Table S1. Training and test sets for derivative method (^{1}D), ratio derivative (^{1}DD), and mean centering ratio (MCR) methods.

Training set[a]			Test set[a]		
Mixture	MF[b]	CP[c]	Mixture	MF	CP
1	5	15	1	20	5
2	15	10	2	24	6
3	15	8	3	5	20
4	10	20	4	16	4
5	25	4	5	10	16
6	20	8			
7	10	2			
8	40	5			
9	35	4			
10	30	5			

[a] Concentration values are expressed as μg/mL; [b] mometasone furoate; [c] calcipotriol

Table S2. Optimized stress condition and percent of degradation for MF and CP

Stress conditions	Stressor and its concentration		Exposure condition		Duration of exposure		% [a]Deg	
Hydrolysis	CP	MF	CP	MF	CP	MF	CP	MF
Acidic	0.0001N HCL	0.1 N HCL	[b]RT		0.5 h	2 days	12	-
			60°C		2.5 h	2.5h	70	10
Alkaline	0. 1N NaOH	0.0001 N NaOH	RT		7 h	4 h	-	54
			60°C		4 h	2.5 h	20	93
Neutral and pH 7	Distilled water and phosphate buffer		RT		24 h	24 h	-	-
Thermal	Methanol		60°C		4 h	1h	20	5
Oxidation	15% H_2O_2		RT		4 h	4 h	9.3	-
Photolysis	UV light		RT		30 min	3 days	17.8	4.5

%[a]Deg: percent of degradation, [b]RT: room temperature

Table S3. The parameters and their levels selected and responses for the optimization HPLC

	Factor1	Factor2	Factor3	Response1	Response2	Response3	Response4	Response5
Run	%Organic solution	ƛ (nm)	Flow rate(mL/min)	t_R[a] MF (min)	t_R CP (min)	AUC[b] MF	AUC CP	R[c]
1	85	247	0.7	6.845	9.55	1627080	68083	6.615
2	85	247	1.3	3.803	5.351	852802.5	36832.5	6.153
3	85	264	1.3	3.8	5.33	736648.5	44323	6.035
4	85	264	0.7	6.901	9.562	1353957	79780.5	6.4
5	90	264	1.3	3.14	3.78	859376	54927	3.197
6	90	247	1.3	3.17	3.8	1073071	50493	3.15
7	90	247	0.7	5.8	6.9	1922681	90257	3.6
8	90	264	0.7	5.78	6.95	1979328	87398	3.6
9	80	247	1.3	4.94	8.5	1005660	45390	10.039
10	80	247	0.7	9.02	15.3	1844899	83278	11.562
11	80	264	0.7	9.01	15.5	1565035	97756	11.3
12	80	264	1.3	4.94	8.48	819333	51581	10.019

[a]Retention times, [b]area under the curves, [c]resolution

Table S4. Statistical comparison between the recovery results of the proposed HPLC method and the chemometrics UV methods to determine MF and CP

StatisticalTerm	MF				CP			
	[1]D	[1]DD	MCR	HPLC	[1]D	[1]DD	MCR	HPLC
mean	99.39	99.96	99.13	100	101	99.96	99.88	99.25
SD	1.925	1.498	1.72	1.77	1.95	1.498	0.9362	1.458
RSD	1.93	1.498	1.742	1.77	1.94	1.50	0.937	1.47
Std. Error of mean	0.6806	0.5295	0.6105	0.6268	0.6928	0.529	0.331	0.5154
[a]N	8	8	8	8	8	8	8	8
[a]p-value	0.8206	0.999	0.6255	-	0.1279	0.7510	0.8107	-

[a]Figures in parentheses are the theoretical P at (P = 0.05), while n is the number of determinations

Table S5. ANOVA test *P*-value and F value for model of responses

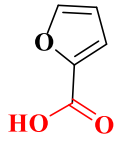
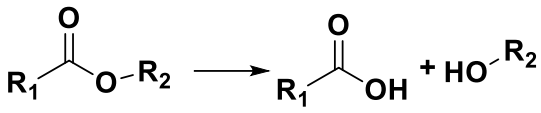
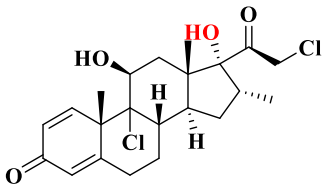
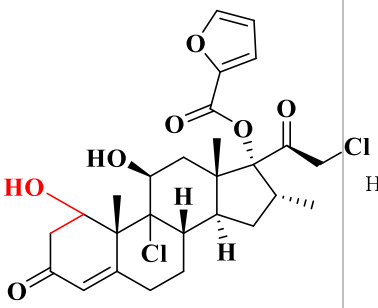
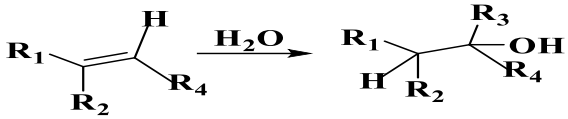
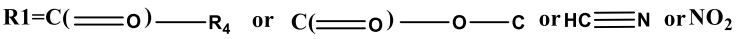
Response	Intercept	A[a]	B[b]	C[c]	AB	AC	BC
t_R[d] MF	5.59575	-1.2525	0.000583333	1.63025	-0.005	0.36	0.0049166
p-values	< 0.0001	< 0.0001	0.9949	<0.001	0.9645	0.0199	0.9572
F- values	83.06	137.52	0.00000	349.47	0.0022	11.36	0.0032
t_R CP	8.25025	-3.29375	0.01675	2.37675	-0.01875	0.94375	-0.0269167
p-values	< 0.0001	0.0002	0.9525	0.0003	0.9566	0.0347	0.9238
F- values	31.34	100.91	0.0039	78.81	0.0033	8.28	0.0101
AUC[e] MF	1.30332E+06	74941.1	-84376.3	412174	38642.9	-48077.6	-1653
p-values	< 0.0001	0.3456	0.2107	0.0009	0.6145	0.5338	0.9787
F- values	8.84	1.08	2.06	49.16	0.2881	0.4460	0.0008
AUC CP	65841.6	633.75	3452.67	18583.8	-2386.75	1478.5	-433.417
p-values	< 0.0001	0.8658	0.2886	0.0014	0.5326	0.6953	0.8874
F- values	7.15	0.0316	1.41	40.8	0.4488	0.1722	0.0200
R[f]	6.80583	-3.67163	0.047333	0.37366	0.041125	0.24387	0.0321667
p-values	< 0.0001	< 0.0001	0.7905	0.0778	0.8502	0.2913	0.8564
F- values	53.61	315.21	0.0786	4.90	0.0395	1.39	0.0363

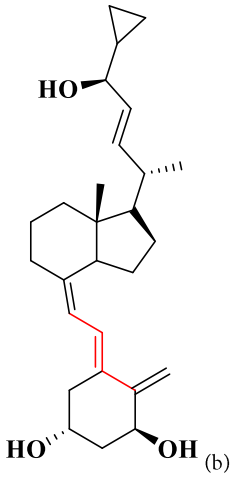
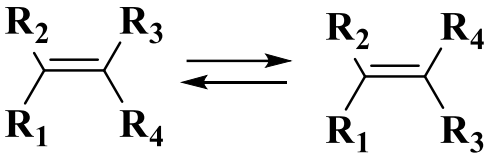
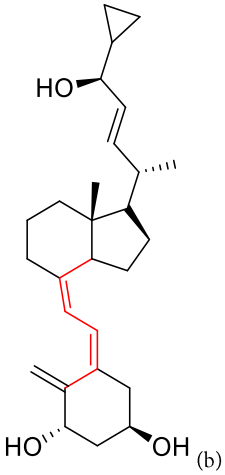
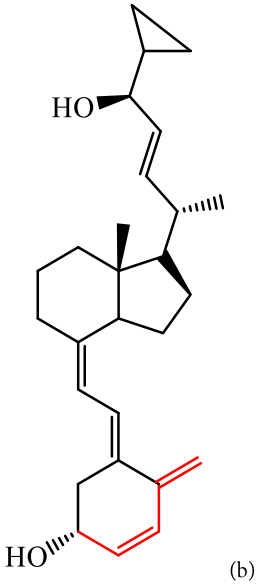
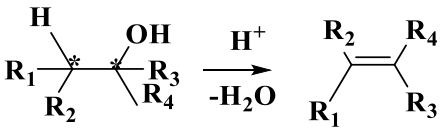
[a]%Organic solution, [b] ƛ (nm), [c]Flow rate(mL/min), [d]retention times, [e]area under the curves, [f]resolution

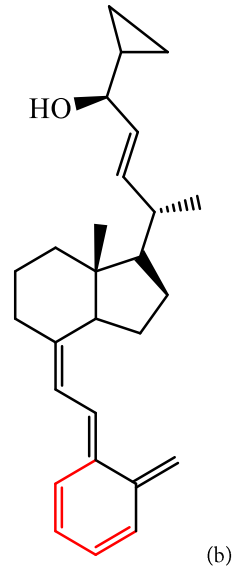
Table S6. Confirmation observed responses by comparing with predicted results

Response	Predicted Mean	Predicted Median	Observed	Std Dev	SE Pred	95% PI low	95% PI high
RT MF	5.59575	5.59575	4.81	0.30209	0.314426	4.78749	6.40401
RT CP	8.25025	8.25025	6.62	0.927411	0.96528	5.76892	10.7316
AUC MF	1.20332E+06	1.20332E+06	1.183205 E+06	203631	211946	758498	1.84815E+06
AUC CP	55841.6	55841.6	42358	10076.7	10488.1	38880.9	92802.2
R	6.80583	6.80583	6.368	0.584926	0.60881	5.24084	8.37083

Table S7. Main products and degradation pathways of MF and CP generated by *in silico* prediction in the Zeneth software

Degradation product	Transformation name	Description
 (a)	Hydrolysis of ester	 R1= carbon or hydrogen R2= aliphatic carbon (not multiply bonded and not attached to another heteroatom) or aromatic carbon. The hydrolysis of acyclic carboxylic esters leads to generation of carboxylic acids and alcohols and can be catalyzed by both acid and base.
 (a)		
 (a)	Hydration of alkene	  R2= hydrogen or carbon or fluorine or chlorine or bromine or iodine R3, R4= carbon or hydrogen Activated alkenes can be hydrated in a Michael addition reaction. The alkenes are activated by an electron withdrawing group such as ketone, aldehyde, ester, cyano or nitro. The reaction takes place readily, even more so in base.

 (b)	Photochemical isomerization of alkene	 R1, R4=aliphatic carbon R3=aromatic carbon R2=hydrogen, carbon, Florine, chlorine, bromine or iodine
 (b)		
 (b)	Dehydration of alcohol	 R1, R2, R3= aliphatic carbon (not multiply bonded to a heteroatom or aromatic carbon or hydrogen R4= aromatic or vinylic or acetylenic Alcohols can be dehydrated in strongly acidic conditions. The reaction involves protonation of the alcohol oxygen followed by loss of water to give a carbonium ion. This carbonium ion then loses a proton from a neighboring carbon atom yielding the alkene.



(b)

(a) Degradation products of MF

(b) Degradation products of CP

Table S8. Fukui index distribution on CP and MF calculated at B3LYP/6-31G(d,p) level

No.	Atom		CP			MF		
	CP	MF	f_k^-	f_k^+	f_k^0	f_k^-	f_k^+	f_k^0
1	C	C	0.0000	-0.0000	0.0000	0.0002	0.0003	0.002
2	C	C	0.0007	0.0004	0.0005	0.0002	0.0002	0.002
3	C	C	0.0006	0.0001	0.0004	0.0002	0.0049	0.0026
4	C	C	0.0003	0.0001	0.0002	0.0000	0.0015	0.0007
5	C	C	0.0000	0.0000	0.0000	0.0000	0.0030	0.0015
6	C	C1	0.0000	0.0000	0.0000	0.0000	0.0013	0.0007
7	C	O	0.0000	0.0000	0.0000	0.0001	0.0002	0.0002
8	C	O	0.0000	0.0000	0.0000	0.0000	0.0404	0.0202
9	C	C	0.0000	0.0000	0.0000	0.0000	0.0847	0.0424
10	C	C	0.0026	0.0024	0.0025	0.0000	0.1775	0.0887
11	C	C	0.0004	-0.0000	0.0002	0.0000	0.0087	0.0044
12	C	C	0.0008	0.0002	0.0005	0.0000	0.1737	0.0869

13	C	C	0.0122	0.0086	0.0104	0.0000	0.0650	0.0325
14	C	C	0.0149	0.0043	0.0096	0.0000	0.0059	0.0030
15	C	C	0.0006	-0.0002	0.0002	0.0000	0.0002	0.0030
16	C	C	0.0022	0.0005	0.0013	0.0001	0.0001	0.0001
17	C	C	0.008	0.0046	0.0067	0.0002	0.0005	0.0001
18	C	C	0.2421	0.1649	0.2035	0.0007	0.0002	0.0004
19	C	C	0.1611	0.0504	0.1057	0.0019	0.0000	0.0004
20	C	C	0.1313	0.1734	0.1523	0.0157	-0.0000	0.0009
21	C	C	0.2250	0.1866	0.2058	0.0212	0.0000	0.0078
22	C	C	0.0089	0.0051	0.0070	0.0949	0.0000	0.0106
23	C	C	0.0099	0.0074	0.0086	0.0372	0.0000	0.0474
24	C	C	0.0008	0.0021	0.0014	0.0912	0.0000	0.0186
25	C	C	0.0066	0.0099	0.0083	0.0186	0.0000	0.0456
26	C	C	0.0144	0.0939	0.0541	0.0065	0.0000	0.0093
27	**C**	C	0.0703	**0.1884**	0.1293	0.0002	0.0000	0.0032
28	O	C	0.0036	0.1884	0.0038	0.0004	0.0000	0.0001
29	O	C	0.0027	0.0040	0.0023	0.0001	0.0000	0.0002
30	C	C	0.0031	0.0018	0.0024	0.0013	0.0001	0.0001
31	H	O	-0.0000	0.0017	0.0000	0.0011	0.0000	0.0006
32	H	C	0.0000	0.0001	0.0000	0.0004	0.0007	0.0005
33	H	O	0.0000	0.0000	-0.0000	0.6791	0.0000	0.3395
34	H	H	0.0001	0.0000	0.0001	0.0000	0.0001	0.0001
35	H	H	0.0001	0.0000	0.0001	0.0001	0.0000	0.0000
36	H	H	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
37	H	H	0.0000	0.0000	0.0000	0.0000	0.0004	0.0002
38	H	H	0.0000	0.0000	0.0000	0.0000	0.0002	0.0001
39	H	H	0.0000	0.0000	0.0000	0.0000	0.0012	0.0006
40	H	H	0.0000	0.0000	0.0000	0.0000	0.0002	0.0001
41	H	H	0.0000	0.0000	0.0000	0.0000	0.0013	0.0007

42	H	H	0.0000	0.0000	0.0000	0.0000	0.0019	0.0009
43	H	H	0.0000	0.0000	0.0000	0.0000	0.0003	0.0002
44	H	H	0.0002	0.0008	0.0005	0.0000	0.0003	0.0002
45	H	H	0.0001	0.0002	0.0001	0.0000	0.0004	0.0002
46	H	H	-0.0000	0.0000	0.0000	0.0000	0.0003	0.0002
47	H	H	0.0027	0.0008	0.0017	0.0000	0.0001	0.0000
48	H	H	0.0003	0.0002	0.0002	0.0000	0.0001	0.0000
49	H	H	0.0181	0.0135	0.0158	0.0000	0.0000	0.0000
50	H	H	0.0005	0.0002	0.0004	0.0014	0.0000	0.0007
51	H	H	0.0001	0.0001	0.0001	0.0003	0.0000	0.0002
52	H	H	0.0017	-0.0001	0.0008	0.0002	0.0000	0.0001
53	H	H	0.0001	0.0004	0.0002	0.0028	0.0000	0.0014
54	H	H	0.0097	0.0173	0.0135	0.0064	0.0000	0.0032
55	H	H	0.0163	0.0166	0.0165	0.0067	0.0000	0.0034
56	H	H	0.0013	0.0032	0.0023	0.0100	0.0000	0.0050
57	H	H	0.0013	0.0029	0.0021	0.0000	0.0000	0.0000
58	H	H	0.0167	0.0107	0.0137	0.0000	0.0000	0.0000
59	H	H	0.0002	0.0018	0.0010	0.0000	0.0000	0.0000
60	H	H	0.0014	0.0002	0.0008	0.0004	0.0000	0.0002
61	H	H	0.0006	0.0023	0.0014	0.0000	0.0000	0.0000
62	H	H	0.0005	0.0016	0.0010	0.0000	0.0000	0.0000
63	H	H	0.0012	0.0051	0.0031	0.0000	0.0002	0.0001
64	H	C	0.0002	0.0029	0.0016	0.0000	**0.2686**	0.1343
65	H	O	0.0011	0.0026	0.0019	0.0000	0.1552	0.0776
66	H		0.0001	0.0020	0.0011			
67	H		0.0004	0.0038	0.0021			
68	H		-0.0000	0.0001	0.0001			
69	H		0.0001	0.0001	0.0001			
70	H		0.0006	0.0001	0.0004			

Table S9. System suitability parameters for HPLC method

Parameter	MF	CP	Reference value
Capacity factor	2.63±0.043	4.31±0.0408	1–10
Theoretical plates	5265.6±55.27	6497.6±69.53	>1000
Resolution (R)	6.68±0.13		>1.5
Tailing factor (T_f)	1.01±0.0262	1.027±0.032	< 2

Table S10. Changing HPLC parameters for the analysis of method robustness

Parameters	compounds	Standard condition[a]	Flow rate (mL/min)		% Methanol		ƛ (nm)	
			0.9	1.1	83	87	252	256
R[b]	MF[c]/CP[d]	6.17	6.24	6.35	8.06	4.9	6.13	6.15
TEP[e]	MF	5208	5208	5085	5540	5285	5387.5	5384
	CP	6470	6693	6445	7341	6353	6765	6777
T_f[f]	MF	1.028	1.030	1.035	1.030	1.062	1.045	1.037
	CP	1.03	1.042	1.046	1.028	1.073	1.048	1.037
Assay%	MF	100	104.917	98.87	104.47	103.55	100.5	102
	CP	100	104.2	98.33	97.92	97.53	97.53	100.5
t_R[g] (min)	MF	4.8	5.35	4.44	5.3	4.8	4.79	4.79
	CP	6.58	7.39	6.18	7.98	6.58	6.15	6.15

[a]Standard condition: Flow rate (1mL/min), % Methanol (85) and ƛ (254nm)
[b]Resolution (R), [c] mometasone furoate; [d] calcipotriol, [e] theoretical plates, [f]tailing factor and [g]retention time