European Journal of Medicinal Chemistry 44 (2009) 2017–2029

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis, anti-tuberculosis activity and 3D-QSAR study of amino acid conjugates of 4-(adamantan-1-yl) group containing quinolines

Amit Nayyar [a,1], Sanjay R. Patel [a], Mushtaque Shaikh [b], Evans Coutinho [b,*], 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 Pharmaceutical Chemistry, Bombay College of Pharmacy, Kalina, Santacruz (E), Mumbai 400 098, India

ARTICLE INFO

Article history:
Received 8 April 2008
Received in revised form
19 September 2008
Accepted 2 October 2008
Available online 11 October 2008

Keywords:
Tuberculosis
Ring-substituted quinolines
CoMFA
Amino acid conjugates
Anti-tuberculosis

ABSTRACT

The synthesis, antimycobacterial activity and 3D-QSAR study of two series of 4-(adamantan-1-yl) group containing quinolines conjugated to amino acids are described. The most potent analogs displayed in vitro antimycobacterial activity ranging between 1.00 and 3.125 μg/mL. To understand the relationship between structure and activity, a 3D-QSAR analysis has been carried out by Comparative Molecular Field Analysis (CoMFA). The activities of molecules in the test sets were nicely predicted by the CoMFA model generated with field alignment. The best model was obtained using atom-fit alignment. Based on the molecular fields the relationships between structure and activity were easily rationalized.

1. Introduction

In 1993, the World Health Organization (WHO) declared tuberculosis (TB) a global public health emergency. The disease has advanced, and currently causes approximately 2 million deaths annually [1]. Several interlinked factors contribute to this progression: (a) development of strains resistant to most commonly used drugs such as isoniazid and rifampicin; (b) the spread of the HIV/AIDS pandemic (one third of the approximately 40 million HIV cases worldwide are coinfected with *Mycobacterium tuberculosis*, and for these individuals, the risk of developing clinical TB is about 10% per year); (c) the difficulty of TB detection in infected individuals (less than 40% of TB cases are detected); and finally; (d) the rising incidence of multidrug-resistant (MDR) TB. To overcome shortcomings of existing regimens of anti-TB drugs, new structural classes of drugs acting via novel biochemical pathways are required [2–4]. Ideally, the new classes of anti-TB drugs must be of low molecular weight, inexpensive for easy availability to poor patients, and possess activity against drug-resistant strains of commonly used anti-TB drugs.

Previously, we had reported the discovery of ring-substituted quinolines as a new structural class of anti-TB compounds [5]. The lead compound 2,8-dicyclopentyl-4-methylquinoline (DCMQ) synthesized in one-step is a promising inhibitor and exhibited encouraging activities against drug-sensitive and several single drug-resistant strains (SDR) of *M. tuberculosis*. The promising activity against SDR strains of several of the currently used anti-TB agents suggests that ring-substituted quinolines exemplified by DCMQ possibly act by new and yet unknown biochemical pathway(s). In attempts to modify the structure of the lead compound DCMQ, we have synthesized several new series of ring-substituted quinolines [6–10]. In one such study, we have reported the synthesis and promising anti-tuberculosis activity of a series of ring-substituted quinolinecarbohydrazides/carboxamides [7]. The most active compounds 4-(adamantan-1-yl)-2-quinolinecarbohydrazide and 4-(adamantan-1-yl)-2-quinolinecarboxamide (Fig. 1) have displayed 99% and 98% inhibition at 6.25 μg/mL, respectively against drug-sensitive *M. tuberculosis H37Rv* strain. Both compounds were synthesized using a facile three-step synthetic process in high yields. Therefore, both compounds were considered ideally suited for further structural optimization. In continuation of our anti-tuberculosis drug discovery program and structural diversification of ring-substituted quinolines, herein we report synthesis of various amino acid derivatives (series 1–2, Fig. 2) of 4-

* Corresponding author. Tel.: +91 22 26670905; fax: +91 22 26670816.
** Corresponding author. Tel.: +91 172 2214682; fax: +91 172 2214692.
E-mail addresses: evans@bcpindia.org (E. Coutinho), rahuljain@niper.ac.in (R. Jain).
[1] Present address: Laboratory of Clinical Infectious Diseases, NIAID, National Institutes of Health, Bethesda, MD 20852, USA.

0223-5234/$ – see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2008.10.004

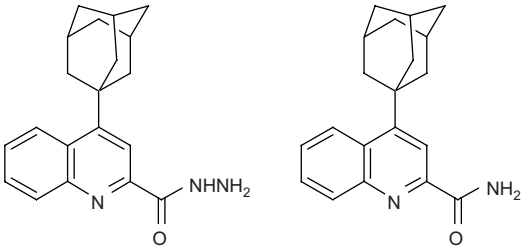


Fig. 1. Structure of promising ring-substituted quinolines.

(adamantan-1-yl)-2-quinolinecarbohydrazide and 4-(adamantan-1-yl)-2-quinolinecarboxamide. Amino acids used were chosen in a way to study the effect of various lipophilic, hydrophilic and cationic groups present on their side chain on the biological activity. As remarked earlier, the exact molecular target for the ring-substituted quinolines remains unknown. Ligand-based techniques have been employed successfully by us and other research groups in the past to help in designing newer classes of antimicrobial agents [8,11–15]. Therefore, we have used the ligand-based approach of 3D-QSAR (CoMFA) for a better understanding of the structure activity relationship of the synthesized ring-substituted quinolines.

2. Results and discussion

2.1. Chemistry

4-(Adamantan-1-yl)-2-quinolinecarbohydrazide (**4**) was synthesized in three convenient steps from commercially available quinoline-2-carboxylic acid (**1**) as described earlier [7]. The latter compound **4** upon reaction with suitably side chain protected commercially available Boc-L-amino acids in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in anhydrous dichloromethane (DCM) as solvent for 8 h at ambient temperature afforded {1-[*N*′-(4-adamantan-1-yl-quinoline-2-carbonyl)hydrazinocarbonyl]alkyl carbamic acid *tert*-butyl esters **6**–**18** (Scheme 1). Compounds **6**–**18** upon reaction with 33% hydrogen bromide (HBr) solution in acetic acid at ambient temperature for 30 min easily and cleanly produced 4-(adamantan-1-yl)-quinoline-2-carboxylic *N*′-(2-aminoalkyl)hydrazides **19–31** as hydrobromide salts (Scheme 1).

The key intermediate 4-(adamantan-1-yl)-2-quinolincarboxylic acid (**5**) required for the synthesis of compounds described in Series 2 was synthesized in three steps from commercially available quinoline-2-carboxylic acid (**1**) as described earlier [10]. We next attempted reaction of **5** with side chain protected L-amino acid methyl esters. Conventional methods using DCC or 1,3-diispropylcarbodiimide (DIC) as coupling reagents in DCM or *N*,*N*-dimethylformamide (DMF) as solvent failed. In situ generated acid chloride mediated coupling method using **5**, thionyl chloride

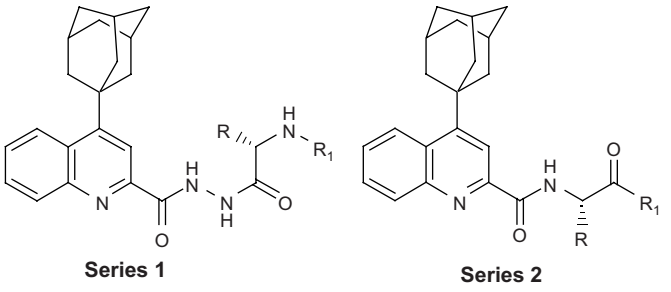


Fig. 2. General structure of newly synthesized ring-substituted quinolines.

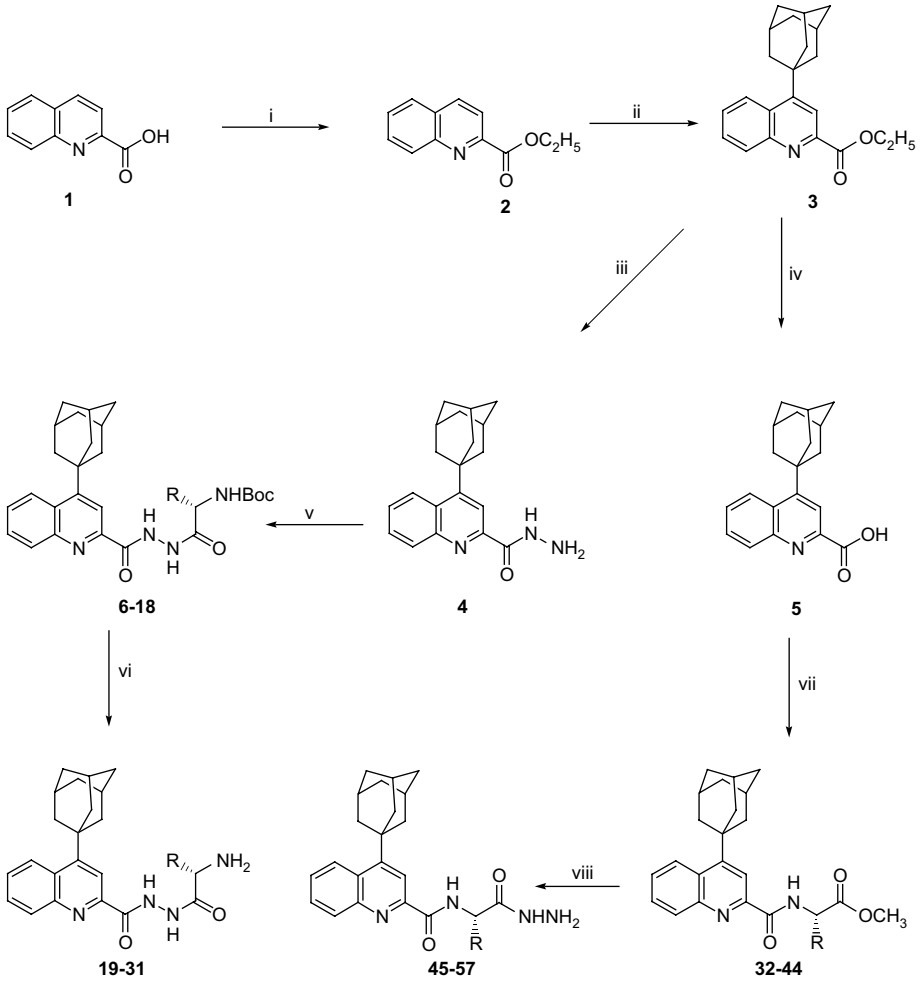
($SOCl_2$) and triethylamine (Et_3N) in dichloroethane (DCE) as solvent at 80 °C also failed. We reasoned that $SOCl_2$ mediated reaction failed presumably due to the instability of the in situ formed acid chloride at elevated temperature. Finally, a highly efficient one-pot protocol for the reaction of **5** with amino acids was devised. In this method, compound **5** upon treatment with $SOCl_2$ in the presence of pyridine and DCM as solvent for 1 min at ambient temperature produced 4-(1-adamantyl)-2-quinolinecarbonyl chloride in situ. This intermediate upon reaction with suitably side chain protected L-amino acid methyl esters in the presence of DMAP in DCM successfully provided methyl 2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]alkanoates **32**–**44** (Scheme 1). Compounds **32**–**38**, **40**–**41** and **44** upon reaction with hydrazine hydrate in the presence of abs. ethanol for 48 h at ambient temperature produced *N*2-[1-hydrazino-carbonylalkyl]-4-(adamantan-1-yl)-2-quinolinecarboxamides **45**–**51**, **53**–**54** and **57**. For, remaining compounds **39** and **42**–**43** (where the side chain functionality was protected, i.e. in cases of Orn, Lys with carbobenzyloxy and Tyr with benzyl) an additional deprotection step was performed. The deprotection at the side chain was achieved by reaction of **39** and **42**–**43** with 33% HBr in acetic acid at ambient temperature for 30 min to produce *N*2-[1-hydrazinocarbonylalkyl]-4-(adamantan-1-yl)-2-quinolinecarboxamides **52** and **55**–**56** as their hydrobromide salts (Scheme 1).

2.2. Biological activity

In vitro activities of the synthesized derivatives (Series 1–2) against *M. tuberculosis H37Rv* strain (ATCC 27294, susceptible both to rifampicin and isoniazid) were initially carried out using the Microplate Alamar Blue Assay (MABA) at a concentration of 6.25 μg/mL [16]. Compounds exhibiting fluorescence were then tested in the BACTEC 460 radiometric system [17] and the (%) inhibition are summarized in Tables 1 and 2. Compounds demonstrating ≥90% inhibition at 6.25 μg/mL in the primary screening were further evaluated at the lower concentration of 3.125 and 1.0 μg/mL to determine MIC value that is the minimum concentration exhibiting 99% inhibition. Isoniazid (99% inhibition, MIC = 1 μg/mL) was included, as a standard drug, for comparison.

From Series 1, analogs **7** [R = H, $R_1 = CO_2C(CH_3)_3$], **8** [$R = CH(CH_3)CH_2CH_3$, $R_1 = CO_2C(CH_3)_3$], **9** [$R = CH_2CH(CH_3)_2$, $R_1 = CO_2C(CH_3)_3$], **12** [$R = CH_2C_6H_5$, $R_1 = CO_2C(CH_3)_3$], **25** ($R = CH_2C_6H_5$, R_1 = H), **28** (R = 1*H*-imidazol-4-yl-methyl, R_1 = H), and **31** [$R = (CH_2)_3NHC(=NH)NH_2$, R_1 = H] exhibited inhibition that ranged between 81 and 92% of *M. tuberculosis H37Rv* at 6.25 μg/mL. While, analogs **14** [R = 1*H*-indol-2-yl-methyl, $R_1 = CO_2C(CH_3)_3$], **15** [R = 1*H*-imidazol-4-yl-methyl, $R_1 = CO_2C(CH_3)_3$], and **18** [$R = (CH_2)_3NHC(=NH)NH_2$, $R_1 = CO_2C(CH_3)_3$] were more potent and displayed 99% inhibition of *M. tuberculosis H37Rv* at the lower tested concentration of 3.125 μg/mL. These analogs upon evaluation at the lower dose of 1 μg/mL inhibited the growth of mycobacteria by <50%. All remaining analogs displayed inhibition that ranged between 36 and 78% against *M. tuberculosis H37Rv* at 6.25 μg/mL. A general observation of the structure activity relationship indicated that the presence of *t*-Boc [$NHCO_2C(CH_3)_3$] group produced compounds with higher potency when compared to compounds with free amino group at the side chain. For example, analog **14** containing a *t*-Boc group was active at 3.125 μg/mL (99% inhibition), while its counterpart analog **27** containing an amino group was comparatively less potent and displayed 56% inhibition at 6.25 μg/mL. Similarly, other *t*-Boc group containing analogs **7**, **8**, **9**, **12**, **14**, **15** and **18** were more potent than their amino group containing counterparts (Table 1).

From Series 2, analogs **34** [$R = CH(CH_3)CH_2CH_3$, $R_1 = OCH_3$], **35** [$R = CH_2CH(CH_3)_2$, $R_1 = OCH_3$], **36** [$R = (CH_2)_2SCH_3$, $R_1 = OCH_3$] and **54** (R = 1*H*-imidazolyl-4-ethyl, $R_1 = NHNH_2$) displayed inhibition that ranged between 83 and 99% of *M. tuberculosis H37Rv* at



Scheme 1. (i) Abs. EtOH, HCl gas, 4 °C, 2 h; (ii) 1-adamantanecarboxylic acid, $AgNO_3$, $(NH_4)_2S_2O_8$, CH_3CN, 10% H_2SO_4, 70–80 °C, 15 min; (iii) $NH_2NH_2 \cdot H_2O$, 95% EtOH, 80 °C, 8 h; (iv) 6 N HCl, 100 °C, 8 h; (v) DCC, DMAP, BocNH-R-CO_2H, DCM, 8 h, rt; (vi) 33% HBr–AcOH, 30 min, rt; (vii) $SOCl_2$, C_5H_5N, DCM, 1 min, rt; DMAP, H_2N–R–OMe, DCM, 20 min, rt; (viii) $NH_2NH_2 \cdot H_2O$, abs. EtOH, 48 h, rt; 33% HBr–AcOH, 30 min, rt.

6.25 μg/mL. At the same time, analogs **41** (R = 1*H*-imidazolyl-4-ethyl, $R_1 = OCH_3$), **44** [$R = (CH_2)_3NHC(=NH)NH_2$, $R_1 = OCH_3$] were comparatively more active, and produced 99% inhibition at the lower tested concentration of 3.125 μg/mL. The most potent compound of both series **57** [$R = (CH_2)_3NHC(=NH)NH_2$, $R_1 = NHNH_2$] displayed promising activity (99% inhibition) against drug-sensitive *M. tuberculosis H37Rv* strain at 1.00 μg/mL and was comparable to standard drug used in this study, isoniazid. The remaining analogs produced inhibition that ranged between 26% and 75% against *M. tuberculosis H37Rv* at 6.25 μg/mL. In this series, we observed that quinoline derivatives conjugated with basic heteroaromatic residue like L-histidine and highly cationic L-arginine residue were more potent compared to the derivatives conjugated to hydrophobic and other residues. However, quinoline derivatives (**42**–**43** and **55**–**56**) conjugated to cationic L-lysine and L-ornithine residues were exceptions to this observation (Table 2).

The most active derivative, *N*2-[(1*S*)-4-amino(imino)-methylamino-1-hydrazinocarbonylbutyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide (**57**), was also evaluated for anti-mycobacterial activity against isoniazid-resistant strain of *M. tuberculosis H37Rv* and exhibited promising activity (99% inhibition at 3.125 μg/mL), and (60% inhibition at 1.00 μg/mL). The most active compounds **14**, **15**, **18**, **41**, **44** and **57** were further evaluated in vitro for cytotoxicity (IC_{50}) in mammalian kidney fibroblast (Vero) cells. None of the compounds were found to exhibit cytotoxic effects up to highest test concentration of 50 μg/mL.

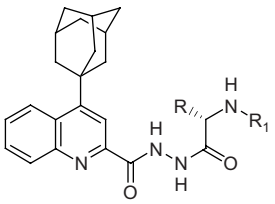
2.3. Computational study

Earlier we had reported the 3D-QSAR studies of analogous molecules based on Comparative Molecular Field analysis (CoMFA) [8–10]. On similar lines, we have employed Comparative Molecular Field Analysis (CoMFA) [18] to understand the structure activity relationship of amino acid derivatives of 4-(adamantan-1-yl)-2-substituted quinolines.

2.3.1. Data set

The molecules were grouped into three sets for the QSAR analysis. The first group (Set I) was composed of 4-(adamantan-1-yl)-2-quinolinecarbohydrazide derivatives (Table 1) while the second set (Set II) comprised 4-(adamantan-1-yl)-2-quinoline-carboxamide derivatives (Table 2). The 52 molecules listed in Tables 1 and 2 were collected into the third set (Set III). The three individual sets were further divided into test and training sets based on chemical as well as biological diversity. For dividing a given set into training and test sets, the chemical characteristics were the interaction energies calculated between a probe and the molecules aligned in a 3D grid and the biological activity was the second property. These two attributes were used to separate the molecules

Table 1
In vitro antimycobacterial activity and pIC_{50}s of {1-[*N*′-(4-adamantan-1-yl-quinoline-2-carbonyl)hydrazinocarbonyl]alkyl carbamic acid *tert*-butyl esters **6–18** and 4-adamantan-1-yl-quinoline-2-carboxylic acid *N*′-(2-aminoalkyl)hydrazides **19–31** (Series 1, Set I) against drug-sensitive *M. tuberculosis H37Rv* strain.



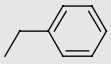
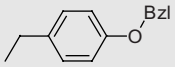
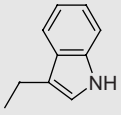
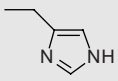
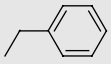
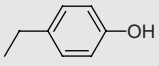
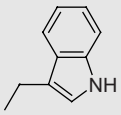
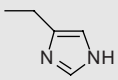
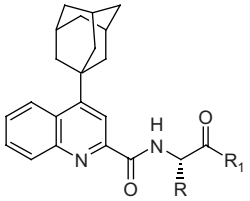
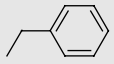
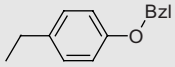
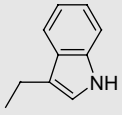
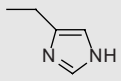
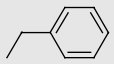
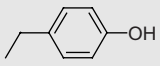
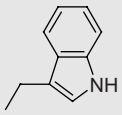
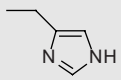
Compound No.	R	R_1	Test Conc. (μg/mL)	(%) inhibition	pIC_{50}
6	H	$CO_2C(CH_3)_3$	6.25	60	5.06
7	CH_3	$CO_2C(CH_3)_3$	6.25	88	5.76
8	$CH(CH_3)CH_2CH_3$	$CO_2C(CH_3)_3$	6.25	90	5.89
9	$CH_2CH(CH_3)_2$	$CO_2C(CH_3)_3$	6.25	90	5.89
10	$(CH_2)_2SCH_3$	$CO_2C(CH_3)_3$	6.25	56	5.05
11	$(CH_2)_2CONH_2$	$CO_2C(CH_3)_3$	6.25	51	4.96
12		$CO_2C(CH_3)_3$	6.25	85	5.71
13		$CO_2C(CH_3)_3$	6.25	42	4.89
14		$CO_2C(CH_3)_3$	3.125	99	7.29
15		$CO_2C(CH_3)_3$	3.125	99	7.25
16	$(CH_2)_3NHZ$	$CO_2C(CH_3)_3$	6.25	75	5.51
17	$(CH_2)_4NHZ$	$CO_2C(CH_3)_3$	6.25	73	5.47
18	$(CH_2)_3NHC(=NH)NH_2$	$CO_2C(CH_3)_3$	3.125	99	7.26
19	H	H	6.25	35	4.52
20	CH_3	H	6.25	41	4.64
21	$CH(CH_3)CH_2CH_3$	H	6.25	75	5.32
22	$CH_2CH(CH_3)_2$	H	6.25	75	5.32
23	$(CH_2)_2SCH_3$	H	6.25	59	5.02
24	$(CH_2)_2CONH_2$	H	6.25	45	4.77
25		H	6.25	81	5.50
26		H	6.25	48	4.86
27		H	6.25	56	5.01
28		H	6.25	88	5.73
29	$(CH_2)_3NH_2$	H	6.25	26	4.39
30	$(CH_2)_4NH_2$	H	6.25	66	5.14
31	$(CH_2)_3NHC(=NH)NH_2$	H	6.25	92	5.94

Table 2
In vitro antimycobacterial activity and pIC_{50}s of methyl 2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]alkanoates **32–44** and *N*2-[1-hydrazinocarbonylalkyl]-4-(adamantan-1-yl)-2-quinolinecarboxamides **45–57** (Series 2, Set II) against drug-sensitive *M. tuberculosis H37Rv* strain.



Compound No.	R	R_1	Test conc. (μg/mL)	(%) Inhibition	pIC_{50}
32	H	OCH_3	6.25	52	4.81
33	CH_3	OCH_3	6.25	73	5.23
34	$CH(CH_3)CH_2CH_3$	OCH_3	6.25	90	5.79
35	$CH_2CH(CH_3)_2$	OCH_3	6.25	83	5.53
36	$(CH_2)_2SCH_3$	OCH_3	6.25	86	5.64
37	$(CH_2)_2CONH_2$	OCH_3	6.25	55	4.94
38		OCH_3	6.25	60	5.05
39		OCH_3	6.25	58	5.10
40		OCH_3	6.25	75	5.38
41		OCH_3	3.125	99	7.16
42	$(CH_2)_3NHZ$	OCH_3	6.25	66	5.23
43	$(CH_2)_4NHZ$	OCH_3	6.25	78	5.50
44	$(CH_2)_3NHC(=NH)NH_2$	OCH_3	3.125	99	6.87
45	H	$NHNH_2$	6.25	70	5.15
46	CH_3	$NHNH_2$	6.25	82	5.45
47	$CH(CH_3)CH_2CH_3$	$NHNH_2$	6.25	70	5.21
48	$CH_2CH(CH_3)_2$	$NHNH_2$	6.25	83	5.53
49	$(CH_2)_2SCH_3$	$NHNH_2$	6.25	68	5.18
50	$(CH_2)_2CONH_2$	$NHNH_2$	6.25	50	4.85
51		$NHNH_2$	6.25	50	4.87
52		$NHNH_2$	6.25	44	4.78
53		$NHNH_2$	6.25	60	5.08
54		$NHNH_2$	6.25	99	6.86
55	$(CH_2)_3NH_2$	$NHNH_2$	6.25	48	4.91
56	$(CH_2)_4NH_2$	$NHNH_2$	6.25	36	4.71
57	$(CH_2)_3NHC(=NH)NH_2$	$NHNH_2$	1.00	99	7.67

into training and test sets based on the Tanimoto similarity coefficient [19].

2.3.2. Biological data

For the QSAR study, the percent inhibition values were transformed, as follows [20].

$$\text{Activity} = -\log c + \log \text{it}$$

where c is molar concentration = concentration (μg/mL) × 0.001/(molecular weight) and $\log \text{it} = \log[\%\ \text{inhibition}/(100 - \%\ \text{inhibition})]$.

2.3.3. Molecular modeling

The CoMFA studies were carried out with the *Sybyl* suite of programs [21] installed on a Pentium 2.8 GHz PC running under the Linux OS (RedHat Enterprise WS 4.0).

The 4-(adamantan-1-yl)quinoline unit is a rigid moiety. At the C_2-position of the quinoline ring, two primary structures –CONHNHCO–amino acid and –CONH–aminoacid, are present. The geometries of the quinolone–CONHNHCO/–CONH segments were based on the crystal structure-sg6059 shown in Fig. 3 [22].

The structures of the molecules were built with the *Builder* module in *Insight II* [23] and energy minimized with the *Discover* module using the steepest descents (SD) and conjugate gradient (CG) methods and the CFF91 [24] force field. The geometries of the R and R1 groups (refer Tables 1 and 2) were optimized by subjecting the molecules to a molecular dynamics (MD) simulation while constraining the 4-(adamantan-1-yl)quinoline moiety and –CONHNHCO or –CONH units to the crystallographic conformation. The MD simulation was carried out through a heating stage to 700 K for 1 ps followed by slowly annealing to 300 K in steps of 100 K for 1 ps at each new temperature. In the simulation, the MD step size was 1 fs and snapshots from the trajectory were captured every 5 fs. The structure in the MD trajectory with the lowest energy (the global minima) was sent through a final round of minimization involving both SD and CG minimizations. The minimization was terminated at a maximum value of 0.01 kcal/mol/Å for the gradient. The molecules were then imported into the *Sybyl* framework and again subjected to constrained minimization where only the amino acid group was allowed to relax. This minimization was done using the Tripos force field and the Gasteiger Hückel charges, until a maximum gradient 0.05 kcal/mol/Å was achieved. These conformations of the molecules were utilized for CoMFA studies.

2.3.4. Alignment

For Set I, molecule **14** (Table 1) was chosen as the template. For both Sets II and III, the template was molecule **57** (Table 2) and all other molecules aligned using the ATOM-FIT alignment method in *Sybyl* (Fig. 4a). The molecules were aligned with reference to the quinoline ring. A second technique of alignment was also carried out using the FIELD-FIT method, wherein the steric and electrostatic fields around the molecules were superimposed over the same fields of the template molecule (Fig. 4b).

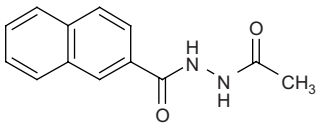


Fig. 3. Structure of sg6059, whose X-day data was used for building the conformation of the molecules.

2.3.5. CoMFA interaction energy calculation

The steric and electrostatic fields in CoMFA were calculated at each lattice intersection of a regularly spaced grid of 2.0 Å in all three dimensions within the defined region. A methyl cation with charge +1.0 was used as the probe. The van der Waals potential and Columbic energy between the probe and the molecules were calculated. A distance-dependent dielectric constant of 1.0r was used in the calculation of the electrostatics. The steric field was truncated at points where the value exceeded ±30.0 kcal/mol, and the electrostatic fields were ignored at those lattice points where the steric interactions were high.

2.3.6. 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 predictive correlation coefficient (r^2_{pred}) based on the test set molecules, is defined as

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

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

2.3.7. Discussion

CoMFA (Comparative Molecular Field Analysis) studies were initially started with a training set of 20 molecules for both the Sets I and II, which were aligned by the atom-fit and field-fit methods. The remaining molecules composed the test set. Some of the molecules (**41**, **43**, and **50**) were found to be outliers in the QSAR study implying that the global minimum energy structures of such molecules is an inappropriate conformation for the QSAR study. For such molecules an alternative conformation (a local minima) was introduced into the dataset and QSAR analysis repeated.

For Set I the best CoMFA model (Model 2, Table 3) was that derived from field-fit alignment, with a correlation coefficient (r^2) of 0.991 and cross-validated $r^2(q^2)$ of 0.434. For Set II, a model with a correlation coefficient of 0.985 and cross-validated $r^2(q^2)$ of 0.450 was obtained again with field-fit alignment of molecules (Model 4, Table 3). The CoMFA model (Model 5, Table 3) generated by atom-fit alignment is a robust model for Set III, as revealed by the statistical parameters (Table 3). Fig. 5 shows plots of predicted versus experimental activity for molecules in the training set based on these three best models.

The CoMFA models were tested for their predictivity on the test sets. The r^2_{pred} of 0.416 for Set I, using Model 2 and 0.45 for Set II based on Model 4 establishes the superiority of these models over their respective atom-fit models (Models 1 and 3, Table 3). Likewise Model 5 obtained by atom-fit alignment was better for Set III with an r^2_{pred} of 0.255. Though the r^2_{pred} is not high, the other statistical parameters repose a high confidence in Model 5. Model 5 was established for the two classes of molecules jointly considered; it represents a unified picture for the exposition of activity of molecules of both types. The steric and electrostatic contours associated with the molecules in Sets I and II are described in the following paragraphs. For the molecules in Set I (e.g. molecule **14**) electropositive contours (blue color) are seen near the C_α and the C_β positions of the amino acid side chain. Electropositive contours are also seen around the acyl hydrazide (–CONHNHCO–) functionality (Fig. 6a). Similarly, for Set II molecules (e.g. molecule **57**) an improvement in the activity will occur if an electronegative substitution is made in the amino acid side chain, especially at the C_β and C_γ positions (Fig. 6b). If the amino acid side chains have an aromatic ring, it π-stacks on to the quinoline ring and according to

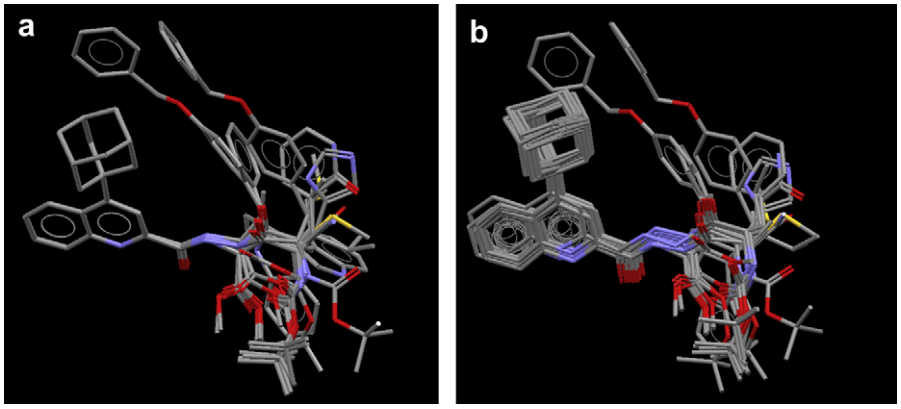


Fig. 4. A view of the molecules of Set III aligned using (a) Atom-Fit, and (b) Field-Fit.

this model such aromatic side chains need to contain electropositive groups.

With regards to the steric contours, for molecules in Set I, the replacement of the hydrogens (*) at the C_α and the N atom bearing the *t*-Boc group (i.e. C_α**H***; N**H***-*t*-Boc) with bulky groups will disfavored activity; the *t*-Boc group seems to satisfy the need for a bulky group in these molecules for good activity (as discussed earlier). No substitution is recommended at the acyl hydrazide functionality (Fig. 7a). The steric contours for Set II show bulky groups at the amino acid side chain are favored but the NH group of the amino acid needs small protecting groups. Similarly bulky groups are also disfavored in the vicinity of the parent structure 4-(adamantan-1-yl)-2-quinolinecarboxamide (Fig. 7b).

3. Conclusions

In the present study, our efforts were directed primarily towards structural optimization of our earlier reported lead compounds, 4-(adamantan-1-yl)-2-quinolinecarbohydrazide and 4-(adamantan-1-yl)-2-quinolinecarboxamide. Analogs **14**, **15**, **18**, **41** and **44** produced inhibitory activity of 99% at 3.125 μg/mL. The most potent analog **57** displayed 99% inhibition at 1.00 μg/mL against drug-sensitive strain, while it exhibited 99% inhibition at 3.125 μg/mL against drug-resistant strain. None of the analog displayed cytotoxicity when tested in mammalian Vero cell line. In general, quinolines conjugated to basic and heteroaromatic residues were more active compared to their hydrophobic and other counterparts. The various 3D-QSAR models built using CoMFA helped to correlate the fine relationship between substitutions on the amino acid side chain of the 4-adamantan-2-substituted quinolines and their anti-tuberculosis activity. The 3D-QSAR study also suggested some novel molecules which may be more potent with aromatic amino acid side chains bearing an electropositive group or aliphatic side chains with electronegative side substitutions. Any increase in the molecular steric bulk appears to affect for the potency. In conclusion, amino acid derivatives of 4-(adamantan-1-yl)-2-substituted quinolines show promising outcomes as anti-tuberculosis agents.

4. Experimental

Melting points were recorded on a Mettler DSC 851 instrument or a capillary melting point apparatus and are uncorrected. ^{1}H spectra were recorded on a 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 a HRMS (Finnigan Mat LCQ) spectrometer (ESI/APCI) mode or MALDI (Bruker Daltonics, Ultraflux MALDI-*tof*/*tof*). Elemental analyses were carried out on an Elementar Vario EL spectrometer. Chromatographic purifications were carried out with silica gel 60 (230–400 mesh) and TLC (silica gel) was done 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 were acquired from commercial sources, were of analytical grade and used without further purification unless otherwise stated.

Table 3
A summary of the statistics of the 3D-QSAR models.

Parameters	Set I		Set II		Set III	
	AF Model 1	FF Model 2	AF Model 3	FF Model 4	AF Model 5	FF Model 6
n	26	26	26	26	52	52
N	4	4	6	6	7	7
r^2	0.987	0.991	0.988	0.985	0.996	0.996
r^2_{cv}	0.407	0.434	0.246	0.450	0.429	0.336
SEE	0.111	0.093	0.029	0.028	0.058	0.063
F-value	284	408	2411	2541	1114	956
r^2_{pred}	0.366	0.416	0.345	0.45	0.255	0.177
r^2_{bs}	0.991 ± 0.007	0.994 ± 0.005	0.995 ± 0.001	0.994 ± 0.001	0.997 ± 0.002	0.997 ± 0.002
Contributions (%)						
Steric	56	55	41	40	46	43
Electrostatic	44	45	59	60	54	57

AF, atom-fit alignment; FF, field-fit alignment; *n*, number of molecules; *N*, optimum number of components; r^2_{cv}, cross-validated correlation coefficient; r^2, conventional (non-cross-validated) correlation coefficient; SEE, standard error of estimate; r^2_{pred}, predictive (test molecules) correlation coefficient; r^2_{bs}, correlation coefficient after 100 runs of bootstrapping analysis; SD, standard deviation from 100 bootstrapping runs.

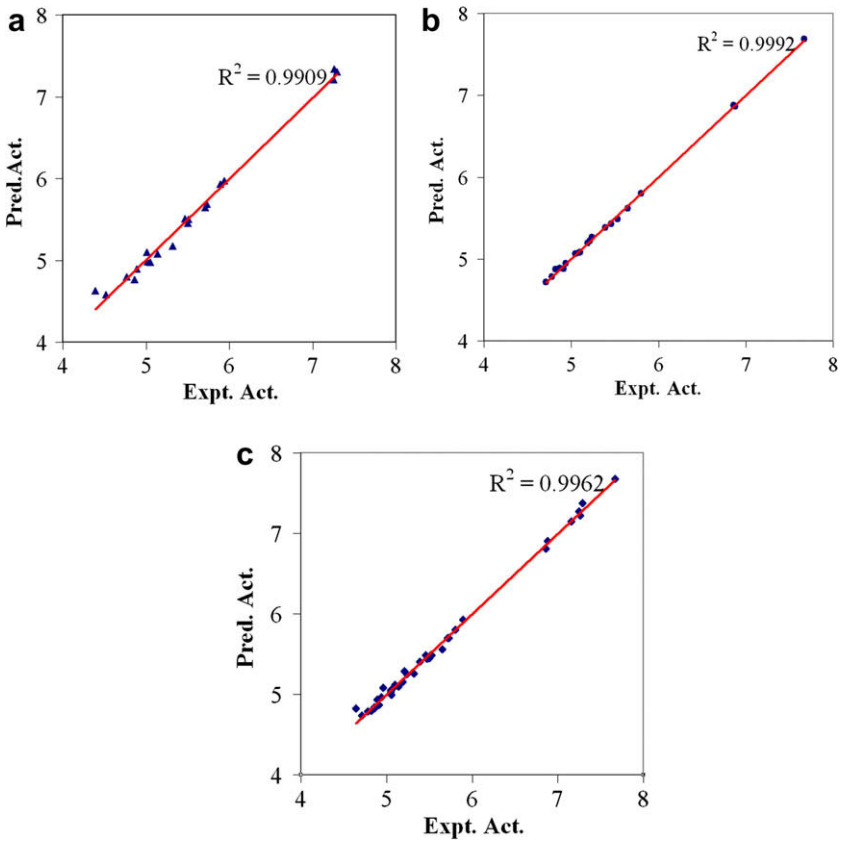


Fig. 5. Predicted versus experimental activity for molecules in the training set based on (a) Model 2, (b) Model 4, and (c) Model 5.

4.1. General procedure for the synthesis of {1-[N′-(4-adamantan-1-yl-quinoline-2-carbonyl)hydrazinocarbonyl]alkyl carbamic acid tert*-butyl esters (**6**–**18**)*

To a solution of 4-(adamantan-1-yl)quinoline-2-carbohydrazide (**4**, 0.1 g, 0.31 mmol) in DCM (15 mL), *N*-α-Boc protected L-amino acid (0.08 g, 0.35 mmol), DCC (0.07 g, 0.35 mmol) and DMAP (0.02 mg, 0.16 mmol) were added. The reaction mixture was stirred for 8 h at ambient temperature. The solvent was removed under reduced pressure to afford a semi-solid residue. This residue was dissolved in ethyl acetate (5 mL) and kept in the refrigerator for 8 h. The precipitated dicyclohexylurea was removed by filtration, and solvent evaporated under reduced pressure to afford the crude product, which upon column chromatographic purification over silica gel (230–400 mesh) using ethyl acetate/hexanes (8:92) gave **6**–**18**.

4.1.1. {2-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazino]-2-oxoethyl}carbamic acid tert*-butyl ester (**6**)*

Yield: 71%; mp: 155–156 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 8.63 (d, 1H, $J = 8.6$ Hz), 8.14 (m, 2H), 7.60 (m, 1H), 7.51 (m, 1H), 3.85 (m, 2H), 1.89 (m, 15H), 1.43 (s, 9H); MALDIMS: *m*/*z* 479 (M + 1); Anal. Calcd for $C_{27}H_{34}N_4O_4$ (478.6): C, 67.76; H, 7.16; N, 11.71. Found: C, 68.04; H, 7.01; N, 11.89.

4.1.2. (S)-{2-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazino]-1-methyl-2-oxoethyl}carbamic acid tert*-butyl ester (**7**)*

Yield: 65%; mp: 173–175 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 8.61 (d, 1H, $J = 8.6$ Hz), 8.10 (m, 2H), 7.64 (m, 1H), 7.54 (m, 1H), 4.56 (m, 1H), 1.88 (m, 15H), 1.51 (d, 3H, $J = 6.7$ Hz), 1.44 (s, 9H); MALDIMS: *m*/*z* 493 (M + 1); Anal. Calcd for $C_{28}H_{36}N_4O_4$ (492.6): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.29; H, 7.39; N, 11.42.

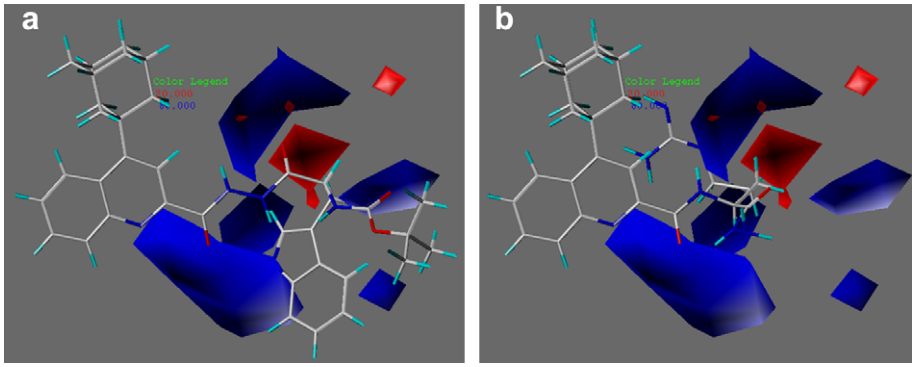


Fig. 6. CoMFA contours based on Model 5 for electrostatic fields drawn around molecules (a) **14** and (b) **57**. The red contour shows regions where electronegative substituents are favored, while the blue contour is associated with positions where electropositive substituents improve activity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

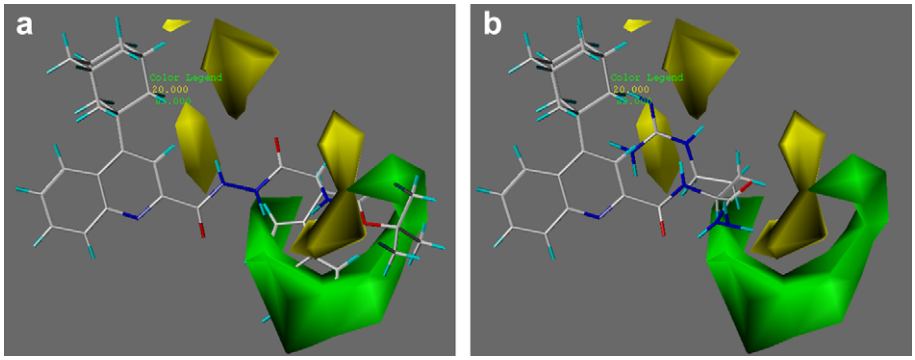


Fig. 7. CoMFA contours based on Model 5 for steric fields drawn around molecules (a) **14** and (b) **57**. The green colored contour favors steric bulk while sites where steric bulk is disfavored are shown in yellow. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4.1.3. (S)-{1-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazinocarbonyl]-2-methylbutyl}carbamic acid tert-*butyl ester (**8**)*

Yield: 62%; mp: 134–136 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 8.61 (d, 1H, $J = 8.8$ Hz), 8.12 (m, 2H), 7.60 (m, 1H), 7.54 (m, 1H), 4.60 (m, 1H), 2.62 (m, 1H), 1.88 (m, 15H), 1.42 (s, 9H), 1.32 (m, 2H), 0.99 (m, 6H); MALDIMS: *m*/*z* 535 (M + 1); Anal. Calcd for $C_{31}H_{42}N_4O_4S$ (534.7): C, 69.64; H, 7.92; N, 10.48. Found: C, 69.79; H, 8.12; N, 10.31.

4.1.4. (S)-{1-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazinocarbonyl]-3-methylbutyl}carbamic acid tert-*butyl ester (**9**)*

Yield: 66%; mp: 121–123 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 8.58 (d, 1H, $J = 8.6$ Hz), 8.11 (m, 2H), 7.62 (m, 1H), 7.50 (m, 1H), 4.56 (m, 1H), 2.01 (m, 1H), 1.94 (m, 2H), 1.88 (m, 15H), 1.42 (s, 9H), 1.08 (m, 6H); MALDIMS: *m*/*z* 535 (M + 1); Anal. Calcd for $C_{31}H_{42}N_4O_4S$ (534.7): C, 69.64; H, 7.92; N, 10.48. Found: C, 69.43; H, 7.66; N, 10.31.

4.1.5. (S)-{1-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazinocarbonyl]-3-methylsulfanylpropyl}carbamic acid tert-*butyl ester (**10**)*

Yield: 60%; mp: 175–177 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 8.63 (d, 1H, $J = 8.7$ Hz), 8.14 (m, 2H), 7.62 (m, 1H), 7.51 (m, 1H), 4.51 (m, 1H), 2.62 (m, 2H), 2.21 (m, 2H), 2.15 (s, 3H), 1.88 (m, 15H), 1.42 (s, 9H); MALDIMS: *m*/*z* 553 (M + 1); Anal. Calcd for $C_{30}H_{40}N_4O_4S$ (552.7): C, 65.19; H, 7.29; N, 10.14. Found: C, 65.23; H, 7.33; N, 10.45.

4.1.6. 4.1.6. (S)-{1-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazinocarbonyl]-3-carbamoylpropyl}carbamic acid tert-*butyl ester (**11**)*

Yield: 55%; mp: 173–175 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 9.88 (br s, 1H) 8.67 (d, 1H, $J = 8.7$ Hz), 8.15 (m, 2H), 7.70 (m, 1H), 7.59 (m, 1H), 4.56 (m, 1H), 1.88 (m, 15H), 1.67 (m, 2H), 1.47 (s, 9H), 1.16 (m, 2H); MALDIMS: *m*/*z* 550 (M + 1); Anal. Calcd for $C_{30}H_{39}N_5O_5$ (549.7): C, 65.55; H, 7.15; N, 12.74. Found: C, 65.59; H, 7.12; N, 12.72.

4.1.7. (S)-{2-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazino]-1-benzyl-2-oxoethyl}carbamic acid tert-*butyl ester (**12**)*

Yield: 75%; mp: 167–169 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 10.27 (br s, 1H), 9.03 (br s, 1H), 8.63 (d, 1H, $J = 8.2$ Hz), 8.13 (m, 2H), 7.67 (m, 1H), 7.55 (m, 1H), 7.22 (m, 5H), 4.56 (m, 1H), 3.18 (d, 2H, $J = 6.4$ Hz), 1.88 (m, 15H), 1.38 (s, 9H); MALDIMS: *m*/*z* 569 (M + 1); Anal. Calcd for $C_{34}H_{40}N_4O_4$ (568.7): C, 71.81; H, 7.09; N, 9.85. Found: C, 71.84; H, 7.05; N, 9.80.

4.1.8. (S)-[2-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazino]-1-(4-benzyloxy-benzyl)-2-oxoethyl]carbamic acid tert-*butyl ester (**13**)*

Yield: 68%; mp: 173–175 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 10.29 (br s, 1H), 8.66 (d, 1H, $J = 8.7$ Hz), 8.16 (m, 2H), 7.70 (m, 1H), 7.58 (m, 1H), 7.36 (m, 5H), 7.23 (d, 2H, $J = 8.5$ Hz), 6.92 (d, 2H, $J = 8.5$ Hz), 5.02 (s, 2H), 4.55 (m, 1H), 3.15 (d, 2H, $J = 6.5$ Hz), 1.88 (m, 15H), 1.42 (s, 9H); MALDIMS: *m*/*z* 675(M + 1); Anal. Calcd for $C_{41}H_{46}N_4O_5$ (674.8): C, 72.97; H, 6.87; N, 8.30. Found: C, 72.95; H, 6.82; N, 8.35.

4.1.9. (S)-[2-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazino]-1-(1H-indol-2-yl-methyl)-2-oxoethyl]carbamic acid tert-*butyl ester (**14**)*

Yield: 52%; mp: 176–178 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 10.19 (br s, 1H), 8.65 (d, 1H, $J = 8.7$ Hz), 8.22 (br s, 1H), 8.14 (m, 2H), 7.69 (m, 2H), 7.52 (m, 1H), 7.50 (m, 3H), 7.37 (d, 1H, $J = 7.7$ Hz), 4.20 (m, 1H), 2.20 (s, 2H), 1.88 (m, 15H), 1.43 (s, 9H); MALDIMS: *m*/*z* 608 (M + 1); Anal. Calcd for $C_{36}H_{41}N_5O_4$ (607.7): C, 71.15; H, 6.80; N, 11.52. Found: C, 71.18; H, 6.85; N, 11.55.

4.1.10. (S)-[2-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazino]-1-(1H-imidazol-4-yl-methyl)-2-oxoethyl]carbamic acid tert-*butyl ester (**15**)*

Yield: 40%; mp: 182–184 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 8.67 (d, 1H, $J = 8.7$ Hz), 8.20 (s, 1H), 8.14 (d, 1H, $J = 8.1$ Hz), 7.70 (m, 1H), 7.58 (m, 2H), 6.90 (s, 1H), 5.62 (br s, 1H), 4.57 (m, 1H), 3.10 (m, 2H), 1.88 (m, 15H), 1.47 (s, 9H); MALDIMS: *m*/*z* 559 (M + 1); Anal. Calcd for $C_{31}H_{38}N_6O_4$ (558.6): C, 66.65; H, 6.86; N, 15.04. Found: C, 66.69; H, 6.89; N, 15.09.

*4.1.11. (S)-{5-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazino]-4-*tert-*butoxy-carbonylamino-5-oxopentyl}carbamic acid* tert-*butyl ester (**16**)*

Yield: 75%; mp: 175–177 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 10.11 (br s, 1H), 9.25 (br s, 1H), 8.65 (d, 1H, $J = 8.6$ Hz), 8.14 (m, 2H), 7.69 (m, 1H), 7.57 (m, 1H), 4.51 (m, 1H), 3.14 (m, 2H), 1.88 (m, 15H), 1.44 (s, 18H), 1.28 (m, 4H); MALDIMS: *m*/*z* 636 (M + 1); Anal. Calcd for $C_{35}H_{49}N_5O_6$ (635.7): C, 66.12; H, 7.77; N, 11.02. Found: C, 66.18; H, 7.79; N, 11.05.

*4.1.12. (S)-{6-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazino]-5-*tert-*butoxy-carbonylamino-6-oxohexyl}carbamic acid benzyl ester (**17**)*

Yield: 77%; mp: 178–180 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 9.48 (br s, 1H), 8.65 (d, 1H, $J = 8.7$ Hz), 8.19 (m, 2H), 7.69 (m, 1H), 7.58 (m, 1H), 7.31 (m, 5H), 5.08 (s, 2H), 4.35 (m, 1H), 3.19 (m, 2H), 1.88 (m, 15H), 1.52 (m, 6H), 1.42 (s, 9H); MALDIMS: *m*/*z* 684 (M + 1); Anal. Calcd for $C_{39}H_{49}N_5O_6$ (683.8): C, 68.50; H, 7.22; N, 10.24. Found: C, 68.54; H, 7.25; N, 10.29.

4.1.13. (S)-{1-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazinocarbonyl]-4-(N,N′-bis-benzyloxycarbonylguanidinobutyl)}carbamic acid tert*-butyl ester (**18**)*

Yield: 37%; mp: 180–182 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 9.60 (br s, 1H), 9.45 (br s, 1H), 9.34 (br s, 1H), 9.13 (br s, 1H), 8.66 (d, 1H, J = 8.7 Hz), 8.11 (m, 2H), 7.70 (m, 1H), 7.58 (m, 1H), 7.25 (m, 10H), 5.25 (s, 2H), 5.23 (s, 2H), 4.45 (m, 1H), 2.04 (m, 2H), 1.88 (m, 15H), 1.72 (m, 2H), 1.45 (s, 9H), 1.33 (m, 2H); MALDIMS: *m*/*z* 846 (M + 1); Anal. Calcd for $C_{47}H_{55}N_7O_8$ (845.9): C, 66.73; H, 6.55; N, 11.59. Found: C, 66.79; H, 6.49; N, 11.55.

4.2. General method for the synthesis of 4-adamantan-1-yl-quinoline-2-carboxylic acid N′*-(2-aminoalkyl)hydrazides (**19**–**31**)*

A solution of 33% HBr in glacial acetic acid (3 mL) was added to **6**–**18** (0.1 mmol), and the reaction mixture was stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure to afford **19**–**31** as hydrobromide salts.

4.2.1. 4-Adamantan-1-yl-quinoline-2-carboxylic acid N′*-(2-aminoacetyl)hydrazide·2HBr (**19**)*

Yield: 95%; mp: 160–162 °C (dec.); ^{1}H NMR (CD_3OD): δ 8.84 (d, 1H, J = 8.7 Hz), 8.40 (d, 1H, J = 8.4 Hz), 8.27 (s, 1H), 7.91 (m, 1H), 7.85 (m, 1H), 4.03 (m, 2H), 1.88 (m, 15H); MALDIMS: *m*/*z* 379 (M + 1); Anal. Calcd for $C_{22}H_{28}Br_2N_4O_2$ (540.3): C, 48.91; H, 5.22; N, 10.37. Found: C, 49.08; H, 5.04; N, 10.55.

4.2.2. (S)-4-Adamantan-1-yl-quinoline-2-carboxylic acid N′*-(2-aminopropionyl)hydrazide·2HBr (**20**)*

Yield: 91%; mp: 175–177 °C (dec.); ^{1}H NMR (CD_3OD): δ 8.89 (d, 1H, J = 8.6 Hz), 8.37 (d, 1H, J = 8.4 Hz), 8.25 (s, 1H), 7.93 (m, 1H), 7.86 (m, 1H), 4.14 (m, 1H), 1.88 (m, 15H), 1.57 (d, 3H, J = 6.8 Hz); MALDIMS: *m*/*z* 393 (M + 1); Anal. Calcd for $C_{23}H_{30}Br_2N_4O_2$ (554.3): C, 49.84; H, 5.46; N, 10.11. Found: C, 49.87; H, 5.49; N, 10.15.

4.2.3. (S)-4-Adamantan-1-yl-quinoline-2-carboxylic acid N′*-(2-amino-3-methyl-pentanoyl)hydrazide·2HBr (**21**)*

Yield: 90%; mp: 170–172 °C (dec.); ^{1}H NMR (CD_3OD): δ 8.92 (d, 1H, J = 8.4 Hz), 8.40 (d, 1H, J = 8.4 Hz), 8.29 (s, 1H), 7.97 (m, 1H), 7.83 (m, 1H), 4.10 (m, 1H), 2.88 (m, 1H), 1.88 (m, 15H), 1.40 (m, 2H), 1.02 (m, 6H); MALDIMS: *m*/*z* 435 (M + 1); Anal. Calcd for $C_{26}H_{36}Br_2N_4O_2$ (596.4): C, 52.36; H, 6.08; N, 9.39. Found: C, 52.12; H, 6.36; N, 9.21.

4.2.4. (S)-4-Adamantan-1-yl-quinoline-2-carboxylic acid N′*-(2-amino-4-methyl-pentanoyl)hydrazide·2HBr (**22**)*

Yield: 90%; mp: 171–173 °C (dec.); ^{1}H NMR (CD_3OD): δ 8.91 (d, 1H, J = 8.4 Hz), 8.40 (d, 1H, J = 8.4 Hz), 8.30 (s, 1H), 7.95 (m, 1H), 7.84 (m, 1H), 4.11 (m, 1H), 2.10 (m, 1H), 1.99 (m, 2H), 1.88 (m, 15H), 1.10 (d, 6H, J = 6.8 Hz); MALDIMS: *m*/*z* 435 (M + 1); Anal. Calcd for $C_{26}H_{36}Br_2N_4O_2$ (596.4): C, 52.36; H, 6.08; N, 9.39. Found: C, 52.66; H, 6.21; N, 9.54.

4.2.5. (S)-4-Adamantan-1-yl-quinoline-2-carboxylic acid N′*-(2-amino-4-methylsulfanyl-butyryl)hydrazide·2HBr (**23**)*

Yield: 93%; mp: 173–175 °C (dec.); ^{1}H NMR (CD_3OD): δ 8.76 (d, 1H, J = 8.3 Hz), 8.33 (d, 1H, J = 8.3 Hz), 8.14 (s, 1H), 7.77 (m, 1H), 7.70 (m, 1H), 4.20 (m, 1H), 2.60 (m, 2H), 2.25 (m, 2H), 2.15 (s, 3H), 1.88 (m, 15H); MALDIMS: *m*/*z* 453 (M + 1); Anal. Calcd for $C_{25}H_{34}Br_2N_4O_2S$ (614.4): C, 48.87; H, 5.58; N, 9.12. Found: C, 48.93; H, 5.61; N, 9.14.

*4.2.6. (S)-5-[N′-(4-Adamantan-1-yl-quinoline-2-carbonyl)hydrazino]-4-amino-5-oxopentanoic acid amide·2HBr (**24**)*

Yield: 95%; mp: 142–144 °C (dec.); ^{1}H NMR (CD_3OD): δ 8.80 (d, 1H, J = 8.4 Hz), 8.39 (d, 1H, J = 8.4 Hz), 8.20 (s, 1H), 7.82 (m, 1H), 7.74 (m, 1H), 4.05 (m, 1H), 2.37 (m, 4H), 1.90 (m, 15H); MALDIMS: *m*/*z* 450 (M + 1); Anal. Calcd for $C_{25}H_{33}Br_2N_5O_3$ (611.4): C, 49.11; H, 5.44; N, 11.46. Found: C, 49.32; H, 5.25; N, 11.37.

4.2.7. (S)-4-Adamantan-1-yl-quinoline-2-carboxylic acid N′*-(2-amino-3-phenylpropionyl)hydrazide·2HBr (**25**)*

Yield: 90%; mp: 172–174 °C (dec.); ^{1}H NMR (CD_3OD): δ 8.78 (d, 1H, J = 8.7 Hz), 8.25 (d, 1H, J = 8.2 Hz), 8.14 (s, 1H), 7.81 (m, 1H), 7.71 (m, 1H), 7.44 (m, 5H), 4.32 (m, 1H), 3.18 (d, 2H, J = 6.4 Hz), 1.88 (m, 15H); MALDIMS: *m*/*z* 469 (M + 1); Anal. Calcd for $C_{29}H_{34}Br_2N_4O_2$ (630.4): C, 55.25; H, 5.44; N, 8.89. Found: C, 55.21; H, 5.44; N, 8.93.

4.2.8. (S)-4-Adamantan-1-yl-quinoline-2-carboxylic acid N′*-[2-amino-3-(4-hydroxyphenyl)propionyl]hydrazide·2HBr (**26**)*

Yield: 90%; mp: 173–175 °C (dec.); ^{1}H NMR (CD_3OD): δ 8.89 (d, 1H, J = 8.8 Hz), 8.33 (d, 1H, J = 8.5 Hz), 8.24 (s, 1H), 7.90 (m, 1H), 7.79 (m, 1H), 7.22 (d, 2H, J = 8.1 Hz), 6.82 (d, 2H, J = 8.2 Hz), 4.20 (m, 1H), 1.96 (d, 2H, J = 6.5 Hz), 1.88 (m, 15H); MALDIMS: *m*/*z* 575 (M + 1); Anal. Calcd for $C_{29}H_{34}Br_2N_4O_3$ (646.4): C, 53.88; H, 5.30; N, 8.67. Found: C, 53.84; H, 5.32; N, 8.69.

4.2.9. (S)-4-Adamantan-1-yl-quinoline-2-carboxylic acid N′*-[2-amino-3-(1*H*-indol-2-yl)propionyl]hydrazide·2HBr (**27**)*

Yield: 94%; mp: 176–178 °C (dec.); ^{1}H NMR (CD_3OD): δ 8.78 (d, 1H, J = 8.6 Hz), 8.24 (d, 1H, J = 8.3 Hz), 8.16 (s, 1H), 7.78 (m, 3H), 7.42 (m, 1H), 7.34 (s, 1H), 7.11 (m, 2H), 4.30 (m, 1H), 2.30 (s, 2H), 1.88 (m, 15H); MALDIMS: *m*/*z* 507 (M + 1); Anal. Calcd for $C_{31}H_{35}Br_2N_5O_2$ (749.4): C, 49.69; H, 4.71; N, 9.35. Found: C, 49.63; H, 4.67; N, 9.33.

4.2.10. (S)-4-Adamantan-1-yl-quinoline-2-carboxylic acid N′*-[2-amino-3-(1*H*-imidazol-4-yl)propionyl]hydrazide·3HBr (**28**)*

Yield: 95%; mp: 165–167 °C (dec.); ^{1}H NMR (CD_3OD): δ 8.77 (d, 1H, J = 8.7 Hz), 8.34 (d, 1H, J = 8.1 Hz), 8.25 (s, 1H), 7.75 (m, 1H), 7.62 (m, 2H), 6.92 (s, 1H), 4.37 (m, 1H), 2.91 (m, 2H), 1.88 (m, 15H); MALDIMS: *m*/*z* 459 (M + 1); Anal. Calcd for $C_{26}H_{33}$ $Br_3N_6O_2$ (701.2): C, 44.53; H, 4.74; N, 11.98. Found: C, 44.56; H, 4.78; N, 11.97.

4.2.11. (S)-4-Adamantan-1-yl-quinoline-2-carboxylic acid N′*-(2,5-diaminopentanoyl)hydrazide·3HBr (**29**)*

Yield: 90%; semi-solid; ^{1}H NMR (CD_3OD): δ 8.76 (d, 1H, J = 8.6 Hz), 8.25 (d, 1H, J = 8.3 Hz), 8.14 (s, 1H), 7.77 (m, 1H), 7.71 (m, 1H), 4.11 (m, 1H), 3.07 (m, 2H), 2.10 (m, 2H), 1.88 (m, 15H), 1.28 (m, 2H); MALDIMS: *m*/*z* 436 (M + 1); Anal. Calcd for $C_{25}H_{36}Br_3N_5O_6$ (678.3): C, 44.27; H, 5.35; N, 10.32. Found: C, 44.23; H, 5.31; N, 10.28.

4.2.12. (S)-4-Adamantan-1-yl-quinoline-2-carboxylic acid N′*-(2,6-diaminohexanoyl)hydrazide·3HBr (**30**)*

Yield: 92%; mp: 172–174 °C (dec.); ^{1}H NMR (CD_3OD): 8.99 (d, 1H, J = 8.7 Hz), 8.33 (d, 1H, J = 8.7 Hz), 8.23 (s, 1H), 7.90 (m, 1H), 7.79 (m, 1H), 4.13 (m, 1H), 3.04 (m, 2H), 2.07 (m, 2H), 1.88 (m, 15H), 1.30 (m, 4H); MALDIMS: *m*/*z* 450 (M + 1); Anal. Calcd for $C_{26}H_{38}Br_3N_5O_2$ (692.3): C, 45.11; H, 5.53; N, 10.12. Found: C, 45.07; H, 5.49; N, 10.09.

*4.2.13. (S)-{5-[N′-(4-Adamantan-1-yl-2-carbonyl)hydrazino]-4-amino-5-oxopentyl}-guanidine·3HBr (**31**)*

Yield: 95%; mp: 140–142 °C (dec.); ^{1}H NMR (CD_3OD): δ 9.15 (br s, 1H), 8.88 (d, 1H, J = 7.9 Hz), 8.57 (br s, 1H), 8.33 (m, 1H, J = 8.4 Hz), 8.23 (s, 1H), 7.90 (m, 1H), 7.80 (m, 1H), 4.20 (m, 1H), 2.04 (m, 2H), 1.88 (m, 15H), 1.72 (m, 2H), 1.33 (m, 2H); MALDIMS: *m*/*z* 478 (M + 1); Anal. Calc for $C_{26}H_{38}Br_3N_7O_2$ (720.3): C, 43.35; H, 5.32; N, 13.61. Found: C, 43.32; H, 5.35; N, 13.64.

4.3. General procedure for the synthesis of methyl 2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]alkanoates (**32**–**44**)

To a mixture of 4-(adamantan-1-yl)-2-quinolincarboxylic acid (**5**, 0.324 g, 0.94 mmol) and pyridine (112 μL, 148 mmol) in anhydrous DCM (15 mL), $SOCl_2$ (95 μL, 1.35 mmol) was added under N_2 atmosphere. The reaction mixture was stirred at ambient temperature for 1 min. To the intermediate acid chloride was added drop wise a solution of the desired L-amino acid methyl ester (0.82 mmol) and DMAP (0.81 mmol) in DCM (10 mL) via a syringe during a period of 5 min under N_2 atmosphere. The reaction mixture was stirred for another 20 min at ambient temperature. The reaction mixture was diluted with DCM (50 mL) and washed with water (2 × 25 mL) and brine solution (1 × 25 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to produce the crude product, which was purified by column chromatography on silica gel using ethyl acetate/hexanes (10:90) as eluant to provide methyl 2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]alkanoates **32**–**44**.

4.3.1. Methyl 2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]acetate (**32**)

Yield: 65%; oil; IR (neat, cm^{-1}): 3380, 1741; ^1H NMR ($CDCl_3$): δ 8.75 (br s, 1H), 8.61 (d, 1H, $J = 8.5$ Hz), 8.24 (m, 2H), 7.75 (m, 1H), 7.58 (m, 1H), 4.17 (m, 2H), 3.81 (s, 3H), 1.88 (m, 15H); ESIMS: *m*/*z* 393 (M + 1); Anal. Calcd for $C_{23}H_{26}N_2O_3$ (378.5), calcd: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.63; H, 6.68; N, 7.77.

4.3.2. Methyl (2S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]propanoate (**33**)

Yield: 50%; oil; IR (neat, cm^{-1}): 3380, 1741; ^1H NMR ($CDCl_3$): δ 8.69 (br s, 1H), 8.66 (d, 1H, $J = 8.7$ Hz), 8.20 (m, 2H), 7.69 (m, 1H), 7.55 (m, 1H), 4.21 (m, 1H), 3.80 (s, 3H), 1.88 (m, 15H), 1.60 (d, 3H, $J = 6.8$ Hz); ESIMS: *m*/*z* 393 (M + 1); Anal. Calcd for $C_{24}H_{28}N_2O_3$ (392.4): C, 73.44; H, 7.19; N, 7.14. Found: C, 73.32; H, 7.17; N, 12.19.

4.3.3. Methyl (2S,3S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]-3-methylpentanoate (**34**)

Yield: 54%; oil; IR (neat, cm^{-1}): 3391, 1701; ^1H NMR ($CDCl_3$): δ 8.74 (br s, 1H), 8.66 (d, 1H, $J = 8.7$ Hz), 8.21 (m, 2H), 7.70 (m, 1H), 7.60 (m, 1H), 4.83 (m, 1H), 3.78 (s, 3H), 1.88 (m, 15H), 1.33 (m, 1H), 1.25 (m, 2H), 1.10 (m, 6H); ESIMS: *m*/*z* 435 (M + 1); Anal. Calcd for $C_{27}H_{34}N_2O_3$ (434.5): C, 74.62; H, 7.89; N, 6.45. Found: C, 74.64; H, 7.75; N, 6.38.

4.3.4. Methyl (2S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]-4-methylpentanoate (**35**)

Yield: 64%; oil; IR (neat, cm^{-1}): 3412, 1720; ^1H NMR ($CDCl_3$): δ 8.66 (d, 1H, $J = 8.7$ Hz), 8.59 (br s, 1H), 8.24 (s, 1H), 8.19 (d, 1H, $J = 7.6$ Hz), 7.70 (m, 1H), 7.57 (m, 1H), 4.89 (m, 1H), 3.78 (s, 3H), 1.88 (m, 15H), 1.81 (m, 2H), 1.25 (m, 1H), 1.10 (m, 6H); ESIMS: *m*/*z* 435 (M + 1); Anal. Calcd for $C_{27}H_{34}N_2O_3$ (434.5): C, 74.62; H, 7.89; N, 6.45. Found: C, 74.65; H, 7.83; N, 6.38.

4.3.5. Methyl (2S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]-4-methylsulfanylbutanoate (**36**)

Yield: 54%; oil; IR (neat, cm^{-1}): 3379, 1731; ^1H NMR ($CDCl_3$): δ 8.78 (br s, 1H), 8.66 (d, 1H, $J = 8.7$ Hz), 8.20 (m, 2H), 7.70 (m, 1H), 7.57 (m, 1H), 4.97 (m, 1H), 3.82 (s, 3H), 2.13 (s, 3H), 1.88 (m, 15H), 1.59 (m, 2H), 1.25 (m, 2H); ESIMS: *m*/*z* 453 (M + 1); Anal. Calcd for $C_{26}H_{32}N_2O_3S$ (452.2): C, 68.99; H, 7.13; N, 6.19. Found: C, 68.93; H, 7.07; N, 6.15.

4.3.6. Methyl (2S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]-4-carbamoylbutanoate (**37**)

Yield: 61%; oil; IR (neat, cm^{-1}): 3385, 1730; ^1H NMR ($CDCl_3$): δ 8.70 (d, 1H, $J = 8.4$ Hz), 8.25 (m, 2H), 7.74 (m, 1H), 7.52 (m, 1H), 4.98 (m, 1H), 3.85 (s, 3H), 2.82 (m, 4H), 1.89 (m, 15H); ESIMS: *m*/*z* 450 (M + 1); Anal. Calcd for $C_{26}H_{31}N_2O_4$ (449.5): C, 69.47; H, 6.95; N, 9.35. Found: C, 69.27; H, 7.21; N, 9.24.

4.3.7. Methyl (2S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]-3-phenylpropanoate (**38**)

Yield: 74%; oil; IR (neat, cm^{-1}): 3350, 1720; ^1H NMR ($CDCl_3$): δ 8.75 (br s, 1H), 8.65 (d, 1H, $J = 8.7$ Hz), 8.22 (s, 1H), 8.15 (d, 1H, $J = 8.4$ Hz), 7.72 (m, 1H), 7.56 (m, 1H), 7.30 (m, 5H), 5.04 (m, 1H), 3.82 (s, 3H), 3.39 (m, 2H), 1.88 (m, 15H); ESIMS: *m*/*z* 469 (M + 1); Anal. Calcd for $C_{30}H_{32}N_3O_2$ (468.6), calcd: C, 76.90; H, 6.88; N, 5.98. Found: C, 76.69; H, 6.49; N, 5.78.

4.3.8. Methyl (2S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]-3-(4-benzyloxyphenyl)propanoate (**39**)

Yield: 50%; oil; IR (neat, cm^{-1}): 3344, 1718; ^1H NMR ($CDCl_3$): δ 8.78 (br s, 1H), 8.67 (d, 1H, $J = 8.7$ Hz), 8.21 (s, 1H), 8.13 (d, 1H, $J = 8.3$ Hz), 7.69 (m, 1H), 7.57 (m, 1H), 7.36 (m, 5H), 7.15 (d, 2H, $J = 8.5$ Hz), 6.91 (d, 2H, $J = 8.6$ Hz), 5.06 (s, 2H), 4.08 (m, 1H), 3.74 (s, 3H), 3.23 (m, 2H), 1.88 (m, 15H); ESIMS: *m*/*z* 575 (M + 1); Anal. Calcd for $C_{37}H_{38}N_2O_4$ (574.7), calcd: C, 77.33; H, 6.66; N, 4.87. Found: C, 77.18; H, 6.52; N, 4.80.

4.3.9. Methyl (2S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]-3-(1H-indolyl)propanoate (**40**)

Yield: 57%; oil; IR (neat, cm^{-1}): 3382, 1725; ^1H NMR ($CDCl_3$): δ 8.75 (br s, 1H), 8.61 (d, 1H, $J = 8.4$ Hz), 8.22 (m, 2H), 7.68 (m, 1H), 7.55 (m, 1H), 7.27 (m, 4H), 6.94 (s, 1H), 5.03 (m, 1H), 3.77 (s, 3H), 3.22 (m, 2H), 1.88 (m, 15H); ESIMS: *m*/*z* 508 (M + 1); Anal. Calcd for $C_{32}H_{33}N_3O_3$ (507.6), calcd: C, 75.71; H, 6.55; N, 8.28. Found: C, 75.64; H, 6.44; N, 8.47.

4.3.10. Methyl (2S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]-(1H-4-imidazol-yl)propaonoate (**41**)

Yield: 58%; oil; IR (neat, cm^{-1}): 3352, 1703; ^1H NMR ($CDCl_3$): δ 9.12 (br s, 1H), 8.72 (d, 1H, $J = 8.7$ Hz), 8.25 (d, 1H, $J = 9.8$ Hz), 8.17 (s, 1H), 7.90 (s, 1H), 7.76 (m, 1H), 7.67 (m, 1H), 6.25 (s, 1H), 4.20 (m, 1H), 3.86 (s, 3H), 2.28 (m, 2H), 1.88 (m, 15H); ESIMS: *m*/*z* 459 (M + 1); Anal. Calcd for $C_{24}H_{30}N_4O_3$ (458.6): C, 70.72; H, 6.59; N, 12.22. Found; C, 70.54; H, 5.47; N, 12.17.

4.3.11. Methyl (2S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]-5-(benzyloxycarbonylamino)pentanoate (**42**)

Yield: 69%; oil; IR (neat, cm^{-1}): 3400, 1715; ^1H NMR ($CDCl_3$): δ 8.72 (br s, 1H), 8.65 (d, 1H, $J = 8.7$ Hz), 8.20 (m, 2H), 7.69 (m, 1H), 7.57 (m, 1H), 7.33 (m, 5H), 5.08 (s, 2H), 4.84 (m, 1H), 3.70 (s, 3H), 3.26 (m, 2H), 1.88 (m, 15H), 1.24 (m, 4H); APCIMS: *m*/*z* 570 (M + 1); Anal. Calcd for $C_{34}H_{39}N_3O_5$ (569.7): C, 71.68; H, 6.90; N, 7.38. Found: C, 71.62; H, 6.55; N, 7.32.

4.3.12. Methyl (2S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]-6-(benzyloxycarbonylamino)hexanoate (**43**)

Yield: 65%; oil; IR (neat, cm^{-1}): 3381, 1728; ^1H NMR ($CDCl_3$): δ 8.72 (br s, 1H), 8.65 (d, 1H, $J = 8.7$ Hz), 8.20 (m, 2H), 7.69 (m, 1H), 7.57 (m, 1H), 7.30 (m, 5H), 5.05 (s, 2H), 4.87 (m, 1H), 3.79 (s, 3H), 3.18 (m, 2H), 1.88 (m, 15H), 1.48 (m, 6H); ESIMS: *m*/*z* 584 (M + 1); Anal. Calcd for $C_{35}H_{41}N_3O_5$ (583.7): C, 72.02; H, 7.08; N, 7.20. Found: C, 72.09; H, 7.15; N, 7.25.

4.3.13. Methyl (2S)-2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]-5-[amino(imino)methylamino]pentanoate (**44**)

Yield: 41%; oil; IR (neat, cm^{-1}): 3380, 1730; ^1H NMR ($CDCl_3$): δ 8.75 (br s, 1H), 8.67 (d, 1H, $J = 8.6$ Hz), 8.25 (m, 2H), 7.70 (m, 1H), 7.52 (m, 1H), 5.01 (M, 1H), 3.78 (s, 3H), 2.90 (m, 2H), 2.03 (m, 2H),

1.88 (m, 17H); ESIMS: *m/z* 478 (M + 1); Anal. Calcd for $C_{27}H_{35}N_5O_3$ (477.6): C, 67.90; H, 7.39; N, 14.66. Found: C, 67.78; H, 7.57; N, 14.41.

4.4. General procedure for the synthesis of N*2-[1-hydrazinocarbonylalkyl]-4-(adamantan-1-yl)-2-quinolinecarboxamides (**45**–**57**)*

To the solution of methyl 2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]alkanoate (**32**–**44**, 0.1 mmol) in abs. ethyl alcohol (10 mL), hydrazine hydrate (0.5 mL, 12.5 mmol) was added and the reaction mixture was stirred for 48 h at ambient temperature. The solvent was removed under reduced pressure to afford **45**–**51**, **53**–**54**, and **57**.

In certain cases where the side chain of the amino acid in methyl 2-[4-(adamantan-1-yl)-2-quinonylcarboxamido]alkanoates was protected (i.e. Orn, Lys with a carbobenzyloxy, and Tyr with a benzyl group), an additional deprotection step as described below was carried out to obtain desired compounds. A solution of 33% HBr in acetic acid (2 mL) was added to intermediates **39**, and **42**–**43** (0.1 mmol) and the reaction mixture was stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure to afford **52**, and **55**–**56** as hydrobromide salts.

4.4.1. N*2-1-Hydrazinocarbonylmethyl-4-(adamantan-1-yl)-2-quinolinecarboxamide (**45**)*

Yield: 95%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 9.12 (br s, 1H), 8.67 (d, 1H, J = 8.8 Hz), 8.25 (s, 1H), 8.17 (d, 1H, J = 8.3 Hz), 7.70 (m, 1H), 7.58 (m, 1H), 3.2 (s, 2H), 1.88 (m, 15H); ESIMS: *m/z* 379 (M + 1); Anal. Calcd for $C_{22}H_{26}N_4O_2$ (378.5): C, 69.82; H, 6.92; N, 14.80. Found: C, 69.85; H, 6.95; N, 14.78.

4.4.2. N*2-[(1S)-1-Hydrazinocarbonylethyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide (**46**)*

Yield: 95%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 8.66 (d, 1H, J = 8.7 Hz), 8.53 (br s, 1H), 8.18 (m, 2H), 7.73 (m, 1H), 7.58 (m, 1H), 4.71 (m, 1H), 1.88 (m, 15H), 1.60 (d, 3H, J = 6.8 Hz); ESIMS: *m/z* 393 (M + 1); Anal. Calcd for $C_{23}H_{28}N_4O_2$ (392.4): C, 70.38; H, 7.19; N, 14.27. Found: C, 70.42; H, 7.21; N, 14.31.

4.4.3. N*2-[(1S,2S)-1-Hydrazinocarbonyl-2-methylbutyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide (**47**)*

Yield: 95%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 8.66 (d, 1H, J = 8.4 Hz), 8.49 (br s, 1H), 8.18 (m, 2H), 7.72 (m, 1H), 7.58 (m, 1H), 4.67 (m, 1H), 1.88 (m, 15H), 1.31 (m, 1H), 1.23 (m, 2H), 1.10 (m, 6H); ESIMS: *m/z* 435 (M + 1); Anal. Calcd for $C_{26}H_{34}N_4O_2$ (434.5): C, 71.86; H, 7.89; N, 12.89. Found: C, 71.89; H, 7.91; N, 12.85.

4.4.4. N*2-[(1S)-1-Hydrazinocarbonyl-3-methylbutyl]-4-(adamantan-1-yl)-2-quinoline-carboxamide (**48**)*

Yield: 95%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 8.67 (d, 1H, J = 8.3 Hz), 8.18 (m, 2H), 7.71 (m, 1H), 7.59 (m, 1H), 7.47 (br s, 1H), 4.44 (m, 1H), 1.88 (m, 15H), 1.61 (m, 2H), 1.25 (m, 1H), 0.99 (m, 6H); ESIMS: *m/z* 435 (M + 1); Anal. Calcd for $C_{26}H_{34}N_4O_2$ (434.5): C, 71.86; H, 7.89; N, 12.89. Found: C, 71.92; H, 7.95; N, 12.87.

4.4.5. N*2-[(1S)-1-Hydrazinocarbonyl-3-methylsulfanylpropyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide (**49**)*

Yield: 95%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 8.72 (br s, 1H), 8.66 (d, 1H, J = 7.9 Hz), 8.17 (m, 2H), 7.69 (m, 1H), 7.59 (m, 1H), 4.85 (m, 1H), 2.64 (m, 2H), 2.13 (s, 3H), 1.88 (m, 15H), 1.25 (m, 2H); ESIMS: *m/z* 453 (M + 1); Anal. Calcd for $C_{25}H_{32}N_4O_2S$ (452.2): C, 66.34; H, 7.13; N, 12.38. Found: C, 66.37; H, 7.14; N, 12.28.

4.4.6. N*2-[(1S)-3-Carbamoyl-1-hydrazinocarbonylpropyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide (**50**)*

Yield: 90%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 8.68 (d, 1H, J = 8.4 Hz), 8.21 (m, 2H), 7.74 (m, 1H), 7.57 (m, 1H), 4.96 (m, 1H), 2.80 (m, 4H), 1.88 (m, 15H); ESIMS: *m/z* 450 (M + 1); Anal. Calcd for $C_{25}H_{31}N_5O_3$ (449.6): C, 66.79; H, 6.95; N, 15.58. Found: C, 66.87; H, 7.15; N, 15.23.

4.4.7. N*2-[(1S)-1-Hydrazinocarbonyl-2-phenylethyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide (**51**)*

Yield: 91%; semi-solid; ^{1}H NMR ($CDCl_3$): 8.69 (d, 1H, J = 8.7 Hz), 8.24 (s, 1H), 8.17 (d, 1H, J = 8.4 Hz), 7.70 (m, 1H), 7.52 (m, 1H), 7.28 (m, 5H), 5.00 (m, 1H), 3.40 (m, 2H), 1.89 (m, 15H); ESIMS: *m/z* 469 (M + 1); Anal. Calcd for $C_{29}H_{32}N_4O_2$ (468.6): C, 74.33; H, 6.88; N, 11.96. Found: C, 74.10; H, 6.59; N, 11.67.

4.4.8. N*2-[(1S)-1-Hydrazinocarbonyl-2-(4-hydroxyphenyl)ethyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide·2HBr (**52**)*

Yield: 96%; mp: 155–157 °C (dec.); ^{1}H NMR (CD_3OD): δ 8.98 (d, 1H, J = 8.8 Hz), 8.37 (d, 1H, J = 8.3 Hz), 8.20 (s, 1H), 8.02 (m, 1H), 7.88 (d, 2H, J = 8.1 Hz), 7.17 (d, 2H, J = 8.1 Hz), 6.74 (d, 2H, J = 7.7 Hz), 3.34 (s, 2H), 1.88 (m, 15H); ESIMS: *m/z* 485 (M + 1); Anal. Calcd for $C_{29}H_{34}Br_2N_4O_3$ (646.4): C, 53.88; H, 5.30; N, 8.67. Found: C, 53.78; H, 5.27; N, 8.63.

4.4.9. N*2-[(1S)-1-Hydrazinocarbonyl-2-(1*H*-indolyl)ethyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide (**53**)*

Yield: 88%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 8.60 (d, 1H, J = 8.4 Hz), 8.24 (m, 2H), 7.65 (m, 1H), 7.52 (m, 1H), 7.29 (m, 4H), 6.96 (s, 1H), 5.05 (m, 1H), 3.20 (m, 2H), 1.88 (m, 15H); ESIMS: *m/z* 508 (M + 1); Anal. Calcd for $C_{31}H_{33}N_5O_2$ (507.6): C, 73.35; H, 6.55; N, 13.80. Found: C, 73.64; H, 6.40; N, 13.90.

4.4.10. N*2-[(1S)-1-Hydrazinocarbonyl-2-(1*H*-4-imidazolyl)ethyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide (**54**)*

Yield: 99%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 8.71 (d, 1H, J = 8.6 Hz), 8.25 (d, 1H, J = 9.6 Hz), 8.17 (s, 1H), 7.91 (s, 1H), 7.75 (m, 1H), 7.65 (m, 1H), 6.23 (s, 1H), 4.19 (m, 1H), 232 (m, 2H), 1.88 (m, 15H); ESIMS: *m/z* 459 (M + 1); Anal. Calcd for $C_{26}H_{30}N_6O_2$ (458.6): C, 68.10; H, 6.59; N, 18.33. Found; C, 68.08; H, 6.57; N, 18.32.

4.4.11. N*2-[(1S)-1-Hydrazinocarbonylbutyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide·3HBr (**55**)*

Yield: 97%; mp: 121–123 °C (dec.); ^{1}H NMR (CD_3OD): δ 9.10 (d, 1H, J = 8.9 Hz), 8.54 (m, 2H), 8.14 (m, 1H), 8.00 (m, 1H), 4.85 (m, 1H), 3.10 (m, 2H), 2.17 (m, 2H), 1.88 (m, 15H), 1.30 (m, 2H); MALDIMS: *m/z* 436 (M + 1); Anal. Calcd for $C_{25}H_{36}Br_3N_5O_2$ (678.3): C, 44.27; H, 5.35; N, 10.32. Found: C, 44.21; H, 5.28; N, 10.27.

4.4.12. N*2-[(1S)-1-Hydrazinocarbonylpentyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide·3HBr (**56**)*

Yield: 98%; mp: 115–117 °C (dec.); ^{1}H NMR (CD_3OD): δ 9.00 (d, 1H, J = 8.8 Hz), 8.41 (d, 1H, J = 8.4 Hz), 8.36 (s, 1H), 7.99 (m, 1H), 7.87 (m, 1H), 4.77 (m, 1H), 2.98 (m, 2H), 2.09 (m, 2H), 1.88 (m, 15H), 1.30 (m, 4H); ESIMS: *m/z* 450 (M + 1); Anal. Calcd for $C_{26}H_{38}Br_3N_5O_2$ (692.3): C, 45.11; H, 5.53; N, 10.12. Found: C, 45.07; H, 5.49; N, 10.07.

4.4.13. N*2-[(1S)-4-Amino(imino)methylamino-1-hydrazinocarbonylbutyl]-4-(adamantan-1-yl)-2-quinolinecarboxamide (**57**)*

Yield: 95%; semi-solid; ^{1}H NMR ($CDCl_3$): δ 8.68 (d, 1H, J = 8.4 Hz), 8.20 (d, 1H, J = 9.2 Hz), 8.17 (s, 1H), 7.75 (m, 1H), 7.65 (m, 1H), 4.50 (m, 1H), 3.02 (m, 2H), 1.62 (m, 4H), 1.88 (m, 15H); ESIMS: *m/z* 478 (M + 1); Anal. Calcd for $C_{26}H_{35}N_7O_2$ (477.6): C, 65.38; H, 7.39; N, 20.53. Found: C, 65.64; H, 7.14; N, 20.23.

Acknowledgements

The authors are thankful to the Tuberculosis Antimicrobial Acquisition and Coordination Facility (TAACF), which provided partial antimycobacterial data through a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases. Amit Nayyar and Sanjay R. Patel thank the Council of Scientific and Industrial Research (CSIR), and the Department of Biotechnology (DBT, grant no. CSH/GIA/1490), India, respectively, for the award of Senior Research Fellowship. The computational facilities at Bombay College of Pharmacy were jointly provided by the All India Council of Technical Education through grant (F. No. 8022/RID/NPROJ/RPS-5/2003-04) and the Department of Science and Technology through their FIST program (SR/FST/LSI–163/2003).

References

[1] World Health Organization, Tuberculosis Fact Sheet, No. 104, 2007; please see: <www.who.int/mediacentre/factsheets/fs104/en>.
[2] A. Nayyar, R. Jain, Curr. Med. Chem. 12 (2005) 1873–1886.
[3] L. Ballell, R.A. Field, K. Duncan, R.J. Young, Antimicrob. Agents Chemother. 49 (2005) 2153–2163.
[4] Y.L. Janin, Bioorg. Med. Chem. 15 (2007) 2479–2513.
[5] R. Jain, B. Vaitilingam, A. Nayyar, P.B. Palde, Bioorg. Med. Chem. Lett. 13 (2003) 1051–1054.
[6] S. Vangapandu, M. Jain, R. Jain, S. Kaur, P.P. Singh, Bioorg. Med. Chem. 12 (2004) 2501–2508.
[7] V. Monga, A. Nayyar, B. Vaitilingam, P.B. Palde, S.S. Jhamb, P.P. Singh, R. Jain, Bioorg. Med. Chem. 12 (2004) 6465–6472.
[8] A. Nayyar, A. Malde, E. Coutinho, R. Jain, Bioorg. Med. Chem. 14 (2006) 847–856.
[9] A. Nayyar, A. Malde, E. Coutinho, R. Jain, Bioorg. Med. Chem. 14 (2006) 7302–7310.
[10] A. Nayyar, V. Monga, A. Malde, E. Coutinho, R. Jain, Bioorg. Med. Chem. 15 (2007) 626–640.
[11] G.F. Yang, X. Huang, Curr. Pharm. Des. 12 (2006) 4601–4611.
[12] F.J. Prado-Prado, H. González-Díaz, L. Santana, E. Uriarte, Bioorg. Med. Chem. 15 (2007) 897–902.
[13] H. González-Díaz, A. Pérez-Bello, E. Uriarte, Y. González-Díaz, Bioorg. Med. Chem. Lett. 16 (2006) 547–553.
[14] M.C. Bagchi, D. Mills, S.C. Basak, J. Mol. Model. 13 (2007) 111–120.
[15] K.E. Hevener, D.M. Ball, J.K. Buolamwini, R.E. Lee, Bioorg. Med. Chem. 16 (2008) 8042–8053.
[16] S.G. Franzblau, R.S. Witzig, J.C. McLaughlin, P. Torres, G. Madico, A. Herandez, M.T. Degnan, M.B. Cook, V.K. Quenzer, R.M. Ferguson, R.H. Gilman, J. Clin. Microbiol. 36 (1998) 362–366.
[17] L. Collins, S.G. Franzblau, Antimicrob. Agents Chemother. 41 (1997) 1004–1009.
[18] R.D. Cramer, D.E. Patterson, J.D. Bunce, J. Am. Chem. Soc. 110 (1988) 5959–5967.
[19] E.J. Martin, J.M. Blaney, M.A. Siani, D.C. Spellmeyer, A.K. Wong, W.H. Moos, J. Med. Chem. 38 (1995) 1431–1436.
[20] CoMFA and QSAR Manual, Sybyl 7.1, Associates Inc., 1699 S Hanley Rd., St. Louis, MO 631444, USA.
[21] Sybyl v.7.1 Tripos Inc., USA.
[22] M.L. Liu, J.M. Diu, D.C. Li, D.Q. Wang, Acta Crystallogr. E 62 (2006) o1009–o1100.
[23] InsightII, Version 2005L, Accelrys, Inc., San Diego, CA, USA, 2005.
[24] J.R. Maple, M.-J. Hwang, T.P. Stockfisch, U. Dinur, M. Waldman, C.S. Ewig, A.T. Hagler, J. Comput. Chem. 15 (1994) 162–182.