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Novel class of hybrid natural products derived from Lupeol/Lupenone (Part-II)

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Triterpene lupeol/lupenone isolated from plant *Crataeva nurvala* has been chemically modified and prototype hybrid forms of lupeol have been prepared.

Keywords: Lupeol, Lupenone, *Crataeva nurvala, Glucal*

In continuation of the ongoing program for development of bioactive compound by modification of abundantly available natural products, we have reported earlier modification of lupeol[1-5] **1**, a known lead molecule from plants as antimalarial[6,7] *in vitro*. These transformations yielded few compounds which were more active than lupeol itself[1]. Lupeol **1**, has been reported to have numerous other pharmacological activities including anticancer[8], antitumor[9], antiarthritis[10], anti-inflammatory[11]. This generated further our interest to prepare hybrid lupeol/lupenone analogues by chemical modification to investigate their biological profiles. Herein is reported further structural transformation of lupeol/lupenone to give prototype **2, 3, 4** and **5** (**Figure 1**).

Results and Discussion

Lupeol **1,** isolated from plant *Crataeva nurvala*[12], was treated with glucal triacetate **6** in the presence of iodine to give **7** (major α isomer) which was separated after acetylation of reaction-mixture followed by chromatography from lupeol acetate **8**. This was deacetylated with methanolic ammonia to give **9** and finally oxidized by manganese dioxide to desired product **2**. Similarily, glactal triacetate **10** under the same sequence of reactions furnished products **11**, **12** and **2**, respectively, as shown in **Scheme I**.

In another structural modification in ring A of lupeol, lupenone oxime **13** prepared from lupeol[1], on reduction with LAH (lithium aluminium hydride) gave 3-amino-3-deoxylupeol **3**, while its rearrangement under acidic condition furnished seven-membered lactone **14** and open chain cyano compound **15** (ref.1). This was converted to amine **4** by LAH reduction which was alkylated with different allyl halides to give **4a-f** or treated with substituted aromatic acids in the presence of DCC/HOBT (Dicyclohexyl carbodiimide/hydroxy benztriazole) to furnish amides **4g-o**.

Cannaric acid **16**, obtained from cyano intermediate **15** by alkaline hydrolysis[1], on treatment with bifunctional amines in the presence of DCC/HOBT gave diamides **17a-c** which were converted by LAH to corresponding amines **5a-c**. The lupenone oxime **13** was also alkylated with epichlorohydrin to give epoxide **18** which was opened with different amines to give **19a-c (Scheme II**).

Experimental Section

Ferier rearrangement: Compound 7

Lupeol **1** (1.065 g, 2.5 mmoles) and D-glucal triacetate **6** (1.25 g, 4.6 mmoles) were stirred with 115 mg of iodine in THF (5 mL) overnight at room temperature under nitrogen atmosphere. After completion of the reaction, the reaction-mixture was washed with 10% aq. sodium thiosulphate, until the solution become colourless. The reaction-mixture was extracted with ether and dried over sodium sulphate. Crude material was purified by flash column chromatography. Column was packed in hexane and was eluted with 2, 5, 10, 15 and 20% of EtOAc in hexane. 10% of EtOAc/hexane gave a mixture of reaction product with lupeol left (400 mg). In TLC, spots of these two compounds were so close that it was not possible to separate them by column chromatography. This mixture was purified by

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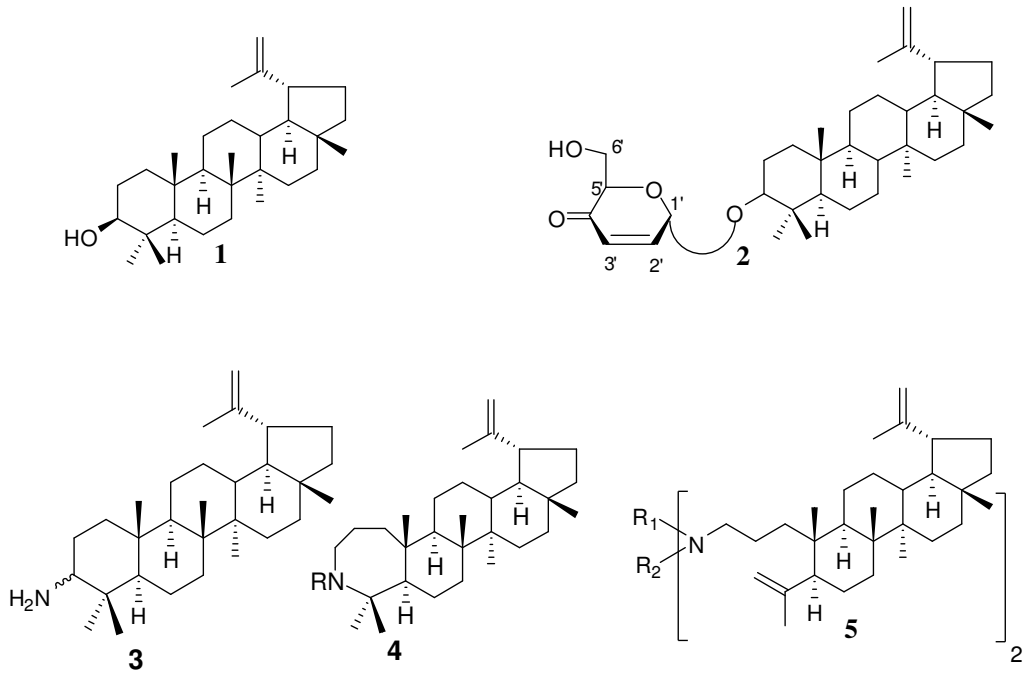


Figure 1

chemical method. The reaction-mixture was treated with acetic anhydride in pyridine, so as to acetylate the remaining lupeol. Now this mixture was again column chromatographed over silica gel column packed in hexane and eluted by 2,4,6,8 and 10% EtOAc in hexane, 4% EtOAc/ hexane gave lupeol acetate **8,** whereas 8% EtOAc/ hexane gave the desired product **7**.

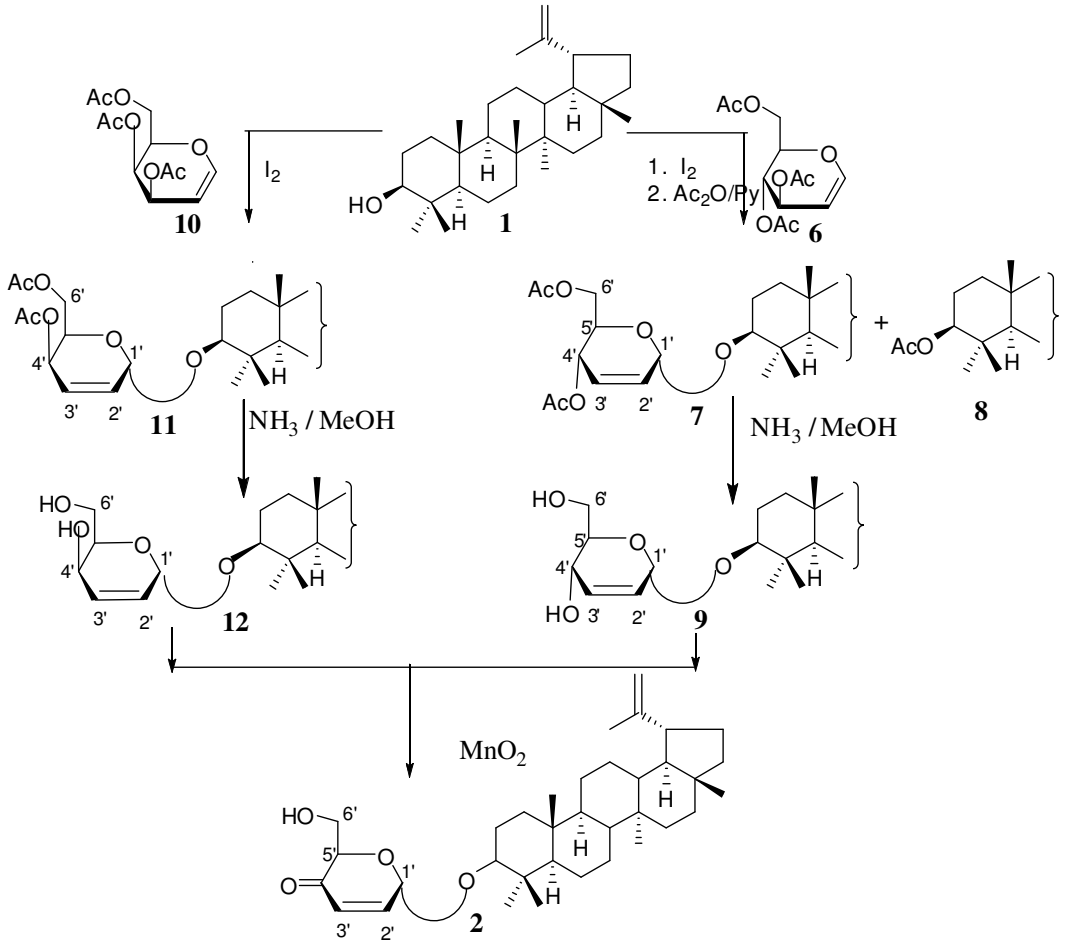
Yield: 22%, m.p. 98-102°C, MS (FAB): *m/z* 661 $(M+23)^+$ ($C_{40}H_{62}O_6$); IR (KBr): 3070, 2944, 2873, 1749 1595, 1458, 1376, 1238, 1099, 1038, 988, 881, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.85 (d, 1H, *J* = 10.5 Hz. H-3′), 5.74 (d, 1H, *J* = 10.2 Hz, H-2′), 5.30 (d, 1H, *J* = 9.3 Hz. H-4′), 5.14 (s, 1H, H-1′), 4.68 and 4.56 (2s, 1H each, H_2-29), 4. 27 - 4. 15 (m, 3H, H-5′ and H_2- 6′), 3.29 (m, 1H, H-3), 2.35 (m, 1H, H-19), 2.08 (s, 6H, 2 CO-CH_3), 1.90 (m, 1H, H-18), 1.68 (s, 3H, H_3-30), 1.65 - 1.13 (m, 23H), 1.02 (s, 3H, Me), 0.98 (s, 3H, Me), 0.93 (s, 3H, Me), 0.84 (s, 3H, Me), 0.78 (s, 6H). Anal. Calcd for $C_{40}H_{62}O_6$: C, 75.19; H, 9.78. Found: C, 74.67; H, 9.73.

Hydrolysis of unsaturated sugar derivative: Compound 9

Above reaction was repeated giving mixture of D-glucal triacetate derivative along with some unreacted lupeol. D-glucal triacetate derivative **7,** present in the reaction-mixture was hydrolyzed directly without purification. The reaction-mixture (250 mg) was stirred with aq. ammonia solution (0.5 mL), in methanol for overnight. Solvent was evaporated and the crude residue was chromatographed over silica gel column, packed in hexane. Column was eluted with 5, 10, 15 and 20% of EtOAc in hexane, 10% EtOAc/hexane gave lupeol and 25% EtOAc/hexane gave the desired compound **9**. Yield: 35%, m.p. 172-74°C, MS (FAB): *m/z* 555 $(M+H)^+$ ($C_{36}H_{58}O_4$); (EI-MS): *m/z* 577.5 $(M+23)^+$; IR (KBr): 3398 (-OH stretching), 3073, 2940, 2879, 1644, 1595, 1455, 1385, 1351, 1039, 882, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.93 (d, 1H, *J* = 10.2, H-3′), 5.69 (m, 1H, H-2′), 5.09 (s, 1H, H-1′), 4.68 and 4.56 (2s, 1H each, H_2-29), 4.22 (br-s, 1H, H-4′) (splits into doublet on D_2O shake *J* = 8.7 Hz), 3.85 (br s, 2H, H_2-6′) (splits into doublet on D_2O shake *J* = 3.9 Hz), 3.75 (m, 1H, H-5′), 3.25 (dd, 1H, 11.7 and 4.2, H-3), 2.38 (m, 1H, H-19), 1.93 (m, 1H), 1.68 (s, 3H, H_3-30), 1.66-1.20 (m, 23H), 1.03 (s, 3H, Me), 0.97 (s, 3H, Me), 0.94 (s, 3H, Me), 0.84 (s, 3H, Me), 0.78 (s, 3H, Me), 0.77 (s, 3H, Me). Anal. Calcd for $C_{36}H_{58}O_4$: C, 77.93; H, 10.54. Found: C, 77.12; H, 10.46.

Ferier rearrangement: Compound 11

Lupeol **1** (1.065 g, 2.5 mmoles) and D-galactal triacetate **10** (1.25 g, 4.6 mmoles) were stirred with 115 mg of iodine in THF (5 mL) at room temperature under nitrogen atmosphere for 14 hr, which after usual work-up gave the crude product. It was purified



Scheme I

over silica gel column packed in hexane and eluted with 2, 4, 6, 8, 10 and 15% EtOAc in hexane, 10% EtOAc/ hexane gave the desired product **11**.

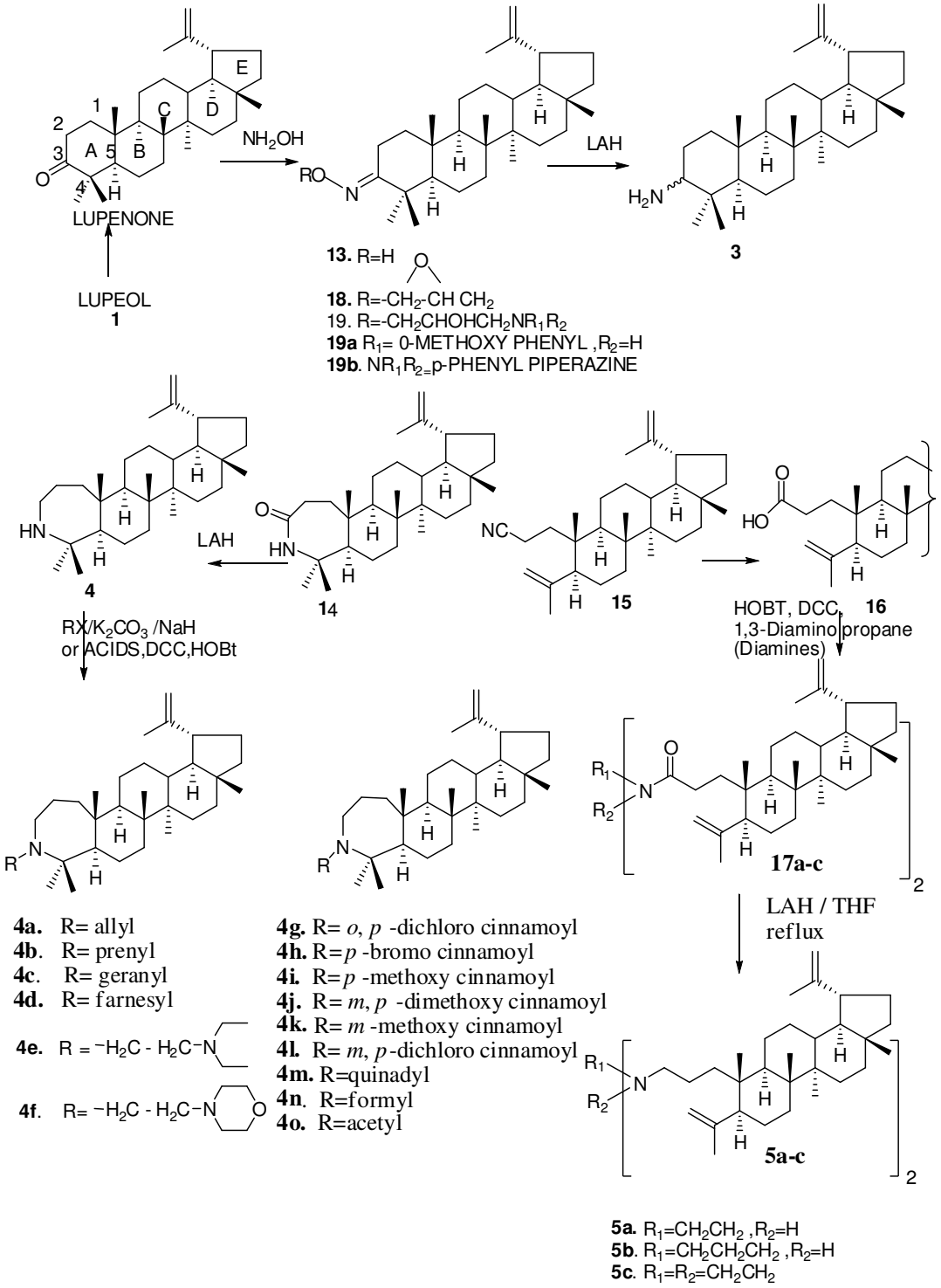
Yield: 12%, m.p. 209-11°C, MS (FAB): *m/z* 661 $(M+23)^+$ ($C_{40}H_{62}O_6$); IR (KBr): 3070, 2944, 2873, 1749, 1595, 1458, 1376, 1238, 1099, 1038, 988, 881, 742 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 6.09 (dd, 1H, *J* = 9.95/5.54 Hz. H-3′), 5.94 (dd, 1H, *J* = 9.99/2.72 Hz, H-2′), 5.18 (d, 1H, *J* = 2.20, H-1′), 5.02 (dd, 1H, *J* = 5.42/2.07, H-4′), 4.68 and 4.56 (2s, 1H each, H_2-29), 4. 44- 4. 37 (m, 1H, H-5′), 4. 29 - 4. 11 (m, 2H, H_2-6′), 3.29 (m, 1H, H-3), 2.35 (m, 1H, H-19), 2.07 (s, 6H, 2 CO-CH_3), 1.90 (m, 1H, H-18), 1.68 (s, 3H, H_3-30), 1.65-1.13 (m, 23H), 1.02 (s, 3H, Me), 0.98 (s, 3H, Me), 0.93 (s, 3H, Me), 0.84 (s, 3H, Me), 0.78 (s, 6H).

Hydrolysis of unsaturated sugar derivative: **Compound 12**

Compound **11** gave deacetylated product **12**, by the same procedure as for **9**. Yield: 32%, m.p. 110-12°C, MS (EI-MS): *m/z* 577.5 $(M+23)^+$ ($C_{36}H_{58}O_4$); IR (KBr): 3398 (-OH stretching), 3073, 2940, 2879, 1644, 1595, 1455, 1385, 1351, 1039, 882, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.34 (m, 1H, H-3′), 6.12 (dd, 1H, *J* = 9.9/5.5 Hz H-2′), 5.85 (dd, 1H, *J* = 9.9/3.0 Hz H-1′), 5.17 (d, 1H, *J* = 2.1 Hz H-4′), 4.68 and 4.56 (2s, 1H each, H_2-29), 4.12 (m, 1H, H-5′), 3.91 (m, 2H, H_2-6′), 3.30 (dd, 1H, 12.0/3.28 Hz, H-3), 2.38 (m, 1H, H-19), 1.93 (m, 1H), 1.68 (s, 3H, H_3-30), 1.66-1.20 (m, 23H), 1.03 (s, 3H, Me), 0.97 (s, 3H, Me), 0.94 (s, 3H, Me), 0.84 (s, 3H, Me), 0.78 (s, 3H, Me), 0.77 (s, 3H, Me).

Allylic Oxidation: **Compound 2**

Allylic alcohol **9** or **12** (1 g, 0.0018 mole) was dissolved in DCM (10 mL) and stirred overnight at room temperature with MnO_2 (3 g, 0.03448 mmole). After completion of the reaction (TLC), the reaction-mixture was passed through celite. Clear solution so obtained was evaporated in vacuum and the crude residue was chromatographed over silica gel column,



Scheme II

packed in hexane. Column was eluted by 5, 10, 15 and 20% of EtOAc in hexane, 20% EtOAc/hexane gave the product **2**, (550 mg). Yield: 55%, m.p. 202-204°C, MS (FAB): *m/z* 553 $(M+1)^+$ ($C_{36}H_{56}O_4$); IR (KBr): 3423 (-OH stretching), 2940, 2365, 1690, 1593, 1456, 1386, 1351, 1037, 877, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.8 (m, 1H, H-2′), 6.1 (d, 1H, J = 10.2 Hz, H-3′), 5.4 (s, 1H, H-1′), 4.69 (2s, 1H, H_2-29_a), 4.56 (br s, 2H, H_2-29_b & H-5′) 3.9 (m, 2H, H_2-6′), (splits into doublet on D_2O shake J = 3.9), 3.3

(dd, 1H, 9.0 and 3.0, H-3), 2.38 (m, 1H, H-19), 1.93 (m, 1H), 1.68 (s, 3H, H_3-30), 1.66-1.20 (m, 23H), 1.03 (s, 3H, Me), 0.97 (s, 3H, Me), 0.94 (s, 3H, Me), 0.84 (s, 3H, Me), 0.78 (s, 3H, Me), 0.77 (s, 3H, Me), (Splits into doublet on D_2O shake J = 3.9 Hz).

Alkylation of lupenoneoxime 13 with epichlorohydrin: **Compound 18**

Lupenoneoxime **13** (2 g, 4.55 mmoles) and NaH (218 mg, 2 eqv.) were stirred at 0°C in THF/DMF. After 30 min. epichlorohydrin (1.053 g, 0.89 mL, 2.5 eqv.) was added to it, and the reaction-mixture was stirred for overnight. After completion of the reaction, it was quenched with water and extracted with ether. Organic layer was concentrated and loaded over normal silica gel column in hexane and was eluted with hexane, 5, 10, 20, 30% chloroform in hexane. 20-30% chloroform in hexane gave the desired product **18**. Yield: 1.65 g. m.p. 110-12°C, MS (FAB): *m/z* 496 $(M+H)^+$ ($C_{33}H_{53}NO_2$); IR (KBr): 3076, 2940, 2867, 1634, 1594, 1455, 1368, 1247, 1054, 969, 912, 879, 834 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.63 (dd, 2H, 2.30 and 2.2, H_2-29), 4.57 (d, 1H, J = 2.3), 4.19 (dd, 1H, J = 12.2 and 3.6 Hz.), 3.97 (dd, 1H, J = 12.2 and 5.7 Hz.) 3.23 (m, 1H), 2.62 - 2.83 (dd, 1H, J = 5.0 and 2.9 Hz.), 2.46 -2.15 (m, 2H), 2.00-1.20 (m, 26H), 1.13 (s, 3H, Me), 1.05 (s, 3H, Me), 1.02 (s, 3H, Me), 0.93 (s, 3H, Me), 0.90 (s, 3H, Me), 0.79 (s, 3H, Me).

Reaction of amines on epoxide: **Compound 19a,b**

19a: Oxime-ether **18** (250 mg, 0.505 mmole) and of *o*-anisidine (124 mg, 0.11 mL, 2 eqv.) in THF/acetonitrile (20 mL, 1:1), were stirred for 24 hr in the presence of anhydrous $ZnCl_2$ (50 mg) at room temperature. After completion of the reaction, crude reaction- mixture was adsorbed over normal silica gel column and eluted with hexane, 2, 5, 8, and 10% ethyl acetate in hexane, 10% ethyl acetate in hexane gave pure product **19a**. Yield: 160 mg, m.p. viscous hygroscopic, MS (FAB): *m/z* 619 $(M+H)^+$ ($C_{40}H_{62}N_2O_3$); IR (KBr): 3420, 3068, 2943, 2866, 1630, 1600, 1517, 1457, 1367, 1249, 1222, 1177, 1136, 1109, 1033, 883, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.87-6.63 (m, 4H, Ar protons), 4.68 and 4.56 (2s, 1H each, H_2-29), 4.15 (bs, 2H), 3.84 (s, 3H, Ph-OMe), 3.71 (bs, 1H) 3.24 (m, 2H), 2.90 (m, 1H), 2.45- 2.16(m, 2H), 2.00 -1.20 (m, 26H), 1.12 (s, 3H, Me), 1.05 (s, 3H, Me), 1.03 (s, 3H, Me), 0.93 (s, 3H, Me), 0.91 (s, 3H, Me), 0.79 (s, 3H, Me).

19b: Oxime-ether **18** (250 mg, 0.505 mmole) and 1-phenyl piperazine (164 mg, 0.154 mL, 2 eqv.) in THF/acetonitrile (20 mL, 1;1) were stirred with anhydrous $ZnCl_2$ for 24 hr at room temperature. After completion of the reaction, crude reaction-mixture was concentrated and chromatographed over normal silica gel column in hexane. 10% ethyl acetate/hexane gave pure product **19b**. Yield: 180 mg, m.p. viscous hygroscopic, MS (FAB): *m/z* 658 $(M+H)^+$ ($C_{43}H_{67}N_3O_2$); IR (KBr): 3411, 2938, 2832, 1629, 1595, 1502, 1455, 1363, 1236, 1147, 1048, 1010, 923, 881, 757, 687 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.25 (m, 2H, Ar protons), 6.94 - 6.80 (m, 3H, Ar protons), 4.68 and 4.56 (2s, 1H each, H_2-29), 4.07 (bs, 3H), 3.21 (m, 4H), 2.90 - 2.15 (m, 9H), 1.92 (m, 1H), 1.75 - 1.22 (m, 27 H), 1.12 (s, 3H, -Me), 1.05 (s, 3H, Me), 1.03 (s, 3H, Me), 0.93(s, 3H, Me), 0.91 (s, 3H, Me), 0.79 (s, 3H, Me).

3-Deoxy 3-aminolupeol: **Compound 3**

Luenoneoxime **13** (2 g, 0.0046 moles), dissolved in dry THF (75 mL) was refluxed with LAH (2 g) for 24 hr, the reaction-mixture was quenched with cold water in ice-cold condition, and extracted with ether, washed the organic layer with water, dried over sodium sulphate and was concentrated to give amine **3**. Yield: 48%, m.p. 115-17ºC, MS (FAB): *m/z* 426 $(M+1)^+$ ($C_{30}H_{51}N$); IR (KBr): 3341, 3068, 2946, 2867, 1636, 1592, 1455, 1380, 1303, 1190, 1106, 1039, 1014, 981, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.68 and 4.56 (2s, 1H each, H_2-29), 2.34-2.31 (m, 1H, CH-NH_2), 1.90 (m, 1H, H-19), 1.68 (s, 3H, H_3-30), 1.62-1.25 (bunch for 24 H), 1.02 (s, 3H, Me), 0.96 (s, 3H, Me), 0.94 (s, 3H, Me), 0.82 (s, 3H, Me), 0.78 (s, 3H, Me), 0.76 (s, 3H, Me); HRMS: Measured mass: 425.4235, Calcd mass: 425.4254 for $C_{30}H_{51}N$.

N-alkylation of cyclic amine 4 with alkyl halides: **Compound 4a-f**

Seven membered amine **4** (425 mg, 1.0 mmole) and of allyl bromide (0.16 mL, 2.0 mmoles) were refluxed with anhydrous potassium carbonate (606 mg, 4.4 mmoles) in dry acetone for 12 hr. After consumption of all the starting amine, potassium carbonate of reaction-mixture was removed by passing through sintered funnel. Filtrate was concentrate and was dissolved in ethyl acetate and washed with water. Organic layer was dried over sodium sulphate, concentrated and purified over normal silica gel column in hexane. Elution with 60%

of chloroform /hexane gave the required product **4a**. Yield: 75%, m.p. 162-63ºC, MS (FAB): *m/z* 464 $(M-1)^+$ ($C_{33}H_{55}N$); IR (KBr): 2955, 2364, 1639, 1455, 1380, 1189, 992, 912, 884, 758, 549 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.8 (m, 1H, N-CH_2-C*H*=), 4.9-5.1 (m, 2H, = CH_2), 4.68 and 4.56 (2s, 1H each, H-29), 3.7 (m, 2H, N-CH_2), 2.2-2.6 (m, 2H, N-CH_2), 2.37 (m, 1H), 1.98 -1.23 (m, 27 H), 1.43 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2× Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me); HRMS: Measured mass: 465.4345, Calcd mass: 465.4334 for $C_{33}H_{55}N$.

4b: As described for **4a,** compound **4** (212 mg, 0.5 mmole) in dry acetone (15 mL), prenyl bromide (0.27 mL, 1.0 mmole), with anhydrous potassium carbonate (304 mg, 2.2 mmol) furnished product **4b** as white amorphous solid. Yield: 76%, m.p. 167-69ºC, MS (FAB): *m/z* 494 $(M+1)^+$ ($C_{35}H_{59}N$); IR (KBr): 2940, 364, 1592, 1456, 1380, 1353, 1165, 881, 669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.2 (m, 1H, N-CH_2-C*H*=), 4.68 and 4.56 (2s, 1H each, H_2-29), 3.2 (m, 2H, N-CH_2), 2.2-2.6 (m, 2H, N-CH_2), 2.37 (m, 1H), 1.98 - 1.23 (m, 27H), 1.7 (s, 6H, 2 × Me), 1.43 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me). Anal. Calcd for $C_{35}H_{59}N$: C, 85.19; H, 11.96; N, 2.84. Found: C, 85.13; H, 12.09; N, 2.75.

4c: Amine **4** (425 mg, 1.0 mmole) and geranyl bromide (0.39 mL, 2.0 mmoles) were refluxed with sodium hydride (72.0 mg, 3 mmoles) in dry THF (25 mL) for 12 hr. After consumption of all the starting amine, reaction-mixture was quenched with cold water in ice-cold condition, and extracted with ether, the organic layer was washed with water. It was dried over sodium sulphate and was column chromatographed over silica gel column in hexane. Elution with 60% of chloroform/hexane gave the product **4c**. Yield: 72%, Oily viscous. MS (FAB): *m/z* 562 $(M+1)^+$ ($C_{40}H_{67}N$); IR (KBr): 2940, 2364, 1592, 1456, 1380, 1353, 1165, 881 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.4 (t, 1H, N-CH_2-CH), 5.10 (m, 1H, -CH_2-CH=), 4.69 and 4.57 (2s, 1H each, H-29), 2.9 (d, 2H, *J* = 15.26, N- CH_2-CH=), 2.3 (m, 2H, N-CH_2), 2.18 (m, 1H), 2.16 -2.02 (m, 4H, CH_2-CH_2), 1.98 - 1.23 (m, 27H), 1.6 (s, 9H, 3 × Me), 1.4 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me). HRMS: Measured mass: 561.4037, Calcd mass: 561.4032 for $C_{40}H_{67}N$.

4d: As described for **4c,** amine **4** (212 mg, 0.5 mmole), in dry THF (15 mL), farnesyl bromide (0.27 mL, 1.0 mmole with sodium hydride (36.0 mg, 1.5 mmole) furnished product **4d** as yellowish oil. Yield: 70%, Oily viscous, MS (FAB): *m/z* 631 $(M+2)^+$ ($C_{45}H_{75}N$); IR (KBr): 2940, 2364, 1592, 1456, 1380, 1353, 1165, 881 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.3 (t, 1H, NCH_2-C*H*=), 5.10 (m, 2H, -CH_2-C*H*=), 4.69 and 4.57(2s, 1H each, H_2-29), 2.9 (d, 2H, *J* = 15.26, N- CH_2-CH=), 2.3 (m, 2H, N-CH_2), 2.18 (m, 1H), 2.17 (m, 4H, CH_2-CH_2), 2.02 (m, 4H, CH_2-CH_2), 1.98 - 1.23 (m, 27H), 1.6 (s, 12H, 4 × Me), 1.4 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me); HRMS: Measured mass: 630.4347, Calcd mass: 630.4342 for $C_{45}H_{75}N$.

4e: As described for **4a**, cyclic amine **4** (212 mg, 0.5 mmole) in dry acetone (20 mL), 2-chloro-ethyl)-diethyl-amine hydrochloride (172 mg, 1.0 mmole) and potassium carbonate (1 g) furnished **4e**. Yield: (180 mg). MS (FAB): *m/z* 525 $(M+H)^+$ ($C_{36}H_{64}N_2$), IR (KBr): 2931.7, 2853.9, 1634.5, 1594.3, 1455.0, 1377.8, 1293.2, 1241.3, 1192.4, 1162.5, 1117.8, 1074.2, 1012.0, 889.4 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.67 and 4.56 (2s, 1H each, H_2-29), 2.88-2.37 (m, 8H, 4 × N- CH_2), 2.17-1.37 (m, 30H), 1.05-0.79 (8 Me, 24H). Anal. Calcd for $C_{36}H_{64}N_2$: C, 82.37; H, 12.29; N, 5.34. Found: C, 8162; H, 12.41; N, 5.25.

4f: As described for **4a**, amine **4** (212 mg, 0.5 mmole), 4-(2-Chloro-ethyl)-morpholin hydrochloride (186 mg, 1 mmole) and potassium carbonate in dry acetone furnished **4f**. Yield: 165 mg. MS (FAB): *m/z* 539 $(M+H)^+$ ($C_{36}H_{62}N_2O$); IR (KBr): 3070, 2947, 2856, 2814, 1596, 1453, 1379, 1293, 1118, 1010, 874 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.68 and 4.56 (2s, 1H each, H_2-29), 3.70 (m 4H, O-CH_2 protons), 3.00-2.77 (m, 2H, N-CH_2 protons), 2.47-2.37 (m, 8H, N-CH_2 protons), 2.19 (m, 1H, H-19), 1.98-1.40 (m, 27H), 1.06 (s, 6H, 2 × Me), 1.00 (s, 3H, Me), 0.94 (s, 6H, Me), 0.79 (s, 3H, Me). Anal. Calcd for $C_{36}H_{62}N_2O$: C, 80.24; H, 11.60; N, 5.20. Found: C, 79.56; H, 11.72; N, 5.12.

Formation of amides of cyclic amine: **Compound 4g-o**

4g: Amine **4** (300 mg, 0.7059 mmole), DMAP (10 mg) and DCC (175 mg, 0.847 mmole) were dissolved in dry DCM (25 mL) and stirred for 30 min at room temperature. 2,4-Dichloro cinnamic acid (184 mg, 0.847 mmole) was added to the reaction-mixture and stirred again for 4 hr. After completion of the reaction, DCU was filtered. Organic layer was washed with water and concentrated. This was purified on a column of silica gel in hexane. Elution with 30% ethyl acetate hexane gave the pure product **4g**.

Yield: 69%. m.p. 120-22ºC, MS (FAB): *m/z* 624 $(M+1)^+$ ($C_{39}H_{55}Cl_2NO$); IR (KBr): 2942, 2363, 1599, 1356, 1192, 976, 876, 758, 668, 553 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.7 (d, 1H, *J* = 15.5, CO-CH=), 7.46 (m, 1H, Ar-H), 7.41 (d, 1H, *J* = 1.98, Ar-H), 7.21 (d, 1H, *J* = 2.04, Ar-H), 6.5 (d, 1H, *J* = 15.5, Ar-CH=), 4.69 and 4.57 (2s, 1H each, H-29), 3.54 (m, 2H, N-CH_2), 2.37 (m, 1H), 1.98-1.23 (m, 27H), 1.43 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me). Anal. Calcd for $C_{39}H_{55}Cl_2NO$: C, 74.97; H, 8.87; N, 2.24%. Found: C, 74.13; H, 8.75; N, 2.25.

4h: As described for **4g,** compound **4** (300 mg, 0.7059 mmole) in dry DCM (15 mL), 4-bromo cinnamic acid (191 mg, 0.847mmole), DCC (175 mg, 0.847 mmole) with catalytic amount of DMAP (10mg) furnished product **4h** as white amorphous solid. Yield: 62%. m.p. 138-40ºC, MS (FAB): *m/z* 634 (M+1) ($C_{39}H_{56}BrNO$), 636 (M+3); IR (KBr): 2945, 2363, 1600, 1383, 1354, 1167, 766 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.50-7.44 (m, 3H, 2 Ar-H, CO-CH=), 7.35-7.31 (m, 2H, Ar-H), 6.5 (d, 1H, *J* = 15.4, Ar-CH=), 4.69 and 4.57 (2s, 1H each, H_2-29), 3.54 (m, 2H, N-CH_2), 2.37 (m, 1H), 1.98 - 1.23 (m, 27H), 1.43 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me); HRMS: Measured mass: 633.2545, Calcd mass: 633.2564 for $C_{39}H_{56}BrNO$.

4i: As described for **4g,** compound **4** (300 mg, 0.7059 mmole) in dry DCM (15 mL), 4-methoxy cinnamic acid (151 mg, 0.847mmole), DCC (175 mg, 0.847 mmole) with catalytic amount of DMAP (10 mg) furnished the product **4i** as white amorphous solid. Yield: 67%. m.p. 98-99ºC MS (FAB): *m/z* 586 $(M+1)^+$ ($C_{40}H_{59}NO_2$), IR (KBr, cm^{-1}):, 2936, 1601, 1512, 1353, 1252, 1169, 1032, 825, 768; ^1H NMR (200 MHz, $CDCl_3$): δ 7.7(d, 1H, *J* =15.5, CO-CH=), 7.4 (d, 2H, *J* = 8.7, Ar-H), 6.8(d, 2H, *J* = 8.4, Ar-H), 6.4 (d, 1H, *J* =15.3, Ar-CH=), 4.69 and 4.57 (2s, 1H each, H-29), 3.82 (s, 3H, OCH_3), 3.54 (m, 2H, N-CH_2), 2.37 (m, 1H), 1.98 - 1.23 (m, 27H), 1.43 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me).

4j: As described for **4g,** amine **4** (300 mg, 0.7059 mmole), in dry DCM (15 mL), 3,4-methoxy cinnamic acid (173 mg, 0.847 mmole), DCC (175 mg, 0.847 mmole) with catalytic amount of DMAP (10mg) furnished product **4j** as white amorphous solid. Yield: 66%, m.p. 109-10ºC MS (FAB): *m/z* 616 (M+1) ($C_{41}H_{61}NO_3$); IR (KBr): 2943, 2364, 1654, 1597, 1398, 1246, 878, 775 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.5 (d, 1H, *J* = 15.5, CO-CH=), 7.0 (dd, 1H, *J* = 1.7, Ar-H), 6.9 (d, 1H, *J* = 1.64, Ar-H), 6.8 (m, 1H, Ar-H), 6.4 (d, 1H, *J* = 15.3, Ar-CH=), 4.69 and 4.58 (2s, 1H each, H_2-29), 3.9 (s, 6H, 2 × OCH_3), 3.5-3.6 (m, 2H, N-CH_2), 2.4 (m, 1H), 1.98- 1.23 (m, 27H), 1.43 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me).

4k: As described for **4g**, amine (**4**, 300 mg, 0.7059 mmole), in dry DCM (15 mL), 3-methoxy cinnamic acid (151 mg, 0.847mmole), DCC (175 mg, 0.847 mmole) with catalytic amount of DMAP (10 mg) furnished the product **4k** as white amorphous solid. Yield: 72%, m.p. 128-29ºC, MS (FAB): *m/z* 586 $(M+1)^+$ ($C_{40}H_{59}NO_2$); IR (KBr): 3080, 2946, 2363, 1597, 1453, 1379, 1189, 1110, 883, 756, 549 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6 (d, 1H, *J* =15.5, CO-CH=), 7.4 - 6.8 (m, 4H, Ar-H), 6.5 (d, 1H, *J* = 15.4, Ar-CH=), 4.69 and 4.57 (2s, 1H each, H_2-29), 3.82 (s, 3H, OCH_3), 3.54 (m, 2H, N-CH_2), 2.37 (m, 1H), 1.98 - 1.23 (m, 27H), 1.43 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me).

4l: As described for **4g,** amine (**4**, 300 mg, 0.7059 mmole), in dry DCM (15 mL), 3, 4-dichlorocinnamic acid (184 mg, 0.847 mmole), DCC (175 mg, 0.847 mmole) with catalytic amount of DMAP (10 mg) furnished product **4l** as white amorphous solid. Yield: 70%, m.p. 88-90ºC MS (FAB): *m/z* 624 (M+1) ($C_{39}H_{55}Cl_2NO$), 628 (M+5), IR (KBr): 2933, 2858, 2363, 1603, 1454, 1353, 1249, 1162, 1045, 885, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.5 (d, 1H, *J* = 15.6, CO-CH=), 7.4 (m, 1H, Ar-H), 7.4 (d, 1H, *J* = 2.16, Ar-H), 7.3 (d, 1H, *J* = 2.0, Ar-H), 6.5 (d, 1H, *J* = 15.4, Ar-CH=), 4.69 and 4.57 (2s, 1H each, H_2-29), 3.54 (m, 2H, N-CH_2), 2.37 (m, 1H), 1.98-1.23 (m, 27H), 1.43 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me).

4m: As described for **4g**, amine (4, 300 mg, 0.7059 mmole), in dry DCM, quinaldic acid (147 mg, 0.847 mmole) with DMAP (10 mg) and DCC (175 mg, 0.847 mmole) furnished product **4m**. Yield: 65%, m.p. 89-90ºC MS (FAB): *m/z* 581 (M+1) ($C_{40}H_{56}N_2O$); IR (KBr): 2943, 2364, 1647, 1513, 1455, 1387, 1260, 1147, 1026, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.1 (d, 1H, *J* = 8.4, Ar-H), 8.0 (d, 1H, *J* = 8.2, Ar-H), 7.5-7.8 (m, 4H, Ar-H), 4.70 and 4.58 (2s, 1H each, H_2-29), 3.4 (m, 2H, N-CH_2), 2.37 (m, 1H), 1.75 (s, 3H, H_3-30), 1.98-1.23 (m, 24H), 1.43 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me); HRMS: Measured mass: 580.4545. Calcd mass: 580.4534 for $C_{40}H_{56}N_2O$.

4n: Amine (**4**, 300 mg, 0.7059 mmole), was refluxed with mixture of acetic anhydride and formic acid 95% 2:1(8.0 mL) for 14 hr. Reaction-mixture was added to water (50 mL), extacted with chloroform (3× 20 mL) which was concentrated and purified as above to give desired product. Yield: 53%, m.p. 120-21ºC, MS (EI): *m/z* 453 (M^+) ($C_{31}H_{51}NO$); IR (KBr): 3074, 2949, 2863, 2369, 1678, 1640, 1592, 1452, 1379, 1194, 1121, 1068. 1026, 951, 882, 687, 649, 543 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.42 (s, 1H, N-CHO), 4.68 and 4.57 (2s, 1H each, H_2-29), 4.1(m, 2H, N-CH_2), 2.37 (m, 1H), 1.68 (s, 3H, H_3-30), 1.98 - 1.23 (m, 24H), 1.43 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me). HRMS: Measured mass: 453.2835, Calcd mass: 453.2854 for $C_{31}H_{51}NO$.

4o: Amine **4** (300 mg, 0.7059 mmole), with acetic anhydride (2.0 mL) in pyridine (5 mL) was kept at room temperature for 4 hr. The reaction worked up by removing pyridine in vaccum and was extracted with chloroform, the organic layer was washed with water, dried over sodium sulphate and concentrated to give crude product which was crystallized with ethyl-acetate-hexane. Yield: 78%, m.p. 182-84ºC, MS (FAB): *m/z* 468 (M+1) ($C_{32}H_{53}NO$); IR (KBr): 3074, 2949, 2863, 2369, 1678, 1640, 1592, 1452, 1379, 1194, 1121, 1068, 1026, 951, 882 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.68 and 4.57 (2s, 1H each, H_2-29), 3.4 (m, 2H, N-CH_2), 2.37 (m, 1H), 2.0 (s, 3H, N-CO-CH_3) 1.98 - 1.23 (m, 27H), 1.43 (s, 3H, Me), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2 × Me), 0.92 (s, 3H, Me), 0.79 (s, 3H, Me). HRMS: Measured mass: 467.2645, Calcd mass: 467.2654 for $C_{32}H_{53}NO$.

Amide formation: **Compounds 17a-c**

17a: Canaric acid **16** (440 mg, 1 mmole) placed in 100 mL round bottomed flask was dissolved in dry DCM (30 mL), HOBT (162 mg, 1.2 mmole) and of DCC (246 mg, 1.2 mmole) was added to reaction-mixture and stirred at room temperature. After 2 hr, ethelenediamine (0.033 mL, 0.5 mmole) was added. The reaction-mixture was stirred for 12 hr. Reaction-mixture was filtered through sintered funnel to remove DCU, and concentrated. Crude reaction-mixture was chromatographed over silica gel in hexane and eluted with 15-20% of ethyl acetate/hexane to give the required amide **17a** as white powder. Yield: 54%, m.p. 255-56ºC, MS (FAB): *m/z* 905 (M+1) ($C_{62}H_{100}N_2O_2$), IR (KBr,): 2938, 2365, 1640, 1576, 1455, 1381, 1241, 888, 757 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 4.81 and 4.63 (2s, 2H each, H_2-24), 4.69 and 4.56 (2s, 2H each, H_2-30), 3.3 (m, 4H, 2 × N-CH_2,), 2.39-2.34 (m, 4H, 2 × CH_2-CO-N), 2.04-0.74 (m, 86H, aliphatic protons).

17b: As described for **17a,** Canaric acid **16** (440 mg, 1.00 mmole) dissolved in dry DCM (25mL), HOBT (162 mg, 1.2 mmole), DCC (246 mg, 1.2 mmole) and 1,3-diamino propane (0.042 mL, 0.5 mmole) furnished product **17b** as white solid. Yield: 70%, m.p: 261-63ºC MS (FAB): *m/z* 919 (M+1) ($C_{63}H_{102}N_2O_2$), IR (KBr): 2938, 2365, 1640, 1576, 1455, 1381, 1241, 888, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.81 and 4.63 (2s, 4H, 2H each, H_2-24), 4.69 and 4.56 (2s, 4H, 2H each, H_2-30), 3.3 (m, 4H, 2 × N-CH_2,), 2.39-2.34 (m, 4H, 2 × CH_2-CO-N), 2.04-0.74 (m, 88H, aliphatic protons).

17c: As described for **17a,** Canaric acid **16** (220 mg, 0.5 mmole) dissolved in dry DCM (25 mL), HOBT (81 mg, 0.6 mmole), DCC (123 mg, 10.6 mmole) and piperazine (22 mg, 0.25 mmole) furnished product **17c** as white solid. Yield: 63%, m.p. 248-50ºC, MS (FAB): *m/z* 931 (M+1) ($C_{64}H_{102}N_2O_2$); IR (KBr,): 2959, 1595, 1461, 1382, 1352, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.81 and 4.63 (2s, 1H each, H-24), 4.69 and 4.56 (2s, 1H each, H_2-30), 3.22-3.13 (m, 8H, 4 × N-CH_2, piperazine protons), 2.39-2.34 (m, 4H, 2 × CH_2-CO-N), 2.04-0.74 (m, 86H, aliphatic protons). Anal. Calcd for $C_{64}H_{102}N_2O_2$: C, 82.52; H, 11.04; N, 3.01. Found: C, 82.01; H, 10.99; N, 2.98.

LAH Reduction of amides: **Compounds 5a-c**

Amide **17a** (200 mg, 0.2212 mmole) dissolved in dry THF was treated with LAH (200 mg). The reaction-mixture was stirred overnight. After completion of the reaction (monitored by TLC) LAH was quenched with water in ice-cold condition, and extracted with ether. Ether layer was dried over sodium sulphate and evaporated to give amine **5a** as oil. Yield: 72%, m.p. viscous oil. MS (FAB): *m/z* 878 $(M+2)^+$ ($C_{62}H_{104}N_2$), IR (KBr): 2939, 2366, 1591, 1458, 1351, 1163, 885, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.82 and 4.68 (2s, 4H, 2H each, H_2-24), 4.61 and 4.57 (d, 4H, 2H each, H_2-30), 2.6-2.1(m, 8H, 4 × N-CH_2), 2.04-0.74 (m, 86H, aliphatic protons).

5b: As described for **5a,** compound **17b** (200 mg, 0.2212 mmole) in dry THF (15 mL), LAH (180 mg) furnished product **5b** as white solid. Yield: 73%, m.p. 105-107ºC. MS (FAB): *m/z* 892 $(M+2)^+$ ($C_{63}H_{106}N_2$); IR (KBr): 3433, 2939, 2366, 1591, 1458, 1351, 1163, 885 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.82 and 4.68 (2s, 4H, 2H each, H_2-24), 4.61 and 4.57 (d, 4H, 2H each, H_2-30), 2.6-2.1(m, 8H, 4 × N-CH_2), 2.04-0.74 (m, 88H, aliphatic protons).

5c: As described for **17a**, compound **17c** (200 mg, 0.224 mmole) in dry THF (15 mL), LAH (200 mg) furnished product **5c** as white solid. Yield: 69%, m.p. 249-50ºC. MS (FAB): *m/z* 904 $(M+2)^+$ ($C_{64}H_{106}N_2$), IR (KBr): 2939, 2366, 1596, 1455, 1353, 1163, 886, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.82 and 4.71 (2s, 4H, 2H each, H_2-24), 4.70 and 4.61 (d, 4H, 2H each, H_2-30), 2.6-2.1 (m, 12H, 6 × N-CH_2), 2.04-0.74 (m, 86H, aliphatic protons).

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