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Synthesis and antimycobacterial activities of ring-substituted quinolinecarboxylic acid/ester analogues. Part 1

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Abstract—Structural optimization of recently discovered new chemical entity, 2,8-dicyclopentyl-4-methylquinoline (DCMQ; MIC = 6.25 μg/mL, *M. tuberculosis H37Rv*) resulted in the synthesis of four new series of ring-substituted quinolinecarboxylic acids/esters constituting 45 analogues. All new derivatives were evaluated for in vitro antimycobacterial activities against *M. tuberculosis H37Rv*. Certain ring-substituted-2-quinolinecarboxylic acid ester and ring-substituted-2-quinoline acetic acid ester analogues described herein showed moderate to good inhibitory activity. In particular, three analogues methyl 4,5-dicyclopentyl-2-quinolinecarboxylate (**3b**), methyl 4,8-dicyclopentyl-2-quinolinecarboxylate (**3c**) and ethyl 2-(2,8-dicyclopentyl-4-quinolyl)acetate (**14g**) exhibited excellent MIC values of 1.00, 2.00 and 4.00 μg/mL, respectively. Results obtained indicate that substitution of the quinoline ring with dicyclopentyl substituent presumably enhances the antimycobacterial activities in the quinoline analogues described herein.

1. Introduction

Tuberculosis (TB) is one of the most devastating diseases in the world primarily due to several decades of neglect and presents a global health problem of escalating proportions. About 32% of the world's population is currently infected with TB. Every year, approximately eight to nine million of these infected people develop clinical pulmonary tuberculosis leading to nearly three million annual deaths.[1,2] If the present trend continues, tuberculosis is likely to claim more than 30 million lives within the next decade. Human immunodeficiency virus (HIV)-associated TB is rampant especially in the sub-Saharan African countries hardest hit by acquired immunodeficiency syndrome (AIDS).[3] Moreover, recent alarming increase in the number of TB cases that are caused by organisms that are resistant to two cheap and effective mainstay drugs, isoniazid and rifampicin has further worsened the situation.[4] Although, widespread use of the bacilli Calmette–Guerin (BCG) vaccine does prevent the development of severe and fatal TB in young children, it has not been effective in reducing the greater number of TB cases in adults. There are now a number of potential vaccine candidates being developed, however marketable and more useful vaccine may still be decades away.[4] Therefore, there exist an urgent need to develop new and effective analogues with structures preferably different from that of all existing anti-tuberculosis drugs.

Sequence of the *Mycobacterium tuberculosis* genome has recently been deciphered and it is expected that this may facilitate the identification of potential new targets for future drug discovery.[5] However, we adapted a more practical approach towards identification of new classes of anti-tuberculosis agents that is based upon broad screening of new chemical structures against the *M. tuberculosis*. This approach proved to be highly rewarding and resulted in the recent discovery of ring-substituted-4-methylquinolines as a new class of anti-tuberculosis agents, and most promising analogue from

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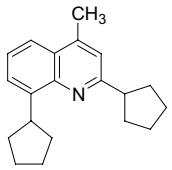


2,8-Dicyclopentyl-4-methylquinoline (DCMQ)

Figure 1.

the series was 2,8-dicyclopentyl-4-methylquinoline (DCMQ) (Fig. 1).[6] Due to the fact that none of the anti-tuberculosis drugs currently used clinically are represented by quinolines; therefore, suggesting that potent activity of the compounds in this series may have been emanated by targeting new biochemical pathways, potentially allowing treatment of multi-drug resistant tuberculosis (MDRTB). More recently, we have also reported synthesis and antimycobacterial activities of nitro and amino group containing ring-substituted quinolines.[7] To discover more efficacious anti-tuberculosis agents based upon quinoline substructure, we have started systematic chemical modification of DCMQ. In continuation of our research on ring-substituted quinolines as potential anti-tuberculosis agents, herein we report the synthesis and antimycobacterial activities of ring-substituted quinolinecarboxylic acids/esters (Series 1–4, Fig. 2).

2. Chemistry

Commercially available 2-quinolinecarboxylic acid (**1**) upon esterification in abs. methanol in the presence of anhydrous hydrogen chloride gas afforded methyl 2-quinolinecarboxylate (**2**). The latter compound **2** upon reaction with various cycloalkylcarboxylic acids in the presence of ammonium persulfate and catalytic silver nitrate in 10% sulfuric acid provided readily separable mixture of methyl 4-substituted/4,5-disubstituted/4,8-disubstituted-2-quinolinecarboxylate (**3a**–**g**) in moderate yield (Scheme 1). The reaction proceeds through a free radical mechanism, and offers a unique and complementary procedure of functionalization of electron-deficient quinoline ring.[8] Reaction involves nucleophilic addition of an alkyl radical (generated from the silver catalyzed oxidative decarboxylation of alkylcarboxylic acid with ammonium persulfate) to a protonated quinoline ring followed by re-aromatization leading to direct carbon alkylation. The utility of the methodology is illustrated by the fact that it allows direct introduction of otherwise difficult propyl, isopropyl, *tert*-butyl, cyclopentyl, adamantyl and many other alkyl groups into the quinoline ring and offer facile access to previously inaccessible functionalized quinoline ring systems. Acidic hydrolysis of methyl ring-substituted-2-quinolinecarboxylate (**3**) in 6 N HCl at reflux temperature for 8 h readily provided ring-substituted-2-quinolinecarboxylic acid (**4a**–**b**) as their hydrochloride salts.

Similarly, methyl 3-quinolinecarboxylate (**6**) and methyl 4-quinolinecarboxylate (**10**) upon free radical reaction with cycloalkylcarboxylic acids in the presence of ammonium persulfate and catalytic silver nitrate in 10% sulfuric acid provided easily separable mixture of methyl 2-substituted/2,4-disubstituted-3-quinolinecarboxylate (**7a**–**e**) and methyl 2-substituted/2,8-disubstituted-4-quinolinecarboxylate (**11a**–**f**), respectively, in moderate yields (Schemes 2 and 3). Acidolysis of the latter compounds **7** and **11** with refluxing 6 N HCl afforded ring-substituted-3-quinolinecarboxylic acid hydrochlorides (**8a**–**b**) and ring-substituted-4-quinolinecarboxylic acid hydrochlorides (**12a**–**c**), respectively, in excellent yields (Schemes 2–4).

On the other hand, methyl 2-(4-quinolyl)acetate (**13a**) and ethyl 2-(4-quinolyl)acetate (**13b**) were prepared in seven steps starting from 2,3-indolinedione (isatin) using procedure reported earlier.[9] Nucleophilic homolytic free radical alkylation of the esters **13a**–**b** produced methyl/ethyl 2-(2-substituted/2,8-disubstituted-4-quinolyl)acetates (**14a**–**j**), which upon acid hydrolysis afforded 2-(2,8-disubstituted-4-quinolyl)acetic acids (**15a**–**b**) in excellent yields as hydrochloride salt.

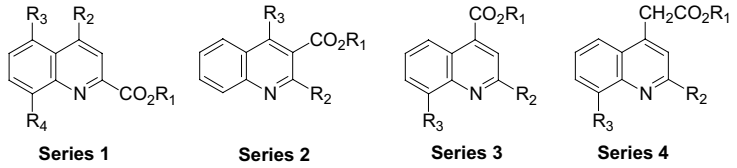
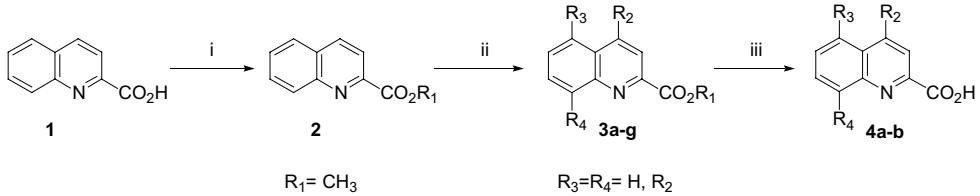
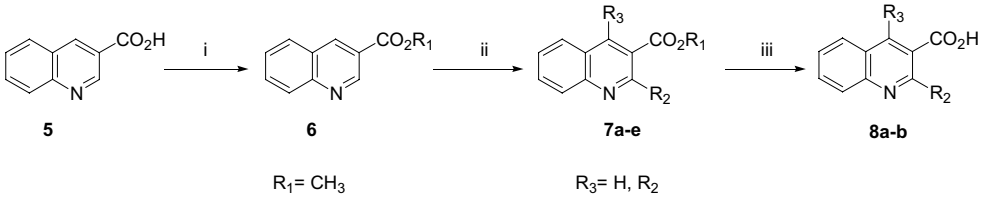


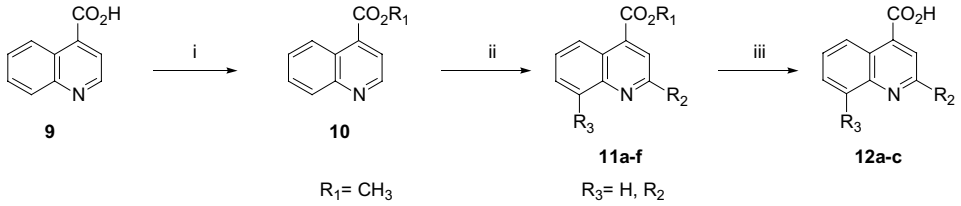
Figure 2.



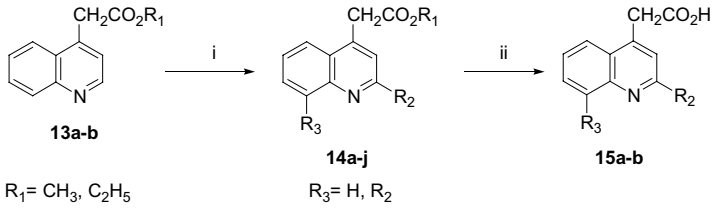
Scheme 1. Reagents and conditions: (i) HCl, CH_3OH, 1 h, 4 °C; (ii) R_2CO_2H, $AgNO_3$, $(NH_4)_2S_2O_8$, 10% H_2SO_4, 70–80 °C; (iii) 6 N HCl, reflux, 8 h.



Scheme 2. Reagents and conditions: (i) HCl, CH_3OH, 1 h, 4 °C; (ii) R_2CO_2H, $AgNO_3$, $(NH_4)_2S_2O_8$, 10% H_2SO_4, 70–80 °C; (iii) 6 N HCl, reflux, 8 h.



Scheme 3. Reagents and conditions: (i) HCl, CH_3OH, 1 h, 4 °C; (ii) R_2CO_2H, $AgNO_3$, $(NH_4)_2S_2O_8$, 10% H_2SO_4, 70–80 °C; (iii) 6 N HCl, reflux, 8 h.

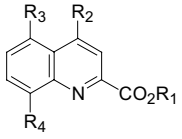


Scheme 4. Reagents and conditions: (i) R_2CO_2H, $AgNO_3$, $(NH_4)_2S_2O_8$, 10% H_2SO_4, 70–80 °C; (ii) 6 N HCl, reflux, 8 h.

3. Biological activity

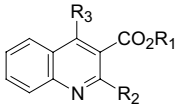
In vitro activities of the synthesized analogues (Series 1–4) for tuberculosis inhibition against *M. tuberculosis H37Rv* strain (ATCC 27294, susceptible both to rifampicin and isoniazid) were initially carried out using the Microplate Alamar Blue Assay (MABA) at a concentration of 6.25 μg/mL.[10] Compounds exhibiting fluorescence were then tested in the BACTEC 460 radiometric system,[11] and activities expressed as Minimum Inhibitory Concentration (MIC, μg/mL) are summarized in Tables 1–4. Compounds demonstrating ⩾90% inhibition at 6.25 μg/mL in the initial screen were retested in the broth microdiluation assay at the lower

Table 1. In vitro antimycobacterial activity evaluation of ring-substituted quinoline-2-carboxylic acid analogues (Series 1) against *M. tuberculosis H37Rv*



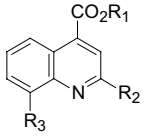
No.	R_1	R_2	R_3	R_4	(%) Inhibition	MIC (μg/mL)
1	H	H	H	H	10	>6.25
2	CH_3	H	H	H	9	>6.25
3a	CH_3	*c*-C_5H_9	H	H	0	>6.25
3b	CH_3	*c*-C_5H_9	*c*-C_5H_9	H	99	1.00
3c	CH_3	H	*c*-C_5H_9	*c*-C_5H_9	97	2.00
3d	CH_3	*c*-C_6H_{11}	H	H	15	>6.25
3e	CH_3	*c*-C_6H_{11}	*c*-C_6H_{11}	H	99	6.25
3f	CH_3	H	*c*-C_6H_{11}	*c*-C_6H_{11}	43	>6.25
3g	CH_3	1-Adamantyl	H	H	34	>6.25
4a	H	*c*-C_6H_{11}	H	H	9	>6.25
4b	H	1-Adamantyl	H	H	15	>6.25
DCMQ					100	6.25
Isoniazid					99	1.00

Table 2. In vitro antimycobacterial activity evaluation of ring-substituted quinoline-3-carboxylic acid analogues (Series 2) against *M. tuberculosis H37Rv*



No.	R_1	R_2	R_3	(%) Inhibition	MIC (μg/mL)
5	H	H	H	74	>6.25
6	CH_3	H	H	0	>6.25
7a	CH_3	*c*-C_5H_9	H	28	>6.25
7b	CH_3	*c*-C_5H_9	*c*-C_5H_9	97	6.25
7c	CH_3	*c*-C_6H_{11}	H	35	>6.25
7d	CH_3	*c*-C_6H_{11}	*c*-C_6H_{11}	95	6.25
7e	CH_3	1-Adamantyl	H	11	>6.25
8a	H	*c*-C_6H_{11}	*c*-C_6H_{11}	0	>6.25
8b	H	1-Adamantyl	H	0	>6.25
DCMQ				100	6.25
Isoniazid				99	1.00

Table 3. In vitro antimycobacterial activity evaluation of ring-substituted quinoline-4-carboxylic acid analogues (Series 3) against *M. tuberculosis H37Rv*



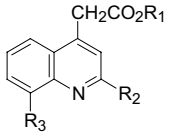
No.	R_1	R_2	R_3	(%) Inhibition	MIC (μg/mL)
9	H	H	H	6	>6.25
10	CH_3	H	H	0	>6.25
11a	CH_3	*c*-C_5H_9	H	2	>6.25
11b	CH_3	*c*-C_5H_9	*c*-C_5H_9	38	>6.25
11c	CH_3	*c*-C_6H_{11}	H	3	>6.25
11d	CH_3	*c*-C_6H_{11}	*c*-C_6H_{11}	44	>6.25
11e	CH_3	1-Adamantyl	H	49	>6.25
11f	CH_3	1-Adamantyl	1-Adamantyl	1	>6.25
12a	H	*c*-C_5H_9	H	4	>6.25
12b	H	*c*-C_6H_{11}	H	10	>6.25
12c	H	1-Adamantyl	H	3	>6.25
DCMQ				100	6.25
Isoniazid				99	1.00

concentrations of 4.0, 2.0, 1.0, 0.5 and 0.25 μg/mL to determine the actual MIC value that is defined as the lowest concentration exhibiting $\geqslant 90\%$ inhibition.

Several derivatives (**3e**, **7b**,**d** and **14i**, Tables 1, 2, 4) appeared to have exhibited good activity (MICs = 6.25 μg/mL) against *M. tuberculosis H37Rv*. Three derivatives, methyl 4,5-dicyclopentyl-2-quinolinecarboxylate (**3b**, Table 1), methyl 4,8-dicyclopentyl-2-quinolinecarboxylate (**3c**, Table 1) and ethyl 2-(2,8-dicyclopentyl-4-quinolyl)acetate (**14g**, Table 4), exhibited excellent activity against *M. tuberculosis H37Rv* with MIC values of 1.00, 2.00 and 4.00 μg/mL, respectively. With the exception of methyl-3-quinolinecarboxylate (**5**, 74% inhibition, MIC, >6.25 μg/mL), none of the starting materials (**1**–**2**, **6**, **9**–**10**, **13a**–**b**) were active at the highest tested concentration of 6.25 μg/mL.

Ester derivatives **3b**–**c** and **14g** were the most active of tested compounds, and it is noteworthy to observe that all of these derivatives contain the dicyclopentyl substituent in the quinoline ring. Though without performing additional studies, we cannot unequivocally predict that dicyclopentyl substitution in the quinoline ring is essential for increase in antimycobacterial activity. Interestingly, for reasons unknown to us at present, none of the carboxylic acid derivatives were found to be active. Two derivatives, methyl 4,5-dicyclopentyl-2-quinolinecarboxylate (**3b**), and methyl 4,8-dicyclopentyl-2-quinolinecarboxylate (**3c**), were also evaluated for antimycobacterial activity against isoniazid resistant strain of *M. tuberculosis H37Rv* using broth microdiluation assay method, and derivative **3c** exhibited good activity (92% inhibition, MIC = 6.25 μg/mL).

Table 4. In vitro antimycobacterial activity evaluation of ring-substituted-quinoline-4-acetic acid analogues (Series 4) against *M. tuberculosis H37Rv*



No.	R_1	R_2	R_3	(%) Inhibition	MIC (μg/mL)
13a	CH_3	H	H	0	>6.25
13b	C_2H_5	H	H	2	>6.25
14a	CH_3	*c*-C_5H_9	H	3	>6.25
14b	CH_3	*c*-C_5H_9	*c*-C_5H_9	3	>6.25
14c	CH_3	*c*-C_6H_{11}	H	4	>6.25
14d	CH_3	*c*-C_6H_{11}	*c*-C_6H_{11}	4	>6.25
14e	CH_3	1-Adamantyl	H	10	>6.25
14f	C_2H_5	*c*-C_5H_9	H	63	>6.25
14g	C_2H_5	*c*-C_5H_9	*c*-C_5H_9	99	4.00
14h	C_2H_5	*c*-C_6H_{11}	H	47	>6.25
14i	C_2H_5	*c*-C_6H_{11}	*c*-C_6H_{11}	99	6.25
14j	C_2H_5	1-Adamantyl	H	47	>6.25
15a	H	*c*-C_5H_9	*c*-C_5H_9	15	>6.25
15b	H	*c*-C_6H_{11}	*c*-C_6H_{11}	9	>6.25
DCMQ				100	6.25
Isoniazid				99	1.00

4. Conclusions

To conclude, in our pursuit towards systemic chemical and biological modification of DCMQ, attempts were made to determine suitability of carboxylic acid and various ester groups placed at the 2, 3 and 4 positions of the ring-substituted quinolines. Several derivatives were found to be more effective when compared to DCMQ. As evident from the results described analogues, which contain an ester functionality placed at C-2 position of the quinoline ring appears to be more beneficial for antimycobacterial activities. One of the most attractive features of the most active analogues is their availability via a facile single step synthetic transformation. Thus these effective derivatives are ideally suited for modification to obtain more efficacious antimycobacterial compounds. Further chemical and biological optimization of the lead molecules reported herein is currently underway in our laboratory.

5. Experimental

Melting points were recorded on Mettler DSC 851 or capillary melting point apparatus and are uncorrected. ^{1}H spectra were recorded on 300 MHz Bruker FT-NMR (Avance DPX300) spectrometer using tetramethylsilane as internal standard and the chemical shifts are reported in δ units. Mass spectra were recorded on either GC–MS (Shimadzu QP 5000 spectrometer) auto sampler/direct injection (EI/CI) or HRMS (Finnigan Mat LCQ spectrometer) (APCI/ESI). FT-IR spectra (λ_{max} in cm^{-1}) were recorded on a Nicolet spectrometer. Elemental analyses were recorded on Elementar Vario EL spectrometer. All chromatographic purification was performed with silica gel 60 (230–400 mesh), whereas all TLC (silica gel) development was performed on silica gel coated (Merck Kiesel 60 F_{254}, 0.2 mm thickness) sheets. All chemicals were purchased from Aldrich Chemical Ltd (Milwaukee, WI, USA). Solvents used for the chemical synthesis acquired from commercial sources were of analytical grade, and were used without further purification unless otherwise stated.

5.1. Synthesis of methyl 2-quinolinecarboxylate (2)

To a mixture of 2-quinolinecarboxylic acid (**1**, 1 mmol) in methanol (100 mL) was passed a slow stream of anhydrous hydrogen chloride gas for 1 h at 4 °C, and reaction mixture was left overnight at ambient temperature. Solvent was removed under reduced pressure, and residue was dissolved in water (20 mL). Neutralized by drop-wise addition of 25% NH_4OH solution that resulted in the precipitation of free ester. Filtration followed by air-drying afforded **2** in good yield.

Yield: 72%; mp 78 °C; IR (KBr) 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.09 (s, 3H), 7.64 (m, 1H), 7.80 (m, 1H), 7.89 (d, 1H, $J = 8.5$ Hz), 8.23 (d, 1H, $J = 8.5$ Hz), 8.30 (m, 2H); EIMS m/z 187 (M^+). Anal. Calcd for $C_{11}H_9NO_2$ (187.2): C, 70.58; H, 4.85; N, 7.45. Found: C, 70.79; H, 5.10; N, 7.43.

5.2. General method for the synthesis of methyl 4-substituted/4,5-disubstituted/4,8-disubstituted-2-quinolinecarboxylate (3a–g)

A freshly prepared solution of ammonium persulfate (3 mmol) in water (5 mL) was added drop wise to a mixture of methyl 2-quinolinecarboxylate (**2**, 1 mmol), silver nitrate (0.6 mmol) and cycloalkylcarboxylic acid (3 mmol) in 10% H_2SO_4 (4 mL) during 15 min at 70–80 °C. The heating source was then removed and the reaction proceeded with evolution of carbon dioxide.

After another 15 min, reaction was terminated by pouring the mixture onto crushed ice. The resulting mixture was made alkaline with 30% NH_4OH solution, and extracted with ethyl acetate (3×50 mL). The combined extracts were washed with brine (2×10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford oil, which on chromatography over silica gel using EtOAc–hexanes (20:80) afforded methyl 4-substituted, 4,5-disubstituted, and 4,8-disubstituted-2-quinolinecarboxylates (**3a**–**g**) in moderate yield.

5.2.1. Methyl 4-cyclopentyl-2-quinolinecarboxylate (3a). Yield: 17%; oil; IR ($CHCl_3$) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–1.90 (m, 8H), 3.30 (m, 1H), 4.08 (s, 3H), 7.65 (m, 1H), 7.76 (m, 1H), 8.15 (m, 2H), 8.30 (d, 1H, $J = 8.5$ Hz); EIMS m/z 255 (M^+). Anal. Calcd for $C_{16}H_{17}NO_2$ (255.3): C, 75.27; H, 6.71; N, 5.49. Found: C, 75.07; H, 6.93; N, 5.17.

5.2.2. Methyl 4,5-dicyclopentyl-2-quinolinecarboxylate (3b). Yield: 10%; oil; IR ($CHCl_3$) 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–2.10 (m, 16H), 2.90 (m, 1H), 3.23 (m, 1H), 3.80 (m, 1H), 4.07 (s, 3H), 7.76 (m, 1H), 7.94 (s, 1H), 8.10 (s, 1H), 8.24 (m, 1H); EIMS m/z 323 (M^+). Anal. Calcd for $C_{21}H_{25}NO_2$ (323.4): C, 77.98; H, 7.79; N, 4.33. Found: C, 78.13; H, 7.91; N, 4.18.

5.3. Methyl 4,8-dicyclopentyl-2-quinolinecarboxylate (3c)

Yield: 12%; oil; IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–2.30 (m, 16H), 3.78 (m, 1H), 4.04 (s, 3H), 4.40 (m, 1H), 7.57 (m, 1H), 7.66 (d, 1H, $J = 7.0$ Hz), 8.0 (d, 1H, $J = 8.4$ Hz), 8.10 (s, 1H); EIMS m/z 323 (M^+). Anal. Calcd for $C_{21}H_{25}NO_2$ (323.4): C, 77.98; H, 7.79; N, 4.33. Found: C, 77.77; H, 7.63; N, 4.57.

5.3.1. Methyl 4-cyclohexyl-2-quinolinecarboxylate (3d). Yield: 22%; oil; IR ($CHCl_3$) 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30–1.80 (m, 10H), 3.37 (m, 1H), 4.08 (s, 3H), 7.65 (m, 1H), 7.76 (m, 1H), 8.12 (m, 2H), 8.30 (d, 1H, $J = 8.5$ Hz); EIMS m/z 269 (M^+). Anal. Calcd for $C_{17}H_{19}NO_2$ (269.3): C, 75.81; H, 7.11; N, 5.20. Found: C, 75.83; H, 7.08; N, 5.41.

5.3.2. Methyl 4,5-dicyclohexyl-2-quinolinecarboxylate (3e). Yield: 12%; oil; IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30–1.90 (m, 20H), 2.71 (m, 1H), 3.34 (m, 1H), 4.07 (s, 3H), 7.53 (d, 1H, $J = 8.7$ Hz), 8.04 (m, 2H), 8.11 (s, 1H); EIMS m/z 351 (M^+). Anal. Calcd for $C_{23}H_{29}NO_2$ (351.5): C, 78.59; H, 8.32; N, 3.99. Found: C, 78.83; H, 8.05; N, 3.73.

5.3.3. Methyl 4,8-dicyclohexyl-2-quinolinecarboxylate (3f). Yield: 11%; oil; IR ($CHCl_3$) 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.570–2.20 (m, 20H), 3.35 (m, 1H), 4.04 (s, 3H), 4.09 (m, 1H), 7.59 (m, 2H), 7.96 (d, 1H, $J = 7.0$ Hz), 8.04 (s, 1H); EIMS m/z 351 (M^+). Anal. Calcd for $C_{23}H_{29}NO_2$ (351.5): C, 78.59; H, 8.32; N, 3.99. Found: C, 78.55; H, 8.38; N, 3.91.

5.3.4. Methyl 4-(1-adamantyl)-2-quinolinecarboxylate (3g). Yield: 60%; mp 93-94 °C; IR (KBr) 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70–2.10 (m, 15H), 4.0 (s, 3H), 7.60 (m, 1H), 7.71 (m, 1H), 8.13 (s, 1H), 8.33 (d, 1H, $J = 8.3$ Hz), 8.68 (d, 1H, $J = 8.0$ Hz); ESIMS m/z 322 (M + 1). Anal. Calcd for $C_{21}H_{23}NO_2$ (321.4): C, 78.47; H, 7.21; N, 4.36. Found: C, 78.55; H, 7.33; N, 4.31.

5.4. General method for the synthesis of ring-substituted-2-quinolinecarboxylic acid hydrochlorides (4a–b)

A mixture of methyl 4-cyclohexyl-2-quinolinecarboxylate (**3d**, 1 mmol) or methyl 4-(1-adamantyl)-2-quinolinecarboxylate (**3g**, 1 mmol) in 6 N HCl (10 mL) was heated under reflux for 8 h. The acid hydrolysis solution was evaporated under reduced pressure to afford the ring-substituted-2-quinolinecarboxylic acids (**4**) in excellent yield as their hydrochloride salts.

5.4.1. Cyclohexyl-2-quinolinecarboxylic acid hydrochloride (4a). Yield: 98%; mp 180–182 °C; IR (KBr) 2356, 1665, 1404, 1039 cm^{-1}; ^1H NMR (CD_3OD) δ 1.60–1.92 (m, 10H), 3.81 (m, 1H), 8.08 (m, 1H), 8.24 (m, 1H), 8.45 (s, 1H), 8.55 (d, 1H, $J = 8.6$ Hz), 8.67 (d, 1H, $J = 8.6$ Hz); EIMS m/z 255 (M^+). Anal. Calcd for $C_{16}H_{18}ClNO_2$ (291.8): C, 65.86; H, 6.22; N, 4.80. Found: C, 65.91; H, 6.02; N, 4.87.

5.4.2. 4-(1-Adamantyl)-2-quinolinecarboxylic acid hydrochloride (4b). Yield: 95%; mp: 195–197 °C; IR (KBr) 2904, 2362, 1718, 1220 cm^{-1}; ^1H NMR (CD_3OD) δ 1.59–1.92 (m, 15H), 7.20 (m, 1H), 7.82 (m, 1H), 8.01 (s, 1H), 8.20 (d, 1H, $J = 8.2$ Hz), 8.75 (d, 1H, $J = 8.5$ Hz); ESIMS m/z 309 (M + 1). Anal. Calcd for $C_{20}H_{22}ClNO_2$ (343.9): C, 69.86; H, 6.45; N, 4.07. Found: C, 70.11; H, 6.17; N, 4.02.

5.4.3. Synthesis of methyl 3-quinolinecarboxylate (6). This compound was synthesized from commercially available 3-quinolinecarboxylic acid (**5**) using procedure reported above for methyl 2-quinolinecarboxylate (**2**).

Yield: 74%; mp 78–79 °C; IR (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02 (s, 3H), 7.63 (m, 1H), 7.79 (m, 1H), 7.94 (d, 1H, $J = 7.6$ Hz), 8.18 (d, 1H, $J = 8.7$ Hz), 8.86 (s, 1H), 9.45 (s, 1H); EIMS m/z 187 (M^+). Anal. Calcd for $C_{11}H_9NO_2$ (187.2): C, 70.58; H, 4.85; N, 7.45. Found: C, 70.51; H, 5.02; N, 7.67.

5.5. General method for the synthesis of methyl 2-substituted/2,4-disubstituted-3-quinolinecarboxylate (7a–e)

These analogues were synthesized from methyl 3-quinolinecarboxylate (**6**) using procedure reported above for methyl ring-substituted-2-quinolinecarboxylates (**3a**–**g**).

5.5.1. Methyl 2-cyclopentyl-3-quinolinecarboxylate (7a). Yield: 24%; oil; IR ($CHCl_3$) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41–1.83 (m, 8H), 3.08 (m, 1H), 3.97 (s, 3H), 7.50 (m, 1H), 7.74 (m, 1H), 7.82 (d, 1H, $J = 9$ Hz), 8.04 (d, 1H, $J = 8.4$ Hz), 8.67 (s, 1H); EIMS m/z 255 $(M)^+$. Anal. Calcd for $C_{16}H_{17}NO_2$ (255.3): C, 75.27; H, 6.71; N, 5.49. Found: C, 75.25; H, 6.79; N, 5.44.

5.5.2. Methyl 2,4-dicyclopentyl-3-quinolinecarboxylate (7b). Yield: 12%; oil; IR ($CHCl_3$) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21–1.67 (m, 16H), 2.99 (m, 2H), 4.04 (s, 3H), 7.44 (m, 1H), 7.64 (m, 1H), 8.04 (m, 2H); EIMS m/z 323 (M^+). Anal. Calcd for $C_{21}H_{25}NO_2$ (323.4): C, 77.98; H, 7.79; N, 4.33. Found: C, 77.87; H, 7.63; N, 4.56.

5.5.3. Methyl 2-cyclohexyl-3-quinolinecarboxylate (7c). Yield: 19%; oil; IR ($CHCl_3$) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43–1.85 (m, 10H), 2.91 (m, 1H), 3.97 (s, 3H), 7.57 (m, 1H), 7.72 (m, 1H), 7.84 (m, 1H), 8.10 (d, 1H, $J = 8.5$ Hz), 8.66 (s, 1H); EIMS m/z 269 (M^+). Anal. Calcd for $C_{17}H_{19}NO_2$ (269.3): C, 75.81; H, 7.11; N, 5.20. Found: C, 75.78; H, 7.34; N, 5.17.

5.5.4. Methyl 2,4-dicyclohexyl-3-quinolinecarboxylate (7d). Yield: 14%; oil; IR ($CHCl_3$) 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.76 (m, 20H), 2.95 (m, 2H), 3.99 (s, 3H), 7.42 (m, 1H), 7.64 (m, 1H), 8.10 (d, 2H); EIMS m/z 351 (M^+). Anal. Calcd for $C_{23}H_{29}NO_2$ (351.5): C, 78.59; H, 8.32; N, 3.99. Found: C, 78.43; H, 8.21; N, 3.74.

5.5.5. Methyl 2-(1-adamantyl)-3-quinolinecarboxylate (7e). Yield: 34%; mp 98–99 °C; IR (KBr) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75–1.94 (m, 15H), 4.01 (s, 3H), 7.73 (m, 1H), 7.81 (m, 1H), 7.88 (d, 1H, $J = 8.6$ Hz), 8.10 (d, 1H, $J = 8.2$ Hz), 8.59 (s, 1H); EIMS m/z 321 (M^+). Anal. Calcd for $C_{21}H_{23}NO_2$ (321.4): C, 78.47; H, 7.21; N, 4.36. Found: C, 78.25; H, 7.09; N, 4.17.

5.6. General method for the synthesis of ring-substituted-3-quinolinecarboxylic acid hydrochlorides (8a–b)

These analogues were synthesized from methyl 2,4-dicyclohexyl-3-quinolinecarboxylate (**7d**) and methyl 2-(1-adamantyl)-3-quinolinecarboxylate (**7e**) using procedure reported above for ring-substituted-2-quinolinecarboxylic acid hydrochlorides (**4a**–**b**).

5.6.1. 2,4-Dicyclohexyl-3-quinolinecarboxylic acid hydrochloride (8a). Yield: 99%; mp 110–111 °C; ^1H NMR (CD_3OD) δ 1.21–1.44 (m, 20H), 3.18 (m, 2H), 7.98 (m, 1H), 8.15 (m, 1H), 8.50 (m, 2H); ESIMS m/z 338 (M + 1). Anal. Calcd for $C_{22}H_{28}ClNO_2$ (373.9): C, 70.67; H, 7.55; N, 3.75. Found: C, 70.81; H, 7.16; N, 3.88.

5.6.2. 2-(1-Adamantyl)-3-quinolinecarboxylic acid hydrochloride (8b). Yield: 98%; mp 106–107 °C; ^1H NMR (CD_3OD) δ 1.87–2.11 (m, 15H), 7.40 (m, 1H), 7.70 (m, 2H), 8.07 (m, 1H), 8.40 (s, 1H); ESIMS m/z 308 (M + 1). Anal. Calcd for $C_{20}H_{22}ClNO_2$ (343.9): C, 69.86; H, 6.45; N, 4.07. Found: C, 70.03; H, 6.52; N, 4.17.

5.6.3. Synthesis of methyl 4-quinolinecarboxylate (10). This compound was synthesized from commercially available 4-quinolinecarboxylic acid (**9**) using the procedure reported above for methyl 2-quinolinecarboxylate (**2**).

Yield: 72%; 73–74 °C; IR (KBr) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.04 (s, 3H), 7.71 (m, 1H), 7.83 (m, 1H), 7.90 (m, 1H), 8.22 (d, 1H, $J = 8.7$ Hz), 8.81 (d, 1H, $J = 8.4$ Hz), 9.02 (d, 1H, $J = 8.7$ Hz); EIMS m/z 187 (M^+). Anal. Calcd for $C_{11}H_9NO_2$ (187.2): C, 70.58; H, 4.85; N, 7.45. Found: C, 70.43; H, 4.67; N, 7.31.

5.7. General method for the synthesis of methyl 2-substituted/2,8-disubstituted-4-quinolinecarboxylate (11a–f)

These analogues were synthesized from methyl 4-quinolinecarboxylate (**10**) using procedure reported above for methyl ring-substituted-2-quinolinecarboxylates (**3a**–**g**).

5.7.1. Methyl 2-cyclopentyl-4-quinolinecarboxylate (11a). Yield: 17%; oil; IR ($CHCl_3$) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31–1.52 (m, 8H), 2.19 (m, 1H), 4.04 (s, 3H), 7.58 (m, 1H), 7.72 (m, 1H), 7.83 (s, 1H), 8.09 (d, 1H, $J = 7.0$ Hz), 8.67 (d, 1H, $J = 7.0$ Hz); EIMS m/z 255 (M^+). Anal. Calcd for $C_{16}H_{17}NO_2$ (255.3): C, 75.27; H, 6.71; N, 5.49. Found: C, 75.03; H, 6.91; N, 5.67.

5.7.2. Methyl 2,8-dicyclopentyl-4-quinolinecarboxylate (11b). Yield: 12%; oil; IR ($CHCl_3$) 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42–1.64 (m, 16H), 2.19 (m, 1H), 2.99 (m, 1H), 4.01 (s, 3H), 7.51 (m, 1H), 7.67 (m, 1H), 7.87 (s, 1H), 8.21 (d, 1H, $J = 7.2$ Hz); EIMS m/z 323 (M^+). Anal. Calcd for $C_{21}H_{25}NO_2$ (323.4): C, 77.98; H, 7.79; N, 4.33. Found: C, 78.31; H, 7.84; N, 4.25.

5.7.3. Methyl 2-cyclohexyl-4-quinolinecarboxylate (11c). Yield: 32%; oil; IR ($CHCl_3$) 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70–1.90 (m, 10H), 2.31 (m, 1H), 4.04 (s, 3H), 7.57 (m, 1H), 7.72 (m, 1H), 7.84 (s, 1H), 8.10 (d, 1H, $J = 8.5$ Hz), 8.66 (d, 1H, $J = 8.7$ Hz); EIMS m/z 269 (M^+). Anal. Calcd for $C_{17}H_{19}NO_2$ (269.3): C, 75.81; H, 7.11; N, 5.20. Found: C, 75.93; H, 7.05; N, 5.08.

5.7.4. Methyl 2,8-dicyclohexyl-4-quinolinecarboxylate (11d). Yield: 20%; oil; IR ($CHCl_3$) 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65–1.85 (m, 20H), 2.89 (m, 2H), 3.99 (s, 3H), 7.49 (m, 1H), 7.77 (m, 1H), 7.89 (s, 1H), 8.30 (d,

1H, $J = 8.2$ Hz); EIMS m/z 351 (M^+). Anal. Calcd for $C_{23}H_{29}NO_2$ (351.5): C, 78.59; H, 8.32; N, 3.99. Found: C, 78.75; H, 8.03; N, 4.11.

5.7.5. Methyl 2-(1-adamantyl)-4-quinolinecarboxylate (11e). Yield: 28%; mp 107–109 °C; IR (KBr) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33–1.56 (m, 15H), 4.04 (s, 3H), 7.57 (m, 1H), 7.71 (m, 1H), 7.81 (s, 1H), 8.12 (d, 1H, $J = 8.4$ Hz), 8.66 (d, 1H, $J = 8.4$ Hz); EIMS m/z 322 (M + 1). Anal. Calcd for $C_{21}H_{23}NO_2$ (321.4): C, 78.47; H, 7.21; N, 4.36. Found: C, 78.77; H, 7.51; N, 4.35.

5.7.6. Methyl 2,8-di(1-adamantyl)-4-quinolinecarboxylate (11f). Yield: 17%; mp 92–93 °C; IR (KBr) 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46–1.67 (m, 30H), 3.93 (s, 3H), 7.57 (m, 1H), 7.78 (m, 1H), 7.83 (s, 1H), 8.31 (d, 1H, $J = 8.1$ Hz); EIMS m/z 456 (M + 1). Anal. Calcd for $C_{31}H_{37}NO_2$ (455.6): C, 81.72; H, 8.19; N, 3.07. Found: C, 81.88; H, 8.09; N, 3.18.

5.8. General method for the synthesis of ring-substituted-4-quinolinecarboxylic acid hydrochlorides (12a–c)

These analogues were synthesized from methyl 2-cyclopentyl-4-quinolinecarboxylate (**11a**), methyl 2-cyclohexyl-4-quinolinecarboxylate (**11c**) and methyl 2-(1-adamantyl)-4-quinolinecarboxylate (**11e**) using procedure reported above for ring-substituted-2-quinolinecarboxylic acid hydrochlorides (**4a**–**b**).

5.8.1. 2-Cyclopentyl-4-quinolinecarboxylic acid hydrochloride (12a). Yield 94%; mp 97–98 °C; IR (KBr) 3405, 2925, 1712, 1638 cm^{-1}; ^1H NMR (CD_3OD) δ 1.71–1.91 (m, 8H), 2.69 (m, 1H), 8.00 (m, 1H), 8.19 (m, 1H), 8.31 (d, 1H, $J = 8.7$ Hz), 8.39 (s, 1H), 8.91 (d, 1H, $J = 8.6$ Hz); ESIMS m/z 242 (M + 1). Anal. Calcd for $C_{15}H_{16}ClNO_2$ (277.8): C, 64.87; H, 5.81; N, 5.04. Found: C, 64.95; H, 5.93; N, 5.17.

5.8.2. 2-Cyclohexyl-4-quinolinecarboxylic acid hydrochloride (12b). Yield 94%; mp 102–104 °C; IR (KBr) 3425, 2925, 1682, 1537 cm^{-1}; ^1H NMR (CD_3OD) δ 1.21–1.31 (m, 10H), 3.32 (m, 1H), 7.96 (m, 1H), 8.15 (m, 1H), 8.26 (d, 1H, $J = 8.3$ Hz), 8.33 (s, 1H), 8.90 (d, 1H, $J = 8.2$ Hz); EIMS m/z 255 (M^+). Anal. Calcd for $C_{16}H_{18}ClNO_2$ (291.8): C, 65.86; H, 6.22; N, 4.80. Found: C, 65.72; H, 6.43; N, 4.81.

5.8.3. 2-(1-Adamantyl)-4-quinolinecarboxylic acid hydrochloride (12c). Yield 97%; mp 112–114 °C; IR (KBr) 3422, 2921, 1680, 1525 cm^{-1}; ^1H NMR (CD_3OD) δ 1.41–1.52 (m, 15H), 7.89 (m, 1H), 8.11 (m, 1H), 8.30 (d, 1H, $J = 8.3$ Hz), 8.38 (s, 1H), 8.83 (d, 1H, $J = 8.3$ Hz); EIMS m/z 307 (M^+). Anal. Calcd for $C_{20}H_{22}ClNO_2$ (343.9): C, 69.86; H, 6.45; N, 4.07. Found: C, 69.68; H, 6.57; N, 4.03.

5.9. General method for the synthesis of methyl/ethyl 2-(2-substituted/2,8-disubstituted-4-quinolyl)acetates (14a–j)

These analogues were synthesized from methyl 2-(4-quinolyl)acetate (**13a**) or ethyl 2-(4-quinolyl)acetate (**13b**) using procedure reported above for methyl ring-substituted-2-quinolinecarboxylate (**3a**–**g**).

5.9.1. Methyl 2-(2-cyclopentyl-4-quinolyl)acetate (14a). Yield: 39%; oil; IR (neat) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) 1.76–1.93 (m, 8H), 2.81 (m, 1H), 3.72 (s, 3H), 4.03 (s, 2H), 7.15 (s, 1H), 7.51 (m, 1H), 7.73 (m, 1H), 7.91 (d, 1H, $J = 8.3$ Hz), 8.05 (d, 1H, $J = 8.3$ Hz); ESIMS m/z 270 (M + 1). Anal. Calcd for $C_{17}H_{19}NO_2$ (269.3): C, 75.81; H, 7.11; N, 5.20. Found: C, 75.74; H, 7.33; N, 5.29.

5.10. Methyl 2-(2,8-dicyclopentyl-4-quinolyl)acetate (14b)

Yield: 12%; oil; IR (neat) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.67–1.87 (m, 16H), 2.73 (m, 2H), 4.01 (s, 2H), 3.92 (s, 3H), 6.93 (s, 1H), 7.52 (m, 1H), 7.60 (d, 1H, $J = 7.9$ Hz), 7.81 (d, 1H, $J = 8.2$ Hz); APCIMS m/z 338 (M + 1). Anal. Calcd for $C_{22}H_{27}NO_2$ (337.5): C, 78.30; H, 8.06; N, 4.15. Found: C, 78.16; H, 7.88; N, 4.37.

5.10.1. Methyl 2-(2-cyclohexyl-4-quinolyl)acetate (14c). Yield: 42%; oil; IR (neat) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) 1.55–1.70 (m, 10H), 2.88 (m, 1H), 3.72 (s, 3H), 4.08 (s, 2H), 7.17 (s, 1H), 7.54 (m, 1H), 7.70 (m, 1H), 7.89 (d, 1H, $J = 8.3$ Hz), 8.01 (d, 1H, $J = 8.3$ Hz); APCIMS m/z 284 (M + 1). Anal. Calcd for $C_{18}H_{21}NO_2$ (283.4): C, 76.29; H, 7.47; N, 4.94. Found: C, 76.22; H, 7.81; N, 4.91.

5.10.2. Methyl 2-(2,8-dicyclohexyl-4-quinolyl)acetate (14d). Yield: 12%; oil; IR (neat) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.65–1.80 (m, 20H), 2.91 (m, 2H), 3.75 (s, 3H), 4.01 (s, 2H), 6.91 (s, 1H), 7.48 (m, 1H), 7.64 (d, 1H, $J = 7.9$ Hz), 7.79 (d, 1H, $J = 8.2$ Hz); ESIMS m/z 366 (M + 1). Anal. Calcd for $C_{24}H_{31}NO_2$ (365.5): C, 78.86; H, 8.55; N, 3.83. Found: C, 78.88; H, 8.54; N, 3.97.

5.10.3. Methyl 2-[(1-adamantyl)-4-quinolyl]acetate (14e). Yield: 35%; mp 52–54 °C; IR (KBr) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) 1.70–1.90 (m, 15H), 3.70 (s, 3H), 4.06 (s, 2H), 6.91 (s, 1H), 7.51 (m, 1H), 7.67 (m, 1H), 7.92 (d, 1H, $J = 8.3$ Hz), 8.10 (d, 1H, $J = 8.3$ Hz); EIMS m/z 335 (M^+). Anal. Calcd for $C_{22}H_{25}NO_2$ (335.4): C, 78.77; H, 7.51; N, 4.18. Found: C, 78.69; H, 7.34; N, 4.41.

5.10.4. Ethyl 2-(2-cyclopentyl-4-quinolyl)acetate (14f). Yield: 45%; oil; IR (neat) 1733cm^{-1}; ^1H NMR ($CDCl_3$) 1.23 (t, 3H, $J = 6.9$ Hz), 1.60–1.90 (m, 8H), 2.88 (m, 1H), 4.03 (s, 2H), 4.15 (m, 2H), 7.21 (s, 1H), 7.50 (m, 1H), 7.67 (m, 1H), 7.94 (d, 1H, $J = 8.4$ Hz),

8.05 (d, 1H, $J = 8.4$ Hz); EIMS m/z 283 (M^+). Anal. Calcd for $C_{18}H_{21}NO_2$ (283.4): C, 76.29; H, 7.47; N, 4.94. Found: C, 76.11; H, 7.26; N, 5.05.

5.10.5. Ethyl 2-(2,8-dicyclopentyl-4-quinolyl)acetate (14g). Yield: 12%; oil; IR (neat) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) 1.22 (t, 3H, $J = 6.9$ Hz), 1.71–1.94 (m, 16H), 2.91 (m, 2H), 3.99 (s, 2H), 4.16 (m, 2H), 7.20 (s, 1H), 7.42 (m, 1H), 7.56 (d, 1H, $J = 7.7$ Hz), 7.76 (d, 1H, $J = 8.4$ Hz); ESIMS m/z 352 (M + 1). Anal. Calcd for $C_{23}H_{29}NO_2$ (351.5): C, 78.59; H, 8.32; N, 3.99. Found: C, 78.62; H, 8.37; N, 4.03.

5.10.6. Ethyl 2-(2-cyclohexyl-4-quinolyl)acetate (14h). Yield: 47%; oil; IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) 1.20 (t, 3H, $J = 7.0$ Hz), 1.60–1.90 (m, 10H), 2.87 (m, 1H), 4.05 (s, 2H), 4.16 (m, 2H), 7.19 (s, 1H), 7.52 (m, 1H), 7.65 (m, 1H), 7.99 (d, 1H, $J = 8.3$ Hz), 8.05 (d, 1H, $J = 8.5$ Hz); ESIMS m/z 298 (M + 1). Anal. Calcd for $C_{19}H_{23}NO_2$ (297.4): C, 76.73; H, 7.80; N, 4.71. Found: C, 76.69; H, 7.84; N, 4.84.

5.10.7. Ethyl 2-(2,8-dicyclohexyl-4-quinolyl)acetate (14i). Yield: 14%; oil; IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) 1.21 (t, 3H, $J = 7.0$ Hz), 2.02–2.22 (m, 20H), 2.88 (m, 2H), 3.99 (s, 2H), 4.15 (m, 2H), 7.19 (s, 1H), 7.43 (m, 1H), 7.51 (d, 1H, $J = 7.2$ Hz), 7.73 (d, 1H, $J = 8.0$ Hz); APCIMS m/z 380 (M + 1). Anal. Calcd for $C_{25}H_{33}NO_2$ (379.5): C, 79.11; H, 8.76; N, 3.69. Found: C, 79.39; H, 8.77; N, 3.23.

5.10.8. Ethyl 2-[2-(1-adamantyl)-4-quinolyl]acetate (14j). Yield: 41%; oil, IR (neat) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) 1.25 (t, 3H, $J = 7.0$ Hz), 1.65–1.92 (m, 15H), 4.04 (s, 2H), 4.17 (m, 2H), 7.43 (s, 1H), 7.50 (m, 1H), 7.66 (m, 1H), 7.94 (d, 1H, $J = 8.3$ Hz), 8.09 (d, 1H $J = 8.1$ Hz); ESIMS m/z 350 (M + 1). Anal. Calcd for $C_{23}H_{27}NO_2$ (349.5): C, 79.05; H, 7.79; N, 4.01. Found: C, 78.83; H, 7.87; N, 4.32.

5.11. General method for the synthesis of 2-(2,8-disubstituted-4-quinolyl)acetic acid hydrochloride (15a–b)

These analogues were synthesized from ethyl 2-(2,8-dicyclopentyl-4-quinolyl)acetate (**14g**) and ethyl 2-(2,8-dicyclohexyl-4-quinolyl)acetate (**14i**) using procedure reported above for ring-substituted-2-quinolinecarboxylic acid hydrochlorides (**4a**–**b**).

5.11.1. 2-(2,8-Dicyclopentyl-4-quinolyl)acetic acid hydrochloride (15a). Yield: 90%; mp 109–111 °C; IR (KBr) 3419, 2925, 1680, 1530 cm^{-1}; ^1H NMR (CD_3OD) 1.40–1.60 (m, 16H), 2.95 (m, 2H), 3.70 (s, 2H) 7.22 (s, 1H), 7.49 (m, 1H), 7.59 (d, 1H, $J = 8.4$ Hz), 7.73 (d, 1H, $J = 8.4$ Hz); ESIMS m/z 324 (M + 1). Anal. Calcd for $C_{21}H_{26}ClNO_2$ (359.9): C, 70.08; H, 7.28; N, 3.89. Found: C, 69.95; H, 7.07; N, 3.79.

5.11.2. 2-(2,8-Dicyclohexyl-4-quinolyl)acetic acid hydrochloride (15b). Yield: 95%; mp 101–103 °C; IR (KBr) 3450, 2930, 1682, 1528 cm^{-1}; ^1H NMR (CD_3OD) 1.67–1.87 (m, 20H), 2.97 (m, 2H), 3.57 (s, 2H), 7.12 (s, 1H), 7.47 (m, 1H), 7.59 (d, 1H, $J = 8.0$ Hz), 7.89 (d, 1H, $J = 8.0$ Hz); APCIMS m/z 352 (M + 1). Anal. Calcd for $C_{23}H_{30}ClNO_2$ (387.9): C, 71.21; H, 7.79; N, 3.61. Found: C, 71.47; H, 7.98; N, 3.55.

Broth Microdilution Assay: A loop full of *M. tuberculosis H37Rv* from Lowenstein–Jensen slants was inoculated into 100 mL of 7H9 broth medium (7H9 medium supplemented with 10% ADC and 0.001% Tween 80), and incubated at 37 °C for two weeks. Two days before the susceptibility testing, the culture was diluted 1:10 in fresh 7H9 broth medium. After two days, the culture was ultrasonicated to make a single cell suspension, and further diluted 1:10 in 7H9 broth just prior to the inoculation of microdilution tubes. This procedure yielded an actively growing culture, which reproducibly contained 5×10^6 CFU/mL as determined by plating. The stock solutions of the compounds were prepared in DMSO diluted 1:3 times in 7H9 broth. Further, serial two-fold dilutions of the compounds were prepared from the stock solutions in 7H9 broth medium to provide the final concentrations of 4.0, 2.0, 1.0, 0.5 and 0.25 μg/mL. The same concentrations were tested for isoniazid (INH), which was taken as the positive control. The autoclaved microdilution tubes contained 1600 μL 7H9 broth medium, 200 μL of drug dilution and 200 μL of 1:10 times diluted and ultrasonicated *M. tuberculosis* inocula. All the test tubes were tightly screw-capped and incubated at 37 °C for 14 days. The tubes were checked for the surface growth layer. The MIC was defined as the lowest concentration of test compounds at which the surface growth layer could not be observed. The negative controls included 7H9 broth with no drug and with equivalent amounts of DMSO as the experimental tubes. DMSO did not inhibit the growth of *M. tuberculosis* in the concentrations used for dissolving the compounds.

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