Efficient Syntheses of Polyamines Bearing 1*H*-Tetrazol-5-yl Units on Their Amino Functions

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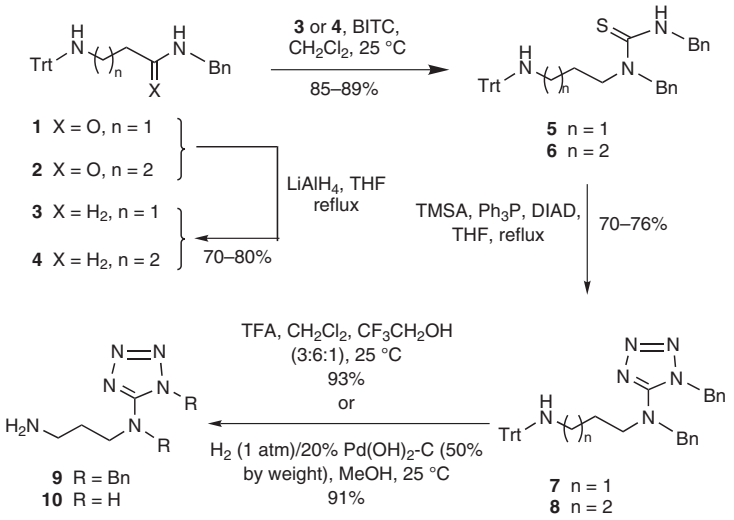
Abstract: Linear *N*-benzyl-*N*′-trityl-α,ω-diamines and N^{α},N^{ω}-ditritylpolyamines were efficiently converted into the corresponding *N*-(1-benzyltetrazol-5-yl)-substituted derivatives upon treatment with benzyl isothiocyanate followed by reaction of the thus-obtained thioureas with azidotrimethylsilane under Mitsunobu reaction conditions.

Key words: polyamines, tetrazoles, Mitsunobu reaction, thiourea derivatives, azidotrimethylsilane

N-Substituted 5-amino-1*H*-tetrazoles have been used as antiallergic or hypocholesterolemic agents, as CCK-B receptor antagonists, or as the prodrug of a selective iNOS inhibitor.[1–4] Commercially available 5-amino-1*H*-tetrazole is used to introduce the required tetrazolyl moiety. On the other hand, a variety of N-substituted 5-amino-1*H*-tetrazoles have been readily obtained in very good yields through the reaction of primary or secondary amines with alkyl or phenyl isothiocyanates, followed by treatment of the thus-obtained thioureas with sodium azide in the presence of mercury(II) chloride.[5]

We have recently shown that polyamines incorporating tetrazole units in their skeleton can be readily obtained by activating suitable polyamino-amides with Lawesson's reagent and then treating the thus-obtained thioamides with azidotrimethylsilane under Mitsunobu reaction conditions.[6] We, therefore, considered it of interest to examine the possibility of obtaining, for the first time, polyamines N-substituted with the tetrazolyl unit. For this purpose, we chose as a model compound the *N*-benzyl-*N*′-tritylpropane-1,3-diamine (**3**), readily available in 80% yield by lithium aluminum hydride mediated reduction of *N*-benzyl-N^3-trityl-β-alaninamide (**1**).[7] The reaction of **3** with benzyl isothiocyanate (BITC) produced unexceptionally the corresponding thiourea **5** in 89% yield. We then reacted this compound with either sodium azide or azidotrimethylsilane (TMSA) in the presence of a variety of reagents, expected to activate the thiourea function towards reaction with azide anion, in order to obtain the corresponding N-tetrazolated diamine derivative **7** (Scheme 1).

The reagents used were the following: mercury(II) chloride,[5] silver nitrate, iodomethane, Mukaiyama's reagent, and the combination of triphenylphosphine with diisopropyl azodicarboxylate (DIAD). Both iodomethane and Mukaiyama's reagent failed to give compound **7** whereas in the case of the inorganic salts incomplete reaction and rather low yields were observed. On the other hand, the



Scheme 1 Synthesis of selectively N-monotetrazolated α,ω-diamines.

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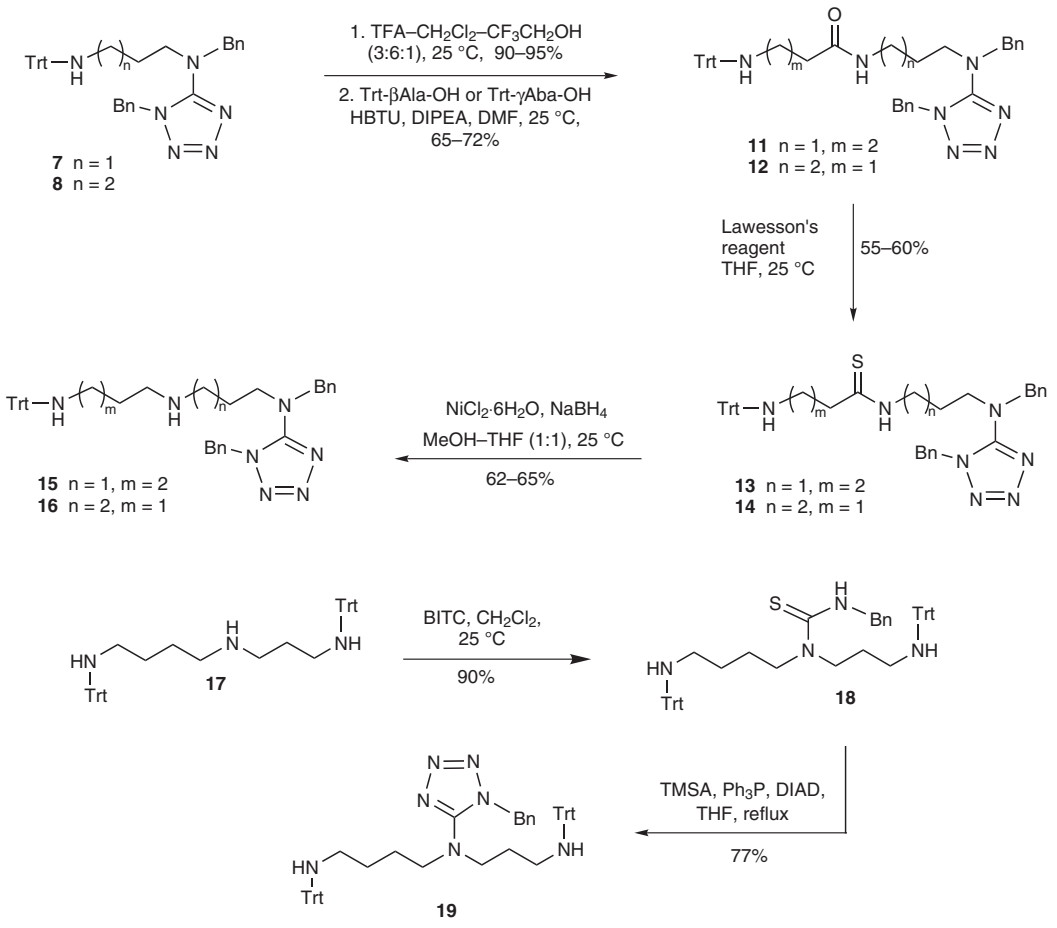
best results were obtained with the system triphenylphosphine/diisopropyl azodicarboxylate, which after two hours in refluxing tetrahydrofuran gave the tetrazolated derivative **7** in 76% yield. Similarly *N*-benzyl-*N*′-tritylbutane-1,4-diamine (**4**), readily obtained in 70% yield by lithium aluminum hydride mediated reduction of amide **2**, was converted into the thiourea derivative **6** in 85% yield, and the latter transformed to the corresponding tetrazolated derivative **8** in 70% yield. From the thus-obtained compound **7**, the detritylated derivative **9** was obtained in 93% yield by trifluoroacetic acid mediated acidolysis, whereas complete deprotection to give 5-(3-aminopropylamino)-1*H*-tetrazole (**10**) in 91% yield was performed by catalytic hydrogenolysis.

Prompted by these results, we decided to develop a methodology for the synthesis of selectively N^1-and N^8-tetrazolated spermidine derivatives **15** and **16**, respectively (Scheme 2, Table 1). Thus, detritylation of the 5-aminotetrazole derivatives **7** and **8** and coupling of the corresponding products with 4-(tritylamino)butanoic acid (Trt-γAba-OH) and *N*-trityl-β-alanine (Trt-βAla-OH) in the presence of the coupling agent *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HBTU) and *N*,*N*-diisopropylethylamine (DIPEA) produced the corresponding amides **11** and **12** in 65 and 72% yields, respectively. Attempted reduction of these amides with lithium aluminum hydride in refluxing tetrahydrofuran, resulted in complex reaction mixtures and failed to give the corresponding triamine derivatives. We then followed an alternative route, which involved the conversion of the amide to the corresponding thioamide by treatment with Lawesson's reagent, followed by reduction under mild reduction conditions, using the system sodium borohydride/nickel(II) chloride hexahydrate.[8]

Indeed, thionation of the amides **11** and **12** with Lawesson's reagent in tetrahydrofuran at ambient temperature produced the corresponding thioamides **13** and **14** in 60% and 55% yields, respectively. These compounds were then reacted with sodium borohydride/nickel(II) chloride hexahydrate in methanol–tetrahydrofuran 1:1 to give the expected amines **15** and **16** in 62% and 65% yields, respectively.

Finally, we turned our attention to extend this methodology to the N-tetrazolation of N^{α},N^{ω}-ditritylated tri- and tetraamines at their free secondary amino function. For this purpose, we chose as model compound the readily available N^1,N^8-ditritylspermidine (**17**).[9] Indeed, this compound was readily converted into the corresponding thiourea derivative **18** in 90% yield and the thus-obtained



Scheme 2 Synthesis of all three N-tetrazolated isomers of linear triamine spermidine.

Table 1 Conversion of Polyamine Derivatives to *N*-Benzylthioureas and the Latter to Polyaminotetrazoles[a]

Entry	Polyamine	*N*-Benzylthiourea	Yield (%)	Polyaminotetrazole	Time (h)	Yield (%)
1	**3**	**5**	89	**7**	2	76
2	**4**	**6**	85	**8**	2	70
3	**17**	**18**	90	**19**	3	77
4	**20**	**25**	90	**30**	16	82
5	**21**	**26**	85	**31**	12	50
6	**22**	**27**	87	**32**	17	47
7	**23**	**28**	73	**33**	14	44
8	**24**	**29**	80	**34**	14	48

[a] Conditions TMSA, Ph_3P, DIAD, THF, reflux.

intermediate was unexceptionally converted into the N^4-tetrazolated spermidine derivative **19** in 77% yield upon treatment with the system azidotrimethylsilane/triphenylphosphine/diisopropyl azodicarboxylate in refluxing tetrahydrofuran for three hours (Scheme 2).

We then extended this methodology to the N^1,N^{12}-ditritylspermine (N^1,N^{12}-Trt_2-SPM, **20**)[7] and the analogous N^{α},N^{ω}-ditritylated aliphatic and aromatic tetraamine derivatives **21**, **22**,[10] **23**,[11] and **24** (Scheme 3, Table 1) which were obtained according to literature procedures previously described by our research group.

Indeed, treatment of the polyamine derivatives **20**–**24** with benzyl isothiocyanate produced the corresponding thiourea derivatives **25**–**29** in 73–90% yields. These intermediates were then treated with azidotrimethylsilane/triphenylphosphine/diisopropyl azodicarboxylate in refluxing tetrahydrofuran for 14–17 hours to obtain the projected, internally N-tetrazolated polyamine derivatives **30**–**34** in 44–82% yields. Similarly to compound **7**, these polyamine derivatives can be readily deprotected as exemplified herein with the preparation of **35** and **36** through partial and complete deprotection of **30**, respectively.

In conclusion, the present methodology provides ease access to polyamines, bearing 1*H*-tetrazol-5-yl units on either their primary or secondary amino functions, by reacting the free amine functions with benzyl isothiocyanate, followed by treatment of the thus-obtained thioureas with azidotrimethylsilane under Mitsunobu reaction conditions.

Tests to determine the biological activity of these novel, fully deprotected, N-tetrazolated polyamines are currently in progress.

Melting points were determined with a Buchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 400.13 MHz and ^{13}C NMR spectra at 100.62 MHz on a Bruker DPX spectrometer. $CDCl_3$ and TMS were used as the solvent and internal standard, respectively, unless otherwise stated. The assignments of the ^{1}H spectra are based on chemical shift arguments, analysis of coupling patterns and signal intensities whereas the ^{13}C spectra were assigned taking into consideration chemical shift arguments. ESI-MS were recorded on a Micromass-Platform LC spectrometer using MeOH as solvent. Microanalyses were performed on a Carlo Erba EA 1108 CHNS elemental analyzer in the Laboratory of Instrumental Analysis of the University of Patras. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh) and TLC on 60 Merck 60 F_{254} films (0.2 mm) precoated on aluminum foil. Spots were visualized with UV light at 254 nm and the ninhydrin agent. All solvents (Merck) were dried and/or purified according to standard procedures prior to use. Anhyd Na_2SO_4 was used for drying organic solvents, unless otherwise indicated. Solvents were routinely removed at ca. 40 °C under reduced pressure (water aspirator). All reagents employed in the present work were purchased from either Aldrich or Fluka and were used without further purification. Tetraamine **24** was obtained in 65% overall yield through condensation of Trt-βAla-OH with 4,4′-(9-fluorenylidene)dianiline in the presence of HBTU/DIPEA, followed by $LiAlH_4$-mediated reduction. Compound **24** had mp 166–167 °C, R_f = 0.23 (toluene–EtOAc, 8:2). With the exception of TFA-mediated deprotections and catalytic hydrogenolysis, all other reactions were routinely carried out under an atmosphere of argon.

Mono- 5, 6, 18 and Bisthiourea Derivatives 25–29; General Procedure

To a soln of *N*-benzyl-*N*′-trityl-α,ω-diamine or N^{α},N^{ω}-ditritylpolyamine (5 mmol) in CH_2Cl_2 (25 mL) was added benzyl isothiocyanate (BITC, 1.3 equiv per free secondary amino group) and the resulting mixture was stirred for 0.5–5 h at r.t. The solvents were then removed under vacuum and the residue was subjected to flash column chromatography (toluene–EtOAc, various combinations from 8:2 to 95:5) to give the corresponding pure thioureas.

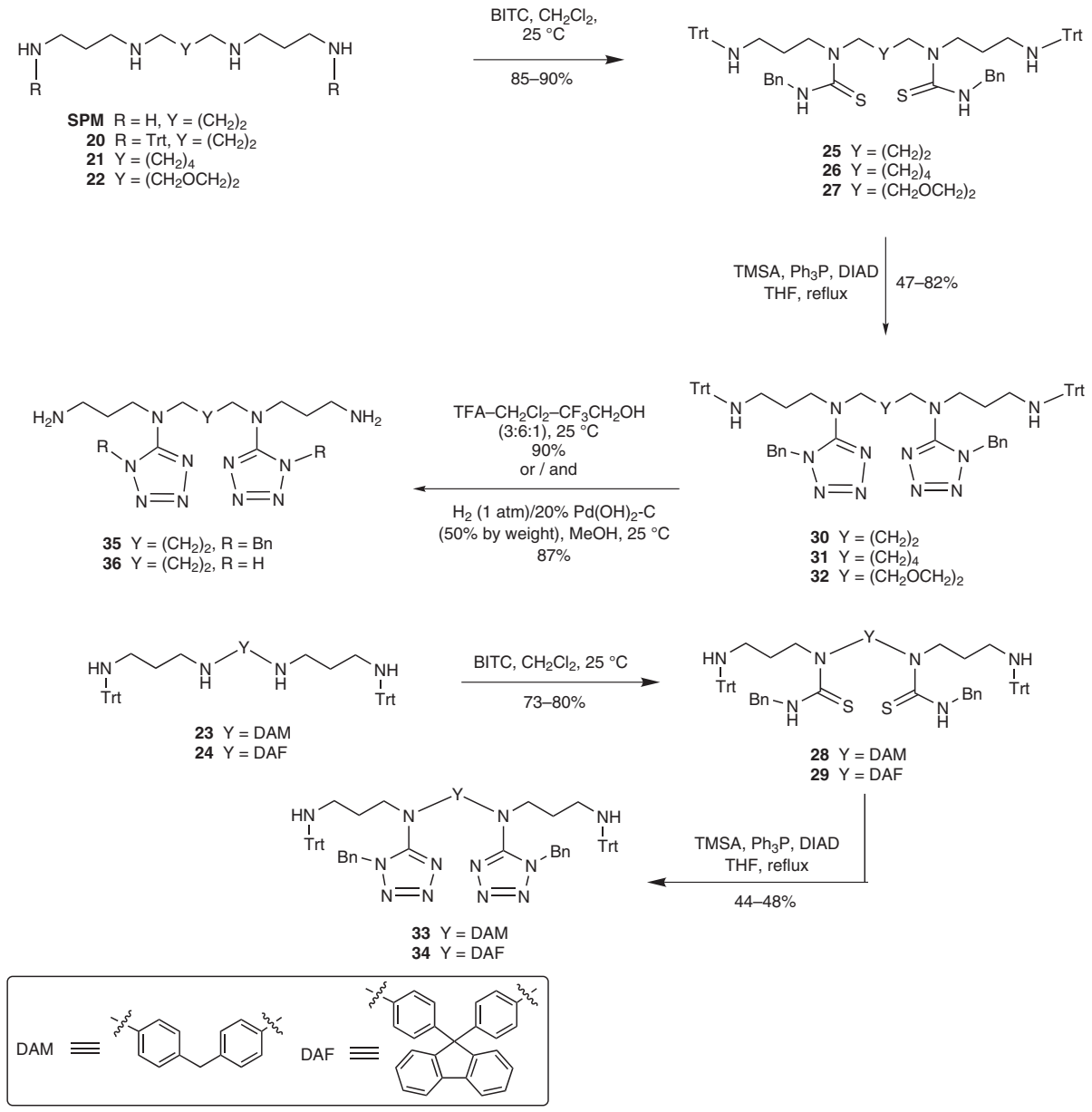
N^1-Benzyl-N^1-[(benzylamino)thiocarbonyl]-N^3-tritylpropane-1,3-diamine (5)

Oil; yield: 89%; R_f = 0.22 (toluene–EtOAc, 95:5).

^{1}H NMR: δ = 7.11–7.38 (m, 25 H), 6.04 (unresolved t, 1 H), 4.89 (s, 2 H), 4.81 (d, *J* = 4.8 Hz, 2 H), 3.82 (t, *J* = 7.2 Hz, 2 H), 2.18 (t, *J* = 6.0 Hz, 2 H), 1.78 (quint, *J* = 6.8 Hz, 3 H).

^{13}C NMR: δ = 182.4, 145.8, 138.2, 136.3, 128.9, 128.6, 127.8, 127.5, 127.4, 126.9, 126.4, 71.1, 54.4, 50.3, 49.5, 40.9, 28.7.

ESI-MS: *m*/*z* = 556.33 ($M + H^+$), 243.11 (Trt^+).



Scheme 3 Synthesis of tetraamines bistetrazolated at their secondary amino function.

N^1-Benzyl-N^1-[(benzylamino)thiocarbonyl]-N^4-tritylbutane-1,4-diamine (6)

Foam; yield: 85%; R_f = 0.18 (toluene–EtOAc, 95:5).

^{1}H NMR: δ = 7.44–7.10 (m, 25 H), 5.57 (t, *J* = 5.2 Hz, 1 H), 4.86 (s, 2 H), 4.81 (d, *J* = 4.8 Hz, 2 H), 3.73 (t, *J* = 7.6 Hz, 2 H), 2.13 (t, *J* = 6.8 Hz, 2 H), 1.74 (quint, *J* = 8.0 Hz, 2 H), 1.50 (quint, *J* = 7.6 Hz, 2 H).

^{13}C NMR: δ = 182.0, 146.8, 137.9, 135.9, 129.0, 128.6, 127.8, 127.6, 127.5, 126.6, 126.2, 70.8, 54.1, 52.0, 50.4, 43.1, 28.0, 25.3.

ESI-MS: *m*/*z* = 570.38 (M + H$^+$), 243.20 (Trt$^+$).

4-[(Benzylamino)thiocarbonyl]-N^1,N^8-ditrityl-4-azaoctane-1,8-diamine (18)

Foam; yield: 90%; R_f = 0.32 (toluene–EtOAc, 9:1).

^{1}H NMR: δ = 7.51–7.15 (m, 35 H), 5.59 (unresolved t, 1 H), 4.83 (d, *J* = 4.8 Hz, 2 H), 3.66 (t, *J* = 8.7 Hz, 2 H), 3.55 (t, *J* = 8.7 Hz, 2 H), 2.19 (t, *J* = 6.4 Hz, 2 H), 2.12 (quint, *J* = 8.0 Hz, 2 H), 1.76 (quint, *J* = 7.3 Hz, 2 H), 1.66 (quint, *J* = 8.4 Hz, 2 H), 1.50 (quint, *J* = 7.2 Hz, 2 H).

^{13}C NMR: δ = 181.4, 146.1, 145.7, 138.5, 128.7, 128.6, 127.9, 127.8, 127.6, 127.5, 126.4, 126.2, 71.9, 71.1, 51.3, 50.1, 48.8, 43.2, 40.9, 28.9, 28.2, 26.4.

ESI-MS: *m*/*z* = 780.49 (M + H$^+$), 243.19 (Trt$^+$).

4,9-Bis[(benzylamino)thiocarbonyl]-N^1,N^{12}-ditrityl-4,9-diazadodecane-1,12-diamine (25)

White solid; yield: 90%; mp 138–139 °C; R_f = 0.27 (toluene–EtOAc, 9:1).

^{1}H NMR: δ = 7.35–7.15 (m, 40 H), 6.53 (t, *J* = 4.8 Hz, 2 H), 4.79 (d, *J* = 4.8 Hz, 4 H), 3.79 (unresolved t, 4 H), 3.62 (unresolved t, 4 H), 2.20 (t, *J* = 6.0 Hz, 4 H), 1.75 (unresolved quint, 6 H), 1.65 (unresolved m, 4 H).

^{13}C NMR: δ = 181.4, 145.7, 138.8, 128.6, 127.9, 127.5, 127.3, 126.4, 71.1, 50.1, 49.7, 45.1, 40.9, 28.8, 24.3.

ESI-MS: *m/z* = 986.88 (M + H$^+$), 243.16 (Trt$^+$).

Anal. Calcd for $C_{64}H_{68}N_6S_2$: C, 78.01; H, 6.96; N, 8.53; S, 6.51. Found: C, 78.23; H, 6.71; N, 8.68; S, 6.29.

4,11-Bis[(benzylamino)thiocarbonyl]-*N*^{1},*N*^{14}-dityrityl-4,11-diazatetradecane-1,14-diamine (26)
Foam; yield: 85%; R_f = 0.16 (toluene–EtOAc, 9:1).

ESI-MS: *m/z* = 1014.98 (M + H$^+$), 243.18 (Trt$^+$).

4,13-Bis[(benzylamino)thiocarbonyl]-*N*^{1},*N*^{16}-dityrityl-7,10-dioxa-4,13-diazahexadecane-1,16-diamine (27)
White solid; yield: 87%; R_f = 0.45 (toluene–EtOAc, 75:25).

^{1}H NMR: δ = 7.49–7.15 (m, 42 H), 4.76 (d, *J* = 4.8 Hz, 2 H), 3.81 (t, *J* = 7.6 Hz, 4 H), 3.50 (unresolved t, 4 H), 3.36 (unresolved t, 4 H), 3.12 (s, 4 H), 2.17 (t, *J* = 6.4 Hz, 4 H), 1.83 (quint, *J* = 7.2 Hz, 4 H).

^{13}C NMR: δ = 183.6, 146.0, 138.6, 128.7, 128.6, 127.8, 127.3, 126.3, 71.0, 70.5, 70.1, 50.8, 50.0, 40.9, 28.4.

ESI-MS: *m/z* = 1046.67 (M + H$^+$), 243.20 (Trt$^+$).

4,4′-Methylenebis{*N*-[(benzylamino)thiocarbonyl]-*N*-[3-(tritylamino)propyl]aniline} (28)
Foam; yield: 73%; R_f = 0.18 (toluene–EtOAc, 95:5).

^{1}H NMR: δ = 7.53–7.13 (m, 44 H), 7.05 (d, *J* = 7.6 Hz, 4 H), 5.46 (t, *J* = 5.2 Hz, 2 H), 4.79 (d, *J* = 5.6 Hz, 4 H), 4.36 (t, *J* = 7.2 Hz, 4 H), 3.97 (s, 2 H), 2.16 (t, *J* = 6.4 Hz, 4 H), 1.83 (quint, *J* = 7.2 Hz, 4 H).

^{13}C NMR: δ = 182.1, 146.2, 140.7, 139.4, 138.2, 131.0, 128.7, 128.6, 128.3, 127.7, 127.3, 127.2, 126.1, 71.0, 53.1, 49.6, 40.8, 28.9.

ESI-MS: *m/z* = 1097.46 (M + H$^+$), 243.24 (Trt$^+$).

4,4′-(9-Fluorenylidene)bis{*N*-[(benzylamino)thiocarbonyl]-*N*-[3-(tritylamino)propyl]aniline} (29)
Foam; yield: 80%; R_f = 0.36 (toluene–EtOAc, 95:5).

ESI-MS: *m/z* = 1246.56 (M + H$^+$), 243.14 (Trt$^+$).

Mono- 7, 8, 19 or Bis-tetrazolated 30–34 Polyamine Derivatives; General Procedure
To a soln of mono- or bisthiourea derivative (2.5 mmol) in THF (2.5 mL) were added DIAD and Ph_3P (2.5 equiv per thiourea group) followed by the addition 5 min later of TMSA (2.5 equiv per thiourea group). The resulting mixture was stirred under reflux for 2–16 h (see Table 1). Then, the solvents were removed under reduced pressure and the residue was subjected to flash column chromatography (toluene–EtOAc, various combinations from 8:2 to 95:5) to give the corresponding pure mono- (**7**, **8**, **19**) or bis-tetrazolated (**30**–**34**) polyamine derivatives.

***N*^{1}-Benzyl-*N*^{1}-(1-benzyl-1*H*-tetrazol-5-yl)-*N*^{3}-tritylpropane-1,3-diamine (7)**
Foam; yield: 76%; R_f = 0.24 (toluene–EtOAc, 9:1).

^{1}H NMR: δ = 7.39–6.98 (m, 25 H), 5.25 (s, 2 H), 4.32 (s, 2 H), 3.30 (t, *J* = 7.6 Hz, 2 H), 1.99 (t, *J* = 6.8 Hz, 2 H), 1.66 (quint, *J* = 6.8 Hz, 2 H).

^{13}C NMR: δ = 158.3, 145.9, 136.5, 134.3, 129.0, 128.8, 128.5, 127.8, 127.5, 126.6, 126.3, 70.9, 55.2, 50.3, 49.7, 40.9, 28.3.

ESI-MS: *m/z* = 565.94 (M + H$^+$), 587.96 (M + Na$^+$), 243.15 (Trt$^+$).

***N*^{1}-Benzyl-*N*^{1}-(1-benzyl-1*H*-tetrazol-5-yl)-*N*^{4}-tritylbutane-1,4-diamine (8)**
Oil; yield: 70%; R_f = 0.32 (toluene–EtOAc, 9:1).

^{1}H NMR: δ = 7.45–7.05 (m, 25 H), 5.33 (s, 2 H), 4.39 (s, 2 H), 3.19 (t, *J* = 7.6 Hz, 2 H), 2.02 (t, *J* = 7.2 Hz, 2 H), 1.50 (quint, *J* = 6.8 Hz, 2 H), 1.26 (quint, *J* = 7.2 Hz, 2 H).

^{13}C NMR: δ = 158.3, 145.8, 136.6, 134.4, 129.1, 128.8, 128.6, 128.5, 127.8, 127.4, 126.6, 126.3, 71.0, 68.0, 55.0, 51.5, 50.5, 43.2, 24.9.

ESI-MS: *m/z* = 579.91(M + H$^+$), 243.14 (Trt$^+$).

4-(1-Benzyl-1*H*-tetrazol-5-yl)-*N*^{1},*N*^{8}-dityrityl-4-azaoctane-1,8-diamine (19)
Oil; yield: 77%; R_f = 0.25 (toluene–EtOAc, 9:1).

^{1}H NMR: δ = 7.55–7.01 (m, 35 H), 5.25 (s, 2 H), 3.23 (t, *J* = 7.6 Hz, 2 H), 3.05 (t, *J* = 6.8 Hz, 2 H), 1.98 (m, 4 H), 1.60 (quint, *J* = 6.8 Hz, 2 H), 1.36 (t, *J* = 6.8 Hz, 2 H), 1.18 (m, 2 H).

ESI-MS: *m/z* = 789.47 (M + H$^+$), 243.16 (Trt$^+$).

4,9-Bis(1-benzyl-1*H*-tetrazol-5-yl)-*N*^{1},*N*^{12}-dityrityl-4,9-diazadodecane-1,12-diamine (30)
Oil; yield: 82%; R_f = 0.25 (toluene–EtOAc, 9:1).

ESI-MS: *m/z* = 1004.51 (M + H$^+$), 243.16 (Trt$^+$).

4,11-Bis(1-benzyl-1*H*-tetrazol-5-yl)-*N*^{1},*N*^{14}-dityrityl-4,11-diazatetradecane-1,14-diamine (31)
Oil; yield: 50%; R_f = 0.34 (toluene–EtOAc, 8:2).

^{1}H NMR: δ = 7.42–6.98 (m, 40 H), 5.28 (s, 4 H), 3.23 (t, *J* = 7.2 Hz, 4 H), 3.04 (t, *J* = 7.6 Hz, 4 H), 2.00 (t, *J* = 6.8 Hz, 4 H), 1.60 (m, 8 H), 1.29 (m, 4 H).

ESI-MS: *m/z* = 1033.02 (M + H$^+$), 243.19 (Trt$^+$).

4,13-Bis(1-benzyl-1*H*-tetrazol-5-yl)-*N*^{1},*N*^{16}-dityrityl-7,10-dioxa-4,13-diazahexadecane-1,16-diamine (32)
Oil; yield: 47%; R_f = 0.21 (toluene–EtOAc, 8:2).

ESI-MS: *m/z* = 1064.65 (M + H$^+$), 243.21 (Trt$^+$).

4,4′-Methylenebis{*N*-(1-benzyl-1*H*-tetrazol-5-yl)-*N*-[3-(tritylamino)propyl]aniline} (33)
Foam; yield: 44%; R_f = 0.16 (toluene–EtOAc, 9:1).

ESI-MS: *m/z* = 1114.52 (M + H$^+$), 243.11 (Trt$^+$).

4,4′-(9-Fluorenylidene)bis{*N*-(1-benzyl-1*H*-tetrazol-5-yl)-*N*-[3-(tritylamino)propyl]aniline} (34)
Foam; yield: 48%; R_f = 0.30 (toluene–EtOAc, 9:1).

^{1}H NMR: δ = 7.85 (d, *J* = 7.6 Hz, 2 H), 7.45–6.94 (m, 46 H), 6.56 (d, *J* = 8.8 Hz, 4 H), 6.47 (d, *J* = 7.6 Hz, 4 H), 4.76 (s, 4 H), 3.88 (t, *J* = 7.2 Hz, 4 H), 2.12 (unresolved t, 4 H), 1.77 (unresolved quint, 4 H).

^{13}C NMR: δ = 155.8, 150.6, 145.7, 142.8, 142.1, 140.2, 133.3, 129.2, 128.6, 128.5, 128.1, 128.0, 127.9, 127.1, 126.4, 125.8, 123.4, 120.6, 71.2, 64.5, 53.3, 50.9, 40.9, 28.8.

ESI-MS: *m/z* = 1264.57 (M + H$^+$), 243.08 (Trt$^+$).

Amides 11 and 12; General Procedure
To a soln of amine **7** or **8** (3 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C were added 2,2,2-trifluoroethanol (0.34 mL) and TFA (1 mL). The resulting mixture was stirred for 20–30 min at the same temperature. The solvents were then removed under vacuum and the residue was treated with warm *n*-hexane to remove Ph_3COH and give the corresponding pure TFA salts in high yields (90–95%). The thus-obtained TFA salts (2 mmol) were further treated with either Trt-βAla-OH or Trt-γAba-OH (2 mmol) in DMF (2 mL) in the presence of HBTU (2 mmol) and DIPEA (6 mmol), for 5 min at 0 °C and at r.t. for 30 min. Then, the mixtures were diluted with EtOAc and washed once with each of cold aq 1 M NaOH, H_2O, cold aq 5% cit-

ric acid, and H_2O. After drying (Na_2SO_4), filtration, evaporation of the solvent under vacuum and flash column chromatography (toluene–EtOAc, various combinations from 1:1 to 2:8) the spermidine derivatives **11** and **12**, respectively, were obtained.

1-[Benzyl(1-benzyl-1*H*-tetrazol-5-yl)amino]-8-(tritylamino)-4-azaoctan-5-one (11)
Oil; yield: 65%; R_f = 0.20 (toluene–EtOAc, 1:1).

ESI-MS: *m*/*z* = 650.55 ($M + H^+$), 243.23 (Trt^+).

8-[Benzyl(1-benzyl-1*H*-tetrazol-5-yl)amino]-1-(tritylamino)-4-azaoctan-3-one (12)
Oil; yield: 72%; R_f = 0.26 (toluene–EtOAc, 2:8).

ESI-MS: *m*/*z* = 650.62 ($M + H^+$), 243.18 (Trt^+).

Thioamide 13 and 14; General Procedure
To a soln of **11** or **12** (1.5 mmol) in THF (3.5 mL) was added Lawesson's reagent (0.8 mmol) and the mixture stirred at r.t. until completion of the reaction (14–16 h). The solvents were removed under vacuum and the corresponding residues were subjected to flash column chromatography (toluene–EtOAc, 8:2 and 75:25, respectively) to give pure thioamides **13** and **14**, respectively.

1-[Benzyl(1-benzyl-1*H*-tetrazol-5-yl)amino]-8-(tritylamino)-4-azaoctane-5-thione (13)
Oil; yield: 60%; R_f = 0.36 (toluene–EtOAc, 1:1).

ESI-MS: *m*/*z* = 665.98 ($M + H^+$), 243.14 (Trt^+).

8-[Benzyl(1-benzyl-1*H*-tetrazol-5-yl)amino]-1-(tritylamino)-4-azaoctane-3-thione (14)
Oil; yield: 55%; R_f = 0.64 (toluene–EtOAc, 2:8).

ESI-MS: *m*/*z* = 666.05 ($M + H^+$), 243.27 (Trt^+).

Reduction of Thioamides 13 and 14; General Procedure
To a soln of **13** or **14** (1 mmol) and $NiCl_2·6H_2O$ (8.5 mmol) in MeOH–THF (1:1, 24 mL) precooled to 0 °C was added $NaBH_4$ (50 mmol) in 5 portions over 15 min and the resulting mixture was stirred at r.t. for 30 min. The mixture was then filtered through Celite and the solvents were removed under vacuum. The resulting residue was diluted with $CHCl_3$ and washed once with each of 5% aq $NaHCO_3$, H_2O, sat. aq EDTA, and H_2O. After drying (Na_2SO_4), filtration, evaporation of the solvent under vacuum and flash column chromatography ($CHCl_3$–MeOH–NH_3, 95:5:0.5) the corresponding spermidine derivatives **15** and **16**, respectively, were obtained.

N^1-Benzyl-N^1-(1-benzyl-1*H*-tetrazol-5-yl)-N^8-trityl-4-azaoctane-1,8-diamine (15)
Oil; yield: 62%; R_f = 0.28 ($CHCl_3$–MeOH–NH_3, 95:5:0.5).

^{1}H NMR: δ = 7.48–7.05 (m, 25 H), 5.37 (s, 2 H), 4.40 (s, 2 H), 3.34 (t, *J* = 7.2 Hz, 2 H), 2.48 (t, *J* = 6.0 Hz, 2 H), 2.45 (t, *J* = 6.8 Hz, 2 H), 2.13 (t, *J* = 6.3 Hz, 2 H), 1.71 (quint, *J* = 7.2 Hz, 2 H), 1.49 (m, 4 H).

^{13}C NMR: δ = 158.3, 146.2, 136.5, 134.4, 129.1, 128.8, 128.6, 128.5, 127.7, 127.2, 126.6, 126.2, 70.1, 54.75, 50.5, 49.7, 49.3, 46.5, 43.4, 28.6, 27.5, 27.2.

ESI-MS: *m*/*z* = 636.87 ($M + H^+$), 243.11 (Trt^+).

N^8-Benzyl-N^8-(1-benzyl-1*H*-tetrazol-5-yl)-N^1-trityl-4-azaoctane-1,8-diamine (16)
Oil; yield: 65%; R_f = 0.16 ($CHCl_3$–MeOH–NH_3, 95:5:0.5).

ESI-MS: *m*/*z* = 636.96 ($M + H^+$), 243.34 (Trt^+).

Detritylation and Complete Deprotection of Polyamino Derivatives 7 and 30; General Procedure
To a soln of polyamino derivative **7** or **30** (1 mmol) in CH_2Cl_2 (1 mL) cooled to 0 °C were added 2,2,2-trifluoroethanol (0.17 mL) and TFA (0.5 mL). The resulting mixture was stirred for 20–30 min at this temperature. The solvents were then removed under vacuum and the residue was treated with warm *n*-hexane to remove Ph_3COH to give the corresponding pure polyamines **9** and **35** as their TFA salts in high yields (90–93%). For complete deprotection compounds **9** and **35** (0.5 mmol) were dissolved in MeOH (10–12 mL) and subjected to catalytic hydrogenolysis using as the catalyst 20% $Pd(OH)_2$-C (50% by weight) for 18–24h. The catalyst was removed by filtration through Celite and the solvents were evaporated to dryness to give **10** and **36** in 91% and 87% yields, respectively.

N^1-Benzyl-N^1-(1-benzyl-1*H*-tetrazol-5-yl)butane-1,4-diamine (9)
Oil; yield: 93%; oil.

^{1}H NMR: δ = 8.32 (br s, 3 H), 7.4–6.95 (m, 10 H), 5.30 (s, 2 H), 4.35 (s, 2 H), 3.52 (t, *J* = 6.4 Hz, 2 H), 2.95 (unresolved m, 2 H), 2.00 (quint, *J* = 6.4 Hz, 2 H).

ESI-MS: *m*/*z* = 323.24 ($M + H^+$).

N^1-(1*H*-Tetrazol-5-yl)butane-1,4-diamine (10)
Oil; yield: 91%.

ESI-MS: *m*/*z* = 142.99 ($M + H^+$).

4,9-Bis(1-benzyl-1*H*-tetrazol-5-yl)-4,9-diazadodecane-1,12-diamine (35)
Oil; yield: 90%; R_f = 0.36 ($CHCl_3$–MeOH–NH_3, 6:4:0.4).

^{1}H NMR (DMSO-d_6): δ = 7.72 (br s, 6 H), 7.36–7.10 (m, 10 H), 5.48 (s, 4 H), 3.20 (t, *J* = 7.2 Hz, 4 H), 2.97 (unresolved t, 4 H), 2.62 (m, 4 H), 1.66 (quint, *J* = 7.2 Hz, 4 H), 0.98 (unresolved m, 4 H).

^{13}C NMR (DMSO-d_6): δ = 157.7, 135.3, 129.3, 128.5, 127.2, 51.1, 50.4, 48.2, 36.9, 25.5, 24.2.

ESI-MS: *m*/*z* = 519.51 ($M + H^+$).

4,9-Bis(1*H*-tetrazol-5-yl)-4,9-diazadodecane-1,12-diamine (36)
Oil; yield: 87%.

^{1}H NMR (DMSO-d_6): δ = 3.39 (t, *J* = 5.7 Hz, 4 H), 3.34 (unresolved m, 4 H), 2.79 (t, *J* = 5.7 Hz, 4 H), 1.82 (unresolved m, 4 H), 1.50 (unresolved m, 4 H).

^{13}C NMR (DMSO-d_6): δ = 158.8, 49.7, 46.9, 36.9, 25.8, 24.6.

ESI-MS: *m*/*z* = 339.26 ($M + H^+$).

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