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]

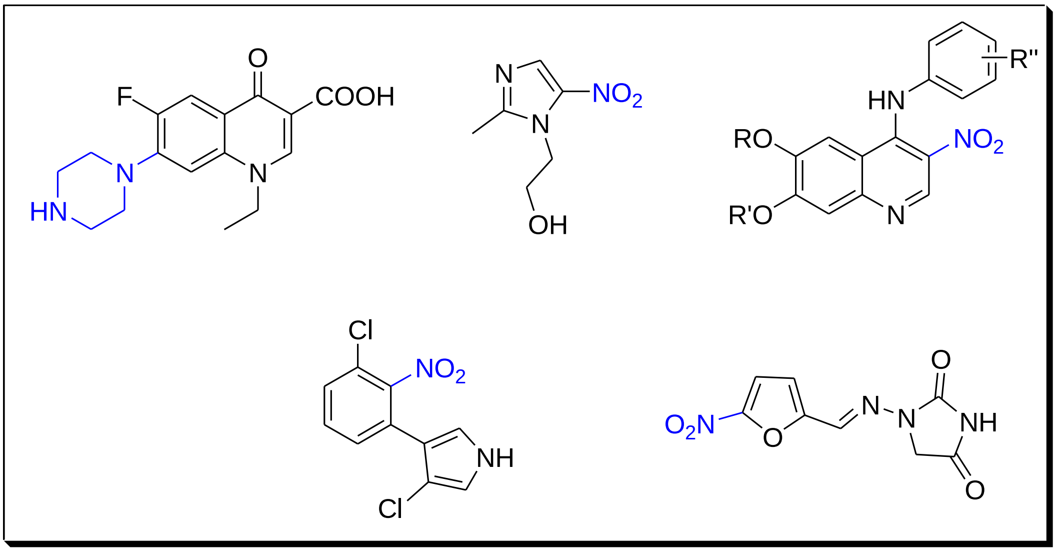


Fig.VII.1. few biologically active nitro derivatives

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.

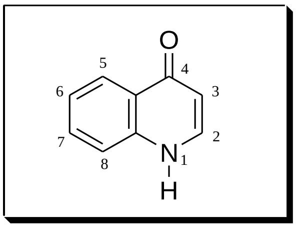
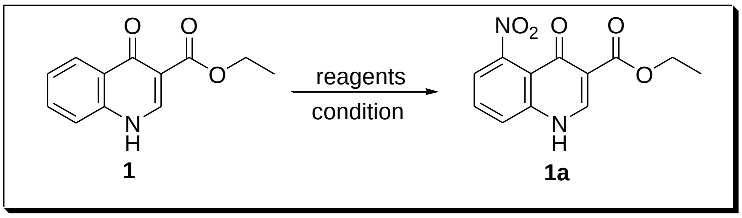


Fig-VII.2. Basic skeleton of 4-quinolone

VII.B.1. Results and Discussion:

Table-VII.1. Optimisation of the reaction conditions



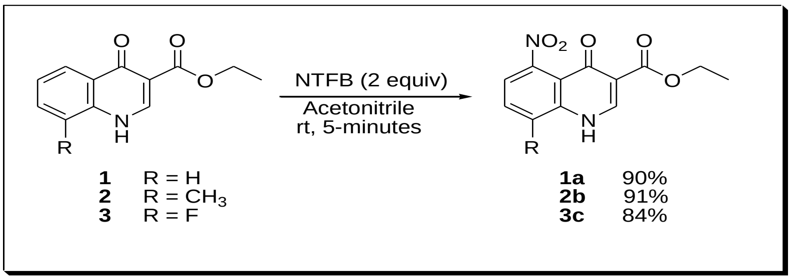
entry	nitrating agent	solvent	temp	time	Yield (%)[a]
1	Mixed acids(Conc^n HNO_3 + Conc^n H_2SO_4)	-	0°C-rt	1 h	78
2	dil HNO_3	-	rt	2 h	30
3	Conc^n HNO_3	-	rt	2 h	52
4	$Cu(NO_3)_2$/p-TSA	DCM	rt	12 h	nr
5	$Fe(NO_3)_3/Ac_2O$	DCM	rt	12 h	nr
6	**NTFB**	**acetonitrile**	**rt**	**5 min**	**90**

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]

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

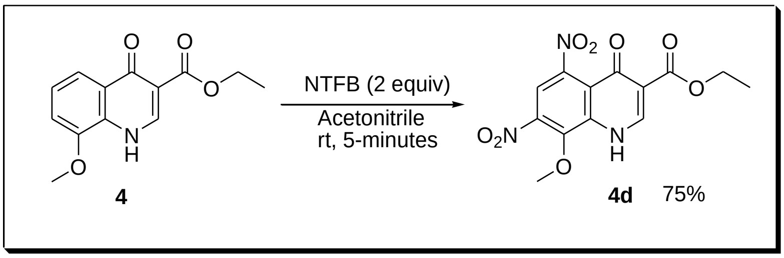
Scheme-VII.1. Scope of various 4-quinolone substrates



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).

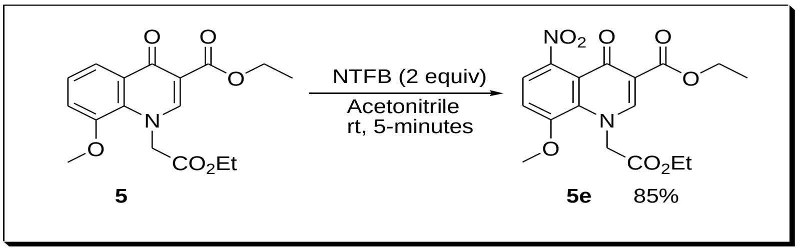
Scheme-VII.2. nitration of 8-methoxy-4-quinolone derivative



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.

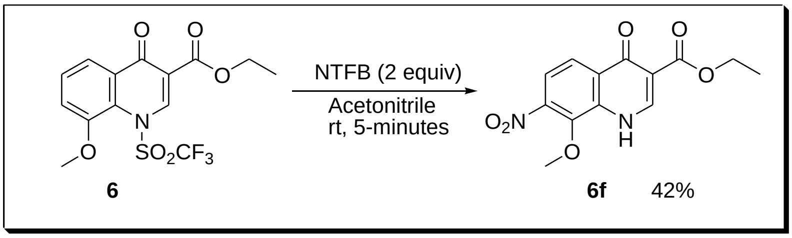
Scheme-VII.3. controlled nitration of compound **5**



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).

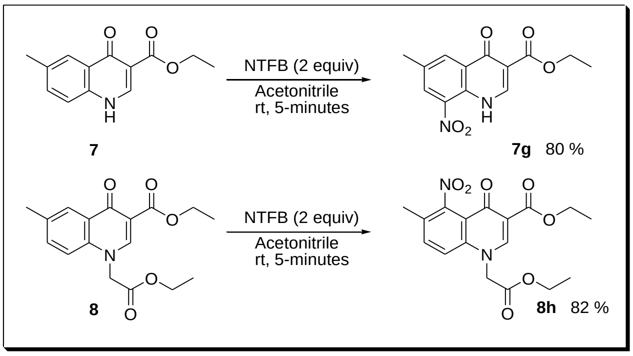
Scheme-VII.4. Selective nitration of *N*-protected 8-methoxy 4-quinolone at C-7 position



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) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.27 ppm). ^{13}C NMR spectra were recorded at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_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

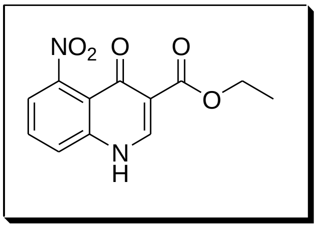
An oven dried round bottomed flask (100 ml) equipped with stir bar was charged with Compound 4 or 7 (1 mmol, 0.247g/ 0.231g) and 1.5 mmol (0.207g) of K_2CO_3 in requisite amount of DMF (solvent) at room temperature. The stirring was continued for half an hour to cease the evolve of hydrogen. Then, ethyl bromoacetate (0.324g/ ~0.3 ml) was the added into the reaction vessel and continued the stirring for next 1h at 60^0C. 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

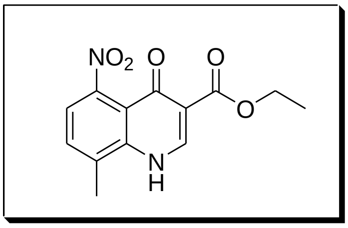
1. Ethyl 1, 4-dihydro-5-nitro-4-oxoquinoline-3-carboxylate (2a)



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-

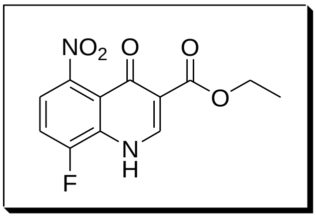
8.55 (m, 2H), 8.61(d, *J*=8.1 Hz, 1H), 12.2 (s, 1H). ^{13}C NMR (75MHz, DMSO-d_6) δ 14.6, 60.4, 111.7, 124.1, 129.5, 130.6, 133.5, 134.2, 137.1, 146.6, 164.2, 172.4, ESI-MS$[M+H]^+$ found m/z 263.10, elemental analysis for $C_{12}H_{10}N_2O_5$ C, 54.97; H, 3.84; N, 10.68; Found: C, 54.76; H, 3.79; N,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

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



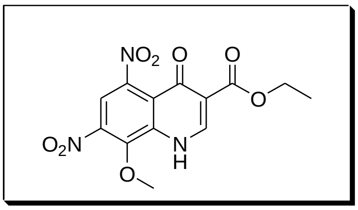
Yellowish white solid, melting point: 225°C-228°C, ^{1}H NMR (300MHz, DMSO-d_6,) δ 1.22 (t, *J*=7.2 Hz, 3H), 2.54 (s, 3H), 4.21 (q, *J*=7.2 Hz, 2H), 7.53 (d, *J*=7.8 Hz, 1H), 7.70 (d, *J*=8.4 Hz, 1H), 8.43 (s, 1H), 11.60 (s, 1H), ^{13}C NMR (75MHz, DMSO-d_6) δ 14.7, 17.7, 60.5, 111.3, 118.3, 119.0, 131.4, 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)



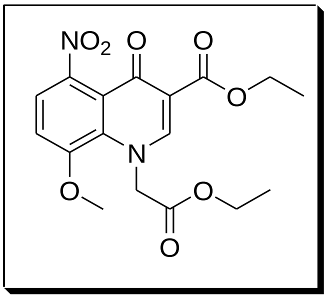
Yellowish white solid, melting point: 234°C-236°C, ^{1}H NMR (300MHz, DMSO-d_6) δ 1.03 (t, *J* =7.2 Hz, 3H), 3.98 (q, *J* =7.2 Hz, 2H), 7.46-7.50 (m, 1H), 7.56-7.62 (m, 1H), 8.19 (s, 1H), 12.80 (s, 1H), ^{13}C NMR (75MHz, DMSO-d_6) δ 14.7, 60.6, 112.3, 117. 7, 117.9, 119.5, 119.6, 120.1, 130.0, 130.2, 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)



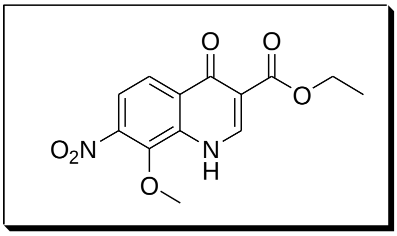
Bright yellow solid, melting point: 175°C-178°C, ^{1}H NMR (300MHz, DMSO-d_6) δ 1.27 (t, *J* =7.2 Hz, 3H), 4.12 (s, 3H), 4.23 (q, *J* =7.2 Hz, 2H), 8.37 (s, 1H), 8.49 (s, 1H), ^{13}C NMR (75MHz, DMSO-d_6) δ 14.7, 60.7, 64.4, 113.2, 114.8, 121.5, 136.8, 142.1, 143.5, 146.1, 146.3, 164.2, 170.3, HRMS (ESI-TOF)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

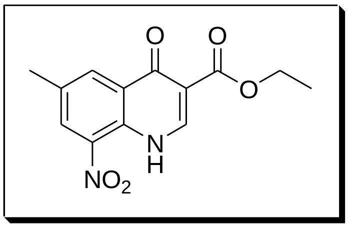
6. Ethyl 1-((ethoxycarbonyl) methyl)-1,4-dihydro-8-methoxy-5-nitro-4-oxoquinoline-3-carboxylate (6f)



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

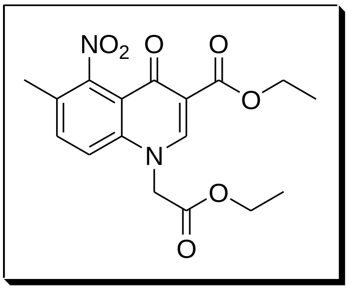
(DMSO-d_6, 75MHz) δ 14.6, 60.3, 64.0, 111.7, 119.8, 121.9, 131.0, 134.7, 143.9, 144.1, 146.1, 164.6, 172.8, (ESI)$^+$[M+H]$^+$ m/z 293.00 [M+H]$^+$, $C_{13}H_{12}N_2O_6$ requires 293.1, elemental analysis for for $C_{13}H_{12}N_2O_6$: C, 53.43; H, 4.14; N, 9.59. Found: C, 52.96; H, 4.21; N, 9.74.

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



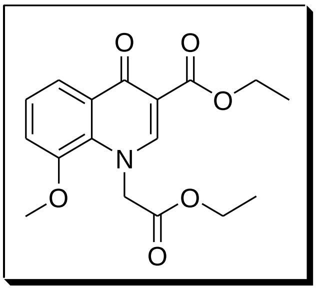
Yellowish white solid, melting point: 239°C-241°C, ^{1}H NMR (300MHz, DMSO-d_6,) δ ppm 1.25 (t, *J* =7.2 Hz, 3H), 2.24 (s, 3H), 4.19 (q, *J* =7.2 Hz, 2H), 7.73 (d, *J* =2.7 Hz, 2H), 8.58 (d, *J* =6.3 Hz, 1H), 12.7 (bs, 1H), ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.2, 15.4, 59.9, 110.8, 117.6, 120.7, 125.6, 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)



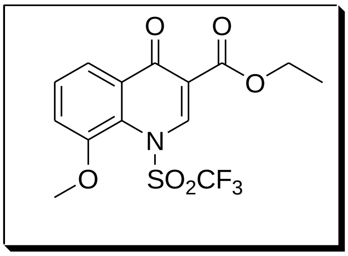
Light yellow solid, melting point: 203°C-206°C, ^{1}H NMR (300MHz, $CDCl_3$) δ 1.09-1.19 (m, 6H), 2.16 (s, 3H), 4.04-4.15 (m, 4H), 5.30 (s, 2H), 7.64 (d, *J* =9 Hz, 1H), 7.72 (d, *J* =9 Hz, 1H), 8.68 (s, 1H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.4, 16.1, 55.0, 61.1, 62.8, 112.3, 117.0, 119.6, 127.1, 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)



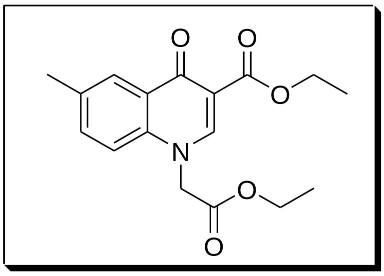
white solid, melting point: 159°C-162°C, ^{1}H NMR (300 MHz $CDCl_3$) δ 1.25 (t, *J* =6.9 Hz, 3H), 1.38 (t, *J* =6.9Hz, 3H), 3.83 (s, 3H), 4.24 (q, *J* =6.9 Hz, 2H), 4.36 (q, *J* =6.9 Hz, 2H), 5.05 (s,2H), 7.07-7.10 (m,1H), 7.27-7.34 (m, 1H), 8.11 (dd, *J* =8.1Hz, 1.2Hz, 1H), 8.25 (s,1H), ^{13}C NMR (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)