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# Synthesis, biological evaluation and 3D-QSAR study of hydrazide, semicarbazide and thiosemicarbazide derivatives of 4-(adamantan-1-yl)quinoline as anti-tuberculosis agents

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ABSTRACT

We report synthesis, anti-tuberculosis activity and 3D-QSAR study of forty nine hydrazide, semicarbazide and thiosemicarbazide derivatives of 4-(adamantan-1-yl)quinoline. The most potent compounds upon evaluation for anti-tuberculosis activity exhibited $MIC_{99}$ of 3.125 μg/mL against *Mycobacterium tuberculosis H37Rv* strain. We applied the *in silico* technique of 3D-QSAR to study structure activity relationship of the synthesized compounds. The developed CoMFA model exhibited excellent $r^2_{ncv}$ of 0.971, and $r^2_{cv}$ of 0.543. The predicted $r^2_{pred}$ of 0.883 showed that the predicted values were in good agreement with the experimental values. Further, the contour map analysis, suggested that the sterically bulky and electronegative substitutions at the *para* position of the phenyl ring are favorable for anti-tuberculosis activity.



## 1. Introduction

The appearance of extreme drug resistance and totally drug resistance strains of tuberculosis (TB) created a need for the new anti-TB agents, which can effectively cure all forms of the disease [1]. The numbers of TB cases are still at a high level with 8.8 million cases annually, and approximately 1.45 million deaths, worldwide [2]. Moreover, development of TB in conjunction with AIDS has further intensified the problems associated with its cure, because both diseases (TB and AIDS) speed up each other progression [3]. The current chemotherapy is inadequate in meeting emerging challenges in the treatment of TB, underling the importance of the discovery process in identifying new classes of compounds.

We have earlier identified 4-(adamantan-1-yl)quinoline-2-carbohydrazide (**2**, Scheme 1) as a promising antimycobacterial from a series of ring-substituted quinoline-carbohydrazides/carboxamides [4]. The compound **2** exhibited $MIC_{99}$ of 3.125 μg/mL, when tested against *Mycobacterium tuberculosis* H37Rv strain. The compound **2** was synthesized in good yield from the inexpensive starting material in a convenient three-step synthesis, making it an ideal structural prototype around which additional structural optimization could be initiated. Moreover, the presence of a novel structure suggests cross-resistance to this structurally different anti-tuberculosis compound with the existing TB drugs is diminished to a greater extent. Therefore, **2** can be considered suitable for the further structural optimization. The semicarbazides and thiosemicarbazide derivatives are known as the effective pharmacophore for anti-tuberculosis activity [5–10]. For example, Fox et al., identified thiosemicarbazones of isonicotinaldehyde (derivative of isoniazid) as the potential anti-TB agents with activity comparable to that of isoniazid [11]. Sriram et al., reported oxazolyl thiosemicarbazones as potent anti-TB compounds, with most promising analogue exhibiting MIC of 0.05 μg/mL, against MTB and MDR-TB *in vitro* [12]. The thiosemicarbazide derivatives of quinoline, when evaluated against a variety of Gram-positive and Gram-negative bacteria and yeast, exhibited activity comparable with the standard drugs used in the assay [13]. Keeping these observations in mind, we have designed a series of hydrazide, thiosemicarbazide and semicarbazide derivatives of 4-(adamantan-1-yl)quinoline-2-carbohydrazide (**2**), and herein, we report their synthesis, antimycobacterial activity and 3D-QSAR studies.

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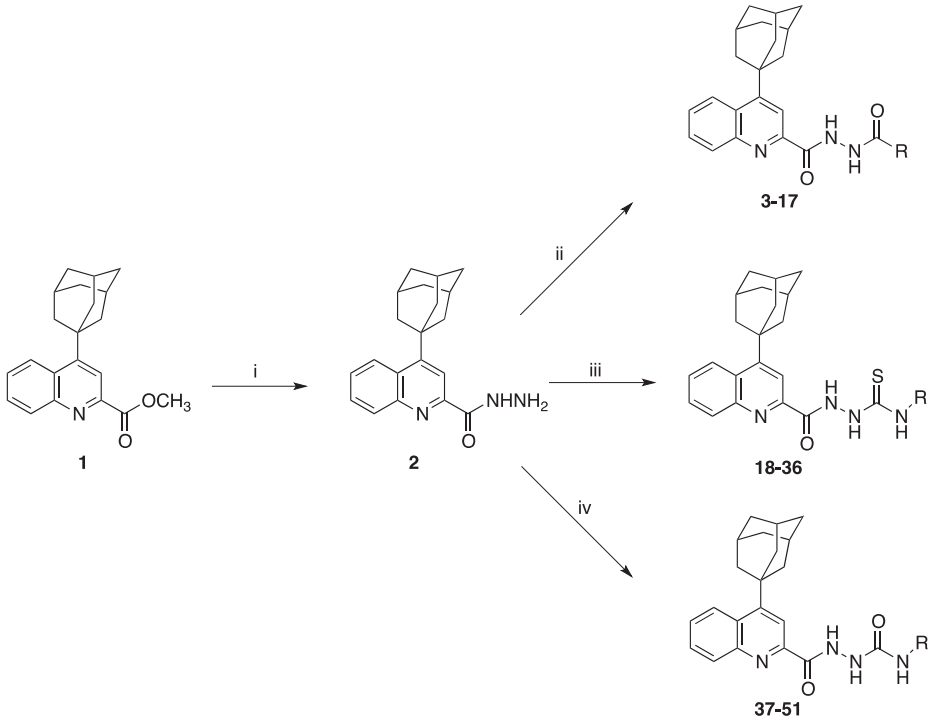
0223-5234/




**Scheme 1.** (i) $NH_2NH_2 \cdot H_2O$, $CH_3OH$, 70 °C, 8 h; (ii) RCOCl, $Et_3N$, $CH_2Cl_2$, RT, 2 h; (iii) R-NCS, THF, RT, 4 h; (iv) R-NCO, THF, RT, 4 h.

## 2. Result and discussion

### 2.1. Chemistry

Methyl 4-(adamantan-1-yl)quinoline-2-carboxylate (**1**, Scheme 1) was conveniently synthesized using a method previously described, using a silver-catalyzed homolytic free radical alkylation reaction [4,14]. The compound **1** was converted to 4-(adamantan-1-yl)quinoline-2-carbohydrazide (**2**, Scheme 1) by reaction with hydrazine hydrate in $CH_3OH$ under reflux temperature for 8 h. Compound **2** upon reaction with various alkyl/aryl/heteroaryl acid chlorides in the presence of triethylamine ($Et_3N$) in anhydrous $CH_2Cl_2$ at ambient temperature gave *N*′-alkyl/aryl/heteroaryl-4-(adamantan-1-yl)quinoline-2-carbohydrazides (**3**–**17**, Series 1, Scheme 1). The reaction of **2** with a library of alkyl/aryl isothiocyanates at ambient temperature cleanly afforded *N*-alkyl/aryl-2-{[4-(adamantan-1-yl)quinolin-2-yl]carbonyl}hydrazinecarbothioamides (**18**–**36**, Series 2, Scheme 1). Likewise, **2** upon reaction with alkyl/aryl isocyanates afforded *N*-alkyl/aryl-2-{[4-(adamantan-1-yl)quinolin-2-yl]carbonyl}hydrazinecarboxamides (**37**–**51**, Series 3, Scheme 1).

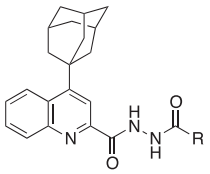
### 2.2. Biological activity

*In vitro* activity of the synthesized analogues for the tuberculosis inhibition against *M. tuberculosis* H37Rv strain (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 [15]. The compounds exhibiting fluorescence were then tested in the BACTEC 460 radiometric system [16], and activities expressed as Minimum Inhibitory Concentration (MIC, μg/mL) are summarized in Tables 1–3. The compounds demonstrating ≥90% inhibition at 6.25 μg/mL in the initial screen were retested at the lower concentrations of 3.125 and 1.56 μg/mL to determine the actual MIC value that is defined as the lowest concentration exhibiting ≥90% inhibition. Standard drugs used for testing were isoniazid and rifampicin, which exhibited $MIC_{99}$ at the concentrations of 0.1 μg/mL and 0.2 μg/mL, respectively.

The carbohydrazide derivatives **3**–**17**, in general exhibited moderate anti-TB activities (Table 1). The most active compound **16** (R = 2-naphthyl) exhibited 90% inhibition, while compound **13** (R = 1-naphthyl) exhibited 88% inhibition at 6.25 μg/mL. The replacement of the naphthyl ring with a phenyl ring (**10**) resulted in the reduction in activity (12% inhibition). The introduction of a 3-pyridyl and 4-pyridyl ring (**12** and **14**, respectively) resulted in an increase in activity (56% and 75% inhibition, respectively) at 6.25 μg/mL. The compounds bearing electron-withdrawing substituent on the phenyl ring, such as **7** (R = pentafluorophenyl) and **11** (R = 3-trifluoromethylphenyl) exhibited modest activity (88% and 69% inhibition at 6.25 μg/mL, respectively). Compounds containing the five membered heteroaromatic rings in the side chain (**5** and **8**) were inactive. On the other hand, the aliphatic side chain containing compounds **3** (R = undecanoyl), **4** (R = undec-10-enoyl) and **6** (R = pentadecanoyl) exhibited moderate inhibitory activity of 32%, 50% and 79% at 6.25 μg/mL, respectively; while, compound **15** (R = adamantan-1-yl) exhibited 87% inhibition at 6.25 μg/mL.

From Series 2, the most active compound **27** (R = 2-chloro-4-nitrophenyl) exhibited 96% inhibition at the test concentration of 6.25 μg/mL (Table 2). The compounds **29** (R = 4-nitrophenyl) and **35** (R = 4-trifluoromethoxyphenyl) also exhibited promising inhibitory activity of 94% and 89%, respectively, at 6.25 μg/mL. The compounds bearing chloro group such as **21** (R = 2,3-dichlorophenyl) and **23** (R = 2,5-dichlorophenyl) exhibited 74% and 43% inhibition at 6.25 μg/mL, respectively. The 2-ethylphenyl group-containing compound (**26**) exhibited 89% inhibition at 6.25 μg/mL; while, 2,6-dimethylphenyl ring containing analogue (**25**) exhibited moderate activity (51% inhibition) at 6.25 μg/mL. The compound **22** (R = 2,5-dimethoxyphenyl) showed inhibitory activity of 81% whereas compound **28** (R = 2-methoxy-5-methylphenyl) exhibited only 12% inhibition at 6.25 μg/mL. The introduction of alkyl groups as in compounds **30** (R = ethyl), **31** (R = allyl) and **32** (R = *tert*-butyl) resulted in 72%, 77% and 90%

**Table 1**
*In vitro* antimycobacterial activity and $pIC_{50}$s of *N′*-alkyl/aryl/heteroaryl-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinoline-2-carbohydrazides (**3**–**17**, **Series 1**) against drug-sensitive *M. tuberculosis H37Rv* strain.



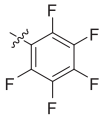
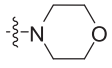
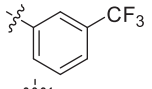
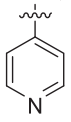
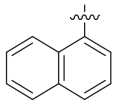
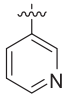
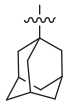
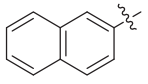
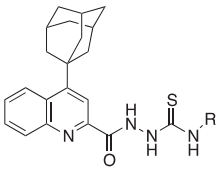
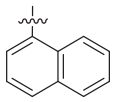
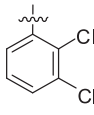
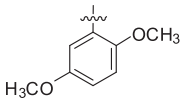
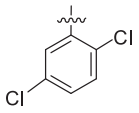
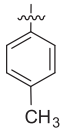
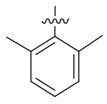
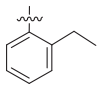
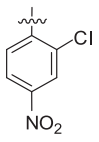
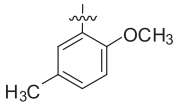
| Compound no. | R | (%) Inhibition | MIC (μg/mL) | $pIC_{50}$ |
|---|---|---|---|---|
| **3** |  | 32 | 6.25 | 4.60 |
| **4** |  | 50 | 6.25 | 4.89 |
| **5** |  | 0 | 6.25 | – |
| **6** |  | 79 | 6.25 | 5.47 |
| **7** |  | 88 | 6.25 | 5.66 |
| **8** |  | 9 | 6.25 | 3.83 |
| **9** |  | 3 | 6.25 | 3.53 |
| **10** |  | 12 | 6.25 | 4.25 |
| **11** |  | 69 | 6.25 | 5.30 |
| **12** |  | 56 | 6.25 | 4.58 |
| **13** |  | 88 | 6.25 | 5.35 |
| **14** |  | 74 | 6.25 | 5.33 |
| **15** |  | 87 | 6.25 | 5.67 |
| **16** |  | 90 | 6.25 | 5.33 |
| **17** |  | 5 | 6.25 | 3.42 |
| **INH** | | 99 | 0.1 | |
| **RIF** | | 99 | 0.2 | |

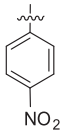
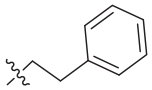
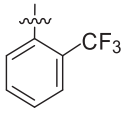
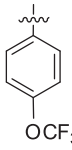
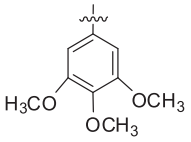
**Table 2**
*In vitro* antimycobacterial activity and $pIC_{50}$s of *N*-alkyl/aryl-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}hydrazinecarbothioamides (**18**–**36**, **Series 2**) against drug-sensitive *M. tuberculosis H37Rv* strain.



| Compound no. | R | (%) Inhibition | MIC (μg/mL) | $pIC_{50}$ |
|---|---|---|---|---|
| **18** |  | 12 | 6.25 | 4.07 |
| **19** |  | 0 | 6.25 | – |
| **20** |  | 44 | 6.25 | 4.72 |
| **21** |  | 74 | 6.25 | 5.15 |
| **22** |  | 81 | 6.25 | 5.55 |
| **23** |  | 43 | 6.25 | 4.85 |
| **24** |  | 23 | 6.25 | 4.34 |
| **25** |  | 51 | 6.25 | 5.08 |
| **26** |  | 89 | 6.25 | 5.82 |
| **27** |  | 96 | 6.25 | 6.38 |
| **28** |  | 12 | 6.25 | 4.14 |

(*continued on next page*)

**Table 2** (*continued*)

| Compound no. | R | (%) Inhibition | MIC (μg/mL) | $pIC_{50}$ |
|---|---|---|---|---|
| **29** |  | 94 | 6.25 | 6.04 |
| **30** |  | 72 | 6.25 | 5.11 |
| **31** |  | 77 | 6.25 | 5.39 |
| **32** |  | 90 | 6.25 | 5.91 |
| **33** |  | 47 | 6.25 | 4.66 |
| **34** |  | 79 | 6.25 | 5.54 |
| **35** |  | 89 | 6.25 | 5.91 |
| **36** |  | 46 | 6.25 | 4.84 |
| **INH** | | 99 | 0.1 | |
| **RIF** | | 99 | 0.2 | |

inhibition of *M. tuberculosis* H37Rv at 6.25 μg/mL, respectively. The remaining compounds of the series exhibited <50% inhibition of *M. tuberculosis* H37Rv at the primary test concentration of 6.25 μg/mL.

The Table 3 showed *in vitro* biological activity of semicarbazide derivatives **37**–**51**. The most active compound **40** (R = 4-trifluoromethoxyphenyl) exhibited $MIC_{99}$ at a concentration of 3.125 μg/mL. Other interesting compounds **47** (R = 4-butoxyphenyl), **48** (R = 4-fluorophenyl), **49** (R = 3-methoxyphenyl) and **51** (R = 3-fluorophenyl) exhibited moderate anti-TB activity (61%, 68%, 78% and 78% inhibition, respectively). It is observed that the compounds containing a cycloalkyl group, for example, **44** (R = cyclopentyl) and **46** (R = cyclododecyl) in general exhibited increased activity when compared to acyclic aliphatic groups containing compounds [for example, **37** (R = pentyl), **42** (R = hexyl) and **43** (R = hexadecyl)]. The compounds **39** (R = 3,4,5-trimethoxyphenyl), **41** (R = 4-*tert*-butylphenyl) and **45** (R = 2,6-diethylphenyl) exhibited weak anti-TB activity (22%, 37% and 27% inhibition, respectively) at 6.25 μg/mL. The most active compound **40** of the series, exhibited 50% inhibition of *M. tuberculosis* H37Rv at the lowest tested concentration of 1.56 μg/mL. All active compounds were further screened for cytotoxicity using an MTT assay with mouse fibroblasts using a procedure described earlier [17]. None of the compounds showed cytotoxic effects up to the highest test concentration used (200 μg/mL), confirming their safety profile.

### 2.3. Quantitative structure activity relationship (QSAR) study

Earlier, we have reported the 3D-QSAR studies of a number of promising ring-substituted quinolines based upon a Comparative Molecular Field Analysis (CoMFA) [18–21]. Similarly, herein, we have employed Comparative Molecular Field Analysis (CoMFA) to understand the structure activity relationship of newly synthesized ring-substituted quinolines.

#### 2.3.1. Dataset

For 3D-QSAR studies, the molecules were divided into test and training sets based upon structural and biological diversity. The number of molecules in training set was 38, while in the test set 9 molecules were selected. Molecules **5** and **19** were not considered for the QSAR study, as they are inactive. The test compounds were selected manually considering the structural diversity and wide range of activity in the dataset.

#### 2.3.2. Biological data

For the QSAR study, the percent inhibition values were transformed into $pIC_{50}$ values using equation given below [22].

$$pIC_{50} = -\log c + \text{logit}$$

where, $c$ is the molar concentration = concentration (μg/mL) × 0.001/(molecular weight) and log it = log[% inhibition/(100 − % inhibition)].

#### 2.3.3. Molecular modeling

All the molecular modeling calculations were performed using SYBYL-X1.2 installed on HP Z800 workstation running under the Linux OS (CentOS 5.4). The 3D structures of all compounds were constructed using the Sketch Molecule module of SYBYL. Compound **40** was selected as a template molecule for the sketching and alignment of all the compounds. Further, applying the Tripos molecular mechanics force field, with conjugate gradient method, minimized the molecules. The minimization was terminated when the energy gradient convergence criterion of 0.05 kcal/mol was reached or when the 10,000-step minimization cycle was exceeded. Finally, Gasteiger-Hückel charges were applied to all the compounds in the dataset, and it was subsequently used for CoMFA studies.

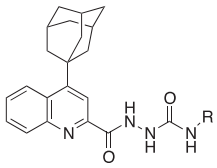
#### 2.3.4. Molecular alignment

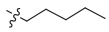
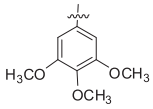
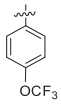
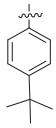
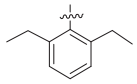
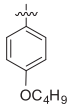
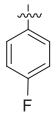
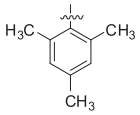
The most important input for the CoMFA is the alignment of molecules. The molecule with the highest biological activity and least conformational flexibility was chosen as the template and all other molecules were aligned to it using the database alignment method in SYBYL. Molecule **40** was taken as a template for alignment and all molecules in the dataset were aligned with reference, 4-(adamantan-1yl)quinoline (Fig. 1).

#### 2.3.5. CoMFA interaction energy calculation

For aligned training set, the steric and electrostatic CoMFA fields at each lattice intersection of a regularly spaced grid of 2.0 Å were calculated using the default probe, a $sp^3$ carbon atom with a charge of +1, and a van der Waals radius of 1.52 Å. The Lennard-Jones potentials and coulombic terms, which represent steric and electrostatic fields, respectively, were calculated using Tripos force field, in which their energy values were truncated at ±30 kcal/mol. The minimum column filtering was set to 2.0 kcal/mol to improve the signal-to-noise ratio by omitting the lattice points, whose energy variation was below this threshold.

**Table 3**
*In vitro* antimycobacterial activity and $pIC_{50}$s of *N*-alkyl/aryl-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}hydrazinecarboxamides (**37**–**51**, **Series 3**) against drug-sensitive *M. tuberculosis H37Rv* strain.



| Compound no. | R | (%) Inhibition | MIC (μg/mL) | $pIC_{50}$ |
|---|---|---|---|---|
| **37** |  | 55 | 6.25 | 4.90 |
| **38** |  | 34 | 6.25 | 4.70 |
| **39** |  | 22 | 6.25 | 4.35 |
| **40**[a] |  | 99 | 3.125 | 6.42 |
| **41** |  | 37 | 6.25 | 4.65 |
| **42** |  | 47 | 6.25 | 4.92 |
| **43** |  | 16 | 6.25 | 4.18 |
| **44** |  | 84 | 6.25 | 5.48 |
| **45** |  | 27 | 6.25 | 4.37 |
| **46** |  | 87 | 6.25 | 5.85 |
| **47** |  | 61 | 6.25 | 5.11 |
| **48** |  | 68 | 6.25 | 5.42 |
| **49** |  | 78 | 6.25 | 5.42 |
| **50** |  | 77 | 6.25 | 5.30 |
| **51** |  | 78 | 6.25 | 5.32 |
| **INH** | | 99 | 0.1 | |
| **RIF** | | 99 | 0.2 | |

[a] Exhibited 50% inhibition at the test concentration of 1.56 μg/mL.

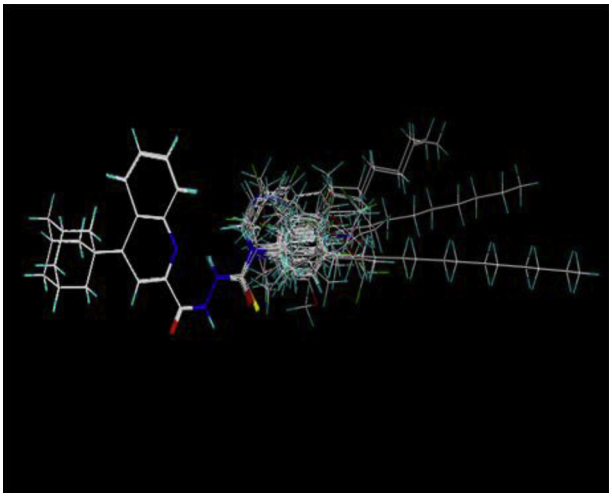


**Fig. 1.** Alignment of molecules used for CoMFA model generation.

### 2.3.6. Partial least squares (PLS) analysis

The PLS analysis was used to linearly correlate the CoMFA fields to the inhibitory activity. The cross validation analysis was performed using the leave-one-out (LOO) method. The non-cross-validated conventional analysis was produced with the optimal number of components equal to that yielding the highest $q^2$, and the corresponding conventional correlation coefficient ($r^2$), its standard error, and the *F* ratio were also calculated.

### 2.3.7. Predictive correlation coefficient

The predictive ability of each 3D-QSAR model was determined from a set of test molecules not included in the model generation. The activity values for the test molecules were predicted by using the developed CoMFA model. The predictive correlation coefficient ($r^2_{pred}$) based on the test set molecules, is defined as.

$$r^2_{pred} = (SD - PRESS)/SD$$

where, SD is the sum of the squared deviations between the inhibitory activities of the test set and mean activities of the training molecules and PRESS is the sum of squared deviations between predicted and actual activity values for each molecule in the test set.

### 2.3.8. CoMFA contour maps

The contour maps were generated as a scalar product of the coefficients and standard deviation (StDev * Coeff) associated with each column. The favored and disfavored levels, fixed at 60.40% and 39.60%, respectively, were used to display the steric and the electrostatic fields. The contours for the steric fields are shown in green (more bulk favored) and yellow (less bulk favored), while the electrostatic field contours are displayed in red (electronegative substituent favored) and blue (electropositive substituent favored) colors.

### 2.3.9. Discussion

The 3D-QSAR model was developed using 38 training set molecules (Table 4), while 9 molecules were kept in the test set (Table 5). The best CoMFA model exhibited correlation coefficient ($r^2$) of 0.971 and cross-validated correlation coefficient ($r^2_{cv}$) of 0.543 (Table 6). The optimum number of components was 7 and column filtering was set to 2. The steric factor contributed about 60.40%, and the electronic factor contributed 39.60% towards the

**Table 4**
The experimental and predicted $pIC_{50}$ values of the training set compounds.

| Compound no. | (%) Inhibition | MIC (μg/mL) | Experimental $pIC_{50}$ | Predicted $pIC_{50}$ |
|---|---|---|---|---|
| **3** | 32 | 6.25 | 4.57 | 4.60 |
| **4** | 50 | 6.25 | 4.89 | 4.89 |
| **6** | 79 | 6.25 | 5.52 | 5.47 |
| **7** | 88 | 6.25 | 5.78 | 5.66 |
| **9** | 3 | 6.25 | 3.33 | 3.53 |
| **10** | 12 | 6.25 | 3.97 | 4.25 |
| **11** | 69 | 6.25 | 5.24 | 5.30 |
| **12** | 56 | 6.25 | 4.94 | 4.58 |
| **14** | 74 | 6.25 | 5.29 | 5.33 |
| **15** | 87 | 6.25 | 5.71 | 5.67 |
| **17** | 5 | 6.25 | 3.49 | 3.42 |
| **18** | 12 | 6.25 | 4.00 | 4.07 |
| **20** | 44 | 6.25 | 4.80 | 4.72 |
| **21** | 74 | 6.25 | 5.38 | 5.15 |
| **22** | 81 | 6.25 | 5.55 | 5.55 |
| **23** | 43 | 6.25 | 4.80 | 4.85 |
| **25** | 51 | 6.25 | 4.91 | 5.08 |
| **26** | 89 | 6.25 | 5.80 | 5.82 |
| **27** | 96 | 6.25 | 6.31 | 6.38 |
| **28** | 12 | 6.25 | 4.04 | 4.14 |
| **29** | 94 | 6.25 | 6.10 | 6.04 |
| **30** | 72 | 6.25 | 5.23 | 5.11 |
| **32** | 90 | 6.25 | 5.80 | 5.91 |
| **33** | 47 | 6.25 | 4.84 | 4.66 |
| **35** | 89 | 6.25 | 5.84 | 5.91 |
| **37** | 55 | 6.25 | 4.93 | 4.90 |
| **38** | 34 | 6.25 | 4.61 | 4.70 |
| **39** | 22 | 6.25 | 4.38 | 4.35 |
| **40** | 99 | 3.125 | 6.37 | 6.42 |
| **42** | 47 | 6.25 | 4.80 | 4.92 |
| **43** | 16 | 6.25 | 4.25 | 4.18 |
| **44** | 84 | 6.25 | 5.56 | 5.48 |
| **45** | 27 | 6.25 | 4.47 | 4.37 |
| **46** | 87 | 6.25 | 5.75 | 5.85 |
| **48** | 68 | 6.25 | 5.19 | 5.42 |
| **49** | 78 | 6.25 | 5.43 | 5.42 |
| **50** | 77 | 6.25 | 5.41 | 5.30 |
| **51** | 78 | 6.25 | 5.42 | 5.32 |

activity. The Fig. 2 shows plot of predicted versus experimental activity for molecules in the training set based on the best model. The CoMFA model was tested for their predictivity on the test set. The model showed $r^2_{pred}$ of 0.883, while the *F*-value and SEE were 141.107 and 0.14, respectively (Table 6). The steric and electronic contours for the compound **40** are shown in Figs. 3 and 4. The analysis of steric contour of **40** (Fig. 3) reveals two green contours (sterically favored) lying on two opposite phase of the phenyl ring and a very small green contour near the *p*-$OCF_3$ group of the phenyl ring. The four yellow contours (sterically not favored) are also observed in the steric contour of **40**. Like **40**, *p*-$OCF_3$ group of the phenyl ring of **35** also lies in the green sterically favored region and hence, accounts for good anti-TB activity. The *tert*-butyl group of

**Table 5**
The experimental and predicted $pIC_{50}$ values of the test set compounds.

| Compound no. | (%) Inhibition | MIC (μg/mL) | Experimental $pIC_{50}$ | Predicted $pIC_{50}$ |
|---|---|---|---|---|
| **8** | 9 | 6.25 | 3.83 | 3.83 |
| **13** | 88 | 6.25 | 5.75 | 5.35 |
| **16** | 90 | 6.25 | 5.84 | 5.33 |
| **24** | 23 | 6.25 | 4.35 | 4.34 |
| **31** | 77 | 6.25 | 5.35 | 5.39 |
| **34** | 79 | 6.25 | 5.50 | 5.54 |
| **36** | 46 | 6.25 | 4.87 | 4.84 |
| **41** | 37 | 6.25 | 4.67 | 4.65 |
| **47** | 61 | 6.25 | 5.11 | 5.11 |

**Table 6**
Summary of the statistical parameter for 3D-QSAR analysis.

| Parameters | |
|---|---|
| *n* (no. of molecules) | 47 |
| Molecule used for alignment | **Compound 40** |
| Total number of training set molecules | 38 |
| Total number of test set molecules | 9 |
| Total number of outlier molecules | 0 |
| *N* (optimum component) | 7 |
| Column filtering use | 2 |
| $r^2$ (non-cross-validated $r^2$) | 0.971 |
| $r^2_{cv}$ (cross-validated $r^2$) | 0.543 |
| SEE (standard error of estimate) | 0.14 |
| *F*-Value | 141.107 |
| $r^2_{pred}$ (test molecules correlation coefficient) | 0.883 |
| Contributions (%) | |
| Steric | 60.40% |
| Electrostatics | 39.60% |

compound **32** is in the proximity of two green regions, and as a result this compound exhibits good inhibitory activity. The good inhibitory activity of the compound **26** may be due to the alkyl substituent at *ortho* position of the phenyl ring, which is completely buried under green region. Similarly, naphthyl ring of **13** and **16**, adamantan-1-yl ring of **15**, cyclopentyl ring of **44** and cyclododecyl ring of **46**, also lies in the green contour and hence, these compounds are active. The phenyl ring of **18** and **33** is close to the sterically not favored yellow contour, thus these compounds show moderate activity. Likewise, $OCH_3$ and $CH_3$ substituents of **28** also fall under the yellow region and therefore, this molecule exhibit moderate inhibitory activity. The electrostatic contour (Fig. 4) shows six red colored contours and three blue colored contours. A big red colored contour near the C-4 and C-3 position of the phenyl ring is observed, which indicates that the electron-withdrawing groups are favored at this position. The *p*-$NO_2$ of **27** and **29** and *p*-$OCF_3$ of **35** and **40** lie near to red contour and hence, these compounds exhibited promising anti-TB activity. Whereas, *tert*-butyl and $CH_3$ groups at the *para* position of the phenyl ring in the compounds **41** and **24**, also lie down near the red contour, which is favored by electronegative group but not by electropositive substituents and therefore, these compounds possess moderate anti-

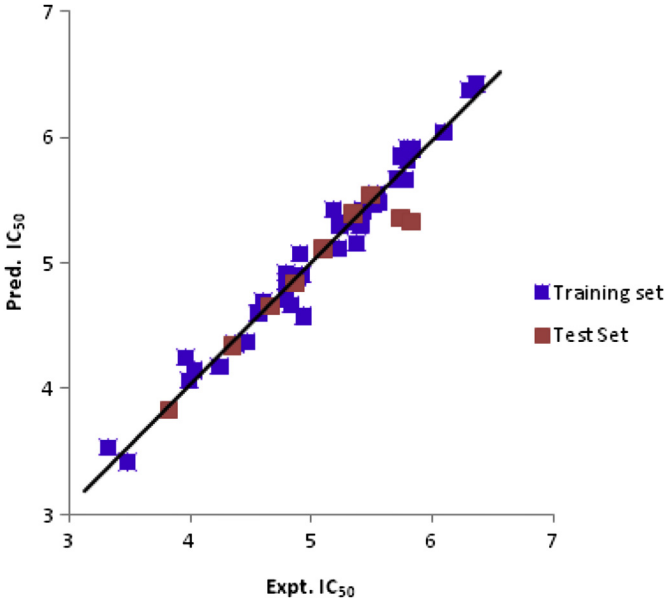



**Fig. 2.** A graph of predicted versus experimental $pIC_{50}$ values.

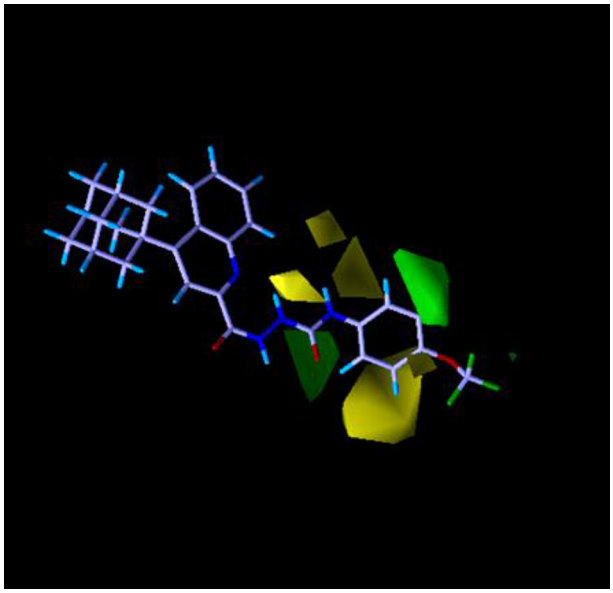


**Fig. 3.** The steric field distribution around compound **40**.

TB activity. The Cl and F groups at the *meta* position of the phenyl ring of **21** and **51**, respectively, lies in the red colored contour and thus, these compounds show good inhibitory activity. The blue colored contour near the *ortho* position of the phenyl ring favored by electropositive substituents like ethyl (**26**) and methyl (**50**), and hence these molecules possess promising anti-TB activity. The adamantan-1-yl, naphthyl and *tert*-butyl groups of compounds **15**, **16** and **32**, respectively, are buried under a blue colored contour, which is reasoned for the exhibition of promising activity.

## 3. Conclusion

The hydrazide, semicarbazide and thiosemicarbazide derivatives of 4-(adamantan-1-yl)quinoline-2-carbohydrazide have exhibited promising anti-tuberculosis activity, when tested against *M. tuberculosis* H37Rv, *in vitro*. Most active analogue **40** exhibited

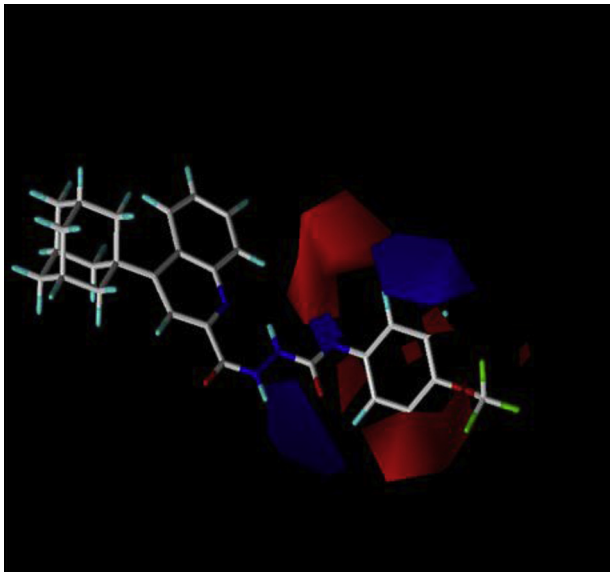


**Fig. 4.** The electrostatic filed distribution around analogue compound **40**.

$MIC_{99}$ of 3.125 μg/mL, and later also produced 50% inhibition at the lower tested concentration of 1.56 μg/mL. Other analogues **16**, **27**, **29** and **32** exhibited MIC of 6.25 μg/mL, when tested *in vitro* against drug-sensitive strain. None of the active analogues exhibited cytotoxicity in an MTT assay using mouse fibroblasts up to the highest tested concentration of 200 μg/mL. The 3D-QSAR model developed using CoMFA exhibits good statistical significance with all values in an acceptable range. The results indicate that the sterically bulky or electronegative substitution at the *para* position of phenyl ring is required for good anti-TB activity.

## 4. Experimental

The synthesized compounds were checked for their purity on pre-coated silica gel $G_{254}$ TLC plates (Merck) and the spots were visualized under UV spectrophotometer and then by exposing them to iodine vapors. Flash chromatography purification was carried out on Merck silica gel (230–400 mesh) using Biotage® SP1 automated flash chromatography system equipped with a UV detector. Melting points were recorded on capillary melting point apparatus or on the Perkin Elmer DSC instrument and are uncorrected. All solvents used for synthesis were of analytical grade and used without any further purification unless otherwise stated. $^1H$ and $^{13}C$ NMR spectra were recorded on 400 MHz Bruker FT-NMR spectrometer using tetramethylsilane as internal standard and the chemical shifts are reported in $\delta$ units. All NMR spectra were processed on the $^1H$ NMR/$^{13}C$ NMR module of ACD 12.0 software. The IR spectra ($\nu_{max}$ in $cm^{-1}$) were recorded on Nicolet FT-IR Impact 410 instrument either in neat or in KBr pellet. The HRMS spectra were recorded on the Bruker Maxis mass spectrometer. Elemental analyses were recorded on Elementar Vario EL spectrometer.

### *4.1. General method for the synthesis of N′-alkyl/aryl/heteroaryl-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinoline-2-carbohydrazides (**3**–**17**)*

To the ice-cold solution of **2** (10 mmol) and $Et_3N$ (20 mmol) in dry $CH_2Cl_2$ (10 mL), alkyl/aryl/heteroaryl acid chloride (12 mmol) was added slowly under $N_2$ atmosphere. The ice bath was removed and the reaction was allowed to proceed at ambient temperature for 2 h. The reaction mixture was poured onto crushed ice and extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic extract was washed with brine (20 mL), dried over sodium sulfate and evaporated under reduced pressure to afford carbohydrazide derivatives **3**–**17**, which were purified through flash column chromatography using EtOAc/hexanes as mobile phase.

#### *4.1.1. 4-(Tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)-N′-undecanoylquinoline-2-carbohydrazide (**3**)*

Yield: 63%; white solid; mp: 168–173 °C; IR (KBr): 2925, 1642 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 10.51 (br s, 1H), 8.90 (br s, 1H), 8.64–8.71 (m, 1H), 8.14–8.19 (m, 2H), 7.64–7.76 (m, 1H), 7.58 (ddd, $J$ = 1.3, 6.9, 8.6 Hz, 1H), 2.20–2.42 (m, 11H), 1.89 (br s, 6H), 1.68–1.78 (m, 2H), 1.65 (br s, 2H), 1.21–1.41 (m, 12H), 0.83–0.96 (m, 3H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 169.8, 161.2, 157.7, 148.0, 147.5, 131.9, 128.8, 128.3, 126.5, 126.3, 115.7, 42.2, 39.1, 36.8, 34.4, 31.8, 29.7, 29.4, 29.4, 29.4, 29.3, 29.0, 25.5, 22.6, 14.1; HRMS (ESI): $m/z$ calcd for $C_{31}H_{43}N_3NaO_2$ $[M+Na]^+$: 498.3096, found: 498.3094; Anal. Calcd for $C_{31}H_{43}N_3O_2$ (476.1): C, 76.03; H, 8.85; N, 8.58; Found: C, 76.00; H, 8.86; N, 8.55.

#### *4.1.2. 4-(Tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)-N′-(undec-10-enoyl)quinoline-2-carbohydrazide (**4**)*

Yield: 71%; light brown solid; mp: 155–161 °C; IR (KBr): 2921, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 10.63 (br s, 1H), 9.58 (br s, 1H), 8.65 (d, $J$ = 8.8 Hz, 1H), 8.12–8.20 (m, 2H), 7.69 (t, $J$ = 7.6 Hz, 1H), 7.52–7.61 (m, 1H), 5.67–5.87 (m, 1H), 4.85–5.08 (m, 2H), 2.42 (t,

$J$ = 7.4 Hz, 2H), 2.28–2.34 (m, 6H), 2.22 (br s, 3H), 1.96–2.07 (m, 2H), 1.88 (br s, 6H), 1.74 (q, $J$ = 7.5 Hz, 2H), 1.21–1.41 (m, 10H); $^{13}$C NMR ($CDCl_3$): $\delta$ 170.0, 161.0, 157.6, 148.0, 147.4, 139.1, 131.9, 128.8, 128.2, 126.5, 126.2, 115.6, 114.1, 114.1, 42.1, 39.1, 36.8, 34.2, 33.7, 29.3, 29.3, 29.3, 29.2, 29.2, 29.1, 29.0, 28.9, 28.9, 25.5; HRMS (ESI): $m/z$ calcd for $C_{31}H_{41}N_3NaO_2$ $[M+Na]^+$: 510.3096, found: 510.3083; Anal. Calcd for $C_{31}H_{41}N_3O_2$ (487.3): C, 76.35; H, 8.47; N, 8.62; Found: C, 76.33; H, 8.48; N, 8.60.

#### 4.1.3. N′-(Furan-2-ylcarbonyl)-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinoline-2-carbohydrazide (**5**)

Yield: 63%; white solid; mp: 223–228 °C; IR (KBr): 2921, 1633 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 9.04 (br s, 1H), 8.91 (br s, 2H), 8.69 (d, $J$ = 8.8 Hz, 1H), 8.17–8.23 (m, 2H), 7.73 (t, $J$ = 7.2 Hz, 1H), 7.57–7.64 (m, 1H), 7.52–7.56 (m, 1H), 7.24 (d, $J$ = 3.5 Hz, 1H), 6.53–6.59 (m, 1H), 2.35 (br s, 6H), 2.24 (br s, 3H), 1.91 (br s, 6H); $^{13}$C NMR ($CDCl_3$): $\delta$ 161.7, 157.7, 155.5, 148.0, 147.4, 145.8, 145.5, 144.9, 144.8, 131.9, 128.8, 128.3, 126.5, 126.3, 116.24, 116.0, 115.8, 112.3, 42.2, 39.2, 36.8, 29.7, 28.9; HRMS (ESI): $m/z$ calcd for $C_{25}H_{25}N_3NaO_3$ $[M+Na]^+$: 438.1794, found: 438.1788; Anal. Calcd for $C_{25}H_{25}N_3O_3$ (415.2): C, 72.27; H, 6.06; N, 10.11; Found: C, 72.22; H, 6.00; N, 10.08.

#### 4.1.4. N′-Pentadecanoyl-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinoline-2-carbohydrazide (**6**)

Yield: 66%; white solid; mp: 150–154 °C; IR (KBr): 2919, 1641 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 10.48 (br s, 1H), 8.62–8.70 (m, 2H), 8.14–8.22 (m, 2H), 7.70 (t, $J$ = 7.2 Hz, 1H), 7.56–7.63 (m, 1H), 2.30–2.41 (m, 8H), 2.23 (br s, 3H), 1.89 (br s, 6H), 1.75 (t, $J$ = 7.4 Hz, 2H), 1.20–1.41 (m, 20H), 0.88 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$): $\delta$ 169.8, 161.2, 157.7, 148.0, 147.4, 131.9, 128.8, 128.3, 126.5, 126.3, 115.7, 42.2, 39.1, 36.8, 34.4, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.3, 29.3, 28.9, 25.5, 22.7, 14.1; HRMS (ESI): $m/z$ calcd for $C_{35}H_{51}N_3NaO_2$ $[M+Na]^+$: 554.3722, found: 554.3715; Anal. Calcd for $C_{35}H_{51}N_3O_2$ (532.4): C, 77.02; H, 9.42; N, 7.70; Found: C, 76.98; H, 9.40; N, 7.68.

#### 4.1.5. N′-(Pentafluorobenzoyl)-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinoline-2-carbohydrazide (**7**)

Yield: 80%; white solid; mp: 256–260 °C; IR (KBr): 2907, 1654 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 9.81 (br s, 1H), 8.68 (d, $J$ = 8.8 Hz, 1H), 8.14–8.22 (m, 1H), 8.05–8.11 (m, 1H), 7.68–7.76 (m, 1H), 7.58–7.66 (m, 1H), 2.31 (br s, 6H), 2.17 (br s, 3H), 1.79–1.97 (m, 9H); $^{13}$C NMR ($CDCl_3$): $\delta$ 161.7, 158.1, 148.0, 146.7, 131.9, 129.1, 128.5, 126.9, 126.4, 115.5, 42.2, 39.2, 36.8, 28.9; HRMS (ESI): $m/z$ calcd for $C_{27}H_{22}F_5N_3NaO_2$ $[M+Na]^+$: 538.1530, found: 538.1517; Anal. Calcd for $C_{27}H_{22}F_5N_3O_2$ (515.2): C, 62.91; H, 4.30; N, 8.15; Found: C, 62.92; H, 4.33; N, 8.13.

#### 4.1.6. N′-(Thiophen-2-ylcarbonyl)-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinoline-2-carbohydrazide (**8**)

Yield: 69%; yellow solid; mp: 224–232 °C; IR (KBr): 2905, 1635 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 10.53 (br s, 1H), 9.51 (br s, 1H), 8.67 (d, $J$ = 8.3 Hz, 1H), 8.14–8.24 (m, 2H), 7.78 (dd, $J$ = 0.88, 3.6 Hz, 1H), 7.71 (ddd, $J$ = 1.1, 6.9, 8.3 Hz, 1H), 7.59 (ddd, $J$ = 1.5, 6.9, 8.7 Hz, 1H), 7.49–7.56 (m, 1H), 7.11 (dd, $J$ = 3.8, 5.0 Hz, 1H), 2.28–2.41 (m, 6H), 2.14–2.26 (m, 3H), 1.81–1.96 (m, 6H); $^{13}$C NMR ($CDCl_3$): $\delta$ 170.5, 157.7, 148.0, 147.4, 131.9, 131.1, 128.9, 128.3, 127.9, 126.6, 126.3, 115.8, 42.1, 39.2, 36.8, 28.9; HRMS (ESI): $m/z$ calcd for $C_{31}H_{30}N_3NaO_2S$ $[M+Na]^+$: 454.1565, found: 454.1558; Anal. Calcd for $C_{25}H_{25}N_3O_2S$ (431.2): C, 69.58; H, 5.84; N, 9.74; Found: C, 69.53; H, 5.81; N, 9.72.

#### 4.1.7. N′-(Morpholin-4-ylcarbonyl)-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinoline-2-carbohydrazide (**9**)

Yield: 80%; white solid; mp: 286–290 °C; IR (KBr): 2906, 1689 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 10.12 (br s, 1H), 8.64 (d, $J$ = 8.8 Hz, 1H), 8.47 (br s, 1H), 8.10–8.19 (m, 2H), 7.68 (ddd, $J$ = 1.0, 6.9, 8.3 Hz, 1H), 7.52–7.61 (m, 1H), 3.67–3.76 (m, 4H), 3.52–3.60 (m, 4H), 2.27–2.39 (m, 6H), 2.21 (br s, 3H), 1.87 (br s, 6H); $^{13}$C NMR ($CDCl_3$): $\delta$ 163.1, 157.1, 156.3, 147.6, 147.5, 131.6, 128.3, 127.8, 126.1, 125.9, 115.4, 66.1, 43.8, 41.8, 38.7, 36.5, 28.6; HRMS (ESI): $m/z$ calcd for $C_{25}H_{30}N_4NaO_3$ $[M+Na]^+$: 457.2216, found: 457.2216; Anal. Calcd for $C_{25}H_{30}N_4O_3$ (434.3): C, 69.10; H, 6.96; N, 12.89; Found: C, 69.05; H, 6.95; N, 12.86.

#### 4.1.8. N′-Benzoyl-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinoline-2-carbohydrazide (**10**)

Yield: 77%; yellow solid; mp: 82–84 °C; IR (KBr): 2907, 1704 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 10.30 (s, 1H), 8.64 (d, $J$ = 8.5 Hz, 1H), 8.19 (s, 1H), 8.12 (dd, $J$ = 1.4, 8.4 Hz, 1H), 7.83–7.90 (m, 3H), 7.68 (ddd, $J$ = 1.3, 7.0, 8.3 Hz, 1H), 7.58 (ddd, $J$ = 1.5, 6.9, 8.7 Hz, 1H), 7.41–7.51 (m, 1H), 7.32–7.41 (m, 2H), 2.26–2.34 (m, 6H), 2.20 (br s, 3H), 1.87 (br s, 6H); $^{13}$C NMR ($CDCl_3$): $\delta$ 171.8, 164.6, 157.7, 147.9, 147.1, 133.8, 132.5, 131.9, 128.9, 128.8, 128.5, 128.4, 126.7, 126.3, 116.1, 42.1, 39.1, 36.8, 28.9; HRMS (ESI): $m/z$ calcd for $C_{27}H_{27}N_3NaO_2$ $[M+Na]^+$: 448.2001, found: 448.1994; Anal. Calcd for $C_{27}H_{27}N_3O_2$ (425.2): C, 76.21; H, 6.40; N, 9.87; Found: C, 76.18; H, 6.38; N, 9.85.

#### 4.1.9. 4-(Tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)-N′-[3-(trifluoromethyl) benzoyl]quinoline-2-carbohydrazide (**11**)

Yield: 40%; white solid; mp: 184–187 °C; IR (KBr): 2914, 1647 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 10.44 (br s, 1H), 8.65 (d, $J$ = 7.8 Hz, 1H), 8.16 (br s, 1H), 8.01–8.12 (m, 3H), 7.98 (br s, 1H), 7.64–7.80 (m, 2H), 7.59 (br s, 1H), 7.53 (br s, 1H), 2.29 (br s, 6H), 2.21 (br s, 3H), 1.88 (br s, 6H); $^{13}$C NMR ($CDCl_3$): $\delta$ 170.5, 164.9, 158.0, 147.8, 147.7, 134.4, 131.9, 131.7, 131.6, 129.2, 129.0, 127.0, 126.3, 125.72, 116.0, 60.41, 42.2, 39.2, 36.8, 28.9; HRMS (ESI): $m/z$ calcd for $C_{28}H_{26}F_3N_3NaO_2$ $[M+Na]^+$: 516.1875, found: 516.1864; Anal. Calcd for $C_{28}H_{26}F_3N_3O_2$ (493.2): C, 68.14; H, 5.31; N, 8.51; Found: C, 68.10; H, 5.34; N, 8.47.

#### 4.1.10. N′-(Pyridin-4-ylcarbonyl)-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinoline-2-carbohydrazide (**12**)

Yield: 60%; yellow solid; mp: 122–126 °C; IR (KBr): 2905, 1629 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 10.84–11.01 (m, 2H), 8.68–8.85 (m, 3H), 8.21 (d, $J$ = 8.0 Hz, 1H), 8.04 (s, 1H), 7.82–7.90 (m, 3H), 7.66–7.80 (m, 1H), 2.28 (br s, 6H), 2.18 (br s, 3H), 1.77–1.95 (m, 6H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 164.4, 164.1, 157.2, 150.8, 149.0, 147.9, 139.9, 131.7, 129.7, 127.6, 127.5, 126.8, 121.7, 115.8, 42.0, 38.6, 36.5, 28.7; HRMS (ESI): $m/z$ calcd for $C_{26}H_{26}N_4NaO_2$ $[M+Na]^+$: 449.1953, found: 449.1950; Anal. Calcd for $C_{26}H_{26}N_4O_2$ (426.2): C, 73.22; H, 6.14; N, 13.14; Found: C, 73.23; H, 6.11; N, 13.12.

#### 4.1.11. N′-(Naphthalen-1-ylcarbonyl)-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinoline-2-carbohydrazide (**13**)

Yield: 76%; white solid; mp: 246–249 °C; IR (KBr): 2906, 1637 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 10.71 (br s, 1H), 8.88 (s, 1H), 8.69 (d, $J$ = 8.5 Hz, 1H), 8.51 (d, $J$ = 8.5 Hz, 1H), 8.22 (dd, $J$ = 1.3, 8.5 Hz, 1H), 8.18 (s, 1H), 7.97 (d, $J$ = 8.3 Hz, 1H), 7.88 (d, $J$ = 7.5 Hz, 1H), 7.84 (dd, $J$ = 1.0, 7 Hz, 1H), 7.70–7.78 (m, 1H), 7.45–7.65 (m, 4H), 2.29–2.40 (m, 6H), 2.23 (br s, 3H), 1.82–1.95 (m, 6H); $^{13}$C NMR ($CDCl_3$): $\delta$ 166.1, 161.8, 157.7, 148.1, 147.4, 133.7, 132.0, 131.7, 130.9, 130.4, 128.9, 128.4, 128.3, 127.6, 126.7, 126.6, 126.6, 126.3, 126.1, 125.3, 124.6, 115.8, 42.2, 39.2, 36.9, 29.0; HRMS (ESI): $m/z$ calcd for $C_{31}H_{30}N_3O_2$ $[M+H]^+$: 476.2338, found: 476.2330; Anal. Calcd for $C_{31}H_{29}N_3O_2$ (475.3): C, 78.29; H, 6.15; N, 8.84; Found: C, 78.22; H, 6.18; N, 8.85.

#### 4.1.12. N′-(Pyridin-3-ylcarbonyl)-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinoline-2-carbohydrazide (**14**)

Yield: 79%; yellow solid; mp: 129–133 °C; IR (KBr): 2908, 1646 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 10.69 (br s, 1H), 9.85 (br s, 1H), 9.16 (d, $J$ = 1.7 Hz, 1H), 8.77 (dd, $J$ = 1.5, 4.8 Hz, 1H), 8.67 (d, $J$ = 8.3 Hz, 1H), 8.21–8.28 (m, 1H), 8.14–8.21 (m, 2H), 7.72 (dt, $J$ = 1.1, 7.6 Hz,

1H), 7.60 (ddd, $J$ = 1.3, 6.9, 8.6 Hz, 1H), 7.41 (dd, $J$ = 4.8, 7.9 Hz, 1H), 2.29–2.41 (m, 6H), 2.22 (br s, 3H), 1.80–1.95 (m, 3H); $^{13}$C NMR ($CDCl_3$): δ 162.7, 162.1, 157.9, 153.0, 148.6, 148.0, 147.2, 135.2, 132.0, 129.0, 128.4, 127.6, 126.7, 126.3, 123.5, 115.8, 77.2, 42.2, 39.2, 36.8, 29.7, 28.9; HRMS (ESI): $m/z$ calcd for $C_{26}H_{26}N_4NaO_2$ $[M+Na]^+$: 449.1953, found: 449.1950; Anal. Calcd for $C_{26}H_{26}N_4O_2$ (426.2): C, 73.22; H, 6.14; N, 13.14; Found: C, 73.20; H, 6.15; N, 13.15.

#### 4.1.13. 4-(Tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)-N′-(tricyclo[3.3.1.1$^{3,7}$]dec-1-ylcarbonyl)quinoline-2-carbohydrazide (**15**)

Yield: 80%; white solid; mp: 249–252 °C; IR (KBr): 2905, 1638 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 10.54 (br s, 1H), 8.66 (d, $J$ = 8.5 Hz, 1H), 8.53 (br s, 1H), 8.12–8.20 (m, 2H), 7.70 (ddd, $J$ = 1.1, 6.9, 8.3 Hz, 1H), 7.58 (ddd, $J$ = 1.5, 6.9, 8.7 Hz, 1H), 2.29–2.38 (m, 6H), 2.22 (br s, 3H), 2.11 (br s, 3H), 2.01 (d, $J$ = 2.7 Hz, 6H), 1.89 (br s, 6H), 1.72–1.81 (m, 6H); $^{13}$C NMR ($CDCl_3$): δ 173.8, 160.8, 157.6, 148.1, 147.5, 131.9, 128.8, 128.2, 126.4, 126.3, 115.6, 42.1, 40.3, 39.1, 38.9, 38.9, 36.8, 36.4, 28.9, 27.9; HRMS (ESI): $m/z$ calcd for $C_{31}H_{37}N_3NaO_2$ $[M+Na]^+$: 506.2783, found: 506.2779; Anal. Calcd for $C_{31}H_{37}N_3O_2$ (483.3): C, 76.98; H, 7.71; N, 8.69; Found: C, 76.94; H, 7.70; N, 8.64.

#### 4.1.14. N′-(Naphthalen-2-ylcarbonyl)-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinoline-2-carbohydrazide (**16**)

Yield: 71%; white solid; mp: 226–229 °C; IR (KBr): 2905, 1644 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 10.85 (br s, 1H), 9.92 (br s, 1H), 8.66 (d, $J$ = 8.5 Hz, 1H), 8.48 (s, 1H), 8.18–8.25 (m, 1H), 8.16 (s, 1H), 7.95–8.02 (m, 1H), 7.80–7.92 (m, 3H), 7.72 (t, $J$ = 7.3 Hz, 1H), 7.45–7.63 (m, 3H), 2.23–2.34 (m, 6H), 2.19 (br s, 3H), 1.86 (br s, 6H); $^{13}$C NMR ($CDCl_3$): δ 164.3, 161.6, 157.7, 148.1, 147.5, 135.1, 132.5, 132.0, 129.2, 128.9, 128.8, 128.6, 128.3, 128.3, 128.0, 127.7, 126.8, 126.6, 126.3, 123.5, 115.8, 42.1, 39.1, 36.8, 28.9; HRMS (ESI): $m/z$ calcd for $C_{31}H_{30}N_3O_2$ $[M+H]^+$: 476.2338, found: 476.2334; Anal. Calcd for $C_{31}H_{29}N_3O_2$ (475.2): C, 78.29; H, 6.15; N, 8.84; Found: C, 78.24; H, 6.12; N, 8.82.

#### 4.1.15. N′-Acetyl-4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinoline-2-carbohydrazide (**17**)

Yield: 66%; colorless solid; mp: 204–207 °C; IR (KBr): 2907, 1727 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 10.03 (s, 1H), 8.69 (d, $J$ = 8.3 Hz, 1H), 8.21 (s, 1H), 8.16 (dd, $J$ = 1.4, 8.4 Hz, 1H), 7.68–7.78 (m, 1H), 7.55–7.66 (m, 1H), 2.52 (s, 3H), 2.33 (d, $J$ = 2.3 Hz, 6H), 2.23 (br s, 3H), 1.89 (t, $J$ = 2.8 Hz, 6H); $^{13}$C NMR ($CDCl_3$): δ 171.6, 165.0, 157.9, 147.9, 147.1, 131.9, 128.9, 128.6, 126.8, 126.4, 116.0, 42.1, 39.2, 36.8, 28.9, 25.1; HRMS (ESI): $m/z$ calcd for $C_{22}H_{25}N_3NaO_2$ $[M+Na]^+$: 386.1844, found: 386.1842; Anal. Calcd for $C_{22}H_{25}N_3O_2$: C, 72.70; H, 6.93; N, 11.56; Found: C, 72.68; H, 6.90; N, 11.54.

### 4.2. General method for the synthesis of N-alkyl/aryl-2-{[4-(tricyclo [3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl} hydrazinecarbothioamides (**18**–**36**)

The alkyl/aryl isothiocyanate (1.2 mmol) was added drop wise to a stirred solution of **2** (1 mmol) in tetrahydrofuran (THF, 5 mL) at ambient temperature. The reaction mixture was stirred at ambient temperature for 4 h. The solvent was evaporated, and the residue was suspended in $C_2H_5OH$. The precipitated solid was filtered, washed with $C_2H_5OH$ and dried under vacuum to produce **18**–**36**.

#### 4.2.1. N-Phenyl-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl] carbonyl}hydrazinecarbothioamide (**18**)

Yield: 77%; white solid; mp: 224–228 °C; IR (KBr): 1637 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 9.94 (br s, 2H), 8.91 (d, $J$ = 8.5 Hz, 1H), 8.34, (d, $J$ = 8.3 Hz), 8.19 (s, 1H), 7.99 (t, $J$ = 7.2 Hz, 1H), 7.87 (t, $J$ = 7.4 Hz, 1H), 7.60 (s, 1H), 7.46 (t, $J$ = 7.8 Hz, 1H), 7.29 (t, $J$ = 7.3 Hz, 1H), 2.43 (br s, 6H), 2.33 (br s, 3H), 1.90–2.04 (m, 6H); $^{13}$C NMR (DMSO-$d_6$) δ 181.2, 164.6, 156.7, 149.4, 147.8, 139.6, 131.7, 129.6, 128.8, 128.4, 127.8, 126.8, 126.0, 125.3, 124.8, 124.1, 115.9, 42.1, 39.2, 36.8, 28.9, 25.1; HRMS (ESI): $m/z$ calcd for $C_{27}H_{28}N_4NaOS$ $[M+Na]^+$: 479.1882, found: 479.1871; Anal. Calcd for $C_{27}H_{28}N_4OS$ (456.2): C, 71.02; H, 6.18; N, 12.27; Found: C, 71.06; H, 6.24; N, 12.30.

#### 4.2.2. N-Cyclohexyl-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}hydrazinecarbothioamide (**19**)

Yield: 75%; colorless solid; mp: 217–220 °C; IR (KBr): 1634 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 10.05 (br s, 1H), 8.68 (d, $J$ = 8.7 Hz, 1H), 8.15–8.19 (m, 2H), 8.07 (br s, 1H), 7.39 (t, $J$ = 7.2 Hz, 1H), 7.61 (t, $J$ = 7.3 Hz, 1H), 6.54 (br s, 1H), 4.23–4.26 (m, 1H), 2.31 (br s, 6H), 2.22 (br s, 3H), 2.03–2.13 (m, 2H), 1.88 (br s, 6H), 1.64–1.73 (m, 6H), 1.33–1.46 (m, 2H), 1.10–1.25 (m, 6H); $^{13}$C NMR ($CDCl_3$): δ 180.9, 163.5, 158.1, 148.0, 147.3, 131.9, 129.1, 128.5, 126.8, 126.4, 115.8, 53.6, 42.2, 39.2, 36.8, 32.7, 29.7, 28.9, 25.5, 24.8; HRMS (ESI): $m/z$ calcd for $C_{27}H_{34}N_4NaOS$ $[M+Na]^+$: 485.2351, found: 485.2348; Anal. Calcd for $C_{27}H_{34}N_4OS$ (462.3): C, 70.09; H, 7.41; N, 12.11; Found: C, 70.04; H, 7.37; N, 12.09.

#### 4.2.3. N-(Naphthalen-1-yl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarbothioamide (**20**)

Yield: 83%; colorless solid; mp: 227–230 °C; IR (KBr): 2906, 1690 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 10.01 (s, 1H), 9.92 (br s, 1H), 8.75 (d, $J$ = 8.8 Hz, 1H), 8.23 (d, 1H, $J$ = 8.3 Hz), 8.06–8.15 (m, 2H), 7.99 (d, $J$ = 7.3 Hz, 1H), 7.86–7.94 (m, 2H), 7.70–7.83 (m, 1H), 7.52–7.64 (m, 3H), 7.42 (br s, 1H), 2.34 (br s, 6H), 2.24 (br s, 3H), 1.80–1.93 (m, 6H); $^{13}$C NMR (DMSO-$d_6$): δ 182.8, 158.6, 156.7, 149.7, 147.8, 133.7, 131.3, 129.5, 128.2, 128.0, 127.5, 127.4, 127.1, 126.7, 126.4, 125.7, 125.4, 116.0, 41.8, 38.5, 36.1, 28.3; HRMS (ESI): $m/z$ calcd for $C_{31}H_{30}N_4NaOS$ $[M+Na]^+$: 529.2038, found: 529.2028; Anal. Calcd for $C_{31}H_{30}N_4OS$ (506.2): C, 73.49; H, 5.97; N, 11.06; Found: C, 73.43; H, 5.95; N, 11.02.

#### 4.2.4. N-(2,3-Dichlorophenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarbothioamide (**21**)

Yield: 76%; red solid; mp: 198–201 °C; IR (KBr): 2918, 1668 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 10.92 (br s, 1H), 10.05 (br s, 1H), 9.76 (br s, 1H), 8.76 (d, $J$ = 8.3 Hz, 1H), 8.21 (d, 1H, $J$ = 8.5 Hz), 8.06 (s, 1H), 7.85 (d, $J$ = 7.4 Hz, 1H), 7.71–7.76 (m, 1H), 7.74 (s, 1H), 7.38 (s, 1H), 7.42 (s, 1H), 2.29 (br s, 6H), 2.19 (br s, 3H), 1.80–1.94 (m, 6H); $^{13}$C NMR (DMSO-$d_6$): δ 182.3, 164.6, 156.8, 149.7, 147.8, 139.4, 131.9, 131.7, 130.2, 129.5, 128.8, 127.8, 127.4, 126.7, 116.0, 41.8, 38.5, 36.5, 28.7; HRMS (ESI): $m/z$ calcd for $C_{27}H_{26}Cl_2N_4NaOS$ $[M+Na]^+$: 547.1102, found: 547.1100; Anal. Calcd for $C_{27}H_{26}Cl_2N_4OS$ (524.1): C, 61.71; H, 4.99; N, 10.66; Found: C, 61.68; H, 4.95; N, 10.62.

#### 4.2.5. N-(2,5-Dimethoxyphenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarbothioamide (**22**)

Yield: 90%; colorless solid; mp: 164–167 °C; IR (KBr): 2903, 1523 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 10.98 (br s, 1H), 8.72 (br s, 1H), 8.67 (d, $J$ = 8.8 Hz, 1H), 8.24 (d, $J$ = 8.5 Hz, 1H), 8.13 (s, 1H), 7.98 (br s, 1H), 7.74 (t, $J$ = 7.6 Hz, 1H), 7.54–7.66 (m, 1H), 6.74–6.85 (m, 2H), 6.63–6.72 (m, 1H), 3.68–3.83 (m, 6H), 3.63 (br s, 1H), 2.26 (br s, 6H), 2.17 (br s, 3H), 1.81–1.94 (m, 6H); $^{13}$C NMR ($CDCl_3$): δ 180.0, 157.1, 152.6, 149.0, 147.8, 145.7131.7, 129.7, 128.9, 127.6, 127.55, 126.7, 119.6, 114.7, 113.5, 111.4, 110.23, 109.9, 79.5, 67.3, 56.7, 55.7 42.7, 38.9, 36.5, 28.7; HRMS (ESI): $m/z$ calcd for $C_{29}H_{32}N_4NaO_3S$ $[M+Na]^+$: 539.2093, found: 539.2089; Anal. Calcd for $C_{29}H_{32}N_4O_3S$ (516.2): C, 67.42; H, 6.24; N, 10.84; Found: C, 67.49; H, 6.32; N, 10.86.

#### 4.2.6. N-(2,5-Dichlorophenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarbothioamide (**23**)

Yield: 91%; yellow solid; mp: 179–183 °C; IR (KBr): 2906, 1647 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 9.09 (br s, 1H), 8.67 (d, $J$ = 8.8 Hz, 1H), 8.38 (br s, 1H), 8.21–8.28 (m, 1H), 8.06 (br s, 1H), 7.72–7.78 (m,

1H), 7.62 (ddd, $J$ = 1.5, 6.9, 8.7 Hz, 1H), 7.28–7.37 (m, 1H), 7.24 (d, $J$ = 2.3 Hz, 1H), 7.13 (dd, $J$ = 2.3, 8.5 Hz, 1H), 2.21 (br s, 6H), 2.13 (br s, 3H), 1.74–1.90 (m, 6H); $^{13}$C NMR ($CDCl_3$): δ 161.9, 158.3, 146.7, 136.0, 132.8, 130.9, 130.1, 129.2, 128.5, 128.0, 126.9, 126.6, 126.4, 115.5, 42.2, 39.3, 36.8, 32.0, 29.7, 29.4, 29.0, 22.7, 14.1; HRMS (ESI): *m/z* calcd for $C_{27}H_{26}Cl_2N_4NaOS$ $[M+Na]^+$: 547.1102, found: 547.1102; Anal. Calcd for $C_{27}H_{26}Cl_2N_4OS$ (524.2): C, 61.71; H, 4.99; N, 10.66; Found: C, 61.70; H, 4.96; N, 10.62.

#### 4.2.7. N-(4-Methylphenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarbothioamide (**24**)

Yield: 90%; pale yellow solid; mp: 225–228 °C; IR (KBr): 2905, 1664 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 10.86 (br s, 1H), 9.70 (br s, 1H), 8.74 (d, $J$ = 9.0 Hz, 1H), 8.18 (d, $J$ = 8.5 Hz, 1H), 8.03 (s, 1H), 7.83 (t, $J$ = 7.5 Hz, 1H), 7.66–7.75 (m, 1H), 7.25–7.37 (m, 2H), 7.11 (d, $J$ = 7.5 Hz, 2H), 2.26 (br s, 10H), 2.17 (br s, 3H), 1.90 (d, $J$ = 12.0 Hz, 3H), 1.81 (d, $J$ = 12.0 Hz, 3H); $^{13}$C NMR (DMSO-$d_6$): δ 181.2, 164.6, 156.8, 148.4, 147.8, 137.0, 134.4, 131.7, 129.6, 128.8, 127.5, 127.4, 126.7, 125.8, 115.9, 41.8, 38.9, 36.5, 28.7, 20.8; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}N_4NaOS$ $[M+Na]^+$: 493.2039, found: 493.2037; Anal. Calcd for $C_{28}H_{30}N_4OS$ (470.6): C, 71.46; H, 6.43; N, 11.90; Found: C, 71.42; H, 6.39; N, 11.88.

#### 4.2.8. N-(2,6-Dimethylphenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarbothioamide (**25**)

Yield: 79%; colorless solid; mp: 207–210 °C; IR (KBr): 2918, 1634 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 10.97 (br s, 1H), 8.65 (d, $J$ = 8.8 Hz, 1H), 8.16–8.26 (m, 1H), 8.05 (br s, 1H), 7.72 (t, $J$ = 7.5 Hz, 1H), 7.59 (t, $J$ = 7.2 Hz, 1H), 7.12–7.23 (m, 3H), 2.31–2.47 (m, 6H), 2.10–2.31 (m, 6H), 1.85 (br s, 6H), 1.61 (br s, 3H); $^{13}$C NMR ($CDCl_3$): δ 179.2, 160.8, 158.0, 148.2, 146.9, 141.2, 134.8, 132.2, 129.2, 129.0, 128.6, 128.3, 128.2, 127.6, 127.0, 126.7, 126.3, 115.3, 42.1, 39.1, 36.8, 29.7, 28.9, 24.6, 14.6; HRMS (ESI): *m/z* calcd for $C_{29}H_{32}N_4NaOS$ $[M+Na]^+$: 507.2195, found: 507.2190; Anal. Calcd for $C_{29}H_{32}N_4OS$ (484.6):C, 71.87; H, 6.66; N, 11.56; Found: C, 71.83; H, 6.62; N, 11.51.

#### 4.2.9. N-(2-Ethylphenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarbothioamide (**26**)

Yield: 81%; colorless solid; mp: 204–207 °C; IR (KBr): 2917, 1638 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 11.19 (br s, 1H), 8.64 (d, $J$ = 8.8 Hz, 1H), 8.45 (br s, 1H), 8.16–8.26 (m, 1H), 8.00 (s, 1H), 7.67–7.76 (m, 1H), 7.59 (ddd, $J$ = 1.5, 6.7, 8.6 Hz, 1H), 7.41–7.51 (m, 1H), 7.28–7.38 (m, 3H), 7.11–7.24 (m, 1H), 2.62–2.79 (m, 2H), 2.07–2.25 (m, 9H), 1.74–1.89 (m, 6H), 1.14–1.31 (m, 3H); $^{13}$C NMR ($CDCl_3$): δ 179.07, 160.7, 157.9, 148.1, 146.9, 141.1, 137.0, 134.9, 132.2, 129.5, 128.9, 128.5, 128.3, 127.9, 127.5, 127.0, 126.7, 126.3, 115.2, 42.0, 39.1, 36.7, 28.9, 25.4, 18.2; HRMS (ESI): *m/z* calcd for $C_{29}H_{32}N_4NaOS$ $[M+Na]^+$: 507.2195, found: 507.2190; Anal. Calcd for $C_{29}H_{32}N_4OS$ (484.2):C, 71.87; H, 6.66; N, 11.56; Found: C, 71.83; H, 6.62; N, 11.51.

#### 4.2.10. N-(2-Chloro-4-nitrophenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]-carbonyl}hydrazinecarbothioamide (**27**)

Yield: red solid; 86%; mp: 178–182 °C; IR (KBr): 1634 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 11.09 (br s, 1H), 10.28 (s, 1H), 9.82 (s, 1H), 8.75 (d, $J$ = 8.8 Hz, 1H), 8.29–8.35 (m, 1H), 8.20 (d, $J$ = 7.5 Hz, 2H), 8.04 (br s, 1H), 7.84 (t, $J$ = 7.4 Hz, 2H), 7.73 (t, $J$ = 7.3 Hz, 1H), 2.27 (br s, 6H), 2.18 (br s, 3H), 1.90 (d, $J$ = 11.5 Hz, 3H), 1.81 (d, $J$ = 12.0 Hz, 3H); $^{13}$C NMR (DMSO-$d_6$): δ 181.9, 164.8, 156.9, 149.2, 147.8, 145.8, 143.5, 131.7, 131.1, 129.7, 127.6, 126.8, 124.8, 122.6, 116.6, 41.8, 39.0, 36.6, 28.8; HRMS (ESI): *m/z* calcd for $C_{27}H_{26}ClN_5NaO_3S$ $[M+Na]^+$: 558.1343, found: 558.1334; Anal. Calcd for $C_{27}H_{26}ClN_5O_3S$ (535.1):C, 60.50; H, 4.89; N, 13.06; Found: C, 60.44; H, 4.82; N, 13.02.

#### 4.2.11. N-(2-Methoxy-5-methylphenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$] dec-1-yl)quinolin-2-yl]-carbonyl}hydrazinecarbothioamide (**28**)

Yield: 88%; colorless solid; mp: 172–175 °C; IR (KBr): 2908, 1655 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 10.93 (br s, 1H), 9.27 (br s, 1H), 8.68 (d, $J$ = 8.5 Hz, 1H), 8.41 (br s, 1H), 8.19–8.29 (m, 1H), 8.09–8.17 (m, 1H), 7.84 (br s, 1H), 7.74 (dt, $J$ = 1.1, 7.6 Hz, 1H), 7.61 (ddd, $J$ = 1.3, 6.7, 8.6 Hz, 1H), 6.92–7.04 (m, 1H), 6.76–6.85 (m, 1H), 3.66–3.78 (m, 3H), 2.34 (s, 3H), 2.24–2.32 (m, 6H), 2.19 (br s, 3H), 1.80–1.94 (m, 6H); $^{13}$C NMR ($CDCl_3$): δ 178.0, 158.4, 149.8, 148.6, 147.7, 131.0, 129.5, 128.9, 127.8, 127.2, 126.9, 126.4, 125.2, 116.2, 111.8, 56.4, 42.7, 39.7, 37.4, 29.5, 21.3; HRMS (ESI): *m/z* calcd for $C_{29}H_{32}N_4NaO_2S$ $[M+Na]^+$: 523.2144, found: 523.2144; Anal. Calcd for $C_{29}H_{32}N_4O_2S$ (500.2):C, 69.57; H, 6.44; N, 11.19; Found: C, 69.50; H, 6.38; N, 11.11.

#### 4.2.12. N-(4-Nitrophenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarbothioamide (**29**)

Yield: 79%; yellow solid; mp: 205–209 °C; IR (KBr): 1637 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 10.11 (br s, 1H), 8.75 (d, $J$ = 8.5 Hz, 1H), 8.19 (d, $J$ = 9.0 Hz, 3H), 8.05 (s, 1H), 7.91 (d, $J$ = 8.0 Hz, 2H), 7.83 (t, $J$ = 7.8 Hz, 1H), 7.66–7.77 (m, 1H), 3.33 (s, 1H), 2.28 (br s, 6H), 2.18 (br s, 3H), 1.91 (d, $J$ = 11.5 Hz, 3H), 1.82 (d, $J$ = 12.1 Hz, 3H); $^{13}$C NMR (DMSO-$d_6$): δ 180.2, 156.6, 155.3, 148.5, 147.3, 145.6, 142.9, 131.1, 128.9, 127.1, 126.8, 126.1, 125.9, 123.6, 122.9, 115.2, 112.2, 42.3, 38.4, 36.0, 28.2; HRMS (ESI): *m/z* calcd for $C_{29}H_{32}N_4NaO_2S$ $[M+Na]^+$: 524.1733, found: 524.1733; Anal. Calcd for $C_{29}H_{32}N_4O_2S$ (501.2): C, 64.65; H, 5.43; N, 13.96; Found: C, 64.69; H, 5.48; N, 13.97.

#### 4.2.13. N-Ethyl-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl] carbonyl}hydrazinecarbothioamide (**30**)

Yield: 78%; colorless solid; mp: 226–230 °C; IR (KBr): 2907, 1655 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 9.95 (br s, 1H), 8.67 (d, $J$ = 8.5 Hz, 1H), 8.11–8.20 (m, 2H), 8.00 (br s, 1H), 7.73 (dt, $J$ = 1.1, 7.6 Hz, 1H), 7.61 (ddd, $J$ = 1.5, 6.9, 8.7 Hz, 1H), 6.69 (br s, 1H), 3.64–3.76 (m, 2H), 2.25–2.35 (m, 6H), 2.21 (br s, 3H), 1.81–1.90 (m, 6H), 1.17–1.33 (m, 3H); $^{13}$C NMR ($CDCl_3$): δ 182.5, 164.2, 158.2, 147.9, 147.3, 131.7, 129.1, 128.5, 126.9, 126.4, 115.9, 42.2, 39.9, 39.2, 36.8, 28.9, 14.2; HRMS (ESI): *m/z* calcd for $C_{23}H_{28}N_4NaOS$ $[M+Na]^+$: 431.1882, found: 431.1875; Anal. Calcd for $C_{23}H_{28}N_4OS$ (408.2): C, 67.61; H, 6.91; N, 13.71; Found: C, 67.59; H, 6.88; N, 13.68.

#### 4.2.14. N-(Prop-2-en-1-yl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarbothioamide (**31**)

Yield: 68%; colorless solid; mp: 234–237 °C; IR (KBr): 2905, 1662 cm$^{-1}$; $^1$H NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 8.62 (d, $J$ = 8.5 Hz, 1H), 8.05–8.11 (m, 2H), 7.67 (t, $J$ = 7.6 Hz, 1H), 7.51–7.59 (m, 1H), 5.77–5.89 (m, 1H), 5.13–5.21 (m, 1H), 5.05–5.12 (m, 1H), 4.21 (d, $J$ = 5.5 Hz, 2H), 2.24 (br s, 6H), 2.15 (br s, 3H), 1.77–1.86 (m, 6H); $^{13}$C NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 182.6, 164.5, 158.4, 147.9, 147.8, 133.3, 131.6, 129.3, 128.5, 127.0, 126.6, 117.0, 116.2, 47.3, 42.7, 39.4, 36.9, 28.9; HRMS (ESI): *m/z* calcd for $C_{24}H_{28}N_4NaOS$ $[M+Na]^+$: 443.1882, found: 443.1882; Anal. Calcd for $C_{24}H_{28}N_4OS$ (420.2): C, 68.54; H, 6.71; N, 13.32; Found: C, 68.54; H, 6.69; N, 13.31.

#### 4.2.15. N-tert-Butyl-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}hydrazinecarbothioamide (**32**)

Yield: 66%; colorless solid; mp: 158–164 °C; IR (KBr): 2907, 1654 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 10.21 (br s, 1H), 8.68 (d, $J$ = 8.5 Hz, 1H), 8.04–8.22 (m, 3H), 7.73 (ddd, $J$ = 1.3, 7, 8.3 Hz, 1H), 7.61 (ddd, $J$ = 1.5, 6.9, 8.7 Hz, 1H), 6.60 (br s, 1H), 2.26–2.39 (m, 6H), 2.22 (br s, 3H), 1.88 (br s, 6H), 1.50–1.60 (m, 9H); $^{13}$C NMR ($CDCl_3$): δ 180.4, 163.4, 158.0, 148.0, 147.2, 131.9, 129.0, 128.5, 126.8, 126.4, 115.8, 54.0, 42.2, 39.2, 36.8, 28.9; HRMS (ESI): *m/z* calcd for $C_{25}H_{32}N_4NaOS$ $[M+Na]^+$: 459.2195, found: 459.2193; Anal. Calcd for $C_{25}H_{32}N_4OS$ (436.3):C, 68.77; H, 7.39; N, 12.83; Found: C, 68.76; H, 7.39; N, 12.82.

*4.2.16. N-(2-Phenylethyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarbothioamide (**33**)*

Yield: 82%; white solid; mp: 201–205 °C; IR (KBr): 2908, 1635 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 9.84 (br s, 1H), 8.69 (d, $J$ = 8.5 Hz, 1H), 8.10–8.18 (m, 2H), 8.07 (br s, 1H), 7.71–7.79 (m, 1H), 7.63 (ddd, $J$ = 1.5, 6.9, 8.7 Hz, 1H), 7.08–7.25 (m, 4H), 6.98–7.08 (m, 1H), 6.73 (br s, 1H), 3.81–3.95 (m, 2H), 2.89–2.98 (m, 2H), 2.30 (s, 6H), 2.22 (br s, 3H), 1.89 (br s, 6H); $^{13}$C NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 182.5, 164.5, 158.3, 147.9, 147.8, 138.8, 138.6, 131.7, 129.3, 129.0, 128.9, 128.8, 128.5, 127.0, 126.6, 126.5, 116.2, 46.2, 42.3, 39.4, 36.9, 35.1, 29.1; HRMS (ESI): $m/z$ calcd for $C_{29}H_{32}N_4NaOS$ [M+Na]$^+$: 507.2195, found: 507.2195; Anal. Calcd for $C_{29}H_{32}N_4OS$ (484.2): C, 71.87; H, 6.66; N, 11.56; Found: C, 71.86; H, 6.65; N, 11.55.

*4.2.17. 2-{[4-(Tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}-N-[2-(trifluoromethyl)-phenyl]hydrazinecarbothioamide (**34**)*

Yield: 75%; yellow solid; mp: 190–193 °C; IR (KBr): 2915, 1635 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 8.86 (br s, 1H), 8.57–8.70 (m, 1H), 8.19–8.26 (m, 1H), 8.01 (br s, 1H), 7.95 (br s, 1H), 7.54–7.76 (m, 5H), 7.39 (t, $J$ = 7.5 Hz, 1H), 2.17 (br s, 6H), 2.10 (br s, 3H), 1.73–1.86 (m, 6H); $^{13}$C NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 180.4, 164.5, 158.1, 148.0, 147.2, 135.9, 133.4, 133.1, 130.5, 129.3, 129.1, 128.9, 127.8, 127.0, 126.9, 125.9, 121.8, 115.7, 68.0, 43.1, 39.2, 36.8, 29.9; HRMS (ESI): $m/z$ calcd for $C_{27}H_{28}F_3N_4NaOS$ [M+Na]$^+$: 547.1756, found: 547.1753; Anal. Calcd for $C_{27}H_{28}F_3N_4OS$ (484.2): C, 64.11; H, 5.19; N, 10.68; Found: C, 64.10; H, 5.14; N, 10.66.

*4.2.18. 2-{[4-(Tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}-N-[4-(trifluoromethoxyphenyl]hydrazinecarbothioamide (**35**)*

Yield: 96%; white solid; mp: 208–211 °C; IR (KBr): 2923, 1665 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 10.84 (br s, 1H), 9.97 (br s, 1H), 9.85 (br s, 1H), 8.74 (d, $J$ = 8.5 Hz, 1H), 8.19 (d, $J$ = 8.5 Hz, 1H), 8.04 (s, 1H), 7.82 (t, $J$ = 7.5 Hz, 1H), 7.72 (t, $J$ = 7.8 Hz, 1H), 7.55–7.68 (m, 2H), 7.25–7.37 (m, 2H), 2.27 (br s, 6H), 2.17 (br s, 3H), 1.86–1.94 (m, 3H), 1.74–1.86 (m, 3H); $^{13}$C NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 181.4, 164.5, 156.9, 149.3, 147.8, 145.4, 138.7, 131.7, 129.6, 129.1, 127.5, 127.4, 126.7, 122.3, 121.2, 118.7, 118.3, 115.4, 41.8, 38.9, 36.5, 28.7; HRMS (ESI): $m/z$ calcd for $C_{27}H_{28}F_3N_4NaO_2S$ [M+Na]$^+$: 563.1705, found: 563.1702; Anal. Calcd for $C_{27}H_{28}F_3N_4O_2S$ (540.2): C, 64.35; H, 4.82; N, 10.72; Found: C, 64.32; H, 4.80; N, 10.70.

*4.2.19. 2-{[4-(Tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}-N-(3,4,5-trimethoxyphenyl)hydrazinecarbothioamide (**36**)*

Yield: 88%; white solid; mp: 259–263 °C; IR (KBr): 2904, 1657 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 8.85 (br s, 1H), 8.69 (br s, 1H), 8.64 (d, $J$ = 8.8 Hz, 1H), 8.19 (d, $J$ = 8.3 Hz, 1H), 8.09 (s, 1H), 7.70 (t, $J$ = 7.6 Hz, 1H), 7.59 (t, $J$ = 7.8 Hz, 1H), 6.68–6.85 (m, 3H), 3.78 (d, $J$ = 8.3 Hz, 9H), 2.24 (br s, 6H), 2.14–2.22 (m, 3H), 1.80–1.90 (m, 6H); $^{13}$C NMR ($CDCl_3$): δ 179.5, 175.7, 158.0, 153.2, 153.0, 148.0, 146.9, 136.2, 133.0, 131.9, 129.0, 128.4, 126.8, 126.3, 115.6, 102.5, 101.8, 60.8, 56.2, 56.1, 42.0, 39.1, 36.7, 28.8; HRMS (ESI): $m/z$ calcd for $C_{30}H_{34}N_4NaO_4S$ [M+Na]$^+$: 569.2199, found: 569.2196; Anal. Calcd for $C_{30}H_{34}N_4O_4S$ (546.2): C, 65.91; H, 6.27; N, 10.25; Found: C, 65.89; H, 6.23; N, 10.23.

*4.3. General method for the synthesis of N-alkyl/aryl-2-{[4-(tricyclo [3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}hydrazinecarboxamides (**37**–**51**)*

To a stirred solution of **2** (1 mmol) in THF (5 mL), alkyl/aryl isocyanate (1.2 mmol) was added. The reaction mixture was stirred at ambient temperature for 4 h. The solvent was evaporated and the residue was suspended in $C_2H_5OH$. The precipitated solid was filtered, washed with $C_2H_5OH$ and dried under vacuum to afford **37**–**51**.

*4.3.1. N-Pentyl-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl] carbonyl}hydrazinecarboxamide (**37**)*

Yield: 80%; white solid; mp: 208–211 °C; IR (KBr): 3435, 1646 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 9.83 (br s, 1H), 8.66 (d, $J$ = 8.5 Hz, 1H), 8.05–8.15 (m, 2H), 7.70 (t, $J$ = 7.3 Hz, 1H), 7.56–7.61 (m, 1H), 7.12 (br s, 1H), 5.52 (br s, 1H), 3.22–329 (m, 2H), 2.34 (br s, 6H), 2.24 (s, 3H), 1.90–1.96 (m, 6H), 1.50–154 (m, 2H), 1.26–131 (m, 4H), 0.84–0.90 (m, 3H); $^{13}$C NMR ($CDCl_3$): δ 164.4, 158.0, 157.8, 147.9, 147.7, 131.8, 128.9, 128.4, 126.7, 126.4, 115.9, 43.1, 42.2, 40.3, 39.7, 39.2, 36.9, 36.8, 29.8, 28.9, 25.4, 14.0; HRMS (ESI): $m/z$ calcd for $C_{26}H_{34}N_4NaO_2$ [M+Na]$^+$: 457.2579, found: 457.2575; Anal. Calcd for $C_{26}H_{34}N_4O_2$ (434.3): C, 71.86; H, 7.89; N, 12.89; Found: C, 71.88; H, 7.84; N, 12.87.

*4.3.2. N-(Tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]-carbonyl}hydrazinecarboxamide (**38**)*

Yield: 90%; yellow solid; mp: 247–250 °C; IR (KBr): 3429, 2929, 1728 cm$^{-1}$; $^1$H NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 8.63 (d, $J$ = 8.8 Hz, 1H), 8.05–8.16 (m, 2H), 7.67 (t, $J$ = 7.6 Hz, 1H), 7.50–7.60 (m, 1H), 2.28 (br s, 6H), 2.18 (br s, 3H), 2.02 (s, 3H), 1.95 (s, 6H), 1.79–1.89 (m, 6H), 1.62 (s, 6H); $^{13}$C NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 164.7, 157.7, 157.1, 147.8, 147.7, 131.4, 128.8, 128.1, 126.5, 126.2, 115.7, 51.1, 51.0, 41.9, 41.6, 39.0, 36.6, 36.1, 29.3, 28.7; HRMS (ESI): $m/z$ calcd for $C_{31}H_{38}N_4NaO_2$ [M+Na]$^+$: 521.2892, found: 521.2890; Anal. Calcd for $C_{31}H_{38}N_4O_2$ (498.7): C, 74.67; H, 7.68; N, 11.24; Found: C, 74.62; H, 7.63; N, 11.20.

*4.3.3. 2-{[4-(Tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}-N-(3,4,5-trimethoxy-phenyl)hydrazinecarboxamide (**39**)*

Yield: 78%; yellow solid; mp: >300 °C; IR (KBr): 3433, 2927, 1737 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 10.11 (br s, 1H), 8.65 (d, $J$ = 8.8 Hz, 1H), 8.22 (br s, 1H), 8.09–8.18 (m, 2H), 7.98 (s, 1H), 7.65–7.75 (m, 1H), 7.52–7.64 (m, 1H), 6.64 (s, 2H), 3.71 (d, $J$ = 9.8 Hz, 9H), 2.24 (br s, 6H), 2.17 (br s, 3H), 1.85 (br s, 6H); $^{13}$C NMR ($CDCl_3$): δ 165.4, 158.0, 155.4, 153.0, 148.0, 147.3, 134.1, 133.9, 131.9, 129.0, 128.4, 126.8, 126.3, 115.7, 97.7, 60.9, 55.9, 42.1, 39.1, 36.8, 28.9; HRMS (ESI): $m/z$ calcd for $C_{30}H_{34}N_4NaO_5$ [M+Na]$^+$: 553.2427, found: 553.2415; Anal. Calcd for $C_{30}H_{34}N_4O_5$ (530.6): C, 67.91; H, 6.46; N, 10.56; Found: C, 67.88; H, 6.43; N, 10.52.

*4.3.4. 2-{[4-(Tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}-N-[4-(trifluoromethoxy)-phenyl]hydrazinecarboxamide (**40**)*

Yield: 69%; red solid; mp: 245–248 °C; IR (KBr): 3307, 2921, 1726 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 10.19 (br s, 1H), 8.60 (d, $J$ = 8.8 Hz, 1H), 8.48 (br s, 2H), 8.13 (dd, $J$ = 1.4, 8.4 Hz, 1H), 8.03 (s, 1H), 7.68 (t, $J$ = 7.6 Hz, 1H), 7.57 (t, $J$ = 7.6 Hz, 1H), 7.30–7.33 (m, 2H), 6.90–6.92 (m, 2H), 2.12 (s, 9H), 1.74–1.86 (m, 6H); $^{13}$C NMR ($CDCl_3$): δ 165.5, 157.9, 155.1, 147.9, 147.1, 144.4, 136.9, 131.9, 129.0, 128.4, 126.8, 126.3, 121.7, 121.3, 120.2, 115.5, 42.0, 39.0, 36.7, 28.8; HRMS (ESI): $m/z$ calcd for $C_{28}H_{27}F_3N_4NaO_3$ [M+Na]$^+$: 547.1933, found: 547.1928; Anal. Calcd for $C_{28}H_{27}F_3N_4O_3$ (524.5): C, 64.11; H, 5.19; N, 10.68; Found: C, 64.07; H, 5.15; N, 10.64.

*4.3.5. N-(4-tert-Butylphenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarboxamide (**41**)*

Yield: 87%; white solid; mp: 208–211 °C; IR (KBr): 3350, 2907, 1720 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 9.90 (br s, 1H), 8.68 (d, $J$ = 8.8 Hz, 1H), 8.10–8.21 (m, 2H), 7.72 (t, $J$ = 7.4 Hz, 1H), 7.57–7.65 (m, 2H), 7.42 (d, $J$ = 6.8 Hz, 1H), 7.12–7.22 (m, 2H), 7.13 (br s, 1H), 6.99 (br s, 1H), 2.31 (br s, 6H), 2.16–2.27 (m, 3H), 1.89 (br s, 6H), 1.35–1.47 (m, 9H); $^{13}$C NMR ($CDCl_3$): δ 163.7, 157.7, 156.0, 148.0, 147.5, 134.9, 131.9, 129.2, 128.9, 128.3, 127.1, 126.8, 126.6, 126.3, 115.8, 77.3, 42.1, 39.1, 36.8, 34.8, 30.7, 30.5, 28.9; HRMS (ESI): $m/z$ calcd for $C_{31}H_{37}N_4O_2$ [M+H]$^+$: 497.2917, found: 497.2911; Anal. Calcd for $C_{31}H_{36}N_4O_2$ (496.6): C, 74.97; H, 7.31; N, 11.28; Found: C, 74.93; H, 7.29; N, 11.24.

*4.3.6. N-Hexyl-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl] carbonyl}hydrazinecarboxamide (**42**)*

Yield: 86%; yellow solid; mp: 277–280 °C; IR (KBr): 3343, 2935, 1657 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 9.76 (br s, 1H), 8.69 (d, $J$ = 8.8 Hz, 1H), 8.13–8.23 (m, 2H), 7.73 (t, $J$ = 7.2 Hz, 1H), 7.62 (t, $J$ = 7.2 Hz, 1H), 6.87 (br s, 1H), 5.41 (t, $J$ = 5.6 Hz, 1H), 3.22–3.32 (m, 2H), 2.31 (s, 6H), 2.21 (s, 3H), 1.89 (s, 6H), 1.52 (q, $J$ = 7.2 Hz, 2H), 1.22–1.36 (m, 6H), 0.78–0.93 (m, 3H); $^{13}$C NMR ($CDCl_3$): δ 164.4, 158.0, 157.7, 148.0, 147.7, 131.8, 128.9, 128.3, 126.6, 126.3, 115.8, 42.2, 40.3, 39.1, 36.8, 31.5, 30.1, 28.9, 26.5, 22.6, 14.0; HRMS (ESI): $m/z$ calcd for $C_{27}H_{34}N_4NaO_2$ $[M+Na]^+$: 471.2736, found: 471.2724; Anal. Calcd for $C_{27}H_{36}N_4O_2$ (448.6): C, 72.29; H, 8.09; N, 12.49; Found: C, 72.25; H, 8.06; N, 12.45.

*4.3.7. N-Hexadecyl-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl] carbonyl}hydrazinecarboxamide (**43**)*

Yield: 79%; white solid; mp: 99–103 °C; IR (KBr): 2923, 1726 cm$^{-1}$; $^1$H NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 8.66 (d, $J$ = 8.8 Hz, 1H), 8.09–8.19 (m, 2H), 7.71 (t, $J$ = 7.4 Hz, 1H), 7.56–7.61 (m, 1H), 3.21 (t, $J$ = 7.0 Hz, 2H), 2.26–2.44 (m, 6H), 2.21 (br s, 3H), 2.02 (br s, 6H), 1.87 (br s, 6H), 1.48 (d, $J$ = 6.8 Hz, 2H), 1.21–1.23 (m, 20H), 0.86 (t, $J$ = 6.7 Hz, 3H); $^{13}$C NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 164.8, 158.5, 158.0, 147.9, 147.8, 131.7, 129.0, 128.4, 126.7, 126.4, 116.0, 42.2, 40.3, 40.2, 39.2, 36.8, 32.0, 30.0, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.0, 26.9, 22.7, 14.1; HRMS (ESI): $m/z$ calcd for $C_{37}H_{57}N_4O_2$ $[M+H]^+$: 589.4482, found: 589.4476; Anal. Calcd for $C_{37}H_{56}N_4O_2$ (588.9): C, 75.47; H, 9.59; N, 9.51; Found: C, 75.45; H, 9.54; N, 9.48.

*4.3.8. N-Cyclopentyl-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}hydrazinecarboxamide (**44**)*

Yield: 95%; yellow solid; mp: 253–256 °C; IR (KBr): 3318, 2930, 1642 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 9.89 (br s, 1H), 8.68 (d, $J$ = 8.8 Hz, 1H), 8.12–8.21 (m, 2H), 7.72 (t, $J$ = 7.3 Hz, 1H), 7.58–7.62 (m, 1H), 7.27 (s, 1H), 5.51 (br s, 1H), 4.11–4.16 (m, 1H), 2.31 (br s, 6H), 2.22 (br s, 3H), 1.94–2.01 (m, 2H), 1.80–1.92 (m, 6H), 1.51–1.71 (m, 4H), 1.43 (dd, $J$ = 6.2, 12.4 Hz, 2H); $^{13}$C NMR ($CDCl_3$): δ 164.2, 158.0, 157.6, 147.8, 147.6, 131.7, 129.0, 128.4, 126.7, 126.4, 115.9, 52.0, 42.2, 39.2, 36.8, 36.1, 33.3, 28.9, 23.6; HRMS (ESI): $m/z$ calcd for $C_{26}H_{33}N_4O_2$ $[M+H]^+$: 433.2604, found: 433.2594; Anal. Calcd for $C_{26}H_{32}N_4O_2$ (432.6): C, 72.19; H, 7.46; N, 12.95; Found: C, 72.15; H, 7.43; N, 12.91.

*4.3.9. N-(2,6-Diethylphenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarboxamide (**45**)*

Yield: 78%; white solid; mp: 250–254 °C; IR (KBr): 3400, 2929, 1727 cm$^{-1}$; $^1$H NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 8.65 (d, $J$ = 8.8 Hz, 1H), 8.11–8.14 (m, 2H), 7.70 (t, $J$ = 7.4 Hz, 1H), 7.53–7.62 (m, 1H), 7.16 (br s, 3H), 2.24 (br s, 6H), 2.17 (br s, 3H), 1.85 (br s, 6H), 1.61 (s, 4H), 1.17–1.31 (m, 6H); $^{13}$C NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 164.7, 158.0, 157.3, 148.0, 147.9, 131.7, 129.0, 128.4, 128.0, 126.7, 126.5, 116.0, 77.4, 42.2, 39.2, 36.9, 29.0, 24.8, 14.6; HRMS (ESI): $m/z$ calcd for $C_{31}H_{36}N_4NaO_2$ $[M+Na]^+$: 519.2736, found: 519.2735; Anal. Calcd for $C_{31}H_{36}N_4O_2$ (496.6): C, 74.68; H, 8.74; N, 10.56; Found: C, 74.63; H, 8.71; N, 10.51.

*4.3.10. N-Cyclododecyl-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}hydrazinecarboxamide (**46**)*

Yield: 86%; white solid; mp: 214–217 °C; IR (KBr): 2927, 1726 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 9.90 (d, $J$ = 3.3 Hz, 1H), 8.66 (d, $J$ = 8.8 Hz, 1H), 8.12–8.18 (m, 2H), 7.71 (dt, $J$ = 1, 7.7 Hz, 1H), 7.56–7.61 (m, 1H), 7.34 (br s, 1H), 5.32 (d, $J$ = 8.5 Hz, 1H), 3.90–4.03 (m, 1H), 2.27–2.38 (m, 6H), 2.21 (br s, 3H), 1.84–1.93 (m, 6H), 1.51–1.67 (m, 2H), 1.20–1.50 (m, 22H); $^{13}$C NMR ($CDCl_3$): δ 163.9, 157.7, 157.3, 148.0, 147.7, 131.8, 128.9, 128.3, 126.6, 126.3, 115.8, 46.9, 42.2, 39.1, 36.8, 31.8, 30.5, 28.9, 25.6, 23.9, 23.7, 23.5, 23.3, 23.2, 23.1, 21.4, 21.0; HRMS (ESI): $m/z$ calcd for $C_{33}H_{46}N_4NaO_2$ $[M+Na]^+$: 553.3518, found: 553.3499; Anal. Calcd for $C_{33}H_{46}N_4O_2$ (530.7): C, 74.68; H, 8.74; N, 10.56; Found: C, 74.63; H, 8.71; N, 10.51.

*4.3.11. N-(4-Butoxyphenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarboxamide (**47**)*

Yield: 64%; yellow solid; mp: 219–222 °C; IR (KBr): 3333, 2906, 1663 cm$^{-1}$; $^1$H NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 8.68 (d, $J$ = 8.8 Hz, 1H), 8.12–8.19 (m, 2H), 7.71 (t, $J$ = 7.5 Hz, 1H), 7.60 (t, $J$ = 7.4 Hz, 1H), 7.32 (d, $J$ = 5.3 Hz, 2H), 6.81 (d, $J$ = 9.0 Hz, 2H), 3.91 (t, $J$ = 6.5 Hz, 2H), 2.30 (br s, 6H), 2.22 (br s, 3H), 1.88 (br s, 6H), 1.67–1.79 (m, 2H), 1.40–1.53 (m, 2H), 0.96 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 164.9, 158.0, 156.2, 155.6, 148.0, 147.8, 131.7, 131.0, 129.1, 128.4, 126.8, 126.4, 122.1, 121.9, 116.0, 114.9, 68.1, 42.2, 39.2, 36.9, 31.4, 29.0, 19.3, 13.9; HRMS (ESI): $m/z$ calcd for $C_{31}H_{37}N_4O_2$ $[M+H]^+$: 513.2866, found: 513.2858; Anal. Calcd for $C_{31}H_{36}N_4O_3$ (512.6): C, 72.63; H, 7.08; N, 10.93; Found: C, 72.61; H, 7.03; N, 10.90.

*4.3.12. N-(4-Fluorophenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarboxamide (**48**)*

Yield: 88%; white solid; mp: 247–250 °C; IR (KBr): 2902, 1654 cm$^{-1}$; $^1$H NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 8.69 (d, $J$ = 8.6 Hz, 1H), 8.15–8.18 (m, 2H), 7.74 (t, $J$ = 7.4 Hz, 1H), 7.62 (t, $J$ = 7.5 Hz, 1H), 7.38–7.43 (m, 2H), 6.95–7.00 (m, 2H), 2.33 (br s, 6H), 2.23 (br s, 3H), 1.90 (br s, 6H); $^{13}$C NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 165.3, 158.1, 157.9, 155.6, 148.1, 148.0, 134.5, 131.7, 129.2, 128.5, 126.9, 126.5, 121.5, 121.4, 116.1, 115.6, 115.4, 42.2, 39.2, 36.9, 29.0; HRMS (ESI): $m/z$ calcd for $C_{27}H_{28}FN_4O_2$ $[M+H]^+$: 459.2126, found: 459.2124; Anal. Calcd for $C_{27}H_{27}FN_4O_2$ (458.5): C, 70.72; H, 5.94; N, 12.22; Found: C, 70.69; H, 5.91; N, 12.18.

*4.3.13. N-(2-Trifluoromethoxyphenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]-carbonyl}hydrazinecarboxamide (**49**)*

Yield: 62%; white solid; mp: 216–219 °C; IR (KBr): 2904, 1648 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 10.14 (br s, 1H), 8.69 (d, $J$ = 8.8 Hz, 1H), 8.49 (br s, 1), 8.13–8.25 (m, 3H), 8.05 (br s, 1H), 7.72 (dt, $J$ = 0.9, 7.6 Hz, 1H), 7.61 (dt, $J$ = 1.2, 7.9 Hz, 1H), 7.11–7.16 (m, 2H), 6.91–7.01 (m, 1H), 2.31 (br s, 6H), 2.21 (br s, 3H), 1.88 (br s, 6H); $^{13}$C NMR ($CDCl_3$): δ 164.9, 157.8, 154.5, 148.0, 147.3, 138.0, 138.0, 138.0, 132.0, 131.2, 128.9, 128.4, 127.3, 126.7, 126.3, 122.9, 121.8, 121.1, 120.3, 119.2, 115.9, 42.1, 39.1, 36.8, 28.9; HRMS (ESI): $m/z$ calcd for $C_{28}H_{27}F_3N_4NaO_3$ $[M+Na]^+$: 547.1933, found: 547.1923; Anal. Calcd for $C_{28}H_{30}N_4O_3$ (470.6): C, 71.47; H, 6.43; N, 11.91; Found: C, 71.44; H, 6.40; N, 11.88.

*4.3.14. 2-{[4-(Tricyclo[3.3.1.1$^{3,7}$]dec-1-yl)quinolin-2-yl]carbonyl}-N-(2,4,6-trimethylphenyl)hydrazinecarboxamide (**50**)*

Yield: 68%; colorless solid; mp: 242–245 °C; IR (KBr): 2925, 1725 cm$^{-1}$; $^1$H NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 8.66 (d, $J$ = 8.5 Hz, 1H), 8.01–8.26 (m, 2H), 7.70 (t, $J$ = 7.2 Hz, 1H), 7.52–7.64 (m, 1H), 6.80–6.97 (m, 2H), 2.15–2.44 (m, 18H), 1.80–1.95 (m, 6H); $^{13}$C NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 164.6, 157.8, 157.1, 147.9, 147.8, 131.6, 128.9, 128.3, 126.6, 126.3, 115.9, 42.1, 39.1, 36.7, 28.9, 20.8, 18.0; HRMS (ESI): $m/z$ calcd for $C_{30}H_{34}N_4NaO_2$ $[M+Na]^+$: 505.2579, found: 505.2571; Anal. Calcd for $C_{30}H_{34}N_4O_2$ (482.6): C, 74.66; H, 7.10; N, 11.61; Found: C, 74.61; H, 7.03; N, 11.58.

*4.3.15. N-(3-Fluorophenyl)-2-{[4-(tricyclo[3.3.1.1$^{3,7}$]dec-1-yl) quinolin-2-yl]carbonyl}-hydrazinecarboxamide (**51**)*

Yield: 72%; white solid; mp: 244–247 °C; IR (KBr): 2929, 1728 cm$^{-1}$; $^1$H NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 8.69 (d, $J$ = 8.8 Hz, 1H), 8.13–8.21 (m, 2H), 7.73 (t, $J$ = 7.4 Hz, 1H), 7.57–7.67 (m, 1H), 7.34–7.43 (m, 1H), 7.17–7.25 (m, 1H), 7.08–7.15 (m, 1H), 6.65–6.77 (m, 1H), 2.32 (br s, 6H), 2.23 (br s, 3H), 1.90 (br s, 6H); $^{13}$C NMR [$CDCl_3$:$CD_3OD$ (5:1)]: δ 165.1, 164.4, 162.0, 158.1, 155.6, 148.1, 147.9, 140.2, 131.7, 130.0, 129.9, 129.1, 128.5, 126.9, 126.5, 116.1, 114.6, 114.5,

109.8, 109.6, 106.7, 106.4, 42.2, 39.3, 36.9, 29.0; HRMS (ESI): *m/z* calcd for $C_{27}H_{28}N_4O_2$ $[M+H]^+$: 459.2196, found: 459.2187; Anal. Calcd for $C_{27}H_{27}FN_4O_2$ (458.5): C, 70.72; H, 5.94; N, 12.22; Found: C, 70.70; H, 5.91; N, 12.20.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.07.100.

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