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Design, Synthesis and Structure–Activity Relationship Studies of Novel 4,4-Bis(trifluoromethyl)imidazolines as Acyl-CoA: Cholesterol Acyltransferase (ACAT) Inhibitors and Antihypercholesterolemic Agents

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Abstract—Novel 4,4-bis(trifluoromethyl)imidazolines have been found to be the potent acyl-CoA cholesterol acyltransferase (ACAT) inhibitors. ACAT is responsible for cholesterol esterification in the intestine, liver, and the arterial wall. These novel imidazolines also inhibit cholesterol ester formation in the macrophage. Several compounds have shown potent serum cholesterol-lowering activity in several animal models. *Para*-substitution of the 2-phenyl is critical for in vitro and in vivo activity. The 4,4-bis(trifluoromethyl)imidazolines with a *para*-cyano group on 2-phenyl and a 4-alkylcyclohexyl amide as the side-chain at the 5-position possess the most potent inhibitory activity in this series. Based on biochemical studies, this series acts as a competitive inhibitor with respect to cholesterol binding at the enzyme, which distinguishes it from most of the ACAT inhibitors discovered to date. Preliminary biological studies supported by X-ray crystal structures, molecular modeling, and structure–activity relationship (SAR) studies suggest that this series may be a cholesterol mimic. © 1997 The DuPont Merck Pharmaceutical Company. Published by Elsevier Science Ltd.

Introduction

Arteriosclerosis, which is the underlying cause of most myocardial infractions, is one of the major cardiovascular diseases in Western countries. Atherosclerosis is the most common sclerosis among three types of arteriosclerosis. An excess accumulation of cholesteryl esters in macrophages and smooth muscle cells in the arterial wall is one of the important factors that causes atherosclerosis. Considerable effort has been directed toward the development of effective hypocholesterolemic agents, and those that control the level of serum cholesterol have proven to be effective in the treatment of atherosclerosis.[1,2] It is known that there are three major sources for the hepatic cholesterol pool: absorption of intestinal cholesterol from the diet and hepatic secretion,[3] LDL uptake from plasma via the LDL receptor, and de novo biosynthesis. Since Acyl-CoA: cholesterol acyltransferase (ACAT)[4,5] is responsible for cholesterol esterification in the intestine, liver, and arterial wall, inhibition of ACAT should have beneficial effects on plasma cholesterol via the prevention of the absorption of dietary cholesterol in the intestine.[8] Systemic ACAT inhibitors may also inhibit foam cell formation in the arterial wall and thus should prevent cholesteryl ester deposition in the macrophage and promote cholesterol efflux,[7] thereby preventing the progression of atherosclerosis.

Although many compounds have been reported as potent ACAT inhibitors during recent years,[1,8–11] much of the attention has focused on amide or urea mimics of the long fatty acid chain. The majority of these compounds are poorly or erratically absorbed orally in the animal. Melinamide (Fig. 1) has a typical structure of those ACAT inhibitors and gives 7–10% reduction of serum cholesterol in hyperlipidemic patients at a dose of 2.25 g/day for 16 weeks and a 20% reduction was observed after six-months' dosing.[12,13] To date, melinamide is the only marketed ACAT inhibitor and is sold by Sumimoto in Japan for the treatment of hypercholesterolemia.[14,15]

We reported[16] that compound **1** and its *R*-enantiomer, **1a**, were stereospecific, systemically active ACAT inhibitors with high oral bioavailability. In this paper we detail the synthesis and structure–activity relationship and in vivo activities of this new class of ACAT inhibitor. We have also extended the scope of structures by variation of the 5-side-chain using extensive molecular modeling studies based on the hypothesis that they are cholesterol mimics. Compound **12b** has been found to be about 20-fold more potent in the in vitro ACAT assay and sixfold more potent in the in vitro J774

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macrophage assay than the previous lead compounds **1** and **1a**.

Results and Discussions

Imidazolines **3a–d** (Scheme 1) were synthesized by a general procedure of oxidative ring cleavage of imidazole **2a–d** by using *m*CPBA or singlet oxygen and subsequent acid-catalyzed dehydrocyclization, which was discovered recently in this laboratory.[17] For *N*-1 unsubstituted imidazoles **2d**, only *m*CPBA was able to provide the desired product **3d** in low yield. Compound **3d** was alkylated with alkyl halides in the presence of NaH in DMF to give **3e–f**. The *exo*-acylimine double bond of **3a** was reduced by $LiAlH_4$ to give **4a** as the only product in 96% yield. When sodium borohydride was used for the reduction of **4a**, a mixture of **4a** and **5** was obtained in 40 and 25% isolated yields, respectively. Alkylation of **4a** with CH_3I furnished the amide **6a** in 94% yield. Reduction of **3e** and **3f** with $LiAlH_4$ followed by methylation, provided **6b** and **6c**.

Treatment of the *para*-fluoro imidazoline **6a** with anhydrous KCN or LiCN and K_2CO_3 in DMSO at 110–140 °C provided the dicyano-substituted imidazoline **1** (Scheme 2). Mono-substituted cyano compounds **7a** and **9g** were also isolated in this reaction when the reaction time was less than 12 h. We found that the *para*-fluorine groups in this series could be displaced by a variety of nucleophiles such as alkoxides, and primary and secondary amines to give **7b** and **7c** in good yield.

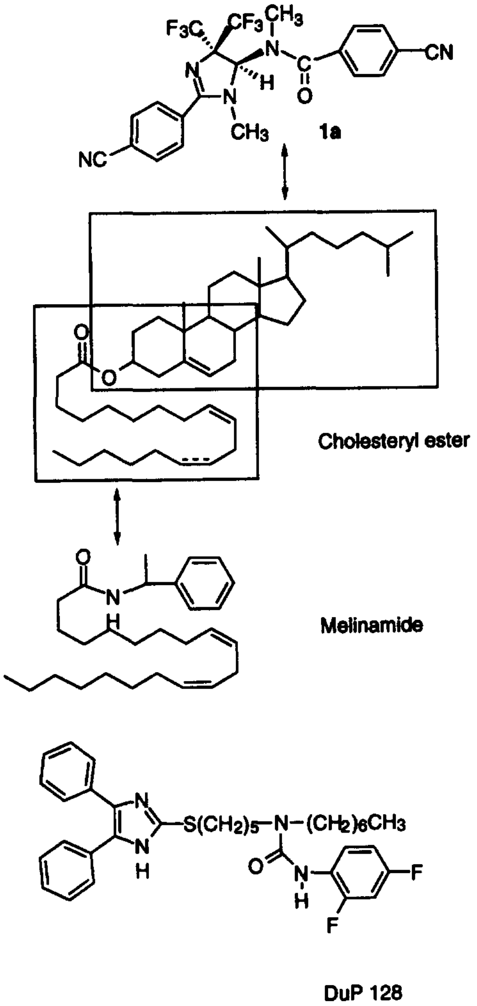
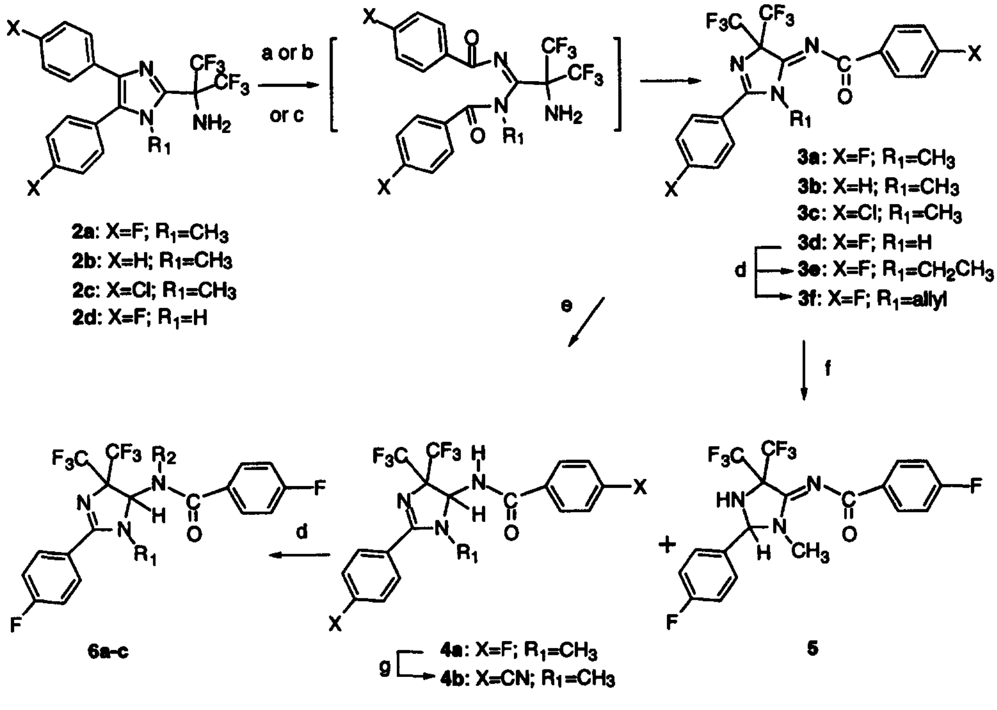
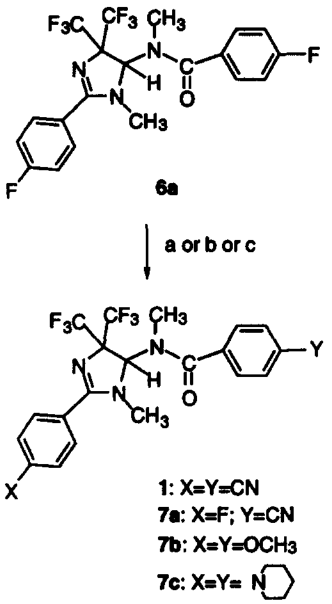


Figure 1.



Scheme 1. Reagents: (a) *m*CPBA, $CHCl_3$, reflux; (b) *m*CPBA, CH_2Cl_2, reflux; (c) (i) oxygen or air, methylene blue, CH_3OH, $CHCl_3$; (ii) HCl in ether; (d) NaH/DMF, alkyl halides; (e) $LiAlH_4$, THF; (f) $NaBH_4$, CH_3OH; (g) LiCN/DMF, KI, K_2CO_3, DMSO, 130–140 °C.

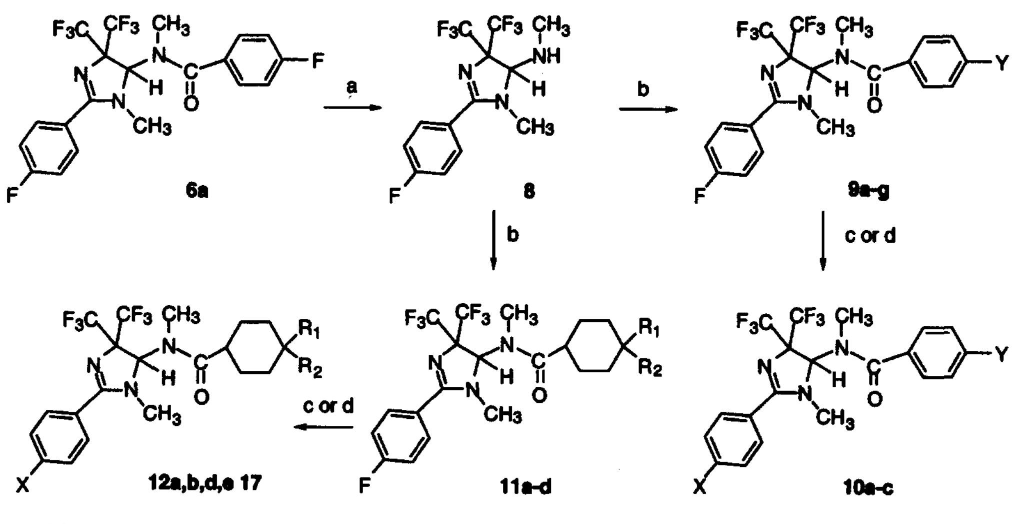


Scheme 2. Reagents: (a) KCN, KI, K_2CO_3, DMSO, 130–140 °C; (b) CH_3ONa, CH_3OH, reflux; (c) piperidine, K_2CO_3, DMSO, 120–140 °C.

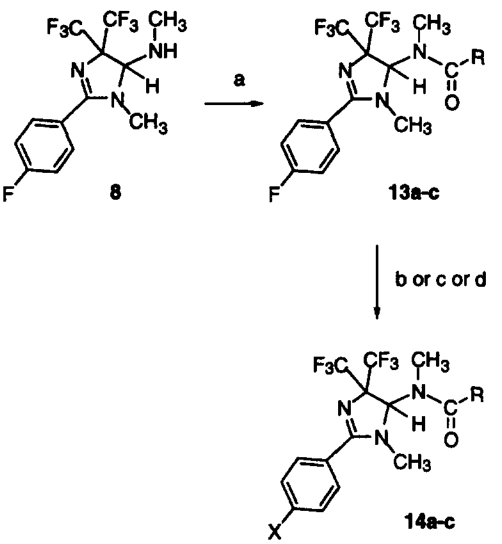
Treatment of 6a with 6 equiv of potassium *tert*-butoxide and 2 equiv of water in ether[18] with vigorous stirring at room temperature gave the corresponding aminal **8** in 98% yield (Scheme 3). This compound was unstable under basic conditions but was stable as the HCl salt. Reaction of the free base or HCl salt of **8** with a series of *p*-substituted benzoyl chlorides or 4-substituted cyclohexanecarbonyl chlorides in the presence of base, generated a series of analogs with different *para*-substituted phenyl (**9a–g**) or 4-substituted cyclohexyl groups (**11a–d**) on the amide side chain. Aminal **8** was also converted to a variety of analogs by treating it with different acyl chlorides to give **13a–c**, which can be further derivatized by nucleophilic displacement of fluorine to give **14a–c** (Scheme 4). All the *para*-fluoro substituted compounds could then be converted to the corresponding *para*-cyano substituted compounds by treating with a LiCN/DMF solution or KCN in DMSO in the presence of base. The amide side chain of cyano-substituted analogs (**1** and **7a**) were also hydrolyzed to give the *para*-cyano substituted imidazoline aminal **15**, which was subsequently derivatized to **16a–h** with different acyl chlorides (Scheme 5).

The compounds **3a–f** (Table 1) with an *exo* imine double bond at the 5-position of imidazoline, showed only moderate activities in both ACAT in vitro and J774 macrophage assays. The substitution at *N*-1 was crucial for the potency of this series. The non-substituted compound (**3d**, R = H) was inactive in the ACAT in vitro assay due to the strong hydrogen bonding between the NH and the carbonyl group on the side chain. This interaction forces the side chain to bend out the position from the cholesterol side chain.[17b] *N*-Substituted derivatives **3a** and **3e–f** showed a moderate increase in ACAT inhibitory activity, due to the fact that **3a** and **3e–f** overlap with cholesterol better than **3d**. When both of the in vitro assays were run with loaded free cholesterol, compound **3a** showed increases in IC_{50} from 20 to 66 μM in the ACAT in vitro assay and from 38 to 100 μM in the J774 assay. This suggested that **3a** might be a competitive inhibitor with respect to cholesterol binding at the ACAT active site. Compound **3a** also showed moderate oral activities in both cholesterol-fed hamster and normolipemic hamster (Table 2). Compound **3a** caused a dose-dependent increase in serum triglycerides. The biological significance of this observation is unclear because of the wide variation historically observed with this lipid fraction. One possible cause of the increase in serum triglycerides may be the decrease of triglyceride transport while inhibiting the ACAT activity.

Reduction of the acylimine to the amide enabled the benzoyl side chain to be relieved from the fixed *cis* configuration. Compounds **4a** and **4b** were very weak ACAT inhibitors in the ACAT in vitro assay and



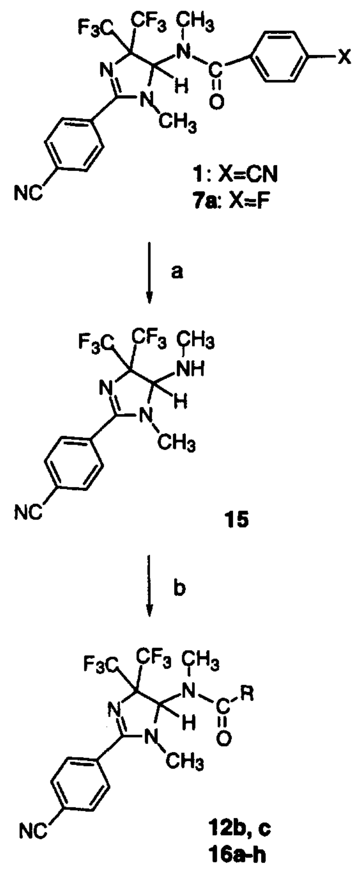
Scheme 3. Reagents: (a) KOBu-*t*, H_2O, ether; (b) RCOCl, pyridine or triethylamine, DMAP, CH_2Cl_2, or CH_2ClCH_2Cl; (c) piperidine, K_2CO_3, DMSO, 120–140 °C; (d) LiCN/DMF, KI, K_2CO_3, DMSO, 130–140 °C; (e) H_2O_2, K_2CO_3, CH_3CH_2OH, DMSO.



Scheme 4. Reagents: (a) RCOCl, pyridine or triethylamine, DMAP, CH_2Cl_2; (b) LiCN/DMF, KI, K_2CO_3, DMSO, 130–140 °C; (c) CH_3ONa, CH_3OH, reflux; (d) piperidine, K_2CO_3, DMSO, 120–140 °C.

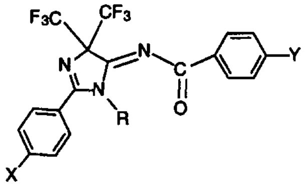
completely inactive in the J774 macrophage assay. This dramatic loss in activity was presumably due to the newly formed acidic hydrogen in the amide moiety, which was absent in cholesterol. The *N*-methyl analogue (**6a**) was able to retain moderate activities in both in vitro assays (Table 3). It appeared that the activity was relatively insensitive to the size of alkyl groups at the *N*-1 position, but both nitrogens at the *N*-1 position, and the side-chain amide had to be fully substituted. Substitutions on both phenyl groups had dramatic effects on biological activities. In general, compounds with *para*-cyano on 2-phenyl were more active than those with *para*-fluoro substituted analogs. It was possible that the cyano group formed a stronger hydrogen bond with the enzyme (ACAT) at the corresponding 3-hydroxyl position of cholesterol. Hetero-atom substitution such as methoxy (**7b**) and piperidyl (**7c**) gave good in vitro activity, but did not generate reasonable blood levels in the rabbits and thus were very weak or inactive in vivo.

The conformationally more flexible analogs with an acyclic carbon chain (**13a–b**) showed a slight improvement in the in vitro ACAT activity but not the in vitro J774 activity (Table 4). Methoxy, piperidinyl, and cyano substitutions at the *para* position on the phenyl group of those compounds with a long fatty side chain (**14b–c**, **16c**) did not improve the activity at all. On the other hand, the steric bulky adamantane analogue**16d** showed significant improvement on the activity in the in vitro ACAT assay. Computer modeling showed that conformationally restrained cyclohexyl side chain with *n*-propyl at the 4-position resembles the cholesterol side chain better than the substituted benzamide side chains (Fig. 2). Single-crystal X-ray structures showed a significant conformational difference of the side chain between benzamide **9b** (Fig. 3) and cyclohexanecarboxamide **11c** (Fig. 4). The substituent size at the 4-position



Scheme 5. Reagents: (a) KOBu-*t*, H_2O, ether; (b) RCOCl, pyridine or triethylamine, DMAP, CH_2Cl_2.

Table 1. Effect on the in vitro ACAT and J774 inhibition by *N*-1 substitution



Compd	X	Y	R	ACAT IC_{50}, μM[a]	J774 IC_{50}, μM[b]
3a	F	F	CH_3	20	38
3a	F	F	CH_3	66[c]	100[d]
3b	H	H	CH_3	76	Inactive
3c	Cl	Cl	CH_3	19.8	59.9
3d	F	F	H	Inactive	38
3e	F	F	CH_2CH_3	10.8	32.1

[a] In vitro rat liver microsomal ACAT inhibition.[19,20] IC_{50} values were determined from assays performed in duplicate containing a minimum of four inhibitor concentrations which bracket the IC_{50}. The average range of replicates was ±17%.

[b] In vitro J774 macrophage cell culture ACAT inhibition.[21-23] The average range of replicates was ±23%.

[c] In vitro rat liver microsomal ACAT inhibition with 25 mM cholesterol.

[d] In vitro cholesterol-loaded J774 macrophage cell culture ACAT inhibition.

Table 2. Effect of **3a** on serum cholesterol

Dose (po)[a] mg/kg/day	Serum cholesterol reduction (%)	Serum triglyceride increase (%)
1[b]	13	29
10[b]	18	36
100[b]	34	128
100[c]	15	40

[a] Male Golden Syrian hamsters ($n = 10$) were orally gavaged with drug suspended in a methylcellulose vehicle. Control animals received vehicle only.

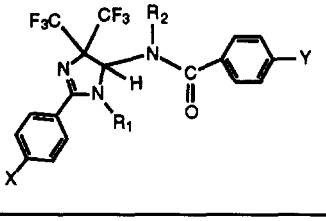
[b] Cholesterol-fed hamsters, 14-day study.

[c] Normolipemic hamsters, no cholesterol in diet, 14-day study.

of cyclohexyl was critical for the activities in both in vitro assays (Table 5). The *n*-propyl group was found to be the best choice with an IC_{50} of 0.09 μM in the in vitro ACAT assay and 2.5 μM in the in vitro J774 macrophage assay. Smaller groups, such as hydrogen or ethyl (**12a** and **16h**), gave little or a slight decrease in the in vitro ACAT activity and a three- to 20-fold decrease in the in vitro J774 macrophage activity. Larger groups, such as *n*-pentyl, *t*-butyl, or spiro[4,5]-decanyl substituted compounds (**12c–e**), had little effect on the in vitro J774 macrophage activity, but some decrease in the in vitro ACAT activity was observed. To our surprise, even the *iso*-propyl-substituted compound (**16g**) was about threefold less potent than **12b** in the in vitro ACAT assay. Oxygen-containing groups, such as OCH_3, were also less potent in the in vitro ACAT assay. It is interesting to note that both *cis* OCH_3 **16e** and *trans* OCH_3 **16f** showed approximately the same activity in the in vitro ACAT assay. The *para*-cyano substituent on 2-phenyl was crucial for ACAT inhibitory activity of this series. Hydrolysis of the cyano group of **12b** to amide **17** caused an approximate 64-fold decrease in the in vitro ACAT activity.

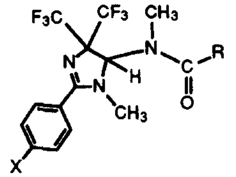
The racemates were resolved into their corresponding enantiomers by chiral HPLC on a Chiralcel OJ column. The absolute stereochemistry of (−)-**1a** and (+)-**1b** was determined by the exciton chirality method based on the exciton-coupled circular dichroism (ECCD) phenomenon.[24–26] The coupling between the two aromatic chromophores in (−)-**1a** gave rise to a positive couplet, thus the chiral center in (−)-**1a** had an *R*-configuration. Vice versa, (+)-**1b** had an *S*-configuration. Compound **12b** was also resolved into its two enantiomers by chiral HPLC. The absolute configurations of (−)-**12g** and (+)-**12h** were not determined at this point. The biological testing results of these pure enantiomers are shown in Table 6. Most of the ACAT activity was found to reside in (−) enantiomers, (−)-**1a** and (−)-**12g**. The high eudismic ratios of the ACAT in vitro IC_{50}s (ranging from 14 to 25) indicated a high degree of stereospecificity in the enzyme inhibition with this series. Molecular modeling studies revealed that the *R*-enantiomers overlap cholesterol structure much better than the *S*-enantiomers.

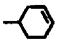
Table 3. Effect on the in vitro ACAT and J774 inhibition by *para*-phenyl substitution



Compd	X	Y	R_1	R_2	ACAT IC_{50}, μM	J774 IC_{50}, μM
1	CN	CN	CH_3	CH_3	1.4–2.0	11.8–19.7
4a	F	F	CH_3	H	41	Inactive
4b	CN	CN	CH_3	H	54.0	Inactive
6a	F	F	CH_3	CH_3	22	105
6b	F	F	CH_2CH_3	CH_3	NTa	44.8
6c	F	F	$CH_2CH{=}CH_2$	CH_3	NTa	81.4
7a	CN	F	CH_3	CH_3	1.6–1.9	34.7–40.0
7b	OCH_3	OCH_3	CH_3	CH_3	9.2	31.0
7c			CH_3	CH_3	8.0	10.7
9a	F	CF_3	CH_3	CH_3	Inactive	NTa
9b	F	OBu-*n*	CH_3	CH_3	2.0	14
9c	F	OCH_3	CH_3	CH_3	6	41.8
9d	F	Bu-*t*	CH_3	CH_3	4.0	18
9e	F	NO_2	CH_3	CH_3	8.0	18.4–28.0
9f	F	Ph	CH_3	CH_3	17	10.8
9g	F	CN	CH_3	CH_3	30.7	47.6
10a	CN	OBu-*n*	CH_3	CH_3	3.0	10.8
10b		Ph	CH_3	CH_3	7.2	8.9
10c	CN	Bu-*t*	CH_3	CH_3	0.8	25.3
16a	CN	OPh	CH_3	CH_3	NT	5.5
16b	CN	OPr-*i*	CH_3	CH_3	2.2	40.0

Table 4. Effect on the in vitro ACAT and J774 inhibition by side-chain substitution



Compd	X	R	ACAT IC_{50}, μM	J774 IC_{50}, μM
13a	F	$-(CH_2)_5CH_3$	2.0	17.0
13b	F	$-(CH_2)_3CH(CH_3)_2$	4.0	36.1
13c	F	$-C_6F_5$	46	35.6
14a	CN		0.77	Inactive
14b		$-(CH_2)_5CH_3$	10	13.4
14c	OCH_3	$-(CH_2)_3CH(CH_3)_2$	9	NT[a]
16c	CN	$-C(CH_3)_2(CH_2)5CH3$	9.9	15.0
16d	CN	$-CH_2-$ 	0.67	32.0

[a]Not tested.

Among all those compounds we have tested so far, we have found that those compounds with the *para*-cyano substitution(s) on the phenyl group(s) showed high blood level following oral administration in general. We further concluded that only those analogs that had good oral bioavailability had antihypercholesterolemic activity in the cholesterol-fed hamster and rabbit. Thus, when compound (−)-**1a** was administered ip to the cholesterol-fed hamster, a greater AHV was found than when administered orally (Table 7). This suggested that this series must be orally absorbed in order to lower total serum cholesterol in the cholesterol-fed hamster, which is not required for most of the known ACAT inhibitors. Dup128 showed no activity at all by ip administration. Both **1** and (−)-**1a** showed greater than 90% AHV suggesting that an essentially complete inhibition of ACAT had been achieved in rabbits. The higher melting polymorph had slightly weaker in vivo activity. This might caused by lower bioavailability of more stable crystals with higher melting point. The *S* enantiomer, (+)-**1b**, showed very weak oral activity in rabbits indicating the nature of high degree stereospecificity in this series again. The stereospecificity extended to the absorption of orally administered racemate **1**. The ratio of the blood concentration of the more active *R*-(−)-**1a** to the *S*-(+)-**1b** remained 5:1 from 1.5 to 48 h following a single oral dose of 25 mg/kg, whereas on iv dosing the ratio of the *R*-(−)-**1a** to the *S*-(+)-**1b** remained 1:1 as determined by chiral HPLC. It is interesting to note that the estimated bioavailability of **1** was about 50%, indicating that only *R*-(−)-**1a** is essentially completely absorbed.

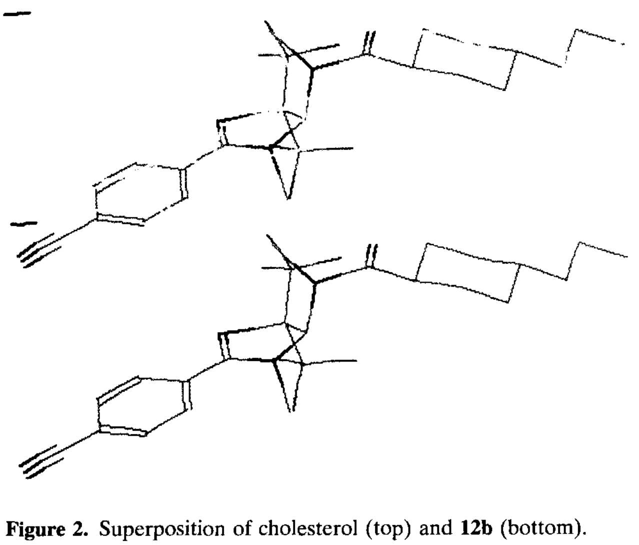


Figure 2. Superposition of cholesterol (top) and **12b** (bottom).

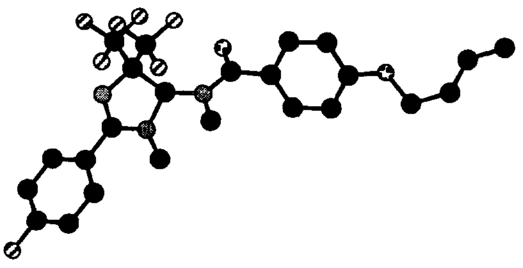
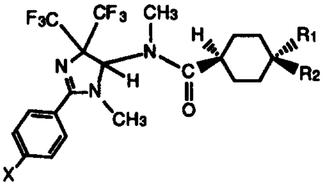


Figure 3. Single-crystal X-ray structure of **9b** (Chem 3-D display based on its PDB file).

Table 5. Effect on the in vitro ACAT and J774 inhibition by cyclohexyl substitution



Compd	X	R_1	R_2	ACATIC$_{50}$ μM	J774IC$_{50}$ μM
11a	F	$(CH_2)_2CH_3$	H	5.0	4.0
11b	F	$(CH_2)_4CH_3$	H	NT	4.0
11c	F	Bu-*t*	H	0.74	1.0
12a	CN	H	H	0.67	49.7
12b	CN	$(CH_2)_2CH_3$	H	0.09	2.5
12c	CN	$-CH_2(CH_2)_2CH_2-$		0.19	8.0
12d	CN	$(CH_2)_4CH_3$	H	0.85	7.0
12e	CN	Bu-*t*	H	0.5	1.0
16e	CN	OCH_3	H	2.6	NT[a]
16f	CN	H	OCH_3	2.0	NT[a]
16g	CN	$CH(CH_3)_2$	H	0.28	NT[a]
16h	CN	CH_2CH_3	H	0.08	NT[a]
17	$CONH_2$	$(CH_2)_2CH_3$	H	5.8	NT[a]

[a] Not tested.

Conclusion

In summary, a structure–activity relationship (SAR) study of a new class of stereospecific, systemic ACAT inhibitors based on 1-alkyl-2-aryl-4,4-bis(trifluoromethyl)imidazolines was conducted, focusing on the *para*-substituents on the 2-phenyl group and the 5-*N*-methylbenzamide side chain or on the 5-*N*-methyl aliphatic carboxamide side chain. A combination of a 2-*p*-cyanophenyl group and a 5-*N*-methyl-*p*-cyanobenzamide side chain gave rise to a very potent antihypercholesterolemic agent with excellent oral bioavailability in the cholesterol-fed hamster and rabbit. The antihypercholesterolemic activity appeared to be the result of a systemic rather than a local effect on the intestinal ACAT. Compound **3a** appeared to be a competitive inhibitor with respect to cholesterol. This result, followed by extensive computer modeling and other biological studies, supported the hypothesis that the series represents a novel cholesterol mimetic.

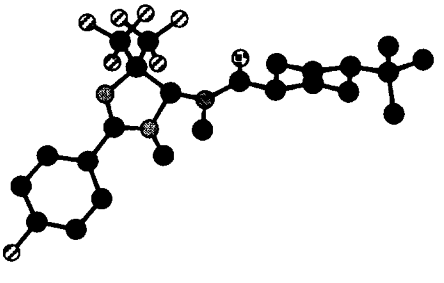


Figure 4. Single-crystal X-ray structure of **11c** (Chem 3-D display based on its PDB file).

Experimental

General

Melting points were measured with a Thomas–Hoover Unimelt apparatus and were uncorrected. IR spectra were obtained on a Perkin–Elmer 1710 series FTIR and were run as KBr pellets. ^1H, ^{19}F, and ^{13}C NMR data were obtained by using a Varian Unity 300 spectrometer. NMR chemical shifts were given in parts per million (ppm) downfield from internal tetramethylsilane (TMS) standard for ^1H NMR, $CDCl_3$ for ^{13}C NMR, and $CFCl_3$ (freon 11) for ^{19}F NMR. ^1H NMR were tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; and c, complex), coupling constant(s) in hertz, and number of protons. High-resolution mass spectra were determined on a Finnegan MAT 8230 spectrometer. Combustion analyses were performed by Quantitative Technologies, Whitehouse, NJ. Solvents and reagents were used as purchased from Aldrich Chemical Co. or other commercial chemical vendors. Column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). All thin layer chromatography (TLC) was performed using E. Merck Kieselgel 60 F_{254} plates with visualization by UV.

General procedure for oxidation of imidazoles (Procedure A)

To a solution of imidazoles **2a–d** (1 equiv) in methylene chloride or chloroform was added portionwise, *m*-chloroperbenzoic acid (*m*CPBA, 80–85%, 3 equiv). The reaction mixture was refluxed under nitrogen for 2–24 h. The solution was cooled to room temperature and

Table 6. Stereospecific in vitro ACAT and J774 inhibition of imidazolines

Compd	Configuration	ACAT IC_{50}, μM	J774 IC_{50}, μM
(−)-**1a**	R	1–2	11.8
(+)-**1b**	S	54.8	54.1
(−)-**12g**	—	0.07	NT[a]
(+)-**12h**	—	1.0	NT[a]

[a] Not tested.

the insoluble solid was filtered off. The organic filtrate was washed successively with satd aqueous sodium sulfite, satd aqueous sodium bicarbonate, and water, dried over anhydrous sodium sulfate, and evaporated under vacuum. The residue was crystallized from methanol–hexane to give the product.

General procedure for *N*-alkylation (Procedure B)

Sodium hydride (1 equiv) 60% suspension in oil was washed with hexane and then it was suspended in anhydrous dimethylformamide. To this suspension was added portionwise *N*-H substrate and the mixture was allowed to stir at room temperature for 1 h. Alkyl iodide or bromide (1.3–2 equiv) was added dropwise and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was poured into water and extracted with ether. The organic layer was washed successively with water and satd aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated to give the product.

General procedure for displacement of aryl fluoro by cyanide (Procedure C)

Potassium iodide (0.5 equiv), potassium carbonate (4–5 equiv), and KCN (powder) or LiCN (0.5 M in DMF, 5–8 equiv) were added to a solution of fluorophenyl derivatives (1 equiv) in dimethyl sulfoxide. The reaction mixture was heated at 135–140 °C for 24–48 h under nitrogen. The solution was cooled to room temperature, poured into water, and extracted with ether. The organic layer was washed with satd aqueous ammonium chloride and satd aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated under vacuum to give the crude product.

General procedure for *N*-acylation (Procedure D)

Acyl chloride (1.2–1.5 equiv) and *N*,*N*-dimethylaminopyridine (DMAP, 0.05 equiv) were added to a solution of 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine hydrogen chloride salt (**8** HCl salt, 1 equiv) or 2-(4-cyanophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**15**, 1 equiv) in dichloromethane and pyridine. The reaction mixture was stirred at room temperature overnight and refluxed for another 1 h under nitrogen. The crude reaction mixture was quenched with water and extracted with ether. The organic layers were washed successively with satd aqueous sodium carbonate, satd aqueous ammonium chloride and brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography eluting with hexane and hexane–ethyl acetate (20:1 to 50:50) to give the product.

Preparation of 4-fluoro-*N*-[2-(4-fluorophenyl)-3,5-dihydro-3-methyl-5,5-bis(trifluoromethyl)-4*H*-imidazol-4-ylidene]benzamide (3a).

Method A. This compound was prepared from α,α-bis(trifluoromethyl)-4,5-bis(4-fluorophenyl)-1-methyl-1*H*-imidazole-2-methanamine (**2a**), following Procedure A described above, as a white solid (71%): mp 112–113 °C; IR (KBr) 1718, 1667, 1595, 1221 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.10 (s, 3H, $NC\underline{H}_3$), 7.16 (t, *J* = 8.7 Hz, 2H), 7.24 (t, *J* = 8.7 Hz, 2H), 7.71 (dd, *J* = 8.7, 5.1 Hz, 2H), 8.02 (dd, *J* = 8.7, 5.5 Hz, 2H); ^{13}C

Table 7. Effect of **1**, **1a**, and **1b** on serum cholesterol

Compd	Animals	Dose mg/kg/day	Dose method	Serum cholesterol[a] reduction (%)	AHV[b] (%)
(−)-**1a**	Hamsters	10	ip[c]	75	77.5
Dup128	Hamsters	10	ip[c]	0	
(−)-**1a**	Hamsters	10	po[c]	63	62.4
(−)-**1a**	Hamsters	10	po[d]	62	
Dup128	Hamsters	10	po[d]	75	
1	Rabbits	2.5	po[c]	79	>90
1[e]	Rabbits	2.5	po[c]	64	
(−)-**1a**	Rabbits	5	po[f]	75	90
(+)-**1b**	Rabbits	5	po[f]	12	15
Dup128	Rabbits	5	po[c]	50	

[a] Blood was obtained from the orbital sinus of each animal and serum cholesterol was analyzed on a Du Pont ACA clinical analyzer.

[b] AHV (%) (antihypercholesterolemic value) is a direct comparison among groups adjusted for differences in an animal's response to dietary cholesterol.

[c] Animals were dosed for seven days.

[d] Animals were dosed for four days.

[e] High melting point polymorph.

[f] Animals were dosed for three days.

NMR (75.4 MHz, $CDCl_3$) δ 172.68, 170.85, 167.74, 166.93, 164.35, 163.55, 152.52, 132.19, 132.06, 131.30, 131.18, 129.87, 129.83, 123.009, 122.96, 116.71, 116.56, 116.42, 116.05, 115.93, 115.76, CF_3 (q, 126.447, 122.661, 118.869, 115.084, J = 272.22 Hz), 75.50–75.58 (m), 33.38; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −72.53 (s, 6F, 2 × CF_3), −104.90 (m, 1F), −105.25 (m, 1F); HRMS for $C_{19}H_{11}F_8N_3O$ calcd 449.0774, found 449.0770. Anal. calcd for $C_{19}H_{11}N_3OF_8$: C, 50.79; H, 2.47; N, 9.35. Found: C, 50.81; H, 2.72; N, 9.10.

Method B. To a solution of α,α-bis(trifluoromethyl)-4,5-bis(4-fluorophenyl)-1-methyl-1*H*-imidazole-2-methanamine (0.5 g, 1.19 mole) in methanol (1.5 L) was added methylene blue (11 mg). Oxygen gas was bubbled through the solution while irradiating with a Tungsten lamp (400 watt) for 8 h. Hydrochloric acid in ether (1 N, 5 mL) was added to the reaction mixture and stirred for 30 min at room temperature. Satd aqueous sodium carbonate (30 mL) and water (300 mL) were added and the mixture was extracted with ether. The combined organic layers were washed with satd aqueous ammonium chloride and sodium chloride, dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was purified by flash column chromatography, eluting with hexane:ethyl acetate (10:1 to 3:1) to give the title compound **3a** (356 mg, 67%), which was identical in all comparable aspects with the sample obtained from *m*CPBA oxidation of **2a**, and 4,5-bis(4-fluorophenyl)-1,5-dihydro-5-methoxy-1-methyl-2*H*-imidazol-2-one as a minor product (23 mg, 6%): mp 209–210 °C; IR (KBr) 1740, 1601, 1509 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.65 (s, 3H, NCH_3), 3.19 (s, 3H, NCH_3), 7.06 (m, 4H), 7.37 (dd, J = 8.7, 5.3 Hz, 2H); 8.10 (dd, J = 8.7, 5.3 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −103.02 (m, 3F, CF_3), −112.02 (m, 3F, CF_3); HRMS for $C_{16}H_{13}N_2O_2F_2$ calcd 303.0945, found 303.0949.

Preparation of *N*-[3,5-dihydro-3-methyl-2-phenyl-5,5-bis(trifluoromethyl)-4*H*-imidazol-4-ylidene]benzamide (3b). This compound was prepared from α,α-bis(trifluoromethyl)-4,5-bisphenyl-1-methyl-1*H*-imidazole-2-methanamine (**2b**), following Procedure A described above, as a white solid: mp 80–81 °C; IR (KBr) 1666, 1622, 1262, 1226, 966 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 3H, NCH_3), 7.46–7.68 (m, 8H), 8.00 (dd, J = 8.4, 1.1 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −71.88 (s, 6F, 2 × CF_3); HRMS for $C_{19}H_{13}N_3OF_6$ calcd 414.1041, found 414.1040.

Preparation of 4-chloro-*N*-[2-(4-chlorophenyl)-3,5-dihydro-3-methyl-5,5-bis(trifluoromethyl)-4*H*-imidazol-4-ylidene]benzamide (3c). This compound was prepared from α,α-bis(trifluoromethyl)-4, 5-bis(4-chlorophenyl)-1-methyl-1*H*-imidazole-2-methanamine (**2c**), following Procedure A described above, as a white solid: mp 94–96 °C; IR (KBr) 1688, 1662, 1628, 1258, 1226, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 3H, NCH_3), 7.46 (t, J = 8.3 Hz, 2H), 7.54 (t, J = 8.3 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.94 (d, J = 8.3 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −71.74 (s, 6F, 2 × CF_3); HRMS for $C_{19}H_{11}Cl_2F_6N_3O$ calcd 482.0262, found 482.0235.

Preparation of 4-fluoro-*N*-[2-(4-fluorophenyl)-3,5-dihydro-5,5-bis(trifluoromethyl)-4*H*-imidazol-4-ylidene]-benzamide (3d). This compound was prepared from α,α-bis(trifluoromethyl)-4,5-bis(4-fluorophenyl)-1*H*-imidazole-2-methanamine (**2d**), following Procedure A described above, as a white solid: mp 163–164 °C; IR (KBr) 1668, 1600, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, J = 8.7 Hz, 2H), 7.27 (t, J = 8.7 Hz, 2H), 8.04 (dd, J = 8.7, 4.9 Hz, 2H), 8.39 (dd, J = 8.7, 5.3 Hz, 2H), 11.71 (s, 1H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −72.10 (s, 6F, 2 × CF_3), −102.99 (m, 1F), 103.94 (m, 1F); HRMS for $C_{18}H_{10}F_8N_3O$ calcd 436.0696, found 436.0684.

Preparation of 4-fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]benzamide (4a). To a solution of lithium aluminum hydride (3.6 g, 95 mmol) in anhydrous tetrahydrofuran (300 mL) was added slowly a solution of 4-fluoro-*N*-[2-(4-fluorophenyl)-3,5-dihydro-3-methyl-5,5-bis(trifluoromethyl)-4*H*-imidazol-4-ylidene]benzamide (**3a**, 35.4 g, 78.8 mmol) in anhydrous tetrahydrofuran (100 mL) under nitrogen at 0 °C. The reaction mixture was stirred at room temperature for 2 h before being cooled to 0 °C and quenched with satd aqueous ammonium chloride (300 mL), and extracted with ether. The combined organic layers were washed successively with water and satd aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solvent was removed under vacuum. The residue was triturated with hexane to give the title compound **4a** (34.1 g, 96%) as a white solid: mp 145–146 °C; IR (KBr) 1658, 1604, 1226 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.97 (s, 3H, NCH_3), 6.44 (d, J = 10.4 Hz, 1H), 6.60 (d, J = 10.4 Hz, 1H), 7.18 (m, 4H), 7.64 (dd, J = 8.7, 5.1 Hz, 2H), 7.84 (dd, J = 8.7, 5.1 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.44, 167.11, 166.33, 165.77, 163.74, 162.97, 131.10, 130.98, 129.69, 129.57, 128.96, 128.92, 128.53, 124.37, 124.32, 117.21, 116.29, 116.19, 115.99, 115.89, CF_3 (q, 128.53, 124.76, 120.99, 117.21, J = 284.5 Hz), 78.40–76.50 (m), 32.95; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −69.63 (q, J = 9.47 Hz, CF_3), −76.59 (q, J = 9.47 Hz, CF_3), −106.23 (m, 1F), −107.564 (m, 1F); MS *m*/*e* 452 $(M+H)^+$. Anal. calcd for $C_{19}H_{13}N_3OF_8$: C, 50.57; H, 2.90; N, 9.31. Found: C, 50.79; H, 3.05; N, 9.61.

Preparation of 4-fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]benzamide (4a) and 4-fluoro-*N*-[2-(4-fluorophenyl)-3-methyl-5,5-bis(trifluoromethyl)-4-imidazolidinylidene]-benzamide (5). Sodium borohydride (170 mg, 4.5 mmol) was added portionwise to a solution of 4-fluoro-*N*-[2-(4-fluorophenyl)-3,5-dihydro-3-methyl-5,5-bis(trifluoromethyl)-4*H*-imidazol-4-ylidene]benzamide (1.8 g, 4 mmol) in ethanol (50 mL) at room temperature under nitrogen. The reaction mixture was heated at reflux for 3 h, and then stirred at room temperature overnight. The reaction mixture was cooled to 0 °C, quenched with water and hydrochloric acid (10 mL, 1 N), made basic with sodium hydroxide (1 N aqueous solution) and then extracted with ether. The organic layer was washed successively with sodium hydroxide

(1 N), water and satd aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue was purified by flash column chromatography, and eluted with hexane followed by hexane:ethyl acetate (20:1 to 50:50) to give two products. The major product (0.8 g, 45%) was characterized as **4a**, which was identical in all comparable aspects with the sample obtained from $LiAlH_4$ reduction of **3a**. The minor product, 4-fluoro-*N*-[2-(4-fluorophenyl)-3-methyl-5,5-bis(trifluoromethyl)-4-imidazolidinylidene]benzamide (**5**), (0.5 g, 27%) was isolated as a solid: mp 132–133 °C; IR (KBr) 3300, 1657, 1601, 1218 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3H, C$\underline{H}_3$), 3.09 (d, 1H, *J* = 3.7 Hz, NH), 5.61 (d, 1H, *J* = 3.7 Hz, C$\underline{H}$), 7.11 (t, 2H, *J* = 8.7 Hz), 7.15 (t, 2H, *J* = 8.7 Hz), 7.44 (dd, 2H, *J* = 5.3, 8.7 Hz), 8.07 (dd, 2H, *J* = 5.3, 8.7 Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −74.07 (m, 3F, CF_3), −74.15 (m, 3F, CF_3), −107.21 (m, 1F), −110.11 (m, 1F); MS *m*/*e* 452 (M+H)$^+$. Anal. calcd for $C_{19}H_{13}N_3OF_8$: C, 50.57; H, 2.90; N, 9.31. Found: C, 50.34; H, 2.68; N, 9.15.

Preparation of 4-cyano-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]benzamide (4b). This compound was prepared from 4-fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]benzamide (**4a**), following Procedure C described above, as an amorphous solid (21%): mp 199–200 °C; IR (KBr) 3300, 2235, 1688, 1672, 1590, 1227 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (s, 3H, NC$\underline{H}_3$), 6.47 (d, *J* = 10.4 Hz, 1H), 6.67 (d, *J* = 10.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.92 (d, *J* = 8.4 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −69.48 (q, *J* = 9.5 Hz, CF_3), −76.42 (q, *J* = 9.5 Hz, CF_3); HRMS for $C_{21}H_{13}F_6N_5O$ (M+H)$^+$ calcd 466.1103, found 466.1096.

Preparation of 4-fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (6a). This compound was prepared from 4-fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]benzamide (**4a**), following Procedure B described above, as a crystalline solid (94%): mp 112–113 °C; IR (KBr) 1658, 1605, 1226 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (s, 3H, NC$\underline{H}_3$), 3.01 (s, 3H, NC$\underline{H}_3$), 6.80 (br s, 1H, C$\underline{H}$), 7.16 (t, 2H, *J* = 8.4 Hz), 7.19 (t, 2H, *J* = 8.4 Hz), 7.46 (dd, 2H, *J* = 5.3, 8.4 Hz), 7.66 (dd, 2H, *J* = 5.3, 8.4 Hz), ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −69.23 (s, 3F, CF_3), −77.24 (s, 3F, CF_3), −106.96 (m, 1F), −109.43 (m, 1F); HRMS for $C_{20}H_{16}N_3OF_8$ (M+H)$^+$ calcd 466.1166, found 466.1185. Anal. calcd for $C_{20}H_{15}N_3OF_8$: C, 51.62; H, 3.25; N, 9.03; F, 32.66. Found: C, 51.63; H, 3.07; N, 8.96; F, 32.71.

Preparation of *N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-4-fluoro-*N*-methylbenzamide (7a) and 4-cyano-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (1). These compounds were prepared from 4-fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (**6a**) following Procedure C described above, and separated by flash column chromatography: *N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-4-fluoro-*N*-methylbenzamide (**7a**, 130 mg, 28%) was isolated as a white solid: mp 189–190 °C; IR (KBr) 2232, 1658, 1588, 1224, 1203 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (s, 3H, NC$\underline{H}_3$), 2.99 (s, 3H, NC$\underline{H}_3$), 6.85 (br s, 1H), 7.16 (t, *J* = 8.7 Hz, 2H), 7.47 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −69.15 (br s, 3F, CF_3), −77.06 (br s, 3F, CF_3), −109.12 (m, 1F); MS *m*/*e* 473 (M+H)$^+$. Anal. calcd for $C_{21}H_{15}N_4OF_7$: C, 53.40; H, 3.20; N, 11.86. Found: C, 53.12; H, 3.16; N, 11.69. 4-Cyano-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (**1**, 40 mg, 8%) was isolated as a white solid: mp 128–129 °C; IR (KBr) 2225, 1659, 1584, 1204 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (s, 3H, NC$\underline{H}_3$), 3.02 (s, 3H, NC$\underline{H}_3$), 6.80 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.80 (m, 6H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −69.13 (m, 3F, CF_3), −77.99 (m, 3F, CF_3); HRMS for $C_{22}H_{16}F_6N_5O$ (M+H)$^+$ calcd 480.1259, found 480.1251. Recrystallization of *N*-[4,4-bis[trifluoromethyl)-4,5-dihydro-1-methyl-2-[4-cyanophenyl]-1*H*-imidazol-5-yl]-*N*-methyl-4-cyanobenzamide from methylene chloride–hexane gave the polymorphic crystalline form that melts at 132–134 °C. Recrystallization from ethyl acetate–hexane gave a polymorphic form melting at 181–183 °C. X-ray powder diffraction showed that each polymorph has a distinct crystalline form. The polymorphs were interconvertible based on the solvent used for recrystallization. Differential scanning calorimetry of the compound of **1** resulted in three peaks at 131.7, 182.6, and 253.5 °C, which corresponded to polymorphic transitions from the 131 °C form to the 182.6 °C form, followed by decomposition at 253.5 °C. The 132–134 °C melting polymorph was threefold more water soluble than the 181–183 °C melting polymorph and had greater oral bioavailability leading to improved systemic ACAT inhibitory activity compared to the higher melting form.

Separation of (*R*) and (*S*) enantiomers of 4-cyano-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (1a and 1b)

The racemic mixture of the title compound (**1**) was separated to the *R*- and *S*-enantiomers using HPLC with a Chiracel-OJ column eluted with 50% ethanol–hexane. On concentration, the enantiomers were triturated with hexane to give an amorphous solid. Compound (*S*)-4-cyano-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide, (+)-**1a**: Peak 1, R_t = 8.4 min (100% ee), [α]+7.32 (*c* 0.82, $CHCl_3$). Compound (*S*)-4-cyano-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide, (−)-**1b**: Peak 2, R_t = 17.7 min (100% ee), [α] −5.32 (*c* 0.32, $CHCl_3$).

Preparation of *N*-[4,5-dihydro-1-methyl-2-[4-methoxyphenyl]-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-methoxybenzamide (7b). This compound was prepared from 4-fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (**6a**) following the method described for the preparation of **14c**: mp 141–142 °C; IR (KBr) 2972, 2940, 2840, 1646, 1612, 1260, 1218 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.95 (s, 3H, NC$\underline{H}_3$), 3.00 (s, 3H, NC$\underline{H}_3$), 3.96 (s, 6H, 2 × OC$\underline{H}_3$), 6.80 (br s, 1H), 6.95 (d, J = 8.8 Hz, 4H), 6.98 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −68.53 (br s, 3F, CF_3), −76.74 (q, J = 10.3 Hz, CF_3); HRMS for $C_{22}H_{21}F_6N_3O_3$ calcd 490.1565, found 490.1570. Anal. calcd for $C_{22}H_{21}F_6N_3O_3$: C, 53.99; H, 4.34; N, 8.60; F, 23.29. Found: C, 54.16; H, 4.10; N, 8.47; F, 23.46.

Preparation of *N*-[4,5-dihydro-1-methyl-2-[4-(1-piperidinyl)phenyl]-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-(1-piperidinyl)benzamide (7c). Potassium carbonate (2.8 g, 20 mmol) and piperidine (1.72 g, 20 mmol) were added to a solution of 4-fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (**6a**, 1.09 g, 2.3 mmol) in dimethyl sulfoxide (15 mL). The reaction mixture was heated at 105 °C for two days under nitrogen. The solution was cooled to room temperature, poured into water (150 mL) and extracted with ether. The organic layer was washed with satd aqueous ammonium chloride and satd aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under vacuum. The residue was purified on silica gel eluting with a mixture of hexane:ethyl acetate (20:1 to 50:50) to give the title product **7c** (1.13 g, 81%) as a white crystalline solid: mp 165–166 °C; IR (KBr) 1638, 1610, 1246, 1210 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.68–1.70 (M, 12H), 2.96 (s, 3H, NC$\underline{H}_3$), 3.01 (s, 3H, NC$\underline{H}_3$), 3.25–3.30 (m, 8H), 6.65 (br s, 1H), 6.91 (d, J = 8.8 Hz, 4H), 7.40 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.23 (br s, 3F, CF_3), −77.40 (q, J = 9.5 Hz, CF_3); HRMS for $C_{30}H_{36}F_6N_5O$ (M+H)$^+$ calcd 596.2824, found 596.2837. Anal. calcd for $C_{30}H_{35}F_6N_5O$: C, 60.50; H, 5.92; N, 11.76; F, 19.14. Found: C, 60.89; H, 6.03; N, 11.46; F, 19.14.

Preparation of 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (8). To a solution of 4-fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (**6a**, 6.46 g, 13.9 mmol) in ether (300 mL) was added potassium *tert*-butoxide (9.35 g, 6 equiv) and water (0.5 mL, 2 equiv). The reaction mixture was stirred vigorously at room temperature overnight, the suspension was poured into water and the phases were separated. The organic layer was washed successively with water, satd aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated under vacuum to give **8** as a yellow oil (4.83 g, 100%). Treatment of **8** with hydrochloric acid (1 M) in ether gave the 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine hydrochloride as a white solid: mp 206–207 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.67 (s, 3H, NC$\underline{H}_3$), 2.93 (s, 3H, NC$\underline{H}_3$), 4.67 (s, 1H), 7.10–7.20 (m, 2H), 7.53–7.63 (m, 2H,); MS *m*/*e* 344 (M+H)$^+$. Anal. calcd for $C_{13}H_{12}N_3F_7\cdot HCl$: C, 41.12; H, 3.45; N, 11.07. Found: C, 41.36; H, 3.79; N, 11.24.

Preparation of 4-trifluoromethyl-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (9a). To a solution of 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**, 0.45 g, 1.3 mmol) in pyridine (10 mL) was added 4-trifluoromethylbenzoyl chloride (0.70 g, 3.4 mmol) and DMAP (20 mg). The reaction mixture was stirred under nitrogen overnight at room temperature (16 h). The crude reaction mixture was quenched with water and extracted with ether. The organic layer was washed successively with sodium hydroxide (1 N aqueous solution), satd aqueous ammonium chloride and satd aqueous sodium chloride, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was crystallized from hexane–chloroform to give the title compound **9a** as a white solid (286 mg, 58%): mp 165–166 °C; IR (KBr) 1661, 1612, 1326, 1228 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.89 (s, 3H, NC$\underline{H}_3$), 3.03 (s, 3H, NC$\underline{H}_3$), 6.78 (s, 1H), 7.20 (t, J = 8.4 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.67 (dd, J = 5.9, 8.4 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −63.523 (s, 3F, CF_3), −69.23 (q, J = 9.6 Hz, CF_3), −76.59 (q, J = 9.6 Hz, CF_3), −106.84 (m, 1F); HRMS for $C_{21}H_{15}F_{10}N_3O$ calcd 515.1056, found 515.1080. Anal. calcd for $C_{21}H_{15}F_{10}N_3O$: C, 48.94; H, 2.93; N, 8.15; F, 36.86. Found: C, 49.01; H, 2.77; N, 8.14; F, 36.69.

Preparation of 4-butoxy-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (9b). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**) and 4-butoxybenzoyl chloride, following Procedure D described above, as a white solid (92%): mp 84–85 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.00 (t, 3H, J = 7 Hz, C$\underline{H}_3$), 1.43–1.60 (m, 2H), 1.73–1.87 (m, 2H), 2.97 (s, 3H, NC$\underline{H}_3$), 3.00 (s, 3H, NC$\underline{H}_3$), 4.00 (t, 2H, J = 7 Hz, OC$\underline{H}_2$), 6.73 (s, 1H, C$\underline{H}$), 6.93 (d, 2H, J = 10 Hz), 7.13–7.27 (m, 2H), 7.43 (d, 2H, J = 7 Hz), 7.63–7.70 (m, 2H,); MS *m*/*e* 520 (M+H)$^+$. Anal. calcd for $C_{24}H_{24}N_3O_2F_7$: C, 55.49; H, 4.66; N, 8.09. Found: C, 55.27; H, 4.56; N, 8.02.

Preparation of *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-4-methoxy-*N*-methylbenzamide (9c). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**) and 4-anisoyl chloride, following Procedure D described above, as a white solid (52%): mp 136–137 °C; MS *m*/*e* 478 (M+H)$^+$; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.93 (s, 3H, NC$\underline{H}_3$), 2.97 (s, 3H, NC$\underline{H}_3$), 3.83 (s, 3H, OC$\underline{H}_3$), 6.73 (s, 1H, C$\underline{H}$), 6.97 (d, 2H, J = 7 Hz), 7.13–7.20 (m, 2H), 7.43 (d, 2H, J = 7 Hz); 7.60–7.70 (m, 2H).

Preparation of 4-(1,1-dimethylethyl)-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (9d). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**) and 4-(*t*-butyl)benzoyl chloride (following Procedure D) as a white solid (79%): mp 129–130 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.33 (s, 9H, 3 × C$\underline{H}_3$), 2.93 (s, 3H, NC$\underline{H}_3$), 3.00 (s, 3H, NC$\underline{H}_3$), 6.83 (s, 1H), 7.17–7.27 (m, 2H), 7.20–7.50 (m, 4H), 7.63–7.70 (m, 2H); MS *m*/*e* 504 (M+H)$^+$. Anal. calcd for $C_{24}H_{24}N_3OF_7$: C, 57.26; H, 4.81; N, 8.35. Found: C, 57.20; H, 4.82; N, 8.29.

Preparation of *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-nitrobenzamide (9e). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**) and 4-nitrobenzoyl chloride (following Procedure D) as a white solid (81%): mp 174–175 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.90 (s, 3H, NC$\underline{H}_3$), 3.07 (s, 3H, NC$\underline{H}_3$), 6.77 (s, 1H, C$\underline{H}$), 7.17–7.27 (m, 2H), 7.60–7.73 (m, 4H), 8.37 (d, 2H, *J* = 7 Hz,); MS *m*/*e* 493 (M+H)$^+$. Anal. calcd for $C_{20}H_{15}N_4O_3F_7$: C, 48.79; H, 3.07; N, 11.38. Found: C, 48.76; H, 2.81; N, 11.27.

Preparation of *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-[1,1(-biphenyl]-4-carboxamide (9f). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**) and 4-biphenyl carbonyl chloride (following Procedure D) as a white solid (17%): mp 186–187 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.00 (s, 3H, NC$\underline{H}_3$), 3.03 (s, 3H, NC$\underline{H}_3$), 6.87 (s, 1H), 7.17–7.77 (m, 14H); MS *m*/*e* 524 (M+H)$^+$. Anal. calcd for $C_{26}H_{20}N_3F_7O$: C, 59.66; H, 3.85; N, 8.03. Found: C, 59.48; H, 3.72; N, 7.89.

Preparation of 4-cyano-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (9g). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**) and 4-cyanobenzoyl chloride (following Procedure D) as a white solid (72%): mp 148–150 °C; IR (KBr) 2232, 1659, 1610, 1227, 1203 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.88 (s, 3H, NC$\underline{H}_3$), 3.03 (s, 3H, NC$\underline{H}_3$), 6.75 (s, 1H), 7.20 (t, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.67 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.19 (q, *J* = 10.3 Hz, C*F*$_3$), −77.17 (q, *J* = 10.3 Hz, C*F*$_3$), 106.65 (m, 1F); HRMS for $C_{21}H_{16}N_4OF_7$ (M+H)$^+$ calcd 473.1212, found 473.1215. Anal. calcd for $C_{21}H_{15}N_4OF_7$: C, 53.40; H, 3.20; N, 11.86; F, 28.15. Found: C, 53.41; H, 3.07; N, 11.75; F, 28.27.

Preparation of 4-butoxy-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (10a). This compound was prepared from 4-butoxy-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (**9b**), following Procedure C described above, as a white solid (64%): mp 183–185 °C; IR (KBr) 2962, 2936, 2874, 2232, 1658, 1256, 1202 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.99 (t, *J* = 7.3 Hz, 3H), 1.52 (m, 2H), 1.80 (m, 2H), 2.95 (s, 3H, NC$\underline{H}_3$), 2.98 (s, 3H, NC$\underline{H}_3$), 4.01 (t, *J* = 6.6 Hz, 2H), 6.82 (br s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −68.39 (br s, C*F*$_3$), −76.38 (q, *J* = 10.4 Hz, C*F*$_3$); HRMS for $C_{25}H_{24}N_4O_2F_6$ calcd 527.1882, found 527.1890. Anal. calcd for $C_{25}H_{24}N_4O_2F_6$: C, 57.03; H, 4.61; N, 10.64; F, 21.65. Found: C, 57.07; H, 4.73; N, 10.48; F, 21.92.

Preparation of *N*-[4,5-dihydro-1-methyl-2-[4-(1-piperidinyl)phenyl]-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-[1,1(-biphenyl]-4-carboxamide (10b). This compound was prepared from *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-[1,1(-biphenyl]-4-carboxamide (**9f**), following the method described for the preparation of compound **7c**, as an off-white solid (45%): mp 189.5–191.5 °C; IR (KBr) 2926, 1640, 1608, 1352, 1212 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.66 (m, 6H), 2.96 (s, 3H, NC$\underline{H}_3$), 3.08 (s, 3H, NC$\underline{H}_3$), 3.31 (m, 4H), 6.77 (br s, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.37–7.69 (m, 11H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.52 (br s, 3F, C*F*$_3$), −76.58 (br s, 3F, C*F*$_3$); HRMS for $C_{31}H_{30}N_4OF_6$ calcd 589.2402, found 589.2386.

Preparation of 4-(1,1-dimethylethyl)-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (10c). This compound was prepared from 4-(1,1-dimethylethyl)-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (**9d**) (following Procedure C) as a white solid (33%): mp 210–211 °C; IR (KBr) 2968, 2232, 1648, 1260, 1216 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.34 (s, 9H), 2.94 (s, 3H, NC$\underline{H}_3$), 2.99 (s, 3H, NC$\underline{H}_3$), 6.88 (br s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −68.44 (br s, 3F, C*F*$_3$), −76.34 (br s, 3F, C*F*$_3$); HRMS for $C_{25}H_{24}N_4OF_6$ calcd 511.1932, found 511.1916.

Preparation of *trans*-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-propylcyclohexanecarboxamide (11a). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine hydrogen chloride salt (**8** HCl) and *trans*-4-*n*-propylcyclohexanecarbonyl chloride (following Procedure D) as a white crystalline solid (88%): mp 92–93 °C; ^{1}H NMR (CDCl$_3$) δ 0.85–1.89 (c, total 16H), 2.49 (m, 1H), 2.92 (s, 3H, NC$\underline{H}_3$), 2.96 (s, 3H, NC$\underline{H}_3$), 6.65 (s, 1H), 7.19 (t, *J* = 8.4 Hz, 2H), 7.65 (dd, *J* = 5.1, 8.4 Hz, 2H); IR (KBr) 2928, 2862, 1666, 1612 cm^{-1}; ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.48 (q, *J* = 9.5 Hz, C*F*$_3$); −77.20 (q, *J* = 9.5 Hz, C*F*$_3$), −107.32 (m, 1F); HRMS for $C_{23}H_{28}F_7N_3O$ calcd 495.2121, found 495.2112.

Preparation of *trans*-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-pentylcyclohexanecarboxamide (11b). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine hydrogen chloride salt (**8** HCl) and *trans*-4-*n*-pentylcyclohexanecarbonyl chloride (following Procedure D) as a white crystalline solid (81%): mp 102–103 °C; IR (KBr) 2926, 2856, 1664, 1612, 1578, 1520, 1302, 1262, 1240, 1224, 1202, 1094, 1064, 980, 848, 742 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.89 (t, *J* = 7.0 Hz, 3H, C$\underline{H}_3$), 0.91–1.89 (m, 17H), 2.49 (m, 1H), 2,92 (s, 3H, NC$\underline{H}_3$), 2.96 (s, 3H, NC$\underline{H}_3$), 6.64 (s, 1H), 7.18 (t, *J* = 8.6 Hz, 2H), 7.66 (dd, *J* = 5.1, 8.6 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.51 (q, *J* = 10.3 Hz, CF_3), −77.21 (q, *J* = 10.3 Hz, CF_3), −107.34 (m, 1F); HRMS for $C_{25}H_{33}F_7N_3O$ (M+H)$^+$ calcd 556.2512, found 556.2515. Anal. calcd for $C_{25}H_{32}F_7N_3O$: C, 57.36; H, 6.16; N, 8.03; F, 25.40. Found: C, 57.55; H, 6.16; N, 7.93; F, 25.23.

Preparation of *trans*-4-(1,1-dimethylethyl)-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylcyclohexanecarboxamide (11c). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine hydrogen chloride salt (**8** HCl) and *trans*-4-*t*-butylcyclohexane carbonyl chloride (following Procedure D) as a white crystalline solid (96%): mp 88–89 °C; IR (KBr) 2942, 2862, 1660, 1610, 1260, 1238, 1226, 1200, 1102, 1062, 980, 852, 744 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.87 (s, 9H, 3 × C$\underline{H}_3$), 1.01–1.07 (m, 3H), 1.42–1.90 (m, 6H), 2.46 (m, 1H), 2.92 (s, 3H, NC$\underline{H}_3$), 2.97 (s, 3H, NC$\underline{H}_3$), 6.73 (s, 1H), 7.19 (t, *J* = 8.4 Hz, 2H), 7.66 (dd, *J* = 5.1, 8.4 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.53 (q, *J* = 10.3 Hz, CF_3), −77.25 (q, *J* = 10.3 Hz, CF_3), −107.37 (m, 1F); HRMS for $C_{24}H_{31}F_7N_3O$ (M+H)$^+$ calcd 510.2355, found 510.2353. Anal. calcd for $C_{24}H_{30}F_7N_3O$: C, 56.58; H, 5.90; N, 8.25; F, 26.10. Found: C, 56.87; H, 5.89; N, 8.12; F, 25.79.

Preparation of *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylcyclohexanecarboxamide (11d). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine hydrogen chloride salt (**8** HCl) and cyclohexanecarbonyl chloride (following Procedure D) as a white crystalline solid (83%): mp 121–122 °C; IR (KBr) 1666, 1611, 1224, 1203 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.27–1.86 (m, 10H), 2.55 (m, 1H), 2.92 (s, 3H, NC$\underline{H}_3$), 2.96 (s, 3H, NC$\underline{H}_3$), 6.65 (s, 1H), 7.18 (t, *J* = 8.4 Hz, 2H), 7.66 (dd, *J* = 5.5, 8.4 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −63.52 (s, 3F, CF_3), −69.23 (q, *J* = 9.6 Hz, CF_3), −76.59 (q, *J* = 9.6 Hz, CF_3), −106.84 (m, 1F); HRMS for $C_{20}H_{22}F_7N_3O$ calcd 453.1651, found 453.1653. Anal. calcd for $C_{24}H_{30}F_7N_3O$: C, 52.98; H, 4.89; N, 9.27; F, 29.33. Found: C, 52.93; H, 4.84; N, 9.13; F, 29.51.

Preparation of *N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylcyclohexanecarboxamide (12a). This compound was prepared from *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylcyclohexanecarboxamide (**12a**) (following Procedure C) as a white crystalline solid (91%): mp 166–167 °C; IR (KBr) 2934, 2232, 1665, 1588, 1258, 1204 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.24–1.86 (m, 10H), 2.55 (m, 1H), 2.91 (s, 3H, NC$\underline{H}_3$), 2.96 (s, 3H, NC$\underline{H}_3$), 6.70 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 1H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.41 (q, *J* = 10.3 Hz, CF_3), −77.01 (q, *J* = 10.3 Hz, CF_3); HRMS for $C_{21}H_{22}F_6N_4O$ calcd 460.1697, found 460.1697.

Preparation of *trans*-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-propylcyclohexanecarboxamide (12b).

Method A. This compound was prepared from *trans*-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-propylcyclohexanecarboxamide (following Procedure C) as a white solid (96%): mp 193–194 °C; IR (KBr) 2954, 2922, 2860, 2232, 1666, 1582, 1554, 1522, 1420, 1400, 1308, 1278, 1260, 1242, 1216, 1202, 1144, 1108, 1096, 1062, 1046, 980, 852, 746, 730 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.86–1.89 (m, 16H), 2.49 (m, 1H), 2.91 (s, 3H, NC$\underline{H}_3$), 2.96 (s, 3H, NC$\underline{H}_3$), 6.70 (s, 1H), 7.78 (q, *J* = 8.5 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.42 (q, *J* = 9.5 Hz, CF_3), −77.02 (q, *J* = 9.5 Hz, CF_3); HRMS for $C_{24}H_{29}F_6N_4O$ calcd 503.2246, found 503.2230. Anal. calcd for $C_{24}H_{28}F_6N_4O$: C, 57.37; H, 5.62; N, 11.15; F, 22.68. Found: C, 57.52; H, 5.65; N, 10.97 F, 22.75.

Method B. To a solution of 2-(4-cyanophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**15**, 4.1 g, 12.8 mmol) in 1,2-dichloroethane (150 mL) and pyridine (2 mL) was added *trans*-4-*n*-propylcyclohexane carbonyl chloride (4.7 g, 30 mmol) and dimethylaminopyridine (40 mg, 0.3 mmol). The reaction mixture was stirred at room temperature overnight and refluxed for another 4 h under nitrogen. The crude reaction mixture was quenched with water and extracted with ether. The organic layer was washed successively with satd aqueous sodium carbonate, satd aqueous ammonium chloride and brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography eluting with hexane and hexane:ethyl acetate (20:1 to 50:50) to give the title compound **12b** (4.6 g, 71%) as a white crystalline solid.

Separation of (+) and (−) enantiomers of *trans*-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-propylcyclohexanecarboxamide (12g and 12h). The racemic mixture of the title compound (**12b**) was separated to the (+) and (−) enantiomers using HPLC with a Chiracel-OJ column eluted with 50% ethanol–hexane. On concentration, the enantiomers were triturated with hexane to give amorphous solid. Compound **12g**: Peak 1, R_t = 7.9 min, mp 72–74 °C, [α]+12.07 (*c* 0.406, MeOH), 98% ee. Compound **12h**: Peak 2, R_t = 9.0 min, mp 76–78 °C, [α]+11.97 (*c* 0.526, MeOH), 92% ee.

Preparation of *N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-spiro(4,5)-decane-8-carboxamide (12c). This compound was prepared from 2-(4-cyanophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**15**) and spiro(4,5)-decane-8-carbonyl chloride (following Procedure D) as a white solid (55%): mp 138–140 °C; ^{1}H NMR (CDCl$_3$) δ 7.81 (d, 2H, *J* = 8.4 Hz), 7.65 (d, 2H, *J* = 8.4 Hz), 6.70 (s, 1H), 2.97 (s, 3H), 2.91 (s, 3H), 2.50 (m, 1H), 1.26–1.80 (c, total 16H); IR (KBr) 2960, 2938, 2862, 2242, 2232, 1662, 1588, 1298, 1260, 1240, 1206 cm^{-1}; HRMS for $C_{25}H_{31}F_6N_4O$ calcd 517.2402, found 517.2409. Anal. calcd for $C_{25}H_{30}F_6N_4O$: C, 58.13; H, 5.85; N, 10.85; F, 22.07. Found: C, 58.44; H, 5.97; N, 10.63; F, 21.83.

Preparation of *trans*-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-pentylcyclohexanecarboxamide (12d). This compound was prepared from *trans*-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-pentylcyclohexanecarboxamide (**11b**) (following Procedure C) as a white solid (87%): mp 179–180 °C; IR (KBr) 2954, 2918, 2850, 2232, 1664, 1098, 1062, 980, 852 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.86–1.90 (m, 20H), 2.49 (m, 1H), 2.91 (s, 3H, NC$\underline{H}_3$), 2.96 (s, 3H, NC$\underline{H}_3$), 6.70 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H); ^{19}F NMR (CDCl$_3$) δ −69.44 (q, *J* = 10.3 Hz, 3F, C*F*$_3$), −77.04 (q, *J* = 10.3 Hz, 3F, C*F*$_3$); HRMS for $C_{26}H_{33}F_6N_4O$ (M+H)$^+$ calcd 531.2559, found 531.2556. Anal. calcd for $C_{26}H_{33}F_6N_4O$: C, 58.86; H, 6.08; N, 10.56; F, 21.48. Found: C, 59.02; H, 6.14; N, 10.43; F, 21.19.

Preparation of *trans*-4-(1,1-dimethylethyl)-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylcyclohexanecarboxamide (12e). This compound was prepared from *trans*-4-(1,1-dimethylethyl)-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylcyclohexanecarboxamide (**11c**) (following Procedure C) as a white solid (82%): mp 183–185 °C; IR (KBr) 2960, 2938, 2862, 2242, 2232, 1662, 1588, 1298, 1260, 1240, 1206, 1060, 978, 852 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.87 (s, 9H, 3 (C$\underline{H}_3$), 1.00–1.96 (m, 9H), 2.50 (m, 1H), 2.91 (s, 3H, NC$\underline{H}_3$), 2.96 (s, 3H, NC$\underline{H}_3$), 6.71 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.81 (d, *J* = 7.8 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.44 (q, *J* = 10.3 Hz, C*F*$_3$), −77.04 (q, *J* = 10.3 Hz, C*F*$_3$); HRMS for $C_{25}H_{31}F_6N_4O$ (M+H)$^+$ calcd 517.2402, found 517.2409. Anal. calcd for $C_{25}H_{30}F_6N_4O$: C, 58.13; H, 5.85; N, 10.85; F, 22,07. Found: C, 58.44; H, 5.97; N, 10.63; F, 21.83.

Preparation of *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylheptanamide hydrochloride (13a). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**) and heptanoyl chloride (following Procedure D) as a white solid (41%): mp 134–136 °C; MS *m*/*e* 456 (M+H)$^+$; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.90 (m, 3H, C$\underline{H}_3$), 1.33 (m, 6H), 1.70 (m, 2H), 2.47 (m, 2H), 3.00 (s, 3H, NC$\underline{H}_3$), 3.23 (s, 3H, NC$\underline{H}_3$), 7.03 (s, 1H, C$\underline{H}$), 7.20–7.40 (m, 2H), 7.93–8.17 (m, 2H).

Preparation of *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*,5-dimethylhexanamide hydrochloride (13b). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**) and 5-methylhexanoyl chloride (following Procedure D) (85%). The viscous oil obtained was then treated with HCl in ether and recrystallized from dichloromethane–methanol–petroleum ether to give the title compound **13b** as a white solid: mp 112–114 °C; MS *m*/*e* 456 (M+H)$^+$; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.90 (s, 3H, C$\underline{H}_3$), 0.93 (s, 3H, C$\underline{H}_3$), 1.27 (m, 2H), 1.67 (m, 3H), 2.47 (m, 2H), 3.00 (s, 3H, NC$\underline{H}_3$), 3.23 (s, 3H, NC$\underline{H}_3$), 7.03 (s, 1H, C$\underline{H}$), 7.33 (m, 2H), 8.00 (m, 2H).

Preparation of 2,3,4,5,6-pentafluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (13c). This compound was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**) and pentafluorobenzoyl chloride (following Procedure D) as a white crystalline solid (49%): mp 112–113 °C; IR (KBr) 1673, 1504, 1336, 1226 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.89 (s, 3H, NC$\underline{H}_3$), 3.03 (s, 3H, NC$\underline{H}_3$), 6.58 (s, 1H), 7.20 (t, *J* = 8.7 Hz, 2H), 7.67 (dd, *J* = 5.3, 8.7 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −66.52 (m, C*F*$_3$), −77.18 (q, *J* = 10.3 Hz, C*F*$_3$), −106.55 (m, 1F), −140.49 (m, 1F), −142.47 (m, 1F), −142.47 (dt, *J* = 23.2, 6.8, 6.8 Hz, 1F), −150.78 (t, *J* = 20.7 Hz, 1F), −158.79 (td, *J* = 22.4, 22.4, 8.6 Hz, 1F), −159.92 (td, *J* = 21.7, 21.7, 8.6 Hz, 1F); HRMS for $C_{20}H_{11}F_{12}N_3O$ calcd 537.0710, found 537.0710. Anal. calcd for $C_{20}H_{11}F_{12}N_3O$: C, 44.71; H, 2.06; N, 7.82. Found: C, 44.72; H, 2.01; N, 7.71.

Preparation of *N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-3-cyclohexene-1-carboxamide (14a). *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-3-cyclohexene-1-carboxamide was prepared from 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**) and 3-cyclohexenecarbonyl chloride (following Procedure D) as a white crystalline solid (44%): mp 103–105 °C; IR (KBr) 2940, 1664, 1612, 1254, 1222, 1202 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.86–2.84 (m, 7H), 2.94 (s, 3H, NC$\underline{H}_3$), 2.99 (s, 3H, NC$\underline{H}_3$), 5.74 (br s, 2H), 6.66 (s, 1H), 7.19 (t, *J* = 8.4 Hz, 2H), 7.67 (dd, *J* = 8.4, 5.4 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −68.74 (q, *J* = 10.3 Hz, C*F*$_3$), −76.47 (q, *J* = 10.3 Hz, C*F*$_3$), −106.54 (m, 1F); HRMS for $C_{20}H_{21}F_7N_3O$ (M+H)$^+$ calcd 452.1573, found 452.1566. Anal. calcd for $C_{20}H_{20}F_7N_3O$: C, 53.22; H, 4.48; N, 9.32; F, 29.46. Found: C, 53.42; H, 4.24; N, 9.30; F, 29.64. The title compound was prepared (following Procedure C) from *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-3-cyclohexene-1-carboxamide (obtained above) as a white crystalline solid: mp 201–202 °C; IR (KBr) 2938, 2230, 1664, 1582, 1254, 1200 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.86–2.81 (m, 7H), 2.93 (s, 3H, NC$\underline{H}_3$), 2.99 (s, 3H, NC$\underline{H}_3$), 5.74 (br s, 2H), 6.72 (s, 1H), 7.77 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.1 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −68.68 (q, J = 10.3 Hz, CF_3), −76.30 (q, J = 10.3 Hz, CF_3); HRMS for $C_{21}H_{20}F_6N_4O$ calcd 459.1620, found 459.1631. Anal. calcd for $C_{21}H_{20}F_6N_4O$ 1/4H$_2$O: C, 54.66; H, 4.64; N, 12.00; F, 24.41. Found: C, 54.60; H, 4.37; N, 11.84; F; 24.77.

Preparation of *N*-[4,5-dihydro-1-methyl-2-[4-(1-piperidinyl)phenyl]-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylheptanamide hydrochloride (14b). To a solution of *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylheptanamide hydrochloride (**13a**, 0.20 g, 0.4 mmol) in dimethyl sulfoxide (5 mL) was added potassium carbonate (0.29 g, 1.2 mmol) and piperidine (0.10 g, 1.2 mmol). The reaction mixture was heated at 145 °C overnight under nitrogen. The solution was cooled to room temperature, poured into water, and extracted with ether. The ether layer was washed with 1 N HCl to give unreacted starting material. The aqueous layer was made basic and it was extracted with ether. The organic layer was washed with water and satd aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under vacuum. The residue was treated with HCl in ether to give the title compound **14b** (50 mg, 22%) as a semi-solid: MS *m*/*e* 521 (M+H)$^+$; IR (KBr) 2932, 2858, 1668, 1608, 1252, 1204 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.90 (m, 3H, C$\underline{H}_3$), 1.30 (m, 8H), 1.67 (m, 6H), 2.40 (t, 2H), 2.90 (s, 3H, NC$\underline{H}_3$), 2.97 (s, 3H, NC$\underline{H}_3$), 3.30 (m, 4H), 6.53 (s, 1H), 6.90 (d, 2H), 7.53 (d, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.02 (br s, CF_3), −76.92 (br s, CF_3); HRMS for $C_{25}H_{35}F_6N_4O$ (M+H−HCl)$^+$ calcd 521.2714, found 521.2715.

Preparation of *N*-[4,5-dihydro-2-(4-methoxyphenyl)-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*,5-dimethyl-hexanamide hydrochloride (14c). To *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*,5-dimethylhexanamide hydrochloride (**13b**, 0.05 g, 0.1 mmol) was added sodium methoxide solution (10 mL, 25%). The reaction mixture was allowed to reflux for 3 h. The solution was cooled to room temperature, poured into water, and extracted with ether. The organic layer was washed successively with water, and satd aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under vacuum. The residue was treated with HCl in ether to give the title compound (50 mg, 99%) as a white solid: mp 68–69 °C; IR (KBr) 2956, 1668, 1612, 1304, 1260, 1202 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.87 (s, 3H, C$\underline{H}_3$), 0.90 (s, 3H, C$\underline{H}_3$), 1.27 (m, 2H), 1.60 (m, 3H), 2.37 (m, 2H), 2.90 (m, 6H, 2 × NC$\underline{H}_3$), 3.83 (s, 3H, OC$\underline{H}_3$), 6.60 (s, 1H,), 6.97 (d, 2H), 7.60 (d, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.27 (q, J = 8.6 Hz, CF_3), −77.08 (q, J = 8.6 Hz, CF_3); MS *m*/*e* 468 (M+H−HCl)$^+$; HRMS for $C_{21}H_{28}F_6N_3O_2$ (M+H−HCl)$^+$ calcd 468.2085, found 468.2086.

Preparation of 2-(4-cyanophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (15).

Method A. This compound was prepared from *N*-[4,4-bis(trifluoromethyl)-2-(4-cyanophenyl)-4,5-dihydro-1-methyl-1*H*-imidazol-5-yl]-*N*-methyl-4-cyanobenzamide (**1**), following the procedure described for the preparation of 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**), as a light-yellow solid (62%): mp 97–98 °C; IR (KBr) 3409, 2945, 2232, 1586, 1289, 1272, 1199 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.60 (br s, 1H), 2.69 (s, 3H, NC$\underline{H}_3$), 2.90 (s, 3H, NC$\underline{H}_3$), 4.69 (br s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −68.74 (q, J = 10.3 Hz, CF_3), −76.47 (q, J = 10.3 Hz, CF_3), −106.54 (m, 1F); HRMS for $C_{14}H_{13}F_6N_4$ (M+H)$^+$ calcd 351.1044, found 351.1033.

Method B. This compound was prepared from *N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-4-fluoro-*N*-methylbenzamide (**7a**), following the procedure described for the preparation of 2-(4-fluorophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**8**), as a light-yellow solid (61%).

Preparation of 4-phenoxy-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (16a). This compound was prepared from 2-(4-cyanophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**15**) and 4-phenoxybenzoyl chloride (following Procedure D) as a white solid: mp 181–182 °C; IR (KBr) 2930, 2236, 1634, 1588, 1486, 1374, 1302, 1266, 1240, 1200, 1074, 1056, 980, 858, 846, 762, 704, 694 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.95 (s, 3H, NC$\underline{H}_3$), 2.99 (s, 3H, NC$\underline{H}_3$), 6.82 (br s, 1H), 7.06 (m, 4H), 7.21 (t, J = 7.7 Hz, 1H), 7.42 (m, 4H), 7.79 (q, 2H); ^{19}F NMR (CDCl$_3$) δ −69.121 (br s, CF_3), −77.087 (q, J = 10.3 Hz, CF_3); HRMS for $C_{27}H_{21}F_6N_4O_2$ (M+H)$^+$ calcd 547.1569, found 547.1563. Anal. calcd for $C_{27}H_{20}F_6N_4O_2$ C, 59.34; H, 3.69; N, 10.25. Found: C, 59.31; H, 3.57; N, 10.19.

Preparation of 4-(1-methylethoxy)-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (16b). This compound was prepared from 2-(4-cyanophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**15**) and 4-(1-methylethoxy)benzoyl chloride (following Procedure D) as a white solid: mp 191–192 °C; IR (KBr) 2982, 2232, 1660, 1582, 1524, 1512, 1422, 1346, 1302, 1256, 1238, 1218, 1200, 1180, 1144, 1098, 1070, 980, 852, 840 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.37 (d, J = 5.9 Hz, 6H), 2.97 (s, 3H, NC$\underline{H}_3$), 2.95 (s, 3H, NC$\underline{H}_3$), 4.64 (m, 1H), 6.80 (br s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.79 (q, 2H); ^{19}F NMR (CDCl$_3$) δ −69.072 (br s, CF_3), −77.135 (q, J = 10.4 Hz, CF_3); HRMS for $C_{24}H_{23}F_6N_4O_2$

(M+H)$^+$ calcd 513.1725, found 513.1732. Anal. calcd for $C_{24}H_{22}F_6N_4O_2$: C, 56.25; H, 4.33; N, 10.93; F, 22.24. Found: C, 56.34; H, 4.18; N, 10.79; F, 22.19.

Preparation of *N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*,2,2-trimethyloctanamide (16c). This compound was prepared from 2-(4-cyanophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**15**) and 2,2-dimethyl octanoyl chloride (following Procedure D) as a white crystalline solid (14%): mp 81–82 °C; IR (KBr) 2932, 2860, 2232, 1650, 1328, 1302, 1258, 1204, 1096, 1060, 1044, 980, 852, 552 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H, C$\underline{H}_3$), 1.15–1.40 (m, 8H), 1.59 (m, 1H), 1.76 (m, 1H), 2.92 (s, 3H, NC$\underline{H}_3$), 3.06 (s, 3H, NC$\underline{H}_3$), 6.74 (s, 1H), 7.81 (q, 2H); ^{19}F NMR (CDCl$_3$) δ −69.21 (q, *J* = 10.3 Hz, C*F*$_3$), −77.03 (q, *J* = 10.3 Hz, C*F*$_3$); HRMS for $C_{24}H_{30}F_6N_4O_2$ calcd 504.2324, found 504.2333. Anal. calcd for $C_{24}H_{30}F_6N_4O$: C, 57.14; H, 5.99; N, 11.11; F, 22.59. Found: C, 57.03; H, 5.82; N, 10.90; F, 22.32.

Preparation of *N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-imidazol-5-yl]-1-adamantanyl-*N*-methylacetamide (16d). This compound was prepared from 2-(4-cyanophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**15**) and 1-adamantaneacetyl chloride (following Procedure D) as a white solid (59%): mp 74–75 °C; IR (KBr) 2904, 2850, 2232, 1706, 1666, 1588, 1482, 1452, 1414, 1358, 1300, 1262, 1246, 1228, 1204, 1144, 1098, 1062, 1044, 980 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.64–2.09 (m, 15H), 2.24 (s, 2H), 2.91 (s, 3H, NC$\underline{H}_3$), 2.94 (s, 3H, NC$\underline{H}_3$), 6.75 (s, 1H), 7.79 (q, 4H); ^{19}F NMR (CDCl$_3$) δ −69.40 (q, *J* = 10.4 Hz, C*F*$_3$), −76.96 (q, *J* = 10.4 Hz, C*F*$_3$); HRMS for $C_{26}H_{29}F_6N_4O$ (M+H)$^+$ calcd 527.2246, found 527.2239. Anal. calcd for $C_{26}H_{28}F_6N_4O$: C, 59.31; H, 5.36. Found: C, 59.60; H, 5.67.

Preparation of *cis*-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-4-methoxy-*N*-methyl-cyclohexanecarboxamide (16e) and *trans*-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-4-methoxy-*N*-methyl-cyclohexanecarboxamide (16f). The title compounds were prepared from 2-(4-cyanophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**15**) and 4-methoxycyclohexanecarbonyl chloride following Procedure D, and the products were separated by flash chromatography eluting with hexane and hexane:ethyl acetate (20:1 to 50:50). For *cis*-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-4-methoxy-*N*-methyl-cyclohexanecarboxamide (**16e**): mp 149–150 °C; IR (KBr) 2936, 2858, 2236, 1658, 1588, 1414, 1296, 1258, 1238, 1204, 1098, 1062, 978, 856 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.18–2.26 (m, 8H), 2.53 (m, 1H), 2.91 (s, 3H, NC$\underline{H}_3$), 2.99 (s, 3H, NC$\underline{H}_3$), 3.19 (m, 1H) 3.38 (s, 3H, OC$\underline{H}_3$), 6.68 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.42 (q, *J* = 10.3 Hz, C*F*$_3$), −77.01 (q, *J* = 10.3 Hz, C*F*$_3$); HRMS for $C_{21}H_{24}F_6N_5O$ (M+H)$^+$ calcd 491.1882, found 491.1880. Anal. calcd for $C_{21}H_{23}F_6N_5O$: C, 58.13; H, 5.85; N, 10.85; F, 22.07. Found: C, 58.44; H, 5.97; N, 10.63; F, 21.83. For *trans*-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-4-methoxy-*N*-methyl-cyclohexanecarboxamide (**16f**): mp 181–182 °C; IR (KBr) 3352, 2934, 2858, 2234, 1632, 1544, 1336, 1308, 1256, 1224, 1204, 1184, 1056, 978, 852 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.06–1.28 (m, 3H), 1.31–1.46 (m, 2H), 1.60–1.80 (m, 3H), 1.94–2.05 (m, 2H), 2.77 (s, 3H, NC$\underline{H}_3$), 2.91 (s, 3H, NC$\underline{H}_3$), 3.72 (m, 1H), 4.49 (d, *J* = 7.7 Hz, 1H), 6.66 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 2H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.01 (q, *J* = 10.7 Hz, C*F*$_3$), −76.41 (q, *J* = 10.7 Hz, C*F*$_3$); HRMS for $C_{21}H_{24}F_6N_5O$ (M+H)$^+$ calcd 476.1885, found 476.1885.

Preparation of *trans*-4-(1-methylethyl)-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylcyclohexanecarboxamide (16g). The title compound was prepared from 2-(4-cyanophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**15**) and 4-*iso*-propylcyclohexanecarbonyl chloride (following Procedure D) as a white solid: mp 89–90 °C; IR (KBr) 2933, 2229, 1665, 1588, 1204 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.88, 0.89 (m, 12H, 4 × C$\underline{H}_3$), 1.00–1.94 (m, 20H), 2.48 (m, 1H), 2.69 (m, 1H), 2.91 (s, 6H, 2 × NC$\underline{H}_3$), 2.96 (s, 6H, 2 × NC$\underline{H}_3$), 6.71 (s, 1H), 6.73 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 4H), 7.81 (d, *J* = 8.3 Hz, 4H); ^{19}F NMR (CDCl$_3$, CFCl$_3$) δ −69.41 (q, *J* = 10.3 Hz, C*F*$_3$), −77.01 (q, *J* = 10.3 Hz, C*F*$_3$); HRMS for $C_{24}H_{29}F_6N_4O$ (M+H)$^+$ calcd 503.2246, found 503.2247. Anal. calcd for $C_{24}H_{28}F_6N_4O$: C, 57.37; H, 5.62; N, 11.15; F, 22.68. Found: C, 56.78; H, 5.59; N, 10.91; F, 22.75.

Preparation of *N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-imidazol-5-yl]-4-ethyl-*N*-methylcyclohexanecarboxamide (16h).

Part A: Preparation of 4-ethylcyclohexanecarboxlic acid. To a suspension of 4-ethylbenzoic acid (5.22 g, 34.8 mmol) in acetic acid (30 mL) was added PtO$_2$ (0.24g). The mixture was hydrogenated at 50 psi for 24 h. The solution was filtered, rinsed with dichloromethane, and concentrated in vacuo. After most of the acetic acid was evaporated, the residue was washed with water, brine, dried with MgSO$_4$, and concentrated to give the title compound as a clear oil (4.90g, 90%). MS *m*/*e* 157.0 (M+H)$^+$; ^{1}H NMR (CDCl$_3$) 12.01 (br, 2H), 2.50 (c, 1H), 2.10 (c, 1H), 1.76–1.85 (c, 6H), 1.40–1.58 (m, 8H), 1.00–1.33 (m, 12H), 0.83 (m, 6H).

Part B: Preparation of 4-ethylcyclohexanecarbonyl chloride. To a solution of 4-ethylcyclohexanecarboxylic acid (0.5 g, 3.2 mmol) in dichloromethane (15 mL) was added oxalyl chloride (0.5 mL, 3.9 mmol) and a catalytic amount of dimethylformamide (small drop). The reaction mixture was stirred at room temperature for 2 h, concentrated and used as is for the subsequent reaction.

Part C: Preparation of *N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-imidazol-5-yl]-4-ethyl-*N*-methylcyclohexanecarboxamide. This compound was prepared from 2-(4-cyanophenyl)-4,5-dihydro-*N*,1-dimethyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (**15**) and 4-ethylcyclohexanecarbonyl chloride (following Procedure D) as a white solid: mp 90.5–91.8 °C; IR (KBr) 2930, 2229, 1665, 1588, 1203 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85–1.91 (c, total 28H) 2.49 (m, 1H), 2.63 (m, 1H), 2.91 (s, 6H, $2 \times NC\underline{H}_3$), 2.96 (s, 6H, $2 \times NC\underline{H}_3$), 6.71 (s, 1H), 6.72 (s, 1H), 7.76 (d, J = 8.3 Hz, 4H), 7.81 (d, J = 8.3 Hz, 4H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −69.41 (q, J = 10.3 Hz, CF_3), −77.01 (q, J = 10.3 Hz, CF_3); HRMS for $C_{23}H_{27}F_6N_4O$ $(M+H)^+$ calcd 489.2089, found 489.2087. Anal. calcd for $C_{23}H_{26}F_6N_4O$: C, 56.55; H, 5.36; N, 11.47; F, 23.34. Found: C, 56.51; H, 5.39; N, 11.31; F, 23.51.

Preparation of *trans*-*N*-[2-(4-carboxamidephenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-propylcyclohexanecarboxamide (17). Hydrogen peroxide (3 mL, 30%) was added slowly to a solution of *trans*-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methyl-4-propylcyclohexanecarboxamide (**12b**, 742 mg, 1.5 mmol) and potassium carbonate (540 mg, 3.9 mmol) in DMSO (3 mL) and ethanol (3 mL). The reaction mixture was stirred at room temperature for 30 min and then poured into water (150 mL). The product was isolated by filtration and dried in a vacuum oven as a white solid (714 mg, 93%): mp 160–164 °C; IR (KBr) 3326, 3194, 2930, 2862, 1670, 1588, 1408, 1388, 1300, 1260, 1244, 1204, 1062, 978, 862, 736 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 0.89 (d, J = 7.0 Hz, 3H, $C\underline{H}_3$), 0.92–1.90 (m, 13H), 2.50 (m, 1H), 2.90 (s, 3H, $NC\underline{H}_3$), 2.98 (s, 3H, $NC\underline{H}_3$), 6.69 (s, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.92 (d, J = 8.1 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −69.635 (q, J = 10.3 Hz, 6F, $2 \times CF_3$), −77.802 (q, J = 10.3 Hz, 3F, CF_3), −77.576 (q, J = 10.3 Hz, 3F, CF_3); HRMS for $C_{24}H_{31}F_6N_4O_2$ $(M+H)^+$ calcd 521.2351; found: 521.2356.

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