Synthesis of 2-Arylquinolin-4(1*H*)-ones and Their Transformation to *N*-Alkylated and *O*-Alkylated Derivatives

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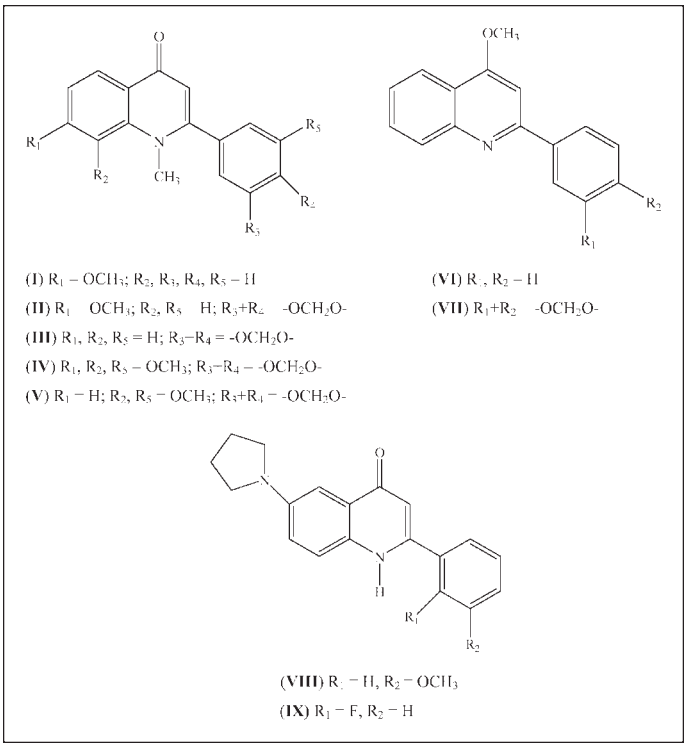

2-Aryl-4-quinolones are versatile synthetic intermediates and several articles continue to appear in literature describing their synthesis, chemical transformation, structural properties, and biological activities. Their versatility as synthetic intermediates is a consequence of 4-quinolone moiety, which contains several reactive centers (positions 1, 3, and 4) for possible functionalization and can also enable different degree of unsaturation. In this review, we describe methods developed to-date for the synthesis of 2-arylquinolin-4(1*H*)-ones and their *N*-alkylated and *O*-alkylated derivatives.

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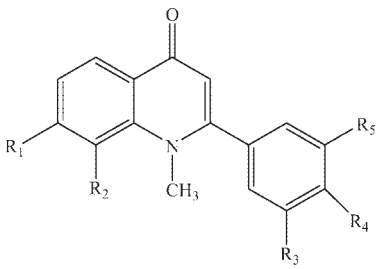
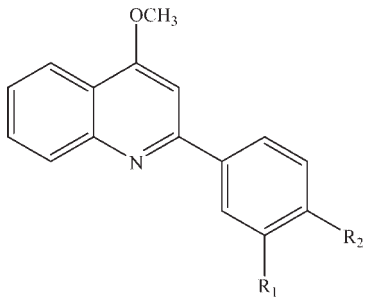
Contents

1. INTRODUCTION

2-Aryl-4-quinolone moiety constitutes important chemical unit in a large variety of naturally occurring compounds and it plays an extremely important role in synthetic and medicinal chemistry. Most of the 2-aryl-4-quinolones and their 2-arylquinoline derivatives are widely distributed in the plant family *Rutaceae*. Eduleine or 7-methoxy-1-methyl-2-phenylquinolin-4(1*H*)-one (**I**) (R_1 = OCH_3; R_2, R_3, R_4, R_5 = H), for example, was first isolated from the bark of the Mexican tree *Casimiroa edulis* [1] and the bark of *Lunasia quercifolia* (Warb) [2]. Eduleine and its 4-methoxy-1-methyl-2-(3,4-methylenedioxyphenyl)quinolin-4(1*H*)-one analogue (**II**) (R_1 = OCH_3; R_2, R_5 = H; R_3+R_4 = —OCH_2O—) were also isolated from the leaves of *Lunasia amara* Blanco of the Philippine origin [2]. Graveoline (**III**) (R_1, R_2, R_5 = H; R_3+R_4 = —OCH_2O—), on the other hand, was first isolated from *Ruta graveolens* and its substituted derivatives methoxygraveoline (**IV**) (R_1, R_2, R_5 = OCH_3; R_3+R_4 = —OCH_2O—) and 3,8-dimethoxygraveoline (**V**) (R = R′ = OMe) were isolated from the roots of the Brazilian plant *Esenbeckia grandiflora* [3]. The isomeric 4-methoxy-2-phenylquinoline (**VI**) (R_1, R_2 = H) and its 4-methoxy-2-(3,4-methylenedioxyphenyl)quinoline analogue (**VII**) (R_1+R_2 = —OCH_2O—) were also isolated from the leaves of *Lunasia amara* Blanco [2].



(**I**) $R_1 = OCH_3$; $R_2, R_3, R_4, R_5 = H$
(**II**) $R_1 = OCH_3$; $R_2, R_5 = H$; $R_3+R_4 = OCH_2O$—
(**III**) R_1, R_2, R_5 = H; R_3+R_4 = —OCH_2O—
(**IV**) R_1, R_2, R_5 = OCH_3; R_3+R_4 = —OCH_2O—
(**V**) $R_1 = H$; $R_2, R_5 = OCH_3$; $R_3+R_4 = $—$OCH_2O$—



(**VI**) R_1, R_2 = H
(**VII**) R_1+R_2 = —OCH_2O—

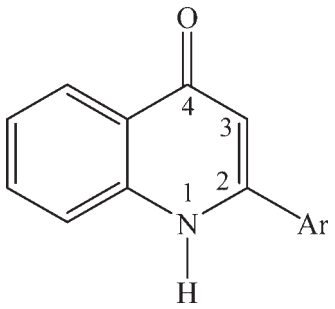
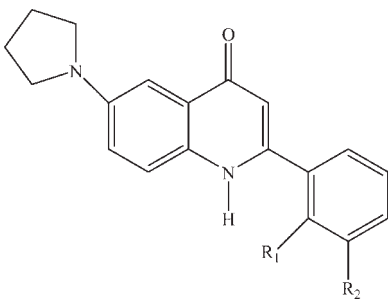


Figure 1. Generalized structure of 2-arylquinolin-4(1*H*)-one.

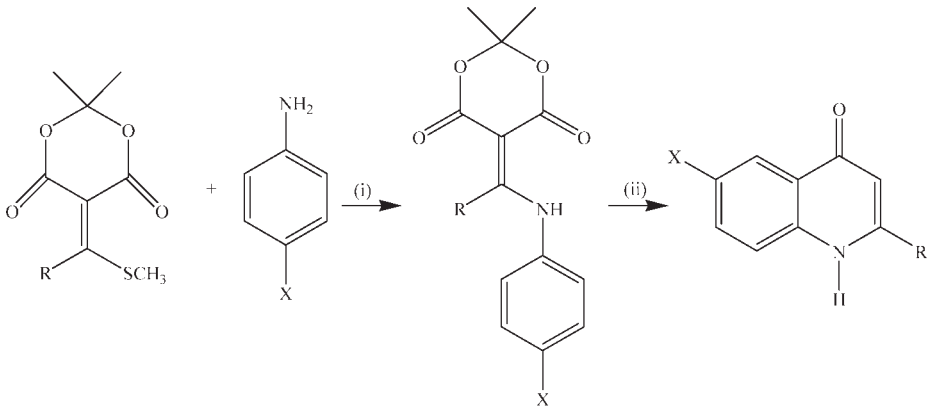
Over the last years, the interest in 2-arylquinolin-4(1*H*)-ones and their analogues have been the subject of extensive study as potential anti-tumor, anti-mitotic, and cytotoxic agents [4–8] as well as anti-platelet agents [9,10]. 2-(3-Methoxyphenyl)-6-(1-pyrrolinyl)quinolin-4(1*H*)-one (**VIII**) (R_1 = H, R_2 = OCH_3) and 2-(2-fluorophenyl)-6-(1-pyrrolinyl)quinolin-4(1*H*)-one analogue (**IX**) (R_1 = F, R_2 = H), for example, are potent inhibitors of tubulin polymerization (IC_{50} = 0.44 μ*M* (**I**); 0.46 μM (**IX**)) and exhibit anti-mitotic anti-tumor activity at low concentrations having effects comparable to those of colchicine, podophyllotoxin, and combretastatin A-4 [4,5]. The 4-substituted quinoline moiety constitutes the framework for several nitrogen-containing heterocycles known to exhibit cytotoxic [11], anti-leishmanial [12], anti-malarial [13], and anti-bacterial properties [14]. Aryl substituted quinolines have also been reported to serve as estrogen receptor modulators [15] and also as potent inhibitors of tyrosine kinase PDGF-RTK [16]. The naturally occurring 4-methoxy-2-phenylquinoline (**VI**) and its 4-methoxy-2-(3,4-methylenedioxyphenyl)quinoline analogue (**VII**) [8] have recently been found to exhibit inhibitory activity against *Mycobacterium tuberculosis* $H_{37}Rv$ [17].



(**VIII**) R_1 = H, R_2 = OCH_3
(**IX**) R_1 = F, R_2 = H

The 2-aryl-4-quinolones are also versatile synthetic intermediates and several articles continue to appear in literature describing their synthesis, chemical transformation, structural properties, and biological activities. Their versatility as synthetic intermediates is a consequence of 4-quinolone moiety (Fig. 1), which contains

Scheme 1. Reagents: (i) $(C_6H_5)_2O$, 140°C, 30 min or EtOH, heat, 2–4 h; (ii) $(C_6H_5)_2O$, 250–260°C.



1 **2** **3** **4**

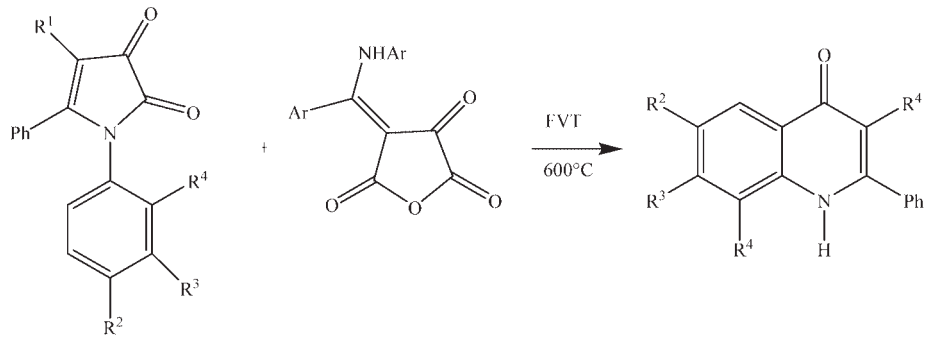
several reactive centers (positions 1, 3, and 4) for possible functionalization and can also enable different degree of unsaturation. They are known to undergo electrophilic substitution with alkyl derivatives to afford *N*- or *O*-alkylated derivatives or a mixture of the two isomers depending on the nature of the electrophile used and steric effect on the quinolone moiety. Aromatization of the 4-quinolone moiety with phosphorus oxychloride occurs with ease to afford 4-chloroquinolines which are important intermediates in the synthesis of 2-arylquinolines bearing a heteroatom group in the 4-position. Their α,β-unsaturated framework allows C-3 halogenation to yield 3-halogeno derivatives, which have been shown to undergo metal-catalyzed C—C formation to yield polysubstituted and polynuclear derivatives.

Although the popularity of variously substituted 2-arylquinolin-4(1*H*)-ones has been increasing over the years, their synthesis and transformation into *N*-alkylated or *O*-alkylated derivatives have never been reviewed. We wish to address this need by reviewing various methods developed to-date for the synthesis of 2-arylquinolin-4(1*H*)-ones and their transformation to *N*-alkylated and *O*-alkylated derivatives.

2. SYNTHESIS OF 2-ARYLQUINOLIN-4 (1*H*)-ONES

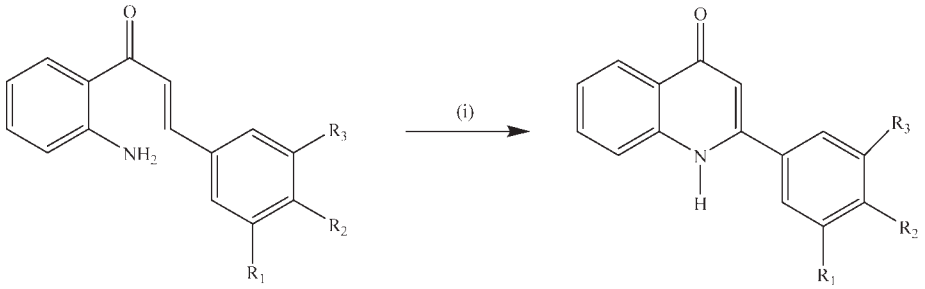
2.1. From arylamines and carbonyl derivatives. Several articles continue to appear in literature describing novel methods for the synthesis of 2-arylquinolin-4(1*H*)-ones. In one of the earliest methods, anthranilic acid or its ester derivative was heated with the acetal of an alkyl aryl ketone to yield the corresponding 2-arylquinolin-4(1*H*)-one [18]. Arylamines were also condensed with an ethyl benzoylacetate derivative in the presence of polyphosphoric acid (PPA) to afford 2-arylquinolin-4(1*H*)-ones [6,9,19]. Both these pathways are, however, not suitable for the synthesis of 2-arylquinolin-4(1*H*)-ones with multiple substituents. Anilinoarylidenemalonates derived from β-chloroarylidenemalonates and sodium diethyl malonate were previously cyclized at 250°C to afford 2-aryl-3(ethoxycarbonyl)-4-quinolones

Scheme 2



5 **6** **7**

Scheme 3. Reagents: (i) $Pd(PPh_3)_2Cl_2$, THF, heat, 2 h.



8 **9**

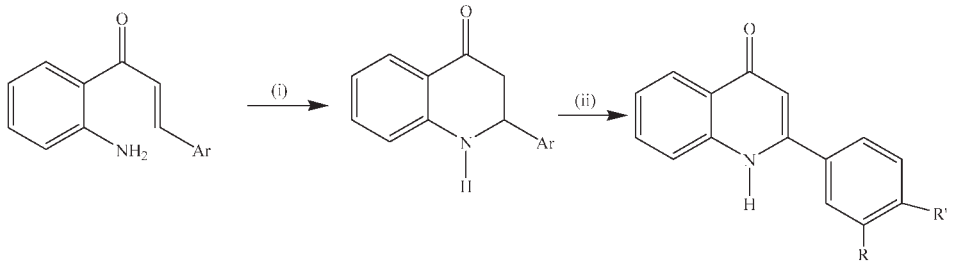
[20]. Lai and coworkers also subjected anilinoarylidenemalonates derived from carboxymidoyl chlorides to thermolysis at 170°C to afford 2-aryl-3(ethoxycarbonyl)-4-quinolones [8]. Thermolysis of the mono-ethoxycarbonyl vinyl derivatives, which are formed in comparable yields along with the anilinoarylidenemalonates afforded the 2-aryl-4-quinolones. In another development, 2,2-dimethyl-5-methylthioalkylidene-1,3-dioxane-4,6-diones **1** (R = Me, Et, Pr, Ph), which are easily prepared from Meldrum's acid (2,2-dimethyl[1,3]dioxane-4,6-dione) were condensed with substituted arylamines **2** (X = H, Me, NO_2, Br, Cl) in refluxing diphenyl ether or ethanol with (isolated yields: 54–57%) or without isolating the resulting intermediate **3** to afford 2-alkyl- and 2-arylquinolin-4(1*H*)-ones **4** (60–96%) upon cyclization in Ph_2O at very high temperature (Scheme 1) [21].

2-Arylquinolin-4(1*H*)-ones were also prepared by condensing ethyl benzoylacetate with aniline in ethanol at 50°C followed by heating the resulting intermediate at 240–250°C in diphenyl ether [22,23]. A series of substituted 2-aryl-4-quinolones **7** has been synthesized in good yields (16–88%) from 1-aryl-5-phenylpyrrole-2,3-diones **5** substituted at the 4-position with cyano (R^1 = CN) or methoxycarbonyl group (R^1 = CO_2Me) and **6** *via* flash thermolysis (FVT) at 600°C (Scheme 2) [24].

2.2. From 2-aminochalcones or 2-aryl-1,2,3,4,-tetrahydroquinol-4-ones. 2′-Amonichalcones and their isomeric 2-aryl-1,2,3,4-tetrahydro-4-quinolone derivatives have also been used as substrates for the synthesis of 2-arylquinolin-4(1*H*)-ones. The 2′-amonichalcones **8**, which are readily accessible *via* Murphy-Watanism's aldol condensation of 2-aminoacetophenone with benzaldehyde derivative [25,26], have been found to undergo intramolecular cyclization in THF in the presence of dichloro-bis(triphenylphosphine)palladium(II) to afford the corresponding 2-arylquinolin-4(1*H*)-ones **9** in good yields (55–85%) (Scheme 3) [27]. The main disadvantage of this reaction is the use of stoichiometric amounts of the organometallic reagent and column chromatographic separation of the NH-4-oxo derivatives that are almost insoluble in many organic solvents.

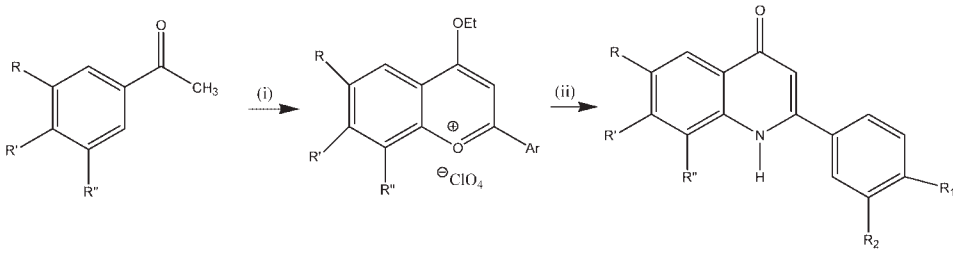
Thallium(III) *p*-tolylsulfonate (TTS) in dimethoxyethane (DME) [28] or iodobenzene diacetate in methanolic KOH [29,30] were used before to dehydrogenate 2-aryl-1,2,3,4-tetrahydro-4-quinolones **10** to 2-aryl-4-quinolones **9** (Scheme 4). The 2-aryl-1,2,3,4-tetrahydro-4-quinolones are themselves easily obtainable through acid-catalyzed cyclization of the isomeric 2-amonichalcones **8** [25,26]. Lee and Youn, recently used zinc chloride in acetonitrile to cyclize series of 2-amonichalcones to afford the corresponding isomeric 2-aryl-1,2,3,4-tetrahydro-4-quinolone derivatives in high yields (>85%) [30]. The 2-aryl-1,2,3,4-tetrahydro-4-quinolones bearing substituents on the fused benzo ring can also be prepared through direct one-pot acid-catalyzed condensation of substituted

Scheme 4. Reagents: (i) H_3PO_4, EtOH, heat; (ii) TTS, DME, heat or toluene, heat.



8 **10** **9**

Scheme 5. Reagents: (i) ArCHO; $HClO_4$, $HC(OEt)_3$; (ii) 25% NH_3 (aq).



11 **12** **13**

R = H, CH_3, t-Bu, $NHCOCF_3$

R' = H; R" = H, $NHCOCF_3$

R_1 = H, OH, OCH_3

R_2 = H, OH, OCH_3

aniline derivatives with ethyl benzoylacetate in refluxing toluene [22,23].

The other approach to 2-arylquinolones makes use of flavylium salts **12** derived from the condensation of 2-hydroxyacetophenones **11** with aryldehydes in ethyl orthoformate in the presence of potentially explosive perchloric acid (Scheme 5) [31]. The resulting flavylium salt is then treated with aqueous ammonia to release the corresponding 2-aryl-4-quinolone **13**. A modification of this procedure employs trifluoroacetic acid or trifluoromethanesulfonic acid in ethyl orthoformate or dichloromethane to afford flavylium salts in high yields, however, the expected 2-aryquinolones are isolated in relatively low yields (18–59%) [32].

2.3. Synthesis from 2-aminoacetophenone and aroylchlorides. The most convenient and high yielding method usually used for the synthesis of 2-arylquinolin-4(1*H*)-ones involves the use of 2-aminoacetophenones **14** and substituted benzoyl chlorides **15** as starting material [5,7,33,34]. The resulting *N*-benzoyl-2-aminoacetophenone **16** is cyclized under reflux using t-BuOK in t-BuOH to afford the corresponding 2-arylquinolin-4(1*H*)-one **17** in high yield (60–80%) and purity (Scheme 6).

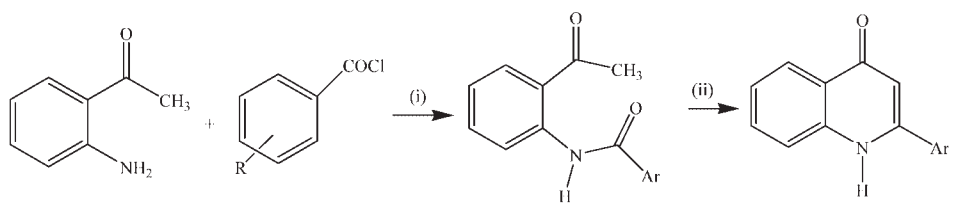
The reaction has also been carried out under microwave conditions involving irradiation of acylated 2′-aminoacetophenone in the presence of sodium hydroxide to afford 2-aryl-4-quinolones [35].

2.4. Methods involving organometallic reagents. Less traditional syntheses of 2-arylquinolin-4(1*H*)-ones, which make use of transitional metals have been developed. Palladium-catalyzed carbonylation of 2-haloaniline **18** in the presence of terminal acetylenes **19** under proper conditions (20 kg/cm^2 of CO at 120°C) afforded a variety of 2-substituted quinolin-4(1*H*)-ones **20** (Scheme 7) [36]. Carbonylation of series of *o*-iodoanilines and terminal alkynes in the presence of palladium catalyst [$PdCl_2$(dppf)] afforded 2-aryl-4-quinolones in good yields (62–83%) [37]. The reaction was found to proceed well in both secondary (diethylamine) and tertiary amines (triethylamine) and in benzene containing 4 equivalent of diethylamine.

Variously substituted 2-arylquinolin-4(1*H*)-ones **23** can also be obtained in appreciable yields (72–97%) *via* sequential Cu-catalyzed amidation of halophenones **21** followed by a base-promoted Camps cyclization of the resulting *N*-(2-ketoaryl)amides **22** (Scheme 8) [38].

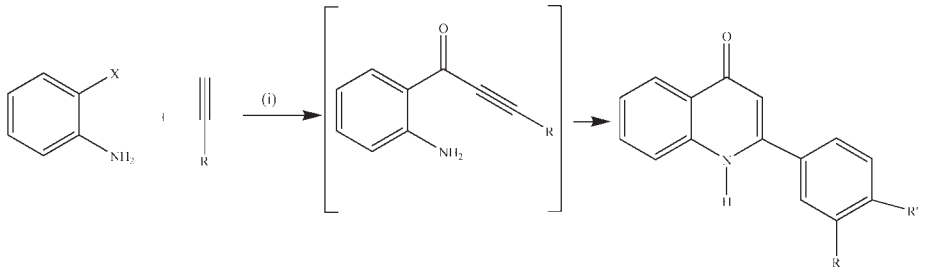
A mild and high yielding (>85%) one-pot synthesis of 2-arylquinolin-4(1*H*)-ones **26** *via* sequential palladium-catalyzed amidation of 2′-bromoacetophenone derivatives **24** followed by base-promoted intramolecular cyclization of **25** has been recently developed (Scheme 9) [39].

Scheme 6. Reagents: (i) NEt_3, THF, 0°C to r.t. 2 h; (ii) t-BuOK, t-BuOH, heat, 20 h.



14 **15** **16** **17**

Scheme 7. Reagents: (i) CO, $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf), $NHEt_2$, 120°C.



18 (X = Br, I) **19** **20**

R, R' = H (90%)

R = H, R' = -OMe (95%)

R = H, R' = -CO_2Et (85%)

R, R' = -OCH_2O- (88%)

These novel methods that make use of organometallic reagents are high yielding and allow synthesis of variously substituted potentially tautomeric 2-arylquinolin-4(1*H*)-ones [40].

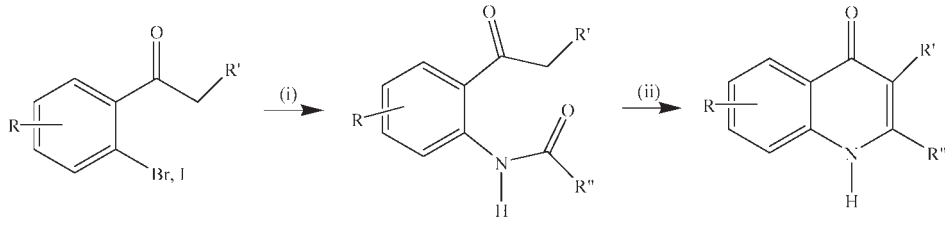
3. REACTIONS OF 2-ARYLQUINOLIN-4(1*H*)-ONES

New findings on the biological properties of 2-aryl-4-quiolones reveal a need to increase the diversity of substituents around the 4-quinolone framework. This moiety contains several reactive centers for possible functionalization to yield novel systems, which can themselves serve as substrates for further chemical transformation. The 2-arylquinolin-4(1*H*)-ones have been found to undergo C-3 halogenation, *N*- or *O*-alkylation, and oxidative aromatization.

3.1. C-3 Halogenation. Halogenated heterocyclic systems continue to attract considerable attention because of the profound effect a halogen atom can have on the physical, chemical, and biological properties of such substances. Iodine–Na_2CO_3 mixture in THF at room temperature was previously used to effect C-3 iodination of 2-arylquinolin-4(1*H*)-ones **27** to afford the corresponding 2-aryl-3-iodoquinolin-4(1*H*)-ones **28** (X = I) in high yield and purity (Scheme 10) [41]. The NH-4-oxo derivatives can also be iodinated using iodine–ammonium cerium nitrate (CAN) mixture in acetonitrile at 70–80°C to afford 2-aryl-3-iodoquinolin-4(1*H*)-ones [42]. On the other hand, the analogous 2-aryl-3-bromoquinolin-4(1*H*)-ones **28** (X = Br) were prepared in high yield and purity from the corresponding 2-arylquinolin-4(1*H*)-ones using pyridinium tribromide in acetic acid at room temperature (Scheme 10) [41].

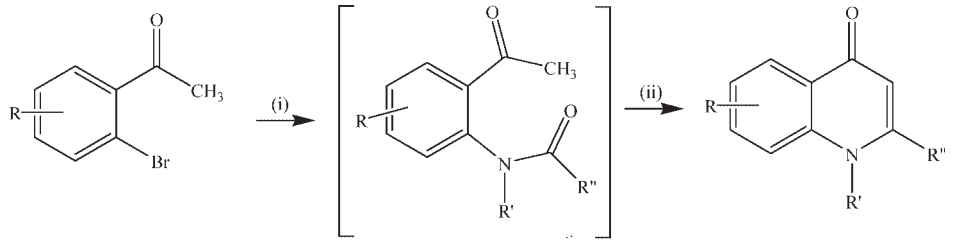
3.2. Alkylation of 2-arylquinolin-4(1H)-ones and their derivatives. The synthetic versatility of the potentially tautomeric 4-quinolone framework enables interconversion between the NH-4-oxo precursors and their *O*- or *N*-methylated derivatives. Comparison of spectroscopic data (IR, NMR, and ms) of these fixed derivatives (*O*- or *N*-alkylated) with those of the corresponding precursors (NH-4-oxo) has been used to resolve uncertainties on the 2-substituted 4-quinolone *versus* 2-substituted 4-quinolinol tautomeric equilibrium [40]. The naturally occurring 4-methoxy-2-phenylquinoline **29**

Scheme 8. Reagents: (i) Amide, CuI, ligand, toluene, heat; (ii) NaOH, 1,4-dioxane, heat.



21 **22** **23**

Scheme 9. Reagents: (i) $Pd_2(dba)_3$, xantphos, amide, Cs_2CO_3, dioxane, heat; (ii) t-BuONa, t-BuOH, heat.



24 **25** **26**

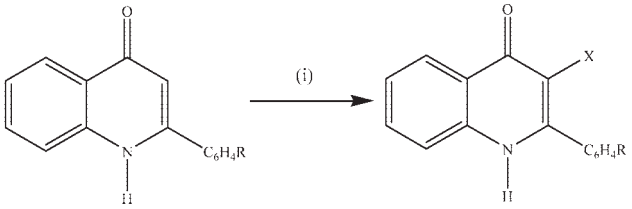
was previously treated with HCl in methanol under reflux to yield the 2-phenylquinol-4-one **30**, which was in turn converted to the NMe-4-oxo derivative **31** using dimethyl sulfate under basic conditions [43]. On the other hand, when heated with MeI, the 4-methoxyquinoline **29** yielded the dimethylated salt **32**, which upon treatment with a base afforded the isomeric 1-methyl-2-phenylquinoline **31** (Scheme 11).

The most classical method used for alkylation of 2-arylquinolin-4(1*H*)-ones involves subjecting the NH-4-oxo derivative to a base followed by quenching with the corresponding alkyl halide. Methylation of the 2-substituted-4(1*H*)-quinolones **33** using MeI-K_2CO_3 mixture in DMF was reported to afford a mixture of the *O*-methylated **34** and *N*-methylated derivatives **35** (Scheme 12) [44] while on the other hand, NaH and MeI in DMF afforded the *O*-methylquinoline derivatives, exclusively [45]. It was, however, discovered by Kuo and coworkers that the product mixture comprised of *N*- and *O*-methylated derivatives in the ratio 2:3 [46]. Alkylation of 2-phenylquinolin-4(1*H*)-one with methyl iodide or various primary alkyl, allyl, and benzyl halides in DMF in the presence of NaH, on the other hand, afforded the corresponding *N*-alkylated derivatives as sole products [47]. Enol ethers were also isolated as sole products when 2-(2-fluorophenyl)-6,7-methylenedioxyquinolin-4(1*H*)-one was treated with NaH in DMF followed by alkylation with ethyl chloroacetate or ethyl 4-chlorobutyrate [5]. Alkylation of 2-arylquinolin-4(1*H*)-ones with various alkyl halides also afforded the corresponding *O*-alkylated derivatives, exclusively [10]. Methylation was, however, found not to be regioselective under these conditions affording mixtures of *O*-methylated and *N*-methylated isomers.

It was also observed that the presence of substituent at C-5 or C-3 position has significant effect on the regioselectivity of alkylation of the quinolone derivatives. Treatment of 5,7-dimethoxy-2-phenylquinolin-4(1*H*)-one **36** (R, R′ = OMe) with MeI-K_2CO_3 mixture in DMF afforded *O*-methylated derivative **37** as the sole product (Scheme 13) [48]. On the other hand, under similar reaction conditions, 5-hydroxy-7-methoxy-2-phenyl-4-quinolone **36** (R = OH, R′ = OMe) afforded both *O*- **37** and *N*-methylated derivatives **38** [46] with *N*-methylated derivative as major product (ratio 9:1 *N*-alkylated *vs*. *O*-alkylated) [49]. Hadjeri *et al*. attributed the observed non-regioselectivity to the tautomeric equilibrium between the NH-4-oxo and its quinolinol isomer which is favored by chelation effect of the 5-OH group [48]. Treatment of the analogous 5-ethyl-2-phenylquinolin-4(1*H*)-one **36** (R = Et, R′ = H) with NaH-MeI mixture in THF afforded both *O*-methylated **37** (R″ = Me) and *N*-methylated isomers **38** (R″ = Me) in the ratio 1:5.4 [10]. On the other hand, under similar reaction conditions ethyl iodide and various ethoxycarbonylalkyl halides afforded only the corresponding *O*-alkylated products **37** (R = Et, R′ = H; R″ = Et, CH_2CO_2Et, CH_2CO_2H) [10].

The 3-halogenated NH-4-oxo derivatives **39** (R′ = Br, I) were treated with NaH in THF to afford the *N*-methylated derivatives **40** as the only products (Scheme 14) [41,50,51]. The observed regioselectivity was attributed to the preponderance of these derivatives as the NH-4-oxo tautomers in polar medium and solid state [40,51]. 2-Aryl-3-bromo-1-methylquinolin-4(1*H*)-ones **40** (X = Br) were also prepared directly from the corresponding 2-aryl-1-methylquinolin-4(1*H*)-one precursors in high yields (77–93%) using pyridinium tribromide in acetic acid at room temperature [41].

Scheme 10. Reagents: (i) I_2, Na_2CO_3, THF, heat for X = I; $C_5H_5NH.Br_3$, AcOH, r.t. for X = Br.

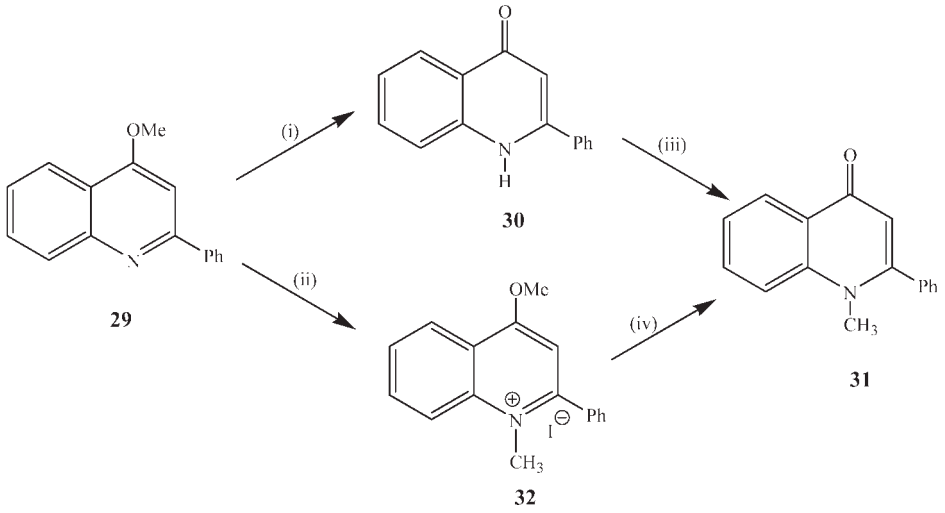


27 **28**

X = I; R = H (85%), 4-F (83%), 4-Cl (90%), 4-OMe (83%)

X = Br; R = H (94%), 4-F (95%), 4-Cl (91%), 4-OMe (90%)

Scheme 11. Reagents: (i) HCl, MeOH, heat; (ii) MeI, heat; (iii) Me_2SO_4, NaOH; (iv) NaOH.



In another development, series of pharmaceutically important *N*-methylated 2-aryl-4-quinolone alkaloids **44** were prepared by methylation of 2-arylquinolines **43** with methyl trifluoromethanesulfonate followed by oxidation with potassium ferricyanate $[K_3Fe(CN)_6]$ (Scheme 15) [52]. 2-Arylquinoline **43** used as substrate in this investigation were, in turn, synthesized by Diels–Alder reaction of substituted 1,2,3-benzotriazine **41** prepared by oxidation of 1-amino-1*H*-indazole with lead tetraacetate, and pyrrolidine enamine of substituted acetophenone **42** in dry chloroform in the presence of zinc bromide under reflux [52].

Although primary alkyl halides and benzyl halides afforded the *O*-alkylated derivatives exclusively, the problem of non-regioselectivity with methylation necessitates the development of sure-fire methods for the direct and regioselective synthesis of either *N*- or *O*-methylated isomers. Very few methods have been developed to-date for the direct synthesis of *N*-alkyl 2-arylquinolin-4(1*H*)-ones.

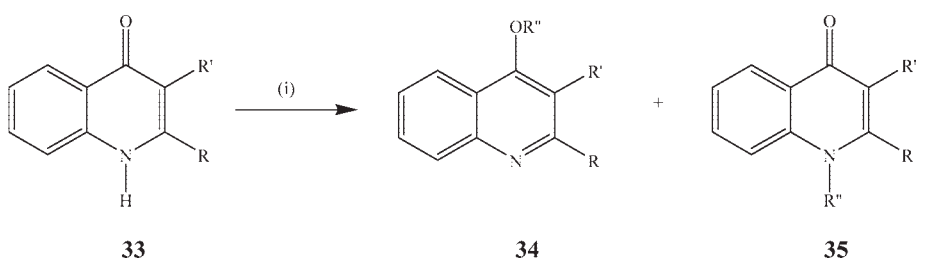
3.2.1. Direct synthesis of N-alkylated 2-arylquino-linones. The shortest route (one-step synthesis) reported to-date for the synthesis of 2-aryl-1-methyl-4-quinolones **47** in appreciable yields involves the condensation of lithium enolates of acetophenone derivatives **46** with substituted *N*-methylisatoic anhydrides **45** (Scheme 16) [46,53]. Although the reaction is high yielding, each reaction when using different substrates has its unique temperature requirements for completion.

Several *N*-methylated 2-aryl-4-quinolinones were prepared in moderate yields by treatment of resin bound flavylium salts with methylamine following a similar procedure outlined in Scheme 5 [32]. In another development involving synthesis of *N*-alkylated 2-arylquinolone derivatives, 2-aminoacetophenone **48** was first condensed with various aldehydes followed by selective reduction using $NaBH_3CN$ to yield **49** (Scheme 17). The alkylated derivatives **49** were, in turn, acylated using various benzoyl chlorides and the resulting amides **50** were cyclized using t-BuOK in refluxing t-BuOH to afford 1-benzyl-2-arylquinolin-4(1*H*)-ones **51** [54].

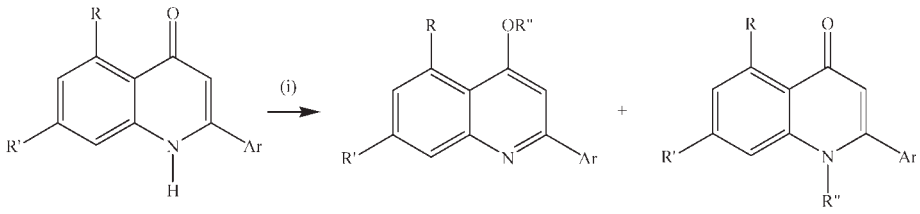
Palladium-catalyzed carbonylation of *N*-ethyl-2-iodoaniline **52** with phenylacetylene **53** in diethylamine afforded a mixture of enamine **54** (52%) and 2-phenylquinoline **55** (20%) (Scheme 18). Further heating of the enamine in THF in the presence of NaH effected smooth cyclization leading to quantitative yield of the quinolone [36].

A direct one-pot synthesis of 2-aryl-1-methylquinolin-4(1*H*)-ones **58**, which involves treatment of *N*-arylamidoacetophenone derivatives **56** with MeI in presence of

Scheme 12. Reagents: (i) MeI, NaH in THF or DMF; MeI, K_2CO_3 in DMF or Acetone.



Scheme 13. Reagents: (i) K_2CO_3, R″X, DMF or NaH, R″X, THF.



36 **37** **38**

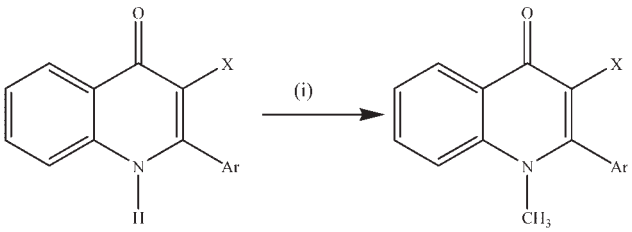
NaH in THF was recently described (Scheme 19) [40]. The corresponding *N*-methylated arylamidoacetophenone derivatives **57** were isolated in trace amounts (>5%).

Friedel-Crafts acylation of **59** using stannic chloride ($SnCl_4$) as catalyst afforded **60,** which upon cyclization with t-BuOK in t-BuOH yielded the corresponding 2-aryl-1-methylquinolin-4(1*H*)-ones **61** (Scheme 20) [55]. This cyclization previously worked well for the synthesis of 2-aryl-3,5,7-trimethoxy-4-quinolones from *N*-phenylamido methoxyacetophenones prepared, in turn, *via* stannic chloride-catalyzed Friedel-Crafts acylation of 3,5-dimethoxyphenyl-*N*-phenylamide with methoxyacetyl chloride in 1,2-dichloroethane [56].

Iodocyclization of the dimethylamino systems **62** using iodine in dichloromethane proved highly selective for the 6-endo-digonal pathway to afford 2-substituted 3-iodo-1-methylquinolin-4(1*H*)-ones **63** in high yield (94%, R = 4-MeO) (Scheme 21) [57].

3.2.2. Direct synthesis of* O*-alkylated 2-arylquinolines. An alkoxide-mediated cyclization of Schiff bases **64** derived from the reaction of trifluoromethylaniline with alkyl or heterophenyl ketones is reported to afford 2-aryl-4-alkoxyquinoline **65**, exclusively [58,59]. In this reaction, the Schiff base is treated with t-KOBu in THF under reflux to afford the alkoxyquinoline derivative (OR = t-BuO) in high yield (83%) (Scheme 22) [58]. On the other hand, under similar reaction conditions, use of sodium or potassium ethoxide afforded the corresponding 4-ethoxy-2-phenylquinoline (R = Et) in lower yield (25%). The 2,3,4-trisubstituted quinoline (R′ = CH_3; R″ = t-Bu) was prepared in 52% yield following similar procedure [58].

Scheme 14. Reagents: (i) NaH, MeI, THF, r.t. 18 h.



39 (X = Br, I) **40**

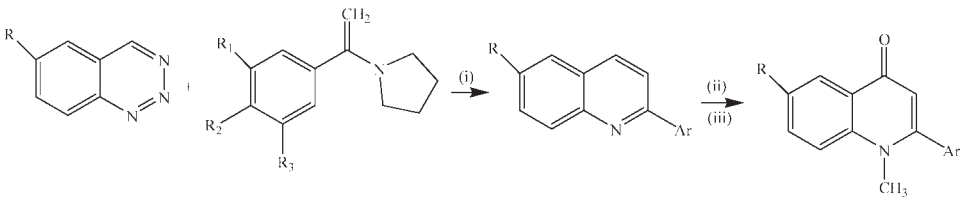
One of the recent developments in the synthesis of 4-alkoxyquinolines involved direct synthesis of the naturally occurring 4-alkoxy-2-arylquinoline derivatives from the corresponding 2-aryl-1,2,3,4-tetrahydro-4-quinolones using oxidative reagents (Scheme 23). Oxidation of 2-aryl-1,2,3,4-tetrahydro-4-quinolones **66** to 2-aryl-4-methoxyquinolines **67** was effected with either thallium(III) nitrate [60] or [hydroxyl(tosyloxy)iodo]benzene [61] in trimethyl orthoformate in the presence of catalytic amount of perchloric acid. Molecular iodine in refluxing methanol was also found to effect oxidative aromatization of 2-aryl-1,2,3,4-tetrahydro-4-quinolones **66** to 2-aryl-4-methoxyquinolines **67** [62]. Recently, Kumar and coworkers used $FeCl_3{\cdot}6H_2O$ in methanol to effect oxidative aromatization of series of 2-aryl-1,2,3,4-tetrahydroquinolin-4-ones to afford 2-aryl-4-methoxyquinolines in 70–85% yields [63]. $FeCl_3{\cdot}6H_2O$ in methanol was later used by these authors to effect direct one-pot synthesis of series of 2-aryl- and 2-heteroaryl-4-methoxyquinolines (55–72%) and their flavones derivatives from the corresponding 2-azachalcones and 2-hydroxychalcones, respectively [64].

Series of 2,4-disubstituted quinolines **69** (X = Br, I, SEt, SPh) including 4-alkoxy-2-arylquinolines (X = OEt, OMe, OAr) were prepared in moderate to high yields (33–98%) from the corresponding β-(2-aminophenyl)-α,β-ynones **68** using various nucleophiles (Scheme 24) [65].

The 4-alkoxy-2-arylquinolines **72** (R′ = Me, Et, i-Pr) were recently prepared in low to moderate yields (10–81%) from 2-(2-(trimethylsilyl)ethynyl)anilines **70** and aryldehydes **71** in the presence of sulfuric acid in alcohols (Scheme 25) [66].

Although simple and efficient, the above reagents used for direct oxidative aromatization of 2-aryl-1,2,3,4-tetrahydro-4-quinolones cannot be used for the synthesis of 2,3-disubstituted 4-alkoxyquinoline derivatives. On the other hand, the Skraup, Döbner-Miller, Friedländer and Combes reactions, which are well known classical methods for the synthesis of polysubstituted quinolines, cannot be adapted for the synthesis of quinoline derivatives bearing 4-alkoxy group [67]. Consequently, indirect methods remain the method of choice for the

Scheme 15. Reagents: (i) $ZnBr_2$, CHCl3, heat, 2 h; (ii) Methyl trifluoromethanesulfonate, heat, 1 h; (iii) $K_3Fe(CN)_6$, 20% NaOH, r.t. 2 h.



41 **42** **43** **44**

$R = R^1 = R^2 = R^3 = H$

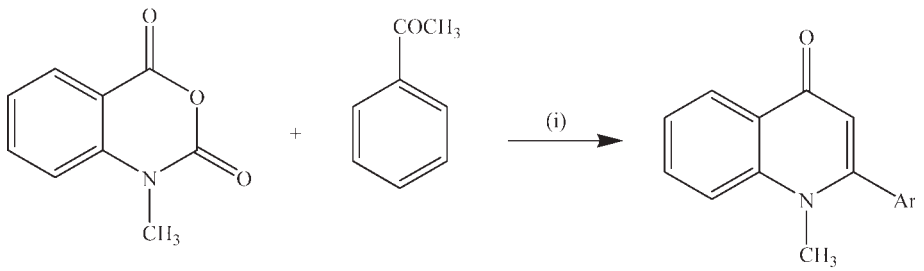
$R = R^3 = H$, $R^1 + R^2 = OCH_2O$

$R = R^1 = R^3 = H$, $R^2 = OH$

$R = OCH_3$, $R^1 = R^2 = R^3 = H$

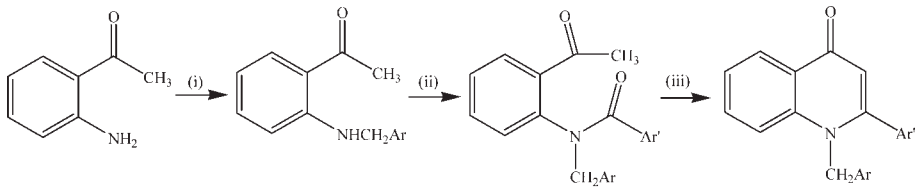
$R = R^1 = R^3 = H$, $R^2 = H$

Scheme 16. Reagents: (i) DIPA, n-BuLi, THF, −65°C, 3.5 h.



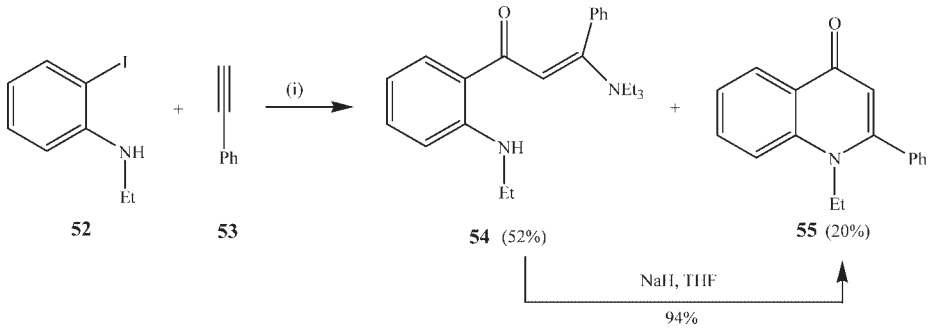
45 **46** **47**

Scheme 17. Reagents: (i) *a*: PhCHO, C_6H_6; *b*: $NaCNBH_3$, PPTS, MeOH. (ii) ArC(O)Cl, NEt_3, CH_2Cl_2. (iii) t-BuOK, t-BuOH.



48 **49** **50** **51**

Scheme 18. Reagents: (i) CO, $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf), $NHEt_2$, 120°C.

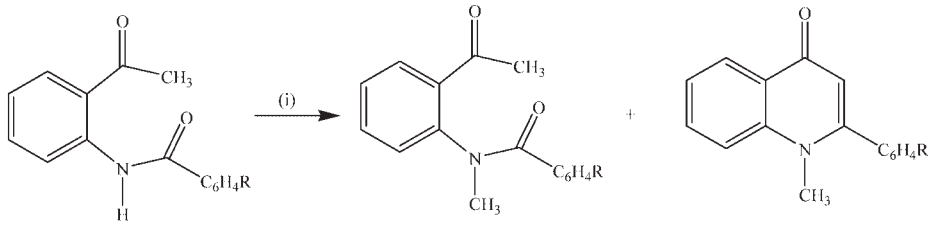


52 **53** **54** (52%) **55** (20%)

NaH, THF

94%

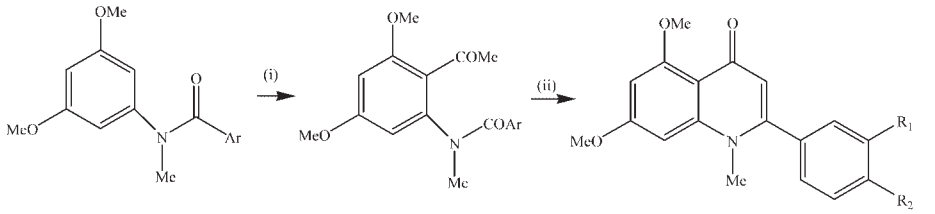
Scheme 19. Reagents: (i) NaH, MeI, THF, r.t.



56 **57** (minor) **58** (major)

Major: R = H (52%), 4-F (54%), 4-Cl (61%), 4-OMe (51%)

Scheme 20. Reagents: (i) $MeCOCl$, $SnCl_4$, CH_2Cl_2, 0°C; (ii) t-BuOK, 30°C.

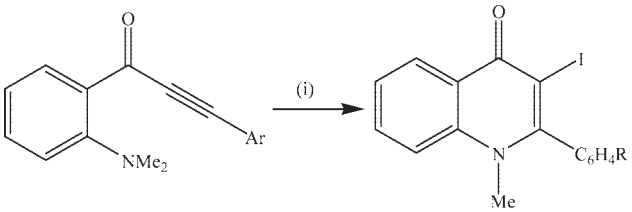


59 **60** **61** ($R_1 = NO_2$, $R_2 = Cl$) ($R_1 = H$, $R_2 = OCOMe$)

synthesis of polysubstituted *O*-alkylated quinoline derivatives.

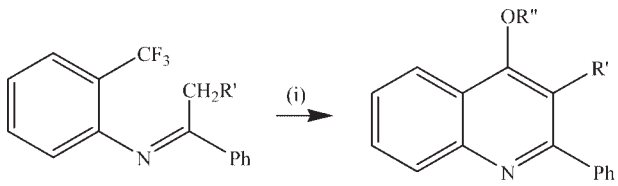
3.2.3. Indirect synthesis of* O-*alkylated 2-arylquinolines. In this approach, the NH-4-oxo derivatives **73** are first converted to the corresponding 4-chloroquinoline derivatives **74** using phosphorus oxychloride under reflux. The C3 unsubstituted 2-aryl-4-chloroquinolines were also prepared by reaction of Vilsmeier reagent with 2′-azidochalcones, which are prepared in turn from the corresponding 2′-amonichalcones by diazotization followed by treatment with NaN_3 [68]. The 4-chloroquinolines **74** are then reacted with alkoxides or phenoxide ions to

Scheme 21. Reagents: (i) I_2, CH_2Cl_2.



62 **63**

Scheme 22. Reagents: (i) KOR″, THF, heat, 2 h.

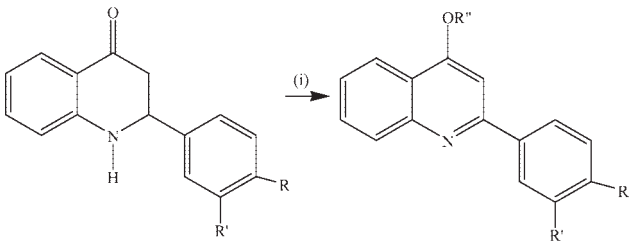


64 **65**

R' = H; R" = t-Bu, Et

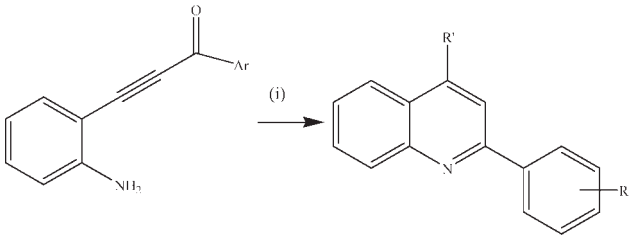
R' = CH_3; R" = t-Bu

Scheme 23. Reagents: (i) TTN, $CH(OR'')_3$, $HClO_4$, 1 h [60]; HTIB, $CH(OR'')_3$, $HClO_4$, 1.5 h [61]; I_2, MeOH, 2 h [62]; or $FeCl_3{\cdot}6H_2O$, MeOH, heat, 3 h [63].



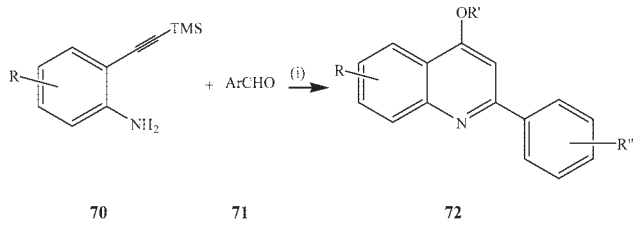
66 **67**

Scheme 24. Reagents: (i) NaOR′, R′OH (R′ = Me, Et).



68 **69** (R' = OMe, OEt)

Scheme 25. Reagents: (i) H_2SO_4, R′OH, heat, 17 h.



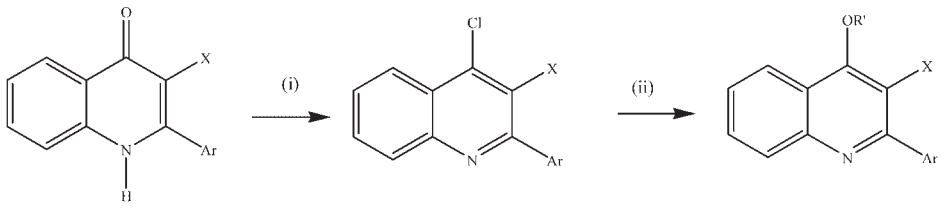
70 71 72

yield the expected 4-phenoxy- or 4-alkoxyquinoline derivatives **75** (Scheme 26) [69,70]. This approach, which takes advantage of the ease of displacement of 4-chlorine atom by nucleophiles has recently been used for the synthesis of 2,3-disubstituted 4-alkoxyquinoline derivatives (R′ = Me) that cannot be easily prepared otherwise. Series of 2-aryl-3-bromo/iodo-4-methoxyquinolines were prepared this way from the corresponding 2-aryl-4-chloro-3-halogenoquinolines [50,51,70].

This indirect approach has also been adapted to involve the use of organometalic reagents in the synthesis of 2,3-disubstituted 4-alkoxyquinolines. The synthesis of 3-aryl-2-(ethyl/phenyl)-4-phenoxyquinolines **78**, involved initial C-2 coupling of 3-aryl-2,4-dichloroquinolines **76** with alkyl- or aryl-zinc reagents (R_2Zn; R = Et, Ph) followed by displacement of the 4-chlorine atom from **77** with bromophenol derivative (Scheme 27) [71].

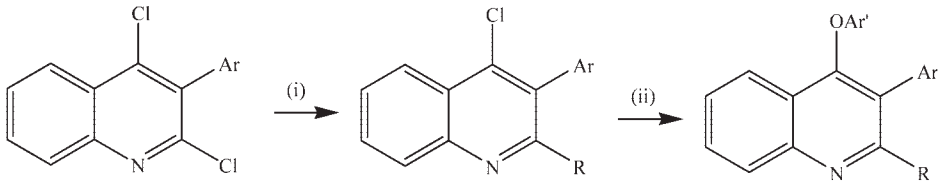
The results of sequential functionalization of 2-aryl-4-chloro-3-iodoquinolines **73** (X = I) *via* palladium-catalyzed cross-coupling with phenylboronic acid followed by displacement of the 4-chloro atom from the resulting 2,3-diaryl-4-chloroquinolines **78** with methoxide ion to yield 2,3-diaryl-4-methoxyquinolines **79** have recently been described (Scheme 28). Compounds **79** were also

Scheme 26. Reagents: (i) $POCl_3$, heat, 2 h; (ii) NaOMe, THF, heat, 18 h.



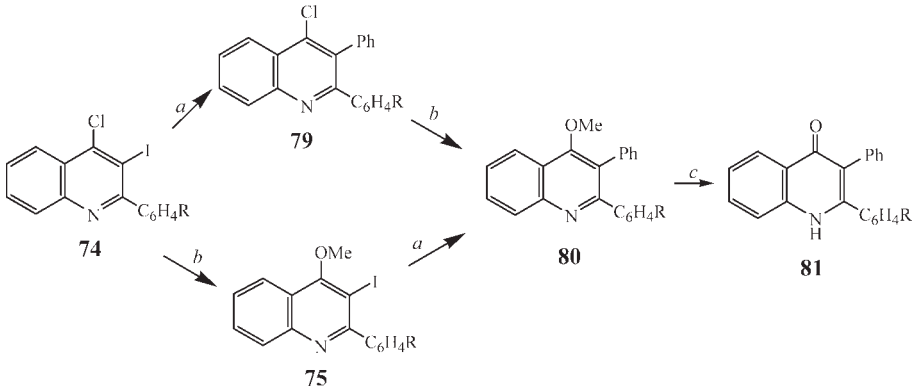
73 (X = H, Br, I) **74** **75**

Scheme 27. Reagents: (i) $Zn(R')_2$, $PdCl_3(dppf)$, K_2CO_3, THF; (ii) *p*-BrC_6H_4OH, NaOH, DMF, 110°C.



76 **77** **78**

Scheme 28. Reagents: (*a*) $Pd(PPh_3)_4$, $PhB(OH)_2$, K_2CO_3, DMF; (*b*) NaOMe, THF or DMF, heat; (*c*) BBr_3, CH_2Cl_2, r.t.



prepared *via* Suzuki–Miyaura cross-coupling of 2-aryl-3-iodo-4-methoxyquinolines **74** (R′ = Me, X = I) with phenylboronic acid [70]. Demethylation of the methoxy compounds **79** with BBr_3 in CH_2Cl_2 gave the 2,3-diaryl-4(1*H*)-quinolinones **80**.

This demethylation represents a convenient synthetic strategy for the construction of 2,3-diarylquinolin-4(1*H*)-ones of potential biological interest that can be obtainable only with difficulty otherwise.

4. CONCLUSIONS

Overall, the methods described in this review present another example showing the potential of 2-arylquinolin-4(1*H*)-ones in the synthesis of 2,3-substituted NH-4-oxo derivatives and their transformation into *N*-alkylated and *O*-alkylated derivatives. Interestingly, *O*-alkylated and *N*-alkylated quinolone derivatives do not feature at all in a recent review on quinolines by Kouznetsov *et al.* [72]. Despite the establishment of structural requirements and optimum reaction conditions suitable for the synthesis of *N*-alkylated quinolone derivatives, there is still a growing need for development of generalized methods for the synthesis of polysubstituted derivatives. On the other hand, indirect methods, which make use of 4-chloroquinolines and take advantage of the ease of displacement of the 4-chloro atom remain the best option for the synthesis of polysubstituted 4-alkoxyquinolines.

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REFERENCES AND NOTES

[1] Sondheimer, F.; Meisels, A. J Org Chem 1958, 23, 762.

[2] Goodwin, S.; Smith, A. F.; Velasquez, A. A.; Horning, E. C. J Am Chem Soc 1959, 81, 6209.

[3] Michael, J. P. Nat Prod Rep 1997, 14, 605.

[4] Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S. C.; Hamel, E.; Hackl, T.; Lee, K. H. J Med Chem 1998, 41, 1155.

[5] Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J.-H.; Lee, K.-H. J Med Chem 2001, 44, 3932.

[6] Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J. H.; Lee, K. H. Bioorg Med Chem Lett 2003, 13, 2891.

[7] Hadjeri, M.; Peiller, E.-L.; Beney, C.; Deka, N.; Lawson, M. A.; Dumontet, C.; Boumendjel, A. J Med Chem 2004, 47, 4964.

[8] Lai, Y.-Y.; Huang, l.-J.; Lee, K.-H.; Xiao, Z.; Bastow, K. F.; Yamori, T.; Kuo, S.-C. Bioorg Med Chem 2005, 13, 265.

[9] Huang, L.-J.; Hsieh, M.-C.; Teng, C.-M.; Lee, K.-H.; Kuo, S.-C. Bioorg Med Chem 1998, 6, 1657.

[10] Ko, T. C.; Hour, M. J.; Lien, J. C.; Teng, C. M.; Lee, K. H.; Kuo, S. C.; Huang, L. J. Bioorg Med Chem 2001, 11, 279.

[11] Chun, M. W.; Olmstead, K. K.; Choi, Y. S.; Lee, C. O.; Kim, J. H.; Lee, J. Bioorg Med Chem Lett 1997, 7, 789.

[12] Fournet, A.; Barrios, A. A.; Munoz, R. H.; Hocquemiller, R.; Cave, A.; Bruneton, J. Antimicrob Agents Chemother 1993, 37, 859.

[13] Michael, J. P. Nat Prod Rep 2006, 24, 223.

[14] Alguinaldo, A. M.; Dalangin-Mallari, V. M.; Macabeo, A. P. G.; Byrne, L. T.; Abe, F.; Yamauchi, T.; Franzblau, S. G. Int J Antimicrobial Agents 2007, 29, 738.

[15] Hoekstra, W. J.; Patel, H. S.; Liang, X.; Blanc, J. E.; Heyer, D. O.; Willson, T. M.; Iannone, M. A.; Kadwell, S. H.; Miller, L. A.; Pearce, K. H.; Simmons, C. A.; Shearin, J. J Med Chem 2005, 48, 2243.

[16] Maguire, M. P.; Sheets, K. R.; McVety, K.; Spada, A. P.; Zilberstein, A. J Med Chem 1994, 37, 2129.

[17] Alguinaldo, A. M.; Dalangin-Mallari, V. M.; Macabeo, A. P. G.; Byrne, L. T.; Abe, F.; Yamauchi, T.; Franzblau, S. G. Int J Antimicrobial Agents 2007, 29, 738.

[18] Fuson, R. C.; Burness, D. M. J Chem Soc 1946, 68, 1270.

[19] Giardina, G. A. M.; Sarau, H. M.; Farina, C.; Medhurst, A. D.; Grugni, M.; Ravereglia, L. F.; Schmidt, D. B.; Rigolio, R.; Luttmann, M.; Vecchietti, V.; Hay, D. W. P. J Med Chem 1997, 40, 1794.

[20] Hormi, O. E. O.; Peltonen, C.; Heikkilä, L. J Org Chem 1990, 55, 2513.

[21] Chen, B.; Huang, X. H.; Wang, J. Synthesis 1987, 482.

[22] Jaroszewski, J. W. J Heterocyclic Chem 1990, 27, 1227.

[23] Park, M.-S.; Lee, J.-I. Bull Korean Chem Soc 2004, 35, 1269.

[24] Rao, V. V. R.; Wentrup, C. J Chem Soc Perkin Trans 1 2002, 1232.

[25] Donnelly, J. A.; Farell, D. F. Tetrahedron 1990, 46, 885.

[26] Donnelly, J. A.; Farell, D. F. J Org Chem 1990, 55, 1757.

[27] Kasahara, A.; Izumi, T.; Watabe, H.; Takahashi, S. Chem Ind 1981, 121.

[28] Singh, O. V.; Kapil, R. S. Synth Commun 1993, 23, 277.

[29] Prakash, O.; Kumar, R. J.; Saini, R. J.; Singh, S. P. Synth Commun 1994, 24, 2167.

[30] Lee, J. I.; Youn, J. S. Bull Korean Chem Soc 2008, 29, 1853.

[31] Sato, S.; Kumagai, H.; Matsuba, S.; Kumazawa, T.; Onodera, J.-I.; Suzuki, M. J Heterocyclic chem 1999, 36, 1345.

[32] Sato, S.; Kubota, Y.; Kumagai, H.; Kumazawa, T.; Matsuba, S.; Kitamura, N.; Onodera, J. I.; Suzuki, M. Heterocycles 2000, 53, 1523.

[33] Li, L.; Wang, H.-K.; Kuo, S.-C.; Wu, T.-C.; Lednicer, D.; Lin, C. M.; Hamel, E.; Lee, K.-H. J Med Chem 1994, 37, 1126.

[34] Li, L.; Wang, H.-K.; Kuo, S.-C.; Wu, T.-C.; Lednicer, D.; Lin, C. M.; Hamel, E.; Lee, K.-H. J Med Chem 1994, 37, 3400.

[35] Ding, D.; Li, X.; Wang, X.; Du, Y.; Shen, J. Tetrahedron Lett 2006, 47, 6997.

[36] Torii, S.; Okumoto, H.; Xu, L. H. Tetrahedron Lett 1991, 32, 237.

[37] Kalanin, V. N.; Shostakovsky, M. V.; Ponomaryov, A. B. Tetrahedron Lett 1992, 33, 373.

[38] Jones, C. P.; Anderson, K. W.; Buchwald, S. L. J Org Chem 2007, 72, 7968.

[39] Huang, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. Org Lett 2008, 10, 2609.

[40] Mphahlele, M. J.; El-Nahas, A. M. J Mol Struct 2004, 688, 2159.

[41] Mphahlele, M. J.; Nwamadi, M. S.; Mabeta, P. J Heterocyclic Chem 2006, 43, 255.

[42] Venkataraman, S.; Barabge, D. K.; Pal, M. Tetrahedron Lett 2006, 47, 7317.

[43] Goodwin, S.; Smith, A. F.; Horning, E. C. J Am Chem Soc 1957, 79, 2239.

[44] Somanathan, R.; Smith, K. M. J Heterocyclic Chem 1981, 18, 1077.

[45] Jaroszewski, J. W. J Heterocyclic Chem 1990, 27, 1227.

[46] Kuo, S. C.; Lee, H. Z.; Juang, J. P.; Lin, Y. T.; Wu, T. S.; Chang, J. J.; Lednicer, D.; Paull, K. D.; Lin, C. M.; Hamel, E.; Lee, K. H. J Med Chem 1993, 36, 1146.

[47] Shim, S. C.; Chae, S. A.; Lee, D. Y.; Lim, H. S.; Kalinin, V. N. J Kor Chem Soc 1994, 38, 774.

[48] Hadjeri, M.; Mariotte, A.-M.; Boumendjel, A. Chem Pharm Bull 2001, 49, 1352.

[49] Pain, C.; Célanire, S.; Guillaumet, G.; Joseph, B. Tetrahedron 2003, 59, 9627.

[50] Mphahlele, M. J. J Chem Res 2002, 196.

[51] Mphahlele, M. J.; Fernandes, M. A.; Ottosson, H.; El-Nahas, A. M.; Ndlovu, S. M.; Sithole, H. M.; Dladla, B. S.; De Waal, D. J Chem Soc Perkin Trans 2 2002, 2159.

[52] Koyama, J.; Toyokuni, I.; Tagahara, K. Chem Pharm Bull 1999, 47, 1038.

[53] Coppola, G. M. J Heterocyclic Chem 1982, 19, 727.

[54] Niedzinski, E. J.; Lashley, M. R.; Nantz, M. H. Heterocycles 2001, 55, 623.

[55] Manfroni, G.; Gatto, B.; Tabarrini, O.; Sabatini, S.; Cecchetti, V.; Giaretta, G.; Parolin, C.; Del Vecchio, C.; Calistri, A.; Palumbo, M.; Fravolini, A. Bioorg Med Chem Lett 2009, 19, 714.

[56] Beney, C.; Hadjeri, M.; Mariotte, A.; Boumendjel, A. Tetrahedron Lett 2000, 41, 7037.

[57] Hessian, K. O.; Flynn, B. L. Org Lett 2006, 8, 243.

[58] Strekowski, L.; Wydra, R. L.; Cegla, M. T.; Czarny, A.; Harden, D. B.; Patterson, S. E.; Battiste, M. A.; Coxon, J. M. J Org Chem 1990, 55, 4777.

[59] Janda, L.; Nguyen, J.; Patterson, S. E.; Strekowski, L. J Heterocyclic Chem 1992, 29, 1753.

[60] Singh, O. V.; Kapil, S. Synlett 1992, 751.

[61] Varma, R. S.; Kumar, D. Tetrahedron Lett 1998, 39, 9113.

[62] Mphahlele, M. J.; Hlatshwayo, S. M.; Mogamisi, F. K.; Tsanwani, M.; Mampa, R. M. J Chem Res 1999, 706.

[63] Kumar, K. H.; Muralidharan, D.; Perumal, P. T. Tetrahedron Lett 2004, 45, 7903.

[64] Kumar, K. H.; Muralidharan, D.; Perumal, P. T. Tetrahedron 2007, 63, 9531.

[65] Acardi, A.; Marinelli, F.; Rossi, E. Tetrahedron 1999, 55, 13233.

[66] Wang, Y.; Peng, C.; Liu, L.; Zhao, J.; Su, L.; Zhu, Q. Tetrahedron Lett 2009, 50, 2261.

[67] Ryabukhin, S. V.; Volochnyuk, D. M.; Plaskon, A. S.; Naumchik, V. S.; Tolmachev, A. A. Synthesis 2007, 1214.

[68] Akila, S.; Selvi, S.; Balasubramanian, K. Tetrahedron 2001, 57, 3465.

[69] Andersen, K. E.; Lundt, B. F.; Jørgensen, A. S.; Braestrup, C. Eur J Med Chem 1996, 31, 417.

[70] Mphahlele, M. J.; Mtshemla, V. J Chem Res 2008, 437.

[71] Hoekstra, W. J.; Patel, H. S.; Liang, X.; Blane, J.-P. E.; Heyer, D. O.; Willson, T. M.; Iannone, M. A.; Kadwell, S. H.; Miller, L. A.; Pearce, K. H.; Simmons, G. A.; Shearin, J. J Med Chem 2005, 48, 2243.

[72] Kouznetsov, V. V.; Méndez, L. Y. V.; Gómez, C. M. M. Curr Org Chem 2005, 9, 141.