Efficient Synthesis of Iminoctadine, a Potent Antifungal Agent and Polyamine Oxidase Inhibitor (PAO)

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Abstract: Iminoctadine (1,17-diguanidino-9-azaheptadecane), isolated from a mixture of polyamines and guanidines known as guazatine that is used in agriculture as a fungicide, showed interesting activity as human antifungal agent and PAO inhibitor. In this paper, we propose a straightforward synthetic strategy for obtaining pure iminoctadine tris(trifluoroacetate) in high overall yield.

Key words: guazatine, antifungal agent, *Candida albicans*, polyamine oxidase inhibitor

The opportunistic human pathogen *Candida albicans* and other non-albicans species have acquired considerable clinical significance as infectious agents in immunocompromised patients. The pathogenic species of *Candida* derive their importance not only from the severity of their infections, but also from their ability to develop resistance against a variety of antifungal agents. In fact, widespread and prolonged use of azoles has led to the rapid development of multidrug resistance (MDR), which poses a major hurdle in antifungal therapy.[1]

Polyamine oxidase is a FAD-containing enzyme that catalyzes the catabolic conversion of spermine (4,9-diazadodecane-1,12-diamine) into spermidine (4-azaoctane-1,8-diamine) and putrescine (butane-1,4-diamine), with the release of 3-aminopropanal and oxygen peroxide.

Spermine, spermidine, and putrescine are present in most living organisms, where they are involved in the growth, differentiation, and death of normal and cancerous tissues cells. Using PAO as a target for modulating cell polyamine concentration it is possible to increase or decrease the progression of a tumor.[2]

Iminoctadine (1,17-diguanidino-9-azaheptadecane, **1**) (Figure 1) is the common name of a component in a mixture of polyamines and guanidines known as guazatine, which is used in agriculture as a fungicide (Table 1).[3]

In preliminary tests, iminoctadine (**1**) showed a micromolar minimal inhibiting concentration (MIC_{50}) against some *Candida* species with potency comparable to that of fluconazole, making it a promising antifungal agent that is different from azole compounds.[3] In addition it showed a nanomolar inhibitor activity against polyamine oxidase (PAO) extracted from maize (*Zea mais*). Recently, a crystal structure of the complex PAO–iminoctadine was described in the literature.[4a–c]

Table 1 Components of Guazatine Acetate[3]

	Component	Proportion (%)
A	$H_2NC(=NH)NH(CH_2)_8NH_2$	9.8
B	$H_2NC(=NH)NH(CH_2)_8NHC(=NH)NH_2$	30
C	$H_2NC(=NH)NH(CH_2)_8NH(CH_2)_8NH_2$	1.7
D	$H_2NC(=NH)NH(CH_2)_8NH(CH_2)_8NHC(=NH)NH_2$	5.1
E	$H_2NC(=NH)NH(CH_2)_8N[C(=NH)NH_2](CH_2)_8NH_2$	8.1
F	$H_2NC(=NH)NH(CH_2)_8N[C(=NH)NH_2](CH_2)_8NHC(=NH)NH_2$	30
G	$NH_2(CH_2)_8NH(CH_2)_8(CH_2)_8NH_2$	3.1
H	$H_2NC(=NH)NH(CH_2)_8N[C(=NH)NH_2](CH_2)_8N[C(=NH)NH_2](CH_2)_8NH_2$	1.4
I	$H_2NC(=NH)NH(CH_2)_8N[C(=NH)NH_2](CH_2)_8N[C(=NH)NH_2](CH_2)_8NHC(=NH)NH_2$	5.1

To extend the knowledge of the biological activity of iminoctadine, a major quantity of this compound was required. Originally iminoctadine was prepared by Evans Medical Ltd. by reaction of 9-azaheptadecane-1,17-diamine with *S*-methylisothiouronium sulfate and it was purified by low-pressure fraction distillation; this purification failed in our hands.[5] Nowadays a difficult purification from guazatine is the only way to obtain pure iminoctadine; moreover, a few milligrams for analysis are extremely expensive.[6]

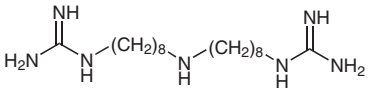

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Figure 1 Iminoctadine

In our first synthetic approach, commercial triamine 9-azaheptadecane-1,17-diamine was reacted with 1,3-bis(*tert*-butoxycarbonyl)-2-methylisothiourea as guanidinylating agent.[7] Surprisingly we obtained only traces of the desired compound and small amount of other products that were difficult to purify.

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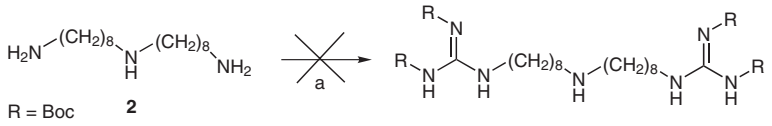
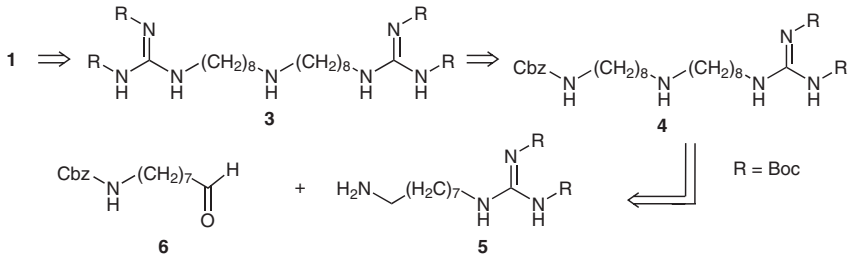


Scheme 1 *Reaction conditions*: (a) BocHNC(=NBoc)SMe, THF–MeOH (5:3), 50 °C.



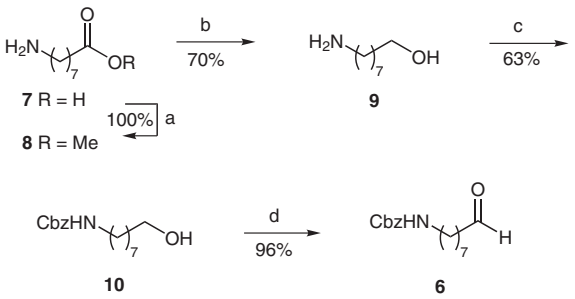
Scheme 2

In order to obtain pure iminoctadine we attempted to synthesize 9-azaheptadecane-1,17-diamine (**2**), no longer commercially available, by a transamination reaction starting from octane-1,8-diamine and using 69% nitric acid with heating to 200 °C. A mixture of linear polyamines was obtained that was purified by low-pressure fraction distillation, as reported in literature, but this was demonstrated by us to be very difficult and low-yielding.[8a,b]

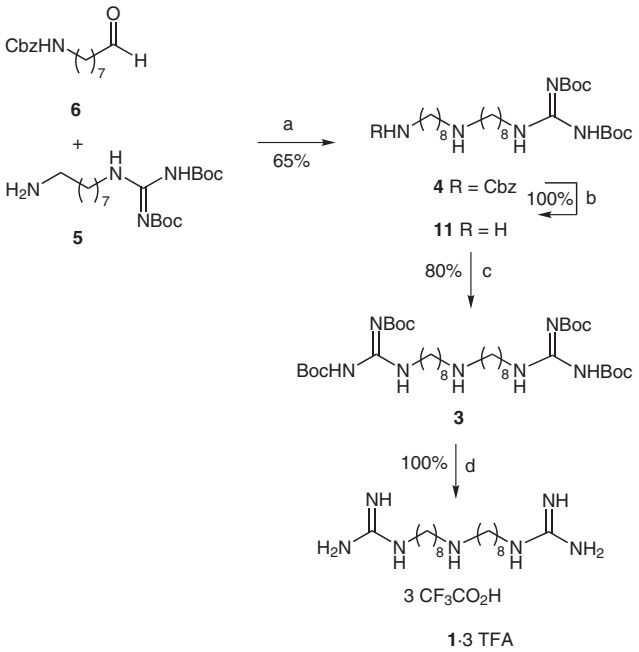
We decided to change our strategy for the synthesis of **1** to the step-by-step synthesis shown in Scheme 2. Our new approach proposes obtaining the final product iminoctadine **1** after simple *tert*-butoxycarbonyl (Boc) deprotection of **3**, which is in turn obtained by guanidinylation of **4** after selective benzyloxycarbonyl (Cbz) deprotection. The intermediate **4** could be prepared by a reductive amination of the aldehyde **6** with protected amine **5** (Scheme 2).

8-[2,3-Bis(*tert*-butoxycarbonyl)guanidino]octan-1-amine (**5**) was synthesized by reaction of octane-1,8-diamine with 1,3-bis(*tert*-butoxycarbonyl)-2-methylisothiourea in tetrahydrofuran–methanol solution at 50 °C as previously described.[7] 8-[(Benzyloxycarbonyl)amino]octanal (**6**) was obtained starting from 8-aminooctanoic acid (**7**) (caprilic acid), which was converted into its methyl ester **8** with acetyl chloride in anhydrous methanol in quantitative yield.[9] Reduction of the amino ester **8** with lithium aluminum hydride in anhydrous tetrahydrofuran gave amino alcohol **9** in very good yield. The amino group of **9** was protected using benzyl chloroformate in tetrahydrofuran–water solution in the presence of sodium hydrogen carbonate to give **10**.[10] Compound **10** was oxidized using Dess–Martin periodinane affording aldehyde **6** in excellent yield (Scheme 3).[11]

The reductive amination between intermediates **5** and **6** in the presence of sodium triacetoxyborohydride was performed in anhydrous 1,2-dichloroethane at room temperature under an argon atmosphere to afford **4** in 65% yield.[12] Hydrogenolysis of **4** with 10% palladium on carbon in methanol yielded the corresponding amine **11**,[13]



Scheme 3 *Reaction conditions*: (a) AcCl, anhyd MeOH, reflux, 3 h; (b) $LiAlH_4$, anhyd THF, reflux, 48 h; (c) CbzCl, $NaHCO_3$, THF, H_2O, r.t., 16 h; (d) Dess–Martin periodinane, anhyd CH_2Cl_2, r.t., 4 h.



Scheme 4 *Reaction conditions*: (a) $NaB(OAc)_3H$, anhyd DCE, r.t., overnight; (b) H_2, 10% Pd/C, MeOH, r.t., 5 h; (c) $(BocHN)_2C{=}NTf$, Et_3N, CH_2Cl_2, r.t., 6 h; (d) 10% TFA–anhyd CH_2Cl_2, r.t., 24 h.

which was treated with 1,3-bis(*tert*-butoxycarbonyl)-2-triflylguanidine as a guanidinylating agent to give protect-

ed iminoctadine **3**.[14] In the last step **3** was deprotected with freshly distilled 10% trifluoroacetic acid in anhydrous dichloromethane solution to give the desired iminoctadine (**1**) as its tris(trifluoroacetate) salt (Scheme 4).

The proposed synthetic approach offers an easy and straightforward way to obtain highly pure iminoctadine tris(trifluoroacetate) in 22% overall yield and on a large scale; this material is required for possible applications as an antifungal agent and a PAO inhibitor.

Reactions requiring anhydrous conditions were carried out in oven-dried or flame-dried glassware. For reactions at low temperatures an acetone–dry ice bath was used. Reagents used were of commercial grade and, when necessary, were purified prior to use. Solvents used were distilled prior to use: THF was distilled from Na/benzophenone under N_2, CH_2Cl_2 and DCE were distilled from CaH_2, MeOH was dried on Mg turnings in the presence of a small amount of I_2.

TLC was carried out on plastic precoated silica gel 60 F_{254} plates (Merck, layer thickness 0.20 mm) containing the fluorescent indicator UV_{254}. Flash chromatography was performed with Merck silica gel 60 (40–63 μm, 230–400 mesh).

Melting points (uncorrected) were determined on a Gallenkap apparatus. IR spectra were recorded with a Perkin-Elmer Spectrum BX as a $CHCl_3$ soln in a KBr cell. ^{1}H NMR spectra were obtained with Bruker AC 200 (200 MHz) and Varian VXR 300 (300 MHz) spectrometers; ^{13}C NMR were recorded with Varian VXR 300 (75 MHz); residual $CHCl_3$ (δ = 7.24) was used as an internal reference. Mass spectra were recorded with the Agilent 1100 series MSD single-quadrupole instrument, equipped with the orthogonal spray API (Agilent Technologies, Palo Alto, CA). N_2 was used as nebulizer and drying gas (350 °C). Mass spectra were acquired over the scan range *m*/*z* 100–1500 using a step size of 0.1 u. The nebulizer gas, the drying gas, the capillary voltage and the vaporizer temperature were set at 2.75 bar, 9 L/min, 300 V, and 350 °C, respectively. Elemental analyses (C, H, N) were performed in-house using a Perkin-Elmer 240C elemental analyzer.

8-[2,3-Bis(*tert*-butoxycarbonyl)guanidino]octan-1-amine (5)
To a stirred soln of octane-1,8-diamine (1.3 g, 9 mmol) in THF–H_2O (5:3, 22 mL) at 50 °C was added dropwise over 1 h a soln of 1,3-bis(*tert*-butoxycarbonyl)-2-methylisothiourea (870 mg, 3 mmol) in THF (16 mL). After 16 h, the mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (MeOH–Et_3N–EtOAc 3:2:95), affording **5** (1.03 g, 89%) as a pale yellow oil.

IR ($CHCl_3$): 330, 2932, 1719, 1635, 1416, 1369, 1134, 1054, 908 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.24 (br s, NH), 3.34–3.27 (m, 2 H), 2.70 (t, *J* = 7 Hz, 2 H), 1.48 (br s, NH_2), 1.42 (s, 9 H), 1.41 (s, 9 H), 1.23 (m, 12 H).

^{13}C NMR ($CDCl_3$): δ = 163.7, 156.3, 153.4, 83.2, 79.4, 41.0, 40.8, 30.4, 30.1, 29.2, 28.6, 28.3, 28.0, 27.8, 27.5, 27.3, 26.9, 26.7, 26.6.

MS (ESI): *m*/*z* = 387.1 $[M + H]^+$, 409.1 $[M + Na]^+$, 287.1 [M – 100]$^+$, 187.2 [M – 200]$^+$.

Anal. Calcd for $C_{19}H_{38}N_4O_4$: C, 59.04; H, 9.91; N, 14.49. Found: C, 59.28; H, 10.14; N, 14.25.

Methyl 8-Aminooctanoate (8)
Freshly distilled AcCl (17.17 mL, 241.5 mmol) was added dropwise to a stirred suspension of 8-aminooctanoic acid (**7**, 15.36 g, 96.6 mmol) in anhyd MeOH (86 mL) under N_2 at 0 °C. The mixture was heated at reflux temperature for 3 h, and the solvent and excess AcCl were evaporated under reduced pressure affording **8** (16.71 g, 100%) as a white solid; mp 129 °C.

IR ($CHCl_3$): 3459, 2976, 1731, 1438, 1391, 1236, 1046, 877 cm^{-1}

^{1}H NMR ($CDCl_3$): δ = 3.66 (s, 3 H), 2.98 (br s, 2 H), 2.30 (t, *J* = 7 Hz, 2 H), 1.76 (br s, NH_2), 1.63–1.58 (m, 2 H), 1.34 (br s, 8 H).

^{13}C NMR ($CDCl_3$): δ = 174.4, 51.7, 40.1, 34.1, 29.0, 28.8, 27.8, 26.4, 24.9.

MS (ESI): *m*/*z* = 174.2 $[M + H]^+$.

Anal. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08. Found: C, 62.21; H, 11.25; N, 8.29.

8-Aminooctan-1-ol (9)
$LiAlH_4$ (1 g, 26.6 mmol) was added in 2 portions (100 + 900 mg) to a stirred suspension of **8** (2.3 g, 13.3 mmol) in anhyd THF (150 mL) in an ice bath. The mixture was heated at reflux for 48 h, cooled to r.t. and poured onto ice. The aqueous layer was extracted a few times with CH_2Cl_2 and the combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give **9** (1.35 g, 70%) as a white solid; mp 65 °C.

IR ($CHCl_3$): 3623, 3358, 2931, 1666, 1586, 1463, 1050, 879 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.60 (t, *J* = 6 Hz, 2 H), 2.60 (t, *J* = 6 Hz, 2 H), 1.53 (br s, 3 H), 1.46–1.42 (br s, 4 H), 1.21–1.16 (m, 8 H).

^{13}C NMR ($CDCl_3$): δ = 63.0, 42.4, 34.0, 33.0, 30.3, 29.6, 27.0, 29.9.

MS (ESI): *m*/*z* = 146.2 $[M + H]^+$.

Anal. Calcd for $C_8H_{19}NO$: C, 66.16; H, 13.19; N, 9.64. Found: C, 65.92; H, 13.44; N, 9.41.

8-[(Benzyloxycarbonyl)amino]octan-1-ol (10)
A stirred soln of **9** (256 mg, 1.76 mmol) and $NaHCO_3$ (163 mg, 1.94 mmol) in THF–H_2O (1:1, 20 mL) was cooled to –5 °C and Cbz-Cl (277 μL, 1.94 mmol) was added dropwise. The mixture was allowed to warm to r.t., and after 16 h the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (petroleum ether–EtOAc, 1:1) affording **10** (310 mg, 63%) as a white solid; mp 60 °C.

IR ($CHCl_3$): 3625, 3452, 3068, 2933, 1715, 1515, 1237, 908 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.31 (br s, 5 H), 5.08 (s, 2 H), 4.90 (br s, 1 H), 3.57 (t, *J* = 6.5 Hz, 2 H), 3.16–3.12 (m, 2 H), 2.39 (br s, 1 H), 1.51–1.45 (m, 4 H), 1.29 (br s, 8 H).

^{13}C NMR ($CDCl_3$): δ = 156.8, 136.9, 128.7, 128.2, 128.0, 66.7, 62.9, 41.3, 32.9, 30.1, 29.5, 29.4, 26.9, 25.9.

MS (ESI): *m*/*z* = 302.1 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 69.01; H, 9.28; N, 4.83.

8-[(Benzyloxycarbonyl)amino]octanal (6)
A stirred suspension of Dess–Martin periodinane (3.41 g, 8.03 mmol) in anhyd CH_2Cl_2 (5 mL) was cooled on an ice bath, and a soln of **10** (1.725 g, 6.18 mmol) in anhyd CH_2Cl_2 (70 mL) was added dropwise. The mixture was allowed to warm to r.t. and it was stirred at r.t. until the reaction had gone to completion. The crude mixture was diluted with pentane (5 mL), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether–EtOAc, 7:30) to give the aldehyde **6** (1.650 g, 96%) as a yellow oil.

IR ($CHCl_3$): 3452, 3069, 2934, 1720, 1515, 1456, 1236, 1046, 870 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.58 (s, 1 H), 7.20 (br s, 5 H), 5.16 (br s, 1 H), 4.95 (s, 2 H), 3.08–3.00 (m, 2 H), 2.29–2.16 (m, 2 H), 1.48–1.43 (m, 2 H), 1.35 (br s, 2 H), 1.17 (br s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 202.7, 156.5, 136.6, 128.3, 127.8, 127.6, 66.30, 43.6, 41.3, 29.7, 28.8, 28.6, 28.5, 26.3.

MS (ESI): *m*/*z* = 300.0 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.06; H, 8.61; N, 4.81.

1-[(Benzyloxycarbonyl)amino]-17-[2,3-bis(*tert*-butoxycarbonyl)guanidino]-9-azaheptadecane (4)

A soln of **5** (810.6 mg, 2.1 mmol) in anhyd DCE (10 mL) was added dropwise to a stirred soln of aldehyde **6** (582 mg, 2.1 mmol) in anhyd DCE (20 mL) at r.t.. The mixture was stirred at r.t. and, after 10 min, $NaB(OAc)_3H$ (623 mg, 2.94 mmol) was added and it was stirred at this temperature overnight. The mixture was concentrated under reduced pressure, diluted with aq sat. $NaHCO_3$ soln, and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (MeOH–Et_3N–EtOAc, 3:2:95), affording amine **4** (886.4 mg, 65%) as a yellow oil.

IR ($CHCl_3$): 3452, 3329, 2932, 1718, 1635, 1515, 1416, 1134, 1027, 914, 808 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.23 (br s, NH), 7.29 (br s, 5 H), 5.04 (s, 2 H), 4.95 (br s, NH), 3.39–3.29 (m, 2 H), 3.17–3.07 (m, 2 H), 2.83–2.75 (m, 4 H), 1.81–1.77 (m, 4 H), 1.45 (br s, 18 H), 1.27 (br s, 20 H).

^{13}C NMR ($CDCl_3$): δ = 163.3, 156.2, 155.8, 153.0, 136.5, 128.2, 128.1, 127.7, 127.5, 127.4, 82.7, 78.9, 66.5, 47.3, 47.1, 40.7, 35.5, 29.6, 29.5, 28.9, 28.8, 28.7, 28.6, 28.0, 27.8, 26.5, 26.4, 25.5, 25.0.

MS (ESI): *m*/*z* = 648.6 $[M + H]^+$, 670.6 $[M + Na]^+$.

Anal. Calcd for $C_{35}H_{61}N_5O_6$: C, 64.88; H, 9.49; N, 10.81. Found: C, 65.14; H, 9.68; N, 11.01.

17-[2,3-Bis(*tert*-butoxycarbonyl)guanidino]-9-azaheptadecan-1-amine (11)

A soln of **4** (335 mg, 0.517 mmol) in MeOH (10 mL) and 10% Pd-C (335 mg) was reacted in a Parr apparatus under H_2 (2.75 bar, 40 psi) at r.t. for 5 h. The mixture was filtered through Celite and the solvent was evaporated under reduced pressure affording **11** (265.2 mg, 100%) as a pale yellow oil.

IR ($CHCl_3$): 3331, 2933, 1715, 1634, 1416, 1369, 1134, 910 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.20 (br s, NH), 3.36–3.30 (m, 2 H), 2.72–2.66 (m, 6 H), 1.41 (br s, 9 H), 1.38 (br s, 9 H), 1.22–1.17 (m, 24 H).

^{13}C NMR ($CDCl_3$): δ = 163.8, 156.3, 153.5, 83.2, 79.4, 50.1, 41.2, 34.1, 29.9, 29.6, 29.4, 29.2, 28.6, 28.4, 28.2, 27.5, 27.0.

MS (ESI): *m*/*z* = 514.3 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{55}N_5O_4$: C, 63.12; H, 10.79; N, 13.63. Found: C, 63.34; H, 10.99; N, 13.4.

1,17-Bis[2,3-bis(*tert*-butoxycarbonyl)guanidino]-9-azaheptadecane (3)

Et_3N (67 μL, 0.48 mmol) and 1,3-bis(*tert*-butoxycarbonyl)-2-triflylguanidine (188 mg, 0.48 mmol) were added to a stirred soln of **11** (226 mg, 0.44 mmol) in CH_2Cl_2 (8 mL), and the mixture was stirred at r.t. for 6 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (MeOH–Et_3N–EtOAc, 3:2:95) affording **3** (265.7 mg, 80%) as a yellow oil.

IR ($CHCl_3$): 3330, 2932, 1720, 1635, 1578, 1416, 1369, 1134, 1026, 908 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.24 (br s, NH), 3.39–3.29 (m, 4 H), 2.55 (t, *J* = 7 Hz, 4 H), 1.44 (br s, 36 H), 1.25 (br s, 24 H).

^{13}C NMR ($CDCl_3$): δ = 163.8, 156.3, 153.5, 83.1, 79.4, 50.0, 41.1, 29.9, 29.5, 29.4, 29.1, 28.5, 28.3, 27.4, 26.9.

MS (ESI): *m*/*z* = 756.8 $[M + H]^+$.

Anal. Calcd for $C_{38}H_{73}N_7O_8$: C, 60.37; H, 9.73; N, 12.97. Found: C, 60.19; H, 9.92; N, 12.77.

1,17-Diguanidino-9-azaheptadecane Tris(trifluoroacetate) [Iminoctadine Tris(trifluoroacetate, 1·3TFA]

A 10% soln of freshly distilled TFA in anhyd CH_2Cl_2 (3 mL) was added to **3** (77 mg, 0.102 mmol) under argon at r.t. The mixture was stirred at r.t. for 24 h and concentrated under reduced pressure giving **1** (71.1 mg, 100%) as a brown oil.

IR ($CHCl_3$): 3467, 3355, 2927, 1662, 1408, 1203, 921 cm^{-1}.

^{1}H NMR (CD_3OD): δ = 3.17 (t, *J* = 7 Hz, 4 H), 2.96 (t, *J* = 8 Hz, 4 H), 1.66–1.61 (m, 4 H), 1.59–1.55 (m, 4 H), 1.36 (br s, 16 H).

^{13}C NMR ($CDCl_3$): δ = 157.5, 48.7, 41.2, 29.5, 28.8, 28.6, 26.3, 26.2, 26.0.

MS (ESI): *m*/*z* = 356.1 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{44}F_9N_7O_6$: C, 41.32; H, 6.36; N, 14.05. Found: C, 41.55; H, 6.6; N, 14.28.

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