Electronic Supplementary Information (ESI) for:

Sustainable methods for the carboxymethylation and methylation of ursolic acid with dimethyl carbonate under mild and acidic conditions

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Content

1 Experimental Process

^{1}H-NMR analysis

The ^{1}H-NMR spectrum results of samples in this research were recorded by a JEOL JNM-ECS 400 MHz spectrometer. Typically, 100 mg sample from the experiment was dissolved in 1 ml chloroform-d. 16 scans were used for the ^{1}H-NMR testing. The data of ^{1}H-NMR was processed and analyzed by ACD/NMR Processor Academic Edition software (Ver. 12.01).

Control experiments for all the substrates investigated in this research

Control experiments run in the absence of catalyst were conducted for all reactants discussed in this research, results are listed in Table S1. This demonstrates that acidic catalysts are vital for the carboxymethylation, methylation and dehydration reaction.

2 Characterisation of structures of products

Cyclohexanol structure and ^{1}H-NMR

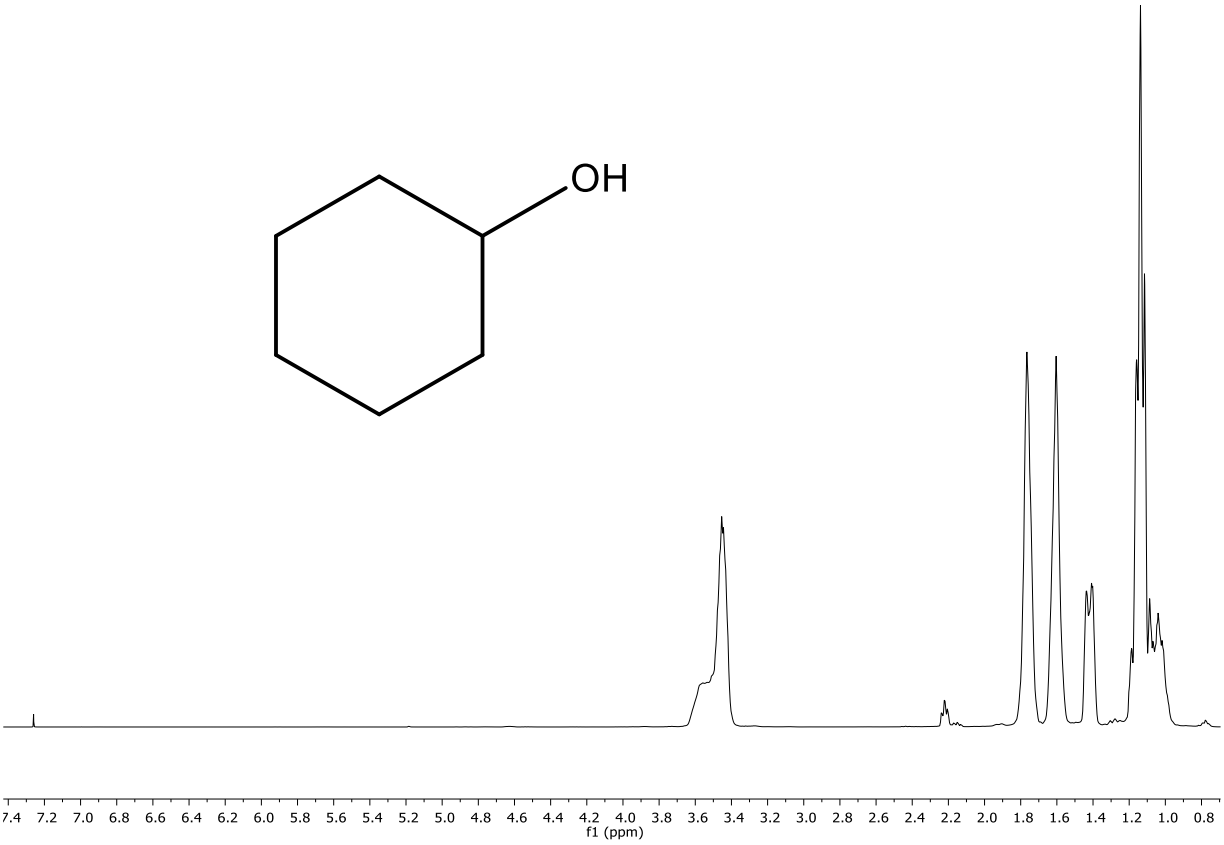


Figure S1. ^{1}HNMR of cyclohexanol in $CDCl_3$

Structure, ^{1}H-NMR and ^{13}C-NMR of ursolic acid

Ursolic acid. ^{1}H-NMR ($CDCl_3$): δ 5.26 (t, 1H), 3.20-3.24 (dd, 1H).

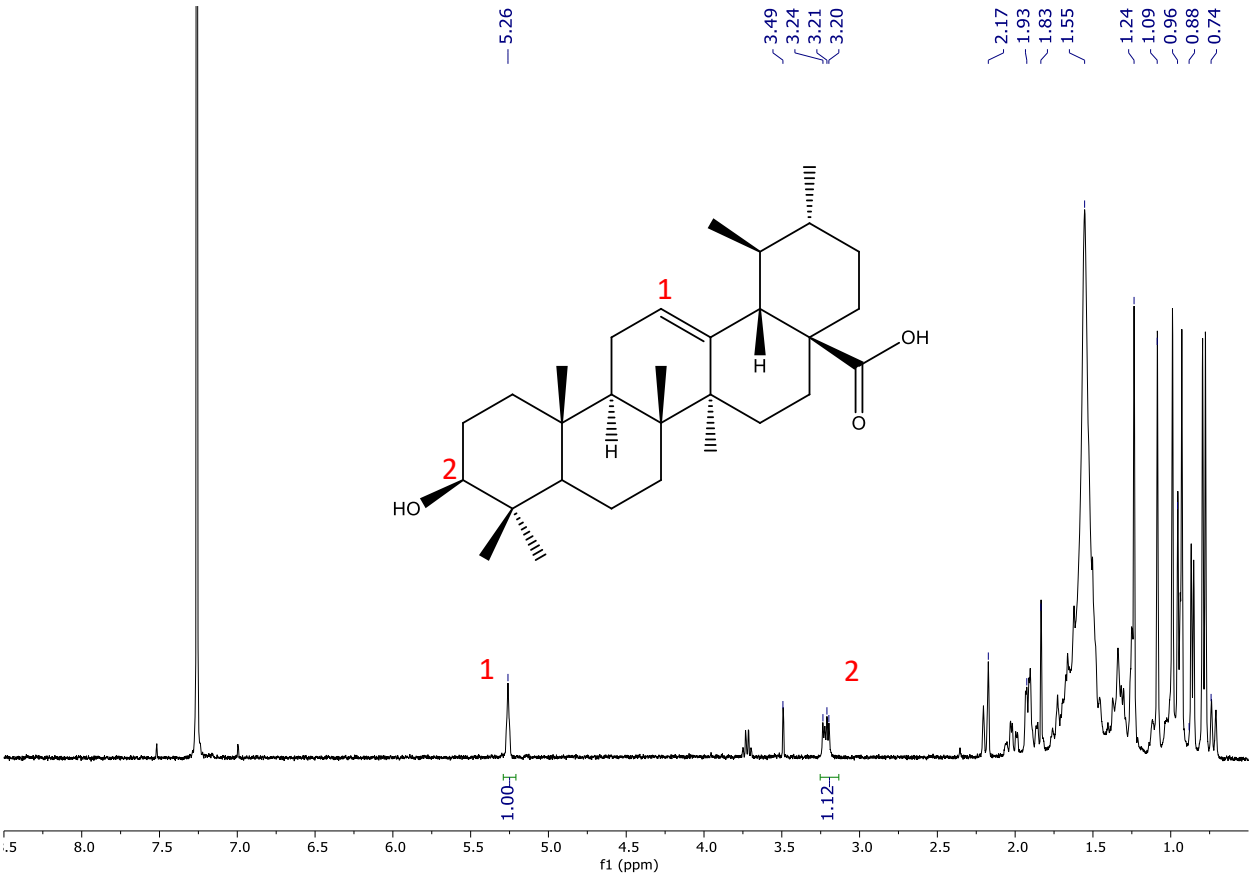


Figure S2. ^{1}HNMR of ursolic acid in $CDCl_3$

Structure, ^{1}H-NMR and ^{13}C-NMR of ursolic acid ester

3β-[[methoxy]carbonyl]oxyurs-12-en-28-oic acid (Carboxymethylation product)

3β-[[methoxy]carbonyl]oxyurs-12-en-28-oic acid. ^{1}H-NMR ($CDCl_3$): δ 5.24-5.25 (t, 1H), 4.31-4.35 (dd, 1H), 3.77(s, 3H).

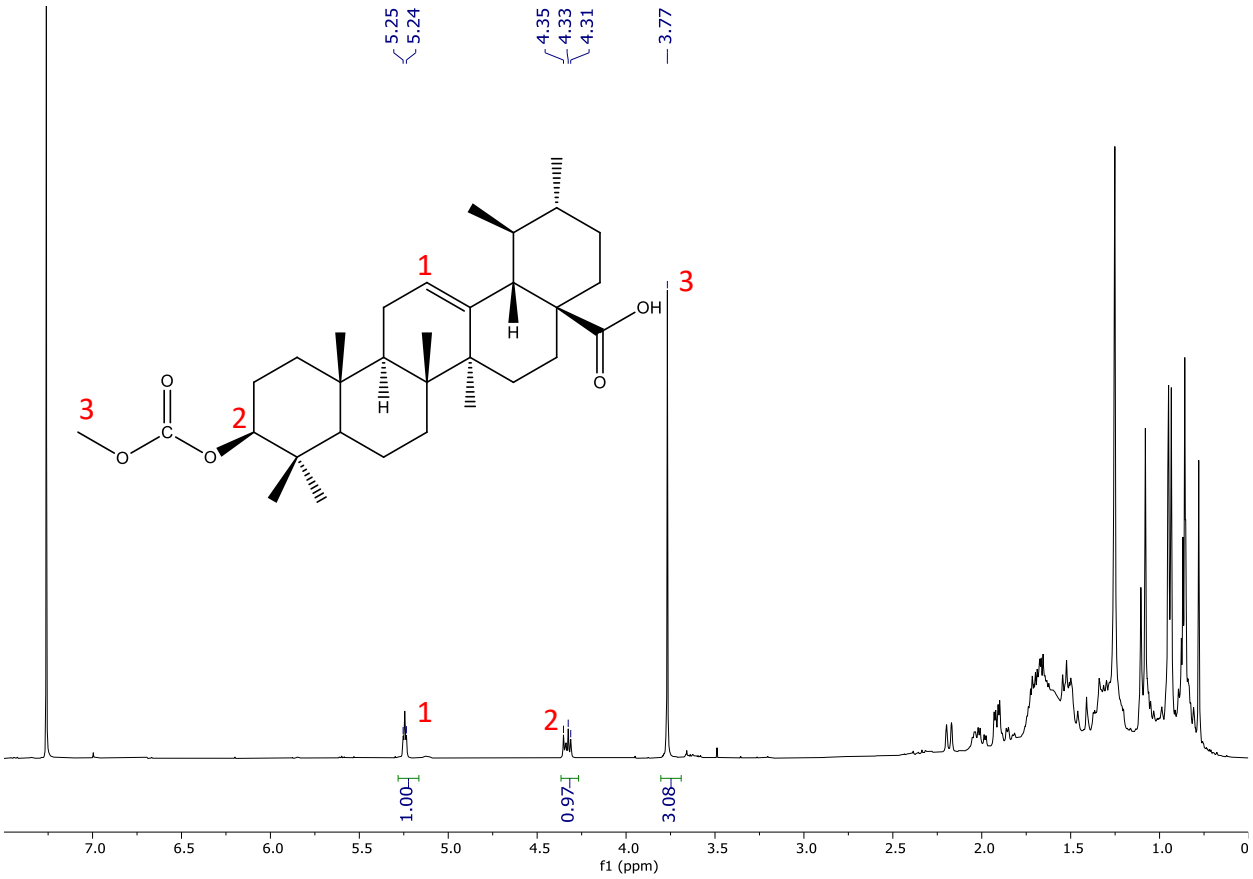


Figure S3. ^{1}HNMR of 3β-[[methoxy]carbonyl]oxyurs-12-en-28-oic acid in $CDCl_3$

3β-methoxyurs-12-en-28-oic acid (Methylation product)

3β-methoxyurs-12-en-28-oic acid. ^{1}H-NMR ($CDCl_3$): δ 5.22-5.26 (t, 1H), 4.25-4.28 (dd, 1H), 3.59(m, 3H).

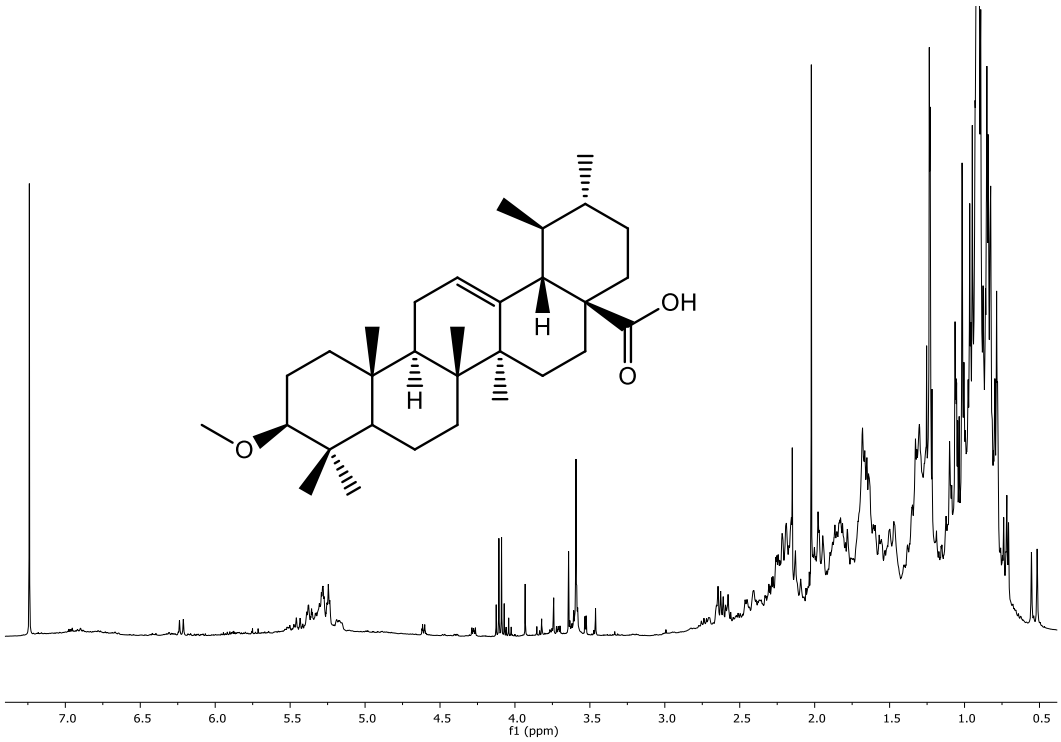


Figure S4. ^{1}HNMR of 3β-methoxyurs-12-en-28-oic acid in $CDCl_3$

3β-formylurs-12-en-28-oic acid (3-formyl ursolic acid ester)

3β-formylurs-12-en-28-oic acid. ^{1}H-NMR ($CDCl_3$): δ 5.2 (t, 1H), 4.6 (dd, 1H), 8.09(s, 1H).

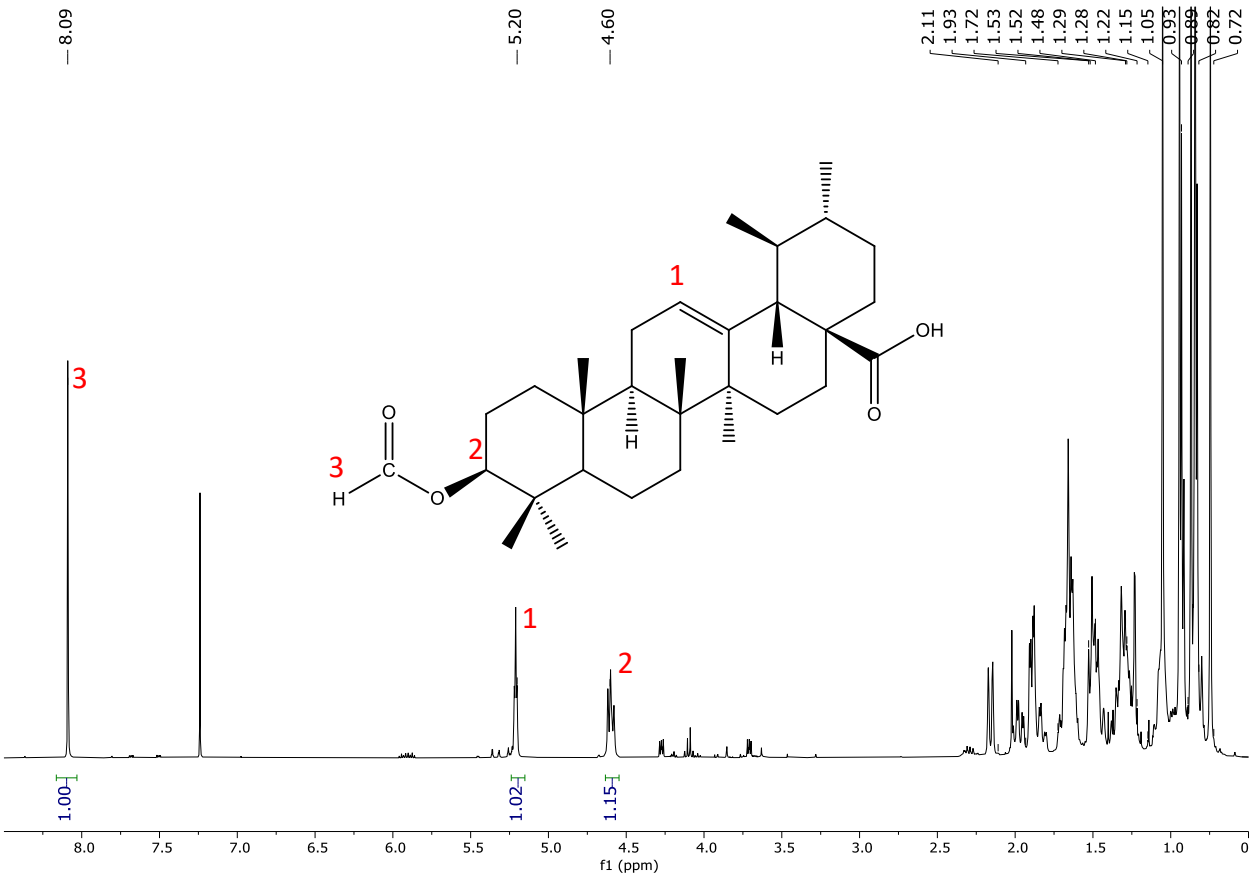


Figure S5. ^{1}HNMR of 3β-formylurs-12-en-28-oic acid in $CDCl_3$

urs-2,12-dien-28-oic acid (Dehydration product)

Urs-2,12-dien-28-oic acid. ^{1}H-NMR ($CDCl_3$): δ 5.40 (t, 1H), 5.23-5.37 (dd, 2H), 2.67(m, 1H).

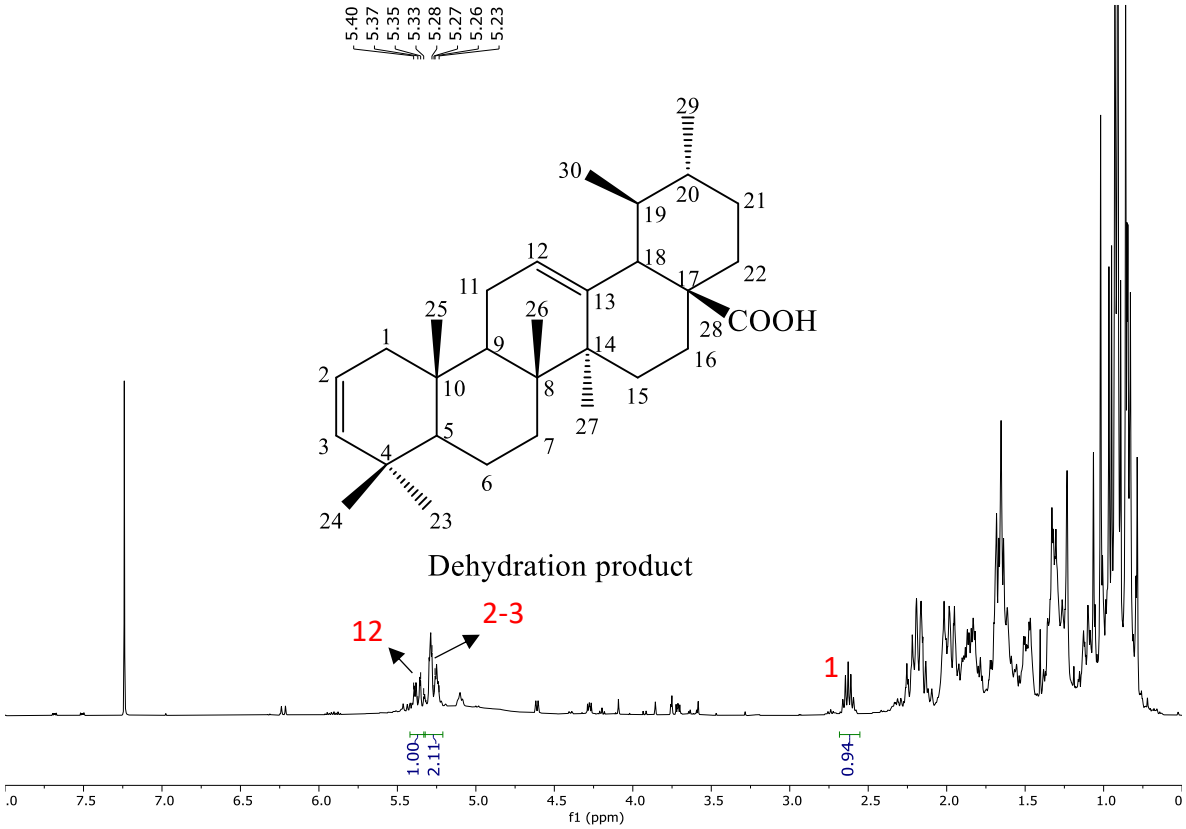


Figure S6. ^{1}HNMR of urs-2,12-dien-28-oic acid in $CDCl_3$

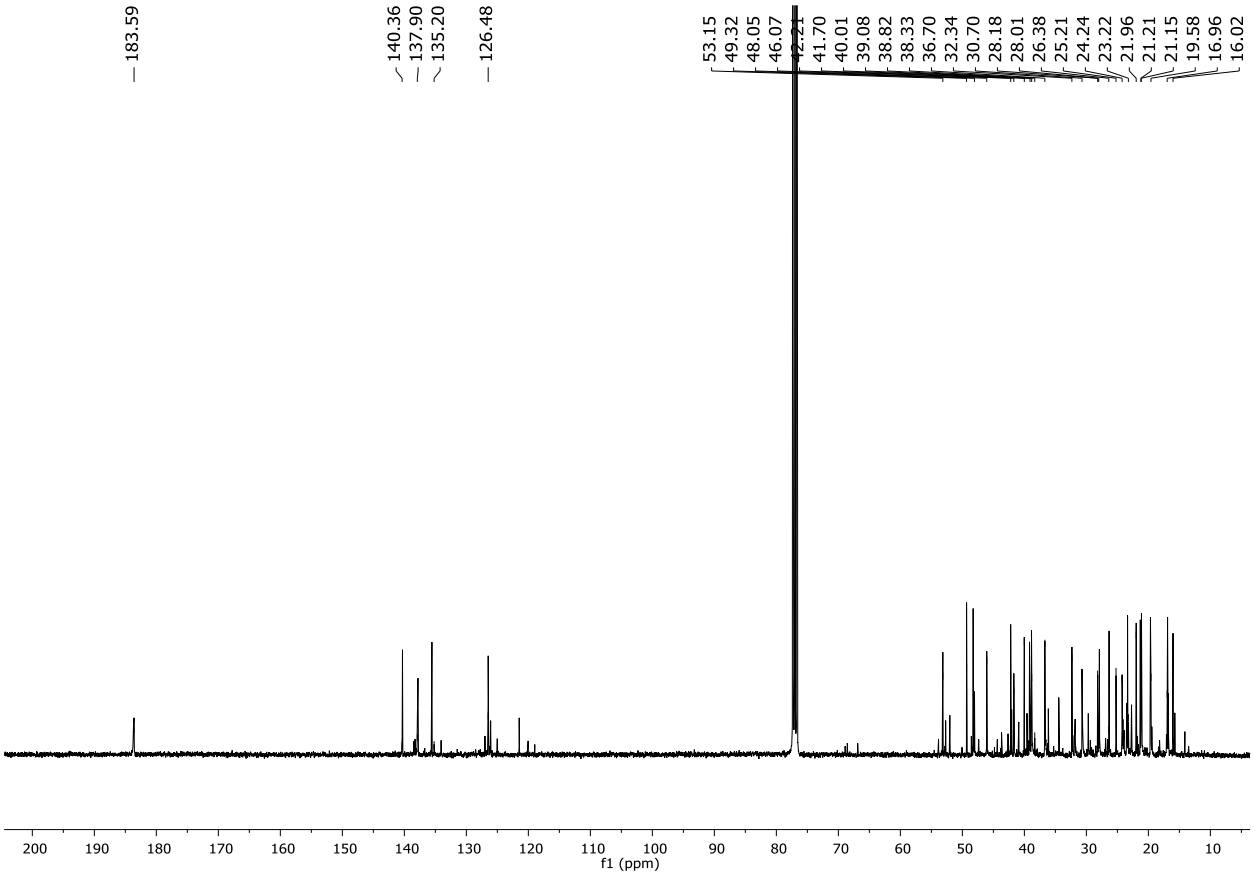


Figure S7. ^{13}CNMR of urs-2,12-dien-28-oic acid in $CDCl_3$

3 Carboxymethylation and/or methylation

Carboxymethylation and/or methylation of cyclohexanol

Table S1 the conversion and selectivity of carboxymethylation and/or methylation reactions with cyclohexanol and acids.

Brønsted acid-catalysed	Conversion (%)	GC-MS Selectivity (%)		
		Methylation product	Carboxymethylation product	other
Formic acid	69	0.00	10.13	89.87 [a]
PTSA	95.3	11.87	85.25	2.88
H_2SO_4	99.7	2.81	0.99	96.20[b]
HCl	53.1	0.00	78.32	21.68
Lewis acid-catalyzed				
$ZnCl_2$	87.9	0.00	87.24	12.76
$FeCl_3$	100	58.26	1.08	40.67
$AlCl_3 \bullet 6H_2O$	55.3	0.00	36.12	63.88
Heterogenous cat.				
H_2SO_4-SiO_2	93.0	5.29	85.90	8.81
$HClO_4$-SiO_2	45.1	0.00	89.29	10.71
Zeolite β (25:1 SiO_2 : Al_2O_3)	38.3	0.00	51.62	48.38

[a] Formyl cyclohexane product

[b] Cyclohexene product

The %conversion and %selectivity were calculated by peak area of GC and GC-MS.

Carboxymethylation and/or methylation of ursolic acid

Table S2 the yield and the conversion of ursolic acid ester synthesized from ursolic acid, acid catalysts, and DMC in various conditions.

Acid	condition	Conversion (%)	Yield to carboxymethylation product (%)	Selectivity (%)			
				Carboxymethylation product	Methylation product	Dehydration product	Etc.
PTSA 1 equivalent	90	38.6	11.01	>99	-	-	-
	150	51.2	36.06	69.72	0	23.37	6.91
PTSA 5 equivalents	90	74	45.54	59.81	0	33.27	6.92
	150	79.8	32.83	40.90	0	55.06	4.04
PTSA 10 equivalents	90	25.4	2.13	8.23	0	56.33	35.44
	150	51.60	15.28	29.31	0	57.97	12.72
$FeCl_3$ 0.5 equivalent	90	-	-	-	-	-	-
	150	52.6	46.6	-	87.7	-	12.3
$FeCl_3$ 1 equivalent	90	-	-	-	-	-	-
	150	>99%	-	<1%	>99%	-	-
$FeCl_3$ 5 equivalents	90	-	-	-	-	-	-
	150	>99%	-	<1%	>99%	-	-
$FeCl_3$ 10 equivalents	90	-	-	-	-	-	-
	150	>99%	-	<1%	>99%	-	-
$ZnCl_2$ 5 equivalents	90	-	-	-	-	-	-
	150	50	11.89	23.56		70.13	6.31
$ZnCl_2$ 10 equivalents	90	-	-	-	-	-	-
	150	80.8	25.20	35.1	-	45.3	19.6
H_2SO_4-SiO_2 5 equivalents	90	87.5	17.40	19.88	-	74.50	5.62
	150	78.27	23.18	29.74	-	40.37	29.81
H_2SO_4-SiO_2 10 equivalents	90	78.4	18.65	23.62	-	54.11	22.27
	150	69.81	9.06	13.10	-	77.46	9.43

Table S3 the yield and the conversion of ursolic acid ester synthesized from ursolic acid, formic acid, and DMC in various conditions.

Acid	condition	Conversion (%)	Yield to Formyl ursolic acid ester product (%)	Selectivity (%)	
				Formyl ursolic acid ester product	Etc.
Formic acid 5 equivalents	90	82.2	69.11	85.52	14.48
	150	58.4	78.39	99.34	0.66
Formic acid Excess without DMC	90	100	100	100	0

The %conversion and %selectivity were calculated by formula below;

$$\%\ Conversion\ of\ alcohol = \frac{Initial\ moles\ of\ alcohol - Final\ moles\ of\ alcohol}{Initial\ moles\ of\ alcohol} x100$$

$$\%\ Selectivity = \frac{Moles\ of\ desired\ product}{Moles\ of\ alcohol\ converted} x100$$

Carboxymethylation mechanism of PTSA

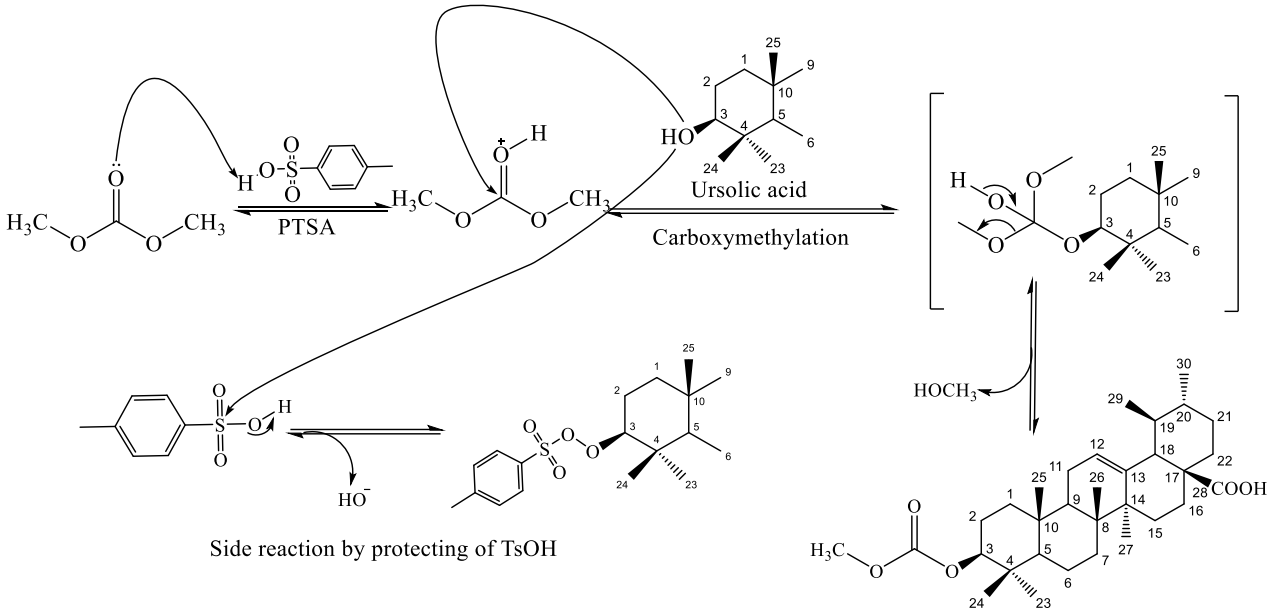


Figure S8. Possible mechanism for carboxymethylation reaction of PTSA and side reaction of high amount of PTSA.

Carboxymethylation mechanism of PTSA

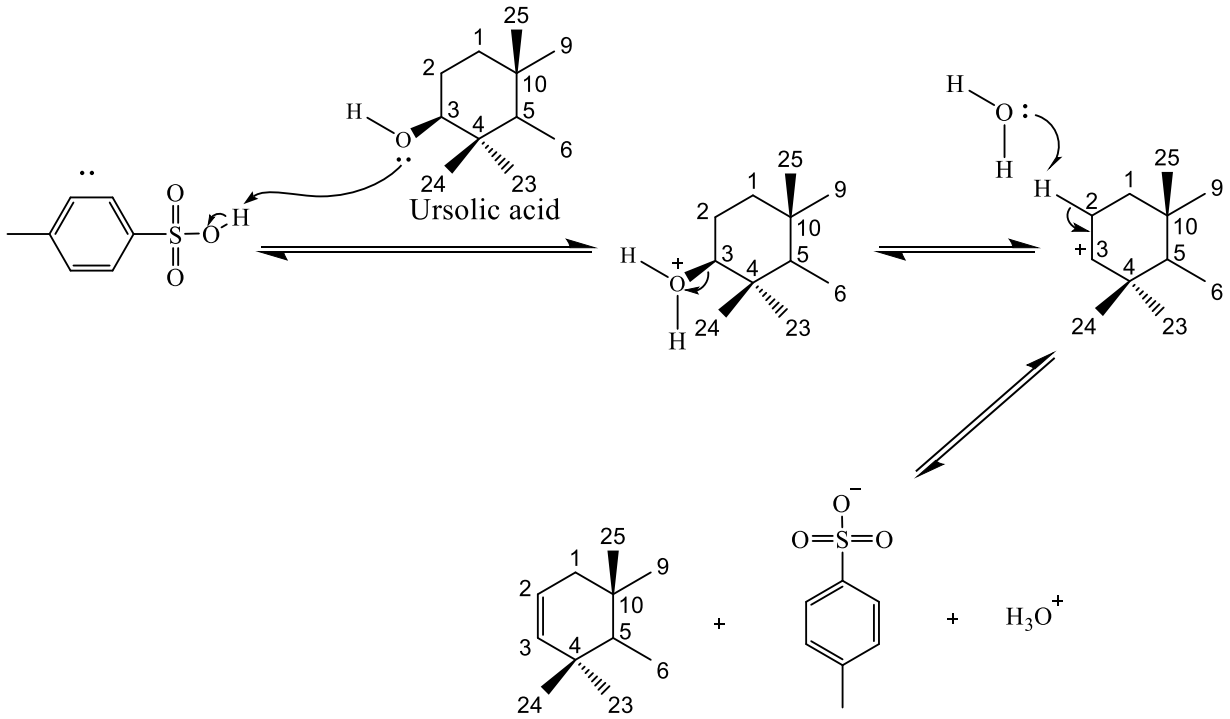


Figure S9. Possible dehydration mechanism of ursolic acid with DMC and PTSA.

Esterification mechanism of formic acid

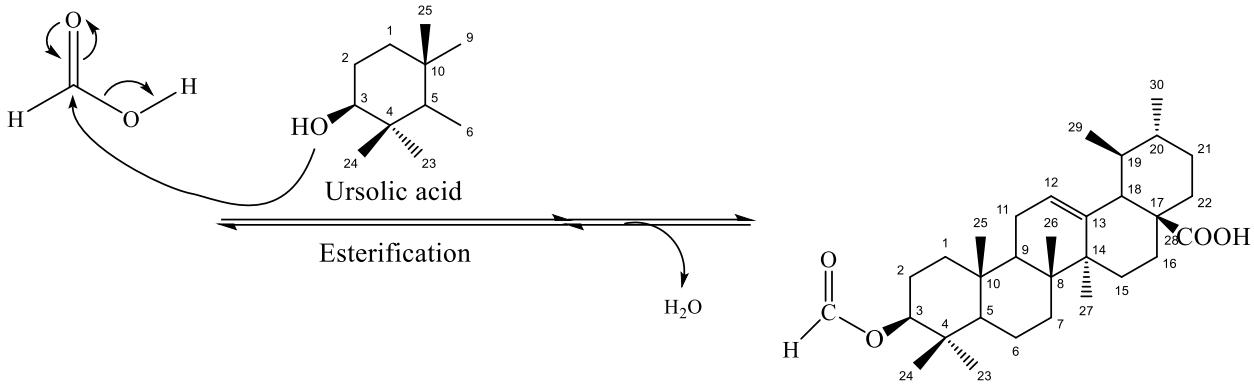


Figure S10. Possible esterification mechanism of ursolic acid with formic acid.

Carboxymethylation mechanism of H_2SO_4-SiO_2

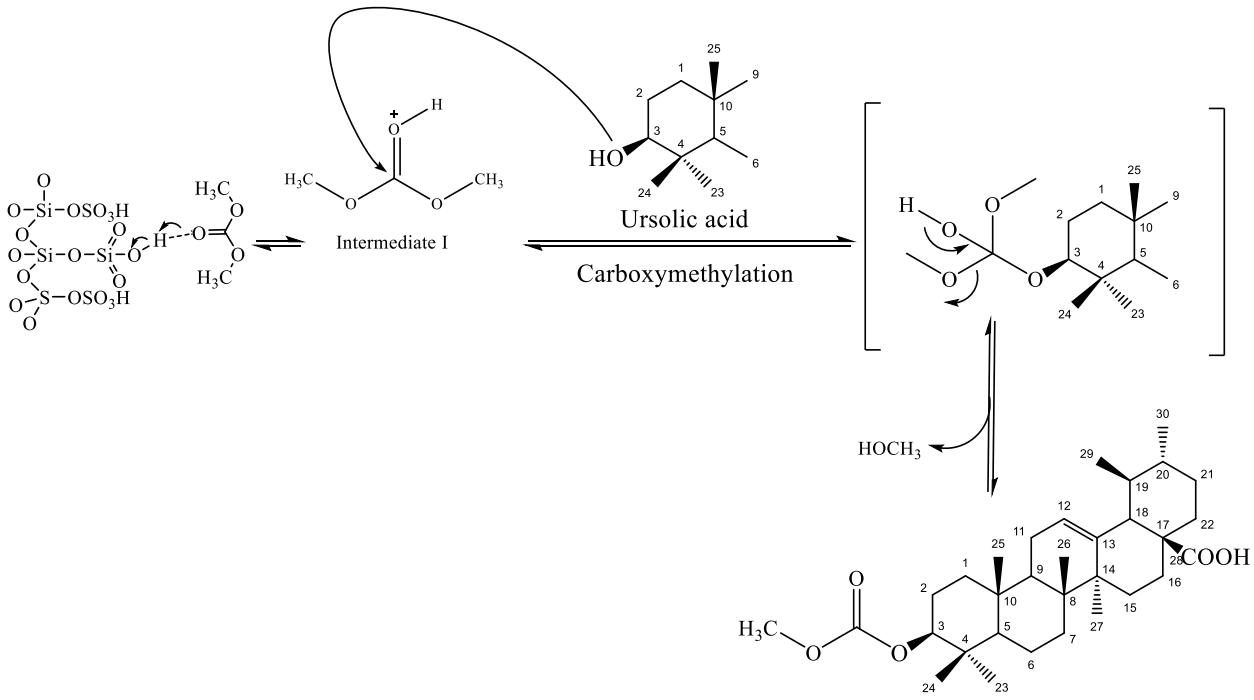
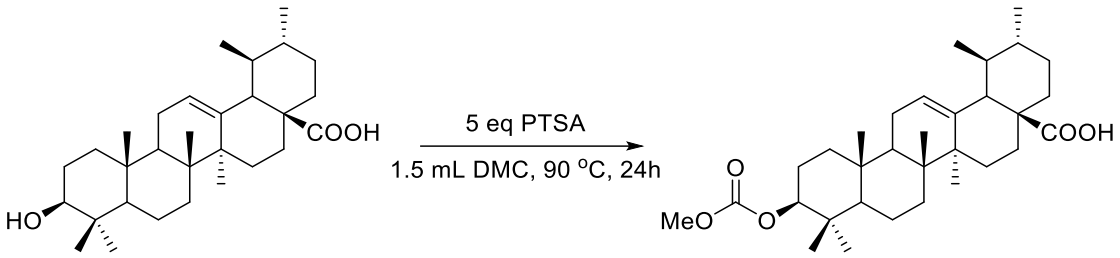


Figure S11. Possible Carboxymethylation mechanism of ursolic acid with DMC and H_2SO_4-SiO_2.

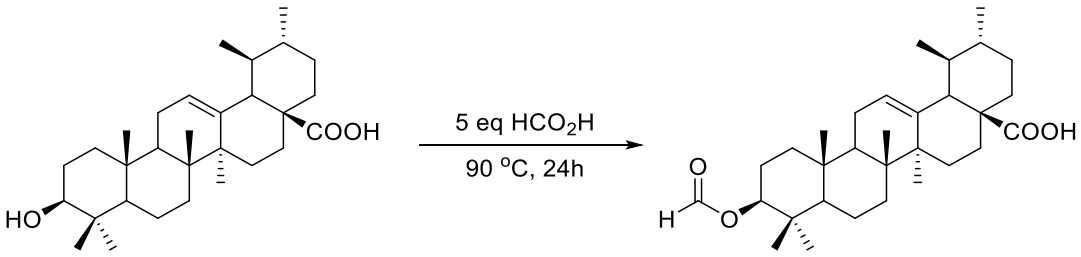
4. Green metrics calculations[1,2]

Current methods (PTSA, HCO_2H and $FeCl_3$)

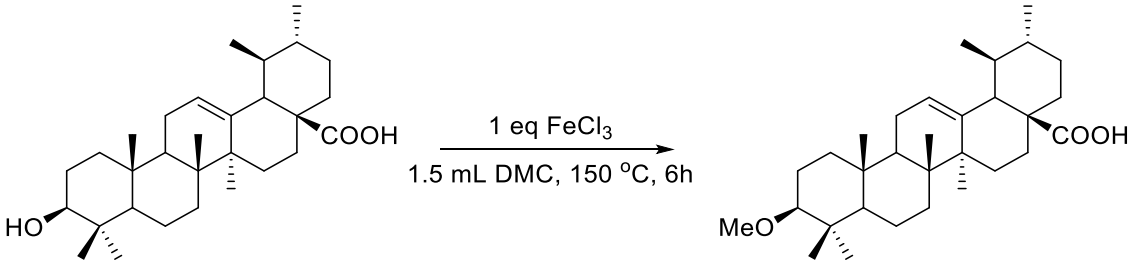
Carboxymethylation



Formylation



Methylation



Role	Chemical	Mass (g)	Volume (mL)	Density (g/mL)
Reaction				
Reactant	Ursolic acid	0.05		
Reactant (1 eq)	DMC	0.013	0.012	1.07
Reagent	PTSA	0.095		
Reactant (1 eq)	HCO_2H	0.005	0.004	1.22
Reagent	$FeCl_3$	0.018		
Solvent	DMC	1.59	1.488	1.07
Solvent (4 eq)	HCO_2H	0.02	0.016	1.22
	Reaction total (PTSA)	1.748		
	Reaction total (HCO_2H)	0.075		
	Reaction total ($FeCl_3$)	1.671		
Work-up				
Extraction solvent	Ethyl acetate	2.255	2.5	0.902
Extraction solvent	Water	2.5	2.5	1.0
CC	Silica-gel column	35		
Solvent	Ethyl acetate	45.1	50	0.902
	Hexane	33.05	50	0.661
	Work-up total (HCO_2H or $FeCl_3$)	4.755		
	Work-up total (PTSA)	117.905		
	Reaction and work-up total (PTSA)	119.653		
	Reaction and work-up total (HCO_2H)	4.83		
	Reaction and work-up total ($FeCl_3$)	6.426		
Product				
Product	Carboxymethylation (PTSA)	0.026		
Product	Formylation (HCO_2H)	0.053		
Product	Methylation ($FeCl_3$)	0.052		

Carboxymethylation (PTSA)

$$\text{PMI (reaction)} = \frac{\text{Total mass in reaction}}{\text{Mass of product}} = \frac{1.748}{0.026} = 67.23$$

$$\text{PMI (workup)} = \frac{\text{Total mass used for workup}}{\text{Mass of product}} = \frac{117.905}{0.026} = 4{,}534.81$$

$$\text{PMI (total)} = \frac{\text{Total mass process}}{\text{Mass of product}} = \frac{119.653}{0.026} = 755.88$$

$$\text{E factor} = \frac{\text{Total mass of waste}}{\text{Mass of product}} = \frac{119.653 - 0.026}{0.026} = 754.88$$

$$\text{SI} = \frac{\text{Total mass of solvent}}{\text{Mass of product}} = \frac{1.59+2.255+45.1+33.05}{0.026} = 4{,}424.81$$

$$\text{WI} = \frac{\text{Total mass of water}}{\text{Mass of product}} = \frac{2.5}{0.026} = 96.15$$

Formylation (HCO_2H)

$$\text{PMI (reaction)} = \frac{\text{Total mass in reaction}}{\text{Mass of product}} = \frac{0.075}{0.053} = 1.42$$

$$\text{PMI (workup)} = \frac{\text{Total mass used for workup}}{\text{Mass of product}} = \frac{4.755}{0.053} = 89.72$$

$$\text{PMI (total)} = \frac{\text{Total mass process}}{\text{Mass of product}} = \frac{4.83}{0.053} = 91.13$$

$$\text{E factor} = \frac{\text{Total mass of waste}}{\text{Mass of product}} = \frac{4.83 - 0.053}{0.053} = 90.13$$

$$\text{SI} = \frac{\text{Total mass of solvent}}{\text{Mass of product}} = \frac{0.02+2.255}{0.053} = 42.92$$

$$\text{WI} = \frac{\text{Total mass of water}}{\text{Mass of product}} = \frac{2.5}{0.053} = 47.17$$

Methylation ($FeCl_3$)

$$\text{PMI (reaction)} = \frac{\text{Total mass in reaction}}{\text{Mass of product}} = \frac{1.671}{0.052} = 32.13$$

$$\text{PMI (workup)} = \frac{\text{Total mass used for workup}}{\text{Mass of product}} = \frac{4.755}{0.052} = 91.44$$

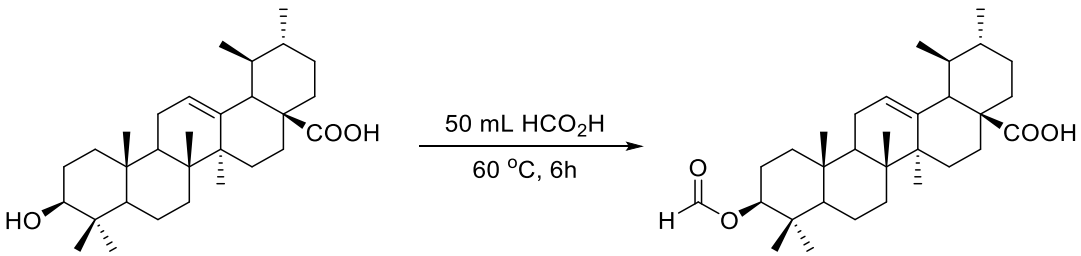
$$\text{PMI (total)} = \frac{\text{Total mass process}}{\text{Mass of product}} = \frac{6.426}{0.052} = 123.58$$

$$\text{E factor} = \frac{\text{Total mass of waste}}{\text{Mass of product}} = \frac{6.426 - 0.052}{0.052} = 122.58$$

$$\text{SI} = \frac{\text{Total mass of solvent}}{\text{Mass of product}} = \frac{1.59+2.255}{0.052} = 73.94$$

$$\text{WI} = \frac{\text{Total mass of water}}{\text{Mass of product}} = \frac{2.5}{0.052} = 48.08$$

Previous method for formylation (HCO_2H)[1]



Experimental Procedures: A mixture of ursolic acid (1) (500 mg, 1.1 mmol) and HCO_2H (50 mL) was stirred at 60°C for 6 h. The solvent was distilled off and the residue was dried at reduced pressure. The crude product was taken up in benzene and percolated through a silica gel column to give formylursolic acid (480 mg, 90%).

Role	Chemical	Mass (g)	Volume (mL)	Density (g/mL)
Reaction				
Reactant	Ursolic acid	0.5		
Reactant (1 eq)	HCO_2H	0.05	0.04	1.22
Solvent	HCO_2H	60.95	49.96	1.22
	Reaction total	61.5		
Work-up				
CC	Silica-gel column	50		
Solvent	Benzene	83.22	95	0.876
	Work-up total	133.22		
	Reaction and work-up total	194.72		
Product				
Product	Formylation	0.48		

PMI (reaction) = $\frac{\text{Total mass in reaction}}{\text{Mass of product}} = \frac{61.5}{0.48}$ = 128.125

PMI (workup) = $\frac{\text{Total mass used for workup}}{\text{Mass of product}} = \frac{133.22}{0.48}$ = 277.54

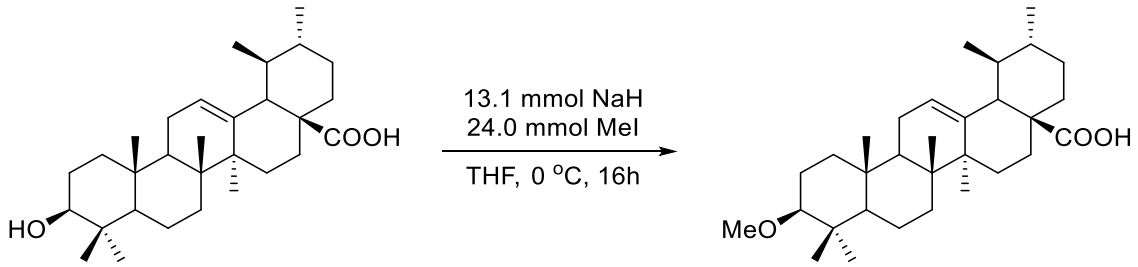
PMI (total) = $\frac{\text{Total mass process}}{\text{Mass of product}} = \frac{194.72}{0.48}$ = 405.67

E = $\frac{\text{Total mass of waste}}{\text{Mass of product}} = \frac{194.72 - 0.48}{0.48}$ = 404.67

SI = $\frac{\text{Total mass of solvent}}{\text{Mass of product}} = \frac{60.95 + 83.22}{0.48}$ = 300.35

WI = $\frac{\text{Total mass of water}}{\text{Mass of product}} = \frac{0}{0.48}$ = 0

Previous method for methylation (NaH, MeI)[2]



Experimental Procedures: To a suspension of NaH (526 mg, 13.1 mmol) in THF (5 mL) was added a solution of ursolic acid (500 mg, 1.09 mmol) in THF (20 mL) at 0 °C, and the mixture was stirred at the same temperature for 1 h. MeI (1.5 mL, 24.0 mmol) was added dropwise, and the solution was stirred in ice-bath for 16 h. The solution was diluted with EtOAc and washed with water and saturated NH_4Cl. The water phases were washed with EtOAc and combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (EtOAc/n-hexane = 1:5) to provide product as a white solid (314 mg, 59%).

Role	Chemical	Mass (g)	Volume (mL)	Density (g/mL)
Reaction				
Reactant	Ursolic acid	0.5		
Reactant	NaH	0.526		
Reagent	MeI	3.42	1.5	2.28

Solvent	THF	22.2	25	0.888
	Reaction total	26.646		
Work-up				
Extraction solvent	EtOAc	45.1	50	0.902
Extraction solvent	NH_4Cl	38.25	25	1.53
CC	Silica-gel column	50		
Solvent	EtOAc	15.334	17	0.902
Solvent	n-Hexane	54.697	83	0.659
	Work-up total	203.381		
	Reaction and work-up total	230.027		
Product				
Product	Methylation	0.314		

$$\text{PMI (reaction)} = \frac{\text{Total mass in reaction}}{\text{Mass of product}} = \frac{26.646}{0.314} = 85.86$$

$$\text{PMI (workup)} = \frac{\text{Total mass used for workup}}{\text{Mass of product}} = \frac{203.381}{0.314} = 647.71$$

$$\text{PMI (total)} = \frac{\text{Total mass process}}{\text{Mass of product}} = \frac{230.027}{0.314} = 732.57$$

$$\text{E} = \frac{\text{Total mass of waste}}{\text{Mass of product}} = \frac{230.027 - 0.314}{0.314} = 731.57$$

$$\text{SI} = \frac{\text{Total mass of solvent}}{\text{Mass of product}} = \frac{22.2 + 45.1 + 15.334 + 54.697}{0.314} = 437.36$$

$$\text{WI} = \frac{\text{Total mass of water}}{\text{Mass of product}} = \frac{38.25}{0.314} = 121.82$$

5. Carboxymethylation, methylation and formylation of Menthol

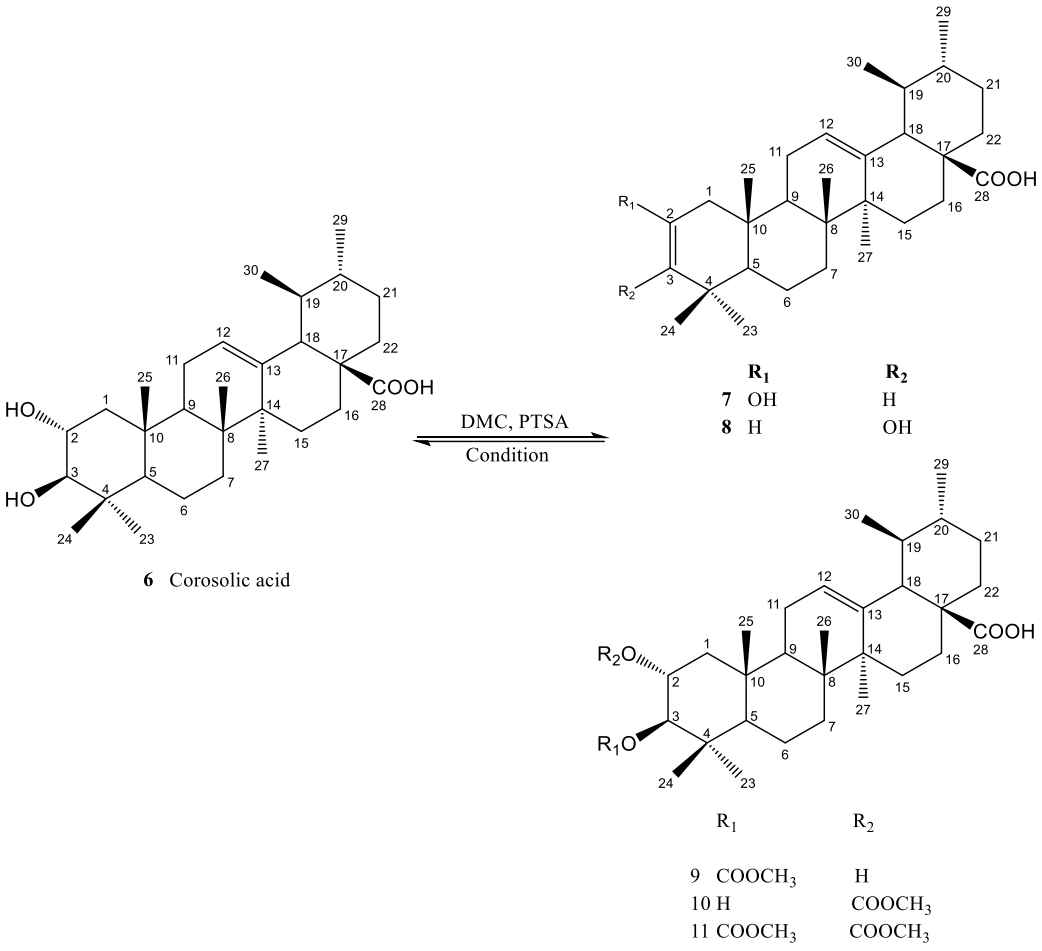
Table S4 the yield, conversion and selectivity of carboxymethylation and methylation of menthol with DMC in difference acidic conditions[a].

Acid	Condition		Conversion (%)	Major product	Yield (%)	GC-MS Selectivity (%)	
	Temperature (°C)	Time (Hour)				Major product	Other
PTSA	90	24	98.84	Carboxymethylation	92.60	93.67	6.33
$FeCl_3$	150	6	93.42	Methylation	54.57	58.41	51.59
Formic acid	90	24	90.63	Formylation	90	>99	<1

[a] condition; Methol : acid = 1:5 in excess DMC.

The %conversion and %selectivity were calculated by peak area of GC-MS.

6. Carboxymethylation, methylation and formylation of Corosolic acid



6 Corosolic acid

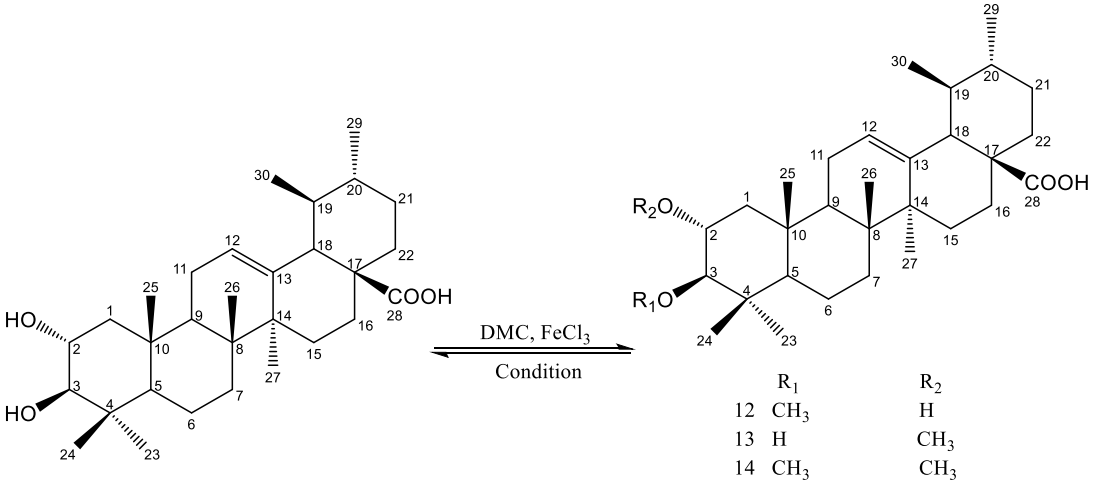
	R_1	R_2
7	OH	H
8	H	OH

	R_1	R_2
9	$COOCH_3$	H
10	H	$COOCH_3$
11	$COOCH_3$	$COOCH_3$

Figure S12 Reaction of corosolic acid with DMC in PTSA condition

Table S5 The yield and selectivity of carboxymethylation and methylation of corosolic acid with DMC in PTSA condition with 63% conversion. (Corosolic acid : PTSA : DMC = 1 : 5 : 160 at 90 °C for 24 hours)

Products	Yield%	Selectivity (%)
7	6.61	10.42
8	8.40	13.23
9	9.26	14.60
10	10.10	15.92
11	3.55	5.60

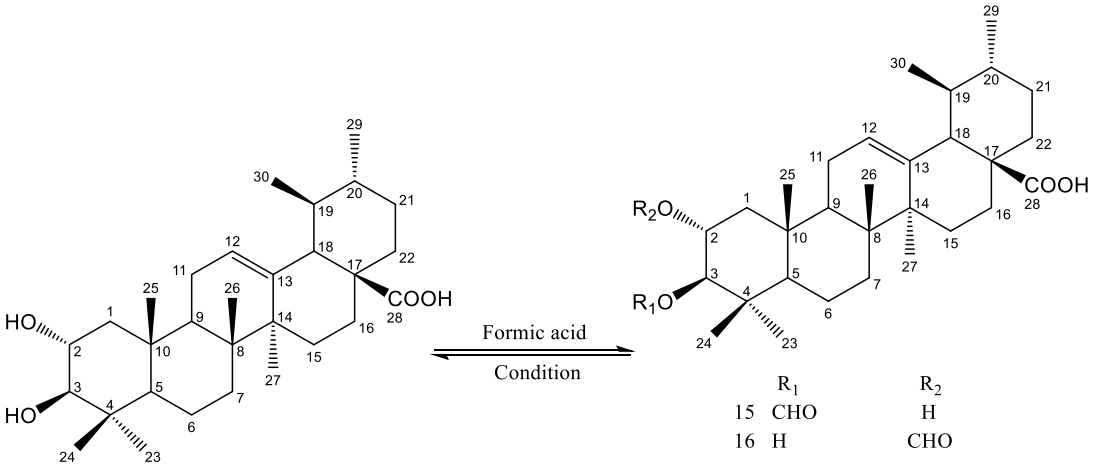


6 Corosolic acid

Figure S13 Reaction of corosolic acid with DMC in $FeCl_3$ condition

Table S6 The yield and selectivity of carboxymethylation and methylation of corosolic acid with DMC in PTSA condition with 85% conversion. (Corosolic acid : $FeCl_3$: DMC = 1 : 5 : 160 at 150 °C for 6 hours)

Products	Yield%	Selectivity (%)
9	21.24	24.98
12	12.33	14.50
13	11.77	13.84
14	3.45	4.06



6 Corosolic acid

Figure S14 Reaction of corosolic acid with DMC in formic acid condition

Table S7 The yield and selectivity of formylation of corosolic acid without DMC in formic acid condition with 83.46% conversion. (Corosolic acid : Formic acid = 1 : 5 at 90 °C for 24 hours)

Products	Yield%	Selectivity (%)
15	35.03	41.97
16	15.44	18.50

Table S8 The yield and selectivity of formylation of corosolic acid with DMC in formic acid condition with 22.20% conversion. (Corosolic acid : Formic acid = 1 : 5 : DMC = 1 : 5 : 160 at 90 °C for 24 hours)

Products	Yield%	Selectivity (%)
15	3.36	15.20
16	11.44	51.51

The %conversion and %selectivity were calculated by formula below;

$$\%\ Conversion\ of\ alcohol = \frac{Initial\ moles\ of\ alcohol - Final\ moles\ of\ alcohol}{Initial\ moles\ of\ alcohol} x100$$

$$\%\ Selectivity = \frac{Moles\ of\ desired\ product}{Moles\ of\ alcohol\ converted} x100$$

Table S9 Physicochemical parameters and Lipinski's rule of five of ursolic acid, corosolic acid and their derivatives using the SwissADME predictive database[a]

Compound	MW	logP	nHBA	nHBD	RO5
1	456.711	7.0895	2	2	1
2	470.738	7.7436	2	1	1
3	514.747	7.8802	4	1	2
4	484.721	7.2702	3	1	1
5	438.696	7.8947	1	1	1
6	472.71	6.0603	3	3	1
7	454.695	7.7804	2	2	1
8	454.965	7.7804	2	2	1
9	528.73	7.8911	5	2	2
10	528.73	7.8911	5	2	2
11	586.766	8.1161	7	1	2
12	484.721	7.7545	3	2	1
13	486.737	6.7144	3	2	1
14	500.764	7.3685	3	1	1
15	500.72	6.241	4	2	1
16	500.72	6.241	4	2	1

[a]MW-molecular weight [Da]; logP-octanol/water partition coefficient; nHBA-number of hydrogen bond acceptors; nHBD-number of hydrogen bond donors; RO5-number of violations of Lipinski's rule of five: molecular weight $\leq$ 500 Da; logP $\leq$ 5; nHBA $\leq$ 10; nHBD $\leq$ 5. A maximum of 1 violation is permitted.[3,4]

Table S10 Result of absorption properties of ursolic acid, corosolic acid and their derivatives by pkCSM

Compound	**Absorption**					
	Caco-2 permeability	**Human intestinal absorption**	**Skin permeability**	**P-glyco-protein substrate**	**P-glyco-protein I inhibitor**	**P-glyco-protein II inhibitor**
Unit	Numeric (log Papp in 10^{-6} cm/s)	Numeric (% Absorbed)	Numeric (log Kp)	Categorical (Yes/No)	Categorical (Yes/No)	Categorical (Yes/No)
Interpretation	High: > 0.90	Poor absorbed: < 30%	Low permeability: > -2.5	Yes/No	Yes/No	Yes/No
1	1.286	100	-2.732	No	No	No
2	-2.732	100	-2.732	No	No	No
3	0.74	100	-2.734	No	No	Yes
4	0.733	100	-2.733	No	No	No
5	1.223	100	-2.725	No	No	No
6	0.9	100	-2.735	Yes	No	No
7	1.318	100	-2.73	No	No	No
8	1.282	100	-2.732	No	No	Yes
9	0.747	81.549	-2.735	No	No	Yes
10	0.729	81.578	-2.735	No	No	Yes
11	0.721	86.545	-2.735	No	No	Yes
12	0.705	100	-2.735	No	No	Yes
13	0.72	100	-2.733	No	No	No
14	1.308	100	-2.733	No	No	No
15	0.84	100	-2.735	No	No	Yes
16	0.753	100	-2.733	No	No	Yes

Table S11 Result of distribution and metabolism properties of ursolic acid, corosolic acid and their derivatives by pkCSM

Compound	Distribution		Metabolism						
	BBB permeability	**CNS permeability**	**CYP2D6 substrate**	**CYP3A4 substrate**	**CYP1A2 inhibitior**	**CYP2C19 inhibitior**	**CYP2C9 inhibitior**	**CYP2D6 inhibitior**	**CYP3A4 inhibitior**
Unit	Numeric (logBB)	Numeric (log PS)	Cate-gorical (Yes/No)	Cate-gorical (Yes/No)	Cate-gorical (Yes/No)	Cate-gorical (Yes/No)	Cate-gorical (Yes/No)	Cate-gorical (Yes/No)	Cate-gorical (Yes/No)
Inter-pretation	Low: < −1; High: > 0.30	Low: < −3; High: > -2	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
1	-0.182	-1.118	No	Yes	No	No	No	No	No
2	-0.19	-2.267	No	Yes	No	No	No	No	No
3	-0.24	-1.053	No	Yes	No	No	No	No	No
4	-0.258	-1.274	No	Yes	No	No	No	No	No
5	0.073	-2.076	No	Yes	No	No	No	No	No
6	-0.592	-1.434	No	Yes	No	No	No	No	No
7	-0.147	-0.973	No	Yes	No	No	No	No	No
8	-0.176	-0.974	No	Yes	No	No	No	No	No
9	0.136	-1.841	No	Yes	No	No	No	No	No
10	0.102	-1.793	No	Yes	No	No	No	No	No
11	-0.909	-1.785	No	Yes	No	No	No	No	No
12	-0.257	-1.012	No	Yes	No	No	No	No	No
13	-0.262	-1.359	No	Yes	No	No	No	No	No
14	-0.163	-1.26	No	Yes	No	No	No	No	No
15	0.301	-1.45	No	Yes	No	No	No	No	No
16	-0.185	-1.564	No	Yes	No	No	No	No	No

Table S12 Result of excretion and toxicity properties of ursolic acid, corosolic acid and their derivatives by pkCSM

Compound	**Excretion**		**Toxicity**			
	Total clearance	**Renal OCT2 Substrate**	**AMES toxicity**	**hERG I and II inhibitors**	**Hepatotoxicity**	**Skin Sensitisation**
Unit	Numeric (log ml/min/kg)	Categorical (Yes/No)	Categorical (Yes/No)	Categorical (Yes/No)	Categorical (Yes/No)	Categorical (Yes/No)
Interpretation	Log ml/min/kg	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
1	0.083	No	No	No	Yes	No
2	0.11	No	No	No	No	No
3	-0.104	No	No	No	No	No
4	0.084	No	No	No	No	No
5	0.041	No	No	No	No	No
6	0.093	No	No	No	No	No
7	-0.067	No	No	No	No	No
8	-0.02	No	No	No	Yes	No
9	-0.264	No	No	No	Yes	No
10	-0.248	No	No	No	Yes	No
11	-0.414	No	No	No	No	No
12	-0.035	No	No	No	No	No
13	0.123	No	No	No	Yes	No
14	0.147	No	No	No	No	No
15	0.092	No	No	No	No	No
16	0.094	No	No	No	No	No

Table S13 Molecular docking results of ursolic acid, corosolic acid and their derivatives with COX-2 enzyme (PDB: 5FDQ)

Compound	Binding affinity (kcal/mol)	Hydrophobic interactions	Hydrogen Bond interactions	Unfavourable interactions
1	-7.2	HIS (A: 207), HIS (A: 386), HIS (A: 388), ALA (A: 446), VAL (A: 447), ALA (A: 450)		
2	-6.7	HIS (A: 207), HIS (A: 214), ILE (A: 274), VAL (A: 291), LEU (A: 294), HIS (A: 386)	THR (A: 212), ASN (A: 382), GLN (A: 454)	
3	-7	HIS (A: 207), HIS (A: 214), ILE (A: 274), VAL (A: 291), LEU (A: 294), MET (A: 458)	ASN (A: 382), HIS (A: 386)	
4	-7.3	HIS (A: 207), HIS (A: 214), ILE (A: 274), VAL (A: 291), LEU (A: 294), HIS (A: 386)	ASN (A: 382), GLN (A: 454)	
5	-6.7	HIS (A: 207), LEU (A: 294), HIS (A: 386), VAL (A: 444), VAL (A: 447)		HIS (A: 214)
6	-7	HIS (A: 207), ILE (A: 274), VAL (A: 291), LEU (A: 294)	ASN (A: 382)	
7	-6.7	HIS (A: 214), VAL (A: 291), LEU (A: 294), LEU (A: 408), VAL (A: 444), VAL (A: 447)	HIS (A: 207), PHE (A: 210)	
8	-6.8	HIS (A: 207), HIS (A: 214), ILE (A: 274), VAL (A: 291), LEU (A: 294), HIS (A: 386)	ASN (A: 382)	
9	-6.8	HIS (A: 214), VAL (A: 291), LEU (A: 294), VAL (A: 295), LEU (A: 391), PHE (A: 395), PHE (A: 407), LEU (A: 408), VAL (A: 444), VAL (A: 447)	PHE (A: 210)	
10	-6.5	HIS (A: 214), VAL (A: 291), LEU (A: 294), LEU (A: 408), VAL (A: 444), VAL (A: 447)	HIS (A: 207)	
11	-6.8	HIS (A: 207), PHE (A: 210), VAL (A: 447)	THR (A: 206), TYR (A: 385), HIS (A: 386)	
12	-6.7	HIS (A: 214), VAL (A: 291), LEU (A: 294), LEU (A: 408), VAL (A: 444), VAL (A: 447)	HIS (A: 207)	
13	-6.6	VAL (A: 444), VAL (A: 447)	HIS (A: 386)	
14	-6.4	HIS (A: 214), VAL (A: 291), LEU (A: 294), LEU (A: 408), VAL (A: 447)	GLN (A: 203), HIS (A: 207)	
15	-6.9	HIS (A: 214), VAL (A: 291), LEU (A: 294), LEU (A: 408)	GLN (A: 203), HIS (A: 207), PHE (A: 210)	
16	-6.9	HIS (A: 214), HIS (A: 386), VAL (A: 444), VAL (A: 447)	HIS (A: 207), ASN (A: 382)	

Table S14 Molecular docking results of ursolic acid, corosolic acid and their derivatives with the EGFR kinase domain (non-small lung cancer, PDB: 2GS2)

Compound	Binding affinity (kcal/mol)	Hydrophobic interactions	Hydrogen Bond interactions	Unfavourable interactions
1	-7.6	LEU (A: 694), VAL (A: 702), ALA (A: 719), LYS (A: 721), LEU (A: 820)	GLY (A: 772), CYS (A: 773)	
2	-7.4	LEU (A: 694), VAL (A: 702), ALA (A: 719), LYS (A: 721)	ASP (A: 776)	
3	-7	LEU (A: 694), VAL (A: 702), ALA (A: 719), LYS (A: 721)	ASP (A: 776)	
4	-7.2	LEU (A: 694), VAL (A: 702), ALA (A: 719), LYS (A: 721)		
5	-7.6	LEU (A: 694), VAL (A: 702), ALA (A: 719), LYS (A: 721), LEU (A: 820)	THR (A: 830)	
6	-7.9	VAL (A: 702), ALA (A: 719), LYS (A: 721)	ASP (A: 776), THR (A: 830)	
7	-7.8	LEU (A: 694), VAL (A: 702), ALA (A: 719), LYS (A: 721)	THR (A: 830)	
8	-7.6	VAL (A: 702), ALA (A: 719), MET (A: 742), CYS (A: 751), CYS (A: 773), LEU (A: 820)	THR (A: 830)	ASP (A: 831)
9	-6.8	ALA (A: 698), VAL (A: 702), ALA (A: 719), LYS (A: 721), CYS (A: 751), LEU (A: 820)	GLY (A: 695), THR (A: 766), THR (A: 830)	SER (A: 696)
10	-8	LEU (A: 694), ALA (A: 698), VAL (A: 702), ALA (A: 719), LEU (A: 768), MET (A: 769), LEU (A: 820)		
11	-6.5	VAL (A: 702), ALA (A: 719), LYS (A: 721), ARG (A: 817), LEU (A: 820)	CYS (A: 773), ARG (A: 817), THR (A: 830)	
12	-7.4	VAL (A: 702), ALA (A: 719), LYS (A: 721)	ASP (A: 776), THR (A: 830)	
13	-7.4	VAL (A: 702), ALA (A: 719), LYS (A: 721), LEU (A: 820)	ASP (A: 776), THR (A: 830)	
14	-7.2	VAL (A: 702), ALA (A: 719), LYS (A: 721), LEU (A: 820)	ASP (A: 776), THR (A: 830)	
15	-7.4	VAL (A: 702), ALA (A: 719), LYS (A: 721)	ASP (A: 776), THR (A: 830)	
16	-7.6	ARG (A: 817), LEU (A: 820)	THR (A: 766), THR (A: 830)	MET (A: 769)

Table S15 Molecular docking results of ursolic acid, corosolic acid and their derivatives with chimaeric Bcl2-xL (breast cancer MCF-7, PDB: 2W3L)

Compound	Binding affinity (kcal/mol)	Hydrophobic interactions	Hydrogen Bond interactions	Unfavourable interactions
1	-6.7	PHE (A: 63), TYR (A: 67), PHE (A: 71), MET (A: 74), ALA (A: 108)	LEU (A: 96)	
2	-7	PHE (A: 63), TYR (A: 67), PHE (A: 71), ALA (A: 108)	ARG (A: 105)	
3	-6.7	TYR (A: 67)	GLU (A: 73)	
4	-7.1	PHE (A: 63), TYR (A: 67), PHE (A: 71), ALA (A: 108)	ARG (A: 105)	
5	-7.1	PHE (A: 63), TYR (A: 67), PHE (A: 71), MET (A: 74), ALA (A: 108)	ARG (A: 105)	
6	-7.3	PHE (A: 63), TYR (A: 67), PHE (A: 71), MET (A: 74), ALA (A: 108)	ARG (A: 105)	
7	-7.1	PHE (A: 63), TYR (A: 67), PHE (A: 71), MET (A: 74)	ARG (A: 105), ALA (A: 108)	
8	-7.2	PHE (A: 63), TYR (A: 67), PHE (A: 71), MET (A: 74), LEU (A: 96), ALA (A: 108)	ARG (A: 105)	
9	-6.7	TYR (A: 67), PHE (A: 71), MET (A: 74)	TYR (A: 67)	
10	-7.1	VAL (A: 92), LEU (A: 96), ARG (A: 105)		
11	-6.5	PHE (A: 63), TYR (A: 67), PHE (A: 71), ALA (A: 108)	ARG (A: 105), ALA (A: 108)	ASN (A: 102), ARG (A: 105)
12	-7	PHE (A: 63), TYR (A: 67), PHE (A: 71)	ARG (A: 105), ALA (A: 108)	ARG (A: 105)
13	-7.1	PHE (A: 63), TYR (A: 67), PHE (A: 71)	ARG (A: 105)	
14	-7	PHE (A: 63), TYR (A: 67), PHE (A: 71)	ASN (A: 102), ARG (A: 105), ALA (A: 108)	
15	-7.2	PHE (A: 63), TYR (A: 67), PHE (A: 71)	ARG (A: 105)	ASN (A: 102), ARG (A: 105)
16	-7.1	PHE (A: 63), TYR (A: 67), PHE (A: 71)	ARG (A: 105)	

Table S16 Molecular docking results of ursolic acid, corosolic acid and their derivatives with kappaB kinase beta (PDB: 3RZF)

Compound	Binding affinity (kcal/mol)	Hydrophobic interactions	Hydrogen Bond interactions	Unfavourable interactions
1	-6.9	VAL (A: 29), ALA (A: 42), MET (A: 96), ILE (A: 165)	THR (A: 23), ASP (A: 103)	
2	-6.8	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), ILE (A: 165)	ASP (A: 103)	
3	-6.3	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), LYS (A: 106), VAL (A: 152), ILE (A: 165)	GLU (A: 149)	
4	-6	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), VAL (A: 152)	GLU (A: 100), GLU (A: 149)	
5	-7.1	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), LYS (A: 106), ILE (A: 165)	GLU (A: 149)	
6	-7.1	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), LYS (A: 106), VAL (A: 152), ILE (A: 165)		ASP (A: 103)
7	-7.1	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), LYS (A: 106), VAL (A: 152), ILE (A: 165)		ASP (A: 103)
8	-7	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), LYS (A: 106), ILE (A: 165)	ASP (A: 103)	
9	-6.3	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), LYS (A: 106), VAL (A: 152), ILE (A: 165)		ASP (A: 103)
10	-7.6	LEU (A: 21), VAL (A: 29), ALA (A: 42), ILE (A: 165)	GLU (A: 100), ASP (A: 103)	
11	-6.3	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), ARG (A: 105), LYS (A: 106), VAL (A: 152), ILE (A: 165)		ASP (A: 103)
12	-6.7	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), VAL (A: 152), ILE (A: 165)	GLU (A: 149)	
13	-6.9	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), ILE (A: 165)	ASP (A: 103)	
14	-6.7	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), LYS (A: 106), VAL (A: 152), ILE (A: 165)	GLU (A: 149)	
15	-6.7	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), LYS (A: 106), VAL (A: 152), ILE (A: 165)		ASP (A: 103)
16	-6.9	LEU (A: 21), VAL (A: 29), ALA (A: 42), TYR (A: 98), LYS (A: 106), ILE (A: 165)		

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