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Ring-substituted quinolines. Part 2: Synthesis and antimycobacterial activities of ring-substituted quinolinecarbohydrazide and ring-substituted quinolinecarboxamide analogues☆

Vikramdeep Monga,[a] Amit Nayyar,[a] Balasubramanian Vaitilingam,[a] Prakash B. Palde,[a] Sarbjit Singh Jhamb,[b] Sukhraj Kaur,[b] Prati Pal Singh[b] and Rahul Jain[a,*]

[a]*Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, S.A.S. Nagar, Punjab 160 062, India*
[b]*Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research, Sector 67, S.A.S. Nagar, Punjab 160 062, India*

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Abstract—Additional structural modifications of the 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 the ring-substituted quinolinecarbohydrazides (series 1–4) constituting 22 analogues. All new derivatives were evaluated for in vitro antimycobacterial activities against drug-sensitive *M. tuberculosis H37Rv* strain. Certain ring-substituted-2-quinolinecarbohydrazide analogues described herein showed good inhibitory activity. In particular, analogues 4-(1-adamantyl)-2-quinolinecarbohydrazide (**2d**), 4,5-dicyclopentyl-2-quinolinecarbohydrazide (**2e**), 4,8-dicyclopentyl-2-quinolinecarbohydrazide (**2f**), and 4,5-dicyclohexyl-2-quinolinecarbohydrazide (**2g**) have exhibited the MIC value of 6.25 μg/mL. Further investigation of the most suitable lead prototype, 4-(1-adamantyl)-2-quinolinecarbohydrazide (**2d**, series 1) led to the synthesis of N2-alkyl/N2,N2-dialkyl/N2-aryl-4-(1-adamantyl)-2-quinolinecarboxamides (series 5) consisting of 13 analogues. Some of the synthesized carboxamides **7a**, **7h**, and **7m** reported herein have exhibited excellent antimycobacterial activities in the range of 6.25–3.125 μg/mL against drug-sensitive and drug-resistant *M. tuberculosis H37Rv* strains.

1. Introduction

Despite the worldwide public health impact of tuberculosis, no new structural class of drug specifically targeting the causative organism, *Mycobacterium tuberculosis* is introduced in the market during the past 40 years.[2] Worldwide emergence of the multi-drug resistant strains of the *M. tuberculosis*, and resurgence of the disease especially in the immuno-compromised individuals are considered as the major factors for increase in the number of mortality cases.[3] The use of the genomic sequencing data[4] of *M. tuberculosis* for the discovery of new specific targets is still not fully developed and may take many more years to provide potentially useful target(s) based anti-tuberculosis drugs.[5–7]

Previously, through a structural-directed antimycobacterial drug-screening program we have reported the discovery of ring-substituted quinolines as a new structural class of anti-tuberculosis agent.[8] The most promising analogue, 2,8-dicyclopentyl-4-methylquinoline (DCMQ) has exhibited interesting anti-tuberculosis activities against both drug-sensitive and drug-resistant *M. tuberculosis H37Rv* strains.[8] Although, DCMQ itself is an attractive molecule for drug development and synthesized via a one-step transformation from lepidine, it suffers due to low yield (24%). With a view to overcome this drawback, we have undertaken a systematic study into the chemical optimization of DCMQ in order to define and determine more suitable pharmacophore(s) that

Keywords: Tuberculosis; Ring-substituted quinolinecarbohydrazides; Ring-substituted quinolinecarboxamides; 2,8-Dicyclopentyl-4-methylquinoline (DCMQ); 4-(1-Adamantyl)-2-quinolinecarbohydrazide (AQCH).
☆ See Ref. 1.
* Corresponding author. Tel.: +91 0172 221 4682; fax: +91 0172 221 4692; e-mail: rahuljain@niper.ac.in

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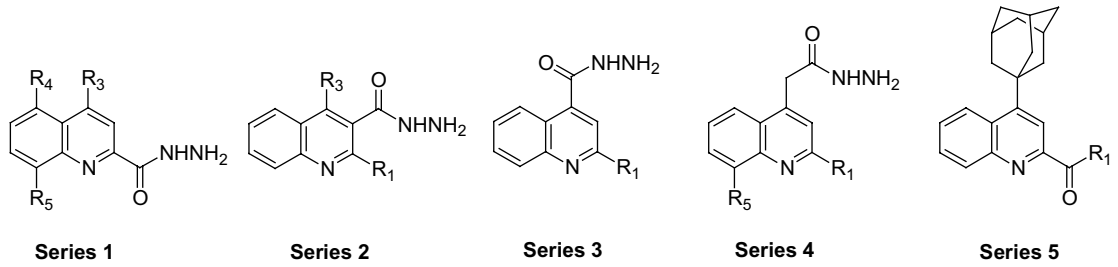
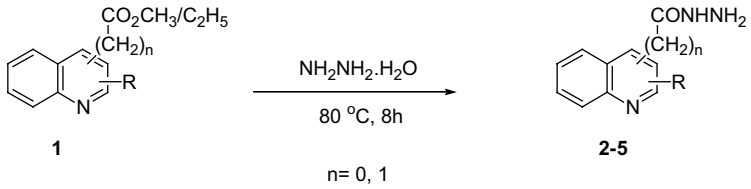


Figure 1.



Scheme 1.

could also result in overall improvement in the biological activity. Initially, we have decided to replace only the methyl group in DCMQ with other easily derivatized functional groups while at the same time retaining the cycloalkyl groups placed at the various positions of the quinoline ring. This strategy seemed particularly appealing since it has demonstrated that replacement of the methyl group by other functionalities like an amino, a nitro, or an ester group largely preserves or enhances the biological activity of the resulting analogues.[1,9] These results have encouraged us to further explore other functionalities as the replacement of methyl group. Herein, we describe synthesis and antimycobacterial activities of several ring-substituted quinolinecarbohydrazides (series 1–4, Fig. 1). It is worthwhile to mention that some of the ring-substituted quinoline esters used for the preparation of ring-substituted quinolinecarbohydrazides reported herein have produced good anti-tuberculosis activities as reported earlier.[1] Preliminary biological activity data indicated that the analogue 4-(1-adamantyl)-2-quinolinecarbohydrazide (**2d**, series 1) has exhibited interesting biological results. In addition, analogue **2d** is synthesized in three convenient steps from commercially available 2-quinolinecarboxylic acid in high overall yields. Hence, analogue **2d** is considered as an excellent lead prototype, and ideally suited to emulate while designing new analogues. Keeping these observations in mind, we decided to further investigate **2d** for structural optimization by synthesizing congeners, which may exhibit potent anti-tuberculosis activities. Thus, herein, we also report synthesis and antimycobacterial activities of several ring-substituted quinolinecarboxamides (series 5, Fig. 1).

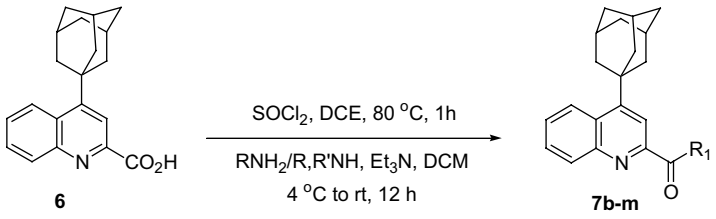
2. Chemistry

Various methyl 4-substituted/4,5-disubstituted/4,8-disubstituted-2-quinolinecarboxylates or methyl 2-substituted/2,4-disubstituted-3-quinolinecarboxylates or methyl 2-substituted-4-quinolinecarboxylates or methyl/ethyl 2-(2-substituted/2,8-disubstituted-4-quinolyl)acetates **1**,[1] upon reaction with hydrazine hydrate in 95% ethyl alcohol at 80 °C for 8 h produced 4-substituted/4,5-disubstituted/4,8-disubstituted-2-quinolinecarbohydrazides **2a**–**h** (series 1), 2-substituted/2,4-disubstituted-3-quinolinecarbohydrazides **3a**–**d** (series 2), 2-substituted-4-quinolinecarbohydrazides **4a**–**d** (series 3), and 2-(2-substituted/2,8-disubstituted-4-quinolyl)ethanohydrazides **5a**–**f** (series 4), respectively, in quantitative yields (Scheme 1).

As discussed above, further structural optimization of analogue **2d** was accomplished by synthesizing various carboxamide analogues **7a**–**m**. Thus, methyl 4-(1-adamantyl)-2-quinolinecarboxylate[1] upon reaction with 7 N NH_3/MeOH for 12 h at reflux temperature readily provided 4-(1-adamantyl)-2-quinolinecarboxamide (**7a**). On the other hand, 4-(1-adamantyl)-2-quinolinecarboxylic acid (**6**) required for the synthesis of N2-alkyl/N2,N2-dialkyl/N2-aryl-4-(1-adamantyl)-2-quinolinecarboxamides **7b**–**m** was prepared in three steps from commercially available 2-quinolinecarboxylic acid as described earlier.[1] Carboxylic acid **6** upon reaction with the excess of thionyl chloride in dichloroethane (DCE) at 80 °C for 1 h easily afforded the corresponding acid chloride, which upon reaction with the several commercially available primary and secondary alkyl amines and the aryl amines in dichloromethane (DCM) at 4 °C in the presence of triethylamine (Et_3N), followed by stirring for 12 h at ambient temperature afforded N2-alkyl/N2,N2-dialkyl/N2-aryl-4-(1-adamantyl)-2-quinolinecarboxamides **7b**–**m** (series 5) in satisfactory yields (Scheme 2).

3. Biological activity

In vitro activity of the synthesized analogues (series 1–5) for tuberculosis inhibition against *M. tuberculosis*

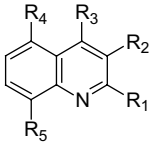


Scheme 2.

H37Rv strain (ATCC 27294, susceptible both to rifampicin and isoniazid) was 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 and 2. Compounds demonstrating ⩾90% inhibition at a concentration of 6.25 μg/mL in the initial screen were then retested at the lower concentrations of 3.125, 1.562, 1.0, 0.5, and 0.25 μg/mL to determine the actual MIC value that is defined as the lowest concentration exhibiting ⩾90% inhibition.

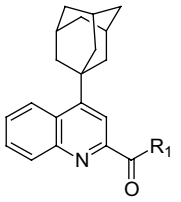
Several derivatives (**3c**, **5e**, and **5f**) appeared to have exhibited moderate inhibitory antimycobacterial activity (<70% inhibition, MICs > 6.25 μg/mL) against drug-sensitive *M. tuberculosis H37Rv* strain (Table 1). Four derivatives, 4-(1-adamantyl)-2-quinolinecarbohydrazide (**2d**), 4,5-dicyclopentyl-2-quinolinecarbohydrazide (**2e**), 4,8-dicyclopentyl-2-quinolinecarbohydrazide (**2f**), and 4,5-dicyclohexyl-2-quinolinecarbohydrazide (**2g**) exhibited excellent inhibitory activity against *M. tuberculosis H37Rv* and produced MIC value of 6.25 μg/mL (series 1, Table 1). In general it is observed that ring-substituted quinoline analogues containing hydrazide group placed at the C-3 and C-4 position of the quinoline ring are less

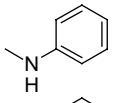
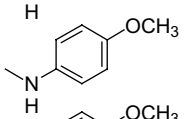
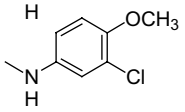
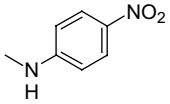
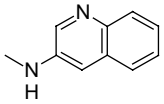
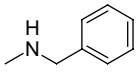
Table 1. In vitro antimycobacterial activity data of ring-substituted quinolinecarbohydrazides **2a**–**h** (series 1), **3a**–**d** (series 2), **4a**–**d** (series 3), and **5a**–**f** (series 4) against drug-sensitive strain of *M. tuberculosis H37Rv*



S. No.	R_1	R_2	R_3	R_4	R_5	(%) Inhibition	MIC (μg/mL)
Series 1							
2a	$CONHNH_2$	H	H	H	H	0	>6.25
2b	$CONHNH_2$	H	*c*-C_5H_9	H	H	0	>6.25
2c	$CONHNH_2$	H	*c*-C_6H_{11}	H	H	0	>6.25
2d	$CONHNH_2$	H	1-Adamantyl	H	H	99	6.25
2e	$CONHNH_2$	H	*c*-C_5H_9	*c*-C_5H_9	H	90	6.25
2f	$CONHNH_2$	H	*c*-C_5H_9	H	*c*-C_5H_9	92	6.25
2g	$CONHNH_2$	H	*c*-C_6H_{11}	*c*-C_6H_{11}	H	91	6.25
2h	$CONHNH_2$	H	*c*-C_6H_{11}	H	*c*-C_6H_{11}	23	>6.25
Series 2							
3a	H	$CONHNH_2$	H	H	H	0	>6.25
3b	1-Adamantyl	$CONHNH_2$	H	H	H	32	>6.25
3c	*c*-C_5H_9	$CONHNH_2$	*c*-C_5H_9	H	H	56	>6.25
3d	*c*-C_6H_{11}	$CONHNH_2$	*c*-C_6H_{11}	H	H	44	>6.25
Series 3							
4a	H	H	$CONHNH_2$	H	H	0	>6.25
4b	*c*-C_5H_9	H	$CONHNH_2$	H	H	2	>6.25
4c	*c*-C_6H_{11}	H	$CONHNH_2$	H	H	2	>6.25
4d	1-Adamantyl	H	$CONHNH_2$	H	H	17	>6.25
Series 4							
5a	H	H	$CH_2CONHNH_2$	H	H	9	>6.25
5b	*c*-C_5H_9	H	$CH_2CONHNH_2$	H	H	1	>6.25
5c	*c*-C_6H_{11}	H	$CH_2CONHNH_2$	H	H	12	>6.25
5d	1-Adamantyl	H	$CH_2CONHNH_2$	H	H	31	>6.25
5e	*c*-C_5H_9	H	$CH_2CONHNH_2$	H	*c*-C_5H_9	67	>6.25
5f	*c*-C_6H_{11}	H	$CH_2CONHNH_2$	H	*c*-C_6H_{11}	56	>6.25
DCMQ						100	6.25
Isoniazid						99	1.00

Table 2. In vitro antimycobacterial activity data of N2-alkyl/N2,N2-dialkyl/N2-aryl-4-(1-adamantyl)-2-quinolinecarboxamides **7a**–**m** (series 5) against drug-sensitive strain of *M. tuberculosis H37Rv*



S. No.	R_1	(%) Inhibition	MIC (μg/mL)
7a	NH_2	98	6.25
7b	$NH(CH_2)_2CH_3$	3	>6.25
7c	$NH(CH_2)_3CH_3$	22	>6.25
7d	$NH(CH_2)_4CH_3$	14	>6.25
7e	$NH(CH_2)_5CH_3$	12	>6.25
7f	$NH(CH_2)_6CH_3$	1	>6.25
7g	$N(CH_2CH_3)_2$	2	>6.25
7h		99	3.125
7i		35	>6.25
7j		35	>6.25
7k		43	>6.25
7l		40	>6.25
7m		99	3.125
DCMQ		100	6.25
Isoniazid		99	1.00

effective compared to the analogues in which hydrazide moiety is placed at the C-2 position. Interestingly though not surprisingly, carbohydrazide analogues **2a**, **3a**, **4a**, and **5a** where quinoline ring is not alkylated were found to be completely inactive. This affirms our earlier observation that the placement of suitable alkyl groups in the quinoline ring is utmost important for anti-tuberculosis activity.

New chemical entity, 4-(1-adamantyl)-2-quinolinecarbohydrazide (AQCH, **2d**) was further investigated, and a series of 13 analogues representing N2-alkyl/N2,N2-dialkyl/N2-aryl-4-(1-adamantyl)-2-quinolinecarboxamides **7a**–**m** was synthesized (series 5). Biological activity data revealed that one analogue 4-(1-adamantyl)-2-quinolinecarboxamide (**7a**) has exhibited good efficacy and exhibited 98% inhibition at a concentration of 6.25 μg/mL (MIC). Whereas, two analogues N2-phenyl-4-(1-adamantyl)-2-quinolinecarboxamide (**7h**) and N2-benzyl-4-(1-adamantyl)-2-quinolinecarboxamide (**7m**) have exhibited excellent antimycobacterial activity and produced 99% inhibition at a concentration of 3.125 μg/mL (MIC) (Table 2).

Two of the most effective derivatives, N2-phenyl-4-(1-adamantyl)-2-quinolinecarboxamide (**7h**) and N2-benzyl-4-(1-adamantyl)-2-quinolinecarboxamide (**7m**) were also evaluated for antimycobacterial activity against isoniazid resistant strain of *M. tuberculosis H37Rv* and derivative **7h** exhibited promising activity (99% inhibition, MIC = 6.25 μg/mL).

4. Conclusions

We have earlier reported the discovery of the 2,8-dicyclopentyl-4-methylquinoline (DCMQ) as a new anti-tuberculosis chemical entity. Our present studies on the systematic structural optimization of the DCMQ led to the synthesis and discovery of 4-(1-adamantyl)-2-quinolinecarbohydrazide (AQCH, **2d**) as another new chemical entity. As discussed earlier although, DCMQ itself is an attractive molecule for drug development; it suffers due to low yield. On the other hand, AQCH is equally potent compared to DCMQ, and is synthesized in high overall yields in three convenient steps. Thus, in our opinion AQCH is a more suitable molecule for lead optimization compared to DCMQ. Earlier we have observed that only dialkylated quinolines exhibit superior antimycobacterial activities as illustrated by DCMQ. The current study has established that a suitable bulky alkyl group containing quinolinecarbohydrazide **2d** also exhibits potent antimycobacterial activity. The results of this study also show that analogue **2d** is attractive for further lead optimization as observed from excellent anti-tuberculosis activities produced by two ring-substituted quinolinecarboxamides **7h** and **7m**. Our investigations on the further structural diversification of 4-(1-adamantyl)-2-quinolinecarbohydrazide (AQCH) are currently underway and results of these studies will be reported in the due course of time.

5. Experimental

Melting points were recorded on Mettler DSC 851 or capillary melting point apparatus and are uncorrected. ^1H 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 GCMS (Shimadzu QP 5000 spectrometer) auto sampler/direct injection (EI/CI) or HRMS (Finnigan Mat LCQ spectrometer) (APCI/ESI). 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. Typical procedure for the synthesis of various 4-substituted/4,5-disubstituted/4,8-disubstituted-2-quinolinecarbohydrazides 2a–h, 2-substituted/2,4-disubstituted-3-quinolinecarbohydrazides 3a–d, 2-substituted-4-quinolinecarbohydrazides 4a–d, and 2-(2-substituted/2,8-disubstituted-4-quinolyl)ethanohydrazides 5a–f

To a solution of methyl 4-substituted/4,5-disubstituted/4,8-disubstituted-2-quinolinecarboxylate or methyl 2-substituted/2,4-disubstituted-3-quinolinecarboxylate or methyl 2-substituted-4-quinolinecarboxylate[1] or methyl/ethyl 2-(2-substituted/2,8-disubstituted-4-quinolyl)acetate (**1**, 5 mmol) in 95% ethyl alcohol (10 mL) hydrazine hydrate (10 mL) was added and reaction mixture was heated under reflux for 8 h. The hydrazides **2a–h**, **3a–d**, **4a–d**, and **5a–f** were obtained in quantitative yields directly after evaporation of the reaction solution without any additional purification step.

5.1.1. 2-Quinolinecarbohydrazide (2a). Yield: 95%; mp 101–102 °C; ^{1}H NMR ($CDCl_3$): δ 5.81 (br s, 2H), 6.71 (m, 1H), 7.40 (br s, 1H), 7.48 (m, 1H), 7.72 (d, 1H, $J = 8.35$ Hz), 7.91 (d, 1H, $J = 8.60$ Hz), 8.40 (d, 1H, $J = 8.35$ Hz); EI MS *m/z* 187 (M^+); Anal. Calcd for $C_{10}H_9N_3O$ (187.2): C, 64.16; H, 4.85; N, 22.45. Found: C, 63.87; H, 5.10; N, 22.27.

5.1.2. 4-Cyclopentyl-2-quinolinecarbohydrazide (2b). Yield: 98%; mp 110–111 °C; ^{1}H NMR ($CDCl_3$): δ 1.63 (m, 8H), 3.30 (m, 1H), 4.11 (br s, 2H), 7.62 (m, 1H), 7.73 (m, 1H), 8.12 (m, 2H), 8.15 (br s, 1H), 8.35 (d, 1H, $J = 8.5$ Hz); EI MS *m/z* 255 (M^+); Anal. Calcd for $C_{15}H_{17}N_3O$ (255.3): C, 70.56; H, 6.71; N, 16.46. Found: C, 70.55; H, 6.68; N, 16.39.

5.1.3. 4-Cyclohexyl-2-quinolinecarbohydrazide (2c). Yield: 98%; mp 112 °C; ^{1}H NMR ($CDCl_3$): δ 1.60 (m, 10H), 3.36 (m, 1H), 4.11 (br s, 2H), 7.65 (m, 1H), 7.78 (m, 1H), 8.19 (m, 2H), 8.25 (br s, 1H), 8.37 (d, 1H, $J = 8.3$ Hz); EI MS *m/z* 269 (M^+); Anal. Calcd for $C_{16}H_{19}N_3O$ (269.3): C, 71.35; H, 7.11; N, 15.60. Found: C, 71.32; H, 7.04; N, 15.66.

5.1.4. 4-(1-Adamantyl)-2-quinolinecarbohydrazide (2d). Yield: 97%; mp 178 °C; ^{1}H NMR ($CDCl_3$): δ 1.88 (m, 15H), 4.13 (br s, 2H), 7.57 (m, 1H), 7.69 (m, 1H), 8.11 (d, 1H, $J = 8.3$ Hz), 8.19 (s, 1H), 8.66 (d, 1H, $J = 8.7$ Hz), 9.19 (br s, 1H); ESI MS *m/z* 322 (M+1); Anal. Calcd for $C_{20}H_{23}N_3O$ (321.4): C, 74.74; H, 7.21; N, 13.07. Found: C, 74.77; H, 7.19; N, 13.02.

5.1.5. 4,5-Dicyclopentyl-2-quinolinecarbohydrazide (2e). Yield: 92%; mp 107–108 °C; ^{1}H NMR ($CDCl_3$): δ 1.70 (m, 16H), 3.22 (m, 1H), 3.99 (m, 1H), 4.20 (br s, 2H), 7.53 (d, 1H, $J = 8.7$ Hz), 7.87 (m, 1H), 8.11 (s, 1H), 8.17 (br s, 1H), 8.25 (d, 1H, $J = 8.5$ Hz); ESI MS *m/z* 324 (M+1); Anal. Calcd for $C_{20}H_{25}N_3O$ (323.4): C, 74.27; H, 7.79; N, 12.99. Found: C, 74.55; H, 7.68; N, 13.05.

5.1.6. 4,8-Dicyclopentyl-2-quinolinecarbohydrazide (2f). Yield: 95%; mp 104–105 °C; ^{1}H NMR ($CDCl_3$): δ 1.68 (m, 16H), 3.21 (m, 1H), 4.02 (m, 1H), 4.15 (br s, 2H), 7.67 (d, 1H, $J = 8.7$ Hz), 7.87 (m, 2H), 8.17 (s, 1H), 8.20 (br s, 1H); ESI MS *m/z* 324 (M+1); Anal. Calcd for $C_{20}H_{25}N_3O$ (323.4): C, 74.27; H, 7.79; N, 12.99. Found: C, 74.21; H, 7.85; N, 12.83.

5.1.7. 4,5-Dicyclohexyl-2-quinolinecarbohydrazide (2g). Yield: 90%; mp 112–113 °C; ^{1}H NMR ($CDCl_3$): δ 1.65 (m, 20H), 3.41 (m, 1H), 4.01 (m, 1H), 4.11 (br s, 2H), 7.66 (d, 1H, $J = 8.4$ Hz), 7.85 (m, 1H), 8.15 (s, 1H), 8.19 (br s, 1H), 8.30 (d, 1H, $J = 8.4$ Hz); ESI MS *m/z* 352 (M+1); Anal. Calcd for $C_{22}H_{29}N_3O$ (351.5): C, 75.18; H, 8.32; N, 11.96. Found: C, 75.27; H, 8.47; N, 11.85.

5.1.8. 4,8-Dicyclohexyl-2-quinolinecarbohydrazide (2h). Yield: 97%; mp 114–115 °C; ^{1}H NMR ($CDCl_3$): δ 1.72 (m, 20H), 3.30 (m, 1H), 4.12 (m, 1H), 4.17 (br s, 2H), 7.69 (d, 1H, $J = 8.3$ Hz), 7.81 (m, 2H), 8.15 (s, 1H), 8.20 (br s, 1H); ESI MS *m/z* 352 (M+1); Anal. Calcd for $C_{22}H_{29}N_3O$ (351.5): C, 75.18; H, 8.32; N, 11.96. Found: C, 75.09; H, 8.31; N, 11.91.

5.1.9. 3-Quinolinecarbohydrazide (3a). Yield: 99%; mp 87–88 °C; ^{1}H NMR ($CDCl_3$): δ 4.99 (br s, 2H), 7.11 (m, 1H), 7.40 (m, 1H), 8.01 (d, 1H, $J = 8.3$ Hz), 8.11 (d, 1H, $J = 8.4$ Hz), 8.51 (s, 1H), 9.31 (s, 1H); EI MS *m/z* 187 (M^+); Anal. Calcd for $C_{10}H_9N_3O$ (187.2): C, 64.16; H, 4.85; N, 22.45. Found: C, 64.22; H, 4.97; N, 22.51.

5.1.10. 2-(1-Adamantyl)-3-quinolinecarbohydrazide (3b). Yield: 100%; mp 101–102 °C; ^{1}H NMR ($CDCl_3$): δ 2.00 (m, 15H), 5.16 (br s, 2H), 7.28 (m, 1H), 7.87 (m, 1H), 8.05 (d, 1H, $J = 8.3$ Hz), 8.20 (d, 1H, $J = 8.2$ Hz), 8.61 (s, 1H); EI MS *m/z* 321 (M^+); Anal. Calcd for $C_{20}H_{23}N_3O$ (321.4): C, 74.74; H, 7.21; N, 13.07. Found: C, 74.89; H, 7.43; N, 13.21.

5.1.11. 2,4-Dicyclopentyl-3-quinolinecarbohydrazide (3c). Yield: 95%; mp 99–100 °C; ^{1}H NMR ($CDCl_3$): δ 1.70 (m, 16H), 3.22 (m, 1H), 3.99 (m, 1H), 5.15 (br s, 2H), 7.75 (m, 1H), 7.81 (m, 1H), 8.11 (d, 1H, $J = 8.1$ Hz), 8.24 (d, 1H, $J = 8.4$ Hz); ESI MS *m/z* 324 (M+1); Anal. Calcd for $C_{20}H_{25}N_3O$ (323.4): C, 74.27; H, 7.79; N, 12.99. Found: C, 74.44; H, 7.61; N, 13.11.

5.1.12. 2,4-Dicyclohexyl-3-quinolinecarbohydrazide (3d). Yield: 98%; mp 104–105 °C; ^{1}H NMR ($CDCl_3$): δ 1.65 (m, 20H), 3.19 (m, 1H), 3.97 (m, 1H), 5.05 (br s, 2H), 7.71 (m, 1H), 7.86 (m, 1H), 8.14 (d, 1H, $J = 8.2$ Hz), 8.21 (d, 1H, $J = 8.3$ Hz); ESI MS *m/z* 352 (M+1); Anal. Calcd for $C_{22}H_{29}N_3O$ (351.5): C, 75.18; H, 8.32; N, 11.96. Found: C, 75.09; H, 8.31; N, 11.97.

5.1.13. 4-Quinolinecarbohydrazide (4a). Yield: 99%; mp 92–93 °C; ^{1}H NMR ($CDCl_3$): δ 5.14 (br s, 2H), 7.55 (m, 1H), 7.65 (m, 1H), 7.70 (s, 1H), 8.05 (d, 1H, $J = 8.4$ Hz), 8.15 (d, 1H, $J = 8.4$ Hz), 9.14 (s, 1H); EI MS *m/z* 187 (M^+); Anal. Calcd for $C_{10}H_9N_3O$ (187.2): C, 64.16; H, 4.85; N, 22.45. Found: C, 64.08; H, 4.77; N, 22.37.

5.1.14. 2-Cyclopentyl-4-quinolinecarbohydrazide (4b). Yield: 100%; mp 87 °C; ^{1}H NMR ($CDCl_3$): δ 1.56 (m, 8H), 3.20 (m, 1H), 4.23 (br s, 2H), 7.3 (s, 1H), 7.54 (m, 1H), 7.73 (m, 1H), 8.09 (d, 1H, J = 8.4 Hz), 8.13 (d, 1H, J = 8.4 Hz); ESI MS *m/z* 256 (M+1); Anal. Calcd for $C_{15}H_{17}N_3O$ (255.3): C, 70.56; H, 6.71; N, 16.46. Found: C, 70.77; H, 6.56; N, 16.44.

5.1.15. 2-Cyclohexyl-4-quinolinecarbohydrazide (4c). Yield: 100%; mp 96 °C; ^{1}H NMR ($CDCl_3$): δ 1.25 (m, 10H), 3.13 (m, 1H), 4.60 (br s, 2H), 7.38 (s, 1H), 7.54 (m, 1H), 7.72 (m, 1H), 8.08 (d, 1H, J = 8.3 Hz), 8.13 (d, 1H, J = 8.3 Hz); ESI MS *m/z* 270 (M+1); Anal. Calcd for $C_{16}H_{19}N_3O$ (269.3): C, 71.35; H, 7.11; N, 15.60. Found: C, 71.51; H, 7.37; N, 15.78.

5.1.16. 2-(1-Adamantyl)-4-quinolinecarbohydrazide (4d). Yield: 100%; mp 108 °C; ^{1}H NMR ($CDCl_3$): δ 1.95 (m, 15H), 4.42 (br s, 2H), 7.51 (m, 2H), 7.71 (m, 1H), 8.11 (m, 2H); ESI MS *m/z* 322 (M+1); Anal. Calcd for $C_{20}H_{23}N_3O$ (321.4): C, 74.74; H, 7.21; N, 13.07. Found: C, 74.63; H, 7.08; N, 13.11.

5.1.17. 2-(4-Quinolyl)ethanohydrazide (5a). Yield: 91%; mp 101 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.81 (br s, 2H), 3.97 (s, 2H), 7.41 (d, 1H, J = 8.4 Hz), 7.58 (m, 1H), 7.72 (m, 1H), 8.09 (d, 1H, J = 8.8 Hz), 8.13 (d, 1H, J = 8.4 Hz), 8.87 (d, 1H, J = 8.4 Hz), 8.99 (br s, 1H); ESI MS *m/z* 202 (M+1); Anal. Calcd for $C_{11}H_{11}N_3O$ (201.2): C, 65.66; H, 5.51; N, 20.88. Found: C, 65.39; H, 5.43; N, 20.78.

5.1.18. 2-(2-Cyclopentyl-4-quinolyl)ethanohydrazide (5b). Yield: 89%; mp 112 °C; NMR ($CDCl_3$): δ 1.99 (m, 8H), 3.77 (m, 1H), 3.85 (br s, 2H), 4.00 (s, 2H), 6.57 (br s, 1H), 7.21 (s, 1H), 7.53 (m, 1H), 7.70 (m, 1H), 7.89 (d, 1H, J = 8.4 Hz), 8.07 (d, 1H, J = 8.4 Hz); APCI MS *m/z* 270 (M+1); Anal. Calcd for $C_{16}H_{19}N_3O$ (269.3): C, 71.35; H, 7.11; N, 15.60. Found: C, 71.67; H, 7.37; N, 15.74.

5.1.19. 2-(2-Cyclohexyl-4-quinolyl)ethanohydrazide (5c). Yield: 88%; mp 105 °C; ^{1}H NMR ($CDCl_3$): δ 1.71 (m, 10H), 3.10 (m, 1H), 3.89 (br s, 2H), 4.08 (s, 2H), 6.54 (br s, 1H), 7.12 (s, 1H), 7.54 (m, 1H), 7.65 (m, 1H), 7.99 (d, 1H, J = 8.3 Hz), 8.05 (d, 1H, J = 8.5 Hz); ESI MS, *m/z* 284 (M+1); Anal. Calcd for $C_{17}H_{21}N_3O$ (283.4): C, 72.06; H, 7.47; N, 14.83. Found: C, 72.31; H, 7.33; N, 14.67.

5.1.20. 2-[2-(1-Adamantyl)-4-quinolyl]ethanohydrazide (5d). Yield: 92%; mp 97 °C; ^{1}H NMR ($CDCl_3$): δ 1.88 (m, 15H), 3.84 (br s, 2H), 4.02 (s, 2H), 6.51 (br s, 1H), 7.39 (s, 1H), 7.52 (m, 1H), 7.69 (m, 1H), 7.88 (d, 1H, J = 8.1 Hz), 8.10 (d, 1H, J = 8.3 Hz); EI MS *m/z* 335 (M^+); Anal. Calcd for $C_{21}H_{25}N_3O$ (335.4): C, 75.19; H, 7.51; N, 12.53. Found: C, 75.44; H, 7.59; N, 12.41.

5.1.21. 2-(2,8-Dicyclopentyl-4-quinolyl)ethanohydrazide (5e). Yield: 100%; mp 88 °C; ^{1}H NMR ($CDCl_3$): δ 1.37 (m, 16H), 3.13 (m, 1H), 3.77 (m, 3H), 4.00 (s, 2H), 6.51 (br s, 1H), 7.20 (s, 1H), 7.51 (m, 1H), 7.74 (m, 1H), 7.87 (d, 1H, J = 8.4 Hz); ESI MS *m/z* 338 (M+1); Anal. Calcd for $C_{21}H_{27}N_3O$ (337.5): C, 74.74; H, 8.06; N, 12.45. Found: C, 74.88; H, 8.21; N, 12.37.

5.1.22. 2-(2,8-Dicyclohexyl-4-quinolyl)ethanohydrazide (5f). Yield: 97%; mp 92–93 °C; ^{1}H NMR ($CDCl_3$): δ 1.35 (m, 20H), 3.11 (m, 1H), 3.74 (m, 3H), 3.99 (s, 2H), 6.47 (br s, 1H), 7.15 (s, 1H), 7.57 (m, 1H), 7.77 (m, 1H), 7.90 (d, 1H, J = 8.3 Hz); ESI MS *m/z* 366 (M+1); Anal. Calcd for $C_{23}H_{31}N_3O$ (365.5): C, 75.58; H, 8.55; N, 11.50. Found: C, 75.41; H, 8.37; N, 11.77.

5.2. Synthesis of 4-(1-adamantyl)-2-quinolinecarboxamide (7a)

A solution of methyl 4-(1-adamantyl)-2-quinolinecarboxylate[1] (500 mg, 1.5 mmol) in 7 N NH_3/MeOH (50 mL) was refluxed for 12 h. The desired product **7a** was obtained directly after evaporation of the solvent without any additional purification step. Yield: 94%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 1.89 (m, 15H), 5.89 (br s, 2H), 7.58 (m, 1H), 7.70 (m, 1H), 8.13 (m, 1H), 8.25 (s, 1H), 8.67 (d, 1H, J = 8.6 Hz); ESI MS *m/z* 307 (M+1); Anal. Calcd for $C_{20}H_{22}N_2O$ (306.4): C, 78.40; H, 7.24; N, 9.14. Found: C, 78.63; H, 7.21; N, 9.27.

5.3. Typical procedure for the synthesis of N2-alkyl/N2,N2-dialkyl/N2-aryl-4-(1-adamantyl)-2-quinolinecarboxamides (7b–m)

To a mixture of 4-(1-adamantyl)-2-quinolinecarboxylic acid hydrochloride[1] (**6**, 5 mmol) in dichloroethane (5 mL), thionyl chloride (10 mL) was added and the reaction mixture was heated with stirring at 80 °C for 1 h. Solvent and excess of $SOCl_2$ were removed under reduced pressure to afford acid chloride. The intermediate acid chloride was immediately dissolved in anhydrous CH_2Cl_2 (5 mL) and cooled to 4 °C. Alkyl/aryl amine (5.5 mmol) and Et_3N (15 mmol) were added to the precooled solution. Reaction mixture was allowed to attain room temperature and stirred for 12 h. The solvent was removed under reduced pressure, and residue was dissolved in chloroform (50 mL). Organic layer was washed with water (2 × 5 mL) and brine (2 × 5 mL). The organic layer was dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by column chromatography using EtOAc/hexanes (20:80) to afford N2-alkyl/N2,N2-dialkyl/N2-aryl-4-(1-adamantyl)-2-quinolinecarboxamides **7b–m** in satisfactory yields.

5.3.1. N2-Propyl-4-(1-adamantyl)-2-quinolinecarboxamide (7b). Yield: 66%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 0.85 (m, 3H), 1.45 (m, 2H), 1.89 (m, 15H), 3.48 (q, 2H, J = 6.8 Hz), 7.56 (m, 1H), 7.68 (m, 1H), 8.13 (d, 1H, J = 8.7 Hz), 8.26 (m, 2H), 8.66 (d, 1H, J = 8.7 Hz); APCI MS *m/z* 349 (M+1); Anal. Calcd for $C_{23}H_{28}N_2O$ (348.5): C, 79.27; H, 8.10; N, 8.04. Found: C, 79.15; H, 8.19; N, 8.14.

5.3.2. N2-Butyl-4-(1-adamantyl)-2-quinolinecarboxamide (7c). Yield: 75%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H, J = 6.8 Hz), 1.49 (m, 4H), 1.89 (m, 15H), 3.45

(q, 2H, $J = 6.7$ Hz), 7.52 (m, 1H), 7.67 (m, 1H), 8.15 (d, 1H, $J = 8.7$ Hz), 8.21 (br s, 1H), 8.27 (s, 1H), 8.69 (d, 1H, $J = 8.5$ Hz); APCI MS *m/z* 363 (M+1); Anal. Calcd for $C_{24}H_{30}N_2O$ (362.5): C, 79.52; H, 8.34; N, 7.73. Found: C, 79.81; H, 8.37; N, 7.98.

5.3.3. N2-Pentyl-4-(1-adamantyl)-2-quinolinecarboxamide (7d). Yield: 56%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 0.92 (m, 7H), 1.40 (m, 2H), 1.89 (m, 15H), 3.51 (q, 2H, $J = 6.8$ Hz), 7.52 (m, 1H), 7.64 (m, 1H), 8.12 (d, 1H, $J = 8.3$ Hz), 8.20 (br s, 1H), 8.27 (s, 1H), 8.64 (d, 1H, $J = 8.7$ Hz); ESI MS *m/z* 377 (M+1); Anal. Calcd for $C_{25}H_{32}N_2O$ (376.5): C, 79.75; H, 8.57; N, 7.44. Found: C, 79.76; H, 8.64; N, 7.29.

5.3.4. N2-Hexyl-4-(1-adamantyl)-2-quinolinecarboxamide (7e). Yield: 49%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 0.91 (m, 7H), 1.88 (m, 19H), 3.52 (q, 2H, $J = 6.7$ Hz), 7.55 (m, 1H), 7.68 (m, 1H), 8.14 (d, 1H, $J = 8.3$ Hz), 8.26 (m, 2H), 8.66 (d, 1H, $J = 8.7$ Hz); APCI MS *m/z* 391 (M+1); Anal. Calcd for $C_{26}H_{34}N_2O$ (390.6): C, 79.96; H, 8.77; N, 7.17. Found: C, 79.85; H, 8.91; N, 7.09.

5.3.5. N2-Heptyl-4-(1-adamantyl)-2-quinolinecarboxamide (7f). Yield: 61%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, $J = 6.5$ Hz), 1.35 (m, 8H), 1.66 (m, 2H), 1.88 (m, 15H), 3.51 (q, 2H, $J = 6.7$ Hz), 7.54 (m, 1H), 7.68 (m, 1H), 8.13 (d, 1H, $J = 8.4$ Hz), 8.29 (m, 2H), 8.66 (d, 1H, $J = 8.7$ Hz); ESI MS *m/z* 405 (M+1); Anal. Calcd for $C_{27}H_{36}N_2O$ (404.6): C, 80.15; H, 8.97; N, 6.92. Found: C, 80.19; H, 8.94; N, 6.78.

5.3.6. N2,N2-Diethyl-4-(1-adamantyl)-2-quinolinecarboxamide (7g). Yield: 44%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 1.25 (m, 6H), 1.88 (m, 15H), 3.42 (q, 2H, $J = 7.0$ Hz), 3.62 (q, 2H, $J = 7.0$ Hz), 7.52 (m, 1H), 7.56 (s, 1H), 7.66 (m, 1H), 8.13 (d, 1H, $J = 8.2$ Hz), 8.63 (d, 1H, $J = 8.7$ Hz); APCI MS *m/z* 363 (M+1); Anal. Calcd for $C_{24}H_{30}N_2O$ (362.5): C, 79.52; H, 8.34; N, 7.73. Found: C, 79.31; H, 8.22; N, 7.89.

5.3.7. N2-Phenyl-4-(1-adamantyl)-2-quinolinecarboxamide (7h). Yield: 69%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 1.90 (m, 15H), 7.16 (m, 1H), 7.42 (m, 2H), 7.60 (m, 1H), 7.73 (m, 1H), 7.86 (m, 2H), 8.22 (d, 1H, $J = 8.1$ Hz), 8.36 (s, 1H), 8.70 (d, 1H, $J = 8.7$ Hz), 10.24 (br s, 1H); APCI MS *m/z* 383 (M+1); Anal. Calcd for $C_{26}H_{26}N_2O$ (382.5): C, 81.64; H, 6.85; N, 7.32. Found: C, 81.93; H, 6.97; N, 7.18.

5.3.8. N2-(4-Methoxyphenyl)-4-(1-adamantyl)-2-quinolinecarboxamide (7i). Yield: 59%; mp 228–230 °C; ^{1}H NMR ($CDCl_3$): δ 1.90 (m, 15H), 3.84 (s, 3H), 6.95 (d, 2H, $J = 8.9$ Hz), 7.59 (m, 1H), 7.74 (m, 3H), 8.21 (d, 1H, $J = 8.4$ Hz), 8.35 (s, 1H), 8.69 (d, 1H, $J = 8.6$ Hz), 10.13 (br s, 1H); ESI MS *m/z* 413 (M+1); Anal. Calcd for $C_{27}H_{28}N_2O_2$ (412.5): C, 78.61; H, 6.84; N, 6.79. Found: C, 78.88; H, 6.71; N, 6.58.

5.3.9. N2-(3-Chloro-4-methoxyphenyl)-4-(1-adamantyl)-2-quinolinecarboxamide (7j). Yield: 66%; mp 242 °C; ^{1}H NMR ($CDCl_3$): δ 1.90 (m, 15H), 3.93 (s, 3H), 6.97 (d, 1H, $J = 8.8$ Hz), 7.60 (m, 1H), 7.74 (m, 2H), 7.92 (s, 1H), 8.20 (d, 1H, $J = 8.3$ Hz), 8.33 (s, 1H), 8.70 (d, 1H, $J = 8.7$ Hz), 10.14 (br s, 1H); EI MS *m/z* 446 (M^+); Anal. Calcd for $C_{27}H_{27}ClN_2O_2$ (446.9): C, 72.55; H, 6.09; N, 6.27. Found: C, 72.67; H, 6.11; N, 6.34.

5.3.10. N2-(4-Nitrophenyl)-4-(1-adamantyl)-2-quinolinecarboxamide (7k). Yield: 48%; mp 191–192 °C; ^{1}H NMR ($CDCl_3$): δ 1.91 (m, 15H), 7.62 (m, 1H), 7.74 (m, 3H), 8.32 (m, 3H), 8.69 (d, 1H, $J = 8.5$ Hz), 9.11 (d, 1H, $J = 8.4$ Hz), 13.10 (br s, IH); ESI MS *m/z* 428 (M+1); Anal. Calcd for $C_{26}H_{25}N_3O_3$ (427.5): C, 73.05; H, 5.89; N, 9.83. Found: C, 73.11; H, 5.79; N, 9.75.

5.3.11. N2-[3-(Quinolyl)-4-(1-adamantyl)]-2-quinolinecarboxamide (7l). Yield: 21%; mp 244–245 °C; ^{1}H NMR ($CDCl_3$): δ 1.92 (m, 15H), 7.62 (m, 3H), 7.77 (m, 1H), 7.88 (d, 1H, $J = 7.9$ Hz), 8.10 (d, 1H, $J = 8.2$ Hz), 8.28 (d, 1H, $J = 9.0$ Hz), 8.39 (s, 1H), 8.72 (d, 1H, $J = 8.7$ Hz), 9.07 (m, 2H), 10.52 (br s, 1H); ESI MS *m/z* 434 (M+1); Anal. Calcd for $C_{29}H_{27}N_3O$ (433.5): C, 80.34; H, 6.28; N, 9.69. Found: C, 80.57; H, 6.15; N, 9.89.

5.3.12. N2-Benzyl-4-(1-adamantyl)-2-quinolinecarboxamide (7m). Yield: 94%; mp 157–159 °C; ^{1}H NMR ($CDCl_3$): δ 1.89 (m, 15H), 4.74 (m, 2H), 7.36 (m, 5H), 7.56 (m, 1H), 7.67 (m, 1H), 8.09 (d, 1H, $J = 7.9$ Hz), 8.30 (s, 1H), 8.61 (br s, 1H), 8.66 (d, 1H, $J = 8.5$ Hz); APCI MS *m/z* 397 (M+1); Anal. Calcd for $C_{27}H_{28}N_2O$ (396.5): C, 81.78; H, 7.12; N, 7.06. Found: C, 81.93; H, 7.02; N, 7.31.

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