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Vistas in the domain of 3-acetyl-4-hydroxy-2-quinolinone derivatives (AHQ) and their applications

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This review discusses the significant advances in the current status and latest synthesis techniques for *N*-substituted 3-acetyl-4-hydroxyquinolinones. They are an important class of alkaloids possessing different electrophilic and nucleophilic centers. In this review, we comprehensively summarize the synthesis of 3-acetylquinolones *via* various reactions, emphasizing recent developments and challenges. Synthetic transformations of quinolone are focused on electrophilic substitution reactions supported by their mechanistic pathways, as well as nucleophilic substitution reactions and cycloaddition reactions, which have allowed access to an extensive scope of binary and fused heterocyclic scaffolds, including pyrazoles, imidazoles, tetrazoles, pyridines, pyrimidines, triazines, azepines, and pyranones. Also, the utilization of quinolone reactions as key intermediates in the ongoing and forthcoming marketed pharmaceutical syntheses is discussed. Additionally, this review covers various potential applications, including complexation, fluorescence sensing, chemical pH sensors, agricultural, and anticorrosion.

1. Introduction and scope

Heterocyclic skeletons which contain a nitrogen atom represent a common unit of a vast amount of marketed drugs,[1] constituting the most extensive and diverse collection of natural, synthetic organic compounds, agrochemicals, and pharmaceuticals.[2–4] Furthermore, the chemistry of heterocycles aggregates an essential branch of the field of drug design and the evolution of novel biologically active compounds,[5–11] including antiparasitic,[12,13] anti-HIV,[14,15] antiepileptic drugs,[16,17] analgesic,[18,19] anthelmintic,[20,21] inhibitors of platelet aggregation, anti-inflammatory,[22–25] antibacterial and antiviral drugs,[26–29] atherosclerosis,[30,31] inhibitors for Parkinson's disease,[32] antiproliferative, pulmonary antifibrotic agents[33] and antitumor.[34–36] Additionally, they provide one of the most fruitful sources for drug discovery and development, owing to synthesizing various scaffolds *via* robust synthetic approaches.[37–40] These are important in synthesizing dyes, pigments, and polymeric materials[41–43] due to their optical and fluorescence properties.[44] The ongoing research in synthetic organic chemistry is dedicated to advancing these goals and addressing the demand for improved and sustainable approaches in synthesizing aromatic heterocyclic compounds.[2–4] Easily accessible nitrogenous scaffolds are fundamental feedstocks; among these, quinoline and quinolones have piqued the interest of scientists since the 19th century, as over 600 quinoline derivatives have been extracted from natural sources to date.

Quinolinones have been perceived for their fascinating structural notions and versatile applications.[45–56] Also, the quinolinones structures are pivotal building blocks,[46] as they are commonly conspicuous scaffolds in a wide range of pharmacologically active synthetic and natural compounds.[57–68] Quinolin-2-one, also referred to as benzo[*b*]pyridine, and 1-azanaphthalene, is important classes of natural product as *N*-based heterocycles which extracted from *Toddalia asiatica* leaves and plants, marine organisms and microorganisms which containing the quinolinone derivatives alkaloid findersine,[52,69–75] consists of a benzene ring fused with a pyridine ring, sharing two carbon atoms between them and nitrogen atom not present as ring junction atom.

Quinoline is a weak base capable of forming salts with acids. It reacts similarly to pyridine and benzene and undergoes either nucleophilic or electrophilic substitution processes.[47,76–81] The importance of the quinoline moiety is being a vital component in many naturally occurring heterocyclic and medicinal plant families. In addition, bucharidine **1** and foliosidine **2** are quinoline alkaloids that are extracted from *Haplophyllum foliosum* and *Haplophyllum bucharicum*, respectively (Fig. 1). Also, both of them have viral-RNA polymerase inhibitory action and estrogenic action, such as compounds **3** and **4**, which strongly inhibit the replication of the hepacivirus C.[82–84]

Additionally, quinolines have various potential biological and pharmacological activities including antimalarial,[84–86] antibacterial,[87] antifungal,[88,89] anticancer,[90–92] anti-HIV (Human

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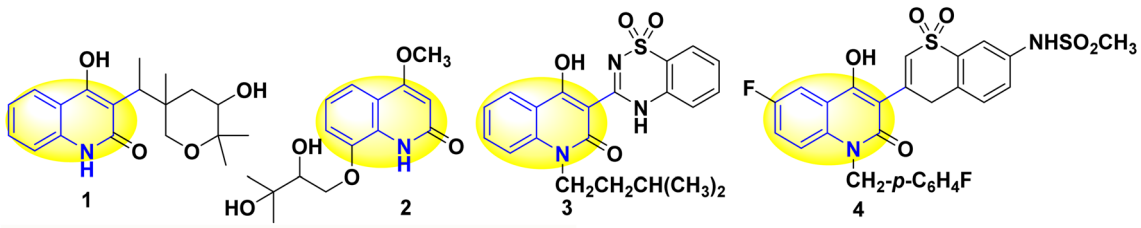


Fig. 1 Some natural alkaloids quinolinone-based molecules.

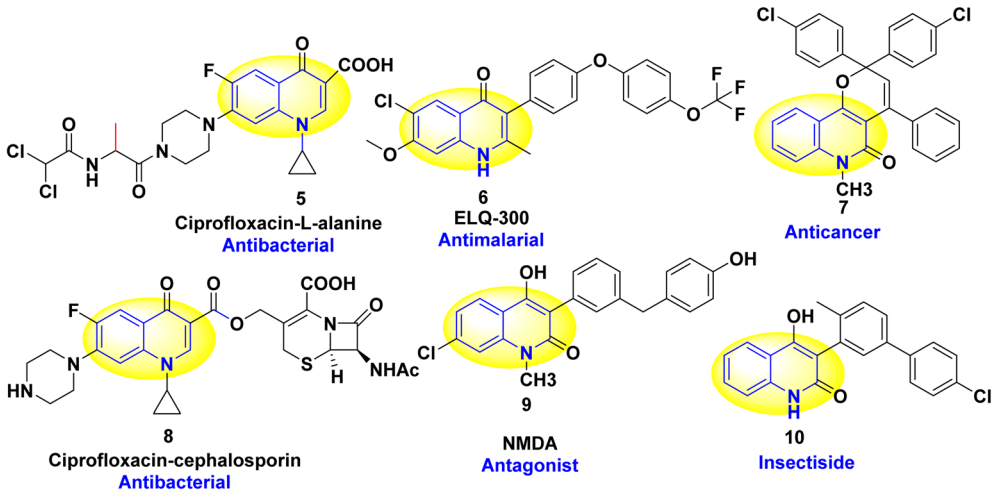


Fig. 2 Chemical structure of biologically active quinolinone scaffolds.

Immunodeficiency Virus),[93] antiviral,[94] antitumor,[95–97] anthelmintic,[98] antioxidant,[49] cardiotonic,[76,99–101] anticonvulsant,[102,103] anti-inflammatory and analgesic properties[76,77,104,105] (Fig. 2).

2. Chemical reactivity

2.1. 3-Acetyl-*N*-substituted/(un)-4-hydroxy-quinolin-2(1*H*) one derivatives (AHQ)

AHQ is the basic ring structure of numerous alkaloids and is a highly versatile scaffold with an extensive range of applications. Progress in synthetic technologies is leading to the production of various functionalized quinolinone derivatives as biosteric analogues to linomide (4-hydroxyquinolinone) derivatives.[82,106–112]

2.2. Structural feature of AHQ

2.2.1. Tautomeric structures. Whereas, the *β*,*β*′-tricarbonyl (TC) group in AHQ compound provides an analogue of 3-acyl pyrrolidine-2,4-diones (tetramic acid), and has suitable sites for interaction with different nucleophilic reagents, with its

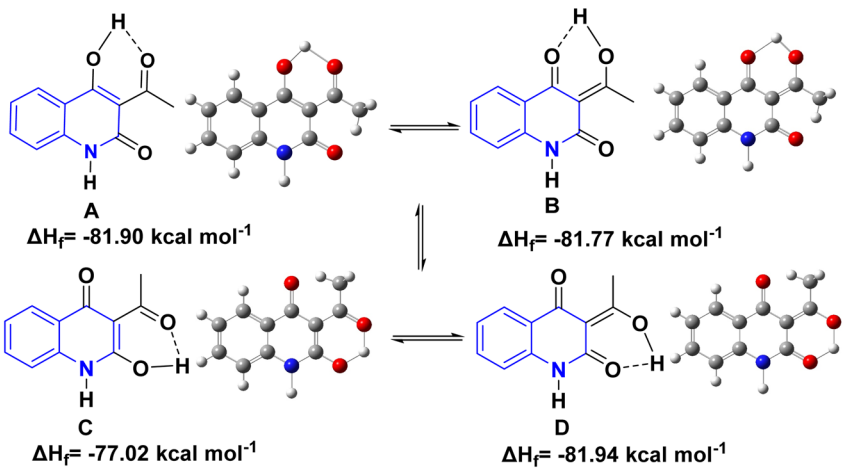
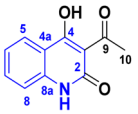
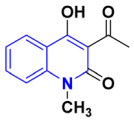
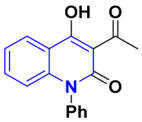


Fig. 3 Tautomeric form of AHQ **12a** and its geometrical structures.

Table 1 Spectral data of AHQ 12a–c

Spectroscopic technique	 12a	 12b	 12c
^{1}H NMR (DMSO-d_6)	2.72 (s, 3H, $COCH_3$), 7.23 (t, 1H, H-6), 7.30 (d, 1H, H-8, J = 8.3 Hz), 7.65 (t, 1H, H-7), 7.99 (dd, 1H, H-5, J = 8.0, J = 1.2 Hz), 11.53 (s, 1H, NH) and 17.04 (s, 1H, OH)[116]	2.79 (s, 3H, $COCH_3$), 3.52 (s, 3H, N–CH_3), 7.30 (t, 1H, H-6), 7.50 (d, 1H, H-8, J = 8.1 Hz), 7.78 (t, 1H, H-7), 7.96 (dd, 1H, H-5, J = 8.4 Hz, J = 1.5 Hz) and 17.04 (s, 1H, OH)[116]	2.77 (3H, s, 3-$COCH_3$), 7.12–7.41 ($9H_{Arom}$), 8.23 (s, OH)[117] Our work 2.79 (s, 3H, $COCH_3$, 6.58 (d, 1H, J = 9 Hz), 7.23 (m, 1H), 7.27 (d, 2H, J = 8 Hz), 7.45 (t, 1H, J = 8 Hz), 7.53 (t, 1H, J = 7 Hz), 7.61 (t, 2H, J = 8 Hz), 8.24 (d, 1H, J = 8 Hz), 17.16 (s, 1H, OH)
^{13}C NMR (DMSO-d_6)	205.7 (C-9), 174.7 (C-4), 161.1 (C-2), 140.5 (C-8a), 134.8 (C-7), 124.7 (C-5), 122.0 (C-6), 115.5 (C-8), 113.3 (C-4a), 105.7 (C-3) and 30.5 (C-10)[116]	206.7 (C-9), 173.3 (C-4), 160.6 (C-2), 141.6 (C-8a), 135.7 (C-7), 125.4 (C-5), 122.3 (C-6), 114.4 (C-8), 115.3 (C-4a), 105.7 (C-3), 31.3 (C-10) and 28.9 (N–CH_3)[116]	206.9 (C-9), 175.0 (C-4), 161.9 (C-2), 142 (1C), 137.4 (1C), 134.4 (1C), 130.3 (2C), 129.0 (2C), 125.8 (1C), 122.3 (1C), 117.7 (1C), 116.0 (1C), 115.2 (1C), 106.0 (1C), 31.4 (1C)
IR (KBr, ν_{max}/cm^{-1})	3360 (OH), 3160 (NH), 1661 (C=O, acetyl), 1622 (C=O, amide), 1606 (C=C)[116]	3250 (OH), 1658 (C=O, acetyl), 1623 (C=O, amide 1598 (C=C)[117]	3072 (CH_{Arom}), 2924 (CH_{Aliph}), 1654(C=O, acetyl, enol form), 1618 (C=O, amide).[114,118]

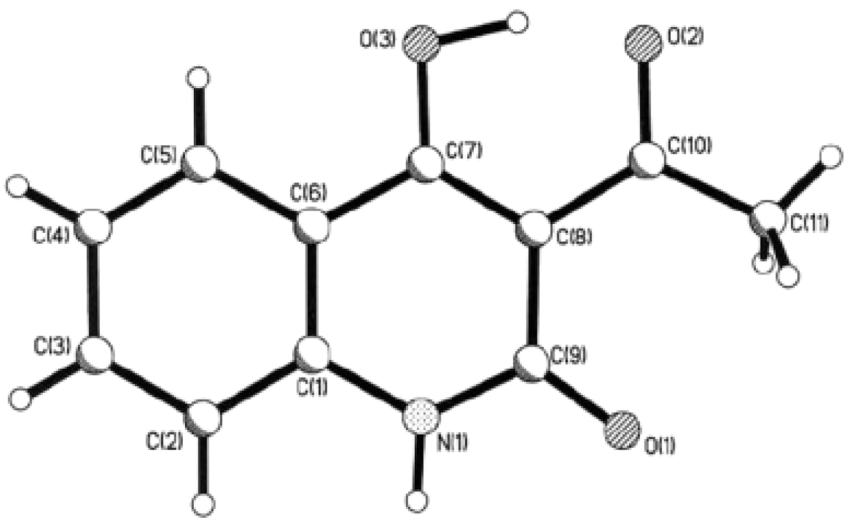


Fig. 4 X-ray structural analysis 12a.[120]

regioselectivity of TC for AHQ [(A)–(D)] given below in a framework of molecular orbital perturbation.[113]

Detsi and coworkers[114] predicting the four tautomeric structures A–D. of AHQ [R=H] **12a** (Fig. 3). The tautomeric equilibrium showed the presence of tautomeric forms that could be in one of four possible structures, A–D (Fig. 3). Whereas, semiempirical quantum calculations showed that the tautomer D was the most stable favorable one according to the total energy values.[114,115] Whereas, the constitutions of AHQ derivatives were fully elucidated *via* different spectroscopic analyses as shown in Table 1.[114,116–118]

2.2.2. X-ray crystallographic. The constitution of AHQ **12a** was supported by X-ray analysis, as the non-hydrogen atoms in compound **12a** are located in a single plane with an accuracy of 0.02 Å, this phenomena indicated the formation of an intramolecular hydrogen bond O(3)–H(3O)···O(2) (H···O 1.41 Å, O–H···O 157°). Also, this phenomenon displayed the re-estimation of the intramolecular electronic charge as shown

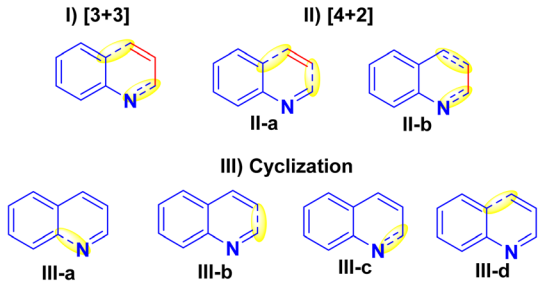


Fig. 5 Common synthetic methods of quinolines.

by the bond lengths O(2)–C(10) 1.255(2) and C(7)–C(8) bonds 1.393(2) (Fig. 4).[119,120]

3. Aspects of the AHQ synthetic approach

Quinolines can be synthesized *via* different synthetic strategies involving [3 + 3], [4 + 2] and cyclization methodologies (I–III).[121]

(I) [3 + 3] Annulation: This strategy includes established procedures, for instance, the Skraup, Conrad-Limpach, Doebner-von Miller, Combes, and Gould-Jacobs syntheses. However, the drawback of these techniques is that they are restricted in regioselectivity for the synthesis of multi-substituted quinolines.[121–123]

(II) [4 + 2] Annulation: There are two techniques to build pyridine nuclei annulated to the benzene ring as shown in designed forms (II-a and II-b), as the first one has minimal regioselectivity with a narrow substrate range.[121,124,125] While the other method is more prevalent and employs easily available substrates to produce products with high regioselectivity as Ptzinger and Friedlander reactions.[121,122,126,127]

(III) Cyclization: There are four distinct ways to generate the pyridine ring of quinolines (III-a to III-d) using cyclization. However, they have not been achieved due to the complicated reaction methodology and the limited availability of the starting substrates (Fig. 5).[128,129]

Synthetic approaches to construct AHQ derivatives have been achieved *via* many routes: aniline, alkaline hydrolysis of pyranoquinoline, anthranilic acid derivatives, heterocyclization of 3,1-benzoxazine-4-one and furo[3,2-*c*]quinoline.

3.1. Synthesis from amines/pyrano[3,2-*c*]quinolindione

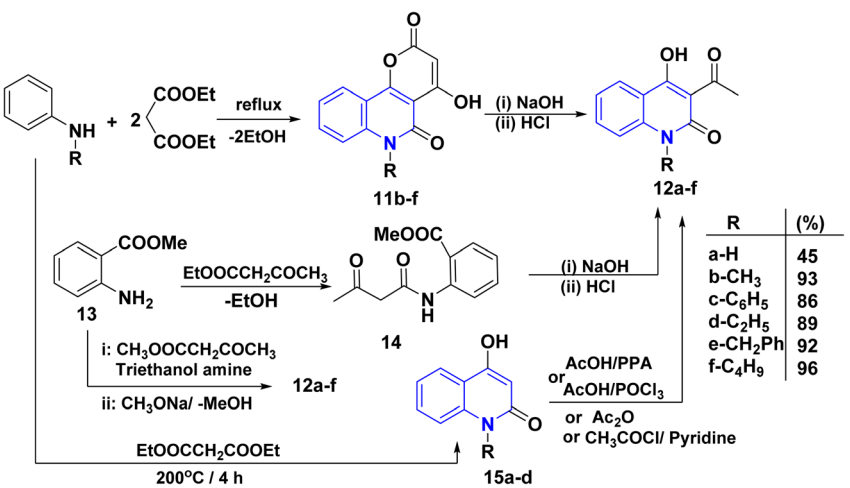
Quinoline derivatives **12a–f** were prepared by cyclocondensation of substituted amines and diethyl malonate in a molar ratio of 1 : 2 for 3–6 h. Till the calculated amount of ethanol was collected using Dean Stark by a short Vigreux column as distillation system afforded the lactone **11**, followed by alkaline hydrolysis [NaOH (2 N)], of lactone **11** and subsequent decarboxylation of the intermediate *β*-oxocarboxylate then acidified with HCl (2 N) to yield the products **12a–f** in high yields (86–96%). In the case of **12b**, compound **11** was synthesized following the methods of Kappe and Stadlbauer, which involved reacting *N*-methylaniline with diethyl malonate in diphenyl ether. However, Kappe's method utilized an excess of diethyl malonate, which served a dual purpose as both a reagent and a solvent (Scheme 1).[115,130–135] Also, the ring opening of **11b–f** by NaOH and subsequent spontaneous decarboxylation afforded 4-hydroxyquinolinone derivatives **12b–f** (Scheme 1).[112,133,135–137]

3.2. Synthesis from 4-hydroxyquinolin-2-ones

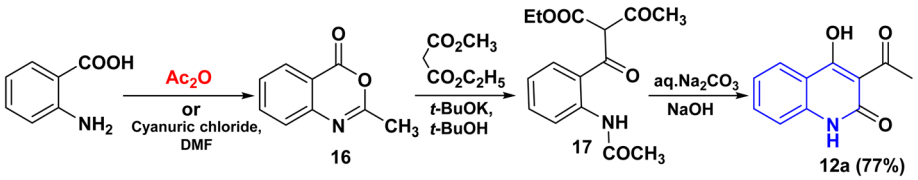
Cyclocondensation reaction of secondary amine and diethyl malonate afforded 4-hydroxyquinolin-2-ones **15a–d**. After that, acetylation reaction of *N*-unsubstituted AHQ **15a–d** with acetyl chloride using acetic acid or pyridine in the presence of polyphosphoric acid (PPA) or AcOH with phosphorus oxychloride ($POCl_3$) yielded acetylquinoline derivatives **12a–d** (Scheme 1).[135–140]

3.3. Synthesis from methyl 2-aminobenzoate/*o*-aminobenzaldehydes/*o*-aminoarylketones

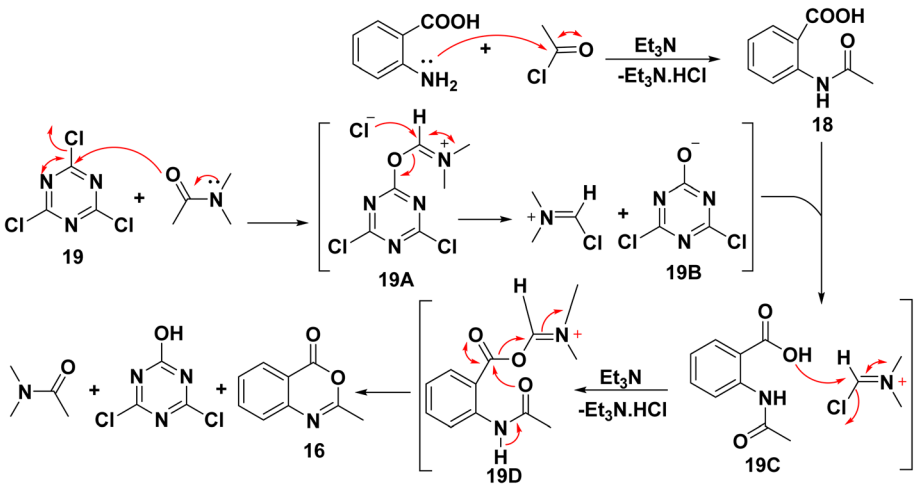
Synthesis of acetylquinoline **12a** was accomplished *via* acylating methyl anthranilate **13** using ethyl acetoacetate or methyl acetoacetate and triethanolamine by continuous removal of



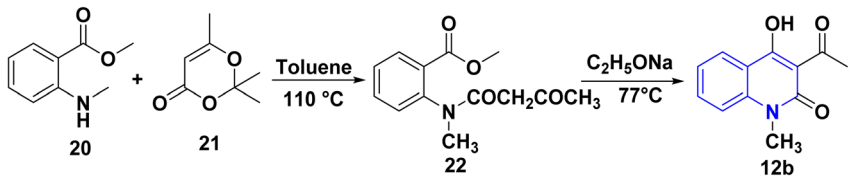
Scheme 1 Synthesis of *AHQ* 12a–f.



Scheme 2 Synthesis of **12a** from anthranilic acid.



Scheme 3 Suggested mechanism for the synthesis of benzoxazinone derivatives **16**.



Scheme 4 Synthesis of **12b** through acylation of **20** followed by cyclization of compound **22**.

methanol or ethanol using Dean–Stark apparatus, resulting in the formation of 2-methoxycarbonyl anilide **13**, followed by Dieckmann intramolecular cyclization of anilide derivative **14** (Scheme 1).[120,141–143]

3.4. Synthesis from 2-methyl-3,1-benzoxazin-4-one

The synthesis of **12a** was performed through a two-step. First, 2-methyl-3,1-benzoxazin-4-one **16** was synthesized by [4 + 2] annulation of anthranilic acid or by using the iminium cation from a mixture of cyanuric chloride and dimethylformamide as a cyclizing agent, and was achieved under mild conditions.[144] Next, C-acylated with ethyl acetoacetate by 3,1-benzoxazin-4-one **16** to form the ester **17**. Finally, cyclization of ester **17** in a basic medium [aqueous Na_2CO_3/NaOH] at room temperature furnished the target compound **12a**. This reaction pathway involves the nucleophilic addition of the active methylene of ethyl acetoacetate (EAA) to the carbonyl group of the benzoxazine ring **16**, followed by intramolecular cyclization (Scheme 2).[108,116,145–147]

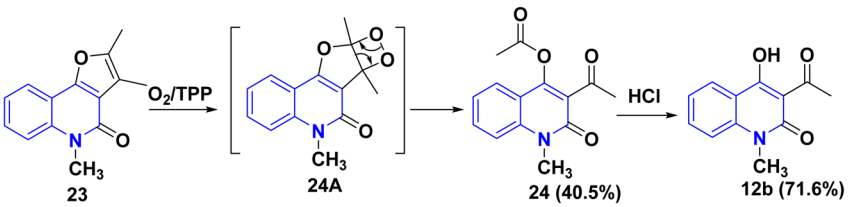
N-Acylated anthranilic acid intermediate **18** is created from anthranilic acid and acid chloride in the presence of a catalytic amount of triethylamine (TEA) as the HCl scavenger *via* N-acylation reaction, affording *N*-acylated anthranilic acid. After that, intramolecular nucleophilic attack at intermediate **18** yielded benzoxazin-4-one ring **16**. The cyclization reaction can be achieved by converting the carboxylic group of acetylated derivative **18** into a dynamic ester through either microwave irradiation or traditional heating (Scheme 3).[144]

3.5. Synthesis from 1,3-dioxinone with methyl 2-(methylamino)benzoate

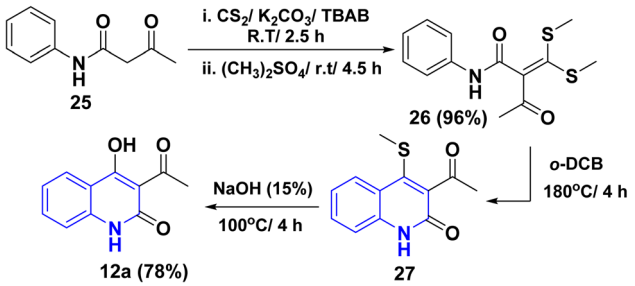
The synthesis of **12b** was accomplished *via* an acylation reaction of secondary amine **20** with trimethyl-1,3-dioxinone **21**, followed by a cyclization reaction of the acylation product **22** under basic conditions (Scheme 4).[108]

3.6. Synthesis from angular furo[3,2-*c*]quinolinone derivatives

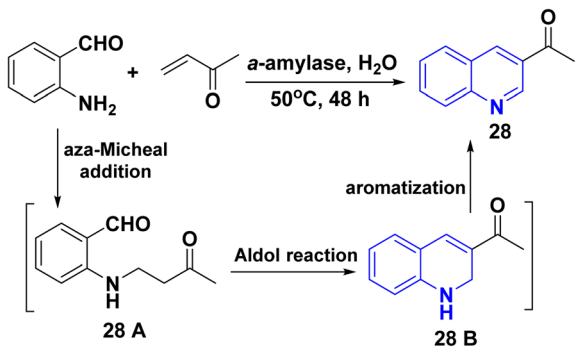
In 2021, the group of Elgogary described the photooxygenation reaction of furo [3,2-*c*] quinolin-4(5*H*)-one derivatives **23** in



Scheme 5 Photooxygenation reaction of 23.



Scheme 6 Synthesis of 12a from acetoacetanilide.



Scheme 7 Synthesis of dehydroxylated-3-acetylquinoline (AQ) 28.

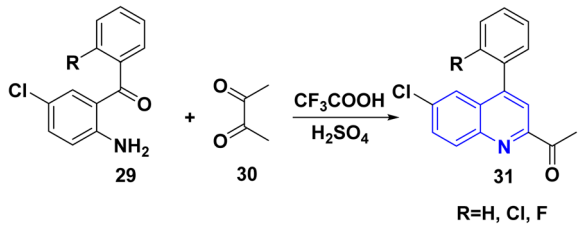
$CHCl_3$ led to the formation of the photocleaved product **24** *via* the intermediate **24A.** Next, acid hydrolysis of quinolinone derivative **24** furnished **12b** (Scheme 5).[139]

3.7. Synthesis from ketene dithioacetal

Compound **12a** was synthesized through *in situ* direct addition of carbon disulfide (CS_2) to acetoacetanilide **25** in the presence of K_2CO_3 and tetrabutylammonium bromide (TBAB) as a green ionic liquid. The alkylation process was achieved using dimethyl sulfate, which yielded the ketene dithioacetal **26.** In the same context, thermal cyclization of ketene **26** afforded the quinolinone **27** in fair yield. Finally, basic hydrolysis of the quinolone **27** furnished 3-acetyl-4-hydroxyquinolinone **12a** (Scheme 6).[140]

3.8. Synthesis of dehydroxylated-3-acetylquinoline (AQ)

Also, synthesis of dehydroxylated-3-acetylquinoline (AQ) **28** *via* the reaction of 2-aminobenzaldehydes with α,β-unsaturated carbonyl compounds as methyl vinyl ketone in high catalytic efficiency (56–86% yield), through sequence process as aza-Michael reaction gave **28 A** followed by Aldol reaction afforded **28 B** then aromatized in presence of α-amylase catalyzed (Scheme 7).[148]



Scheme 8 Synthesis of 2-acetylquinoline 31.

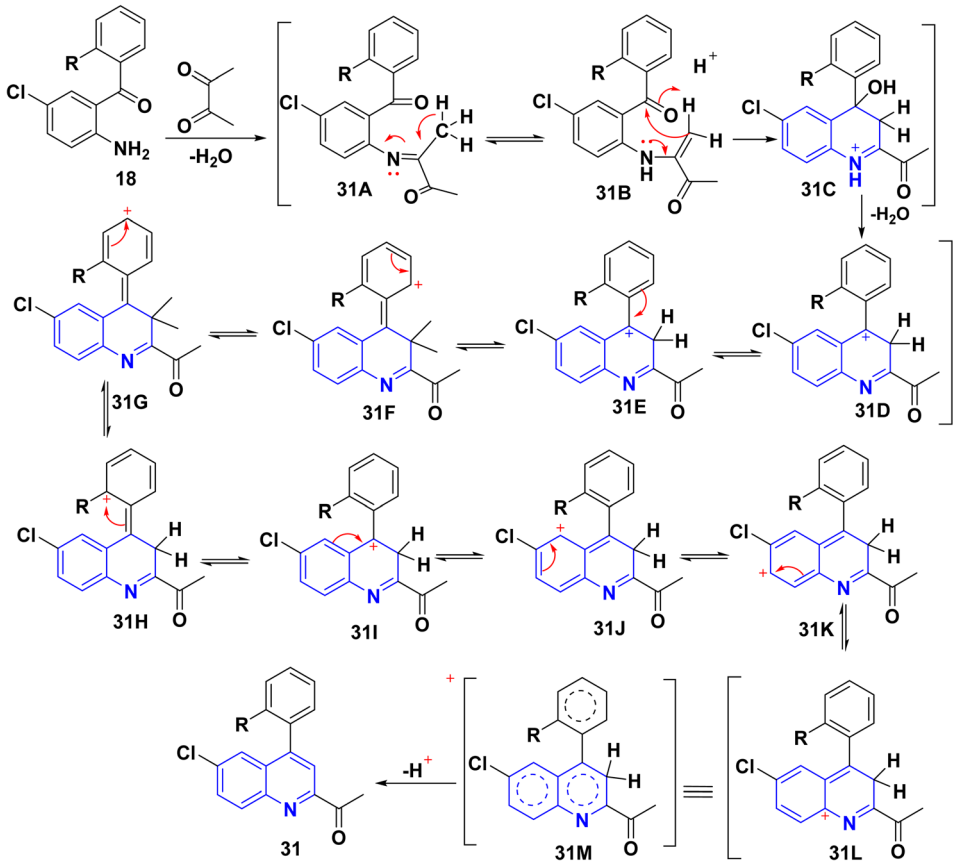
3.9. Synthesis of 2-acetylquinoline derivatives

The reaction of *o*-aminoarylketones **29** with butanedione as a symmetrical 1,2-diketone **30** according to Friedländer synthesis. Similarly, *o*-aminoarylketones condensed with pentanedione (unsymmetrical 1,2-diketone) under acidic conditions led to the formation of regioselective 2-acetylquinoline derivatives **31** (Scheme 8). The suggested reaction mechanism (Scheme 9) is analyzed using density functional theory calculations at the B3LYP/6-311G (d,p) level. It was determined that all relative energy barriers and activation energies for the reaction steps are minimized at these theoretical levels.[149]

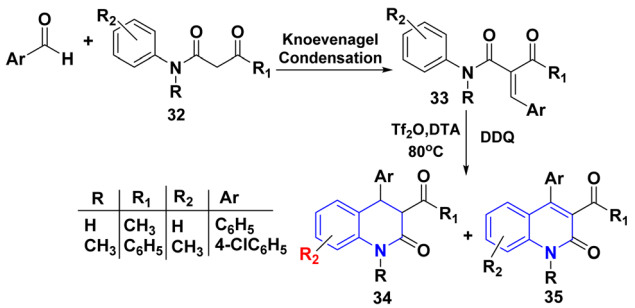
A plausible mechanism for forming product **31** is shown in Scheme 9. Initially, *o*-aminoaryl ketone (**29**) condenses with butan-2,3-dione (**30**) in the presence of TFA with conc. H_2SO_4 to give an imine intermediate **31A** as geometrical isomer **E** by eliminating H_2O. Then, tautomerization of the **31A** into a more activated form, the enamine intermediate **31B.** Followed by nucleophilic attack of β-position of enamino group on the carbonyl carbon and this gives the benzylic carbocation (which stabilise through eight resonance hybrid structures **31(G-H)** and subsequently loses a proton to form final product subsequently loses a proton *via* aromatization to form final product **31.**

3.10. Synthesis of quinolinones

Zhang *et al.*[150] reported an efficient methodology for preparing of 3,4-dihydroquinolinone **34** and quinolinone derivatives **35** through intramolecular cyclization of *N*-aryl cinnamides **33.** Compound **33** was synthesized through Knoevenagel condensation of β-oxo-amides **32** with various aryl aldehydes, which were then subjected to intramolecular cyclization. The



Scheme 9 Proposed mechanism for synthesis of 2-acetylquinoline **31**.

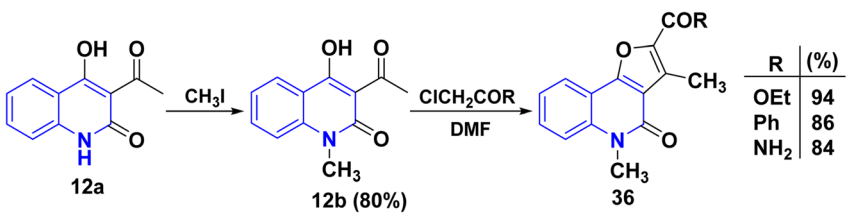


Scheme 10 Triflic anhydride-mediated synthesis of quinolinone.

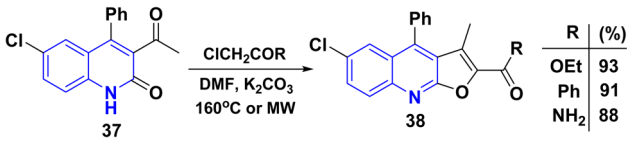
optimized conditions for cyclization, including solvent, the reaction temperature, and various catalysts such as Tf_2O and DDQ, were investigated, whereas the optimum temperature is 80 °C, and *N*,*N*-dimethyl trifluoroacetamide (DTA) as solvent afforded the most satisfactory results. Under the optimised conditions, the reaction of a wide range of substrates such as α-acetyl-*N*-aryl cinnamides and α-benzoyl *N*-aryl secondary cinnamides proceeded efficiently to afford the corresponding quinoline-2(1*H*)-ones **34** and **35** (Scheme 10).[150]

4. Reactivity of AHQ

According to the current literature survey, the reactivity of AHQ **12a–f** is part of scientific research with many reagents, as illustrated below. AHQ is a quinolin-2-one derivative with a unique chemical structure consisting of a β,β'-tricarbonyl (TC) group and thus a quinolinone ring with a carbonyl (acetyl), hydroxyl (enolate), and carbonyl (lactamic) group attached to it.



Scheme 11 Formation of angular *N*-methylfuro[3,2-*c*]quinolinones **36**.



Scheme 12 Formation of linear furo[2,3-*b*]quinolinones **38**.

4.1. Electrophilic substitution reactions

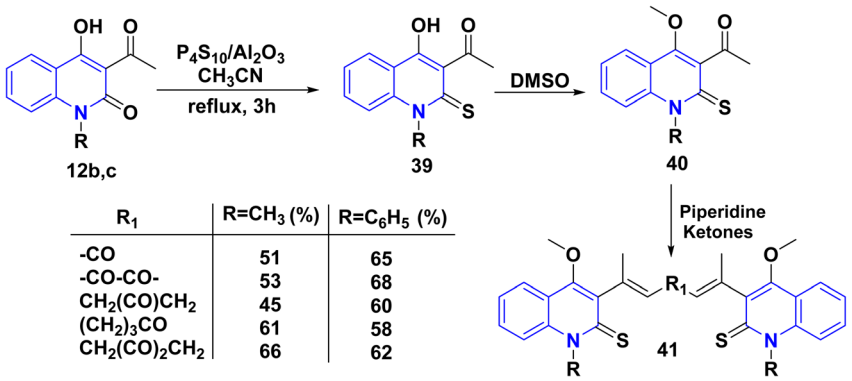
An electrophilic substitution reaction is a chemical reaction in which an electrophile replaces a functional group attached to a compound, typically displacing a hydrogen atom. These reactions usually follow a three-step mechanism that includes forming an electrophile, forming a carbocation (an intermediate), and removing a proton from this intermediate. AHQ derivatives can efficiently undergo electrophilic substitution reactions such as alkylation, halogenation, Friedel–Crafts, and formylation.[151]

4.1.1. Alkylation

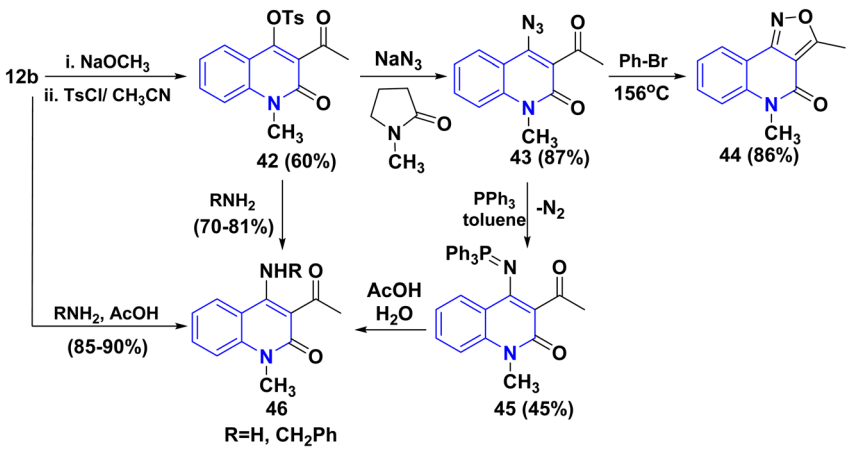
4.1.1.1. N_1-Alkylation. Compound **12a** can potentially undergo methylation at either the nitrogen atoms at positions 1 or the oxygen atom at C_4. However, the methylation exclusively occurs at the nitrogen atom rather than the oxygen atom.[115,116,143,145] Following that, angular *N*-methylfuro[3,2-*c*] quinolinone derivatives **36** were synthesized from **12b** through the Rap–Stöermer reaction, with *α*-chlorocarbonyl substrates in the presence of K_2CO_3 in DMF (Scheme 11).

Whereas, the reaction of 3-acetyl-6-chloro-4-phenylquinolinone **37** with different *α*-halocarbonyl compounds afforded linear tetrasubstituted furo[2,3-*b*]quinolines **38** (Scheme 12). Thus, angular fluoroquinolinones **36** have been synthesized *via* the reaction of **12b** derivatives with *α*-chlorocarbonyl compounds, as applied to the Rap–Stöermer reaction through both conventional and/or microwave methods. Thus, the microwave irradiation provided higher yields (88–93%) compared to the conventional method (64–72%) (Scheme 12).[143,152,153]

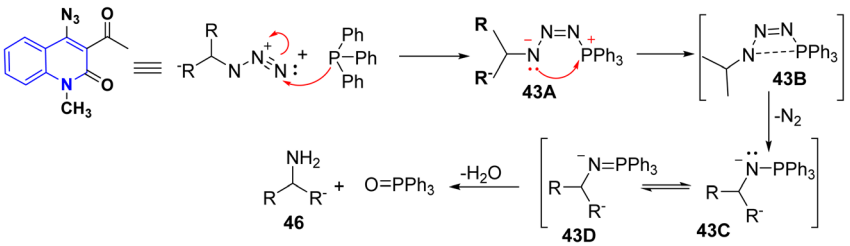
4.1.1.2. O-Alkylation and its transformation. Compounds **12b,c** underwent thionation using phosphorus pentasulfide, aluminum oxide as a catalyst/CH_3CN. The thionated compound **39** by dimethyl sulfoxide (DMSO) underwent *o*-methylation of the hydroxyl group (enol), yielding **40** as a sole product, which prevents keto–enol tautomerism at the 3rd and 4th positions, which could have interfered with the Aldol condensation reaction. Whereby, compound **40** was further reacted with various ketones through Aldol condensation in piperidine as a basic medium, to produce 1-(4-methoxy-2-thioxoquinolin-3-yl) ethenone **41** (Scheme 13).[154]



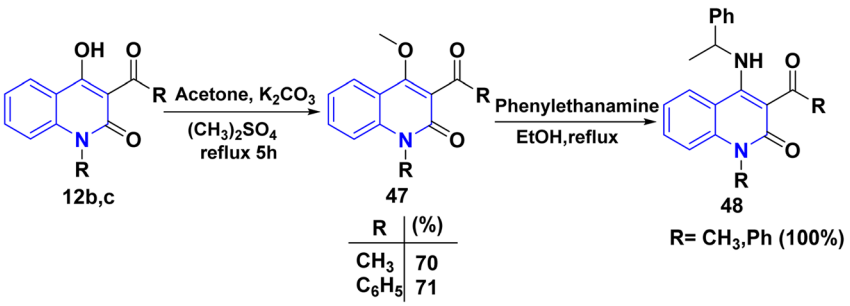
Scheme 13 Synthetic route of **41** from **12b,c**.



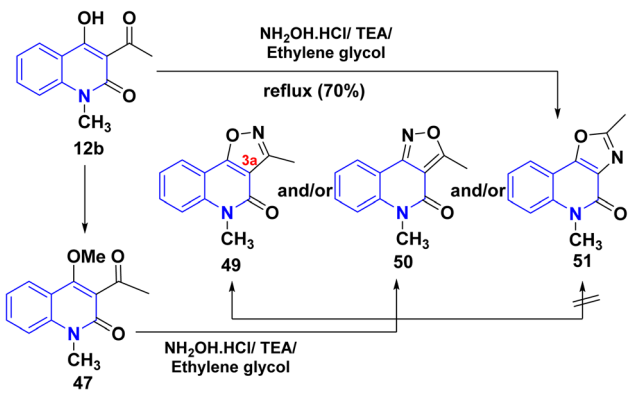
Scheme 14 Transformation of the hydroxyl group of **12b**.



Scheme 15 Mechanism of the Staudinger reaction.



Scheme 16 Synthesis of phenylethylaminoquinolinone **48**.

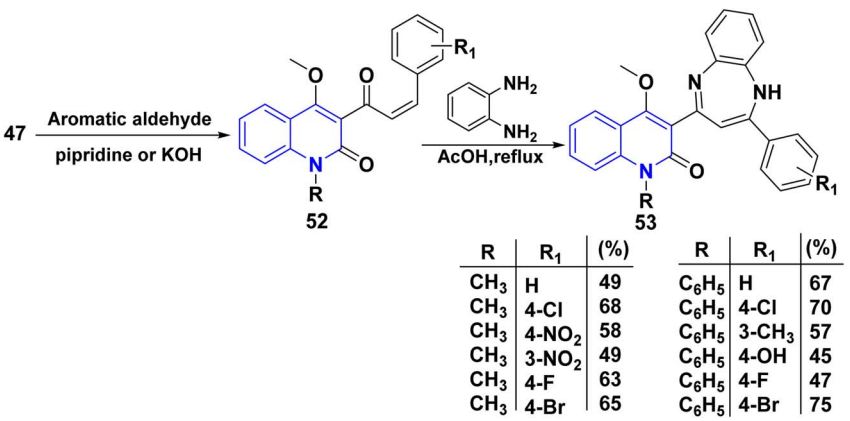


Scheme 17 Synthesis of isoxazoloquinolinone.

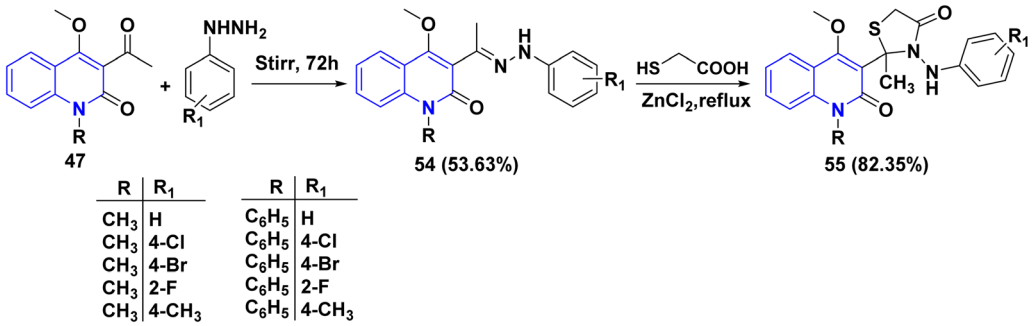
Tosylation of the sodium salt of **12b** furnished a very reactive compound 3-acetyl-4-tosyloxyquinolone **42**, which was used as the key compound to synthesize *o*-acetylazido-quinolinone **43** *via* transformation of the tosyloxy group to the azido group by using NaN_3/*N*-methylpyrrolidone as solvent. Followed by ring closure through elimination of nitrogen gas by thermal heating in bromobenzene at 156 °C, 3-acetylazido-quinolinone afforded angular isoxazolo[4,3-*c*]quinolones **44**. The azide **43** undergoes the Staudinger reaction with triphenylphosphane, yielding the phosphazene **45** *via* nitrogen loss. The hydrolysis of **45** in AcOH (80%) produced the 4-aminoquinolone **46**. This amine can also be produced by reacting tosyloxyquinolone **42** with ammonia. Similarly, benzylamine combines with **42** to yield substituted quinoline **46** (Scheme 14).[155–157]

Mechanism of Staudinger reaction *via* very mild reduction of the azide **43** with triphenylphosphane yields the phosphazene **43B** by loss of nitrogenous gas. The hydrolysis of **43C**/**43D** in AcOH (80%) produced the 4-aminoquinolone **46** (Scheme 15).[155]

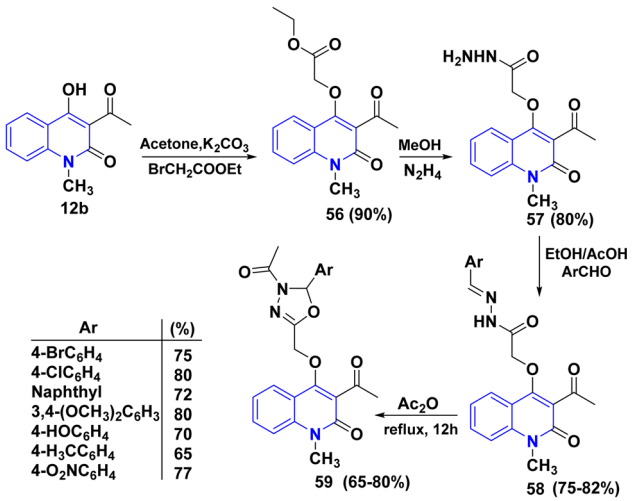
Whereas, methylation of compound **12b,c** by dimethyl sulphate, a potent methylating agent, in acetone, which replaced a hydrogen atom in the hydroxyl group. This process



Scheme 18 Claisen–Schmidt reaction of compound **47**.



Scheme 19 Cyclization reaction of **54** to yield 4-thiazolidinone derivatives **55**.



Scheme 20 Synthesis of oxadiazolylquinolinone derivatives **59**.

yielded a single product 3-acetyl-4-methoxyquinolinone **47**.[158,159] Following this interpretation, the product reacted with a primary amine in EtOH, yielding phenylethylaminoquinolin-2-one **48** (Scheme 16).[158]

Treatment of 3-acetyl-4-methoxyquinolinone **47** was observed by the Chimichi group[158] with 1,2-bisnucleophiles, such as hydroxylamine, to synthesize fused isoxazolo[4,5-*c*]-and/or isoxazolo[4,3-*c*]quinolin-4(5*H*)ones, which gave three different products **49–51** depending on the conditions (Scheme 17). As a result, the utilization of either hydroxylamine hydrochloride or its free base leads to the formation of two distinct products. The obtained product was through a reaction of **47** with $NH_2OH \cdot HCl$ is structurally assigned to the regioisomeric isoxazolo[4,5-*c*] or isoxazolo[4,3-*c*]quinolin-4(5*H*)one in the following ways:

(a) The presence of a three-bond connection between C-3a and the methyl group at position 3 of compounds **49** and **50** led to the exclusion of the oxazole structure **51**.

(b) The chemical shift of the C-3 atom being analyzed, which resembles that of a 3-substituted isoxazole more than a 5-substituted one, was used as a preliminary criterion to distinguish between the two regioisomeric isoxazole skeletons. In contrast, compound **47** exclusively and preferentially generates the regioisomeric isoxazolo[4,5-*c*]- or isoxazolo[4,3-*c*]quinolin-4(5*H*)on e (compounds **49** and **50**, respectively).[158]

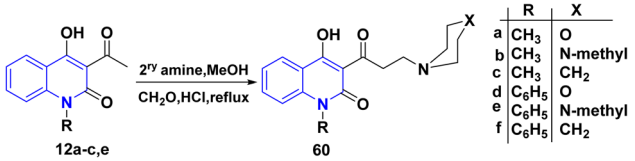
Whereby, synthesis of *α*,*β*-unsaturated ketones **52** was achieved through Claisen–Schmidt reaction of compound **47** with various aromatic aldehydes in glacial AcOH. Michael addition reaction of *o*-phenylenediamine to *α*,*β*-unsaturated ketone **52** afforded binary diazepin-quinolinones **53** (Scheme 18), whereas derivatives of **53** have shown gratifying sedative, anxiolytic, and muscle relaxant activities.[159]

Methylated compound **47** was reacted with substituted phenylhydrazines, which resulted in the formation of hydrazone **54**, which were then cyclized with thioglycolic acid in methanol using zinc chloride ($ZnCl_2$) as catalyst, affording 4-thiazolidinone derivatives **55** (Scheme 19).[160]

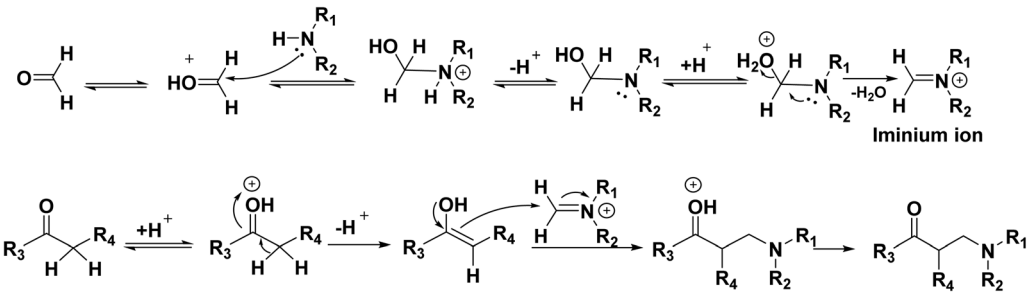
The *o*-alkylation of **12b** with ethyl bromoacetate in anhydrous acetone and K_2CO_3 led to the formation of ethyl oxoquinolinoxyacetate **56**. Hydrazinolysis of **56** with hydrazine hydrate in methanol at room temperature (RT) yielded hydrazide compounds **57** in 80%, after which heating hydrazide compound **57** with different aromatic aldehydes in refluxing EtOH yielded derivatives **58**. Finally, compounds **58** were refluxed with Ac_2O to obtain the corresponding substituted 1,3,4-oxadiazolyl)methoxy)-1-methylquinolinone **59** (Scheme 20).[161]

4.1.1.3. Aminoalkylation. AHQ **12a–f** were subjected to Mannich reaction with formaldehyde and morpholine salt in boiling MeOH for 6 h, furnishing Mannich base 4-hydroxy-3-(3-morpholinopropanoyl) quinolinone **60** (Scheme 21).[162]

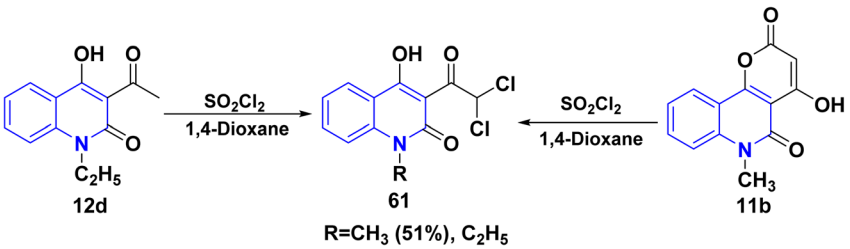
The Mannich reaction mechanism starts with the reaction between formaldehyde and amine, leading to the formation of the iminium ion. The enol form of the organic compound is obtained *via* tautomerization of the ketone form. The reactive iminium ion is attacked by this enol form, which ultimately



Scheme 21 Synthesis of Mannich base 4-hydroxy-3-(3-morpholinopropanoyl)quinolinone **60**.



Scheme 22 The proposed Mannich reaction mechanism.



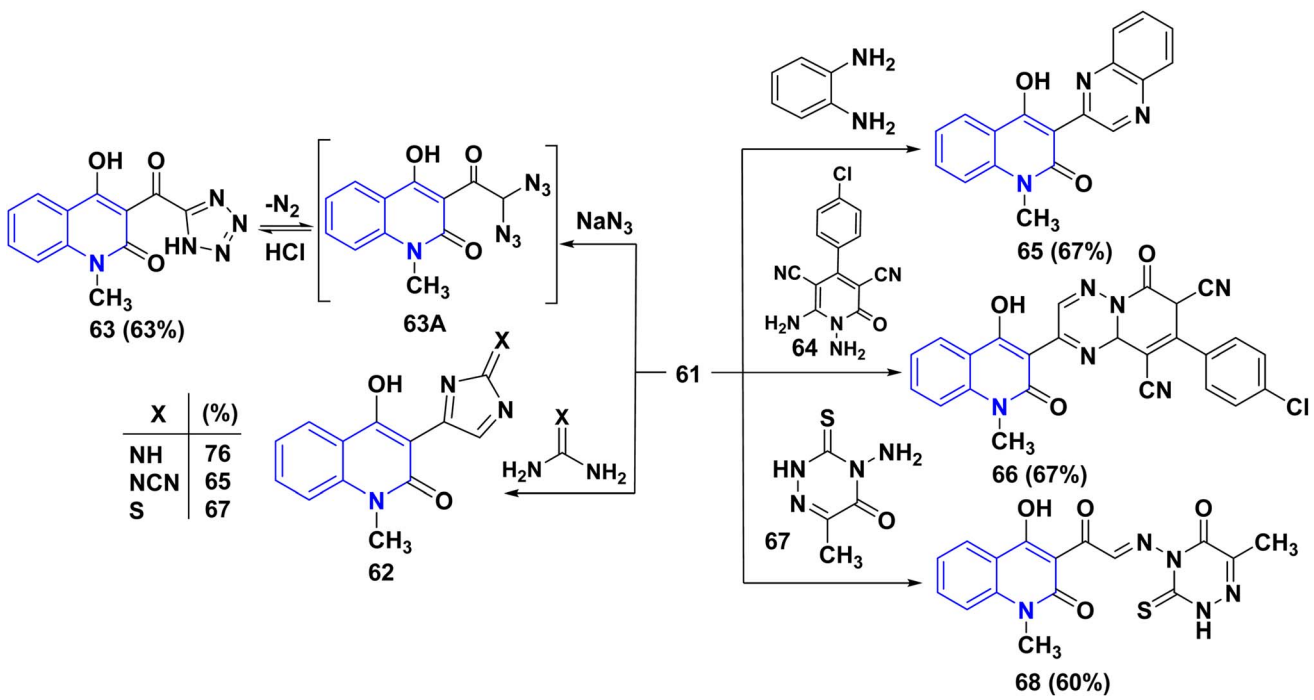
Scheme 23 Chlorination of acetylquinolinone **12d** and pyranoquinolindione **11b**.

produces the necessary β-amino-carbonyl molecule or Mannich base (Scheme 22).

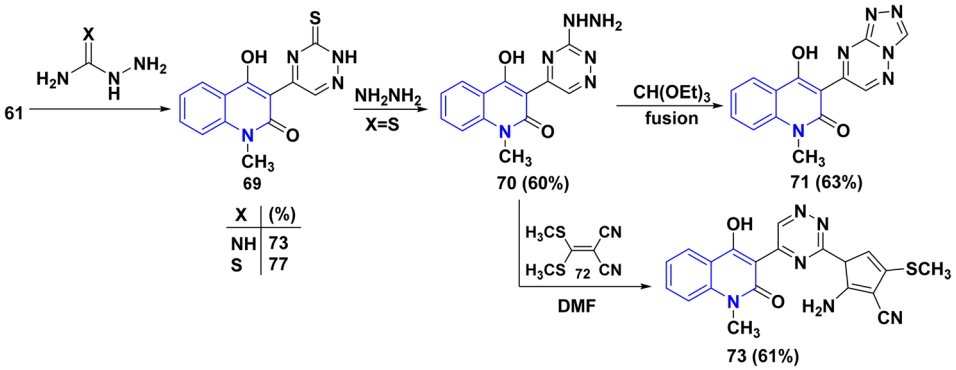
4.1.2. Halogenation and its synthetic value for constructing various heterocyclic systems

4.1.2.1. Synthesis of 3-dichloroacetyl derivative and its utility. Among organic synthesis transformations, chlorination holds one of the most fundamental reactions that can be achieved directly by using molecular chlorine or chlorinating agents. Thus, the electrophilic chlorination reaction of **12b,d** with sulfuryl chloride (SO_2Cl_2) in 1,4-dioxane yielding 3-dichloroacetyl derivative **61**, also by heating pyranoquinolindione **11b** with SO_2Cl_2 (Scheme 23).[163,164]

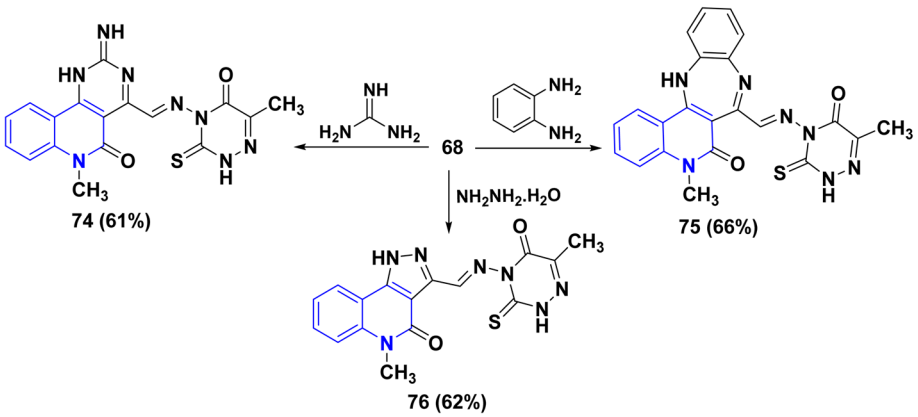
Treatment of compound **61** with some 1,3-binucleophilic reagents, namely, guanidine hydrochloride, cyanoguanidine, and thiourea, was carried out under reflux in DMF, to afford the corresponding 3-imidazolylquinolinones **62.** While the reaction



Scheme 24 Treatment of 3-dichloroacetyl **61** with nucleophilic nitrogenous reagents.



Scheme 25 Hydrazinolysis of the 1,2,4-triazine derivative **69**.



Scheme 26 Synthesis of pyrimidine, diazepine, and pyrazole heterocycles from **68**.

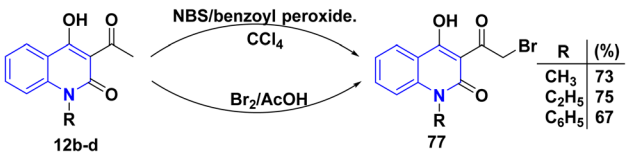
of **61** with NaN_3 in DMF occurred at ambient temperature, the intermediate diazido compound **63A** yielded the tetrazole **63** under loss of N_2 gas. Condensation of compound **61** with 1,4-*N*,*N*-binucleophiles such as *o*-phenylenediamine and 1,6-diaminopyridine derivative **64** under reflux in DMF, afforded the quinoxalinylquinolinone **65** and the pyridotriazine derivative **66**, respectively.[163]

Reaction of **61** with 4-aminotriazine derivative **67** was carried out in boiling pyridine. Interestingly, the only product that was obtained revealed the absence of chlorine; analysis results indicate that a nucleophilic replacement took place with the leaving of a chlorine atom, which is followed by elimination of hydrogen chloride, leading to the α-iminone **68** (Scheme 24).[164]

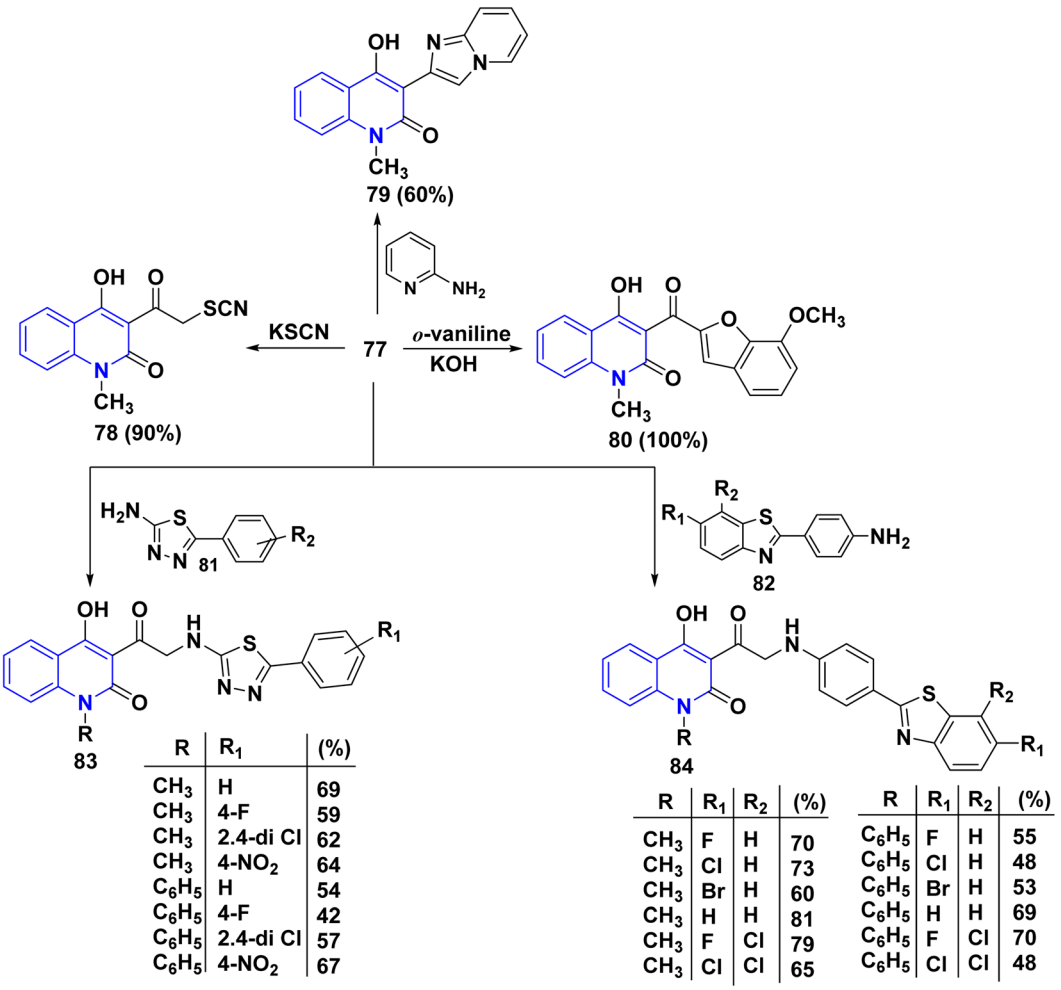
Reaction of compound **61** with aminoguanidine and thiosemicarbazide as 1,4-binucleophiles, under reflux in DMF, yielded the corresponding 1,2,4-triazine derivatives **69**. Hydrazinolysis of **69** in DMF produced the hydrazinotriazine **70**, Thermal cyclocondensation reaction of **70** with $CH(OEt)_3$ under fusion condition was carried out to get the triazolotriazine derivative **71** whereas, reaction with [*bis*(methylthio)methylene] malononitrile **72**, in DMF under reflux, gave the compound **73** (Scheme 25).[163]

α-Iminone **68**, as an interesting starting material, was subjected to interaction with some binucleophilic reagents to synthesize new quinolinone systems fused with pyrimidine, benzodiazepine, and pyrazole heterocycles. Therefore, treatment of α-iminone **68** with guanidine, *o*-phenylenediamine, and hydrazine hydrate, in DMF under reflux, afforded the pyrimidoquinolinone **74** and benzodiazepinoquinolinone **75**, and pyrazoloquinolinone **76**, respectively (Scheme 26).[163]

4.1.2.2. Synthesis of 3-(bromoacetyl)-4-hydroxyquinolinone and its benefits. The bromination of AHQs **12b–d** can be performed using bromine or *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide. 3-(Bromoacetyl)-4-hydroxyquinolinone derivatives **77** were synthesized by the free radical bromination mechanism of acetyl **12b–d** using NBS in dry carbon tetrachloride (CCl_4) with a catalytic amount of benzoyl peroxide (3 mol%) *via* homolytic fission,[165] also reaction of **12b–d** with bromine in the presence of AcOH *via* electrophilic bromination gave the same product **77** (Scheme 27).[115,134,166,167]



Scheme 27 Bromination of *N*-substituted-3-acetyl-4-hydroxyquinolinones **12b–d**.

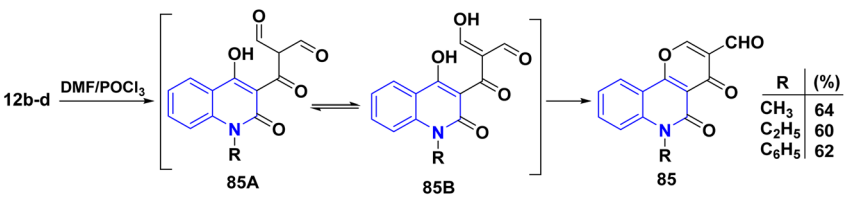


R	R_1	(%)
CH_3	H	69
CH_3	4-F	59
CH_3	2.4-di Cl	62
CH_3	4-NO_2	64
C_6H_5	H	54
C_6H_5	4-F	42
C_6H_5	2.4-di Cl	57
C_6H_5	4-NO_2	67

R	R_1	R_2	(%)
CH_3	F	H	70
CH_3	Cl	H	73
CH_3	Br	H	60
CH_3	H	H	81
CH_3	F	Cl	79
CH_3	Cl	Cl	65

R	R_1	R_2	(%)
C_6H_5	F	H	55
C_6H_5	Cl	H	48
C_6H_5	Br	H	53
C_6H_5	H	H	69
C_6H_5	F	Cl	70
C_6H_5	Cl	Cl	48

Scheme 28 Reactions of bromo-derivatives 77 with variable reagents.

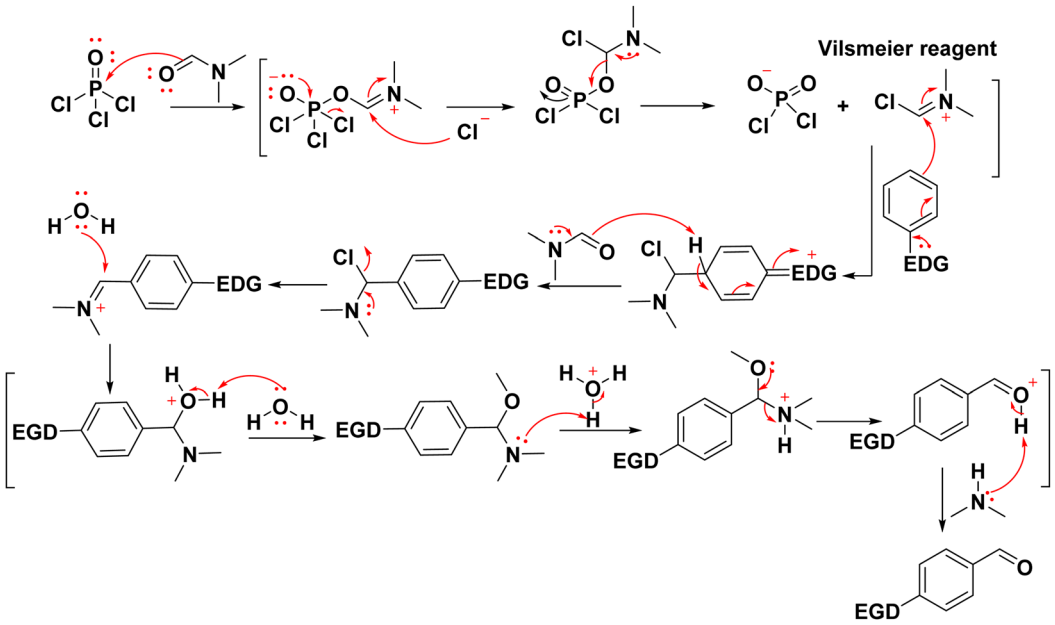


R	(%)
CH_3	64
C_2H_5	60
C_6H_5	62

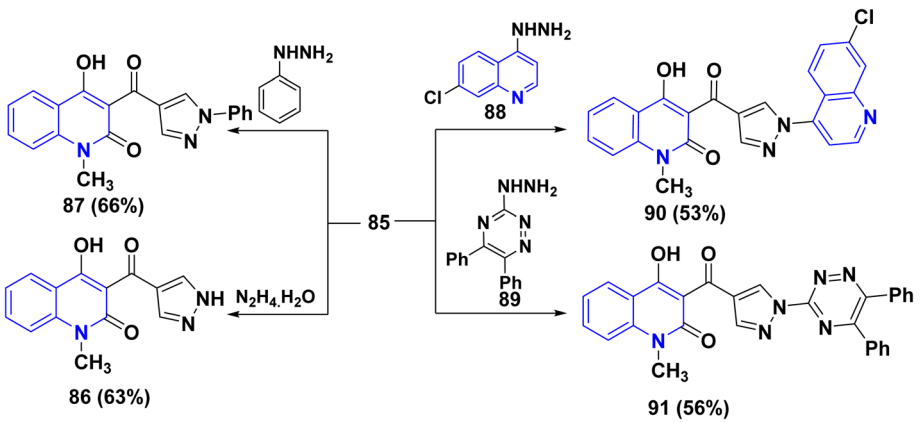
Scheme 29 Vilsmeier–Haack reaction of skeletons 12b–d.

The desired thiocyanate **78** was obtained from the reaction of 77 with potassium thiocyanate. Meanwhile, phenacyl halides were used for the alkylation of 2-aminopyridine, followed by cyclization to imidazo[1,2-*a*]pyridines. Thus, when 77 was heated with 2-aminopyridine in ethanol, 4-hydroxy-3-imidazoyl methylquinolinone **79** was formed.[167] Moreover, condensation of bromo-derivatives 77 with *o*-vaniline gave 4-hydroxy-3-(7-methoxybenzofuran-2-carbonyl)-1-methylquinolin-2(1*H*)-one **80**. Whereas, compound 77 is a versatile intermediate in synthesizing compounds **83** and **84**. So that, the synthesis of **83** were achieved through condensation reaction of 77 with various thiadiazole **81** and the observed compound benzo[*d*]thiazol-2-yl-phenylglycylquinolinone **84** were synthesized in good yield (60–81%) through the reaction of disubstituted-2-benzo[*d*]thiazole **82** with 77 in the presence of AcOH (Scheme 28).[166,168]

4.1.3. Formylation of AHQ and its uses. The Vilsmeier–Haack reaction was known since 1927,[169] which uses DMF, an acid chloride and an aqueous work-up to change an aromatic ring with a lot of electrons into an aryl aldehyde. The "Vilsmeier reagent" is an iminium salt that is created when DMF reacts with acid chloride at the start of the mechanism (Scheme 30). Moreover, double formylation of the methyl group present in acetylquinolone **12b–d** with subsequent *in situ* cyclization of intermediates **85A** and **85B** yielded pyrano[3,2-*c*]quinoline-3-carboxylaldehyde derivatives **85** *via* Vilsmeier–Haack reaction of acetylquinolinones **12b–d** (Scheme 29).[137,170]



Scheme 30 Plausible mechanism of Vilsmeier reaction.



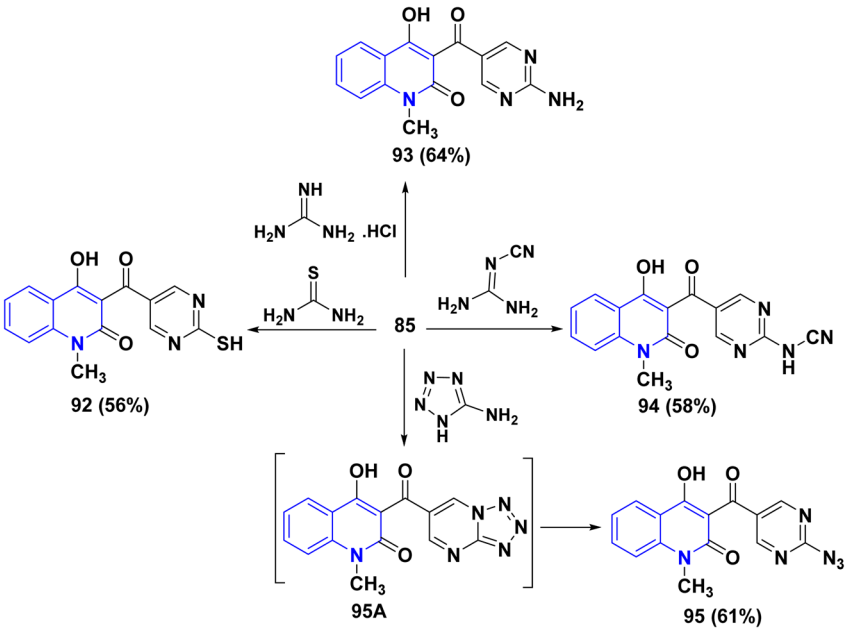
Scheme 31 Synthesis of pyrazolylquinolinone skeletons.

Ibrahim *et al.*[170] independently reported the treatment of **85** with various nucleophilic reagents affording pyrano[3,2-*c*] quinolines *via* ring-opening followed by ring closure (RORC).

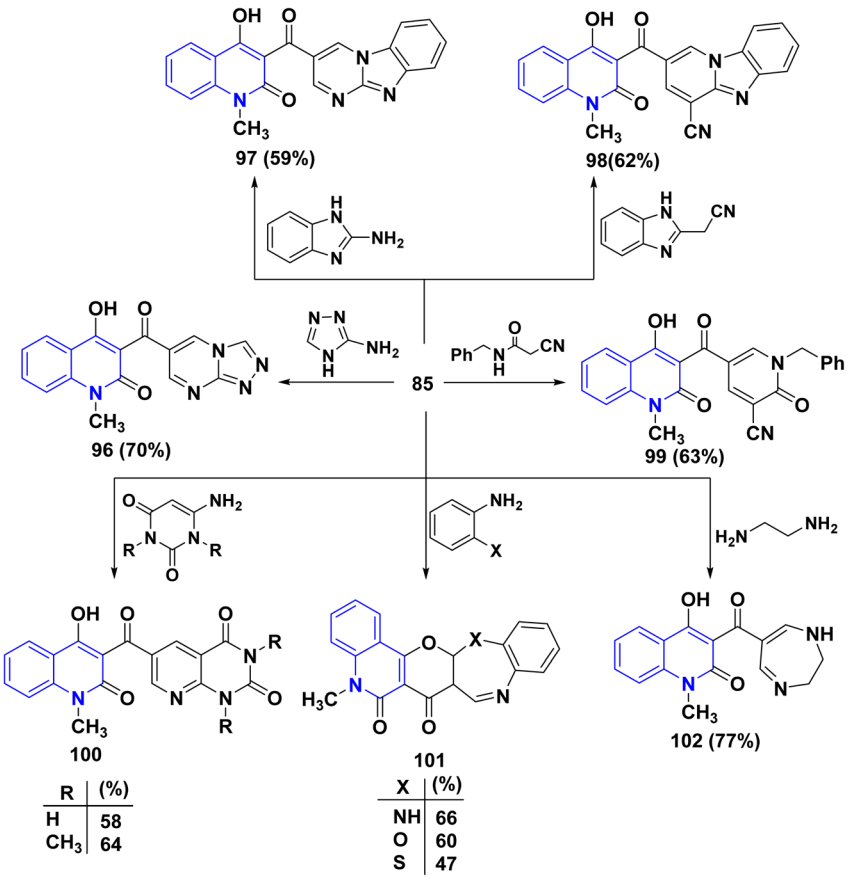
Also, reaction of carboxaldehyde **85** with hydrazine hydrate in refluxing EtOH yielded 4-hydroxypyrazol-4-ylcarbonylquinolin-2-one **86**, *via* the non-isolable hydrazone intermediate, which underwent intramolecular nucleophilic attack of NH_2 at the C-2 position with concomitant γ-pyrone ring opening *in situ*. In the same way, the condensation reaction of **85** with phenyl hydrazine in EtOH containing a catalytic amount of TEA afforded phenylpyrazole derivative **87**. Whereby, the condensation of carboxaldehyde **85** with hydrazinylquinoline quinoline **88** and 3-hydrazinyl-1,2,4-triazine-1,2,4-triazine **89** under the same reaction conditions was achieved yielding quinolinylpyrazolylquinolinone **90** and triazinylpyrazolylquinolinone **91**, respectively (Scheme 31).[170]

Furthermore, aldehyde **85** was subjected to react with some 1,3-*N*,*N*-binucleophiles such as thiourea, guanidine hydrochloride and cyanoguanidine in ethanolic KOH yielded the corresponding pyrimidine derivatives **92**, **93** and **94**, respectively. Whereby, refluxing of **85** with 5-aminotetrazole in EtOH afforded 3-[(2-azidopyrimidin-5-yl)carbonyl]4-hydroxyquinolin-2-one **95** through non-isolable tetrazolo[1,5-*a*]pyrimidine intermediate **95A** (Scheme 32).

Meanwhile, condensation of aldehyde **85** with 3-aminotriazole in EtOH yielded triazolo[4,3-*a*]pyrimidine **96** containing the quinolinylcarbonyl moiety. Ultimately, condensation of **85** with 2-aminobenzimidazole in EtOH containing one crystal of *p*-toluenesulfonic acid afforded pyrimido[1,2-*a*]pyrimidine derivative **97**. Also, reaction of **85** with 1*H*-benzimidazol-2-ylacetonitrile and *N*-benzyl-2-cyanoacetamide in EtOH containing catalytic drops of TEA yielded **98** and **99**, respectively.

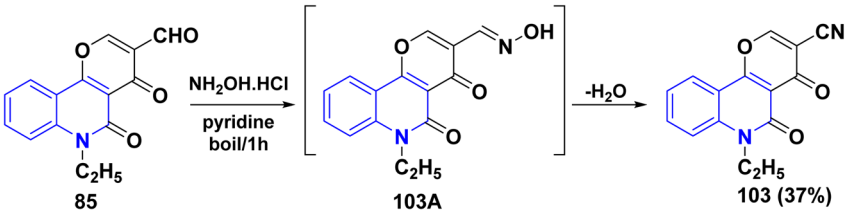


Scheme 32 Synthesis of six-membered heterocyclic scaffolds.

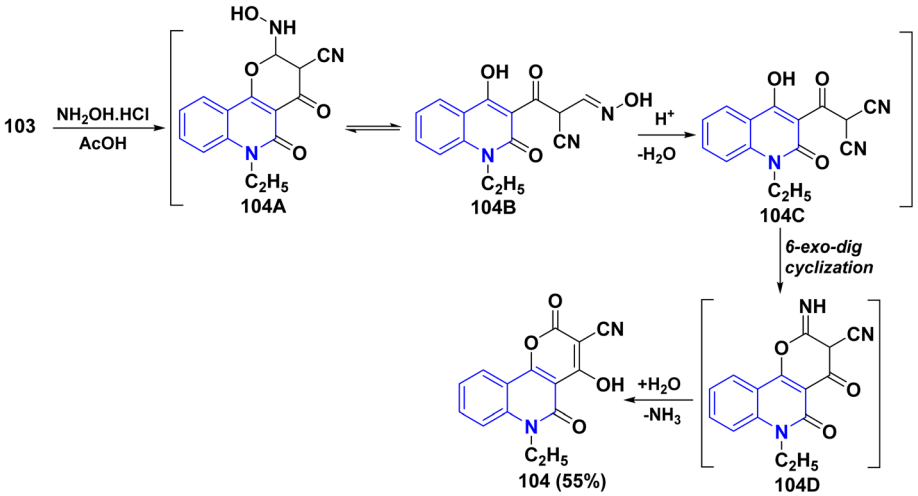


Scheme 33 Synthesis of different heterocyclic systems containing quinolone scaffolds.

Next, condensation reaction **85** with *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol in AcOH yielded the corresponding heteroannulated pyrano[3,2-*c*]quinoline derivatives **101.** Whereby, reaction of **85** with 6-aminouracil and 6-amino-1,3-dimethyluracil in EtOH afforded pyrido[2,3-*d*] pyrimidines **100.** Furthermore, the chemical reactivity of **85** was



Scheme 34 Synthesis of tricyclic carbonitrile derivative **103**.

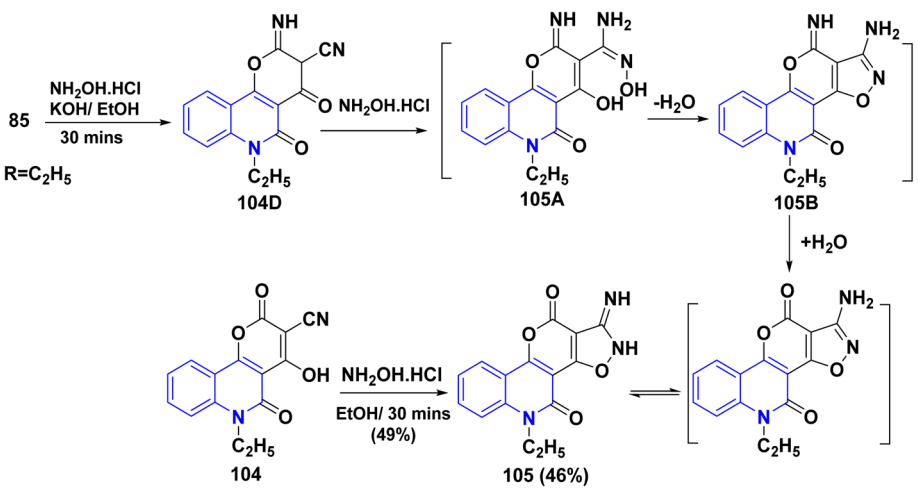


Scheme 35 Synthesis of 4-hydroxypyrano[3,2-*c*]quinoline-3-carbonitrile derivative **104**.

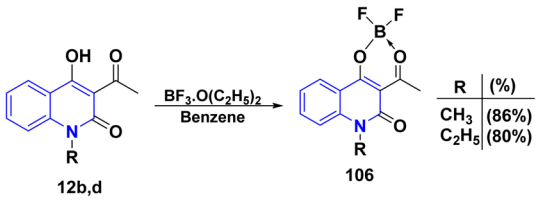
investigated towards different 1,4-binucleophiles. By the way, the condensation reaction of **85** with ethylenediamine in EtOH yielded 1,4-diazepinylcarbonylquinolin-2-one **102**. The reaction was accomplished through the synthesis of the corresponding Schiff base intermediate, followed by an intramolecular nucleophilic addition at the C-2 position associated with γ-pyrone ring opening to afford **102** as the final product (Scheme 33).[170]

In refluxing pyridine, the reaction of tricyclic aldehyde **85** with $NH_2OH{\cdot}HCl$ yielded the corresponding carbonitrile derivative **103**, through the formation of non-isolable oxime **103A**, after *in situ* dehydration step (Scheme 34).[137]

Reaction of aldehyde **85** with $NH_2OH{\cdot}HCl$, in AcOH, did not yield either oxime **103A** or carbonitrile **103** but gave unexpected product showed that dioxopyrano[3,2-*c*]quinoline-3-carbonitrile **104** through two molecules of hydroxylamine reacted stepwisely with **85** yielded **103** which is regarded as a highly reactive cyclic push–pull system that quickly produces the adduct **104B**, which exists in equilibrium due to ring-chain tautomerism. The dehydration of oxime tautomer readily afforded the



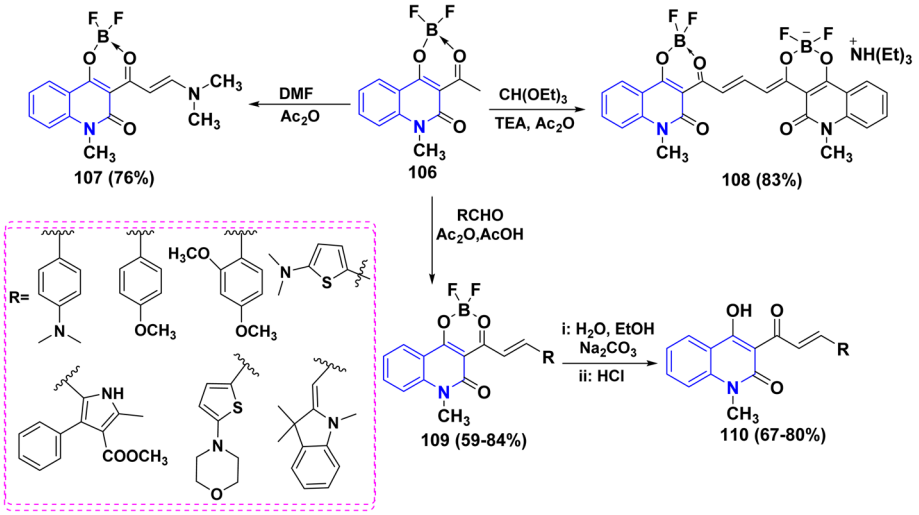
Scheme 36 Formation of 1-amino-5-ethylisoxazolopyrano[3,2-*c*]quinolindione **105**.



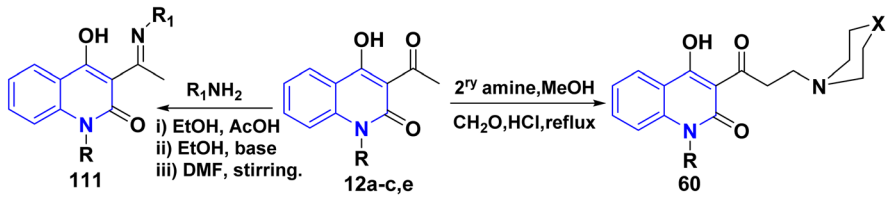
Scheme 37 Complexation of compounds 12b,d.

corresponding intermediate **104C**. Intramolecular 6-*exo-dig* cyclization type of intermediate **104C** gave 2-iminopyranoquinoline **104D** following that hydrolysis of **104D** yielded the final product **104** (Scheme 35).[137]

Reaction of aldehyde **85** with $NH_2OH \cdot HCl$, in ethanolic KOH (1%) as a basic catalyst, instead of an acidic medium, gave **105** in 46% yield. The reaction gave the same intermediate **104D**, in a basic catalyzed route, which underwent the addition of another molecule of $NH_2OH \cdot HCl$ led to the formation of 2-



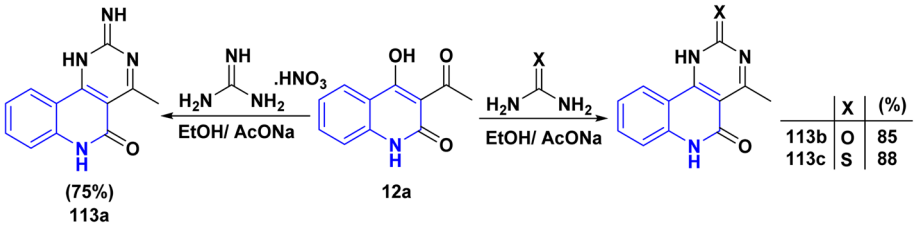
Scheme 38 Condensation reactions on complex 106.



R	R_1	(%)
H	4-methylpyridin-2-amine	72
H	5-methylpyridin-2-amine	75
H	6-methylpyridin-2-amine	74
H	4-methyl-3-nitropyridin-2-amine	70
H	Pr	52
H	i-Pr	63
H	Bu	17
H	i-Bu	78
H	sec-Bu	56
H	$(CH_2)_2OH$	70
H	CH_2Cy	72
H	$(CH_2)_4CH_3$	11
CH_3	C_6H_5-NH-	85
CH_3	4-Cl-C_6H_4-NH-	89
CH_3	4-Br-C_6H_4-NH-	78
CH_3	Bu	86
CH_3	CH_2Ph	51
CH_3	Ph	58
C_6H_5	C_6H_5-NH-	82
C_6H_5	4-Cl-C_6H_4-NH-	79
C_6H_5	4-Br-C_6H_4-NH-	84
CH_2Ph	CH_2Ph (64%)	64
CH_2Ph	Ph	61

R	R_1	X	(%)
CH_3	C_6H_5-NH-	O	81
CH_3	4-Cl-C_6H_4-NH-	O	93
CH_3	C_6H_5-NH-	N-methyl	84
CH_3	4-Cl-C_6H_4-NH-	N-methyl	88
CH_3	C_6H_5-NH-	CH_2	92
C_6H_5	C_6H_5-NH-	O	90
C_6H_5	4-Cl-C_6H_4-NH-	O	88
C_6H_5	4-NO_2-C_6H_4-NH-	N-methyl	86
C_6H_5	4-Cl-C_6H_4-NH-	N-methyl	79
C_6H_5	C_6H_5-NH-	CH_2	81

Scheme 39 Synthesis of imine 111, Mannich base (QVIR) 60 and its imine analogue 112.



Scheme 40 Synthesis of pyrimido[5,4-*c*]quinolinones **113a–c**.

imino-5-oxopyrano[3,2-*c*]quinoline-3-carboximidamide **105A**. Whereas, the cyclization of imidamide through a condensation reaction yielded isoxazole derivative **105B**. After that, hydrolysis of imine **105B** was achieved, leading to the final product **105**. Additionally, compound **105** was accurately prepared from the reaction of **104** with $NH_2OH{\cdot}HCl$ in refluxing EtOH (Scheme 36).[137]

4.1.4. Synthesis of 1,3,2-dioxaborinino[5,4-*c*]quinolinone *via* metallation and its utility. The metallation reaction of acetylquinolinone **12b,d** with boron trifluoride etherate $BF_3{\cdot}(OC_2H_5)_2$ in benzene gave its boron difluoride chelate complex **106** (Scheme 37).[171]

Reaction of complex **106** with DMF gave enamine **107**, which can serve as a valuable synthon for transformations of the two-quinolinone fragment. Moreover, complex **106** was treated with different carbonyl compounds to yield the corresponding condensation products at the methyl group. For example, a reaction of two moles of complex **106** with $CH(OEt)_3$ with a catalytic amount of TEA afforded symmetric polymethine dye **108**. In acetonitrile, complex **108** absorbs at 581 nm, displaying noticeable fluorescence. Lastly, boron-containing styryl dyes **109** were produced by the condensation reaction of several aromatic and heterocyclic aldehydes with complex **106**. Compounds **109** were hydrolyzed to produce novel 4-hydroxy-2-quinolinone derivatives **110**, which exhibit fluorescence in both solid and solution states (Scheme 38).[171]

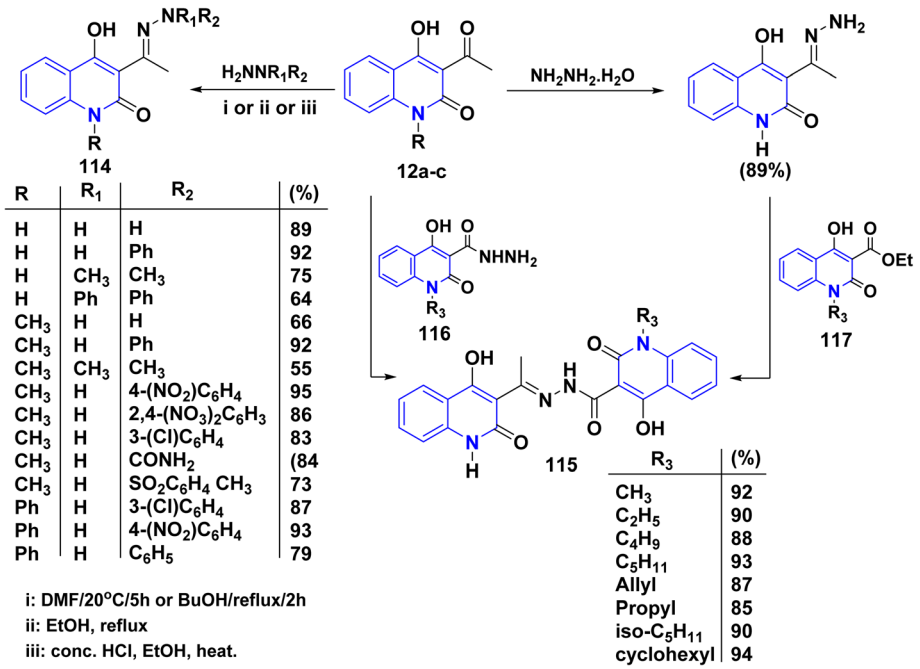
4.2. Nucleophilic substitution reactions

The substitution of a nucleophile at a tetrahedral or sp^3 carbon is known as aliphatic nucleophilic substitution. Substitutions involving aliphatic nucleophiles are not glamorous or essential in the field of chemistry. The way carbonyl additions and carboxyloid replacements seem to occur in biochemistry, they do not occur in all significant processes. Rather, they are commonplace, minor reactions with significant, minor effects everywhere.

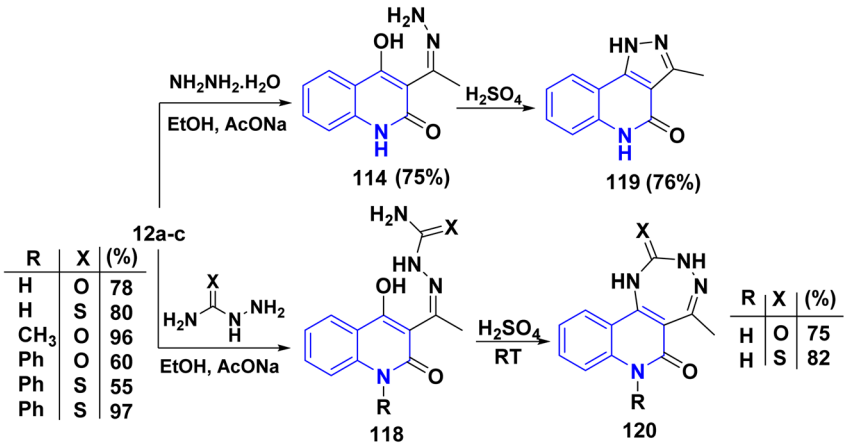
4.2.1. Reactions with nitrogen bases

4.2.1.1. With amines. Condensation reaction of *N*-substituted (un)acetylquinolinone **12a–c,e** with different amines under various conditions afforded enaminones **111**.[143,155,162,172,173] While, addition of a solution of substituted aniline in dimethylformamide (DMF) and pyridine to **60** and refluxed for 17–24 h to give **112** (Scheme 39).[162,173]

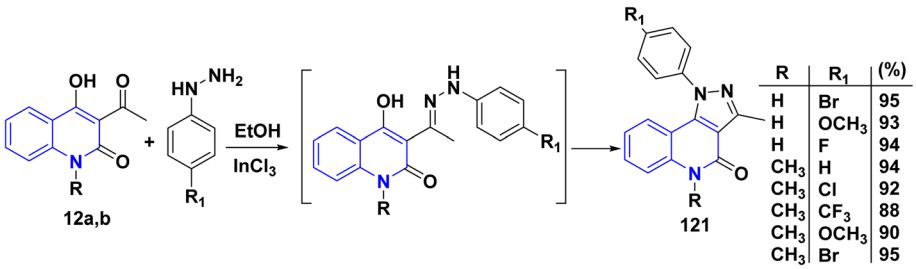
The reaction of quinolinone **12a** with nitrogen bases derivatives such as guanidine nitrate, urea and thiourea in boiling ethanol using AcONa as a catalyst through nucleophilic



Scheme 41 Reactions of quinolinones **12a–c** with variable hydrazines.



Scheme 42 Condensation and cyclization of **114** and **118** to synthesize compounds **119** and **120**.



Scheme 43 Synthesis of pyrazolo[4,3-*c*]quinoline **121**.

addition of the amino group with the regioselectively at the C=O of acetyl function of **12a** accompanied by intramolecular cyclocondensation afforded regioisomer pyrimido[5,4-*c*]quinolinones **113a–c** (Scheme 40).[174]

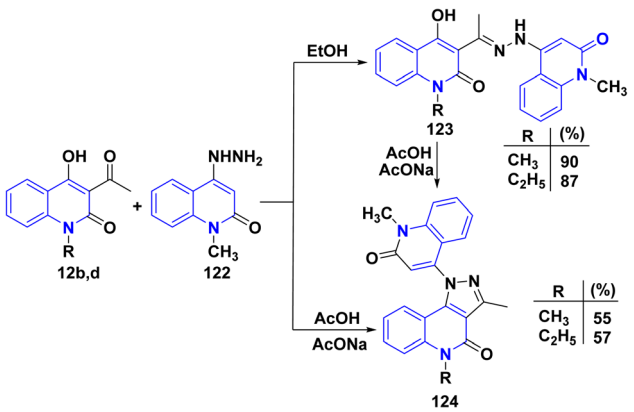
4.2.1.2. With hydrazines. Condensation reaction of hydrazines and arylhydrazines with AHQ derivatives **12a–c** in boiling EtOH or DMF yielded corresponding hydrazones **114**.[115,118,134,172] The reaction conditions varied depending on the aryl substituents, with phenylhydrazine reacting in dimethylformamide (DMF) at ambient temperature, while nitro- and chlorophenyl hydrazines required refluxing in BuOH (Scheme 41).[135,155]

The formation of compound **115** can be accomplished through various methods. This reaction involves two straightforward and efficient approaches. The first method involves a one-step condensation of acetylquinoline **12a** with hydroxyquinolone-3-carboxylic acids hydrazides **116**, resulting in high yields. The second method consists of two stages: initially, treatment of acetylquinoline **12a** to quinolinone, followed by acylation using ethyl hydroxyquinoline-3-carboxylates **117**. This method also proves to be effective in the production of the hydrazones **115** described in this study; both methods were found to be equally valuable (Scheme 41).[115,120,134]

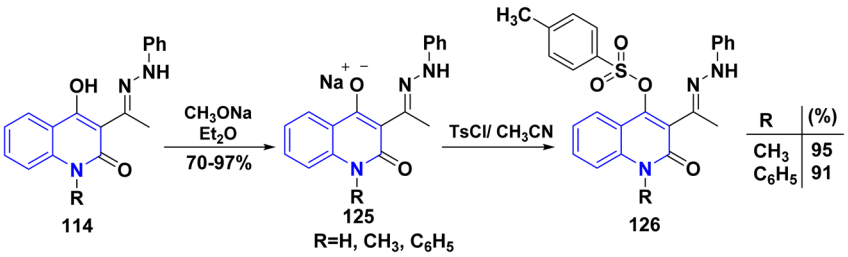
Similarly, compounds **119** and **120** were not achieved immediately by the condensation of **12a–c** with the following hydrazines as hydrazine hydrate, semicarbazide, or thiosemicarbazide but gave acyclized hydrazone **114** and **118**, respectively. These products were cyclized with Conc. H_2SO_4 to yield angular fused pyrazoloquinolinone **119** and angular triazepinoquinolinone **120** (Scheme 42).[118,174]

Angular pyrazolo[4,3-*c*]quinoline derivatives **121** were synthesized under *via* enolizable 3-acetylquinolinone **12a,b** with phenylhydrazine derivatives, utilizing $InCl_3$ as an effective Lewis acid in providing greater yields of products **121** under microwave irradiation (Scheme 43).[175]

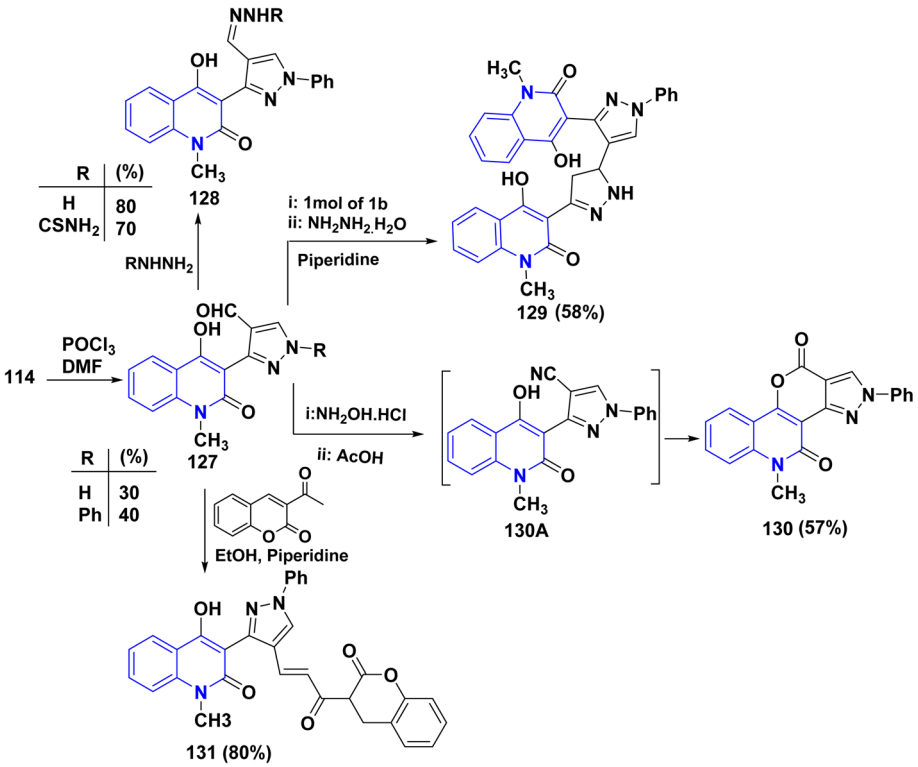
Also, bis quinolinone **123** and **124** were obtained by reaction of **12b,d** with hydrazinyl derivative **122** in different conditions,



Scheme 44 Synthesis of compounds **123** and **124** through condensation and cyclization.



Scheme 45 Synthesis of phenylhydrazonoquinolinylmethylbenzenesulfonate **126**.



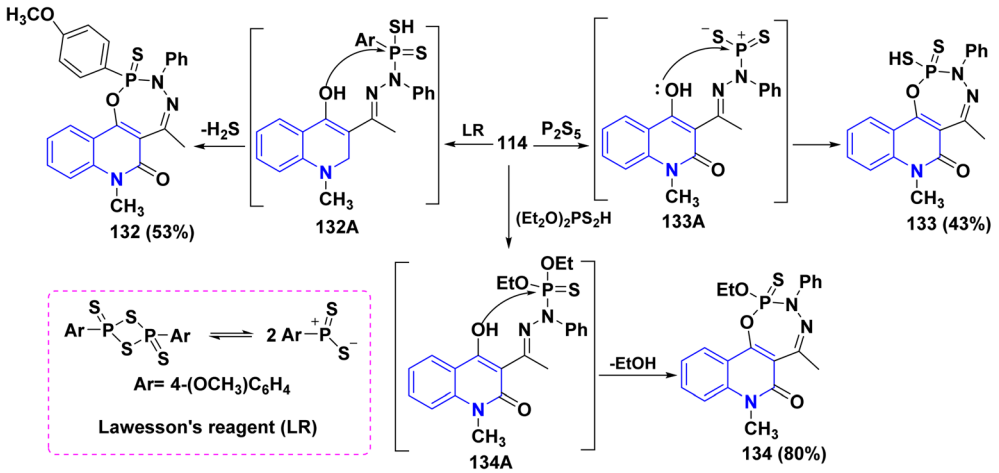
Scheme 46 Synthesis of functionalized quinolone derivatives **128–131**.

in hot ethanol or glacial acetic acid and sodium acetate (AcONa) (Scheme 44).[176]

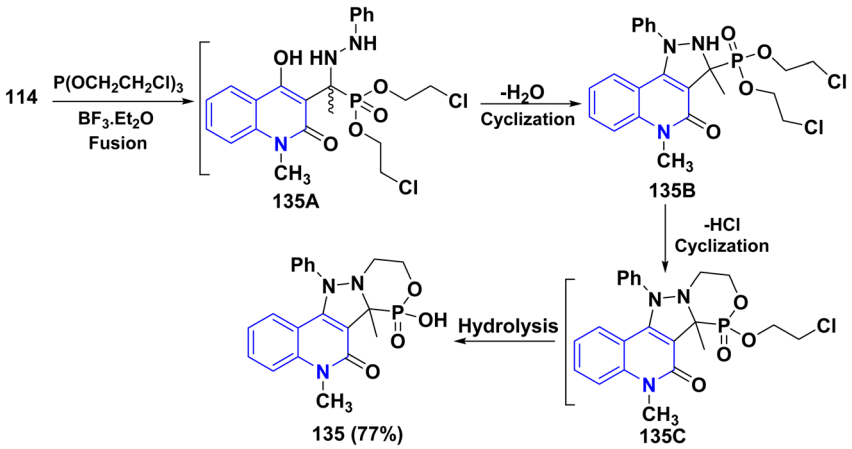
Initially, the reaction of hydrazone derivatives **114** with CH_3ONa in diethyl ether converted the hydroxy group at position 4 to the sodium enolate group, affording **125**. The reaction of sodium salts with toluenesulfonyl chloride in dry CH_3CN yielded targeted toluenesulfonyloxy quinolones **126**. Conversely, the attempts to obtain the toluenesulfonyloxy compounds **126** (R=H) were not avail However, the separation of sodium salts **125** (R=H) in good yields may be attributed to the high reactivity, in both cases, after reaction with TsCl yielded non-isolable mixture of products (Scheme 45).[135]

For the synthesis of pyrazole-4-carbaldehydes **127**, the hydrazones **114** were exposed to Vilsmeier–Haack reagent ($DMF\text{-}POCl_3$).[177,178] While traditional condensation of pyrazole-4-carbaldehydes **127** with hydrazine hydrate or thiosemicarbazide furnished hydrazone derivatives **128** in acceptable yields. Another system in this area was created in two steps. Condensing acetylquinolinone **12b** with aldehyde **127** (R = Ph) furnished the α, β-unsaturated ketone, which was then treated with NH_2NH_2, affording polynuclear heterocyclic skeleton **129** (Scheme 46).

Unexpectedly, the condensation of **127** (R = Ph) with $NH_2\text{-}OH\cdot HCl$ in AcOH did not produce the predicted oxime or the likely carbonitrile **130A** but yielded phenylpyrazolopyrano[3,2-*c*] quinolindione **130**, while the oxime transformed to carbonitrile *via* a dehydration process. The carbonitrile **130A** was then cycloadditionally converted to an iminopyranoquinolinone, hydrolyzed to yield the isolated tetracyclic system **130**. Another option is that the hydrolysis of the intermediate **130A** into the equivalent carboxylic acid causes the pyrone ring to form *via* intramolecular condensation. Anyway, both routes are rational and feasible.[178] Condensation of equimolar amounts of carbaldehyde **127** (R = Ph) with the 3-acetylcoumarin in the presence



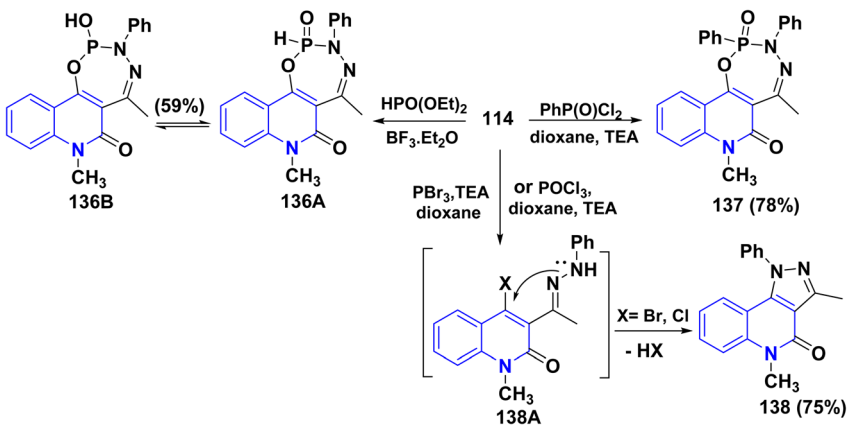
Scheme 47 Reaction of hydrazone **114** with sulfur-containing phosphorus reagents.



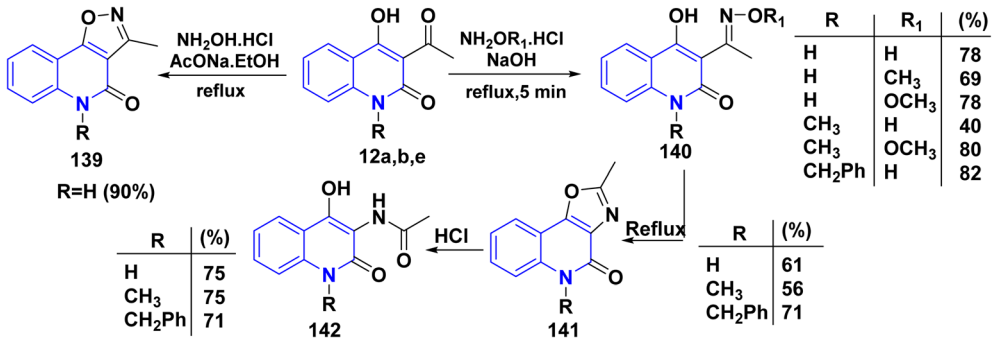
Scheme 48 Treatment of hydrazone **114** with $P(OCH_2CH_2Cl)_3$.

of piperidine as catalyst afforded the corresponding chalcone **131** (Scheme 46).[177]

Additionally, the synthesis of fused phosphorus heterocycles with quinolinone moieties was achieved through an efficient protocol *via* the reaction of hydrazone **114** with some phosphorus reagents. As the treatment of hydrazone **114** with Lawesson's reagent (LR) [which forms two reactive dithiophosphine ylides ($R–PS_2$)], phosphorus pentasulfide (P_2S_5) and diethyldithiophosphoric acid in refluxing dioxane afforded the



Scheme 49 Annulation of hydrazone **114** with diethyl phosphite and phosphohalogenating agents.



Scheme 50 Condensation and thermal Beckmann rearrangement of oxime product.

corresponding fused tricyclic oxadiazaphosphepino[6,7-*c*]quinolinones **132–134** (Scheme 47).[179]

Synthesis of cyclic phosphonic ester **135** was accomplished through treatment of hydrazone **114** with tris(2-chloroethyl) phosphite $P(OCH_2CH_2Cl)_3$. The credible mechanism for synthesis of compound **135** starting with Michael addition of the phosphite to the azomethine bond to produce the non-isolatable intermediate **135A**, which undergoes cyclization through nucleophilic attack of NH functionality at position 4 of the quinoline ring to remove a water molecule yielding the pyrazolyl non-isolatable intermediate **135B** which underwent cyclization through elimination of HCl, followed by acidic hydrolysis yielding **135** as final product (Scheme 48).[179]

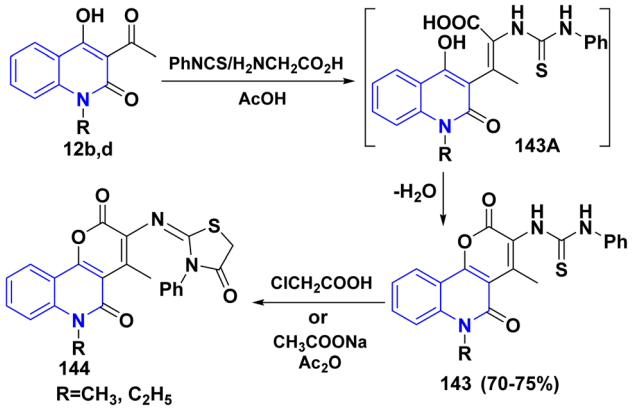
Furthermore, Pudovik reaction of hydrazone **114** with diethyl phosphite in the presence of BF_3 etherate at 80–90 °C furnished oxadiazophosphepino[6,7-*c*]quinolinone **136A,B**. The plausible mechanism involves a cyclization of hydrazone **114** through the nucleophilic attack of OH and NH groups at the phosphorus atom, followed by stripping off two molecules of EtOH. Additionally, heterocyclization of hydrazone **114** with phenylphosphonic dichloride ($C_6H_5Cl_2PO$) in dioxane afforded the corresponding oxadiazaphosphepinoquinolinone **137**(Scheme 49).[179]

Finally, reaction of hydrazone **114** with equimolar amounts of with diethyl phosphite, $PhPOCl_2$, phosphorus tribromide (PBr_3) or $POCl_3$ in dry dioxane in molar ratio (1 : 1) containing catalytic amount of TEA afforded **138**, The proposed mechanism for the synthesis of fused tricyclic **138** may be attributed to halogenation of OH group process through the at C_4. A phosphorus halide of the quinolinone ring, cascade by cyclization of intermediate **138A** through dehydrohalogenation elimination of HX using TEA yielding **138** (Scheme 49).[179]

4.2.1.3. With hydroxylamine. Reaction of acetylquinolinone **12a** with $NH_2OH \cdot HCl$ was accomplished in an ethanolic solution in the presence of AcONa furnished the corresponding oxazole **139**. Whereas, repeating the reaction in the presence of NaOH instead of AcONa furnished corresponding oxime **140** (Scheme 50).[115,118,134,145,172,174]

3-Oximatoacyl-4-hydroxyquinolones **140** were synthesized by reacting AHQ **12a,b,e** with excess hydroxylammonium chloride and hydrogencarbonate, yielding hydroxyiminoquinolones **140** (R_1 = H). To obtain the oximethers **140** (R_1 = methyl), quinolinone **12a,b** were reacted with methyloxyammonium chloride and hydrogencarbonate. Both types of compounds **140** structurally resemble biologically active compounds like alloxydim or sethoxy. When oximes are thermolyzed according to Beckmann rearrangement and converted into isomeric oxazolo[5,4-*c*] quinolinones **141** in high-boiling solvents like 1,2-dichlorobenzene and diphenyl ether. Whereby, the hydrolysis process of oxazole derivatives **141** with dil. HCl led to formation of 3-acylamino-4-hydroxyquinolones **142** (Scheme 50).[172]

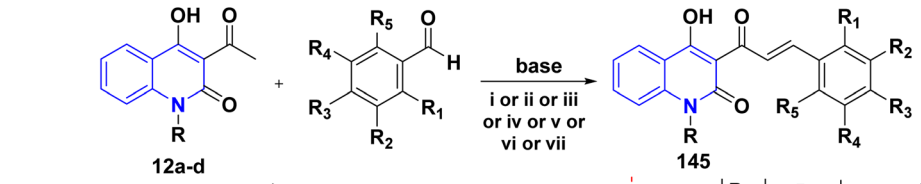
4.2.2. With phenylisothiocyante. Multicomponent reaction (MCR) of **12b,d**, phenylisothiocyanate and glycine furnished *N*-pyrano[3,2-*c*]quinolinedion phenylthiourea **143** in acceptable yields *via* condensation of the carbonyl group of **12b,d** with the active methylene group in glycine to yield the intermediates **143A** which readily cyclized through stripping off water molecule to afford **143**. Whereas, the condensation of **143** with chloroacetic acid and Ac_2O afforded thiazolidine derivatives **144** (Scheme 51).[151]



Scheme 51 Formation of thiazolidine derivatives **144**.

4.3. Condensation reactions

4.3.1. With aldehydes (synthesis of *α*,*β*-unsaturated ketones). A series of *α*,*β*-unsaturated ketones of quinolinone analogues **145** were synthesized through Claisen–Schmidt condensation of **12a–d** with aldehydes under reflux or microwave irradiation.[115,131,146,180–184] The mechanism of the reaction started by reacting of formyl group with L-proline to form an

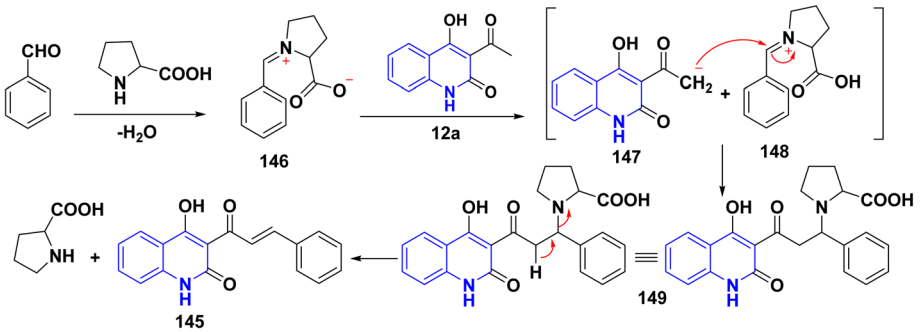


R	R_1	R_2	R_3	R_4	R_5	(%)
H	H	H	H	H	H	89
H	H	OCH_3	OH	H	H	
H	H	OCH_3	OCH_3	H	H	92
H	H	H	$(OCH_3)_2$	H	H	72
H	H	$C(CH_3)_3$	OH	$C(CH_3)_3$	H	
H	H	H	NO_2	H	H	
H	H	H	$N(CH_3)_2$	H	H	78
H	OCH_3	H	$(CH=CH)_2$	$(CH=CH)_2$	H	89
H	H	H	Cl	H	H	86
H	$(CH=CH)_2$	$(CH=CH)_2$	H	H	OCH_3	88
H	H	OCH_3	OH	H	H	58
H	Cl	H	Cl	H	H	90
H	OCH_3	H	H	H	H	78
H	H	OCH_3	OCH_3	H	H	68
H	H	H	$N(C_2H_5)_2$	H	H	90
H	OCH_3	H	OCH_3	H	H	91
H	H	H	CO_2CH_3	H	H	72

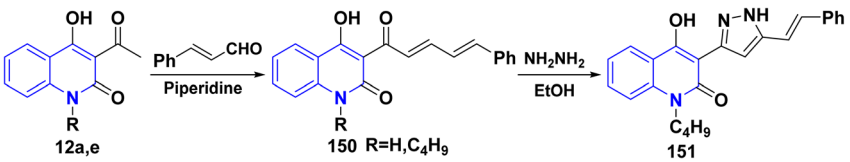
R	R_1	R_2	R_3	R_4	R_5	(%)
H	H	Br	H	H	H	60
CH_3	H	H	H	H	H	74
CH_3	Cl	H	H	H	H	
CH_3	H	H	Cl	H	H	63
CH_3	F	H	H	H	H	
CH_3	H	H	OCH_3	H	H	85
CH_3	H	H	OH	H	H	78
CH_3	H	H	CH_3	H	H	70
CH_3	H	CH_3	H	H	H	87
CH_3	H	Cl	H	H	H	78
CH_3	H	H	Br	H	H	85
CH_3	H	OCH_3	OCH_3	H	H	71
CH_3	H	OCH_3	OH	H	H	48
CH_3	H	H	Cl	H	H	72
C_2H_5	H	H	Cl	H	H	65
C_6H_5	H	H	Cl	H	H	75
C_6H_5	H	H	F	H	H	
C_6H_5	H	H	OCH_3	H	H	65

i) C_2H_5ONa,MW/320 W/1 min or 12h stirring; ii) piperidine, EtOH; iii) BuOH, drops piperidine and reflux
iv) neutral alumina and ultrasonic waves; v) L-Proline/ DMSO/ 30-40 min/ RT;vi) 5% aq.NaOH, 24 h /RT
vii) 5% Alc.NaOH, 12 h/ RT

Scheme 52 Synthesis of α,β-unsaturated ketones **145**.



Scheme 53 Proposed mechanism for the synthesis of α,β-unsaturated ketone **145** in the presence of L-proline.



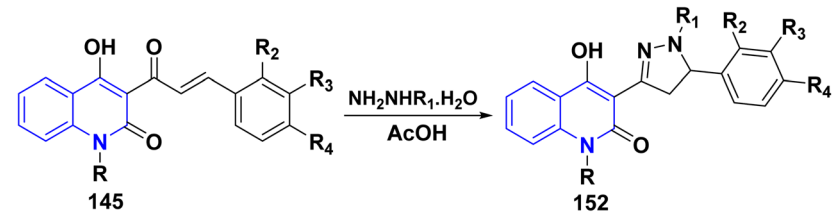
Scheme 54 Reaction of quinolinone **12a,e** with cinnamaldehyde.

iminium carboxylate ion **146**, after that this ion eliminating a proton from active methylene of **12a** affording the carboxylic acid containing iminium ion **148** and quinoline anion **147** as ion pairs that combine to form the adduct **149** which loses proline to afford α,β-unsaturated ketone **145** (Schemes 52 and 53).[183]

Similarly, reaction of quinolone **12a,e** with cinnamaldehyde in the presence of piperidine in refluxing EtOH afforded α,β-unsaturated ketone **150**. After that, treatment of **150** with hydrazine hydrate led to the formation of styrylpyrazolylquinolinone **151** (Scheme 54).[146,185]

The predominant transformations for generating pyrazole rings typically involve the use of α,β-unsaturated carbonyl group derivatives as parent skeletons. Chalcones **145** were treated with appropriate hydrazines in AcOH, furnished functionalized pyrazoline analogues **152** (Scheme 55).[108,146,184,186]

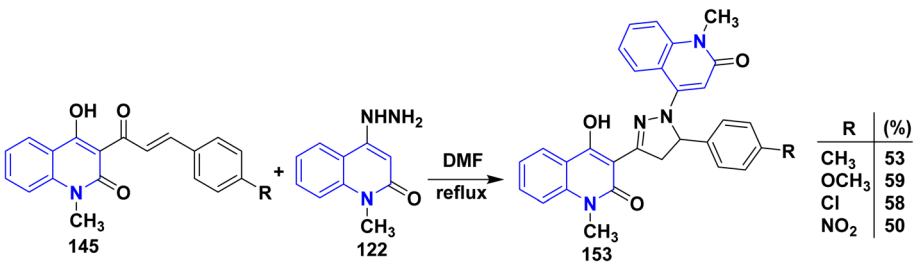
Whereby, the hydrazinoquinolinone **122** underwent condensation followed by cycloaddition reaction with α,β-



R	R_1	R_2	R_3	R_4
H	4-CN-C_6H_4	H	OCH_3	OCH_3
H	4-(OCH_3)C_6H_4	H	OCH_3	OCH_3
H	4-(CN)C_6H_4	H	OCH_3	OH
H	4-(Cl)C_6H_4	H	OCH_3	OH
H	4-(benzyloxy)C_6H_4	H	OCH_3	OCH_3
H	4-(benzyloxy)C_6H_4	H	OCH_3	OH
H	C_6H_5	H	OCH_3	OH
H	C_6H_5	H	OCH_3	OCH_3
H	$COCH_3$	H	H	H
CH_3	4-(CN)C_6H_4	H	OCH_3	OCH_3
CH_3	3,4-$(CH_3)_2C_6H_3$	H	OCH_3	OCH_3
CH_3	4-(CN)C_6H_4	H	OCH_3	OCH_3
CH_3	3,4-$(CH_3)_2C_6H_3$	H	OCH_3	OH
CH_3	4-(OCH_3)C_6H_4	H	OCH_3	OH
CH_3	4-(Cl)C_6H_4	H	OCH_3	OH
CH_3	4-(benzyloxy)C_6H_4	H	OCH_3	OH
CH_3	3-(OCH_3)C_6H_4	H	H	OCH_3
CH_3	4-(OCH_3)C_6H_4	H	H	OCH_3

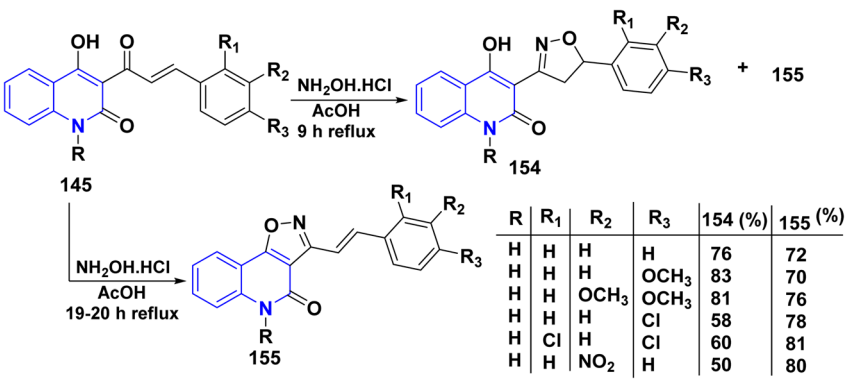
R	R_1	R_2	R_3	R_4
CH_3	H	H	H	H
CH_3	H	Cl	H	H
CH_3	H	H	H	Cl
CH_3	H	F	H	H
CH_3	H	H	H	F
CH_3	H	Cl	H	Cl
CH_3	H	H	H	OCH_3
CH_3	Ph	H	OCH_3	OH
Ph	H	H	H	H
Ph	H	Cl	H	H
Ph	H	H	H	Cl
Ph	H	F	H	H
Ph	H	H	H	F
Ph	H	Cl	H	Cl

Scheme 55 Synthesis of pyrazolylquinolinones through the reaction of **145** with hydrazines.



R	(%)
CH_3	53
OCH_3	59
Cl	58
NO_2	50

Scheme 56 Synthesis of binary pyrazolylquinolinone derivatives.

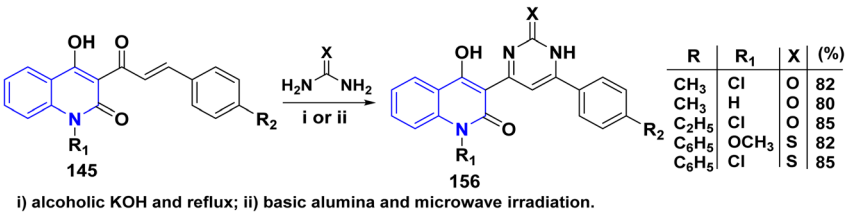


R	R_1	R_2	R_3	154 (%)	155 (%)
H	H	H	H	76	72
H	H	H	OCH_3	83	70
H	H	OCH_3	OCH_3	81	76
H	H	H	Cl	58	78
H	Cl	H	Cl	60	81
H	H	NO_2	H	50	80

Scheme 57 Synthesis of fused and binary isoxazolo and isoxazolyl quinolinone **154** and **155**.

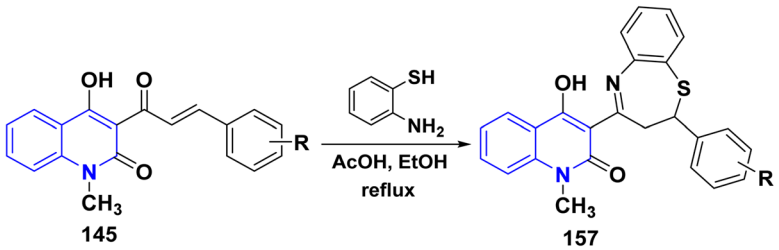
unsaturated ketone derivatives **145**, affording binary quinolinylpyrazoloquinolinone derivatives **153** up to yield 59% (Scheme 56).[176]

Whereas, the reaction of **145** with $NH_2OH{\cdot}HCl$ in glacial AcOH yielded a mixture of two products **154** and **155**. Conversely, repeating the same reaction in other solvents such



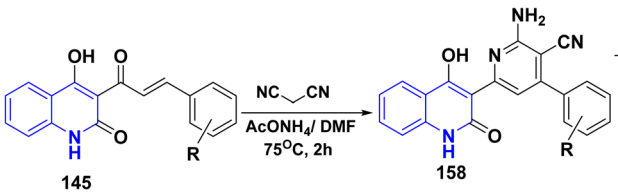
R	R_1	X	(%)
CH_3	Cl	O	82
CH_3	H	O	80
C_2H_5	Cl	O	85
C_6H_5	OCH_3	S	82
C_6H_5	Cl	S	85

Scheme 58 Synthesis of pyrimidinylquinolinone **156**.



R	(%)
3-Cl	67
$3-CH_3$	82
$4-OCH_3$	72
4-Br	78
$4-N(CH_3)_2$	78
$4-OH-3-OCH_3$	62

Scheme 59 Synthesis of 1,5-benzothiazepin ylquinolinones **157** anchored on quinolone.



R	(%)
H	76
2-F	63
2-Cl	76
2-Br	79
$2-OCH_3$	80
3-Cl	82

R	(%)
$3-OCH_3$	76
4-F	75
4-Cl	68
4-Br	83
$4-OCH_3$	69
4-isobutyl	85

Scheme 60 Synthesis of 4-hydroxy-oxoquinolin-4-arylpyridine-3-carbonitriles **158**.

as benzene, MeOH, and EtOH was unsuccessful. Since the isoxazolo[4,5-*c*]quinolin-4(5*H*)-ones **155** formation could not be controlled to get only isoxazolines **154**, increasing the reaction duration to 19–20 h led to isoxazoles **155** as major products, and the minor products could not be isolated (Scheme 57).[180]

Pyrimidinylquinolinone quinolinyl pyrimidine derivatives **156** have been synthesized through both traditional methods and microwave irradiation. These compounds were obtained *via* condensing *α*,*β*-unsaturated ketone derivatives **145** with urea or thiourea in basic media (Scheme 58).[182]

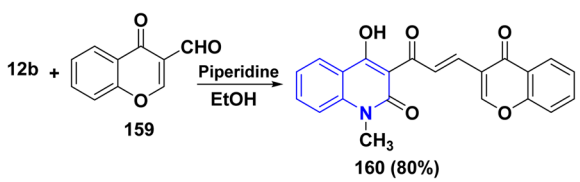
Furthermore, substituted 1,5-benzothiazepinylquinolinones **157** were synthesized by cyclocondensation reaction followed by Michael addition. Whereas, a mixture of *α*,*β*-unsaturated ketone **145**, *o*-aminothiophenol in absolute EtOH then added glacial AcOH (5 mol%). The obtained reaction mixture was refluxed for 5–7 h, furnishing the target product 1,5-benzothiazepinylquinolinones **157** in yields 62–82% (by the optimized condition) (Scheme 59).[133]

MCRs of *α*,*β*-unsaturated ketone **145**, malononitrile, and ammonium acetate in DMF at 75 °C afforded functionalized pyridine binary with quinoline systems **158** (Scheme 60).[187]

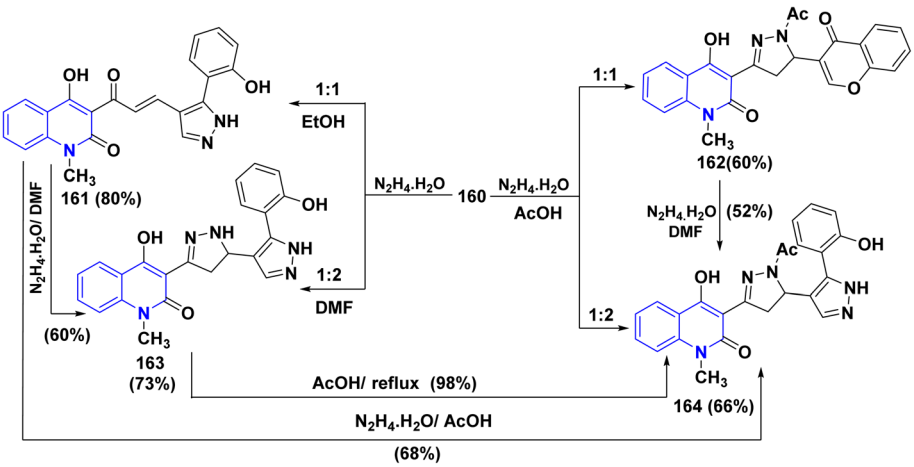
The desired precursor chromenacryloylquinolinone **160** was obtained smoothly *via* a one-pot Aldol condensation dehydration reaction of **12b** with 3-formylchromone **159** (Scheme 61).[188]

In refluxing EtOH, the treatment of compound **160** with an equimolar amount of hydrazine hydrate led to the opening of the pyrone ring and the enone side chain unaffected, affording a new product assigned as 4-hydroxy-3-[3-(2-hydroxyphenyl) pyrazolyl]acryloylg quinolineone **161**. Whereas, using AcOH as the solvent oriented the reaction away from the γ-pyrone nucleus, yielding 3-[1-acetyl-5-(4-oxo-4*H*-chromen-3-yl)-4,5dihydropyrazolyl]-4-hydroxyquinolinone **162**.

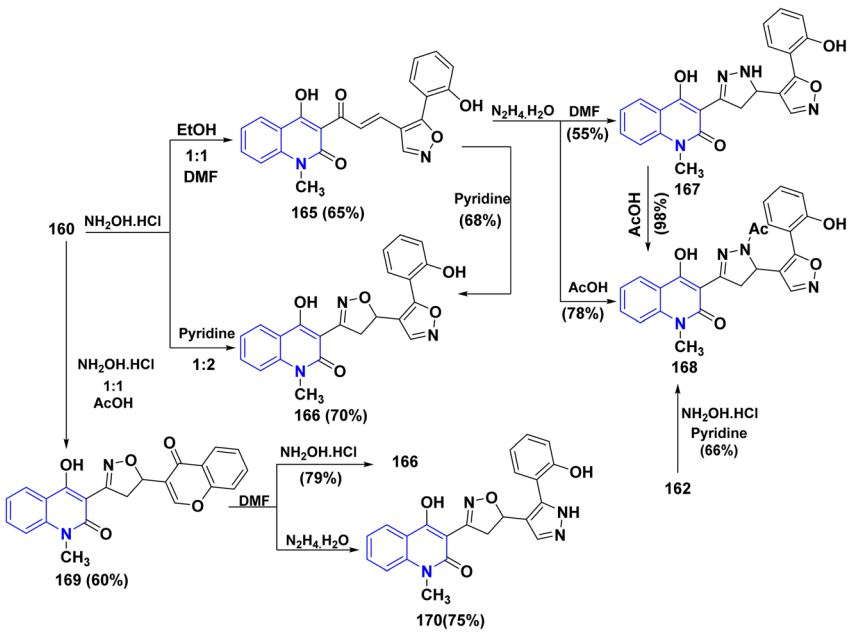
While by, compound **160** was reacted with of hydrazine hydrate (1 : 2) in refluxing DMF affording 4-hydroxy-3-[30-(2-hydroxyphenyl)bipyrazolyl]quinolinone **163** in 73% yield, through double nucleophilic attack at both the *α*,*β*-unsaturated ketone side chain and chromone ring, where by, the same product was prepared by reacting the pyrazolylacryloylquinolinone **161** with an excess amount of hydrazine hydrate in boiling DMF in 60% yield. Interestingly, the reaction of compound **160** with hydrazine (1 : 2) in AcOH did



Scheme 61 Reaction of quinolinone **12b** with 3-formylchromone **159**.



Scheme 62 Synthetic pathway to generate pyrazolo and bipyrazoloquinolone.

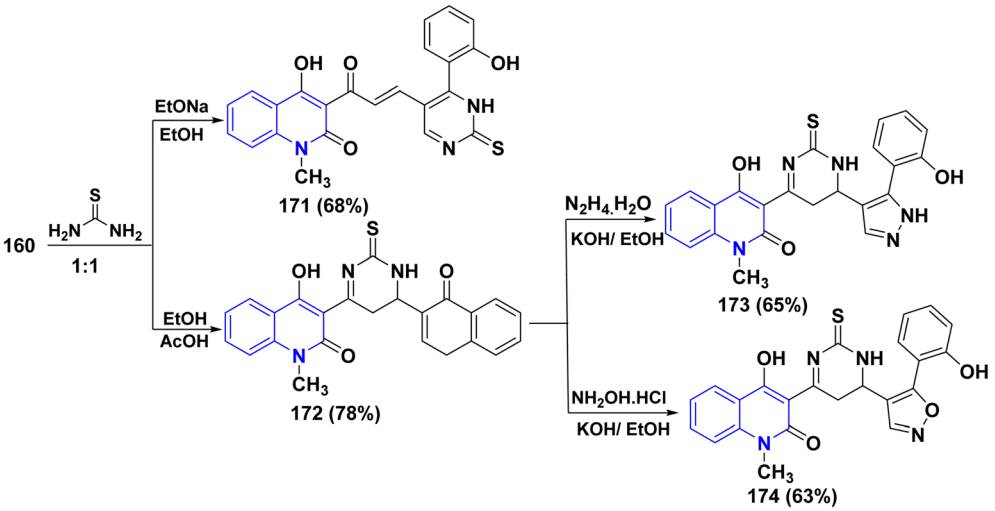


Scheme 63 Reaction of 160 with $NH_2OH \cdot HCl$ in different conditions.

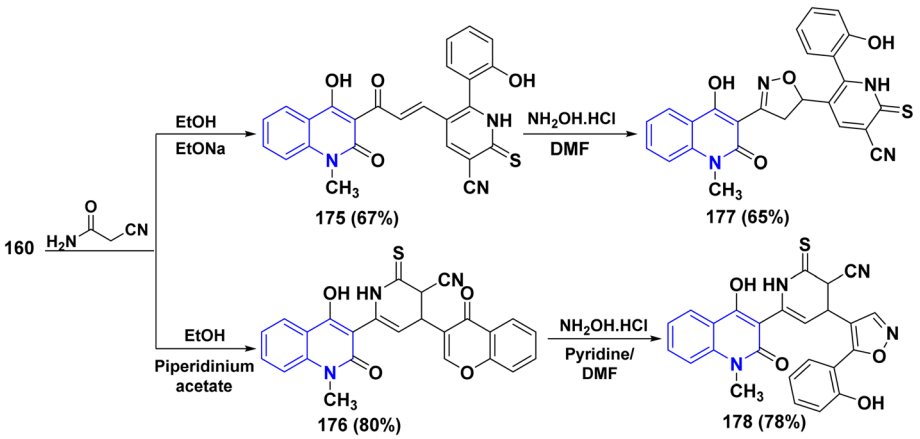
not give either compound **162** or compound **163** but yielded the *N*-acetyl derivative of compound **163** and formulated as binary bipyrazoles **164**. Annotative synthesis of **164** was preceded by reaction of **161** with NH_2NH_2 in AcOH or treatment of compound **162** with NH_2NH_2 in boiling DMF (Scheme 62).[188]

Reaction of equimolar amounts of **160** with $NH_2OH \cdot HCl$ in a mixed solvent of ethanol–DMF led to the formation of 4-hydroxy[5-(2-hydroxyphenyl)isoxazolyl]acryloylgquinolinone **165**. Additionally, the reaction of both compounds **165** with $NH_2OH \cdot HCl$ in boiling DMF or pyridine afforded 4-hydroxy-3-[5-(2-hydroxypheny1)biisoxazoly1]quinolinone **166**, which is obtained directly from **160**, when using an excess of $NH_2OH \cdot HCl$ (1 : 2) in refluxing pyridine. Additionally, polycyclic skeleton **167** was obtained upon reacting isoxazolylacryloy1quinolinone **165** with NH_2NH_2 in boiling DMF. Moreover, boiling compound **167** in AcOH led to acetylation, yielding acetyl-5-[5-(2-hydroxypheny1)isoxazol-4-y1]pyrazol-3-y1-4-hydoxyquinolinone **168**, a compound that was also obtained during heterocyclization of the acryloy1 derivative **165** by means of hydrazine hydrate in AcOH. In the same line, the reaction of *N*-acetylpyrazoline **162** with $NH_2OH \cdot HCl$ furnished the same compound **168** (Scheme 63).

Whereas, the reaction of **160** with an equimolar amount of $NH_2OH \cdot HCl$ in AcOH proceeds in a different manner, and afforded 4-hydroxy-1-methy1-3-[5-(4-oxochromeny1)isoxazol-3-yl)quinolinone] **169**. After that, the reaction of chromeny1isoxazoliny1quinolinone **169** with $NH_2OH \cdot HCl$ in boiling DMF afforded 4-hydroxy-3-[5-(2-hydroxypheny1)biisoxazol-y1] quinolinone **166**. Also, chromeny1isoxazoliny1quinolinone **169** was treated with NH_2NH_2 in boiling DMF yielded 4-hydroxy



Scheme 64 Synthetic pathway to generate pyrimidine, pyrazole and oxazole scaffolds.



Scheme 65 Reaction of 160 with cyano thioacetamide in different reaction conditions.

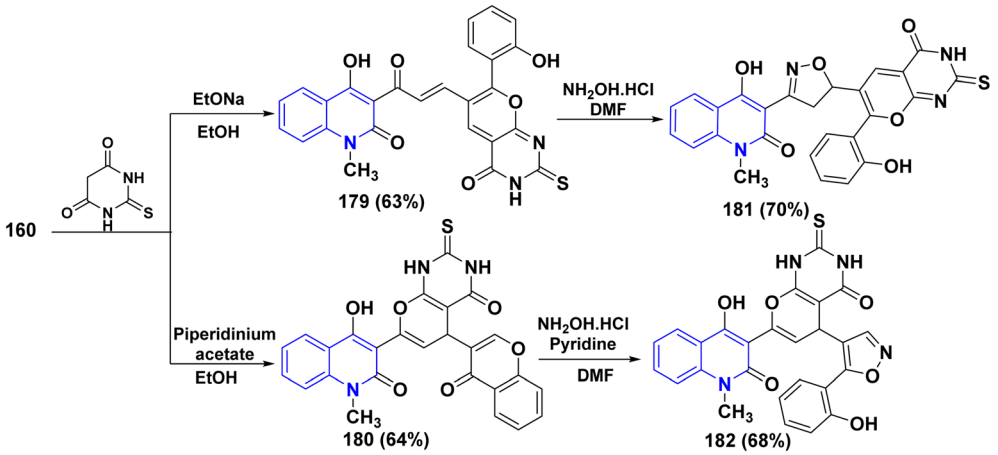
[3-(2-hydroxy phenyl) -pyrazol-4-yl]isoxazol-3-y1-quinolinone **170** (Scheme 63).[188]

Equimolar ratio of **160** and thiourea was refluxed in the presence of sodium ethoxide, affording thioxopyrimidinquinolin-2-one **171** under various reaction conditions. In refluxing EtOH containing a catalytic amount of HCl or in refluxing AcOH, the same reaction resulted in the formation of chromenthioxopyrimidinquinolinone **172**. The reaction of compound **172** with both hydrazine hydrate and $NH_2OH \cdot HCl$ proceeded smoothly using ethanolic potassium hydroxide to afford pyrazolyl **173** and its isoxazolyl analogue **174**, respectively (Scheme 64).[188]

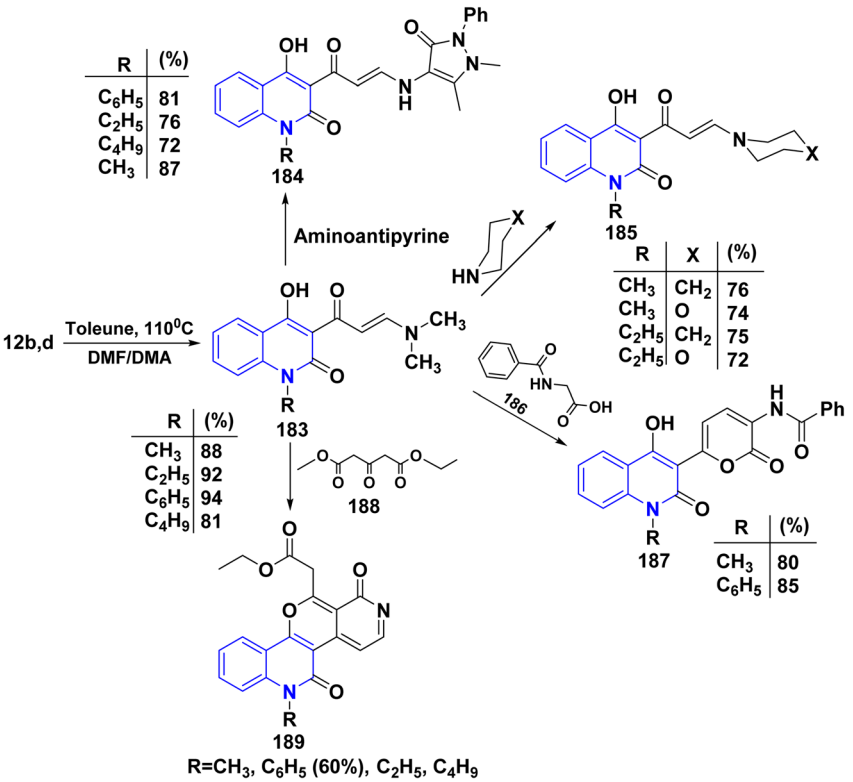
2-Thioxopyridine-3-carbonitriles have great interest due to their usage as intermediates for the synthesis of various medicines. Thus, synthesis of 4-hydroxy-1-methyl-2-oxoquinolin thioxo-3-carbonitrile **175** was achieved by reaction of an equimolar amount of cyano thioacetamide with compound **160**, using sodium ethoxide as a catalyst. Whereas, in a relatively moderate basic medium using piperidinium acetate, the reaction approaching another possible product accessible by a Michael route led to the formation of 6-(4-hydroxy-2-oxo-1,2-dihydroquinolinyl)-4-(4-oxo-4*H*-chromen-3-yl)-2-thioxopyridine-3-carbonitrile **176.** The heterocyclization reaction of both compounds **175** and **176** with $NH_2OH \cdot HCl$, in boiling pyridine and/or DMF, yielded two important triheterocyclic systems: 5-[3-(4-hydroxy-2-oxo-quinolin-3-yl)-4,5-dihydro-isoxzolyl]-6-(2-hydroxyphenyl)-2-thioxopyridine-3-carbonitrile **177** and 6-(4-hydroxyl-2-oxoquinolin-3-yl)-4-[5-(2-hydroxyphenyl)-isoxazolyl]-2-thioxopyridine-3-carbonitnile **178** (Scheme 65).[188]

2-Thiobarbituric acid is recognized as a reactive cyclic methylene compound of the 1,3-dione type, which is utilized to synthesize pyranopyrimidines when cyclized with enone systems or 1,3-dicarbonyl compounds, and more recently with 3-substituted chromones.[189] When compound **160** was treated with 2-thiobarbituric acid in an equimolar ratio in the presence of sodium ethoxide, it yielded (4-hydroxy-2-oxoquinolin-3-yl)-3-oxopropenyl]thioxopyrano[2,3-*d*]pyrimidinone **179**.

While by, the same reaction occurred in the presence of piperidinium acetate, a polycyclic molecule, thioxopyrano[2,3-*d*] pyrimidinone derivative **180** was obtained. Furthermore, both



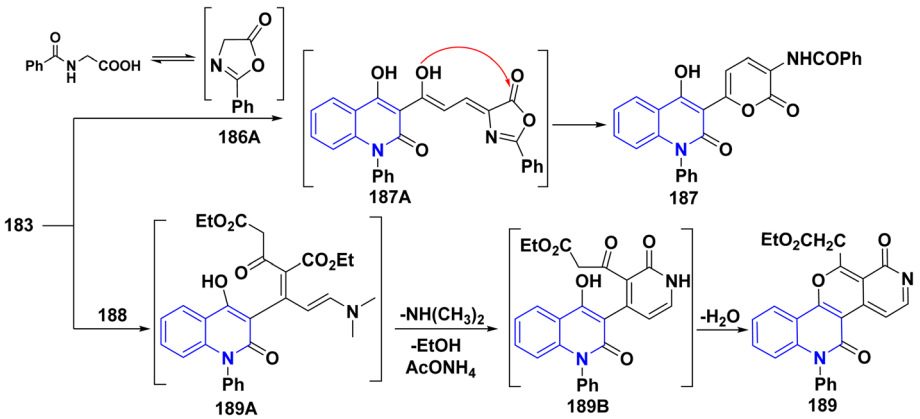
Scheme 66 Reaction of **160** with thiobarbituric acid in different reaction conditions.



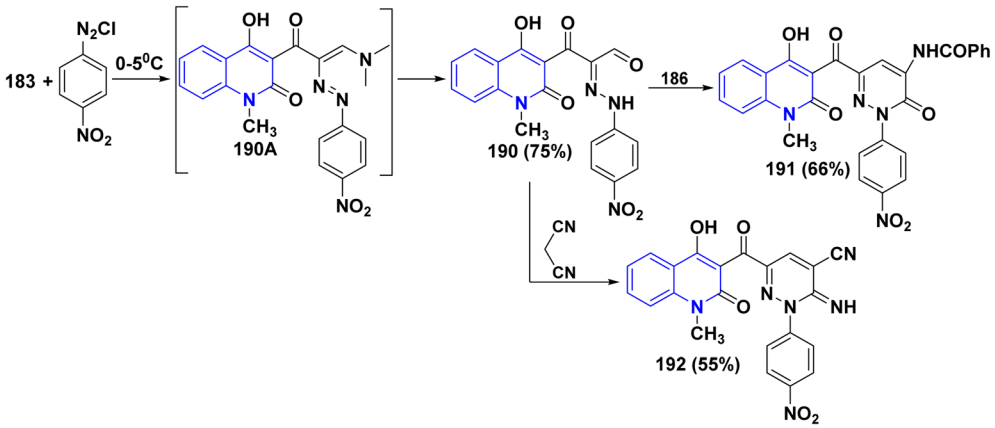
Scheme 67 Reaction series of enaminone **183** with different heterocyclic reagents.

179 and **180** were reacted with $NH_2OH \cdot HCl$ in DMF affording the [3-(4-hydroxy-2-oxoquinolin-3-yl)isoxazol-5-yl]-7-(2-hydroxyphenyl)-2-thioxopyrano[2,3-*d*]-pyrimidinone **181** and (4-hydroxy-2-oxo-quinolin-3-yl)-5-[5-(2-hydroxyphenyl)isoxazol-4-yl]-2-thioxopyrano[2,3-d]pyrimidinone **182**, respectively (Scheme 66).[188]

4.3.2. With DMF/DMA. *N*,*N*-Dimethylformamide dimethyl acetal (DMFDMA), also known as 1,1-dimethoxy-*N*,*N*-dimethylmethanamine, The chemical structure of DMF/DMA has two significant sites: a partially positive carbon that functions as an electrophile in condensation processes and a partially negative nitrogen that acts as a nucleophile. Owing to its structure, DMF/DMA reacts with a wide range of organic groups and can be a useful reagent as a C1 synthon, particularly in the production of heterocycles. Also, it is used to formylate aromatic compounds. The process involves initial conversion of DMF to a chloroiminium ion, $[(CH_3)_2N{=}CH(Cl)]^+$, known as a Vilsmeier reagent, which attacks arenes. Thermal condensation of **12b,d** with DMF/DMA, afforded the corresponding dimethylaminoacryloylquinolinone derivatives as (enaminone compound) **183**.[190] Reaction of enaminone **183** with 4-aminoantipyrine, furnished 3-(3-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-



Scheme 68 Plausible mechanism for synthesis of compound **187** and **189**.



Scheme 69 Coupling of enaminone **183** with 4-nitrobenzenediazonium chloride followed by cyclization.

pyrazol-4-yl)amino)acryloyl)-4-hydroxyquinolinone **184**. Whereas, the reaction of the enaminone **183** with morpholine and piperidine as cycloaliphatic secondary amines smoothly proceeded, leading to the corresponding 4-hydroxy-1-alkyl-3-(3-morpholino/piperidinoacryloyl)quinolinone **185**.

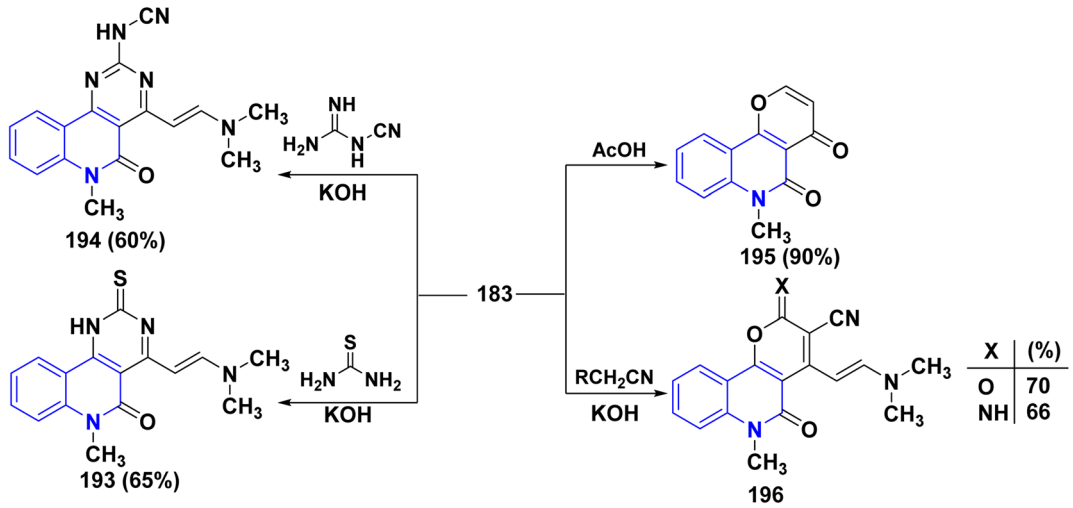
While by, treating enaminone with hippuric acid (*N*-benzoylglycine) or aceturic acid (*N*-acetylglycine) **186** in Ac_2O resulted in the production of **187**. It is suggested that this process begins with the cyclization of **186** into oxazolone, which then adds to the activated double bond system of enaminone **183**, followed by further spontaneous rearrangement yielding **187**.[177,191]

Furthermore, compound **189** was synthesized through condensing the active methylene group in diethyl acetonedicarboxylate **188** with the carbonyl group in compound **183**, *via* water elimination and the formation of an intermediate **189B**. This intermediate is then cyclized in the presence of $AcONH_4$, resulting in the stripping of a water molecule yielding angular tetracyclic compound **188** (Scheme 67).[190]

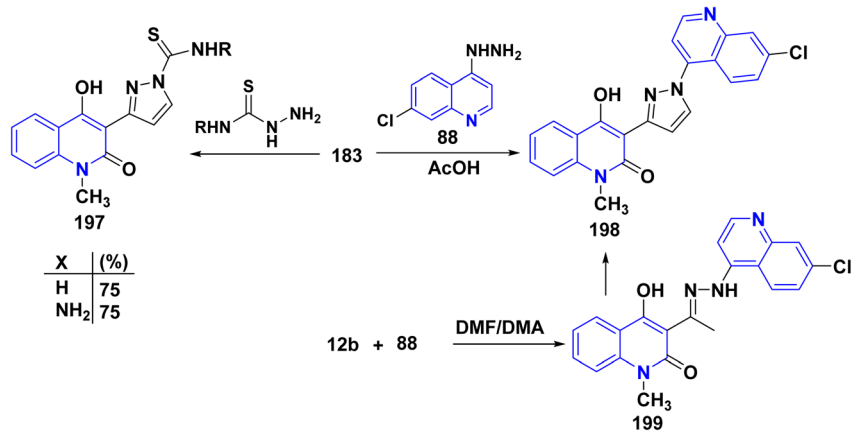
A probable mechanism for the synthesis of **187** started with the cyclization of hippuric acid into oxazolone **186A**, which then adds to the activated double bond system of the enaminone **183**, yielding **187A**, followed by further rearrangement of this intermediate to give **187**. Whereas, compound **189** is thought to be formed *via* condensation of the active methylene in **188** with the carbonyl function in **183** with water elimination, forming the intermediate **189A** that was cyclized in the presence of ammonium acetate *via* elimination of a molecule of EtOH and water to afford the final product **189** (Scheme 68).

Biological activities of pyridazinone ring systems represent one of the most active classes of heterocycles. Consequently, enaminone **183** was employed as a promising building block for synthesizing pyridazinone **191**. Compound **183** coupled with 4-nitrobenzenediazonium chloride, leading to the formation of the arylazo intermediate **190A**, which undergoes hydrolysis during the reaction to produce α-hydrazono-β-oxopropanal **190**. Cyclization of the hydrazone derivative **190** with hippuric acid **186** in Ac_2O produced the 4-benzoylamino-6-[(quinolin-3-yl) carbonyl]-pyridazinone **191** in 66% yield. Whereas, the reaction of compound **183** with malononitrile in absolute ethanol in the presence of piperidine yielded carbonitrile derivative **192** in 55% yield (Scheme 69).[178]

Additionally, treatment of the enaminone **183** with thiourea in ethanolic potassium hydroxide solution did not give the expected pyrimidinylquinolinone **193**. Similarly, reaction of enaminone **183** with cyanoguanidine as amidine reagent gave



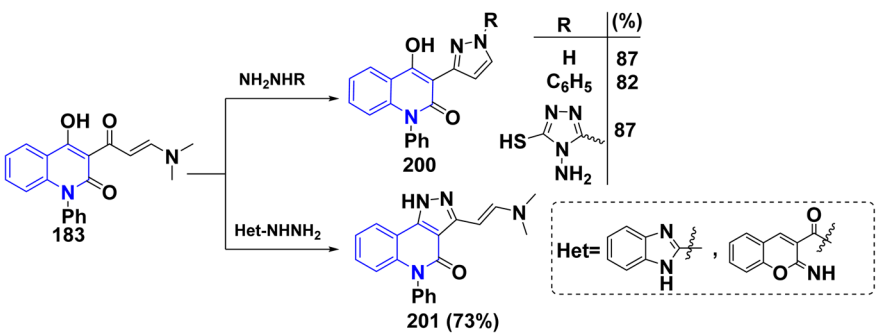
Scheme 70 Reaction series of enaminone **183** analogues synthesis.



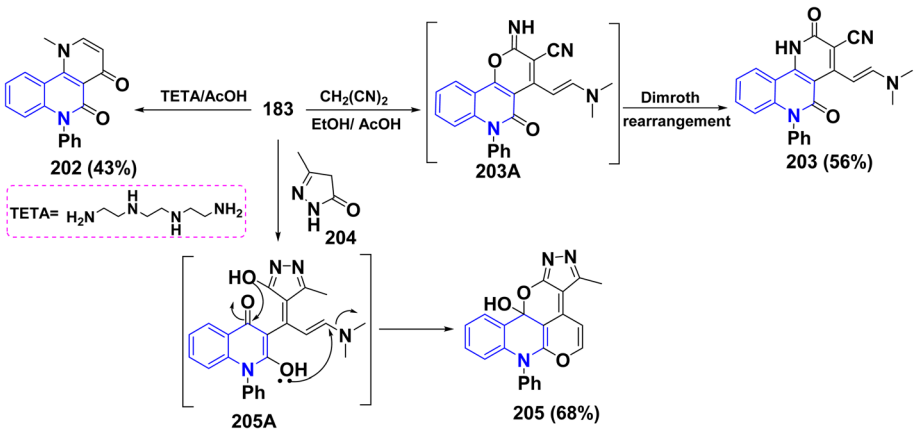
Scheme 71 Reaction of enaminone **183** with binucleophilic reagents.

another pyrimido[5,4-*c*]quinolinone derivative **194**. Moreover, when enaminone **183** was heated in AcOH, it went through intramolecular cyclocondensation, resulting in the formation of 6-methylpyrano[3,2-*c*]quinolindione **195**. Finally, when enaminone **183** was reacted with compounds containing active methylene like malononitrile and ethyl cyanoacetate in the presence of KOH, it yielded the pyranoquinolinone derivatives **196** (Scheme 70).[178]

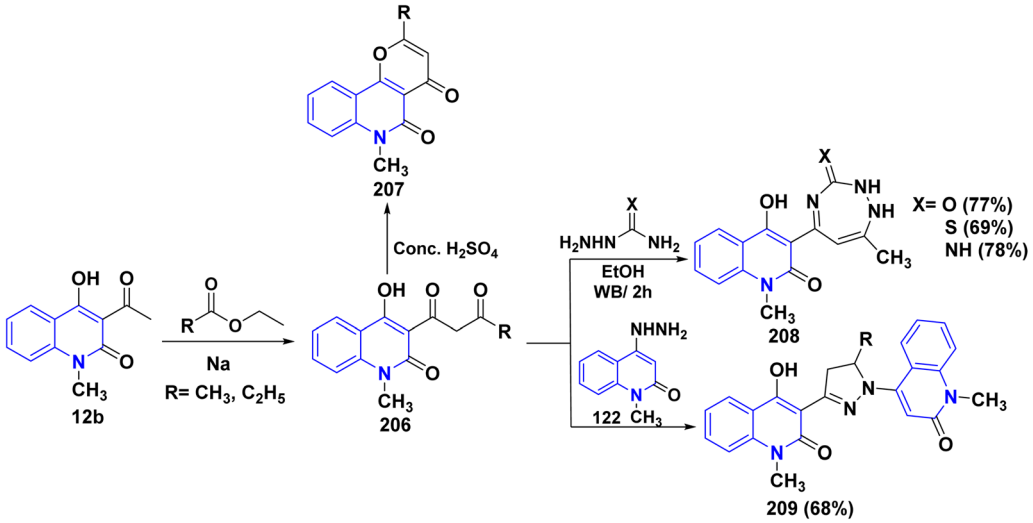
Moreover, treatment of the enaminone **183** with thiosemicarbazide and thiocarbodihydrazide yielded **197**. The cyclocondensation of 7-chloro-4-hydrazinoquinoline **88** with enaminone **183** in acetic acid resulted in the formation of 4-hydroxy-1-methyl-3-[1-(7-chloroquinolin-4-yl)-1*H*-pyrazol-3-yl] quinolinone **198**. The proposed structure for compound **198** was further validated through an alternative synthesis starting from acetylquinolinone **12b**. Specifically, treating compound



Scheme 72 Reaction of enaminone **183** with different hydrazine derivatives.



Scheme 73 Synthesis of fused heterocyclic scaffolds **202**, **203**, and **205**.



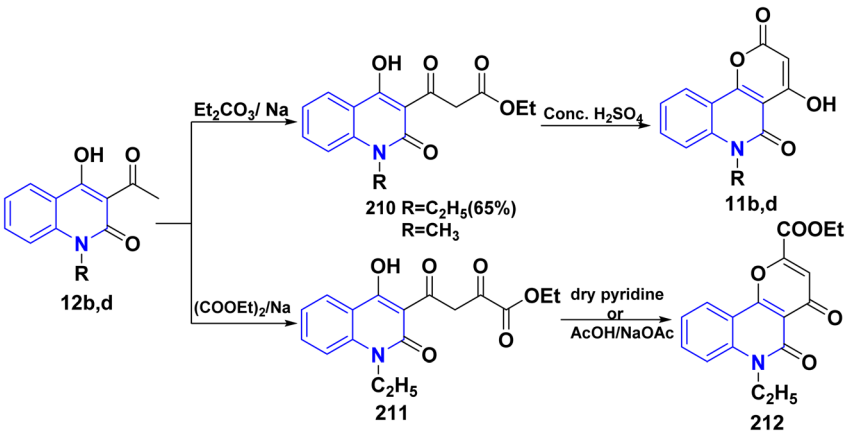
Scheme 74 Synthesis and cyclization reactions of compound **206**.

12b with compound **88** yielded hydrazone **199**. Subsequently, the *in situ* thermal condensation of hydrazone **199** with DMF/DMA smoothly produced compound **198** (Scheme 71).[178]

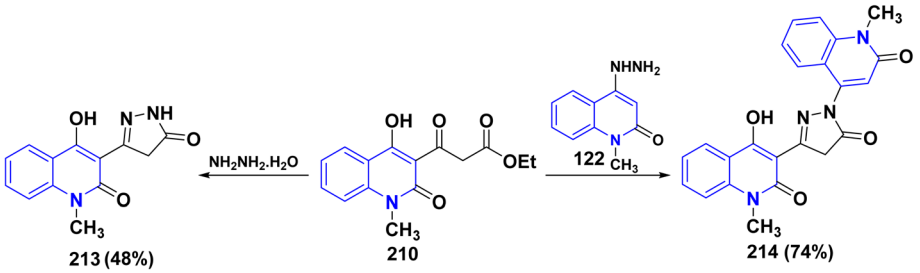
Reaction of enaminone **183** with different hydrazines and hydrazides, such as hydrazine hydrate, phenylhydrazine, and 4-amino-5-hydrazineyl-4*H*-1,2,4-triazole-3-thiol afforded binary pyrazole **200** in good yield. Whereas, treatment of **183** with heterocyclic hydrazine as 2-hydrazineyl-1*H*-benzo[*d*]imidazole or 2-imino-2*H*-chromene-3-carbohydrazide yielded chemoselective fused pyrazole (*E*)-3-(2-(dimethylamino)-5-phenyl-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (**201**) (Scheme 72).[192]

Reaction of enaminone **183** with triethylenetetramine (TETA) as highly active linear polyamines in CH_2Cl_2 led to the formation of benzo[*h*][1,6]naphthyridine-4,5-dione derivative **202** instead of the anticipated transamination products. Furthermore, refluxing of **183** with malononitrile led to the formation of tetrahydrobenzo-[*h*][1,6]naphthyridine-3-carbonitrile **203** through 1,2-addition mechanism followed by the nucleophilic attack of OH group to the cyano function. After that, the Dimroth rearrangement was achieved instead of an alternative path involving the replacement of the active methylene with the dimethylamino group (Scheme 73). Refluxing of enaminone **183** with pyrazolone **204** in AcOH gave fused triazaindenoanthracenol **205** (Scheme 73). The mechanistic pathway for the formation of **205** was recognized through a condensation reaction afforded 1,5-dicarbonyl intermediate **205A**, followed by cyclization reactions of intermediate **205A** through double nucleophilic attacks of the both two OH groups to the endo-ketonic carbonyl group of quinolinone and *β*-position of enaminone led to affording the fused polycyclic system **205** in 68% yield (Scheme 73).[192]

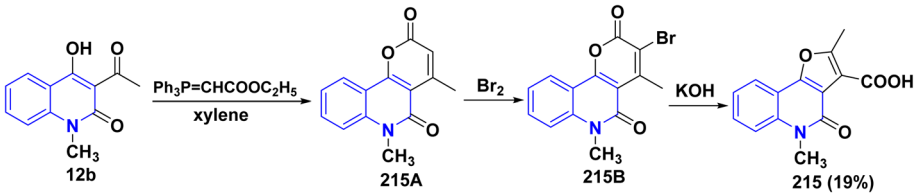
4.3.3. With esters. Compound **206** was synthesized through the condensation of quinolinone derivative **12b** with methyl/ethyl propionate in the presence of Na metal. This reaction occurred through the nucleophilic attack of the active methylene group on the carbonyl group of the ester reagent. Cyclization of compound **206** with sulfuric acid gave 2-ethyl-6-methylpyrano[3,2-*c*]quinolindione **207** (Scheme 74).[151] The bifunctional ammonia derivatives such as semicarbazide, thiosemicarbazide or aminoguanidine reacted with **206** in



Scheme 75 Claisen condensation of compound **12b,d** with different esters.



Scheme 76 Synthesis of pyrazolonyl moiety anchored on quinolone **213** and **214**.



Scheme 77 Synthesis of furo[3,2-*c*]quinolone **215**.

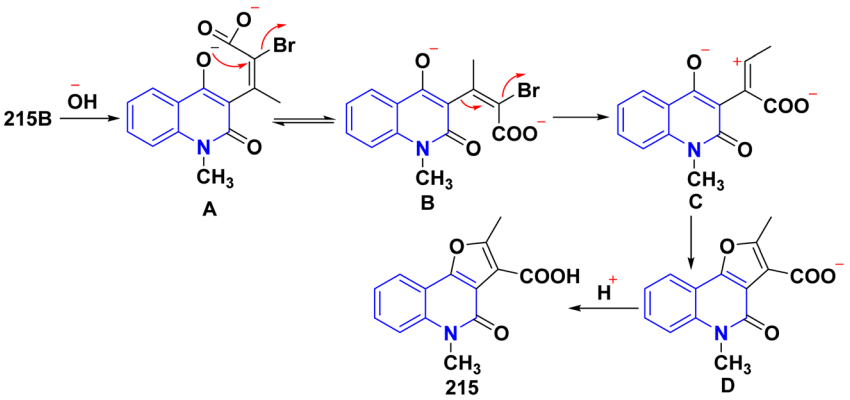
refluxing ethanol to furnish a binary triazepinone, triazepinthione and iminotriazepine **208**, respectively. Furthermore, reaction of compound **206** with hydrazinoquinolinone **122** afforded the intended dihydromethylquinolinyl)-3-pyrazolyl)-4-hydroxyquinolinones **209** (Scheme 74).[176]

Additionally, Claisen condensation reaction of **12b,d** with diethyl carbonate led to 1,3-diketone; 3-ethoxycarbonylacetyl-4-hydroxyquinolin-2-one **210** in the presence of sodium metal. Cyclization of compound **210** with sulfuric acid afforded 4-hydroxypyrano[3,2-*c*]quinolindione **11b,d.** In a similar process, Claisen condensation of compound **12d** with diethyl oxalate in the presence of Na metal produced the diketo-ester; (ethylhydroxy-1,2-dihydroquinolinyl)dioxobutyrate **211**. Cyclization of **211**, in dry pyridine, or AcOH/AcONa (freshly fused) yielded ethyl 6-ethyldihydropyrano[3,2-*c*]quinoline-2-carboxylate **212** (Scheme 75).[151]

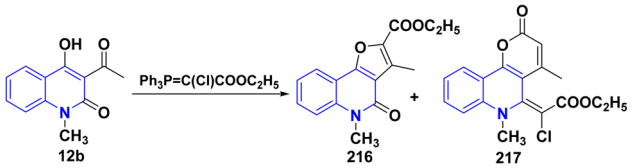
The synthesis of binary pyrazolylquinolinone **213** was achieved by reacting the *β*-ketoester **210** with hydrazine hydrate to give the target compound **213** in 48% yield.[193a] While, direct treatment of pyranoquinolindione **11** with hydrazine hydrate gave the desired pyrazolylquinoline **213** in 92% yield. The possibility of forming the isomeric quinolinylpyrazolin-3-yl) quinolinone **214** was ruled out by independently synthesizing this derivative through the cyclization of hydrazinoquinolinone **122** with 3-ethoxycarbonylacetyl-4-hydroxy-1-methylquinolinone **210** in 74% yield (Scheme 76).[176b]

Whereas, the reaction of acetylquinolinone **12b** with ethyl (triphenylphosphoranylidene)acetate in refluxing xylene afforded **215A** followed by bromination to give compound **215B** that underwent hydrolysis gave furo[3,2-*c*]quinolinone **215** (Scheme 77).[193b]

The proposed reaction mechanism for the molecular rearrangement of **215B** to acids **215** begins with the opening of the pyrane ring in a basic medium, resulting in the formation of dianion **A.** Tautomer **B** is considered more likely than **A** due to the greater distance between the two negatively charged



Scheme 78 Plausible mechanism for the synthesis of **215**.



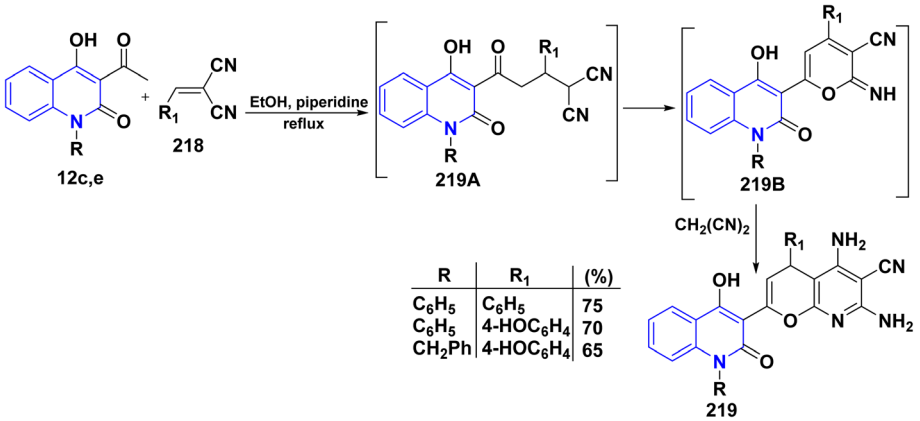
Scheme 79 Reaction of quinolone **12b** with ethyl (triphenylphosphoranylidene)chloroacetate.

functional groups. Following this, the elimination of a halogen atom from the sp^2 hybridized carbon atom occurs alongside the migration of the substituent in a *trans* position relative to the departing halogen. This migrating group exhibits partial carbanionic character due to its potential tautomerism. This rearrangement, which can be classified as a Wagner–Meerwein type, leads to the formation of intermediate **C**, which subsequently yields compound **D** and ultimately product **215** after acidification (Scheme 78).

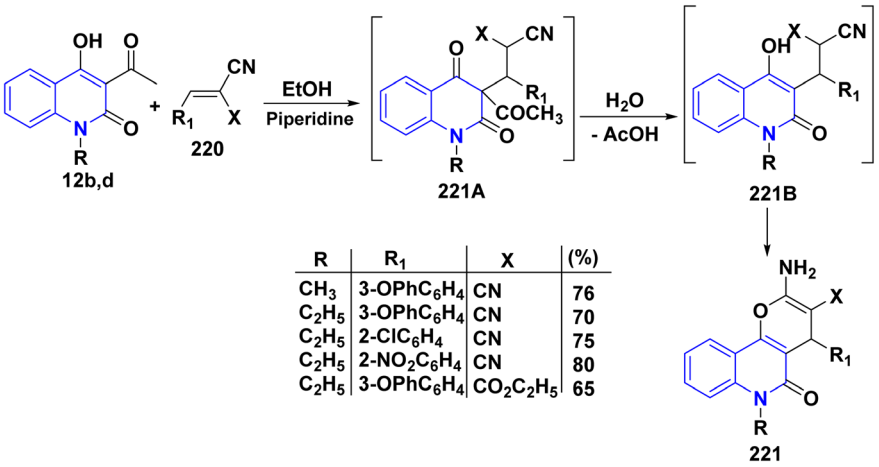
Treatment of **12b** with ethyl (triphenylphosphoranylidene) chloroacetate in refluxing xylene afforded a complex mixture of compounds **216** and **217**. Compound **216** was isolated by repeated column chromatography and identified as an ethyl ester. The second reaction product **217** contained an unsaturated lactone moiety (Scheme 79).[193,194]

4.3.4. With activated olefins as synthetic routes to pyrano skeletons and their benefits (ylidene nitriles). A Michael reaction refers to a type of organic chemistry reaction involving the addition of a nucleophile (Michael donor) to an activated olefin or alkyne (Michael acceptor), such as an acrylate. This reaction is known for its rapid occurrence, tolerance of various functional groups, and its utility in synthesizing novel step-growth compounds with tailored macromolecular architectures. Derivatives **219** are similarly synthesized *via* Michael type addition of the anion ion of the acetyl group in **12c,e** to the activated double bond in ylidenenitriles **218** in (1 : 1) or (1 : 2) molar ratios in ethanol/piperidine to yield the acyclic intermediate **219A**, which dehydrogenated and undergo cyclization into the adducts **219B** which afford compounds **219** under basic conditions by adding one molecule of $CH_2(CN)_2$, which exists in equilibrium with two moles (Scheme 80).[191]

On the other hand, the nucleophilic addition of 3-acetylquinolinones **12b,d** to **220** in EtOH, using piperidine as a catalyst, produced intermediate **221A**. This intermediate underwent hydrolysis, losing the acetyl group, to form quinolone intermediate **221**. Subsequently, cyclization of this

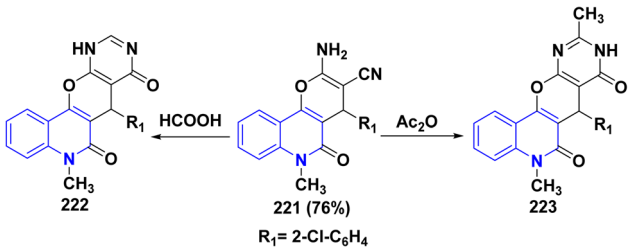


Scheme 80 Michael addition of compounds **12c,e**.



R	R_1	X	(%)
CH_3	3-$OPhC_6H_4$	CN	76
C_2H_5	3-$OPhC_6H_4$	CN	70
C_2H_5	2-ClC_6H_4	CN	75
C_2H_5	2-$NO_2C_6H_4$	CN	80
C_2H_5	3-$OPhC_6H_4$	$CO_2C_2H_5$	65

Scheme 81 Catalyzed nucleophilic addition of 3-acetylquinolinones 12b,d.



Scheme 82 Synthetic pathway to access tetracyclic systems 222 and 223.

intermediate yielded 2-amino-5-oxopyrano[3,2-*c*]quinoline derivatives **221** (Scheme 81).[115,134,195]

2-Amino-4-(2-chlorophenyl)oxopyrano[3,2-*c*]quinolinecarbonitrile **221**, as a typical enaminonitrile derivative, reacted with HCOOH to afford tetracyclic 5-methylpyrimidopyrano[3,2-*c*] quinolindione **222**. Compound **221** also reacted with Ac_2O to yield 5,10-dimethylpyrimidopyrano[3,2-*c*]quinolindione **223** (Scheme 82).[195]

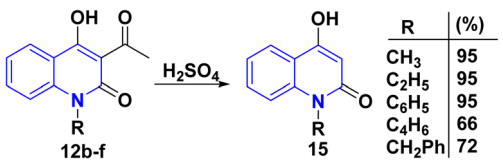
6-Methyldioxodihydrospiro[indoline-3,4′-pyrano[3,2-*c*]-quinoline]-3′-carboxylate **225** was synthesized through the reaction of compound **12b** with **224** in EtOH, pyridine (Scheme 83).[115]

4.4. Miscellaneous reactions

4.4.1. Deacetylated quinolinone (HQ) and its utility. Hydrolysis reaction of acetylquinolinone **12b–f** with sulfuric acid, accompanied by deacetylation produced 4-hydroxyquinoline derivatives (HQ) **15** (Scheme 84).[115,130,132,141,145,155]

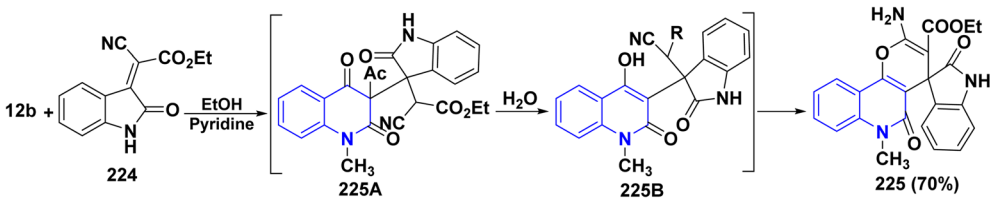
Refluxing of 4-hydroxyphenylquinolinone **15** with $POCl_3$ for 2 h yielded the corresponding 4-chloroquinolinone derivative **226**, reaction of **226** with three equivalent piperazine in DMF in the presence of TEA was heated at 80 °C for 6 h yielded 4-piperazinylquinolinone **227**, heating **227** with formaldehyde and the appropriate amine in EtOH at reflux then leave overnight afforded the target *N*-Mannich bases **228.** Alkylation of the piperazinyl nitrogen of compounds **227** with 2-bromo-*N*-phenylacetamide derivatives **229** was achieved by stirring overnight in DMF using K_2CO_3 as a base to yield the target compounds **230** (Scheme 85).[194]

Refluxing of **15** with propargyl bromide in acetone in the presence of anhydrous K_2CO_3 for 14–16 h afforded a mixture of **231**, **232**, and **233**, which were separated by HPLC.[196] Base-catalysed Claisen rearrangement of propynyloxyquinolone **231** in hexamethylphosphoric triamide (HMPT) in the presence of $NaHCO_3$ (2 equiv), refluxed for 10–18 h afforded angular furo [3,2-*c*]quinolinone **234** according to the shown mechanism (Schemes 86 and 87). Whereas, **231** products followed by

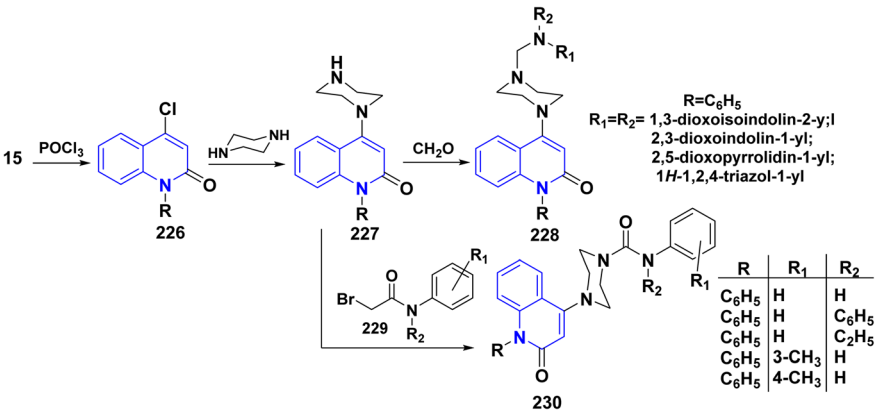


R	(%)
CH_3	95
C_2H_5	95
C_6H_5	95
C_4H_6	66
CH_2Ph	72

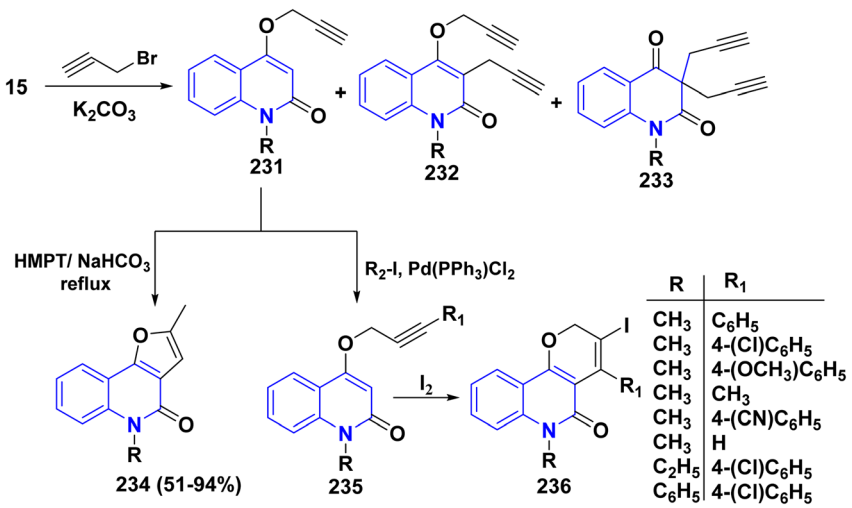
Scheme 84 Deacetylation of 3-acetyl-4-hydroxyquinolone derivatives 12b–f.



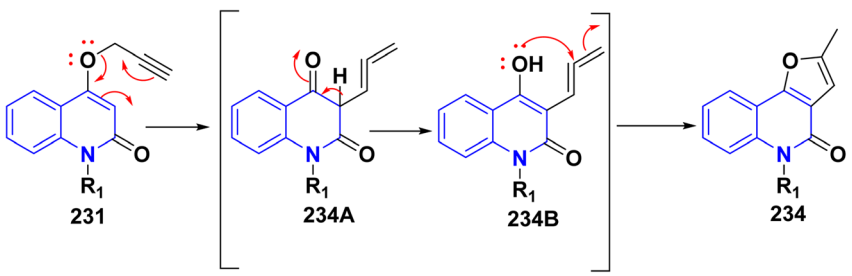
Scheme 83 Synthetic approach of spiro compound 225.



Scheme 85 Chloronation of **15** followed by synthesis of *N*-Mannich base.



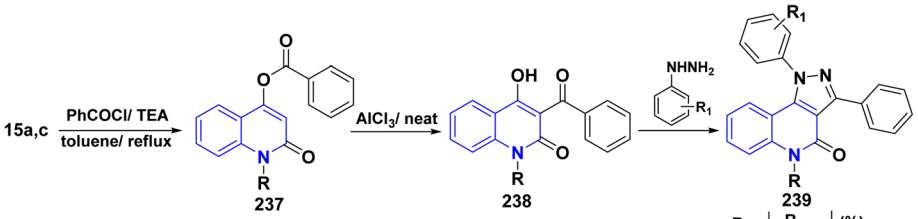
Scheme 86 *O*-alkylation followed by Suzuki coupling reaction.



Scheme 87 Mechanistic pathway for the synthesis of **234**.

Sonogashira coupling yielded 4-((3-arylprop2-yn-1-yl)oxy) quinolin-2-onederivatives **235** in good yield. Then, electrophilic cyclization between **235** and iodine to obtain **236**, the reaction was initially performed in various solvents (DMF, CH_3CN, CH_3OH, THF, DCM, and CH_3NO_2) at 25 °C, using sodium bicarbonate as a base (Scheme 86).[197]

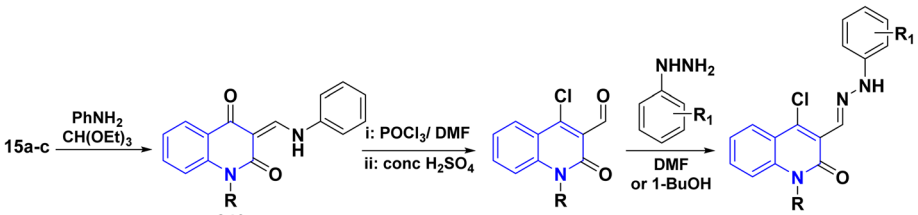
Benzoylation reaction of **15a–c** with benzoyl chloride and a catalytic amount of TEA afforded 4-benzoyloxy-2-quinolinones **237**.[198] Compound **237** underwent Fries rearrangement with $AlCl_3$, yielding 3-benzoyl-4-hydroxy-2-quinolinones **238** in excellent yields. Reaction of *β*-hydroxyketone compound **238** with phenylhydrazines in dimethylformamide (DMF) at room temperature and also at 0 °C yielded mixtures of compounds that can be separated, which contained cyclized pyrazolo[4,3-*c*] quinolinones **239**. To obtain pyrazolo[4,3-*c*]quinolinones **239** directly from 3-benzoyl-4-hydroxy-2-quinolinones **240** pure and in good yield (87–99%). A suspension of 3-benzoyl compounds **238** was treated in AcOH with a few drops of conc. H_2SO_4 to



R	(%)
CH_3	90
C_6H_5	99

R	R_1	(%)
H	3-Cl	52
CH_3	H	72
CH_3	4-NO_2	85
C_6H_5	H	68
C_6H_5	4-NO_2	95
C_6H_5	3-Cl	98

Scheme 88 Synthesis of pyrazolo[4,3-*c*]quinolinones **239** through *o*-benzoylation.



R	(%)
H	91
CH_3	62
C_6H_5	66

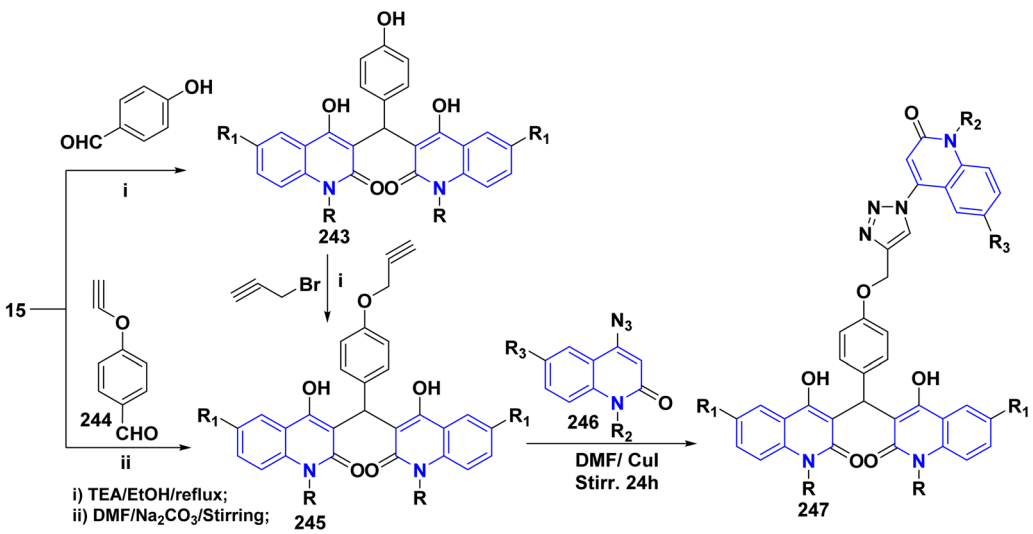
R	(%)
H	63
CH_3	84
C_6H_5	95

R	R_1	(%)
H	H	85
CH_3	H	84
C_6H_5	H	62
C_6H_5	NO_2	91

Scheme 89 Synthesis of chlorohydrazonoquinolinones **242**.

enhance the reaction rate and obtain good to excellent yields. Heating for 2 h yielded pyrazolo[4,3-*c*]quinolones **239** (Scheme 88).[135]

The synthetic pathway for compound **242** begins from 3-phenylaminomethylene quinolindiones **240**, which were synthesized from 4-hydroxy 2-quinolones, aniline and triethyl

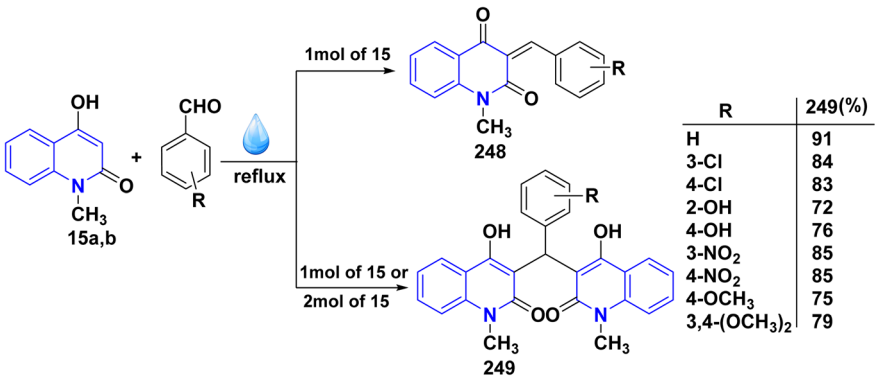


R	R_1	(%)
H	H	85
H	OCH_3	90
CH_3	H	78

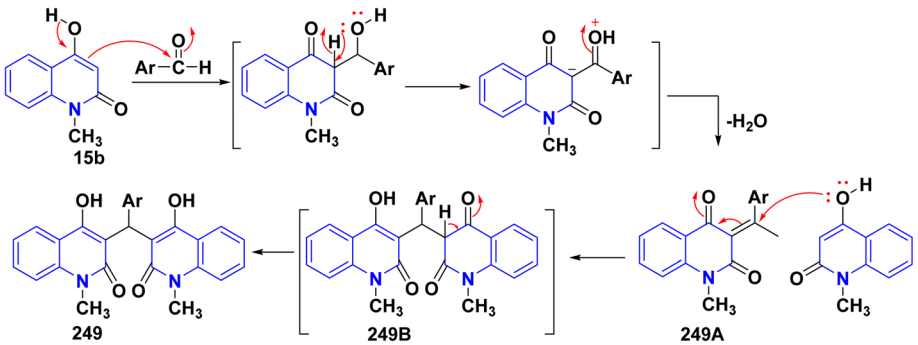
R	R_1	R_2	R_3	(%)
H	H	H	H	75
H	H	H	CH_3	80
H	H	H	OCH_3	82
H	H	CH_3	H	70
H	OCH_3	H	H	77
H	OCH_3	H	CH_3	82

R	R_1	R_2	R_3	(%)
H	OCH_3	H	OCH_3	83
H	OCH_3	CH_3	H	69
CH_3	H	H	H	72
CH_3	H	H	CH_3	77
CH_3	H	H	OCH_3	71
CH_3	H	CH_3	H	66

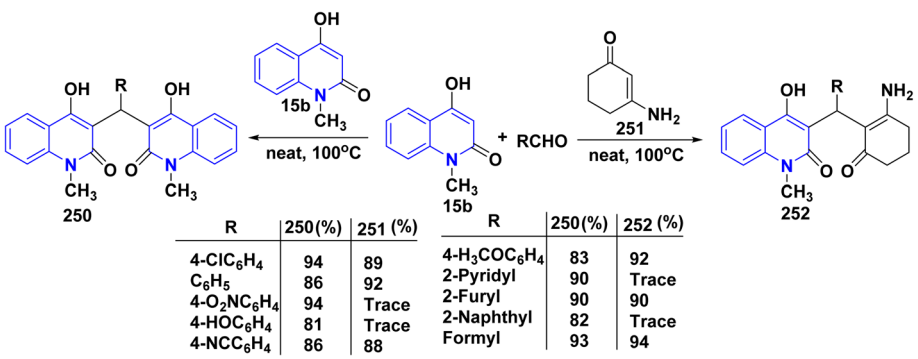
Scheme 90 Synthesis of triazolyl-*bis*(4-hydroxy-quinolin-2(1*H*)-ones) **247**.



Scheme 91 Reaction of 4-hydroxyquinoline derivatives **15** with various aromatic aldehydes.



Scheme 92 Mechanistic pathway for the synthesis of **249**.

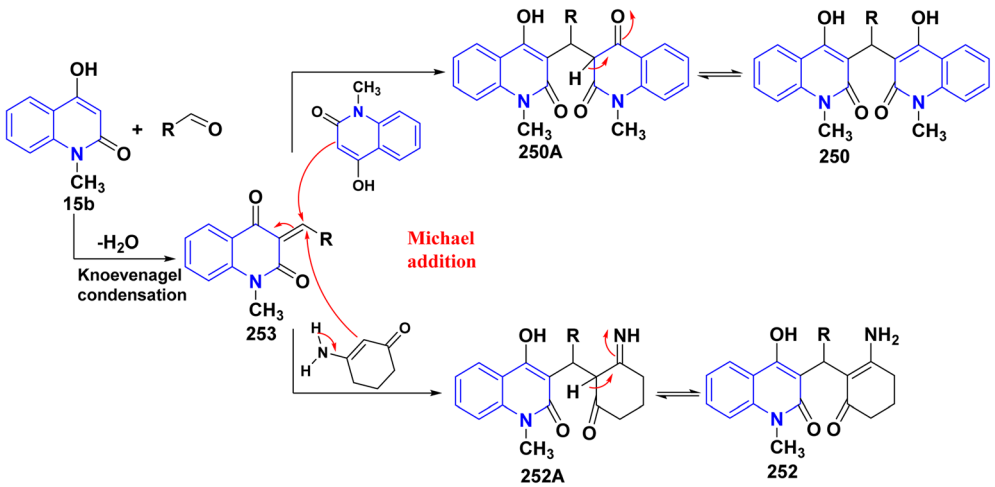


Scheme 93 Synthesis of **250** and **252** *via* Knoevenagel–Michael reaction.

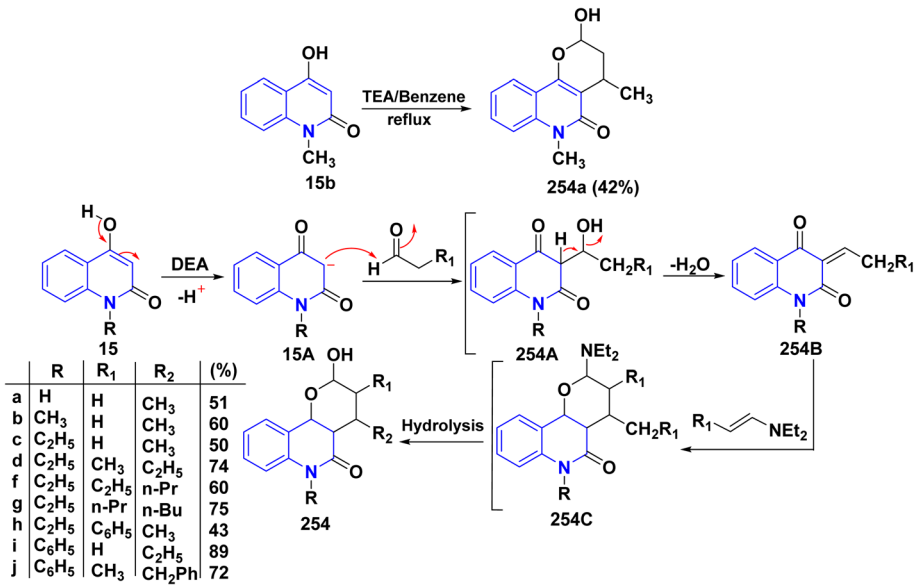
orthoformate ($CH(OEt)_3$), after that converted to 4-chloro-3-formylquinolinones **241**.[135,199] The reaction of carboxaldehydes **241** with a specific amount of phenylhydrazines in a solution of DMF at room temperature or in refluxing BuOH afforded 4-chloro-3-arylhydrazinonoquinolinones **242** in good to excellent yields (Scheme 89).[135]

The synthesis of a new series of triazolylquinolinones, specifically 3,3′–(oxoquinolin-4-yl)-1,2,3-triazol-4-yl)methoxy) phenyl)methylene)bis(4-hydroxyquinolinones) **247**, was achieved by reacting 4-azido-2-quinolinones **246** with 3,3′–(prop-2-yn-1-yloxy)phenyl)methylene)bis(4-hydroxyquinolinones) **245** through a Cu-catalyzed [3 + 2] cycloaddition (Huisgen–Meldal–Sharpless reaction). Initially, the synthesis of terminal alkynes **245** was performed *via* interaction between 4-hydroxyquinoline-2-ones **15** and *p*-hydroxybenzaldehyde in different molar ratios under reflux to afford 3,3′–(hydroxy-phenyl)methylene)*bis*(4-hydroxyquinolin-2-ones) **243**. Phenol compound **243** reacts with propargyl bromide in DMF to produce alkynes **245**. On the other hand, 4-hydroxy-2-quinolinones **15**, interacted with aldehyde **244** in different molar ratios (2 : 1) to produce the desired terminal alkynes **245** (Scheme 90).[200]

Reaction of compound **15** with several aromatic and heterocyclic aldehydes, which contain both electron-withdrawing and electron-donating groups, was investigated



Scheme 94 Suggested mechanism for the synthesis of **250** and **252**.



	R	R_1	R_2	(%)
a	H	H	CH_3	51
b	CH_3	H	CH_3	60
c	C_2H_5	H	CH_3	50
d	C_2H_5	CH_3	C_2H_5	74
f	C_2H_5	C_2H_5	n-Pr	60
g	C_2H_5	n-Pr	n-Bu	75
h	C_2H_5	C_6H_5	CH_3	43
i	C_6H_5	H	C_2H_5	89
j	C_6H_5	CH_3	CH_2Ph	72

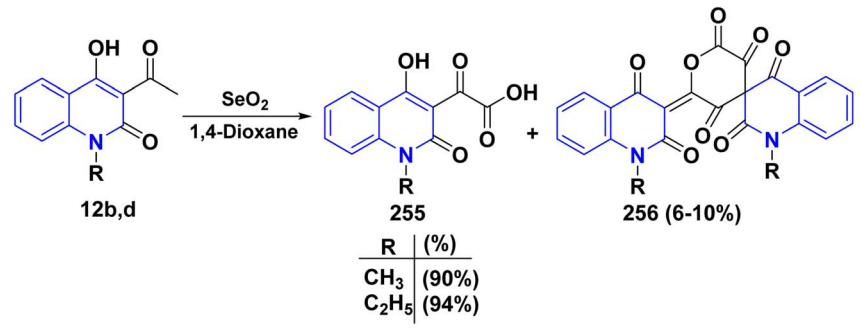
Scheme 95 Photoinduced reaction of compound **15b** with TEA producing **254a** and the Plausible mechanism.

under catalyst-free conditions using water as the eco-medium to produce compound **249**, through Knoevenagel condensation followed by a Michael-type addition with compound **15**, leading to the smooth formation of a wide range of substituted bis-quinolinones. In these cases, aldehydes with electron-withdrawing groups produced higher product yields, ranging from 85% to 90%. The study revealed that compound **249** was the primary product, rather than compound **248**, when using different moles of compound **15** (Scheme 91).[201–204]

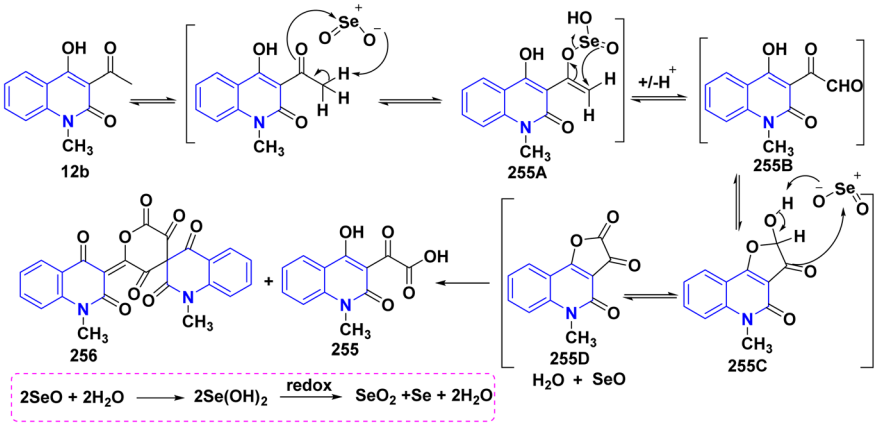
A believable mechanism for the formation of compound **15** has been suggested. Initially, one equivalent of HQ **15b** undergoes a straightforward Knoevenagel condensation with aromatic and heterocyclic aldehydes to produce carbonyl intermediate **249A.** This intermediate serves as a strong Michael acceptor and reacts with another equivalent of **15b** through Michael addition, resulting in the keto–enol intermediate **249B**, followed by isomerization to yield the final product (Scheme 92).[201]

Furthermore, treatment of **15b** with the aromatic and heterocyclic aldehydes in different molar ratios (2 : 1) led to the formation of **250.** Whereas, the three-component Knoevenagel–Michael reaction of **15b**, aldehyde, and aminocyclohex-2-enone **251** produced skeleton **252.** But, when the reactants were added sequentially, only a small amount of the desired product **252** was obtained, with compound **250** being the major product (Scheme 93).[203]

A plausible mechanism for the formation of compounds **250** and **252** started with simple Knoevenagel condensation of **15** with the aromatic or heterocyclic aldehydes (known to occur under solvent and catalyst-free conditions) to generate an adduct **253**, which acts as a strong Michael acceptor. After that, another molecule of HQ **15** (two-component reaction) or 3-



Scheme 96 Oxidation of quinolone derivatives **12b,d**.



Scheme 97 Proposed mechanism for the synthesis of **255** and **256**.

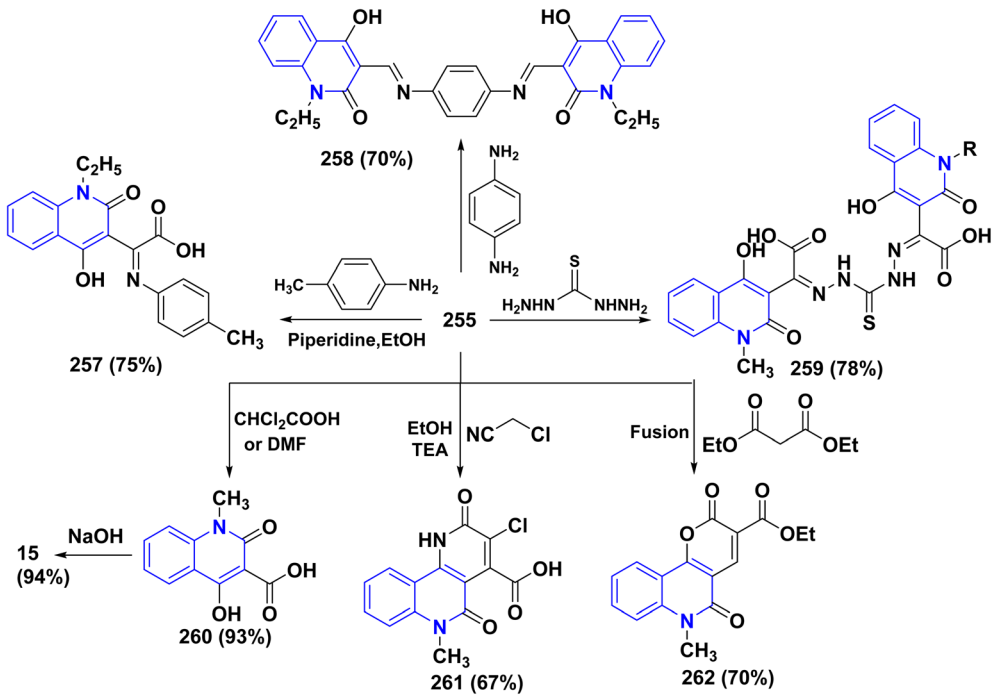
aminocyclohex-2-enone (three-component reaction) attacks the electron-deficient β position of **253** in a Michael addition fashion to afford **250** and **252** (Scheme 94).[203]

Pyrano[3,2-*c*]quinolinone derivatives represent a significant category of naturally occurring alkaloids. As their synthetic counterparts are currently the focuses of research due to their diverse biological activities with potential medicinal applications. Additionally, these compounds are frequently employed as synthetic precursors in producing dimeric quinoline and polycyclic heterocycles.[205] While by, 2-hydroxydimethylpyrano [3,2-*c*]quinolin-5-one (**254a**) was synthesized by a photoinduced reaction of **15b** in the presence of TEA, which generated DEA and acetaldehyde derivatives *in situ*, whereas, photoinduced electron–transfer reactions with TEA as an monodentate electron donating through a redox reactions were achieved according sketeched mechanism in Scheme 93.[206] Reaction of 4-hydroxyquinolinone **15** with aliphatic aldehyde gave the corresponding quinolone methide, base-catalyzed condensation of a quinolinone **15** with an aldehyde yields the corresponding 4-hydroxy-3-(1-hydroxyethyl)quinolin-2-one **254A** which underwent dehydration in basic medium to furnish the highly electrophilic quinone methide intermediate **254B**. After that, Michael's addition reaction at the exocyclic methylene carbon of quinone methide **254B** by the generated enamine (from DEA and the aldehyde) and the carbanion **15A** derived from the deprotonation of **15**. The Michael-type addition of the enamine proceeds in a 1,4-fashion and results in an intramolecular cyclization to yield 2-(diethylamino)pyrano[3,2-*c*]quinolin-5-one **254C** which hydrolyzed to afford **254** (Scheme 95).[206]

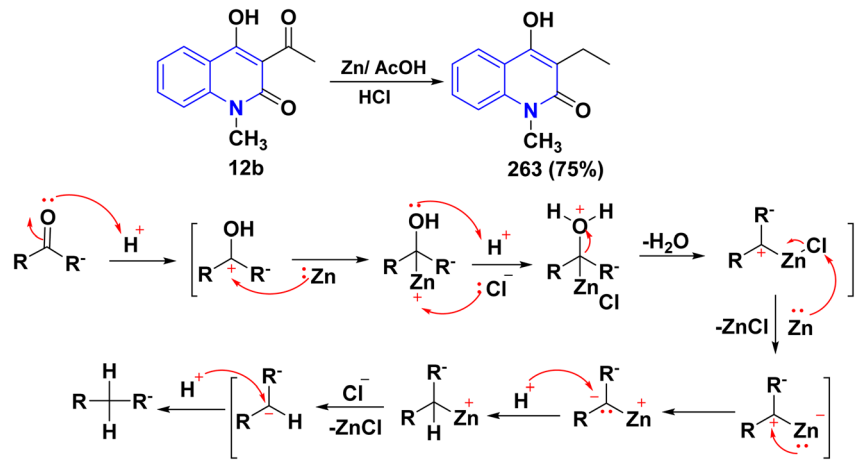
4.4.2. Oxidation. Oxidation of quinolone derivatives **12b,d** under the classic Riley conditions afforded a mixture of two products: α-keto acid **255** and its dehydrated dimer derivatives **256**. The major product is soluble in aq. Na_2CO_3; besides, it can be isolated after neutralization to yield the α-keto acid **255**, whereby the minor product is insoluble in aq. Na_2CO_3 solution, but soluble in boiling NaOH and crystallizable from AcOH and identified as spiropolyketonic scaffold **256** (Scheme 96).[207]

A probable mechanism for the synthesis of the α-keto acids **255** can be simply explained by the fast oxidation of quinolone derivatives **12b,d** to α-keto aldehyde intermediates **255A**, which cyclize into the hemiacetal intermediates **255B**, which can afford the corresponding 5-alkylfuro[3,2-*c*]quinolinetriones **255C**. These furoquinolinetriones **255C** and **255D** are easily hydrolyzed, furnishing the formation of **255** as a major product and **256** as a minor product (Scheme 97).

Specifically, the reactivity of **255** with various nucleophilic reagents was investigated, as the reaction of **255** with *p*-toluidine in refluxing EtOH with a few drops of piperidine produced (4-hydroxy-2-oxoquinolin-3-yl)-*p*-tolyliminoacetic acid **257**. Similarly, reaction of **255** with *p*-phenylenediamine in DMF yielded *bis*[(hydroxy-1,2-dihydroquinolinyl)methylidene]-1,4-phenylenediamine **258**. While condensing α-ketoacid **255** with



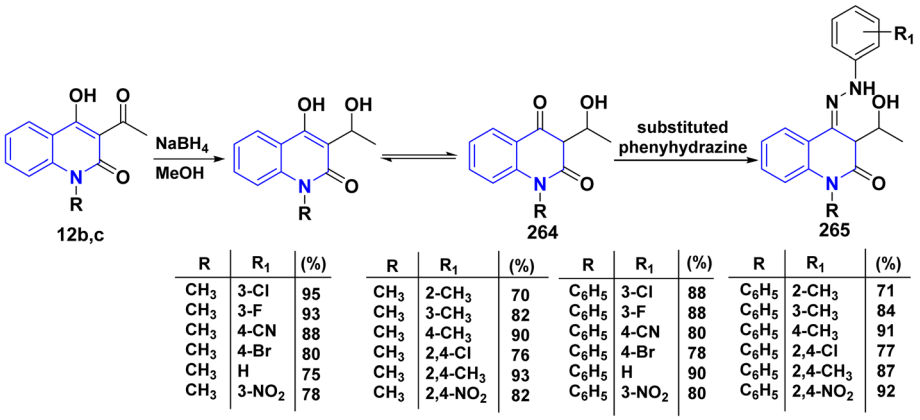
Scheme 98 Reaction of α-keto acids **255** with different reagents.



Scheme 99 Reduction of the acetyl group of **12b** to form compound **263**, in addition to the plausible mechanism of the Clemmensen reduction.

thiocarbohydrazide in different molar ratios in boiling EtOH containing TEA afforded *bis*[2-(4-hydroxy-2-oxoquinolin-3-yl)-2-oxoacetic acid]thiocarbohydrazone **259**. Additionally, the reaction of α-ketoacid **255** with various carbon nucleophiles was explored through its reaction with active methylene such as dichloroacetic acid, chloroacetonitrile, and diethyl malonate, which led to the synthesis of quinoline-3-carboxylic acids **260** and fused tricyclic scaffolds (3-chloro-2-hydroxymethylbenzo) carboxylic acid **261** and 2,5-dioxopyrano[3,2-*c*]quinoline **262**, respectively. Whereas, the hydrolysis process of quinoline-3-carboxylic acids **260** by NaOH was continued for a day, yielding 4-hydroxy-2-oxoquinoline **15** (Scheme 98).[208]

4.4.3. Reduction of AHQ. Whereas, the reduction is one of the most effective chemical transformation processes in organic chemistry[209] as the development in this field has been tremendous, progressing from the use of stoichiometric reagents to get novel organic systems, whereas, Clemmensen-type reduction of acetylquinolinone **12b** in the presence of zinc dust (particle size <45 μm) afforded 3-ethyl-4-hydroxyquinolinone **263** in acceptable yield 75% (Scheme 99).[210] The Clemmensen reduction is a chemical reaction used to convert a carbonyl group (C=O) into a methylene group directly. Firstly, the carbonyl group is protonated by acidic hydrogen to be more electrophilic and easily attacked. Then, nucleophilic Zn attacks the protonated carbocation, leading to the formation of a tetrahedral carbinol containing the carbon–zinc bond, which is protonated by HCl through a carbenoid mechanism. After that, the reduction process happens on the surface of the zinc metal, leading to the



R	R_1	(%)
CH_3	3-Cl	95
CH_3	3-F	93
CH_3	4-CN	88
CH_3	4-Br	80
CH_3	H	75
CH_3	3-NO_2	78

R	R_1	(%)
CH_3	2-CH_3	70
CH_3	3-CH_3	82
CH_3	4-CH_3	90
CH_3	2,4-Cl	76
CH_3	2,4-CH_3	93
CH_3	2,4-NO_2	82

R	R_1	(%)
C_6H_5	3-Cl	88
C_6H_5	3-F	88
C_6H_5	4-CN	80
C_6H_5	4-Br	78
C_6H_5	H	90
C_6H_5	3-NO_2	80

R	R_1	(%)
C_6H_5	2-CH_3	71
C_6H_5	3-CH_3	84
C_6H_5	4-CH_3	91
C_6H_5	2,4-Cl	77
C_6H_5	2,4-CH_3	87
C_6H_5	2,4-NO_2	92

Scheme 100 Reduction of compounds **12b,c** using $NaBH_4$.

formation of the corresponding alkane through undergoing two sequential $2e^-$ reduction steps involving a dehydration step and anionic intermediates (Scheme 99).[211]

Reduction of derivatives **12b,c** *via* using sodium borohydrate ($NaBH_4$) as hydrogen source and electron donor afforded 4-hydroxy-3-(hydroxyethyl)quinolinones **264**. Whereby, a chemo-selective reduction of **264** was achieved by the treatment of **264** with substituted phenylhydrazines, yielding hydrazono-3-(1-hydroxyethyl)quinolin-2-one derivatives **265** (71–92%) (Scheme 100).[212]

5. Applications

5.1. Medicinal perspective of quinolinones

Quinolinone derivatives are significant heterocyclic systems with multiple medicinal applications.[84] As these compounds possess various pharmacological properties,[213,214] including analgesic effects,[106,215] anti-inflammatory,[108,216–219] antiallergenic,[107,220,221] diuretic,[222,223] cardiovascular agents,[47,224] orally active antagonists,[225–228] antimicrobial,[161,229–232] anticonvulsant,[110,233–235] acetylcholinesterase reactivators,[236–239] antitumor, anticancer,[136,240] Farnesyl transferase inhibitor,[241]

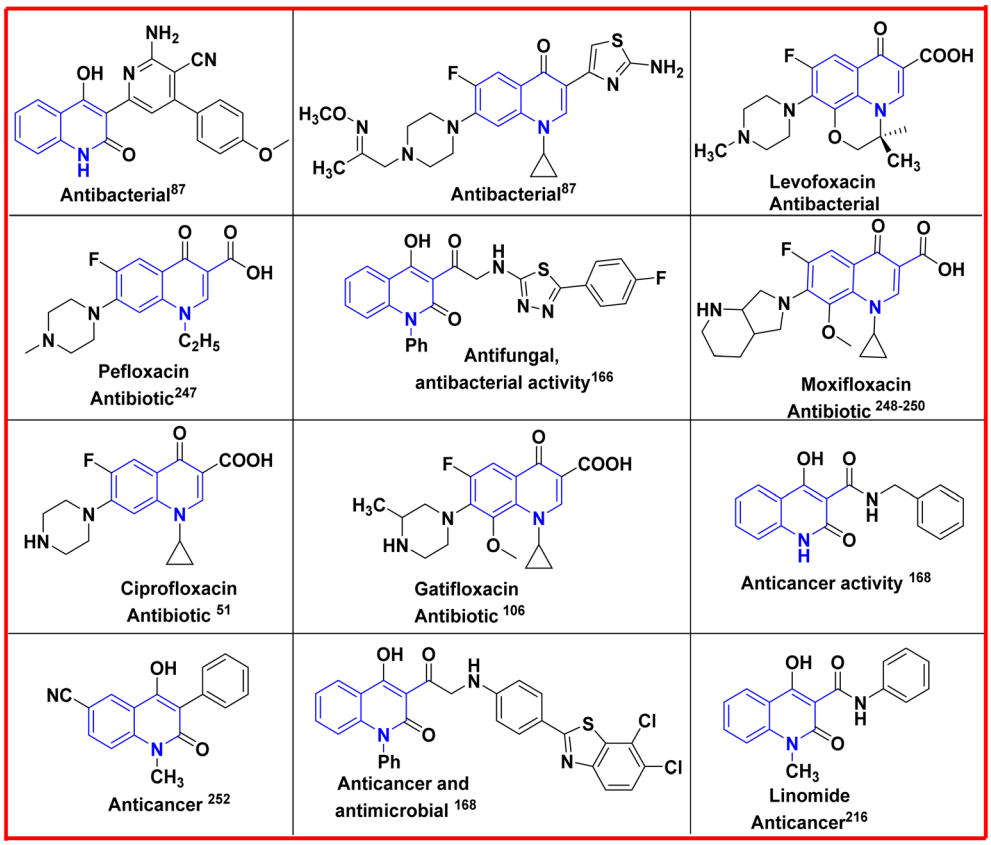


Fig. 6 Biologically active compounds containing quinolinone scaffolds.

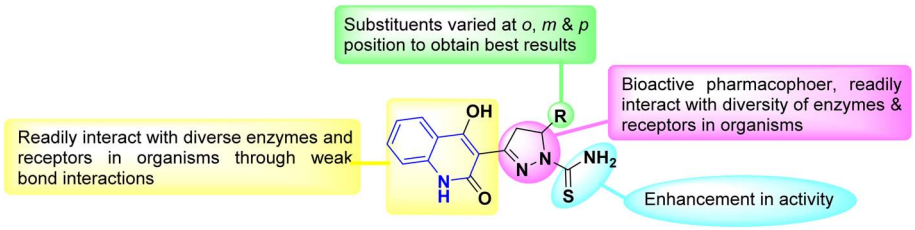


Fig. 7 Design an approach to increase anti-tuberculosis activity.

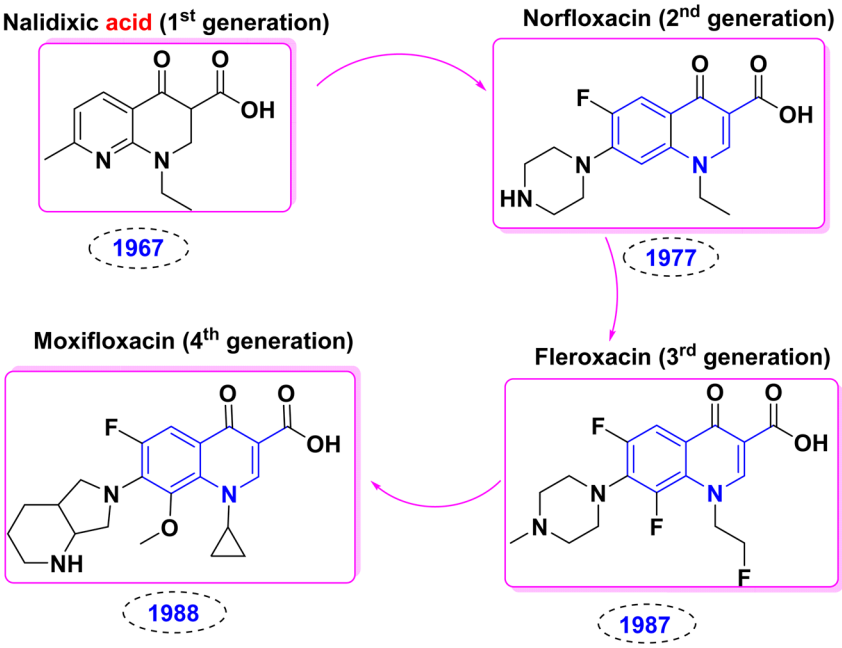


Fig. 8 The history of quinolinones and modifications to improve their pharmacokinetics.

antioxidant,[107,192,216,242] anti-tubercular activity[106,243–246] and other potential biological applications [247–252] as shown in Fig. 6.

Globally, tuberculosis (TB) is a highly lethal infectious disease caused by the bacterium *Mycobacterium tuberculosis*, which is responsible for approximately three million deaths. The recent report from the World Health Organization (WHO) identifies TB as the second leading cause of death from infectious diseases worldwide. About one-third of the global population is at risk due to latent infections with *Mycobacterium tuberculosis*, according to the WHO.[106,253,254] On the other hand, quinolines are a crucial active pharmaceutical ingredient that plays a vital role in discovering new drug candidates. Many quinoline-based compounds are currently in clinical and preclinical development for tuberculosis treatment. Additionally, several quinoline-derived medications, such as moxifloxacin, gatifloxacin, and TMC207, are utilized to treat tuberculosis.[255–257] Interestingly the incorporation of pyrazole derivatives into the quinolinone scaffold enhances its biological efficacy, as it alters modes of action, improves selectivity profiles, and reduces unwanted side effects. Those compounds may be further changed to have better pharmacokinetics and oral bioavailability (Fig. 7).[106,258]

The accidental discovery of nalidixic acid during chloroquine synthesis and its role in the development of numerous quinolinone analogues, including flumequine, rosoxacin, ofloxacin, ciprofloxacin, moxifloxacin, levofloxacin, trovafloxacin, and marbofloxacin. All of the aforementioned pharmaceutical candidates demonstrated significant antibiotic activities.[259–261] Over the years, the history of quinolones is characterized by numerous iterations, innovations, and expansions, as evidenced by the many potent drugs available today. In 1962, nalidixic acid (1st generation) was discovered and then approved in 1967 for treating uncomplicated urinary tract infections (UTIs), but resistance quickly developed among various species.[262] Due to adverse bioeffects as low serum concentrations and high minimum inhibitory concentrations, nalidixic acid was largely abandoned till the emergence of fluoroquinolones in the 1970s and 1980s.[263,264] Modifying quinolones to fluoroquinolone scaffolds improved their pharmacokinetics and expanded their antimicrobial spectrum.[263,264] Interestingly, certain second-generation marketed antibiotics, such as ofloxacin, ciprofloxacin, and norfloxacin, are still in use today (Fig. 8).[250]

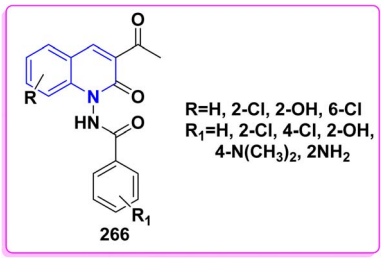


Fig. 9 Quinolinone scaffolds with biological efficacy.

Fleroxacin signifies the start of the "3rd generation" of quinolinones, which demonstrated meaningfully enhanced antimicrobial activity due to various modifications in its chemical structure, as shown to be photocarcinogenic and photomutagenic.[265] Finally, Moxifloxacin, the "4th generation" of quinolones, is characterized by robust antimicrobial activity, including high efficacy against pathogens due to improved anaerobic coverage.[250,263,266,267]

Also synthesized *N*-(3-acetyl-2-oxoquinolin-1(2*H*)-yl)benzamide derivatives **266** were tested for their antitubercular and antimicrobial activities. The majority of the tested derivatives exhibited encouraging antitubercular efficacy in comparison to the standard drugs (isoniazid and streptomycin). The inclusion of electron-donating groups such as methyl, amino, hydroxy, and dimethylamino has enhanced its antitubercular activity. Notably, most of the investigated derivatives of **266** displayed considerable antibacterial efficacy against both Gram-positive and Gram-negative microorganisms. They also showed marked antifungal efficacy against *C. albicans* and *A. niger* (Fig. 9).[268]

Krishnakumar *et al.*[269] reported the evaluation of *in vitro* antibacterial properties for ethyl-2-oxoquinoline-3-carboxylate **267**, showing moderate activity against the *Vibrio cholerae* and *Bacillus subtilis*. Likewise, 1-methyl-3-(3-oxo-3-phenylprop-1-enyl) quinoline-2-(1*H*)-ones **268** were examined *in vitro* as antimicrobial agents exhibiting significant antibacterial activity against *S. Typhi*,*S. aureus*, *P. aeruginosa*, and *B. subtilis* (Fig. 10).[270]

Whereas, the next generation of anticancer, antimicrobial, and anti-HIV-1 drugs is expected to be characterized by quinolinone-pyrimidine-based. Anticancer evaluation of pyrimidoquinolinone **269** and pyrimidotetrazinoquinoline **270** was examined *in vitro* against the human liver cancer cell line

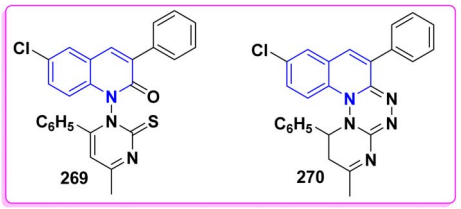


Fig. 11 Quinolone-pyrimidine based molecular hybrids as potential anticancer agents.

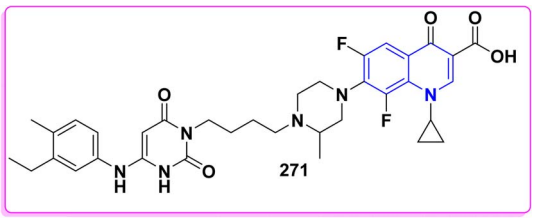


Fig. 12 Quinolone-pyrimidine based molecular hybrids as potential antibacterial agents.

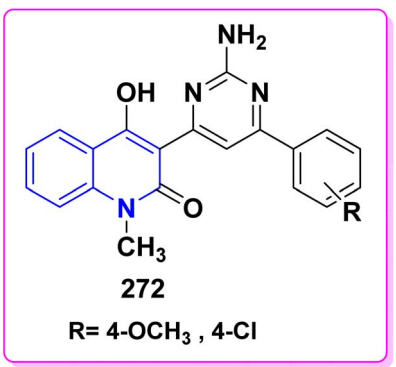


Fig. 13 Pyrimidinylquinolinones based molecular hybrids as potential anticancer agents.

(HEPG2). The anticancer activity results indicated that these compounds showed inhibitory activity against the tested cell line with IC_{50} values of 38.30 μM for **269** skeleton and 39.8 μM for **270** (Fig. 11).[271]

Compound anilinouracil-fluoroquinolone **271** demonstrated Gram-positive antibacterial potency at least 15 times that of the corresponding [3-(4-hydroxybutyl)-6-(3-ethyl-4-methylanilino)

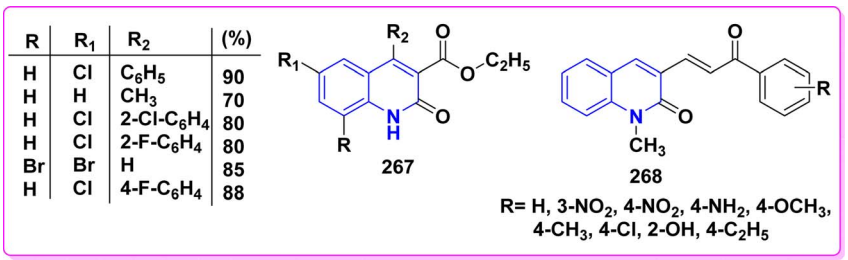


Fig. 10 Quinolinone skeletons with antibacterial activity.

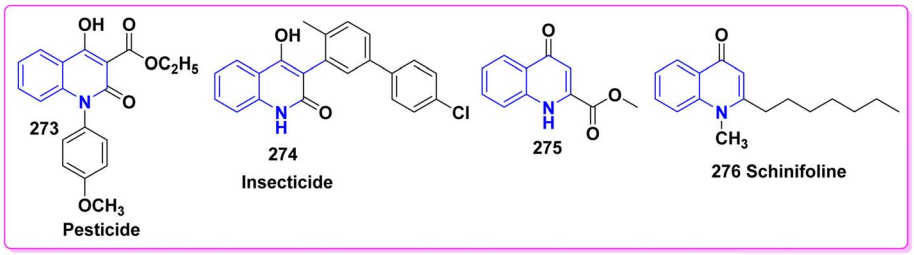


Fig. 14 Agrochemical compounds with quinolinone scaffolds.

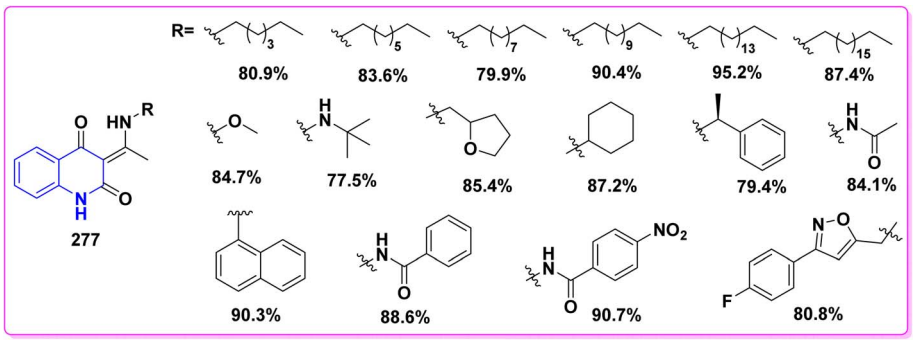


Fig. 15 Quinolinone scaffolds with agrochemical efficacy.

uracil], effectively inhibited pol IIIC and topoisomerase/gyrase, inhibited gyrase and *B. subtilis* topoisomerase IV with IC_{50} of 31 and 43.6 μM, respectively, and, as anticipated, had a selective effect on bacterial DNA. Additionally, this compound showed the ability to attack both of its possible targets in the bacterium by being active against a wide range of Gram-positive pathogens that were resistant to antibiotics, as well as a number of Gram-negative organisms. It was also active against Gram-positive organisms that were resistant to fluoroquinolones and anilinouracils. Moreover, it lacked toxicity *in vitro* and was bactericidal for Gram-positive bacteria. With a unique dual mechanism of action and strong activity against Gram-positive bacteria that are both susceptible to and resistant to antibiotics, this class of anilinouracil–fluoroquinolone hybrids offers a promising new pharmacophore (Fig. 12).[272]

Furthermore, the synthesized derivatives of 3-(2-amino-6-arylpyrimidin-4-yl)-4-hydroxy-1-methylquinolin-2(1*H*)-ones **272** had shown the best activity in the series, with anticancer efficacy against HepG2 cell lines (IC_{50} values of 1.32 and 1.33 μM, respectively) (Fig. 13).[131]

5.2. Agricultural applications

In recent years, the discovery of agrochemicals based on the quinoline scaffold structure has led to great progress. Some new quinoline pesticides that have been commercialized or are under development not only inject new vitality into the market but also can replace unfriendly old pesticides.[51] For example, ethyl-4-hydroxy-1-(4-methoxyphenyl)quinolinone-3-carboxylate **273**, has been investigated for the first time as a sensitization chromophore for Tb(III) to improve selectivity and sensitivity for organophosphorus pesticide detection.[273]

The insecticidal activity of pyrazoloquinolone compounds was investigated, both *in vitro* and *in vivo*, against the cotton leafworm, *S. littoralis*, and cotton aphids. The most effective compounds were (*E*)-4-(2-(dimethylamino)phenyl)-2,5-dioxo-6-phenyl-1,2,5,6-tetrahydrobenzo[*h*][1,6] naphthyridin-3-carbonitrile **203** and 3-(1-(4-amino-5-mercapto-4*H*-1,2,4-trizol-3-yl)-1*H*-pyrazol-3-yl)-4-hydroxy-1-phenylquinoline-2(1*H*)-one **200**, with LC_{50s} of 119.79 and 164.63 mg L^{-1} against *S. littoralis*.[192] Additionally, 1,4-dihydro-quinolinecarboxylate **275** is isolated from *Beauveria* sp. for the first time and has insecticidal activity against *Bemisia tabaci* with remarkable toxicity in contact and feeding assays, as its LC_{50} values were 10.59 μg mL^{-1} (contact) and 5.66 μg mL^{-1} for feeding. Whereas, no adverse effect on plant height/growth or phytotoxicity was detected on pepper, tomato, cotton, and cucumber during the treatment.[274] Also, Liu *et al.*[275] reported that the utilization of Schinifoline **276**, the fruit pericarp of *Zanthoxylum schinifolium* possessed remarkable feeding toxicity against *Sitophilus zeamais* and *Tribolium castaneum* through reducing their food consumption and growth rate, leading to weakness of their reproductive ability and low resistance (Fig. 14).[275]

Additionally, a series of (*E*)-3-acyl-quinoline-2,4-(1*H*,3*H*)-dione imine derivatives **277** displayed remarkable herbicidal activity against monocot and dicot species by affecting PSII electron transport inhibitors and inhibiting the electron transport chain, leading to the prevention of the production of NADPH and ATP. As the majority of the compounds showed good to excellent herbicidal activities against a number of dicot or monocot species, with an inhibition percentage of over 50%

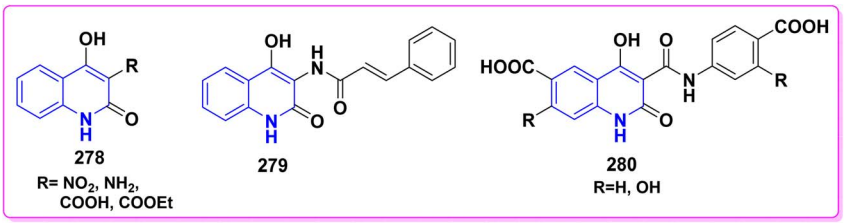


Fig. 16 Quinolinone scaffolds with photosynthesis-inhibiting activity.

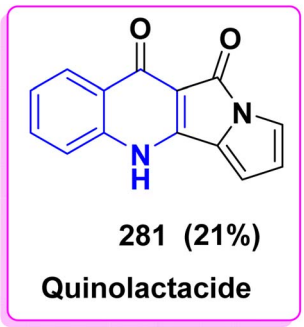


Fig. 17 Quinolinone scaffolds with insecticidal activity.

at a dosage of 94 g per ha or even lower. Notably, the compounds featuring short straight-chain alkyl groups display the highest activity, comparable with the longer alkyl chains; insecticidal activity diminishes with increasing chain length (Fig. 15).[276]

A series of substituted 4-hydroxy-1*H*-quinolin-2-one derivatives **278–280** were analyzed using RP-HPLC to determine lipophilicity and photosynthesis-inhibiting activity (the inhibition of photosynthesis in *Spinacia oleracea* L. As the synthesized quinolinones displayed high to moderate inhibitory effects on the photosynthesis activity process. In addition, *in vitro* antifungal screening of these scaffolds was evaluated against various fungal strains, displaying moderate efficacy (Fig. 16).[277]

Quinolactacide **281** is structurally analogous to quinolactacins derived from *Penicillium* species, which are recognized for exhibiting various biological activities, particularly insecticidal properties. This compound exhibited 88% mortality against the green peach aphid (*Myzus persicae*) at a concentration of 250 ppm. The insecticidal and miticidal efficacy of quinolactacide was assessed against five distinct insects and one mite at a concentration of 500 ppm. The insects utilized for the experiments included the green peach aphid, silverleaf whitefly (*Bemisia argentifolii*), diamondback moth (*Plutella xylostella*), common cutworm (*Spodoptera litura*), western flower thrips (*Frankliniella occidentalis*), and two-spotted spider mite (*Tetranychus urticae*). The synthetic quinolactacide exhibited no activity against the other insects, but it demonstrated 100% and 42% mortality against the green peach aphid and diamondback moth, respectively (Fig. 17).[278]

5.3. Complex formation

Quinolinones bind metal ions to create complexes where they can function as bidentate, unidentate, or bridging ligands. Quinolinone molecules have a basic side nucleus that becomes

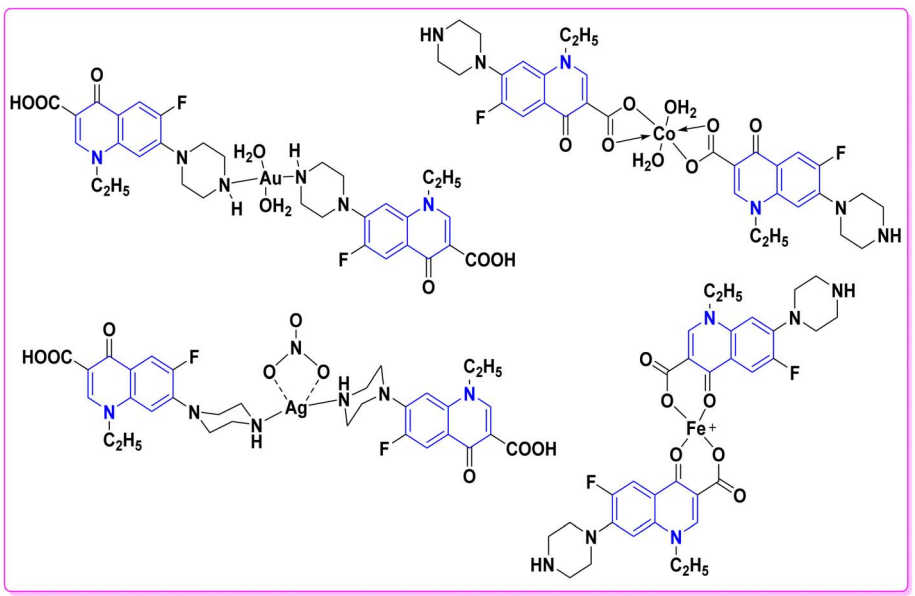


Fig. 18 Coordination modes of quinolinone complexes with high biological activity.

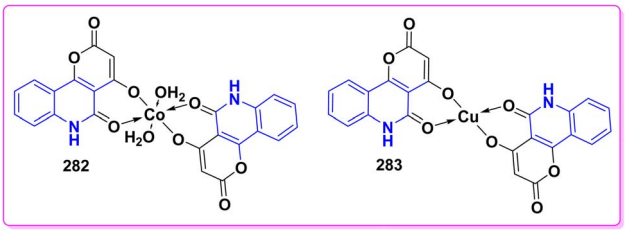


Fig. 19 Bioactive complexes with quinolinone scaffolds.

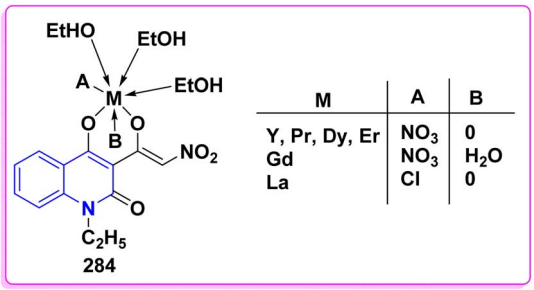


Fig. 21 The chemical structures of lanthanide complexes.

protonated and shows up as cations in the ionic complexes under highly acidic conditions. Quinolone solubility, pharmacokinetics, and bioavailability are all significantly impacted by interaction with metal ions, which also plays a role in the bactericidal agents' mode of action. Many metal complexes have shown various biological activities, including antifungal, anticancer, antiparasitic, and antimicrobial (Fig. 18).[279]

A series of Cu(II) **282** and Co(II) **283** complexes were designed and synthesized by Khalaf *et al.*[280] as 4-hydroxy-2*H*-pyrano[3,2-*c*] quinolin-2,5(6*H*)-dione acts as monobasic didentate ligand and form tetrahedral and octahedral complexes at molar ratio of 1 : 2. Interestingly, the synthesized complexes displayed greater efficacy as antibacterial, antifungal and antioxidant candidates in comparison with the free pyrano[3,2-*c*]quinolin-2,5(6*H*)-dione as ligand (Fig. 19).[280]

The potential antibacterial and antifungal properties of the quinoline ligands (SL_1–SL_4) and their Cu(II) and Zn(II) complexes (Fig. 20) were evaluated *in vitro*. The ligands (SL_1–SL_4) demonstrated moderate antibacterial activity against Gram-positive bacteria but exhibited no effectiveness against Gram-negative bacteria or fungal strains. Among them, the SL_3 ligand displayed the highest activity, achieving a zone of inhibition of 24 mm against *S. aureus.* However, the antibacterial activity of these ligands was significantly lower than that of the standard drugs amoxicillin and fluconazole. These metal complexes generally enhanced antibacterial activity against both Gram-positive *S. aureus* and *E. faecalis* strains. On comparing the metal complexes, it was found that $[Cu(SL_1)_2]$ was the most harmful substance to Gram-positive bacteria and had moderate antifungal properties.[281]

Fouad *et al.*[282] studied lanthanide nano-complexes (Gd^{3+}, Er^{3+}, Pr^{3+}, Y^{3+}, Dy^{3+}, and La^{3+}) containing quinolinone. The obtained results reveal that the quinolinone **284** acts as a bidentate *via* OO donor sites, creating octahedral complexes. The complexes are nanoscale, having crystalline or amorphous structures. The synthesized nano-complexes have acceptable anticancer efficacy against the hepatocellular carcinoma cell line. Whereby, the maximum anticancer activity of Pr^{3+} nano-complex (Fig. 21).[282]

A series of quinolinone-derived Schiff bases **286** were synthesized *via* the condensation of 7-amino-4-methylquinolinone **285** with different aromatic aldehydes. Then, complexation of Schiff ligands with cupric salts involving Cu(II) acetate or Cu(II) perchlorate hexahydrate was achieved, affording Cu(II) complexes of the corresponding ligands **287** (Scheme 101). These complexes showed significant antifungal effects, suppressing *C. albicans* growth by 50% at a dosage of 4 μM.[283]

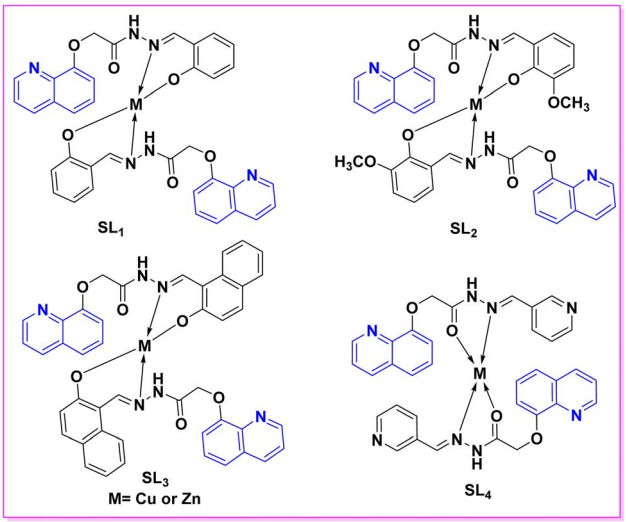
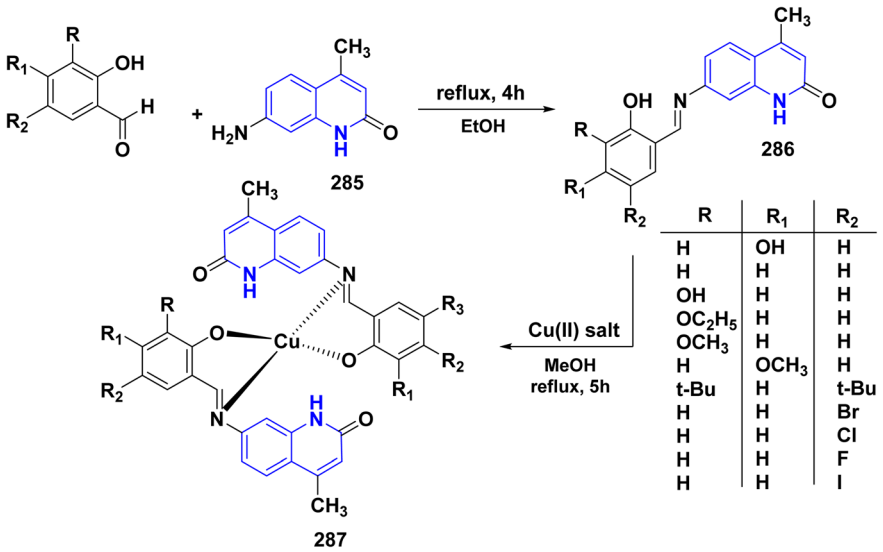


Fig. 20 Hydroxyquinoline functionalized Schiff base copper and zinc complexes SL_{1-4}.

5.4. Corrosion inhibitors

Hussein *et al.*[185] reported the utilization of 4-hydroxyquinolinone derivatives as antioxidant agents for various lubricating oils through using the ASTM D-942 and ASTM D-664 tests. The compositions that they synthesized are: dichlorophenyl-pyrazol-4-hydroxy-1-methylquinolinone **288**, 4-hydroxy-8-methyl-2-oxoquinolin-1-phenyl-2-hydroxyhydropyrimidin-4,6-dione **289**, and 1-butyl-4-hydroxy-3-1*H*-pyrazol-3-yl)quinolinone **290** (Fig. 22). The obtained results indicate that the hydroxyquinolinone scaffolds reduce both the total acid number and the oxygen pressure drop in lubricating oils. On the other hand, it has been discovered that the antioxidant activity is most efficient when quinolinones have both butyl and hydroxyl groups. These quinoline scaffolds (**288–290**) inhibit radical processes during oil oxidation, as well as their continuation and production. A comparison of the antioxidant activity of compounds **288**, **289**, and **290** reveals that the efficacy and antioxidant benefits of the third compound.[184,284]

Quinolinone chalcone (PPQ) **291** showed effective corrosion inhibition for high carbon steel (HCS) in 1.0 M HCl, and the



Scheme 101 Complexation of ligand **286** with Cu(II) salts.

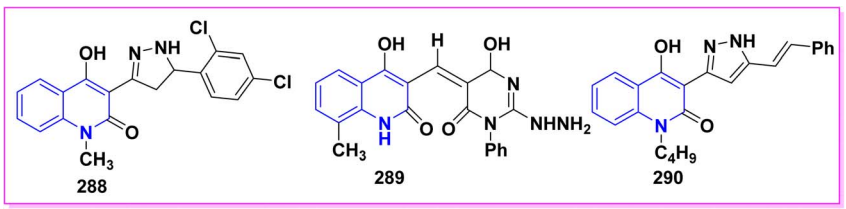


Fig. 22 Quinolinone scaffolds with antioxidant effect in lubricating oils.

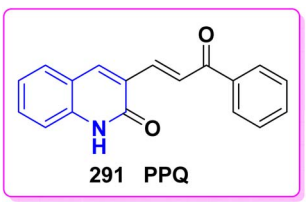


Fig. 23 Quinolinone scaffolds as corrosion inhibitors.

inhibition efficiency improved as the inhibitor concentration was raised. The compound's efficiency is attributed to the presence of heteroatoms and phenyl rings with delocalized π electrons that can act as adsorption centers. These factors support both physical and chemical interactions and adsorption of inhibitor scaffolds with the metal surface according to the Langmuir adsorption isotherm (Fig. 23).[285,286]

The dihydroquinoline-3-carboxylate derivatives **292** and **293** (**NODC**, **AODC**, **CODC**, and **MODC**) display potential corrosion inhibition for carbon steel in 1 M HCl, due to the presence of a substituent attached to the benzene portion of the 4-quinolinone (Fig. 24).[287]

Imino quinolinone IQ **294** acts as a corrosion inhibitor on low carbon steel (LCS) in 0.5 M HCl solution with inhibition efficiency 93.2% at the optimal concentration of IQ (30×10^{-3} Mm), adhered to the Langmuir adsorption model, signifying a monolayer adsorption mechanism. The characterization of IQ as a mixed-type inhibitor was evidenced due to its capacity to impede both cathodic and anodic processes, predominantly functioning as an anodic inhibitor (Fig. 25).[288]

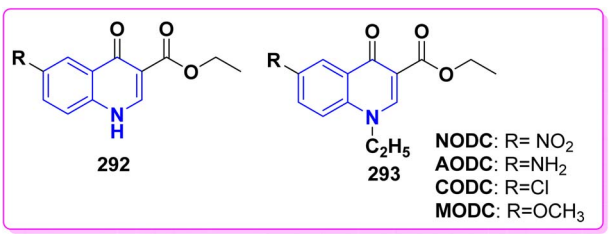


Fig. 24 Quinolinones scaffolds as potential corrosion inhibitors.

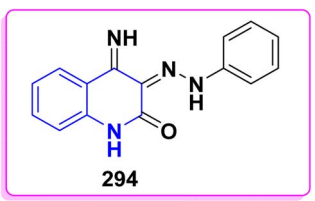


Fig. 25 Imino quinolinone IQ **294**.

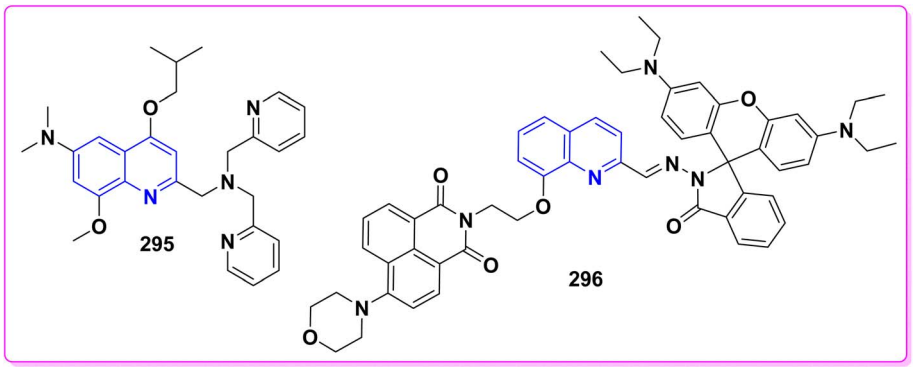
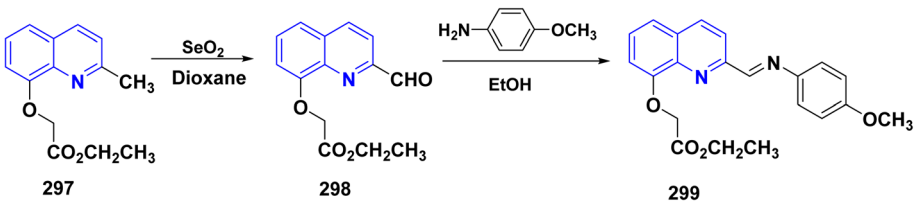
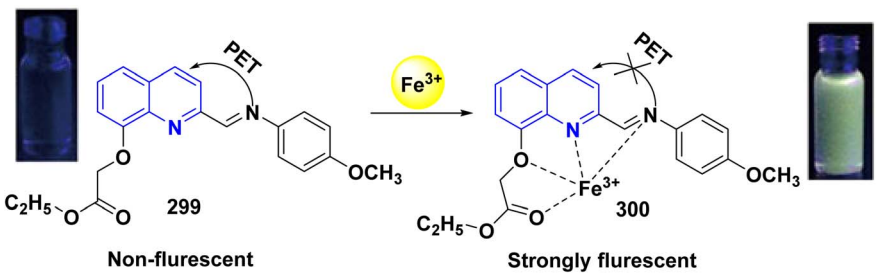


Fig. 26 Quinolinone/hydroxyquinoline scaffolds as chemosensors.



Scheme 102 Hydroxyquinoline scaffolds as fluorescence sensors.



Scheme 103 Complexation mechanism of sensor **299** and Fe^{3+} ions.

5.5. Sensors

5.5.1. Chemosensors. Quinolinone derivative-based chemosensors designed to detect various metal ions were discussed. There is considerable interest in improving these chemosensors due to their ease of synthesis, high sensitivity, and stability. Nonetheless, there remains substantial potential for enhancement in their *in vivo* applications, particularly regarding water solubility, selectivity, and fluorescent bioimaging capabilities. Consequently, the development of receptors tailored for different ions is essential. For instance, skeleton **295** employed an alternative bonding model to identify Zn^{2+} and Cd^{2+}. Also, **296** act as a Cr^{3+} chemosensor. Additionally, two-photon laser sources can be used to excite an extended conjugated quinoline system (Fig. 26).[289]

5.5.2. Fluorescence sensors. Fluorescence-based techniques have become essential tools in metalworking because of their sensitivity and selectivity benefits.[290–292] A lot of work has gone into creating fluorescent Fe^{3+} indicators that are highly sensitive and selective. The majority of documented fluorescent sensors for Fe^{3+} are based on a fluorescence quenching mechanism due to the paramagnetic nature of Fe^{3+},[293,294] and the majority of these have interference issues brought on by transition metal cations like Cu^{2+}, Co^{2+}, or Hg^{2+}. Thus, looking for highly selective chemosensors for Fe^{3+} based on the fluorescence enhancement is crucial. While using the ether derivative **297** as a starting material, the synthesis of Schiff base **299** was utilized. Whereby, quinoline **299** is a chemosensor that made up of the quinoline fluorophore **298** and *p*-anisidine binding site led to formation of bearing polarized C–C, C–N and C–O bonds conjugated to the quinoline moiety, it displays a strong fluorescence increase of Fe^{3+} ions, demonstrating excellent sensitivity and good selectivity for Fe^{3+} over a broad spectrum of other ecologically and physiologically significant metal ions (Schemes 102 and 103).[295]

Sensor **299** is an excellent sensitive chemosensor for the Fe^{3+} ion as it exhibits no fluorescence in MeOH, but when Fe^{3+} is added, it affords a highly effective fluorescence sensor **300**, and there is a noticeable increase in fluorescence of about 44-fold

(Scheme 103). As a result, the fluorescence response is explained by Fe^{3+} blockage of electron transfer to the quinoline group, which encouraged sensor **299** to produce high fluorescence. A color shift from colorless to brown that is readily apparent to the unaided eye resulted from the identification of Fe^{3+}. Consequently, the Fe^{3+} ion can be readily distinguished in visible light from all other metal ions. Additionally, under light from a 365 nm UV lamp, Fe^{3+} shows an increase in the intensity of fluorescence, vivid green, while other metal ions show no change under the same circumstances.[295]

6. Conclusion

With the ever-increasing importance of 3-acetyl-4-hydroxyquinolinone and its *N*-substituted derivatives as structurally decisive scaffolds in bioactive natural products and pharmaceutical drugs, so in this review enormous efforts have been made to summarize the synthesis, structural features and chemical reactivity of 3-acetyl-4-hydroxy-2-quinolinone entities and its *N*-substituted derivatives as structurally decisive scaffolds in bioactive natural products and pharmaceutical drugs, accredited by reaction mechanisms. Also, we highlight the most important breakthroughs of 3-acetyl-4-hydroxy-2-quinolinone derivatives as an auspicious class displaying a wide range of potential pharmacological activities and their developments in the various clinical stages. Generally, this review supplies an overview of the chemistry for 3-acetyl-4-hydroxy-2-quinolinone derivatives and documents more than two hundred references over the last decade of research, covering mainly the period from 2020 to the beginning of 2025.

Abbreviations

AcOH	Acetic acid
AHQ	3-Acetyl-4-hydroxyquinolinone
BQB	1,4-*Bis*-(quinolin-6-ylimino methyl)benzene
$BF_3 \cdot (OC_2H_5)_2$	Boron trifluoride etherate
CS_2	Carbon disulfide
CCl_4	Carbon tetrachloride
DMF	Dimethylformamide
DMA	Dimethylamine
DMSO	Dimethyl sulfoxide
EAA	Ethyl acetoacetate
HCS	High carbon steel
$NH_2OH \cdot HCl$	Hydroxylamine hydrochloride
HMPT	Hexamethylphosphoric triamide
HQ	4-Hydroxyquinoline
LCS	Low-carbon steel
LR	Lawesson's reagent
MCR	Multicomponent reaction
DMF/DMA	*N*,*N*-Dimethylformamide dimethyl acetal
DTA	*N*,*N*-Dimethyl trifluoroacetamide
NBS	*N*-Bromosuccinimide
$POCl_3$	Phosphorous oxychloride
P_2S_5	Phosphorus pentasulfide
PBr_3	Phosphorus tribromide
$PhPOCl_2$	Phosphonic dichloride
PPA	Polyphosphoric acid
RORC	Ring opening and ring closure
RT	Room temperature
AcONa	Sodium acetate
SO_2Cl_2	Sulfuryl chloride
$NaBH_4$	Sodium borohydrate
$CH(OEt)_3$	Triethyl orthoformate
TEA	Triethylamine
$P(OCH_2CH_2Cl)_3$	Tris(2-chloroethyl)phosphite
TB	Tuberculosis
TC	β,β-Tricarbonyl
TBAB	Tetrabutylammonium bromide
TsCl	Toluenesulfonyl chloride
WHO	World Health Organization
$ZnCl_2$	Zinc chloride

Data availability

No primary research results, software or code have been included, and no new data were generated or analyzed as part of this review.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review.

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