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SOLUTION PARALLEL SYNTHESIS OF CYCLIC GUANIDINES

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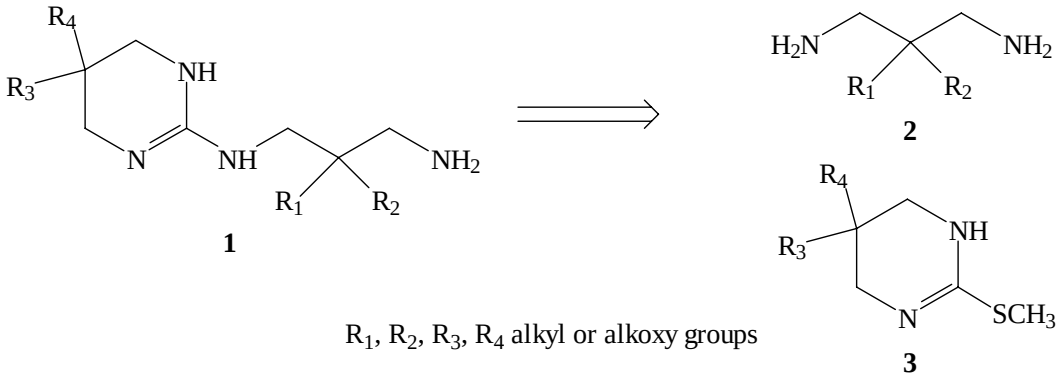
Abstract- An efficient method for the solution phase synthesis of cyclic guanidines is presented. A variety of 2-substituted monoprotected propanediamines react with a set of 5-substituted 2-methylthio-3,4,5,6-tetrahydropyrimidines under Rathke conditions for the construction of a potential library of 81 cyclic guanidines.

The guanidine moiety is present in many active drugs with uses covering large therapeutic areas:[1] cardiovascular, antihistaminic, anti-inflammatory, antidiabetic, antibacterial and fungicidal. Recent development in combinatorial chemistry on solid phase as well as in solution[2] have largely demonstrated the parallel synthesis of numbers of compounds.[3] We report here the solution phase synthesis of 6-membered cyclic guanidines with variable lipophilicity. Many reagents have been used to prepare protected and unprotected guanidines including carbodiimide derivatives,[4] formamidinesulfinic acid,[5] pyrazole-1-carboxamide derivatives[6] and isothiourea derivatives.[7] The latter gave access to the more adapted method to synthesise the new cyclic guanidine **(1)** from propanediamines **(2)** and cyclic isothioureas **(3)**, as depicted in scheme 1.

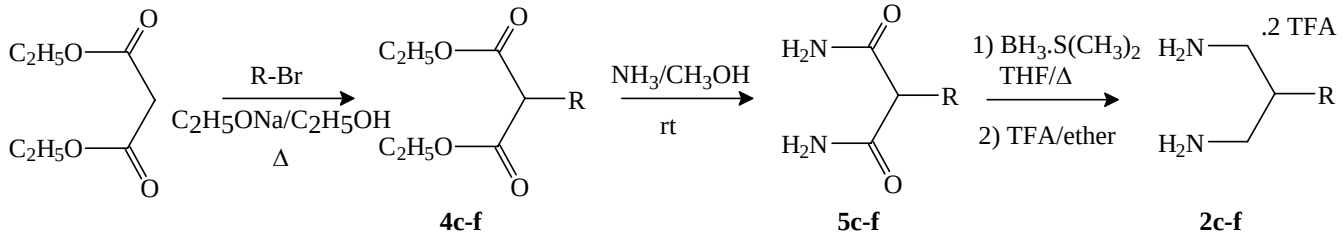


Scheme 1 : *Retrosynthetic way for the preparation of 6-membered cyclic guanidines*

	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**
R_1, R_3	H	CH_3	$(CH_2)_2C_6H_5$	$(CH_2)_5CH_3$	$(CH_2)_9CH_3$	$(CH_2)_{17}CH_3$	$pOC_6H_4CF_3$	$O(CH_2)_9CH_3$	$O(CH_2)_{17}CH_3$
R_2, R_4	H	CH_3	H	H	H	H	H	H	H

Table 1: *Alkyl and alkoxy substitutions of propanediamines **(2)** and isothioureas **(3)**.*

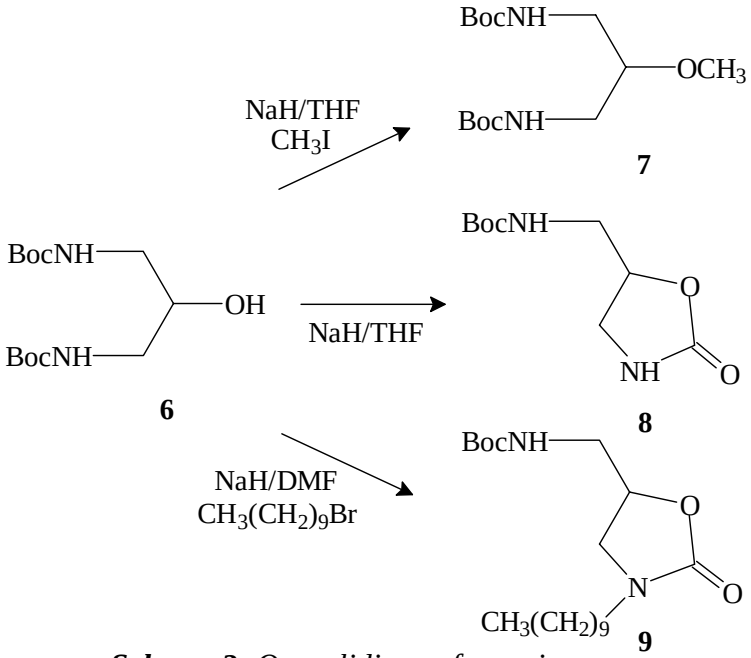
Following this scheme, we have first synthesised[8] nine propanediamines **(2a-i)** (Table 1) substituted in position 2 with lipophilic alkyl- and alkoxy-groups and then the correspondent isothioureas **(3a-i)**.
Only propanediamines **(2a)** and **(2b)** are commercially available. 2-Alkylpropanediamines **(2c-f)** were obtained *via* malonic synthesis (Scheme 2), and 2-alkoxypropanediamines were prepared using 2-hydroxypropanediamine as starting material.



4c-f **5c-f** **2c-f**

Scheme 2: *2-Alkylpropanediamines synthesis*

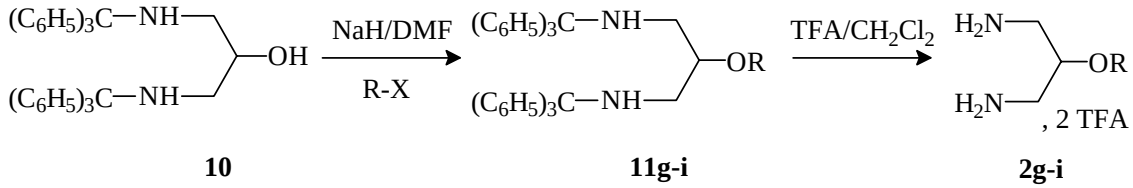
Alkylation[9] of diethyl malonate was carried out with the corresponding alkyl halide and sodium ethoxide under reflux. Diamides **(5c-f)** were finally obtained by shaking diesters **(4c-f)** in a saturated methanolic solution of ammonia. Reduction[10] of the amide functions with boran-methyl sulfide complex in THF gave the diamines **(2c-f)** which were isolated as diammonium salt after treatment with a 50% solution of TFA in methylene chloride. Many of these salts were found to be hygroscopic.
2-Alkoxypropanediamines **(2g-i)** were obtained by *O*-alkylation of the *N*-protected 1,3-diaminopropan-2-ol since the amino function protection is necessary to overcome the preferential *N*-alkylation. In the literature, Ramalingam *et al*.[9] described the synthesis of *N*,*N'*-di-*tert*-Boc-2-methoxy-1,3-diaminopropane **(7)** with 89% yield (Scheme 3). *N*,*N'*-di-*tert*-Boc-diaminopropan-2-ol **(6)** reacts with methyl iodide in presence of sodium hydride. Practice of this alkylation method from **6** with a longer alkyl halide like 1-bromodecane led to the oxazolidinone **(8)**. Such cyclisation also occurs with 1-iododecane and without any alkyl halide. Sodium hydride pulled out first the OH hydrogen and then the formed alkoxide quickly attacked the Boc-carbonyl function which is more electrophilic than the alkyl halide. In DMF, the *tert*-butoxide anion formed in the mixture pull out the NH hydrogen of the oxazolidinone to give the *N*-alkylated derivative **(9)**.



7 **6** **8** **9**

Scheme 3: *Oxazolidinone formation*

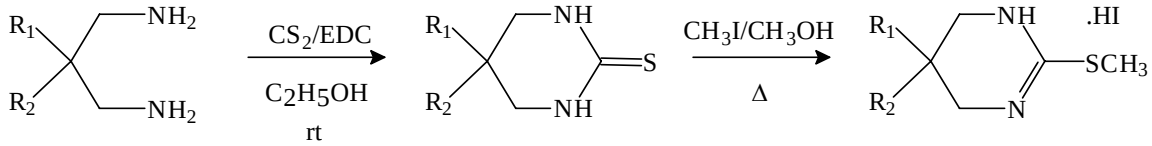
At last, we put a trityl function on 2-hydroxypropanediamine in place of the Boc-protecting group (Scheme 4). *O*-Alkylation of **10** with the correspondent alkyl or aryl halide in presence of NaH in DMF led to compounds **(11g-i)**. Diammonium salts **(2g-i)** were obtained after deprotection in acidic conditions.



10 **11g-i** **2g-i**

Scheme 4: *2-Alkoxypropanediamines synthesis*

The isothiourea library was obtained in two steps from and the already described propanediamines **(2b-i)** (Scheme 5) and the commercial thiourea **(12a)** for compound **3a**.

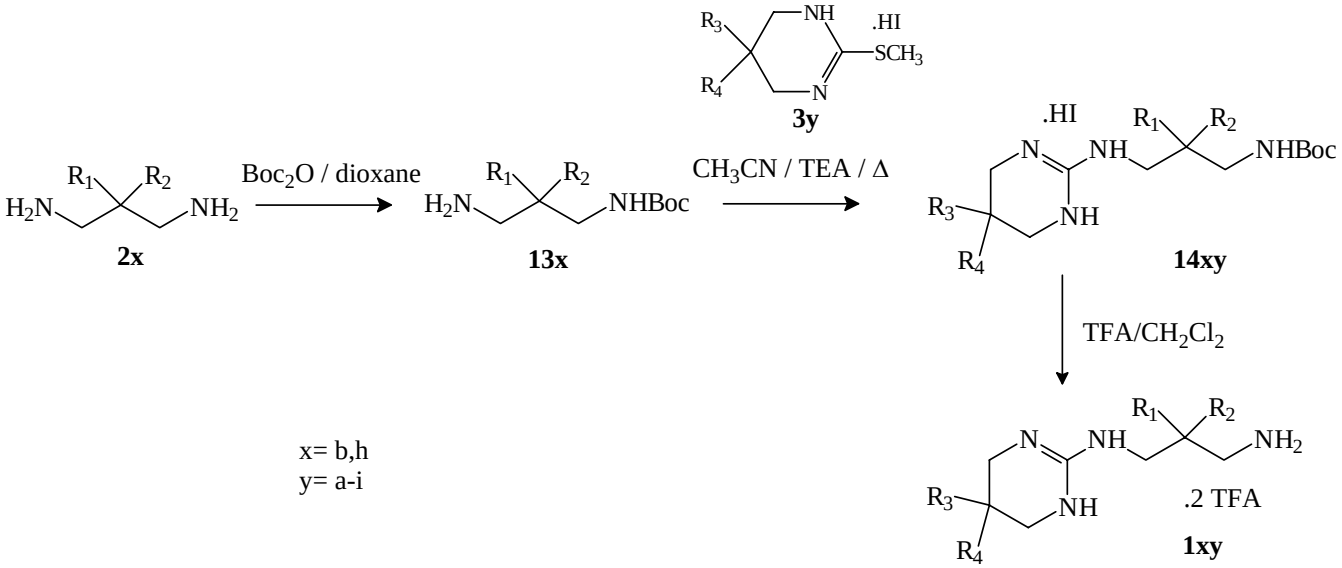


2b-i **12b-i** **3b-i**

Scheme 5: *Isothioureas synthesis*

Cyclisation step[11] is allowed with 1-[3-dimethylamino propyl]-3-ethylcarbodiimide hydrochloride (EDC) and carbon disulfide in ethanol at room temperature according to the following mechanism: amine nucleophilic attack of **2b-i** on CS_2 led to the thiocarbamate which is activated by reaction with EDC. Rearrangement of this intermediate to an isothiocyanate, which then undergo a nucleophilic attack from the other amine function, gave cyclic compounds **(12b-i)**. The activation is carried out with methyl iodide in methanol under reflux to afford isothiourea salts **(3a-i)**.

The synthetic method to produce the family of guanidines **(1)** is depicted in Scheme 6:



Scheme 6: *Guanidine synthesis*

The monoprotection[12] of **2x** (x and y are depicted in Table 2) was carried out with a large excess of propanediamine and one equivalent of Boc_2O in dioxane. Addition and elimination of the isothiouronium salt **(3y)** on the protected propanediamine **(13x)**, in the presence of one equivalent of triethylamine, led to

the guanidine **(14xy)** in acetonitrile under reflux. Desired compounds **(1xy)** were obtained by treatment of **5** with a solution of trifluoroacetic acid in dichloromethane.
From these building blocks (Table 1) such procedure allowed us the potential construction of a library of 81 guanidines **(1)**. In order to study the influence of R_1, R_2, R_3 and R_4 groups on this synthetic method, eight guanidines **(1xy)** were synthesised (Table 2): seven compounds from 2,2-dimethylpropanediamine **(2b)** and isothiouronium salts **(3a-c, 3e , 3g-i)** yielding compounds **(13b(a-c), 5be, 5b(g-i))** and the last one **(5hc)** from 2-decyloxypropanediamine **(13h)** and **3c**. As indicated on Table 2 the yield of these reactions were good, at global 60-87%. Treatment of **14xy** with a solution trifluoroacetic acid in dichloromethane quantitatively yielded guanidiniums salts **(1xy)** after washing with ether. The purity of these crude guanidiniums salts were good enough for their further application except for compounds **(1bg)** and **(1ba)** which had to be purified by column chromatography. By this way and using this procedure, with a variety of R_1, R_2, R_3 and R_4 groups in different substituted propanediamines **(2)** and 2-methylthio-3,4,5,6-tetrahydropyridinium salts **(3)**, we have demonstrated the efficacy of our approach to built a library of 81 cyclic guanidines.

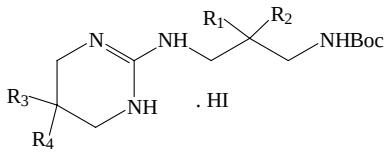
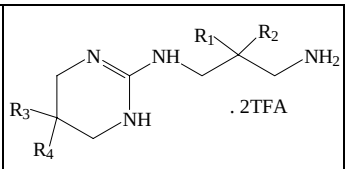
R_1	**R_2**	**R_3**	**R_4**			
				14xy	**Yield %**	**1xy**
CH_3	CH_3	O*p*$C_6H_4CF_3$	H	**14bg**	60	**1bg**
CH_3	CH_3	$O(CH_2)_9CH_3$	H	**14bh**	67	**1bh**
CH_3	CH_3	$(CH_2)_2C_6H_5$	H	**14bc**	83	**1bc**
CH_3	CH_3	$O(CH_2)_{17}CH_3$	H	**14bi**	61	**1bi**
CH_3	CH_3	$(CH_2)_5CH_3$	H	**14bd**	85	**1be**
CH_3	CH_3	H	H	**14ba**	60	**1ba**
CH_3	CH_3	CH_3	CH_3	**14bb**	85	**1bb**
$O(CH_2)_9CH_3$	H	$(CH_2)_2C_6H_5$	H	**14hc**	87	**1hc**

Table 2 : *Synthesised guanidines and intermediates*

In summary, we have demonstrated a synthetic route to build a library of 81 cyclic guanidines from 2-substituted propanediamines and 5-substituted 2-methylthio-3,4,5,6-tetrahydropyrimidines. MonoBoc-protected propanediamines were converted to guanidines in good yield with reasonable purity.

EXPERIMENTAL

Melting points were determined in open capillary tubes with a Büchi apparatus and are uncorrected. ^{1}H-NMR were recorded at 100 MHz (Brüker AC 100) or 360 MHz (Brüker AC 360), while ^{13}C-NMR at 25 or 90 MHz. Chemical shifts are reported relative to TMS as internal standard and the *J* values in Hz. Elemental analysis were calculated with 1108.ERBA.SCIENCE apparatus. MS spectra were recorded with JEOL JMS DX300 (FAB+) and Plaform Micromass (ESI+) apparatus by Science University of Montpellier. Macherey Nagel precoated silica gel SIL G-25UV_{254} plates were employed for analytical thin layer chromatography and silica gel Matrex 35-70µ (200-400 mesh) for column chromatography.

Diethyl 2-alkylmalonate (4c-f) were prepared according to published procedure.[9]

4c. 74%. bp 117°C (10^{-2} mbar); ^{1}H-NMR ($CDCl_3$): 1.25 (t, 3H, CH_3, J=7.1 Hz); 2.23 (m, 2H, CH-C$\underline{H}_2$); 2.66 (m, 2H, C$\underline{H}_2$-C_6H_5); 3.32 (t, 1H, CH, J=7.3 Hz); 4.18 (q, 4H, CH_2-O J= 7.1 Hz); 7.21 (m, 5H, C_6H_5.) ppm; ^{13}C-NMR: 14.1 (CH_3); 30.4 ($\underline{C}H_2$-CH); 33.3 ($\underline{C}H_2$-C_6H_5); 51.2 (CH); 61.3 (CH_2-O); 126.2 (p-C_6H_5); 128.5 (o,m-C_6H_5); 140.6 (C); 169.3 (C=O) ppm; Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.18; H, 7.58. Found: C, 68.14; H, 7.60.
4d. 75%. bp 110°C (10^{-2} mbar); ^{1}H-NMR ($CDCl_3$): 0.75 (t, 3H, CH_3, J=5.5 Hz); 1.14 (m, 14H, CH_2, C$\underline{H}_3$-CH_2-O); 1.78 (m, 2H, CH-C$\underline{H}_2$); 3.19 (t, 1H, CH, J=7.4 Hz); 4.07 (q, 4H, CH_2-O, J=7.1 Hz) ppm; ^{13}C-NMR: 13.9 (CH_3); 22.4 (CH_3-$\underline{C}H_2$-); 27.1; 28.6; 28.7; 31.4 (CH_2); 51.9 (CH); 61.0 (CH_2-O); 169.4 (C=O) ppm; Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.93; H, 9.84. Found: C, 63.96; H, 9.82.
4e. 88%. bp 134°C (10^{-2} mbar); ^{1}H-NMR ($CDCl_3$): 0.80 (t, 3H, CH_3, J=5.5 Hz); 1.18 (m, 20H, CH_2, C$\underline{H}_3$-CH_2-O); 1.80 (m, 4H, CH-C$\underline{H}_2$-C$\underline{H}_2$-); 3.23 (t, 1H, CH, J=7.4 Hz); 4.11 (q, 4H, O-CH_2, J=7.4 Hz) ppm; ^{13}C-NMR: 14.1 (CH_3); 22.6 (CH_3-$\underline{C}H_2$); 27.3; 28.7; 29.3; 29.5; 31.9 (CH_2); 52.0 (CH); 61.1 (O-CH_2); 169.5 (C=O) ppm; Anal. Calcd for $C_{17}H_{32}O_4$: C, 68.00; H, 10.67. Found: C, 68.04; H, 10.64.
4f. was purified over silica gel column (hexane/ ethyl acetate 95:5) 46%. bp 117°C (10^{-2} mbar); ^{1}H-NMR ($CDCl_3$): 0.80 (t, 3H, CH_3, J=5.5 Hz); 1.18 (m, 36H, CH_2, C$\underline{H}_3$-CH_2-O); 1.80 (m, 4H, CH-C$\underline{H}_2$-C$\underline{H}_2$-); 3.23 (t, 1H, CH, J=7.4 Hz); 4.11 (q, 4H, O-CH_2, J=7.4 Hz) ppm; ^{13}C-NMR: 14.1 (CH_3); 22.6 (CH_3-$\underline{C}H_2$); 27.4; 28.8; 29.4; 29.7; 32.0 (CH_2); 52.1 (CH); 61.2 (O-CH_2); 169.6 (C=O) ppm; Anal. Calcd for $C_{25}H_{48}O_4$: C, 72.81; H, 11.65. Found: C, 72.80; H, 11.63.

2-Alkylmalonamide (5c-f) were prepared according to published procedure.[9]
5c. white powder; 95%; mp 235-236°C (methanol); MS-FAB+: $[M+H]^+$: 207; Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.08; H, 6.80; N, 13.59. Found: C, 64.05; H, 6.82; N, 13.58.
5d. white powder; 99%; mp 201-203°C (methanol); MS-FAB+: $[M+H]^+$: 187; Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.06; H, 9.68; N, 15.05. Found: C, 58.11; H, 9.65; N, 15.00.
5e. white powder; 68%; mp 200-203°C (methanol); Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.69; H, 10.36; N, 11.60. Found: C, 64.63; H, 10.65; N, 11.21.
5f. white powder; 97%; mp 123-125°C (methanol); Anal. Calcd for $C_{21}H_{42}N_2O_2$: C, 71.19; H, 12.14; N, 7.91. Found: C, 71.36; H, 11.95; N, 7.89.

Synthesis of propanediamines (2c-f): typical procedure.[10]
Borane-dimethyl sulfide complex (66 mmol) was added dropwise to the suspension of malonamide (22 mmol) in THF (85 mL) under reflux. After 24 h under reflux, the reaction mixture was cooled at rt. Methanol was added dropwise to destroy excess of borane complexe. THF was removed and the mixture was heated 5 h in *1N* HCl methanolic solution to destroy all the borane complexes. Methanol was then removed and the mixture was poured in an aqueous *1N* solution of NaOH and extract with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated under reduce pressure. The residue was then tritured in TFA (110 mmol) ether solution affording diammonium salts **(2c-f)** as hygroscopic white solids. In view of solubility problems, NMR analysis were done in CD_3OD. However, in this solvent, resolution of ^{1}H-NMR was imperfect resulting in ^{13}C-NMR characterisation of **2c-f**.
2c. 58%; mp 119°C (ethanol/ether); MS-FAB+: $[M+H]^+$: 179; ^{13}C-NMR: 29.9 ($\underline{C}H_2CH$) ; 31.5 ($\underline{CH}_2$-C_6H_5) ; 39.3 (CH_2N) ; 125.2 (p-C_6H_5) ; 128.2 (o,m-C_6H_5) ; 141.7 (C) ppm; Anal. Calcd for $C_{15}H_{20}N_2O_4F_6$: C, 44.33; H, 4.93; N, 6.90; F, 28,08. Found: C, 44.28; H, 4.95; N, 6.84; F, 28.12.
2d. 82%; mp 118-120°C (ethanol/ether); MS-FAB+: $[M+H]^+$: 159; ^{13}C-NMR: 14.2 (CH_3) ; 23.2 ($\underline{C}H_2CH_3$) ; 27.7 ; 29.9 ; 32.2 (CH_2) ; 36.1 (CH) ; 41.3 (CH_2N) ppm; Anal. Calcd for $C_{13}H_{24}N_2O_4F_6$: C, 40.41; H, 6.22; N, 7.25; F, 29,53. Found: C, 40.48; H, 6.23; N, 7.22; F, 29.51.
2e. 64%; mp 143-145°C (ethanol/ether); MS-FAB+: $[M+H]^+$: 215; ^{13}C-NMR: 14.4 (CH_3) ; 23.7 ($\underline{C}H_2CH_3$) ; 27.1 ; 29.9 ; 30.4 ; 30.7 ; 33.0 (CH_2) ; 36.9 (CH) ; 41.4 (CH_2N) ppm; Anal. Calcd for $C_{17}H_{32}N_2O_4F_6$: C, 46.15; H, 7.24; N, 6.34; F, 25,79. Found: C, 46.18; H, 7.18; N, 6.32; F, 25.82.

2f. 56%; mp 151°C (ethanol/ether); MS-FAB+: $[M+H]^+$: 327; ^{13}C-NMR: 12.6 (CH_3) ; 21.7 ($\underline{C}H_2CH_3$) ; 25.9 ; 27.8 ; 28.4 ; 28.7 ; 31.0 (CH_2) ; 37.5 (CH) ; 42.6 (CH_2N) ppm; Anal. Calcd for $C_{25}H_{48}N_2O_4F_6$: C, 54.15; H, 8.66; N, 5.05; F, 20,58. Found: C, 54.22; H, 8.61; N, 5.02; F, 20.59.

4-(*N*-*tert*-Butyloxycarbonylaminomethyl)oxazolidin-2-one (8) :
50 mg (2 mmol) of sodium hydride (dry, 95%) was added to a stirred solution of 500 mg (1.7 mmol) of *N,N'-tert*-butyloxycarbonyl-2-hydroxy-1,3-diaminopropane **(6)** in 10 mL of dry THF. After stirring 15 h at rt, THF was removed and the residue poured into water, extracted with CH_2Cl_2 and dried (Na_2SO_4). The crude product was chromatographied over silica gel (ethyl acetate). Yield: 330 mg (89%) of colorless oil which crystallized. mp 102°C (ethyl acetate); ^{1}H-NMR ($CDCl_3$) : 1.32 (s, 9H, CH_3); 3.31-3.53 (m, 4H, CH_2); 4.61 (m, 1H, CH); 5.37 (s, 1H, NHBoc); 6.62 (ls, 1H, NH) ppm. ^{13}C-NMR: 28.1 (CH_3); 42.9 ($\underline{C}H_2$-NHBoc); 43.2 (CH_2); 75.6 (CH); 79.8 ($\underline{C}(CH_3)_3$); 156.2 (C=O Boc); 159.9 (C=O) ppm. Anal. Calcd for $C_9H_{16}N_2O_4$: C, 50.22; H, 7.07; N, 13.01. Found: C, 50.28; H, 7.10; N, 13.03.

4-(*N*-*tert*-Butyloxycarbonylaminomethyl)-*N*-decyl-oxazolidin-2-one (9) :
23 mg (0.96 mmol) of sodium hydride (dry, 95%) and 174 mg (0.79 mmol) of 1-bromodecane were added to a stirred solution of 230 mg (0.79 mmol) of *N,N'-tert*-butyloxycarbonyl-2-hydroxy-1,3-diaminopropane **(6)** in 8 mL of dry DMF. After stirring 15 h at rt, DMF was removed and the residue poured into water, extracted with CH_2Cl_2. The organic layer was washed with a aqueous saturated $NaHCO_3$ solution (2x), dried over Na_2SO_4 and removed under vacuum. The crude product was chromatographied over silica gel (ethyl acetate:hexane 90:10) affording 420 mg (67%) of **9** as a colorless oil. ^{1}H-NMR ($CDCl_3$) : 0.81 (t, 3H, CH_3, J=5.7 Hz) ; 1.20 (m, 16H, CH_2) ; 1.37 (s, 9H, $\underline{C}H_3$ Boc) ; 3.09-3.51 (m, 6H, CH_2-N) ; 4.54 (m, 1H, CH) ; 5.00 (s, 1H, NH) ppm. ^{13}C-NMR: 14.1 (CH_3) ; 22.6 ($\underline{C}H_2$-CH_3) ; 26.6 ; 27 .2 ; 29.2 ; 29.5 ; 31.8 (CH_2) ; 28.3 (CH_3 Boc) ; 43.4 ; 44.1 ; 46.6 (CH_2-N) ; 72.2 (CH) ; 79.9 ($\underline{C}(CH_3)_3$) ; 156.2 (C=O Boc); 159.9 (C=O) ppm; Anal. Calcd for $C_{19}H_{36}N_2O_4$: C, 64.04; H, 10.11; N, 7.87. Found: C, 64.08; H, 10.10; N, 7.84.

***N,N'*-Di(triphenylmethyl)-2-hydroxy-1,3-diaminopropane (10) :**
To a solution of 2-hydroxy-1,3-diaminopropane (20.0 g, 0.22 mol) in dry DMF (355 mL) was added triethylamine (61.9 mL, 0.44 mol) and stepwise trityl chloride (136.0 g, 0.484 mol). After stirring overnight at rt, DMF was removed and the residue poured into water, extracted with CH_2Cl_2. The organic layer was washed with an aqueous saturated $NaHCO_3$ solution (2x), dried over Na_2SO_4 and evaporated under reduce pressure. The residue was then tritured in methanol affording a precipitate which was filtered and washed with methanol and ether to give 87.9 g (69%) of **10** as a beige powder. mp 186-187°C (methanol); ^{1}H-NMR ($CDCl_3$) : 2.40 (d, 4H, CH_2-N, J=4.5 Hz); 3.87 (t, 1H, CH, J=4.5 Hz); 7.30-7.48 (m, 30H, C_6H_5) ppm ; ^{13}C-NMR: 47.9 (CH_2); 70.3 ($\underline{C}(C_6H_5)_3$); 70.5 (CH-O); 125.4; 126.7; 128.2 (C_6H_5); 140.6 (C) ppm; Anal. Calcd for $C_{41}H_{38}N_2O$: C, 85.71; H, 6.62; N, 4.88. Found: C, 85.75; H, 6.63; N, 4.83.

***N,N'*-Di(triphenylmethyl)-2-(4-benzotrifluorure)-1,3-diaminopropane (11g) :**
Sodium hydride (dry, 95%) (334 mg, 13.9 mmol) was added in small portions to a solution of *N,N'*-di(triphenylmethyl)-2-hydroxy-1,3-diaminopropane (**10)** (2.0 g, 3.5 mmol) in dry DMF (35 mL). After 1 h stirring, 4-chlorobenzotrifluoride (0.7 ml, 5.22 mmol) was added and the reaction mixture was heated in an oil bath at 120-130°C for 15 h. DMF was removed under vacuum, the residue poured into water and extracted with CH_2Cl_2. The organic layer was washed with an aqueous saturated $NaHCO_3$ solution (2x), dried over Na_2SO_4 and evaporated under reduce pressure. The crude product was chromatographied over silica gel (petroleum ether:ethyl acetate 95:5) to yield 1.97 g (78%) of **11g** as a colorless oil. ^{1}H-NMR $CDCl_3$) : 2.66 (d, 4H, CH_2, J=2.5 Hz); 4.80 (m, 1H, CH); 6.88 (d, 2H, *o*-$OC_6H_4CF_3$, A_2B_2, J=8.8 Hz); 7.28-7.71 (m, 32H, *m*-$OC_6H_4CF_3$, C_6H_5) ppm ; ^{13}C-NMR: 45.5 (CH_2); 70.8 ($\underline{C}(C_6H_5)$); 78.6 (CH); 121.4

(CF_3); 126.4-128.6 (CH); 145.7 (C); 160.8 (C-O) ppm; Anal. Calcd for $C_{48}H_{41}N_2OF_3$: C, 80.22; H, 5.71; N, 3.90; F, 7.94. Found: C, 80.28; H, 5.66; N, 3.87; F, 8.00.

***N,N'*-Di(triphenylmethyl)-2-decyloxy-1,3-diaminopropane (11h) :**
Sodium hydride (dry, 95%) (351 mg, 14.6 mmol) was added in small portions to a solution of *N,N'*-di(triphenylmethyl)-2-hydroxy-1,3-diaminopropane (**10)** (2.51 g, 4.4 mmol) in dry DMF (20 mL). After ¼ h stirring, 1-bromodecane (1.3 mL, 6.54 mmol) was added and the reaction mixture was stirred for 96 h at rt. DMF was removed under vacuum, the residue poured into water and extracted with CH_2Cl_2. The organic layer was washed with an aqueous saturated $NaHCO_3$ solution (2x), dried over Na_2SO_4 and evaporated under reduce pressure. Yield: 2.15 g (69%) of **11h** as a yellow oil. ^{1}H-NMR ($CDCl_3$) : 1.00 (t, 3H, CH_3, J=6.0 Hz); 1.42 (m, 16H, CH_2); 2.56 (d, 4H, CH_2-N, J=5.0 Hz); 3.26 (t, 2H, CH_2-O, J=6.0 Hz); 3.38 (t, 1H, CH, J=5.0 Hz); 7.37-7.69 (m, 30H, C_6H_5) ppm ; ^{13}C-NMR: 14.2 (CH_3); 22.7 ($\underline{C}H_2$-CH_3); 26.3; 29.6; 30.1; 31.9 (CH_2); 45.0 (CH_2-N); 69.5 (CH_2-O); 70.6 ($\underline{C}(C_6H_5)_3$); 79.4 (CH); 126.2; 127.8; 128.7 (C_6H_5); 146.1 (C) ppm; Anal. Calcd for $C_{51}H_{58}N_2O$: C, 85.72; H, 8.12; N, 3.92. Found: C, 85.75; H, 8.11; N, 3.91.

***N,N'*-Di(triphenylmethyl)-2-octadecyloxy-1,3-diaminopropane (11i) :**
11i was prepared according to procedure of **11h**. Yield: 62% (white oil). ^{1}H-NMR ($CDCl_3$) : 1.00 (t, 3H, CH_3, J=6.0 Hz); 1.42 (m, 32H, CH_2); 2.56 (d, 4H, CH_2-N, J=5.0 Hz); 3.26 (t, 2H, CH_2-O, J=6.0 Hz); 3.38 (t, 1H, CH, J=5.0 Hz); 7.37-7.69 (m, 30H, C_6H_5) ppm ; ^{13}C-NMR: 14.2 (CH_3); 22.7 ($\underline{C}H_2$-CH_3); 26.3; 29.5; 29.8; 30.1; 32.0; 33.9 (CH_2); 45.1 (CH_2-N); 69.5 (CH_2-O); 70.6 ($\underline{C}(C_6H_5)_3$); 79.4 (CH); 126.2; 127.8; 128.7 (C_6H_5); 146.1 (C) ppm; Anal. Calcd for $C_{59}H_{74}N_2O$: C, 85.71; H, 8.96; N, 3.39. Found: C, 85.72; H, 8.98; N, 3.36.

Synthesis of propanediamines (2g-i): typical procedure.
Trityl derivatives **(11g-i)** were treated with trifluoroacetic acid (TFA) in methylene chloride (50/50) and allowed to stir 1 h. Methylene chloride and excess of TFA were removed under vacuum and the residue was triturated in ether affording respectively diammonium salts **(2g-i)** as hygroscopic white powders. NMR analyses were done in CD_3OD.
2g : 92%; mp 169°C (ethanol/ether); ^{1}H-NMR : 3.10 (m, 2H, CH_2N) ; 4.8 (m, 1H, CH) ; 7.12 (d, 2H, *o*-C_6H_5, A_2B_2, J=8.8 Hz) ; 7.51 (d, 2H, *m*- C_6H_5, A_2B_2, J=8.8 Hz) ppm ; ^{13}C-NMR: 40.8 (CH_2N) ; 72.0 (CH) ; 117.4 (*o*-C_6H_5) ; 112.3 ;123.9 (CF_3) ; 128.2 ;128.3 (*m*-C_6H_5, $\underline{C}CF_3$) ; 160.2 (C-O) ppm; Anal. Calcd for $C_{14}H_{15}N_2O5F_9$: C, 36.36; H, 3.25; N, 6.06; F, 37.01. Found: C, 36.28; H, 3.26; N, 6.04; F, 37.08.
2h : 73%; mp 236-238°C (ethanol/ether); ^{13}C-NMR: 14.4 (CH_3) ; 23.7 ($\underline{C}H_2CH_3$) ; 26.8 ;30.6 ; 33.0 (CH_2) ; 40.8 (CH_2N) ; 71.8 (CH_2O) ; 73.5 (CH) ppm; Anal. Calcd for $C_{17}H_{32}N_2O_5F_6$: C, 44.54; H, 6.99; N, 6.11; F, 24.89. Found: C, 44.53; H, 6.97; N, 6.10; F, 24.92.
2i: 56%; mp 100-102°C (ethanol/ether); ^{13}C-NMR: 14.7 (CH_3) ; 23.7 ($\underline{C}H_2CH_3$) ; 26.7 ;30.8 ; 33.1 (CH_2) ; 40.7 (CH_2N) ; 71.7 (CH_2O) ; 73.2 (CH) ppm; Anal. Calcd for $C_{25}H_{48}N_2O_5F_6$: C, 52.63; H, 8.42; N, 4.91; F, 20.00. Found: C, 52.57; H, 8.40; N, 4.91; F, 20.06.

Synthesis of cyclic thioureas (12b-i): typical procedure.
To a solution of propanediamine derivatives **(2b-i)** (83 mmol) in absolute ethanol (50 mL) were added carbon disulfide (167 mmol) and EDC (83 mmol). The mixture was stirred 3 h at rt. Ethanol was removed under vacuum, the residue poured into water, extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated under reduced pressure affording **12b-i**.
12b : white powder (93%); mp 225-227°C (acetone); ^{1}H-NMR ($CDCl_3$) : 0.91 (s, 6H, CH_3); 2.88 (d, 4H, CH_2, J=2.1 Hz); 7.46 (s, 2H, NH) ppm ; ^{13}C-NMR : 24.2 (CH_3); 26.3 (C); 52.0 (CH_2); 174.8 (C=S) ppm; Anal. Calcd for $C_6H_{12}N_2S$: C, 50.00; H, 8.33; N, 19.45; S, 22.22. Found: C, 49.96; H, 8.32; N, 19.44; S, 22.27.

12c : yellow solid (64%) which was recrystallized (acetone); mp 187°C; MS-ES+: $[M+H]^+$: 235; ^{1}H-NMR (DMSO-d_6) : 1.63 (m, 2H, C$\underline{H_2}$-CH) ; 1.94 (m, 1H, CH) ; 2.62 (m, 2H, C$\underline{H_2}$-C_6H_5) ; 2.94 (m, 2H, H_a, CH_2N) ; 3.17 (m, 2H, H_e, CH_2N) ; 7.20 (m, 5H, C_6H_5) ppm ; ^{13}C-NMR : 28.8 (CH_2- C_6H_5) ; 32.4 (CH) ; 32.8 (CH_2-CH) ; 45.6 (CH_2N) ; 126.2 (p-C_6H_5) ; 128.2 (o-C_6H_5) ; 128.6 (m-C_6H_5) ; 141.0 (C) ; 176.1 (C=S) ppm; Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.45; H, 7.27; N, 12.73; S, 14.55. Found: C, 65.40; H, 7.25; N, 12.74; S, 14.61.

12d : white solid (62%) which was recrystallized (ethanol); mp 115-117°C; ^{1}H-NMR ($CDCl_3$) : 0.84 (m, 3H, CH_3, J=5.8 Hz) ; 1.28 (m, 10H, CH_2) ; 1.90 (m, 1H, CH) ; 2.91 (m, 2H, H_a, CH_2N) ; 3.28 (m, 2H, H_e, CH_2N) ; 7,0 (s, 2H, NH) ppm ; ^{13}C-NMR : 13.3 (CH_3) ; 21.4 ; 25.5 ; 28.3 ; 29.6 (CH_2) ; 30.5 (CH) ; 44.4 (CH_2N) ; 174.9 (C=S) ppm; Anal. Calcd for $C_{10}H_{20}N_2S$: C, 59.96; H, 10.07; N, 13.99; S, 15.98. Found: C, 59.98; H, 10.06; N, 13.95; S, 16.01.

12e : white fluffy solid (65%); mp 126°C (ethanol) ; ^{1}H-NMR ($CDCl_3$) : 0.84 (m, 3H, CH_3, J=5.8 Hz) ; 1.22 (m, 18H, CH_2) ; 1.89 (m, 1H, CH) ; 2.90 (m, 2H, H_a, CH_2N) ; 3.26 (m, 2H, H_e, CH_2N) ; 7.00 (s, 2H, NH) ppm ; ^{13}C-NMR : 14.1 (CH_3) ; 22.7 ; 26.7 ; 29.6 (CH_2) ; 30.8 (CH) ; 45.9 (CH_2N) ; 176.4 (C=S) ppm; Anal. Calcd for $C_{14}H_{28}N_2S$: C, 65.62; H, 10.94; N, 10.94; S, 12.50. Found: C, 65.65; H, 10.92; N, 10.90; S, 12.53.

12f : white solid (67%); mp 106°C (ethanol) ; ^{1}H-NMR ($CDCl_3$) : 0.92 (m, 3H, CH_3, J=5.8 Hz) ; 1.30 (m, 18H, CH_2) ; 1.92 (m, 1H, CH) ; 2.93 (m, 2H, H_a, CH_2N) ; 3.32 (m, 2H, H_e, CH_2N) ; 7.00 (s, 2H, NH) ppm ; ^{13}C-NMR : 14.1 (CH_3) ; 22.7 ; 26.5 ; 29.4 ; 29.7 (CH_2) ; 31.5 (CH) ; 45.9 (CH_2N) ; 176.4 (C=S) ppm; Anal. Calcd for $C_{22}H_{44}N_2S$: C, 71.74; H, 11.96; N, 7.61; S, 8.69. Found: C, 71.80; H, 11.93; N, 7.59; S, 8.72.

12g : white solid (52%) after chromatography over silica gel (CH_2Cl_2:CH_3OH 95:5); mp 221-223°C (ethanol) ; ^{1}H-NMR (DMSO-d_6) : 3.54 (m, 4H, CH_2N) ; 5.02 (m, 1H, CH) ; 7.18 (d, 2H, *o*-OC_6H_5, A_2B_2, J=8.2 Hz) ; 7.64 (d, 2H, *m*-OC_6H_5, A_2B_2, J=8.2 Hz) ppm ; ^{13}C-NMR : 43.2 (CH_2N) ; 64.6 (CH) ; 116.3 (CH *o*-OC_6H_4) ; 121.2 ;122.5 ($\underline{C}$-CF_3) ; 108.5 ; 119.3 ; 130.0 ;140.8 (CF_3) ; 127.2 ; 127.3 (CH m-O C_6H_4) ; 159.6 (C-O) ; 175.7 (C=S) ppm; Anal. Calcd for $C_{11}H_{11}N_2F_3OS$: C, 47.83; H, 3.99; N, 10.14; F, 20.65; S, 11.59. Found: C, 47.89; H, 3.98; N, 10.12; F, 20.59; S, 11.62.

12h : orange thick oil (61%) after chromatography over silica gel (CH_2Cl_2:CH_3OH 95:5); ^{1}H-NMR ($CDCl_3$) : 1.06 (t, 3H, CH_3, J=5.8 Hz) ; 1.45-1.66 (m, 16H, CH_2) ; 3.48-3.74 (m, 6H, CH_2N, CH_2O) ; 3.97 (m, 1H, CH) ppm ; ^{13}C-NMR : 14.1 (CH_3) ; 22.6 ($\underline{C}H_2$-CH_3) ; 26.0 ; 29.3 ; 29.4 ; 29.5 ; 29.7 ; 31.8 (CH_2) ; 44.4 (CH_2N) ; 66.4 (CH) ; 69.2 (CH_2O) ; 176.1 (C=S) ppm; Anal. Calcd for $C_{14}H_{28}N_2OS$: C, 61.76; H, 10.29; N, 10.29; S, 11.77. Found: C, 61.82; H, 10.26; N, 10.27; S, 11.82.

12i : precipitate formed in the reaction mixture was filtered, washed with ethanol and ether affording **12i** (80%) as a white solid. mp 125°C (acetone) ; ^{1}H-NMR ($CDCl_3$) : 1.06 (t, 3H, CH_3, J=5.8 Hz) ; 1.45-1.66 (m, 32H, CH_2) ; 3.48-3.74 (m, 6H, CH_2N, CH_2O) ; 3.97 (m, 1H, CH) ; 6.75 (s, 2H, NH) ppm ; ^{13}C-NMR : 14.1 (CH_3) ; 22.6 ($\underline{C}H_2$-CH_3) ; 26.0 ; 29.3 ; 29.4 ; 29.7 ; 31.8 (CH_2) ; 44.4 (CH_2N) ; 66.4 (CH) ; 69.2 (CH_2O) ; 176.1 (C=S) ppm; Anal. Calcd for $C_{22}H_{44}N_2S$: C, 68.75; H, 11.46; N, 7.29; S, 8.33. Found: C, 68.80; H, 11.42; N, 7.30; S, 8.36.

Synthesis of isothioureas (3a-i): typical procedure.

Respectively thiourea **(12a-i)** (0.1 mol) and methyl iodide (0.12 mol) in methanol (10 mL/g) were heated 5 h under reflux. After cooling, methanol and excess of methyl iodide were removed under vacuum affording quantitatively **3a-i**, as solids which were washed with acetone and petroleum ether.

3a : brown powder; mp 146-148°C (ethanol/ether); ^{1}H-NMR (DMSO-d_6) : 1.94 (m, 2H, CH_2) ; 2.66 (s, 3H, SCH_3) ; 3,44 (t, 4H, CH_2N, J=5.7 Hz) ; 9.53 (s, 2H, NH) ppm ; ^{13}C-NMR : 13.1 (SCH_3) ; 17.6 (CH_2) ; 39.4 (CH_2N) ; 162.1 (C=N) ppm ; Anal. Calcd for $C_5H_{11}N_2IS$: C, 23.26; H, 4.26; N, 10.85; S, 12.40. Found: C, 23.16; H, 4.28; N, 10.84; S, 12.38.

3b : yellow amorphous solid; ^{1}H-NMR ($CDCl_3$) : 0.95 (s, 6H, CH_3); 2.62 (s, 3H, SCH_3); 3.11 (s, 4H, CH_2), 8.76 (s, 2H, NH) ppm ; ^{13}C-NMR : 13.6 (SCH_3) ; 23.2 (CH_3) ; 25.7 ($\underline{C}(CH_3)_2$) ; 50.5 (CH_2) ; 162.0

(C=N) ppm ; Anal. Calcd for $C_7H_{15}N_2IS$: C, 29.37; H, 5.24; N, 9.79; S, 11.19. Found: C, 29.31; H, 5.25; N, 9.77; S, 11.17.

3c : white powder; mp 161-162°C (ethanol/ether); ^{1}H-NMR (CD_3OD) : 1.70 (m, 2H, C$\underline{H_2}$-CH) ; 2.04 (m, 1H, CH) ; 2.63 (s, 3H, SCH_3) ; 2.74 (m, 2H, C$\underline{H_2}C_6H_5$) ; 3.24 (m, 2H, CH_2N) ; 3.59 (m, 2H, CH_2N) ; 7.28 (m, 5H, C_6H_5) ppm ; ^{13}C-NMR : 13.1 (SCH_3) ; 29.7 ($\underline{C}H_2$-CH) ; 33.1 ($\underline{C}H_2$-C_6H_5) ; 33.6 (CH) ; 46.3 (CH_2N) ; 127.1 (*p*-C_6H_5) ; 129.4 (*m*-C_6H_5) ; 129.5 (*o*-C_6H_5) ; 142.6 (C) ; 165.7 (C=N) ppm ; Anal. Calcd for $C_{13}H_{19}IN_2S$: C, 43.09; H, 5.25; N, 7.73; S, 8.84. Found: C, 42.99; H, 5.25; N, 7.74; S, 8.86.

3d : brown thick oil; ^{1}H-NMR (CD_3OD) : 0.89 (t, 3H, CH_3, J=6.0 Hz) ; 1.34 (m, 10H, CH_2) ; 2.06 (m, 1H, CH) ; 2.65 (s, 3H, SCH_3) ; 3.04-3.67 (m, 4H, CH_2N) ppm ; ^{13}C-NMR : 13.1 (SCH_3) ; 14.4 (CH_3) ; 23.5 ($\underline{C}H_2CH_3$) ; 29.9 (CH) ; 27.4 ; 30.2 ; 31.3 ; 32.6 (CH_2) ; 46.4 (CH_2N) ; 165.3 (C=N) ppm; Anal. Calcd for $C_{11}H_{22}N_2IS$: C, 38.60; H, 6.72; N, 8.19; S, 9.36. Found: C, 38.58; H, 5.26; N, 8.16; S, 9.34.

3e : yellow oil; ^{1}H-NMR (CD_3OD) : 0.89 (t, 3H, CH_3, J=6.0 Hz) ; 1.30 (m, 20H, CH_2) ; 2.06 (m, 1H, CH) ; 2.66 (s, 3H, SCH_3) ; 3.04-3.37 (m, 4H, CH_2N) ppm ; ^{13}C-NMR : 13.1 (SCH_3) ; 14.4 (CH_3) ; 23.5 ($\underline{C}H_2CH_3$) ; 29.9 (CH) ; 27.4 ; 29.0 ; 30.2 ; 30.7 ; 31.4 ; 32.6 (CH_2) ; 46.4 (CH_2N) ; 165.3 (C=N) ppm ; Anal. Calcd for $C_{15}H_{31}N_2IS$: C, 45.23; H, 7.79; N, 7.03; S, 8.04. Found: C, 45.15; H, 7.81; N, 7.03; S, 8.02.

3f : beige amorphous solid; ^{13}C-NMR (CD_3OD) : 13.1 (SCH_3) ; 14.4 (CH_3) ; 23.3 ($\underline{C}H_2CH_3$) ; 29.9 (CH) ; 27.4 ; 30.2 ; 31.3 ; 32.6 (CH_2) ; 46.4 (CH_2N) ; 165.4 (C=N) ppm ; Anal. Calcd for $C_{23}H_{47}N_2IS$: C, 54.12; H, 9.22; N, 5.49; S, 6.27. Found: C, 54.05; H, 9.25; N, 5.49; S, 6.26.

3g : yellow amorphous solid; ^{1}H-NMR (DMSO-d_6) : 2.71 (s, 3H, SCH_3) ; 3.78 (m, 4H, CH_2N) ; 5.40 (m, 1H, CH) ; 7.35 (d, 2H, *o*-$OC_6H_4CF_3$, A_2B_2, J=8.0 Hz) ; 7.75 (d, 2H, *m*-$OC_6H_4CF_3$, A_2B_2, J=8.0 Hz) ; 9.39 (s, 2H, NH) ppm ; ^{13}C-NMR : 13.0 (SCH_3) ; 42.9 (CH_2N) ; 64.4 (CH) ; 115.9 (CH *o*-OC_6H_4) ; 121.2 ;122.5 ($\underline{C}$-CF_3) ; 108.5 ; 119.3 ; 130.0 ;140.8 (CF_3) ; 126.5 ; 126.6 (CH *m*-C_6H_4) ; 158.2 (C-O) ; 162.8 (C=N) ppm ; Anal. Calcd for $C_{11}H_{22}N_2OF_3IS$: C, 34.45; H, 3.35; N, 6.70; S, 7.66. Found: C, 34.43; H, 3.36; N, 6.71; S, 7.66.

3h : orange solid; mp 55°C (ethanol/ether); ^{1}H-NMR (CD_3OD) : 0.97 (t, 3H, CH_3, J=5.8 Hz) ; 1.37-1.63 (m, 16H, CH_2) ; 2.72 (s, 3H, SCH_3) ; 3.64 (m, 6H, CH_2N, CH_2O) ; 4.15 (m, 1H, CH) ppm ; ^{13}C-NMR : 14.0 (SCH_3) ; 14.5 (CH_3) ; 23.7 ($\underline{C}H_2$-CH_3) ; 27.2 ; 30.5 ; 30.7 ; 33.0 (CH_2) ; 45.2 (CH_2N) ; 66.2 (CH) ; 69. 8 (CH_2O) ;165.6 (C=N) ppm ; Anal. Calcd for $C_{15}H_{31}N_2OIS$: C, 43.48; H, 7.49; N, 6.76; S, 7.73. Found: C, 43.44; H, 7.50; N, 6.75; S, 7.71.

3i : colorless amorphous solid; ^{1}H-NMR (DMSO-d_6) : 0.97 (t, 3H, CH_3, J=5.8 Hz) ; 1.37-1.63(m, 32H, CH_2) ; 2.72 (s, 3H, SCH_3) ; 3.64 (m, 6H, CH_2N, CH_2O) ; 4.15 (m, 1H, CH) ; 7.88 (s, 1H, NH ppm ; ^{13}C-NMR : 14.0 (SCH_3) ; 14.5 (CH_3) ; 23.7 ($\underline{C}H_2$-CH_3) ; 27.2 ; 30.5 ; 30.7 ; 33.0 (CH_2) ; 45.2 (CH_2N) ; 66.2 (CH) ; 69. 8 (CH_2O) ;165.6 (C=N) ppm ; Anal. Calcd for $C_{23}H_{47}N_2OIS$: C, 52.47; H, 8.94; N, 5.32; S, 6.08. Found: C, 52.40; H, 8.97; N, 5.32; S, 6.05.

***N-tert*-Butyloxycarbonyl-2,2-dimethyl-1,3-propanediamine (13b)**

Di-*tert*-butyldicarbonate (7.59 g, 34.8 mmol) in dioxane (80 mL) was added dropwise to a solution of 2,2-dimethyl-1,3-propanediamine **(2b)** (15.1 mL, 174 mmol) in dioxane (90 mL) over a period of 2 h. The reaction mixture was stirred 16 h at rt and dioxane was removed under reduce pressure. The residue was poured into water and the formed precipitate, di-Boc derivative (0.25 g, 2%), was filtered. The filtrate was extracted with CH_2Cl_2 (4x), the organic layer washed with a saturated NaCl aqueous solution, dried over Na_2SO_4 and evaporated to give compound **13b** as a colorless oil which solidified on standing and was recrystallized (hexane-ether). Yield: 6.74 g (96%). mp 78°C; ^{1}H-NMR ($CDCl_3$) : 0.75 (s, 6H, CH_3) ; 1.36 (s, 9H, $(CH_3)_3C$) ; 2.37 (m, 2H, CH_2NH_2) ; 2.90 (m, 2H, CH_2NH) ppm ; ^{13}C-NMR : 23.1 (($\underline{C}H_3)_2$)C) ; 28.2 (($\underline{C}H_3)_3$)C) ; 35.6 ($\underline{C}(CH_3)_2$) ; 48.2 (CH_2NH) ; 50.5 (CH_2NH_2) ; 78.8 ($\underline{C}(CH_3)_3$) ; 156.3 (C=O) ppm ; Anal. Calcd for $C_{10}H_{22}N_2O_2$: C, 59.41; H, 10.89; N, 13.86. Found: C, 59.45; H, 10.88; N, 13.82.

***N-tert*-Butyloxycarbonyl-2-decyloxy-1,3-propanediamine (13h)**

13h was prepared according to procedure of **13b**. Yield: 63% (yellow oil). ^{1}H-NMR ($CDCl_3$) : 0.85 (t, 3H, CH_3, J=5.1 Hz) ; 1.22-1.40 (m, 25H, $(CH_3)_3$, $CH_3(C\underline{H}_2)_8$) ; 3.11-3.59 (m, 6H, CH_2N, CH_2O) ppm ; ^{13}C-NMR : 14.1 (CH_3) ; 22.7 ($\underline{C}H_2$-CH_3) ; 28. 4 (($\underline{C}H_3)_3C$) ; 26.0 ; 29.4 ; 29.8 ; 29.9 ; 31.9 (CH_2) ; 40.3 (CH_2NH_2) ; 40.4 (CH_2NH) ; 70.4 (CH_2O) ; 73.9 (CH) ; 79.9 ($\underline{C}(CH_3)_3$) ; 156.4 (C=O) ppm ; Anal. Calcd for $C_{18}H_{38}N_2O_3$: C, 65.45; H, 11.52; N, 8.48. Found: C, 65.48; H, 11.49; N, 8.47.

Synthesis of compounds (14xy) : typical procedure

Isothiourea hydroiodide **(3y)** (3.1 mmol) was added to amine **(13x)** (3.1 mmol) in dry acetonitrile (10 mL). The reaction mixture was heated 72 h under reflux, CH_3CN was removed under vacuum and the residue poured into water. 1N NaOH was added up to basic pH and these solution was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, evaporated under reduce pressure affording **14xy** obtained after chromatography over silica gel (CH_2Cl_2 :CH_3OH :NH_4OH 90 :10 :1).

14bg : yellow oil; 60%; ^{1}H-NMR ($CDCl_3$) : 0.78 (s, 6H, CH_3) ; 1.33 (s, 9H, $(\underline{C}H_3)_3C$) ; 2.88 (m, 4H, CH_2N) ; 3.48 (m, 4H, CH_2N_{cyc}) ; 4.56 (m, 1H, CH) ; 7.35 (d, 2H, *o*-$OC_6H_4CF_3$, A_2B_2, J=8.0 Hz) ; 7.75 (d, 2H, *m*-$OC_6H_4CF_3$, A_2B_2, J=8.0 Hz) ppm ; ^{13}C-NMR : 23.6 (CH_3) ; 28.4 (($\underline{C}H_3)_3C$) ; 36.3 ($\underline{C}(CH_3)_2$) ; 44.7 (CH_2N_{cyc}) ; 46.8 (CH_2NHBoc) ; 47.6 (CH_2N) ; 68,2 (CH) ; 79.4 ($\underline{C}(CH_3)_3$) ; 115.7 (CH, *o*-OC_6H_4) ; 123.2 (CF_3) ; 126.9 (CH, *m*-OC_6H_4) ; 127.0 ($\underline{C}$-CF_3) ; 151.9 (C=N) ; 157.0 (C=O) ; 159.9 (C-O) ppm ; Anal. Calcd for $C_{20}H_{30}N_4O_3F_3I$: C, 43.01; H, 5.38; N, 10.04. Found: C, 43.07; H, 5.39; N, 10.08.

14bh : yellow oil; 67%; ^{1}H-NMR ($CDCl_3$) : 0.85 (s, 3H, $C\underline{H}_3(CH_2)_9$, J=5.1 Hz) ; 0.94 (s, 6H, $(CH_3)_2C$) ; 1.21-1.38 (m, 25H, $(C\underline{H}_2)_8CH_3$, $(C\underline{H}_3)_3C$) ; 2.93 (m, 2H, CH_2NHBoc) ; 3.08 (m, 2H, CH_2NH) ; 3.42 (m, 6H, CH_2N_{cyc}, CH_2O) ; 3.75 (m, 1H, CH) ppm ; ^{13}C-NMR : 14.1 ($\underline{C}H_3$-$(CH_2)_9$) ; 22.6 ($\underline{C}H_2$-CH_3) ; 23.5 (($\underline{C}H_3)_2C$) ; 26.0 ; 28.4 ; 29.3 ; 31.7 (CH_2) ; 29.5 (($\underline{C}H_3)_3C$) ; 36.7 ($\underline{C}(CH_3)_2$) ; 42.3 (CH_2N cycle) ; 47.7 (CH_2NHBoc) ; 49.2 (CH_2NH) ; 66.5 (CH) ; 67.9 (CH_2O) ; 79.4 ($\underline{C}(CH_3)_3$) ; 153.2 (C=N) ; 156.8 (C=O) ppm ; MS-ES+ *:* $[M+H]^+$: 441 ; Anal. Calcd for $C_{20}H_{30}N_4O_3I$: C, 49.81; H, 8.48; N, 10.11. Found: C, 49.78; H, 8.50; N, 10.13.

14bc : yellow thick oil; 83%; ^{1}H-NMR ($CDCl_3$) : 0.90 (s, 6H, $(CH_3)_3$) ; 1.53 (m, 2H, $C\underline{H}_2$-CH) ; 1.82 (m, 1H, CH) ; 2.56 (m, 2H, $C\underline{H}_2$-C_6H_5) ; 2.88-3.42 (m, 8H, CH_2N) ; 7.11 (m, 5H, C_6H_5) ppm ; ^{13}C-NMR : 23.0 (CH_3) ; 28.1 (($CH_3)_3$) ; 29.4 (CH) ; 31.9 ($\underline{C}H_2$-CH) ; 32.4 (CH_2-C_6H_5) ; 36.4 ($\underline{C}(CH_3)_2$) ; 43.1 (CH_2N_{cyc}) ; 47.7 (CH_2NHBoc) ; 49.3 (CH_2NH) ; 79.4 ($\underline{C}(CH_3)_3$) ; 126.0 (*p*-C_6H_5) ; 127.9 (*o*-C_6H_5) ; 128.3 (*m*-C_6H_5) ; 140.5 (C) ; 153.3 (C=N) ; 156.8 (C=O) ppm ; Anal. Calcd for $C_{22}H_{37}N_4O_2I$: C, 51.16; H, 7.17; N, 10.85. Found: C, 51.09; H, 7.18; N, 10.83.

14bi : yellow thick oil; 61%; ^{1}H-NMR ($CDCl_3$) : 0.85 (t, 3H, $C\underline{H}_3$, J=5.1 Hz) ; 0.94 (s, 6H, $(CH_3)_2$) ; 1.13-1.38 (m, 41H, $CH_3(C\underline{H}_2)_{16}$, $C(CH_3)_3$) ; 2.93 (m, 2H, CH_2NHBoc) ; 3.08 (m, 2H, CH_2NH) ; 3.42 (m, 6H, CH_2N_{cyc}, CH_2O) ; 3.75 (m, 1H, CH) ppm ; ^{13}C-NMR : 14.1 (CH_3) ; 22.6 ($CH_3\underline{C}H_2$) ; 23.5 (($CH_3)_2$) ; 29.4 (($CH_3)_3$) ; 25.8 ; 28.1 ; 29.0 ; 31.6 (($\underline{C}H_2)_{15}CH_2O$) ; 36.5 ($\underline{C}(CH_3)_3$) ; 42.0 ($CH_2N_{cyc}$) ; 47.7 ($CH_2NHBoc$) ; 49.2 ($CH_2NH$) ; 66.2 (CH) ; 68.8 ($CH_2O$) ; 79.4 ($\underline{C}(CH_3)_3$) ; 153.2 (C=N) ; 156.8 (C=O) ppm ; Anal. Calcd for $C_{32}H_{65}N_4O_3I$: C, 56.47; H, 9.56; N, 8.23. Found: C, 56.42; H, 9.55; N, 8.21.

14bd : brown oil; 85%; ^{1}H-NMR ($CDCl_3$) : 0.88 (m, 9H, CH_3, $(CH_3)_2$) ; 1.12-1.26 (m, 19H, CH_2, $(CH_3)_3$) ; 1.83 (m, 1H, CH) ; 2.81-3.42 (m, 8H, CH_2N) ppm ; ^{13}C-NMR : 14.1 (CH_3) ; 22.6 ($CH_3\underline{C}H_2$) ; 23.5 (($CH_3)_2$) ; 26.9 ; 28.8 ; 29.6 ; 32.0 (($\underline{C}H_2)_4CH$) ; 31.0 (CH) ; 36.5 ($\underline{C}(CH_3)_3$) ; 44.0 (CH_2N_{cyc}) ; 47.7 (CH_2NHBoc) ; 49.3 (CH_2NH) ; 79.4 ($\underline{C}(CH_3)_3$) ; 153.3 (C=N) ; 156.9 (C=O) ppm ; Anal. Calcd for $C_{20}H_{41}N_4O_2I$: C, 48.39; H, 8.27; N, 11.29. Found: C, 48.34; H, 8.27; N, 11.27.

14ba : colorless oil; 60% ; ^{1}H-NMR ($CDCl_3$) : 0.92 (s, 6H, $(CH_3)_2C$) ; 1.35 (s, 9H, $(C\underline{H}_3)_3C$) ; 1.98 (m, 2H, CH_2) ; 3.00-3.10 (m, 4H, CH_2NH) ; 3.33 (m, 4H, CH_2N_{cyc}) ppm ; ^{13}C-NMR : 19.2 (CH_2) ; 23.3 (($\underline{C}H_3)_2C$) ; 28.3 (($\underline{C}H_3)_3C$) ; 36.6 ($\underline{C}(CH_3)_2$) ; 39.8 (CH_2N_{cyc}) ; 48.1 (CH_2NHBoc) ; 49.5 (CH_2NH) ; 79.8 ($\underline{C}(CH_3)_3$) ; 152.8 (C=N) ; 156.8 (C=O) ppm ; Anal. Calcd for $C_{14}H_{29}IN_4O_2$: C, 40.78; H, 7.04; N, 13.59; O, 7.67. Found: C, 40.73; H, 7.07; N, 13.57; O, 7.66.

14bb : yellow oil; 85%; ^{1}H-NMR ($CDCl_3$) : 0.89 (s, 3H, $(C\underline{H}_3)_2C_{cyc}$) ; 0.94 (s, 6H, $(CH_3)_2C$) ; 1.30 (s, 9H, $(C\underline{H}_3)_3C$) ; 2.90 (m, 8H, CH_2N) ppm ; ^{13}C-NMR : 23.2 (($\underline{C}H_3)_2C$) ; 23.9 (($\underline{C}H_3)_2C_{cyc}$) ; 27.1 (($CH_3)_2\underline{C}_{cyc}$) ;

28.3 (($\underline{C}H_3)_3C$) ; 36.6 ($\underline{C}(CH_3)_2$) ; 44.6 (CH_2N_{cyc}) ; 48.0 (CH_2NHBoc) ; 49.2 (CH_2NH) ; 79.5 (($CH_3)_3\underline{C}$) ; 152.8 (C=N) ; 156.8 (C=O) ppm ; MS-ES+ : $[M+H]^+$: 313 ; Anal. Calcd for $C_{16}H_{33}N_4O_2I$: C, 43.64; H, 7.50; N, 12.73. Found: C, 43.56; H, 7.51; N, 12.70.

14hc : brown oil; 87%; ^{1}H-NMR ($CDCl_3$) : 0.85 (t, 3H, CH_3, J=5.1 Hz) ; 1.18 (m, 16H, $CH_3(C\underline{H}_2)_{\underline{8}}$) ; 1.36 (s, 9H, $(CH_3)_3$) ; 1.58 (m, 2H, CH_2-CH) ; 1.92 (m, 1H, CH) ; 2.60 (m, 2H, CH_2-C_6H_5) ; 2.92-3.69 (m, 11H, CH_2N, CH_2O, CH-O) ; 7.12 (m, 5H, C_6H_5) ppm ; ^{13}C-NMR : 14.1 (CH_3) ; 22.6 ($CH_3\underline{C}H_2$) ; 28.3 (($CH_3)_3$) ; 26.0 ; 29.6 ; 31.1 (($\underline{C}H_2)_{\underline{7}}CH_2O$) ; 29.4 (CH) ; 31.9 ($\underline{C}H_2$-CH) ; 32.4 ($CH_2$-$C_6H_5$) ; 41.6 ($CH_2N_{cyc}$) ; 45.1 ($CH_2NHBoc$) ; 53.5 ($CH_2NH$) ; 70.3 ($CH_2O$) ; 73.9 (CH-O) ; 79.4 ($\underline{C}(CH_3)_3$) ; 126.0 (*p*-$C_6H_5$) ; 127.9 (*o*-$C_6H_5$) ; 128.3 (*m*-$C_6H_5$) ; 141.0 (C) ; 154.6 (C=N) ; 156.8 (C=O) ppm ; Anal. Calcd for $C_{30}H_{53}N_4O_3I$: C, 55.90; H, 8.23; N, 8.70. Found: C, 55.86; H, 8.21; N, 8.69.

Synthesis of compounds (1xy): typical procedure

Compound **(14xy)** (0.167 mol) was stirred 2 h in 10 mL of a CH_2Cl_2:TFA 9:1 mixture. CH_2Cl_2 and excess of TFA were then removed under reduce pressure; residual thick oil was tritured (3x) with ether, followed by drying *in vacuo*, affording quantitatively **1xy.**

1bg : yellow thick oil; ^{1}H-NMR (CD_3OD) : 1.08 (s, 6H, CH_3) ; 2.91 (m, 2H, CH_2NH_2) ; 3.17 (m, 2H, CH_2NH) ; 3.64 (m, 4H, CH_2N_{cyc}) ; 3.96 (m, 1H, CH) ; 7.13 (d, 2H, *o*-$OC_6H_4CF_3$, A_2B_2, J=8.0 Hz) ; 7.61 (d, 2H, *m*-$OC_6H_4CF_3$, A_2B_2, J=8.0 Hz) ppm ; ^{13}C-NMR : 22.5 (CH_3) ; 36.0 ($\underline{C}(CH_3)_2$) ; 43.0 (CH_2N_{cyc}) ; 47.9 (CH_2NH_2) ; 49.2 (CH_2NH) ; 66.1 (CH) ; 117.3 (*o*-OC_6H_4) ; 117.8 (CF_3) ; 128.1 (*m*-OC_6H_4) ; 128.2 ($\underline{C}$-CF_3) ; 154.8 (C=N) ; 160.3 (C-O) ppm ; MS-ES+ : $[M+H]^+$: 345 ; $[M+2H]^{++}/2$: 173 ; Anal. Calcd for $C_{20}H_{25}F_9N_4O_5$: C, 41.96; H, 4.37; N, 9.79. Found: C, 41.94; H, 4.32; N, 9.77.

1bh : brown oil; ^{1}H-NMR (CD_3OD) : 0.89 (s, 3H, $C\underline{H}_3(CH_2)_9$, J=5.1 Hz) ; 1.06 (s, 6H, $(CH_3)_2C$) ; 1.29 (m, 16H, (CH_2) ; 2.90 (s, 2H, CH_2NH_2) ; 3.14 (s, 2H, CH_2NH) ; 3.45 (m, 6H, CH_2N_{cyc}, CH_2O) ; 3.91 (m, 1H, CH) ppm ; ^{13}C-NMR : 14.5 ($\underline{C}H_3$-$(CH_2)_9$) ; 22.6 (($\underline{C}H_3)_2C$) ; 23.7 ; 27.2 ; 30.7 ; 30.9 ; 33.1 (CH_2) ; 36.0 ($\underline{C}(CH_3)_2$) ; 43.3 (CH_2N_{cyc}) ; 47.9 (CH_2NH_2) ; 49.3 (CH_2NH) ; 67.6 (CH) ; 69.7 (CH_2O) ; 154.9 (C=N) ppm ; MS-ES+ : $[M+H]^+$: 341 ; $[M+2H]^{++}/2$: 171 ; Anal. Calcd for $C_{22}H_{40}N_4O_5F_6$: C, 47.65; H, 7.22; N, 10.11. Found: C, 47.82; H, 7.18; N, 10.03.

1bc : brown thick oil; ; ^{1}H-NMR (CD_3OD) : 1.05 (s, 6H, $(CH_3)_2$) ; 1.69 (m, 2H, $C\underline{H}_2$-CH) ; 1.93 (m, 1H, CH) ; 2.69 (m, 2H, $C\underline{H}_2$-C_6H_5) ; 2.88-3.49 (m, 8H, CH_2N) ; 7.21 (m, 5H, C_6H_5) ppm ; ^{13}C-NMR : 22.4 (($CH_3)_2$) ; 30.9 (CH) ; 33.0 ($\underline{C}H_2$-CH) ; 33.6 ($\underline{C}H_2$-C_6H_5) ; 35.6 ($\underline{C}(CH_3)_2$) ; 44.3 (CH_2N_{cyc}) ; 48.2 (CH_2NH_2) ; 50.0 (CH_2NH) ; 126.9 (*p*-C_6H_5) ; 129.2 (*o*-C_6H_5) ; 129.3 (*m*-C_6H_5) ; 142.4 (C) ; 154.7 (C=N) ppm ; MS-ES+ : $[M+H]^+$: 289 ; $[M+2H]^{++}/2$: 145 ; Anal. Calcd for $C_{21}H_{30}N_4O_4F_6$: C, 48.84; H, 5.81; N, 10.85. Found: C, 48.74; H, 5.62; N, 10.80.

1bi : yellow powder; mp 88°C; ^{1}H-NMR (DMSO-d_6) : 1.31 (m, 9H, CH_3) ; 1.66 (m, 32H, $(C\underline{H}_2)_{16}CH_3$) ; 2.96 (s, 2H, CH_2NH_2) ; 3.18 (s, 2H, CH_2NH) ; 3.76-3.88 (m, 6H, CH_2N_{cyc}, CH_2O) ; 4.47 (m, 1H, CH) ; 8.08 (sl, 1H, NH) ; 8.37 (ls, 2H, NH_2) ppm ; ^{13}C-NMR : 13.4 (CH_3) ; 21.5 (($\underline{C}H_3)_2C$) ; 21.7 ($CH_3\underline{C}H_2$) ; 25.3 ; 28.4 ; 28.7 ; 31.0 (($\underline{C}H_2)_{\underline{15}}CH_2O$) ; 34.4 ($\underline{C}(CH_3)_2$) ; 41.3 ($CH_2N_{cyc}$) ; 45.6 ($CH_2NH_2$) ; 47.0 ($CH_2NH$) ; 65.3 (CH) ; 67.3 ($CH_2O$) ; 152.6 (C=N) ppm ; MS-ES+ : $[M+H]^+$: 453 ; $[M+2H]^{++}/2$: 227 ; Anal. Calcd for $C_{31}H_{58}N_4O_5F_6$: C, 54.71; H, 8.53; N, 8.24. Found: C, 54.50; H, 8.41; N, 8.20.

1bd : brown oil; ^{1}H-NMR (CD_3OD) : 0.87 (t, 3H, CH_3, J=5.3 Hz) ; 1.04 (s, 6H, $(CH_3)_2$) ; 1.31 (m, 10H, CH_2) ; 1.96 (m, 1H, CH) ; 2.87-3.50 (m, 8H, CH_2N) ppm ; ^{13}C-NMR : 14.3 (CH_3) ; 22.6 ($CH_3\underline{C}H_2$) ; 23.5 (($CH_3)_2$) ; 27.6 ; 30.3 ; 31.4 ; 32.7 (CH_2) ; 33.2 (CH) ; 35.6 ($\underline{C}(CH_3)_3$) ; 44.6 (CH_2N_{cyc}) ; 47.8 (CH_2NH_2) ; 49.2 (CH_2NH) ; 154.8 (C=N) ppm ; MS-ES+ : $[M+H]^+$: 269 ; $[M+2H]^{++}/2$: 135 ; Anal. Calcd for $C_{19}H_{34}N_4O_4F_6$: C, 45.97; H, 6.85; N, 11.29. Found: C, 45.85; H, 6.83; N, 11.17.

1ba : yellow oil; ^{1}H-NMR (CD_3OD) : 0.92 (s, 6H, $(CH_3)_2C$) ; 1.98 (m, 2H, CH_2) ; 2.29 (s, 2H, CH_2NH_2) ; 2.83 (s, 2H, CH_2NH) ; 3.33 (m, 4H, CH_2N_{cyc}) ppm ; ^{13}C-NMR : 19.2 (CH_2) ; 23.3 (CH_3) ; 36.6 ($\underline{C}(CH_3)_2$) ; 39.8 (CH_2N_{cyc}) ; 46.8 (CH_2NH_2) ; 49.5 (CH_2NH) ; 153.8 (C=N) ppm ; MS-ES+ : $[M+H]^+$: 185 ; $[M+2H]^{++}/2$: 93 ; Anal. Calcd for $C_{13}H_{22}N_4O_4F_6$: C, 37.86; H, 5.34; N, 13.59. Found: C, 37.84; H, 5.32; N, 13.57.

1bb : yellow oil; ^{1}H-NMR (CD_3OD) : 1.06 (s, 12H, CH_3) ; 2.90-3.15 (m, 8H, CH_2N) ppm ; ^{13}C-NMR : 22.5 (($\underline{C}H_3)_2C$) ; 24.0 (($\underline{C}H_3)_2C_{cyc}$) ; 28.0 (($CH_3)_2\underline{C}_{cyc}$) ; 35.9 ($\underline{C}(CH_3)_2$) ; 48.0 ($CH_2N_{cyc}$) ; 49.4 ($CH_2NH_2$) ; 50.8 ($CH_2NH$) ; 154.3 (C=N) ppm ; MS-ES+ : $[M+H]^+$: 213 ; $[M+2H]^{++}/2$: 107 ; Anal. Calcd for $C_{15}H_{26}N_4O_4F_6$: C, 40.91; H, 5.91; N, 12.73. Found: C, 40.75; H, 5.80; N, 12.70.
1hc : brown oil; ^{1}H-NMR (CD_3OD) : 0.88 (t, 3H, CH_3, J=5.1 Hz) ; 1.18 (m, 16H, $CH_3(C\underline{H}_2)_8$) ; 1.60 (m, 2H, $C\underline{H}_2$-CH) ; 1.92 (m, 1H, CH) ; 2.66 (m, 2H, $C\underline{H}_2$-C_6H_5) ; 2.92-3.64 (m, 11H, CH_2N, CH_2O, CH-O) ; 7.13 (m, 5H, C_6H_5) ppm ; ^{13}C-NMR : 14.1 (CH_3) ; 22.6 ($CH_3\underline{C}H_2$) ; 26.0 ; 29.6 ; 31.1 (($\underline{C}H_2)_7CH_2O$) ; 29.4 (CH) ; 31.9 (CH_2-CH) ; 32.4 (CH_2-C_6H_5) ; 41.6 (CH_2N_{cyc}) ; 45.1 (CH_2NH_2) ; 53.5 (CH_2NH) ; 70.3 (CH_2O) ; 73.8 (CH-O) ; 126.0 (p-C_6H_5) ; 127.9 (o-C_6H_5) ; 128.3 (m-C_6H_5) ; 141.0 (C) ; 154.6 (C=N) ppm ; MS-ES+ : $[M+H]^+$: 417 ; $[M+2H]^{++}/2$: 209 ; Anal. Calcd for $C_{29}H_{46}N_4O_5F_6$: C, 54.04; H, 7.14; N, 8.70. Found: C, 53.82; H, 7.10; N, 8.67.

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