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Novel hybrid natural products derived from solanesol as wound healing agents[†]

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A series of compounds **2a-g, 3a**,**b**, **4a-n** have been synthesized from solanesol **1**, an acyclic terpenoid alcohol, extracted from tobacco waste. These compounds have been evaluated for antioxidant, angiogenesis and wound healing activity. Compounds **3b** and **4h** exhibit better wound healing activity in comparison to 3,3-dimethylacryl shikonin. These results indicate that Solanesol derivatives can be further developed as wound healing agents.

Keywords: Solanesol, angiogenesis, antioxidant, wound healing activity

Solanesol **1**, an acyclic trisesquiterpenoid alcohol, extracted from tobacco waste[1] has been reported to exhibit antiulcer activity[2] and its derivatives were evaluated for various biological activities. For example, solanesyl (5-amino, 4-nitro) benzoate is as effective as chlofibrate in reducing serum cholesterol and is also associated with same bioactivity[3]. Substituted solanesyl sulphates and their salts are useful as antiinflammatories, antiallergics and are described as reverse transcriptase inhibitors for treatement of AIDS[4]. *N*-solanesyl-*N*,*N*-bis (3,4-dimethoxy benzyl) ethylene diamine (SDB-ethylene diamine) inhibits the colony formation of multidrug resistant mutant cell lines derived from Chinese hamster V79 (V79/ADM) and human hepatoma PLC/PRF/5 (PLC/COL) cells to a greater extent than that of the parental cells when combined with other derivatives useful as antitumor agents. It potentiated the cytotoxic activity of almost all kinds of drugs tested including adriamycin (ADM), actinomycin D, Vincristrine, Cytoxine arabinoside and 5-fluorocil urea (5-FU, Ref. 5). Isomeric solanesol (2-Z) prepared from solanesol was reported as antihypertensive, antihyperlepidemic and antitumor-agents[6]. *S*-(2,3)-dihydrosolanesol and *S*-(2,3)-dihydrosolanesyl mono-phosphate are used in inhibiting the metastasis of cancers[7]. Some substituted solanesyl amine and its ether derivatives have been synthesized and tested for antiviral and antitumor activities in rats and interferon inducing activity in humans[8,9]. Solanesol derivatives are also known to prevent ulcer[10] and liver disease[11]. The in-built number of unsaturation in this natural product suggests its possible role as an antioxidant to augment wound healing process because a wound causes enormous oxidative stress leading to depletion of endogenous antioxidant stores. It is therefore, logical to presume that solanesol derivatives with appropriate angiogenic and antioxidant activities may furnish an effective and useful wound healing compound. The ultimate aim of this wound healing agent is its use in the treatment of wounds in diabetic subjects.

The design of the present solanesol derivatives aims at generating “Hybrid Natural Products” in which the added component structure in the hybrid molecule is expected to contribute towards wound healing process which involves a series of overlapping cellular and molecular events[12-36].

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Results and Discussion

Chemistry

Solanesol was reacted with different acid bearing sub-structural units of wound healing agents such as substituted cinnamic acids, acrylic acid, furyl acrylic acids and immunomodulatory iridoid glycoside such as loganic acid pentaacetate[37] using dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethyl amino pyridine (DMAP) to yield the solanesol esters **2a-g** **(Scheme I)**.

In another strategy solanesol was modified into the reactive intermediate solanesol chloroacetyl ester **3** **(Scheme II)**, which could then be elaborated in a manner to incorporate required pharmacophores in the molecular architecture of the envisaged wound healing agents. In this strategy solanesol was reacted with chloroacetyl chloride and triethylamine, to provide chloroacetyl ester of solanesol **3**. This was then linked with coumarins in acetone and K_2CO_3 to yield **3a**,**b** .

Similarly, solanesol was reacted with succinic anhydride to obtain a hemisuccinate **4** **(Scheme III)** and the free carboxylic group of this hemi-succinate was reacted with different amines, in presence of DCC and catalytic amount of DMAP to yield amides **4a-l**, and the carboxylic acid group of the hemisuccinate **4** was also reacted with loganin tetraacetate[37], and with the primary alcoholic group of the tri-O-acetyl- methylglucopyranoside[38] to yield compounds **4m**,**n**.

Biology

Evaluation of wound healing activity: in vitro and in vivo models

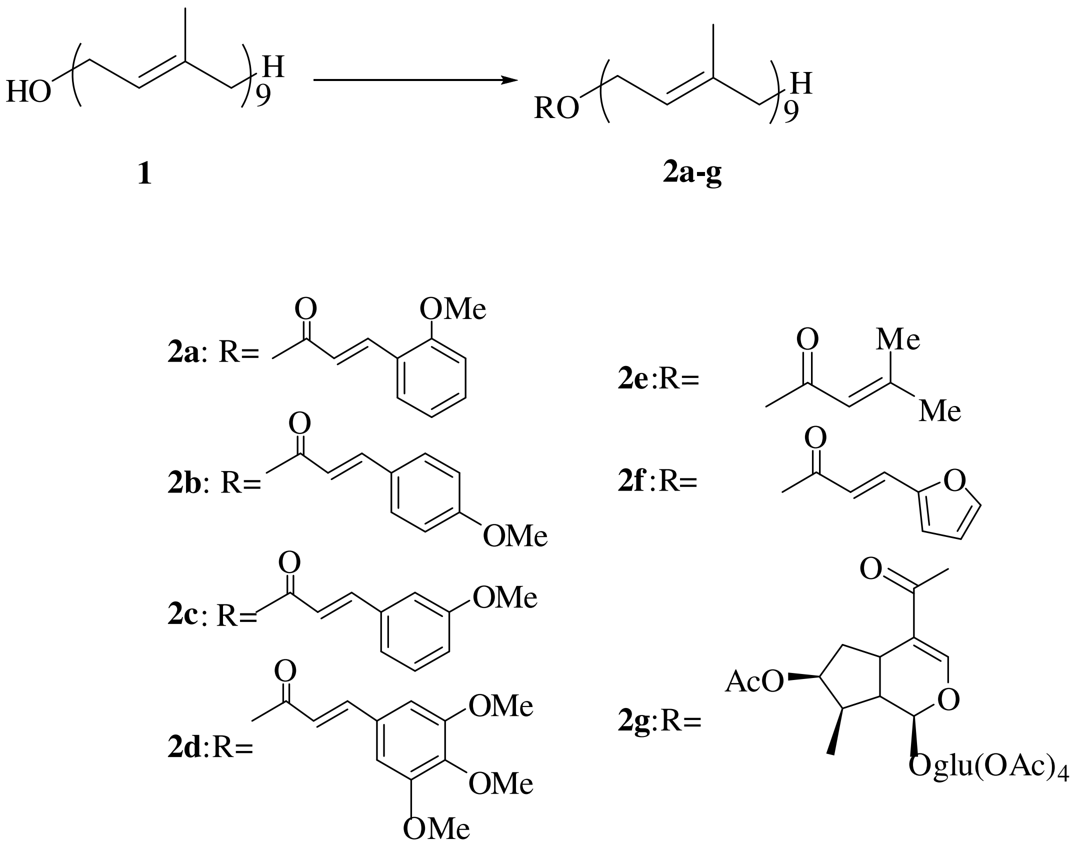
Effect of synthetic compounds on generation of hydroxyl radicals: *in vitro* model of antioxidant activity: Effect of test samples on generation of hydroxyl radicals ($OH^\bullet$) was studied by non enzymatic method. Briefly OH^- ions were generated in a non-enzymatic system comprising $FeSO4.7H_2O$ (0.2 mmole), deoxyribose (2.8 mmole), sodium ascorbate (2 mmole) and hydrogen peroxide (2.8 mmole) in 50 mm K_2HPO_4 buffer, *p*H = 7.4, to a final volume of 2.5 mL. Total reaction-mixture was incubated at 37°C for 90 min. Reference tubes and reagent blanks were also run simultaneously. The reaction was stopped by the addition of EDTA (2.8 mmole). Formation of malonildialdehyde (in both the experimental and reference tube) was estimated as thiobarbituric acid reactive substances (TBARS). Briefly the reaction-mixture was added with 0.5 mL of SDS (8% w/v), 0.5 mL glacial acetic acid and 1.5 mL thiobarbituric acid (0.8% w/v), was heated at 100°C (in a water-bath) for 1 hr in the dark. After cooling to RT, optical density of reaction-mixture was read at 532 nm with respective reagent blank (**Table I**).

Chick chorioallantoic membrane (CAM) model: This model was used to assess the angiogenic activity of compounds[39]. Nine days old fertilized chick eggs were selected and a small window of 1.0 cm^2 made in the shell. A small hole was drilled at the air space and air was sucked out using a rubber bulb, as a result of which the membrane disk of methyl cellulose loaded with different amounts of test compounds 20 μg to 80 μg was placed in at the junction of two big vessels. The window was resealed by tape and the eggs were incubated at 37°C in a well humidified chamber for 72 hr. The eggs were then opened. New vessel formation was observed and compared with that in eggs containing disks without the test compound.

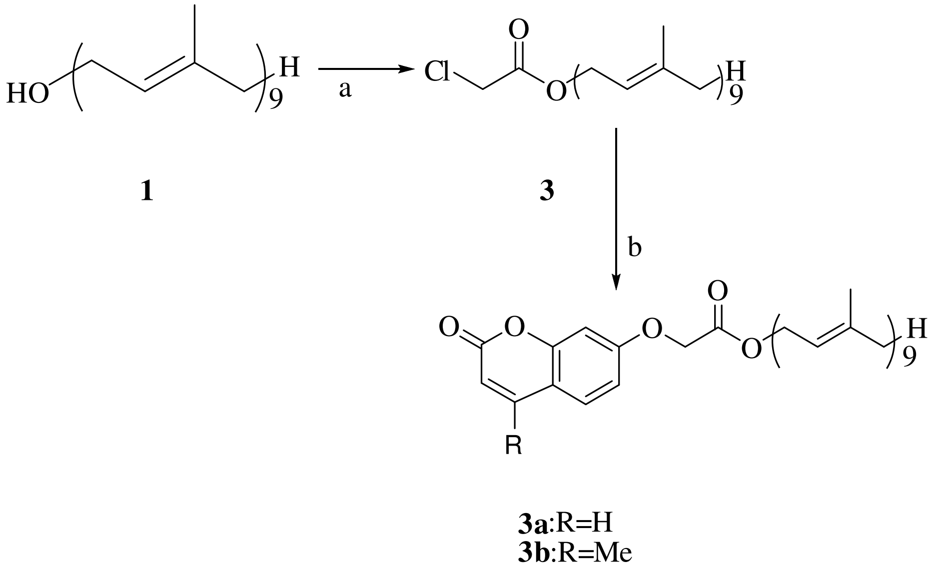
***In vivo* cutaneous punch wound model**: Guinea pigs (male, 300-325 g) were used in the study. Four cutaneous (full thickness, completely transdermal) circular wounds of 8 mm diameter were made on the pre-shaved, sterile (wiped with 70% alcohol) dorsal surface of the animal with the help of a biopsy punch (Acuderm, Louderole, USA). All surgical procedures were carried out under thiopentane sodium (25 mg/kg, i.p.) anaesthesia. Animals were allowed to recover and were housed individually in metallic cages containing autoclaved paper cuttings. They received food and water *ad libitum.* Solution of synthetic compounds (20 μL/wound) was applied topically in concentrations of 0.1% twice daily for 7 days. The control group received an equal amount of vehicle. Wound tissue excision on the 7th day after making the wound was also done using biopsy punch. This procedure excises only the newly formed (regenerated) tissues in the wounded area, thus avoiding contamination from surrounding tissues. The animals were anaesthesized before excision as described in the preceding section[40].

Assessment of healing: In each animal study, eight animals were taken. From each animal, two wounds were pooled to make one sample for the estimation of hydroxyproline content and one each was used for histology.

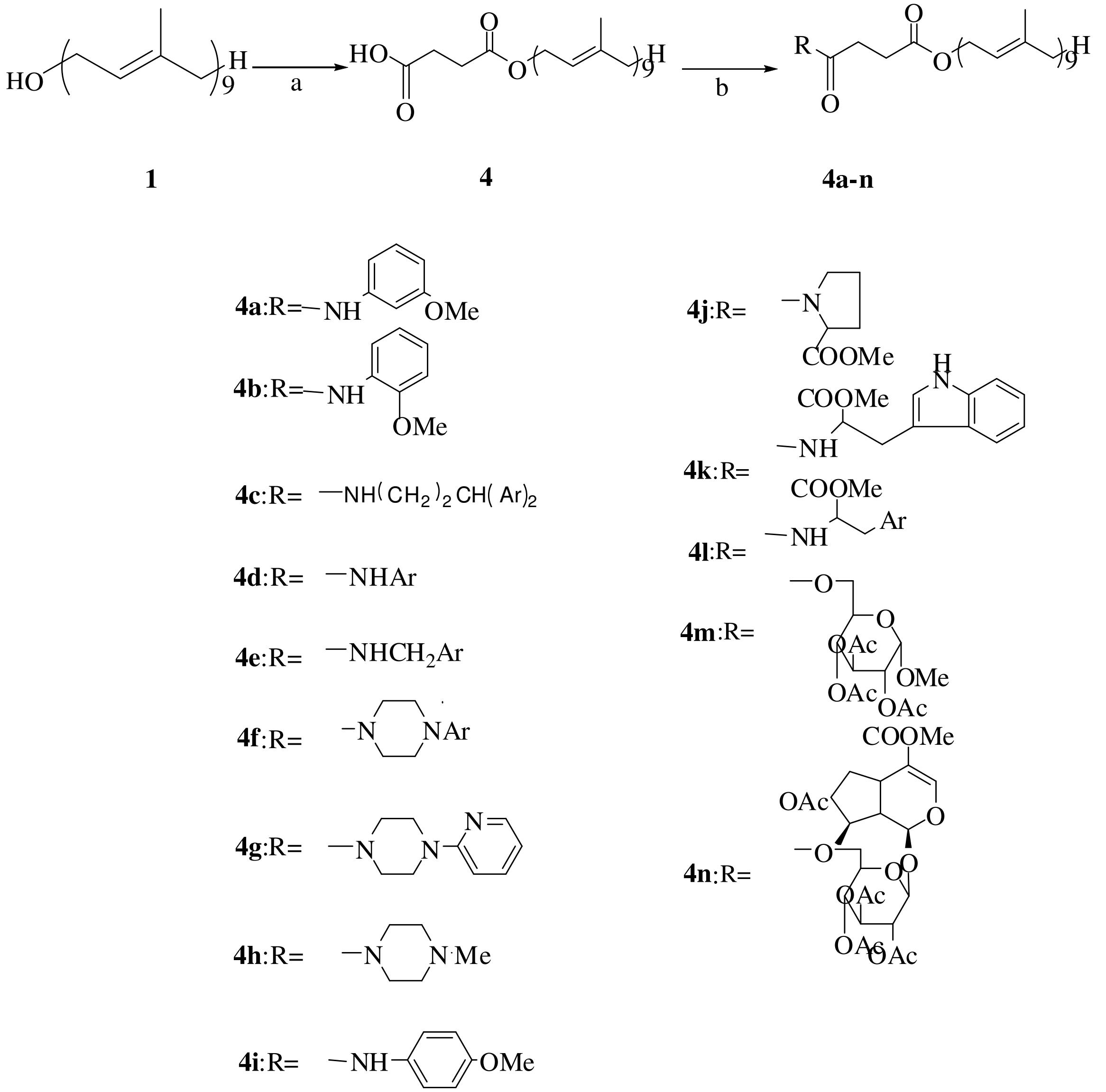
Area of wound: The surface area of healing (7 and 10 day) wound was measured by tracing the boundary of still open wound on semi-transparent paper and calculation of area was done by using a graph paper[41].



Scheme I — Reagents and conditions: RCOOH, DCM, DCC, DMAP, RT, 6 hr



Scheme II — Synthesis of compounds **3** and **3a**,**b**: Reagents and conditions: (a) Chloroacetyl chloride, benzene, Et_3N, 5°C, 4 hr; (b) Coumarins, K_2CO_3, acetone, 4 hr, reflux



Scheme III — Synthesis of compounds **4** and **4a-n** Reagents and conditions: (a) Succinic anhydride, Pyridine, DMAP, RT, 6 hr; (b) **4a-h** Amines, DCM, DCC, DMAP, RT, 4 hr; **4i**: *p*-anisidine, DCM, DCC, HOBT, RT, 3 hr; **4j-l**: Amino acid hydrochloride salt, DCM, Et_3N, DCC, DMAP, RT, 4 hr; **4m,n**: Partially protected sugar/loganin pentaacetate, DCM, DCC, DMAP, 0°C, 5 hr

Collagen estimation: Wound tissues were analyzed for hydroxyproline content, which is a basic constituent of collagen. Tissues were dried in a hot air oven at 60-70°C to constant weight and were hydrolyzed in 6*N* HCl at 130°C for 4 hr in sealed tubes. The hydrolysate was neutralized to *p*H 7.0 and was subjected to Chloramine-T oxidation for 20 min. The reaction was terminated by addition of 0.4 *M* perchloric acid and colour was developed with the help of Ehrlich reagent at 60°C, which was then measured at 557 nm using a Pye Unicam Spectrophotometer[42]. The angiogenesis and wound healing activities are presented in **Table II**.

It can be seen from **Table I** that solanesol **1** shows antioxidant activity (48% inhibition of free radical generation). This activity increased to 96% in compounds **3** and **4** and in most of the compounds the antioxidant activity for the *in vitro* assay was better than solanesol. However, compounds **2d, 2f, 3b, 4, 4a, 4j-l,** and **4n** were inferior to solanesol for inhibiting the generation of radicals. It was also observed from **Table II** that compounds which have wound healing activities **(1, 2d, 2e, 3, 3b, 4, 4a, 4e, 4h, 4k, 4i, 4n)** possess different profile of antioxidant activity (24-96%), indicating antioxidant activity alone is not essential for wound healing activity.

Table I — Effect of test compounds on the generation of hydroxyl radicals (OH): *in vitro* antioxidant activity dose of compounds used = 250nmole

Compd	Ref. MDA/hr nmole	Exp. MDA/hr nmole	% Inh.
1	55.33± 0.86	28.51± 0.88	48
2a	28.56 ± 0.43	3.12 ± 0.57	89
2b	28.81 ± 0.57	29.06 ± 1.50	-
2c	31.20 ± 0.89	1.51 ± 0.37	95
2d	43.07 ± 0.61	27.82 ± 0.86	35
2e	35.52 ± 0.53	1.10 ± 0.21	97
2f	21.75 ± 0.79	15.22 ± 0.17	30
3	30.09 ± 0.86	1.20 ± 0.09	96
3a	25.54 ± 0.62	0.91 ± 0.14	96
3b	48.71 ± 2.16	37.01 ± 0.98	24
4	30.74 ± 0.77	1.20 ± 0.07	96
4a	32.06 ± 2.70	24.42 ± 0.91	24
4b	29.04 ± 0.43	3.61 ± 0.07	87
4c	33.48 ± 0.40	12.92 ± 0.93	61
4d	28.46 ± 0.53	5.48 ± 0.21	80
4e	30.30 ± 0.96	14.48 ± 0.55	52
4f	29.04 ± 0.43	3.61 ± 0.07	87
4g	25.35 ± 1.32	3.85 ± 0.63	84
4h	32.64 ± 0.33	9.13 ± 0.24	72
4i	27.44 ± 0.38	0.07 ± 0.04	97
4j	35.41 ± 2.00	19.83 ± 0.67	44
4k	29.58 ± 0.43	21.21 ± 0.45	2 8
4l	29.96 ± 0.48	17.62 ± 3.89	41
4m	51.54 ± 0.72	20.96 ± 1.11	59
4n	47.15 ± 0.32	33.55 ± 0.60	29

MDA = malonildialdehyde

Table-II — *In vivo* evaluation of compounds for angiogenesis and wound healing activity

Compd	Angiogenesis 40µg	80µg	H.P. (%)	W.A. (%).
1			-13.16	-3.61
2a	++	-	-14.83	+50.00
2b	-	-	-20.52	+34.00
2c	-	-	-23.46	+67.00
2d	-	++	+68.00	-8.94
2e	-	-	-27.00	-28.80
2f	**-**	-	-7.74	+23.00
3	±	±	-	- 3.80
3a	±	±	-34.00	-
3b	+	++	+75.00	-38.70
4	±	±	+35.00	-7.65
4a	+	+	-19.70	-15.80
4b	+	-	-13.80	-
4c	+	++	-5.69	+10.00
4d	-	-	-8.98	+53.20
4e	-	+	-6.57	-13.10
4f	+	+	N.C.	-
4g	+	-	N.C.	-
4h	-	-	+7.63	-38.00
4i	+	+	-8.37	-25.00
4k	-	±	+2.66	-30.00
4l	-	+	-38.49	+7.00
4m	-	-	+36..50	+52.70
4n	+	-	+9.82	-6.0
Ref			+31.8	-30.00

Angiogenesis; ±, Slight; +, Moderate; ++, Maximal; - , H. P. = Hydroxy Proline; Reference = 3, 3 - Dimethylacryl Shikonin; N.C. = No Change, W.A.; wound area.

It was observed that there is increase in hydroxylproline content and decrease in wound area when treated with compounds **2d, 3b, 4, 4h, 4k, 4n,** contrary to these compounds **2a-c, 2f, 4c, 4d, 4l** show decrease in hydroxyproline content and the increase in wound area by the treatment of these compounds. These results indicate that increase in hydroxyproline content is nessessary for wound healing activity but the extent of the increase in hydroxyproline content cannot be quantitatively correlated with the healed wound. However, some of these compounds tested for angiogenic response at 40/80µg concentration indicate that compounds **2d, 3b, 4, 4k, 4n,** show angiogenesis and increase in hydroxyproline content and finally lead to decrease the wound area. But this spectrum of activities is not uniform with other compounds. For example compounds **2a, 4c, 4l** show angiogenesis and decrease in hydroxyproline content but increased wound area. Similarily, compounds **4a, 4e** and **4i** which are angiogenic and decrease the hydroxyproline content are able to decrease the wound area. Likewise, compound **4m** increases the proline content and also the overall wound area.

Experimental Section

The melting points were recorded on an electrically heated melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Perkin-Elmer 90 MHz, Bruker Advance DRX 300, Bruker DPX 200 FT and Bruker WM-400 MHz spectrometers using TMS as an internal reference and $CDCl_3$ as solvent unless specified. FAB mass spectra were recorded on a JEOL SX 102/DA 6000 mass spectrometer using Argon/Xenon (6 KV, 10 mA) as the FAB gas. EI mass spectra were recorded on JEOL JMS-D-300 spectrometer with the ionization potential of 70 eV and ES mass on Quantro-II, micromass instrument. Elemental analyses were carried out on a Carlo-Erba-EA-1108 analyzer. Silica gel (60-120 mesh) for column chromatography and Silica gel (230-400 mesh) for column chromatography were used. Room temperature mentioned are in the range between 20-40°C unless stated otherwise.

General procedure for the synthesis of compounds, 2a-g

To a solution of solanesol **1** (1.0 g, 1.5 mmole) in dry dichloromethane (30 mL) were added various substituted aromatic acids (1.0 eq), dicyclohexylcarbodiimide (1.0 eq) and dimethyl amino pyridine (0.1 eq) stirred for 6 hr at RT. Seperated dicyclohexylurea (DCU) was filtered off and the filtrate was evaporated to dryness *in vacuo* to give a white foamy mass which was purified by column chromatography using ethyl acetate/hexane (2:98 v/v) as eluent. The product was purified by recrystallization from hexane/ methanol at 0-4°C.

3-(2-Methoxy-phenyl)-acrylic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 2a

Yield: 61%; m. p. 60°C; IR (KBr): 1710 (C=O), 1260, 1160 cm^{-1} (C-O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.99 (d, 1H, J = 16 Hz, Ar-C*H*), 7.49-6.93 (m, 4H, Ar-H), 6.53 (d, 1H, J = 16 Hz, Ar-CH=C*H*), 5.42 (t, 1H, OCH_2-C*H*), 5.08 (m, 8H, 8 × CH_2- C*H*), 4.72 (d, 2 H, J = 6.8 Hz, OCH_2-CH), 3.88 (s, 3H, OMe), 2.09-2.00 (m_e, 32H, 8 × CH_2-CH_2), 1.74-1.55 (m_e, 30 H, 10 × = C(CH_3). Anal. Calcd for $C_{55}H_{82}O_3$. 0.5 H_2O: C, 82.60; H, 10.38. Found: C, 82.83; H, 10.60%.

3-(4-Methoxy-phenyl)-acrylic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 2b

Yield: 64%; m.p. 63°C; IR (KBr): 1700 (C=O), 1252, 1166 cm^{-1} (C-O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.64 (d, 1H, J = 16 Hz, Ar-C*H*), 7.46 (d, 2H, J = 8.6 Hz, Ar-H), 6.89 (d, 2 H, J = 8.6 Hz, Ar-H), 6.31 (d, 1 H, J = 16 Hz, Ar-CH=C*H*), 5.41 (t, 1 H, OCH_2-C*H*), 5.08 (t, 8H, 8 × CH_2-C*H*), 4.79 (d, 2H, J = 6.8 Hz, OCH_2-CH), 3.83 (s, 3H, OMe), 2.09-2.00 (m, 32 H, 8 × CH_2-CH_2), 1.74-1.59 (m, 30 H, 10 × C(CH_3). Anal. Calcd for $C_{55}H_{82}O_3$. 0.5 H_2O: C, 82.60; H, 10.38. Found: C, 82.77; H, 10.69%.

3-(3-Methoxy-phenyl)-acrylic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 2c

Yield: 80%; m.p. 42°C; IR (KBr): 1718 (C=O), 1254, 1164 cm^{-1} (C-O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.65 (d, 1H, J = 16 Hz, Ar-C*H*), 7.30-6.80 (m, 4H, Ar-*H*), 6.43 (d, 1H, J = 16Hz, Ar-CH=C*H*), 5.42 (t, 1H, OCH_2-C*H*), 5.11 (m, 8H, 8 × CH_2-C*H*), 4.72 (d, 2 H, J = 7 Hz, OCH_2-CH), 3.83 (s, 3H, OMe), 2.09-2.00 (m, 32H, 8 × CH_2 -CH_2), 1.74-1.59 (m, 30H, 10 × = C(CH_3). Anal. Calcd for $C_{55}H_{82}O_3.0.5H_2O$: C, 82.60; H, 10.38. Found: C, 82.70; H, 10.25% .

3-(3,4,5-Trimethoxy-phenyl)-acrylic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 2d

Yield: 60%; m.p. 50°C; IR (KBr): 1701 (C=O), 1249, 1195 cm^{-1} (C-O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.60 (d, 1H, J = 16 Hz, Ar-C*H*), 6.74 (s, 2H, Ar-H), 6.35 (d, 1H, J = 16 Hz, Ar-CH=C*H*), 5.42 (t, 1H, OCH_2-C*H*), 5.11 (m, 8H, 8 × CH_2-C*H*), 4.72 (d, 2H, J = 6.0 Hz, OCH_2-CH), 3.87 (s, 9H, 3 × OCH_3), 2.09-2.00 (m, 32H, 8 × CH_2-CH_2_), 1.74-1.55 (m, 30H, 10 × = C(CH_3). Anal. Calcd for $C_{57}H_{86}O_5$. 0.5 H_2O: C,79.62; H, 10.12. Found: C, 79.72; H, 10.26%.

3-Methyl-but-2-enoic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 2e

Yield: 66.3%; m.p. 42°C; IR (KBr): 1714 (C=O), 1145, 1228 cm^{-1} (C-O); ^1H NMR (200 MHz, $CDCl_3$): δ 5.68 (s,1H, $(Me)_2C$=CH), 5.36 (t, 1H, OCH_2-C*H*), 5.11 (m, 8H, 8 × CH_2-C*H*), 4.60 (d, 2H, J = 6.0 Hz, OCH_2-CH), 2.16-1.88 (m, 38H, 8 × CH_2-CH_2, $(CH_3)_2C$= , 1.71-1.55 (m, 30H, 10 × = C(CH_3); FAB-MS (LiCl): *m/z* 719 $[M + Li]^+$. Anal. Calcd for $C_{50}H_{80}O_2.H_2O$: C, 82.19; H, 11.23. Found: C, 82.64; H, 11.21% .

3-Furan-2-yl-acrylic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 2f

Yield: 50%; m.p. 57°C; IR (KBr): 1708 (C=O), 1296, 1160 cm^{-1} (C-O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.46 (d, 1 H, J = 1.7 Hz, Fu-H), 7.42 (d, 1 H, J = 16 Hz, C*H*=CHCO), 6.58 (d, 1H, J = 3.2 Hz, Fu-H), 6.44 (dd, J = 3.2 and 1.7 Hz, Fu-H), 6.32 (d, 1H, J = 16 Hz, CH=C*H*CO), 5.40 (t,1H, J = 7.0 Hz, OCH_2-CH), 5.11 (m, 8H, 8 × CH_2-C*H)*, 4.70 (d, 2H, J = 7.0 Hz, OCH_2-CH), 2.00 (m, 32H, 8 × CH_2-CH_2), 1.59

(m, 30H, 10 × = C(CH_3). Anal. Calcd for $C_{52}H_{78}O_3$: C, 83.20; H, 10.40. Found: C, 83.03; H, 10.79% .

6-Acetoxy-1-(3,4,5,-triacetoxy-6-ethyl--tetrahydro-pyran-2-yloxy)-7-methyl-1,4a,5,6,7,7a-hexahydro-cyclopenta[c]pyran-4-carboxylic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 2g

Yield: 60%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.35-4.82 (m, 15H, H-1, H-7, H-1′, H-2′, H-3′, H-4′, OCH_2-C*H*, 8 × CH_2-C*H*), 4.81 (d, 2 H, *J* = 6.8 Hz, OCH_2-CH), 4.30 (dd, 1 H, *J* = 12, and 4.4 Hz, H-6′), 4.11 (dd, 1 H, *J* = 14, and 5.4 Hz, H- 6′), 3.73 (m, 1H, H-5′), 3.00 (m, 1 H, H-5), 2.35-2.16 (m, 2 H, H-6, H-9), 2.09-1.94 (m, 47 H, 5 × COCH_3, 8 × CH_2-CH_2), 1.86 (m, 1 H, H-8), 1.76 (m, 1 H, H-9), 1.69-1.59 (m, 30 H, 10 ×= C(CH_3), 1.00 (d, 3H, *J* = 8 Hz, H-10). Anal. Calcd for $C_{71}H_{106}O_{15}$: C, 71.11; H, 8.84. Found: C, 70.93; H, 9.05%.

The synthesis of chloro-acetic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 3

To a stirred solution of solanesol **1** (1.0 g, 1.5 mmole) and benzene (30 mL) was added chloroacetyl chloride (0.12 mL, 1.0 eq.) followed by triethylamine (1.0 eq) at 5°C and stirred for 4 hr. Benzene was removed *in vacuo* and the residue was extracted with methylene chloride (4 × 25 mL). Combined organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to give a thick mass which was purified by flash column chromatography using ethyl acetate:hexane (2:98 v/v) as eluent. The product was purified by recrystallization from chloroform/ methanol at 10°C. Yield: 80.3%; m.p. 46°C; IR (KBr): 1730 (C=O), 1150 cm^{-1} (C-O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (t, 1H, OCH_2-C*H*), 5.10 (m, 8H, CH_2 -C*H*), 4.70 (d, 2H, *J* = 6.0 Hz, OCH_2-CH), 4.06 (s, 2H, Cl-CH_2), 2.03-1.90 (m, 32H, 8 × CH_2-CH_2), 1.70-1.52 (m, 30H, 10 × = C(CH_3); FAB-MS: *m/z* 707 $[M + 1]^+$. Anal. Calcd for $C_{47}H_{75}O_2Cl.1.5\ H_2O$: C, 76.94; H, 10.64. Found: C, 77.02; H, 10.78%.

General procedure for the synthesis of compounds, 3a,b

To a solution of chloroacetyl ester of solanesol **3,** (0.56 mmole), in dry acetone (50mL) was added coumarins (1.0 eq), and anhydrous potassium carbonate (5.6 mmole) and refluxed for 4 hr. Reaction-mixture was then filtered. Filtrate was concentrated on a thin film rotary evaporator and dried *in vacuo* to a give thick syrup which was purified on silica gel column using chloroform:hexane (3:1 v/v) as eluent. The obtained product was purified by recrystallization from dichloromethane/methanol at 10°C.

(2-Oxo-2*H*-chromen-7-yloxy)-acetic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 3a

Yield: 76%; m. p. 51°C; IR (KBr): 1740 (C=O), 1138 cm^{-1} (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, 1 H, *J* = 9.0 Hz, H-4), 7.39 (d, 1H, *J* = 9.0 Hz, H-5), 6.88 (d, 1H, *J* = 9.0 Hz, H-6), 6.78 (s, 1H, H-8), 6.27 (d, 1 H, *J*= 9.0 Hz, H-3), 5.36 (t, 1H, OCH_2-C*H*), 5.11 (m, 8H, 8 × CH_2-C*H*), 4.74 (d, 2H, *J* = 6.0 Hz, OCH_2-CH), 4.68 (s, 2H, CH_2-CO), 2.07- 2.00 (m, 32H, 8 × CH_2-CH_2), 1.72-1.59 (m, 30H, 10 × = C(CH_3); FAB-MS: *m/z* 833 $[M + 1]^+$. Anal. Calcd for $C_{56}H_{80}O_5$: C, 80.76; H, 9.61. Found: C, 80.80; H, 9.69%.

(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-acetic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-6,10,14,18,22,26,30,34-nonaen-1-yl ester, 3b

Yield: 73%; m.p. 60°C; IR (KBr): 1710 (C=O), 1151 cm^{-1} (C-O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.51 (d, 1H *J* = 8.8 Hz, H-4), 6.90 (d, 1H, *J* = 8.8 Hz, H-6), 6.78 (s, 1H, H-8), 6.15 (s, 1H, H-3), 5.35 (t, 1H, OCH_2-C*H*), 5.11 (m, 8H, 8 × CH_2-C*H*), 4.73 (d, 2H, *J* = 6.0 Hz, OCH_2-CH), 4.67 (s, 2H, CO-CH_2), 2.39 (s, 3H, H-11), 2.07- 2.00(m, 32H, 8 × CH_2-CH_2), 1.72-1.59 (m, 30H, 10 × =C(CH_3); FAB-MS: *m/z* 853 $[M + Li]^+$. Anal. Calcd for $C_{57}H_{82}O_5$. 0.5 H_2O: C, 80.00; H, 9.70. Found: C, 79.82; H, 9.93%.

The synthesis of Succinic acid mono-(3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 4

To solution of solanesol (6.0 g, 9.5 mmole) in dry pyridine (100 mL) was added succinic anhydride (1.0 eq), and DMAP (1.0 eq) at RT and stirred for 6 hr. Pyridine was removed *in vacuo* and the residue was extracted with chloroform (3 × 100 mL). Combined organic layer was dried over anhydrous sodium sulphate. The filtrate was evaporated *in vacuo* to give a thick residue which was purified through flash column chromatography using ethyl acetate:hexane (4:96 v/v) as eluent . The product was purified by recrystallization from methylene chloride/methanol at 10°C.

Yield: 80%; m. p. 50°C; IR (KBr): 1737 (C=O, ester), 1164 (C-O), 3415 cm^{-1} (O-H); ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.30 (t, 1H, OCH$_2$-C*H*), 5.10 (m, 8H, 8 × CH$_2$-C*H*), 4.60 (d, 2H, *J* = 6.0 Hz, OC*H*$_2$-CH), 2.61 (m, 4H, 2 × C*H*$_2$-CO), 1.92-1.24 (m, 32H, 8 × C*H*$_2$-C*H*$_2$), 1.78-1.52 (m, 30H, 10 × =C(C*H*$_3$); FAB-MS (LiCl): *m/z* 729 [M$^+$ -1]. Anal. Calcd for $C_{49}H_{78}O_4$. H_2O: C, 78.60; H, 10.69. Found: C, 78.27; H, 10.69%.

General procedure for the synthesis of compounds, 4a-h

To the stirred ice cold solution of solanesol hemisuccinate **4** (1.0 g, 1.3 mmole), in dry dichloromethane (30 mL), was added dicyclohexylcarbodiimide (1.0 eq), DMAP (0.1 eq) followed by desired amine (1.0 eq) at RT and the reaction-mixture stirred for 4 hr. On completion, DCU was filtered, washed with chilled dichloromethane (2 × 20 mL) and filtrate was concentrated to dryness. The dry residue was purified through column chromatography using ethyl acetate:hexane (6:94 v/v) as eluent. The fractions containing the desired compound were concentrated *in vacuo* which yielded the crude compound, which was then purified by recrystallization from methylene chloride:methanol (0-4°C).

N-3-Methoxy phenyl-succinamic acid 3,7,11,15,19, 23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14, 18, 22,26,30,34-nonaen-1-yl ester, 4a

Yield: 61.4%; IR (KBr): 1732 (C=O, ester), 1161 (C-O, ester), 1666 (C=O, amide), 3303 cm^{-1} (N-H); ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.26-6.62 (m, 4H, Ar-H), 5.30 (t, 1H, OCH$_2$-C*H*), 5.11 (m, 8H, 8 × CH$_2$-C*H*), 4.63 (d, 2H, *J* = 8.0 Hz, OC*H*$_2$-CH), 3.79 (s, 3H, OCH$_3$), 2.70 (m, 4H, 2 × C*H*$_2$CO), 2.01 (m, 32H, 8 × C*H*$_2$-C*H*$_2$), 1.60 (m, 30 H, 10 × =C(C*H*$_3$); FAB-MS: *m/z* 842 [M + Li]$^+$. Anal. Calcd for $C_{56}H_{85}O_4N.H_2O$: C, 78.78; H, 10.19; N, 1.64. Found: C, 78.52; H, 10.16; N, 1.19%.

N-2-Methoxy phenyl-succinamic acid 3,7,11,15,19, 23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14, 18,22,26,30,34-nonaen-1-yl ester,4b

Yield: 60.3%; m.p. 60°C; IR (KBr): 1738 (C=O, ester), 1170 (C-O, ester), 1644 cm^{-1} (C=O, amide), 3290 cm^{-1} (N-H); ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.19 (d, 2 H, *J* = 8.6 Hz, Ar-H), 6.85 (d, 2H, *J* = 8.6 Hz, Ar-H), 5.32 (t, 1H, *J* = 7.0 Hz, OCH$_2$-C*H*), 5.11(m, 8H, 8 × CH$_2$-C*H*), 4.59 (d, 2H, *J* = 7.0 Hz, OC*H*$_2$-CH), 4.36 (d, 2H, *J* = 5.6 Hz, Ar-C*H*$_2$), 3.79 (s, 3H, OCH$_3$), 2.69-2.48 (m, 4H, 2 × COC*H*$_2$), 2.00 (m, 32H, 8 × C*H*$_2$-C*H*$_2$), 1.60 (m, 30H, 10 × =C(C*H*$_3$). Anal. Calcd for $C_{57}H_{87}O_4N$. 0.5 H_2O: C, 79.72; H, 10.25; N, 1.63. Found: C, 79.59; H, 10.22; N, 1.86%.

N-(3,3-Diphenyl-propyl)-succinamic acid 3,7,11, 15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6, 10,14,18,22,26,30,34-nonaen-1-yl ester, 4c

Yield: 63.5%; IR (KBr): 1726 (C=O, ester), 1109 (C-O, ester), 1676 (C=O, amide), 3020 cm^{-1} (N-H); ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.26-7.08 (m, 10H 2 × Ar-H), 5.58 (s, 1H, NH), 5.31 (t, 1H, OCH$_2$-C*H*), 5.11 (m, 8H, 8 × CH$_2$-C*H*), 4.59 (d, 2H, *J* = 7.2 Hz, OC*H*$_2$-CH), 3.95 (t, 1H, *J* = 7.8 Hz, (Ar)$_2$-C*H*), 3.23 (m, 2H, (Ar)$_2$ CH-C*H*$_2$), 2.63 (t, 2H, *J* = 6.6 Hz, NH-C*H*$_2$), 2.28 (m, 4H, 2 × COC*H*$_2$), 2.00 (m, 32H,8 × C*H*$_2$-C*H*$_2$), 1.60 (m, 30H,10 ×=C(C*H*$_3$). Anal. Calcd for $C_{64}H_{93}O_3N.1.5\ H_2O$: C, 80.84; H,10.10; N,1.46. Found: C, 81.16; H, 10.16; N, 1.47%.

N-Phenyl-succinamic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30, 34-nonaen-1-yl ester, 4d

Yield: 68%; m.p.50°C; IR (KBr): 1732 (C=O, ester), 1106 (C-O, ester), 1668 (C=O, amide), 3334 cm^{-1} (N-H); ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.60-7.10 (m, 5H, Ar-H), 5.33 (t, 1H, OCH$_2$-C*H*), 5.11 (m, 8H, 8 × CH$_2$-C*H*), 4.62 (d, 2H, *J* = 7.0 Hz, OC*H*$_2$-CH), 2.70 (m, 4H, 2 × COC*H*$_2$), 2.00 (m, 32H, 8 × C*H*$_2$-C*H*$_2$), 1.60 (m, 30H, 10 × =C(C*H*$_3$); FAB-MS: *m/z* 828 [M + Na]$^+$. Anal. Calcd for $C_{55}H_{83}O_3N$: C, 81.98; H, 10.31; N, 1.73. Found: C, 81.67; H, 10.59; N, 1.90%.

N-Benzyl-succinamic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30, 34-nonaen-1-yl ester, 4e

Yield: 80%; m.p. 52°C; IR (KBr): 1739 (C=O, ester), 3313 cm^{-1} (N-H); ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.29 (m, 5H, Ar-H), 5.32 (t, 1H, *J* = 6.6 Hz, OCH$_2$-C*H*), 5.11 (m, 8H, 8 × CH$_2$-C*H*), 4.60 (d, 2H, 6.6 Hz, OC*H*$_2$-CH), 4.44 (d, 2H, *J* = 6.0 Hz, Ar-C*H*$_2$), 3.49 (s, 1H, NH), 2.71 (m, 4H, 2 × COC*H*$_2$), 2.51 (m, 2H, NHCOC*H*$_2$), 2.00 (m, 32H, 8 × C*H*$_2$-C*H*$_2$), 1.60 (m, 30H,10 × =C(CH$_3$). Anal. Calcd for $C_{56}H_{85}O_3N$: C, 80.36; H, 10.77; N, 1.13. Found: C, 80.28; H, 10.39; N, 1.67%.

4-Oxo-4-(4-phenyl-piperazin-1-yl)-butyric acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 4f

Yield: 60%; m.p. 60°C; IR(KBr): 1734 (C=O, ester), 1664 (C=O, amide), 1172 cm^{-1} (C-O, ester); ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.29-6.92 (m, 5H, Ar-H), 5.43 (m, 1H, OCH$_2$-C*H*), 5.20 (m, 8H, 8 × CH$_2$ -C*H*), 4.67 (d, 2H, *J* = 7.0 Hz, OC*H*$_2$-CH), 3.82 (t, 4H, CON(C*H*$_2$)$_2$, 3.28 (t, 4H, Ar-N(C*H*$_2$)$_2$, 2.69 (m, 4H, 2 × C*H*$_2$CO), 2.00 (m, 32H, 8 × C*H*$_2$-C*H*$_2$), 1.60 (m, 30H, 10 × = C(C*H*$_3$); FAB-MS: *m/z* 881[M + Li]$^+$. Anal. Calcd for $C_{59}H_{90}O_3N_3$: C, 81.00; H, 10.29; N, 3.20. Found: C, 81.20; H, 10.56; N, 3.26%.

4-Oxo-4-(4-pyridin-2-yl-piperazin-1-yl)-butyric acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 4g

Yield: 63%; m.p. 55°C; IR (KBr): 1730 (C=O, ester), 1658 (C=O, amide), 1174 cm^{-1} (C-O, ester); ^{1}H NMR (200 MHz, CDCl$_3$): δ 8.19-6.66 (m, 4H, Ar-H), 5.34 (t, 1H, OCH$_2$-C*H*), 5.11 (m, 8H, 8 × CH$_2$-C*H*), 4.62 (d, 2H, *J* = 6.6 Hz, OC*H*$_2$-CH), 3.75 (t, 2H, COC*H*$_2$), 3.63 (s, 4H, N(CH$_2$)$_2$), 3.50 (t, 2H, NCOC*H*$_2$), 2.69 (s, 4H, N(CH$_2$)$_2$, 2.00 (m, 32H, 8 × C*H*$_2$-C*H*$_2$), 1.60 (m, 30H, 10 × C(CH$_3$). Anal. Calcd for $C_{58}H_{89}O_3N_3$: C, 79.54; H,10.17; N, 4.80. Found: C, 79.69; H, 10.35; N, 4.90%.

4-(4-Methyl-piperazin-1-yl)-4-oxo-butyric acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 4h

Yield: 63%; IR (KBr): 1732 (C=O, ester), 1654 (C=O, amide), 1164 cm^{-1} (C-O, ester); ^{1}H NMR (200 MHz, CDCl$_3$): δ 5.34 (t, 1H, OCH$_2$C*H*), 5.11 (m, 8H, 8 × CH$_2$C*H)*, 4.61 (d, 2 H, *J* = 6.8 Hz, OC*H*$_2$-CH), 3.63-3.51 (m, 4H, 2 × COC*H*$_2$), 2.66 (m, 4H, CON(CH$_2$)$_2$), 2.39 (m, 4H, N(CH$_2$)$_2$), 2.30 (s, 3H, NCH$_3$), 2.00 (m, 32H, 8 × C*H*$_2$ -C*H*$_2$), 1.60 (m, 30H, 10 × =C(C*H*$_3$). Anal. Calcd for $C_{54}H_{88}O_3N_2$. H$_2$O: C, 78.00; H, 10.84; N, 3.37. Found: C, 77.8; H, 10.77; N, 3.30%.

The synthesis of *N*- 3 methoxy phenyl-succinamic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 4i

To the stirred ice cold solution of solanesol hemisuccinate (0.1 g, 0.13 mmole), in dry dichloromethane (10 mL), was added dicyclohexylcarbodiimide (1.0 eq), HOBT (1.0 eq) and *p*-anisidine (1.0 eq) and the reaction-mixture was stirred at RT for 3 hr. The solid DCU was filtered off and filtrate was concentrated to dryness. The dry residue was purified by column chromatography using ethyl acetate:hexane (6:94 v/v) as eluent. The fractions containing the desired compound were concentrated *in vacuo* which yielded the crude compound, which was then purified by recrystallization from methylene chloride: methanol (0-4°C).

Yield: 60%; m.p. 56°C; IR (KBr): 1730 (C=O, ester), 1170 (C-O, ester), 1664 (C=O, amide), 3324 cm^{-1} (N-H); ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.39 (d, 2H, *J* = 9.0 Hz, Ar-H), 6.84 (d, 2H, *J* = 9.0 Hz, Ar-H), 5.33 (t, 1H, OCH$_2$-C*H*), 5.11 (m, 8H, 8 × CH$_2$.C*H*), 4.62 (d, 2H, *J* = 7.2 Hz,OCH$_2$-C*H*), 3.78 (s, 3H, OC*H*$_3$), 2.70 (m, 4H, 2 × COC*H*$_2$), 2.00 (m, 32H, 8 × C*H*$_2$-C*H*$_2$), 1.60 (m, 30H, 10 × =C(CH$_3$). Anal. Calcd for $C_{56}H_{87}O_4N$: C, 82.06; H,10.37; N, 1.70. Found: C, 82.17; H, 10.64; N, 1.94%.

General procedure for the synthesis of 4j-l

To the stirred solution of desired amino acid hydrochloride salt (1.3 mmole) in dichloromethane (20 mL) was added triethylamine (1.0 eq) and stirred for 10 min followed by addition of solanesol hemisuccinate **4** (1.0 eq), dicyclohexylcarbodiimide (1.0 eq) and DMAP (0.1 eq). The reaction-mixture was stirred at RT for 4 hr. The solid DCU was filtered off and filtrate was washed with water. The organic layer was collected and dried over anhydrous sodium sulphate and concentrated to dryness which was then purified by column chromatography using ethyl acetate:hexane (15:85 v/v) as eluent. The crude product was purified by recrystallization from methylene chloride:methanol (0-4°C).

1-[3-(3,7,11,15,19,23,27,31,35-Nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaenyloxy-carbonyl)-propionyl] - pyrolysis-2-carboxylic acid methyl ester, 4j

Yield: 65%; IR (KBr): 1739 (C=O, ester), 1649 (C=O, amide), 1168 cm^{-1} (C-O, ester); ^{1}H NMR (200 MHz, CDCl$_3$): δ 5.30 (t, 1 H, OCH$_2$-C*H*), 5.11 (m, 8H, 8 × CH$_2$-C*H*), 4.59 (d, 2 H, *J* = 6.0 Hz, OC*H*$_2$-CH), 4.50 (m, 1H, C*H*), 2.66 (m, 4H, 2 × COC*H*$_2$), 3.71 (s, 3 H, OCH$_3$), 2.00 (m, 32 H, 8 × C*H*$_2$-C*H*$_2$), 1.60 (m, 30 H, 10 × = C(CH$_3$); FAB-MS: *m/z* 864 [M + Na]$^+$. Anal. Calcd for $C_{55}H_{87}O_5N$: C, 78.47; H, 10.34; N, 1.66. Found: C, 78.17; H, 10.57; N, 1.31%.

N-[2- (1*H*- Indol-3- yl)-1-methoxycarbonyl-ethyl]-succinamic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 4k

Yield: 75%; IR (KBr): 3372 (N-H), 1734 (C=O, ester), 1674 cm^{-1} (C=O, amide); ^1H NMR (200 MHz, $CDCl_3$): δ 7.54-7.08 (m, 4H, Ar-H), 7.03 (s, 1H, NC*H*=), 5.32 (t, 1H, OCH_2-C*H*), 5.11 (m, 8H, CH), 4.90 (m, 1H, CH), 4.52 (d, 2H, *J* = 7 Hz, OCH_2), 3.67 (s, 3 H, OMe), 3.29 (d, 2H, *J* = 5.4 Hz, CH_2), 2.50 (m, 4H, CO-CH_2), 2.00 (m, 32H, CH_2), 1.60 (m, 30H, CH_3); FAB-MS: *m/z* 937 $[M + Li]^+$. Anal. Calcd for $C_{61}H_{90}O_5N_2$: C, 78.59; H, 9.72; N, 3.01. Found: C, 78.7; H, 9.67; N, 2.58%.

N-(1-Methoxycarbonyl-2-phenyl-ethyl)-succinamic acid 3,7,11,15,19,23,27,31,35-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 4l

Yield: 50%; IR (KBr): 3300 (N-H), 1739 (C=O, ester), 1656 cm^{-1} (C=O, amide); ^1H NMR (200 MHz, $CDCl_3$): δ 7.56-7.08 (m, 5 H, Ar-H), 5.33 (t, 1H, OCH_2.C*H*), 5.11 (m, 8 H, 8 × CH_2-C*H*), 4.90 (m, 1H, C*H*), 4.59 (d, 2H, *J* = 7.0 Hz, OCH_2-CH), 3.72 (s, 3H, OMe), 3.11 (m, 2H, ArCH_2), 2.63 (m, 4H, CH_2CO), 2.00 (m, 32 H, 8 × CH_2-CH_2), 1.60 (m, 30H, 10 × =C(CH_3)); FAB-MS: *m/z* 937 $[M + Li]^+$. Anal. Calcd for $C_{59}H_{87}O_4N$: H_2O: C, 78.23; H, 10.05; N, 1.54. Found: C, 78.42; H, 10.39; N, 1.44%.

General procedure for the synthesis of 4m,n

To the solution of solanesol hemisuccinate **4** (1.0 g, 1.3 mmole) in methylene chloride (30 mL) was added dicyclohexylcarbodiimide (1.0 eq) and DMAP (0.1 eq) followed by addition of partially protected sugar alcohol or loganin pentaacetate (1.0 eq) at 0°C and stirred for 5 hr. The solid DCU was filtered off. The filtrate was concentrated *in vacuo* to a thick residue which was purified by flash column chromatography using ethyl acetate:hexane (1:99 v/v) as eluent. The crude compound was purified by recrystallization from methylene chloride and methanol at 0-4°C.

Succinic acid 2-(3,4,5-triacetoxy, 6-methoxy-tetrahydro-pyran-2-yl)-ethyl ester 2,6,10,14,18,22,26, 30,34-nonamethyl-hexatriaconta-2,6,10,14,18,22, 26, 30,34-nonaen-1-yl ester, 4m

Yield: 82%; ^1H NMR (200 MHz, $CDCl_3$): δ 5.47 (t, 1H, *J* = 9.8 Hz, H-3), 5.33 (t, 1H, OCH_2-C*H*), 5.18-4.80 (m, 11H, H-4, H-2, H-1, 8 × CH_2-C*H*), 4.61 (d, 2H, *J* = 7.0 Hz, OCH_2-CH), 4.30- 4.05 (m, 2H, H-6), 3.95 (m, 1H, H-5), 3.41 (s, 3H, OMe), 2.68 (m, 4H, 2 × CO-CH_2), 2.00 (m, 41H, 3 × COCH_3, 8 × CH_2-CH_2), 1.69-1.59 (m, 30 H, 10 × = C(CH_3); FAB-MS: *m/z* 1039 $[M + Li]^+$. Anal. Calcd for $C_{62}H_{96}O_{12}$.2 H_2O: C, 69.66; H, 9.36. Found: C, 69.79; H, 9.28%.

Succinic acid 2-[6-(6-acetoxy-4-methoxycarbonyl-5-methyl-1,4a,5,6,7,7a-hexahydro-cyclopenta[*c*]-pyran-1-yloxy)-3,4,5-trimethoxy-tetrahydro-pyran-2-yl]-ethyl ester 2,6,10,14,18,22,26, 30,34-nonamethyl-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl ester, 4n

Yield: 66%; ^1H NMR (200 MHz, $CDCl_3$): δ 7.28 (s, 1H, H-3), 5.30 (t,1H, OCH_2-C*H*), 5.25- 4.80 (m, 14H, H-7, H-1, H-1′, H-2′, H-3′, H-4′, 8 × CH_2-C*H*), 4.58 (d, 2H, *J* = 7.0 Hz, OCH_2-CH), 4.29 (dd, 1H, *J* = 12.0 and 6.0 Hz , H-6′), 4.15 (dd, 1H, *J* = 12.0 and 6.0 Hz, H-6′), 3.71 (m, 1H, H-5′), 3.69 (s, 3 H, OMe), 3.00 (m, 1 H, H-5), 2.57 (s, 4H, 2 × COCH_2), 2.30-1.80 (m, 48H, H-6, H-8, H-9, 4 × COCH_3, 8 × CH_2-CH_2), 1.69-1.59 (m, 30H, 10 × C(CH_3); FAB-MS: *m/z* 1277 $[M + Li]^+$. Anal. Calcd for $C_{74}H_{110}O_{17}$.1.5 H_2O: C, 68.2; H, 8.76. Found: C, 68.1; H, 8.94%.

Conclusion

Solanesol is extremely interesting for wound healing activity. Simulation of this pharmacophore with or without a spacer with other molecules does elicit promising wound healing activity. However, profile of wound healing activity seems to be affected by structural changes indicating specificity of the molecules.

Antioxidant activity (*in vitro*) of the synthetic compounds **2a-4n** was tested to observe the effect of the test compounds on the generation of hydroxyl radicals and angiogenesis activity (CAM) of these compounds was tested to assess the angiogenic profile and its impact on hydroxyproline content followed by wound healing activity (wound area). The wound healing activity of active compounds, was therefore, evaluated in Punch wound model. The wound healing activity of these compounds was determined on the basis of the area of the wound. It is concluded that hydroxyproline content and the ability of the compounds to exhibit antioxidant and angiogenic activities are good markers for wound healing activity evaluation. The compounds **3b**, **4h**, when compared to 3,3-dimethylacryl shikonin, exhibit better wound healing activity.

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