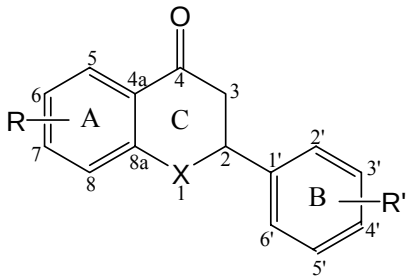
CHAPTER ONE

INTRODUCTION

1.1 Brief description of quinolones and related analogues

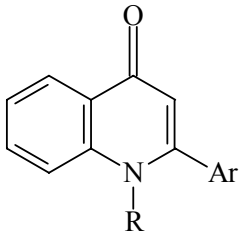
Quinolones are analogues of flavanones and thiaflavanones which are characterized by a fused benzo ring A and phenyl substituent B at position 2 of the heterocyclic ring C as shown by the generalized structure **1**. Flavanones have an ether linkage (X = O)[1,2,3] whereas the quinolones have an aza linkage (X = NR; R = H, acetyl and sulfonyl)[3,4] and thiaflavanones have a thioether linkage (X = S).[3,5] Quinolones[3] and flavanones[1,6,7] are widely distributed in plants and can also be synthesized in the laboratory using various methods. On the other hand, thiaflavanones are only accessible in the laboratory by the reaction of cinnamic acid and thiophenol to afford the 3-(phenylmercapto)propanoic acid which when converted to acid chloride undergoes Friedel-Crafts cyclization to afford thiaflavanone.[5]



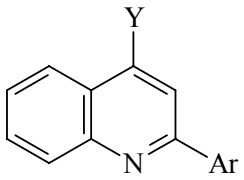
1

The C ring of quinolones **1** contain several reactive sites (positions 1, 3 and 4) and can also allow different degree of unsaturation in the heterocyclic ring, as observed in quinolin-4(1*H*)-ones **2** and the fully aromatic quinoline derivatives **3**.[6,8-11] The A-ring

of structure **1** (R = Cl, Br) can also be modified by nucleophilic substitution at either position 6 or 8.[12,13]



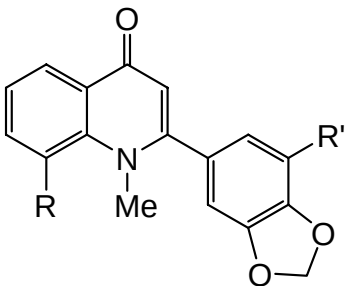
2
R = H, alkyl, acetyl or sulfonyl



3
Y = Alkoxy, amino

1.2 Natural sources of quinolone and their derivatives

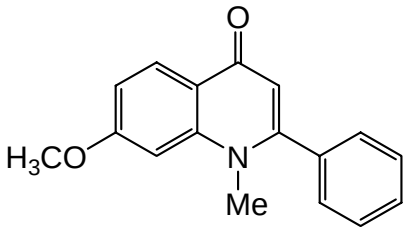
Most of the 2-phenylquinoline and 2-phenylquinolone alkaloids are widely distributed in the plant family *Rutaceae*.[14-16] Graveoline (R = R' = H) **4a**, for example, was first isolated from *Ruta graveolens*[14,15] and its substituted derivatives, the 3'-methoxygraveoline (R = H, R' = OMe) **4b** and 3',8-dimethoxygraveoline (R = R' = OMe) **4c** were also isolated from the roots of the Brazilian plant *Esenbeckia grandiflora*.[15-17] Edulein **5** a derivative of 2-phenyl-4-quinolone, on the other hand, was isolated from the bark of the Mexican tree *Casimiroa edulis* and the leaves of *Lunasia amara*.[18,19]



4a Graveoline R = R' = H

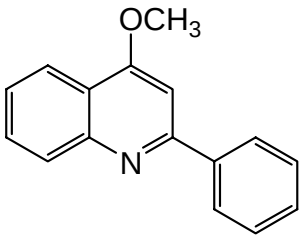
b R = H, R' = OMe

c R = R' = OMe



5

The isomeric 4-methoxy-2-phenylquinoline **6** and the 4-methoxy-2-(3',4'-methylenedioxyphenyl)quinoline **7** were isolated from the leaves of *Lunasia amara.*[16,19] Compound **6** was also isolated from the bark of *Galipea longiflora*.[16]



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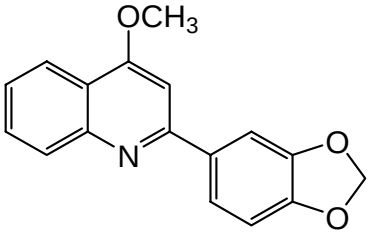

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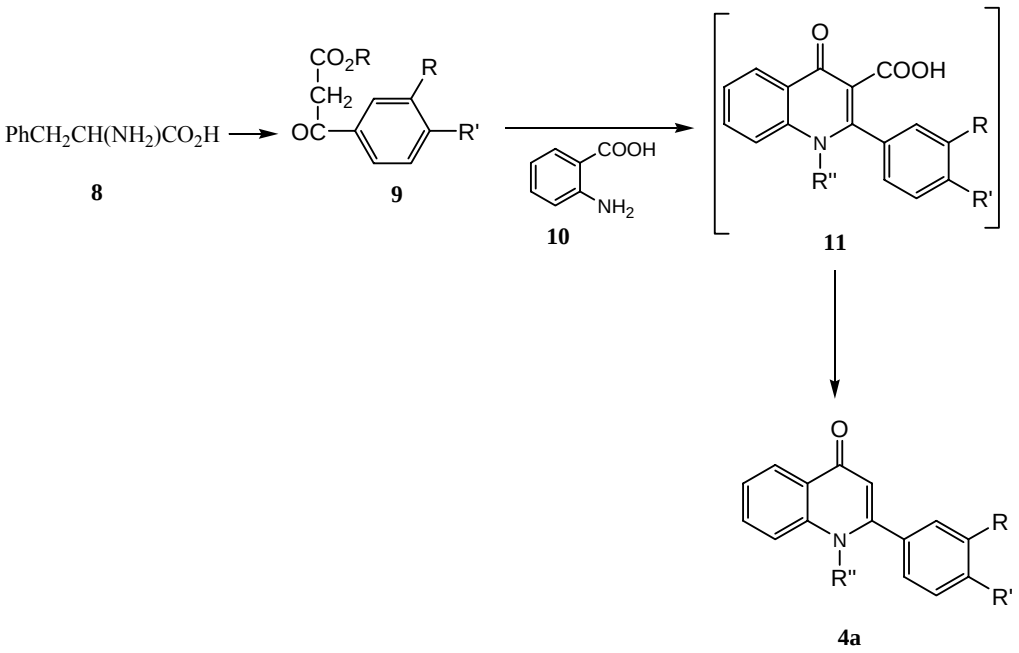
1.3 Biosynthesis of quinolones and their derivatives

The biosynthesis of 2-alkylquinoline, 2-arylquinoline and 2-arylquinolone alkaloids is believed to involve the condensation of anthranilic acid[20-23] and either phenylalanine[20] or acetate[22] as precursors. Graveoline **4a** (R and R' = CH_2O_2, R'' = CH_3), for example, is believed to be the product of the condensation of β-Keto ester **9** and anthranilic acid **10** through an intermediate 3-carboxyquinolone **11**.[20] On the other hand, the analogous *O*-methylated derivative **7,** is believed to be the product of the reaction

between 2-aminobenzoylacetic acid and appropriate aldehyde followed by dehydrogenation and methylation.[10]



Scheme 1

1.4 Laboratory methods for the synthesis of 2-aryl-4-quinolone derivatives

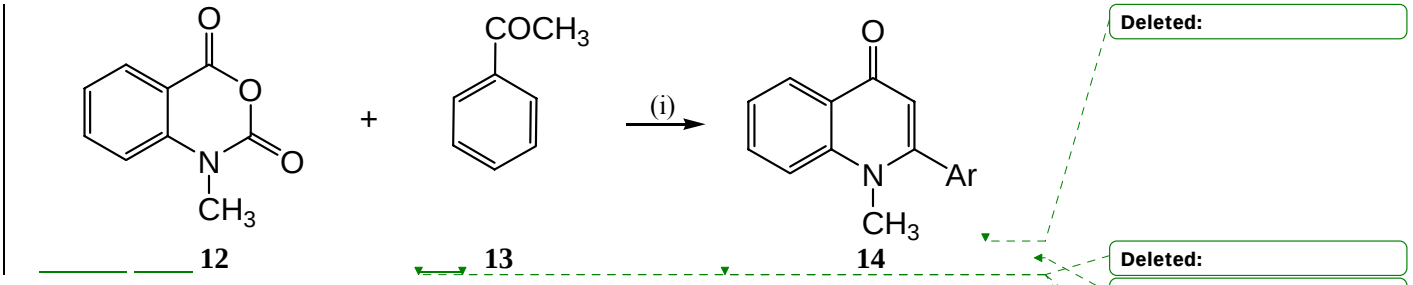
Most of these plant-based compounds are usually isolated in small amounts from large quantities of plant material and this in some cases may lead to extensive harvesting and/ or extinction of some species of plants. Alternative methods are therefore continuously being developed in the laboratory for the synthesis of medicinally important quinolone derivatives and their analogues.

There are several pathways described in literature for the synthesis of 2-aryl-4-quinolone derivatives.[24] Laboratory preparations of 2-aryl-4-quinolinone derivatives

mostly involve the reaction of commercially available reagents, such as aniline[24,25] or aminoacetophenone derivatives[26] with carbonyl compounds.

1.4.1 Classical methods for the synthesis of 2-aryl-4-quinolone derivatives

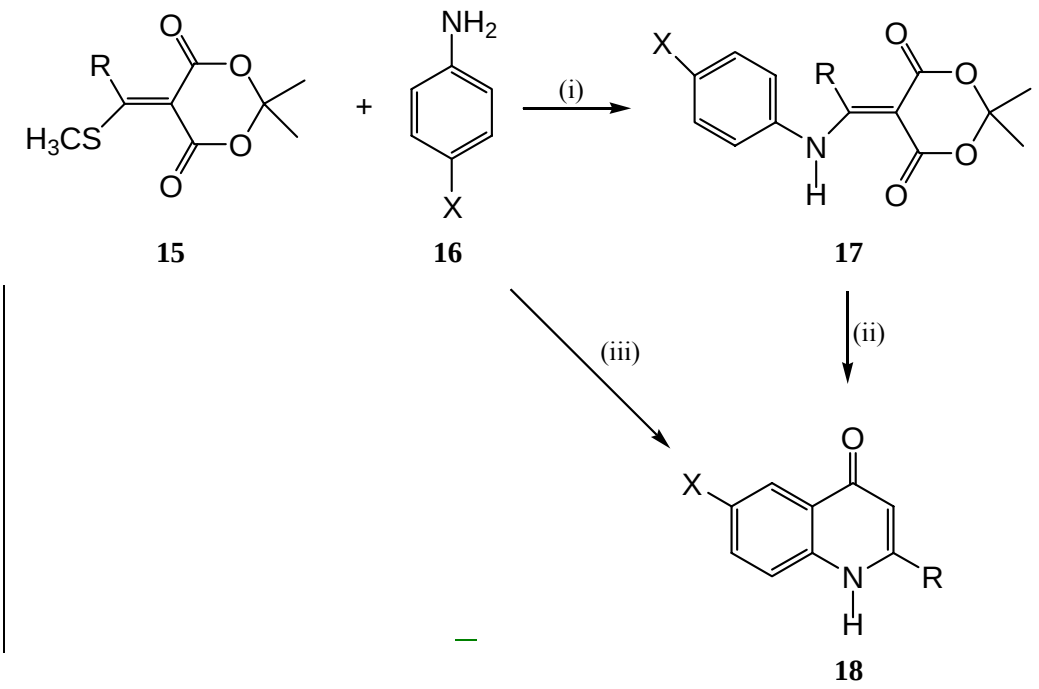
The 1-methyl-2-phenyl-4-quinolone **14** and its derivatives were previously prepared by the reaction of *N*-methylisatoic anhydride **12** with acetophenone **13** (Scheme 2).[14] Although the reaction involves a minimum number of steps, some of the yields are relatively low.



Reagents: (i) DIPA, n-BuLi, THF, -65° C, 2.5 h

Scheme 2

The reaction of 2,2-dimethyl-5-ethoxymethylene-1,3-dioxane-4,6-diones **15** and phenylamines **16** in diphenyl ether, a single step [route (iii)] without isolating the intermediate compound **17** was reported to give 2-alkyl and 2-phenyl-4-quinolones **18** in 81% yield (Scheme 3).[27] The reaction involves relatively short time with high yields of systems **18**, however, the very high temperatures used constitute drawbacks to this pathway.[27]



X = H, CH_3, NO_2, Cl, Br; R = CH_3, Ar

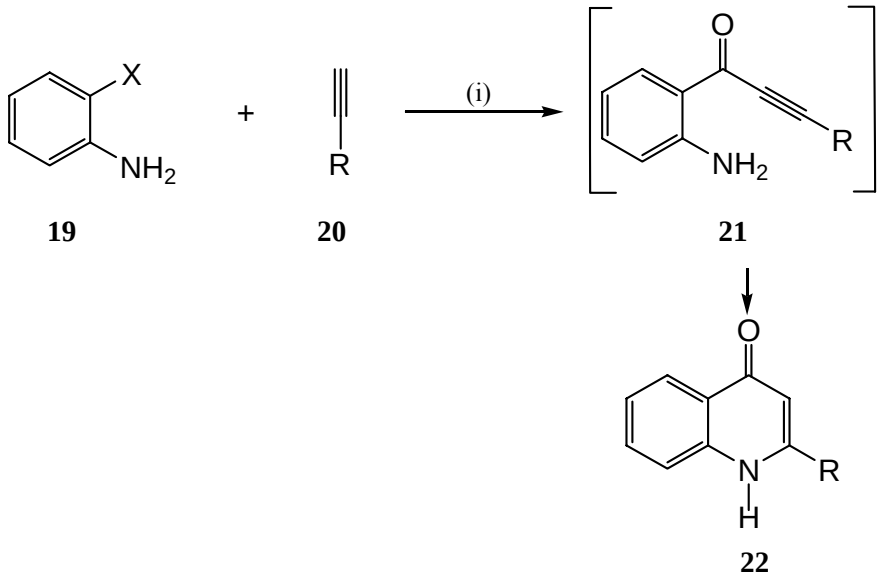
Reagents: (i) $(C_6H_5)_2O$, 140° C, 30 min./ C_2H_5OH, heat, 2-4 h

(ii) $(C_6H_5)_2O$, 250-260° C, N_2(g), 15-20 min

(iii) $(C_6H_5)_2O$, 250-260° C, 50 min.

Scheme 3

The formation of a variety of carbonyl compounds has been investigated using carbon monoxide with catalytic amount of palladium.[28,29] The carbonylative coupling reaction of 2-haloaniline **19** with terminal acetylenes **20** in diethylamine through system **21** is reported to afford products **22** in good yields (Scheme 4). The change of the base and solvent type were found to affect the formation of the desired product while carbonylation in diethylamine with $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf) as a catalyst gave the best results. A decrease in reaction temperature, on the other hand, leads to decrease in the reaction rate.[29]



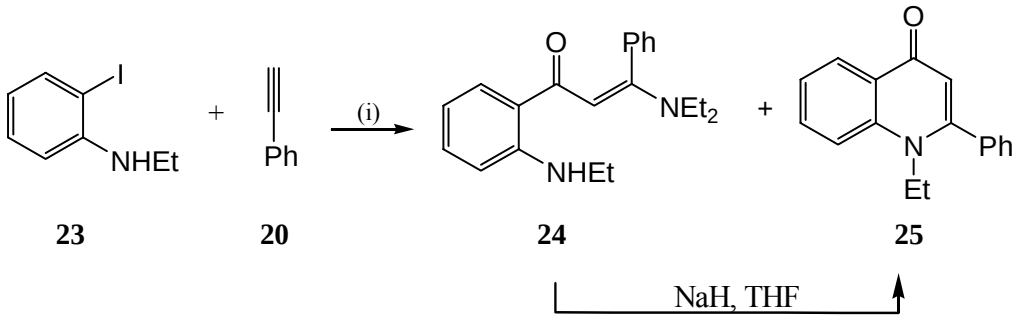
19 **20** **21** **22**

X = I, Br; R = H, Et, Ph, *p*-MeOPh

Reagents: (i) $PdCl_2(PPh_3)_2$, Et_2NH, CO, 120° C, 6 h

Scheme 4

The reaction of alkylated aniline **23** with phenyl acetylene **20** under similar reaction conditions employed for the synthesis of **22** gives a mixture of the corresponding derivative **24** and quinolone **25** in 52% and 20% yield, respectively (Scheme 5).[28] Systems **24** can however be treated with sodium hydride in THF to afford product **25** quantitatively (94%).

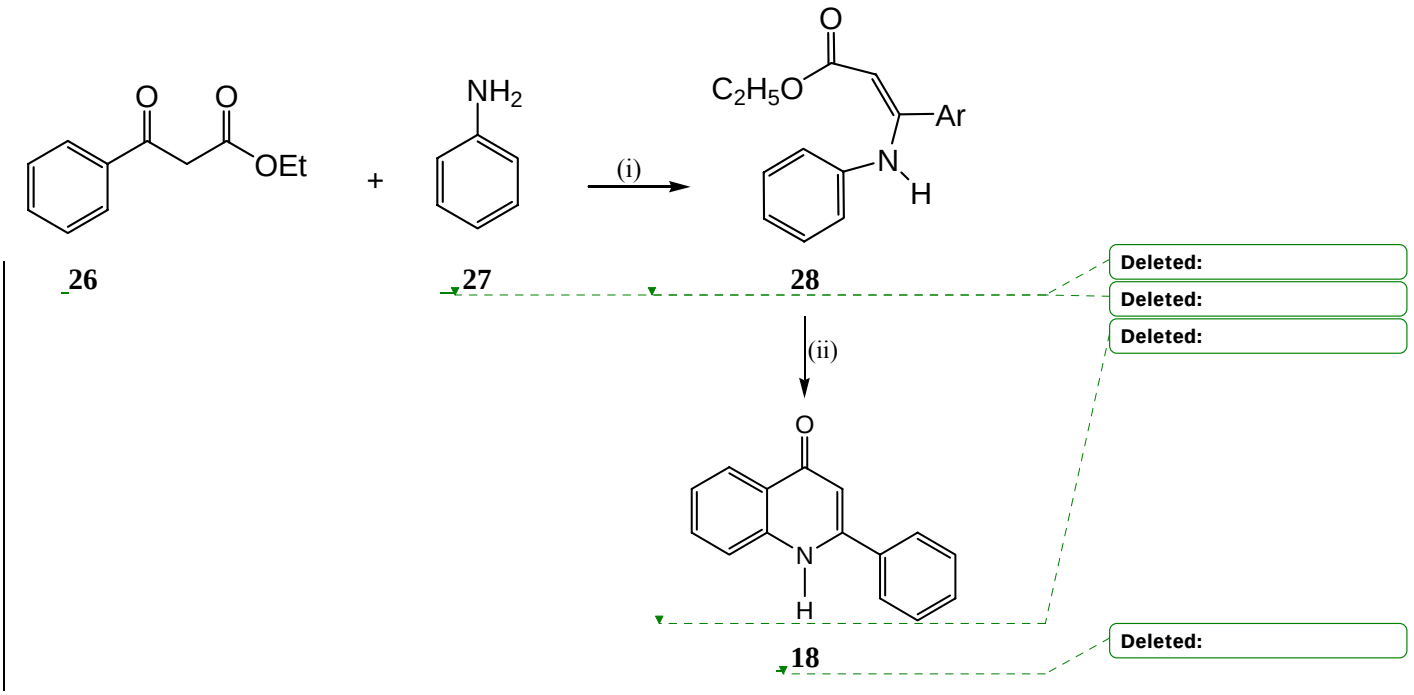


23 **20** **24** **25**

Reagents: (i) $PdCl_2(PPh_3)_2$, Et_2NH, CO,120° C, 6 h

Scheme 5

The 2-phenylquinolin-4(1*H*)-one **18** and its A- and B-ring substituted derivatives are prepared by thermal cyclization of system **28** in diphenyl ether at 240-250° C.[30] Substrate **28** is a product of condensation of benzoylacetate **26** and aniline **27** in ethanol at 50° C (Scheme 6).[30] In addition to the desired target compound **18**, small amounts of the 5-substituted isomers are obtained from the *meta*-substituted aniline derivatives **27** thus resulting in low to moderate yields of the desired product.



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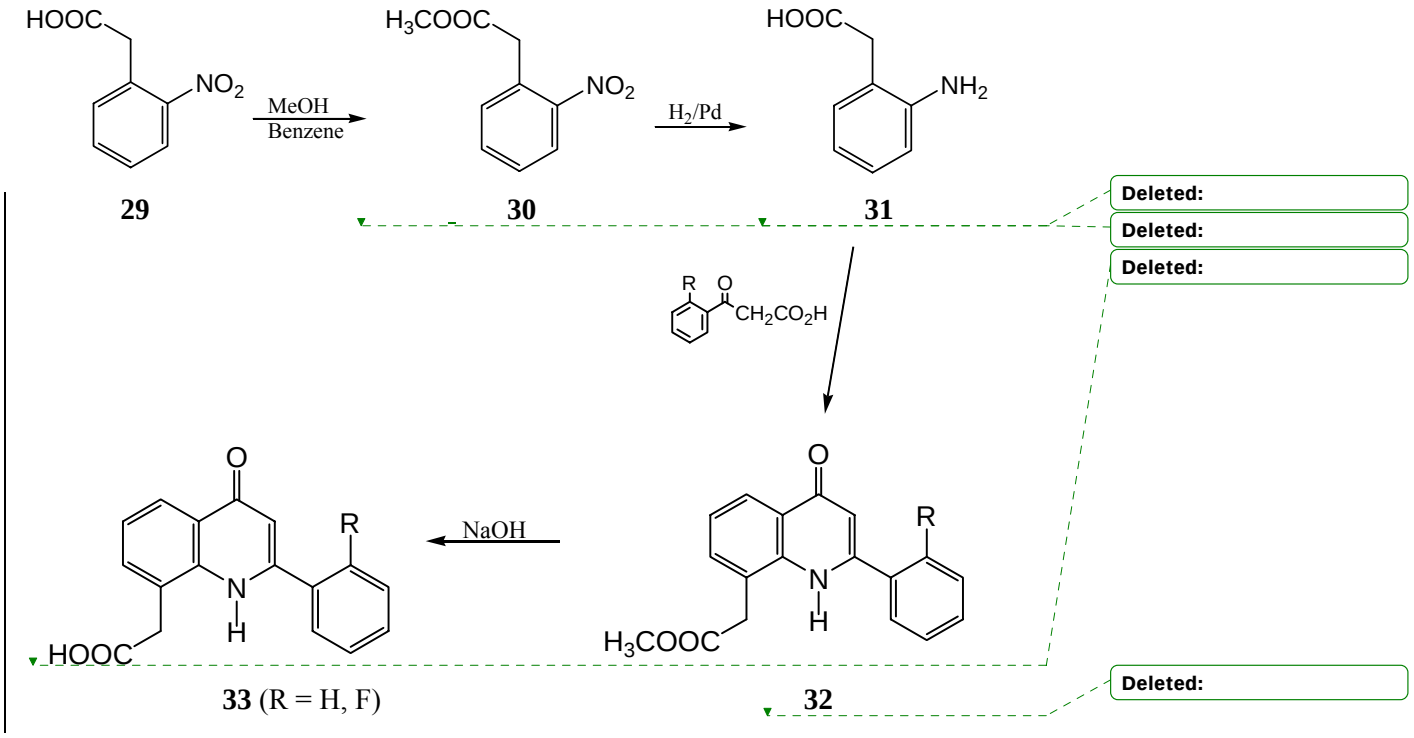
Reagents: (i) AcOH, EtOH, 50° C, 24 h (ii) diphenyl ether, 240° C, then 250° C, 10 min

Scheme 6

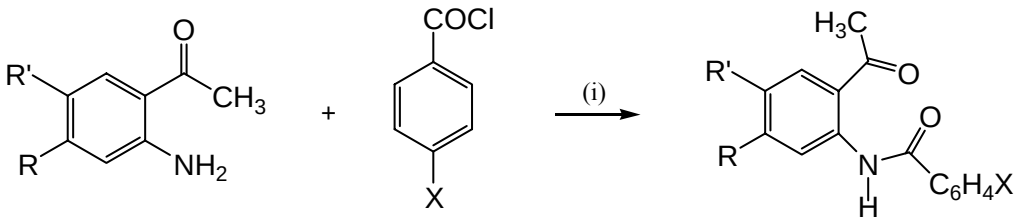
The 2-arylquinolin-4(1*H*)-one derivatives **32** are prepared by acid-catalysed cyclization of 2-(methylacetate)aniline **31** and ethyl benzoylacetate (Scheme 7).[31] The 2-(methylacetate)aniline **31** is, in turn, prepared by the reduction of methyl 2-

nitrophenylacetate **30** as described in literature.[31] The overall yields of the products obtained through this procedure are reasonable (*ca.* 66%), however, the multiple steps and different work-up conditions required for each product constitute drawbacks for this pathway.

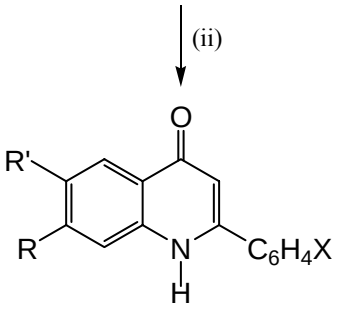


Scheme 7

Systems **18** are easily accessible by cyclization of *N*-benzoyl-2-aminoacetophenone derivatives **36** under basic conditions as described in literature (Scheme 8).[26,32-34] Compounds **36** are, in turn, prepared by condensation of 2-aminoacetophenone **34** and benzoyl chloride derivatives **35** with NEt_3 in THF.[32,33]



34 **35** **36**



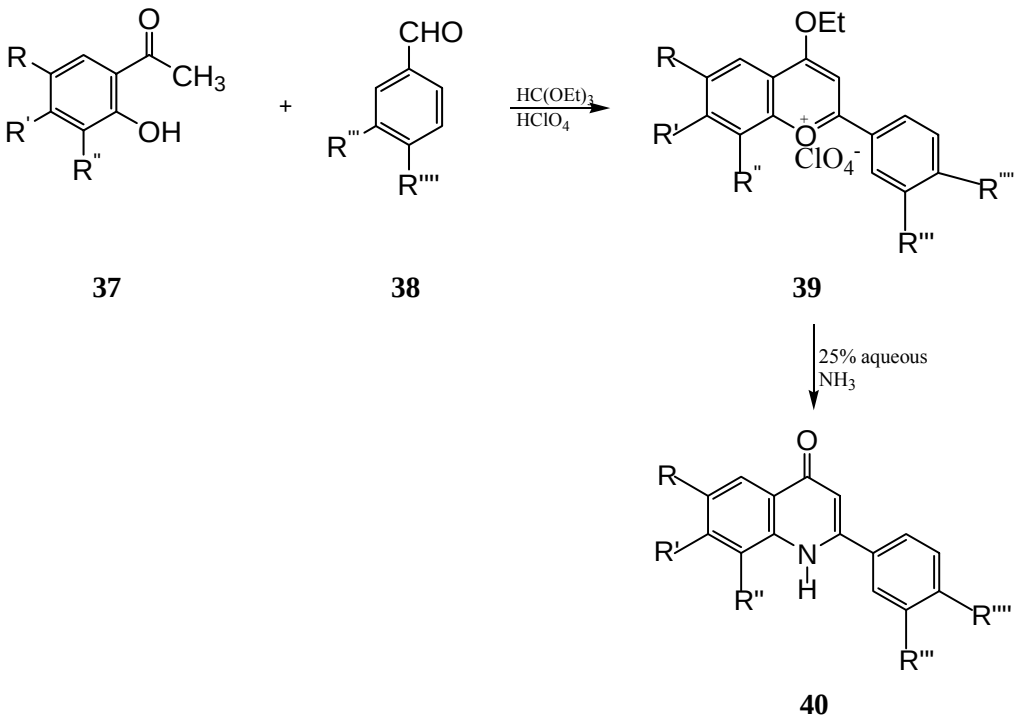
18

R= R' = H, OCH_2O; X = H, F, Cl, OCH_3

Reagents: (i) NEt_3, THF, 0^o C-r.t., 2 h (ii) ^{tert}BuOK, ^{tert}BuOH, heat, 12 h.

Scheme 8

The A- and B-ring substituted quinolone derivatives **40** were recently prepared by the reaction of flavylium salt **39** with aqueous ammonia (Scheme 9).[35-37] Systems **39** are, in turn, prepared by condensing substituted 2-hydroxyacetophenones **37** and benzaldehyde derivatives **38** using potentially explosive perchloric acid.[35] An alternative method that avoids the use of perchloric acid involves the treatment of a mixture of **37** and **38** with trifluoroacetic acid or trifluoromethanesulfonic acid in ethyl orthoformate or dichloromethane to afford flavylium salts **39** in high yield.[37]



37 **38** **39**

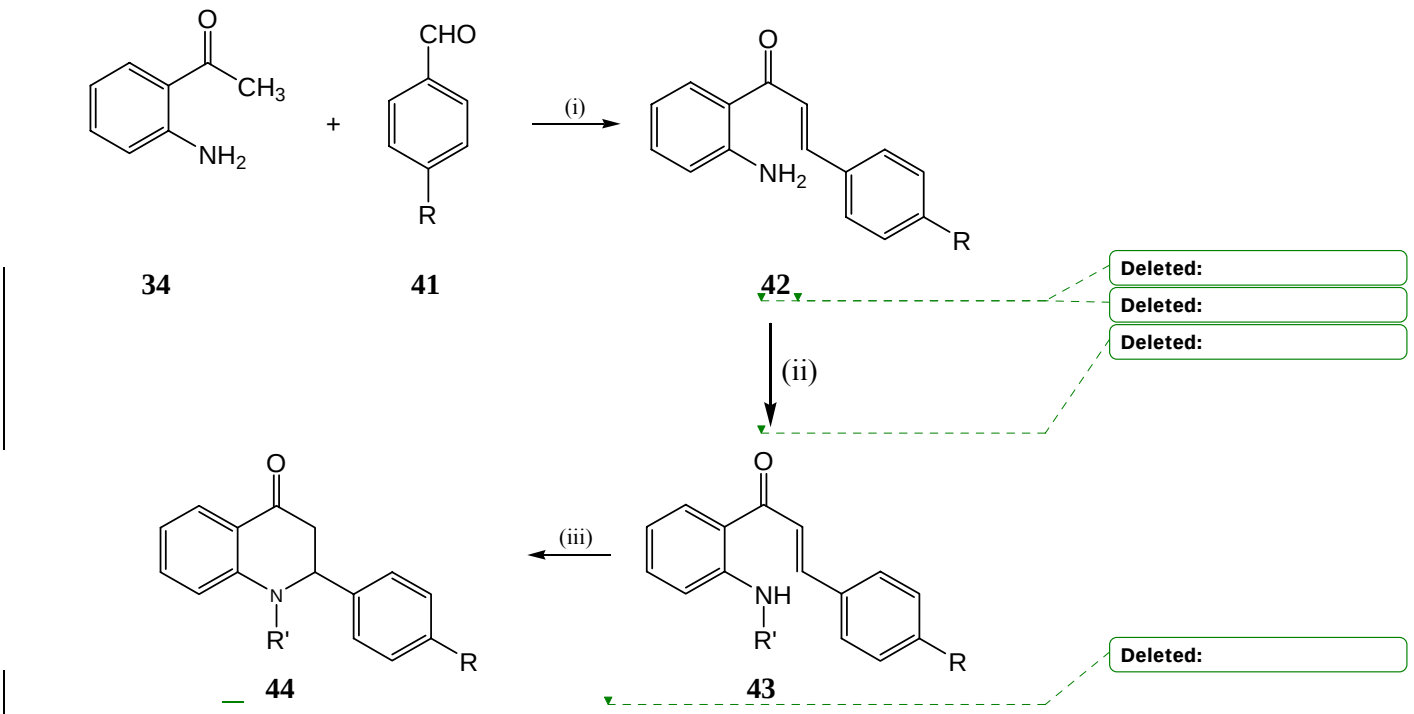
40

R = H, CH_3, t-Bu, $NHCOCF_3$; R' = H, CH_3; R'' = H, $NHCOCF_3$;

R''' = H, OH, OCH_3 and R'''' = H, OH, OCH_3

Scheme 9

The 2-aryl-1,2,3,4-tetrahydro-4-quinolone derivatives **44** (R' = H), which are also precursors for the synthesis of systems **18** through C2-C3 dehydrogenation using $PhI(OAc)_2$-KOH in methanol,[38,39]or TTS in DME,[40] are prepared in high yields by acid-catalyzed cyclization of the corresponding 2-aminochalcones **43** (Scheme 10).[41,42] The 2-aminochalcones **42** are, in turn, prepared by Murphy-Watanism's aldol condensation of 2-aminoacetophenone **34** and benzaldehyde derivatives **41** under basic conditions. The *N*-acetyl (R = Ac)[42] and benzenesulfonyl (R = $PhSO_2$)[41] derivatives are accessible via base-catalyzed cyclisation of corresponding 2-*N*-substituted chalcone derivatives **43**.



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R' = H, Ac, $PhSO_2$; R = H, F, Cl, Br, OCH_3

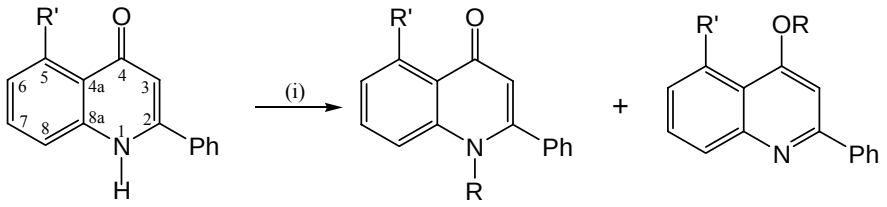
Reagents: (i) NaOH, EtOH, 5° C (ii) Ac_2O, C_5H_5N or $PhSO_2Cl$, C_5H_5N (iii) H_3PO_4, AcOH, heat; Ac_2O, heat; NaOH, EtOH, heat

Scheme 10

Treatment of system **42** with thallium(III) *p*-tolylsulphonate (TTS) in DME[40] or $PhI(OAc)_2$ (IBD), KOH in MeOH[39] under reflux afford 2-phenylquinolin-4(1*H*)-one **18** (X = H, R = Ar, see Scheme 3 on page 6) in high yield. The latter are suitable substrates for the synthesis of *N*-alkylated **2** and *O*-alkylated **3** derivatives.[8,30,43]

1.4.2 Literature methods for the synthesis of isomeric *N*-alkylated quinolones derivatives

A decade ago, the *N*-alkylated derivatives **45** were claimed to be afforded regioselectively by the reaction of systems **18**, NaH and alkyl halide mixture in DMF at room temperature (Scheme 11).[44] However, it has recently been reported that under similar reaction conditions, systems **18** produce mixture of *N*-methylated **45** and *O*-methylated **46** derivatives in the ratio 2:3.[30] Alkylation of systems **18** with ethyl halide or higher alkyl halide afforded the *O*-alkylated derivatives **46** regioselectively.[43] Ethyl group at position 5 of ring **A** (R' = Et) was found to have no effect on the regioselective alkylation of this derivatives[43] whereas the hydroxy and methoxy group have a remarkable effect due to the chelation of the enol isomer (R' = OH, OMe).[8]



18 **45** **46**

R = -CH_3, -Et, -CH_2COOEt, -CH_2COOH; R' = OH, OMe

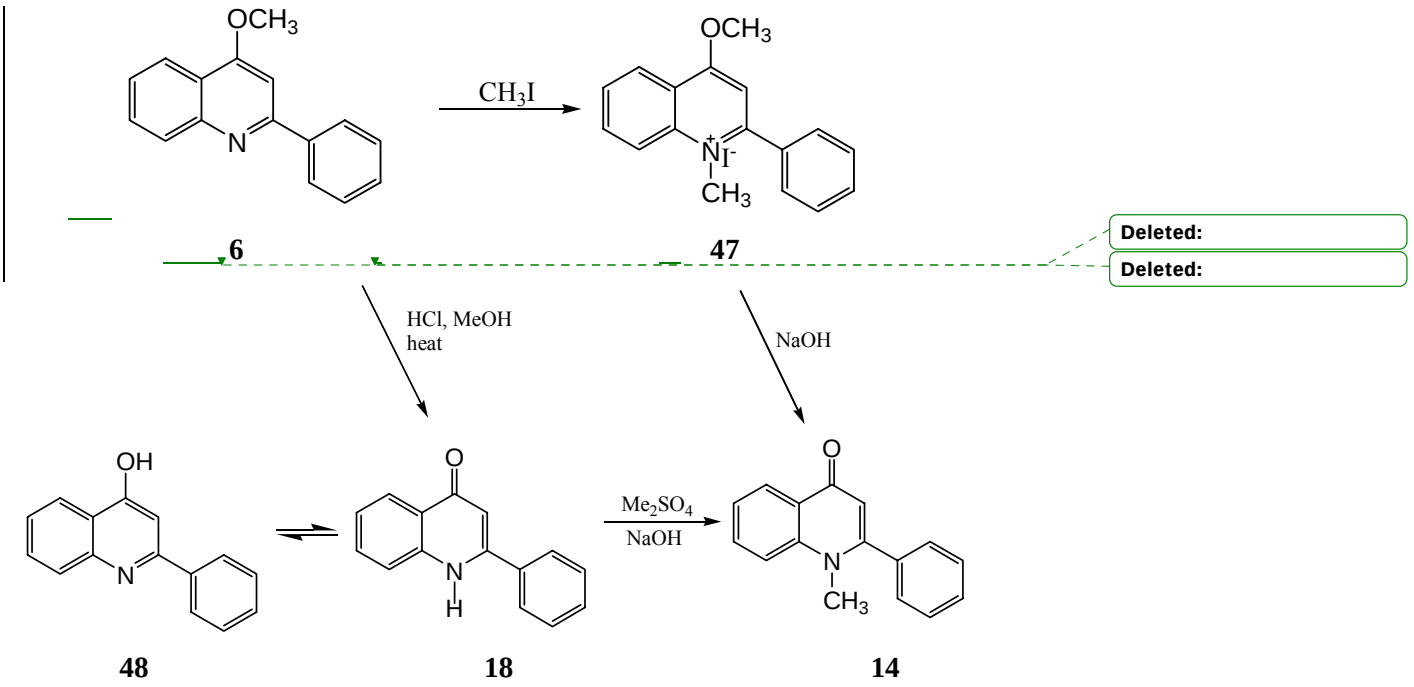
Reagents: (i) NaH, DMF, Alkyl halide or NaH, THF, Alkyl halide

Scheme 11

For the 5-methoxy derivatives (R' = OMe), the 4-alkoxy-2-phenylquinoline **46** is produced as the sole product whereas the hydroxylated quinolone produces a mixture of product **45** and **46** as well as the diakylated product. Potassium carbonate and

dimethylformamide (DMF) mixture was found to give the highest yields but without any significant influence on the regioselectivity of the reaction.

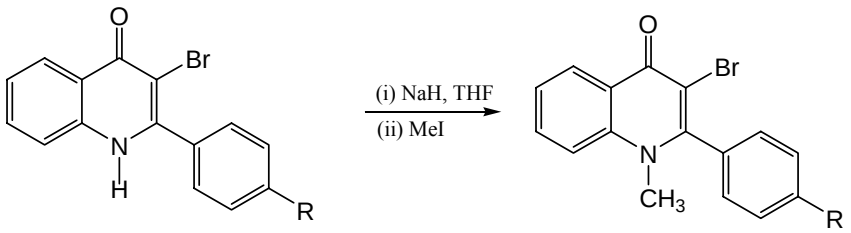
The naturally occurring 4-methoxy-2-phenylquinoline **6** was previously heated with methanol to give **47** which upon treatment with a base afforded the isomeric *N*-methyl derivatives **14** (Scheme 12).[45] On the other hand, treatment of 4-methoxy-2-phenylquinoline **6** with hydrochloric acid in methanol followed by heating at 180° C affords the demethylated potentially tautomeric NH-4-oxo derivative **18**. The latter reacts with dimethyl sulphate in the presence of sodium hydroxide to afford the NCH_3-4-oxo derivative **14**.[45]



Scheme 12

Methylation of 2-aryl-3-bromoquinolin-4(1*H*)-one **49** derivatives using iodomethane and NaH in THF is reported to afford the *N*-methylated derivatives **50** in acceptable

yields (Scheme 13).[46,47] The presence of the bromine at C-3 position of the quinolone favors the formation of the *N*-alkylated derivatives. The *O*-alkylated isomers are not formed presumably due to the steric interaction of the bromine atom at C-3 position of systems **49**.

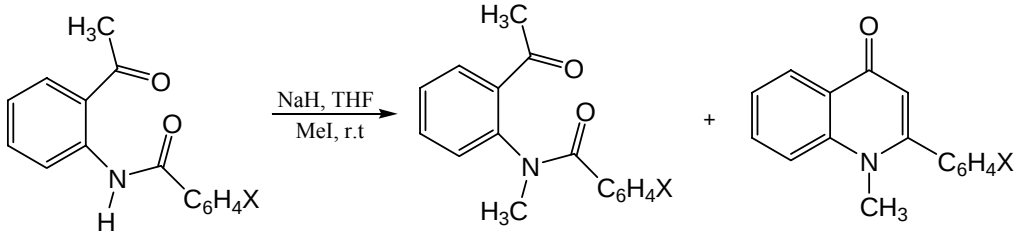


49 **50**

R = H, F, Cl, Br, OMe

Scheme 13

In order to circumvent the problem of formation of a mixture of *N*-methylated **45** (R = Me) and *O*-methylated **46** (R = Me) products shown in Scheme 11 (see page 13), an alternative method was developed in our laboratory before and it makes use of substrates **36**, NaH and MeI in THF to afford systems **51** and the target product **14** in reasonable yields (Scheme 14).[26]



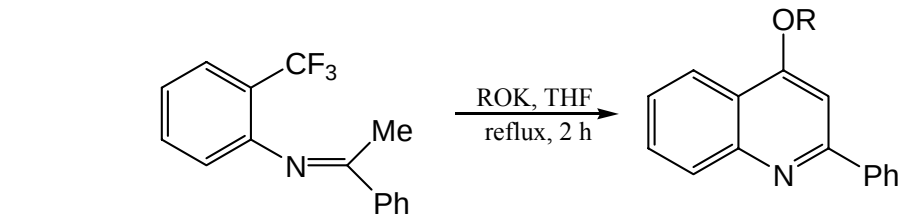
36 **51** **14**

X = H, F, Cl, OCH_3

Scheme 14

1.4.3 Literature methods for the synthesis of isomeric *O*-alkylated derivatives

An alkoxide-mediated cyclization of Schiff base **53** derived from 2-trifluoromethylaniline and alkyl or heterophenyl ketones is reported to afford product **54** exclusively (Scheme15).[48] Treatment of **53** with potassium *tert*-butoxide in THF afforded a cyclized product **54** in high yield.[48,49] Similar treatment of **53** with either sodium or potassium ethoxide afford product **54** (R = Et) in lower yield. The *tert*-butyl derivatives were obtained in high yields through this method, however, the effectiveness of the method is reported to decrease with the decrease in the size of the alkyl groups of the bases.

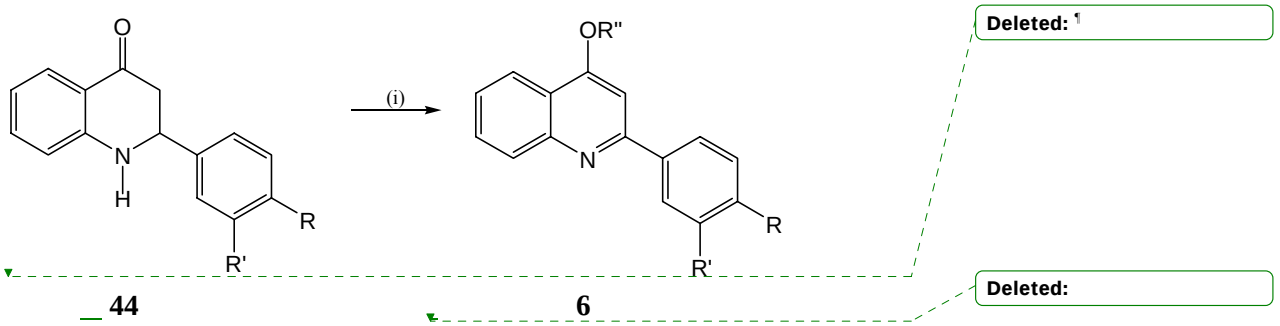


53 **54**

R = t-Bu, Et

Scheme 15

The oxidative aromatization of system **44** using thallium(III) nitrate[50] or hydroxyl(tosyloxy)iodobenzene (HTIB)[9] in trimethyl orthoformate and catalytic amount of perchloric acid ($HClO_4$) afford compounds **6** in high yield (Scheme 16). Previously in our laboratory, systems **44** were treated with iodine in methanol under reflux to afford the corresponding 2-aryl-4-methoxyquinoline derivatives **6** (R" = Me) as sole products (Scheme 16).[10] Recently Kumar and co-workers, have reported the oxidation of system **44** using $FeCl_3.6H_2O$ in methanol to afford the 2-aryl-4-methoxyquinolines **6** exclusively.[51]



44 **6**

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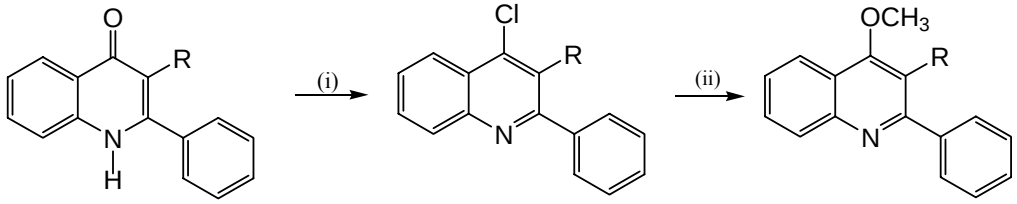
R = H, Me, Cl, OMe; R' = H, -OCH_2O- ; R" = Me, Et

Reagents: (i) HTIB, $CH(OR")_3$, $HClO_4$, 1.5 h[9] or TTN, $CH(OR")_3$, $HClO_4$, 1 h[50]

or I_2, MeOH[10] or $FeCl_3.6H_2O$, MeOH/EtOH[44]

Scheme 16

Compound **56** can be prepared by an alternative method which involves treatment of systems **49** with phosphorus oxychloride to form **55** followed by nucleophilic substitution of chlorine by methoxide ion as shown in scheme 17.[45-47]



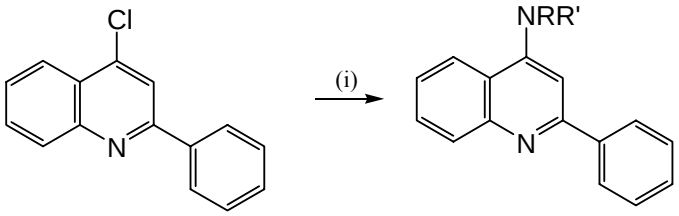
49 **55** **56**

R = H,[45] Br[47]

(i)$POCl_3$, reflux, 12 h (ii) NaOMe, MeOH, reflux

Scheme 17

On the other hand, the reaction of **57** with nitrogen-containing reagents such as aniline ($PhNH_2$) and ammonia derivatives affords systems **58** (Scheme 18).[52-61]



57 **58**

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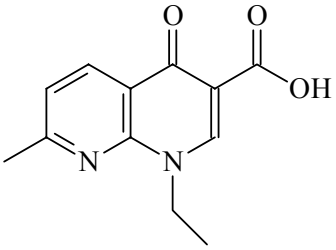
R = H; R' = Ph; R, R' = -$(CH_2)_4$-

Reagents: (i) R'NH_2/ RR'NH, heat.

Scheme 18

1.5 Pharmacological and structural activity relationships of 4-quinolones

The antimicrobial activity of quinolones and quinolines derivatives is well-documented[10,46] and some of the synthetic analogues are in clinical use as antimalarial agents.[10] Over the last years, the interest in 2-arylquinolin-4(1*H*)-ones and related compounds has been the subject of extensive study because of their antiplatelet,[8,25,43] antimitotic,[12,13,31] antibacterial,[8,62] antileishmanial,[8] cytotoxic,[8,13,30,63,64] antifungal[65] and antitumor activities.[66,67] Quinolones form a class of antimicrobial agents that are structurally related to nalidixic acid **59**.[68]



59

The higher antitumor activity of 2-phenylquinolone derivatives is enhanced by change in substituents on the quinolone ring than on the 2-phenyl group and also by the position of the phenyl group.[37] The synthesis of the selectively fluorinated heterocyclic compounds continues to attract a great attention because of the profound effect the introduction of a halogen atom into a heterocyclic ring can have on the physical, chemical and biological properties of such substrates.[65]

Most fluoroquinolones are effective against gram negative organisms such as enterobacteria and pseudomonas organisms.[69] Ciprofloxacin **60** is the most potent of the fluoroquinolones and has a similar antibacterial spectrum to that of norfloxacin **61**. The latter is used for the treatment of pseudomonas infections associated with cystic fibrosis. Norfloxacin **61** is also effective against both gram-negative and gram-positive organisms in the treatment of complicated and uncomplicated urinary tract infections (UTIs) and prostatitis, but not systematic infections.[69] Fleroxacin **62** is used as skin tumor antibiotic whereas nalidixic acid **59** is used as antibacterial agent for urinary tract infections.[69]

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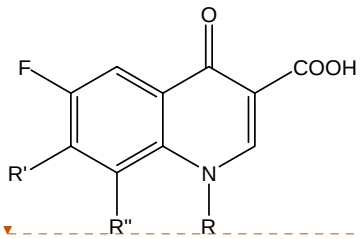

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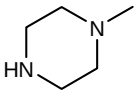
R' = 

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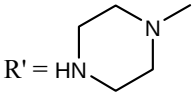
60

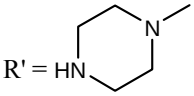
R = $-CH_2CH_3$

R' = 

R" = H

61

R = $-CH_2CH_2$-F

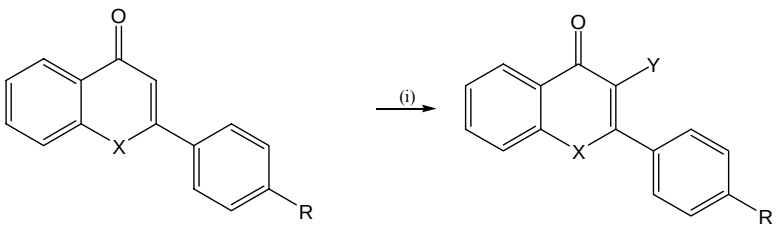
R' = 

R" = F

62

1.6 Previous work related to this investigation

Most of the halogenated heterocyclic compounds can be easily transformed into other derivatives.[70] Rho and co-workers have previously reported the synthesis of 3-bromoflavone derivatives **64** (X = O) in quantitative yields using $Bu_4NBr/PhI(OAc)_2$ in dichloromethane at room temperature for 8-10 h.[70] Bromination of thiochromones **63** (X = S) using H_2O_2, hν and Br_2 in $CHCl_3$, on the other hand, afford the 3-bromo-2-phenylthiochromone-1,1-dioxides **64** (X = SO_2, Y = Br) in relatively low yield (*ca.* 43%).[71] The 3-bromoflavone **64** (X = O, Y = Br) and 3-iodoflavone **64** (X = O, Y = I) are produced in excellent yields by treatment of system **63** with NBS in $CHCl_3$ and iodine with bis(trifluoroacetoxyiodo)benzene (BTI), respectively (Scheme 19).[72-73] Chlorination of system **63** (X = O, S; Y = Cl)[74] and iodination of system **63** (X = S, Y = I)[75] have been reported before.



63 **64**

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X = O, S, SO_2; Y = Br, I

R = H, CH_3, Cl, Br, OCH_3, SCH_3, SO_2CH_3

Reagents: (i) $Bu_4NBr/PhI(OAc)_2/CH_2Cl_2$;[70] H_2O_2, *hv*, $Br_2/CHCl_3$;[71] NBS, $CHCl_3$ and I_2, BTI;[72] PHPB, C_4H_4N/CH_2Cl_2, rt.[73]

Scheme 19

Although the heterocyclic ketones **14**, **18** and **63** share common structural features, to our knowledge, direct C-3 halogenation of the NCH_3-4-oxo **14** and NH-4-oxo **18** have not been reported before. This prompted us to investigate the possible method for the direct bromination and iodination of systems **14** and **18** to produce compounds that can be further transformed into other derivatives.

Systems **64** (X = NH/ NCH_3, Y = I or Br) can serve as substrates for a carbon-carbon bond formation following Suzuki cross-coupling reactions which is mostly applied for the synthesis of biphenyls.[76,77]

1.7 Aims and Objectives

Although the C-3 brominated compounds **49** and **50** are known, the direct C-3 bromination of systems **14** and **18** have not been reported before. This prompted us to investigate the possibility of direct C-3 bromination and iodination of compounds **14** and **18.**

The aims and objectives of the project are

- To effect regioselective C-3 bromination and iodination of the 2-arylquinolin-(1*H*)-ones and their NCH_3-4-oxo derivatives.
- To subject the C-3 halogenated NH-4-oxo and NCH_3-4-oxo derivatives to Suzuki coupling reactions.
- To undertake transformation of the C-3 brominated NH-4-oxo derivatives to 4-*N*-(4-chlorophenyl)quinoline derivatives.
- To characterize the resulting products using spectroscopic techniques (NMR, FT-IR and mass spectroscopy) and elemental analysis.

CHAPTER TWO

RESULTS AND DISCUSSION

The *N*-(2-acetylaryl)benzamides **36** were prepared from 2-aminoacetophenone **34** and benzoyl chloride derivatives **35**. Systems **36** were converted to 2-arylquinolin-4(1*H*)-one derivatives **18** using t-BuOK in t-BuOH. Compounds **36** were subjected to NaH in THF followed by quenching with methyl iodide to afford mixture of *N*-benzoyl-*N*-methyl-2-aminoacetophenones **51** and 2-aryl-1-methyl-4-quinolones **14**. Regioselective C-3 bromination was achieved by the treatment of products **14** and **18** with pyridinium tribromide in acetic acid at room temperature to afford products **49** and **50**, respectively. The reaction of systems **18** with sodium carbonate and iodine in THF gave the corresponding 2-aryl-3-iodoquinolin-4(1*H*)-one derivatives **65**. The latter were, in turn, subjected to NaH in THF followed by quenching with methyl iodide to afford the 2-aryl-3-iodo-1-methyl-4-quinolones **66**.

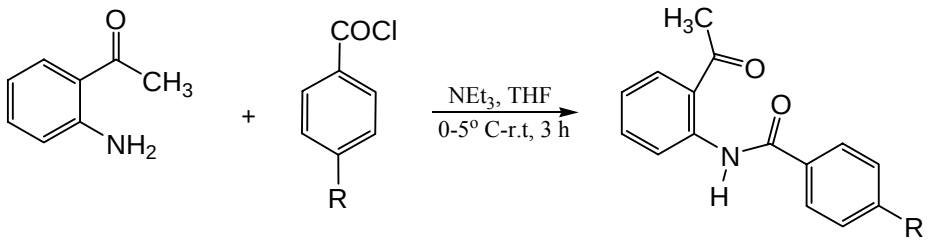
The 2-aryl-3-iodoquinolin-4(1*H*)-one derivatives **65** and **66** were coupled with phenyl boric acid to yield the 2,3-diarylquinolin-4(1*H*)-one derivatives. Chlorination of systems **49** using phosphorus oxychloride under reflux afforded the 2-aryl-3-bromo-4-chloroquinoline derivatives **55** which served as substrates for the synthesis of 4-aminoquinoline derivatives **69**.

The products were characterised using a combination of ^{1}H NMR, ^{13}C NMR, IR, mass spectroscopic techniques and elemental analysis.

2.1 Synthesis of substrates

2.1.1 Synthesis of *N*-benzoyl-2-aminoacetophenones 36

The *N*-(2-acetylaryl)benzamides **36** were prepared by condensing 2-aminoacetophenone **34** with benzoyl chloride derivatives **35** in tetrahydrofuran following literature methods (Scheme 20).[26,33] The ^{1}H NMR spectra of systems **36** (Figure 1, page 28) are characterised by the presence of intense singlet at δ *ca*. 2.67 ppm corresponding to the methyl group, a group of aromatic proton signals in the region δ 7.08-8.97 ppm and the amide proton signal at δ *ca.* 12.7 ppm. The ^{13}C NMR spectra of products **36** are characterised by the presence of two carbonyl signals at δ *ca*. 166.3 ppm (C=O) and 203.5 (C=O, Table 1). The dicarbonyl nature of compounds **36** is further confirmed by the presence of two C=O absorption stretches at ν_{max} *ca*. 1643.3 and 1673.9 cm^{-1} and a broad absorption band at ν_{max} *ca*. 3221 cm^{-1} which corresponds to the NH group in their IR spectra.



34 **35** **36**

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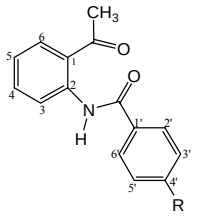
36	R	% yield	m.p. °C (lit.[ref])
a	H	97	96 – 98 (95-96)[78]
b	F	94	99 – 101(92 – 95)[79]
c	Cl	97	113 – 115 (106 – 108)[79]
d	OMe	88	121 – 123 (125-127)[78]

Scheme 20

Table 1: ^{13}C NMR chemical shift values (ppm) of systems **36** in $CHCl_3$ (at 75 MHz)

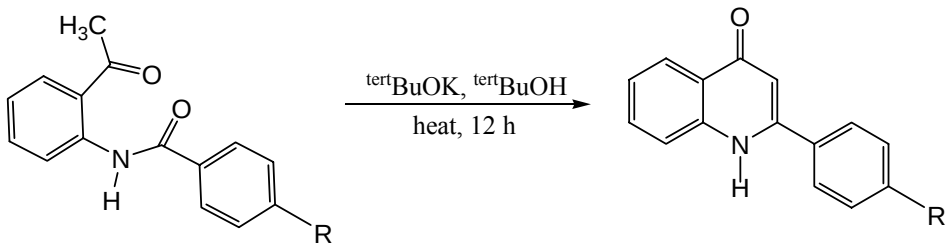


36

nucleus	**36a (R = H)**	**36b (R = F)**	**36c (R = Cl)**	**36d (R = OMe)**
CH_3	28.8	28.4	28.5	28.5
OCH_3	-	-	-	55.3
C-1	122.1	121.7	121.7	126.9
C-2	141.6	141.2	141.1	141.5
C-3	120.9	120.5	120.6	120.5
C-4	122.7	122.4	122.6	122.0
C-5	132.1	131.8	131.8	131.7
C-6	132.2	135.3	135.3	135.2
C-1'	135.0	130.8 (d, $^4J_{CF}$ 3.0 Hz)	133.0	132.7
C-2',6'	127.7	129.8 (d, $^3J_{CF}$ 9.2 Hz)	128.9	129.3
C-3',5'	135.6	115.8 (d, $^2J_{CF}$ 21.8 Hz)	128.8	113.8
C-4'	135.6	166.6 (d, $^1J_{CF}$ 251.2 Hz)	138.2	162.5
NC=O	166.3	164.7	164.7	165.5
C=O	203.5	203.3	203.3	203.1

2.1.2 Synthesis of 2-arylquinolin-4(1*H*)-ones 18

The *N*-(2-acetylaryl)benzamides **36** were cyclized with t-BuOK in t-BuOH to afford the 2-arylquinolin-4(1*H*)-ones **18** in high yield following the literature method (Scheme 21).[26,33,34] The ^{1}H NMR spectra of compounds **18** (Figure 2, page 28) are characterised by a singlet at δ *ca.* 6.35 ppm which corresponds to the olefinic proton (3-H), aromatic proton signals in the region δ *ca.* 7.32-8.11 ppm and the imine proton signal at δ *ca.* 11.8 ppm. The signal corresponding to 5-H proton is shifted downfield to δ *ca.* 8.08-8.11 ppm due to the deshielding effect of the carbonyl group in the *peri*-position.[80] The presence of a group of resonances in the aromatic region and the carbonyl group signal at δ *ca.* 177.5 ppm (C=O) in their ^{13}C NMR spectra further confirm the structures of the products **18** (Table 2). The IR spectra of products **18** are characterized by the absorption band at ν_{max} *ca.* 1631.3 cm^{-1} corresponding to the C=O and a broad absorption band at ν_{max} *ca*. 3240.2 cm^{-1} corresponding to amine group (NH). The observed melting points of systems **18c** and **18d** differ from those reported in literature,[26] however, the NMR and FT-IR spectroscopic data are consistent with the assigned structures.



36 **18**

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18	R	% yield	m.p. °C (lit.[ref])
a	H	61	252 – 254 (252 – 254[30])
b	F	80	315 – 317 (322 – 325[26])
c	Cl	77	332 – 334 (270 – 273[26])
d	OMe	75	306 – 308 (290 – 293[26])

Scheme 21

Table 2: ^{13}C NMR chemical shift values (ppm) of systems **18** in DMSO-d_6 (at 75 MHz)

nucleus	**18a (R = H)**	**18b (R = F)**	**18c (R = Cl)**	**18d (R = OMe)**
OCH_3	-	-	-	55.4
C-2	149.2	149.3	149.2	149.7
C-3	107.6	107.7	107.6	106.5
C-4	177.7	177.3	177.6	177.3
C-4a	119.5	122.0	124.3	122.8
C-5	125.2	125.1	125.0	125.2
C-6	124.0	123.7	123.8	123.9
C-7	129.9	132.2	132.2	132.1
C-8	118.5	119.1	119.5	118.4
C-8a	139.1	140.1	141.2	139.0
C-1'	135.5	131.0 (d, $^4J_{CF}$ 3.1 Hz)	133.5	127.1
C-2',6'	129.0	131.6 (d, $^3J_{CF}$ 8.7 Hz)	129.6	130.7
C-3',5'	128.4	116.4 (d, $^2J_{CF}$ 21.6 Hz)	129.4	113.7
C-4'	132.2	163.8 (d, $^1J_{CF}$ 246.5 Hz)	135.6	160.4

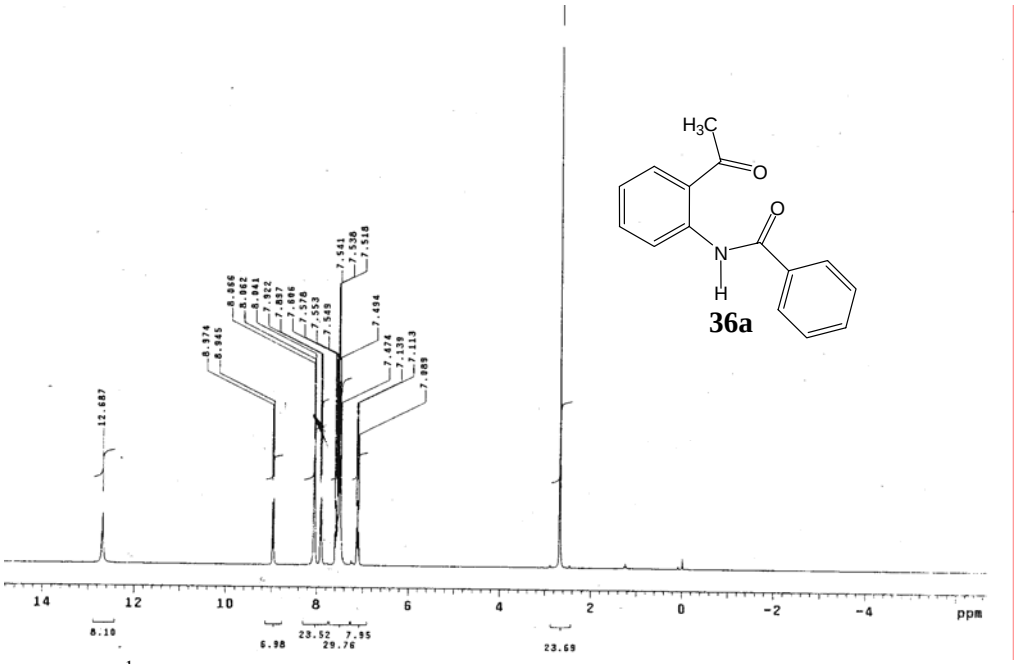


Figure 1: ^{1}H NMR spectrum of *N*-benzoyl-2-aminoacetophenone **36a** in $CDCl_3$

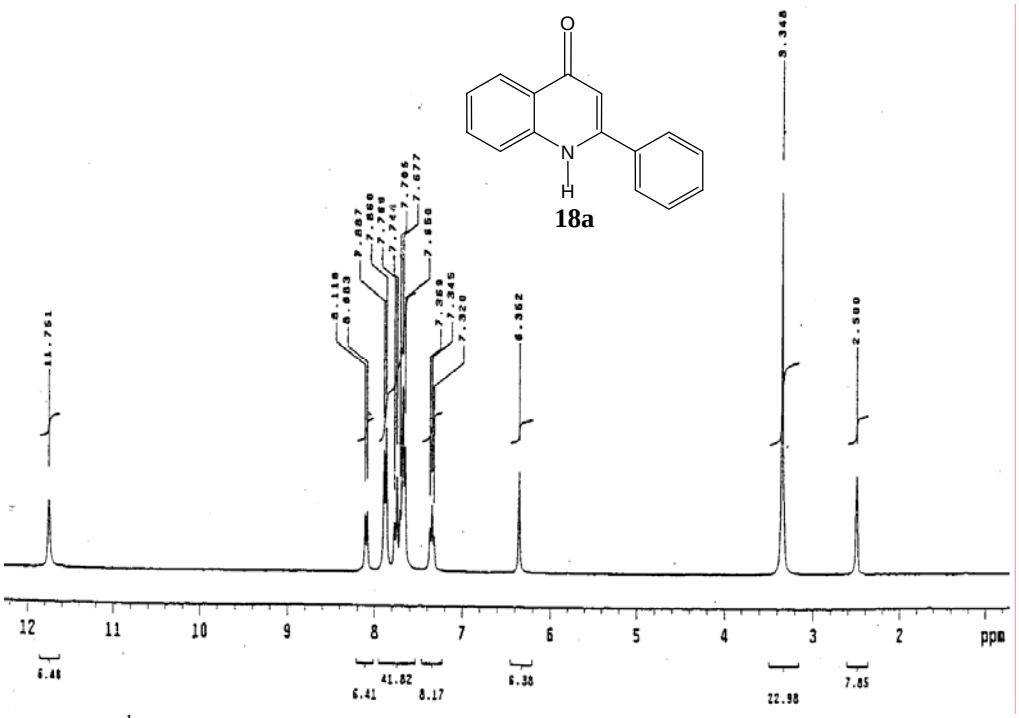
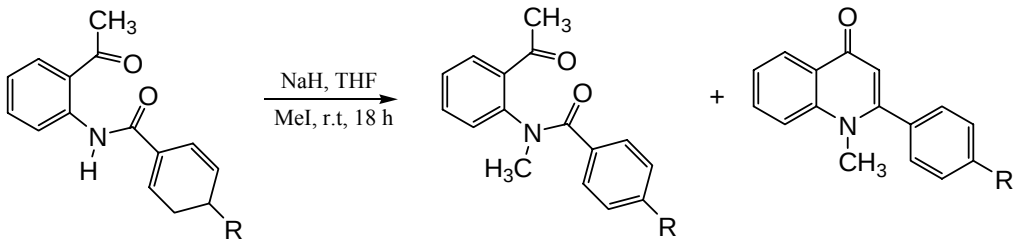


Figure 2: ^{1}H NMR spectrum of 2-phenylquinolin-4(1*H*)-one **18a** in DMSO-d_6

2.1.3 Synthesis of *N*-benzoyl-*N*-methyl-2-aminoacetophenone 51 and 2-aryl-1-methyl-4-quinolones 14

Systems **36** were converted to the *N*-benzoyl-*N*-methyl-2-aminoacetophenones **51** and 1-methyl-2-phenyl-4-quinolones **14** (Scheme 22) following the procedure previously developed in our laboratory.[26] Other methods reported previously for the synthesis of systems **14** either involve multiple steps with reduced overall yields[14] or produce mixtures of *O*-methylated and *N*-methylated derivatives that are difficult to separate by conventional column chromatographic techniques.[26,30,43] The ^{1}H NMR spectra of compounds **51** are characterized by the presence of two sets of methyl signals at δ *ca*. 1.84 ppm ($COCH_3$) and δ *ca*. 3.45 ppm (NCH_3) and a group of signals in the aromatic region (Figure 3, page 32). On the other hand, the ^{1}H NMR spectra of compounds **14** reveal the presence of the *N*-methyl signal at δ *ca.* 3.44 ppm, the vinylic proton (3-H) signal at δ *ca.* 6.51 ppm and the aromatic proton signals at δ *ca.* 7.25-8.48 ppm (Figure 4, page 32). The ^{13}C NMR spectra of compounds **51** are characterized by two sets of methyl signals at δ *ca*. 13.3 ppm ($COCH_3$) and δ *ca.* 37.2 ppm (NCH_3), a group of resonances in the aromatic region and the carbonyl carbon signals at δ *ca*. 151.0 ppm and δ *ca*. 177.4 ppm (Table 3). The ^{13}C NMR spectra of the cyclized derivatives **14** are characterized by the *N*-methyl signals at δ *ca*. 37.6 ppm, signals corresponding to aromatic carbons and the carbonyl carbon at δ *ca*. 177.6 ppm (Table 4). A sharp IR absorption band at ν_{max} *ca*. 1614.4 cm^{-1} corresponding to the carbonyl carbons confirm the structures of the products **14**.



36 **51** **14**

		51		**14**	
R		% yield	m.p. ° C (lit.[ref])	% yield	m.p. ° C (lit.[ref])
a	H	4	129 – 131 (63-65[79])	52	147 – 149 (143 – 145[26])
b	F	6	161 – 163 (168 – 170[26])	54	190 – 192 (178 – 180[26])
c	Cl	5	167 – 169 (108 – 111[26])	61	177 – 179 (174 – 178[26])
d	OMe	8	181 – 183 (179 – 182[26])	51	148 – 150 (144 – 146[26])

Scheme 22

Table 3: ^{13}C NMR chemical shift values (ppm) of systems **51** in $CHCl_3$ (at 75 MHz)

nucleus	**51a (R = H)**	**51b (R = F)**	**51c (R = Cl)**	**51d (R = OMe)**
CH_3	37.2	37.2	37.2	37.1
NCH_3	13.4	13.2	13.4	13.4
OCH_3	-	-	-	55.2
C-1	141.8	140.6	140.8	140.8
C-2	118.0	125.0	124.8	124.9
C-3	115.4	115.4	115.4	115.5
C-4	131.7	123.1	131.9	122.8
C-5	126.8	126.9	123.1	126.7
C-6	129.0	131.9	126.8	131.6
C-1'	125.0	131.6 (d, $^4J_{CF}$ 3.1 Hz)	118.1	118.3
C-2',6'	128.3	130.4 (d, $^3J_{CF}$ 7.9 Hz)	129.9	129.7
C-3',5'	129.1	116.4 (d, $^2J_{CF}$ 21.8 Hz)	129.5	114.4
C-4'	123.0	162.8 (d, $^1J_{CF}$ 241.9 Hz)	133.9	151
NC=O	140.0	149.9	149.8	159.8
C=O	177.4	177.3	177.3	177.3

Table 4: ^{13}C NMR chemical shift values (ppm) of systems **14** in $CHCl_3$ (at 75 MHz)

nucleus	**14a (R = H)**	**14b (R = F)**	**14c (R = Cl)**	**14d (R = OMe)**
NCH_3	37.2	37.2	37.2	37.2
OCH_3	-	-	-	55.3
C-2	154.6	153.6	153.3	154.6
C-3	112.6	112.8	112.6	112.6
C-4	177.5	177.5	177.7	177.5
C-4a	126.6	141.8	134.1	126.7
C-5	123.5	123.7	123.7	123.4
C-6	129.5	126.6	126.5	126.5
C-7	132.2	132.4	132.4	132.1
C-8	115.9	115.9	115.0	115.1
C-8a	141.8	141.8	141.8	141.8
C-1'	135.7	131.9 (d, $^4J_{CF}$ 3.8 Hz)	135.8	128
C-2',6'	128.4	130.5 (d, $^3J_{CF}$ 8.2 Hz)	129.9	129.9
C-3',5'	128.7	116.0 (d, $^2J_{CF}$ 21.8 Hz)	129.9	114.1
C-4'	126.6	163.3 (d, $^1J_{CF}$ 249.1 Hz)	160.4	160.4

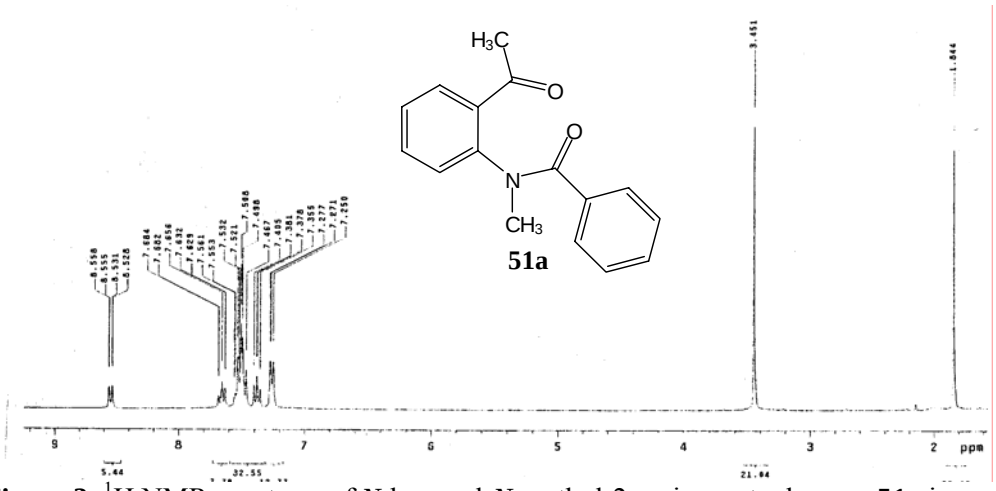


Figure 3: ^{1}H NMR spectrum of *N*-benzoyl-*N*-methyl-2-aminoacetophenone **51a** in $CDCl_3$

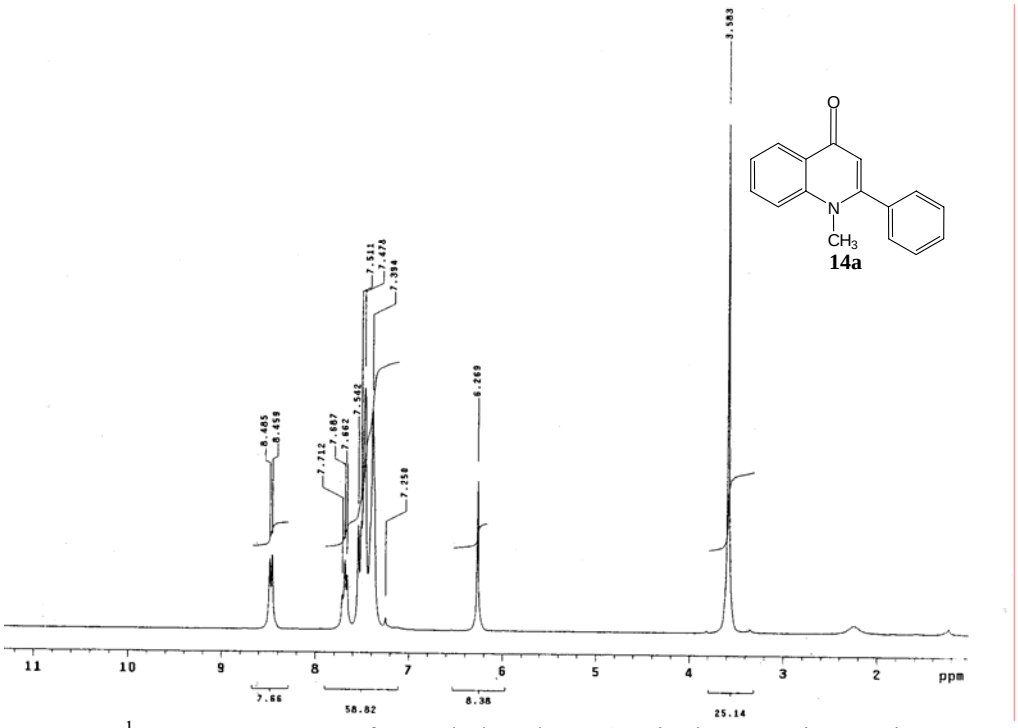
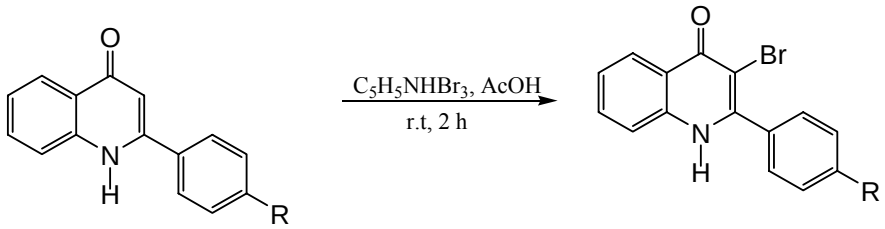


Figure 4: ^{1}H NMR spectrum of 1-methyl-2-pheny-4-quinolone **14a** in $CDCl_3$

2.2 C-3 Bromination of 2-arylquinolin-4(1*H*)-ones 18

Compounds **18** were subjected to pyridinium tribromide (2 equiv.) in glacial acetic acid at room temperature to afford the 2-aryl-3-bromoquinolin-4(1*H*)-ones **49** in high yields and purity (Scheme 23). The ^{1}H NMR spectra of systems **49** (Figure 5) are characterized by the absence of olefinic proton (3-H) signal at δ *ca*. 6.35 ppm present in the spectra of the precursors, the presence of aromatic proton signals in the region δ *ca*. 7.38-8.17 ppm and a strongly hydrogen-bonded imine proton signal at δ *ca*. 12.3 ppm. The presence of a group of resonances in the aromatic region and carbonyl group signal at δ *ca.* 171.6 ppm (C=O) in the ^{13}C NMR spectra of products **49** further confirm the assigned structures (Table 5). The sharp IR absorption band at ν_{max} *ca*. 1626.5 cm^{-1} corresponding to carbonyl group (C=O) and a broad IR absorption band at ν_{max} *ca*. 3259.3 cm^{-1} corresponding to and NH confirm the NH-4-oxo nature of products **49**. Although the melting points of compounds **49** differ from the literature values,[46] the NMR spectroscopic data are consistent with the assigned structures.



18 **49**

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50	R	% yield	m.p.° C (lit.[ref])
a	H	94	219 – 221 (292 – 294[46])
b	F	95	231 – 233 (267 – 269[46])
c	Cl	91	233 – 235 (270 – 272[46])
d	OMe	90	206 – 208 (267 – 269[46])

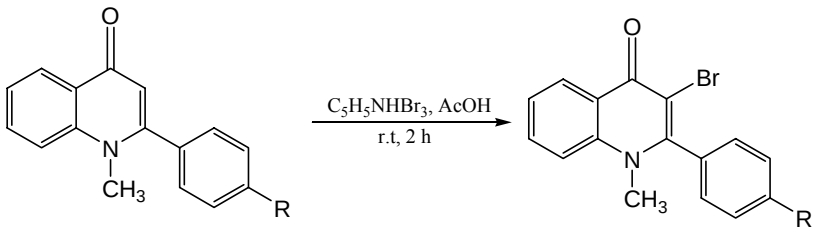
Scheme 23

Table 5: ^{13}C NMR chemical shift values (ppm) of systems **49** in DMSO-d_6 (at 75 MHz)

nucleus	**49a (R = H)**	**49b (R = F)**	**49c (R = Cl)**	**49d (R = OMe)**
OCH_3	-	-	-	55.4
C-2	149.2	148.9	148.7	149.7
C-3	105.3	105.5	105.4	105.4
C-4	171.7	171.7	171.6	171.7
C-4a	122.9	112.9	122.9	122.8
C-5	125.2	125.3	125.2	125.2
C-6	124.0	124.1	124.1	123.9
C-7	129.9	132.2	132.2	132.1
C-8	118.5	118.5	118.5	118.4
C-8a	139.1	138.9	138.9	139.0
C-1'	135.5	131.4 (d, $^4J_{CF}$ 3.0 Hz)	134.8	127.1
C-2',6'	129.0	131.6 (d, $^3J_{CF}$ 8.8 Hz)	131.1	130.7
C-3',5'	128.4	115.4 (d, $^2J_{CF}$ 21.0 Hz)	128.5	113.7
C-4'	132.2	162.8 (d, $^1J_{CF}$ 246.7 Hz)	133.7	160.4

2.3 C-3 Bromination of 2-aryl-1-methyl-4-quinolones 14

Systems **14** were treated with two equivalents of pyridinium tribromide at room temperature to produce the 2-aryl-3-bromo-1-methyl-4-quinolones **50** in high yields (Scheme 24). Treatment of 2-aryl-3-bromoquinolin-4(1*H*)-ones **49** with NaH in dry THF, followed by quenching with MeI at room temperature is reported to afford systems **50** in moderate yields.[46,47] The ^{1}H NMR spectra of compounds **50** (Figure 6) are characterized by the presence of the *N*-methyl signal at δ *ca*. 3.52 ppm, the absence of the vinylic proton signal (3-H) confirming the incorporation of bromine, and the aromatic proton signals at δ *ca* 7.29-8.51 ppm. Their ^{13}C NMR spectra are characterized by the *N*-methyl signal at δ *ca*. 37.6 ppm, signals corresponding to aromatic carbons in the region δ *ca*. 115.8-161.4 ppm, the presence of the C-3 signal at δ *ca.* 107.5 ppm and the carbonyl carbon signal at δ *ca.* 171.5 ppm (Table 6). The sharp IR absorption band at ν_{max} *ca*. 1618.7 cm^{-1} confirms the presence of the carbonyl group (C=O) in compounds **50**. Even though the melting points of compounds **50** differ somewhat from the literature values, the ^{1}H NMR, ^{13}C NMR and IR spectral data are consistent with the assigned structures. Although systems **49** and **50** have been prepared before,[46,47] the method described in this report involves reduced steps with high yields and purity.



14 **50**

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50	R	% yield	m.p. ° C (lit.[ref])
a	H	92	171 – 173 (186 – 188[46])
b	F	77	181 – 183 (195 – 198[47])
c	Cl	93	221 – 223 (250 – 253[46])
d	OMe	93	201 – 203 (205 – 207[46])

Scheme 24

Table 6: ^{13}C NMR chemical shift values (ppm) of systems **50** in $CDCl_3$ (at 75 MHz)

nucleus	**50a (R = H)**	**50b (R = F)**	**50c (R = Cl)**	**50d (R = OMe)**
NCH_3	38.6	38.4	38.5	38.7
OCH_3	-	-	-	55.6
C-2	153.0	151.5	151.7	152.8
C-3	107.5	109.3	107.6	109.8
C-4	170.9	172.4	170.9	172.8
C-4a	124.2	124.7	124.3	124.5
C-5	124.2	124.4	117.2	125.7
C-6	125.9	127.5	124.2	125.0
C-7	132.7	132.6	132.5	132.7
C-8	117.5	115.8	125.9	116.8
C-8a	140.3	140.4	140.3	140.8
C-1'	136.0	131.4 (d, $^4J_{CF}$ 3.6 Hz)	160.6	160.6
C-2',6'	128.3	130.5 (d, $^3J_{CF}$ 8.6 Hz)	130.2	130.0
C-3',5'	129.0	116.6 (d, $^2J_{CF}$ 22.1 Hz)	129.0	114.7
C-4'	129.5	164.8 (d, $^1J_{CF}$ 249.3 Hz)	134.5	126.6

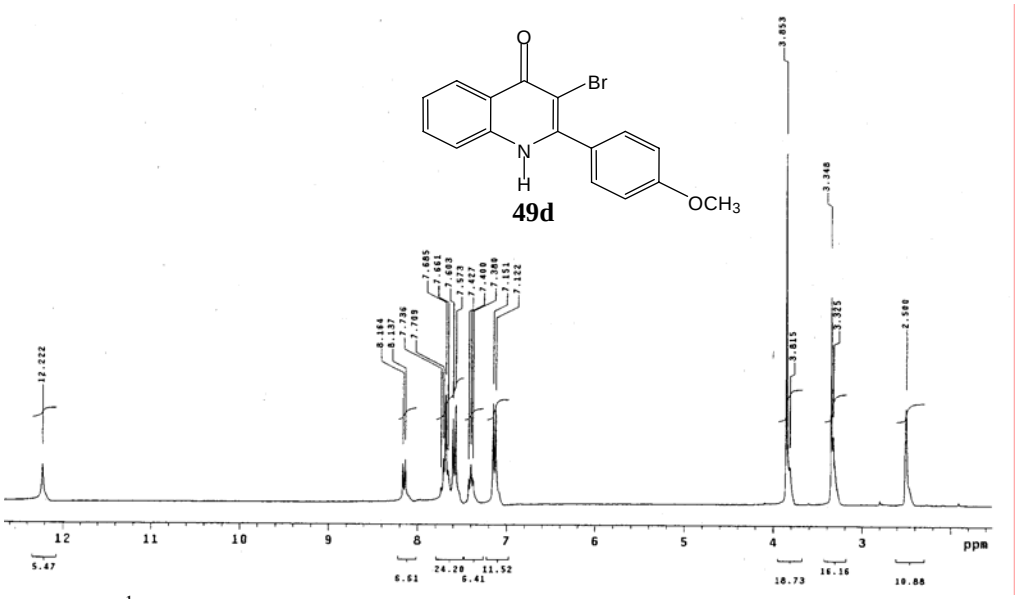


Figure 5: ^{1}H NMR spectrum of 3-bromo-2-phenylquinolin-4(1*H*)-one **49d** in DMSO-d_6

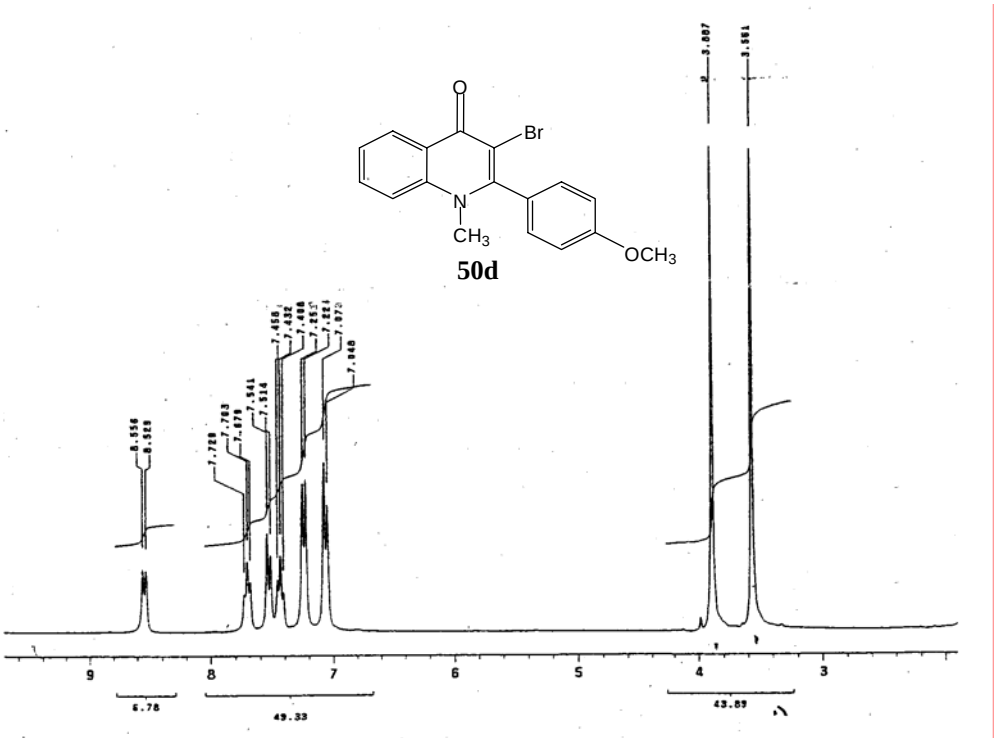
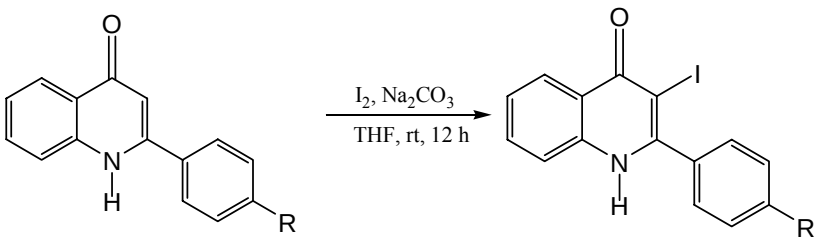


Figure 6: ^{1}H NMR spectrum of 3-bromo-1-methyl-2-phenyl-4-quinolone **50d** in $CDCl_3$

2.4 C-3 Iodination of 2-arylquinolin-4(1*H*)-ones 18

The reactions of the systems **18** with Na_2CO_3 (1.5 equiv.) and iodine (2 equiv.) in THF at room temperature, a procedure developed in our laboratory, afforded the previously undescribed 2-aryl-3-iodoquinolin-4(1*H*)-ones **65** in high yields and purity (Scheme 25). Campos and co-workers previously reported that iodination of 2-arylthioflavone affords the 2-aryl-3-iodothioflavone in 58% yields after 20 h.[81] The ^{1}H NMR spectra of systems **65** are characterised by the absence of olefinic proton signal (3-H), the presence of the aromatic proton signals in the region δ 7.39-8.15 ppm and the imine proton signal at δ *ca.* 12.3 ppm (Figure 7, page 42)). Their ^{13}C NMR spectra are characterized by the presence of the iodinated carbon atom (C-3) at δ *ca*. 85.9 ppm, a group of resonance in the aromatic region and the carbonyl carbon at δ *ca*. 173.5 ppm (Table 7). The NH-4-oxo nature of the products is further confirmed by a sharp IR absorption band ν_{max} *ca*. 1624.8 cm^{-1} which corresponds to the carbonyl group (C=O) and a broad NH band at ν_{max} *ca*. 3361.9 cm^{-1}.



18 **65**

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65	R	% yield	m.p. °C
a	H	85	267 – 269
b	F	83	265 – 268
c	Cl	91	291 – 293
d	OMe	83	276 – 279

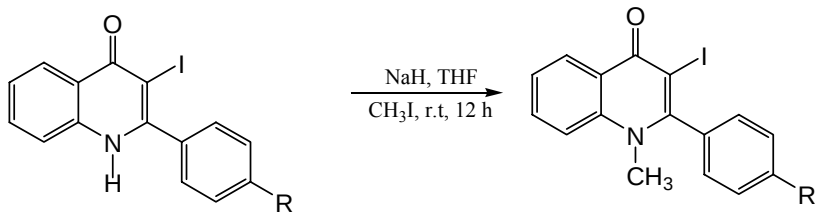
Scheme 25

Table 7: ^{13}C NMR chemical shift values (ppm) of systems **65** in DMSO-d_6 (at 75 MHz)

nucleus	**65a (R = H)**	**65b (R = F)**	**65c (R = Cl)**	**65d (R = OMe)**
OCH_3	-	-	-	55.4
C-2	153.1	152.4	152.0	152.9
C-3	85.9	86.2	86.0	86.2
C-4	173.4	173.5	173.7	173.6
C-4a	120.8	120.9	120.9	120.7
C-5	125.5	125.4	125.5	125.4
C-6	124.1	124.1	124.4	124.1
C-7	132.1	132.0	132.3	132.1
C-8	118.4	118.6	118.4	118.3
C-8a	139.9	139.5	139.3	139.3
C-1'	137.9	134.6 (d, $^4J_{CF}$ 3.2 Hz)	136.7	130.1
C-2',6'	128.9	131.5 (d, $^3J_{CF}$ 8.6 Hz)	131.0	130.6
C-3',5'	128.4	115.3 (d, $^2J_{CF}$ 21.9 Hz)	128.5	113.6
C-4'	129.8	162.7 (d, $^1J_{CF}$ 245.3 Hz)	134.7	160.3

2.5 *N*-Methylation of 2-aryl-3-iodoquinolin-4(1*H*)-ones 65

Compounds **65** were treated with sodium hydride in THF at room temperature followed by quenching with iodomethane to afford the 2-aryl-3-iodo-1-methyl-4-quinolones **66** in high yields as sole products (Scheme 26). It has been reported that methylation of 2-alkylquinolin-4(1*H*)-ones using iodomethane and K_2CO_3 in DMF afford a mixture of *N*-alkylated and *O*-alkylated derivatives that are difficult to separate by conventional column chromatography.[46,47] The presence of iodine atom at C-3 position of the quinolone favors the formation of the *N*-alkylated derivatives. The *O*-alkylated isomers are not formed presumably due to the steric interaction of the iodine atom at C-3 position of systems **65**. The ^{1}H NMR spectra of compounds **66** are characterized by the presence the *N*-methyl signal at δ *ca*. 3.58 ppm and the aromatic signals in the region δ 7.26-8.56 ppm (Figure 8). The absence of the imine proton signal at δ *ca*. 12.7 ppm further distinguishes products **66** from their corresponding precursors **65**. Their ^{13}C NMR spectra are characterized by the *N*-methyl signal at δ *ca*. 39.1 ppm, the signals corresponding to aromatic carbons and also the C-3 iodinated nucleus at δ *ca*. 89.2 ppm (Table 8). The comparable chemical shifts of the C-4 nuclei of compounds **65** and **66** (*ca*. 174.1 ppm), also confirm the carbonyl nature of systems **66**. The carbonyl band of the latter at ν_{max} *ca*. 1616.3 cm^{-1}, an absorption band at ν_{max} *ca*. 1593.2 cm^{-1} corresponding to the aromatic C=C and the C-H bands at ν_{max} *ca*. 3055.2 cm^{-1} in their IR spectra confirm the structures of products **66**. The structures of compounds **65** and **66** were confirmed by a combination of ^{1}H NMR, ^{13}C NMR, IR, elemental analysis and mass spectroscopic techniques and the latter is discussed in chapter 3.



65 **66**

66	R	% yield	m.p.° C
a	H	89	230 – 232
b	F	88	218 – 220
c	Cl	75	253 – 255
d	OMe	73	196 – 198

Scheme 26

Table 8: ^{13}C NMR chemical shift values (ppm) of systems **66** in $CDCl_3$ (at 75 MHz)

nucleus	**66a (R = H)**	**66b (R = F)**	**66c (R = Cl)**	**66d (R = OMe)**
NCH_3	39.1	39.1	39.1	39.2
OCH_3	-	-	-	55.4
C-2	155.2	154.2	154.0	140.7
C-3	89.1	89.6	89.3	89.9
C-4	174.1	173.9	173.9	174.1
C-4a	122.9	122.8	122.9	122.8
C-5	127.5	124.5	127.9	124.3
C-6	129.7	127.8	124.4	127.8
C-7	132.6	132.6	132.7	132.5
C-8	124.4	115.6	115.6	115.9
C-8a	140.7	135.4	140.7	137.7
C-1'	139.3	135.4 (d, $^4J_{CF}$ 3.7 Hz)	137.6	155.2
C-2',6'	128.2	130.4 (d, $^3J_{CF}$ 8.2 Hz)	129.8	129.7
C-3',5'	129.2	116.6 (d, $^2J_{CF}$ 21.9 Hz)	129.6	114.4
C-4'	115.6	163.1 (d, $^1J_{CF}$ 249.3 Hz)	135.9	160.3

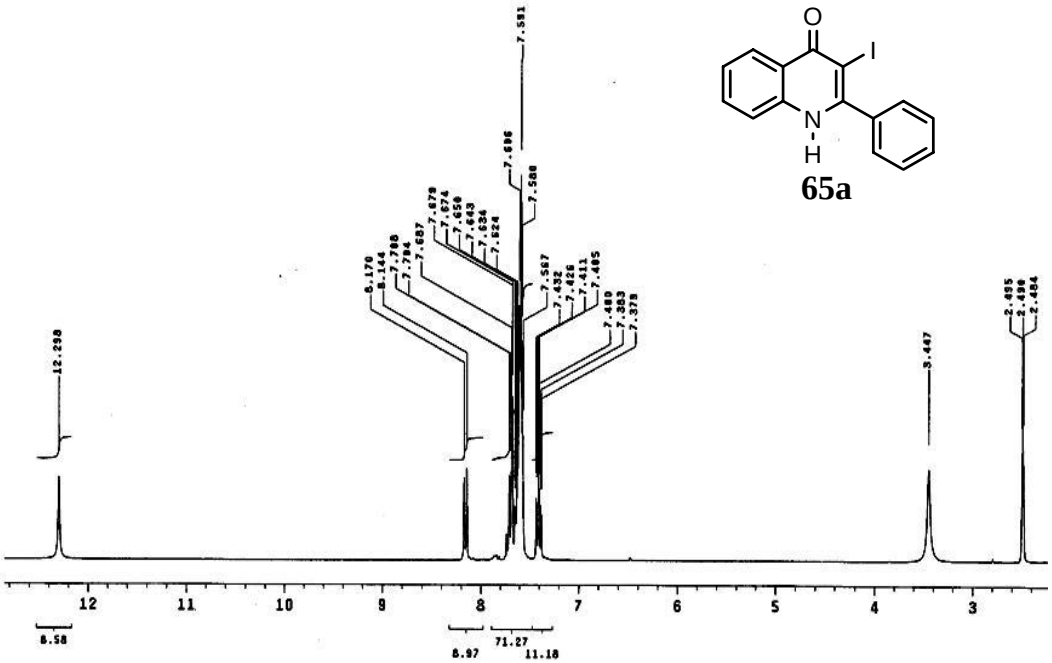


Figure 7: ^{1}H NMR spectrum of 3-iodo-2-phenylquinolin-4(1*H*)-one **65a** in DMSO-d_6

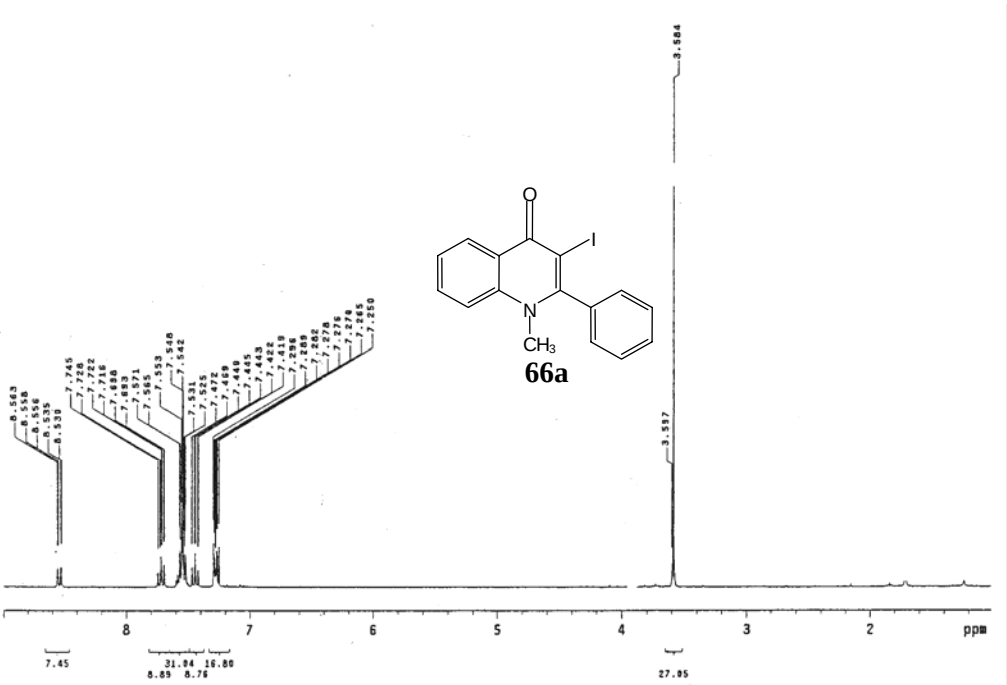


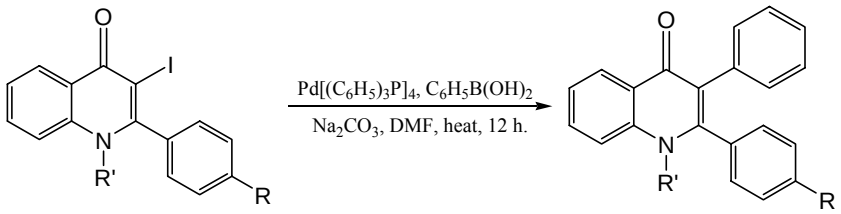
Figure 8: ^{1}H NMR spectrum of 3-iodo-1-methyl-2-phenyl-4-quinolone **66a** in $CDCl_3$

Suzuki coupling reactions of 2-aryl-3-iodoquinolin-4(1*H*)-ones 65a and 66(a-d)

Palladium-catalysed carbon-carbon bond forming reactions continue to attract considerable attention in recent years[77] and biaryls are reported to constitute important building blocks for the synthesis of substances that serve as pharmaceuticals and herbicides.[82]

Suzuki coupling reactions of 3-iodo-NH-4-oxo system **65a** with a phenyl boric acids in DMF using catalytic amount of $Pd[(C_6H_5)_3P]_4$ afforded the 2,3-diphenylquinolin-4(1*H*)-one **67** in 53% yield (Scheme 27). On the other hand, under similar reaction conditions applied to system **65a,** 3-iodo-NH-4-oxo systems (**65b-c**) failed to afford the expected products. It is reported that at pH 10 the unprotected acidic N-1 proton may be deprotonated to give an anion that can coordinate to palladium.[83] On the other hand, 3-iodo-NCH_3-4-oxo derivatives **66** afforded the corresponding 2,3-diaryl-1-methyl-4-quinolone derivatives in reasonable yields. The structure of product **67** is characterised by the increased number of aromatic proton signals in the region δ 7.03-8.16 ppm and the imine proton signal at δ *ca.*11.8 ppm (Figure 9). On the other hand, the ^{1}H NMR spectra of compounds **68** are characterized by the presence of the *N*-methyl signal at δ *ca*. 3.52 ppm, the increased number of aromatic proton signals in the region δ 7.01-8.58 ppm (Figure 10). The ^{13}C NMR spectrum of **67** is characterized by the increased number of resonances in the aromatic region and the carbonyl carbon at δ *ca*. 175.4 ppm (Table 9). The absence of signal corresponding to the C-3 iodinated nucleus which resonates at δ *ca*. 89.2 in spectrum of the precursor further confirms the structure of product **67**. The ^{13}C NMR spectra of compounds **68** are characterized by the presence of the *N*-methyl signal at δ *ca*. 37.58 ppm and signals

corresponding to aromatic regions. The carbonyl carbon at δ *ca*. 176.2 ppm and the absence of the signals corresponding to C-3 iodinated nucleus also further confirm the structures of products **68** (Table10). A sharp IR absorption band at ν_{max} *ca*. 1622.1 cm^{-1} for carbonyl stretch and a broad band at ν_{max} *ca*. 3200.9 cm^{-1} corresponding to the amine stretch confirm the structure to correspond to product **67**. A sharp IR absorption band at ν_{max} *ca*. 1614.4 cm^{-1} which corresponds to the carbonyl group further confirms the structures of products **68**. The fragmentation patterns of systems **67** and **68** are discussed later in chapter 3.



65 (R' = H), **66** (R' = CH_3) **67** (R' = H), **68** (R' = CH_3)

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	R	R'	% yield	m.p.° C (lit.[ref])
67	H	H	53	351–353 (337-338[84,85])
68a	H	CH_3	58	251–253
68b	F	CH_3	52	284–286
68c	Cl	CH_3	74	268-270
68d	OMe	CH_3	63	266–268

Scheme 27

Table 9: ^{13}C NMR chemical shift values (ppm) of systems **67** in DMSO-d_6 (at 75 MHz)

nucleus	**67 (R = H)**
OCH_3	-
C-2	148.4
C-3	120.5
C-4	175.3
C-4a	135.2
C-5	125.3
C-6	123.2
C-7	131.7
C-8	118.4
C-8a	139.6
C-1'	124.6
C-1"	135.7
C-4'	128.9
C-4"	125.9
C-2',6'	131.8
C-2",6"	127.2
C-3',5'	128.1
C-3",5"	129.5

Table 10: ^{13}C NMR chemical shift values (ppm) of systems **68** in $CDCl_3$ (at 75 MHz)

nucleus	**68a (R = H)**	**68b (R = F)**	**68c (R = Cl)**	**68d (R = OMe)**
NCH_3	37.5	37.6	37.6	37.1
OCH_3	-	-	-	55.2
C-2	141.3	141.4	141.3	140.9
C-3	124.2	124.6	124.3	123.3
C-4	176.1	176.2	176.1	174.9
C-4a	126.5	126.6	126.5	125.8
C-5	126.0	126.2	126.3	125.3
C-6	123.5	123.6	123.6	122.8
C-7	132.1	132.3	132.3	131.7
C-8	115.7	115.4	115.7	116.1
C-8a	151.9	150.9	150.7	151.7
C-1'	134.9	131.0 (d, $^4J_{CF}$ 3.5 Hz)	134.8	126.5
C-1"	135.7	135.6	135.3	135.9
C-4'	128.6	162.5 (d, $^1J_{CF}$ 248.8 Hz)	133.3	158.8
C-4"	127.3	127.4	127.3	125.9
C-2',6'	131.3	131.5 (d, $^3J_{CF}$ 8.0 Hz)	130.9	130.9
C-2",6"	127.3	127.6	127.6	113.1
C-3',5'	129.5	115.6 (d, $^2J_{CF}$ 21.6 Hz)	131.2	130.4
C-3",5"	128.2	131.2	128.6	126.7

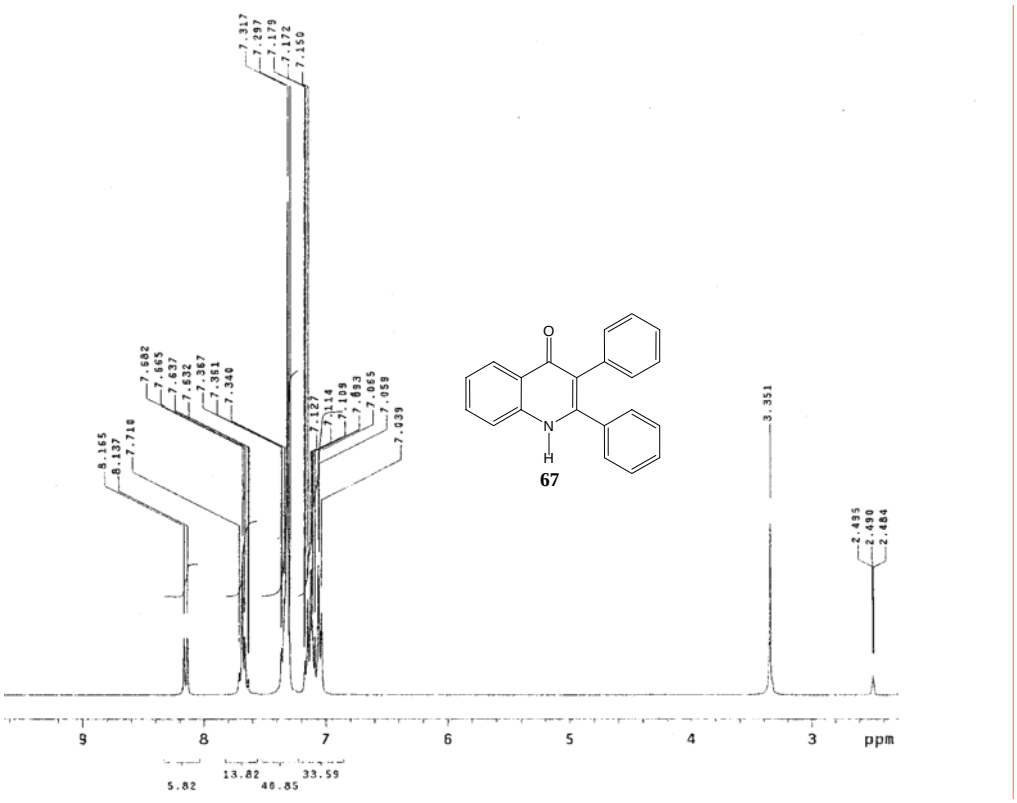


Figure 9: ^{1}H NMR spectrum of 2,3-diphenylquinolin-4(1*H*)-one **67** in DMSO-d_6

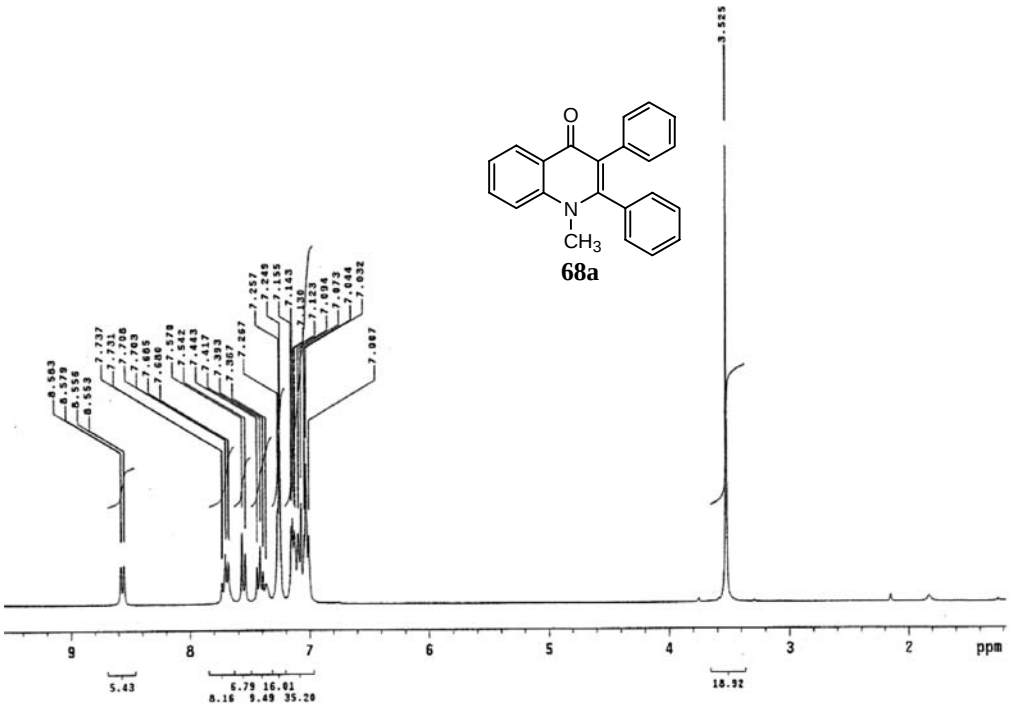
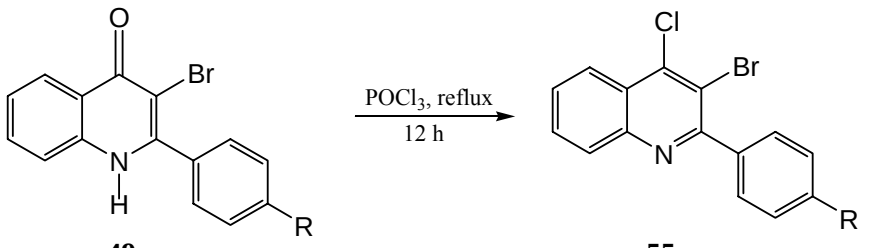


Figure 10: ^{1}H NMR spectrum of 1-methyl-2,3-diphenyl-4-quinolinone **68a** in $CDCl_3$

2.7 Chlorination of 2-aryl-3-bromoquinolin-4(1*H*)-ones 49

The reactions of 2-aryl-3-bromoquinolin-4(1*H*)-ones **49** with phosphorus oxychloride under reflux afforded the previously described 2-aryl-3-bromo-4-chloroquinolines **55** (Scheme 28).[46,47] Their ^{1}H NMR spectra are characterized by signals in the aromatic region at δ 7.50-8.27 ppm (Figure 11). Their ^{13}C NMR spectra reveal the presence of a group of resonances in the aromatic region and the absence of the carbonyl carbon signal at δ *ca.* 177.0 ppm (Table 11, Figure 12). The absence of the sharp IR carbonyl absorption band and the broad band corresponding to NH stretch further distinguish structures **55** from those of the corresponding precursors. The melting points of compounds **55** differ from the literature values, nevertheless, their ^{1}H NMR, ^{13}C NMR and IR spectral data are consistent with the assigned structures.



49 **55**

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55	R	% yield	m.p. °C (lit.[ref])
a	H	65	147 – 149 (134–136[46])
b	F	71	168 – 170 (165-167[46])
c	Cl	84	216 – 218 (224–226[46])
d	OMe	81	177 – 179 (188–190[47])

Scheme 28

Table 11: ^{13}C NMR chemical shift values (ppm) of systems **55** in DMSO-d_6 (at 75 MHz)

nucleus	**55a (R = H)**	**55b (R = F)**	**55c (R = Cl)**	**55d (R = OMe)**
OCH_3	-	-	-	53.3
C-2	158.7	158.1	157.9	157.9
C-3	118.0	118.2	118.0	116.1
C-4	142.1	143.4	138.8	140.2
C-4a	125.4	126.3	126.4	123.4
C-5	129.1	129.8	129.8	127.5
C-6	128.6	128.6	128.6	128.8
C-7	131.3	130.7	130.8	129.1
C-8	124.2	124.6	124.6	122.3
C-8a	145.9	146.5	146.5	144.1
C-1'	140.1	130.3 (d, $^4J_{CF}$ 3.6 Hz)	135.2	130.4
C-2',6'	127.9	131.3 (d, $^3J_{CF}$ 8.3 Hz)	130.7	128.9
C-3',5'	129.2	115.1 (d, $^2J_{CF}$ 21.6 Hz)	128.3	111.2
C-4'	129.5	163.2 (d, $^1J_{CF}$ 247.6 Hz)	129.2	156.3

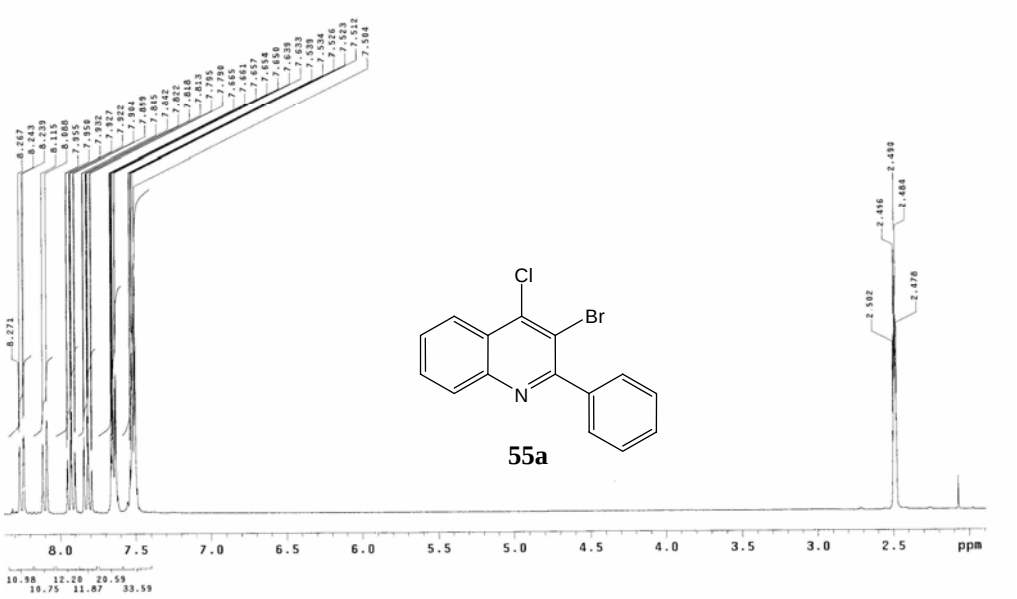


Figure 11: ^{1}H NMR spectrum of the 3-bromo-4-chloro-2-phenylquinolines **55a** in DMSO-d_6

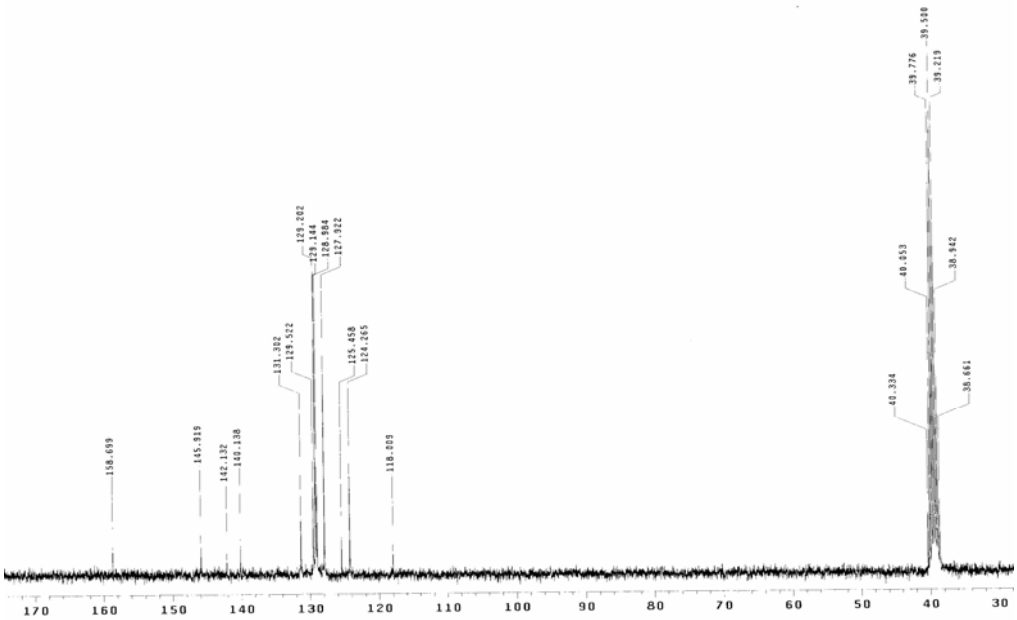
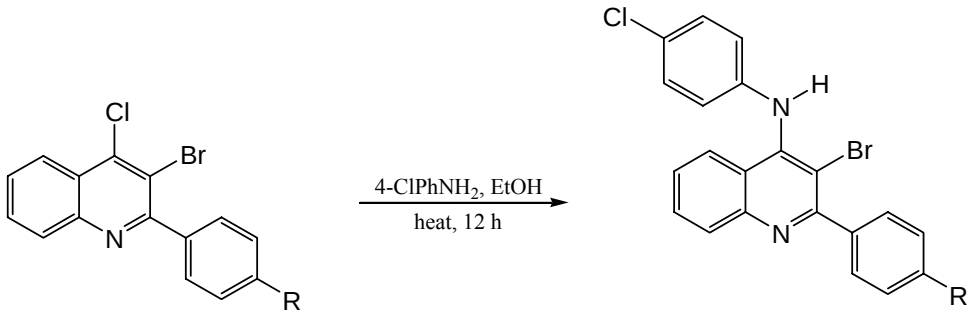


Figure 12: ^{13}C NMR spectrum of 3-bromo-4-chloro-2-phenylquinolines **55a** in DMSO-d_6

2.8 Amination of 2-aryl-3-bromo-4-chloroquinolines 55

Systems **55** were converted in reasonable yields to the corresponding 3-bromo-4-(*N*-4"-chloroaryl)-2-aryl-4-aminoquinolines **69** using 4-chloroaniline in ethanol under reflux (Scheme 29). The ^{1}H NMR spectra of systems **69** are characterised by the presence of a singlet at δ *ca.* 6.65 ppm (NH), two doublets at δ *ca.* 6.82 and 7.20 ppm corresponding to 2"-H & 6"-H and 3"-H & 5"-H of 4-chloroaniline group and other signals corresponding to aromatic protons (Figure 13). The ^{13}C NMR spectra of systems **69** are further distinguished from those of their precursors **55** by the increased number of resonance in the aromatic region (Table 12, Figure 14). The incorporation of aniline group is further confirmed by the amine absorption band at ν_{max} *ca.* 3059.1 cm^{-1} in the IR spectra of systems **69**.



55 **69**

69	R	% yield	m.p.° C
a	H	62	190–192
b	F	68	181–183
c	Cl	52	188–190
d	OMe	52	192–194

Scheme 29

Table 12: ^{13}C NMR chemical shift values (ppm) of systems **69** in $CDCl_3$ (at 75 MHz)

nucleus	**69a (R = H)**	**69b (R = F)**	**69c (R = Cl)**	**69d (R = OMe)**
OCH_3	-	-	-	55.3
C-2	147.5	127.9	157.8	158.6
C-3	110.4	110.2	109.9	110.3
C-4	159.0	163.0	127.9	127.6
C-4a	121.4	121.3	121.3	121.3
C-5	128.7	130.0	126.1	130.0
C-6	125.9	126.1	134.6	125.8
C-7	130.1	130.1	130.5	129.8
C-8	124.5	124.5	124.5	124.5
C-8a	140.7	141.9	141.9	142.1
C-1'	144.7	147.5 (d, $^4J_{CF}$ 3.5 Hz)	147.5	133.2
C-1"	127.7	136.7	139.1	147.5
C-4'	129.9	163.0 (d, $^1J_{CF}$ 246.5 Hz)	134.9	160.4
C-4"	142.0	144.9	144.9	144.7
C-2',6'	129.2	131.2 (d, $^3J_{CF}$ 8.2 Hz)	130.7	130.7
C-2",6"	129.1	129.3	129.3	129.2
C-3',5'	128.3	115.3 (d, $^2J_{CF}$ 21.6 Hz)	128.2	113.4
C-3",5"	120.2	120.0	120.3	120.1

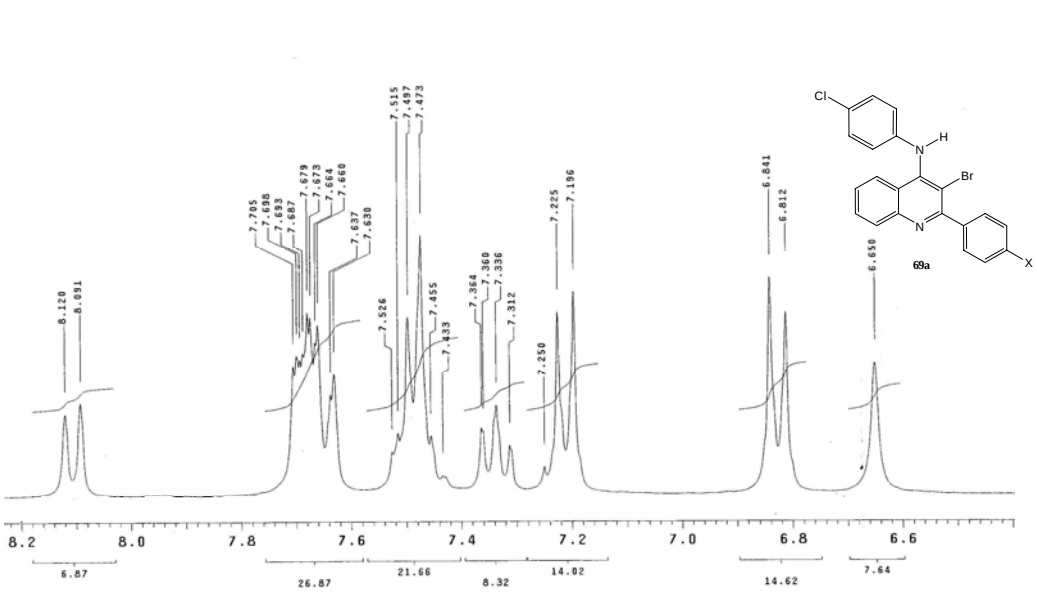


Figure 13: ^{1}H NMR spectrum of the 3-bromo-4-(*N*-4"-chlorophenyl-4-amino)-2-phenylquinolines **69a** in $CDCl_3$

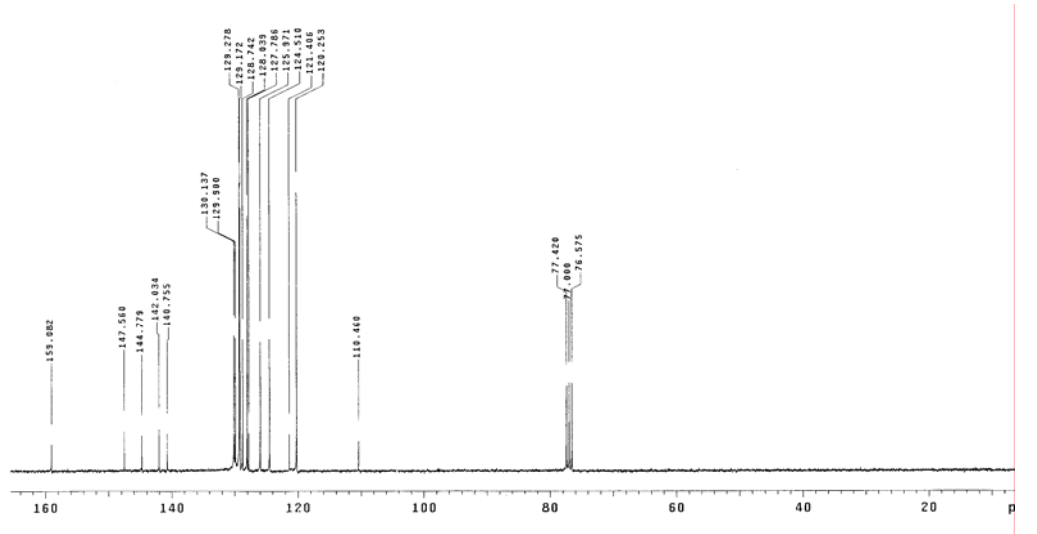


Figure 14: ^{13}C NMR spectrum of the 3-bromo-4-(*N*-4"-chlorophenyl-4-amino)-2-phenylquinolines **69a** in $CDCl_3$

CHAPTER THREE

MASS SPECTROMETRIC ANALYSIS

In addition to the characterization of the synthesized products using NMR and FT-IR spectroscopy, the low resolution mass spectra of compounds prepared in this investigation were also recorded and are discussed below.

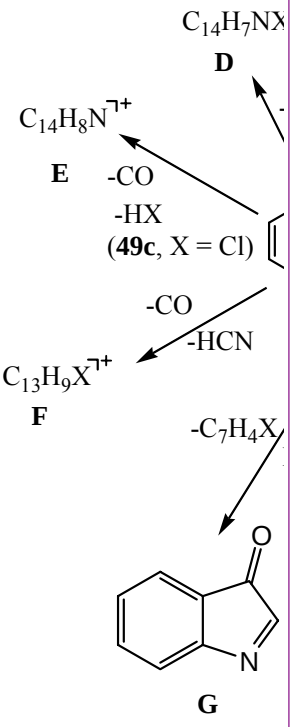
3.1 The electron impact induced mass fragmentation of the 2-aryl-3-halogenoquinolin-4(1*H*)-ones 49 and 65

During electron impact (EI) in addition to molecular ion, the 2-arylquinolin-4(1*H*)-one derivatives are cleaved into many intact A- and B- ring fragments in a pattern similar to that observed for flavones.[86] They both display some common features, such as the loss of carbon monoxide (M-28). The mass spectra of systems **49** are characterized by the molecular ion peak **A** and other major fragments as shown in the Scheme 30 below and their mass-to-charge ratios (m/z) are summarized in Table 12. The main fragmentation involves the cleavage of the C-Y bond (Y = Br or I) to afford a cation fragment **C** which constitutes a base peak for systems **49**. On the other hand, the parent ion of **49** loses CO to afford 2-aryl-3-bromoindole fragment **B** which was also observed in the mass spectra of anilidoquinolones[87] and some alkyl(aryl)-4-quinolones.[88]

Loss of carbon monoxide and two hydrogen atoms from **C** affords fragment **D**. The chlorinated derivative **49** (X = Cl) loses CO and HX to yield fragment **E**. Loss of hydrogen atom, CO and CN give fragment **F**. The cleavage of fragment **C** at a

Deleted: position α to the carbonyl carbon followed by rearrangement and a proton shift with subsequent loss of C_7H_4X affords cation fragment **G**. Retro Diels-Alder (RDA) rearrangement of fragment **C** affords fragment **H** in a process parallel to the pattern observed for 2-aryl-1,2,3,4-tetrahydro-4-quinolones,[4] flavones[89] and isoflavones.[90] The tropylium ion **I** is also produced from cation fragment **C**. Sequential loss of C_6H_3 and C_6H_4 from **C** afford the fragment **J**. The latter constitutes a base peak in the mass spectrum of system **65a** (Y = I, X = H). Benzene cation **K** which is formed from **C** subsequently loses CHX to afford **L**.¶

¶



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Scheme 30

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Table 12: Mass fragmentation data for selected peaks in the electron impact mass spectra of systems **49** and **65**¶

¶

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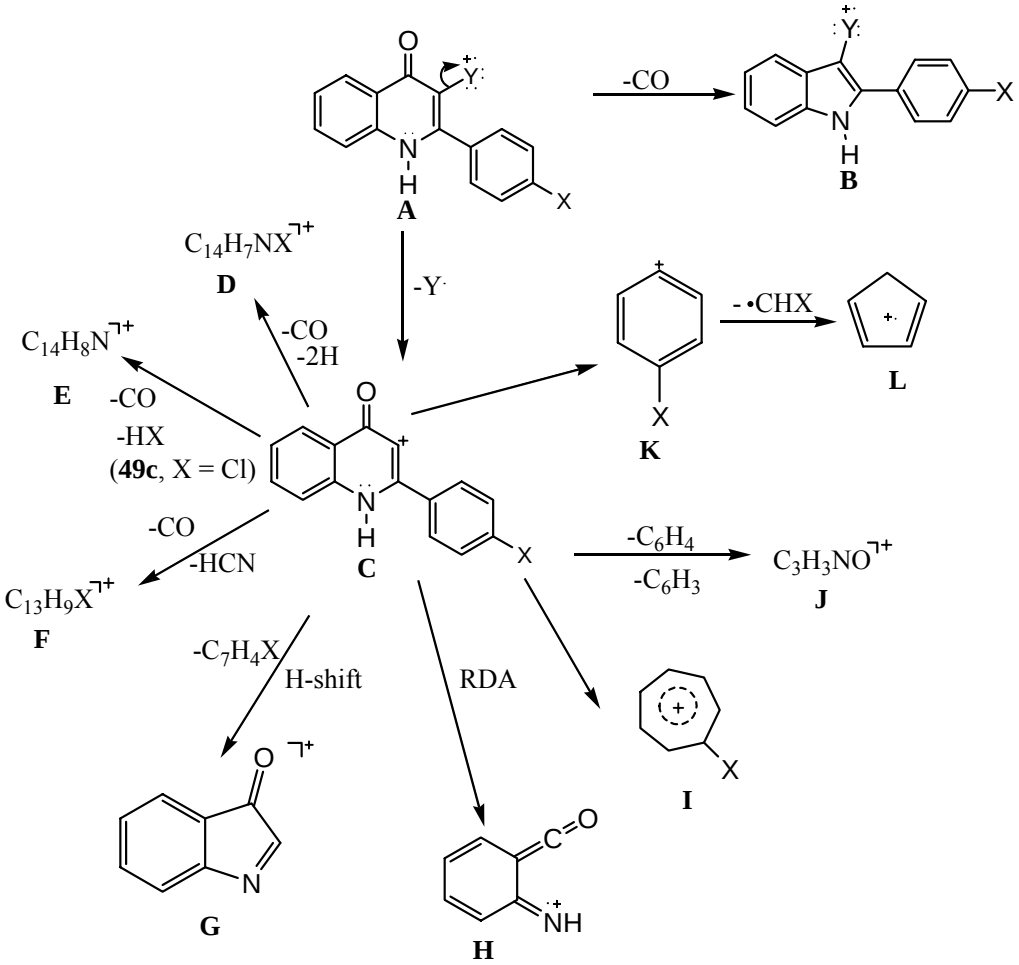
position α to the carbonyl carbon followed by rearrangement and a proton shift with subsequent loss of C_7H_4X affords cation fragment **G**. Retro Diels-Alder (RDA) rearrangement of fragment **C** affords fragment **H** in a process parallel to the pattern observed for 2-aryl-1,2,3,4-tetrahydro-4-quinolones,[4] flavones[89] and isoflavones.[90] The tropylium ion **I** is also produced from cation fragment **C**. Sequential loss of C_6H_3 and C_6H_4 from **C** afford the fragment **J**. The latter constitutes a base peak in the mass spectrum of system **65a** (Y = I, X = H). Benzene cation **K** which is formed from **C** subsequently loses CHX to afford **L**.



Scheme 30

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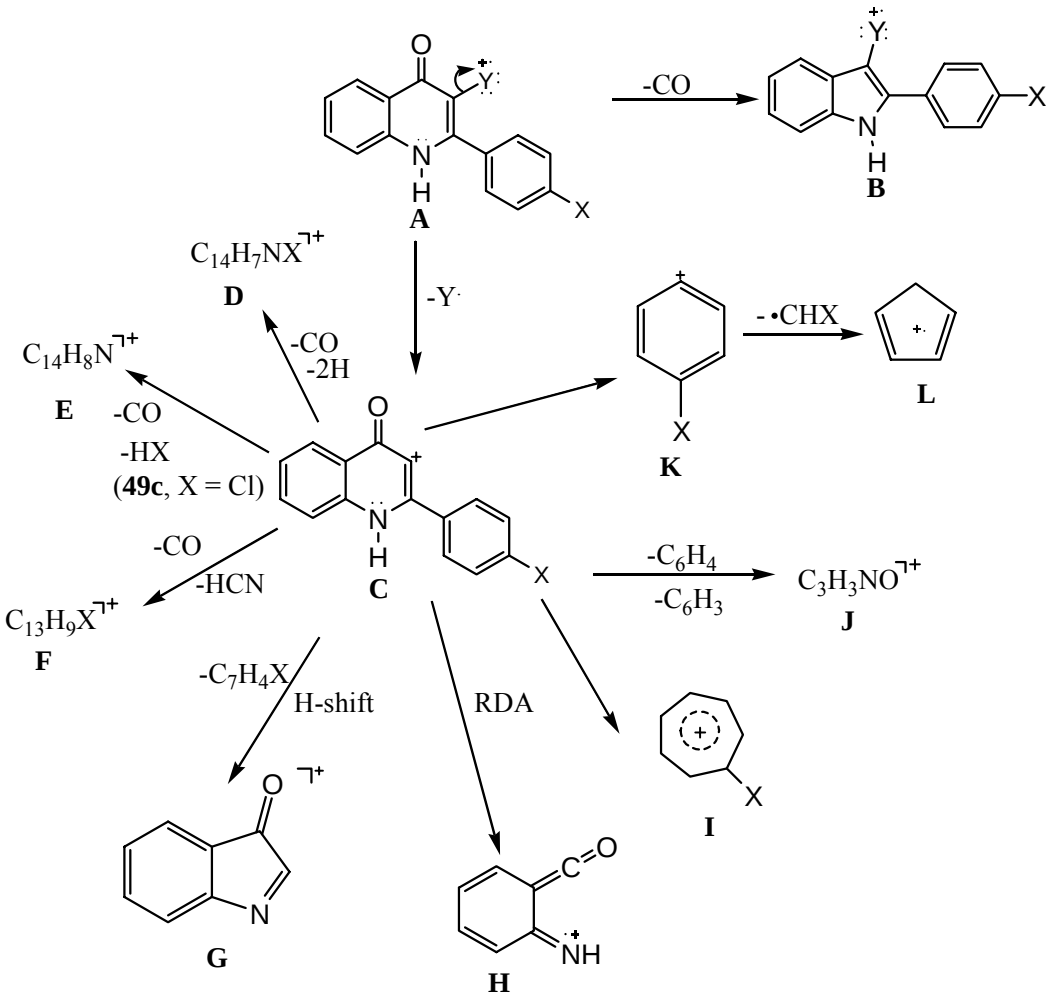
position α to the carbonyl carbon followed by rearrangement and a proton shift with subsequent loss of C_7H_4X affords cation fragment **G**. Retro Diels-Alder (RDA) rearrangement of fragment **C** affords fragment **H** in a process parallel to the pattern observed for 2-aryl-1,2,3,4-tetrahydro-4-quinolones,[4] flavones[89] and isoflavones.[90] The tropylium ion **I** is also produced from cation fragment **C**. Sequential loss of C_6H_3 and C_6H_4 from **C** afford the fragment **J**. The latter constitutes a base peak in the mass spectrum of system **65a** (Y = I, X = H). Benzene cation **K** which is formed from **C** subsequently loses CHX to afford **L**.



Scheme 30

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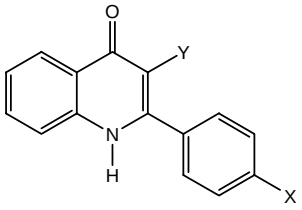
Table 12: Mass fragmentation data for selected peaks in the electron impact mass spectra of systems **49** and **65**



49 (Y = Br)**, 65** (Y = I**)**

Compd	**X**	**Y**	A (%)	B (%)	C (%)	D (%)	E (%)	F (%)	G (%)	H (%
49a	H	Br	299 (59)	277 (9)	220 (100)	190 (16)	-	165 (30)	-	-
49b	F	Br	317 (59)	289 (9)	238 (100)	208 (16)	-	183 (28)	-	119(9
49c	Cl	Br	333 (55)	304 (7)	254 (100)	225 (7)	190 (24)	199 (13)	-	-
49d	OMe	Br	329 (88)	301 (5)	250 (100)	-	190 (4)	195 (2)	-	-
65a	H	I	347 (83)	319 (3)	220 (62)	190 (21)	-	165 (36)	131 (29)	119 (
65b	F	I	365 (90)	337 (2)	238 (43)	208 (12)	-	183 (26)	131 (14)	119 (
65c	Cl	I	381(68)	353 (4)	254 (32)	224 (1)	190 (18)	199 (10)	131(9)	119 (

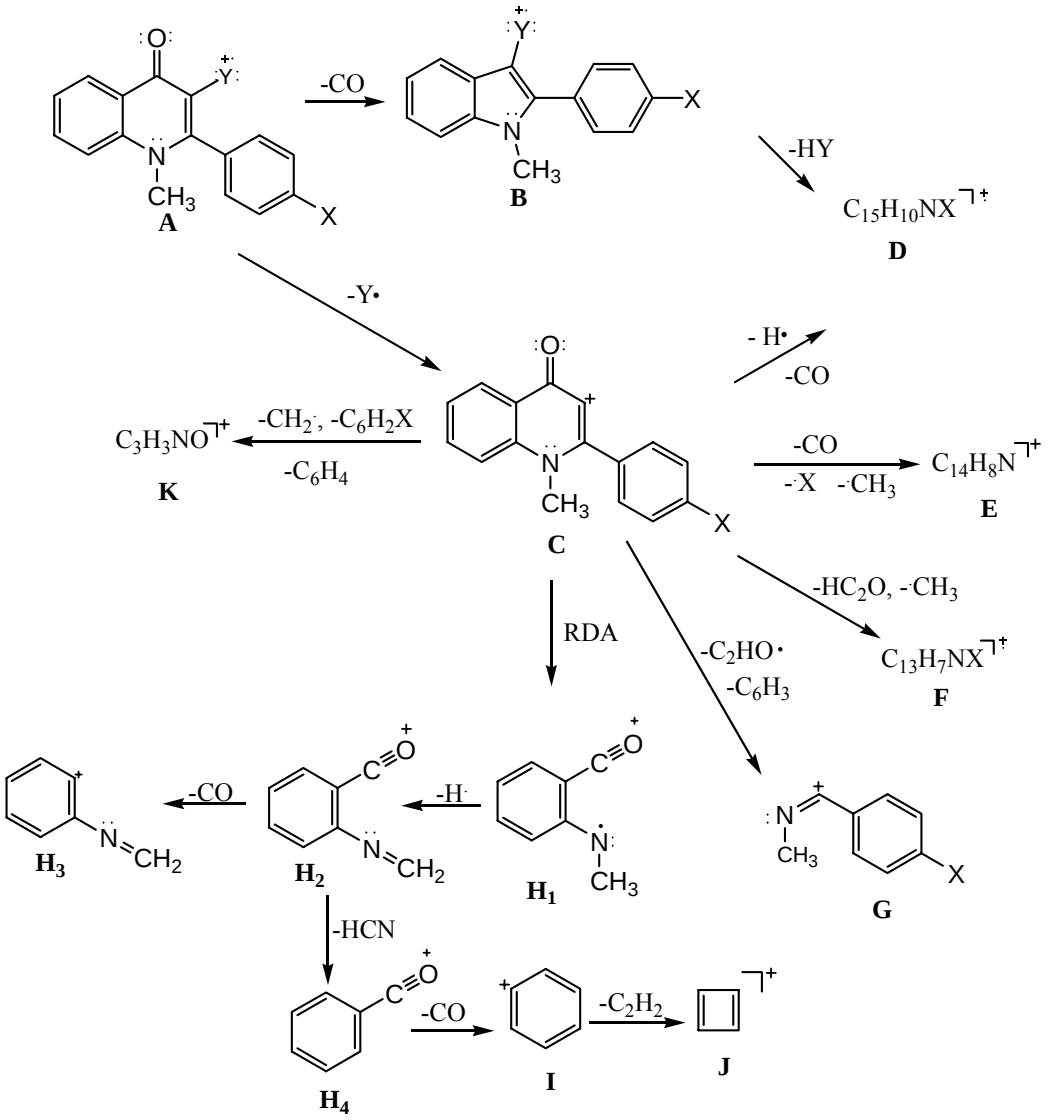
65d	OMe	I	377(100)	349 (3)	250 (36)	220 (4)	190 (5)	195 (7)	131 (11)	119 (

The electron impact induced mass fragmentation of the 2-aryl-3-halogeno-1-methyl-4-quinolones 50 and 66

The parent ion **A** which constitutes a base peak in the mass spectra of systems **50b,d** and **66a-c** undergoes loss of carbon monoxide to afford 2-aryl-3-iodoindole derivatives **B** (Scheme 31, Table 13). The analogous pathway was observed before for anilidoquinolones[87] and alkyl(aryl)-4-quinolones.[88] The parent ion **A** also loses a halogen atom to afford a cation species **C,** which in turn, loses hydrogen atom and CO to afford fragment **D**. The latter may also be the result of loss of HY from **B**. Fragment **E** is probably the result of loss of CO, HX and methyl radical from fragment **C**. On the other hand, loss of HC_2O and methyl radical afford **F** from **C**. Fragment **G** is presumably derived from **C** by loss of C_2HO radical and C_6H_3 group.

Fragment **C** also undergoes the RDA rearrangement to afford fragment $\mathbf{H_1}$ in analogy with the fragmentation pattern reported for 2-aryl-1,2,3,4-tetrahydro-4-quinolones,[4] flavones,[89] isoflavones[90] and glycerine.[91] Fragment $\mathbf{H_1}$ may, in turn, lose hydrogen atom to afford $\mathbf{H_2}$ which loses carbon monoxide to afford fragment $\mathbf{H_3}$. In another pathway, $\mathbf{H_2}$ presumably loses HCN to afford $\mathbf{H_4}$. Fragment **I** is probably the result of loss of CO from $\mathbf{H_4}$ as observed for glycorine.[91] Fragment **I**, in turn, may lose C_2H_2 to

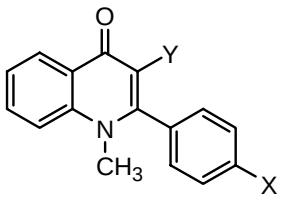
yield fragment **J**.[92] The cation species **K** is presumably the result of loss of benzene radical, C_6H_4X and methylene radical from **C**.



Scheme 31

Table 13: Mass fragmentation data for selected peaks in the electron impact mass spectra of systems **50** and **66**

Cation or reaction type

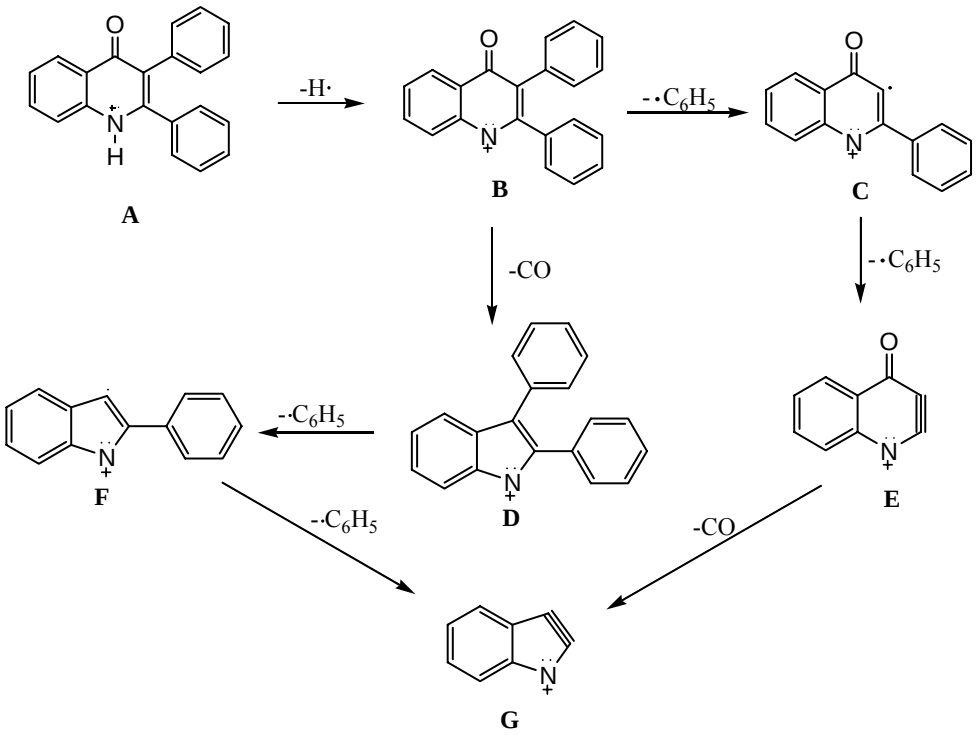


50 (Y = Br), **66** (Y = I)

Compound	X	Y	M^+A (%)	B (%)	C (%)	D (%)	E (%)	F (%)	G (%)	
50a	H	Br	-	-	-	-	-	-	-	
50b	F	Br	331 (100)	303 (28)	252 (56)	222 (14)	-	196 (6)	-	
50c	Cl	Br	-	-	-	-	-	-	-	
50d	OMe	Br	343 (100)	315 (23)	264 (57)	234 (3)	190 (2)	206 (3)	-	
66a	H	I	361 (100)	333 (12)	234 (49)	204 (17)	190 (11)	178 (7)	117 (10)	
66b	F	I	379 (100)	351 (9)	252 (51)	222 (14)	-	196 (6)	-	
66c	Cl	I	395 (89)	367 (7)	268 (20)	-	190 (7)	-	-	
66d	OMe	I	391 (100)	363 (9)	265 (45)	234 (1)	190 (1)	-	147 (1	

3.3 The electron impact induced mass fragmentation of the 2,3-diarylquinolin-4(1*H*)-one 67

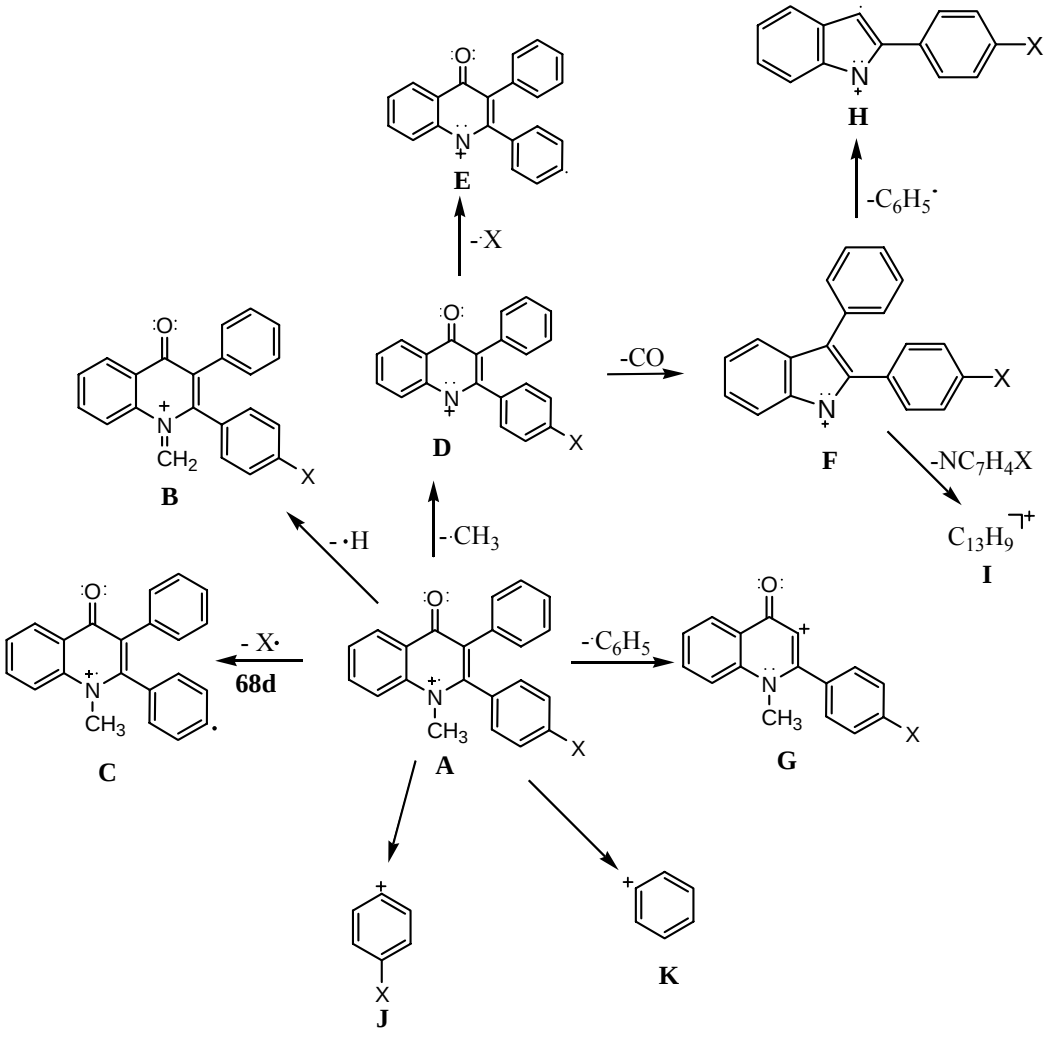
The molecular ion **A** of system **67** loses hydrogen atom to afford a cation fragment **B** and this constitutes the base peak (Scheme 32, Table 14). Fragment **B** loses carbon monoxide to give rise to a cation fragment which is tentatively assigned as the 2,3-diphenylindole ion **D** and this mode of fragmentation was also observed before for 2-methyl-4-quinolones.[88] On the other hand, **B** loses benzene radical to yield fragment **C**, which in turn loses benzene radical to yield **E**. The carbon-carbon bond of the indole moiety **D** cleaves to extrude benzene radical to afford the 2-phenylindole fragment **F**. The cation fragment **G** is presumably derived from **E** and/ or **F** by loss of carbon monoxide and phenyl radical, respectively.



Scheme 32

3.4 The electron impact induced mass fragmentation of the 2,3-diaryl-1-methyl-4-quinolones 68

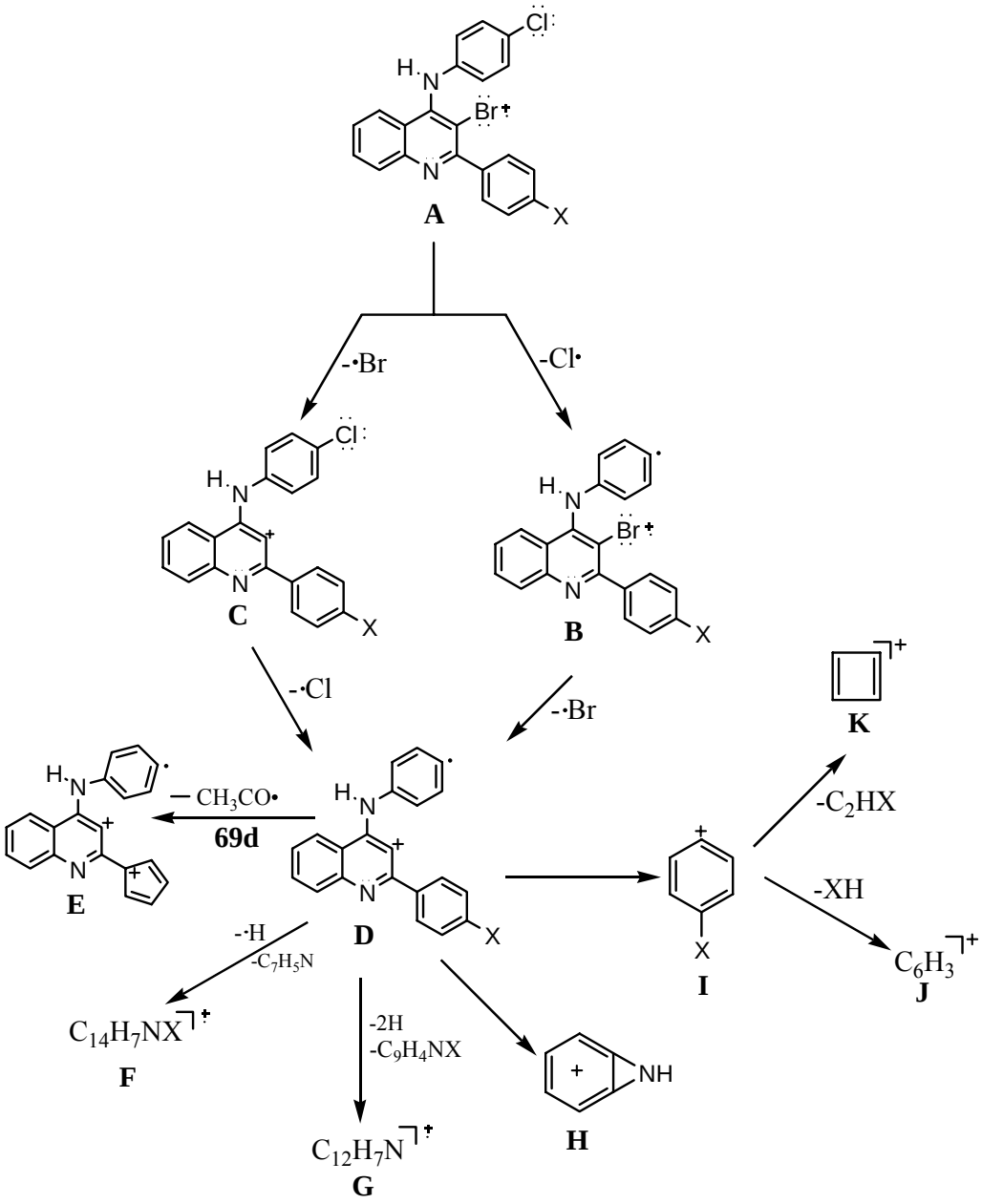
The molecular ion **A** of **68** loses a hydrogen atom to yield fragment **B** (Scheme 33, Table 14). On the other hand, **A** may lose a methyl radical by cleavage of N-C bond to afford a cation fragment **D**, as observed in the electron impact mass spectra of 6- and 8-methoxy flavonoids.[93] Fragment **D** loses a halogen atom to afford cation-radical **E** as reported for 5,6,7,8-tetrahydro-4*H*-chromenes.[94] Fragment **D** may lose carbon monoxide to afford a diphenylindole fragment **F** as observed for anilidoquinolones[87] and 2-methyl-4-quinolones.[88] Fragment **H** is probably the results of the loss of phenyl radical from **F**. Elimination of NC_7H_4X group from fragment **F** affords a cation fragment **I**. On the other hand, a methoxylated derivative **68** (X = OMe) may lose CH_3O radical to afford fragment **C**. Fragment **G** is a result of **A** by loss of a phenyl radical as observed for the 5,6,7,8-tetrahydro-4*H*-chromenes.[94] The molecular ion **A** may also afford a benzene cation fragments **J** and **K** in the process.



Scheme 33

3.5 The electron impact induced mass fragmentation of the 2-aryl-3-bromo-4-(4"-chloroaniline)quinolines 69

The molecular ion **A** of systems **69** which constitutes a base peak in the mass spectra of **69a-c** (Scheme 34, Table 14) undergoes cleavage of the C-Cl bond of the 4-chloroaniline with the loss of chlorine atom to afford fragment **B** in a similar pattern to that observed for 5,6,7,8-tetrahydro-4*H*-chromenes.[94] On the other hand, **A** may lose a bromine atom to afford fragment **C**. Fragment **D** presumably results from both **B** and **C** by loss of bromine and chlorine atoms, respectively. The methoxylated derivative **69d** (X = OMe) loses a CH_3CO radical to afford fragment **E** similar to literature observation for 7-methoxyquinoline.[91] The loss of hydrogen atom and C_7H_5N group from fragment **D** affords **F**. On the other hand, **D** affords fragment **G** by loss of two hydrogen atoms and C_9H_4NX group. The cleavage of the C-N bond at C-4 position of the quinoline moiety of **D** affords fragment **H**, *m/z* = 91 as observed for quinoline *N*-oxide.[95] Fragment **D** affords **I** by cleavage of the carbon-carbon bond between C-2 and C-1 of benzene ring. Fragment **J** is the results of loss of HX from **I** and the latter also loses C_2HX group to afford fragment **K**.



Scheme 34

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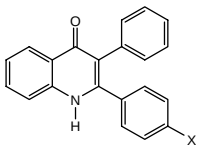
Table 14: Mass fragmentation data for selected peaks in the electron impact mass spectra of systems **67**, **68** and **69**



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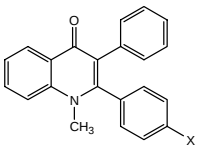

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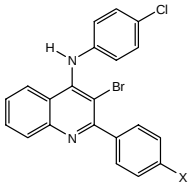

69

Compound	M^+A(%)	B (%)	C (%)	D (%)	E	F (%)	G (%)	H (
67	297 (63)	296 (100)	218 (0.8)	268 (4)	140 (1)	190 (4)	112 (0.2)	-
68a (X = H)	311 (89)	310 (100)	-	296 (12)	-	267 (26)	234 (6)	19
68b (X = F)	329 (100)	328 (42)	-	314 (11)	-	286 (13)	-	-
68c (X = Cl)	345 (60)	344 (97)	310 (14)	330 (-9)	294 (6)	302 (1)	267 (7)	19
68d (X =OMe)	341 (50)	340 (71)	-	326 (26)	296 (7)	298 (4)	264 (1)	19
69a (X = H)	409(100)	374 (2)	329 (39)	293 (41)	-	191 (6)	165 (7)	91
69b (X = F)	427(100)	392 (2)	347 (36)	311 (36)	-	209 (1)	164 (3)	91

69c (X = Cl)	443(100)	408 (3)	362 (45)	327 (25)	-	226 (3)	164 (7)	91
69d (X =OMe)	439 (94)	404 (1)	359 (20)	314 (10)	280 (22)	220 (21)	164 (9)	91

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CONCLUSION

Pyridium tribromide in acetic acid and I_2-Na_2CO_3 mixture in THF were found to be highly useful reagents for the bromination and iodination of variety of 2-arylquinolin-4(1*H*)-one derivatives, respectively. The C-3 brominated derivatives were previously obtained in multiple steps and lower yields.[46] An efficient method for the direct C-3 bromination of 2-aryl-1-methyl-4-quinolone **14** and 2-arylquinolin-4(1*H*)-one **18** in high yields has thus been developed. The new 3-iodo-2-arylquinolin-4(1*H*)-one derivatives **65** were prepared in excellent yield using relatively cheap reagents such as iodine and Na_2CO_3 at room temperature and systems **65** were, in turn, converted to 2-aryl-3-iodo-1-methyl-4-quinolone derivatives **66** in quantitative yields. The ^{1}H NMR, ^{13}C NMR and IR spectral data of systems **14**, **18**, **49** and **50** are comparable to those reported in the literature for the NH-4-oxo and NCH_3-4-oxo products.[26] The 2-aryl-3-iodoquinolin-4(1*H*)-one **65** and 2-aryl-3-iodo-1-methyl-4-quinolone **66** were further confirmed by mass spectroscopy and elemental analysis.

Transformation of 2-aryl-3-iodo-1-methyl-4-quinolone **66** to 2,3-diaryl-1-methyl-4-quinolone **68** was achieved in good yields. On the other hand, 2-aryl-3-iodoquinolin-4(1*H*)-one **65** afforded the expected product in relatively low yields due the unprotected acidic *N*-1 proton. Thus, to achieve high yields of the 2,3-diaryl-4-quinolones, *N*-1 protected substrates such as **68** should be used**.** The reactions of the 2-aryl-3-bromo-4-chloroquinoline **55** derivatives with 4-chloroaniline afforded the 2-aryl-3-bromo-4-(4"-chloroaniline)quinoline derivatives **62**. Although the bromine at C-3 is bulky, it is shown that transformation of 2-aryl-3-bromo-4-chloroquinoline **55** derivatives to 2-aryl-3-bromo-4-(*N*-4"-chloroaniline)quinoline derivatives **62** is possible. In general, the compounds reported in this investigation can serve as substrates for further study of chemical transformation.

Future research from this investigation is expected to include the following:

Thionation of the 2-aryl-3-bromoquinolin-4(1*H*)-ones **49** and 2-aryl-3-bromo-1-methyl-4-quinolone **50**.

Dimerization of the 2-aryl-3-halogenoquinolin-4(1*H*)-ones derivatives **49**, **50**, **65** and **66**.

Chlorination of 2-aryl-3-iodoquinolin-4(1*H*)-ones derivatives **65**.

Transformation of the 2-aryl-3-iodo-4-chloroquinolines to 4-azido and 4-alkoxy derivatives.

CHAPTER FOUR

EXPERIMENTAL

General

Solvents and commercially available reagents were purified by conventional methods before use. Melting points were recorded on Gallenkamp melting point apparatus and are uncorrected. Thin layer column chromatography (TLC) was carried out on silica gel plates Merck silica gel 60 F_{254} as the stationary phase. Fourier Transform Nuclear Magnetic Resonance (FT-NMR) spectra were recorded on Varian Mercury 300 MHz NMR spectrometer with $CDCl_3$ and DMSO-d_6 as solvents and the chemical shifts are quoted relative to the solvents peak expressed in parts per million (ppm) (δ_H 7.25 ppm or δ_C 77.0 ppm). Fourier Transform Infrared (FT-IR) spectra were recorded neat as powder using a Digilab FTS 7000 spectrometer. Low- and high-resolution mass spectra were recorded at an ionisation potential of 70e V using Micro Auto-TOF (double focusing high resolution) instrument.

4.1 Preparation of *N*-benzoyl-2-aminoacetophenone derivatives

4.1.1 Preparation of *N*-benzoyl-2-aminoacetophenone 36a

Benzoyl chloride **35a** (3.9 ml, 27.8 mmol) was added dropwise to a mixture of 2-aminoacetophenone **34** (3.13 g, 23.2 mmol) and triethylamine (4.68 g, 46.4 mmol) in

THF (40 ml) at 0° C. After 30 minutes at 0° C, the mixture was stirred at room temperature for 2 hours and then poured into ice-cold water (113.8 ml). The resulting precipitate was filtered and then was taken into chloroform (50 ml). The solution was washed with water and dried over sodium sulphate, filtered and the solvent was evaporated under reduced pressure to afford **36a**, solid (5.40 g, 97%), m.p. 96-98° C (lit.[78] 95-96° C); ^{1}H NMR (300 MHz, $CDCl_3$) 2.67 (3H, s, CH_3), 7.11 (1H, t, *J* 7.5 Hz, 4-H), 7.47-7.54 (2H, m, 5-H, 4'-H), 7.57 (2H, t, *J* 8.3 Hz, 3'-H and 5'-H), 7.91 (1H, d, *J* 7.5 Hz, C-3), 8.05 (2H, d, *J* 6.9 Hz, 2'-H and 6'-H), 8.96 (1H, d, *J* 8.7 Hz, 6-H), 12.68 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 28.8 (CH_3), 120.9 (C-3), 122.1 (C-1), 122.7 (C-4), 127.7 (C-2' and C-6'), 129.0 (C-3' and C-5'), 132.1 (C-5), 132.2 (C-6), 135.0 (C-1'), 135.6 (C-4'), 141.6 (C-2), 166.3 (C=O), 203.54 (C=O); ν_{max}/cm^{-1} 760.0, 962.9, 1242.2, 1446.6, 1533.4, 1606.7, 1643.3 (C=O), 1672.9 (C=O), 3221.1.

4.1.2 Preparation of *N*-(4'-fluorobenzoyl)-2-aminoacetophenone 36b

The experimental procedure employed for the synthesis of **36a** was followed using a mixture of 2-aminoacetophenone **34** (3.0 g, 22.2 mmol); triethylamine (4.5 g, 44.4 mmol) and 4-fluorobenzoyl chloride **35b** (4.2 g, 26.6 mmol) in THF (40 ml). Work-up afforded **36b**, solid (5.20 g, 94%), m.p. 99-101° C (lit.[78] 92-95° C); ^{1}H NMR (300 MHz, $CDCl_3$) 2.64 (3H, s, CH_3), 7.06-7.16 (3H, m, 3'-H and 5'-H, 3-H), 7.54 (1H, t, *J* 8.0 Hz, 4-H), 7.88 (2H, d, *J* 8.1 Hz, 2'-H and 6'-H), 8.02 (1H, t, *J* 6.9 Hz, 5-H), 8.88 (1H, d, *J* 8.4 Hz, 6-H), 12.7 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 28.4 (CH_3), 115.8 (C-3' and C-5', d, $^{2}J_{CF}$ 21.8 Hz), 120.5 (C-3), 121.7 (C-1), 122.4 (C-4), 129.8 (C-2' and C-6'; d, $^{3}J_{CF}$ 9.2 Hz),

130.8 (C-1', d, $^{4}J_{CF}$ 3.0 Hz), 131.8 (C-5), 135.3 (C-6), 141.2 (C-2), 164.7 (C=O), 164.9 (C-4', d, $^{1}J_{CF}$ 251.2 Hz), 203.3 (C=O); ν_{max}/cm^{-1} 750.2, 846.7, 1163.1, 1231.2, 1448.5, 1504.4, 1588.8, 1649.1 (C=O), 1671.8 (C=O), 3187.8.

4.1.3 Preparation of *N*-(4'-Chlorobenzoyl)-2-aminoacetophenone 36c

The experimental procedure employed for the synthesis of **36a** was followed using a mixture of 2-aminoacetophenone **34** (3.07 g, 22.7 mmol), triethylamine (4.6 g, 45.5 mmol) and 4-chlorobenzoyl chloride **35c** (4.7 g, 27.2 mmol) in THF (40 ml). Work-up afforded **50c**, solid (6.03 g, 97%), m.p. 113-115^{o} C (lit.[79] 106-108^{o} C); ^{1}H NMR (300 MHz, $CDCl_3$) 2.66 (3H, s, CH_3), 7.11 (1H, t, *J* 7.5 Hz, 4-H), 7.44 (1H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.56 (1H, t, *J* 7.7 Hz, 5-H), 8.02 (1H, d, *J* 8.4 Hz, 3-H), 7.96 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 8.89 (1H, d, *J* 8.4 Hz, 6-H), 12.7 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 28.5 (CH_3), 120.6 (C-3), 121.7 (C-1), 122.6 (C-4), 128.8 (C-3' and C-5'), 128.9 (C-2' and C-6'), 131.8 (C-5), 133.0 (C-1'), 135.3 (C-6), 138.2 (C-4'), 141.1 (C-2), 164.7 (C=O), 203.3 (C=O); ν_{max}/cm^{-1} 744.1, 1010.7, 1244.1, 1316.1, 1448.5, 1533.4, 1587.8, 1647.2 (C=O), 1669.4 (C=O), 3226.5.

4.1.4 Preparation of *N*-(4'-methoxybenzoyl)-2-aminoacetophenone 36d

The experimental procedure employed for the synthesis of **36a** was followed using a mixture of 2-aminoacetophenone **34** (3.64 g, 26.9 mmol), triethylamine (5.4 g, 53.9

mmol) and 4-methoxybenzoyl chloride **35d** (5.55 g, 32.4 mmol) in THF (40 ml). Work-up afforded **36d**, solid (6.80 g, 94%), m.p.126-128^{o} C (lit.[78] 125-127^{o} C); ^{1}H NMR (300 MHz, $CDCl_3$) 2.65 (3H, s, CH_3); 3.82 (3H, s, OCH_3), 6.96 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.07 (1H, t, *J* 7.5 Hz, 4-H), 7.55 (1H, t, *J* 7.7 Hz, 5-H), 7.88 (1H, d, *J* 7.5 Hz, 3-H), 7.99 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 8.93 (1H, d, *J* 8.7 Hz, 6-H), 12.59 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 28.5 (CH_3), 55.3 (OCH_3), 113.8 (C-3' and C-5'), 120.5 (C-3), 122.0 (C-4), 121.6 (C-1), 129.3 (C-2' and C-6'), 131.7 (C-5), 132.7 (C-1'), 135.2 (C-6), 141.5 (C-2), 162.5 (C-4'), 165.5 (C=O), 203.1 (C=O); ν_{max}/cm^{-1} 758.0, 1018.4, 1158.4, 1188.1, 1249.9, 1313.5, 1508.3, 1604.8, 1644.9 (C=O), 1669.0 (C=O), 3225.0.

4.2 Preparation of the 2-phenylquinolin-4(1*H*)-one derivatives 18

4.2.1 Preparation of 2-phenylquinolin-4(1*H*)-one 18a

A stirred mixture of *N*-2-acetophenonebenzamide **36a** (2.50 g, 10.5 mmol) and 1M solution of potassium *tert*-butoxide (1M solution in THF, 20.9 ml, 20.9 mmol) in *tert*-butanol (20 ml) was heated under reflux for 12 h. The mixture was allowed to cool to room temperature and was poured into saturated aqueous ammonium chloride solution (40 ml). The precipitate was collected and washed several times with water and ice-cold ethanol (10 ml) and then was dried to afford **18a**, solid (1.50 g, 61%), m.p. 252–253° C (lit.[30] 252-254° C); ^{1}H NMR (300 MHz, DMSO-d_6) 6.33 (1H, s, 3-H), 7.33 (1H, t, *J* 7.2 Hz, 7-H), 7.42 (2H, t, *J* 9 Hz, 2'-H and 6'-H), 7.67 (1H, d, *J* 8.1 Hz, 8-H), 7.88-7.93 (2H, m, 3'-H and 5'-H), 8.10 (1H, d, *J* 8.1 Hz, 5-H), 11.8 (1H, s, NH); ^{13}C NMR (75 MHz,

DMSO-d_6) 107.6 (C-3), 118.5 (C-8), 119.5 (C-4a), 124.0 (C-6), 125.2 (C-5), 128.4 (C-3' and C-5'), 129.0 (C-2' and C-6'), 129.9 (C-7), 132.2 (C-4'), 135.5 (C-1'), 139.1 (C-8a), 149.2 (C-2), 177.7 (C-4); ν_{max}/cm^{-1} 754.9, 767.7, 839.0, 1253.7, 1471.2, 1499.0, 1545.0, 1581.6, 1629.8 (C=O), 2969.2, 3066.8, 3090.2, 3259 (NH).

4.2.2 Preparation of 2-(4'-fluorophenyl)quinolin-4(1*H*)-one 18b

The experimental procedure employed for the synthesis of **18a** was followed using a mixture of *N*-(4'-fluorobenzoyl)-2-aminoacetophenone **36b** (2.50 g, 9.72 mmol) and potassium *tert*-butoxide (1M solution in THF, 20 ml, 19.5 mmol) in *tert*-butanol (20 ml). Work-up afforded **18b**, solid (1.85 g, 80%), m.p. 315-317° C (lit.[26] 322-325° C); ^{1}H NMR (300 MHz, DMSO-d_6) 6.33 (1H, s, 3-H), 7.33 (1H, t, *J* 7.2 Hz, 7-H), 7.41 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.67 (1H, t, *J* 7.1 Hz, 6-H), 7.76 (1H, d, *J* 8.1 Hz, 8.-H), 7.91 (2H, d, *J* 8.1 Hz, 2'-H and 6'-H), 8.10 (1H, d, *J* 8.1 Hz, 5-H), 11.7 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 107.7 (C-3), 116.4 (C-3' and C-5', d, ^2J 21.6 Hz), 119.1 (C-8), 122.0 (C-4a), 123.7 (C-6), 125.1 (C-5), 131.0 (C-1', d, ^4J 3.1 Hz), 130.3 (C-2' and C-6', d, ^3J 8.7 Hz), 132.2 (C-7), 140.9 (C-8a), 149.3 (C-2), 163.8 (C-4', d, ^1J 246.5 Hz), 177.3 (C-4); ν_{max}/cm^{-1} 763.7, 794.8, 827.5, 1229.0, 1503.6, 1547.7, 1591.3, 1631.8 (C=O), 2972.6, 3068.7, 3258.0 (NH).

4.2.3 Preparation of 2-(4'-chlorophenyl)quinolin-4(1*H*)-one 18c

The experimental procedure employed for the synthesis of **18a** was followed using a mixture of *N*-(4'-chlorobenzoyl)-2-aminoacetophenone **36c** (2.50 g, 9.21 mmol) and potassium *tert*-butoxide (1M solution in THF, 18.3 ml, 18.3 mmol) in *tert*-butanol (20 ml). Work-up afforded **18c**, solid (2.0 g, 85%), m.p. 332–334° C (lit.[26] 270-273); ^{1}H NMR (300 MHz, DMSO-d_6) 6.39 (1H, s, 3-H), 7.34 (1H, t, *J* 7.5 Hz,7-H), 7.57-7.70 (3H, m, 3'-H, 5'-H and 6-H), 7.78 (1H, d, *J* 8.1 Hz,8-H), 7.88 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 8.90 (1H, dd, *J* 0.6 and 8.1 Hz, 5-H); ^{13}C NMR (75 MHz, DMSO-d_6) 107.6 (C-3), 119.5 (C-8), 123.8 (C-6), 124.3 (C-4a), 125.0 (C-5), 129.4 (C-3' and C-5'), 129.6 (C-2' and C-6'), 132.2 (C-7), 133.5 (C-1'), 135.6 (C-4'), 141.2 (C-8a), 177.6 (C-4); ν_{max}/cm^{-1} 763.7, 794.8, 827.5, 1229.0, 1503.6, 1547.7, 1547.3, 1591.3, 1631.8 (C=O), 1972.6, 3068.7, 3238.0 (NH).

4.2.4 Preparation of 2-(4'-methoxyphenyl)quinolin-4(1*H*)-one 18d

The experimental procedure employed for the synthesis of **18a** was followed using a mixture of *N*-(4'-methoxybenzoyl)-2-aminoacetophenone **36d** (2.50 g, 9.31 mmol) and potassium *tert*-butoxide (1M solution in THF, 18.6 ml, 18.6 mmol) in *tert*-butanol (20 ml). Work-up afforded **18d**, solid (1.80 g, 75%), m.p. 306–308° C (lit.[26] 290-293); ^{1}H NMR (300 MHz, DMSO-d_6) 3.84 (3H, s, OCH_3), 6.30 (1H, s, 3-H), 7.12 (2H, d, *J* 8.7 Hz, 3'-H and 5'-H), 7.31 (1H, dt, *J* 1.2 and 7.5 Hz, 7-H), 7.65 (1H, dt, *J* 1.8 and 7.5 Hz, 6-H), 7.75 (1H, d, *J* 8.1 Hz, 8-H), 7.80 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 8.07 (1H, dd, *J* 1.2 and 8.4 Hz, 5-H), 11.6 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 55.4 (OCH_3), 107.4

(C-3), 113.7 (C-3' and C-5'), 118.4 (C-8), 122.8 (C-4a), 123.9 (C-6), 125.2 (C-5), 127.1 (C-1'), 130.7 (C-2' and C-6'), 132.1 (C-7a), 139.0 (C-8a), 149.7 (C-2), 160.4 (C-4'), 171.7 (C-4); ν_{max}/cm^{-1} 752.2, 801.8, 1028.1, 1244.11503.4, 1543.1, 1580.7, 1631.8 (C=O), 2986.7, 3076.8, 3101.5, 3259.1 (NH).

4.3 Cyclization to N-*methyl and quinolone derivatives*

4.3.1 Preparation of *N*-benzoyl-*N*-methyl-2-aminoacetophenone 51a and 2-Aryl-1-methyl-4-quinolones 14a

A stirred solution of *N*-benzoyl-2-aminoacetophenone **36a** (2.50 g, 10.5 mmol) in dry THF (30 ml) was treated with NaH (0.38 g, 15.8 mmol) at room temperature. Methyl iodide (2.23 g, 15.7 mmol) was added to the reaction mixture after 30 minutes and stirring was continued for 18 hours at room temperature. The mixture was concentrated under reduced pressure and the residue was taken into chloroform (50 ml) and washed with water (20 ml). The organic solution was dried over sodium sulphate, filtered and the solvent was evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (elution with 2:3 hexane-EtOAc, v/v) to afford

sequentially the starting material, *N*-methylated derivative **51a** and 1-methyl-2-phenyl-4-quinolone **14a**.

***N*-Methylated derivative 51a**, solid (0.08 g, 4%), m.p. 127-129° C (lit.[79] 63-65° C); ^{1}H NMR (300 MHz, $CDCl_3$) 1.84 (3H, s, NCH_3), 3.44 (3H, s, CH_3), 7.26 (2H, dd, *J* 1.7 and 7.7 Hz, 2'-H and 6'-H), 7.37 (1H, dt, *J* 0.9 and 7.5 Hz, 4-H), 7.46-7.56 (4H, m, 3'-H, 5'-H, 4'-H), 7.65 (1H, dt, *J* 1.5 and 7.8 Hz, 5-H), 8.5 (1H, dd, *J* 1.7 and 8.3 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.3 (NCH_3), 37.2 (CH_3), 115.4 (C-3), 118.0 (C-2), 123.0 (C-4'), 125.0 (C-1'), 126.8 (C-5), 128.3 (C-2' and C-6'), 129.0 (C-6), 129.1 (C-3' and C-5'), 131.7 (C-4), 135.6 (C-1), 140.0 (C=O), 151.0 (C-4'), 177.4 (C=O); ν_{max}/cm^{-1} 754.6, 829.4, 1278.8, 1363.7, 1488.2, 1545.0, 1573.0, 1585.5, 1615.9 (C=O), 2918.2, 3053.6.

1-Methyl-2-phenyl-4-quinolone 14a, solid (1.10 g, 52%), m.p. 147-149° C (lit.[26] 143-145° C); ^{1}H NMR (300 MHz, $CDCl_3$) 3.60 (3H, s, NCH_3), 6.28 (1H, s, 3-H), 7.39-7.51 (6H, m, 2'-H and 6'-H, 3'-H and 5'-H, 4'-H, 7-H), 7.55 (1H, d, *J* 8.4 Hz, 8-H), 7.71 (1H, dt, *J* 0.9 and 7.8 Hz, 6-H), 8.5 (1H, dd, *J* 1.4 and 8.0 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 37.2 (NCH_3), 112.6 (C-3), 115.9 (C-8), 123.5 (C-5), 126.6 (C-4'), 126.7 (C-4a), 128.4 (C-2' and C-6'), 128.7 (C-3' and C-5'), 129.5 (C-6), 132.2 (C-7), 135.7 (C-1'), 141.8 (C-8a), 154.6 (C-2), 177.5 (C-4); ν_{max}/cm^{-1} 768.0, 1275.5, 1446.6, 1506.4, 1556.7, 1594.6, 1615.4 (C=O), 2918.2, 3053.6.

4.3.2 Preparation of *N*-(4'-fluorobenzoyl)-*N*-methyl-2-aminoacetophenone 51b and 1-methyl-2-(4'-fluorophenyl)-4-quinolone 14b

The experimental procedure employed for the synthesis of **14a** was followed using a mixture of *N*-(4'-fluorobenzoyl)-2-aminoacetophenone **36b** (2.50 g, 9.71 mmol), NaH (0.47 g, 19.4 mmol) and methyl iodide ((2.07 g, 14.6 mmol) in THF (30 ml). Work-up afforded **51b** and **14b**.

***N*-Methylated derivative 51b**, solid (0.15 g, 6%), m.p. 161-163° C (lit.[26] 168-170° C); ^{1}H NMR (300 MHz, $CDCl_3$) 1.85 (3H, s, NCH_3), 3.47 (3H, s, CH_3), 7.22-7.31 (4H, m, 2'-H and 6'-H, 3'-H and 5'-H), 7.40 (1H, t, *J* 7.5 Hz, 4-H), 7.49 (1H, d, *J* 8.4 Hz, 3-H), 7.68 (1H, dt, *J* 1.5 and 7.9 Hz, 5-H), 8.55 (1H, dd, *J* 1.7 and 8.3 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.3 (NCH_3), 37.2 (CH_3), 115.4 (C-3), 116.4 (C-3' and C-5', d, $^{2}J_{CF}$ 21.8 Hz), 118.4 (C-1), 123.1 (C-4), 125.0 (C-1), 126.9 (C-5), 130.4 (C-2' and C-6', d, $^{3}J_{CF}$ 7.9 Hz), 131.6 (C-1', d, $^{4}J_{CF}$ 3.7 Hz), 131.9 (C-6), 140.9 (C-2), 149.9 (NC=O), 162.8 (C-4', d, $^{1}J_{CF}$ 248.5 Hz), 164.5 (C=O), 177.3 (C=O); ν_{max}/cm^{-1} 767.7, 845.5, 1225.1, 1471.4, 1495.2, 1568.5, 1590.6, 1614.6 (C=O), 2922.2.

2-(4'-Fluorophenyl)-1-methyl-4-quinolone 14b, solid (1.39 g, 54%), m.p. 190-192 ° C (lit.[26] 178-180° C); ^{1}H NMR (300 MHz, $CDCl_3$) 3.58 (3H, s, NCH_3), 6.24 (1H, s, 3-H), 7.18 (1H, t, *J* 7.7 Hz, 7-H), 7.38-7.46 (4H, m, 3'-H and 5'-H, 2'-H and 6'-H), 7.53 (1H,d, *J* 8.4 Hz, 8-H), 7.70 (1H, t, *J* 7.1 Hz, 6-H), 8.47 (1H,d, *J* 7.2 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 37.2 (NCH_3), 112.8 (C-3), 115.9 (C-8), 116.0 (C-3' and C-5', d, $^{2}J_{CF}$ 21.8 Hz), 123.7 (C-5), 126.6 (C-6), 126.8 (C-4a), 130.5 (C-2' and C-6', d, $^{3}J_{CF}$ 8.2 Hz), 131.9 (C-1', d, $^{4}J_{CF}$ 3.8 Hz), 132.4 (C-7), 141.8 (C-8a) 153.6 (C-2), 163.3 (C-4', d, $^{1}J_{CF}$ 249.1 Hz), 177.5 (C-4); ν_{max}/cm^{-1} 769.6, 835.3, 848.7, 1466.2, 1492.7, 1571.5, 1591.9, 1622.1 (C=O), 2937.6.

4.3.3 Preparation of *N*-(4'-chlorobenzoyl)-2-aminoacetophenone 51c and 2-(4'-chlorophenyl)-1-methyl-4-quinolone 14c

The experimental procedure employed for the synthesis of **14a** was followed using a mixture of *N*-(4'-chlorobenzoyl)-2-aminoacetophenone **36c** (2.52 g, 9.20 mmol), NaH (0.33 g, 13.8 mmol) and methyl iodide (1.96 g, 13.8 mmol) in THF (30 ml). Work-up afforded **51c** and **14c**.

***N*-methylated derivative 51c**, solid (0.13 g, 5%), m.p. 167-169˚ C (lit.[26] 108-111˚ C); ^{1}H NMR (300 MHz, $CDCl_3$) 1.83 (3H, s, NCH_3), 3.45 (3H, s, CH_3), 7.22 (2H, d, *J* 8.1 Hz, 3'-H and 5'-H), 7.37 (1H, t, *J* 7.7 Hz, 4-H), 7.46 (1H, d, *J* 8.4 Hz, 3-H), 7.52 (2H, d, *J* 8.1 Hz, 2'-H and 6'-H), 7.65 (1H, t, *J* 8.0 Hz, 5-H), 8.51 (1H, d, *J* 8.1 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.3 (NCH_3), 37.2 (CH_3), 115.4 (C-3), 118.1 (C-1'), 123.1 (C-5), 124.9 (C-1), 126.8 (C-6), 129.5 (C-3' and C-5'), 129.9 (C-2' and C-6'), 131.9 (C-4), 133.9 (C-4'), 140.8 (C-2), 149.8 (C=O), 177.3 (C=O). ν_{max}/cm^{-1} 753.7, 1008.5, 1369.3, 1570.8, 1622.1 (C=O), 2924.1.

2-(4'-chlorophenyl)-1-methyl-4-quinolone 14c, solid (1.54 g, 61%), m.p. 177-179° C (lit.[26] 174-178° C); ^{1}H NMR (300 MHz, $CDCl_3$) 3.61 (3H, s, NCH_3), 6.30 (1H, s, 3-H), 7.37 (2H, d, *J* 8.1 Hz, 3'-H and 5'-H), 7.41 (1H, t, *J* 7.8 Hz, 7-H), 7.43 (1H, t, *J* 7.2 Hz,), 7.50 (2H, d, *J* 8.0 Hz, 2'-H and 6'-H), 7.56 (1H, d, *J* 8.1 Hz, 8-H), 7.71 (1H, t, *J* 7.8 Hz, 6-H), 8.47 (1H, d, *J* 7.8 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 37.2 (NCH_3), 112.6 (C-3), 115 (C-8), 123.7 (C-5), 126.5 (C-6), 129.9 (C-3' and C-5'), 129.9 (C-2' and C-6'), 132.4 (C-7), 134.1 (C-4a), 135.8 (C-1'), 141.8 (C-8a) 153.3 (C-4'), 160.4 (C-2), 177.5 (C-4);

ν_{max}/cm^{-1} 760.0, 833.7, 846.7, 1093.2, 1404.2, 1490.5, 1572.0, 1595.0, 1618.3 (C=O), 3053.3.

4.3.4 Preparation of 2-(4'-methoxyphenyl)-1-methyl-4-quinolone 14d

The experimental procedure employed for the synthesis of **14a** was followed using a mixture of *N*-(4'-methoxybenzoyl)-2-aminoacetophenone **36d** (2.52 g, 9.37 mmol), NaH (0.34 g, 14.1 mmol) and methyl iodide ((2.0 g, 14.1 mmol) in THF (30 ml). Work-up afforded **51d** and **14d**.

***N*-methylated derivative 51d**, solid (0.10 g, 3.8%), m.p. 181-183° C (lit.[26] 179-182° C); ^{1}H NMR (300 MHz, $CDCl_3$) 1.85 (3H, s, NCH_3), 3.47 (3H, s, CH_3), 7.22-7.31 (4H, m, 2'-H and 6'-H, 3'-H and 5'-H), 7.40 (1H, t, *J* 7.5 Hz, 4-H), 7.49 (1H, d, *J* 8.4 Hz, 3-H), 7.68 (1H, dt, *J* 1.2 and 7.8 Hz, 5-H), 8.55 (1H, dd, *J* 1.8 and 8.3 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.4 (NCH_3), 37.1 (CH_3), 55.2 (OCH_3), 114.4 (C-3' and C-5'), 115.5 (C-3), 118.3 (C-1'), 122.8 (C-4), 124.9 (C-1), 126.7 (C-5), 127.7 (C-2), 129.7 (C-2' and C-6'), 131.6 (C-6), 140.8 (C-2), 151.0 (C-4'), 159.8 (C=O), 177.3 (C=O); ν_{max}/cm^{-1} 756.1, 846.7, 1246.0, 1291.0, 1546.2, 1569.1, 1589.3, 1612.2 (C=O), 2936.6.

1-methyl-2-(4'-methoxyphenyl)-4-quinolone 14d, solid (1.32 g, 53%), m.p. 146–148° C (lit.[26] 144–146° C); ^{1}H NMR (300 MHz, $CDCl_3$) 3.66 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 6.41 (1H, s, 3-H), 7.02 (2H, d, *J* 9 Hz, 3'-H and 5'-H), 7.36 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 7.43 (1H, t, *J* 7.2 Hz, 7-H), 7.58 (1H, d, *J* 8.7 Hz, 8-H), 7.72 (1H, dt, *J* 7.2 Hz, 6-H), 8.50 (1H,dd, *J* 1.5 and 6.9 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 37.2 (NCH_3), 55.3

(OCH_3), 112.6 (C-3), 114.1 (C-3' and C-5'), 115.9 (C-8), 123.4 (C-5), 126.5 (C-6), 126.7 (C-4a), 128 (C-1'), 129.9 (C-2' and C-6'), 132.1 (C-7), 141.8 (C-8a) 154.6 (C-2), 160.4 (C-4'), 177.5 (C-4); ν_{max}/cm^{-1} 769.1, 841.1, 1182.4, 1251.8, 1493.2, 1562.5, 1592.8, 1614.4 (C=O).

4.4 C-3 Bromination of quinolone derivatives

4.4.1 Preparation of 2-phenyl-3-bromoquinolin-4(1*H*)-one 49a

A stirred suspension of 2-phenylquinolin-4(1*H*)-one **18a** (1.0 g, 4.50 mmol) in acetic acid (10 ml) was treated with pyridinium tribromide (2.9 g, 9.11 mmol) at room temperature. The mixture was stirred for 2 hours at room temperature and then was poured into aqueous sodium thiosulphate solutions. The resulting precipitate was filtered to dryness to afford **49a**, solid (1.28 g, 94%), m.p. 219–221° C (lit.[46] 292-294° C); ^{1}H NMR (300 MHz, DMSO-d_6) 7.41 (1H, dt, *J* 1.5 and 7.4 Hz, 6-H), 7.57-7.74 (7H, m, 2'-H and 6'-H, 3'-H and 5'-H, 4'-H, 7-H, 8-H), 8.16 (1H, d, *J* 7.8 Hz, 5-H), 12.32 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 105.3 (C-3), 118.5 (C-8), 122.9 (C-4a), 124.0 (C-6), 125.2 (C-5), 128.4 (C-3' and C-5'), 129.0 (C-2' and C-6'), 129.9 (C-7), 132.2 (C-4'), 135.5 (C-1'), 139.1 (C-8a), 149.9 (C-2), 171.7 (C-4); ν_{max}/cm^{-1} 754.9, 864.8, 1123.3, 1352.4, 1470.0, 1492.4, 1543.4, 1626.5 (C=O), 2902.9, 3059.1, 3372.5.

4.4.2 Preparation of 3-bromo-2-(4'-fluorophenyl)quinolin-4(1*H*)-one 49b

The experimental procedure employed for the synthesis of **47a** was followed using a mixture of 2-(4'-fluorophenyl)quinolin-4(1*H*)-one **18b** (1.0 g, 4.21 mmol), pyridinium tribromide (2.67 g, 8.40 mmol) in glacial acetic acid (10 ml). Work-up afforded **47b**, solid (1.26 g, 95%), m.p. 231-233° C (lit.[46]267–269); ^{1}H NMR (300 MHz, DMSO-d_6) 7.41 (1H, dt, *J* 1.8 and 6.3 Hz, 6-H), 7.45 (2H, d, 2'-H and 6'-H, *J* 9 Hz), 7.64 -7.74 (4H, m, 7-H, 8-H, 3'-H and 5'-H), 8.17 (1H, dd, *J* 0.9 and 8.1 Hz, 5-H), 12.3 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 105.5 (C-3), 115.4 (C-3' and C-5', d, ^{2}J 21.0 Hz), 118.5 (C-8), 122.9 (C-4a), 124.1 (C-6), 125.3 (C-5), 131.4 (C-1', d, ^{4}J 3.0 Hz), 131.6 (C-2' and C-6', d, ^{3}J 8.8 Hz), 132.2 (C-7), 138.9 (C-9), 148.9 (C-2), 162.8 (C-4', d, ^{1}J 245.7 Hz), 171.7 (C-4); ν_{max}/cm^{-1} 759.0, 839.8, 1130.8, 1352.3, 1467.8, 1489.2, 1537.9, 1626.0 (C=O), 2912.5, 3059.0, 3372.3.

4.4.3 Preparation of 3-bromo-2-(4'-chlorophenyl)quinolin-4(1*H*)-one 49c

The experimental procedure employed for the synthesis of **49a** was followed using a mixture of 2-(4'-chlorophenyl)quinolin-4(1*H*)-one **18c** (1.0 g, 3.90 mmol), pyridinium tribromide (2.51 g, 7.80 mmol) in glacial acetic acid (10 ml). Work-up afforded **49c**, solid (1.19 g, 91%), m.p. 233-235° C (lit.[46] 270–272° C); ^{1}H NMR (300 MHz, DMSO-d_6) 7.35 (1H, dt, *J* 1.8 and 7.20 Hz, 6-H), 7.59-7.68 (6H, m, 2'-H and 6'-H, 3'-H and 5'-H, 7-H and 8-H), 8.13 (1H, d, *J* 8.4 Hz, 5-H), 12.3 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 105.5 (C-3), 118.5 (C-8), 122.9 (C-4a), 124.1 (C-6), 125.2 (C-5), 128.5 (C-3' and C-5'), 131.1 (C-2' and C-6'), 132.2 (C-7), 133.7 (C-4'), 134.8 (C-1'), 138.9 (C-8a), 148.7 (C-

2), 171.6 (C-4); ν_{max}/cm^{-1} 758.0, 1014.6, 1092.1, 1348.2, 1491.1, 1570.1, 1626.0 (C=O), 3059.0, 3259.3.

4.4.4 Preparation of 3-bromo-2-(4'-methoxyphenyl)quinolin-4(1*H*)-one 49d

The experimental procedure employed for the synthesis of **49a** was followed using a mixture of 2-(4'-methoxyphenyl)quinolin-4(1*H*)-one (1.0 g, 3.98 mmol), pyridinium tribromide (2.55 g, 7.97 mmol) in glacial acetic acid (10 ml). Work-up afforded **49d**, solid (1.18 g, 90%), m.p. 206-208° C (lit.[46] 267-269° C); ^{1}H NMR (300 MHz, DMSO-d_6) 3.84 (3H, s, OCH_3), 7.13 (2H, d, *J* 8.7 Hz, 3'-H and 5'-H), 7.38 (1H, dt, *J* 2.4 and 7.0 Hz, 6-H), 7.57 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 7.64 -7.72 (2H, m, 7-H and 8-H), 8.14 (1H, d, *J* 7.8 Hz, 5-H), 12.19 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 55.4 (OCH_3), 105.4 (C-3), 113.7 (C-3' and C-5'), 118.4 (C-8), 122.8 (C-4a), 123.9 (C-6), 125.2 (C-5), 127.1 (C-1'), 130.7 (C-2' and C-6'), 132.1 (C-7a), 139.0 (C-8a), 149.7 (C-2), 160.4 (C-4'), 171.7 (C-4); ν_{max}/cm^{-1} 758.6, 829.5, 877.6, 1022.3, 1252.1, 1467.8, 1493.4, 1528.3, 1608.6, 1626.8 (C=O), 2890.3, 3059.1, 3470.0, 3544.8.

4.5 Preparation of 3-bromo-1-methyl-2-phenyl-4-quinolones

4.5.1 Preparation of 3-bromo-1-methyl-2-phenyl-4-quinolones 50a

A stirred suspension of 1-methyl-2-phenyl-4-quinolone **14a** (1.0 g, 4.30 mmol) in acetic acid (10 ml) was treated with pyridinium tribromide (2.74 g, 8.60 mmol) at room temperature. The mixture was stirred for 2 hours at room temperature and then quenched with ice-cold water. The resulting precipitate was filtered to dryness and was taken into chloroform (20 ml). The chloroform solution was washed sequentially with sodium hydrogen carbonate and sodium thiosulphate solutions and then dried over sodium sulphate, filtered and the solvent evaporated under reduced pressure to afford **50a**, solid (1.20 g, 90%), m.p. 171–173° C (lit.[46] 186-188° C); ^{1}H NMR (300 MHz, $CDCl_3$) 3.55 (3H, s, NCH_3), 7.33 (2H, d, *J* 5.7 Hz, 2'-H and 6'-H), 7.43-7.48 (4H, t, *J* 7.5 Hz, 3'-H and 5'-H, 4'-H, 7-H), 7.55 (1H, d, *J* 6.9 Hz, 8-H), 7.72 (1H, t, *J* 6.9 Hz, 6-H), 8.59 (1H, dd, *J* 1.5 and 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 38.6 (NCH_3), 107.5 (C-3), 117.5 (C-8), 124.2 (C-4a), 124.2 (C-5), 125.9 (C-6), 128.3 (C-2' and C-6'), 129.0 (C-3' and C-5'), 129.5 (C-4'), 132.7 (C-7), 136.0 (C-1') 140.3 (C-8a), 153.0 (C-2), 170.9 (C-4); ν_{max}/cm^{-1} 760.7, 868.9, 1082.1, 1157.3, 1263.9, 1394.5, 1485.1, 1591.3, 1618.7 (C=O), 3053.5.

4.5.2 Preparation of 3-bromo-2-(4'-fluorophenyl)-1-methyl-4-quinolone 50b

The experimental procedure employed for the synthesis of **50a** was followed using a mixture of 2-(4'-fluorophenyl)-1-methyl-4-quinolone **14b** (1.0 g, 4.0 mmol), pyridinium tribromide (2.53 g, 8.0 mmol) in glacial acetic acid (10 ml). Work-up afforded **50b**, solid

(1.14 g, 87%), m.p. 193-195 °C (lit.[47] 195-198); ^{1}H NMR (300 MHz, $CDCl_3$) 3.57 (3H, s, NCH_3), 7.27-7.37 (4H, m, 2'-H and 6'-H, 3'-H and 5'-H), 7.47 (1H, t, *J* 7.8 Hz, 7-H), 7.56 (1H, d, *J* 8.7 Hz, 8-H), 7.74 (1H,dt, *J* 1.5 and 5.1 Hz, 6-H), 8.58 (1H, dd, *J* 1.5 and 6.9 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 38.4 (NCH_3), 109.3 (C-3), 115.8 (C-8), 116.6 (C-3' and C-5', d, $^{2}J_{CF}$ 22.1 Hz), 124.4 (C-5), 124.7 (C-4a), 127.5 (C-6), 130.5 (C-2' and C-6', d, $^{3}J_{CF}$ 8.6 Hz), 132.1 (C-1', d, $^{4}J_{CF}$ 3.6 Hz), 132.6 (C-7), 140.4 (C-8a), 151.5 (C-2), 163.1 (C-4', d, $^{1}J_{CF}$ 249.3 Hz), 172.4 (C-4); ν_{max}/cm^{-1} 753.1, 806.3, 860.5, 1080.1, 1154.6, 1224.5, 1492.6, 1589.2, 1612.5 (C=O), 3047.7.

4.5.3 Preparation of 3-bromo-2-(4'-chlorophenyl)-1-methyl-4-quinolone 50c

The experimental procedure employed for the synthesis of **50a** was followed using a mixture of 2-(4'-chlorophenyl)-1-methyl-4-quinolone **14c** (1.0 g, 3.70 mmol), pyridinium tribromide (2.38 g, 7.40 mmol) in glacial acetic acid (10 ml). Work-up afforded **50c**, solid (1.13 g, 88%), m.p. 236-238° C (lit.[46] 250–253° C); ^{1}H NMR (300 MHz, $CDCl_3$) 3.54 (3H, s, NCH_3), 7.29 (2H, d, *J* 8.7 Hz, 3'-H and 5'-H), 7.44 (1H, t, *J* 7.5 Hz, 7-H), 7.53 (3H, t, *J* 8.1 Hz, 2'-H and 6'-H, 8-H), 7.71 (1H, dt, *J* 0.9 and 7.2 Hz, 6-H), 8.53 (1H, d, *J* 7.2 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 38.5 (NCH_3), 107.6 (C-3), 117.2 (C-5), 124.2 (C-6), 124.3 (C-4a), 125.9 (C-8), 129 (C-3' and C-5'), 130.2 (C-2' and C-6'), 132.5 (C-7), 134.5 (C-4'), 140.3 (C-8a), 151.7 (C-2), 160.6 (C-1'), 170.9 (C-4); ν_{max}/cm^{-1} 766.0, 862.9, 1081.1, 1155.4, 1397.0, 1483.4, 1591.3, 1591.3, 1616.3 (C=O), 2929.6.

4.5.4 Preparation of 3-bromo-2-(4'-methoxyphenyl)-1-methyl-4-quinolone 50d

The experimental procedure employed for the synthesis of **50a** was followed using a mixture of 2-(4'-methoxyphenyl)-1-methyl-4-quinolone **14d** (1.0 g, 3.80 mmol), pyridinium tribromide (2.42 g, 7.60 mmol) in glacial acetic acid (10 ml). Work-up afforded **50d**, solid (1.04 g, 80%), m.p. 222-224° C (lit.[46] 205-207° C); ^{1}H NMR (300 MHz, $CDCl_3$) 3.56 (3H, s, NCH_3), 3.88 (3H, s, OCH_3), 7.07 (2H, d, *J* 7.5 Hz, 3'-H and 5'-H), 7.25 (2H, d, *J* 7.0 Hz, 2'-H and 6'-H), 7.43 (1H, t, *J* 7.8 Hz, 7-H), 7.54 (1H, d, *J* 8.7 Hz, 8-H), 7.70 (1H, t, *J* 7.0 Hz, 6-H), 8.55 (1H, d, *J* 8.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 38.7 (NCH_3), 55.6 (OCH_3), 109.8 (C-3), 114.7 (C-3' and C-5'), 116.8 (C-8), 124.5 (C-4a), 125.0 (C-6), 128.6 (C-4'), 125.7 (C-5), 130 (C-2' and C-6'), 132.7 (C-7), 140.8 (C-8a), 152.8 (C-2) ,160.6 (C-1'), 172.8 (C-4); ν_{max}/cm^{-1} 767.7, 827.5, 1080.8, 1155.4, 1244.1, 1462.0, 1489.9, 1593.9, 1618.3 (C=O), 2960.7, 2934.5, 3452.5.

4.6 C-3 iodination of 2-phenylquinolin-4(1*H*)-ones

4.6.1 Preparation of 3-iodo-2-phenylquinolin-4(1*H*)-one 65a

A mixture of 2-phenylquinolin-4(1*H*)-one **18a** (0.5 g, 2.26 mmol), iodine (1.15 g, 4.52 mmol) and sodium carbonate (0.36 g, 3.43 mmol) in THF (20 ml) was stirred at room temperature for 12 hours and poured into saturated ice-cold aqueous sodium thiosulphate solution. The precipitate was collected, washed with water and recrystallized to afford **65a**, solid (0.59 g, 75%), m.p. 267-269° C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) 7.39

(1H, t, *J* 8.1 Hz, 7-H), 7.66 (7H, m, 2'-H and 6'-H, 3'-H and 5'-H, 4'-H, 6-H, 8-H), 8.28 (1H, d, *J* 8.1 Hz 5-H), 12.3 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 85.9 (C-3), 118.4 (C-8), 120.8 (C-4a), 124.1 (C-6), 125.5 (C-5), 128.4 (C-3' and C-5'), 128.9 (C-2' and C-6'), 129.8 (C-4'), 132.1 (C-7), 137.9 (C-1'), 139.9 (C-8a), 153.1 (C-2), 173.4 (C-4); ν_{max}/cm^{-1} 755.6, 869.7, 1350.2, 1468.3, 1490.5, 1539.5, 1566.2, 1624.8 (C=O), 2899.0, 3056.2, 3361.9 (N-H); MS: m/z 347 (M^+, 86), 220 (62), 165 (37), 131 (29), 69 (100).

Anal. Calcd. for $C_{15}H_{10}NOI$: C, 49.34; H, 2.90; N, 4.03. Found: C, 49.28; H, 3.40; N, 3.85.

4.6.2 Preparation of 2-(4'-fluorophenyl)-3-iodoquinolin-4(1*H*)-one 65b

The experimental procedure employed for the synthesis of **65a** was followed using a mixture of 2-(4'-fluorophenyl)quinolin-4(1*H*)-one **18b** (0.5 g, 2.10 mmol), iodine (1.06 g, 4.20 mmol) and sodium carbonate (0.33 g, 3.10 mmol) in THF (15 ml). Work-up afforded **65b**, solid (0.65 g, 85%), m.p. 265-267° C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) 7.40 (3H, m, 3'-H and 5'-H, 7-H), 7.65 (4H, m, 2'-H and 6'-H, 6-H, 8-H), 8.13 (1H, d, *J* 7.8 Hz, 5-H), 12.3 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 86.2 (C-3), 115.3 (C-3' and C-5', d, $^2J_{CF}$ 21.9 Hz), 118.6 (C-8), 120.9 (C-4a), 124.1 (C-6), 125.4 (C-5), 131.6 (C-2' and C-6', d, $^3J_{CF}$ 8.6 Hz), 132.0 (C-7), 134.6 (C-1', d, $^4J_{CF}$ 3.2 Hz), 139.6 (C-8a), 152.4 (C-2), 162.7 (C-4', d, $^1J_{CF}$ 245.3 Hz), 173.5 (C-4); ν_{max}/cm^{-1} 754.7, 8180.0, 1157.8, 1224.8, 1466.3, 1492.9, 1535.3, 1622.1 (C=O), 2924.7, 3063.1, 3414.4; MS: m/z 365 (M^+, 89), 238 (45), 183 (27), 69 (56), 28 (100).

Anal. Calcd. for $C_{15}H_9NOFI$: C, 48.34; H, 2.48; N, 3.84. Found: C, 47.30; H, 3.03; N, 3.71.

4.6.3 Preparation of 3-iodo-2-(4'-chlorophenyl)quinolin-4(1*H*)-one 65c

The experimental procedure employed for the synthesis of **65a** was followed using a mixture of 2-(4'-chloropheny)quinolin-4(1*H*)-one **18c** (0.5 g, 2.0 mmol), iodine (0.99 g, 4.0 mmol) and sodium carbonate (0.25 g, 3.0 mmol) in THF (15 ml). Work-up afforded **65c**, solid (0.68 g, 91%), m.p. 291-293° C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) 7.39 (1H, t, *J* 7.2 Hz, 7-H), 7.57–7.73 (6H, m, 3'-H and 5'-H, 2'-H and 6'-H, 6-H and 8-H), 8.13 (1H, d, *J* 7.8 Hz, 5-H), 12.3 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 86.0 (C-3), 118.4 (C-8), 120.9 (C-4a), 124.4 (C-6), 125.5 (C-5), 128.5 (C-3' and C-5'), 131.0 (C-2' and C-6'), 132.3 (C-7), 134.7 (C-4'), 136.7 (C-1'), 139.3 (C-8a), 152.0 (C-2), 173.7 (C-4); ν_{max}/cm^{-1} 758.6, 995.7, 1090.0, 1165.2, 1487.4, 1539.5, 1626.2 (C=O), 2900.8, 3060.6, 3401.0 (N-H); MS: m/z 381 (M^+, 68), 254 (32), 69 (31), 28 (100).

Anal. Calcd. for $C_{15}H_9NOClI$: C, 45.21; H, 2.38; N, 3.67. Found: C, 45.57; H, 2.31; N, 3.62.

4.6.4 Preparation of 3-iodo-2-(4'-methoxyphenyl)quinolin-4(1*H*)-one 65d

The experimental procedure employed for the synthesis of **65a** was followed using a mixture of 2-(4'-methoxyphenyl)-1-methyl-4-quinolone **18d** (0.20 g, 0.80 mmol) and

iodine (0.41 g, 1.6 mmol) in THF (15 ml). Work-up afforded **65d**, solid (0.25 g, 83%), m.p. 276-278° C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) 3.84 (3H, s, CH_3), 7.11 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.37 (1H, t, *J* 7.2 Hz, 7-H), 7.51 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 7.66 (2H, m, 6-H and 8-H), 8.12 (1H, d, *J* 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 55.4 (OCH_3), 86.2 (C-3), 113.6 (C-3' and C-5'), 118.3 (C-8), 120.7 (C-4a), 124.1 (C-6), 125.4 (C-5), 130.1 (C-1'), 130.6 (C-2' and C-6'), 132.1 (C-7), 139.3 (C-8a), 152.9 (C-2), 160.3 (C-4'), 173.6 (C-4); ν_{max}/cm^{-1} 759.8, 1024.2, 1178.9, 1253.6, 1467.8, 1544.3, 1624.1 (C=O), 2929.9, 3061.3, 3390.7; MS: m/z 377 (M^+, 100), 250 (36), 69 (28).

Anal. Calcd. for $C_{15}H_{12}NO_2I$: C, 49.47; H, 3.21; N, 3.71. Found: C, 50.95; H, 3.49; N, 3.35.

4.7 Preparation of 2-aryl-3-iodo-1-methyl-4-quinolone derivatives 66

4.7.1 Preparation of 3-iodo-1-methyl-2-phenyl-4-quinolone 66a

A stirred mixture of 3-iodo-2-phenylquinolin-4(1*H*)-one **65a** (0.5 g, 1.4 mmol) in dry THF was treated with NaH (0.041 g, 1.7 mmol) at room temperature. Methyl iodide (0.31 g, 2.2 mmol) was added to the reaction mixture after 30 minutes and stirring was continued for 12 hours at room temperature. The mixture was quenched with water and extracted with chloroform. The organic phase was dried over anhydrous sodium sulphate, filtered and solvent evaporated to dryness in a *vacuo* to afford **66a**, solid (0.46 g, 89%), m.p. 230-232° C; ^{1}H NMR (300 MHz, $CDCl_3$) 3.56 (3H, s, CH_3), 7.28 (2H, dd, *J* 1.5 and 7.7 Hz, 2'-H and 6'-H), 7.47 (1H, dt, *J* 1.1 and 7.2 Hz, 7-H), 7.53-7.60 (4H, m, 3'-H and

5'-H; 4'-H; 8-H), 7.72 (1H, dt, *J* 1.5 and 7.9 Hz, 6-H), 8.55 (1H, dd, *J* 1.5 and 8.4 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 39.1 (NCH_3), 89.1 (C-3), 115.6 (C-4'), 122.9 (C-4a), 124.4 (C-8), 127.8 (C-5), 128.2 (C-2' and C-6'), 129.2 (C-3' and C-5'), 129.7 (C-6), 132.6 (C-7), 139.3 (C-1'), 140.7 (C-8a), 155.2 (C-2), 174.1 (C-4); ν_{max}/cm^{-1} 750.3, 862.2, 1074.3, 1151.5, 1394.5,1460.0, 1524.4, 1593.0, 1616.3 (C=O), 2930.7, 3055.2; MS: m/z 361 (M^+, 100); 234 (49).

Anal. Calcd. for $C_{16}H_{12}NOI$: C, 53.21; H, 3.35; N, 3.89. Found: C, 54.08; H, 3.59; N, 3.93.

4.7.2 Preparation of 2-(4'-fluorophenyl)-3-iodo-1-methyl-4-quinolone 66b

The experimental procedure employed for the synthesis of **66a** was followed using a mixture of 3-iodo-2-(4'-fluorophenyl)quinolin-4(1*H*)-one **65b** (0.5 g, 1.40 mmol), NaH (0.039 g, 1.60 mmol) and CH_3I (0.29 g, 2.10 mmol) in THF (15 ml). Work-up afforded **66b**, solid (0.46 g, 88%), m.p. 218-220° C; ^{1}H NMR (300 MHz, $CDCl_3$) 3.56 (3H, s, CH_3), 7.22 (4H, d, *J* 2.1 Hz, 2'-H and 6'-H, 3'-H and 5'-H), 7.42 (1H, t, *J* 7.5 Hz, 7-H), 7.50 (1H, d, *J* 8.7 Hz, 8-H), 7.69 (1H, dt, *J* 1.7 and 7.71 Hz, 6-H), 8.50 (1H, dd, *J* 1.5 and 8.3 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 39.1 (NCH_3), 89.7 (C-3), 115.6 (C-8), 116.6 (C-3' and C-5', d, $^2J_{CF}$ 21.9 Hz), 122.8 (C-4a), 124.5 (C-5), 127.8 (C-6), 130.4 (C-2' and C-6', d, $^3J_{CF}$ 8.3 Hz), 132.6 (C-7), 135.4 (C-1', d, $^4J_{CF}$ 3.7 Hz), 140.7 (C-2), 154.2 (C-2), 163.1 (C-4', d, $^1J_{CF}$ 249.3 Hz), 174.1 (C=O); ν_{max}/cm^{-1} 765.7, 859.6, 1151.5, 1217.9, 1394.8, 1488.7, 1589.0, 1612.6 (C=O), 3063.3; MS: m/z 379 (M^+, 100), 252 (52).

Anal. Calcd. for $C_{16}H_{11}NOFI$: C, 50.68; H, 2.92; N, 3.69. Found: C, 50.92; H, 3.11; N, 3.62.

4.7.3 Preparation of 2-(4'-chlorophenyl)-3-iodo-1-methyl-4-quinolone 66c

The experimental procedure employed for the synthesis of **66a** was followed using a mixture of 3-iodo-2-(4'-chlorophenyl)quinolin-4(1*H*)-one 6**5c** (0.5 g, 1.30 mmol), NaH (0.038 g, 1.60 mmol) and CH_3I (0.28 g, 2.0 mmol) in THF (15 ml). Work-up afforded **59c**, solid (0.39g, 75%), m.p. 253-255° C; ^{1}H NMR (300 MHz, $CDCl_3$) 3.58 (3H, s, NCH_3), 7.23 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.44 (1H, dt, *J* 0.9 and 7.5 Hz, 7-H), 7.54 (3H, m, 2'-H and 6'-H, 8-H), 7.72 (1H, dt, *J* 1.8 and 7.8 Hz, 6-H), 8.52 (1H, dd, *J* 1.5 and 8.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 39.1 (NCH_3), 89.3 (C-3), 115.6 (C-3' and C-5'), 122.9 (C-8), 124.6 (C-5), 127.9 (C-6), 129.8 (C-2' and C-6'), 132.7 (C-7), 135.9 (C-8a), 137.6 (C-2), 140.7 (C-1'), 154 (C-4'), 173.9 (C-4); ν_{max}/cm^{-1} 767.7, 860.2, 1008.8, 1087.8, 1153.6, 1396.5, 1482.4, 1590.1, 1613.6 (C=O), 2926.2; MS: m/z 395 (M^+, 89), 268 (43), 28 (100).

Anal. Calcd. for $C_{16}H_{11}NOClI$: C, 48.58; H, 2.80; N, 3.54. Found: C, 48.79; H, 2.93; N, 3.47.

4.7.4 Preparation 3-iodo-2-(4'-methoxyphenyl)-1-methyl-4-quinolone 66d

The experimental procedure employed for the synthesis of **66a** was followed using a mixture of 3-iodo-2-(4'-methoxyphenyl)quinolin-4(1*H*)-one 6**5d** (0.5 g, 1.3 mmol), NaH

(0.038 g, 1.6 mmol) and CH_3I (0.28 g, 2.0 mmol) in THF (15 ml). Work-up afforded **66d**, solid (0.38 g, 73%), m.p. 196-198° C; ^{1}H NMR (300 MHz, $CDCl_3$) 3.66 (3H, s, NCH_3), 3.96 (3H, s, OCH_3), 7.13 (2H, d, *J* 8.7 Hz, 3'-H and 5'-H), 7.26 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 7.50 (1H, dt, *J* 0.9 and 7.4 Hz, 7-H), 7.59 (1H, d, *J* 8.7 Hz, 8-H), 7.78 (1H, dt, *J* 1.8 and 7.8 Hz, 6-H), 8.60 (1H, dd, *J* 0.9 and 7.9 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 39.2 (NCH_3), 55.4 (OCH_3), 89.9 (C-3), 114.4 (C-3' and C-5'), 115.9 (C-8), 122.8 (C-4a), 124.4 (C-5), 127.8 (C-6), 129.7 (C-2' and C-6'), 131.8 (C-8a), 132.5 (C-7), 140.7 (C-2), 155.3 (C-1'), 160.3 (C-4'), 174.1 (C-4); ν_{max}/cm^{-1} 762.3, 852.4, 1029.7, 1248.2, 1460.1, 1502.4, 1590.3, 1614.4 (C=O), 3008.7, 3446.8; MS: m/z (M^+, 90).

Anal. Calcd. for $C_{17}H_{14}NO_2I$: C, 52.19; H, 3.61; N, 3.58. Found: C, 52.40; H, 3.93; N, 3.53.

4.8.1 Preparation of 2,3-diphenylquinolin-4(1*H*)-one 67

$Pd(PPh_3)_4$ (0.07 g, 0.0576 mmol, 2.3 mmol%) was added to a solution of 3-iodo-2-phenylquinolin-4(1*H*)-one **65a** (0.4 g, 1.2 mmol), sodium carbonate (2.6 ml, 2M aq. soln.) and phenylboric acid (0.28 g, 2.3 mmol) in DMF (6 ml) under nitrogen. The mixture was stirred and heated under reflux for 12 hours, cooled to room temperature and poured into ice-cold aqueous sodium thiosulphate solution. The precipitate was collected and purified by column chromatography (elution with 1:3 hexane-EtOAc, v/v) to afford **67,** solid (0.18 g, 53%), m.p. 351-353° C (lit.[84,85] 337-338° C); ^{1}H NMR (300 MHz, DMSO-d_6) 7.04-7.18 (5H, m, 2''-H and 6''-H and 3''-H and 5''-H, 4''-H), 7.25 – 7.36 (6H,

m, 2'-H and 6'-H, 4'-H, 6-H, 7-H, 8-H), 7.68 (2H, t, *J* 8.4 Hz, 3'-H and 5'-H), 8.15 (1H, d, *J* 8.4 Hz, 5-H), 11.8 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 37.6 (CH_3), 118.4

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2 (C-2" and C-6"), 128.1

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(C-4'), 129.5 (C-3" and C-5"), 131.7

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(C-4); ν_{max}/cm^{-1} 756.2, 1350.3, 1516.0, 1552.9, 1622.1 (C=O), 3101.7; MS: m/z 296 (M^+, 100), 28 (34).

Anal. Calcd. for $C_{21}H_{15}NO$: C, 84.82; H, 6.08; N, 3.71. Found: C, 83.10; H, 6.56; N, 3.77.

4.9.1 Preparation of 2,3-diphenyl-1-methyl-4-quinolone 68a

$Pd(PPh_3)_4$ (0.016 g, 0.0139 mmol, 2.3 mmol%) was added to a solution of 3-iodo-1-methyl-2-phenylquinolone **66a** (0.1 g, 0.277 mmol), sodium carbonate (2 ml, 1M aq. soln.) and phenylboric acid (0.068 g, 0.0554 mmol) in DMF (3 ml) under nitrogen. The mixture was stirred and heated under reflux for 12 hours, cooled to room temperature and poured into ice-cold water. The precipitate was collected and taken up into chloroform (30 ml), washed with water and the organic phase was dried over anhydrous sodium sulphate, filtered and the solvent evaporated in a *vacuo*. The residue was recrystallized to

afford **68a**, solid (0.05 g, 58%), m.p. 241–243 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) 3.52 (3H, s, CH_3), 7.00-7.15 (6H, m, 2"-H and 6"-H, 3"-H and 5"-H, 7-H and 4"-H), 7.26 (3H, m, 4'-H, 2'-H and 6'-H), 7.41 (2H, dt, *J* 0.9 and 7.55 Hz, 3'-H and 5'-H), 7.56 (1H, d, *J* 8.4 Hz, 8-H), 7.71 (1H, dt, *J* 1.8 and 8.6 Hz, 6-H), 8.55 (1H, dd, *J* 1.1 and 8.7 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 37.6 (CH_3), 115.7 (C-8), 123.5 (C-6), 124.2 (C-3), 126.0 (C-5), 126.5 (C-4a), 127.3 (C-4", 127.4 (C-2" and C-6"), 128.2 (C-3" and C-5"), 128.6 (C-4'), 129.5 (C-3' and C-5'), 131.3 (C-2' and C-6'), 132.1 (C-7), 134.9 (C-1'), 135.7 (C-1"), 141.3 (C-2), 151.9 (C-8a), 176.2 (C-4); ν_{max}/cm^{-1} 752.9, 1069.5, 1319.3, 1434.3, 1481.6, 1569.5, 1587.5, 1614.4 (C=O), 3059.2; MS: m/z 311 (M^+, 100), 294 (52), 267 (25), 262 (41), 183 (26), 77 (30), 69 (28).

Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.49. Found: C, 85.47; H, 5.42; N, 4.45.

4.9.2 Synthesis of 2-(4'-fluorophenyl)-1-methyl-3-phenyl-4-quinolone 68b

The experimental procedure employed for the synthesis of **68a** was followed using a mixture of 2-(4'-fluorophenyl)-3-iodo-1-methyl-4-quinolone **66b** (0.2 g, 0.528 mmol), $Pd(PPh_3)_4$ (0.0140 g, 0.0122 mmol, 2.3 mmol%), sodium carbonate (2.5 ml, 1M aq. soln.) and phenylboric acid (0.129 g, 1.06 mmol) in DMF (6 ml) to afford **68b**, solid (0.09 g, 52%), m.p. 284–286° C; ^{1}H NMR (300 MHz, $CDCl_3$) 3.53 (3H, s, CH_3), 6.93-7.25 (9H, m, 2'-H and 6'-H, 3'-H and 5'-H, 2"-H and 6"-H and 3"-H and 5"-H, and 4"-H), 7.42 (1H, t, *J* 1.2 and 7.5 Hz, 7-H), 7.55 (1H, d, *J* 8.7 Hz, 8-H), 7.72 (1H, dt, *J* 1.5 and 6.9 Hz, 6-

H), 8.55 (1H, d, *J* 8.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 37.6 (CH_3), 115.4 (C-8), 115.6 (C-3' and C-5', d, $^2J_{CF}$ 21.7 Hz), 123.6 (C-6), 124.5 (C-3), 126.2 (C-5), 126.6 (C-4a), 127.4 (C-4"), 127.6 (C-2" and C-6"), 131.0 (C-1', d, $^4J_{CF}$ 3.5 Hz), 131.2 (C-3" and C-5"), 131.5 (C-2' and C-6', d, $^3J_{CF}$ 8.0 Hz), 132.3 (C-7), 135.6 (C-1"), 141.4 (C-2), 150.9 (C-8a), 162.5 (C-4', d, $^1J_{CF}$ 248.8 Hz), 176.2 (C-4); ν_{max}/cm^{-1} 760.0, 839.6, 1216.6, 1319.9, 1489.4, 1571.7, 1587.4, 1614.4 (C=O), 3063.0; MS: m/z 329 (M^+, 100), 77 (26). *Anal*. Calcd. for $C_{22}H_{16}NOF$: C, 80.22; H, 4.89; N, 4.25. Found: C, 79.68; H, 4.90; N, 4.10.

4.9.3 Synthesis of 2-(4'-chlorophenyl)-3-phenyl-1-methyl-4-quinolone 68c

The experimental procedure employed for the synthesis of **68a** was followed using a mixture of 3-iodo-2-(4'-chlorophenyl)-1-methyl-4-quinolone **66c** (0.2 g, 0.51 mmol), $Pd(PPh_3)_4$ (0.0293 g, 0.0253 mmol, 2.3 mmol%), sodium carbonate (2.5 ml, 1M aq. soln.) and phenylboric acid (0.123 g, 1.01 mmol) in DMF (6 ml). Work-up afforded **68c**, solid (0.11 g, 63%), m.p. 284–286° C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) 3.53 (3H, s, CH_3), 7.01 (2H, d, *J* 7.2, 3'-H and 5'-H), 7.05-7.16 (5H, m, 2"-H and 6"-H, 3"-H and 5"-H, and 4"-H), 7.26 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 7.44 (1H, t, *J* 7.5 Hz, 7-H), 7.57 (1H, d, *J* 8.7 Hz, 8-H), 7.73 (1H, dt, *J* 1.5 and 7.8 Hz, 6-H), 8.56 (1H, dd, *J* 1.4 and 8.0 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 37.6 (CH_3), 115.7 (C-8), 123.7 (C-6), 124.3 (C-3), 126.3 (C-5), 126.5 (C-4a), 127.3 (C-4"), 127.6 (C-2" and C-6"), 128.6 (C-3" and C-5"), 130.9 (C-3' and C-5'), 132.3 (C-7), 133.3 (C-4'), 134.8 (C-1'), 135.3 (C-1"), 141.4 (C-2), 150.7 (C-

8a), 176.1 (C-4)); ν_{max}/cm^{-1} 758.4, 871.8, 1006.7, 1088.6, 1308.9, 1476.0, 1590.5, 1615.1 (C=O), 3034.0; MS: m/z 344 (M^+, 98), 28 (100).

Anal. Calcd. for $C_{22}H_{16}NOCl$: C, 76.41; H, 4.66; N, 4.05. Found: C, 76.70; H, 4.83; N, 4.10.

4.9.4 Preparation of 2-(4'-methoxyphenyl)-3-phenyl-1-methyl-4-quinolone 68d

The experimental procedure employed for the synthesis of **68a** was followed using a mixture of 3-iodo-2-(4'-methoxyphenyl)-1-methyl-4-quinolone **66d** (0.2 g, 0.511 mmol), $Pd(PPh_3)_4$ (0.0457 g, 0.0256 mmol, 2.3 mmol%), sodium carbonate (2 ml, 2M aq. Soln.) and phenylboric acid ((0.125 g, 1.026 mmol) in DMF (6 ml). Work-up afforded **68d**, solid (0.11 g, 63%), m.p. 266–268° C (EtOH); ^1H NMR (300 MHz, $CDCl_3$) 3.49 (3H, s, CH_3), 3.69 (3H, s, OCH_3), 6.74 (2H, d, *J* 6 Hz, 3'-H and 5'-H), 6.91-7.01 (5H, m, 2''-H and 6''-H, 3''-H and 5''-H and 4''-H), 7.04 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 7.35 (2H, dt, *J* 1.2 and 7.5 Hz, 7-H), 7.62 (1H, d, *J* 7.8 Hz, 8-H), 7.69 (1H, dt, *J* 8.4 Hz, 6-H), 8.32 (1H, dd, *J* 1.5 and 8.0 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 37.2 (CH_3), 54.6 (OCH_3), 113.1 (C-2'' and C-6''), 116.1 (C-8), 122.8 (C-6), 123.3 (C-3), 125.3 (C-5), 125.8 (C-4a), 125.9 (C-4''), 126.5 (C-1'), 126.7 (C-3'' and C-5''), 130.4 (C-3' and C-5'), 130.9 (C-2' and C-6'), 131.7 (C-7), 135.9 (C-1''), 140.9 (C-2), 151.7 (C-8a), 158.8 (C-4'), 174.9 (C-4); ν_{max}/cm^{-1} 752.9, 1069.5, 1319.3, 1434.3, 1481, 1587.5, 1614.4 (C=O), 3059.2; MS: m/z 340 (M^+, 73), 326 (26), 28 (100).

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 81.45; H, 5.80; N, 4.36.

4.10.1 Preparation of 3-bromo-4-chloro-2-phenylquinoline 55a

A stirred mixture of 3-bromo-2-phenylquinolin-4(1*H*)-one **47a** (1.0 g, 3.33 mmol) and phosphoryl chloride (10 ml) was heated under reflux for 12 hours. The mixture was allowed to cool to room temperature and poured into ice-cold water (20 ml) and alkalinized with 25% ammonia solution (5 ml). The precipitate was collected, washed with water and dried to afford 4-chloro-2-phenylquinoline **55a**, solid (0.67 g, 63%), m.p. 134–136° C (lit.[46] 134-136° C); ^{1}H NMR (300 MHz, $CDCl_3$) 7.50-7.54 (3H, m, 2'-H, 4'-H and 6'-H), 7.63-7.61 (2H, m, 3'-H and 5'-H), 7.81 (1H, dt, *J* 1.5 and 6Hz, 7-H), 7.92 (1H, dt, *J* 1.5 and 5.4,Hz, 6-H), 8.11 (1H, d, *J* 8.1Hz, 8-H)), 8.27 (1H, dd, *J* 1.2 and 7.2 Hz, 5-H); ^{13}C NMR (75 MHz, DMSO-d_6) 118.0 (C-3), 124.2 (C-5), 125.4 (C-4a), 127.9 (C-2' and C-6'), 128.9 (C-8), 129.0 (C-6), 129.2 (C-3' and C-5'), 129.5 (C-4'), 131.3 (C-7), 140.1 (C-1'), 142.1 (C-4), 145.9 (C-8a), 158.6 (C-2); ν_{max}/cm^{-1} 694.8, 761.8, 849.7, 884.1, 986.9, 1095.7, 1348.4, 1478.9, 1560.8, 3066.8.

4.10.2 Preparation of 3-bromo-4-chloro-2-(4'-fluorophenyl)quinoline 55b

The experimental procedure employed for the synthesis of **55a** was followed using a mixture of 3-bromo-2-(4'-fluorophenyl)quinolin-4(1*H*)-one **47b** (1.0 g, 3.14 mmol) and phosphoryl chloride (10 ml). Work-up afforded **55b**, solid (0.56 g, 51%); m.p. 161–163° C (lit.[46] 134-136° C); ^{1}H NMR (300 MHz, DMSO-d_6) 7.19 (1H, dt, *J* 2.1 and 8.7 Hz, 7-H), 7.25 (2H, dd, *J* 11.7 Hz, 3'-H and 5'-H), 7.65-7.72 (3H, m, 3'-H and 5'-H, 8-H), 7.80 (1H, dt, *J* 1.5 and 8.4 Hz, 6-H), 8.13 (1H, d, *J* 8.1 Hz, 8-H), 8.26 (1H, d, *J* 8.0 Hz, 5-H);

^{13}C NMR (75 MHz, DMSO-d_6) 115.1 (C-3' and C-5', d, $^{2}J_{CF}$ 21.6 Hz), 118.2 (C-3), 124.6 (C-8), 126.3 (C-4a), 128.5 (C-6), 129.8 (C-5), 130.3 (C-1', d, $^{4}J_{CF}$ 3.6 Hz), 130.7 (C-7), 131.3 (C-2' and C-6', d, $^{3}J_{CF}$ 8.3 Hz), 143.4 (C-4), 146.5 (C-8a), 158.1 (C-2), 163.2 (C-4', d, $^{1}J_{CF}$ 247.6 Hz); ν_{max}/cm^{-1} 731.0, 755.5, 827.5, 887.3, 1095.6, 1159.4, 1220.3, 1347.9, 1476.0, 1508.3, 1598.8, 3057.2.

4.10.3 Preparation of 3-bromo-4-chloro-2-(4'-chlorophenyl)quinoline 55c

The experimental procedure employed for the synthesis of **55a** was followed using a mixture of 3-bromo-2-(4'-chlorophenyl)quinolin-4(1*H*)-one **49c** (1.0 g, 2.99 mmol) and phosphoryl chloride (10 ml). Work-up afforded **55c**, solid (0.75 g, 71%), m.p. 209–211° C (lit.[46] 224-226° C); ^{1}H NMR (300 MHz, DMSO-d_6) 7.60 (2H, d, *J* 8.7Hz, 3'-Hand 5'-H), 7.71 (2H, d, *J* 8.4Hz, 2'-H and 6'-H), 7.83 (1H, dt, *J* 1.5 and 5.4Hz, 7-H), 7.93 (1H, dt, *J* 1.2 and 7.2 Hz, 6-H), 8.12 (1H, d, *J* 8.1 Hz, 8-H), 8.27 (1H, dd, *J* 1.2 and 7.2 Hz, 5-H); ^{13}C NMR (75 MHz, DMSO-d_6) 118.0 (C-3), 124.6 (C-8), 126.4 (C-4a), 128.3 (C-3' and 5'), 128.6 (C-6), 129.2 (C-4'), 129.9 (C-5), 130.7 (C-2' and C-6'), 130.8 (C-7), 135.2 (C-1'), 138.8 (C-4), 146.5 (C-8a), 157.9 (C-2); ν_{max}/cm^{-1} 725.2, 755.7, 823.9, 854.5, 886.2, 1012.6, 1093.6, 1346.3, 1473.3, 1561.2, 3059.0.

4.10.3 Preparation of 3-bromo-4-chloro-2-(4'-methoxyphenyl)quinoline 55d

The experimental procedure employed for the synthesis of **55a** was followed using a mixture of 2-(4'-chlorophenyl)quinolin-4(1*H*)-one **47d** (1.0 g, 2.99 mmol) and phosphoryl chloride (10 ml). Work-up afforded **55d**, solid (0.85 g, 81%), m.p. 177–179° C (lit.[34] 188-190° C); ^{1}H NMR (300 MHz, DMSO-d_6) 3.83 (OCH_3), 7.06 (2H, d, *J* 9.3 Hz, 3'-H and 5'-H), 7.64 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 7.78 (1H, dt, *J* 1.2 and 7.7 Hz, 6-H), 7.91 (1H, dt, *J* 1.5 and 7.7 Hz, 7-H), 8.08 (1H, dd, *J* 0.8 and 8.8 Hz, 8-H), 8.22 (1H, dd, *J* 0.9 and 8.7 Hz, 5-H); ^{13}C NMR (75 MHz, DMSO-d_6) 53.3 (OCH_3), 111.2 (C-3' and 5'), 116.1 (C-3), 122.3 (C-8), 123.4 (C-4a), 126.8 (C-6), 127.5 (C-5), 128.9 (C-2' and C-6'), 129.1 (C-7), 130.4 (C-1'), 140.2 (C-4), 144.1 (C-8a), 156.3 (C-4'), 157.9 (C-2); ν_{max}/cm^{-1} 759.9, 822.5, 999.8, 1082.6, 1180.2, 1247.7, 1345.6, 1512.2, 1602.8, 2833.3, 2922.9.

4.11.1 Preparation of 3-bromo-4-(4''-chlorophenyl)-2-phenylquinoline

A stirred mixture of 3-bromo-4-chloro-2-phenylquinoline **55a** (0.20 g, 0.63 mmol) and 4-chloroaniline (0.39 g, 7.9 mmol) in ethanol (10 ml) was heated under reflux for 12 h. The mixture was allowed to cool to room temperature and extracted with chloroform (30 ml). The organic phase was dried over magnesium sulphate, filtered and solvent evaporated under reduced pressure. The residue was purified by column chromatography (elution with 3:1 hexane-EtOAc, v/v) to afford **69a**, solid (0.12 g, 47%), m.p. 189-191^o C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.64 (1H, s, NH), 6.84 (2H, d, *J* 9 Hz, 3''-H and 5''-H), 7.22 (2H, d, *J* 9 Hz, 2''-H and 6''-H), 7.33 (1H, dt, *J* 0.9 and 5.7 Hz, 6-H), 7.44-7.52 (3H, m, 4'-H, 2'-H and 6'-H), 7.62-7.70 (4H, m, 3'-H and 5'-H, 6-H, 8-H), 8.11 (1H, d, *J* 8.1 Hz, 5-

H); ^{13}C NMR (75 MHz, $CDCl_3$) 110.4 (C-3), 120.2 (C-3" and C-5"), 121.4 (C-4a), 124.5 (C-8), 125.9 (C-6), 127.7 (C-1"), 128.3 (C-3' and C-5'), 128.7 (C-5), 129.1 (C-2" and C-6"), 129.2 (C-2' and C-6'), 129.9 (C-4'), 130.1 (C-7), 140.7 (C-4a), 142.0 (C-4"), 144.7 (C-1'), 147.5 (C-2), 159.0 (C-4); ν_{max}/cm^{-1} 698.2, 760.3, 809.6, 931.6, 1394.5, 1487.9, 1573.4, 2924.2, 3059.1, 3379.3; MS: m/z 409 (M^+, 100), 329 (39), 293 (31), 146 (29). *Anal*. Calcd. for $C_{21}H_{14}N_2ClBr$: C, 61.60; H, 3.44; N, 6.84. Found: C, 61.99; H, 3.46; N, 6.82.

4.11.2 Synthesis of 3-bromo-4-(4"-chlorophenyl)-2-(4'-fluorophenyl)quinoline 69b

The experimental procedure employed for the synthesis of **69a** was followed using a mixture of 3-bromo-4-chloro-2-(4'-fluorophenyl)quinoline **55b** (0.25 g, 0.74 mmol) and 4-chloroaniline (0.47 g, 3.72 mmol) in ethanol (10 ml). Work-up afforded **69b**, solid (0.19 g, 68%); m.p. 181–183° C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.64 (1H, s, NH), 6.84 (2H, d, *J* 9 Hz, 3"-H and 5"-H), 7.14-7.22 (4H, m, 2"-H and 6"-H, 2'-H and 6'-H), 7.33 (1H, dt, *J* 1.2 and 7.2 Hz, 7-H), 7.62-7.72 (4H, m, 4'-H, 3'-H and 5'-H, 6-H, 8-H), 8.09 (1H, d, *J* 8.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 110.2 (C-3), 115.1 (C-3'and C-5', d, $^2J_{CF}$ 21.6 Hz), 120 (C-3" and C-5"), 121.3 (C-4a), 124.5 (C-8), 126.1 (C-5), 127.9 (C-4), 129.3 (C-2" and C-6"), 130.4 (C-7), 131.2 (C-2' and C-6', d, $^3J_{CF}$ 8.3 Hz), 136.7 (C-1"), 141.9 (C-8a), 144.9 (C-4"), 147.5 (C-1', d, $^4J_{CF}$ 3.5 Hz), 157.9 (C-2), 163.0 (C-4', d, $^1J_{CF}$ 246.5 Hz); ν_{max}/cm^{-1} 767.7, 815.9, 1157.3, 1394.5, 1482.0, 1508.3, 1568.5, 2924.1, 2959.7, 3256.2 (N-H); MS: m/z 427 (M^+, 100), 347 (37), 311 (46), 28 (65).

Anal. Calcd. for $C_{21}H_{13}N_2ClBrF$: C, 58.97; H, 3.06; N, 6.55. Found: C, 59.15; H, 3.13; N, 6.50.

4.11.3 Synthesis of 3-bromo-4-(4''-chlorophenyl)-2-(4'-chlorophenyl)quinoline 69c

The experimental procedure employed for the synthesis of **69a** was followed using a mixture of 3-bromo-4-chloro-2-(4'-chlorophenyl)quinoline **55c** (0.25 g, 0.71 mmol) and 4-chloroaniline (0.45 g, 3.55 mmol) in ethanol (10 ml). Work-up afforded **69c**, solid (0.20 g, 63%), m.p. 188-190° C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.65 (1H, s, NH), 6.84 (2H, d, *J* 9 Hz, 3''-H and 5''-H),), 7.22 (2H, d, *J* 8.7 Hz, 2''-H and 6''-H), 7.33 (1H, t, *J* 7.5 Hz, 6-H), 7.47 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 7.61-7.69 (4H, m, 3'-H and 5'-H, 6-H, 8-H), 8.08 (1H, d, *J* 8.1 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 109.9 (C-3), 120.3 (C-3' and C-5'), 121.3 (C-4a), 124.5 (C-8), 126.1 (C-5), 127.9 (C-4), 128.2 (C-3'' and C-5''), 129.3 (C-2'' and C-6''), 130.5 (C-7), 130.7 (C-2' and C-6'), 134.8 (C-6), 139.1 (C-1''), 141.9 (C-8a), 144.9 (C-4''), 147.5 (C-1'), 157.8 (C-2); ν_{max}/cm^{-1} 762.6, 825.5,1084.7, 1394.5, 1486.6, 1574, 2924.1, 3064.9, 3369.6 (N-H); MS: m/z 443 (M^+, 100), 362 (46).

Anal. Calcd. for $C_{21}H_{13}N_2Cl_2Br$: C, 56.79; H, 2.95; N, 6.31. Found: C, 56.97; H, 3.28; N, 5.94.

4.11.4 Synthesis of 3-bromo-4-(4''-chlorophenyl)-2-(4'-methoxyphenyl)quinoline 69d

The experimental procedure employed for the synthesis of **69a** was followed using a mixture of 3-bromo-4-chloro-2-(4'-methoxyphenyl)quinoline **55d** (0.20 g, 0.58 mmol) and 4-chloroaniline (0.37 g, 2.87 mmol) in ethanol (10 ml). Work-up afforded **69d**, solid (0.14 g, 56%), m.p. 192–194° C; ^{1}H NMR (300 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 6.62 (1H, s, NH), 6.82 (2H, d, *J* 8.4 Hz, 3''-H and 5''-H),), 7.02 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.21 (1H, d, *J* 9 Hz, 2''-H and 6''-H), 7.31 (2H, dt, *J* 0.9 and 7.2 Hz, 7-H), 7.61-7.68 (4H, m, 2'-H and 6'-H, 6-H, 8-H), 8.09 (1H, d, *J* 8.7 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) 110.3 (C-3), 113.4 (C-3' and C-5'), 120.1 (C-3'' and C-5''), 121.3 (C-4a), 124.5 (C-8), 125.8 (C-5), 127.6 (C-4), 129.2 (C-2'' and C-6''), 129.8 (C-7), 130.7 (C-2' and C-6'), 133.2 (C-1'), 142.1 (C-8a), 144.7 (C-4''), 147.5 (C-1''), 158.6 (C-2', 160.0 (C-4'); ν_{max}/cm^{-1} 767.7, 929.7, 1032.6, 1178.5, 1486.5, 1573.0, 2928.8, 2956.9, 3378.0 (N-H); MS: m/z 439 (M^+, 95), 91 (57), 57 (40), 43 (38), 28(100).

Anal. Calcd. for $C_{22}H_{16}N_2OClBr$: C, 60.09; H, 3.67; N, 5.37. Found: C, 59.83; H, 3.30; N, 5.10.

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CHAPTER FIVE

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APPENDIX

Mass spectra of systems **65c**, **66a**, **67**, **68a** and **69a**

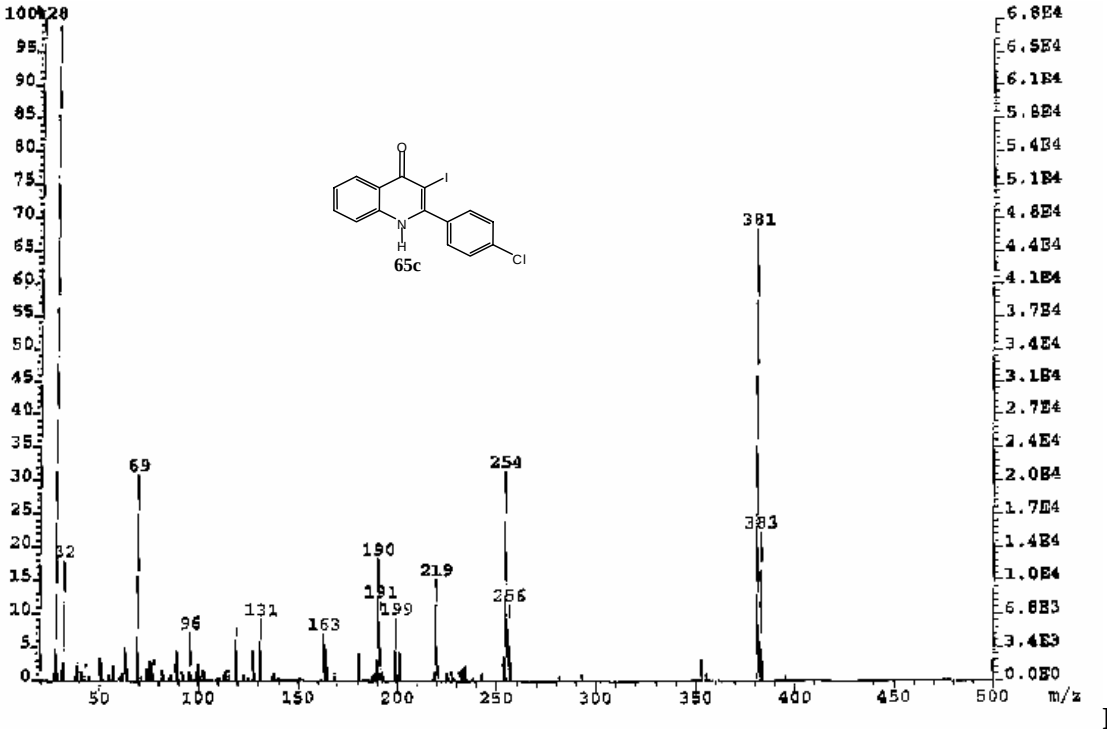

Fig ure 15: Mass spectrum of 3-iodo-2-(4'-chlorophenyl)quinolin-4(1*H*)-one **65c**

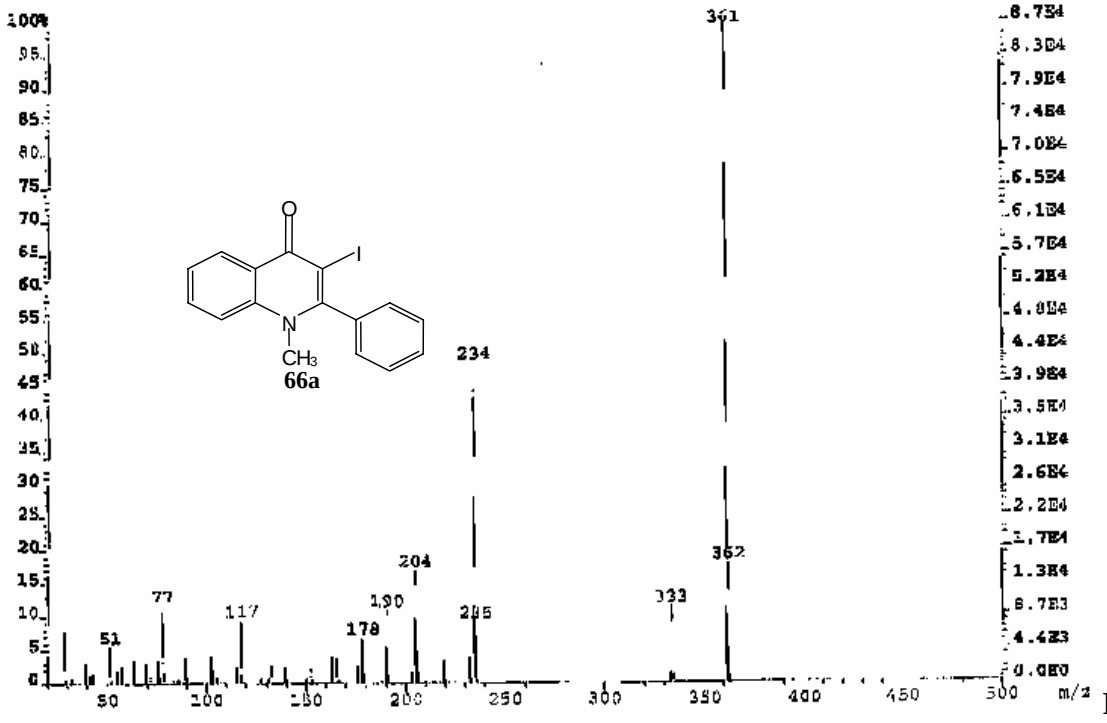

Fig ure 16: Mass spectrum of 3-iodo-1-methyl-2-phenyl-4-quinolone **66a**

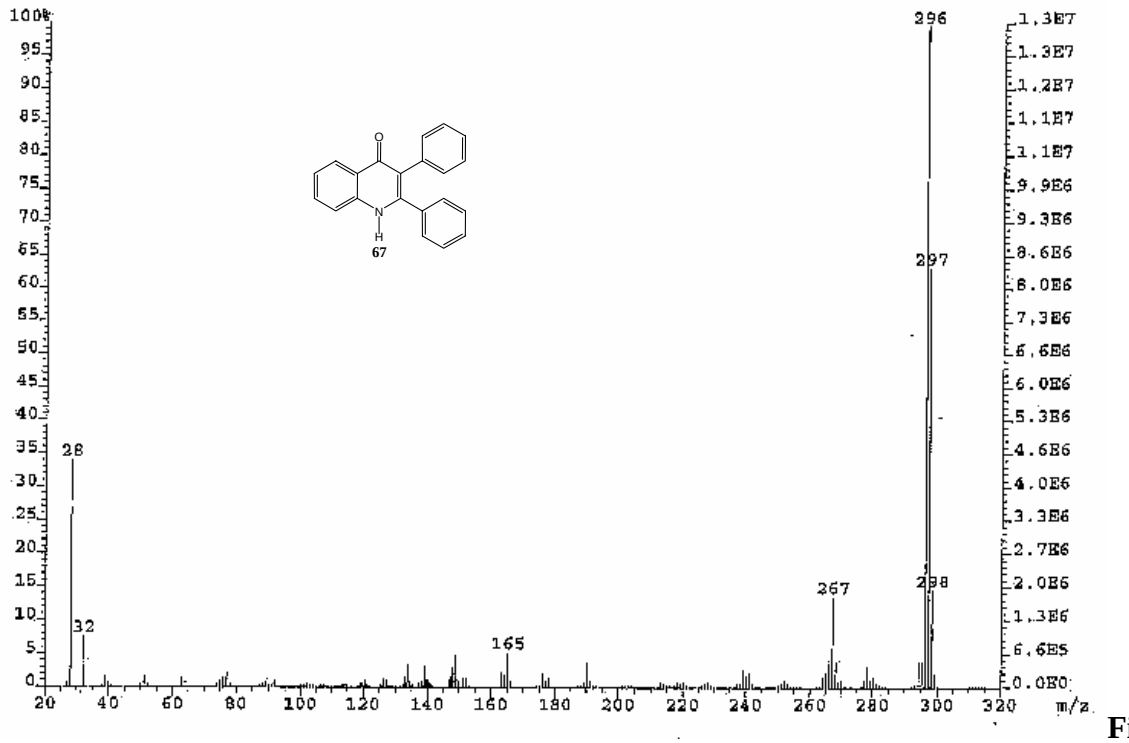

Figure 17: Mass spectrum of 2,3-diphenylquinolin-4(1*H*)-one **67**

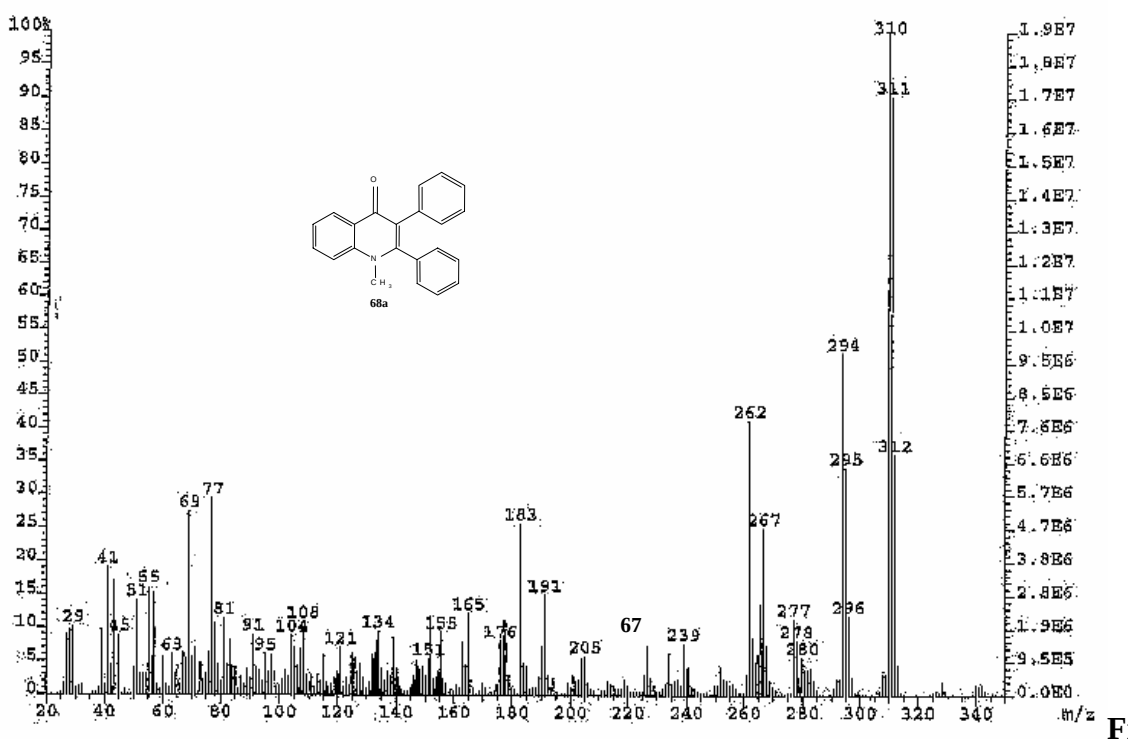

Figure 18: Mass spectrum of 2,3-diphenyl-1-methyl-4-quinolone **68a**

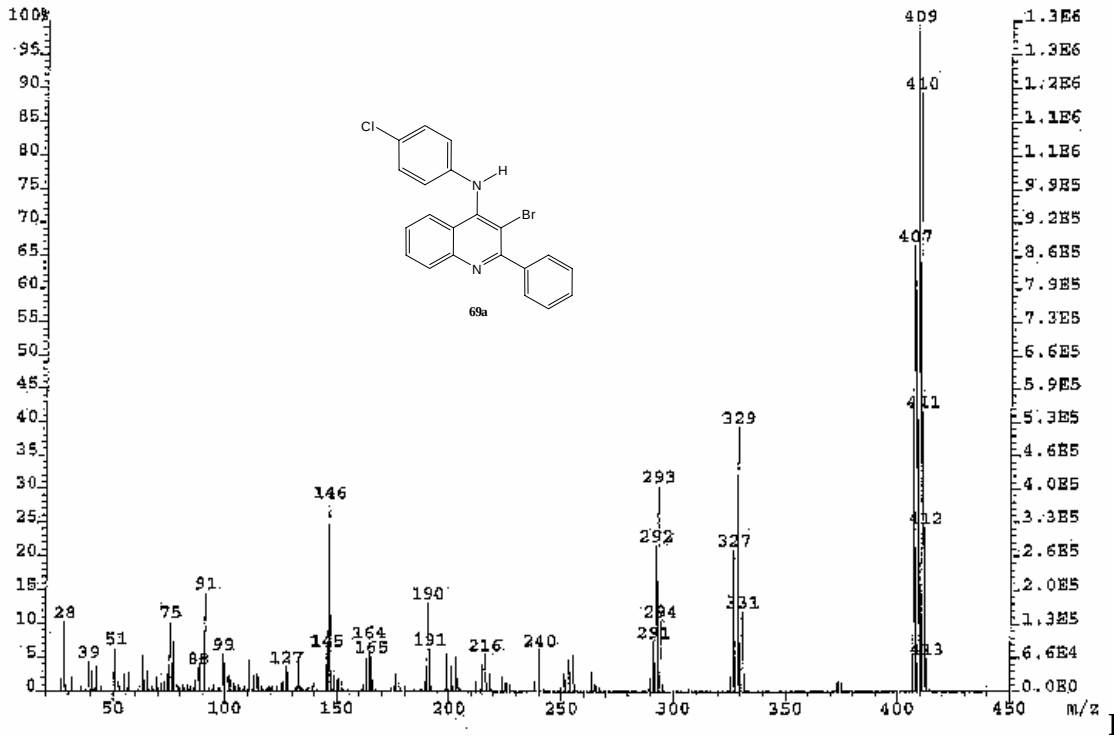

Figure 19: Mass spectrum of 3-bromo-2-phenyl-4-(*N*-4”-chlorophenyl)-4-aminoquinoline **69a**