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Synthesis of potent water soluble forskolin analogues†

Bansi Lal [a]*, Ashok Kumar Gangopadhyay [a], Ramesh M Gidwani [a],
Ramanujam Rajagopalan [b,c] & Anil V Ghate [b]

[a]Department of Chemistry, [b]Department of Pharmacology, Quest Institute of Life Sciences, Mulund (W), Mumbai 400 080, India

[c]Dr.Reddy's Research Foundation, Bollaram Road, Miyapur, Hyderabad 500138, India

Email: bansilal@nicholaspiramal.co.in

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The coupling of ω-halo acid or acrylic acid with 6β-2-hydroxyacyl forskolin **1** in the presence of DCC and DMAP gives 6β-ω-haloacyloxy or acryloxy derivatives **10**-**12**. These derivatives undergo halogen displacement or Michael addition reaction with aliphatic or heterocyclic amine to afford compounds **13**-**28**. Alternatively, **1** is coupled with N-trityl protected amino acid to give corresponding intermediates **2**-**5**. Removal of trityl group could be achieved by TFA diluted with ether and subsequent salt formation with HCl in ether yields **6**-**9** as hydrochloride salt. Compound **6** has shown excellent *in vitro* and *in vivo* positive inotropic activity.

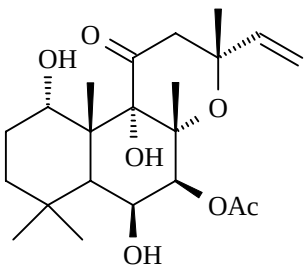
Keywords: forskolin, water soluble, ω-halo acid, acrylic acid, hydroxyacyl forskolin, aliphatic amine, Michael addition, heterocyclic amine, inotropic activity

IPC: **Int.Cl.**[7] **C 07 C**

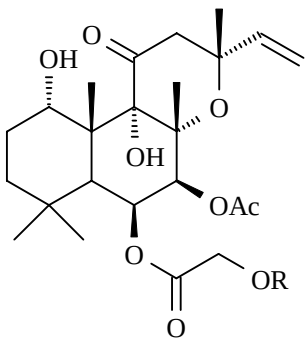
During our endeavour to develop forskolin molecule with better positive inotropic activity we have introduced a novel hydroxyacetyl chain, at 6β-position of forskolin that maintains to a great extent the activity of forskolin[1]. Further, when the hydroxy group was substituted with acetoxy or formyloxy group the positive inotropic activity was either retained or increased sharply as shown in **Figure 1**. Since these compounds were water insoluble, further development could not be undertaken. Thus, we undertook a synthetic programme to prepare water-soluble forskolin derivatives based on these novel skeletons. In this paper84 the synthesis and biological activity of these compounds have been described.

Chemistry

The approach we adopted to make these compounds water soluble was to introduce a variety of substituted or unsubstituted α-or ω-aminoacyl chain at primary –OH group of 6β-(2-hydroxy-acetyloxy)forskolin and subsequent formation of hydrochloride salt. The introduction of amino acid residues such as glycine, sarcosine, *S*-alanine and α-aminoisobutyric acid could be achieved through the



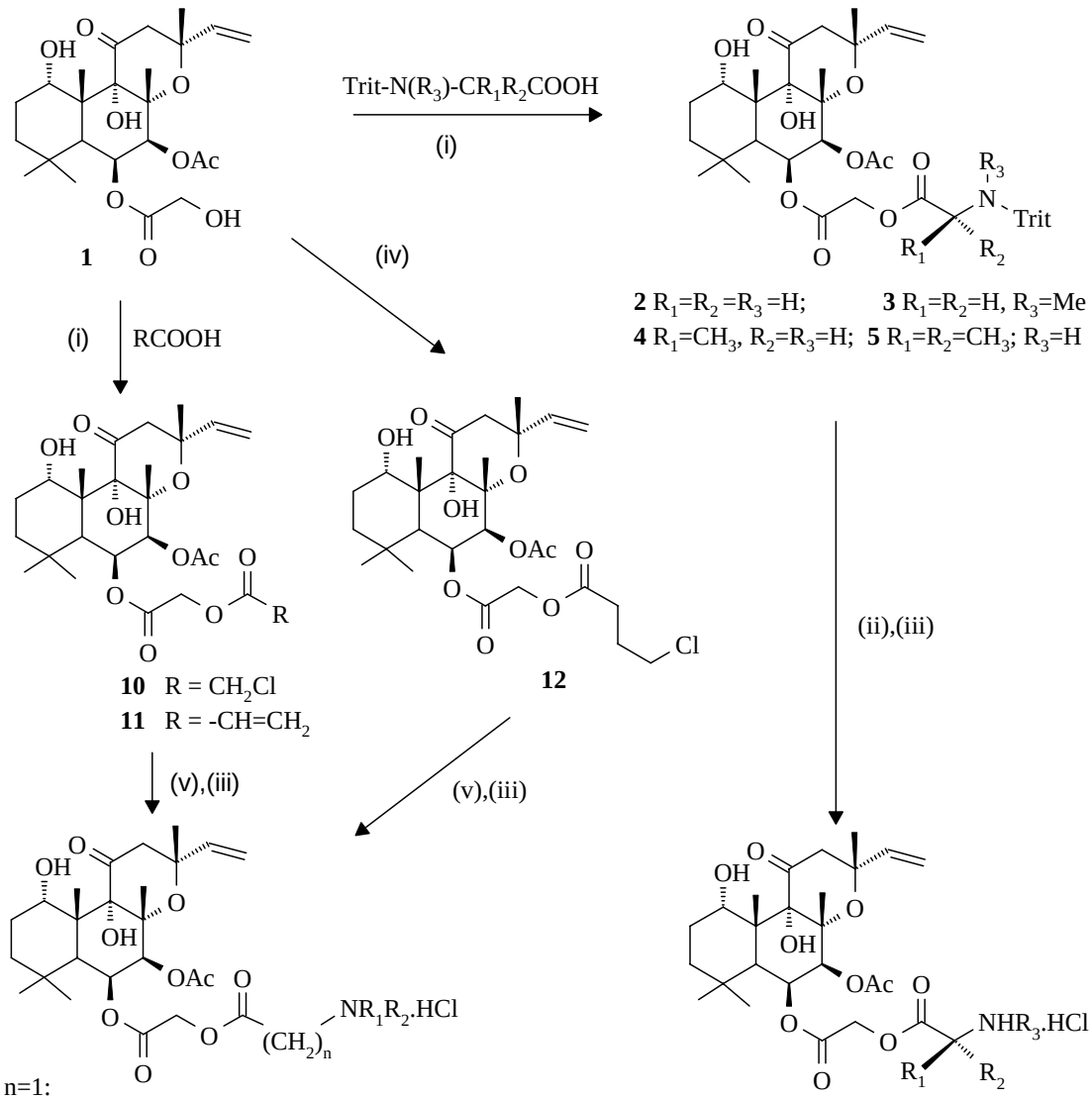
Forskolin; EC_{50}=0.02 μg/ml



R = H ; EC_{50}=0.16 μg/ml
R = COCH$_3$; EC_{50}=0.16 μg/ml
R = COH; EC_{50}=0.01 μg/ml

Figure 1

† This work was carried out at Research Centre, Hoechst Marrion Roussel Limitted, Mulund (W), Mumbai 400 080, India



Scheme I-(i)DCC, DMAP, EtOAc - DMF, CH_2Cl_2 - DMF. (ii). TFA, ether. (iii). HCl - ether. (iv). $ClCH_2CH_2CH_2COCl$, Py, CH_2Cl_2, O^oC; (v). R_1R_2NH, CH_2Cl_2, rt.

coupling of the corresponding trityl-protected amino acid[2-4], in the presence of DCC-DMAP to obtain **2**-**5** as shown in **Scheme I**, followed by deprotection of trityl group by TFA in ether under dilution[5]. The final products **6**-**9** were isolated as hydrochloride salt. For the synthesis of dialkylaminoacetyl ($COCH_2NR_2$) derivatives, compound **1** was first converted to 2-chloroacetyl derivative **10** by reacting 2-chloroacetic

acid in the presence of DCC and DMAP. The resulting chloro derivative was treated with the appropriate amine in dichloromethane at room temperature. After purification of these compounds as free base, they were converted into soluble hydrochloride salt by treatment with HCl in dry ether from a suitable solvent to yield compounds **13**-**20** as shown in **Scheme I**. The higher homologue of α-aminoacetyl chain such as 3-dialkylaminopropanoyl and 4-dialkylaminobutanoyl chains were also incorporated as shown in **Scheme I**. Thus, 3-dialkylaminopropanoyl derivatives were synthesized by first coupling acrylic acid with **1** in the presence of DCC-DMAP to get **11** followed by Michael addition of different secondary amines across the conjugated double bond in dichloromethane resulting final compounds **21**-**25**. Introduction of 4-dialkylamino-butanoyl residues was achieved through condensation of 4-chlorobutanoyl chloride to obtain **12**. Compound **12** was converted into compounds **26**-**28** by treatment with the required amine as described earlier. Compound **6** was found to be the most potent (see biological activity), was further converted to amidine derivative **30** as shown in **Scheme II** by treatment with dimethylformamide acetal in DMF following a literature method [6]. It was also interesting to ascertain the role of double bond at position 14 in terms of activity. Compound **6** was subjected to hydrogenation with 10% Pd-C in methanol to obtain **29**. It was observed that compound **6** was not very stable in aqueous solution. At room temperature in 24 hr ~15-20% of hydrolysed product **1** was formed. This was due to the presence of aminoacyl moiety on primary hydroxy group. To stabilize the molecule, one of the approaches adopted was to replace $CH_2OCOCH_2NH_2$ by $CH_2NHCOCH_2NH_2$ and subsequently evaluate its stability and more importantly its biological efficacy. Therefore, it was decided to synthesize the target compound **35** as described in **Scheme II**. Treatment of 1α-*tert*-butyldimethylsilyl-7β-deacetyl-forskolin with Trit-Gly-Gly in the presence of DCC-DMAP resulted **31**, which on treatment with Na_2CO_3 in DMF-CH_3CN and water at room temperature gave **32**. The free hydroxyl group at 7β-position was acetylated through the coupling of AcOH by DCC-DMAP method to yield **33**. The *tert*-butyldimethylsilyl group was removed by treatment with 1*M* *n*-$Bu_4N^+F^-$ in THF[7] to give compound **34** which was finally converted into **35** by removal of trityl group in TFA-ether as described earlier [5].

Biological activity

The positive inotropic activity of all compounds was assessed *in vitro* using spontaneously beating isolated guinea pig atrial preparation. Compounds with EC_{50} <0.1 μg/mL and good water solubility were tested *in vivo* for their ability to cause increase in cardiac force of contraction by administering them intravenously, as an infusion and in bolus doses. Those compounds that showed interesting activity on intravenous administration were tested for oral efficacy in conscious dog model.

Isolated G.pig atria

As described earlier[8], spontaneously beating atria were suspended in Ringer solution, at 32°C, in 10 mL capacity organ bath. The force of contraction was recorded isometrically. Test compounds were dissolved in distilled water or propylene glycol to prepare solutions of 1mg/mL concentration. After recording the control response, test compounds were added to get 0.01-30μg/mL concentrations, cumulatively. EC_{50} values were calculated from the dose response curves.

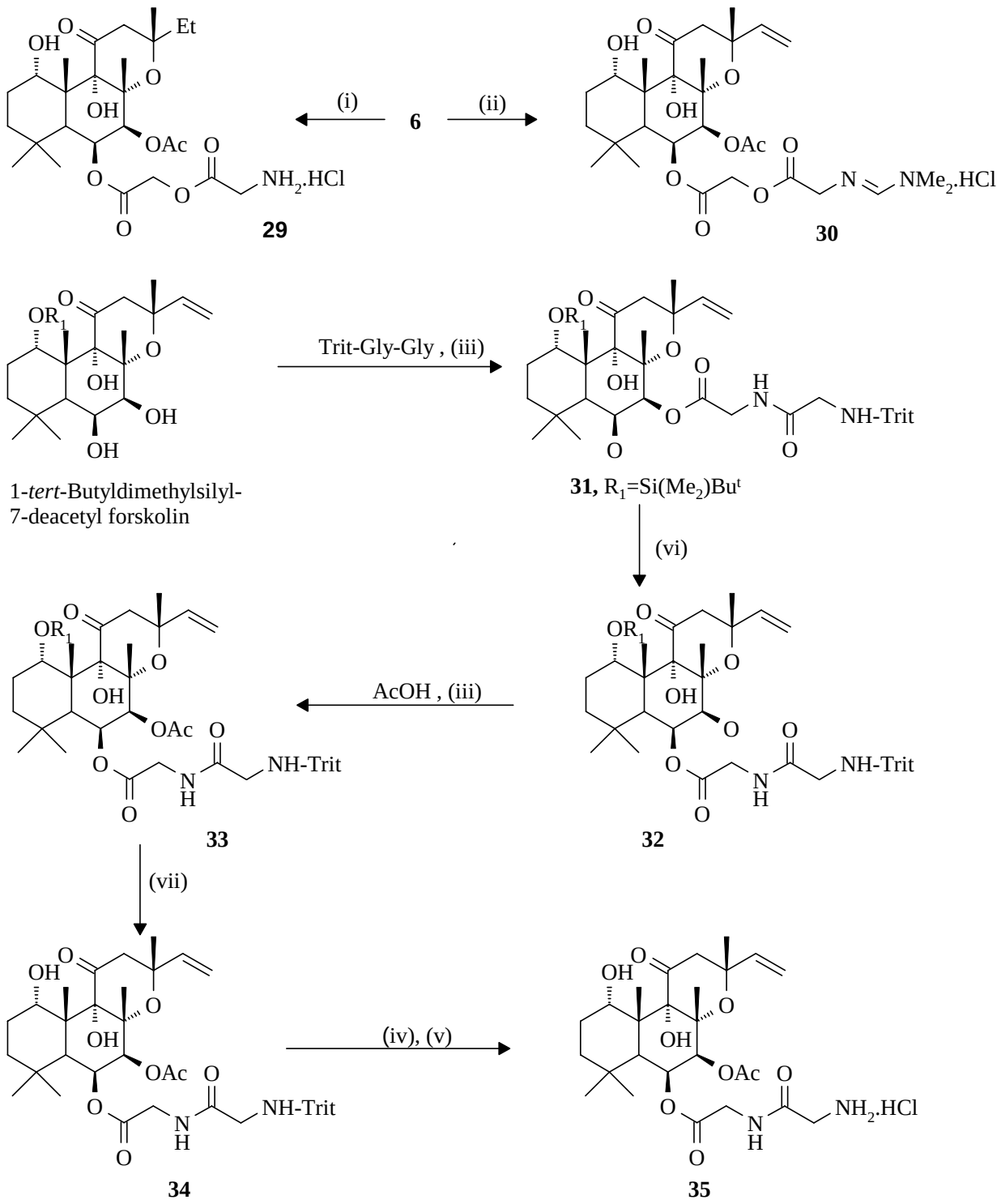
Intravenous administration in anaesthetized dogs

(a) Intravenous infusion study. Male mongrel dogs (18-22 kg body weight) were anaesthetized with pentobarbital sodium (35 mg/kg i.p.) and prepared as described earlier[8]. Briefly, after tracheal, venous, arterial and left ventricular cannulations parameter like heart rate (HR), lead II ECG, mean arterial blood pressure (MBP), left ventricular pressure (LVP) and its differentiated form LV dP/dt max were recorded continuously throughout the infusion period of 60 min. Test compounds were dissolved in distilled water (1mg/mL concentration). Further dilutions were made as per the body weight of the animal so as to adjust the infusion volume to 0.2 mL/min containing dose of 0.5 μg or 1 μg/kg/min.

(b) Intravenous bolus dose study. The animals were prepared as described earlier[8] and above. In a volume of 0.1 mL/kg/dose, various doses (0.01mg to 3mg/kg depending upon *in vitro* EC_{50}), were administered intravenously 10-30 min apart. ED_{50} for percent increase in LV dP/dt max was calculated from the dose-effect relationship.

Oral activity in conscious dog

Both beagle and mongrel dogs of either sex (body wt. 10-17 kg) were used. The animals received



Scheme II- (i). H_2, 10% Pd-C,MeOH; (ii). $(MeO)_2CHNMe_2$, DMF. (iii). DCC, DMAP, EtOAc; (iv). TFA, ether. (v). HCl, ether. (vi). Na_2CO_3, DMF; CH_3CN, Water, rt. (vii). $nBu_4N^+F^-$, THF, rt.

antibiotic Streptopenicillin (1g) (Dicristin-S, Sarabhai Merck), intramuscularly twenty-four hours before, as pre surgical antibiotic treatment. Next day, the dog was anaesthetized with pentobarbital sodium (35 mg/kg i.v.). Through a small incision in the neck, left carotid artery was partially isolated and through it a sterile, heparinised saline filled catheter was introduced into left ventricle. The wound was sutured and dressed properly. Post-surgically, the animal received Novalgin (HMR) injection 0.5 mL, i.m. and a repeat antibiotic treatment. Conscious animal was used for the experiment 24-30 hr later. Left ventricular pressure (LVP) and its differentiated form (LV dP/dt max) were recorded via a pressure transducer (Statham, p23XL) on a polygraphic recorder (Nihon Kohden). Heart rate (HR) was monitored through LVP signals fed into the heart rate meter (Maqlab). Control values for the parameters were recorded before test compound solutions (10 mg/mL in distilled water) were administered through an intragastric catheter. Changes in LVP, LV dP/dt max and HR were recorded at different time intervals for 60 min.

Results and Discussion

Isolated G. pig atrium

The compounds **2**-**5**, and **10**–**12** were not tested for biological activity since these compounds were not water-soluble. **Table I** shows the positive inotropic activity of compounds tested. A number of compounds viz. **6**, **13**, **14**, **16**, **20**, **21**, **23** showed *in vitro* activity. The IC_{50} values range from 0.008 μg/mL to 0.093 μg/mL, compared to IC_{50} values of forskolin at 0.02 μg/mL. Among the compounds synthesized, **20** and **6** showed excellent *in vitro* positive inotropic activity, with IC_{50} 0.006 μg/mL and 0.0084 μg/mL respectively **(Table I)**. *In vitro* positive inotropic activity of compound **6** in spontaneously beating isolated G.pig atria is shown in **Figure 2**.

Intravenous infusion study in anaesthetized dogs

On slow intravenous infusion (1μg / kg / min) of the compounds in anaesthetized dogs, only 5 compounds showed significant positive inotropic activity **(Table I)**. Of these, **6** was the most potent compound causing 136% increase in LV dP/dt max. In earlier experiments, under similar conditions, forskolin could produce only 59% rise in cardiac contractility. In both 0.5 μg/kg/min and 1 μg/ kg/min infusion doses, **6** produced significant ($P<0.05$) increase in cardiac force of contraction without changing the heart rate significantly.

Table I – Positive ionotropic activity of tested compounds

Compd	Positive inotropic activity		
	in vitro G. pig atrium EC50 μg / mL	*in vivo* I.V. infusion (1μg / kg /min)	Oral effect
6	0.008	136%	3 mg/kg : 74%
7	ND	20%*	
8	ND	20%*	
9	NA		
13	0.093	74%	5 mg / kg : 60%
14	0.03	22%	5 mg / kg : 78%
15	0.14	ND	
16	0.04	NA	3 mg / kg : 63%
17	NA	ND	
18	0.072	NA	
19	>30	ND	
20	0.006	84%	5 mg / kg : 45%
21	0.058	97%	
23	0.086	54%	
24	0.3	ND	
25	0.31	ND	
27	NA	ND	
28	0.26	ND	
31	NA	ND	
34	NA	ND	
35	NA	ND	
Forskolin	0.02	59%	3 mg / kg : 31%
	NA=Not active	ND=Not done	* 3 μg / kg /min

Intravenous bolus dose study in anaesthetized dogs

The most interesting compound **6** had caused dose dependent effects on intravenous administration of multiple successive bolus doses in anaesthetized dogs. It was observed that at 3 μg and 10 μg/kg doses, none of the parameters was significantly affected. At 30 μg dose, LV dP/dt max increased significantly ($P<0.05$), without affecting HR and MBP. All the three parameters were significantly changed ($P<0.05$), for 5-10 min after 100 μg / kg and 300μg / kg doses. Forskolin, the parent compound showed an ED_{50} of 0.007 μg/kg while compound **6** has an ED_{50} of 0.0075 μg/kg.

Oral efficacy in conscious dogs

The experiment revealed that at 3mg/kg p.o. dose, both **6** and the standard cardiotonic Milrinone

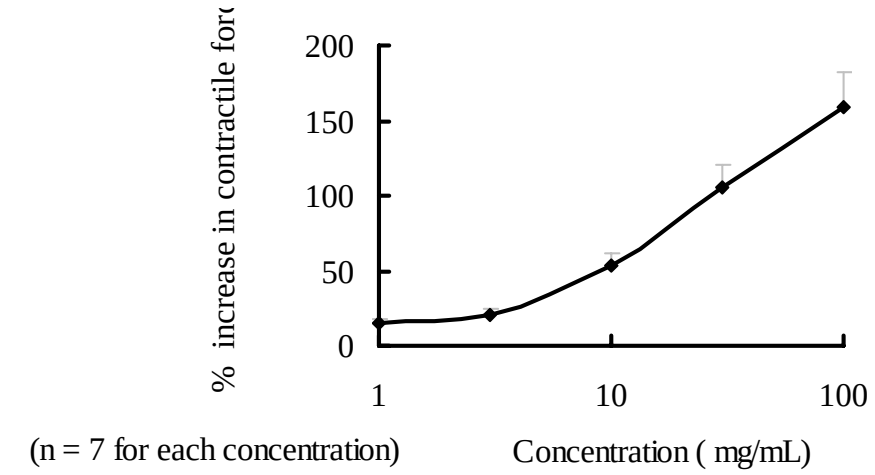


Figure 2 — *In vitro* Positive inotropic activity of compound **6** in spontaneously beating isolated G.Pig atria

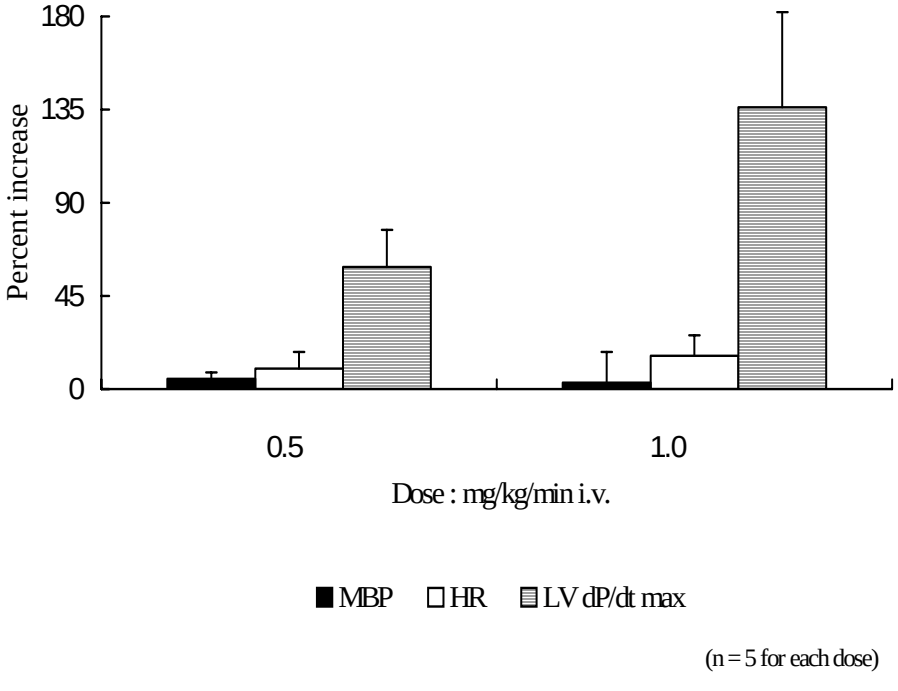


Figure 3 — Haemodynamic effects of compound **6** in anaesthetized dog (i.v. infusion study)

had similar effects in conscious dog. Compound **6** increased the heart rate slightly (35±12%, n=3, P>0.05) as did Milrinone (29±10%, n=3, P>0.05). However, both the compounds increased cardiac contractility significantly (P<0.05) and comparably (74+.11% and 99±15). Forskolin, at 3 mg / kg oral dose, produced 31% rise in LV dP/dt max (data not shown), while **6** under similar experimental conditions increased it by 74%.

The encouraging result of compound **6** prompted us to synthesize compounds **7**-**9** wherein the glycine part was replaced by N-methylglycine, L-alanine and 2,2-dimethyl glycine. To our surprise these compounds showed very low *in vivo* activity **(Table I)**.

Structure–activity correlation

The biological activity data suggest that as the chain length of the substituent on 6β–2-hydroxyacyl group increases, the biological activity decreases. The best activity is seen for n = 1, whereas for n = 3 all the compounds were found to be inactive. However, for n = 2, only one compound **23** showed activity with IC_{50} = 0.086 and *in vivo* activity 54% through i.v. infusion at 1μg/kg/min but failed to show oral activity. The most active compound belongs to the series for n=1. Attempt of single substitution on the amino group of glycine viz. sarcosine resulted in loss of activity. Substitution of α-position of glycine by mono-or di-methyl group also resulted in loss of activity. Conversion of **6** to a highly polar formamidine **30** resulted in complete loss of activity. The compound **35** in which the O atom of hydroxy-acetyl spacer was replaced by N atom was totally inactive.

All these results possibly suggest that substituted or unsubstituted 2-aminoacyl chain substituted on 2-hydroxylacyl spacer chain behaving like water soluble prodrug of 6β-2-hydroxyacyl-forskolin analogs which were earlier described by us to have good positive inotropic activity (**Figure I**)[1]. In case of compound **35** the amide bond does not cleave in a similar manner *in vivo*. Therefore, this compound failed to show any activity.

Conclusion

Earlier, we have successfully shown the use of 2-hydroxyacyl chain for the synthesis of compounds with specificity towards positive inotropic activity[1]. In this paper, we have demonstrated the design and synthesis of water-soluble analogs using one such scaffold to generate selective positive inotropic agent.

Among all the water-soluble forskolin derivatives from this group, **6** has the most interesting profile **(Table I)**. Compared to the parent compound forskolin, **6** is 2.6 times more potent *in vitro*, while *in vivo,* on intravenous infusion and oral administration it is 2.3 times superior. The compound **6** appears to be almost as potent as forskolin in an intravenous bolus study. Incidentally colforsin daropate (NKH 477), another water-soluble forskolin derivative, currently in clinical use is reported to be about 1.2 times more potent than forskolin in an i.v. bolus study[9] .

Thus, **6** shows potent *in vitro* as well as *in vivo* positive inotropic activity (without much chronotropic and hypotensive effects), good oral efficacy and low toxicity (LD_{50} 47.5 mg/kg, i.p. in mice) make it an ideal candidate for further development.

Experimental Section

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 157 Spectrophotometer as KBr film unless otherwise mentioned; ^{1}H NMR spectra in $CDCl_3$ unless otherwise mentioned on a Jeol FT-90 Spectrometer with TMS as internal standard (chemical shifts in δ, ppm). Petroleum ether refers to the fraction of b.p. 60-80°C. For flash column chromatography silica gel (finer than 0.08 mm particle size) was used. Pre-coated (silica gel 60 F_{254}) TLC plates were used for checking purity of compounds. Vaniline-50% orthophosphoric acid or anisaldehyde-H_2SO_4 spray reagents were used and heated the plates at 110°C for visualization. All compounds were homogeneous on TLC and gave proper spectral characteristics.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-(2-tritylaminomethylcarbonyloxyacetyloxy)labd-14-en-11-one 2. To a solution of compound **1** (2.33g, 5 mmoles) and DCC (1.25 g, 6.05 mmoles) in EtOAc (60 mL), Trit-Gly (1.74 g, 5.5 mmoles) was added followed by DMAP (0.61 g, 5 mmoles) under stirring at room temperature. After 6 hr DCC was filtered off and the filtrate was washed with dil. aq. $NaHCO_3$ followed by brine. The EtOAc layer was dried over anhydrous Na_2SO_4 and the solvent was removed. The residue was purified by flash chromatography with 20% EtOAc-light petroleum, yield 3.2 g (83.4%), mp. 218-20°C (EtOAc-light petroleum); IR (KBr): 3500 (br), 3340 (br), 2970 (br), 1768, 1758, 1730 cm^{-1}; ^{1}H NMR: 0.92, 1.01, 1.30, 1.34, 1.53, (5×s, 15H, 5×CH_3), 2.01 (s, 3H,-$COCH_3$), 2.39 (d, 1H, J=3.04, H-5), 2.44 (d, 1H, J_{gem}=17.21, 12βH), 3.19 (d, 1H,

J_{gem}=17.21, 12αH), 3.21 (s, 2H, $COCH_2N$-), 4.45, 4.65 (2×d, 2H, J_{gem}=16.2, $COCH_2O$), 4.46 (1H, br, 1H), 4.92 (1H, dd, J_{cis} =10.13, J_{gem} =1.62, $15H_{cis}$), 5.18 (dd, 1H, J_{trans} =16.7, J_{gem} =1.62, $15H_{trans}$), 5.45 (d, 1H, *J*=4.56, H-7), 5.82 (dd, 1H, *J*=4.56, 3.04, H-6), 5.92 (dd, 1H, J_{trans}=16.71, J_{cis}=10.13, H-14), 7.14-7.49 (m,15H, 15 x Ph-H). Anal. Calcd for $C_{45}H_{53}NO_{10}$: C, 70.38; H, 6.96; N, 1.82. Found: C, 70.11; H, 7.13; N, 1.89%.

Compounds **3-5** were also prepared by the same method after reacting compound **1** with appropriate N-Trit protected amino acids.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-[2-methyl(trityl)aminomethylcarbonyloxy acetyloxy]-labd-14-en-11-one 3. The crude product was purified by flash chromatography with 10% CH_3CN-$CHCl_3$, yield 72% (semisolid); IR (KBr): 3440-3300 (br), 2940 (br), 1765 (br), 1725 cm^{-1}; ^1H NMR: 1.0, 1.04, 1.39 (6H), 1.64 (4×s, 15H, 5×CH_3), 2.10 (s, 3H, $COCH_3$), 2.19 (s, 3H, NCH_3), 2.43 (d, 1H, *J*=3.04, H-5), 2.46 (d, 1H, J_{gem} =16.7, 12βH), 3.14 (s, 2H, $COCH_2N$-), 3.23 (d, 1H, J_{gem} =16.7, 12αH), 4.52, 4.80 (2×d, 2H, J_{gem} =17.2, $COCH_2O$-) 4.60 (br, 1H, H-1), 4.94 (dd, 1H, J_{cis} =10.13, J_{gem} =2.03, $15H_{cis}$), 5.22 (dd, 1H, J_{trans} =17.2, J_{gem} =2.03, $15H_{trans}$), 5.52 (d, 1H, *J* = 4.05, H-7), 5.86 (dd, 1H, *J* = 4.05, 3.04, H-6), 5.96 (dd,1H, J_{trans} =17.2, J_{cis} =10.13, H-14), 7.11-7.59 (m,15H, 15 × Ph-H). Anal. Calcd for $C_{46}H_{55}NO$: C, 70.66; H, 7.09; N, 1.79. Found: C, 70.52; H, 7.21; N, 1.77%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-[(S)-2-(tritylaminoethylcarbonyloxyacetyloxy)labd-14-en-11-one 4: The crude product was purified by flash chromatography with 10% CH_3CN-$CHCl_3$, yield 78% (foam); IR (KBr): 3450 (br), 2935, 1750 (br), 1718 cm^{-1}; ^1H NMR: 0.91, 0.99, 1.39, 1.40 (4×s, 12H, 4×CH_3), 1.41 (d, 3H, J=8.1, $CHCH_3$), 1.59 (s, 3H, CH_3), 2.0 (s, 3H, $COCH_3$), 2.39 (d, 1H, *J*=3.04, H-5), 2.45 (d, 1H, J_{gem} =17.2, 12βH), 3.21 (d, 1H, J_{gem} =17.2, 12αH), 3.44 (q, 1H, *J* = 8.1, C*H*CH_3), 3.96, 4.11 (2×d, 2H, J_{gem} =16.2, $COCH_2O$), 4.59 (br, 1H, H-1), 4.95 (dd, 1H, J_{cis}.=3, J_{gem} =.6, $15H_{cis}$), 5.21 (dd, 1H, J_{trans} =17.2, J_{gem} =1.6, $15H_{trans}$), 5.49 (d, 1H, *J* = 4.05, H-7), 5.79 (t, 1H, *J* = 3.5, H-6), 5.95 (dd, 1H, J_{trans} =17.2, J_{cis} =10.13, H-14), 7.20-7.54 (m, 15H, 15 × Ph-H). Anal Calcd for $C_{46}H_{55}NO_{10}$: C, 70.66; H, 7.09; N, 1.79. Found: C, 70.56; H, 6.90; N, 1.51%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-[2-(methyl-tritylaminoethylcarbonyloxyacetyloxy)-labd-14-en-11-one 5: The reaction was carried out in CH_2Cl_2-DMF (10:1) instead of EtOAc-DMF (which gave very poor yield). The crude product was purified by flash chromatography with 25% EtOAc-light petroleum, yield 56% (foam); IR (KBr): 3500-3300 (br), 2940, 1755 (br), 1725-1710 (br) cm^{-1}; ^1H NMR: 0.89, 1.0 (2×s, 6H, 2×CH_3), 1.26-1.43 (m, 9H, 3×CH_3), 1.54, 1.64 (2×s, 6H, 2×CH_3), 1.94 (s, 3H, $COCH_3$) 2.39 (d, 1H, *J* 3.52, H-5), 2.45 (d, 1H, J_{gem}=17.2, 12βH), 3.21 (d, 1H, J_{gem}=17.2, 12αH), 4.01 (m, 2H, $COCH_2O$), 4.59 (br, 1H, H-1), 4.94 (dd, 1H, J_{cis}=10.13, J_{gem}.= .62,H_{cis}5,20 (1H, dd, J_{trans}=17.2, J_{gem}=1.62, $15H_{trans}$), 5.47 (d, 1H, *J*=4.56, H-7), 5.77 (t, 1H, *J*=4.05, H-6), 5.94 (dd, 1H, J_{trans}=17.2, J_{cis}=10.13, H-14), 7.36 (m, 15H, 15×Ph-H). Anal. Calcd for $C_{47}H_{57}NO_{10}$: C, 70.92; H, 7.22; N, 1.76. Found: C, 70.75; H, 7.31; N, 1.74%.

General method for the deprotection of trityl group from compounds 2-5 to prepare compounds 6-9. The required starting compound (1 mmoles) was dissolved in dry ether (25 mL) and freshly distilled TFA (1.3 mL) was added. The clear solution was kept at room temperature. After the reaction was over (~3 hr), dry HCl in ether (saturated) was added dropwise till further precipitation occurred. The white solid was filtered and washed with dry ether and dried. The solid was recrystallized from MeOH-dry ether.

7β-Acetoxy-6β-aminomethylcarbonyloxyactyl-oxy-1α,9α-dihydroxy-8,13-epoxy-labd-14-en-11-one 6: Yield 92%; m.p.218-20°C; IR (KBr): 3280 (br), 2980 (br), 1770, 1750, 1725 cm^{-1}; ^1H NMR (CD_3OD): 1.01 (6H), 1.34, 1.44, 1.63 (4×s, 15H, 5×CH_3), 2.0 (s, 3H, $COCH_3$), 2.40 (d, 1H, J_{gem}=16.2, 12βH), 2.04 (d, 1H, *J*=2.53, H-5), 3.26 (d, 1H, J_{gem}=16.2, 12αH), 3.96 (s, 2H, $COCH_2NH_2$.HCl), 4.49 (br, 1H, H-1), 4.79, 5.0 (2×d, 2H, J_{gem}=15.2, $COCH_2O$), 4.86 (dd, 1H, J_{cis}=10.13, J_{gem}=1.62 $15H_{cis}$), 5.09 (dd, 1H, J_{trans}= 17.21, J_{gem}=1.62, $15H_{trans}$), 5.45 (d, 1H, *J*=4.46, H-7), 5.86 (t, 1H, *J*=2.6, H-6), 6.05 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14). Anal Cald for $C_{26}H_{40}NO_{10}Cl$: C, 55.56; H, 7.18; N, 2.49; Cl, 6.31. Found: C, 55.72; H, 6.94, N, 2.21; Cl, 6.42%.

7β-Acetoxy-6β-(2-methylaminomethylcarbonyl-oxyacetyloxy)-1α,9α-dihydroxy-8,13-epoxy-labd-14-en-11-one 7: Yield 75%; m.p. 237-40°C; IR (KBr): 3200 (br), 2970 (br), 1785, 1763, 1755, 1745, 1722 cm^{-1}; ^1H NMR ($CDCl_3$+CD_3OD): 1.01, 1.04, 1.39, 1.44, 1.63 (5×s, 15H, 5×CH_3), 2.06 (s, 3H, $COCH_3$), 2.41 (d, 1H, J_{gem}=16.2, 12βH), 2.47 (d, 1H, *J*=3.04, H-5), 2.87 (s, 3H, NCH_3), 3.30 (d, 1H, J_{gem} =16.2, 12αH), 4.0 (s, 2H, $COCH_2NH$), 4.51 (br, 1H, H-1),

4.63 (m, 2H, $COCH_2O$), 4.93 (dd, 1H, J_{cis}=11.14, J_{gem}=2.0, $15H_{cis}$), 5.17 (dd, 1H, J_{trans} = 17.2, J_{gem}=2.0, $15H_{trans}$), 5. 57 (d,1H, *J*=4.05, H-7), 5.89 (t, 1H, *J*=3.04, H-6), 6.0 (dd, 1H, J_{trans} = 17.2, J_{cis}=11.14, H-14). Anal. Calcd for $C_{27}H_{42}NO_{10}Cl$: C, 56.29; H, 7.35, N, 2.43; Cl, 6.15. Found: C, 56.03; H, 7.36; N, 2.34; Cl, 6.44%.

7β-Acetoxy-6β-[(S)-2-aminoethylcarbonyloxy-acetyloxy]-1α,9α-dihydroxy-8,13-epoxy-labd-14-en-11-one hydrochloride 8: Yield 74.4%; m.p. 235-37°C; IR (KBr): 3320 (br), 2960 (br), 1773, 1763, 1758, 1717, 1712 cm^{-1}; ^1H NMR: 1.01, 1.06, 1.37, 1.43, 1.61 (5×s, 15H, $5\times CH_3$), 1.69 (d, 3H, *J*=7.09, $CHCH_3$), 2.04 (s, 3H, $COCH_3$), 2.39 (d, 3H, J_{gem}=16.2, 12βH), 2.47 (d, 1H, *J*=2.53, H-5), 3.31 (d, 1H, J_{gem}=16.2, 12αH), 4.17 (m, 1H, $CHCH_3$), 4.50 (br, 1H, H-1), 4.77 (s, 2H, $COCH_2O$), 4.92 (dd, 1H, J_{cis}=11.14, J_{gem}=2, $15H_{cis}$); 5.17 (dd, 1H, J_{trans}=17.21, J_{gem}=2, $15H_{trans}$), 5.56 (d, 1H, *J*=4.05, H-7), 5.89 (dd, 1H, *J*=4.05, 2.53, H-6), 6.0 (dd, 1H, J_{trans}=17.21, J_{cis}=11.14, H-14). Anal. Calcd for $C_{27}H_{42}ClNO_{10}$: H_2O: C, 54.59; H, 7.46; N, 2.36; Cl, 5.97. Found: C, 56.46; H, 7.55; N, 2.28; Cl, 6.14%.

7β-Acetoxy-6β-2(methyl-aminoethylcarbonyl-oxyacetyloxy)-1α,9α-dihydroxy-8,13-epoxy-labd-14-en-11-one; hydrochloride 9: Yield 72%; m.p. 222-25°C: IR (KBr): 3435 (br), 2960 (br), 1760 (br), 1728, 1722 cm^{-1}; ^1H NMR: 0.99, 1.01, 1.36, 1.41, 1.61, 1.71 (6H) (6×s, 21H, $7\times CH_3$), 2.03 (s, 3H, $COCH_3$), 2.37 (d, 1H, J_{gem}=16.2, 12βH), 2.43 (d, 1H, *J*=3.04, H-5), 3.27 (d, 1H, J_{gem}=16.2, 12αH), 4.50 (br, 1H, H-1), 4.62, 4.86 (2×d, 2H, J_{gem}=17.2, $COCH_2O$), 4.90 (dd, 1H, J_{cis}=10.13, J_{gem}=1.8, $15H_{cis}$), 5.14 (dd, 1H, J_{trans}=17.2, J_{gem}=1.8, $15H_{trans}$), 5.51 (d, 1H, *J*=4.05, H-7), 5.84 (t, 1H, *J*=3.04, H-6), 5.97 (dd, 1H, J_{trans}=17.2, J_{cis}=10.13, H-14). Anal. Calcd for $C_{28}H_{44}NO_{10}Cl$. 1.5 H_2O: C, 54.49; H, 7.68; N, 2.27; Cl, 5.75. Found: C, 54.14; H, 7.89; N, 2.30; Cl, 5.52%.

7β-Acetoxy-6β-(chloroacetyloxy)acetyloxy-1α, 9α-dihydroxy-8,13-epoxy-labd-14-en-11-one 10. The compound **1** (3.75g, 8 mmoles) and DCC (1.98g, 9.7 mmoles) were dissolved in EtOAc (50 mL) and DMF (5 mL). To this solution, 2-chloroacetic acid (0.832 g, 8.8 mmoles) was added followed by DMAP (0.98g, 8 mmoles) under vigorous stirring at room temperature. After 2.5 hr the reaction was worked up (cf. compound. **4**; S**cheme I**), and the crude product was purified by flash chromatography with 10% CH_3CN-$CHCl_3$, yield, 3.91 g (89.8%); m.p. 145-47°C (EtOAc-light petroleum); IR (KBr): 3300 (br), 2965 (br), 1768; 1760, 1727 cm^{-1}; ^1H NMR: 0.99, 1.03, 1.36, 1.42, 1.63, (5×s, 15H, $5\times CH_3$), 2.04 (s, 3H, $COCH_3$), 2.44 (d, 1H, *J*=2.53, H-5), 2.45 (d, 1H, J_{gem}=16.2, 12βH, 3.22 (d, 1H, J_{gem}=16.2, 12αH), 4.13 (s, 2H, $COCH_2Cl$), 4.57 (br, 1H, H-1), 4.61, 4.82 (2×d, 2H, J_{gem}=16.2, $COCH_2O$), 4.93 (dd, 1H, J_{cis}=10.13, J_{gem}=1.6, $15H_{cis}$), 5.19 (dd, 1H, J_{trans} = 17.21, J_{gem}=1.6, $15H_{trans}$), 5.5 (d, 1H, *J*=4.46, H-7), 5.85 (dd, 1H *J*=4.46, 2.53, H-6), 5.93 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14). Anal. Calcd for $C_{26}H_{37}O_{10}Cl$: C, 57.29; H, 6.84; Cl, 6.50. Found: C, 57.43; H, 7.33; Cl, 6.72%.

7β-Acetoxy-6β-(acryloyloxy)-acetyloxy-1α,9α-dihydroxy-8,13-epoxy-labd-14-en-11-one 11. The compound **1** (2.34 g, 5 mmoles) and DCC (1.24g, 6 mmoles) were dissolved in EtOAc (25 mL) and DMF (10 mL). Acrylic acid (0.38 mL, 5.5 mmoles) was added at room temperature, followed by DMAP (0.175 g). After 6 hr stirring at room temperature, further amount of acrylic acid (0.07 mL) and DCC (0.206 g), after mixing separately, was added to the reaction mixture and stirring continued for 12 hr. After work-up (see Experimental for **1**), the crude product was purified by flash chromatography with 8% CH_3CN in $CHCl_3$, yeild 2.05 g (78.5%), m.p.

197-99°C (EtOAc-light petroleum); IR (KBr): 3340 (br), 2950 (br), 1760, 1720 cm^{-1}; ^1H NMR ($CDCl_3$ +CD_3OD): 0.99, 1.03, 1.36, 1.40, 1.59, (5×s, 15H, $5\times CH_3$), 2.04 (s, 3H, $COCH_3$), 2.37 (dd, 1H, J_{gem}=16.2, 12βH), 2.46 (d, 1H, *J*=3.04, H-5), 3.30 (dd, 1H, J_{gem}=16.2, 12αH), 4.49 (br, 1H, H-1), 4.61, 4.82 (2×d, 2H, J_{gem}=16.2 $COCH_2O$), 4.91 (dd, 1H, J_{cis}11.14, J_{gem}=1.6, $15H_{cis}$), 5.16 (dd, 1H, J_{trans} = 17.21, J_{gem}=1.6, $15H_{trans}$), 5.54 (d, 1H, *J*=4,05, H-7), 5.86-6.60 (m, 5H, $COCH=CH_2$, H-6 & H-14); Anal. Calcd. for $C_{27}H_{38}O_{10}$: C, 62.06; H, 7.33. Found: C, 62.11; H, 7.28%.

7β-Acetoxy-6β-(4-chlorobutanoyloxyacetyloxy)-1α,9α-dihydroxy-8,13-epoxy-labd-14-en-11-one 12. To a solution of compound **1** (4.1g, 8.76 mmoles), pyridine (0.71 mL, 8.8 mmoles) in dichloromethane (10 mL) at 0°C, 4-chlorobutanoyl chloride (1 mL, 11.2 mmoles), was added dropwise (10 min) with vigorous stirring. After 2 hr the reaction mixture was diluted with CH_2Cl_2 (50 mL) and poured over ice containing dil. HCl (sufficient to neutralize excess pyridine). The dichloromethane layer was separated and was washed with brine. It was dried over anhydrous Na_2SO_4. Solvent was removed and the crude product was

purified by flash chromatography with 7% CH_3CN-$CHCl_3$, yield 2.06 g (52%). IR (KBr): 3340 (br), 2950 (br), 1760, 1720 cm^{-1}, ^1H NMR: 1.0, 1.04, 1.36, 1.43, 1.64, (5×s, 15H, 5×CH_3), 2.04 (s, 3H, $COCH_3$), 2.11 (quintet, 2H, *J*=6.08,-$CH_2CH_2CH_2Cl$), 2.43 (d, 1H, *J*=3.04, H-5), 2.46 (d, 1H, J_{gem}=17.20, 12βH), 2.61 (t, 2H, *J*=6.08, $COCH_2CH_2$), 3.22 (d, 1H, J_{gem}=17.21, 12αH), 3.61 (t, 2H, *J*=6.08, CH_2CH_2Cl) 4.51, 4.74 (2×d, 2H, J_{gem}=16.2, $COCH_2O$), 4.60 (br, 1H, H-1), 4.94 (dd, 1H, J_{cis}=11.14, J_{gem}=1.82, $15H_{cis}$), 5.22 (dd, 1H, J_{trans}=17.2, J_{gem}=1.8, $15H_{trans}$), 5.51 (d, 1H, *J*=4.5, H-7), 5.86 (br, 1H, *H-6*), 5.95 (dd, 1H, J_{trans}=17.21, J_{cis}=11.14, H-14). Anal. Calcd for $C_{28}H_{41}O_{10}Cl$: C, 58.68; H, 7.21; Cl, 6.19. Found: C, 58.51; H, 7.11; Cl, 6.31%.

Compounds **13** to **20** were prepared from starting material **10**, compounds **21** to **25** were prepared from starting material **11** while starting material was **12** for the synthesis of compounds **26** to **28**.

General method for the synthesis of compounds 13 to 28. The required starting material **10** or **11** or **12** (0.5 mmoles) was dissolved in dichloromethane (3 mL) and appropriate amine was added at room temperature (with the exception of diisopropyl amine that required reflux without using dichloromethane and dimethyl amines which was used as saturated toluene solution). After the reaction was over (checked by TLC, 2 hr), the solvent was removed. The residue was purified by flash chromatography. The pure products were isolated as free-base or hydrochloride salt. The isolation of products, yield, and physico-chemical characteristics are described below for all the compounds.

7β-Acetoxy-1α, 9α-dihydroxy-6β-(2-dimethyl-aminomethylcarbonyloxyacetyloxy)-8,13-epoxy-labd-14-en-11-one 13. The crude material was partitioned between aq. HCl and ether. The aqueous layer was basified with $NaHCO_3$ and extracted with ether and was washed with brine. The ether layer was dried over anhydrous Na_2SO_4 and solvent was evaporated to a small volume. Dry HCl in ether was added. Solid filtered off and washed with dry ether. Finally, it was crystallized from dry MeOH-ether, yield 36%; m.p. 156-58°C; IR (KBr): 3500-3200 (br), 2965 (br), 1775, 1762, 1755, 1722 cm^{-1}; ^1H NMR (CD_3OD):1.0, 1.03,1.34, 1.46, 1.63 (5×s, 15H, 5×CH_3), 2.0 (s, 3H, CH_3), 2.38 (d, 1H, J_{gem}=16.2, 12βH), 2.45 (d, 1H, *J*=2.54, H-5), 3.01 (s, 6H, $N(CH_3)_2$], 3.25 (d, 1H, J_{gem}=16.2, 12αH), 4.29 (s, 2H, $COCH_2N$), 4.49 (br, 1H, H-1), 4.81, 5.02 (2×d, 2H, J_{gem}=16.2, $COCH_2O$), 4.84 (dd, 1H, J_{cis}=10.13, J_{gem}=1.62, $15H_{cis}$), 5.08 (dd, 1H, J_{trans}=17.21, J_{gem}=1.62, $15H_{trans}$), 5.47 (d, 1H, *J*=4.56, H-7), 5.89 (dd, 1H, *J*=4.56, 2.54, H-6), 6.03 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14). Anal. Cald. for $C_{28}H_{44}NO_{10}Cl$. $2H_2O$: C, 53.71; H, 7.73; N, 2.24; Cl. 5.66. Found: C, 53.76; H, 7.94; N, 2.14; Cl, 5.84%.

7β-Acetoxy-1α,9α-dihydroxy-6β-(2-diethylamino-methylcarbonyloxyacetyloxy)-8,13-epoxy-labd-14-en-11-one, hydrochloride 14. The crude product was purified by flash chromatography with 10% CH_3CN-$CHCl_3$ followed by 20% CH_3CN-$CHCl_3$.The pure product was converted into hydrochloride salt from dry ether and was finally crystallized from dry MeOH-ether, yield 65%, m.p. 189-91°C; IR (KBr): 3500-3200 (br), 2970 (br), 1780, 1762, 1725 cm^{-1}; ^1H NMR (CD_3OD): 1.01, 1.04 (2×s, 6H, 2×CH_3), 1.36 (s, 9H, *J*=7.09, 2×CH_2CH_3 + CH_3), 1.46, 1.64 (2×s, 6H, 2×CH_3), 2.0 (s, 3H, $COCH_3$), 2.38 (d, 1H, J_{gem}=16.2, 12βH), 2.44 (d, 1H, J_{gem}=2.43, H-5), 3.25 (d, 1H, J_{gem}=1.6, 12αH), 3.33 (quartet, 4H, *J*=7.09, 2×NCH_2CH_3), 4.31 (s, 2H, $COCH_2N$), 4.49 (br, 1H, H-1), 4.81, 5.03 (2×d, 2H, J_{gem}=16.2, $COCH_2O$), 4.87 (dd, 1H, J_{cis}=10.13, J_{gem}=1.62, $15H_{cis}$), 5.10 (dd, 1H, J_{trans}=16.71, J_{gem}=1.62, $15H_{trans}$), 5.45 (dd, 1H, *J*=4.56, H-7), 5.86 (d, 1H, J_{gem}=4.56, 3.04, *H-6*) 6.03 (dd, 1H, J_{trans}=16.71, J_{cis}=10.13, H-14). Anal. Calcd for $C_{30}H_{48}NO_{10}Cl.H_2O$: C, 56.64, H, 7.92, N, 2.20, Cl, 5.57. Found: C, 56.84, H, 8.12, N, 1.98, Cl, 5.46%.

7β-Acetyl-1α,9α-dihydroxy-6β-(2-diisopropyl-aminomethylcarbonyloxyacetyloxy) - 8, 13 - epoxy-labd-14-en-11-one hydrochloride 15. The crude product was purified by acid-base treatment as described for the synthesis of compound **13**. Hydrochloride salt was crystallized from dry MeOH-ether, yield 43%; m.p. 137-39°C; IR (KBr): 3470 (br), 2980 (br), 1750 (br), 1730 cm^{-1}; ^1H NMR (CD_3OD): 1.0, 1.03, 1.35 (3×s, 9H, 3×CH_3) 1.36 [d, 12H, *J*=6.08, 2×$CH(CH_3)_2$], 1.46, 1.63, (2×s, 6H, 2×CH_3), 2.0 (s, 3H, $COCH_3$), 2.38 (d, 1H, J_{gem}=16.2, 12βH), 2.44 (d, 1H, J_{gem}=2.54, H-5), 3.25 (d, 1H, J_{gem}=16.2, 12αH), 3.71 (m, 2H, 2× $CHPr^i_2$), 4.23 (s, 2H,$COCH_2N$), 4.49 (br, 1H,H-1), 4.80, 5.03 (2×d, 2H, J_{gem}=1.62, 15H-$_{trans}$), 4.91 (dd, 1H, J_{cis}=10.13, J_{gem}=1.62, $15H_{cis}$), 5.15 (dd, 1H, J_{trans}=17.21, J_{gem}=1.62, $15H_{trans}$), 5.47 (d, 1H, *J*= 4.56, H-7), 5.86 (br, 1H, H-6) 6.04 (dd, 1H, J_{trans} =17.21, J_{cis}=10.13, H-14). Anal. Calcd for $C_{32}H_{52}NO_{10}Cl.H_2O$: C, 57.86; H, 8.19; N, 2.11; Cl, 5.34. Found: C, 57.73; H, 8.37, N, 1.95; Cl, 5.46%.

7β-Acetoxy-1α, 9α-dihydroxy-8, 13-epoxy-6β-(2-piperidinomethylcarbonyloxyacetyloxy)labd-14-en-11-one, hydrochloride 16. The crude product was purified by flash chromatography with 10% CH_3CN-$CHCl_3$ followed by 20% CH_3CN-$CHCl_3$. The pure product was converted into hydrochloride salt from ether solution and was finally crystallized from dry MeOH-ether, yield 86%; m.p. 233-35°C; IR (KBr): 3120 (br), 2960, 1787, 1762, 1745, 1725 cm^{-1}; ^{1}HNMR (CD_3OD): 0.99, 1.04, 1.36, 1.46, 1.64 (15H, 5×s, 5×CH_3), 1.71-2.11 (6H, m, $NCH_2(CH_2)_3CH_2$], 2.0 (3H, s, $COCH_3$), 2.39 (1H, d, J_{gem}=16,2, 12βH), 2.46 (1H, d, *J*=3.04, H-5), 3.26 (1H, d, J_{gem}=16.2, 12αH), 3.0-3.83 (4H, m,-CH_2NCH_2-), 4.29 (2H, s, $COCH_2N$), 4.51 (1H, br, H-1), 4.79, 5.01 (2H, 2×d, J_{gem}=17.2, $COCH_2O$), 4.90 (1H, dd, J_{cis}=11.14, J_{gem}=1.82, $15H_{cis}$), 5.11 (1H, dd, J_{trans}=17.2, J_{gem}=1.82, $15H_{trans}$), 5.49 (1H, d, J=5.06, H-7), 5.89 (1H, br, H-6), 6.06 (1H, dd, J_{trans}=17.2, J_{cis}=11.14, H-14). Anal Calcd for $C_{31}H_{48}NO_{10}Cl$: C, 59.08; H, 7.68; N, 2.22; Cl, 5.63. Found: C, 58.91; H, 7.48; N, 2.20; Cl, 5.90%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-[2-(4-phenylpiperidino)methylcarbonyloxyacetyloxy)-labd-14-en-11-one, hydrochloride 17. The crude product was purified by flash chromatography with 30% EtOAc-light petroleum. The pure product was converted into hydrochloride salt from dry ether and HCl-ether. It was finally crystallized from MeOH-ether (dry), yield 70%, m. p. 140-41°C; IR (KBr): 3450-3240 (br), 2960 (br), 1770 (br), 1725 cm^{-1}; ^{1}H NMR: 1.0, 1.03, 1.36, 1.41, 1.61 (5×s, 15H, 5×CH_3), 2.06 (s 3H, $COCH_3$), 1.76-2.23 (m, 5H, 3'-CH_2, 4'-CH-Ph, 5'-CH_2), 2.44 (d, 1H, J_{gem}=17.21, 12βH), 2.49 (d, 1H, *J*=3.04, H-5), 2.56-2.79 and 3.23-3.73 (2×m, 4H, 2'-CH_2 & 6'-CH_2), 4.06 (br, 2H, $COCH_2N$), 4.62 (br 1H, H-1), 4.77 (br, 2H, $COCH_2O$), 4.94 (dd, 1H, J_{cis}=10.13, J_{gem}=1.82, $15H_{cis}$) 5.19 (dd, 1H, J_{trans}=17.21, J_{gem}=1.82, $15H_{trans}$), 5.56 (d, 1H, *J*=5.06, H-7), 5.86 (m, 1H, H-6), 5.97 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14). Anal. Calcd for $C_{37}H_{52}NO_{10}Cl$: C, 62.92; H, 7.42; N, 1.98; Cl, 5.02. Found: C, 63.38; H, 8.18; N, 2.29; Cl, 5.34%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-(2-morpholinomethylcarbonyloxyacetyloxy)-labd-14-en-11-one 18. The crude product was purified by flash chromatography with 10% CH_3CN-$CHCl_3$ followed by 20% CH_3CN-$CHCl_3$. The slightly impure material (contaminated by hydrolyzed product viz., 7β-$COCH_2OH$) was converted into hydrochloride salt from dry ethereal HCl-ether. It was finally crystallized from dry MeOH-ether in 43% yield; m.p. 173-75°C. IR (KBr): 3180 (br), 3000, 2960, 1760 (br) 1723 cm^{-1}; ^{1}H NMR (CD_3OD): 1.0, 1.04, 1.35, 1.46, 1.63 (5×s, 15H, 5×CH_3), 2.0 (s, 3H, $COCH_3$), 2.38 (d, 1H, J_{gem}=16.2, 12βH), 2.44 (d, 1H, *J*=3.04, H-5), 3.24 (d, 1H, J_{gem}=16.2, 12αH), 3.41 (t, 4H, *J*=4.56, CH_2-N-CH_2-), 3.93 (t, 4H, *J*=4.56, CH_2OCH_2), 4.34 (s, 2H, $COCH_2N$), 4.48 (br, 1H, H-1), 4.84 (dd, 1H, J_{cis}=10.13, *J*=1.62, $15H_{cis}$), 4.89 (s, 2H, $COCH_2O$), 5.09 (dd, 1H, J_{trans}=17.21, J_{gem}=1.62, $15H_{trans}$), 5.47 (dd, 1H, *J*=4.25, H-7), 5.86 (t. 1H, *J*=2.53, H-6), 6.03 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14). Anal. Calcd for $C_{30}H_{46}NO_{11}Cl$: C, 56.99; H, 7.33; N, 2.22; Cl, 5.61. Found: C, 57.11; H, 7.40; N, 2.11; Cl, 5.86%.

7β-Acetoxy-1α, 9α-dihydroxy-6β-[2-(2, 6-dimethylmorpholino)methylcarbonyloxyacetyloxy]-8,13-epoxy-labd-14-en-11-one, hydrochloride 19. The crude product was purified by flash chromatography with 6% CH_3CN-$CHCl_3$. Hydrochloride salt was prepared from ether and recrystallized from MeOH-ether, yield 30%; m.p.146-48°C; IR (KBr): 3450 (br), 3360 (br), 3000, 2960, 1765 (br) 1725 cm^{-1}; ^{1}H NMR: 1.0, 1.4 (2×s, 6H, 2×CH_3), 1.26[t, 6H, *J*=7.09, 2×CH_3 (morpholino ring)] 1.36, 1.41, 1.61 (3×s, 9H, 3×CH_3), 2.03 (s, 3H, $COCH_3$), 2.45 (d, 1H, J_{gem}=17.21, 12βH) 2.46 (d, 1H, *J*=3.04, H-5), 3.24 (d, 1H, J_{gem}=17.21, 12αH), 2.94-3.40 (m, 4H, CH_2NCH_2), 3.94 [m, 2H, 2×CH(Me)-O], 4.31 (m, 2H,$COCH_2N$), 4.61 (br, 1H, H-1), 4.76 (br, 2H, $COCH_2O$-) 4.94 (dd, 1H, J_{cis}=10.13, J_{gem}=1.82, $15H_{cis}$), 5.20 (dd, 1H, J_{trans}=17.21, J_{gem}=1.82, $15H_{trans}$), 5.54 (d, 1H, *J*=5.06, H-7), 5.86 (dd, 1H, *J*=5.06, 3.04, H-6), 5.97 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14); Anal. Calcd for $C_{32}H_{50}NO_{11}Cl$: C, 58.22; H, 7.63; N, 2.12, Cl, 5.37. Found: C, 58.09; H, 7.33; N, 2.01; Cl, 5.31%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-[2-(4-methylpiperazino)-methylcarbonyloxyacetyloxy]-labd-14-en-11-one, hydrochloride 20. The crude product was purified by flash chromatography with 10-20% CH_3CN-$CHCl_3$ followed by 5% MeOH-$CHCl_3$. The pure product was converted into hydrochloride salt from ether and recrystallized from MeOH-ether, yield 66%; m.p. 176-78°C; IR (KBr): 3430 (br), 2960 (br), 1750 (br), 1720 cm^{-1}; ^{1}H NMR (CD_3OD): 1.0, 1.03, 1.36, 1.46, 1.64 (5×s, 15H, 5×CH_3), 2.0 (s, 3H, NCH_3), 2.38 (d, 1H, J_{gem}=16.2, 12βH), 2.45 (d, 1H, *J*=3.04, H-5), 2.97 (s, 3H, NCH_3), 3.24 (d, 1H, J_{gem}=16.2, 12αH), 3.51 [br, 8H, 4×CH_2 of

piperazine], 4.08 (s, 2H, $COCH_2N$), 4.48 (br, 1H, H-1), 4.76, 4.96 (2×d, 2H, J_{gem}=16.2, $COCH_2O$), 4.84 (dd, 1H, J_{cis}=10.13, J_{gem}=2.03, $15H_{cis}$), 5.09 (dd, 1H, J_{trans}=17.21, J_{gem}=2.03, $15H_{trans}$), 5.46 (d, 1H, *J*=4.56, H-7), 5.85 (t, 1H, *J*=3.04, H-6), 6.04 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14); Anal. Calcd for $C_{31}H_{50}N_2O_{10}Cl_2$. 1.5 H_2O: C, 52.54; H, 7.54; N, 3.95; Cl, 10.01. Found: C, 52.37; H, 7.90; N, 3.66; Cl, 10.12%.

7β-Acetoxy-1α,9α-dihydroxy-6β-[2-(3-dimethyl-aminopropyl)-carbonlyoxyacetyloxy]-8,13-epoxy-labd-14-en-11-one, hydrochloride 21. The crude product was purified by flash chromatography with 20% CH_3CN-$CHCl_3$ by 15% MeOH-$CHCl_3$. The pure material was converted into hydrochloride salt, yield 30%; mp 173-75°C (MeOH-ether); IR (KBr): 3570-3200 (br), 2970 (br), 1775, 1755 (br), 1725 cm^{-1}; ^{1}H NMR: 1.0, 1.03, 1.36, 1.41, 1.63 (5×s, 15H, 5×CH_3), 2.04 (s, 3H, $COCH_3$), 2.45 (d, 1H, J_{gem}=16.2, 12βH) 2.44 (d, 1H, *J*=3.04, 12αH), 2.86 [s, 6H, N $(CH_3)_2$], 3.14-3.43 (m, 5H, CH_2NCH_2 + 12αH), 4.47-4.71 (m, 3H, $COCH_2O$ & H-1), 4.94 (dd, 1H, J_{cis}=11.14, J_{gem}=1.82, $15H_{cis}$), 5.21 (dd, 1H, J_{trans}=17.21, J_{gem}=1.82, $15H_{trans}$), 5.53 (d, 1H, *J*=4.56, H-7), 5.84 (br, 1H, H-6), 5.96 (dd, 1H, J_{trans}=17.21, J_{cis}=11.14, H-14), Anal. Calcd for $C_{29}H_{46}NO_{10}Cl$ 1.5 H_2O: C, 55.19; H, 7.83; N, 2.22; Cl, 5.62. Found C, 55.21; H, 7.75; N, 2.05; Cl, 5.34%.

7**β-Acetoxy-1α,9α-dihydroxy-6β-[2-(3-dipentyl-aminopropyl)-carbonyloxyacetyloxy]-8,13-epoxy-labd-14-en-11-one, hydrochloride 22**: Yield 42%; m.p. 105-07°C; IR (KBr): 3220 (br), 2980 (br), 1765 (br), 1728 cm^{-1}; ^{1}H NMR: 0.86-1.06 (m, 18H, 2×$NCH_2(CH_2)_3CH_3$, 2×CH_3], 1.37, 1.43, 1.63 (3×s, 9H, 3×CH_3), 2.44 (d, 1H, *J*=3.04, H-5), 2.45 (d, 1H, J_{gem}=16.2, 12βH), 2.86-3.49 [m, 9H, $COCH_2CH_2N$, 2×$NCH_2(CH_3)_3$ & 12αH], 4.56,4.76 (2×d, 2H, J_{gem}=16.2, $COCH_2O$), 4.94 (dd, 1H, J_{cis}=11.14, J_{gem}=2.03, $15H_{cis}$), 5.21 (dd, 1H, J_{trans}=17.21, J_{gem}=2.03, $15H_{trans}$), 5.53 (d, 1H, *J*=4.05, H-7), 5.87(dd, 1H, *J*=4.05, 3.04, H-6), 5.96 (dd, 1H, J_{trans}=17.21, J_{cis}=11.14, H-14); Anal. Calcd for $C_{37}H_{62}NO_{10}Cl$: C, 62.05; H, 8.72; N, 1.96; Cl, 4.95. Found: C, 61.85; H, 8.59; N, 1.63; Cl, 4.90%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-[2-(3-piperidinopropyl)carbonyloxy-acetyloxy]-labd-14-en-11-one, hydrochloride 23: Yield 45%; m.p. 231-33°C (MeOH-ether); IR (KBr): 3245 (br), 2990, 1755 (br), 1730 cm^{-1}; ^{1}H NMR (free base): 1.0, 1.04, 1.37, 1.43, 1.64 (5×s, 15H, 5×CH_3), 2.04 (s, 3H, $COCH_3$), 2.44 (d, 1H, *J*=3.04, H-5), 2.46 (dd, 1H, J_{gem}=17.21, 12βH) 3.37-3.49 (m, 7H, CH_2N, 2'-CH_2, 6'-CH_2 & 12αH), 4.53, 4.74 (2×d, 2H, J_{gem}=16.2, $COCH_2O$), 4.94 (dd, 1H, J_{cis}=11.14, J_{gem}=1.62, $15H_{cis}$), 5.19 (dd, 1H, J_{trans}=17.21, J_{gem}=1.62, $15H_{trans}$), 5.52 (d, 1H, 5.06, H-7), 5.86 (br, 1H, H-6), 5.96 (dd, 1H, J_{trans}=17.21, J_{cis}=11.14, H-14); Anal. Calcd for $C_{32}H_{50}NO_{10}Cl$. 0.5 H_2O: C, 58.84; H, 7.86; N, 2.14; Cl, 5.43. Found: C, 58.74; H, 7.90; N, 2.03; Cl, 5.80%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-[2-(3-morpholinopropyl)carbonyloxyacetyloxy]-labd-14-en-11-one, hydrochloride 24: Yield 53.3%; m.p.228-30°C IR (KBr): 3440 (br), 2960 (br), 1765, 1750 (br), 1720 cm^{-1}; ^{1}H NMR: 1.0, 1.03, 1.33, 1.41, 1.63 (5×s, 15H, 5×CH_3), 2.04 (s, 3H, $COCH_3$), 2.44 (d, 1H, *J*=3.04, H-5), 2.45 (d, 1H, J_{gem}=17.21, 12βH), 3.14-3.37 (m, 9H, 12αH, $COCH_2CH_2N$, 3'-CH_2 & 5'CH_2), 4.07 (br, t after D_2O, 4H, *J*=5.06, 2'-CH_2, 6'-CH_2) 4.55, 4.76 (2×d, 2H, J_{gem}=16.2, $COCH_2O$), 4.94 (dd, 1H, J_{cis}=10.13, J_{gem}=1.82, $15H_{cis}$), 5.16 (dd, 1H, J_{trans}=17.21, J_{gem}=1.82, $15H_{trans}$), 5.54 (dd, 1H, *J*=4.05, H-7), 5.87 (br, 1H, H-6) 5.96 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14), Anal. Calcd for $C_{31}H_{48}NO_{11}Cl$. 2.5 H_2O: C, 53.87; H, 7.73; N, 2.03; Cl, 5.13. Found: C, 53.79; H, 8.05; N, 2.05; Cl, 5.38%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-[2-{3-(4-methylpiperazino)propylcarbonyloxy}acetyl-oxy]-labd-14-en-11-one, hydrochloride 25: Yield 34%; m.p.175-77°C (MeOH-ether); IR (KBr): 3460 (br), 2970 (br), 1760, 1728 (br), cm^{-1}; ^{1}H NMR: 1.0, 1.03, 1.37, 1.43, 1.61 (5×s, 15H, 5×CH_3), 2.06 (s, 3H, $COCH_3$), 2.39 (d, 1H, J_{gem}=17.21, 12 βH), 2.46 (d, 1H, *J*=3.04, H-5), 2.17-3.11 and 3.29-3.66 [2×m, 15H, $COCH_2CH_2N$, 4×CH_2 of piperazine & NCH_3), 3.29 (d, 1H, J_{gem}=16.2, 12αH,), 4.50 (br, 1H, H-1), 4.67 (br, 2H, $COCH_2O$), 4.92 (dd, 1H, J_{cis}=10.13, J_{gem}=2.03, $15H_{cis}$), 5.17 (dd, 1H, J_{trans}=17.21, J_{gem}=2.03, $15H_{trans}$), 5.54 (dd, 1H, *J*=5.06, H-7), 5.89 (br, 1H, H-6) 6.01 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14), Anal. Calcd for $C_{32}H_{52}N_2O_{10}Cl_2$. 3$H_2O$: C, 51.27; H, 7.79; N, 3.74; Cl, 9.46. Found: C, 51.25; H, 8.02; N, 3.58; Cl, 9.63%.

7β-Acetoxy-1α,9α-dihydroxy-6β-2-[(4-diethyl-aminobutylcarbonyloxy)-acetyloxy]-8,13-epoxy-labd-14-en-11-one, hydrochloride 26. After work-up, the crude product was purified by flash chromatography with 10% MeOH-$CHCl_3$ and converted into HCl salt from dry ether, yield 40%; m.p. 233-35°C (dry MeOH-ether); IR (KBr): 3220 (br), 2950 (br), 1758, 1748,

1720 cm^{-1}; ^1H NMR (CD_3OD): 1.01, (s, 6H, 2×CH_3), 1.33 (t, 6H, *J*=7.09, 2×CH_2CH_3), 1.34, 1.45, 1.63 (3×s, 9H, 3×CH_3), 1.99 (s, 3H, $COCH_3$), 2.38 (d, 1H, J_{gem}=16.2, 12βH), 2.42 (d, 1H, *J*=3.04, H-5), 2.59 (t, 2H, *J*=6.5, $COCH_2CH_2CH_2$-), 3.09-3.37 (m, 7H, 2×NCH_2CH_3, $COCH_2CH_2CH_2N$ & 12 αH), 4.49 (br, 1H, H-1), 4.60 (br, 2H, $COCH_2O$), 4.85 (dd, 1H, J_{cis}=10.13, J_{gem}=1.62, $15H_{cis}$), 5.09 (dd, 1H, J_{trans}=17.21, J_{gem}=1.62, $15H_{trans}$), 5.45 (d, 1H, *J*=4.56, H-7), 5.89 (dd, 1H, *J*=4.56, 3.04, H-6), 5.97 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14), Anal. Calcd for $C_{32}H_{52}NO_{10}Cl$. 0.5 H_2O: C, 58.66; H, 8.15; N, 2.14; Cl, 5.41. Found: C, 58.59; H, 8.18; N, 2.01; Cl, 5.48%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-2-[(4-piperidinobutylcarbonyloxy)acetyloxy]-labd-14-en-11-one, hydrochloride 27. The crude product was purified by flash chromatography with 20% CH_3CN-$CHCl_3$ and was converted into hydrochloride salt from ether, yield 30%; m.p. 134-35°C (MeOH-ether); IR (KBr): 3425 (br), 3230 (br), 2950 (br), 1750 (br) 1720 cm^{-1}; ^1H NMR: 1.0, 1.03, 1.36, 1.41, 1.90 (5×s, 15H, 5×CH_3), 2.03 (s, 3H, $COCH_3$), 1.71-3.14 (4×m,19H), 4.51, 4.74 (2×d, 2H, J_{gem}=16.2, $COCH_2O$), 4.94 (dd, 1H, J_{cis}=10.13, J_{gem}=2.03, $15H_{cis}$), 5.20 (dd, 1H, J_{trans}=16.71, J_{gem}=2.03, $15H_{trans}$), 5.53 (d, 1H, *J*=5.06, H-7), 5.87 (dd, 1H, *J*=5.06, 3.04, H-6), 6.01 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14); Anal. Calcd for $C_{33}H_{52}NO_{10}Cl.H_2O$: C, 58.61; H, 8.05; N, 2.07; Cl, 5.24. Found: C, 58.41; H, 8.13; N, 2.03; Cl, 5.68%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-2-[{4-(4-methylpiperizino)butylcarbonyloxy}-acetyloxy]-labd-14-en-11-one, hydrochloride 28. The crude product was purified by flash chromatography with 8% CH_3CN-$CHCl_3$ and was converted into hydrochloride salt from ether, yield 37%; m.p. 134-35°C (MeOH-ether); IR (KBr): 3450 (br), 2970 (br), 1745 (br) 1718 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD): 1.0, 1.03, 1.37, 1.43, 1.63 (5×s, 15H, 5×CH_3), 2.06 (s, 3H, $COCH_3$), 2.38 (d, 1H, J_{gem}=16,2, 12βH), 2.46 (d, 1H, *J*=3.04, H-5), 2.63 (t, 2H, *J*=7.09, $COCH_2CH_2$), 2.97 (s, 3H, NCH_3), 3.60-3.94 (br, 11H, CH_2CH_2N, 4×CH_2 of piperazine, & 12αH), 4.49 (br, 1H, H-1), 4.53 (s, 2H, $COCH_2O$), 4.92 (dd, 1H, J_{cis}=10.13, J_{gem}=1.82, $15H_{cis}$), 5.16 (dd, 1H, J_{trans}=17.21, J_{gem}=1.82, $15H_{trans}$), 5.55 (d, 1H, *J*=5.06, H-7), 5.89 (dd, 1H, *J*=5.06, 3.04, H-6), 6.02 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14); Anal. Calcd for $C_{33}H_{54}N_2O_{10}Cl_2.$ H_2O: C, 54.46; H, 7.76; N, 3.85; Cl, 9.74. Found: C, 54.04; H, 7.97; N, 3.83; Cl, 10.40%.

7β-Acetoxy-6β-(aminomethylcarbonyloxy) acetyloxy-1α, 9α-dihydroxy-8, 13-epoxy-labd-11-one 29. A solution of compound **6** (0.15 g) in MeOH (10 mL) was hydrogenated over 10% Pd-C (15 mg) for 1 hr. Catalyst was filtered off and the filtrate was concentrated. The residue was crystallized twice from dry MeOH-ether, yield 0.1 g (70%); m.p.228-30°C; IR (KBr): 3300 (br), 2980 (br), 1765, 1748, 1715 cm^{-1};$1H^{NMR}$: 0.89 (t, 3H, *J*=8.1, CH_2CH_3), 1.0, 1.03, 1.23, 1.49, 1.59 (5×s, 15H, 5×CH_3), 1.33-1.66 (m, 2H, CH_2CH_3), 2.01 (s, 3H, $COCH_3$), 2.10 (d, 1H, J_{gem}=15.19, 12βH), 2.45 (d, 1H, *J*=3.04, H-5), 3.34 (d, 1H, J_{gem}=15.19, 12αH), 3.99 (s, 2H, $COCH_2NH_2.HCl$), 4.40 (br, 1H, H-1), 4.86 (br, 2H, $COCH_2O$), 5.48 (d, 1H, *J*=5.06, H-7), 5.86 (dd, 1H, *J*=5.06, 3.04, H-6): Anal. Calcd for $C_{26}H_{42}NO_{10}Cl$. 0.5 H_2O: C, 54.49; H, 7.56; N, 2.44; Cl, 6.19; found: C, 54.51; H, 7.32, N, 2.12; Cl, 5.99%.

7β-Acetoxy-1α, 9α-dihydroxy-6β-(2-dimethylaminomethyleneaminoacetyloxy)acetyloxy-8, 13-Epoxy-labd-14-en-11-one 30. A clear solution of compound **6** (0.52 g; 0.93 mmoles), Et_3N (0.14 mL,1 mmoles) and N,N-dimethylformamide acetal (0.2 mL) in CH_2Cl_2 (10 mL) was stirred at room temperature for 16 hr. Solvent was removed and the residue was triturated with dry EtOAc (3×5 mL) and dried. The solid thus obtained was crystallized from dry MeOH-ether, yield 0.4 g (69.8%); m.p.255-57°C; IR (KBr): 3440, 3260 (br), 2950 (br), 1765, 1755, 1720 cm^{-1}; $^1H^{NMR}$ ($CDCl_3$ + CD_3OD): 1.0, 1.01, 1.39, 1.44, 1.63 (5×s, 15H, 5×CH_3), 2.06 (s, 3H, $COCH_3$), 2.41 (d, 1H, J_{gem}=16.2, 12βH), 2.49 (d, 1H, *J*=3.04, H-5), 3.29 (d, 1H, J_{gem}=16.2, 12αH), 3.31, 3.34 [2×s, 6H, N $(CH_3)_2$], 4.43 (s, 2H, $COCH_2N$), 4.53 (br, 1H, H-1), 4.64, 4.83 (2×d, 2H, J_{gem}=16.2, $COCH_2O$), 4.93 (dd, 1H, J_{cis}=10.13, J_{gem}=1.6, $15H_{cis}$), 5.17 (dd, 1H, J_{trans}=17.2, J_{gem}=1.6, $15H_{trans}$), 5.54 (d, 1H, *J*=4.05, H-7), 5.89 (br, 1H, H-6), 5.99 (dd, 1H, J_{trans}=17.2, J_{cis}=10.13, H-14); Anal. Calcd for $C_{29}H_{45}N_2O_{10}Cl$. H_2O: C, 54.84; H, 7.46; N, 4.41; Cl, 5.58. Found: C, 54.60; H, 7.57, N, 4.30; Cl, 5.93%.

6β,9α-Dihydroxy-8,13-epoxy-1α-tertiarybutyldimethylsilyloxy-7β-(2-tritylaminomethylcarboxamidoacetyloxy)-labd-14-en-11-one 31. This compound was prepared according to the method adopted for the synthesis of compounds **2-5**. The crude product was purified by flash chromatography with 20% EtOAc-light petroleum, yield 70.2%; m.p.258-60°C; IR (KBr): 3350 (br), 2955 (br), 1770, 1760, 1728 cm^{-1}; $^1H^{NMR}$: 0.11 [s, 6H, SiC $(CH_3)_2$],

0.87 [s, 9H, SiC $(CH_3)_3$], 1.0, 1.21, 1.34, 1.41, 1.64 (5×s, 15H, 5×CH_3), 2.16 (d, 1H, *J*=2.63, H-5), 2.32 (d, 1H, J_{gem}=16.2, 12βH), 2.97 (br, 2H, CH_2NHTrit), 3.23 (d, 1H, J_{gem}=16.2, 12αH), 4.08 (d, 2H, *J*=5.57, $COCH_2N$), 4.53 (br, 2H, H-1 & H-6), 4.86 (dd, 1H, J_{cis}=10.13, J_{gem}=1.82, $15H_{cis}$), 5.09 (dd, 1H, J_{trans}=17.21, J_{gem}=1.82, $15H_{trans}$), 5.45 (d, 1H, *J*=4.05, H-7), 6.01 (dd, 1H, J_{trans}=17.2, J_{cis}=10.13, H-14), 7.09-7.43 (m, 15H, 15×Ph-H); Anal. Calcd for $C_{49}H_{66}N_2O_8Si$: C, 70.13; H, 7.93; N, 3,34. Found: C, 70.28; H, 7.98, N, 3.40%.

7β,9α-Dihydroxy-8,13-epoxy-1α-tertiarybutyldimethylsilyloxy-6β-(2-tritylaminomethylcarboxamidoacetyloxy)-labd-14-en-11-one 32. A solution of **31** (2.5 g, 2.98 mmoles) in a mixture of acetonitrile (60 mL), DMF (100 mL) and water (130 mL) was treated with Na_2CO_3 (0.82g, 7.74 mmoles) while stirring at room temperature for 3 hr. Solvent was removed under reduced pressure after neutralizing with dil. HCl. The residue was extracted with CH_2Cl_2 (50 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed. The crude product was purified by flash chromatography with 30% EtOAc-light petroleum followed by 20% CH_3CN-$CHCl_3$, yield,1.1 g (70.2%); m.p.138-40°C; IR (KBr): 3370 (br), 2975 (br), 2930, 1758, 1755, 1728 cm^{-1}; $^1H^{NMR}$: 0.07, 0.18 [2×s, 6H, SiC $(CH_3)_2$], 0.90 [s, 9H, SiC $(CH_3)_3$], 1.01, 1.11, 1.41 (6H), 1.55 (4×s, 15H, 5×CH_3), 2.36 (d, 1H, *J*=2.54, H-5), 2.41 (d, 1H, J_{gem}=17.21, 12βH), 3.0 (s, 2H, CH_2NHTrit), 3.18 (d, 1H, J_{gem}=17.21, 12αH), 4.06 (m, 2H, $COCH_2N$), 4.33 (d, 1H, *J*=4.56, H-7), 4.63 (br, 1H, H-1*)*, 4.91 (dd, 1H, J_{cis}=10.13, J_{gem}=1.01, $15H_{cis}$), 5.06 (dd, 1H, J_{trans}=17.21, J_{gem}=1.01, $15H_{trans}$), 5.91 (t, 1H, *J*=4.05, H-6), 6.13 (dd, 1H, J_{trans}=17.2, J_{cis}=10.13, H-14), 7.11-7.46 (m, 15H, 15×Ph-H); Anal. Calcd for $C_{49}H_{66}N_2O_8Si$: C, 70.13; H, 7.93; N, 3.34. Found: C, 70.08; H, 7.83, N, 3.19%.

7β-Acetoxy-8,13-epoxy-9α-hydroxy-1α-tertiarybutyldimethylsilyloxy-6β-(2-trityl-aminomethylcarboxamidoacetyloxy)-labd-14-en-11-one 33. This was prepared from **32** and acetic acid by following the same procedure as described for the synthesis of compound **2**. The crude product after usual work-up was purified by flash chromatography with 30% EtOAc-light petroleum, yield 97.3%; m.p.135-37°C; IR (KBr): 3365 (br), 2970 (br), 2930, 1765, 1732, cm^{-1}; $^1H^{NMR}$: 0.13, 0.15 [s, 6H, SiC $(CH_3)_2$], 0.90 [s, 9H, SiC $(CH_3)_3$], 0.98, 1.05, 1.31 1.41, 1.56 (5×s, 15H, 5×CH_3), 2.0 (s, 3H, $COCH_3$), 2.34 (d, 1H, J_{gem}=17.21, 12βH), 2.46 (d, 1H, *J*=2.5, H-5), 3.0 (s, 2H, CH_2NHTrit), 3.21 (d, 1H, J_{gem}=16.2, 12αH), 4.05 (m, 2H, $COCH_2N$), 4.60 (br, 1H, H-1), 4.84 (dd, 1H, J_{cis}=10.13, J_{gem}=1.62, $15H_{cis}$), 5.07 (dd, 1H, J_{trans}=17.21, J_{gem}=1.62, $15H_{trans}$), 5.55 (d, 1H, *J*=4.56, H-7), 5.89 (dd, 1H, J=4.05, 2.54, H-6), 5.98 (dd, 1H, J_{trans}=17.2, J_{cis}=10.13, H-14), 7.11-7.43 (m, 15H, 15×Ph-H), 7.60 (br, 1H exchangeable, NH); Anal. Calcd for $C_{51}H_{68}N_2O_9Si$: C, 69.52; H, 7.78; N, 3.18. Found: C, 69.42; H, 7.83, N, 3.19%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-(2-trityl-aminomethylcarboxamidoacetyloxy)-labd-14-en-11-one 34. To a solution of **33** (5 g; 5.68 mmoles) in THF (200 mL), 1*Mn*=$Bu_4N^+F^-$in THF (kept over molecular seive 4Å type) (6.25 mL; 6.25 mmoles) was added under vigorous stirring for 10 min. The solvent was removed. The residue was dried and purified by flash chromatography with 7.5% CH_3CN in $CHCl_3$, yield 92% (foam); IR (KBr): 3400-3340 (br), 2955 (br), 1760, 1730 (br) cm^{-1}; $^1H^{NMR}$: 1.0, 1.06, 1.34 1.41, 1.62 (5×s, 15H, 5×CH_3), 2.02 (s, 3H, $COCH_3$), 2.43 (d, 1 H, *J*=2.63, H-5), 2.44 (d, 1H, J_{gem}=17.21, 12βH), 3.01 (s, 2H, CH_2NHTrit), 3.19 (d, 1H, J_{gem}=17.2, 12αH), 3.94, 4.20 (2×dd, 2H, J_{gem}=18.2, $J_{CH\text{-}NH}$=5.06, $COCH_2N$), 4.56 (br, 1H, H-1), 4.93 (dd, 1H, J_{cis}=10.63, J_{gem}=2.03, $15H_{cis}$), 5.19 (dd, 1H, J_{trans}=17.21, J_{gem}=2.03, $15H_{trans}$), 5.50 (d, 1H, *J*=4.06, H-7), 5.86 (br, 1H, H-6), 5.93 (dd, 1H, J_{trans}=17.2, J_{cis}=10.13, H-14), 7.13-7.43 (m, 15H, 15×Ph-H), 7.62 (br 1H exchangable, NH); Anal. Cald. for $C_{45}H_{54}N_2O_9$: C, 70.48; H, 7.10; N, 3.65. Found: C, 70.10; H, 7.06, N, 3.50%.

7β-Acetoxy-6β-(2-aminomethylcarboxamidoacetyloxy)-1α,9α-dihydroxy-8,13-epoxy-labd-14-en-11-one 35. Compound **34** was converted to **35** by the method as described for the synthesis of compound **13,** yield 44%; m.p. 186-89°C; IR (KBr): 3400 (br), 3270 (br), 2960 (br), 1765, 1760, 1755, 1728 cm^{-1}; $^1H^{NMR}$ (CD_3OD): 1.02, 1.04, 1.37 1.47, 1.66 (5×s, 15H, 5×CH_3), 2.01 (s, 3H, $COCH_3$), 2.38 (d, 1H, J_{gem}=16.2, 12βH), 2.43 (d, 1H, *J*=2.54, H-5), 3.25 (d, 1H, J_{gem}=16.2, 12αH), 3.71 (s, 2H, $CH_2NH_2.HCl$), 3.96, 4.17 (2×d, 2H, J_{gem}=17.7, $COCH_2NHCO$), 4.49 (br, 1H, H-1), 4.85 (dd, 1H, J_{cis}=10.13, J_{gem}=2.03, $15H_{cis}$), 5.09 (dd, 1H, J_{trans}=17.21, J_{gem}=2.03, $15H_{trans}$), 5.45 (d, 1H, *J*=4.56, H-7), 5.84 (dd, 1H, *J*=4.56, 2.54, H-6), 6.04 (dd, 1H, J_{trans}=17.21, J_{cis}=10.13, H-14); Anal. Calcd. for $C_{26}H_{41}N_2O_9Cl$. $1.5H_2O$: C, 53.10; H, 7.54; N, 4.76; Cl, 6.03. Found: C, 52.96; H, 7.53, N, 4.59; Cl, 6.12%.

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