

**A facile method for the large-scale synthesis of
6,7,4'-trihydroxyisoflavanone**

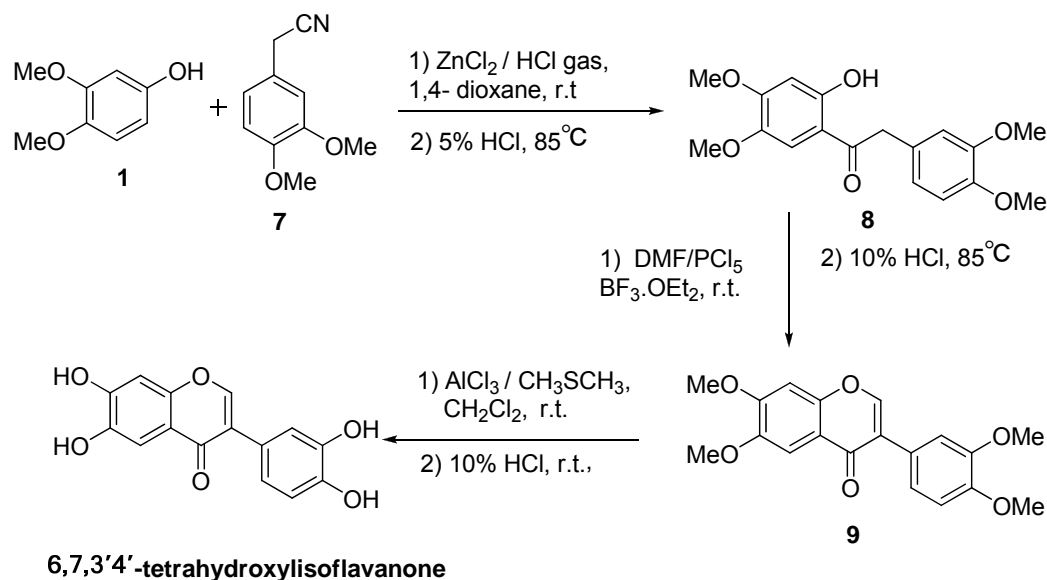
Jing Liu, Zhangyou Yang, Shenglin Luo, Yuhui Hao, Jiong Ren, Yongping Su, Rong Li *

Institute of Combined Injury, State Key Laboratory of Trauma, Burns and Combined Injury, Chongqing Engineering Research Center for Nanomedicine, College of Preventive Medicine, Third Military Medical University, 30, Gaotanyan Road, Chongqing 400038, China.

Contents:

- 1. Synthesis and characterization of 6,7,3',4'-tetrahydroxyisoflavanone**
- 2. Multi-factor experimental designs**
- 3. Spectra graphs for characterization of 6,7,4'-trihydroxyisoflavanone**
- 4. HPLC analysis of 6,7,4'-trihydroxyisoflavanone**
- 5. Spectra graphs for characterization of 6,7,3',4'-tetrahydroxyisoflavanone**

1. Synthesis and characterization of 6,7,3',4'-tetrahydroxyisoflavanone



Scheme S1. Large-scale synthesis of 6,7,3',4'-tetrahydroxyisoflavanone-an analog of 6,7,4'-trihydroxyisoflavanone with the same method

Synthesis of 3, 4-dimethoxyl-3',4'- dimethoxyl-deoxybenzoin(8)

Dry HCl gas was bubbled into a mixture of anhydrous ZnCl_2 (2 kg, 14.7 mol) and 1,4-dioxane (3 L) to saturation. After the reaction mixture was stirred for 6 hours at room temperature, 3,4-dimethoxyl benzyl cyanide (**7**) (2.64 kg, 14.9 mol) was added portionwise. After 6 hours, the 3, 4-dimethoxyphenol (**1**) (2 kg, 13 mol) was added portionwise. The mixture was then stirred at room temperature for 24 h. The rest procedure was consistent to that for 3, 4-dimethoxyl-4'-hydroxyl-deoxybenzoin (**3**), giving **8** (3.10 kg, yield 72%). Melting point: $136.9\text{--}137.7^\circ\text{C}$; ^1H NMR (400 MHz, DMSO) δ ppm: 12.467(1H, s), 7.428(1H, s), 6.929(1H, s), 6.885(1H, d, $J=8.0\text{Hz}$), 6.801(1H, s, $J=8.0\text{Hz}$), 6.542(1H, s), 4.27(2H, s), 3.813(3H, s), 3.761(3H,

s); ,3.711(3H, s), 3.682(3H, s), ^{13}C NMR (100 MHz, DMSO) δ ppm:44.193,55.393, 55.431,55.930, 56.166, 100.365, 110.658, 111.847, 112.296, 113.344, 121.510, 127.375, 141.623, 147.571. 148.570, 156.339, 158.805, 202.238.

Synthesis of 6,7,3',4'-tetramethoxyl isoflavanone(9)

A solution: $\text{BF}_3\text{Et}_2\text{O}$ (5.6 L) was added dropwise into a mixture of **(8)** (2 kg, 6 mol) and DMF (12 L) under 0~10°C with stirring. **B** solution: in another flask, DMF (18 L) was cooled to 0~10°C and PCl_5 (2.58 kg, 12.4 mol) was added portionwise, stirred at 55°C for 45 min. Then **B** solution was added into **A** solution slowly. The rest procedure was consistent to that for 6, 7-dimethoxyl-4'-hydroxylisoflavanone(**4**), giving **9** (1.79 kg, yield 87%). Melting point: 186.6-187.7°C, ^1H NMR (400 MHz, DMSO) δ ppm: 8.457(1H, s), 7.445(1H, s), 7.224(1H, s), 7.214(1H, s), 7.140(1H, d, $J=8.0\text{Hz}$), 7.016 (1H, d, $J=8.0\text{Hz}$), 3.919 (3H, s), 3.864(3H, s), 3.780(3H, s), 3.78(3H, s); ^{13}C NMR (100MHz, DMSO) δ ppm: 55.454, 55.503, 55.717, 56.345, 100.259, 104.062, 111.523, 112.681, 116.896, 121.122, 122.878, 124.563, 147.385, 148.234, 148.535, 151.630, 153.276, 154.198, 174.223.

Synthesis of 6,7,3',4'-tetrahydroxyisoflavanone

Dimethyl sulfide (2.1L, 30 mol) was added dropwise into a mixture of AlCl_3 (7 kg, 52.6 mol) and CH_2Cl_2 (24 L) under 10°C with strongly stirring. The reaction was added **9** (2 kg, 6.7 mol) portionwise and stirred at room temperature (10~30°C) for 12h.

The rest procedure was consistent to that for **6**,

7-dimethoxyl-4'-hydroxyisoflavanone(**4**), giving 6,7,3',4'-tetrahydroxyisoflavanone (1.554 kg, yield 93%); Melting point: 294.3-296.4°C; ^1H NMR (400 MHz,DMSO) δ ppm: 8.20(1H, s), 7.373(1H, s), 7.011(1H,s), 6.890 (1H, s), 6.770(2H, d, J=8.0Hz); ^{13}C NMR(100MHz, DMSO) δ ppm: 102.694, 108.074, 115.200, 115.269, 116.557, 116.614, 119.861, 122.852, 123.404, 144.542, 144.908, 150.780, 152.011, 152.361, 174.402; HRMS (ESI) m/z: $[\text{M}+\text{H}]^+$,calcd for $\text{C}_{15}\text{H}_{10}\text{NaO}_5$: 287.0556, found 287.0546.

2. Multi-factor experimental designs

Multi-factor experimental designs including reactant ratio between compound **1** and **2**, reaction temperature and time for the modified Hoesch reaction, were conducted to simplify the practical operation.

Table s1. Multi-factor experimental designs in Hoesch reaction

Entry	Ratio (Compd. 1:2)	Hoesch reaction Temperature(□)	Time (h)	Hydrolysis reaction Temperature(□)	Yield (%)
1	1:1	r.t.	15	85	65%
2	1:1.2	r.t.	15	85	79%
3	1:1.5	r.t.	15	85	80%
4	1:1.2	0	15	85	55%
5	1:1.2	10	15	85	60%
6	1:1.2	24	15	85	83%
7	1:1.2	r.t.	10	85	72%
8	1:1.2	r.t.	20	85	85%
9	1:1.2	r.t.	40	85	86%

As shown in **Table S1**, 1.2 of reactant ratio between compound **1** and **2**, room temperature and 20h reaction time, were evaluated as the optimal and simplified reaction conditions for the Hoesch reaction.

3. Spectra graphs for characterization of 6,7,4'-trihydroxyisoflavanone

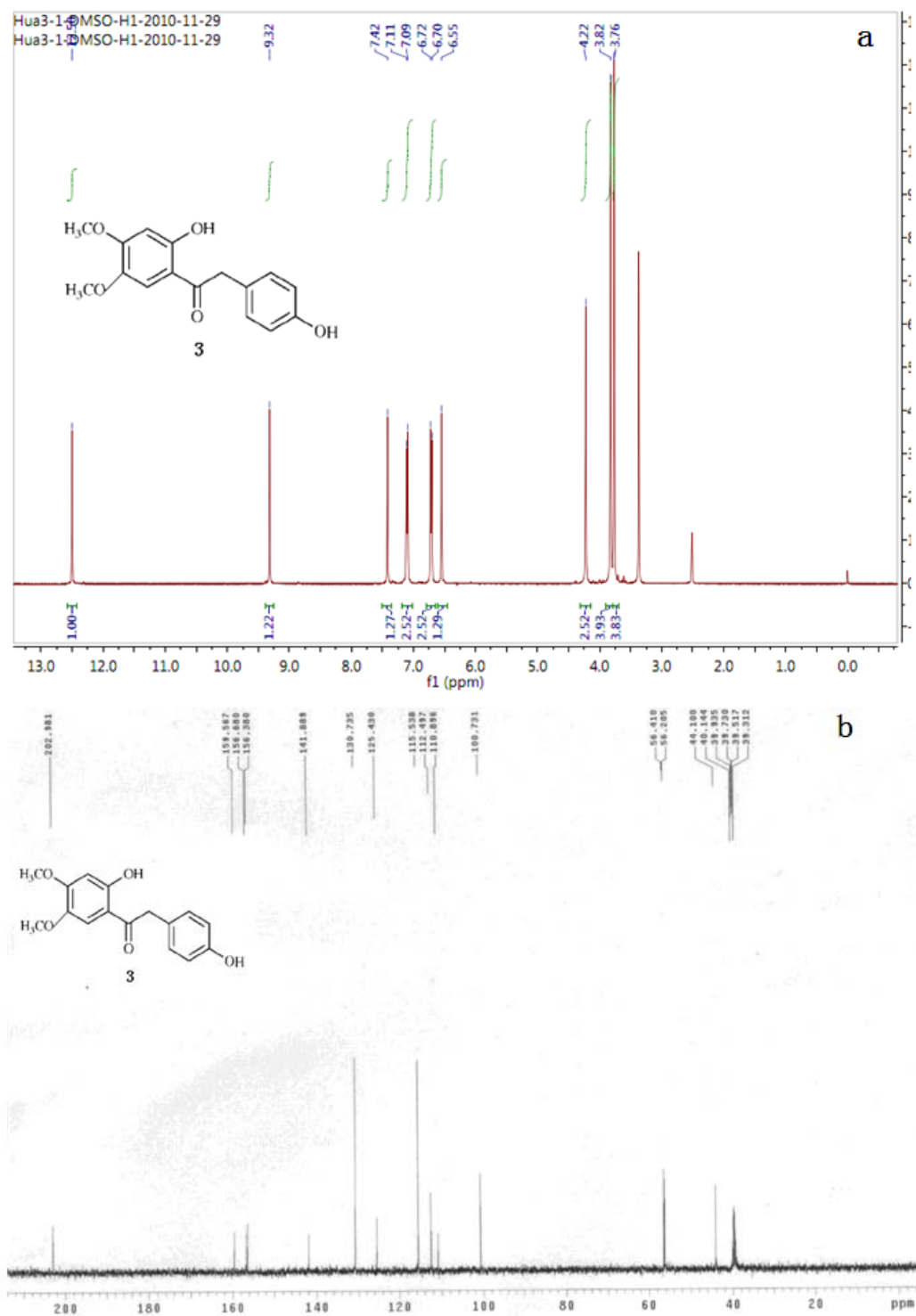


Fig.S1. $^1\text{H-NMR}$ (a) and $^{13}\text{C-NMR}$ (b) of 3, 4-dimethoxyl-4'-hydroxyl-deoxybenzoin(3)

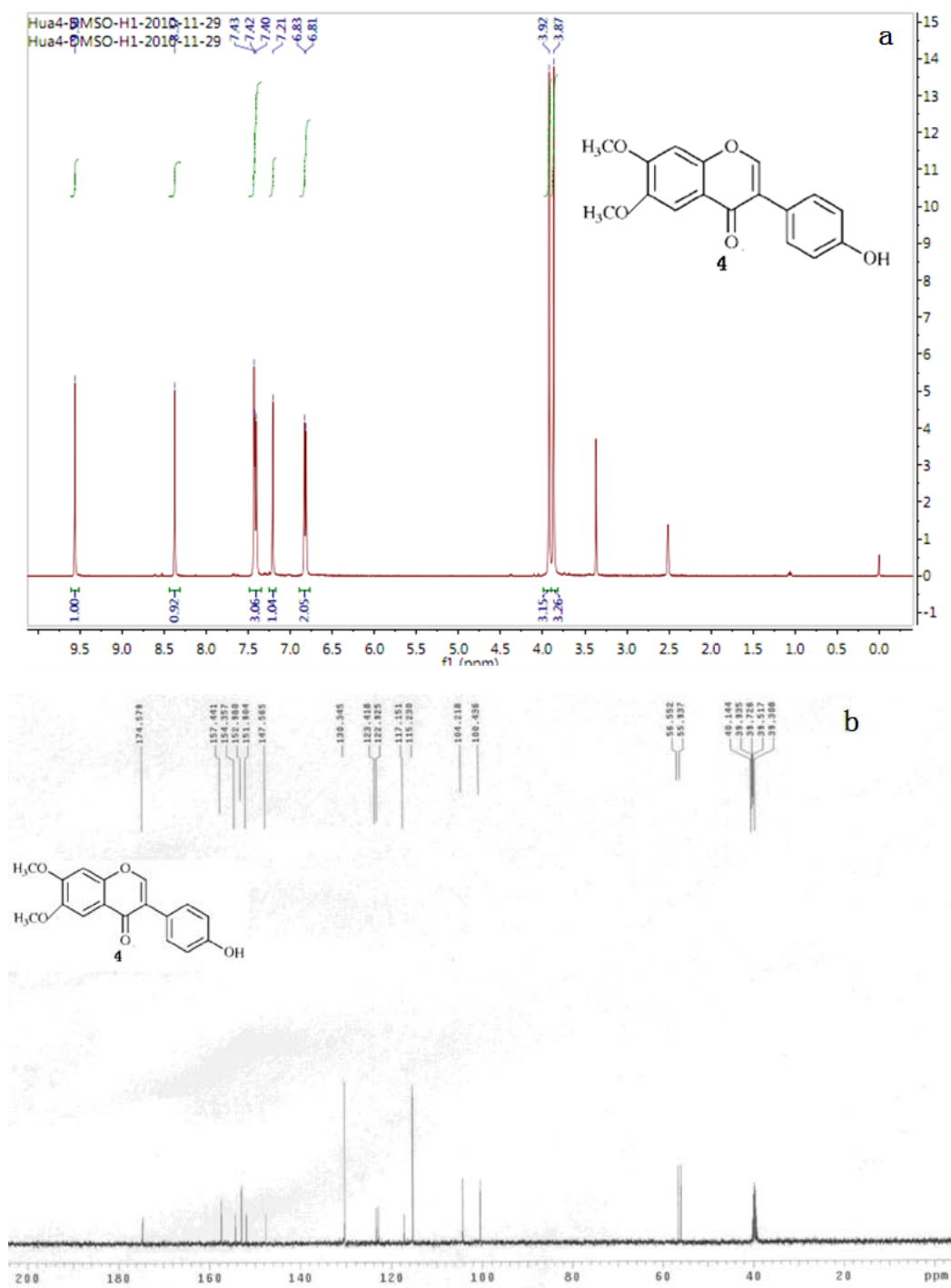


Fig.S2. ^1H NMR(a) and ^{13}C NMR(b) of 6, 7-dimethoxy-4'-hydroxyisoflavone(4)

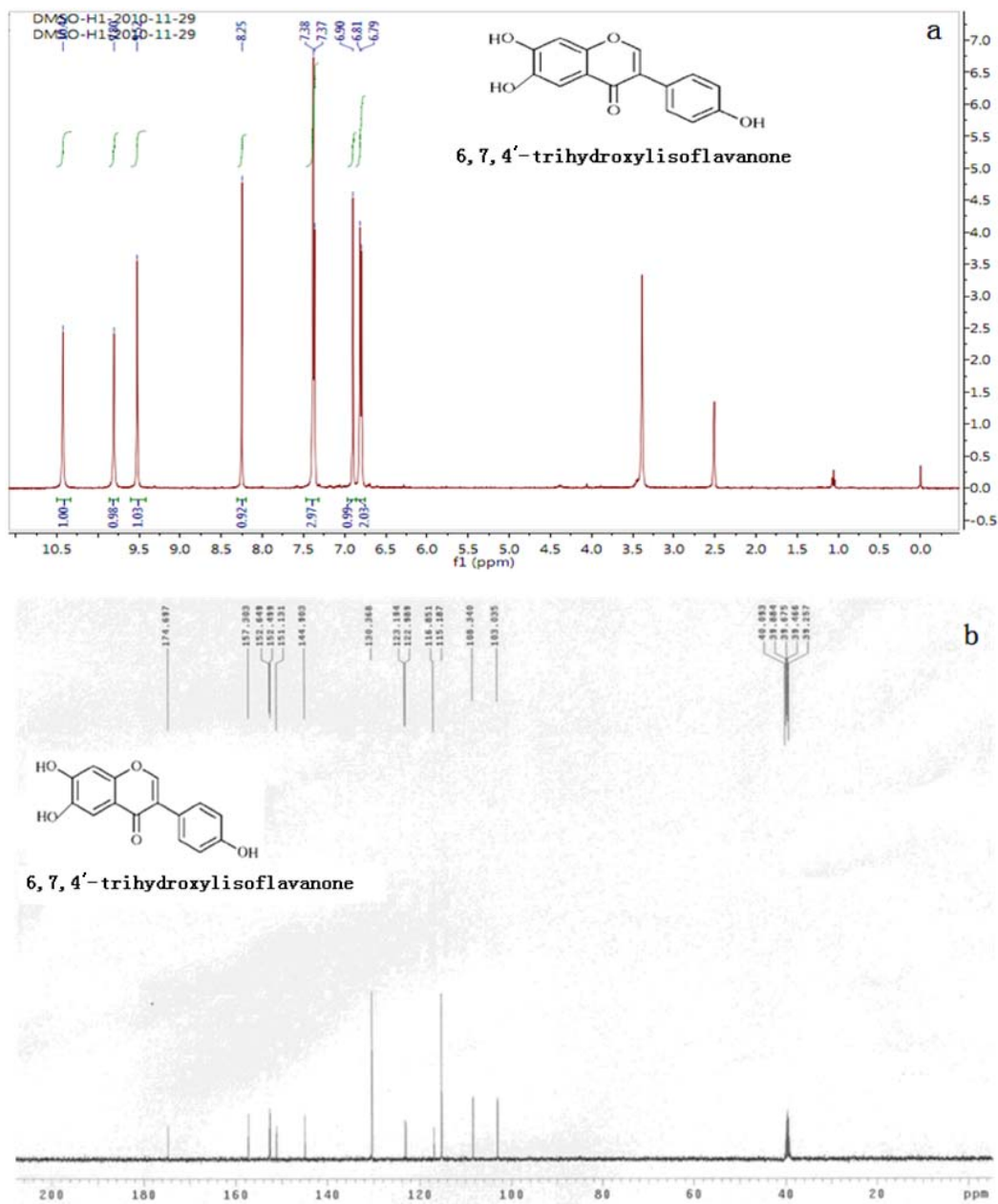
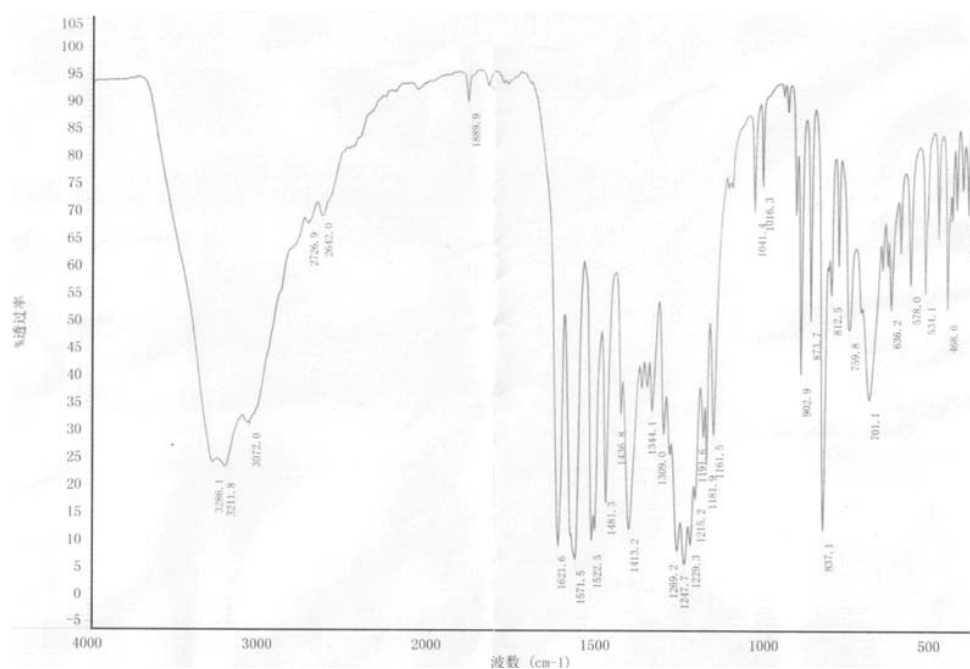
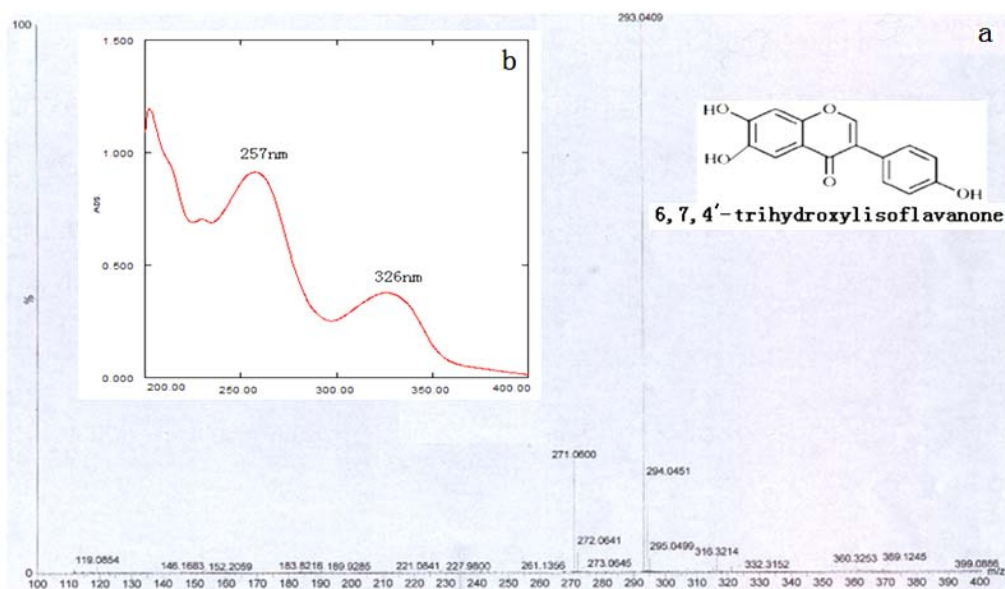


Fig.S3. ¹H NMR(a) and ¹³C NMR(b) of 6,7,4'-trihydroxyisoflavanone



中国科学院成都分院分析测试中心
分析测试结果报告单

送样单位	四川大学	送样时间	2011.4.6						
样品名称 编 号	T2								
分析测试 要 求	C、H 含量测定								
分析仪器	意大利 CARLO ERBA 1106 元素分析仪								
分 析 测 试 结 果	<table style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>C %</th> <th>H %</th> </tr> </thead> <tbody> <tr> <td>66.42</td> <td>3.77</td> </tr> <tr> <td>66.56</td> <td>3.76</td> </tr> </tbody> </table>			C %	H %	66.42	3.77	66.56	3.76
C %	H %								
66.42	3.77								
66.56	3.76								
分 析 人	 [Signature]	分 析 时 间	2011.4.8						
备 注	本结果只对来样负责								

单位盖章

2011 年 4 月 8 日

Fig.S6. Elemental analysis of 6,7,4'- trihydroxyisoflavanone

4. HPLC analysis of 6,7,4'-tetrahydroxyisoflavanone

Shimadzu CLASS-VP V6.14 SP1

Area % Report

Page 1 of 3

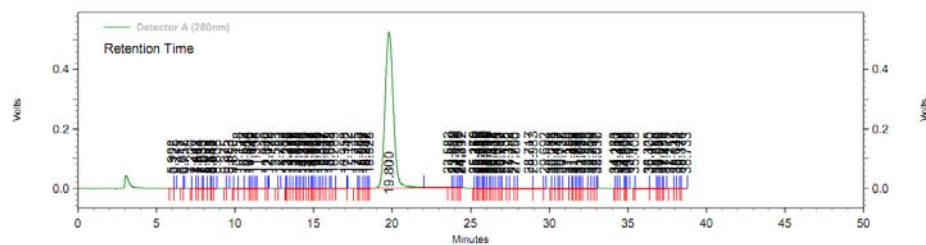
Method Name: C:\CLASS-VP\Methods\zjy.met

Data Name: T2-一毫克每毫升

User: System

Acquired: 2011-4-14

Printed: 2011-4-15



Detector A (260nm)					
Pk #	Retention Time	Area	Area %	Height	Height %
1	5.992	918	0.005	91	0.017
2	6.125	265	0.001	59	0.011
3	6.617	380	0.002	55	0.010
4	6.758	164	0.001	63	0.012
5	7.200	100	0.001	52	0.010
6	7.442	520	0.003	56	0.010
7	7.583	226	0.001	44	0.008
8	7.850	522	0.003	72	0.013
9	7.933	170	0.001	51	0.010
10	8.092	794	0.004	74	0.014
11	8.383	572	0.003	73	0.014
12	8.458	186	0.001	68	0.013
13	8.542	312	0.002	64	0.012
14	8.808	311	0.002	48	0.009
15	9.375	236	0.001	38	0.007
16	9.583	177	0.001	45	0.008
17	9.850	135	0.001	53	0.010
18	10.158	309	0.002	46	0.009
19	10.542	783	0.004	82	0.015
20	10.808	996	0.005	77	0.014
21	10.900	428	0.002	96	0.018
22	11.042	448	0.002	77	0.014
23	11.142	490	0.003	73	0.014
24	11.308	200	0.001	51	0.010
25	11.900	1433	0.007	79	0.015
26	12.042	372	0.002	70	0.013
27	12.125	88	0.000	36	0.007
28	12.583	241	0.001	49	0.009
29	12.783	330	0.002	47	0.009
30	13.208	51	0.000	33	0.006
31	13.292	94	0.000	45	0.008
32	13.375	497	0.003	74	0.014
33	13.617	913	0.005	115	0.021
34	13.725	616	0.003	84	0.016
35	13.883	178	0.001	58	0.011
36	14.008	232	0.001	45	0.008

37	14.158	252	0.001	50	0.009
38	14.283	284	0.001	65	0.012
39	14.375	293	0.002	66	0.012
40	14.617	285	0.001	66	0.012
41	14.708	312	0.002	53	0.010
42	14.867	191	0.001	49	0.009
43	14.983	172	0.001	57	0.011
44	15.058	329	0.002	73	0.014
45	15.183	259	0.001	39	0.007
46	15.392	318	0.002	62	0.012
47	15.517	298	0.002	65	0.012
48	15.667	322	0.002	48	0.009
49	15.942	391	0.002	55	0.010
50	16.083	95	0.000	42	0.008
51	16.283	407	0.002	51	0.010
52	16.958	1089	0.006	44	0.008
53	17.142	62	0.000	41	0.008
54	17.725	430	0.002	56	0.010
55	17.883	289	0.001	67	0.013
56	18.092	662	0.003	83	0.015
57	18.267	661	0.003	75	0.014
58	18.342	462	0.002	76	0.014
59	18.525	364	0.002	82	0.015
60	19.800	18852497	99.507	525792	98.187
61	23.583	3413	0.018	302	0.056
62	23.850	1037	0.005	164	0.031
63	23.967	992	0.005	114	0.021
64	24.200	509	0.003	90	0.017
65	24.317	200	0.001	57	0.011
66	24.392	91	0.000	39	0.007
67	25.175	80	0.000	33	0.006
68	25.250	218	0.001	36	0.007
69	25.417	122	0.001	44	0.008
70	25.533	172	0.001	52	0.010
71	25.625	362	0.002	77	0.014
72	25.767	189	0.001	62	0.012
73	25.850	121	0.001	46	0.009
74	25.950	319	0.002	60	0.011
75	26.058	320	0.002	70	0.013
76	26.217	231	0.001	54	0.010
77	26.317	255	0.001	57	0.011
78	26.433	336	0.002	56	0.010
79	26.608	380	0.002	42	0.008
80	26.783	125	0.001	38	0.007
81	26.917	170	0.001	50	0.009
82	27.158	530	0.003	64	0.012
83	27.392	453	0.002	63	0.012
84	27.708	1340	0.007	105	0.020
85	27.850	934	0.005	106	0.020
86	28.717	15227	0.079	423	0.079
87	28.983	7983	0.041	384	0.072
88	29.692	180	0.001	31	0.006
89	30.083	123	0.001	38	0.007
90	30.275	316	0.002	48	0.009

91	30.433	463	0.002	65	0.012
92	30.617	257	0.001	75	0.014
93	30.758	539	0.003	82	0.015
94	31.150	1972	0.010	125	0.023
95	31.350	897	0.005	108	0.020
96	31.492	344	0.002	103	0.019
97	31.558	672	0.003	87	0.016
98	31.708	357	0.002	89	0.017
99	31.842	573	0.003	95	0.018
100	31.950	155	0.001	68	0.013
101	32.025	444	0.002	67	0.013
102	32.325	1592	0.008	108	0.020
103	32.550	1210	0.006	111	0.021
104	32.708	1072	0.006	115	0.021
105	32.917	507	0.003	82	0.015
106	33.050	100	0.001	51	0.010
107	34.133	127	0.001	37	0.007
108	34.250	220	0.001	51	0.010
109	34.417	251	0.001	46	0.009
110	34.692	471	0.002	60	0.011
111	34.800	167	0.001	62	0.012
112	34.892	139	0.001	58	0.011
113	35.025	162	0.001	41	0.008
114	35.408	197	0.001	36	0.007
115	36.325	11799	0.061	380	0.071
116	36.400	6808	0.035	352	0.066
117	36.850	683	0.004	167	0.031
118	36.958	657	0.003	120	0.022
119	37.075	594	0.003	92	0.017
120	37.233	202	0.001	59	0.011
121	37.425	373	0.002	43	0.008
122	37.717	360	0.002	39	0.007
123	38.033	233	0.001	43	0.008
124	38.142	365	0.002	63	0.012
125	38.375	236	0.001	70	0.013
126	38.733	585	0.003	44	0.008

Totals		18947922	100.000	535499	100.000
--------	--	----------	---------	--------	---------

Fig.S7. HPLC analysis of 6,7,4'-trihydroxyisoflavanone

a

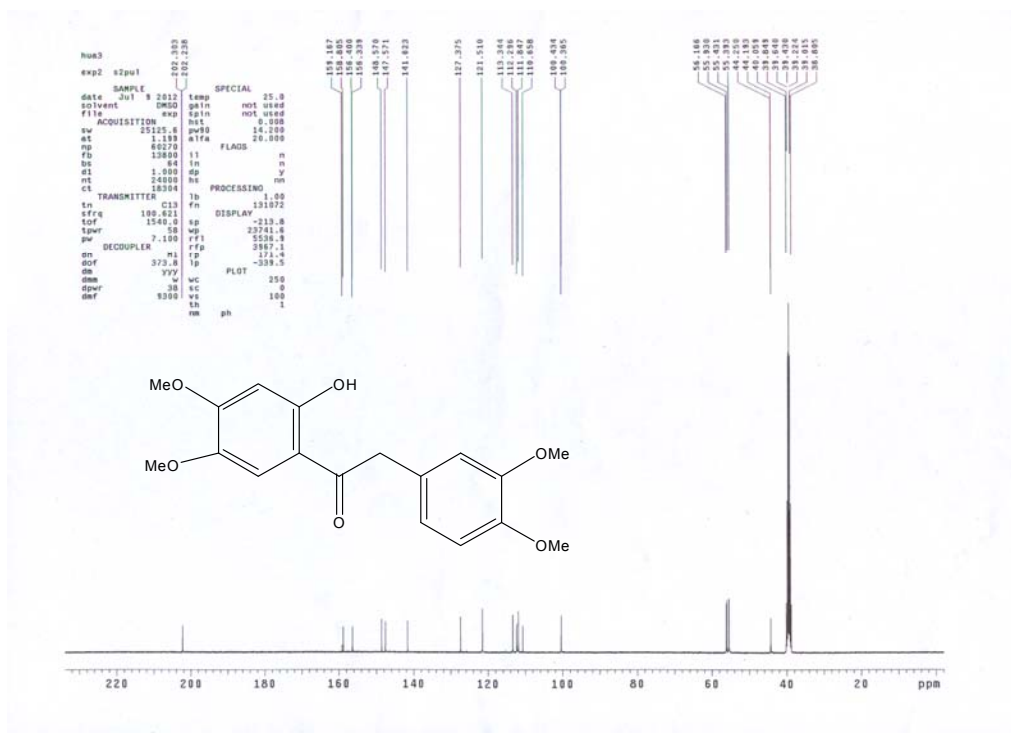


Fig.S8. ^1H -NMR(a) and ^{13}C -NMR(b) of 3,4-dimethoxyl-3',4'- dimethoxyl-deoxybenzoin (**8**)

COc1ccc(cc1C(=O)Oc2cc(OC)c(OC)cc2)C(=O)O

Name: 4-(3,4,5-trimethoxyphenyl)-3-methoxybenzoic acid
 MW: 284.30
 SMILES: COc1ccc(cc1C(=O)Oc2cc(OC)c(OC)cc2)C(=O)O

1H NMR (400 MHz, DMSO-d6):
 11.80 (s, 1H, COOH), 7.80 (d, 2H, ArH), 7.60 (d, 2H, ArH), 7.40 (d, 2H, ArH), 7.20 (d, 2H, ArH), 7.00 (d, 2H, ArH), 6.80 (d, 2H, ArH), 6.60 (d, 2H, ArH), 6.40 (d, 2H, ArH), 6.20 (d, 2H, ArH), 6.00 (d, 2H, ArH), 5.80 (d, 2H, ArH), 5.60 (d, 2H, ArH), 5.40 (d, 2H, ArH), 5.20 (d, 2H, ArH), 5.00 (d, 2H, ArH), 4.80 (d, 2H, ArH), 4.60 (d, 2H, ArH), 4.40 (d, 2H, ArH), 4.20 (d, 2H, ArH), 4.00 (d, 2H, ArH), 3.80 (d, 2H, ArH), 3.60 (d, 2H, ArH), 3.40 (d, 2H, ArH), 3.20 (d, 2H, ArH), 3.00 (d, 2H, ArH), 2.80 (d, 2H, ArH), 2.60 (d, 2H, ArH), 2.40 (d, 2H, ArH), 2.20 (d, 2H, ArH), 2.00 (d, 2H, ArH), 1.80 (d, 2H, ArH), 1.60 (d, 2H, ArH), 1.40 (d, 2H, ArH), 1.20 (d, 2H, ArH), 1.00 (d, 2H, ArH), 0.80 (d, 2H, ArH), 0.60 (d, 2H, ArH), 0.40 (d, 2H, ArH), 0.20 (d, 2H, ArH), 0.00 (d, 2H, ArH).

13C NMR (100 MHz, DMSO-d6):
 165.0, 155.0, 154.0, 153.0, 152.0, 151.0, 150.0, 149.0, 148.0, 147.0, 146.0, 145.0, 144.0, 143.0, 142.0, 141.0, 140.0, 139.0, 138.0, 137.0, 136.0, 135.0, 134.0, 133.0, 132.0, 131.0, 130.0, 129.0, 128.0, 127.0, 126.0, 125.0, 124.0, 123.0, 122.0, 121.0, 120.0, 119.0, 118.0, 117.0, 116.0, 115.0, 114.0, 113.0, 112.0, 111.0, 110.0, 109.0, 108.0, 107.0, 106.0, 105.0, 104.0, 103.0, 102.0, 101.0, 100.0, 99.0, 98.0, 97.0, 96.0, 95.0, 94.0, 93.0, 92.0, 91.0, 90.0, 89.0, 88.0, 87.0, 86.0, 85.0, 84.0, 83.0, 82.0, 81.0, 80.0, 79.0, 78.0, 77.0, 76.0, 75.0, 74.0, 73.0, 72.0, 71.0, 70.0, 69.0, 68.0, 67.0, 66.0, 65.0, 64.0, 63.0, 62.0, 61.0, 60.0, 59.0, 58.0, 57.0, 56.0, 55.0, 54.0, 53.0, 52.0, 51.0, 50.0, 49.0, 48.0, 47.0, 46.0, 45.0, 44.0, 43.0, 42.0, 41.0, 40.0, 39.0, 38.0, 37.0, 36.0, 35.0, 34.0, 33.0, 32.0, 31.0, 30.0, 29.0, 28.0, 27.0, 26.0, 25.0, 24.0, 23.0, 22.0, 21.0, 20.0, 19.0, 18.0, 17.0, 16.0, 15.0, 14.0, 13.0, 12.0, 11.0, 10.0, 9.0, 8.0, 7.0, 6.0, 5.0, 4.0, 3.0, 2.0, 1.0, 0.0.

Hua-4
exp2 v2pu1

SAMPLE
date Jul 24 2012 temp SPECIAL 25.0
solvent DMSO gain not used
file exp spin not used
ACQUISITION
sw 25125.4 pw90 14.200
at 1.151 alpha 0.100
rg 80270 ii FLAGS 20.000
fb 13800 ii
bs 64 in
d1 1.000 dp
nt 30000 hs
ct 7456 PROCESSING
tx TRANSMITTER lb 1.90
tn C13 fn 131071
tfrq 100.621 rn DISPLAY -50.0
told 1540.0 sp 5537.1
tpwr 7.100 wp 23439.1
DECOUPLER rfp 3967.1
dn 81 rf 154.1
dor 373.8 lb -220.1
dm yyy
dm w vc
dprf 38 cc
dprf 9300 vs 241
dm ph 4

154.188
153.276
152.850
150.535
148.234
147.385
126.563
125.849
125.372
118.486
112.681
111.523
104.882
100.259
55.395
55.217
55.103
55.054
40.000
39.995
39.940
39.820
39.611
39.405

154
153
152
150
148
147
126
125
125
118
112
111
104
100
55
55
55
55
40
39
39
39
39
39

MeO

MeO

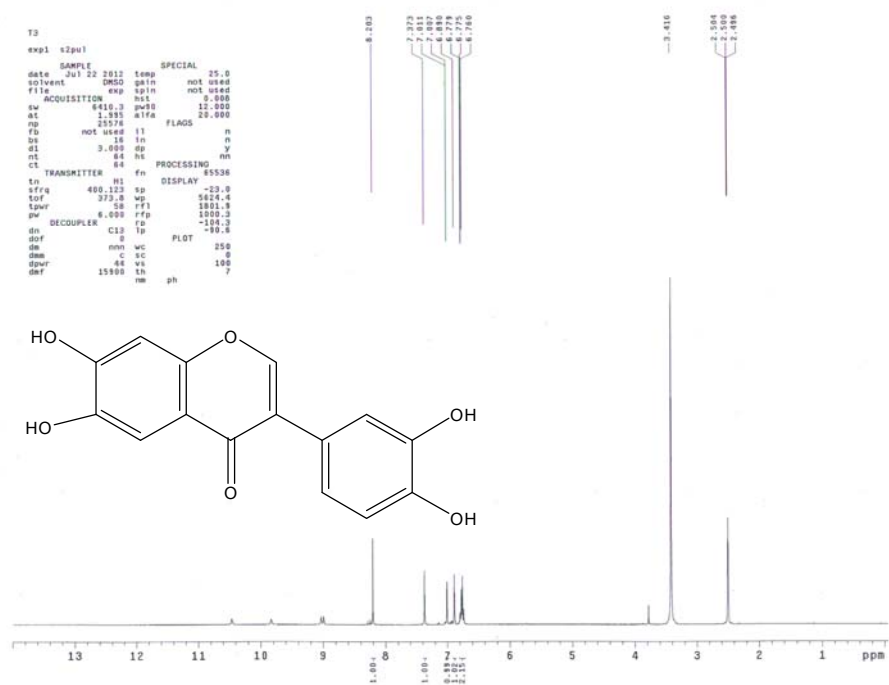
Me

Me

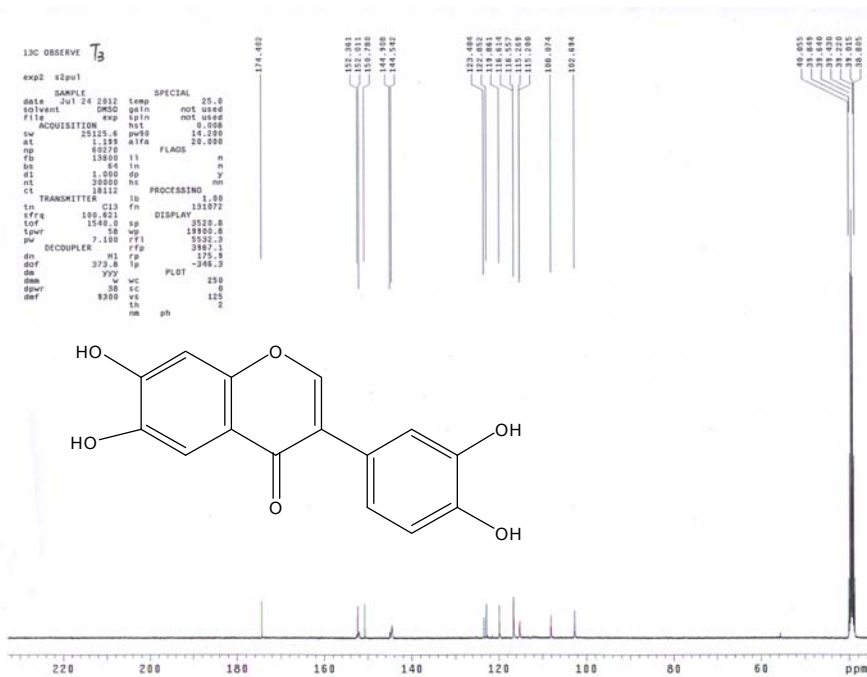
ppm

Fig.S9. ^1H -NMR(a) and ^{13}C -NMR(b) of 6,7,3',4'-tetramethoxyl isoflavanone(**9**)

a



b



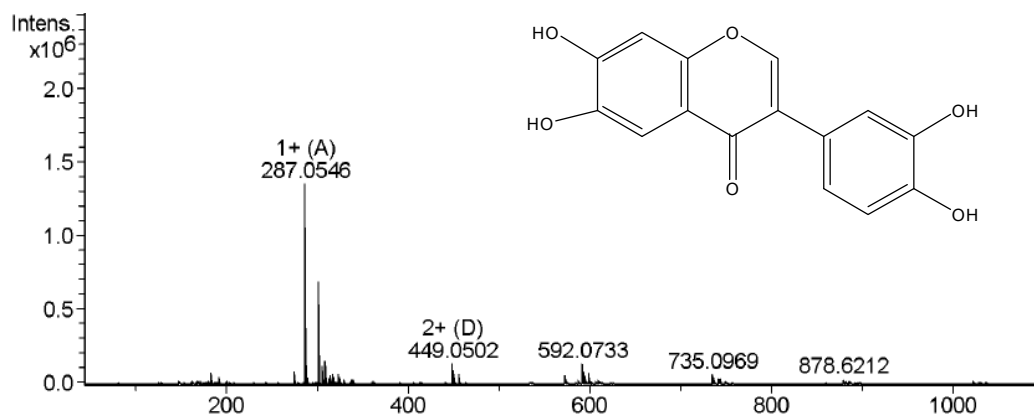


Fig.S11.HRMS of 6,7,3',4'-tetrahydroxyisoflavanone