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A one-pot four-component reaction providing quinoline-based 1,4-dihydropyridines

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Abstract In this work, highly functionalized novel quinolinyl 1,4-dihydropyridines were synthesized in a facile and efficient method. A variety of quinoline-based dihydropyridines were obtained via a one-pot four-component condensation of 2-chloroquinoline-3-carbaldehydes, arylamines, acetylenedicarboxylates and malononitrile or ethyl cyanoacetate in moderate to excellent yields. The atom-efficiency, high-yielding, mild reaction conditions, use of simple experimental procedure and prompt isolation of the products are the main advantages of these reactions.

Keywords 2-Chloroquinoline-3-carbaldehyde · 1,4-Dihydropyridine · Multicomponent reactions

Introduction

Multicomponent reactions (MCRs) are processes in which at least three different simple substrates react in one pot to give the target materials [1–3]. These reactions, which have gained significant attention during the past years, do not occur through a single-step procedure, but rather via several sequential steps involving cascades or domino reactions [4]. Simplicity, greater efficiency, and atom economy with generation of diverse and complex "drug-like" heterocyclic compounds in one-pot transformation are some of the advantages of these reactions [5–7]. These reactions are highlighted as diversity-oriented syntheses and can be extended to combinatorial strategies [8–14].

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1,4-Dihydropyridines (1,4-DHPs) as privileged pharmacophores have gained a vital place in the field of pharmaceuticals, in view of the abundance of naturally occurring DHPs and presence in many valuable commercial drugs such as nifedipine [15–19], cilnidipine [20–23], nicardipine [24, 25], and nimodipine [26–28], and as calcium channel blockers with useful effects on cardiovascular disorders including, hypertension or cardiac arrhythmias [29–38]. In addition to these, functionalized 1,4-DHPs are common to numerous bioactive compounds, which exhibit a broad range of considerable biological activities such as antidiabetic [39, 40], antitumor [41, 42], antitubercular [43, 44], radioprotective [45], neuroprotective [46, 47], bronchodilator [48], and as anti-ischemic for the treatment of Alzheimer's disease [49–51], as well as several other potentially useful activities [52–61]. Replacement of the 4-aryl group of the DHPs with the bioactive heterocyclic compounds leads to the formation of scaffolds with variant biological properties. For example, isoxazolyldihydropyridine I exhibits inhibition of the multidrug-resistance transporter [62]. Moreover, coumarin and pyrazole-based 1,4-DHPs such as II and III are known as bone anabolic [63] and potential antitubercular [64] agents, respectively (Fig. 1).

Since quinoline is a core structure present in various natural products and pharmaceuticals, compounds containing this scaffold have been extensively used in medicinal chemistry. Therefore, quinolines and their analogues are widely utilized as anticancer [65–68], antihypertensive [69, 70], bactericidal [71–75], analgesic [76, 77], antituberculosis [78, 79], and anti-inflammatory [80–82]. The diarylquinoline TMC207 (Fig. 1), developed at Johnson & Johnson Pharmaceutical Research and Development was shown to possess a new mechanism of action based on the interaction with the enzyme adenosine triphosphate (ATP) synthase, the energy source for the bacterium [83, 84]. This

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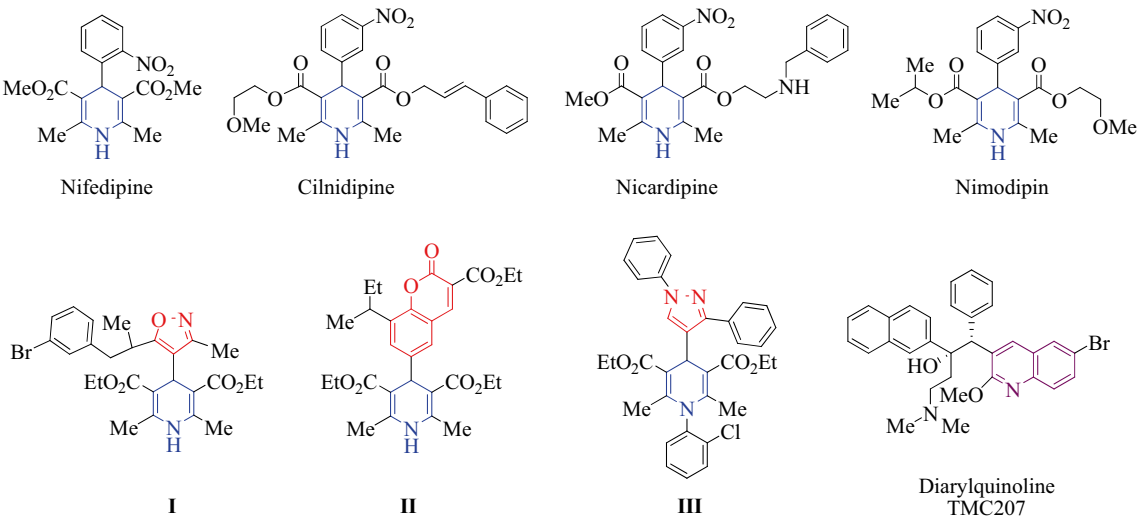


Fig. 1 Examples of some 1,4-DHPs and quinoline derivative as potential antitubercular agents

drug which is very promising against multidrug-resistant tuberculosis (MDR-TB), is currently in phase 2 clinical trials [78, 79]. It should be emphasized that the preparation of quinoline derivatives to be evaluated against TB were malaria drugs, such as quinine [85], chloroquine [86–88], mefloquine [89–91], primaquine [92, 93], and amodiaquine [94–96], which possessed moderate biological activity against TB using the Microplate Alamar Blue Assay (MABA).

Since substitution of the various functional groups on the 1,4-DHP ring often results in remarkable changes on pharmacological properties of these compounds [97–101], it is not surprising that an increasing interest has always been on the synthesis of functionalized 1,4-DHPs to organic chemists because of the biological importance associated with these compounds [102–111].

Based on the reported antitubercular activity of some 4-aryl substituted DHPs and a series of quinoline derivatives as mentioned earlier [112], we became interested in the synthesis of new compounds possessing both DHP and quinoline scaffolds in their molecular structures in order to potentially enhance their biological activities. Herein, we report the one-pot four-component synthesis of some novel 4-quinoline substituted 1,4-DHP derivatives.

Experimental

General information

All commercially available chemicals and reagents were purchased from Merck Chemical Company and used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer, in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500-AVANCE spectrometer at 300 (^{1}H) and 75 MHz (^{13}C) using $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and 77.0 ppm). Mass spectra of the products were obtained with an HP (Agilent Technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA).

Representative procedure for the synthesis of **7a–t**

To a stirred solution of 2-chloroquinoline-3-carbaldehyde (1 mmol) and malononitrile or ethyl cyanoacetate (1 mmol) in EtOH (5 mL) was added triethylamine (0.101 g, 1 mmol), and the solution was stirred at room temperature for 10 min. A solution of amine (1 mmol) and dialkylacetylenedicarboxylate (1 mmol) in EtOH (2 mL) was then added and the mixture stirred for 10 h. After completion of the reaction as indicated by TLC, the resulting solid was filtered and washed with EtOH to afford pure compounds **7a–t**.

*Dimethyl 6-amino-4-(2-chloroquinoline-3-yl)-5-cyano-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (***7a***)* White solid, mp 271–273 °C, yield: 0.41 g (86 %). IR (KBr) (ν_{max}, cm^{-1}): 3,449 (NH), 3,281 (NH), 2,171 (CN), 1,747 (C=O), 1,711 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta_H = 3.33$ (s, 3H, OMe), 3.44 (s, 3H, OMe), 5.23 (s, 1H, CH), 5.71 (s, 2H, NH_2), 7.42–7.45 (m, 2H, Ar), 7.53–7.55 (m, 3H, Ar), 7.68 (t, 1H, $J = 7.5$ Hz, Ar), 7.83 (t, 1H, $J = 7.6$ Hz, Ar),

7.84 (d, 1H, $J = 8.4$ Hz, Ar), 8.17 (d, 1H, $J = 8.0$ Hz, Ar), 8.36 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta_C = 36.7$ (CH), 51.9 (OMe), 52.4 (OMe), 58.1 (C-5 of DHP), 102.4 (C-3 of DHP), 120.4 (CN), 127.4, 127.5, 127.5, 128.0, 129.6 (2C), 130.2, 130.5 (2C), 130.9, 134.9, 137.3, 138.5, 143.1, 146.0, 149.1, 151.0 (C–Ar), 162.6 (C=O), 164.7 (C=O); EI-MS: *m/z* (%): 476 (7, M^++2), 474 (21, M^+), 415 (43), 355 (7), 312 (100), 288 (13), 176 (15), 162 (7), 139 (47), 127 (10), 111 (20), 101 (14), 77 (77); Anal. Calcd for $C_{25}H_{19}ClN_4O_4$ (474.11): C, 63.23; H, 4.03; N, 11.80 %. Found: C, 63.12; H, 4.05; N, 11.62 %.

*Dimethyl 6-amino-4-(2-chloroquinoline-3-yl)-5-cyano-1-p-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (***7b***)* White solid, mp 275–278 °C, yield: 0.46 g (94 %). IR (KBr) (ν_{max}, cm^{-1}): 3,453 (NH), 3,279 (NH), 2,169 (CN), 1,743 (C=O), 1,709 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta_H = 2.36$ (s, 3H, Me), 3.36 (s, 3H, OMe), 3.44 (s, 3H, OMe), 5.23 (s, 1H, CH), 5.68 (s, 2H, NH_2), 7.32 (s, 4H, Ar), 7.67 (t, 1H, $J = 7.4$ Hz, Ar), 7.82 (t, 1H, $J = 7.4$ Hz, Ar), 7.97 (d, 1H, $J = 8.4$ Hz, Ar), 8.15 (d, 1H, $J = 8.0$ Hz, Ar), 8.36 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta_C = 20.8$ (Me), 36.6 (CH), 51.9 (OMe), 52.4 (OMe), 58.0 (C-5 of DHP), 102.2 (C-3 of DHP), 120.4 (CN), 127.4, 127.4, 127.5, 128.0, 130.1 (2C), 130.2 (2C), 130.9, 132.3, 137.4, 138.4, 139.9, 143.3, 146.0, 149.1, 151.1 (C–Ar), 162.7 (C=O), 164.8 (C=O); EI-MS: *m/z* (%): 490 (10, M^++2), 488 (29, M^+), 429 (61), 415 (12), 370 (7), 326 (100), 312 (87), 288 (11), 252 (9), 208 (19), 176 (29), 162 (19), 139 (41), 127 (22), 111 (17), 101 (28), 91 (91), 77 (33 %), Anal. Calcd for $C_{26}H_{21}ClN_4O_4$ (488.13): C, 63.87; H, 4.33; N, 11.46 %. Found: C, 63.79; H, 4.35; N, 11.42 %.

*Dimethyl 6-amino-4-(2-chloroquinoline-3-yl)-5-cyano-1-(3,4-dimethylphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (***7c***)* White solid, mp 271–273 °C, yield: 0.46 g, (92 %). IR (KBr) (ν_{max}, cm^{-1}): 3,469 (NH), 3,423 (NH), 2,196 (CN), 1,728 (C=O), 1,714 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta_H = 2.27$ (s. 6H, 2Me), 3.47 (s, 3H, OMe), 3.50 (s, 3H, OMe), 4.37 (s, 2H, NH_2), 5.32 (s, 1H, CH), 7.06–7.09 (m, 2H, Ar), 7.21 (d, 1H, $J = 7.7$ Hz, Ar), 7.54 (t, 1H, $J = 7.3$ Hz, Ar), 7.69 (t, 1H, $J = 7.5$ Hz, Ar), 7.84 (d, 1H, $J = 8.0$ Hz, Ar), 7.98 (d, 1H, $J = 8.4$ Hz, Ar), 8.14 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta_C = 19.6$ (Me), 19.8 (Me), 36.4 (CH), 52.1 (OMe), 52.6 (OMe), 60.2 (C-5 of DHP), 103.1 (C-3 of DHP), 120.2 (CN), 127.0, 127.3, 127.5, 127.6, 128.2, 130.4, 130.8, 130.9, 132.1, 136.7, 138.4, 138.8, 139.8, 143.2, 146.8, 149.8, 150.7 (C–Ar), 163.3 (C=O), 165.4 (C=O); EI-MS: *m/z* (%): 504 (7, M^++2), 502 (21, M^+), 443 (38), 383 (5), 340 (100), 326 (10), 312 (6), 176 (14), 162 (9), 127 (10), 91 (10), 77 (38 %). Anal. Calcd for $C_{27}H_{23}ClN_4O_4$: C, 64.48; H, 4.61; N, 11.14 %. Found: C, 64.46; H, 4.52; N, 11.17 %.

*Dimethyl 6-amino-4-(2-chloro-6-methylquinoline-3-yl)-1-(4-chlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (***7d***)* Pale yellow solid, mp 241–243 °C, yield: 0.44 g (84 %). IR (KBr) (ν_{max}, cm^{-1}): 3,454 (NH), 3,282 (NH), 2,171 (CN), 1,749 (C=O), 1,703 (C=O); ^{1}H-NMR (300 MHZ, $CDCl_3$): $\delta_H = 2.52$ (s, 3H, Me), 3.49 (s, 3H, OMe), 3.50 (s, 3H, OMe), 4.31 (s, 2H, NH_2), 5.24 (s, 1H, CH), 7.32 (d, 2H, $J = 8.2$ Hz, Ar), 7.45 (d, 2H, $J = 8.2$ Hz, Ar), 7.52 (d, 1H, $J = 8.5$ Hz, Ar), 7.60 (s, 1H, Ar), 7.86 (d, 1H, $J = 8.5$ Hz, Ar), 8.01 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta_C = 21.6$ (Me), 36.6 (CH), 52.2 (OMe), 52.9 (OMe), 61.0 (C-5 of DHP), 103.8 (C-3 of DHP), 119.8 (CN), 126.4, 127.6, 127.8, 130.3 (2C), 131.7 (2C), 132.8, 133.2, 136.0, 137.0, 137.2, 138.0, 142.6, 145.4, 148.7, 150.1 (C–Ar), 163.2 (C=O), 165.2 (C=O); EI-MS: *m/z* (%): 526 (1, M^++4), 524 (10, M^++2), 522 (14, M^+), 487 (9), 463 (25), 421 (9), 369 (11), 346 (100), 304 (13), 247 (12), 176 (18), 140 (16), 111 (24), 75 (21 %). Anal. Calcd for $C_{26}H_{20}Cl_2N_4O_4$ (522.09): C, 59.67; H, 3.85; N, 10.71 %. Found: C, 59.69; H, 3.85; N, 10.68 %.

*Dimethyl 6-amino-4-(2-chloro-6-methylquinoline-3-yl)-5-cyano-1-(3,4-dimethylphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (***7e***)* Pale yellow solid, mp 257–259 °C, yield: 0.46 g (89 %). IR (KBr) (ν_{max}, cm^{-1}): 3,450 (NH), 3,282 (NH), 2,170 (CN), 1,750 (C=O), 1,707 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta_H = 2.29$ (s, 6H, 2Me), 2.53 (s, 3H, Me), 3.48 (s, 3H, OMe), 3.50 (s, 3H, OMe), 4.32 (s, 2H, NH_2), 5.30 (s, 1H, CH), 7.07–7.11 (m, 2H, Ar), 7.23 (d, 1H, $J = 7.8$ Hz, Ar), 7.52 (d, 1H, $J = 8.4$ Hz, Ar), 7.61 (s, 1H, Ar), 7.88 (d, 1H, $J = 8.5$ Hz, Ar), 8.05 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta_C = 19.6$ (Me), 19.8 (Me), 21.6 (Me), 36.4 (CH), 52.0 (OMe), 52.6 (OMe), 60.4 (C-5 of DHP), 103.2 (C-3 of DHP), 120.2 (CN), 126.4, 127.3, 127.7, 127.9, 130.8, 130.9, 132.1, 132.6, 136.6, 137.1, 137.9, 138.8, 139.8, 143.2, 145,4, 148.8, 150.6 (C–Ar), 163.3 (C=O), 165.4 (C=O); EI-MS: *m/z* (%): 518 (7, M^++2), 516 (21, M^+), 457 (38), 340 (100), 310 (22), 282 (23), 222 (9), 176 (20), 160 (70), 140 (18), 123 (36), 105 (29), 91 (13), 77 (49 %). Anal. Calcd for $C_{28}H_{25}ClN_4O_4$ (516.16): C, 65.05; H, 4.87; N, 10.84 %. Found: C, 65.11; H, 4.76; N, 10.87 %.

*Dimethyl 6-amino-4-(2-chloro-6-methoxyquinoline-3-yl)-5-cyano-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (***7f***)* White solid, mp 213–215 °C, yield: 0.42 g (83 %). IR (KBr) (ν_{max}, cm^{-1}): 3,457 (NH), 3,340 (NH), 2,185

(CN), 1,745 (C=O), 1,693 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 3.41 (s, 3H, OMe), 3.48 (s, 3H, OMe), 3.90 (s, 3H, OMe), 4.36 (s, 2H, NH_2), 5.25 (s, 1H, CH), 7.07 (d, 1H, J = 2.4 Hz, Ar), 7.29-7.45 (m, 6H, Ar), 7.85 (d, 1H, J = 9.2 Hz, Ar), 8.01 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 36.6 (CH), 52.1 (OMe), 52.7 (OMe), 55.7 (OMe), 60.4 (C-5 of DHP), 103.2 (C-3 of DHP), 105.0 (C-5 of quinoline), 120.1 (CN), 123.2, 128.7, 129.5, 130.0 (2C), 130.3 (2C), 130.7, 134.7, 136.6, 137.4, 142.8, 142.9, 147.1, 150.4, 158.1 (C–Ar), 163.3 (C=O), 165.3 (C=O); EI-MS: *m/z* (%): 506 (5, M^++2), 504 (15, M^+), 445 (33), 403 (14), 340 (20), 312 (100), 282 (9), 254 (24), 236 (7), 192 (12), 176 (18), 160 (32), 136 (19), 120 (64), 104 (9), 77 (73 %). Anal. Calcd for $C_{26}H_{21}ClN_4O_5$ (504.12): C, 61.85; H, 4.19; N, 11.10 %. Found: C, 61.93; H, 4.17; N, 11.15 %.

*Dimethyl 6-amino-4-(2-chloro-6-methoxyquinoline-3-yl)-5-cyano-1-m-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (***7g***)* White solid, mp 252–255 °C, 0.41 g (79 %). IR (KBr) (ν_{max}, cm^{-1}): 3,465 (NH), 3,344 (NH), 2,182 (CN), 1,742 (C=O), 1,694 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 2.39 (s, 3H, Me), 3.47 (s, 3H, OMe), 3.51 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.31 (s, 2H, NH_2), 5.30 (s, 1H, CH), 7.09 (d, 1H, J = 2.7 Hz, Ar), 7.17 (br s, 2H, Ar), 7.28–7.40 (m, 3H, Ar), 7.88 (d, 1H, J = 9.2 Hz, Ar), 8.01 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 21.2 (Me), 36.6 (CH), 52.1 (OMe), 52.6 (OMe), 55.7 (OMe), 60.5 (C-5 of DHP), 103.3 (C-3 of DHP), 105.0 (C-5 of quinoline), 120.1 (CN), 123.1, 127.2, 128.7, 129.6, 129.7, 130.7, 131.5, 134.6, 136.6, 137.4, 140.4, 142.8, 143.0, 147.2, 150.4, 158.1 (C–Ar), 163.3 (C=O), 165.4 (C=O); EI-MS: *m/z* (%): 520 (6, M^++2), 518 (18, M^+), 459 (33), 417 (10), 365 (9), 346 (14), 326 (100), 268 (9), 236 (7), 208 (11), 192 (8), 176 (14), 157 (10), 133 (9), 91 (62 %). Anal. Calcd for $C_{27}H_{23}ClN_4O_5$ (518.14): C, 62.49; H, 4.47; N, 10.80 %. Found: C, 62.64; H, 4.37; N, 10.86 %.

*Dimethyl 6-amino-4-(2-chloro-6-methoxyquinoline-3-yl)-1-(4-chlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (***7h***)* White solid, mp 214–216 °C, yield: 0.43 g (80 %). IR (KBr) (ν_{max}, cm^{-1}): 3,579 (NH), 3,459 (NH), 2,184 (CN), 1,732 (C=O), 1,701 (C=O); ^{1}H-NMR (300 MHZ, $CDCl_3$): δ_H = 3.48 (s, 3H, OMe), 3.49 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.36 (s, 2H, NH_2), 5.23 (s, 1H, CH), 7.08 (d, 1H, J = 2.6 Hz, Ar), 7.30–7.33 (m, 3H, Ar), 7.43 (d, 2H, J = 8.6 Hz, Ar), 7.85 (d, 1H, J = 9.2 Hz, Ar), 7.99 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 36.7 (CH), 52.2 (OMe), 52.9 (OMe), 55.7 (OMe), 60.8 (C-5 of DHP), 103.6 (C-3 of DHP), 105.0 (C-5 of quinoline), 119.9 (CN), 123.3, 128.7, 129.5, 130.2 (2C), 131.8 (2C), 133.2, 136.2, 136.9, 137.5, 142.6, 142.8, 147.0, 150.1, 158.2 (C–Ar), 163.2 (C=O), 165.2 (C=O); EI-MS: *m/z* (%): 542 (1, M^++4), 540 (6, M^++2), 538 (9, M^+), 503 (9), 479 (23), 437 (6), 385 (9), 346 (100), 288 (6), 228 (9), 204 (10), 192 (13), 176 (15), 157 (13), 111 (30 %). Anal. Calcd for $C_{26}H_{20}Cl_2N_4O_5$ (538.08): C, 57.90; H, 3.74; N, 10.39 %. Found: C, 57.88; H, 3.75; N, 10.39 %.

*Diethyl 6-amino-4-(2-chloroquinoline-3-yl)-5-cyano-1-(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (***7i***)* Pale yellow solid, mp 220–222 °C, yield: 0.47 g (88 %).IR (KBr) (ν_{max}, cm^{-1}): 3,461 (NH), 3,296 (NH), 2,167 (CN), 1,737 (C=O), 1,696 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 1.00 (t, 6H, J = 7.1 Hz, $2OCH_2\underline{Me}$), 3.82 (s, 3H, O$\underline{Me}$), 3.86-4.00 (m, 4H, $2OC\underline{H}_2Me$), 4.31 (s, 2H, NH_2), 5.33 (s, 1H, CH), 6.95 (d, 2H, J = 8.8 Hz, Ar), 7.30 (d, 2H, J = 8.8 Hz, Ar), 7.54 (t, 1H, J = 7.5 Hz, Ar), 7.69 (t, 1H, J = 7.6 Hz, Ar), 7.84 (d, 1H, J = 8.0 Hz, Ar), 7.99 (d, 1H, J = 8.4 Hz, Ar), 8.14 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 13.5 ($OCH_2\underline{Me}$), 13.8 ($OCH_2\underline{Me}$), 36.7 (CH), 55.6 (OMe), 60.3 (O$\underline{C}H_2$Me), 61.0 (O$\underline{C}H_2$Me), 62.1 (C-5 of DHP), 103.2 (C-3 of DHP), 114.9 (2C), 120.2 (CN), 126.8, 127.0, 127.5, 127.6, 128.2, 130.3, 131.8 (2C), 136.7, 138.7, 143.4, 146.7, 149.9, 150.8, 160.9 (C–Ar), 162.8 (C=O), 164.8 (C=O); EI-MS: *m/z* (%): 534 (10, M^++2), 532 (27, M^+), 459 (57), 431 (9), 395 (9), 370 (100), 342 (14), 296 (9), 270 (67), 255 (8), 227 (13), 209 (6), 181 (8), 162 (9), 127 (9), 92 (14), 77 (16 %). Anal. Calcd for $C_{28}H_{25}ClN_4O_5$ (532.15): C, 63.10; H, 4.73; N, 10.51 %. Found: C, 63.02; H, 4.78; N, 10.49 %.

*Diethyl 6-amino-4-(2-chloroquinoline-3-yl)-5-cyano-1-p-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (***7j***)* Pale yellow solid, mp 208–210 °C, yield: 0.46 g (89 %). IR (KBr) (ν_{max}, cm^{-1}): 3,462 (NH), 3,295 (NH), 2,169 (CN), 1,740 (C=O), 1,694 (C=O); ^{1}H-NMR (300 MHZ, $CDCl_3$): δ_H = 0.96-1.03 (m, 6H, $2OCH_2\underline{Me}$), 2.39 (s, 3H, Me), 3.84-4.00 (m, 4H, $2OC\underline{H}_2Me$), 4.29 (s, 2H, NH_2), 5.35 (s, 1H, CH), 7.27 (s, 4H, Ar), 7.55 (t, 1H, J = 7.5 Hz, Ar), 7.70 (t, 1H, J = 7.6 Hz, Ar), 7.84 (d, 1H, d, J = 7.9 Hz, Ar), 8.00 (d, 1H, J = 8.4 Hz, Ar), 8.15 (s,1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 13.4 ($OCH_2\underline{Me}$), 13.8 ($OCH_2\underline{Me}$), 21.3 (Me), 36.7 (CH), 60.4 (O$\underline{C}H_2$Me), 61.0 (O$\underline{C}H_2$Me), 62.1 (C-5 of DHP), 103.3 (C-3 of DHP), 120.1 (CN), 127.0, 127.5, 127.6, 128.2, 130.2 (2C), 130.3, 130.5 (2C), 132.0, 136.8, 138.7, 141.1, 143.2, 146.8, 149.9, 150.5 (C–Ar), 162.8 (C=O), 164.8 (C=O); EI-MS: *m/z* (%): 518 (4, M^++2), 516 (12, M^+), 443 (38), 400 (53), 354 (100), 316 (17), 281 (22), 254 (46), 215 (12), 199 (18), 171 (20), 162 (7), 157 (23), 127 (9), 115 (28), 93 (39), 77 (14 %); Anal. Calcd for $C_{28}H_{25}ClN_4O_4$ (514.14): C, 65.05; H, 4.87; N, 10.84 %. Found: C, 64.81; H, 4.72; N, 10.84 %.

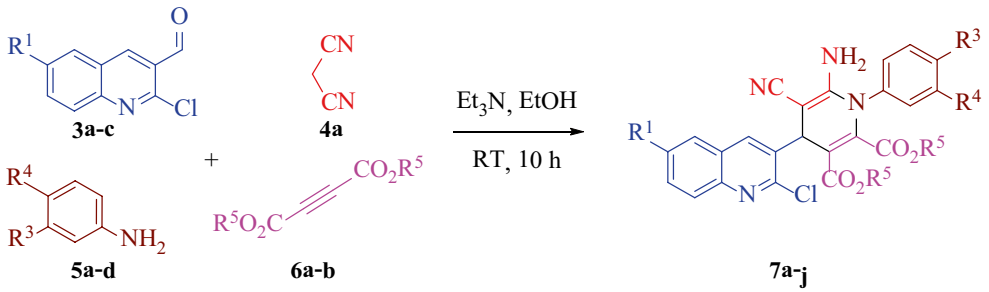
*5-Ethyl 2,3-dimethyl 6-amino-4-(2-chloroquinoline-3-yl)-1-p-tolyl-1,4-dihydropyridine-2,3,5-tricarboxylate (**7k**)* White solid, mp 228–230 °C, yield: 0.49 g, (91 %). IR (KBr) (ν_{max}, cm^{-1}): 3,409 (NH), 3,258 (NH), 1,740 (C=O), 1,685 (C=O), 1,660 (C=O); ^{1}H-NMR (300 MHZ, $CDCl_3$): δ_H = 1.12 (t, 3H, J = 7.1 Hz, $OCH_2\underline{Me}$), 2.40 (s, 3H, Me), 3.42 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.90-4.08 (m, 2H, $OC\underline{H}_2Me$), 5.52 (s, 1H, CH), 6.40 (br s, 2H, NH_2), 7.31 (s, 4H, Ar), 7.51 (t, 1H, J = 7.5 Hz, Ar), 7.66 (t,1H, J = 7.6 Hz, Ar), 7.81 (d, 1H, J = 8.1 Hz, Ar), 7.98 (d, 1H, J = 8.4 Hz, Ar), 8.23 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 14.5 ($OCH_2\underline{Me}$), 21.3 (Me), 36.0 (CH), 52.7 (OMe), 52.5 (OMe), 59.5 ($O\underline{C}H_2Me$), 78.9 (C-5 of DHP), 105.6 (C-3 of DHP), 126.6, 127.3, 127.6, 128.1, 129.9, 130.3 (2C), 130.5 (2C), 132.1, 139.6, 139.4, 140.8, 142.3, 146.3, 150.7, 151.7 (C–Ar), 163.8 (C=O), 166.1 (C=O), 169.5 (C=O); EI-MS: *m/z* (%): 537 (3, M^++2), 535 (9, M^+), 476 (29), 462 (79), 426 (12), 387 (13), 373 (100), 340 (53), 327 (11), 308 (8), 295 (27), 267 (9), 235 (7), 162 (7), 91 (43 %). Anal. Calcd for $C_{28}H_{26}ClN_3O_6$ (535.15): C, 62.75; H, 4.89; N, 7.84 %. Found: C, 62.68; H, 4.89; N, 7.82 %.

*5-Ethyl 2,3-dimethyl 6-amino-4-(2-chloroquinoline-3-yl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (**7l**)* White solid, mp 234–237 °C, yield: 0.47 g (85 %). IR (KBr) (ν_{max}, cm^{-1}): 3,417 (NH), 3,259 (NH), 1,741 (C=O), 1,686 (C=O), 1,657 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 1.11 (t, 3H, J = 7.0 Hz, $OCH_2\underline{Me}$), 3.43 (s, 3H, OMe), 3.57 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.90-4.07 (m, 2H, $OC\underline{H}_2Me$), 5.51 (s, 1H, CH), 6.41 (br s, 2H, NH_2), 6.98 (d, 2H, J = 8.6 Hz, Ar), 7.34 (d, 2H, J = 8.6 Hz, Ar), 7.50 (t, 1H, J = 7.3 Hz, Ar), 7.65 (t, 1H, J = 7.5 Hz, Ar), 7.79 (d, 1H, J = 8.0 Hz, Ar), 7.97 (d, 1H, J = 8.4 Hz, Ar), 8.22 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 14.5 ($OCH_2\underline{Me}$), 36.1 (CH), 51.7 (OMe), 52.5 (OMe), 55.6 (OMe), 59.5 ($O\underline{C}H_2Me$), 78.8 (C-5 of DHP), 105.4 (C-3 of DHP), 114.9 (2C), 126.3, 127.0, 127.3, 127.6, 128.1, 129.9, 131.8 (2C), 139.5, 139.9, 142.6, 146.3, 150.7, 151.9, 160.7 (C–Ar), 163.8 (C=O), 166.0 (C=O), 169.4 (C=O); EI-MS: *m/z* (%): 553 (3, M^++2), 551 (9, M^+), 492 (22), 478 (70), 449 (8), 420 (24), 403 (9), 389 (100), 361 (17), 343 (12), 311 (24), 247 (74), 173 (67), 162 (6), 101 (20), 77 (22 %). Anal. Calcd for $C_{28}H_{26}ClN_3O_7$ (551.15): 60.93; H, 4.75; N, 7.61 %. Found: C, 60.84; H, 4.59; N, 7.67 %.

*5-Ethyl 2,3-dimethyl 6-amino-1-(4-chlorophenyl)-4-(2-chloroquinoline-3-yl)-1,4-dihydropyridine-2,3,5-tricarboxylate (**7m**)* White solid, mp 242–243 °C, yield: 0.49 g (88 %). IR (KBr) (ν_{max}, cm^{-1}): 3,403 (NH), 3,226 (NH), 1,740 (C=O), 1,689 (C=O), 1,662 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 1.10 (t, 3H, J = 7.1 Hz, $OCH_2\underline{Me}$), 3.45 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.93–4.08 (m, 2H, $OC\underline{H}_2Me$), 5.51 (s, 1H, CH), 6.37 (br s, 2H, NH_2), 7.40 (d, 2H, J = 8.5 Hz, Ar), 7.46-7.54 (m, 3H, Ar), 7.67 (t, 1H, J = 7.3 Hz, Ar), 7.81 (d, 1H, J = 7.8 Hz, Ar), 7.98 (d, 1H, J = 8.4 Hz, Ar), 8.20 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 14.4 ($OCH_2\underline{Me}$), 36.3 (CH), 51.8 (OMe), 52.6 (OMe), 59.6 ($O\underline{C}H_2Me$), 79.1 (C-5 of DHP), 106.0 (C-3 of DHP), 126.7, 127.3, 127.5, 128.1, 130.0, 130.2 (2C), 132.0 (2C), 133.4, 136.7, 138.9, 140.0, 141.8, 146.3, 150.6, 151.3 (C–Ar), 163.6 (C=O), 165.9 (C=O), 169.4 (C=O); EI-MS: *m/z* (%): 559 (0.4, M^++4), 557 (2, M^++2), 555 (4, M^+), 496 (15), 482 (39), 446 (8), 407 (5), 393 (100), 365 (7), 347 (6), 315 (9), 287 (6), 261 (9), 162 (6), 152 (8), 127 (6), 111 (12 %). Anal. Calcd for $C_{27}H_{23}Cl_2N_3O_6$ (555.10): C, 58.28; H, 4.17; N, 7.55 %. Found: C, 58.48; H, 3.99; N, 7.52 %.

*5-Ethyl 2,3-dimethyl 6-amino-4-(2-chloro-6-methylquinoline-3-yl)-1-phenyl-1,4-dihydropyridine-2,3,5-tricarboxylate (**7n**)* Pale yellow solid, mp 188–190 °C, yield: 0.45 g (86 %). IR (KBr) (ν_{max}, cm^{-1}): 3,337 (NH), 3,257 (NH), 1,756 (C=O), 1,705 (C=O), 1,656 (C=O); ^{1}H-NMR (300 MHZ, $CDCl_3$): δ_H = 1.13 (t, 3H, J = 7.1 Hz, $OCH_2\underline{Me}$), 2.52 (s, 3H, Me), 3.39 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.94–4.09 (m, 2H, $OC\underline{H}_2Me$), 5.51 (s, 1H, CH), 6.38 (br s, 2H, NH_2), 7.44-7.57 (m, 7H, Ar), 7.88 (d, 1H, J = 8.5 Hz, Ar), 8.15 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 14.5 ($OCH_2\underline{Me}$), 21.5 (Me), 36.1 (CH), 51.7 (OMe), 52.4 (OMe), 59.5 ($O\underline{C}H_2Me$), 79.1 (C-5 of DHP), 105.9 (C-3 of DHP), 126.1, 127.5, 127.6, 127.8, 129.9 (2C), 130.5, 130.7 (2C), 132.2, 135.0, 136.6, 139.3, 142.1, 144.9, 149.8, 151.1 (C–Ar), 163.7 (C=O), 166.0 (C=O), 169.5 (C=O); EI-MS: *m/z* (%): 537 (3, M^++2), 535 (9, M^+), 476 (21), 462 (65), 426 (16), 359 (100), 331 (15), 313 (12), 281 (23), 253 (9), 221 (6), 176 (7), 140 (16), 115 (9), 77 (41 %). Anal. Calcd for $C_{28}H_{26}ClN_3O_6$ (535.15): C, 62.75; H, 4.89; N, 7.84 %. Found: C, 62.75; H, 4.91; N, 7.84 %.

*5-Ethyl 2,3-dimethyl 6-amino-4-(2-chloro-6-methylquinoline-3-yl)-1-p-tolyl-1,4-dihydropyridine-2,3,5-tricarboxylate (**7o**)* Pale yellow solid, mp 125–128 °C, yield: 0.49 g (89 %). R_f (33 % EtOAc/hexane) 0.60; IR (KBr) (ν_{max}, cm^{-1}): 3,402 (NH), 3,261 (NH), 1,741 (C=O), 1,689 (C=O), 1,658 (C=O); ^{1}H-NMR (300 MHZ, $CDCl_3$): δ_H = 1.13 (t, 3H, J = 7.1 Hz, $OCH_2\underline{Me}$), 2.41 (s, 3H, Me), 2.52 (s, 3H, Me), 3.42 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.91-4.09 (m, 2H, $OC\underline{H}_2Me$), 5.50 (s, 1H, CH), 6.41 (br s, 2H, NH_2), 7.32 (s, 4H, Ar), 7.50 (d, 1H, J = 8.6 Hz, Ar), 7.56 (s, 1H, Ar), 7.87 (d, 1H, J = 8.6 Hz, Ar), 8.14 (s, 1H,



Scheme 2 Synthesis of quinoline-based DHPs **7a–j**

Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 14.5 ($OCH_2\underline{Me}$), 21.3 (Me), 21.6 (Me), 36.0 (CH), 51.7 (OMe), 52.4 (OMe), 59.5 ($O\underline{C}H_2Me$), 79.0 (C-5 of DHP), 105.7 (C-3 of DHP), 126.1, 127.6, 127.8, 130.3 (2C), 130.5 (2C), 132.2 (2C), 136.6, 139.3, 139.5, 140.8, 142.3, 144.9, 149.8, 151.7 (C–Ar), 163.8 (C=O), 166.1 (C=O), 169.5 (C=O); EI-MS: *m/z* (%): 551 (2, M^++2), 549 (6, M^+), 490 (13), 476 (34), 440 (7), 415 (10), 373 (100), 345 (7), 327 (5), 295 (11), 267 (4), 176 (3), 140 (8), 115 (5), 91 (18 %). Anal. Calcd for $C_{29}H_{28}ClN_3O_6$ (549.17): C, 63.33; H, 5.13; N, 7.64 %. Found: C, 63.31; H, 5.33; N, 7.92 %.

Triethyl 6-amino-4-(2-chloroquinoline-3-yl)-1-m-tolyl-1,4-dihydropyridine-2,3,5-tricarboxylate (**7p**) Pale yellow solid, mp 120–123 °C, yield: 0.48 g (85 %). IR (KBr) (ν_{max}, cm^{-1}): 3,258 (NH), 3,189 (NH), 1,743 (C=O), 1,703 (C=O), 1,658 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 0.92 (t, 3H, *J* = 7.0 Hz, $OCH_2\underline{Me}$), 1.12 (t, 6H, *J* = 7.0 Hz, $2OCH_2\underline{Me}$), 2.41 (s, 3H, Me), 3.79-4.07 (m, 6H, $3OC\underline{H}_2Me$), 5.52 (s, 1H, CH), 6.41 (br s, 2H, NH_2), 7.26–7.31 (m, 3H, Ar), 7.36-7.41 (m, 1H, Ar), 7.52 (t, 1H, *J* = 7.4 Hz, Ar), 7.66 (t, 1H, *J* = 7.6 Hz, Ar), 7.81 (d, 1H, *J* = 8.0 Hz, Ar), 7.98 (d, 1H, *J* = 8.4 Hz, Ar), 8.24 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 13.4 ($OCH_2\underline{Me}$), 14.0 ($OCH_2\underline{Me}$), 14.5 ($OCH_2\underline{Me}$), 21.2 (Me), 36.5 (CH), 59.4 ($O\underline{C}H_2Me$), 60.8 ($O\underline{C}H_2Me$), 61.7 ($O\underline{C}H_2Me$), 78.5 (C-5 of DHP), 105.5 (C-3 of DHP), 126.6, 127.3, 127.5, 127.8, 128.1, 129.6, 129.8, 131.1, 131.3, 134.9, 139.1, 140.1, 140.3, 142.3, 146.3, 150.7, 151.8 (C–Ar), 163.8 (C=O), 166.1 (C=O), 169.5 (C=O); EI-MS: *m/z* (%): 566 (3, M^++2), 564 (9, M^+), 518 (6), 490 (56), 444 (3), 418 (5), 401 (100), 373 (5), 354 (6), 308 (4), 255 (10), 209 (5), 162 (3), 152 (4), 127 (4), 91 (14 %). Anal. Calcd for $C_{30}H_{30}ClN_3O_6$ (563.18): C, 63.88; H, 5.36; N, 7.45 %. Found: C, 63.81; H, 5.38; N, 7.45 %.

Triethyl 6-amino-4-(2-chloroquinoline-3-yl)-1-(3,4-dimethylphenyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (**7q**) White solid, mp 153–155 °C, yield: 0.53 g (92 %). IR (KBr) (ν_{max}, cm^{-1}): 3,398 (NH), 3,255 (NH), 1,734 (C=O), 1,659 (C=O), 1,637 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 0.93 (t, 3H, *J* = 7.0 Hz, $OCH_2\underline{Me}$), 1.12 (t, 6H, *J* = 7.0 Hz, $2OCH_2\underline{Me}$), 2.29 (s, 6H, 2Me), 3.83-4.06 (m, 6H, $3OC\underline{H}_2Me$), 5.51 (s, 1H, CH), 6.43 (b s, 2H, NH_2), 7.14–7.25 (m, 3H, Ar), 7.50 (t, 1H, *J* = 7.3 Hz, Ar), 7.65 (t, 1H, *J* = 7.6 Hz, Ar), 7.80 (d, 1H, *J* = 8.0 Hz, Ar), 7.97 (d, 1H, *J* = 8.3 Hz, Ar), 8.23 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 13.4 ($OCH_2\underline{Me}$), 14.0 ($OCH_2\underline{Me}$), 14.5 ($OCH_2\underline{Me}$), 19.8 (Me), 19.8 (Me), 36.4 (CH), 59.4 ($O\underline{C}H_2Me$), 60.7 ($O\underline{C}H_2Me$), 61.6 ($O\underline{C}H_2Me$), 78.5 (C-5 of DHP), 105.3 (C-3 of DHP), 126.6, 127.3, 127.5, 127.9, 128.1, 129.8, 130.8, 131.4, 132.4, 138.5, 139.3, 139.4, 140.2, 142.5, 146.3, 150.7, 152.0 (C–Ar), 163.3 (C=O), 165.6 (C=O), 169.5 (C=O); EI-MS: *m/z* (%): 580 (3, M^++2), 578 (9, M^+), 532 (6), 504 (59), 415 (100), 404 (3), 387 (6), 370 (13), 354 (17), 323 (72), 296 (45), 281 (7), 269 (13), 217 (6), 177 (5), 161 (7), 121 (9), 105 (9), 77 (9 %). Anal. Calcd for $C_{31}H_{32}ClN_3O_6$ (577.20): C, 64.41; H, 5.58; N, 7.27 %. Found: C, 64.37; H, 5.55; N, 7.23 %.

Triethyl 6-amino-1-(4-chlorophenyl)-4-(2-chloroquinoline-3-yl)-1,4-dihydropyridine-2,3,5-tricarboxylate (**7r**) Pale yellow solid, mp 165–167 °C, Yield: 0.51 g (87 %). IR (KBr) (ν_{max}, cm^{-1}): 3,400 (NH), 3,241 (NH), 1,733 (C=O), 1,663 (C=O), 1,608 (C=O); ^{1}H-NMR (300 MHZ, $CDCl_3$): δ_H = 0.97 (t, 3H, *J* = 7.1 Hz, $OCH_2\underline{Me}$), 1.11 (t, 6H, *J* = 7.1 Hz, $2OCH_2\underline{Me}$), 3.83–4.05 (m, 6H, $3OC\underline{H}_2Me$), 5.51 (s, 1H, CH), 6.37 (br s, 2H, NH_2), 7.40 (d, 2H, *J* = 8.7 Hz, Ar), 7.44-7.53 (m, 3H, Ar), 7.66 (t, 1H, *J* = 7.4 Hz, Ar), 7.79 (d, 1H, *J* = 8.1 Hz, Ar), 7.98 (d, 1H, *J* = 8.5 Hz, Ar), 8.20 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 13.4 ($OCH_2\underline{Me}$), 14.0 ($OCH_2\underline{Me}$), 14.4 ($OCH_2\underline{Me}$), 36.7 (CH), 59.5 ($O\underline{C}H_2Me$), 60.9 ($O\underline{C}H_2Me$), 61.9 ($O\underline{C}H_2Me$), 78.7 (C-5 of DHP), 105.8 (C-3 of DHP), 126.7, 127.2, 127.4, 128.1, 129.9, 130.1 (2C), 132.3 (2C), 133.6, 136.7, 138.9, 140.4, 141.9, 146.3, 150.6, 151.5 (C–Ar), 163.2 (C=O), 165.4 (C=O), 169.4 (C=O); EI-MS: *m/z* (%): 587 (0.8, M^++4), 585 (5, M^++2), 583 (7, M^+), 538 (6), 510 (65), 438 (6), 421 (100), 393 (7), 374 (10), 356

Scheme 1 Preparation of 2-chloroquinoline-3-carbaldehydes **3a–c**

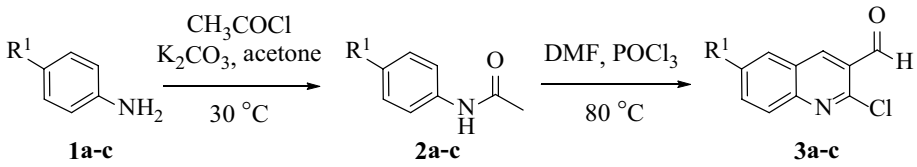
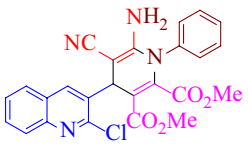
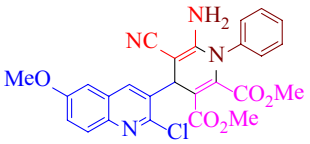
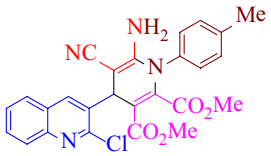
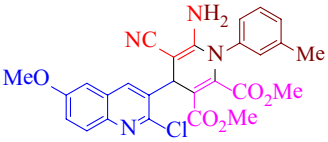
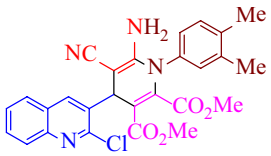
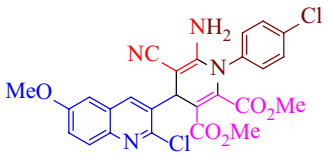
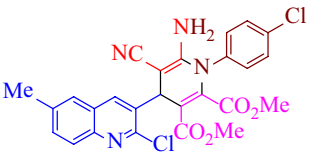
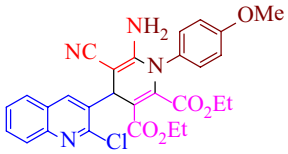
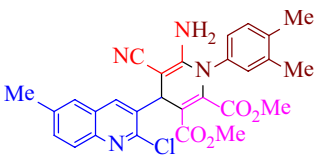
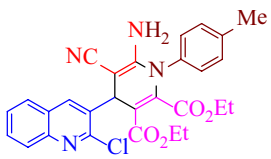


Table 1 Structure of quinoline-based DHPs **7a–j** from reactions of malononitrile

Entry	Product structure	Yield (%)	Entry	Product structure	Yield (%)[a]
1	 **7a**	86	6	 **7f**	83
2	 **7b**	94	7	 **7g**	79
3	 **7c**	92	8	 **7h**	80
4	 **7d**	84	9	 **7i**	88
5	 **7e**	89	10	 **7j**	89

[a] Isolated yields

(5), 321 (6), 393 (10), 275 (20), 229 (7), 162 (4), 152 (7), 128 (6), 111 (7), 93 (13 %). Anal. Calcd for $C_{29}H_{27}Cl_2N_3O_6$ (583.13): C, 59.60; H, 4.66; N, 7.19 %. Found: C, 59.56; H, 4.66; N, 7.20 %.

Triethyl 6-amino-4-(2-chloro-6-methylquinoline-3-yl)-1-(3,4-dimethylphenyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (**7s**) Pale yellow solid, mp 194–196 °C, yield: 0.54 g (91 %). IR (KBr) (ν_{max}, cm^{-1}) 3,360 (NH), 3,290

Scheme 3 Synthesis of quinoline-based DHPs **7k–t**

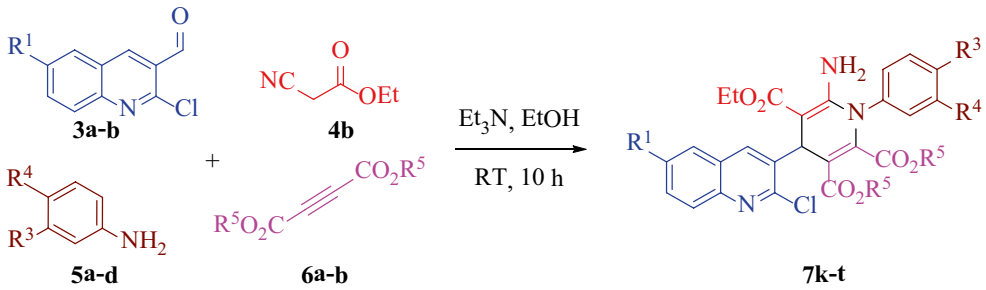
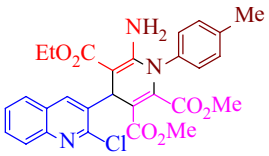
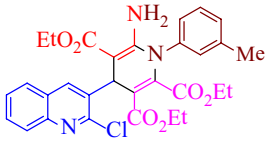
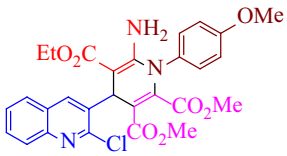
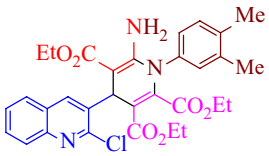
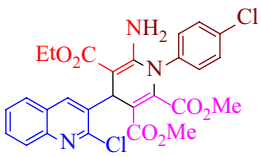
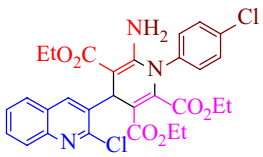
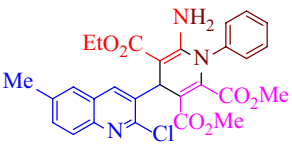
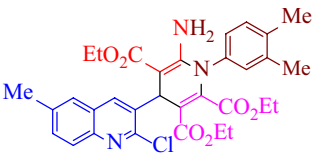
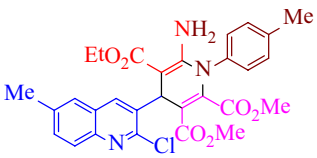
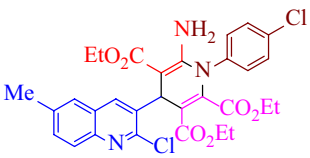
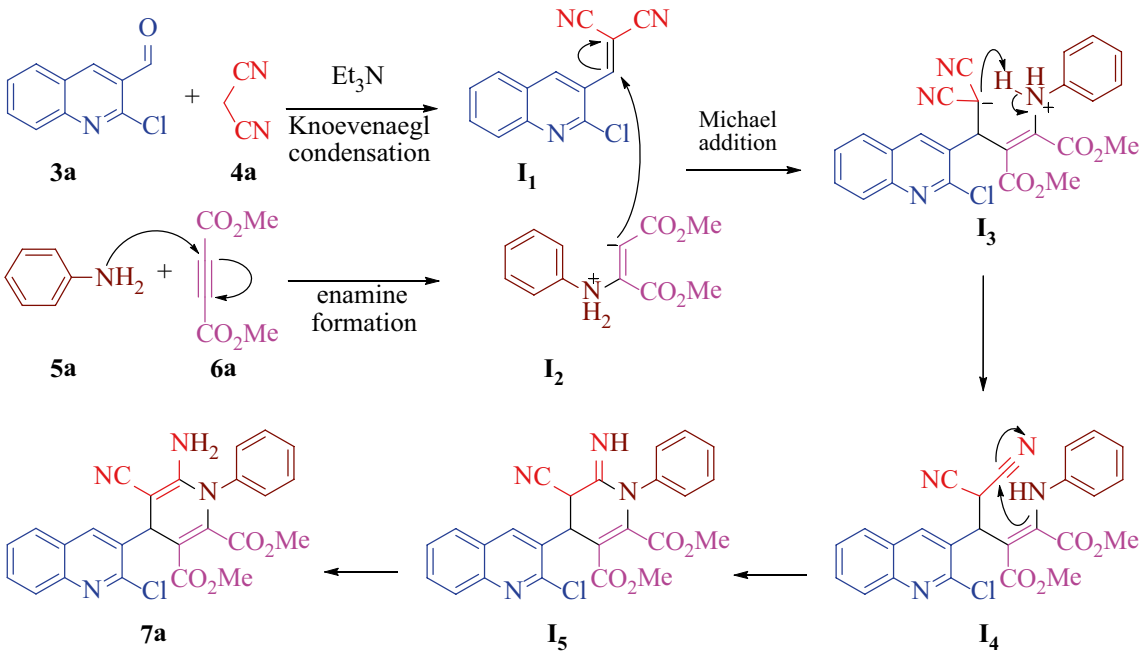


Table 2 Structure of quinoline-based DHPs **7k–t** from reactions of ethyl cyanoacetate

Entry	Product structure	Yield (%)	Entry	Product structure	Yield (%)[a]
11	 **7k**	91	16	 **7p**	85
12	 **7l**	85	17	 **7q**	92
13	 **7m**	88	18	 **7r**	87
14	 **7n**	86	19	 **7s**	91
15	 **7o**	89	20	 **7t**	87

[a] Isolated yields

(NH), 1,745 (C=O), 1,703 (C=O), 1,656 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 0.94 (t, 3H, J = 7.1 Hz, $OCH_2\underline{Me}$), 1.12 (t, 6H, J = 7.1 Hz, $2OCH_2\underline{Me}$), 2.29 (s, 3H, Me), 2.30 (s, 3H, Me), 2.51 (s, 3H, Me), 3.84-4.06 (m, 6H, $3O\underline{CH_2}Me$), 5.50 (s, 1H, CH), 6.40 (br s, 2H, NH_2), 7.15-7.19 (m, 2H, Ar), 7.25 (d, 1H, J = 8.5 Hz, Ar), 7.48



Scheme 4 Proposed mechanism for the formation of DHP **7a**

(d, 1H, J = 8.6 Hz, Ar), 7.55 (s, 1H, Ar), 7.87 (d, 1H, J = 8.6 Hz, Ar), 8.14 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 13.4 ($OCH_2\underline{Me}$), 14.1 ($OCH_2\underline{Me}$), 14.5 ($OCH_2\underline{Me}$), 19.6 (Me), 19.8 (Me), 21.6 (Me), 36.4 (CH), 59.3 ($O\underline{C}H_2Me$), 60.7 ($O\underline{C}H_2Me$), 61.6 ($O\underline{C}H_2Me$), 78.6 (C-5 of DHP), 105.5 (C-3 of DHP), 126.0, 127.6, 127.8, 127.9, 130.8, 131.5, 132.0, 132.5, 136.5, 138.4, 139.1, 139.3, 139.6, 142.4, 144.9, 149.8, 152.0 (C–Ar), 163.3 (C=O), 165.6 (C=O), 169.5 (C=O); EI-MS: *m/z* (%): 593 (1, M^++2), 591 (3, M^+), 518 (37), 415 (100), 400 (2), 387 (3), 341 (3), 315 (2), 297 (3), 269 (12), 251 (3), 223 (6), 140 (6), 105 (9 %). Anal. Calcd for $C_{32}H_{34}ClN_3O_6$ (591.21): C, 64.91; H, 5.79; N, 7.10 %. Found: C, 64.87; H, 5.82; N, 7.10 %.

Triethyl 6-amino-4-(2-chloro-6-methylquinoline-3-yl)-1-(4-chlorophenyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (**7t**) Pale yellow solid, mp 185–187 °C, yield: 0.52 g (87 %). IR (KBr) (ν_{max}, cm^{-1})3,332 (NH), 3,182 (NH), 1,751 (C=O), 1,705 (C=O), 1,659 (C=O); ^{1}H-NMR (300 MHZ, $CDCl_3$): δ_H = 0.96 (t, 3H, J = 7.1 Hz, $OCH_2\underline{Me}$), 1.10 (t, 6H, J = 7.1 Hz, $2OCH_2\underline{Me}$), 2.50 (s, 3H, Me), 3.85–4.03 (m, 6H, $3O\underline{C}H_2Me$), 5.47 (s, 1H, CH), 6.36 (br s, 2H, NH_2), 7.39 (d, 2H, J = 8.6 Hz, Ar), 7.46-7.49 (m, 3H, Ar), 7.54 (s, 1H, Ar), 7.86 (d, 1H, J = 8.6 Hz, Ar), 8.10 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 13.4 ($OCH_2\underline{Me}$), 14.0 ($OCH_2\underline{Me}$), 14.4 ($OCH_2\underline{Me}$), 21.6 (Me), 36.6 (CH), 59.5 ($O\underline{C}H_2Me$), 60.9 ($O\underline{C}H_2Me$), 61.9 ($O\underline{C}H_2Me$), 78.7 (C-5 of DHP), 105.8 (C-3 of DHP), 126.0, 127.4, 127.7, 130.1 (2C), 132.2, 132.3 (2C), 133.6, 136.6, 136.7, 138.3, 139.8, 141.9, 144.9, 149.7, 151.5 (C–Ar), 163.2 (C=O), 165.4 (C=O), 169.4 (C=O); EI-MS: *m/z* (%): 602 (0.4, M^++4), 600 (3, M^++2), 598 (5, M^+), 524 (5), 421 (100), 388 (8), 349 (6), 303 (6), 275 (16), 237 (9), 178 (10), 140 (12), 111 (9 %). Anal. Calcd for $C_{30}H_{29}Cl_2N_3O_6$ (597.14): C, 60.21; H, 4.88; N, 7.02 %. Found: C, 60.63; H, 4.85; N, 6.97 %.

Results and discussion

Initially, 2-chloroquinoline-3-carbaldehydes 3a–c were prepared using the traditional Vilsmeier–Haack cyclization of acetanilides 2a–c (Scheme 1) [113, 114].

Subsequent four-component reactions employing 3a–c, malononitrile 4a, various aromatic amines 5a–d and dialkylacetylenedicarboxylates 6a–b in the presence of triethylamine in ethanol at ambient temperature afforded 7a–j in moderate to excellent yields (Scheme 2; Table 1).

To demonstrate the versatility of these reactions, we replaced malononitrile 4a with ethylcyanoacetate 4b in order to test it in our new one-pot four-component method (Scheme 3). As illustrated in Table 2, 7k–t were obtained in moderate to good yields.

The structure of compounds **7a–t** was confirmed by their analytical and spectral data. The mass spectra of **5a**

displayed the molecular ion peak at 474 for M^+ ([^{35}Cl]) and 476 for M^+ ([^{37}Cl]) consistent with the molecular structure. The IR spectrum of 7a displayed characteristic absorption bands at 3,449 and 3,281, 2,171, 1,747, and 1,711 cm^{-1} due to NH_2, CN and CO_2Me groups stretching vibrations, respectively. The ^{1}H NMR spectrum of **7a** exhibited four singlets at δ 3.33 (3H), 3.44 (3H), 5.23 (1H), and 5.71 (2H) for two CO_2Me, CH, and NH_2, respectively. The presence of two C=O groups was further confirmed by the appearance of two signals δ 162.6 and 164.7 in the ^{13}C NMR spectrum of **7a**. The ^{1}H NMR and ^{13}C NMR spectra of **7b–t** were similar to that of **7a**.

Although the precise mechanism is not known, a mechanistic postulate as shown in Scheme 4 may be invoked to rationalize the formation of **7a**. It is conceivable that the zwitterionic intermediate I_2, formed by the 1:1 interaction between the amine **5a** and acetylenedicarboxylate (DMAD) **6a** attacks the Knoevenagel adduct $\mathbf{I}_1$ obtained from condensation of the aldehyde **3a** with malononitrile **4a**, leading to 1,5-dipolar intermediate $\mathbf{I}_3$. The subsequently generated $\mathbf{I}_4$ is transformed into $\mathbf{I}_5$ and finally **7a** presumably upon ring closure and tautomerization processes, respectively (Scheme 4).

Conclusion

In conclusion, we have developed a novel, basic domino four-component reactions employing 2-chloroquinoline-3-carbaldehydes, malononitrile or ethyl cyanoacetate, various aromatic amines and dialkylacetylenedicarboxylates in ethanol at ambient temperature. A variety of quinolinyl 1,4-dihydropyridines were synthesized in a facile and efficient method in moderate to excellent yields. These new structures broaden the scaffolds that are accessible through Knoevenagel condensation and enamine formation followed by Michael addition and intramolecular cyclization tandem sequences and many of them may represent interesting pharmacophores. This protocol is simple, high-yielding, and does not involve any purification techniques like column chromatography.

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