

Table S1. The concentration of cinobufagin and its metabolites ($\mu\text{g/L}$)

Time (h)	Cinobufagin			3-epi-cinobufagin			Desacetylcinobufagin			Hydroxyl-desacetylcinobufagin (0.94 min)			Hydroxyl-desacetylcinobufagin (1.54 min)			Hydroxyl-desacetylcinobufagin (1.84 min)			
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
0.083	51.1	43.2	43.2	0.06	0.04	0.02	5.46	6.65	1.86	0	0	0	0	0	0	0	0	0	0
0.25	14.6	10.2	12.8	2.40	5.74	2.39	142.02	240.70	182.59	0.88	0.82	0.58	0.86	1.79	1.29	0.10	0.41	0.10	
0.5	8.32	4.8	4.81	6.91	8.81	4.79	548.83	661.99	638.34	11.96	12.63	11.68	4.52	6.11	8.91	3.56	3.27	2.96	
0.75	4.64	11.5	3.55	7.19	4.79	7.49	731.19	749.82	837.66	22.78	23.54	28.95	6.00	9.11	11.24	8.13	7.29	6.72	
1	6.19	5.34	4.98	4.18	8.91	6.82	657.05	905.23	1131.58	24.58	27.76	35.97	6.16	10.47	10.13	9.37	9.28	8.57	
2	4.53	10.6	5.29	1.33	7.56	8.00	334.40	918.74	1337.66	12.70	33.61	58.95	3.76	10.23	12.86	9.31	16.31	20.60	
4	3.74	3.09	2.87	1.45	8.14	5.94	99.93	331.58	959.28	2.86	12.76	49.15	1.72	5.09	11.61	6.53	14.82	31.82	
6	1.86	2.05	1.12	1.12	3.01	2.29	70.67	192.05	506.58	1.33	6.28	20.97	1.11	3.54	6.99	4.28	12.63	27.02	
8	3.5	1.07	5.59	2.84	1.61	1.46	164.06	80.91	104.55	3.56	2.30	5.30	1.53	1.75	2.72	5.64	7.66	13.95	
10	2.61	1.63	0.24	0.82	0.61	0.40	50.83	26.78	8.61	1.40	0.61	0.91	1.16	0.75	0.79	3.92	3.20	5.20	

Table S2. Pharmacokinetic parameters of metabolites of cinobufagin after a single intragastric administration with 20 mg/kg cinobufagin to rats (n = 3, mean \pm SD)

Metabolite	t _{1/2} (h)	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (ng/mL*h)	MRT _{0-t} (h)
3-epi-cinobufagin	2.83 \pm 0.29	6.84 \pm 2.01	1.25 \pm 0.66	33.40 \pm 14.97	3.22 \pm 0.16
Hydroxyl-desacetylcinobufagin (m/z 417, 0.94 min)	1.33 \pm 0.20	35.08 \pm 23.16	1.67 \pm 0.58	146.46 \pm 108.71	2.79 \pm 0.53

Hydroxyl-desacetylcinobufagin (m/z 417, 1.54 min)	2.70 ± 1.78	8.95 ± 4.68	1.33 ± 0.58	48.10 ± 26.10	3.55 ± 0.20
Hydroxyl-desacetylcinobufagin (m/z 417, 1.84 min)	3.48 ± 2.83	17.72 ± 12.89	2.33 ± 1.53	118.50 ± 65.77	4.63 ± 0.20
Desacetylcinobufagin (m/z 401, 5.05 min)	2.93 ± 3.04	897.95 ± 237.35	1.58 ± 0.72	3952.88 ± 2167.49	3.10 ± 0.25
