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.

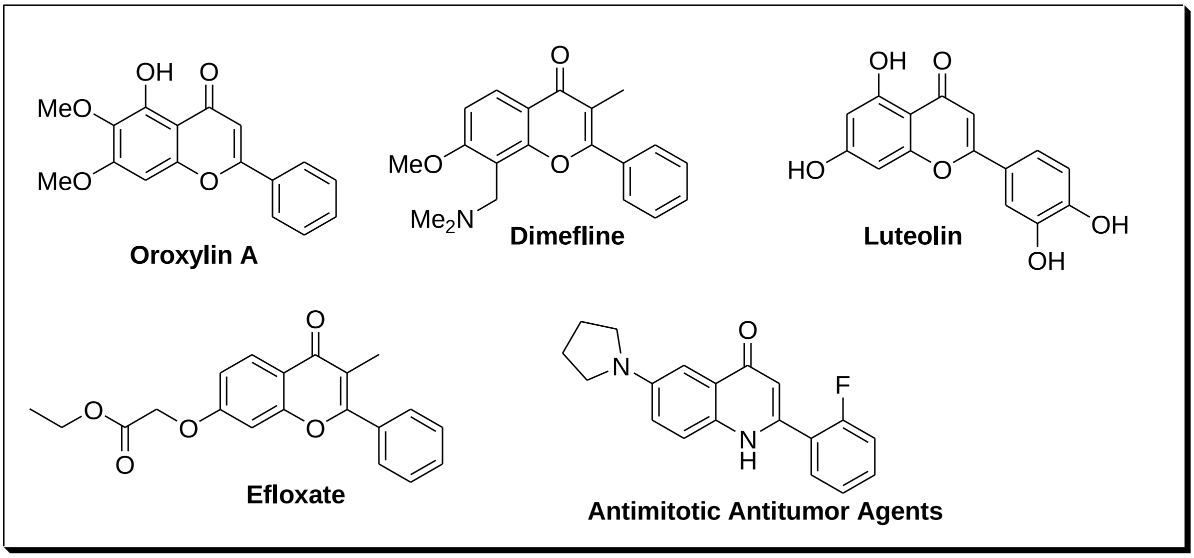
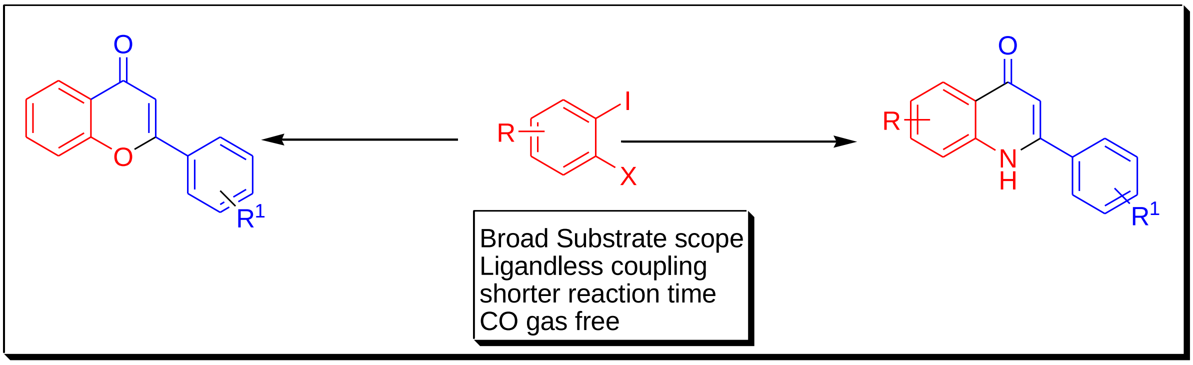


Fig-II.1. Biologically active flavones and 4-quinolone scaffolds

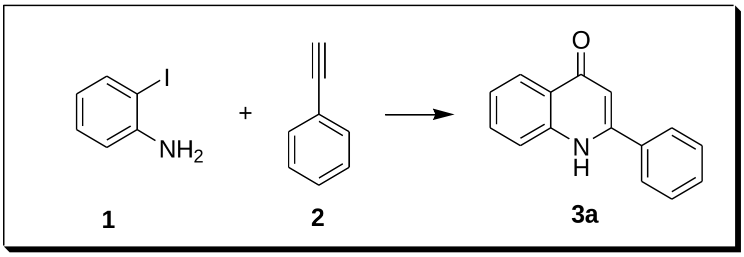
II.B. Present work: Background & objectives

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:

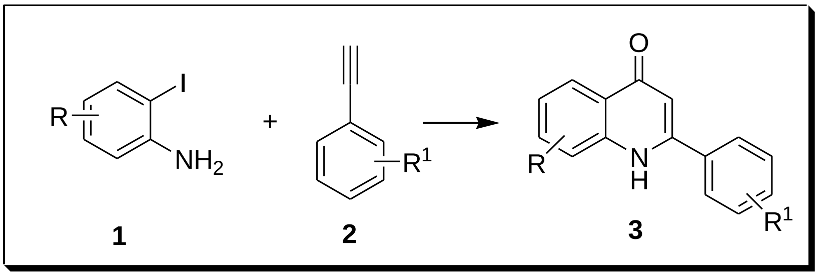


1 2 3a

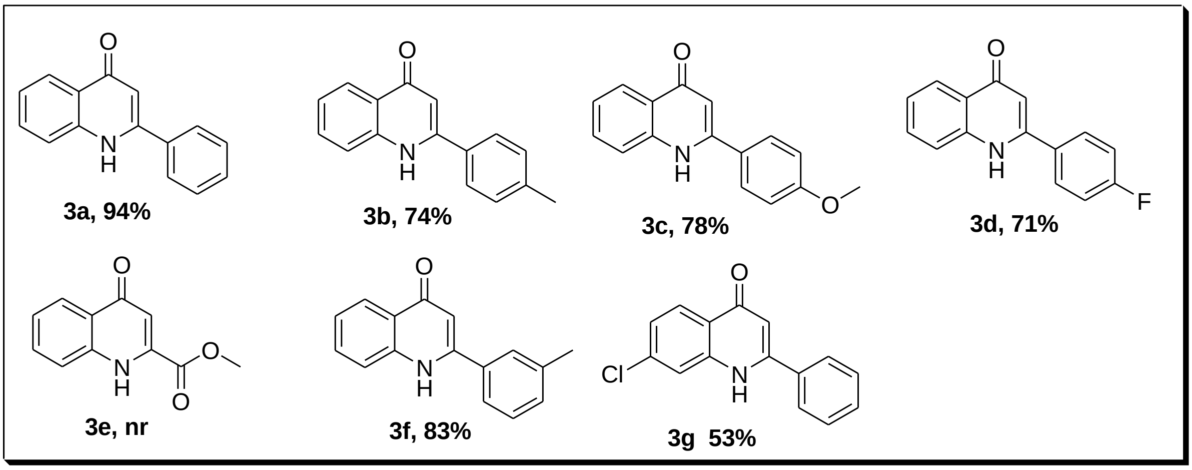
entry	Catalyst (mol %)	Base (equiv)	CO source (equiv)	Temp (°C)	solvent	Time (h)	Yield (%)
1	Pd-NHC 2	Et_3N	$Mo(CO)_6$	95	DMF	15	75
2	Pd-NHC 2	K_2CO_3	$Mo(CO)_6$	95	Anisole	15	25
3	Pd-NHC 2	K_2CO_3	$Mo(CO)_6$	95	Toluene	15	No desired product
4	Pd-NHC 2	Et_3N	$Mo(CO)_6$	95	Anisole	20	45
5	Pd-NHC 2	K_2CO_3	$Mo(CO)_6$	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 $95^{\circ}C$ 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 $95^{\circ}C$ (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).

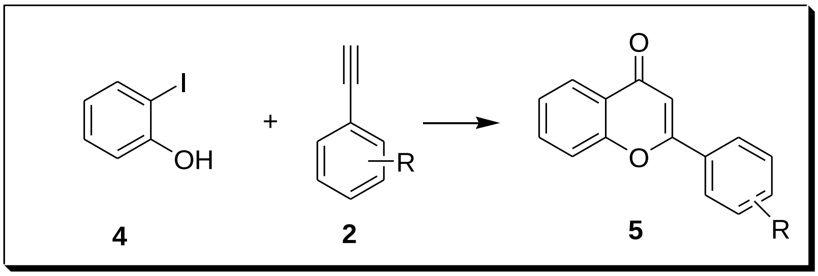


Scheme-II.1. Scope of various phenyl acetylene and 2-iodoaniline in the carbonylative sonogashira coupling of 4-quinolones

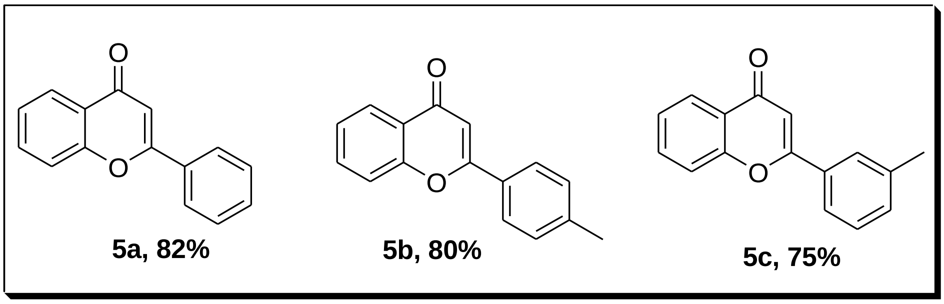


Reaction condition: Various 2-iodo aniline (0.25 mmol), Phenyl acetylene (0.5 mmol), Me_2NH (4 equiv), $Mo(CO)_6$ (0.5 mmol, 132mg), Pd-NHC (2mol%), DMF (2 ml) stirred at 95°C under N_2 atm .Yield = Isolated yield after column chromatography

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


5a, 82% **5b, 80%** **5c, 75%**

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:

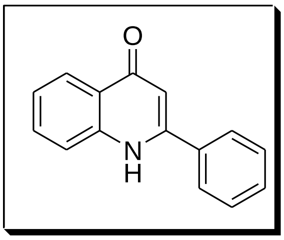
Initially, 2-iodoaniline (0.25 mmol, 55mg), phenylacetylene (0.5mmol), $Mo(CO)_6$ (0.5 mmol, 132mg), Pd-NHC (2 mol%, 4.8mg), Me_2NH (1 mmol, 180mg) and DMF (2ml) were taken in sealed tube. Then, it was evacuated with nitrogen three times and stirred the reaction mixture at 95°C for 15hr. After completion 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).

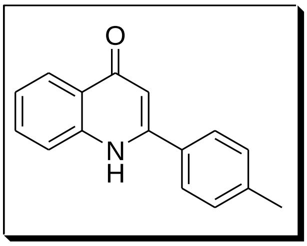
II.D.4. Physical characteristics and spectral data of compounds:

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



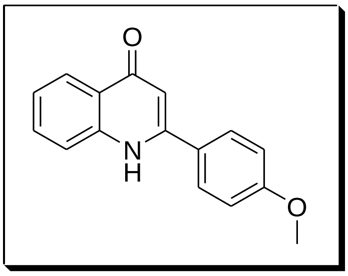
tan powder; ^1H NMR (DMSO-d_6, 300 MHz) δ 6.34 (d, *J* = 1.8 Hz, 1H), 7.32-7.37 (m, 1H), 7.58-7.60 (m, 3H), 7.68 (dt, *J* = 6.9Hz, 1.5Hz, 1H), 7.76-7.85 (m, 3H), 8.10 (d, *J* = 7.8Hz, 1H), 11.75 (s, 1H); ^{13}CNMR (DMSO-d_6, 75 MHz) δ 107.8, 119.2, 123.8, 125.2, 125.3, 127.9, 129.5, 130.9, 132.3, 134.7,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

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



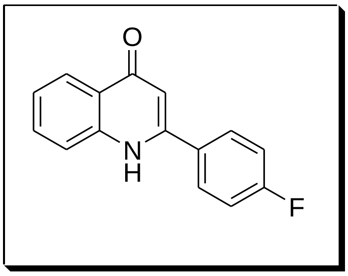
Tan powder, ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.38 (s, 3H), 6.32 (s, 1H), 7.29-7.39 (m, 3H), 7.62-7.77 (m, 4H), 8.06-8.09 (m, 1H), 11.65 (s, 1H); ^{13}CNMR (DMSO-d_6, 75 MHz) δ 21.4, 107.3, 119.2, 123.7, 125.1, 127.7, 130.0, 131.7, 132.2, 140.8, 141.0, 150.5, 177.4.

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



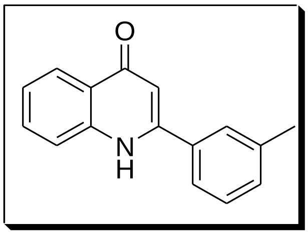
Tan powder, ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.85 (s, 3H), 6.33 (s, 1H), 7.14 (d, *J* = 8.8Hz, 2H), 7.33 (t, *J* = 7.5Hz, 1H), 7.63-7.68 (m, 1H), 7.75-7.83 (m, 3H), 8.09 (d, *J* = 7.2Hz, 1H), 11.65 (s, 1H); ^{13}CNMR (DMSO-d_6, 75 MHz) δ 55.9, 106.8, 114.8, 119.3, 123.6, 125.1, 125.2, 126.8, 129.3, 132.1,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

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



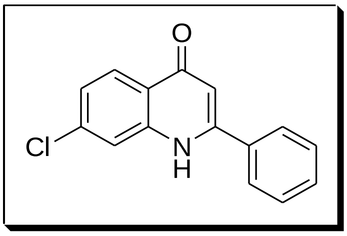
Tan powder, ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.33 (d, *J* = 1.8Hz, 1H), 7.35 (t, *J* = 7.2Hz, 1H), 7.44 (t, *J* =8.7Hz, 2H), 7.58-7.77 (m, 2H), 7.88-7.93 (m, 2H), 8.10 (d, *J* =7.8Hz, 1H), 11.65 (s, 1H); ^{13}CNMR (DMSO-d_6, 75 MHz) δ 107.8, 116.3, 116.6, 119.1, 123.7, 125.2, 125.3, 130.3, 130.4, 131.1,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

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



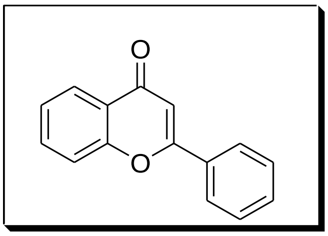
Brownish white solid, ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.44 (s, 3H), 6.32(s, 1H), 7.32-7.42 (m, 2H), 7.48 (t, *J* = 7.5Hz, 1H), 7.61-7.70 (m, 3H), 7.76-7.79 (m, 1H), 8.10 (d, *J* = 8.1Hz, 1H), 11.69(s, 1H); ^{13}CNMR (DMSO-d_6, 75 MHz) δ 21.5, 107.7, 119.1, 123.6, 124.8, 125.0, 125.2, 128.3, 129.4, 131.5,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

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



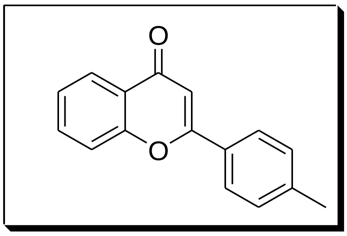
Tan powder, ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.38 (s, 1H), 7.37 (dd, *J* = 8.7Hz, 2.1Hz, 1H), 7.58-7.62 (m, 3H), 7.80-8.09 (m, 3H), 8.10 (d, *J* = 8.7Hz, 1H), 11.74 (s, 1H). ^{13}CNMR (DMSO-d_6, 75 MHz) δ 104.1, 118.0, 119.2, 125.3, 128.3, 128.5, 129.3, 130.8, 132.7, 140.5, 141.3, 156.7, 169.9.

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



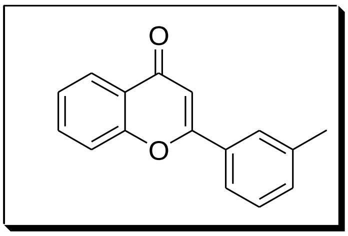
White solid, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.84 (s, 1H), 7.43 (dt, *J* = 8.1Hz, 1.2Hz, 1H), 7.53-7.60 (m, 4H), 7.68-7.71 (m, 1H), 7.92-7.96 (m, 2H), 8.24 (dd, *J* = 7.8Hz, 1.5Hz, 1H); ^{13}CNMR ($CDCl_3$, 75 MHz) δ 107.6, 118.1, 124.0, 125.3, 125.7, 126.3, 129.1, 131.6, 131.8, 133.8, 156.3, 163.4,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

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



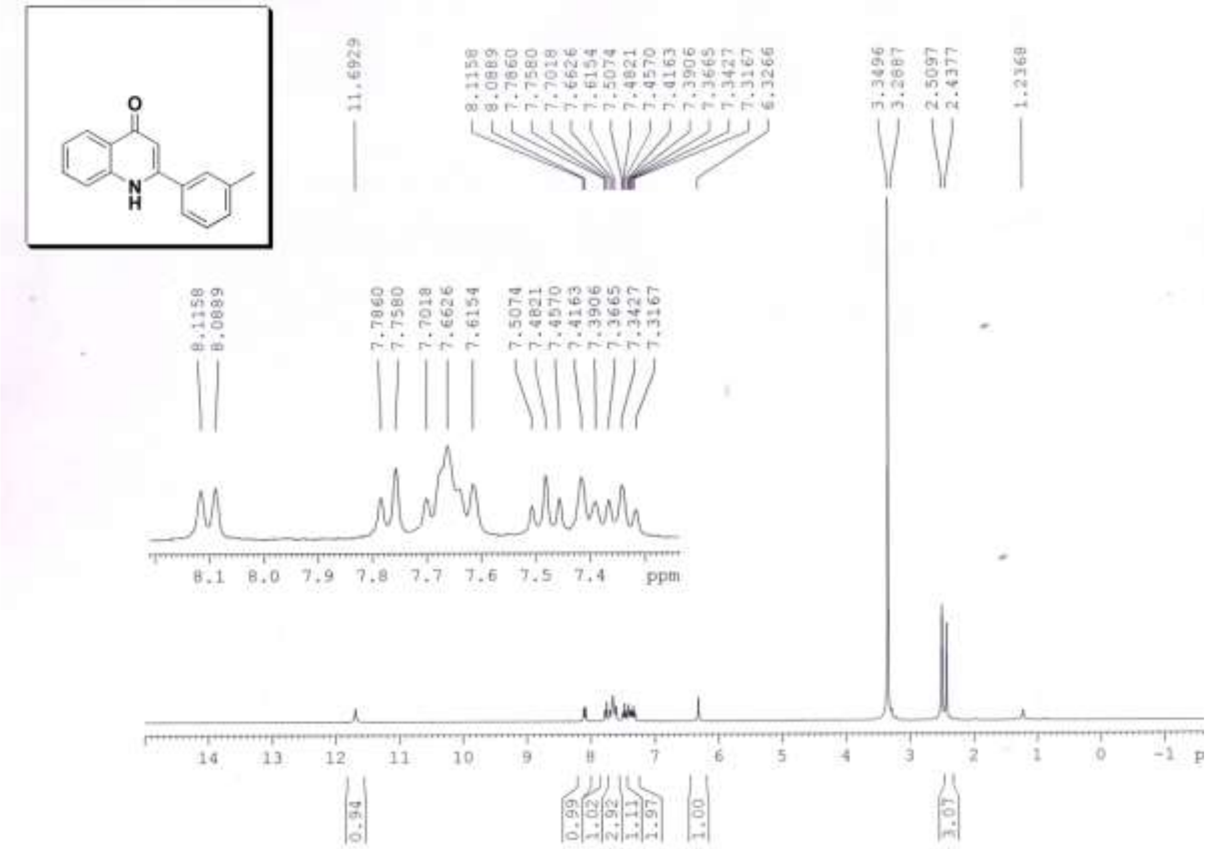
White solid, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 6.80 (s, 1H), 7.32 (d, *J*= 8.1Hz, 2H), 7.39-7.44 (m, 1H), 7.55-7.57 (m, 1H), 7.66-7.72 (m, 1H), 7.82 (d, *J*= 8.4Hz, 2H), 8.22 (dd, *J*= 7.8Hz, 1.2Hz, 1H); ^{13}CNMR ($CDCl_3$, 75 MHz) δ 21.5, 107.0, 118.7, 124.0, 125.1, 125.7, 126.3, 129.0,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

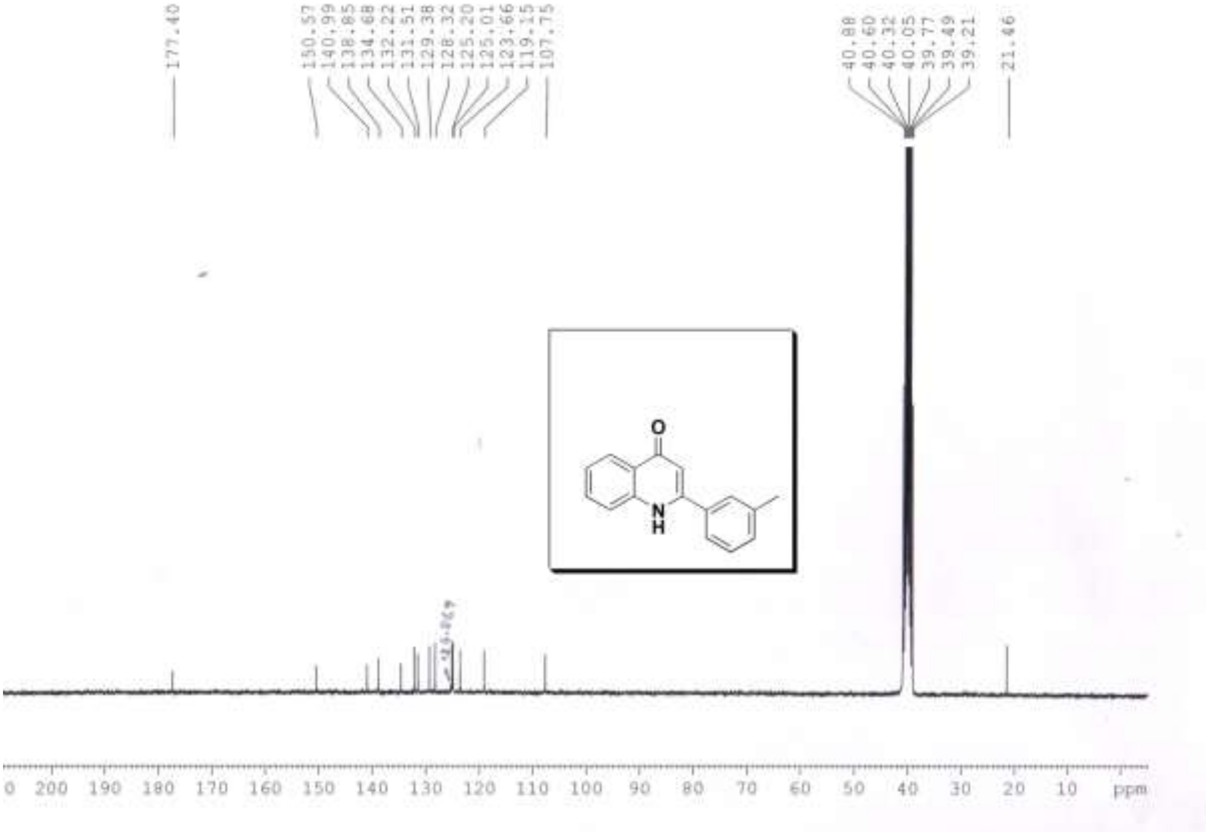
9. 2-*m*-tolyl-4*H*-chromen-4-one (5c)[19]



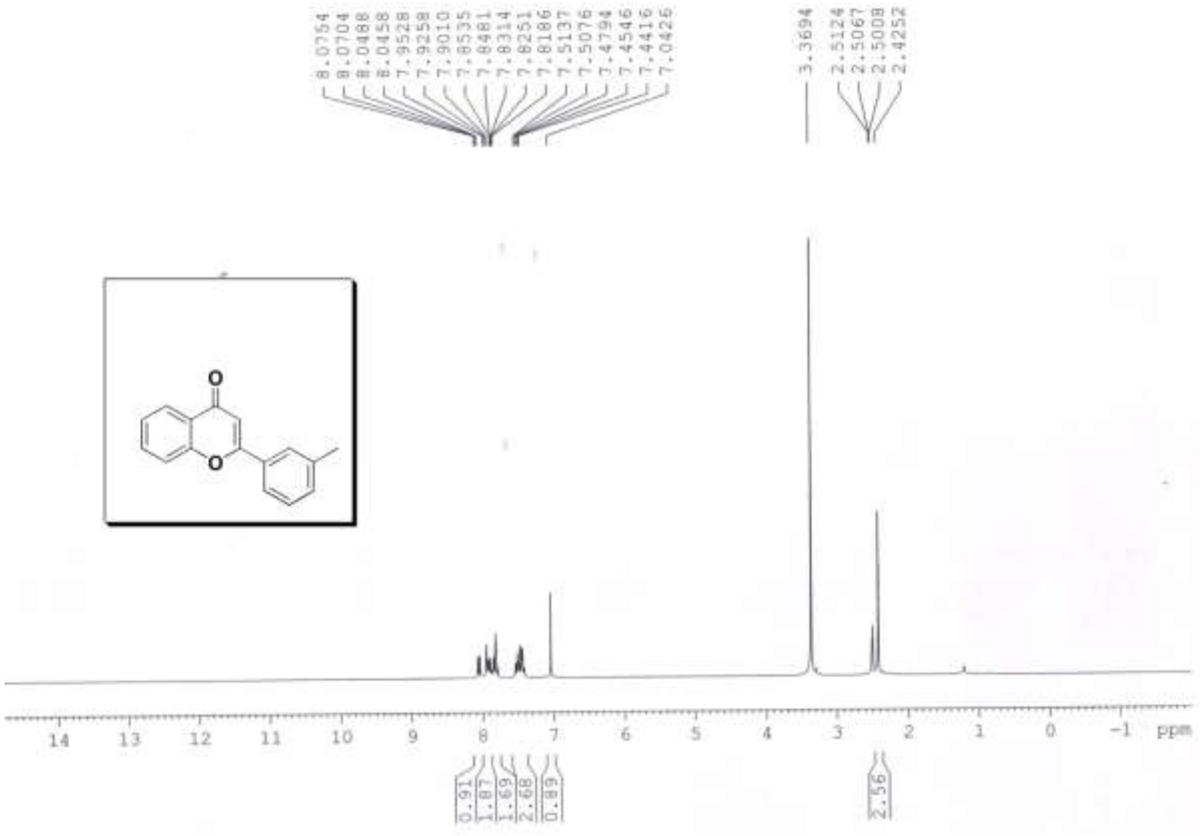
Pale yellow solid, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 7.04 (s, 3H), 7.44-7.51 (m, 3H), 7.82-7.85 (m, 2H), 7.90-8.04 (m, 2H), 8.07 (d, J = 1.5Hz, 1H); ^{13}CNMR ($CDCl_3$, 300 MHz) δ 21.4, 107.3, 119.0, 123.8, 124.0, 125.2, 126.0, 127.2, 129.5, 131.5, 133.0, 134.8, 139.0, 156.1, 163.2, 177.6.

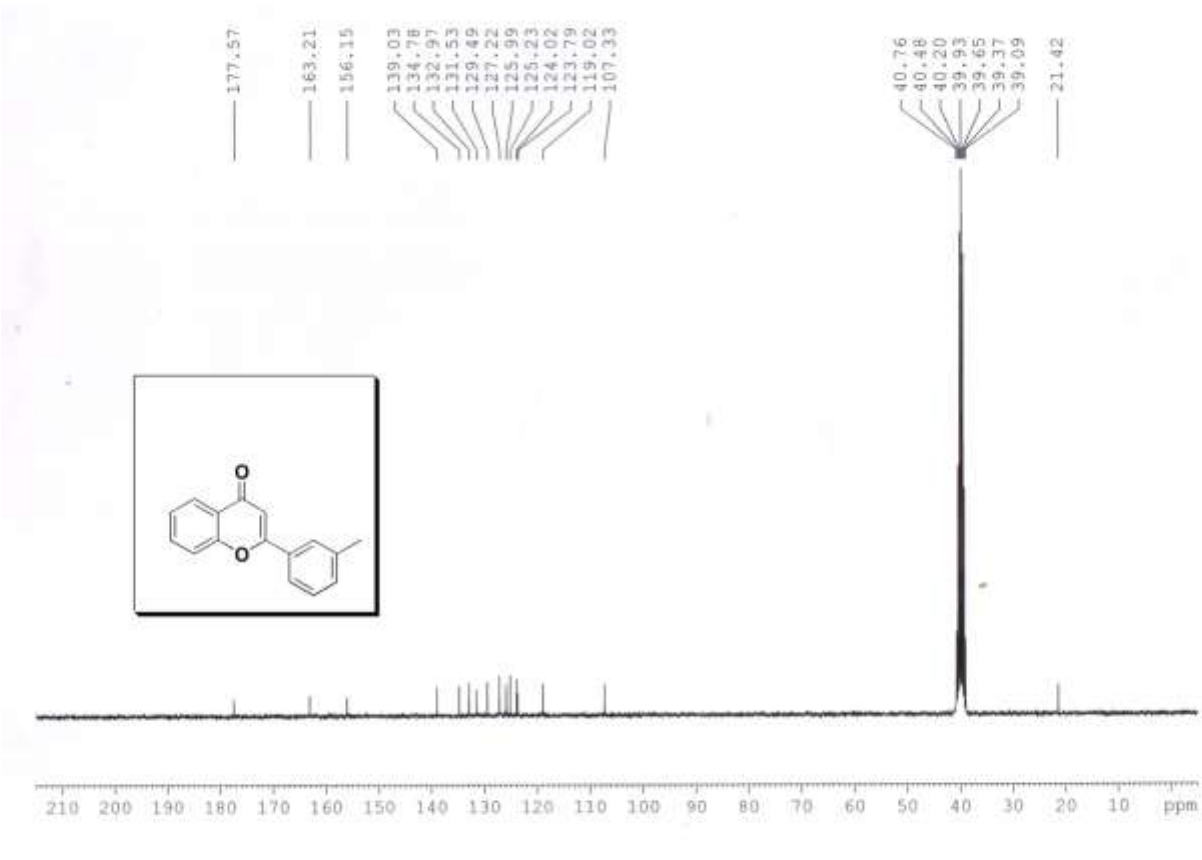
^{1}H and ^{13}C NMR spectra of entry 3f (Scheme-II.1.) in DMSO-d_6





^{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)