Synthesis of (2-{4-[4-Fluoro-3-(trifluoromethyl)phenyl]-2-piperidin-4-yl-1*H*-imidazol-1-yl}ethyl)dimethylamine

Radhe K. Vaid,*[a] Sathish Boini,[a] Jeremy T. Spitler,[a] Yangwei John Pu,[a] Scott A. May,[a] Hannah Yu,[a] Wu Sizhong,[b] Jie Fu,[b] Guoliang Zhang[b]

[a] Chemical Product Research and Development, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA
Fax +1(317)2764507; E-mail: vaid_radhe_k@lilly.com

[b] Shanghai PharmExplorer, Shanghai, 20120, P. R. of China

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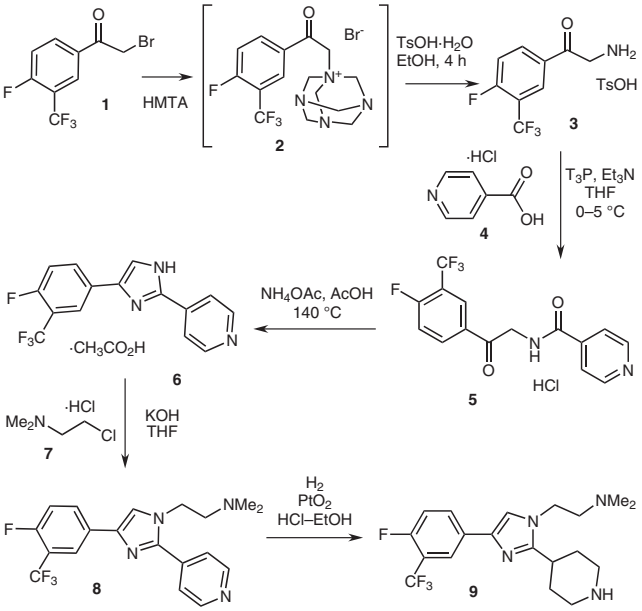
Abstract: An efficient eight-step synthesis of the title compound, starting from oxoacetic acid monohydrate, was developed. Condensation of oxoacetic acid monohydrate with *N*,*N*-dimethylethanamine followed by reductive amination and protection gave *N*-(*tert*-butoxycarbonyl)-*N*-[2-(dimethylamino)ethyl]glycine. Activation of this intermediate with 1,1′-carbonylbis-1*H*-imidazole followed by treatment with (methoxyamino)methane gave *tert*-butyl [2-(dimethylamino)ethyl]{2-[methoxy(methyl)amino]-2-oxoethyl}carbamate, which upon reaction with [4-fluoro-3-(trifluoromethyl)phenyl]magnesium bromide, generated in situ, and subsequent deprotection gave 2-{[2-(dimethylamino)ethyl]amino}-1-[4-fluoro-3-(trifluoromethyl)phenyl]ethanone dihydrochloride. Coupling of this diamine with an activated carboxylic acid gave *tert*-butyl 4-{1-[2-(dimethylamino)ethyl]-4-[4-fluoro-3-(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl}piperidine-1-carboxylate, which on treatment with sodium acetate in ethanol followed by deprotection *in situ* and neutralization gave the title compound in good yield.

Key words: alkylation, heterocycles, imidazoles

Syntheses of substituted imidazoles have received considerable attention, not only because these heteroaromatic compounds exhibit a broad range of biological properties,[1–11] such as antifungal activity,[1] analgesic activity,[2,3] and antiinflammatory activity in inhibiting the release of p38 MAP kinase and cytokines,[4,5] but also because they are important building blocks found in naturally occurring compounds. Because of our interest in kinase inhibitors,[11] we were interested in developing an efficient synthesis of (2-{4-[4-fluoro-3-(trifluoromethyl)phenyl]-2-piperidin-4-yl-1*H*-imidazol-1-yl}ethyl)dimethylamine (**9**), and we recently reported a synthesis of the title compound through hydrogenation of its pyridinyl analogue **8** (Scheme 1).[12]

Although, this is a practical synthesis, it involves the use of the lachrymator **1**, which requires special handling in large-scale production. Also, the synthesis of amine **3** from intermediate **2** produces formaldehyde, the handling of which required special controls with respect to personnel exposure and disposal. In addition, alkylation of intermediate **6** results in the formation of isomer **10** (Figure 1), so that additional purification is required.



Scheme 1 Original synthesis of (2-{4-[4-fluoro-3-(trifluoromethyl)phenyl]-2-piperidin-4-yl-1*H*-imidazol-1-yl}ethyl)dimethylamine (**9**)

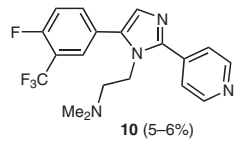


Figure 1 Structure of impurity **10**

We were therefore interested in developing a route that would avoid the use of lachrymator **1** and eliminate the need for selective alkylation of the imidazole intermediate **6**. Here we report an efficient synthesis of the title compound starting from oxoacetic acid monohydrate (**11**) (Scheme 2).

A retrosynthetic analysis of the protected intermediate **21** (Scheme 3) revealed that it might be synthesized either by *N*-alkylation of amide **23** (path a)[11] or by acylation of diamine **19** with carboxylic acid **20** (path b). Diamine (**19**) could be obtained through reductive amination of keto aldehyde **24**.[13]

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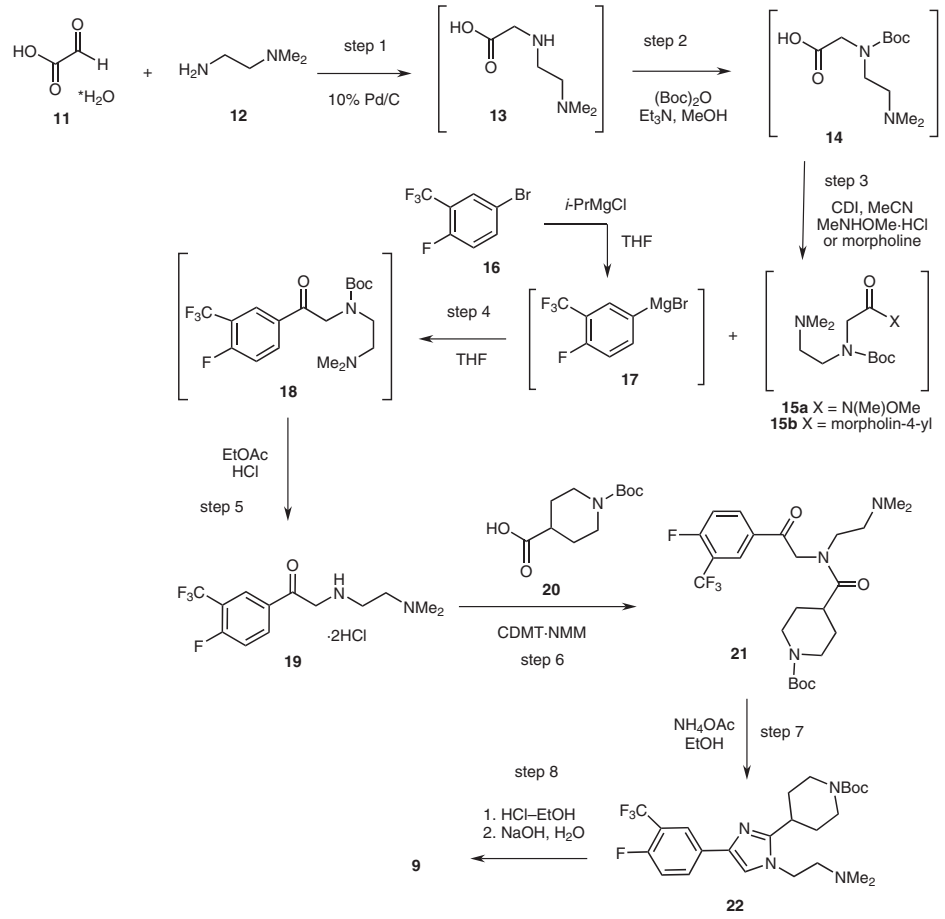
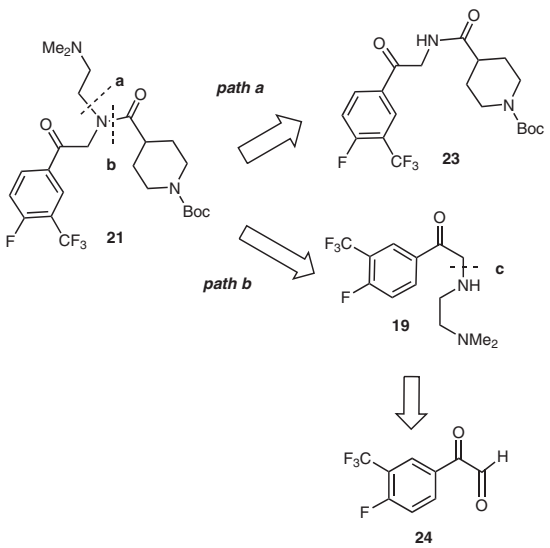
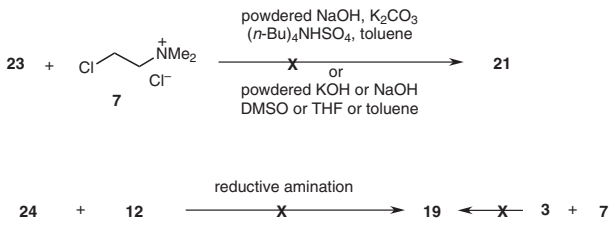


Scheme 2 Synthesis of (2-{4-[4-fluoro-3-(trifluoromethyl)phenyl]-2-piperidin-4-yl-1*H*-imidazol-1-yl}ethyl)dimethylamine (**9**) from oxoacetic acid monohydrate (**11**)



Scheme 3 Retrosynthetic analysis for the protected intermediate **21**

A survey of the literature revealed that N-alkylation of unsubstituted or N-substituted carboxamides with alkyl halides under basic conditions can be accomplished in good yields.[14–16] We therefore attempted to synthesize intermediate **21** by alkylation of amide **23** with chloro amine **7** in the presence of a powdered mixture of sodium hydroxide, potassium carbonate and tetrabutylammonium hydrogen sulfate in toluene or in the presence of sodium hydroxide or potassium hydroxide in various solvents (Scheme 4). N-Alkylation of **23** under these conditions led to the formation of complex mixtures of products, possibly as a result of competing reactions at the methylene group in the position α to the ketone group.



Scheme 4 Attempted syntheses of the protected intermediate **21** and diamine **19**

On the basis of a report in the literature,[17] we attempted an alternative synthesis of diamine **19** by reductive amination on a palladium/carbon catalyst of the imine generated in situ by condensing keto aldehyde **24** with *N*,*N*-dimeth-

ylethane-1,2-diamine (**12**) in methanol, but this was unsuccessful. Similarly, attempts to synthesize diamine **19** by direct alkylation of amino ketone **3** with chloro amine **7** failed.[18] Finally, we focused our efforts on synthesizing diamine **19** from oxoacetic acid hydrate (**11**; Scheme 2). Because the isolated yield of diamino acid **13** was low, we planned to synthesize this intermediate from oxoacetic acid hydrate (**11**) and diamine **12** by reductive amination in the presence of a palladium-on-carbon catalyst and then to protect the intermediate **13** in situ to obtain the protected derivative **14** for subsequent use in formation of the active amide **15**. We performed a screening study to identify a suitable coupling agent for activation of acid **14**, the results of which are reported in Table 1.

The results in Table 1 show that both 1-propanephosphonic acid cyclic anhydride (T_3P) and 1,1′-carbonylbis-1*H*-imidazole (CDI) gave similar yields of **15a**. We therefore prepared the active amide **15a** by activation of the acid with CDI followed by addition of (methoxyamino)methane hydrochloride and extractive workup. Similarly, the active amide **15b** was successfully synthesized by activation of diamino acid **14** with CDI followed by the addition of morpholine. Active amides **15a** and **15b** were not purified and were used as prepared in the synthesis of aroyl derivative **18**.

The synthesis of the diamine **19** began with preparation of the arylmagnesium bromide **17** by the reaction of aryl bromide **16** with isopropylmagnesium chloride in tetrahydrofuran.[19] Addition of **17** *in situ* to the activated amide **15** in tetrahydrofuran, subsequent deprotection of the resulting diamine **18**, and formation of the dihydrochloride salt by treatment with hydrogen chloride gas in ethyl acetate gave the required diamine dihydrochloride **19**. The effect of the stoichiometry of the aryl bromide **16** was studied to determine the optimal conditions, and the results of this study are listed in Table 2. On the basis of these results, we synthesized the protected diamine **18** by using 2.3 equivalents of **17** generated in situ.

We also conducted a second screening study to identify a suitable acid-activating agent for coupling of acid **20** with diamine **19**. The results of this study are listed in Table 3. On the basis of these results, we chose 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) for the synthesis of amide **21** by coupling of acid **20** with amine **19** in tetrahydrofuran.

We studied the cyclization of amide **21** by ammonium acetate to give the imidazole **22** in methanol, ethanol, or isopropyl alcohol. The reaction was slow and did not go to completion in refluxing methanol. Solvents ethanol and isopropyl alcohol gave similar in situ yields of **21**. On the basis of the high solubility of **21** and **9** in ethanol, we developed the synthesis of **9** from **21** by using ethanol as a solvent. Thus, reaction of amide **21** with ammonium acetate in refluxing ethanol gave an excellent conversion (>99%). Solvent exchange with ethanol was performed and deprotection of the *tert*-butoxycarbonyl group was completed in ethanol by using concentrated hydrochloric acid. Concentration of the reaction mixture followed by neutralization with aqueous sodium hydroxide gave the desired product **9** in excellent yield and purity. The results obtained for the syntheses of **22** and **9** are listed in Table 4.

In conclusion, we have developed an efficient and streamlined synthesis of (2-{4-[4-fluoro-3-(trifluoromethyl)phenyl]-2-piperidin-4-yl-1*H*-imidazol-1-yl}ethyl)dimethylamine starting from oxoacetic acid monohydrate; this route avoids the use of a lachrymatory compound and of hexamethyltetramine, and it eliminates the need for N-alkylation of an imidazole.

Table 1 Screening of Acid Activating Agents for Synthesis of Intermediate **15a**

Entry	1	2	3	4	5
Compound **14** (g) (equiv)	2 (1.0)	2 (1.0)	2 (1.0)	259 (1.0)	274 (1.0)
MeNHOMe·HCl (equiv)	1.1	1.1	1.1	1.1	1.1
Coupling agent (equiv)	T_3P[a] 1.1	EDCI[b] (1.5) HOBt[c] (1.0)	CDI[d] (1.5)	CDI (1.5)	CDI (1.5)
Solvent	EtOAc	THF	MeCN	MeCN	MeCN
Temp (°C)	50	30	15	15	18
Time (h)	19	15	16	19	18
Yield of **15**a (g)	2.3	0.78	2.4	259	274
Three-step yield of **15**a (%)	68.0	23.0	69.0	68.0	69.0

[a] 1-Propanephosphonic acid cyclic anhydride.
[b] *N*-[3-(Dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride.
[c] 1*H*-Benzotriazol-1-ol.
[d] 1,1′-Carbonylbis-1*H*-imidazole.

Table 2 Synthesis of Compounds **18** and **19:** Screening Study of Aryl Bromide Stoichiometry

(Step 4)	Quantity of **15** (g) (equiv)	4 (1)	20 (1)	100 (1)	200 (1)
	16 (equiv)	1.7	2.2	2.3	2.3
	i-PrMgCl (equiv)	1.7	2.2	2.5	2.5
	THF (L)	0.02	0.14	1.00	2.00
	Temp (°C)	30	30	30	30
	Time (h)	2	6	17	17
(Step 5)	EtOAc (L)	0.04	0.20	1.00	2.00
	HCl (equiv)	2.3	2.3	2.3	2.3
	Two-step yield of **19** (%)	36	45	48	49
	HPLC purity of **19** (%)	98.0	94.0	95.4	96.2

Table 3 Results of a Screening Study of Acid-Activating Agents for the Synthesis of Amide **21**

Entry	Coupling agent (equiv)	Base (equiv)	Solvent	Conditions[a]		Yield (%) of **21**	HPLC purity (%) of **21**
1	CDI (1.2)	–	MeCN	A	30 °C, 16 h	0	0
2	T_3P (1.5)	NMM (5)	THF	B	10 °C, 3 h	50.0	57.9
3	*i*-BuO_2CCl (1.0)	NMM (4)	THF	C	0 °C, 4 h	65.0	72.7
4	*i*-BuO_2CCl (1.0)	NMM (4)	THF	C	0 °C, 4 h	56.0	68.0
5	CDMT[b] (1.2)	NMM (6)	CH_2Cl_2	D	22 °C, 1 h then –30 °C to 3 °C, 6 h	42.0	47.6
6	CDMT (1.2)	NMM (6)	MeCN	D	22 °C, 1 h then –30 °C to 3 °C, 6 h	58.0	67.1
7	CDMT (1.2)	NMM (6)	THF	D	22 °C, 1 h then –30 °C to 3 °C, 6 h	78.0	99.2

[a] A = **20** mixed with CDI then added to **19**; B = **20** mixed with T_3P and NMM; C = **20** mixed with *i*-BuO_2CCl then **19** added, followed by NMM; D = **20** mixed with CDMT and NMM for 1 h then **19** added.
[b] CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine.

Table 4 Results for Syntheses of **22** and **9**

	Synthesis[a] of **22**				Synthesis[b] of **9**			
Scale (g)	NH_4OAc (equiv)	EtOH (L)	HPLC areas for **21** and **22** (%)	HPLC purity (%)	Concd HCl (mL)	HPLC areas for **22** and **9** (%)	HPLC purity (%)	Yield (%)
5	20	0.05	ND[c], 99.5	99.2	4.5	ND, 98.7	99.5	90.4
114	20	1.14	ND, 99.2	99.0	103	ND, 98.8	99.0	92.9
245	20	2.15	ND/ 99.4	99.4	224	ND, 99.4	99.0	87.7

[a] 76–80 °C, 4 h.
[b] 50–60 °C, 4 h
[c] ND = not detected.

Melting points were measured on a Buchi R-535 apparatus and are uncorrected. All reagents were purchased from Aldrich and were used as received without further purification. IR spectra were recorded on Shimadzu 100 FTIR and Nicolet Magna 550-FTIR spectrophotometers. ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. Chemical shifts (δ) are expressed in ppm downfield relative to TMS (0 ppm). High-resolution mass spectra were obtained by using a Waters GCT Premier TOF mass spectrometer with an EI source. Elemental analyses were performed using a Carlo Erba-106 elemental analyzer.

_N_-[2-(Dimethylamino)ethyl]glycine (13)
A 1-L, three-necked, round-bottomed flask was charged with oxoacetic acid hydrate (**11**; 60.0 g, 0.652 mol) and MeOH (500 mL). The mixture was stirred at 22 °C for 0.2 h then cooled to 0 °C. *N*,*N*-Dimethylethane-1,2-diamine (**12**, 57.0 g; 0.646 mol) was added to the mixture over 0.2 h, and then 10% Pd/C (8.2 g) was added, followed by MeOH (10 mL). The mixture was degassed three times with H_2 and then stirred at 24–28 °C for 18 h under an H_2-filled balloon. Analysis of the reaction mixture by LC/MS indicated the presence of the desired product **13**. The reaction was stopped and the soln of **13** was filtered through diatomite and washed with MeOH (150 mL). The filtered soln of **13** was used without further purification in the synthesis of **14**; in situ yield (HPLC): 93 g (98%).

_N_-[2-(Dimethylamino)ethyl]glycine Dihydrochloride (13·2HCl)
A sample of the soln of **13** (15 mL) was concentrated and purified as the dihydrochloride salt by treatment with concd HCl; mp 202–213 °C

IR (KBr): 1720 (sharp) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.80 (s, 6 H), 3.42 (m, 2 H), 3.46 (m, 2 H), 3.92 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.60, 51.96, 45.96, 42.33, 41.02.

_N_-(*tert*-Butoxycarbonyl)-_N_-[2-(dimethylamino)ethyl]glycine (14)
A three-necked round-bottomed flask was charged with the soln of **13** (95.3 g, 0.650 mol) and MeOH (600 mL), and the mixture was stirred for 0.2 h at 10 °C. Et_3N (132.0 g, 1.3 mol) followed by di-*tert*-butyl dicarbonate (142.2 g, 0.652 mol) were added over 0.5 h and the mixture was stirred for 2 h. Analysis of the mixture by LC/MS indicated consumption of the starting material and formation of the desired product. The mixture was then concentrated to dryness under vacuum at 45 °C, and toluene (200 mL) was added. The mixture was again concentrated under vacuum at 50–55 °C to give a brown oil that was used in the synthesis of **15a** or **15b** without further purification; yield: 147 g (92% based upon HPLC purity); purity: 96.0% (HPLC).

***tert*-Butyl [2-(Dimethylamino)ethyl]{2-[methoxy(methyl)amino]-2-oxoethyl}carbamate (15a)**
Product **14** (550 g, 2.2 mol) and MeCN (2.75 L) were placed in a dry, three-necked, round-bottomed flask at 15–25 °C. The mixture was cooled to 10–15 °C, CDI (542.5 g, 3.4 mol) was added over 0.2 h under N_2, and the mixture was stirred at r.t. for 1 h. MeNHOMe·HCl (326.5 g, 3.4 mol) was added under N_2 and the mixture was stirred at 10–15 °C for 21 h. The mixture was then concentrated under reduced pressure at 50–55 °C. H_2O (3.4 L) was added to dissolve the residue, followed by EtOAc (2.8 L). The resulting mixture was stirred at 15–35 °C for 1 h, then the aqueous layer was separated and the EtOAc layer was discarded. The aqueous layer was washed with EtOAc (2.8 L) then extracted with CH_2Cl_2 (3 × 3.4 L). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under vacuum to give a yellow oil that was used in next step without further purification; yield: 791 g (87%); purity: 96.0% (HPLC).

IR (neat): 1697, 1684 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.21 and 1.28 (s, 9 H), 2.02 and 2.03 (s, 6 H), 2.24 (m, 2 H), 2.97 and 2.99 (s, 3 H), 3.13 (m, 2 H), 3.55 and 3.57(s, 3 H), 3.99 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8, 155.24, 79.09, 61.34, 57.75, 57.48, 48.51, 47.98, 45.99, 45.62, 45.59, 32.43, 28.33, 28.30.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{13}H_{28}N_3O_4$: 290.2074; found: 290.2074.

***tert*-Butyl [2-(Dimethylamino)ethyl](2-morpholin-4-yl-2-oxoethyl)carbamate (15b)**
A 2-L round-bottomed flask was charged with product **14** (147.4 g, 0.598 mol), CDI (106.7 g, 0.658 mol) and MeCN (1.2 L) at 10–15 °C, and the mixture was stirred at 10–15 °C for 2 h. Morpholine (52.0 g, 0.596 mol) was added, and the mixture was stirred for 3 h. Analysis of the resulting mixture by LC/MS indicated the presence of 92.0% of the desired product. The mixture was then concentrated under vacuum, and H_2O (400 mL) was added with stirring. The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 300 mL). The organic layers were combined, washed with 27% aq NH_4Cl (2 × 200 mL), dried (Na_2SO_4), and concentrated to give a brown oil that was used in next step without further purification; yield: 108 g (86%); purity: 96.8% (HPLC).

IR (neat): 1697, 1647 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.32 and 1.39 (s, 9 H), 2.12 (s, 3 H), 2.13 (s, 3 H), 2.31 (m, 2 H), 3.20 (m, 2 H), 3.41 (m, 4 H), 3.55 (m, 4 H), 4.03 (d, *J* = 11.9 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.1, 154.9, 78.5, 66.1, 57.1, 48.2, 45.2, 44.5, 41.7, 27.9.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{15}H_{30}N_3O_4$: 316.2231; found: 316.2231.

***tert*-Butyl [2-(Dimethylamino)ethyl]{2-[4-fluoro-3-(trifluoromethyl)phenyl]-2-oxoethyl}carbamate (18)**
A 20-L, three-necked, round-bottomed flask was charged with 4-bromo-1-fluoro-2-(trifluoromethyl)benzene (1.0 L, 4.1 mol) and THF (6.0 L) under an inert atmosphere, and the mixture was stirred for 0.5 h at 10–23 °C. A 1.3 M soln of *i*-PrMgCl in THF (3.18 L; 4.1 mol) was added at 10–23 °C and the mixture was then stirred for 2 h at 10–23 °C. The formation of the Grignard reagent was monitored by GC/MS analysis of a sample of the soln of the Grignard reagent quenched with a soln of PhCHO in MeCN. A soln of the active amide **15**a (474.6 g, 1.6 mol) or **15**b (620 g, 1.6 mol) in THF (1 L) was added dropwise over 0.5 h to the soln of the Grignard reagent at 23–30 °C, and then the resulting mixture was stirred for 3 h until no starting material was detected by LC/MS. H_2O (2.0 L) was added and the mixture was stirred at 23 °C for 0.5 h. The solvent was evaporated, the residue was dissolved in 18% aq NH_4Cl (4.0 L), and the mixture was extracted with EtOAc (2 × 2.25 L). The organic layers were combined, washed with H_2O (2 × 1.25 L), dried (Na_2SO_4), and concentrated under vacuum to give a brown oil that was used as such in next step without further purification; yield: 625 g (97%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.25 and 1.42 (s, 9 H), 2.73 (s, 3 H), 2.74 (s, 3 H), 3.18 (m, 2 H), 3.61 (m, 2 H), 4.88 (s, 2 H), 7.75 (t, *J* = 10.1 Hz, 1 H), 8.35 (m, 1 H), 8.40 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): 193.96, 162.13 (d, *J* = 263.4 Hz), 155.34, 135.93, 132.19, 127.65, 122.61 (q, *J* = 272.8 Hz), 118.56, 80.56, 80.09, 54.87, 54.57, 54.18, 43.32, 43.08, 42.61, 28.34, 28.14.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –60.39, –108.46.

HRMS: *m/z* [M]$^+$ calcd for $C_{18}H_{24}F_4N_2O_3$: 392.1723; found: 392.1728.

2-{[2-(Dimethylamino)ethyl]amino}-1-[4-fluoro-3-(trifluoromethyl)phenyl]ethanone Dihydrochloride (19)
A 5-L round-bottomed flask was charged with carbamate **18** (625 g, 1.593 mol) and EtOAc (1.25 L), and the mixture was stirred and

cooled to 4–6 °C. A 4.44 M soln of HCl gas in EtOAc (3.5 L, 15.5 mol) was added at 5 °C, and the mixture was warmed to r.t. and stirred for 3 h. The resulting slurry was cooled to 10 °C and stirred at 10 °C for 2 h to give an off-white slurry. The product was recovered by filtration, washed with EtOAc (1.5 L), and dried in a vacuum oven at 50 °C; yield: 304 g (52%); purity: 95.4% (HPLC); mp 125–127 °C.

IR (KBr): 3393 (br), 1701 (sharp) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.83 (s, 6 H), 3.47 (m, 2 H), 3.57 (m, 2 H), 4.97 (s, 2 H), 7.81 (t, *J* = 9.7 Hz, 1 H), 8.18 (m, 1 H), 8.23 (d, *J* = 6.6 Hz, 1 H), 10.07 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 190.33, 163.83, 162.52 (d, *J* = 263.4 Hz), 136.11, 136.06, 130.99, 130.96, 128.18, 121.72 (q, *J* = 272.6 Hz), 118.80, 118.57, 52.70, 52.39, 42.73, 41.60.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –60.41, –107.03.

Anal. Calcd for $C_{13}H_{18}Cl_2F_4N_2O$: C, 42.76; H, 4.97; Cl, 19.42; F, 20.81; N, 7.67. Found: C, 42.74; H, 4.93; Cl, 19.40; F, 20.81; N, 7.64.

tert-Butyl 4-[([2-(dimethylamino)ethyl]{2-[4-fluoro-3-(trifluoromethyl)phenyl]-2-oxoethyl}amino)carbonyl]piperidine-1-carboxylate (21)

A three-necked, 2-L, round-bottomed flask was charged with acid **20** (62.8 g, 0.27 mole) and THF (1 L). The mixture was cooled to 0–5 °C and CDMT (48.1 g, 0.27 mole) was added, followed by NMM (41.5 g, 0.41 mole) added dropwise over 0.4 h. The mixture was then warmed to r.t., stirred at 20–30 °C for 3 h, and cooled to –30 °C. Diamine **19** (100 g, 0.27 mol) was added followed by dropwise addition of NMM (83.1 g, 0.822 mole) over 0.2 h. The mixture was then slowly warmed to 10–15 °C and stirred for 18 h, when a sample drawn for HPLC analysis showed the presence of 0.3% of **18** and 92.2% of the desired product **21**. The mixture was then concentrated to 1–2 volumes under reduced pressure at 40–50 °C and the residue was dissolved in CH_2Cl_2 (600 mL). H_2O (500 mL) and 7% aq $NaHCO_3$ (500 mL) were added, and the mixture was stirred for 0.5 h. The organic layer was separated, washed with 7% aq $NaHCO_3$ (1.0 L), transferred to a flask, and concentrated to 1–2 volumes. EtOAc (200 mL) was added and the mixture was concentrated to 1–2 volumes under reduced pressure at 30–50 °C to give the crude product that was dissolved in EtOAc (500 mL) at 70–80 °C. Slow dropwise addition of heptane (500 mL) gave a slurry that was cooled to 0–5 °C over 2 h. The product was then collected by filtration and dried under vacuum at 55 °C; yield: 114 g (78%); purity: 99.2% (HPLC); mp 146–151 °C.

IR (KBr): 1697, 1674, 1647 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.27, 1.28 (s, 9 H), 1.35–1.58 (m, 4 H), 1.81 (s, 3 H), 2.03 (s, 3 H), 2.12 (m, 1 H), 2.39 (m, 1 H), 2.40–2.8 (m, 4 H), 3.27 (m, 1 H), 3.39 (m, 1 H), 3.8 (m, 2 H), 4.71 (s, 1 H), 5.01 (s, 1 H), 7.62 (m, 1 H), 8.19–8.26 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.82, 192.32, 175.70, 174.71, 162.4 (d, *J* = 263.4 Hz), 154.25, 154.20, 135.58, 132.70, 127.59, 122.38 (*J* = 272.6 Hz), 118.34, 78.88, 58.60, 57.42, 53.36, 46.63, 45.64, 44.81, 44.31, 43.15, 37.39, 28.78, 28.43.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –60.36, –109.28.

HRMS: *m/z* $[M + H]^+$ calcd for $C_{24}H_{34}F_4N_3O_4$: 504.2477; found: 504.2480.

(2-{4-[4-Fluoro-3-(trifluoromethyl)phenyl]-2-piperidin-4-yl-1*H*-imidazol-1-yl}ethyl)dimethylamine (9)

A 5-L, four-necked, round-bottomed flask was charged with amide **21** (245 g, 0.486 mol), EtOH (2.15 L), and NH_4OAc (750 g, 9.7 mol), and the mixture was stirred and refluxed for 4 h until HPLC analysis indicated consumption of the starting material and the presence of 99.0% of the desired intermediate **22**. The mixture was then cooled to r.t. and concentrated to 1.2 L under vacuum at 50 °C. H_2O (1.4 L) was added and the mixture was stirred for 0.2 h. EtOAc (1.8 L) was then added and the mixture was stirred for a further 0.5 h then transferred to a 5-L separatory funnel. The EtOAc layer was separated and the aqueous layer was extracted with EtOAc (1.4 L). The organic layers were combined and concentrated under vacuum at 45 °C. EtOH (780 mL) was added and the mixture was stirred for 5 min. Concd aq HCl (220 mL; 2.7 mol) was added dropwise over 0.5 h at r.t. and the resulting mixture was heated to 50–55 °C for 4 h until analysis by HPLC indicated consumption of the starting material and the presence of 99.37% of the desired product. H_2O (480 mL) was added and the soln was transferred to a dropping funnel and added over 3 h to a 5-L, three-necked, round-bottomed flask charged with 5 M aq NaOH (750 mL) and H_2O (2.08 L) while the temperature was maintained at 0–5 °C. During the initial addition, a pale-yellow slurry formed and after complete addition, a slurry was obtained; the pH of the final reaction mixture was 11. The product was recovered by filtration, washed with H_2O (1.2 L), and dried under vacuum at 50 °C for 72 h to give a white solid; yield: 149 g (88%); purity: 99.0% (HPLC); mp 92–93 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.70 (m, 4 H), 2.17 (s, 6 H), 2.54 (m, 4 H), 2.81 (m, 1 H), 3.00 (d, *J* = 11.9 Hz, 2 H), 3.15 (br s, 1 H), 3.99 (t, *J* = 6.6 Hz, 2 H), 7.44 (t, *J* = 10.1 Hz, 1 H), 7.69 (s, 1 H), 8.01 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 32.32, 33.59, 43.08, 45.30, 46.08, 59.45, 116.38, 117.41, 121.75, 124.15, 129.88, 129.96, 132.11, 132.15, 135.91, 152.21, 155.72, 158.19.

^{19} F NMR (376 MHz, DMSO-d_6): δ = –60.0, –120.6.

HRMS: *m/z* $[M + H]^+$ calcd for $C_{19}H_{25}F_4N_4$: 385.2009; found: 385.2010.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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