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Preliminary communication

Ring-substituted imidazoles as a new class of anti-tuberculosis agents

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Abstract

We describe in vitro anti-*Mycobacterium tuberculosis* activities of ring-substituted-1*H*-imidazole-4-carboxylic acid derivatives (**1–6**), and 3-(2-alkyl-1*H*-imidazol-4-yl)-propionic acid derivatives (**7–13**) against drug-sensitive and drug-resistant *M. tuberculosis H37Rv* strains. The most effective analogues, **2f** (R=R_1=*c*-C_5H_9), and **2h** (R=R_1=*c*-C_6H_{11}) have produced >90% inhibition at a concentration of <6.25 μg/ml in the drug-sensitive screen. Upon further evaluation against drug-resistant strains, both analogues **2f** and **2h** produced an MIC value of 25.0 μg/ml. The observation of significant anti-tuberculosis activity in some of these analogues describes the discovery of novel ring-substituted-1*H*-imidazole-4-carboxylic acid ethyl esters as a new class of anti-tuberculosis agents.

Keywords: Tuberculosis; Homolytic free radical reaction; Ring-substituted-1*H*-imidazole-4-carboxylic acid derivatives; 3-(2-Alkyl-1*H*-imidazol-4-yl)-propionic acid derivatives

1. Introduction

Tuberculosis is a devastating worldwide problem, whose control is complicated by a number of confounding factors including development of multi-drug-resistant (MDR) strains to commonly used drugs, substantially long course of therapy, and lack of affordable cheap drugs in the cases involving patients suffering due to MDR tuberculosis [1–3]. These factors combined with shortage of new structural classes of drugs has made tuberculosis second leading infectious cause of death in the world today behind only to HIV/AIDS. *Mycobacterium tuberculosis*, the causative organism claims approximately three million human lives each year. Recently, World Health Organization (WHO) reported that the global figure of total deaths by infectious diseases is 17 million, of which tuberculosis accounts for approximately 20% of mortality. The gravity of the problem increases even more by the fact that one new case of tuberculosis is reported every 4 s, and one patient dies every 10 s [4]. It is commonly known that *M. tuberculosis* has developed resistance to the majority of the existing drugs, and no new drug has been introduced specifically to combat tuberculosis in the past 40 years. Thus, there is an urgent need to discover drugs, preferably belonging to new structural classes to combat drug-resistant cases, and to assist in decreasing the duration of therapy [5]. In pursuit of this goal, our research efforts are directed towards discovery of new chemical entities that are effective as anti-tuberculosis agents, and to optimize the structure to display the potent efficacy [6–7]. In continuing our anti-tuberculosis drug discovery program, this preliminary communication describes the synthesis and hitherto unknown in vitro anti-*M. tuberculosis* activities of new structural class of ring-substituted-1*H*-imidazole-4-carboxylic acid derivatives (Series 1, Fig. 1), and 3-(2-alkyl-1*H*-imidazol-4-yl)-propionic acid derivatives (Series 2, Fig. 1).

Fig. 1. Ring-substituted imidazoles.

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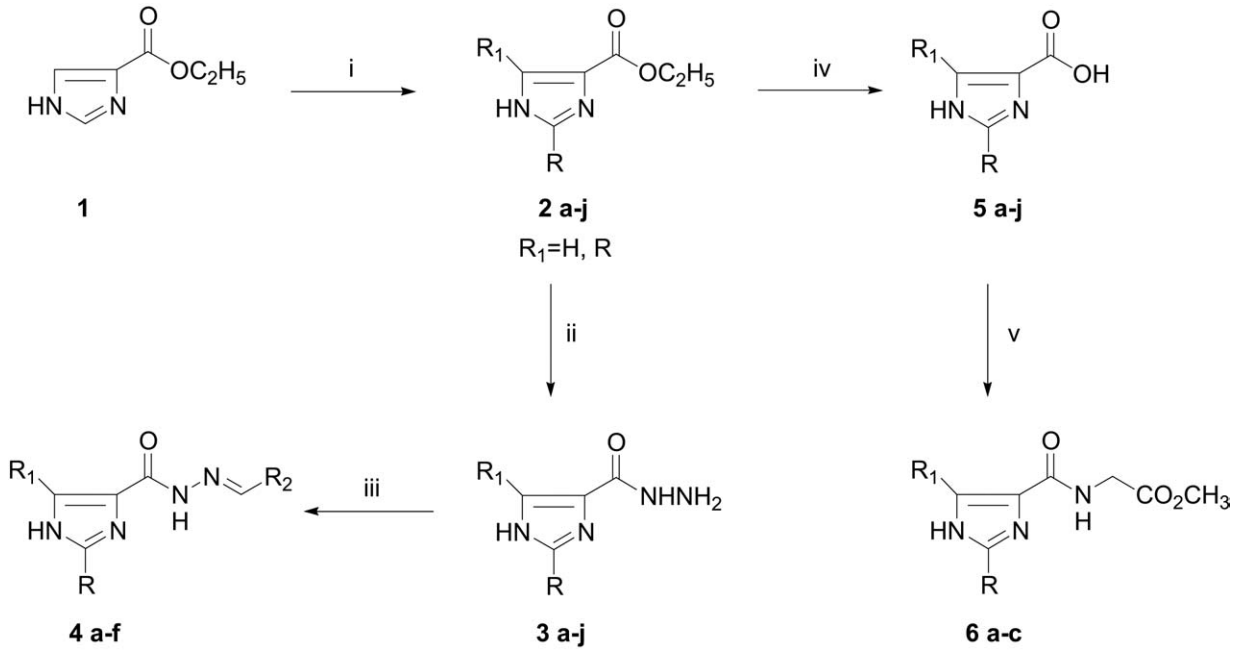


Scheme 1. Conditions: (i) RCO_2H, $AgNO_3$, $(NH_4)_2S_2O_8$, 10% H_2SO_4, 70–80 °C; (ii) NH_2NH_2, EtOH, reflux, 8 h; (iii) R_2CHO, EtOH, reflux, 2 h; (iv) 6 N HCl, 100 °C, 8 h; (v) H-Gly-OMe, Et_3N, DCC, DMF, 12 h.

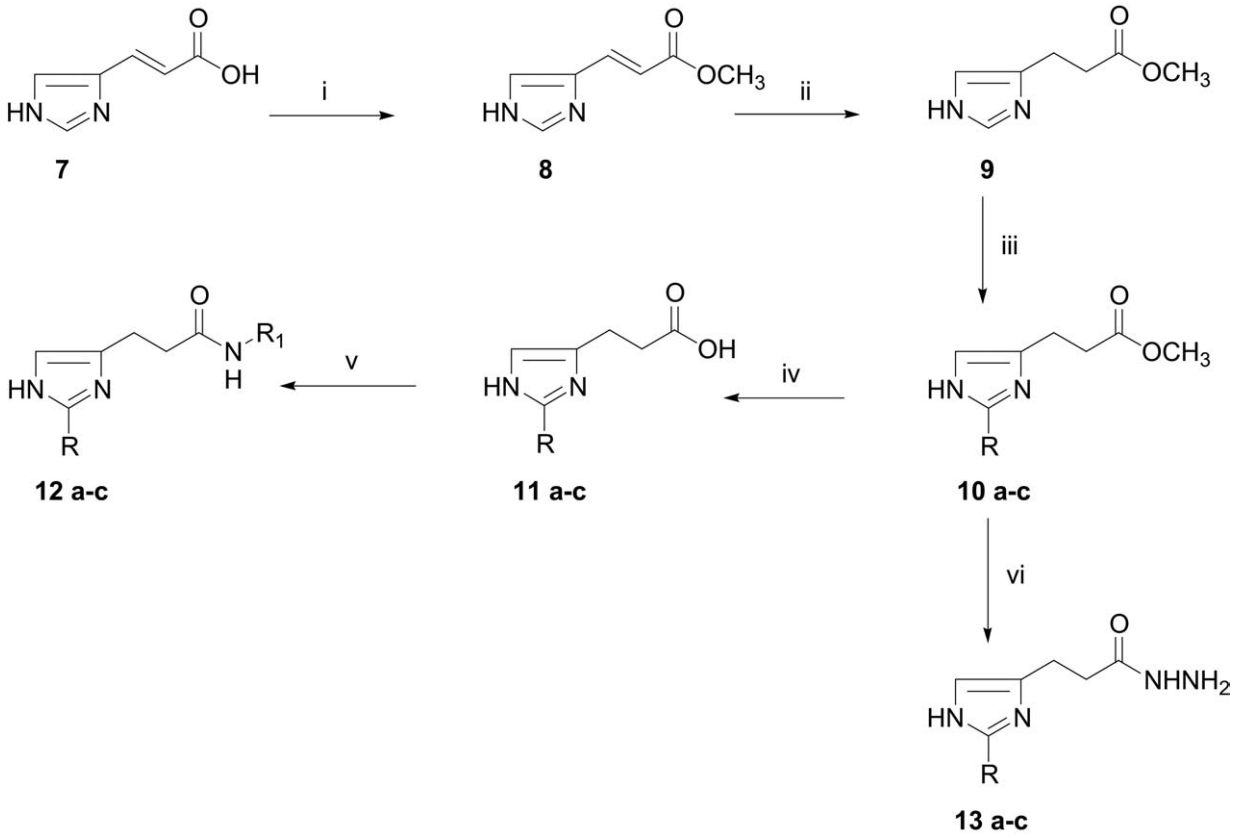
2. Chemistry

Commercially available 1*H*-imidazole-4,5-dicarboxylic acid upon partial decarboxylation with refluxing aniline followed by acidic hydrolysis with refluxing aqueous HCl, and finally esterification with abs. ethanol in the presence of dry HCl gas afforded desired starting material, 1*H*-imidazole-4-carboxylic acid ethyl ester (**1**) in excellent yield as reported earlier [8]. 1*H*-Imidazole-4-carboxylic acid ethyl ester (**1**) upon homolytic free radical reaction with various commercially available alkyl/cycloalkylcarboxylic acids in the presence of ammonium persulfate and catalytic amount of silver nitrate in 10% sulfuric acid provided readily separable mixture of 2-substituted and 2,5-disubstituted-1*H*-imidazole-4-carboxylic acid ethyl esters (**2a–j**) in moderate yield (Scheme 1). The reaction, as mentioned earlier is known to proceed through a homolytic free radical mechanism, and highly efficient in introducing otherwise difficult and previously unrealizable bulky alkyl/cycloalkyl groups directly into the imidazole ring [9–12]. 2-Substituted/2,5-disubstituted-1*H*-imidazole-4-carboxylic acid ethyl esters (**2a–j**) upon reaction with hydrazine hydrate in refluxing 95% ethyl alcohol produced 2-substituted/2,5-disubstituted-1*H*-4-imidazole carbohydrazides (**3a–j**) in quantitative yields. The reaction of latter compounds (**3a–j**) with various commercially available aromatic/aliphatic aldehydes at 80 °C for 2 h in 95% ethyl alcohol gave hydrazones (**4a–f**) in excellent yields. On the other hand, 2-substituted/2,5-disubstituted-1*H*-imidazole-4-carboxylic acid ethyl esters (**2a–j**) upon acidic hydrolysis with refluxing 6 N HCl for 8 h provided 2-substituted/2,5-disubstituted-1*H*-imidazole-4-carboxylic acids (**5a–j**) as hydrochloride salts. Condensation reaction of the acids (**5**) with glycine methyl ester hydrochloride (Gly-OMe) in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and triethylamine (Et_3N) in dimethylformamide (DMF) for 12 h at ambient temperature afforded [(2-substituted/2,5-disubstituted-1*H*-imidazole-4-carbonyl)amino]acetic acid methyl esters (**6a–c**) in good yield (Scheme 1).

On the other hand, intermediate 3-(1*H*-imidazol-4-yl)propionic acid methyl ester (**9**) was obtained in two steps from commercially available 3-(1*H*-imidazol-4-yl)acrylic acid (**7**) (Scheme 2). The latter compound **9** upon homolytic free radical reaction with various alkylcarboxylic acids in the presence of ammonium persulfate and catalytic amount of silver nitrate in 10% sulfuric acid provided 3-(2-alkyl-1*H*-imidazol-4-yl)propionic acid methyl esters (**10a–c**) in moderate yield. Acidic hydrolysis with 6 N HCl at reflux temperature produced 3-(2-alkyl-1*H*-imidazol-4-yl)propionic acids (**11a–c**), which upon reaction with various primary amines in the presence of DCC in dichloromethane (DCM) at ambient temperature for 12 h provided 3-(2-alkyl-1*H*-imidazol-4-yl)-*N*-alkyl-propionamides (**12a–c**) in good yield. Finally, 3-(2-alkyl-1*H*-imidazol-4-yl)propionic acid methyl esters (**10a–c**) upon reaction with hydrazine hydrate in refluxing 95% ethyl alcohol for 8 h produced 3-(2-alkyl-1*H*-imidazol-4-yl)propionic acid hydrazides (**13a–c**) in quantitative yield (Scheme 2).

3. Microbiology

In vitro activities of the synthesized compounds for tuberculosis inhibition against *M. tuberculosis H37Rv* strain (ATCC 27294, susceptible both to rifampin and isoniazid) were carried out using the Microplate Alamar Blue Assay (MABA) [13]. Compounds exhibiting fluorescence were



Scheme 2. Conditions: (i) CH_3OH, HCl; (ii) Pd-C/H_2, Et_3N, RTP, 24 h; (iii) RCO_2H, $AgNO_3$, $(NH_4)_2S_2O_8$, 10% H_2SO_4, 70–80 °C; (iv) 6 N HCl, reflux, 8 h; (v) R_1NH_2, DCC, DCM, 4 h; (vi) NH_2NH_2, EtOH, reflux, 8 h.

then tested in the BACTEC 460 radiometric system [13] and/or in broth microdilution assay, and activities expressed as minimum inhibitory concentration (MIC, μg/ml) are summarized in Tables 1–2. Compounds demonstrating at least 90% inhibition are re-tested at lower concentrations in the broth microdilution assay to determine the actual MIC, a value defined as the lowest concentration inhibiting ~90% of the inoculum relative to controls.

4. Results and discussion

Among the ring-substituted-1*H*-imidazole-4-carboxylic acid derivatives (**1–6**), esters **2f** (R=R_1=*c*-C_5H_9), and **2h** (R=R_1=*c*-C_6H_{11}) produced highest efficacy and exhibited >90% inhibition at a concentration of 6.25 μg/ml (MIC < 6.25 μg/ml) (Table 1). On the other hand, analogue **3h** (R=R_1=*c*-C_6H_{11}) exhibited moderate activity (MIC > 6.25 μg/ml) (see Table 1).

These results clearly demonstrated that the presence of two cycloalkyl groups at the imidazole ring cause improvement in anti-tuberculosis activity. Most surprisingly, these results are identical and in agreement with our earlier observation as in the case of ring-substituted quinolines that presence of two cycloalkyl groups in the ring is utmost important for potent anti-tuberculosis activity [6]. Furthermore, analogues (**3–6**) prepared by synthetic modification on the ethyl ester group have exhibited decrease of activity. However, replacement of the ethyl ester group in the effective analogues with long chain esters, and other electron-withdrawing groups may impart additional information on their role and provide inputs regarding most suitable group required at the C-4 position of the imidazole ring. The most effective analogues **2f** (R=R_1=*c*-C_5H_9), and **2h** (R=R_1=*c*-C_6H_{11}) upon further evaluation against isoniazid and rifampin resistant *M. tuberculosis H37Rv* strains exhibited similar results and produced 90% inhibition at a concentration of 25.0 μg/ml (MIC = 25.0 μg/ml).

At the same time, none of the 3-(2-alkyl-1*H*-imidazol-4-yl)propionic acid analogues (**7–13**) exhibited significant anti-tuberculosis activity (Table 2), thereby establishing the fact that placement of any spacer between the ring-substituted imidazole moiety and the ester functionality is detrimental for enhancement in biological activity.

5. Conclusions

To summarize, we have uncovered ring-substituted-1*H*-imidazole-4-carboxylic acid ethyl esters as a new class of anti-tuberculosis agents. The most effective analogues have demonstrated good anti-tuberculosis activities against both drug-sensitive and drug-resistant strains of *M. tuberculosis*, and are easily synthesized through a simple single step reaction. These properties make ring-substituted imidazole derivatives interesting lead molecules for further synthetic and

Table 1
In vitro antimycobacterial activity evaluation of ring-substituted-1*H*-4-imidazole carboxylic acid derivatives (**1–6**) against drug-sensitive *M. tuberculosis H37Rv* strain

S. No.	R	R_1	R_2	(%) Inhibition	MIC (μg/ml)
1	H	H	–	21	>6.25
2a	$CH(CH_3)_2$	H	–	20	>6.25
2b	$CH(CH_3)_2$	$CH(CH_3)_2$	–	5	>6.25
2c	$C(CH_3)_3$	H	–	0	>6.25
2d	$C(CH_3)_3$	$C(CH_3)_3$	–	0	>6.25
2e	*c*-C_5H_9	H	–	16	>6.25
2f	*c*-C_5H_9	*c*-C_5H_9	–	91	<6.25
2g	*c*-C_6H_{11}	H	–	22	>6.25
2h	*c*-C_6H_{11}	*c*-C_6H_{11}	–	99	<6.25
2i	adamantan-1-yl	H	–	0	>6.25
2j	adamantan-1-yl	Adamantan-1-yl	–	0	>6.25
3a	$CH(CH_3)_2$	H	–	0	>6.25
3b	$CH(CH_3)_2$	$CH(CH_3)_2$	–	ND	ND
3c	$C(CH_3)_3$	H	–	10	>6.25
3d	$C(CH_3)_3$	$C(CH_3)_3$	–	20	>6.25
3e	*c*-C_5H_9	H	–	1	>6.25
3f	*c*-C_5H_9	*c*-C_5H_9	–	0	>6.25
3g	*c*-C_6H_{11}	H	–	37	>6.25
3h	*c*-C_6H_{11}	*c*-C_6H_{11}	–	54	>6.25
3i	adamantan-1-yl	H	–	ND	ND
3j	adamantan-1-yl	adamantan-1-yl	–	ND	ND
4a	adamantan-1-yl	H	$CH(CH_3)_2$	27	>6.25
4b	adamantan-1-yl	H	C_6H_5	9	>6.25
4c	adamantan-1-yl	H	*p*-OCH_3-C_6H_4	11	>6.25
4d	adamantan-1-yl	H	C_6F_5	5	>6.25
4e	adamantan-1-yl	adamantan-1-yl	$CH(CH_3)_2$	0	>6.25
4f	adamantan-1-yl	adamantan-1-yl	*p*-OCH_3-C_6H_4	0	>6.25
5a	$CH(CH_3)_2$	H	–	3	>6.25
5b	$CH(CH_3)_2$	$CH(CH_3)_2$	–	0	>6.25
5c	$C(CH_3)_3$	H	–	0	>6.25
5d	$C(CH_3)_3$	$C(CH_3)_3$	–	0	>6.25
5e	*c*-C_5H_9	H	–	0	>6.25
5f	*c*-C_5H_9	*c*-C_5H_9	–	0	>6.25
5g	*c*-C_6H_{11}	H	–	0	>6.25
5h	*c*-C_6H_{11}	*c*-C_6H_{11}	–	1	>6.25
5i	adamantan-1-yl	H	–	0	>6.25
5j	adamantan-1-yl	adamantan-1-yl	–	0	>6.25
6a	$C(CH_3)_3$	H	–	12	>6.25
6b	$C(CH_3)_3$	$C(CH_3)_3$	–	11	>6.25
6c	adamantan-1-yl	H	–	21	>6.25
Isoniazid					0.05

ND, not done.

biological exploration. Additional studies on the role of ester functionality and replacement of cycloalkyl group present at the imidazole ring with substituted cycloalkyl groups are currently underway in our laboratory. It can be concluded that this class of compounds certainly hold great promise towards pursuit to discover new structural class of anti-tuberculosis agents.

6. Experimental

6.1. Chemistry

Melting points were recorded on Mettler DSC 851 or capillary melting point apparatus and are uncorrected. ^1H spectra were recorded on 300 MHz Bruker FT-NMR (Avance DPX300) spectrometer using tetramethylsilane as internal standard and the chemical shifts are reported in δ units. Mass spectra were recorded on either GCMS (Shimadzu QP 5000 spectrometer) auto sampler/direct injection (EI/CI) or HRMS (Finnigan Mat LCQ spectrometer) (APCI/ESI). IR spectra (λ_{max} in cm^{-1}) were recorded on a Nicolet spectrometer. Elemental analyses were recorded on Elementar Vario EL spectrometer. All chromatographic purification was performed with silica gel 60 (230–400 mesh), whereas all TLC (silica gel) development was performed on silica gel coated (Merck Kiesel 60 F_{254}, 0.2 mm thickness) sheets. All chemicals were purchased from Aldrich Chemical Ltd (Milwaukee,

Table 2
In vitro antimycobacterial activity evaluation of 3-(2-alkyl-1*H*-imidazol-4-yl)-propionic acid derivatives (**7–13**) against drug-sensitive *M. tuberculosis H37Rv* strain

S. No.	R	R_1	(%) Inhibition	MIC (μg/ml)
7	–	–	22	>6.25
8	–	–	0	>6.25
9	–	–	24	>6.25
10a	*c*-C_5H_9	–	0	>6.25
10b	*c*-C_6H_{11}	–	2	>6.25
10c	adamantan-1-yl	–	21	>6.25
11a	*c*-C_5H_9	–	0	>6.25
11b	*c*-C_6H_{11}	–	0	>6.25
11c	adamantan-1-yl	–	2	>6.25
12a	adamantan-1-yl	$(CH_2)_4CH_3$	25	>6.25
12b	adamantan-1-yl	$(CH_2)_5CH_3$	23	>6.25
12c	adamantan-1-yl	$(CH_2)_6CH_3$	8	>6.25
13a	*c*-C_5H_9	–	20	>6.25
13b	*c*-C_6H_{11}	–	21	>6.25
13c	adamantan-1-yl	–	14	>6.25
Isoniazid				0.05

WI, USA). Solvents used for the chemical synthesis acquired from commercial sources were of analytical grade, and were used without further purification unless otherwise stated.

7. Synthesis of 1*H*-imidazole-4-carboxylic acid ethyl ester (1)

To a solution of 1*H*-imidazole-4-carboxylic acid (1 mmol) in abs. ethanol (200 ml) was passed anhydrous HCl gas for 2 h. The reaction mixture evaporated under reduced pressure, and residue is dissolved in water and neutralized with solid sodium bicarbonate. The separated solid filtered, washed with cold water, and air-dried. The aqueous filtrate extracted with ethyl acetate (4 × 50 ml), dried over Na_2SO_4, and evaporated under reduced pressure to yield additional quantities of product.

Yield: 72%; m.p. 156–158 °C; IR (KBr): 1714 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.03 (s, 1H, H-2), 7.77 (s, 1H, H-5), 4.40 (q, 2H, J = 7.1 Hz, CH_2), 1.37 (t, 3H, J = 7.1 Hz, CH_3); EIMS: *m/z* 140 (M^+); Anal. $C_6H_8N_2O_2$ (C, H, N).

8. General method for the synthesis of 2-alkyl and 2,5-dialkyl-1*H*-4-imidazole carboxylic acid ethyl esters (2a–j)

1*H*-Imidazole-4-carboxylic acid ethyl ester (**1**, 1 mmol), was added to a mixture of silver nitrate (0.6 mmol) and alkyl/cycloalkylcarboxylic acid (3 mmol) in 10% H_2SO_4 (10 ml). Reaction mixture was stirred vigorously and heated to 70–80 °C. A freshly prepared solution of ammonium persulfate (3 mmol) in water (10 ml) was added drop wise over 15 min. The heating source was then removed and the reaction proceeded with evolution of carbon dioxide. After 15 min, the reaction was terminated by pouring it onto ice. The resulting mixture was made alkaline with 30% NH_4OH solution and extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with brine (2 × 10 ml), and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford oil, which upon chromatography over silica using ethyl acetate/hexanes (4:6) first eluted 2,5-dialkyl followed by 2-alkyl-1*H*-4-imidazole carboxylic acid ethyl esters in 9–33% yield.

*8.1. 2-Isopropyl-1*H*-4-imidazole carboxylic acid ethyl ester (**2a**)*

Yield: 9%; m.p. 166–168 °C; IR (KBr): 1709 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.61 (s, 1H, 5-H), 4.34 (q, 2H, J = 7.1 Hz, CH_2), 3.11 (m, 1H, CH), 1.36 (m, 6H, 2 × CH_3), 1.35 (t, 3H, J = 7.1 Hz, CH_3); APCIMS: *m/z* 183 (M + 1); Anal. $C_9H_{14}N_2O_2$ (C, H, N).

*8.2. 2,5-Diisopropyl-1*H*-4-imidazole carboxylic acid ethyl ester (**2b**)*

Yield: 11%; m.p. 135–136 °C; IR (KBr): 1705 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.34 (q, 2H, J = 7.1 Hz, CH_2), 3.11 (m, 1H, CH), 1.70 (m, 1H, CH), 1.33 (m, 6H, 2 × CH_3), 1.27 (m, 9H, 3 × CH_3); APCIMS: *m/z* 225 (M + 1); Anal. $C_{12}H_{20}N_2O_2$ (C, H, N).

*8.3. 2-tert-Butyl-1*H*-4-imidazole carboxylic acid ethyl ester (**2c**)*

Yield: 24%; m.p. 185–186 °C; IR (KBr): 1717 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.59 (s, 1H, 5-H), 4.34 (q, 2H, J = 7.2 Hz, CH_2), 1.40 (s, 9H, 3 × CH_3), 1.36 (t, 3H, J = 7.2 Hz, CH_3); ESIMS: *m/z* 197 (M + 1); Anal. $C_{10}H_{16}N_2O_2$ (C, H, N).

*8.4. 2,5-Di-tert-butyl-1*H*-4-imidazole carboxylic acid ethyl ester (**2d**)*

Yield: 13%; m.p. 144–146 °C; IR (KBr): 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.33 (q, 2H, J = 7.2 Hz, CH_2), 1.44 (s, 9H, 3 × CH_3), 1.40 (s, 9H, 3 × CH_3), 1.36 (t, 3H, J = 7.2 Hz, CH_3); ESIMS: *m/z* 253 (M + 1); Anal. $C_{14}H_{24}N_2O_2$ (C, H, N).

*8.5. 2-Cyclopentyl-1*H*-4-imidazole carboxylic acid ethyl ester (**2e**)*

Yield: 17%; m.p. 131–132 °C; IR (KBr): 1722 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.61 (s, 1H, 5-H), 4.33 (q, 2H, J = 7.1 Hz, CH_2), 3.18 (m, 1H, CH), 1.84 (m, 8H, 4 × CH_2), 1.37 (t, 3H, J = 7.1 Hz, CH_3); APCIMS: *m/z* 209 (M + 1); Anal. $C_{11}H_{16}N_2O_2$ (C, H, N).

*8.6. 2,5-Dicyclopentyl-1*H*-4-imidazole carboxylic acid ethyl ester (**2f**)*

Yield: 11%; m.p. 154–155 °C; IR (KBr): 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.33 (q, 2H, J = 7.1 Hz, CH_2), 2.77 (m, 1H, CH), 1.91 (m, 1H, CH), 1.81 (m, 16H, 8 × CH_2), 1.36 (t, 3H, J = 7.1 Hz, CH_3); APCIMS: *m/z* 277 (M + 1); Anal. $C_{16}H_{24}N_2O_2$ (C, H, N).

*8.7. 2-Cyclohexyl-1*H*-4-imidazole carboxylic acid ethyl ester (**2g**)*

Yield: 13%; m.p. 151–152 °C; IR (KBr): 1722 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60 (s, 1H, 5-H), 4.34 (q, 2H, *J* = 7.2 Hz, CH_2), 2.78 (m, 1H, CH), 1.61 (m, 10H, 5 × CH_2), 1.37 (t, 3H, *J* = 7.2 Hz, CH_3); ESIMS: *m/z* 223 (M + 1); Anal. $C_{12}H_{18}N_2O_2$ (C, H, N).

*8.8. 2,5-Dicyclohexyl-1*H*-4-imidazole carboxylic acid ethyl ester (**2h**)*

Yield: 10%; m.p. 147–159 °C; IR (KBr): 1703 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.32 (q, 2H, *J* = 7.2 Hz, CH_2), 3.17 (m, 1H, CH), 2.77 (m, 1H, CH), 1.84 (m, 20H, 10 × CH_2), 1.36 (t, 3H, *J* = 7.2 Hz, CH_3); ESIMS: *m/z* 305 (M + 1); Anal. $C_8H_{28}N_2O_2$ (C, H, N).

*8.9. 2-Adamantan-1-yl-1*H*-4-imidazole carboxylic acid ethyl ester (**2i**)*

Yield: 33%; m.p. 218–220 °C; IR (KBr): 1717 cm^{-1}; ^1H NMR (CD_3OD): δ 7.56 (s, 1H, 5-H), 4.32 (q, 2H, *J* = 7.2 Hz, CH_2), 1.81 (m, 15H, adamantyl protons), 1.35 (t, 3H, *J* = 7.2 Hz, CH_3); APCIMS: *m/z* 275 (M + 1); Anal. $C_{16}H_{22}N_2O_2$ (C, H, N).

*8.10. 2,5-Diadamantan-1-yl-1*H*-4-imidazole carboxylic acid ethyl ester (**2j**)*

Yield: 22%; m.p. 164–165 °C: IR (KBr): 1694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.32 (q, 2H, *J* = 7.2 Hz, CH_2), 1.88 (m, 30H, adamantyl protons), 1.32 (t, 3H, *J* = 7.2 Hz, CH_3); APCIMS: *m/z* 409 (M + 1); Anal. $C_{26}H_{36}N_2O_2$ (C, H, N).

9. General procedure for synthesis of 2-alkyl and 2,5-dialkyl-1*H*-4-imidazole carbohydrazides 3(a–j)

To a solution of 2-alkyl or 2,5-dialkyl-1*H*-4-imidazole carboxylic acid ethyl ester (**2a–j**, 1 mmol) in ethanol (2 ml), hydrazine hydrate (2 ml) was added, and reaction mixture was heated under reflux for 8 h. The carbohydrazides (**3a–j**) were obtained in quantitative yields directly after evaporation of the reaction solution.

*9.1. 2-Isopropyl-1*H*-4-imidazole carbohydrazide (**3a**)*

Yield: 92%; m.p. 208–209 °C; ^1H NMR ($CDCl_3$): δ 8.43 (bs, 1H, NH), 7.49 (s, 1H, 5-H); 3.62 (bs, 2H, NH_2), 1.48 (m, 1H, CH), 1.35 (m, 6H, 2 × CH_3); APCIMS: *m/z* 169 (M + 1); Anal. $C_7H_{12}N_4O$ (C, H, N).

*9.2. 2,5-Diisopropyl-1*H*-4-imidazole carbohydrazide (**3b**)*

Yield: 91%; m.p. 108–110 °C; ^1H NMR ($CDCl_3$): δ 8.95 (bs, 1H, NH), 3.91 (m, 1H, CH), 3.49 (bs, 2H, NH_2), 2.96 (m, 1H, CH), 1.32 (m, 6H, 2 × CH_3), 1.27 (m, 6H, 2 × CH_3); APCIMS: *m/z* 211 (M + 1); Anal. $C_{10}H_{18}N_4O$ (C, H, N).

*9.3. 2-tert-Butyl-1*H*-4-imidazole carbohydrazide (**3c**)*

Yield: 91%; m.p. 159–160 °C; ^1H NMR ($CDCl_3$): δ 8.80 (bs, 1H, NH), 7.56 (s, 1H, 5-H), 3.49 (bs, 2H, NH_2), 1.25 (s, 9H, 3 × CH_3); APCIMS: *m/z* 183 (M + 1); Anal. $C_8H_{14}N_4O$ (C, H, N).

*9.4. 2,5-Di-tert-butyl-1*H*-4-imidazole carbohydrazide (**3d**)*

Yield: 78%; m.p. 76–78 °C; ^1H NMR ($CDCl_3$): δ 8.55 (bs, 1H, NH), 3.48 (bs, 2H, NH_2), 1.48 (s, 9H, 3 × CH_3), 1.25 (s, 9H, 3 × CH_3); APCIMS: *m/z* 239 (M + 1); Anal. $C_{12}H_{24}N_4O$ (C, H, N).

*9.5. 2-Cyclopentyl-1*H*-4-imidazole carbohydrazide (**3e**)*

Yield: 92%; m.p. 228–230 °C; ^1H NMR ($CDCl_3$): δ 8.21 (bs, 1H, NH), 7.43 (s, 1H, 5-H), 3.75 (bs, 2H, NH_2), 2.75 (m, 1H, CH), 1.81 (m, 8H, 4 × CH_2); APCIMS: *m/z* 195 (M + 1); Anal. $C_9H_{14}N_4O$ (C, H, N).

*9.6. 2,5-Dicyclopentyl-1*H*-4-imidazole carbohydrazide (**3f**)*

Yield: 93%; m.p. 118–120 °C; ^1H NMR ($CDCl_3$): δ 8.35 (bs, 1H, NH), 3.95 (bs, 2H, NH_2), 2.77 (m, 1H, CH), 2.33 (m, 1H, CH), 1.80 (m, 16H, 8 × CH_2); APCIMS: *m/z* 263 (M + 1); Anal. $C_{14}H_{22}N_4O$ (C, H, N).

*9.7. 2-Cyclohexyl-1*H*-4-imidazole carbohydrazide (**3g**)*

Yield: 93%; m.p. 82–84 °C; ^1H NMR ($CDCl_3$): δ 8.25 (bs, 1H, NH), 7.51 (s, 1H, 5-H), 4.01 (bs, 2H, NH_2), 2.71 (m, 1H, CH), 1.61 (m, 10H, 5 × CH_2); APCIMS: *m/z* 209 (M + 1); Anal. $C_{10}H_{16}N_4O$ (C, H, N).

*9.8. 2,5-Dicyclohexyl-1*H*-4-imidazole carbohydrazide (**3h**)*

Yield: 93%; m.p. 218–219 °C; ^1H NMR ($CDCl_3$): δ 8.60 (bs, 1H, NH), 3.92 (bs, 2H, NH_2), 3.54 (m, 1H, CH), 2.63 (m, 1H, CH), 1.65 (m, 20H, 10 × CH_2); ESIMS: *m/z* 291 (M + 1); Anal. $C_{16}H_{26}N_4O$ (C, H, N).

*9.9. 2-Adamantan-1-yl-1*H*-4-imidazole carbohydrazide (**3i**)*

Yield: 96%; m.p. 116–117 °C; ^1H NMR ($CDCl_3$): δ 8.08 (bs, 1H, NH), 7.51 (s, 1H, 5-H), 3.82 (bs, 2H, NH_2), 1.94 (m, 15H, adamantyl protons); APCIMS: *m/z* 261 (M + 1); Anal. $C_{14}H_{20}N_4O$ (C, H, N).

*9.10. 2,5-Diadamantan-1-yl-1*H*-4-imidazole carbohydrazide (**3j**)*

Yield: 98%; m.p. 144–145 °C; ^1H NMR ($CDCl_3$): δ 8.59 (bs, 1H, NH), 3.82 (bs, 2H, NH_2), 1.93 (m, 30H, adamantyl protons); ESIMS: *m/z* 395 (M + 1); Anal. $C_{24}H_{34}N_4O$ (C, H, N).

10. General procedure for the synthesis of 2-adamantan-1-yl and 2,5-diadamantan-1-yl-1*H*-imidazole-4-carboxylic acid alkylidene/ benzylidene-hydrazides (4a–f)

A mixture of 2-adamantan-1-yl-1*H*-imidazole carbohydrazide (**3i**, 1 mmol) or 2,5-diadamantan-1-yl-1*H*-imidazole carbohydrazide (**3j**, 1 mmol) and the appropriate commercially available aldehyde (1 mmol) in ethanol (2 ml) was heated at reflux for 2 h. Solvent was removed under reduced pressure and crude product purified on silica using EtOAc/hexanes (40:60) to afford 2-adamantan-1-yl-1*H*-imidazole-4-carboxylic acid alkylidene/benzylidene-hydrazides (**4a–d**) and 2,5-diadamantan-1-yl-1*H*-imidazole-4-carboxylic acid alkylidene/benzylidene-hydrazides (**4e–f**) in good yields.

*10.1. 2-Adamantan-1-yl-1*H*-imidazole-4-carboxylic acid isobutylidene-hydrazide (**4a**)*

Yield: 55%; m.p. 111–112 °C; ^{1}H NMR ($CDCl_3$): δ 7.65 (s, 1H, CH), 7.50 (s, 1H, 5-H), 5.10 (bs, 1H, NH), 2.70 (m, 1H, CH), 1.80 (m, 15H, adamantyl protons), 0.90 (m, 6H, 2 × CH_3); ESIMS: *m/z* 315 (M + 1); Anal. $C_{18}H_{26}N_4O$ (C, H, N).

*10.2. 2-Adamantan-1-yl-1*H*-imidazole-4-carboxylic acid benzylidene-hydrazide (**4b**)*

Yield: 75%; m.p. 171–173 °C; ^{1}H NMR ($CDCl_3$): δ 8.20 (s, 1H, CH), 8.10 (s, 1H, 5-H), 7.76 (m, 2H, Ar–H), 7.39 (m, 3H, Ar–H), 4.93 (bs, 1H, NH), 1.81 (m, 15H, adamantyl protons); APCIMS: *m/z* 349 (M + 1); Anal. $C_{21}H_{24}N_4O$ (C, H, N).

*10.3. 2-Adamantan-1-yl-1*H*-imidazole-4-carboxylic acid (4-methoxy-benzylidene)hydrazide (**4c**)*

Yield: 57%; m.p. 218–219 °C; ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1H, CH), 7.75 (s, 1H, 5-H), 7.71 (m, 2H, Ar–H), 6.92 (m, 2H, Ar–H), 5.20 (bs, 1H, NH), 3.84 (s, 3H, OCH_3), 1.81 (m, 15H, adamantyl protons); ESIMS: *m/z* 379 (M + 1); Anal. $C_{22}H_{26}N_4O_2$ (C, H, N).

*10.4. 2-Adamantan-1-yl-1*H*-imidazole-4-carboxylic acid pentafluorophenylmethylene-hydrazide (**4d**)*

Yield: 60%; m.p. 97–99 °C; ^{1}H NMR ($CDCl_3$): δ 8.15 (s, 1H, CH), 8.10 (s, 1H, 5-H), 4.46 (bs, 1H, NH), 1.80 (m, 15H, adamantyl protons); APCIMS: *m/z* 439 (M + 1); Anal. $C_{21}H_{19}F_5N_4O$ (C, H, N).

*10.5. 2,5-Diadamantan-1-yl-1*H*-imidazole-4-carboxylic acid isobutylidene-hydrazide (**4e**)*

Yield: 59%; m.p. 112–114 °C; ^{1}H NMR ($CDCl_3$): δ 8.10 (s, 1H, CH), 5.31 (bs, 1H, NH), 3.10 (m, 1H, CH), 1.71 (m, 30H, adamantyl protons), 0.87 (m, 6H, 2 × CH_3); APCIMS: *m/z* 449 (M^+); Anal. $C_{28}H_{40}N_4O$ (C, H, N).

*10.6. 2,5-Diadamantan-1-yl-1*H*-imidazole-4-carboxylic acid (4-methoxy-benzylidene)hydrazide (**4f**)*

Yield: 68%; m.p. 158–159 °C; ^{1}H NMR ($CDCl_3$): δ 8.20 (s, 1H, CH), 7.67 (m, 2H, Ar–H), 6.92 (m, 2H, Ar–H), 5.19 (bs, 1H, NH), 3.83 (s, 3H, OCH_3), 1.40 (m, 30H, adamantyl protons); APCIMS: *m/z* 513 (M + 1); Anal. $C_{32}H_{40}N_4O_2$ (C, H, N).

11. General procedure for synthesis of 2-alkyl and 2,5-dialkyl-1*H*-4-imidazole carboxylic acids (5a–j)

A solution of 2-alkyl or 2,5-dialkyl-1*H*-4-imidazole carboxylic acid ethyl ester (**2a–j**, 1 mmol) in 6 N HCl (5 ml) was heated under reflux for 8 h. 2-Alkyl and 2,5-dialkyl-1*H*-4-imidazole carboxylic acids (**5a–j**) were obtained directly after evaporation of the acids hydrolysis solutions as hydrochloride salts.

*11.1. 2-Isopropyl-1*H*-4-imidazole carboxylic acid hydrochloride (**5a**)*

Yield: 85%; m.p. 171–173 °C (dec.); ^{1}H NMR (DMSO-d_6): δ 7.75 (s, 1H, 5-H), 3.50 (m, 1H, CH), 1.75 (m, 6H, 2 × CH_3); APCIMS: *m/z* 155 (M + 1); Anal. $C_7H_{11}ClN_2O_2$ (C, H, N).

*11.2. 2,5-Diisopropyl-1*H*-4-imidazole carboxylic acid hydrochloride (**5b**)*

Yield: 86%; m.p. 206–207 °C (dec.); ^{1}H NMR (D_2O): δ 3.55 (m, 1H, CH), 2.81 (m, 1H, CH), 0.85 (m, 6H, 2 × CH_3), 0.76 (m, 6H, 2 × CH_3); APCIMS: *m/z* 197 (M + 1); Anal. $C_{10}H_{17}ClN_2O_2$ (C, H, N).

*11.3. 2-tert-Butyl-1*H*-4-imidazole carboxylic acid hydrochloride (**5c**)*

Yield: 80%; m.p. 119–121 °C (dec.); ^{1}H NMR (D_2O): δ 7.78 (s, 1H, 5-H), 1.30 (s, 9H, 3 × CH_3); APCIMS: *m/z* 169 (M + 1); Anal. $C_8H_{13}ClN_2O_2$ (C, H, N).

*11.4. 2,5-Di-tert-butyl-1*H*-4-imidazole carboxylic acid hydrochloride (**5d**)*

Yield: 85%; m.p. 177–179 °C (dec.); ^{1}H NMR (D_2O): δ 1.55 (s, 9H, 3 × CH_3), 1.30 (s, 9H, 3 × CH_3); APCIMS: *m/z* 225 (M + 1); Anal. $C_{12}H_{21}ClN_2O_2$ (C, H, N).

*11.5. 2-Cyclopentyl-1*H*-4-imidazole carboxylic acid hydrochloride (**5e**)*

Yield: 76%; m.p. 127–129 C (dec.); ^{1}H NMR (CD_3OD): δ 7.50 (s, 1H, 5-H), 3.30 (m, 1H, CH), 1.91 (m, 8H, 4 × CH_2); APCIMS: *m/z* 181 (M + 1); Anal. $C_9H_{13}ClN_2O_2$ (C, H, N).

*11.6. 2,5-Dicyclopentyl-1*H*-imidazole-4-carboxylic acid hydrochloride (**5f**)*

Yield: 71%; m.p. 227–229 °C (dec.); ^{1}H NMR (D_2O): δ 4.21 (m, 1H, CH), 2.61 (m, 1H, CH), 1.80 (m, 16H, 8 × CH_2); APCIMS: *m/z* 249 (M + 1); Anal. $C_{14}H_{21}ClN_2O_2$ (C, H, N).

*11.7. 2-Cyclohexyl-1*H*-4-imidazole carboxylic acid hydrochloride (**5g**)*

Yield: 73%; m.p. 169–170 °C (dec.); ^{1}H NMR (CD_3OD): δ 7.72 (s, 1H, 5-H), 2.99 (m, 1H, CH), 1.60 (m, 10H, 5 × CH_2); ESIMS: *m/z* 195 (M + 1); Anal. $C_{10}H_{15}ClN_2O_2$ (C, H, N).

*11.8. 2,5-Dicyclohexyl-1*H*-4-imidazole carboxylic acid hydrochloride (**5h**)*

Yield: 75%; m.p. 171–173 °C; ^{1}H NMR (DMSO-d_6): δ 3.97 (m, 1H, CH), 2.77 (m, 1H, CH), 1.61 (m, 20H, 10 × CH_2); ESIMS: *m/z* 277 (M + 1); Anal. $C_{16}H_{25}ClN_2O_2$ (C, H, N).

*11.9. 2-Adamantan-1-yl-1*H*-4-imidazole carboxylic acid hydrochloride (**5i**)*

Yield: 78%; m.p. 227–229 °C (dec.); ^{1}H, NMR (D_2O): δ 7.84 (s, 1H, 5-H), 1.80 (m, 15H, adamantyl protons); APCIMS: *m/z* 247 (M + 1); Anal. $C_{14}H_{19}ClN_2O_2$ (C, H, N).

*11.10. 2,5-Diadamantan-1-yl-1*H*-4-imidazole carboxylic acid hydrochloride (**5j**)*

Yield: 73%; m.p. 273–274 °C (dec.); ^{1}H NMR (D_2O): δ 1.73 (m, 30H, adamantyl protons); APCIMS: *m/z* 381 (M + 1); Anal. $C_{24}H_{33}ClN_2O_2$ (C, H, N).

12. General procedure for the synthesis of [(2-alkyl/2,5-dialkyl-1*H*-imidazole-4-carbonyl)amino]acetic acid methyl esters (6a–c)

To a solution of 2-alkyl or 2,5-dialkyl-1*H*-imidazole-4-carboxylic acid hydrochloride (**5a,b,i**, 1 mmol) in anhydrous DMF (5 ml) was added glycine methyl ester dihydrochloride (1.1 mmol) followed by triethylamine (1 ml), and reaction mixture stirred for 15 min at 5 °C. 1,3-Dicyclohexylcarbodiimide (1.2 mmol) was added in one portion to the reaction mixture, and stirring continued overnight at ambient temperature. Solvent was removed under reduced pressure, and residue was dissolved in ethyl acetate (25 ml). Organic layer was washed with water (2 × 5 ml) followed with brine (2 × 5 ml), and dried over Na_2SO_4. Evaporation of the organic solvent provided crude product, which was purified by column chromatography using EtOAc/hexanes (50:50) to afford pure compounds (**6a–c**).

*12.1. [(2-tert-Butyl-1*H*-imidazole-4-carbonyl)amino]acetic acid methyl ester (**6a**)*

Yield: 33%; m.p. 178–180 °C; ^{1}H NMR ($CDCl_3$): δ 9.19 (bs, 1H, NH), 7.51 (s, 1H, 5-H), 3.77 (s, 2H, CH_2), 3.48 (s, 3H, OCH_3), 1.30 (s, 9H, 3 × CH_3); APCIMS: *m/z* 240 (M + 1); Anal. $C_{11}H_{17}N_3O_3$ (C, H, N).

*12.2. [(2,5-Di-tert-butyl-1*H*-imidazole-4-carbonyl)amino] acetic acid methyl ester (**6b**)*

Yield: 42%; m.p. 184–185 °C, ^{1}H NMR ($CDCl_3$): δ 8.58 (bs, 1H, NH), 3.76 (s, 2H, CH_2), 3.49 (s, 3H, OCH_3), 1.67 (s, 9H, 3 × CH_3), 1.36 (s, 9H, 3 × CH_3); APCIMS: *m/z* 296 (M + 1); Anal. $C_{15}H_{25}N_3O_3$ (C, H, N).

*12.3. [(2-Adamantan-1-yl-1*H*-imidazole-4-carbonyl)amino] acetic acid methyl ester (**6c**)*

Yield: 50%; m.p. 211–213 °C; ^{1}H NMR ($CDCl_3$): δ 9.18 (bs, 1H, NH), 7.55 (s, 1H, 5-H), 3.77 (s, 2H, CH_2), 3.48 (s, 3H, OCH_3), 1.64 (m, 15H, adamantyl protons); APCIMS: *m/z* 318 (M + 1); Anal. $C_{17}H_{23}N_3O_3$ (C, H, N).

13. Synthesis of 3-(1*H*-imidazol-4-yl)acrylic acid methyl ester (8)

To a chilled solution of 3-(1*H*-imidazol-4-yl)acrylic acid (**7**, 3.6 mmol) in anhydrous methanol (200 ml), a slow continuous stream of dry HCl gas was passed for 1 h. Reaction mixture was left overnight at ambient temperature. Solvent was evaporated under reduced pressure to yield **8** as hydrochloride salt.

Yield: 98%; m.p. 213–214 °C (dec.); IR (KBr): 1711 cm^{-1}; ^{1}H NMR (D_2O): δ 7.70 (s, 1H, 2-H), 7.61 (d, 1H, *J* = 15.7 Hz, CH), 7.27 (s, 1H, 5-H), 6.49 (d, 1H, *J* = 15.7 Hz, CH), 3.78 (s, 3H, OCH_3); EIMS: *m/z* 152 (M^+); Anal. $C_7H_8N_2O_2$ (C, H, N).

14. Synthesis of 3-(1*H*-imidazol-4-yl)propionic acid methyl ester (9)

To a solution of 3-(1*H*-imidazol-4-yl)acrylic acid methyl ester (**8**, 3.3 mmol) in methanol (75 ml) was added 10% Pd–C (250 mg) and triethylamine (1 ml). The reaction mixture was hydrogenated at ambient temperature and atmospheric pressure for 24 h. Catalyst filtered through a pad of celite, and filtrate was evaporated under reduced pressure to afford **9** as oil. Yield: 93%; oil; IR ($CHCl_3$) 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.55 (s, 1H, 2-H), 6.80 (s, 1H, 5-H), 3.80 (s, 3H, OCH_3), 2.68 (t, 2H, *J* = 7.0 Hz, CH_2), 2.93 (t, 2H, *J* = 7.0 Hz, CH_2); EIMS: *m/z* 154 (M^+); Anal. $C_7H_{10}N_2O_2$ (C, H, N).

15. General method for the synthesis of 3-(2-alkyl-1*H*-imidazol-4-yl)propionic acid methyl esters (10a–c)

3-(1*H*-Imidazol-4-yl)propionic acid methyl ester (**9**, 1 mmol), was added to a mixture of silver nitrate (0.6 mmol) and alkylcarboxylic acid (3 mmol) in 10% H_2SO_4 (10 ml) while reaction mixture was heated to 70–80 °C. A freshly prepared solution of ammonium persulfate (3 mmol) in water (5 ml) was added drop wise over 10 min. The heating source

was removed and reaction proceeded with evolution of carbon dioxide. After the effervescence ceases, the reaction was terminated by pouring it onto ice. The resulting mixture was made alkaline with 30% ammonia solution, and extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with brine (2 × 20 ml) and dried over Na_2SO_4.The solvent was removed under reduced pressure to afford oil, which upon flash column chromatography over silica gel using ethyl acetate/hexane (70:30) gave compounds **10a–c** in 9–36% yield.

*15.1. 3-(2-Cyclopentyl-1*H*-imidazol-4-yl)propionic acid methyl ester (**10a**)*

Yield: 9%; oil; IR ($CHCl_3$): 1731 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.64 (s, 1H, 5-H), 3.68 (s, 3H, OCH_3), 3.30 (m, 1H, CH), 2.87 (t, 2H, *J* = 6.9 Hz, CH_2), 2.64 (t, 2H, *J* = 6.9 Hz, CH_2), 1.88 (m, 8H, 4 × CH_2); EIMS: *m/z* 222 (M^+); Anal. $C_{12}H_{18}N_2O_2$ (C, H, N).

*15.2. 3-(2-Cyclohexyl-1*H*-imidazol-4-yl)propionic acid methyl ester (**10b**)*

Yield: 10%; oil; IR ($CHCl_3$): 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.64 (s, 1H, 5-H), 3.68 (s, 3H, OCH_3), 3.30 (m, 1H, CH), 2.87 (t, 2H, *J* = 7.1 Hz, CH_2), 2.65 (t, 2H, *J* = 7.1 Hz, CH_2), 1.90 (m, 10H, 5 × CH_2); ESIMS: *m/z* 237 (M + 1); Anal. $C_{13}H_{20}N_2O_2$ (C, H, N).

*15.3. 3-(2-Adamantan-1-yl-1*H*-imidazol-4-yl)propionic acid methyl ester (**10c**)*

Yield: 36%; m.p. 76–78 °C; IR (KBr): 1742 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.67 (s, 1H, 5-H), 3.69 (s, 3H, OCH_3), 2.88 (t, 2H, *J* = 6.8 Hz, CH_2), 2.64 (t, 2H, *J* = 6.8 Hz, CH_2), 1.93 (m, 15H, adamantyl protons); CIMS (CH_4): *m/z* 289 (M + 1); Anal. $C_{17}H_{24}N_2O_2$ (C, H, N).

16. General method for the synthesis of 3-(2-alkyl-1*H*-imidazol-4-yl)propionic acids (11a–c)

A solution 3-(2-alkyl-1*H*-imidazol-4-yl)propionic acid methyl ester (**10a–c**, 1 mmol) in 6 N HCl (5 ml) was heated under reflux for 8 h. The solvent was evaporated under reduced pressure to afford **11a–c** as the hydrochloride salt.

*16.1. 3-(2-Cyclopentyl-1*H*-imidazol-4-yl)propionic acid hydrochloride (**11a**)*

Yield: 90%; m.p. 82–84 °C (dec.); IR (KBr): 1666 cm^{-1}; ^1H NMR (CD_3OD): δ 7.20 (s, 1H, 5-H), 3.21 (m, 1H, CH), 2.91 (t, 2H, *J* = 6.9 Hz, CH_2), 2.68 (t, 2H, *J* = 6.9 Hz, CH_2), 1.85 (m, 8H, 4 × CH_2); ESIMS: *m/z* 209 (M + 1); Anal. $C_{11}H_{17}ClN_2O_2$ (C, H, N).

*16.2. 3-(2-Cyclohexyl-1*H*-imidazol-4-yl)propionic acid hydrochloride (**11b**)*

Yield: 85%; m.p. 76–78 °C (dec.); IR (KBr): 1666 cm^{-1}; ^1H NMR (CD_3OD): δ 7.15 (s, 1H, 5-H), 3.10 (m, 1H, CH), 2.95 (t, 2H, *J* = 6.9 Hz, CH_2), 2.70 (t, 2H, *J* = 6.9 Hz, CH_2), 1.86 (m, 10H, 5 × CH_2); ESIMS: *m/z* 223 (M + 1); Anal. $C_{12}H_{19}ClN_2O_2$ (C, H, N).

*16.3. 3-(2-Adamantan-1-yl-1*H*-imidazol-4-yl)propionic acid hydrochloride (**11c**)*

Yield: 87%; m.p. 73–74 °C (dec.); IR (KBr): 1695 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.59 (s, 1H, 5-H), 2.49 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 1.87 (m, 15H, adamantyl protons); ESIMS: *m/z* 275 (M + 1); Anal. $C_{16}H_{23}ClN_2O_2$ (C, H, N).

17. General method for the synthesis of 3-(2-adamantan-1-yl-1*H*-imidazol-4-yl)-*N*-alkyl-propionamides (12a–c)

To an ice cooled stirred solution of 3-(2-adamantan-1-yl-1*H*-imidazol-4-yl)propionic acid (**11c**, 1.8 mmol) and alkyl amine (2.7 mmol) in dichloromethane (5 ml), 1,3-dicyclohexylcarbodiimide (2.7 mmol) was added in one portion. The reaction mixture was allowed to attain room temperature and stirring continued for another 4 h. The reaction mixture was kept in refrigerator overnight, and separated 1,3-dicyclohexylurea (DCU) was filtered. The filtrate was concentrated under reduced pressure, and ethyl acetate (50 ml) was added to the residue. The additional separated DCU was filtered, and the filtrate was washed with saturated $NaHCO_3$ solution (3 × 10 ml), water (2 × 10 ml) and dried over Na_2SO_4. Solvent removed in vacuo to yield crude product that was purified by flash column chromatography over silica gel (230–400 mesh) using $CH_3OH/CHCl_3$ (2:98) to afford **12a–c** in good yield.

*17.1. 3-(2-Adamantan-1-yl-1*H*-imidazol-4-yl)-*N*-pentylpropionamide (**12a**)*

Yield: 75%; oil; IR ($CHCl_3$): 1680 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.66 (s, 1H, 5-H), 3.30 (t, 2H, *J* = 7.8 Hz, CH_2), 2.91 (t, 2H, *J* = 6.2 Hz, CH_2), 2.73 (t, 2H, *J* = 6.2 Hz, CH_2), 1.79 (m, 6H, 3 × CH_2), 1.18 (m, 15H, adamantyl protons), 0.89 (t, 3H, *J* = 7.8 Hz, CH_3); EIMS: *m/z* 343 (M^+); Anal. $C_{21}H_{33}N_3O$ (C, H, N).

*17.2. 3-(2-Adamantan-1-yl-1*H*-imidazol-4-yl)-*N*-hexylpropionamide (**12b**)*

Yield: 80%; oil; IR ($CHCl_3$): 1677 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.63 (s, 1H, 5-H), 3.27 (t, 2H, *J* = 7.5 Hz, CH_2), 2.95 (t, 2H, *J* = 6.3 Hz, CH_2), 2.71 (t, 2H, *J* = 6.3 Hz, CH_2), 1.72 (m, 8H, 4 × CH_2), 1.14 (m, 15H, adamantyl protons), 0.88 (t, 3H, *J* = 7.8 Hz, CH_3); EIMS: *m/z* 357 (M^+); Anal. $C_{22}H_{35}N_3O$ (C, H, N).

*17.3. 3-(2-Adamantan-1-yl-1*H*-imidazol-4-yl)-*N*-heptylpropionamide (**12c**)*

Yield: 83%; oil; IR ($CHCl_3$): 1673 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.67 (s, 1H, 5-H), 3.29 (t, 2H, *J* = 7.6 Hz, CH_2),

2.90 (t, 2H, J = 6.2 Hz, CH_2), 2.76 (t, 2H, J = 6.2 Hz, CH_2), 1.75 (m, 10H, 5 × CH_2), 1.15 (m, 15H, adamantyl protons), 0.85 (t, 3H, J = 8.0 Hz, CH_3); EIMS: *m/z* 371 (M^+); Anal. $C_{23}H_{37}N{=}O$ (C, H, N).

18. General method for the synthesis of 3-(2-alkyl-1*H*-imidazol-4-yl)propionic acid hydrazides (13a–c)

To a solution of 3-(2-alkyl-1*H*-imidazol-4-yl)propionic acid methyl ester (**10a–c**, 1 mmol) in ethanol (2 ml), hydrazine hydrate (2 ml) was added, and reaction mixture was heated under reflux for 8 h. The hydrazides (**13a–c**) were obtained in quantitative yields directly after evaporation of the reaction solution.

*18.1. 3-(2-Cyclopentyl-1*H*-imidazol-4-yl)propionic acid hydrazide (**13a**)*

Yield: 91%; m.p. 122–124 °C; ^{1}H NMR (CD_3OD): δ 8.07 (bs, 1H, NH), 6.67 (s, 1H, 5-H), 3.10 (m, 1H, CH), 2.87 (t, 2H, J = 7.5 Hz, CH_2), 2.49 (t, 2H, J = 7.5 Hz, CH_2), 2.10 (bs, 2H, NH_2), 1.82 (m, 8H, 4 × CH_2); ESIMS: *m/z* 223 (M + 1); Anal. $C_{11}H_{18}N_4O$ (C, H, N).

*18.2. 3-(2-Cyclohexyl-1*H*-imidazol-4-yl)propionic acid hydrazide (**13b**)*

Yield: 97%; m.p. 117–118 °C; ^{1}H NMR (CD_3OD): δ 8.13 (bs, 1H, NH), 6.65 (s, 1H, 5-H), 3.15 (m, 1H, CH), 2.80 (t, 2H, J = 7.5 Hz, CH_2), 2.47 (t, 2H, J = 7.5 Hz, CH_2), 2.03 (bs, 2H, NH_2), 1.85 (m, 10H, 5 × CH_2); ESIMS: *m/z* 237 (M + 1); Anal. $C_{12}H_{20}N_4O$ (C, H, N).

*18.3. 3-(2-Adamantan-1-yl-1*H*-imidazol-4-yl)-propionic acid hydrazide (**13c**)*

Yield: 95%; m.p. 111–112 °C; ^{1}H NMR (CD_3OD): δ 8.20 (bs, 1H, NH), 6.62 (s, 1H, 5-H), 2.83 (t, 2H, J = 7.5 Hz, CH_2), 2.43 (t, 2H, J = 7.5 Hz, CH_2), 2.11 (bs, 2H, NH_2), 1.89 (m, 15H, adamantyl protons); ESIMS: *m/z* 289 (M + 1); Anal. $C_{16}H_{24}N_4O$ (C, H, N).

19. Microbiological assays

19.1. Broth microdilution assay

A loop full of *M. tuberculosis H37Rv* strain (ATCC 27294, susceptible both to rifampin and isoniazid) from Lowenstein–Jensen slants was inoculated into 100 ml of 7H9 broth medium (7H9 medium supplemented with 10% ADC and 0.001% Tween 80), and incubated at 37 °C for two weeks. Two days before the susceptibility testing, the culture was diluted 1:10 in fresh 7H9 broth medium. After two days, the culture was ultrasonicated to make a single cell suspension, and further diluted 1:10 in 7H9 broth just prior to the inoculation of microdilution tubes. This procedure yielded an actively growing culture, which reproducibly contained 5 × 106 CFU/ml as determined by plating. The stock solutions of the compounds were prepared in DMSO diluted 1:3 times in 7H9 broth. Further, serial twofold dilutions of the compounds were prepared from the stock solutions in 7H9 broth medium to provide the final concentrations of 4.0, 2.0, 1.0, 0.5, and 0.25 μg/ml. The same concentrations were tested for isoniazid (INH), which was taken as the positive control. The autoclaved microdilution tubes contained 1600 μl 7H9 broth medium, 200 μl of drug dilution, and 200 μl of 1:10 times diluted and ultrasonicated *M. tuberculosis* inocula. All the test tubes were tightly screw-capped and incubated at 37 °C for 14 days. The tubes were checked for the surface growth layer. The MIC was defined as the lowest concentration of test compounds at which the surface growth layer could not be observed. The negative controls included 7H9 broth with no drug and with equivalent amounts of DMSO as the experimental tubes. DMSO did not inhibit the growth of *M. tuberculosis* in the concentrations used for dissolving the compounds.

References

[1] D.B. Young, Nature 393 (1998) 515–516.
[2] L.A. Mitscher, W. Baker, Med. Res. Rev. 98 (1998) 363–374.
[3] E. Manoharam, K.R. John, A. Joseph, K.S. Jacob, Ind. J. Tub. 48 (2001) 77–80.
[4] S.H.E. Kaufmann, Nature Rev. Immun. 1 (2001) 20–30.
[5] D.E. Schraufnagel, Int. J. Tuber. Lung. Dis. 3 (1999) 651–662.
[6] R. Jain, B. Vaitilingam, A. Nayyar, P.B. Palde, Bioorg. Med. Chem. Lett. 13 (2003) 1051–1054.
[7] S. Vangapandu, M. Jain, R. Jain, S. Kaur, P.P. Singh, Bioorg. Med. Chem. 12 (2004) 2501–2508.
[8] T.Y. Shen, A. Matzuk, C.P. Dorn, Chem. Abstr. 71 (1969) 61386t US Patent 3,438,992, 1969.
[9] F. Minisci, R. Bernardi, F. Bertini, R. Galli, M. Perchinummo, Tetrahedron 27 (1971) 3575–3579.
[10] R. Jain, L.A. Cohen, Tetrahedron 53 (1997) 2365–2370.
[11] R. Jain, L.A. Cohen, Tetrahedron 53 (1997) 4539–4548.
[12] S. Narayanan, S. Vangapandu, R. Jain, Bioorg. Med. Chem. Lett. 11 (2001) 1133–1136.
[13] L. Collins, S.G. Franzblau, Antimicrob. Agents Chemother. 41 (1997) 1004–1009.