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Comprehensive methodologies for synthesizing tricyclic fused pyrimidoquinolines of biological relevance: a review

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Among quinoline-fused heterocycles, tricyclic pyrimidoquinoline nuclei have received considerable attention from synthetic chemists and medicinal and materials scientists over many years because they occur commonly in various biologically important natural products and potent drugs that exhibit anticancer, antibacterial, anti-inflammatory, antilipidemic, antioxidant and antimalarial activities. This study will be beneficial for medicinal chemists in the field of drug discovery to synthesize new fused tricyclic pyrimidoquinolines as potent therapeutic agents. This review provides a comprehensive compilation of the methodologies developed for the synthesis of all six known types of pyrimidoquinolines reported thus far. This article includes synthesis *via* solvent-free reactions, Vilsmeier–Haack reaction, Lewis and Brønsted acid catalysis, Pictet–Spengler reaction, the use of metal oxide nanoparticles as a green catalyst, multicomponent reactions (MCR), the use of L-proline as an environmentally friendly organocatalyst, aza-Wittig reaction, the use of β-cyclodextrin (β-CD) as a supramolecular catalyst, ultrasound irradiation, microwave-assisted reaction and ultraviolet light (UV_{365}) irradiation. To the best of our knowledge, this is the first review that focuses on the synthesis of all six types of pyrimidoquinolines along with mechanistic aspects. Some medicinal applications are also mentioned.

1. Introduction

Pyrimidine and its derivatives have been studied for over a century due to their chemical and biological significance. They occur widely in nature[1] as substituted and ring-fused compounds and derivatives, including nucleotides, alloxan and thiamine (vitamin B1). They are also found in many synthetic compounds, such as zidovudine and barbiturates. In medicinal chemistry, pyrimidines are well known for their therapeutic applications. One possible explanation for this activity is the presence of a pyrimidine base in uracil, cytosine, and thymine, which are essential binding blocks for nucleic acids, DNA, and RNA. The literature indicates that pyrimidines and heterocyclic annulated pyrimidines have a broad range of fascinating biological and pharmacological properties, such as antiproliferative,[2] antitumor,[3,4] antibacterial,[5] anti-inflammatory,[6] antimycobacterial,[7,8] antifungal,[9] anticancer,[10] sedative,[11] anti-HIV,[12,13] antimicrobial and antitubercular,[14] antimalarial,[15] antineoplastic,[16] and antibiotic[17,18] activities.

Quinoline derivatives are an important class of N-heteroaromatic compounds used in the development of new drugs. Many theoretical and experimental studies have shown that the quinoline ring system is an important structural unit widely found in natural products, pharmaceuticals, dyestuffs, materials, agrochemicals and synthetic analogues. Furthermore, many quinolines have been shown to have various useful pharmacological and biological activities, such as anti-leishmanial activity,[19] antifungal activity,[20,21] antidiabetic activity[22] anti-Alzheimer activity,[23] antiasthmatic activity,[24] antipsychotic activity,[25] antibiotic activity,[26] the presence of potent melaninconcentrating hormone 1 receptor (MCH1R) antagonists 1,[27–31] antiprotozoal activity,[32–37] the potential to treat lupus[38,39] and neurodegenerative diseases,[36] Src kinase inhibition activity,[40] and antihypertensive activity.[41]

In the last few decades, the chemistry of fused heterocycles has remained a promising area in organic synthesis owing to their abundance in various biologically important natural products and synthetic molecules with wide applications for various purposes, such as biological materials, potent drugs, chemosensors, agrochemicals and pharmaceuticals, polymers and ligands.[42–48] In particular, pyrimidine-fused quinoline derivatives are found in several drugs and bioactive natural products.[49,50] Hybrid molecules having a pyrimidine ring fused with quinoline, as shown in Fig. 1, are also known as 5-

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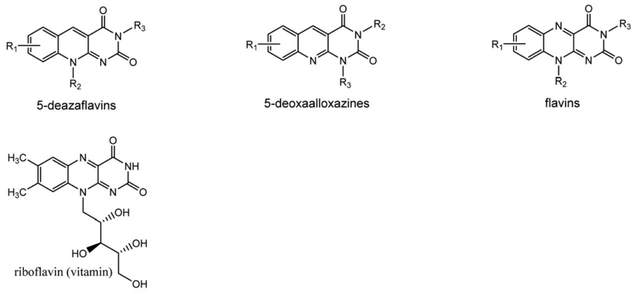


Fig. 1 Names and structures of representative-fused pyrimidoquinolines and their naturally available analogues.

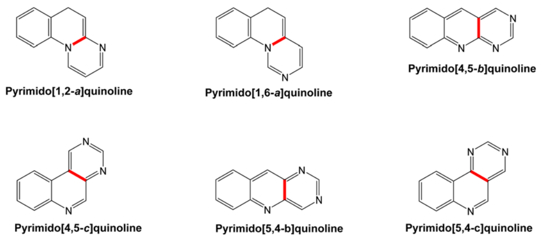


Fig. 2 Six most known types of pyrimidoquinolines ring system.

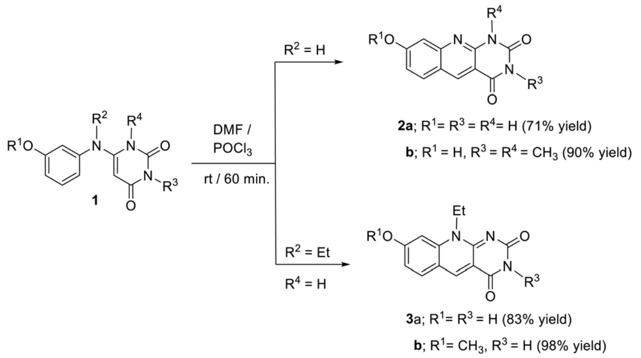
deazaisoalloxazines or deazaflavins. The N-5 analogues of these molecules are known as flavins and are available in the biomolecule riboflavin and flavin adenine dinucleotide (FAD). Considering their structural resemblance to flavins, they are very useful molecules in medicinal chemistry. The compounds with a pyrimidoquinoline core demonstrate several significant and therapeutically useful biological activities, such as antiallergic,[51,52] antifolate,[53] radioprotective,[54] antimitotic,[55] antioxidant,[56,57] antiproliferative,[58] anticancer,[59,60] antimicrobial,[61,62] antitumor,[63,64] antiviral,[65] analgesic[66] and antimalarial[67] activities. Given their tremendous applications, the design and development of new and efficient protocols for the synthesis of pyrimidoquinoline derivatives remains an important topic.

The six known types of pyrimidine fused to quinoline according to the sites of fusion at the quinoline substrate are pyrimido[1,2-*a*]quinoline, pyrimido[1,6-*a*]quinoline, pyrimido[4,5-*b*]quinoline, pyrimido[4,5-*c*]quinoline, pyrimido[5,4-*b*]quinoline and pyrimido[5,4-*c*]quinoline, as shown in Fig. 2. To the best of our knowledge, there is no review article about the synthetic procedures of the reported 6 types of pyrimidoquinoline derivatives, and only a few review articles highlighting the synthesis of pyrimido[5,4-*c*]quinolines and pyrimido-[4,5-*b*]quinoline have been published very recently.[68–72] Therefore, we here wish to report, for the first time, this review to present a comprehensive survey of the literature on the synthetic approaches employed for the synthesis of all 6 types of pyrimidoquinolines.

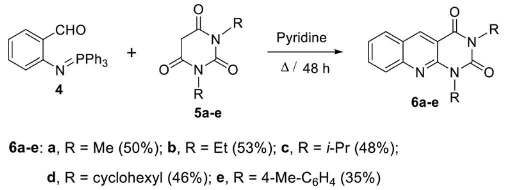
2. Synthesis of pyrimidoquinolines

2.1. Synthesis of pyrimido[4,5-*b*]quinolines

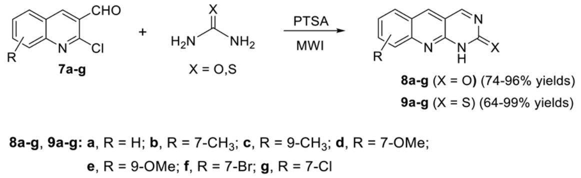
Pyrimido[4,5-*b*]quinolines are considered an important class of heterocyclic compounds because the pharmacological and biological properties displayed by these compounds mainly depend on the position and nature of substituents, and they also possess antiallergic,[52] antimicrobial,[73] anti-inflammatory[74] and antitumor[75] activities.



Scheme 1 Synthesis of 2,4-dioxopyrimido[4,5-*b*]quinolines **2a,b** and **3a,b** from 6-(arylamino)-uracil **1**.



Scheme 2 Synthesis of pyrimido[4,5-*b*]quinolines **6a–e** *via* the reaction of iminophosphorane **4** with *N*,*N*′-dialkylbarbituric acids **5a–e**.



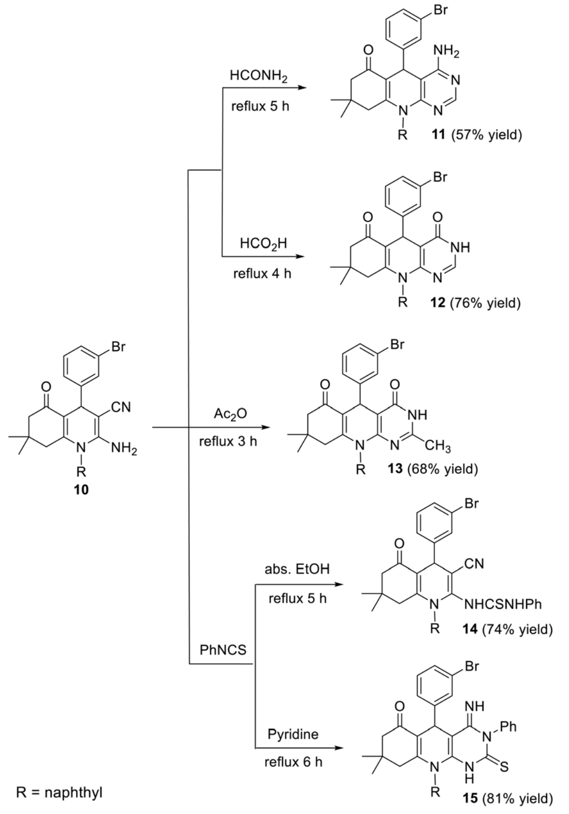
Scheme 3 Green method for the synthesis of 2-oxopyrimido[4,5-*b*]-**8a–g** and 2-thioxo-pyrimido[4,5-*b*]quinolines **9a–g** under microwave heating.

In 1982, Yamazaki and coworkers[76] developed an efficient synthesis of 2,4-dioxo-pyrimido[4,5-*b*]-quinolines **2,3** by Vilsmeier–Haack cyclization of 6-(arylamino)uracil **1**. The reactions were carried out by treating 6-(arylamino)uracil **1** with a mixture of dimethylformamide (DMF) and phosphorus oxychloride ($POCl_3$) at room temperature under an argon atmosphere for 60 min. The desired 2,4-dioxopyrimido[4,5-*b*]quinolines **2a,b** and **3a,b** were obtained in very good to excellent yields (Scheme 1).

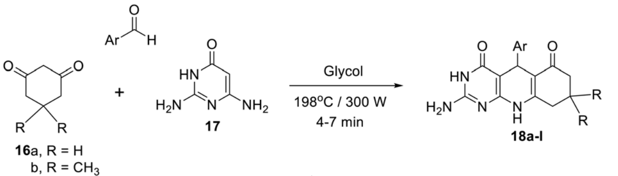
On heating iminophosphorane **4** with *N*,*N*′-dialkylbarbituric acids **5a–e** in pyridine under reflux for 48 h, pyrimido[4,5-*b*]quinoline derivatives **6a–e** were obtained in 35–53% yields (Scheme 2).[77]

Selvi *et al.*[61] developed eco-friendly, solvent free and microwave-induced techniques for the synthesis of a series of 2-oxopyrimido[4,5-*b*]- **8a–g** and 2-thioxopyrimido[4,5-*b*] quinolines **9a–g** as antibacterial and antifungal agents. The condensation of 2-chloro-3-formylquinolines **7a–g** with urea (or thiourea) in the presence of *p*-toluenesulfonic acid (PTSA) as a catalyst under microwave heating for 5 min. Afforded the required 2-oxopyrimido[4,5-*b*]- **8a–g** and 2-thioxo-pyrimido[4,5-*b*]quinolines **9a–g** in good to excellent yields (Scheme 3).

The synthesis of a new series of pyrimido[4,5-*b*]quinolines **11–15** was reported, starting from 2-amino-4-(3-bromophenyl)-7,7-dimethyl-1-(naphthalen-1-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**10**).[78] When compound **10** was heated with formamide at reflux temperature for 5 h, 4-amino-5-(3-bromophenyl)-8,8-dimethyl-10-(naphthalen-1-yl)-5,8,9,10-tetrahydropyrimido[4,5-*b*]quinolin-6(7*H*)-one (**11**) was obtained in 57% yield. Heating compound **10** with formic acid for 4 h caused intramolecular cyclization to give the corresponding 5-(3-bromophenyl)-8,8-dimethyl-10-(naphthalen-1-yl)-5,8,9,10-tetrahydro-pyrimido[4,5-*b*]quinoline-4,6(3*H*,7*H*)-dione (**12**) in 76% yield. When compound **10** was made to reflux with acetic anhydride for 3 h, the 5-(3-bromo-phenyl)-2,8,8-trimethyl-10-(naphthalen-1-yl)-5,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-4,6(3*H*,7*H*)-dione (**13**) was isolated in 68% yield. In addition, the behavior of **10** towards phenyl isothiocyanate under different conditions was investigated. Thus, the reaction of equimolar amounts of **10** and phenyl isothiocyanate in boiling absolute ethanol for 5 h afforded 1-(4-(3-bromophenyl)-3-cyano-7,7-dimethyl-1-(naphthalen-1-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinolin-2-yl)-3-phenylthiourea (**14**) in 74% yield. However, the reaction of **10** with phenyl isothiocyanate in absolute pyridine under reflux conditions for 6 h led to the formation of 5-(3-bromophenyl)-4-imino-8,8-dimethyl-10-(naphthalen-1-yl)-3-phenyl-2-thioxo-2,3,4,5,7,8,9,10-octahydropyrimido[4,5-*b*]quinolin-6(1*H*)-one (**15**) in 81% yield (Scheme 4).



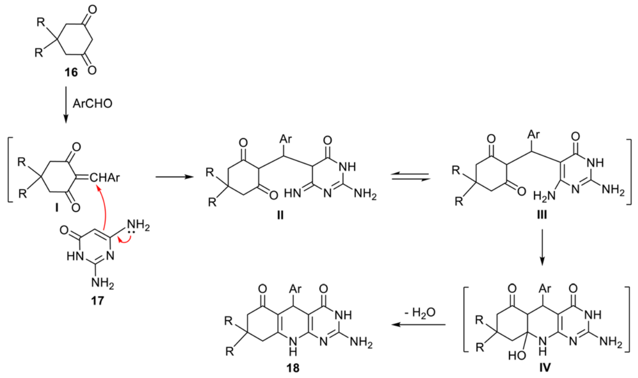
Scheme 4 Synthesis of new derivatives of tetrahydropyrimido[4,5-*b*]quinolines **11–15**.



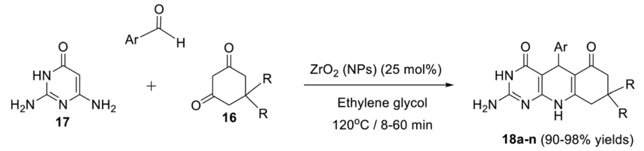
18	Ar	R	Yield (%)
a	4-Cl-C_6H_4	CH_3	95
b	2-Cl-C_6H_4	CH_3	91
c	4-NO_2-C_6H_4	CH_3	93
d	3-NO_2-C_6H_4	CH_3	92
e	3,4-$(OMe)_2$-C_6H_3	CH_3	95
f	3,4-OCH_2O-C_6H_3	CH_3	95
g	4-Cl-C_6H_4	H	92
h	3-NO_2-C_6H_4	H	92
i	4-NO_2-C_6H_4	H	94
j	4-Br-C_6H_4	H	91
k	4-OMe-C_6H_4	H	91
l	1,3-Cl_2-C_6H_3	H	90

Scheme 5 Microwave-assisted synthesis of 2-amino-5-aryl-8-substituted-5,8,9,10-tetrahydro-pyrimido[4,5-*b*]quinoline-4,6(3*H*,7*H*)-diones **18a–l**.

In 2005, a clean and expeditious microwave-mediated one-pot methodology for the synthesis of a new series of pyrimido[4,5-*b*]quinolines was reported by Tu and his coworkers.[79] A mixture of aromatic aldehyde, cyclic 1,3-dicarbonyl compound **16a,b** and 2,6-diamino-pyrimidin-4(3*H*)-one (**17**) in glycol was irradiated in a microwave at 198 °C (300 W) for 4–7 min to provide different linear 2-amino-5-aryl-8-substituted-5,8,9,10-tetrahydropyrimido[4,5-*b*]-quinoline-4,6(3*H*,7*H*)-diones **18a–l** (Scheme 5). The protocol in the absence of a catalyst has the advantage of short reaction time, excellent yield (90–95%) and an environmentally friendly technique. A plausible mechanism for the formation of **18** is given in Scheme 6. The reaction may

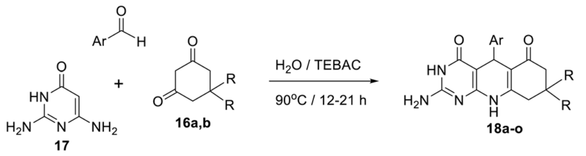


Scheme 6 Plausible mechanism for the formation of 2-amino-5-aryl-8-substituted-5,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-4,6(3*H*,7*H*)-diones **18a–l**.



18	R	Ar	Time (min)	Yield (%)
a	H	$4-O_2N-C_6H_4$	10	94
b	H	$2-O_2N-C_6H_4$	12	90
c	H	C_6H_5	9	94
d	H	$4-Cl-C_6H_4$	9	96
e	H	$2-Cl-C_6H_4$	10	93
f	H	$2,4-Cl_2C_6H_3$	8	96
g	H	$4-Br-C_6H_4$	8	96
h	H	$4-F-C_6H_4$	10	94
i	H	$4-Me-C_6H_4$	8	95
j	H	$4-MeO-C_6H_4$	8	98
k	H	$4-MeS-C_6H_4$	8	98
l	H	1-naphthlene-1-yl	9	96
m	CH_3	$4-F-C_6H_4$	35	95
n	CH_3	$3-O_2N-C_6H_4$	60	93

Scheme 7 Synthesis of 2-amino-5-aryl-pyrimido[4,5-*b*]quinolinediones **18a–n** *via* ZrO_2 (NPs) catalyzed reaction.



18	R	Ar	Yield %
a	H	$4-F-C_6H_4$	95
b	H	$4-HO-C_6H_4$	93
c	H	$3-NO_2-C_6H_4$	94
d	H	$4-NO_2-C_6H_4$	90
e	H	$4-Cl-C_6H_4$	92
f	H	$4-Br-C_6H_4$	86
g	CH_3	$4-Cl-C_6H_4$	95
h	CH_3	$4-OH-C_6H_4$	86
i	CH_3	$4-NO_2-C_6H_4$	86
j	CH_3	$3,4-(MeO)_2C_6H_3$	92
k	CH_3	$3,4-Cl_2-C_6H_3$	96
l	CH_3	$3-NO_2-C_6H_4$	94
m	CH_3	$4-Br-C_6H_4$	94
n	CH_3	$3,4-OCH_2OC_6H_3$	92
o	CH_3	pyridine-3-yl	88

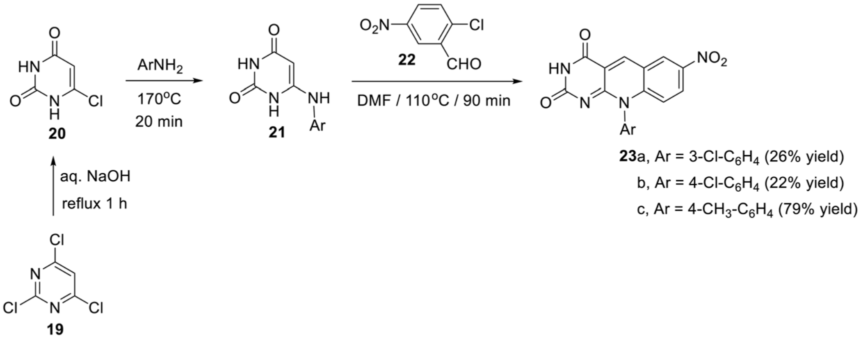
Scheme 8 Clean and one-pot synthesis of 2-amino-5-aryl-8,9-dihydropyrimidino[4,5-*b*]-quinoline-4,6-(1*H*, 3*H*, 5*H*, and 10*H*)-diones **18a–o**.

occur *via* a condensation, addition, cyclization, or elimination mechanism. The initial condensation between cyclic 1,3-dicarbonyl compound **16** and aldehyde afforded the corresponding 2-arylidene-5,5-dimethyl-1,3-cyclohexane-dione **I**. Then, Michael addition between **I** and 2,6-diaminopyrimidin-4-one **17** furnished the intermediate **II**, which isomerized to **III.** Intramolecular dehydration of **IV** yielded the desired tricyclic product **18.**

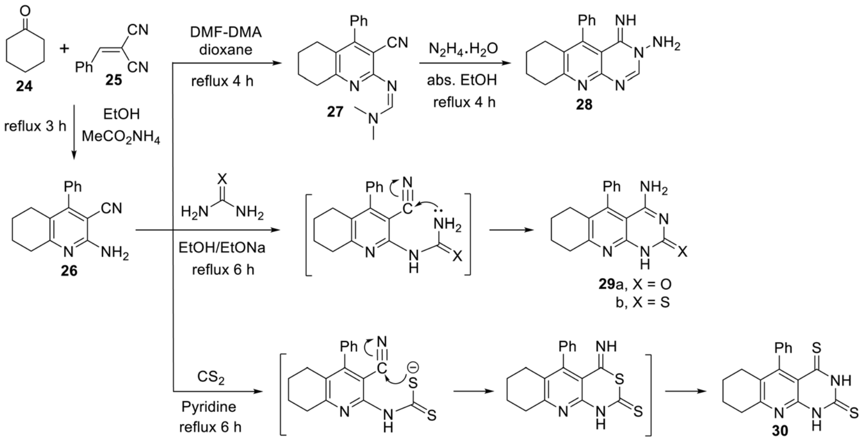
In 2017, Mamaghani *et al.*[80] described an ecofriendly and efficient multi-component reaction for the green synthesis of 2-amino-5-aryl-pyrimido[4,5-*b*]quinolinediones using metal oxide nanoparticles [ZrO_2 (NPs)] as a green catalyst. On heating equimolar amounts of 2,6-diamino-pyrimidin-4(1*H*)-one (**17**), aromatic aldehydes and 1,3-cyclohexane-dione or 5,5-dimethyl-1,3-cyclohexanedione (**16**) in the presence of ZrO_2 (NPs) (25 mol%) in ethylene glycol at 120 °C for 8–60 min, the desired 2-amino-5-aryl-pyrimido[4,5-*b*]quinoline-4,6(1*H*,5*H*,7*H*,10*H*)-diones **18a–n** were obtained in excellent yields (90–98%) (Scheme 7).

An efficient, clean, one-pot, three-component reaction of 2,6-diaminopyrimidin-4(3*H*)-one (**17**), aromatic aldehyde and 1,3-cyclohexanedione (**16a**) or 5,5-dimethyl-1,3-cyclo-hexanedione (**16b**) in water in the presence of triethylbenzylammonium chloride (TEBAC) as a catalyst under conventional heating conditions at 90 °C for 12–21 h produced the pyrimidine fused quinoline (PFQ), namely 2-amino-5-aryl-8,9-dihydropyrimidino [4,5-*b*]quinoline-4,6-(1*H*,3*H*,5*H*,10*H*)-diones **18a–o**, in high yields (Scheme 8). This new method has the advantages of mild reaction conditions, the use of inexpensive reagents, easy work-up, high yields, and environmentally friendly procedures.[81]

In 2007, Wilson *et al.*[82] described a short and efficient synthesis of 10-aryl-7-nitro-pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones **23a–c**. The starting 6-chlorouracil (**20**) was synthesized by heating 2,4,6-trichloropyrimidine (**19**) with a solution of sodium hydroxide under reflux for 1 h. The next stage involves a two-step convergent approach where 6-chloro-uracil (**20**) was fused at the melt temperature (170 °C for 20 min) with the appropriate arylamine, followed by heating the resulting 6-*N*-aryl-aminouracils **21** with 2-chloro-5-nitrobenzaldehyde (**22**) in DMF at 110 °C for 90 min to give 10-(3-chlorophenyl)-7-nitro-10*H*-pyrimido[4,5-*b*]-quinoline-2,4-dione (**23a**), 10-(4-chlorophenyl)-7-nitro-10*H*-pyrimido[4,5-*b*] quinoline-2,4-dione (**23b**) and 10-(4-methylphenyl)-7-nitro-10*H*-



Scheme 9 Efficient synthesis of 10-aryl-7-nitro-pyrimido[4,5-*b*]quinoline-2,4(3*H* and 10*H*)-diones **23a–c**.



Scheme 10 Facile synthesis of new 6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolines **28–30**.

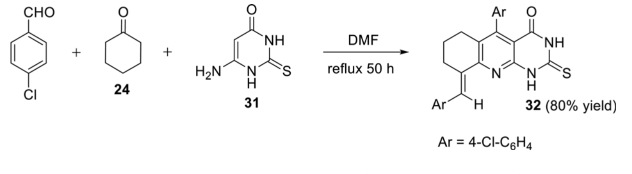
pyrimido-[4,5-*b*]quinoline-2,4-dione (**23c**) in 26%, 22% and 79% yields, respectively, in two steps (Scheme 9).

A facile synthesis of new 6,7,8,9-tetrahydropyrimido[4,5-*b*] quinoline derivatives **28–30**, a family of new pyrimido[4,5-*b*] quinolines with potential antifungal activity, was developed by Elkholy and Morsy in 2006.[83] Refluxing a solution of cyclohexanone (**24**) and 2-benzylidenemalononitrile (**25**) in absolute ethanol containing an excess of ammonium acetate for 3 h yielded the 2-amino-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**26**). Heating **26** with dimethylformamide dimethylacetal (DMF–DMA) in dioxane at reflux temperature for 4 h afforded 2-dimethylaminomethelenimino-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**27**). Reacting **27** with hydrazine hydrate in refluxing absolute ethanol for 4 h produced 3-amino-4(3*H*)-imino-5-phenyl-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline (**28**). The reactivity of compound **26** towards urea, thiourea and carbon disulfide was also investigated. Thus, heating a mixture of **26** with urea (or thiourea) and sodium ethoxide in absolute EtOH at reflux temperature for 6 h gave 4-amino-5-phenyl-6,7,8,9-tetrahydro-pyrimido[4,5-*b*]quinoline-2(1*H*)-one/thione derivatives **29a,b.** However, reacting **26** with carbon disulphide in dry pyridine under reflux conditions for 6 h afforded the corresponding 5-phenyl-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dithione (**30**) (Scheme 10). The yields of the products were not reported.

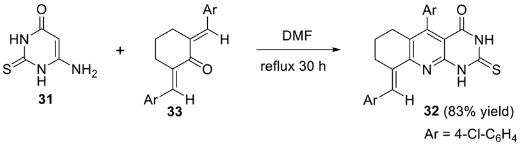
A one-pot synthesis of 5-(4-chlorophenyl)-9-(4-chlorophenylmethylene)-2-thioxo-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4-one (**32**) was reported by El-Gazzar *et al.* in 2009.[84] This synthetic approach proceeded by heating a mixture of 4-chlorobenzaldehyde, cyclohexanone (**24**) and 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**31**) in DMF at reflux temperature for 50 h to give **32** in 80% yield (Scheme 11). In the same year, they developed a new synthetic strategy for the preparation of **32** by refluxing a solution of 6-aminothiouracil (**31**) and α,β-unsaturated ketone **33** in DMF for 30 h. The respective tricyclic **32** was obtained in 83% yield (Scheme 12).[85]

Dow *et al.* described a general synthetic route for the synthesis of pyrimido[4,5-*b*]quinolin-4(3*H*)-ones **36a–e** and **38a,b**, which are potent and selective inhibitors of the tyrosine-specific kinase activity associated with pp6Oc-src.[86] The reactions were performed in three steps, starting with *o*-nitrobenzaldehyde **34.** First, condensation of *o*-nitrobenzaldehyde **34** with ethyl cyanoacetate or cyanoacetamide under basic conditions was followed by reductive cyclization, which gave the corresponding 2-aminoqninolines **35a,b.** Reaction of ethyl 2-amino-quinoline-3-carboxylates **35a** with carboxamides at elevated temperatures; alternatively, treatment of carboxamides **35b** with an ortho ester in the presence of an acid catalyst provided fully-aromatized tricyclic pyrimido[4,5-*b*]quinolin-4(3*H*)-ones **36a–e.** Synthesis of the corresponding *N*-3 functionalized analogs was performed by the condensation of **35a** with dimethylformamide dimethylacetal (MDF–DMA) to give the corresponding ethyl 2-(((dimethylamino)methylene)amino) quinoline-3-carboxylate **37.** When compound **37** was reacted with the appropriate amine, it underwent intramolecular cyclization to give *N*-3 substituted pyrimido[4,5-*b*]quinoline-4-ones **38a,b** (Scheme 13). The yields of the products were not reported.

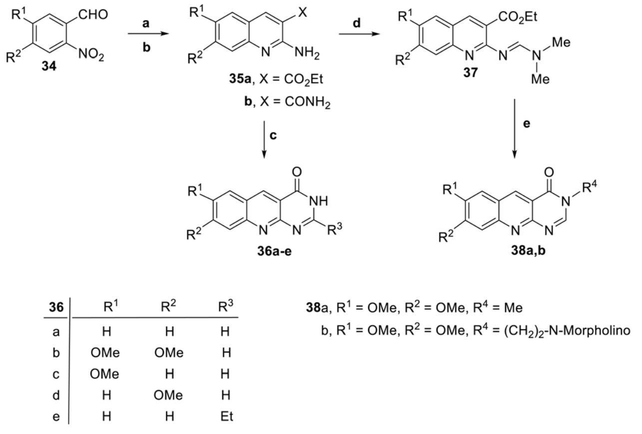
In 2008, El-Gazzar and his coworkers[66] developed a new approach for the synthesis of a novel series of pyrimido[4,5-*b*]



Scheme 11 One-pot synthesis of 5-(4-chlorophenyl)-9-(4-chlorophenyl-methylene)-2-thioxo-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4-one (**32**).



Scheme 12 New synthetic strategy for the synthesis of 9-(4-chlorobenzylidene)-5-(4-chloro-phenyl)-2-thioxo-2,3,6,7,8,9-hexahydropyrimido[4,5-*b*]quinolin-4(1*H*)-one (**32**).



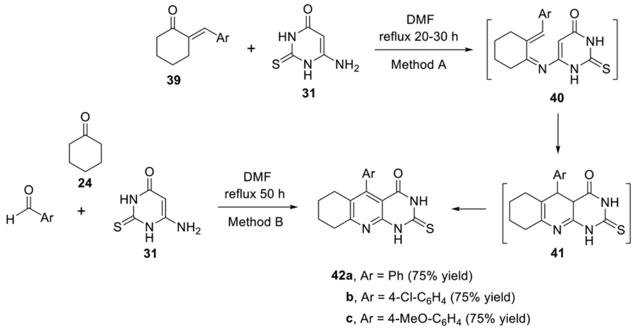
36	R^1	R^2	R^3
a	H	H	H
b	OMe	OMe	H
c	OMe	H	H
d	H	OMe	H
e	H	H	Et

38a, R^1 = OMe, R^2 = OMe, R^4 = Me
b, R^1 = OMe, R^2 = OMe, R^4 = $(CH_2)_2$-N-Morpholino

Scheme 13 General synthetic route for the synthesis of 5,10-dihydropyrimido[4,5-*b*]quinolin-4(3*H*)-ones **36a–e** and **38a,b**. Reagents and reaction conditions: (a) $CNCH_2CO_2Et$ or $CNCH_2CONH_2$/piperdine/EtOH, reflux; (b) zinc or iron dust AcOH/reflux; (c) R^3-$CONH_2$/over 150 °C or R^3-$CH(OEt)_3$/PTSA/reflux; (d) $(MeO)_2CHNMe_2$/PTSA/toluene/reflux; (e) R^4-NH_2/EtOH/reflux.

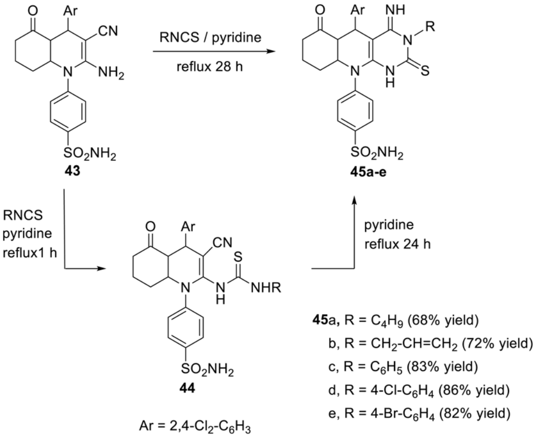
quinolines **42a–c** in good yields. The reaction was accomplished by heating a mixture of arylidene cyclohexanone **39** and 6-amino-thiouracil **31** in DMF under reflux for 20–30 h to give 5-aryl-2-thioxo-2,3,6,7,8,9-hexahydro-1*H*,4*H*-pyrimido-[4,5-*b*]quinoline-4-ones **42a–c** *via* intermediacies **40** and **41** (Method A). Alternatively, compound **42** could also be obtained by a one-pot synthesis by refluxing a solution of 6-aminothiouracil (**31**), cyclohexanone (**24**) and aromatic aldehydes in DMF for 50 h (Method B) (Scheme 14).

In 2010, Alqasoumi and his workers[63] investigated the reaction of 2-amino-quinoline-3-carbonitrile derivatives **43**, bearing biologically active sulfonamide with isothiocyanates, and they found that the type of products depends on the reaction conditions. Thus, the nucleophilic reaction of compound **43** on the highly positive carbon of the isothiocyanates (RNCS) in dry pyridine under reflux conditions for 1 h afforded the corresponding thioureido derivatives **44** (Scheme 15), while a 28 h reaction time gave the novel tricyclic system pyrimido[4,5-*b*]quinoline derivatives **45a–e** in one step. Alternatively, compound **45** could also be obtained by boiling compound **44** in dry pyridine for 24 h (Scheme 15). Product **45** exhibited higher activity with IC50 values (5.5, 6.9, and 7 mg ml^{-1}) when compared with doxorubicin as a reference drug (IC50 value of 38 mg ml^{-1}).



42a, Ar = Ph (75% yield)
b, Ar = 4-Cl-C_6H_4 (75% yield)
c, Ar = 4-MeO-C_6H_4 (75% yield)

Scheme 14 Synthesis of a novel series of pyrimido[4,5-*b*]quinolines 42a–c.

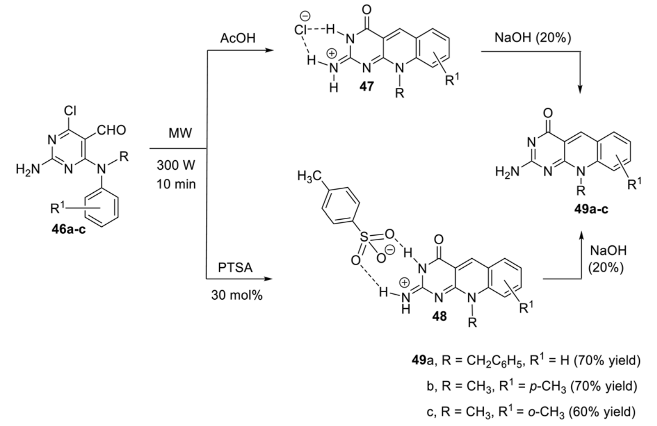


45a, R = C_4H_9 (68% yield)
b, R = CH_2-CH=CH_2 (72% yield)
c, R = C_6H_5 (83% yield)
d, R = 4-Cl-C_6H_4 (86% yield)
e, R = 4-Br-C_6H_4 (82% yield)

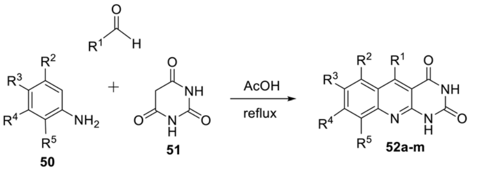
Scheme 15 Synthesis of novel pyrimido[4,5-*b*]quinoline derivatives 45a–e.

An efficient microwave-assisted synthesis of a series of pyrimido[4,5-*b*]quinolines **49a–c**, flavin analogues, *via* intramolecular cyclization of 2,4-diamino-6-chloro-pyrimidine-5-carbaldehydes **46a–c**, was reported by Trilleras *et al.*[87] When 2,4-diamino-6-chloro-pyrimidine-5-carbaldehydes **47a–c** were heated with an excess of acetic acid under microwave irradiation (maximum power 300 W for 10 min at a controlled temperature of 300 °C) using a focused microwave reactor, they underwent intramolecular cyclo-condensation to furnish the 4-oxo-4,10-dihydropyrimido[4,5-*b*]quinolin-2(3*H*)-iminium chlorides **47**. To avoid substituting the chloro atom to maintain the possibility of adding molecular diversity and complexity to the molecule, the same reaction was carried out using an excess of 4-toluenesulfonic acid (PTSA). Thus, compounds **46a–c** (1 mmol) were reacted with an excess of PTSA monohydrate (1.3 mmol) under the same conditions described above. Reaction products were characterized from the spectroscopic data and X-ray analysis as 1 : 1 salt 2-amino-pyrimido[4,5-*b*]quinolin-4(10*H*)-one:PTSA **48**. The treatment of salts **47** and **48** with aqueous NaOH (20%) was carried out to directly give the neutral tricyclic ring system 2-amino-pyrimido[4,5-*b*]quinolin-4(10*H*)-one derivatives **49a–c** in good yields (Scheme 16).

A new synthetic approach to polyfunctionally substituted pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **52** *via* a three-component one-pot reaction of aromatic amines **50**, barbituric acid (**51**) and aromatic aldehydes is reported.[88] The use of commercially available aniline derivatives allowed the facile syntheses of pyrimido[4,5-*b*]quinolinediones **52** to be substituted in all the positions on the benzene ring with electron donor or electron withdrawing groups. On heating an equimolar mixture of aniline **50**, compound **51** and aromatic aldehydes in AcOH at reflux temperature, a wide range of the desired tricyclic pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **52a–m** were obtained in 25–77% yields (Scheme 17).

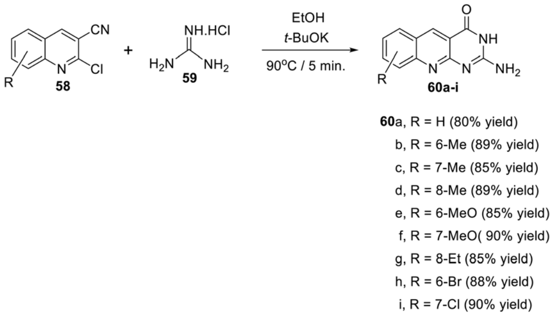


Scheme 16 Efficient microwave-assisted synthesis of a series of 2-amino-pyrimido[4,5-*b*]-quinolin-4(10*H*)-ones **49a–c**.



52	R¹	R²	R³	R⁴	R⁵	Time (h)	Yield (%)
a	H	H	O-CH$_2$-O		H	19	75
b	Me	H	O-CH$_2$-O		H	4.5	44
c	H	H	H	OMe	H	2	70
d	Me	H	H	OMe	H	24	77
e	H	H	H	Me	H	2	56
f	H	H	H	NHAc	H	7	70
g	H	H	H	OBn	H	8	66
h	H	H	H	Cl	H	100	50
i	H	H	H	CF$_3$	H	1	51
j	H	H	Me	H	H	72	45
k	H	H	H	H	H	1	25
l	H	H	Me	Me	H	12	54
m	H	OMe	OMe	OMe	H	2	73

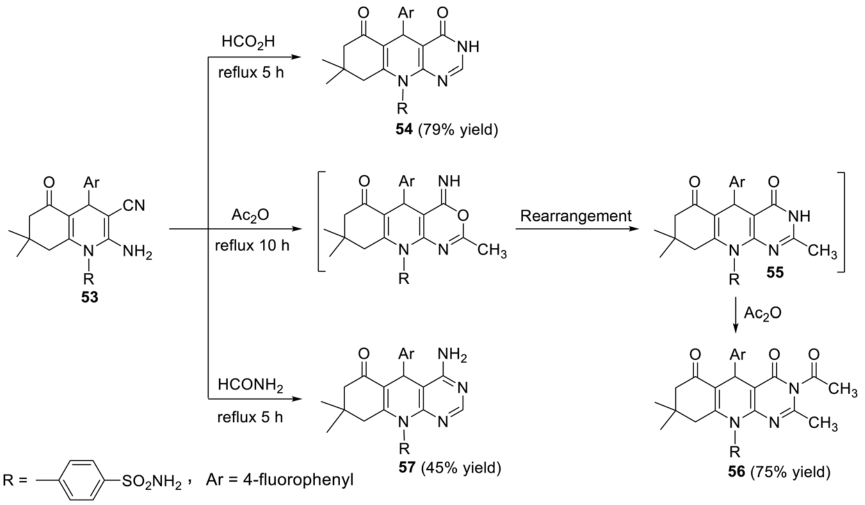
Scheme 17 One-pot procedure for the synthesis of polyfunctionally substituted pyrimido-[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **52a–m**.



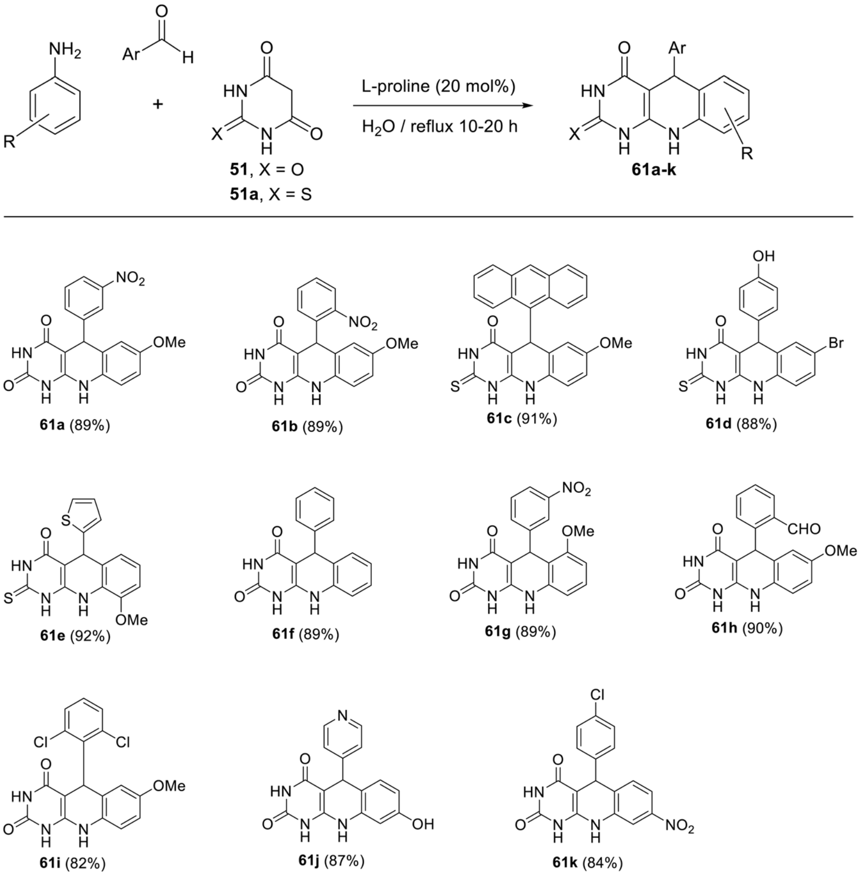
Scheme 19 Simple and rapid synthesis of 2-amino-3*H*-pyrimido[4,5-*b*]quinolin-4(3*H*)-ones **60a–i**.

Ghorab *et al.*[89] reported the synthesis of new pyrimido[4,5-*b*]quinoline derivatives **54**, **56**, **57** using 4-(2-amino-3-cyano-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)benzenesulfonamide (**53**) as the starting material. Refluxing a solution of **53** in formic acid for 5 h furnished 4-(5-(4-fluorophenyl)-8,8-dimethyl-4,6-dioxo-3,4,6,7,8,9-hexahydropyrimido[4,5-*b*]quinolin-10(5*H*)-yl)benzenesulfonamide (**54**) in 79% yield. However, heating **53** with acetic anhydride and formamide at reflux temperature gave the new fused pyrimido[4,5-*b*]quinolines **56** (*via* the intermediacy of **55**) and **57** in 75% and 45% yields, respectively (Scheme 18). The products showed significant anticancer activity.

In 2011, Chandra and his coworkers[90] developed a simple and rapid synthesis of 2-amino-3*H*-pyrimido[4,5-*b*]quinolin-4(3*H*)-ones **60a–i** *via t*-BuOK-catalyzed cyclization of 2-chloroquinoline-3-carbonitriles **58** with guanidine hydrochloride (**59**) in a very short reaction time in good yields. On heating 2-chloroquinoline-3-carbonitriles **58** (1 equiv.) with guanidine hydrochloride (**59**) (1 equiv.) in the presence of *t*-BuOK (0.5 equiv.) in EtOH at 90 °C for 5 min, the cyclized products **60a–i** were obtained in 80–90% yields (Scheme 19). The electron-donating and -withdrawing substituents at the benzene ring of the quinoline moiety show better yields of the cyclized products.



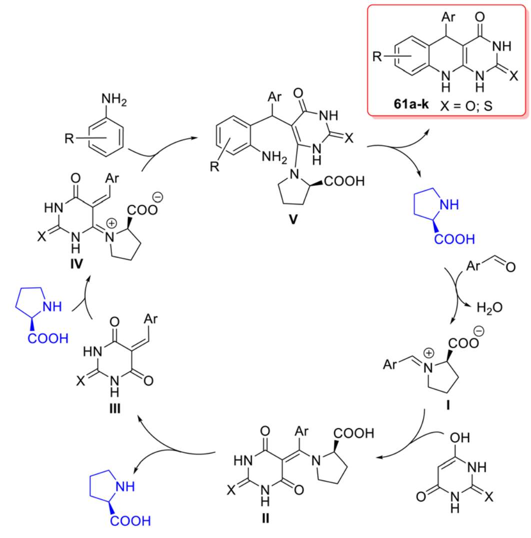
Scheme 18 Synthesis of new pyrimido[4,5-*b*]quinoline derivatives **54**, **56**, and **57**.



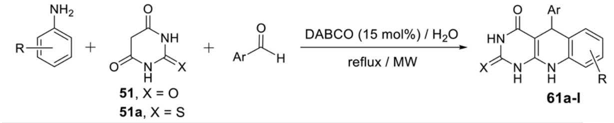
Scheme 20 Green, convenient and efficient synthesis of 5-aryl-pyrimido[4,5-*b*]quinoline-diones **61a–k**.

A green, convenient and efficient procedure for the regioselective synthesis of 5-aryl-pyrimido-[4,5-*b*]quinoline-diones **61a–k** using the three-component coupling reaction involving aromatic amines, aldehydes, and barbituric acids **52a,b** was reported by Khalafi-Nezhad *et al.* in 2012.[91] This protocol was accomplished efficiently using L-proline, an environmentally friendly organocatalyst, in an aqueous medium to produce the desired tricyclic products in high yields. The MCRs showed good regioselectivity, and computational studies were used to investigate selectivity. Thus, when a mixture of aromatic amines, barbituric acid (**51**) or thiobarbituric acid (**51a**), aromatic aldehydes and L-proline (20 mol%), as catalysts, in refluxing H_2O was stirred for 10–20 h, the 5-aryl-pyrimido[4,5-*b*] quinolines **61a–k** were obtained in high yields (82–92%) (Scheme 20). As is clearly shown in Scheme 20, this multicomponent route can be used for both aromatic aldehydes with electron-donating and electron-withdrawing groups. Similarly, heterocyclic aldehydes can be used under optimized conditions. Furthermore, a wide range of aromatic amines were applied successfully in this reaction with excellent results.

The proposed mechanism to explain the formation of **61** is shown in Scheme 21. First, the aldehyde is activated by L-proline. Simultaneously, L-proline acts as a Brønsted acid/base, assisting the enolization of barbituric acids **51**, which is subsequently reacted with adduct **I** to generate intermediate **II**. Intermediate **II** can lose one molecule of L-proline, so barbiturate **III**, as an unsaturated carbonyl compound, is formed. However, L-proline can activate adduct **III** to produce intermediate **IV**, which undergoes a reaction with aniline derivatives to



Scheme 21 Plausible mechanism for the one-pot three-component synthesis of 5-aryl-pyrimido[4,5-*b*]quinoline-diones **61a–k** using L-proline as a catalyst.



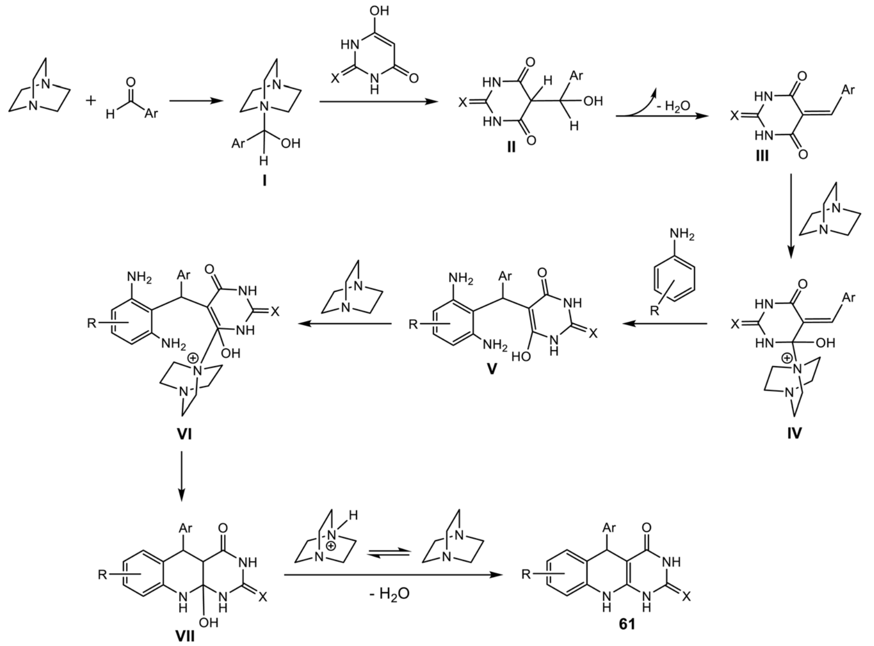
61	R	Ar	X	Δ (h)		MWI	
				Time (h)	Yield (%)	Time (Sec)	Yield (%)
a	H	4-Br-C_6H_4	O	12	95	30	97
b	H	4-CH_3-C_6H_4	O	12	96	30	98
c	4-Me	4-Br-C_6H_4	O	12	96	30	97
d	4-OMe	3-NO_2-C_6H_4	O	12	85	30	94
e	4-Br	4-OH-C_6H_4	S	12	86	30	93
f	4-OMe	Naphthy-	S	12	90	30	92
g	H	C_6H_5	O	12	90	30	95
h	2,5-$(OMe)_2$	3-NO_2-C_6H_4	O	12	86	30	92
i	2-OMe	thienyl	S	12	85	30	92
j	4-OMe	3,5-Cl_2-C_6H_3	O	12	86	30	90
k	3-NO_2	4-Cl-C_6H_4	O	12	83	30	91
l	3-OH	pyridyl	O	12	83	30	92

Scheme 22 Green and efficient synthesis of new 5-aryl-(1*H*,3*H*,5*H*,10*H*)-pyrimido[4,5-*b*]-quinoline-2,4-diones **61a–l**.

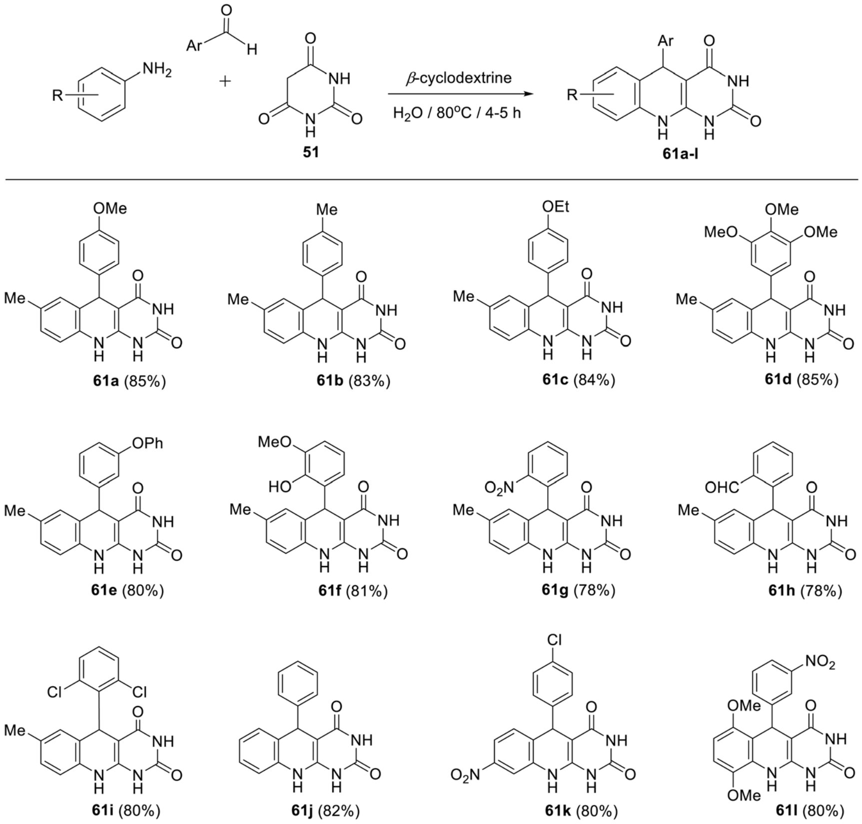
afford intermediate **V**. Then, intermediate **V** undergoes an intramolecular cyclization reaction to form the desired product **61**. Although L-proline plays a key role in this reaction, it does not affect the formation of a chiral center, so stereoselectivity does not occur.

In 2014, Mosslemina and his coworkers[92] reported a green and efficient synthesis of 5-aryl-(1*H*,3*H*,5*H*,10*H*)-pyrimido[4,5-*b*] quinoline-2,4-diones **61a–l** *via* a one-pot, three-component reaction of anilines, barbituric acids **51** and aldehydes catalyzed by 1,4-diaza-bicyclo[2.2.2]octane (DABCO) in H_2O. This synthetic approach proceeded by heating a mixture of equimolar amounts of anilines, (thio)barbituric acids **51** and aldehydes in the presence of a catalytic amount of DABCO (15 mol%) in H_2O at a reflux temperature for 12 h to give the new derivatives of 5-aryl-(1*H*,3*H*,5*H*,10*H*)-pyrimido[4,5-*b*] quinoline-2,4-diones **61a–l** in 83–96% yields (Scheme 22). Using microwave heating (at 90 °C, 400 W), reaction times were shortened from 12 h to under a minute (30 s) and yields were generally higher (Scheme 22). A suggested mechanism for the formation of **61** is illustrated in Scheme 23. DABCO initially activated the aldehyde. Simultaneously, DABCO as Brønsted acid/base assists the enolization of the barbituric acids **51**, which is subsequently reacted with adduct **I** to give intermediate **II.** The latter intermediate can lose one molecule of H_2O, so barbiturate **III**, as an unsaturated carbonyl compound, is formed. However, DABCO can activate adduct **III** to generate intermediate **IV** to undergo a reaction with aniline, resulting in the production of adduct **V.** DABCO could act as a nucleophilic catalyst, reacting with adduct **V** to produce intermediate **VI.** Subsequently, intermediate **VI** undergoes an intramolecular cyclization reaction to afford intermediate **VII.** DABCO can assist **VII** to lose one molecule of H_2O and give the final products **61a–l.**

Recently, an efficient, fast and straightforward protocol towards the construction of various new derivatives of 5-aryl-pyrimido[4,5-*b*]quinolinedione **61** *via* a three-component condensation of electronically different aromatic amines, aromatic aldehydes and barbituric acid (**51**) promoted by β-cyclodextrin (β-CD), as a supramolecular catalyst, in water has been developed, for the first time, by Reddy and his group.[93] This strategy provides a benign method for building pyrimido-[4,5-*b*]quinolinediones in an environmentally safer reaction medium. The reactions were carried out by heating a mixture of equimolar amounts of aromatic amines, aromatic aldehydes

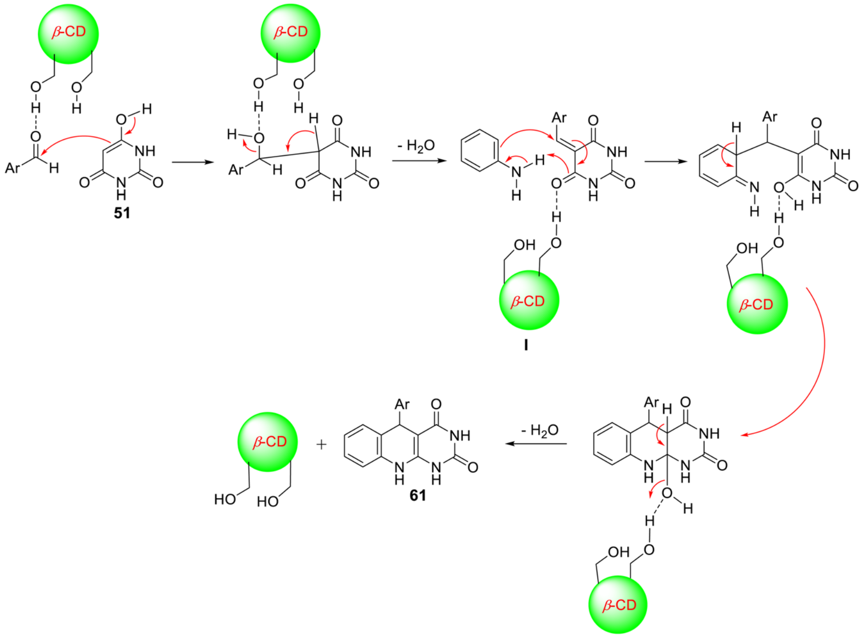


Scheme 23 Plausible reaction mechanism for DABCO-catalyzed synthesis of 5-aryl-pyrimido[4,5-*b*]quinoline-diones **61**.

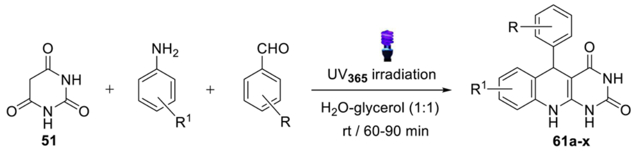


Scheme 24 Green approach for the synthesis of 5-aryl-pyrimido[4,5-*b*]quinolinediones **61a–l**.

and barbituric acid (**51**) in H_2O in the presence of β-cyclodextrin (β-CD), as a supramolecular catalyst, at 80 °C for 4–5 h to afford new 5-aryl-pyrimido[4,5-*b*]quinoline-diones **61a–l** in good to excellent yields (Scheme 24). A plausible mechanism to account for the formation of **61** is suggested in Scheme 25. A hydrophobic environment of the catalyst (β-CD facilitated the reaction by forming the β-CD-aldehyde complex). This complex reacts with barbituric acid (**51**) to give enone **I**. The latter reacts



Scheme 25 Plausible mechanism for the β-CD catalyzed synthesis of pyrimido[4,5-*b*]-quinoline-diones **61a–l**.

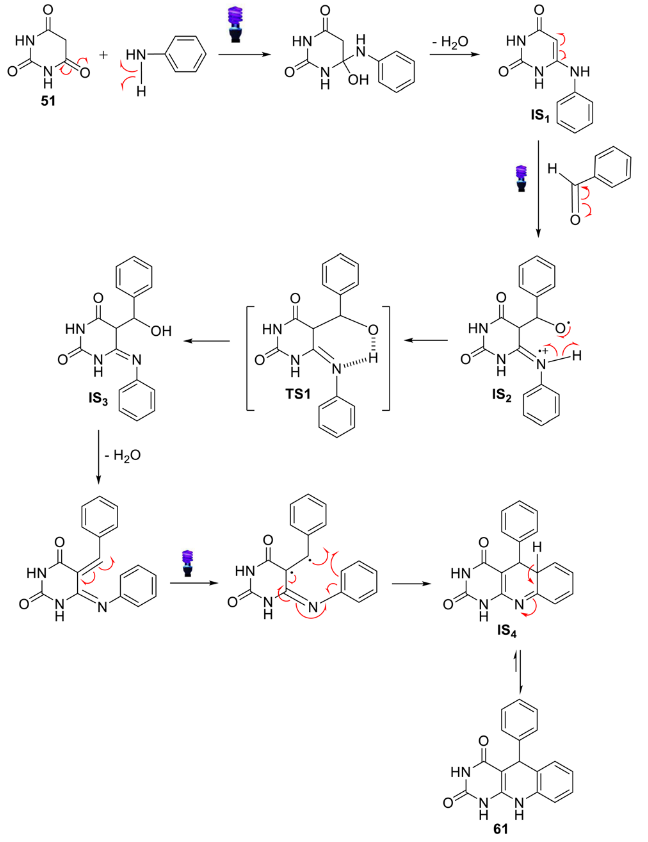


61	R	R^1	Time (min)	Yield (%)
a	H	H	60	98
b	4-F	H	60	95
c	3-Br	H	60	93
d	4-Br	H	60	94
e	4-NO$_2$	H	60	90
f	2-Cl	H	60	90
g	2-Cl	4-CH$_3$	90	87
h	H	4-OMe	60	97
i	4-CH$_3$	H	60	91
j	4-CH$_3$	4-CH$_3$	90	88
k	4-NO$_2$	4-OMe	60	95
l	3-Cl	4-CH$_3$	90	89
m	2-Cl	4-Cl	90	85
n	3-Br	4-CH$_3$	90	90
o	4-CH$_3$	4-OMe	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

Scheme 26 Synthesis of pyrimido[4,5-*b*]quinoline-2,4-diones **61a–x** under UV$_{365}$ irradiation.

with aromatic amines *via* the Michael addition reaction, followed by intramolecular cyclization, giving the corresponding 5-aryl-pyrimido[4,5-*b*]quinolinedione **61**.

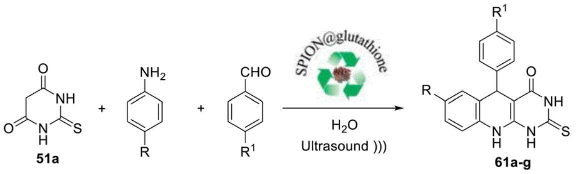
In 2018, Nongthombam and his coworkers[94] developed a green, highly efficient and environmentally benign UV$_{365}$ light-mediated synthesis of several biologically important pyrimido[4,5-*b*]quinoline-2,4-diones **61** from barbituric acid (**51**), aromatic amines and aromatic aldehyde. Thus, when a mixture of barbituric acid (**51**), aryl amines and aryl aldehydes in water–glycerol (1 : 1) was irradiated by long ultraviolet light (UV$_{365}$) for 60–90 min, the desired pyrimido[4,5-*b*]quinoline-2,4-diones **61a–x** were obtained in 85–98% yields (Scheme 26). This synthetic approach operates at room temperature under direct irradiation from a UV$_{365}$ light source in a water–glycerol medium and in the absence of a photocatalyst. This reported method shows several merits, such as clean reaction conditions, chromatography-free synthesis, and the use of an inexpensive water–glycerol solvent system, which is also environmentally friendly and results in high yields. The proposed mechanism to explain the formation of **61a–x** is shown in Scheme 27.



Scheme 27 Suggested mechanism for UV$_{365}$-aided synthesis of **61a–x** *via* a free radical pathway.

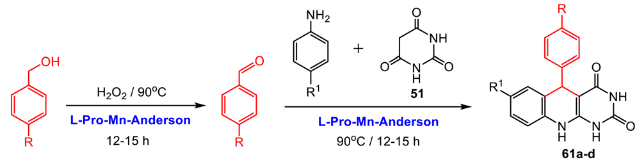
In the same year, Nongthombam and Nongkhlaw[95] reported an efficient, economical and environment benign protocol for the synthesis of 5-aryl-2-thioxo-2,3,5,10-tetrahydropyrimido[4,5-*b*]quinolin-4(1*H*)-ones **61a–g** utilizing glutathione on superparamagnetic iron-oxide nanoparticle (SPION) (SPION@glutathione) as a nano-organo-catalyst and ultrasound irradiation as an energy source. When a mixture of thiobarbituric acid (**51a**), aniline derivatives, aryl aldehyde, and SPION@glutathione (10 mg) in H$_2$O was ultrasonicated for 15 min, the desired tricyclic 5-aryl-2-thioxo-2,3,5,10-tetrahydropyrimido[4,5-*b*]quinolin-4(1*H*)-ones **61a–g** were obtained in 92–98% yields (Scheme 28). In this strategy, the nano-organocatalyst (SPION@glutathione) was successfully recovered and reused without any loss in its activity.

In 2023, Dai and his group[96] reported a one-pot alcohol oxidation/three-component green synthesis of new 5-aryl-



61	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

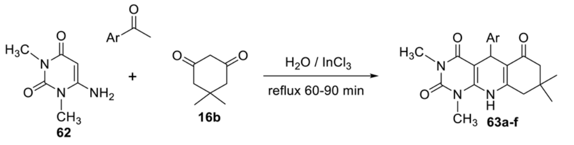
Scheme 28 Synthesis of 5-aryl-2-thioxo-2,3,5,10-tetrahydropyrimido[4,5-*b*]quinolin-4(1*H*)-ones **61a–g** using SPION@ glutathione as a nano-organocatalyst under ultrasonic conditions.



61	R	R^1	Yield (%)
a	CH_3	Cl	90
b	OCH_3	CH_3	91
c	Et	Cl	93
d	F	F	85

Scheme 29 L-Pro-Mn-Anderson catalyzed a one-pot alcohol oxidation/three-component condensation reaction from alcohols to 5-aryl-pyrimido[4,5-*b*]quinoline-diones **61**.

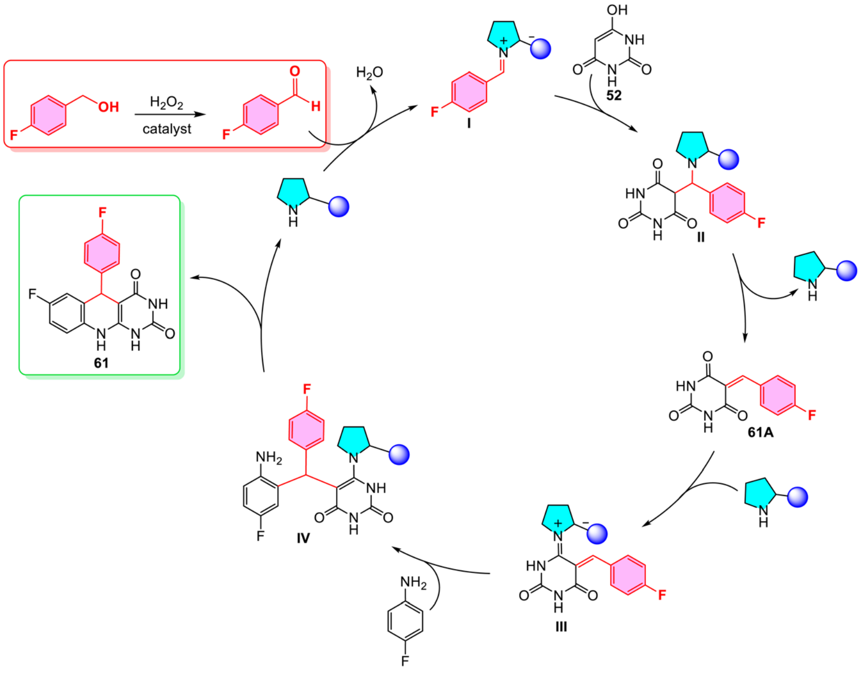
pyrimido[4,5-*b*]quinolinedione derivatives **61**, for the first time, utilizing a bifunctional nanomolecular catalyst L-Pro-Mn-Anderson by grafting L-proline onto an Mn-Anderson POM (polyoxometalate). This synthetic method involves heating a mixture of alcohol (1 mmol), catalyst (L-Mn-Anderson POM, 0.5 mol%) and aqueous H_2O_2 (30%, 3 mmol) in H_2O at 90 °C for 12–15 h to give the corresponding aldehyde, followed by *in situ* reaction with aromatic amine compound (1 mmol) and barbituric acid (**51**) (1 mmol) in H_2O at a reflux temperature for 12–15 h to afford **61a–d** in excellent yields (85–93%) (Scheme 29). A postulated reaction mechanism for the formation of **61** is presented, as shown in Scheme 30. First, the Mn-Anderson skeleton of the L-Pro modified compound catalyzes the oxidation of alcohol to aldehyde. The pyrrolidine grafted on the POM may activate the aldehyde to form intermediate **I**. Meanwhile, L-Pro-Mn-Anderson Brønsted acid/base helps the enolization of barbituric acid **51** and then reacts enolate with intermediate **I** to give intermediate **II**. 5-(4-Fluorobenzylidene)-pyrimidine-2,4,6-trione (**61A**) is generated (the compound was successfully isolated) after removing L-Pro-Mn-Anderson from intermediate **II.** Subsequently, L-Pro-Mn-Anderson can activate **61A** to generate intermediate **III** to facilitate the reaction with 4-fluoroaniline, resulting in the formation of intermediate **IV.** Finally, the latter intermediate **IV** undergoes an intramolecular cyclization reaction to afford the target product **61**.



63a, Ar = 4-Cl-C_6H_4 (91% yield)
b, Ar = 4-Br-C_6H_4 (90% yield)
c, Ar = 4-HO-C_6H_4 (90% yield)
d, Ar = 4-CH_3O-C_6H_4 (89% yield)
e, Ar = 4-O_2N-C_6H_4 (91% yield)
f, Ar = 2-thienyl (89% yield)

Scheme 31 Indium trichloride catalyzed the synthesis of pyrimido[4,5-*b*]quinolines **63a–f**.

Khurana *et al.*[97] described a new, simple, environmentally benign one-pot and three-component protocol for the synthesis of novel pyrimido[4,5-*b*]quinolines **63** using indium trichloride ($InCl_3$) as a catalyst in water. The condensation of 6-amino-1,3-dimethyluracil (**62**), 5,5-dimethylcyclohexane-1,3-dione (**16b**) and various aromatic aldehydes in water in the presence of $InCl_3$ (20 mol%), as a catalyst, at reflux temperature for 60–90 min afforded a series of novel pyrimido[4,5-*b*]quinolines **63a–f** in excellent yields (Scheme 31). The advantages of this

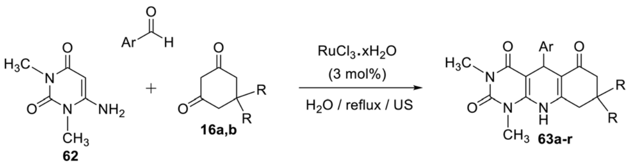


Scheme 30 Proposed mechanism for the synthesis of 5-aryl-pyrimido[4,5-*b*]quinoline-diones **61** *via* a one-pot alcohol oxidation/three-component condensation reaction.

method include operational simplicity, the reusability of the catalyst and high yields.

In 2014, Tabatabaeian and his group[98] described a novel, convenient, efficient and environmentally benign one-pot three-component coupling reaction of 6-amino-1,3-dimethyluracil (**62**), aromatic aldehydes and cyclic 1,3-diketones **16a,b** for the synthesis of bioactive pyrimido[4,5-*b*]quinoline derivatives **63** utilizing $RuCl_3 \cdot xH_2O$ as a reusable homogenous catalyst in the absence of any organic solvents and H_2O as a green solvent. The main advantages of this route are (i) high atom economy of the reaction by avoiding the use of toxic organic solvents, (ii) clean and simple work-up for the isolation and purification of products using non-chromatographic methods, (iii) short reaction time, (iv) energy saving by employing multicomponent reactions, (iv) excellent yields, (v) environmentally benign procedures, and (vi) reusability of the catalyst. Several derivatives of pyrimido[4,5-*b*]quinolines **63** showed extremely high levels of antibacterial activity.

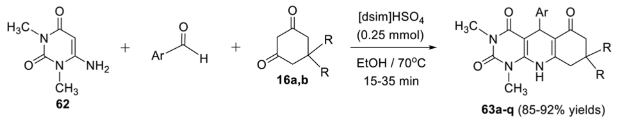
In this investigation, 6-amino-1,3-dimethyluracil (**62**) was used as an important partner in the synthesis of tricyclic fused rings. This compound provided C_5 and C_6 carbons in products **63**. 1,3-Cyclohexanedione (**16a**) or dimedone (**16b**) as a cyclic ketone with strong nucleophilic properties provided C_2 and C_3 carbons in products **63**. The reaction was carried out by heating equimolar amounts of 6-amino-1,3-dimethyluracil (**62**), aromatic aldehydes and cyclic 1,3-diketones **16a,b** in deionized H_2O in the presence of a catalytic amount of $RuCl_3 \cdot xH_2O$ (3 mol%) either *via* long reflux or by short time ultrasound (US) irradiations (40 kHz, 40 °C) to furnish the desired tricyclic pyrimido[4,5-*b*]quinolines **63a–r**. This reaction under ultrasound (US) irradiation gave an excellent yield of products and increased the reaction rate (Scheme 32). It was found that the electronic nature of the substituents on the phenyl ring of the applied aromatic aldehydes significantly affected this reaction. Aromatic aldehydes with electron-withdrawing groups (EWG) (such as nitro and halide groups) reacted at a faster rate and in better yields compared to electron-donating groups (EDG) (such as methoxy and methyl groups). When an aliphatic aldehyde, such as acetaldehyde, reacted with cyclic ketone and 6-amino-1,3-dimethyluracil under the same reaction conditions mentioned above, the desired product, pyrimido[4,5-*b*]quinoline **63**, was not obtained.



63	R	Ar	Ultrasound Time (min)	Ultrasound Yield (%)	Reflux Time (min)	Reflux Yield (%)
a	CH_3	$4\text{-MeO-}C_6H_4$	6	82	50	80
b	CH_3	$4\text{-}O_2N\text{-}C_6H_4$	3	96	30	95
c	CH_3	$2\text{-MeO-}C_6H_4$	10	73	65	75
d	CH_3	$4\text{-Cl-}C_6H_4$	4	91	30	90
e	CH_3	$2,4\text{-}Cl_2\text{-}C_6H_3$	3	92	25	91
f	CH_3	$4\text{-Me-}C_6H_4$	8	80	55	78
g	CH_3	$2\text{-Cl-6-F-}C_6H_3$	3	92	20	93
h	CH_3	$3\text{-}O_2N\text{-}C_6H_4$	5	91	35	90
i	CH_3	$2\text{-Cl-}C_6H_4$	4	87	35	88
j	CH_3	$4\text{-}(CH_3)_3C\text{-}C_6H_4$	12	66	75	60
k	H	$4\text{-Cl-}C_6H_4$	5	92	30	90
l	H	$2\text{-Cl-6-F-}C_6H_3$	3	95	18	93
m	H	$4\text{-}O_2N\text{-}C_6H_4$	4	92	25	91
n	H	$4\text{-F-}C_6H_4$	3	90	25	89
o	H	$4\text{-Me-}C_6H_4$	8	80	45	78
p	H	$4\text{-}(CH_3)_2N\text{-}C_6H_4$	6	87	30	88
q	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	3	92	22	90
r	H	$4\text{-}(CH_3)_3C\text{-}C_6H_4$	10	65	70	62

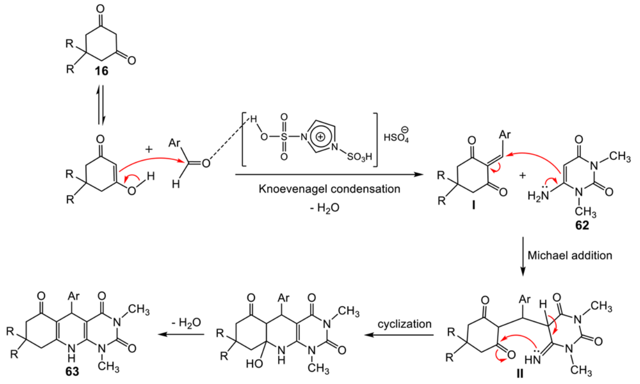
Scheme 32 $RuCl_3 \cdot xH_2O$ catalyzed the synthesis of pyrimido[4,5-*b*] quinolines **63a–r**.

In 2015, Mohammadi *et al.*[99] described a green, efficient and convenient method for the synthesis of pyrimido[4,5-*b*]quinolines *via* a three-component one-pot cyclo-condensation of 6-amino-1,3-dimethyluracil (**62**), aromatic aldehydes and cyclic 1,3-dicarbonyl compounds **16a,b** in the presence of a catalytic amount of 1,3-disulfonic acid imidazolium hydrogen sulfate $[dsim]HSO_4$ as an environmentally benign and reusable catalyst. The reactions were carried out by heating a mixture of 6-amino-1,3-dimethyluracil (**62**), aromatic aldehydes and cyclic 1,3-dicarbonyl compounds **16a,b** in EtOH in the presence of a catalytic amount of $[dsim]HSO_4$ at 70 °C for 15–35 min to afford the polyfunctionalized pyrimido[4,5-*b*]quinolines **63a–q** in 85–92% yields (Scheme 33). The notable advantages of the present methodology are mild conditions, excellent yields of the products, efficiency, short reaction times, easy work-up procedures and non-chromatographic purification of the products, making this method an attractive and useful process for the synthesis of pyrimido[4,5-*b*]quinolines as biologically interesting compounds. Moreover, the catalyst is recyclable and can be reused several times without a significant loss of activity. A probable mechanism for the formation of pyrimido-[4,5-*b*] quinolines **63a–q** is outlined in Scheme 34. Initially, the [dsim]



63	R	Ar	Time (min)	Yield (%)
a	CH_3	$4\text{-MeO-}C_6H_4$	25	85
b	CH_3	$4\text{-}O_2N\text{-}C_6H_4$	15	92
c	CH_3	$4\text{-Cl-}C_6H_4$	15	91
d	CH_3	$2\text{-}O_2N\text{-}C_6H_4$	35	87
e	CH_3	$3\text{-}O_2N\text{-}C_6H_4$	30	90
f	CH_3	$3\text{-Br-}C_6H_4$	30	89
g	CH_3	$2\text{-Cl-}C_6H_4$	35	88
h	CH_3	$2\text{-Cl-6-F-}C_6H_3$	20	90
i	CH_3	$4\text{-F-}C_6H_4$	20	90
j	CH_3	$4\text{-Br-}C_6H_4$	20	90
k	H	$3\text{-}O_2N\text{-}C_6H_4$	30	89
l	H	$4\text{-F-}C_6H_4$	18	88
m	H	$4\text{-Cl-}C_6H_4$	15	90
n	H	$4\text{-}O_2N\text{-}C_6H_4$	15	92
o	H	$2\text{-Cl-6-F-}C_6H_3$	18	90
p	H	$4\text{-}(CH_3)_2NC_6H_4$	30	88
q	H	$4\text{-Me-}C_6H_4$	35	86

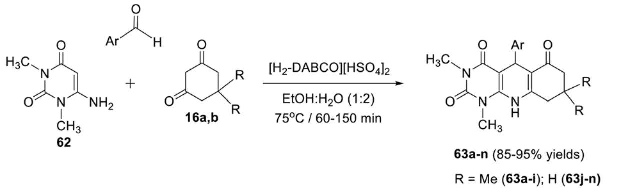
Scheme 33 $[dsim]HSO_4$ catalyzed the synthesis of polyfunctionalized pyrimido[4,5-*b*]-quinolines **63a–q**.



Scheme 34 Proposed mechanistic pathway for the [dsim]HSO_4 catalyzed formation of polyfunctionalized pyrimido[4,5-*b*]quinolines **63a–q**.

HSO_4-catalyzed Knoevenagel condensation between the aldehyde and cyclic 1,3-diketone gave adduct **I**. Then, the 6-amino-1,3-dimethyluracil (**62**) attacks adduct **I** through a Michael addition to provide an open chain intermediate **II**. Subsequently, the latter intermediate **II** undergoes intramolecular cyclization by the reaction of nucleophilic amino function (NH_2) to the C═O group, followed by dehydration, to produce pyrimido[4,5-*b*]quinolines **63**.

A novel methodology for the synthesis of pyrimido[4,5-*b*] quinolines **63** utilizing a new ionic liquid (IL), [H_2-DABCO] [HSO_4]$_2$ from the reaction of 1,4-diazabicyclo[2.2.2]octane (DABCO) and H_2SO_4, as a catalyst, was developed by Shirini *et al.* in 2017.[100] The results show the applicability of the prepared ionic liquid as a reusable catalyst without losing its activity. This protocol has some advantages such as short reaction times, excellent yields and use of non-toxic and affordable catalyst. This synthetic procedure proceeded by stirring a mixture of the 6-amino-1,3-dimethyluracil (**62**), aromatic aldehyde and 1,3-diketone **16** and in the presence of a catalytic amount of [H_2-DABCO][HSO_4]$_2$ in EtOH–H_2O (1 : 2) at 75 °C for 60–150 min to give the tricyclic pyrimido[4,5-*b*]quinolines **63a–n** in 85–95% yields (Scheme 35). A plausible mechanism to account for the formation of **63a–n** is suggested in Scheme 36. The ionic liquid [H_2-DABCO] [HSO_4]$_2$ may activate the aldehyde *via* hydrogen bonding formation. Then, 6-amino-1,3-dimethyluracil (**62**) was engaged in a Michael addition with intermediate **IV** to afford intermediate **V.** Subsequently, the ionic liquid promotes intramolecular cyclization by removing a hydrogen proton (H^+) from intermediate **V**, resulting in

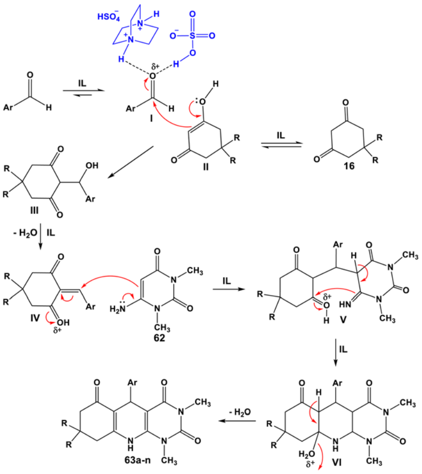


63a-n (85-95% yields)

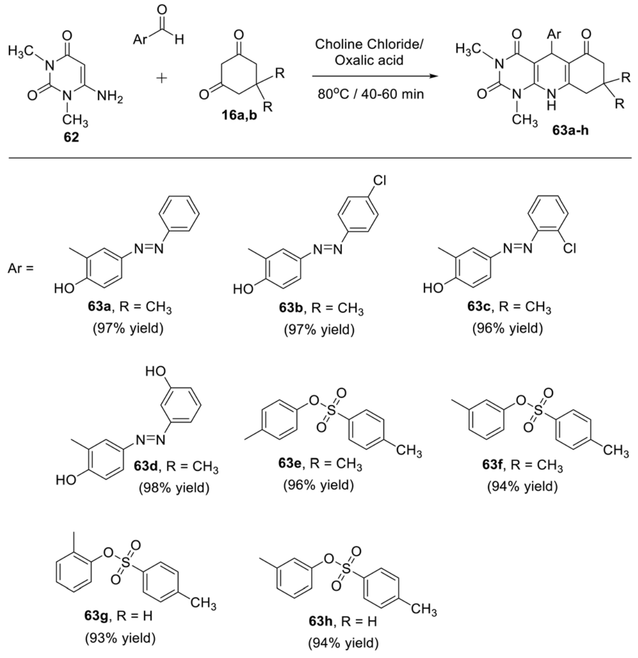
R = Me (**63a-i**); H (**63j-n**)

63	Ar	Yield (%)
a	C_6H_5	90
b	4-Cl-C_6H_4	93
c	2-Cl-C_6H_4	85
d	4-Br-C_6H_4	95
e	3-F-C_6H_4	90
f	4-NO_2-C_6H_4	90
g	3-NO_2-C_6H_4	92
h	2-NO_2-C_6H_4	85
i	4-Me-C_6H_4	90
j	4-Cl-C_6H_4	95
k	4-F-C_6H_4	90
l	4-NO_2-C_6H_4	90
m	3-NO_2-C_6H_4	85
n	4-Me-C_6H_4	95

Scheme 35 Synthesis of pyrimido[4,5-*b*]quinolines **63a–n** utilizing [H_2-DABCO][HSO_4]$_2$ as the catalyst.



Scheme 36 Suggested mechanism for the synthesis of pyrimido[4,5-*b*]quinolines **63a–n** catalyzed by [H_2-DABCO][HSO_4]$_2$.

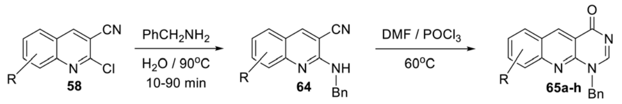


Scheme 37 Synthesis of novel azo and sulfonated pyrimido[4,5-*b*] quinolines **63a–h** catalyzed by ChCl : Oxa.

intermediate **VI**. Finally, the latter intermediate **VI** loses one molecule of H_2O to afford the desired products **63a–n**.

Very recently, Gholami and his group[101] reported a one-pot, three-component synthesis of novel azo and sulfonated pyrimido[4,5-*b*]quinoline derivatives **63** by the reaction of azo or sulfonated aldehydes, 6-amino-1,3-dimethyluracil (**62**) and 1,3-cyclohexadione (**16a**) or dimedone (**16b**). The reaction occurred in choline chloride/oxalic acid (ChCl : Oxa), as a green solvent and catalyst, at 80 °C for 40–60 min, delivering pyrimido[4,5-*b*] quinolines **63a–h** (Scheme 37). This approach has several advantages, including high efficiency, excellent yields over short reaction times and a low cost. The catalytic role of ChCl : Oxa in the synthesis of pyrimido[4,5-*b*]quinolines **63** is indicated by the mechanistic pathway (Scheme 38). Hydrogen bonding with the acidic hydrogen of oxalic acid increases the electrophilicity of the carbonyl group of aldehydes. It is supposed that the reaction may proceed at first by the reaction of 1,3-diketone **16a,b** with aldehyde by Knoevenagel condensation to produce the required intermediate **I**. The 6-amino-1,3-dimethyluracil (**62**) then attacks intermediate **I** in a Michael-type reaction to form intermediate **II**. Finally, the latter intermediate **II** underwent intramolecular cyclization *via* attack of the NH group to a carbonyl group, followed by dehydration to form novel pyrimido[4,5-*b*]quinoline **63**.

In 2012, Singh and his coworkers[102] developed a two-step synthesis of pyrimido[4,5-*b*]quinoline-4-ones **65a–h** from 2-chloroquinoline-3-carbonitriles **58** *via* amination and cyclization reactions. The amination reactions proceeded much faster in water *via* the simple S_NAr displacement reactions of chlorine atoms at C-2 in **58.** The cyclization reactions using the Vilsmeier reagent at lower temperatures gave the best yield of the products. When a mixture of 2-chloroquinoline-3-carbonitriles **58** (1 equiv.) and benzylamine (3 equiv.) was heated in water at 90 °C for 10–90 min, the corresponding 2-benzylamino-quinoline-3-carbonitriles **64** were formed. The authors examined the scope of the Vilsmeier reagent for the cyclization of 2-benzylaminoquinoline-3-carbonitriles **64**, and they found that the Vilsmeier reaction with 1 : 3 molar ratios of DMF and $POCl_3$ at 60 °C was the best optimal reaction conditions for cyclization to afford excellent yields of the desired products pyrimido-[4,5-*b*]quinoline-4-ones **65a–h** (Scheme 39). The electron donating substituents at position 7 afforded better yields of the products than the substituents at position 6. Notably, the ethyl group gave a better product yield than the CH_3 group at position 8. However, the electron-withdrawing substituent at position-6/7 afforded a better yield of the product. Notably, the faster reaction rates with the methoxy group could be attributed to the resonance effect of the group. A plausible mechanism for the formation of **65** is depicted in Scheme 40.

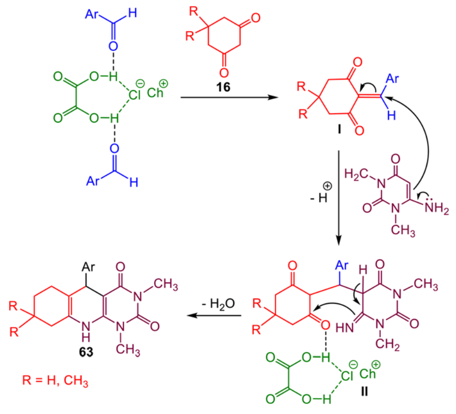


65	R	Time (min)	Yield (%)
a	6-CH$_3$	35	82
b	6-OCH$_3$	15	85
c	7-CH$_3$	42	90
d	7-OCH$_3$	20	92
e	8-CH$_3$	40	86
f	8-Et	45	95
g	6-Br	45	90
h	7-Cl	40	85

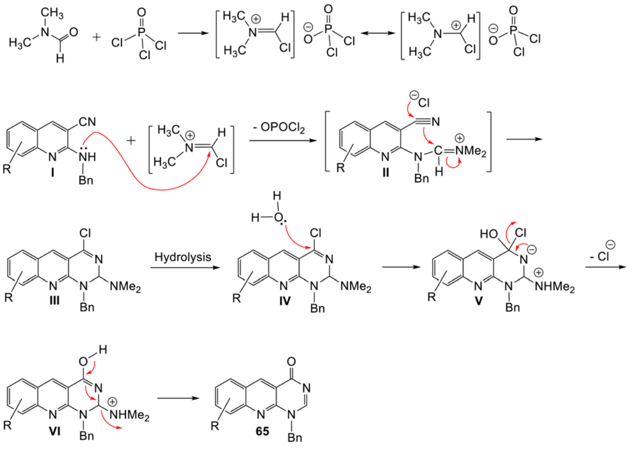
Scheme 39 Two-step synthesis of 1-benzyl-pyrimido[4,5-*b*]quinoline-4-ones **65a–h**.

The synthesis of new pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones **68a–u** was developed by Dickens *et al.*[103] in 2013. Reactions were carried out by heating 6-chlorouracil (**20**) (1 equiv.) with a wide variety of anilines (6 equiv.) at 180–200 °C for 1.5–3 h to afford the corresponding 6-anilinouracils **66**, which were then refluxed with 2-halo-benzaldehydes **67** in DMF for 4 h to give the desired pyrimido-[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones **68a–u** in 11–79% yields (Scheme 41).

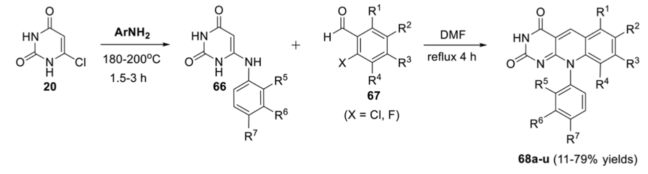
In 2013, El-Gohary[104] described the synthesis of a series of new pyrimido[4,5-*b*]quinolines as potential antitumor agents. Reactions were carried out by heating the key 2-amino-4-aryl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitriles **69a,b** with ammonium thiocyanate (NH_4SCN) in glacial acetic acid at reflux



Scheme 38 Proposed mechanism for the synthesis of azo and sulfonated pyrimido[4,5-*b*]-quinolines **63** by ChCl : Oxa.



Scheme 40 Plausible mechanism for the formation of 1-benzyl-pyrimido[4,5-*b*]quinoline-4-ones **65a–m**.

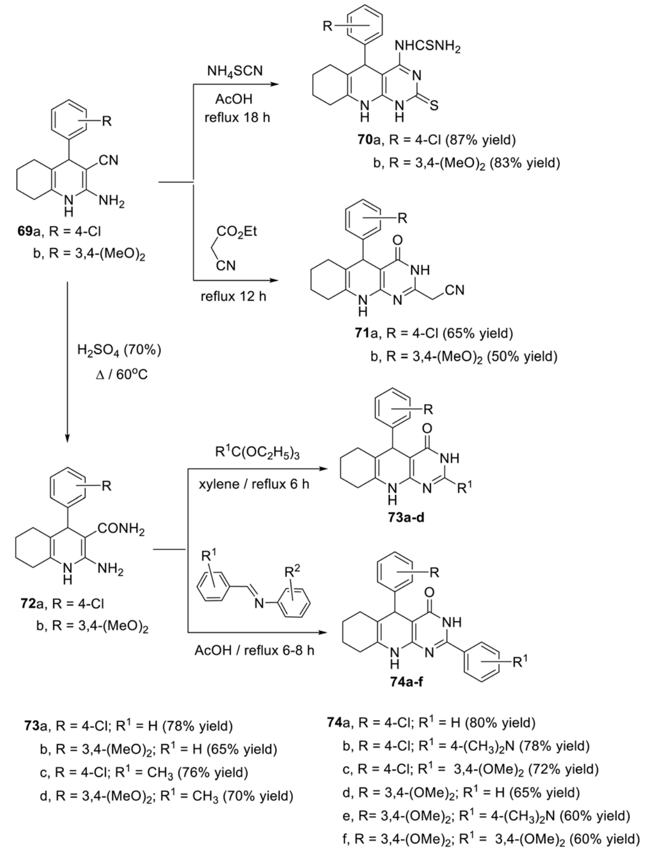


68	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)
a	H	H	H	NO_2	F	H	H	23
b	H	H	H	H	H	H	Cl	24
c	H	H	CF_3	H	F	H	H	39
d	H	H	H	CF_3	F	H	H	66
e	CF_3	H	H	H	H	H	Cl	11
f	H	H	CF_3	H	H	H	Cl	51
g	H	H	H	CF_3	H	H	Cl	28
h	H	H	H	CF_3	H	Cl	H	55
i	H	H	H	CF_3	H	Cl	Cl	62
j	H	H	H	CF_3	H	H	F	46
k	H	H	H	CF_3	H	Me	H	39
l	H	H	H	CF_3	H	H	Me	52
m	H	H	H	CF_3	H	H	H	39
n	H	Cl	H	CF_3	F	H	H	79
o	Cl	H	H	H	H	H	Cl	38
p	H	H	H	Cl	H	H	Cl	15
q	H	H	H	Cl	H	Cl	H	30
r	H	H	H	Cl	H	F	H	71
s	H	H	Me	H	H	H	Cl	24
t	H	H	H	Br	H	H	H	29
u	H	H	H	Br	H	H	Cl	36

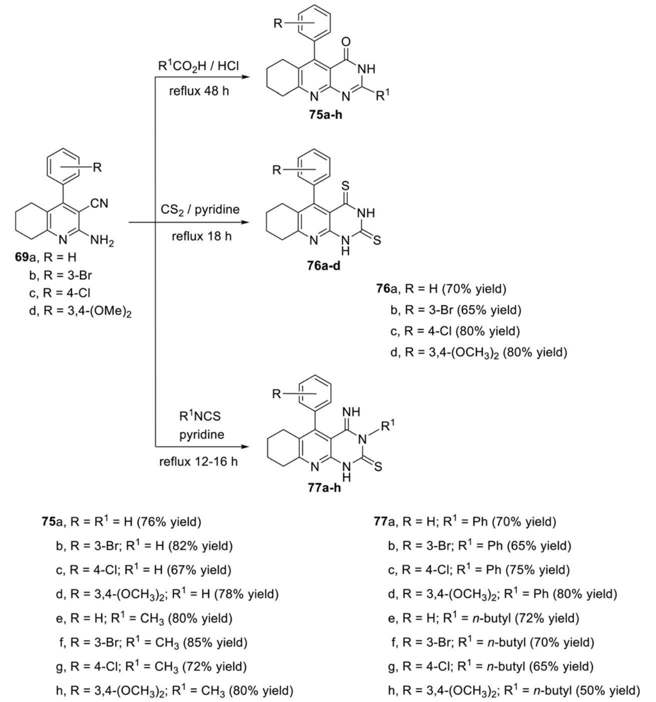
Scheme 41 Synthesis of new pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones **68a–u**.

temperature for 18 h to give 5-aryl-1,2,5,6,7,8,9,10-octahydro-2-thioxopyrimido[4,5-*b*]quinolins **70a,b** in very good yields. When compounds **69a,b** were refluxed with an excess of ethyl cyanoacetate for 12 h, new 5-aryl-2-(cyanomethyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4(3*H*,5*H*,10*H*)-ones **71a,b** were formed in moderate yields (Scheme 42). However, the hydrolysis of compounds **69a,b** using H_2SO_4 (70%) at 60 °C gave the corresponding 2-amino-quinoline-3-carboxamides **72a,b** (Scheme 42). Refluxing **72a,b** with an appropriate triethyl orthoester in xylene for 6 h gave 5-aryl-6,7,8,9-tetrahydro-2-(unsubstituted or methyl)pyrimido[4,5-*b*]quinolin-4(3*H*,5*H*,10*H*)-ones **73a–d** in 65–78% yields. However, when **72a,b** (1 equiv.) were refluxed with the appropriate benzylideneaniline (2 equiv.) in glacial AcOH for 6–8 h, tricyclic products **74a–f** were obtained in 60–80% yields, as a new derivative of pyrimido[4,5-*b*]quinolin-4-ones (Scheme 42).

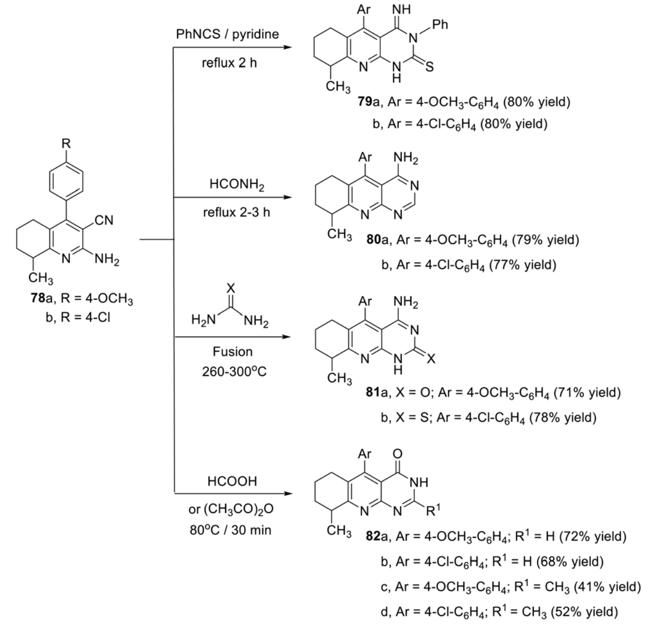
In another report, El-Gohary and his coworkers[105] described the synthesis of a new series of tricyclic pyrimido[4,5-*b*]quinolines *via* a reaction of 2-amino-quinoline-3-carbonitriles **69a–d** with different reagents, as shown in Scheme 38. Thus, heating compounds **69a–d** with aliphatic acids (HCO_2H and CH_3CO_2H) in the presence of a catalytic amount of conc. HCl at reflux temperature for 48 h gave 5-aryl-6,7,8,9-tetrahydro-2-(unsubstituted or methyl)-pyrimido[4,5-*b*]quinolin-4(3*H*,5*H*,10*H*)-ones **75a–h** in 67–85% yields. When compounds **69a–d** (1 equiv.) were refluxed with carbon disulfide (CS_2) (1 equiv.) in pyridine on a water bath (80 °C) for 18 h, they underwent a cyclo-condensation reaction to afford 5-aryl-5,6,7,8,9,10-hexahydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dithiones **76a–d** in 65–80% yields. On heating compounds **69a–d** with isothiocyanates in pyridine at reflux temperature for 12–



Scheme 42 Synthesis of 2-thioxopyrimido[4,5-*b*]quinolins **70a,b** and pyrimido[4,5-*b*]-quinolin-4-ones **71a,b**, **73a–d** and **74a–f**.



Scheme 43 Synthesis of new series of pyrimido[4,5-*b*]quinolin-4-ones **75a–h**, pyrimido-[4,5-*b*]quinoline-2,4-dithiones **76a–d** and 4-imino-pyrimido[4,5-*b*]quinoline-2-thiones **77a–h**.

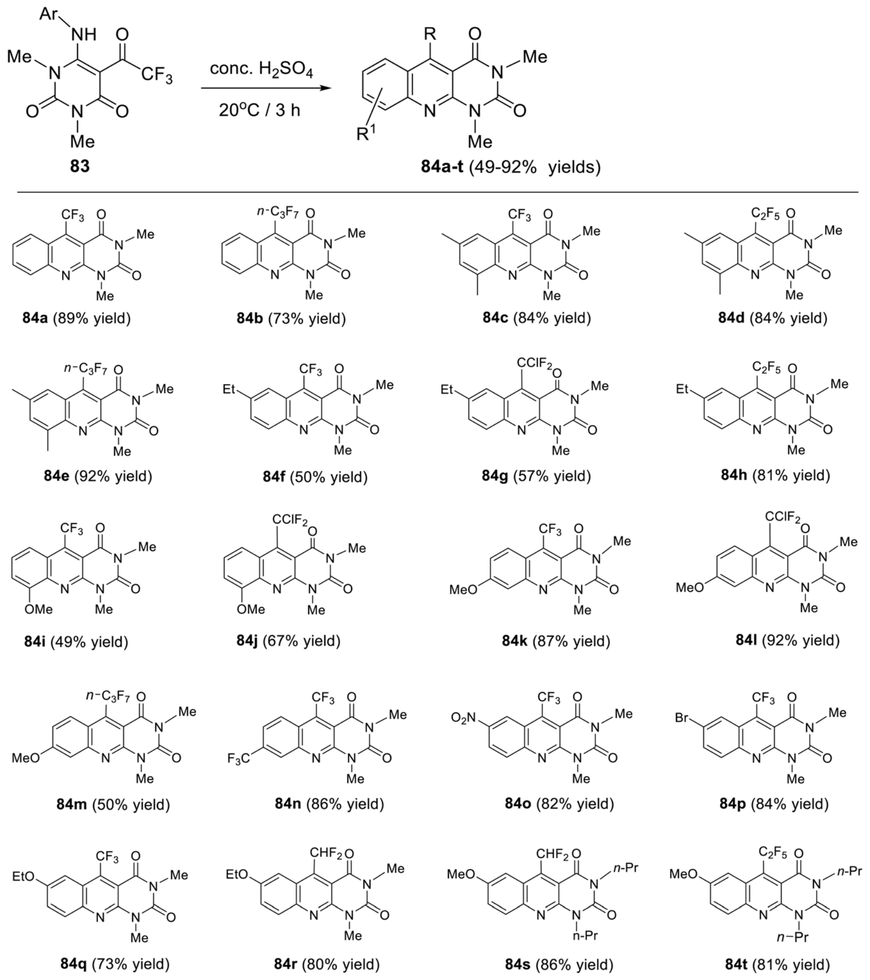


Scheme 44 Synthesis of some new derivatives of tetrahydropyrimido[4,5-*b*]quinolines **79–82**.

16 h, 5-aryl-3,4,5,6,7,8,9,10-octahydro-4-imino-3-(*n*-butyl or phenyl)-pyrimido[4,5-*b*]-quinoline-2(1*H*)-thiones **77a–h** were obtained in 50–80% yields (Scheme 43).

In the same year, Faidallah and Rostom[75] reported the synthesis of some new derivatives of tetrahydropyrimido[4,5-*b*] quinolines utilizing 2-amino-8-methyl-4-substituted-5,6,7,8-tetrahydro-quinoline-3-carbonitriles **78a,b** as the key precursors. The reaction of **78a,b** with phenyl isothiocyanate in pyridine under reflux for 2 h afforded the corresponding substituted tricyclic thiones **79a,b**. The cyclization of compound **78a,b** with formamide led to the formation of the required 4-amino-9-methyl-5-substituted-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolines **80a,b**. Moreover, the fusion of **78a,b** (1 equiv.) either with urea or thiourea (5 equiv.) at 260–300 °C using a sand bath for 1 h was used as a fruitful way for a one-step synthesis of the target tricyclic compounds **81a,b**. However, reacting compounds **78a,b** with either formic acid or acetic anhydride at 80 °C for 30 min gave the targeted tetrahydropyrimido-[4,5-*b*] quinolin-4-ones **82a,b** and their 2-methyl analogs **82c,d** (Scheme 44).

Dudkin *et al.*[106] developed a new, simple and general methodology for the synthesis of novel 1,3-dimethyl-5-

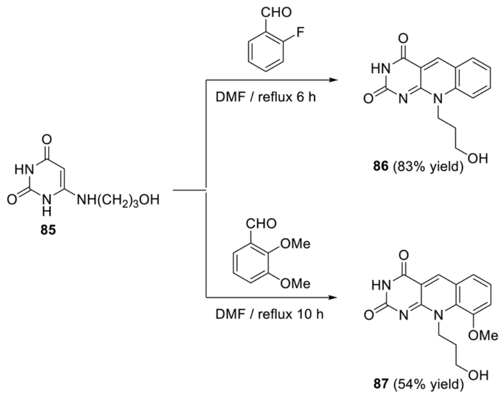


Scheme 45 Synthetic route to 1,3-dialkyl-5-(polyfluoroalkyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **84a–t**.

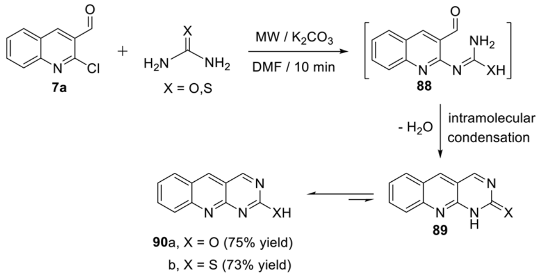
(polyfluoroalkyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **84**. This approach was based on the intramolecular cyclization reaction of 6-anilino-5-(polyfluoroacyl)-1,3-dimethyluracils **83** under acidic conditions. Thus, when uracils **83** were dissolved in conc. H_2SO_4 and allowed to stand at room temperature for 3 h, the tricyclic 1,3-dimethyl-5-(polyfluoroalkyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **84a–t** were obtained in good to excellent yields (49–92%) (Scheme 45).

Cyclocondensation of 6-*N*-(3-hydroxypropyl)aminouracil (**85**) with 2-fluoro-benzaldehyde in DMF at reflux temperature for 6 h provided the desired 10-(3-hydroxypropyl)-pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)dione (**86**) in 83% yield. However, the reaction of **85** with 2,3-dimethoxybenzaldehyde under the same reaction conditions mentioned above gave the corresponding 10-(3-hydroxypropyl)-9-methoxy-pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione (**87**) in 54% yield (Scheme 46).[107]

Naik *et al.*[108] described a versatile and useful access to different scaffolds of biologically significant pyrimido[4,5-*b*]quinoline-2-ol/thiol **90a,b** utilizing a simple and efficient methodology based on the microwave (MW) irradiation technique. The reaction was carried out by heating 2-chloroquinoline-3-carbaldehyde (**7a**) (1 equiv.) with urea or thiourea (1 equiv.) in the presence of anhydrous K_2CO_3 (2 equiv.) in DMF for 10 min under microwave irradiation to give pyrimido[4,5-*b*]quinoline-2-ol (**90a**) and pyrimido[4,5-*b*]quinoline-2-thiol (**90b**) *via* intermediacy of **88** in 75% and 73% yields, respectively (Scheme 47). The efficiency of this methodology can be explained by the fact that MW energy is much higher than the activation energy required for each reaction, so the rate of reaction increases and yields are higher. The DNA binding properties of these two newly synthesized **90a,b** were investigated using viscosity, absorption spectra and thermal denaturation experiments. The results showed that sulfur-containing **90b** had more interaction with CT-DNA compared to **90a**. Additionally, the authors carried out DNA cleavage *via* an oxidative route. The cleavage study results demonstrated that sulfur-containing **90b** is more nuclease than **90a**.



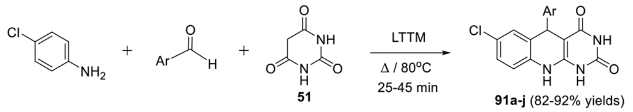
Scheme 46 Synthesis of new pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones **86** and **87**.



Scheme 47 Microwave-induced one-pot synthesis of pyrimido[4,5-*b*]quinoline-2-ol/thiol **90a,b**.

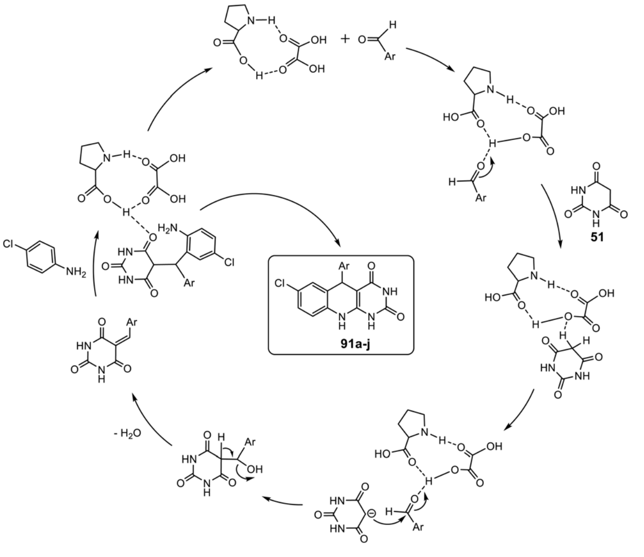
Mohire *et al.*[109] developed a new, green, highly efficient cost-effective and atom-economic approach for the synthesis of 5-aryl-7-chloro-5,10-dihydropyrimido[4,5-*b*]-quinoline-2,4(1*H*,3*H*)-diones **91** *via* one-pot three-component condensation of 4-chloroaniline, aromatic aldehyde and barbituric acid (**51**) utilizing oxalic acid dihydrate:proline, as a low transition temperature mixture (LTTM), as new generation and green solvents instead of the hazardous organic solvents. This methodology was accomplished using ecofriendly and recyclable reaction media, easy work-up procedures, simple methodology, high atom economy and no chromatographic purification with high yields. The reactions were carried out by heating a mixture of 4-chloroaniline, aromatic aldehydes and barbituric acid (**51**) in oxalic acid:proline (LTTM), as a solvent, at 80 °C for 25–45 min to afford the new tricyclic 5-aryl-7-chloro-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **91a–j** in 82–92% yields (Scheme 48).

A plausible mechanism for the formation of 5-aryl-7-chloro-5,10-dihydropyrimido-[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione derivatives **91** is shown in Scheme 49. Owing to the hydrogen bonding nature of LTTM, it facilitates the electrophilic activation of the carbonyl group of aromatic aldehydes. Then, Knoevenagel condensation of aromatic aldehydes and barbituric acid (**51**) occurs to form 5-arylidene-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones. Subsequently, the aza-Michael addition forms the ring nitrogen of 4-chloroaniline, resulting in the formation of an intermediate aza-Michael adduct, which is then cyclized to the



91	Ar	Yield (%)
a	2-Cl-C_6H_4	88
b	3-Cl-C_6H_4	85
c	4-Cl-C_6H_4	92
d	C_6H_5	92
e	3-Br-C_6H_4	86
f	3-NO_2-C_6H_4	82
g	3-MeO-C_6H_4	84
h	4-CN-C_6H_4	90
i	4-OH-C_6H_4	88
j	2,4-Cl_2-C_6H_3	90

Scheme 48 Oxalic acid dihydrate:proline (LTTM)-mediated synthesis of 5-aryl-7-chloro-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **91a–j**.

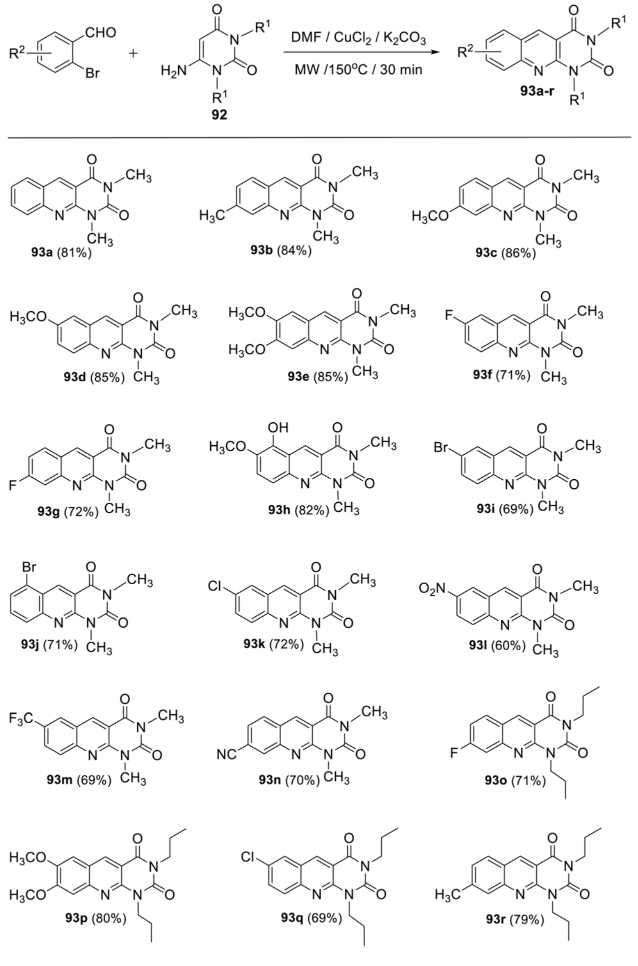


Scheme 49 Plausible mechanism for the one-pot synthesis of 5-aryl-pyrimido[4,5-*b*]-quinolinediones **91** using oxalic acid dihydrate:proline (LTTM) as a solvent.

tricyclic product *via* intramolecular nucleophilic attack from the *endo*-nitrogen on the amino heterocycle species. Finally, air auto-oxidation leads to the desired products **91a–j**.

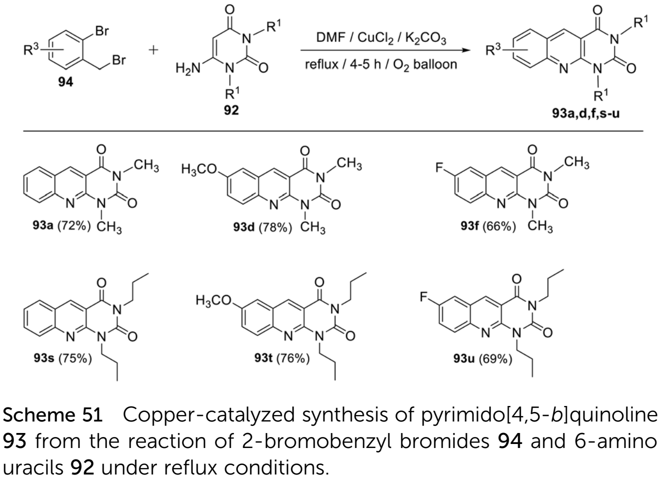
Panday and his group[110] developed two efficient and convenient methodologies for the synthesis of new 1,3-dialkylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **93** *via* the Cu-catalyzed coupling reaction of 6-aminouracils **92** and 2-bromobenzaldehydes/2-bromo-benzyl bromides **94**. The reaction of 2-bromo-benzaldehydes with 6-aminouracils **92** in the presence of K_2CO_3 as base and a catalytic amount of $CuCl_2$ (10 mol%) in DMF under microwave (MW) heating afforded the corresponding 1,3-dialkyl-pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **93a–r**, in 60–86% yields, within 30 min (Scheme 50). Alternatively, 1,3-dialkyl-pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **93a,d,f,s–u** were synthesized by reacting 2-bromobenzyl bromides **97** with 6-aminouracils **95** in the presence of molecular oxygen, K_2CO_3 as base and $CuCl_2$ (10 mol%) in DMF at reflux temperature for 4–5 h (Scheme 51). A plausible mechanism (a) for the synthesis of **93** from 2-bromo benzaldehydes and **92** under MW heating and mechanism (b) for the formation of **93** from **94** and **92** under reflux conditions are outlined in Schemes 52 and 53, respectively.

In 2017, El-Gamal[111] described the synthesis of a new series of pyrimido[4,5-*b*]-quinolines **96–101** *via* the reaction of the key 2-aminoquinoline-3-carbonitrile (**95**) with various reagents. Thus, the reaction of **95** with chloroacetic chloride, formamide, DMF–DMA/N_2H_4, urea (or thiourea), formic acid and acetic anhydride (or acetyl chloride) gave the corresponding pyrimido[4,5-*b*]quinoline derivatives **96–101** (Scheme 54). The results of the *in vitro* cancer activity and docking study revealed that the synthesized compounds have potential cancer activity.

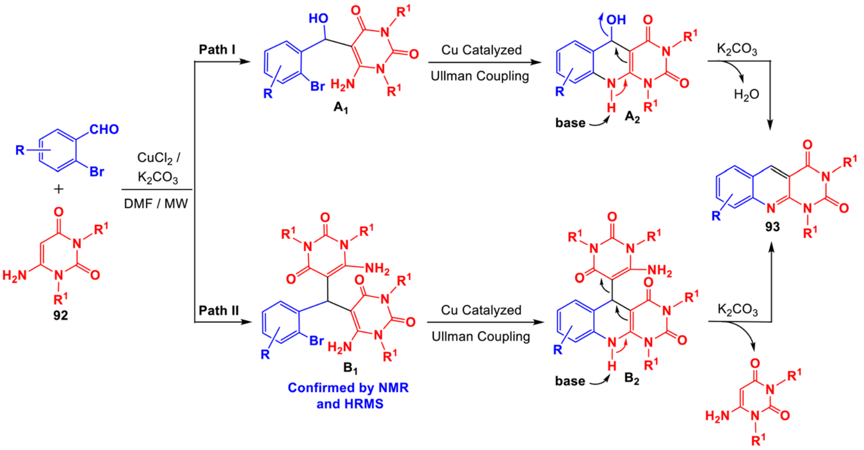


Scheme 50 Copper-catalyzed synthesis of pyrimido[4,5-*b*]quinolines **93a–r** from the reaction of 2-bromobenzaldehyde and 6-aminouracils **92** under MW heating.

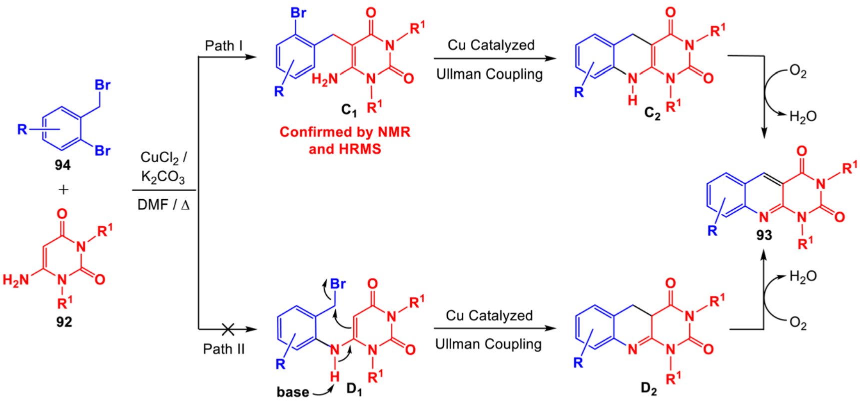
In the same year, Husain and his coworkers[112] designed and synthesized a new class of pyrimido-[4,5-*b*]quinolines **105a–j** utilizing the starting materials, 5-(bis(methylthio)-methylene)-1,3-diphenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**104a**) and 5-(bis(methylthio)-methylene)-1,3-diphenyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (**104b**), as efficient α,α-ketene dithioacetals. α,α-Ketene dithioacetals **104a,b** were synthesized



Scheme 51 Copper-catalyzed synthesis of pyrimido[4,5-*b*]quinolines **93** from the reaction of 2-bromobenzyl bromides **94** and 6-aminouracils **92** under reflux conditions.



Scheme 52 Proposed mechanism for the formation of **93** from 2-bromobenzaldehydes and **92** under MW heating.

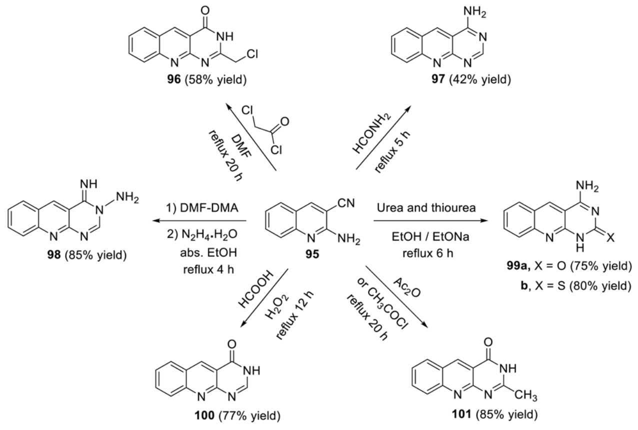


Scheme 53 Proposed mechanism for the formation of **93** from **92** and **94** under reflux conditions.

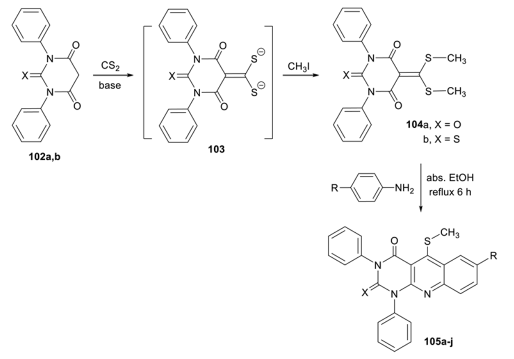
from 1,3-diphenyl-barbituric acid (**102a**) and 1,3-diphenyl-2-thiobarbituric acid (**102b**), as shown in Scheme 55. Thus, heating the desired starting materials **104a,b** with different *para*-substituted anilines in absolute EtOH at reflux temperature for 6 h afforded the novel tricyclic pyrimido[4,5-*b*]quinoline derivatives **105a–j** in high yields (Scheme 55). Some of these compounds exhibited outstanding antibacterial activity (100%) against the strains *E. coli* and *S. aureus*, comparable to that of the standard drug Ciprofloxacin at the same concentration, while the others revealed significant antifungal activity.

2.2. Synthesis of pyrimido[5,4-*c*]quinolines

Pyrimido[5,4-*c*]quinoline derivatives are found in a wide range of biologically important natural products and potent drugs. Compounds with pyrimido[5,4-*c*]quinoline cores exhibit various important and therapeutically useful biological activities, including antioxidant,[57] antiherpetic,[113] and antimalarial activities[114] and potent 5-HT1A/2A and 5-HT7 receptor ligands.[115] The synthesis of novel 2-imino-4-methyl-2,6-dihydropyrimido[5,4-*c*]quinolin-5(1*H*)-one (**107**), 4-methyl-pyrimido[5,4-*c*]quinoline-2,5(1*H*,6*H*)-dione (**108a**) and 4-methyl-2-thioxo-2,6-dihydropyrimido[5,4-*c*]quinolin-5(1*H*)-one (**108b**) was developed by Sankaran *et al.*[57] utilizing 3-acetyl-4-hydroxy-quinoline-2-one (**106**) as the key precursor. The reaction of **106** with guanidine nitrate, urea and thiourea (as nitrogen bases) in refluxing EtOH in the presence of a catalytic amount of sodium acetate afforded the corresponding pyrimido[5,4-*c*]quinolines **107** and **108a,b**

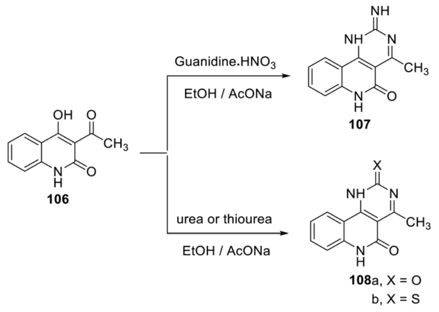


Scheme 54 Synthesis of pyrimido[4,5-*b*]quinolines **96–101** *via* the reaction of **95** with different reagents.

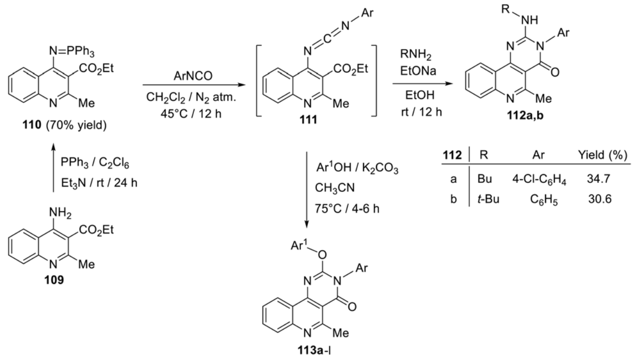


105a, X = O, R = CH_3 (90% yield)
b, X = O, R = OCH_3 (88% yield)
c, X = O, R = $-N(CH_3)_2$ (79% yield)
d, X = O, R = OH (51% yield)
e, X = O, R = NO_2 (81% yield)
f, X = S, R = CH_3 (72% yield)
g, X = S, R = OCH_3 (84% yield)
h, X = S, R = $-N(CH_3)_2$ (88% yield)
i, X = S, R = OH (70% yield)
j, X = S, R = NO_2 (64% yield)

Scheme 55 Synthesis of some novel functionalized pyrimido[4,5-*b*]quinoline derivatives **105a–j** from α,α-ketene dithioacetals **104a,b**.



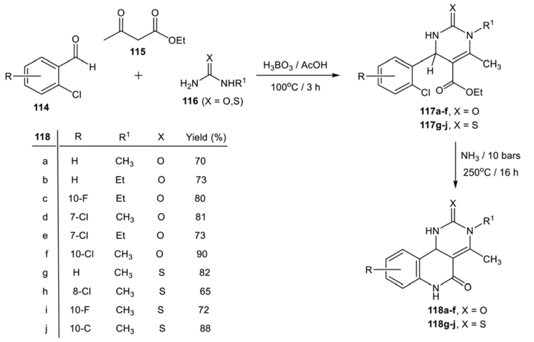
Scheme 56 Synthesis of pyrimido[5,4-*c*]quinolines **107** and **108a,b** from 3-acyl-4-hydroxy-quinoline-2-one (**106**).



112	R	Ar	Yield (%)
a	Bu	4-Cl-C_6H_4	34.7
b	*t*-Bu	C_6H_5	30.6

113	Ar^1	Ar	Yield (%)
a	4-Br-C_6H_4	4-F-C_6H_4	39
b	2,4-Cl_2-C_6H_3	4-Cl-C_6H_4	33.8
c	2,5-$(Me)_2$-C_6H_3	4-Cl-C_6H_4	35.2
d	C_6H_5	4-Cl-C_6H_4	31.4
e	naphthyl	4-Cl-C_6H_4	33.8
f	2-OMe-C_6H_4	4-Cl-C_6H_4	32.2
g	4-Br-C_6H_4	4-Cl-C_6H_4	30.2
h	2-Cl-4-NO_2-C_6H_3	4-Cl-C_6H_4	34.6
i	4-F-C_6H_4	4-F-C_6H_4	30.5
J	4-Cl-2-Me-C_6H_3	4-F-C_6H_4	34.5
K	2-Cl-C_6H_4	4-F-C_6H_4	33.6
l	2-OMe-C_6H_4	C_6H_5	35.5

Scheme 57 Synthesis of 2-(amino/aroxy)-5-methyl-pyrimido[5,4-*c*]quinolin-4(3*H*)-ones **112a,b** and **113a–l** *via* an aza-Wittig reaction.



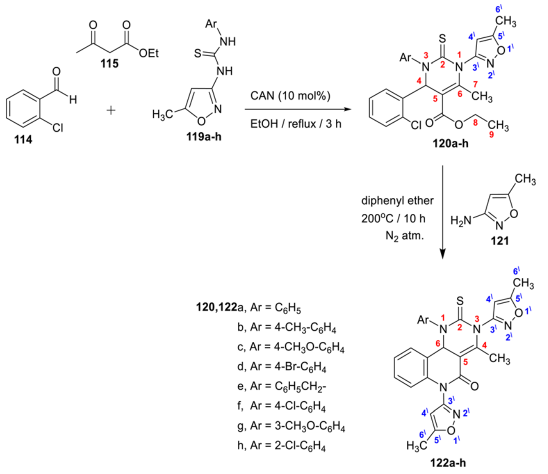
118	R	R^1	X	Yield (%)
a	H	CH_3	O	70
b	H	Et	O	73
c	10-F	Et	O	80
d	7-Cl	CH_3	O	81
e	7-Cl	Et	O	73
f	10-Cl	CH_3	O	90
g	H	CH_3	S	82
h	8-Cl	CH_3	S	65
i	10-F	CH_3	S	72
j	10-C	CH_3	S	88

Scheme 58 Synthesis of new hexahydropyrimido[5,4-*c*]quinoline-2,5-diones **118a–f** and 2-thioxohexahydropyrimido[5,4-*c*]quinoline-5-ones **118g–j**.

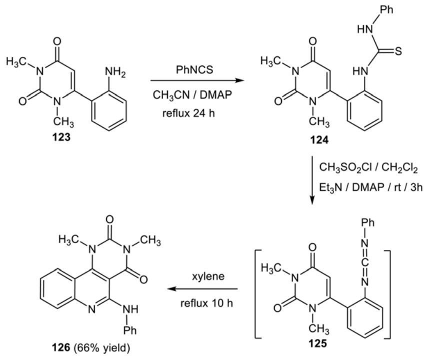
(Scheme 56). The yields of the products and the reaction times were not reported. These compounds were screened for their *in vitro* antioxidant activities against Trolox equivalent antioxidant capacity (TEAC), radical scavenging capacity using DPPH$^{\cdot}$, superoxide radical ($O_2^{\cdot -}$) scavenging activity, total antioxidant activity by FRAP, nitric oxide scavenging activity and metal chelating activity, and they exhibited significant antioxidant activities.

Ai and his group[58,116] designed and synthesized new derivatives of 2-(amino/aroxy)-5-methyl-pyrimido[5,4-*c*]quinolin-4(3*H*)-ones **112a,b** and **113a–i** *via* an aza-Wittig reaction, starting from ethyl 4-amino-2-methyl-quinoline-3-carboxylate (**109**), as shown in Scheme 57. Treatment of key intermediate **109** with triphenylphosphine, hexachloroethane and triethylamine at room temperature for 24 h afforded iminophosphorane **110** in a satisfactory yield (70% yield). Aza–Wittig reaction between iminophosphorane **110** and substituted phenyl isocyanate in dry methylene chloride under a nitrogen atmosphere at 45 °C for 12 h provided the corresponding carbodiimides **111**, which were used directly without further purification in the next step. Reacting **111** with alkyl amines in absolute EtOH in the presence of EtONa at room temperature for 12 h gave the desired tricyclic 2-(alkylamino)-3-aryl-5-methyl-pyrimido[5,4-*c*]quinoline-4(3*H*)-ones **112a,b.** Meanwhile, the reaction of carbodiimide **111** with substituted phenols in CH_3CN in the presence of a catalytic amount of K_2CO_3 at 75 °C for 4–6 h produced new 5-methyl-2-aryloxy-pyrimido[5,4-*c*]quinolin-4(3*H*)-ones **113a–l** in 30–39% yields. The products showed potential antiproliferative activity with broad spectrum against several human cancer cell lines.

In 2008, Ismaili *et al.*[56] developed a simple and general methodology for the synthesis of several new hexahydropyrimido[5,4-*c*]quinoline-2,5-diones **117a–f** and 2-thioxo-hexahydropyrimido[5,4-*c*]quinoline-5-ones **117g–j** by Biginelli reaction in two steps from ethyl 4-aryl-6-methyl-2-oxo-



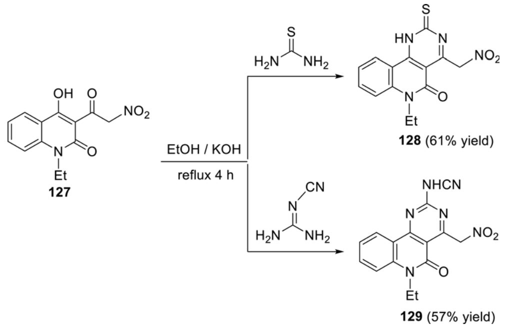
Scheme 59 Synthesis of new 1-aryl-4-methyl-3,6-bis-(5-methylisoxazol-3-yl)-2-thioxo-2,3,6,10*b*-tetrahydro-1*H*-pyrimido-[5,4-*c*]quinolin-5-ones **122a–h**.



Scheme 60 Synthesis of new 1,3-dimethyl-5-(phenylamino)-pyrimido[5,4-*c*]quinoline-2,4(1*H*,3*H*)-dione (**126**) *via* ring closure reaction of carbodiimide **125**.

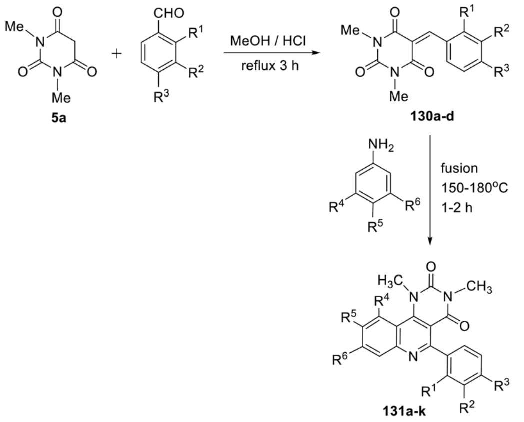
tetrahydropyrimidine-5-carboxylates **116a–f** or ethyl 4-aryl-6-methyl-2-thioxotetrahydropyrimidine-5-carboxylates **116g–j**, as good precursors. When a mixture of 2-chlorobenzaldehyde derivatives **114**, ethyl acetoacetate (**115**), urea or thiourea derivatives **116** and boric acid (H_3BO_3) in glacial CH_3CO_2H was heated at 100 °C for 3 h, they underwent condensation reactions to give the corresponding **117a–f** and **117g–j.** Intramolecular cyclization of **117** was achieved by heating in ammonia at 250 °C under 10 bars for 16 h to afford the desired tricyclic compounds **118a–j** in 65–90% yields (Scheme 58).

In 2010, Rajanarendar *et al.*[117] reported the synthesis of a novel series of 1-aryl-4-methyl-3,6-bis-(5-methylisoxazol-3-yl)-2-thioxo-2,3,6,10b-tetrahydro-1*H*-pyrimido[5,4-*c*]quinolin-5-ones **122a–h**, as antibacterial and antifungal agents, utilizing ethyl 3-aryl-4-(2-chloro-phenyl)-6-methyl-1-(5-methyl-isoxazol-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **120a–h** as starting materials, which were obtained by Biginelli reaction, through CAN-catalyzed one-pot condensation reaction of 2-chloro-benzaldehyde (**114**), ethyl acetoacetate (**115**) and isoxazolyl thioureas **119** (Scheme 59). The compounds **120a–h** when heated with 3-amino-5-methyl-isoxazole (**121**) in diphenyl ether under a nitrogen atmosphere at 200 °C for 10 h underwent intramolecular cyclization to give directly the new tricyclic ring system **122a–h** (Scheme 59). The yields of the products were not reported.



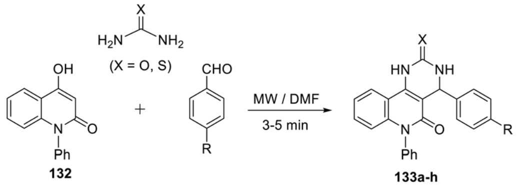
Scheme 61 Synthesis of 6-ethyl-4-(nitromethyl)-2-thioxo-2,6-dihydropyrimido[5,4-*c*]-quinolin-5(1*H*)-one (**128**) and 6-ethyl-4-(nitromethyl)-pyrimido[5,4-*c*]quinolin-5(6*H*)-one derivative **129**.

Krajsovszky and his coworkers[118] described the synthesis of a new 1,3-dimethyl-5-(phenylamino)-pyrimido[5,4-*c*]quinoline-2,4(1*H*,3*H*)-dione (**126**) *via* a carbodiimide intermediate by electrocyclic ring closure. The reactions were carried out by refluxing 6-(2-aminophenyl)-1,3-dimethyl-pyrimidine-2,4(1*H*,3*H*)-dione (**123**) with phenylisothio-cyanate in acetonitrile catalyzed by 4-(dimethylamino)-pyridine (DMAP) for 24 h to produce the thiourea derivative **124. By stirring a solution of 124** with methane-sulfonylchloride in dichloromethane in the presence of triethylamine and 4-dimethylamino-pyridine



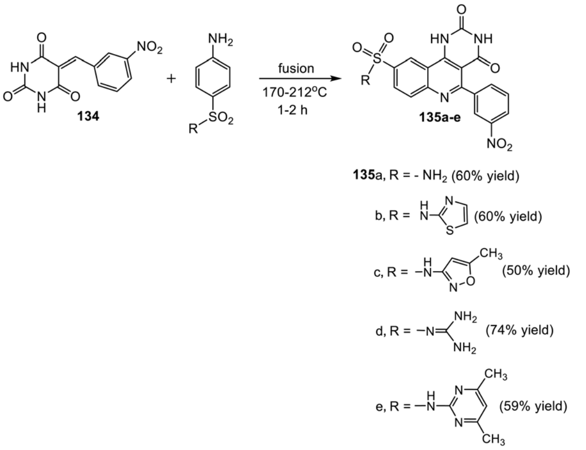
131	R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)
a	H	H	H	H	CH_3	H	42
b	H	H	OMe	H	CH_3	H	50
c	H	OMe	OMe	H	CH_3	H	53
d	H	OMe	OMe	H	Cl	H	47
e	H	OMe	OMe	OMe	H	OMe	40
f	H	H	OMe	OMe	H	OMe	38
g	H	H	H	H	Cl	H	45
h	H	H	H	OMe	H	OMe	40
i	H	OMe	OMe	H	OMe	H	43
j	H	H	OMe	H	OMe	H	55
k	OEt	H	H	H	OMe	H	46

Scheme 62 Efficient procedure for the synthesis of a series of pyrimido[5,4-*c*]quinoline-2,4-dione derivatives **131a–k**.

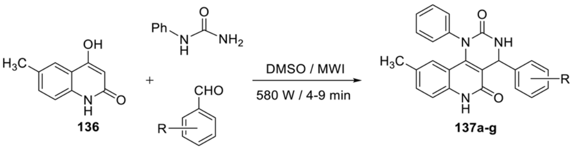


133 a, R = H; X = O (80% yield)
b, R = Cl; X = O (79% yield)
c, R = OMe; X = O (82% yield)
d, R = NO_2; X = O (83% yield)
e, R = H; X = S (82% yield)
f, R = Cl; X = S (85% yield)
g, R = OMe; X = S (79% yield)
h, R = NO_2; X = S (81% yield)

Scheme 63 Synthesis of 4-aryl-6-phenyl-4,6-dihydropyrimido[5,4-*c*]quinoline-2,5(1*H*,3*H*)-diones **133a–d** and 4-aryl-6-phenyl-2-thioxo-2,3,4,6-tetrahydropyrimido[5,4-*c*]quinolin-5(1*H*)-ones **133e–h**.



Scheme 64 Synthesis of highly functionalized 5-(-3-nitrophenyl)-pyrimido[5,4-*c*]quinoline-2,4(1*H*,3*H*)-diones **135a–e**.



137	R	Yield (%)
a	*o*-Cl	97.73
b	*m*- Cl	79.43
c	*p*-Cl	86.25
d	*p*-NO_2	92.47
e	*m*-NO_2	93.15
f	*p*-OH	92.78
g	H	96.23

Scheme 65 Synthesis of 4-aryl-9-methyl-1-phenyl-1,4-dihydropyrimido[5,4-*c*]quinolin-2,5(3*H*,6*H*)-diones **137a–g**.

(DMAP) at ambient temperature for 3 h, the corresponding carbodiimide **125** was generated *in situ*, which was transformed by refluxing in xylene to the cyclized product pyrimido[5,4-*c*]quinoline **126** (Scheme 60).

An efficient and straightforward synthesis of pyrimido[5,4-*c*]quinoline-5(1*H*)-ones by cyclocondensation method utilizing 1-ethyl-4-hydroxy-3-(2-nitroacetyl)quinolin-2(1*H*)-one (**127**), as a promising building block, with thiourea and cyanoguanidine was described by Ibrahim and his group in 2012.[119] Thus, refluxing **127** with thiourea and cyanoguanidine in ethanolic KOH solution for 4 h afforded the corresponding 6-ethyl-4-(nitromethyl)-2-thioxo-2,6-dihydropyrimido[5,4-*c*]quinolin-5(1*H*)-one (**128**) and 6-ethyl-4-(nitromethyl)-pyrimido[5,4-*c*]-quinolin-5(6*H*)-one derivative **129** in 61% and 57% yields, respectively (Scheme 61).

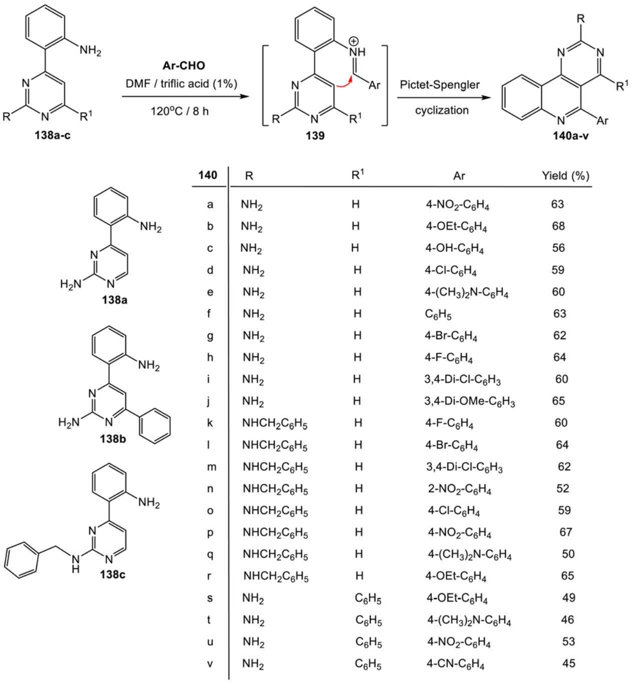
In 2013, Ismail *et al.*[120] developed an efficient procedure for the synthesis of a series of pyrimido-[5,4-*c*]quinoline-2,4-diones **131a–k** with different substituents on the quinoline ring as a useful scaffold for the synthesis of antimicrobial agents *via* a thermolysis reaction of an equimolar ratio of 5-arylidene-1,3-dimethylbarbituric acid derivatives **130a–d** with different aromatic amines at 150–180 °C for 1–2 h (Scheme 62).

4-Aryl-6-phenyl-4,6-dihydropyrimido[5,4-*c*]quinoline-2,5(1*H*,3*H*)-diones **133a–d** and 4-aryl-6-phenyl-2-thioxo-2,3,4,6-tetrahydropyrimido[5,4-*c*]quinolin-5(1*H*)-ones **133e–h** were synthesized *via* Biginelli condensation reactions of 4-hydroxy-1-phenyl-quinolin-2(1*H*)-one (**132**), aromatic aldehydes and urea or thiourea in DMF under microwave irradiation for 3–5 min (Scheme 63).[121]

A simple and solvent free reaction of 5-(3-nitrobenzylidene) pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**134**) with various sulfanilamides to synthesize highly functionalized 5-(3-nitro-phenyl) pyrimido-[5,4-*c*]quinoline-2,4(1*H*,3*H*)-diones **135a–e** was developed by Mubeen in 2018.[122] Thus, fusion of **134** with sulfanilamide derivatives in a sealed tube at 170–212 °C for 1–2 h in an oil bath afforded the desired tricyclic pyrimido[5,4-*c*]quinoline-2,4(1*H*,3*H*)-diones **135a–e** in 50–74% yields (Scheme 64). The synthesized compounds are potential drug candidates for the development of new antibacterial and antiviral agents.

Recently, Nadaraj and his coworkers[123] developed a new synthetic method for the synthesis of 4-aryl-9-methyl-1-phenyl-1,4-dihydropyrimido[5,4-*c*]quinolin-2,5(3*H*,6*H*)-diones **137a–g** by the reaction of 6-methyl-4-hyrdoxyquinolin-2(1*H*)-one (**136**), an aromatic aldehyde, with phenyl urea *via* the Biginelli reaction. A mixture of 6-methyl-4-hydroxy-quinolin-2(1*H*)-one (**136**), aromatic aldehydes and phenyl urea in dimethyl sulphoxide (DMSO) was irradiated in a microwave (580 W) for 4–9 min to provide 4-aryl-9-methyl-1-phenyl-1,4-dihydro-pyrimido[5,4-*c*]quinolin-2,5(3*H*,6*H*)-diones **137a–g** in very good to excellent yields (Scheme 65). The notable features of this protocol are mild reaction conditions, easy work of the products, excellent yields, cleaner reactions and short reaction times.

The synthesis of pyrimido[5,4-*c*]quinolines **140**, structurally analogous to biologically active benzonaphthyridines present in alkaloids, was described by Agarwal *et al.* in 2009.[124] This synthetic strategy is based on the modified Pictet–Spengler reaction. The 2-amino-pyrimidine substrates **138a–c** when heated with various aldehydes in DMF in the presence of

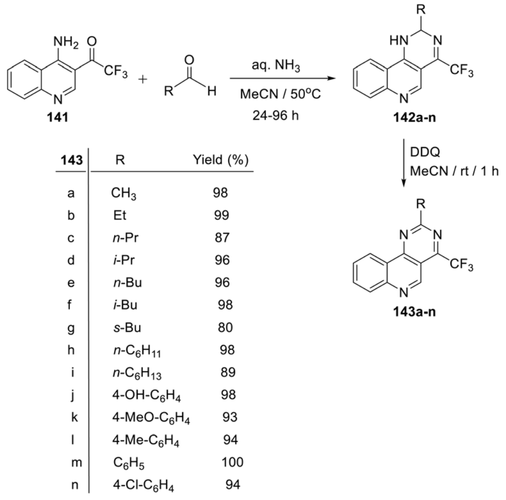


140	R	R^1	Ar	Yield (%)
a	NH_2	H	4-NO_2-C_6H_4	63
b	NH_2	H	4-OEt-C_6H_4	68
c	NH_2	H	4-OH-C_6H_4	56
d	NH_2	H	4-Cl-C_6H_4	59
e	NH_2	H	4-$(CH_3)_2N$-C_6H_4	60
f	NH_2	H	C_6H_5	63
g	NH_2	H	4-Br-C_6H_4	62
h	NH_2	H	4-F-C_6H_4	64
i	NH_2	H	3,4-Di-Cl-C_6H_3	60
j	NH_2	H	3,4-Di-OMe-C_6H_3	65
k	$NHCH_2C_6H_5$	H	4-F-C_6H_4	60
l	$NHCH_2C_6H_5$	H	4-Br-C_6H_4	64
m	$NHCH_2C_6H_5$	H	3,4-Di-Cl-C_6H_3	62
n	$NHCH_2C_6H_5$	H	2-NO_2-C_6H_4	52
o	$NHCH_2C_6H_5$	H	4-Cl-C_6H_4	59
p	$NHCH_2C_6H_5$	H	4-NO_2-C_6H_4	67
q	$NHCH_2C_6H_5$	H	4-$(CH_3)_2N$-C_6H_4	50
r	$NHCH_2C_6H_5$	H	4-OEt-C_6H_4	65
s	NH_2	C_6H_5	4-OEt-C_6H_4	49
t	NH_2	C_6H_5	4-$(CH_3)_2N$-C_6H_4	46
u	NH_2	C_6H_5	4-NO_2-C_6H_4	53
v	NH_2	C_6H_5	4-CN-C_6H_4	45

Scheme 66 Synthesis of pyrimido[5,4-c]quinolines **140a–v** *via* Pictet–Spengler reaction from 2-amino-pyrimidine substrates **138a–c**.

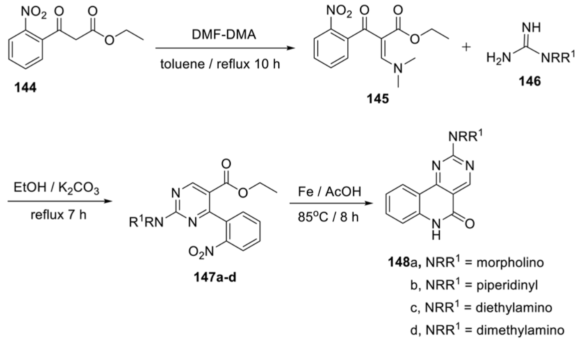
a catalytic amount of triflic acid (1%) at 120 °C for 8 h underwent Pictet–Spengler cyclization to give the corresponding tricyclic pyrimido-[5,4-*c*]quinolines **140a–v** in good yields *via* intermediacy of **139** (Scheme 66).

A novel three-component synthesis of fluorine-containing pyrimido[5,4-*c*]quinolines **143** *via* the condensation reactions of 4-amino-3-trifluoroacetyl-quinoline (**141**) with different aldehydes and aq. NH_3 was developed by Okada and his coworkers in 2014.[125] Thus, stirring a mixture of **141** (1 mmol) with aldehydes (5 mmol) and aq. NH_3 [28% (w/w)] (3 to 10 mmol) in MeCN at 50 °C for 24–96 h gave the corresponding fluorine-containing dihydropyrimido-[5,4-*c*]quinolines **142a–n**. Treatment of **142a–n** with DDQ in MeCN at room temperature for 1 h led to successful dehydrogenation to afford the desired 2-substituted-4-(trifluoromethyl)-pyrimido[5,4-*c*]quinolines **143a–n** in 80–100% yields (Scheme 67).



143	R	Yield (%)
a	CH_3	98
b	Et	99
c	*n*-Pr	87
d	*i*-Pr	96
e	*n*-Bu	96
f	*i*-Bu	98
g	*s*-Bu	80
h	*n*-C_6H_{11}	98
i	*n*-C_6H_{13}	89
j	4-OH-C_6H_4	98
k	4-MeO-C_6H_4	93
l	4-Me-C_6H_4	94
m	C_6H_5	100
n	4-Cl-C_6H_4	94

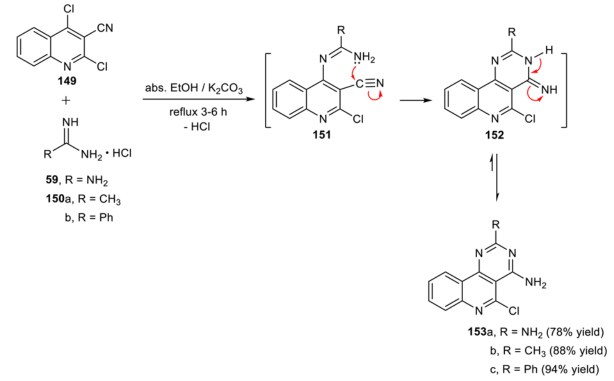
Scheme 67 Synthesis of 2-substituted-4-(trifluoromethyl)-pyrimido[5,4-c]quinolines **143** *via* three-component condensation reactions of 4-amino-3-trifluoroacetylquinoline (**141**) with different aldehydes and aq. NH_3.



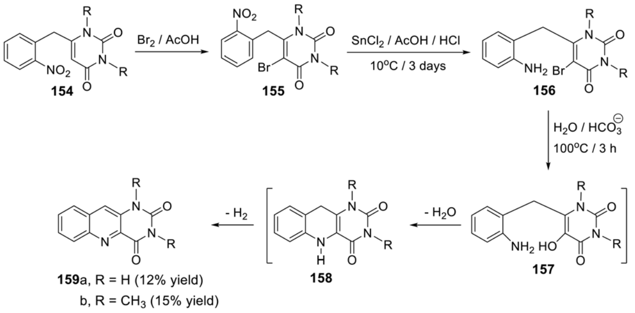
Scheme 68 Synthesis of 2-substituted-pyrimido[5,4-c]quinolin-5(6*H*)-ones **148a–d**.

Zhang *et al.*[126] synthesized a new series of 2-substituted-pyrimido[5,4-*c*]-zquinolin-5(6*H*)-one derivatives **148** and evaluated their cytotoxic activity against human lung carcinoma (H460), human colorectal cancer (HT-29) and human breast cancer (MDA-MB-231) cell lines. The results showed that most of these compounds exhibited stronger activity in the three selected cell lines. The condensation of ethyl 3-(2-nitrophenyl)-3-oxopropanoate (**144**) with dimethylformamide dimethylacetal (DMF–DMA) in toluene at reflux temperature for 10 h afforded ethyl 3-(dimethylamino)-2-(2-nitrobenzoyl)acrylate (**145**). When compound **145** was heated with various guanidines **146** in EtOH in the presence of K_2CO_3 at reflux temperature for 7 h, it underwent intermolecular cyclization to produce ethyl 2-substituted-4-(2-nitrophenyl)-pyrimidine-5-carboxylates **147a–d**. Finally, the reduction of the nitro group in **147** with Fe in AcOH at 85 °C for 8 h and ring-closure in one pot gave the target tricyclic 2-substituted-pyrimido-[5,4-*c*]quinolin-5(6*H*)-ones **148a–d** in 45–75% yields (Scheme 68).

In 2022, Mekheimer and his group[127] developed a new, affordable, simple, and one-step methodology for the construction of a novel series of pyrimido[5,4-*c*]quinolines variously substituted at positions 2 and 5, as potential anti-proliferative agents with multitarget actions, *via* a rapid base-catalyzed cyclization reaction of 2,4-dichloro-quinoline-3-carbonitrile (**149**) with guanidine hydrochlorides **59; 150a,b**. The reactions were carried out by refluxing compound **149** (1 mmol) with **59; 150a,b** (4 mmol) in the presence of anhydrous K_2CO_3 (4 mmol) in absolute EtOH for 3–6 h, as inferred by TLC. The reaction occurred *via* an initial nucleophilic attack of the guanidine on the quinoline C-4, followed by 6-*exo*-dig cyclization to afford the new tricyclic 4-amino-5-chloro-2-substituted-pyrimido[5,4-*c*]quinolines **153a–c** in one step *via* intermediacies **151** and **152** in very good to excellent yields (Scheme 69).



Scheme 69 One-step synthesis of new 4-amino-5-chloro-2-substituted-pyrimido[5,4-*c*]quinolines **153a–c**.

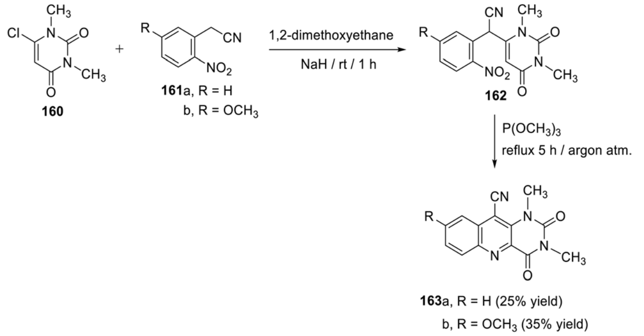


Scheme 70 Synthesis of 1,3-disubstituted-pyrimido[5,4-*b*]quinoline-2,4(3*H*)-diones **159a,b**.

2.3. Synthesis of pyrimido[5,4-*b*]quinolines

Fenner and Teichmann[128] developed a synthetic route for the synthesis of pyrimido[5,4-*b*]quinoline derivatives as analogues of lumichrome. The bromination of **154** in glacial AcOH gave the corresponding 5-bromo-1,3-disubstituted-6-(2-nitrobenzyl)-pyrimidine-2,4(1*H*,3*H*)-diones **155**. The reduction of **155** with stannous chloride in glacial acetic acid/HCl at 10 °C for 3 days gave 6-(2-aminobenzyl)-5-bromo-1,3-disubstituted-pyrimidine-2,4(1*H*,3*H*)-dione derivatives **156**. When compound **156** was warmed in a saturated $NaHCO_3$ solution at 100 °C for 3 h, the desired tricyclic 1,3-disubstituted-pyrimido-[5,4-*b*]quinoline-2,4(3*H*)-diones **159a,b** were obtained in low yields as fluorescent substances (Scheme 70).

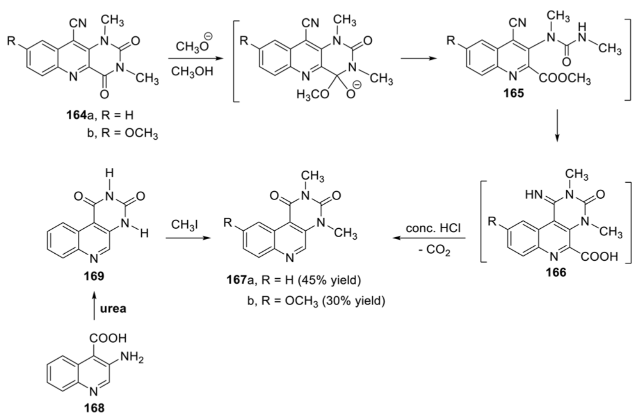
Fenner *et al.*[129] described the synthesis of 1,3-dimethyl-2,4-dioxo-8-substituted-1,2,3,4-tetrahydropyrimido[5,4-*b*]quinoline-10-carbonitriles **163a,b** by the trimethylphosphite cyclization of 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-2-(2-nitro-5-substituted-phenyl)acetonitrile derivatives **162**. As shown in Scheme 71, the reactions were achieved in two steps. Stirring a mixture of 6-chloro-1,3-dimethyluracil (**160**) (1 equiv.), 2-nitro-phenylacetonitrile (**161a**) or 5-methoxy-2-nitro-phenylacetonitrile (**161b**) (1 equiv.) and NaH (5.8 equiv.) in 1,2-dimethoxyethane at room temperature for 1 h gave **162**. The reductive cyclization of nitro-substituted aromatics in **162** was performed by heating **162** in trimethylphosphite at reflux temperature under an argon atmosphere for 5 h to obtain the desired tricyclic products **163a,b** directly in low yields.



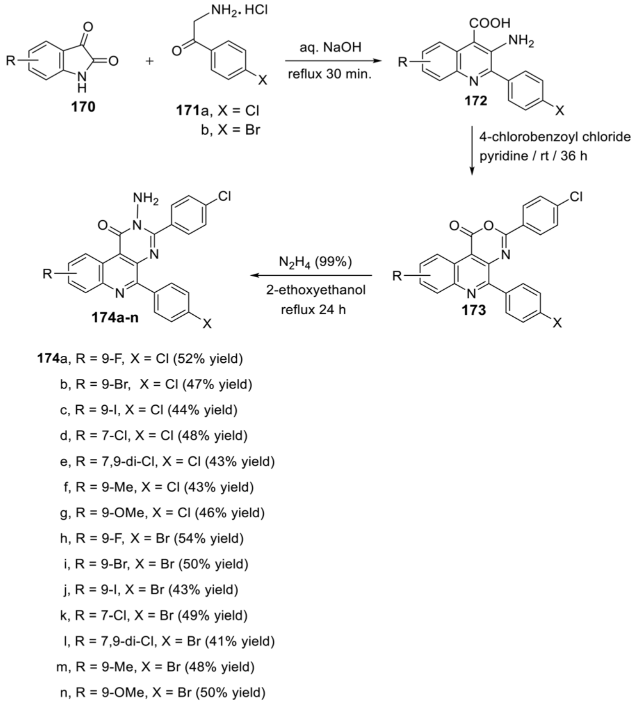
Scheme 71 Synthesis of 1,3-dimethyl-2,4-dioxo-8-substituted-1,2,3,4-tetrahydropyrimido-[5,4-*b*]quinoline-10-carbonitriles **163a,b**.

2.4. Synthesis of pyrimido[4,5-*c*]quinolines

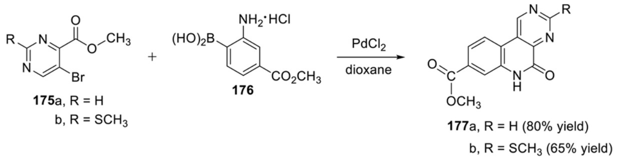
In 1986, Fenner and his coworkers[130] described a facile and unexpected transformation of the pyrimido[5,4-*b*]quinoline ring system to pyrimido[4,5-*c*]quinoline derivatives. They reported that investigations of the reactivity of deazaalloxazines towards nucleophiles showed that in the case of 5-deazaalloxazine and 10-deazaalloxazine, ring-opening reactions occur at the pyrimidine-2,4-dione system and preferably occur by attack in the 2-position. Unexpectedly, with the 10-cyano substitution of the 10-deazaalloxazine system, ring opening follows exclusively under attack in the 4-position. The reaction was performed by adding sodium methoxide solution dropwise to a suspension of 1,3-dimethyl-2,4-dioxo-pyrimido[5,4-*b*]quinoline-10-carbonitriles **164a,b** in absolute MeOH until the substances dissolved and a dark color appeared. Then, acidification with conc. HCl resulted in the formation of the tricyclic products, namely 2,4-dimethylpyrimido[4,5-*c*]quinoline-1,3(2*H*,4*H*)-diones **167a,b**, in moderate yields *via* intermediates **165** and **166** (Scheme 72). The following mechanism is proposed based on the structure of the end product. First, ring opening to **165**



Scheme 72 Facile and unexpected transformation of pyrimido[5,4-*b*] quinolines **164a,b** to pyrimido[4,5-*c*]quinolines **167a,b**.



Scheme 73 Synthesis of new 2-amino-pyrimido[4,5-*c*]quinolin-1(2*H*)-ones **174a–n**.



Scheme 74 One-pot procedure for the synthesis of novel substituted pyrimido[4,5-*c*]quinolines **177a,b**.

occurs, which results in a rapid subsequent relationship action to form the angularly annulated pyrimido[4,5-*c*]quinoline **166**. Upon acidification, the hydrolysis of imine **166** occurs, followed by decarboxylation to **167** (Scheme 72). This unexpected transformation of pyrimido[5,4-*b*]quinoline **164** to pyrimido[4,5-*c*] quinoline **167** is supported by the independent synthesis of **167a**. The condensation of 3-amino-quinoline-4-carboxylic acid (**168**) with urea afforded pyrimido[4,5-*c*]quinoline-1,3(2*H*,4*H*)-dione (**169**), which reacted with methyl iodide to produce a product identical to **167a** (Scheme 72).

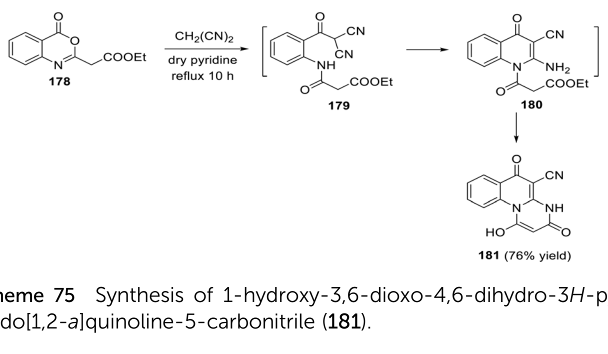
In 2010, Metwally *et al.*[131] described the synthesis of a novel series of 2-amino-pyrimido[4,5-*c*]quinolin-1(2*H*)-ones **174a–n** having several substituents with various electronic and steric properties at different positions of the pyrimidine and quinoline rings (positions 3,5,7 and 9) as potent cytotoxic antimitotic agents. The synthetic route to the target 2-amino-pyrimido[4,5-*c*]quinolin-1(2*H*)-ones **174** is illustrated in the general reaction sequence depicted in Scheme 73. The starting 3-amino-2-aryl-quinoline-4-carboxylic acids **172** were synthesized by refluxing isatins **170** with 4-chloro- (**171a**) or 4-bromo-phenacyl-amine hydrochloride (**171b**) in aq. NaOH for 30 min. The treatment of acids **172** with 4-chlorobenzoyl chloride in pyridine at room temperature for 36 h led to the formation of the lactones, [1,3] oxazino[4,5-*c*]-quinolin-1-ones **173**. Finally, the hydrazinolysis of the lactones **173** by heating with hydrazine hydrate (99%) in 2-ethoxyethanol, as a high boiling solvent, at reflux temperature for 24 h afforded the desired pyrimido[4,5-*c*]quinolin-1(2*H*)-ones **174a–n** in 41–54 yields.

In 2011, Pierre *et al.*[132] described the first one-pot synthesis of novel substituted pyrimido[4,5-*c*]-quinolines, which act mechanistically as ATP-competitive inhibitors of protein kinase CK2. Palladium-catalyzed coupling between methyl 5-bromo-2-substituted-pyrimidine-4-carboxylates **175a,b** and 2-amino-4-(methoxycarbonyl)-phenylboronic acid hydrochloride (**176**) in dioxane at reflux temperature resulted in the one-pot formation of cyclized methyl 5-oxo-5,6-dihydropyrimido[4,5-*c*]quinoline-8-carboxylates **177a,b** (Scheme 74). Reaction times were not reported.

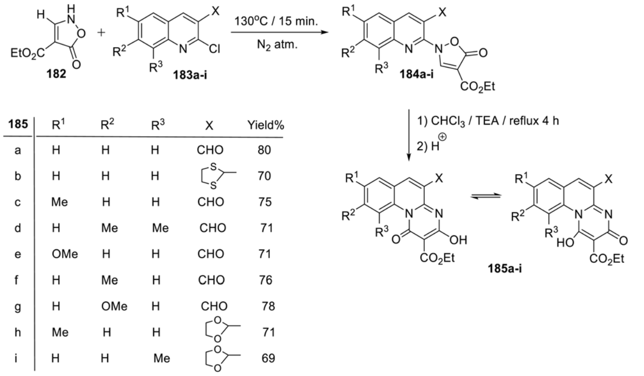
2.5. Synthesis of pyrimido[1,2-*a*]quinolines

In 2007, Ukrainets and his group[133] described the synthesis of 1-hydroxy-3,6-dioxo-4,6-dihydro-3*H*-pyrimido[1,2-*a*]quinoline-5-carbonitrile (**181**) in 76% yield *via* the reaction of ethyl 2-(4-oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)acetate (**178**) with malononitrile in dry pyridine at reflux temperature for 10 h (Scheme 75). In the proposed reaction mechanism, benzoxazinone **178** reacted with the highly nucleophilic carbanion generated from malononitrile to give the acylmalononitrile intermediate **179**, which was cyclized into the corresponding aminoquinolone intermediate **180.** The isolation of **180** was unsuccessful because under the reaction conditions of the synthesis, the amino group was subject to intramolecular acylation with the formation of the desired tricyclic product 1-hydroxy-3,6-dioxo-4,6-dihydro-3*H*-pyrimido[1,2-*a*]quinoline-5-carbonitrile (**181**) (Scheme 75).

In 2011, Marjani *et al.*[134,135] reported a short, facile and highly effective method for the synthesis of functionalized pyrimido [1,2-*a*]quinoline derivatives **185a–i** by the rearrangement of *N*-quinolinyl-isoxazol-5(2*H*)-ones **184a–i** under mild basic conditions (Scheme 76). Heating a neat mixture of ethyl 5-oxo-2,5-dihydroisoxzole-4-carboxylate (**182**) with 2-chloroquinolines **183a–i** at 130 °C under nitrogen atmosphere for 15 min afforded the corresponding *N*-quinolinylisoxazolones **184a–i.** When compounds **184a–i** were refluxed in $CHCl_3$ in the presence of a catalytic amount of triethylamine for 4 h, the desired ethyl 3-hydroxy-5,8,9,10-tetrasubstituted-1-oxo-1*H*-pyrimido[1,2-*a*]

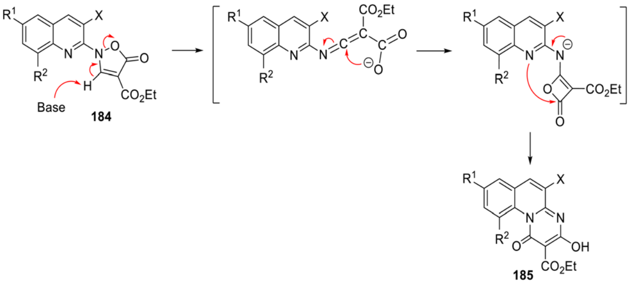


Scheme 75 Synthesis of 1-hydroxy-3,6-dioxo-4,6-dihydro-3*H*-pyrimido[1,2-*a*]quinoline-5-carbonitrile (**181**).

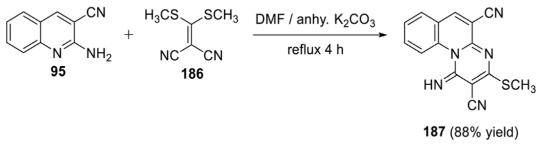


185	R^1	R^2	R^3	X	Yield%
a	H	H	H	CHO	80
b	H	H	H		70
c	Me	H	H	CHO	75
d	H	Me	Me	CHO	71
e	OMe	H	H	CHO	71
f	H	Me	H	CHO	76
g	H	OMe	H	CHO	78
h	Me	H	H		71
i	H	H	Me		69

Scheme 76 Facile synthesis of a new series of ethyl 3-hydroxy-5,8,10-trisubstituted-1-oxo-1*H*-pyrimido[1,2-*a*]quinoline-2-carboxylates **185a–i**.



Scheme 77 Plausible mechanism for the formation of **185**.

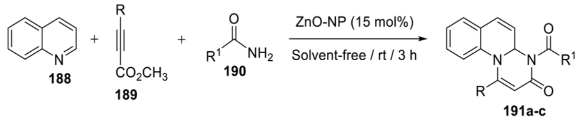


Scheme 78 Novel and simple route for the synthesis of 1-imino-3-(methylthio)-1*H*-pyrimido[1,2-*a*]quinoline-2,5-dicarbonitrile (**187**).

quinoline-2-carboxylates **185a–i** were produced in 69–80% yields (Scheme 76). A mechanism for the formation of **185a–i** is outlined in Scheme 77.

In 2013, Jadhav and Halikar[136] reported for the first time a simple route for the synthesis of 1-imino-3-(methylthio)-1*H*-pyrimido[1,2-*a*]quinoline-2,5-dicarbonitrile (**187**) under mild conditions with good yield, exhibiting significant antibacterial and antifungal activities. On reacting 2-amino-quinoline-3-carbonitrile (**185**) with 2-(bis-(methylthio)-methylene) malononitrile (**186**) in *N*,*N*-dimethylformamide in the presence of a catalytic amount of anhydrous K_2CO_3 under reflux for 4 h, 1-imino-3-(methylthio)-1*H*-pyrimido[1,2-*a*]quinoline-2,5-dicarbonitrile (**187**) was obtained in 88% yield (Scheme 78).

Recently, Soleimani-Amiri and co-workers[137] reported a green and one-pot synthesis of pyrimido[1,2-*a*]-quinolin-3-ones **191a–c** in high yields from the reaction of quinoline (**188**), dialkylacetylene-dicarboxylate or propiolate **189** and amides **190** in the presence of ZnO nanorods (ZnO-NRs) (15 mol%), as an efficient catalyst, under solvent-free conditions at room temperature (Scheme 79). The ease of use, solvent-free conditions, and reusability of the catalyst make this method an interesting alternative to others. The current method has several advantages, including high atom economy and yield, clean and mild reaction conditions, a short reaction time and low catalyst loading.

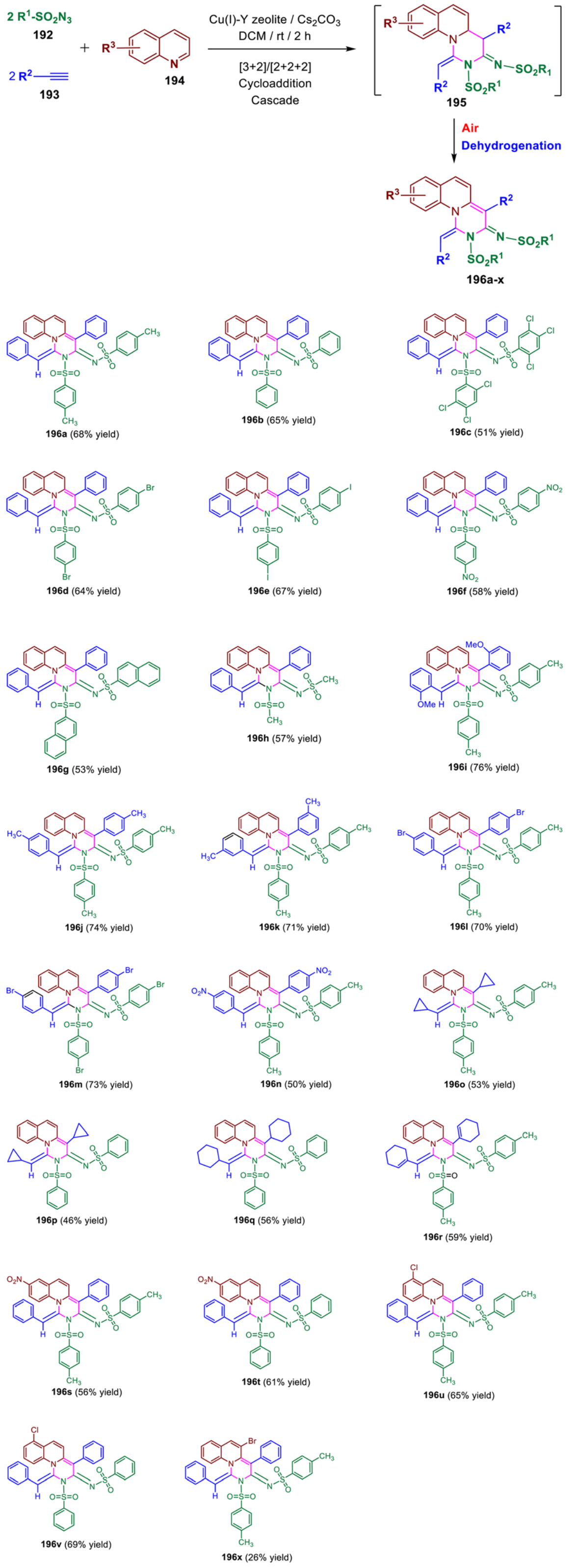


191	R	R^1	Yield %
a	CO_2Me	H	87
b	CO_2Me	CH_2Cl	85
c	H	3-pyridyl	83

Scheme 79 Green and one-pot synthesis of pyrimido[1,2-*a*]quinolin-3-ones **192a–c**.

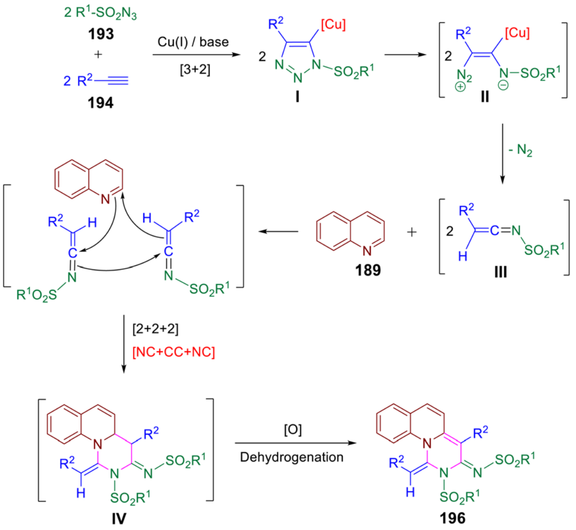
2.6. Synthesis of pyrimido[1,6-*a*]quinolines

In 2015, Ramanathan and Pitchumani[138] reported for the first time an unprecedented copper(I)–Y zeolite-catalyzed tandem process involving ketenimine-based termolecular [2 + 2 + 2]/[NC + CC + NC] cycloaddition using sulfonyl azides **192**, alkynes **193** and quinoline derivative **194** to synthesize highly functionalized pyrimido[1,6-*a*]quinolines **196a–x** (Scheme 80). In this simple, highly atom- and step-economical protocol, copper(I) promotes azide–alkyne [3 + 2] cycloaddition, which is followed by ring-rearrangement/ketenimine formation/regio- and stereoselective [2 + 2 + 2] termolecular cycloaddition and dehydrogenation cascade to afford selectively the *E*-isomer of pyrimido[1,6-*a*] quinoline. The advantages of performing two cycloaddition reactions ([3 + 2] [2 + 2 + 2]) in one operation, remarkable simplicity of operation and significant molecular complexity generated render this catalytic system environmentally friendly and potentially cost-effective. The reaction was carried out by adding alkyne **193** (2 equiv.) to a mixture of Cu(I)–Y zeolite (20 mg, 10 mol%), sulfonyl azide **192** (2 equiv.), quinoline derivative **194** (1 equiv.) and Cs_2CO_3 (1.2 equiv.) in DCM under an open air atmosphere at room temperature. The methodology furnished the desired tricyclic **196**, *via* intermediacy of **195** in 26–76% yields (Scheme 80). The plausible mechanistic pathway for the formation of **196** is described in Scheme 81. Sulfonyl azide **192** and alkyne **193** in the presence of Cs_2CO_3 and Cu(I)–Y zeolite form copper triazolyl intermediate **I**. This is followed by a ring opening reaction to give **II**, which undergoes rearrangement and extrusion of nitrogen to yield *N*-sulfonyl-ketenimine **III**, simultaneously regenerating the copper catalyst. The *N*-sulfonyl-ketenimine **III** as an energetic dipolar intermediate, reacting simultaneously as an electrophile (across C=N) and nucleophile (across C=C bond), undergoes addition to the C=N bond of quinoline in a novel termolecular [2 + 2 + 2] cycloaddition reaction. The observed [NC + CC + NC] termolecular cycloaddition reaction occurs regioselectively and stereoselectively to form



Scheme 80 Synthesis of highly functionalized pyrimido[1,6-*a*]quinolines **196a–x**.

a dihydro intermediate **IV** in a concerted manner. The subsequent dehydrogenation of intermediate **IV** by air oxidation generates pyrimido[1,6-*a*]quinolines **196**.



Scheme 81 Plausible mechanism for the formation of pyrimido[1,6-*a*]quinolines **196a–x**.

3. Conclusion

In this review, we highlighted the synthesis of all six known types of pyrimidoquinolines with notable pharmacological and biological properties. Rapid progress in the chemistry of pyrimidoquinoline derivatives over the past two decades has led to a wide range of valuable synthetic methods for all major classes of these ring systems. Because of the established biological and pharmaceutical activities of the synthesized ring systems, we hope that this review will attract more research efforts to this field and provide a useful aid to crop protection, medicinal and other chemists dealing with heterocyclic systems daily. In addition, the lack of a comprehensive literature overview on the synthesis of all six known types of pyrimidoquinolines is behind the present attempt to provide for the first time a detailed literature survey and summarize the synthesis of these ring systems.

Data availability

No primary research results, software, or code are included, and no new data are generated or analyzed in this review.

Conflicts of interest

There are no conflicts to declare.

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