

Figure S1.

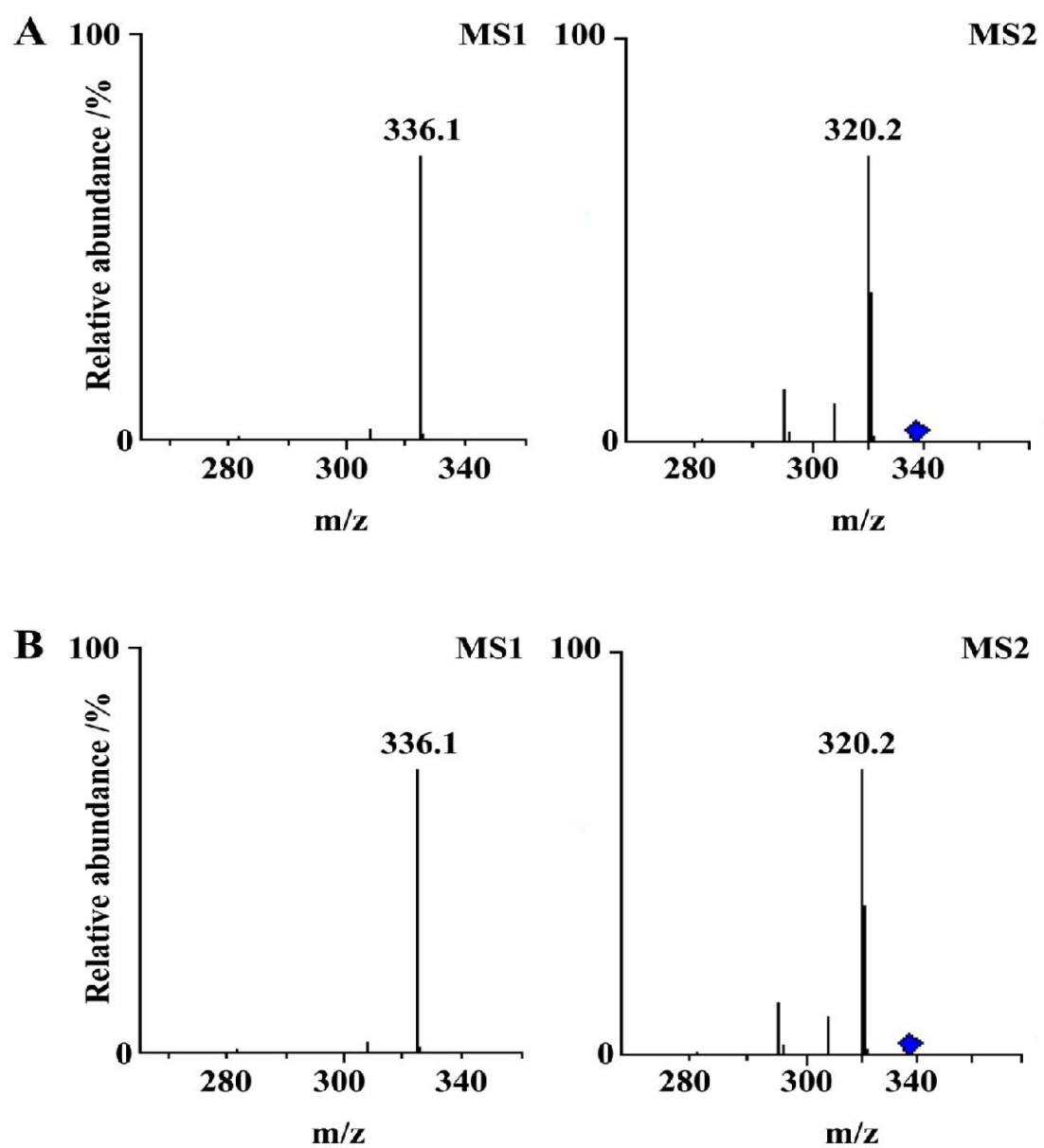


Figure S1 The secondary mass spectrometry of EPI (A) and berberine (B) in the positive mode.

Figure S2.

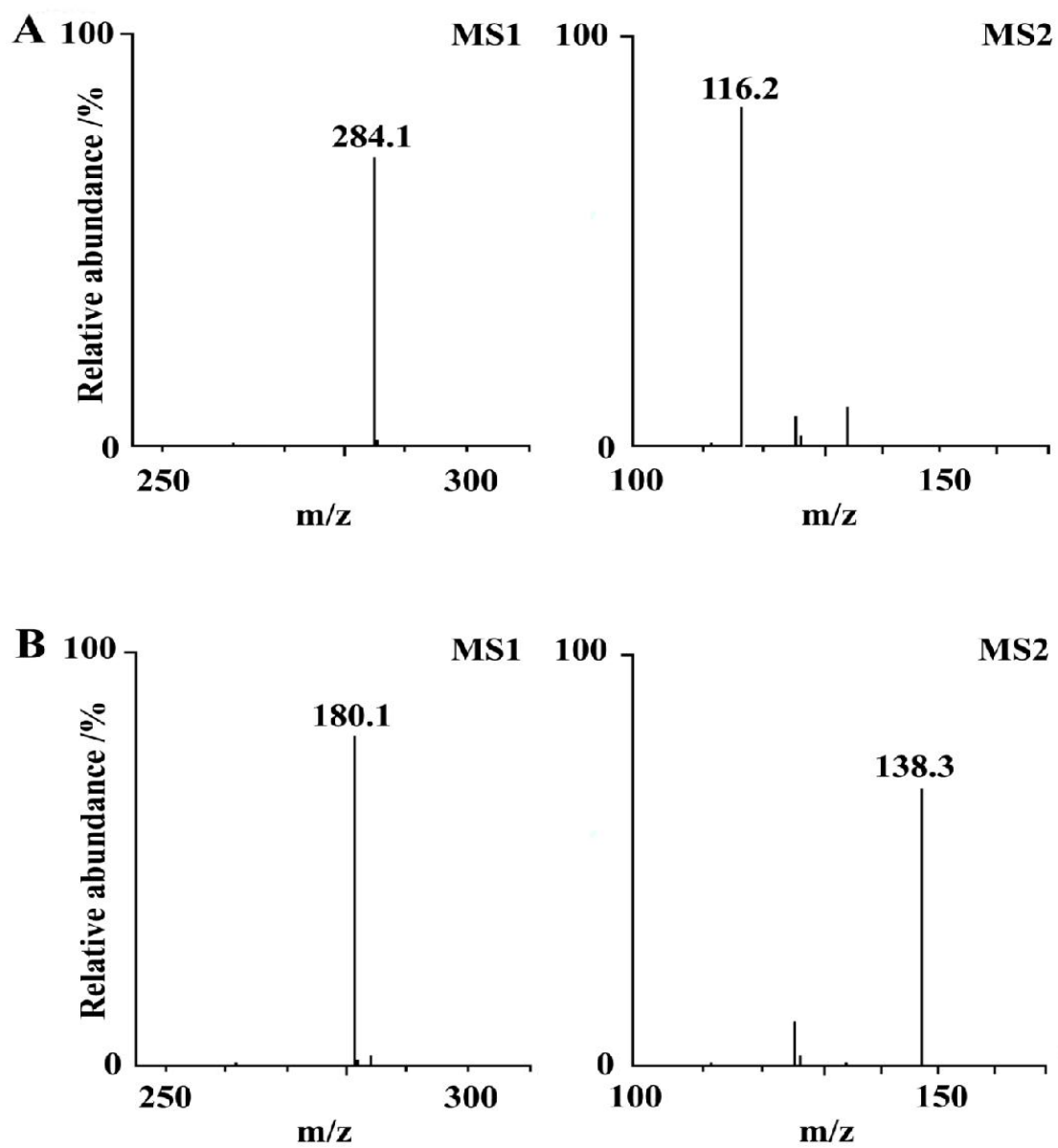


Figure S2 The secondary mass spectrometry of α -hydroxymetoprolin (A) and phenacetin (IS)

Figure S3.

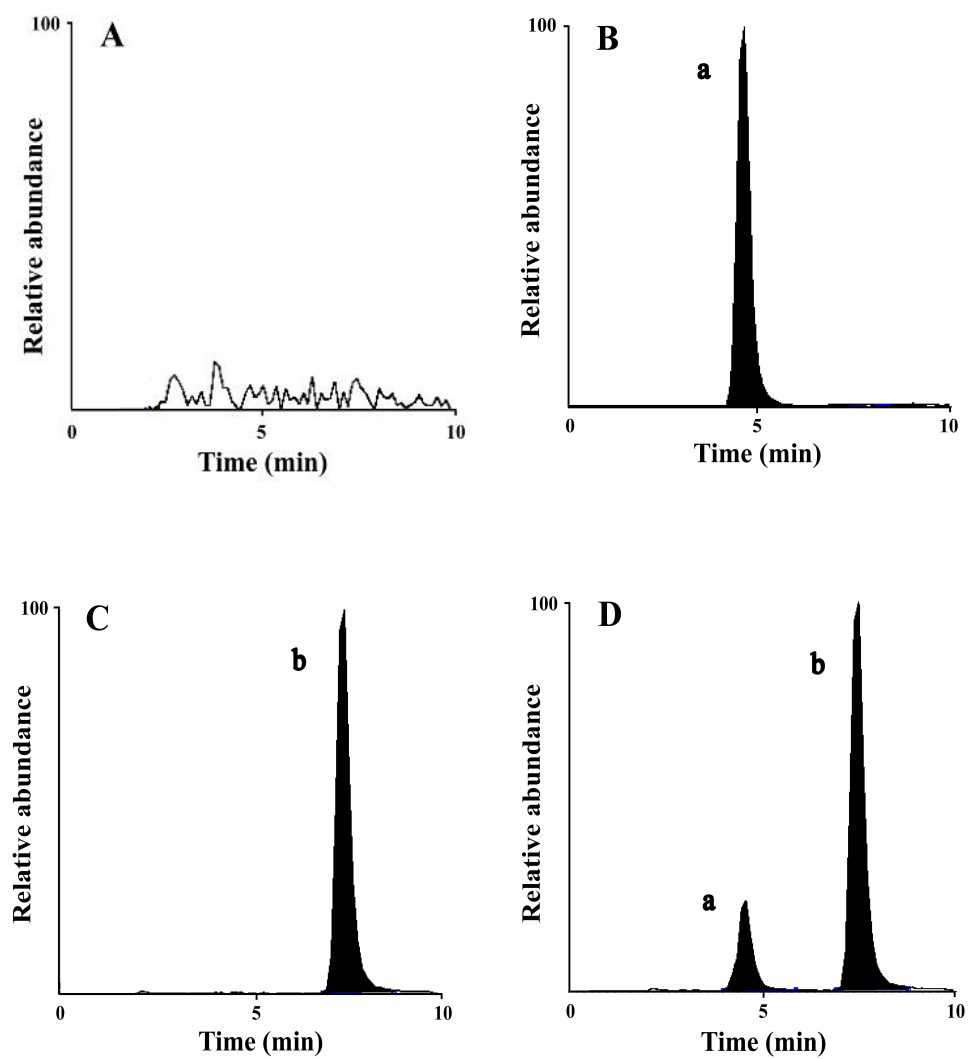


Figure S3. SRM chromatograms of plasma samples.

Notes: (A) Blank; (B) Blank spiked with EPI; (C) Blank spiked with IS; (D) Sample;

a. EPI; b. Berberine (IS).

Figure S4.

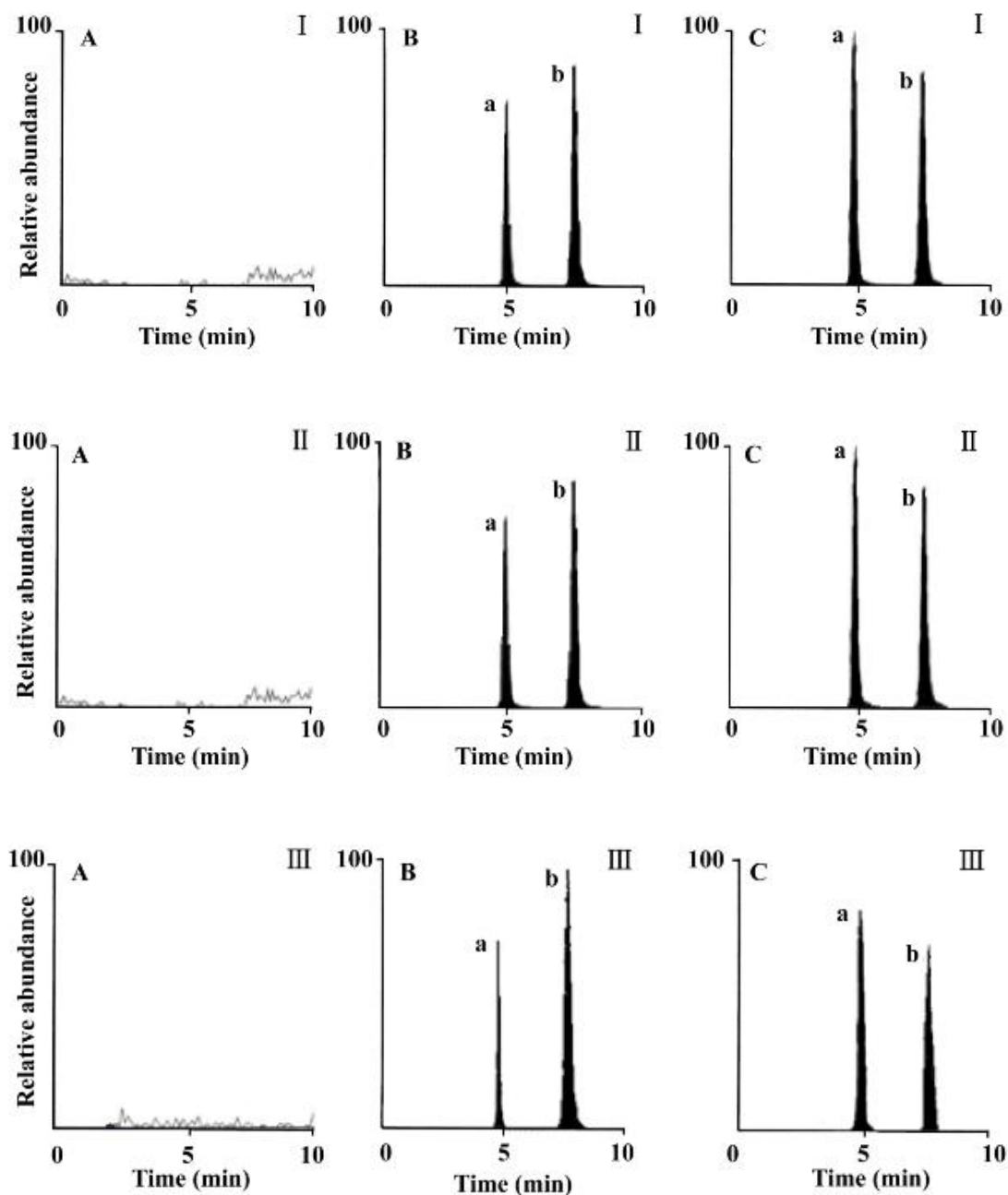


Figure S4 SRM chromatograms of rat biological samples. **Notes:** (A) Blank; (B) Blank spiked with EPI and IS; (C) Samples; a. EPI; b. Berberine (IS); I . Urine; II . Feces; III. Bile;

Figure S5.

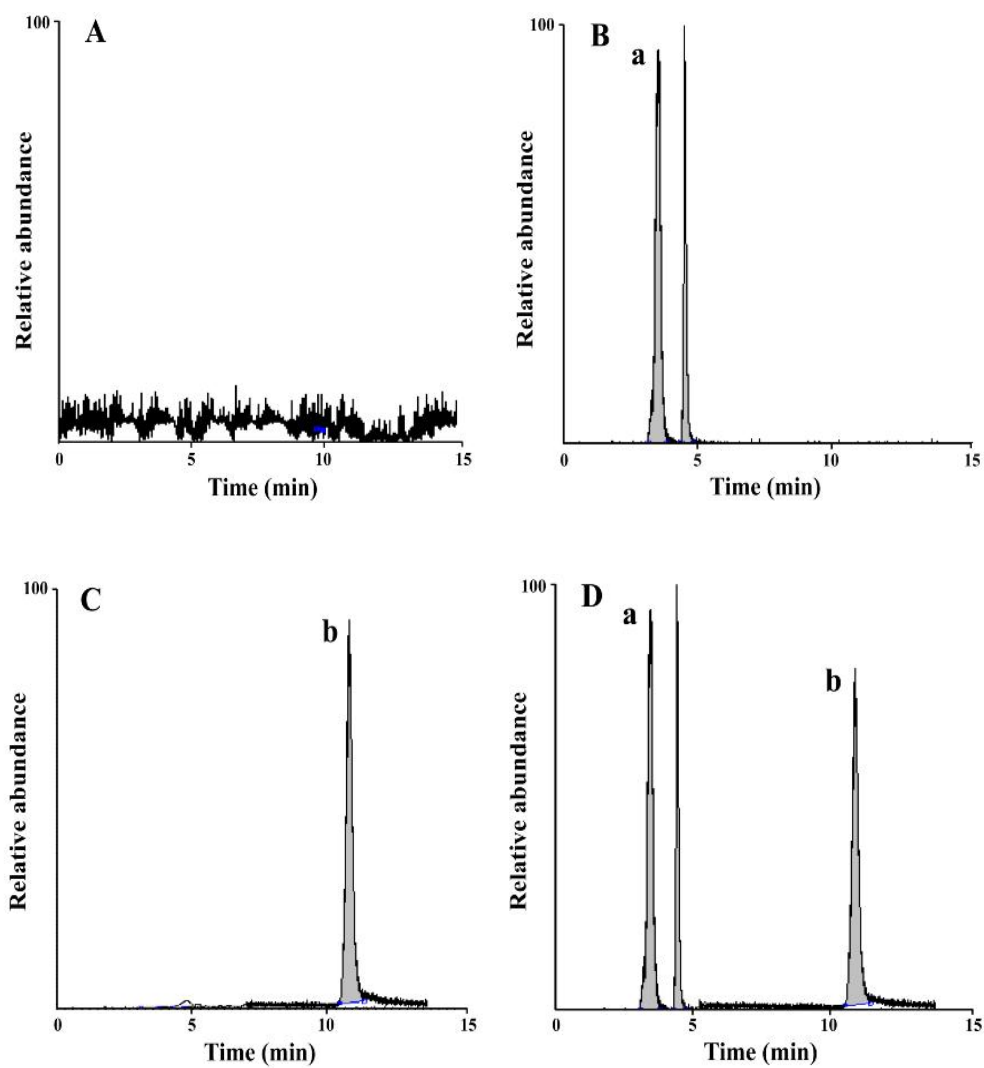


Figure S5. SRM chromatograms of α -hydroxymetoprol in HLM.

Notes: (A) Blank HLM; (B) Blank HLM spiked with α -hydroxymetoprol; (C) Blank HLM spiked with phenacetin; (D) Samples. a. α - Hydroxymetoprol(enantiomers); b. Phenacetin (IS).

Figure S6.

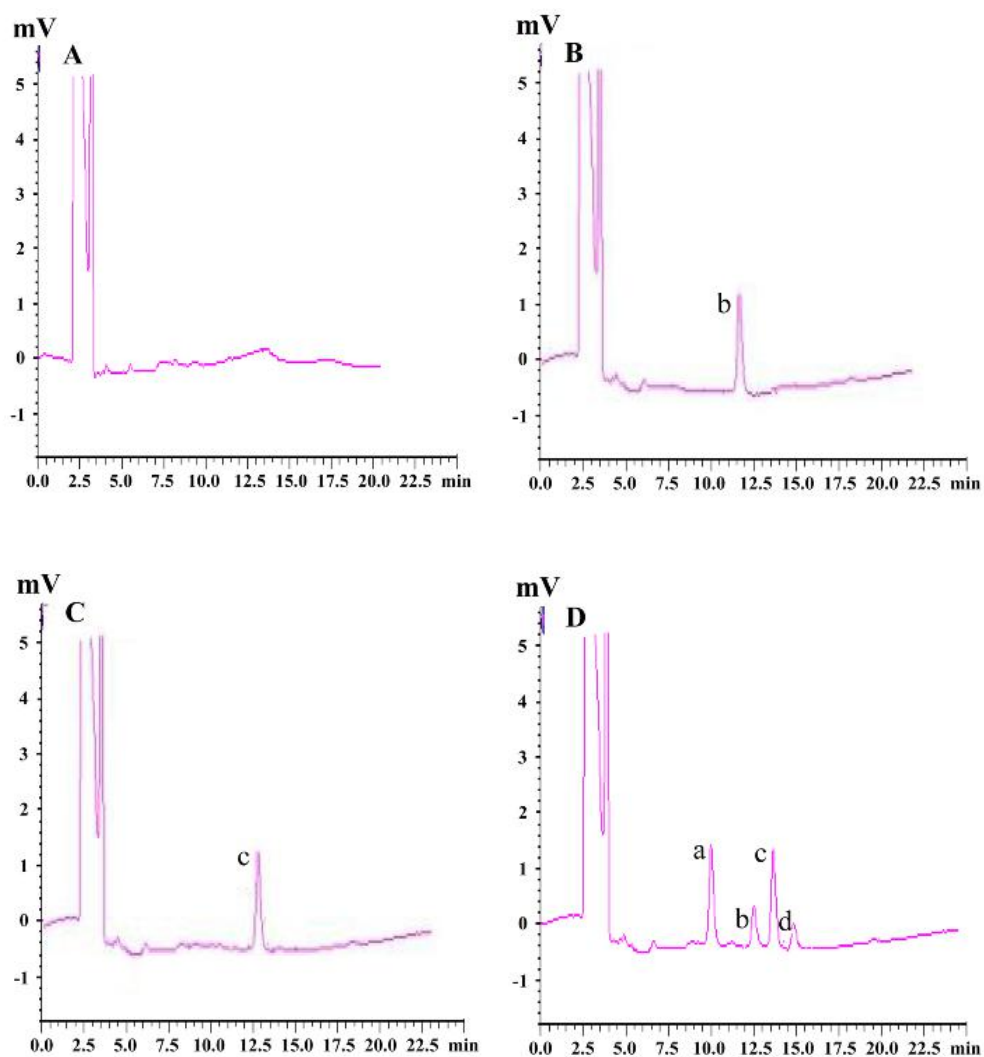


Figure S6 The HPLC chromatograms of 4-hydroxytolbutamide in HLM.

Notes: (A) Blank HLM; (B) Blank HLM spiked with 4-hydroxytolbutamide; (C) Blank HLM spiked with IS; (D) Sample. a. EPI; b. 4-Hydroxytolbutamide; c. Phenacetin (IS); d. Tolbutamide

Figure S7.

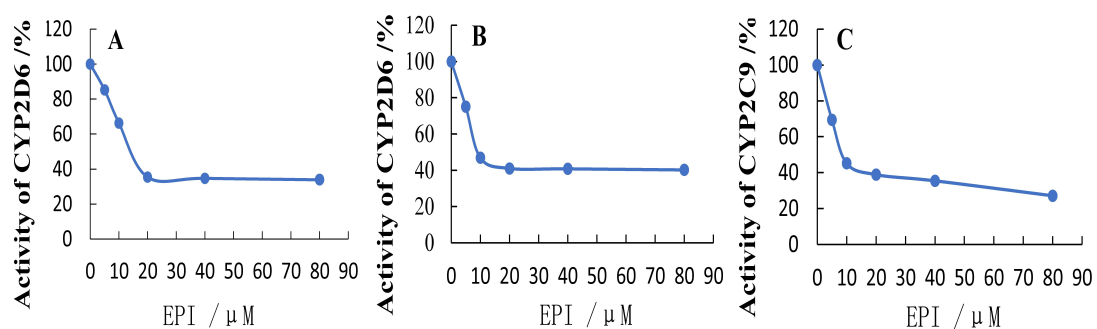


Figure S7 The inhibition of EPI on CYP isoforms mediated metabolism of substances in RLM and HLM. Clearance of substrates (10 μM metoprolol or tolbutamide) represented activity of CYP2D6 and CYP2C9. Values are presented as mean ± SD ($n=6$).

Notes: (A) Metoprolol in RLM; (B) Metoprolol in HLM; (C) Tolbutamide in HLM

Table S1.

Table S1. The calibration curves, regression equations and linear ranges of EPI in rat blood, urine, feces and bile ($n=5$).

Samples	Concentration ranges (ng/mL)	Regression equations	Correlation coefficients r^2	LLOQ (ng/mL)
Blood	1.67-26784.0	$Y=3.80X+2.61$	0.9998	1.67
Urine	39.0-2500	$Y=1.62X+0.0012$	0.9992	39.0
Feces	39.0-2500	$Y=1.68X-0.0096$	0.9990	39.0
Bile	39.0-2500	$Y=1.62X+0.0012$	0.9995	39.0

Table S2.

Table S2. The calibration curves, regression equations and linear ranges of α -hydroxylmetoprolol and 4-hydroxytolbutamide in RLM ($n=3$)

Compounds	Concentration ranges ($\mu\text{mol/L}$)	Regression equations	Correlation coefficients/ r^2	LLOQ ($\mu\text{mol/L}$)
4-Hydroxytolbutamide	0.069-1.09	$Y=0.10X-0.0013$	0.9993	0.069
α -Hydroxymetoprololin	0.017-0.55	$Y=28.44X-0.76$	0.9922	0.017