# Synthesis of functionalized 4-quinolones and their reactions: Approaches towards bioactive molecules

A Thesis submitted to the University of North Bengal

For the Award of

Doctor of Philosophy

in

Chemistry

BY

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GUIDE

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**March-2017**

*Dedicated to*

*My parents*

*&*

*Family members*

# DECLARATION

I declare that the thesis entitled **Synthesis of functionalized 4-quinolones and their reactions: Approaches towards bioactive molecules** has been prepared by me under the guidance of Dr. Sajal Das, Assistant Professor of Chemistry, University of North Bengal. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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## CERTIFICATE

I certify that Mr. Prasanjit Ghosh has prepared the thesis entitled **Synthesis of functionalized 4-quinolones and their reactions: Approaches towards bioactive molecules** for the award of Ph.D. degree of the University of North Bengal, under my guidance. He has carried out the work at the Department of Chemistry, University of North Bengal. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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The single largest contribution is properly shaping me what I am today comes from the faith, hope and pride of parents. Words are inadequate for expressing such feelings.

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Prasanjit Ghosh

PRASANJIT GHOSH

# ABSTRACT

The Present Thesis entitled as **Synthesis of functionalized 4-quinolones and their reactions: Approaches towards bioactive molecules** has made some efforts to synthesize the diverse 4-quinolone scaffolds and functionalization of its various position. The work was started in January, 2012 as UGC-NET-JRF. Based on different facets and contents of the work; the thesis has been divided into eight chapters.

As a prelude to present work, the **Chapter I** summarizes a brief review on the development of synthesis and functionalization of 4-quinolones.

**Chapter II** describes our work Pd-NHC catalysed carbonylative Sonogashira coupling for the formation of 4-quinolones and 4*H*-chromen-4-one. We reported a very mild, operationally simple, ligand free carbonylative method for the synthesis of biologically active motifs 4-quinolones and flavones. Our protocol avoids the use toxic CO gas, high catalyst loading and use of any expensive salt. Moreover, the cyclocarbonylation of both 2-iodophenol and 2-iodoaniline with phenylacetylene was excellent and the corresponding products were obtained from moderate to promising yield. Herein, we also wish to report the first time $Mo(CO)_6$ was used as solid CO source for the synthesis of flavones.

**Chapter III** delineates Pd-NHC catalysed ligand free carbonylative Suzuki coupling reactions of aryl halides and arylboronic acids and its application towards the synthesis of biologically active 4-quinolone scaffolds. Notably, this method offers various advantages such as free of toxic CO gas, shorter reaction time, good to excellent yield of the desired product and broad substrate scope availability. Several functional groups (-COMe, -COOMe,-F,-Cl) were well tolerated in this reaction. This approach was quite effective in the biological active 4-quinolone scaffold to synthesize the 3-Aroylquinolin-4(1*H*)-ones.

**Chapter IV** describes an efficient protocol of Pd-NHC catalysed thioetherification of 3-iodo-2-aryl substituted 4-quinolone derivatives. Simultaneously, our synthesized thioether substituted 4-quinolone derivatives are under investigation for their biological activity. However, we have disclosed a new, simple and efficient route of Pd-NHC catalysed thioetherification of 3-iodo-2-aryl substituted-4-quinolones in promising yield under rapid and aerobic condition. Our method is free of –NH protection of 4-quinolones and harsh reaction condition as reported earlier.

**Chapter V** deals an efficient nickel catalysed C-S coupled protocol for the synthesis of thioether linkage in 4-quinolone scaffolds from 3-iodo-2-aryl substituted-4-quinolone derivatives. This methodology enables the production of diverse ArS-substituted 4-quinolone derivatives in excellent yield under short span of time, which may enhance the drug efficacy of quinolone scaffolds.

**Chapter VI** depicts the microwave assisted synthesis of 6-aryl substituted 4-quinolones via regioselective bromination at C-6 position. We have unfolded also a suitable synthetic way to provide 6-aryl substituted 4-quinolones. Our approach has some distinct advantages of easily forming substrates, regioselective bromination at C-6 position and corresponding arylation via Suzuki coupling reaction. The 6- bromo and 6- arylated entities isolated (**3→4**) are all newly synthesized compounds which are anticipated to be important components in drug designing. Various biological activities of these compounds are still going on in our laboratory.

**Chapter VII** demonstrates the NTFB (nitronium tetrafluoroborate) induced regioselective synthesis of nitro derivatives of 4-quinolone at ambient condition. This newly developed protocol for introducing nitro group in the various position of the 4-quinolone ring with maximum yield was not reported before in the literature. This method may be very helpful for the designing the newly bioactive molecules based on 4-quinolone scaffold. The whole study explored the selective insertion of nitro group which is predominantly governed by the free –NH of 4-quinolones. Other investigations to develop various substituted derivative on this moiety is currently underway.

**Chapter VIII** describes ligandless copper catalysed rapid and selective C-$NH_2$ arylation of 4-quinolone at ambient condition. We have developed a protocol of copper catalysed selective C-$NH_2$ arylation of 4-quinolones under ambient condition. This method offers several advantages such as room temp stirring, rapid reaction and ligand free condition. Our catalytic system is well tolerable with various functional groups (-Br, -Cl,-$NO_2$). Moreover, we have synthesized a broad array of functionally diverse 4-quinolone derivatives which may possess some biological activity and it will be reported in due course.

# PREFACE

The ever increasing demand for efficient syntheses and functionalization of biologically active 4-quinolone scaffolds remains the major interest to the synthetic chemist. In the area of antibiotics, the 4-quinolone ring has been heavily investigated and is an attractive synthetic target in organic synthesis. It is found in numerous natural product structures as the core structural motif of many antibacterial agents. So the development of suitable protocol to functionalize the 4-quinolone scaffold of its various positions in organic transformations is well accepted.

The present research work describes the suitable approaches towards the synthesis and the functionalization of 4-quinolone moiety. This thesis begins with **Chapter I**, which depicts a brief review on the development of methodologies for the synthesis as well as functionalization of 4-quinolone scaffold. **Chapter II** deals with Pd-NHC catalysed carbonylative sonogashira annulations for the synthesis of 4-quinolone and flavones. **Chapter III** contains a rapid and simple carbonylative Suzuki coupling for the synthesis of biaryl ketones and its application towards the synthesis biologically active 4-quinolone scaffolds. Newer methodologies for the synthesis of C-S linkage 4-quinolone derivatives using Pd-NHC and Ni catalyst has been described in **Chapter IV** and **Chapter V**. Rather, the **Chapter VI** is to focus on the synthesis of 6-aryl substituted 4-quinolones *via* regioselective bromination. The last two chapters (**VII** and **VIII**) demonstrates the regiocontrolled nitration and selective C-$NH_2$ arylation of 4-quinolone under ambient condition.

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## APPENDIX-A

**List of Publications**: (**Thesis related**)

1. "Pd-NHC catalysed carbonylative Sonogashira coupling for the formation of 4-quinolones and 4*H*-chromen-4-one" **Prasanjit Ghosh** and Sajal Das (Manuscript under process of submission).
2. "Pd-NHC catalysed carbonylative Suzuki coupling reactions of aryl halides and arylboronic acids and its application towards the synthesis of biologically active 4-quinolone scaffolds" **Prasanjit Ghosh**, Bhaskar Ganguly and Sajal Das. (Manuscript under process of submission).
3. "Pd-NHC catalysed thioetherification of 3-iodo-2-aryl substituted 4-quinolone derivatives *via* C-S cross couplings" **Prasanjit Ghosh** and Sajal Das (Manuscript under process of submission).
4. "Ni catalysed C-S cross-coupling of 3-iodo-2-aryl substituted-4-quinolone derivatives" **Prasanjit** Ghosh and Sajal Das (Manuscript under process of submission).
5. "Synthesis of 6-aryl substituted 4-quinolones *via* Suzuki cross coupling" Sumanta Gupta, **Prasanjit Ghosh**, Seema Dwivedi and Sajal Das. *RSC.Adv*, **2014**, *4*, 6254-6260.
6. "Regiocontrolled nitration of 4-quinolones at ambient condition" Sonali sarkar, **Prasanjit Ghosh**, Anirban Misra and Sajal Das, *Synth.Comm*, **2015**, *45*, 2386-2393.
7. "Ligandless copper catalysed rapid and selective C-$NH_2$ arylation of 4-quinolone at ambient condition" **Prasanjit** Ghosh and Sajal Das (Manuscript under process of submission).
8. "Synthesis and functionalisation of 4-quinolones-a progressing story" **Prasanjit** Ghosh and Sajal Das (Manuscript under process of submission).

**(Non Thesis Publications)**:

9. "A green etiquette for Pd catalyzed ligand free homocoupling reaction of arylboronic acids at ambient conditions" Seema Dwivedi, Soumik Bardhan, **Prasanjit Ghosh** and Sajal Das, *RSC. Adv*, **2014**, *4*, 41045-41050.
10. "A Fast and Additive Free C–C Homo/Cross-Coupling Reaction in Reverse Micelle: An Understanding of Role of Surfactant, Water Content and Base on the Product Yield and Reaction Site" Barnali Kar, Soumik Bardhan, **Prasanjit Ghosh**, Bhaskar

Ganguly, Kaushik Kundu, Sonali Sarkar, Bidyut Kumar Paul, and Sajal Das, *Chemistry select*, **2017**, 2, 1079-1088.

11. "Microemulsion Mediated Organic Synthesis and the Possible Reaction Site" **Prasanjit Ghosh**, Barnali Kar, Soumik Bardhan, Kaushik Kundu, Swapan Kumar Saha, Bidyut K. Paul and Sajal Das, *J. Surface Sci. Technol*. **2016**, 32, 8–16.
12. "A synthesis of Biaryl Ketones *via* the C-S bond cleavage of Thiol esters by a Cu/Ag salt" **Prasanjit Ghosh**, Bhaskar Ganguly, Eliyahu Perl and Sajal Das (Manuscript Communicated).
13. "Microemulsion (mEs) mediated rapid synthesis of Imidazo[1,2 *a*]pyridine and its late-stage functionalization." **Prasanjit Ghosh**, Bhaskar Ganguly, Barnali Kar and Sajal Das (Manuscript Communicated).
14. "A novel Pd-NHC catalysed carbonylation of aryl halides towards the synthesis of thioesters, acids, ketones, amides and its application towards 4-quinolone scaffolds" **Prasanjit Ghosh**, Bhaskar Ganguly, and Sajal Das (Manuscript under process of submission).
15. "Formation of High-Temperature Stable Benzimidazolium Ionic Liquid-in-Oil Microemulsion and Regioselective Nitration Reaction Therein" Barnali Kar, Soumik Bardhan, Kaushik Kundu, **Prasanjit Ghosh**, Bidyut K. Paul and Sajal Das (Manuscript communicated).

# APPENDIX-B

## Oral Presentations

1. "Synthesis of Biaryl ketones *via* C-S bond cleavage of Thiol ester" in the National Seminar "Frontier in Chemistry –2017" organized by the Department of Chemistry, NBU and funded by UGC and SAP (DRS–III), held at University of North Bengal, Darjeeling, India, February 20-21, 2017.
2. "Synthesis of 6-aryl substituted 4-quinolones via Pd-NHC complex catalysed Suzuki cross coupling" in the National Seminar "Frontier in Chemistry –2015" organized by the Department of Chemistry, NBU and funded by UGC and SAP (DRS–III), held at University of North Bengal, Darjeeling, India, February 17–18, 2015.

## Poster Presentations

1. "Synthesis of Biaryl ketones *via* C-S bond cleavage of Thiol ester" **Prasanjit Ghosh**, Bhaskar Ganguly, Barnali Kar and Sajal das in 19$^{th}$ CRSI National Symposium in Chemistry, held at University of North Bengal, Darjeeling, India, July 13–16, 2016.
2. "Synthesis of 6-aryl substituted 4-quinolones" **Prasanjit Ghosh**, Sumanta Gupta, Bhaskar Ganguly, Barnali Kar, Seema dwivedi and Sajal das in National Symposium on recent trends and perspectives in chemistry (RTPC-2015), National Institute of Technology, Sikkim, India, January 23-24, 2015.

## ABBREVIATION

| | |
|---|---|
| Ac | Acetyl |
| AMBH | aza-Morita-Baylis Hilmann |
| ANRORC | Addition of the Nucleophile Ring Opening, and Ring Closure |
| CB1 | Cannabinoid-1 |
| CB2 | Cannabinoid-2 |
| d | Doublet |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCM | Dichloro methane |
| dd | Doublet of a doublet |
| DDQ | 2,3-dichoro-5,6-dicyano-1,4-benzoquinone |
| DFT | Density functional theory |
| DMA | Dimethyl acetamide |
| DMEDA | N,N'-dimethylethylenediamine |
| DMF | N,N-dimethyl formamide |
| DMSO | Dimethyl sulpfoxide |
| DPEPhos | (Oxydi-2,1-Phenylene) bis(Diphenylphosphine) |
| ee | enantiomeric excess |
| EGFR | Epidermal growth factor receptor |
| EMME | Diethyl (ethoxymethylene)malonate |
| Et | Ethyl |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| KCC-1 | Potassium chloride cotransporter 1 |
| m | multiplet |
| MCM-41 | Mobil Composition of Matter No. ***41*** |
| Me | Methyl |
| MHz | Mega Hertz |
| NTFB | Nitronium tetrafluoroborate |
| per-6-ABCD | Per-6-amino-β-cyclodextrin |
| PPA | Poly phosphoric acid |
| q | Quartet |
| QSAR | Quantitative structure activity relationship |
| RT | Room Temperature |
| s | Singlet |
| SAR | Structure–activity relationship |
| SET | Single electron transfer |

| | |
|---|---|
| t | Triplet |
| TBAB | Tetrabutylammonium bromide |
| TBAHS- | Tetrabutyl ammonium hydrogen sulphate |
| t-BuO | Tert-butoxide |
| TC | Thiophen Carboxylate |
| TEMPO- | (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl |
| TFA | Tri fluoro acetic acid |
| THF | Tetrahydrofuran |
| TIPS-EBX | 1-{[Tris-(1-methylethyl)silyl]ethynyl]}-1,2-benziodoxol-3(1H)-one |
| TLC | Thin layer chromatography |
| TMP | 2,2,6,6-tetramethylpiperidyl |
| TMS | Tetra methyl silane |
| UTI | Urinary tract infections |

# Chapter I

# *A brief review on synthesis and functionalization of 4-quinolones*

# INTRODUCTION

## I.A. 4-quinolone

In the 20th century, the most leading cause for human illness and death was bacterial infections.[1] Over 200 million cases of malaria and 600,000 deaths were recorded in each year.[2] Several therapies were applied but the introduction of antibiotic agents brought a new route for the treatment of these bacterial infections. Synthesis of sulfonamide, penicillin by Alexander Fleming and also the synthesis of quinolones were the great success in science at that time.[3,4] George Lesher and his colleagues were first isolated the nalidixic acid (1962), the first member of quinolone drug as a byproduct in the synthesis Chloroquine.[5] In 1960's, the nalidixic acid was used for the treatment Urinary tract infections (UTI) caused by enteric bacteria.[6] Afterwards in 1970's, several new generation of quinolones such as oxolinic acid, pipemedic acid, cinoxacin and flumequine were synthesized and oxolinic acid proved itself as most prominent and notable drug.[6,7,8] Until 1980's, quinolones were little-used drugs and later second generation of quinolones were developed.[6,9,13] In search for better quinolones, the substitution at C-6 and C-8 displayed the remarkable activity against the antibacterial infections.[9] Most importantly, the position of fluorine atom at C-6 position and nitrogen heterocycles (piperazine, pyrollidinyl, piperadinyl moiety) at C-7 position remarkably enhanced the pharmacokinetic and pharmacodynamic properties e.g., Norfloxacin, ofloxacin etc.[10,11,12]

Norfloxacin, a fluoro containing quinolone, was utilized as first broad-spectrum quinolone but due to low serum level and poor tissue penetration, its applicability became restricted into the Urinary tract infections (UTI) and sexually transmitted diseases. Then, Ciprofloxacin used as the most commonly prescribed antibacterial drugs.[6,7,9] It showed its efficacy towards a variety of Gram-negative bacteria. Many fluoro quinolones have broad array of medical application in the treatment of Urinary tract infections (UTI), sexually transmitted diseases, tissue infections, pelvic infections and intra-abdominal infections. [14]

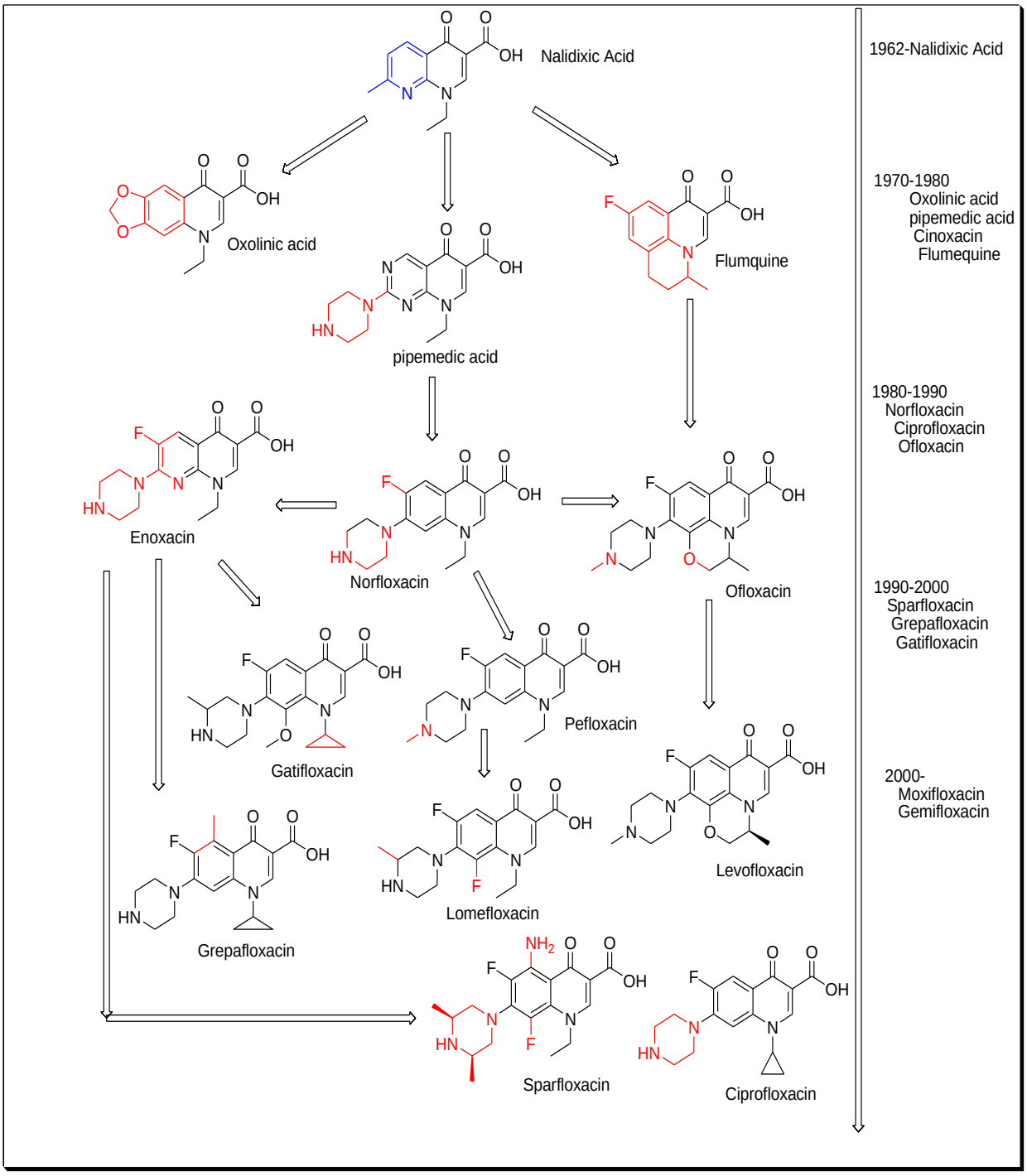


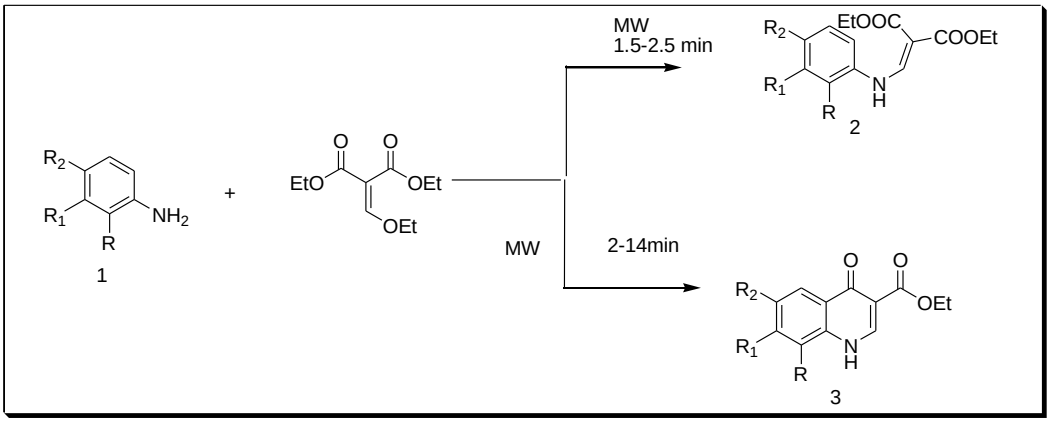

**Figure-I.1** Chemical structure of 4-quinolones

### I.A.1 Development of the Synthesis of 4-quinolones:

Quinolones are very omnipotent class drug due its broad-spectrum antibacterial, antimalarial and anti cancer activity. The development of the synthesis of 4-quinolones as well as its functionalisation at different position is still going on to increase its activity. Generally, these procedures involve harsh condition, domino reaction, and multi-step strategy, use of lewis acid and base, expensive transition metal catalyst or metal free condition. In this review, we mainly highlight the different route of synthesis part of 4-quinolones and functionalisation.

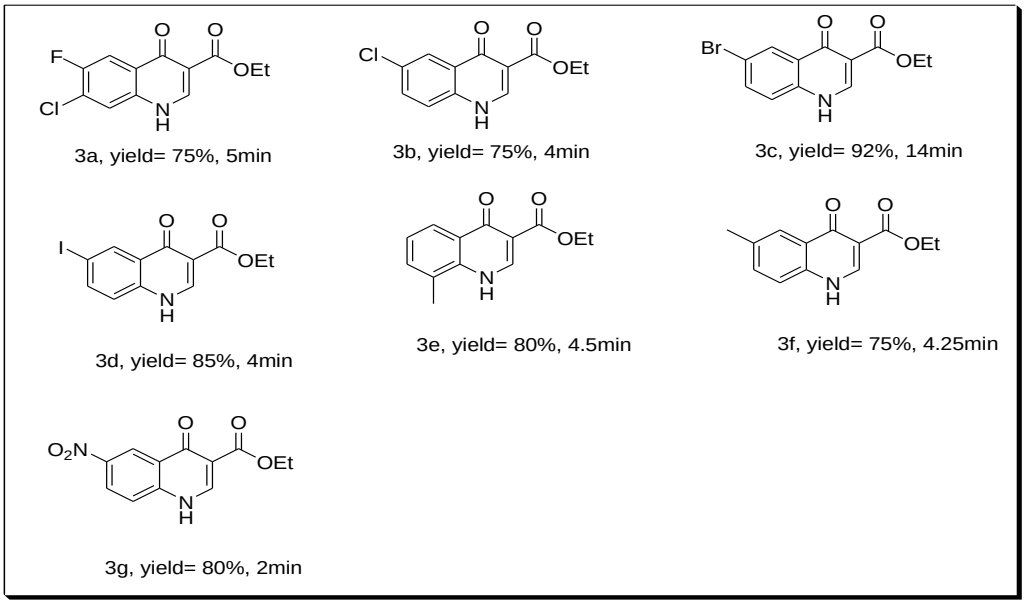
#### I.A.1.a Metal free synthesis of 4-quinolones

In 2002, Dave firstly reported the microwave assisted 4-quinolone synthesis under solvent free condition.[15] This method involved the condensation between aromatic amines and diethyl ethoxy methylenemalonates to afford the intermediate (2) in 1.5-2.5 min and corresponding cyclised product (3) in 2-14 min. Generally, this process was quite superior to Gould-Jacob method with respect to reaction time and product isolation.

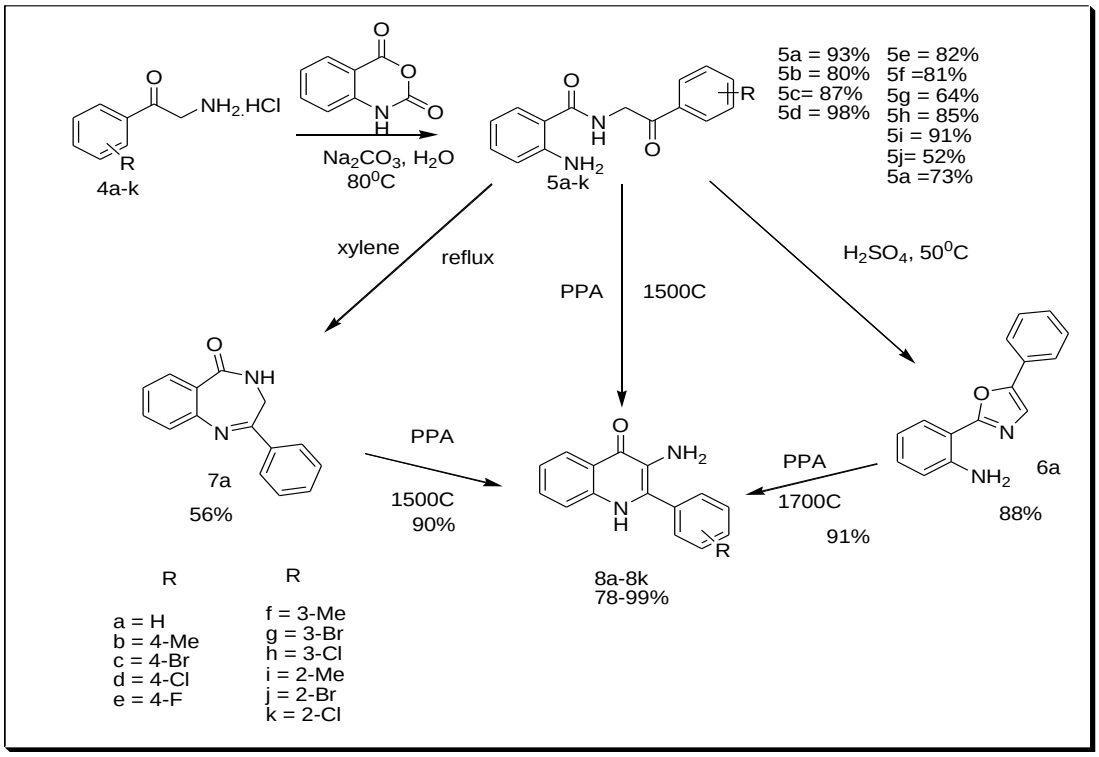



**Scheme-I.1.** Microwave assisted synthesis of 4-quinolones under solvent free Conditions

**Selected examples**

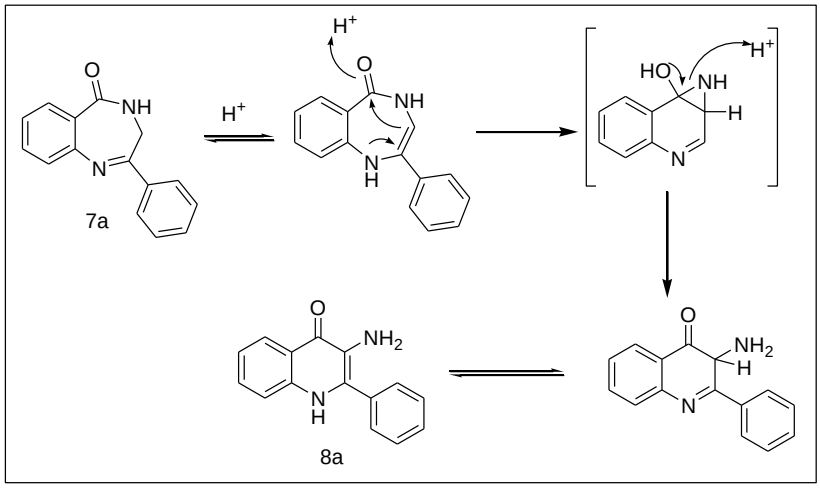



In 2006, Hradil and his coworkers developed a straight forward method for the synthesis of 3-Amino-2-phenyl-4(1H)-quinolinones from Anthranilamides in presence of PPA (poly phosphoric acid) at 150°C.[16]



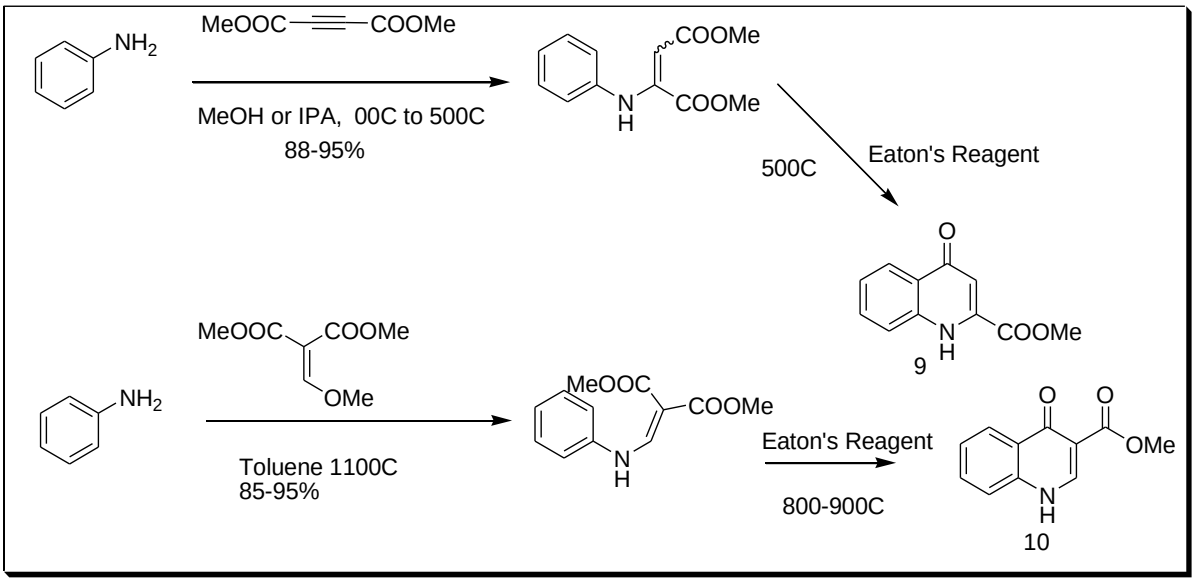

**Scheme-I.2.** PPA mediated synthesis of 3-Amino-2-phenyl-4(1H)-quinolinones from Anthranilamides

**Plausible Mechanism**




They proposed a plausible mechanism in which primarily 2-aminoacetophenones were reacted with isatoic anhydride to form anthranilamide derivatives. Afterwards, in presence of PPA (polyphosphoric acid) at 150°C resulted the diazepinone (7a) a seven memebered ring .Then it rearranged itself in presence of acid to afford the final 3-amino-2-phenyl-4-1(H)-quinolinone 8a . In presence of $H_2SO_4$ anthranilamide 5a afforded oxazole 6a due to intermolecular dehydration. Further, the oxazole 6a with PPA at 170°C gave aminoquinolone 8a with high yield.

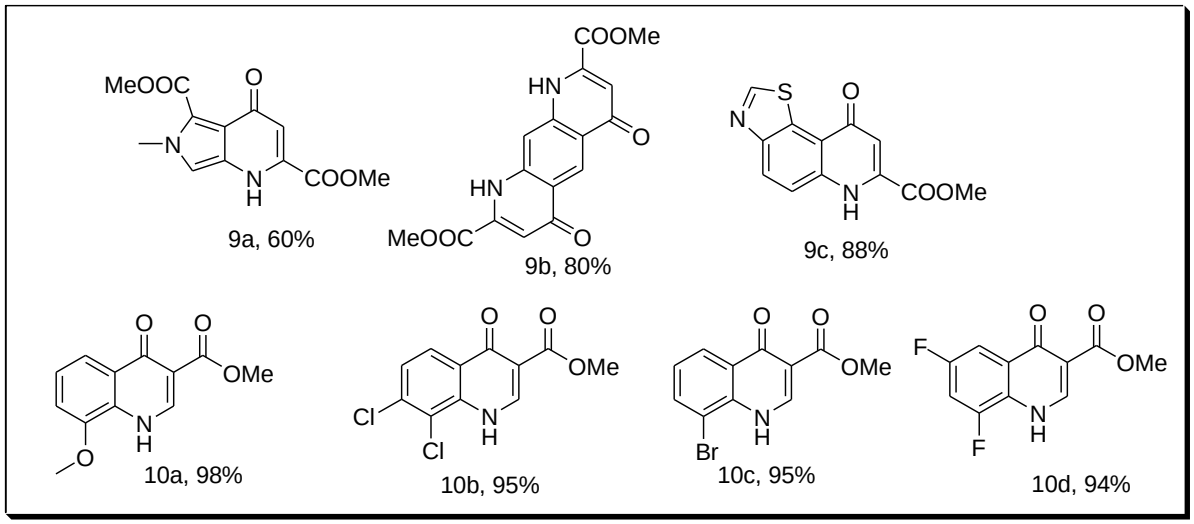
In 2007, Zewge and his co workers demonstrated the utility of Eaton's reagent (a mixture of $P_2O_5$ and $MeSO_3H$) for the cycloacylation of aniline derivatives to 4-quinolones. This present protocol has several advantages in compare to traditional approaches, like high yielding methodology, low reaction temperature and easy product isolation.[17]




**Scheme-I.3.** Eatons reagent mediated synthesis of 4-quinolones

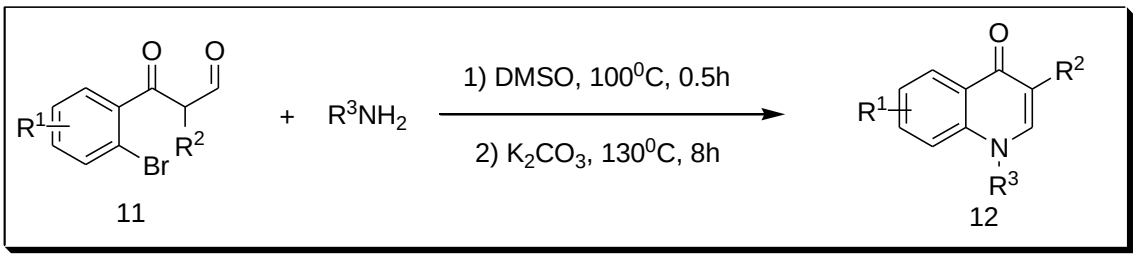
They had focused their attention on the application of the cyclisation protocol towards the synthesis of the 4-quinolone molecules such as tetracyclic bis quinolones and quinolone heterocycles (9a).

**Selected examples**



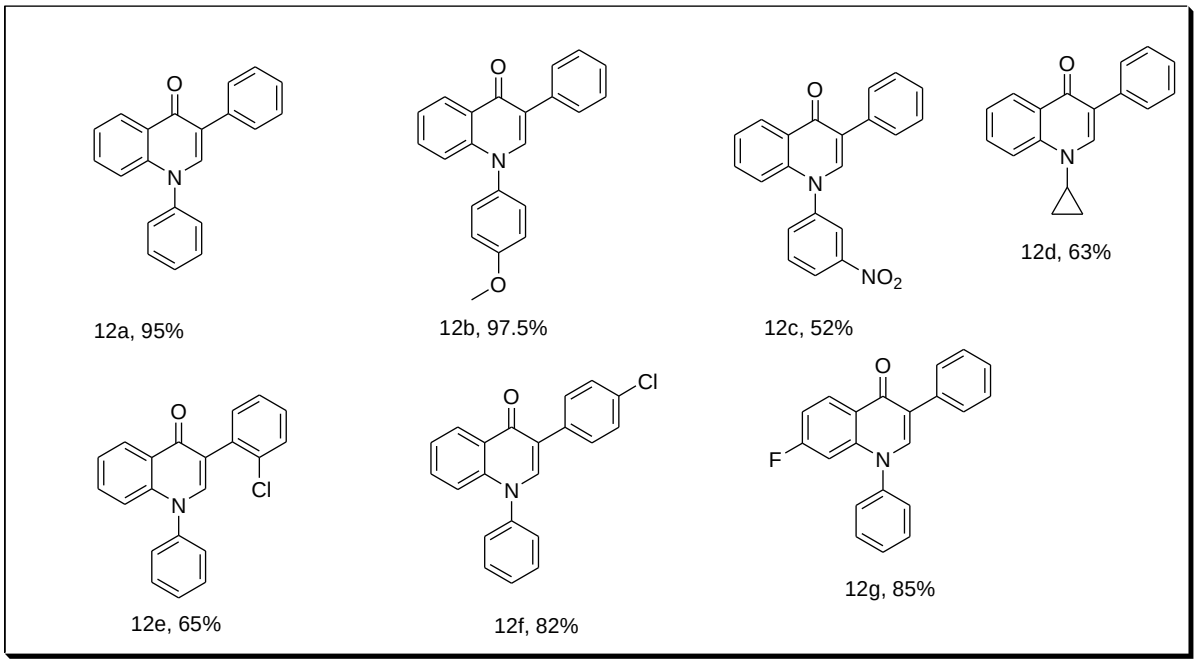

Most importantly, the cyclization of 1, 8-naphthalene diamine derivative resulted in 85% of quinolinoquinolinedione after isolation whereas the same transformation at 230 °C in diphenyl ether gave only 58% yield of product. In spite of this applicability, it had certain limitations such as regioselectivity and resulted several products when this protocol applied to derivatives.

Herein, an efficient one-pot metal-free process for the synthesis of 3-substituted 4-quinolones using amines and 3-(2-bromophenyl)-3-oxopropanal derivatives was described.[18]

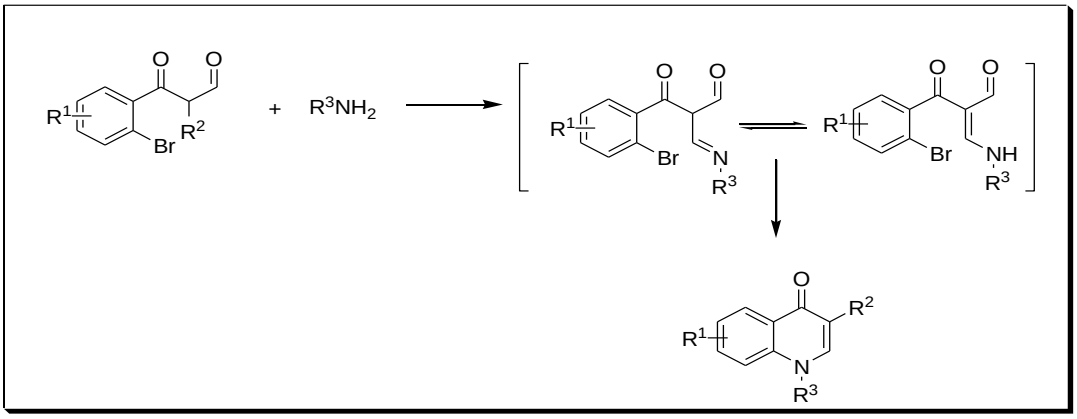



**Scheme-I.4.** Metal free synthesis of 3-substituted 4-quinolones from 3-(2-bromophenyl)-3-oxopropanal derivatives

**Selected examples**

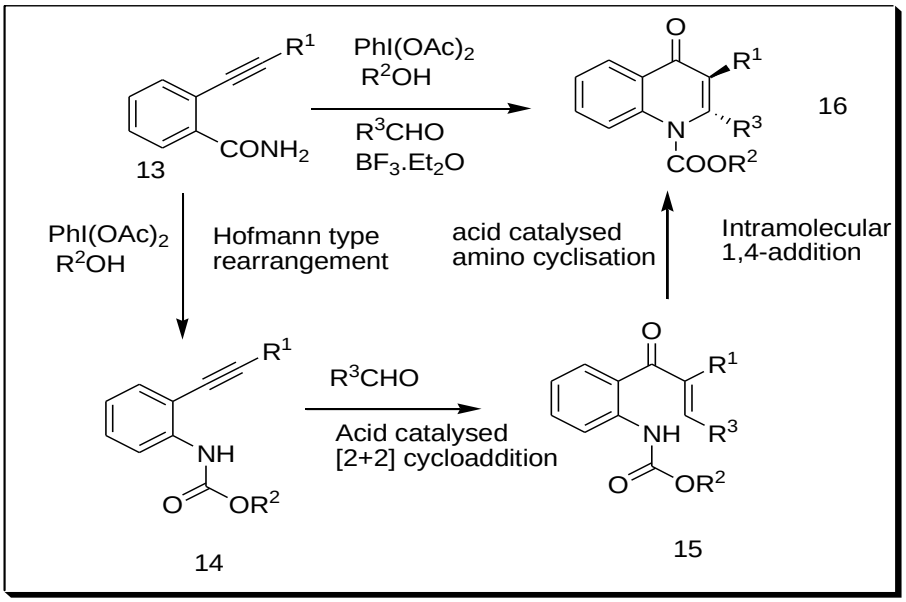



**Plausible mechanism**



A plausible mechamism was depicted which involved intramolecular cyclization/ amination of the enamines formed insitu (Figure). Actually, the base promoted the enamine-imine transformation and facilitated the dehydrobromination process to undergo the cyclization reaction. Electron rich amine furnished better yields than the electron poor counterparts.

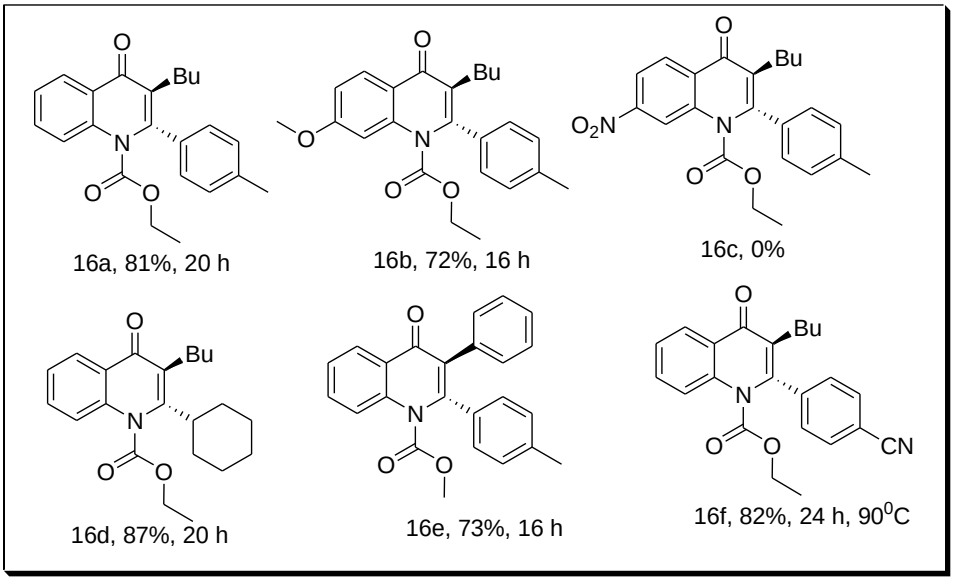
Yanada et.al reported the one-pot tandem process for the synthesis of various trans-2,3-disubstituted-2,3-dihydro-4-quinolones from 2-alkynylbenzamide derivatives.[19]

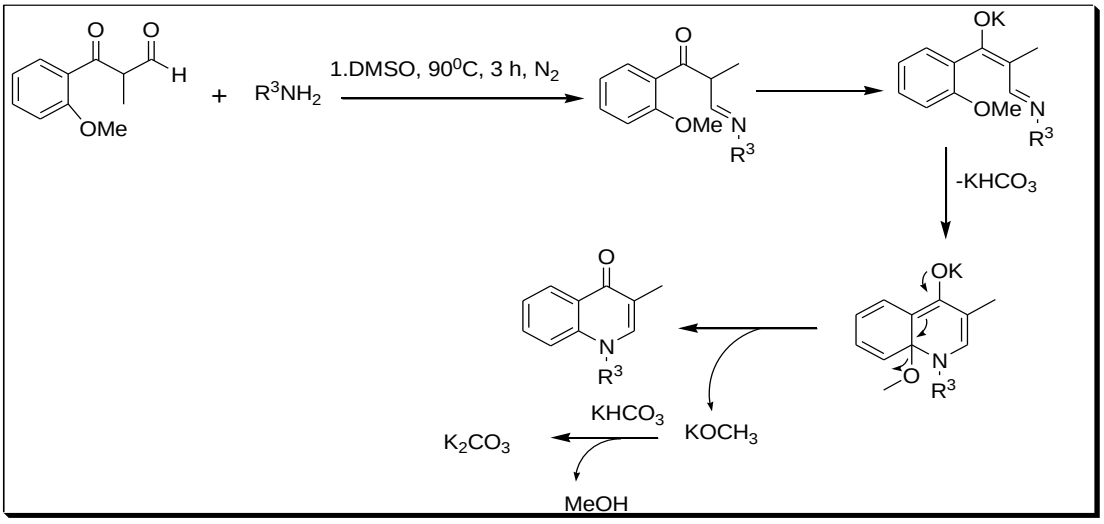



**Scheme-I.5.** $PhI(OAc)_2$ mediated synthesis of trans-2,3-disubstituted-2,3-dihydro-4-quinolones from 2-alkynylbenzamide derivatives

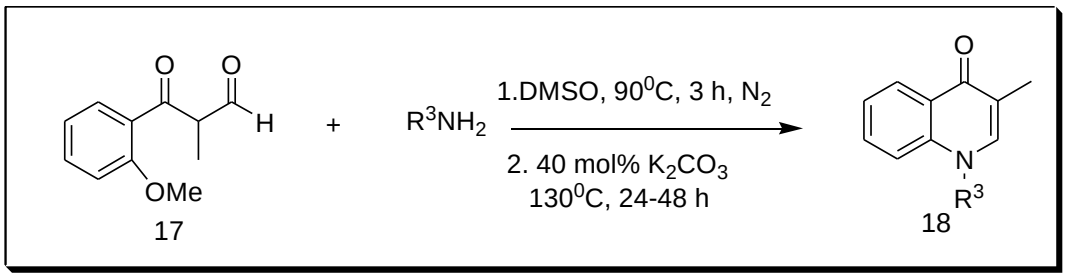
This tandem process comprised of following sequential steps. Compound 13 in the presence of hypervalent iodine underwent Hoffmann-type rearrangement followed by the addition of alkoxide resulted the intermediate 14. Then, intermolecular cycloaddition [2+2] took place in between the aldehyde and the triple bond of the alkyne. Finally, the desired product 16 obtained via the intramolecular aminocyclization of intermediate 15 and α,β-unsaturated ketones. Some selected examples of synthesized compounds were shown below.

**Selected examples**



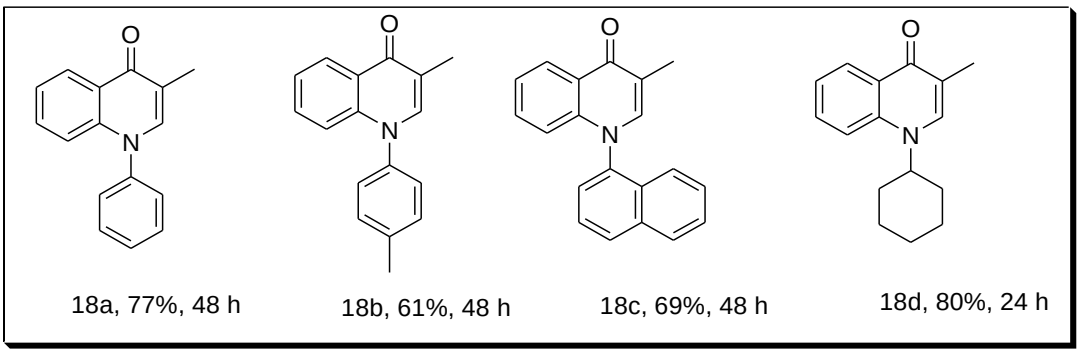



In 2012, Fu *et al.* accomplished the selective cleavage aromatic C-O bonds under base catalysed and metal free condition to synthesize the 4-quinolone in moderate yields. The whole process followed via coupling of aldehyde with primary amine to form imine intermediate, 3-(alkylimino)-1-(2-methoxyphenyl)2-methylpropan-1-one (III), and then it underwent intramolecular cyclization providing the 4-quinolone derivative.[20]



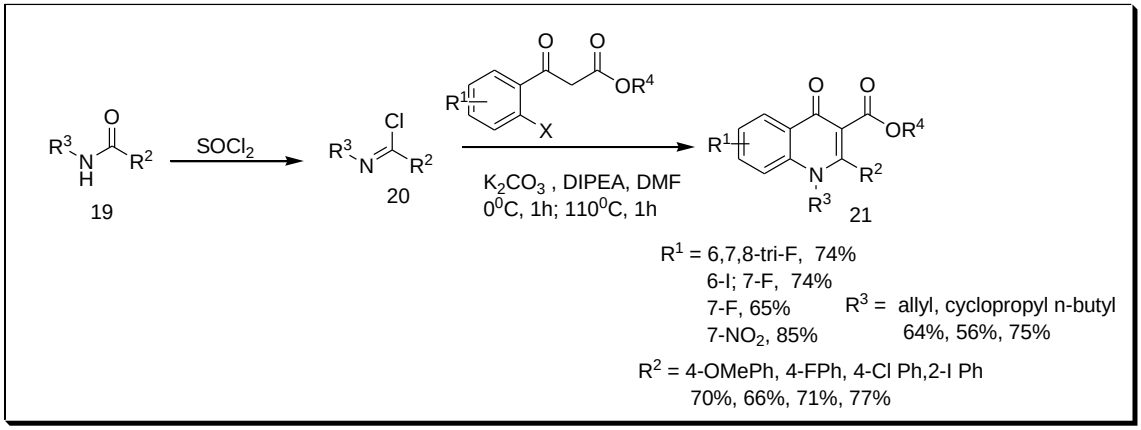

**Scheme-I.6.** $K_2CO_3$-Catalyzed synthesis of 4-quinolones through the Cleavage of Aromatic C-O Bonds

**Selected examples**



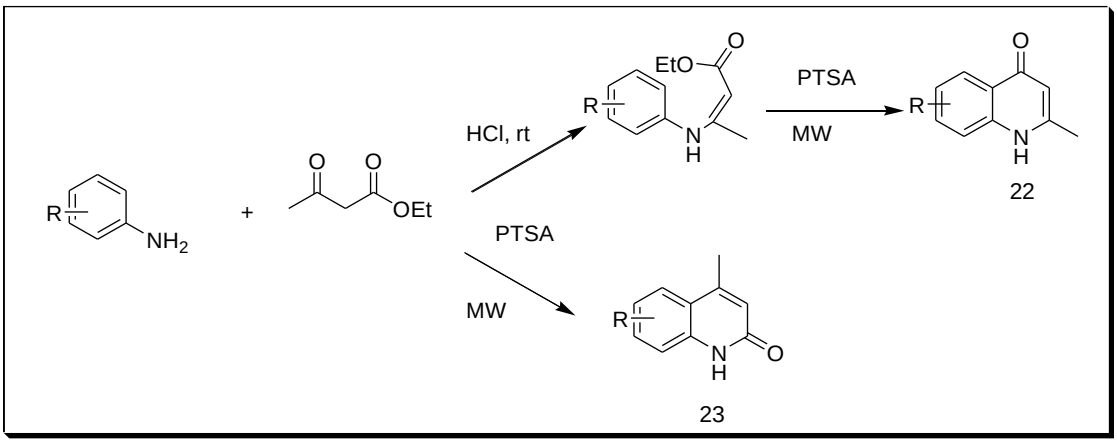
**Plausible mechanism**

Long.et.al reported the novel and efficient route of transition metal free synthesis of structurally diverse 2-substituted 3-carboxy-4-quinolone derivatives from 3-oxo-3-arylpropanoates and amides in a one pot approach. The methodology involves the intramolecular N-arylation in presence of base.[21]



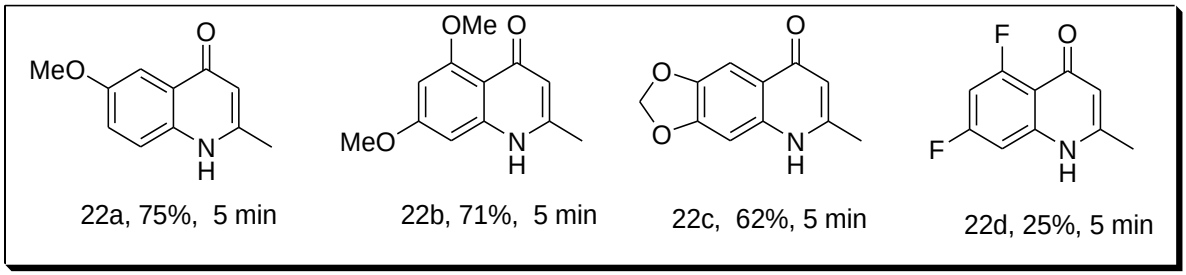

**Scheme-I.7.** Metal free synthesis of 2-substituted 3-carboxy-4-quinolone derivatives from 3-oxo-3-arylpropanoates and amides

Corrêa and his coworkers reported the microwave assisted synthesis of 4-quinolones in one step reaction between ethyl acetoacetate and electron rich anilines with diphenyl ether as a solvent.[22]

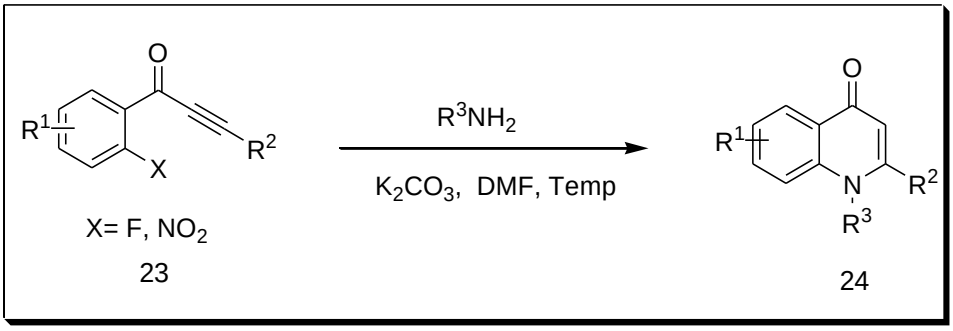



**Scheme-I.8.** Microwave assisted synthesis of 4-quinolones

**Selected examples**




Herein, Iaroshenko et.al described the catalyst free approach for the synthesis of functionalized quinolin-4-ones via tandem amination/conjugated Michael addition in between 1-(2-fluoro/2-nitrophenyl)prop-2-yn-1ones with amines.[23]

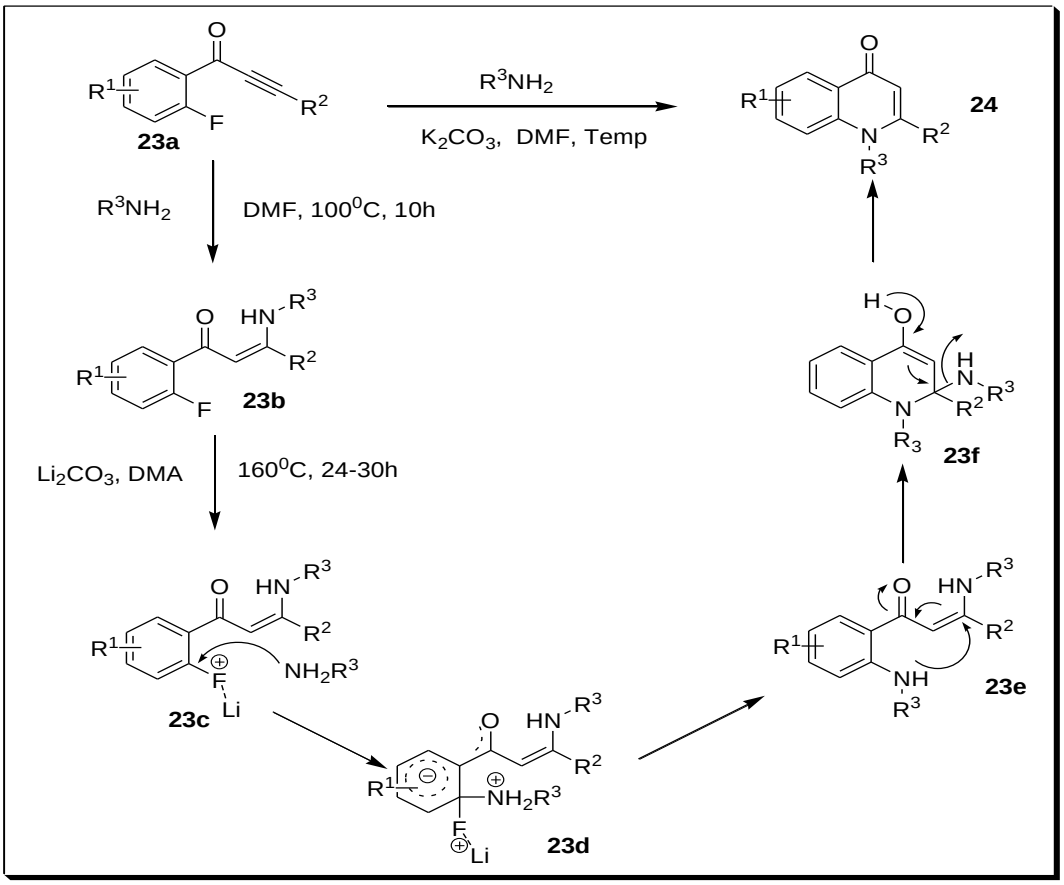



**Scheme-I.9.** Metal free synthesis of functionalized quinolin-4-ones from 1-(2-fluoro/2-nitrophenyl)prop-2-yn-1ones

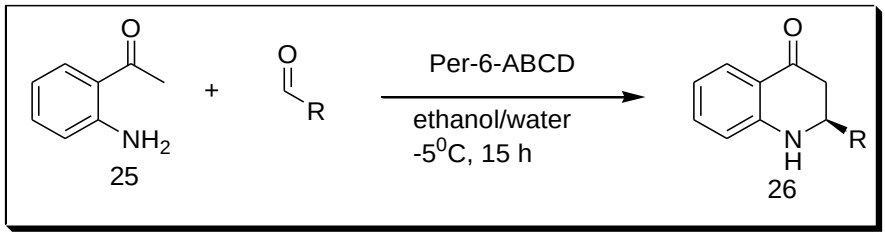
Generally, aliphatic amines responded well and gave moderate to excellent yields of the corresponding products, but anilines gave good yields. Electron-deficient heteroaromatic amines such as benzo[d]thiazol-2-amine, pyrimidin-2-amine, or pyridine-2-amine did not respond under this optimized condition.

**Plausible mechanism**

They proposed a stepwise mechanism for the one-pot synthesis of 4-quinolones 24 was shown above. Preliminary, the alkynone 23a underwent hydroamination reaction gave intermediates 23b. In the next, the lithium cation coordinated with the fluorine atom of the intermediate 23b to produce the intermediate 23C, which readily transformed into the Meisenheimer complex 23d via an aromatic nucleophilic substitution reaction. The fluorine anion eliminated as lithium fluoride to give the intermediate 23e. Further, it underwent an intermolecular Michael addition to generate the quinolin-4-one 24 via forming an intermediate 23f.

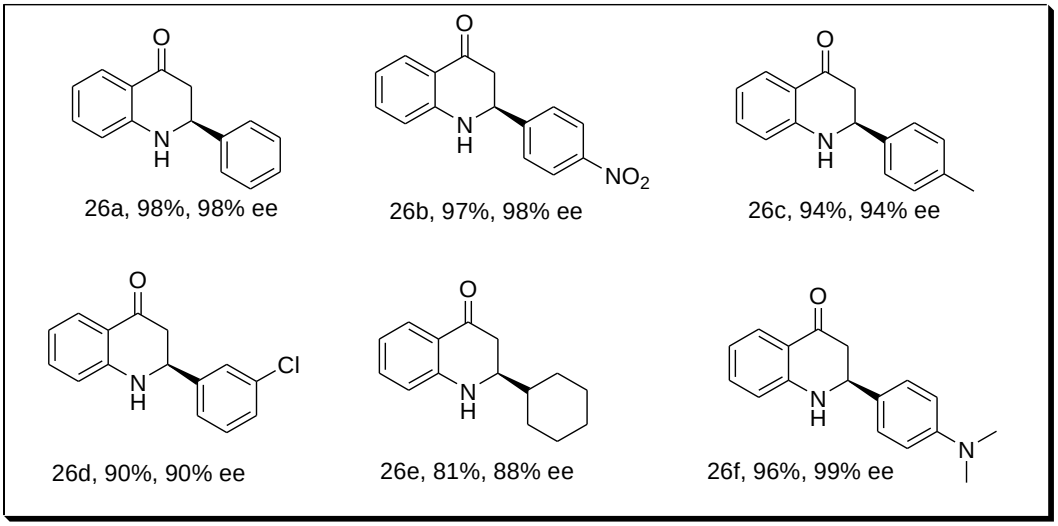



Pitchumani demonstrated the novel and efficient one-pot synthesis of enantiomerically enriched 2-aryl-2,3-dihydroquinolin-4(1H)-ones from o-aminoacetophenone and substituted aldehyde in the presence of per-6-ABCD (per-6-amino-β-cyclodextrin) which acted as a supramolecular host, chiral base catalyst, and also a reusable promoter to give the desired scaffold with excellent yield (up to 99%) and enantiomeric excess (up to 99%).[24]



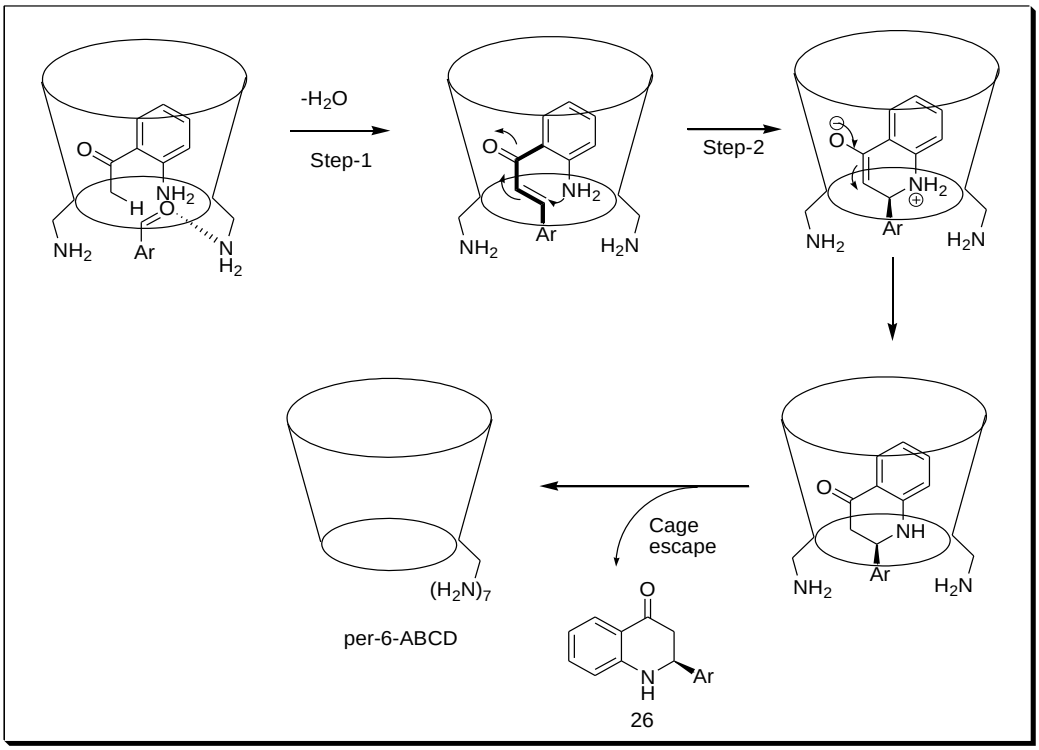

**Scheme-I.10.** Per-6-ABCD induced synthesis of enantiomerically enriched 2-aryl-2,3-dihydroquinolin-4(1H)-ones

**Selected examples**



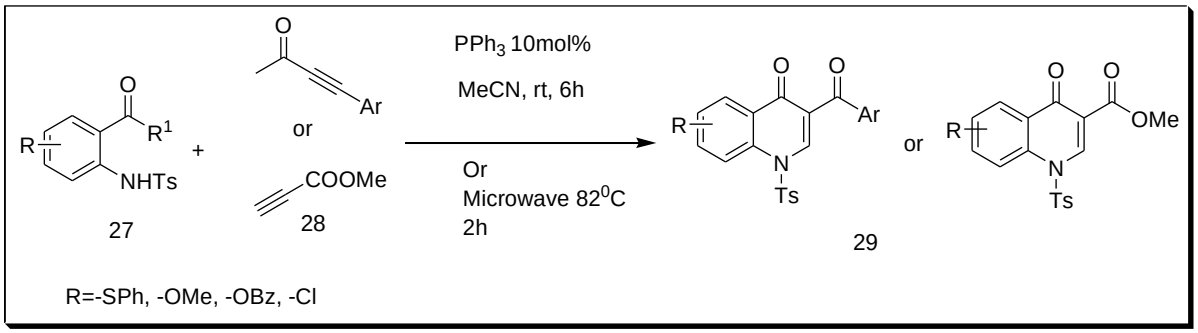

Both heterocyclic and cyclic aldehydes participated in reaction very well and resulted the products with high yield and excellent enantioselectivity. Electron releasing group and electron with drawing group possessing aldehydes were well tolerated in the reaction. Para-substituted aldehydes accomplished better yield than the ortho and meta substituted aldehydes due to stronger binding and deeper inclusion in the cyclodextrin cavity. Electronic factor was not very prominent than the steric factor in enhancing the enantiomeric excess (ee).

**Plausible mechanism**



A plausible mechanism was proposed to provide the asymmetric synthesis of 2-Aryl-2,3-dihydro-4-quinolone. Initially, o-aminoacetophenone and aldehydes underwent the condensation reaction to form chalcone. Then, isomerization of chalcone occurred via Aza-michael addition and readily it tautomerized to provide the 2-aryl-2, 3-dihydro-4-quinolone with high enantioselectivity (ee > 99%). The amino group of per-6-ABCD activated the Aza-michael addition into the cavity through its *Si*-face and resulted the stereochemical outcome.

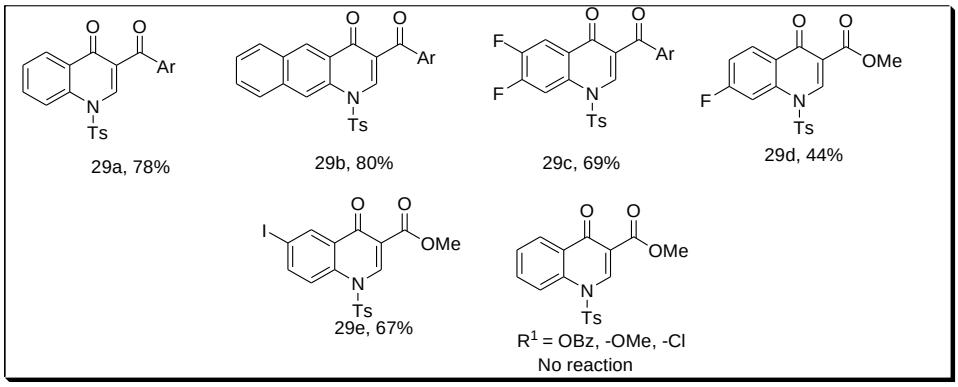
Kwon *et al.* reported a metal free approach for the synthesis of 3-substituted 4-Quinolones using an inexpensive cheap phosphine catalyst.[25]



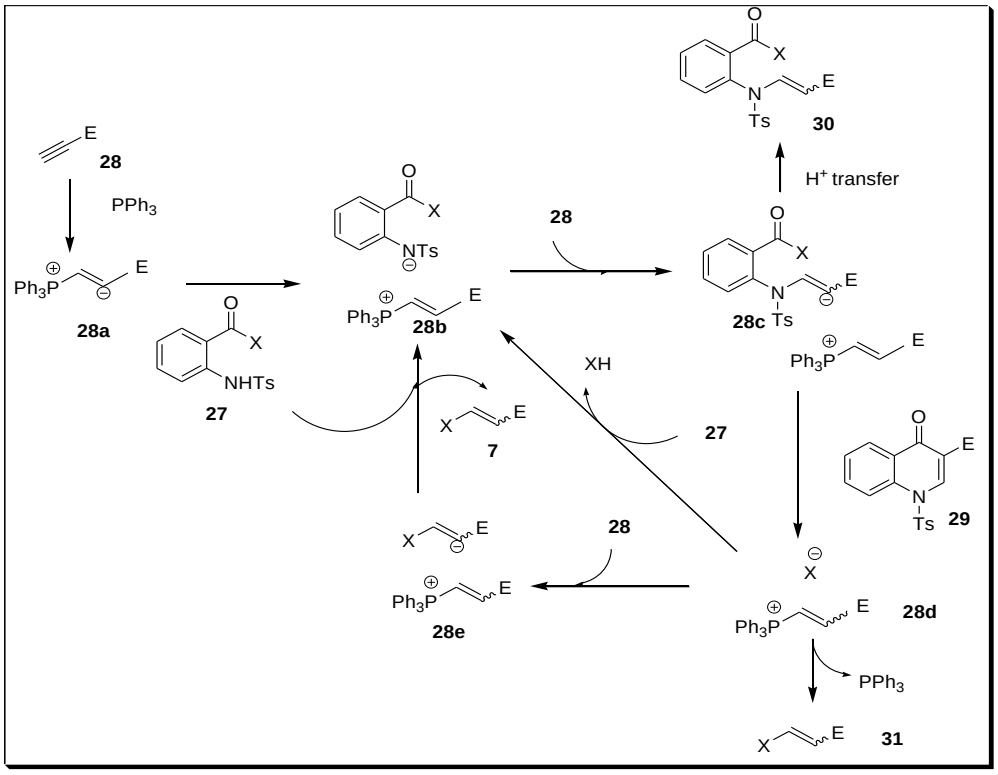

**Scheme-I.11.** $PPh_3$ catalysed synthesis of 4-quinolones

The reaction took 6h at rt to complete conversion whereas under microwave irradiation at 82°C it completed within 2h and resulted in the decent yield of the final product. Using this reaction condition, they synthesized a number quinolone structures in which electron-deficient aromatic rings gave the lower reaction yields than the electron-rich aromatic rings. Particularly, the electron-withdrawing halide substituents, at the meta position showed a contradictory trend in the reaction. More electron-withdrawing halides led the better reaction yields of quinolone formation.

**Selected examples**



**Plausible mechanism**



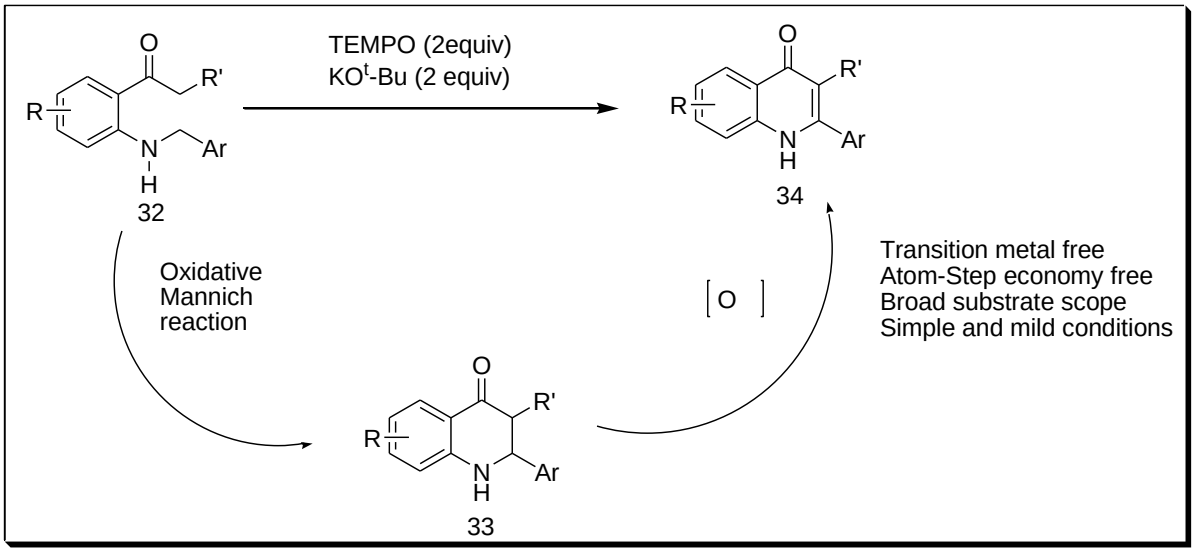

A mechanistic pathway was proposed by Kwon et.al where reaction began with the nucleophilic addition of triphenyl phosphine to the activated alkyne 28 and subsequently generated the phosphonium based zwitterions 28a. By deprotonation, the intermediate 28a activated the pronucleophile 27. The resulting nucleophile in 28b readily added to the activated alkyne 28 to form the ion pair 28C.

Then, it underwent the cyclization to generate the desired 4-quinolone 29 via acyl substitution (X=SPh) pathway whereas it also formed to the Michael adduct 30 as a byproduct. During the formation of the quinolone 29, the leaving group X in the ion pair 28d further added to the activated acetylene **28** to regenerate the $PPh_3$ derived base for continuing the catalytic cycle.

Other possibility, the departing group $X^-$ might be functioning as a base to activate the starting pronucleophile 27. In this case , the proton donor HX would also generate the byproduct 30 via proton transfer mechanism. Lastly, the $Ph_3P$ initiator might be reformed from the ion pair 28d followed by addition/elimination reaction.

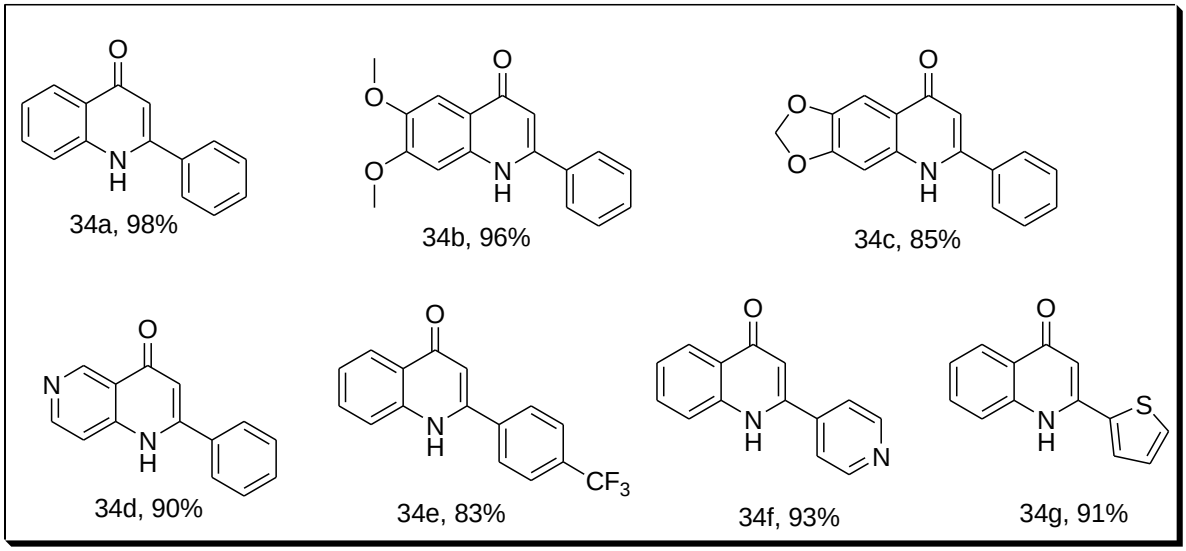
In 2015, a novel approach for the synthesis of diverse 2-aryl-4-quinolone derivatives via a TEMPO-mediated intramolecular oxidative Mannich reaction from N-arylmethyl-2-aminophenyl ketones was reported by Long et al.[26] This transition metal-free oxidative Mannich reaction followed a tandem oxidative $C(sp^3)–H/C(sp^3)–H$

coupling and aromatization to afford a broad range of 2-arylquinolin-4(1H)-ones as a final product.



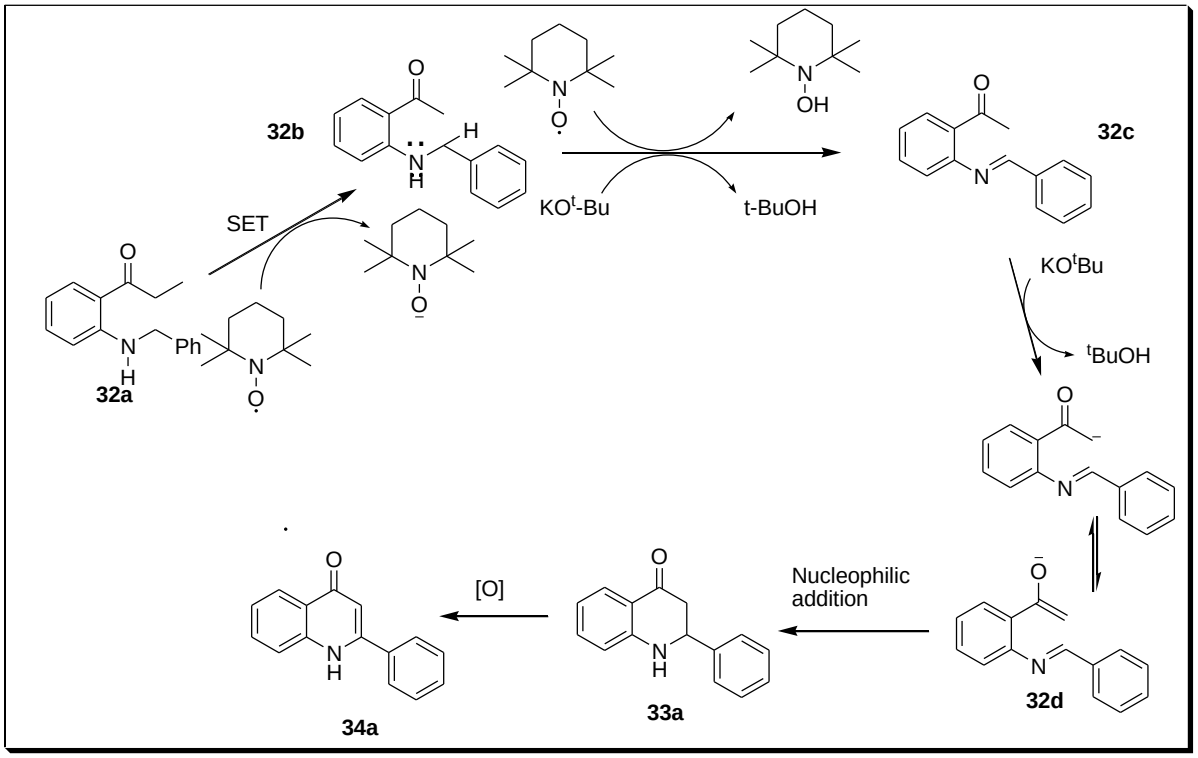

**Scheme-I.12.** TEMPO catalysed intramolecular tandem oxidative C(SP$^3$)-H/ C(SP$^3$)-H coupling

**Selected examples**



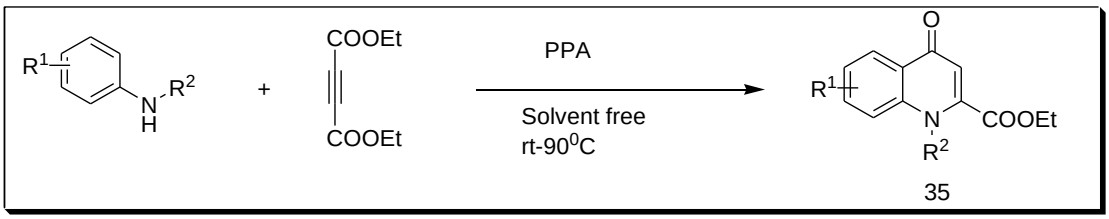

Aromatic rings possessing the electron-donating or -withdrawing or sterically hindered groups, all underwent the oxidative cyclization smoothly and furnished the desired 4-quinolone products in good to excellent yields. Aliphatic substituent could not be incorporated at the 2-position of 4-quinolone using this protocol rather it gave an oxidized cleavage benzoic acid derivative.

**Plausible mechanism for the TEMPO promoted oxidative annulations**




A plausible mechanism for this protocol was given in above figure. Initially followed by the SET pathway, TEMPO generated an anilinium radical cation 32b. This radical cation yielded an iminium-type intermediate via a hydrogen transfer from the adjacent carbon. Afterwards under the basic conditions, it rapidly converted to imine 32c and subsequently to an enolate form 32d. Finally, nucleophilic addition occured to the imine and the annulated product 33a is readily oxidized to give the desired quinolone product 34a.

In 2015, Huang and his co workers designed a protocol for the construction of 4-quinolone-2carboxylates via a cascade reaction between commercially available aromatic amines and diethyl acetylene dicarboxylate.[27]

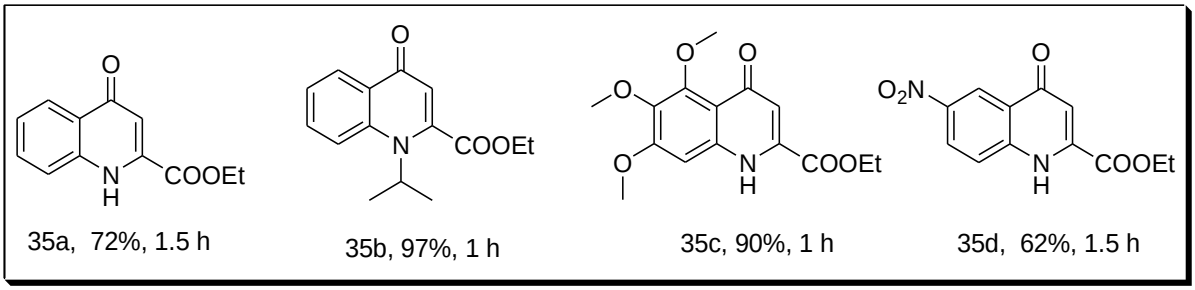



**Scheme-I.13.** PPA catalysed synthesis of 4-quinolones.

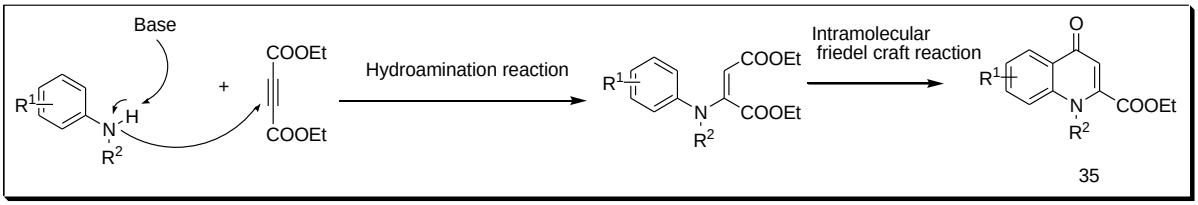
Electron density effect of aromatic amines plays the pivotal role for the formation of 4-quinolone. As the electron density on the nitrogen atom increases, the yield of the product gradually increases. Electron withdrawing group substituted primary amine

took longer reaction time than those for electron donating groups. The steric hindrance and electron density of diphenylamine and benzylamine failed to give the desired product.

**Selected examples**

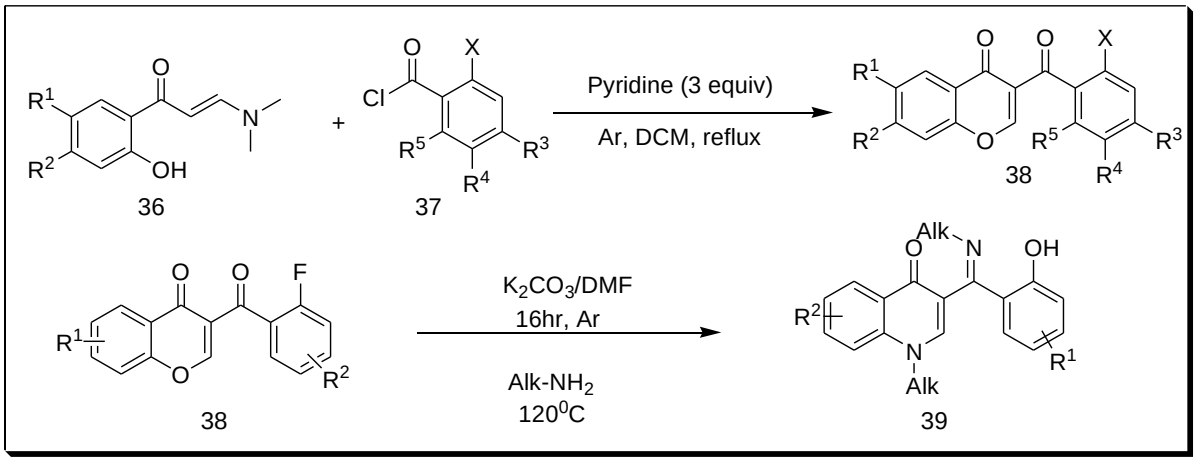



**Plausible mechanism**




A plausible mechanism for the formation of the desired product 35 is mentioned in following scheme. The activated non-terminal alkyne participated in hydroamination reaction with diethyl acetylenedicarboxylate in presence of aromatic amine affording the intermediate. Subsequently, the intermediate underwent an intramolecular Friedel–Crafts reaction to furnish the product 35 with PPA as catalyst. Due to the effect of electron density and steric hindrance of nitrogen atom, the structure of aromatic amine had a significant influence in the protocol.

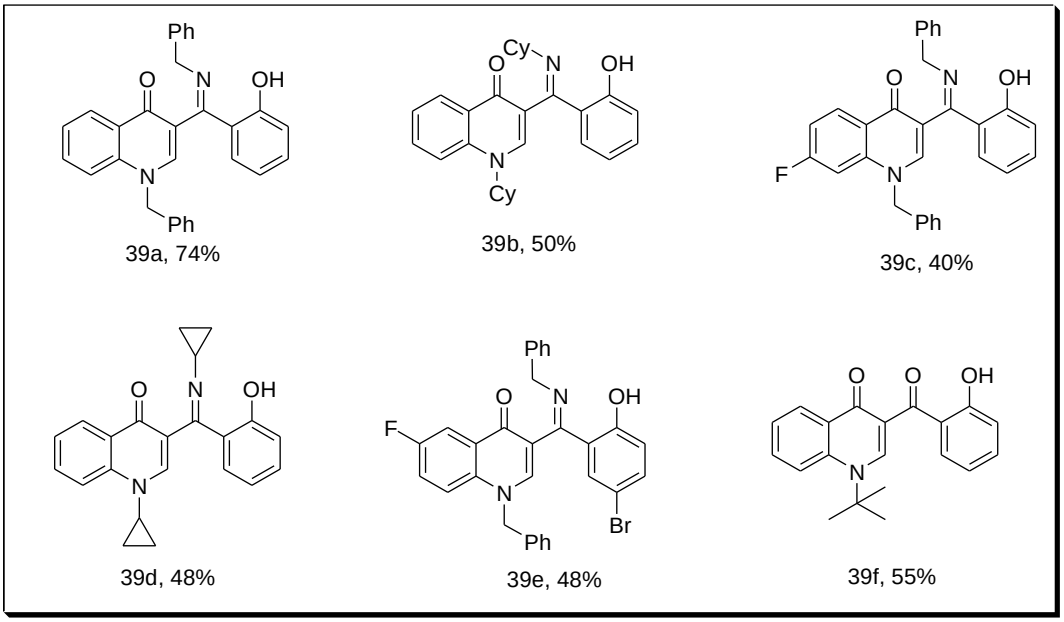
A transition metal free strategy for the synthesis of 4-quinolones *via* domino reaction of 3-benzoyl-chromones with aliphatic amines, anilines was demonstrated.[28]



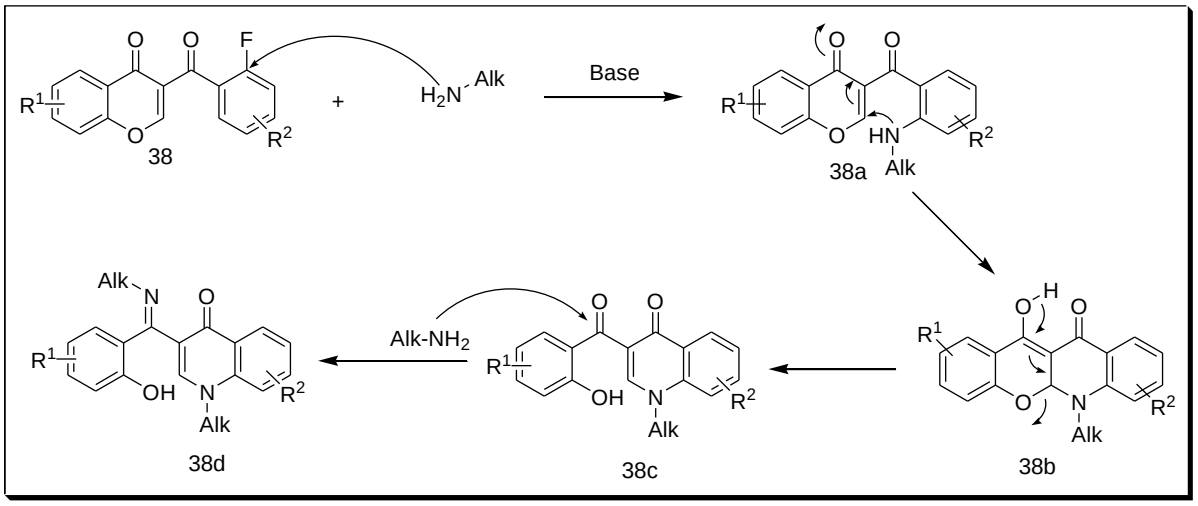

**Scheme-I.14.** Transition metal free synthesis of 4-quinolones *via* domino reaction of 3-benzoyl-chromones with aliphatic amines, anilines

All reactions responded well and provided the desired products ranging from moderate to excellent yields, with excellent chemoselectivity. Sensitive functional groups on the chromone were well tolerated.

**Selected examples**

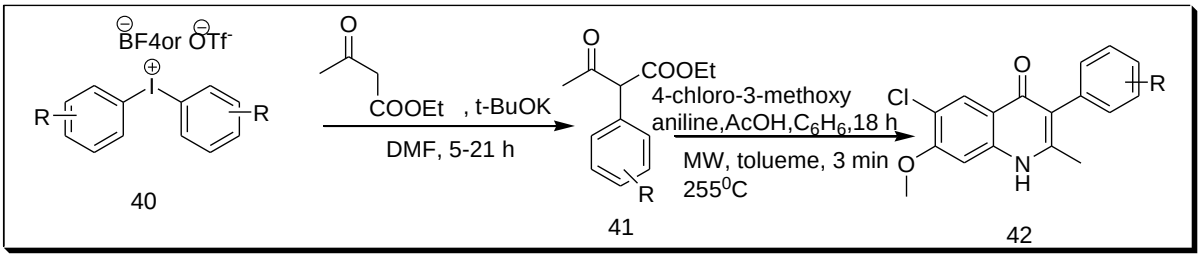


**Plausible mechanism**



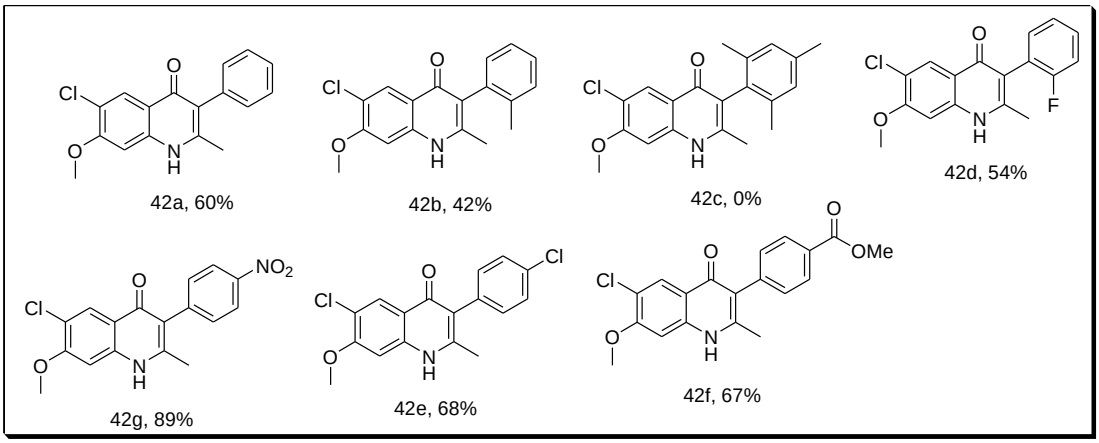

This domino sequence was initiated by the aromatic nucleophilic substitution of fluorine atom. This was followed by the intramolecular attack of amino group to the position 2 of chromone moiety. Finally the ANRORC (Addition of the Nucleophile, Ring Opening, and Ring Closure) transformation of the pyrone ring delivered the desired 4-quinolones. In most of the cases the reaction proceeded further with second molecule of amine leading to the formation of corresponding Schiff bases.

Manetsch et al. recently reported a new convenient and operationally simple protocol for the arylation of ethylacetoacetate under metal free and mild condition in the presence of hypervalent iodine reagents. Further, this technology was applied by them to prepare the antimalarial ELQ-300 compound under modified Conrad Limpach cyclisation.[29]



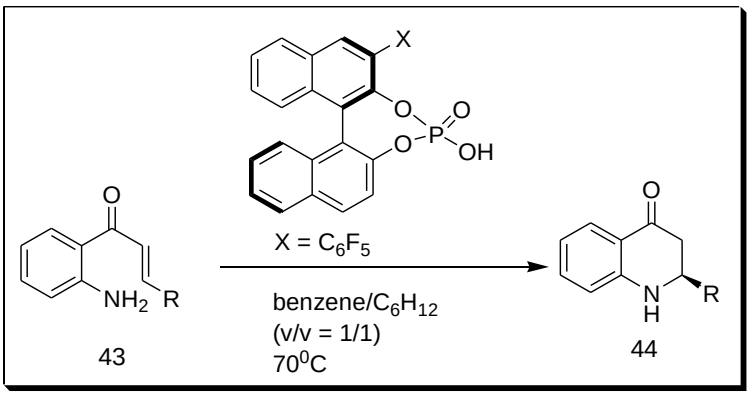

**Scheme-I.15.** Hypervalent iodine reagent mediated arylation of ethylacetoacetate

**Selected examples**



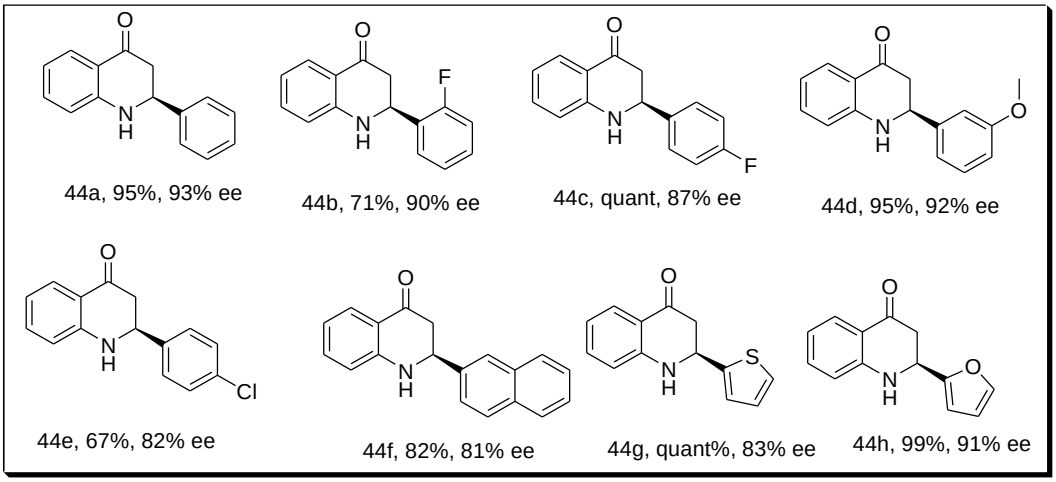

Major advantage of this protocol was that ortho substituted substrates were well tolerated and converted to moderate yield of the arylated product. 4-methoxy substituted aryliodonium salt did not provide any product after prolonged reaction because +R effect of methoxy group reduced the electrophilicity of the iodine centre. In contrast, electron withdrawing group substituted iodonium salt reacted in a very short time and provided excellent yield.

In 2015, Akiyama and his coworkers developed a new method to synthesize the asymmetric 2-substituted 2,3-dihydro-4-quinolones via chiral phosphoric acid catalyzed intramolecular aza-Michael addition reaction from *N*-unprotected 2-aminophenyl vinyl ketones . This method furnished the broad array products with high enantioselectivities and yield.[30]



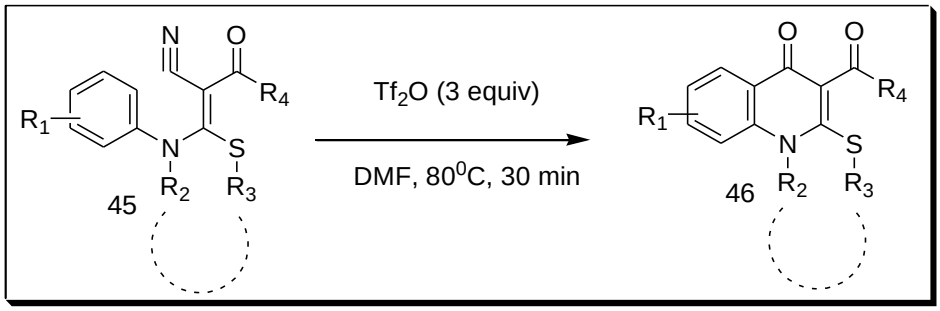

**Scheme-I.16.** chiral phosphoric acid catalyzed synthesis of 2-substituted 2,3-dihydro-4quinolones via intramolecular aza-Michael addition reaction from N-unprotected 2-aminophenyl vinyl ketones

**Selected examples**



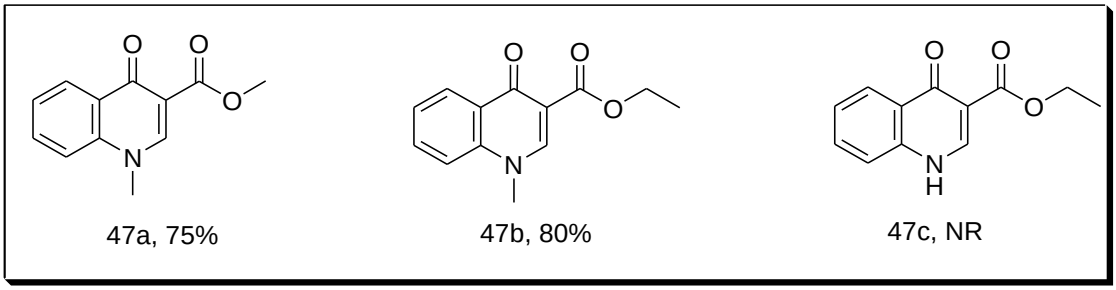

Ortho substituted arenes at the β-position furnished both high yield and excellent enantioselectivity. Electron with drawing and electron donating group substituted substrates were easily converted into the desired products with high enantiomeric excess.

Huang and Ge reported an efficient approach to synthesize the 4-quinolones via intramolecular Houben-Hoesch reaction of β-arylamino acrylonitriles mediated by triflic anhydride in N,N-dimethylformamide.[31]

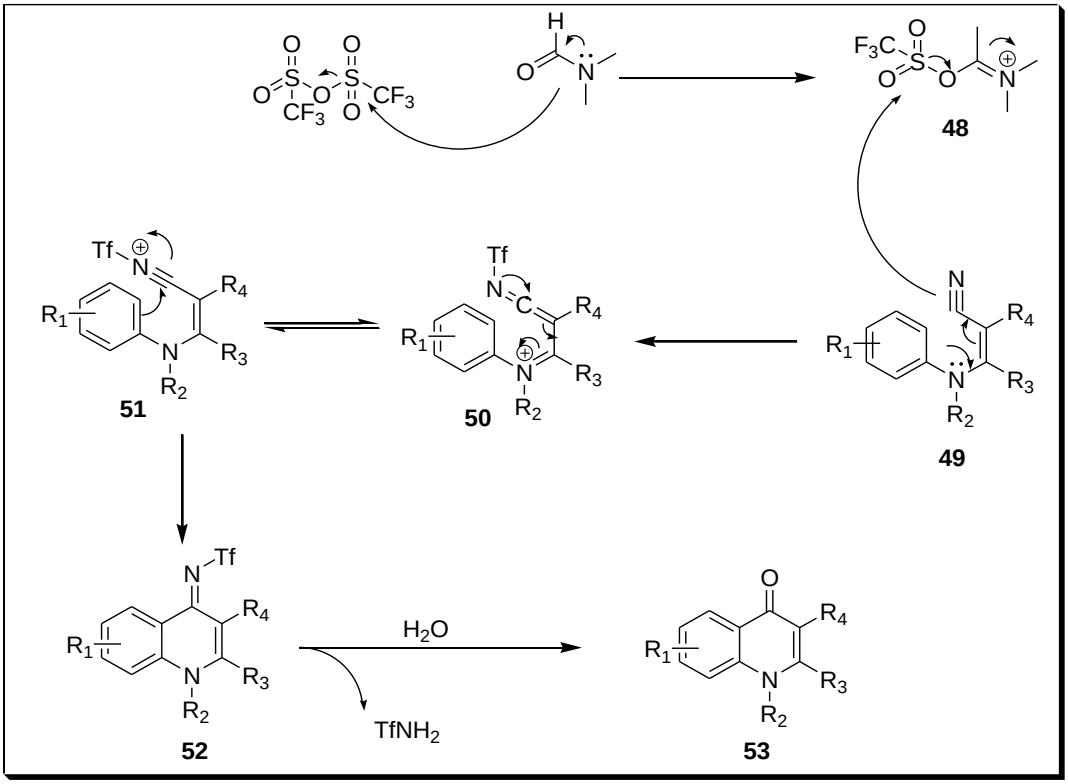



**Scheme-I.17.** Synthesis of 4-quinolones from N-aryl ketene-N,S-acetals

**Selected Examples**

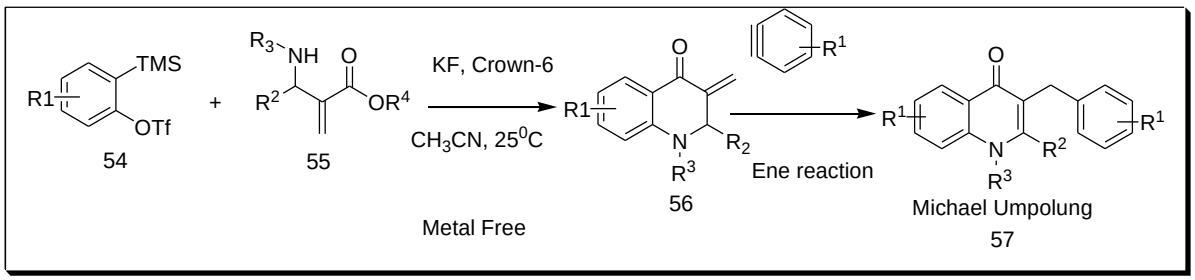


**Plausible reaction mechanism**



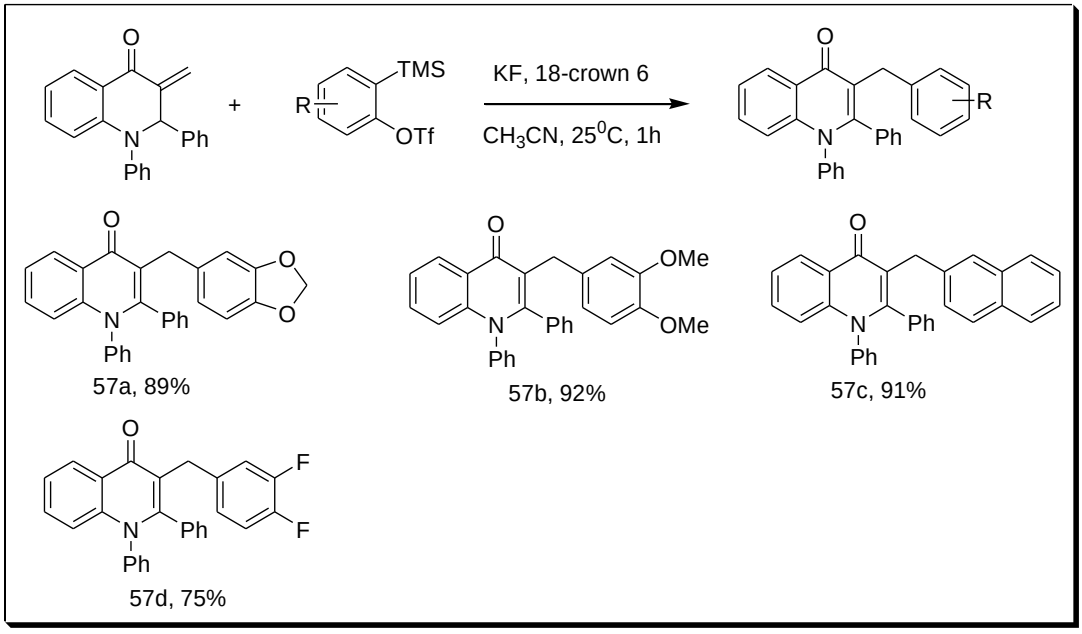

Initially, iminium triflate derived in situ via the reaction between DMF and $Tf_2O$. Then, the triflation of β-arylacryloaminonitrile occurred with iminium triflate to produce the intermediate 50 and its tautomer 51. Subsequently, the intermediate 51 underwent intramolecular Houben-Hoesch reaction which leads to the intermediate 52. Then, intermediate 52 hydrolyzed to provide the final product 53.

Here in , a mild and novel one pot aryne transformation for the construction of various substituted 4-quinolones through a cascade –insertion cyclisation followed by a rare inverse electron demand ene reaction was demonstrated by He et al. [32]

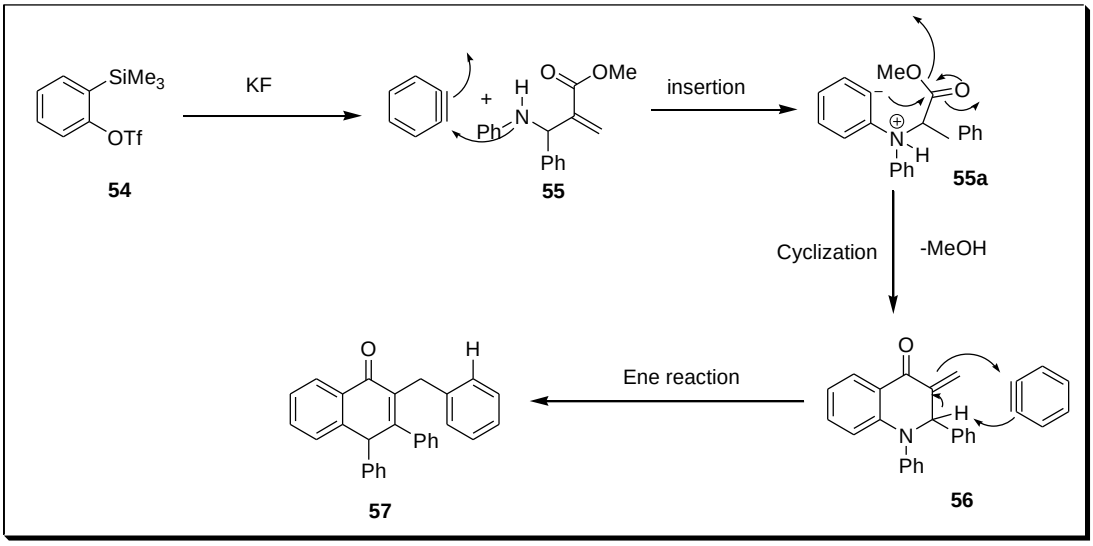



**Scheme-I.18.** Cascade Reaction of Aryne and AMBH (aza-Morita-Baylis Hilmann) Adduct

**Selected examples**



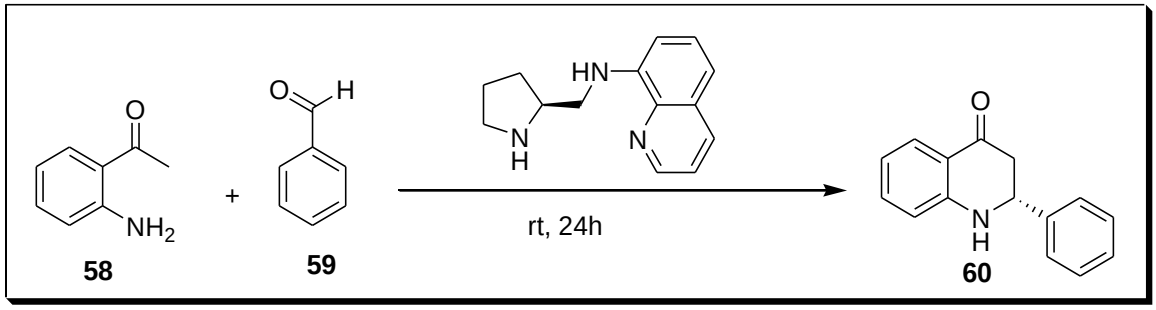

**Plausible mechanism**




A probable mechanism for the synthesis of 4-quinolone derivatives was outlined in the above Scheme. The reaction of the AMBH adduct with an aryne generated the intermediate 5a followed by a cascade insertion−cyclization process.[44] Subsequently, intermediate 56 reacted with another molecule of electrophilic aryne in a concerted way proceeding through an inverse electron demand ene reaction to furnish the product 57.

In recent years, Wang and his group accomplished the highly efficient organocatalytic one-pot enantioselective synthesis of (R)-2-aryl-2,3-dihydro-4-quinolones from o-amino

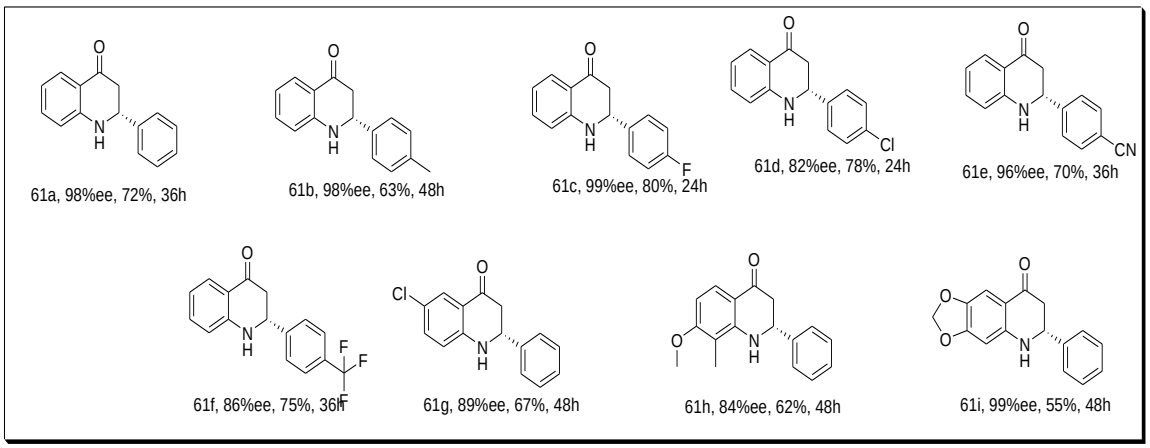
acetophenones and aryl aldehydes under metal free, solvent free and protecting group free approach.[33]



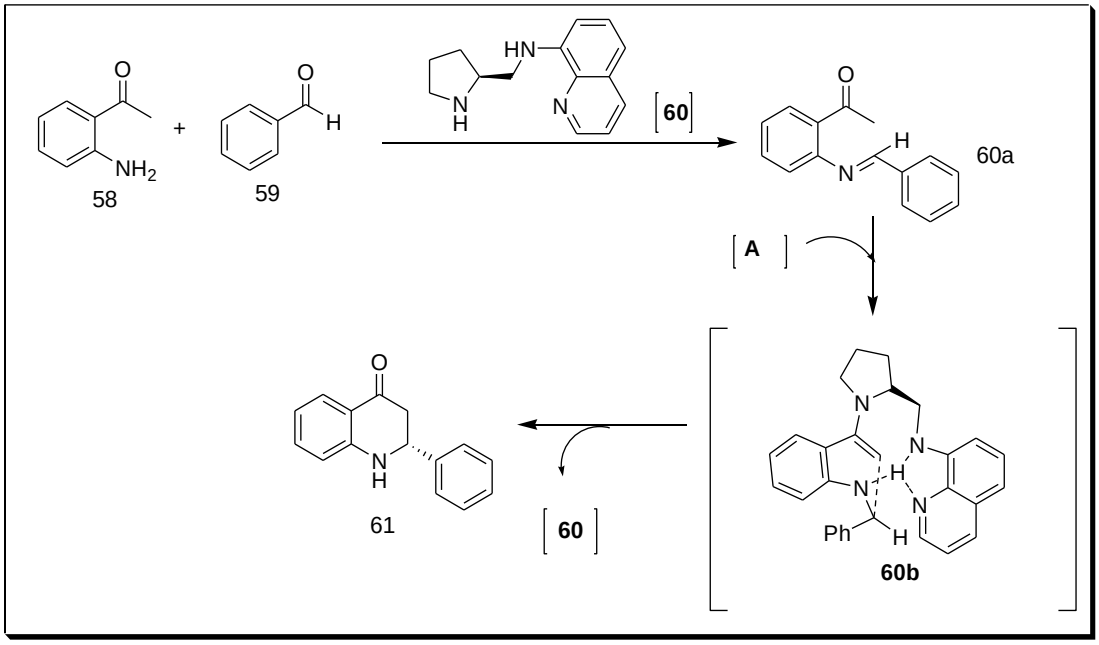

**Scheme-I.19.** Metal free, solvent free enantioselective synthesis of dihydro 4-quinolones

Electron-donating groups or electron withdrawing groups substituted aryl aldehydes reacted nicely and provided the corresponding (*R*)-2-aryl-2,3-dihydro-4-quinolones in moderate to excellent yields and ee values. Sterically hindered substituted aryl aldehyde gave much lower yield. 5-chloro-2-aminoacetophenone, 3-methyl-4-methoxyl-2-aminoacetophenone and 4,5 methylenedioxy-2-aminoacetophenone reacted smoothly with benzaldehyde, resulting the desired products (67% yield, 89% ee), (62% yield, 84% ee) and (55% yield, 99% ee), respectively.

**Selected examples**

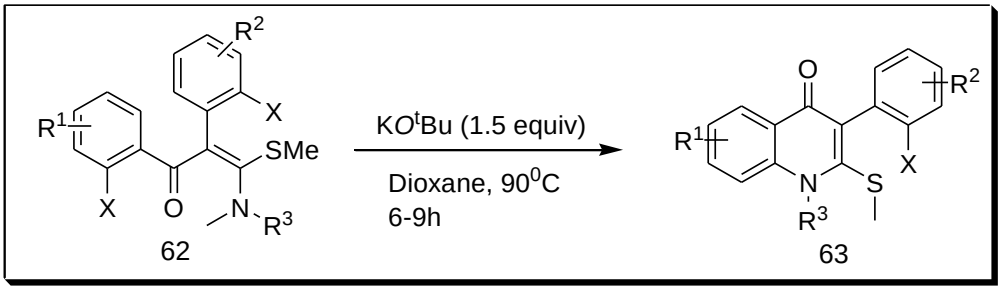


**Plausible mechanism**




Probably this one pot approach formed via imine formation and it underwent the intramolecular asymmetric Mannich reaction to give the 2-aryl-2,3 dihydro-4-quinolone. Catalyst [60] might be promoted the subsequent Mannich reaction followed by the intermediate 60b, in which the C=O group of imine was readily activated by the catalyst [60] via formation of an enamine. Also the hydrogen-bond between the nitrogen atom and the N–H activated the C=N of the imine. From the molecular modeling studies, the author believed that phenyl ring of the substrate and quinolinyl ring of the catalyst possess arene pi–pi stacking which contributed to the high enantioselectivities.

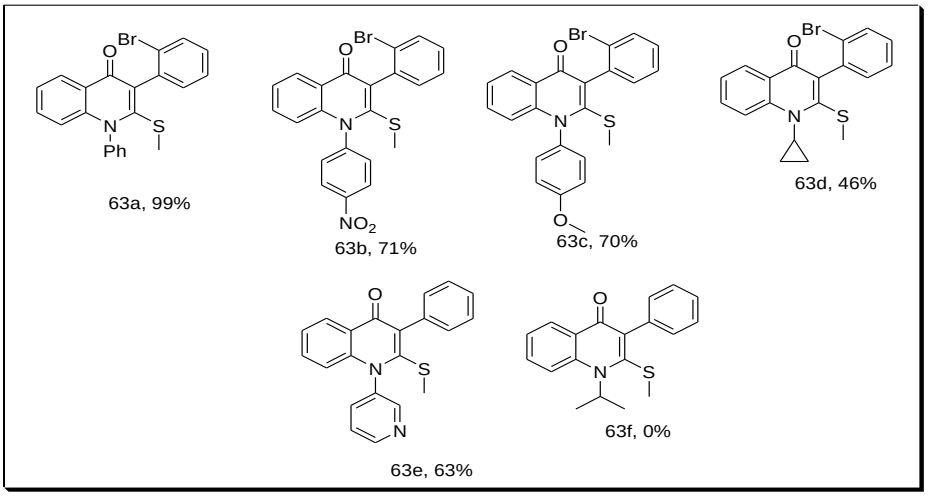
Recently, Peruncheralathan and his coworkers unfolded a new method to prepare the quinolone fused heterocycles under transition metal free condition from single S, N-acetal precursors *via* double heteroannulation.[34]



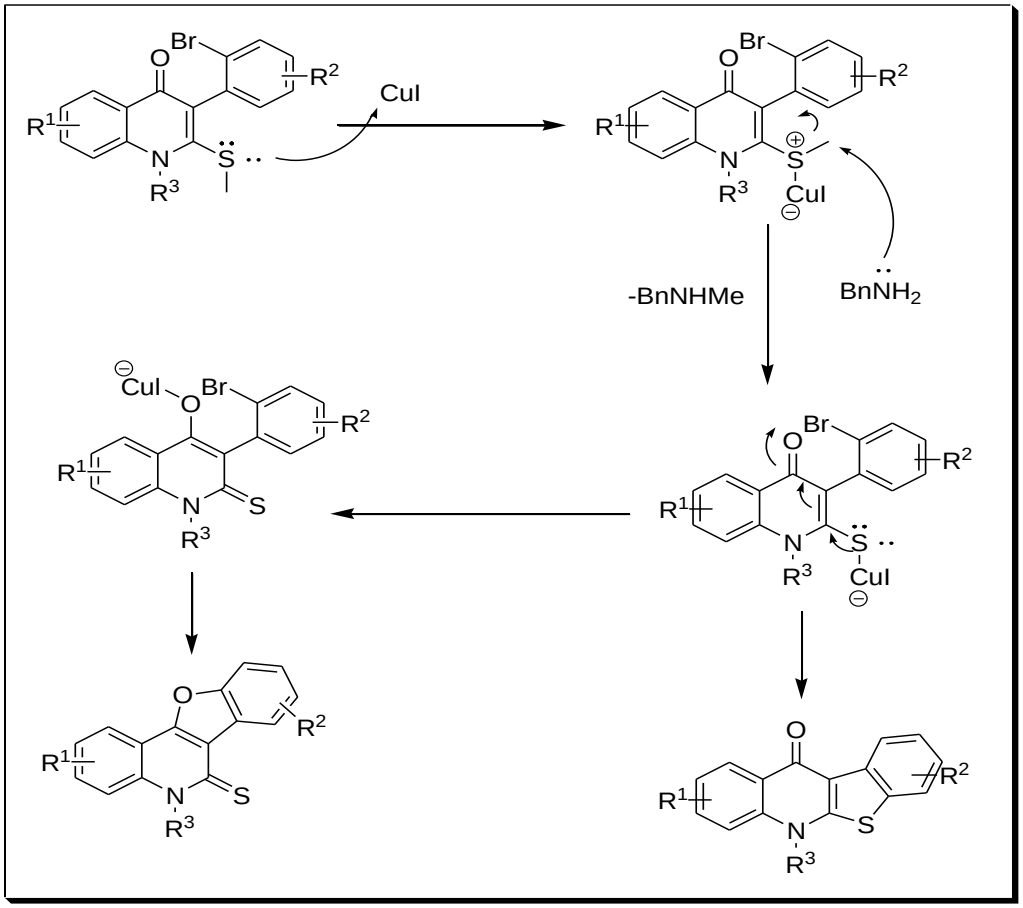

**Scheme-I.20.** KO-*t*Bu catalysed synthesis of 4-quinolones

It has been found that the substituted aniline nitrogen atom of S,N acetals bearing both Electron withdrawing and electron releasing group responded equally. Unfortunately, aliphatic amino *S,N* acetals gave poor yield. In the amination process, Steric hindrance effect profoundly.

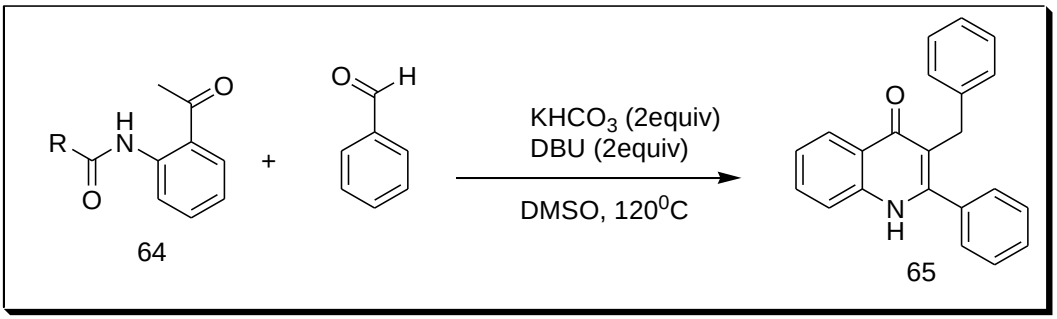
**Selected examples**




**Plausible pathway for the formation fused heterocycles**



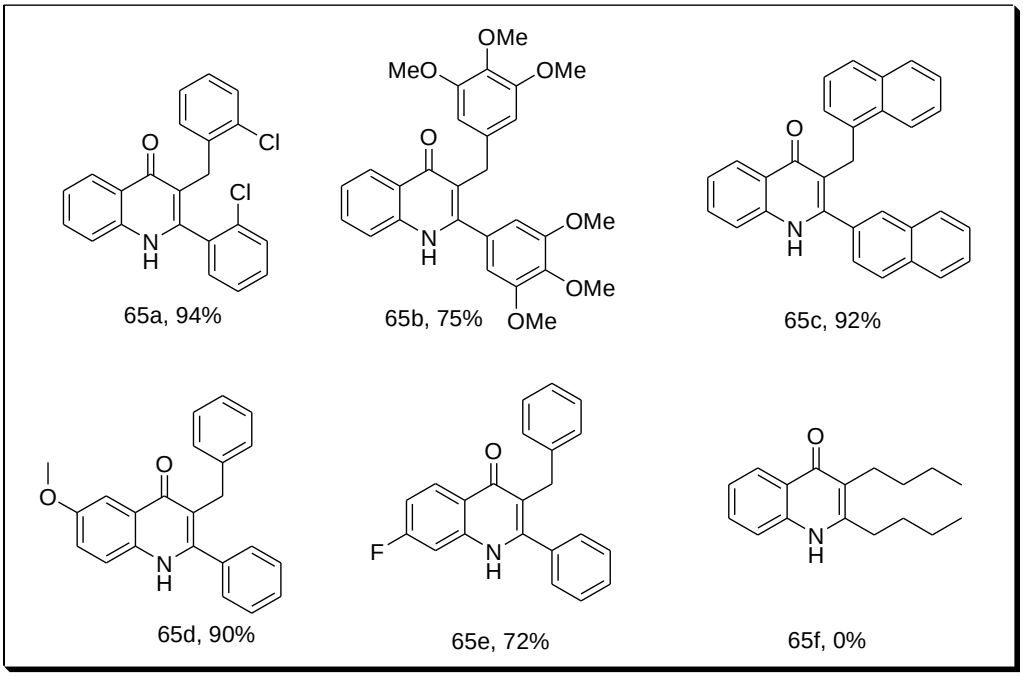
More recently Huang *et al.* described an efficient strategy for the transition metal free synthesis of 3-Benzyl-2-phenylquinolin-4(1H)-ones via $KHCO_3$ and DBU promoted cascade reaction. [35]



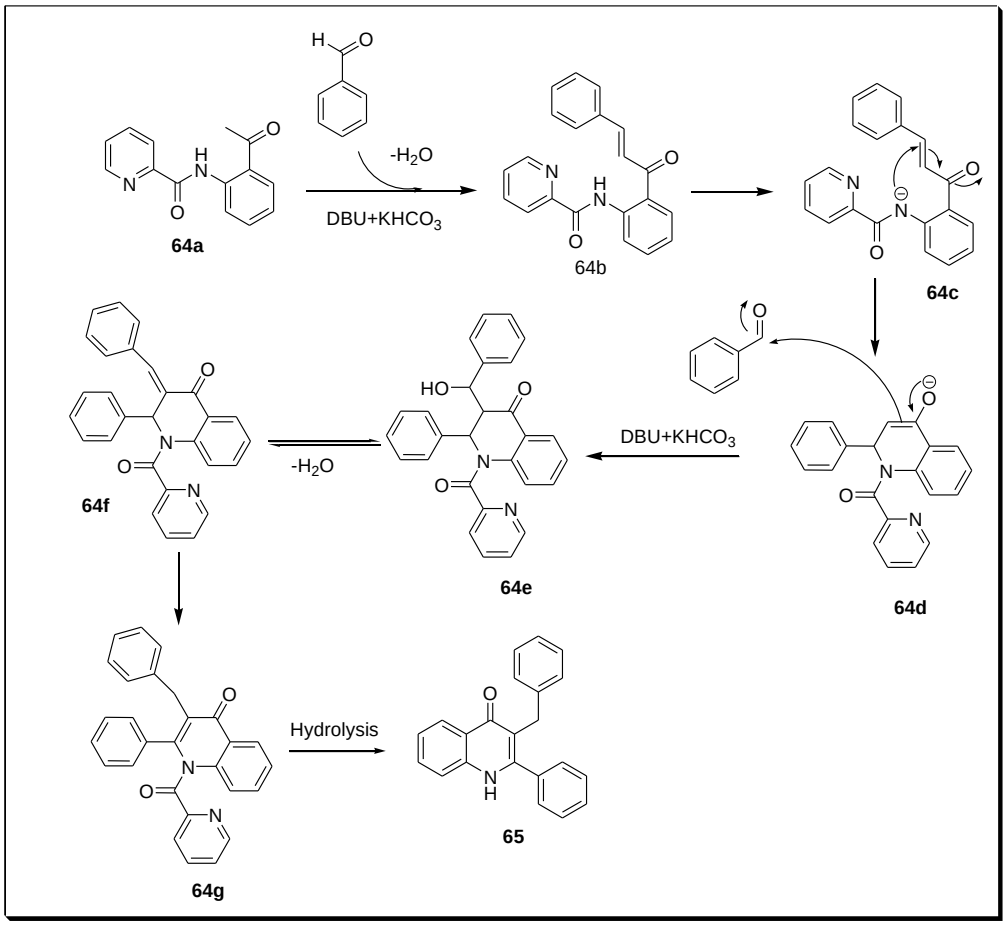

**Scheme-I.21.** Synthesis of 3-benzyl-2-phenylquinolin-4(1H)ones *via* cascade reaction

Due to the greater stability of iminium intermediate the starting material N-picolinoyl amide responded very well in the reaction and gave very good results. The aldehydes possessing the electron withdrawing group took participated in the reaction very smoothly than comparison to electron donating groups.

**Selected examples**

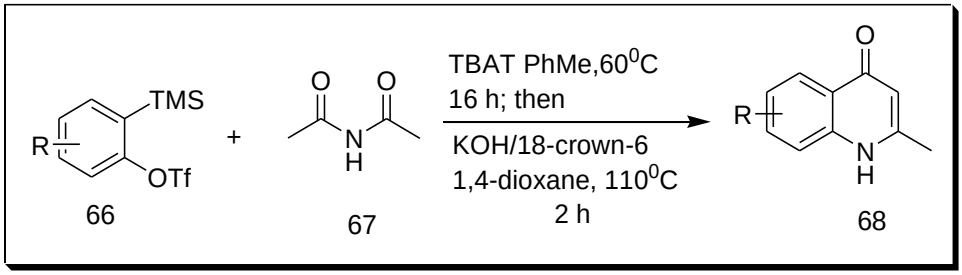


**Plausible Mechanism**



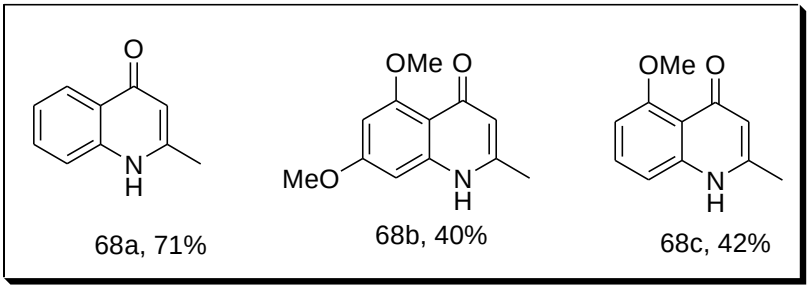

In this reaction, primarily the starting material 64a and benzaldehyde formed the intermediate 64b through aldol reaction in presence of DBU and $KHCO_3$. Then, the intermediate 64b readily converted to the 64c *via* abstraction of proton in presence of DBU and $KHCO_3$. Rather, the intermediate 64d might be underwent the intramolecular cyclization reaction to form the intermediate 64d through the Michael addition.The starting material benzaldehyde and intermediate 64d participated in aldol reaction to generate the intermediate 64e. Intermediate 64f readily formed in situ *via* elimination of hydroxyl group, it afforded the 64g through isomerisation. Finally, the intermediate 64g could be hydrolysed to result the desired products 65.

More recently, Stoltz *et al.* demonstrated the insertion of arynes into acyclic imides and anhydrides to provide aryl ketoamides under mild conditions. Further, the aryl keto amides were converted into 2-substituted 4-quinolones *via* base-catalysed Camps cyclization.[36]



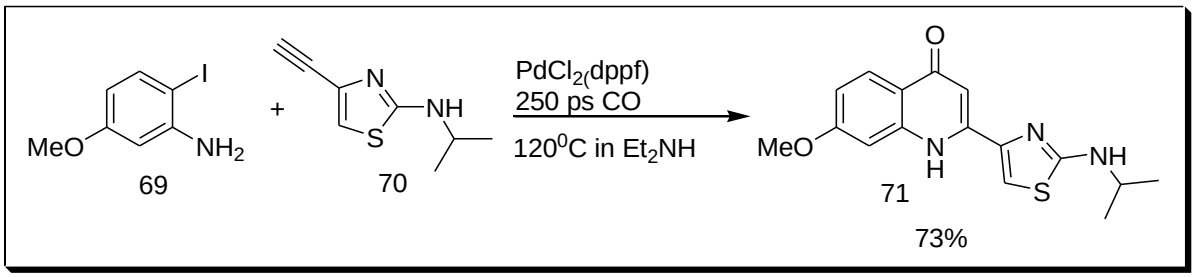

**Scheme-I.22.** Camps cyclization of ketoamide insertion products to provide quinolones.

**Selected examples**



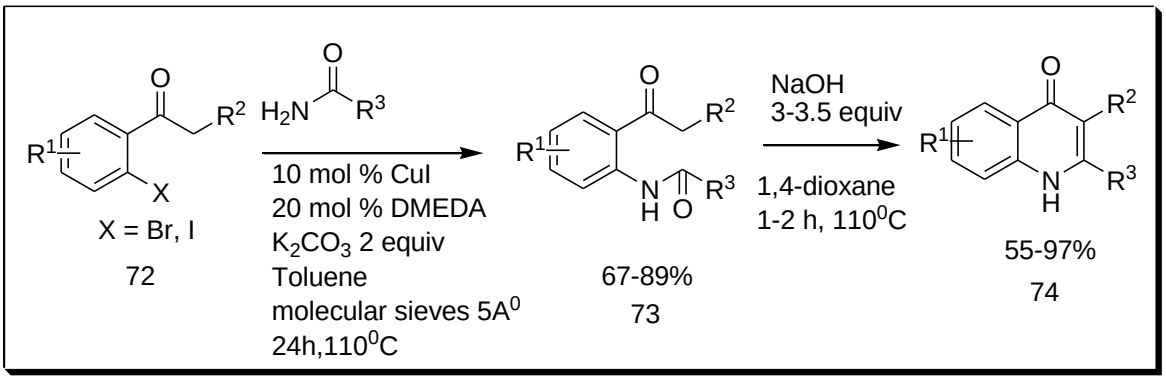

### I.A.1.b Metal catalysed synthesis of 4-quinolones

Haddad. et al. also described the synthesis of the 4-quinolone Substructure of **BILN 2061** via Carbonylative Sonogashira Coupling/Cyclization of 2-iodo-5-methoxyaniline with thiazolylacetylene.[37]



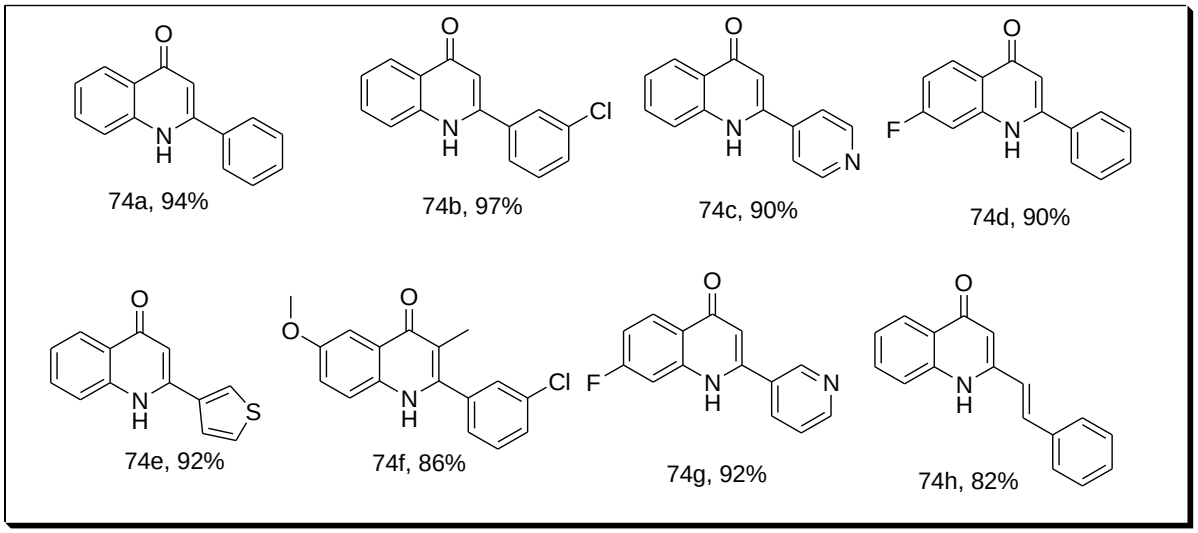

**Scheme-I.23.** $PdCl_2$ catalysed Carbonylative sonogashira coupling

In 2007, Buchwald *et al.* developed a new method for the synthesis of 2-vinyl and 2-aryl quinolones from N-(2-ketoaryl)amides under the base catalysed camps cyclization . The reaction offered two step processes. Initially, the starting material N-(2-ketoaryl)amides was synthesized by Cu catalysed amidation of 2-halophenones in excellent yields.[38]

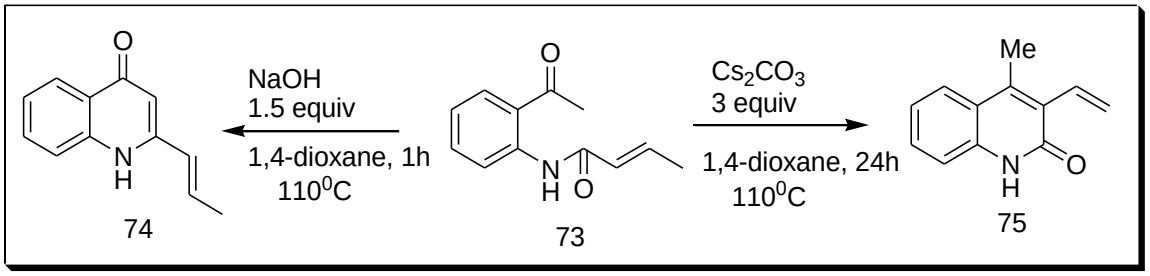



**Scheme-I.24.** CuI catalysed Camps cyclisation to synthesize 2-vinyl and 2-aryl quinolones from *N*-(2-ketoaryl)amides

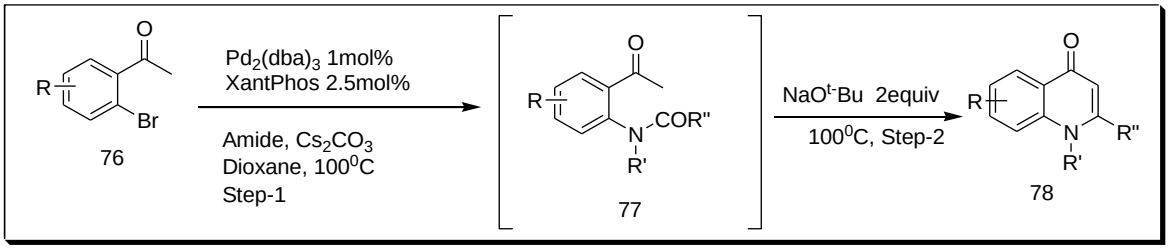
**Selected examples**




Depending on the nature of the base utilized, the derivative of N-(2-ketoaryl)amides was able to cyclise to afford the 2-quinolone and 4-quinolone. In presence of stronger base NaOH, deprotonation occurred at the α-position of keto methyl group of N-(2-ketoaryl)amides which underwent aldol condensation to furnish the 2-quinolone whereas $Cs_2CO_3$ abstracted the Y-proton of the amide to afford the 4-quinolones respectively.



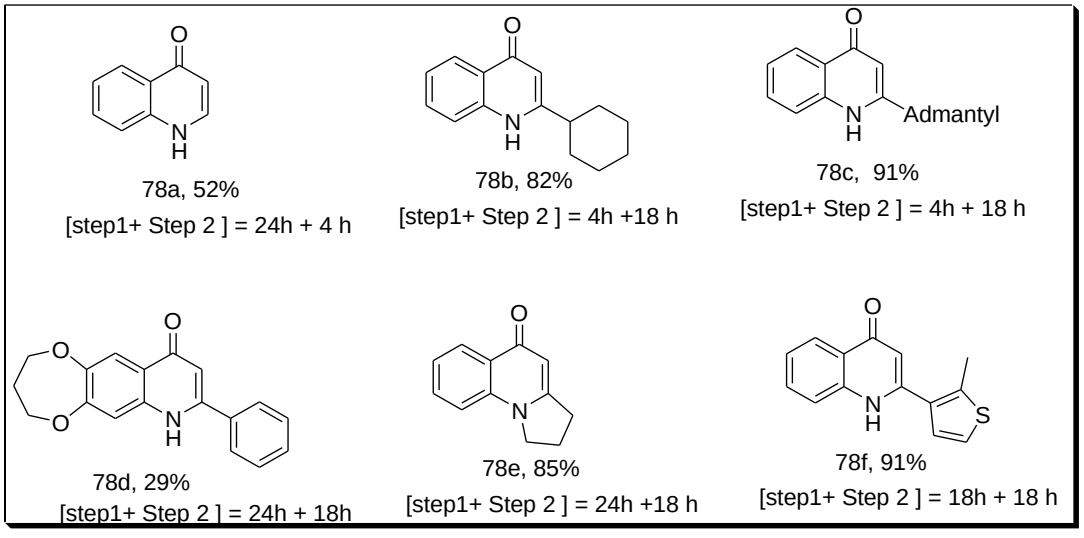
Huang and his coworkers reported the efficient route for a wide range of 4-quinolones synthesis in one pot reaction from base-catalysed cyclization N-(o-ketoaryl) amides. The starting material derived formed Pd-catalyzed amidation of 2-acetylbromoarenes.[39]




**Scheme-I.25.** Synthesis of 4-quinolones from base catalysed cyclisation of N-(o-ketoaryl) amides.

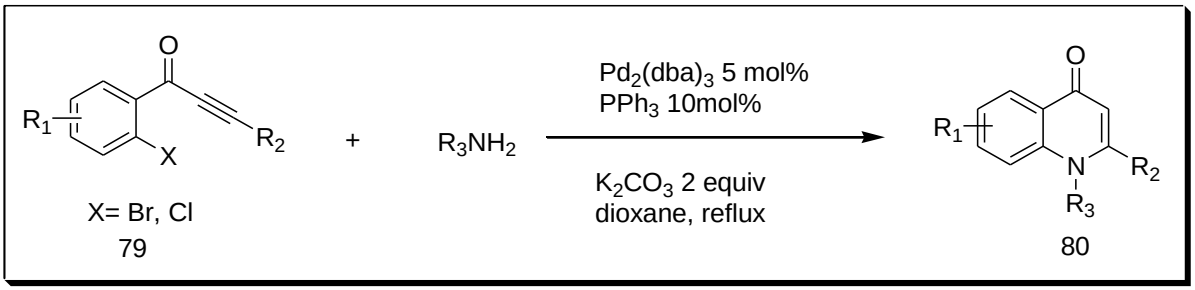
Initially, they used a mild base $Cs_2CO_3$, appropriate ligand XantPhos and the solvent dioxane to suppress the side reaction of ketone arylation. Then, the stronger base sodium tertiary butoxide performed the cyclization step. Dioxane proved to be a better solvent for the highest yield of both amide and quinolone. Alkyl, aryl, and heterocyclic amides afforded very good yields. Alkylamides with one or no proton (R) substrates provided promising yield of the desired quinolone products.

**Selected Examples**



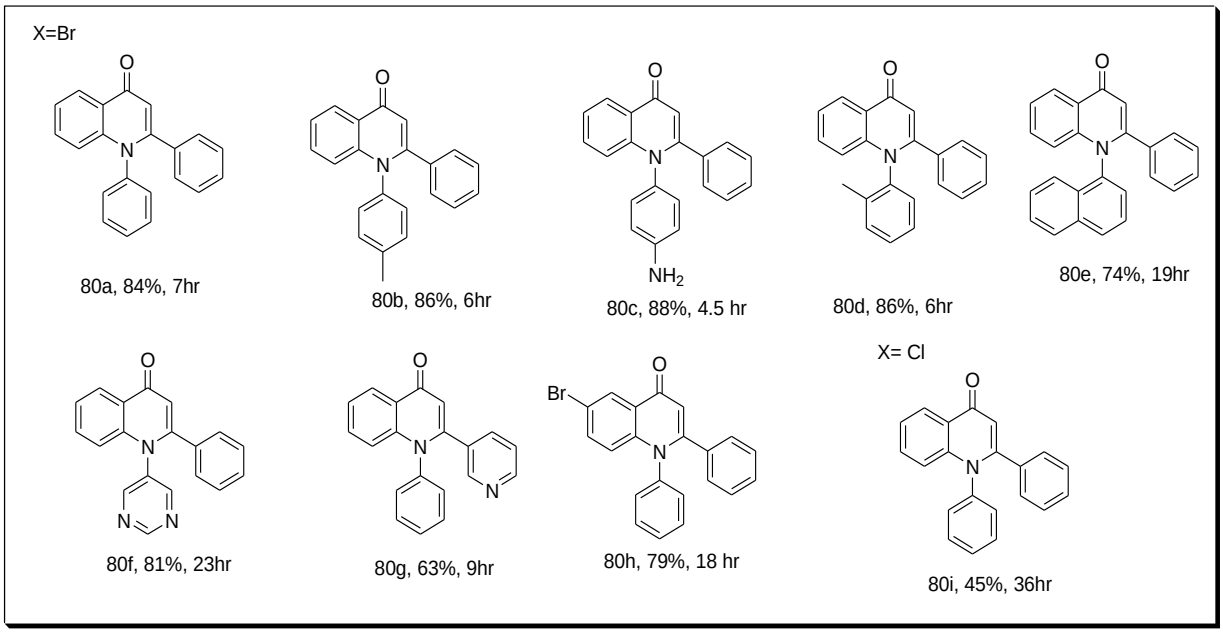

Zhao and Xu have developed a new procedure for synthesizing the substituted 4-quinolones *via* palladium-catalyzed tandem reaction. The reaction followed the sequential double C-N

bond formation from easily available o-haloaryl acetylenic ketones and primary amines.[40]

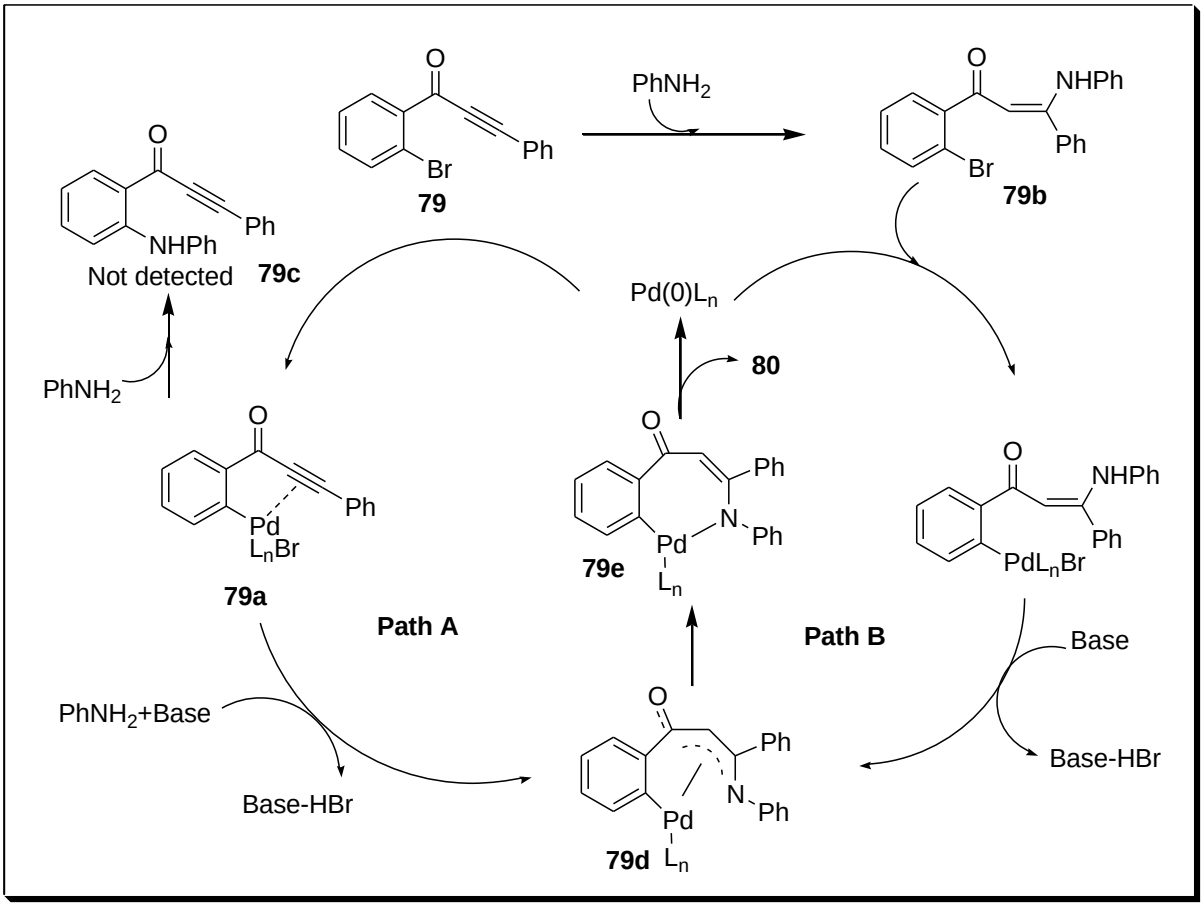



**Scheme-I.26.** Pd catalysed tandem reaction of o-haloaryl acetylinic ketones and primary amines.

**Selected Examples**



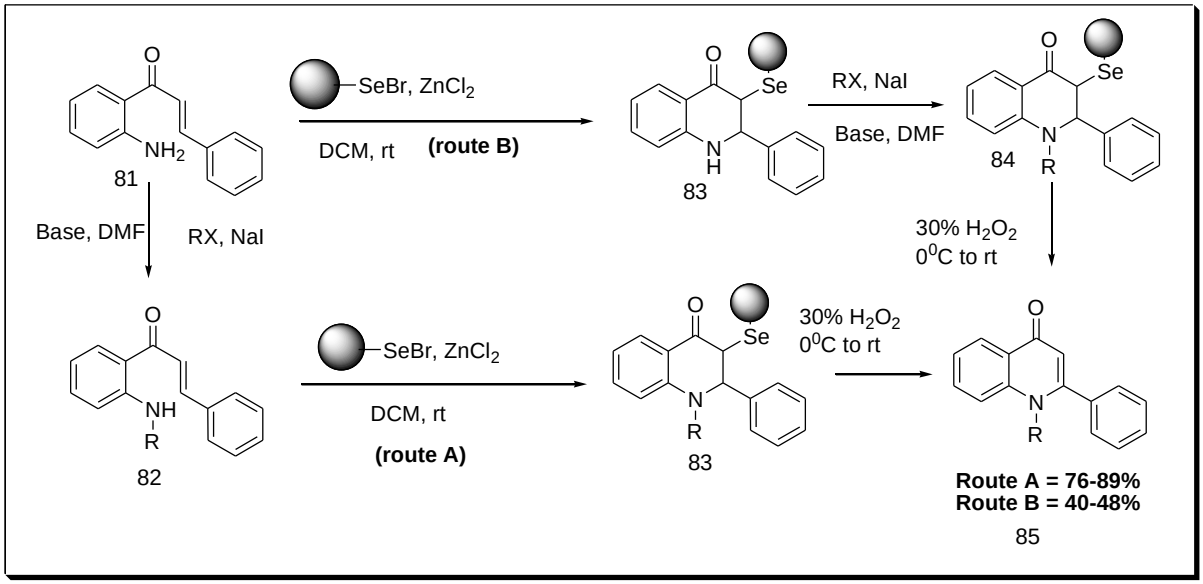
**Plausible reaction mechanism**




The authors postulated the mechanism for the above mentioned reaction which follows the two different routes (Route A & Route B). Initially in the 1st step, the reaction may proceeds via the oxidative addition of Pd(0) to the C-Br bond in 79 (intermediate 79a in Route A)or direct conjugate addition of aniline may takes place to 79 (intermediate 79b in Path B).[41]Most probably, the intermediate 79c formed from 79a through the Buchwald-Hartwig amination.[42] In another case, the intermediate 79d formed via the activation of triple bond in alkynone followed by the coordination to the palladium and simultaneous attacked by aniline. [43] These two pathways will go through intermediates 79d and 79e,[44] followed by reductive elimination of Pd(0) to give product 80.

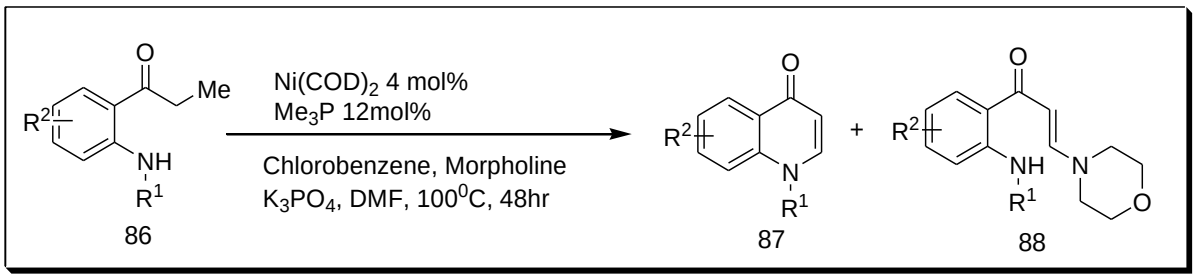
Herein, Tang et al. reported the $ZnCl_2$ mediated intramolecular cyclization of 2-aminochalcones to the solid phase synthesis of of 2-aryl-4-quinolones and 2-phenyl-2,3-dihydroquinolin-4(1H)-ones. Polymer supported organoselenium reagents mainly

induced the total transformation process. The conversion generally proceeded via oxidation, elimination reaction of selenides or free-radical hydrogenation and allylation reaction of selenides.[45]



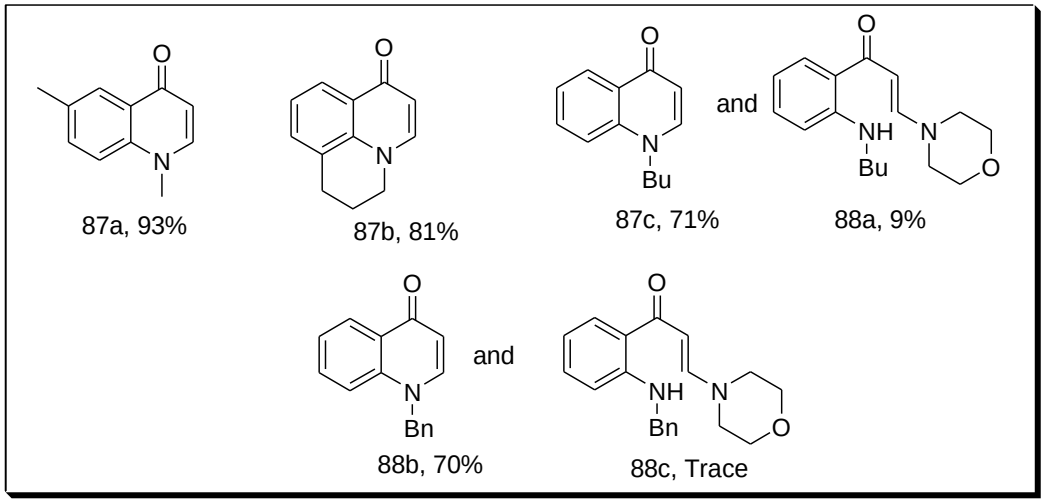

**Scheme-I.27** $ZnCl_2$ mediated intramolecular cyclisation of 2-amino chalcones to the solid phase synthesis 4-quinolones

Ueno et al. reported the methodology for the conversion of o-(N-Alkylamino) propiophenones into 4-quinolones in the presence of chlorobenzene, potassium phosphate, morpholine, and nickel(0) catalyst. The reaction proceeds through the nickel-catalyzed formation of β-enaminones from o-(N-alkylamino)propiophenones and morpholine, followed by the intramolecular transamination. [46]



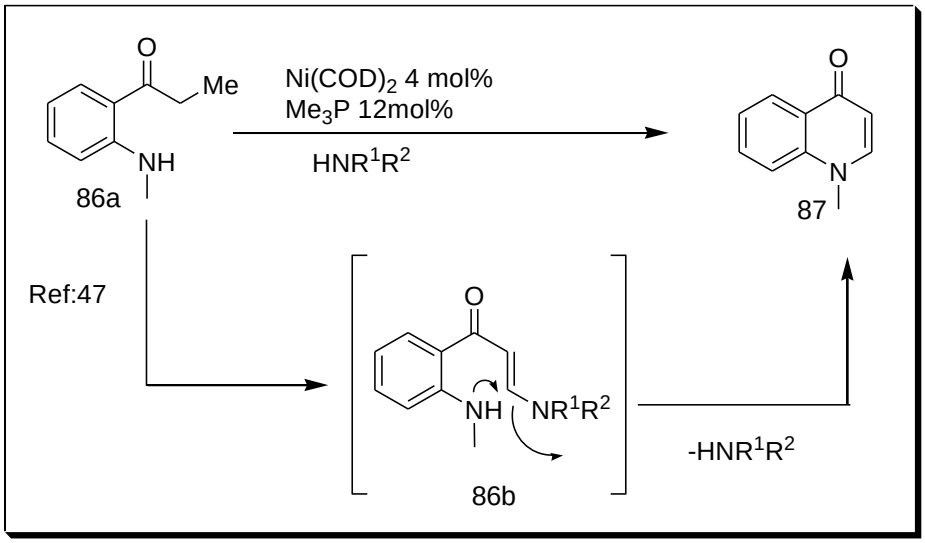

**Scheme-I.28.** Ni(0) catalysed synthesis of 4-quinolones from o-(N-Alkylamino) propiophenones

**Selected examples**



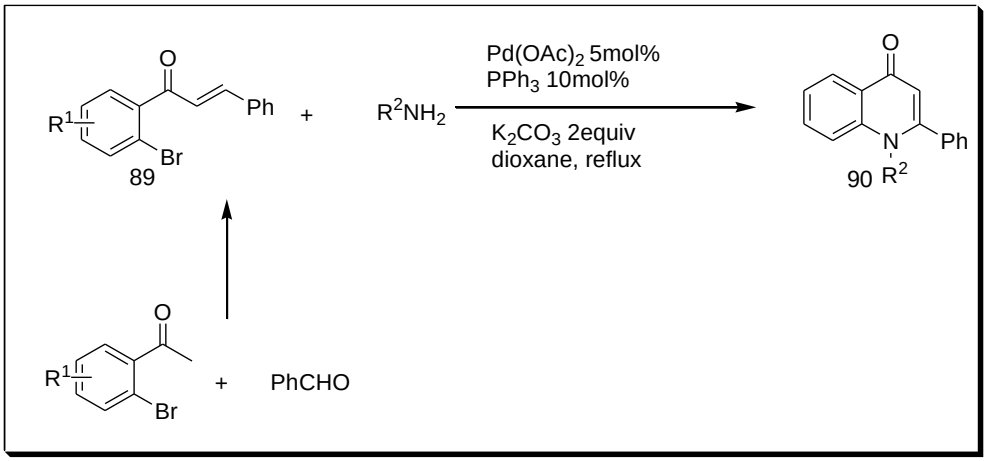

Morpholine was the effective additive for the above cyclisation whereas piperdine, pyrrolidine, acyclic amines failed to produce the 4-quinolone.

**Plausible pathway**




The N-benzyl-protected 4-quinolone was obtained in 70% yield In contrast, the reaction of possessing of the bulkier isopropyl group on the nitrogen atom, gave undesirable β-enaminone as the major product.

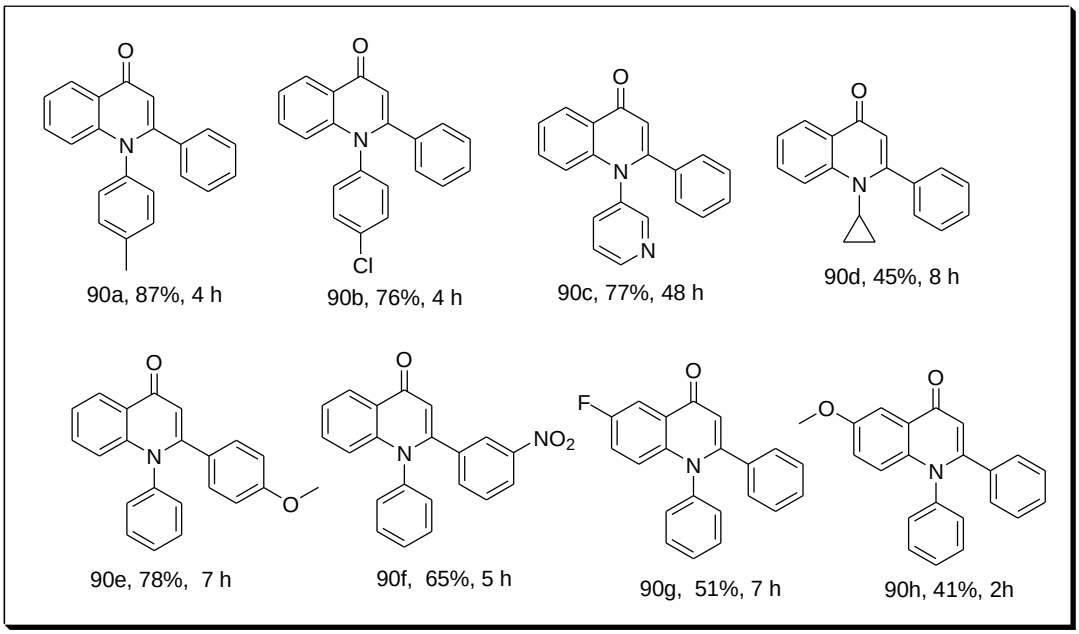
A more general strategy for the synthesis of 1,2-disubstituted 4-quinolones by Palladium catalysed tandem amination reaction using chalcones as substrates was reported here. [48]



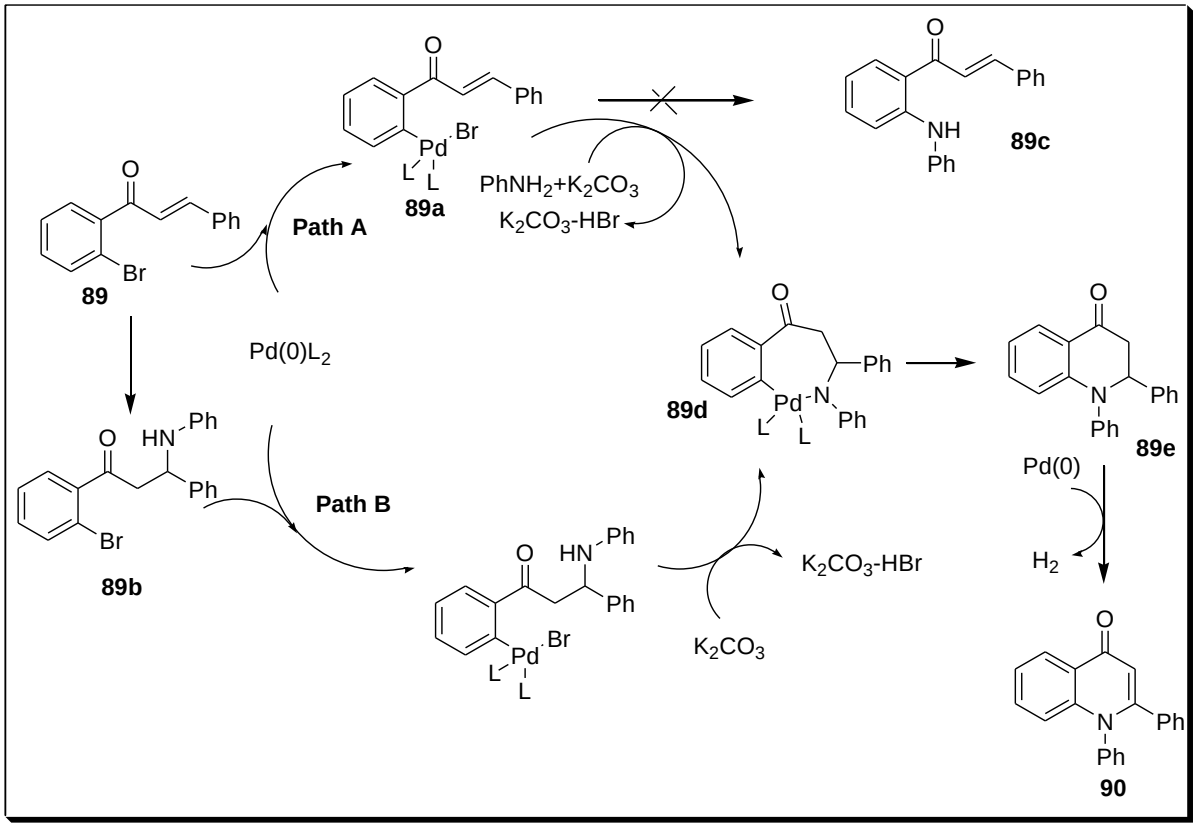

**Scheme-I.29.** Pd catalysed tandem amination reaction

Arylamines containing electron-donating groups gave higher yields than those with electron-withdrawing groups. However, this reaction was not limited to simple aromatic amines; the pyridine-containing substrate also afforded in good yield.

**Selected examples**

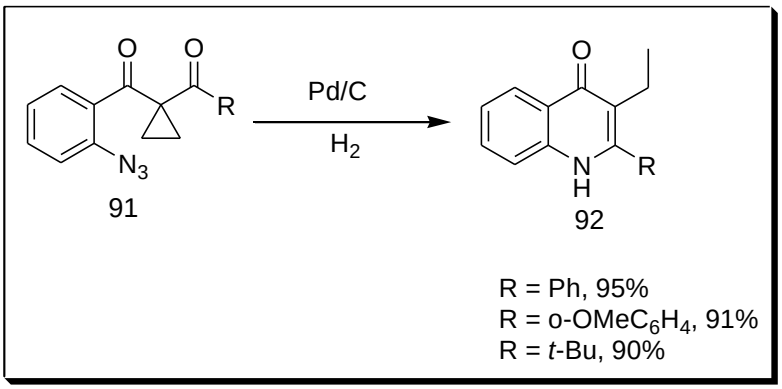


**Plausible mechanism**



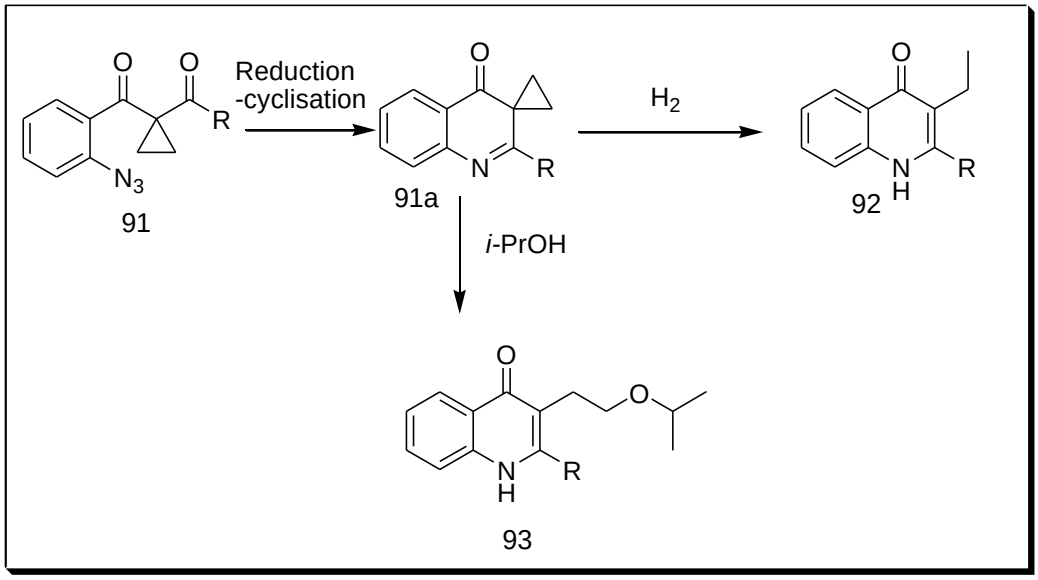

A plausible reaction mechanism for this one-pot synthesis of 1,2-disubstituted 4-quinolones was proposed in Scheme 2 (Paths A and B).[49] In Path A, oxidative addition of 89 to the Pd(0) catalyst leads to palladium complex 89a. The C=C bond in 89a can be activated through coordination to the Pd(II) and attacked by aniline to form intermediate D. Note, intermediate C was not formed from complex A under these conditions. Path B involves the Michael addition of aniline to 89 and oxidative addition, and then intermediate 89d is formed by elimination of HBr. Both pathways proceed via intermediate 89d, followed by reductive elimination of Pd(0) to yield 89e. Intermediate 89e leads to 90 by catalytic dehydrogenation of Pd(0), which is the key step.

Ren and his coworkers successfully reported a useful method to synthesize the 4-quinolone derivatives via reduction of azido-cyclopropyl ketones.[52]

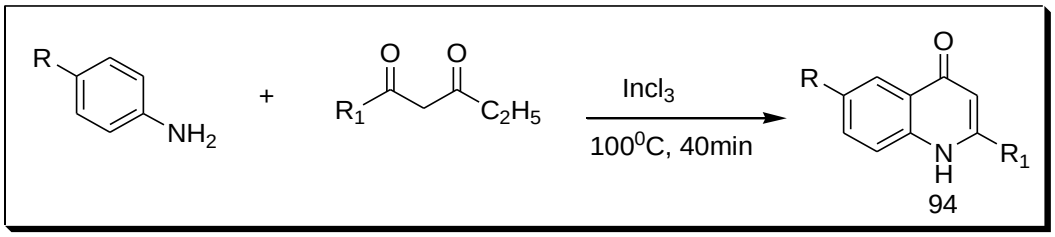



**Scheme-I.30.** Synthesis of 4-quinolones from azido cyclopropyl ketones

**Plausible mechanism**

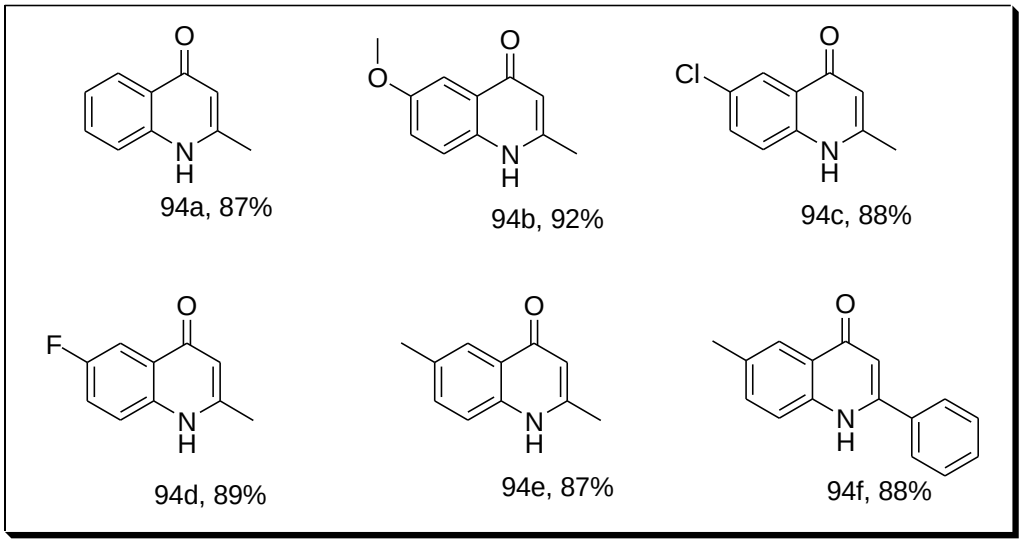



In 2013, Bhupathi and his coworkers derived a facile and efficient one pot method for the synthesis of 4-quinolones in high yields under solvent-free conditions at $100^0$C. The reaction generally employed substituted amines and β-ketoesters to prepare the 2-aryl or 2-alkyl quinolones *via* Conrad-Limpach reaction in presence of Indium (III) chloride. The advantage of the reaction is that the catalyst is reusable and easily recoverable.[51]

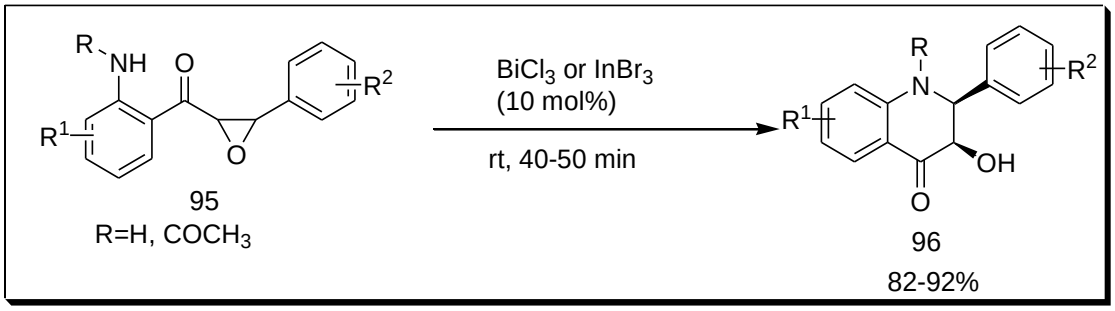



**Scheme-I.31.** $InCl_3$ mediated synthesis of 4-quinolone

**Selected Examples**

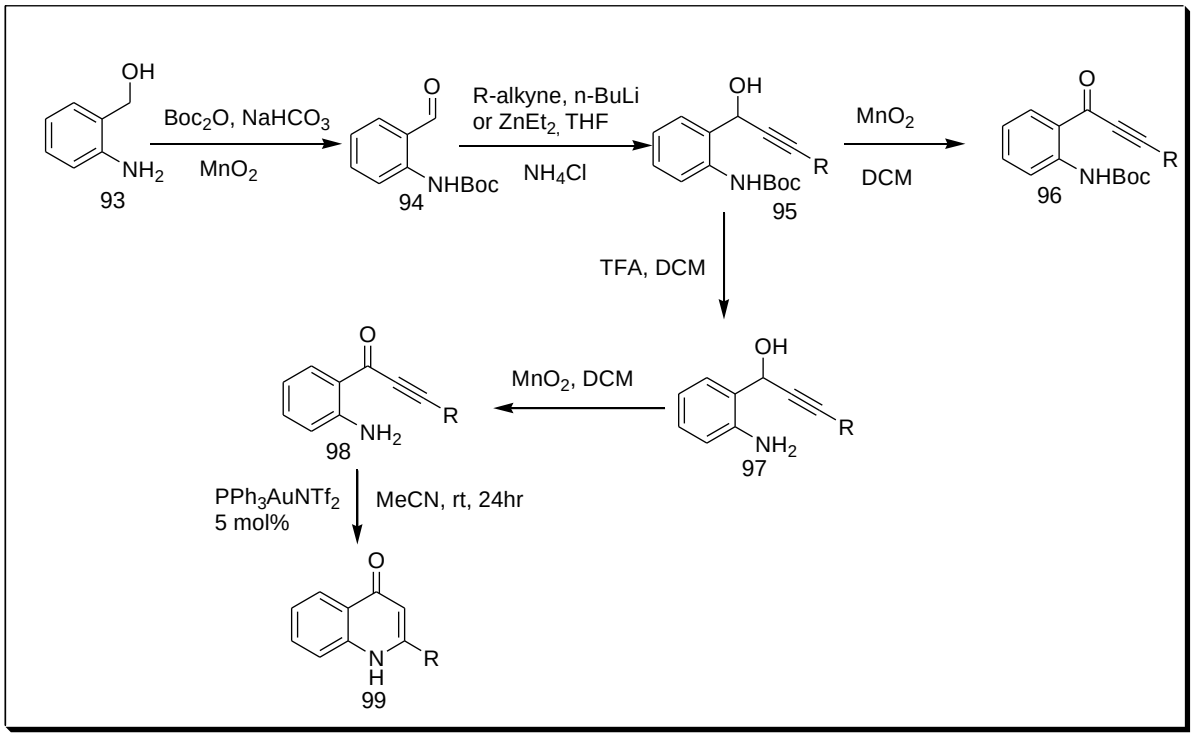



In 2013, Ahmed and his coworkers reported the $BiCl_3$ or $InBr_3$ catalyzed the ring opening of 2-aminochalcone epoxides followed by intramolecular aminolysis under mild conditions. The reactions proceed efficiently at room temperature to afford highly functionalized 2-aryl-3-hydroxy-2,3-dihydro-4-quinolones (aza-flavanones) in excellent yields (82– 92%).[52]




**Scheme-I.32.** $BiCl_3$ or $InBr_3$ induced ring opening reactions of 2-amino chalcone epoxides.

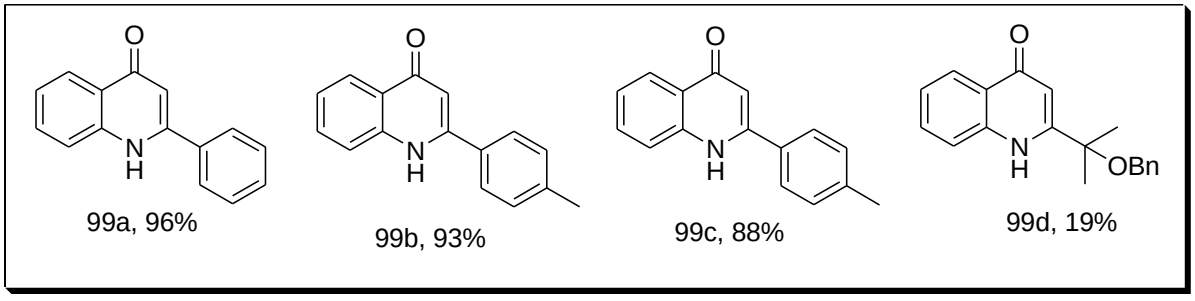
In 2014, Helaja and his coworkers prepared the 2-substituted 4-quinolones from the 1-(*o*-aminophenyl)-2-propyn-1-ones in the presence of gold catalyst. [53]




**Scheme-I.33.** Gold catalysed synthesis of 4-quinolones

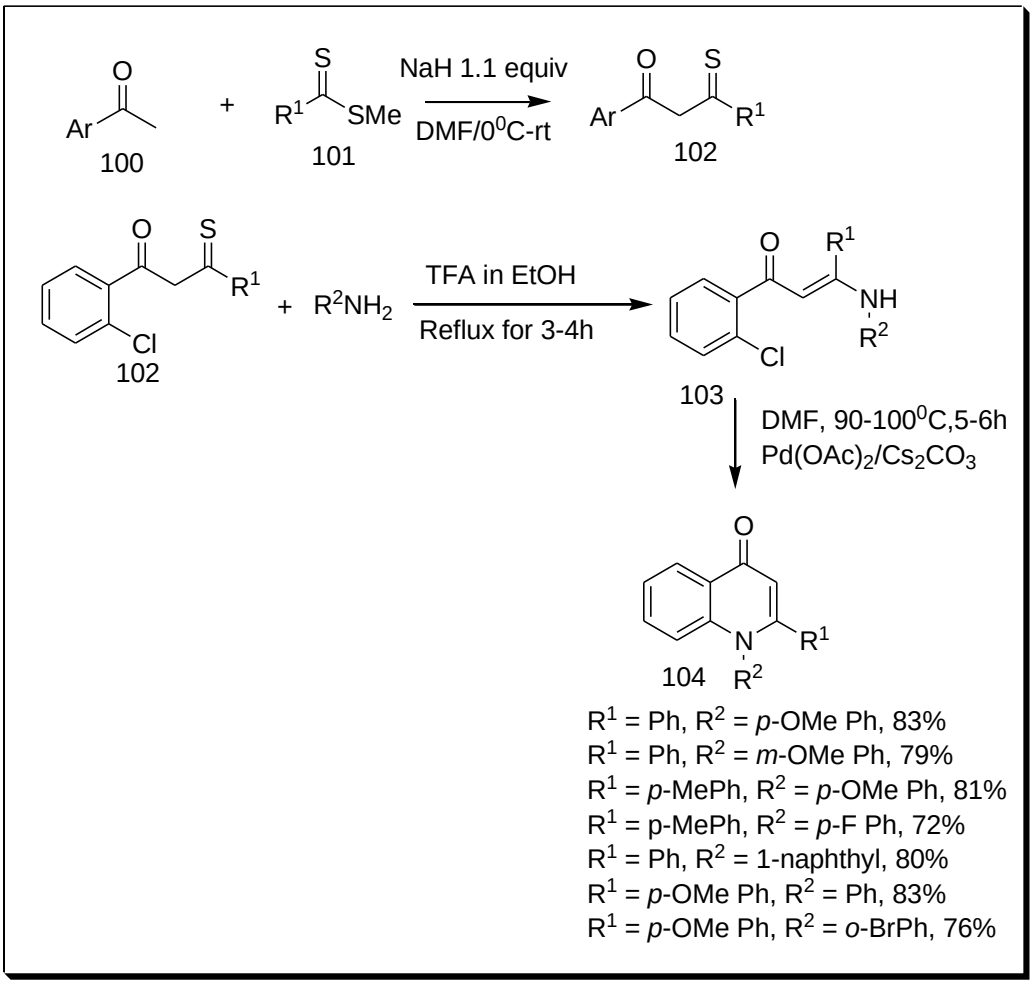
It has been found that the both electron-withdrawing and donating substituents 2-Aryl-4-quinolones could be isolated with excellent yields. Similarly, straight chain alkyl substitution gave high yields. Cyclization protocol did not proceed at all with a simple TMS protected substrate. Rather in absence of the gold catalyst, the unprotected derivative underwent oligomerization to tar.

**Selected examples**



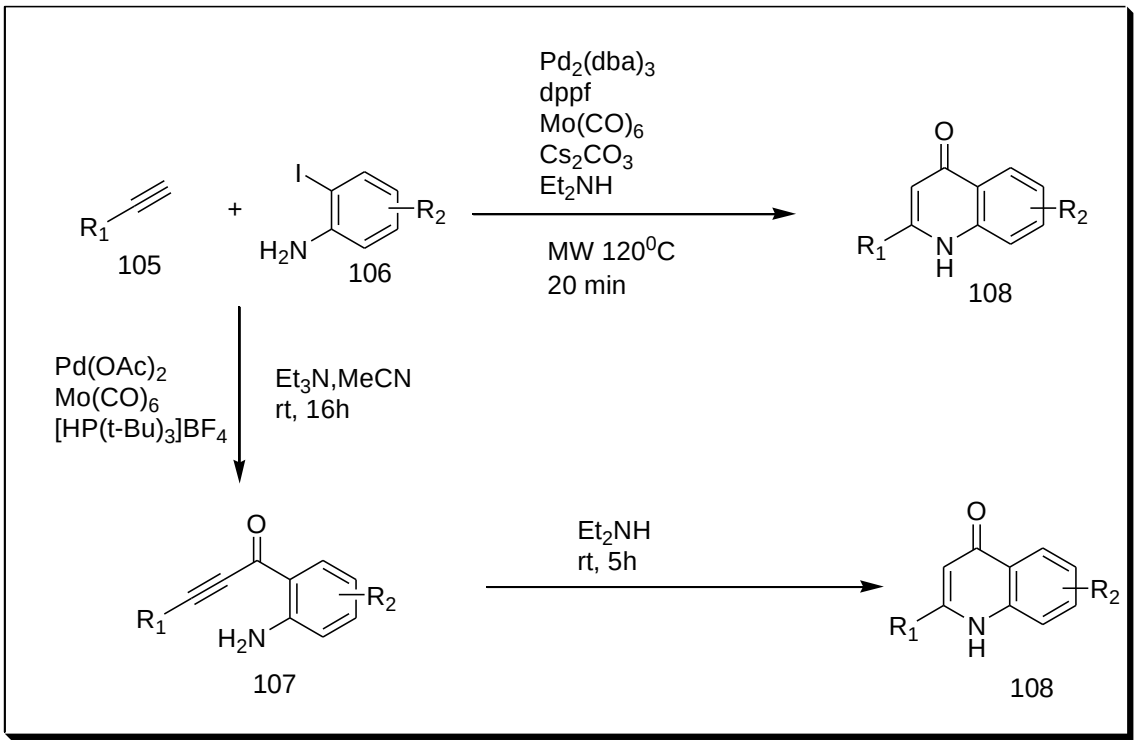

A novel strategy for the synthesis of 1, 2-disubstituted 4-quinolones in moderate to excellent yield from 1,3-bisaryl-monothio-1,3-diketone and arylamine substrates was reported. This protocol involved two steps for providing the cyclised quinolone products. Initially, enaminones were formed by condensation of the substrates in

presence of TFA. Then, it underwent cyclisation using the $Pd(OAc)_2$ catalyst and the $Cs_2CO_3$ base. In the cyclisation step, the substituents had no profound impacts on the yield.[54]



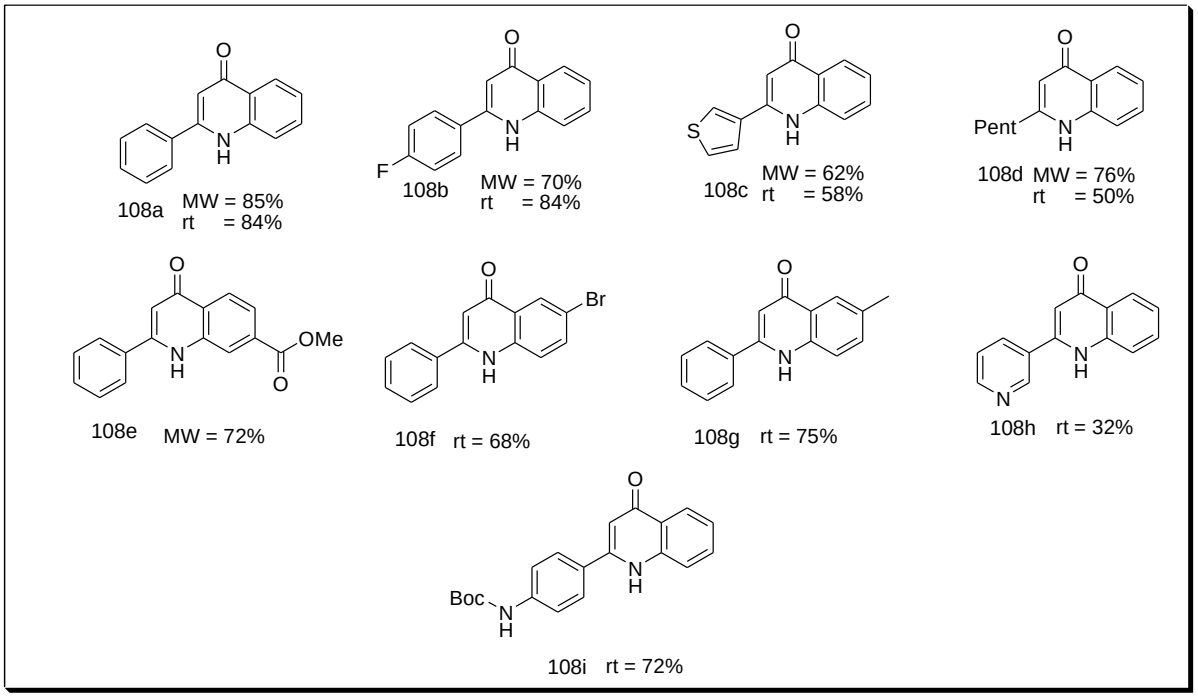

**Scheme-I. 34.** Synthesis of 1, 2 –disubstituted 4-quinolones from monothio-$\beta$-diketones.

Here in, $Mo(CO)_6$ has been used as a solid CO source instead of toxic CO gas for the synthesis 4-quinolones *via* two pathway. The first route encountered the desired compound in a very short time under microwave irradiation whereas the one-pot two-step approach (second method) preceded the reaction at ambient temperature. Both the methods are usually effective to synthesize the large variation 4-quinolones in moderate to excellent yields. [55]

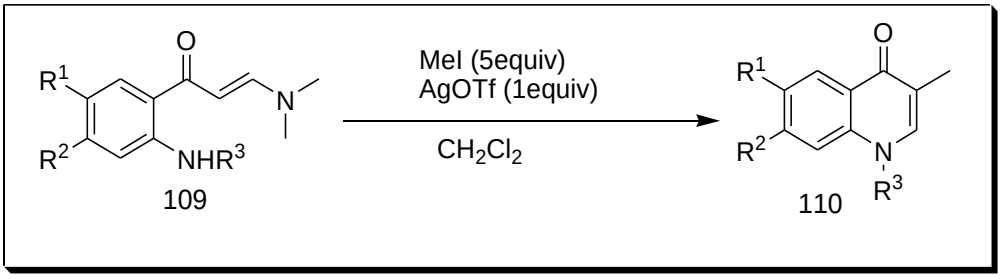



**Scheme-I.35.** $Mo(CO)_6$ as CO source for synthesis of 4-quinolone

**Selected Examples**

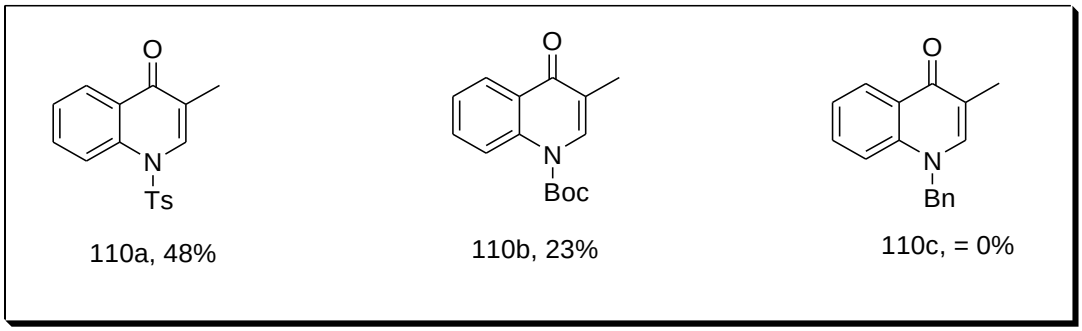



Here in, Joussot *et al.* described a method to synthesize the 3-substituted quinolones easily in a one-pot technique which involved the cyclization of appropriate enaminones and subsequently quenched with diverse electrophiles.[56]

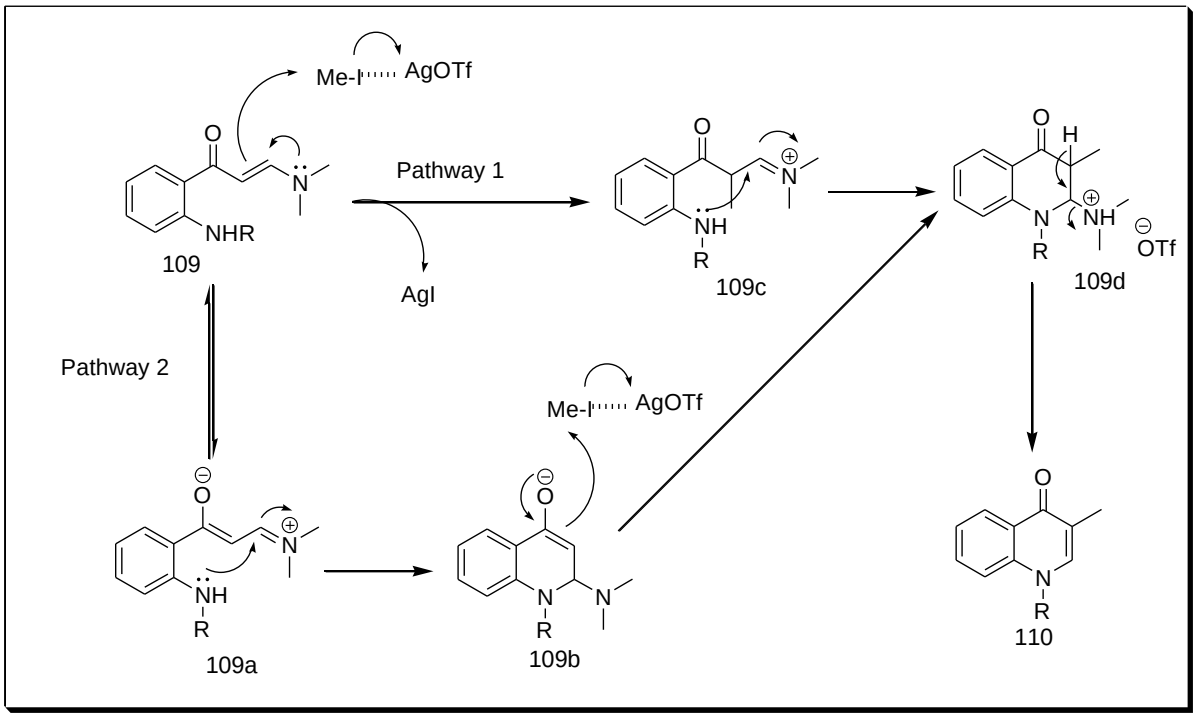



**Scheme-I.36.** Ag(I) catalysed cyclisation of enaminones to 4-quinolones

**Selected examples**




**Plausible mechanism**



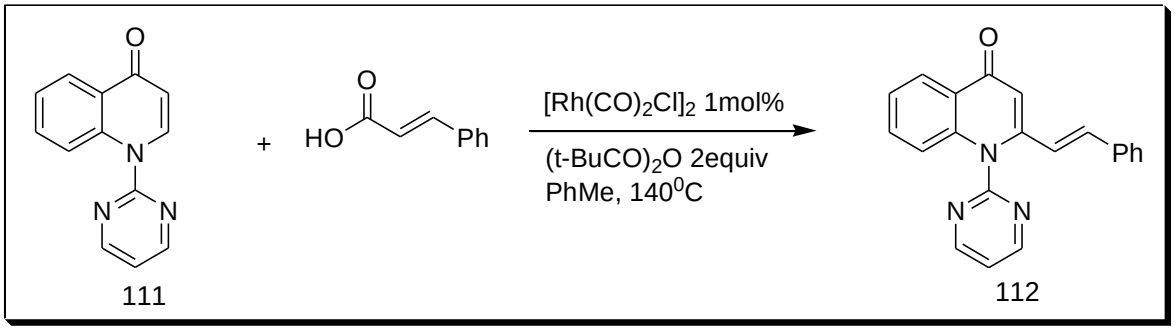

The cyclization procedure proceeded via two pathways as predicted in the above scheme. In pathway 1, the alkylation occured first, leading to form iminium salt, and then underwent the cyclization to generate a new iminium salt. In pathway 2, the

cyclization occured first followed by alkylation to result the same iminium salt. Lastly, the 3-substituted quinolone was formed with the elimination of the dimethyl amine.

### I.B. Functionalization of 4-quinolones

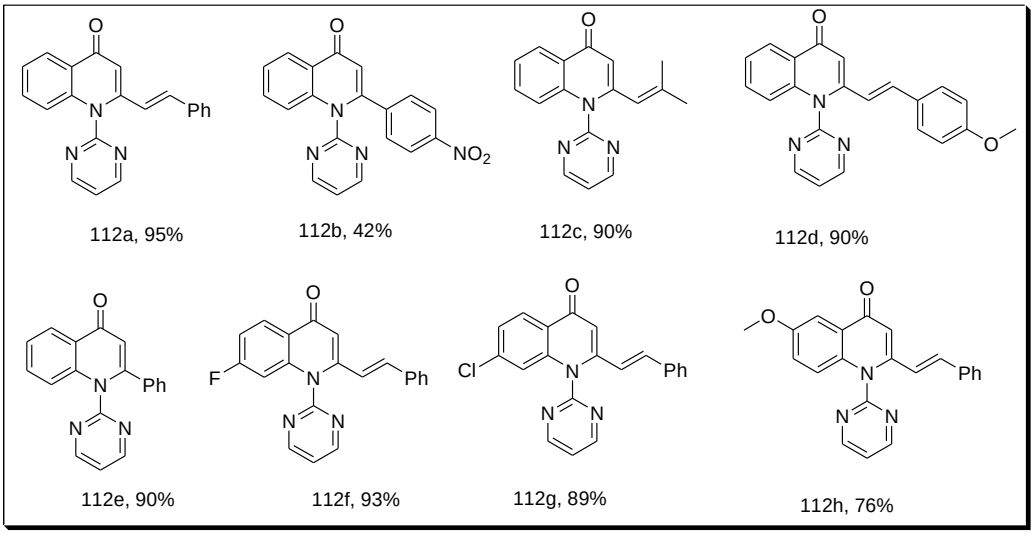
#### I.B.1. Decarbonylative cross coupling reaction

Kwon *et al.* established a site-selective decarbonylative cross-coupling method to promote the direct C-H functionalisation at the 2-position of 4-quinolones *via* the presence of N-pyrimidyl group on the quinolone nitrogen atom. [57] Under the optimized protocol, decarbonylative coupling reactions were successful in between various functionalized quinolones and alkenes. Fluoro, chloro substituted quinolones smoothly underwent the C-2 alkenylation with cinnamic acid.

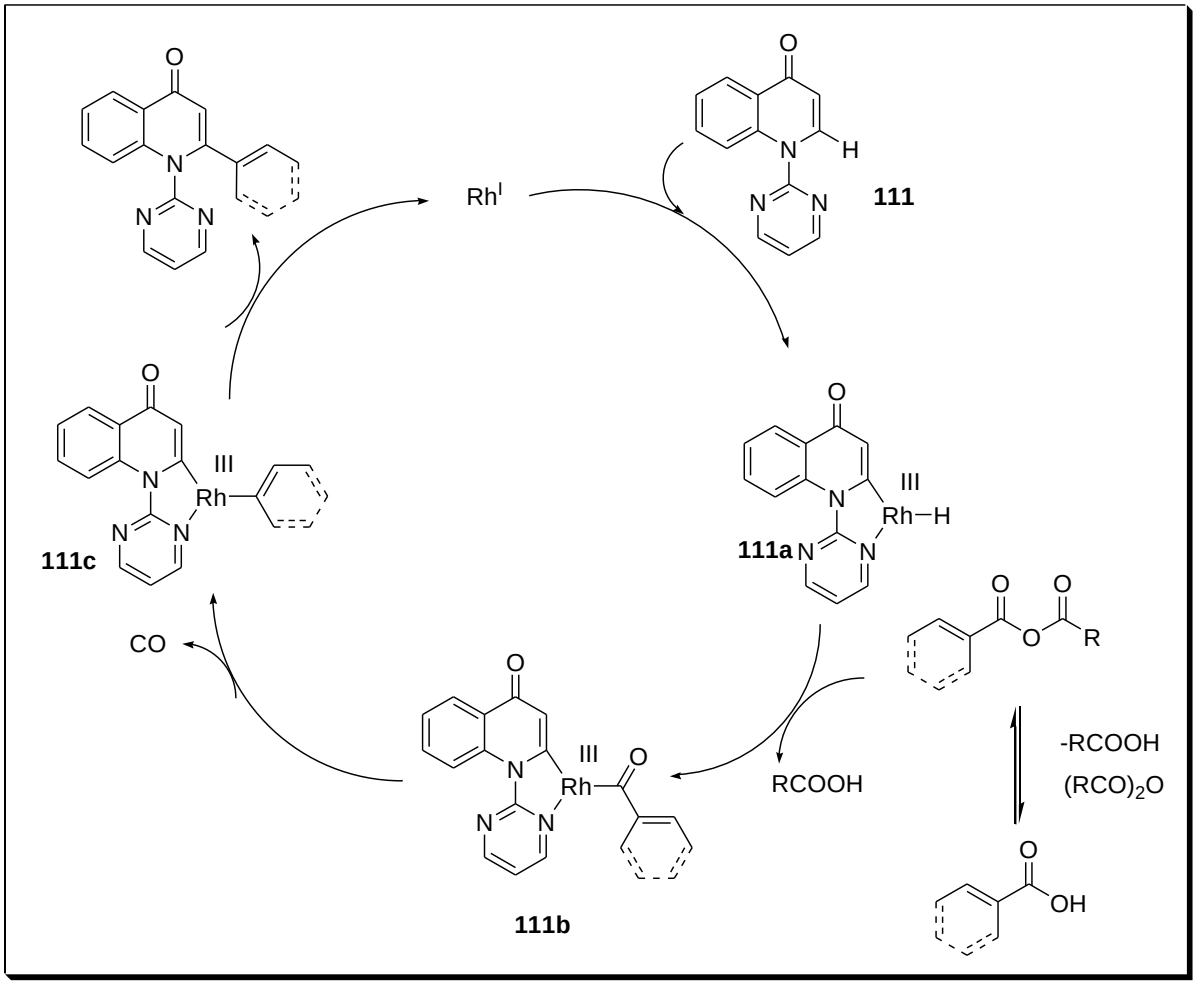



**Scheme-I. 37.** Rhodium-catalyzed decarbonylative cross couplings of 4-quinolones

**Selected examples**



**Plausible mechanism**

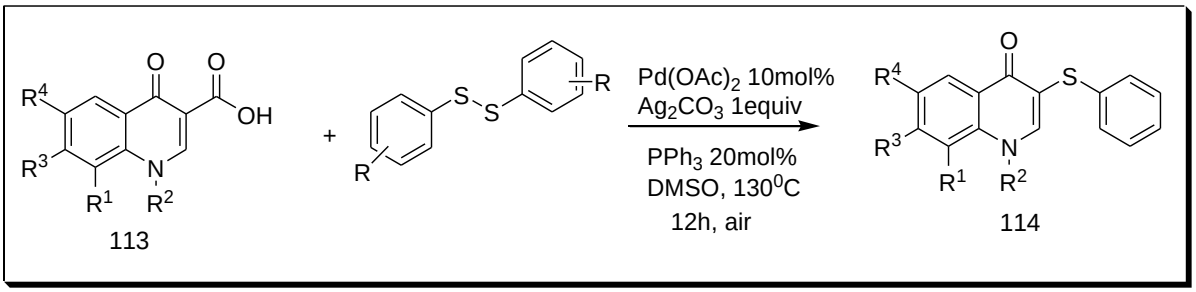



A plausible mechanism was proposed for the decarbonylative C–H coupling reaction. Preliminary, Pyrimidyl directing group inserted the Rh(I) into the C-2–H bond, which gives rhodacycle 111a (Scheme above). An appropriate anhydride which is formed by the equilibrium of the anhydride and acid underwent the oxidative addition to the substrate. Then, it produces the acyl rhodium species 111b. Later, complex 111c is generated *via* the extrusion of carbon monoxide. Finally, reductive elimination occurred and resulted the desired product 112 with the regeneration of active Rh(I) catalyst.

### I.B.2. Decarboxylative C-S coupling reaction

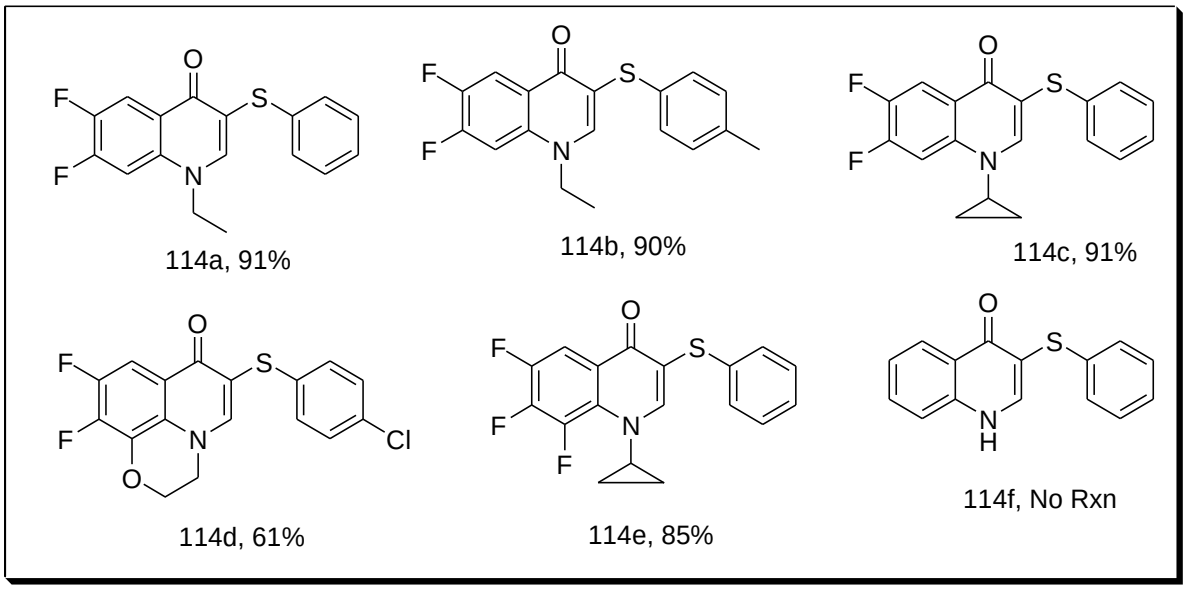
Palladium catalysed direct thioetherification of quinolone derivatives with diaryl disulfides was firstly reported by Zhang and his coworkers. They have inserted the –SPh group into the scaffold *via* decarboxylation technique in the presence of $Pd(OAc)_2$ and $Ag_2CO_3$ in DMSO.[58] The yield of the product was high in case of diaryl disulfides bearing an electron-donating

group such as diphenyl disulfide, *p*-tolyldisulfide, and bis(4-methoxyphenyl)disulfide whereas bis(4-chlorophenyl)disulfide substituted with an electron-withdrawing group gave a lower yield. However, the prime requirement of the protocol was the quinolone carboxylic acids containing a halogen substituent.

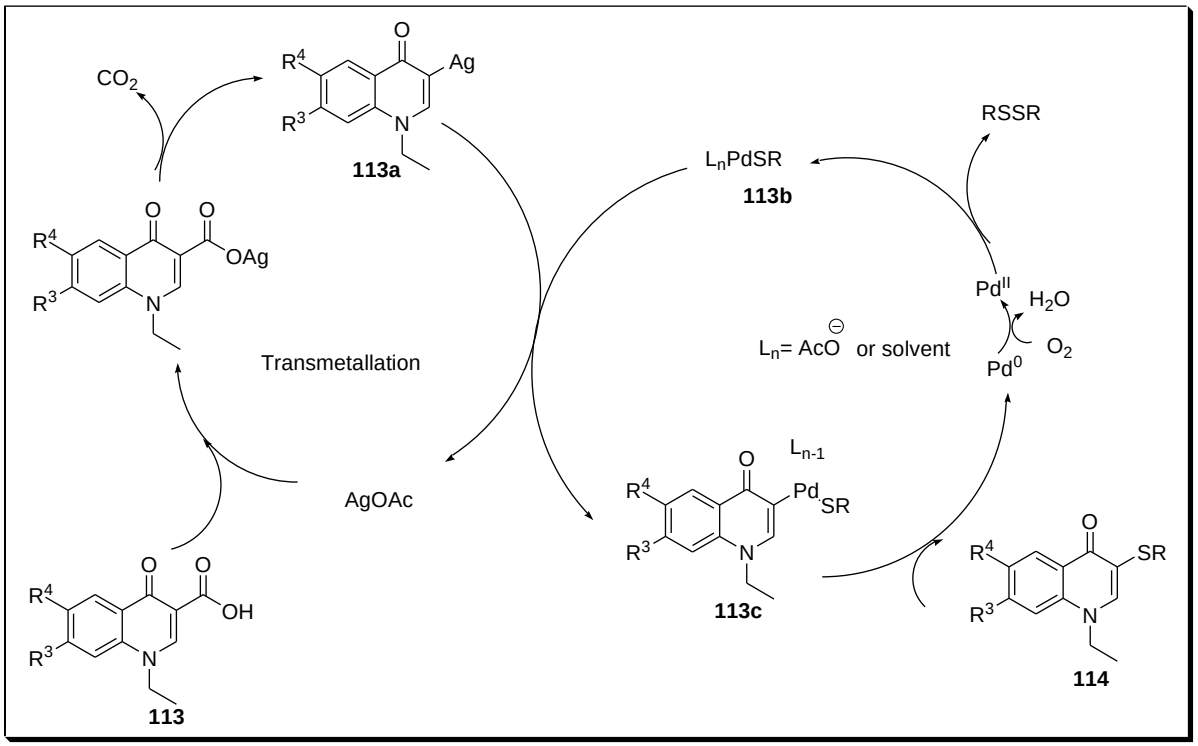



**Scheme–I.38.** Palladium catalyzed thioetherification of quinolones *via* C-S coupling

**Selected examples**

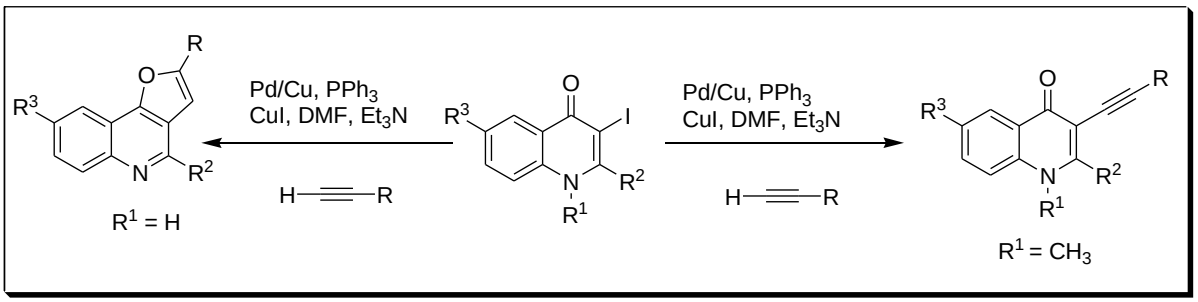


**Plausible mechanism**



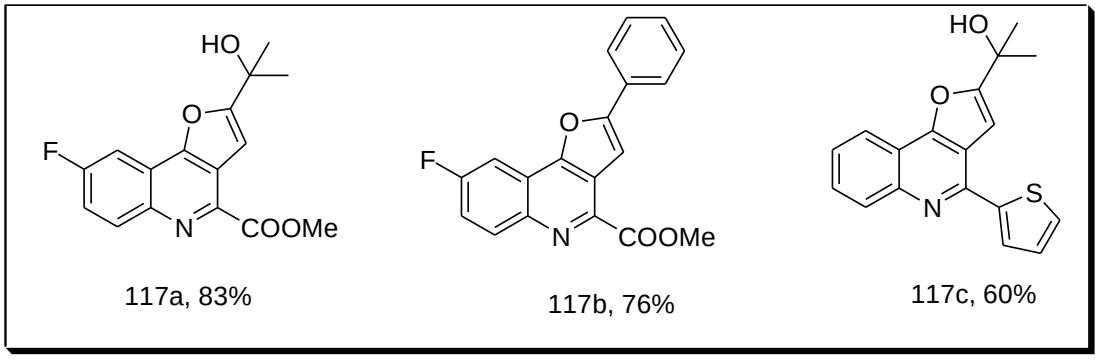

**I.B.3. Sonogashira coupling reaction**

Pal *et al.* synthesized of 2-substituted furo[3,2-c]quinolines *via* tandem sonogashira coupling–cyclization under Pd/C-copper catalysis. These reactions underwent under mild conditions and formed the furo[3,2-c]quinolines with significant regioselectivity . Rather, the reaction became irrespective of the nature of the substituent present at C-2 of the starting quinolone.[59]

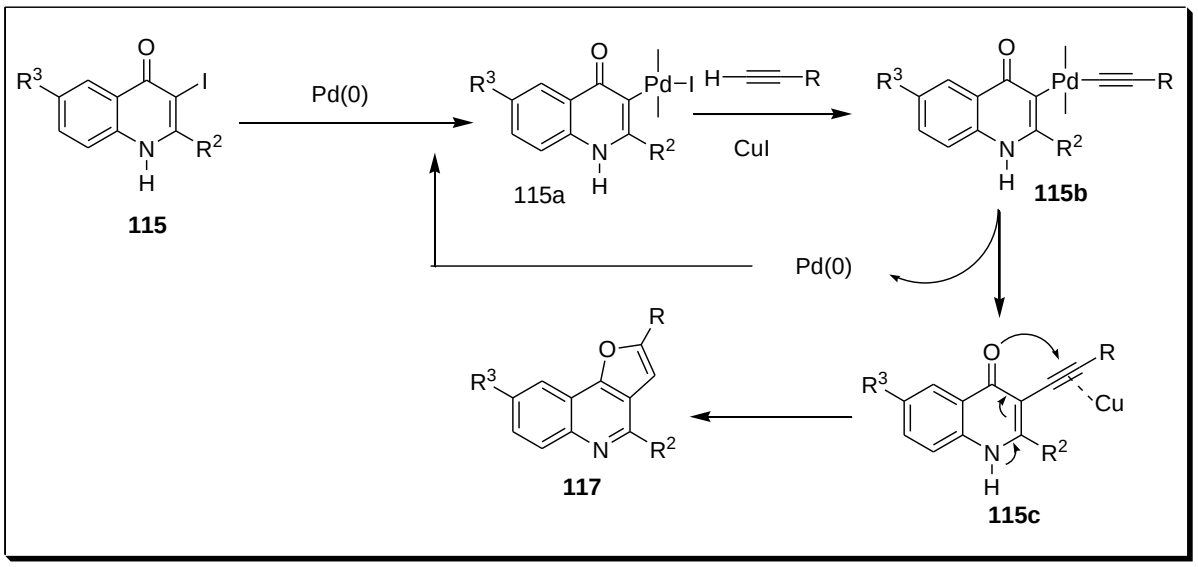



**Scheme-I.39.** Pd/C-copper catalysed One-pot synthesis of 2-substituted furo[3,2-c]quinolones

**Selected Examples**



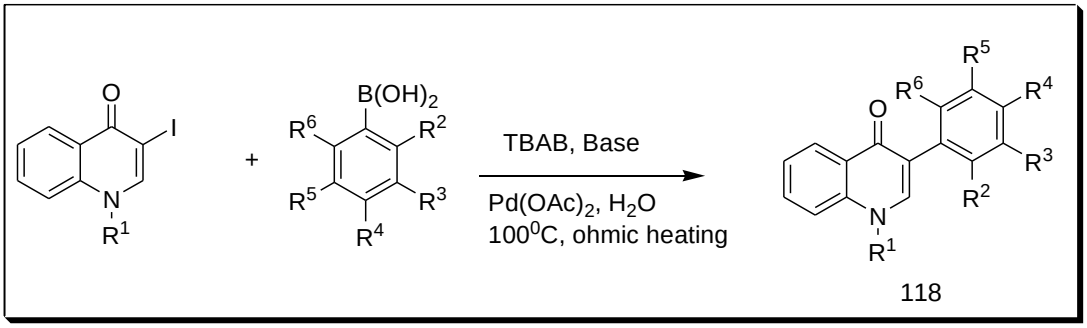

**Plausible mechanism**




The main highlight of this tandem coupling–cyclization process was the formation of furoquinoline. Initially, palladium metal-mediated activation of the triple bond of the 3-alkynyl quinoline generated *insitu* followed by an intramolecular attack of the oxygen on the activated triple bond with subsequent proton transfer and release of the metal ion to give the desired product. The –NH group of the quinolone ring played a crutial role in the cyclization step and perhaps facilitated the preferential participation of the C-4 quinoline oxygen. N-methylated quinolones afforded only the sonogashira coupled product instead of forming the fused cyclic product.

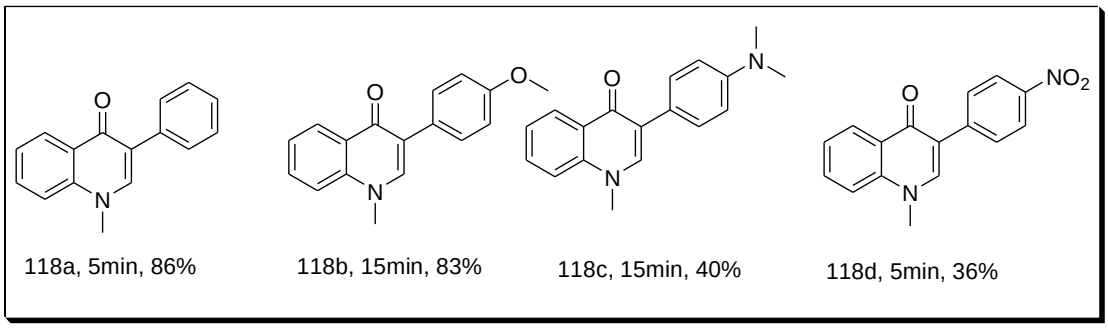
### I.B.4. Suzuki cross coupling

Potential bioactive 3-arylquinolin-4(1H)-ones were synthesized under ohmic heating using an efficient, reusable, and ligand-free protocol *via* the Suzuki−Miyaura coupling of 1-substituted-3-iodoquinolin-4(1H)-ones with several boronic acids in water using $Pd(OAc)_2$ as a catalyst and tetrabutylammonium bromide (TBAB) as the phase transfer catalyst.[60]



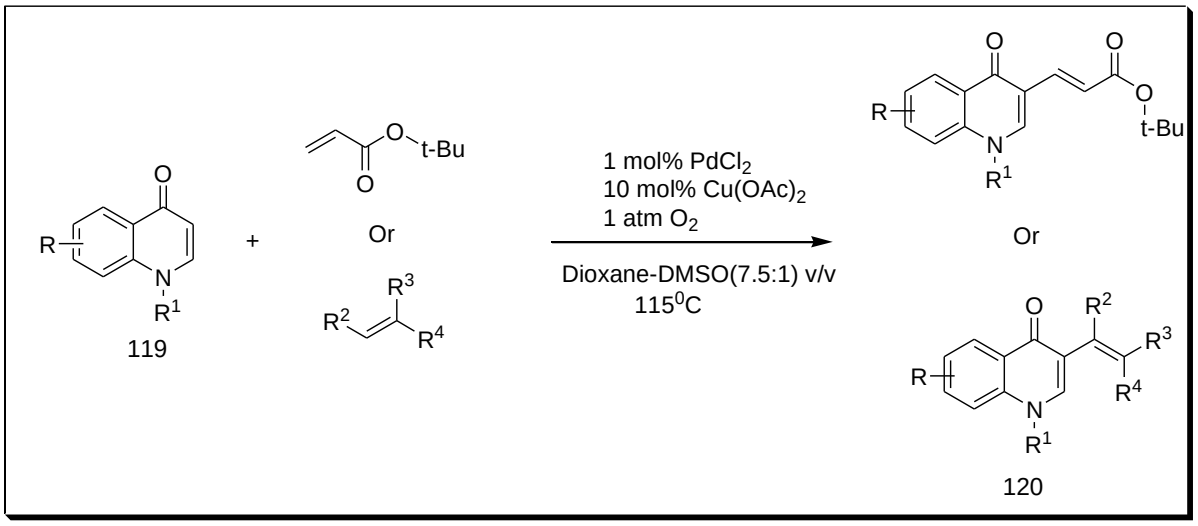

**Scheme-I.40.** Ohmic heating induced Suzuki cross coupling reaction

**Selected Examples**



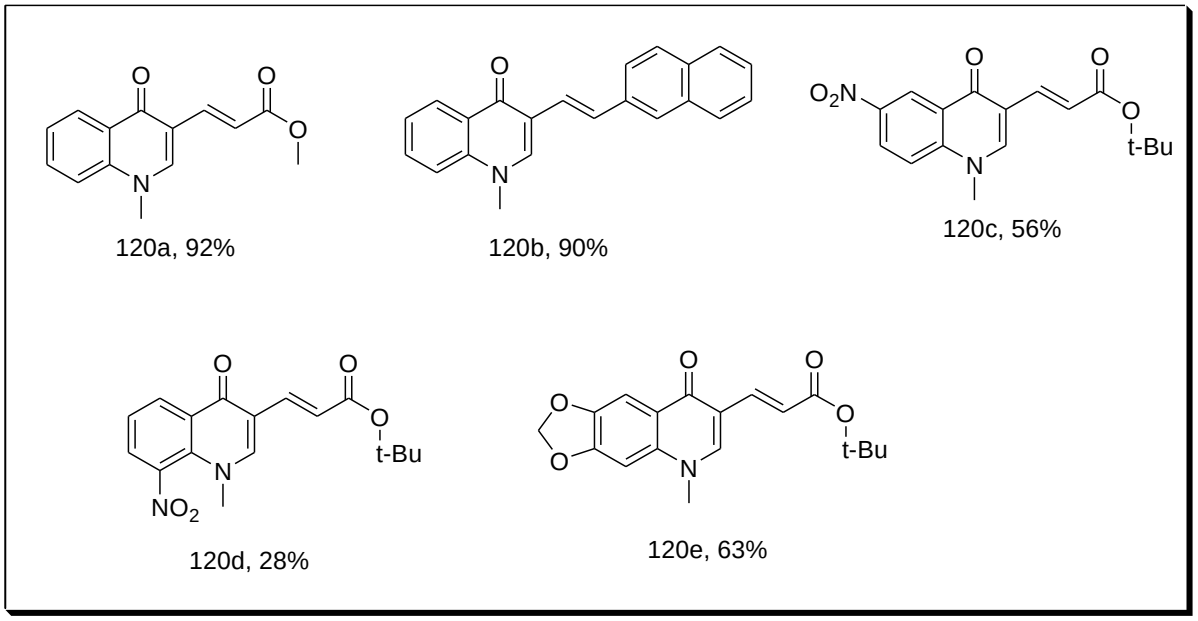

### I.B.5 Alkenylation coupling

Herein, Ge and his coworker successfully developed an unprecedented Pd catalysed C-3 alkenylation of 4-quinolones with low catalyst loading. [61]




**Scheme-I.41.** Pd catalysed C-3 alkenylation of 4-quinolones

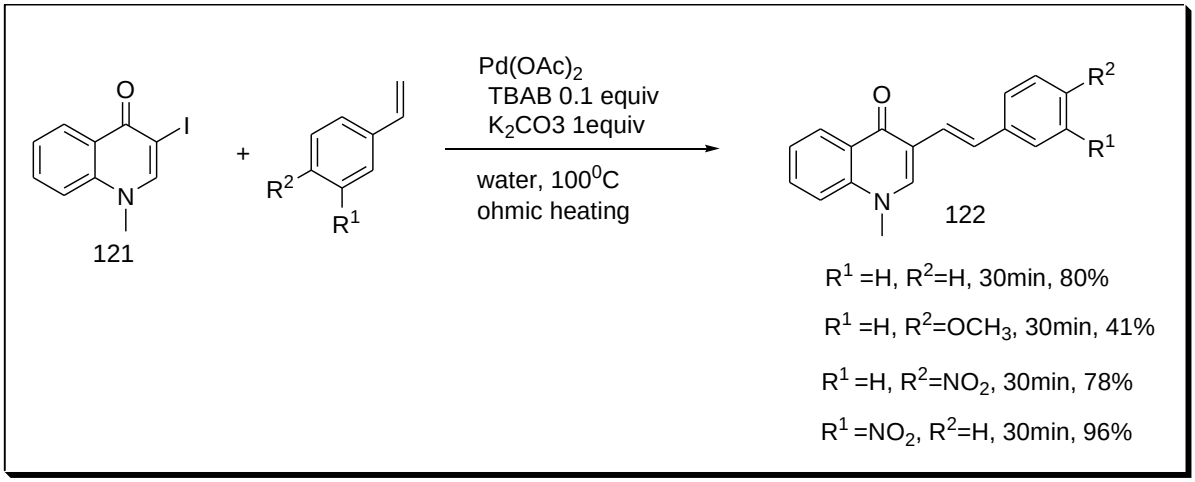
**Selected Examples**




It has been found that all terminal acrylates, sterically hindered acrylates both undergo the reaction smoothly. Rather, the reaction did not proceed well in the presence of electron releasing group at C-6 position on the quinolone ring. Steric factor also prevents the reaction in C-8 substituted 4-quinolones to give the high yield of the product. Most importantly, -NH protection was essential requirement for this reaction.

### I.B.6. Heck Coupling

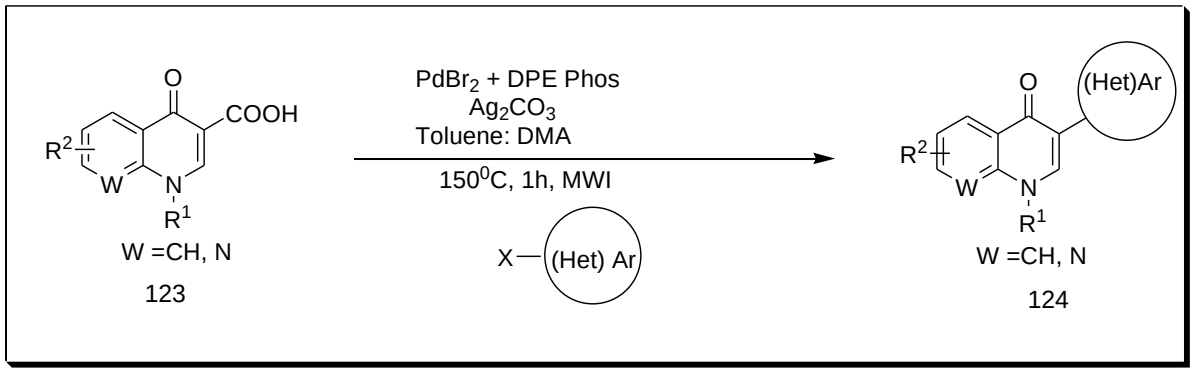
In 2016, Silva *et al.* reported the synthesis of (E)-3-Styrylquinolin-4(1H)-ones by heck coupling reaction in water from 3-iodo substituted 4-Quinolones. The reaction was performed in the presence of ohmic heating, [$Pd(OAc)_2$ as a catalyst, TBAB as a Phase Transfer catalyst] instead of classical heating procedure.[62] They have mentioned several advantages to this method, such as use of universal solvent water instead of other toxic solvent, avoid of additional ligands, more rapid reaction and short span of time .Moreover, ΩH (ohmic heating) resulted the better yields in comparison to previous method in the literature.




**Scheme-I.42.** Ohmic heating induced Heck cross-coupling reaction

### I.B.7. Decarboxylative cross coupling

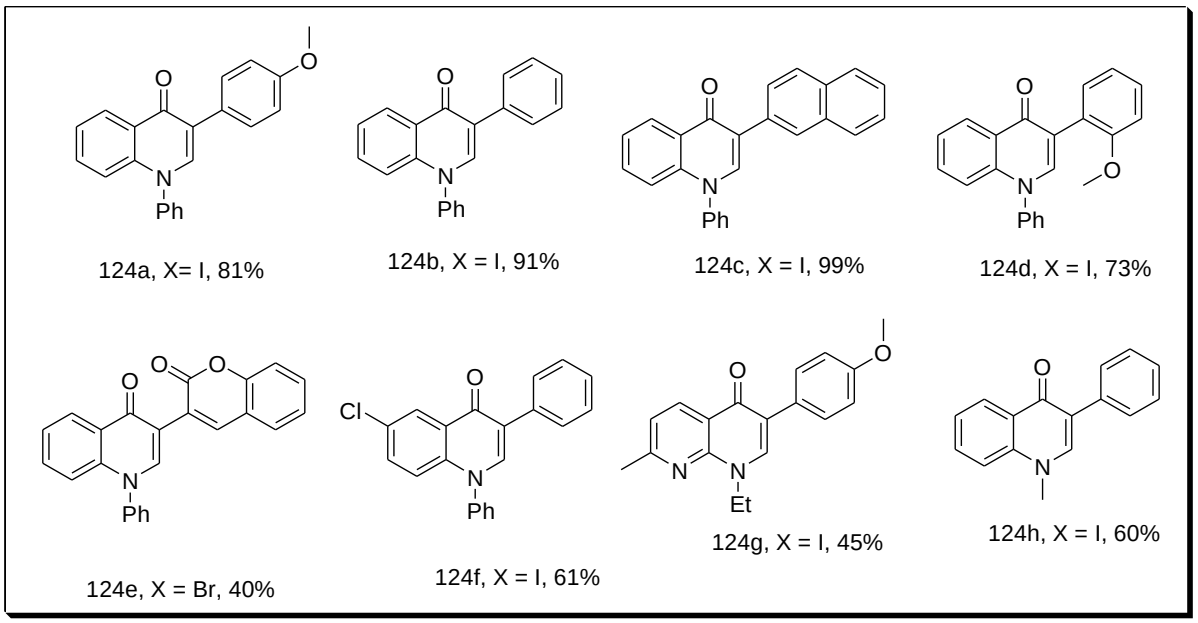
In 2012, an efficient and practical decarboxylative cross-coupling reaction of quinolin-4(1H)-one 3-carboxylic acids with (hetero)aryl halides has been established by using a bimetallic system of $PdBr_2$ and silver carbonate. [63]



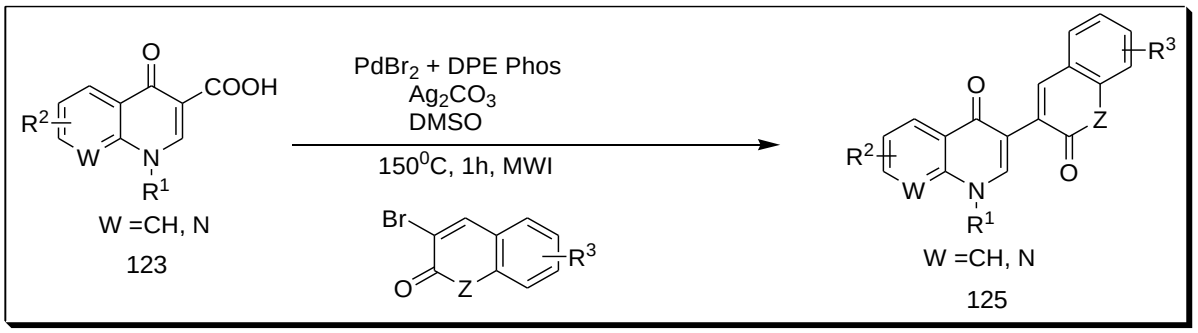

**Scheme-I.43.** Pd/Ag catalysed decarboxylative cross-coupling reaction of aryl halides with 4-quinolones

They attempted to choose microwave irradiation to enhance the reaction rate and to reduce the reaction time as well as to increase the yield of the product. Many screening had been done by using various Pd catalyst, ligand, solvent, base and temperature. The combination of $PdBr_2$ and $Ag_2CO_3$ along with DPEPhos served the promising result. Both aryl iodide and bromide participated in the reaction well. Aryl chloride became less effective as a coupling partner. Steric factor did not influence the decarboxylation reaction so well. Electron-donating or -withdrawing groups substituted N-alkyl- and N-arylquinolin4 (1H)-one 3-carboxylic acids converted into the corresponding product in good yields.

**Selected Examples**



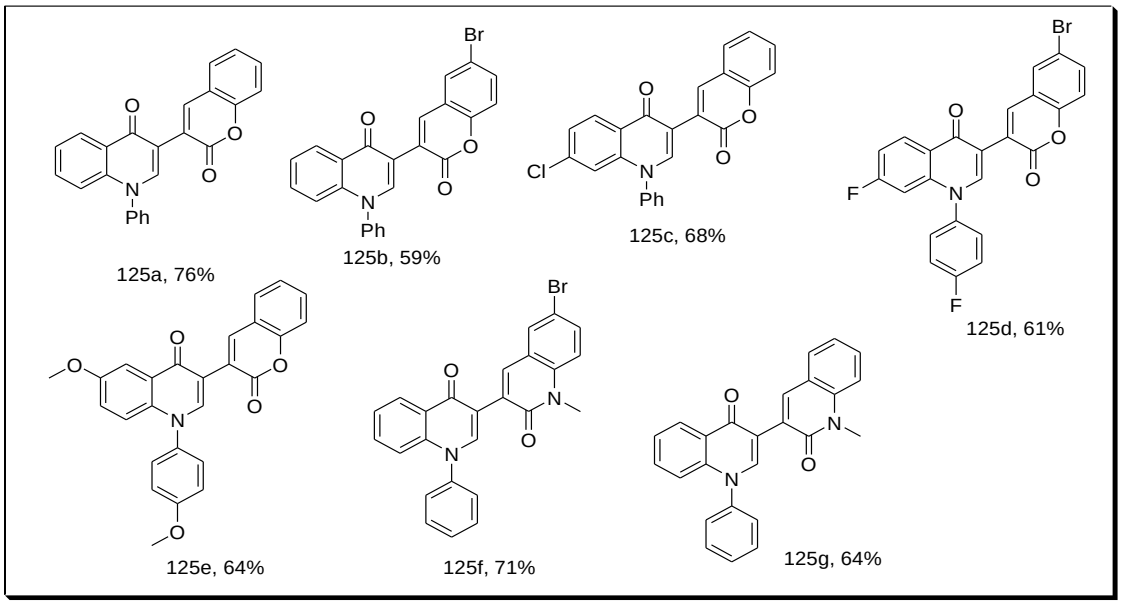

Following the procedures of the above development, the same research group discovered the the similar type of Pd catalysed decarboxylative coupling reaction of heterocyclic carboxylic acids with heterocyclic halides.[64]



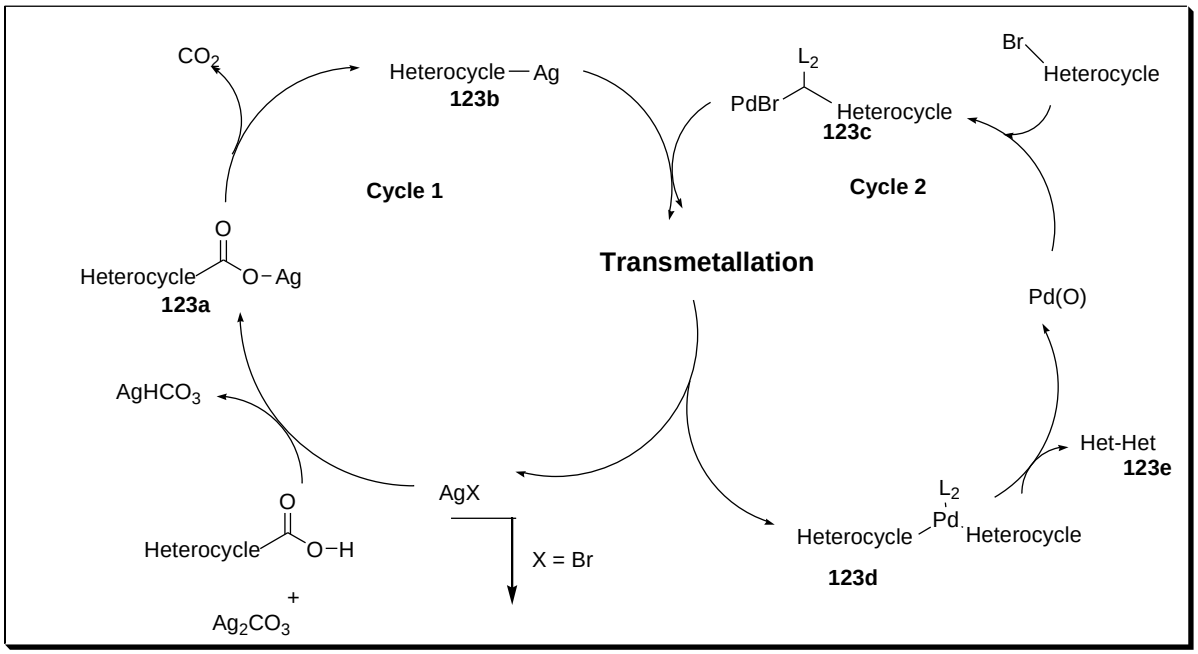
**Scheme-I.44.** Pd catalysed decarboxylative of 4-quinolone with heterocyclic halides cross coupling reaction

They performed the reaction by using their previously reported procedure [$PdBr_2$ (5 mol %), DPEphos (10 mol %); $Ag_2CO_3$ (1 equiv) in toluene/DMA] at 150°C for 1 h under microwave irradiation], but it resulted poor yield of the desired product. By optimizing several conditions, they had found that DMSO was the optimal solvent for this decarboxylative coupling. They investigated the scope of the Pd-catalyzed decarboxylative coupling of various substituted quinolin-4-ones 3-carboxylic acids with 3-bromocoumarins and 3-bromoquinolin-2-ones possessing different steric and electronic properties. Gratifyingly, all the couplings proceeded cleanly and selectively in good to excellent yields regardless of the nature of the substituents on the aromatic ring of the quinolin-4-one 3-carboxylic acid .

**Selected Examples**

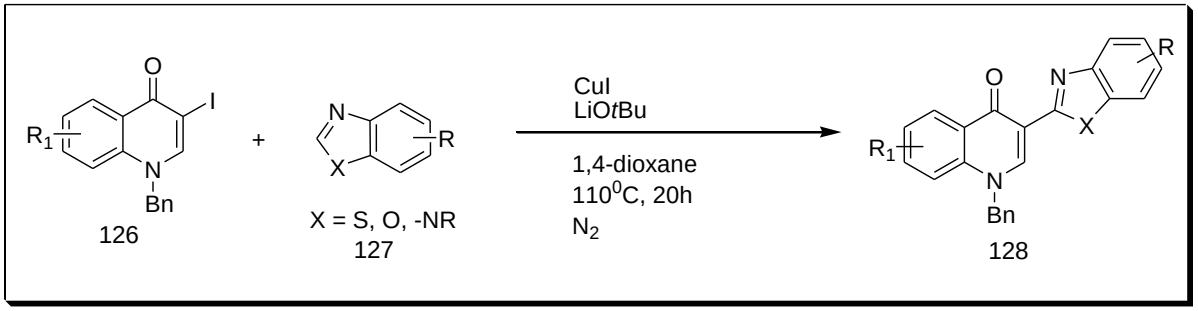


**Mechanistic pathway**




**I.B.8. C-H bond activation**

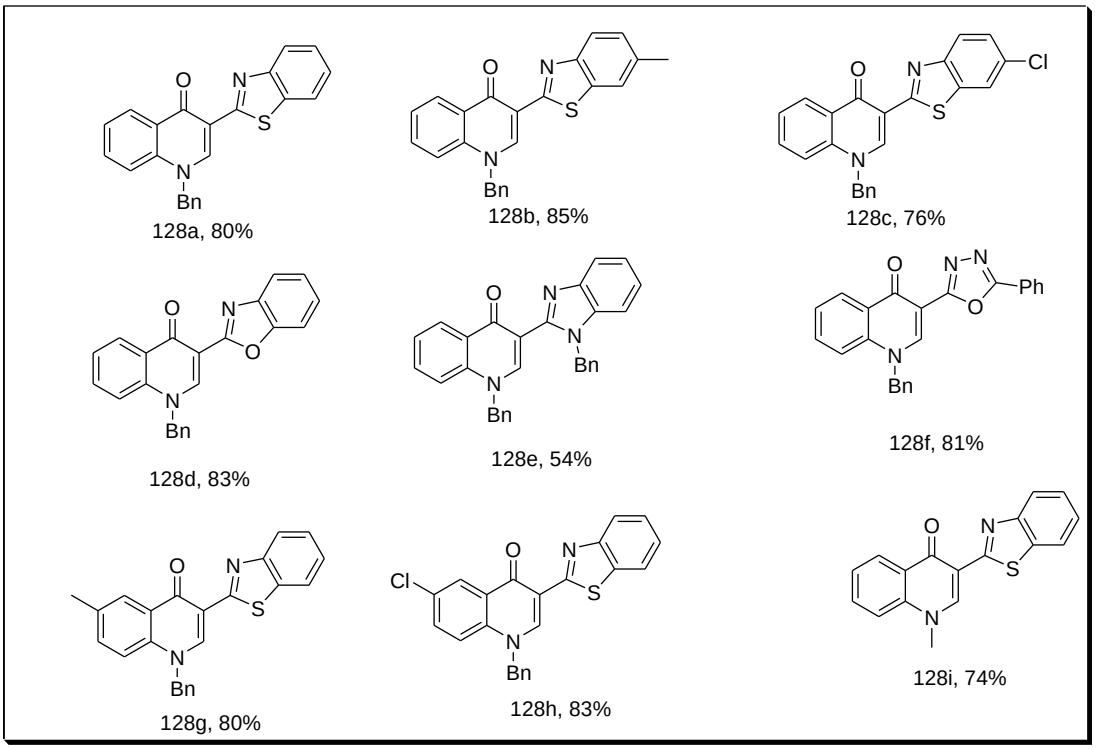
Hong and his coworkers developed an efficient and practical method for the direct insertion of azoles into the 4-quinolones via C–H functionalization in presence of copper catalyst. [65]



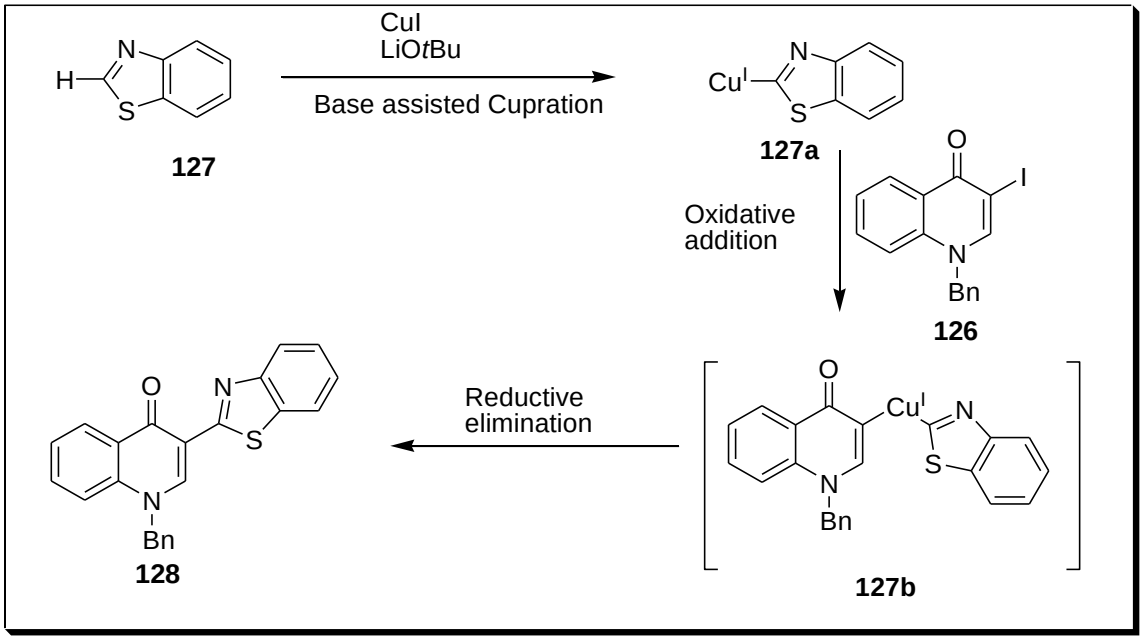

**Scheme-I.45.** Cu catalysed C-H functionalisation of azoles with 4-quinolones.

Interestingly, Pd catalyst and KO*t*Bu have no such promising effect for the formation as well as the product yield. Rather, the combination of CuI and LiO*t*Bu showed the better efficacy for such C-H bond functionalisation. A broad array of azoles, including variously substituted benzothiazoles, benzoxazoles, and imidazole were efficiently coupled with quinolone to prepare the diverse coupling products in moderate to good yields.

**Selected Examples**




**Plausible Mechanism**

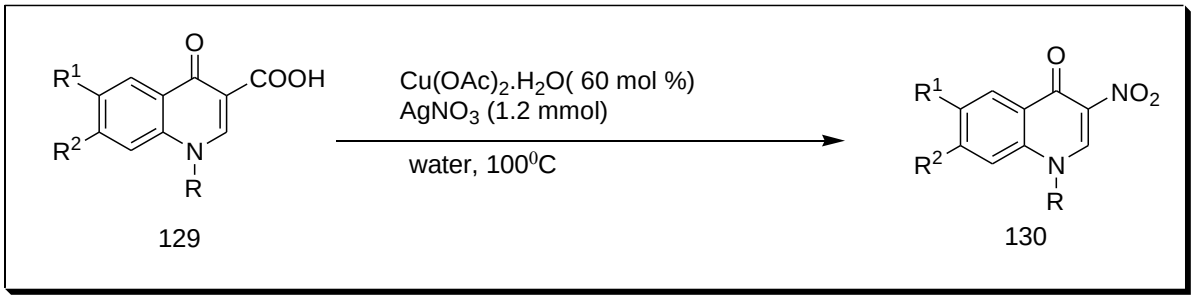



They proposed a plausible mechanism for the C-H bond functionalizing of azoles with N-benzyl-quinolone. Base-assisted cupration of benzothiazole took place at the first stage. Then, Cu species 127a would undergo the oxidative addition to provide the

copper species of higher oxidation state. Subsequently, reductive elimination of intermediate 127b yielded the desired coupled product.

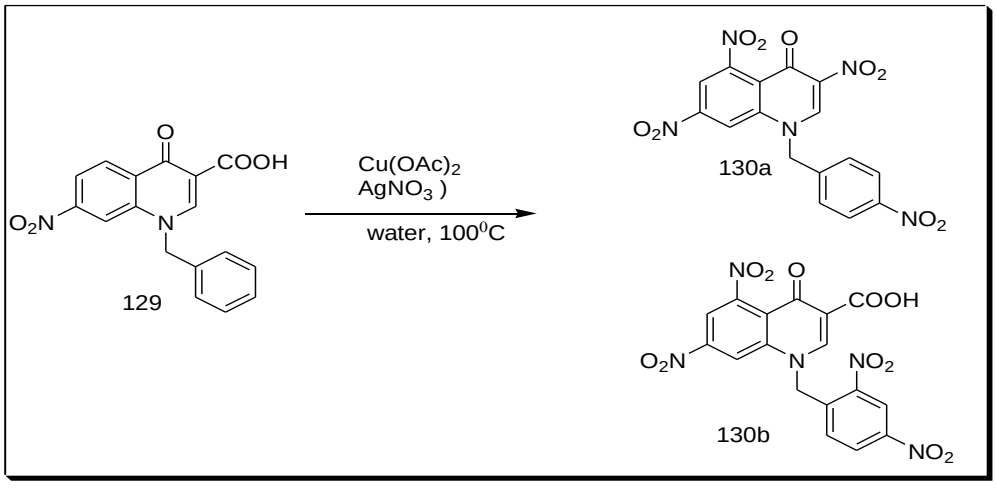
**I.B.9. Decarboxylative ipso nitration**

In 2015, Saxena *et al.* successfully developed a methodology to convert the 3-carboxy-4-quinolones to 3-nitro-4-quinolones using silver nitrate as a nitrating agent in presence of copper acetate.[66]

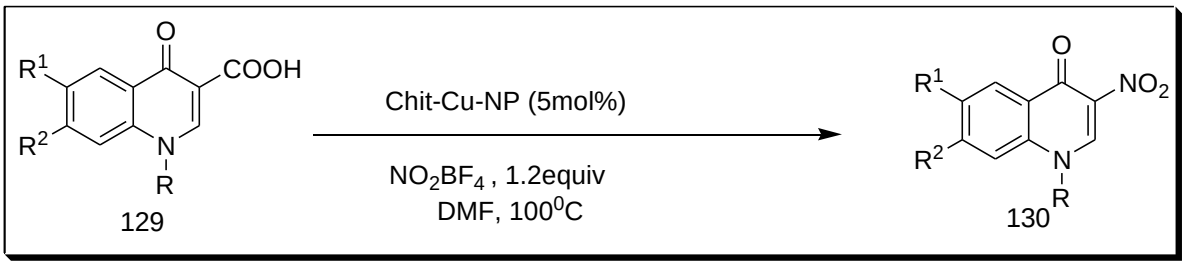



**Scheme-I.46.** Cu/Ag catalysed decarboxylative ipso nitration of 4-Quinolones

**Selected Example**



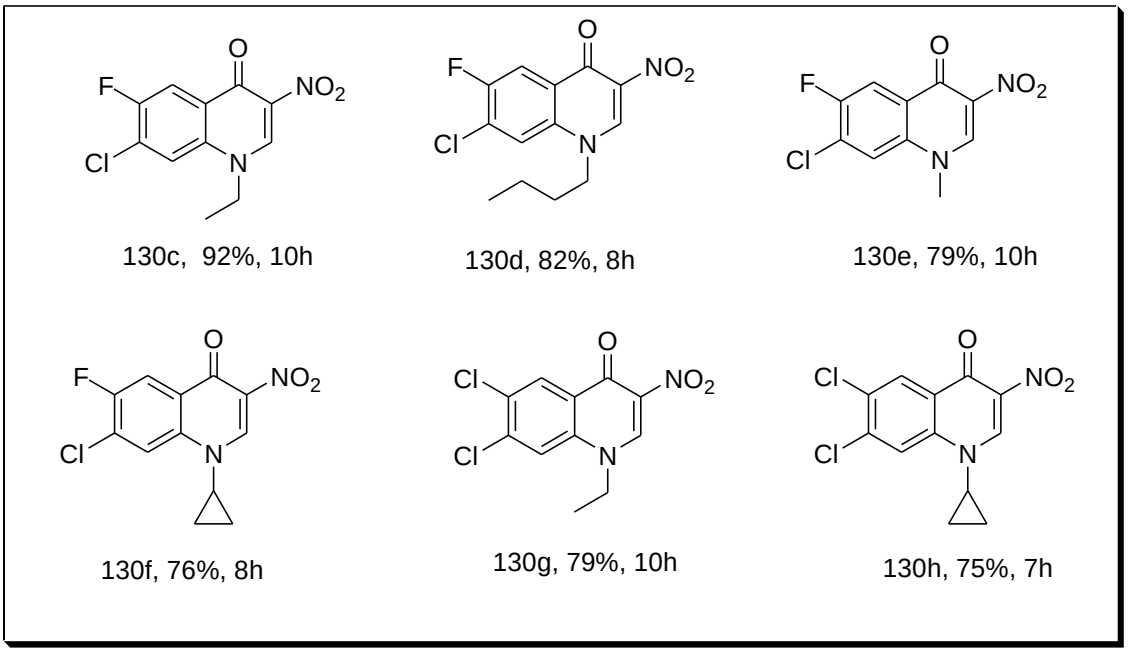

Recently, Narula and his co worker demonstrated the ipso nitration of 3-carboxy-4-quinolones in aid of NTFB via decarboxylative nitration using polysaccharide supported copper nanoparticles.[67]



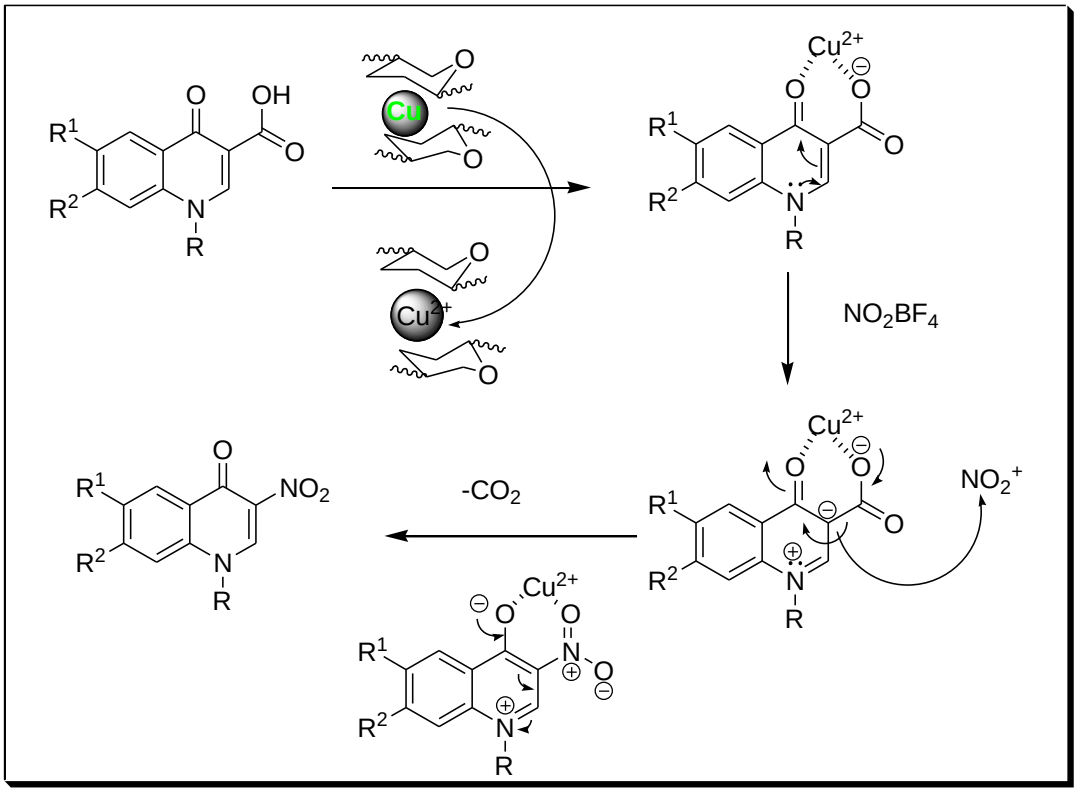

**Scheme-I.47.** Chitosan Cu-NP catalysed ipso nitration of 4-Quinolones.

The bi-functional groups such as hydroxyl and amine in chitosan are responsible for providing the excellent stability to the metal nanopartcles. In catalysis, it has shown its versatile potential. The high stoichiometric ratio of chit-Cu-NP (30 mol %) did not provide the profound impact on the yield. Many metal nitrates were employed but $NO_2BF_4$ which generated $NO_2^+$ in the reaction medium, is responsible for the nitration to give modest yield.

**Selected Examples**



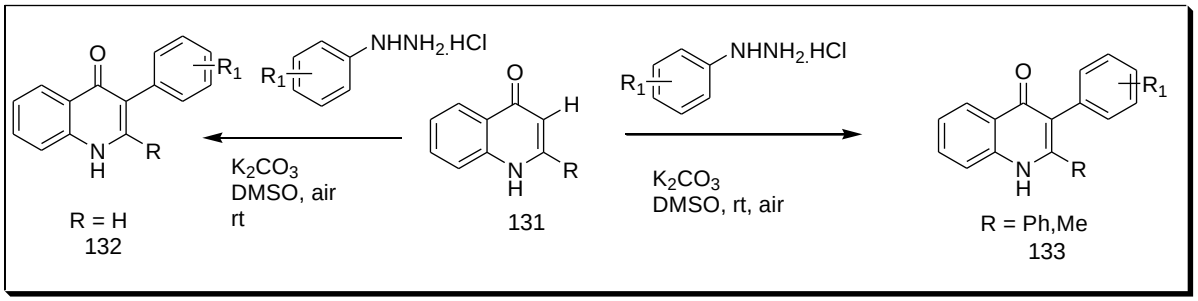
**Plausible Mechanism**




A plausible reaction mechanism was explained for the copper-nano particle decarboxylative nitration of the quinolones (Scheme above). -mediated chelation of β-keto acid assisted. Initially the Cu oxidized to $Cu^{2+}$ in the presence of atmospheric oxygen. Then the two carbonyl groups of the quinolones chelated with $Cu^{2+}$ ions through oxygen. The decarboxylative nitration proceeded through a concerted step, in which $NO_2^+$ from nitronium tetrafluoroborate attacks on the C-3 carbon. Simultaneously, decarboxylation takes place which leads to product formation.

### I.B.10. Transitional metal free C-3 arylation reaction

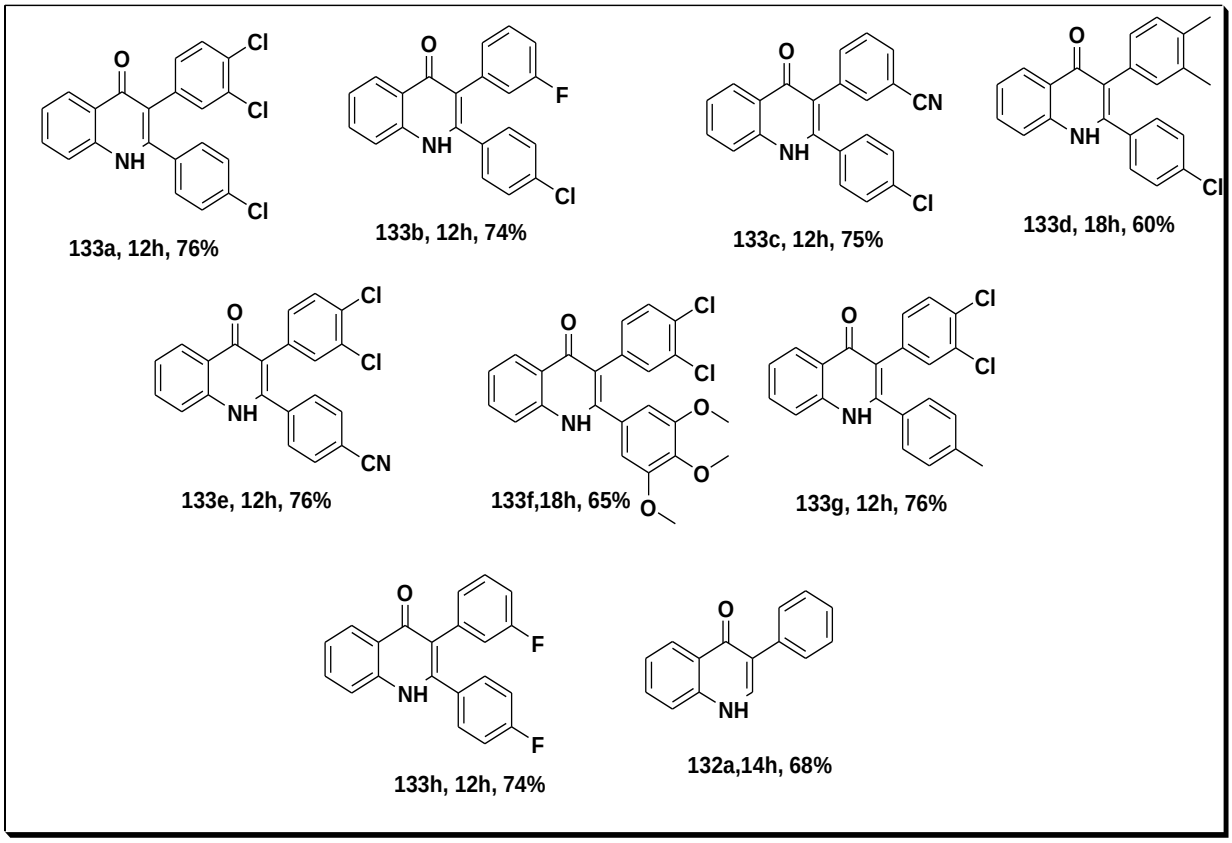
Yadav and his coworkers described the transition-metal-free C-3-arylation of quinolin-4-ones in the presence of base by using arylhydrazines as aryl radical source and air as oxidant. The reaction proceeds smoothly at room temperature and does not require any prefunctionalization and N-protection of quinoline-4-ones.[68]



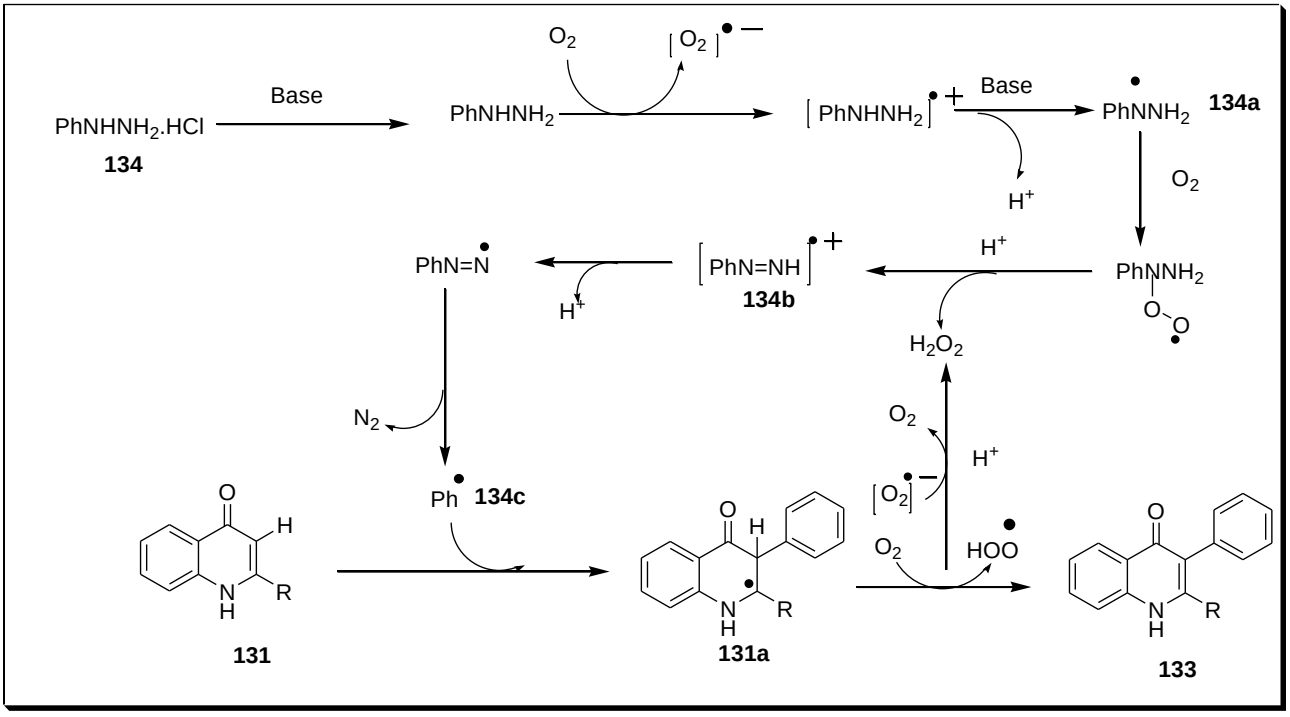

**Scheme-I.48.** Metal free C-3 arylation of 4-quinolones.

Phenylhydrazines bearing electron-withdrawing groups such as chloro, fluoro, cyano underwent the reaction smoothly to result the 3-arylated product in good yields. Moreover hydrazines having electron-releasing groups such as methoxy and dimethyl were well tolerated. Both the electron withdrawing and electron-donating groups on 2-phenyl ring were participated in arylation in quite well.

**Selected Examples**



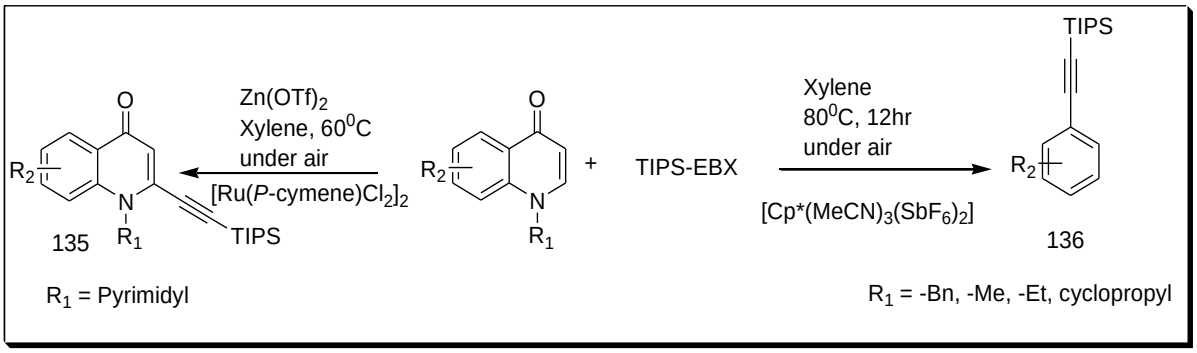
**Plausible Mechanism**




The group had proposed a plausible mechanism in which the free phenylhydrazine formed from its hydrochloride salt (134) in the presence of base at the initial stage. In presence of air/oxygen, it underwent single electron transfer[69] to generate the phenylhydrazine cation radical intermediate. Simultaneously, it lost $H^+$ in the presence of base which leads to phenylhydrazyl radical [134a]. Then, the radical [134a] converted into cation radical of phenyldiazene [134b] and hydrogen peroxide via passing through radical peroxide intermediate.[70] Due to unstable nature of the phenyl cation radical intermediate, it rapidly transformed into aryl radical [134c] and $N_2$ by losing the $H^+$. Later the aryl radical reacted with the quinoline-4-ones (131) to give the intermediate [131a] which afforded the desired product upon oxidation.[71]

### I.B.11. Alkynylation of 4-quinolones

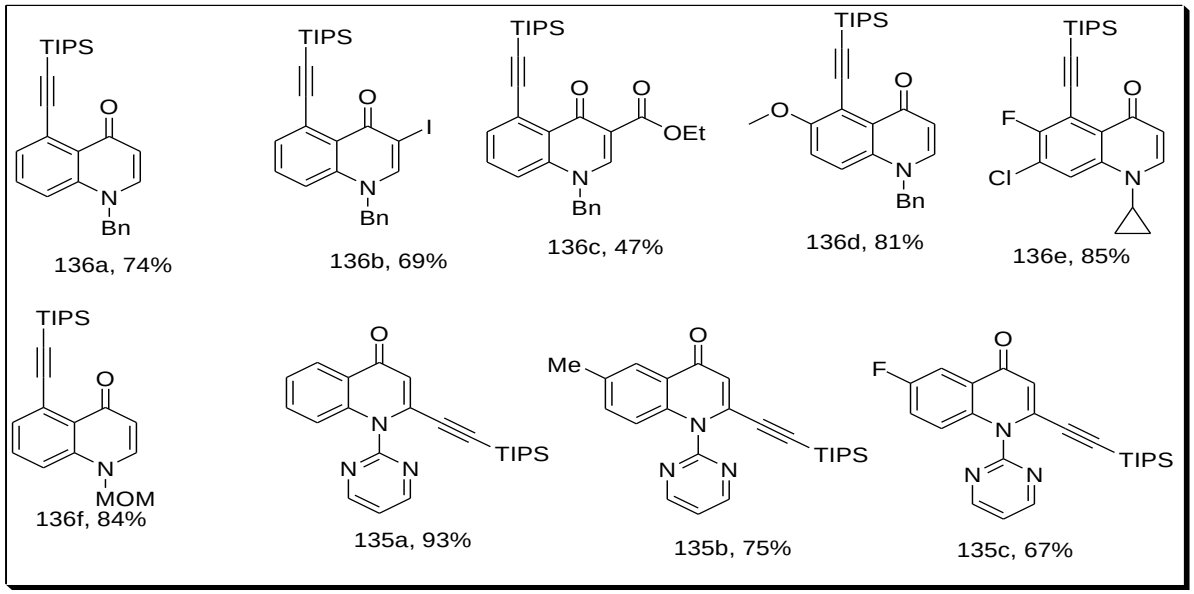
Hong *et.al* reported the two different efficient strategies for site selective C-5 alkynylation of 4-quinolones directed by the weakly coordinating carbonyl group and Ru(II) catalyzed C-2 selective alkynylation via N-pyrimidyl directing group using TIPS-EBX (an alkylating agent)[72]



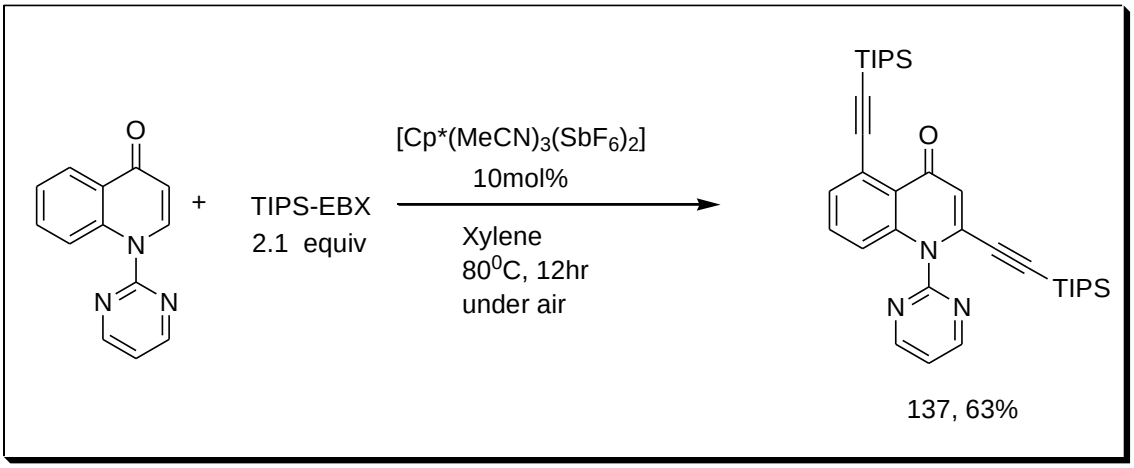

**Scheme-I.49.** Ru (II) catalysed site selective alkynylation of 4-Quinolones

Generally, N-Benzyl 4-quinolones containing bromo, iodo, ester and imide groups at the C-3 position smoothly participated to afford the corresponding C-5 alkynylated derivatives. Interestingly, the size and electronic properties of the substituents had no significant influence on the reaction efficiency. In addition, benzyl, methyl, ethyl, cyclopropyl, and MOM groups protected N-quinolones were easily underwent the reaction. In case of C-2 alkynylation, N-pyrimidyl group showed the high regioselectivity to the 4-quinolone moiety. Electron releasing group (Me− and OMe−) and electron withdrawing groups (F−, Cl−, Br−, $CF_3$−, and $NO_2$) on the 4-quinolone moiety were feasible to provide the C-2 alkynylated products.They had used these strategies in one-pot reaction to achieve both C-2 and C-5 alkynylation on the 4-quinolone scaffold.

**Selected Examples**

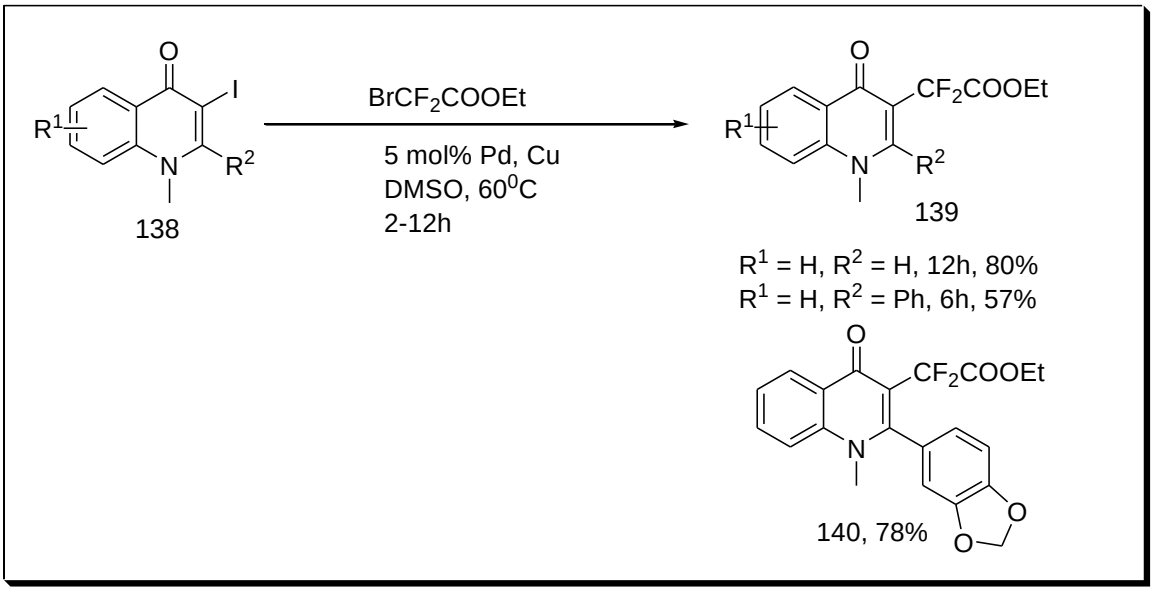


**One pot catalytic C-2/C-5 alkynylation of 4-Quinolones**




**I.B.12. –$CF_2$ unit insertion of 4-Quinolones**

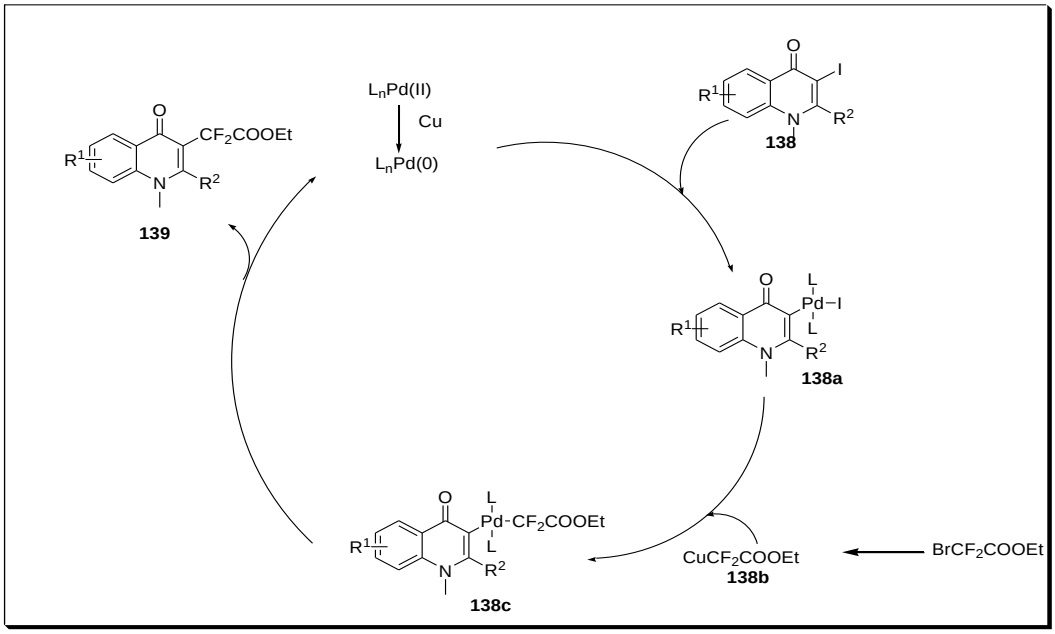
In 2013**,** Yang et al. reported the insertion of –$CF_2$ unit in the 3-position of 4-quinolone derivatives via palladium catalysed cross coupling in presence of copper mediator. [73]




**Scheme-I.50.** Pd/Cu catalysed–$CF_2$ group insertion of 4-Quinolones

Graveolinine, natural quinolone alkaloid[74] isolated from Ruta graveolens have interesting antibacterial, spasmolysis, and antitumor activities. They have inserted the –$CF_2$ unit into the scaffold via generating the 3-iodo-graveolonine primarily.[75]

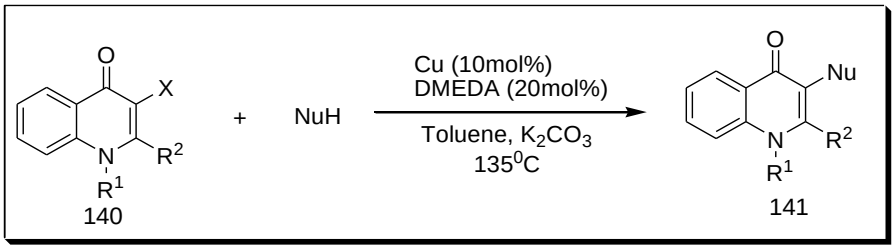
**Plausible Mechanism**




They have proposed a mechanism in which Pd (II) catalyst may be reduced by copper into an active Pd(0) species initially which then undergo the oxidative addition into the C−I bond of compound 138 to form intermediate 138a. In the meantime, the unstable copper ethyl difluoroacetate complex 138b was easily formed which performed a reaction with the intermediate 138a to form the intermediate 138c rapidly. In last step, the reduction elimination occurred which afforded the desired product 139 via regeneration of Pd(0) catalyst.

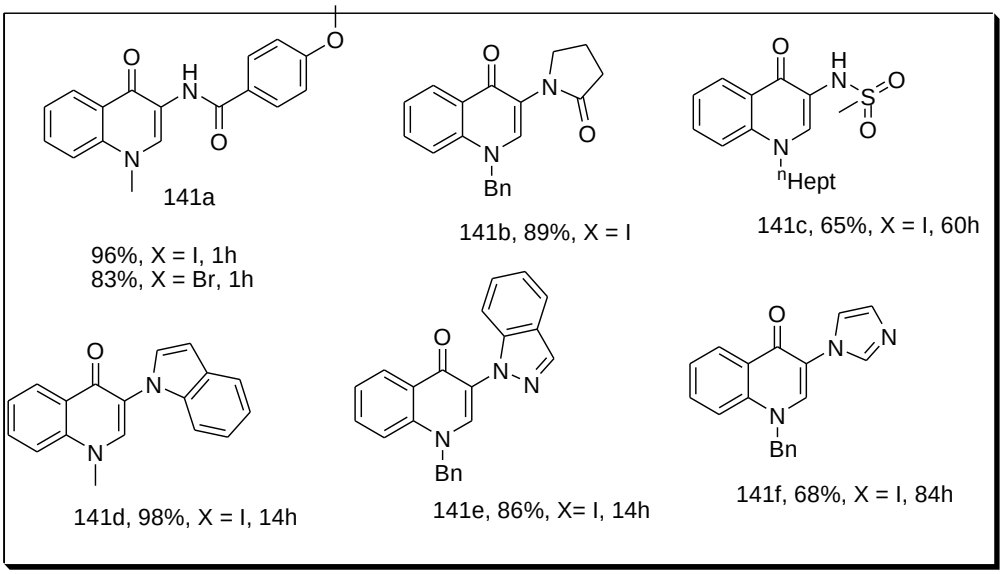
**I.B.13. C-N coupling**

Mouâd Alami *et al.* first reported the C-N coupling reaction of 3-halo-4(1H)-quinolones with various nucleophiles including amides, lactams, sulfonamides and NH-containing azoles in moderate to good yields. Copper powder, the catalyst plays the pivotal role for this Ullmann C-N bond forming strategy in presence of DMEDA (as a ligand) and $K_2CO_3$ (as a base) at 135 °C. [76]



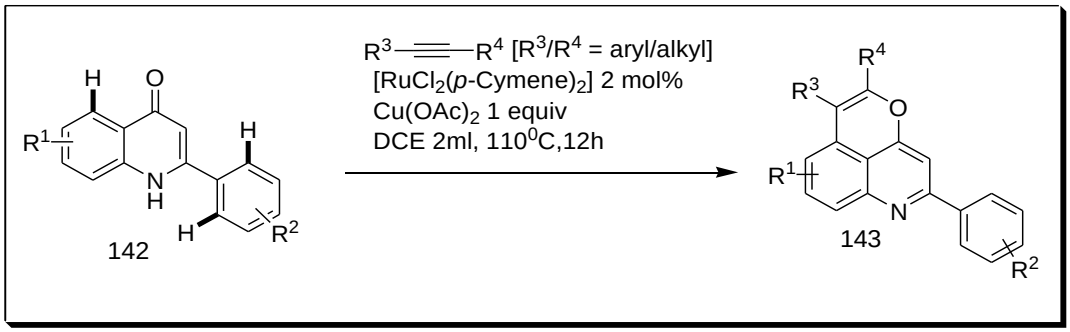

**Scheme-I.51.** Cu catalysed C-N coupling of 4-quinolones

**Selected Examples**



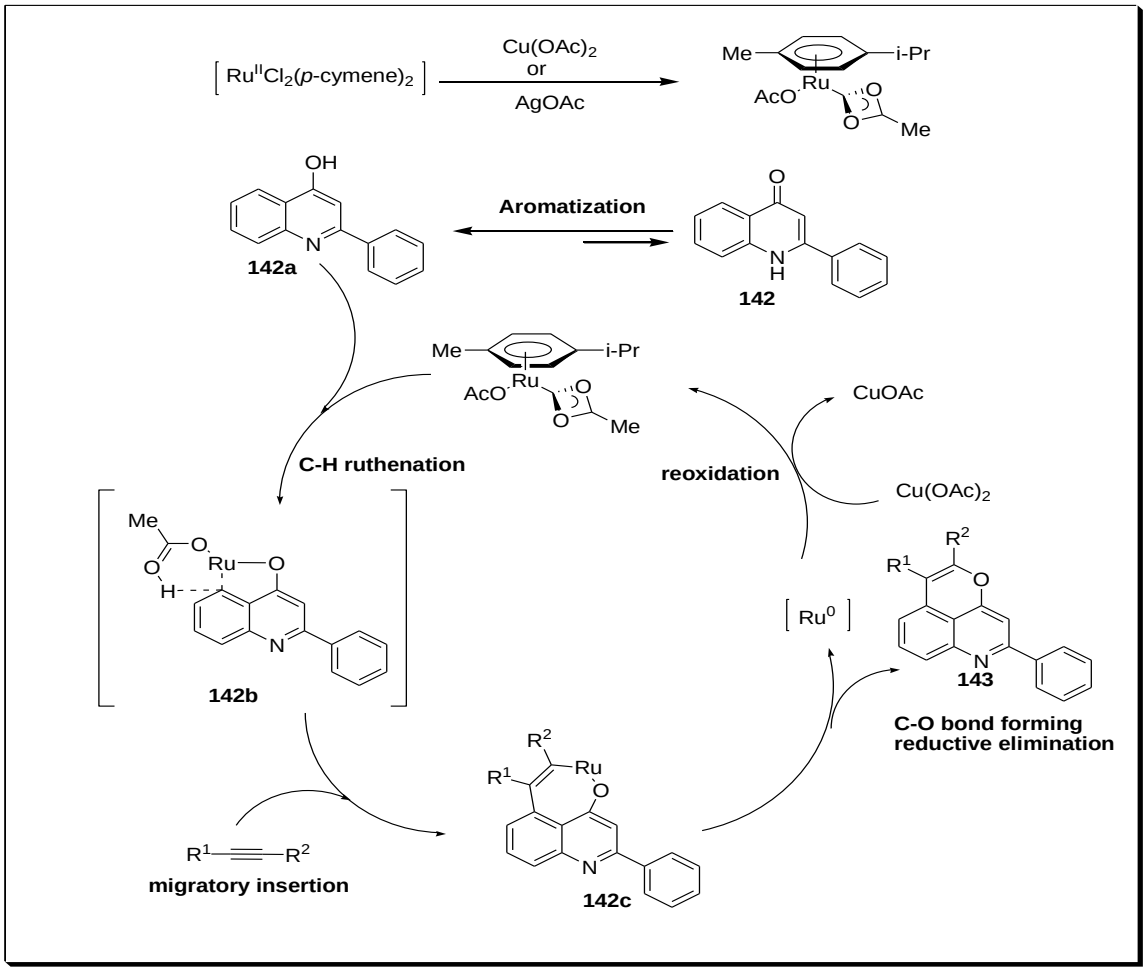

## I.B.14. Ru catalysed C-H annulations of 2-arylquinolinone

Patel and his coworkers successfully done the C-H annulations of 2-arylquinolinone with internal alkyne *via* weak coordination in the presence of ruthenium catalyst.[77] electron-donating substituents such as *p*-Me in the 2-aryl ring of Arylquinolinone furnished their expected annulated products in moderate yields whereas Electron-withdrawing groups such as *p*-F and *o*-Cl present in the 2-aryl ring of 2arylquinolinone also provide their annulations products in decent yields.



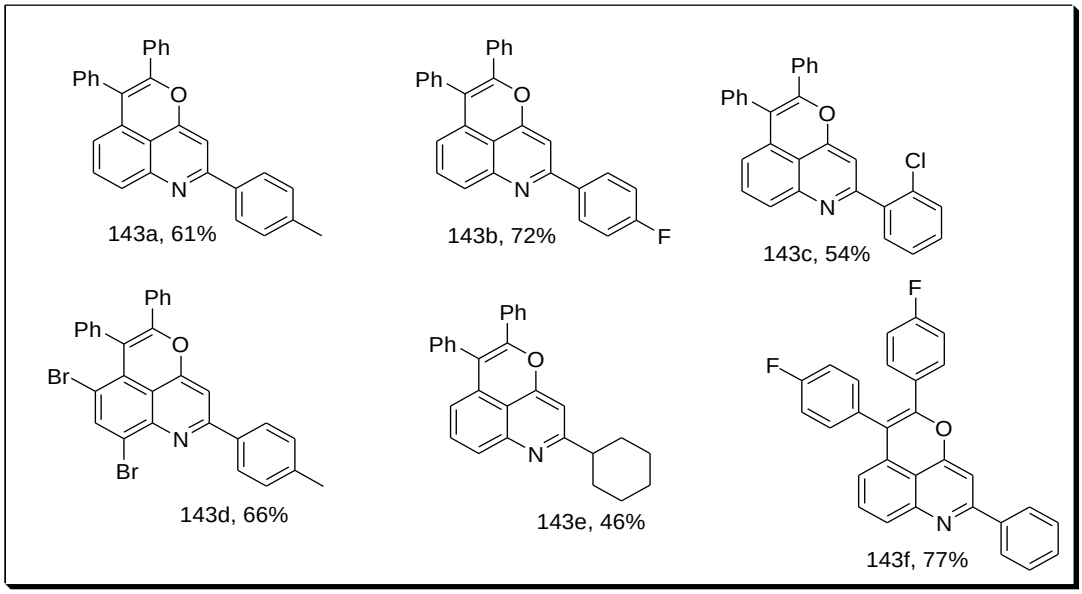

**Scheme-I.52.** C-H annulations of 2-arylquinolinone with internal alkyne in the presence Ru catalyst

**Plausible mechanism**



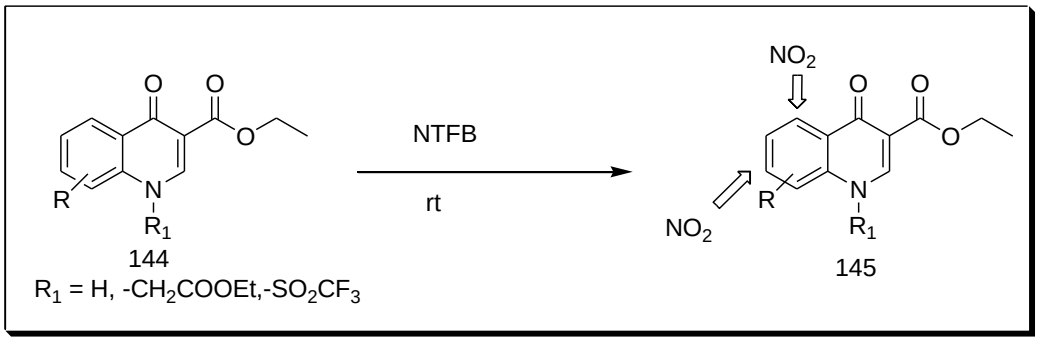

Initially, the chloride ligand of the ruthenium catalyst exchanged via the reactions with an acetate anion either from AgOAc or $Cu(OAc)_2$. Then, aromatization of 2-phenylquinolinone (142) provided the 4-hydroxy-2-phenylquinoline (142a). Afterwards, a five-membered ruthenacycle intermediate (B) is formed from (A). Then, migratory insertion of alkyne took place into the Ru-carbon bond of intermediate (142b) and resulted the intermediate (142c). For unsymmetrical alkynes, the alkyne carbon having higher electron density favoured the insertion into the Ru-carbon bond which accounted for the regioselectivity. Finally, reductive elimination resulted the expected annulated product (143) with the regeneration of catalyst Ru(0) . This Ru(0) is further oxidized to an active Ru(II) catalyst with the aid of oxidant $Cu(OAc)_2$ or by an areal oxidation.

**Selected Examples**



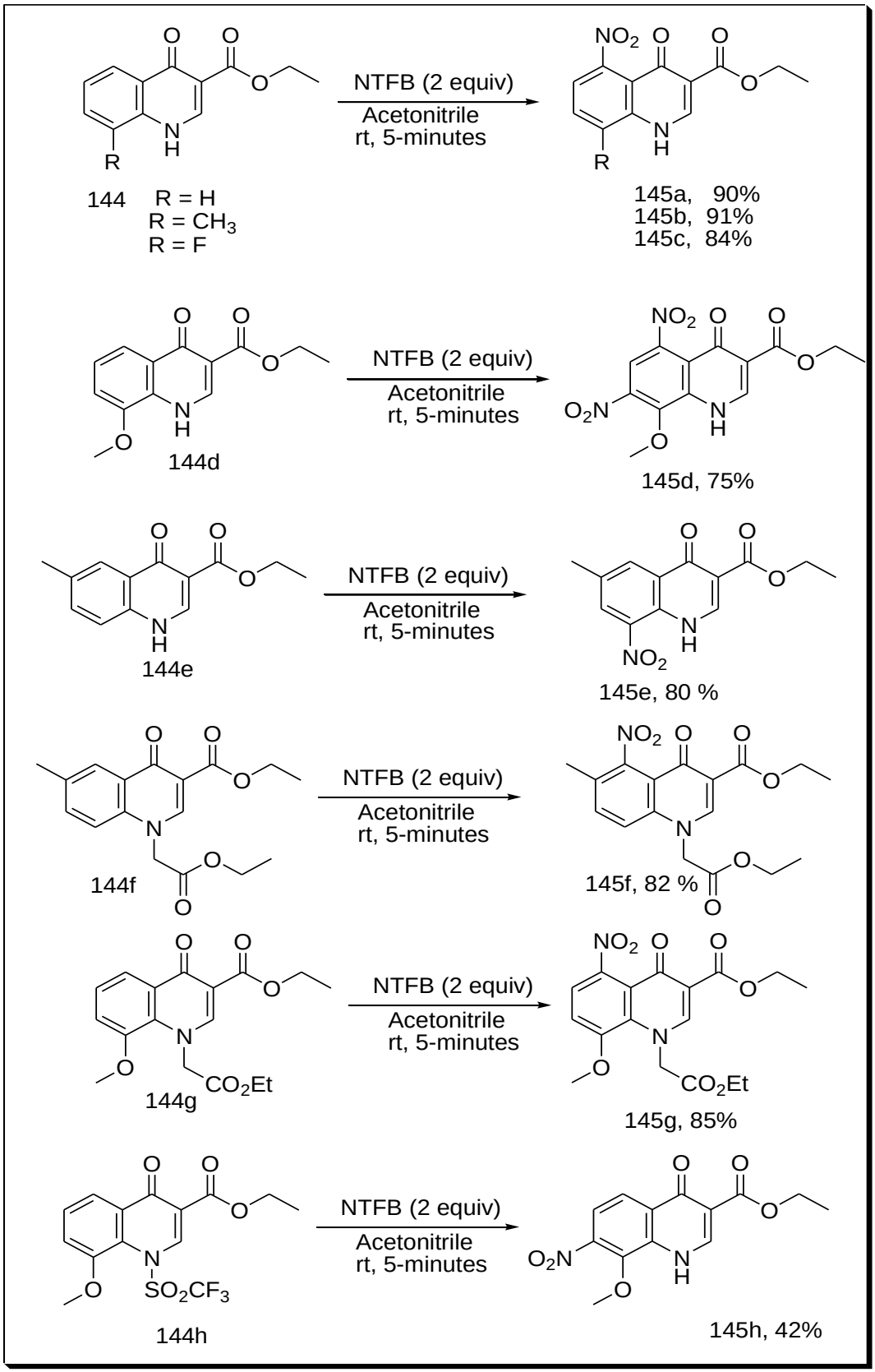

**I.B.15. Regiocontrolled nitration of 4-quinolones at ambient temperature**

A complete regio-controlled nitration of 4-quinolones at ambient conditions with the aid of NTFB (nitronium tetrafluoroborate) was described. We had tuned the selectivity by the selective functionalization of free N-H group of 4-quinolone. Analyzing the DFT (density functional theory) calculation, the profound impacts of the free N-H and other substituents in the nitration process of 4-quinolones have been screened .Theoretical prediction and experimental observations were well synchronized below this reaction.[78]



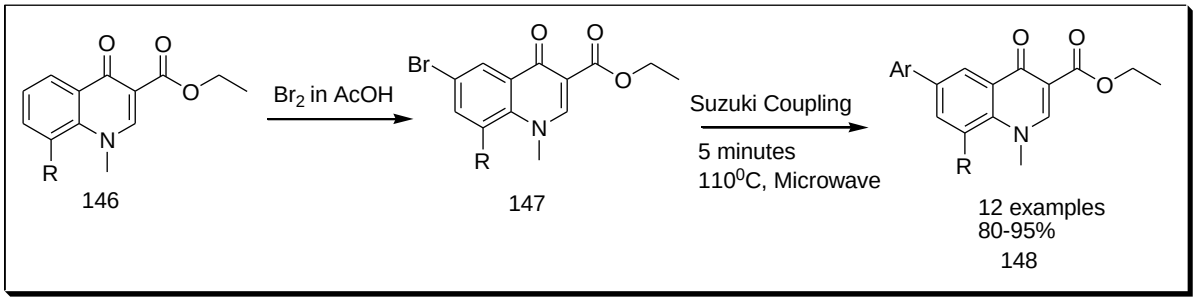

**Scheme-I.53.** Regiocontrolled nitration of 4-quinolones

**Selected Examples**



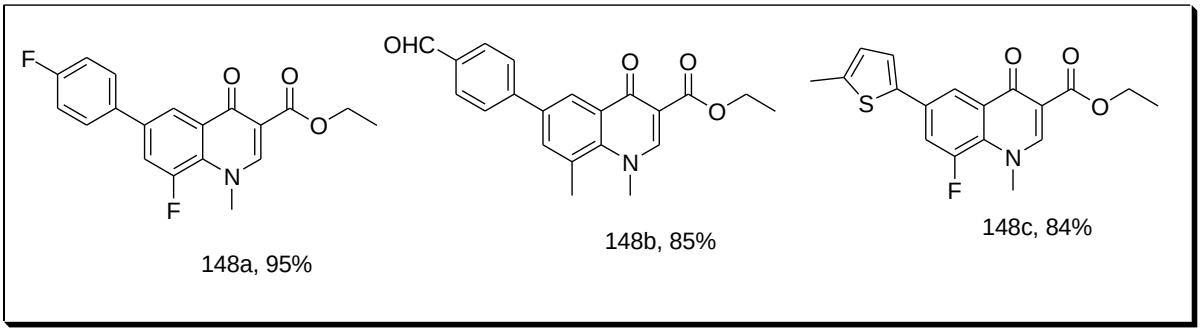
### I.B.16. Synthesis of 6-aryl substituted 4-quinolones

Here in, we reported the regioselective bromination at C-6 position and subsequent arylation by Suzuki cross-coupling using Pd-NHC catalyst to prepare a broad array of 6-aryl substituted-4-quinolones. The desired cross-coupled product easily formed in only 10 minutes under microwave irradiation at 110 °C.[79]



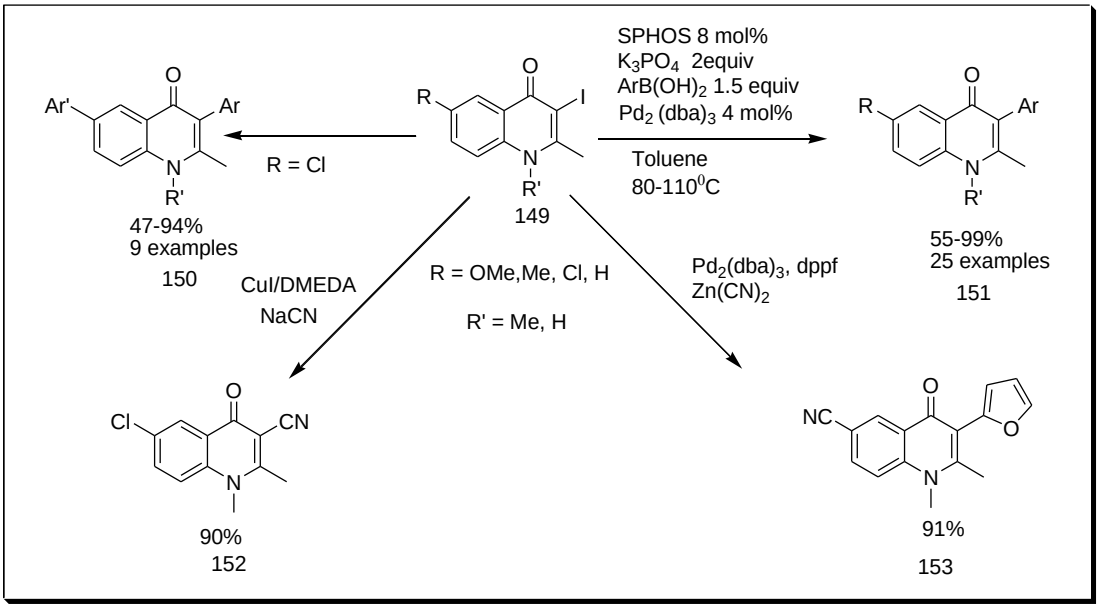

**Scheme-I.54.** Synthesis of 6-aryl substituted 4-quinolones *via* Suzuki cross coupling

**Selected Examples**




### I.B.17. Suzuki coupling & cyanation

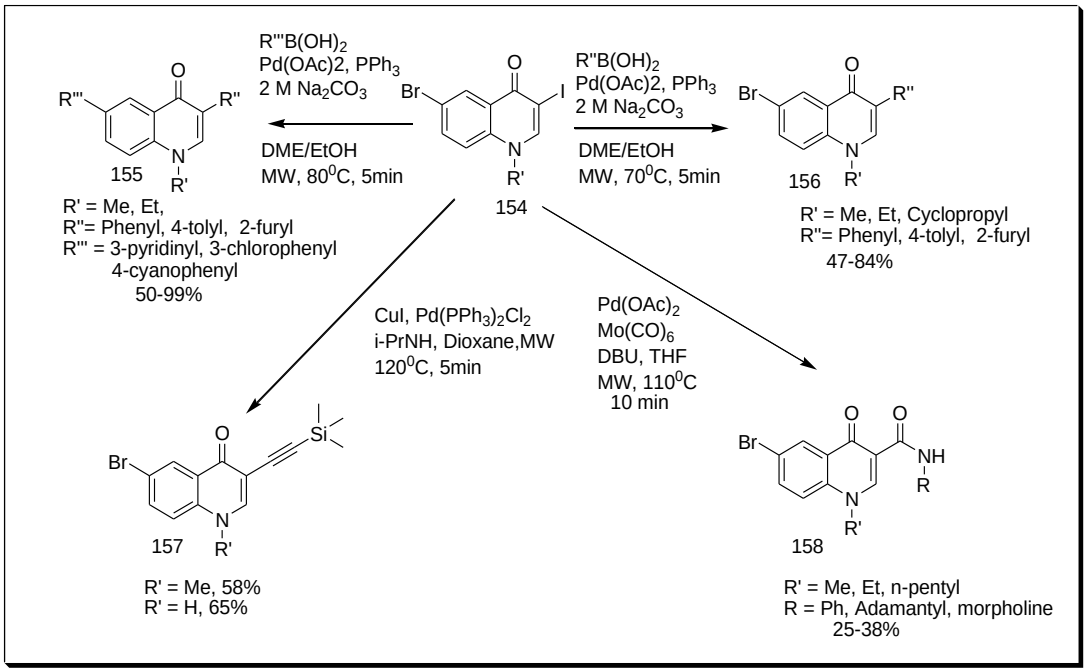
Manetsch *et al.* demonstrated the divergent route to access the structurally diverse 4-Quinolones via sequential Suzuki coupling and cyanation reaction in presence of palladium as well as copper catalyst. A large variety of aryl(Het)boronic acid successfully coupled with 6-chloro-3-iodo substituted 4-quinolone with very good yield. [80]




**Scheme-I.55.** Synthesis of different substituted 4-Quinolones via Suzuki cross coupling & cyanation reaction.

### I.B.18. Regioselective Suzuki, sonogashira & aminocarbonylation reaction

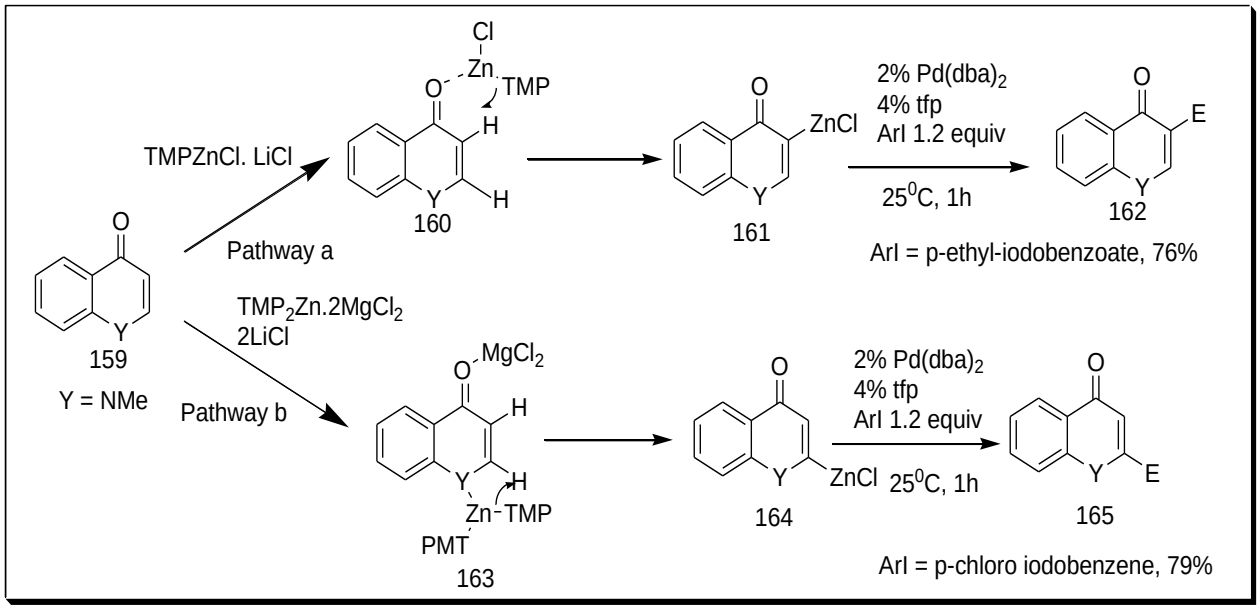
In 2011, Corelli and his coworkers similarly synthesized the1,3,6-trisubstituted quinolin-4(1H)-ones starting from 1-alkyl-6-bromo-3-iodoquinolin-4(1H)-one via regioselective Suzuki coupling, sonogashira coupling and aminocarbonylation reaction. All the reaction proceeded under microwave irradiation in a very short span.[81]



**Scheme-I.56.** Regioselective Suzuki, sonogashira coupling & aminocarbonylation reaction

### I.B.19. Regioselective zincation of C-2 & C-3 position of 4-Quinolones

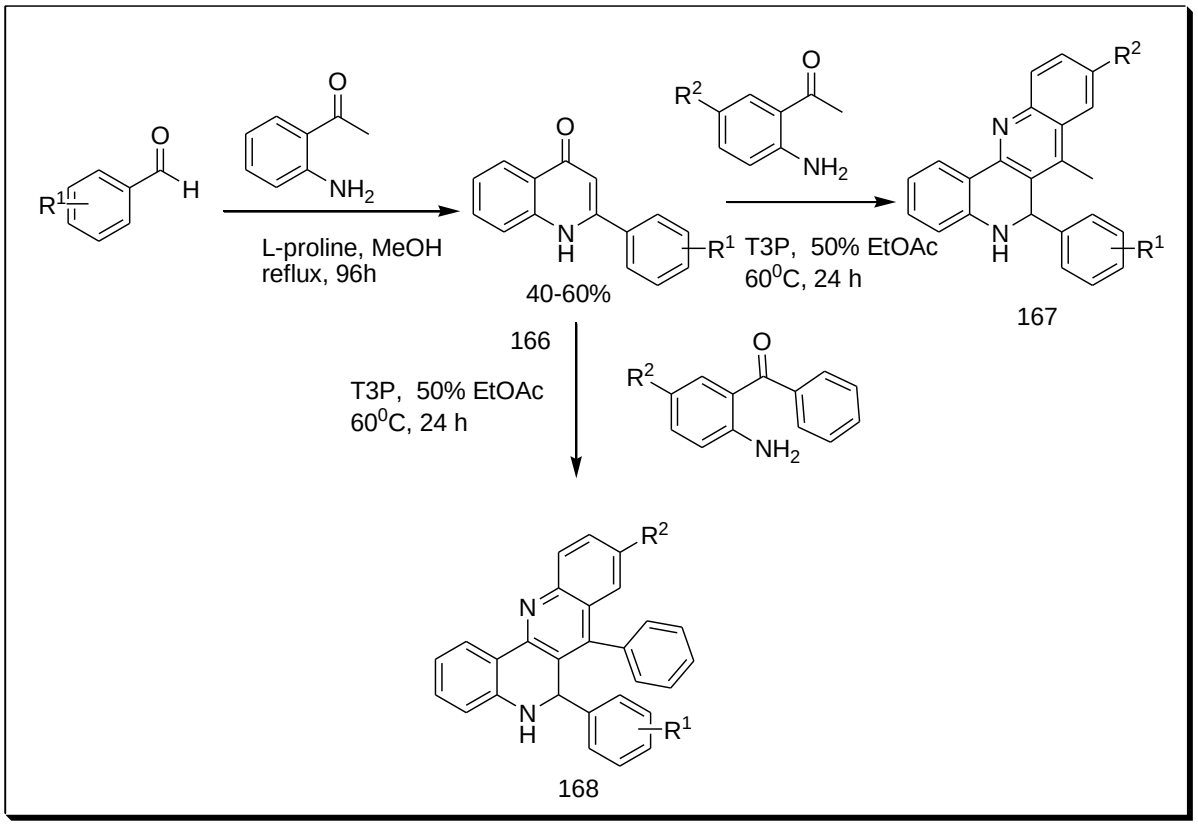
Knochel have employed the regioselective zincation at C-2 and C-3 position of quinolones in presence or absence of $MgCl_2$ lewis acid. For achieving the regioselectivity, they have used highly chemoselective TMP (2,2,6,6-tetramethylpiperidyl) bases such as TMPZnCl.LiCl and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ by which several quinolone units have been synthesized. [82]




**Scheme-I.57.** Regioselective electrophile insertion at C-2 & C-3 position of 4-quinolones.

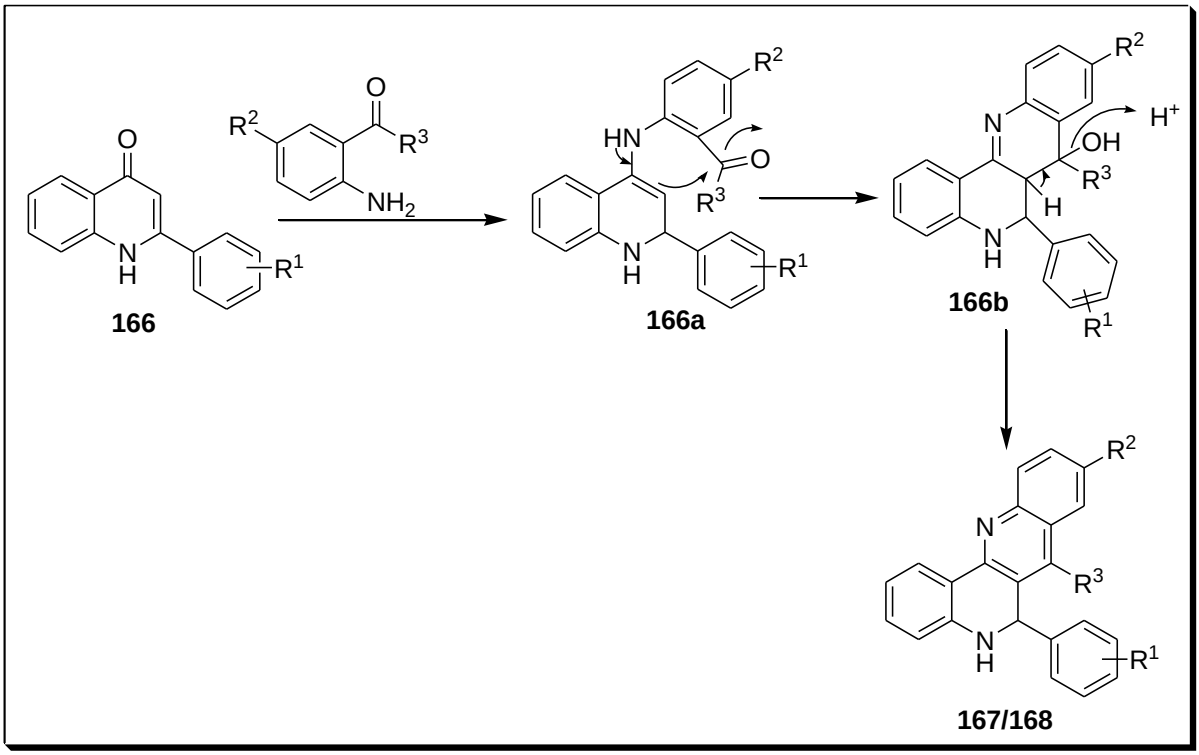
### I.C. Miscellaneous reactions of 4-quinolones

More recently, Kumar and his group finished a two step protocol for the synthesis of substituted dibenzo[*b,h*][1,6]naphthyridine derivatives generated from the coupling of 2-aminoacetophenones and 2-aminobenzophenones with dihydroquinolin-4ones using propyl phosphonic anhydride solution as a catalyst (T3P). A diverse analogues of dibenzo[*b,h*][1,6]naphthyridine derivatives was isolated in good yield under expensive catalyst free condition.[83]



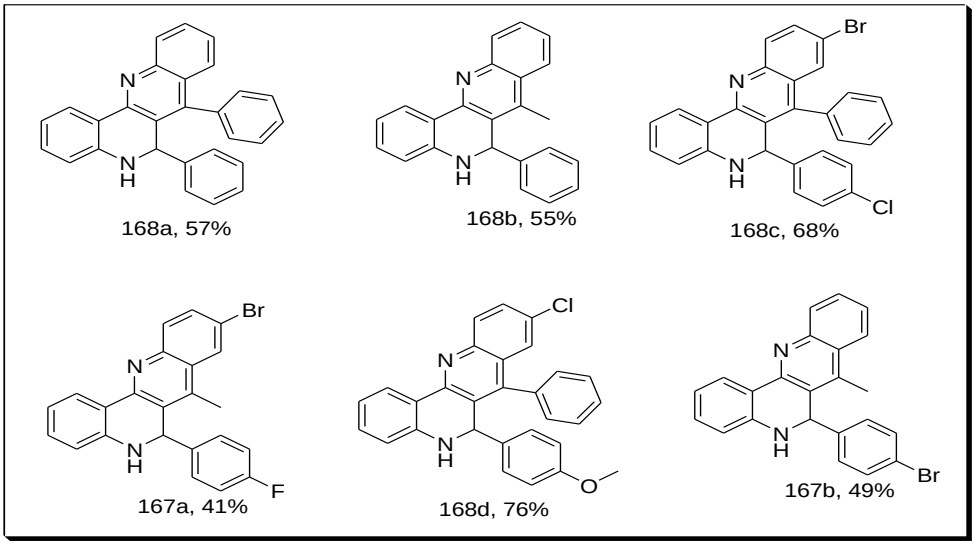

**Scheme-I.58.** Synthesis of dibenzo[*b*,*h*][1,6]naphthyridine derivatives using T3P as a catalyst

**Plausible Mechanism:**

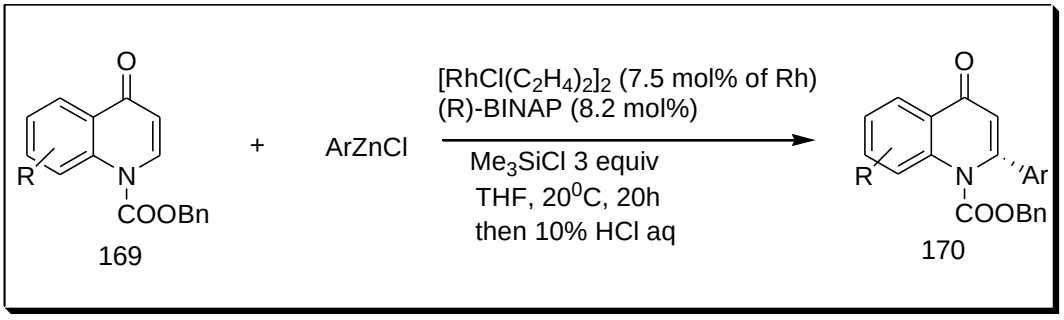


The above reaction proceeded via the formation of 4-acylamino-dihydroquinoline intermediate 166a initially. Then, the enamine group of intermediate 166a attacked the nearby ketone functional group to provide the intermediate 166b. Finally, the desired product generated upon dehydration reaction of intermediate 166b.

**Selected Examples**

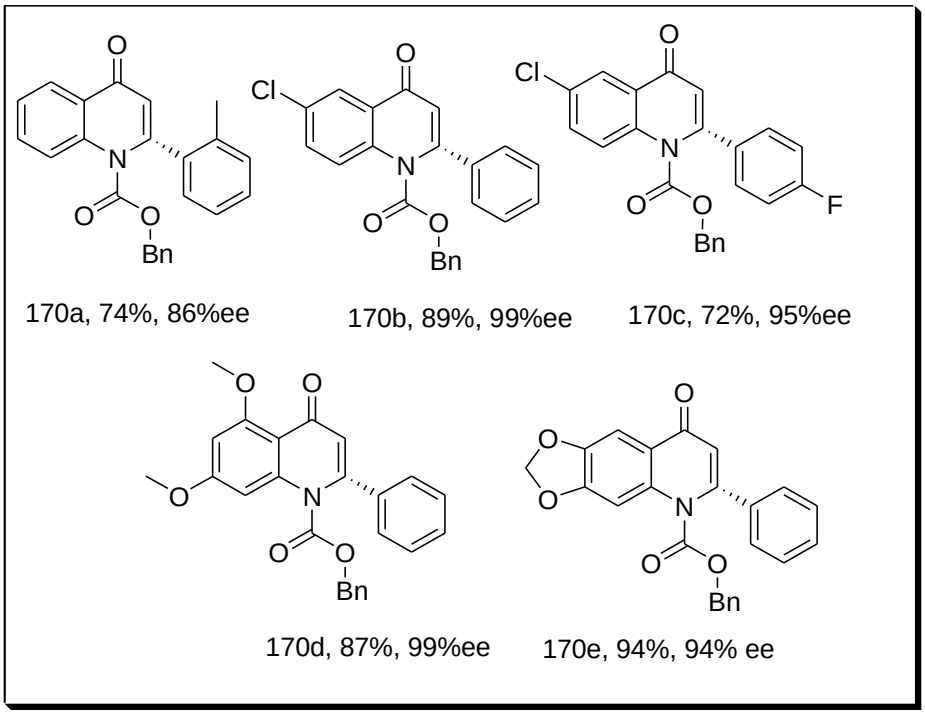



In 2005, Hayashi *et al*. first reported the asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones via rhodium catalysed 1,4-addition of arylzinc reagent to the 4-quinolone moiety with high enantioselectivity. [84]

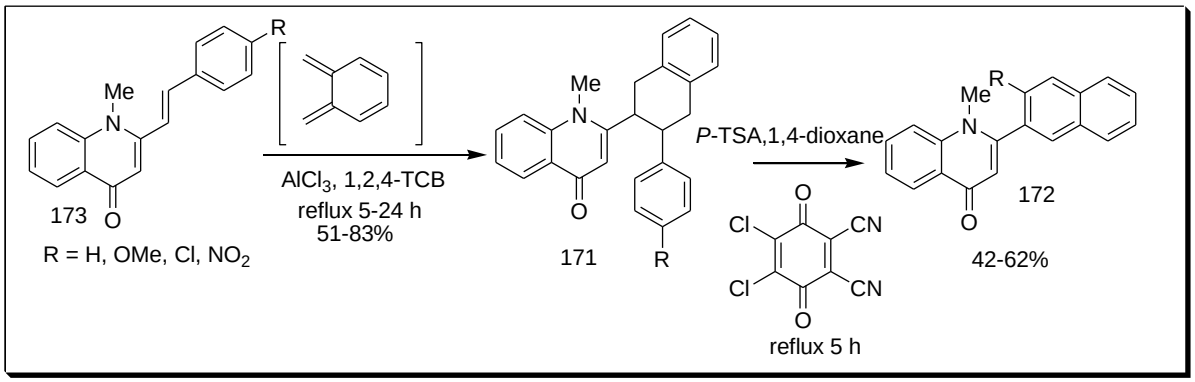



**Scheme-I.59.** Rh catalysed asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones via 1,4-addition of arylzinc reagent

**Selected examples**




Very recently, Silva *et al.* reported the synthesis of trans-2-(3-aryl-1,2,3,4-tetrahydronaphthalen-2-yl)-1-methylquinolin-*4*(1H)-ones from the cycloaddition reactions in between (E)-1-methyl 2-styrylquinolin-4(1H)-ones and very reactive diene ortho-benzoquinodimethane in presence of lewis acid. Further, they converted this adduct into the 2-(3-arylnaphthalen-2yl)-1-methylquinolin-4(1H)-ones with the aid DDQ in moderate yield.[85]




**Scheme-I.60.** Lewis Acid Catalyzed Diels–Alder Reactions of (E)-1-Methyl-2-styrylquinolin-4(1H)-ones with ortho-Benzoquinodimethane

The electron donating group (-OMe) decreases the reactivity of of (E)-1-methyl-2-styrylquinolin-4(1*H*)-ones to participate in cycloaddition reaction whereas the electron

withdrawing group showed higher reactivity to afford excellent yield of the desired product.

## I.D. Conclusion

In this introduction part, several approaches to the transition metal catalyzed and metal free synthesis of 4-quinolones are briefly discussed. This review also includes various aspect of functionalization of the 4-quinolone precursor *via* C-C coupling (Suzuki, Sonogashira), C-N coupling, nitration, ipso-nitration, decarboxylative C-S coupling, and C-H bond activation etc. The use of these processes has become a lively area of research because 4-quinolone unit is a common structural unit widely encountered in biologically active molecules and natural products. The review describes the latest improvements in the substrate scope, mildness of the procedures, catalyst loading and catalytic cycle in the area of transition metal catalyzed functionalisation.

## I.E. References

References of chapter I are given in the Bibliography (pp-223-227)

# Chapter II

# *Pd-NHC catalysed carbonylative Sonogashira coupling for the formation of 4-quinolones and 4H-chromen-4-one*

## II.A. Introduction:

4-quinolones are mainly occurred in many natural products and bio-active drug molecules due to its wide applicability as a "privileged building unit" in medicinal chemistry.[1]As a consequence, the synthesis of 4-quinolone has remained a great interest and several procedures are readily available in the literature. [2] Generally, the most useful method is the condensation of anilines with β-keto esters via cyclisation of in situ formed β-amino acrylates. This reaction became ineffective in the case of electro deficient anilines.[3] Later strategies involved the heterocyclisation of 2-amino chalcone[4] and carbonylation reaction of allenes with *N*-tosyl-o-iodo anilines.[5]Naturally occurring the chromone moiety and its derivatives possessed diverse pharmaceutical[6] and biological activities.[7] It also exhibited some interesting fluorescence characteristics.[8]Therefore, the development as well as enrichment of the methods for their synthesis is an important task in organic synthesis.

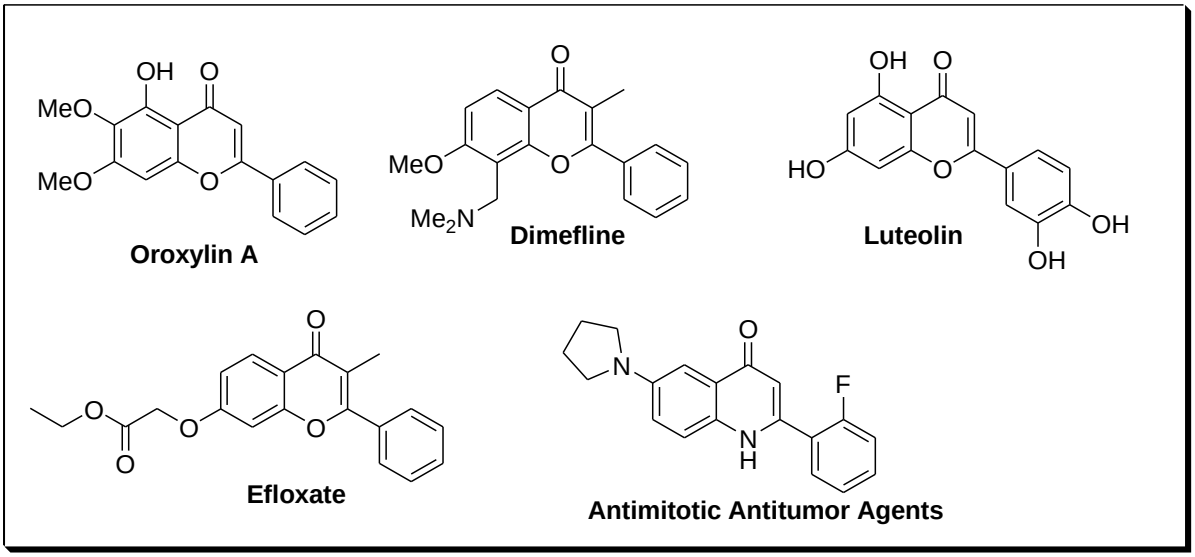
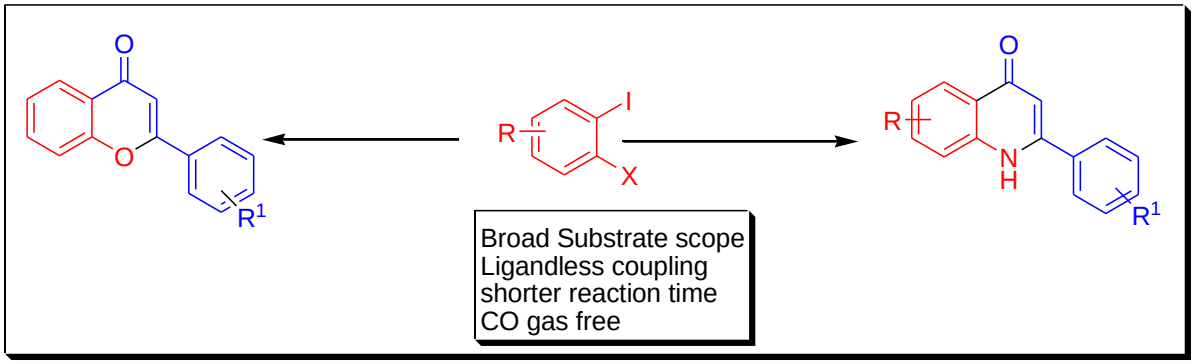



**Fig-II.1.** Biologically active flavones and 4-quinolone scaffolds

## II.B. Present work: Background & objectives

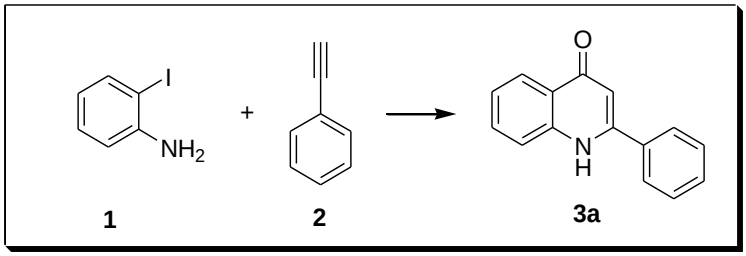
Three classical non-catalytic routes such as Kostanecki–Robinson reaction[9] Claisen condensation[10]and Baker–Venkatamaran rearrangement[11]for the preparation of chromone derivatives is very much well known to the chemist. However, these pathways suffer from various disadvantages which involved harsh reaction condition, multistep process, poor functional group tolerance and formation of by-products. Using of Palladium as a catalyst for the heterocyclic moiety syntheses has been a profound arena for its research in last two decades.[12] Recently, palladium catalysed cyclocarbonylation methodology between aryl

halides, CO and a nucleophile became more attractive due to its versatility because this protocol has been applied for the syntheses of multitude arylcarbonyl derivatives (e.g.-ester, amide, acids, ketones).[13] In addition, Palladium (0) catalysed multicomponent cyclocarbonylation reaction of terminal acetylenes with 2-iodo phenol and 2-iodo aniline under elevated pressure of carbon monoxide has been a general method to synthesize both chromone[14]and 4-quinolone[15] derivatives. Genelot and his co-workers used a two step protocol to synthesize the serine protease inhibitor BILN-2061.[16] Although, this method bears the use of highly toxic, flammable, invisible and tasteless CO gas. In addition, it requires above atmospheric pressure and special equipment to safe handling the CO gas. Lizuka *et al.* developed a nongaseous carbonylative sonogashira technique to provide alkynones using $Mo(CO)_6$ as CO source.[17]Very recently, Larhed *et al.* reported nongaseous carbonylative Sonogashira annulations to form the 2-substituted 4-quinolone derivative under microwave irradiation as well as room temperature method.[18] Rather, the method requires high loading of palladium catalyst, expensive ligand and salt. Wu *et al*. also synthesized the flavones derivatives *via* ligand free Pd/C catalysed cyclocarbonylation reaction in excellent yields under the carbon monoxide gas.[19] Herein, we report the carbonylative Sonogashira annulations sequence for the syntheses of flavones and 4-quinolone scaffolds in the presence of Pd-NHC catalyst using $Mo(CO)_6$ as CO source.



**II.B.1. Present work: Result and Discussion**

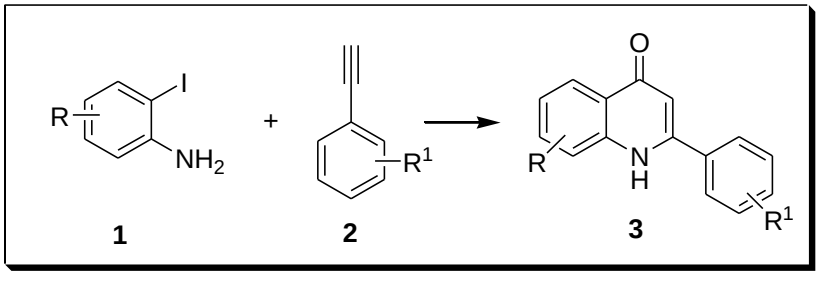
**Table-II.1. Optimization of the reaction condition:**



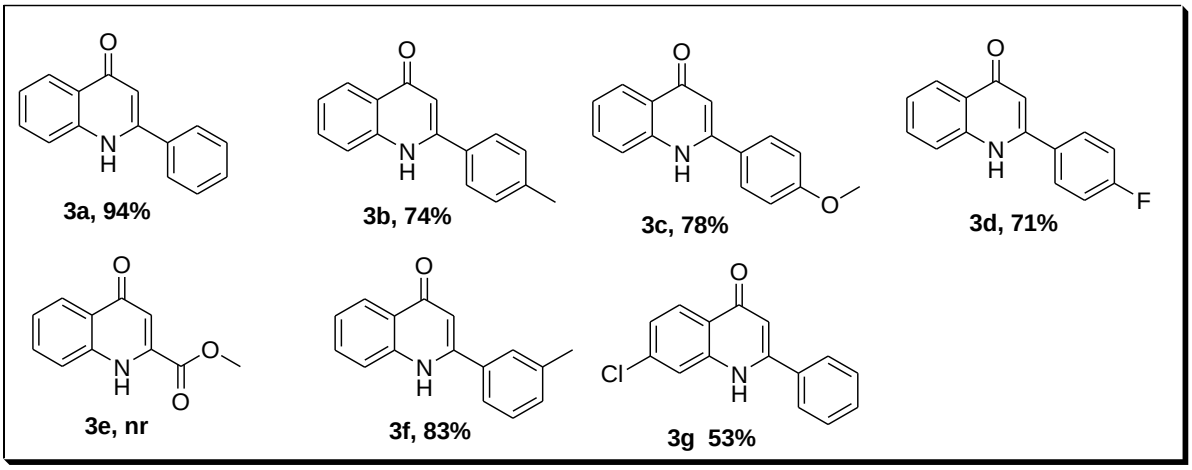

| entry | Catalyst ( mol %) | Base ( equiv) | CO source ( equiv) | Temp (°C) | solvent | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | Pd-NHC 2 | $Et_3N$ | $Mo(CO)_6$ | 95 | DMF | 15 | 75 |
| 2 | Pd-NHC 2 | $K_2CO_3$ | $Mo(CO)_6$ | 95 | Anisole | 15 | 25 |
| 3 | Pd-NHC 2 | $K_2CO_3$ | $Mo(CO)_6$ | 95 | Toluene | 15 | No desired product |
| 4 | Pd-NHC 2 | $Et_3N$ | $Mo(CO)_6$ | 95 | Anisole | 20 | 45 |
| 5 | Pd-NHC 2 | $K_2CO_3$ | $Mo(CO)_6$ | 95 | DMF | 15 | trace |
| 6 | $Pd(OAc)_2$ 5 | $Et_3N$ | $Mo(CO)_6$ | 95 | DMF | 22 | No desired product |
| 7 | $PdCl_2$ 5 | $Et_3N$ | $Mo(CO)_6$ | 95 | DMF | 20 | 58 |
| **8** | **Pd-NHC 2** | **$Me_2NH$** | **$Mo(CO)_6$** | **95** | **DMF** | **15** | **94** |
| 9 | Pd-NHC 2 | $Cs_2CO_3$ | $Mo(CO)_6$ | 95 | DMF | 15 | 41 |
| 10 | Pd-NHC 2 | $Me_2NH$ | $Fe_3(CO)_{12}$ | 95 | DMF | 15 | No desired product |
| 11 | Pd-NHC 2 | DBU | $Mo(CO)_6$ | 95 | DMF | 15 | No desired product |
| 12 | $Pd(PPh_3)_4$ | $Me_2NH$ | $Mo(CO)_6$ | 95 | DMF | 15 | 41 |
| 13 | Pd-NHC 2 | $Me_2NH$ | $Mo(CO)_6$ | 80 | DMF | 15 | 77 |
| 14 | Pd-NHC 2 | $Me_2NH$ | $Mo(CO)_6$ | 60 | DMF | 15 | 64 |
| 15 | Pd-NHC 2 | $Me_2NH$ | $Mo(CO)_6$ | rt | DMF | 15 | 21 |
| 16 | Pd-NHC 1 | $Me_2NH$ | $Mo(CO)_6$ | 95 | DMF | 15 | 79 |
| 17 | Pd-NHC 2 | $Me_2NH$ | $Mo(CO)_6$ | 95 | DMF | 6 | 56 |
| 18 | Pd-NHC 2 | $Me_2NH$ | $Mo(CO)_6$ | 95 | DMF | 9 | 68 |
| 19 | Pd-NHC 2 | $Cs_2CO_3$ | $Mo(CO)_6$ | 95 | Toluene | 15 | No desired product |
| 20 | - | $Me_2NH$ | $Mo(CO)_6$ | 95 | DMF | 15 | No desired product |

**Reaction condition:** 2- iodo aniline (0.25 mmol, 55mg), Phenyl acetylene (0.5 mmol, 50 mg), Base (3 equiv) , $Mo(CO)_6$ ( 0.5 mmol, 132mg), Solvent (2 ml) stirred at 95°C under $N_2$ atm . Isolated yield after column chromatography.

Initially, we attempted the feasibility of carbonylative Sonogashira coupling with 2-iodo aniline and phenyl acetylene as a model substrates using DMF as a solvent at 95°C under $Mo(CO)_6$. In presence of our pre developed Pd-NHC (2 mol%) catalyst and $Et_3N$ (as a base), it afforded the 75% yield of the desired 4-quinolone product (Table-II.1; entry 1). When Pd-NHC was employed as a catalyst using $K_2CO_3$ as base, the product **3a** was obtained in only 25% in anisole (Table-II.1; entry 2). Changing the solvent system from DMF to toluene, no effective result was obtained ((Table-II.1; entry 3). Pd-NHC was found to be more effective catalyst than comparison to $Pd(OAc)_2$ and $PdCl_2$ to form the **3a** (Table-II.1; entries-1,6,7 and 75%, 0%, 58% respectively) . Different bases were screened to find the best result of the reaction. $Me_2NH$ gave the best result and 94% of the desired product **3a** (Table-II.1; entry-8) was formed in DMF. DBU showed no suitable result under this reaction condition (Table-II.1; entry-11). Interestingly, we checked the source of CO by replacing the $Mo(CO)_6$ with $Fe_3(CO)_{12}$ and it afforded no result of the desired 4-quinolone (Table-II.1; entry-10). We also performed the reaction at different temperatures (Table-II.1; entry 13-15) and the most promising result was found at 95°C (Table-II.1; entry-8). Rather without the presence of any palladium catalyst, a control reaction was done but no desired conversion of iodo aniline was found (Table-II.1; entry-20). Based on the following observations, the following combination 2 mol% Pd-NHC catalyst at 95°C in presence of $Me_2NH$ was found to be the optimal for carbonylative sonogashira annulations (Table-II.1; entry-8).

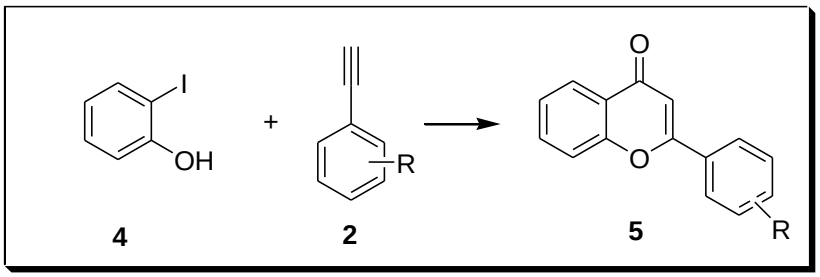



**Scheme-II.1.** Scope of various phenyl acetylene and 2-iodoaniline in the carbonylative sonogashira coupling of 4-quinolones

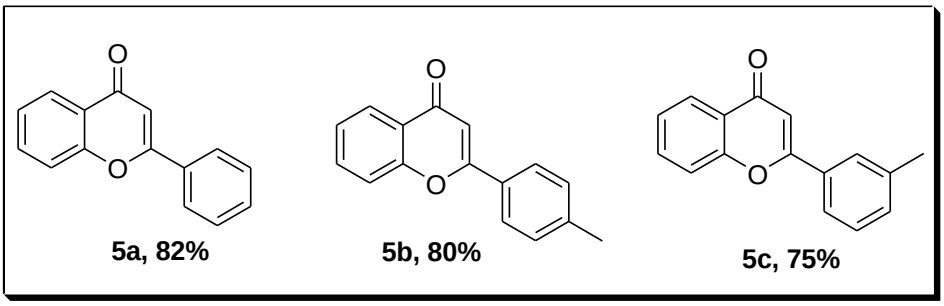



**Reaction condition:** Various 2-iodo aniline (0.25 mmol), Phenyl acetylene (0.5 mmol), $Me_2NH$ (4 equiv), $Mo(CO)_6$ (0.5 mmol, 132mg), Pd-NHC (2mol%), DMF (2 ml) stirred at 95°C under $N_2$ atm .Yield = Isolated yield after column chromatography

With the optimized protocol in our hand, the scope of carbonylative sonogashira annulations was investigated next. Both electron donating and electron with drawing group containing phenyl acetylene participated in the reaction very well and resulted the product in excellent yields (scheme-II.1; entry **3a**-**3d**). Moreover, when 1-ethynyl-3-methylbenzene was used in the reaction, **3f** was obtained in 83% yield. In contrast, methyl propiolate did not respond in our optimized condition to afford the desired product (scheme-II.1; entry-**3e**).Surprisingly, chloro substituted 2-iodoaniline furnished the moderate yield of the corresponding product (scheme-II.1; entry-**3g**).




**Scheme-II. 2.** Scope of various phenyl acetylene in the carbonylative sonogashira coupling of 4*H*-chromen-4-one synthesis




**Reaction condition:** 2- iodophenol (0.25 mmol, 55mg), Various Phenyl acetylene (0.5 mmol), $Me_2NH$ (4 equiv), $Mo(CO)_6$ (0.5 mmol, 132mg), DMF (2 ml) stirred at 95°C under $N_2$ atm .Yield = Isolated yield after column chromatography

To further explore our protocol in the formation of flavone, we initiated our journey with 2-iodophenol and phenyl acetylene as coupling partners. The cyclocarbonylations of *o*-iodophenol and electron rich aromatic acetylene proceeded very well and the desired product was formed in excellent yield (scheme-II.2; entry-**5b)**. 1-ethynyl-3-methylbenzene reacted very facile with 2-iodophenol and resulted **5c** in 75% yield.

## II.C. Conclusion:

In summary, we reported a very mild, operationally simple, ligand free carbonylative method for the synthesis of biologically active motifs 4-quinolones and flavones. Our protocol avoids the use toxic CO gas, high catalyst loading and use of any expensive salt. Moreover, the cyclocarbonylation of both 2-iodophenol and 2-iodoaniline with phenylacetylene was excellent and the corresponding products were obtained from moderate to promising yield. Herein, we also wish to report the first time $Mo(CO)_6$ was used as solid CO source for the synthesis of flavones.

## II. D. Experimental Section:

### II.D.1.General information:

NMR spectra were recorded on 300 MHz spectrometer at 298 K with calibration done on the basis of solvent residual peak. Unless stated otherwise, all reagents such as *o*-iodophenol, *o*-iodoaniline, various acetylenes were purchased from sigma Aldrich and solvents were purchased from commercial suppliers Products were purified using column chromatography on silica gel (60-120 mesh) and a mixture of petroleum ether (60-80°C)/ethyl acetate was used as an eluent. Progress of reaction was monitored by silica gel TLC.

**II.D.2. Preparation of various 4-quinolone derivatives:**

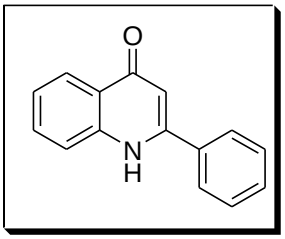
Initially, 2-iodoaniline (0.25 mmol, 55mg), phenylacetylene (0.5mmol), $Mo(CO)_6$ (0.5 mmol, 132mg), Pd-NHC (2 mol%, 4.8mg), $Me_2NH$ (1 mmol, 180mg) and DMF (2ml) were taken in sealed tube. Then, it was evacuated with nitrogen three times and stirred the reaction mixture at 95°C for 15hr. After completion of the reaction by monitoring the TLC, it was cooled. The mixture was diluted with water and the product was extracted with ethyl acetate (3 x 20 mL). Organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude product was then purified using column chromatography as petroleum ether and ethyl acetate as eluents (80% ethyl acetate).

**II.D.3. Preparation of various flavone derivatives:**

Initially, 2-iodophenol (0.25 mmol, 55mg), phenylacetylene (0.5mmol), $Mo(CO)_6$ (0.5 mmol, 132mg), Pd-NHC (2 mol%, 4.8mg), $Me_2NH$ (1 mmol, 180mg) and DMF (2ml) were taken in sealed tube. Then, it was evacuated with nitrogen three times and stirred the reaction mixture at 95°C for 15hr. After completion of the reaction by monitoring the TLC, it was cooled. The mixture was diluted with water and the product was extracted with DCM (3 x 20 mL). Organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude product was then purified using column chromatography as petroleum ether and ethyl acetate as eluents (80% ethyl acetate).

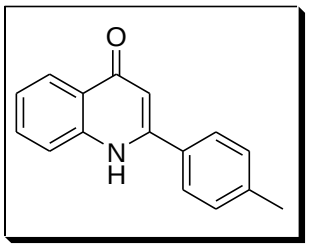
**II.D.4. Physical characteristics and spectral data of compounds:**

1. **2-phenylquinolin-4(1*H*)-one (3a)**[18]



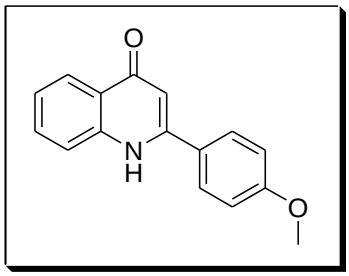

tan powder; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 6.34 (d, *J* = 1.8 Hz, 1H), 7.32-7.37 (m, 1H), 7.58-7.60 (m, 3H), 7.68 (dt, *J* = 6.9Hz, 1.5Hz, 1H), 7.76-7.85 (m, 3H), 8.10 (d, *J* = 7.8Hz, 1H), 11.75 (s, 1H); $^{13}$CNMR (DMSO-$d_6$, 75 MHz) δ 107.8, 119.2, 123.8, 125.2, 125.3, 127.9, 129.5, 130.9, 132.3, 134.7, 141.0, 150.5, 177.5.

**2. 2-*p*-tolyl quinolin-4(1*H*)-one (3b)**[19]



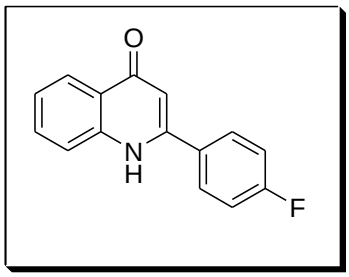
Tan powder, $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 2.38 (s, 3H), 6.32 (s, 1H), 7.29-7.39 (m, 3H), 7.62-7.77 (m, 4H), 8.06-8.09 (m, 1H), 11.65 (s, 1H); $^{13}$CNMR (DMSO-$d_6$, 75 MHz) δ 21.4, 107.3, 119.2, 123.7, 125.1, 127.7, 130.0, 131.7, 132.2, 140.8, 141.0, 150.5, 177.4.

**3. 2-(4-methoxyphenyl) quinolin-4(1*H*)-one (3c)**[18]



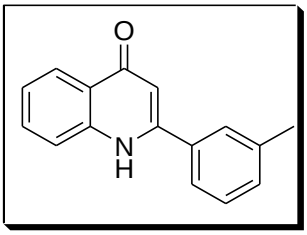
Tan powder, $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 3.85 (s, 3H), 6.33 (s, 1H), 7.14 (d, *J* = 8.8Hz, 2H), 7.33 (t, *J* = 7.5Hz, 1H), 7.63-7.68 (m, 1H), 7.75-7.83 (m, 3H), 8.09 (d, *J* = 7.2Hz, 1H), 11.65 (s, 1H); $^{13}$CNMR (DMSO-$d_6$, 75 MHz) δ 55.9, 106.8, 114.8, 119.3, 123.6, 125.1, 125.2, 126.8, 129.3, 132.1, 141.1, 150.3, 161.5, 177.1.

**4. 2-(4-fluorophenyl) quinolin-4(1*H*)-one (3d)**[18]



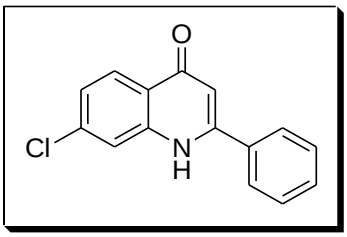
Tan powder, $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 6.33 (d, *J* = 1.8Hz, 1H), 7.35 (t, *J* = 7.2Hz, 1H), 7.44 (t, *J* =8.7Hz, 2H), 7.58-7.77 (m, 2H), 7.88-7.93 (m, 2H), 8.10 (d, *J* =7.8Hz, 1H), 11.65 (s, 1H); $^{13}$CNMR (DMSO-$d_6$, 75 MHz) δ 107.8, 116.3, 116.6, 119.1, 123.7, 125.2, 125.3, 130.3, 130.4, 131.1, 132.3, 140.9, 149.4,162.5, 165.5, 177.4.

**5. 2-*m*-*tolyl*quinolin-4(1*H*)one (3f)**[20]



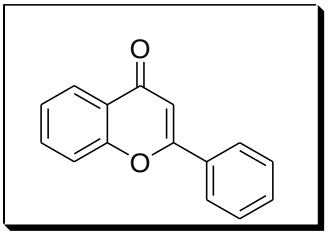
Brownish white solid, $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 2.44 (s, 3H), 6.32(s, 1H), 7.32-7.42 (m, 2H), 7.48 (t, *J* = 7.5Hz, 1H), 7.61-7.70 (m, 3H), 7.76-7.79 (m, 1H), 8.10 (d, *J* = 8.1Hz, 1H), 11.69(s, 1H); $^{13}$CNMR (DMSO-$d_6$, 75 MHz) δ 21.5, 107.7, 119.1, 123.6, 124.8, 125.0, 125.2, 128.3, 129.4, 131.5, 132.2, 134.7, 138.8, 141.0, 150.6, 177.5.

**6. 7-chloro-2-phenylquinolin-4(1*H*)-one (3g)**[18]



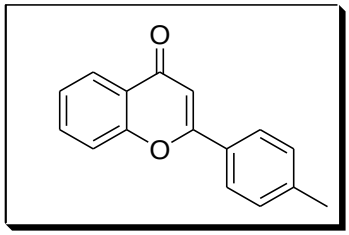
Tan powder, $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 6.38 (s, 1H), 7.37 (dd, *J* = 8.7Hz, 2.1Hz, 1H), 7.58-7.62 (m, 3H), 7.80-8.09 (m, 3H), 8.10 (d, *J* = 8.7Hz, 1H), 11.74 (s, 1H). $^{13}$CNMR (DMSO-$d_6$, 75 MHz) δ 104.1, 118.0, 119.2, 125.3, 128.3, 128.5, 129.3, 130.8, 132.7, 140.5, 141.3, 156.7, 169.9.

**7. 2-phenyl-4H-chromen-4-one (5a)**[21]



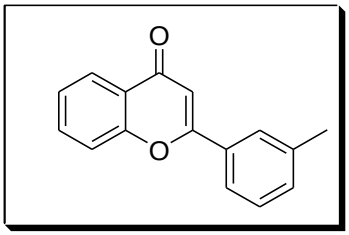
White solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 6.84 (s, 1H), 7.43 (dt, *J* = 8.1Hz, 1.2Hz, 1H), 7.53-7.60 (m, 4H), 7.68-7.71 (m, 1H), 7.92-7.96 (m, 2H), 8.24 (dd, *J* = 7.8Hz, 1.5Hz, 1H); $^{13}$CNMR ($CDCl_3$, 75 MHz) δ 107.6, 118.1, 124.0, 125.3, 125.7, 126.3, 129.1, 131.6, 131.8, 133.8, 156.3, 163.4, 178.5.

**8. 2-*p*-tolyl-4*H*-chromen-4-one (5b)**[22]



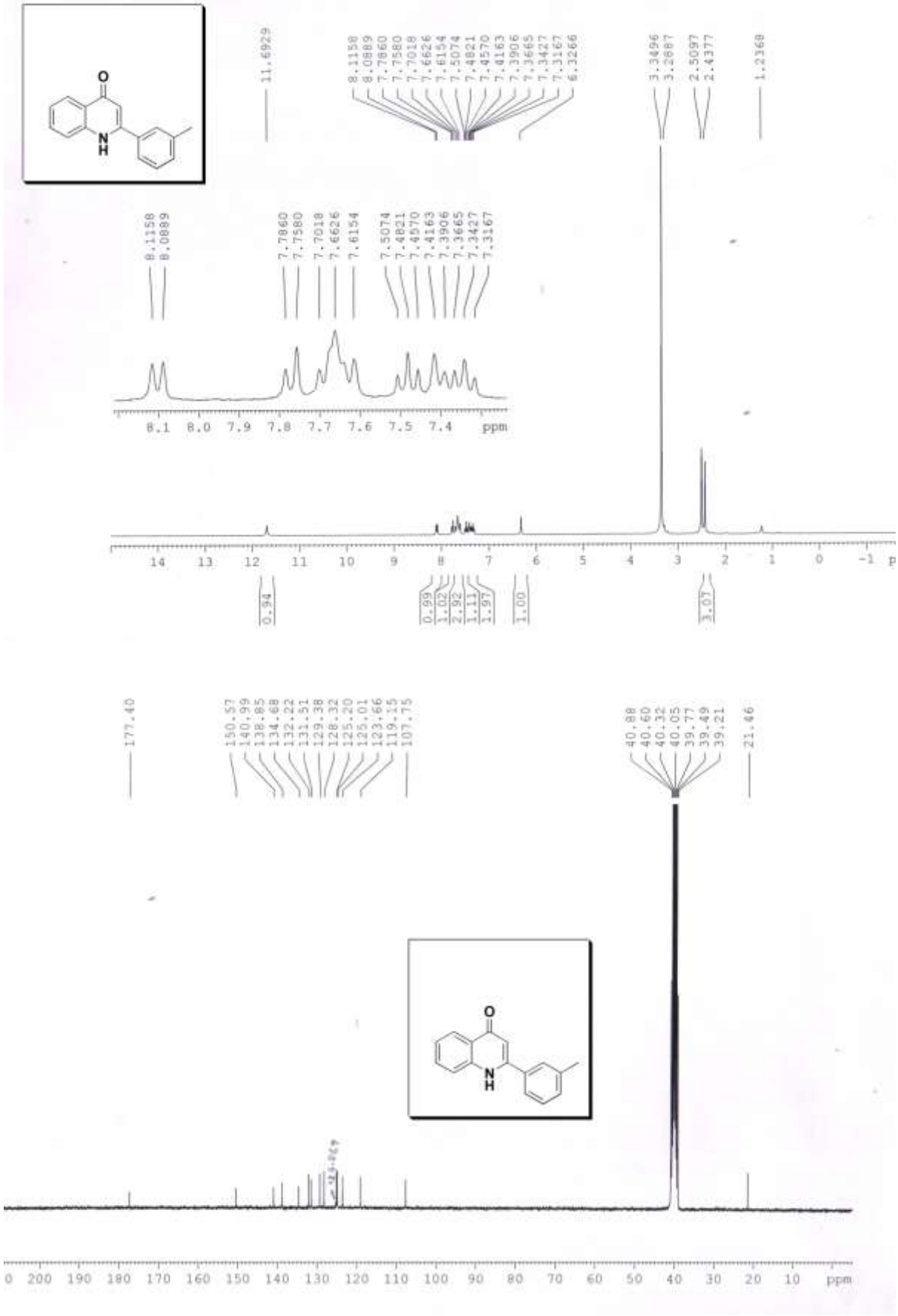
White solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 6.80 (s, 1H), 7.32 (d, *J*= 8.1Hz, 2H), 7.39-7.44 (m, 1H), 7.55-7.57 (m, 1H), 7.66-7.72 (m, 1H), 7.82 (d, *J*= 8.4Hz, 2H), 8.22 (dd, *J*= 7.8Hz, 1.2Hz, 1H); $^{13}$CNMR ($CDCl_3$, 75 MHz) δ 21.5, 107.0, 118.7, 124.0, 125.1, 125.7, 126.3, 129.0, 129.8, 133.7, 142.3, 156.3, 163.7, 178.5.

**9. 2-*m*-tolyl-4*H*-chromen-4-one (5c)**[19]

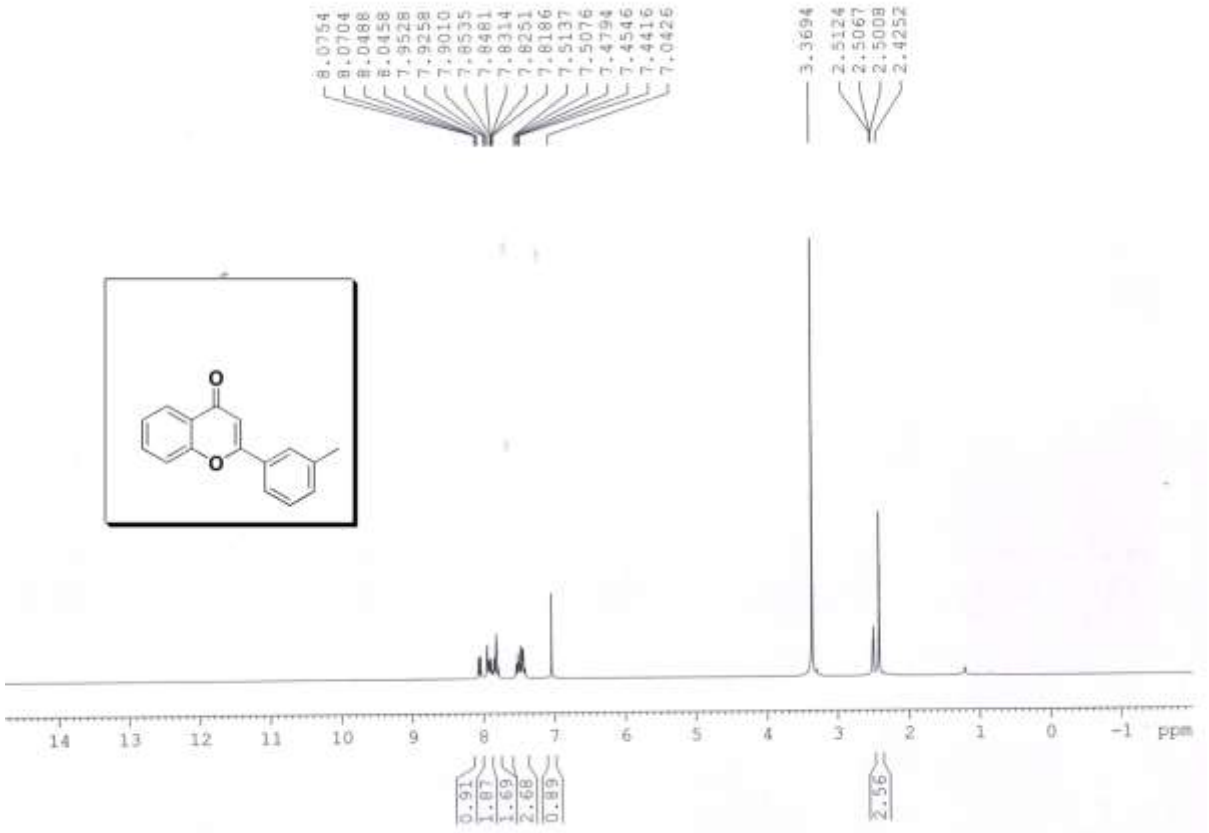


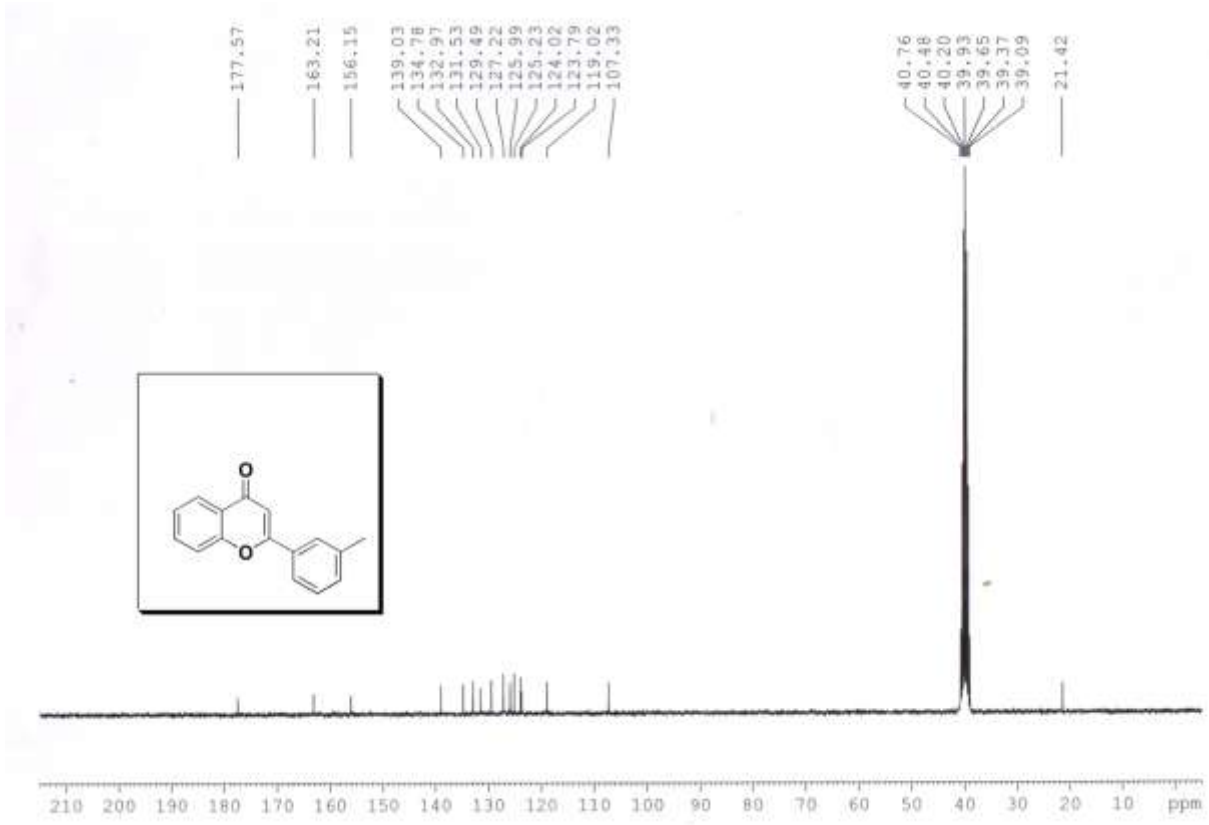
Pale yellow solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 7.04 (s, 3H), 7.44-7.51 (m, 3H), 7.82-7.85 (m, 2H), 7.90-8.04 (m, 2H), 8.07 (d, J = 1.5Hz, 1H); $^{13}$CNMR ($CDCl_3$, 300 MHz) δ 21.4, 107.3, 119.0, 123.8, 124.0, 125.2, 126.0, 127.2, 129.5, 131.5, 133.0, 134.8, 139.0, 156.1, 163.2, 177.6.

**$^{1}$H and $^{13}$C NMR spectra of entry 3f (Scheme-II.1.) in DMSO-$d_6$**



**$^{1}H$ and $^{13}C$ NMR spectra of entry 5c (Scheme-II.2.) in $CDCl_3$**



## II.E. References

References are given in BIBLIOGRAPHY under Chapter II (pp-227-229)

# Chapter III

# *Pd-NHC catalysed carbonylative Suzuki coupling reactions of aryl halides and arylboronic acids and its application towards the synthesis biologically active 4-quinolone scaffolds*

# III.A. Introduction

Biaryl ketones are found in numerous photosensitizers, advanced organic materials, natural products, and pharmaceutically apposite agents.[1] For instance Evista,[2] Tricor[3] and Sector[4], which contain biaryl ketone cores, are commonly prescribed medications, due to their extraordinary biological and therapeutic properties (e.g., in selective estrogen receptor modulation, cholesterol regulation, and anti-inflammation, respectively). Predictably, the development of methodologies towards the synthesis of functionally diverse biaryl ketones that are economical, practical, synthetically effective, and nonhazardous is of both great importance and interest to medicinal chemists. Traditionally, transition metal catalyzed cross-coupling methods, such as acylative Suzuki couplings, Friedel-Crafts acylations, and nucleophilic additions of an organometallic to a carbonyl moiety, are commonly used for the synthesis of aryl ketones. However, the cross coupling of arylboronic acids with carboxylic acid derivatives is far superior to these previous methods, not only with respect to the reaction's conditions and reagent compatibility, but also with regard to its regioselectivity and efficiency.[5] Bumagin and colleagues introduced Pd-catalyzed cross-coupling reactions of acid chlorides in 1997 for the synthesis of aryl ketones.[6] Later, this method was extended to acylative Suzuki couplings with anhydrides,[7] esters,[8] and carboxylic acids, in the presence of activating agents.[7c-9] More recently, a Pd-catalyzed thiol ester–boronic acid coupling towards the synthesis of biaryl ketones was developed by Liebeskind and Srogl.[10] Catalytic amount of Pd(0) salt and stoichiometric amount of Cu(I)TC [Copper(I)-thiophene-2-carboxylate], an expensive salt are essential requirements of this thioorganic–boronic acid coupling reaction.[10]

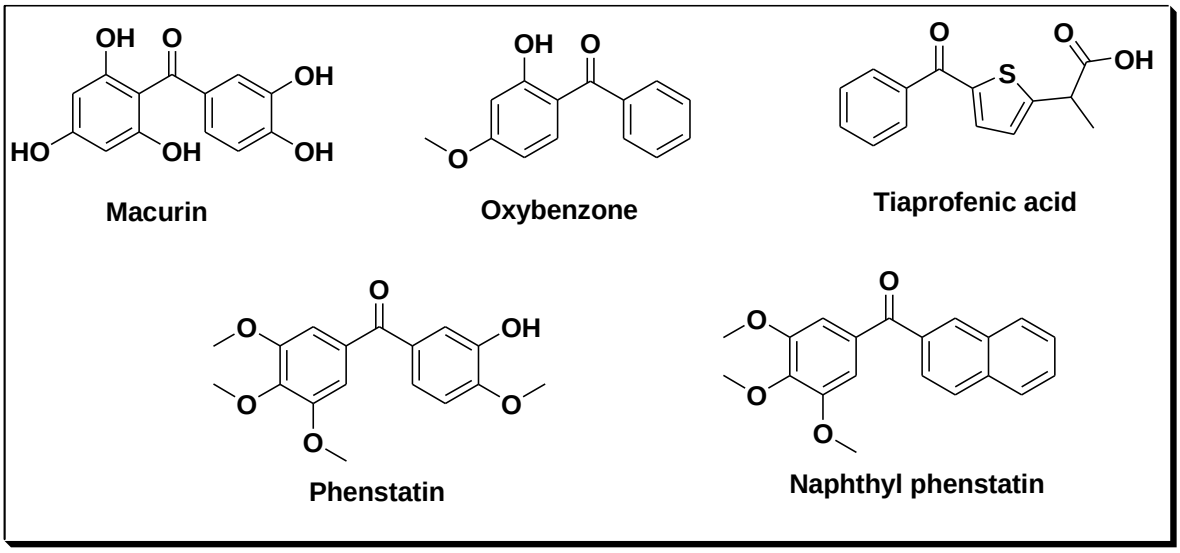
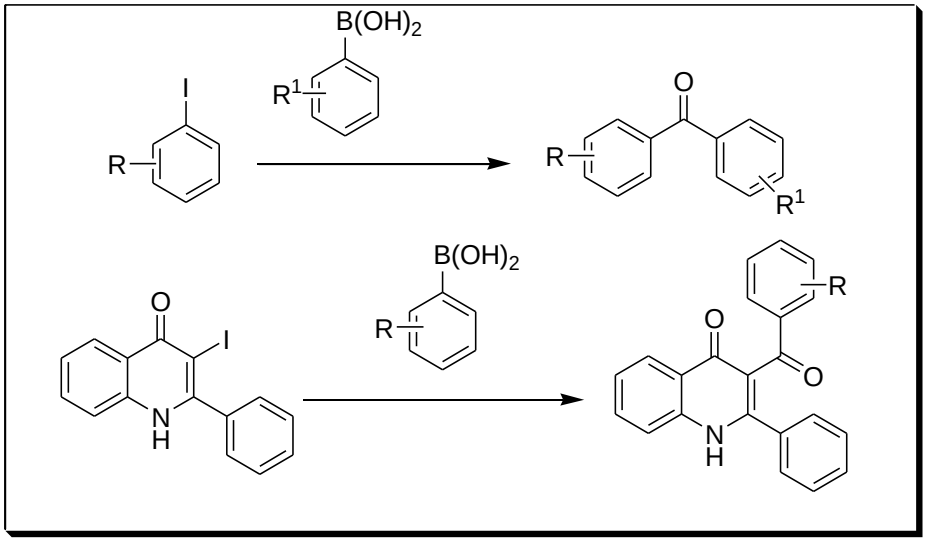



**Fig: III.1.** Some biologically active biaryl ketone compounds

**III. B. Present work: Background & Objective:**

However, the traditional transition metal catalysed carbonylative cross coupling reactions between aryl electrophiles, carbon monoxide and organometallic reagent is supposed to be the more convenient route for the synthesis of wide range of biaryl ketones. Several aryl metal reagents have been preferably used such as silicon[11], aluminium[12], tin [13]and magnesium [14]etc. The main disadvantage of this carbonylative cross coupling reaction is the formation several by products without carbon monoxide insertion, generally in the case of electron deficient aryl halides. Suzuki et.al firstly developed a facile protocol to synthesize the biaryl ketones from arylboronic acid, carbon monoxide and aryl halides in presence of palladium catalyst[15].In general, this method becomes quite effective due to the versatile nature of boronic acid which is non-toxic and stable to moisture and air. Afterwards, various research groups reported several methods for the synthesis of biaryl carbonyl scaffolds by using different palladium based catalyst such as $PdCl_2(PPh_3)_2$,[16]$PdCl_2(PPh_3)_2$/ $PdCl_2$(dppf),[17] $Pd(OAc)_2$-imidazolium salts,[18]$Pd(OAc)_2$/ N,N-bis(2,6-diisopropylphenyl)dihydroimidazolium chloride,[19] an MCM-41-supported bidentate phosphane palladium complex,[20] $Pd(OAc)_2$/di-1-adamantyl-n-butylphosphane[21][and Pd/thiourea,[22]. In spite of huge potential applicability, this method suffers from main disadvantage such as the use of air/moisture sensitive and expensive, phosphane donating ligands. Very recently, Bhanage et al. reported the Suzuki carbonylation of aryl and heterocyclic halides using palladacyle complex [23] and KCC-1supported palladium nanoparticles[24] using carbon monoxide gas as CO source. Applicability of CO gas at higher pressure reduces the formation of biaryl side products, but *insitu* generation of carbon monoxide in carbonylation process would much more effective in organic synthesis. In this context, several newly developed protocols are available in the literature such as formic acid, formates, formamides, chloroform, formic anhydride, and aldehydes, as well as metal carbonyls were used as CO source. Interestingly, the incorporation of carbon monoxide *via* metal carbonyl is much appealing and effective than any other methods.

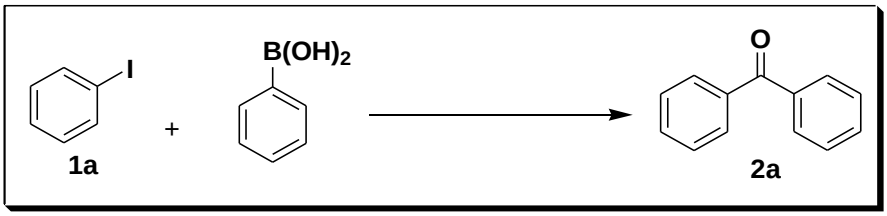



**Scheme-III.1.** Approach for the Biaryl ketones synthesis

Preliminary, we have focused our approach to insert the CO in situ in carbonylation process by using simple molybdenum hexacarbonyl as a solid handling reagent. Previously, Jafarpour et.al also reported the carbonylative Suzuki coupling of aryl halides and aryl boronic acid in presence of $Mo(CO)_6$ and Palladium acetate.[25]However, this method generally suffers from various disadvantages such as use high loading Pd catalyst (10 mol%), longer reaction time and high temperature. As a part of our ongoing efforts to develop the simple protocol for the formation of C-C bond, C-hetero atom bond formation, herein we explore the methodology of carbonylative Suzuki coupling reaction in between different aryl halides and arylboronic acids by using our pre-synthesized Pd-NHC[26] catalyst in low catalyst loading. Further, we apply this protocol to the biologically active 4-quinolone scaffold for developing its better pharmacokinetic properties. Our approach is free from microwave heating as well as using of toxic carbon monoxide gas.

### III.B.1. Present work: Results and Discussion

**Table-III.1. Optimization of the reaction condition for the carbonylative Suzuki coupling**



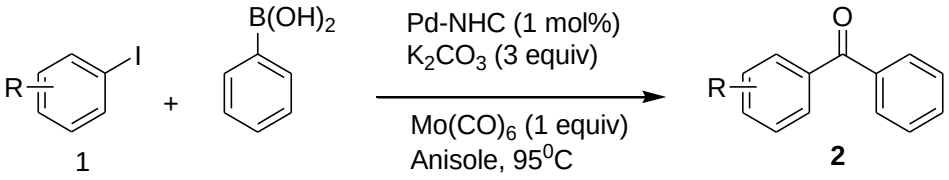

| entry | Catalyst (mol %) | solvent | Base (equiv) | Temp (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | Pd-NHC 1 | DMF | $K_2CO_3$ | 95 | 24 | 15 |
| 2 | Pd-NHC 1 | THF | $K_2CO_3$ | 95 | 24 | 20 |
| 3 | Pd-NHC 1 | 1,4-dioxane | $K_2CO_3$ | 95 | 24 | NR |
| **4** | **Pd-NHC 1** | **anisole** | **$K_2CO_3$** | **95** | **1** | **85** |
| 5 | Pd-NHC 1 | toluene | $K_2CO_3$ | 95 | 24 | 30 |
| 6 | Pd-NHC 1 | anisole | t-BuOK | 95 | 24 | 10 |
| 7 | Pd-NHC 1 | anisole | DBU | 95 | 24 | NR |
| 8 | Pd-NHC 1 | anisole | $Cs_2CO_3$ | 95 | 24 | 10 |
| 9 | Pd-NHC 1 | anisole | $Et_3N$ | 95 | 24 | 25 |
| 10 | $Pd(OAc)_2$ 5 | anisole | $K_2CO_3$ | 95 | 7 | 64 |
| 11 | $PdCl_2$ 5 | anisole | $K_2CO_3$ | 95 | 7 | 68 |
| 12 | $Pd_2(dba)_3$ 5 | anisole | $K_2CO_3$ | 95 | 7 | 73 |
| 13 | Pd-NHC 1 | anisole | $K_2CO_3$ | 80 | 4 | 65 |
| 14 | Pd-NHC 1 | anisole | $K_2CO_3$ | 60 | 12 | 52 |
| 15 | Pd-NHC 1 | anisole | $K_2CO_3$ | 120 | 1 | 84 |

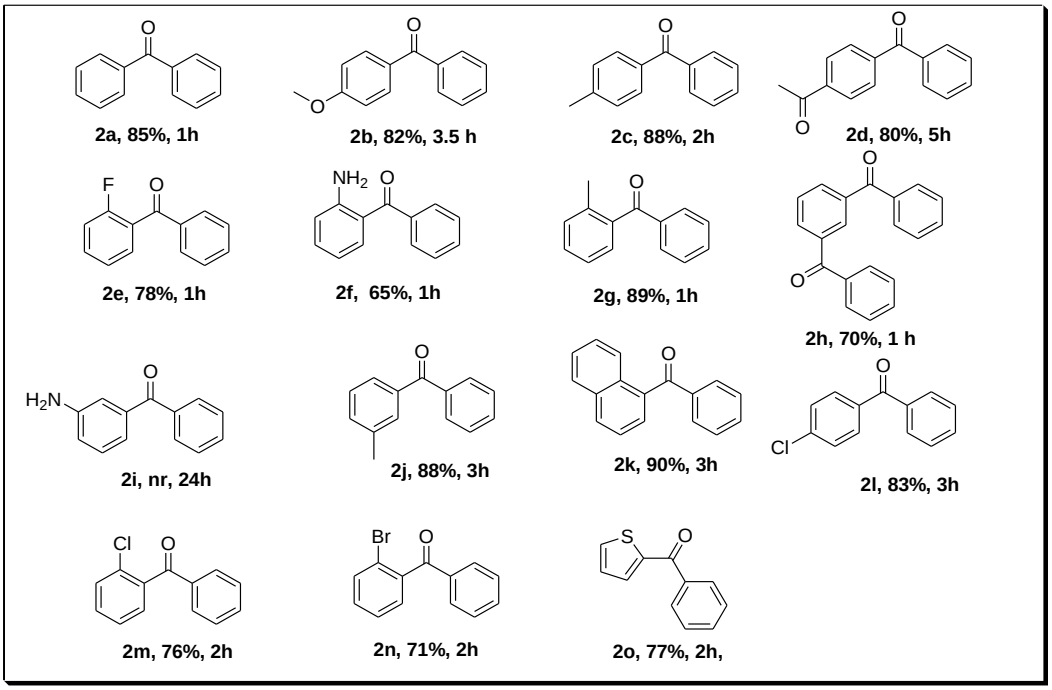
**Reaction conditions**: 0.25 mmol of iodobenzene, 0.375 mmol of phenylboronic acid, base (3 equiv), $Mo(CO)_6$ (1 equiv), were heated . Yield = Isolated yields.

To investigate the feasibility of the reaction, we commenced our journey *via* the carbonylative cross coupling reactions in between phenylboronic acid and iodobenzene using Pd-NHC (1 mol%) as catalyst in DMF in presence of $K_2CO_3$. However, only 15% yield of the desired biaryl ketone was obtained (Table-III.C.1; entry-1). Next, we screened the different solvents (Table-III.C.1; entry-1-5). Anisole as a solvent media served the better yields of

biaryl ketone whereas other solvents such as DMF, Toluene, 1, 4-dioxane and THF led to the biaryl as a predominant product. The combination of $K_2CO_3$/anisole proved to be the most suitable combination as base/ solvent for the carbonylative Suzuki coupling (Table-III.C.1; entry-4). Most surprisingly, the reaction completed within 1h only and yielded 85% of the desired product. We next turned our attention to choose the better base other than $K_2CO_3$. Inferior results of desired product was obtained by using several bases such as DBU, t-BuOK, $Cs_2CO_3$ and $Et_3N$ (Table-III.C.1; entry-6-9). Further, we evaluated the catalytic activity of different palladium catalyst but not getting so much promising result as Pd-NHC (Table-III.C.1; entry 10-12). Rather, we also optimize the temperature and 95°C gave the best result (Table-III.C.1; entry-4). By lowering the temperature, the yield of the biaryl ketone decreases due to the low liberation of carbon monoxide (Table-III.C.1; entry 13, 14). By comparison, the same reaction, at 120°C resulted in only 84% yield of **2a** after 1h also (Table-III.C.1; entry 15). Eventually, the combination of Pd-NHC (1mol %) and $K_2CO_3$ (3 equiv), in DMF at 95 °C, was found to be optimal for the coupling of iodobenzene and arylboronic acids, leading to benzophenone in high yield (85%) after only 1h.

**Scheme-III.2.** Scope of various iodobenzene in the carbonylative Suzuki coupling

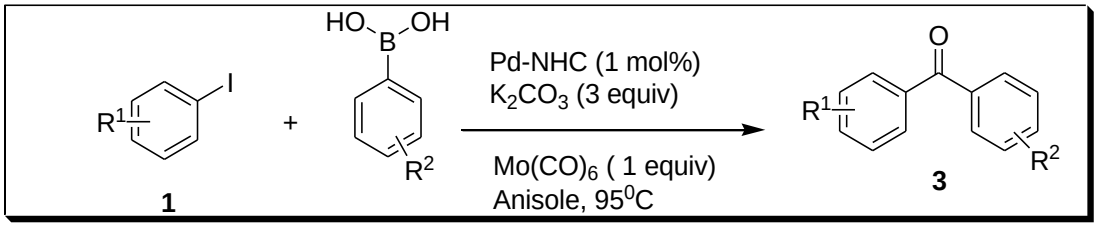


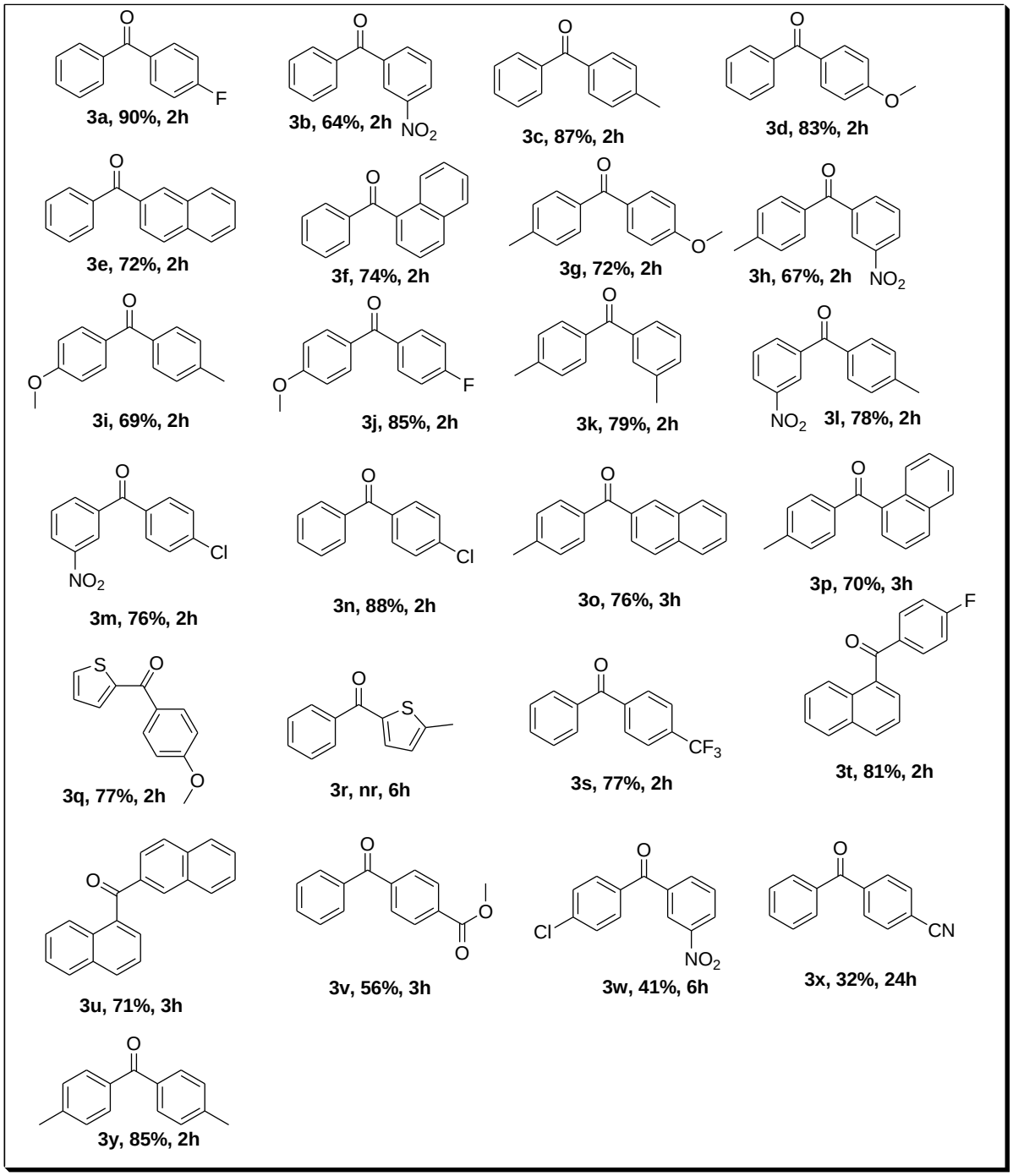



**Reaction conditions**: 0.25 mmol of various iodoarenes, 0.375 mmol of phenylboronic acid, base (0.75mmol,104mg) and Pd-NHC (3mg, 1mol%), $Mo(CO)_6$ (1 equiv), were heated in anisole . Yield = Isolated yield after column chromatography.

Encouraged by the above observation, the scope of the reaction with a broad range of aryl iodide was explored. Various iodoarenes possessing both electron withdrawing and electron releasing group participated in the reaction very well and afforded moderate to excellent yields (scheme-III.2; entry **2a-2o**). Iodobenzene reacted with phenyl boronicacid in a short span of time and resulted in 85% yield of benzophenone. Employment of *p*-methoxy and *p*-methyl substituted iodobenzene in carbonylative Suzuki coupling led to the promosing yield of the desired product (scheme-III.2, entry **2b, 2c**). 4-iodocetophenone took longer time and resulted 80% yield of the desired product. (scheme-III.2, entry **2d).** We also covered the aspect of steric hindrance in making the biaryl ketones via this coupling reaction. Such as ortho substituted -F, $-NH_2$,-Cl,-Br and –Me groups afforded the corresponding biaryl ketones in moderate to good yields respectively (scheme-III.2, entry **2e, 2f, 2g, 2m, 2n**). Whereas bulky 1-naphthyl iodoarenes responded very well and yielded 90% yield of the desired product in just 1h only. Nevertheless, 3-iodotoluene proved to be a good coupling partner for this coupling methodology (scheme-III.2, entry-**2j**). Surprisingly, 3-iodo aniline did not afford the corresponding biaryl ketone over 24h stirring (scheme-III.2, entry **2i**). Heterocyclic iodoarene (2-iodothiophene) was very prone to undergo the reaction and resulted 77% yield of the corresponding product (scheme-III.2, entry-**2o)**.

**Scheme-III.3.** Substrate scope of various iodoarenes and aryl(Het)boronic acid



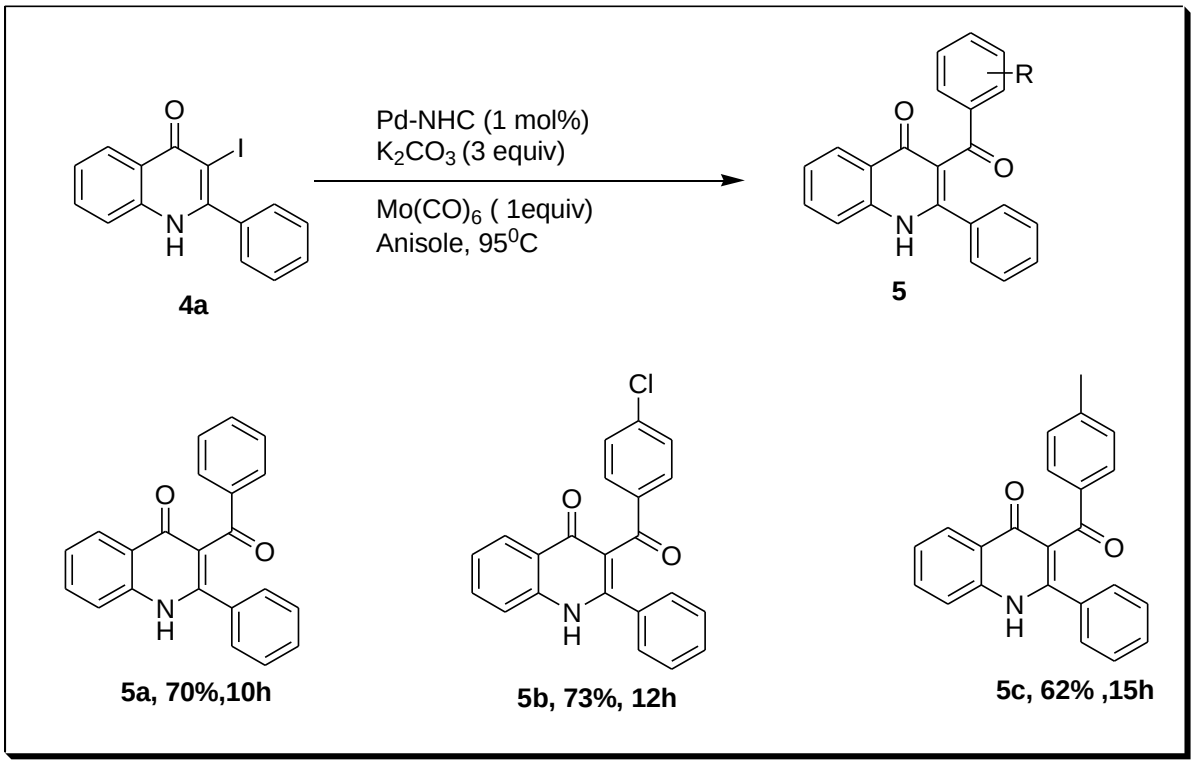



**Reaction conditions**: 0.25 mmol of various iodobenzene, 0.375 mmol of substituted arylboronic acid, base (3 equiv) and Pd-NHC (3mg, 1mol%), $Mo(CO)_6$ (66mg, 1 equiv), were heated in anisole . Yield = Isolated yields.

To further investigate the scope, we extensively surveyed the carbonylative Suzuki coupling with various iodoarenes and arylboronic acids under our optimized reaction condition. A broad array of arylboronic acid possessing both electron donating and electron releasing group were well tolerated in this reaction. Our protocol was quite compatible with various functional groups like methoxy, chloro, fluoro, ester and cyano. Bulky naphthylboronic acid (1-naphthyl and 2-naphthyl) were quite effectively coupled with iodobenzene and 4-

iodoarenes and afforded the desired products with much higher yields (scheme-III.3; entry **3e**, **3f**, **3o**, **3p**). We were also pleased to find that a heterocyclic iodoarenes (2-iodo thiophene) coupled with 4-methoxyphenyl boronic acid effectively (scheme-III.3; entry-**3q**). Importantly, 1-iodonaphthalene quite successfully underwent the carbonylative Suzuki coupling with 2-naphthylboronic acid and 4-fluoro phenylboronic acid (scheme-III.3; entry **3t**, **3u**). Surprisingly, 4-cyano phenylboronic acid afforded only 32% yield of the desired biaryl ketone when it coupled with normal iodobenzene (scheme-III.3; entry **3x**). To our delight, iodoarene possessing nitro group at meta position did not hamper the process and coupled with both electron deficient and electron rich arylboronic acid (scheme-III.3; **3l**, **3m**). More interestingly, 4-iodotoluene coupled with *p*-tolylboronic acid excellently and furnished the corresponding product **3y** (85%) in a very short span.

**Scheme-III.4.** Scope of the carbonylative Suzuki coupling in 4-quinolone scaffold




**Reaction conditions**: 0.25 mmol of 3-iodo substituted 4-quinolone (86mg), 0.375 mmol of substituted arylboronic acid, base (3 equiv) and Pd-NHC (3mg, 1mol%), $Mo(CO)_6$ (66mg, 1 equiv), were heated in anisole . Yield = Isolated yields.

Next, we explored the scope of the reaction into the biologically active 4-quinolone scaffold. Very recently, Alfonsi et.al synthesized the 3-Aroylquinolin-4(1*H*)-ones which act as a inhibitors of the Hedgehog Signaling Pathway.[27]3-iodo-2-aryl substituted 4-quinolone participated well in this carbonylative Suzuki coupling. Both electron withdrawing and electron donating arylboronic acid effectively underwent the reaction and resulted in the desired products respectively (scheme-III.4; entry **5b** and **5c**).

## III.C. Conclusion

In summary, we have developed a simple mild protocol for the synthesis of biaryl ketones via carbonylative Suzuki coupling. Notably, this method offers various advantages such as free of toxic CO gas, shorter reaction time, good to excellent yield of the desired product and broad substrate scope availability. Several functional groups (-COMe, -COOMe,-F,_Cl) were well tolerated in this reaction. This approach was quite effective in the biological active 4-quinolone scaffold to synthesize the 3-Aroylquinolin-4(1*H*)-ones.

## III.D. Experimental section:

### III.D.1. General Information:

Unless stated otherwise, all reagents such as various Iodoarenes, aryl(Het)boronic acid, $K_2CO_3$, Anisole, $Mo(CO)_6$ and solvents were used as received from commercial suppliers. NMR spectra were recorded on 300 MHz spectrometer at 298 K with calibration done on the basis of solvent residual peak. Products were purified using column chromatography on silica gel (60-120 mesh). Ethyl acetate and petroleum ether ($60\text{-}80^0$C) were used as eluents. Progress of reaction was monitored using silica gel TLC.

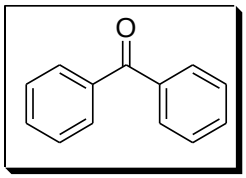
### III.D.2. Preparation of Biaryl ketones from the carbonylative Suzuki coupling of various iodoarenes and arylboronic acids:

Initially, various iodoarenes (0.25 mmol), aryl(Het) boronicacid (0.375 mmol), $K_2CO_3$ (0.75 mmol, 103.5 mg) $Mo(CO)_6$ (0.25 mmol, 66mg), Pd-NHC (1 mol%, 2.5mg) and anisole (2 ml) were taken in a sealed tube under $N_2$ atmosphere and heated at 95°C. The reaction was continued for 1h to several hours for completion of the reaction. After monitoring the TLC analysis, the reaction mixture was diluted with 30 ml water and the organic layer was extracted with DCM (30 ml). Then, it was dried over anhydrous sodium

sulphate and concentrated under reduced pressure. The crude residue was purified through column chromatography using pet.ether and ethyl acetate as an eluents.

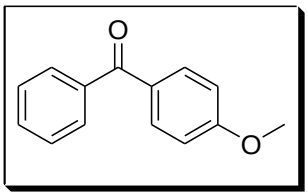
**III.D.3. Physical characteristics and spectral data of compounds:**

1**. Benzophenone (2a)**[28]



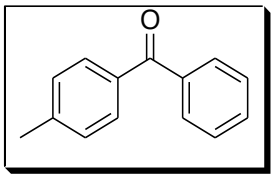
White solid, Melting point: 47-48 °C, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.47-7.53 (m,4H), 7.58-7.64 (m, 2H), 7.80-7.84 (m, 4H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 128.3, 130.1, 132.4, 137.6, 196.8.

**2**. **(4-methoxy phenyl) phenyl methanone (2b and 3d)**[28]



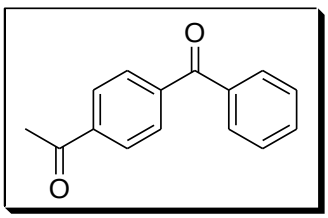
White solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 3.89 (s, 3H), 6.95-6.98 (m, 2H), 7.44-7.49 ( m, 2H), 7.53-7.59 (m, 1H), 7.73-7.76 ( m, 2H), 7.77-7.84 ( m, 2H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 55.5, 113.6, 128.2, 129.7, 130.2, 131.9, 132.5, 138.3, 163.2, 195.6.

**3**. **Phenyl (*p*-tolyl)methanone (2c and 3c)**[28]



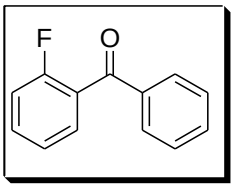
White solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 7.26-7.30 (m, 2H), 7.44-7.50 (m, 2H), 7.54-7.60 (m,1H), 7.70-7.74 (m, 2H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 21.6,128.3, 129.0, 129.9, 130.3, 132.1, 134.9, 138.0, 143.2, 196.5.

**5. 1-(4-Benzoylphenyl)ethan-1-one** (2d)[29a]



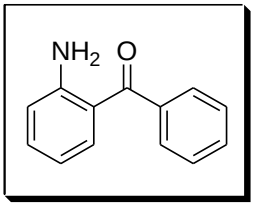
yellow oil, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.69 (s, 3H), 7.50-7.55 (m, 2H), 7.62-7.65 (m, 1H), 7.81-7.84 (m, 2H), 7.87-7.90 (m, 2H), 8.07-8.09 (m, 2H),$^{13}$C NMR ($CDCl_3$, 75 MHz) δ 26.8, 128.1, 128.4, 130.0, 130.1, 132.9, 136.9, 139.6, 141.4, 195.9, 197.5.

**6. (2-fluoro phenyl)(phenyl)methanone (2e)**[30]



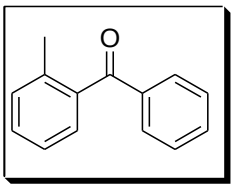

Liquid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.53-7.57 (m, 2H), 7.69-7.73 (m, 1H), 7.82 (s, 2H), 7.93 (s, 2H), 8.20 (d, *J* = 8.0Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 124.0, 125.3, 128.8, 129.0, 130.6, 134.8, 134.9, 162.0, 189.6.

**7. (2-aminophenyl)(phenyl)methanone (2f)**[30]



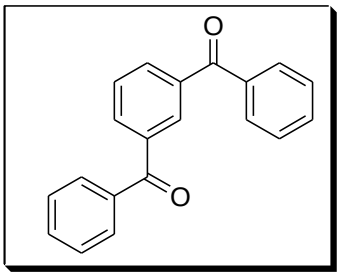

Yellow solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 6.00 (s, 2H), 6.57-6.72 (m, 1H), 6.73-6.75 (m, 1H), 7.26-7.32 (m, 1H), 7.43-7.65 (m, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 115.5, 117.0, 118.2, 128.1, 129.1, 131.1, 134.2, 134.6, 140.1, 150.9, 199.1.

**8. phenyl(o-tolyl)methanone (2g)**[28]



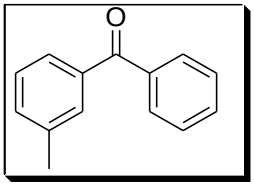

Colorless liquid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 7.24-7.35 (m, 3H), 7.37 (t, *J* = 7.5Hz, 1H), 7.44 (t, *J* = 7.5Hz, 2H), 7.57 (t, *J* = 7.5Hz, 1H), 7.78 (d, *J* = 7.5Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 19.5, 124.7, 127.8, 128.1, 129.5, 129.7, 130.5, 132.7, 136.3, 137.3, 138.3, 197.9.

**9. (2h)** [28]



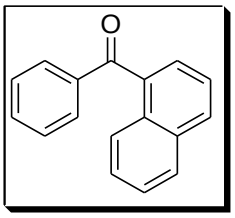
White solid, $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 7.57-7.62 (m, 1H), 7.68-7.70 (m, 3H), 7.79-7.82 (m, 4H), 8.00-8.04 (m, 1H), 8.05-8.08 (m, 2H), $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 129.1, 129.7, 130.2, 131.2, 133.5, 133.9, 136.9, 137.5, 195.5.

**10. Phenyl (m-tolyl)methanone (2j)[28]:**



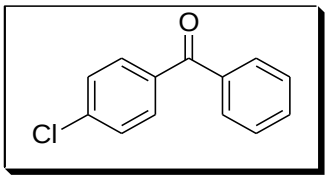
Colourless liquid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 7.39-7.40 (m 2H), 7.49-7.51 (m, 2H), 7.57-7.64 (m, 3H), 7.79-7.82 (m, 2H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 20.8, 126.8, 127.6, 127.7, 129.5, 130.0, 131.8, 132.6, 137.2, 137.3, 137.6, 196.4.

**11. (Naphthalen-2-yl)(phenyl)methanone (2k and 3f)[28]**:



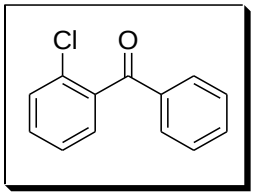
Colourless oil, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.64 (m, 7H), 7.88-7.97 (m, 3H), 8.01-8.03 (m, 1H), 8.10-8.14 (m,1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 124.4, 125.7, 126.5, 127.3, 127.97, 128.4, 128.51, 130.5, 131.0, 131.4, 133.3, 133.7, 138.3, 198.1.

**12. (4-chloro phenyl)(phenyl) methanone (2l and 3n)[28]**



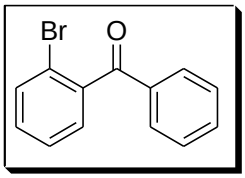
White solid, 1H NMR ($CDCl_3$, 300 MHz) δ 7.44-7.52 (m, 4H), 7.58-7.63 (m, 1H), 7.74-7.79 (m, 4H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 128.4, 128.6, 129.9, 131.5, 132.6, 135.9, 137.2, 138.9, 195.2.

**13.** ( **2-chlorophenyl)phenyl methanone (2m)[30]:**



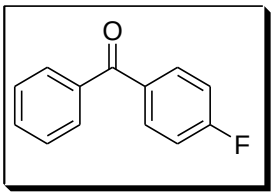

Colourless oil, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.83-7.85 (d, *J* =7.8 Hz, 2H), 7.60-7.65 (t, *J* =7.5 Hz, 1H), 7.46-7.51 (m, 4H), 7.38-7.44 (m, 2H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 129.1, 128.6, 126.7,128.6, 129.1, 130.1, 130.2, 131.1, 131.3, 133.7, 136.4, 138.5, 195.4.

**14. (2-bromophenyl)(phenyl)methanone (2n)[31]:**



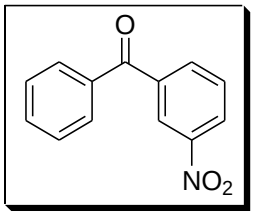

Yellow solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.50 (m, 5H), 7.58-7.66(m, 2H), 7.80-7.83(m, 2H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 119.5, 127.2, 128.6, 129.0, 130.2, 131.2, 133.2, 133.8, 136.1, 140.7, 195.9.

**15**. **4-Fluoro phenyl) phenyl methanone (3a)[31]**



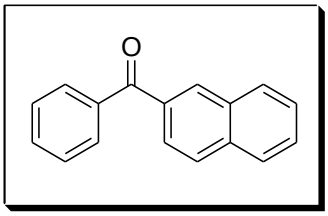

Yellow oil, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.13-7.20 (m, 2H), 7.46-7.51 (m, 2H), 7.57-7.62 (m, 1H), 7.75-7.79 (m, 2H), 7.82-7.87 (m, 2H),$^{13}$C NMR ($CDCl_3$, 75 MHz) δ 115.3, 115.6, 127.5, 128.3, 128.7, 129.2, 129.8, 132.4, 132.6, 132.7, 133.8, 137.5, 163.7, 167.1, 195.2.

**16. (3-nitrophenyl)(phenyl)methanone (3b)[32]**:



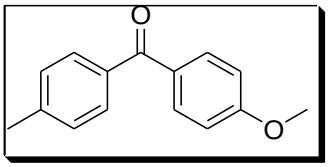

Yellow solid; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.53-7.57 (m, 2H), 7.64-7.74 (m, 2H), 7.79-7.83 (m, 2H), 8.15 (td, *J*= 3.0 Hz, 1.2Hz, 1H), 8.45 (m, 1H), 8.62 (t, *J*=1.8Hz, 1H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 124.3, 126.3, 128.3, 129.2, 129.6, 133.0, 135.0, 138.7, 147.7, 193.7.

**17. (Naphthalen-3-yl)(phenyl) methanone (3e)**[28]



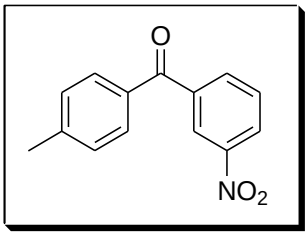
White solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.41-7.60 (m, 7H), 7.84-7.92 (m, 3H), 7.97-7.99 (m,1H), 8.07-8.10 (m, 2H),$^{13}$C NMR ($CDCl_3$, 75 MHz) δ 124.4, 125.7, 126.5, 127.3, 127.8, 128.4, 128.5, 130.4, 131.0, 131.3, 133.3, 133.7, 136.4, 138.3, 198.1.

**18. 4-methoxy phenyl(p-tolyl) methanone (3g & 3i)**[28]



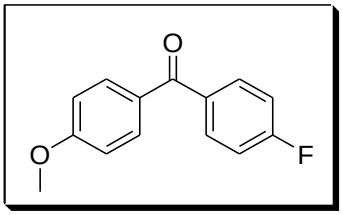
White solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.88 (s, 3H), 6.95 (dt, *J* =4.8Hz, 2.7Hz, 2H), 7.26-7.29 ( m, 2H), 7.67 (dd, *J*=8.1Hz, 1.8Hz, 2H), 7.78-7.82 (m, 2H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 21.6, 55.5, 113.5, 128.9, 130.0, 130.5, 132.5, 135.5, 142.6, 163.0, 195.4.

**19. (3-nitrophenyl)(p-tolyl)methanone (3h and 3l)**[33]



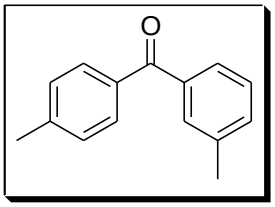
Yellow solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.47 (s, 3H), 7.32-7.34 (m, 2H), 7.67-7.73 (m, 3H), 8.12 (td, *J* =2.7Hz, 1.5Hz, 1H), 8.43 (qd, *J* = 3.6Hz, 1.2Hz, 1H), 8.60(t, *J* =1.8Hz, 1H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 21.7, 124.6, 126.4, 129.4, 129.5, 130.2, 133.6, 135.3, 139.5, 144.4, 148.1, 193.8.

**20. (4-fluorophenyl)(4-methoxyphenyl)methanone (3j)**



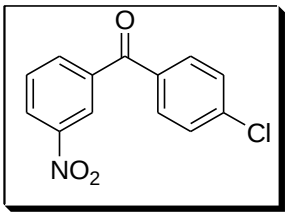
White solid, $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 7.08-7.11(m, 2H), 7.38 (dt, *J* = 6.9Hz, 1.8Hz, 2H), 7.72-7.79 (m, 2H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 56.0, 114.4, 115.8, 116.1, 129.7, 132.6, 132.7, 134.6, 134.7, 163.1,163.4, 166.4, 193.5.

**21. *m*-tolyl(*p*- tolyl) methanone (3k)**[34]



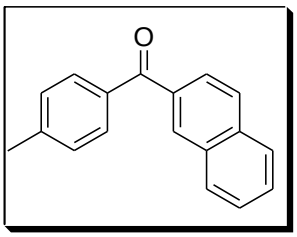

White solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 7.25-7.38 (m, 4H), 7.53-7.60 ( m, 2H), 7.70-7.73 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 21.4, 21.6, 127.2, 128.0, 128.9, 130.3, 130.3, 132.9, 135.1, 138.0, 138.1, 143.1, 196.7.

**22. (4-chloro phenyl)(m-nitro) methanone (3m)**[35]



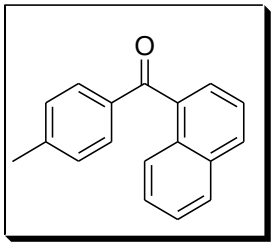

Yellow solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.51(td, *J*=4.2Hz, 2,1Hz, 2H), 7.70-7.78 (m, 3H), 8.12 (td, *J* =3.0Hz, 1.5Hz, 1H), 8.46 (qd, *J* =2.4Hz, 1.2Hz, 1H), 8.59 (t, *J*=1.8Hz, 1H),$^{13}$C NMR ($CDCl_3$, 75 MHz) δ 124.6, 126.9, 129.1, 129.4, 129.8, 131.4, 134.5, 135.3, 138.7, 140.0, 148.1, 193.0.

**23. (Naphthalen-2-yl)(*p*-tolyl)methanone (3o)**[36]



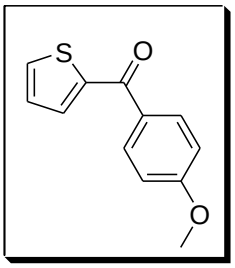

White solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.47 (s,3H), 7.32 (d, *J*=8.1Hz, 2H), 7.54-7.63 (m, 2H), 7.78 (dd, *J*=1.8Hz, 2H), 7.90-7.93 (m, 4H), 8.25 (s, 1H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 21.7, 125.9,126.7, 127.8, 128.1, 128.2, 129.1, 129.4, 130.4, 131.5, 132.4, 135.2, 135.3, 143.2, 196.5.

**24.** (**Naphthalen-1-yl)(*p*-tolyl)methanone (3p)**[28]**



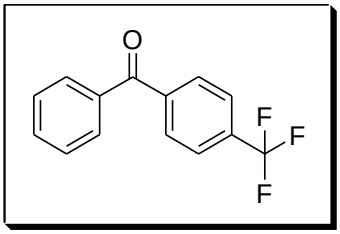

White solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.41(s, 3H), 7.22-7.25 (m, 2H), 7.44-7.56 (m, 4H), 7.77 (d, *J*=8.1Hz, 2H), 7.90 (dd, *J*=7.5Hz, 2.4Hz, 1H), 7.96-7.98 (m, 1H), 8.02-8.06 (m, 1H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 21.8, 124.4, 125.7, 126.4, 127.1, 127.4, 128.4, 129.2, 130.6, 130.9, 131.0, 133.7, 135.7, 136.8, 144.2, 197.8.

**25. (4-methoxyphenyl)(thiophen-2-yl)methanone (3q)**[24]



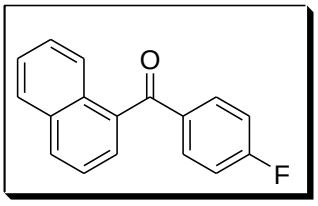

white solid, $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 3.89 (s, 3H), 6.99 (dd, *J* = 4.8Hz, 2.1Hz, 2H), 7.14-7.17 (m, 1H), 7.64-7.70 (m, 2H), 7.90 (dd, *J* = 4.8 Hz, 2.1Hz, 2H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 55.5, 113.7, 127.8, 130.7, 131.6, 133.4, 134.0, 143.8, 163.1, 186.9.

**26. 4-trifluoromethyl-benzophenone (3s)**[31]




white solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.51 (t, *J* = 7.5Hz, 2H), 7.64 (t, *J* = 7.2Hz, 1H), 7.75 (d, *J* = 8.4Hz, 2H), 7.81 (d, *J* = 7.2Hz, 2H), 7.90 (d, J = 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 123.7, 125.4, 128.5, 130.1, 133.1, 133.7, 136.7, 140.7, 195.6.

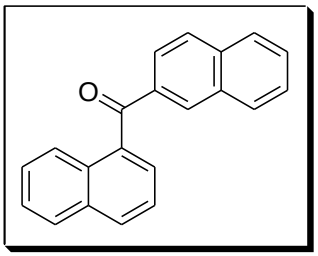
**27. (4-fluorophenyl)(naphthalene-4-yl)methanone (3t)**[23]




white solid, $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 7.35-7.41 (m, 2H), 7.55-7.64 (m, 4H), 7.83-7.92 (m, 3H), 8.06-8.09 (m, 1H), 8.16-8.19 (m,1H); $^{13}$C NMR

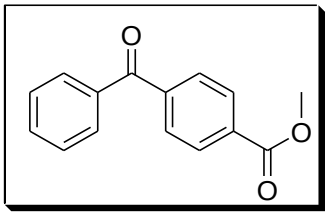
(DMSO-$d_6$, 75 MHz) δ 116.3, 116.5, 125.2, 126.2, 127.1, 127.9, 128.6, 129.1, 130.5, 131.7, 133.3, 133.4, 133.7, 134.7, 134.7, 136.0, 164.0, 167.3, 196.2.

**28. (napthalen-2-yl)(napthalen-5-yl)methanone (3u)**[37]



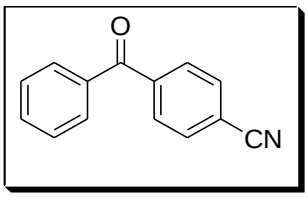

white solid; $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.48-7.54 (m, 4H), 7.57-7.66 (m, 2H), 7.83 (d, *J* = 8.1Hz, 1H), 7.89-7.97 (m, 3H), 8.03-8.13 (m, 3H), 8.24 (s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 124.4, 125.4, 125.7, 126.5, 126.8, 127.3, 127.7, 127.8, 128.4, 128.5, 128.7, 129.7, 131.0, 13 1.2, 132.4, 132.9, 133.8, 135.6, 135.7, 136.6, 198.0.

**29. Methyl-4-benzoylbenzoate (3v)**[29b].



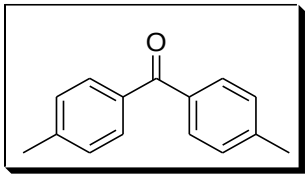

white solid, $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.96 (s, 3H), 7.47-7.52 (m, 2H), 7.59-7.61 (m, 1H), 7.78-7.85 (m, 4H), 8.13-8.16 (m, 2H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 52.5, 128.5, 129.5, 129.8, 130.2, 133.0, 133.2, 136.9, 141.3, 166.3, 196.0.

**30. (4-cyano phenyl) (phenyl) methanone (3x)**[28]



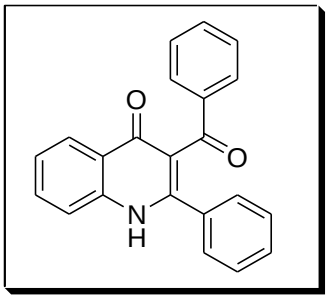

White solid, $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.49-7.54 (m, 2H), 7.62-7.64 (m, 1H), 7.71-7.81(m, 4H), 7.86-7.89 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 115.7, 118.0, 128.6, 130.1, 130.2, 132.2, 133.3, 136.3, 141.2, 195.0.

**31. di(*p*-tolyl)methanone (3y)**[28]



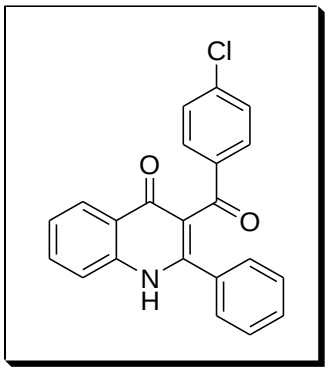
White solid, $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 6H), 7.26 (d, J = 8.4Hz, 4H), 7.70 (d, J = 8.1Hz, 4H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 21.5, 128.8, 130.1, 135.2, 142.8, 196.2.

**32. 3-benzoyl-2-phenyl-quinolin-4-(1*H*)-one (5a)** [38]



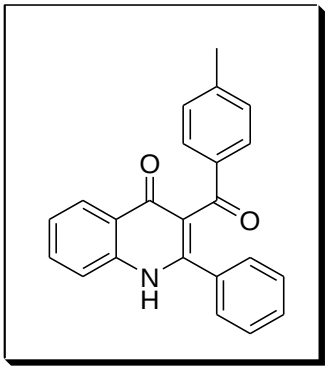
white solid, melting point:>260°C; $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 7.38-7.53 (m, 8H), 7.56 (t, *J* = 7.5Hz, 1H), 7.75-7.79 (m, 4H), 8.10 (d, *J* = 8.1Hz, 1H), 12.2 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 119.3, 120.7, 124.5, 125.2, 125.3, 128.9, 129.0, 129.1, 129.4, 130.5, 132.9, 133.5, 134.0, 138.4, 140.3, 149.9, 175.5, 196.2.

**33. 3-benzoyl-(4-chlorophenyl)-quinolin-4-(1*H*)-one (5b)** [38]



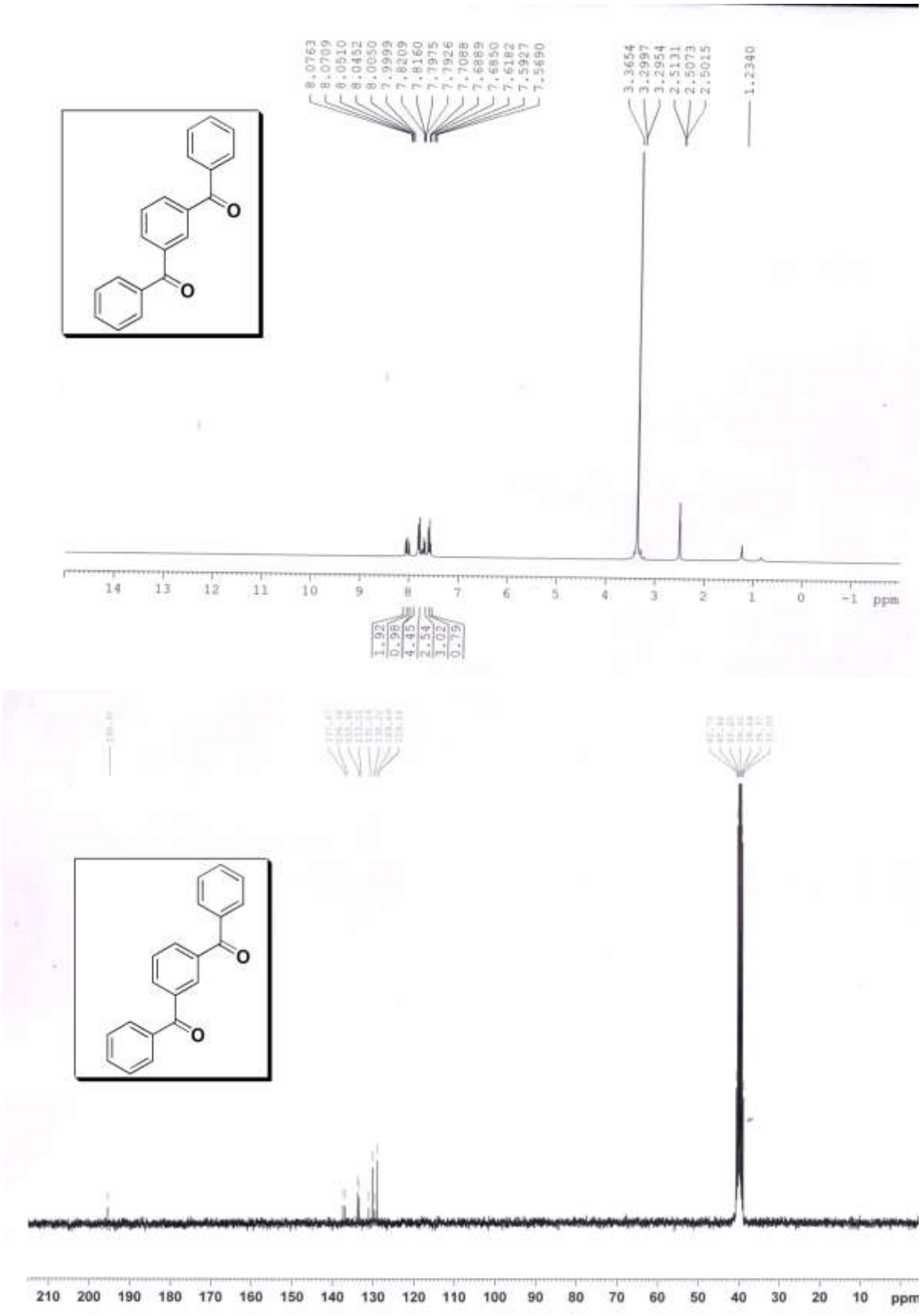
Pale yellow solid, melting point:>260°C; $^{1}$H NMR (DMSO-$d_6$, 300 MHz) δ 7.41-7.51 (m, 8H), 7.75-7.81 (m, 4H), 8.10 (d, *J* = 8.1Hz, 1H), 12.2 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 119.4, 120.2, 120.2, 124.5, 125.3, 129.0, 129.1, 129.2, 130.5, 131.3, 133.0, 134.0, 137.2, 138.3, 140.4, 150.5, 175.5, 195.1.

**34. 3-(4-Methylbenzoyl)-2-phenylquinolin-4(1*H*)-one (5c)**[38]

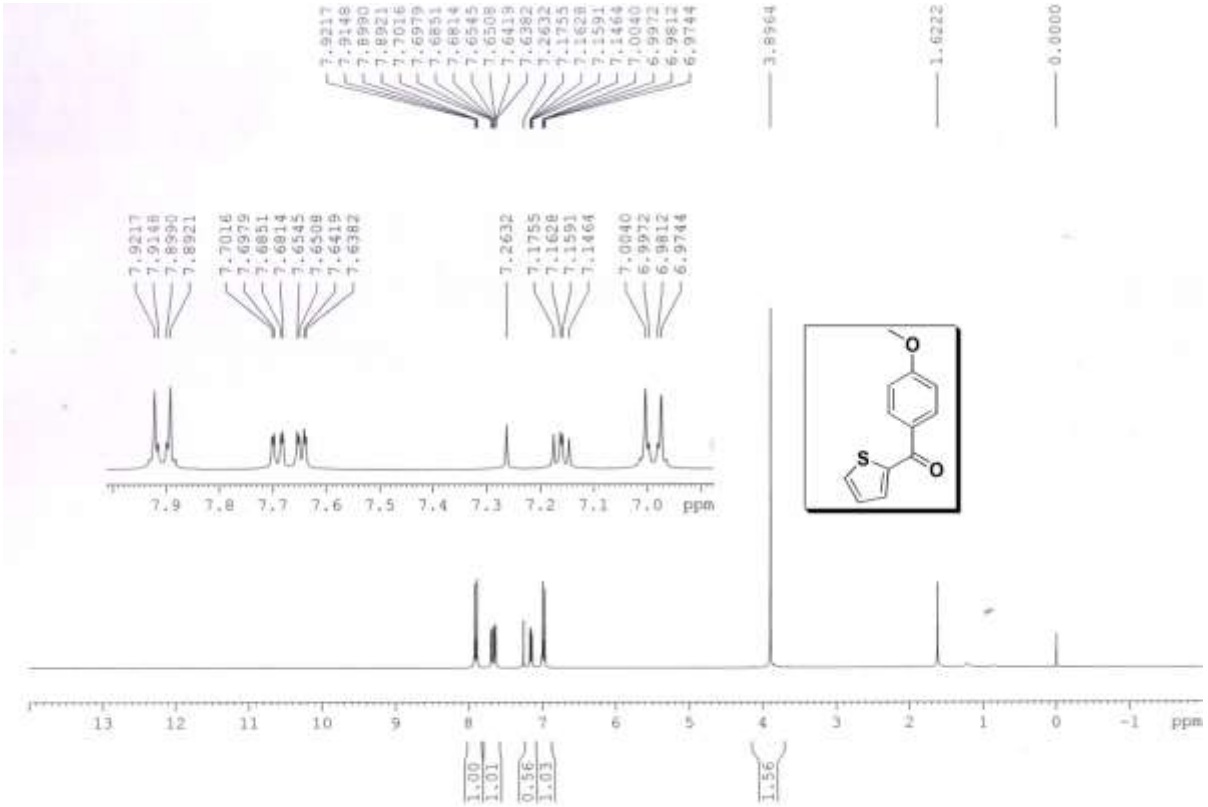


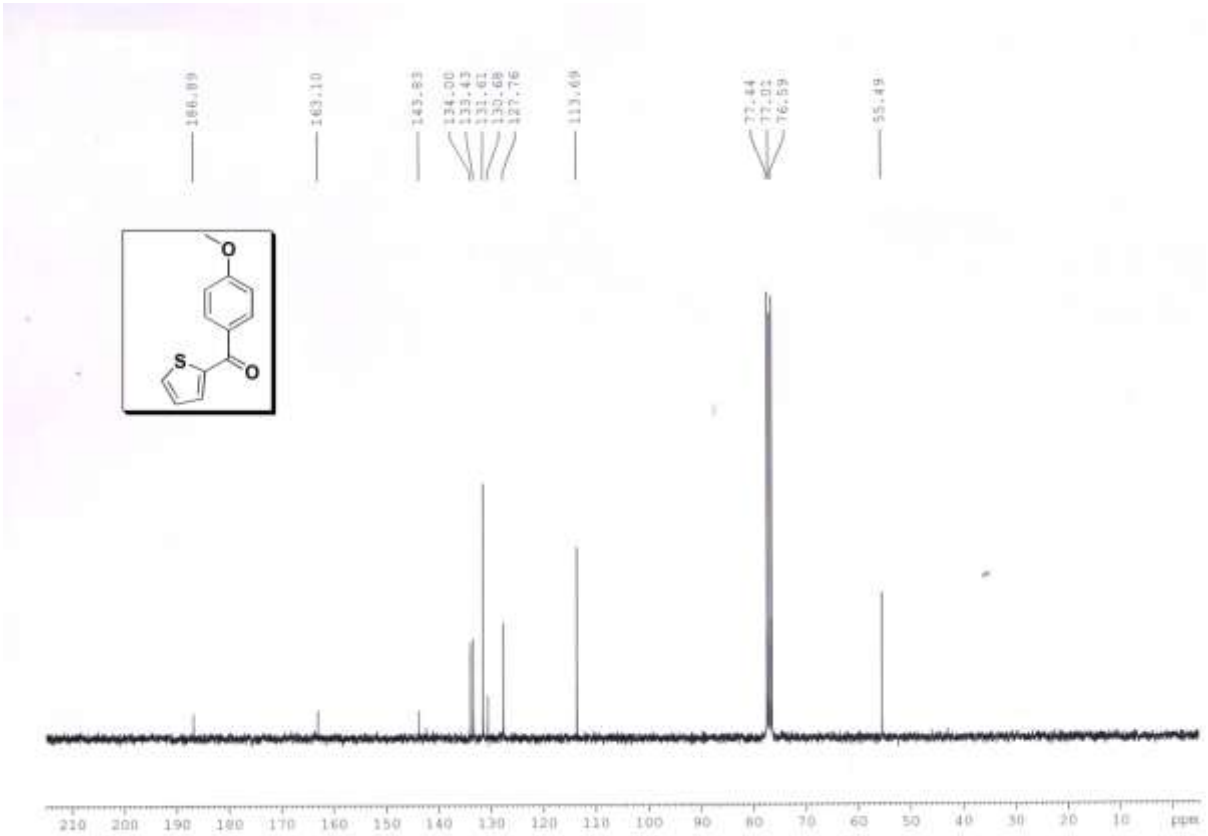

Brown solid, melting point: >260°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 2.33 (s, 3 H),7.22 (d, *J* = 8.0 Hz, 2 H), 7.40−7.49 (m, 6 H),7.67 (d, *J* = 8.0 Hz, 2 H), 7.75−7.79 (m, 2 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 12.12 (s, 1 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 21.5, 119.3, 120.7, 124.5, 125.2, 125.3, 128.9, 129.0, 129.1, 129.4, 130.5, 132.9, 133.5, 134.0, 138.4, 140.3, 149.9, 175.5, 196.2.

**$^{1}$H and $^{13}$C NMR spectra of entry 2h (Scheme-III.2.) in DMSO-$d_6$**

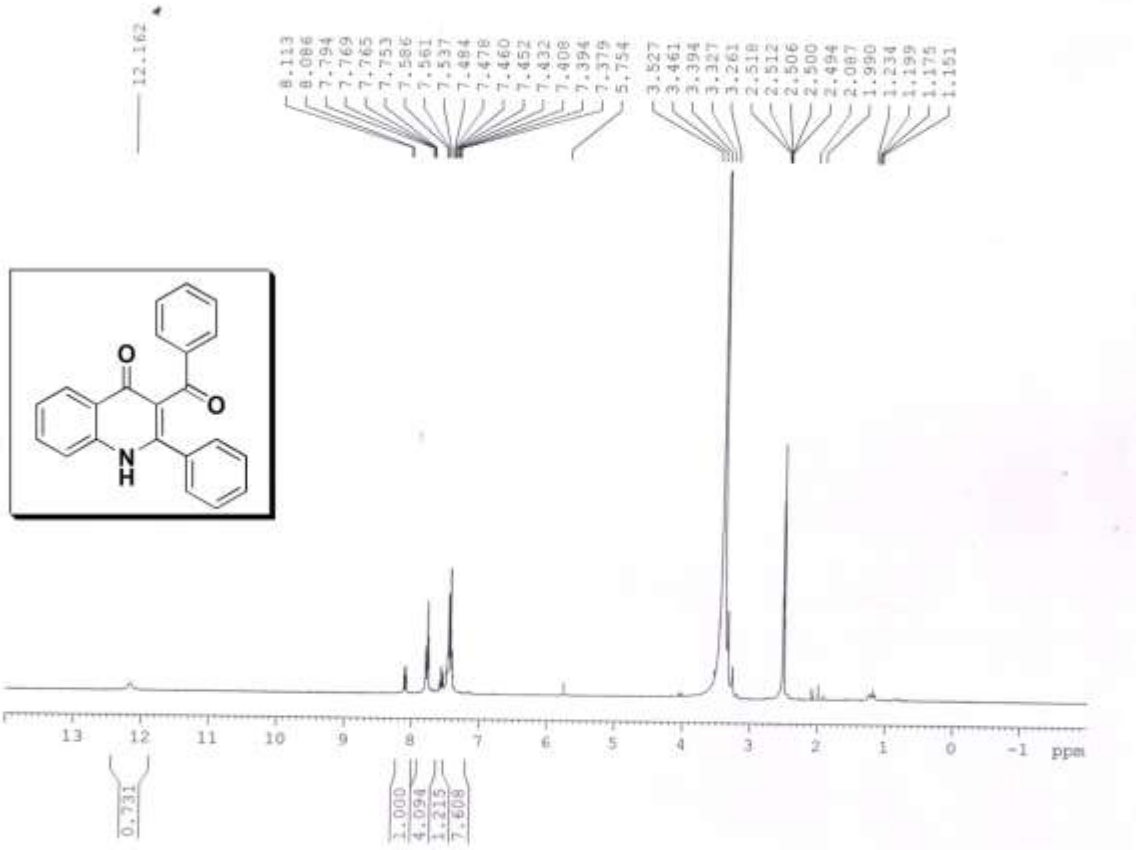


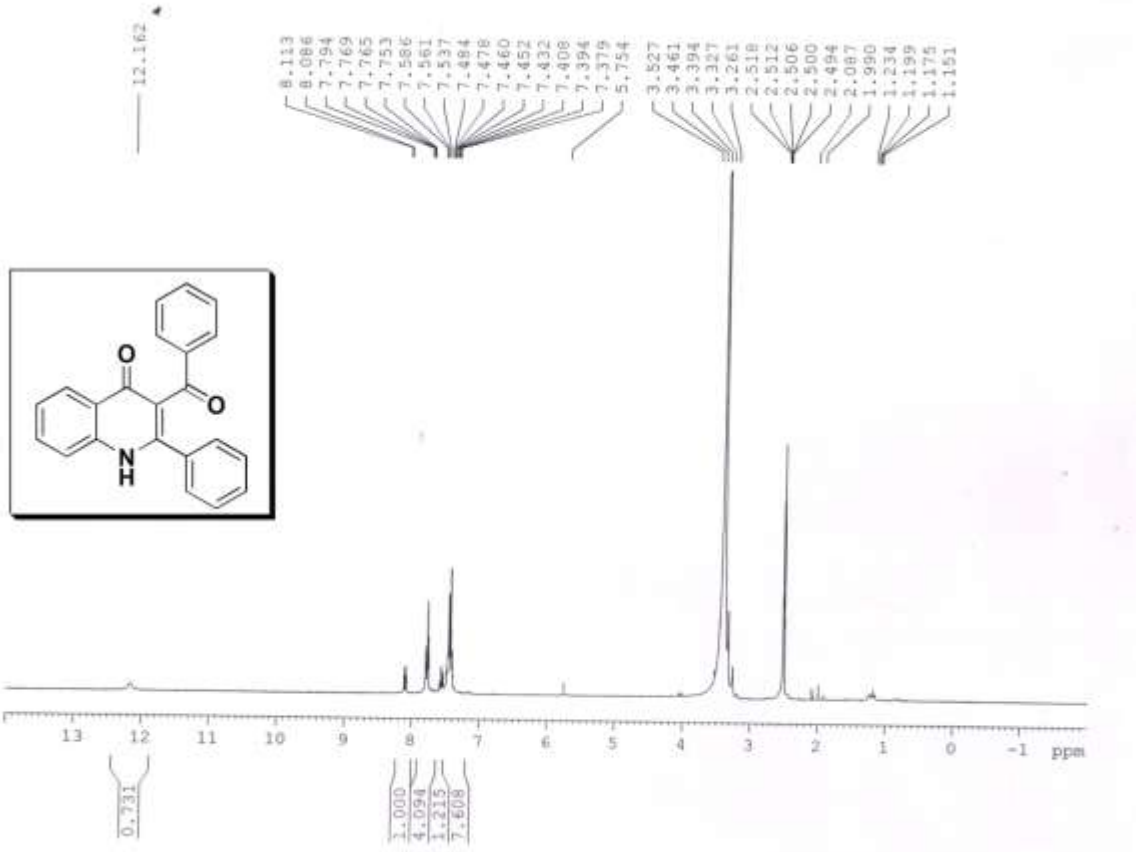
**$^{1}$H and $^{13}$C NMR spectra of entry 3q (Scheme-III.3.) in DMSO-$d_6$**



**$^{1}$H and $^{13}$C NMR spectra of entry 5a (Scheme-III.4.) in DMSO-$d_6$**



## III.E. References

References are given in BIBLIOGRAPHY under Chapter III (pp-229-231)

# Chapter IV

## *Pd-NHC catalysed thioetherification of 3-iodo-2-aryl substituted 4-quinolone derivatives via C-S cross coupling*

## IV.A. Introduction

Sulfenylation in organic molecules has received much attention due to its importance in organic dyes, pharmaceuticals, material chemistry, agrochemicals and many bioactive products.[1] Diaryl sulfides also have tremendous applications in the treatment of Parkinson's, [2] Alzheimer's [3]diseases and HIV infections,[4], Breast cancer[5] etc. Therefore, the development of highly efficient, novel, simple pathway for the formation C-S bond linkage in many biologically active molecules is still a great challenge for all over the world.[6]Till now, many methods have been well recognized for generating the C-S bond . Migita et.al. firstly developed the carbon-sulfur bond formation between aryl halides and thiols in the presence of $Pd(PPh_3)_4$.[7]

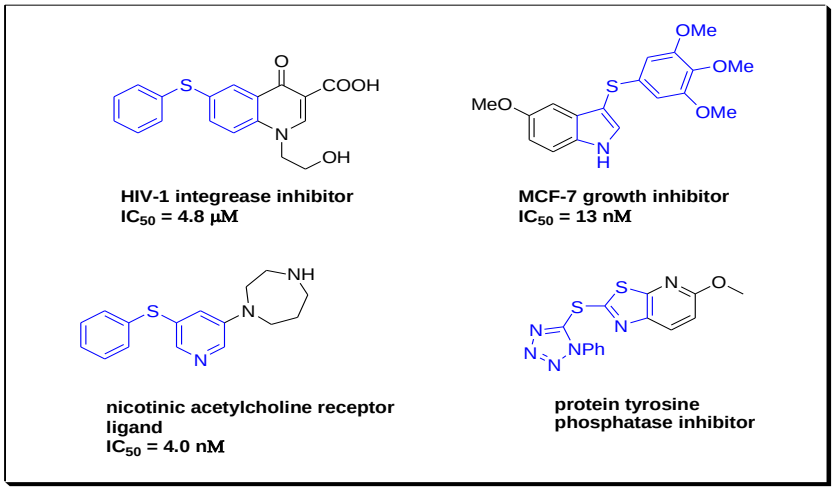


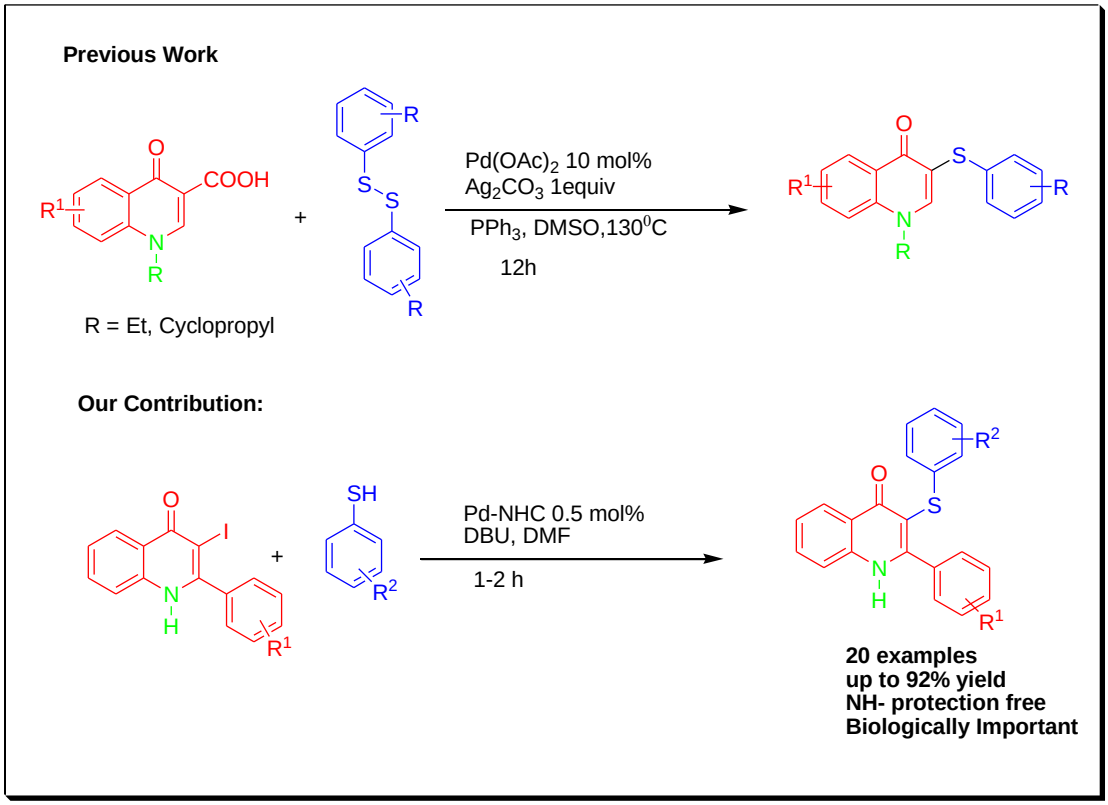

**Fig-IV.1** Important biologically active diaryl sulfide scaffolds

## IV.B. Present work: Background and Objective

4-quinolones are mainly found in the pharmaceutical chemistry on owing to its various biological activities, e.g., antibacterial,[8] antimalarial, [9] and anticancer.[10] As a consequence, the synthesis of 4-quinolones and its derivatives has involved considerable interest. Therefore, many synthetic procedures are commonly available in the literature.[11] 3-aryl- or 3-heteroaryl-substituted quinolones have been widely explored because of their profound biological activities. Despite 3-aryl substituted quinolones have some advantages; coupling reactions at C-3 of quinolin-4-ones remains a challenging task due to the requirement of pre – NH functionalisation and protection. In recent year, Zhang and his coworkers introduce the thioether linkage at the C-3 position of 4-quinolones via decarboxylative thioetherification.[12]

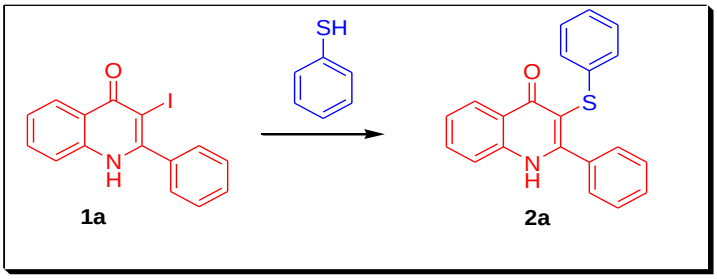
But still, this method has some disadvantages such as harsh reaction condition, longer reaction time; halogen substituted starting material and prerequisite protection of –NH group.

In this arena, we have previously reported the regio-controlled nitration at C-5, C-7 position of 4-quinolones under ambient condition[13] and regioselective bromination at C-6 position and its subsequent arylation via Suzuki cross coupling reactions.[14] However in this chapter, we have disclosed a new, simple and efficient route of Pd-NHC catalysed thioetherification of 3-iodo-4-quinolones in promising yield under rapid and aerobic condition. To the best of our knowledge, no such study has not been well documented before.



## IV.B.1. Present work: Result and Discussion

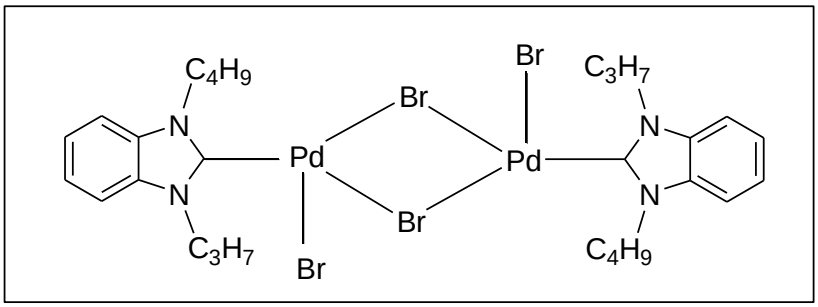
**Table-IV.1. Optimization of the reaction condition for the C-S cross coupling**




| entry | catalyst ( mol %) | base | solvent | temp (°C) | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (5 ) | DBU | DMF | 80 | 4 | 80 |
| 2 | $Pd(OAc)_2$ (5 ) | $K_2CO_3$ | DMF | 80 | 4 | 71 |
| 3 | $PdCl_2$ (5 ) | $K_2CO_3$ | DMF | 80 | 4 | 73 |
| 4 | $Pd(acac)_2$ (5 ) | $K_2CO_3$ | DMF | 80 | 4 | 70 |
| 5 | Pd-NHC (2 ) | $K_2CO_3$ | DMF | 80 | 2 | 75 |
| 6 | Pd-NHC (1) | DBU | DMF | 80 | 2 | 83 |
| 7 | Pd-NHC (1) | $Et_3N$ | DMF | 80 | 2 | 79 |
| 8 | Pd-NHC (1) | $Cs_2CO_3$ | DMF | 80 | 2 | 52 |
| 9 | Pd-NHC (1) | DBU | Dioxane | 80 | 2 | 70 |
| 10 | Pd-NHC (1) | DBU | DMF | 40 | 2 | 67 |
| 11 | Pd-NHC (1) | DBU | DMF | rt | 2 | 59 |
| 12 | Pd-NHC (0.5) | $K_2CO_3$ | DMF | 80 | 2 | 72 |
| **13** | **Pd-NHC (0.5)** | **DBU** | **DMF** | **80** | **2** | **86** |

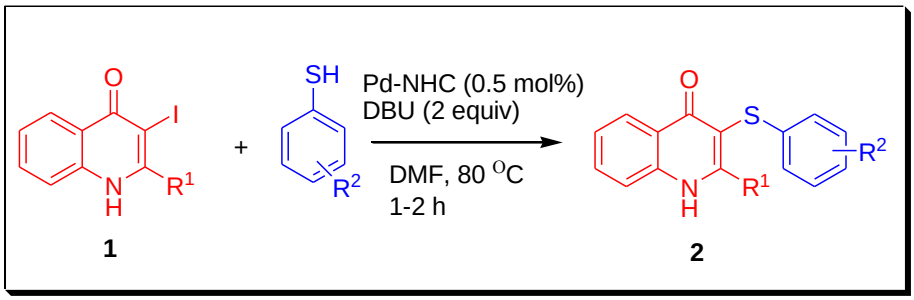
All reactions were carried out using 0.25 mmol of 3-iodo-2-aryl substituted 4-quinolones and 0.375 mmol benzene thiol in 2 mL DMF for stirring at 80 °C. Yield = Isolated yields

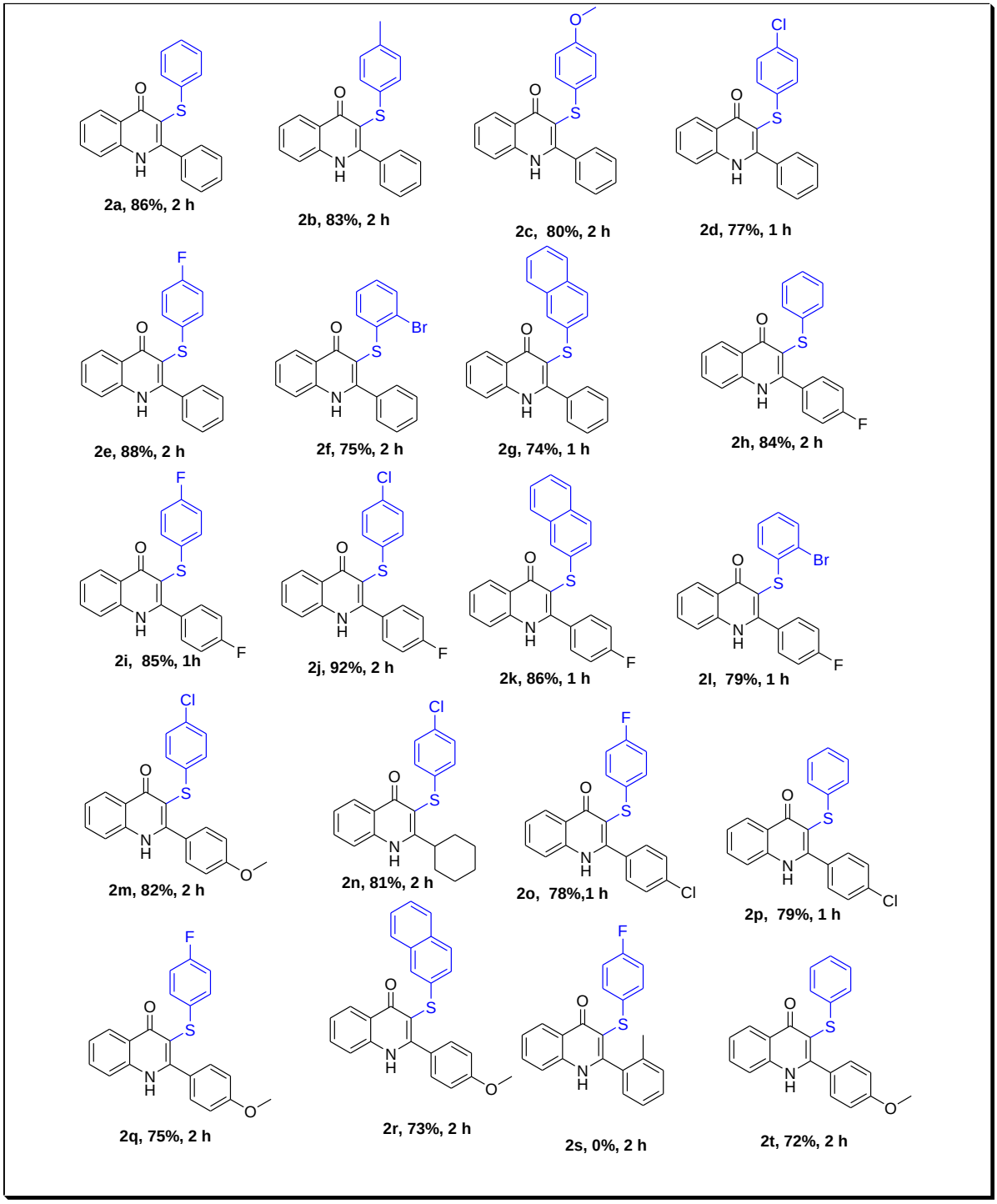
**Fig: IV.2.** Structure of the Benzimidazole based Pd-NHC catalyst A




To optimize the reaction condition, we investigated our journey by the reaction of 3-iodo -2-aryl substituted-4-quinolone and benzene thiol in DMF, as a model reaction. Delightfully, thioetherification at C-3 position of 4-quinolone took place in the presence of $Pd(OAc)_2$ and DMF, afforded 80% yield in 4 h (Table-IV.1, entry1). Subsequently, various palladium catalysts such as $PdCl_2$, $Pd(acac)_2$, Pd-NHC were screened to proceed the reaction; (Table-IV.1, entry 3,4) among them Pd-NHC[15]served the best results (Table-IV.1, entry 13). Only 0.5 mol % of our pre-developed Pd-NHC catalyst required to catalyse the reaction. Furthermore, various solvents were also examined to achieve the fruitful result. Among them DMF proved to be the best suited solvent, affording 86% yield of **2a** in 2 h (Table-IV.1, entry 13). The reaction temperature 80°C was found to be the optimal to furnish the highest yield of **2a** (Table-IV.1, entry 13). The base have also a profound role in this transformation, DBU found to be superior to the other bases such as $K_2CO_3$, $Cs_2CO_3$, $Et_3N$ etc (Table-IV.1, entry 5-8**)**. After investigating the various catalysts, solvent, catalyst loading and reaction temperature, the combination of Pd-NHC (0.5 mol %), DBU (2 equiv) in DMF at 80°C for 2 h served the optimal reaction condition for this transformation.

**Scheme-IV.1.** Substrate scope of Pd-NHC catalysed thioetherification






All reactions were carried out using 0.25 mmol of various 3-iodo-2-aryl substituted 4-quinolones and 0.375 mmol substituted benzene thiols in 2 mL DMF for stirring at 80 °C. Yield = Isolated yields.

With the optimized reaction conditions in our hand, we explored the substrate scope of both 3-iodo substituted-4-quinolone and various substituted benzene thiols as shown in (Scheme IV.1.) A broad range of benzene thiols were allowed to react with various 3-iodo-2-phenylquinolin-4-(1*H*)one, affording the corresponding product 3-aryl sulfide-4-quinolone in good to excellent yields. Both electron donating and electron withdrawing groups containing benzene thiols were performed very well in this transformation. 4-fluoro substituted benzene thiol was successfully coupled with 3-iodo-2-phenylquinolin-4-(*1H*)one, resulting the 88% yield of the desired product (Scheme-IV.1, entry **2e**). However, 2-naphthyl thiol furnished moderate to excellent yield (73%-86%) respectively (Scheme-IV.1, entry **2g, 2k 2r**). Steric hindrance of naphthyl ring with the phenyl group at C-2 position of 4-quinolone might play a key role for lowering the yield in **2g** and **2r**. Next, we examined the influence of various groups in the C-2 substituted phenyl ring of 4-quinolone. It has been found that electron withdrawing group substituted phenyl afforded much higher yield in comparison to electron releasing group (Scheme-IV.1, entry **2h-2l, 2m, 2q, 2r**). Cyclohexyl group substituted 4-quinolone also proved to be a good coupling partner with 4-chloro benzene thiol (scheme 1, entry **2n**). Highest yield 92% was obtained when 2-(4-fluorophenyl)-3-iodoquinolin-4-(1*H*)-one was coupled with 4-fluoro benzene thiol (Scheme-IV.1, entry **2j**). Surprisingly, meta substituted phenyl ring at C-2 position of 4-quinolone did not afford the corresponding product (scheme 1, entry **2t**) under this optimized condition. Interestingly in various cases, the reaction completed within 1 h and afforded the promising yield of the desired C-S coupled product (Scheme-IV.1, entry **2d, 2j, 2k, 2l**).

**IV.C. Conclusion**:

In summary, an efficient protocol of Pd-NHC catalysed rapid thioetherification of 4-quinolone is developed. This method should attract much attention to the synthetic and pharmaceutical chemistry for the synthesis of large compound production. Simultaneously, our synthesized thioether substituted 4-quinolone derivatives are under investigation for their biological activity.

## IV.D. Experimental section

### IV.D.1. General Informations

NMR spectra were recorded on 300 MHz spectrometer at 298 K with calibration done on the basis of solvent residual peak. Products were purified using column chromatography on silica gel (60-120 mesh). Ethyl acetate and petroleum ether (60-80$^0$C) were used as eluents. Progress of reaction was monitored using silica gel TLC.

### IV.D.2. Preparation of Various 3-iodo-2- aryl substituted 4-quinolones (1a-1f)

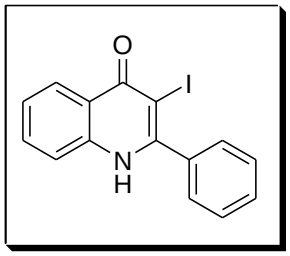
Initially, 2-aryl quinolin-4(1*H*)-one (1a, 0.25mmol), iodine (2 equiv.) and sodium carbonate (1.5 equiv.) in THF (2 ml) was stirred at room temperature for 18 hours. Then, the reaction mixture was quenched with sodium thiosulphate and the precipitate was collected by filtration and washed with ice-cold water. Afterwards, the crude product was purified through column chromatography.

### IV.D.3. Preparation of various thioether substituted 4-quinolones:

Initially, various 3-iodo-2-aryl substituted 4-quinolone (0.25mmol), thiophenol (0.375mmol), DBU (0.5 mmol, 76mg) and Pd-NHC (0.5 mol%, 1.2mg) were taken in DMF (2ml) in 25 ml round bottomed flask. Afterwards, the reaction mixture was heated at 80°C for 1-2 hr. Then, it was cooled and diluted with water and the product was extracted with ethyl acetate (3 x 20 mL). Organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude product was then purified using column chromatography.

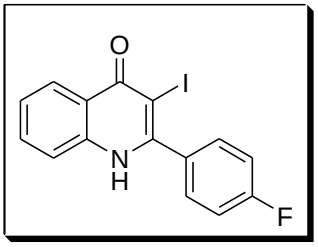
### IV.D.4. Physical characteristics and spectral data of compounds:

1. **3-iodo-2-phenylquinolin-4(1*H*)-one (1a)**[15]



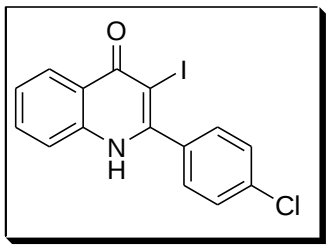

Light Yellow solid, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.36-7.42 (m, 1H), 7.53-7.58 (m, 5H), 7.63-7.69 (m, 2H), 8.13 (dd, *J* = 8.1Hz, 0.9Hz, 1H), 12.29 (s,1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 86.3, 118.8, 121.3, 124.7, 125.9, 128.8, 129.4, 130.3, 132.6, 139.7, 153.6, 174.1.

**2. 2-(4-fluorophenyl)-3-iodo-quinolin-4(1*H*)-one (1b)**[15]



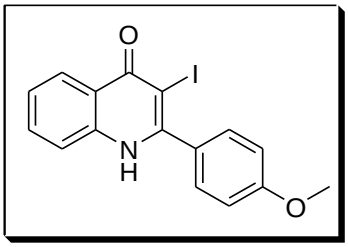

Light Yellow solid, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.38-7.45 (m, 3H), 7.62-7.71 (m, 4H), 8.15 (d, *J* = 8.0Hz, 1H), 12.3 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 86.6, 115.7, 115.9, 118.9, 121.4, 124.6, 125.9, 131.9, 132.1, 132.6, 134.8, 134.9, 139.8, 152.7, 161.5, 164.8, 174.0.

**3. 2-(4-chlorophenyl)-3-iodo-quinolin-4(1*H*)-one (1c)**[15]



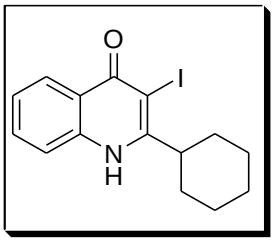

Light Yellow solid, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.37-7.42 (m, 1H), 7.59-7.73 (m, 5H), 8.15 (d, *J* = 9.9Hz, 1H), 12.13 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 86.4, 119.3, 121.6, 124.5, 125.9, 128.8, 131.5, 132.4, 134.9, 137.5, 152.9, 173.8.

**4. 3-iodo-2-(4-methoxyphenyl) quinolin-4(1*H*)-one (1d)**[15]




Light Yellow solid, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.56 (s, 3H), 7.13 (d, *J* = 8.7Hz, 2H), 7.39-7.42 (m, 1H), 7.53 (d, *J* = 8.7Hz, 2H), 7.67-7.70 (m, 2H), 8.13 (d, *J* = 7.8Hz, 1H), 12.20 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 55.8, 86.6, 114.1, 118.8, 121.3, 124.5, 125.9, 130.7, 131.1, 132.5, 139.8, 153.4, 160.7, 174.0.

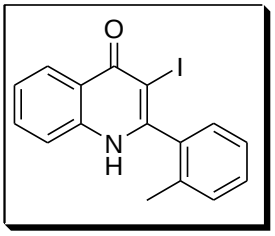
**5. 2-cyclohexyl-3-iodo-quinolin-4(1*H*)-one (1e)**




Light Yellow solid, melting point:222-224°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.35 (s, 3H), 1.82 (dd, *J* = 18.9Hz, 9.6Hz, 7H), 7.34 (t, *J* = 7.2Hz,

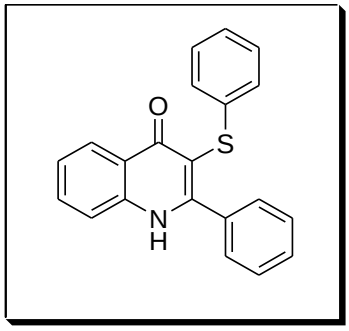
1H), 7.65-7.70 (m, 1H), 7.82 (d, *J* = 8.3Hz, 1H), 8.07 (d, *J* = 8.0Hz, 1H), 11.25 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 25.6, 26.4, 29.9, 40.8, 49.0, 87.1, 118.7, 121.4, 124.3, 125.8, 132.3, 139.8, 157.5, 173.7.

**6. 3-iodo-2-*o*-tolyl- quinolin-4(1*H*)-one (1f)**



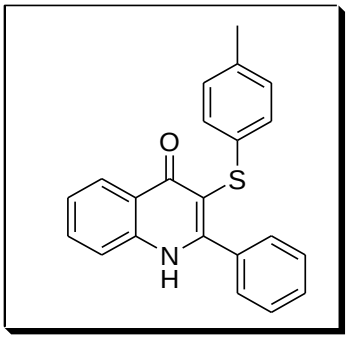

Light Yellow solid, melting point: 220-222°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 2.17 (s, 3H), 7.31-7.47 (m, 5H), 7.61-7.70 (m, 2H), 8.16 (d, J = 7.6Hz, 1H), 12.31 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 19.2, 87.1, 118.9, 121.5, 125.9, 126.5, 129.0, 130.1, 130.6, 132.5, 135.4, 138.5, 153.8, 173.8.

**7. 2-phenyl-3-(phenylthio)quinolin-4(1*H*)-one (2a)**




White solid, melting point: 245-247°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 6.97-7.05 (m, 3H), 7.14-7.20 (m, 2H), 7.41 (s, 1H), 7.48-7.54 (m, 5H), 7.71-7.73 (m, 2H), 8.11 (d, *J* = 7.8Hz, 1H), 12.29 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 108.5, 119.2, 124.5, 124.7, 124.8, 125.5, 125.9, 128.5, 129.0, 129.1, 130.2, 132.8, 135.5, 138.8, 139.9, 175.5.

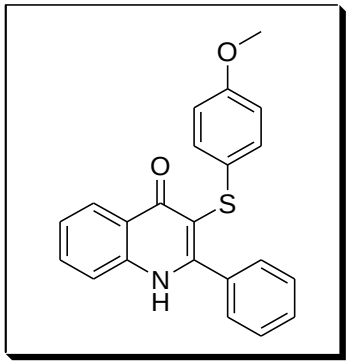
**8. 3-(4-methylphenylthio)-2-phenylquinolin-4(1*H*)-one (2b)**




White solid, melting point:185-187°C,$^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 2.20 (s, 3H), 6.95 (d, *J* = 8.4Hz, 2H), 6.99 (d, *J* = 8.4Hz, 2H), 7.38-7.73 (m,

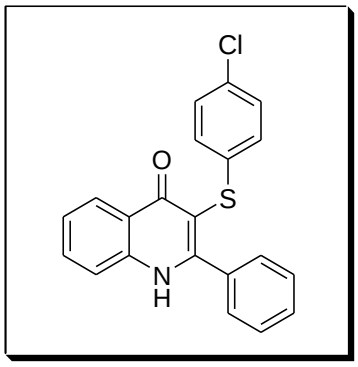
8H), 8.10-8.16 (m, 1H), 12.24 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 20.8, 109.1, 119.2, 124.5, 124.6, 125.9, 128.5, 128.9, 129.1, 129.4, 129.8, 130.1, 130.3, 132.8, 134.1, 135.2, 135.6, 139.9, 156.8, 175.6.

**9. 3-(4-methoxyphenylthio)-2-phenylquinolin-4(1*H*)-one (2c)**



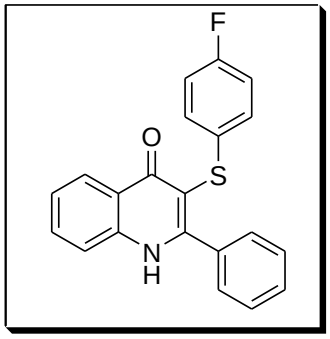

White solid, melting point:225-227°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.67 (s, 3H), 6.78 (dd, *J* = 6.9Hz, 1.8Hz, 2H), 6.98 (dd, *J* = 6.9Hz, 1.8Hz, 2H), 7.40-7.43 (m, 1H), 7.51-7.55 (m, 5H), 7.70-7.72 (m, 2H), 8.11 (d, *J* = 8.1Hz, 1H), 12.22 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 52.1, 107.0, 111.4, 115.7, 121.1, 121.1, 122.4, 124.9, 125.0, 125.7, 125.8, 126.7, 129.3, 132.1, 136.4, 153.0, 154.2, 172.2.

**10. (4-chlorophenylthio)-2-phenylquinolin-4(1*H*)-one (2d)**



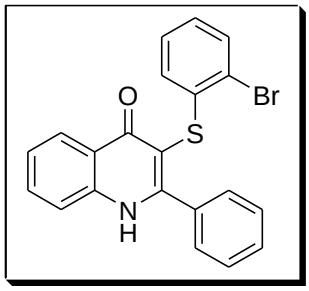

White solid, melting point: 235-237°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 6.96 (d, *J* = 1.5Hz, 2H), 6.99 (d, *J* = 1.8Hz, 2H), 7.17-7.20 (m, 1H), 7.38-7.49 (m, 5H), 7.68-7.70 (m, 2H), 8.07 (d, *J* = 7.8Hz, 1H). $^{13}$C NMR (75 MHz DMSO-$d_6$) δ 107.7, 118.7, 124.1, 124.3, 125.4, 126.8, 128.1, 128.5, 128.8, 129.7, 132.4, 134.9, 137.4, 139.4, 156.5, 174.9.

**11. 3-(4-fluorophenylthio)-2-phenylquinolin-4(1*H*)-one (2e)**



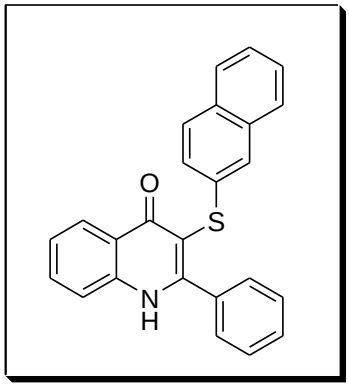

White solid, melting point: 240-242°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.02-7.05 (m, 4H), 7.39-7.44 (m, 1H), 7.50-7.54 (m, 5H), 7.71-7.74 (m, 2H), 8.12 (d, *J* = 7.5Hz, 1H), 12.28 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 105.8, 105.9, 112.4, 112.7, 115.7, 121.2, 122.4, 124.4, 124.5, 124.7, 125.1, 125.6, 126.7, 129.3, 130.7, 132.0, 136.5, 153.4, 155.5, 158.7, 172.0. HRMS (ESI$^{+}$): $[M+H]^{+}$, found 348.0855. $C_{21}H_{15}FNOS$ requires 348.0853.

**12. 3-(2-bromophenylthio)-2-phenylquinolin-4(1*H*)-one (2f)**



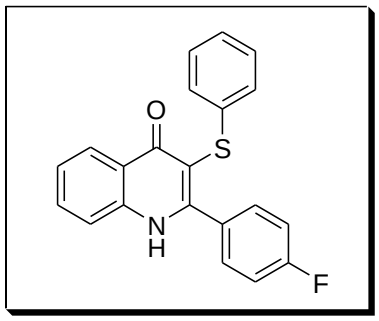

White solid, melting point:> 260°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 6.86 (dd, *J* = 8.1Hz, 1.5Hz, 1H), 6.99 (dt, *J* = 7.5Hz, 1.5Hz, 1H), 7.18 (dt, *J* = 7.8Hz, 1.2Hz, 1H), 7.41-7.54 (m, 7H), 7.74-7.76 (m, 2H), 8.13 (d, *J* = 7.8Hz, 1H), 12.38 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 107.8, 119.3, 119.5, 124.6, 124.8, 125.9, 126.2, 126.3, 128.3, 128.6, 128.9, 130.3, 132.8, 132.9, 135.3, 139.5, 140.0, 157.4, 175.3. HRMS (ESI$^{+}$): $[M+H]^{+}$ , found 408.0053. $C_{21}H_{15}BrNOS$ requires 408.0052.

**13. 3-(naphthalen-2-ylthio)-2-phenylquinolin-4(1*H*)-one (2g)**



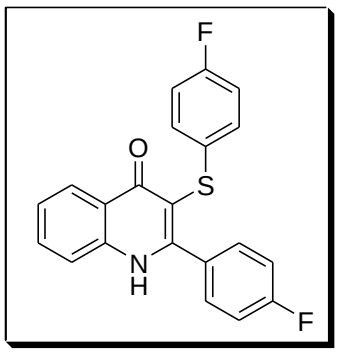
White solid, melting point:>260°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.19-7.22 (m, 1H), 7.38-7.52 (m, 7H), 7.57-7.60 (m, 2H), 7.71-7.82 (m, 5H), 8.13 (d, J = 8.1Hz, 1H), 12.35 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 107.9, 118.7, 122.2, 124.1, 124.2, 124.3, 124.9, 125.4, 126.4, 126.6, 127.5, 128.0, 128.1, 128.5, 129.7, 130.7, 132.4, 133.3, 135.0, 136.1, 139.5, 156.6, 175.1.

**14. 2-(4-fluorophenyl)-3-(phenythio)quinolin-4(1*H*)-one (2h)**



White solid, melting point: 236-238°C,$^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 6.99-7.07 (m, 3H), 7.15-7.20 (m, 2H), 7.30-7.44 (m, 3H), 7.57-7.62 (m, 2H), 7.69-7.77 (m, 2H), 8.12 (d, *J* = 7.5Hz, 1H), 12.30 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 108.8, 115.4, 115.6, 119.2, 124.5, 124.7, 124.9, 125.6, 125.9, 129.2, 131.5, 131.6, 131.8, 131.9, 132.9, 138.6, 139.9, 156.0, 161.6, 14.9, 175.5.

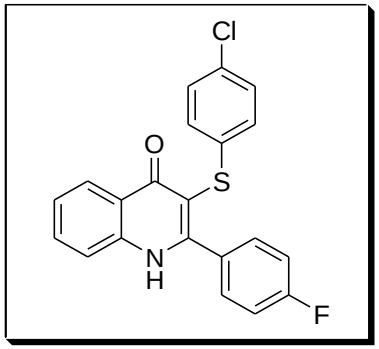
**15. 3-(4-fluorophenylthio)-2-(4-fluorophenyl)quinolin-4(1*H*)-one (2i)**



White solid, melting point: 230-232°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.02-7.03 (m, 3H), 7.05-7.44 (m, 3H), 7.58-7.74 (m, 4H), 8.12 (d, *J* =

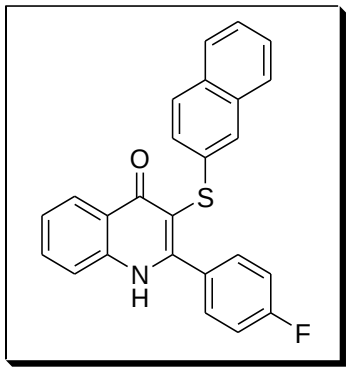
8.1Hz, 1H), 12.29 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 106.0, 111.9, 112.2, 112.5, 112.8, 115.3, 115.7, 117.9, 121.2, 121.3, 122.5, 124.5, 124.6, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 129.2, 129.4,130.5, 130.6, 131.4, 136.3, 136.4, 149.2, 152.4, 155.5, 158.2, 161.4, 170.6, 172.0. HRMS (ESI$^+$): $[M+H]^+$ , found 366.0762. $C_{21}H_{14}F_2NOS$ requires 366.0759.

**16. 3-(4-chlorophenylthio)-2-(4-fluorophenyl)quinolin-4(1*H*)-one (2j)**



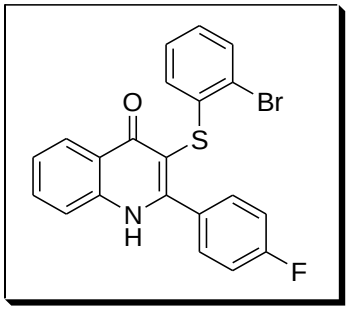

White solid, melting point : 158-160°C,$^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.01-7.04 (m, 2H), 7.22-7.25 (m, 2H), 7.32-7.45 (m, 3H), 7.57-7.62 (m, 2H), 7.69-7.75 (m, 2H), 8.12 (d, *J* = 8.1Hz, 1H), 12.22 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 107.9, 114.9, 115.2, 118.8, 124.1, 124.3, 125.4, 126.8, 128.5, 128.9, 130.9, 131.1, 131.2, 131.3, 132.4, 137.3, 139.4, 156.6, 161.1, 164.4, 174.8.

**17. 2-(4-fluorophenyl)-3-(naphthalene-2-ylthio)quinolin-4(1*H*)-one (2k)**



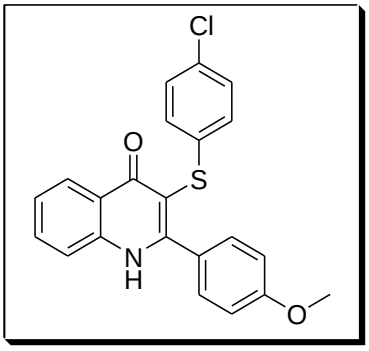

White solid, melting point: 170-172°C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.21 (dd, *J* = 8.4Hz, 2.1Hz, 1H), 7.30-7.47 (m, 6H), 7.62-7.82 (m, 7H), 8.12 (d, *J* = 7.8Hz, 1H), 12.34 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 108.8, 115.4, 115.7, 119.2, 122.9, 124.7, 124.9, 125.4, 125.9, 126.9, 127.1, 127.9, 128.5, 131.2, 131.5, 131.6, 131.9, 132.8, 133.9, 136.4, 140.0, 156.1, 161.6, 164.9, 175.6.

**18. 3-(2-bromophenylthio)-2-(4-fluorophenyl)quinolin-4(1*H*)-one (2l)**



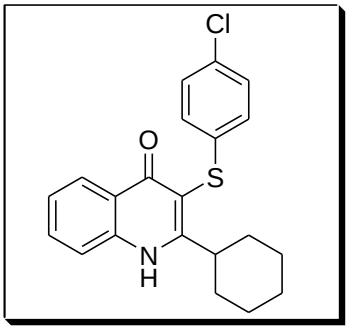

White solid, melting point: 250-252°C.$^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 6.85 (dd, *J* = 7.8Hz, 1.5Hz, 1H), 7.00(dt, *J* = 7.5Hz, 1.5Hz, 1H0, 7.15-7.20 (m, 1H), 7.31-7.37 (m, 2H), 7.41-7.61 (m, 6H), 7.73-7.76 (m, 2H), 8.13 (dd, J = 7.8Hz, 1.2Hz, 1H), 12.30 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 108.0, 115.5, 115.7, 119.3, 119.5, 124.6, 124.9, 125.9, 126.2, 126.3, 128.4, 131.4, 131.5, 131.6, 131.7, 132.8, 133.0, 139.4, 140.0, 156.5, 161.7, 162.8, 165.0, 175.3. HRMS (ESI$^{+}$): $[M+H]^{+}$, found 425.9960. $C_{21}H_{14}BrFNOS$ requires 425.9958.

**19. 3-(4-chlorophenylthio)-2-(4-methoxyphenyl)quinolin-4(1*H*)-one (2m)**



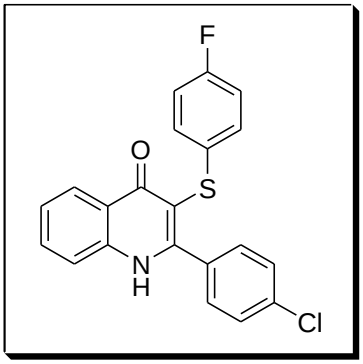

White solid, melting point: 220-222°C,$^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.81(s, 3H), 7.00-7.07 (m, 4H), 7.22-7.24 (m, 2H), 7.47 (d, *J*= 8.7Hz, 3H), 7.71 (s, 2H), 8.10 (d, *J* = 8.1Hz, 1H), 12.35 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 55.8, 109.2, 114.1, 116.5, 119.2, 126.5, 127.3, 129.2, 129.8, 130.6, 130.7, 131.1, 133.1, 135.4, 141.6, 148.8, 159.8, 176.1.

**20. 3-(4-chlorophenylthio)-2-cyclohexylquinolin-4(1*H*)-one (2n)**



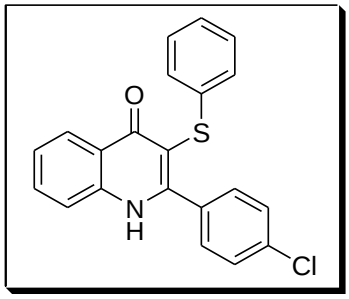

White solid, melting point: 238-240°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.17-1.29 (m, 3H), 1.63-1.83 (m, 7H), 7.02-7.13 (m, 4H), 7.35 (t, *J* = 7.2Hz, 1H), 7.59 (dt, *J* = 7.2Hz, 1.5Hz, 1H), 7.80-7.83 (m, 1H), 8.05 (dd, *J* = 8.1Hz, 1.2Hz, 1H), 11.29 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 25.6, 26.3, 30.5, 42.5, 108.8, 116.1, 116.4, 118.9, 124.3, 124.4, 125.8, 128.3, 128.4, 132.6, 134.1, 134.2, 139.9, 162.5, 175.4.

**21. 3-(4-fluorophenylthio)-2-(4-chlorophenyl)quinolin-4(1*H*)-one (2o)**




White solid, melting point:165-167°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.00-7.03 (m, 4H), 7.37-7.43 (m, 1H), 7.52-7.58(m, 4H), 7.65-7.72 (m, 2H), 8.1 (dd, *J* = 6.9Hz, 1.5Hz, 1H), 12.30 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 115.5, 115.7, 120.8, 124.1, 124.2, 125.4, 127.6, 127.7, 128.1, 128.4, 130.6, 132.4, 133.4, 133.7, 134.5, 139.5, 147.4, 152.0, 155.2, 158.5, 161.7, 174.9.

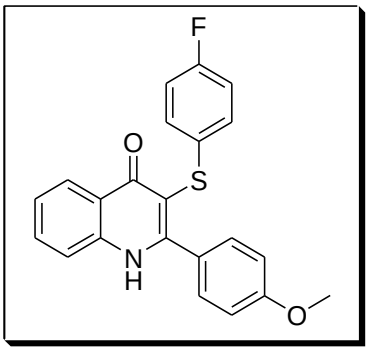
**22. 2-(4-chlorophenyl)-3-(phenythio)quinolin-4(1*H*)-one (2p)**




White solid, melting point: 243-245°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 6.99-7.07 (m, 3H), 7.16-7.21 (m, 2H), 7.40-7.45 (m, 1H), 7.57 (s, 4H), 7.68-

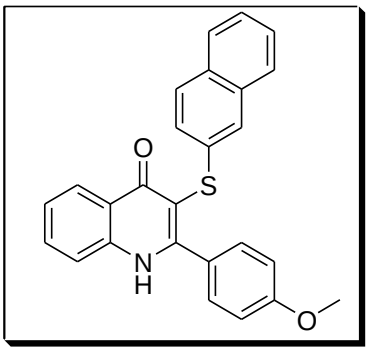
7.77 (m, 2H), 8.12 (d, *J* = 7.2Hz, 1H), 12.30 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 108.7, 119.2, 124.6, 124.7, 124.9, 125.6, 125.9, 128.6, 129.2, 131.0, 132.9, 134.2, 135.0, 138.5, 139.9, 155.8, 175.4.

**23. 3-(4-fluorophenylthio)-2-(4-methoxyphenyl)quinolin-4(1*H*)-one (2q)**



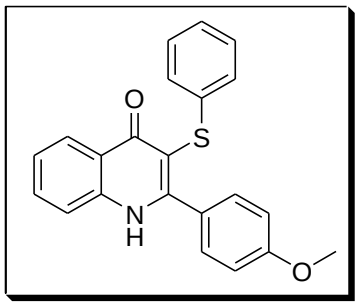

White solid, melting point : 190-192°C,$^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.82 (s, 3H), 7.02-7.07 (m, 7H), 7.40-7.41(m, 1H), 7.48 (dd, J = 4.8Hz, 1.8Hz, 2H), 7.70-7.73 (m, 2H), 8.10 (d, J = 8.1Hz, 1H), 12.20 (s, 1H); $^{13}$C NMR (75MHz, DMSO-$d_6$)δ 55.8, 109.2, 113.9, 115.9, 116.2, 119.1, 124.5, 125.9, 127.7, 127.8, 127.9, 130.8, 132.7, 134.4, 139.9, 156.7, 160.9, 175.5

**24. 2-(4-methoxyphenyl)-3-(naphthalene-2-ylthio)quinolin-4(1*H*)-one (2r)**



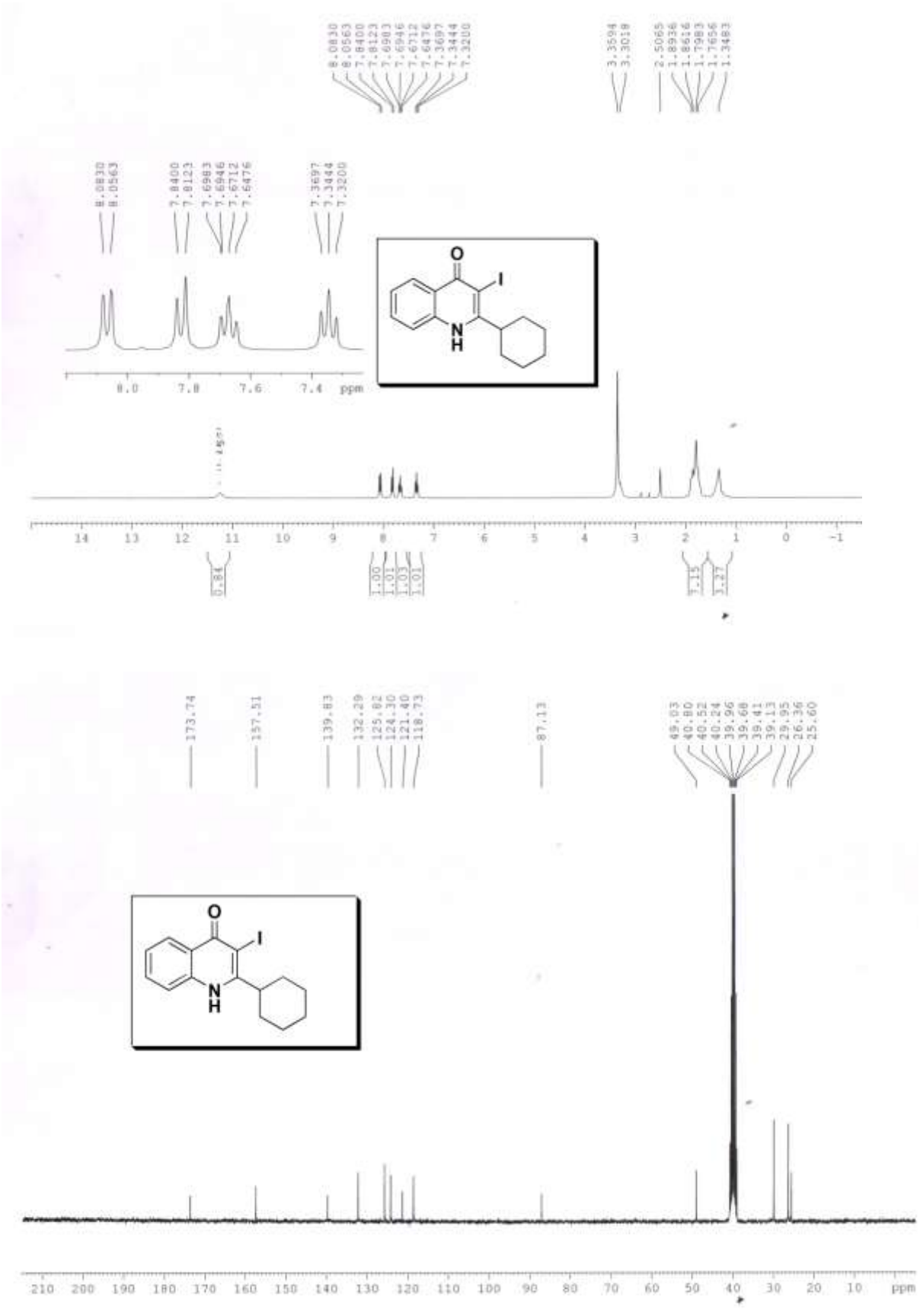

White solid, melting point:>260°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.78 (s, 3H), 7.03 (dd, *J* = 6.6Hz, 2.1Hz, 2H), 7.20 (dd, *J* = 8.7Hz, 1.8Hz, 1H), 7.37-7.46 (m, 4H), 7.53 (dd, *J* = 6.9Hz, 2.1Hz, 2H), 7.70-7.82 (m, 6H), 8.11 (d, *J* = 7.8Hz, 1H), 12.23 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 55.8, 108.3, 113.9, 119.2, 122.5, 124.5, 124.6, 124.8, 125.4, 125.9, 126.9, 127.1, 127.7, 128.0, 128.5, 130.7, 131.2, 132.8, 133.9, 136.8, 140.0, 156.9, 160.9, 175.6.

**25. 2-(4-methoxyphenyl)-3-(phenylthio)quinolin-4(1*H*)-one (2t)**

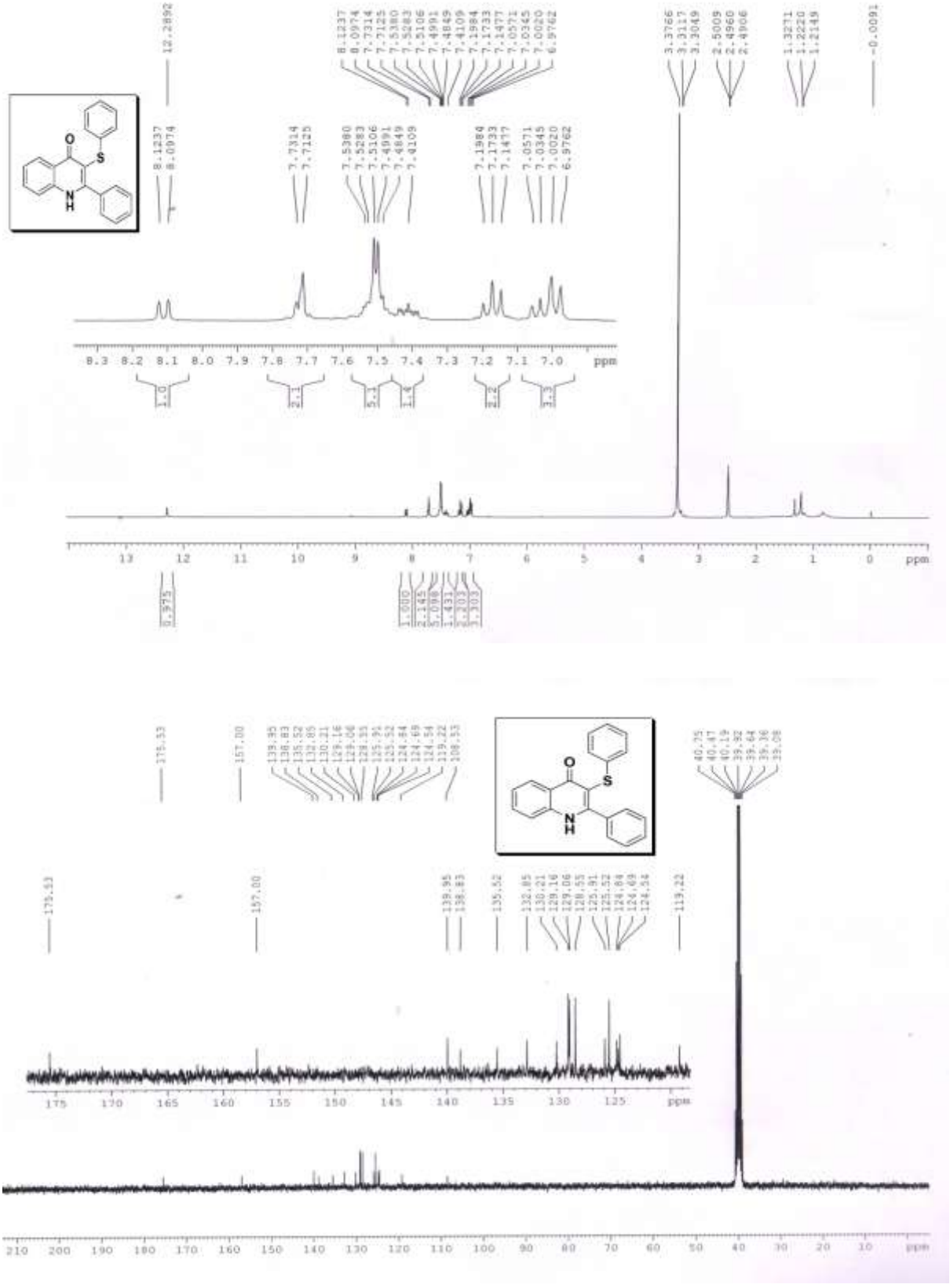



White solid, melting point: 228-230°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.76 (s, 3H), 6.78 (dd, *J* = 6.9Hz, 1.8Hz, 2H), 6.96 (dd, *J* = 6.9Hz, 1.8Hz, 2H), 7.40-7.45 (m, 1H), 7.52-7.56 (m, 5H), 7.70-7.74 (m, 2H), 8.11 (d, *J* = 8.1Hz, 1H), 12.23 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 55.8, 109.0, 111.4, 115.7, 121.1, 122.4, 124.9, 125.0, 125.7, 125.8, 126.7, 130.7, 132.7,134.0, 139.9, 153.0, 156.8, 160.9, 175.5.

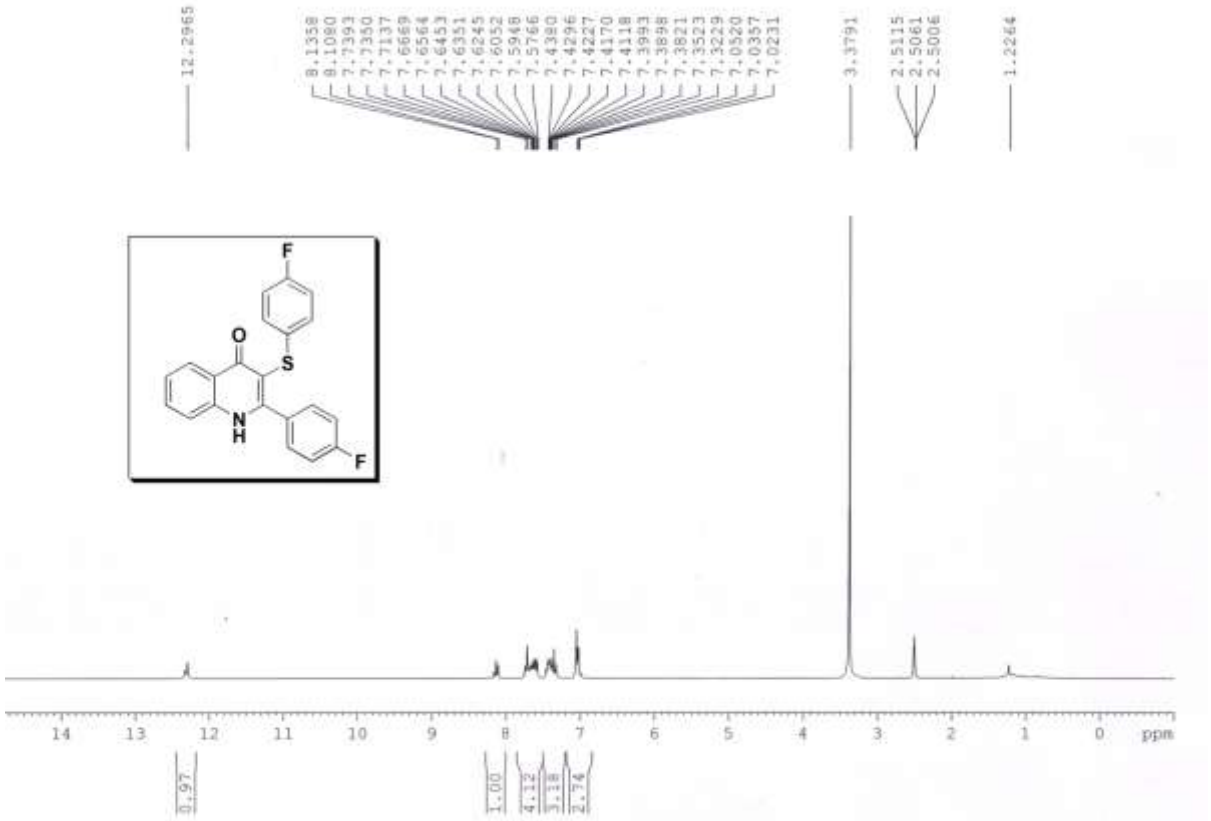
**$^{1}$H and $^{13}$C NMR spectra of entry 1e in DMSO-$d_6$**

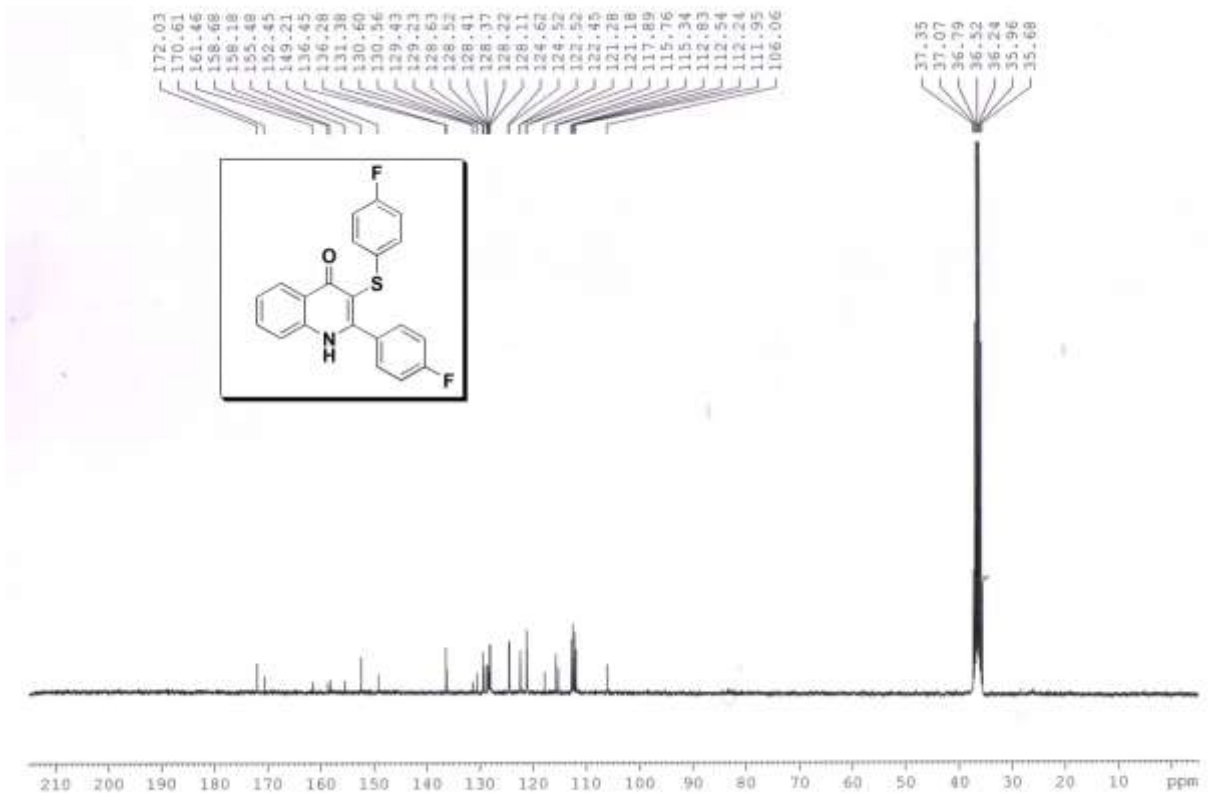


**$^{1}$H and $^{13}$C NMR spectra of entry 2a (Scheme-IV.1.) in DMSO-$d_6$**

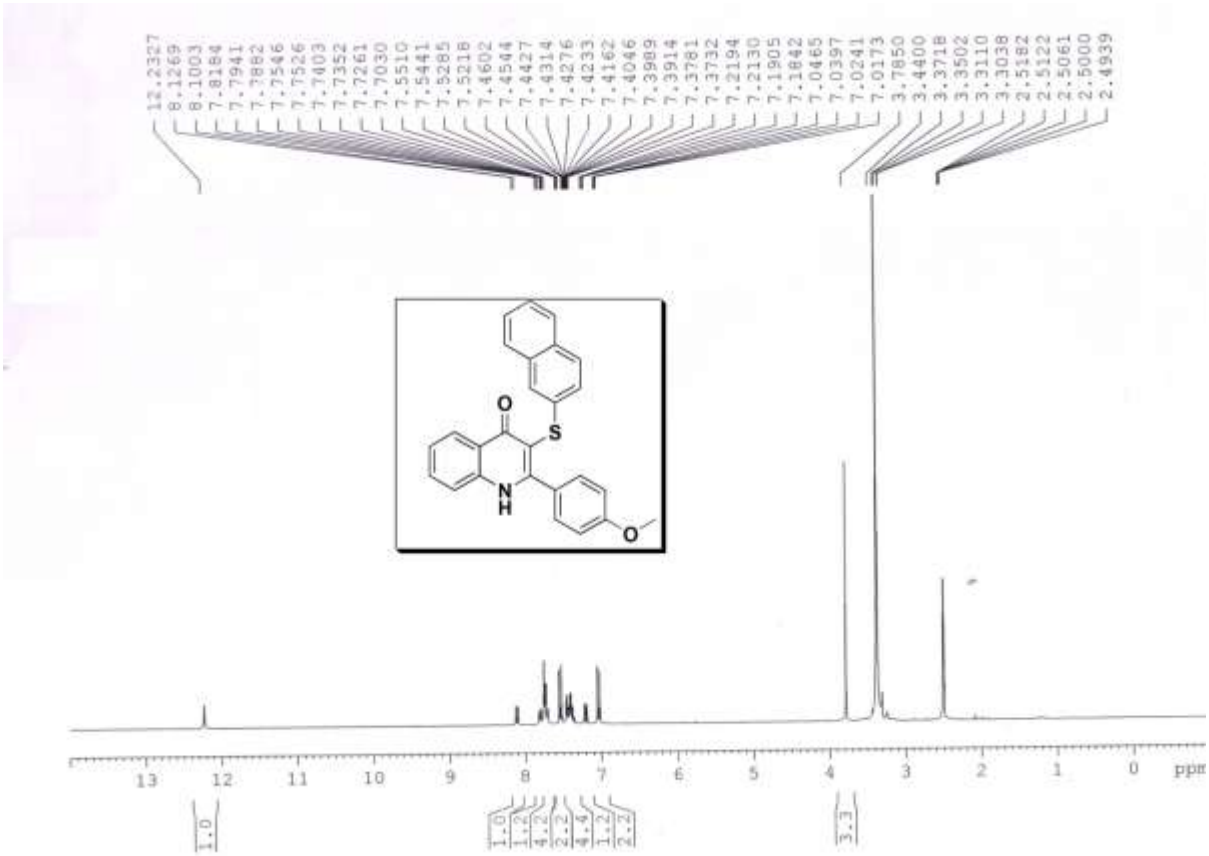


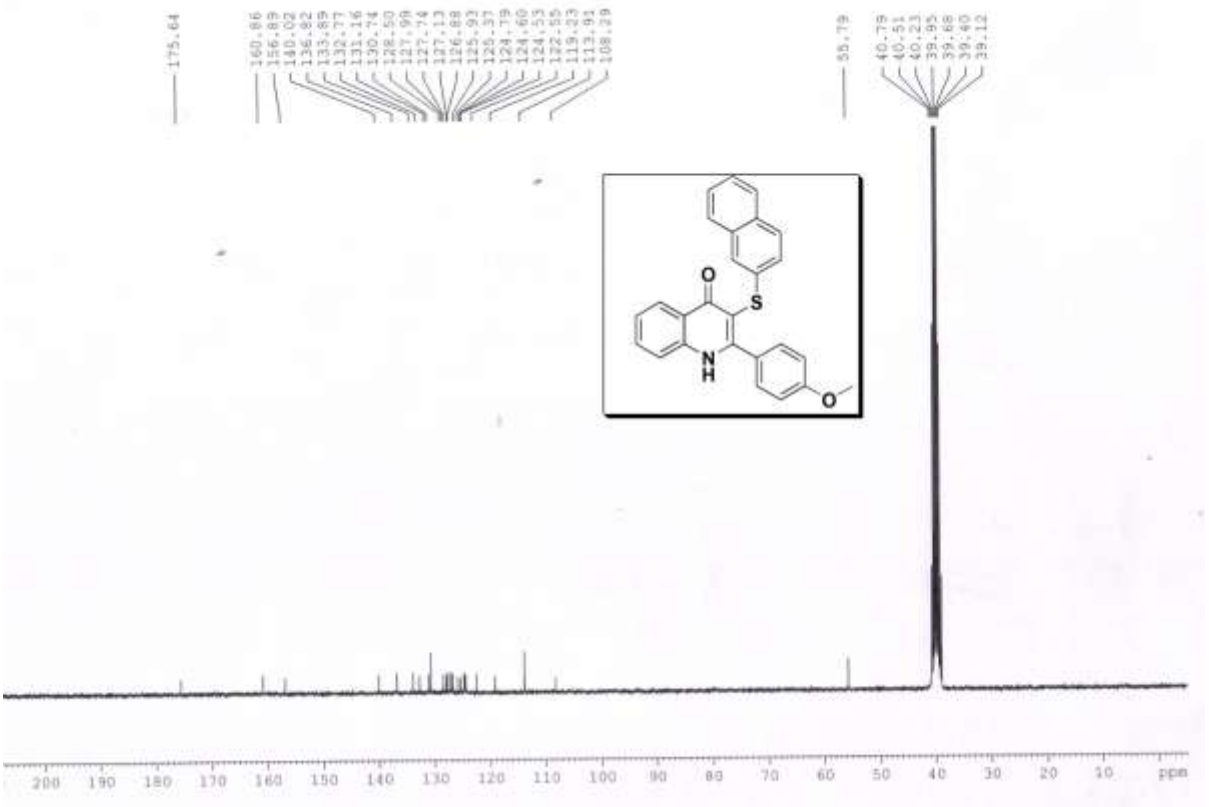
**$^{1}$H and $^{13}$C NMR spectra of entry 2i (Scheme-IV.1.) in DMSO-$d_6$**



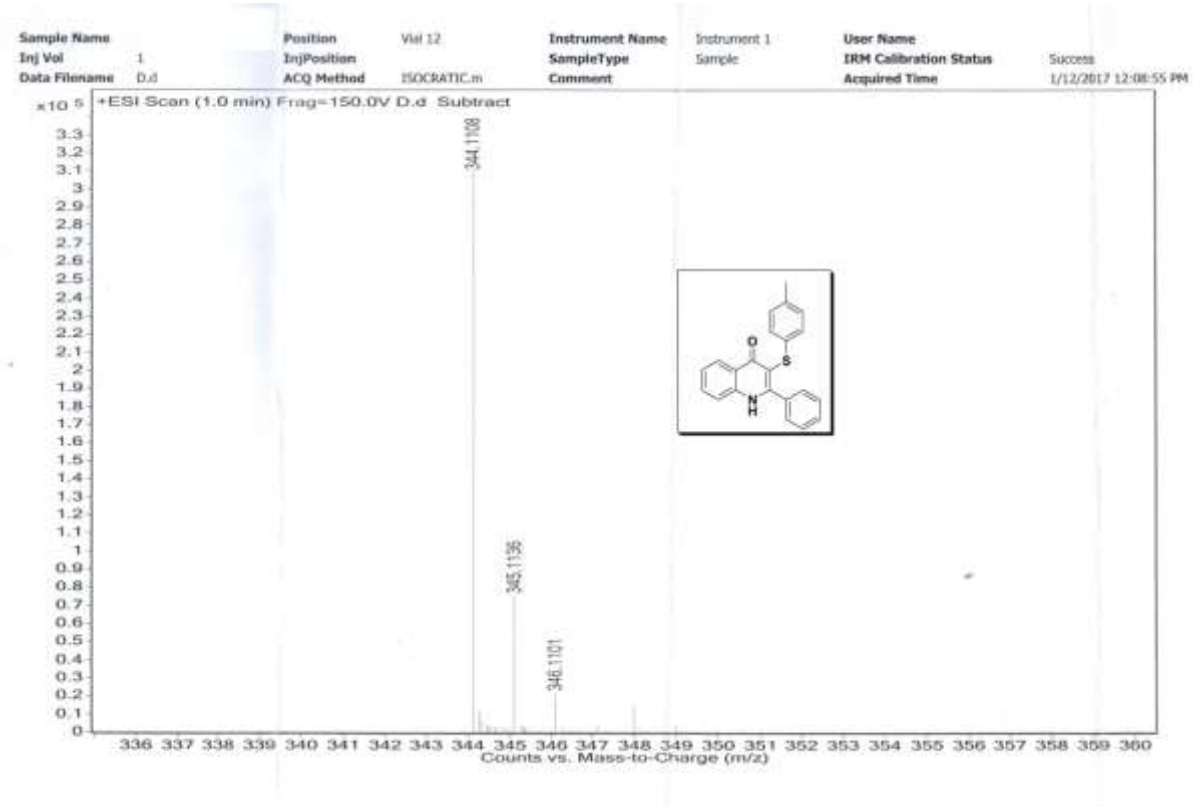



**$^{1}$H and $^{13}$C NMR spectra of entry 2r (Scheme-IV.1.) in DMSO-$d_6$**

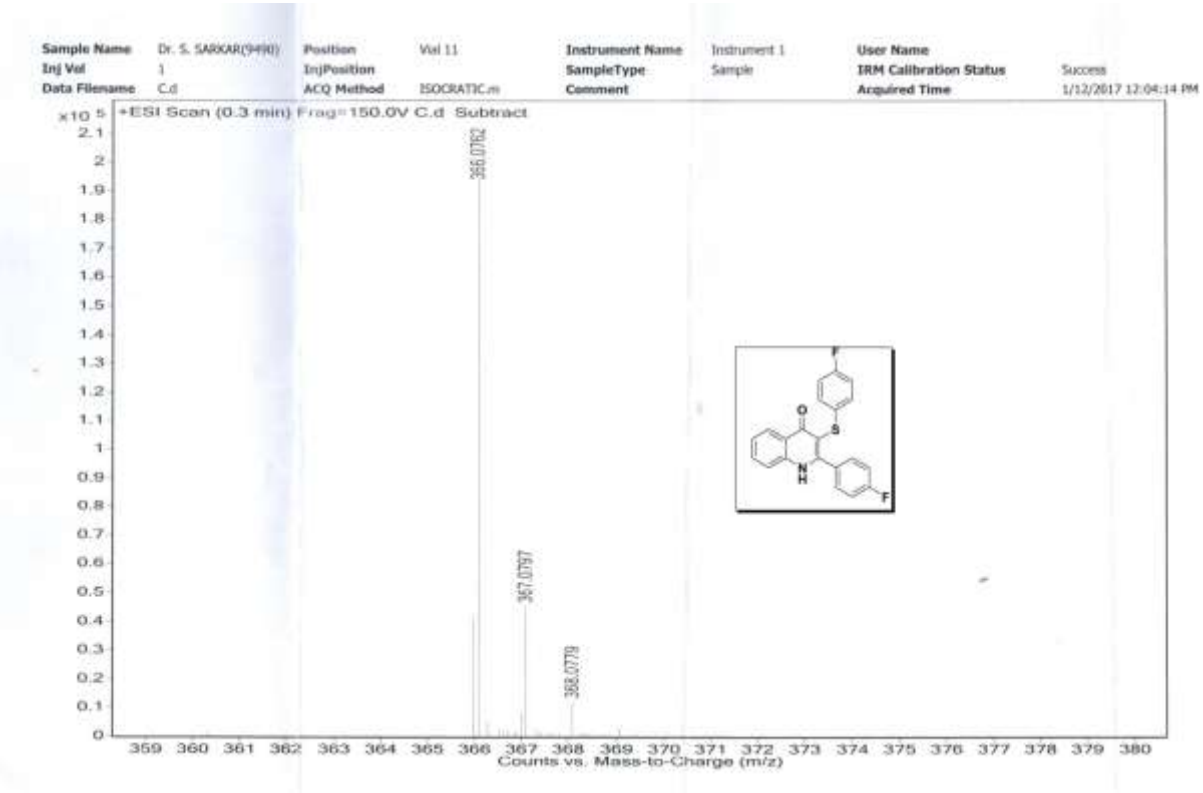


**Scan copy HRMS of entry 2b (Scheme-IV.1)**




**Scan copy HRMS of entry 2i (Scheme-IV.1)**



## IV.E. References

References are given in BIBLIOGRAPHY under Chapter IV (pp-232-233)

# Chapter V

# *Ni catalysed C-S cross coupling of 3-iodo-2-aryl substituted 4-quinolone derivatives*

## V.A. Introduction

In organic syntheses, the formation of C-S bond has experienced a lot of attention due to its profound impact in pharmaceuticals, organic dyes, material chemistry and agrochemicals etc.[1] Therefore, the generation of new methodology to enrich the chemistry of C-S coupling is still a challenge . But until now, various techniques are easily found in the literature. Traditional approaches followed the reaction of aryl halides, aryl boronic acids or pseudo halides with disulfides or thiols in presence of transitional metal.[2]4-quinolone skeleton has been occurred in many biologically active molecules, drugs, natural products for its anti malarial[3], anti cancer[4], antimitotic[5]and xanthine oxidase activities.[6] Few biologically active thioether containing molecules are shown below.

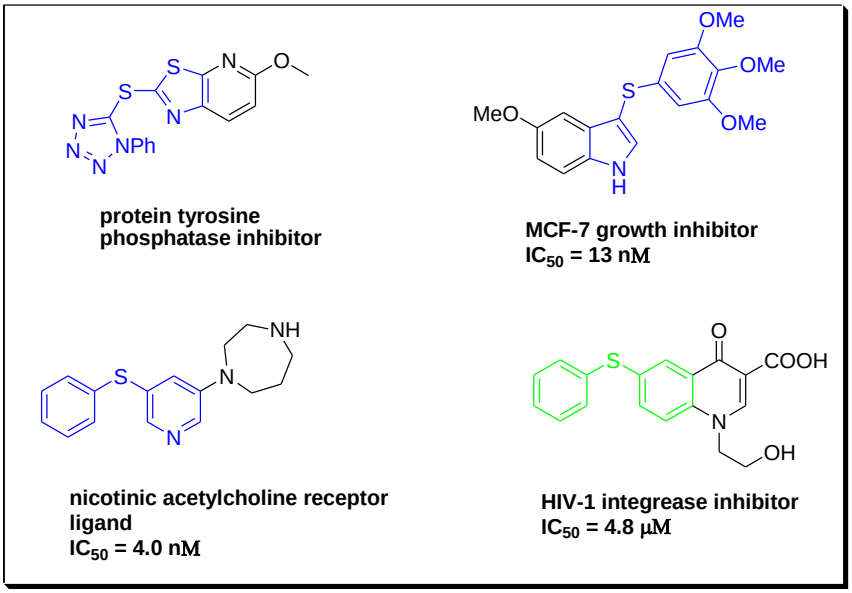
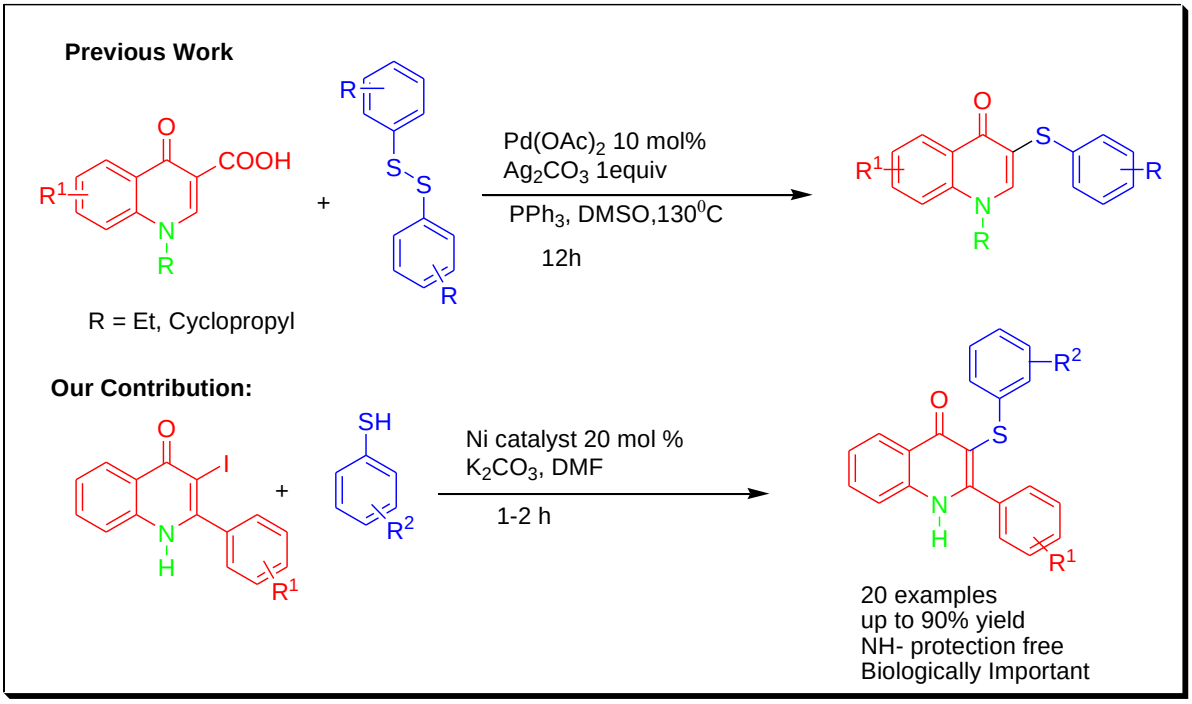



**Fig-V. 1**. Some Important C-S linkage containing biologically active molecules

## V.B. Present work: Background & objectives

Very recently, Zhang and his coworkers reported the direct insertion of –SPh moiety into the 4-quinolone precursor *via* Pd catalyzed decarboxylation protocol.[7] Nevertheless, this approach has some drawbacks like harsh reaction condition, longer reaction time; essentially requires halogen substituted starting material and prerequisite protection of –NH functional group. An efficient nickel catalysed C-S coupled protocol for the synthesis of thioether linkage in 4-quinolone from 3-iodo-4-quinolone is developed. This methodology enables the production of diverse ArS-substituted 4-quinolone derivatives in excellent yield under short span of time, which may enhance the drug efficacy of quinolone scaffolds.



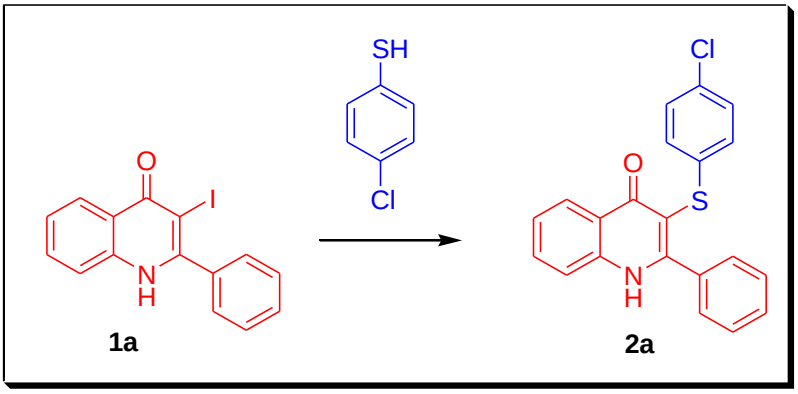

**Scheme-V.1.** Approach for the C-S cross coupling of 4-quinolone derivatives

### V.B.1. Present work: Result and Discussion

To optimize the reaction condition, we commenced our investigation by the reaction of 3-iodo-2-aryl substituted-4-quinolone and benzene thiol in DMF, as a model reaction under nitrogen atmosphere. Delightfully, thioetherification at C-3 position of 4-quinolone took place in the presence of $NiCl_2.6H_20$ and DMF, afforded 87% yield in 2 h (Table-V.1, entry 1). Subsequently, various Nickel catalyst such as $Ni(OAc)_2.4H_20$, $NiSO_4.6H_20$ were screened to proceed the reaction; among them Nickel chloride served the best results (Table-V.1, entry 1 *vs* 3,6**)**. Only 20 mol % of Nickel chloride required to catalyse the reaction. Furthermore, various solvents were also examined such as DMF, toluene, DMSO, 1,4-dioxane, and to achieve the fruitful result (Table-V.1, entry-1 and 7-9). Among them DMF proved to be the best suited solvent, affording 87% yield of **2a** in 2 h (Table-V.1, entry-1). The reaction temperature 80°C was found to be the optimal to furnish the highest yield of **2a** (Table-V.1, entry-1). The base has also a profound role in this transformation, $K_2CO_3$ found to be superior to the other bases such as KOH and $Cs_2CO_3$ Table-V.1, entry-1, 2-4). It has also been found that without nitrogen atmosphere the C-S coupled reaction afforded low yield of the desired product (Table-V.1, entry-11). After investigating the various catalysts, solvent, catalyst loading and reaction temperature, the combination of $NiCl_2.6H_20$ (20 mol %), $K_2CO_3$

(2 equiv) in DMF at 80°C for 2 h served the optimal reaction condition for this transformation under $N_2$ atm.

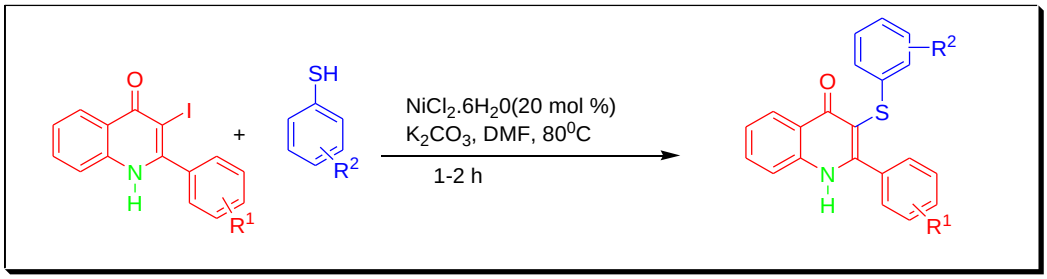
**Table-V.1. Screening of the reaction conditions**

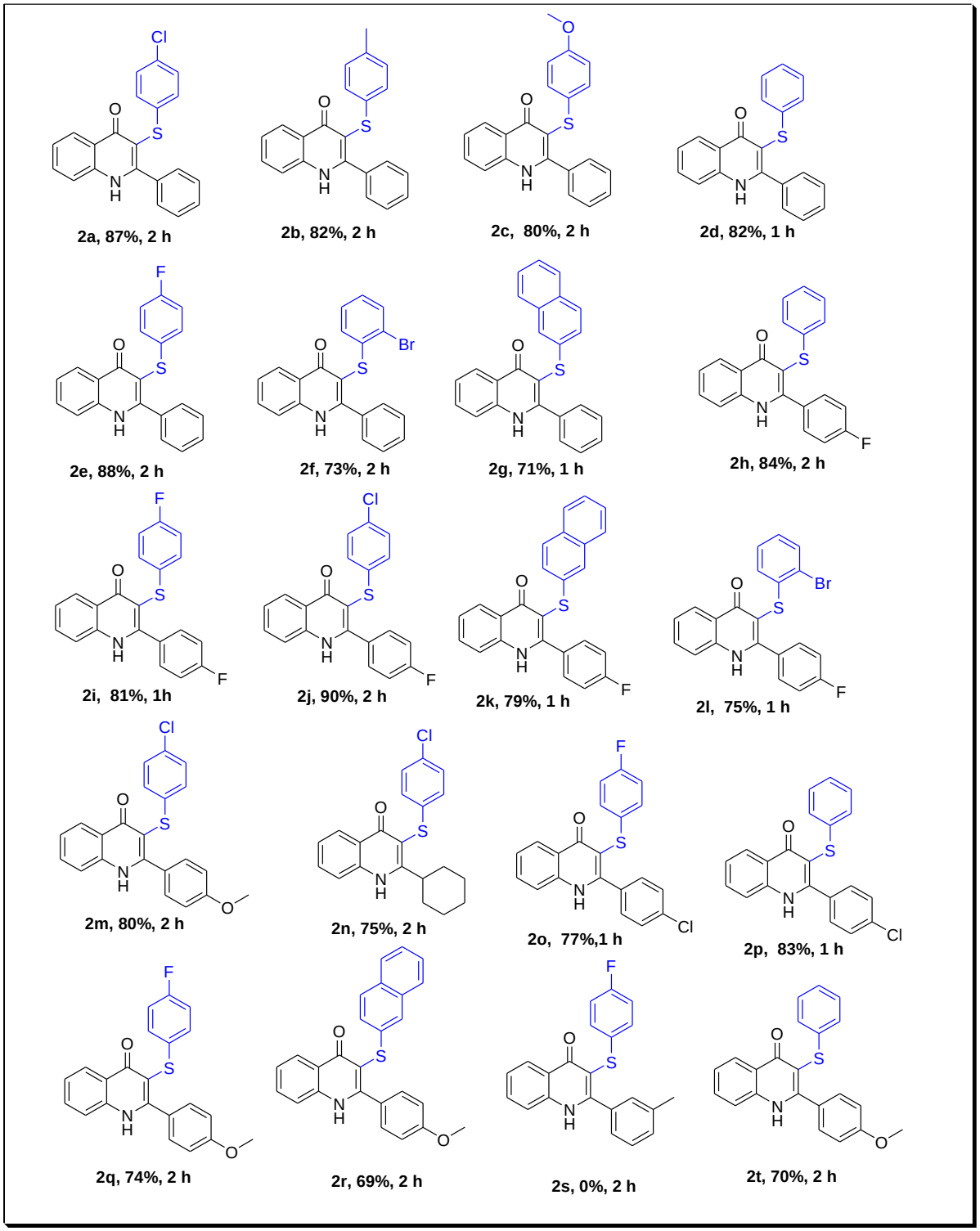



| entry | catalyst (mol %) | base (equiv) | time (h) | temp( °C) | solvent | yield ( %) |
|---|---|---|---|---|---|---|
| 1 | **$NiCl_2.6H_2O$ (20)** | **$K_2CO_3$** | **2** | **80** | **DMF** | **87** |
| 2 | $NiCl_2.6H_2O$ (20) | $Cs_2CO_3$ | 2 | 80 | DMF | 64 |
| 3 | $Ni(OAc)_2.4H_2O$ (20) | $Cs_2CO_3$ | 2 | 80 | DMF | 60 |
| 4 | $NiCl_2.6H_2O$ (20) | KOH | 2 | 80 | DMF | 74 |
| 5 | $NiCl_2.6H_2O$ (40) | $K_2CO_3$ | 2 | 80 | DMF | 80 |
| 6 | $NiSO_4.6H_2O$ (40) | $K_2CO_3$ | 2 | 80 | DMF | 58 |
| 7 | $NiCl_2.6H_2O$ (20) | $K_2CO_3$ | 8 | 80 | toluene | 55 |
| 8 | $NiCl_2.6H_2O$ (20) | $K_2CO_3$ | 4 | 80 | DMSO | 79 |
| 9 | $NiCl_2.6H_2O$ (20) | $K_2CO_3$ | 2 | 80 | Dioxane | 71 |
| 10 | $NiCl_2.6H_2O$ (20) | $K_2CO_3$ | 2 | 100 | DMF | 85 |
| 11 [a] | $NiCl_2.6H_2O$ (20) | $K_2CO_3$ | 2 | 80 | DMF | 65 |

**Reaction conditions**: 0.25 mmol of 1a and 0.375 mmol of thiophenol was stirred at 80 °C under $N_2$ atm. Yield = Isolated yields. [a] without $N_2$ atmosphere.

**Scheme-V.2. Substrate scope of the C-S coupling reaction:**






**Reaction conditions**: 0.25 mmol of 3-iodo substituted 4-quinolones, 0.375 mmol of various thiophenol and 20 mol% $NiCl_2.6H_20$ (12 mg) was stirred in DMF (2ml) under nitrogen atmosphere at 80°C. Yield = Isolated yield after column chromatography.

With the optimized reaction conditions in our hand, the scope of nickel catalysed C-S coupling reaction of both 3-iodo-2-aryl substituted-4-quinolone and various substituted benzene thiols as shown in Scheme-V.2. A broad array of benzene thiols were successfully coupled with various 3-iodo-2-phenylquinolin-4-(*1H*)one, affording the corresponding product 3-aryl sulfide-4-quinolone in good to excellent yields. Likewise, the benzene thiols bearing both electron releasing and electron withdrawing groups were performed very well manner in this transformation. *p*-fluoro substituted benzene thiol was coupled with 3-iodo-2-phenylquinolin-4-(*1H*)one, resulted the 88% yield of the desired product (Scheme-V.2, entry **2e**). *p*-chloro substituted thiol coupled with the 3-iodo-2-aryl substituted-4-quinolone excellently in a very short span of time (Scheme-V.2, entry- **2a**). However, bulkier 2-naphthyl thiol furnished moderate to excellent yield of the desired products (69%-79%) respectively (Scheme-V.2, entry **2g, 2k, 2r**). The moderate yield of **2g** and **2r** is basically due to the steric hindrance of naphthyl ring with the phenyl group at C-2 position of 4-quinolone. Also, we investigated the role of various groups in the C-2 substituted phenyl ring of 4-quinolone. It has been found that electron withdrawing group possessing benzene (*p*-F), resulted much higher yield than the electron releasing group (Scheme-V.2, entry **2h-2l, 2p, 2m, 2q, 2r**). Cyclohexyl group substituted 4-quinolone also proved to be a good coupling partner with 4-chloro benzene thiol (Scheme-V.2, entry **2n**). Highest yield was obtained when 2-(4-fluorophenyl)-3-iodoquinolin-4-(*1H*)-one was coupled with 4-fluoro benzene thiol (Scheme-V.2, entry **2j**). Interestingly, meta substituted phenyl ring at C-2 position of 4-quinolone did not afford the corresponding product (scheme V.2, entry **2s**) under this optimized condition. More significantly, the most of the reaction completed within 1 h and afforded the promising yield of the desired C-S coupled product (Scheme-V.2, entry **2a, 2g, 2i, 2k, 2l, 2o** and **2p**).

**V.C. Conclusion:**

In summary, we have developed a simple protocol for the synthesis of a library of ArS substituted 4-quinolone skeletons. This method is simple and does not require any expensive catalyst for the isolation of desired products in very good yields. These compounds will be evaluated for their biological activities and reported in due course.

## V.D. Experimental section:

### V.D.1.General Information:

Unless stated otherwise, all reagents such as thiophenols, $NiCl_2.6H_2O$, bases and solvents were used as received from commercial suppliers. NMR spectra were recorded on 300 MHz spectrometer at 298 K with calibration done on the basis of solvent residual peak. Mass spectra were performed using ion trap mode. Products were purified using column chromatography on silica gel (60-120 mesh). Ethyl acetate and petroleum ether (60-80$^oC$) were used as eluents. Progress of reaction was monitored using silica gel TLC.

### V.D.2. Preparation of Various 3-iodo-2-phenyl substituted 4-quinolones (1a-1f)[8]

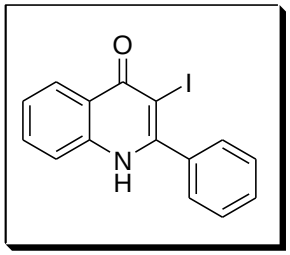
Initially, 2-aryl quinolin-4(1*H*)-one (1a, 0.25mmol), iodine (2 equiv.) and sodium carbonate (1.5 equiv.) in THF (2 ml) was stirred at room temperature for 18 hours. Then, the reaction mixture was quenched with sodium thiosulphate and the precipitate was collected by filtration and washed with ice-cold water. Afterwards, the crude product was purified through column chromatography.

### V.D.3. Preparation of various thioether substituted 4-quinolones

Initially, various 3-iodo-2-aryl substituted 4-quinolone (0.25mmol), thiophenol (0.375mmol), $K_2CO_3$ (0.5 mmol, 69mg) and 20mol% $NiCl_2.6H_20$ (12mg) were taken in DMF (2ml) in 25 ml round bottomed flask. Then, it was filled with nitrogen atmosphere for 3 times. Afterwards, the reaction mixture was heated at 80°C for 1-2 hr. Then, it was cooled and diluted with water and the product was extracted with ethyl acetate (3 x 20 mL). Organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude product was then purified using column chromatography.

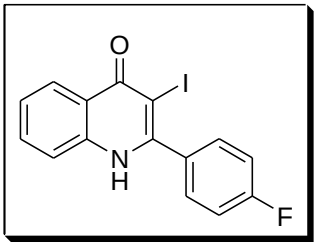
### V.D.4. Physical characteristics and spectral data of compounds

1. **3-iodo-2-phenylquinolin-4(1*H*)-one (1a)**[8]



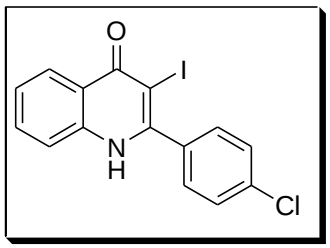

Light Yellow solid, $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7.36-7.42 (m, 1H), 7.53-7.58 (m, 5H), 7.63-7.69 (m, 2H), 8.13 (dd, *J* = 8.1Hz, 0.9Hz, 1H), 12.29 (s,1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ 86.3, 118.8, 121.3, 124.7, 125.9, 128.8, 129.4, 130.3, 132.6, 139.7, 153.6, 174.1.

**2. 2-(4-fluorophenyl)-3-iodo-quinolin-4(1*H*)-one (1b)**[8]



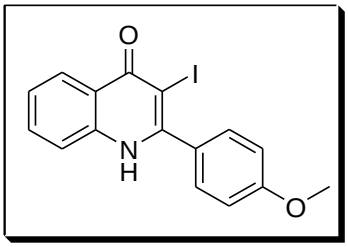

Light Yellow solid, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.38-7.45 (m, 3H), 7.62-7.71 (m, 4H), 8.15 (d, *J* = 8.0Hz, 1H), 12.3 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 86.6, 115.7, 115.9, 118.9, 121.4, 124.6, 125.9, 131.9, 132.1, 132.6, 134.8, 134.9, 139.8, 152.7, 161.5, 164.8, 174.0.

**3. 2-(4-chlorophenyl)-3-iodo-quinolin-4(1*H*)-one (1c)**[8]



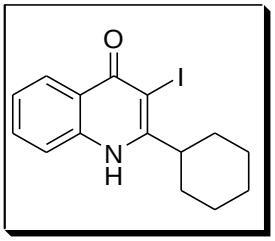

Light Yellow solid, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.37-7.42 (m, 1H), 7.59-7.73 (m, 5H), 8.15 (d, *J* = 9.9Hz, 1H), 12.13 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 86.4, 119.3, 121.6, 124.5, 125.9, 128.8, 131.5, 132.4, 134.9, 137.5, 152.9, 173.8.

**4. 3-iodo-2-(4-methoxyphenyl) quinolin-4(1*H*)-one (1d)**[8]



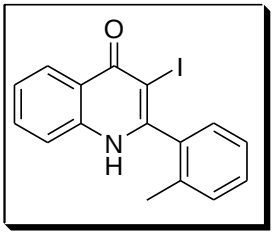

Light Yellow solid, Melting point: $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.56 (s, 3H), 7.13 (d, *J* = 8.7Hz, 2H), 7.39-7.42 (m, 1H), 7.53 (d, *J* = 8.7Hz, 2H), 7.67-7.70 (m, 2H), 8.13 (d, *J* = 7.8Hz, 1H), 12.20 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 55.8, 86.6, 114.1, 118.8, 121.3, 124.5, 125.9, 130.7, 131.1, 132.5, 139.8, 153.4, 160.7, 174.0.

**5. 2-cyclohexyl-3-iodo-quinolin-4(1*H*)-one (1e)**



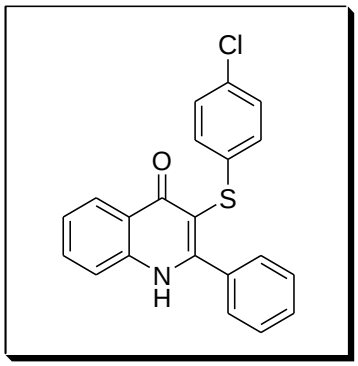

Light Yellow solid, melting point:222-224°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.35 (s, 3H), 1.82 (dd, *J* = 18.9Hz, 9.6Hz, 7H), 7.34 (t, *J* = 7.2Hz, 1H), 7.65-7.70 (m, 1H), 7.82 (d, *J* = 8.3Hz, 1H), 8.07 (d, *J* = 8.0Hz, 1H), 11.25 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 25.6, 26.4, 29.9, 40.8, 49.0, 87.1, 118.7, 121.4, 124.3, 125.8, 132.3, 139.8, 157.5, 173.7.

**6. 3-iodo-2-*o*-tolyl- quinolin-4(1*H*)-one (1f)**



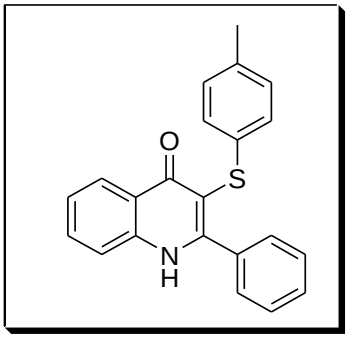

Light Yellow solid, melting point: 220-222°C;$^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 2.17 (s, 3H), 7.31-7.47 (m, 5H), 7.61-7.70 (m, 2H), 8.16 (d, *J* = 7.6Hz, 1H), 12.31 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 19.2, 87.1, 118.9, 121.5, 125.9, 126.5, 129.0, 130.1, 130.6, 132.5, 135.4, 138.5, 153.8, 173.8.

**7. (4-chlorophenylthio)-2-phenylquinolin-4(1*H*)-one (2a)**



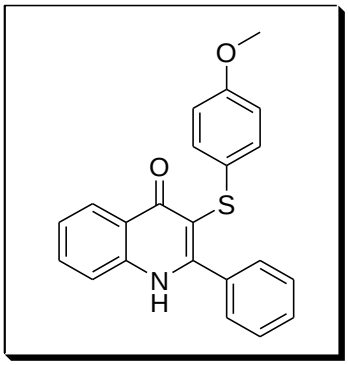

White solid, melting point: 235-237°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 6.96 (d, *J* = 1.5Hz, 2H), 6.99 (d, *J* = 1.8Hz, 2H), 7.17-7.20 (m, 1H), 7.38-7.49 (m, 5H), 7.68-7.70 (m, 2H), 8.07 (d, *J* = 7.8Hz, 1H). $^{13}$C NMR (75 MHz DMSO-$d_6$,) δ 107.7, 118.7, 124.1, 124.3, 125.4, 126.8, 128.1, 128.5, 128.8, 129.7, 132.4, 134.9, 137.4 , 139.4, 156.5, 174.9.

**8. 3-(4-methylphenylthio)-2-phenylquinolin-4(1*H*)-one (2b)**



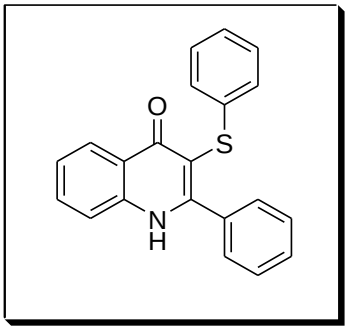
White solid, melting point:185-187°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 2.20 (s, 3H), 6.95 (d, *J* = 8.4Hz, 2H), 6.99 (d, *J* = 8.4Hz, 2H), 7.38-7.73 (m, 8H), 8.10-8.16 (m, 1H), 12.24 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 20.8, 109.1, 119.2, 124.5, 124.6, 125.9, 128.5, 128.9, 129.1, 129.4, 129.8, 130.1, 130.3, 132.8, 134.1, 135.2, 135.6, 139.9, 156.8, 175.6.

**9. 3-(4-methoxyphenylthio)-2-phenylquinolin-4(1*H*)-one (2c)**



White solid, melting point: 225-227°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.67 (s, 3H), 6.78 (dd, *J* = 6.9Hz, 1.8Hz, 2H), 6.98 (dd, *J* = 6.9Hz, 1.8Hz, 2H), 7.40-7.43 (m, 1H), 7.51-7.55 (m, 5H), 7.70-7.72 (m, 2H), 8.11 (d, *J* = 8.1Hz, 1H), 12.22 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 52.1, 107.0, 111.4, 115.7, 121.1, 121.1, 122.4, 124.9, 125.0, 125.7, 125.8, 126.7, 129.3, 132.1, 136.4, 153.0, 154.2, 172.2.

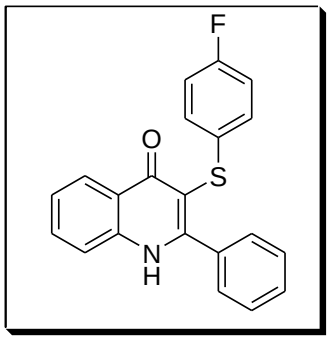
**10. 2-phenyl-3-(phenylthio)quinolin-4(1*H*)-one (2d)**



White solid, melting point: 245-247°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 6.97-7.05 (m, 3H), 7.14-7.20 (m, 2H), 7.41 (s, 1H), 7.48-7.54 (m, 5H), 7.71-

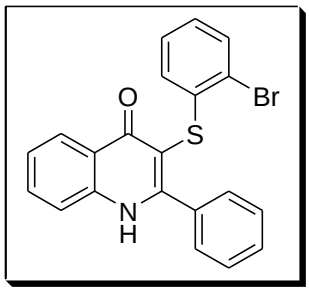
7.73 (m, 2H), 8.11 (d, *J* = 7.8Hz, 1H), 12.29 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 108.5, 119.2, 124.5, 124.7, 124.8, 125.5, 125.9, 128.5, 129.0, 129.1, 130.2, 132.8, 135.5, 138.8, 139.9, 175.5.

**11. 3-(4-fluorophenylthio)-2-phenylquinolin-4(1*H*)-one (2e)**



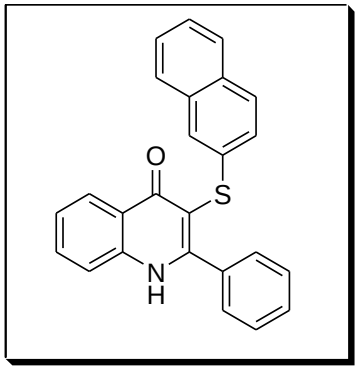

White solid, melting point: 240-242°C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.02-7.05 (m, 4H), 7.39-7.44 (m, 1H), 7.50-7.54 (m, 5H), 7.71-7.74 (m, 2H), 8.12 (d, *J* = 7.5Hz, 1H), 12.28 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 105.8, 105.9, 112.4, 112.7, 115.7, 121.2, 122.4, 124.4, 124.5, 124.7, 125.1, 125.6, 126.7, 129.3, 130.7, 132.0, 136.5, 153.4, 155.5, 158.7, 172.0. HRMS (ESI$^+$): $[M+H]^+$ , found 348.0855. $C_{21}H_{15}FNOS$ requires 348.0853.

**12. 3-(2-bromophenylthio)-2-phenylquinolin-4(1*H*)-one (2f)**



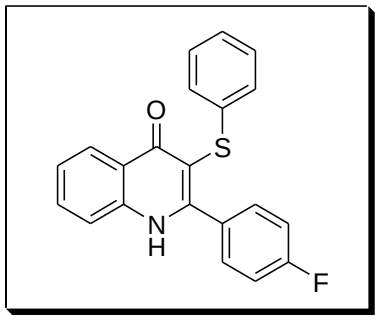

White solid, melting point:> 260°C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 6.86 (dd, *J* = 8.1Hz, 1.5Hz, 1H), 6.99 (dt, *J* = 7.5Hz, 1.5Hz, 1H), 7.18 (dt, *J* = 7.8Hz, 1.2Hz, 1H), 7.41-7.54 (m, 7H), 7.74-7.76 (m, 2H), 8.13 (d, *J* = 7.8Hz, 1H), 12.38 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 107.8, 119.3, 119.5, 124.6, 124.8, 125.9, 126.2, 126.3, 128.3, 128.6, 128.9, 130.3, 132.8, 132.9, 135.3, 139.5, 140.0, 157.4, 175.3. HRMS (ESI$^+$): $[M+H]^+$ , found 408.0053. $C_{21}H_{15}BrNOS$ requires 408.0052.

**13. 3-(naphthalen-1-ylthio)-2-phenylquinolin-4(1*H*)-one (2g)**



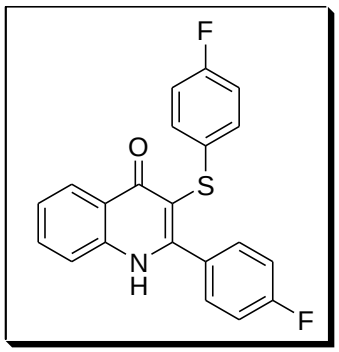

White solid, melting point:>260°C,$^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.19-7.22 (m, 1H), 7.38-7.52 (m, 7H), 7.57-7.60 (m, 2H), 7.71-7.82 (m, 5H), 8.13 (d, *J* = 8.1Hz, 1H), 12.35 (s, 1H);$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 107.9, 118.7, 122.2, 124.1, 124.2, 124.3, 124.9, 125.4, 126.4, 126.6, 127.5, 128.0, 128.1, 128.5, 129.7, 130.7, 132.4, 133.3, 135.0, 136.1, 139.5, 156.6, 175.1.

**14. 2-(4-fluorophenyl)-3-(phenythio)quinolin-4(1*H*)-one (2h)**




White solid, melting point:236-238°C,$^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 6.99-7.07 (m, 3H), 7.15-7.20 (m, 2H), 7.30-7.44 (m, 3H), 7.57-7.62 (m, 2H), 7.69-7.77 (m, 2H), 8.12 (d, *J* = 7.5Hz, 1H), 12.30 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 108.8, 115.4, 115.6, 119.2, 124.5, 124.7, 124.9, 125.6, 125.9, 129.2, 131.5, 131.6, 131.8, 131.9, 132.9, 138.6, 139.9, 156.0, 161.6, 14.9, 175.5.

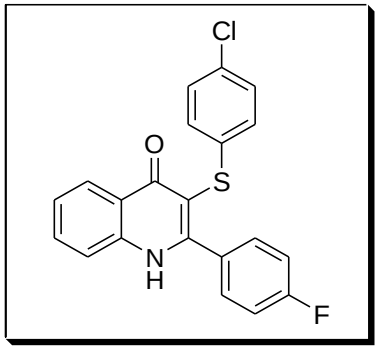
**15. 3-(4-fluorophenylthio)-2-(4-fluorophenyl)quinolin-4(1*H*)-one (2i)**




White solid, melting point: 230-232°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.02-7.03 (m, 3H), 7.05-7.44 (m, 3H), 7.58-7.74 (m, 4H), 8.12 (d, *J* =

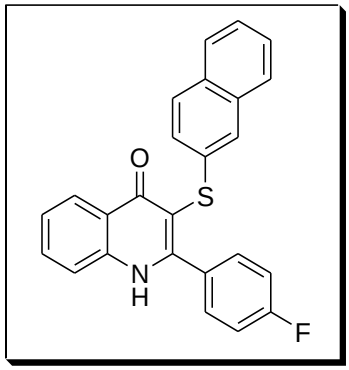
8.1Hz, 1H), 12.29 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 106.0, 111.9, 112.2, 112.5, 112.8, 115.3, 115.7, 117.9, 121.2, 121.3, 122.5, 124.5, 124.6, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 129.2, 129.4,130.5, 130.6, 131.4, 136.3, 136.4, 149.2, 152.4, 155.5, 158.2, 161.4, 170.6, 172.0. HRMS (ESI$^+$): $[M+H]^+$ , found 366.0762. $C_{21}H_{14}F_2NOS$ requires 366.0759.

**16. 3-(4-chlorophenylthio)-2-(4-fluorophenyl)quinolin-4(1*H*)-one (2j)**



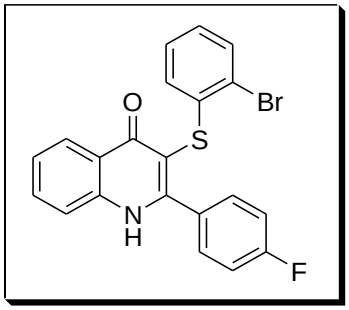

White solid, melting point:158-160°C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.01-7.04 (m, 2H), 7.22-7.25 (m, 2H), 7.32-7.45 (m, 3H), 7.57-7.62 (m, 2H), 7.69-7.75 (m, 2H), 8.12 (d, *J* = 8.1Hz, 1H), 12.22 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 107.9, 114.9, 115.2, 118.8, 124.1, 124.3, 125.4, 126.8, 128.5, 128.9, 130.9, 131.1, 131.2, 131.3, 132.4, 137.3, 139.4, 156.6, 161.1, 164.4, 174.8.

**17. 2-(4-fluorophenyl)-3-(naphthalene-2-ylthio)quinolin-4(1*H*)-one (2k)**



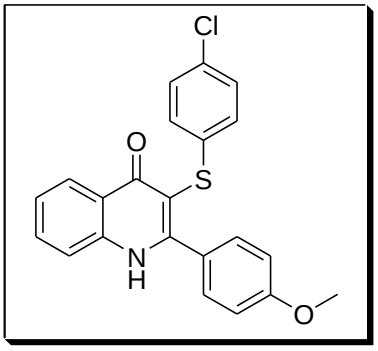

White solid, melting point: 170-172°C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.21 (dd, *J* = 8.4Hz, 2.1Hz, 1H), 7.30-7.47 (m, 6H), 7.62-7.82 (m, 7H), 8.12 (d, *J* = 7.8Hz, 1H), 12.34 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 108.8, 115.4, 115.7, 119.2, 122.9, 124.7, 124.9, 125.4, 125.9, 126.9, 127.1, 127.9, 128.5, 131.2, 131.5, 131.6, 131.9, 132.8, 133.9, 136.4, 140.0, 156.1, 161.6, 164.9, 175.6.

**18. 3-(2-bromophenylthio)-2-(4-fluorophenyl)quinolin-4(1*H*)-one (2l)**



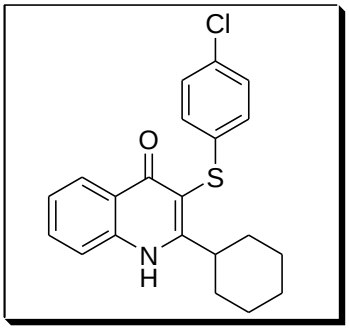

White solid, melting point: 250-252°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 6.85 (dd, *J* = 7.8Hz, 1.5Hz, 1H), 7.00(dt, *J* = 7.5Hz, 1.5Hz, 1H0, 7.15-7.20 (m, 1H), 7.31-7.37 (m, 2H), 7.41-7.61 (m, 6H), 7.73-7.76 (m, 2H), 8.13 (dd, *J* = 7.8Hz, 1.2Hz, 1H), 12.30 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 108.0, 115.5, 115.7, 119.3, 119.5, 124.6, 124.9, 125.9, 126.2, 126.3, 128.4, 131.4, 131.5, 131.6, 131.7, 132.8, 133.0, 139.4, 140.0, 156.5, 161.7, 162.8, 165.0, 175.3. HRMS (ESI$^{+}$): $[M+H]^{+}$, found 425.9960. $C_{21}H_{14}BrFNOS$ requires 425.9958.

**19. 3-(4-chlorophenylthio)-2-(4-methoxyphenyl)quinolin-4(1*H*)-one (2m)**



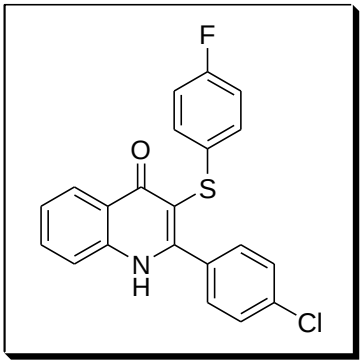

White solid, melting point: 220-222°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.81(s, 3H), 7.00-7.07 (m, 4H), 7.22-7.24 (m, 2H), 7.47 (d, J= 8.7Hz, 3H), 7.71 (s, 2H), 8.10 (d, J= 8.1Hz, 1H), 12.35 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 55.8, 109.2, 114.1, 116.5, 119.2, 126.5, 127.3, 129.2, 129.8, 130.6, 130.7, 131.1, 133.1, 135.4, 141.6, 148.8, 159.8, 176.1.

**20. 3-(4-chlorophenylthio)-2-cyclohexylquinolin-4(1*H*)-one (2n)**



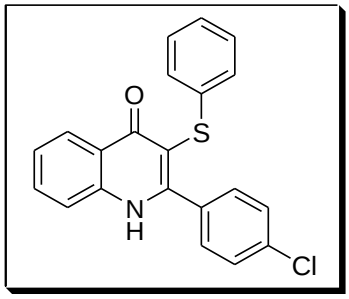

White solid, melting point: 238-240°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.17-1.29 (m, 3H), 1.63-1.83 (m, 7H), 7.02-7.13 (m, 4H), 7.35 (t, *J* = 7.2Hz, 1H), 7.59 (dt, *J* = 7.2Hz, 1.5Hz, 1H), 7.80-7.83 (m, 1H), 8.05 (dd, *J* = 8.1Hz, 1.2Hz, 1H), 11.29 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 25.6, 26.3, 30.5, 42.5, 108.8, 116.1, 116.4, 118.9, 124.3, 124.4, 125.8, 128.3, 128.4, 132.6, 134.1, 134.2, 139.9, 162.5, 175.4.

**21. 3-(4-fluorophenylthio)-2-(4-chlorophenyl)quinolin-4(1*H*)-one (2o)**




White solid, melting point: 165-167°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.00-7.03 (m, 4H), 7.37-7.43 (m, 1H), 7.52-7.58(m, 4H), 7.65-7.72 (m, 2H), 8.1 (dd, *J* = 6.9Hz, 1.5Hz, 1H), 12.30 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 115.5, 115.7, 120.8, 124.1, 124.2, 125.4, 127.6, 127.7, 128.1, 128.4, 130.6, 132.4, 133.4, 133.7, 134.5, 139.5, 147.4, 152.0, 155.2, 158.5, 161.7, 174.9.

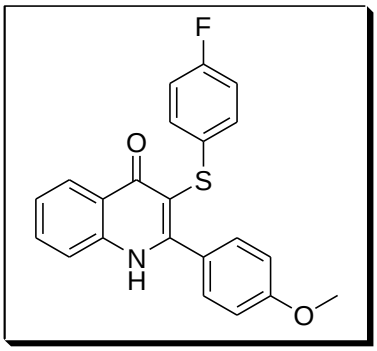
**22. 2-(4-chlorophenyl)-3-(phenythio)quinolin-4(1*H*)-one (2p)**




White solid, melting point:243-245°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 6.99-7.07 (m, 3H), 7.16-7.21 (m, 2H), 7.40-7.45 (m, 1H), 7.57 (s, 4H), 7.68-

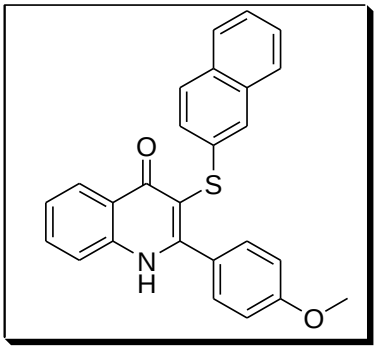
7.77 (m, 2H), 8.12 (d, *J* = 7.2Hz, 1H), 12.30 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 108.7, 119.2, 124.6, 124.7, 124.9, 125.6, 125.9, 128.6, 129.2, 131.0, 132.9, 134.2, 135.0, 138.5, 139.9, 155.8, 175.4.

**23. 3-(4-fluorophenylthio)-2-(4-methoxyphenyl)quinolin-4(1*H*)-one (2q)**



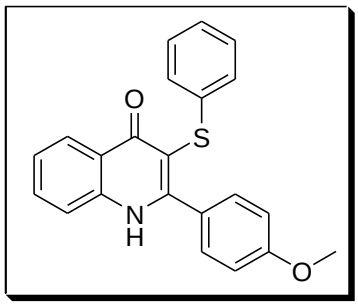

White solid, melting point:190-192°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.82 (s, 3H), 7.02-7.07 (m, 7H), 7.40-7.41(m, 1H), 7.48 (dd, *J* = 4.8Hz, 1.8Hz, 2H), 7.70-7.73 (m, 2H), 8.10 (d, *J* = 8.1Hz, 1H), 12.20 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 55.8, 109.2, 113.9, 115.9, 116.2, 119.1, 124.5, 125.9, 127.7, 127.8, 127.9, 130.8, 132.7, 134.4, 139.9, 156.7, 160.9, 175.5.

**24. 2-(4-methoxyphenyl)-3-(naphthalene-2-ylthio)quinolin-4(1*H*)-one (2r)**



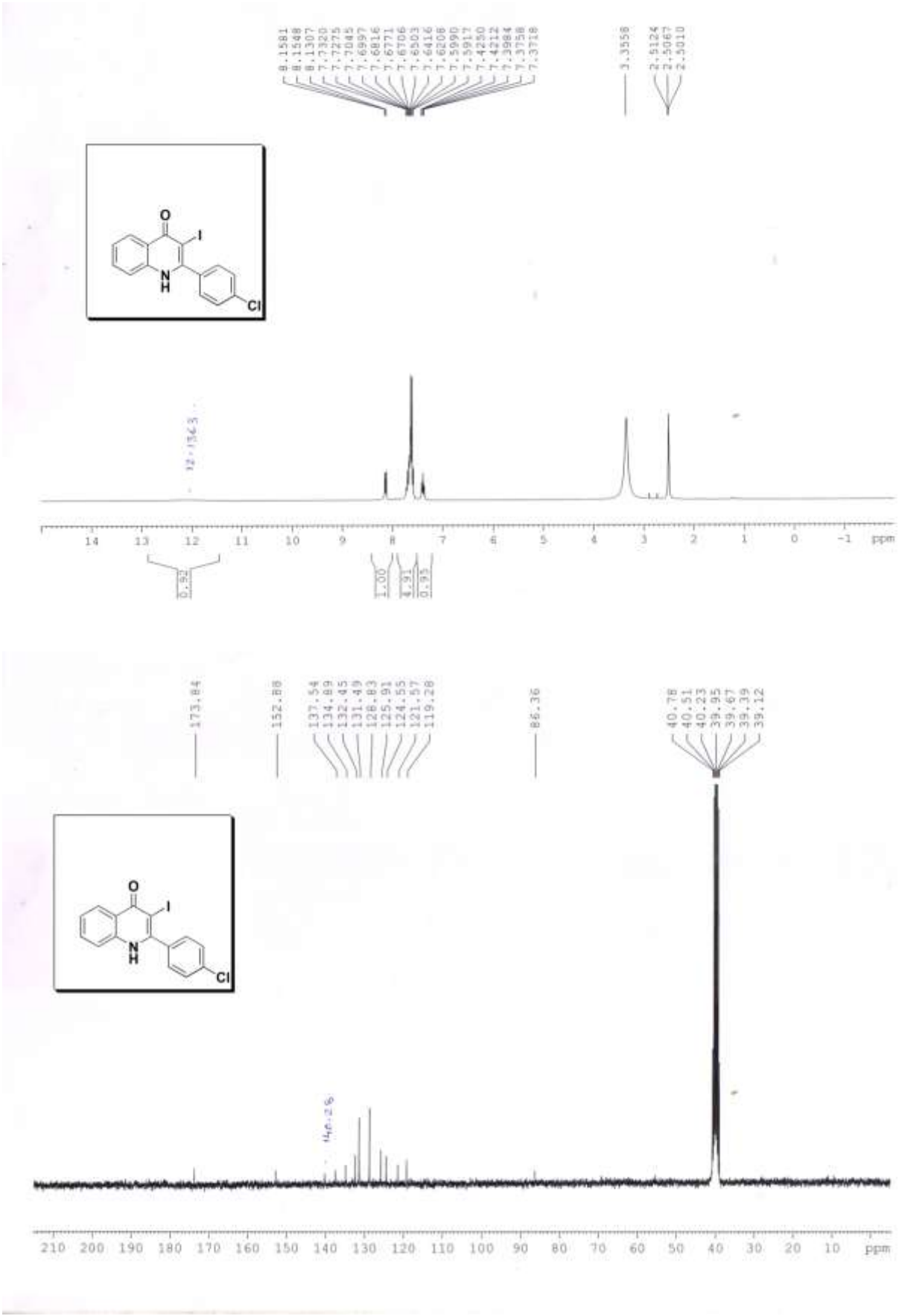

White solid, melting point:>260°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.78 (s, 3H), 7.03 (dd, *J* = 6.6Hz, 2.1Hz, 2H), 7.20 (dd, *J* = 8.7Hz, 1.8Hz, 1H), 7.37-7.46 (m, 4H), 7.53 (dd, *J* = 6.9Hz, 2.1Hz, 2H), 7.70-7.82 (m, 6H), 8.11 (d, *J* = 7.8Hz, 1H), 12.23 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 55.8, 108.3, 113.9, 119.2, 122.5, 124.5, 124.6, 124.8, 125.4, 125.9, 126.9, 127.1, 127.7, 128.0, 128.5, 130.7, 131.2, 132.8, 133.9, 136.8, 140.0, 156.9, 160.9, 175.6.

**24. 2-(4-methoxyphenyl)-3-(phenylthio)quinolin-4(1*H*)-one (2t)**

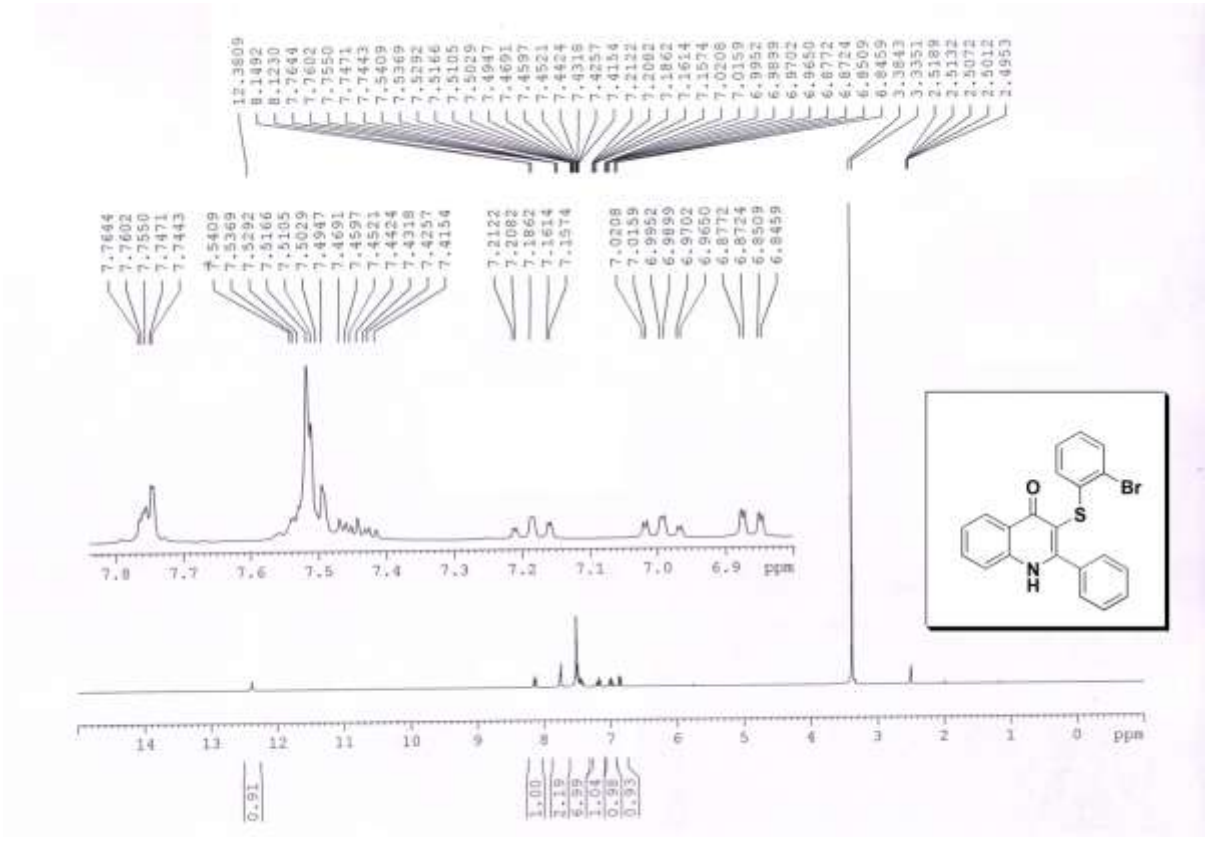


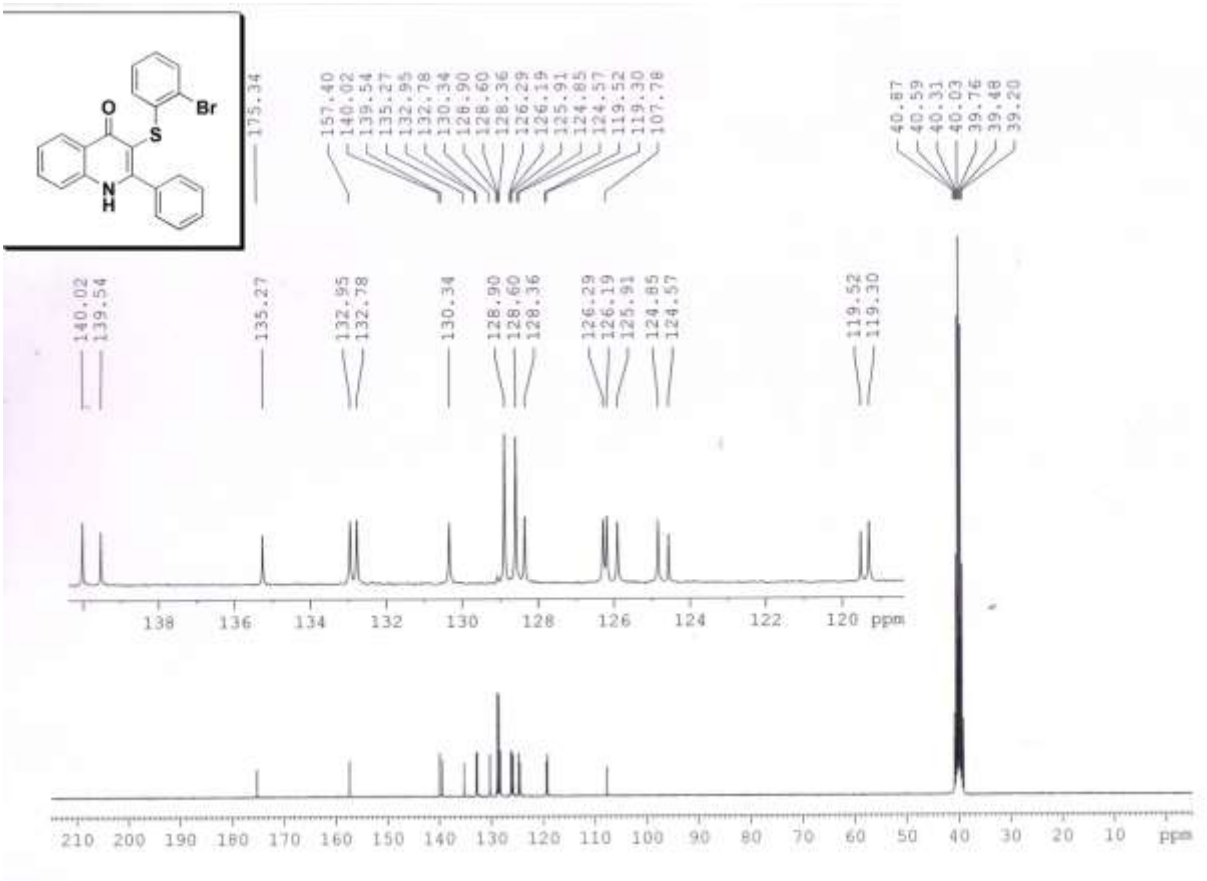

White solid, melting point:228-230°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 3.76 (s, 3H), 6.78 (dd, *J* = 6.9Hz, 1.8Hz, 2H), 6.96 (dd, *J* = 6.9Hz, 1.8Hz, 2H), 7.40-7.45 (m, 1H), 7.52-7.56 (m, 5H), 7.70-7.74 (m, 2H), 8.11 (d, *J* = 8.1Hz, 1H), 12.23 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 55.8, 109.0, 111.4, 115.7, 121.1, 122.4, 124.9, 125.0, 125.7, 125.8, 126.7, 130.7, 132.7,134.0, 139.9, 153.0, 156.8, 160.9, 175.5.

**$^{1}$H and $^{13}$C NMR spectra of entry 1c in DMSO-$d_6$**

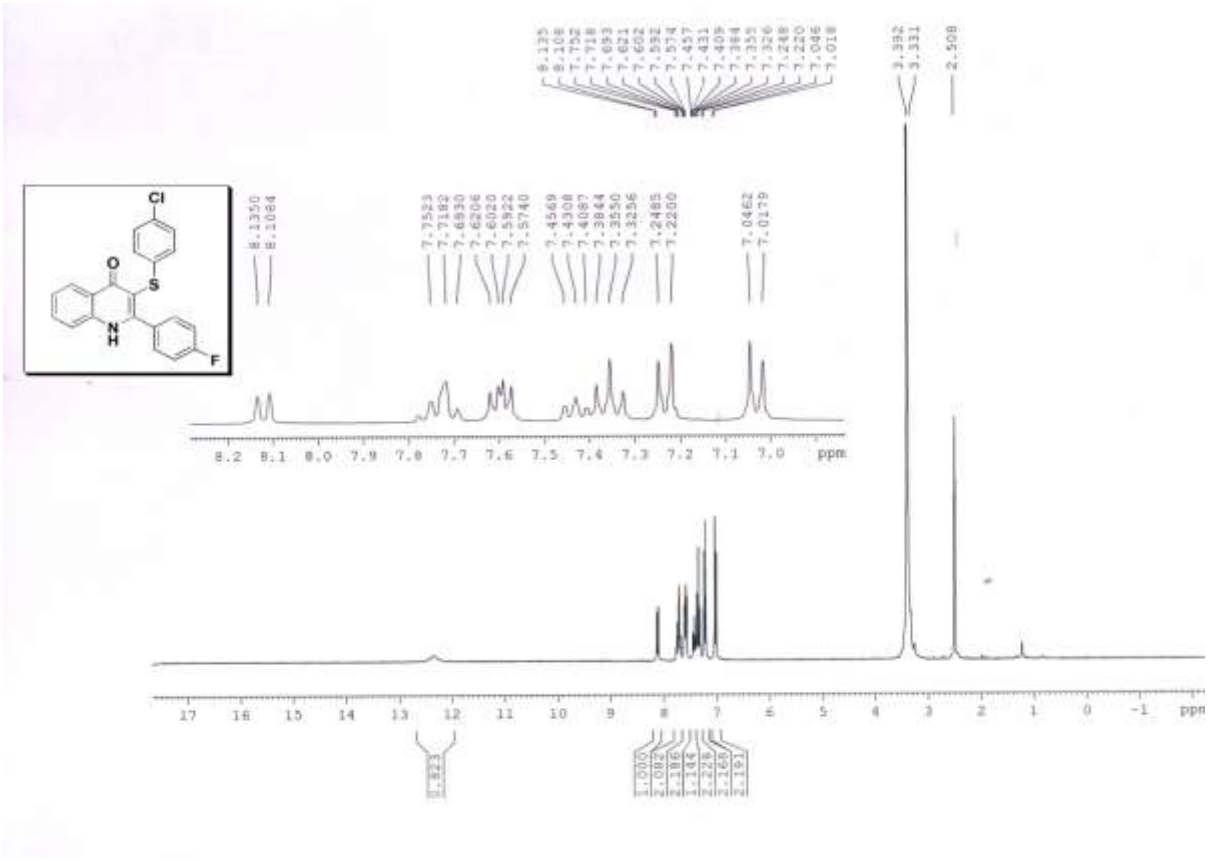


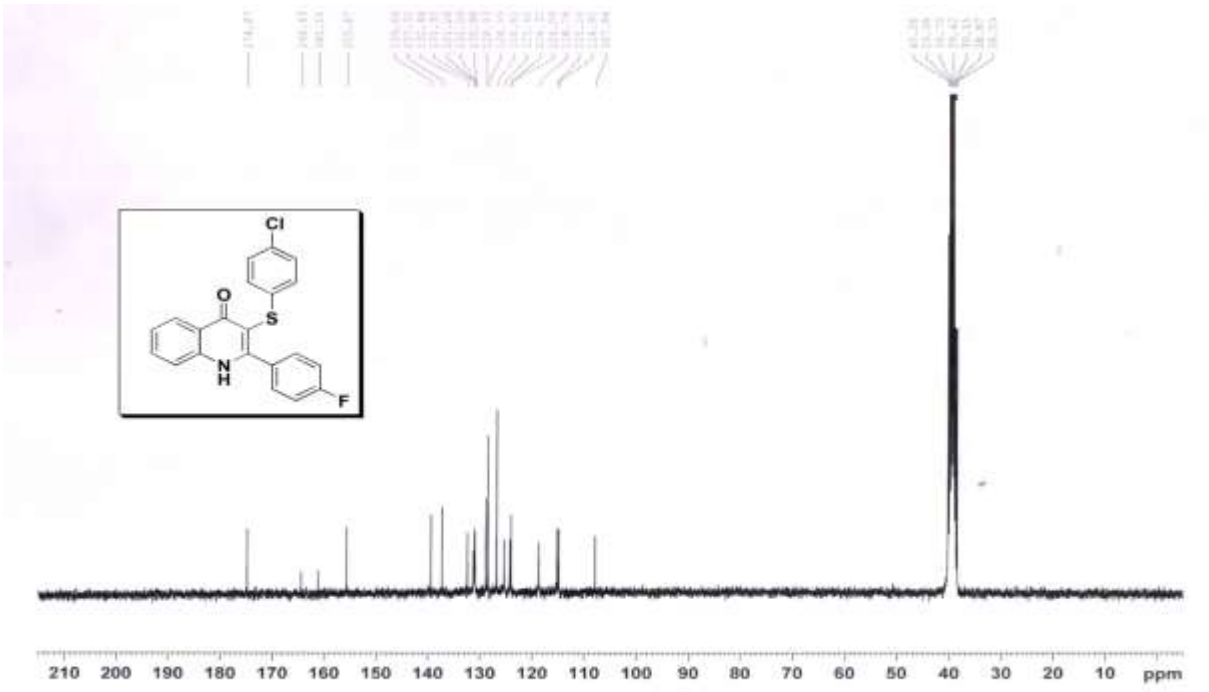
**$^{1}H$ and $^{13}C$ NMR spectra of entry 2f (Scheme-V.1.)in DMSO-$d_6$**



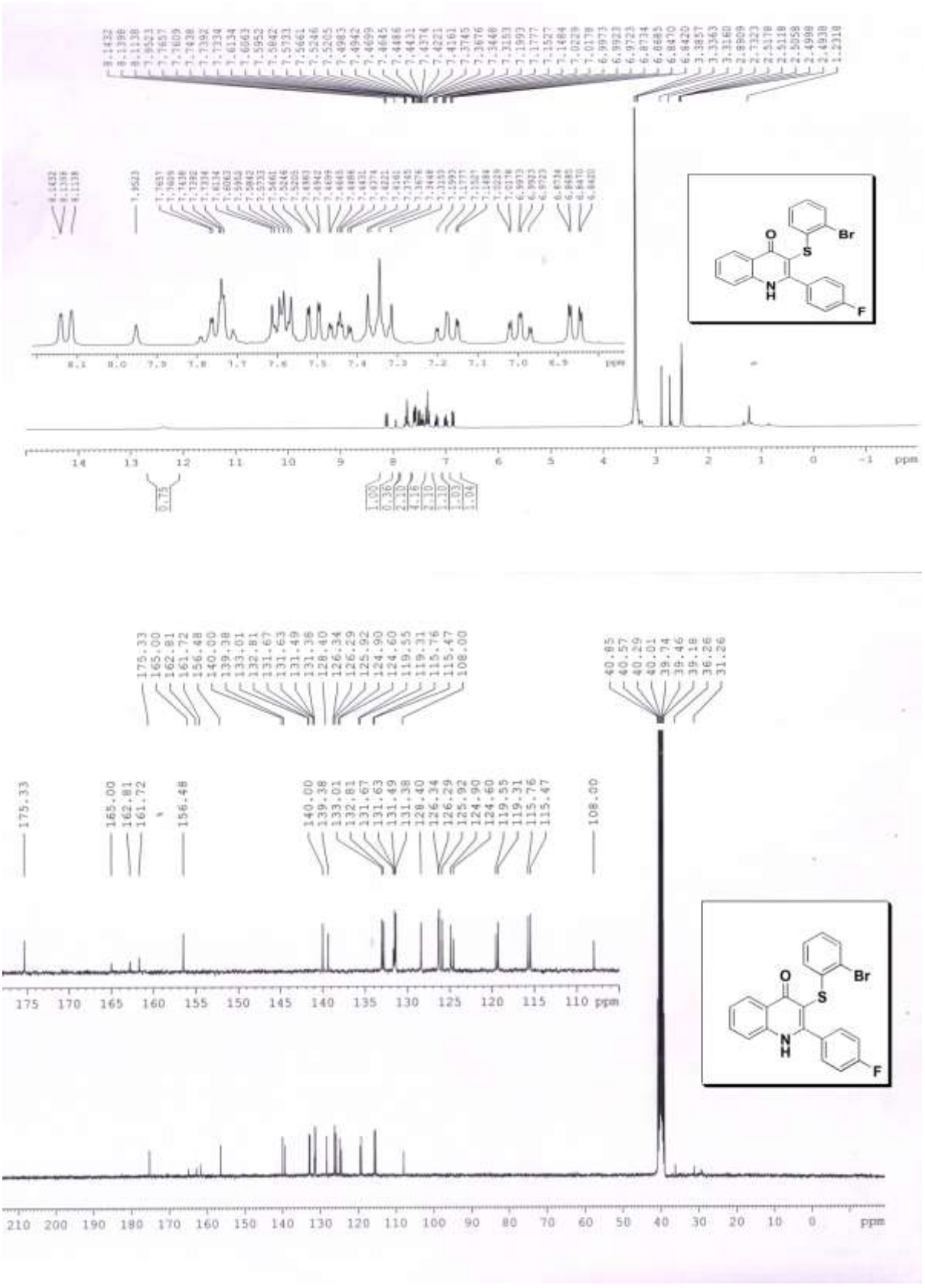



**$^{1}$H and $^{13}$C NMR spectra of entry 2j (Scheme-V.1.) in DMSO-$d_6$**

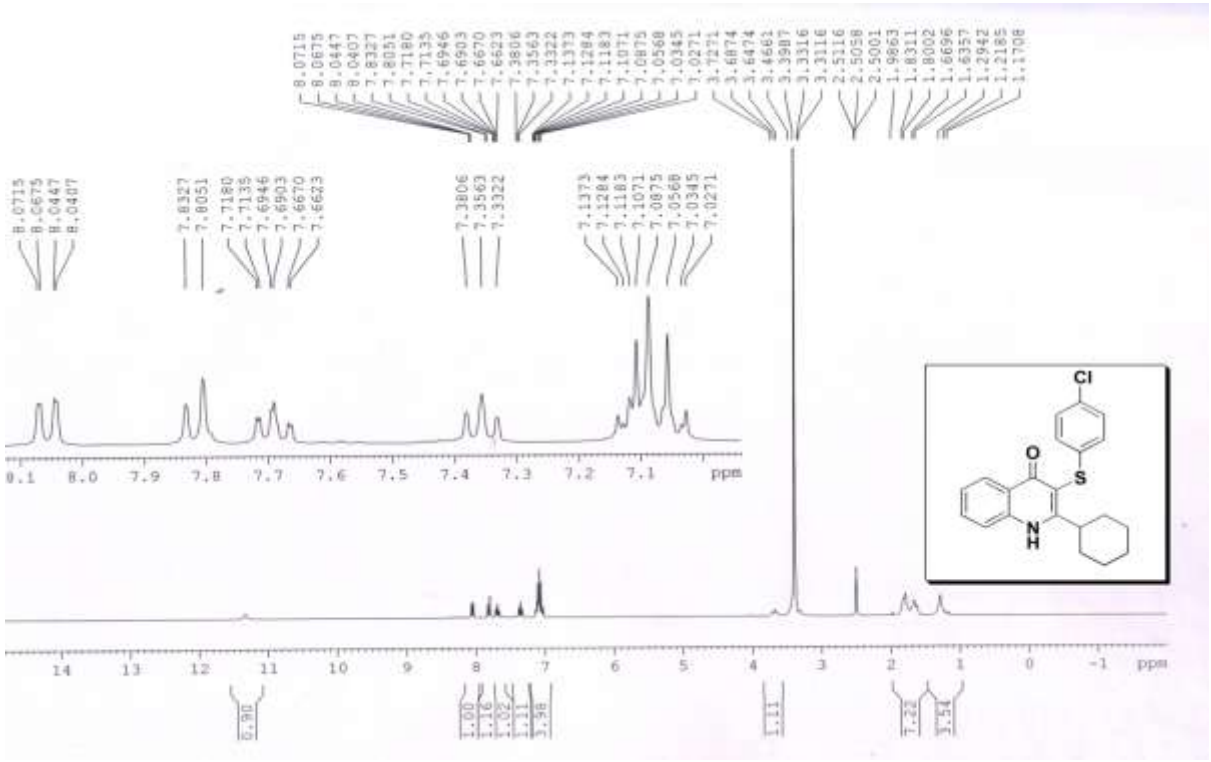


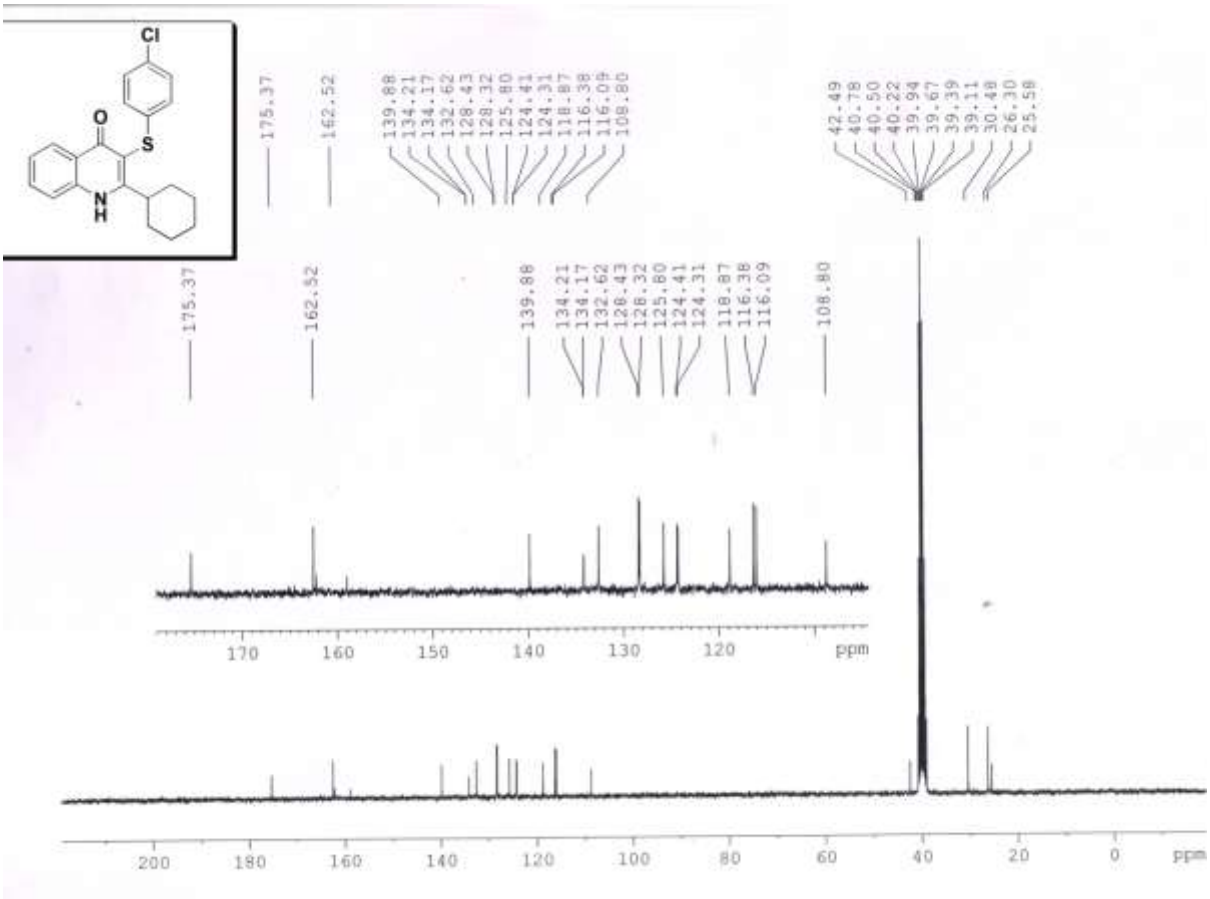



**$^{1}$H and $^{13}$C NMR spectra of entry 2l (Scheme-V.1.) in DMSO-$d_6$**

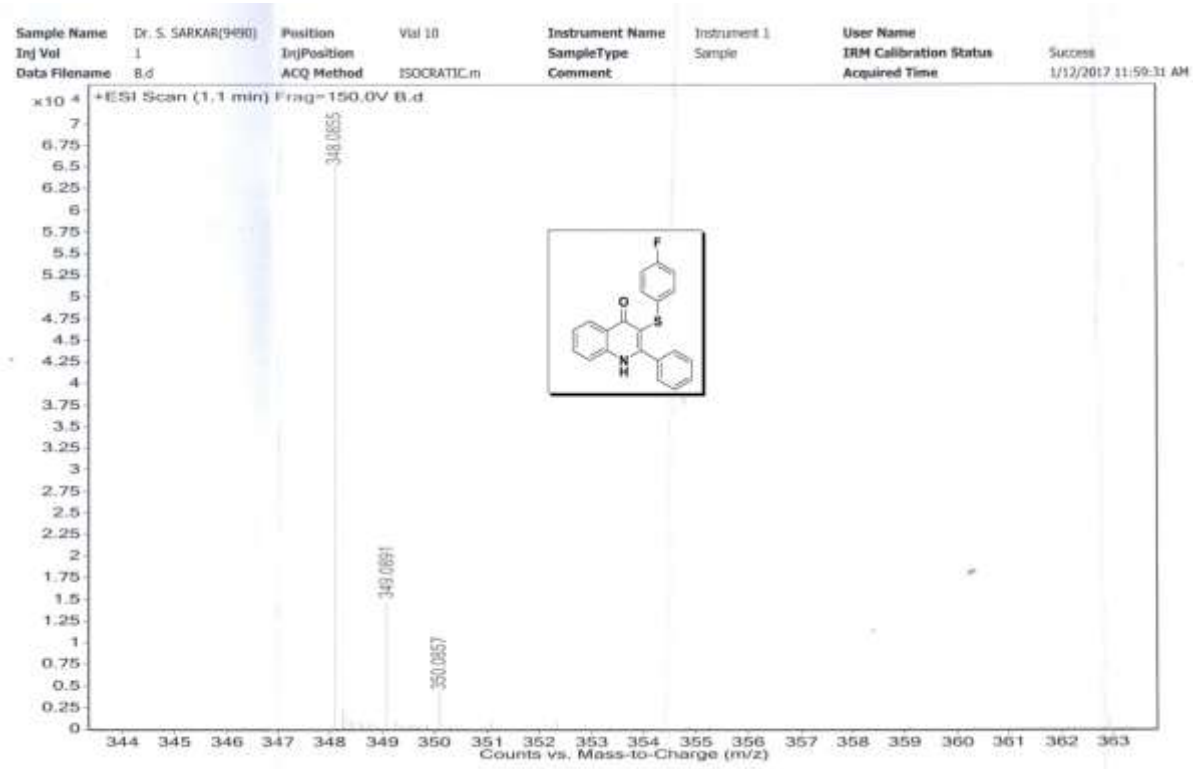


**$^{1}$H and $^{13}$C NMR spectra of entry 2n (Scheme-V.1.) in DMSO-$d_6$**

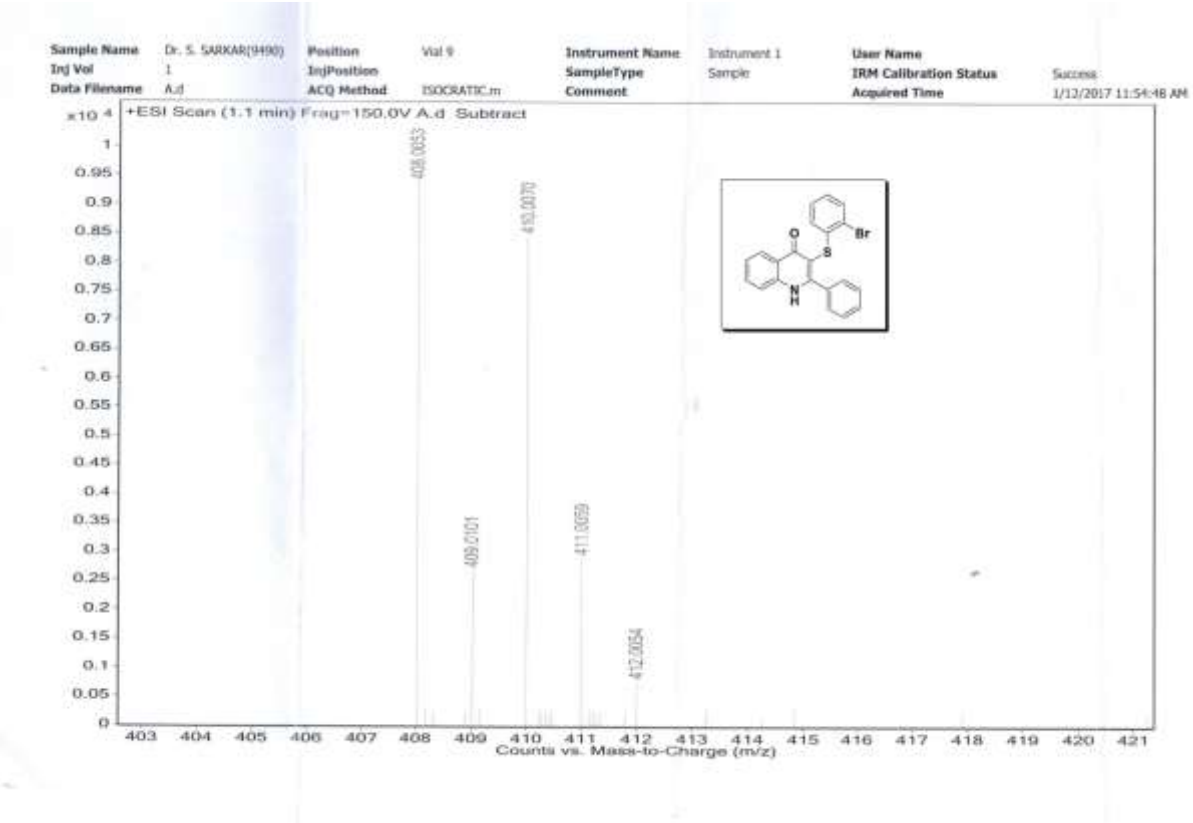


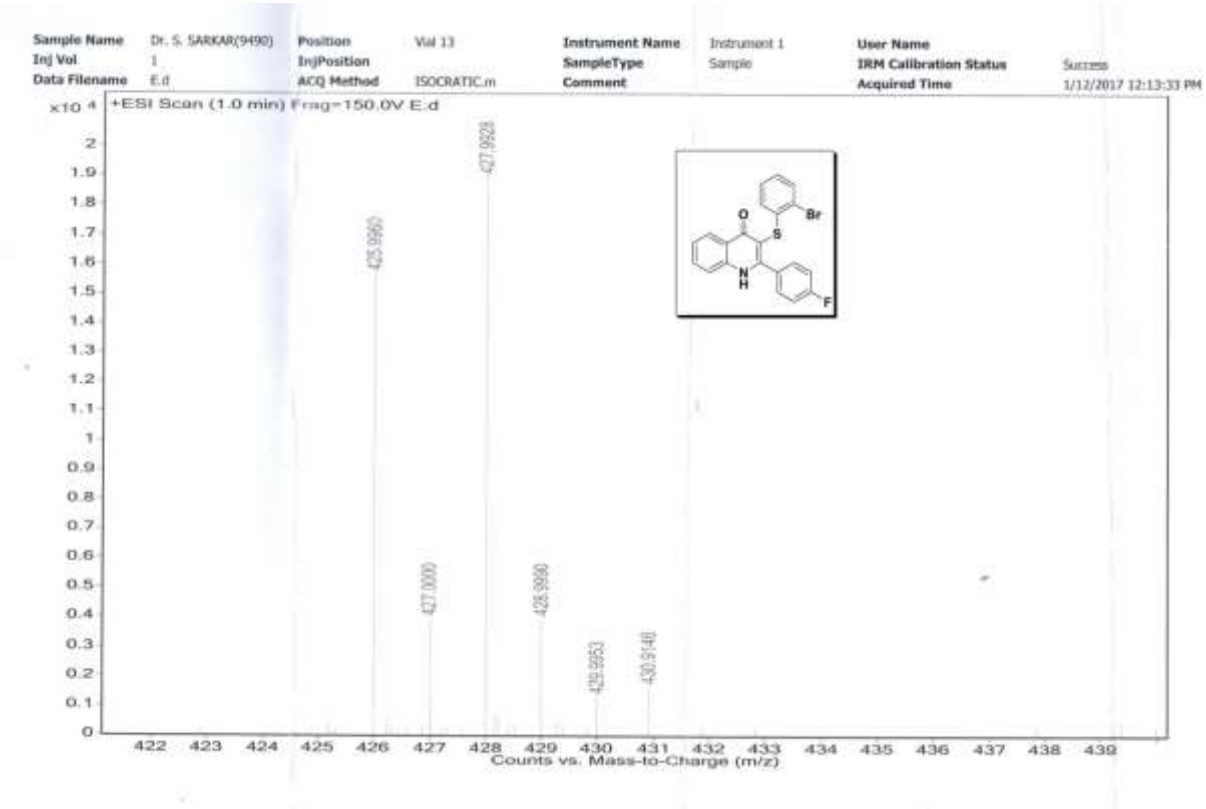
**Scan copy of HRMS of entry 2e (Scheme-V.2.)**




**Scan copy of HRMS of entry 2f (Scheme-V.2.)**



**Scan copy of HRMS of entry 2l (Scheme-V.2.)**




## V.E. References

References are given in BIBLIOGRAPHY under Chapter V (pp-233-234)

# Chapter VI

# *Microwave assisted synthesis of 6-aryl substituted 4-quinolones via regioselective bromination at C-6 position-"precursor of bioactive molecules"*

## VI.A. Introduction

4-quinolones scaffold has been widely occurred in both biologically active molecules and natural products. After the isolation of first quinolone antibiotic i.e.; nalidixic acid, it attracted a lot of attention in the medicinal chemistry.[1] Later, QSAR ( quantitative structure activity relationship) studies have made a pitch for the development of quinolones with enhanced pharmacokinetic and pharmacodynamic properties.[2] Nowadays, these potent scaffolds are mainly serving as active components in various drugs such as antiviral,[3] antimalarial,[4] antibacterial,[5] antitumor[6],anticancer,[7]and anti-HIV[4a,8] agents. Some quinolone based drug molecules are shown below (figure 1). These potent quinolone based drugs also have some limitations such as oral side effects and poor adsorption etc.[9] Therefore; efforts are still going on to synthesize the efficient drug molecule with good oral absorption, minimal secondary effects and selective binding ability.

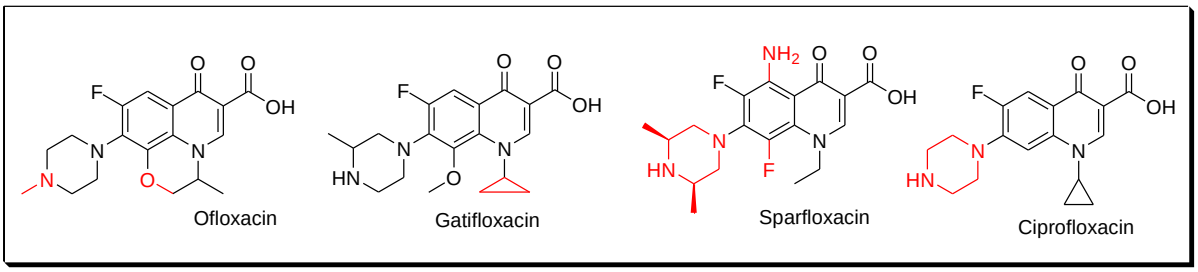
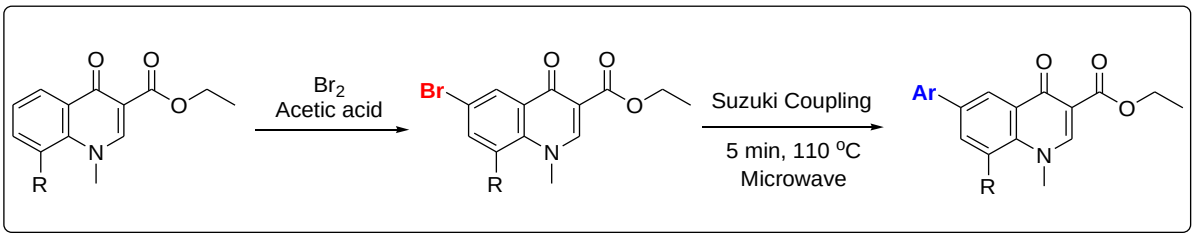



**Fig –VI.1.** Various quinolone base effective drug molecules

## VI.B. Present work: Background & objectives

Many facile and well developed methods are easily available in the literature for the synthesis of 4-quinolones.Unfortunately, these methods allied with some drawback that the substituents needed on the quinolone scaffold could only be incorporated/launched during the formation of the main skeleton.[10] So, it is desirable to design the new strategies for introducing the substituents on the quinolone moiety as per our requirement. In recent years, researchers have been synthesized many quinolone derivatives bearing diverse C-6 substituents with high active therapeutic capabilities.[10f,11,12] Previous studies were mainly the introduction of aryl group at 1 and 2-postion of quinolone moiety. C-6 aryl substituted 4-quinolone derivatives acts as an inhibitors of hepatitis C virus (HCV), reported by Chen and his co-workers. [11b] It was reported that 6-substituted 4-quinolone-3-carboxamides showed high selective affinity for the human CB2 (cannabinoid-2) receptor over CB1.[11c] such reports inspired us to design a library of newly 6-aryl substituted 4-quinolone scaffolds. We execute selective

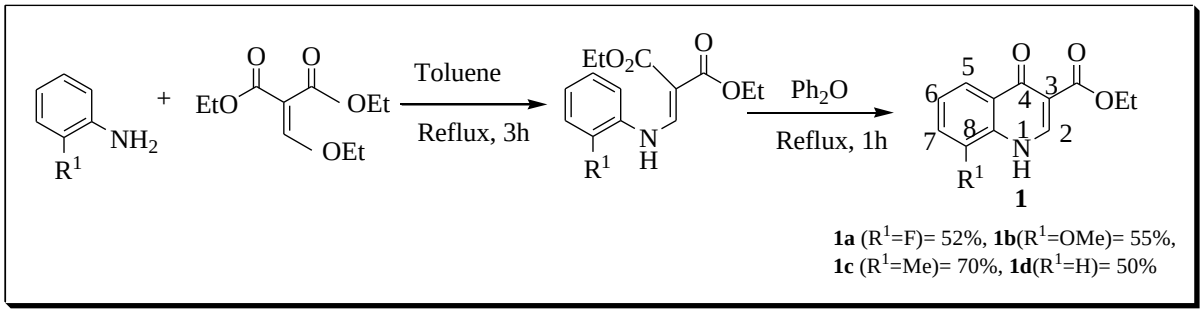
functionalization at C-6 atom of quinolone skeleton *via* regioselective bromination at C-6 position and followed by Suzuki miyaura cross coupling reaction. (Scheme-VI.1).




**Scheme-VI.1**

## VI.B. Present work: Result and discussion

Preliminary, we started our journey with the synthesis of starting material [ethyl-4-quinolone-3-carboxylate] compound **1** *via* the classic Gould-Jacobs method[10a] (Scheme-VI.2). It is found that the C-8 substituents of 4-quinolone increases the antibacterial activity.[9b] Again, fluoro group at C-8 position gave better oral absorption of the drug molecules.[13] In this regard, we took various substituents at C-8 position that could be isosteres and synthesized the compounds (**1a-1c**) as the starting materials of our present work (Scheme-VI.2).



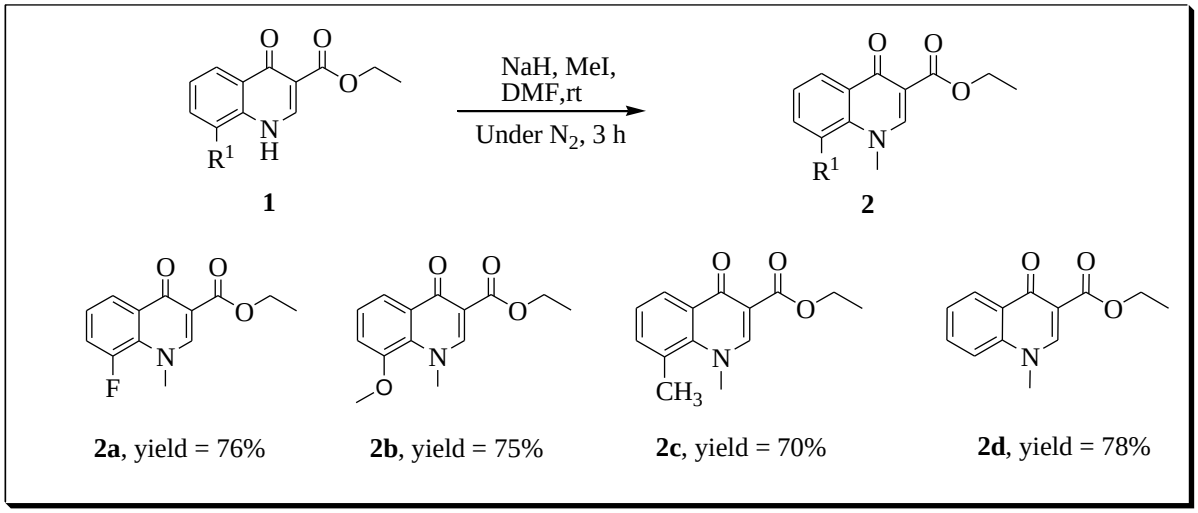

[All the entries were performed by the presenting author P. Ghosh]

**Scheme-VI.2**. General method for the synthesis of 4-quinolones **1.**

Most of the potent and effective quinolone drug molecules possessed with pre-functionalised –NH with smaller alkyl groups like ethyl, methyl and cyclopropyl groups. [14] Therefore before going for further functionalization of **1,** we replaced the -NH of compound with a methyl substituent. Several synthetic procedures for N-alkylation are well known in literature. [15]

After optimizing the reaction condition, NaH (sodium hydride) as a base and DMF as a solvent were found to be suitable in our system. Thus, to proceed the N-methylation, compound **1** was dissolved in DMF (*N*,*N*-dimethyl formamide) followed by gradual

addition of MeI (methyl iodide) under inert atmosphere at 60ºC. No side product (O-methylated) was obtained. Electron donating or withdrawing group at C-8 position showed no significant change in the yield of N-methylated product.

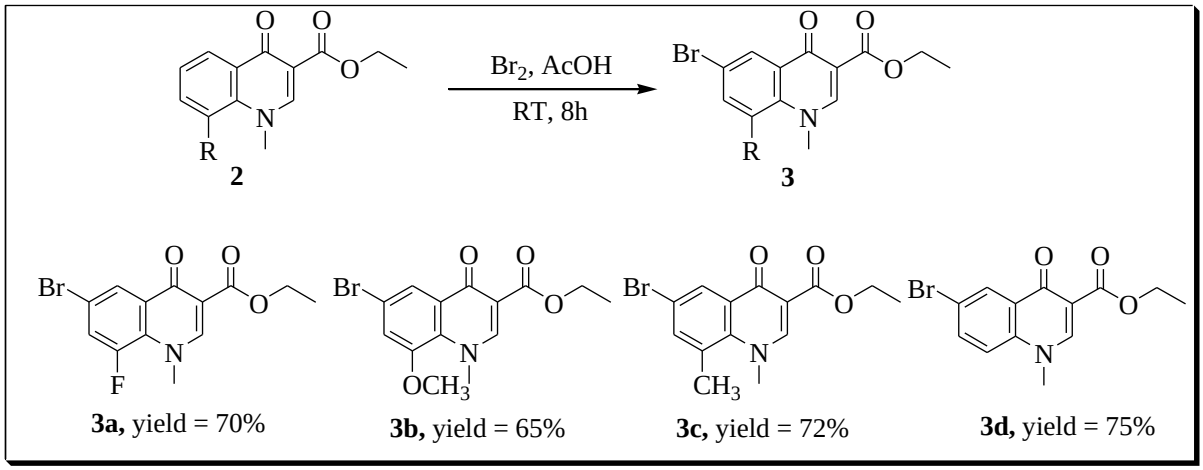



[Entries 2a-2b were performed by the co–author S. Gupta and rest of the entries were performed by the presenting author P. Ghosh]

**Scheme-VI.3.** Synthesis of *N*-methylated derivatives **2** from compound **1**

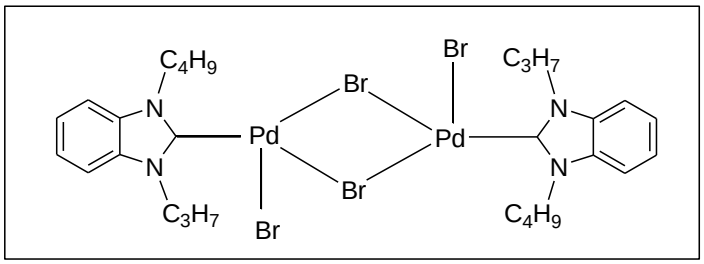
### VI.C. Regioselective bromination at C-6 position

Bromination is one of the most imperative transformations in organic synthesis and can be carried out using bromine and many other brominating agents. Initially, we tried the bromination of compound **2** with NBS (*N*-Bromosuccinimide) in $CHCl_3$ (chloform) at ambient condition but yield of the desired product was not up to the benchmark. Then, performing the same reaction at higher temperature (50ºC) afforded only poor yield (yield<50%) of desired product even after 24 hours. Finally, Bromine in acetic acid medium at room temperature resulted regioselectively C-6 bromo derivatives with moderate yields (65-75%) (Scheme-VI.4)




[Entries 3a-3b were performed by the co–author S. Gupta and rest of the entries were performed by the presenting author P. Ghosh]

**Scheme-VI.4**. Regioselective synthesis of C-6 substituted bromo derivatives **3**



After successful bromination of 4-quinolone at C-6 position, we attempted the functionalisation of **3** *via* transitional metal catalysed Suzuki Miyuara cross coupling reaction. In quest of appropriate conditions for the Suzuki coupling reaction we initiated the coupling of phenyl boronic acid with **3d** using various solvents and catalysts (common palladium salts) in the presence of $K_2CO_3$ (potassium carbonate). The results are shown below (Table-VI.1). Preferably, the combination of DMF as solvent and $K_2CO_3$ (potassium carbonate) as base was optimum for this cross-coupling reaction in presence of our pre-developed Pd-NHC catalyst (catalyst-A).

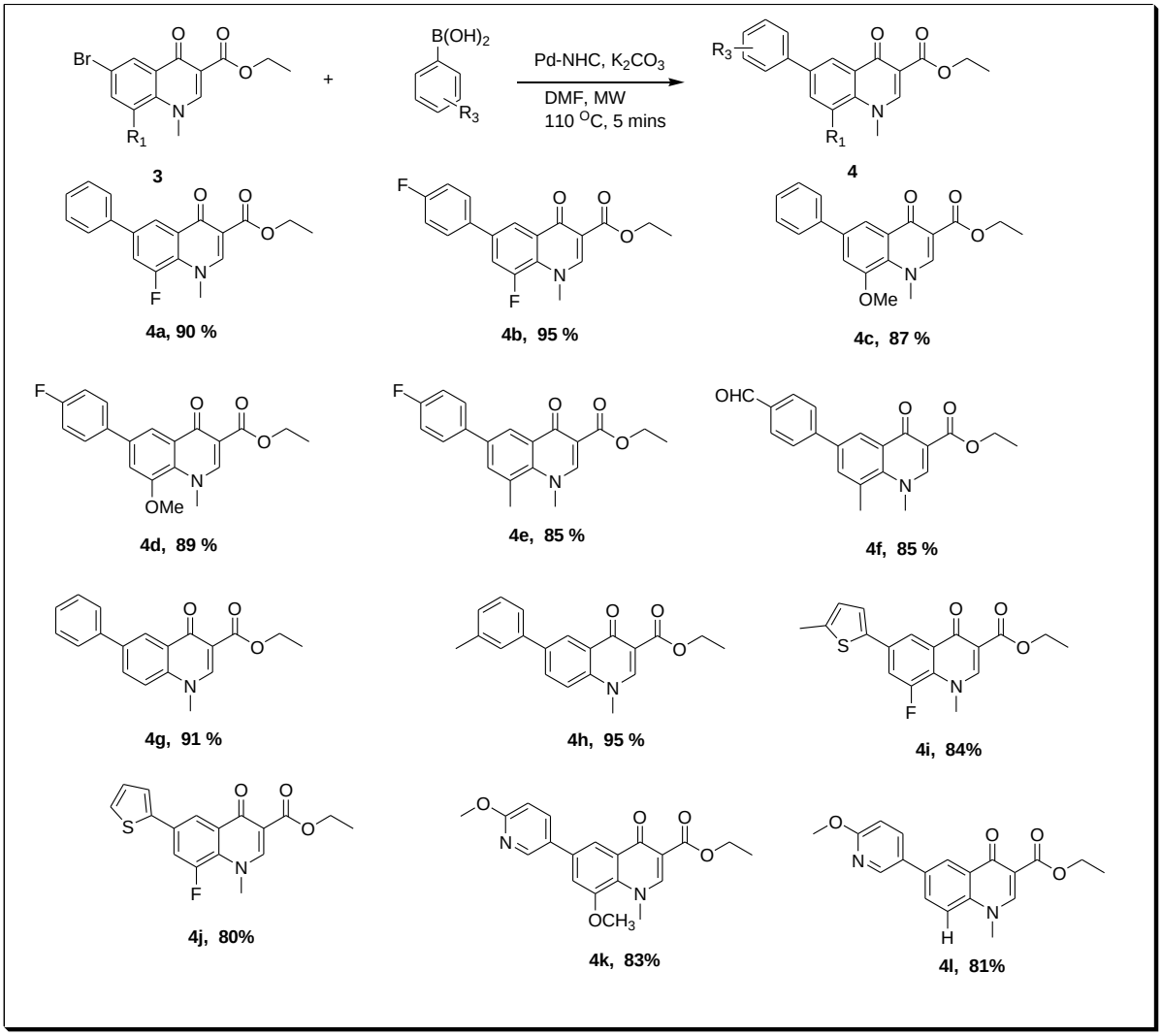
**Table-VI.1. Screening of Suzuki coupling**

| entry | Pd-Catalyst | solvent | yield (%) |
|---|---|---|---|
| 1 | $Pd(OAc)_2$ | DMF | 73 |
| 2 | $PdCl_2$ | DMF | NR |
| 3 | $Pd(OAc)_2$ | Toluene | 63 |
| 4 | $Pd_2(dba)_3$ | DMF | 64 |
| 5 | Pd-NHC | DMF | 91 |
| 6 | Pd-NHC | DMF+$H_2O$ (1:1) | 55 |

**Reaction conditions**: compound **3d** (310 mg, 1 mmol), Phenylboronic acid (146 mg, 1.2 mmol), $K_2CO_3$ (276mg, 2 mmol), Pd-catalyst (19.2 mg, 2 mol%), 110ºC (microwave). Yield = Isolated yield after purification.

The desired cross-coupled product **4g** was rapidly formed within 5 minutes under microwave irradiation at 110ºC. Under our optimized condition, the compound **3** participated in Suzuki cross-coupling reaction with different arylboronic acids in a very facile manner to provide corresponding products in excellent yields (Scheme-VI.5). Compounds **3a** and **3b** furnished **4a** and **4c** in 90% and 87% yield. 4-fluorophenyl boronic acid effectively coupled with **3b, 3c** and **3d** to afford the **4d, 4e** and **4d** in 95%, 85% and 89% yields respectively.Sensitive functional group bearing phenyl boronic acid such as 4-formyl phenylboronic acid easily coupled with **3c** to give the cross-coupling product **4f** in excellent yield (85%). Substrates containing both electron-donating and withdrawing groups underwent smooth coupling to furnish the desired products within a short span of time (5 minutes).

In the literature, it was found that the heterocyclic ring substituent in quinolone ring showed profound anti-bacterial activity,[13] xanthine oxidase inhibition.[14] tubulin based assays,[15] and increased activity in-vitro cytotoxicity. Therefore, we explored our approach towards the cross-coupling reaction with heteroarylboronic and achieved prominent yields of corresponding coupled products (Scheme-VI.5). Compound **3a** suitably coupled with 5-methyl-2-thienylboronic acid and 2-thienylboronic acid and resulted the desired compounds **4i** and **4j** in 84% and 80% yields respectively. 6-methoxy-3-pyridinylboronicacid also effectively coupled with **3b** and **3a** to afford **4k** and **4l** in 83% and 81% yields respectively. A library of 6-aryl and heteroaryl substituted quinolones have been easily synthesized utilizing the regioselective bromination approach.




**Reaction conditions**: compound **3** (1 mmol), aryl(Het)boronic acid (1.2 mmol), $K_2CO_3$ (2 mmol), Pd-NHC (0.0192g, 2 mol%), DMF (3 mL), Microwave, 110ºC, 5 min. Yield = Isolated yields after column chromatography purification. [Entries 4a–4e were performed by the co–author S. Gupta and rest of the entries were performed by the presenting author P. Ghosh]

**Scheme-VI.5.** Suzuki cross coupling with heteroarylboronic acids forming products **4**

## VI.D. Conclusion

We have unfolded a suitable synthetic way to provide 6-aryl substituted 4-quinolones. Our approach has some distinct advantages of easily forming substrates, regioselective bromination at C-6 position and corresponding arylation via Suzuki coupling reaction. The 6- bromo and 6- arylated entities isolated (**3→4**) are all newly synthesized compounds which are anticipated to be important components in drug designing. Various biological activities of these compounds are still going on in our laboratory.

## VI.E. Experimental

### VI.E.1. General Consideration

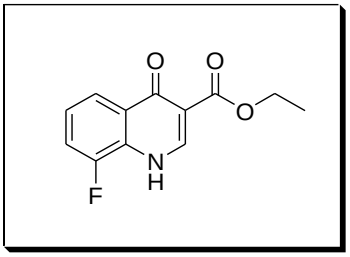
Unless stated otherwise, all reagents such as aromatic anilines, EMME, Palladium acetate, boronic acids and solvents were used as received from commercial suppliers. NMR spectra were recorded on 300 MHz spectrometer at 298 K with calibration done on the basis of solvent residual peak. Mass spectra were performed using ion trap mode. Products were purified using column chromatography on silica gel (60-120 mesh). Ethyl acetate and petroleum ether (60-80$^{o}$C) were used as eluents. Progress of reaction was monitored using silica gel TLC.

### VI.E.2. Preparation of Compound 1

A reaction mixture of aniline (10 mmol), EMME (11 mmol) and toluene (30 mL) was refluxed in a 250 ml round bottom flask for 5 hours. It was then cooled and washed with 3(N) 100 mL $H_2SO_4$. Toluene was distilled out afterwards. The mixture was scratched vigorously to get solid anil product. This product (**5g**) was refluxed with biphenyloxide (50 mL) for 2 hours at 280 ºC. It was then cooled and stirred for an hour after addition of small amount (100 mL) of petroleumether. Crude compound **1** was obtained by filtration on Buchner funnel.

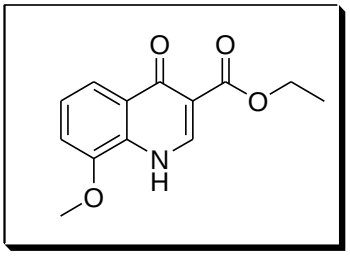
### VI.E.3. Physical characteristics and spectral data of compounds

1. **Ethyl 8-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (1a)**



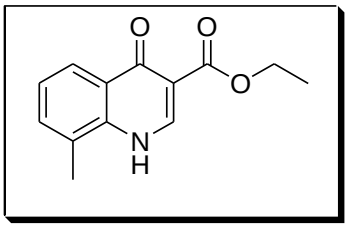

White solid; m.p. 217ºC-219ºC; $^{1}$H NMR (300MHz, DMSO-$d_6$,25ºC, TMS):δ=1.28 (t, *J*=6.9 Hz, 3H), 4.22(q, *J*=6.9 Hz, 2H), 7.40 (m, 1H), 7.65 (t, *J*=9 Hz, 1H), 7.96 (d, *J*=7.8 Hz, 1H), 8.39 (s, 1H), 12.5 (bs, 1H);$^{13}$C NMR (75MHz,DMSO-$d_6$, 25ºC, TMS,): δ 14.23, 59.78, 110.47, 117.17, 117.40, 121.28, 121.33, 124.48, 124.57, 128.08, 128.26, 129.09, 144.67, 150.12, 153.41, 164.38, 172.53; HRMS (EI$^{+}$): $[M]^{+}$ , found 235.0634. $C_{12}H_{10}FNO_3$ requires 234.0645.

**2. Ethyl 1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylate (1b)**



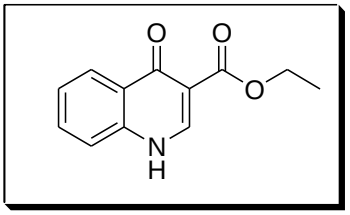
Greyish white; m.p. 243ºC-245ºC; $^{1}$HNMR (300MHz, DMSO-$d_6$,25ºC, TMS): δ=1.26 (t, *J*=7.2Hz, 3H), 3.99 (s, 3H), 4.20 (q, *J*=7.2Hz, 2H), 7.29-7.37 (m, 2H), 7.70 (dd, *J*=7.2Hz, 1.2 Hz, 1H), 8.34 (s, 1H), 11.9 (s, 1H); $^{13}$C NMR (75MHz, DMSO-$d_6$, 25ºC, TMS):δ=14.81, 56.81, 60.09, 110.44, 117.26, 125.06, 128.61, 129.79, 144.34, 144.66, 149.17, 165.12, 173.68; MS(ESI$^{+}$) m/z 270.31[M+Na]$^{+}$, elemental analysis calcd (%) for $C_{13}H_{13}NO_4$ : C, 63.15; H, 5.30; N, 5.67. found C, 63.11; H, 5.34; N, 5.64.

**3. Ethyl 1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (1c)**



White solid; m.p. 249ºC-251ºC; $^{1}$H NMR (300 MHz, DMSO-$d_6$,25ºC, TMS):δ=1.28 (t, *J*=7.2 Hz, 3H), 4.22 (q, *J*=7.2 Hz, 2H), 7.31 (t, *J*=7.8 Hz, 1H), 7.55 (d, *J*=6.9 Hz, 1H), 8.03 (d, *J*=7.8 Hz, 1H), 8.39 (s, 1H), 11.63 (s, 1H); $^{13}$C NMR (75MHz, DMSO-$d_6$,25ºC, TMS):δ=14.77, 17.43, 60.11, 110.12, 124.02, 124.83, 127.45, 127.90, 133.71, 137.94, 145.01, 165.23, 174.11; HRMS (EI$^{+}$): [M]$^{+}$ , found 231.0891. $C_{13}H_{13}NO_3$ requires 231.0895.

**4. Ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate (1d)**

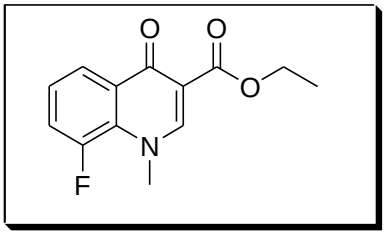


White solid; m.p. 251ºC-253ºC; $^{1}$H NMR (300 MHz, DMSO-$d_6$,25ºC, TMS): δ=1.27 (t, *J*=7.2 Hz, 3H),4.21 (q, *J*=7.2Hz, 2H), 7.41 (t, *J*=6.9 Hz, 1H), 7.68 (m, 2H), 8.16 (dd, *J*=6.9 Hz, 0.9 Hz, 1H), 8.55(s,1H), 12.3 (s, 1H); $^{13}$C NMR (75MHz, DMSO-$d_6$,25ºC, TMS):δ=14.80, 60.04, 110.22, 119.25, 125.17, 126.09, 127.72, 132.38, 139.42, 145.38, 165.28, 173.92.

**VI.E.4. Preparation of N-methylated derivatives (2)**

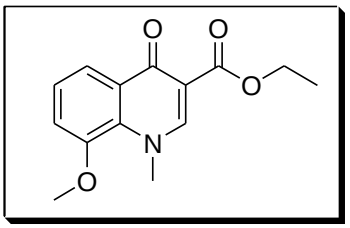
Compound **1** (1 mmol) and DMF (5 ml) were taken in a round bottom flask fitted with guard tube. NaH (36 mg, 1.5 mmol) was added and the reaction mixture was stirred at room temperature until $H_2$ gas ceased to evolve. Methyl iodide (284 mg, 2mmol) was then introduced drop-wise into the reaction mixture and it was further stirred at 60$^{o}$C for 4 hours. The mixture was diluted with water and the product was extracted with DCM (3 x 20 mL). Organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude product was then purified using column chromatography.

**5. Ethyl 8-fluoro 1, 4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (2a)**



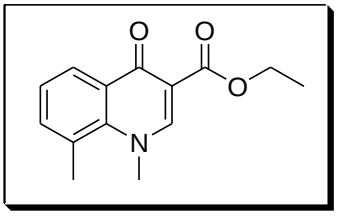

White solid; m.p. 121ºC-124ºC; $^{1}$H NMR (300MHz,$CDCl_3$, 25ºC, TMS):δ=1.40 (t, *J*=7.2Hz, 3H), 4.10(d, *J*=8.1Hz, 3H), 4.38 (q, *J*=7.2Hz, 2H), 7.37 (m, 2H), 8.31 (m, 1H), 8.36 (s, 1H); $^{13}$C NMR (75MHz,$CDCl_3$, 25ºC, TMS):δ=14.33, 46.06, 46.27, 61.06, 109.48, 120.34, 120.63, 122.47, 122.51, 126.30, 126.41, 129.22, 129.31, 130.44, 150.83, 152.51, 154.16, 165.10, 173.26; MS(ESI$^{+}$) m/z 271.95 $[M+Na]^{+}$ , elemental analysis calcd (%) for $C_{13}H_{12}FNO_3$ : C, 62.65; H, 4.85; N, 5.62. found C, 62.51; H, 4.88; N, 5.64.

**6. Ethyl 1,4-dihydro-8-methoxy-1-methyl-4-oxoquinoline-3-carboxylate (2b)**



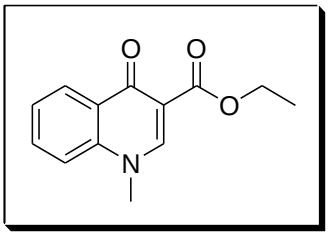

Light brown solid; m.p. 113ºC-116ºC;$^{1}$H NMR(300MHz,$CDCl_3$,25ºC, TMS):δ=1.23 (t, *J*=7.2Hz, 3H), 3.75 (s, 3H), 3.98 (s, 3H), 4.20 (q, *J*=7.2Hz, 2H), 6.96 (d, *J*=7.8Hz, 1H), 7.14 (m, 1H), 7.96 (d, *J*=8.1Hz, 1H), 8.16(s, 1H); $^{13}$C NMR (75MHz,$CDCl_3$,25ºC, TMS):δ=14.78, 47.60, 57.24, 60.11, 109.64, 115.90, 118.57, 125.92, 130.98, 131.15, 151.12, 152.37, 164.98, 172.55; MS(ESI$^{+}$) m/z 284.31 $[M+Na]^{+}$, elemental analysis calcd (%) for $C_{14}H_{15}NO_4$ : C, 64.36; H, 5.79; N, 5.36. found C, 64.40; H, 5.75; N, 5.39.

**7. Ethyl 1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (2c)**



White solid; m.p. 91ºC-93ºC;$^{1}$H NMR (300MHz,$CDCl_3$,25ºC, TMS):δ=1.41(t, *J*=7.2Hz, 3H), 2.80(s, 3H), 4.11(s, 3H), 4.38(q, *J*=7.2Hz, 2H), 7.29 (m, 1H), 7.43 (m, 1H), 8.37(s, 1H), 8.42(d, *J*=8.1Hz, 1H);$^{13}$CNMR (75MHz,$CDCl_3$,25ºC, TMS): δ=14.45, 24.20, 46.99, 60.93, 110.23, 125.31, 126.38, 126.43, 130.66, 137.45, 140.36, 152.48, 165.83, 174.23; MS($ESI^+$) m/z 268.32 $[M+Na]^+$, elemental analysis calcd (%) for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. found C, 68.40; H, 6.05; N, 5.74.

**8. Ethyl 1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (2d)**

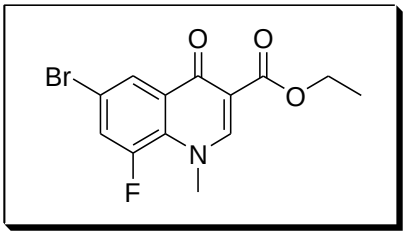


Brown solid; m.p.102ºC-105ºC; $^{1}$H NMR (300MHz, $CDCl_3$, 25ºC, TMS): δ=1.44 (t, *J*=7.2Hz, 3H), 4.00 (s, 3H), 4.43 (q, *J*=7.2Hz, 2H), 7.53 (m, 2H), 7.78 (m, 1H), 8.55 (m, 1H), 8.80 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25ºC, TMS): δ=14.44, 41.40, 60.81, 110.66, 115.72, 125.23, 127.66, 128.78, 132.66, 139.66, 149.70, 165.63, 174.44.

**VI.E.5 Preparation of bromo derivatives (3)**

N-methylated product (compound **2**) was dissolved in minimum amount of acetic acid and equivalent quantity of bromine was added drop wise. The resulting mixture was stirred at room temperature for 8 hours. Then it was poured into water and the organic layer was extracted with DCM and concentrated under reduced pressure. The crude material was further purified using column chromatography.

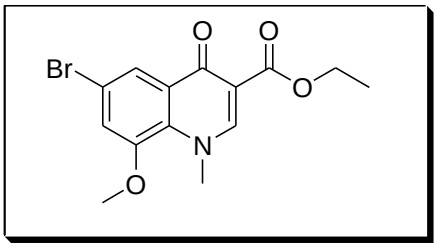
**9. Ethyl 6-bromo-8-fluoro-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (3a)**



White solid; m.p. 150$^{o}$C-153$^{o}$C; $^{1}$H NMR (300MHz $CDCl_3$,25ºC, TMS):δ=1.27 (t, *J*=7.2 Hz, 3H), 4.02 (d, *J*=8.7 Hz, 3H), 4.20 (q, *J*=7.2 Hz, 2H), 7.91 (dd, *J*=13.5Hz, 2.4 Hz, 1H), 8.03 (d, *J*=1.2 Hz, 1H), 8.52( s, 1H);$^{13}$C NMR (75

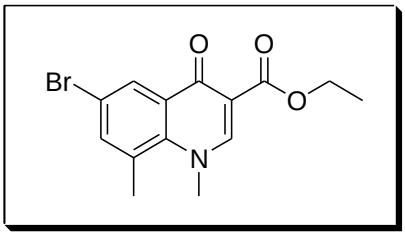
MHz,$CDCl_3$,25ºC, TMS):δ=14.75, 45.56, 60.43, 110.44, 117.23, 117.36, 122.74, 123.17, 124.90, 125.09, 129.08, 129.18, 131.93, 151.07, 152.35, 152.65, 154.46, 164.41, 170.48; HRMS (ESI+): $[M+1]^+$ , found 327.9902. $C_{13}H_{11}BrFNO_3$ requires 327.9906.

**10. Ethyl 6-bromo-1,4-dihydro-8-methoxy-1-methyl-4-oxoquinoline-3-carboxylate (3b)**



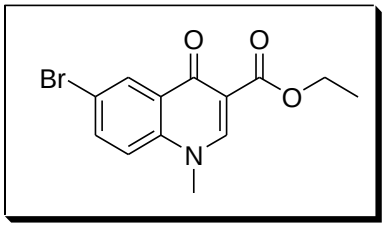

Yellowish white solid; m.p. 155ºC-157ºC; $^1$H NMR (300MHz, $CDCl_3$, 25ºC, TMS):δ=1.40 (t, *J*=7.2Hz, 3H), 3.93 (s, 3H), 4.17 (s, 3H), 4.38 (q, *J*=7.2Hz, 2H), 7.18(d, *J*=2.1Hz, 1H), 8.20 (d, *J*=2.1Hz, 1H), 8.43 (s, 1H); $^{13}$C NMR (75MHz, $CDCl_3$, 25ºC, TMS):δ=14.46, 48.32, 56.80, 61.30, 110.12, 117.75, 119.56, 121.96, 130.02, 131.71, 151.20, 152.12, 165.62, 172.09; HRMS ($ESI^+$): $[M+1]^+$ , found 340.0119. $C_{14}H_{14}BrNO_4$ requires 340.0106.

**11. Ethyl 6-bromo-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (3c)**




Yellowish white solid, m.p. 205ºC-208ºC; $^1$H NMR (300MHz,$CDCl_3$,25ºC, TMS):δ=1.40 (t, *J*=7.2 Hz, 3H), 2.76 (s, 3H), 4.09 (s, 3H), 4.37 (q, *J*=7.2 Hz, 2H), 7.49 ( d, *J*=2.4 Hz, 1H), 8.30 ( s, 1H), 8.43 (d, *J*=2.4 Hz, 1H); $^{13}$C NMR (75MHz,$CDCl_3$,25ºC, TMS): δ=14.43, 23.94, 47.08, 60.96, 110.36, 119.01, 128.52, 129.06, 131.69, 139.18, 139.65, 152.40, 165.09, 172.74; HRMS ($ESI^+$): $[M+1]^+$ , found 324.0129. $C_{14}H_{14}BrNO_3$ requires 324.0157.

**12. Ethyl 6-bromo-1,4-dihydro-4-oxoquinoline-3-carboxylate (3d)**




White solid, m.p. 108ºC-111ºC; $^1$H NMR (300MHz,$CDCl_3$,25ºC, TMS):δ=1.39 (t, *J*=7.2 Hz, 3H), 3.85 (s, 3H), 4.36 (q, *J*=7.2 Hz, 2H), 7.28 (d, *J*=2.1 Hz, 1H), 7.70 (dd, *J*=9.0 Hz , 2.4 Hz, 1H), 8.36 (s, 1H), 8.49 (d, *J*=2.4 Hz,

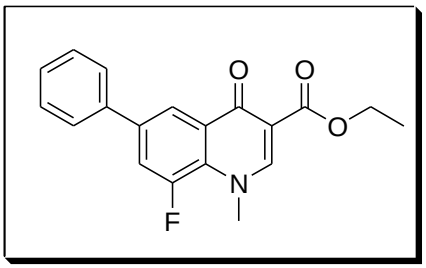
1H); $^{13}$C NMR (75 MHz,$CDCl_3$,25ºC, TMS):δ=14.43, 41.52, 60.91, 111.04, 117.74, 119.27, 129.89, 130.06, 135.56, 138.44, 149.69, 165.02, 172.94; MS($ESI^+$) m/z 332.05( $[M+Na]^+$ , $^{79}$Br), 334.04 ($[M+Na]^+$, $^{81}$Br), elemental analysis calcd (%) for $C_{14}H_{14}BrNO_3$: C, 50.34; H, 3.90; N, 4.52. found C, 50.31; H, 3.94; N, 4.48.

**VI.E.6. Preparation of 6-arylated derivatives (4)**

Compound **3** (1 mmol), aryl boronic acid (1.2 mmol), $K_2CO_3$ (276 mg, 2 mmol), Pd-NHC (0.0096 g, 1 mol %) and DMF (2 mL) were taken in a microwave reaction vessel. The mixture was placed in the focused microwave reactor and heated at 110℃ for 5 minutes. Then the solution was diluted with water and extracted with DCM (3 x 10 ml). The combined organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography.

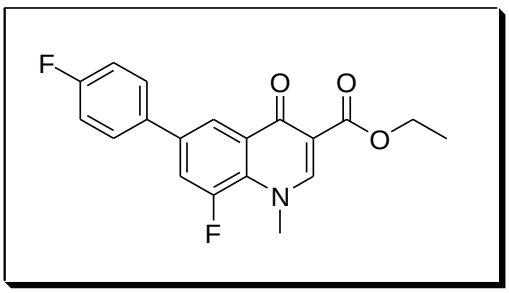
**Spectral Analysis of 6-aryl substituted 4-quinolones**

**13. Ethyl 8-fluoro-1,4-dihydro-1-methyl-4-oxo-6-phenylquinoline-3-carboxylate (4a)**




Light brown solid; m.p. 168ºC-170ºC; $^1$H NMR (300MHz, $CDCl_3$, 25ºC, TMS): δ=1.43 (t, *J*=7.2 Hz, 3H), 4.14 (d, *J*=8.1Hz, 3H), 4.41 (q, *J*=7.2Hz, 2H), 7.47 ( m, 3H ), 7.67 (m, 3H), 8.40 (s, 1H), 8.59 (d, *J*=2.4 Hz, 1H); $^{13}$C NMR (75MHz, $CDCl_3$, 25ºC, TMS): δ=14.43, 45.94, 46.15, 61.19, 110.85, 117.98, 118.29, 121.18, 127.03, 128.47, 129.16, 129.32, 131.68, 138.04, 138.72, 138.82, 151.01, 151.47, 165.62, 166.50, 173.00; MS($ESI^+$) m/z 347.91 $[M+Na]^+$, $C_{19}H_{16}FNO_3$, elemental analysis calcd (%) for $C_{19}H_{16}FNO_3$ : C, 70.14; H, 4.96; N, 4.31. found C, 70.07; H, 5.01; N, 4.33.

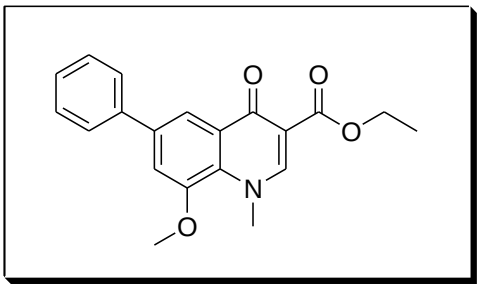
**14. Ethyl8-fluoro-6-(4-fluorophenyl)-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (4b)**




White solid; m.p. 184ºC-187ºC; $^1$H NMR (300MHz, $CDCl_3$,25ºC, TMS):δ=1.41(t, *J*=7.2Hz, 3H), 4.10 (d, *J*=8.1Hz, 3H), 4.39 (q, *J*=7.2 Hz, 2H),

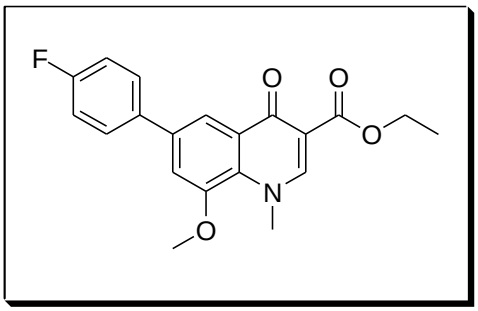
7.15 (m, 2H), 7.58 (m, 3H), 8.33 (s, 1H), 8.48 (d, *J*=1.5Hz 1H); $^{13}$C NMR (75MHz, $CDCl_3$, 25ºC, TMS):δ=14.47, 46.05, 46.24, 61.20, 110.96, 115.99, 116.28, 116.51, 117.80, 118.11, 121.01, 128.12, 128.21, 128.69, 128.80, 128.96, 131.76, 134.21, 137.66, 137.76, 151.01, 151.57, 154.32, 161.46, 164.76, 165.48, 166.39, 172.91; HRMS(ESI$^+$): $[M+Na]^+$, found 366.0868. $C_{19}H_{15}F_2NO_3Na$ requires 366.0918.

**15. Ethyl 1,4-dihydro-8-methoxy-1-methyl-4-oxo-6-phenylquinoline-3-carboxylate (4c)**



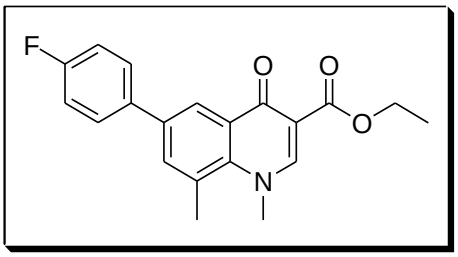

White solid; m.p. 182ºC-185ºC; $^1$H NMR (300MHz, $CDCl_3$, 25ºC, TMS): δ=1.38 (t, *J*=7.2 Hz, 3H), 3.78 (s, 3H), 4.05 (s, 3H), 4.35 (q, *J*=7.2Hz, 2H), 7.21 (d, *J*=1.8Hz, 1H), 7.39 (m, 3H), 7.62 (d, *J*=7.2 Hz, 2H), 8.17 (s, 1H) 8.31(d, *J*= 1.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$,75MHz) δ 14.44, 47.82, 56.37, 60.68, 109.88, 112.91, 116.94, 126.87, 127.92, 128.91, 129.87, 131.35, 137.89, 139.19, 150.76, 151.48, 165.55, 173.55 ; MS(ESI+): m/z 337.95 $[M]^+$, elemental analysis calcd (%) for $C_{20}H_{19}NO_4$ : C, 71.20; H, 5.68; N, 4.15. found C, 71.13; H, 5.60; N, 4.16.

**16. Ethyl-6-(4-fluorophenyl)-1,4-dihydro-8-methoxy-1-methyl-4-oxoquinoline-3-carboxylate (4d)**



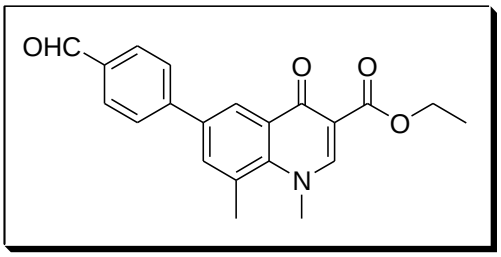

White solid; m.p. 178ºC-180ºC; $^1$H NMR (300 MHz, $CDCl_3$, 25ºC, TMS): δ=1.44 ( t, *J*=7.2 Hz, 3H), 4.03 (s, 3H), 4.22 (s, 3H), 4.42 (q, *J*=7.2 Hz, 2H), 7.17 (m, 2H), 7.32 (d, *J*=2.1 Hz, 1H), 7.65 (m, 2H), 8.35 (d, *J*=2.1Hz, 1H), 8.40 (s, 1H); $^{13}$C NMR (75 MHz,$CDCl_3$,25ºC, TMS): δ=14.44, 47.87, 56.51, 60.93, 110.18, 113.07, 115.73, 116.02, 117.34, 128.66, 128.77, 130.04, 131.56, 135.56, 135.60, 137.40, 150.90, 151.71, 161.16, 164.44, 165.85, 173.60; MS(ESI$^+$): m/z 355.89 $[M]^+$, elemental analysis calcd (%) for $C_{20}H_{18}FNO_4$ : C, 67.60; H, 5.11; N, 3.94. found C, 67.49; H, 5.01; N, 3.98.

**17. Ethyl-6-(4-fluorophenyl)-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (4e)**



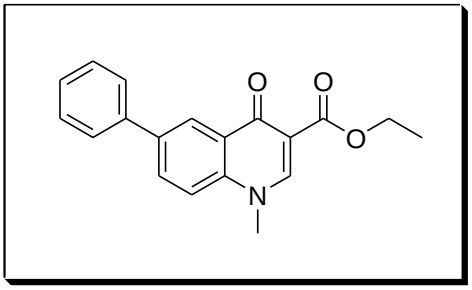

Light yellow solid; m.p. 217°C-220°C; $^{1}$H NMR (300 MHz, $CDCl_3$, 25ºC, TMS): δ=1.41 (t, *J*=7.2Hz, 3H), 2.83 (s, 3H), 4.11 (s, 3H), 4.38 (q, *J*=7.2 Hz, 2H), 7.13 (t, *J*=8.7 Hz, 2H), 7.60 (m, 3H), 8.34 (s, 1H), 8.56 (d, *J*= 2.4 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25ºC, TMS):δ=14.43, 24.34, 47.03, 60.86, 110.14, 115.71, 115.99, 123.61, 127.26, 128.51, 128.62, 130.89, 135.00, 135.77, 136.52, 139.38, 152.18, 161.09, 164.37, 165.46, 174.21; MS(ESI$^+$): m/z 361.92 $[M+Na]^+$, elemental analysis calcd (%) for $C_{20}H_{18}FNO_3$: C, 70.78; H, 5.35; N, 4.13. found C, 70.75; H, 5.08; N, 4.11.

**18. Ethyl 6-(4-formylphenyl)-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (4f)**



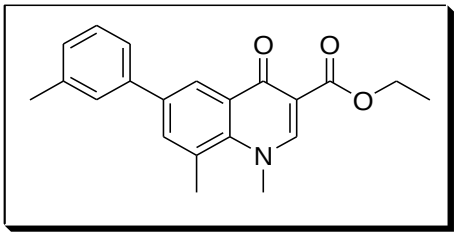

White solid; m.p. 230ºC-233ºC;$^{1}$H NMR (300 MHz, $CDCl_3$, 25ºC, TMS): δ=1.39 ( t, *J*=7.2 Hz, 3H), 2.87 (s, 3H), 4.14 (s, 3H),4.38 (q, *J*=7.2 Hz, 2H), 7.70 ( s, 1H), 7.80 ( d, *J*=8.1Hz, 2H), 7.95 (d, *J*=8.1Hz, 2H), 8.38 (s, 1H), 8.68 (s, 1H), 10.04 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25ºC, TMS): δ=14.43, 24.38, 47.04, 61.02,110.62, 124.66, 127.53, 130.39, 131.00 ,135.50, 135.94, 136.01, 140.31, 144.84, 152.48, 165.49, 174.13, 191.85; MS(ESI$^+$) m/z 372.23 $[M+Na]^+$, elemental analysis calcd (%) for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. found C, 72.11; H, 5.40; N, 3.98.

**19. Ethyl 1,4-dihydro-1-methyl-4-oxo-6-phenylquinoline-3-carboxylate (4g)**



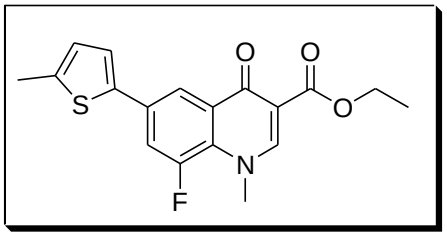
White solid, m.p. 137ºC-140ºC; $^{1}$H NMR (300 MHz, $CDCl_3$, 25ºC, TMS): δ=1.31 (t, *J*=7.2Hz, 3H), 3.77 (s, 3H), 4.27 (q, *J*=7.2Hz, 2H), 7.35 (m, 4H), 7.55 (m, 2H), 7.76 (dd, *J*=8.7Hz, 2.1Hz, 1H), 8.29 (s, 1H), 8.58 (d, *J*=2.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25ºC, TMS): δ=13.34, 40.42, 59.76, 109.40, 115.44, 123.97, 125.95, 126.84, 127.64, 127.93, 130.28, 136.80, 137.69, 137.89, 148.35, 164.38, 173.34; MS(ESI+): m/z 329.94 $[M+Na]^+$, elemental analysis calcd (%) for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. found C, 74.21; H, 5.62; N, 4.60.

**20. Ethyl 1, 4-dihydro-1-methyl-4-oxo-6-m-tolylquinoline-3-carboxylate (4h)**



Light yellow solid; m.p. 98ºC-101ºC; $^{1}$H NMR (300MHz, $CDCl_3$, 25ºC, TMS):δ=1.41(t, *J*=7.2 Hz, 3H), 2.44 (s, 3H), 3.97 (s, 3H), 4.42 (q, *J*=7.2 Hz, 2H), 7.21 (d, *J*=7.5 Hz, 1H), 7.36 (t, *J*=7.8 Hz, 1H), 7.51 (m, 3H), 7.97 (dd, *J*=8.7 Hz, 2.1 Hz, 1H), 8.61 (s, 1H), 8.75 (d, *J*=2.4 Hz, 1H); $^{13}$CNMR (75MHz, $CDCl_3$, 25ºC, TMS):δ=14.43, 21.56, 41.64, 61.00, 110.54, 116.53, 125.12, 125.37, 127.81, 128.03, 128.69, 138.27, 138.71, 138.84, 139.00,149.37, 149.68, 165.79, 174.34; HRMS ($EI^+$): $[M]^+$ , found 321.1366. $C_{20}H_{19}NO_3$ requires 321.1365.

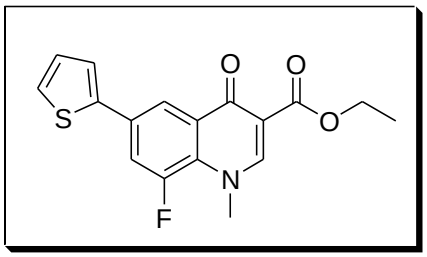
**21. Ethyl 8-fluoro-1, 4-dihydro-1-methyl-6-(5-methylthiophen-2-yl)-4-oxoquinolone-3-carboxylate (4i)**



Light yellow solid; m.p. 158$^{o}$C-161$^{o}$C; $^{1}$H NMR (300MHz, $CDCl_3$, 25ºC, TMS): δ=1.37 (t, *J*=6.9 Hz, 3H), 2.49 (s, 3H), 4.03 (m, 3H), 4.36 (q, *J*=6.9 Hz, 2H), 6.72 (m , 1H), 7.16 (d, *J*=3.6 Hz, 1H), 7.44 (dd, *J*=15Hz, 2.4 Hz, 1H), 8.23 (s,

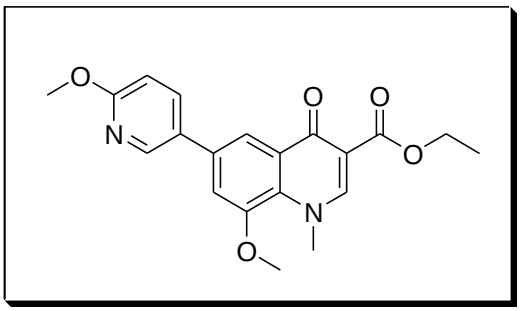
1H), 8.36 (m, 1H); $^{13}$C NMR (75MHz, $CDCl_3$, 25ºC, TMS): δ=14.42, 15.54, 45.91, 46.12, 61.15, 110.62, 116.25,116.57, 119.00, , 124.70, 126.72,127.54, 127.64, 131.65, 132.61,132.73, 138.87, 141.56, 150.87, 151.21, 154.18, 165.60, 172.70; HRMS ($EI^+$): $[M]^+$ , found 345.0832. $C_{18}H_{16}FNO_3S$ requires 345.0835.

**22. Ethyl 8-fluoro-1,4-dihydro-1-methyl-4-oxo-6-(thiophen-2-yl) quinolone-3-carboxylate (4j)**



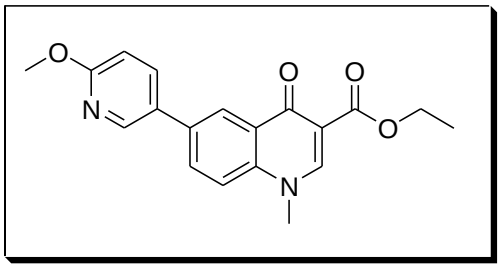

Light yellow solid; m.p. 185ºC-188ºC; $^1$H NMR (300MHz, $CDCl_3$, 25ºC, TMS): δ=1.42 (t, *J*=7.2 Hz, 3H), 4.10 (d, *J*=8.1 Hz, 3H), 4.40 (q, *J*=7.20 Hz, 2H), 7.10-7.13 (m, 1H), 7.36 (dd, *J*=5.1Hz, 0.9 Hz, 1H), 7.44 (dd, *J*=3.6Hz, 1.2 Hz, 1H), 7.61 (dd, *J*=15Hz, 2.1 Hz, 1H), 8.34 (s, 1H), 8.54 (m, 1H); $^{13}$C NMR(75 MHz, $CDCl_3$,25ºC, TMS):δ=14.43, 45.91, 46.12, 61.14, 110.78, 116.62, 116.94, 119.63, 119.67, 124.70, 126.46, 127.97, 128.47, 131.80, 132.16, 132.27, 141.37, 150.87, 151.31, 154.17, 165.51, 172.75; HRMS ($EI^+$): $[M]^+$ , found 331.0676. $C_{17}H_{14}FNO_3S$ requires 331.0678.

**23. Ethyl 1,4-dihydro-8-methoxy-6-(6-methoxypyridin-3-yl)-1-methyl-4-oxoquinoline-3-carboxylate (4k)**




White solid; m.p. 181ºC-184ºC;$^1$H NMR (300MHz, $CDCl_3$, 25ºC, TMS): δ=1.42 (t, *J*=7.2 Hz, 3H), 4.00 (s, 6H), 4.18 (s, 3H), 4.40 (q, *J*=7.2 Hz, 2H), 6.85 (d, *J*=8.4 Hz, 1H), 7.27 (s, 1H), 7.90 (dd, *J*=5.4, 2.1 Hz, 1H), 8.31 (m, 2H), 8.46 (s, 1H); $^{13}$C NMR (75MHz,$CDCl_3$,25ºC, TMS):δ=14.45, 47.87, 53.77, 56.52, 60.92, 110.28, 111.12, 112.55, 117.03, 128.55, 130.08, 131.76, 135.12, 137.54, 144.89, 151.04, 151.74, 163.91, 165.81, 173.57; MS(ESI+): m/z 391.20 $[M+Na]^+$, elemental analysis calcd (%) for $C_{20}H_{20}N_2O_5$ : C, 65.21; H, 5.47; N, 7.60. found C, 65.23; H, 5.45; N, 7.62.

**24. Ethyl 1,4-dihydro-6-(6-methoxypyridin-3-yl)-1-methyl-4-oxoquinoline-3-carboxylate (4l)**



White solid; m.p. 169°C-171°C; $^{1}$H NMR (300MHz, $CDCl_3$,25ºC, TMS):δ 1.40 (t, *J* = 7.2 Hz, 3H), 3.88 (s, 3H), 3.99 (s,3H), 4.37(q, *J*=7.2Hz, 2H), 6.82 (d, *J*=8.7Hz, 1H), 7.46 (d, *J*=8.7Hz, 1H), 7.82(m, 2H), 8.39 (d, *J*=10.8Hz, 2H), 8.56 (d, *J*=1.5Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75MHz) δ : 14.42, 41.45, 53.66, 60.79, 110.71, 116.69, 124.56, 128.08, 128.97, 130.62, 134.64, 138.74, 144.98, 149.91, 163.88, 165.39, 174.18; MS($ESI^+$): m/z 361.24 $[M+Na]^+$, elemental analysis calcd (%) for $C_{19}H_{18}N_2O_4$ : C, 67.44; H, 5.79; N, 5.36. found C, 67.41; H, 5.82; N, 5.39.

## VI.F. References

References are given in BIBLIOGRAPHY under Chapter VI (pp-234-236)

# Chapter VII

# *NTFB (nitronium tetrafluoroborate) induced regioselective synthesis of nitro derivatives of 4-quinolone at ambient condition*

## VII.A. Introduction

From the last few decades, quinolones belong to the most commonly prescribed antibacterial drugs in the world.[1] High potency, low toxicity and better pharmacokinetic properties make the quinolones are highly demanded in now a days. Basically, most of the nitro quinolone derivatives served as a potential antifilarial, antiallergic, antiviral, antibacterial and antitumor agent.[2] Hai-Hong Li also reported that 3-nitro quinolone 5 has the ability to inhibit the epidermal growth factor receptor (EGFR).[3] In medicinal chemistry, the nitro compounds can easily formed various heterocycles by transforming into the diverse functionalities. Different 3-nitro quinolones derivatives have been also investigated for their antiprotozoal, antihistaminic, and antimalarial activities.[4]

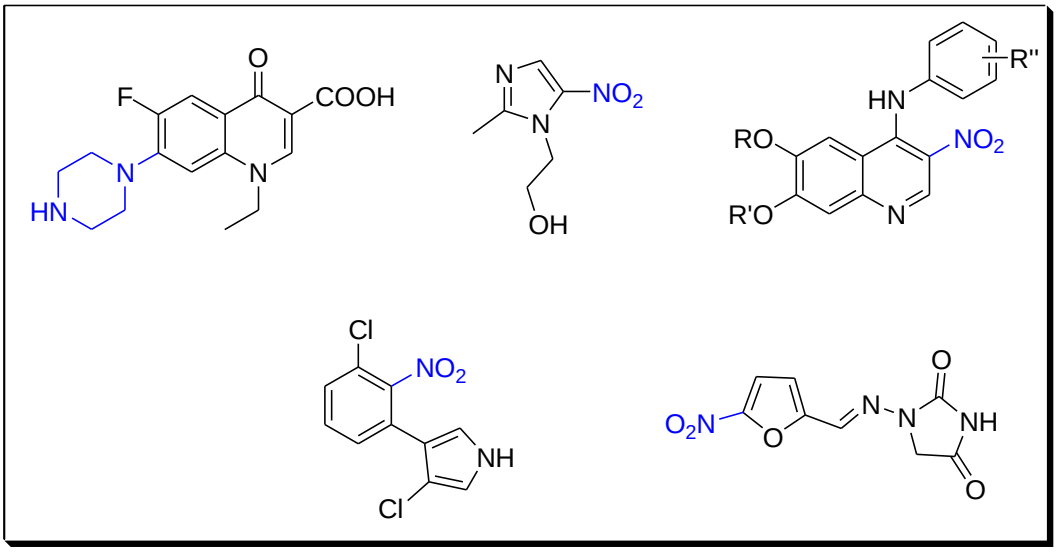



**Fig.VII.1.** few biologically active nitro derivatives

## VII.B.Present work: Background and objective

As 4-quinolones are most potent bioactive molecules so their regioselective functionalization remains a challenging task. So we have focused our aim towards the regioselective functionalisation of this bioactive molecule.[5] It has been found that the nature and position of various substituent brings magnificent potency to this drug. Till now very limited number of 6-nitro derivatives of 4-quinolones have been isolated and their medicinal values are totally examined so far.[6] It might be the problems associated with common reported methodologies as these include the cyclization of nitro-substituted anilines to form the desired nitro derivatives of 4-quinolone. Many methods have been reported but it is complicated to opt the process for aiming to get 5- or 7-nitro 4-quinolone because the starting unsymmetrical nitro

derivatives of anilines upon cyclization always resulted the mixture products (isomers) which lead to problematic separation process as well as low yield. No such direct protocol for the selective nitration of 4-quinolone is well documented in the literature. The regio-selection in the nitration reaction is mainly favoured by various factors like nature of solvent, electronic effects, steric effects and interaction between substrate and reagents.[7] Herein, we first disclosed a NTFB (nitronium tetrafluoroborate) induced regioselective synthesis of nitro derivatives of 4-quinolone at ambient condition. We have easily tuned the regio selectivity of the nitration reaction via proper selective protection of free -NH group of 4-quinolone. Using DFT (density functional theory) method, we have synchronized both the theoretical predictions with experimental observations.

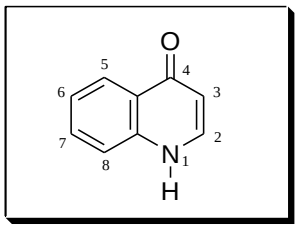
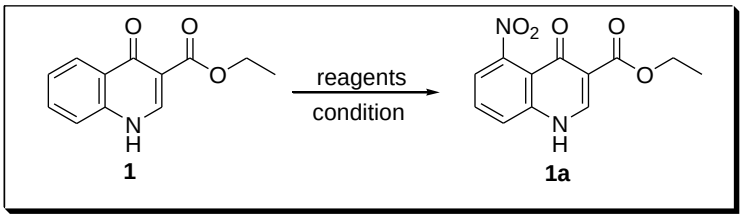



**Fig-VII.2.** Basic skeleton of 4-quinolone

### VII.B.1. Results and Discussion:

**Table-VII.1. Optimisation of the reaction conditions**



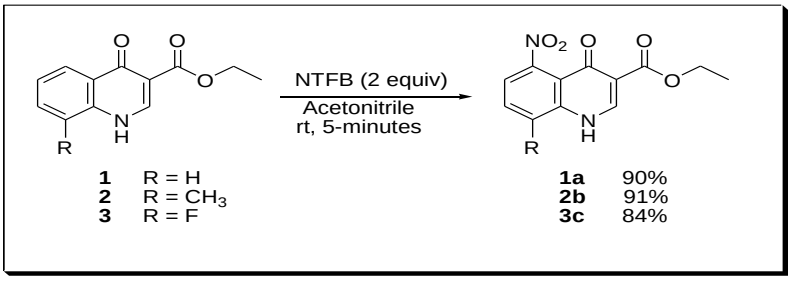

| entry | nitrating agent | solvent | temp | time | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | Mixed acids(Conc$^n$ $HNO_3$ + Conc$^n$ $H_2SO_4$) | - | 0°C-rt | 1 h | 78 |
| 2 | dil $HNO_3$ | - | rt | 2 h | 30 |
| 3 | Conc$^n$ $HNO_3$ | - | rt | 2 h | 52 |
| 4 | $Cu(NO_3)_2$/p-TSA | DCM | rt | 12 h | nr |
| 5 | $Fe(NO_3)_3$/$Ac_2O$ | DCM | rt | 12 h | nr |
| **6** | **NTFB** | **acetonitrile** | **rt** | **5 min** | **90** |

**Reaction conditions:** compound **1** (1mmol) taken in all cases. [a]yield = isolated yields after column chromatography

Initially, our journey began with the unsubstituted 4-quinolone 3-carboxylate as a model substrate for screening the optimal reaction condition. Five positions (C-2, C-5, C-6, C-7 and C-8) are available for nitration in the 4-quinolone scaffold. When nitration of compound 1, was conducted in the presence of mixed acids at ambient conditions resulted 78% yield of the desired 5-nitro-4-quinolone derivative upon isolation (Table-VII.1). Inspired by this observations, we optimized the reaction condition by using both dilute and concentrated nitric acid but the reaction did not provide any good result (Table-VII.1). Furthermore in presence of acid sensitive group, we changed our pathway to develop the nitration reaction under neutral conditions. Additional experiments with different well-known nitrating reagents furnished the corresponding product summarized in Table-VII.1. Finally, It was very much evident that the nitronium tetrafluoroborate (NTFB) was best suited nitrating agent in presence of acetonitrile (Table-VII.1, entry 6) in this present study which resulted 90 % yield of the desired product within few minutes at ambient conditions. Generally, nitration via NTFB proceeded followed the equation.[8]

$$ArH + NO_2^+ BF_4^- \longrightarrow ArNO_2 + HF + BF_3 \quad \text{..... (1)}$$

**Scheme-VII.1.** Scope of various 4-quinolone substrates

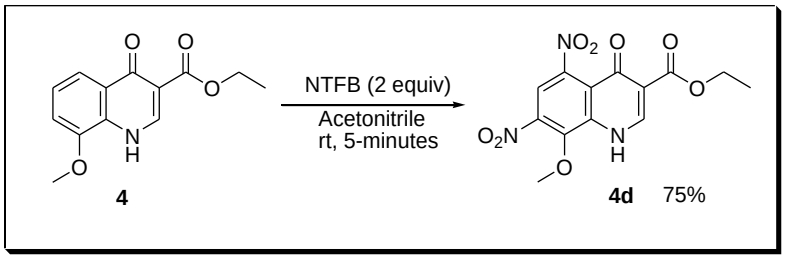



**Reaction conditions:** Compound 1, 2, 3 (1mmol) and NTFB (2 mmol. 0.266g) was stirred in 5 ml dry acetonitrile at room temp. Yield = isolated yields after column chromatography

With the optimized system in our hand, the scope of selective nitration was fully examined (Scheme-VII.1). Interestingly, the substrate bearing the –Me and –F at the 8- position (entry 2 and 3) of the scaffold enabled selective nitration and afforded the 5-nitro derivative in excellent yield. From this result, it was obvious that the presence of electron withdrawing group (-F) and electron releasing group (-$CH_3$) has no significant role in defining the

selective position of incoming electrophile (nitronium group). But the problem started with the derivative of 8-methoxy-4-quinolone (compound 4) while attempted the nitration. Our optimized reaction condition furnished the corresponding 5, 7-dinitro derivatives (Scheme-VII.2) upon nitration on Compound 4. Probably, the inherent +R effect of methoxy group facilitated the second nitration in its orthoposition (C-7).

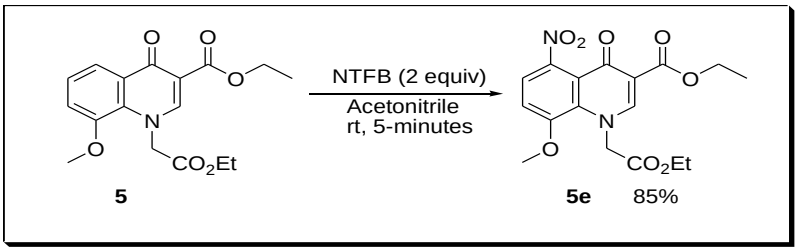
**Scheme-VII.2.** nitration of 8-methoxy-4-quinolone derivative




**Reaction conditions:** Compound **4** (1mmol) and NTFB (2 mmol. 0.266g) was stirred in 5 ml dry acetonitrile at room temp. Yield = isolated yields after column chromatography

Next to investigate as well as control the nitration reaction, we simply tuned the reactivity of compound 4 via functionalising of the free-NH with additional group so that it could slow down the reactivity of the staring compound 4 and thereby hindered the second addition of nitronium ion. From theoretical investigation, it was very evident that either introducing an alkylester or -$CH_2Ph$ group for the pre-functionalization of free N-H could restrict the second nitration of the compound 4. To test the feasibility of this strategy, we have choosen the alkylester group to protect the free –NH. The resulted product 5 can also be treated as an amino acid precursor. Afterwards, Compound 5 afforded the selective 5-nitroderivative of 4-quinolone in excellent yield.

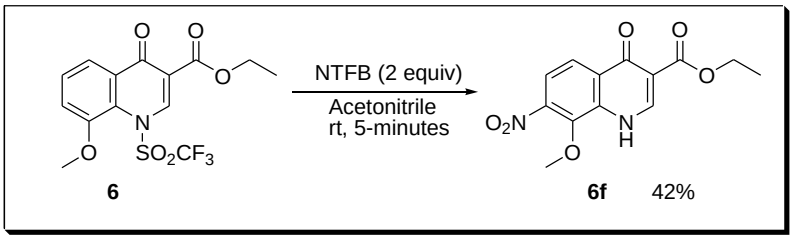
**Scheme-VII.3.** controlled nitration of compound **5**




**Reaction conditions:** Compound **5** (1mmol) and NTFB (2 mmol. 0.266g) was stirred in 5 ml dry acetonitrile at room temp. Yield = isolated yield after column chromatography.

The major challenge is to synthesize the selectively 7-nitro derivative of the same compound 4. With the aid of DFT calculation, it might be assumed that the $–SO_2CF_3$ protecting group can bring the selective nitration on C-7 position than the other protecting group. Finally, we have achieved the $–SO_2CF_3$ protected derivative of compound 4 in good yield by using triflic anhydride in presence of (TBAHS). tetrabutyl ammonium hydrogen sulphate. A noteworthy mono nitro-derivative of compound 6 had been isolated after *insitu* deprotection. Rather, the yield was not so much promising but it introduced the regioselection of the nitration under the optimized reaction condition (Scheme-VII.3).

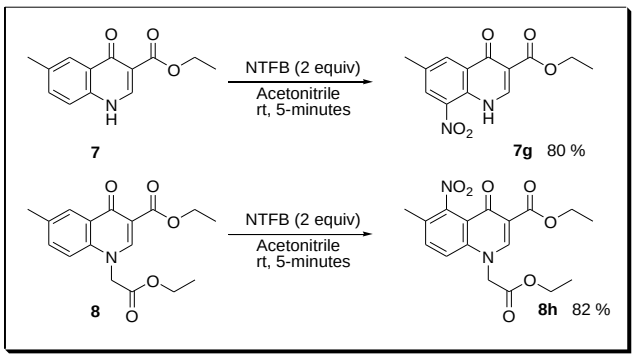
**Scheme-VII.4.** Selective nitration of *N*-protected 8-methoxy 4-quinolone at C-7 position




**Reaction conditions:** Compound **6** (1mmol) and NTFB (2 mmol. 0.266g) was stirred in 5 ml dry acetonitrile at room temp. Yield = isolated yield after column chromatography

From our previous results, it definitely showed that -NH group played the significant role for introducing the nitro group in the selective position of 4-quinolone moieties. Having establishment the selective nitration protocol, we readily explored the reactivity of 4-quinolone derivatives in the nitration reaction *via* selection of another compound **7** where methyl group resides at the C-6 position. The result of DFT calculation clearly indicated that the C-8 position is the most electron dense than the other possible sites for the electrophilic substitution.

**Scheme-VII.5.** Selective nitration of 6-methyl 4-quinolone




**Reaction conditions:** Compound **7, 8** (1mmol) and NTFB (2 mmol. 0.266g) was stirred in 5 ml dry acetonitrile at room temp. Yield = isolated yield after column chromatography

Additionally, the pre-functionalization of free N-H of compound 7 with both alkylester or $–SO_2CF_3$ changed the reactivity and selected the C-5 position for the attack of electrophile. By DFT analysis, the alkylester showed the highest reactivity indices than the - $SO_2CF_3$. Accordingly, we have done the prefunctionalisation of compound 7 with an alkyl ester followed the previous method (compound 5). Both the compounds 7 and 8 were underwent in the nitration reaction and furnished the correspondingC-8 and C-5 nitro derivatives in excellent yields.

## VII.C. Conclusion

Finally, the newly developed protocol for introducing nitro group in the various position of the 4-quinolone ring with maximum yield was not reported before in the literature. This method may be very helpful for the designing the newly bioactive molecules based on 4-quinolone scaffold. The whole study explored the selective insertion of nitro group which is predominantly governed by the free –NH of 4-quinolones. Other investigations to develop various substituted derivative on this moiety is currently underway.

## VII.D. Experimental section

### VII.D.1. General information

$^{1}H$ NMR spectra were recorded on Bruker Avance AV–300 spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) ($\delta_H$ = 0.00 ppm) or $CHCl_3$ ($\delta_H$ = 7.27 ppm). $^{13}C$ NMR spectra were recorded at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [$\delta_C$ = 77.00 ppm (central line of triplet)]. In the $^{1}H$ NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet and m = multiplet. Unless stated otherwise, all reagents such as *o*-anisidine, *p*-toluidine, aniline, 2-F-aniline, *o*-toluidine, EMME, potassium carbonate, tetrabutylammniumhydrogensulfate (TBAHS), NTFB (nitronium tetrafluoroborate), $(CF_3SO_2)O$ and solvents were purchased from commercial suppliers. Mass spectra were performed using ion trap mode. Products were purified using column chromatography on silica gel (60-120 mesh) and a mixture of petroleum ether (60-80°C)/ethyl acetate was used as an eluent. Progress of reaction was monitored by silica gel TLC.

### VII.D.2. Preparation of Compound (1 - 4)[5]

Initially, A mixture of aniline (10 mmol), EMME (11 mmol) and toluene (30 ml) was taken in a 250 ml round bottom flask for 5 hours at reflux temperature. Then it was cooled and washed with 3(N) 100 ml $H_2SO_4$. Afterwards toluene was distilled out. The resulting mixture was scratched continuously to get the solid anil product. The anil product (5g) was refluxed with diphenylether (50 ml) for 2 hours at 280ºC. It was further cooled and stirred with addition of 100 ml of petroleum ether for an hour. By filtration technique, Compound (1 - 4) was isolated on Buchner funnel. All products were fully characterized by $^{1}H$, $^{13}C$ NMR and melting points (for solid compounds).

### VII.D.3. General Procedure of Nitration Reaction (Compound 1a -8h)

In a 25 ml round bottom flask, 4-quinolone-3-carboxylate (1 mmol) was taken in 5ml dry acetonitrile. Then, NTFB (nitronium tetrafluroborate) 2 mmol (0.266 g) was rapidly added to it and stirred at ambient condition for 5 minutes. The progress as well as completion of the reaction was monitored by TLC. The reaction mixture was mixed with ice-water and immediately a yellow solid generated. The yellow solid product was filtered out and dried.

Furthermore, it was purified through column chromatography using petroleum ether and ethyl acetate as an eluent. All products were fully characterized by $^{1}H$, $^{13}C$ NMR, mass spectrometry, C, H, N analysis and melting points (for known solid compounds).

### VII.D.4. Preparation of compound 5 and 8

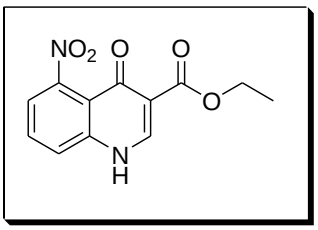
An oven dried round bottomed flask (100 ml) equipped with stir bar was charged with Compound 4 or 7 (1 mmol, 0.247g/ 0.231g) and 1.5 mmol (0.207g) of $K_2CO_3$ in requisite amount of DMF (solvent) at room temperature. The stirring was continued for half an hour to cease the evolve of hydrogen. Then, ethyl bromoacetate (0.324g/ ~0.3 ml) was the added into the reaction vessel and continued the stirring for next 1h at $60^0$C. After completion of reaction as monitored by the TLC, the reaction mixture was completely diluted with water and the desired product was extracted with DCM (3 x10 ml). The organic layer was further dried over anhydrous $Na_2SO_4$ and concentrated under high vacuum. The crude residue was purified by silica gel column chromatography using the mixture of ethyl acetate and petroleum ether as eluent.

### VII.D.5. Preparation of compound 6

An oven dried round bottomed flask (25 ml) equipped with a stir bar was charged with Compound **4 (**1 mmol, 0.247g), TBAHS (0.01 mmol, 3.23mg) and powdered NaOH (2.5 mmol, 100 mg) in 8 ml of DCM. Then 1.5 mmol (0.423 g) of $(CF_3SO_2)_2O$ in 1 ml DCM was rapidly added in a single portion and continued the stirring at room temperature for 30 minutes. Immediately after completion of reaction by monitoring TLC, solid $NaHCO_3$ was added to neutralize the reaction mixture. The crude material was filtered out and purified by the silica gel column chromatography.

### VII.D.6. Physical characteristic and spectral analysis of compounds

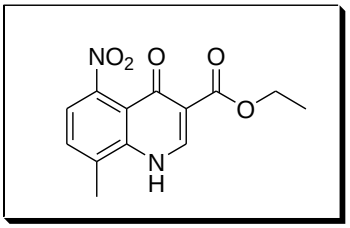
**1. Ethyl 1, 4-dihydro-5-nitro-4-oxoquinoline-3-carboxylate (2a)**




Greenish yellow solid, melting point: >253°C, $^{1}H$ NMR (300MHz, DMSO-$d_6$) δ 1.26 (t, *J*=7.2 Hz, 3H), 4.23 (q, *J*=7.2 Hz, 2H), 7.56 (t, *J*=8.1 Hz, 1H), 8.53-

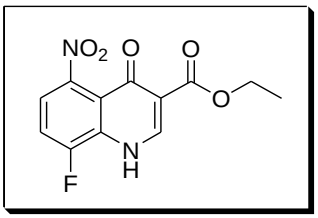
8.55 (m, 2H), 8.61(d, *J*=8.1 Hz, 1H), 12.2 (s, 1H). $^{13}$C NMR (75MHz, DMSO-$d_6$) δ 14.6, 60.4, 111.7, 124.1, 129.5, 130.6, 133.5, 134.2, 137.1, 146.6, 164.2, 172.4, ESI-MS$[M+H]^+$ found m/z 263.10, elemental analysis for $C_{12}H_{10}N_2O_5$ C, 54.97; H, 3.84; N, 10.68; Found: C, 54.76; H, 3.79; N, 10.51.

**2. Ethyl 1, 4-dihydro-8-methyl 5-nitro-4-oxoquinoline-3-carboxylate (2b)**



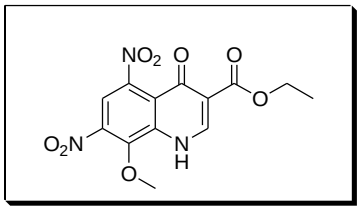

Yellowish white solid, melting point: 225°C-228°C, $^1$H NMR (300MHz, DMSO-$d_6$,) δ 1.22 (t, *J*=7.2 Hz, 3H), 2.54 (s, 3H), 4.21 (q, *J*=7.2 Hz, 2H), 7.53 (d, *J*=7.8 Hz, 1H), 7.70 (d, *J*=8.4 Hz, 1H), 8.43 (s, 1H), 11.60 (s, 1H), $^{13}$C NMR (75MHz, DMSO-$d_6$) δ 14.7, 17.7, 60.5, 111.3, 118.3, 119.0, 131.4, 133.3, 139.1, 145.6, 147.5, 164.6, 171.2, ESI-MS$[M+Na]^+$ found m/z 298.95, elemental analysis for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14; Found: C, 56.38; H, 4.32; N, 9.96.

**3. Ethyl 8-fluoro 1, 4-dihydro- 5-nitro-4-oxoquinoline-3-carboxylate (3c)**



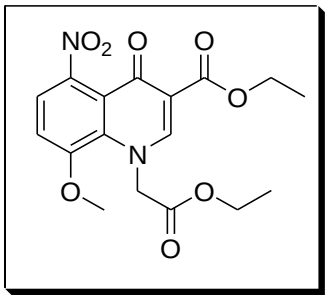

Yellowish white solid, melting point: 234°C-236°C, $^1$H NMR (300MHz, DMSO-$d_6$) δ 1.03 (t, *J* =7.2 Hz, 3H), 3.98 (q, *J* =7.2 Hz, 2H), 7.46-7.50 (m, 1H), 7.56-7.62 (m, 1H), 8.19 (s, 1H), 12.80 (s, 1H), $^{13}$C NMR (75MHz, DMSO-$d_6$) δ 14.7, 60.6, 112.3, 117. 7, 117.9, 119.5, 119.6, 120.1, 130.0, 130.2, 144.9, 145.0, 145.6, 151.1, 154.5, 164.3, 170.2, HRMS (ESI-TOF) [M+H] m/z: $[M+H]^+$ found 281.0486. $C_{12}H_9FN_2O_5$ requires 281.0574.

**4. Ethyl 1,4-dihydro-8-methoxy-5,7-dinitro-4-oxoquinoline-3-carboxylate (4d)**



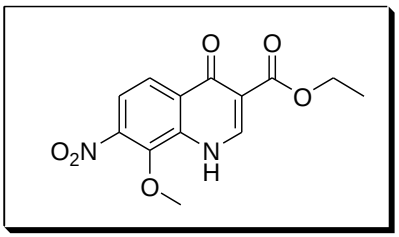
Bright yellow solid, melting point: 175°C-178°C, $^{1}$H NMR (300MHz, DMSO-$d_6$) δ 1.27 (t, *J* =7.2 Hz, 3H), 4.12 (s, 3H), 4.23 (q, *J* =7.2 Hz, 2H), 8.37 (s, 1H), 8.49 (s, 1H), $^{13}$C NMR (75MHz, DMSO-$d_6$) δ 14.7, 60.7, 64.4, 113.2, 114.8, 121.5, 136.8, 142.1, 143.5, 146.1, 146.3, 164.2, 170.3, HRMS (ESI-TOF) $[M+H]^+$ m/z: [M+H]+, found 338.0522. $C_{13}H_{11}N_3O_8$ requires 338.0624.

**5. Ethyl 1-((ethoxycarbonyl) methyl)-1,4-dihydro-8-methoxy-5-nitro-4-oxoquinoline-3-carboxylate (5e)**



Yellow solid, melting point: 148°C-150°C, $^{1}$H NMR (300MHz, DMSO-$d_6$) δ 1.26-1.36 (m, 6H), 3.91 (s, 3H), 4.22-4.35 (m, 4H), 5.07 (s, 2H), 7.03 (d, *J*=8.7 Hz,1H), 7.24 (d, *J*=8.4 Hz, 1H), 8.19 (s,1H), $^{13}$C NMR (75MHz, DMSO-$d_6$) δ 14.3, 56.6, 60.2, 61.1, 61.9, 112.0, 112. 7, 120.4, 130.8, 143.3, 151.0, 152.3, 164.1, 167.3, 170.3, HRMS(EI)$^+$[M]$^+$, found 378.1041. $C_{17}H_{18}N_2O_8$ requires 378.1063.

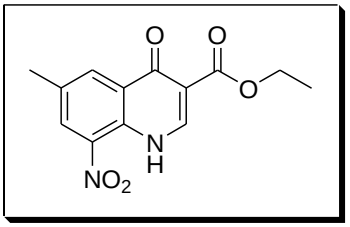
**6. Ethyl 1-((ethoxycarbonyl) methyl)-1,4-dihydro-8-methoxy-5-nitro-4-oxoquinoline-3-carboxylate (6f)**



Yellow solid, melting point: 190°C-193°C, $^{1}$H NMR (DMSO-$d_6$, 300MHz) δ 1.27 (t, *J* =7.2 Hz, 3H), 3.98 (s, 3H), 4.22 ( q, *J* =7.2 Hz, 2H), 7.87 (dd, *J* =9.0Hz, 0.9 Hz, 1H), 8.00 (dd, *J* =9.0Hz, 0.9Hz, 1H), 8.44 (s, 1H), 12.40 (s, 1H), $^{13}$C NMR

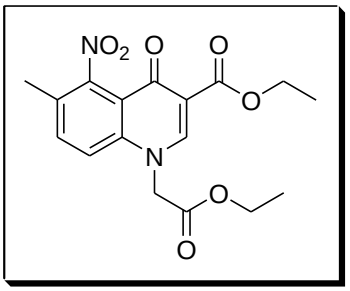
(DMSO-$d_6$, 75MHz) δ 14.6, 60.3, 64.0, 111.7, 119.8, 121.9, 131.0, 134.7, 143.9, 144.1, 146.1, 164.6, 172.8, $(ESI)^+[M+H]^+$ m/z 293.00 $[M+H]^+$, $C_{13}H_{12}N_2O_6$ requires 293.1, elemental analysis for for $C_{13}H_{12}N_2O_6$: C, 53.43; H, 4.14; N, 9.59. Found: C, 52.96; H, 4.21; N, 9.74.

**7. Ethyl 1-((ethoxycarbonyl) methyl)-1,4-dihydro-8-methoxy-5-nitro-4-oxoquinoline-3-carboxylate (7g)**



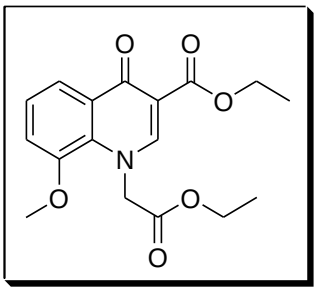

Yellowish white solid, melting point: 239°C-241°C, $^1$H NMR (300MHz, DMSO-$d_6$,) δ ppm 1.25 (t, *J* =7.2 Hz, 3H), 2.24 (s, 3H), 4.19 (q, *J* =7.2 Hz, 2H), 7.73 (d, *J* =2.7 Hz, 2H), 8.58 (d, *J* =6.3 Hz, 1H), 12.7 (bs, 1H), $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 14.2, 15.4, 59.9, 110.8, 117.6, 120.7, 125.6, 135.1, 138.1, 145.0, 147.3, 164.3, 170.3, $(ESI)^+[M+H]^+$ m/z 277.00 $[M+H]^+$, $C_{13}H_{12}N_2O_5$ requires 277.1, elemental analysis for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. found: C, 56.32; H, 4.29; N, 9.65.

**8. Ethyl 1-((ethoxycarbonyl) methyl)-1, 4-dihydro-6-methyl-5-nitro-4-oxoquinoline-3-carboxylate (8h)**



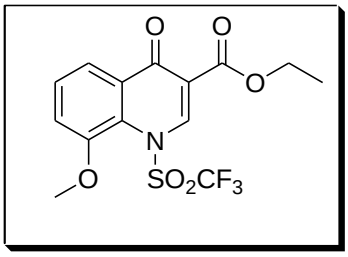

Light yellow solid, melting point: 203°C-206°C, $^1$H NMR (300MHz, $CDCl_3$) δ 1.09-1.19 (m, 6H), 2.16 (s, 3H), 4.04-4.15 (m, 4H), 5.30 (s, 2H), 7.64 (d, *J* =9 Hz, 1H), 7.72 (d, *J* =9 Hz, 1H), 8.68 (s, 1H), $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.4, 16.1, 55.0, 61.1, 62.8, 112.3, 117.0, 119.6, 127.1, 135.1, 138.3, 148.9, 149.8, 164.3, HRMS$(EI)^+[M]^+$ found 362.1123. $C_{17}H_{18}N_2O_7$ requires 362.1114.

**9. Ethyl 1-((ethoxycarbonyl) methyl)-1, 4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylate (5)**



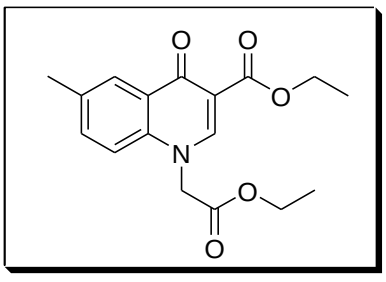
white solid, melting point: 159°C-162°C, $^{1}$H NMR (300 MHz $CDCl_3$) δ 1.25 (t, *J* =6.9 Hz, 3H), 1.38 (t, *J* =6.9Hz, 3H), 3.83 (s, 3H), 4.24 (q, *J* =6.9 Hz, 2H), 4.36 (q, *J* =6.9 Hz, 2H), 5.05 (s,2H), 7.07-7.10 (m,1H), 7.27-7.34 (m, 1H), 8.11 (dd, *J* =8.1Hz, 1.2Hz, 1H), 8.25 (s,1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.4, 56.2, 60.1, 60.9, 61.8, 110.8, 114.4, 119.9, 125.5, 130.1, 131.0, 149.4, 152.1, 165.5, 167.6, 173.8.

**10. Ethyl 1,4-dihydro-8-methoxy-1-trifluoromethanesulfonate-4-oxoquinoline-3-carboxylate (6)**



Colourless liquid, $^{1}$H NMR (300 MHz, $CDCl_3$) δ ppm 1.50 (t, *J* =7.2 Hz, 3H), 4.17 (s,3H), 4.60 (q, *J* =7.2 Hz, 2H), 7.46 (d, *J* =7.5 Hz, 1H), 7.75-7.80 (m, 1H), 8.01 (dd, *J* =8.4 and 0.6 Hz, 1H), 9.41 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.0, 57.0, 64.4, 105.3, 115.1, 115.2, 118.4, 121.2, 130.3, 131.2, 145.2, 150.2, 167.9, 172.6.

**11. Ethyl 1-((ethoxycarbonyl) methyl)-1, 4-dihydro-6-methyl-4-oxoquinoline-3-carboxylate (8)**



white solid, melting point: 205°C-208°C, $^{1}$H NMR(300 MHz, $CDCl_3$) δ ppm 1.26 (t, *J* =6.9 Hz, 3H), 1.41(t, *J* =6.9 Hz, 3H), 4.26 (q, *J* =6.9 Hz, 2H), 4.39 (q, *J* =6.9 Hz, 2H), 4.89 (s, 2H), 7.12(d, *J* =8.4 Hz, 1H), 7.48 (dd, *J* =8.7 and 2.1 Hz 1H), 8.31 (s, 1H), 8.46 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.4, 21.0, 54.7, 61.0, 62.6, 110.9, 115.0, 127.5, 128.5, 134.4, 135.8, 137.3, 149.6, 165.5, 166.6, 174.5.

## VII.E. References

References are given in BIBLIOGRAPHY under Chapter VII (pp-236-237)

# Chapter VIII

# *Ligandless copper catalysed rapid and selective C-$NH_2$ arylation of 4-quinolone at ambient condition*

## VIII.A. Introduction

The development of aromatic C–N bond is one of the most important breakthrough in organic synthesis due to the pervasiveness of N-arylamine derivatives in various molecules of biological importance.[1]Particularly, the formation of N-aryl bond formation can actually determine the biological activity of the molecules during structure–activity relationship (SAR) studies.[2]Now a days, significant development has been done on the transition-metal-catalyzed C(aryl)–N bond formations.[3]Generally, these studies have primarily based on the Ullmann (Cu –mediated)[4]or Buchwald–Hartwig cross-coupling reactions (Pd-promoted).[5]In recent years, Cham-Lam coupling through Cu-mediated N-,O- and S-arylation with aryl or aliphatic boronic acids is paid main attention for C-heteroatom bond synthesis.[6,7]Main highlight of this coupling reaction is the mild reaction conditions such as weak base, room temperature and an ambient condition. Several researchers have engrossed their thinking's to find the various aspects of this coupling method.[8]

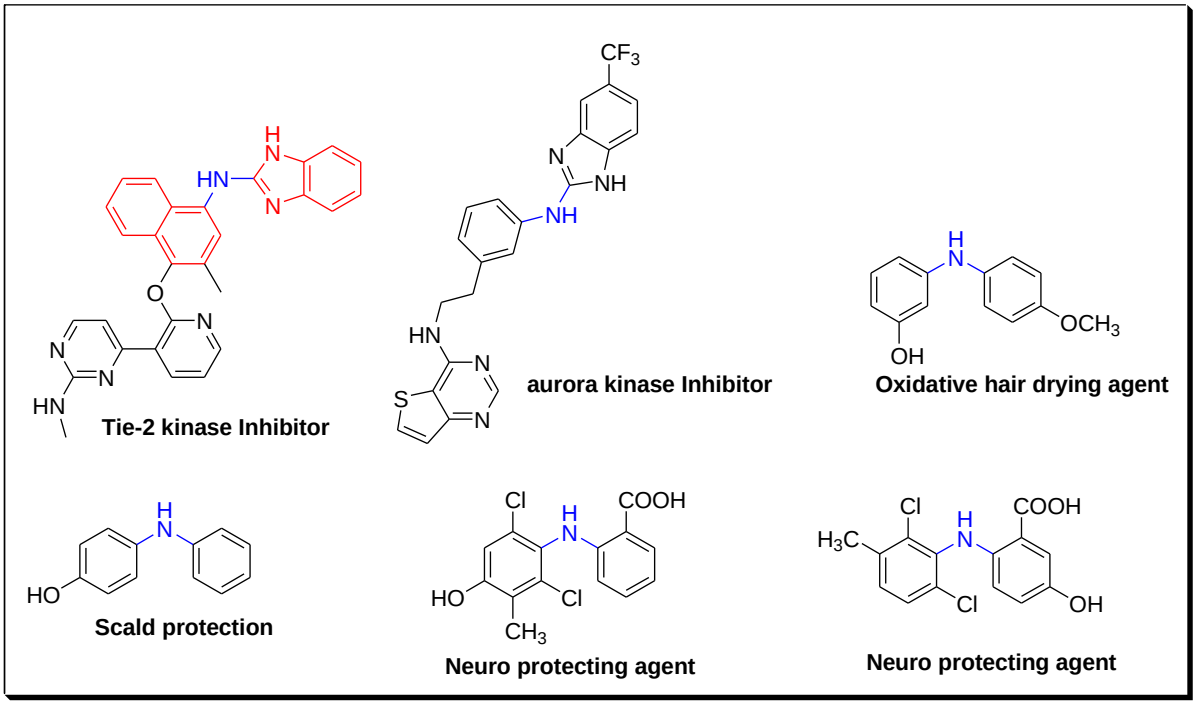
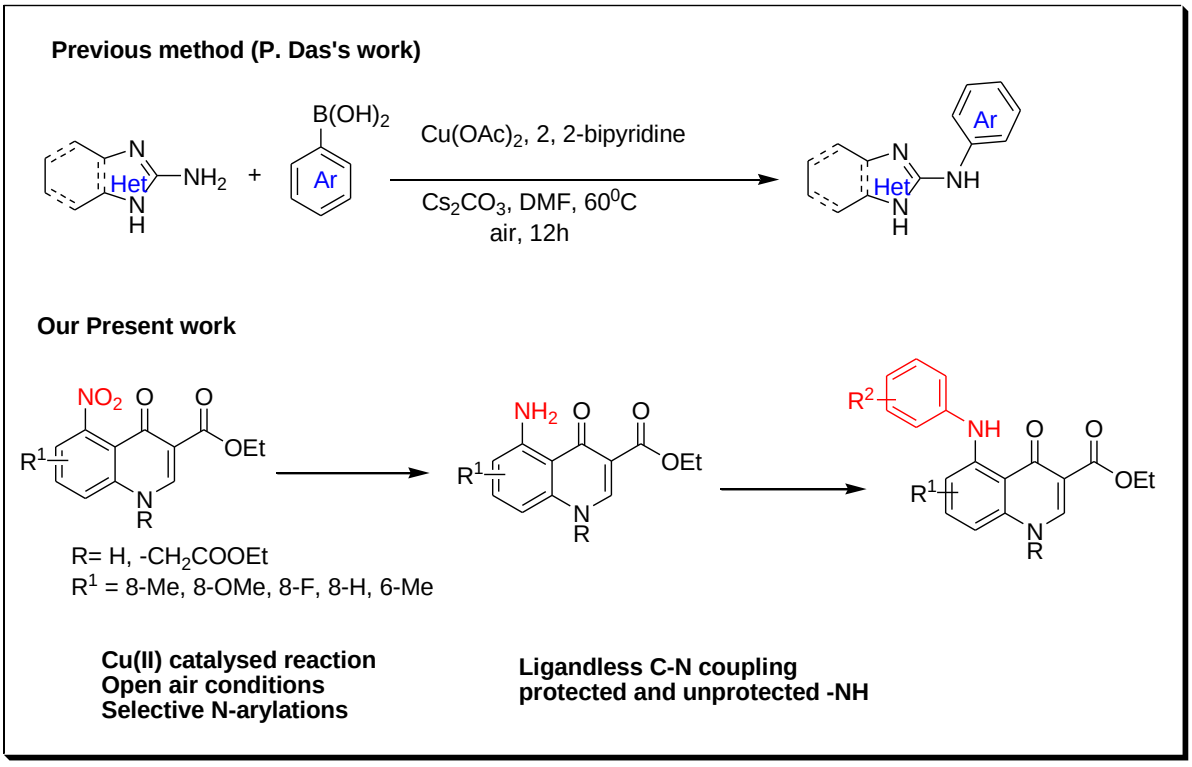


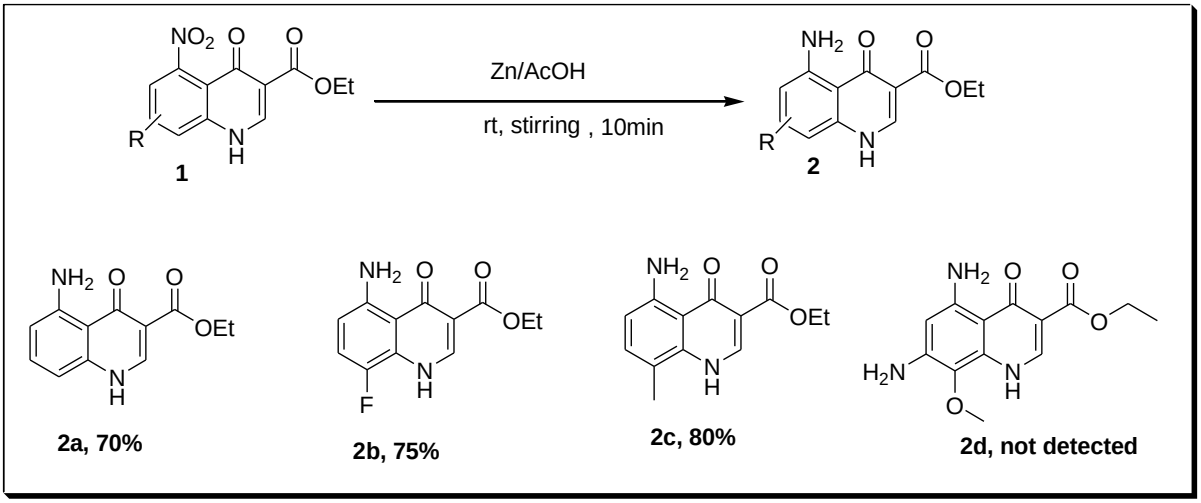

**Fig-VIII.1.** Biologically important N-arylated 2-aminobenzimidazole and N-arylated amino phenols

## VIII.B. Present work: Background and objective

Derivatives of 4-quinolones are widely accepted owing to its impressive antibiotic activity. Now a day's tremendous investigations are continued on this due to its prolific activity as an anticancer, anti-HIV, anti malarial, anti diabetic agent etc. Most of the biologically active potent quinolones enriched with amino, nitro group or any other alkylating group at C-5, C-6 and N-1 position. In our previous papers, we mainly accomplished to synthesize the highly functionalized 6-arylsubstituted-4-quinolones via regioselective bromination[9] and regiocontrolled nitration under ambient condition.[10] Afterwards, it has opened an avenue for the quest of newly better functionalized quinolone moieties. In recent times, our laboratory has also been focused on the development of N-arylated derivatives of 4-quinolones via the Chan–Lam type cross-coupling reactions because various N-arylated heterocyclic motifs such as 2-amino benzimidazole[11] N-arylated amino phenols [12] are found in numerous medicinally important compounds. In this context, we have unfolded a copper (II) catalysed rapid selective C-$NH_2$ arylation of both unprotected and protected 4-quinolone derivatives under ambient condition.



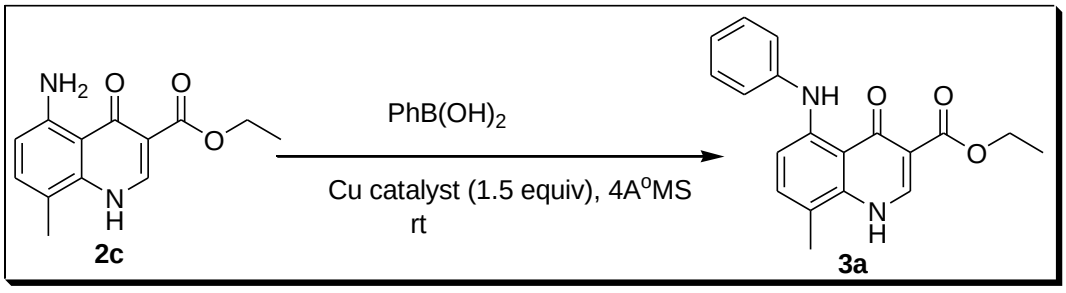
**VIII.B.1. Present work: Result and Discussion**




**Scheme-VIII.1** reduction of nitro derivatives of 4-quinolones at ambient condition.

To accomplish our pathway, we reduced the nitro group to amine (2) in presence of zinc and acetic acid because most of the biologically active quinolone scaffolds contained the amine group, cyclic amine, or heterocyclic amine moiety etc. Most promising finding of this reaction was to complete the reduction fully in just 10 minutes. Both electron rich (-Me) and electron deficient (-H, -F) substituted nitro derivatives easily reduced and the corresponding amine derivatives were formed in good yields (Scheme-VIII.1; entry **2a-2c**). Unfortunately, no desired product was detected in case of 8-methoxy-5-nitro 4-quinolone derivative (Scheme-VIII.1; entry **2d**).

**Table-VIII.1. Optimization of the reaction condition**

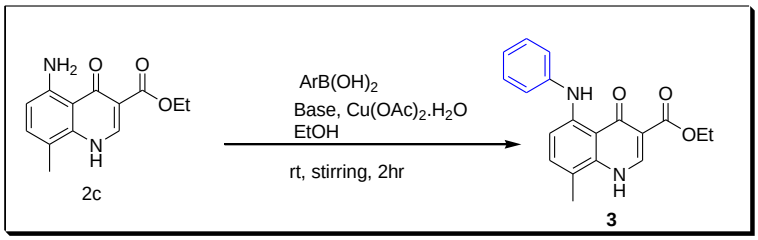


| entry | catalyst (equiv) | base (equiv) | solvent (ml) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | EtOH | 12 | 80 |
| 2 | $Cu(OAc)_2.H_2O$ | $Cs_2CO_3$ | EtOH | 12 | 25 |
| 3 | $Cu(OAc)_2.H_2O$ | $K_3PO_4$ | EtOH | 12 | 15 |
| 4 | $Cu(OAc)_2.H_2O$ | $Et_3N$ | EtOH | 12 | 56 |
| 5 | $Cu(OAc)_2.H_2O$ | $Na_2CO_3$ | EtOH | 12 | 42 |
| 6 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | DCM | 24 | - |
| 7 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | 1,4-dioxane | 24 | - |
| 8 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | toluene | 24 | trace |
| 9 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | THF | 24 | NR |
| 10 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | DMF | 12 | 60 |
| 11 | $Cu(OTf)_2$ | $K_2CO_3$ | EtOH | 12 | 66 |
| 12 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | EtOH | 9 | 79 |
| 13 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | EtOH | 6 | 72 |
| **14** | **$Cu(OAc)_2.H_2O$** | **$K_2CO_3$** | **EtOH** | **2** | **81%** |
| 15 | CuI | $K_2CO_3$ | EtOH | 24 | - |
| 16 | CuBr | $K_2CO_3$ | EtOH | 24 | - |
| 17 | $CuSO_4.5H_20$ | $K_2CO_3$ | EtOH | 24 | - |

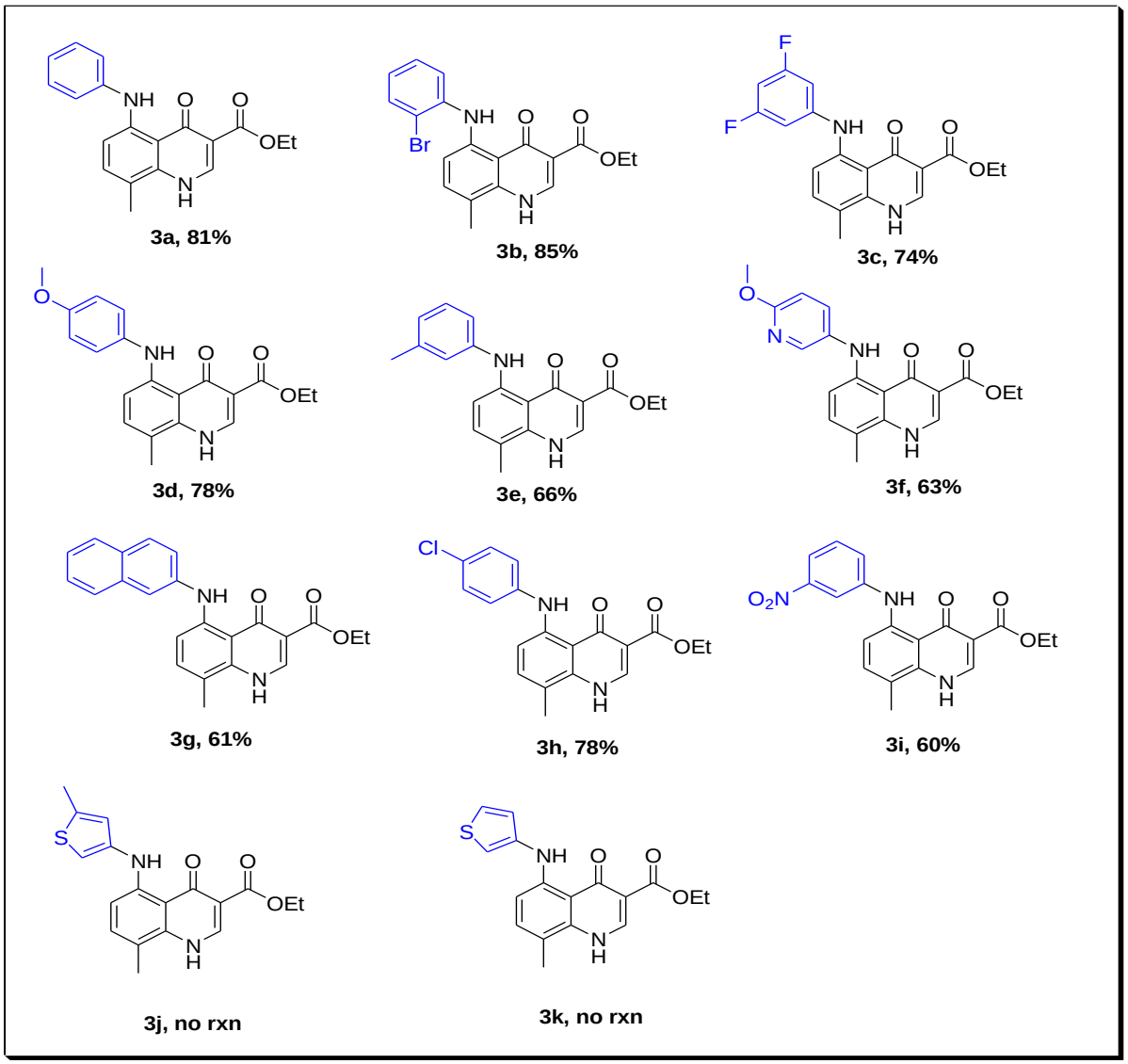
**Reaction condition:** 0.25 mmol (62 mg) of **2c**, $ArB(OH)_2$ (0.375 mmol, 46mg), Base (2 equiv), Cu catalyst (1.5 equiv), 4A°MS (100 mg) in 2ml solvent at rt stirring in air . Yield = Isolated yield after column chromatography.

To accomplish our journey, we initially screened the reaction conditions with **2c** and phenylboronic acid as coupling partners by using $Cu(OAc)_2.H_2O/K_2CO_3$ combination in EtOH at room temperature and we isolated the major N-5 arylated product (**3a**) in 80% yield after 12h (Table-VIII.1; entry-1). Next, we change the bases ($Cs_2CO_3$, $K_3PO_4$ and $Et_3N$) for the improvement of the result but the product yield was not quite promising (Table-VIII.1; entries 2, 3 and 4). $Na_2CO_3$ was remained inferior to the combination of $Cu(OAc)_2.H_2O/K_2CO_3$ in EtOH at room temperature (Table-VIII.1; entry-5). We also tried our reaction in various solvents (DCM, THF, 1,4-dioxane and DMF) but all gave trace to moderate yield of the corresponding product(Table-VIII.1; entry 6-10). Different Cu sources were employed to furnish better yield of the product, only $Cu(OAc)_2.H_2O$ served the best result (Table-VIII.1; entries-11, 14-17). Furthermore by varying the time it was observed that

only 2h was required for this smooth coupling (Table-VIII.1; entry-14). Eventually, it was evident that the combination of $Cu(OAc)_2.H_2O/K_2CO_3$ in EtOH at room temperature for 2h afforded the highest yield of the desired N-arylated product (Table-VIII.1; entry-14).

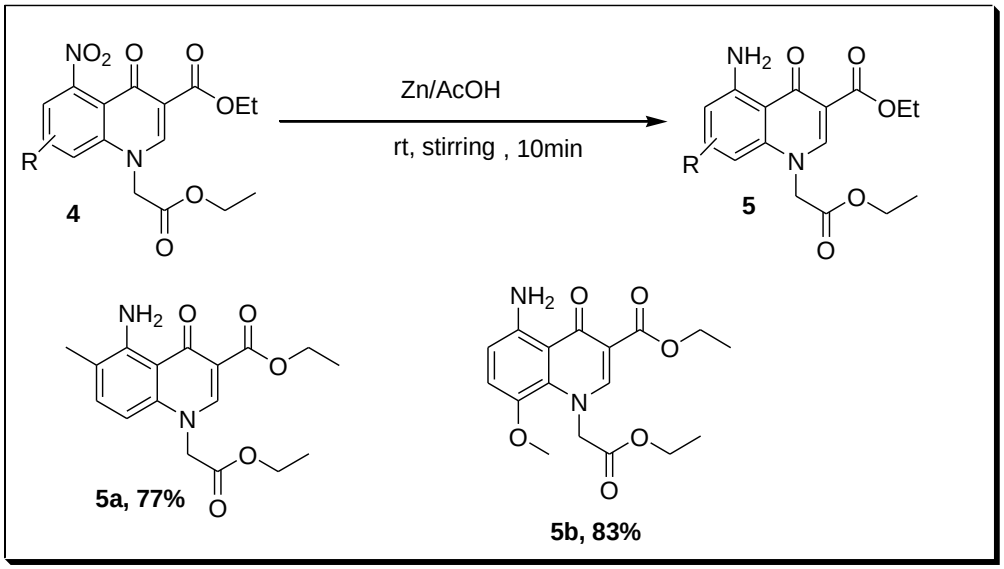



**Scheme-VIII.2** Scope of Cu catalysed C-5 $NH_2$ arylation of 4-quinolone derivative




**Reaction condition:** 0.25 mmol (62 mg) of **2c** , $ArB(OH)_2$ (0.375 mmol, 46mg), $K_2CO_3$ (0.5 mmol, 69 mg), Cu $(OAc)_2.H_2O$ (0.375 mmol, 75mg), 4A°MS (100 mg) in 2ml EtOH at rt stirring for 2h . Yield = Isolated yield.

With the optimized condition in our hand, we examined the scope of various arylboronic acids with 5-amino derivatives of 8-methyl substituted 4-quinolone. The reaction proceeded smoothly with different arylboronic acid and afforded the N-arylated quinolones (**3a**-**3i**) in excellent yields (60-81%). Electronic factors of arylboronic acid did not influence so much towards the product yield. Rather both electron donating (4-OMe, 3-Me) groups and electron withdrawing group (4-Cl) substituted arylboronic acids proved to be a good coupling partners for this coupling (scheme-VIII.2.; entry-**3d, 3e** and **3h**). ortho bromo substituted phenylboronic acid afforded the desired N-arylated derivative in excellent yield (**3b**). 5-methyl-2-thienyl and 2-thienyl boronic acid did not produce any result due to the formation of complex in between 4-quinolone derivatives and Cu(II) species.

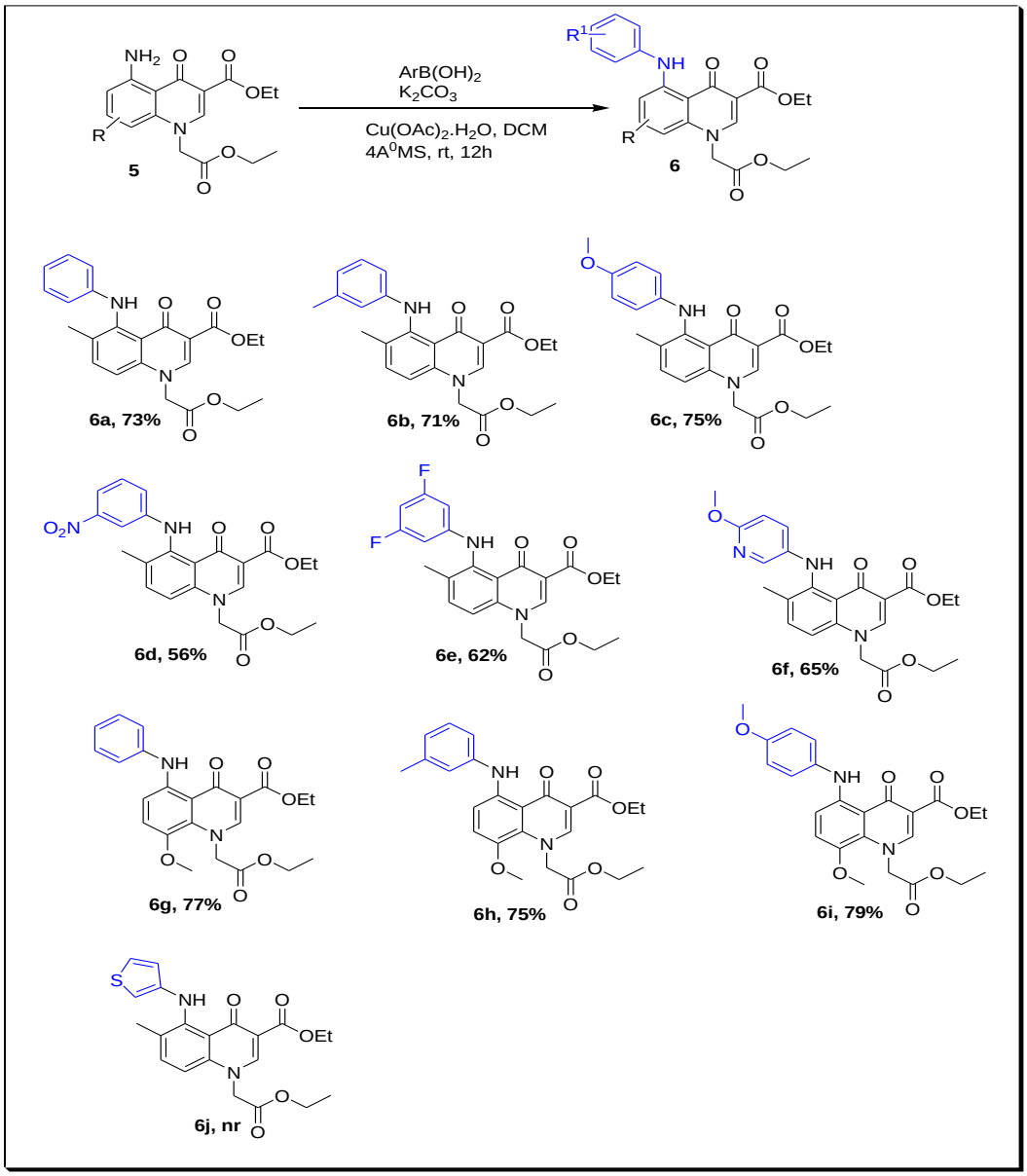



**Scheme-VIII.3.** reduction of N-protected nitro derivatives of 4-quinolones at ambient condition

To establish our proof of concept for N-arylation at 5-$NH_2$ instead of N-H, we proceeded our journey with N-protected nitro derivative (4). Primarily, we reduced the nitro derivative to amine *via* employing similar technique as stated earlier.6-methyl and 8-methoxy substituted 4-quinolone derivatives afforded the corresponding amine product with excellent yields in a very short span.

Next, we further investigated scope of the Cu catalysed N-arylation of 5-$NH_2$ with protected 4-quinolone and substituted arylboronic acid. Our catalytic system performed very well with both electron releasing and electron deficient arylboronic acid. *m*-tolylboronic acid and 4-methoxyboronic acid coupled with (Scheme-VIII.3.entry-**5a)** in a very facile manner and

produced the desired products with good yields (Scheme-VIII.4, entry **6b** and **6c**). Electron-withdrawing group such as –F, -$NO_2$ have an effect to reduce the yield of the N-arylated product (Scheme-VIII.4, entry **6d-6e**) on the cross-coupling reaction than compared to electron-donating group.2-methoxy-pyridin-5-boronic acid participated in cross-coupling reaction with **5a** and afforded 65% yield of the product (Scheme-VIII.4, entry **6f**). The optimized condition also employed with **5b** and it furnished the corresponding N-arylated derivatives in 75-79% yield respectively. Surprisingly, 2-thienylboronic acid could not afford any product due to the formation of complex.




**Scheme-VIII.4.** Scope of Cu catalysed C-5 $NH_2$ arylation of -NH protected 4-quinolone derivative

## VIII.C. Conclusion:

In conclusion, we have developed the copper catalysed selective C-$NH_2$ arylation of 4-quinolones under ambient condition. This method offers several advantages such as room temperature, short reaction and ligand free condition. Various functional groups (-Br, -Cl,-$NO_2$) are well tolerable in this present protocol. Moreover, we have synthesized a broad array of functionally diverse 4-quinolone derivatives which may possess some biological activity and it will be reported in due course.

## VIII.D. Experimental section:

### VIII.D.1. General Information

Unless stated otherwise, all reagents such as Copper acetate, boronic acids and solvents were used as received from commercial suppliers. NMR spectra were recorded on 300 MHz spectrometer at 298 K with calibration done on the basis of solvent residual peak. Mass spectra were performed using ion trap mode. Products were purified using column chromatography on silica gel (60-120 mesh). Ethyl acetate and petroleum ether (60-80$^oC$) were used as eluents. Progress of reaction was monitored using silica gel TLC

### VIII.D.2. Preparation of Amine derivatives of 4-quinolones (2a-2d, 5a-5b):

At first, various 5-nitro derivatives (1, 4) of 4-quinolone (0.5 mmol), Zn (0.75 mmol, 47.5mg) and AcOH (2ml) were taken in 5ml methanol in a 25 ml round bottomed flask. Then it was stirring at room temp for 10 minutes. The reaction became exothermic. After completion of the reaction, it was cooled and diluted with water. The excess acetic acid was neutralized by $NaHCO_3$ solution. Then, it was extracted with 30 ml ethyl acetate and dried over $Na_2SO_4$. The crude product was then purified using column chromatography.

### VIII.D.3 Preparation of N-arylated derivatives of 4-quinolones (3a-3i):

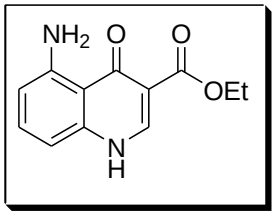
0.25 mmol (62 mg) of 2c, $ArB(OH)_2$ (0.375 mmol, 1.5 equiv), $K_2CO_3$ (0.5 mmol, 69 mg), Cu $(OAc)_2.H_2O$ (0.375 mmol, 75mg), 4A°MS (100 mg) were dissolved in 5ml ethanol. Then, the reaction mixture was stirred for 2h under ambient condition for the completion of reaction. Afterwards, it was evaporated to dryness under reduced pressure. Then, it was diluted with water and extracted via 30ml ethyl acetate. The crude reaction mixture was dried over $Na_2SO_4$. The crude product was then purified using column chromatography.

**VIII.D.4. Preparation of N-arylated derivatives of 4-quinolones (6a-6i):**

0.25 mmol) of 5, $ArB(OH)_2$ (0.375 mmol, 1.5 equiv), $K_2CO_3$ (0.5 mmol, 69 mg), Cu $(OAc)_2.H_2O$ (0.375 mmol, 75mg), 4A°MS (100 mg) were dissolved in 5ml DCM . Then, the reaction mixture was stirred for 12h under ambient condition for the completion of reaction. Then, it was diluted with water and extracted via 30ml ethyl acetate. The crude reaction mixture was dried over $Na_2SO_4$ and evaporated to dryness under reduced pressure. The crude product was then purified using column chromatography.

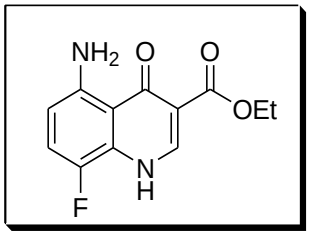
**VIII.D.5. Physical characteristics and spectral data of compounds**

1. **Ethyl-5-amino-1,4-dihydro-4-oxoquinoline-3-carboxylate (2a)**



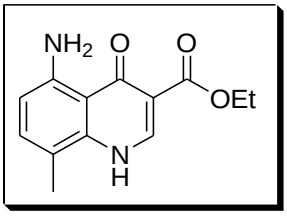

Brown solid, melting point:225-227°C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 4.24 (q, *J* = 7.2Hz, 2H), 7.59 (t, *J* = 8.1Hz, 1H), 8.56-8.66 (m, 3H), 12.20 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.7, 60.5, 111.9, 124.2, 124.6, 130.7, 133.6, 134,3, 137.2, 146.7, 164.3, 172.5.

2. **Ethyl-5-amino-1,4-dihydro-8-fluoro-4-oxoquinoline-3-carboxylate (2b)**



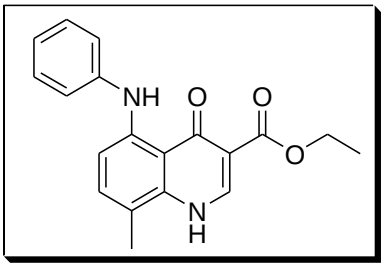

Black solid, melting point: 212-215°C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.16 (t, *J* = 7.2 Hz, 3H), 4.08 (q, *J* = 7.2Hz, 2H), 6.25 (dd, *J* = 9.0Hz, 4.2Hz, 1H), 8.09 (s, 1H),7.14-7.20 (m, 1H), 7.28 (s, 2H), 11.80 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.8, 60.1, 107.2, 107.3, 110.6, 112.2, 116.1, 119.2, 119.4, 129.1, 140.0, 143.1, 144.4, 148.3, 164.7, 177.8 HRMS ($ESI^+$): $[M+H]^+$, found 251.0739. $C_{12}H_{12}FN_2O_3$ requires 251.0753.

**3. Ethyl-5-amino-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (2c)**



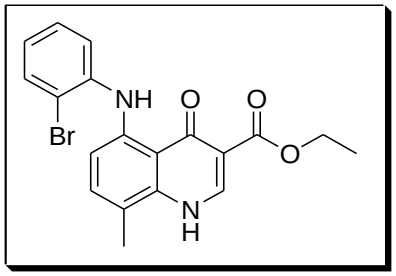

Yellow solid, melting point: 236-238°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 2.20 (s, 3H), 4.16 (q, *J* = 7.2Hz, 2H), 6.34 (d, *J* = 8.1Hz, 1H), 7.09 (d, *J* = 8.4Hz, 1H), 7.40 (s, 2H), 8.18 (d, *J* = 5.1Hz, 1H), 11.00 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.8, 16.7, 59.9, 108.9, 109.9, 110.0, 112.7, 134.8, 139.1, 144.2, 150.3, 165.0, 178.7.

**4. Ethyl-1,4-dihydro-8-methyl-4-oxo-5-(phenylamino)quinolone-3-carboxylate (3a)**




Light Yellow solid, Melting point: 262-264°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.31 (s, 3H), 4.20 (q, *J* = 7.2Hz, 2H), 6.96-6.98 (m, 2H), 7.25-7.34 (m, 5H), 8.30 (s, 1H), 11.45 (s, 1H), 11. 80 (s, 1H) , $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.8, 17.0, 60.2, 106.2, 110.5, 113.6, 113.6, 121.2, 123.0, 129.9, 134.9, 139.6, 141.3, 144.4, 145.7, 164.8, 179.0. HRMS (ESI$^{+}$): $[M+H]^{+}$, found 323.1388. $C_{19}H_{18}N_2O_3$ requires 322.3578.

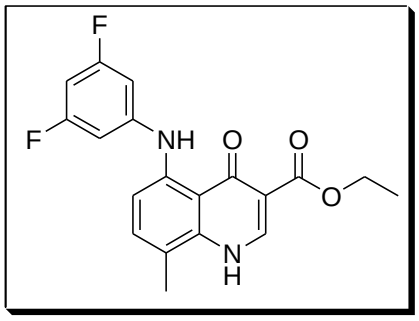
**5. Ethyl-5-(2-bromophenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3b)**




Light Yellow solid, melting point:235-237°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2Hz, 3H), 2.34 (s, 3H), 4.22 (q, *J* = 7.2Hz, 2H), 6.87 (d, *J* = 8.4Hz, 1H), 7.00 ( t, *J* = 6.1 Hz, 1H), 7.29-7.34 (m, 2H), 7.57-7.60 (m, 1H), 7.69 (dd, *J* = 7.8Hz, 1.2Hz, 1H), 8.32 (s, 1H), 11.50 (s, 1H), 11.90 (s, 1H), $^{13}$C NMR (75

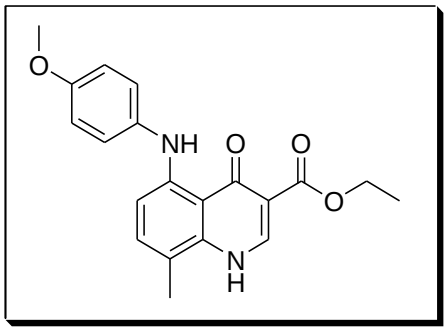
MHz, DMSO-$d_6$) δ 14.8, 17.0, 60.2, 107.0, 110.6, 114.1, 114.9, 116.7, 121.9, 124.6 , 128.8, 133.8, 134.7, 139.6, 139.8, 144.4, 144.7.

**6. Ethyl-5-(3,5-difluorophenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3c)**



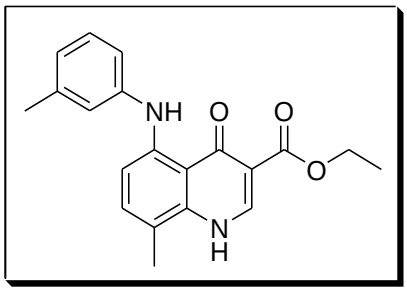

Light Yellow solid, melting point:240-242°C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2Hz, 3H), 2.36 (s, 3H), 4.21 (q, *J* =7.2Hz, 2H), 6.75 (s, 1H), 6.96 (d, *J* = 7.8Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 11.50 (s, 1H), 12.10 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 11.3, 13.6, 56.8, 93.5, 98.5, 98.9, 105.1, 107.4, 111.0, 112.8, 131.4, 136.1, 140.0, 141.0, 141.3, 158.5, 158.7, 161.3, 162.0, 175.4. HRMS (ESI$^+$): $[M+H]^+$, found 359.1206. $C_{19}H_{17}F_2N_2O_3$ requires 359.1202.

**7. Ethyl-5-(4-methoxyphenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3d)**



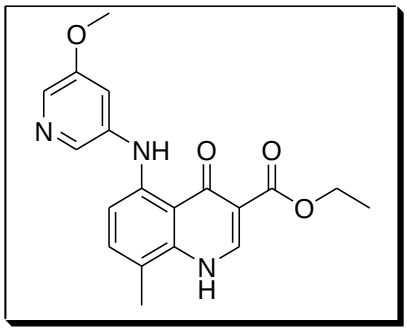

Yellow solid, melting point:260-262°C,$^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.29 (s, 3H), 3.40 (s, 3H), 4.21 (q, *J* = 7.2Hz, 2H), 6.68 (d, *J* = 7.8Hz, 1H), 6.95 (d, *J* = 8.8Hz, 2H), 7.21 (t, *J* = 9.0Hz, 3H), 8.28 (s, 1H), 11.37 (s, 1H), 11.58 (s, 1H) , $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.8, 16.9, 55.7, 60.1, 105.1, 110.4, 112.2, 113.0, 115.2, 124.7, 133.9, 135.0, 139.5, 144.3, 147.54, 156.1, 164.8, 179.0.

**8. Ethyl-5-(m- tolylphenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3e)**



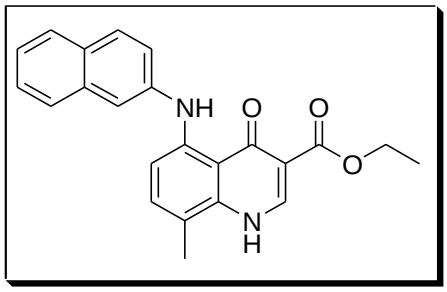

Yellow solid, melting point: 252-254°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2Hz, 3H), 2.30 (s, 3H), 2.33 (s, 3H), 4.22 (q, *J* = 7.2Hz, 2H), 6.85 ( d, *J* = 7.2Hz, 1H), 6.98 (d, *J* = 8.3Hz, 1H), 7.08 (s, 2H), 7.20-7.23 (m, 1H), 7.30 (d, *J* = 8.5Hz, 1H), 8.31 (s, 1H), 11.45 (s, 1H), 11.85 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ11.3, 13.5, 18.0, 56.7, 102.9, 107.2, 110.1, 110.2, 114.8, 118.4, 120.4, 126.2, 131.4, 135.8, 136.3, 137.9, 140.9, 142.5, 161.4, 175.5.

**9. Ethyl-5-(5-methoxypyridin-3-ylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3f)**



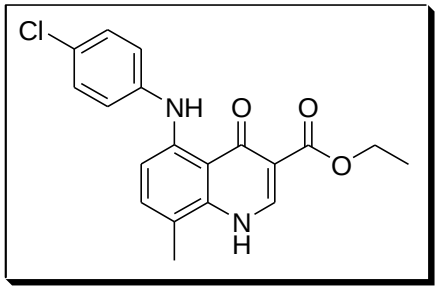

Yellow solid, melting point:235-237°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.27 (t, *J* = 7.2Hz, 3H), 2.30 (s, 3H), 3.85 (s, 3H), 4.21 (q, *J* = 7.2Hz, 2H), 6.58 ( d, J = 8.4 Hz, 1H), 6.85 (d, *J* = 8.7Hz, 1H), 7.23 (d, *J* = 8.4Hz, 1H), 7.66 (dd, *J* = 8.7Hz, 2.7Hz, 1H), 8.08 (d, *J* = 2.6Hz, 1H), 8.30 (s, 1H), 11.45 (s, 1H), 11.55 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 11.3, 13.4, 50.2, 56.7, 101.7, 107.0, 107.9, 109.6, 109.8, 128.3, 131.6, 132.3, 136.1, 138.5, 141.0, 143.9, 157.2, 161.4, 175.5.

**10. Ethyl-1,4-dihydro-8-methyl-5-(naphthalene-3-ylamino) 4-oxo-quinolone-3-carboxylate (3g)**



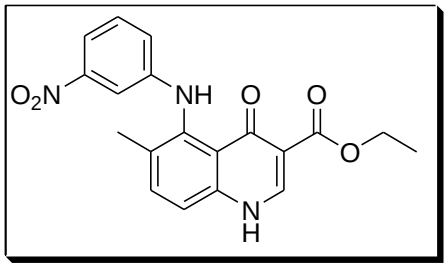

Yellow solid, melting point:>260°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2Hz, 3H), 2.33 (s, 3H), 4.22 (q, *J* = 7.2Hz, 2H), 7.16 (d, *J* = 8.4Hz, 1H), 7.33-7.45 (m, 4H), 7.75-7.89 (m, 4H), 8.33 (s, 1H), 11.50 (s, 1H), 12.13 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.7, 17.0, 60.2, 106.8, 110.6, 113.8, 114.2, 115.2, 122.4, 124.6, 126.9, 127.2, 127.9, 129.5, 129.9, 134.5, 135.0, 139.1, 139.6, 144.4, 145.3, 164.8, 179.0.

**11. Ethyl-5-(4-chlorophenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3h)**




Yellow solid, melting point: 246-248°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.27 (t, *J* = 7.2Hz, 3H), 2.33 (s, 3H), 4.20 (q, *J* = 7.2Hz, 2H), 6.98 (d, *J* = 8.4Hz, 1H), 7.27-7.38 (m, 5H), 8.31 (s, 1H), 11.50 (s, 1H), 11.94 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.7, 17.0, 60.2, 106.6, 110.6, 113.8, 114.4, 122.4, 126.1, 129.7, 134.9, 139.7, 140.5, 144.5, 145.1, 164.8, 178.9.

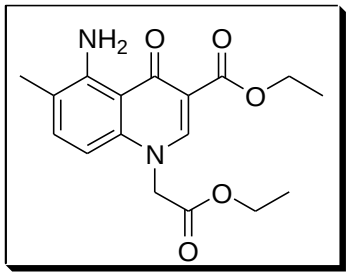
**12. Ethyl-5-(3-nitrophenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3h)**




Yellow solid, melting point:238-240°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2Hz, 3H), 2.36 (s, 3H), 4.32 (q, *J* = 7.2Hz, 2H), 7.13 (d, *J* = 8.4Hz, 1H), 7.38 (d, *J* = 8.1Hz, 1H), 7.58 (d, *J* = 8.1Hz, 1H), 7.67 (d, *J* =

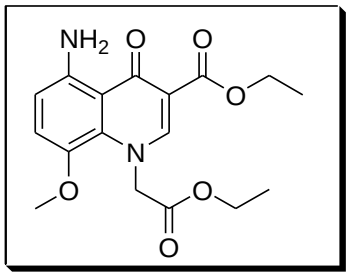
7.8Hz, 1H), 7.78 (d, *J* = 7.8Hz, 1H), 8.04 (s, 1H), 8.33 (s, 1H), 12.20 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.7, 17.1, 60.2, 107.7, 110.7, 113.1, 114.4, 116.1, 116.5, 126.2, 131.2, 134.7, 139.7, 143.2, 143.8, 144.5, 149.1, 164.7, 178.8. HRMS (ESI$^+$): $[M+H]^+$ , found 368.1243. $C_{19}H_{18}N_3O_5$ requires 368.1241.

**13. Ethyl-1-((ethoxycarbonyl)methyl-5-amino-1,4-dihydro-6-methyl-4-oxo-quinoline-3-carboxylate (5a)**



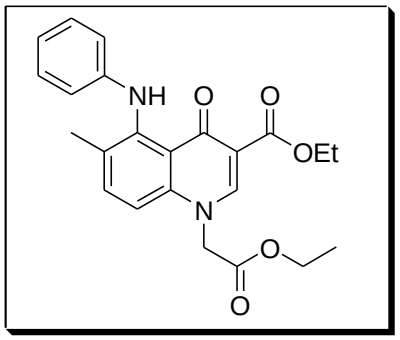

Brownish white, melting point:200-202°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2Hz, 2H), 2.08 (s, 3H), 4.16 (q, *J* = 7.2Hz, 2H), 4.21 (q, *J* = 7.2Hz, 2H), 6.30 (d, *J* = 8.4Hz, 1H), 7.24 (d, *J* = 8.4Hz, 1H), 8.50 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.5, 14.8, 17.4, 100.4, 110.4, 111.8, 117.0, 134.7, 140.2, 149.5, 150.3, 164.8, 168.4, 168.5, 178.4.

**14. Ethyl-1-((ethoxycarbonyl)methyl-5-amino-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylate (5b)**



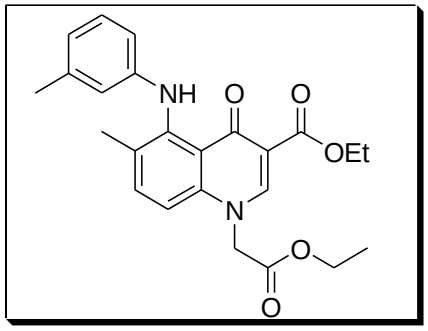

Yellow solid, melting point:182-184°C, $^1$H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2Hz, 3H), 1.40 (t, *J* = 7.2Hz, 3H), 3.78 (s, 3H), 4.29 (q, *J* = 7.2Hz, 2H), 4.39 (q, *J* = 7.2Hz, 2H), 4.99 (s, 2H), 6.85 (d, *J* = 8.7Hz, 1H), 7.10 (d, *J* = 9.0Hz, 1H), 8.20 (s,1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.3, 56.6, 60.2, 61.1, 61.9, 112.0, 112. 6, 120.3, 130.5, 143.1, 152.0, 152.3, 164.2, 167.2, 170.5.

**15. Ethyl-1-((ethoxycarbonyl)methyl)-1,4-dihydro-6-methyl-4-oxo-5-(phenylamino)-quinoline-3-carboxylate (6a)**



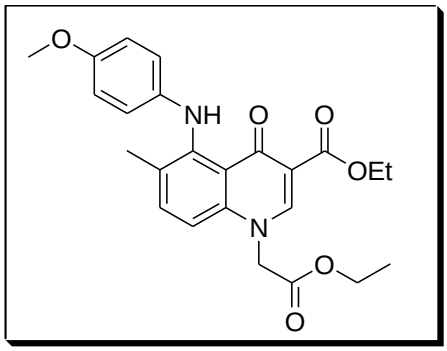

Yellow solid, melting point: 172-174°C, $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.28(t, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.98 (s, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.80 (s, 2H), 6.63 (d, *J* = 8.7 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.90-6.94 (m , 1H), 7.19 (t, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 8.31 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.5, 20.2, 55.2, 60.8, 62.6, 106.2, 111.3, 119.8, 121.7, 128.6, 136.5, 139.4, 143.6, 146.6, 148.6, 166.80, 178.7

**16. Ethyl-1-((ethoxycarbonyl)methyl)-5-(*m*-tolylamino)-1,4-dihydro-6-methyl-4-oxoquinoline-3-carboxylate (6b)**



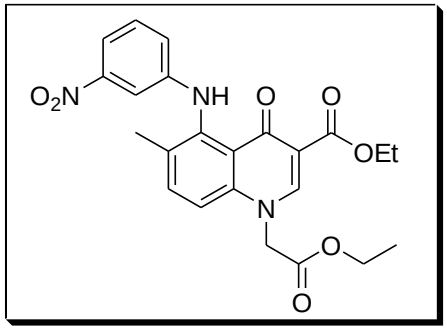

Light Yellow solid, melting point: 158-160°C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.25(t, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 2.04 (s, 3H), 2.26 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.78 (s, 2H), 6.58-6.65 (m, 3H), 6.73 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 8.28 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.5, 20.2, 21.4, 55.2, 60.8, 62.5, 106.0, 111.30, 116.7, 120.5, 122.4, 125.7, 128.3, 136.4, 138.3, 139.4, 143.5, 146.5, 148.7, 166.80.

**17. Ethyl-1-((ethoxycarbonyl)methyl)-5-(4-methoxyphenylamino)-1,4-dihydro-6-methyl-4-oxoquinoline-3-carboxylate (6c)**



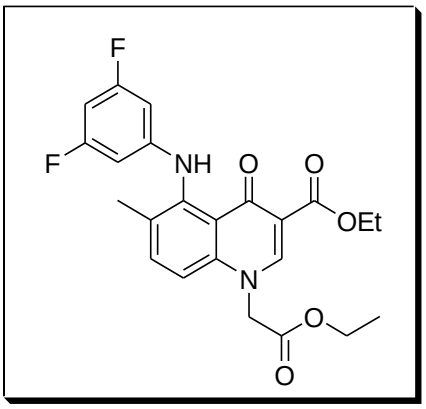

Yellow solid, melting point:184-186°C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.33(t, *J* = 7.2 Hz, 3H), 1.91 (s, 3H), 3.72 (s, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.78 (s, 2H), 6.55 (d, J = 8.4 Hz, 1H), 6.70-6.83 (m, 4H), 7.21 (s, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 8.32 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.5, 14.7, 54.4, 55.6, 60.4, 62.0,107.7, 111.1, 114.6, 117.7, 121.3, 124.2, 136.9, 137.4, 140.0, 146.5, 149.6, 154.8, 164.7, 168.4, 178.3.

**18. Ethyl-1-((ethoxycarbonyl)methyl)-5-(3-nitrophenylamino)-1,4-dihydro-6-methyl-4-oxoquinoline-3-carboxylate (6d)**



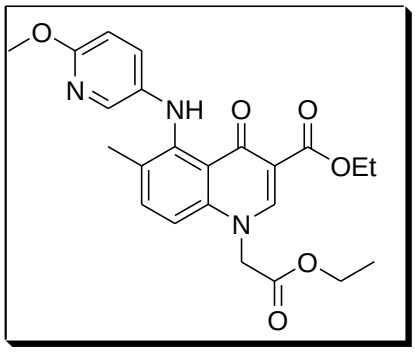

Yellow solid, melting point: 138-140°C, $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 2.04 (s, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.85 (s, 2H), 6.81 (d, *J* = 8.7 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.43-7.49 (m, 2H), 7.73 ( dd, *J* = 8.1Hz, 1.2 Hz, 1H), 8.38 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.5, 29.7, 55.3, 61.0, 62.8, 108.0, 111.8, 112.3, 115.7,116.1,125.1, 126.3, 129.3, 136.7, 139.5, 144.6, 145.0, 148.8, 148.9, 166.5,168.7, 178.5.

**19. Ethyl-1-((ethoxycarbonyl)methyl)-5-(3,5-difluorophenylamino)-1,4-dihydro-6-methyl-4-oxoquinoline-3-carboxylate (6e)**



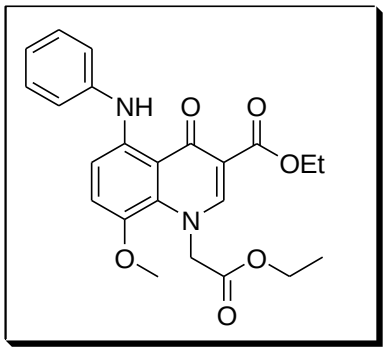

Yellow solid, melting point:162-164°C, $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.29(t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 2.08 (s, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.82 (s, 2H), 6..25-6.28 (m, 3H), 6.79 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 8.35 (s, 1H), 11.50 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.4, 29.7, 55.3, 61.0, 62.7, 95.9, 96.2, 96.6, 101.5, 101.7, 101.8, 107.9, 111.7, 126.8, 136.5, 139.4, 144.8, 146.4, 148.8, 161.8, 162.0, 165.0, 165.2, 166.5,178.5.

**20. Ethyl-1-((ethoxycarbonyl)methyl)-5-(6-pyridin-3-ylamino)-1,4-dihydro-6-methyl-4-oxoquinoline-3-carboxylate (6f)**



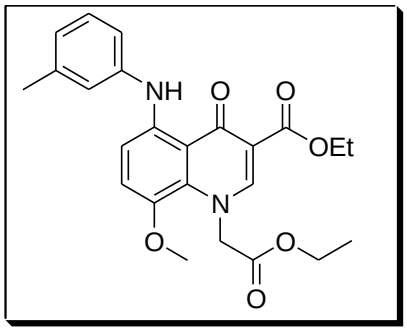

Greenish yellow solid, melting point:175-177°C, $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.21-1.30 (m, 6H), 1.88 (s, 3H), 3.80 (s, 3H), 4.17-4.25 (m, 4H), 5.32 (s, 2H), 6.73 (d, *J* = 8.7Hz, 1H), 6.96 (s, 1H), 7.18 (dd, *J* = 9.0Hz, 2.7Hz, 1H), 7.49 (d, J = 8.7Hz, 1H), 7.72 (d, *J* = 8.7Hz, 1H), 8.68 (s, 1H), 11.46 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.5, 14.8, 17.6, 20.0, 53.5, 60.4, 62.0, 86.2, 110.7, 111.1, 123.9, 131.9, 135.0, 137.1, 138.2, 140.1, 145.9,149.8, 159.4, 164.6, 168.3, 178.3.

**21. Ethyl-1-((ethoxycarbonyl)methyl)-1,4-dihydro-8-methoxy-4-oxo-5-(phenylamino)- quinoline-3-carboxylate (6g)**



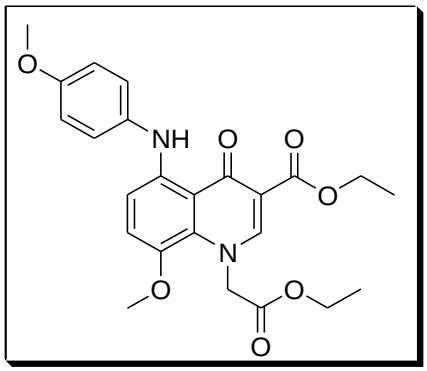

Yellow solid, melting point:162-164°C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 3.72 (s, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.95 (s, 2H), 6.98-7.11 (m, 3H), 7.23-7.32 (m, 4H), 8.14 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.5, 57.3, 60.3, 60.8, 61.7, 108.5, 111.9, 115.6, 118.7, 122.0, 123.0, 129.2, 131.9, 139.5, 141.5, 151.6, 164.7, 167.5, 178.7.

**22. Ethyl-1-((ethoxycarbonyl)methyl)-5-(*m*-tolylamino)-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylate (6h)**



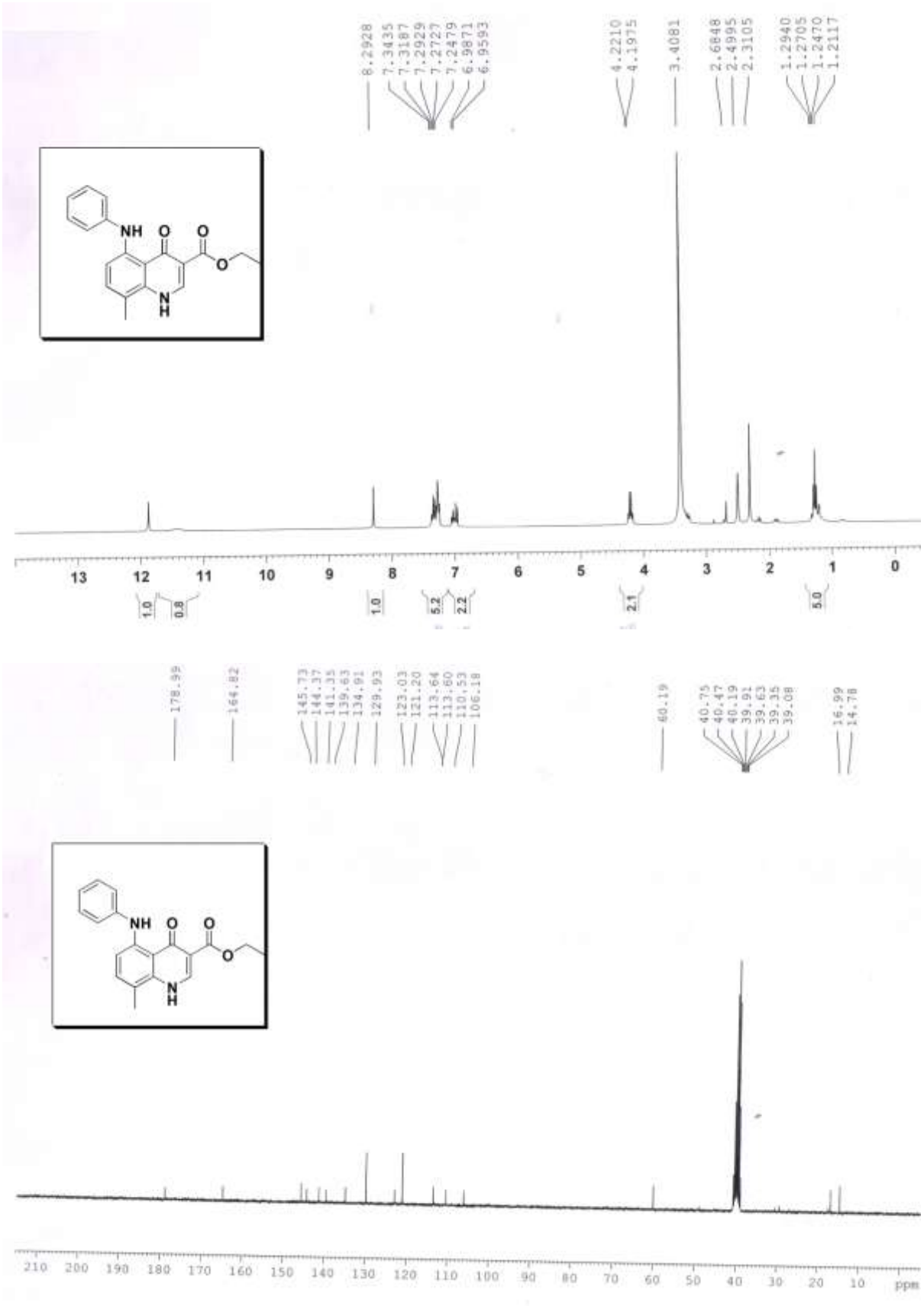

Yellow solid, melting point: 155-157°C; $^{1}$H NMR ($CDCl_3$, 300 MHz,) δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 2.32 (s, 3H), 3.74 (s, 3H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.96 (s, 2H), 6.86 (d, *J* = 7.2 Hz, 1H), 7.00-7.18 (m, 5H), 8.15 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.5, 21.4, 57.4, 60.2, 60.8, 60.9, 61.7, 108.9, 111.0, 115.7, 118.8, 118.8, 119.2, 123.0, 124.0, 129.0, 132.0, 139.1, 139.5, 141.3, 143.3, 143.4, 151.6, 167.4, 178.6.

**23. Ethyl-1-((ethoxycarbonyl)methyl-5-(4-methoxyphenylamino)-)-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylate (6i)**

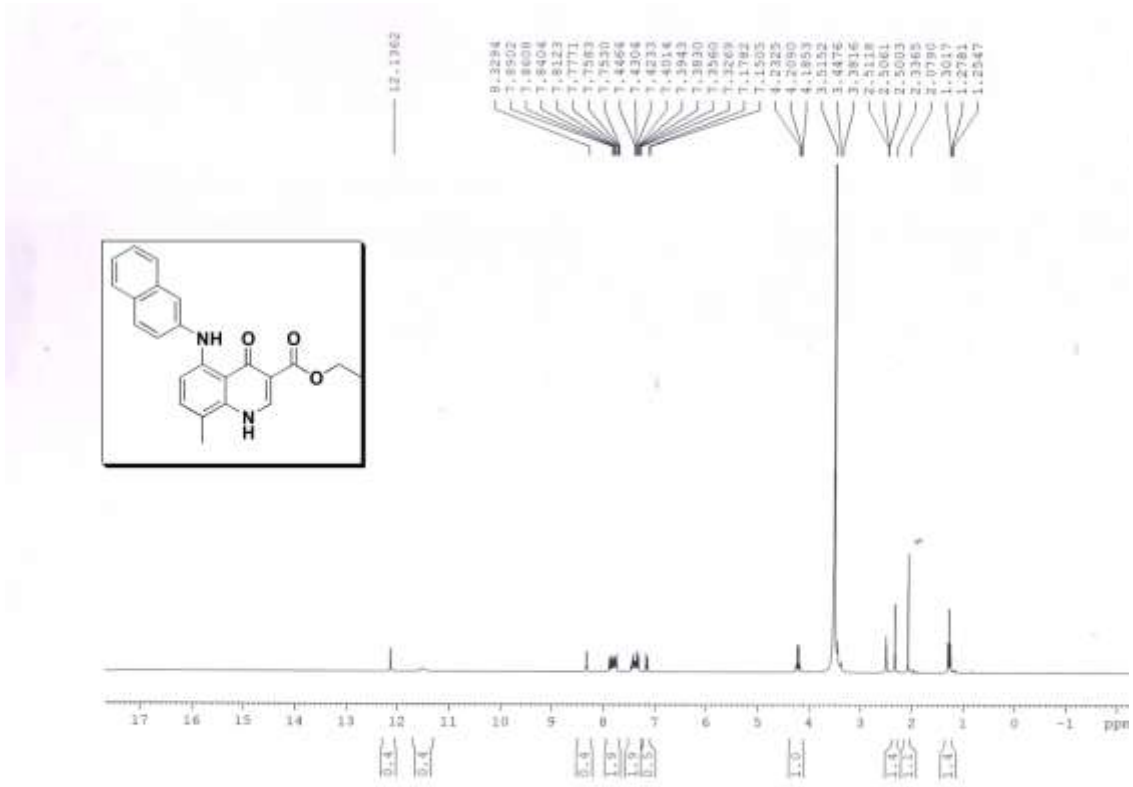


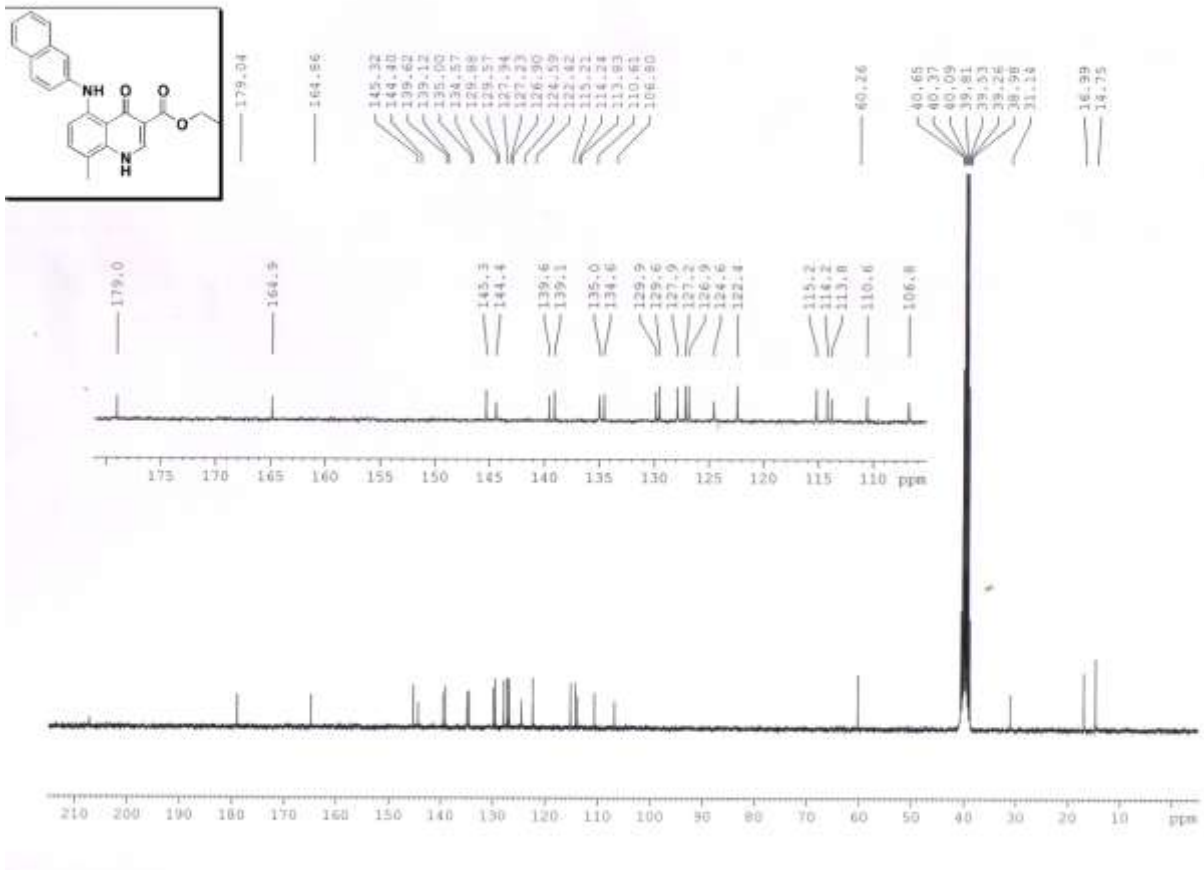

Yellow solid, melting point:170-172°C,$^{1}$H NMR ($CDCl_3$,300 MHz) δ 1.25 (t, *J* = 7.2Hz, 3H), 1.36 (t, *J* = 7.2Hz, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 4.28 (q, *J* = 7.2Hz, 2H), 4.37 (q, *J* = 7.2Hz, 2H), 4.94 (s, 2H), 6.82-6.88 (m, 3H), 6.97 (d, *J* = 9.3Hz, 1H), 7.16 (d, *J* = 8.7Hz, 2H), 8.12 (s, 1H), 11.50 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.5, 55.5, 57.5, 60.2, 60.8, 61.7, 107.3, 110.8, 114.6, 114.8, 119.4, 125.4, 131.9, 134.2, 138.5, 145.4, 151.6, 156.3, 164.9, 167.5, 178.8.

**$^{1}$H and $^{13}$C NMR spectra of entry 3a (Scheme-VIII.2.) in DMSO-$d_6$**

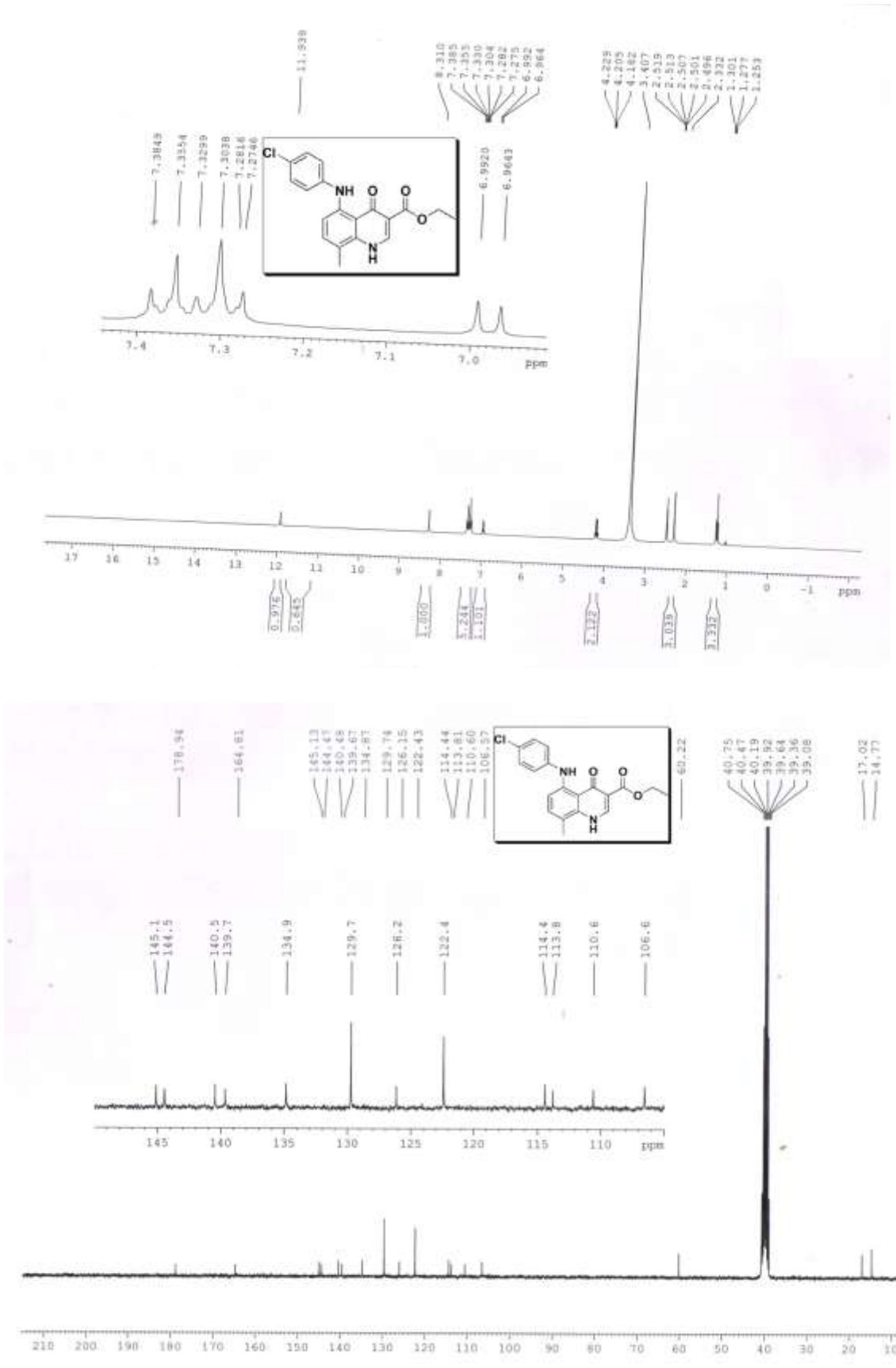


**$^{1}$H and $^{13}$C NMR spectra of entry 3g (Scheme-VIII.2.) in DMSO-$d_6$**

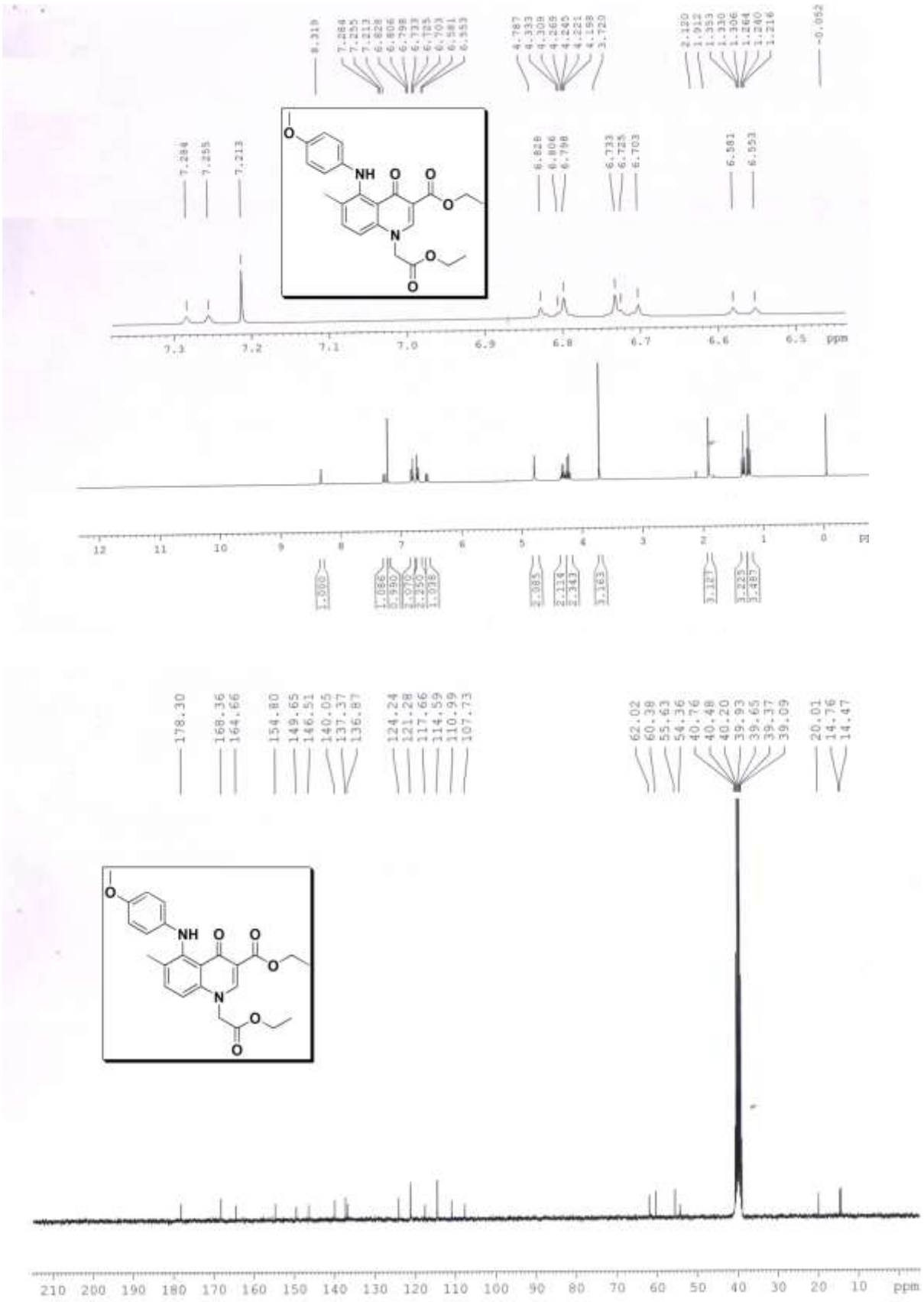




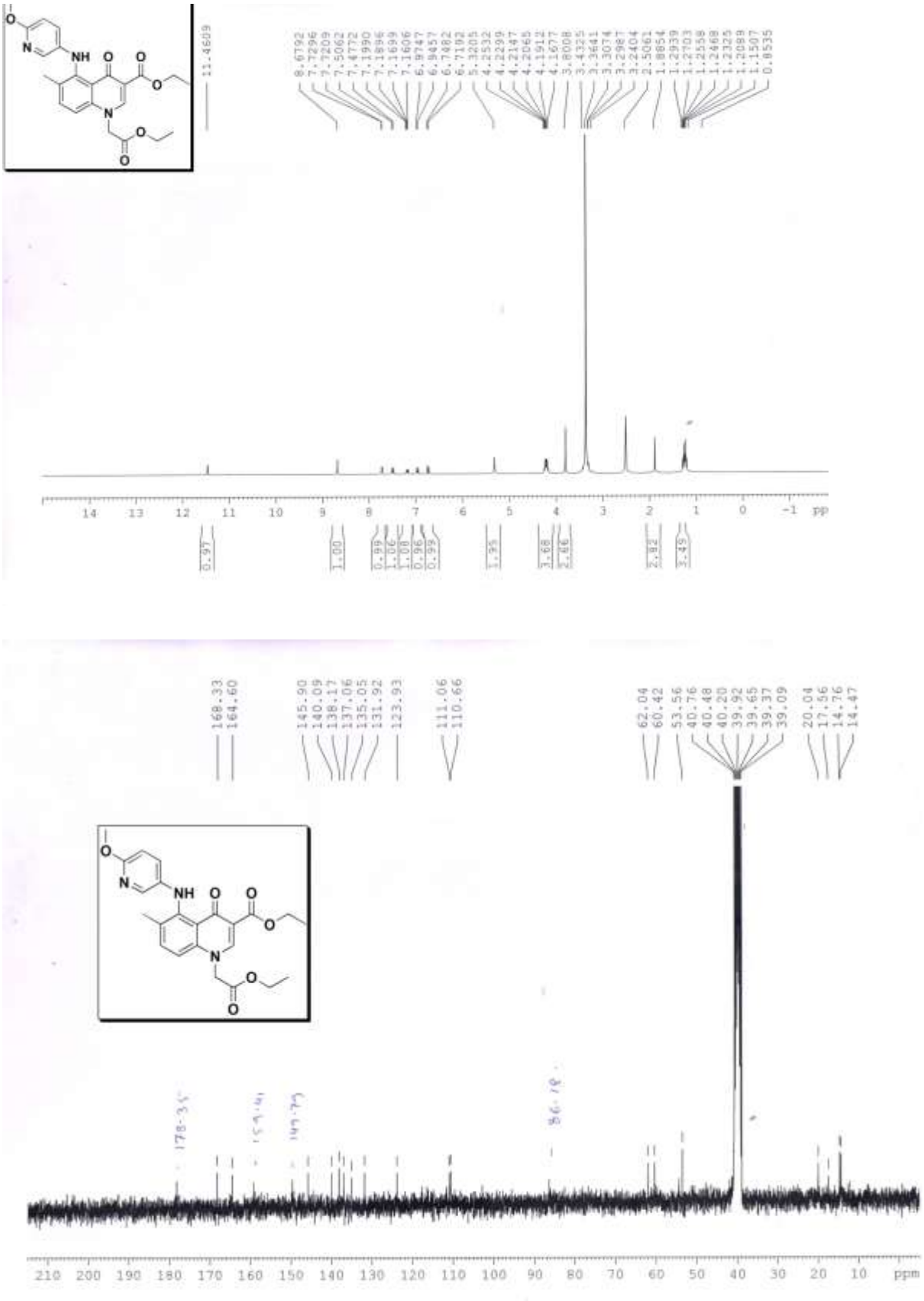
**$^{1}$H and $^{13}$C NMR spectra of entry 3h (Scheme-VIII.2.) in DMSO-$d_6$**



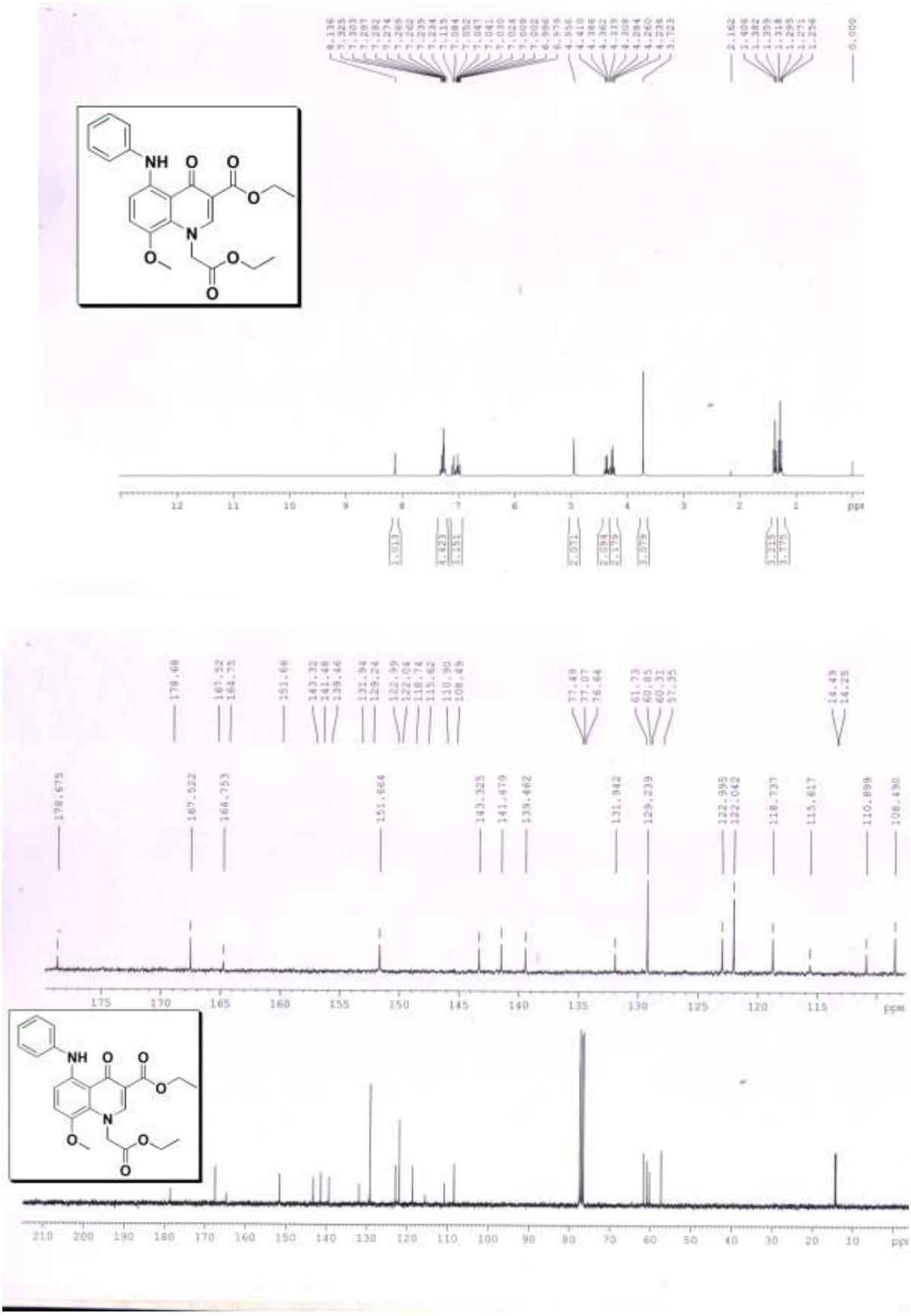
**$^{1}$H and $^{13}$C NMR spectra of entry 6c (Scheme-VIII.4.) in DMSO-$d_6$**



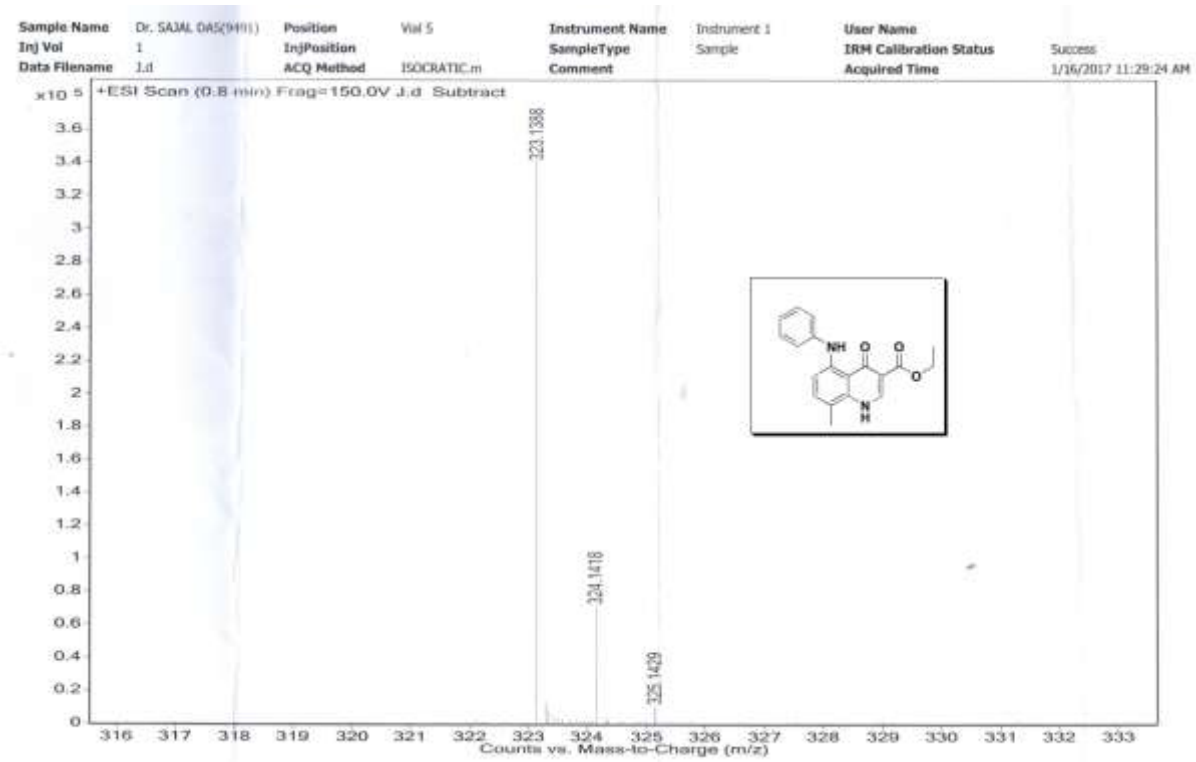
**$^{1}$H and $^{13}$C NMR spectra of entry 6f (Scheme-VIII.4.) in DMSO-$d_6$**



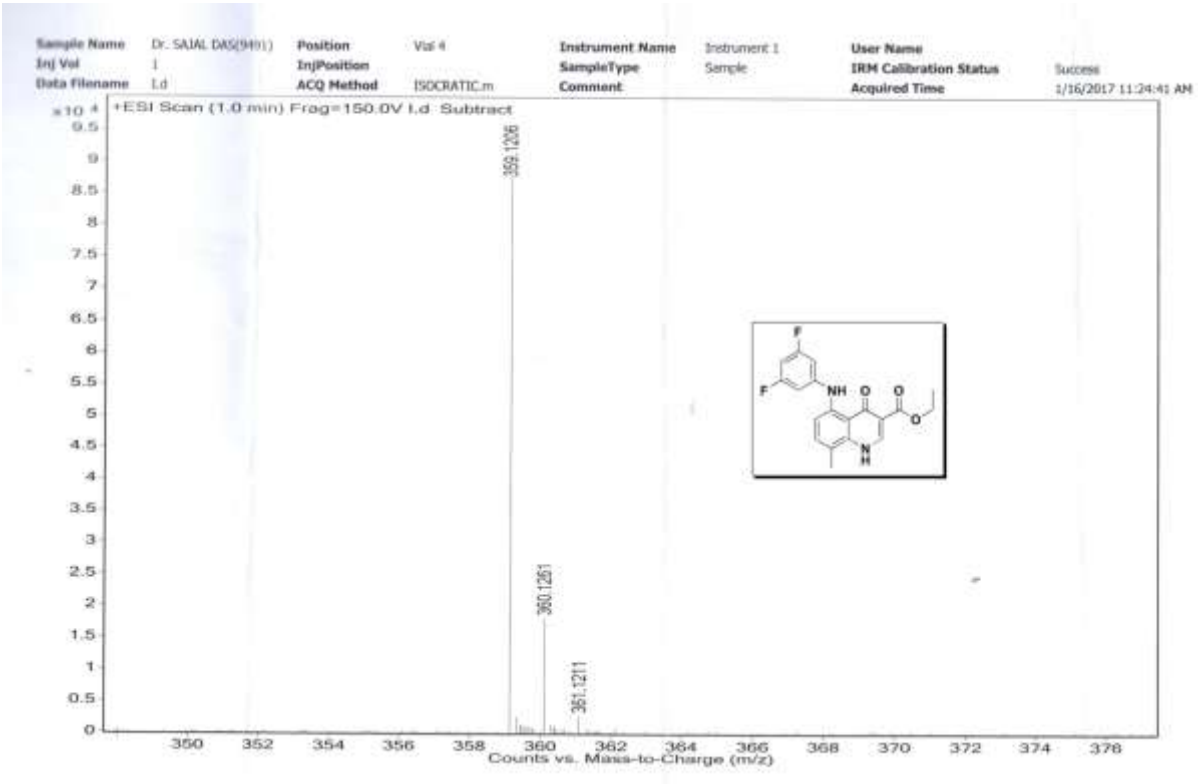
**$^{1}$H and $^{13}$C NMR spectra of entry 6g (Scheme-VIII.4.) in DMSO-$d_6$**



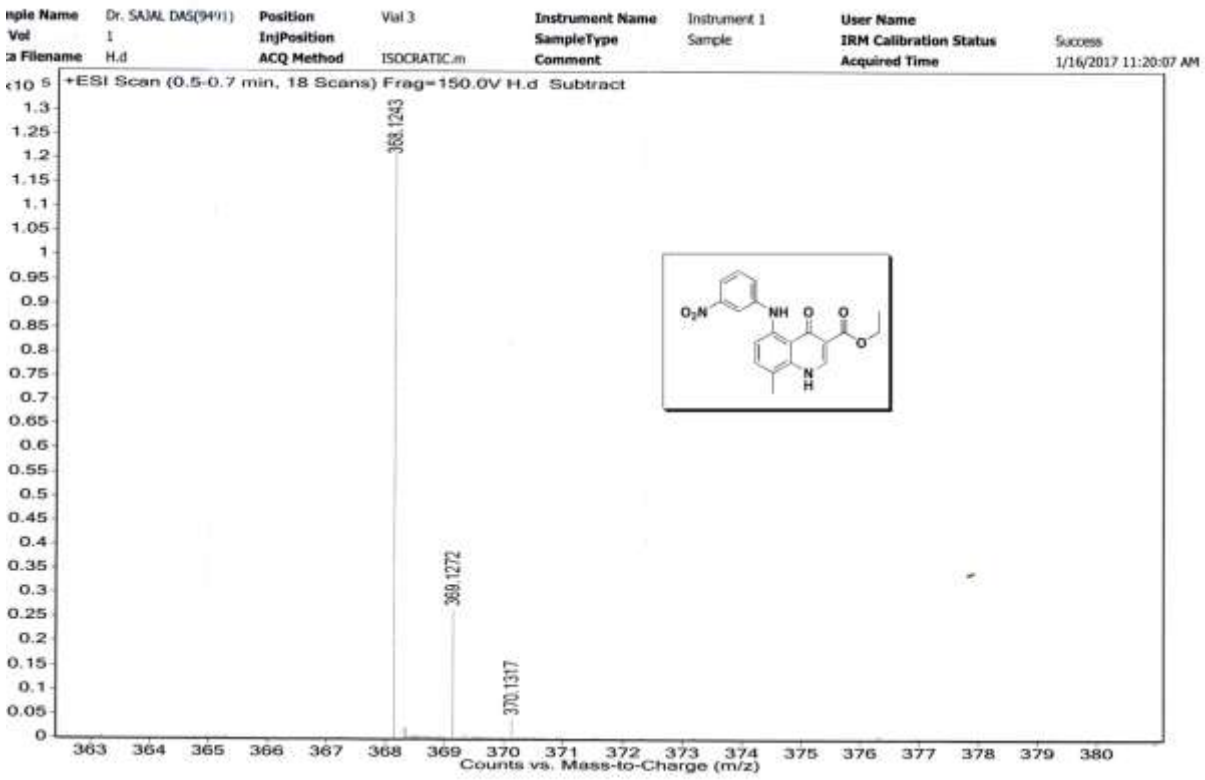
**Scan copy of HRMS of entry-3a (Scheme-VIII.2.)**




**Scan copy of HRMS of entry-3c (Scheme-VIII.2.)**



**Scan copy of HRMS of entry-3i (Scheme-VIII.2.)**




## VIII.E. References

References of chapter VIII are given in the Bibliography (pp-237-239)

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**CHAPTER-I (I.E)**

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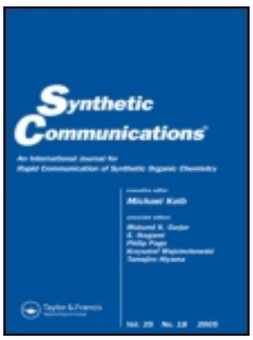

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# Regiocontrolled Nitration of 4-Quinolones at Ambient Conditions

Sonali Sarkar, Prasanjit Ghosh, Anirban Misra & Sajal Das

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# REGIOCONTROLLED NITRATION OF 4-QUINOLONES AT AMBIENT CONDITIONS

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## GRAPHICAL ABSTRACT


**Abstract** *Regiocontrolled nitration of 4-quinolone, the highly privileged scaffold, has been developed at ambient conditions. The nitro group can selectively be introduced at diverse positions simply by tuning the reactivity of the moiety. Discrimination is being achieved through the selective functionalization of the free N-H group. The functional group has been screened theoretically with the help of Fukui function and local softness calculation. Theoretical predictions are synchronized well with the experimental findings. Finally, this nitration technique allows quick access to the structurally diverse 4-quinolones.*

**Keywords** Ambient conditions; Fukui function; local softness; 4-quinolones; regiocontrolled nitration

## INTRODUCTION

Nitration has been extensively studied since its discovery in 1834.[1] Nitro compounds are significantly beneficial synthetic intermediates and have potential application in various fields, especially in the chemical industry and pharmaceuticals.[2] A variety of aromatic nitro compounds are used for the treatment of insomnia, angina, Parkinson, and trypanosomatid diseases.[2b] Various methodologies have been employed to synthesize the aromatic nitro compounds. Nitration using mixed acids is most widely used technique and results in a mixture of products. Afterward, many regioselective nitration techniques such as *ipso*-nitration/oxidation of amine[3]

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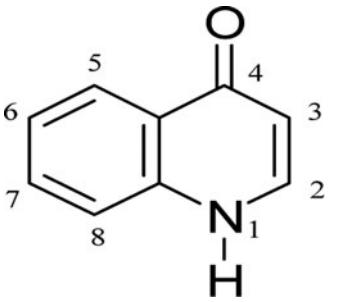



**Figure 1.** Basic 4-quinolone scaffold.

or azide,[4] functional group directed nitration,[5] etc., have been developed to overcome those shortcomings. However, these modern and sophisticated techniques are not always helpful for designing target molecules.

In the arena of 4-quinolones, multisubstituted 4-quinolones are prominent in bioactive molecules and their selective functionalization remains a challenge. Our main effort was directed toward the regioselective functionalization of 4-quinolones.[6] Slight variation in the substituent nature or position (Fig. 1) greatly varies the potency of the quinolone-based drugs.[7]

Nitro-quinolone derivatives have been reported to possess antifilarial, antiviral, antiallergic, antitumor, and antibacterial capabilities.[8] So far, very limited and mostly 6-nitro derivatives of 4-quinolones have been synthesized and their medicinal values evaluated.[8,9] This might be due to the problems associated with common synthetic methodologies, as these include the cyclization of nitro-substituted anilines to form the desired nitro-quinolone.[8,9] It is difficult to use the literature method if one aims to get 5- or 7-nitro 4-quinolone because the starting unsymmetrical nitro anilines upon cyclization always result in the formation of mixture products (isomers), in turn leading to cumbersome separation process as well as poor yield. No such direct technique for the selective nitration of 4-quinolone has been reported in the literature. Selectivity in the nitration reaction is governed by various factors such as steric effects, nature of solvent, and interaction between substrate with reagents and electronic effects.[10] Under the identical reaction conditions, regioselectivity is governed by the electronic effects of the substrate.

Herein for the first time, we report a complete regiocontrolled nitration of 4-quinolones at ambient conditions. Selectivity can easily be tuned by the selective functionalization of free N-H group of 4-quinolone. The profound impacts of the free N-H and other substituents in the nitration process of 4-quinolones have been screened with the help of density functional theory (DFT) calculation using a synchronized study based on theoretical prediction and experimental observations.

## RESULTS AND DISCUSSION

Our study began with the nitration of 4-quinolone 3-carboxylate using mixed acids at ambient conditions. The unsubstituted 4-quinolone 3-carboxylate **1** has been selected as a model compound for this study. There are five positions (C-2, C-5, C-6, C-7, and C-8) available for nitration. Compound **1** on nitration with mixed acids at

ambient conditions results in 78% yield of the corresponding 5-nitro derivative upon isolation (Table 1). Carrying out the reaction in the presence of both dilute and concentrated nitric acid did not provide any good result (Table 1). During the modification of reaction conditions, keeping the presence of the acid-sensitive group in mind, we focused on developing the nitration reaction in neutral conditions. Various sets of well-known nitrating reagents were used and corresponding results are summarized in Table 1. It is clear from the table that the combination of nitronium tetrafluoroborate [NTFB] and acetonitrile (Table 1, entry 6) is best suited in the present study, which results in 90% yield of the desired product within 5 min at ambient conditions. Nitration using NTFB generally proceeds via Eq. (1).[11]

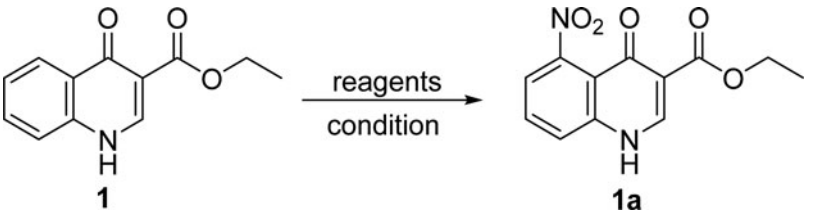
$$\mathrm{ArH} + \mathrm{NO_2^+BF_4^-} \longrightarrow \mathrm{ArNO_2} + \mathrm{HF} + \mathrm{BF_3} \tag{1}$$

With the optimized conditions in our hand, the scope of selective nitration was investigated (Scheme 1). Different substituted 4-quinolones **2** and **3** smoothly underwent selective nitration to furnish the desired 5-nitro product in excellent yield. The results clearly showed that the presence of an electron-donating group (-$CH_3$) and electron-withdrawing group (-F) has no significant role in defining the position of incoming electrophile (nitronium group).

The problem begins while attempting the nitration of compound **4**, which has a methoxy group present at the C-8 position. Compound **4** on nitration under the optimized conditions always results in the corresponding 5,7-dinitro derivatives (Scheme 2). This is probably due to the +R effect of methoxy group, which facilitated the second nitration in its *ortho*-position.

This observation made us develop a regioselective nitration technique. To control the nitration reaction we thought to tune the reactivity of compound **4**. Accordingly, an additional functional group has been introduced (functionalization of free N-H) into the moiety so that it could trim down the reactivity of the parent

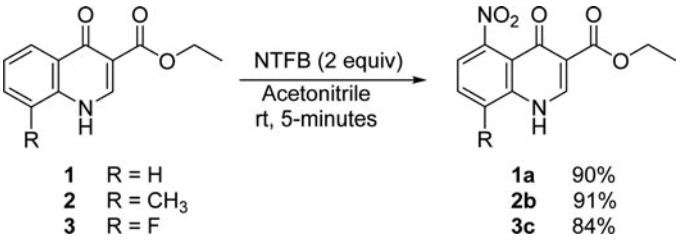
**Table 1.** Optimization of the reaction conditions




**1** **1a**

| No. | Reagent(s)–Solvent | Time | Temperature | Yield (%)[a] |
|---|---|---|---|---|
| 1 | Mixed acids | 1 h | 0 °C rt | 78 |
| 2 | $HNO_3$ (dil.) | 2 h | rt | 30 |
| 3 | $HNO_3$ (conc.) | 2 h | rt | 52 |
| 4 | $Cu(NO_3)_2$, p-TSA –DCM | 12 h | rt | No reaction |
| 5 | $Fe(NO_3)_3$, $Ac_2O$-DCM | 12 h | rt | No reaction |
| 6 | NTFB | 5 min | rt | 90 |

[a]Isolated yield after column chromatography purification.

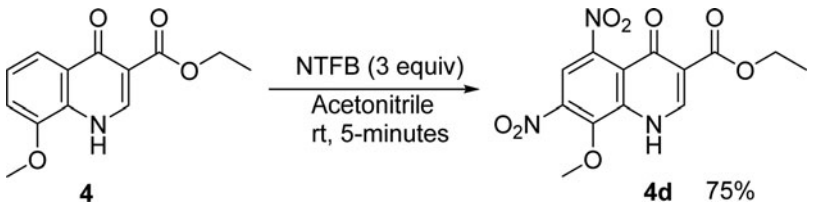



**Scheme 1.** Substrate scope of selective nitration of 4-quinolones.

compound **4** and thereby restrict the second nitration. Selection of the functional group has been done with the help of B3LYP density functional theory (DFT) calculation using the Gaussian 03 W quantum chemical package.[12] Among the different density functionals, the hybrid functional B3LYP is by far the most popular in chemistry.[13] It is well documented that the B3LYP functional along with 6-31G(D) or 6-31G(D, P) basis function can be used in studying various organic reactions.[14] Here we have chosen the 6-31G(D,P) basis function for our computation. Regioselectivity as well as reactivity of any molecule can be ascertained through evaluation of Fukui function[15] and local softness.[16] The Fukui function ($f_k^i$), instigated in density functional theory (DFT) by Parr and Yang,[15,16a] is the most important local reactivity index. For electrophilic attack it is defined as $f_k^- = [\rho_k(N) - \rho_k(N-1)]$, where $\rho(N)$ and $\rho(N-1)$ are the electron densities of the N and $(N-1)$ electron systems respectively. Local softness ($sk^-$) is another parameter in analyzing the regioselectivity, which is related to Fukui function as $s_k^i = f_k^i$. S with $i = +$ or $-$, where S is the global softness given as $S = 1/2\eta$, where $\eta$ is the global hardness.

The detail results of the nucleophilic Fukui function ($f_k^-$) and local softness ($s_k^-$) calculation are shown in Tables 2 and S-I (see supporting information). It is clear from theoretical analysis that either an alkylester or -$CH_2$Ph group can be chosen for the functionalization of free N-H to restrict the second nitration. Herein, we have selected the alkylester group as the resulting moiety **5** can serve as an amino acid precursor. Nitration of compound **5** under the optimized condition selectively results in the corresponding 5-nitroderivative in excellent yield upon isolation (Scheme 3).

Now the remaining major challenge is the introduction of nitro group selectively at the 7-position of the same moiety (compound **4**). After screening several protecting groups with the help of conceptual DFT, we found –$SO_2CF_3$ may be chosen in this case (Table 2). As for –$SO_2CF_3$ N-protecting group C7 is susceptible for electrophilic attack, having greater reactivity indices ($f_k^- = 0.027, s_k^- = 0.158$) than the other




**Scheme 2.** Dinitration of 8-methoxy-4-quinolone.

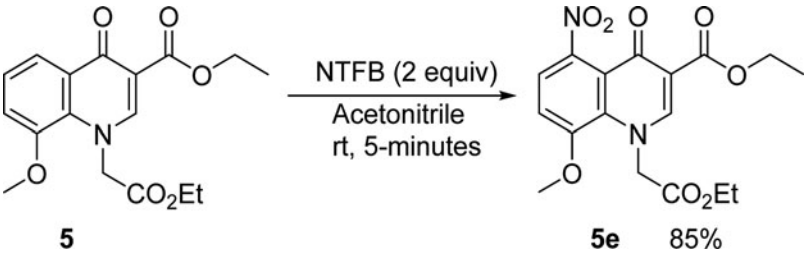
**Table 2.** Fukui function ($fk^-$) and local softness ($sk^-$) calculation at B3LYP/6-31G(d,p)

| | Fukui functions | | | | Local softness | | | | Theoretically preferred reaction center | Experimentally preferred reaction center |
|---|---|---|---|---|---|---|---|---|---|---|
| Compound | C-5 | C-6 | C-7 | C-8 | C-5 | C-6 | C-7 | C-8 | | |
| 1 | 0.043 | 0.030 | 0.015 | — | 0.248 | 0.173 | 0.085 | — | C-5 | C-5 |
| 2 | 0.038 | 0.027 | 0.020 | — | 0.220 | 0.156 | 0.113 | — | C-5 | C-5 |
| 3 | 0.042 | 0.027 | 0.020 | — | 0.238 | 0.150 | 0.111 | — | C-5 | C-5 |
| 4 | 0.037 | 0.025 | 0.027 | — | 0.217 | 0.145 | 0.156 | — | C-5 | C-5 and C-7 |
| 5 | 0.033 | 0.027 | 0.019 | — | 0.193 | 0.160 | 0.113 | — | C-5 | C-5 |
| 6 | 0.020 | 0.015 | 0.027 | — | 0.120 | 0.091 | 0.158 | — | C-7 | C-7 |
| 7 | 0.041 | — | 0.018 | 0.042 | 0.238 | — | 0.105 | 0.240 | C-8 | C-8 |
| 8 | 0.038 | — | 0.015 | 0.037 | 0.220 | — | 0.088 | 0.218 | C-5 | C-5 |

probable sites C5 (0.020, 0.120) and C6 (0.015, 0.091). Accordingly, the parent compound **4** on treatment with triflic anhydride in the presence of tetrabutyl ammonium hydrogen sulfate (TBAHS) results in the desired *N*-protected 4-quinolone **6** in good yield. The protected quinolone (**6**) on nitration under the optimized conditions results in the corresponding mono nitro-derivative after in situ deprotection. The 7-nitro derivative of compound **6** has been isolated selectively in moderate yield (Scheme 4).

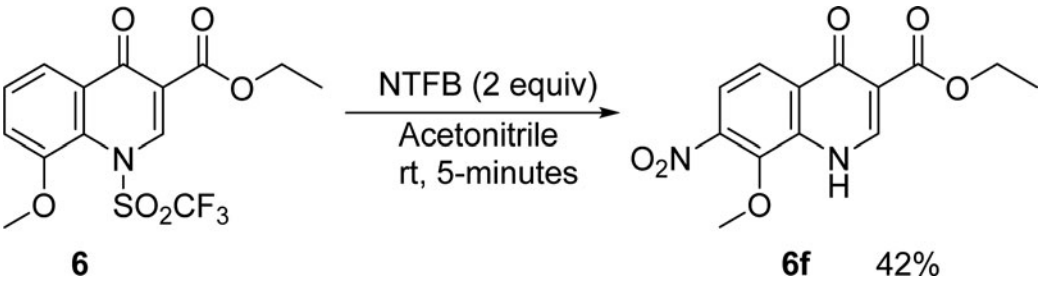
This study showed that the *N-H* group plays a pivotal role in defining the position of the nitro group in the nitration reaction of 4-quinolone moieties. Tuning of the reactivity in the nitration reaction was further justified using another model compound **7** where the methyl group is present in the C-6 position. The DFT calculation of compound **7** showed that the most reactive position for the electrophilic attack is C-8, as it has greater reactivity index ($f_k^- = 0.042, s_k^- = 0.240$) than the other possible sites (C-5 and C-7, Table 2).

Functionalization of free N-H either with alkylester or $-SO_2CF_3$ changes the reactivity and C-5 becomes the most susceptible position for the attack of nitronium ion (Tables 2 and S-I). Among alkylester and $-SO_2CF_3$, the former has greater reactivity indices and accordingly, the free N-H of compound **7** was protected with alkylester (compound **8**) following the previous method (compound **5**). Both the compounds **7** and **8** were subjected to the nitration reaction in our optimized conditions and resulted in the corresponding 8 and 5 nitro derivatives in 80 and 82% yields respectively.

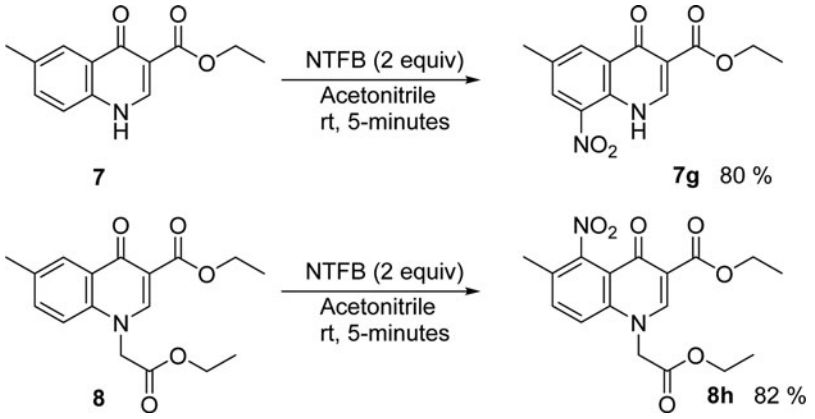



**5** **5e** 85%

**Scheme 3.** Controlled nitration of compound **5**.




**Scheme 4.** Selective nitration of *N*-protected 8-methoxy 4-quinolone at the C-7 position.




**Scheme 5.** Selective nitration of 6-methyl 4-quinolone.

## CONCLUSION

Finally, the newly developed technique allows introducing the nitro group in diverse positions of the 4-quinolone ring with maximum efficiency. This method would be very useful for the target synthesis of new bioactive molecules based on a 4-quinolone system. The study showed that the N-H functional group plays a pivotal role in defining the position of incoming electrophile. Judicial functionalization of free N-H brings the discrimination and allows selective nitration of 4-quinolones. Other part of the development based on this moiety is currently under way.

## EXPERIMENTAL

Unless stated otherwise, all reagents such as *o*-anisidine, *p*-toluidine, aniline, *o*-F-aniline, *o*-toluidine, diethylethoxy methylene malonate (EMME), potassium carbonate, tetrabutylammniumhydrogensulfate (TBAHS), nitronium tetrafluoroborate (NTFB), $(CF_3SO_2)O$ and solvents were used as received from commercial suppliers. NMR spectra were recorded on a 300-MHz spectrometer at 298 K and calibrations were done on the basis of solvent residual peak. Mass spectra were performed using ion trap mode. Products were purified using column chromatography on silica gel

(60–120 mesh) and a mixture of petroleum ether (60–80 °C)/ethyl acetate was used as an eluent. Progress of reaction was monitored by silica-gel thin-layer chromatography (TLC).

### Preparation of Compounds 1–4[6]

A mixture of aniline (10 mmol), EMME (11 mmol), and toluene (30 mL) was refluxed in a 250-ml round-bottom flask for 5 h. It was then cooled and washed with 3 (N) 100 mL $H_2SO_4$. Toluene was distilled off afterward. The mixture was scratched vigorously to get solid anil product. This product (5 g) was refluxed with biphenyl-oxide (50 mL) for 2 h at 280 °C. It was then cooled and stirred for an hour after addition of a small amount (100 mL) of petroleum ether. Compounds **1–4** were obtained by filtration on Buchner funnel.

### General Procedure of Nitration Reaction (Compounds 1a–8h)

A mixture 4-quinolone-3-carboxylate (1 mmol) in 5 ml dry acetonitrile was taken in a 25-ml round-bottom flask. Then, 2 mmol (0.266 g) of NTFB (nitronium tetrafluroborate) was added into it at a time. The reaction mixture was stirred at room temperature for 5 min. The progress of reaction was monitored by TLC, and upon completion the reaction mixture was poured into the ice water and a yellow solid appeared. The yellow solid material was collected and dried completely. The crude material was further purified by the silica-gel column chromatography using ethyl acetate and petroleum ether as an eluent.

### Ethyl 1,4-Dihydro-8-methoxy-5,7-dinitro-4-oxoquinoline-3-carboxylate (4d)

Bright yellow solid, melting point 175–178 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 1.27 (t, $J = 7.2$ Hz, 3H), 4.12 (s, 3H), 4.23 (q, $J = 7.2$ Hz, 2H), 8.37 (s, 1H), 8.49 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 14.66, 60.75, 64.38, 113.25, 114.83, 121.48, 136.79, 142.12, 143.54, 146.13, 146.30, 164.18, 170.26. HRMS (ESI-TOF) $m/z$: $[M + H]^+$, found 338.0522. $C_{13}H_{11}N_3O_8$ requires 338.0624.

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## SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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RSC Advances

PAPER

# Synthesis of 6-aryl substituted 4-quinolones *via* Suzuki cross coupling†

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A convenient way to introduce aryl functionalization in the 6-position of 4-quinolones is developed *via* selective bromination and subsequent arylation by Suzuki cross-coupling. Ethyl 4-quinolone 3-carboxylates were subjected to selective bromination at C-6 followed by arylation under microwave irradiation that yielded the desired cross-coupling products within 5 minutes. This approach can expediently be used for library synthesis of the aryl functionalized 4-quinolone derivative, an important class of biologically active compounds.

## Introduction

4-Quinolones are the most privileged scaffolds found in both natural products and biologically active molecules. They have experienced prolific development after the accidental discovery of the first synthetic antibiotic *i.e.*; nalidixic acid in 1962.[1] Further, SAR (structure activity relationship) studies have facilitated the development of quinolones with better pharmacokinetic properties and good tolerability.[2] These potent quinolone derivatives now serve as active components in diverse families of drugs such as antibacterial,[3] antiviral,[4] antimalarial,[5] anticancer,[6] antitumor[7] and anti-HIV[4a,8] agents. A few important biologically active moieties based on the quinolone scaffold are shown in Fig. 1. In spite of the wide applicability of quinolone based drugs, they are often associated with limitations like poor absorption, side effects *etc.*[9] Hence, efforts are still required to synthesize highly efficient drugs with good oral absorption, selective binding ability and minimal secondary effects.

Many reliable and well established methods are available for the library synthesis of 4-quinolones, but majority of them are allied with the drawback that the substituents required on the quinolone moiety can only be introduced during the synthesis of the main skeleton.[10] This confines the scope of fine tuning of the structure activity relationships. As substituents play a crucial role in deciding drug efficacy, for an effective library synthesis of 4-quinolones, it is desirable to develop new strategies that permit the introduction of substituents at later stage or as per the requirements. So, we endeavored to create a way to undertake sequential functionalization of quinolones. Many research works in the recent past have reported quinolone derivatives bearing diverse C-6 substituents that exhibit highly active therapeutic capabilities.[10f,11,12] This fostered our interest to execute selective functionalization at the C-6 atom of the quinolone skeleton. In this context, herein, we disclose a simple and convenient route for the selective bromination of compound **2** which effectively yields 6-bromo-4-quinolones. These bromoquinolones can then participate in various kinds of organic transformations, and the access of structurally diverse 6-substituted quinolones is prevailed. Here we have studied only the Suzuki coupling reactions for the synthesis of 6-aryl substituted 4-quinolones.

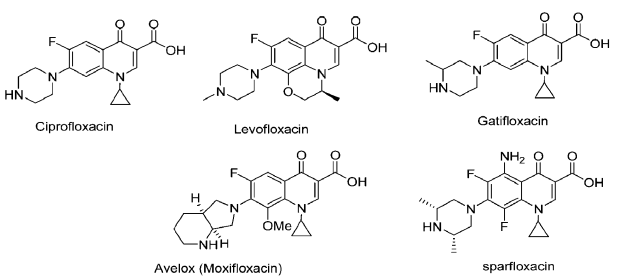
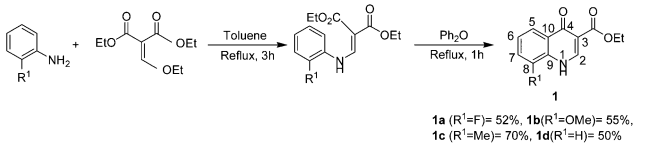



Fig. 1 Structures of several biologically active quinolones.

## Results and discussion

We began by synthesising the starting scaffolds [ethyl-4-quinolone-3-carboxylate] compound **1** *via* the classic Gould–Jacobs approach[10a] (Scheme 1). It is reported that the presence of the substituent at the C-8 position of 4-quinolone enhances the




Scheme 1 General synthesis of 4-quinolones **1**.

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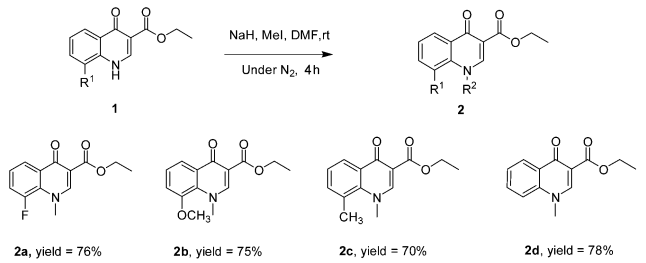
† Electronic supplementary information (ESI) available: Copies of $^{1}H$ and $^{13}C$ NMR of all compounds. See DOI: 10.1039/c3ra45056b

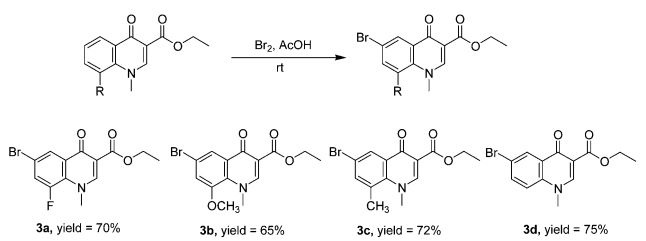



Scheme 2 Synthesis of *N*-methylated derivatives **2** from compound **1**. *Reaction conditions*: compound **1** (1 mmol), NaH (0.036 mg, 1.5 mmol), MeI (0.284 g, 2 mmol) in DMF at 60 °C. Stirring under $N_2$ atmosphere, 4 h. Isolated yields after column chromatography.

antibacterial activity.[9b] Again, the fluoro group at C-8 owes better oral absorption of the drug.[13] So, we considered different substituents at the C-8 position that can be isosteres or analogues and accordingly synthesized compounds (**1a–1c**) as the starting materials (8-substituted-4-quinolones) for this present work.

It is known that the protection of the N–H of compound **1** with alkyl group (preferable smaller alkyl groups like methyl, ethyl and cyclopropyl) is essential to enhance drug potency and efficiency.[14] Therefore we have replaced the N–H of compound **1** with a methyl substituent. Synthetic procedures of *N*-alkylation are well documented in literature.[15] After screening of standard techniques, use of NaH (sodium hydride) as base was found to be best suited in our system. Hence, to carry out *N*-methylation, compound **1** was treated with NaH in dry DMF (*N*,*N*-dimethyl formamide) followed by the addition of methyliodide under inert atmosphere at 60 °C. The desired *N*-methylated product **2** was obtained in good yields (Scheme 2) without formation of the possible side product (*O*-methylated). Presence of electron donating or withdrawing group at C-8 position literally has no significant role in this reaction. Selective bromination followed by the Suzuki coupling was studied next to access the structurally diverse 4-quinolones.

Initially, we attempted the bromination of compound **2** with NBS (*N*-bromosuccinimide) in chloroform at room temperature. Here the rate of the reaction as well as the yield of desired product was not satisfactory. Conducting the reaction at higher temperature (50 °C) which also resulted poor yield (yield < 50%) of the desired compound even after continuing the reaction up to 24 hours. Finally, the treatment of compound **2** with bromine



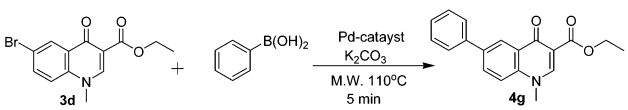

Scheme 3 Synthesis of 6-bromo-4-quinolone derivatives. *Reaction conditions*: **2** (1 mmol), bromine (1.2 equiv., 0.1 mL), AcOH (4 mL), stir rt (8 h). Isolated yields after column chromatography.

in acetic acid medium at room temperature resulted in the corresponding 6-bromo derivatives selectively in satisfactory yields (65–75%, Scheme 3).

Aryl substituted 4-quinolones are known to be effective drugs as *Plasmodium falciparum* Type II NADH,[16] M1 positive allosteric modulators with reduced plasma protein binding,[17] selective agonists of somatostatin receptor subtype 2,[12a] antimitotic and antitumor agents.[7b] Earlier studies include aryl substitution mostly at the 1 and 2 positions of the quinolone moiety. Scientists are now investigating the influence of 6-aryl substitution on the therapeutic applications of quinolones which are yet to be well explored. Recent work by Chen and co-workers reported C-6 aryl substituted 4-quinolone derivatives as inhibitors of the hepatitis C virus (HCV).[12b] 6-Substituted 4-quinolone-3-carboxamides having high selective affinity for the human CB2 (cannabinoid-2) receptor over CB1 are also reported.[12c] Such promising perspectives of 6-arylated-4-quinolones inspired us to synthesize such entities *via* Suzuki cross coupling of compounds **3**. This method offered the opportunity to enrich the library of 6-aryl substituted quinolone scaffolds.

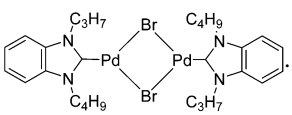
In the search for suitable conditions for the Suzuki coupling reaction, we first examined the coupling of phenylboronic acid with **3d** using different solvents and catalysts (common palladium salts) in the presence of potassium carbonate. The results are shown in Table 1. Notably, the combination of DMF as solvent and $K_2CO_3$ (potassium carbonate) as base was best suited for this coupling reaction in presence of our newly developed Pd-NHC catalyst.[18] The desired coupled product **4g** was formed within 5 minutes under microwave irradiation at 110 °C. Suzuki cross-coupling reaction of compound **3** with different aryl boronic acids under this optimized condition furnished the corresponding cross-coupled products in excellent yields (Scheme 4). Compounds **3a** and **3b** were successfully coupled with phenylboronic acid and correspondingly produced **4a** and **4c** in 90% and 87% yield. With 4-fluorophenylboronic acid they provided coupled products **4b** and **4d**

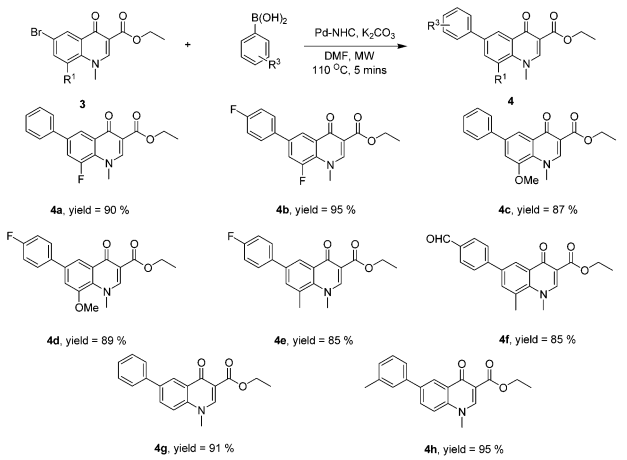
Table 1 Standardization of Suzuki coupling[a]




| Entry | Pd-catalyst | Solvent | Yield[b] (%) |
|---|---|---|---|
| 1 | $Pd(OAc)_2$ | DMF | 73 |
| 2 | $PdCl_2$ | DMF | NR |
| 3 | $Pd(OAc)_2$ | Toluene | 63 |
| 4 | $Pd_2(dba)_3$ | DMF | 64 |
| 5 | Pd-NHC[c] | DMF | 91 |
| 6 | Pd-NHC[c] | DMF + $H_2O$ (1 : 1) | 55 |

[a] *Reaction conditions*: compound **3d** (310 mg, 1 mmol), phenylboronic acid (146 mg, 1.2 mmol), $K_2CO_3$ (276 mg, 2 mmol), Pd-catalyst (19.2 mg, 2 mol%), 110 °C (microwave). [b] Isolated yield after purification.

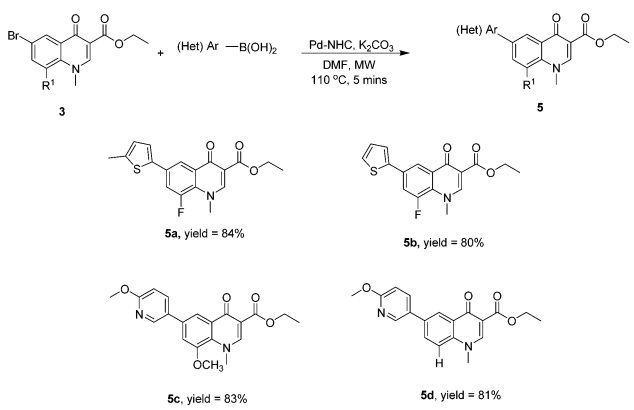
[c] Structure of Pd-NHC = 




Scheme 4 Synthesis of 6-aryl-4-quinolones. *Reaction conditions*: compound **3** (1 mmol), aryl boronic acid (1.2 mmol), $K_2CO_3$ (2 mmol), Pd-NHC (0.0192 g, 2 mol%), dry DMF (3 mL), Microwave, 110 °C, 5 min. Isolated yields after column chromatography purification.

in 95% and 89% yields respectively. The compound **3c** coupled with 4-fluoroboronic acid to afford **4e** in 85% yield. The compound **3d** underwent smooth coupling with phenylboronic acid and 3-methyl phenylboronic acid to yield the desired cross-couple products in 91% and 95% respectively. Highly active, 4-formyl phenylboronic acid was also successfully coupled with **3c** to furnish the cross-coupling product **4f** in high yield (85%). Hence, our potential catalytic system allowed the smooth coupling of compound **3** with different aryl boronic acids under optimized conditions. Substrates having both electron-donating and withdrawing groups easily participated in the reaction to afford the desired couple products within a short time (5 minutes).

It is reported that the presence of heterocyclic ring substituents in many quinolone derivatives attribute enhanced antibacterial activity,[13] increased activity in *in vitro* cytotoxicity and tubulin based assays,[19] and xanthine oxidase inhibition.[20] Therefore, we further explored the influence of heteroarylboronic acids on the reaction performance and employed similar reaction conditions to couple thienyl and pyridinyl boronic acid derivatives with 6-bromoquinolones **3**. The corresponding coupling products with the general structure **5** were achieved in high yields. Compound **3a** coupled with 5-methyl thienylboronic acid and thienylboronic acid and furnished compounds **5a** and **5b** in 84% and 80% yields respectively. 6-Methoxy-3-pyridinylboronicacid also coupled to provide **5c** and **5d** in 83% and 81% yields respectively. Hence, our reaction system was found compatible with variety of substituted aryl and heteroarylboronic acids. A family of 6-aryl and heteroaryl substituted quinolones have successfully been synthesized utilizing the 6-bromoquinolones **3** (Scheme 5).




Scheme 5 Suzuki cross coupling with heteroarylboronic acids forming products **5**. *Reaction conditions*: compound **3** (1 mmol), heteroarylboronic acid (1.2 mmol), $K_2CO_3$ (2 mmol), Pd-NHC (0.0192 g, 2 mol%), DMF (3 mL), microwave, 110 °C, 5 min. Isolated yields after column chromatography purification.

## Conclusions

In summary, we have demonstrated a suitable synthetic approach to obtain bromo and aryl substitution at 6-position of 4-quinolones. The bromo group may easily be substituted by different functional groups using various common synthetic reactions, thus opening opportunity to access variety of substituted quinolones. For instance we employed these bromoquinolones to Suzuki cross coupling reaction and produced a set of arylated quinolones. Both electron donating and withdrawing groups are well tolerated to provide excellent yields. Heterocyclic groups (thiophene and pyridine derivatives) were also successfully coupled in high yields. The 6-bromo and 6-arylated entities synthesized (**3** → **5**) are all new compounds which are anticipated to be valuable components for drug design. Exploring antimicrobial activities of these compounds in future may also add to the current knowledge about their structural activity relationships.

## Experimental

### General methods

Unless stated otherwise, all reagents such as aromatic anilines, EMME, palladium acetate, boronic acids and solvents were used as received from commercial suppliers. NMR spectra were recorded on a 300 MHz spectrometer at 298 K with calibration on the basis of the solvent residual peak. Mass spectra were performed using an ion trap mode. Products were purified using column chromatography on silica gel (60–120 mesh). Ethyl acetate and petroleum ether (60–80 °C) were used as eluents. Progress of the reaction was monitored using silica gel TLC.

### Preparation of compound 1

A mixture of aniline (10 mmol), EMME (11 mmol) and toluene (30 mL) was refluxed in a 250 mL round bottom flask for 5 hours. It was then cooled and washed with 3(N) 100 mL $H_2SO_4$. Toluene was distilled out afterwards. The mixture was scratched vigorously to get solid aniline product. This product (**5g**) was refluxed with biphenyloxide (50 mL) for 2 hours at 280 °C. It was then cooled and stirred for an hour after the addition of a small

amount (100 mL) of petroleum ether. Crude compound **1** was obtained by filtration on a Buchner funnel.

### Preparation of *N*-methylated derivatives (2)

Compound **1** (1 mmol) and DMF (5 mL) were placed in a round bottom flask fitted with a guard tube. NaH (36 mg, 1.5 mmol) was added and the reaction mixture was stirred at room temperature until $H_2$ gas ceased to evolve. Methyliodide (284 mg, 2 mmol) was then introduced drop-wise into the reaction mixture and it was further stirred at 60 °C for 4 hours. The mixture was diluted with water and the product was extracted with DCM (3 × 20 mL). The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude product was then purified using column chromatography.

### Preparation of bromo derivatives (3)

The *N*-Methylated product (compound **2**) was dissolved in a minimum amount of acetic acid and an equivalent quantity of bromine was added drop-wise. The resulting mixture was stirred at room temperature for 8 hours. Then it was poured into water and the organic layer was extracted with DCM and concentrated under reduced pressure. The crude material was further purified using column chromatography.

### Preparation of 6-arylated derivatives (4 and 5)

Compound **3** (1 mmol), aryl boronic acid (1.2 mmol), $K_2CO_3$ (276 mg, 2 mmol), Pd-NHC (0.0096 g, 1 mol %) and DMF (2 mL) were p[laced in a microwave reaction vessel. The mixture was placed in the focused microwave reactor and heated at 110 °C for 5 minutes. Then the solution was diluted with water and extracted with DCM (3 × 10 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography.

### Spectral analysis

**Ethyl 8-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (1a).** White solid, yield 52% (1.220 g); m.p. 217–219 °C; $^1$H NMR (300 MHz, DMSO-$d_6$, 25 °C, TMS): $\delta = 1.28$ (t, $J = 6.9$ Hz, 3H), 4.22 (q, $J = 6.9$ Hz, 2H), 7.40 (m, 1H), 7.65 (t, $J = 9$ Hz, 1H), 7.96 (d, $J = 7.8$ Hz, 1H), 8.39 (s, 1H), 12.5 (bs, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$, 25 °C, TMS): $\delta$ = 14.2, 59.8, 110.5, 117.17, 117.4, 121.3, 121.3, 124.5, 124.6, 128.1, 128.3, 129.1, 144.7, 150.1, 153.4, 164.4, 172.5; HRMS (EI$^+$): $[M]^+$, found 235.0634. $C_{12}H_{10}FNO_3$ requires 235.0645.

**Ethyl 1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylate (1b).** Greyish white, yield 55% (1.358 g); m.p. 243–245 °C; $^1$H NMR (300 MHz, DMSO-$d_6$, 25 °C, TMS): $\delta = 1.26$ (t, $J = 7.2$ Hz, 3H), 3.99 (s, 3H), 4.20 (q, $J = 7.2$ Hz, 2H), 7.29–7.37 (m, 2H), 7.70 (dd, $J = 7.2$ Hz, 1.2 Hz, 1H), 8.34 (s, 1H), 11.9 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$, 25 °C, TMS): $\delta$ = 14.8, 56.8, 60.1, 110.4, 117.3, 125.1, 128.6, 129.8, 144.3, 144.7, 149.2, 165.1, 173.7; MS (ESI$^+$) *m*/*z* 270.31[M + Na]$^+$, elemental analysis calcd (%) for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67, found C, 63.11; H, 5.34; N, 5.64.

**Ethyl 1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (1c).** White solid, yield 70% (1.617 g); m.p. 249–251 °C; $^1$H NMR (300 MHz, DMSO-$d_6$, 25 °C, TMS): $\delta = 1.28$ (t, $J = 7.2$ Hz, 3H), 4.22 (q, $J = 7.2$ Hz, 2H), 7.31 (t, $J = 7.8$ Hz, 1H), 7.55 (d, $J = 6.9$ Hz, 1H), 8.03 (d, $J$ = 7.8 Hz, 1H), 8.39 (s, 1H), 11.63 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$, 25 °C, TMS): $\delta = 14.8, 17.4, 60.1, 110.1, 124.0, 124.8, 127.4, 127.9, 133.7, 137.9, 145.0, 165.2, 174.1$; HRMS (EI$^+$): $[M]^+$, found 231.0891. $C_{13}H_{13}NO_3$ requires 231.0895.

**Ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate (1d).**[21] White solid, yield 50% (1.085 g); m.p. 251–253 °C; $^1$H NMR (300 MHz, DMSO-$d_6$, 25 °C, TMS): $\delta$ = 1.27 (t, $J$ = 7.2 Hz, 3H), 4.21 (q, $J$ = 7.2 Hz, 2H), 7.41 (t, $J$ = 6.9 Hz, 1H), 7.68 (m, 2H), 8.16 (dd, $J$ = 6.9 Hz, 0.9 Hz, 1H), 8.55 (s, 1H), 12.3 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$, 25 °C, TMS): $\delta$ = 14.8, 60.0, 110.2, 119.2, 125.2, 126.1, 127.7, 132.4, 139.4, 145.4, 165.3, 173.9.

**Ethyl 8-fluoro 1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (2a).** White solid, yield 76% (0.189 g); m.p. 121–124 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta$ = 1.40 (t, $J$ = 7.2 Hz, 3H), 4.10 (d, $J$ = 8.1 Hz, 3H), 4.38 (q, $J$ = 7.2 Hz, 2H), 7.37 (m, 2H), 8.31 (m, 1H), 8.36 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta$ = 14.33, 46.1, 46.3, 61.1, 109.5, 120.3, 120.6, 122.47, 122.51, 126.3, 126.4, 129.2, 129.3, 130.4, 150.8, 152.5, 154.2, 165.1, 173.3; MS (ESI$^+$) *m*/*z* 271.95 [M + Na]$^+$, elemental analysis calcd (%) for $C_{13}H_{12}FNO_3$: C, 62.65; H, 4.85; N, 5.62, found C, 62.51; H, 4.88; N, 5.64.

**Ethyl 1,4-dihydro-8-methoxy-1-methyl-4-oxoquinoline-3-carboxylate (2b).** Light brown solid, yield 75% (0.196 g); m.p. 113–116 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta$ = 1.23 (t, $J$ = 7.2 Hz, 3H), 3.75 (s, 3H), 3.98 (s, 3H), 4.20 (q, $J$ = 7.2 Hz, 2H), 6.96 (d, $J$ = 7.8 Hz, 1H), 7.14 (m, 1H), 7.96 (d, $J$ = 8.1 Hz, 1H), 8.16 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta$ = 14.8, 47.6, 57.2, 60.1, 109.6, 115.9, 118.6, 125.9, 131.0, 131.1, 151.1, 152.4, 165.0, 172.5; MS (ESI$^+$) *m*/*z* 284.31 [M + Na]$^+$, elemental analysis calcd (%) for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36, found C, 64.40; H, 5.75; N, 5.39.

**Ethyl 1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (2c).** White solid, yield 70% (0.171 g); m.p. 91–93 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta$ = 1.41 (t, $J$ = 7.2 Hz, 3H), 2.80 (s, 3H), 4.11 (s, 3H), 4.38 (q, $J$ = 7.2 Hz, 2H), 7.29 (m, 1H), 7.43 (m, 1H), 8.37 (s, 1H), 8.42 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta$ = 14.4, 24.2, 47.0, 60.9, 110.2, 125.3, 126.38, 126.43, 130.7, 137.4, 140.4, 152.5, 165.8, 174.2; MS (ESI$^+$) *m*/*z* 268.32 [M + Na]$^+$, elemental analysis calcd (%) for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71, found C, 68.40; H, 6.05; N, 5.74.

**Ethyl 1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (2d).**[21] Brown solid, yield 78% (0.180 g); m.p.102–105 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta$ = 1.44 (t, $J$ = 7.2 Hz, 3H), 4.00 (s, 3H), 4.43 (q, $J$ = 7.2 Hz, 2H), 7.53 (m, 2H), 7.78 (m, 1H), 8.55 (m, 1H), 8.80 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta$ = 14.4, 41.4, 60.8, 110.7, 115.7, 125.2, 127.7, 128.8, 132.7, 139.7, 149.7, 165.6, 174.4.

**Ethyl 6-bromo-8-fluoro-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (3a).** White solid, yield 70% (0.229 g); m.p. 150–153 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.27$ (t,

$J = 7.2$ Hz, 3H), 4.02 (d, $J = 8.7$ Hz, 3H), 4.20 (q, $J = 7.2$ Hz, 2H), 7.91 (dd, $J = 13.5$ Hz, 2.4 Hz, 1H), 8.03 (d, $J = 1.2$ Hz, 1H), 8.52 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.7$, 45.6, 60.4, 110.4, 117.2, 117.4, 122.7, 123.2, 124.9, 125.1, 129.1, 129.2, 131.9, 151.1, 152.3, 152.6, 154.5, 164.4, 170.5; HRMS (ESI-TOF) $m/z$: $[M + H]^+$, found 327.9902. $C_{13}H_{12}BrFNO_3$ requires 327.9985.

**Ethyl 6-bromo-1,4-dihydro-8-methoxy-1-methyl-4-oxoquinoline-3-carboxylate (3b).** Yellowish white solid, yield 65% (0.221 g); m.p. 155–157 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.40 (t, $J = 7.2$ Hz, 3H), 3.93 (s, 3H), 4.17 (s, 3H), 4.38 (q, $J = 7.2$ Hz, 2H), 7.18 (d, $J = 2.1$ Hz, 1H), 8.20 (d, $J = 2.1$ Hz, 1H), 8.43 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.5$, 48.3, 56.8, 61.3, 110.1, 117.7, 119.6, 122.0, 130.0, 131.7, 151.2, 152.1, 165.6, 172.1; HRMS (ESI-TOF) $m/z$: $[M + H]^+$, found 340.0119. $C_{14}H_{15}BrNO_4$ requires 340.0184.

**Ethyl 6-bromo-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (3c).** Yellowish white solid, yield 72% (0.232 g); m.p. 205–208 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.40$ (t, $J = 7.2$ Hz, 3H), 2.76 (s, 3H), 4.09 (s, 3H), 4.37 (q, $J = 7.2$ Hz, 2H), 7.49 (d, $J = 2.4$ Hz, 1H), 8.30 (s, 1H), 8.43 (d, $J = 2.4$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 23.9, 47.1, 61.0, 110.4, 119.0, 128.5, 129.1, 131.7, 139.2, 139.6, 152.4, 165.1, 172.7; HRMS (ESI-TOF) $m/z$: $[M + H]^+$, found 324.0129. $C_{14}H_{15}BrNO_3$ requires 324.0235.

**Ethyl 6-bromo-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (3d).** White solid, yield 75% (0.232 g); m.p. 108–111 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.39$ (t, $J = 7.2$ Hz, 3H), 3.85 (s, 3H), 4.36 (q, $J = 7.2$ Hz, 2H), 7.28 (d, $J = 2.1$ Hz, 1H), 7.70 (dd, $J = 9.0$ Hz, 2.4 Hz, 1H), 8.36 (s, 1H), 8.49 (d, $J = 2.4$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 41.5, 60.9, 111.0, 117.7, 119.2, 129.9, 130.1, 135.6, 138.4, 149.7, 165.0, 172.9; MS ($ESI^+$) $m/z$ 332.05 ($[M + Na]^+$, $^{79}$Br), 334.04 ($[M + Na]^+$, $^{81}$Br), elemental analysis calcd (%) for $C_{13}H_{12}BrNO_3$: C, 50.34; H, 3.90; N, 4.52, found C, 50.31; H, 3.94; N, 4.48.

**Ethyl 8-fluoro-1,4-dihydro-1-methyl-4-oxo-6-phenylquinoline-3-carboxylate (4a).** Light brown solid, yield 90% (0.292 g); m.p. 168–170 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.43 (t, $J = 7.2$ Hz, 3H), 4.14 (d, $J = 8.1$ Hz, 3H), 4.41 (q, $J = 7.2$ Hz, 2H), 7.47 (m, 3H), 7.67 (m, 3H), 8.40 (s, 1H), 8.59 (d, $J = 2.4$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 45.9, 46.1, 61.2, 110.8, 118.0, 118.3, 121.2, 127.0, 128.5, 129.2, 129.3, 131.7, 138.0, 138.7, 138.8, 151.0, 151.5, 165.6, 166.5, 173.0; MS ($ESI^+$) $m/z$ 347.91 $[M + Na]^+$, $C_{19}H_{16}FNO_3$, elemental analysis calcd (%) for $C_{19}H_{16}FNO_3$: C, 70.14; H, 4.96; N, 4.31, found C, 70.07; H, 5.01; N, 4.33.

**Ethyl 8-fluoro-6-(4-fluorophenyl)-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (4b).** White solid, yield 95% (0.326 g); m.p. 184–187 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.41$ (t, $J = 7.2$ Hz, 3H), 4.10 (d, $J = 8.1$ Hz, 3H), 4.39 (q, $J =$ 7.2 Hz, 2H), 7.15 (m, 2H), 7.58 (m, 3H), 8.33 (s, 1H), 8.48 (d, $J =$ 1.5 Hz 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.5$, 46.0, 46.2, 61.2, 111.0, 116.0, 116.3, 116.5, 117.8, 118.1, 121.0, 128.1, 128.2, 128.7, 128.8, 129.0, 131.8, 134.2, 137.7, 137.8, 151.0, 151.6, 154.3, 161.5, 164.8, 165.5, 166.4, 172.9; HRMS ($ESI^+$): $[M + Na]^+$, found 366.0868. $C_{19}H_{15}F_2NO_3Na$ requires 366.0918.

**Ethyl 1,4-dihydro-8-methoxy-1-methyl-4-oxo-6-phenylquinoline-3-carboxylate (4c).** White solid, yield 87% (0.293 g); m.p. 182–185 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.38$ (t, $J = 7.2$ Hz, 3H), 3.78 (s, 3H), 4.05 (s, 3H), 4.35 (q, $J = 7.2$ Hz, 2H), 7.21 (d, $J = 1.8$ Hz, 1H), 7.39 (m, 3H), 7.62 (d, $J = 7.2$ Hz, 2H), 8.17 (s, 1H) 8.31 (d, $J = 1.8$ Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.4, 47.8, 56.4, 60.7, 109.9, 112.9, 116.9, 126.9, 127.9, 128.9, 129.9, 131.3, 137.9, 139.2, 150.8, 151.5, 165.5, 173.5; MS (ESI+): $m/z$ 337.95 $[M]^+$, elemental analysis calcd (%) for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15, found C, 71.13; H, 5.60; N, 4.16.

**Ethyl-6-(4-fluorophenyl)-1,4-dihydro-8-methoxy-1-methyl-4-oxoquinoline-3-carboxylate (4d).** White solid, yield 89% (0.316 g); m.p. 178–180 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.44 (t, $J = 7.2$ Hz, 3H), 4.03 (s, 3H), 4.22 (s, 3H), 4.42 (q, $J = 7.2$ Hz, 2H), 7.17 (m, 2H), 7.32 (d, $J = 2.1$ Hz, 1H), 7.65 (m, 2H), 8.35 (d, $J = 2.1$ Hz, 1H), 8.40 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 47.9, 56.5, 60.9, 110.2, 113.1, 115.7, 116.0, 117.3, 128.7, 128.8, 130.0, 131.6, 135.56, 135.60, 137.4, 150.9, 151.7, 161.2, 164.4, 165.8, 173.6; MS($ESI^+$): $m/z$ 355.89 $[M]^+$, elemental analysis calcd (%) for $C_{20}H_{18}FNO_4$: C, 67.60; H, 5.11; N, 3.94, found C, 67.49; H, 5.01; N, 3.98.

**Ethyl-6-(4-fluorophenyl)-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (4e).** Light yellow solid, yield 85% (0.288 g); m.p. 217–220 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.41 (t, $J = 7.2$ Hz, 3H), 2.83 (s, 3H), 4.11 (s, 3H), 4.38 (q, $J = 7.2$ Hz, 2H), 7.13 (t, $J = 8.7$ Hz, 2H), 7.60 (m, 3H), 8.34 (s, 1H), 8.56 (d, $J = 2.4$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 14.4, 24.3, 47.0, 60.9, 110.1, 115.7, 116.0, 123.6, 127.3, 128.5, 128.6, 130.9, 135.0, 135.8, 136.5, 139.4, 152.2, 161.1, 164.4, 165.5, 174.2; MS($ESI^+$): $m/z$ 361.92 $[M + Na]^+$, elemental analysis calcd (%) for $C_{20}H_{18}FNO_3$: C, 70.78; H, 5.35; N, 4.13, found C, 70.75; H, 5.08; N, 4.11.

**Ethyl 6-(4-formylphenyl)-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (4f).** White solid, yield 85% (0.296 g); m.p. 230–233 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.39$ (t, $J = 7.2$ Hz, 3H), 2.87 (s, 3H), 4.14 (s, 3H), 4.38 (q, $J = 7.2$ Hz, 2H), 7.70 (s, 1H), 7.80 (d, $J = 8.1$ Hz, 2H), 7.95 (d, $J = 8.1$ Hz, 2H), 8.38 (s, 1H), 8.68 (s, 1H), 10.04 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 24.4, 47.0, 61.0, 110.6, 124.7, 127.5, 130.4, 131.0, 135.5, 135.9, 136.0, 140.3, 144.8, 152.5, 165.5, 174.1, 191.8; MS($ESI^+$) $m/z$ 372.23 $[M + Na]^+$, elemental analysis calcd (%) for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01, found C, 72.11; H, 5.40; N, 3.98.

**Ethyl 1,4-dihydro-1-methyl-4-oxo-6-phenylquinoline-3-carboxylate (4g).** White solid, yield 91% (0.279 g); m.p. 137–140 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.31$ (t, $J = 7.2$ Hz, 3H), 3.77 (s, 3H), 4.27 (q, $J = 7.2$ Hz, 2H), 7.35 (m, 4H), 7.55 (m, 2H), 7.76 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H), 8.29 (s, 1H), 8.58 (d, $J = 2.1$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 13.3$, 40.4, 59.8, 109.4, 115.4, 124.0, 125.9, 126.8, 127.6, 127.9, 130.4, 136.8, 137.7, 137.9, 148.3, 164.4, 173.3; MS (ESI+): $m/z$ 329.94 $[M + Na]^+$, elemental analysis calcd (%) for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56, found C, 74.21; H, 5.62; N, 4.60.

**Ethyl 1, 4-dihydro-1-methyl-4-oxo-6-*m*-tolylquinoline-3-carboxylate (4h).** Light yellow solid, yield 95% (0.305 g); m.p. 98–101 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.41$ (t,

$J = 7.2$ Hz, 3H), 2.44 (s, 3H), 3.97 (s, 3H), 4.42 (q, $J = 7.2$ Hz, 2H), 7.21 (d, $J = 7.5$ Hz, 1H), 7.36 (t, $J = 7.8$ Hz, 1H), 7.51 (m, 3H), 7.97 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H), 8.61 (s, 1H), 8.75 (d, $J = 2.4$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 21.6, 41.6, 61.0, 110.5, 116.5, 125.1, 125.4, 127.8, 128.0, 128.7, 138.3, 138.7, 138.8, 139.0, 149.4, 149.7, 165.8, 174.3; HRMS ($EI^+$): $[M]^+$, found 321.1366. $C_{20}H_{19}NO_3$ requires 321.1365.

**Ethyl 8-fluoro-1, 4-dihydro-1-methyl-6-(5-methylthiophen-2-yl)-4-oxoquinolone-3-carboxylate (5a).** Light yellow solid, yield 84% (0.290 g); m.p. 158–161 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.37$ (t, $J = 6.9$ Hz, 3H), 2.49 (s, 3H), 4.03 (m, 3H), 4.36 (q, $J = 6.9$ Hz, 2H), 6.72 (m, 1H), 7.16 (d, $J = 3.6$ Hz, 1H), 7.44 (dd, $J = 15$ Hz, 2.4 Hz, 1H), 8.23 (s, 1H), 8.36 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 15.5, 45.9, 46.1, 61.1, 110.6, 116.2, 116.6, 119.0, 124.7, 126.7, 127.54, 127.6, 131.6, 132.6, 132.7, 138.9, 141.6, 150.9, 151.2, 154.2, 165.6, 172.7; HRMS ($EI^+$): $[M]^+$, found 345.0832. $C_{18}H_{16}FNO_3S$ requires 345.0835.

**Ethyl 8-fluoro-1,4-dihydro-1-methyl-4-oxo-6-(thiophen-2-yl)-quinolone-3-carboxylate (5b).** Light yellow solid, yield 80% (0.265 g); m.p. 185–188 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.42$ (t, $J = 7.2$ Hz, 3H), 4.10 (d, $J = 8.1$ Hz, 3H), 4.40 (q, $J = 7.20$ Hz, 2H), 7.10–7.13 (m, 1H), 7.36 (dd, $J = 5.1$ Hz, 0.9 Hz, 1H), 7.44 (dd, $J = 3.6$ Hz, 1.2 Hz, 1H), 7.61 (dd, $J = 15$ Hz, 2.1 Hz, 1H), 8.34 (s, 1H), 8.54 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 45.9, 46.1, 61.1, 110.8, 116.6, 116.9, 119.6, 119.7, 124.7, 126.5, 128.0, 128.5, 131.8, 132.2, 132.3, 141.4, 150.9, 151.3, 154.2, 165.5, 172.7; HRMS ($EI^+$): $[M]^+$, found 331.0676. $C_{17}H_{14}FNO_3S$ requires 331.0678.

**Ethyl 1,4-dihydro-8-methoxy-6-(6-methoxypyridin-3-yl)-1-methyl-4-oxoquinoline-3-carboxylate (5c).** White solid, yield 83% (0.305 g); m.p. 181–184 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.42$ (t, $J = 7.2$ Hz, 3H), 4.00 (s, 6H), 4.18 (s, 3H), 4.40 (q, $J = 7.2$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 1H), 7.27 (s, 1H), 7.90 (dd, $J = 5.4$, 2.1 Hz, 1H), 8.31 (m, 2H), 8.46 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 47.9, 53.8, 56.5, 60.9, 110.3, 111.1, 112.5, 117.0, 128.5, 130.1, 131.8, 135.1, 137.5, 144.9, 151.0, 151.7, 163.9, 165.8, 173.6; MS (ESI+): $m/z$ 391.20 $[M + Na]^+$, elemental analysis calcd (%) for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60, found C, 65.23; H, 5.45; N, 7.62.

**Ethyl 1,4-dihydro-6-(6-methoxypyridin-3-yl)-1-methyl-4-oxo-quinoline-3-carboxylate (5d).** White solid, yield 81% (0.274 g); m.p. 169–171 °C; $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.40$ (t, $J = 7.2$ Hz, 3H), 3.88 (s, 3H), 3.99 (s, 3H), 4.37 (q, $J = 7.2$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 1H), 7.46 (d, $J = 8.7$ Hz, 1H), 7.82 (m, 2H), 8.39 (d, $J = 10.8$ Hz, 2H), 8.56 (d, $J = 1.5$ Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 14.4, 41.4, 53.7, 60.8, 110.7, 116.7, 124.6, 128.1, 129.0, 130.6, 134.6, 138.7, 145.0, 149.9, 163.9, 165.4, 174.2; MS ($ESI^+$): $m/z$ 361.24 $[M + Na]^+$, elemental analysis calcd (%) for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28, found C, 67.48; H, 5.32; N, 8.22.

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