetate as constituent synthons using tetrabutyl ammonium bromide (TBAB) as a catalyst, or by using dry ammonia gas in ethanol, to obtain 2-amino-3-quinolinecarbaldehyde 51, which was condensed with cyclopentanone in the presence of acetic and sulfuric acids to give 2,3-dihydro-1H-benzo[g]cyclopenta[b][1,8]naphthyridine 52 (Scheme 17).

Aldehyde 2 was converted into 2-oxoquinoline-3-carbaldehyde 53 when refluxed in 70% acetic acid, followed by reaction with substituted hydrazides, to afford the corresponding aroyl hydrazone 54 (Scheme 18).
The synthesis of 2-azidoquinoline-3-carbaldehydes 55 from reaction of aldehydes 2 with sodium azide in DMSO or DMF is reported, and their ring-chain tautomerism discussed (Scheme 19). The 3-formyl-2-(3-hydroxy-1,4-naphthoquinon-2-yl)-quinoline 57 was synthesized by reaction of aldehydes 2 with 2-hydroxy-1,4-naphthoquinone 56 in basic alumina using microwave irradiation (MWI) (Scheme 20). The synthesized compound showed promising antibacterial activity.
3.2. Addition reactions at the aldehyde group

2-Chloroquinoline-3-carbaldehyde 2 was reacted with ethyl lithiodiazoacetate 58 in THF to afford ethyl 3-(2-chloroquinolin-3-yl)-2-diazo-3-hydroxypropanoate 59 in 97% yields followed by mild oxidation with the Dess–Martin periodinane 60 to give ethyl 3-(2-chloroquinolin-3-yl)-2-diazo-3-oxopropanoate (Scheme 21). 50

\[
\begin{align*}
\text{N} & \backslash \text{Cl} \quad & \text{CHO} & \text{Li} & \text{N}_2 & \text{CO}_2\text{Et} \\
2 & & & 58 & \text{THF} & -78^\circ\text{C} \\
& & & & \xrightarrow{\text{DMP}} & \text{CH}_2\text{Cl}_2, \text{rt} \\
& & & & & \text{60, 92%}
\end{align*}
\]

Scheme 21

Epoxy ester 63 and β-hydroxy ester 62 were prepared in moderate yields from reaction of aldehyde 2 with ethyl 2-bromoacetate 61 according to Darzens condensation reaction (Scheme 22). 51

\[
\begin{align*}
\text{N} & \backslash \text{Cl} \quad & \text{CHO} & \text{Br} & \text{CO}_2\text{Et} \\
2 & & & 61 & \xrightarrow{\text{a}} & \text{62} & \text{63, 32%}
\end{align*}
\]

a) t-BuOK, DMSO, 15 - 20 °C, 1 h; rt, 24 h; pentane, aq.NH₄Cl

Scheme 22

Morita-Baylis-Hillman reaction of aldehyde 2 with methyl or ethyl acrylate and acrylonitrile 64 under ultrasonic irradiation to provide the corresponding MBH adducts 65 in good yield. The later adducts were reacted with tert-butyldimethylsilyl triflate (TBSOTf) or with acetyl chloride to give silylated 66, 52 or acetated 67, 53 Morita-Baylis-Hillman adducts, respectively in good yield (Scheme 23).
Scheme 23

Ethyl 2-[(2-chloroquinolin-3-yl)(hydroxy)methyl]acrylate 65 was treated with tris(dibenzylideneacetone)dipalladium(0) [Pd$_2$(dba)$_3$] and carbon monoxide to give quinoline-phthalide 68 as major product and tetrasubstituted olefin 69 as minor product (Scheme 24). The phthalide 68 showed a potent effect on the proliferation of human tumor cell lines.$^{54,55}$

Scheme 24
The reaction of ethyl aminocrotonate 70a or 3,3-diaminoacrylate 70b with aldehyde 2 in DMF at room temperature gave diethyl 4-(2-chloroquinolin-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate 71a,b and ethyl 2-amino-5-chlorobenzo[hl][1,6]naphthyridine-3-carboxylate 72 via intermediates A and B, respectively (Scheme 25).

![Scheme 25](image)

The Wittig reaction of cholesteryl triphenylphosphonioacetate chloride 73a with aldehyde 2 in ethanol in the presence of Et₃N gave the cholesteryl 3-(2-chloroquinolin-3-yl)acrylate 74 (Scheme 26).

![Scheme 26](image)

Condensation of aldehyde 2 with stabilized phosphonium ylides 73b,c in refluxing 1,2-dimethoxyethane (DME) gave the corresponding (E)-quinolyl α,β-unsaturated esters 75 with high stereoselectivity in good yields. 1,3-Dipolar cycloaddition of azomethine ylides, generated in situ from sarcosine and paraformaldehyde, to α,β-unsaturated esters 75, gave pyrrolidine...
derivatives 76A followed by oxidation to pyrrole 76B with activated MnO$_2$ in refluxing THF (Scheme 27).$^{58}$

$$\begin{align*}
\text{CHO} & \quad + \quad \text{Ph$_3$P=CHCO$_2$R} \\
\text{R}^2 \quad \text{R}^1 \quad \text{R}^3 \quad \text{R}^4 \quad \text{Cl} & \quad \text{DME, reflux, 4-5 h} \\
\text{73B, } R = \text{Me} & \quad \text{75a,b} \\
\text{c, } R = \text{Et} & \\
\text{76A} & \\
\text{76B} \\
\end{align*}$$

(a) R$^1$= R$^2$ = R$^3$ = R$^4$ = H; (b) R$^1$ = Me, R$^2$ = H, R$^3$ = Me, R$^4$ = H; (c) R$^1$ = Me, R$^2$ = R$^3$ = R$^4$ = H; (d) R$^1$ = Me, R$^2$ = H, R$^3$ = Me, R$^4$ = H; (e) R$^1$ = Me, R$^2$ = R$^3$ = H, R$^4$ = Me; (f) R$^1$ = R$^2$ = H, R$^3$ = OMe, R$^4$ = H; (g) R$^1$ = R$^2$ = H, R$^3$ = Me, R$^4$ = H; (h) R$^1$ = H, R$^2$, R$^3$ = OCH$_2$O, R$^4$ = H

**Scheme 27**

The Abramov reaction between aldehyde 2 and triethyl phosphite, to synthesize α-hydroxyphosphonate 77, was performed either by traditional or ultrasound irradiation using several catalyst such as chlorotrimethylsilane at room temperature$^{59}$ (yield: 96%) as well as at reflux temperature (yield 77-83%),$^2$ ammonium metavanadate (NH$_4$VO$_3$) at room temperature (yield 94%),$^{60}$ potassium dihydrogen phosphate (KH$_2$PO$_4$) (yield 90%),$^{61}$ or sulfamic acid (NH$_2$SO$_3$H) under ultrasound irradiation (yield 88%).$^{62}$ Treatment α-hydroxyphosphonate 77 with acetic anhydride in the presence of DBU catalyst afford α-acetyloxyphosphonates 78 (yield 95%) (Scheme 28). α-Hydroxy 77 as well as α-acetyloxyphosphonate 78 were screened for antibacterial.

$$\begin{align*}
\text{CHO} & \quad \text{P(OEt)$_3$} \\
\text{2} & \quad \text{77} \\
\text{OH} & \quad \text{Ac$_2$O} \\
\text{DBU, rt} & \quad \text{78} \\
\text{DBU = 1,8-Diazabicyclo-undec-7-ene} & \\
\end{align*}$$

**Scheme 28**
The formation of tetrazoloquinoline-3-ylmethyl α-alkoxy-79 and α-hydroxy-phosphonates80 from reaction of 2-azidoquinoline-3-carbaldehydes55 with trialkyl phosphites and dialkyl hydrogenphosphonates, respectively was recently reported (Scheme 29). The anti-inflammatory activity of the prepared compounds were determined in vivo by their effect on the acute carrageenin-induced paw edema in rats.9

Scheme 29

A three-component reaction of aldehyde 2, amine, and triethyl phosphite was carried out under solvent-free conditions in the presence of either alum [KAl(SO₄)₂·12H₂O]63 or yttria-zirconia as a catalyst64 to afford the corresponding α-aminophosphonate 81 in 94% or 75%, respectively (Scheme 30).

Scheme 30

Synthesis of 3-[bis(2-phenyl-1H-indol-3-yl)methyl]-2-chloroquinoline 83 by a sequential approach involving gold(I) chloride catalyzed cycloisomerization/bis-addition and conjugate addition of 2-(phenylethynyl)aniline 82 to aldehyde 2 has been reported (Scheme 31).65,66
Allylation of 2-oxoquinoline-3-carbaldehyde 53 to give 3-homoallyl-2-quinolones 84 in excellent yields (89–94%) was achieved by reaction with in situ generated allylindium bromide in aqueous DMF at room temperature. Intramolecular electrophilic cyclization of 84 with I₂ in THF in the presence of sodium bicarbonate at room temperature gave 88% yield of a mixture of 4-hydroxy-2-iodomethylpyrano[2,3-b]quinolines 85/86, exclusively, or predominantly, racemic cis-diastereoisomers 85 (Scheme 32).

The reaction of aldehydes 2 with allyl bromide in the presence of indium powder yielded 2-chloro-3-(1-hydroxybut-3-en-1-yl)quinolines 88 in good yield, followed by Pd(0)-catalyzed intramolecular cyclization to afford 3-methylene-2,3-dihydro-1H-cyclopenta[b]quinolin-1-ols 89 (Scheme 33).
3.3. Reduction of the aldehyde group

2-Chloroquinoline-3-carbaldehydes 2 were reduced with sodium borohydride NaBH₄ to (2-chloroquinolin-3-yl)methanol 92 either by using microwave irradiation,⁶⁹-⁷² or at room temperature.⁷³-⁷⁶ Subsequently, compound 92 was converted into iodomethyl quinoline 93 through PPh₃ and imidazole with iodine. Further, azidomethylquinoline 94 was obtained by treating 93 with NaN₃ in the presence of DMF. Azidomethylquinoline 94 was subjected to catalytic hydrogenation at room temperature using 10% Pd/C for 2 h to afford quinoline isothiocyanate 95, which was coupled with substituted amino acid in the presence of N-methyl morpholine in dry CH₂Cl₂ to give quinolinepeptidylthiourea esters 96 (Scheme 34).⁷⁵

2-Chloroquinolin-3-ylmethanols 92 were converted into O,O-diethyl O-(2-chloroquinolin-3-yl)-methyl phosphorothioates 98 by treatment with O,O-diethyl phosphorochloridothioate 97 in acetone in the presence of sodium hydroxide (Scheme 35).⁷⁶

Synthesis of 4-[[5-(difluoromethyloxy)-1H-benzimidazol-2-ylthio]methyl]tetrazolo[1,5-α]-quinolines 102 was reported from substituted aldehydes 55 via reduction to the corresponding alcohols 99, followed by conversion into chlorides 100 with thionyl chloride, and finally coupling with 5-(difluoromethyloxy)-1H-benzimidazole-2-thiol 101 (Scheme 36). The synthesized compounds were screened for the antibacterial activity against gram positive and gram negative bacteria.⁴⁷
Scheme 34

Scheme 35

Scheme 36
3.4. Condensation Reactions

3.4.1 Reactions with active methylene compounds. Perkin–type condensation of aldehyde 55 with tetraethyl methylenebisphosphonate 103 provided the corresponding tetrazoloquinoline-based bisphosphonate esters 104 (Scheme 37).\(^9\)

\[
\begin{align*}
&\text{R}^1 \text{C} = \text{O} \\
&\text{55, R}^1 = \text{H, Me} \\
&\text{O} \\
&\text{P(}\text{OEt\text{)2}} \\
&\text{103} \\
&\text{Na/EtOH, rt} \\
&\text{R}^1 \text{C} = \text{O} \\
&\text{P(}\text{OEt\text{)2}} \\
&\text{104}
\end{align*}
\]

Scheme 37

\((E)\)-Ethyl 3-(2-chloroquinolin-3-yl)acrylate 106 was synthesized by aldol and elimination reactions of aldehyde 2 with ethyl trifluoroacetoacetate 105 under basic conditions with high stereoselectivity (Scheme 38).\(^77\)

\[
\begin{align*}
&\text{C} = \text{O} \\
&\text{2} \\
&\text{F_3C} \text{C} = \text{O} \\
&\text{105} \\
&\text{piperidine} \\
&\text{CH}_2\text{Cl}_2, 40 \degree\text{C} \\
&\text{C} = \text{O} \\
&\text{106, 85}\%
\end{align*}
\]

Scheme 38

Multi-component reaction of aldehyde 2, \(p\)-bromophenol 108, 2-benzothiazolethiol 107, and malononitrile was carried out under microwave irradiated in aq. \(\text{K}_2\text{CO}_3\) to synthesize 2-amino-6-(benzothiazol-2-ylthio)-4-(2-chloroquinolin-3-yl)-4\(H\)-chromene-3-carbonitrile 110 (Scheme 39). The synthesized compound was screened for their antibacterial activities against gram positive and gram negative pathogenic strains of bacteria.\(^78\)
Scheme 39

Claisen-Schmidt condensation of aldehydes 2 either with 3-(trifluoromethyl)-1H-pyrazol-5(4H)-ones 111 in refluxing acetic acid or 5,7-dimethoxy-1-indanone 112 in methanolic sodium hydroxide at room temperature, afforded \((E)\)-4-((2-chloroquinolin-3-yl)methylene)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-ones 113\(^7\) and \((E)\)-2-((2-chloroquinolin-3-yl)methylene)-5,7-dimethoxy-2,3-dihydro-1H-inden-1-ones 114\(^8\) in good yields, respectively (Scheme 40). The latter compounds were evaluated in vitro for inhibition of \(\beta\)-hematin formation and hemoglobin hydrolysis and in vivo for efficacy against \textit{Plasmodium berghei} suggest the antimalarial activity is derived from inhibition of hemoglobinolytic proteases.\(^8\)

Scheme 40

\[
\begin{align*}
\text{R} = \text{H, 6-Me; 7-Me; 8-Me; 5,8-Me; 6-OMe; 7-OMe; 6,7-OMe; 5,6,7- OMe; 6-Br}
\end{align*}
\]
Condensations of aldehydes 2 or 55 with aryl (heterocycles) methyl ketones either by using microwaves under solvent-free conditions or by using conventional methods, to give quinoline chalcones 116 was reported.\textsuperscript{10-18,81-88} Michael addition of tetraethyl methylenebisphosphonate to compounds 116 (R = Cl, N\textsubscript{3}, R\textsubscript{1} = Ph, thienyl, furyl, pyrryl) in EtOH/EtONa at refluxing temperature gave bisphosphonate adduct 117 (Scheme 41).\textsuperscript{10}

![Scheme 41](image)

Aldehydes 2 were treated with chromanones 118 in ethanol in the presence of sodium methoxide gave chalcones 119. The later compounds were reacted either with o-aminothiophenol in the presence of catalytic quantity of acetic acid to afford benzothiazepine system flanked by quinoline and chromanone moieties 120 or with ammonium acetate in acetic acid at reflux to give the amino chalcone 121 (Scheme 42).\textsuperscript{22}

6-Amino-4-(2-chloroquinolin-3-yl)-3-methyl-1-phenyl-1,4-dihydropyran[2,3-c]pyrazole-5-carbonitriles 124 were prepared by reaction between aldehyde 2 and 3-methyl-1-phenyl-1\textsubscript{H}-pyrazol-5(4\textsubscript{H})-one 122 to afford 4-((2-chloroquinolin-3-yl)methylene)-3-methyl-1-phenyl-1\textsubscript{H}-pyrazol-5(4\textsubscript{H})-ones 123 followed by cyclocondensation with malononitrile (Scheme 43). All the synthesized compounds have shown significant antimicrobial activity.\textsuperscript{89,90}
Synthesis of 3-phenyl-2\(H\)-pyrano[2,3-\(b\)]quinolin-2-one 125 by the Perkin type reaction of aldehyde 2 with sodium 2-phenylacetate was reported (Scheme 44).\(^9\)

\[
\begin{align*}
2 & \quad + \quad \text{PhCH}_2\text{CO}_2\text{Na} \\
\phantom{2} & \quad \rightarrow \\
\end{align*}
\]

R = H, 6-Me, 7-Me, 6-MeO

Scheme 43

Scheme 44
Condensation of aldehyde 2 with nitroalkane 126 at room temperature in the presence of benzyltrimethylammonium hydroxide to give 2-chloro-3-(2-nitroalk-1-enyl)quinoline 127 in good yield (Scheme 45).\(^92\)

\[
\begin{align*}
\text{N} & \text{C} \text{O} \\
\text{Cl} & \text{R} \\
2 & 126 \quad \text{BzN(Me)}_3\text{OH}^+ \\
\rightarrow & \\
\text{N} & \text{C} \text{O} \\
\text{Cl} & \text{R} \\
127 & \\
R = \text{H, Me, Et}
\end{align*}
\]

**Scheme 45**

Condensation reaction of 4-hydroxy-2-methylquinolines 128 with aldehyde 2 in the presence of acetic anhydride, acetic acid and sodium acetate afforded the corresponding 2-[2-(2-chloroquinolin-3-yl)ethenyl]quinolin-4(1H)-ones 129, which on cyclization using alcoholic KOH yields the quinacridine systems 130 in 72-83% yields (Scheme 46).\(^93\)

\[
\begin{align*}
\text{N} & \text{C} \text{O} \\
\text{Cl} & \text{R} \\
2 & 128 \quad \text{Ac}_2\text{O}, \text{HOAc}, \text{NaOAc} \\
\rightarrow & \\
\text{N} & \text{C} \text{O} \\
\text{Cl} & \text{R} \\
129 & , 82-95\%
\end{align*}
\]

**Scheme 46**

The pyrimidine derivatives 131 were synthesized by the cyclocondensation of \(\alpha,\beta\)-unsaturated ketones 116b, which were prepared from reaction of aldehyde 55 with substituted acetophenone in the presence of KOH, with thiourea (Scheme 47).\(^48\)
One-pot synthesis of 3-(2,6-diarylpyrid-4-yl)quinolin-2(1H)-ones 133 in high yield was reported by cyclocondensation reaction under Kröhnke's reaction conditions using aldehyde 2, aryl methyl ketone, and various N-phenacylpyridinium bromides 132 in a mixture of ammonium acetate and acetic acid under microwave irradiation (Scheme 48). The synthesized compounds were screened for their antimicrobial activities.94-95

The interaction of aldehydes 2 with either 1H-benzimidazol-2-ylacetonitrile 134a,96 or 2-(4-oxo-3,4-dihydroquinazolin-2-yl)acetonitriles 134b,97 in DMF in the presence of Et3N at reflux temperature, gave benzimidazo[1,2-a]benzo[g][1,8]naphthyridine-6-carbonitrile 135a and 15-oxo-15H-benzo[6,7][1,8]naphthyridino[2,1-b]quinazoline-6-carbonitrile 135b, respectively (Scheme 49).
Scheme 49

12-(2-Chloro-6-quinolin-3-yl)-2,3,4,12-tetrahydro-1H-benzothiazolo[2,3-b]quinazolin-1-one 138 was synthesized in one pot by condensing aldehyde 2, 2-amino-6-methoxybenzothiazole 136, and 5-dimethyl-1,3-cyclohexanedione 137a in ethanol (Scheme 50). 98

Scheme 50

Biginelli reaction of aldehyde 2 with urea or thiourea and active methylene compounds such as ethyl acetoacetate 139, 99 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one 140, 100 4-hydroxy-2H-chromen-2-one 141, 101 dimedone 137a, 102 or cyclohexane-1,3-dione 137b, 103 was performed by using either microwave irradiation, 99-101,103 or by traditional methods in the presence of yttria-zirconia-based Lewis acid, 104 silica-supported (HO)₃Si(CH₂)₃SO₃H, 105 silica-supported zinc chloride catalyst, 106 or hydrochloric acid, 102 to give 4-(2-chloro-3-quinolinyl)-2-oxo/thio-
pyrimidine 142-145 (Scheme 51). Compounds 143 and 145 were found to be active anticancer agents against lung, breast and CNS carcinomas, and were screened for their antimicrobial activities, respectively.

Scheme 51
Similarly, pyrimido[4,5-d]pyrimidine derivatives 147 were synthesized by reaction of aldehyde 2, barbituric acid 146 and urea/thiourea using either solid support of alumina\textsuperscript{107} or water\textsuperscript{108} under microwave irradiation (Scheme 52).

![Scheme 52](image)

Scheme 52

2'-Chloro-2,3'-biquinolin-4(1H)-ones 148 were obtained by one-pot microwave-mediated multicomponent reaction of aldehyde 2, aryl methyl ketone, and ammonium acetate using piperidine as a catalyst (Scheme 53). The antibacterial activity of the synthesized compounds were determined against gram-positive and gram-negative bacteria and their antifungal activity was determined\textsuperscript{109}.

![Scheme 53](image)

Scheme 53

Biquinoline adducts 151 were synthesized in high yields by cyclization of [(2-chloro-3-quinolyl)methylene]methane-1,1-dicarbonitrides 149, which was provided from reaction between aldehyde 2 and malononitrile, with 3-arylamino-5,5-dimethyl-cyclohex-2-en-1-ones 150 under microwave irradiation catalyzed by 4-(N,N-dimethylamino)pyridine (DMAP) (Scheme 54). The synthesized compound was screened for their antifungal and antibacterial activity\textsuperscript{110}.
Scheme 54

Synthesis of β-acetamido ketone 152 in high yields was described by one-pot three-component reaction of aldehyde 2, 4-bromoacetophenone and acetonitrile using cerium (IV) sulfate as a catalyst (Scheme 55).\(^{111}\)

Scheme 55

Condensation of chloromethylphenyl sulfone 153 with aldehyde 2 using solid sodium hydroxide as catalyst in methanol at room temperature to yield 2-chloro-3-(2-chloro-2-(phenylsulfonyl)vinyl)quinoline 154 was reported (Scheme 56). The later compound showed antimalarial activity against cultured *Plasmodium falciparum*, hemozoin formation, Hb hydrolysis, and murine malaria model.\(^{112}\)

Scheme 56
The 3-arylidenaeindolinone 156 was synthesized by refluxing 1-(2,6-dichlorophenyl)indolin-2-one 155 with aldehyde 2 in ethanol using piperidine as catalyst (Scheme 57). The synthesized compound was screened for their \textit{in vitro} cytotoxic activity on SW620 colon cancer cell lines.\textsuperscript{113}

\begin{center}
\includegraphics[width=\textwidth]{scheme_57}
\end{center}

\textbf{Scheme 57}

Condensation of aldehyde 2 with 4-hydrazonopentan-2-one 157 in the presence of alc. KOH led to 4-acetyl-3-methyl[1,2]diazepino[3,4-\textit{b}]quinoline 158 (Scheme 58). The later compound was screened for antimicrobial activity.\textsuperscript{114}

\begin{center}
\includegraphics[width=\textwidth]{scheme_58}
\end{center}

\textbf{Scheme 58}

A direct three component Mannich-type reaction of aldehyde 2, aniline, and acetophenone was efficiently catalyzed by an yttria-zirconia based strong Lewis acid in aqueous acetonitrile to give 3-(2-chloroquinolin-3-yl)-1-phenyl-3-(phenylamino)propan-1-one 159 (Scheme 59).\textsuperscript{115}

\begin{center}
\includegraphics[width=\textwidth]{scheme_59}
\end{center}

\textbf{Scheme 59}
The Knoevenagel condensation reaction of aldehyde 2 with ethyl cyanoacetate was carried out under ultrasonic irradiation catalyzed by 1,8-diazabicyclocundec-7-ene (DBU) at room temperature under solvent-free conditions to afford \((E)\)-ethyl 3-(2-chloroquinolin-3-yl)-2-cyanoacrylate 160 (Scheme 60).\(^{116}\)

![Scheme 60](image)

The reaction between aldehyde 2 and thioglycolic acid in refluxing ethanol containing sodium hydroxide and potassium iodide, afforded a mixture of \([(3\text{-formylquinolin-2-yl})\text{thio}]\text{acetic acids} 162\) and thieno[2,3-\(b\)]quinoline-2-carboxylic acids 161. The uncyclized compounds 162, on refluxing with POCl\(_3\) in various alcoholic media, gave \([(3\text{-formylquinolin-2-yl})\text{thio}]\text{acetates} 163\). Further cyclization was achieved by refluxing them with DMF to produce thieno[2,3-\(b\)]quinoline derivatives 164.\(^{117}\) On the other hand, thieno[2,3-\(b\)]quinoline-2-carboxylic acids and its alkyl esters 164 were synthesized by condensation of aldehyde 2 with thioglycolic acid/alkyl esters under microwave irradiation using anhydrous potassium carbonate (Scheme 61).\(^{118}\) The synthesized compounds showed moderate antimicrobial activity,\(^{118}\) and evaluated for their activity to inhibit \(\beta\)-hematin formation and Hb hydrolysis \textit{in vitro} and \textit{in vivo}.\(^{119}\)

![Scheme 61](image)
Reaction of 2,4,6-trichloropyrimidine 165 with sodium hydroxide to give 6-chlorouracil 166 in 71% yield. Next, 6-chlorouracil 166 was heated at melt temperature with the aniline followed by heating the resulting 6-N-aryl-aminouracil 167 with aldehyde 2 in DMF to afford 5-deazaflavin 168 (Scheme 62). The compound act as a low molecular weight inhibitor of the E3 activity of HMD2 in tumors that retain wild-type p53.

```
\begin{center}
\includegraphics[width=\textwidth]{scheme62}
\end{center}
```

Scheme 62

The three-component reaction of aldehyde 2, malononitrile, and either 4-hydroxycoumarin 141 or resorcinol was performed in aqueous K₂CO₃ under microwave irradiation to give 2-amino-4-(2-chloroquinolin-3-yl)-5-oxo-4,5-dihydropyran-3-carbonitrile 169 and 2-amino-4-(2-chloroquinolin-3-yl)-7-hydroxy-4H-chromene-3-carbonitrile 170 respectively, in excellent yields (Scheme 63). Compound 170 was shown to possess antibacterial activity as tested *in vitro* against strains of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.122
Scheme 63

A three-component one-pot condensation reaction of aldehyde 2, β-naphthol, and urea (thiourea) in the presence of montmorillonite K10 clay under solvent free conditions to afford 1-(2-chloroquinolin-3-yl)-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-one (thione) 171 in excellent yields (Scheme 64). \(^\text{123}\)

Scheme 64

Pyridine derivatives 172-174 were synthesized via Hantzsch reaction of aldehyde 2, barbituric acid \(^\text{146}\),\(^\text{124}\) or dimedone \(^\text{137a}\),\(^\text{97}\) and ammonium salts, either under microwave or under conventionally method using water as the solvent. Aromatization was observed when ammonium nitrate was used as the source of nitrogen (Scheme 65).
Knoevenagel reaction of aldehyde 2 with CH-acidic compounds, such as benzoyl acetonitrile 175 and 1-phenyl-2-(phenylsulfonyl)ethanone 176 in boiling methanol containing few drops of piperidine, afforded 4-(2-oxo-1,2-dihydroquinolin-3-yl)-2,6-diphenyl-4H-pyran-3,5-dicarbonitrile 179 and 3-(2-chloroquinolin-3-yl)-1-phenyl-2-(phenylsulfonyl)prop-2-en-1-one 180, respectively in good yield as the sole reaction products (Scheme 66). Similarly, aldehyde 2 was reacted with 1-indanone 177 in boiling ethanol containing few drops of piperidine, reportedly to afford 12,13-dihydroindeno[5,6]pyrano[2,3-b]quinoline 183, via intermediate 182. On the other hand, treatment of aldehyde 2 with 2-cyano-N'-((1-(furan-2-yl)ethylidene)acetohydrazide 178 in refluxed methanol containing piperidine, gave 3-(2-chloroquinolin-3-yl)-2-cyano-N'-((1-(furan-2-yl)ethylidene)acrylohydrazide 184 (Scheme 66).  

Scheme 65
3.4.2 Reactions with hydrazine, hydroxylamine, hydrazides, (thio)semicarbazide, and (thio)urea. 2-Chloroquinoline-3-carbaldehyde 2 reacted with hydroxylamine, hydrazine or aryl-hydrazine, urea, thiourea, either by traditional methods in acetic acid or by solvent-free microwave-induced techniques using PTSA as a catalyst, or potassium carbonate in DMF, to afford isoxazolo[5,4-b]quinoline 185, pyrazolo[3,4-b]quinolines 186, pyrimido[4,5-b]quinolin-2-ol 187a, and pyrimido[4,5-b]quinoline-2-thiol 187b, respectively in good to excellent yields (Scheme 67). The synthesized compounds have higher analgesic activity than
noramidopyrine (NAP),¹⁵ and they were evaluated for their antibacterial and antifungal activities, most of them showing activity against *Escherichia coli* and *Pseudomonas aeruginosa*.¹²⁶,¹²⁹

On the other hand, pyrazolo[3,4-b]quinolines 186 (R₁ = H, Ph) were obtained with better to excellent yield (91%), when one-pot condensation of aldehyde 2 and molar excess of hydrazine hydrate/phenyl hydrazine was carried in water for 7 h using thermal energy.⁴³,¹³⁰ The same condensation take place when the reaction is carried out in water under microwave irradiation (93%, 1.5 h) (Scheme 67).⁴³

![Scheme 67](image)

R = H, 6-Me, 7-Me, 8-Me, 6-OMe, 7-OMe, 8-OMe, 6-Br, 6-Cl, 7-Br, 7-Cl

R₁ = H, Ph, 2,4-NO₂C₆H₄, 4-MeC₆H₄SO₂

**Scheme 67**

One-pot synthesis of pyrimido[4,5-b]quinolines 189 were achieved from reaction of aldehydes 2 and guanidinium nitrate 188 (Scheme 68). All the synthesized compounds were biologically screened for their antibacterial activity.¹³¹

![Scheme 68](image)
One-step synthesis of 1-phenylpyrimido[4,5-b]quinoline-2(1H)-thiones 191a,132 or -ones 191b 90 were achieved from reaction of aldehydes 2 with N-phenylthiourea 190a or N-phenylurea 190b, respectively (Scheme 69). The synthesized compounds were biologically screened for their antibacterial and antifungal activities.

Scheme 69

Synthesis of pyrazolo[3,4-b]quinolines 193 was reported from direct reaction of aldehydes 2 with hydrazine was unsuccessful, because the formed hydrazone had E geometry and thus was sterically prevented from attacking the quinoline C-2. In order to avoid this difficulty, the aldehydes 2 were converted into acetals 91, that reacted with hydrazine hydrate in refluxing ethanol gave the quinolin-2-ylhydrazines 192 in good yields. Finally, mild aqueous acidic removal of the acetal protection led directly, in one pot, to the cyclized 1H-pyrazolo[3,4-b]-quinolines 193 (Scheme 70).133,134

Scheme 70

2-Chloroquinoline-3-carbaldehyde [arylmethylene]hydrazones 195 were synthesized from reaction of aldehyde 2 with hydrazine to give hydrazone 194 followed by reaction with substituted aldehydes (Scheme 71). The synthesized derivatives were screened for antibacterial and antifungal activities.135
Scheme 71

1,8-Naphthyridinyl pyrazolo[3,4-b]quinolines 197 were synthesized by reaction of 2-hydrazino-3-(4-methoxyphenyl)-1,8-naphthyridine 196 with aldehydes 2 followed by cyclization with DMF/KOH either by microwave irradiation or by conventional methods. The reaction rate is enhanced tremendously under microwave irradiation as compared to conventional method with improved yields (Scheme 72).\(^{136}\)

Scheme 72

The aldehydes 2 underwent condensation with thiosemicarbazide 198 to give the corresponding thiosemicarbazones 199, which on treatment with phenacyl bromides, gave thiazoles 200. The dehydrogenative cyclization of 200 was achieved with chloranil, in refluxing toluene, resulting in 3-(2-chloroquinolin-3-yl)-5-arylthiazolo[2,3-c][1,2,4]triazoles 161 (Scheme 73).\(^{137}\)
5-(2-Chloroquinolin-3-yl)-6-hydroxy-8-mercapto-4,5-dihydro-1H-pyrimido[4,5-e][1,2,4]triazepine-2(3H)-thione 202 was prepared under microwave irradiation either by one pot reaction of aldehyde 2, thiosemicarbazide 198a, and thiobarbituric acid 146b using montmorillonite K-10 clay or by two steps. Firstly, thiosemicarbazide 198a was condensed with aldehyde 2 using neutral alumina/montmorillonite K-10 clay resulting in thiosemicarbazone 199. Then in the second step, the later compound was allowed to react with thiobarbituric acid 146b, over alumina/clay that cyclized to afford target compounds (Scheme 74).
2-Hydrazinyl[1,3,4]thiadiazepino[7,6-b]quinolines 204 were obtained in good yields by one pot reaction of aldehyde 2 with carbidimide 202 in DMF in the presence of p-TsOH as a catalyst under microwave irradiation (Scheme 75).^{139,140}

![Scheme 75](image)

R = H, R = 7-Me, 6-Me, 8-Me, 6-Cl, 7-OMe, 8-OMe, 6-OMe

Scheme 75

Condensation of tetrazolo[1,5-a]quinoline-4-carbaldehyde 55 with substituted thiosemicarbazides 205 afforded the corresponding thiosemicarbazones 206. The later compounds underwent cyclization with malonic acid in the presence of acetyl chloride to give the pyrimidine derivatives 207. Condensation of 207 with the appropriate aromatic aldehyde gave rise to arylidene derivatives 208 (Scheme 76).^{48}

![Scheme 76](image)

R¹ = Ph, 4-MeC₆H₄, 4-ClC₆H₄; R² = Ph, 4-(Me)₂NC₆H₄

Scheme 76
The reaction of aldehyde 2 with \( N'-(2\text{-aminobenzoyl})\text{methanesulfonohydrazide} \) 209 in refluxing propanol gave \( N-(2\text{-}(2\text{-chloroquinolin-3-yl})-4\text{-oxo-1,2-dihydroquinazolin-3(4H)-yl})\text{-methanesulfonamide} \) 210 (Scheme 77).

\[
\begin{align*}
\text{CHO} & \quad \text{H}_{\text{N-SO}_{3}\text{Me}} \\
\text{Cl} & \quad \text{Cl} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

\( 2 \quad \text{PrOH, reflux} \quad 210, 62\% \)

Scheme 77

The reaction of aldehyde 2 with 2-cyanoacetohydrazide 211 in boiling ethanol containing a few drops of acetic acid to afford \( N'-(2\text{-chloroquinolin-3-yl})\text{methylene}-2\text{-cyanoacetohydrazide} \) 212 in good yield. Condensation of 212 with 2,4-dihydroxybenzaldehyde, 4-fluorobenzaldehyde, and 1-phenyl-3(2-thienyl)-1\text{-H-pyrazole-4-carbaldehyde}, in methanol in the presence of a few drops of piperidine at reflux temperature, gave \( N'-(2\text{-chloroquinolin-3-yl})\text{methylene}-7\text{-hydroxy-2-imino-2H-chromene-3-carbohydrazide} \) 213, \( N'-(2\text{-chloroquinolin-3-yl})\text{methylene}-2\text{-cyano-3-(1-phenyl-3(2-thienyl)-1\text{-H-pyrazol-4-yl})acyrolyhydrazide} \) 214a, and \( N'-(2\text{-chloroquinolin-3-yl})\text{methylene}-2\text{-cyano-3-(4-fluorophenyl)acrylohydrazide} \) 214b, respectively (Scheme 78). The \textit{anti}-inflammatory and analgesic activities of the synthesized compounds were evaluated.

\[
\begin{align*}
\text{CHO} & \quad \text{CN} \\
\text{OH} & \quad \text{OH} \\
\text{Cl} & \quad \text{Cl} \\
\text{CN} & \quad \text{CN} \\
\text{MeOH/piperidine} & \quad \text{MeOH/piperidine} \\
\text{Ar-CHO} & \quad \text{Ar-CHO} \\
\text{214a, Ar} = 1\text{-phenyl-3-(thiophen-2-yl)-1\text{-H-pyrazole-4-yl}} \\
\text{b, Ar} = 4\text{-FC}_{6}\text{H}_{4} \\
\end{align*}
\]

Scheme 78
(4-(1H-Pyrrol-1-yl)phenyl)(1H-pyrazolo[3,4-b]quinolin-1-yl)methanone 217 was synthesized by reaction of aldehydes 2 with 4-(1H-pyrrol-1-yl)benzohydrazide 215a in microwave irradiation to give $N'$-((2-chloroquinolin-3-yl)methylene)-4-(1H-pyrrol-1-yl)benzohydrazide 216 followed by intramolecular cyclization. Compound 217 exhibited moderate to good antibacterial and antitubercular activities (Scheme 79).^{142}

![Scheme 79](image)

2-(Phenylamino)-1-(1H-pyrazolo[3,4-b]quinolin-1-yl)ethanone 218a, 1H-pyrazolo[3,4-b]-quinoline-1-carbothioamide 218b, and 1H-pyrazolo[3,4-b]quinoline-1-carboxamide 218c were synthesized by the condensation of aldehyde 2 with 2-(phenylamino)acetohydrazide 215b, thiosemicarbazide 198a, or semicarbazide 198b, respectively (Scheme 80). The synthesized compounds have antibacterial and antifungal activity.^{143}

![Scheme 80](image)

Naphtho[2,1-b]furan-2-carboxydrazide 215c was treated with substituted aldehydes 2 in the presence of catalytic amount of acetic acid in absolute ethanol to give the hydrazone 219, which on treatment with chloroacetyl chloride in dioxane in the presence of triethylamine gave $N$-(3-chloro-2-(2-chloroquinolin-3-yl)-4-oxoazetidin-1-yl)naphtho[2,1-b]furan-2-carboxamide 220.
(Scheme 81). The synthesized compounds were screened for their antibacterial and antifungal activities.\(^{144}\)

\[
\begin{align*}
\text{R} & = \text{H, 7-Me, 6-Me, 8-Me, 6-OMe, 7-OMe, 8-OMe, 6-Br, 6-Cl, 7-Cl, 6,7-(OMe)\_2, 5,6,7-(OMe)\_3} \\
\end{align*}
\]

**Scheme 81**

Treatment of aldehyde 2 with aroyl hydrazides 215d in ethanol gave quinoline hydrazones 221. The latter compounds, on reaction with acetic anhydride at reflux, yielded 2-(2-chloro-3-quinolyl)-5-aryl-2,3-dihydro-1,3,4-oxadiazoles 222 (Scheme 82).\(^{23}\)

\[
\begin{align*}
\text{R} & = \text{H, 7-Me, 6-Me, 8-Me, 6-OMe, 7-OMe, 8-OMe, 6-Br, 6-Cl, 7-Cl, 6,7-(OMe)\_2, 5,6,7-(OMe)\_3} \\
\end{align*}
\]

**Scheme 82**

\(N'\)-[(2-Chloroquinolin-3-yl)methylene]-2-arylp propanehydrazide 224 was synthesized and evaluated for their anti-inflammatory activity from reaction of aldehyde 2 with arylp propanehydrazide 223 (Scheme 83).\(^{100,145}\)
Treatment of [1-(5-bromobenzofuran-2-yl)ethylidene]hydrazine 225 with aldehyde 2 in refluxed ethanol containing few drops of acetic acid, gave the corresponding Schiff base 226 (Scheme 84).\(^\text{146}\)

\[
\begin{align*}
\text{Reflux, 5-6 h} & \quad \text{AcOH/ EtOH} \\
223 & \quad 225 \\
\end{align*}
\]

Scheme 84

Reaction of 3-chloro-2-hydrazono-1,2-dihydroquinoxaline 227 with aldehyde 2 under microwave irradiation yielded 3-chloro-2-((2-chloroquinolin-3-yl)methylene)hydrazono)-1,2-dihydroquinoxaline 228 (Scheme 85).\(^\text{147}\)

\[
\begin{align*}
\text{MWI} & \quad 2 \text{ min} \\
227 & \quad 226, 83\% \\
\end{align*}
\]

Scheme 85

3.4.3. Reactions with amines and amides

Condensation of aldehydes 2 with 2-aminophenol was reported either by traditional methods\(^\text{148,149}\) or under the influence of microwave irradiation using 1,8-diazabicycloundec-7-ene-silica gel as a catalyst\(^\text{150}\) to afford quinolino[2,3-b][1,5]benzoxazepine 229 in excellent
yield. The later compound reacted with triethyl phosphite in the presence of \( p \)-toluenesulfonic acid (\( p \)-TSA) under the influence of ultrasound irradiation under solvent-free conditions to give the \( \alpha \)-aminophosphonate 230 in high yield (Scheme 86). The synthesized compound showed antibacterial activity against gram-positive and gram-negative bacteria.\(^{148}\)

![Scheme 86](image)

**Scheme 86**

Synthesis of 2-(2-chloroquinolin-3-yl)-3-phenylthiazolidin-4-ones 233 were reported either by DCC (dicyclohexylcarbodiimide) mediated three-component one-pot reaction of aldehyde 2, amine, and mercaptoacetic acid 232 \(^{151}\) or by cyclocondensation of mercaptoacetic acid 232 with Schiff bases 231 which in turn were prepared by the action of amines on aldehyde 2 (Scheme 87).\(^{152}\) The synthesized compounds were studied for interaction with calf thymus DNA by electronic spectra, viscosity measurements as well as thermal denaturation studies \(^{151}\) and screened for their antimicrobial activity against several microbes.\(^{152}\)

![Scheme 87](image)

**Scheme 87**

The aldehydes 2 when reacted with aniline in DMF afford dibenzo[\( b, g \)][1,8]naphthyridines 234 (Scheme 88).\(^{153}\)
$N$-[\text{2-chloroquinolin-3-yl}methylene]prop-2-yn-1-amine 236 was synthesized in excellent yield by condensation of aldehyde 2 with prop-2-yn-1-amine 235 in either benzene or THF in the presence of magnesium sulfate (Scheme 89).$^{154}$

2-(2-Chloroquinolin-3-yl)-10-ethyl-4-phenyl-10$H$-pyrido[2,3-$b$]carbazole 239 was obtained from cyclization of imine 238, derived from reaction of aldehyde 2 and 9-ethyl-9$H$-carbazol-3-amine 237, with phenylacetylene in the presence of CuI/La(OTf)$_3$ in [Bmim][BF$_4$] followed by aromatization (Scheme 90).$^{155}$

**Scheme 88**

**Scheme 89**

**Scheme 90**
Synthesis of \( \alpha \)-aminophosphonate 241 in excellent yields from reaction of imine 240, which obtained from reaction of aldehyde 2 and 3-fluoroaniline with triethyl phosphite in the presence of chlorotrimethylsilane (Scheme 91)\(^{156} \)

\[
\text{CHO} \quad + \quad \text{F-PhNH}_2 \quad \xrightarrow{\text{AcOH, EtOH, 20 min, rt}} \quad \text{Cl-Ph} \quad \text{N-Ph} \quad \text{F} \quad 240, \text{96%}
\]

\[
\text{(EtO)}_3\text{P} \quad \rightarrow \quad \text{EtO-P} \quad \text{EtO-} \quad \text{N-Ph} \quad \text{F} \quad 241
\]

3-Aryl-1\(H\)-[1,2,4]triazolo[4′,3′:2,3][1,2,4]triazepino[5,6-b]quinolines 243 were synthesized via heterocyclization of 5-aryl-3,4-diamino-1,2,4-triazoles 242 and aldehydes 2 in DMF in the presence of \( p \)-TsOH with either microwave irradiation or oil-bath heating at 80\(^\circ\)C (Scheme 92)\(^{157} \)

\[
\text{CHO} \quad + \quad \text{N=N-N=NH}_2 \quad \xrightarrow{p\text{-TsOH, DMF}} \quad \text{N=N-N=N} \quad 243, \text{60%}
\]

\[
\text{R} = \text{H, 3-Me, 4-OMe; } R^1 = \text{Ph, 4-O}_2\text{NC}_6\text{H}_4, \text{ 2-ClC}_6\text{H}_4
\]

Stereoselective synthesis of \( N^1,N^2 \)-bis[(2-chloroquinolin-3-yl)methylene]ethane-1,2-diamine 244 was reported by reaction of aldehyde 2 with ethylenediamine in ethanol at reflux temperature (Scheme 93)\(^{158} \)

\[
\text{CHO} \quad + \quad \text{H}_2\text{N-NH}_2 \quad \xrightarrow{\text{EtOH, reflux, 3-4 h}} \quad \text{N=N-N=N} \quad 244, \text{94%}
\]
One-pot synthesis of 3-(1H-benzimidazol-2-yl)quinolin-2(1H)-one 245 was performed in 70% aqueous acetic acid in the presence of Amberlyst-15 (20% wt./wt.) by the direct reaction of aldehyde 2 with o-phenylenediamine (Scheme 94). Antitumor studies against sixty different cancer cell lines showed the potential of these kinds of compound.159

![Scheme 94](image)

2-Phenyl-2H-[1,3]thiazino[6,5-b]quinolines 246 were synthesized in good to excellent yields by one pot reaction between aldehyde 2 and thiobenzamide using p-TsOH catalyst under microwave irradiation (Scheme 95).125-160

![Scheme 95](image)

1H-Pyrazolo[3,4-b]quinoline-3-amines 249 were prepared by dehydration of 2-chloro-3-quinolinecarbaldehyde oxime 247 with thionyl chloride followed by cyclization with hydrazine hydrate in ethanol. The fused pyrazole intermediates 249 were diazotized to give the diazonium salt 250. Subsequent coupling reactions took place with various heterocyclic compounds to obtain 251.161 Furthermore, 1-aryl-1H-pyrazolo[3,4-b]quinolin-3-amine 249 (R = H) were reacted with 1,3-thiazinan-4-one 252 and thiazolidin-4-one 254 to give Schiff base adducts 253 and 255, respectively (Scheme 96). The antimicrobial activity was evaluated for most of the prepared compounds.162

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Scheme 96

Reaction of aldehyde 2, 1-vinylpyrrolidin-2-one 256, and substituted aniline at room temperature in a water-acetonitrile mixture (1:1) in the presence of 5 mol % ceric ammonium nitrate (CAN) for ~ 50 min. afforded tetrahydroquinolines 257 in good yields as single regioisomers and diastereoisomers. Subsequently, the tetrahydroquinolines 257 were oxidized to the corresponding 2'-chloro-2,3'-biquinoline 258 by reaction with 2.5 equivalent of CAN in acetonitrile at 0 °C (Schemes 97).[^163]
The condensation of aldehyde 2 with various derivatives of 4-amino-5-aryl-4H-1,2,4-triazole-3-thiol 259 either by using microwave irradiated in the presence of Montmorillonite K-10 clay in DMSO or by traditional method was reported to give 3-aryl-[1,2,4]-triazolo[3′,4′:2,3][1,3,4]thiadiazepino[7,6-b]quinolines 260. The base catalyzed facile intramolecular rearrangement of 260 to s-triazolothiazinoquinolines 261 involving N-N bond scission (Scheme 98).

The condensation of aldehyde 55 with 1-amino-2-mercapto-5-aryl-1,3,4-triazole 259 either by microwave irradiating using basic alumina as solid support or by stirring in DMF to give 3-substituted-6-(tetrazolo[1,5-a]quinolin-4-yl)-5,6-dihydro-[1,2,4]triazolo[3,4-b]-[1,3,4]thiadiazole 262 (Scheme 98). Compounds 261 and 262 were screened for their antibacterial and antifungal activity.

\[
\text{R} = \text{R}^1 = \text{H (85%)}; \text{R} = \text{H}, \text{R}^1 = \text{Cl (82%)}; \text{R} = \text{Me}, \text{R}^1 = \text{H (87%)}; \text{R} = \text{OMe}, \text{R}^1 = \text{H (86%)}
\]
Condensation of aldehyde 2 with ethyl 2-aminoacetate hydrochloride gave imine 263, which on cyclization in either sulfuric acid or Dowtherm A, furnished 5-chlorobenzo[c][2,7]-naphthyridin-1-ol 264 (Scheme 99). An improved yield was observed in Dowtherm A.\(^{167}\)

![Scheme 99](image1)

The reaction of aldehyde 2 with sarcosine 265 in refluxing xylene gave 2-methyl-5,9b-dihydro-1H-pyrrolo[3,4-c]quinolin-4(2H)-ones 269 in acceptable yields via 1,5-electrocyclisation reaction accompanied by hydrolysis of the chlorine function under the applied reaction conditions in the presence of the water formed in the first step. The intermediate of azomethine ylides 266 were shown by trapping the proposed dipoles with N-phenylmaleimide to give the two isomeric cycloadducts 268a and 268b (endo-exo ratio1:1) in quantitative yield (Scheme 100).\(^{20-168}\)

![Scheme 100](image2)
3.4.4 Miscellaneous reactions. Aldehyde 2 was transformed into 2-chloroquinoline-3-carbonitrile 270 by using either propylphosphonic anhydride or hydroxylamine\textsuperscript{169} (98%) or iodine and aqueous ammonia in THF at room temperature (82%) (Scheme 101).\textsuperscript{170}

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{(PrP(O)O)}_3, \text{NH}_2\text{OH} \cdot \text{HCl}} \text{CN} \\
\text{Et}_3\text{N, DMF, 100 °C, 1 - 3 h} & \text{or} \\
\text{NH}_3, \text{I}_2, \text{H}_2\text{O, THF, rt, 75 min} & \Rightarrow \\
\text{Cl} & \xrightarrow{} \\
\end{align*}
\]

Scheme 101

The aldehyde 2 was reacted with Grignard reagent (MeMgBr, 98%) followed by oxidation by MnO\textsubscript{2} (80%) to give the methyl ketone. Finkelstein reaction on the latter compound yielded the iodo derivative 271 (80%). Action of TBSOTf with Et\textsubscript{3}N on 271 gave the O-TBS protected derivative 272 (77%), which underwent efficient Sonogashira reaction with several alkynes: 1-hexyne (273a, 70%), phenylacetylene (273b, 60%), tetrahydro-2-(2-propynyloxy)-2H-pyran (273c, 70%), 3,3-diethoxy-1-propyne (273d, 72%). The Rh(I)-catalyzed cyclization produced the corresponding 1,3-disubstituted acridines 274a (60%), 274b (50%), 274c (60%), 274d (40%) (Scheme 102).\textsuperscript{171}

\[
\begin{align*}
\text{CHO} & \xrightarrow{a-c} \text{Me} \\
\text{Cl} & \xrightarrow{d} \text{CH}_2 \\
\text{I} & \xrightarrow{e} \text{CH}_2 \\
\text{OTBS} & \xrightarrow{f} \\
\end{align*}
\]

\begin{itemize}
  \item \text{R = Bu, Ph, CH}_2\text{-O-THP, CH(OEt)}_2
\end{itemize}

(a) 3 equiv MeMgBr, THF, 40 °C, 98%; (b) 10 equiv MnO\textsubscript{2}, toluene, 80 °C, quant.; (c) NaI, CH\textsubscript{3}CN, 0.5 equiv HCl 4N, reflux, 80–98%; (d) 2.2 equiv TBSOTf, 3 equiv Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 77%; (e) 1-alkyne, 0.07 equiv PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}, 0.3 equiv Cul, 1.5 equiv Et\textsubscript{3}N, toluene, rt; (f) 10 mol% [Rh(CO)]\textsubscript{2}Cl\textsubscript{2}, toluene, 2–4 h, 120 °C.

Scheme 102
Similarly, the reaction of 1-(2-(pyridin-2-ylethynyl)quinolin-3-yl)ethanone 275 with pyrrolidine in refluxed dichloromethane in the presence of powdered molecular sieves gave 3-(pyridin-2-yl)-1-(pyrrolidin-1-yl)acridine 276 via the enamine synthesis and the aminobenzannulation step took place subsequently (Scheme 103).\(^{172}\)

![Scheme 103](image)

2,4,5-Trisubstituted imidazoles 278 were synthesized from reaction between benzil 277, aldehydes 2 and excess of ammonium acetate either by traditional method using refluxed acetic acid,\(^{21}\) or by solvent-free microwave irradiation. Similarly, 1,2,4,5-tetrasubstituted imidazoles 279\(_{a,b}\) were also obtained in high yields within few minutes by the four-component condensation of benzil, the aldehyde 2, a primary amine and ammonium acetate under microwave irradiation (Scheme 104).\(^{173}\)

![Scheme 104](image)
Julia olefination between aldehyde 2 and α-halomethyl sulfones 280a,b in THF in the presence of lithium bis(trimethylsilyl)amide afforded 2-chloro-3-(2-halovinyl)quinoline 281a,b in good yields with high E/Z stereoselectivities (Scheme 105).\textsuperscript{174}

\[
\begin{align*}
\text{CHO} &+ \begin{array}{c}
\text{Cl} \\
\text{N-N=S-O-X}
\end{array} \xrightarrow{\text{LiHMDS, HMPA}} \begin{array}{c}
\text{Cl} \\
\text{H}
\end{array}
\end{align*}
\]

\[
280a,b \rightarrow 281a, X = \text{Cl (62\%), (E:Z, 52:48)} \quad 281b, X = \text{Br (50\%), (E:Z, 50:50)}
\]

LiHMDS = Lithium bis(trimethylsilyl)amide  
HMPA = Hexamethylphosphoramide

Scheme 105

\textit{meso-Tetrakis}(2-chloroquinolin-3-yl)porphyrins 283 were synthesized from reaction of aldehyde 2 with pyrrole 282 in 1:1 ratio in propionic acid at 140°C for 4 h (Scheme 106).\textsuperscript{175}

\[
\begin{align*}
\text{CHO} &+ \begin{array}{c}
\text{Cl} \\
\text{R}
\end{array} \xrightarrow{\text{propionic acid}} \begin{array}{c}
\text{Cl} \\
\text{R}
\end{array}
\end{align*}
\]

\[
282 \rightarrow 283, \text{10-12\%}
\]

R = 6-Me, 6-OMe, 7-OMe

Scheme 106

3-[(4-(Dimethylamino)phenylamino)methyl]-5,6,7-trimethoxyquinolin-2(1H)-one 284 was prepared from reaction between 5,6,7-trimethoxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde via reductive amination with $N^1,N^1$-dimethylbenzene-1,4-diamine in 1,2-dichloroethane containing NaBH(OAc)$_3$.\textsuperscript{176}
The Ugi four-component reaction of aldehyde 2, 2-halo-5-nitrobenzoic acid, (4-methoxy-phenyl)methanamine, and isonitrile resulted in formation of the classical U-4CC product, followed by intramolecular cyclization to produce 3-oxoisooindoline adduct in 73% yield (Scheme 107).\(^{177}\)

![Scheme 107](image_url)

4. Conclusions

2-Chloroquinoline-3-carbaldehydes are easily available and have high chemical reactivity due to the presence of both chloro and aldehyde groups. This survey is attempted to summarize the synthetic methods and reactions of 2-chloroquinoline-3-carbaldehydes during the last twelve
years. We will publish the literature survey of the chemistry of 2-chloroquinoline-3-carbaldehydes from the first to the end of 1999 in a separate review article in the near future.

5. References

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**Professor Abdel-Aziz Sayed El-Ahl** was born in Mansoura, Egypt in 1958. He received his M. Sc. degree from the University of Mansoura in1985 under the supervision of Professor A. M. Khalil. He performed his Ph.D. thesis on model studies for synthesis of mitomycin C in the research group of Professor H. J. Knoelker in Hannover, Germany under the scientific channel system between Egypt and Germany where he graduated in 1992. Since 1992, he has been a
lecturer at the University of Mansoura, Egypt. In 1997 he has became associate professor at the same institution. Professor A. S. El-Ahl has awarded the Fulbright fellowship January 1998- July 1998 to join the group of Professor William A. Donaldson for studying the application of tricarbonylriron diene complexes in synthesis of Macrolactin A at the chemistry department, Marquette University, Milwaukee, Wisconsin, USA. Since 2002 he moved to the chemistry department, University College Makkah, Umm Al-Qura University, Makkah, Saudi Arabia and he was promoted to full professor in 2004. His research interest is the synthesis of heterocyclic compounds with pharmaceutical interest using a variety of Silicon reagents derived from tetrachlorosilane and soft nucleophiles.