ADDITION –ELIMINATION PROCESS OF 2,4-DICHLOROQUINOLINE SYNTHESIS AND PHARMACOLOGICAL IMPORTANCE

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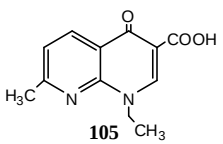
ASTRACT

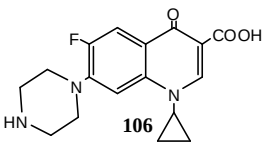
In terms of the diversity of quinolines, 2,4-dichloro compounds can play a role as key intermediates in synthesis of 2,4-disubstituted quinolines by possible stepwise substitution at C4 and C2 positions, where the chance for study of regioselectivity is more. This obvious significance prompted us to study the selectivity referred to 2,4-dichloroquinolines, in which one of the chlorine is selectively replaced under controlled temperature to yield new molecular structures with high pharmacological importance or with interesting properties.

INTRODUCTION

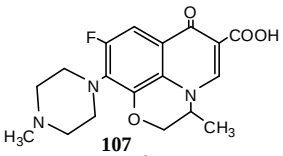
The quinoline having nitrogen atoms have been ubiquitously found in plant, microbial, and animal sources, Ciprofloxacin 106, Ofloxacin 107, and Levofloxacin biological potential (Michael 2000 & 2001).[12a] the 4-quinolones had improved activity against limited range of Gram-negative bacteria. synthetic antibiotics, fluroquinolines Ciprofloxacin 106, Ofloxacin 107, and Levofloxacin are used to ge genitourinary, respiratory, and gastrointestinal tracts, skin and soft tissues, and other structures.



105
Naldixic acid



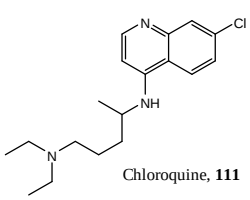
106
Ciprofloxacin



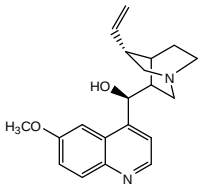
107
Ofloxacin

chloroquine (CQ, 111), quinine (112), piperaquine (113), amodiaquine (114) and primaquine (115) (Fig 3.1) were used for the treatment of malaria (Foley and Tilley 1999).[4] antimalarial chloroquine (CQ, 111), quinine (112), piperaquine (113), amodiaquine (114) and

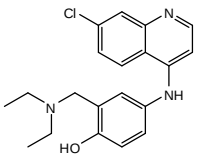
primaquine (115) (Fig 3.1) were used for the treatment of malaria (Foley and



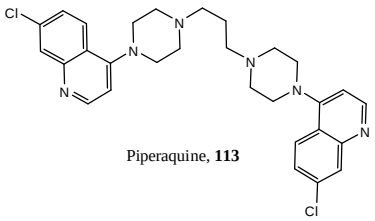
Chloroquine, **111**



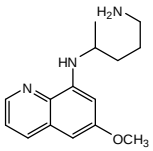
Quinine, **112**



Amodiaquine, **114**

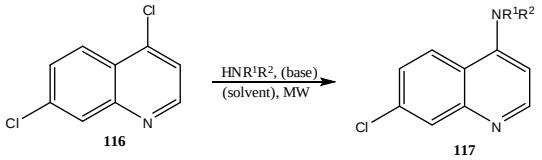


Piperaquine, **113**



Primaquine, **115**

Tilley 1999).[4]



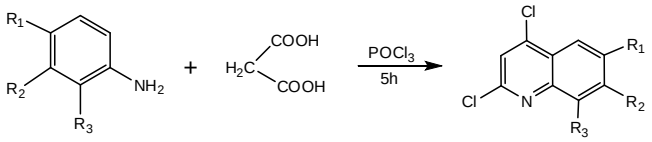
116 **117**

aniline with malonic acid in an excess of phosphorus oxychloride at reflux to give 2,4-dichloroquinoline 120 Quinolines with low-molecular weight, especially 2-alkylquinolines, 2-alkenylquinolines and 2- arylquinolines, isolated from plants (Fournet et al., 1993) [55] or prepared by synthesis (Fakhfakh et al., 2001 & 2002) [56-58] exhibited a variety of biological properties such as leishmanicidal (Fournet et al., 1996) [59], trypanocidal (Nakayama et al., 2001) [60], antimalarial (Gantier et al., 1996) [61] and were found to be potent inhibitors of the human immunodeficiency virus of type-1 (HIV-1) integrase (Mekouar et al., 1998; Zouhiri et al., 2000) [62,63], as well as active against HTLV-1 transformed cell lines (HUT-102) (Fakhfakh et al., 2003; Fournet et al., 2003) [64,65]. Mercedes Martinez Grueiro and his coworkers (Grueiro et al., 2005) synthesized various 2-substituted quinolines (Fig 3.4) and evaluated in vitro and in vivo against the nematodes *Caenorhabditiselegans*, *Heligmosomoidespolygyrus*and the protozoa *Trichomonasvaginali*s. Some of them have shown in vitro nematocide activity at 10 μM and their trichomonacidal activity reached 50% reduction at only 100 μM. The in vivo activity on *Trichinellaspiralis*model was also evaluated for some of the most in vitro active quinolines.

RESULT AND DISCUSSION

Scheme 3.7: Synthesis of 2,4-dichloroquinoline derivatives

Initially, 2,4-dichloroquinolines 140a-l (scheme 3.7) were synthesized by refluxing substituted anilines (0.02 mol), malonic acid (0.02 mol) and POCl3 (15 ml) under dry condition for 5 h.



140 (a-l)

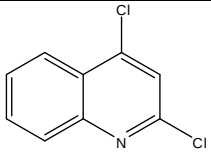
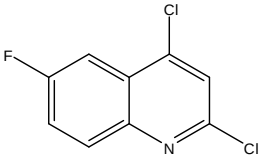
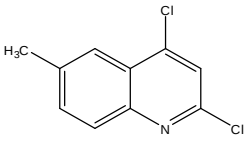
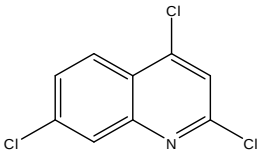
The progress of the reaction was monitored by TLC. After the completion of reaction, excess of POCl3 was removed under reduced pressure, solution was cooled to room temperature and poured over crushed ice carefully with vigorous stirring and allowed to stand overnight.

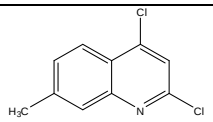
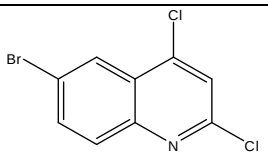
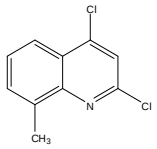
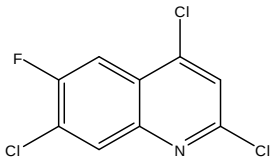
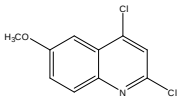
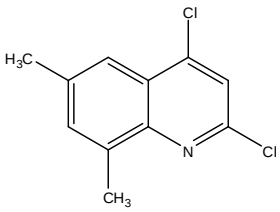
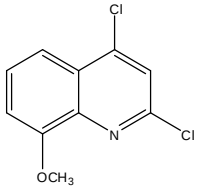
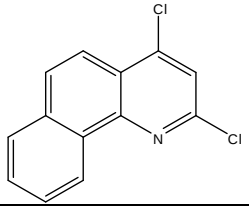
In order to bring highly functionalized structural molecules, we tried incorporate quinoline moiety with varied substitutions and a halogen in the quinoline in to a new hetero atom molecule, which could result new structural moieties with high pharmacological importance or with interesting properties, where we can have the prolonged activity of both the heterocycles chosen. As a consequence we had chosen 1,4-dihydropyridines to react with 2,4-dichloroquinolines to yield new molecular structures

The solid settled was filtered to dryness and purified over a column of silica gel (60-120 *mesh*) using hexane:ethylacetate (9.5:0.5) mixture as eluent, which afforded the product 140a-l in pure form.Yields of the compounds ranges from 36 to 74% (Table 3.1). The ^{1}H NMR of 2,4,7-trichloroquinoline (140h) shows chemical shift values at 7.54 (s, 1H, H-3), 7.72 (d, 1H, *J* = 8.5 Hz, H-6), 7.97 (d, 1H, *J* = 8.5 Hz, H-8), 8.17 (s, 1H, H-8) confirms the product formation.

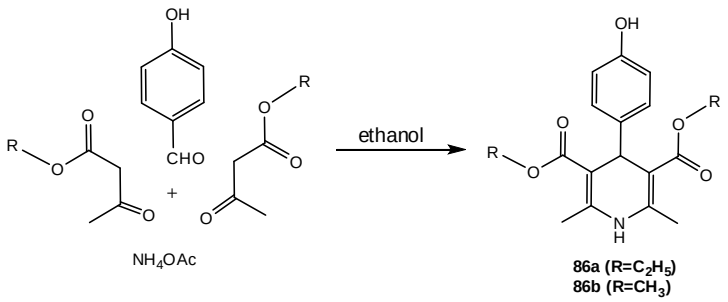
Scheme 3.8: Synthesis of diethyl and dimethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-

Table 3.1: Physical data of 2,4-dichloroquinolines

Entry	Product	M.P. (°C) [Lit]	Yield (%)	Entry	Product	M.P. (°C) [Lit]	Yield (%)
140a		65-66 [66-67]	48	140g		~~146-148~~	52
140b		92-93 [91-93]	56	140h		114-116	50

140c		80	51	140i		134	42
140d		81-82 [81-82]	55	140j		114-116	36
140e		167 [168-170]	57	140k		102-104	52
140f		133-134 [132-135]	34	140l		131	40

dicarboxylate (86a,b).



One pot three components reaction of β-ketoester (2 mmol), *p*-hydroxybenzaldehyde (1 mmol) and ammonium acetate (1.1 mmol) in the presence of ethanol afforded the corresponding 1,4-dihydropyridines (1,4-DHP's) (86a,b) in good yield. Similarly, reaction of β-ketoester (1 mmol), *m* (or) *p*-hydroxybenzaldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexadione (1 mmol) and ammonium acetate (1.1 mmol) in the presence of ethanol afforded the corresponding 1,4-dihydropyridines (1,4-DHP's) (141, 142) (Table 3.2).

EXPERIMENTAL SECTION

CHEMICALS AND APPARATUS

Solvents and reagents were commercially sourced and used without further purification. Melting points were taken on Elchem Microprocessor based DT apparatus in open capillary tubes and are uncorrected. IR spectra were obtained on an Avatar-330 FTIR spectrophotometer (Thermo Nicolet) using KBr pellets, and only noteworthy absorption levels (reciprocal centimeters) are listed. The NMR spectra were recorded on a Bruker 200, 300 & 500 MHz spectrometer using TMS as internal standard (chemical shifts δ in ppm). Mass spectra were recorded on HRMS and LCMS by Agilent 1200 series LC and MicromasszQ spectrometer. Thin-layered chromatography (TLC) was performed on preparative plates of silica gel (s.d.fine). Visualization was made with iodine chamber. Column chromatography was performed by using silica gel (*60-120 mesh*).

GENERAL PROCEDURE FOR THE SYNTHESIS OF 2,4-DICHLOROQUINOLINES (140a-l).

A mixture of substituted anilines (0.02 mol), malonic acid (0.02 mol) was taken in a round bottomed flask and phosphorous oxychloride was added drop wise to the round bottomed flask with constant stirring under ice cold condition then the mixture was stirred well for half an hour by using magnetic stirrer. The mixture was then refluxed under dry condition for 5 hours on the heating mantle. The completion of the reaction was monitored by TLC. Then the mixture was cooled to room temperature and poured on crushed ice, stirred for 10 minutes and allowed to stand overnight. The solid separated out was filtered to dryness and purified the products through column chromatography of silica gel (60-120 mesh) using pet ether and ethyl acetate (9.5:0.5) mixture as eluent, which afforded the products 140a-l in pure form.

SPECTRAL DATA

2,4-dichloroquinoline (140a).

Yield: 48%. M.p. 65-66 °C [Lit: 66-67]. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 7.49 (s, 1H, H-3), 7.63 (t, 1H, *J* = 5.7 Hz, H-6), 7.77 (t, 1H, *J* = 5.4 Hz, H-7), 8.01 (d, 1H, *J* = 6.3 Hz, H-8), 8.17 (d, 1H, *J* = 6.3 Hz, H-5).

2,4-dichloro-6-methylquinoline (140b).

Yield: 56%. M.p. 92-93 °C [Lit: 91-93]. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 2.58 (s, 3H, H-6'), 7.48 (s, 1H, H-3), 7.62 (d, *J* = 6 Hz, 1H, H-7), 7.93 (d, *J* = 6 Hz, 1H, H-8), 7.95 (s, 1H, H-5). MS: *m/z* 212 [M+1].

2,4-dichloro-6-fluoroquinoline (140g).

Yield: 52%. M.p. 65-66 °C [Lit: 66-67]. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 7.54 (s, 1H, H-3), 7.54-7.58 (m, 1H, H-7), 7.82 (dd, *J* = 9.5 Hz, 1H, H-5), 8.05 (dd, *J* = 9.5 Hz, 1H, H-8).

2,4-dichloro-7-chloroquinoline (140h).

Yield: 50%. M.p. 114-116 °C.^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 7.54 (s, 1H, H-3), 7.73 (d, *J* = 9 Hz, 1H, H-6), 7.97 (d, *J* = 8.5 Hz, 1H, H-5), 8.17 (s, 1H, H-8).

2,4-dichloro-6-bromoquinoline (140i).

Yield: 42%. M.p. 134 °C.^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 7.53 (s, 1H, H-3), 7.85-7.91 (m, 2H, H-7,8), 8.35 (s, 1H, H-5).

2,4,7-trichloro-6-fluoroquinoline (140j).

Yield: 36%. M.p. 114-116 °C.^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 7.53 (d, *J* = 8.1 Hz, 1H, H-3), 7.87 (d, *J* = 8.3 Hz, 1H, H-5), 8.09 (d, *J* = 6.9 Hz, 1H, H-8). MS: *m/z* 249 [M+1].

2,4-dichloro-6,8-dimethylquinoline (140k).

Yield: 52%. M.p. 102-104 °C.^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 2.49 (s, 3H, H-8'), 2.69 (s, 3H, H-6'), 7.39 (s, 1H, H-3), 7.41 (s, 1H, H-7), 7.71 (s, 1H, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C: 17.89 (C-8'), 21.67 (C-6'), 120.71 (C-5), 121.39 (C-3), 124.95 (C-9), 133.69 (C-8), 136.62 (C-7), 137.47 (C-5), 143.38 (C-4), 145.73 (C-2), 147.45 (C-10).

2,4-dichlorobenzo[*h*]quinoline (140l).

Yield: 40%. M.p. 131 °C.^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 7.62 (s, 1H, H-3), 7.74-7.77 (m, 2H), 7.91-7.95 (m, 2H), 8.08 (d, *J* = 9.3 Hz, 1H), 9.20-9.23 (m, 2H).

GENERAL PROCEDURE FOR SYNTHESIS OF 1,4-DHP's.

Synthesis of diethyl & dimethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (86a,b)

Amixture of *p*-hydroxybenzaldehyde (10 mmol, 1.0 equiv.), β-ketoester (20 mmol, 2.0 equiv.) and ammonium acetate (12 mmol, 1.2 equiv.) were heated for 15 min in the presence of ethanol (10 ml). The progress of the reaction was monitored by TLC. After

completion of the reaction, the reaction mixture was left aside for the formation of product, filtered to remove the insoluble solids and then the filter cake was washed with diethyl ether. The solid was recrystallised from absolute ethanol to yield respective 1,4-dihydropyridine derivatives as a yellow solid.

SPECTRAL DATA

Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (86a)

Yellow solid (recrystallised from ethanol). R_f (pet ether/EtOAc, 6:4) = 0.83. M.p. 228-230 °C (Lit. 230-232 °C). IR (KBr, cm^{-1}): 3345, 2981, 1662, 1486. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* =7.5 Hz, 6H), 2.77 (s, 6H), 3.66-3.76 (q, *J* = 6.0 Hz, 4H), 4.49 (s, 1H), 6.30 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 7.60 (s, -NH, 1H), 8.27 (s, -OH, 1H). HRMS: *m/z*345.1582 (M^+).

Dimethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (86b)

Yellow solid (recrystallised from ethanol). R_f (pet ether/EtOAc, 6:4) = 0.8. M.p. 230-232 °C (Lit. 231-233 °C). IR (KBr, cm^{-1}): 3339, 3003, 2950, 1680, 1647, 1611. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.86 (s, 6H), 3.28 (s, 6H), 4.51 (s, 1H), 6.31 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 7.73 (s, -NH, 1H), 8.35 (s, -OH, 1H). HRMS: *m/z* 317.1270 (M^+).

4.3.2. Synthesis of ethyl 4-(3-(2-chloroquinolin-4-yloxy) phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (141)

A mixture of *m*-hydroxybenzaldehyde (10 mmol, 1.0 equiv.), ethyl acetoacetate (10 mmol, 1.0 equiv.), 5,5-dimethyl-1,3-cyclohexadione (10 mmol, 1.0 equiv.) and ammonium acetate (12 mmol, 1.2 equiv.) were heated for 15 min in the presence of ethanol (10 ml). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was left aside for the product formation, filtered to remove the insoluble solids and then the filter cake was washed with diethyl ether. The solid was recrystallised from absolute ethanol to yield respective 1,4-dihydropyridine derivative as a yellow solid.

SPECTRAL DATA

Yellow solid (recrystallised from ethanol). M.p. 204-206 °C (Lit. 230-232 °C). IR (KBr, cm^{-1}): 3345, 2981, 1662, 1486. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.72 (s, 3H), 0.84 (s, 3H), 0.99 (t, 3H, *J* =7.0 Hz), 1.92 (m, 2H), 2.09-2.12 (m, 5H), 3.82 (q, 2H, *J* = 7.5 Hz), 4.73 (s, 1H), 6.34 (d, 1H, *J* = 8 Hz), 6.53-6.56 (m, 2H), 7.92 (s, 1H, -NH), 8.29 (s, 1H, -OH). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.64, 18.74, 27.03, 29.60, 32.59, 36.05, 50.77, 59.49, 104.09, 110.37, 113.08, 115.03, 118.63, 128.98, 145.17, 149.42, 149.90, 157.29, 167.41, 194.73.

Synthesis of methyl 4-(4-(2-chloroquinolin-4-yloxy) phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate derivatives (142)

A mixture of *p*-hydroxybenzaldehyde (10 mmol, 1.0 equiv.), methyl acetoacetate (10 mmol, 1.0 equiv.), 5,5-dimethyl-1,3-cyclohexadione (10 mmol, 1.0 equiv.) and ammonium acetate (12 mmol, 1.2 equiv.) were heated for 15 min in the presence of ethanol (10 ml). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was left aside for the formation of product, filtered to remove the insoluble solids and then the filter cake was washed with diethyl ether. The solid was recrystallised from absolute ethanol to yield respective 1,4-dihydropyridine derivative as a yellow solid.

SPECTRAL DATA

Yellow solid (recrystallised from ethanol). M.p. 228-230 °C (Lit. 230-232 °C). IR (KBr, cm^{-1}): 3345, 2981, 1662, 1486. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.84 (s, 3H), 1.00 (s, 3H), 1.97 (d, 1H, *J* =16 Hz), 2.16 (d, 1H, *J* =16 Hz), 2.27 (d, 1H, *J* =16.5 Hz), 2.26 (s, 3H), 2.40 (d, 1H, *J* = 17 Hz), 3.34 (s, 3H), 3.52 (s, 3H), 4.75 (s, 1H), 6.55 (d, 2H, *J* = 8.5 Hz), 6.91 (d, 2H, *J* = 8.5 Hz), 9.00 (s, 1H), 9.04 (s, 1H).

GENERAL PROCEDURE FOR THE SYNTHESIS OF DIETHYL 4-(4-(2-CHLOROQUINOLIN-4-YLOXY)PHENYL)-2,6-DIMETHYL-1,4-DIHYDRO PYRIDINE-3,5-DICARBOXYLATE (143a-j).

A mixture of substituted 2,4-dichloroquinolines 140a-j (1 mol), powdered K_2CO_3 (1.2 mol) and diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (86a) (1 mol) in DMF was stirred at 70°C for 48h. Progress of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was poured into a beaker containing ice cold water and stirred well. The solid separated out was filtered to dryness and purified the products through column chromatography of silica gel (60-120 mesh) using pet ether and ethyl acetate (7:3) mixture as eluent, which afforded the products 143a-j in pure form.

SPECTRAL DATA

Diethyl 4-(4-(2-chloroquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (143a).

Yield: 71%. M.p. 172 °C. IR (KBr,cm^{-1}): 3348 (-NH stretching), 2978 (aromatic -CH stretching), 1696 (-C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 1.25 (t, *J* = 7 Hz, 6 protons at H-

10, 10'), 2.38 (s, 6 protons at H-7, 7'), 4.15 (q, *J* = 6.6 Hz, 4 protons at H-9, 9'), 5.06 (s, 1 proton at H-4), 5.62 (bs, 1 proton at -NH), 6.50 (s, 1 proton at H-16), 7.03 (d, *J* = 8 Hz, 2 arom. protons at H-13, 13'), 7.41 (d, *J* = 8 Hz, 2 arom. protons at H-12, 12'), 7.57 (t, *J* = 7 Hz, 1 arom. proton at H-20), 7.76 (t, *J* = 7 Hz, 1 arom. proton at H-21), 7.98 (d, *J* = 8 Hz, 1 arom. proton at H-22), 8.30 (d, *J* = 8 Hz, 1 arom. proton at H-19). MS: *m/z*Calcd. For $C_{28}H_{27}ClN_2O_5$: 506.1; found. 507.0 [M+1].

Diethyl 4-(4-(2-chloro-6-methylquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate (143b).

Yield: 73%. M.p. 174-176 °C. IR (KBr,cm^{-1}): 3347 (-NH stretching), 2977 (aromatic –CH stretching), 1694 (-C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 1.25 (t, *J* = 7 Hz, 6 protons at H-10, 10'), 2.38 (s, 6 protons at H-7, 7'), 2.55 (s, 3 protons at H-20'), 4.15 (q, *J* = 6.7 Hz, 4 protons at H-9, 9'), 5.06 (s, 1 proton at H-4), 5.63 (bs, 1 proton at -NH), 6.47 (s, 1 proton at H-16), 7.02 (d, *J* = 8 Hz, 2 arom. protons at H-13, 13'), 7.30 (d, *J* = 8 Hz, 2 arom. protons at H-12, 12'), 7.58 (d, *J* = 8 Hz, 1 arom. proton at H-21), 7.87 (d, *J* = 10 Hz, 1 arom. proton at H-22), 8.06 (s, 1 arom. proton at H-19). LCMS: *m/z*Calcd. For $C_{29}H_{29}ClN_2O_5$: 520.1; found. 521.2 [M+1].

Diethyl 4-(4-(2-chloro-7-methylquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate (143c).

Yield: 67%. M.p. 180-182 °C. IR (KBr,cm^{-1}): 3305 (-NH stretching), 2980 (aromatic -CH stretching), 1695 (-C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 1.26 (t, *J* = 7 Hz, 6 protons at H-10, 10'), 2.38 (s, 6 protons at H-7, 7'), 2.56 (s, 3 protons at H-21'), 4.12 (q, *J* = 7.3 Hz, 4 protons at H-9, 9'), 5.06 (s, 1 proton at H-4), 5.63 (s, 1 proton at -NH), 6.48 (s, 1 proton at H-16), 7.03 (d, *J* = 8 Hz, 2 arom. protons at H-13, 13'), 7.42 (d, *J* = 8 Hz, 2 arom. protons at H-12, 12'), 7.66 (s, 1 arom. proton at H-22), 7.84 (d, *J* = 8 Hz, 1 arom. proton at H-20), 8.16 (d, *J* = 8 Hz, 1 arom. proton at H-19). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 14.33 (C-10, 10'), 19.62 (C-7, 7'), 24.21 (C-21'), 39.37 (C-4), 59.84 (C-9, 9'), 104.04 (C-3, 5), 105.86 (C-16), 120.30 (C-13, 13'), 121.87 (C-18), 126.72 (C-19), 129.07 (C-22), 130.02 (C-12, 12'), 130.44 (C-20), 135.61 (C-11), 141.75 (C-21), 144.05 (C-2, 6), 145.87 (C-23), 150.47 (C-17), 151.86 (C-14), 165.82 (C-15), 167.50 (C-8, 8'). MS: *m/z*Calcd. For $C_{29}H_{29}ClN_2O_5$: 520.1; found. 521.1 [M+1].

Diethyl 4-(4-(2-chloro-8-methylquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate (143d).

Yield: 80%. M.p. 172 °C. IR (KBr,cm^{-1}): 3348 (-NH stretching), 2977 (aromatic -CH stretching), 1695 (-C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 1.26 (t, *J* = 7 Hz, 6 protons at H-10, 10'), 2.38 (s, 6 protons at H-7, 7'), 2.62 (s, 3 protons at H-22'), 4.12 (q, *J* = 7.3 Hz, 4 protons at H-9, 9'), 5.06 (s, 1 proton at H-4), 5.63 (s, 1 proton at -NH), 6.49 (s, 1 proton at H-16), 7.12 (d, *J* = 8 Hz, 2 arom. protons at H-13, 13'), 7.42 (d, *J* = 8 Hz, 2 arom. protons at H-12, 12'), 7.49 (t, *J* = 6 Hz, 1 arom. proton at H-20), 7.63 (d, *J* = 6 Hz, 1 arom. proton at H-21), 8.12 (d, *J* = 8 Hz, 1 arom. proton at H-19). HRMS: *m/z*Calcd. For $C_{29}H_{29}ClN_2O_5$: 520.1765; found. 520.1758 [M^+].

Diethyl 4-(4-(2-chloro-8-methoxyquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate (143e).

Yield: 62%. M.p. 178-180 °C. IR (KBr,cm^{-1}): 3329 (-NH stretching), 2976 (aromatic -CH stretching), 1686 (-C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 1.26 (t, *J* = 7 Hz, 6 protons at H-10, 10'), 2.38 (s, 6 protons at H-7, 7'), 4.06 (s, 3 protons at H-22'), 4.13 (q, *J* = 7.3 Hz, 4 protons at H-9, 9'), 5.06 (s, 1 proton at H-4), 5.71 (s, 1 proton at -NH), 6.54 (s, 1 proton at H-16), 7.03 (d, *J* = 8 Hz, 2 arom. protons at H-13, 13'), 7.41 (d, *J* = 8 Hz, 2 arom. protons at H-12, 12'), 7.13 (d, *J* = 8 Hz, 1 arom. proton at H-21), 7.49 (t, *J* = 7 Hz, 1 arom. proton at H-20), 7.86 (d, *J* = 8 Hz, 1 arom. proton at H-19). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 14.32 (C-10, 10'), 19.53 (C-7, 7'), 39.33 (C-4), 56.02 (C-22'), 59.80 (C-9, 9'), 103.90 (C-3, 5), 105.50 (C-16), 109.60 (C-21), 113.55 (C-19), 120.33 (C-3,13'), 121.57 (C-18), 126.52 (C-20), 130.04 (C-12, 12'), 140.37 (C-11), 144.22 (C-2, 6), 146.12 (C-23), 150.50 (C-17), 151.77 (C-14), 154.50 (C-22), 163.53 (C-15), 167.53 (C-8, 8'). MS: *m/z*Calcd. For $C_{29}H_{29}ClN_2O_6$: 536.1; found. 537.1 [M+1].

Diethyl 4-(4-(2-chloro-6-fluoroquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate (143f).

Yield: 70%. M.p. 176 °C. IR (KBr,cm^{-1}): 3350 (-NH stretching), 2979 (aromatic -CH stretching), 1693 (-C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 1.25 (t, *J* = 7 Hz, 6 protons at H-10, 10'), 2.39 (s, 6 protons at H-7, 7'), 4.14 (q, *J* = 7.3 Hz, 4 protons at H-9, 9'), 5.06 (s, 1 proton at H-4), 5.63 (s, 1 proton at -NH), 6.52 (s, 1 proton at H-16), 7.02 (d, *J* = 8 Hz, 2 arom. protons at H-13, 13'), 7.41 (d, *J* = 8 Hz, 2 arom. protons at H-12, 12'), 7.87-8.02 (m, 2 arom. proton at H-19, 22), 7.52 (t, 1 arom. proton at H-21). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 14.33 (C-10, 10'), 19.67 (C-7, 7'), 39.41 (C-4), 59.85 (C-9, 9'), 104.06 (C-3, 5), 105.18 (C-16), 106.16 (C-19), 120.30 (C-13, 13'), 121.16 (C-18), 121.11 (C-21), 130.15 (C-12, 12'), 130.66 (C-22), 143.98 (C-2, 6), 145.62 (C-23), 146.26 (C-11), 150.61 (C-15), 151.53 (C-17),

159.47 (C-14), 162.25 (C-20), 167.45 (C-8, 8'). HRMS: *m/z*Calcd. For $C_{28}H_{26}ClFN_2O_5$: 524.1514; found. 524.1527 [M^+].

Diethyl 4-(4-(2,7-dichloroquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate (143g).

Yield: 74%. M.p. 186-188 °C. IR (KBr,cm^{-1}): 3347 (-NH stretching), 2978 (aromatic -CH stretching), 1694 (-C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 1.25 (t, *J* = 7 Hz, 6 protons at H-10, 10'), 2.38 (s, 6 protons at H-7, 7'), 4.12 (q, *J* = 8 Hz, 4 protons at H-9, 9'), 5.06 (s, 1 proton at H-4), 5.63 (s, 1 proton at -NH), 6.48 (s, 1 proton at H-16), 7.01 (d, *J* = 8 Hz, 2 arom. protons at H-13, 13'), 7.40 (d, *J* = 8 Hz, 2 arom. protons at H-12, 12'), 7.67 (d, *J* = 8 Hz, 1 arom. proton at H-20), 7.90 (d, *J* = 8 Hz, 1 arom. proton at H-19), 8.27 (s, 1 arom. proton at H-22). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 14.33 (C-10, 10'), 19.68 (C-7, 7'), 39.42 (C-4), 59.85 (C-9, 9'), 104.07 (C-3, 5), 105.36 (C-16), 120.28 (C-13, 13'), 121.15 (C-18), 121.28 (C-19), 129.79 (C-20), 130.17 (C-12, 12'), 132.00 (C-21), 132.37 (C-22), 143.96 (C-2, 6), 146.32 (C-11), 147.02 (C-23), 151.45 (C-17), 151.63 (C-14), 162.70 (C-15), 167.44 (C-8, 8'). MS: *m/z*Calcd. For $C_{28}H_{26}Cl_2N_2O_5$: 540.1; found. 541.1 [M+1].

Diethyl 4-(4-(6-bromo-2-chloroquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (143h).

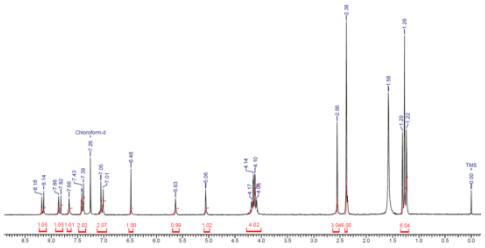
Yield: 78%. M.p. 182 °C. IR (KBr,cm^{-1}): 3349 (-NH stretching), 2978 (aromatic -CH stretching), 1696 (-C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 1.25 (t, *J* = 7 Hz, 6 protons at H-10, 10'), 2.39 (s, 6 protons at H-7, 7'), 4.12 (q, *J* = 8 Hz, 4 protons at H-9, 9'), 5.06 (s, 1 proton at H-4), 5.60 (s, 1 proton at -NH), 6.51 (s, 1 proton at H-16), 7.02 (d, *J* = 8 Hz, 2 arom. protons at H-13, 13'), 7.41 (d, *J* = 8 Hz, 2 arom. protons at H-12, 12'), 7.83-7.88 (m, 2 arom. proton at H-21, 22), 8.46 (s, 1 arom. proton at H-19). HRMS: *m/z*Calcd. For $C_{28}H_{26}BrClN_2O_5$: 584.0714; found. 584.0726 [M^+], 586.0699 [M+2].

Diethyl 4-(4-(2,7-dichloro-6-fluoroquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (143i).

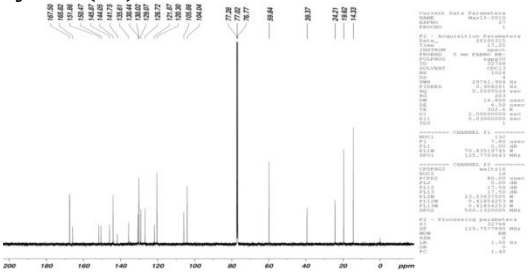
Yield: 67%. M.p. 184-186 °C. IR (KBr,cm^{-1}): 3347 (-NH stretching), 2970 (aromatic -CH stretching), 1697 (-C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 1.26 (t, *J* = 7 Hz, 6 protons at H-10, 10'), 2.38 (s, 6 protons at H-7, 7'), 4.12 (q, *J* = 8 Hz, 4 protons at H-9, 9'), 5.06 (s, 1 proton at H-4), 5.64 (s, 1 proton at -NH), 6.62 (s, 1 proton at H-16), 7.02 (d, *J* = 8 Hz, 2 arom. protons at H-13, 13'), 7.42 (d, *J* = 8 Hz, 2 arom. protons at H-12, 12'), 7.57-7.61 (m, 1 arom. proton at H-22), 7.87-8.07 (m, 1 arom. proton at H-19). MS: *m/z*Calcd. For $C_{28}H_{25}Cl_2FN_2O_5$: 558.1; found. 559.0 [M+1].

Diethyl 4-(4-(2-chlorobenzo[*h*]quinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (143j).

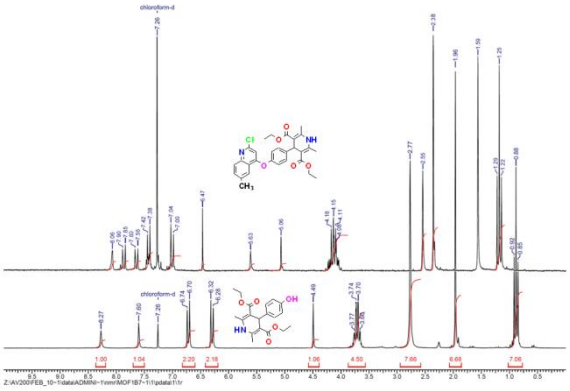
Yield: 65%. M.p. 198-200 °C. IR (KBr,cm^{-1}): 3340 (-NH stretching), 2965 (aromatic -CH stretching), 1697 (-C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ_H: 1.26 (t, *J* = 7 Hz, 6 protons at H-10, 10'), 2.38 (s, 6 protons at H-7, 7'), 4.13 (q, *J* = 8 Hz, 4 protons at H-9, 9'), 5.06 (s, 1 proton at H-4), 5.62 (s, 1 proton at -NH), 6.68 (s, 1 proton at H-16), 7.05 (d, *J* = 8 Hz, 2 arom. protons at H-13, 13'), 7.41 (d, *J* = 8 Hz, 2 arom. protons at H-12, 12'), 7.69-7.95 (m, 4 arom. proton at H-20, 21', 21'', 22''), 8.18 (d, *J* = 8 Hz, 1 arom. proton at H-19), 9.19 (d, *J* = 8 Hz, 1 arom. proton at H-22'). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 14.30 (C-10, 10'), 19.70 (C-7, 7'), 39.43 (C-4), 59.85 (C-9, 9'), 104.11 (C-3, 5), 106.39 (C-16), 117.57 (C-18), 120.29 (C-13, 13'), 120.73 (C-19), 125.05 (C-22'), 127.23 (C-21'), 127.78 (C-21''), 128.73 (C-22''), 130.07(C-12, 12'), 130.28 (C-20), 130.61 (C-22), 134.25 (C-11), 143.97 (C-2, 6), 145.90 (C-23), 147.48 (C-21), 150.41 (C-17), 152.10 (C-14), 163.35 (C-15), 167.49 (C-8, 8'). MS: *m/z*Calcd. For $C_{32}H_{29}ClN_2O_5$: 556.1; found. 557.1 [M+1].



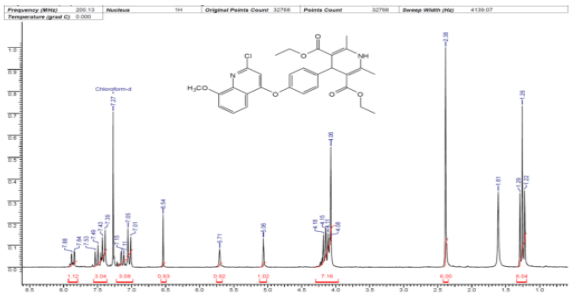
7-methylquinolin-4-yloxy) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3c).



^{13}C NMR spectrum of diethyl 4-(4-(2-chloro-7-methylquinolin-4-yloxy) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3c).

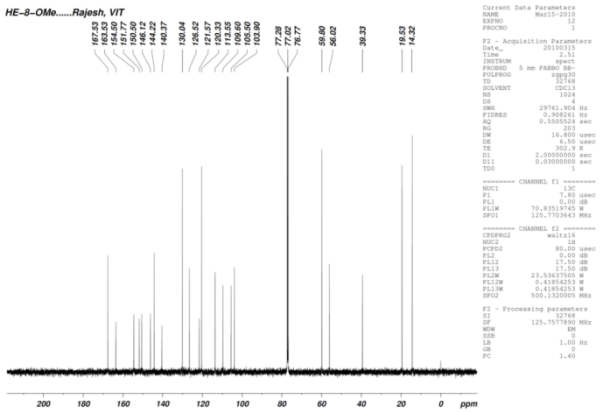


Comparative ^{1}H NMR spectra of diethyl 4-(4-(2-chloro-6-methylquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate (3b) & diethyl 4-(4-hydroxyphenyl)-

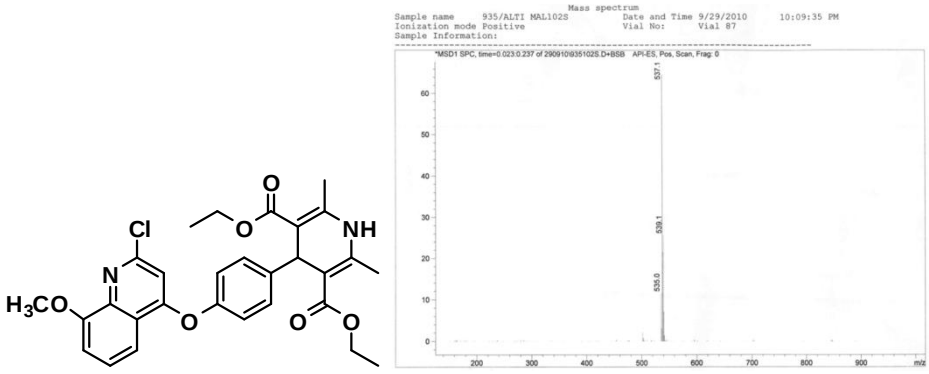


2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (2a).

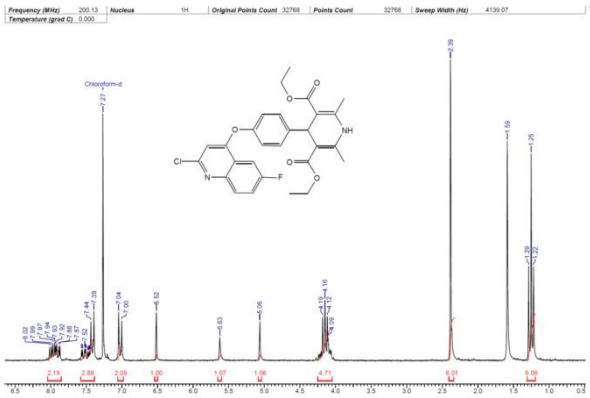
^{1}H NMR spectrum of diethyl 4-(4-(2-chloro-8-methoxyquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3e).



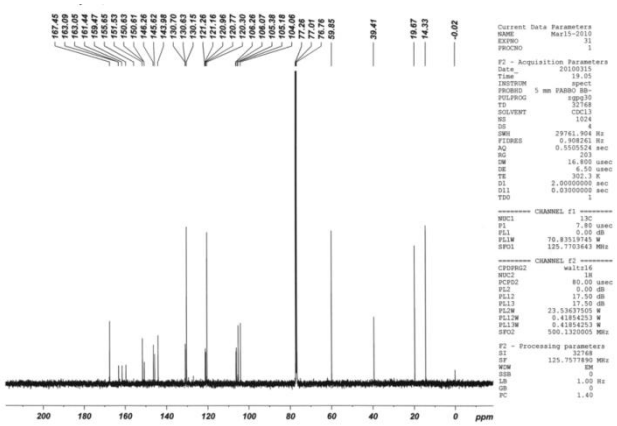
^{13}C NMR spectrum of diethyl 4-(4-(2-chloro-8-methoxyquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3e).



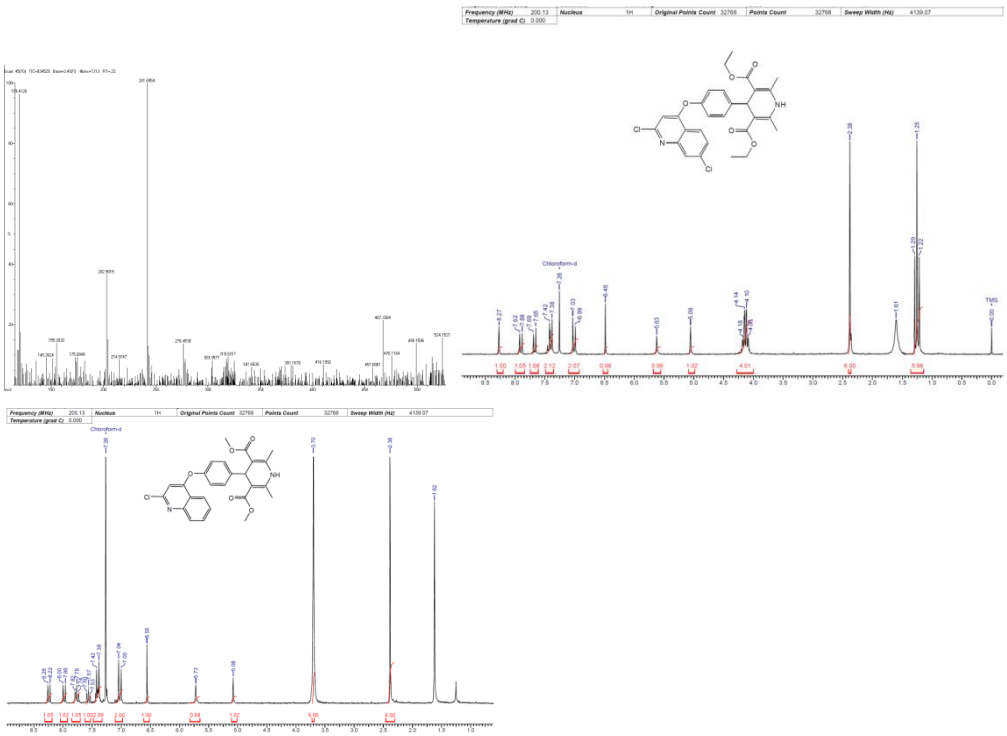
Mass spectrum of diethyl 4-(4-(2-chloro-8-methoxyquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3e).



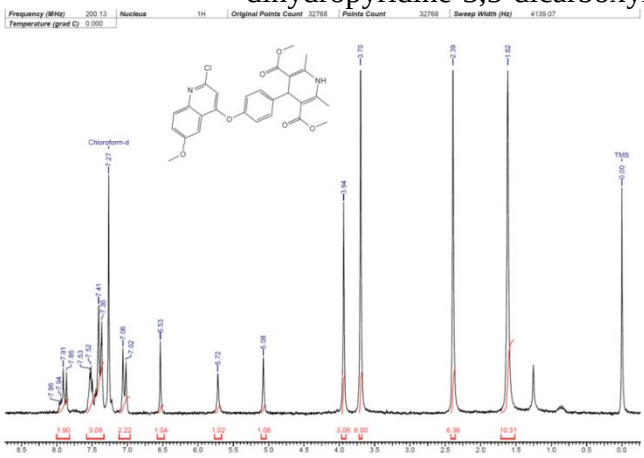
^{1}H NMR spectrum of diethyl 4-(4-(2-chloro-6-fluoroquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3f).



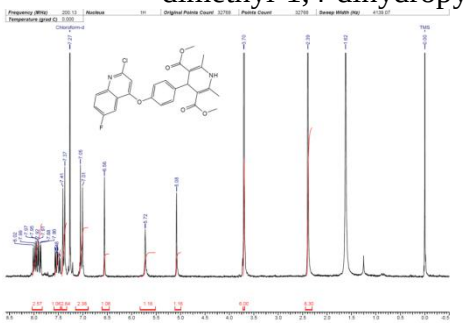
Mass spectrum of diethyl 4-(4-(2-chloro-6-fluoroquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3f).



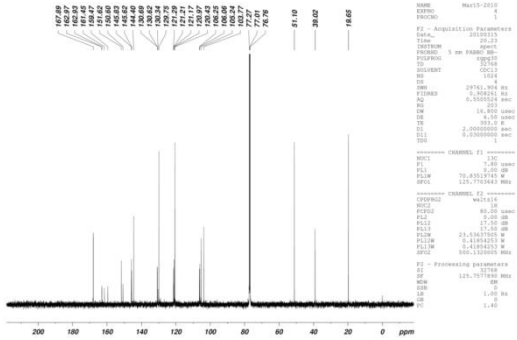
^{1}H NMR spectrum of dimethyl 4-(4-(2-chloroquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4a).



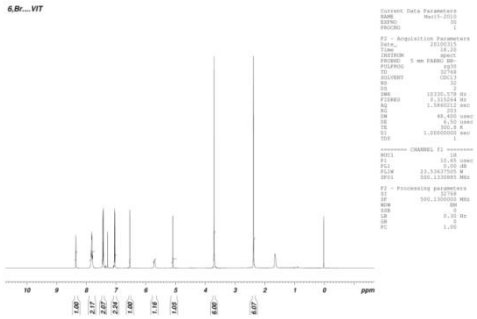
^{1}H NMR spectrum of dimethyl 4-(4-(2-chloro-6-methoxyquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4e).



^{1}H NMR spectrum of dimethyl 4-(4-(2-chloro-6-fluoroquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4f).

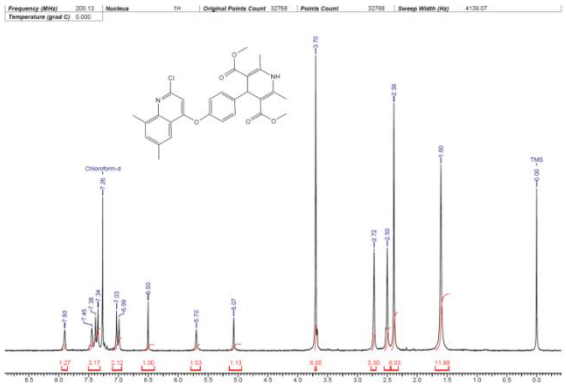


^{13}C NMR spectrum of dimethyl 4-(4-(2-chloro-6-fluoroquinolin-4-yloxy)phenyl)-2,6-dimethyl

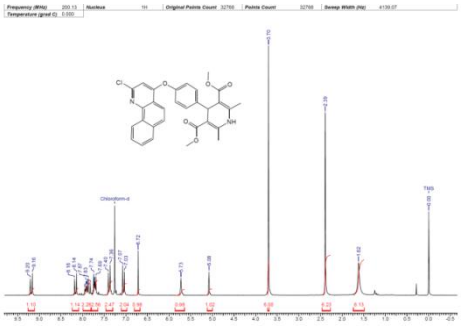


1,4-dihydropyridine-3,5-dicarboxylate (4f).

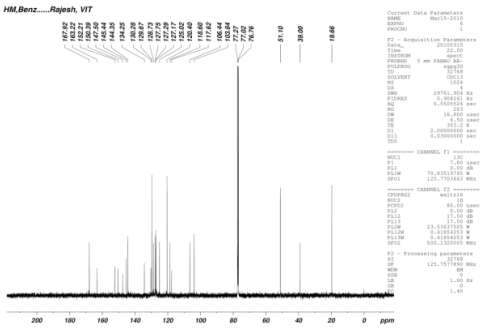
^{1}H NMR spectrum of dimethyl 4-(4-(6-bromo-2-chloroquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4h).



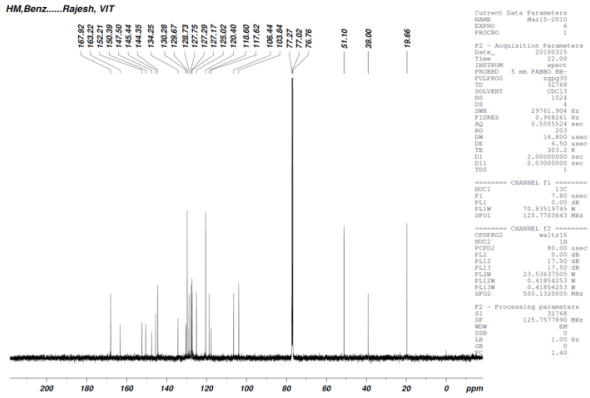
^{1}H NMR spectrum of dimethyl 4-(4-(2-chloro-6,8-dimethylquinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4i).



^{1}H NMR spectrum of dimethyl 4-(4-(2-chlorobenzo[*h*]quinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4j).



^{1}H NMR spectrum of dimethyl 4-(4-(2-chlorobenzo[*h*]quinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4j).



^{13}C NMR spectrum of dimethyl 4-(4-(2-chlorobenzo[*h*]quinolin-4-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4j).

CONCLUSION

Reaction of substituted anilines, malonic acid and $POCl_3$ gave 2,4-dichloroquinolines,which served as a building blocks for the construction of novel differentially substituted Hantzsch quinolones derivatives. Substitution at C4 of quinolone is known to be favored and the substitution at C2 is drawn to zero during the course of reaction .the azidation reaction of2,4-dichloro-6-methyl quinolones towards nucleophilic substitution at both 2 and4 positions also indicate that 4 chloro atom of dichloroquinolines is more reactive towards nucleophiles and predominately an addition- elimination process occurred.All the synthesized compounds were characterized through spectral data

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