Received: 6 November 2023 | Revised: 26 February 2024 | Accepted: 15 March 2024

DOI: 10.1002/jhet.4815

REVIEW

JOURNAL OF HETEROCYCLIC CHEMISTRY WILEY

Synthetic methodology of pyrimido[4,5-*b*]quinoline derivatives

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Abstract

This review discusses the synthetic pathways of an important class of quinolines known as pyrimido[4,5-b]quinoline. Due to their profound range as biologically active compounds, they attracted the attention of medical/organic researchers. The construction of pyrimido[4,5-b]quinolines involved the intermolecular cyclization of diamino chloropyrimidine carbaldehyde and intramolecular cyclization of 2-amino-3-cyanotetra/hexahydroquinoline, 2-aminoquinoline-3-carbonitriles, ester or amide. That class of organic compounds was constructed from the reaction between 2-chloro-3-formylquinoline with amidine, urea, and thiourea. Also, barbituric acid and uracil and their analogous play an important role in synthesizing pyrimidoquinolines via multicomponent reaction strategies (MCR).

1 | INTRODUCTION

The nucleus of pyrimidoquinoline consists of three rings: a benzene ring fused to a pyridine ring, which fused to a pyrimidine ring so that it may be named benzopyridopyrimidine but due to the trivial name of the quinoline ring (benzene fused pyrimidine), the widely used name according to Hantzsch-Widman was pyrimidoquinoline (Figure).

Some quinoline-containing and pyrimidine-containing compounds, or both of them in their structure, are important in pharmaceutical chemistry due to their significant biological activities [1], such as antitumor [2], antihistaminic [3], anti-inflammatory [4], anticancer [5], antimalarial properties [6], and antimicrobial [7]. Moreover, some pyrimidine-containing compounds in their structure have been used as inhibitors of AbI kinase and PTP1B [8] and applied as antimicrobial agents [9]. On the other hand, Some quinoline-containing compounds have shown biological activities such as DNA binding [10] and DNA intercalating carrier [11].

As for other planar nitrogen-rich heterocyclen, pyrimido[4,5-*b*]quinolines could enable various H-bond donors and acceptors. In particular, if carbonyl groups are involved and they resemble nucleic acid bases. As such, the bonding domain is crucial. In pyrimido[4,5-*b*]quinolines, various derivatives with a carbonyl group were prepared, in particular in the 2 and 4 positions (Figure 1).

In the thesis review, MCRs (multicomponent reactions) play the method of choice for synthesizing pyrimidoquinolines because they offer significant advantages over conventional linear-type syntheses for a high degree of atom economy, convergence, ease of execution, and broad application character. The most widely used starting material for synthesizing pyrimidoquinolines considered the main building block, is barbituric acid derivatives. On the other hand, 2-chloroquinoline-3-carbaldehyde, aminouracil, and 2-amino-3-carbonitrile are important in synthesizing pyrimido[4,5-*b*]quinolines. As mentioned in Figure 2, the skeleton of the pyrimidoquinoline contains

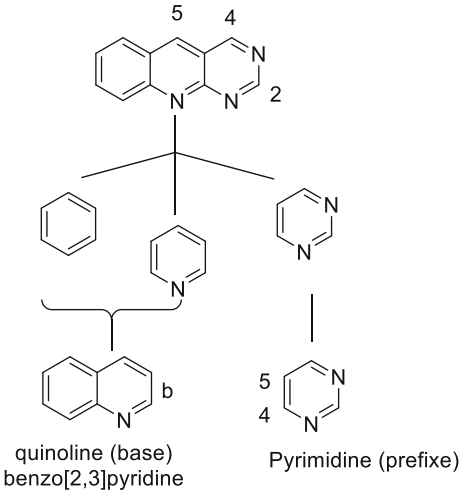


FIGURE 1 The nomenclature of pyrimidoquinoline.

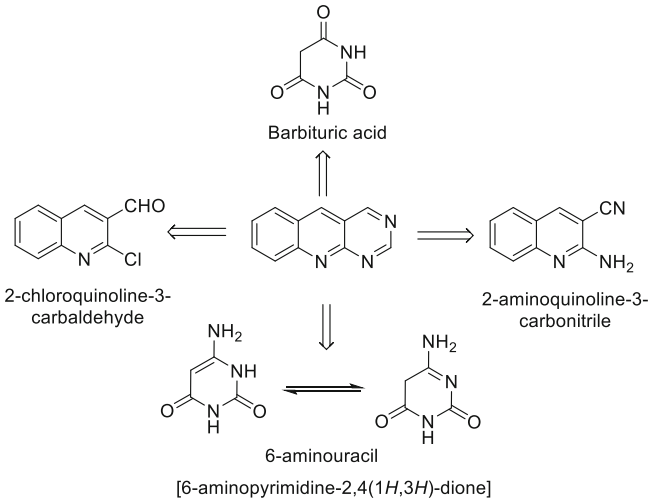


FIGURE 2 The main building cycles for pyrimido[4,5-b] quinolines.

two main units: the quinoline unit and the pyrimidine unit, which, to be fission, requires the formation of N-C and C-C bond formations [12–21].

Accordingly, the synthesis of pyrimido[4,5-*b*]quinolines was accomplished with the utility of various catalysts for the MCRs such as SBA-15/PrN($CH_2PO_3H_2$) [22] [H_2-DABCO]-[ClO_4] [23] nano-[Fe_3O_4@SiO_2/*N*-propyl-1-(thiophen-2-yl)-ethanimine][$ZnCl_2$] [24], nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$]-[H_2PO_4] [25], Fe_3O_4@Cellulose sulfuric acid [26], *N*,*N*-diethyl-*N*-sulfoethanaminium chloride [27], [bmim]Br [28], glycolic acid supported cobalt ferrite [29], nanocrystalline MgO [30], [C_4(DABCO)$_2$] · 2OH [31], and agar-entrapped sulfonated DABCO [32].

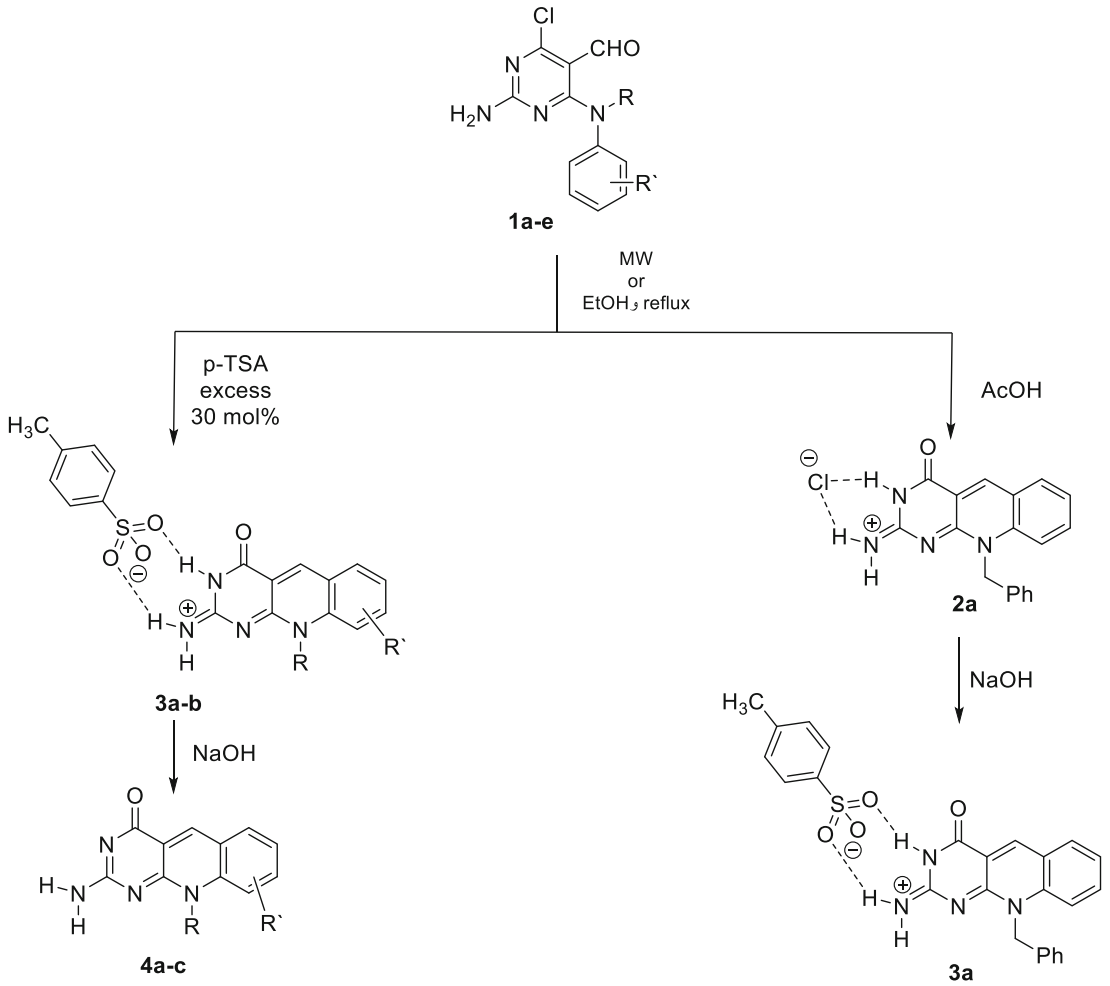
In the next paragraphs, we have listed the main building blocks for pyrimido[4,5-*b*]quinolines.

2 | SYNTHETIC STRATEGIES

2.1 | From 2,4-diamino-6-chloro-pyrimidine-5-carbaldehyde

N^4–Benzyl–N^4–phenyl–2,4–diamino–6–chloropyrimidine–5–carbaldehyde (**1a**) and acetic acid were heated both under MW irradiation and by conventional heating. The reaction product corresponded to the deazaflavin analog 10-benzyl-4-oxo-4,10-dihydro pyrimido[4,5-*b*] quinolin-2(3*H*)-iminium chloride (**2**). Treatment of salt **2a** with aqueous NaOH (20%) was carried out to give the neutral derivative **4a-c** in a good yield (Scheme 1). To avoid substituting the chloro-atom to maintain the possibility of adding complexity and molecular diversity to the molecule, the same reaction was carried out using an excess of 4-toluenesulfonic acid (PTSA). Thus, compound **1** (1.0 mmol) and an excess of PTSA monohydrate (1.3 mmol) were subjected to microwave irradiation or conventional heating in refluxing ethanol. The reaction product was characterized from the spectroscopic data as the 1:1 salt 2-amino-10-benzylpyrimido[4,5-*b*]quinolin-4(10*H*)-one PTSA (**3a**). The same type of salt **3b** was obtained using the 2,4-diamino-6-chloropyrimidine-5-carbaldehyde (**1b**). When the reaction was carried out by conventional heating of aldehydes **1** and acid (PTSA), reactions proceeded similarly, affording products **2a** and **3**. The only difference between those methods was that microwave irradiation makes the reaction time shorter than conventional heating, 10 versus 60 min, respectively (Scheme 1) (Table 1) [33].

A straightforward synthesis of 2-aminopyrimido [4,5-*b*]quinoline derivatives **7a-c** has been attempted through the reaction of N^4-ethyl-N^4-phenyl-2,4-diamino-6-chloro-pyrimidine-5-carbaldehyde **5c** and PTSA monohydrate under MW irradiation or by conventional heating. The same type of salts **6a**,**b** were obtained using the 2,4-diamino-6-chloro-pyrimidine-5-carbaldehydes **5a**,**b**, respectively. The same results were obtained when trifluoroacetic acid (TFA) was used instead of PTSA (Scheme 2). A direct attempt to the deazaflavines **8a-i** proceeded by reacting in acetic acid (CH_3COOH). The intramolecular cyclization of 6-chloropyrimidine-5-carbaldehydes **5a–c** afforded deazaflavin analogs **7a-c**, with the hydrolysis of both Cl and NH_2 groups (Scheme 2). The same procedure was applied to various 6-chloro pyrimidinecarbaldehydes **5d–i,** obtaining the series of compounds **8d–i** [34].



Entry	Compound **1**		Reaction conditions	Yield (%)					
	R	R`		MW (10min)			/ethanol (60 min)		
				2a	**3a-b**	**4a-c**	**2a**	**3a-b**	**4a-c**
A	$CH_2C_6H_5$	H	AcOH	80	-	-	85	-	-
			PTSA (1.3 mmol)	-	70	-	-	72	-
			(i) PTSA (1.3 mmol) (ii) NaOH	-	-	70	-	-	68
B	CH_3	*p*-CH_3	PTSA (1.3 mmol)	-	70	-	-	70	-
			PTSA (1.3 mmol) (ii) NaOH	-	-	70	-	-	68
C	CH_3	*o*-CH_3		-	-	60	-	-	62

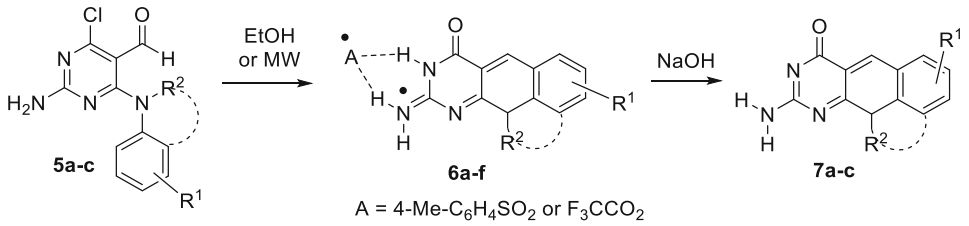
SCHEME 1 Synthesis of 2-aminopyrimido[4,5-*b*]quinoline-4-one **4a-c** from 2,4–diamino–6–chloropyrimidine–5–carbaldehyde derivatives **1**.

TABLE 1 Optimized conditions of the reaction between 4-chlorobenzaldehyde, 6-amino-1,3-dimethyl uracil **97b** (1 mmol), and dimedone **91a,b** to synthesize pyrimidoquinoline derivatives **99a-s**.

Entry	Solvent	Time (h)	Yield (%)
1	Ethanol	45 min	97
2	Ethyl acetate	4	40
3	n-Hexane	6	35
4	Chloroform	5	40
5	Acetonitrile	4	55

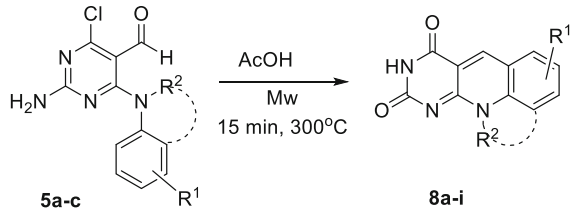
2.2 | From 2-amino-3-cyano-tetra/hexahydroquinoline

Treatment of cyclohexanone (**9**) with 2-benzylidenemalononitrile **10** in the presence of ammonium acetate (CH_3COONH_4) afforded 2-amino-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**11**). Treatment of compound (**11**) with DMF-DMA in dioxane afforded compound **12**. When compound **12** was refluxed with hydrazine hydrate in absolute ethanol, the corresponding 3–amino–4(3*H*)-imino–5-phenyl–6,7,8,9–tetrahydropyri

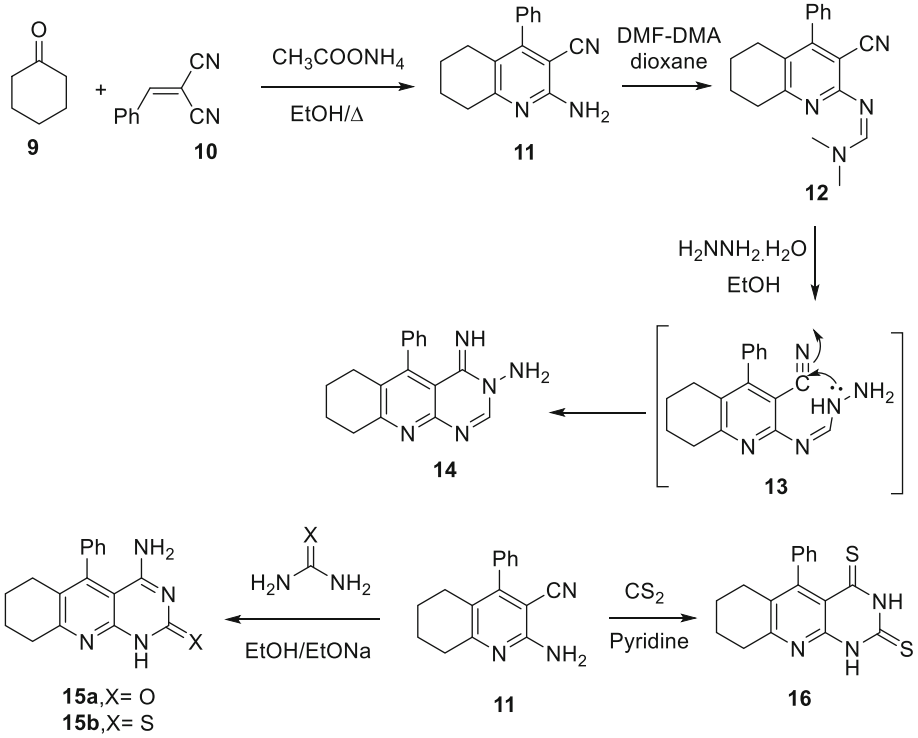


SCHEME 2 Synthesis of pyrimido[4,5-*b*]quinolines **7a-c** and **8a-I** from 2,4–diamino–6–chloropyrimidine–5–carbaldehyde derivatives **5a-i**.

Entry	Compound **7**		Yield (%)
	R^1	R^2	
a		2-$CH_2CH_2CH_2$-	80
b		2-CH_2CH_2-	50
c	H	CH_2CH_3	60

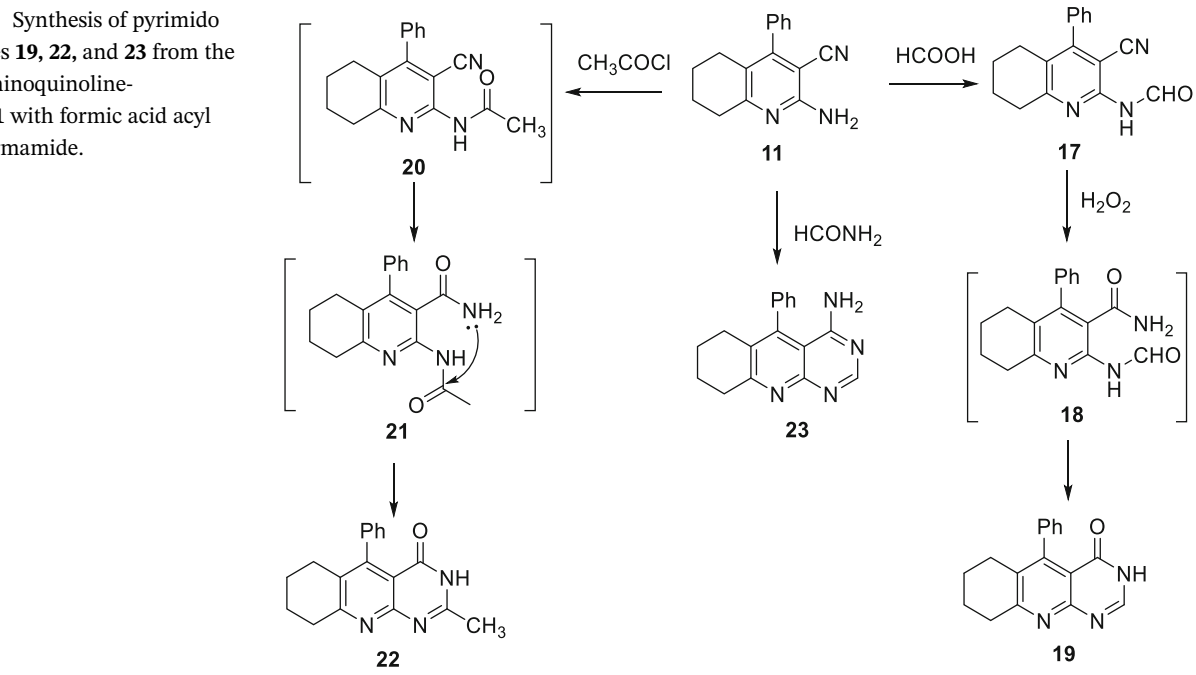


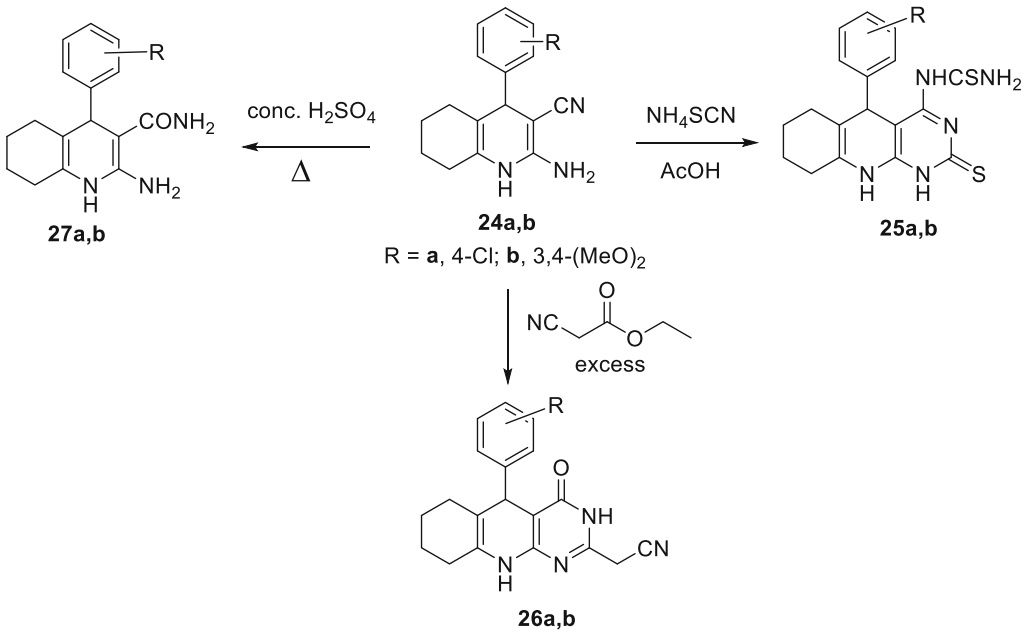
Entry	Compound **8**		Yield (%)
	R^1	R^2	
a	H	2-$CH_2CH_2CH_2$-	70
b	H	2-CH_2CH_2-	70
c	H	CH_2CH_3	60
d	H	CH_3	70
e	H	$CH_2C_6H_5$	80
f	7-CH_3	CH_3	70
g	9-CH_3	CH_3	70
h	7-OCH_3	CH_3	60
i	9-OCH_3	CH_3	70

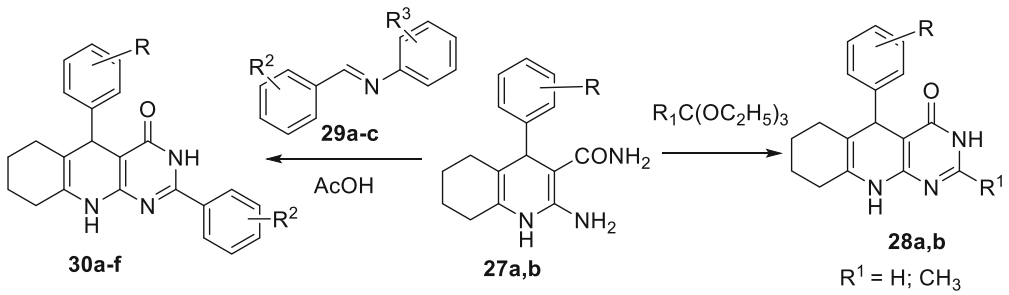


SCHEME 3 Synthesis of tetrahydropyrimidoquinolone analogues **14–16** from 2-amino-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**11**).

SCHEME 4 Synthesis of pyrimido [4,5-*b*]quinolines **19, 22,** and **23** from the reaction of 2-aminoquinoline-3-carbonitrile **11** with formic acid acyl chloride and formamide.

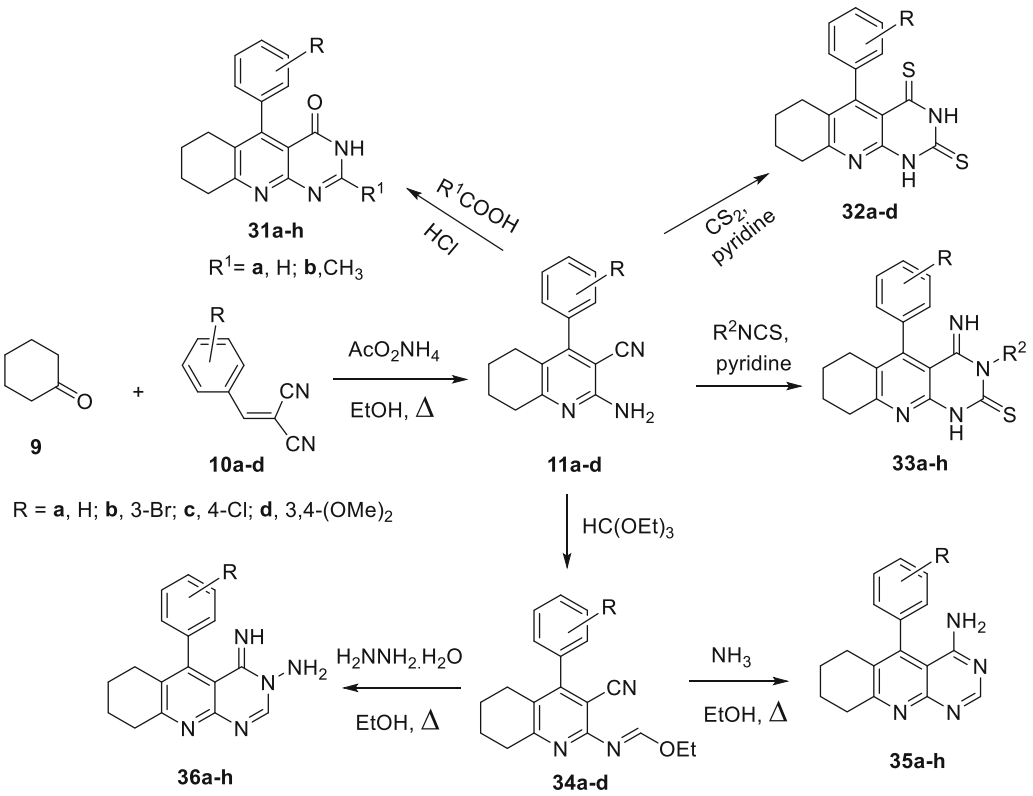




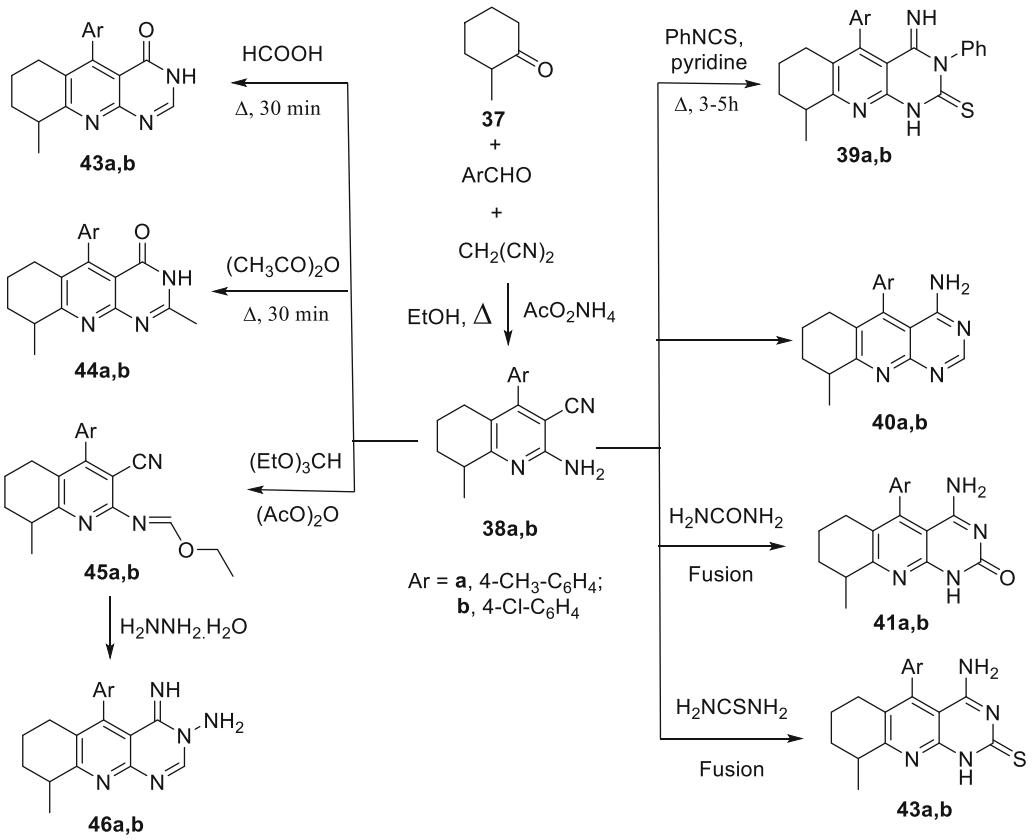


30a-f: **a**, R= 4-Cl; R^2 = 4-NO_2-C_6H_4; **b**, R= 4-Cl; R^2 = 4-CH_3-C_6H_4;
c, R= 4-Cl; R^2 = 4-OMe-C_6H_4; **d**, R= 3,4-$(OMe)_2$; R^2 = 4-NO_2-C_6H_4;
e, R= 3,4-$(OMe)_2$; R^2 = 4-CH_3-C_6H_4; **f**, R= 3,4-$(OMe)_2$; R^2 = 4-OMe-C_6H_4

SCHEME 5 Synthesis of pyrimido[4,5-b]quinolines from 2-aminoquinoline-3-carbonitriles **24a,b** and quinoline-3-carboxamides **27a,b**.

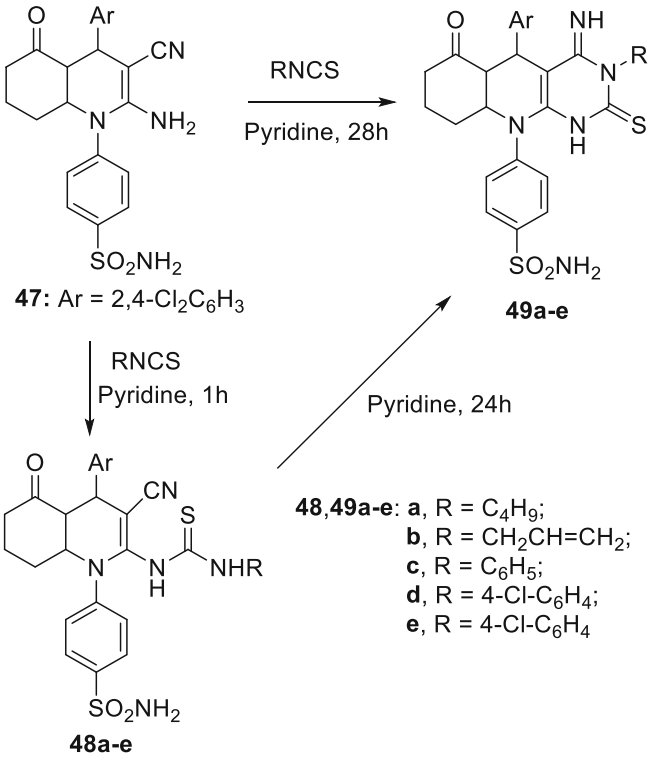


SCHEME 6 Synthesis of series of different pyrimido[4,5-b]quinolines from 2-aminoquinoline-3-carbonitriles **11a–d** and ethyl *N*-[3-cyano-4-arylquinolin-2-yl]formimidates **34a–d**.



SCHEME 7 Synthesis of pyrimido[4,5-b]quinolines from 2-amino-3-cyano-8-methyl-4-substituted-5,6,7,8-tetrahydroquinolines **38**.

mido[4,5-*b*]quinoline (**14**) was formed from the intermediate **13** (Scheme 3). Compound **11** was reacted with thiourea or urea in an ethanol/sodium ethoxide mixture to afford the 4–amino–10–phenyl–6,7,8,9–tetrahydropyrimido[4,5-*b*]quinoline–2(1*H*)–thione/one derivative **15a** and **15b** (Scheme 3). On the other hand, compound **11** was reacted with carbon disulfide (CS_2) in pyridine

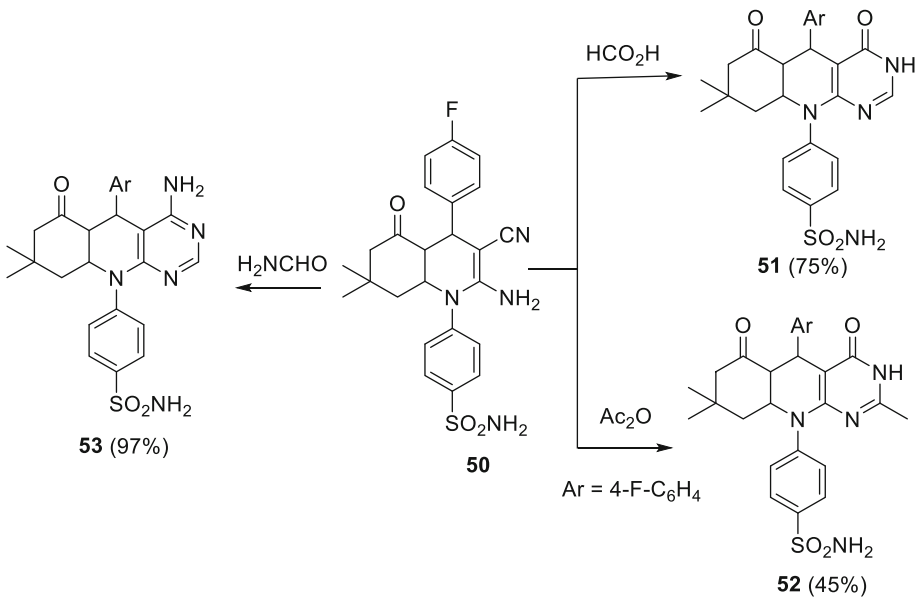


SCHEME 8 Synthesis of pyrimido[4,5-*b*]quinoline derivatives **49a-e**.

to give 5-phenyl-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dithione (**16**) (Scheme 3) [35].

Also, compound **11** was subjected to react with formic acid to yield *N*-(3-cyano-4-phenyl-5,6,7,8-tetrahydroquinolin-2-yl)formamide (**17**), which on treatment with alkaline hydrogen peroxide gave the corresponding 5-phenyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4(3H)-one (**19**) via the intermediate **18**. The reaction proceeds by initial hydration of the nitrile group to give a carboxamide, which then undergoes cyclization in the alkaline medium. Meanwhile, acylation of **11** with acid chloride gave 2–methyl–5–phenyl–6,7,8,9-tetrahydro pyrimido[4,5-*b*]quinolin–4–(3*H*)one (**22**) through the intermediates **20** and **21**. The reaction of compound **11** with formamide gave the corresponding 5-phenyl-6,7,8,9-tetrahydropyrimido[4,5-b] quinolin-4-amine (**23**) (Scheme 4) [35].

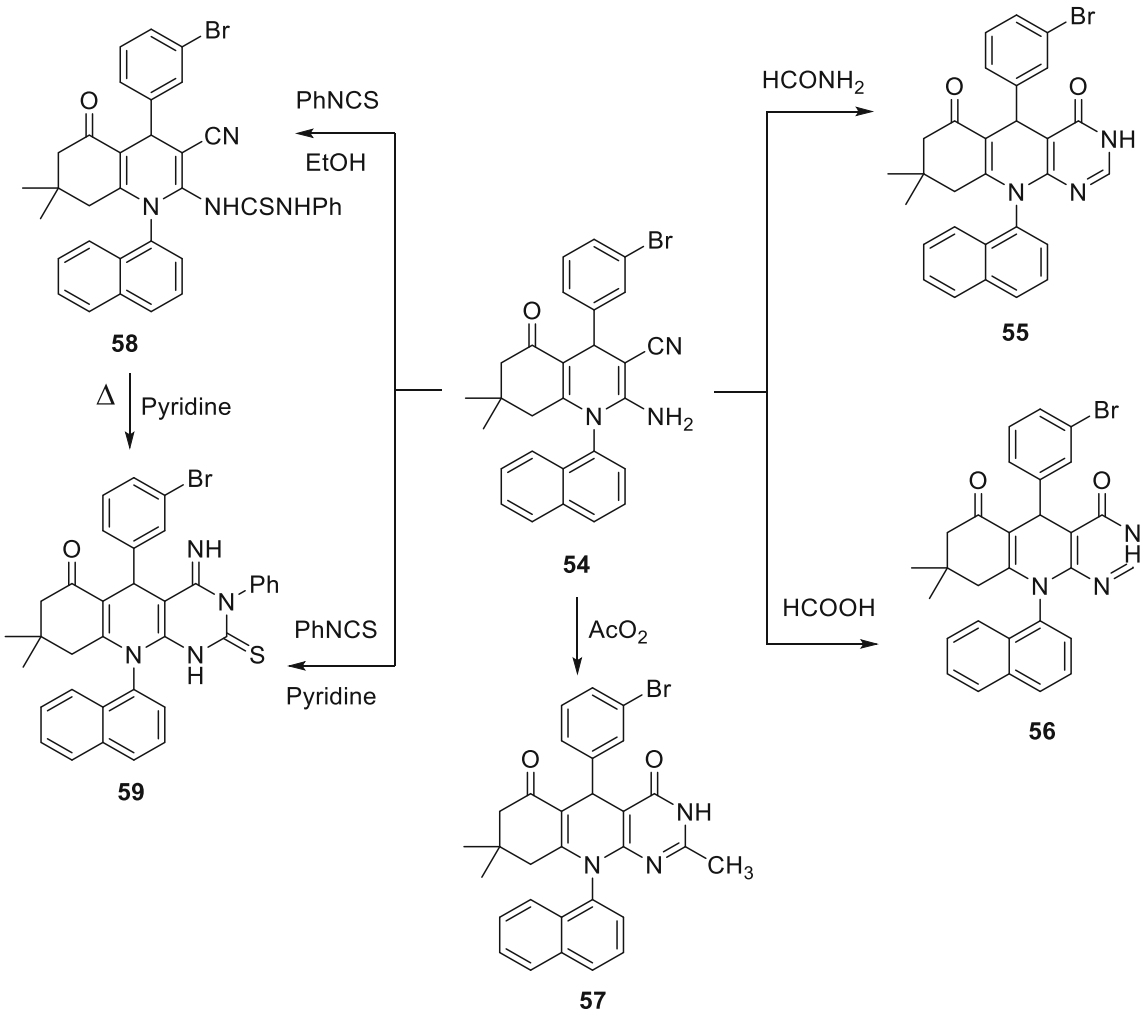
El Gohary has reported a general approach to synthesize pyrimido[4,5-*b*]quinoline analogous from 2-amino-4-(substituted phenyl)quinoline-3-carbonitriles **24a,b**, as the precursor. The ortho aminonitriles **24a,b** were further utilized for another cyclo-condensation reaction using ammonium thiocyanate in refluxing glacial acetic acid to afford the thiourea derivatives of pyrimidoquinolines **25a,b**. Heating compounds **24a,b** with excess ethyl cyanoacetate yielded the 2-cyanomethylpyrimido[4,5-*b*]quinoline derivatives **26a,b**. Hydrolysis of compounds **24a,b** using 70% sulfuric acid at 60°C afforded 2-amino-4-(substituted phenyl)quinoline-3-carboxamides **27a,b** in 70 and 55% yield, respectively (Scheme 5). The reaction of quinoline-3-carboxamides **27a,b** with triethyl ortho-esters in refluxing xylene yielded the pyrimido[4,5-*b*]quinolin-5-one derivatives **28a,b**. The benzylideneanilines **29a-c** were reacted with **27a,b** to provide **30a–f** in one step (Scheme 5) [36].



SCHEME 9 Synthesis of pyrimido [4,5-*b*]quinoline derivatives **51–53**.

Reacting compounds **11a-d** with aliphatic formic and acetic acids in the presence of a catalytic amount of concentrated hydrochloric acid yielded 2-(unsubstituted or methyl)-5-aryl pyrimido[4,5-*b*]quinolin-4-ones **31a-h**. On the other hand, compounds **11a-d** underwent a cyclocondensation reaction with carbon disulfide in pyridine to give 5-arylpyrimido[4,5-*b*]quinoline-2,4-dithiones **32a-d**. Upon heating, compounds **11a-d** with *n*-butyl or phenyl isothiocyanate in pyridine, furnished 4-imino-3-(n-butyl or phenyl)-5-aryl pyrimido[4,5-*b*]quinoline-2(1H)-thiones **33a-h**, while condensing compounds **11a-d** with triethyl orthoformate gave the corresponding ethyl *N*-[3-cyano-4-arylquinolin-2-yl]formimidates **34a-d**. The reaction of compound **34a-d** with 35% ammonia solution in ethanol yielded the corresponding pyrimidoquinoline derivatives **35a-d**. The treatment of compounds **34a-d** with hydrazine hydrate ($NH_2NH_2.H_2O$) gave 3-amino-4-imino-5-arylpyrimido[4,5-*b*]quinolines **36a–d** (Schemes 6 and 7**)** [37].

The precursor 2-amino-3-cyano-8-methyl-4-substituted-5,6,7,8-tetrahydro-quinolines **38** was synthesized from the multicomponent one-pot reaction of 2-methylcyclohexanone (**37**), aromatic aldehyde, malononitrile and an excess of CH_3COONH_4 in boiling ethanol. Reacting compound **38** with phenyl isothiocyanate gave corresponding substituted tricyclic thiones **39**. Cyclization of compound **38** with formamide resulted in the formation of the targeted 4-amino-9-methyl-5-substituted-pyrimido[4,5-*b*]quinolines **40**. Furthermore, fusion of the tetrahydroquinoline derivatives **38a,b** with urea or thiourea yielded via one-step synthesis of the tricyclic compounds **41** and **42**, respectively. Moreover, when compound **38** was reacted with either formic acid or acetic anhydride, the targeted tetrahydropyrimido[4,5-*b*]quinolin-4-ones **43** and their 2-methyl analogs **44**, respectively, were obtained. Finally, reacting **38** with triethyl orthoformate gave the 2-ethoxymethylidineamino derivatives **45**. Compound

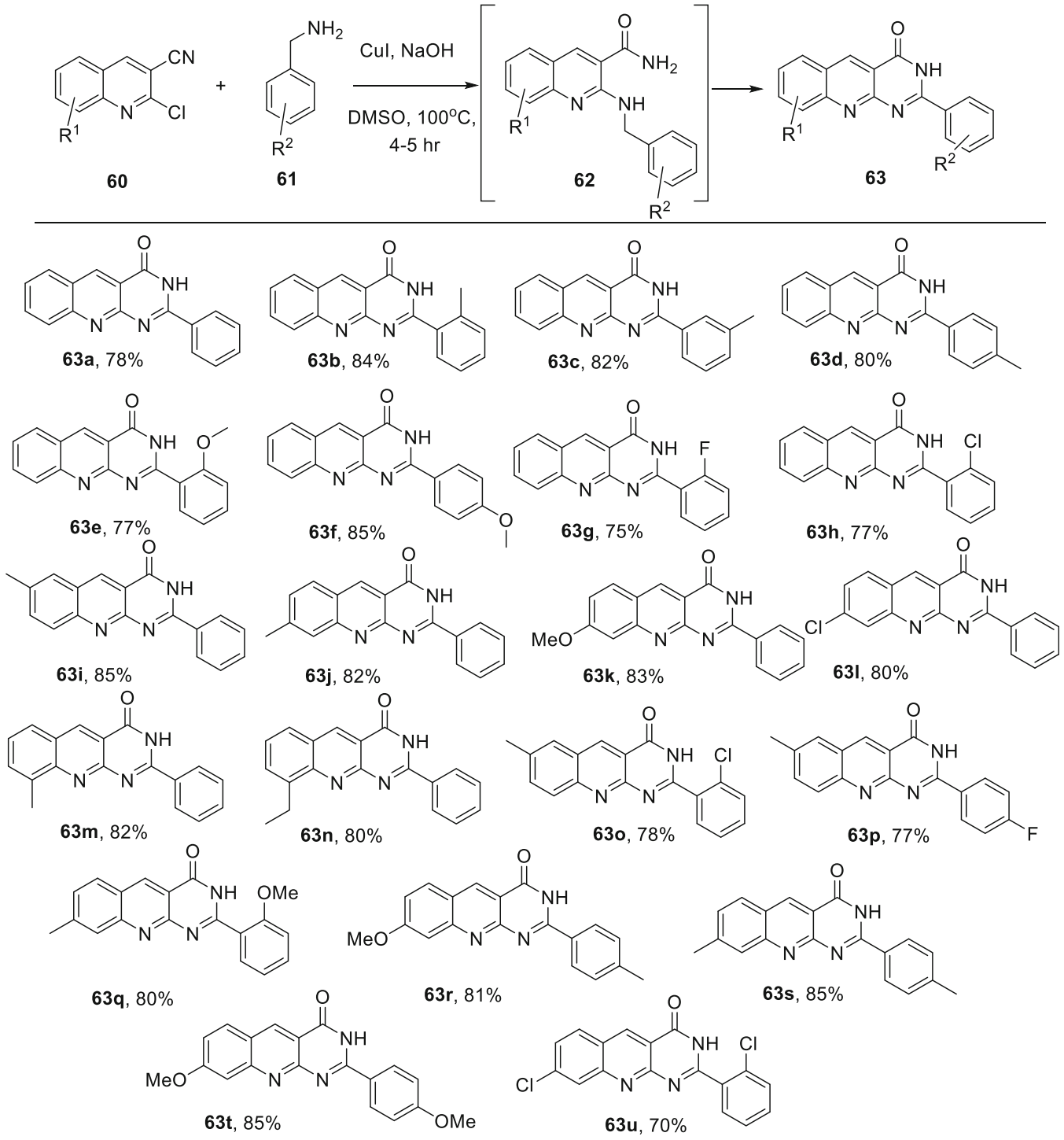


SCHEME 10 Reaction of 2-amino-4-(3-bromophenyl)-7,7-dimethyl-1-(naphthalen-1-yl)-5-oxo-quinoline-3-carbonitrile **54** with formamide, formic acid, acetic anhydride and phenylisothiocyanate.

45, in its turn, was allowed to react with hydrazine hydrate to produce the tricyclic 3-amino-4-imino-9-methyl-5-substituted-pyrimido[4,5-*b*]quinolines **46** (Scheme 7) [38].

The reaction of 4-(2-amino-3-cyano-4-(2,-4-dichlorophenyl)-5-oxo-4a,5,6,7,8,8a-hexahydroquinolin-1(4H)-yl)benzenesulfonamide **47** with isothiocyanate was studied. Thus, the nucleophilic reaction of compound **47** on the highly positive carbon of the isothiocyanate (RNCS) in dry pyridine for 1 h yielded the corresponding thioureido derivatives **48a-e** (Scheme 8), while 24 h reaction time furnished the cyclic system pyrimido[4,5-*b*] quinoline derivatives **49a-e** (Scheme 8) [7].

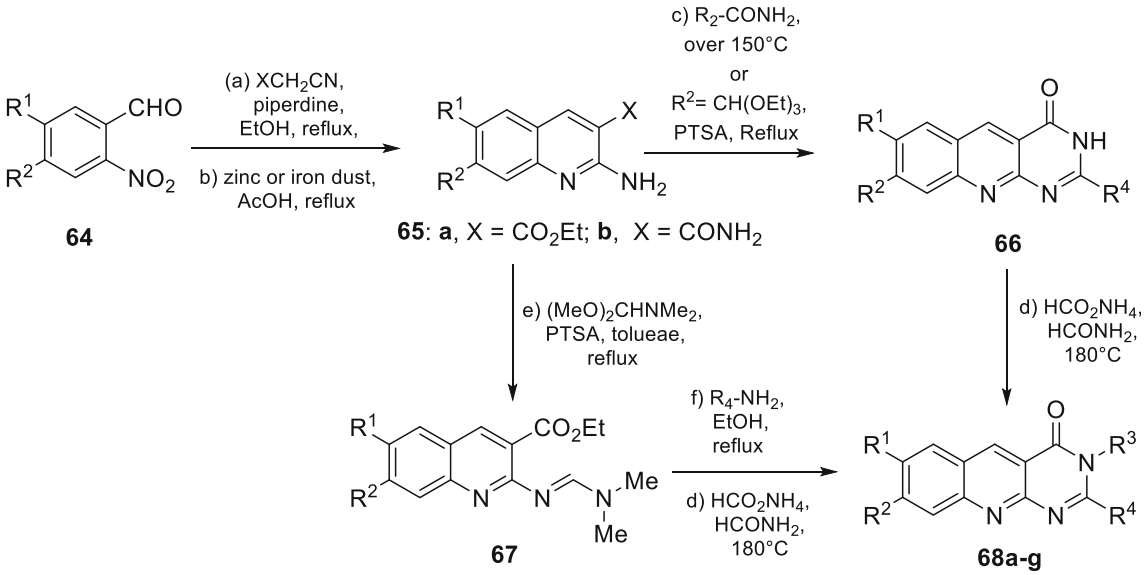
Pyrimido[4,5-*b*]quinoline derivative **51** was obtained upon refluxing 4-(2-amino-3-cyano-4-aryl-7,7-dimethyl-5-oxo-hexahydroquinolin-1(4H)-yl)benzene-sulfonamide



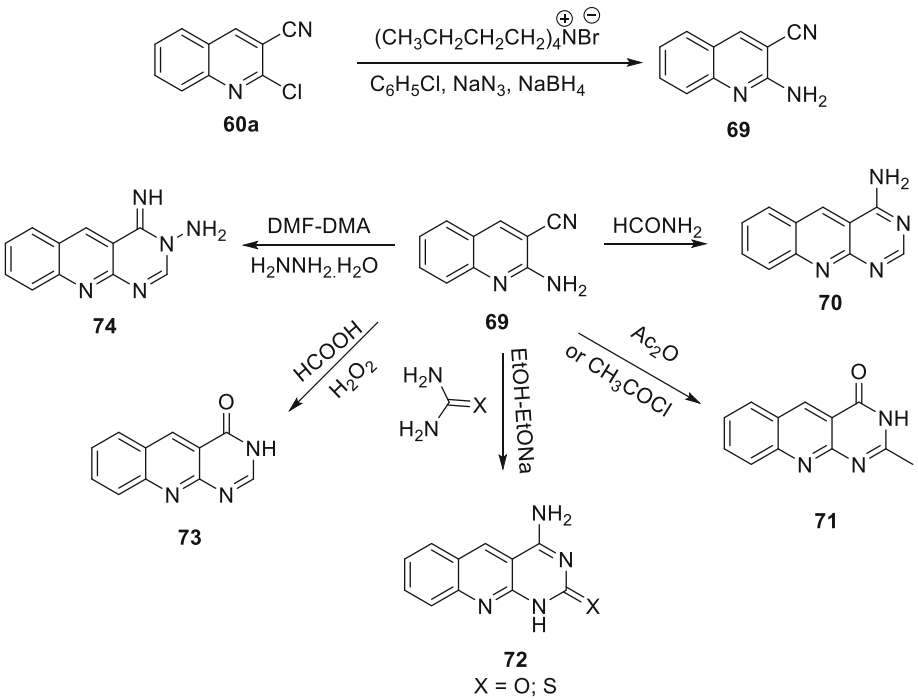
SCHEME 11 Reaction of 2-chloroquinoline-3-carbonitriles **60** with benzylamines **61** pyrimido[4,5-*b*]quinoline-4-ones **63**.

50 with formic acid. Also, compound **50** was refluxed in acetic anhydride, yielding the fused pyrimido[4,5-*b*]quinoline system **52**, while the pyrimido[4,5-*b*]quinoline derivative **53** was obtained by reacting compound **50** with formamide (Scheme 9) [39, 40].

The pyrimidoquinoline derivative **55** was synthesized from the reaction of 2-amino-4-(3-bromophenylquinoline)-3-carbonitrile **54** with formamide. Heating compound **54** with formic acid caused cyclization, giving pyrimidoquinoline derivative **56**. When compound **54**



SCHEME 12 Synthesis of substituted pyrimido[4,5-*b*]quinolin-4(1*H*)-one **68a-g** from *o*-nitrobenzaldehyde (**64**).

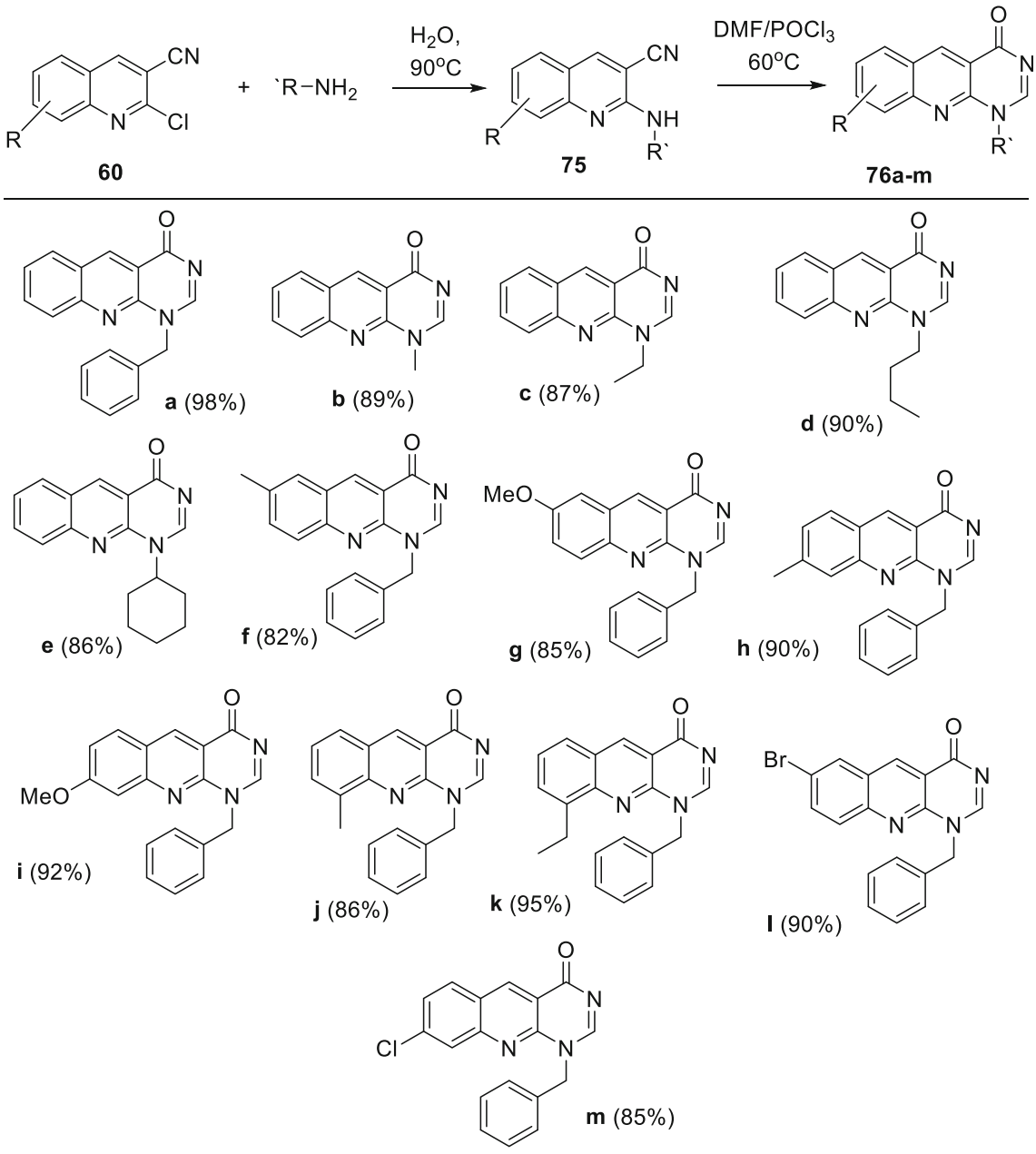


SCHEME 13 Synthesis of pyrimido[4,5-*b*]quinoline derivatives **71–74** from 2-chloro/aminoquinoline-3-carbonitrile.

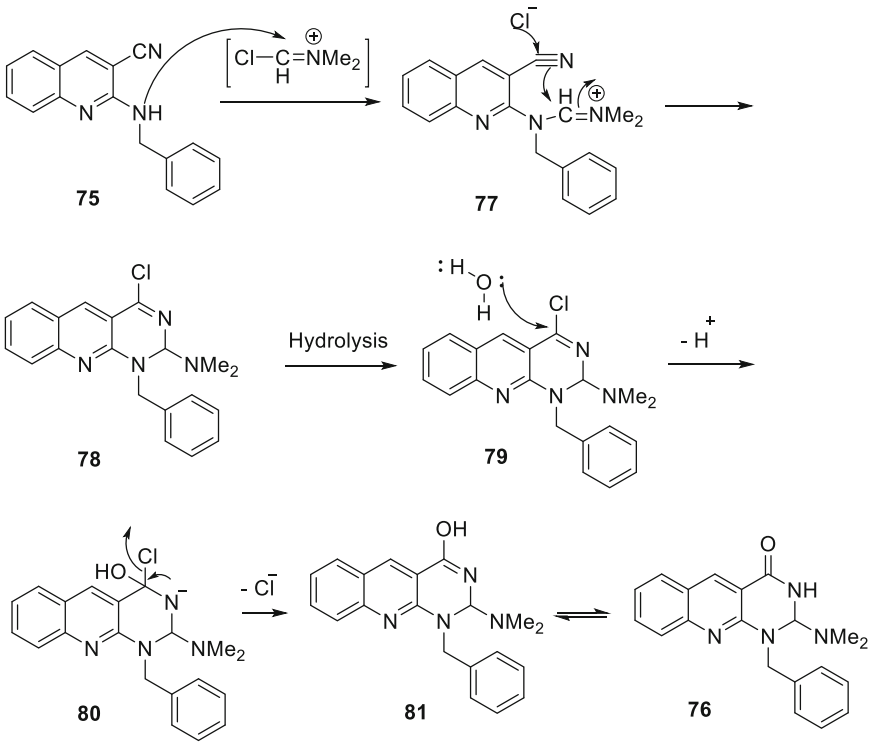
reacted with acetic anhydride, the fused system pyrimidoquinoline **57** was isolated. The behavior of **54** towards phenyl isothiocyanate under different conditions was also studied. Thus, the reaction of **54** with phenyl isothiocyanate in boiling ethanol afforded a product ($C_{35}H_{29}N_4OSBr$) for which two structures, **58** and **57**, seemed possible. Compound **54** also reacted with phenyl isothiocyanate in pyridine to give a pyrimidoquinoline derivative **59**. Compound **59** was also obtained by heating **58** in pyridine (Scheme 10) [41].

Singh et al. reported synthesizing pyrimidoquinolines **63** using CuI in a strong basic medium upon reacting 2-chloroquinoline-3-carbonitriles **60** with benzylamines **61**. The reaction proceeds sequentially via Ullmann-coupling and conversion of nitrile to amide intermediate **62**, followed by nucleophilic addition of amide nitrogen onto iminium carbon and air oxidation (Scheme 11) [42].

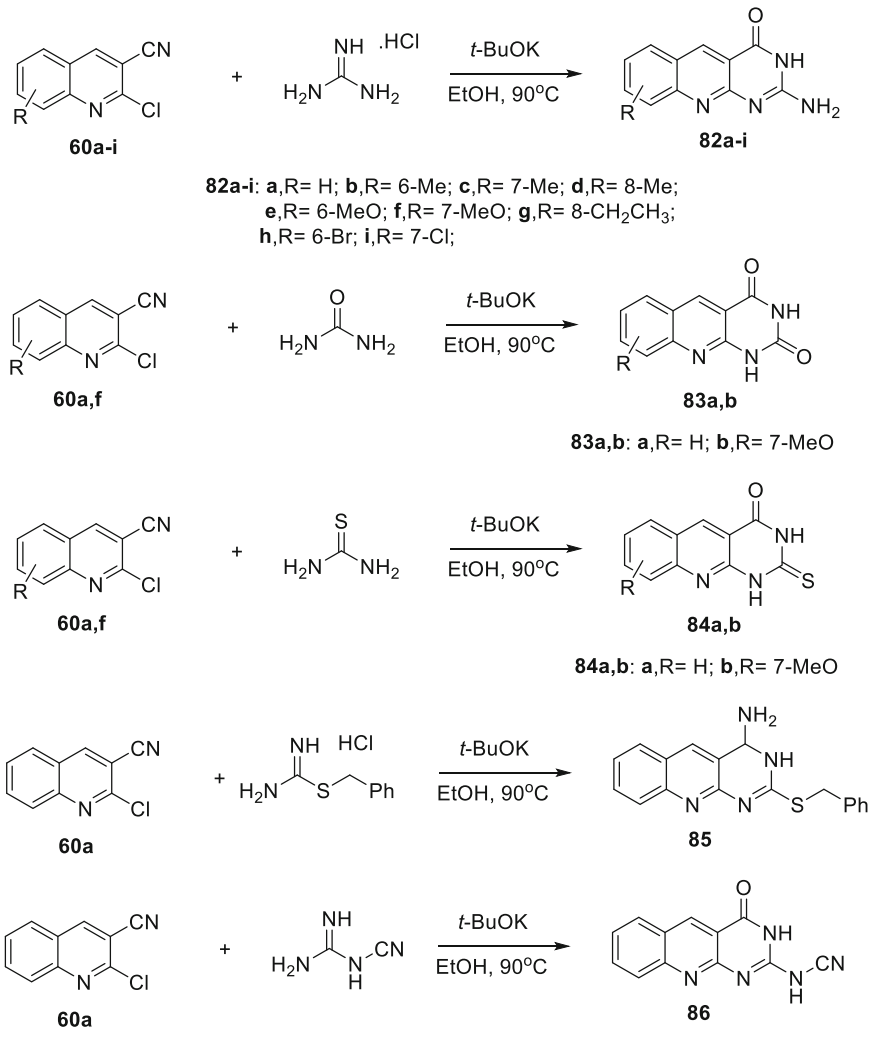
The synthetic routes utilized to prepare 5,10-dihydro-pyrimido[4,5-*b*]quinolin-4(1*H*)-one (**70a**) backbone, as well as C-2 and N-3, substituted variants **68b-g** were as depicted in Scheme 12. Condensation of an *o*-nitrobenzaldehyde (**64**) with ethyl cyanoacetate or cyanoacetamide, followed by reductive cyclization, afforded the corresponding 2-aminoquinoline intermediate **65**.



SCHEME 14 Protocol for synthesizing pyrimido[4,5-*b*]quinoline-4-ones **76a-m** from 2-chloroquinoline-3-carbonitriles **60**.



SCHEME 15 Mechanism for the formation of 1-benzyl-pyrimido[4,5-*b*] quinoline-4-ones **76a-m**.



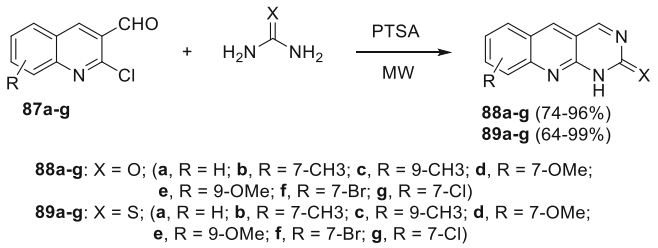
SCHEME 16 Synthesis of 2-amino-3*H*-pyrimido[4,5-*b*]quinolin-4-one **82–86** from the reaction between 2-chloroquinoline-3-carbonitriles **60** with urea, thiourea, amidine and cyanoguanidine.

The reaction of ester **65a** with carboxamides at high temperatures or treatment of carboxamides **65b** with an ortho ester in the presence of an acid catalyst provided the fully aromatized tricyclic core **66**. Reduction to the dihydro-targets **6** was efficiently accomplished by heating **66** with an excess of ammonium formate in formamide. Preparation of the corresponding N-3 functionalized analogs is initiated by condensation of **65a** with dimethylformamide (DMF) dimethyl acetal. Cyclization of **67** with amine afforded N-3 substituted analogs of **68a-g** (Scheme 12) [43].

The synthetic method adopted to obtain pyrimido[4,5-*b*]quinoline derivatives from 2-aminoquinoline-3-carbonitrile (**69**) was as shown in Scheme 14. Compound **69** was reacted with formamide to afford pyrimido[4,5-*b*]quinolin-4-amine **70**. When compound **69** was refluxed with acetic anhydride, 2-methylpyrimido[4,5-*b*]quinolin-4(3*H*)-one **71**, the same compound was obtained when 2-aminoquinoline-3-carbonitrile (**69**) was reacted with acetyl chloride. Moreover, compound **69** reacted with thiourea or urea to afford pyrimido[4,5-*b*]quinoline–2(1*H*)–one/thione derivatives **72a**,**b** (Scheme 13). Another pyrimido[4,5-*b*]quinoline derivative **73** was obtained on refluxing compound **69** in formic acid. Furthermore, pyrimido[4,5-b]quinoline derivative **74** was obtained by a reaction of **69** with dimethyl amine and hydrazine hydrate (Scheme 13) [44].

Synthesis of pyrimido[4,5-*b*]quinoline-4-ones from 2-chloroquinoline-3-carbonitriles **60** involved the metal-free amination reaction with aliphatic amines in water and subsequent cyclization reaction of compound **75** via Vilsmeier-Haack reagent (DMF/$POCl_3$) (Scheme 14). The mechanistic equations for forming pyrimido[4,5-*b*]quinoline-4-ones **76a-m** from 2-chloroquinoline-3-carbonitriles **60** were as depicted in Scheme 15. Firstly, amination of 2-chloroquinoline-3-carbonitriles to 2-(benzylamino) quinoline-3-carbonitrile **75**, which was converted to the corresponding imine **77** with the ease of $POCl_3$ and DMF (Vilsmeier-Haack reaction) followed by cyclization to 1-benzyl-4-chloro-*N*,*N*-dimethyl-1,2-dihydropyrimido[4,5-*b*]quinolin-2-amine **78**. The latter was hydrolyzed to 1-benzyl-2-(dimethylamino)-1,-2-dihydropyrimido[4,5-b]quinolin-4-ol **81** tautomerized to the target compound pyrimido[4,5-*b*]quinoline-4-ones **76** (Scheme 15) [45].

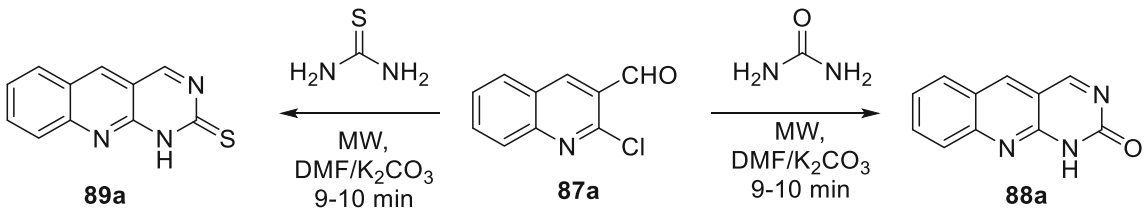
2-Chloroquinoline-3-carbonitriles **60a-i** were reacted with guanidine hydrochloride using *t*-BuOK as a base in ethanol under reflux to afford the corresponding 2-amino-3*H*-pyrimido[4,5-*b*]quinolin-4-one **82a-i** in good yields (80–90%). On the other hand, the reaction of 2-chloroquinoline-3-carbonitriles **60a,f** with binucleophiles such as urea and thiourea were examined to furnish pyrimido[4,5-*b*]quinoline-2,4-diones **83a,b** (79% and 82%) and 4-amino-pyrimido[4,5-*b*]quinoline-2-thione **84a,b** (62% and 72%) respectively. While, when 2-chloroquinoline-3-carbonitrile **60a** was reacted with both *S*-benzyl isothiourea chloride and cyanoguanidine under the same conditions 2-benzylsulfanyl-pyrimido[4,5-*b*]quinolin-4-ylamine **85a** (79%) and 4-amino-pyrimido[4,5-*b*]quinolin-2-yl-cyanamide **86a** (70%) were obtained respectively as illustrated in Scheme 16 [46].



SCHEME 17 Synthesis of pyrimido[4,5-*b*]quinoline-2(1H)-ones/thiones **88/89a-g**.

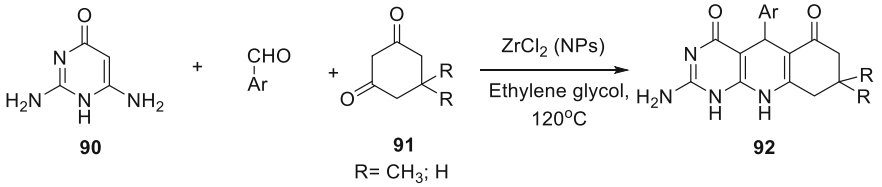
2.3 | From 2-chloro-3-formylquinoline

Pyrimido[4,5-*b*]quinoline-2(1H)-ones **88a-g** were synthesized by the condensation reaction of 2-chloro-3-formylquinoline (**87a**) with urea in the presence of PTSA (*p*-toluene sulfonic acid). The thio-analogues **89a–g** were similarly synthesized from **87a–g** and thiourea under the same conditions (Scheme 17) [47].



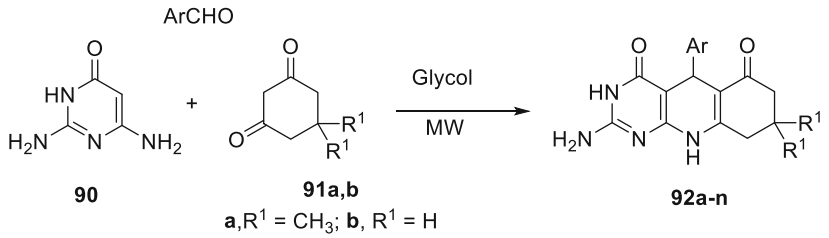
SCHEME 18 Microwave irradiation accessed synthesis of pyrimido[4,5-*b*]quinoline-2-thiol (**89a**),pyrimido[4,5-*b*]quinolin-2-one (**88a**).

Microwave irradiation accessed synthesis of pyrimido[4,5-*b*]quinoline-2-thiol (**89a**),pyrimido[4,5-*b*]quinolin-2-one (**88a**) via cyclization between 2-chloroquinoline-3-carbaldehyde (**87a**) with urea and thiourea under microwave irradiation in the presence of anhydrous potassium carbonate as catalyst (Scheme 18) [48].



Product **92**	R	Ar	Time (min)	Yield (%)
a	H	4-$O_2NC_6H_4$	10	94
b	H	2-$O_2NC_6H_4$	12	90
c	H	C_6H_5	9	94
d	H	4-ClC_6H_4	9	96
e	H	2-ClC_6H_4	10	93
f	H	2,4-$Cl_2C_6H_4$	8	96
g	H	4-BrC_6H_4	8	96
h	H	4-FC_6H_4	10	94
i	H	4-MeC_6H_4	8	95
j	H	4-$MeOC_6H_4$	8	98
k	H	4-$MeSC_6H_4$	8	98
l	H	1naphthlene-1-yl	9	96
m	CH_3	4-FC_6H_4	35	95
n	CH_3	3-$O_2NC_6H_4$	60	93

SCHEME 19 Synthesis of 2-amino-pyrimido[4,5-*b*]quinolines **92a-n** from 2,6-diamino pyrimidin-4(1*H*)-one.



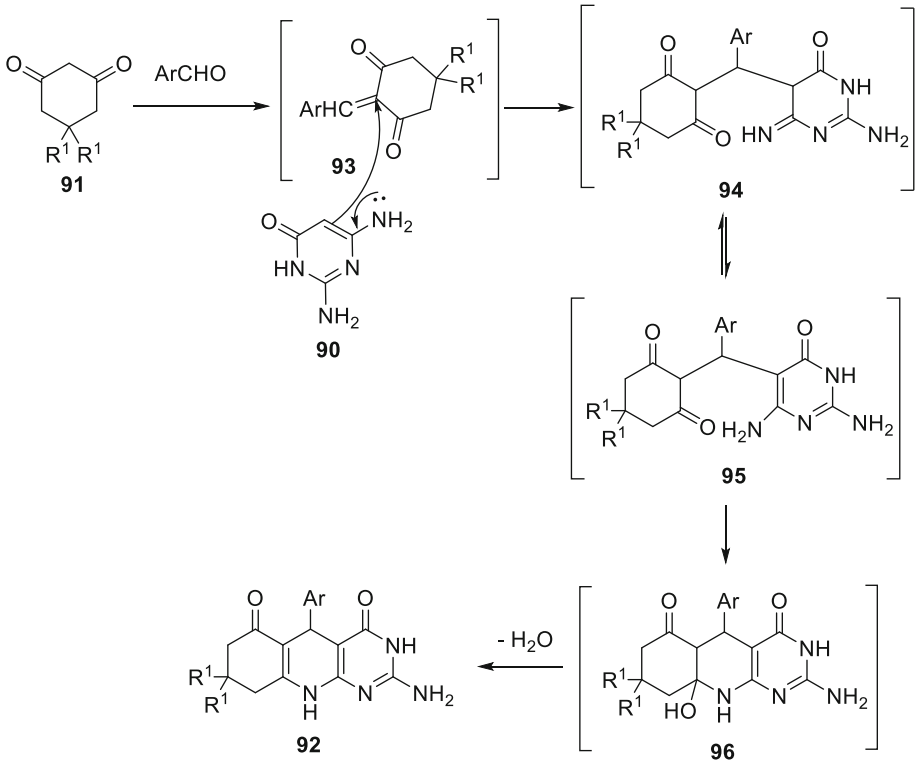
Entry	Ar	R^1	Yield (%)
a	4-Cl-C_6H_4	CH_3	95 (91)^T
b	2-Cl-C_6H_4	CH_3	91 (90)^T
c	4-NO_2-C_6H_4	CH_3	93
d	3-NO_2-C_6H_4	CH_3	92
e	3,4-$(OMe)_2$-C_6H_3	CH_3	95
f	3,4-OCH_2O-C_6H_3	CH_3	95
g	$CH_3CH_2CH_2$	CH_3	91
h	4-Cl-C_6H_4	H	92
i	3-NO_2-C_6H_4	H	92
j	4-NO_2-C_6H_4	H	94
k	4-Br-C_6H_4	H	91
l	4-OMe-C_6H_4	H	91
m	1,3-Cl_2-C_6H_3	H	90
n	$CH_3CH_2CH_2CH_2$	H	87

SCHEME 20 Synthesis of pyrimido[4,5-b]quinoline derivatives **92a-n**, form the reaction of 2,6-diaminopyrimidin-4-one **90** with the cyclic 1,3-dicarbonyl compound **91** and appropriate aldehyde.

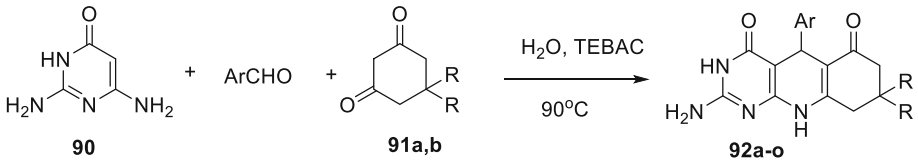
2.4 | From 2,6-diaminopyrimidine-4-one and 6-amino uracil

Mamaghani et al. reported the synthesis of 2-amino-pyrimido[4,5-b]quinolines **92a-n** via a one-pot, three-component reaction of aldehydes, 2,6-diaminopyrimidin-4(1*H*)-one (**90**) and cyclic 1,3-dicarbonyl compounds **91a,b** using ZrO_2 nanoparticles as a catalyst (Scheme 19) [49].

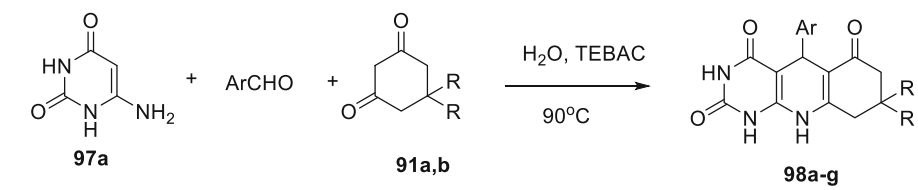
Pyrimidoquinoline derivatives **92a-n** were synthesized by reacting 2,6-diaminopyrimidin-4-one **90** with the cyclic 1,3-dicarbonyl compound **91** and appropriate aldehyde without catalyst in a small amount of glycol under microwave irradiation (Scheme 20). After 4–



SCHEME 21 Mechanism for the formation of pyrimidoquinone derivatives **90**.



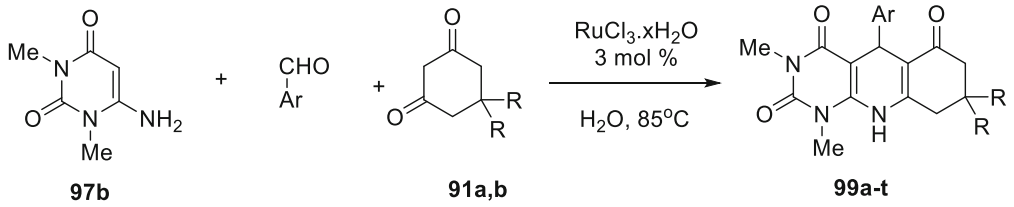
92a-o: a, R= H, Ar = 4-FC_6H_4 (95%); **b**, R = H, Ar = 4-HOC_6H_4 (93%);
c, R = H, Ar = 3-$NO_2C_6H_4$ (94%); **d**, R = H, Ar = 4-$NO_2C_6H_4$ (90%);
e, R = H, Ar = 4-ClC_6H_4 (92%); **f**, R = H, Ar= 4-BrC_6H_4 (86%);
g, R= Me, A r= 4-ClC_6H_4 (95%); **h**,R= Me, Ar= 4-HOC_6H_4 (86%);
i, R= Me, Ar= 4-$NO_2C_6H_4$ (86%); **j**, R= Me, Ar= 3,4-$(MeO)_2C_6H_4$ (92%);
k, R= Me, Ar= 3,4-$Cl_2C_6H_4$ (96%); **l**, R= Me, Ar= 3-$NO_2C_6H_4$ (94%);
m, R= Me, Ar= 4-BrC_6H_4 (94%); **n**, R= Me, Ar= 3,4-$OCH_2OC_6H_3$ (92%);
o, R= Me, Ar= pyridine-3-yl (88%);



98a-g: a, R= H, Ar= 3,4-$Cl_2C_6H_4$ (76%); **b**, R= H, Ar= 3-$NO_2C_6H_4$ (98%);
c, R= H, Ar= 2,4-$Cl_2C_6H_4$ (75%); **d**, R= H, Ar= 2-$NO_2C_6H_4$ (93%);
e, R= H, Ar= 4-$NO_2C_6H_4$ (86%); **f**, R= Me, Ar= 3,4-$(MeO)_2C_6H_4$ (91%);
g, R= Me, Ar= 4-HOC_6H_4 (98%);

SCHEME 22 Synthesis of 2-amino-5-aryl-pyrimidino[4,5-*b*]quinoline-4,6-dione **92** and 5-aryl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6-trione **98**.

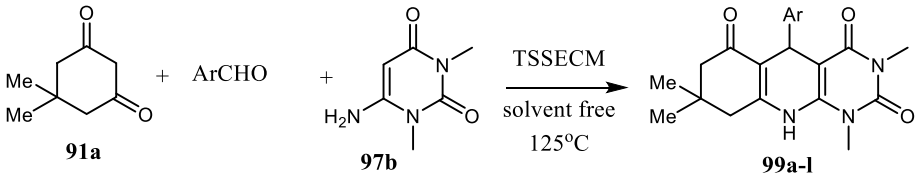
7 min irradiation, the pyrimidoquinoline derivatives **92** with pyrimidine unit were obtained in excellent yields. The results obtained via the irradiation process were compared with those obtained from the traditional heating methodology. This reaction may occur via a condensation, addition, cyclization, or elimination mechanism



97b **91a,b** **99a-t**

Product **99**	R	Ar	Ultrasound Yield (%)	Reflux Yield (%)
a	CH_3	4-$MeOC_6H_4$	82	80
b	CH_3	4-$O_2NC_6H_4$	96	95
c	CH_3	2-$MeOC_6H_4$	73	75
d	CH_3	4-ClC_6H_4	91	90
e	CH_3	2,4-$Cl_2C_6H_3$	92	91
f	CH_3	4-MeC_6H_5	80	78
g	CH_3	2-Cl-6-FC_6H_3	92	93
h	CH_3	3-$O_2NC_6H_4$	91	90
i	CH_3	2-ClC_6H_4	87	88
j	CH_3	4-$(CH_3)_3CC_6H_4$	66	60
k	CH_3	CH_3	Traces	-
l	H	4-ClC_6H_4	92	90
m	H	2-Cl-6-FC_6H_3	95	93
n	H	4-$O_2NC_6H_4$	92	91
o	H	4-FC_6H_4	90	89
p	H	4-MeC_6H_5	80	78
q	H	4-$(CH_3)_2NC_6H_4$	87	88
r	H	2,4-$Cl_2C_6H_3$	92	90
s	H	Me	Traces	-
t	H	4-$(CH_3)_3CC_6H_4$	65	62

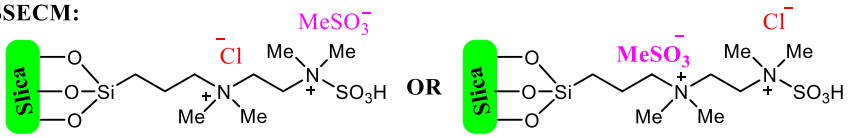
SCHEME 23 Synthesis of pyrimido[4,5-*b*]quinoline derivatives **99a-t** via a three-component reaction of cyclic 1,3-diketones **91a,b** aminouracil **97a** and aldehydes.



91a **97b** **99a-l**

Ar = **a**, C_6H_5 (93%); **b**, 4-Br-C_6H_4 (86%); **c**, 4-Cl-C_6H_4 (92%);
d, 2,4-diCl-C_6H_4 (93%); **e**, 3-Cl-C_6H_4 (91%); **f**, 3-NO_2-C_6H_4 (84%);
g, 2-NO_2-C_6H_4 (92%); **h**, 4-Me-C_6H_4 (94%); **i**, 3,4-diOMe-C_6H_3 (93%);
j, 2,5-diOMe-C_6H_3 (83%); **k**, 4-OMe-C_6H_4 (95%); **l**, 4-OH-C_6H_4 (91%);

TSSECM:



SCHEME 24 TSSECM promoted the synthesis of pyrimido[4,5-*b*] quinoline derivatives **99a-l**.

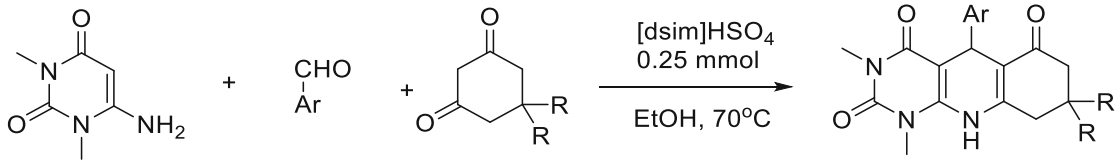
(Scheme 22). The condensation between aldehyde and cyclic 1,3-dicarbonyl compound gave 2-arylidene-5,5-dimethyl-1,3-cyclohexanedione **93**. Michael addition between 9**5** and 2,6-diaminopyrimidin-4-one **91** furnished the intermediate **94**, which isomerized to **95**. Intramolecular cyclodehydration of **96** gave **92** (Scheme 21) [50].

Three-component reaction of 2,6-diaminopyrimidine-4-one **90**, aromatic aldehyde, and 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione **91a,b** was performed in water in the presence of TEBAC at 90°C, 2-amino-5-aryl-8,9-dihydropyrimidino[4,5-*b*]quinoline-4, 6(1*H*,3*H*,5*H*,10*H*)-dione **92** were obtained in high yields (Scheme 23). On replacing 2,6-diaminopyrimidine-4-one **90** with 6-aminopyrimdine-1,3-dione **97a**, another series of 5-aryl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6 (1*H*,3*H*,5*H*,10*H*)-trione **98** were obtained under the same reaction conditions (Scheme 22) [51].

Tabatabaeian et al. have reported the utility of $RuCl_3.xH_2O$ as an efficient and effective catalyst without any toxic solvent in the synthesis of pyrimido[4,5-*b*]quinoline derivatives **99a-t** via three-component reaction conditions. In this methodology, cyclic 1,3-diketones **91a,b** aminouracil **97b,** and aldehyde react in one step in the presence of Lewis acid $RuCl_3.xH_2O$ in water. The reaction was carried out under reflux and ultrasonication, and the results were compared. It was found that the yields were improved by applying the ultrasound method (Scheme 23) [52, 53].

Recently, pyrimido[4,5-*b*]quinoline derivatives **99a-l** have been obtained from the reaction of various arylaldehydes with dimedone **91a** and 6-amino-1,-3-dimethyluracil **97b** using TSSECM as a novel silica-based organic–inorganic hybrid material namely *N,N,N′*, *N′*-tetramethyl-*N*-(silica-*n*-propyl)-*N′*-sulfonic acid-ethylenediaminium chloride/ mesylate, which acts as a dual-functionalized catalyst (it has acidic and basic groups the SO_3H is acid, and the mesylate is weak base). (Scheme 24) [1].

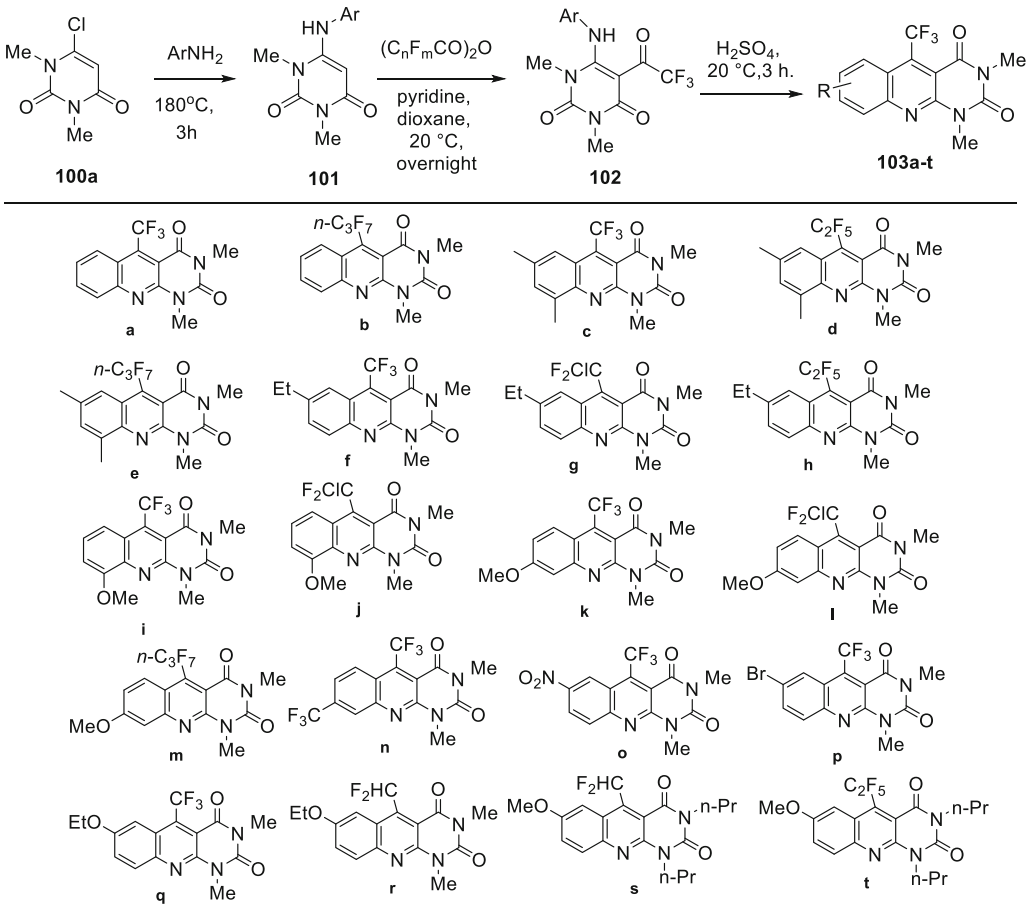
In continuation of the use of catalytic procedures for the synthesis of pyrimidoquinolines **99a-q,** a one-pot, three-component reaction of aldehydes, 6-amino-1,-3-dimethyluracil **97b** and cyclic 1,3-dicarbonyl compounds **91a,b** using $[dsim]HSO_4$ as a recyclable catalyst in ethanol at 70°C (Scheme 25) [54].



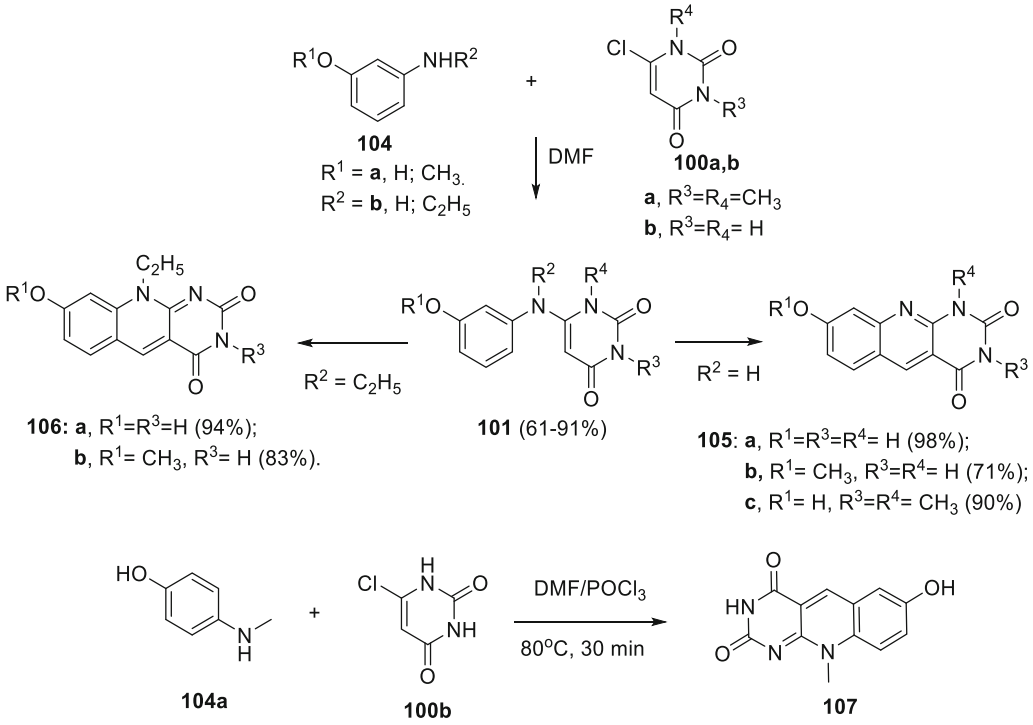
97b **91a,b** **99a-q**

Product **99**	R	Ar	Time (min)	Yield (%)
a	CH_3	4-$MeOC_6H_4$	25	85
b	CH_3	4-$O_2NC_6H_4$	15	92
c	CH_3	4-ClC_6H_4	15	91
d	CH_3	2-$O_2NC_6H_4$	35	87
e	CH_3	3-$O_2NC_6H_4$	30	90
f	CH_3	3-BrC_6H_4	30	89
g	CH_3	2-ClC_6H_4	35	88
h	CH_3	2-Cl-6-FC_6H_3	20	90
i	CH_3	4-FC_6H_4	20	90
j	CH_3	4-BrC_6H_4	20	90
k	H	3-$O_2NC_6H_4$	30	89
l	H	4-FC_6H_4	18	88
m	H	4-ClC_6H_4	15	90
n	H	4-$O_2NC_6H_4$	15	92
o	H	2-Cl-6-FC_6H_3	18	90
p	H	4-$(CH_3)_2NC_6H_4$	30	88
q	H	4-MeC_6H_4	35	86

SCHEME 25 Synthesis of pyrimidoquinolines **99a-q** via a one-pot, three-component reaction.

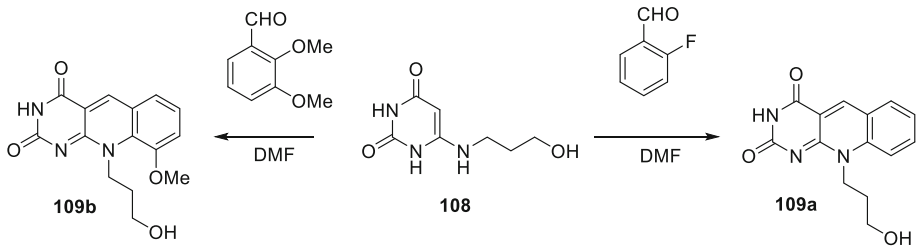


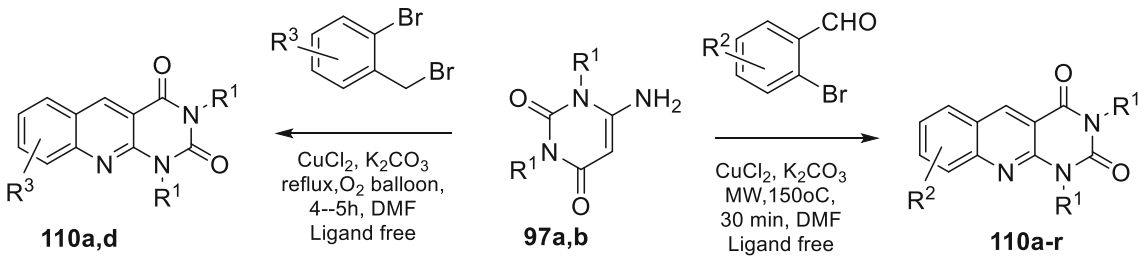
SCHEME 26 Pyrimidoquinolines **103a-x** from 6-chloro-1,3-dimethyluracil **100**.

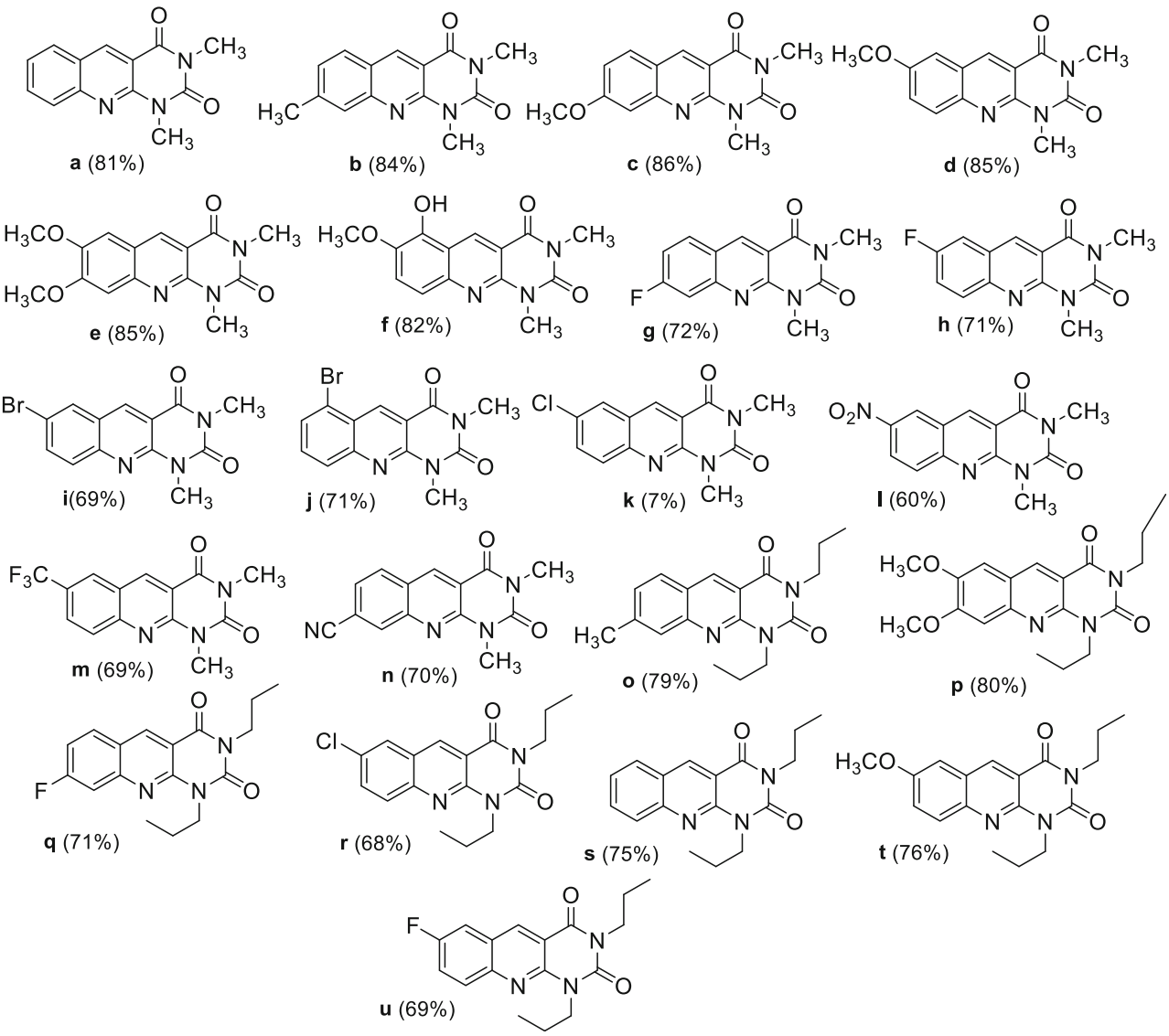


SCHEME 27 2,4-Dioxopyrimido[4,5-*b*]quinolines **105** and **106** and 7-Hydroxy-10-methyl-2,4-dioxopyrimid[4,5-*b*]quinoline (**107**).

SCHEME 28 Synthesis of 5-deazaflavin **109a,b** from the reaction of 6-aminouracyl with substituted aromatic aldehydes.



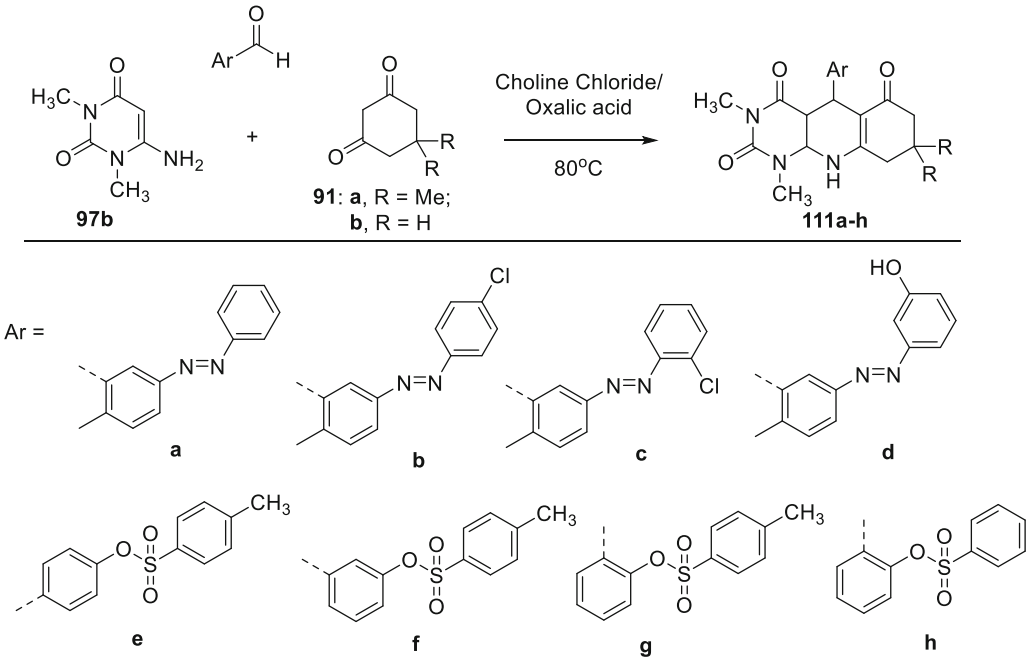




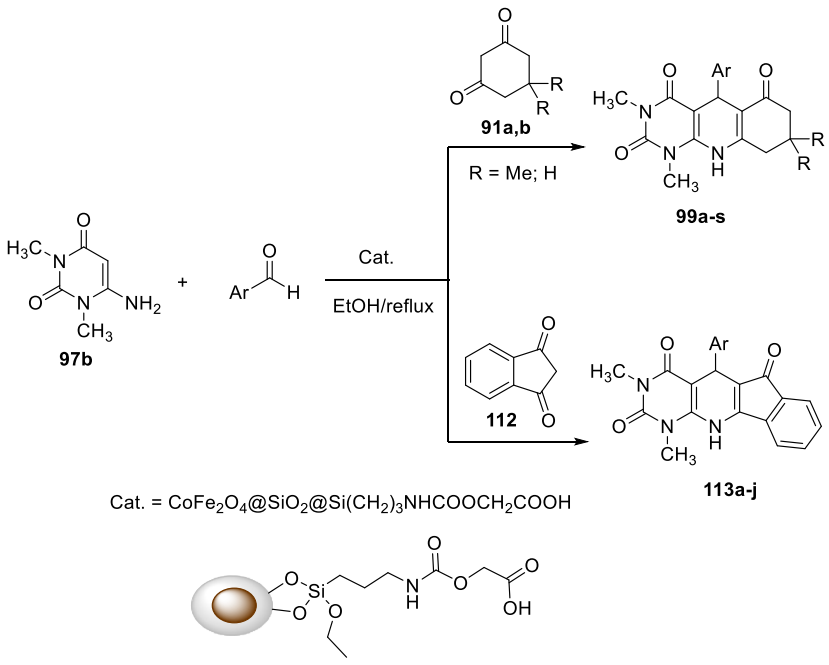
SCHEME 29 Synthesis of pyrimido[4,5-*b*]quinolinone derivatives **110a-r** from the reaction of aminouracil derivatives with bromobenzaldehydes and 2-bromobenzyl bromides.

6-Anilino-1,3-dialkyluracils **101** were prepared by nucleophilic displacement of 6-chloro-1,3-dimethyluracil **100a** with arylamines. Treatment of 6-aminouracils **100** with the corresponding polyfluorinated carboxylic acid anhydride (or acid chloride, if $R^F = n\text{-}C_3F_7$) in dioxane and the presence of pyridine resulted in the formation of 6-anilino-5-(polyfluoroacyl)-1,3-dimethyluracils **102a-x** in excellent yields (79–99%). Dissolving the uracils **102a-x** in concentrated H_2SO_4 at room temperature for 3 h gave corresponding pyrimidoquinolines **103a-x** in good to excellent yields (49–92%), as shown in Scheme 26 [55].

2,4-Dioxopyrimido[4,5-*b*]quinolines **105** and **106** were obtained from 6-ary1-aminouracil in DMF and phosphorus oxychloride ($POCl_3$) under argon. 7-Hydroxy-10-methyl-2,4-dioxopyrimid[4,5-*b*]quinoline (**107**) was synthesized from *p*-(methylamino)phenol **104** and



SCHEME 30 Synthesis of azo and sulfonated pyrimido[4,5-*b*]quinoline derivatives **111a-h**.



SCHEME 31 Synthesis of pyrimido[4,5-*b*] quinoline **99a-s** and indenopyrido[2,3-*d*] pyrimidine derivatives **113a-j**.

6-chlorouracil **100b** by the same procedure, except that the cyclization step required heating at 80°C for 30 min (Scheme 27) [56].

Condensation of 6-((3-hydroxypropyl)amino) pyrimidine-2,4-dione **108** with 2-fluoro-benzaldehyde in boiling DMF for 5–6 h, through dehydration and dehydrofluorination gave the corresponding 10-(3-hydroxypropyl) pyrimido[4,5-b]quinoline-2,4-dione **109a** in good yield. Applying this method to 2,3-dimethoxybenzaldehyde, instead of halogen-containing aldehyde in the ortho-position, the corresponding 10-(3-hydroxypropyl)-9-methoxy pyrimido[4,5-b]quinoline-2,4(3H,10H)-dione **109b** was performed (Scheme 28) [57].

Two methods for the synthesis of pyrimidine fused quinolines using a one-pot C – C and C – N bond-forming strategy from the reaction of 6-aminouracils with 2-bromobenzaldehydes or 2-bromobenzyl bromide derivatives in the presence of 10 mol % $CuCl_2$ without using any ligand were mentioned in Scheme 30. The reaction of 2-bromobenzaldehyde or its derivatives with 6-aminouracils **97a,b** in the presence of K_2CO_3 as the base and a catalytic amount of $CuCl_2$ in DMF medium under microwave heating conditions provide corresponding pyrimidine fused quinoline derivatives **110a-r** in good yields within 30 min. Alternatively, pyrimidine fused quinoline derivatives **110a,d** were synthesized from the reaction of 2-bromobenzyl bromides with 6-aminouracil derivatives **97a,b** in the presence of molecular oxygen, $CuCl_2$ (10 mol %), and K_2CO_3 as base in DMF under reflux conditions (Scheme 29) [58].

Azo and sulfonated pyrimido[4,5-*b*]quinoline derivatives **111a-h** were synthesized via a three-component reaction of azo and sulfonated aldehydes, 6-amino-1,-3-dimethyluracil **97b**, and dimedone or 1,3-cyclohexadione **91a,b** in the presence of choline chloride/oxalic acid at 80°C (Scheme 30) [59].

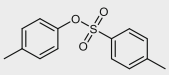
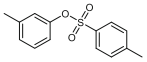
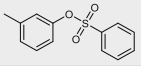
Recently, Gholami et al. reported the one-pot synthesis of pyrimido[4,5-*b*]quinoline **99** and indenopyrido [2,3-*d*]pyrimidine derivatives **113** from the three-component reaction of aldehydes, 6-amino-1,-3-dimethyluracil **97a** and dimedones **91a,b** or indandione **112** in the presence of glycolic acid-supported cobalt ferrite $CoFe_2O_4@SiO_2@Si(CH_2)_3$ $NHCOOCH_2COOH$ as a magnetic catalyst in ethanol at refluxing conditions (Scheme 31). To optimize the reaction conditions, the reaction of 4-chlorobenzaldehyde, 6-amino-1,3-dimethyl uracil **97b** (1 mmol), and dimedone **91a,b** was examined as a model reaction in the various solvents as shown in Table 1, it was observed that ethanol was selected as the more efficient solvent under reflux conditions concerning the reaction time and yield of the desired product (Table 1). Carrying the model reaction using different amounts of catalyst (0.01, 0.02, 0.03, and 0.04 g), the studies resulted in using 0.03 g of catalyst as a favorable one (Scheme 31). The yields of the obtained products **99a-s** and **113a-j** were mentioned in Tables 2 and 3, respectively [27].

An efficient protocol for the synthesis of pyrimido [4,5-*b*]quinolines (**99a-f, 114a,b** and **115a,b**) was

TABLE 2 Synthesis of pyrimidoquinoline derivatives **99a-s**.

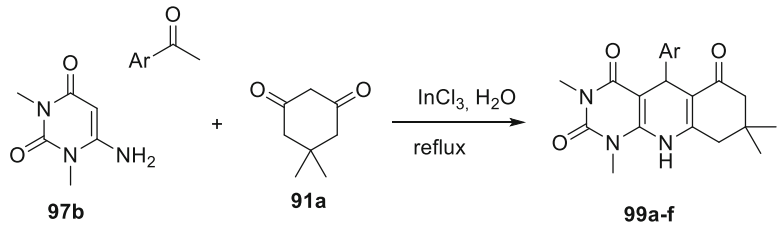
Product	Ar	R	Yield (%)
a	4-Cl-C_6H_4	CH_3	97
b	2-Cl-C_6H_4	CH_3	96
c	2,4-$(Cl)_2$-C_6H_3	CH_3	97
d	4-NO_2-C_6H_4	CH_3	98
e	3-NO_2-C_6H_4	CH_3	96
f	3-MeO-C_6H_4	CH_3	94
g	4-MeO-C_6H_4	CH_3	93
h	3-Me-C_6H_4	CH_3	93
i	4-Me-C_6H_4	CH_3	94
j	2-HO-C_6H_4	CH_3	93
k	4-HO-C_6H_4	CH_3	94
l	2-NO_2-furyl	CH_3	95
m	4-CHO-C_6H_4	CH_3	96
n	4-Cl-C_6H_4	H	96
o	3-NO_2-C_6H_4	H	95
p	3-MeO-C_6H_4	H	93
q	4-HO-C_6H_4	H	92
r	3-Me-C_6H_4	H	92
115 s	4-CHO-C_6H_4	H	95

TABLE 3 Synthesis of indenopyrido[2,3-d]pyrimidine derivatives **113a-j**.

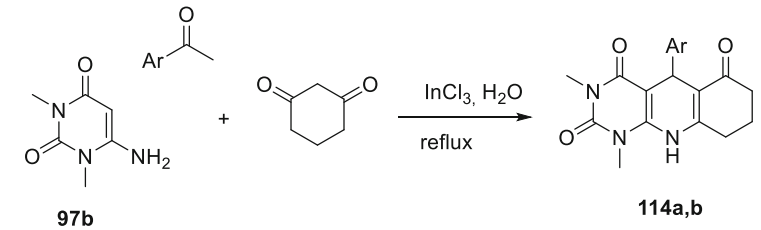
Product	Ar	Yield (%)
a	4-Cl-C_6H_4	95
b	4-Br-C_6H_4	94
c	2-Br-C_6H_4	92
d	2,4-$(Cl)_2$-C_6H_3	96
e	4-MeO-C_6H_4	91
f	4-Me-C_6H_4	91
g	Naphthyl	93
h		96
i		94
j		95

performed via three-component condensation of aldehydes, 1,3-dicarbonyl compounds and electron-rich amino heterocycles like 6-amino-1,3-dimethyl uracil **97b** catalyzed by indium trichloride in water under reflux (Scheme 32) [60].

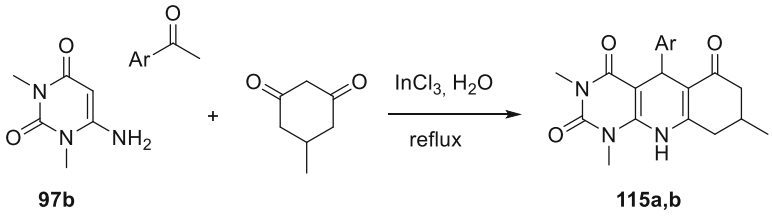
A one-pot synthesis of 5-(4-chlorophenyl)-9-(4-chlorophenylmethylene)-2-thioxopyrimido[4,5-*b*]quinolin-4-one **118a-c** was as described below. 4-Chlorobenzaldehyde was condensed with cyclohexanone and 6-aminothiouracil **97a** in dimethyl formamide (DMF)



99a-f: Ar = **a**,4-ClC_6H_4 (91%); **b**,4-BrC_6H_4 (90%); **c**,4-HOC_6H_4 (90%); **d**,4-$CH_3OC_6H_4$ (89%), **e**, 4-$O_2NC_6H_4$ (91%); **f**, 2-Thiophenyl (89%);

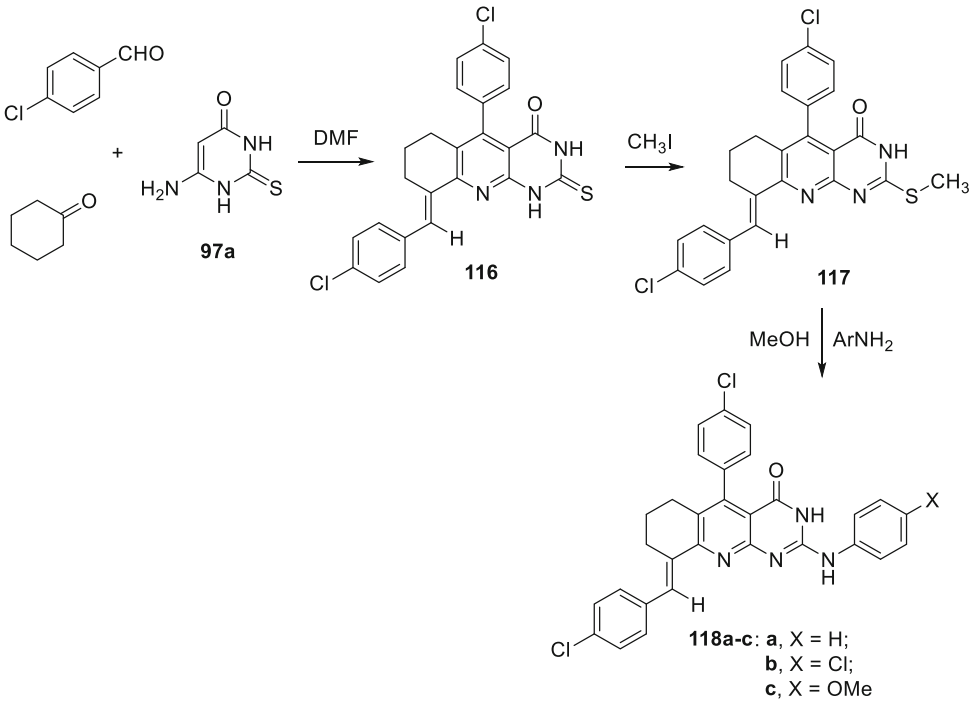


114a,b: Ar = **a**,4-ClC_6H_4 (92%); **b**,4-O_2N-C_6H_4 (93%);



115a,b: Ar = **a**, 4-ClC_6H_4 (91%); **b**, 4-O_2N-C_6H_4 (92%); **c**, 4-Br-C_6H_4 (91%);

SCHEME 32 Synthesis of pyrimido[4,5-*b*] quinolines (**99a-f, 114a,b** and **115a,b**).



SCHEME 33 Synthesis of 2-arylamino-5-(4-chloro-phenyl)-9-(4-chlorophenylmethylene)-6,7,8,9-tetrahydropyrimido[4,5-*b*] quinolin-4-one derivatives **118a–c**.

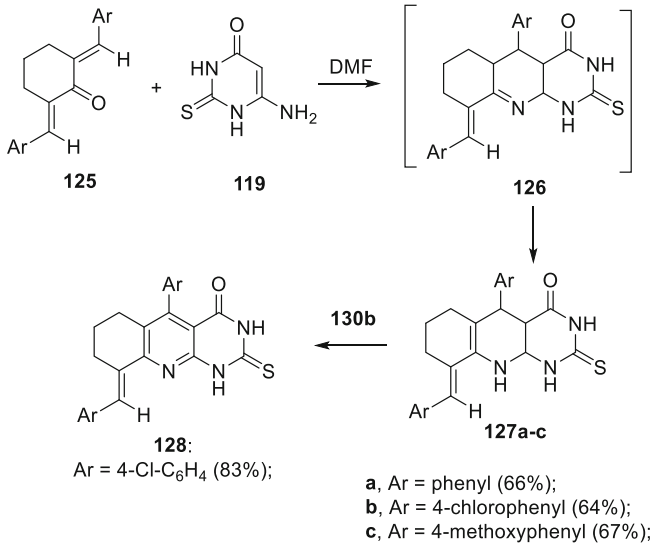
solution, affording **116** in good yield (80%) (Scheme 33). It is known that positions 2 and 4 in pyrimidine and fused pyrimidines showed distinct activities towards nucleophiles. Therefore, 2-methylthio-5-(4-chlorophenyl)-9-(4-chlorophenyl methylene)-pyrimido[4,5-*b*]quinolin-4-one (**117**) was prepared, and its activity towards nucleophiles such as primary aromatic and secondary aliphatic amines (piperazine, morpholine) was investigated. Thus heating under reflux of 2-methylthiopyrimido [4,5-*b*]quinolin-4-one (**117**) with aniline, 4-chloroaniline, and *p*-anisidine in methanol gave 2-arylamino-5-(4-chloro-phenyl)-9-(4-chlorophenyl methylene)-pyrimido[4,5-*b*]quinolin-4-one derivatives **118a–c** with evolution of methanethiol (Scheme 33) [61].

Heating under reflux of 6-aminothiouracil **119** with *α*,*β*-unsaturated ketones **120a-c** gave 5-aryl-2-thioxo-2,-3,6,7,8,9-hexahydro-1*H*,4*H*-pyrimido[4,5-*b*]quinolin-4-ones **123a–c** and the non-oxidized form 2-thioxo-5,-10-dihydro-1*H*,4*H*-pyrimido[4,5-*b*]quinolin-4-ones **124a–c** were isolated (Method A). Depending on the reaction conditions, the prolonged reaction time in refluxing DMF furnished the oxidized forms **123a–c** in good yield in the cyclo-condensation process. Also, the latter pyrimido [4,5-*b*]quinoline **123a–c** was obtained by the cyclo-condensation reaction of 6-aminothiouracil **119** with cyclohexanone and aromatic aldehydes via one-pot synthesis (Method B) as shown in Scheme 34 [62].

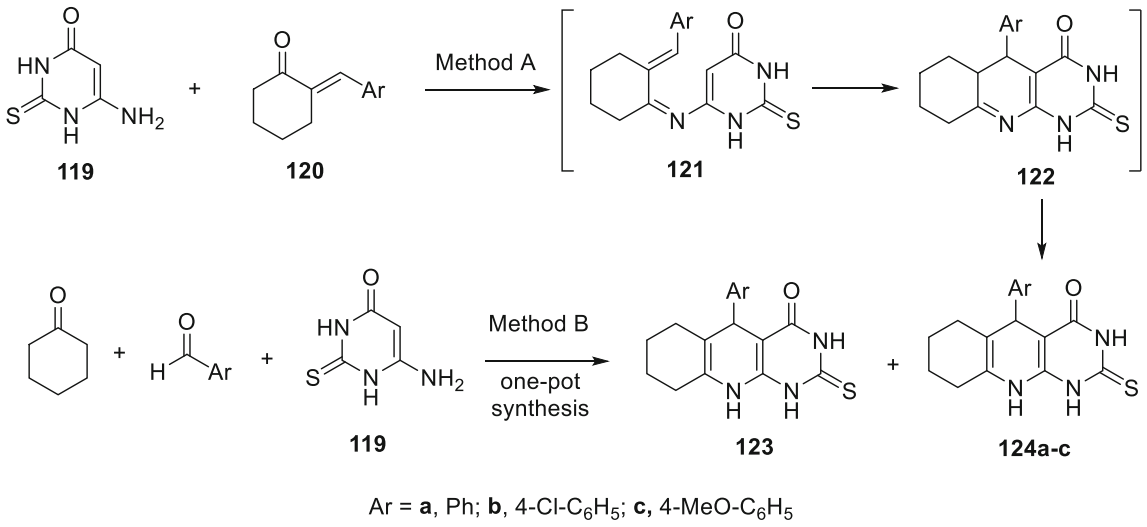
5-(4-Chlorophenyl)-9-(4-chlorophenylmethylene)-2-thioxo-pyrimido[4,5-*b*]quinolin-4-one **128** was obtained by the reaction of an *α*,*β*-unsaturated ketone (**125**) and 6-amino-2-thioxopyrimidin-4-one (**119**) in refluxing DMF for a long time via intermediate **126** and the isolated product **127a-c** (Scheme 35) [63].

The 5-deazaflavins were prepared as shown in Scheme 35. The 6-chlorouracil **100a**, prepared by hydrolysis of 2,4,6-trichloropyrimidine **129**, was allowed to be fused with the appropriate anilines or other primary amines to give the 6-anilinouracils **130**. These were then subjected to cyclocondensation with *ortho*-halobenzaldehydes to give the corresponding 5-deazaflavins **132** and **133** (Scheme 36) [64].

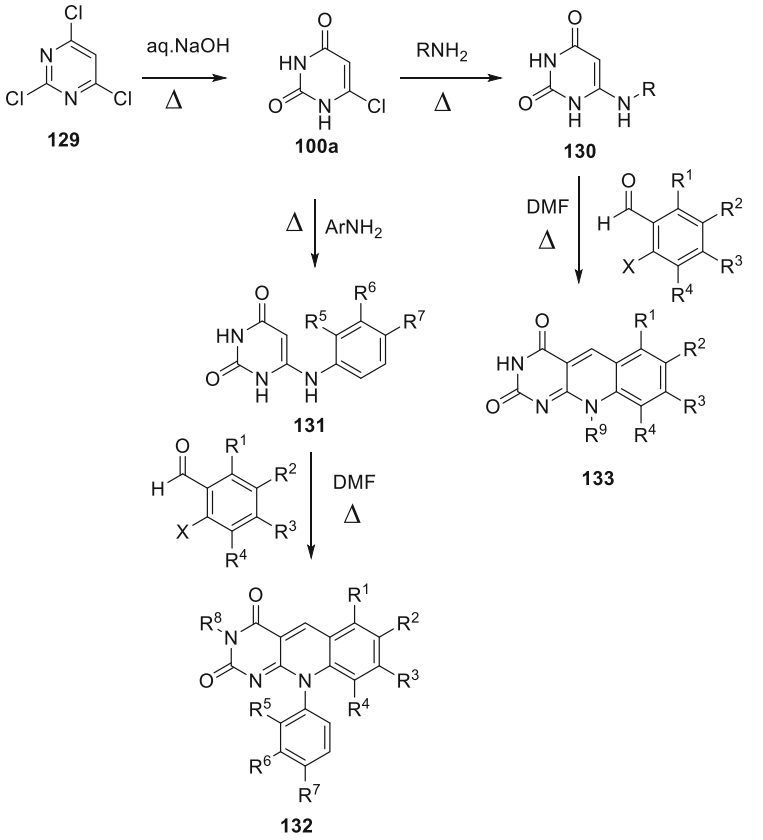
Similarly, the reaction of 2,4,6-trichloropyrimidine (**129**) with sodium hydroxide gave 6-chlorouracil (**100a**) in 71% yield. The next stage involved a two-step convergent approach where 6-chlorouracil **(100a)** was fused at melt temperature with the corresponding arylamines,



SCHEME 35 Synthesis of 2-thioxo-6,7,8,9-tetrahydopyrimido [4,5-*b*]quinolin-4-one (**128**).



SCHEME 34 Synthesis of thioxopyrimidoquinoline derivatives **123a-c**.

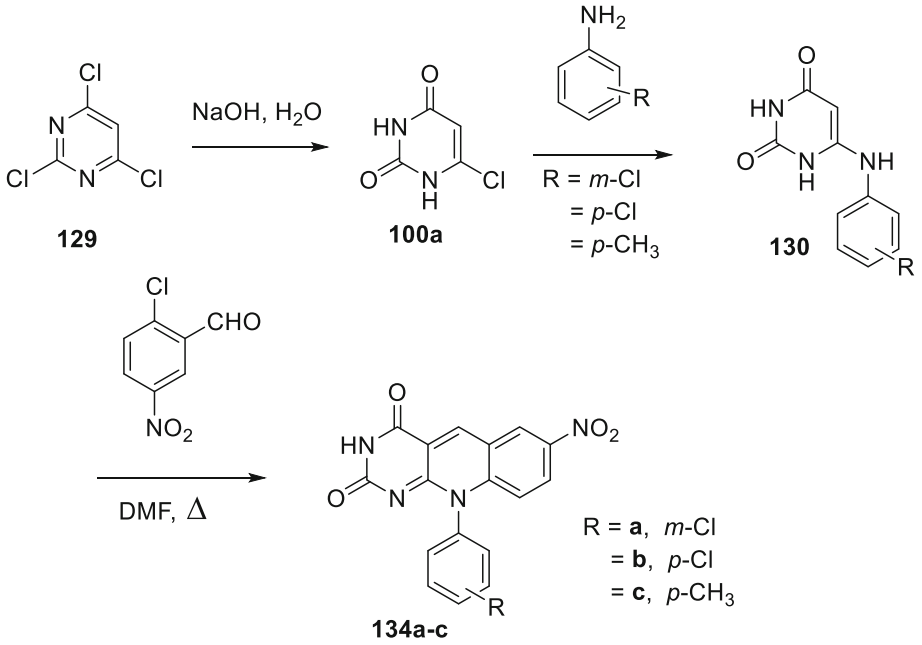


SCHEME 36 Synthesis of 5-deazaflavins **132a-p** and **133a-j**.

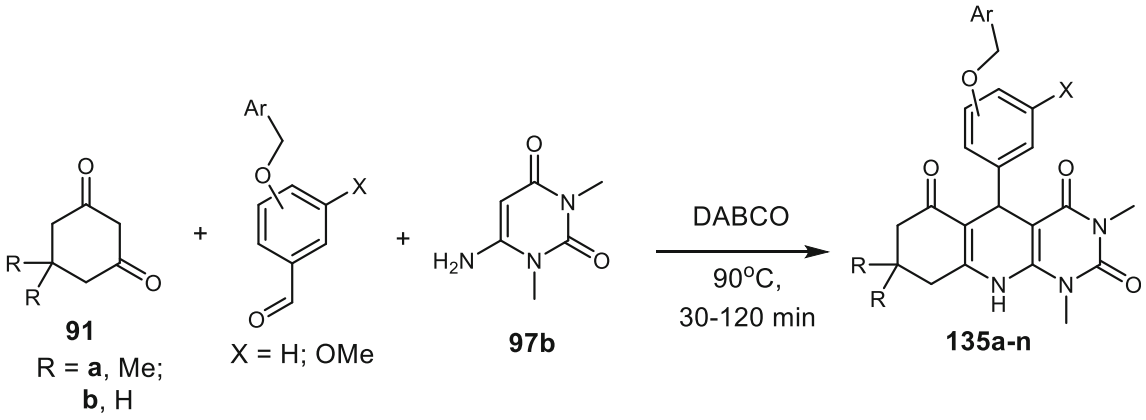
Entry	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
132a	H	H	H	NO_2	F	H	H	H	-
b	H	NO_2	H	H	H	H	Cl	H	-
c	H	H	H	NO_2	H	H	Cl	H	-
d	H	H	H	CF_3	H	H	H	H	-
e	H	H	CF_3	H	F	H	H	H	-
f	H	H	H	CF_3	F	H	H	H	-
g	CF_3	H	H	H	H	H	Cl	H	-
h	H	CF_3	H	H	H	H	Cl	H	-
i	H	H	CF_3	H	H	H	Cl	H	-
j	H	H	H	CF_3	H	Cl	H	H	-
k	H	H	H	CF_3	H	Cl	Cl	H	-
l	H	H	H	Cf_3	H	Cl	Cl	H	-
m	H	H	H	CF_3	H	F	H	H	-
n	H	H	H	CF_3	H	H	F	H	-
o	H	H	H	CF_3	H	Me	H	H	-
p	H	H	H	CF_3	H	H	Me	H	-
133a	H	H	H	CF_3	-	-	-	H	Bn
b	H	H	H	Cl	H	H	H	H	-
c	H	Cl	H	H	F	H	H	H	-
d	Cl	H	H	H	H	H	Cl	H	-
e	H	H	H	Cl	H	H	Cl	H	-
f	H	H	H	Cl	H	Cl	H	H	-
g	H	H	H	Cl	H	F	H	H	-
h	H	H	Me	H	H	H	Cl	H	-
i	H	H	H	Br	H	H	H	H	-
j	H	H	H	Br	H	H	Cl	H	

followed by heating the resulting 6-*N*-aryl-aminouracils **130** with 2-chloro-5-nitrobenzaldehyde in DMF furnished the 10-(3-chlorophenyl)-7-nitropyrimido[4,5-*b*]quinoline-2,4-dione **134a**, 10-(4-chlorophenyl)-7-nitro-10*H*-pyrimido[4,5-*b*]quinoline-2,4-dione (**134b**) and 10-(4-methyl phenyl)-7-nitro-10*H*-pyrimido[4,5-b]quinoline-2,4-dione (**134c**) in 26%, 22%, and 79% yields, respectively, over the two steps (Scheme 37) [65].

Recently, Esmaili et al [66]. have reported the synthesis of pyrimido[4,5-*b*]quinolinetriones **135a-n** using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a basic catalyst on applying a one-pot MCR of various



SCHEME 37 Synthesis of 10-(substituted phenyl)-7-nitro-10*H*-pyrimido[4,5-*b*]quinoline-2,4-dione derivatives **134a-c**.



135a-n:

p-benzyloxy derivatives **a-i**

X = H: **a**, R = Me, Ar = C_6H_5 (84%); **b**, R = H, Ar = C_6H_5 (90%);
c, R = Me, Ar = 4-MeC_6H_4 (95%); **d**, R = H, Ar = 4-ClC_6H_4 (84%);
e, R = Me, Ar = 2-FC_6H_4 (93%);
X = OMe: **f**, R = Me, Ar = C_6H_5 (45%); **g**, R = Me, Ar = 4-BrC_6H_4 (81%);
h, R = Me, Ar = 2-FC_6H_4 (90%); **i**, R = Me, Ar = 4-ClC_6H_4 (65%).

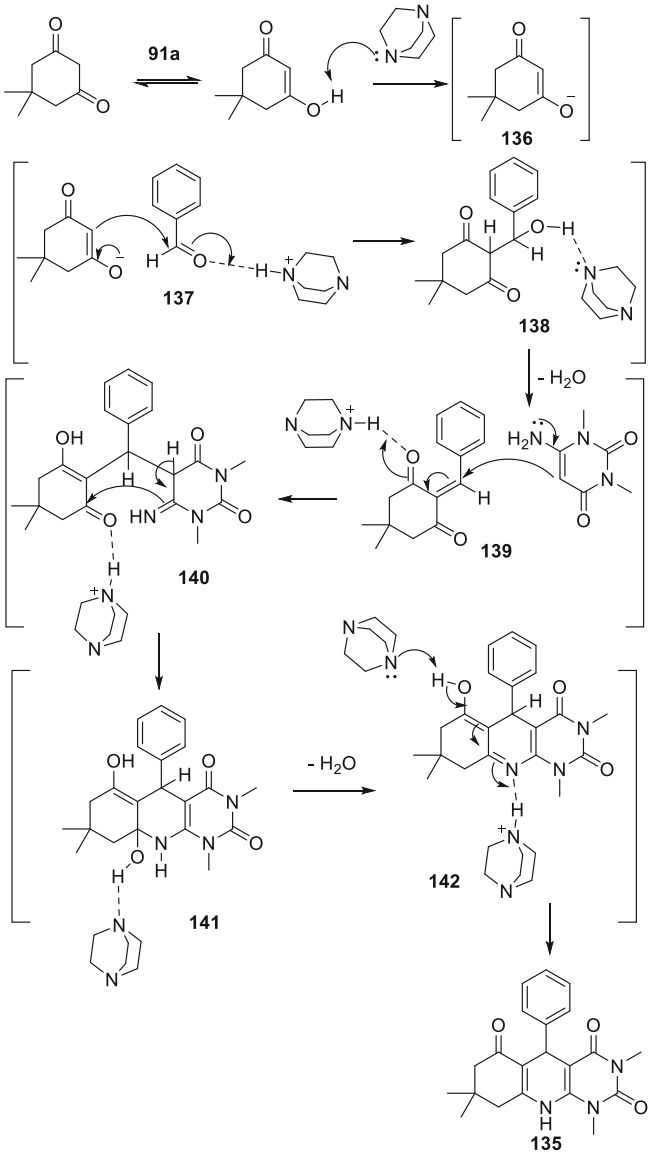
m-benzyloxy derivatives **j-n**

X = H: **j**, R = Me, Ar = C_6H_5 (78%); **k**, R = Me, Ar = 4-MeC_6H_4 (90%);
l, R = Me, Ar = 4-MeC_6H_4 (95%); **m**, R = Me, Ar = 4-FC_6H_4 (92%);
n, R = Me, Ar = 4-ClC_6H_4 (95%);

SCHEME 38 Synthesis of 6-benzyloxypyrimido[4,5-*b*]quinolines **135a-n**.

benzyloxybenzaldehydes with dimedones **91a,b** and 6-amino-1,3-dimethyluracil **97b** at 90°C under the solvent-free condition (Scheme 38) [66].

The proposed mechanism for the formation of pyrimidoquinolines **135a-n** with the utility of DABCO as a bifunctional catalyst was initiated by the formation of the enolate **137** of the diketone **91a,b** (acidic character of DABCO), followed by protonation (acidic character of DABCO) of the aldehyde with nucleophilic attack on the carbonyl carbon to form the intermediate **138**. The loss of a water molecule from intermediate **138** gave intermediate **139**, which was reacted with aminouracil **97b** to give intermediate **140**. The latter underwent heterocyclization to intermediate **141**. Losing another water molecule from intermediate **141** gave intermediate **142**, which was tautomerized to the target compound **135** by the ease of DABCO (Scheme 39).



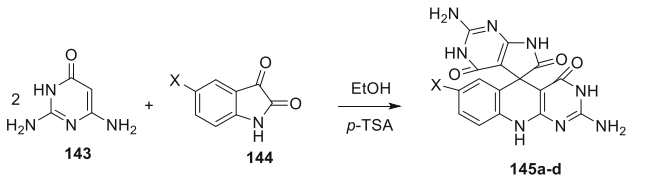
SCHEME 39 Proposed mechanism for the preparation of pyrimido[4,5-b]quinolines **135a-n** catalyzed by DABCO.

Mixing 2,6-diaminopyrimidin-4(3*H*)-one **143** and isatin **144a**, in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) afforded 2,2′-diamino-3*H*-spiro [pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]-4,4′,6′-trione **145a** in 85% yield (Scheme 1). On continuation, isatins **144b–d** under similar conditions (using EtOH/*p*-TSA) furnished the respective 2,20-diamino-3*H*-spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]-4,4′,6′-triones **145b–d** in good yields (85–90%) (Scheme 40) [67].

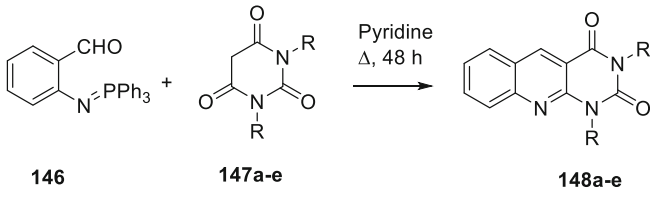
2.5 | From barbituric acid and its derivatives

Pyrimido[4,5-*b*]quinolones **148a-e** were synthesized from the reaction between imino-phosphorane **146** and *N*,*N*′-dialkylbarbituric acids **147a-e** in moderate yields (35–50%) as shown in Scheme 41 [68].

Barbituric acids **147a,b** underwent a three-component reaction with anilines and aldehydes in the presence of L-proline as a catalyst in water to give 5-arylpyrimido [4,5-*b*]quinoline **149a-k** in high yields as depicted in the following Scheme 41. Furthermore, when the aldehydes were replaced by cyclohexanone using the same protocol,

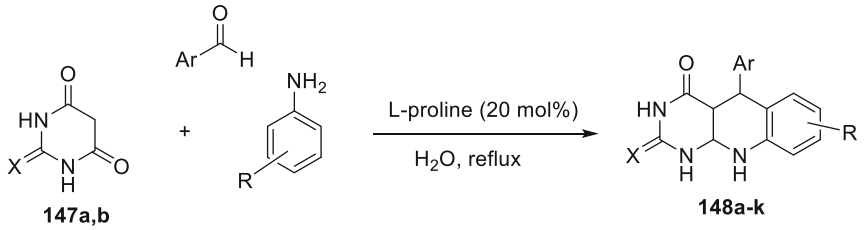


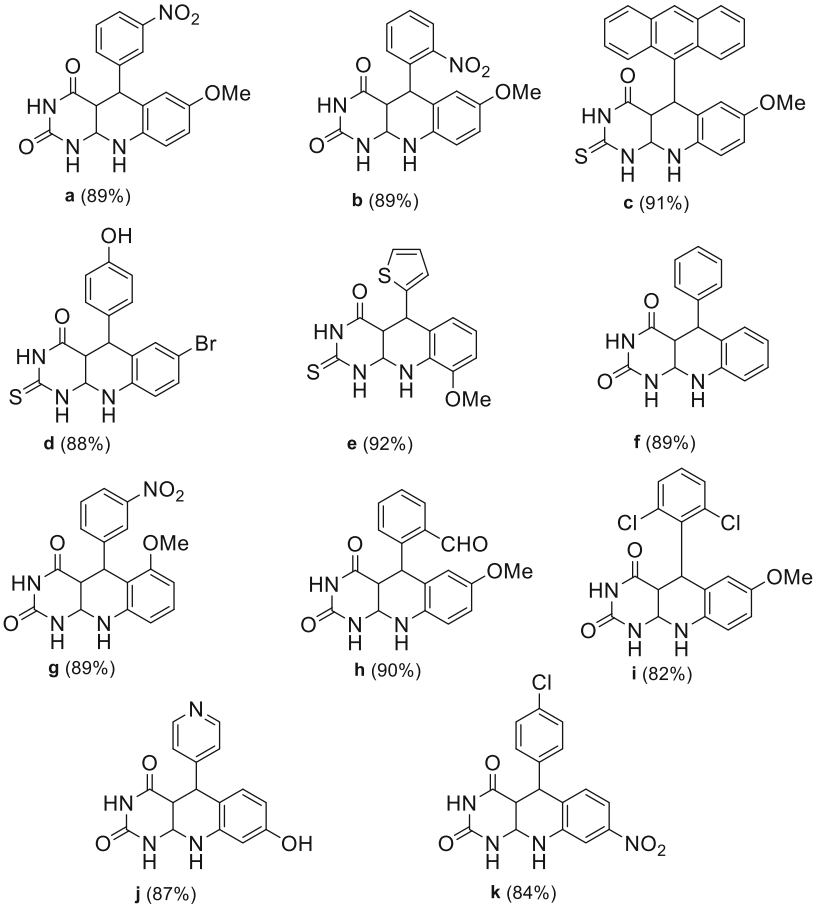
SCHEME 40 Synthesis of spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine **145a-d** from 2,6-diaminopyrimidin-4(3*H*)-one **143a-d** and isatin **144a**.



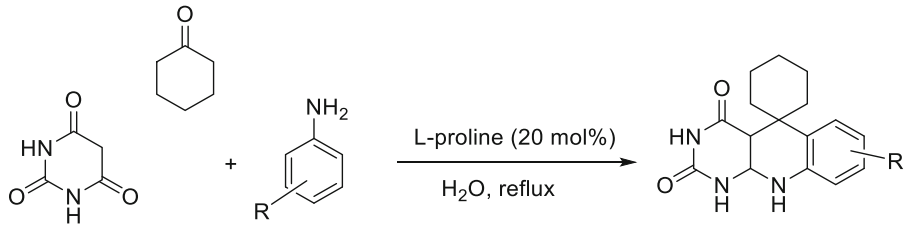
SCHEME 41 Synthesis of pyrimido[4,5-*b*]quinolones **148a-e** from the reaction of imino-phosphorane **146** and barbituric acid derivatives **147a-e**.

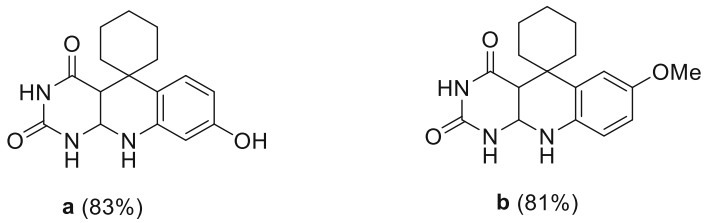
SCHEME 42 Synthesis of 5-arylpyrimido[4,5-*b*]quinoline **149a-k**.

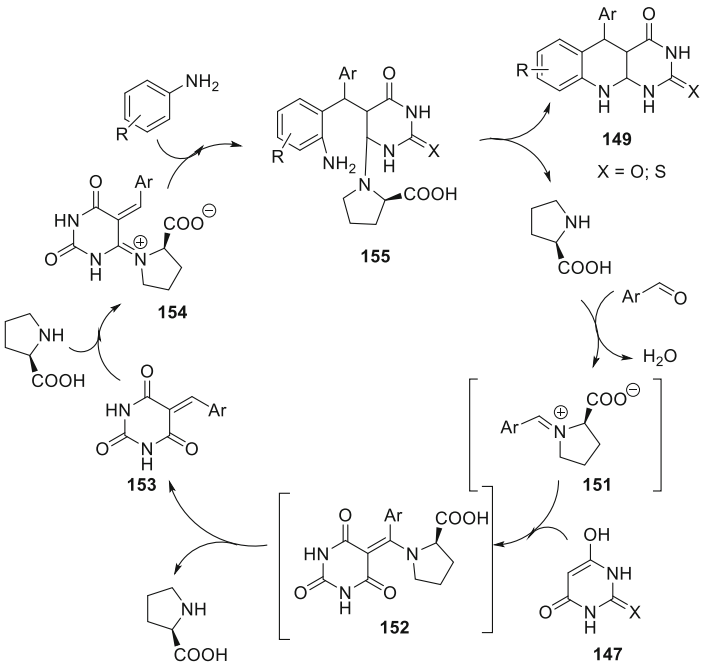




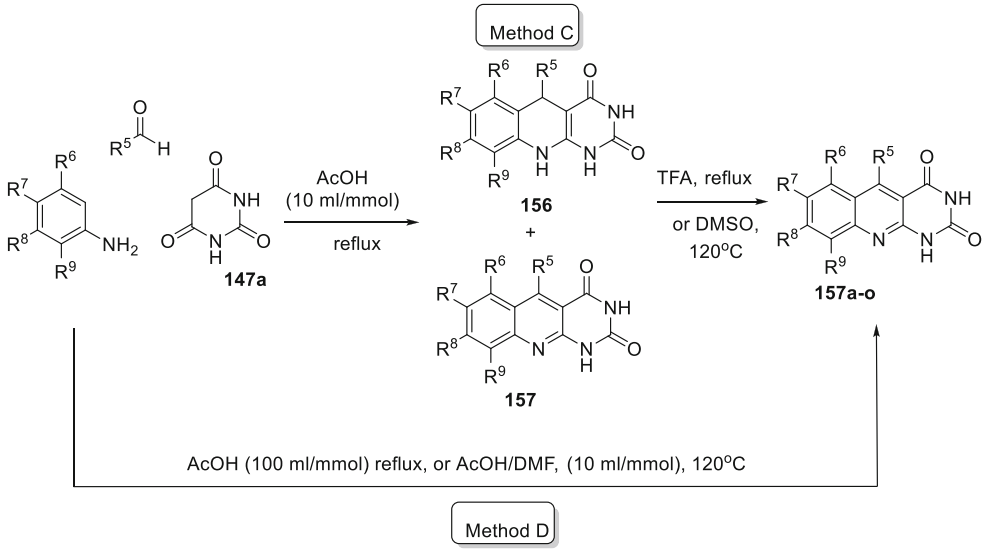
SCHEME 43 Spiro-pyrimido[4,5-*b*] quinoline-dione derivatives **150a,b**.







SCHEME 44 The proposed mechanism for the one-pot three-component synthesis of 5-aryl-pyrimido[4,5-*b*] quinolinediones **149a-k** using L-proline as a catalyst.



						Method C			Method D		
Product **160a-o**	R^5	R^6	R^7	R^8	R^9	Solvent 2nd step	Time (h)	Yield (%)	Solvent	Time	Yield (%)
a	H	H	O-CH_2-O		H	DMSO	4.5	44	AcOH	19	75
b	Me	H	O-CH_2-O		H	TFA	8	64	AcOH	4.5	44
c	3,4,5-MeOPh	H	O-CH_2-O		H	DMSO	4.5	90	AcOH	67	88
d	H	H	H	OMe	H	TFA	3	12	AcOH/DMF	2	70
e	Me	H	H	OMe	H	TFA	24	45	AcOH	24	77
f	H	H	H	Me	H	TFA	12	10	AcOH/DMF	2	56
g	H	H	H	NHAc	H	TFA	5	22	AcOH	7	70
h	H	H	H	OBn	H	-	-	-	AcOH/DMF	8	66
i	H	H	H	Cl	H	-	-	-	AcOH	100	50
j	H	H	H	CF_3	H	-	-	-	AcOH	1	51
k	H	H	Me	H	H	-	-	-	DMSO	72	45
l	H	H	H	H	H	-	-	-	AcOH	1	25
m	H	CH=CH-CH=CH		H	Me	-	-	-	AcOH	48	65
n	H	H	Me	Me	H	-	-	-	AcOH	12	54
o	H	OMe	OMe	OMe	H	-	-	-	AcOH	2	73

SCHEME 45 Synthesis of the substituted pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **157a-o**.

spiro-pyrimido[4,5-*b*]quinolinedione derivatives **150a,b** were synthesized in good yield (Schemes 42 and 43) [69].

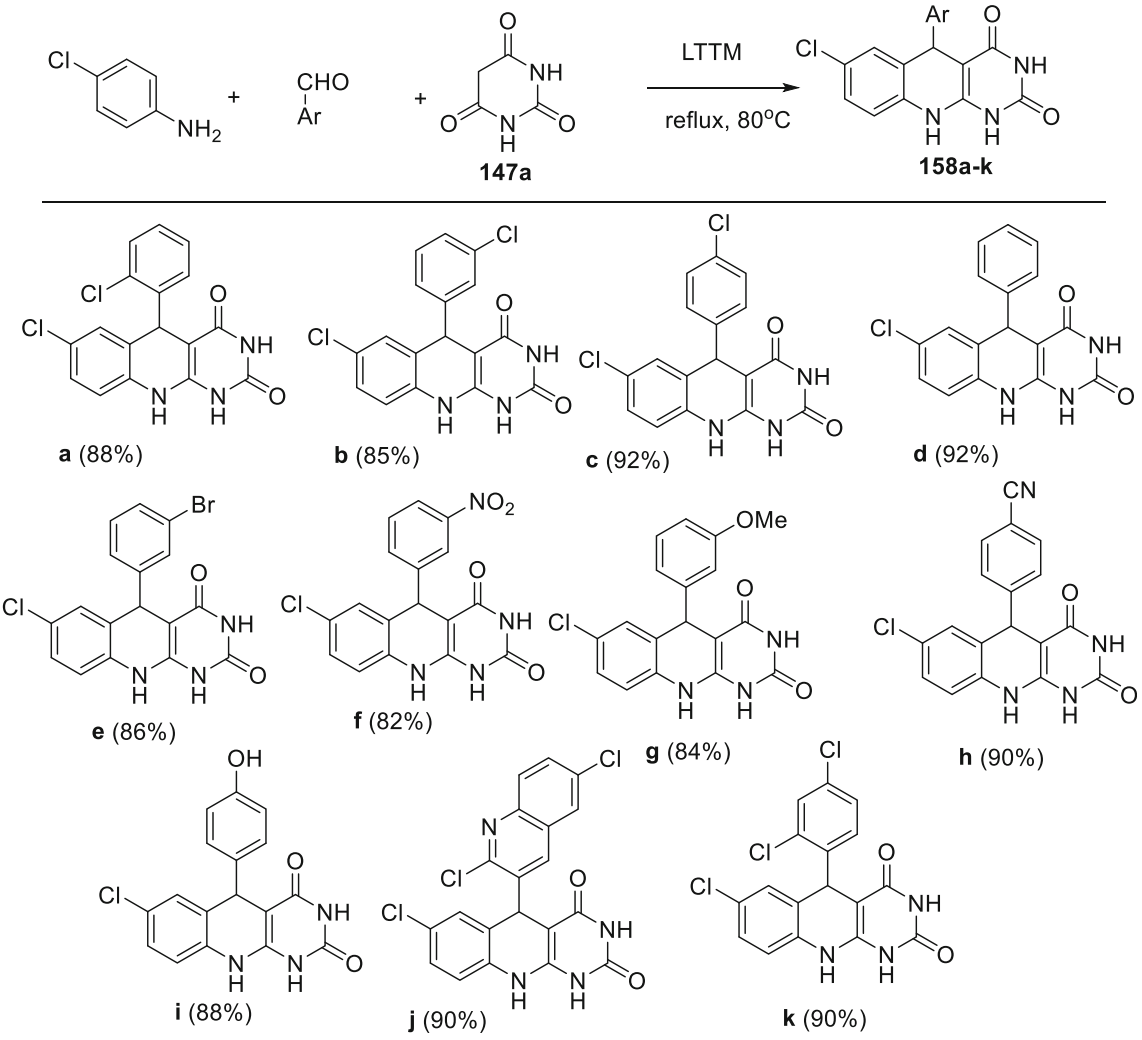
The proposed mechanism for forming 5-arylpyrimido [4,5-*b*]quinolines **149a-k** (Scheme 2). Activation of the aldehyde was achieved by L-proline. Simultaneously, L-proline as Brønsted acid/base assisted in the enolization of the barbituric acid. Barbituric acid in its enol form was reacted with adduct **151** to form intermediate **152**. Intermediate **152** lost the L-proline molecule to generate the barbiturate **153**. Contentiously, L-proline activated the adduct **153** to react with aniline, and the intermediates **154** and **155** were formed. Intramolecular cyclization intermediate **155** gave the desired product **149** (Scheme 44) [69].

Synthesis of pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **157a-o** consisted of refluxing in AcOH equimolecular amounts of an aniline, barbituric acid (**147**), and either formaldehyde, or aliphatic, or an aromatic aldehyde. The resulting mixtures of dihydroquinoline and quinoline **156**, or **157** were filtered, and the dihydropyrimidoquinoline **147** was oxidized to compound **157** on heating the mixture in DMSO or TFA (Method C) (Scheme 45) [12].

Mohir et al. reported a green protocol to synthesize pyrimidoquinolines **158a-k** via one-pot three-component condensation of 4-chloroaniline, aromatic aldehyde, and barbituric acid **147a** using oxalic acid dihydrate: proline as a low transition temperature mixtures (LTTM) yields 82–92% (Scheme 46) [70].

Synthesis of pyrimido[4,5-*b*]quinolines **99a-n** using ionic liquid catalyst formulated as $[H_2\text{-DABCO}][HSO_4]_2$, which was prepared from 1,4-diazabicyclo [2.2.2]octane (DABCO) and sulfuric acid (H_2SO_4) via three-component reaction between aldehydes, 1,3-diketone **91a,b**, and 6-amino-1,3-dimethyluracil **147b** in aqueous ethanol (Scheme 47) [71].

Mixing of an aniline, aldehydes (aromatic or heterocyclic), and (thio)barbituric acid **147a,c** in water and the

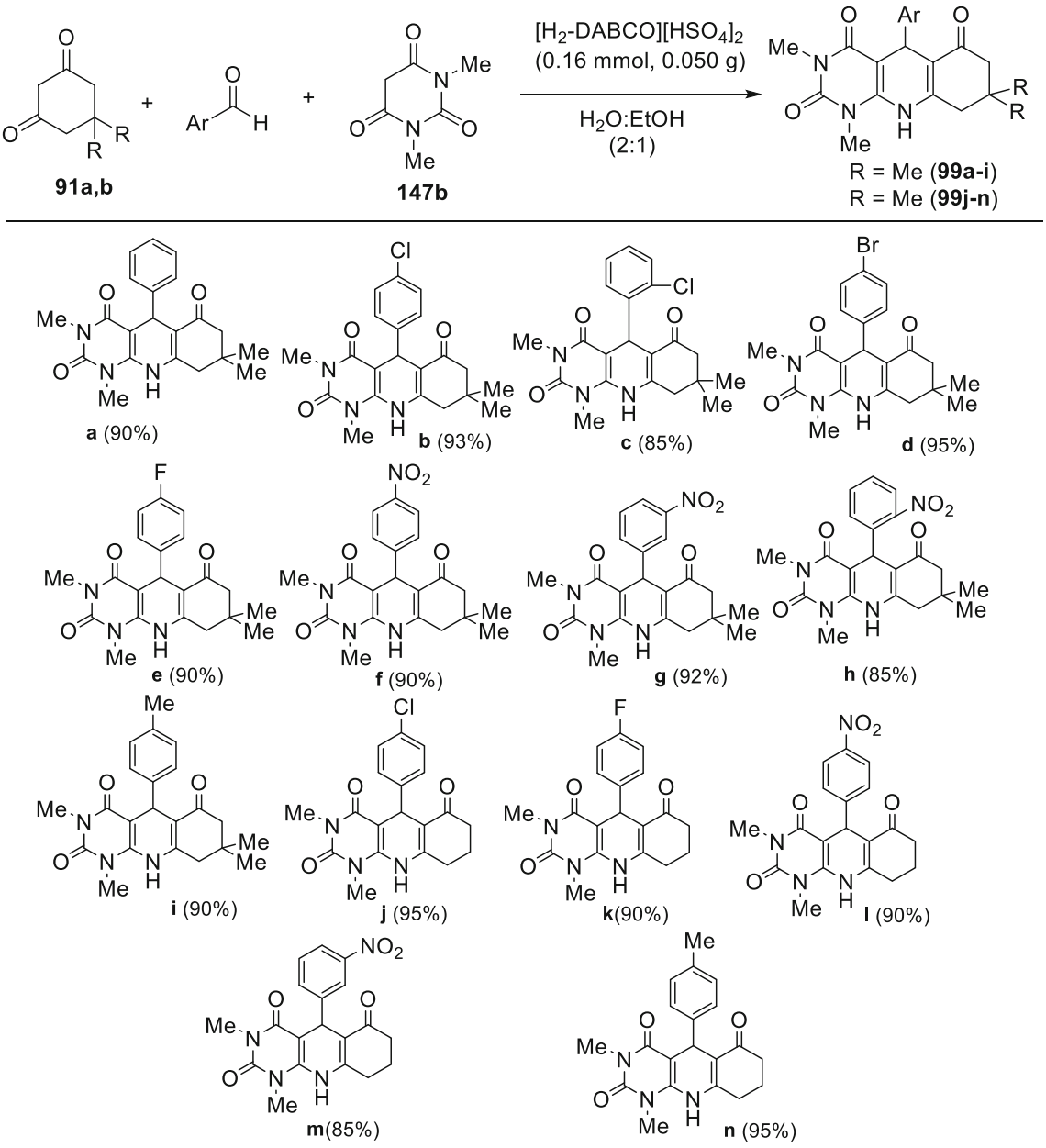


SCHEME 46 Oxalic acid dihydrate:proline (LTTM)-mediated synthesis of pyrimido[4,5-b]quinolinediones **158a-k**.

presence of a catalytic amount of DABCO afforded 5-arylpyrimido[4,5-*b*]quinoline-2,4-diones **159a–m** (Scheme 48). Then, the reaction was repeated with a small volume of water (2 mL), using microwave irradiation to decrease the reaction time and improve the yield of 5-arylpyrimido [4,5-*b*]quinoline-2,4-diones **159a-m**. The results were compared with conventional heating in the listed table. As observed, microwave heating yields were generally higher than those of conventional heating, and, importantly, reaction times were reduced from 12 h to 30 s (Scheme 48) [72].

The construction of pyrimido[4,5-*b*]quinolinediones **160a-o** was achieved via the three-component condensation reaction of aldehyde, aniline, and barbituric acid **147a**, which was catalyzed by a supramolecular catalyst *β*-cyclodextrin (*β*-CD) in aqueous media (Scheme 49). The proposed mechanism for synthesizing pyrimido [4,5-*b*]quinolinediones was mentioned below in Scheme 50 [73].

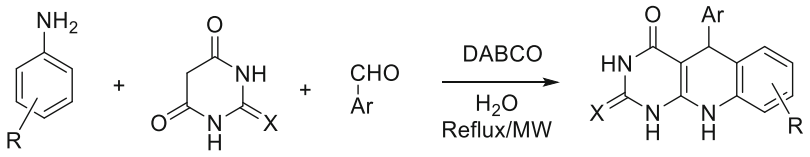
The postulated mechanism for forming pyrimidoquinolines **160a-o** was as depicted in Scheme 50. Firstly, *β*-cyclodextrin promoted the Michael-type addition of barbituric acid to aldehyde to give adducts **161** and **162,** respectively. Adduct **162** was reacted with amines to give intermediate 167, which was cyclized to intermediate **166**. Intermediate **166** lost a water



SCHEME 47 Ionic liquid catalyst formulated as $[H_2\text{-DABCO}][HSO_4]_2$ promoted the synthesis of pyrimido[4,5-*b*]quinolines **99a-n**.

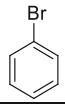
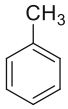
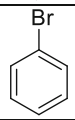
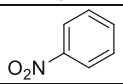
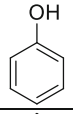
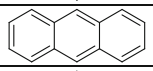
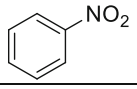
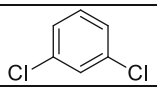
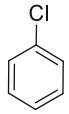
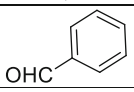
molecule by the ease of *β*-cyclodextrin to give the final product **160** (Scheme 50) [73].

Nongthombam et al. have reported a convenient synthetic protocol for pyrimido[4,5-*b*]quinoline-2,4-diones **165a-x** from aromatic amines, barbituric acid **147a,** and aryl aldehyde by the use of a catalyst-free irradiation from UV_{365} light source in the absence of a photocatalyst in water-glycerol solvent system. The free radical reaction

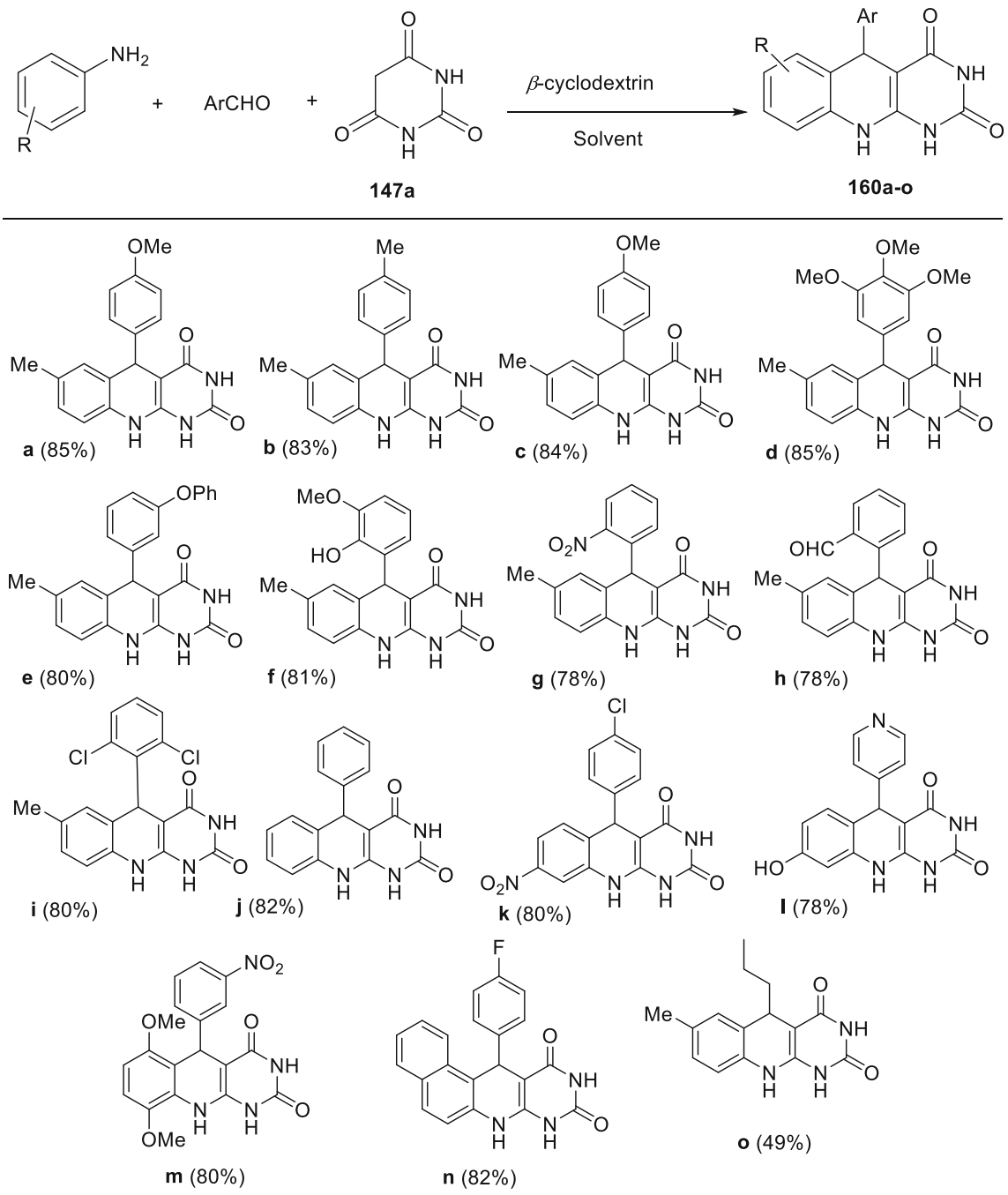


147a,c
X= **a**, O; **c**, S

159-m

Product **159**	R	Ar	X	Classical Heating		Microwave Irradiation	
				T (h)	Yield (%)	T (h)	Yield (%)
a	H		O	12	95	30	97
b	H		O	12	96	30	98
c	4-Me		O	12	96	30	97
d	4-OMe		O	12	85	30	94
e	4-Br		S	12	86	30	93
f	4-OMe		S	12	0	30	92
g	H		O	12	90	30	95
h	2,5-di-OMe		O	12	86	30	92
i	2-OMe		S	12	85	30	92
j	4-OMe		O	12	86	30	90
k	3-NO_2		O	12	83	30	91
l	3-OH		O	12	83	30	92
m	4-OMe		O	12	78	30	89

SCHEME 48 DABCO-catalyzed the multicomponent synthesis of 5-aryl-pyrimido[4,5-*b*]quinoline-2,4-diones **159a–m**.



SCHEME 49 Synthesis of pyrimido[4,5-*b*] quinolinediones **160a-o**.

mechanism for the synthetic pathway for compounds **165a** (Schemes 51 and 52) [74].

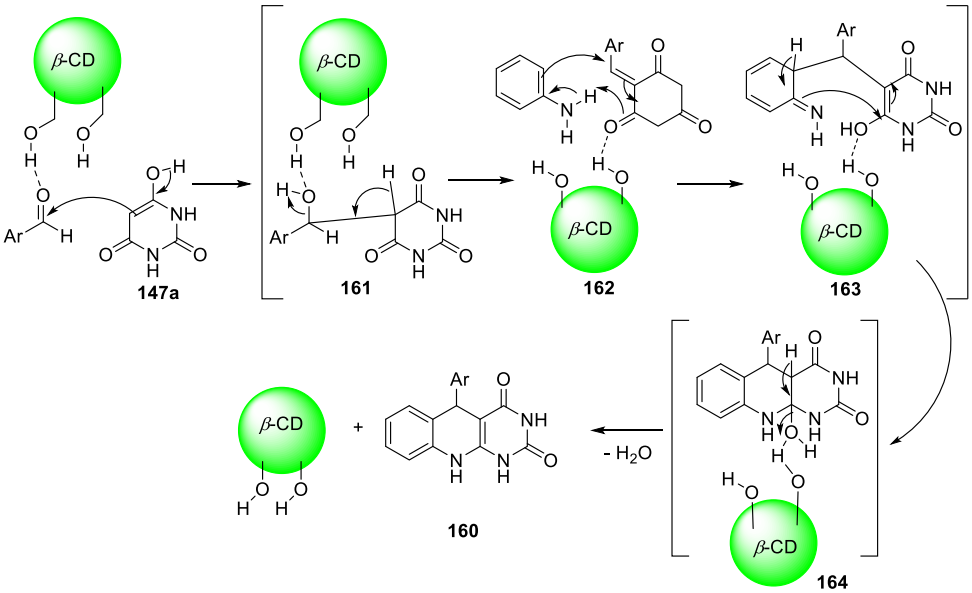
Three-component interaction between thiobarbituric acid (**147c**), aniline derivatives, and aryl aldehyde, using SPION@glutathione (10 mg) as catalyst under ultrasonicated for 15 min afforded pyrimido[4,5-*b*]quinoline derivatives **177a-g** (Scheme 53) [75].

A bifunctional nanomolecular catalyst L-Pro-Mn by grafting L-proline onto an Mn-Anderson-type POM (Polyoxometalate). It has been shown that L-Pro-Mn-Anderson can realize the one-pot alcohol oxidation/three-component reaction between aldehydes, arylamines, and barbituric acid **147a** to synthesize 5-aryl-pyrimido[4,5-b]quinolinediones **178a-k** (Scheme 54) [76].

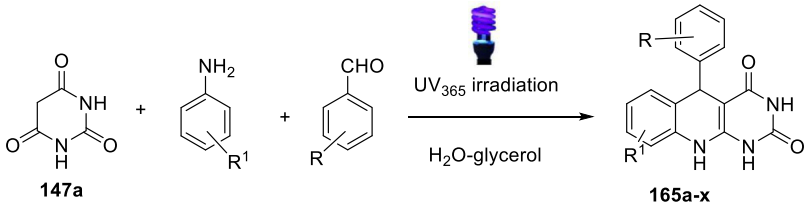
2.6 | Miscellaneous

The reaction of 5-aminothiazolo[3,2-*a*]pyrimidin-7-one **179**, aromatic aldehyde, and dimedone **91b** in ethylene glycol at 100°C, furnished thiazolo [2′,3′:2,3]pyrimido [4,5-*b*]quinoline **180a-s** (Scheme 55) [77].

SCHEME 50 Proposed mechanism for synthesizing pyrimido[4, 5-*b*]quinolinediones **160a-o**.

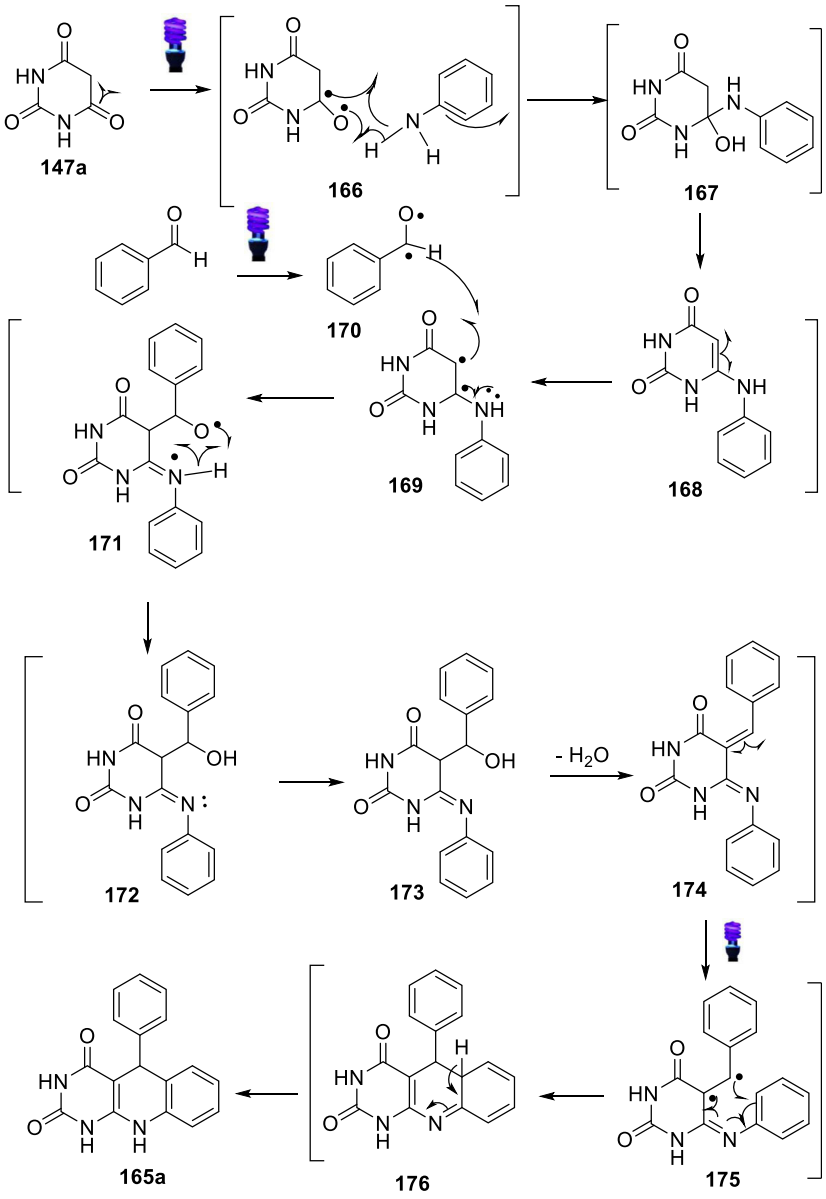


SCHEME 51 Synthesis of pyrimidoquinoline-2,4-diones **165a-x** catalyzed by UV_{365} light source.

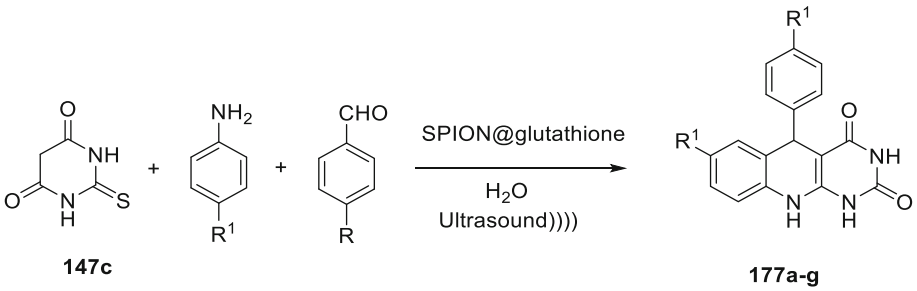


Entry	R	R^1	Time (min)	Yield (%)
a	H	H	60	98
b	4-F	H	60	95
c	3-Br	H	60	93
d	4-Br	H	60	94
e	4-NO_2	H	60	90
f	2-Cl	H	60	90
g	2-Cl	4-CH_3	90	87
h	H	4-OMe	60	97
i	4-CH_3	H	60	91
j	4-CH_3	4-CH_3	90	88
k	4-NO_2	4-OMe	60	95
l	3-Cl	4-CH_3	90	89
m	2-Cl	4-Cl	90	85
n	3-Br	4-CH_3	90	90
o	4-CH_3	4-OMe	60	93
p	4-Cl	4-CH_3	90	87
q	3-F	H	90	93
r	3-F	4-CH_3	90	91
s	4-F	4-OMe	60	96
t	4-NO_2	4-Br	90	91
u	4-F	4-CH_3	90	87
v	2-Cl	4-Br	90	88
w	3-Cl	H	60	85
x	4-Cl	H	60	93

Liu et al. have reported the synthesis of spiro[indoline-3110-pyrazolo[3,4-f]pyrimido[4,5-b]quinoline] derivatives **182a-r** from a one-pot three-component reaction between 1*H*-indazol-6-amine **181**, isatin derivatives **144** and barbituric acid **147a** or 2-thiobarbituric acid **147c**, in the presence of L-proline in refluxing EtOH (Scheme 56).



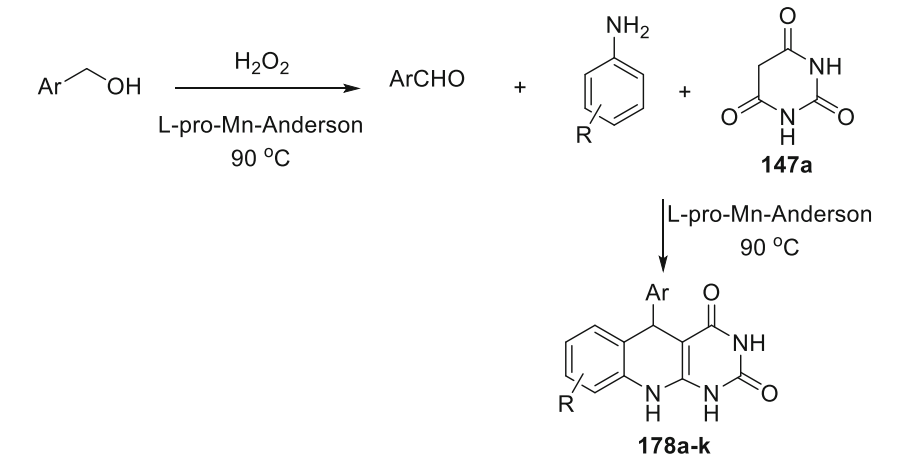
SCHEME 52 Proposed mechanism for UV_{365}-aided synthesis of **165a** via *a* free radical pathway.

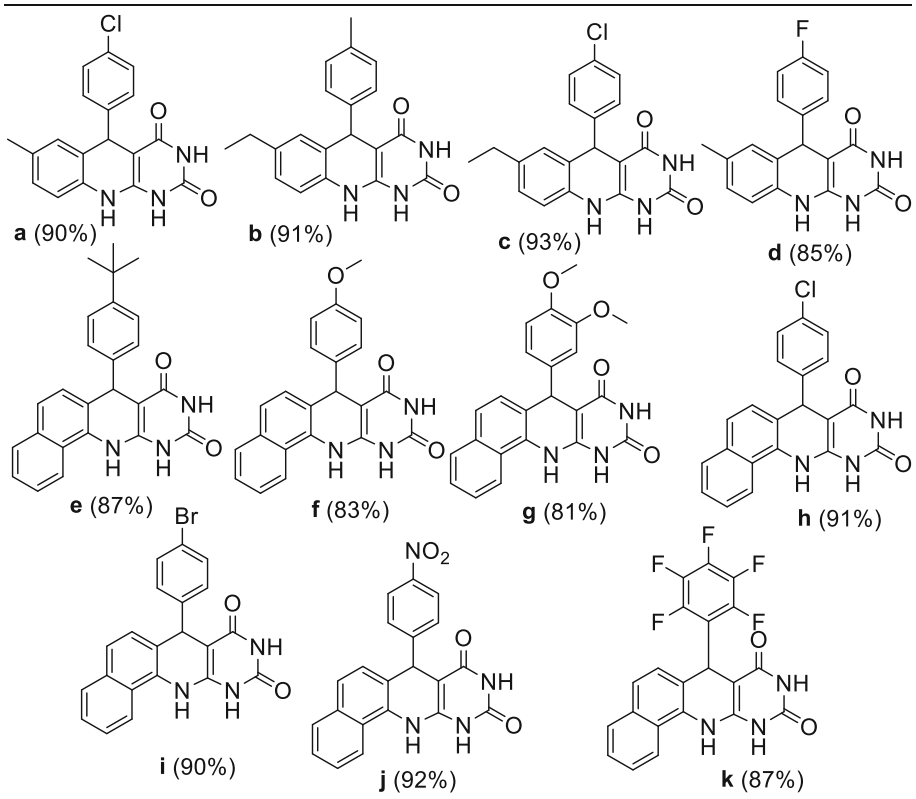


SCHEME 53 SPION@glutathione catalyzed the synthesis of pyrimidoquinoline derivatives **177a-g**.

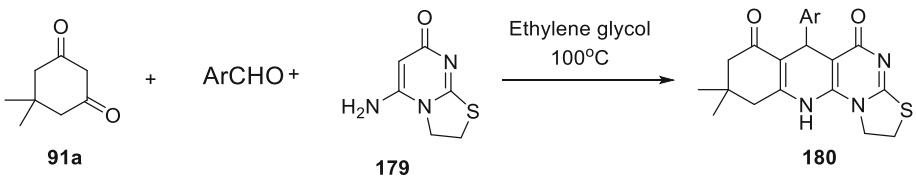
Product	R	R^1	Yield
a	H	H	97
b	NO_2	H	96
c	H	OMe	98
d	NO_2	OMe	98
e	H	Br	95
f	H	Cl	94
g	OH	H	92

SCHEME 54 Synthesis of 5-aryl-pyrimido[4,5-b]quinolinedione derivatives **178a-k**.



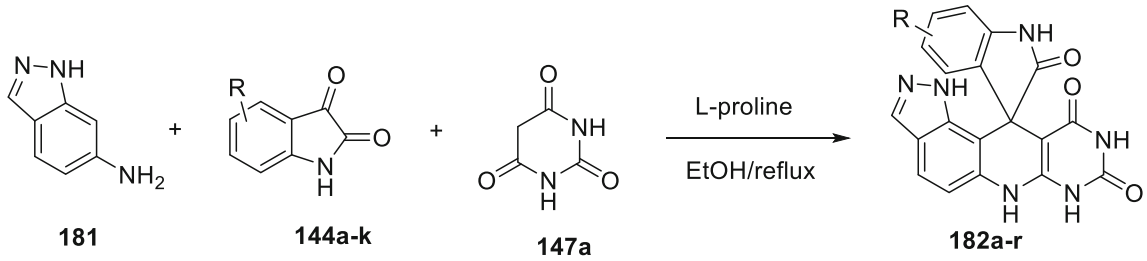


SCHEME 55 Synthesis of thiazolo[2′,3′:2,3]pyrimido[4,5-*b*]quinoline **179a-s**.



Ar = **a**, 4-NO_2-C_6H_4 (90%); **b**, 3-NO_2-C_6H_4 (93%); **c**, 3,4-diCl-C_6H_3 (82%); **d**, 2,3-$(OH)_2$-C_6H_3 (77%); **e**, 4-OH-C_6H_4 (90%); **f**, 2,4-diCl-C_6H_3 (85%); **g**, C_6H_5 (84%); **h**, 4-Cl-C_6H_4 (80%); **i**, 3-OH-C_6H_4 (84%); **j**, 5-Br-2-OH-C_6H_3 (87%); **k**, 4-Me-C_6H_4 (70%); **l**, 2-naphthyl (69%); **m**, 1-naphthyl (67%); **n**, 2-OH-C_6H_4 (74%); **o**, 4-OMe-C_6H_4 (81%); **p**, 3-OMe-C_6H_4 (78%); **q**, 3-Br-C_6H_4 (72%); **r**, 4-Pyridyl (89%); **s**, 2-thienyl (91%).

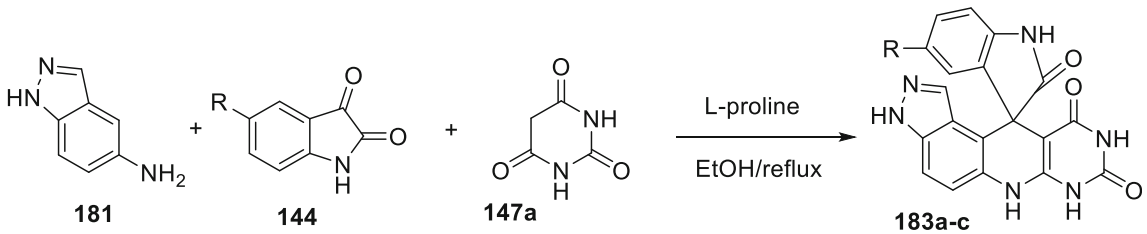
The authors have examined the effect of solvents and catalysts on the reaction time and the yield and found that the optimal reaction condition is to use L-proline as a catalyst and ethanol as the appropriate solvent. It was observed that the 4-chloro derivative of isatin exhibited no reaction. Also, the reaction was carried out using



144a-: R = **a**, H; **b**, 5-NO_2; **c**, Br; **d**, 5-Me; **e**, Cl; **f**, 5-Cl; **g**, 5-F; **h**, 5-OMe; **i**, 6-Br; **j**, 7-Cl; **k**, 7-F.

182a-r: X = O; [R = **a**, H (80%); **b**, 5-Cl (81%); **c**, 5-Br (81%), **d**, 5-F (87%); **e**, 5-Me (85%); **f**, 5-OMe (84%); **g**, 6-Br (87%); **h**, 7-Cl (89%); **i**, 7-F (84%)]
X = S; [R = **j**, H (88%); **k**, 5-Cl (89%); **l**, 5-Br (88%), **m**, 5-F (86%); **n**, 5-NO_2 (86%); **o**, 5-Me (85%); **p**, 5-OMe (85%); **q**, 6-Br (87%); **r**, 7-F (90%)]

SCHEME 56 Synthesis of spiro[indoline-3110-pyrazolo[3,4-f]pyrimido[4,5-b]quinoline] derivatives **182a-s**.



R = **a**, H;
c, Br;
e, Cl

a, R = H (80%);
b, R = Cl (81%);
c, R = Br (81%)

SCHEME 57 Synthesis of the isomeric spiro derivatives **183a-c**.

5-amino-1*H*-indazole instead of 6-amino-1*H*-indazol under the same conditions to react with isatin (R = H; Cl; Br) and barbituric acid to give the corresponding isomeric spiro compounds **183a-c** as shown in Scheme 57 [78].

3 | OUTLOOK

In our review, we presented the synthetic pathways of pyrimido[4,5-b]quinoline derivatives using a variety of organic compounds to be the synthons of the target compounds as well as different organic reagents and catalysts. The review also includes some mechanistic equations to explain the behavior of both reagents and catalysts.

Interestingly, most of the multi-component reactions do not take advantage of chiral catalysts (such as proline) targeting chiral, non-racemic pyrimido[4,5-b]quinoline.

ACKNOWLEDGMENT

Open Access funding enabled and organized by Projekt DEAL [Correction added on 20 July 2024, after first online publication: Projekt DEAL funding statement has been added.]

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: H. N. Tawfeek, T. H. A. Hasanin, S. Bräse, *J. Heterocycl. Chem.* **2024**, *61*(6), 971. https://doi.org/10.1002/jhet.4815