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

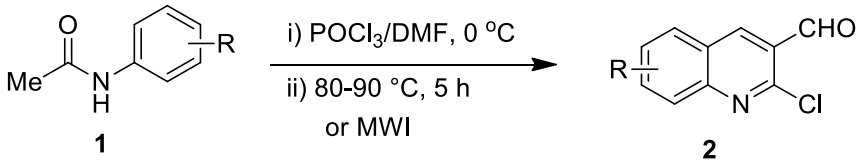
Interesting pharmacological properties have been associated with 2-chloroquinoline-3-carbaldehydes and their derivatives.[1,2] These compounds have shown antimicrobial,[1-3] antimalarial,[4,5] anti-inflammatory,[6-9] antitumor,[10,11] and anti-parasitic activity.[12] Despite this versatile importance, 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

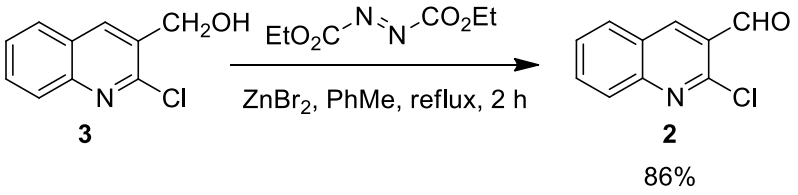
2-Chloroquinoline-3-carbaldehydes **2** were synthesized from acetanilides **1** *via* a Vilsmeier-Haack reaction either by traditional methods [14-23] or by microwave,[24] or ultrasonic irradiation (Scheme 1).[25]



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 $ZnBr_2$ in refluxing toluene (Scheme 2).[26]

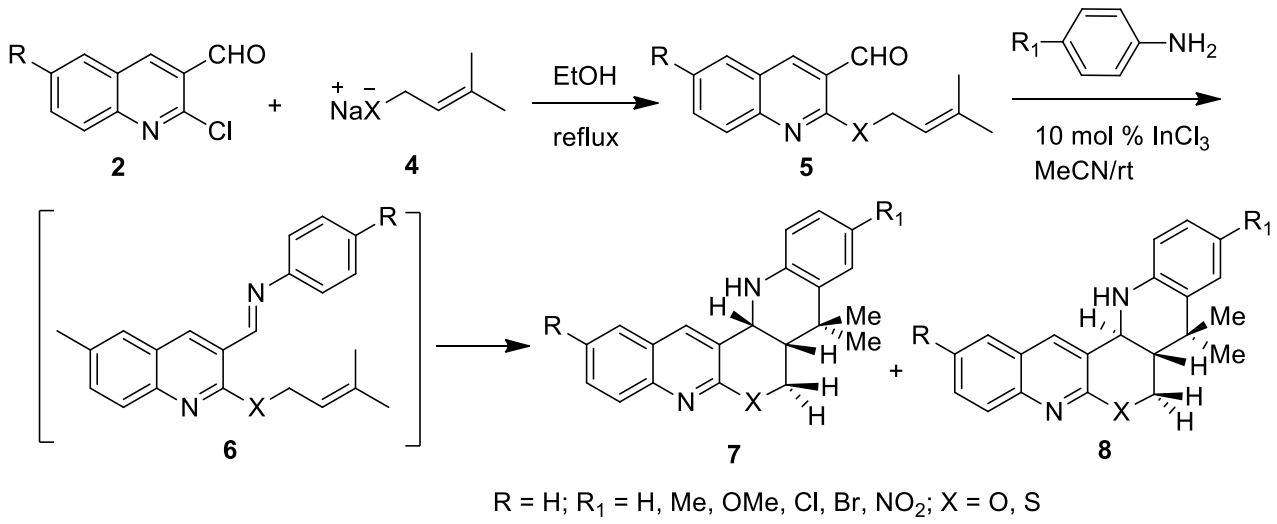


Scheme 2

3 Chemical Reactions

3.1. Substitution reactions

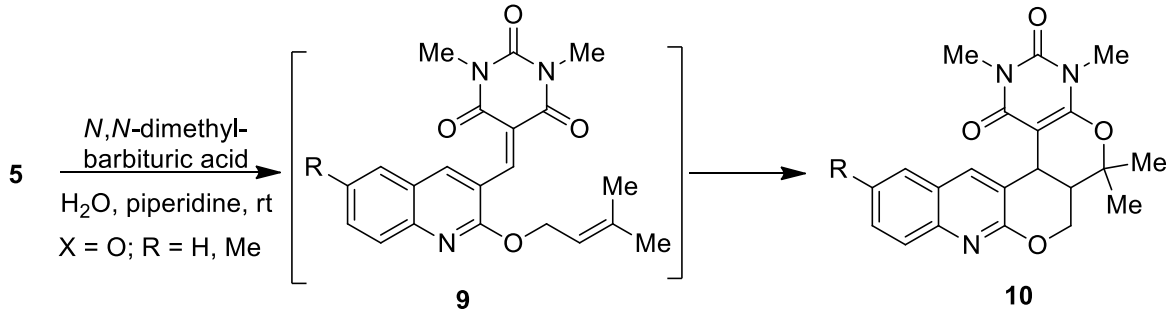
Treatment of 2-chloroquinoline-3-carbaldehydes **2** with prenyl thiolate or prenyl alcoholate **4** in the presence of sodium hydroxide or potassium *t*-butoxide, furnished *S*/*O*-prenyl aldehydes **5** in 72-84% yield, respectively. *S*/*O*-prenyl aldehyde **5**, underwent imino Diels-Alder reactions with various substituted anilines in the presence of $InCl_3$ 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]



Scheme 3

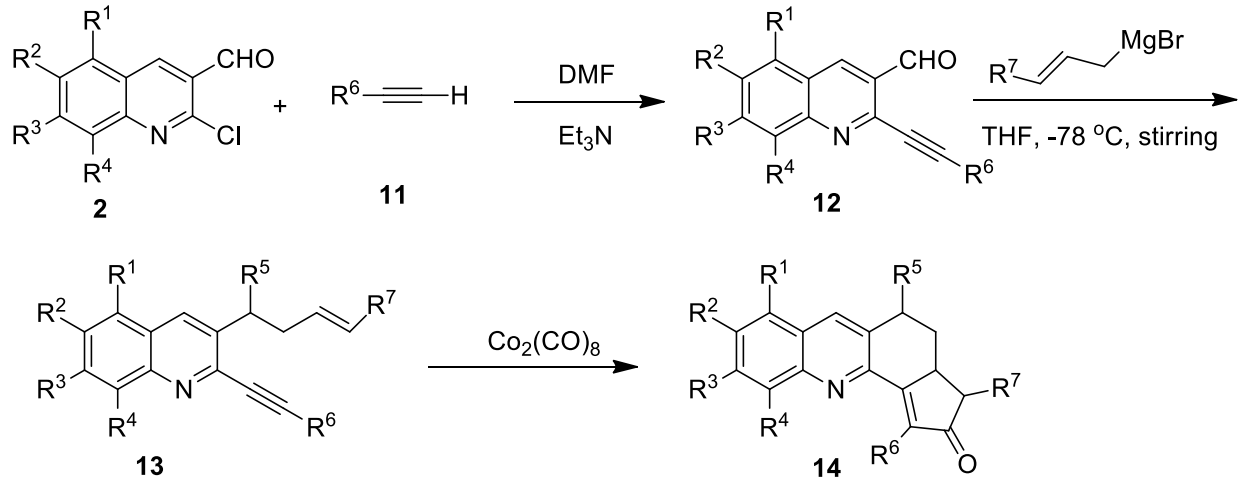
Knoevenagel hetero Diels-Alder reaction of **5** (X = O) with *N*,*N*′-dimethylbarbituric acid in water was carried out in the presence of piperidine at room temperature. The intermediate

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]



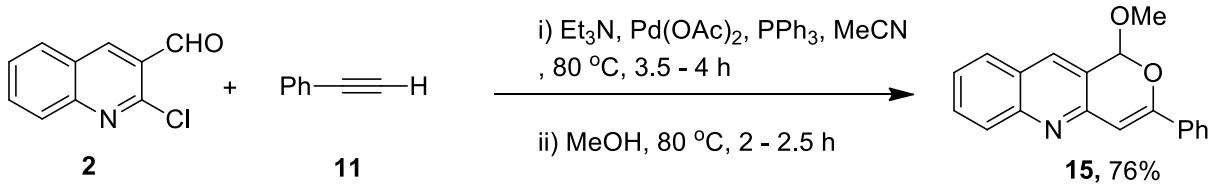
Scheme 4

Recently, tetrahydrocyclopenta[*c*]acridines **14** were synthesized from reaction of substituted aldehyde **2** with alkyne **11** in DMF in the presence of Et_3N to afford alkynyl quinolines **12** which were reacted with allyl magnesium bromide followed by Pauson-Khand cyclization using $Co_2(CO)_8$ (Scheme 5). The synthesized compounds were used as kinase inhibitors in particular for treating cancer.[11,12]



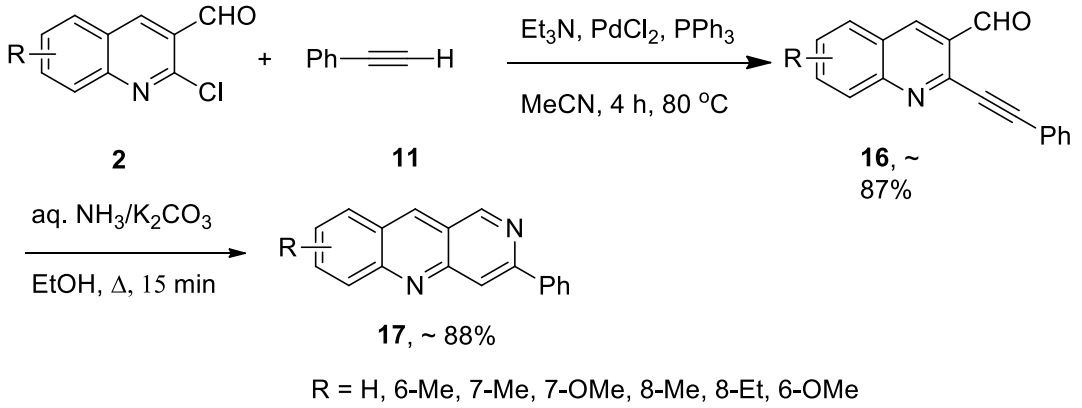
Scheme 5

Similarly, a convenient and one-pot synthesis of 1-methoxy-3-phenyl-1*H*-pyrano[4,3-*b*]-quinoline **15** from reaction of aldehyde **2** with phenyl acetylene **11** (R_6 = Ph) in acetonitrile in the presence of $Pd(OAc)_2$ and triphenylphosphine was reported (Scheme 6).[28]



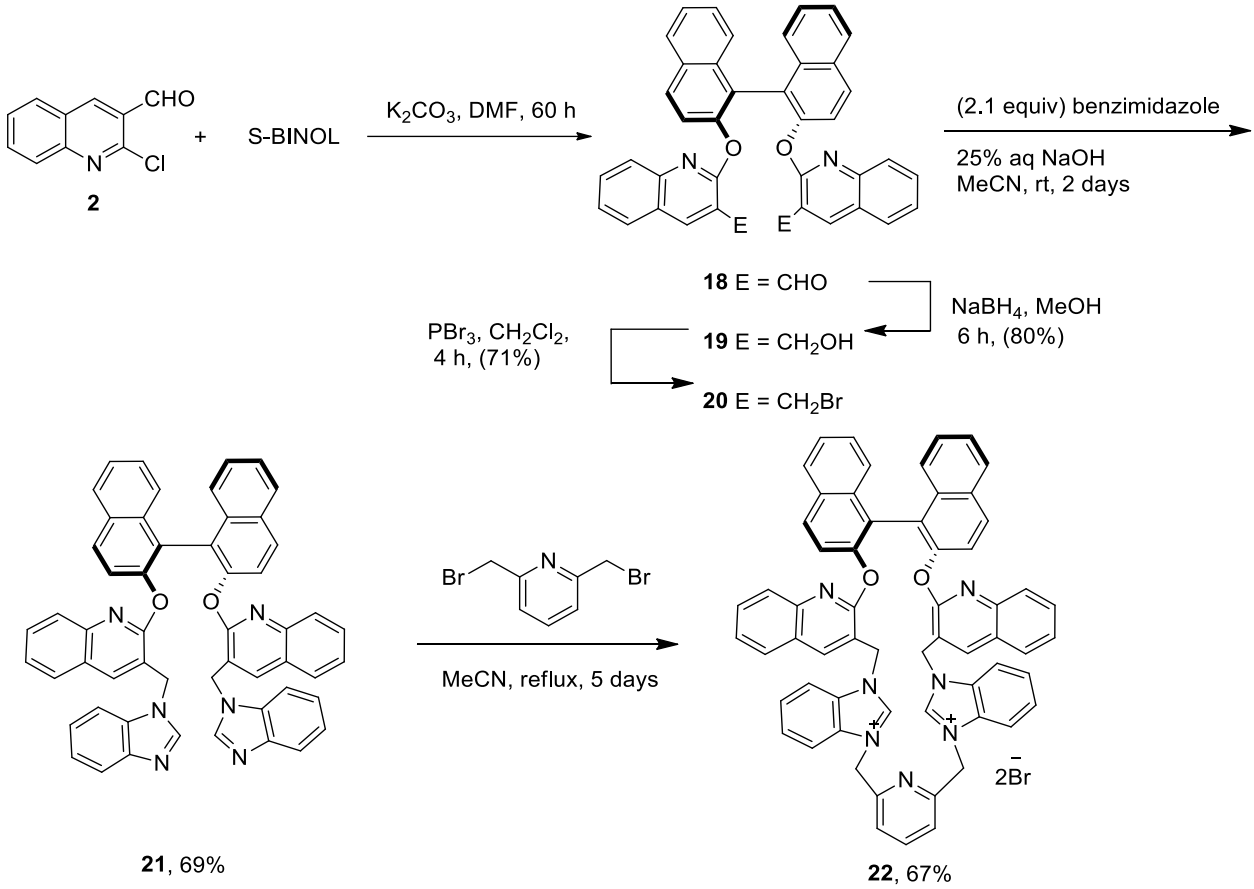
Scheme 6

Reaction of aldehydes **2** with phenylacetylene **11**(R_6 = Ph) was carried out in the presence of $PdCl_2$, 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]



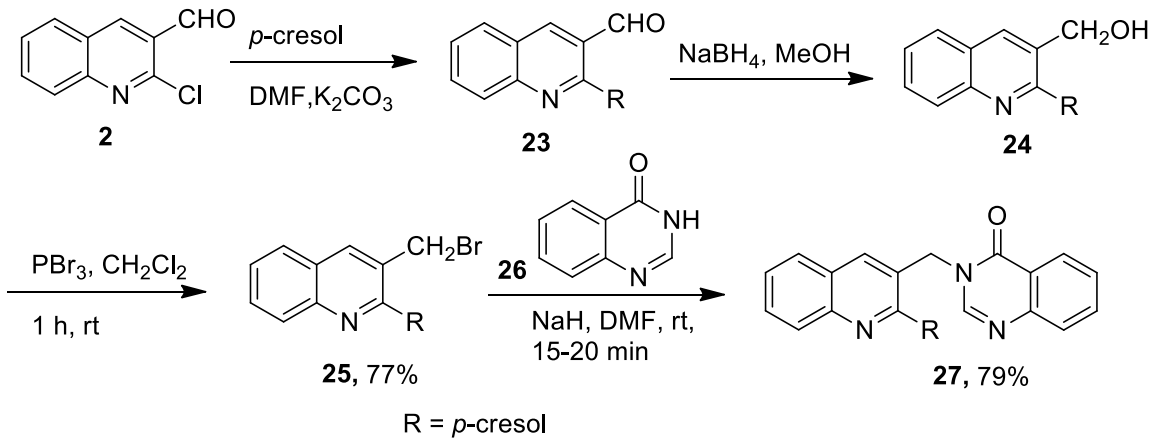
Scheme 7

Reaction of one equivalent of *S*-(–)-BINOL with 2.1 equivalent of aldehyde **2** in DMF in the presence of K_2CO_3 gave the dialdehyde **18**, which was reduced to diol **19** using $NaBH_4$ in methanol, followed by reaction with phosphorus tribromide (PBr_3) 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]



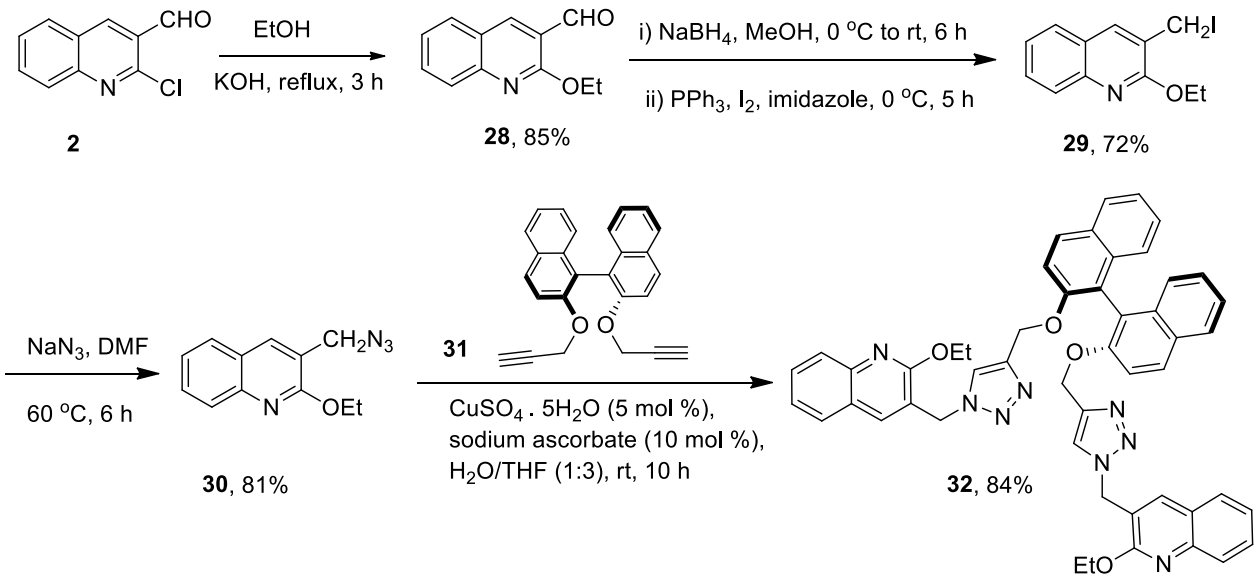
Scheme 8

3-(Quinolin-3-ylmethyl)quinazolin-4(3*H*)-one **27** (79%) was synthesized *via* reaction of 3-(bromomethyl)quinoline 25 with quinazolin-4(3*H*)-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 K_2CO_3, in methanol in the presence of $NaBH_4$ followed by treated with PBr_3 in dichloro-methane under ice cold condition (Scheme 9). The synthesized compound was screened in vitro for antimicrobial activity.[33]



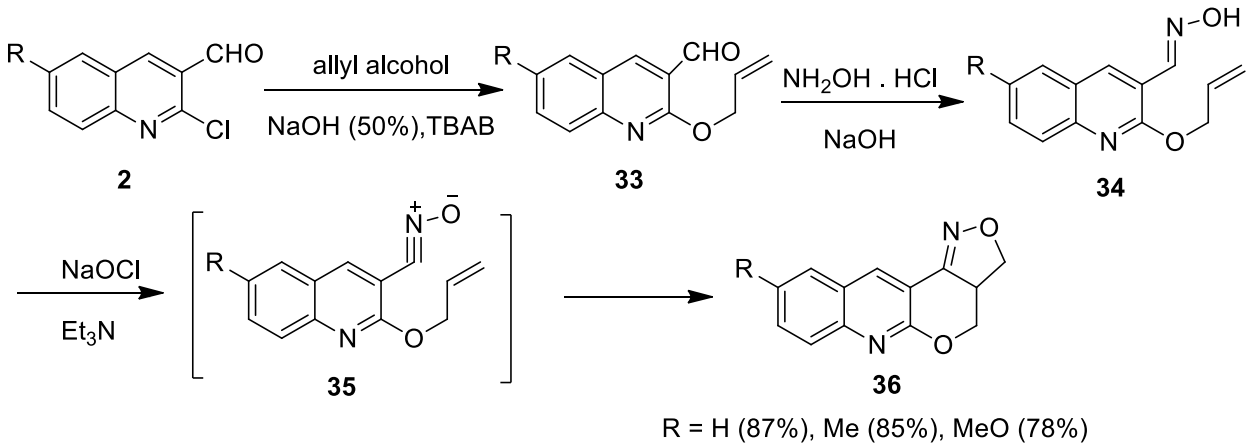
Scheme 9

The reaction of aldehyde **2** with ethanol in the presence of KOH, afforded 2-ethoxy-3-formylquinoline **28** which was reduced with $NaBH_4$ in methanol to give the alcohol which on further reaction with PPh_3 and I_2 in the presence of imidazole in dry CH_2Cl_2 gave 2-ethoxy-3-(iodomethyl)quinoline **29** in good yield. The later compound when reacted with sodium azide in DMF at 60 ^oC 3-(azidomethyl)-2-ethoxyquinoline **30** was obtained. Quinoline azide **30** was reacted with bis(propargyloxy)-(*S*)(-)-BINOL **31** in the presence of $CuSO_4$.$5H_2O$ 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).[34]



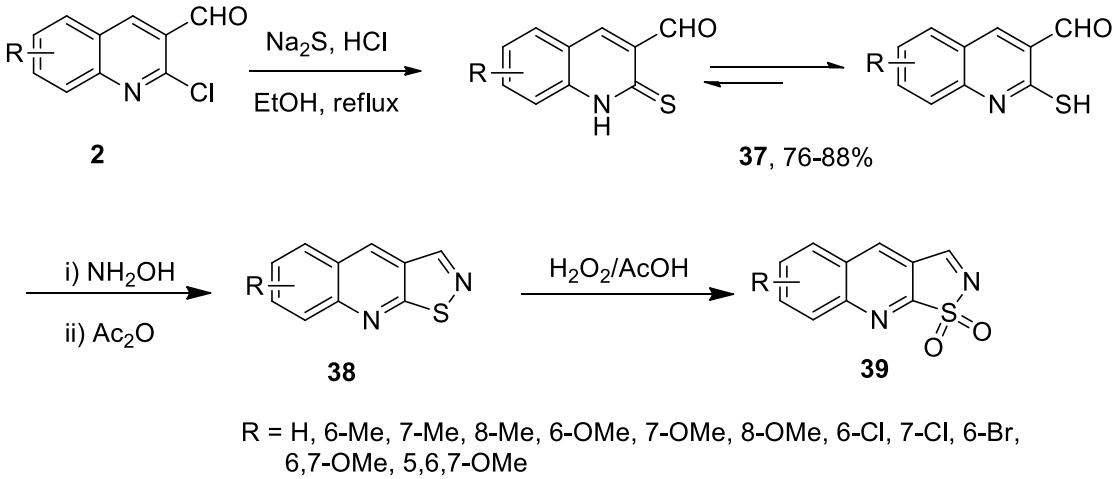
Scheme 10

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 Et_3N at 0-20 ºC afforded dihydro-3*H*-[1,2]oxazolo[3',4':4,5]pyrano[2,3-*b*]quinoline **36** in excellent yields *via* 1,3-dipolar cycloaddition of the nitrile oxides (Scheme 11).[35]



Scheme 11

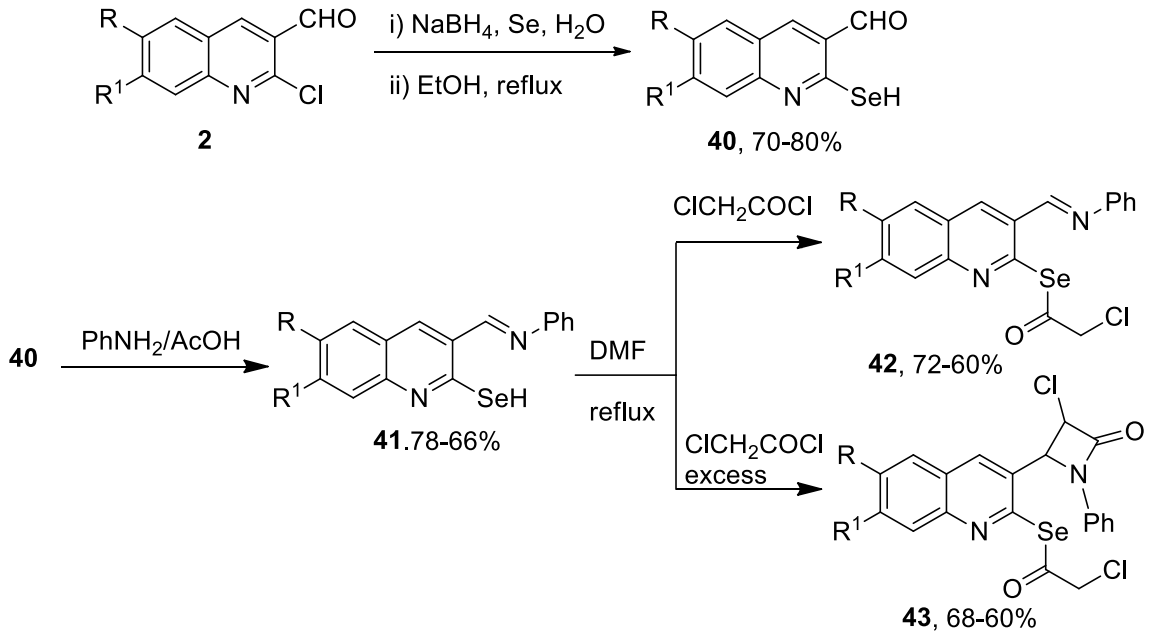
3-Formyl-2-mercaptoquinolines **37** were synthesized in good yields by one-pot reaction of aldehyde **2** with sodium sulfide and hydrochloric acid in hot ethanol.[36-38] Isothiazolo[5,4-*b*]-quinolines **38** were obtained by reaction between **37** and hydroxylamine followed by cyclization with Ac_2O. Subsequently, compound **38** was oxidized with H_2O_2 in acetic acid to give 2*H*-isothiazolo[5,4-*b*]quinoline 1,1-dioxides **39** (Scheme 12).[38]



Scheme 12

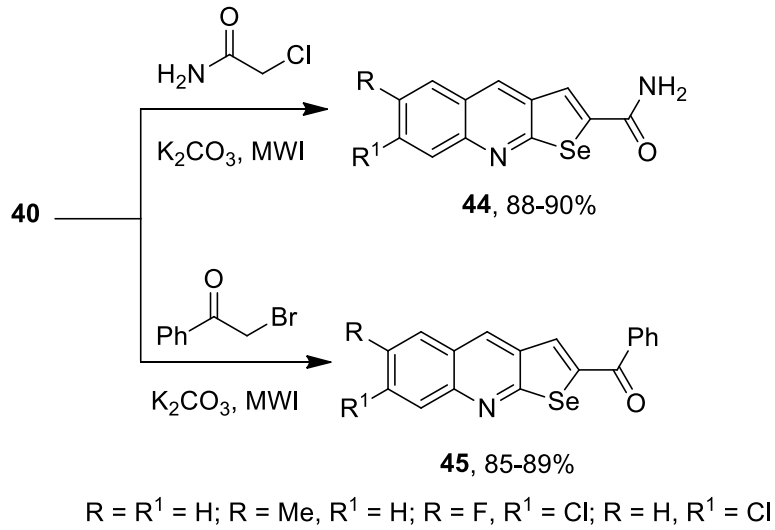
2-hydroselenoquinoline-3-carbaldehydes **40** were synthesized in a quantitative yield by reaction of aldehydes **2** with sodium hydrogen selenide in ethanol. 2-hydroselenoquinoline-3-carbaldehydes **40** were reacted with aniline in glacial acetic acid to give 3-[(phenylimino)methyl]quinoline-2-selenol **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]



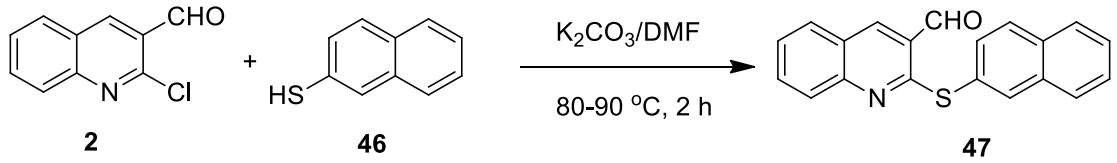
R = R^1 = H; R = Me, R^1 = H; R = F, R^1 = Cl; R = H, R^1 = Cl

Scheme 13



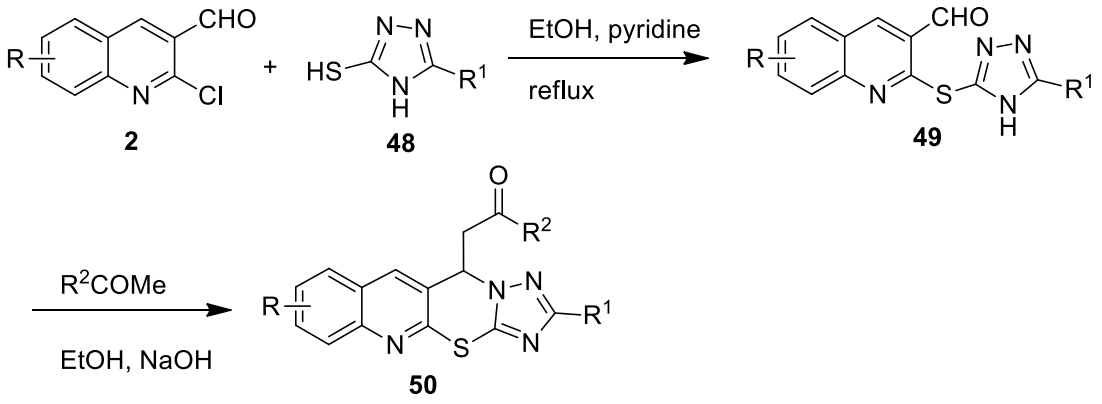
Scheme 14

2-(Naphthalen-2-ylthio)quinoline-3-carbaldehyde **47** was prepared from reaction between aldehyde **2** and naphthalene-2-thiol **46** in K_2CO_3/DMF (Scheme 15).[41]



Scheme 15

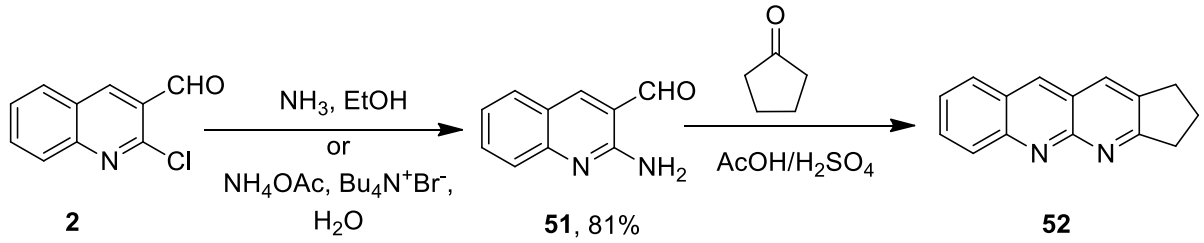
2-(5-Aryl-4*H*-1,2,4-triazol-3-ylthio)quinoline-3-carbaldehydes **49** were prepared by reaction of aldehyde **2** with 5-aryl-4*H*-1,2,4-triazole-3-thiol **48** in refluxing ethanol in the presence of pyridine. The later compound on reaction with substituted acetophenone gave 1-aryl-2-(2-aryl-9*H*-[1,2,4]triazolo[3,2-*b*][1,3]thiazino[6,5-*b*]quinolin-9-yl)ethanones **50** (Scheme 16).[42]



R = H, 6-Me, 8-Me; R^1 = Ph, 4-OHC_6H_4; R^2 = Ph, 4-ClC_6H_4

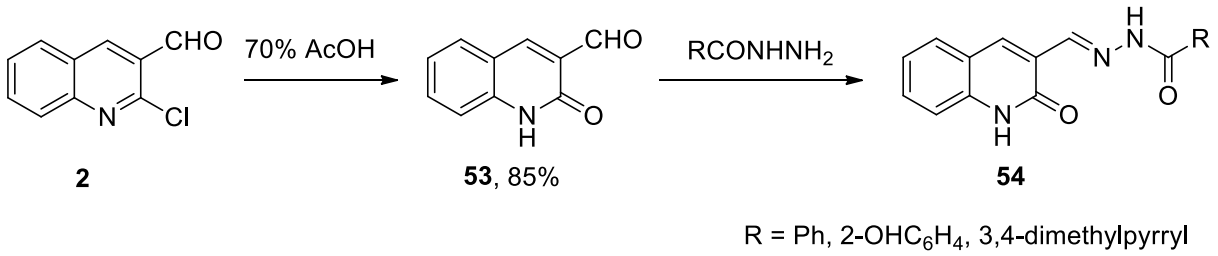
Scheme 16

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.[43] or by using dry ammonia gas in ethanol, to obtain 2-amino-3-quinolinecarbaldehyde **51**,[44] which was condensed with cyclopentanone in the presence of acetic and sulfuric acids to give 2,3-dihydro-1*H*-benzo[*g*]cyclopenta[*b*][1,8]naphthyridine **52** (Scheme 17).[44]



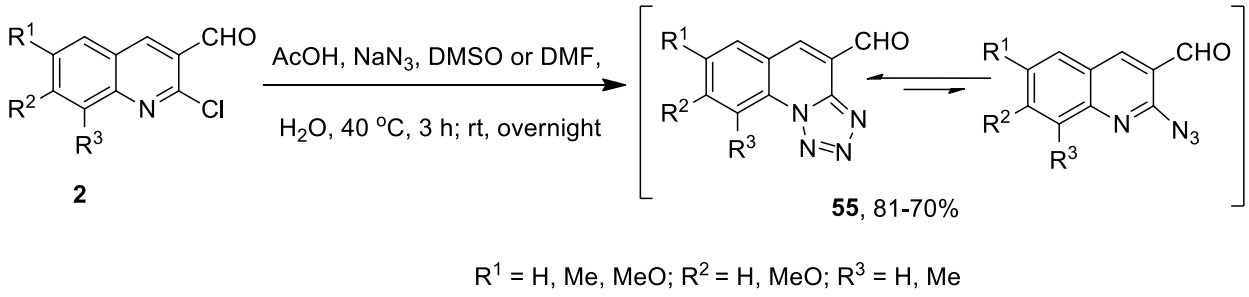
Scheme 17

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).[45]



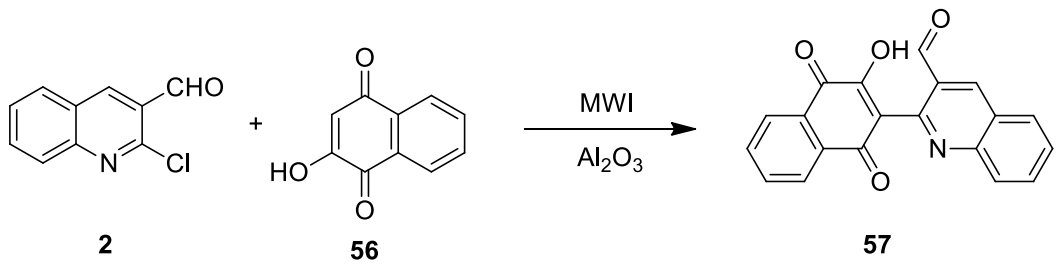
Scheme 18

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).[9,10,46-48]



Scheme 19

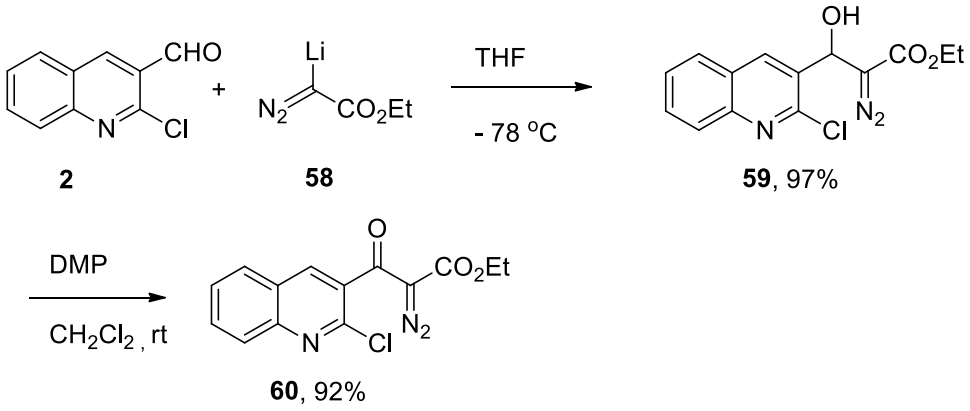
3-Formyl-2-(3-hydroxy-1,4-naphthoquinon-2-yl)-quinoline **57** was synthesized by reaction of aldehydes **2** with 2-hydroxy-1,4-naphthoquinone **56** in basic alumina using microwave irradiation (MWI) (Scheme 20). The synthesized compound showed promising antibacterial activity.[49]



Scheme 20

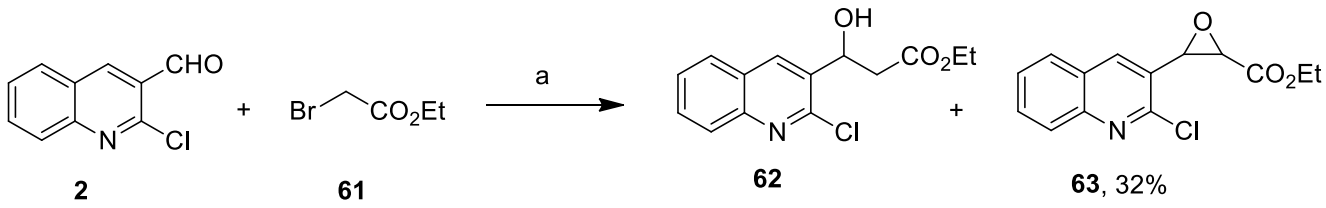
3.2. Addition reactions at the aldehyde group

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]



Scheme 21

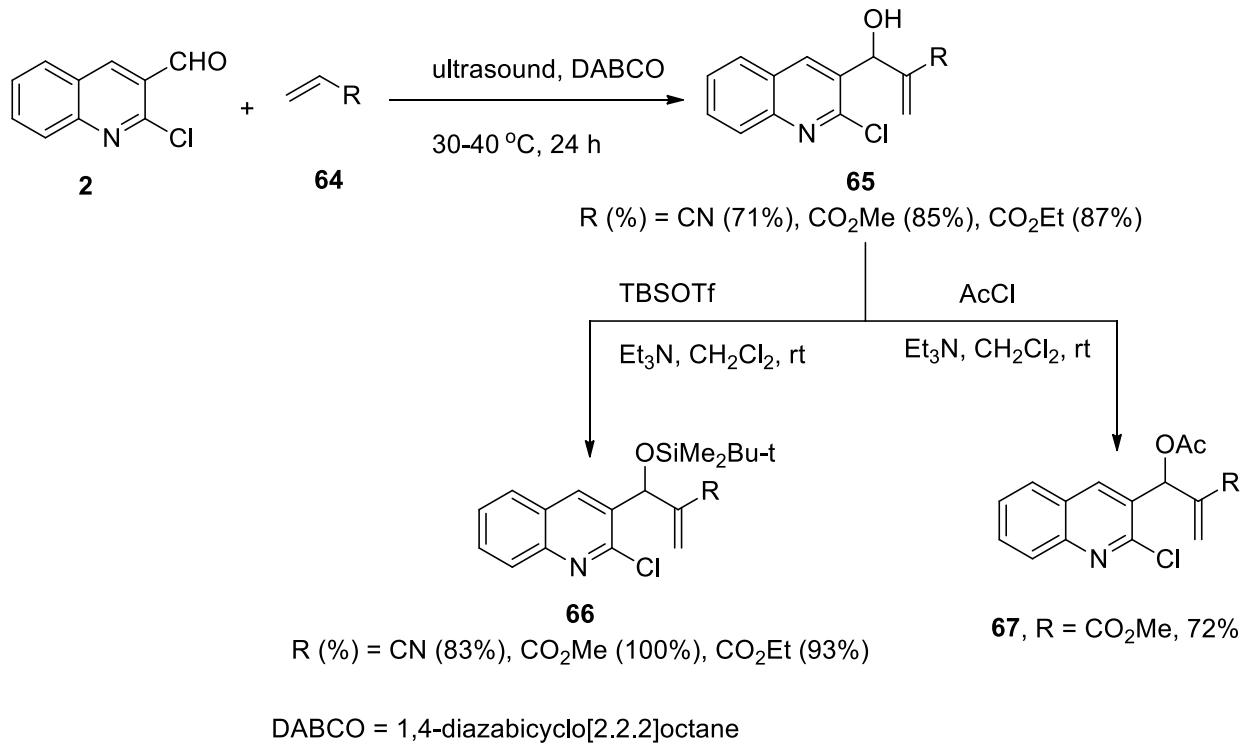
Epoxy ester **63** and *β*-hydroxy ester **62** were prepared in moderate yields from reaction of aldehyde **2** with ethyl 2-bromoacetate **61** according to Darzens condensation reaction (Scheme 22).[51]



a) *t*-BuOK, DMSO, 15 - 20 °C,1 h; rt, 24 h; pentane, aq.NH_4Cl

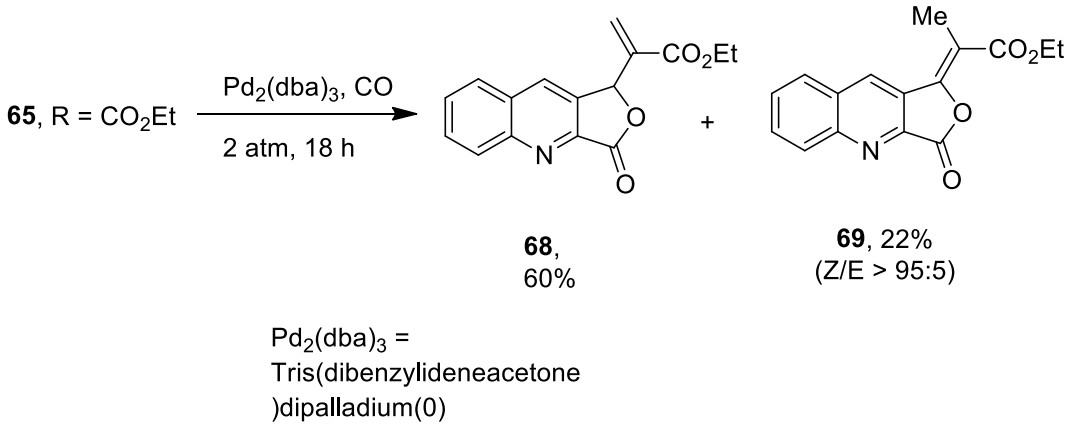
Scheme 22

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).



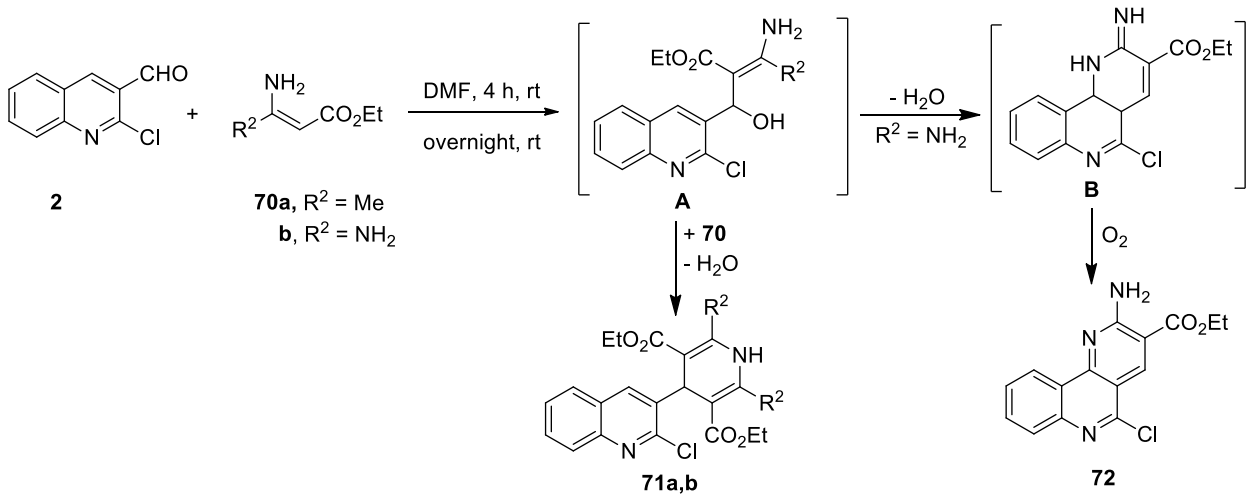
Scheme 23

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]



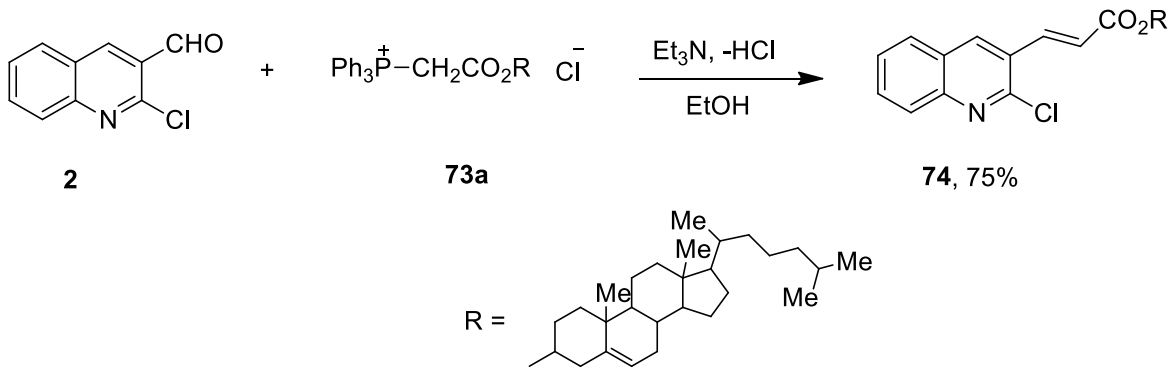
Scheme 24

The reaction of ethyl aminocrotonate **70a** [21] or 3,3-diaminoacrylate **70b**[56] 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[*h*][1,6]naphthyridine-3-carboxylate **72** *via* intermediates **A** and **B**, respectively (Scheme 25).



Scheme 25

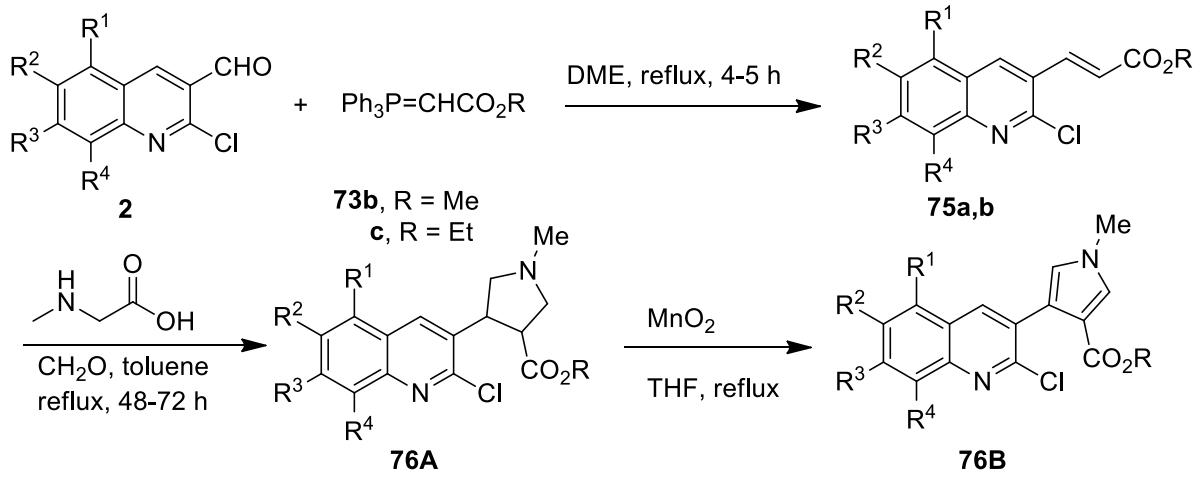
The Wittig reaction of cholesteryl triphenylphosphonioacetate chloride **73a** with aldehyde **2** in ethanol in the presence of Et_3N gave the cholesteryl 3-(2-chloroquinolin-3-yl)acrylate **74** (Scheme 26).[57]



Scheme 26

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

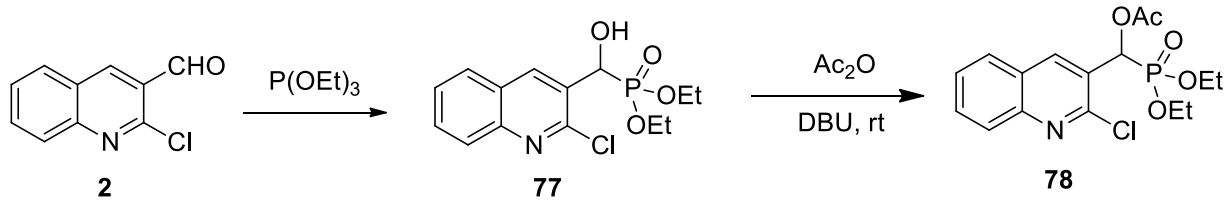
derivatives **76A** followed by oxidation to pyrrole **76B** with activated MnO_2 in refluxing THF (Scheme 27).[58]



(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, $R^3 = OCH_2O$, R^4 = H

Scheme 27

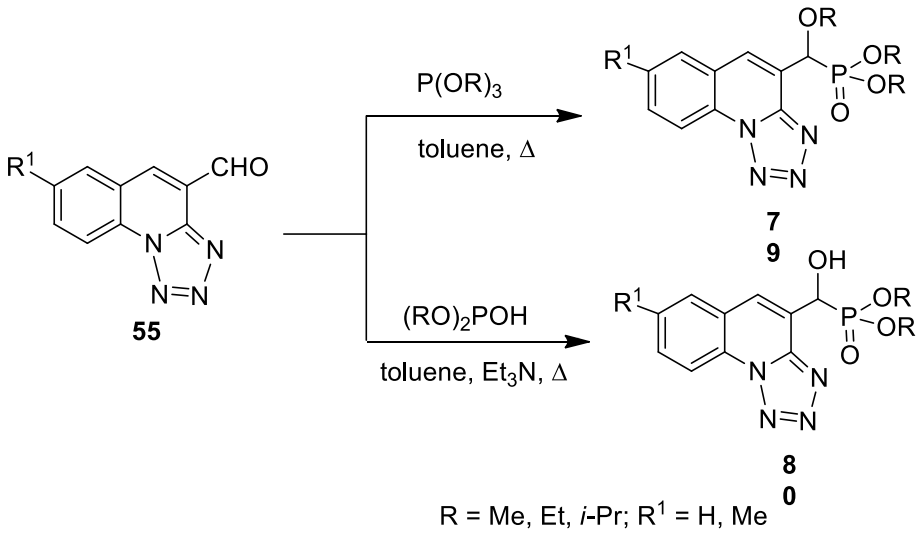
The Abramov reaction between aldehyde **2** and triethyl phosphite, to synthesize *α*-hydroxyphosphonate **77**, was performed either by traditional or ultrasound irradiation using several catalyst such as chlorotrimethylsilane at room temperature [59] (yield: 96%) as well as at reflux temperature (yield 77-83%),[2] ammonium metavanadate (NH_4VO_3) at room temperature (yield 94%),[60] potassium dihydrogen phosphate (KH_2PO_4) (yield 90%),[61] or sulfamic acid (NH_2SO_3H) 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.



DBU = 1,8-Diazabicyclo-undec-7-ene

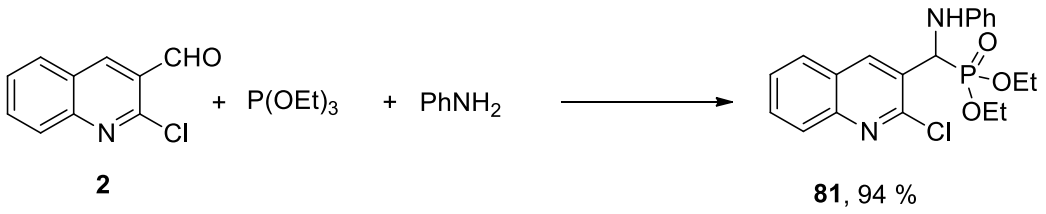
Scheme 28

The formation of tetrazoloquinoline-3-ylmethyl α-alkoxy- **79** and α-hydroxy-phosphonates **80** from reaction of 2-azidoquinoline-3-carbaldehydes **55** 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]



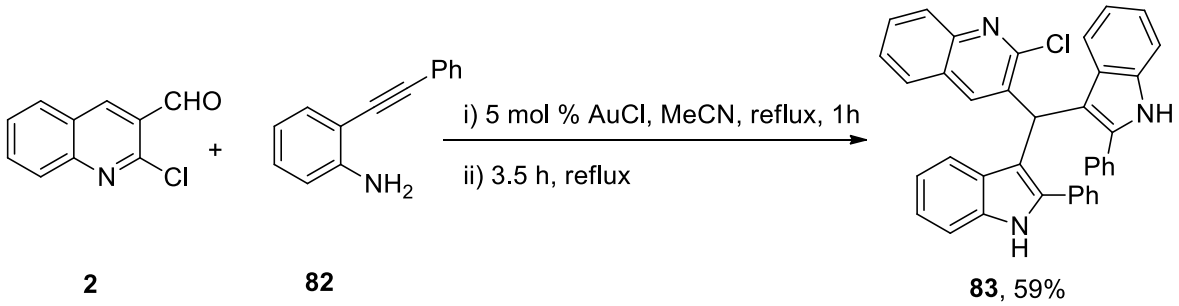
Scheme 29

A three-component reaction of aldehyde **2**, amine, and triethyl phosphite was carried out under solvent-free conditions in the presence of either alum [$KAl(SO_4)_2.12H_2O$] [63] or yttria-zirconia as a catalyst [64] to afford the corresponding *α*-aminophosphonate **81** in 94% or 75%, respectively (Scheme 30).



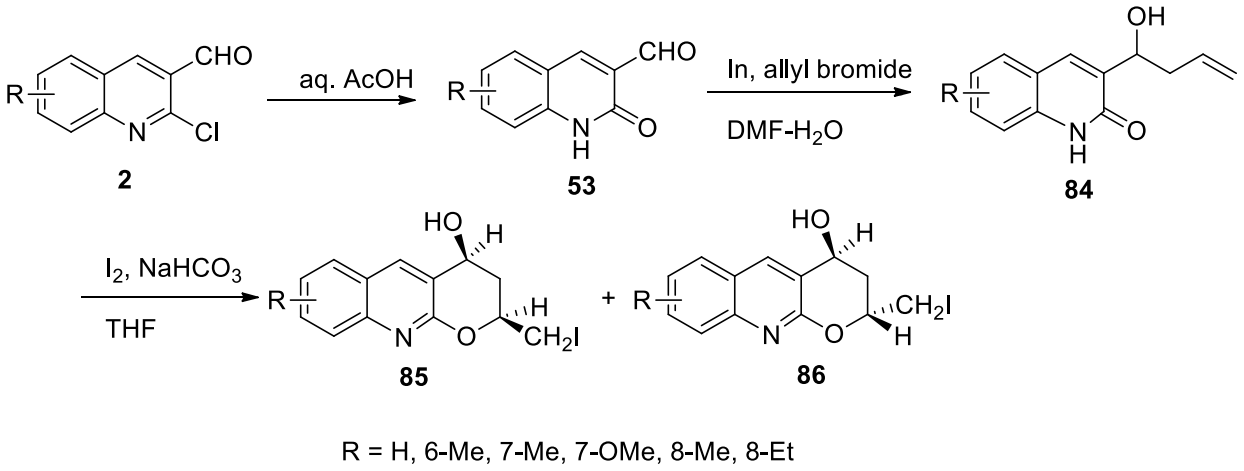
Scheme 30

Synthesis of 3-[bis(2-phenyl-1*H*-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]



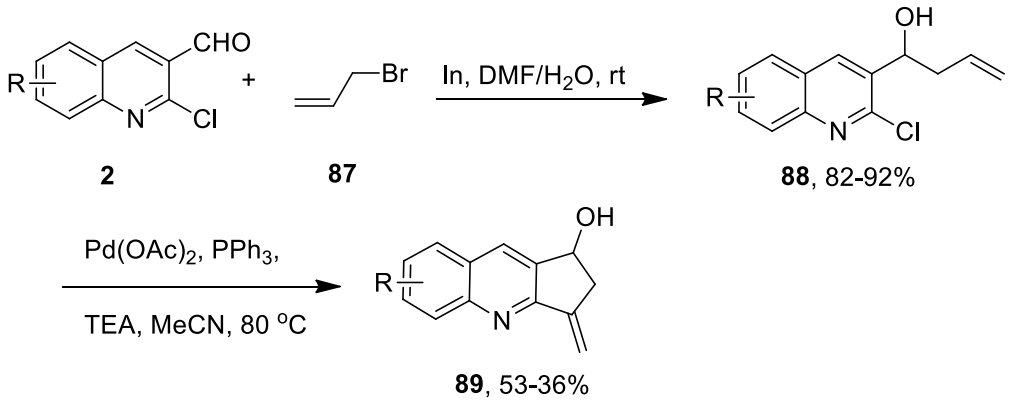
Scheme 31

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 I_2 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).[67]



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-1*H*-cyclopenta[*b*]quinolin-1-ols **89** (Scheme 33). [68]



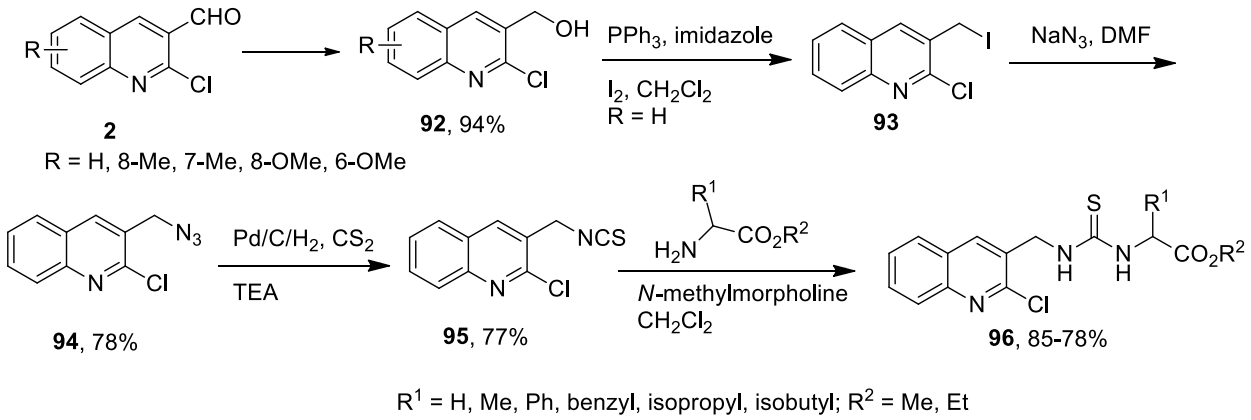
Scheme 33

3.3. Reduction of the aldehyde group

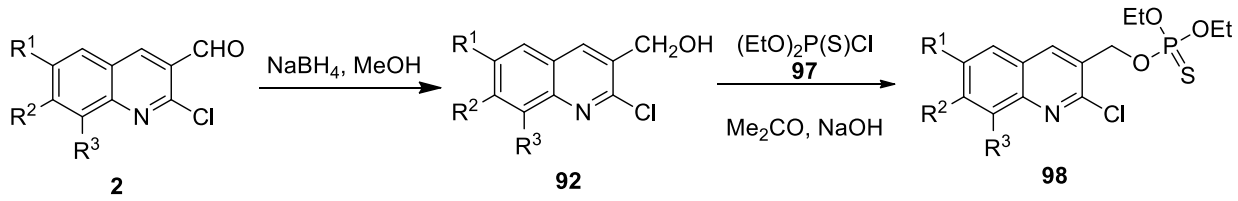
2-Chloroquinoline-3-carbaldehydes **2** were reduced with sodium borohydride $NaBH_4$ to (2-chloroquinolin-3-yl)methanol **92** either by using microwave irradiation,[69-72] or at room temperature.[73-76] Subsequently, compound **92** was converted into iodomethyl quinoline **93** through PPh_3 and imidazole with iodine. Further, azidomethylquinoline **94** was obtained by treating **93** with NaN_3 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 CH_2Cl_2 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)-1*H*-benzimidazol-2-ylthio]methyl]tetrazolo[1,5-*a*]-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)-1*H*-benzimidazole-2-thiol **101** (Scheme 36). The synthesized compounds were screened for the antibacterial activity against gram positive and gram negative bacteria.[47]

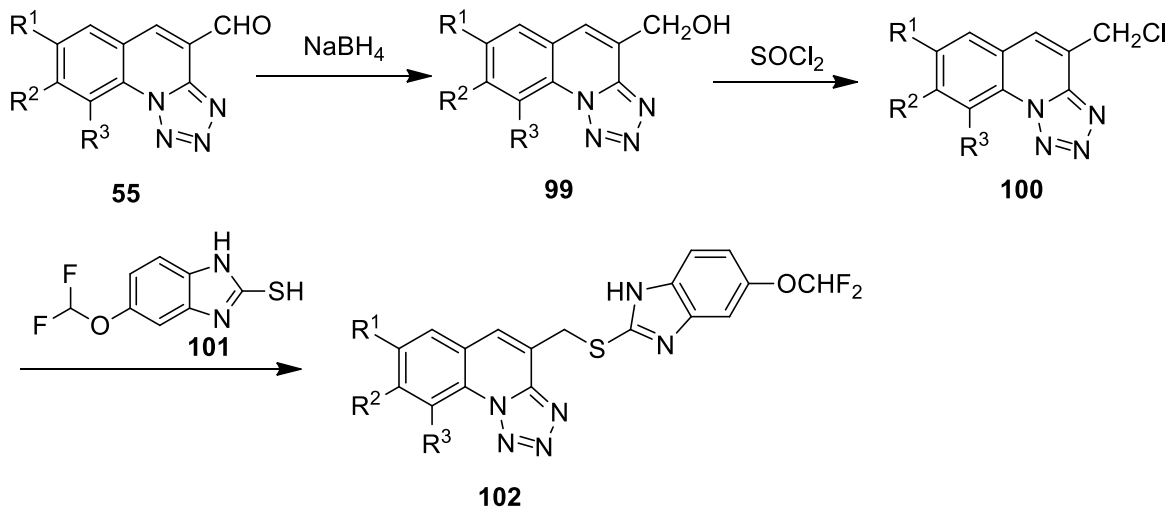


Scheme 34



2,92,98; $R^1 = R^2 = R^3 = H$ (a); R^1 = Me, $R^2 = R^3 = H$ (b); $R^1 = R^3 = H$, R^2 = Me (c); $R^1 = R^2 = H$, R^3 = Me (d); R^1 = MeO, $R^2 = R^3 = H$ (e); $R^1 = R^3 = H$, R^2 = MeO (f); $R^1 = R^2 = H$, R^3 = Et (g); R^1 = EtO, $R^2 = R^3 = H$ (h).

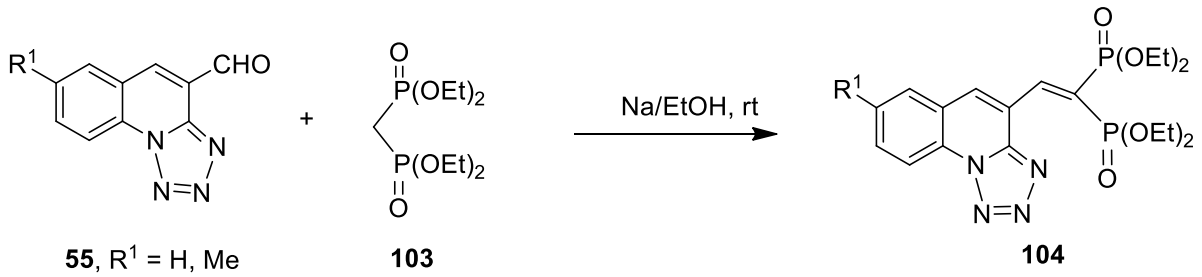
Scheme 35



Scheme 36

3.4. Condensation Reactions

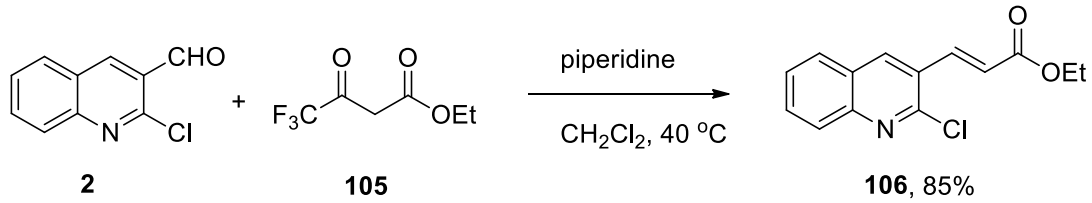
3.4.1 Reactions with active methylene compounds. Perkin–type condensation of aldehyde 55 with tetraethyl methylenebisphosphonate 103 provided the corresponding tetrazoloquinoline-based bisphosphonate esters 104 (Scheme 37).[9]



55, R^1 = H, Me **103** **104**

Scheme 37

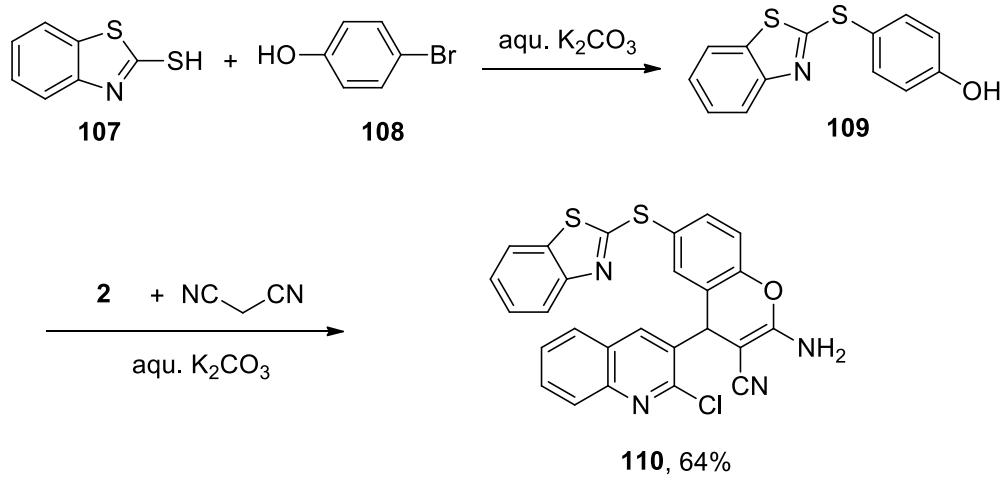
(*E*)-Ethyl 3-(2-chloroquinolin-3-yl)acrylate **106** was synthesized by aldol and elimination reactions of aldehyde **2** with ethyl trifluoroacetoacetate **105** under basic conditions with high stereoselectivity (Scheme 38).[77]



2 **105** **106**, 85%

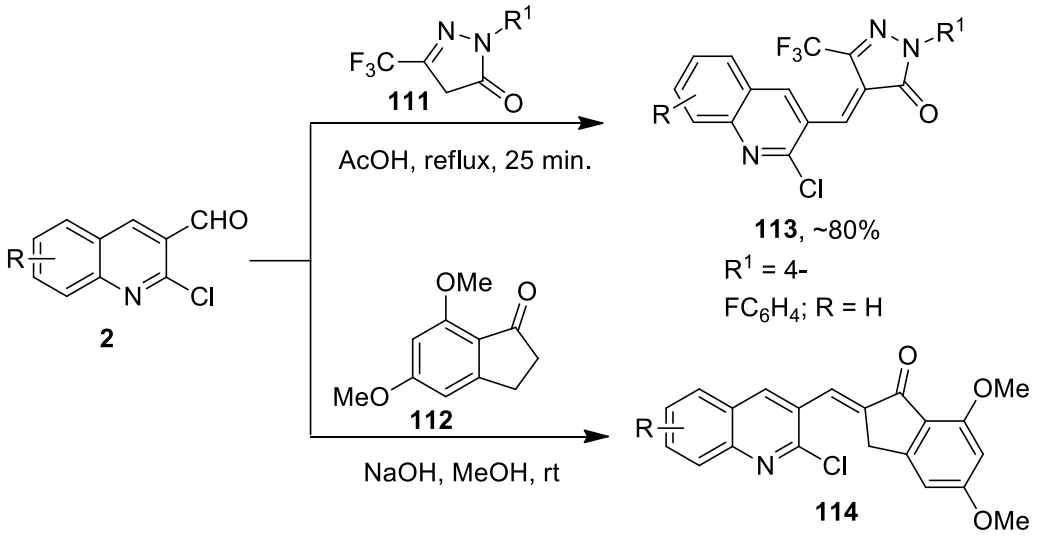
Scheme38

Multi-component reaction of aldehyde **2**, *p*-bromophenol **108**, 2-benzothiazolethiol **107**, and malononitrile was carried out under microwave irradiated in aq. K_2CO_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]



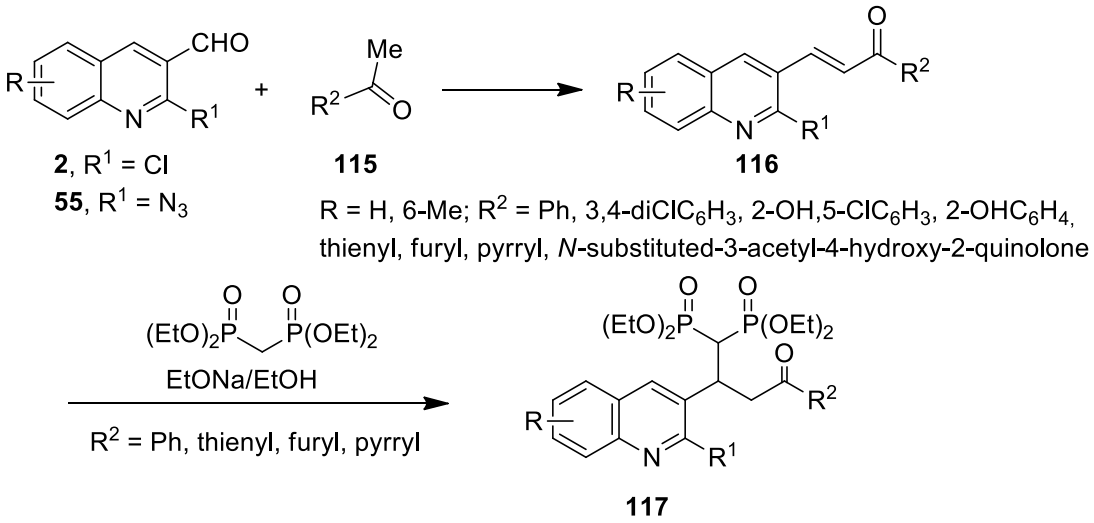
Scheme 39

Claisen-Schmidt condensation of aldehydes **2** either with 3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-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)-1*H*-pyrazol-5(4*H*)-ones **113**[79] and (*E*)-2-((2-chloroquinolin-3-yl)methylene)-5,7-dimethoxy-2,3-dihydro-1*H*-inden-1-ones **114**,[80] in good yields, respectively (Scheme 40). The latter compounds were evaluated in vitro for inhibition of *β*-hematin formation and hemoglobin hydrolysis and *in vivo* for efficacy against *Plasmodium berghei* suggest the antimalarial activity is derived from inhibition of hemoglobinolytic proteases.[80]



Scheme 40

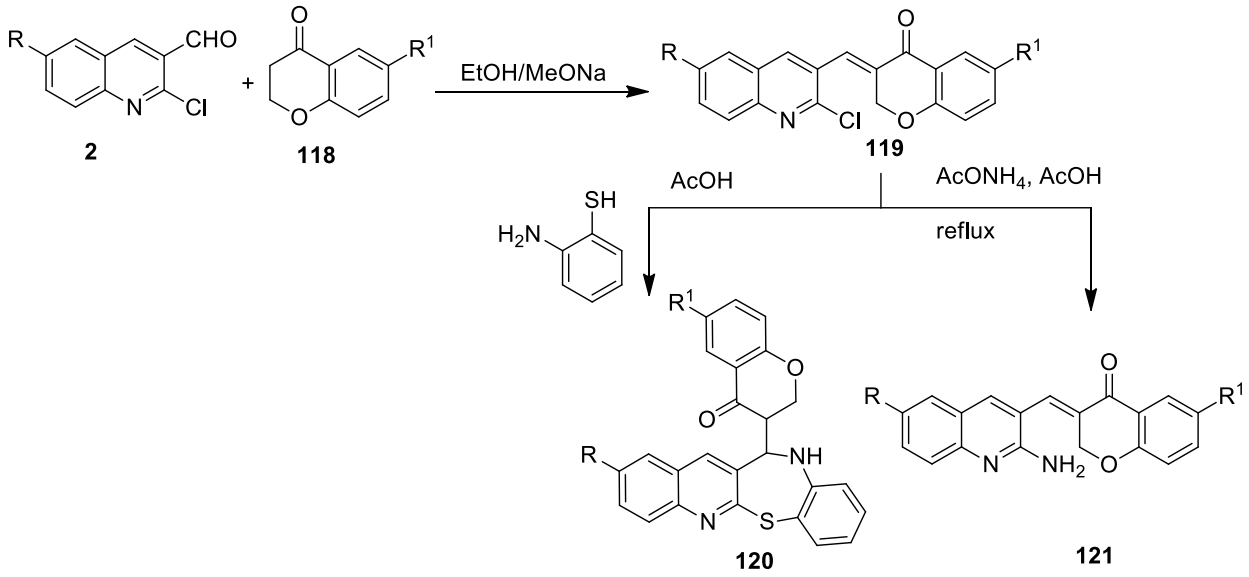
Condensations of aldehydes **2** or **55** with aryl (heterocycles) methyl ketones either by using microwaves under solvent-free conditions or by using conventional methods, to give quinoline chalcones **116** was reported.[10-18,81-88] Michael addition of tetraethyl methylenebisphosphonate to compounds **116** (R = Cl, N_3, R^1 = Ph, thienyl, furyl, pyrryl) in EtOH/EtONa at refluxing temperature gave bisphosphonate adduct **117** (Scheme 41).[10]



Scheme 41

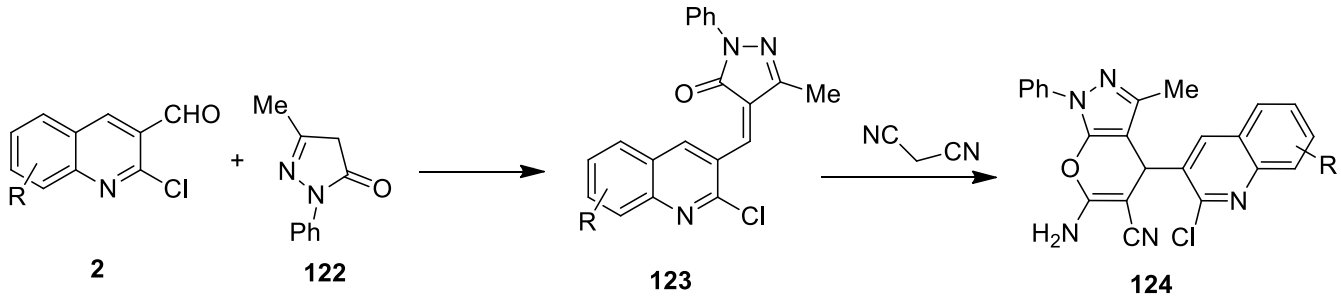
Aldehydes **2** were treated with chromanones **118** in ethanol in the presence of sodium methoxide gave chalcones **119**. The later compounds were reacted either with *o*-aminothiophenol in the presence of catalytic quantity of acetic acid to afford benzothiazepine system flanked by quinoline and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

6-Amino-4-(2-chloroquinolin-3-yl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles **124** were prepared by reaction between aldehyde **2** and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **122** to afford 4-((2-chloroquinolin-3-yl)methylene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-ones **123** followed by cyclocondensation with malononitrile (Scheme 43). All the synthesized compounds have shown significant antimicrobial activity.[89,90]



R = H, Me, OMe; R^1 = H, Cl, Me, $CH(Me)_2$, Et

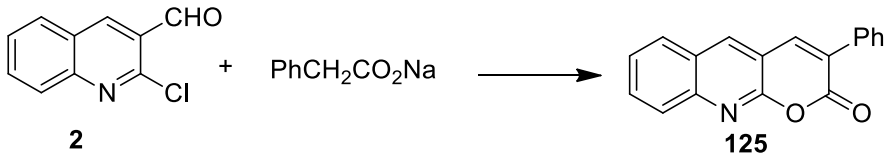
Scheme 42



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

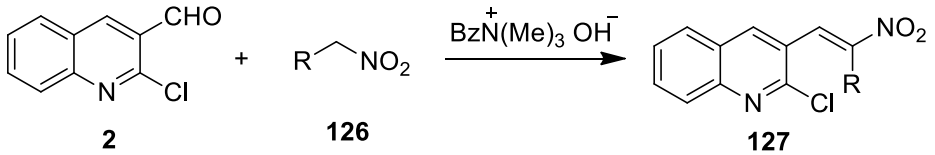
Scheme 43

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).[91]



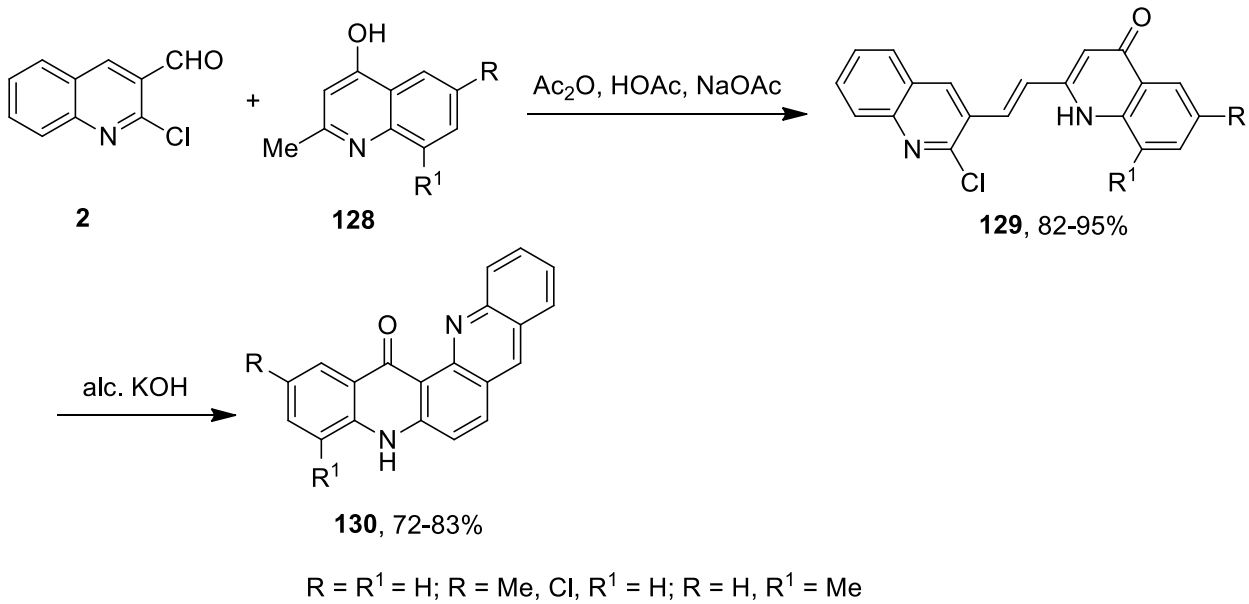
Scheme 44

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]



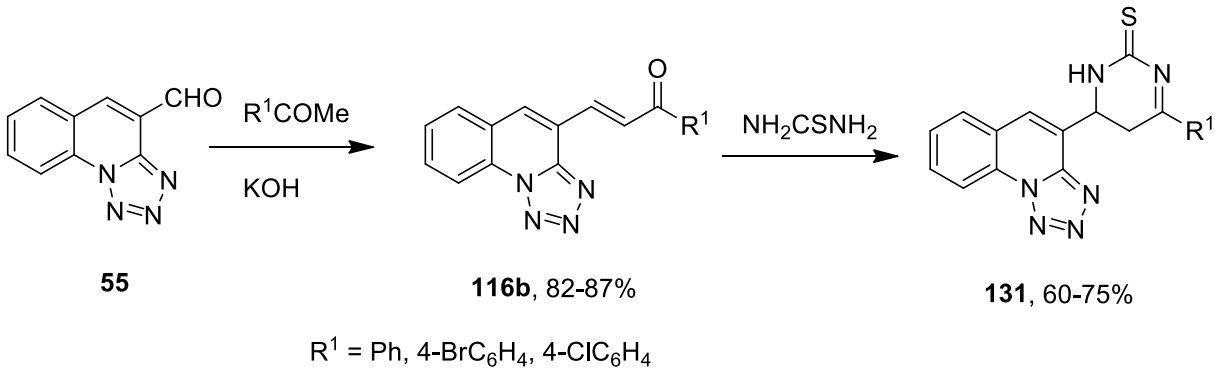
Scheme 45

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(1*H*)-ones **129**, which on cyclization using alcoholic KOH yields the quinacridine systems **130** in 72-83% yields (Scheme 46).[93]



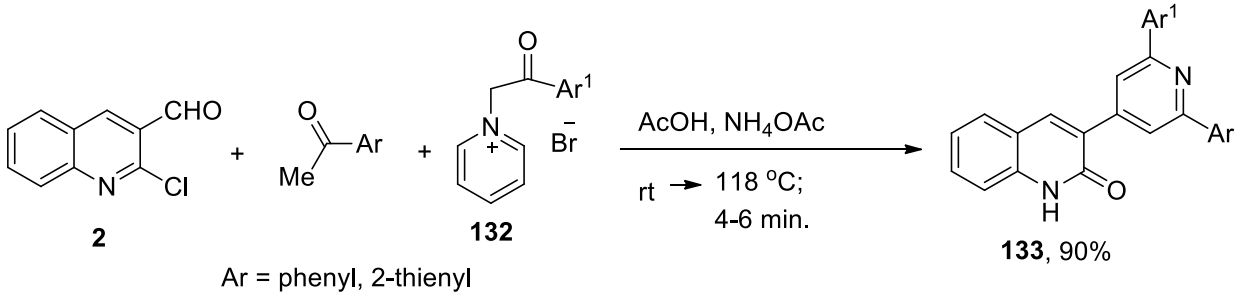
Scheme 46

The pyrimidine derivatives **131** were synthesized by the cyclocondensation of *α*,*β*-unsaturated ketones **116b**, which were prepared from reaction of aldehyde 55 with substituted acetophenone in the presence of KOH, with thiourea (Scheme 47).[48]



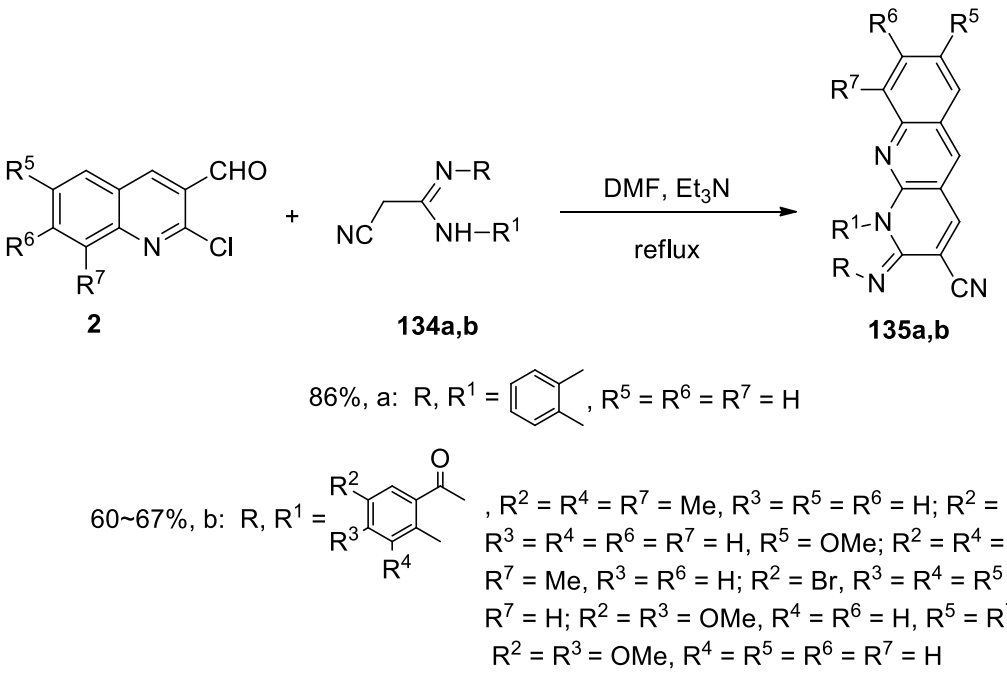
Scheme 47

One-pot synthesis of 3-(2,6-diarylpyrid-n-4-yl)quinolin-2(1*H*)-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]



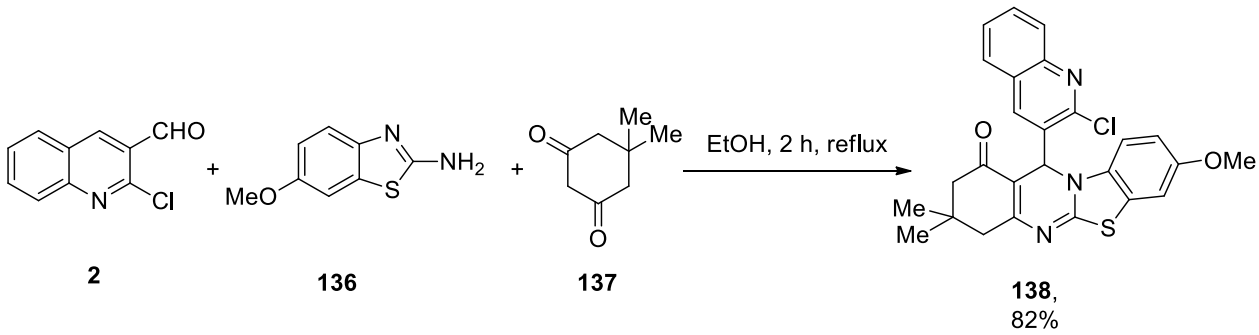
Scheme 48

The interaction of aldehydes **2** with either 1*H*-benzimidazol-2-ylacetonitrile **134a**,[96] or 2-(4-oxo-3,4-dihydroquinazolin-2-yl)acetonitriles **134b**,[97] in DMF in the presence of Et_3N at reflux temperature, gave benzimidazo[1,2-*a*]benzo[*g*][1,8]naphthyridine-6-carbonitrile **135a** and 15-oxo-15*H*-benzo[6,7][1,8]naphthyridino[2,1-*b*]quinazoline-6-carbonitrile **135b**, respectively (Scheme 49).



Scheme 49

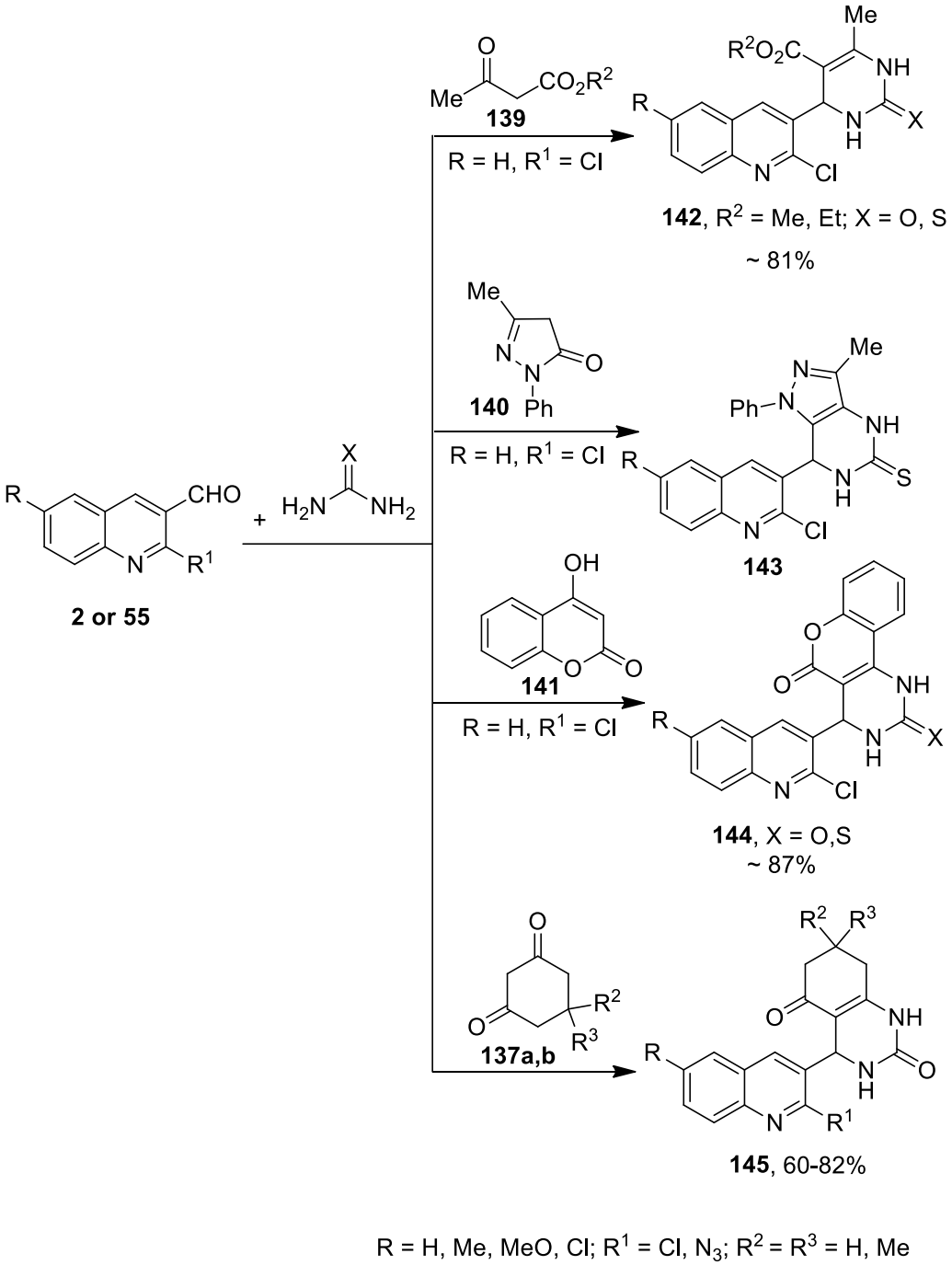
12-(2-Chloro-6-quinolin-3-yl)-2,3,4,12-tetrahydro-1*H*-benzothiazolo[2,3-*b*]quinazolin-1-one **138** was synthesized in one pot by condensing aldehyde **2**, 2-amino-6-methoxybenzothiazole **136**, and 5-dimethyl-1,3-cyclohexanedione **137a** in ethanol (Scheme 50).[98]



Scheme 50

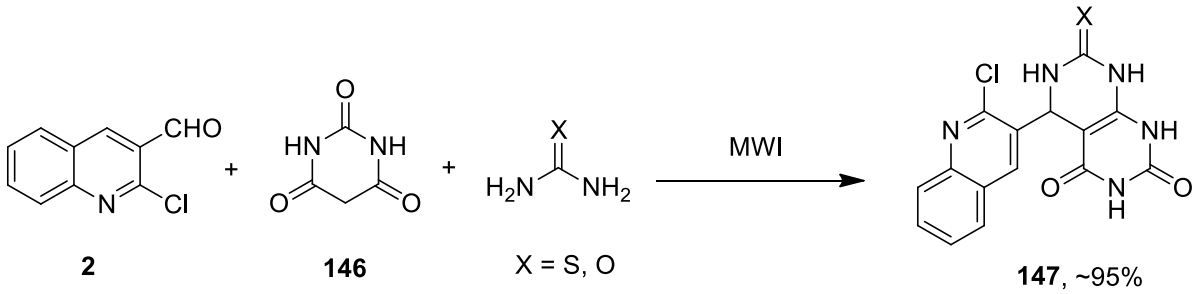
Biginelli reaction of aldehyde **2** with urea or thiourea and active methylene compounds such as ethyl acetoacetate **139**,[99] 3-methyl-1-phenyl-1*H*-pyrazol-5(4H)-one **140**,[100] 4-hydroxy-2*H*-chromen-2-one **141**,[101] dimedone **137a**,[102] or cyclohexane-1,3-dione **137b**,[103] was performed by using either microwave irradiation,[99-101-103] or by traditional methods in the presence of yttria-zirconia-based Lewis acid,[104] silica-supported $(HO)_3Si(CH_2)_3SO_3H$,[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,[100] and were screened for their antimicrobial activities, respectively.[102]



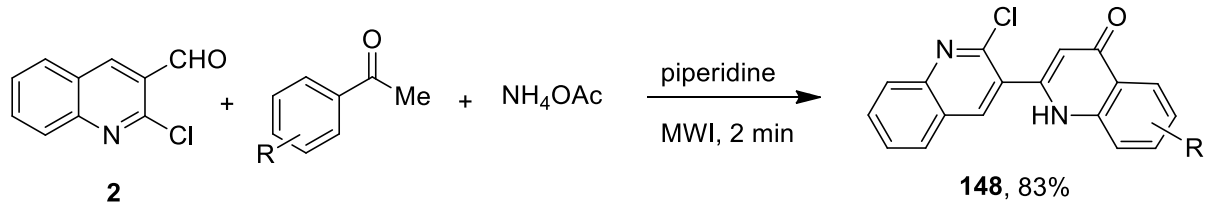
Scheme 51

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[107] or water[108] under microwave irradiation (Scheme 52).



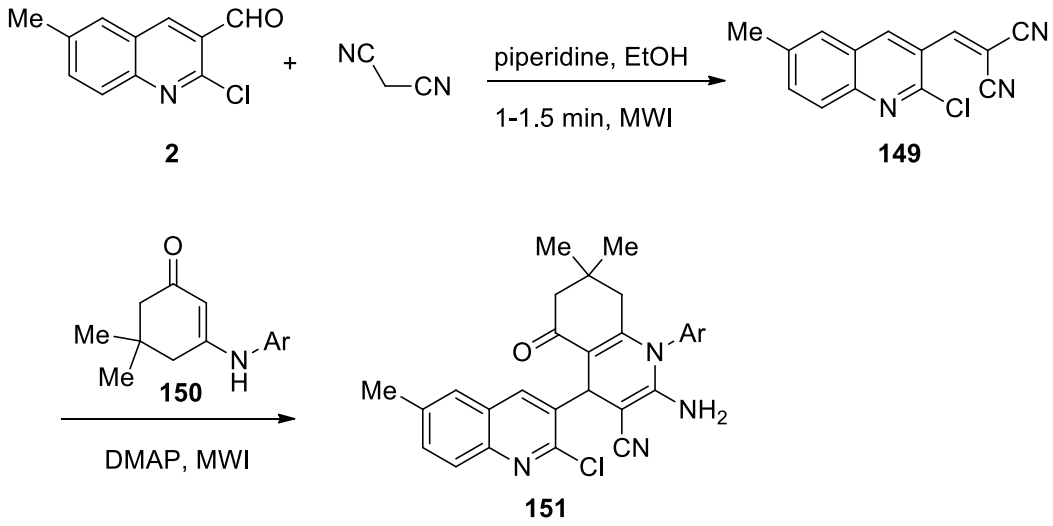
Scheme 52

2'-Chloro-2,3'-biquinolin-4(1*H*)-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.[109]



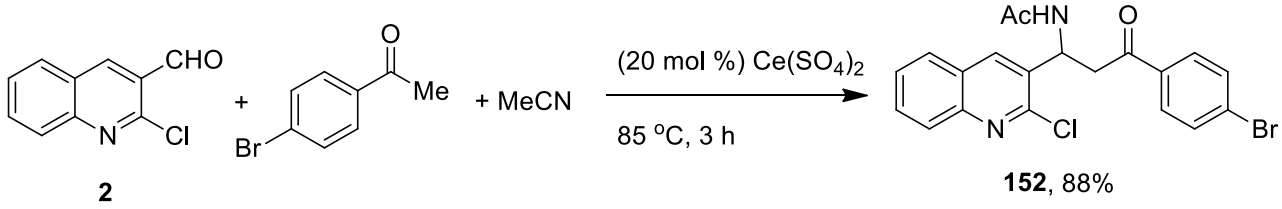
Scheme 53

Biquinoline adducts **151** were synthesized in high yields by cyclization of [(2-chloro-3-quinolyl)methylene]methane-1,1-dicarbonitriles **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.[110]



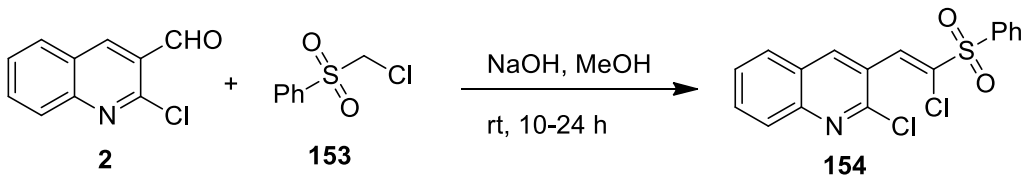
Scheme 54

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]



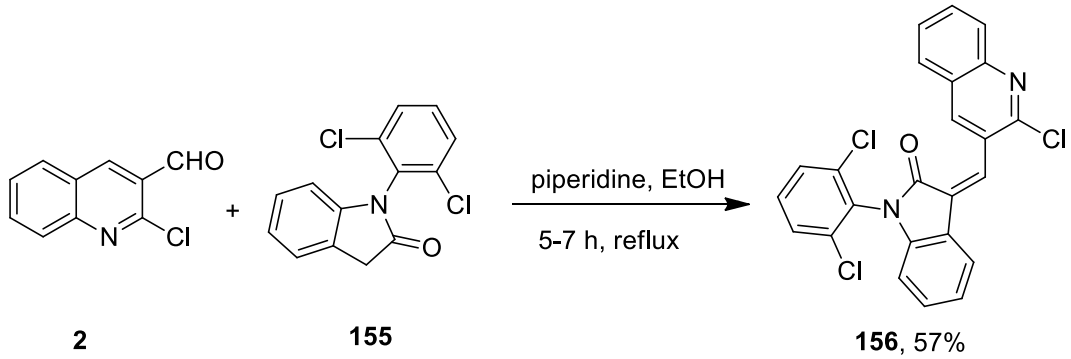
Scheme 55

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]



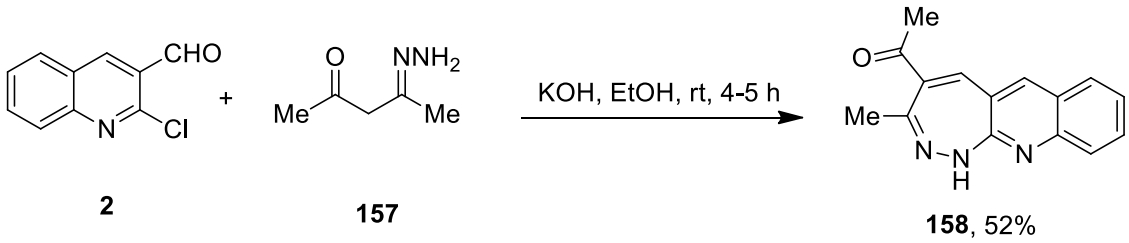
Scheme 56

The 3-arylideneindolinone **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 *in vitro* cytotoxic activity on SW620 colon cancer cell lines.[113]



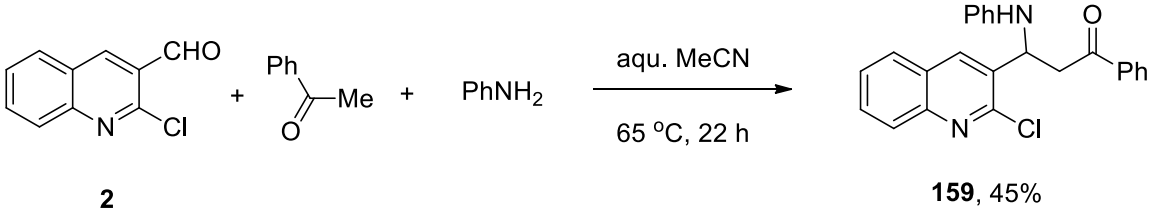
Scheme 57

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-*b*]quinoline **158** (Scheme 58). The later compound was screened for antimicrobial activity.[114]



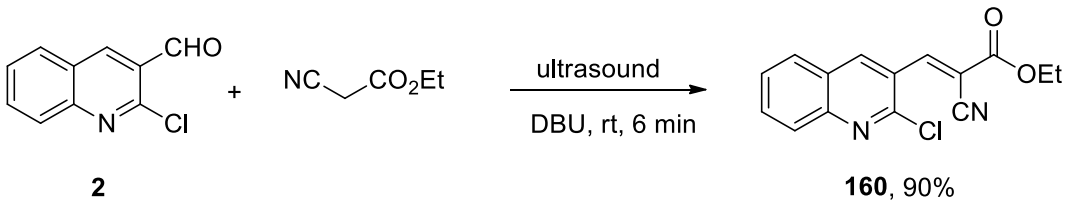
Scheme 58

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).[115]



Scheme 59

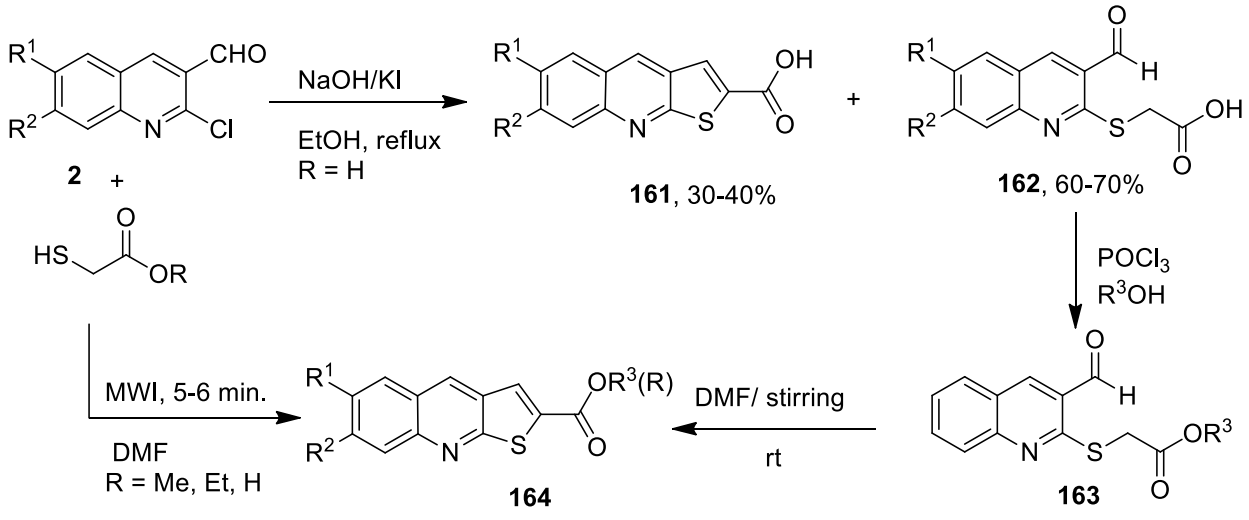
The Knoevenagel condensation reaction of aldehyde **2** with ethyl cyanoacetate was carried out under ultrasonic irradiation catalyzed by 1,8-diazabicycloundec-7-ene (DBU) at room temperature under solvent-free conditions to afford (*E*)-ethyl 3-(2-chloroquinolin-3-yl)-2-cyanoacrylate **160** (Scheme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



2 **160**, 90%

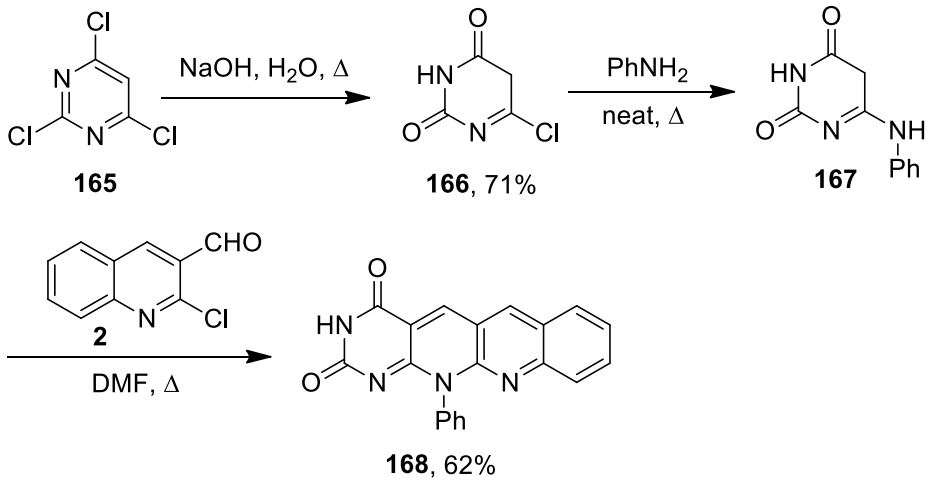
Scheme 60

The reaction between aldehyde **2** and thioglycolic acid in refluxing ethanol containing sodium hydroxide and potassium iodide, afforded a mixture of [(3-formylquinolin-2-yl)thio]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-formylquinolin-2-yl)thio]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 *β*-hematin formation and Hb hydrolysis *in vitro* and *in vivo*.[119]



Scheme 61

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).[120] The compound act as a low molecular weight inhibitor of the E3 activity of HMD2 in tumors that retain wild-type p53.[120]

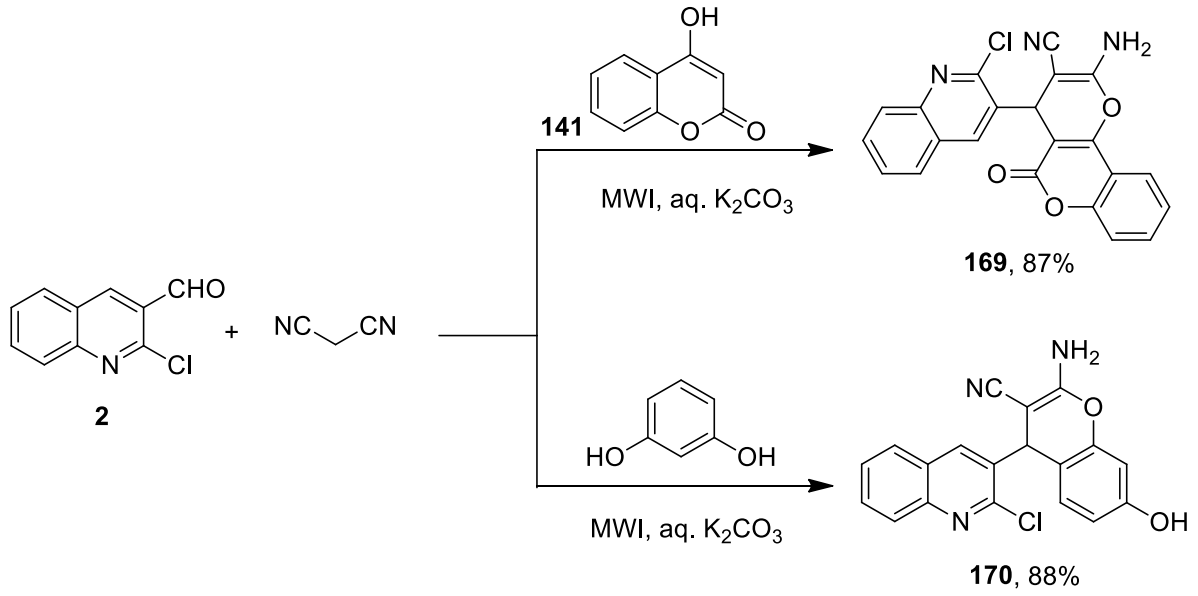


165 **166**, 71% **167**

168, 62%

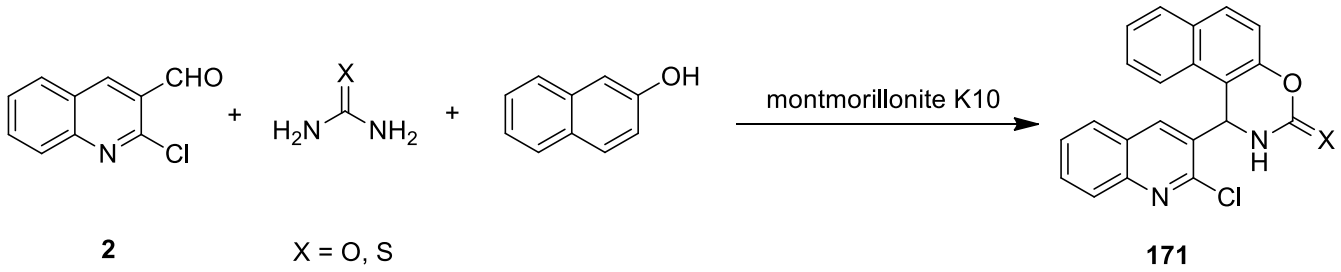
Scheme 62

The three-component reaction of aldehyde **2**, malononitrile, and either 4-hydroxycoumarin **141** or resorcinol was performed in aqueous K_2CO_3 under microwave irradiation to give 2-amino-4-(2-chloroquinolin-3-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile **169**[121] and 2-amino-4-(2-chloroquinolin-3-yl)-7-hydroxy-4*H*-chromene-3-carbonitrile **170**[122] 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]



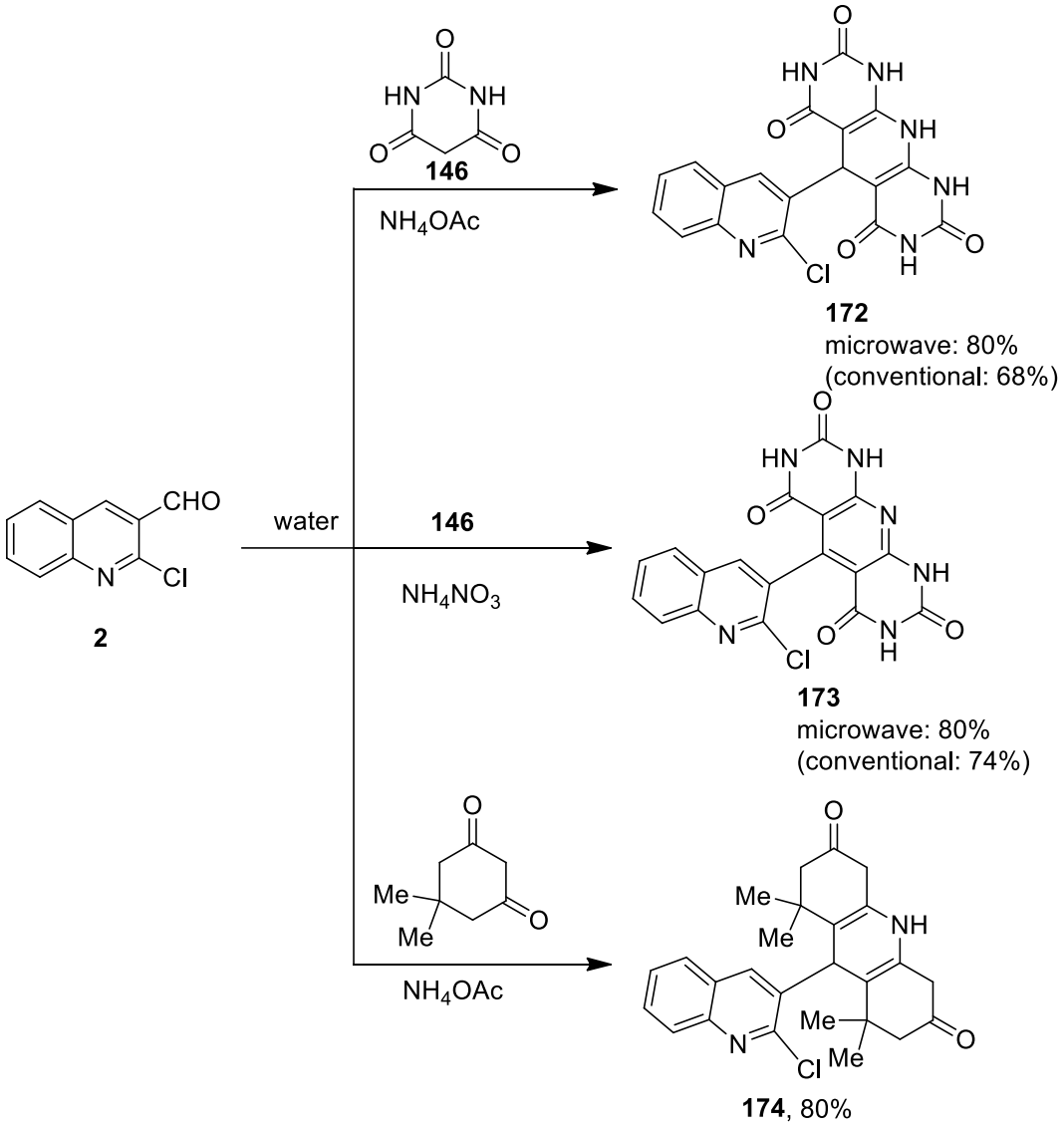
Scheme 63

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)-1*H*-naphtho[1,2-*e*][1,3]oxazin-3(2*H*)-one (thione) **171** in excellent yields (Scheme 64).[123]



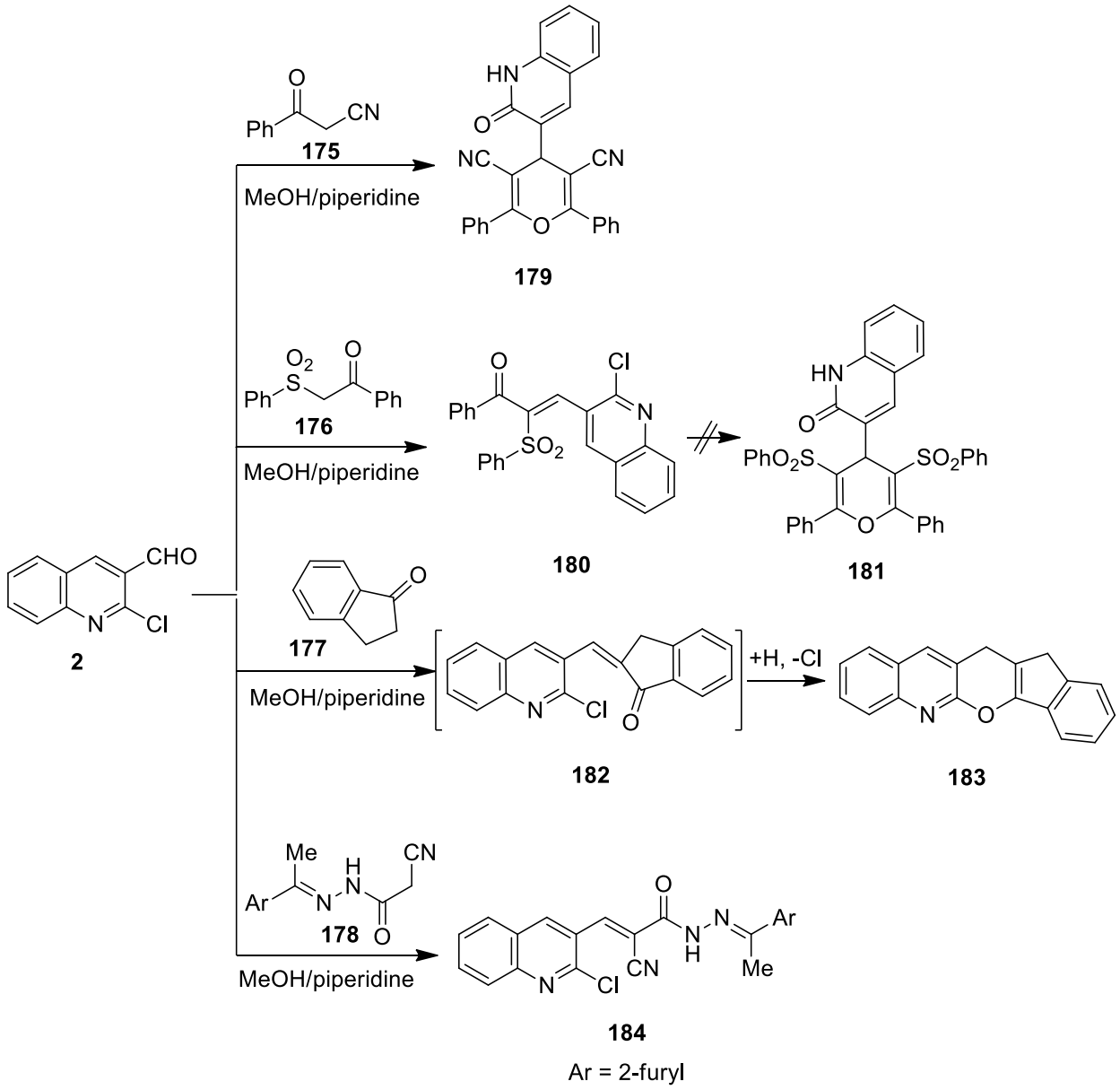
Scheme 64

Pyridine derivatives **172-174** were synthesized *via* Hantzsch reaction of aldehyde **2**, barbituric acid **146**,[124] or dimedone **137a**,[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).



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-4*H*-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).[6]

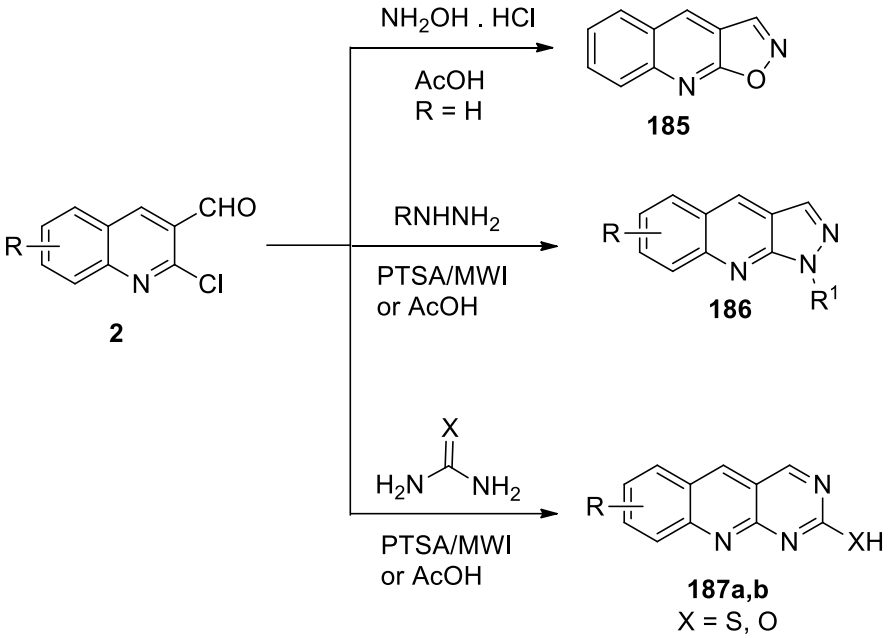


Scheme 66

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,[125] either by traditional methods[15] in acetic acid or by solvent-free microwave-induced techniques using PTSA as a catalyst,[126,127] or potassium carbonate in DMF,[128] 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

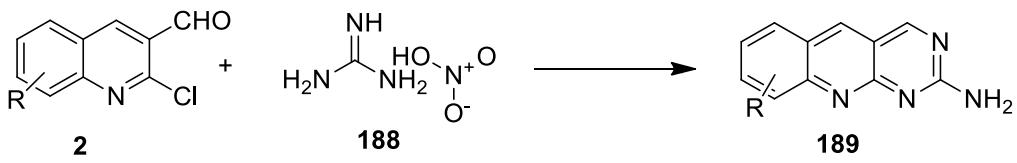
noramidopyrine (NAP),[15] and they were evaluated for their antibacterial and antifungal activities, most of them showing activity against *Escherichia coli* and *Pseudomonas aeruginosa*.[126,129]

On the other hand, pyrazolo[3,4-*b*]quinolines **186** (R_1 = 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]



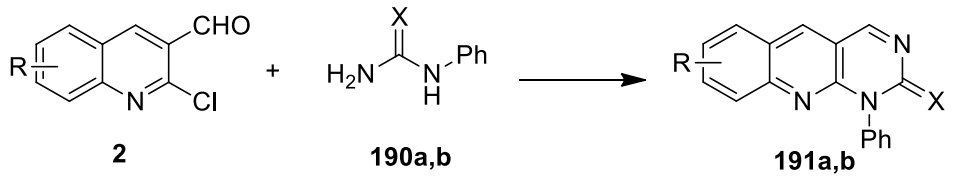
Scheme 67

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

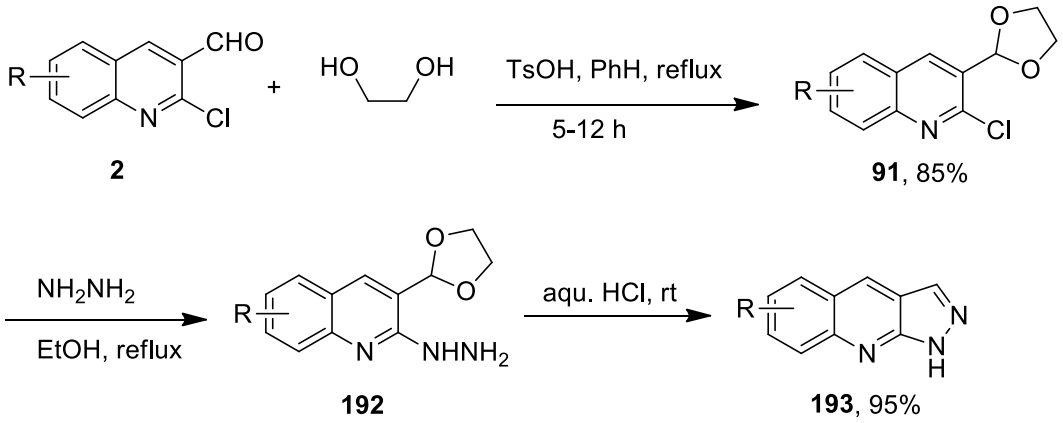
One-step synthesis of 1-phenylpyrimido[4,5-*b*]quinoline-2(1*H*)-thiones **191a**,[132] or -ones **191b** [90] were achieved from reaction of aldehydes **2** with *N*-phenylthiourea **190a** or *N*-phenylurea **190b**, respectively (Scheme 69). The synthesized compounds were biologically screened for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



R = alkyl, alkoxy, halo; X = (a) S, (b) O

Scheme 69

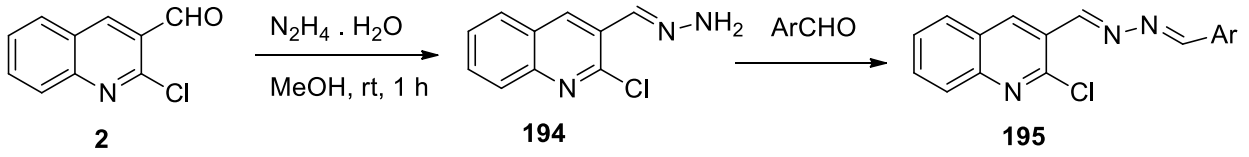
Synthesis of pyrazolo[3,4-*b*]quinolines **193** was reported from direct reaction of aldehydes **2** with hydrazine was unsuccessful, because the formed hydrazone had *E* geometry and thus was sterically prevented from attacking the quinoline C-2. In order to avoid this difficulty, the aldehydes **2** 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 1*H*-pyrazolo[3,4-*b*]-quinolines **193** (Scheme 70).[133,134]



R = 8-Me, 7-Me, 6-Me, 7-MeO, 6-MeO

Scheme 70

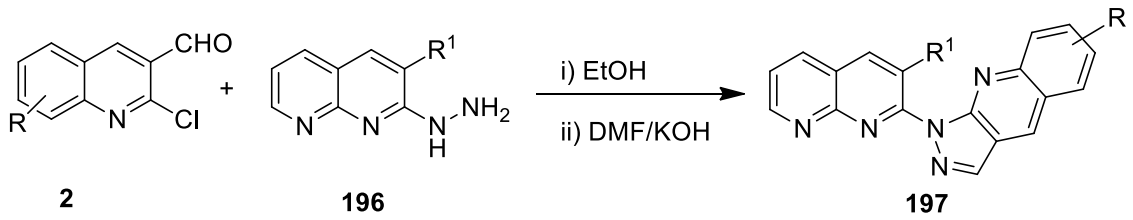
2-Chloroquinoline-3-carbaldehyde [arylmethylene]hydrazones **195** were synthesized from reaction of aldehyde **2** with hydrazine to give hydrazone **194** followed by reaction with substituted aldehydes (Scheme 71). The synthesized derivatives were screened for antibacterial and antifungal activities.[135]



Ar = 6-$(NMe_2)C_6H_4$, 2-hydroxy-1-naphthyl

Scheme 71

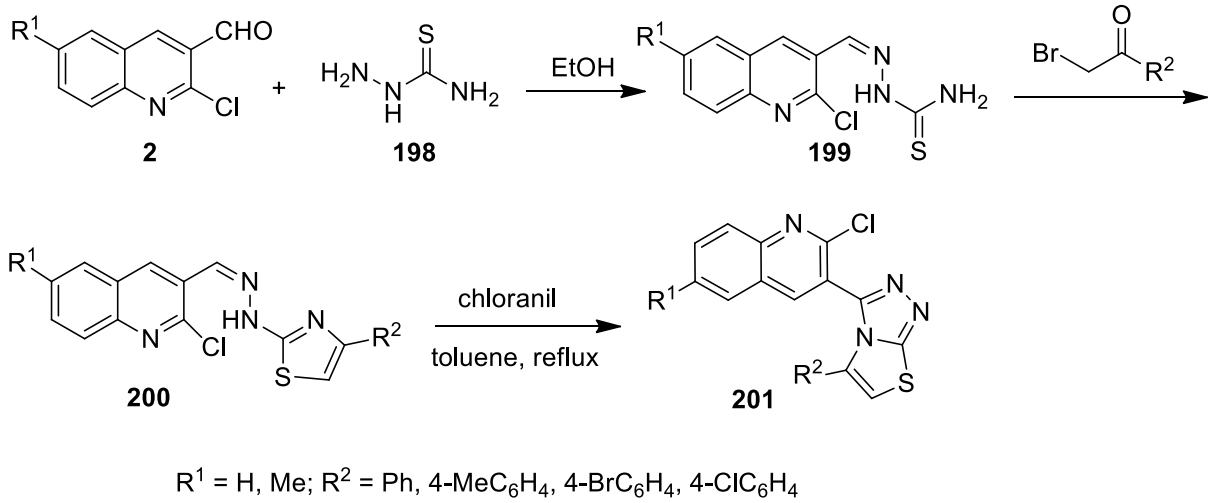
1,8-Naphthyridinyl pyrazolo[3,4-*b*]quinolines **197** were synthesized by reaction of 2-hydrazino-3-(4-methoxyphenyl)-1,8-naphthyridine **196** with aldehydes **2** followed by cyclization with DMF/KOH either by microwave irradiation or by conventional methods. The reaction rate is enhanced tremendously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



R = H, 6-Me, 7-Me, 8-Me, 8-MeO, 6-Cl, 6-Br; R^1 = 4-$MeOC_6H_4$

Scheme 72

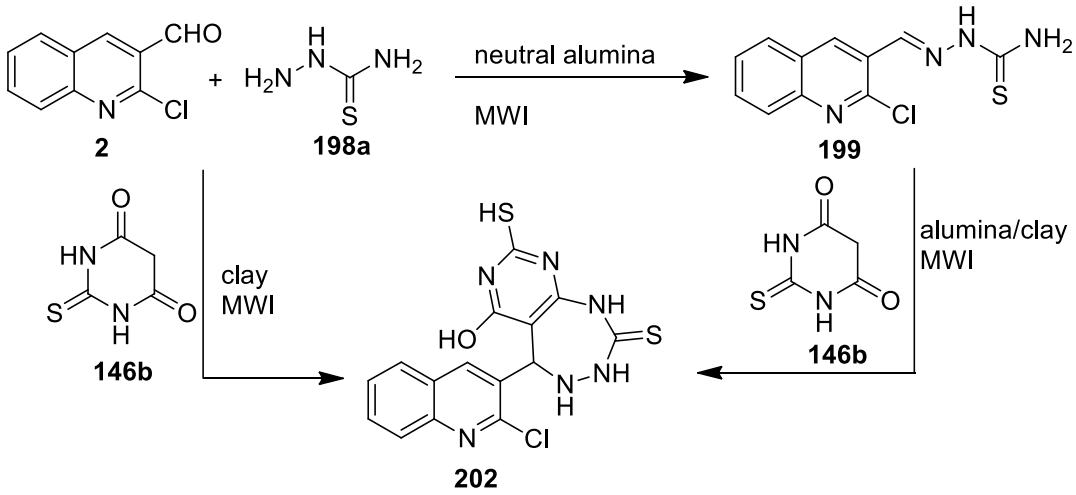
The aldehydes **2** underwent condensation with thiosemicarbazide **198** to give the corresponding thiosemicarbazones **199**, which on treatment with phenacyl bromides, gave thiazoles **200**. The dehydrogenative cyclization of **200** was achieved with chloranil, in refluxing toluene, resulting in 3-(2-chloroquinolin-3-yl)-5-arylthiazolo[2,3-*c*][1,2,4]triazoles **161** (Scheme 73).[137]



R^1 = H, Me; R^2 = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4

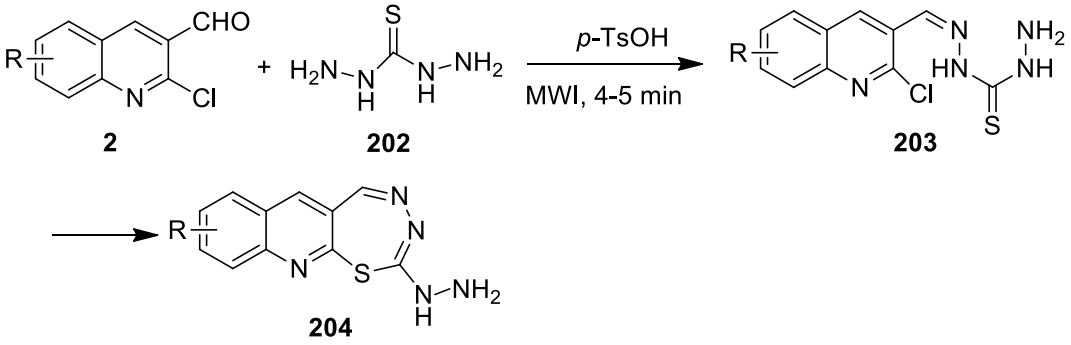
Scheme 73

5-(2-Chloroquinolin-3-yl)-6-hydroxy-8-mercapto-4,5-dihydro-1*H*-pyrimido[4,5-*e*][1,2,4]triazepine-2(3*H*)-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).[138]



Scheme 74

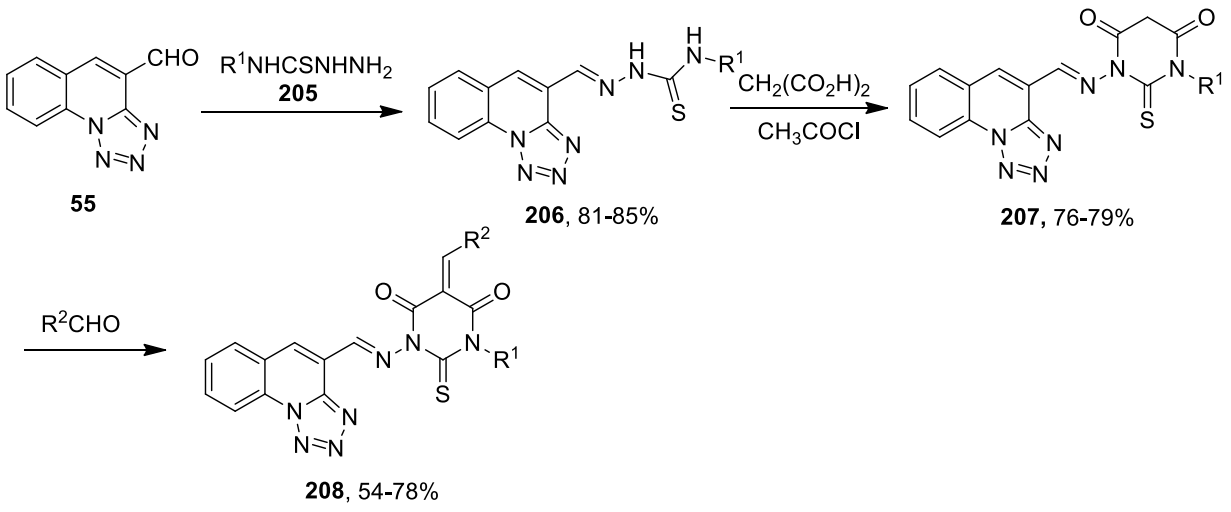
2-Hydrazinyl[1,3,4]thiadiazepino[7,6-*b*]quinolines **204** were obtained in good yields by one pot reaction of aldehyde **2** with carbidimide **202** in DMF in the presence of *p*-TsOH as a catalyst under microwave irradiation (Scheme 75).[139,140]



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

Scheme 75

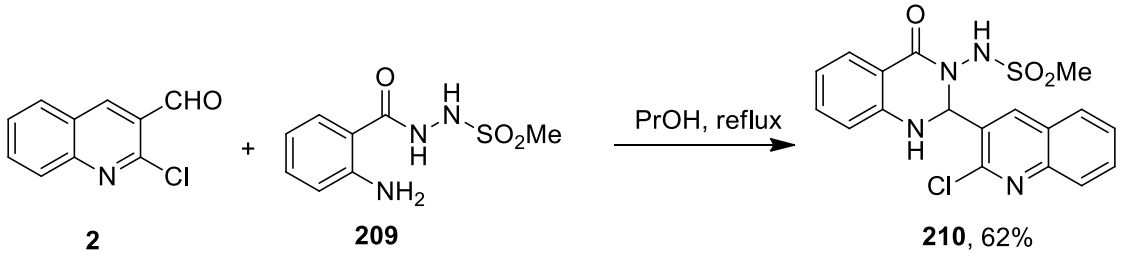
Condensation of tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **55** with substituted thiosemicarbazides **205** afforded the corresponding thiosemicarbazones **206**. The later compounds underwent cyclization with malonic acid in the presence of acetyl chloride to give the pyrimidine derivatives **207**.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



R^1 = Ph, 4-MeC_6H_4, 4-ClC_6H_4; R^2 = Ph, 4-$(Me)_2NC_6H_4$

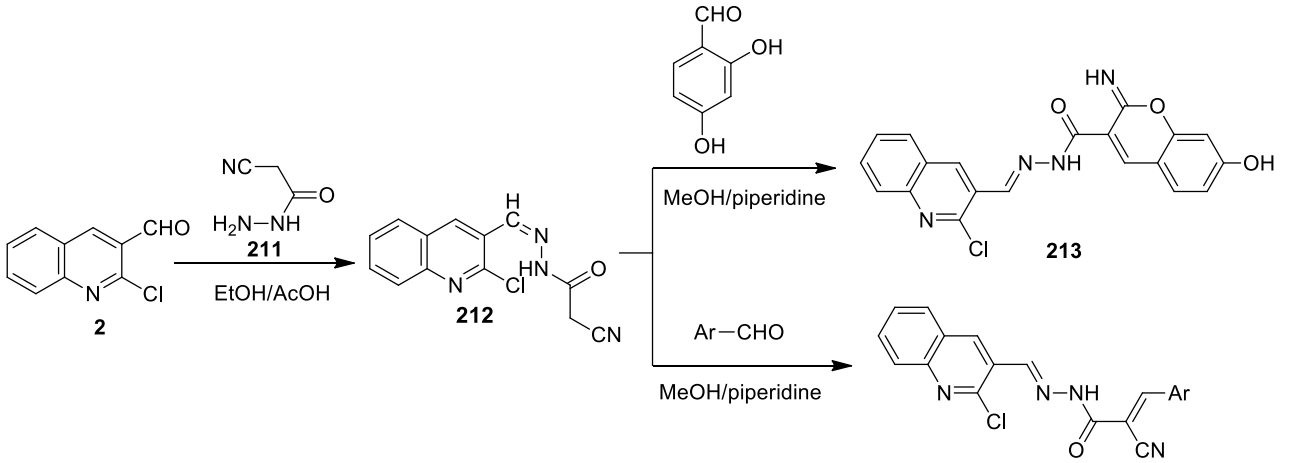
Scheme 76

The reaction of aldehyde **2** with *N*′-(2-aminobenzoyl)methanesulfonohydrazide **209** in refluxing propanol gave *N*-(2-(2-chloroquinolin-3-yl)-4-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)-methanesulfonamide **210** (Scheme 77).[141]



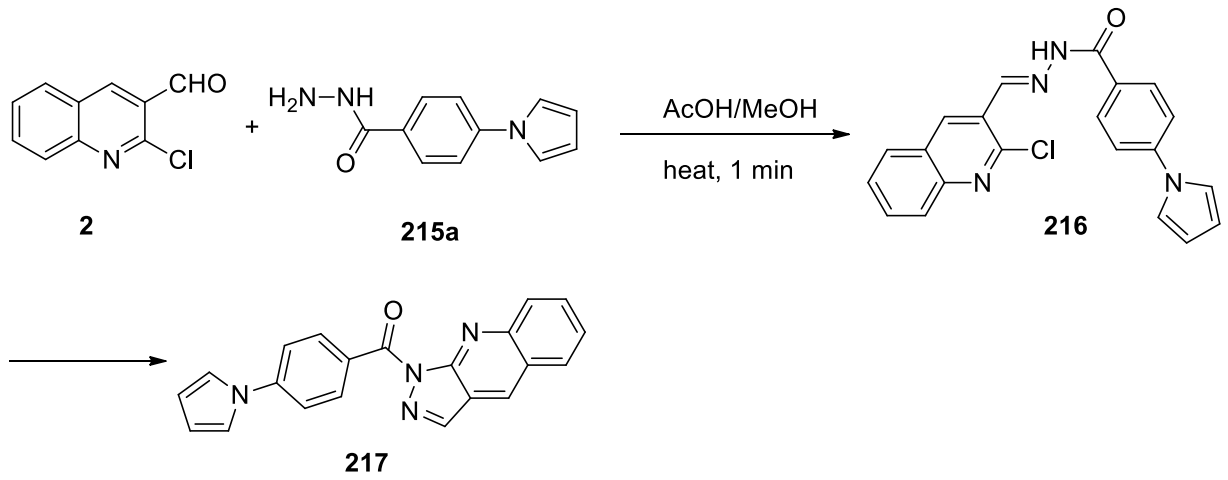
Scheme 77

The reaction of aldehyde **2** with 2-cyanoacetohydrazide **211** in boiling ethanol containing a few drops of acetic acid to afford *N*′-[(2-chloroquinolin-3-yl)methylene]-2-cyanoacetohydrazide **212** in good yield. Condensation of **212** with 2,4-dihydroxybenzaldehyde, 4-fluorobenzaldehyde, and 1-phenyl-3(2-thienyl)-1*H*-pyrazole-4-carbaldehyde, in methanol in the presence of a few drops of piperidine at reflux temperature, gave *N*′-[(2-chloroquinolin-3-yl)methylene]-7-hydroxy-2-imino-2*H*-chromene-3-carbohydrazide **213**, *N*′-((2-chloroquinolin-3-yl)methylene)-2-cyano-3-(1-phenyl-3(2-thienyl)-1*H*-pyrazol-4-yl)acrylohydrazide **214a**, and *N*′-((2-chloroquinolin-3-yl)methylene)-2-cyano-3-(4-fluorophenyl)acrylohydrazide **214b**, respectively (Scheme 78). The *anti*-inflammatory and analgesic activities of the synthesized compounds were evaluated.[6]



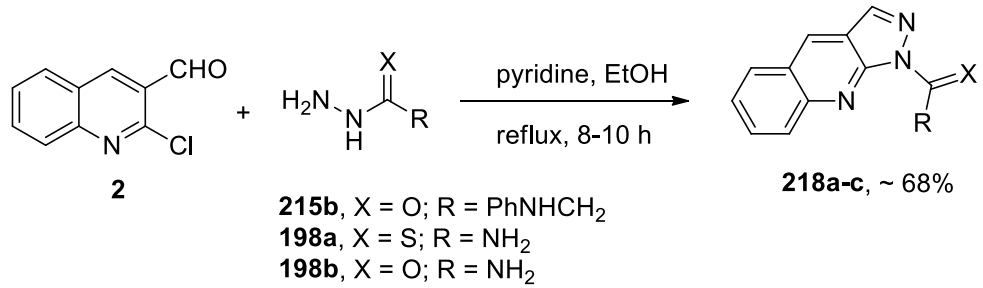
Scheme 78

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



Scheme 79

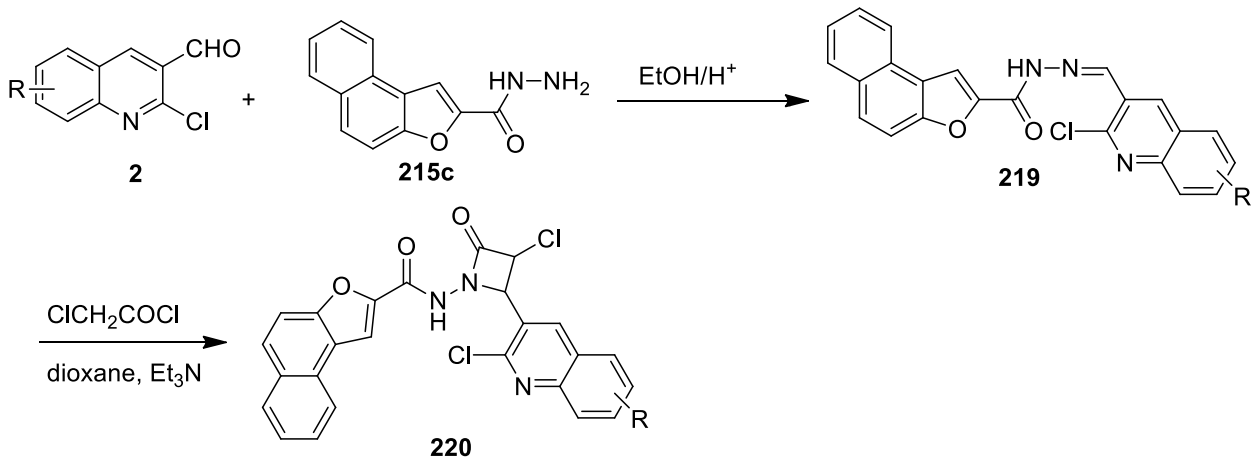
2-(Phenylamino)-1-(1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)ethanone **218a**, 1*H*-pyrazolo[3,4-*b*]-quinoline-1-carbothioamide **218b**, and 1*H*-pyrazolo[3,4-*b*]quinoline-1-carboxamide **218c** were synthesized by the condensation of aldehyde **2** with 2-(phenylamino)acetohydrazide **215b**, thiosemicarbazide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



Scheme 80

Naphtho[2,1-*b*]furan-2-carbohydrazide **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**

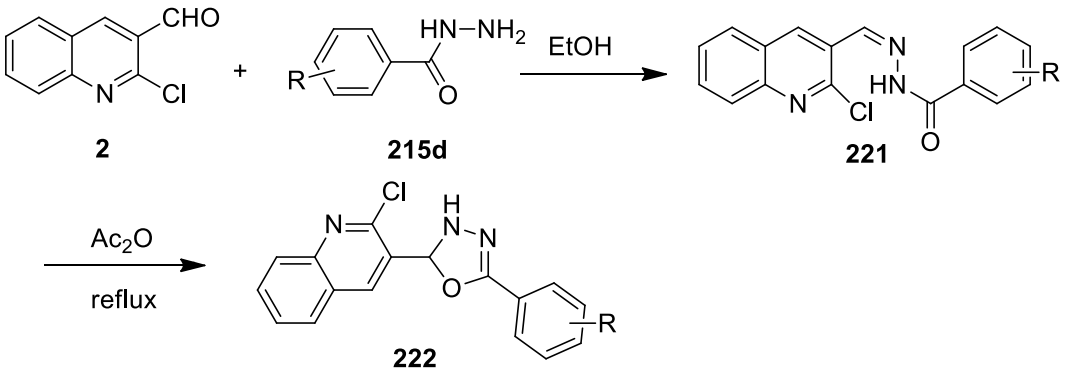
(Scheme 81). The synthesized compounds were screened for their antibacterial and antifungal activities.[144]



R = 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-$(OMe)_3$

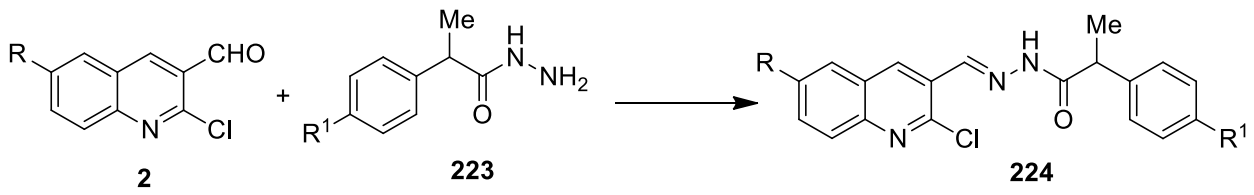
Scheme 81

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]



Scheme 82

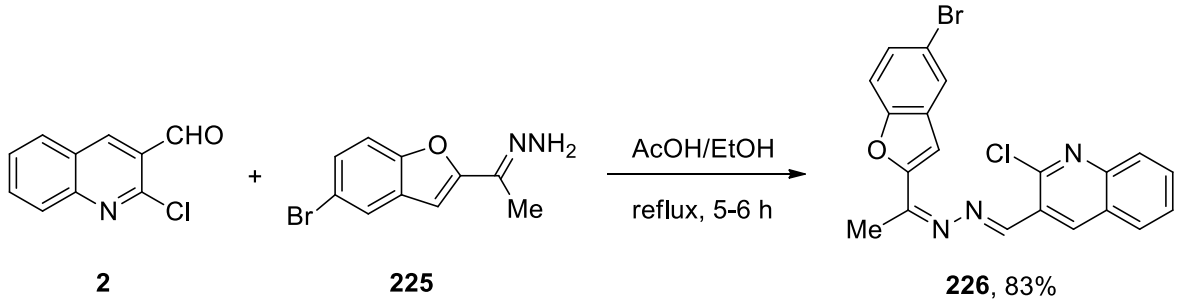
N′-[(2-Chloroquinolin-3-yl)methylene]-2-arylpropanehydrazide **224** was synthesized and evaluated for their anti-inflammatory activity from reaction of aldehyde **2** with arylpropanehydrazide **223** (Scheme 83).[100,145]



R = H, R^1 = $(CH_3)_2CHCH_2$; R = Me, OMe, Cl; R^1 = MeO

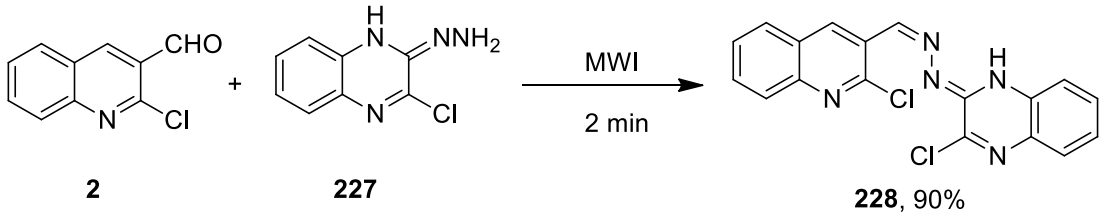
Scheme 83

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).[146]



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).[147]

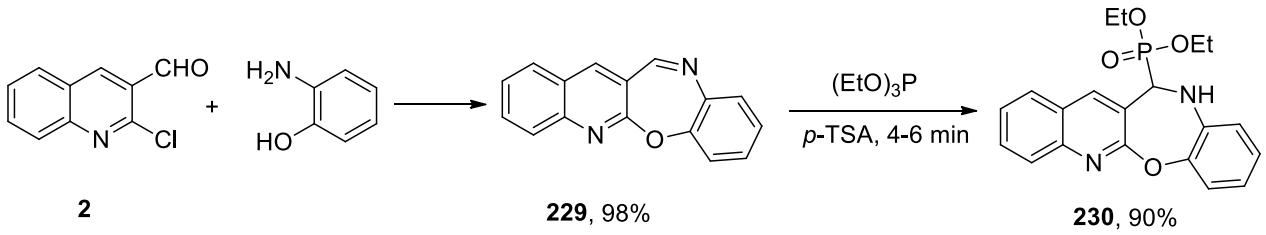


Scheme 85

3.4.3. Reactions with amines and amides

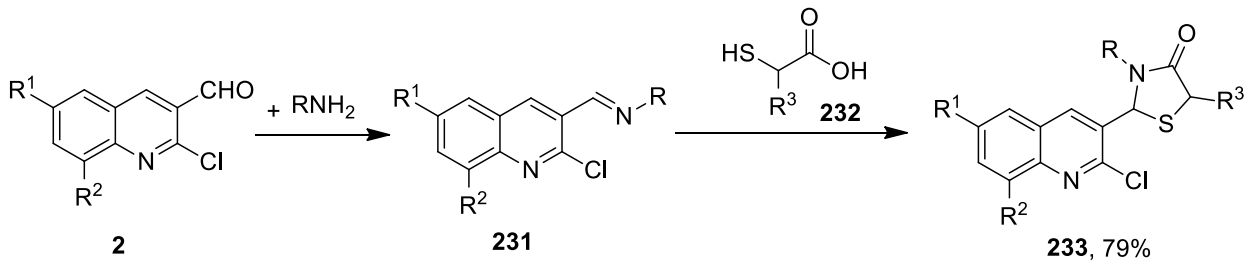
Condensation of aldehydes **2** with 2-aminophenol was reported either by traditional methods[148,149] or under the influence of microwave irradiation using 1,8-diazabicycloundec-7-ene-silica gel as a catalyst,[150] to afford quinolino[2,3-*b*][1,5]benzoxazepine **229** in excellent

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 *α*-aminophosphonate **230** in high yield (Scheme 86). The synthesized compound showed antibacterial activity against gram-positive and gram-negative bacteria.[148]



Scheme 86

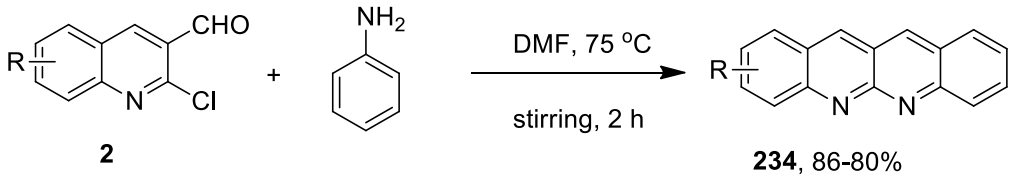
Synthesis of 2-(2-chloroquinolin-3-yl)-3-phenylthiazolidin-4-ones **233** were reported either by DCC (dicyclohexylcarbodiimide) mediated three-component one-pot reaction of aldehyde **2**, amine, and mercaptoacetic acid **232** [151] or by cyclocondensation of mercaptoacetic acid **232** with Schiff 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]



R = Ph, 4-$AsO(OH)_2C_6H_4$, 4- antipyrinyl, 4-$EtO_2CC_6H_4$, 2-ClC_6H_4, 3-Cl-4-FC_6H_4, 2,4-$Cl_2C_6H_4$, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-$O_2NC_6H_4$, C_5H_5N ; R^1 = H, Me, MeO; R^2 = H, Me; R^3 = H, Me

Scheme 87

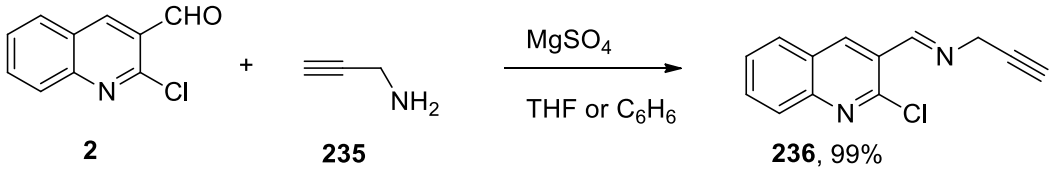
The aldehydes **2** when reacted with aniline in DMF afford dibenzo[*b*,*g*][1,8]naphthyridines **234** (Scheme 88).[153]



R = H; 5-Me;8-Me;8-Me, 6-Me; 6-OMe; 7-OMe; 8-OMe; 8-OMe, 5-OMe

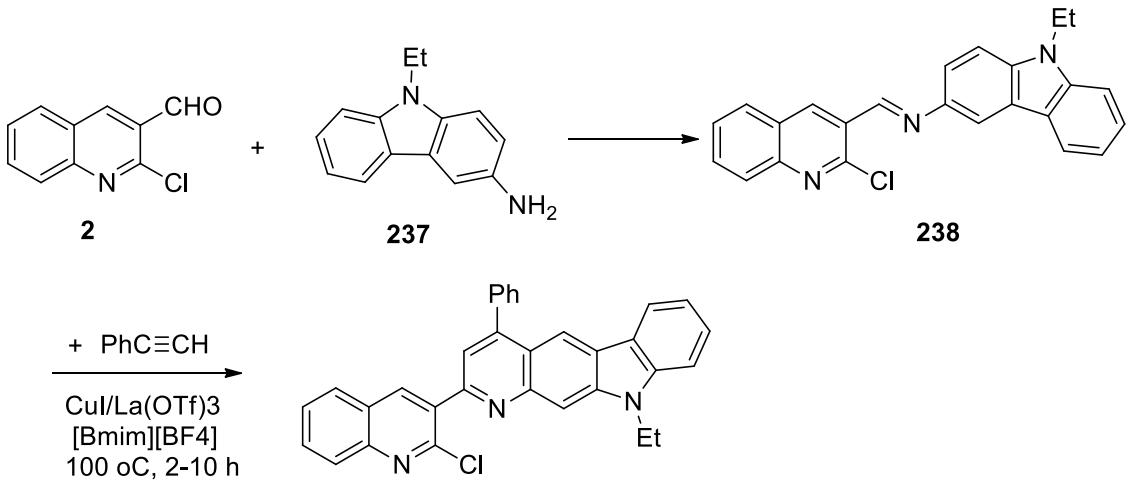
Scheme 88

N-[(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]



Scheme 89

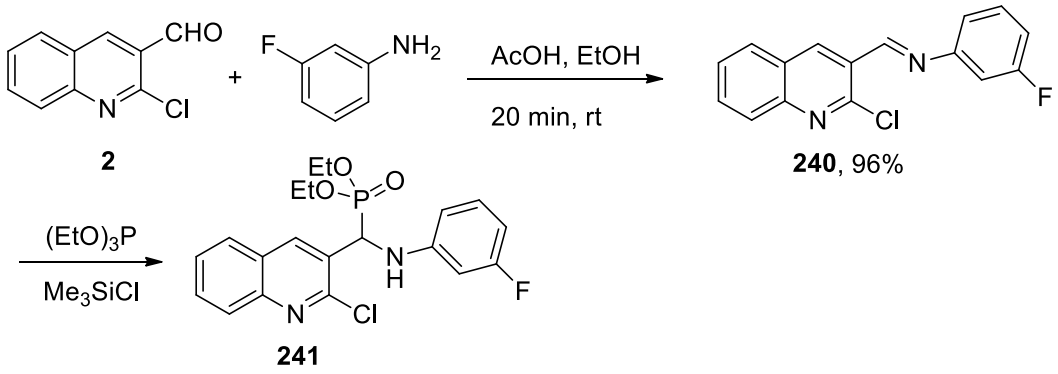
2-(2-Chloroquinolin-3-yl)-10-ethyl-4-phenyl-10*H*-pyrido[2,3-*b*]carbazole **239** was obtained from cyclization of imine **238**, derived from reaction of aldehyde **2** and 9-ethyl-9*H*-carbazol-3-amine **237**, with phenylacetylene in the presence of CuI/La(OTf)$_3$ in [Bmim][BF$_4$] followed by aromatization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



[Bmim][BF4] = 1-butyl-3-methylimidazolium tetrafluoroborate

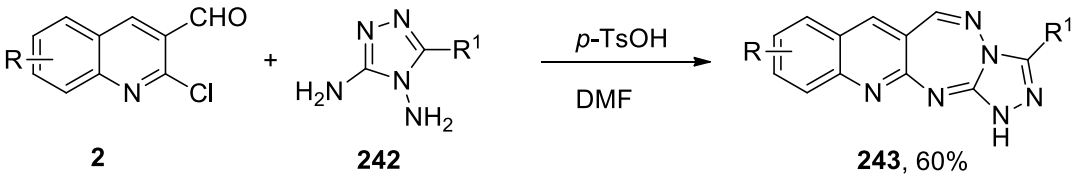
Scheme 90

Synthesis of α-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]



Scheme 91

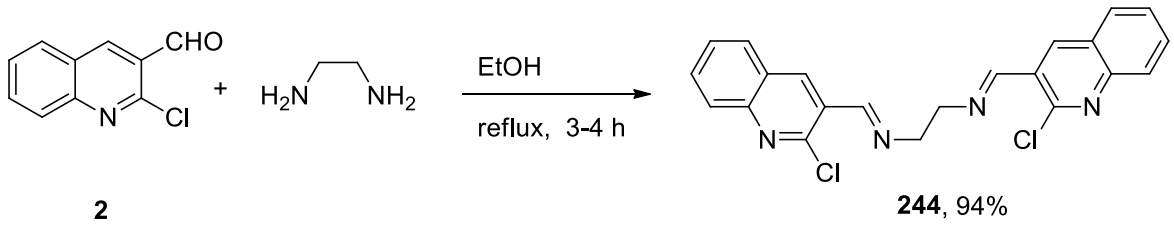
3-Aryl-1*H*-[1,2,4]triazolo[4′,3′:2,3][1,2,4]triazepino[5,6-b]quinolines **243** were synthesized *via* heterocyclization of 5-aryl-3,4-diamino-1,2,4-triazoles **242** and aldehydes **2** in DMF in the presence of *p*-TsOH with either microwave irradiation or oil-bath heating at 80°C (Scheme 92).[157]



R = H, 3-Me, 4-OMe; R^1 = Ph,4-$O_2NC_6H_4$, 2-ClC_6H_4

Scheme 92

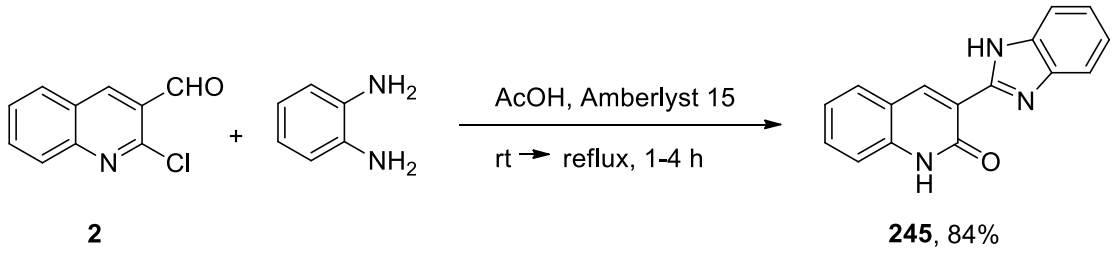
Stereoselective synthesis of N^1,N^2-bis[(2-chloroquinolin-3-yl)methylene]ethane-1,2-diamine **244** was reported by reaction of aldehyde **2** with ethylenediamine in ethanol at reflux temperature (Scheme 93).[158]



2

Scheme 93

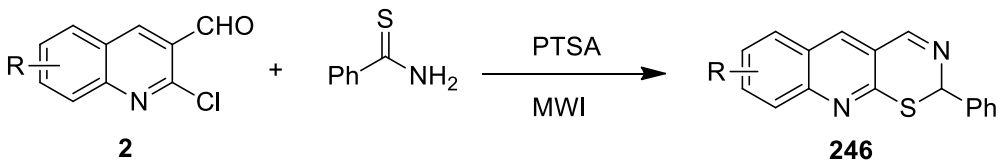
One-pot synthesis of 3-(1*H*-benzimidazol-2-yl)quinolin-2(1*H*)-one **245** was performed in 70% aqueous acetic acid in the presence of Amberlyst-15 (20% wt./wt.) by the direct reaction of aldehyde **2** with *o*-phenylenediamine (Scheme 94). Antitumor studies against sixty different cancer cell lines showed the potential of these kinds of compound.[159]



2 **245**, 84%

Scheme 94

2-Phenyl-2*H*-[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]

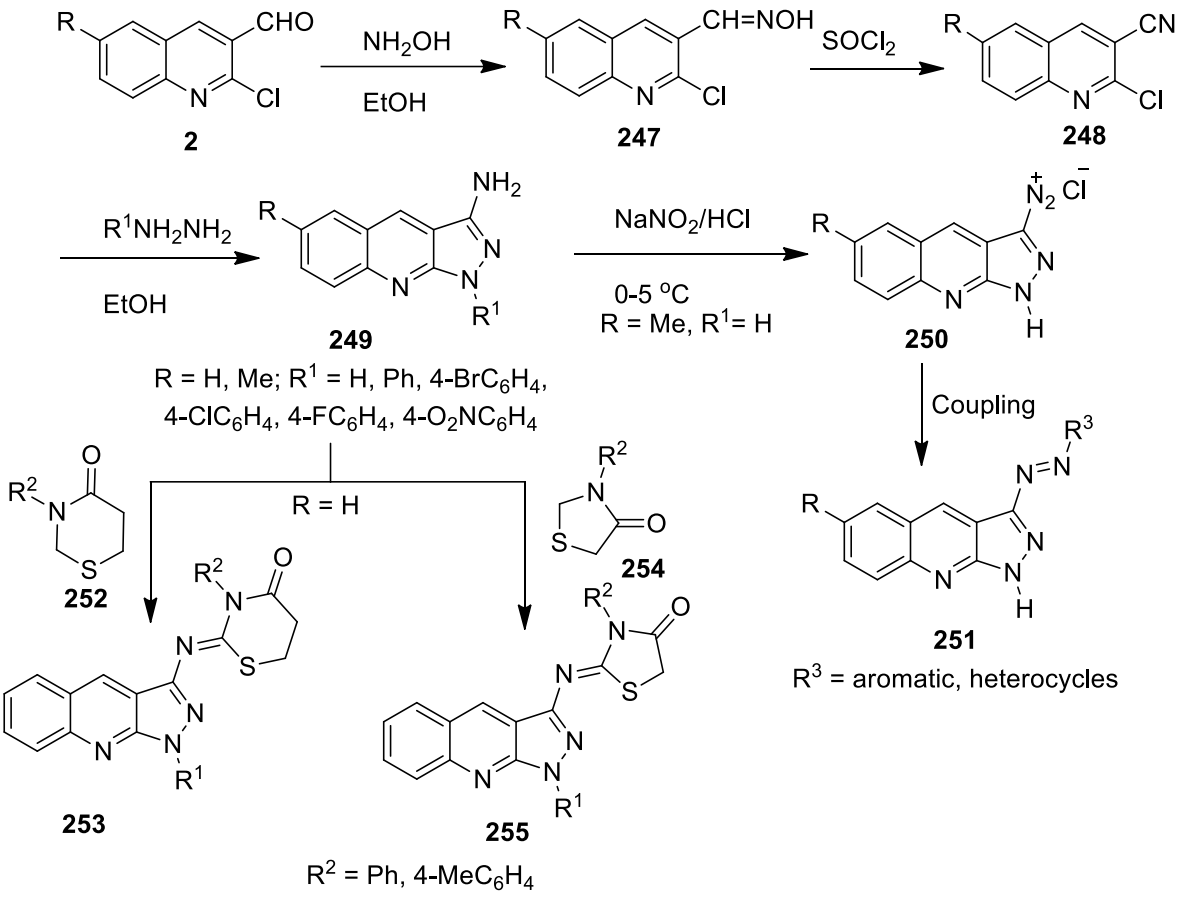


2 **246**

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

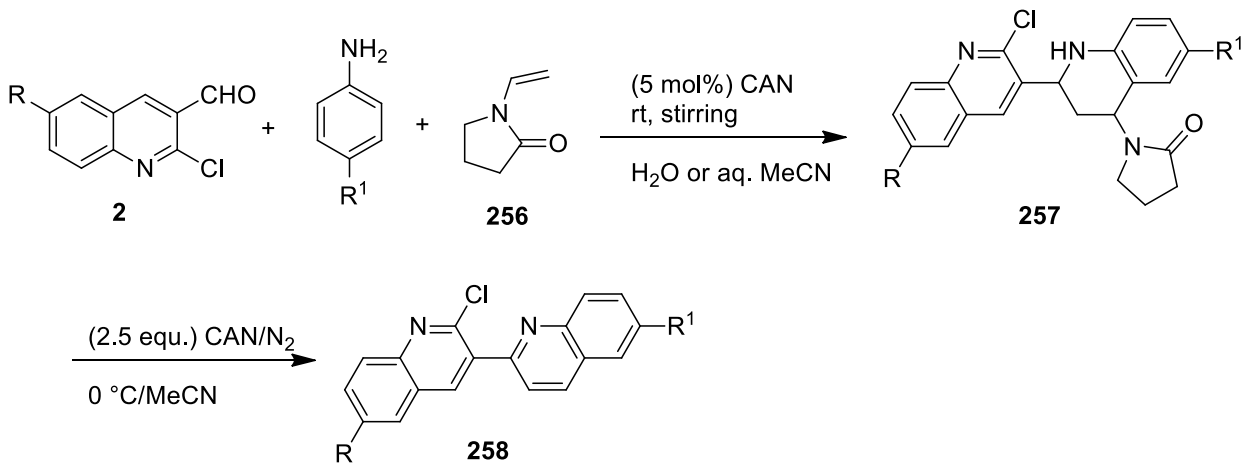
Scheme 95

1*H*-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-1*H*-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]



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 ºC (Schemes 97).[163]



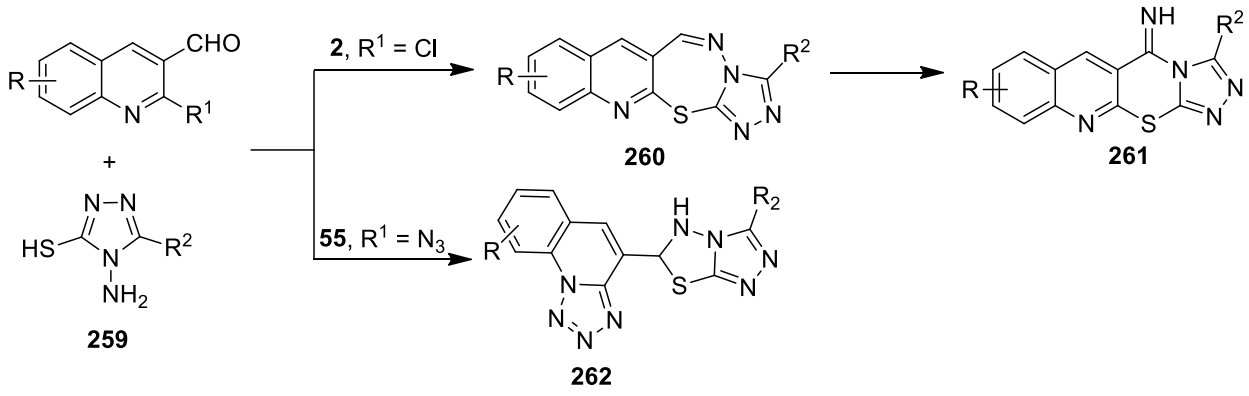
2 **256** **257** **258**

R = R^1 = H (85%); R = H, R^1 = Cl (82%); R = Me, R^1 = H (87%); R = OMe, R^1 = H (86%)

Scheme 97

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[164] or by traditional method[89,165] 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 intra-molecular 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 irradiation 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).[166] Compounds **261** and **262** were screened for their antibacterial and antifungal activity.[165,166]

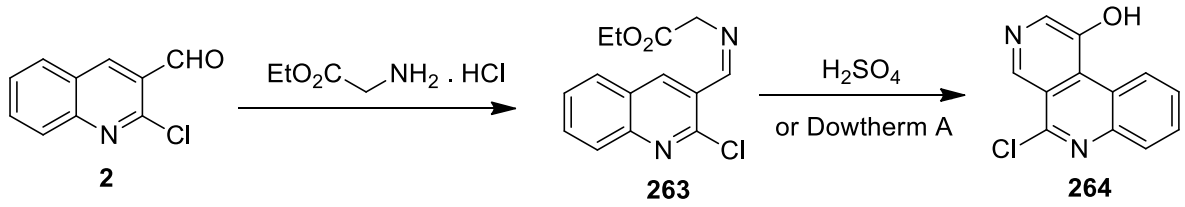


259 **260** **261** **262**

R = H,6-F, 8-Cl, 6-Br, 6-Me, 6-MeO; R^2 = Me, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, $ArNHCH_2$

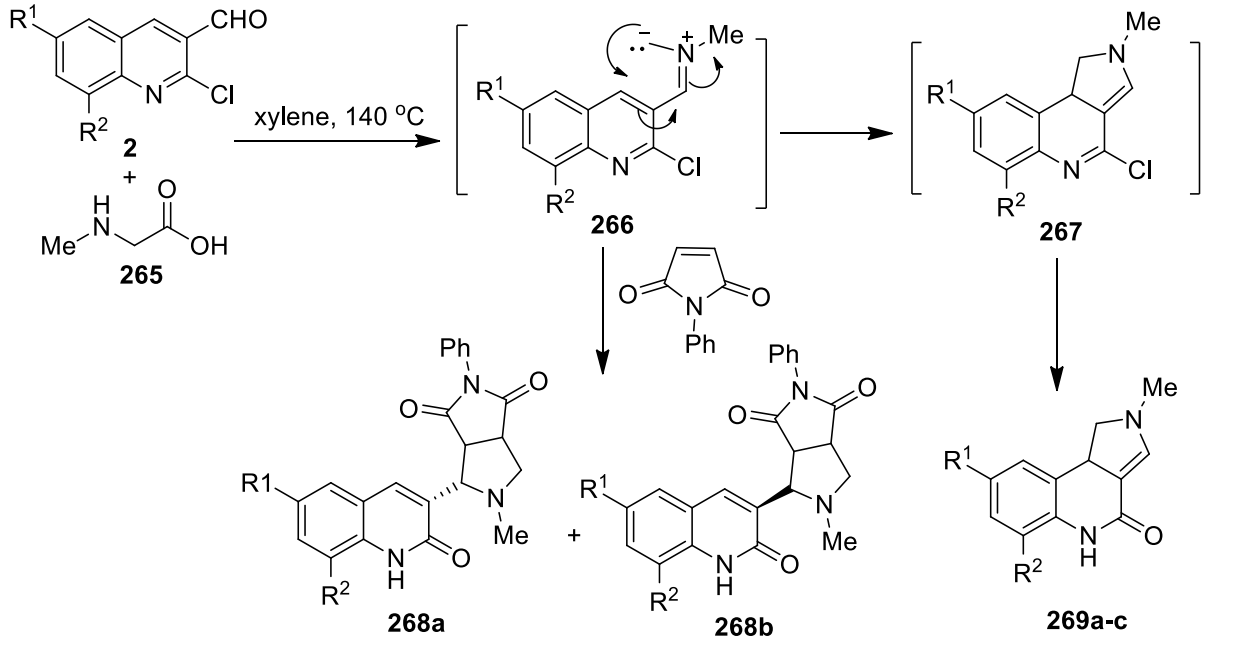
Scheme 98

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]



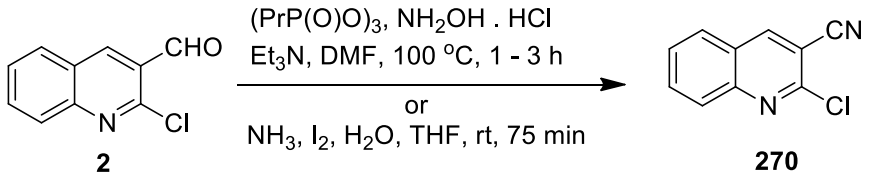
Scheme 99

The reaction of aldehyde **2** with sarcosine **265** in refluxing xylene gave 2-methyl-5,9*b*-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-4(2*H*)-ones **269** in acceptable yields *via* 1,5-electro-cyclisation 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]



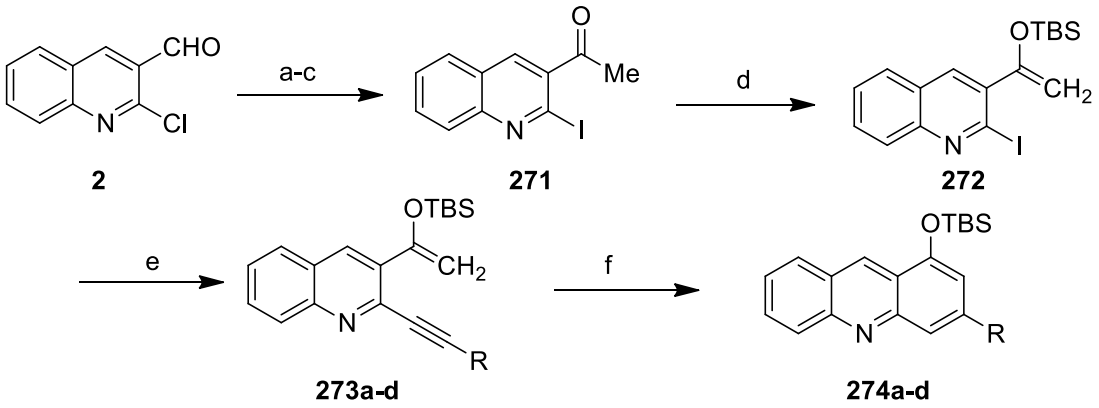
Scheme 100

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



Scheme 101

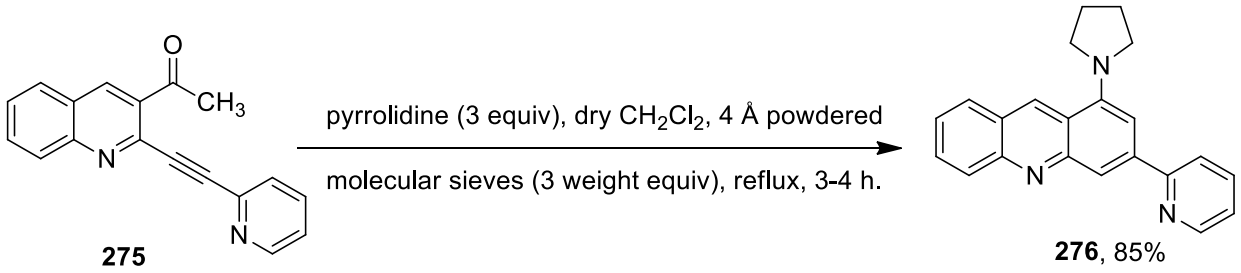
The aldehyde **2** was reacted with Grignard reagent (MeMgBr, 98%) followed by oxidation by MnO_2 (80%) to give the methyl ketone. Finkelstein reaction on the latter compound yielded the iodo derivative **271** (80%). Action of TBSOTf with Et_3N on **271** gave the *O*-TBS protected derivative **272** (77%), which underwent efficient Sonogashira reaction with several alkynes: 1-hexyne (**273a**, 70%), phenylacetylene (**273b**, 60%), tetrahydro-2-(2-propynyloxy)-2*H*-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).[171]



(a) 3 equiv MeMgBr, THF, 40 °C, 98%; (b) 10 equiv MnO_2, toluene, 80 °C, quant.; (c) NaI, CH_3CN, 0.5 equiv HCl 4N, reflux, 80–98%; (d) 2.2 equiv TBSOTf, 3 equiv Et_3N, CH_2Cl_2, 77%; (e) 1- alkyne, 0.07 equiv $PdCl_2(PPh_3)_2$, 0.3 equiv CuI, 1.5 equiv Et_3N, toluene, rt; (f) 10 mol% $[Rh(CO)_2Cl]_2$, toluene, 2–4 h, 120 °C.

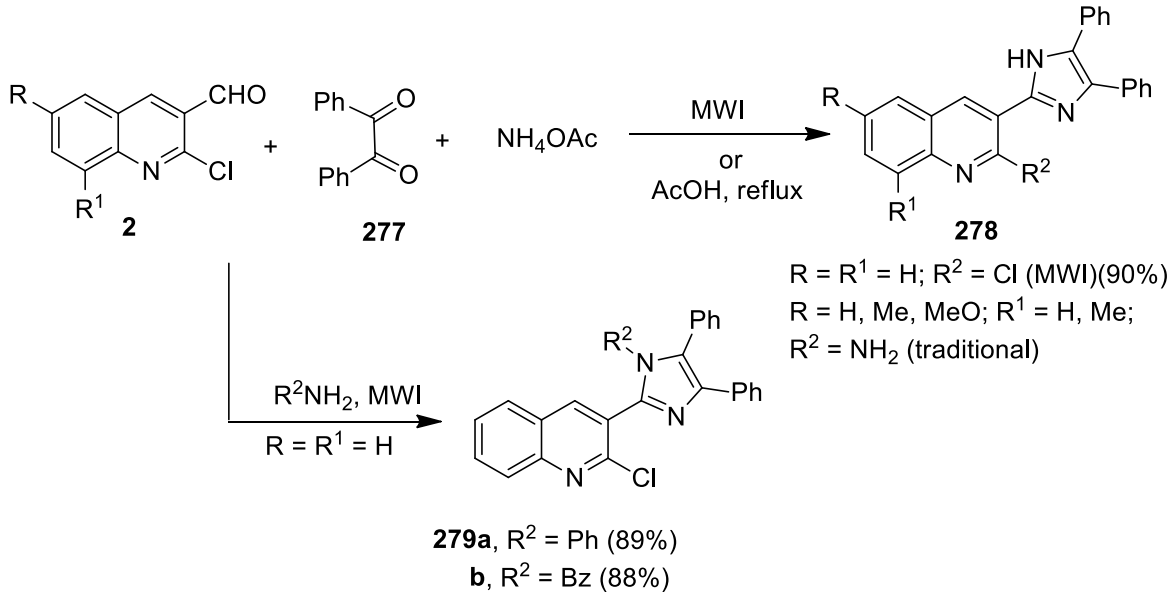
Scheme 102

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 aminobenz-annulation step took place subsequently (Scheme 103).[172]



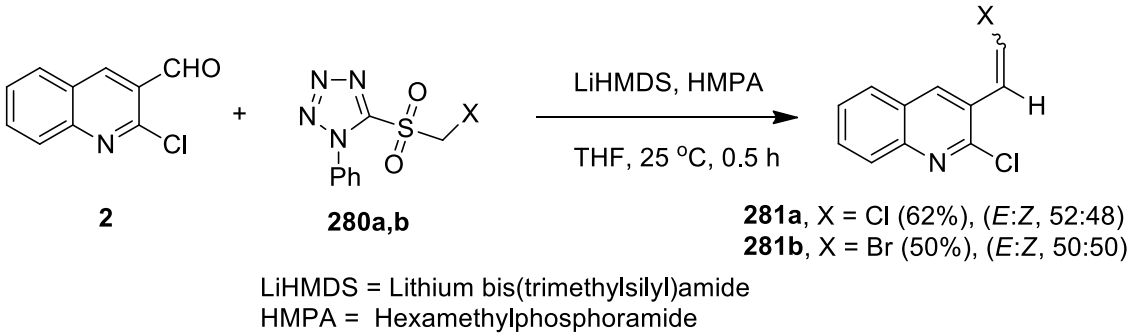
Scheme 103

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 **279a,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]



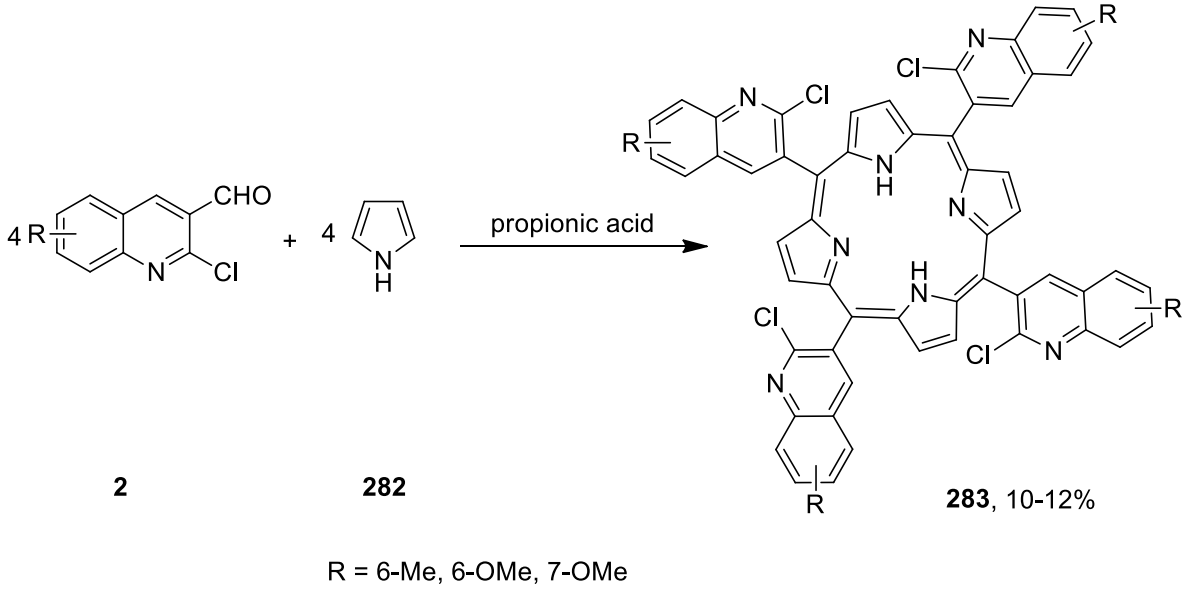
Scheme 104

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).[174]



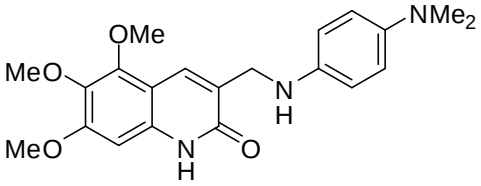
Scheme 105

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).[175]



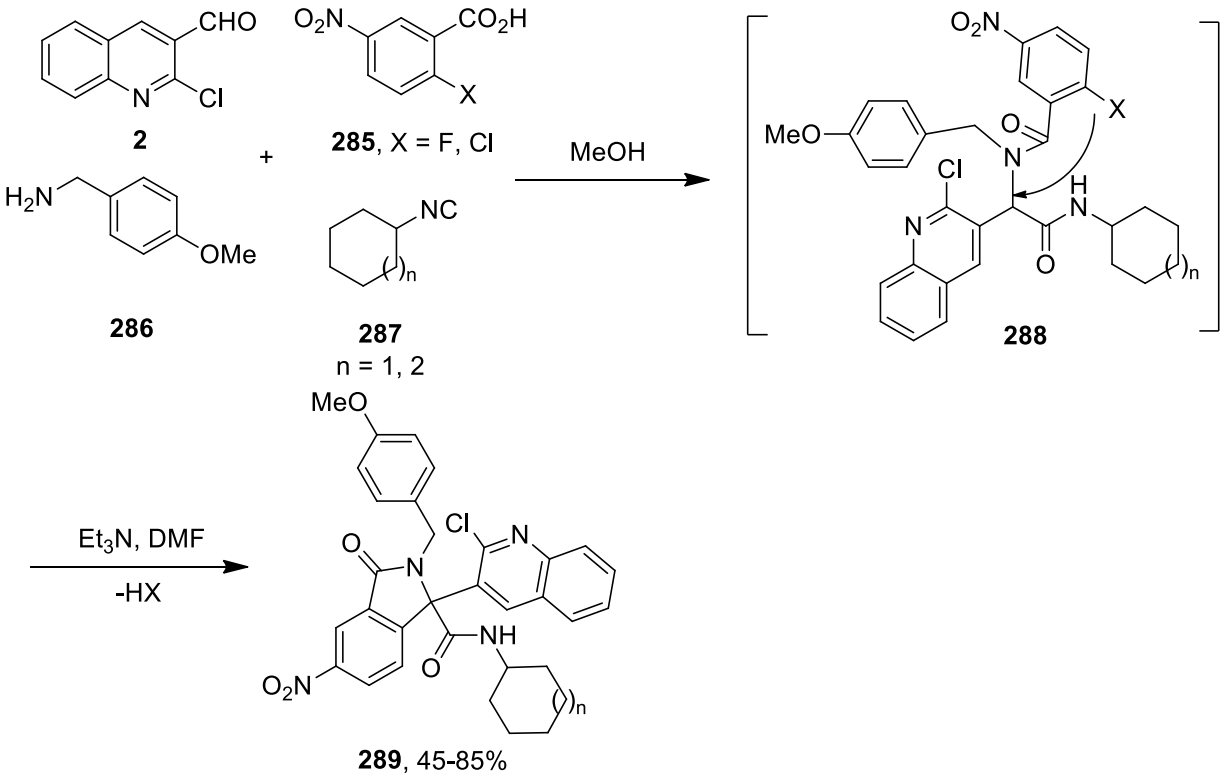
Scheme 106

3-[(4-(Dimethylamino)phenylamino)methyl]-5,6,7-trimethoxyquinolin-2(1*H*)-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 $NaBH(OAc)_3$.[176]



284

The Ugi four-component reaction of aldehyde **2**, 2-halo-5-nitrobenzoic acid, (4-methoxyphenyl)methanamine, and isonitrile resulted in formation of the classical U-4CC product, followed by intramolecular cyclization to produce 3-oxoisoindoline adduct in 73% yield (Scheme 107).[177]



Scheme 107

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.

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