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2-Chloroquinoline-3-carbaldehydes: synthesis and reactions (2012-2017)

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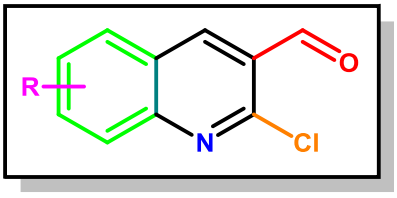
Abstract

This review discuss in details the synthesis and reactions of 2-chloroquinoline-3-carbaldehydes during years of 2012-2017. The reactions are subdivided into groups, according to type of reaction, including reactions of both chloro and/or aldehyde substituents. Most applied reactions have been successfully utilized for synthesis of different biologically and pharmacologically active derivatives.



Keywords: Aldehydes, aromatic nucleophilic substitution, 2-chloroquinoline-3-carbaldehydes, cyclization, quinolines, Vilsmeier-Haack reaction

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1. Introduction

In the recent years, the chemistry of 2-chloroquinoline-3-carbaldehydes has received considerable attention owing to their synthetic and reactions versatility, in addition to a wide variety of biological activity.[1] These aldehydes were also used as synthetic intermediates for the preparation of large numbers of heterocyclic systems[2] and stereoselective ligands[3,4] of various importance.

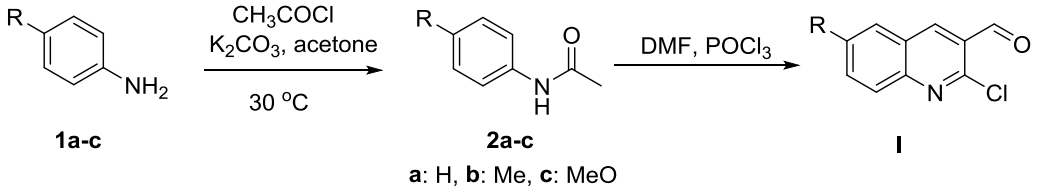
Polyfunctionalized heterocyclic compounds play important roles in the drug discovery and drug analysis processes; about 68% of available market drugs are containing heterocyclic ring system.[5] Hence it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received significant attention. The quinolone or 1-azanaphthalene ring system represent a wide occurrence in the nature as substituted and fused ring derivatives, Its derivatives have been known to display a wide range of pharmacological activities such as antimalarial[6], anti-bacterial[7], anticancer[8], antifungal[9], anthelmintic[10], cardiotonic[11], anticonvulsant and antihypertensive[12], anti-inflammatory and analgesic activity.[13] In addition, Quinoline has a privileged scaffold in cancer drug discovery.[14] 2-Chloroquinoline-3-carbaldehydes has been reviewed during the period from 1979 to 1999[15] and from 1999 to 2011[16], Herein, in this review, we cover the versatile synthetic methods and reactions from 2012 until 2017.

2. Synthetic Methods

Two important general procedures are used for synthesis of 2-chloroquinoline-3-carbaldehyde and its derivatives **I**.

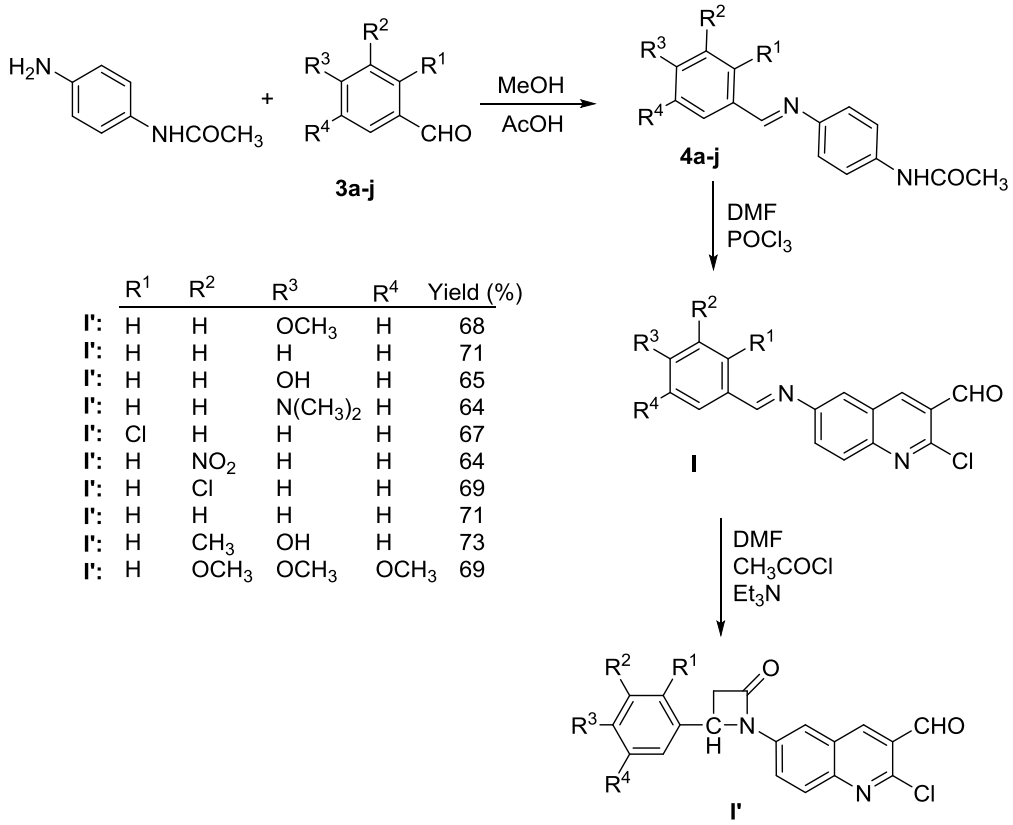
2.1. The classical Vilsmeier-Haack reaction

It is the most convenient and traditional route for the synthesis of 2-chloroquinoline-3-carbaldehydes. This strategy consists of a multicomponent reaction that involves processes of chlorination, formylation and cyclization of acetanilides by the action of the Vilsmeier´s reagent DMF/$POCl_3$ to afford 2-chloroquinoline-3-carbaldehydes **I** (Scheme 1).[17,18]



Scheme 1

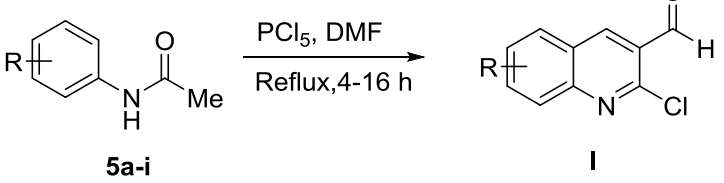
Vilsmeier formylation of acetamide derivatives **4a-j** afforded the corresponding 2-chloroquinoline-3-carbaldehydes **I**, which upon treatment with CH_3COCl and triethyl amine in DMF, furnished the respective 4-oxazetidin-1-yl derivatives **I'** (Scheme 2).[19]



	R^1	R^2	R^3	R^4	Yield (%)
I':	H	H	OCH_3	H	68
I':	H	H	H	H	71
I':	H	H	OH	H	65
I':	H	H	$N(CH_3)_2$	H	64
I':	Cl	H	H	H	67
I':	H	NO_2	H	H	64
I':	H	Cl	H	H	69
I':	H	H	H	H	71
I':	H	CH_3	OH	H	73
I':	H	OCH_3	OCH_3	OCH_3	69

Scheme 2

An alternative, convenient and efficient procedure for the synthesis of 2-chloroquinoline-3-carbaldehydes **I** was carried out by the action of Vilsmeier´s reagent on acetanilides **5a-i** using PCl_5 as chlorinating agent in place of $POCl_3$ was developed (Scheme 3).[20]



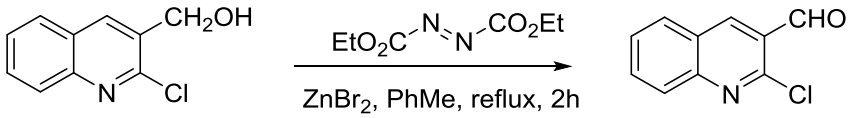
5a-i **I**

	R	Yield (%)
I:	H	78
I:	6-CH_3	74
I:	7-CH_3	66
I:	8-CH_3	67
I:	6-OCH_3	54
I:	7-OCH_3	65
I:	6-Br	30
I:	7-Cl	35
I:	6-NO_2	0

Scheme 3

2.2. Oxidation of the corresponding alcohol

2-Chloroquinoline-3-carbaldehyde **I** was obtained by oxidizing its corresponding alcohol **6** using diethyldiazene-1,2-dicarboxylate (DEAD) and catalytic $ZnBr_2$ in refluxing toluene (Scheme 4).[21]



6 **I,** 86%

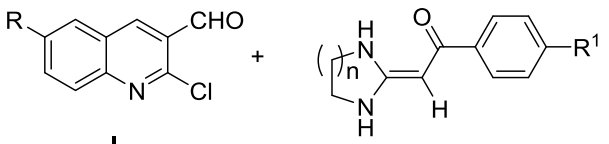
Scheme 4

3. Chemical Reactions

3.1 Cyclization reactions

3.1.1. Cyclization at both aldehyde and chloro groups. A mixture of 2-chloroquinoline-3-carbaldehyde **I** and heterocyclic ketene **7a-o** was stirred for 20 h at 75 °C in 1,4-dioxane and in presence of catalytic piperidine to afford of 1,3-diazaheterocycle fused naphthyridine derivatives **8a-y**, regioselectively (Scheme 5).[22]

A series of pyrazolo[3,4-*b*]quinolines **10a-h** was synthesized using one-pot water mediated synthetic route under microwave irradiation involving the condensation of 2-chloroquinoline-3-carbaldehydes **I** with semicarbazide or 2,4-dinitrophenyl hydrazine (Scheme 6).[23]



I **7a-o**

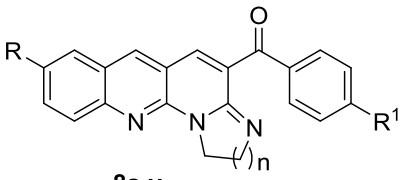
I: R=H
I: R= OCH_3

a-e n=1, **f-g** n=2, **k-o** n=3
$\mathbf{R^1}$= H, F, Cl, Me, OMe.

Piperidine
1,4-Dioxane
75 °C, 20 h

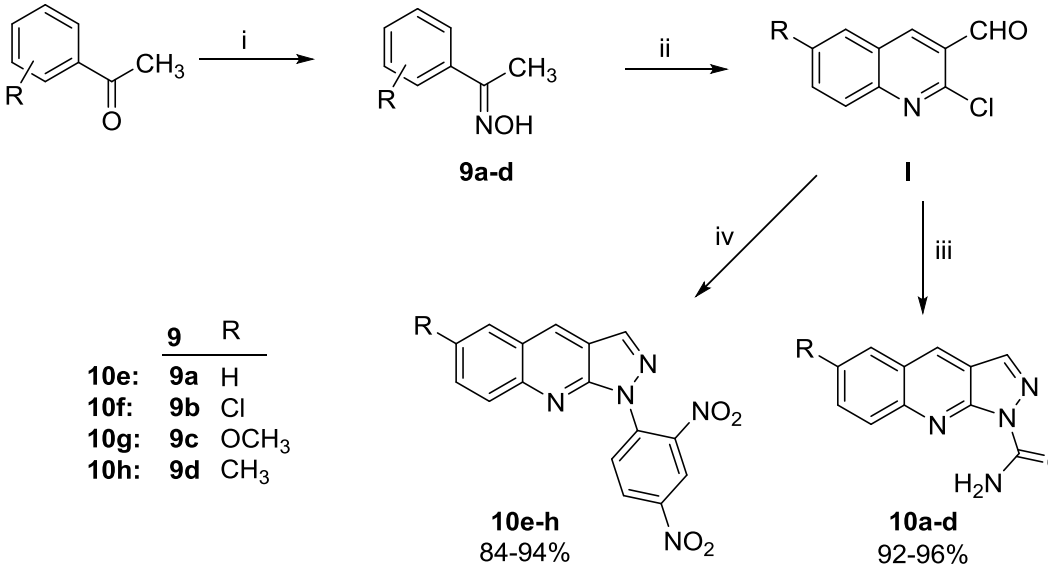
R	7	n/R^1	8	Yield (%)
H	**7a**	1/H	**8a**	76
H	**7b**	1/F	**8b**	73
H	**7c**	1/Cl	**8c**	70
H	**7d**	1/Me	**8d**	80
H	**7e**	1/OMe	**8e**	83
OMe	**7a**	1/H	**8f**	84
OMe	**7b**	1/F	**8g**	81
OMe	**7c**	1/Cl	**8h**	78
OMe	**7d**	1/Me	**8i**	86
OMe	**7e**	1/OMe	**8j**	89
H	**7F**	2/H	**8k**	83
H	**7g**	2/F	**8l**	80
H	**7h**	2/Cl	**8m**	79

R	7	n/R^1	8	Yield (%)
H	**7i**	2/Me	**8n**	86
H	**7j**	2/OMe	**8o**	89
OMe	**7F**	2/H	**8p**	88
OMe	**7g**	2/F	**8q**	85
OMe	**7h**	2/Cl	**8r**	81
OMe	**7i**	2/Me	**8s**	91
OMe	**7j**	2/OMe	**8t**	95
OMe	**7k**	3/H	**8u**	64
OMe	**7l**	3/F	**8v**	61
OMe	**7m**	3/Cl	**8w**	57
OMe	**7n**	3/Me	**8x**	66
OMe	**7o**	3/OMe	**8y**	70



8a-y

Scheme 5



9a-d **I**

	9	R
10e:	**9a**	H
10f:	**9b**	Cl
10g:	**9c**	OCH_3
10h:	**9d**	CH_3

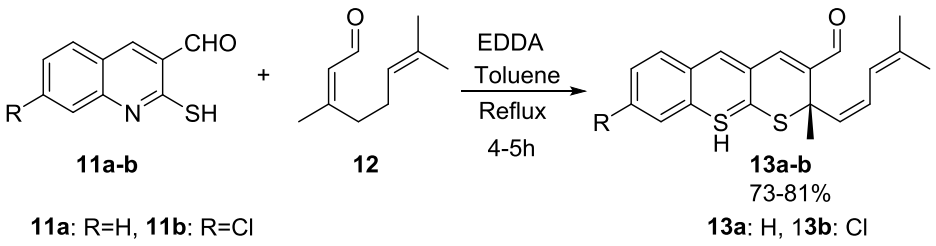
10e-h 84-94%

10a-d 92-96%

Reagents and Condition: i. Sodium acetate, Hydroxylamine, HCl; ii.DMF, $POCl_3$; iii. Semicarbazide, water, MW -1000 W; iv. 2,4-dinitrophenylhydrazine, water, MW -1000 W.

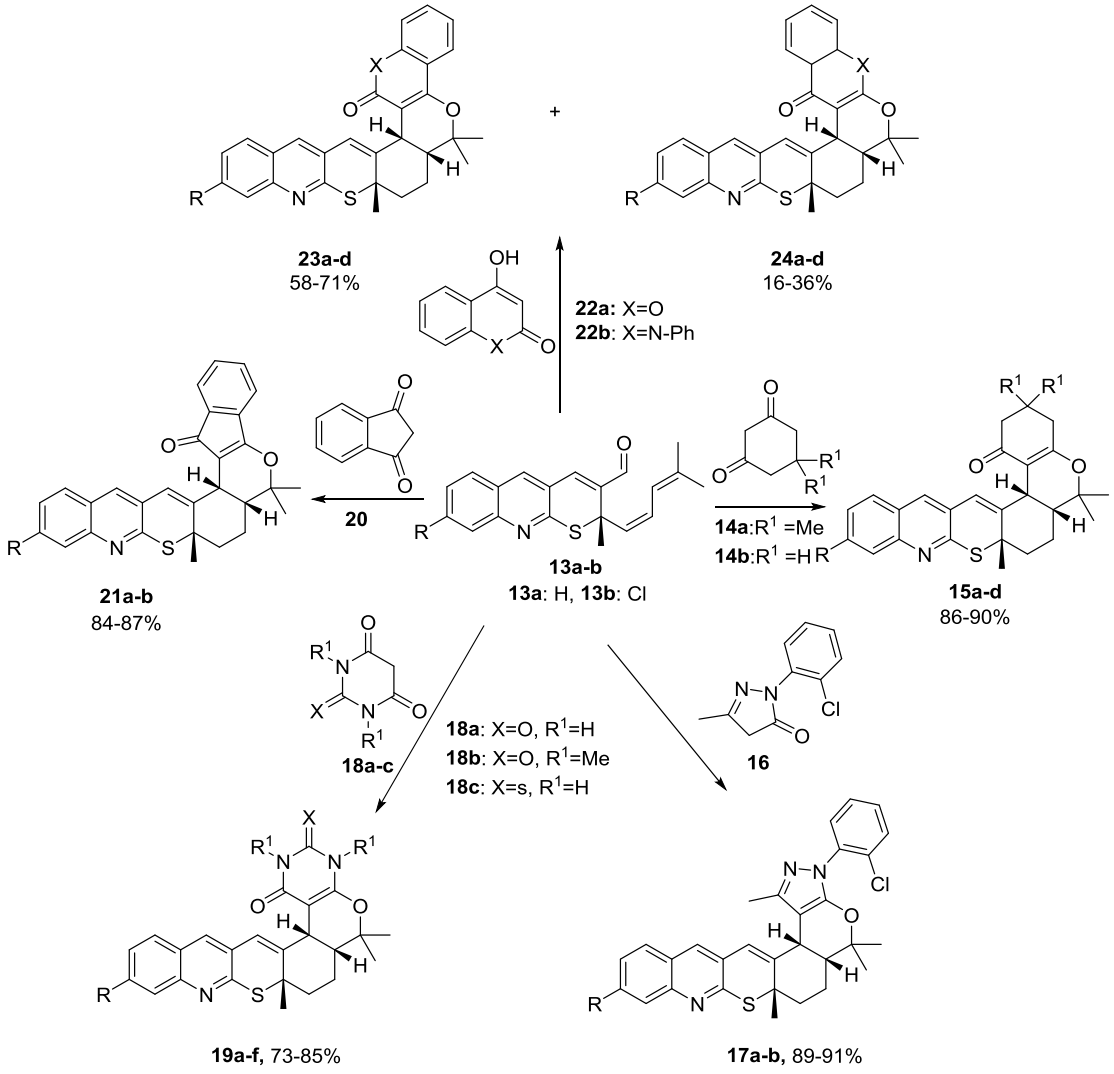
Scheme 6

Both thiopyrano[2,3-*b*]quinoline-3-carbaldehydes **13a** and **13b** were obtained as new Domino Knoevenagel/hetero-Diels-Alder (dienophile-tethered-aldehyde substrates) in 73% and 81% yields, respectively. The reaction proceeds through thia-Michael-Aldol reaction of the corresponding 2-mercaptoquinoline-3-carbaldehydes **11a** and **11b** with **12** in ethylenediamine diacetate (EDDA) in refluxing toluene (Scheme 7).[24-29]



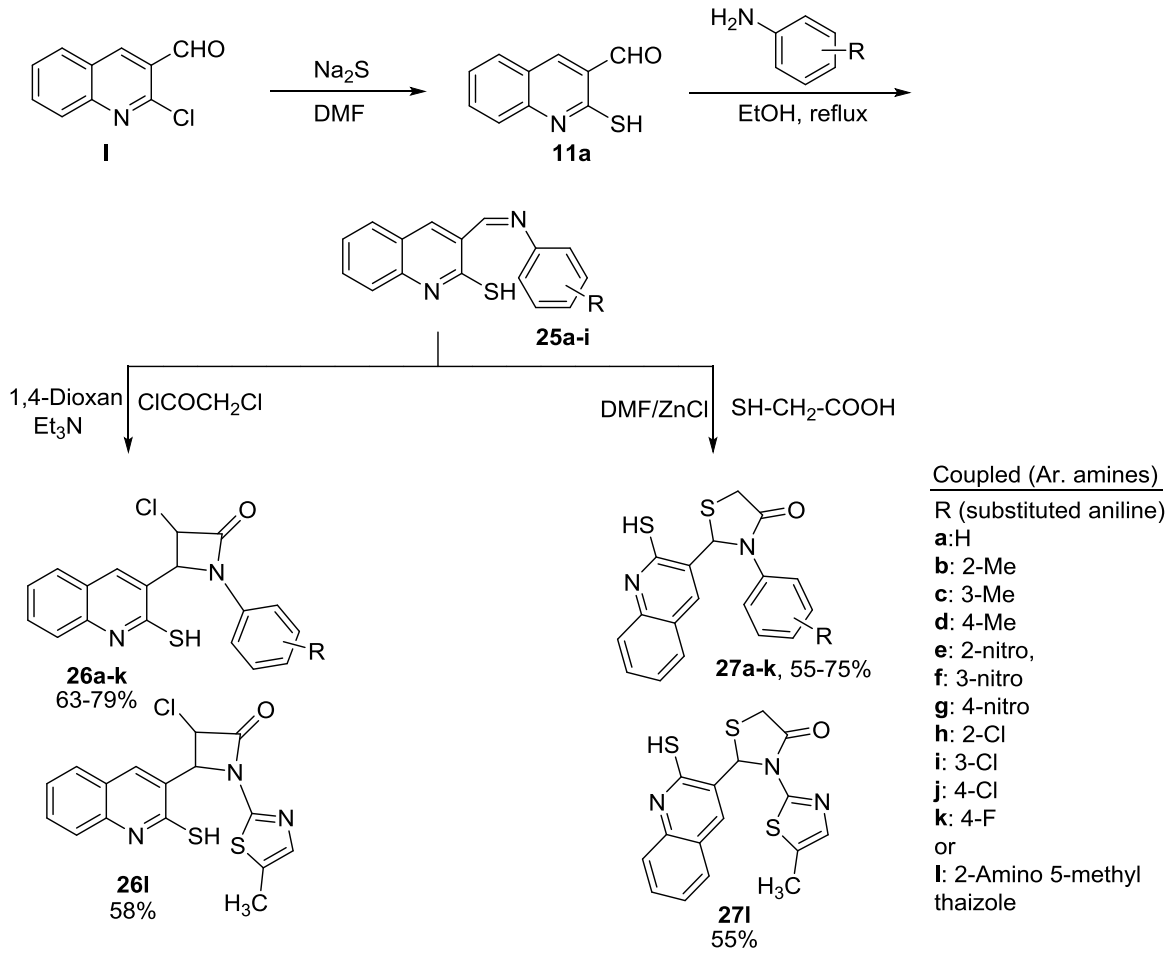
Scheme 7

2-Alkenylthiopyranoquinoline-3-carbaldehydes **13a-b** with heterocyclic mono- or diketones in tetrabutylammonium hydrogensulfate, under solvent-free conditions, afforded a new class of thiochromenoquinoline-fused heterocycles in good yields. The reaction is highly diasteroselective (Scheme 8).[30]



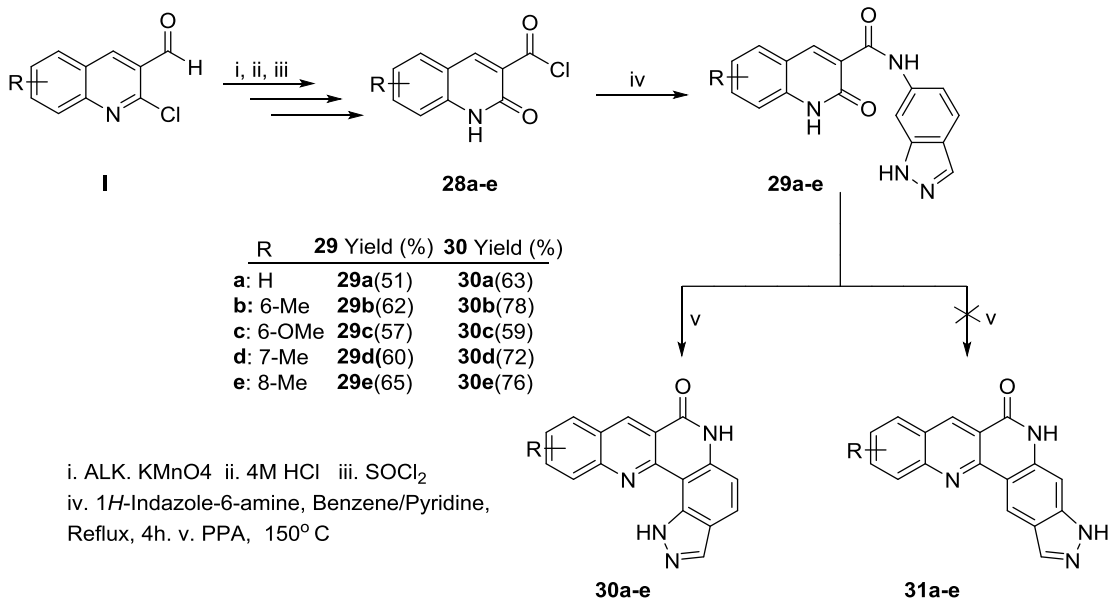
Scheme 8

3.1.2. **Cyclization at aldehyde group.** A new series of quinoline-based azetidinones **26a-l** and thiazolidinone **27a-l** analogs was developed by a simple and efficient synthetic protocol. The thione nucleus was obtained from 2-chloroquinoline-3-carbaldehyde **I** using sodium sulphide in DMF followed by reaction with various substituted amine to form the corresponding Schiff base intermediates **25a-i**. Attempt has been made to derive final azetidinone and thiazolidinone analogs from Schiff's bases by using chloroacetyl chloride and 2-mercaptoacetic acid, respectively (Scheme 9).[31]



Scheme 9

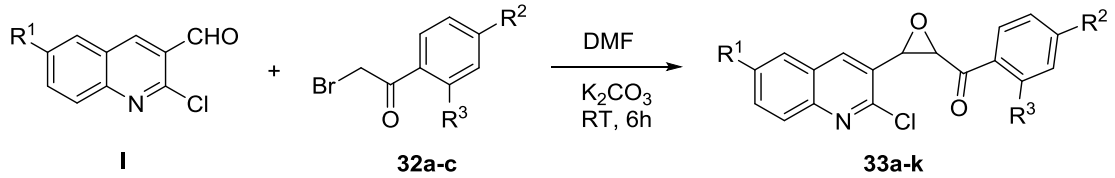
Efficient synthesis of 3-(6'-amidoindazoloquinoline-2-(1*H*)-ones **29a-e** was reported *via* addition of 1*H*-Indazole-6-amine to a solution of the corresponding acid chlorides **28a-e** in dry benzene in presence of few drops of pyridine under reflux. Benzo[*b*]-1*H*-indazolo[6,7-*h*][1,6]naphthyridin-7-(6*H)*-ones **30a-e** were prepared by heating **29a-e** in polyphosphoric acid (PPA) at 150 °C for 5 h (Scheme 10).[32]



R	**29** Yield (%)	**30** Yield (%)
a: H	**29a**(51)	**30a**(63)
b: 6-Me	**29b**(62)	**30b**(78)
c: 6-OMe	**29c**(57)	**30c**(59)
d: 7-Me	**29d**(60)	**30d**(72)
e: 8-Me	**29e**(65)	**30e**(76)

Scheme 10

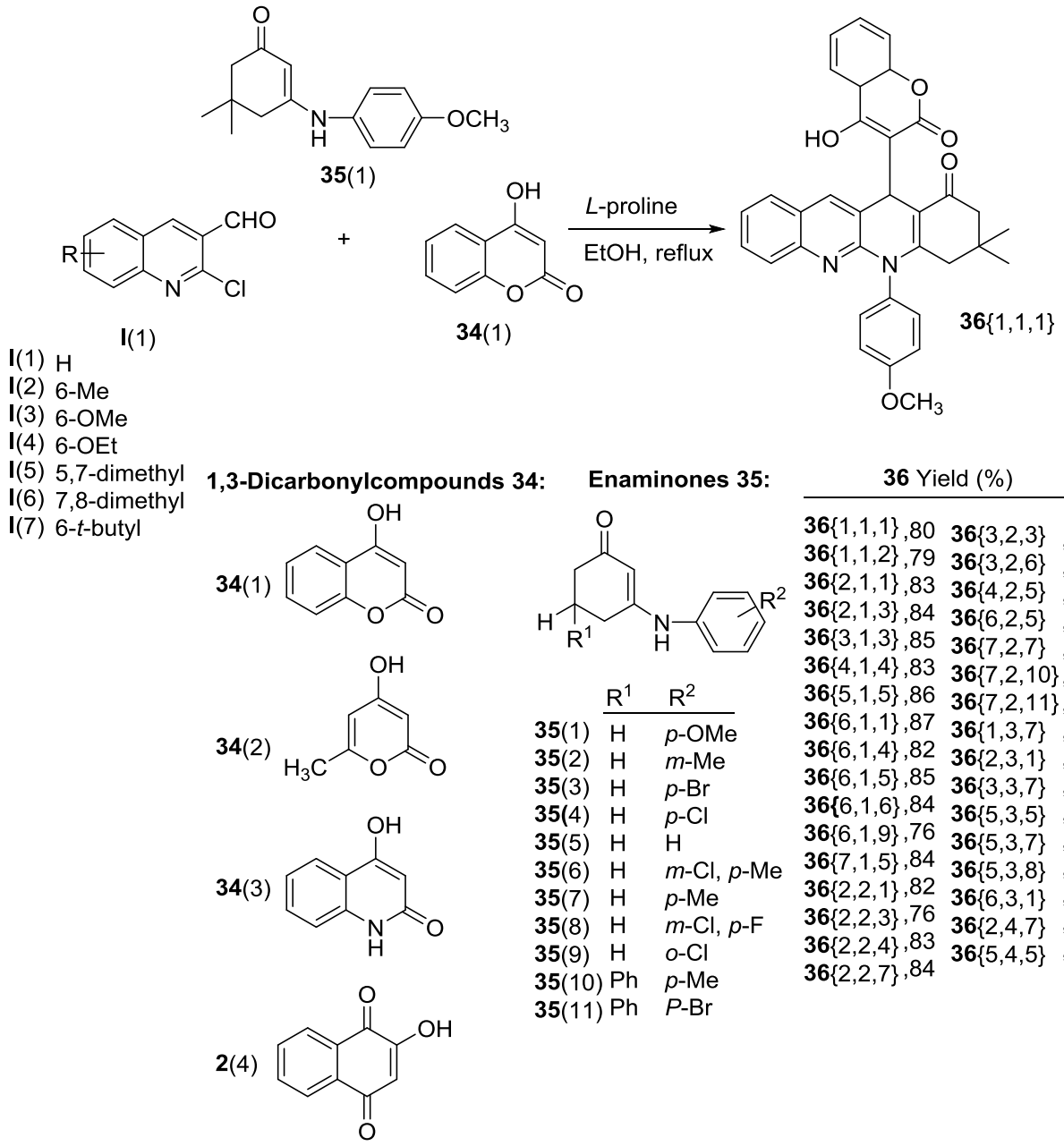
The parent epoxide 3-(2-chloroquinolin-3-yl)oxiran-2-yl)(phenyl)methanone **33a** and ten of its substituted derivatives **33b-k** were synthesized *via* Darzens reaction of 2-chloroquinoline-3-carbaldehydes and its 6-substituted derivatives **I** with phenacyl bromide and its 2- and 4-mono- and 2,4-disubstituted derivatives **32a-c**. (Scheme 11).[33]



	R^1	R^2	R^3	Yield (%)
33a	H	H	H	87
33b	CH_3	H	H	90
33c	OCH_3	H	H	91
33d	H	Cl	Cl	81
33e	CH_3	Cl	Cl	83
33f	OCH_3	Cl	Cl	86
33g	H	CH_3	H	94
33h	CH_3	CH_3	H	88
33i	OCH_3	CH_3	H	88
33j	Cl	Cl	Cl	68
33k	Cl	CH_3	H	63

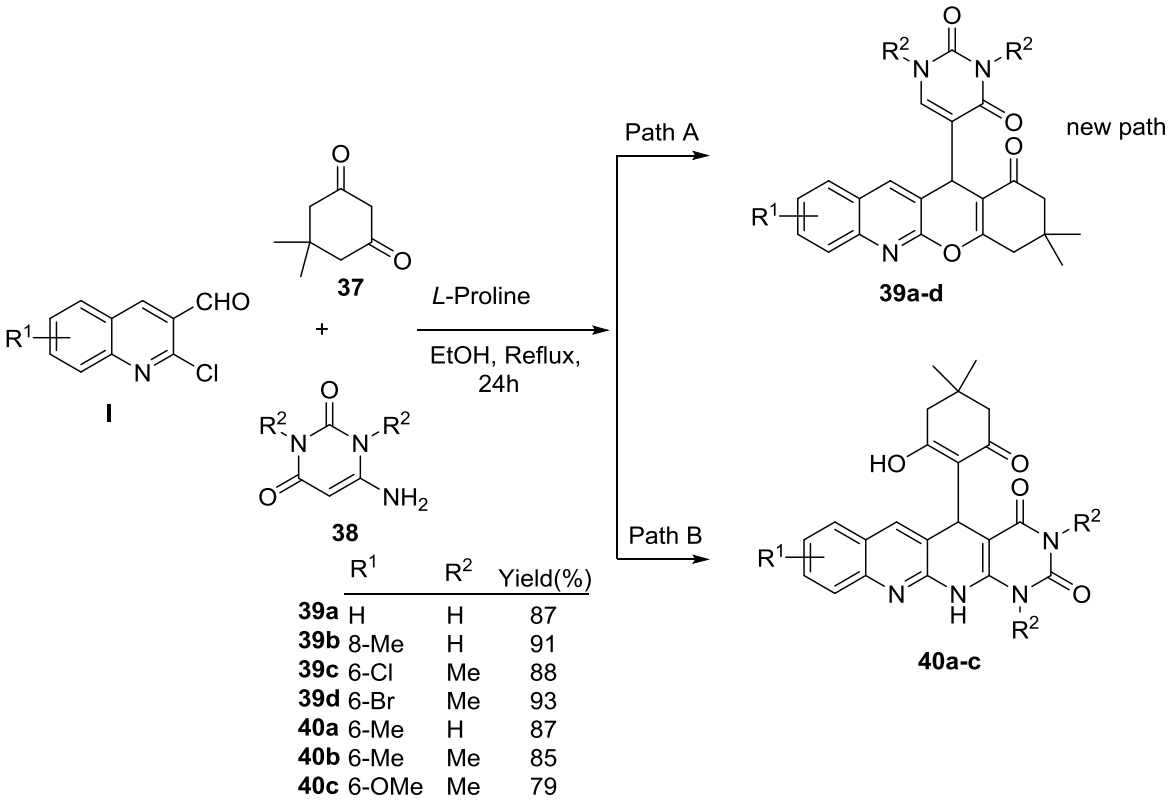
Scheme 11

3.1.3. **Cyclization *via* multicomponent reactions (MCRs). 3.1.3.1**. **Three component reactions.** A facile and efficient one-pot procedure for the preparation of functionalized benzo[*b*][1,8]naphthyridine **36{1,1,1}** by three-component reaction of 2-chloroquinoline-3-carbaldehyde **I(1)**, 1,3-dicarbonyl compound (4-hydroxycoumarin) **34(1)**, and enaminone **35(1)** catalyzed by *L*-proline was described (Scheme 12).[34]



Scheme 12

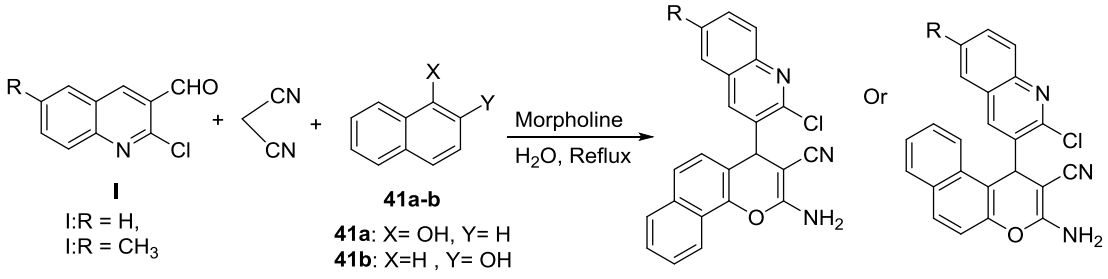
The aforementioned procedure was further applied *via* one-pot reaction of 2-chloroquinoline-3-carbaldehydes **I**, 6-aminouracils **38** and dimedone **37**. Interestingly, the 6-Me and 6-OMe substituted quinoline aldehydes gave rise to products **40a-c** proceeding through intramolecular nucleophilic attack by nitrogen, while the other aldehydes gave products **39a-d** resulting from attack by oxygen. The exact reason for this selectivity is at present unclear (Scheme 13).[35]



	R^1	R^2	Yield(%)
39a	H	H	87
39b	8-Me	H	91
39c	6-Cl	Me	88
39d	6-Br	Me	93
40a	6-Me	H	87
40b	6-Me	Me	85
40c	6-OMe	Me	79

Scheme 13

An environmentally benign strategy to the synthesis of 2-amino-3-cyano 4-*H*-chromenes **42a-d**, *via* one-pot reaction involving malononitrile, various *α*- or *β*-naphthol and aldehydes **I** in the presence of morpholine in water was developed. It was found that employing this approach, aromatic aldehydes bearing electron-withdrawing groups gave higher yields of the corresponding products in shorter reaction times. (Scheme 14).[36]

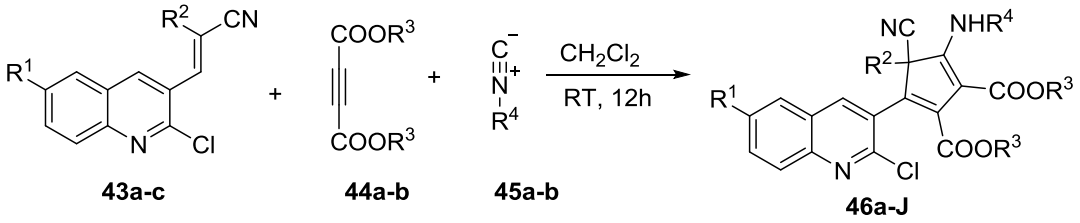


	R	Yield(%)
42a:	H	88
42b	CH_3	85

	R	Yield(%)
42c:	H	84
42d	CH_3	80

Scheme 14

Synthesis of highly substituted cyclopentadienes containing quinoline nucleus **46a-j**, was described. The initially prepared Knöevenagel adducts **43a-b** of 2-chloroquinoline-3-carbaldehydes and malononitrile or ethyl cyanoacetate underwent reaction with acetylenecarboxylates **44a-b** and isocyanide **45a-b** in dichloromethane at room temperature within 12 h, affording the products in moderate to good yields. Mild reaction condition and prompt isolation of the products are some advantages of this protocol (Scheme 15).[37]

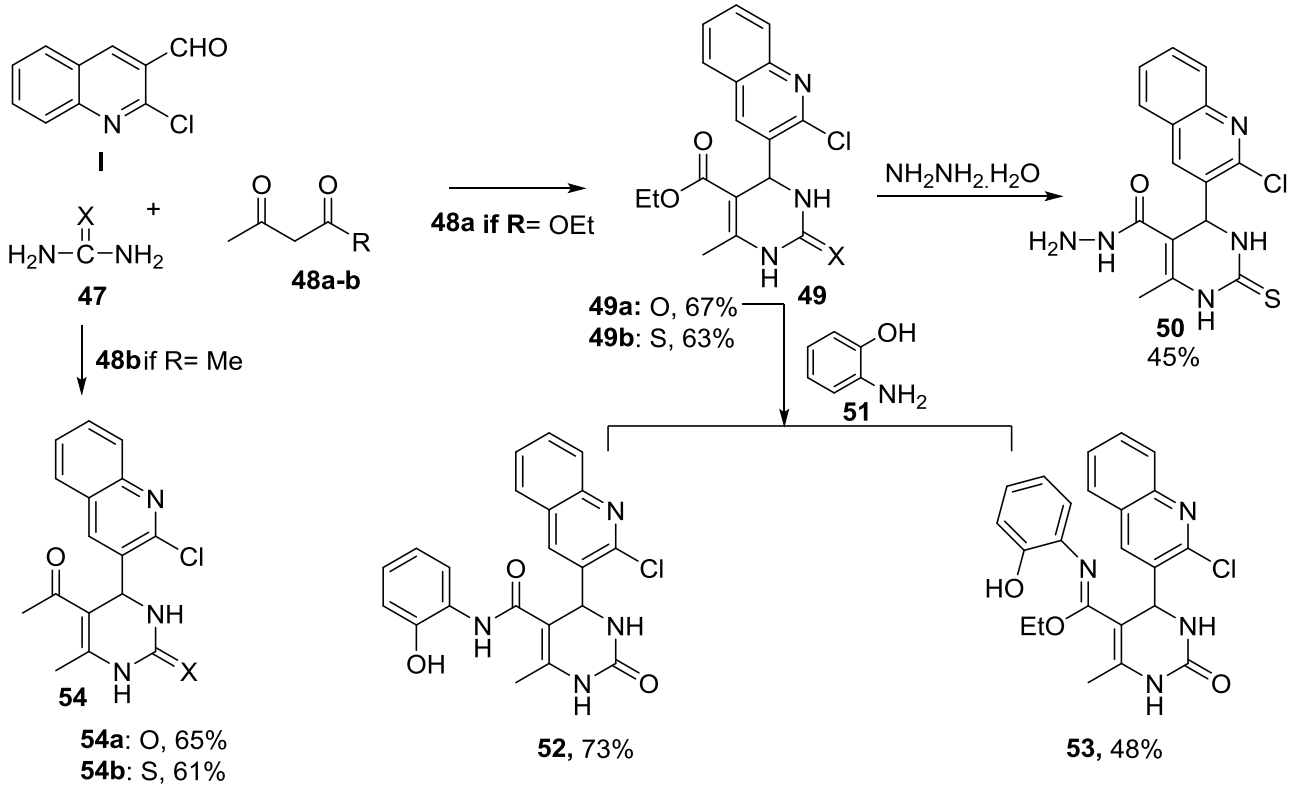


43a-c **44a-b** **45a-b** **46a-J**

	R^1	R^2	R^3	R^4	Yield (%)
46a	H	CO_2Et	Me	cyclohexanyl	62
46b	H	CO_2Et	Me	2,2,4-trimethylpentane-2-yl	68
46c	H	CO_2Et	Et	2,2,4-trimethylpentane-2-yl	71
46d	Me	CO_2Et	Me	cyclohexanyl	74
46e	Me	CO_2Et	Et	cyclohexanyl	69
46f	Me	CO_2Et	Me	2,2,4-trimethylpentane-2-yl	79
46g	Me	CO_2Et	Et	2,2,4-trimethylpentane-2-yl	73
46h	Me	CN	Me	2,2,4-trimethylpentane-2-yl	63
46i	Me	CN	Et	2,2,4-trimethylpentane-2-yl	66
46j	Me	CN	Me	cyclohexanyl	61

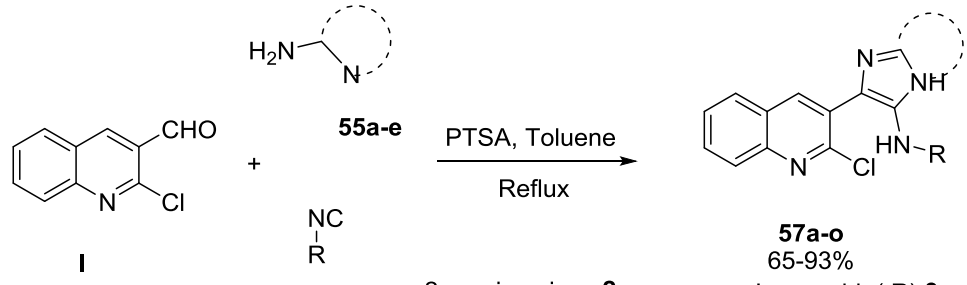
Scheme 15

When the aldehyde **I** was reacted with urea or thiourea **47a,b** and active methylene compounds **48a-b** in ethanol and in the presence of drops of acetic acid as a catalyst in one-pot reaction namely *Biginelli* reaction[38,39], the corresponding compounds **49a-b** and **54a-b** was obtained respectively. The carbohydrazide **50** was afforded by reaction of hydrazine hydrate with the ester derivative **49b**. Moreover, condensation of **49a** with 2-aminophenol **51** in the presence of acetic acid afforded the tetrahydropyrimidine-5-carboxamide derivative **52**; while the carbimidate derivative **53** was afforded, if the same reaction was carried out in ethanol (Scheme 16).[40]



Scheme 16

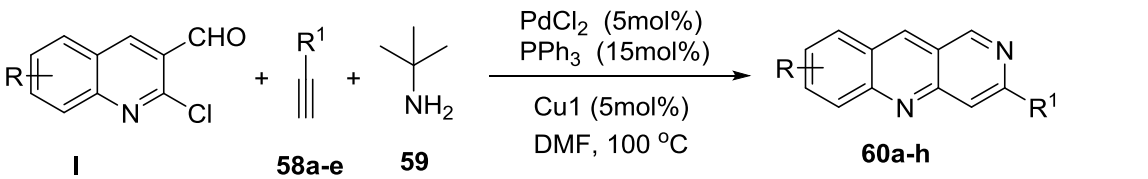
A series of 2-chloroquinoline-based imidazopyridines **57a-i** and imidazothiazoles **57m-o** bearing a bulky alkylamine side chain were synthesized as soybean 15-LOX inhibitors. The target compounds of quinoline-based imidazole-fused heterocycles **57a-o** were prepared via one-pot reaction of 2-chloroquinoline-3-carbaldehyde **I**, heteroaromatic amine **55**, and alkyl isocyanides **56**, in the presence of NH_4Cl (Scheme 17).[41]



	2-amnio azines **2**	Isocyanide(R) **3**
57a	2-amino pyridine	*c*-Hex
57b	2-amino pyridine	*t*-But
57c	2-amino pyridine	1,1,3,3-tetramethylbutyl
57d	2-amino-3-methyl pyridine	*c*-Hex
57e	2-amino-3-methyl pyridine	*t*-But
57f	2-amino-3-methyl pyridine	1,1,3,3-tetramethylbutyl
57g	2-amino-4-methyl pyridine	*c*-Hex
57h	2-amino-4-methyl pyridine	*t*-But
57i	2-amino-4-methyl pyridine	1,1,3,3-tetramethylbutyl
57j	2-amino-5-Chloro pyridine	*c*-Hex
57k	2-amino-5-Chloro pyridine	1,1,3,3-tetramethylbutyl
57l	2-amino-5-Bromo pyridine	*t*-But
57m	2-amino thiazole	*c*-Hex
57n	2-amino thiazole	*t*-But
57o	2-amino thiazole	1,1,3,3-tetramethylbutyl

Scheme 17

Via Sonogashira conjoined electrophilic cyclization, the three component reaction of *o*-halo aldehydes **I**, alkynes **58a-e** and tert-butylamine **59** led to the synthesis of biologically active benzo[*b*][1,6]naphthyridine derivatives **60a-h,** using a bimetallic Pd/Cu catalytic system. (Scheme 18).[42]



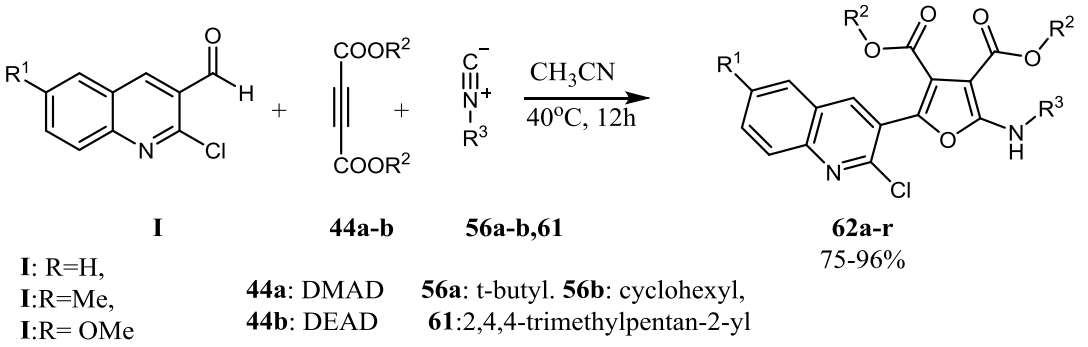
I:R=H
I:R=6-Me
I:R=6-OMe

58a	Phenyl
58b	Thiophen-3-yl
58c	*p*-Methylphenyl
58d	p-Butylphenyl
58e	p-Ethylphenyl

	R	R^1	Yield (%)
60a	H	Phenyl	75
60b	H	*p*-Methylphenyl	82
60c	H	*p*-Butylphenyl	76
60d	H	Thiophen-3-yl	80
60e	6-Me	*p*-Methylphenyl	78
60f	6-Me	*p*-Ethylphenyl	77
60g	6-OMe	Phenyl	77
60h	6-OMe	*p*-Butylphenyl	78

Scheme 18

A facile and efficient method for synthesis of novel furylquinolines **62a-r** was developed *via* the condensation of 2-chloroquinoline-3-carbaldehydes **I** with acetylenecarboxylates **44a-b** and isocyanides **56a-b** and **61**. The mixture was stirred in acetonitrile for 12 h at 40 ^{o}C. After completion of the reaction, the mixture was cooled to room temperature to afford **62a-r (**Scheme 19).[43]



I **44a-b** **56a-b,61** **62a-r**
75-96%

I: R=H,
I:R=Me,
I:R= OMe

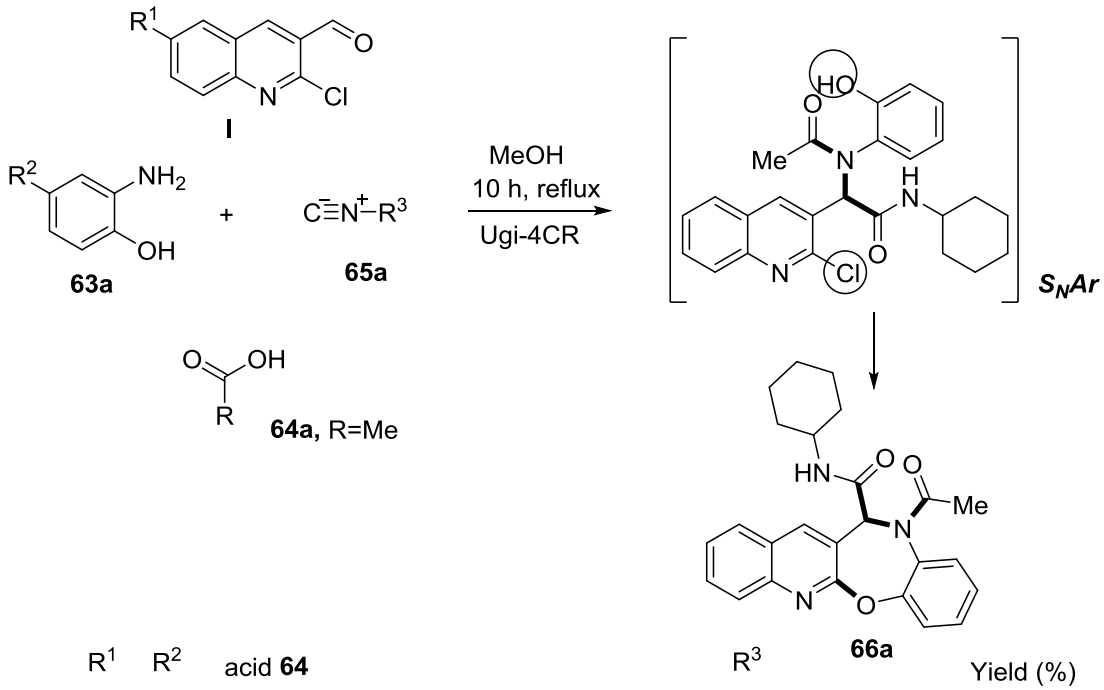
44a: DMAD **56a**: t-butyl. **56b**: cyclohexyl,
44b: DEAD **61**:2,4,4-trimethylpentan-2-yl

Scheme 19

3.1.3.2. **Four component reactions.** A convenient and facile method for synthesis of diverse quino[2,3-*b*][1,5]benzoxazepines **66a-t** was developed. The reaction proceeds through a one-pot sequential Ugi-4CR/base-free intramolecular aromatic nucleophilic substitution reaction (S_NAr) in moderate to good yields from readily available starting materials. Upon treating 2-chloroquinoline-3-carbaldehyde **I** with 2-aminophenol **63a**, acetic acid **64a**, and cyclohexyl isocyanide, **65a** was directly obtained as a sole product in 83% yield (Scheme 20).[44]

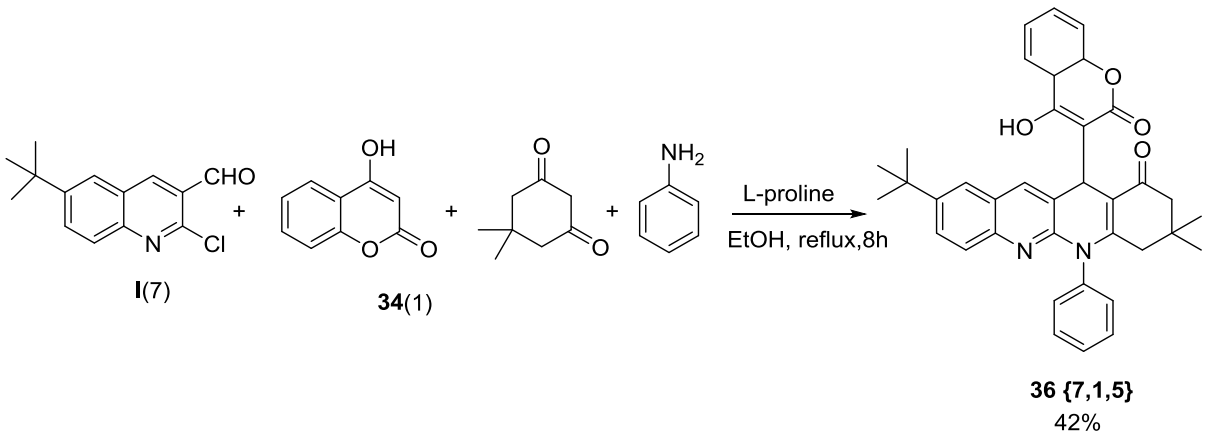
Also benzo[*b*][1,8]naphthyridine derivative **36{7,1,5}** were obtained in low yield (42% yield) *via* four-component reaction of 6-tert-butyl-2-chloroquinoline-3-carbaldehyde **I(7)**, 4-hydroxycoumarin **34(1)**, dimedone, and aniline. After completion of the reaction, the reaction mixture was cooled to room temperature. The crystalline solids were collected and purified by recrystallization from DMF and water to give pure products **36{7,1,5}** (Scheme 21).[34]

In an extended work at the same context, the synthesis of diverse naphthyridinone derivatives **68a-h** was presented. When 2-chloroquinoline-3-carbaldehydes **I**, 3-methyl-1*H*-pyrazol-5(4*H*)-one **67**, enaminone **35**, *L*-proline was stirred and refluxed in ethanol (Scheme 22).[45]

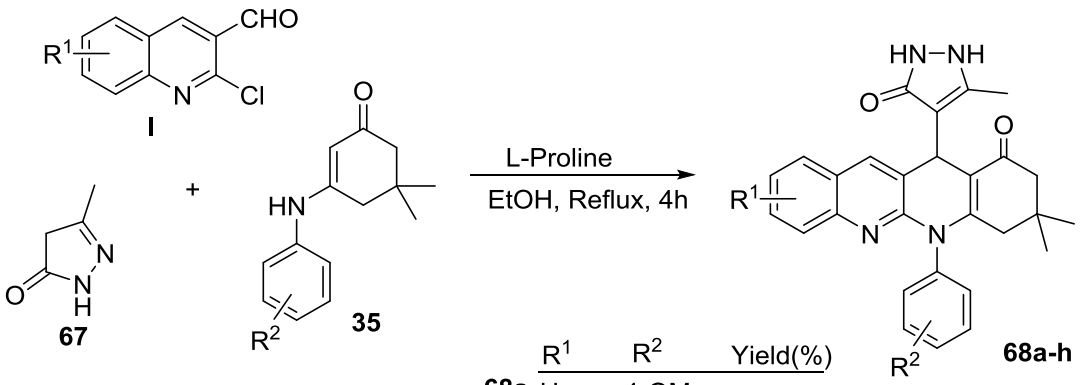


	R^1	R^2	acid **64**	R^3	Yield (%)
66a	H	H	Acetic acid	-cyclohexyl	83
66b	H	H	Acetic acid	-tert-butyl	81
66c	H	H	Acetic acid	-2,4,4-trimethylpentan-2-yl	80
66d	Me	h	Acetic acid	-cyclohexyl	81
66e	Me	H	Acetic acid	-tert-butyl	82
66f	Me	H	Acetic acid	-2,4,4-trimethylpentan-2-yl	79
66g	Me	H	2-oxo-2*H*-chromene-3-carboxylic acid	-tert-butyl	77
66h	Me	H	2-oxo-2*H*-chromene-3-carboxylic acid	-2,4,4-trimethylpentan-2-yl	75
66i	Me	H	2-oxo-2*H*-chromene-3-carboxylic acid	-cyclohexyl	76
66j	Me	H	2-oxo-2*H*-chromene-3-carboxylic acid	-tert-butyl	74
66k	Me	H	2-oxo-2*H*-chromene-3-carboxylic acid	-2,4,4-trimethylpentan-2-yl	74
66l	Me	H	benzoic acid	-cyclohexyl	71
66m	H	H	2-chloronicotinic acid	-cyclohexyl	81
66n	H	H	2-chloronicotinic acid	-tert-butyl	77
66o	H	Cl	Acetic acid	-cyclohexyl	85
66p	H	Cl	benzoic acid	-cyclohexyl	74
66q	H	Cl	2-chloronicotinic acid	-cyclohexyl	83
66r	Me	Cl	2-chloronicotinic acid	-cyclohexyl	79
66s	OMe	Cl	2-chloronicotinic acid	-cyclohexyl	58
66t	H	Cl	2-bromonicotinic acid	-tert-butyl	81

Scheme 20



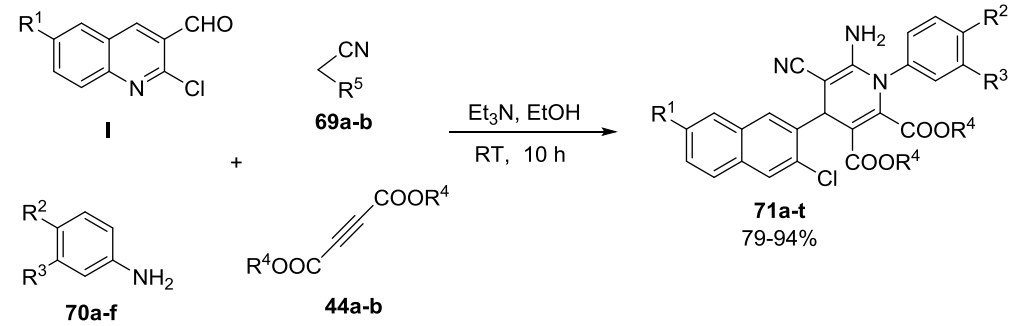
Scheme 21



	R^1	R^2	Yield(%)
68a	H	4-OMe	95
68b	H	4-Me	85
68c	H	4-Cl	83
68d	6-Me	4-Cl	86
68e	6-Br	4-OMe	56
68f	8-Me	4-Me	89
68g	8-Me	4-OMe	94
68h	8-Me	4-Cl	87

Scheme 22

A one-pot reaction providing quinoline-based 1,4-dihydropyridines **71a-t** was developed through reaction of 2-chloroquinoline-3-carbaldehyde **I** and malononitrile or ethyl cyanoacetate **69a-b** in EtOH, TEA followed by addition of amine **70a-f** and dialkylacetylenedicarboxylate **44a-b** (Scheme 23).[46]



I:R^1 = H,
I:R^1 = Me,
I:R^1 =OCH_3

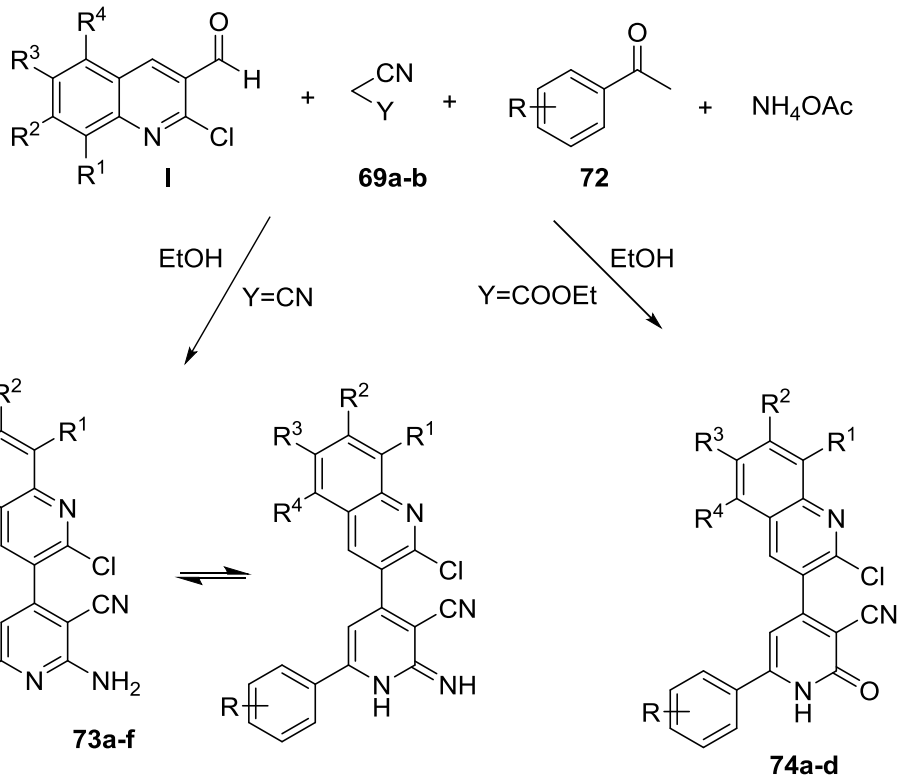
	R^2	R^2
70a	H	H
70b	Me	H
70c	Me	Me
70d	Cl	H
70e	H	Me
70f	OCH_3	H

	R^1	R^2	R^3	R^4	R^5
71a	H	H	H	Me	CN
71b	H	Me	H	Me	CN
71c	H	Me	Me	Me	CN
71d	Me	Cl	H	Me	CN
71e	Me	Me	Me	Me	CN
71f	OCH_3	H	H	Me	CN
71g	OCH_3	H	Me	Me	CN
71h	OCH_3	Cl	H	Me	CN
71i	H	OCH_3	H	Et	CN
71j	H	Me	H	Et	CN

	R^1	R^2	R^3	R^4	R^5
71k	H	H	H	Me	$-CO_2Et$
71l	H	Me	H	Me	$-CO_2Et$
71m	H	Me	Me	Me	$-CO_2Et$
71n	Me	Cl	H	Me	$-CO_2Et$
71o	Me	Me	Me	Me	$-CO_2Et$
71p	OCH_3	H	H	Me	$-CO_2Et$
71q	OCH_3	H	Me	Me	$-CO_2Et$
71r	OCH_3	Cl	H	Me	$-CO_2Et$
71s	H	OCH_3	H	Et	$-CO_2Et$
71t	H	Me	H	Et	$-CO_2Et$

Scheme 23

Recently, an one-pot method has been used for the synthesis of new polycyclic compounds articulated around 3-cyanopyridine derivatives **73a-f** and **74a-d** from 2-chloroquinolin-3- carbaldehydes **I**, acetophenone derivatives **72**, active methylene compounds **69a-b**, and ammonium acetate as a source of ammonia in the presence of catalytic amounts of PPh_3 at room temperature (Scheme 24).[47]



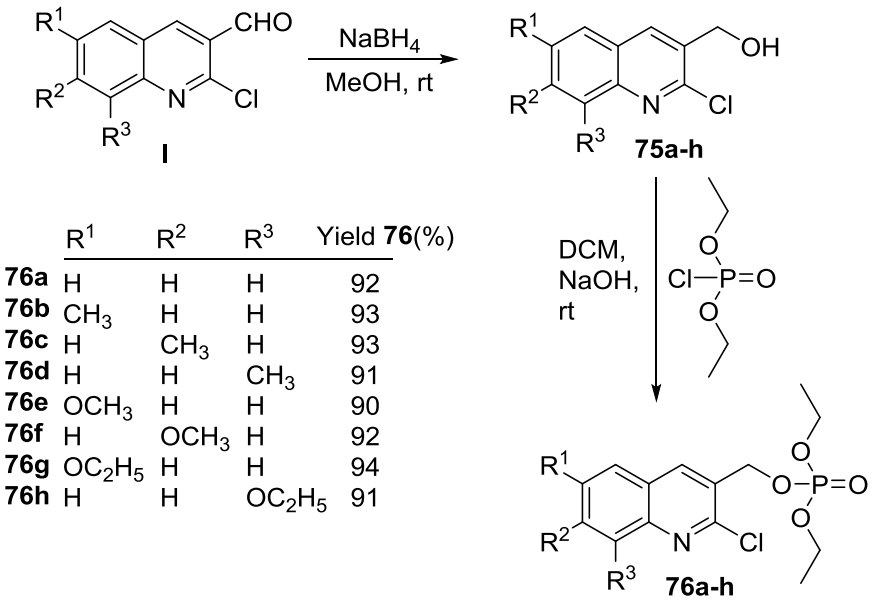
	R^1	R^2	R^3	R^4
I:	H	H	H	H
I:	H	OMe	H	H
I:	H	H	OMe	H
I:	OMe	H	H	OMe
I:	H	H	Me	H

	R^1	R^2	R^3	R^4	R	Yield (%)
73a	H	H	H	H	H	28
73b	H	OMe	H	H	H	40
73c	H	H	Me	H	H	43
73d	OMe	H	H	OMe	OMe	38
73e	H	H	H	H	OMe	36
73f	H	OMe	H	H	OMe	33
74a	H	H	Me	H	OMe	44
74b	H	OMe	H	H	OMe	36
74c	H	H	OMe	H	OMe	33
74d	OMe	H	H	OMe	OMe	31

Scheme 24

3.2. Reduction of the aldehyde group

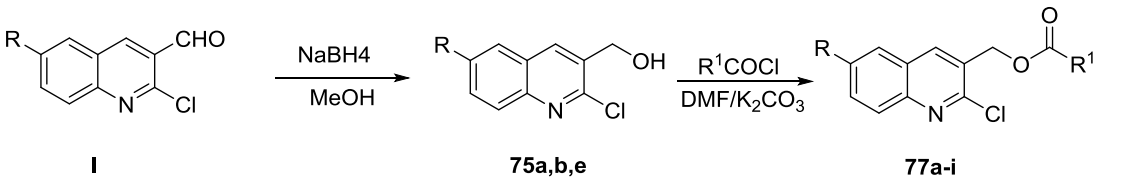
A simple and high yielding method was developed for the synthesis of new (2-chloroquinolin-3-yl)methyl diethyl phosphate **76a-h** from the corresponding alcohol derivatives **75a-h**, that obtained from the aldehydes **I**, by using *O,O*-diethyl chlorophosphate in the presence of NaOH and methylene chloride at ambient temperature (Scheme 25).[48]



	R^1	R^2	R^3	Yield **76**(%)
76a	H	H	H	92
76b	CH_3	H	H	93
76c	H	CH_3	H	93
76d	H	H	CH_3	91
76e	OCH_3	H	H	90
76f	H	OCH_3	H	92
76g	OC_2H_5	H	H	94
76h	H	H	OC_2H_5	91

Scheme 25

The synthesis of a new series of 2-chloroquinolin-3-yl ester derivatives **77a-i** was reported *via* a two-steps protocol from 2-chloroquinoline-3-carbaldehydes **I**. Firstly, **I** was reduced using $NaBH_4$ in methanol to yield the corresponding alcohol derivatives **75a,b,e**, which is then reacted with acid chloride in DMF along with activated K_2CO_3 at room temperature to afford target compounds **(Scheme 26)**.[49]



I

I: R = H
I: R = CH_3
I: R = OCH_3

75a,b,e

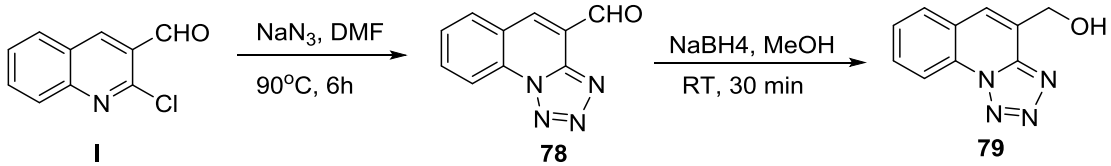
75a: R = H
75b: R = CH_3
75e: R = OCH_3

77a-i

	R	R^1	Yield(%)
77a	H	CH_3	56
77b	H	$-C_6H_5$	70
77c	H	-2,4-dichlorobenzoyl	73
77d	H	-2,6-dichlorobenzoyl	70
77e	CH_3	CH_3	50
77f	CH_3	$-C_6H_5$	74
77g	CH_3	-2,6-dichlorobenzoyl	74
77h	OCH_3	CH_3	76
77i	OCH_3	-2,4-dichlorobenzoyl	73

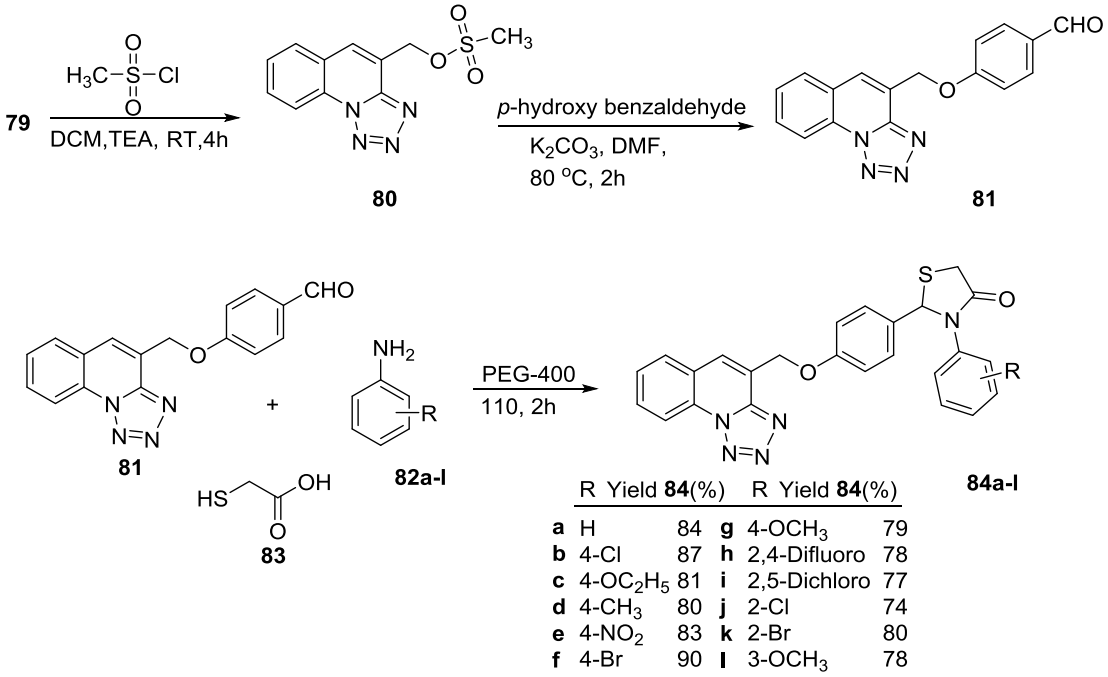
Scheme 26

Condensation of 2-chloroquinoline-3-carbaldehyde **I** with NaN_3 in DMF afforded tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **78**, which was reduced by $NaBH_4$ to obtain tetrazolo[1,5-*a*]quinolin-4-yl methanol **79** (Scheme 27).[50,51]



Scheme 27

The quinolinyl methanol **79**, when allowed to react with methane sulfonyl chloride in presence of TEA in DCM at 0 °C, yielded the corresponding tetrazolo[1,5-*a*]quinolin-4-ylmethyl methanesulfonate ester **80**, which on condensation with p-hydroxybenzaldehyde in DMF in presence of K_2CO_3, afforded the required precursor aldehyde **81**. One-pot cyclocondensation of the **81** with anilines **82a-l** and mercaptoacetic acid **83** was carried out in PEG-400 at 110 °C to obtain the thiazolidin-4-ones **84a-l** in moderate to good yield (Scheme 28).[52]

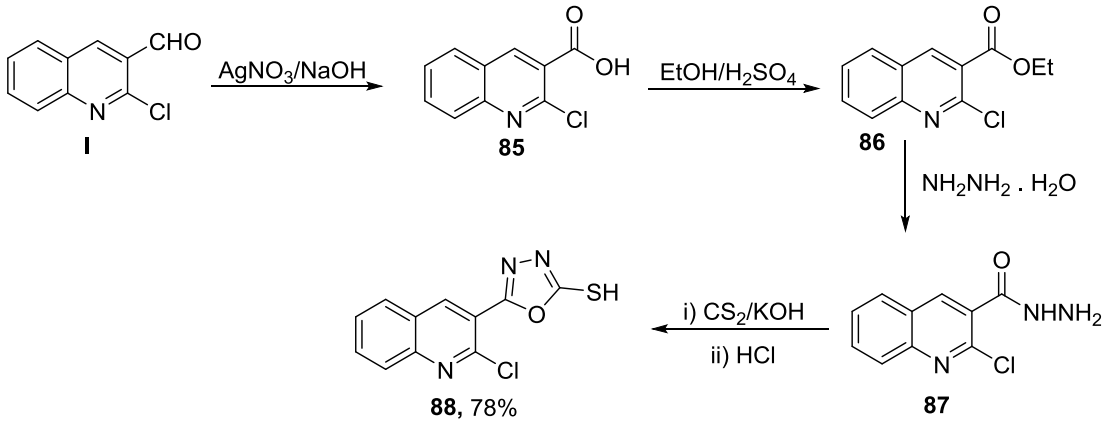


	R	Yield **84**(%)		R	Yield **84**(%)
a	H	84	**g**	4-OCH_3	79
b	4-Cl	87	**h**	2,4-Difluoro	78
c	4-OC_2H_5	81	**i**	2,5-Dichloro	77
d	4-CH_3	80	**j**	2-Cl	74
e	4-NO_2	83	**k**	2-Br	80
f	4-Br	90	**l**	3-OCH_3	78

Scheme 28

3.3. Oxidation of the aldehyde group

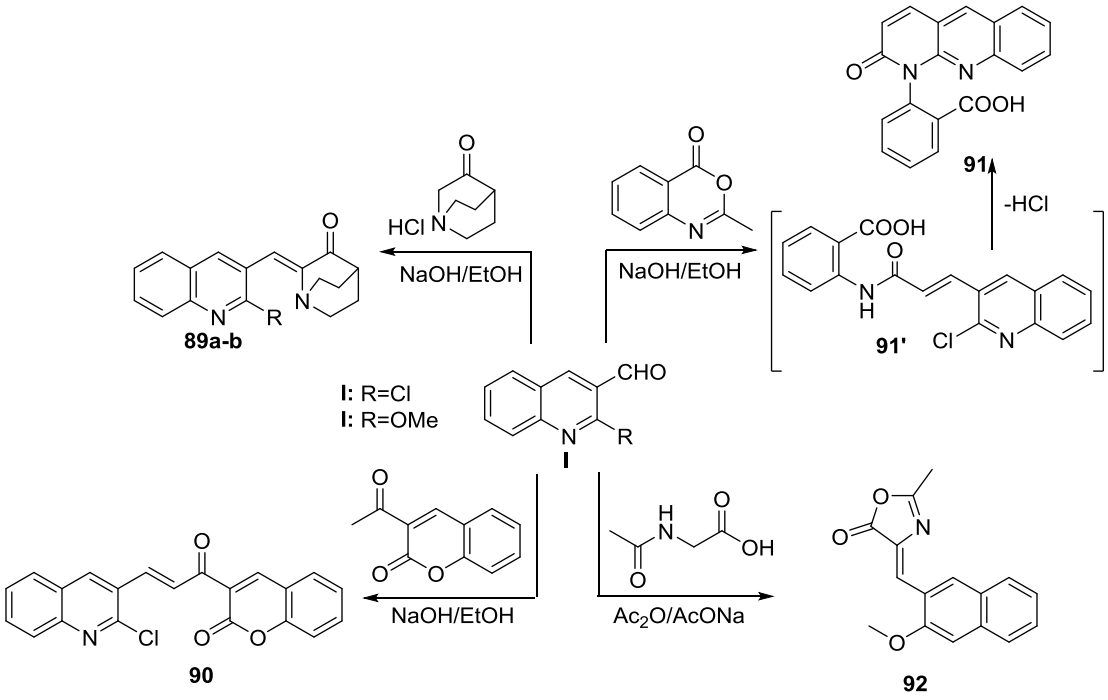
2-Chloroquinoline-3-carboxylic acid was prepared by oxidation of **I** using silver nitrate in the presence of sodium hydroxide.[53] Esterification of the carboxylic acid derivative **85** using absolute ethanol and sulfuric acid afforded the ester derivative **86**, in a good yield, followed by subsequent hydrazinolysis in boiling ethanol to afford 2-chloroquinoline-3-carbohydrazide **87**. The later compound **87** was subjected to react with carbon disulfide in ethanol in the presence of KOH under reflux followed by acidification using diluted HCl to give 5-(2-chloro-quinolin-3-yl)-1,3,4- oxadiazole-2-thiol **88** (Scheme 29).[6]



Scheme 29

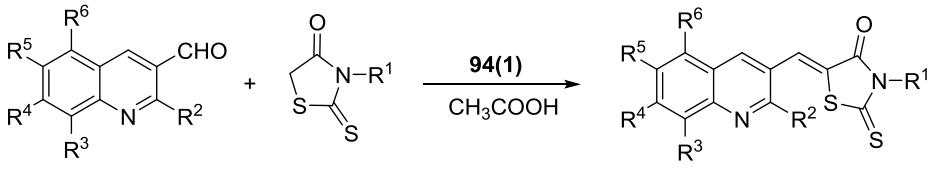
3.4. Condensation reactions

3.4.1. Reactions with active methylene compounds. A series of α,β-unsaturated carbonyl compounds **89a-b** and **90** were synthesized through the Claisen–Schmidt condensation of equimolar amounts of the aldehydes **I** with different active methylene compounds and methyl respectively, in ethanol in the presence of NaOH as catalyst. In addition, the Knoevenagel condensation of **I** with 2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one led to the formation of non-isolable quionoline intermediate **91'**, which underwent cyclization *via* elimination of HCl to afford 2-(2- oxobenzo[*b*][1,8]naphthyridin-1(2*H*)-yl)benzoic acid **91**. While the azlactone **92** was obtained by reaction of *N*-acetylglycine with **I** in the presence of acetic anhydride and sodium acetate (Scheme 30).[54]



Scheme 30

Substituted 2-chloroquinoline-3-carbaldehydes **I,** or substituted 2-(piperidin-1-ylmorpholino) quinoline-3-carbaldehydes **93(1-5)** were reacted with rhodanine derivatives **94(1-3)** in the presence of sodium acetate and acetic acid to afford new rhodanine analogs **95(1-31)** as anticancer agents. Replacement of chlorine group with piperazine or morpholine, improved anticancer activity. While, replacement of rhodanine with rhodanine acetic acid does not change much in the anticancer activity (Scheme 31).[55]



I , 93(1-5) **94(1-3)** **95(1-31)** 66-85%

I(1) R^2=Cl, R^3=R^4=R^5=R^6=H
I(2') R^2=Cl, R^3=Me, R^4=R^5=R^6=H
I(3') R^2=Cl, R^3=Et, R^4=R^5=R^6=H
I(4') R^2=Cl, R^3= R^5=R^6=H, R^4=Me
I(5') R^2=Cl, R^3= R^4=R^6=H, R^5=Me
I(6') R^2=Cl, R^3= R^5=Me, R^4=R^6=H
I(7') R^2=Cl, R^3= R^6=Me, R^4=R^5=H
I(8') R^2=Cl, R^3= R^4=R^6=H, R^5=OMe
I(9') R^2=Cl, R^3= R^6=OMe, R^4=R^5=H
I(10') R^2=Cl, R^3= R^6=H, R^4=R^5=OMe
I(11') R^2=Cl, R^3= R^6=H, R^4=R^5= -OCH_2O-
I(12') R^2=Cl, R^3= R^4=ph, R^5=R^6=H
93 (1) R^2=piperidin-1-yl, R^3=Me, R^4=R^5=R^6=H
93 (2) R^2=morpholino, R^3= R^4=R^6=H, R^5=Me
93 (3) R^2=piperidin-1-yl, R^3=R^4=R^5=R^6=H
93 (4) R^2=piperidin-1-yl, R^3=Et, R^4=R^5=R^6=H
93 (5) R^2=piperidin-1-yl, R^3= R^4=R^6=H,R^5=Me

R^1	
94(1)	H
94(2)	-CH_2COOH
94(3)	-ph

	I	94
95(1)	**I(1)**	**94(1)**
95(2)	**I(2')**	**94(1)**
95(3)	**I(3')**	**94(1)**
95(4)	**I(4')**	**94(1)**
95(5)	**I(5')**	**94(1)**
95(6)	**I(6')**	**94(1)**
95(7)	**I(7')**	**94(1)**
95(8)	**I(8')**	**94(1)**
95(9)	**I(9')**	**94(1)**
95(10)	**I(10')**	**94(1)**
95(11)	**I(11')**	**94(1)**
95(12)	**I(12')**	**94(1)**

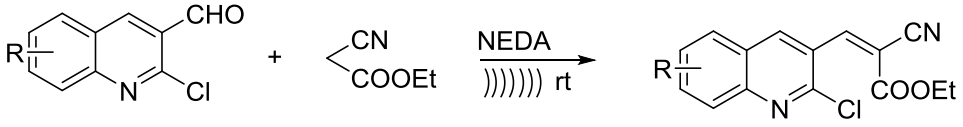
	I	94
95(13)	**I(1)**	**94(2)**
95(14)	**I(2')**	**94(2)**
95(15)	**I(3')**	**94(2)**
95(16)	**I(5')**	**94(2)**
95(17)	**I(6')**	**94(2)**
95(18)	**I(7')**	**94(2)**
95(19)	**I(8')**	**94(2)**
95(20)	**I(9')**	**94(2)**
95(21)	**I(10')**	**94(2)**
95(22)	**I(11')**	**94(2)**
95(23)	**I(12')**	**94(2)**

	I	94
95(24)	**I(6')**	**94(3)**
95(25)	**I(7')**	**94(3)**
95(26)	**I(12')**	**94(3)**

	93	94
95(27)	**93(1)**	**94(1)**
95(28)	**93(2)**	**94(1)**
95(29)	**93(3)**	**94(2)**
95(30)	**93(4)**	**94(2)**
95(31)	**93(5)**	**94(2)**

Scheme 31

An efficient, eco-friendly method for rapid Knoevenagel condensation of 2-chloroquinoline-3-carbaldehydes **I** with ethyl cynoacetate **69b** under ultrasonic irradiation in solvent-free medium by using *N*-ethyl diisopropyl amine (NEDA) as catalyst within short time period (14-20 min) at room temperature was reported. Compared with traditional method, this method is more convenient and reaction can be carried out in higher yield, shorter reaction time and milder condition, without generation of pollution and safer to analyst (Scheme 32).[56]



I **69b** **96a-h**

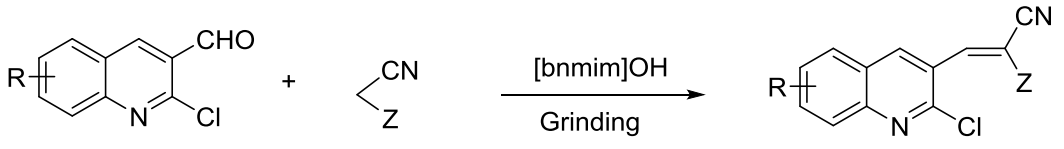
I: R= 8-CH_3
I: R= H
I: R=6-OCH_3
I; R= 7-OCH_3
I: R= 6-CH_3
I: R= 7-CH_3
I: R= 6-C_2H_5
I: R= 7-C_2H_5

	R	Yield(%)
96a	8-CH_3	89
96b	H	85
96c	6-OCH_3	88
96d	7-OCH_3	84
96e	6-CH_3	87
96f	7-CH_3	89
96g	6-C_2H_5	82
96h	7-C_2H_5	91

Scheme 32

In addition, a facile, efficient and green methodology for the Knoevenagel condensation reaction was reported by grinding a mixture of hetero aryl aldehydes **I** and various active methylene compounds **69a,b** and **97a,b** with catalytic amount of [bnmim]OH, at room temperature. The product was extracted twice from

diethyl ether, leaving behind [bnmim]OH. Organic layer washed by brine solution (2×10 mL) and dried over sodium sulfate and the solvent was evaporated under reduced pressure (Scheme 33).[57]



I **69(a,b),97a,b** **98a-o**

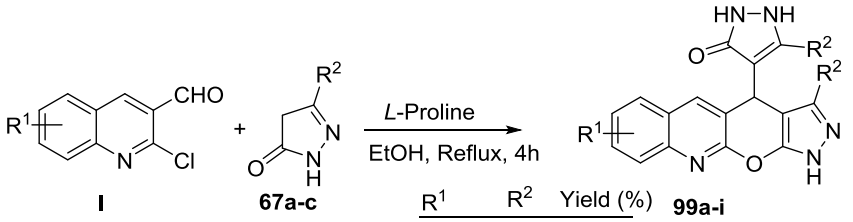
	Z
69a	CN
69b	COOEt
97a	COOH
97b	$CONH_2$

	R	Z	Yield (%)
98a	-H	CN	96
98b	6-Cl	CN	95
98c	7-Me, 8-Cl	CN	94
98d	6-Me	COOH	94
98e	6-Br	COOH	95
98f	7-Me, 8-Cl	COOH	92
98g	6-Me	$CONH_2$	93
98h	6-Cl	$CONH_2$	94

	R	Z	Yield (%)
98i	7-Me, 8-Cl	$CONH_2$	95
98i	H	COOEt	92
98k	7-OMe	COOEt	90
98l	6-Me	COOEt	85
98m	7-Me	COOEt	92
98n	8-Me	COOEt	93
98o	6-Et	COOEt	90

Scheme 33

Description of the synthesis of novel 1,4-dihydropyrazolo-pyrano-[2,3-*b*]quinoline derivatives **99a-i**, by reacting 2-chloroquinoline-3-carbaldehydes **I** with 3-substituted-1*H*-pyrazol-5(4*H*)-one **67a-c** in refluxing ethanol mediated by *L*-proline was reported. This procedure was found efficient for various 2-chloroquinoline-3-carbaldehydes **Ia-e** bearing electron donating and electron withdrawing groups (Scheme 34).[45]

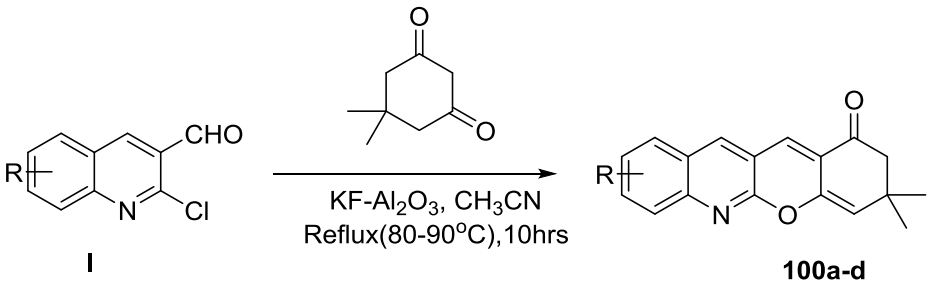


I **67a-c** **99a-i**

	R^1	R^2	Yield (%)
99a	6-OMe	Me	93
99b	H	Me	88
99c	6-Me	Me	93
99d	H	Ph	80
99e	8-Me	Ph	85
99f	6-Me	Ph	82
99g	6-OMe	Ph	87
99h	H	CH_2Cl	73
99i	6-Cl	Me	88

Scheme 34

The reaction of 2-chloroquinoline-3-carbaldehyde derivatives **I** and dimedone in the presence of KF-Al_2O_3 to afford new pyranoquinolines **100a-d** was reported. In this approach, a mechanism was proposed for the reaction course. Reasonable yields (41-50%), easily available starting materials and less expensive efficient catalyst are the key features of this method (Scheme 35).[58]



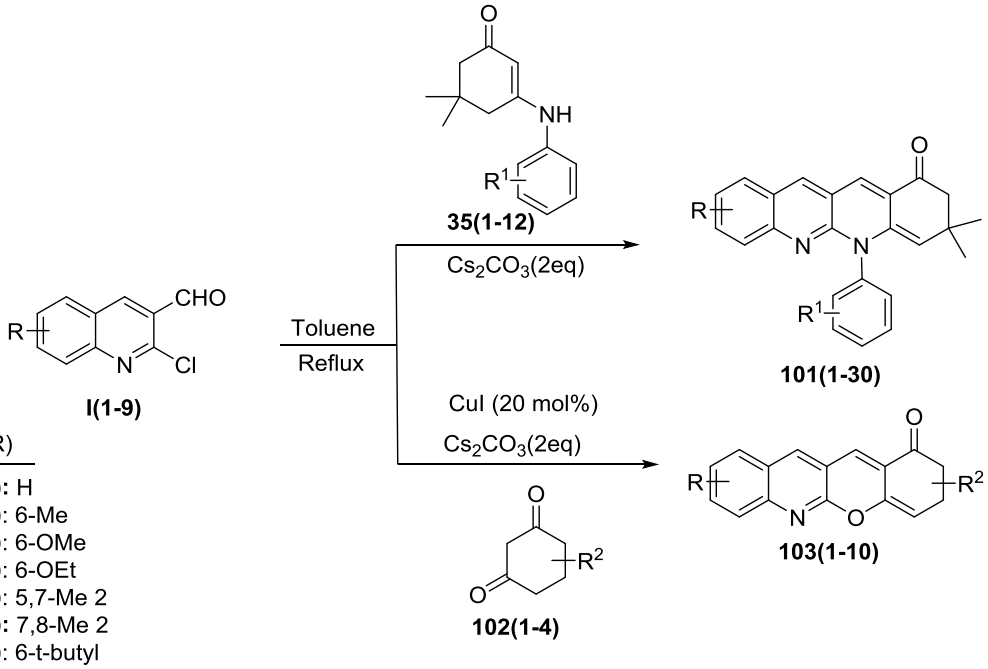
I

I: R = H
I: R = 5,7-Me 2
I: R = 6-Br
I: R = 7-OCH_3

100a-d

	R	Yield (%)
100a	H	50
100b	5,7-Me 2	46
100c	6-Br	44
100d	7-OCH_3	41

Scheme 35



I(R)

I(1): H
I(2): 6-Me
I(3): 6-OMe
I(4): 6-OEt
I(5): 5,7-Me 2
I(6): 7,8-Me 2
I(7): 6-t-butyl
I(8): 6-isopropyl
I(9): 8-Et

35(R^1)

35(1): *p*-Me
35(2): H
35(3): *p*-OMe
35(4): *p*-*t*-butyl
35(5): *p*-Cl
35(6): *p*-Br
35(7): *p*-NO_2
35(8): *p*-F,*m*-Cl
35(9): *m*-Me2
35(10): *o*-Cl
35(11): *o*-Et
35(12): benzo[2-3]

Entry	**3**(R,R^1)	Yield(%)	Entry	**3**(R,R^1)	Yield(%)
1	**101**(1,1)	79	**16**	**101**(7,1)	87
2	**101**(1,2)	80	**17**	**101**(7,2)	82
3	**101**(1,6)	83	**18**	**101**(7,3)	85
4	**101**(1,7)	84	**19**	**101**(7,4)	86
5	**101**(1,10)	85	**20**	**101**(7,5)	78
6	**101**(1,12)	83	**21**	**101**(7,6)	75
7	**101**(2,1)	87	**22**	**101**(7,7)	82
8	**101**(2,8)	82	**23**	**101**(7,8)	85
9	**101**(3,1)	84	**24**	**101**(7,9)	84
10	**101**(3,2)	85	**25**	**101**(7,11)	83
11	**101**(4,2)	82	**26**	**101**(7,12)	82
12	**101**(4,3)	76	**27**	**101**(8,1)	84
13	**101**(5,1)	83	**28**	**101**(8,2)	83
14	**101**(6,1)	84	**29**	**101**(8,7)	82
15	**101**(6,5)	84	**30**	**101**(9,9)	84

4(R^2)

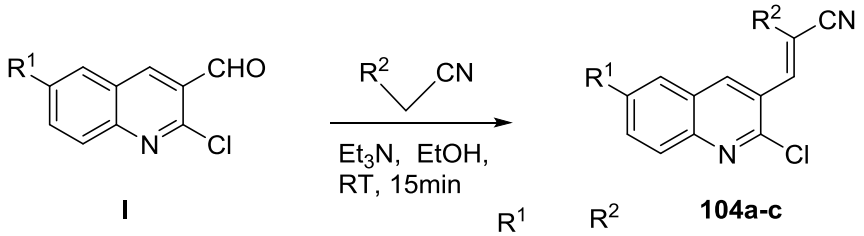
102(1): 5-Me2
102(2): 5-Me
102(3): 5-p
102(4): **5**-propyl

Entry	**5**(R,R^2)	Yield(%)
1	**103**(1,1)	87
2	**103**(2,1)	89
3	**103**(3,1)	89
4	**103**(4,1)	92
5	**103**(5,1)	89
6	**103**(7,1)	85
7	**103**(8,1)	94
8	**103**(9,1)	87
9	**103**(7,2)	81
10	**103**(7,3)	84

Scheme 36

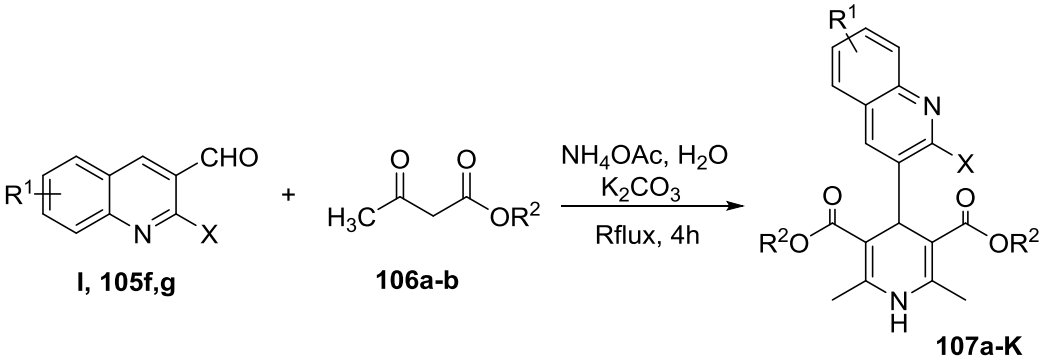
An efficient synthesis of novel functionalized 1,8-naphthyridine **101(1-30)** and chromeno[2,3-*b*]quinolines **103(1-10)** derivatives *via* cascade reaction of 2-chloroquinoline-3-carbaldehyde **I(1-9)** and enaminones **35(1-12)** or cyclic 1,3-dicarbonyl compounds **102(1-4)** was introduced. The crude products of **101(1-30)** were purified by recrystallization from 95% ethanol, while the crude products of **103(1-10)** were purified by column chromatography to afford the pure products. All of the newly synthesized compounds were evaluated for their in *vitro* antiproliferative properties against cancer; several compounds were found to have high activities (Scheme 36).[59]

A synthetic route of novel highly substituted cyclopentadienes containing quinoline nucleus was described, in which a Knoevenagel adducts **104a-c** of 2-chloroquinoline-3-carbaldehydes **I** and malononitrile or ethyl cyanoacetate were prepared. The reaction mixture was stirred in ethanol for 15 min at room temperature. After completion of the reaction, the solid was separated by filtration (Scheme 37).[37]



	R^1	R^2
104a	H	CO_2Et
104b	Me	CO_2Et
104c	Me	CN

Scheme 37



	R^1	X
I:	H	Cl
I:	6-Me	Cl
I:	6-OMe	Cl
I:	8-Me	Cl
I:	7-OMe	Cl
105f	H	I
105g	H	O

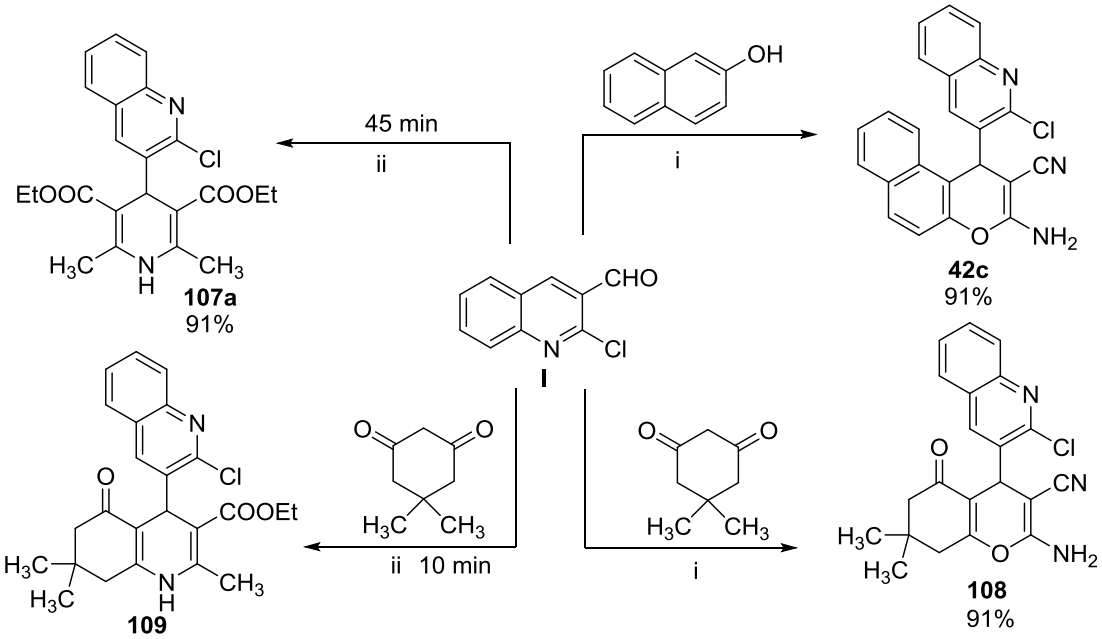
106a: Et
106b: Me

	R^1	R^2	X	Yield (%)
107a	H	Et	Cl	78
107b	6-Me	Me	Cl	79
107c	H	Me	Cl	82
107d	6-OCH_3	Et	Cl	85
107e	6-OCH_3	Me	Cl	88
107f	8-Me	ET	Cl	75
107g	8-Me	Me	Cl	78
107h	7-OCH_3	Me	Cl	84
107i	H	Et	I	85
107j	H	Me	I	83
107k	H	Me	O	87

Scheme 38

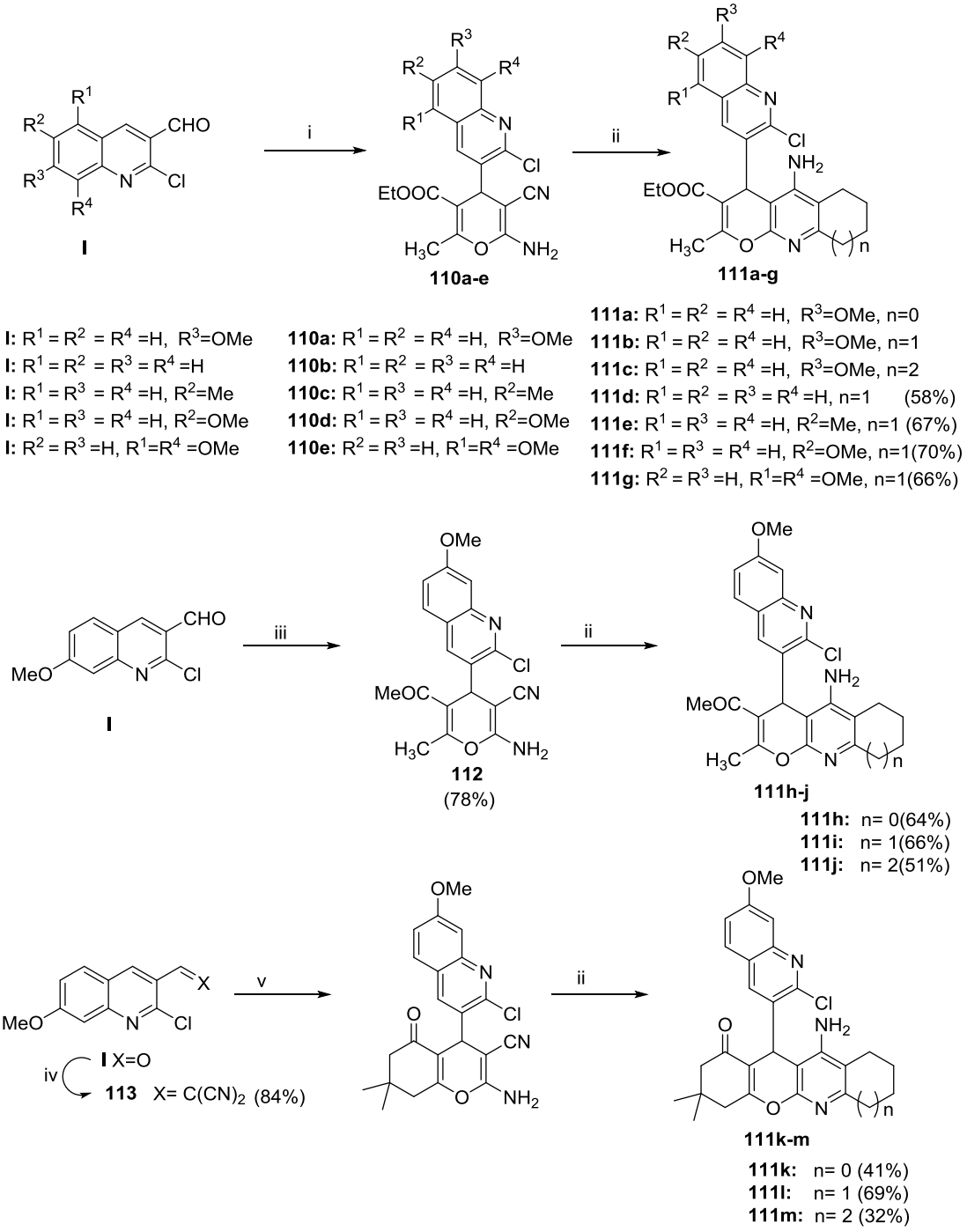
The synthesis of a novel series of substituted 1,4-dihydropyridines **107a-k** was achieved in aqueous media by a base-catalyzed Hantzsch reaction of 2-chloroquinoline-3-carbaldehydes (**I and 105f,g**), ammonium acetate, and alkyl acetoacetate **106a-b** in good to high yields was achieved (Scheme 38).[60]

Functionalized 2-amino-4*H*-benzo[*b*]pyran **42c** and **108**, dihydropyridine **107a**, polyhydroquinoline **109**, derivatives were synthesized at ambient temperature in aqueous medium, in the presence of Bi_2WO_6 (5 mol %) as a catalyst. Bi_2WO_6 nanoparticle mediated multicomponent reactions (at RT, in aq. medium) afforded good yields in a short period of time (10–45 min; 5 mol% of catalyst) (Scheme 39).[61]



Scheme 39

Herein, thirteen new racemic, diversely functionalized 2-chloroquinolin-3-yl substituted Pyrano Tacrines (PTs) **111a-m** were synthesized from the corresponding readily available 4*H*-pyrans and diverse commercial cycloalkanones, by using a Friedländer-type reaction[62], under standard reaction conditions (Scheme 40).[63]

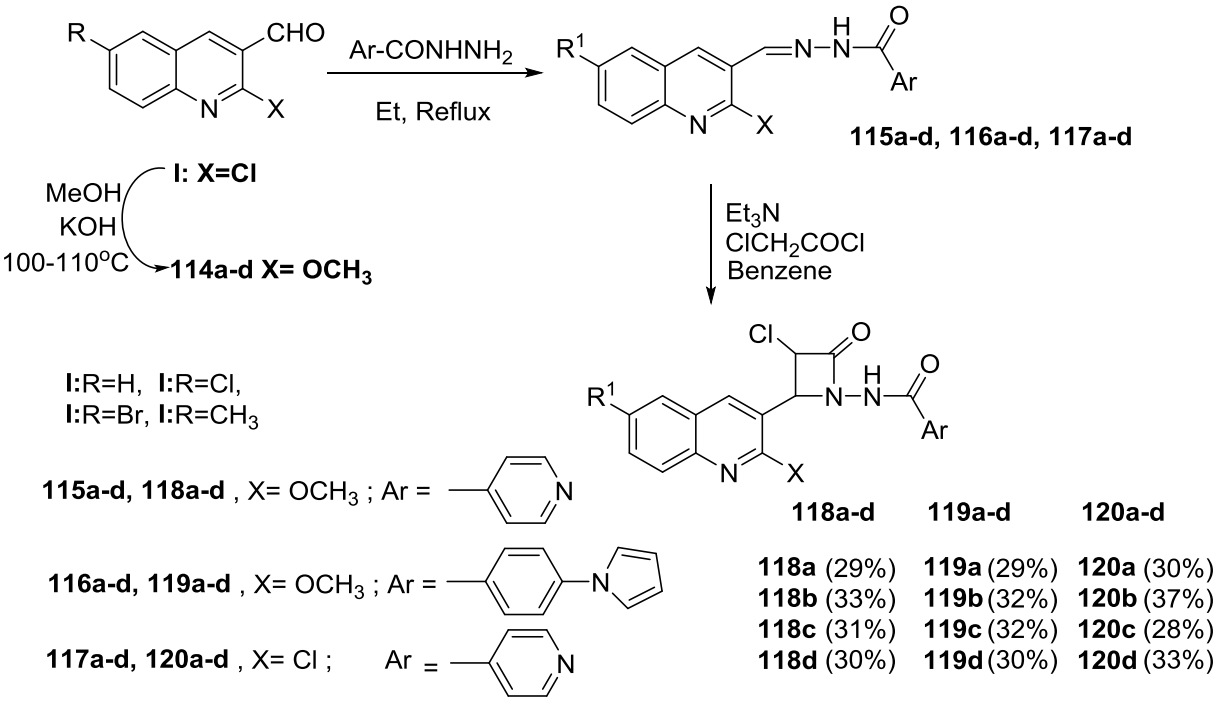


Reagents and conditions: **i**: a. $CNCH_2CN$, piperidine (cat.), EtOH, rt, 20 min; b. ethyl acetoacetate, piperidine(cat.); **ii.** Cycloalkanone, 1,2-dichloroethane, $AlCl_3$, reflux; **iii**: a. $CNCH_2CN$, piperidine (cat.), EtOH, rt, 20 min; b. 2,4-pentanedione, piperidine (cat.); **iv.** $CNCH_2CN$, piperidine (cat.), EtOH, rt, 20 min; **v**: dimedone, Et_3N (cat.), EtOH, rt, 1 h.

Scheme 40

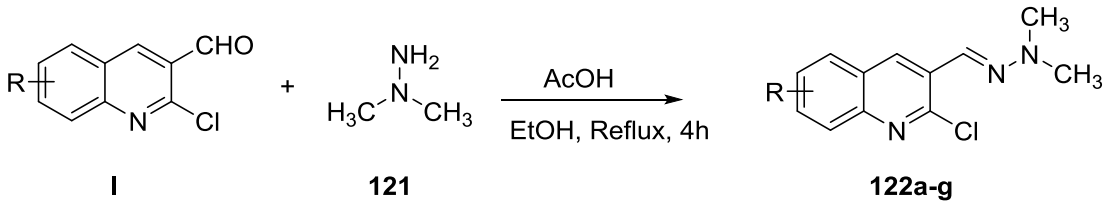
3.4.2. Reactions with hydrazine, hydroxylamine, hydrazides, (thio)semicarbazide, and urea. The synthesis of new series of quinolinyl Schiff's bases and azetidinones was reported. The aldehydes **I**, upon treatment with methanol in the presence of KOH furnished the corresponding 2-methoxyquinoline-3-carbaldehydes **114a-d**. The Schiff's bases **115a-d** and **116-d** were prepared by reacting **114a-d** with isoniazid and 4-(1*H*-pyrrol-1-yl)benzohydrazide in the presence of glacial acetic acid, respectively. While the Schiff's bases **117a-d** were

prepared by reacting **I** with isoniazid in ethanol in the presence of glacial acetic acid. Compounds **115a-d**, **116a-d**, and **117a-d** upon treatment with monochloroacetyl chloride in the presence of TEA in dry benzene gave **118a-d**, **119a-d**, and **120a-d**, respectively (Scheme 41).[64]



Scheme 41

A new series of quinoline derivatives **122a-g** were synthesized by refluxing a mixture of 2-chloroquinoline-3-carbaldehydes **I**, 1,1-dimethylhydrazine **121**, few drops of glacial acetic acid in EtOH for 4 h. After completion of the reaction, distilled water was added to the reaction mixture, the resulting solid was separated by filtration, and recrystallized from ethanol to afford pure products (Scheme 42).[65]

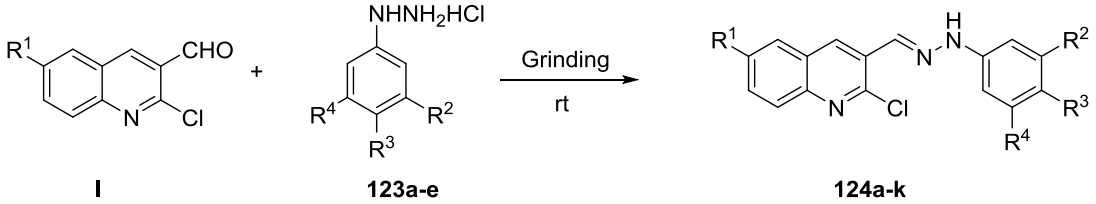


	R	Yield (%)
122a	H	70
122b	6-Me	72
122c	6-OMe	75
122d	6-Cl	69
122e	7-Me	80
122f	6-isopropyl	70
122g	7-Cl	69

Scheme 42

The synthesis of 2-chloroquinoline-3-carbaldehyde phenyl hydrazone derivatives **124a-k** by two methods was described. The first method is in solution, by stirring substituted aldehyde **I** and substituted

phenyl hydrazine **123a-c** in MeOH at room temperature over 2-15 h, while the second method is in solid state by grinding reactants to form products in short time (Scheme 43).[66]



I: R^1 = H
I: R^1 = CH_3
I: R^1 = OCH_3

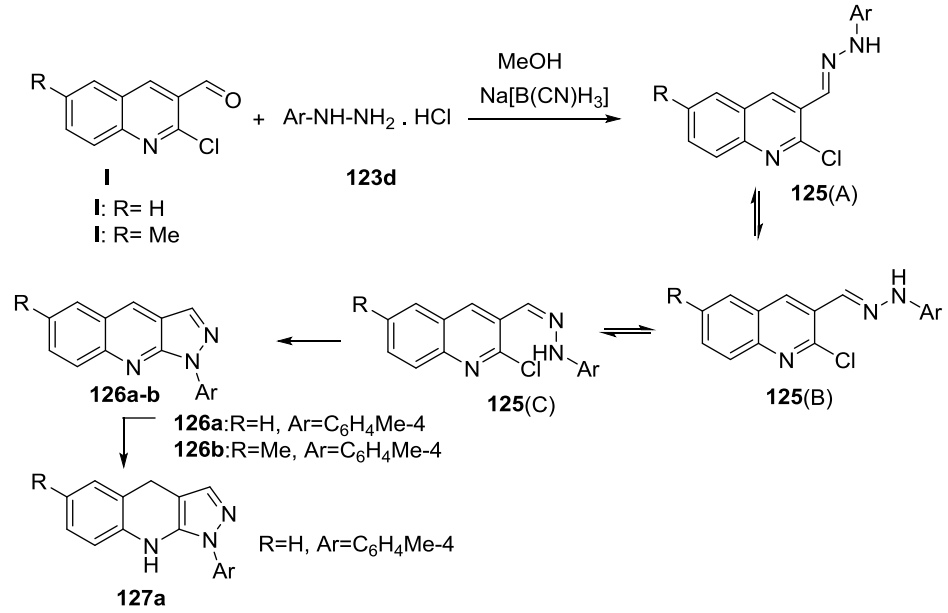
	R^2	R^3	R^4
123a	H	H	H
123b	F	H	H
123c	F	H	F
123d	H	CH_3	H
123e	NO_2	H	H

a: Yield (%) in Methanol at rt
b: Yield (%) in solvent-free at rt

	R^1	R^2	R^3	R^4	Yield(%)[a]	Yield(%)[b]
124a	H	H	H	H	90	98
124b	H	F	H	H	92	97
124c	H	F	H	F	94	99
124d	H	H	CH_3	H	90	97
124e	CH_3	H	H	H	90	97
124f	CH_3	F	H	H	90	99
124g	CH_3	F	H	F	94	97
124h	OCH_3	H	H	H	88	96
124i	OCH_3	F	H	H	90	98
124j	OCH_3	H	CH_3	H	93	96
124k	H	NO_2	H	H	90	95

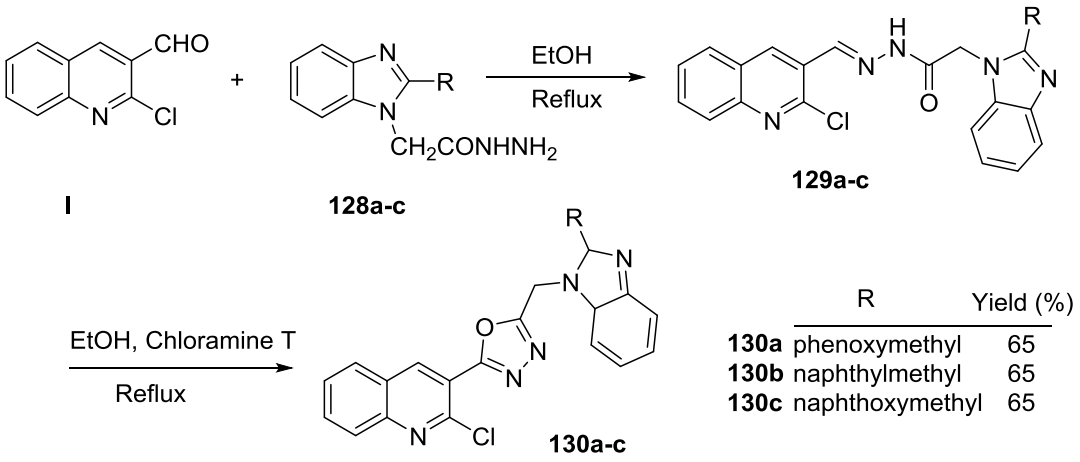
Scheme 43

Dry grinding of a mixture of the aldehydes **I** and 4-methylphenylhydrazinium chloride **123d** afforded the hydrazone derivative **125(A,B)**, while the same reagents in methanol in the presence of sodium cyanoborohydride gave the 1*H*-pyrazolo[3,4-*b*]quinoline **127a** (Scheme 44).[66,67]



Scheme 44

On refluxing the benzimidazolylacetohydrazides **128a-c** with **I** in ethanol, the acetohydrazides **129a-c** were afforded. 1,3,4-Oxadiazoles **130a-c** were prepared by refluxing *N*'-((2-chloroquinolin-3-yl)methylene)-2-(2-substituted-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide **129a-c** with chloramine-T in ethanol (Scheme 45).[8,68]

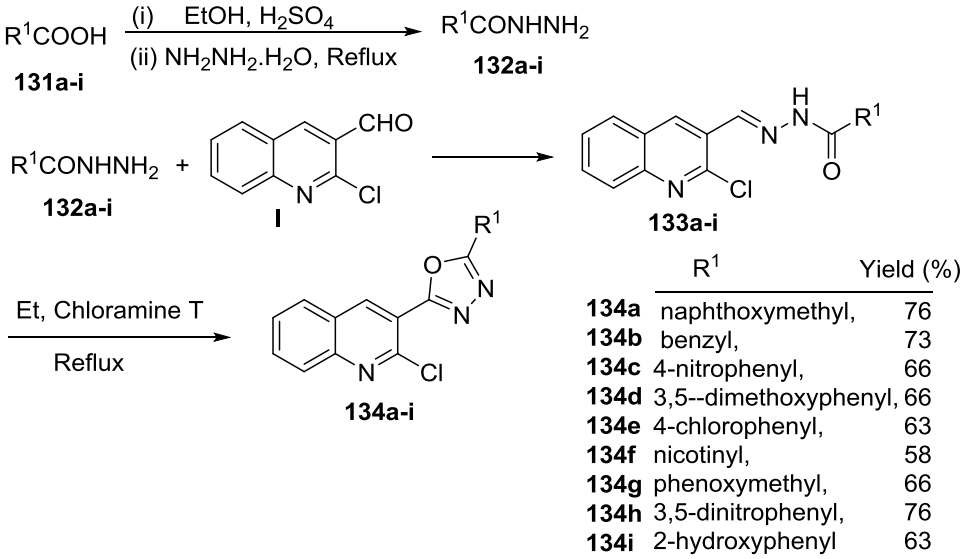


I **128a-c** **129a-c** **130a-c**

	R	Yield (%)
130a	phenoxymethyl	65
130b	naphthylmethyl	65
130c	naphthoxymethyl	65

Scheme 45

Similarly, the different hydrazides **132a-i** were synthesized starting from aromatic acids **131a-i**. The benzohydrazide derivatives **133a–i** were synthesized by reacting the aldehyde **I** and the appropriate hydrazide **132a-i**. In the final step, the oxadiazol-2-ylquinolines **134a-i** were synthesized with chloramine-T as aforementioned (Scheme 46).[68,69]

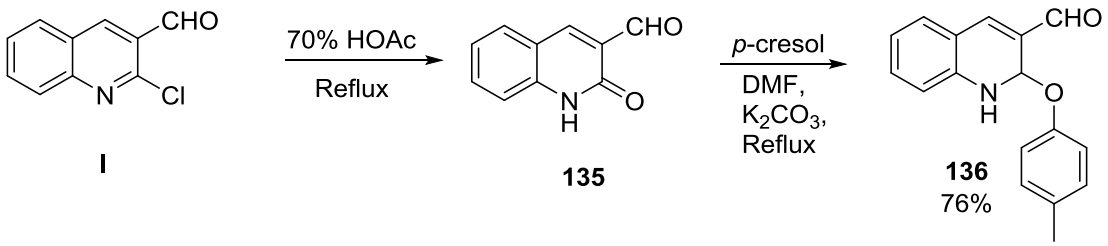


131a-i **132a-i** **I** **133a-i** **134a-i**

	R^1	Yield (%)
134a	naphthoxymethyl,	76
134b	benzyl,	73
134c	4-nitrophenyl,	66
134d	3,5--dimethoxyphenyl,	66
134e	4-chlorophenyl,	63
134f	nicotinyl,	58
134g	phenoxymethyl,	66
134h	3,5-dinitrophenyl,	76
134i	2-hydroxyphenyl	63

Scheme 46

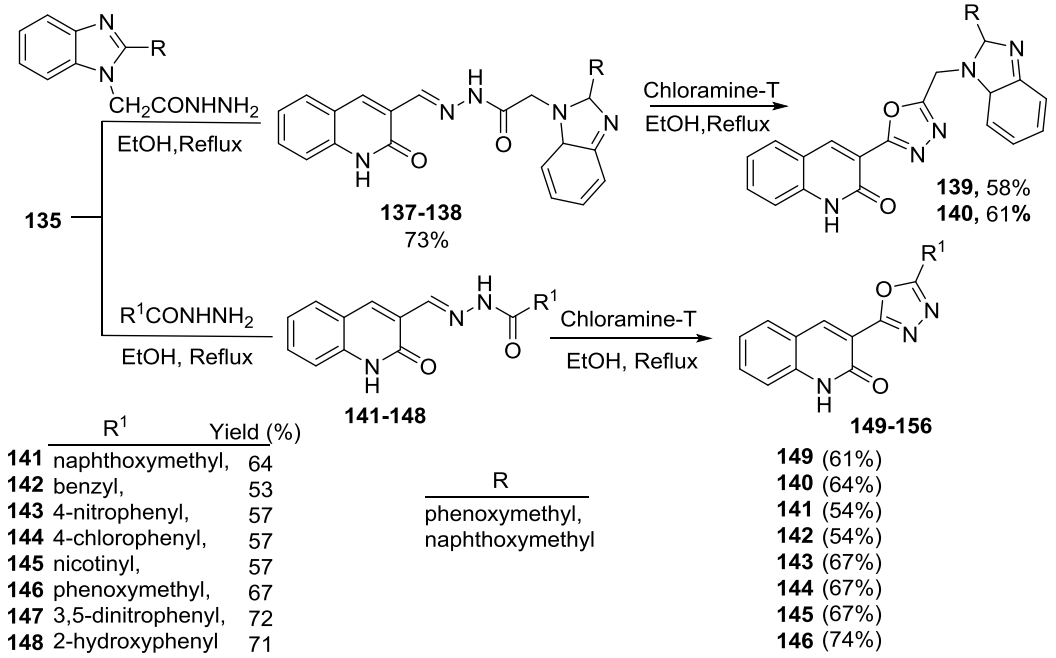
2-Oxo-1,2-dihydroquinoline-3-carbaldehyde **135** was obtained by refluxing 2-chloroquinoline-3-carbaldehyde **I** in 70% acetic acid. While 2-(*p*-tolyloxy)quioline-3-carbaldehyde **136** was prepared by refluxing **135** with *p*-cresol in DMF and using catalytic amount of K_2CO_3 (Scheme 47).[8]



I **135** **136**

Scheme 47

2-Oxo-1,2-dihydroquinoline-3-carbaldehyde **135** was used for preparation of the series of 2,5-disubstituted 1,3,4-oxadiazoles **139-140** and **149-156**. This series were synthesized in search of potential therapeutics for cancer. The corresponding 1,3,4-oxadiazoles has been synthesized by chloramine-T and refluxing in ethyl alcohol. (Scheme 48).[8]

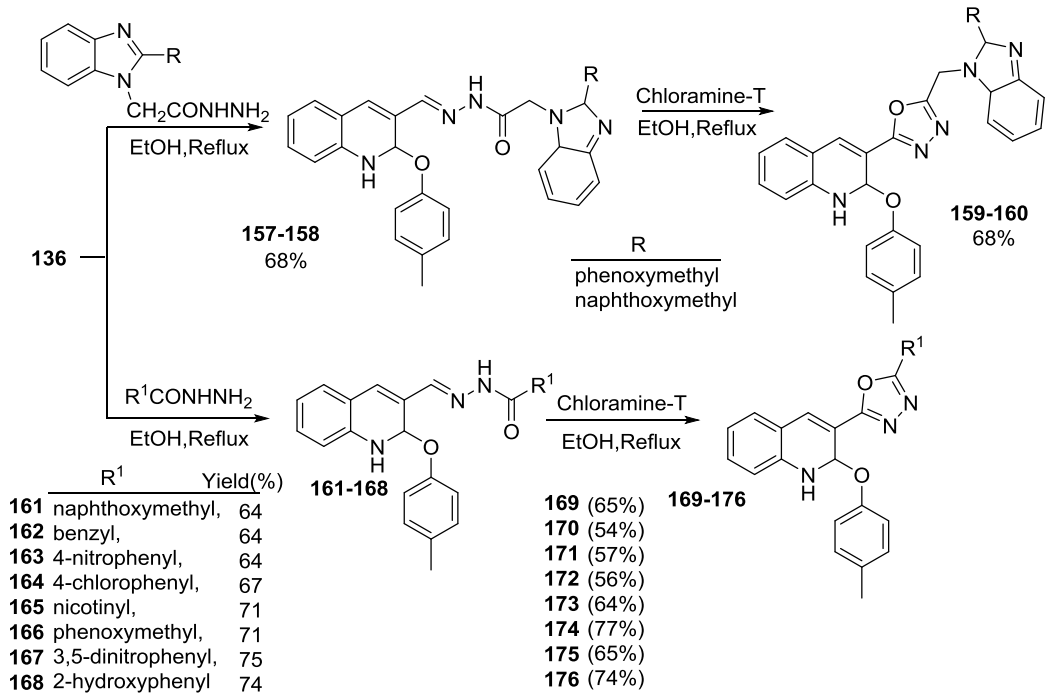


	R^1	Yield (%)
141	naphthoxymethyl,	64
142	benzyl,	53
143	4-nitrophenyl,	57
144	4-chlorophenyl,	57
145	nicotinyl,	57
146	phenoxymethyl,	67
147	3,5-dinitrophenyl,	72
148	2-hydroxyphenyl	71

149 (61%)
140 (64%)
141 (54%)
142 (54%)
143 (67%)
144 (67%)
145 (67%)
146 (74%)

Scheme 48

For the synthesis of the second series of 2,5-disubstituted 1,3,4-oxadiazoles **159-160**, **169-176**, 2-(*p*-tolyloxy)quioline-3-carbaldehyde **136** was used as a starting aldehyde. This series had also been synthesized using chloramine-T and refluxing in ethanol. The study revealed that compound **159** is a potent lead compound for anticancer drug discovery (Scheme 49).[8]

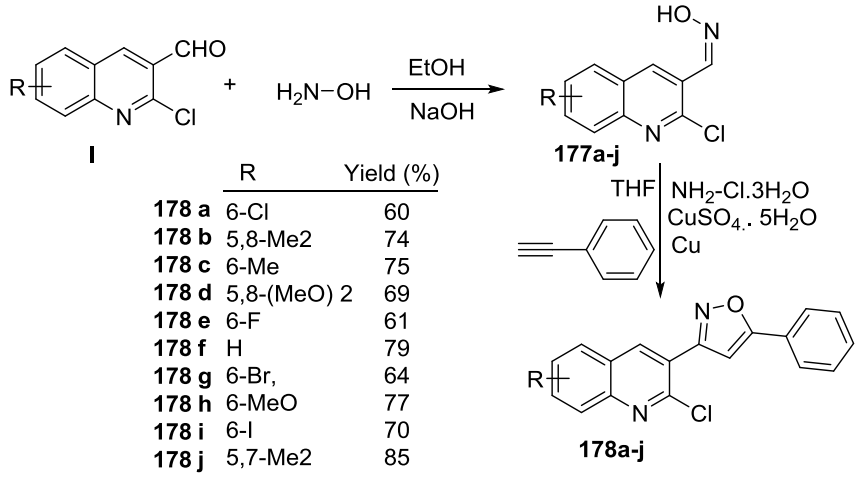


	R^1	Yield(%)
161	naphthoxymethyl,	64
162	benzyl,	64
163	4-nitrophenyl,	64
164	4-chlorophenyl,	67
165	nicotinyl,	71
166	phenoxymethyl,	71
167	3,5-dinitrophenyl,	75
168	2-hydroxyphenyl	74

169 (65%)
170 (54%)
171 (57%)
172 (56%)
173 (64%)
174 (77%)
175 (65%)
176 (74%)

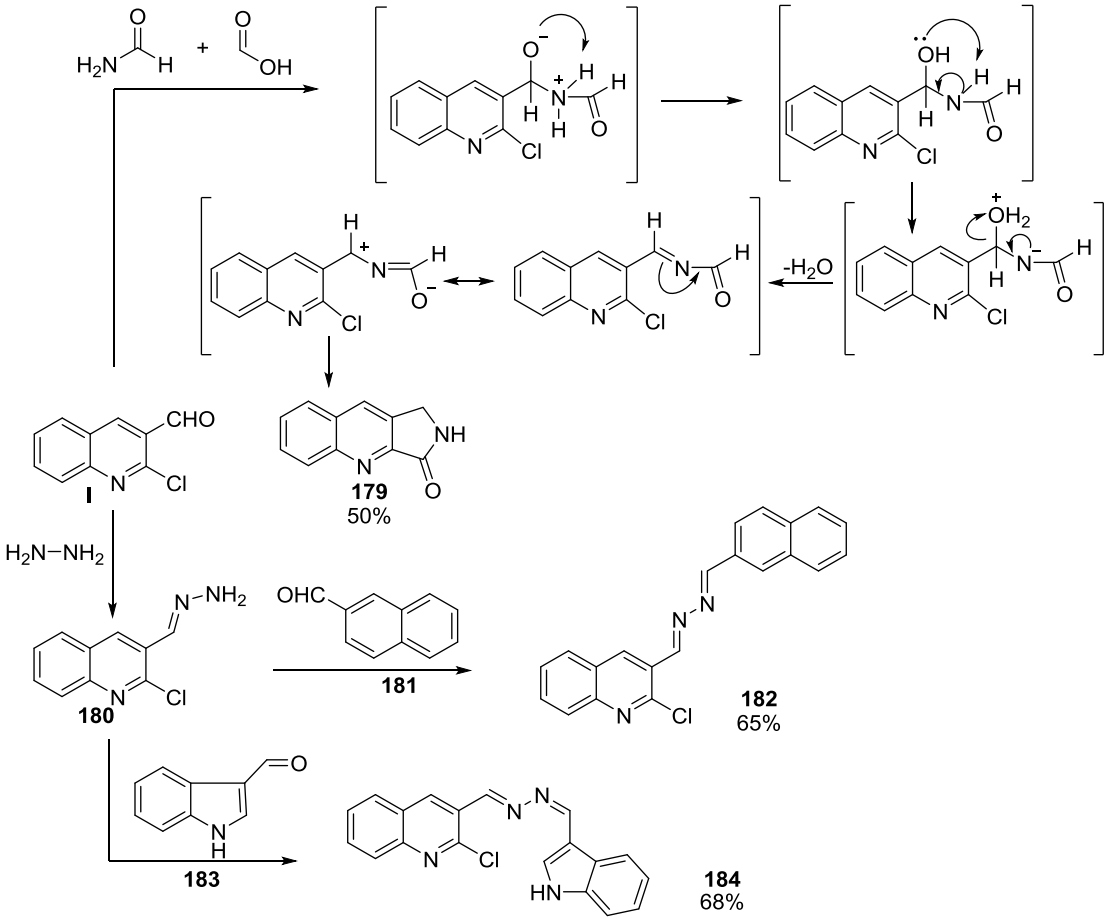
Scheme 49

A procedure was described for the synthesis of 3-(2-chloroquinolin-3-yl)-5-phenylisoxazoles **178a-j**. The appropriate aldehyde **I** was added to a hydroxylamine solution in ethanol to afford the oxime **177a-g**, which upon reaction with chloramine-T trihydrate, $CuSO_4.5H_2O$, Cu and phenylacetylene afforded the corresponding phenylisoxazoles **178a-j** (Scheme 50).[7]



	R	Yield (%)
178 a	6-Cl	60
178 b	5,8-Me2	74
178 c	6-Me	75
178 d	5,8-(MeO) 2	69
178 e	6-F	61
178 f	H	79
178 g	6-Br,	64
178 h	6-MeO	77
178 i	6-I	70
178 j	5,7-Me2	85

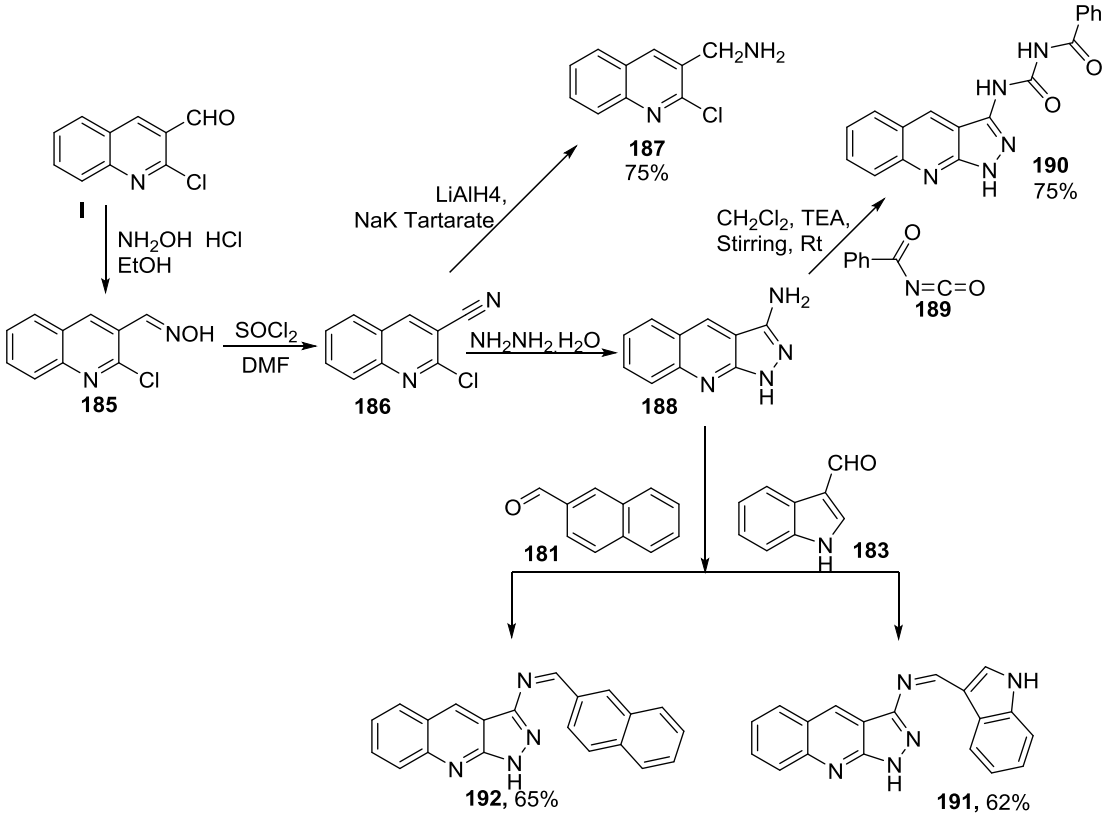
Scheme 50



Scheme 51

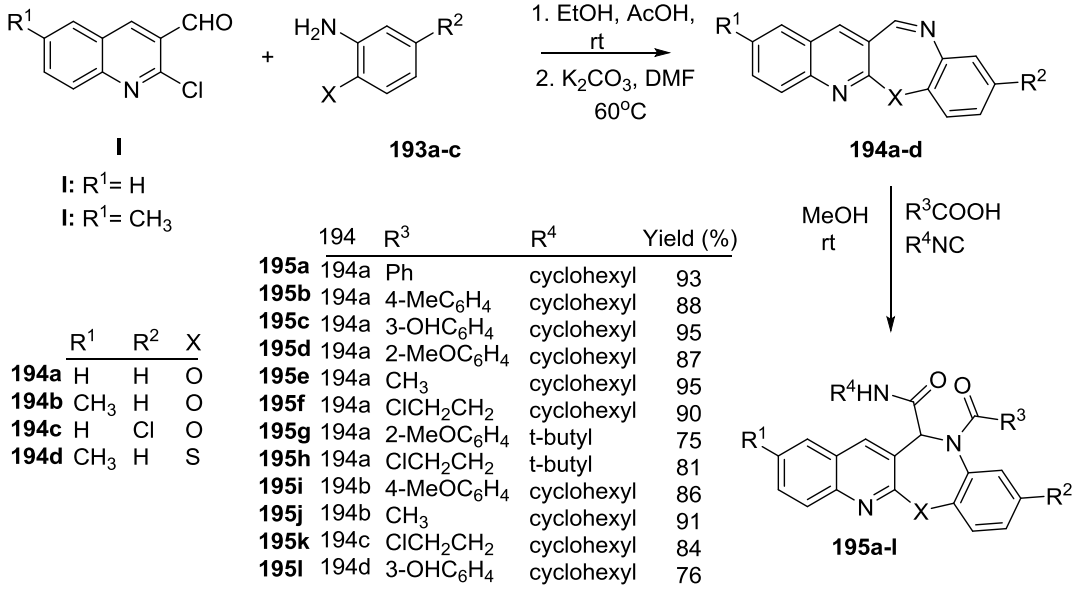
When carbaldehyde **I** was treated with formamide and formic acid, the pyrrolo[3,4-*b*]quinolin-3-one **179** was obtained, the reaction occurs *via Leuckart* reaction[70] by using formamide as a formylating agent. On treating **I** with hydrazine hydrate, the hydrazone **180** was afforded, which then treated with aromatic aldehydes **181** and **183** to give 3-((naphthalen-2-yl/1*H*-indol-3-yl)methylene)hydrazono)methyl)quinoline **182** and **184**, respectively (Scheme 51).[40]

Furthermore, the carbaldehyde group in **I** was transformed to a nitrile group *via* condensation reaction with hydroxylamine hydrochloride and sodium acetate to afford oxime **185**. Dehydration of the aldoxime **185** with thionyl chloride gave the cyanoquinoline **186**. The cyanoquinoline **186** was reacted with lithium aluminium hydride and potassium sodium tartarate in THF afforded the corresponding amine **187**. In addition, cyclization of **186** with hydrazine hydrate afforded **188**. Compound **190** was obtained from the reaction of **188** with benzoylisocyanate **189**. In the same manner pyrazoloquinoline Schiff's base derivatives **191** and **192** were obtained in moderate yield by condensation reaction of **188** with naphthaldehyde **181** or indol-3-aldehyde **183** (Scheme 52).[40]



Scheme 52

3.4.3. Reactions with amines and amides. 2-Chloroquinoline-3-carbaldehyde **I** was reacted with amines **193a-c** to form an imine intermediate, which was subsequently cyclized to afford tetracyclic thio- and oxazepino derivatives **194a-d**.[71-73] While benzo[2,3][1,4]thia- or oxazepino[7,6-*b*]quinolones **195a-i** was afforded by reacting carboxylic acid, isocyanide and **194a-d** in methanol. The reaction mixture was stirred for 48 h at room temperature (Scheme 53).[74]



I

I: R^1= H

I: R^1= CH_3

193a-c

194a-d

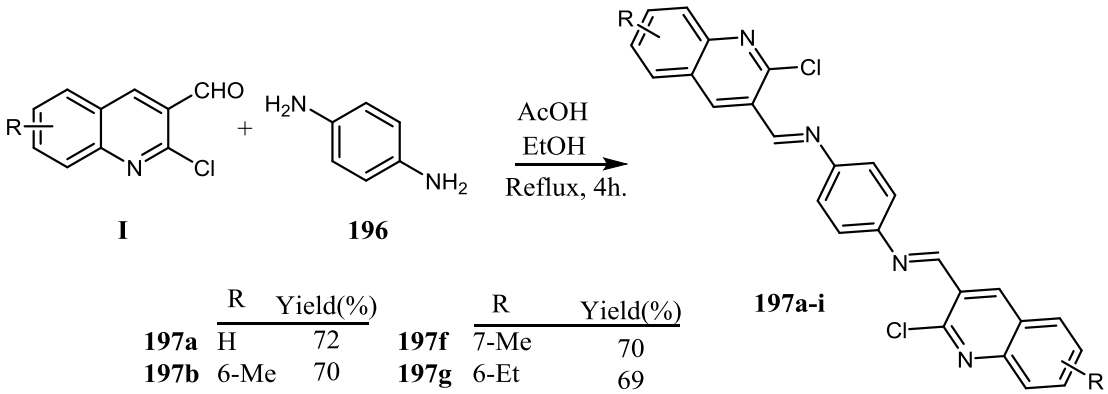
	R^1	R^2	X
194a	H	H	O
194b	CH_3	H	O
194c	H	Cl	O
194d	CH_3	H	S

	194	R^3	R^4	Yield (%)
195a	194a	Ph	cyclohexyl	93
195b	194a	4-MeC_6H_4	cyclohexyl	88
195c	194a	3-OHC_6H_4	cyclohexyl	95
195d	194a	2-$MeOC_6H_4$	cyclohexyl	87
195e	194a	CH_3	cyclohexyl	95
195f	194a	$ClCH_2CH_2$	cyclohexyl	90
195g	194a	2-$MeOC_6H_4$	t-butyl	75
195h	194a	$ClCH_2CH_2$	t-butyl	81
195i	194b	4-$MeOC_6H_4$	cyclohexyl	86
195j	194b	CH_3	cyclohexyl	91
195k	194c	$ClCH_2CH_2$	cyclohexyl	84
195l	194d	3-OHC_6H_4	cyclohexyl	76

195a-l

Scheme 53

Formation of mono and di Schiff's bases derivatives **197a-i** derivatives was reported. The reaction took place between 2-chloroquinoline-3- carbaldehydes **I** and benzene-1,4-diamine **196** in ethanol under reflux. The reaction was catalyzed with acetic acid (Scheme 54).[1]



I **196**

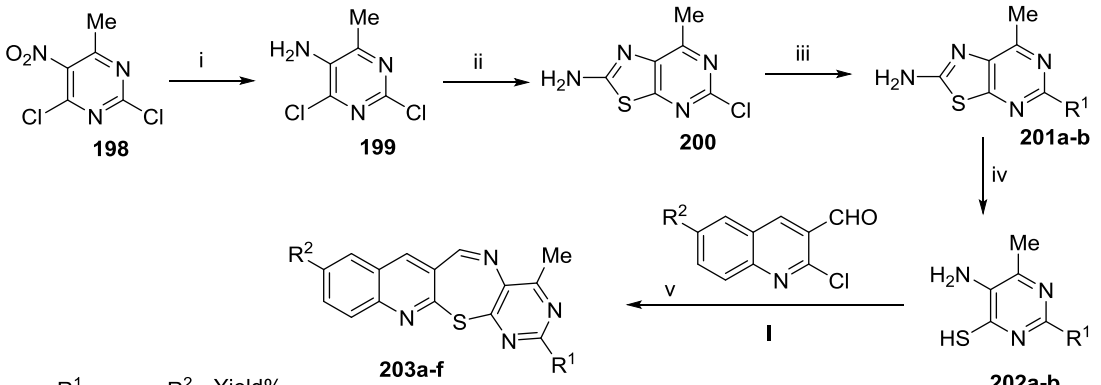
197a-i

	R	Yield(%)		R	Yield(%)
197a	H	72	**197f**	7-Me	70
197b	6-Me	70	**197g**	6-Et	69
197c	6-OMe	69	**197h**	6-Isopropyl	68
197d	6-OEt	68	**197i**	7-Cl	75
197e	6-Cl	74			

Scheme 54

Derivatives of novel pyrimido[4',5':2,3][1,4]thiazepino[7,6-*b*]quinoline ring **203a-f** system have been synthesized through cyclocondensation of 5-amino-6-methylpyrimidine-4-thiols **202a,b** and 2-chloroquinoline-3-carbaldehydes **I** in the presence of K_2CO_3 in DMF (Scheme 55).[75]

Synthesis of a series of 23 novel unsymmetrical bis-heterocycles having either imidazo[2,1-*b*]thiazoles **207a-k** or benzo[*d*]imidazo[2,1-*b*]thiazole **209a-l** frameworks bound with chromone, quinoline or julolidine in good to excellent yields by an acid-free Groebke-Blackburn-Bienaymé reaction (GBBR) under microwave-heating conditions, was reported (Scheme 56).[76]



	R^1	R^2	Yield%
203a	morpholino	H	65%
203b	morpholino	Cl	70%
203c	morpholino	Me	55%

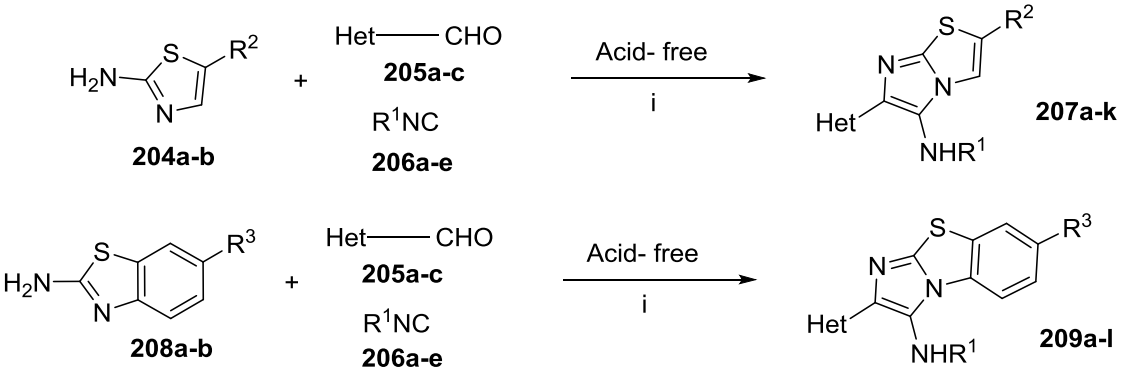
	R^1	R^2	Yield%
203d	piperidino	H	65
203e	piperidino	Cl	72
203f	piperidino	Me	70

I: R^2 = H
I: R^2 = Cl
I: R^2 = Me

201a, 202a R^1=morpholino
201a, 202a R^1=piperidino

Reagents and conditions: (i) Fe powder, HOAc, rt, 2 h; (ii) KSCN, DMF, reflux, 3 h; (iii) morpholine or piperidine, EtOH, reflux, 6 h; (iv) KOH(aq), reflux, 10 h; (v) K_2CO_3, DMF, reflux, 8-12 h.

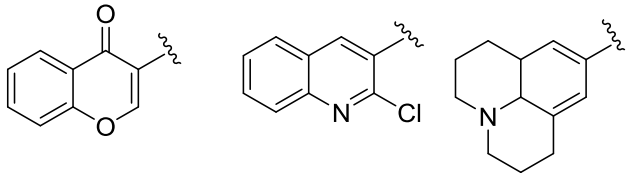
Scheme 55



i = PhMe, MW(150W, 150°c), 10 min

R^1 = *t*-But, c-Hex, Bn, 4-OMeBn, 3,4-diOMePhEt; R^2= H, CN, R^3 = H, F

Het =

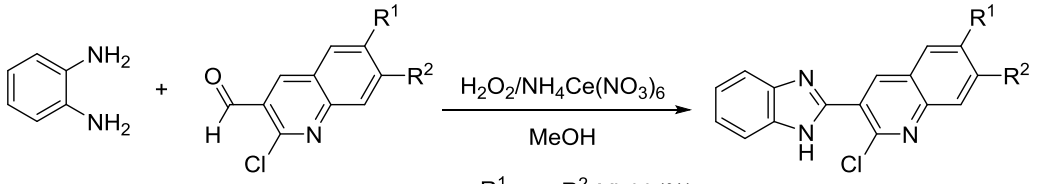


	204R^2	**205**(Het)	**206**R^2	**208**R^3	Yield(%)
207a	H	Chromone	*t*-Bu	-	96
207b	H	Chromone	c-Hex	-	95
207c	H	Chromone	Bn	-	93
207d	H	Chromone	4-OMeBn	-	91
207e	H	Chromone	3,4-diOMePhEt	-	92
207f	H	Quinoline	*t*-Bu	-	96
207g	H	Quinoline	c-Hex	-	95
207h	CN	Quinoline	*t*-Bu	-	92
207i	CN	Quinoline	c-Hex	-	90
207j	H	Julolidine	*t*-Bu	-	84
207k	H	Julolidine	c-Hex	-	82

	204R^2	**205**(Het)	**206**R^2	**208**R^3	Yield(%)
209a	-	Chromone	*t*-Bu	H	97
209b	-	Chromone	c-Hex	H	96
209c	-	Chromone	Bn	H	92
209d	-	Chromone	4-OMeBn	H	95
209e	-	Chromone	3,4-diOMePhEt	H	90
209f	-	Chromone	*t*-Bu	F	97
209g	-	Chromone	c-Hex	F	96
209h	-	Quinoline	*t*-Bu	H	96
209i	-	Quinoline	c-Hex	H	97
209j	-	Quinoline	*t*-Bu	F	97
209k	-	Quinoline	c-Hex	F	96
209l	-	Julolidine	c-Hex	H	72

Scheme 56

The benzene-1,2-diamine **210** was added to the solution of 2-chloro-6,7-substituted quinoline-3-carbaldehydes **I** in methanol. Ceric ammonium nitrate as a catalyst and hydrogen peroxide as an oxidant were then added to this solution. After completion of the reaction, the reaction mixture was cooled at room temperature and poured into crushed ice. The separated solid product was filtered and recrystallized from methanol to afford 59-79% yield of The benzo[*d*]imidazole ligands **211a-g** (Scheme 57).[77]

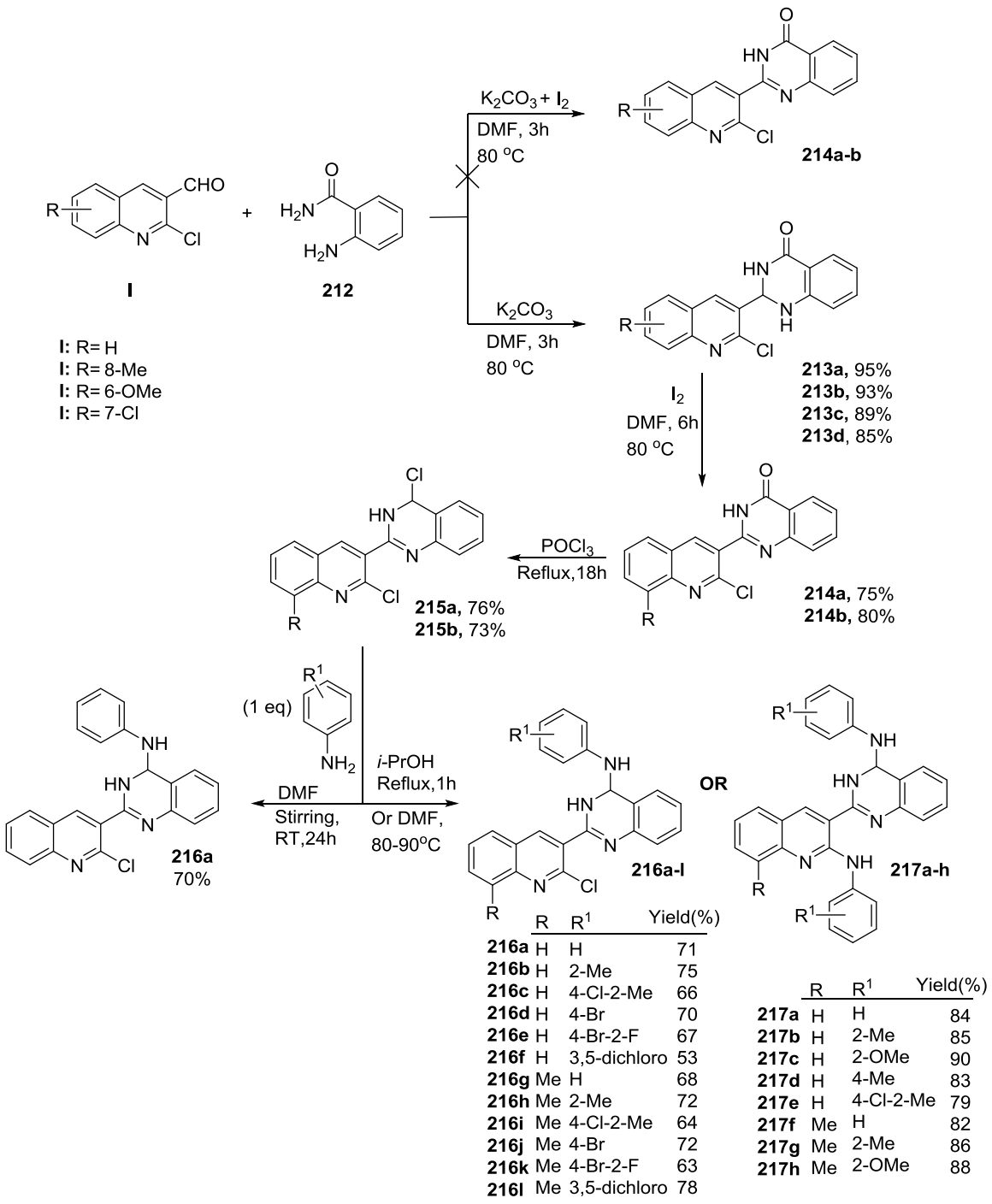


210 **I** **211a-g**

	R^1	R^2	Yield (%)
211a	H	H	68
211b	OCH_3	H	70
211c	CH_3	H	65
211d	Cl	Cl	74
211e	Br	H	60
211f	I	H	59
211g	NO_2	H	79

Scheme 57

An efficient and high yielding protocol is reported for the synthesis of new class of 4-anilinoquinolino-quinazoline hybrids **216a-l**, **217a-h**. The target compounds were prepared first by the reaction of 2-aminobenzamide **2** with 2-chloroquinoline-3-carbaldehydes **I**. After oxidation and chlorination, the key 2-quinolyl-4-chloroquinazolines **215a-b** were converted to the corresponding 2-(2-arylaminoquinolyl)-4-arylaminoquinazolines **216a-l** and *N*-heteroaryl-2-(2-(heteroarylamino)quinolin-3-yl)quinazolin-4-amines **217a-h** (Scheme 58).[78]

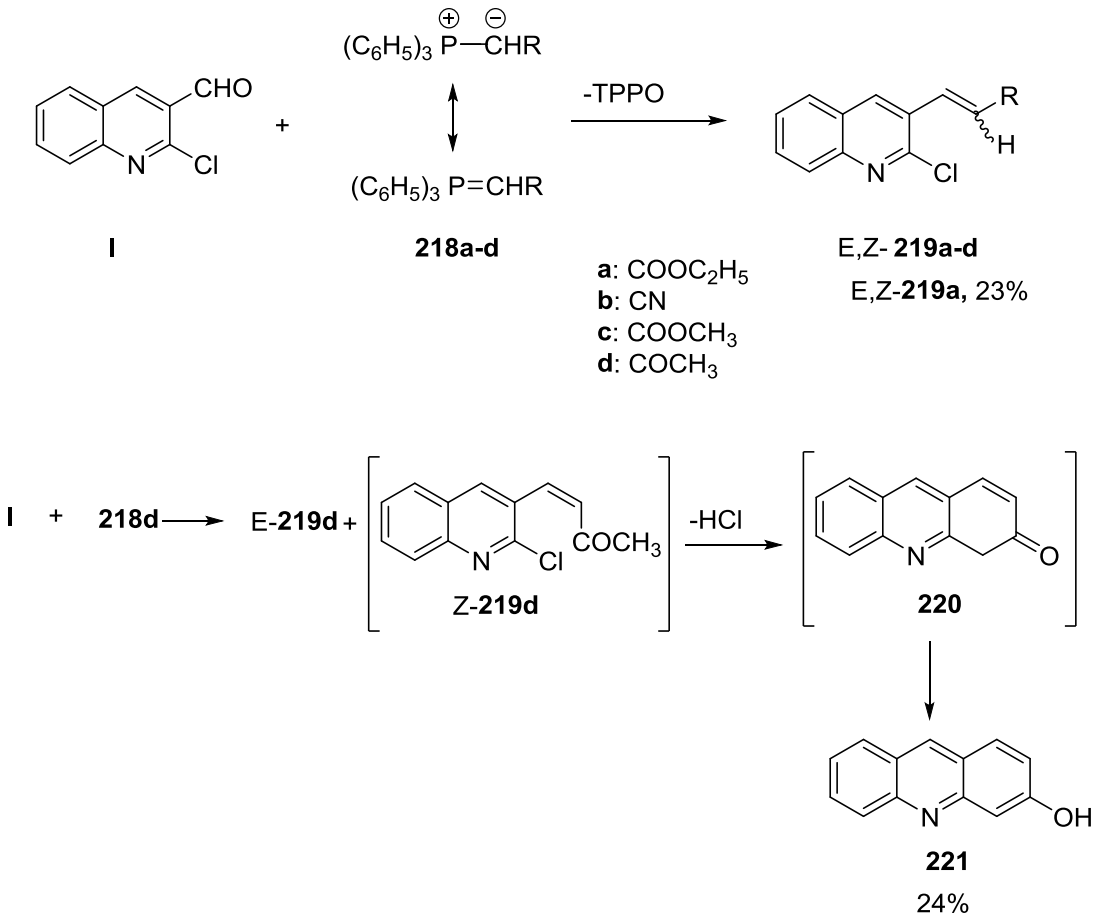


	R	R^1	Yield(%)
216a	H	H	71
216b	H	2-Me	75
216c	H	4-Cl-2-Me	66
216d	H	4-Br	70
216e	H	4-Br-2-F	67
216f	H	3,5-dichloro	53
216g	Me	H	68
216h	Me	2-Me	72
216i	Me	4-Cl-2-Me	64
216j	Me	4-Br	72
216k	Me	4-Br-2-F	63
216l	Me	3,5-dichloro	78

	R	R^1	Yield(%)
217a	H	H	84
217b	H	2-Me	85
217c	H	2-OMe	90
217d	H	4-Me	83
217e	H	4-Cl-2-Me	79
217f	Me	H	82
217g	Me	2-Me	86
217h	Me	2-OMe	88

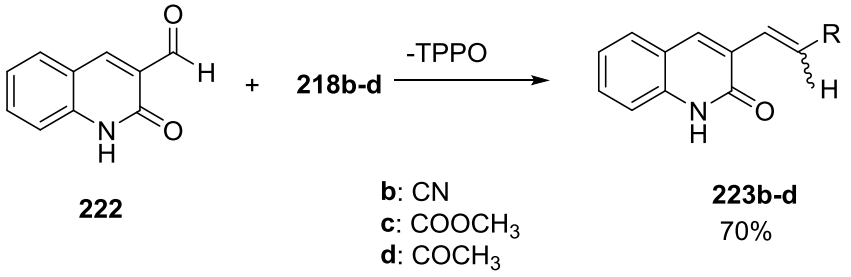
Scheme 58

3.4.4. Miscellaneous reactions. Condensation of 2-chloroquinoline-3-carbaldehyde **I** with some selected stabilized phosphonium ylides (Wittig reagent) **218a-d** yielded a mixture of the corresponding *E* and *Z* olefins in each case along with triphenylphosphine oxide (TPPO), *via* Wittig carbonyl olefination reaction. However, the reaction of **I** with **218d** produced the (*E*) form olefin **219d** together with acridin-3-ol **221** (Scheme 59).[79]



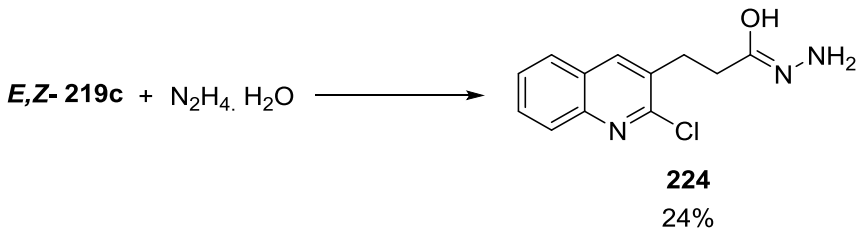
Scheme 59

A mixture of 2-oxoquinoline-3-carbaldehyde **222** and stabilized ylides **218b-d** in absolute ethanol was stirred at room temperature for 2 h. The formed colorless precipitate was filtered and recrystallized from absolute ethanol to give the corresponding Z-**223b-d** isomers. Pure Z-**223b-d** were obtained by chromatography (Scheme 60).[79]



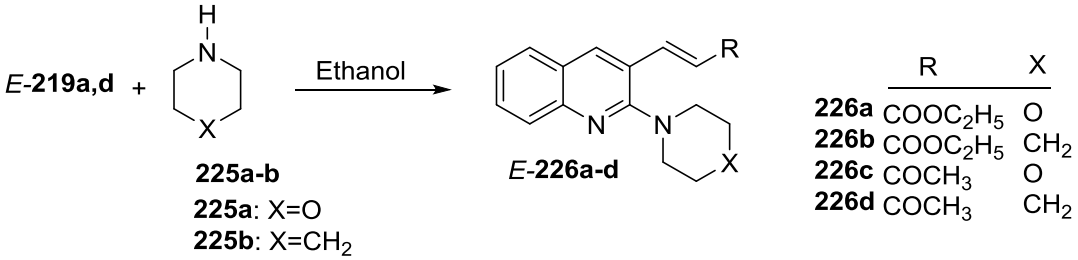
Scheme 60

The behavior of compounds *E,Z*-**219c** toward hydrazine hydrate was also investigated. In which hydrazine hydrate was added to a solution of compound *Z*-**219c** and/or *E*-**219c** in ethanol. The reaction mixture was heated under reflux for about 3h. The solvent was evaporated under reduced pressure and the residue was recrystallized from chloroform/n-hexane to give 3-(2-chloroquinolin-3-yl)propanehydrazonic acid **224** (Scheme 61).[79]



Scheme 61

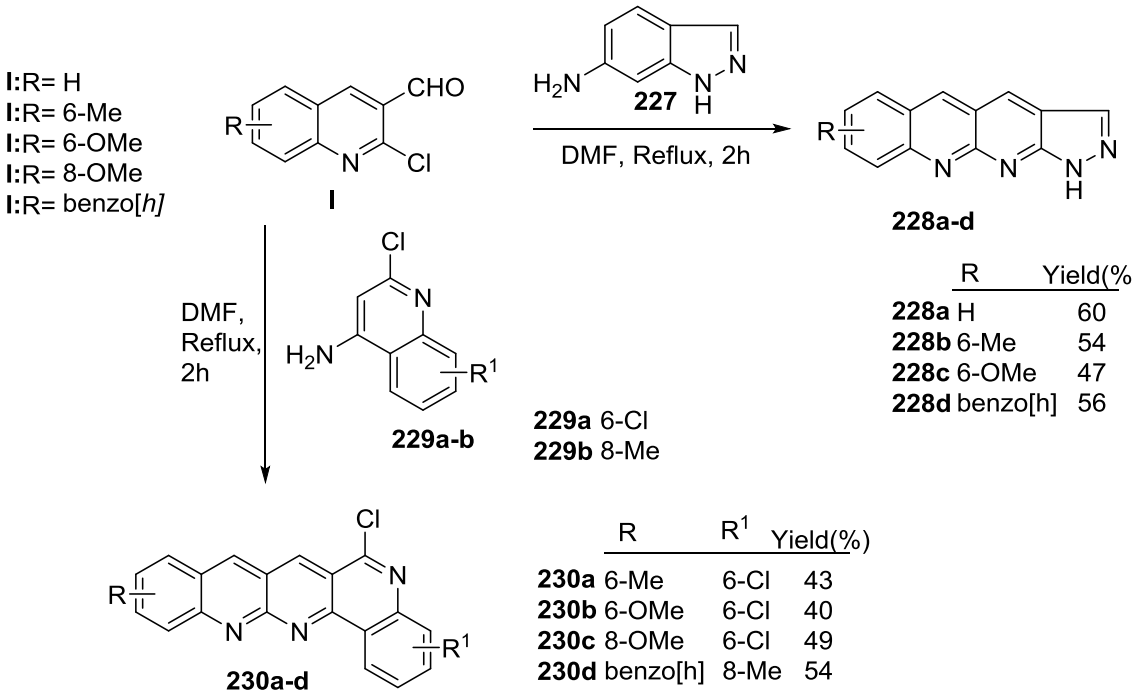
On the other hand, heating under reflux a mixture of *E*-**219a** or *E*-**219d** with the appropriate secondary amine (morpholine **225a** or piperidine **225b**) for 7–10 h, followed by evaporation of the volatile materials and triturating the residue with diethyl ether afforded colorless **226a-d** (Scheme 62).[79]



	R	X
226a	$COOC_2H_5$	O
226b	$COOC_2H_5$	CH_2
226c	$COCH_3$	O
226d	$COCH_3$	CH_2

Scheme 62

Finally, a direct and efficient approach to the synthesis of benzo[*g*][1,8]naphthyridines **228a-d, 230a-d** from simple synthons 2-chloroquinoline-3-carbaldehydes **I**, 1*H*-Indazole-6-amine **227** and 2-chloroquinolne-4-amines **229a-b**, has been developed. The reaction proceed by simple condensation under basic medium conditions without any catalyst furnishing the naphthyridine derivatives **228a-d** and **230a-d**, respectively (Scheme 63).[80]



	R	Yield(%)
228a	H	60
228b	6-Me	54
228c	6-OMe	47
228d	benzo[h]	56

	R	R^1	Yield(%)
230a	6-Me	6-Cl	43
230b	6-OMe	6-Cl	40
230c	8-OMe	6-Cl	49
230d	benzo[h]	8-Me	54

Scheme 63

4. Conclusions

2-Chloroquinoline-3-carbaldehydes were used extensively, as an interesting versatile intermediate, due to the presence of both chloro and aldehyde groups, for synthesis of many chemical compounds possessing diverse biological activities. This survey is an attempt to collect, summarize and organize the different synthetic methods and reactions of 2-chloroquinoline-3-carbaldehydes from 2012 through 2017. Most of 2-chloroquinoline-3-carbaldehydes reactions are multi component reaction (MCR), either in a step-wise manner or in a one pot has been achieved successfully. Hence these protocols provide convenient strategies to annelate different heterocyclic nuclei with widespread bioactive pyrans and pyrimidines thereby extending the categories of heterocyclic systems. The strategies may also provide valuable information for further design and development of more active biological agents through various modifications and derivatizations.

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