

Figure S1. Double cannulation in rats. The cannulas are placed inside the jugular vein for plasma sample collection and the hepatic portal vein for both administration and plasma sample collection.

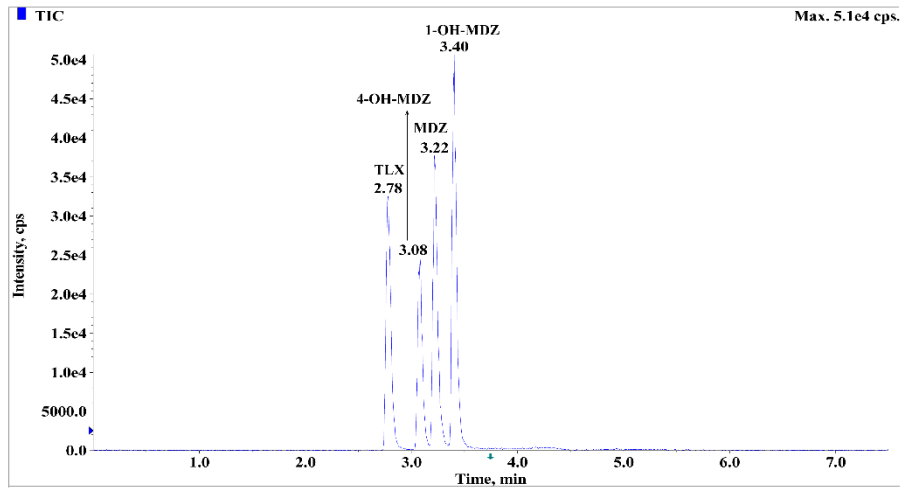


Figure S2. Total ion chromatogram (TIC) from the LC-MS/MS analysis of Tamsulosin (TLX) (5 ng/ml), MDZ, 1-OH-MDZ, and 4-OH-MDZ at 50 ng/ml for plasma sample.

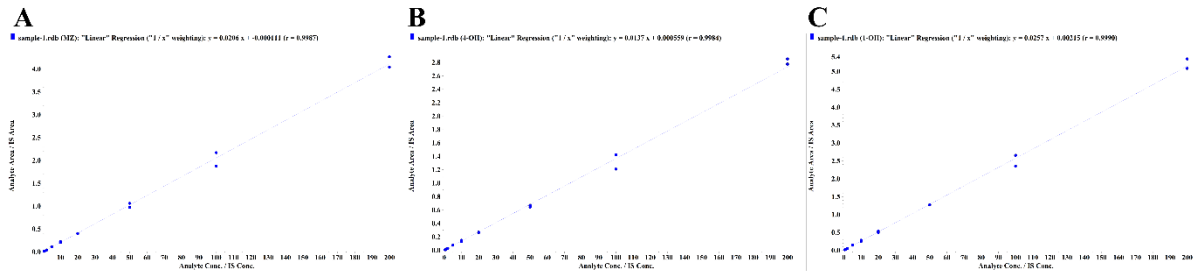


Figure S3. The calibration curves of MDZ (A), 1-OH-MDZ (B), and 4-OH-MDZ (C) with the coefficient of determination ( $r^2$ ) values  $> 0.99$ .

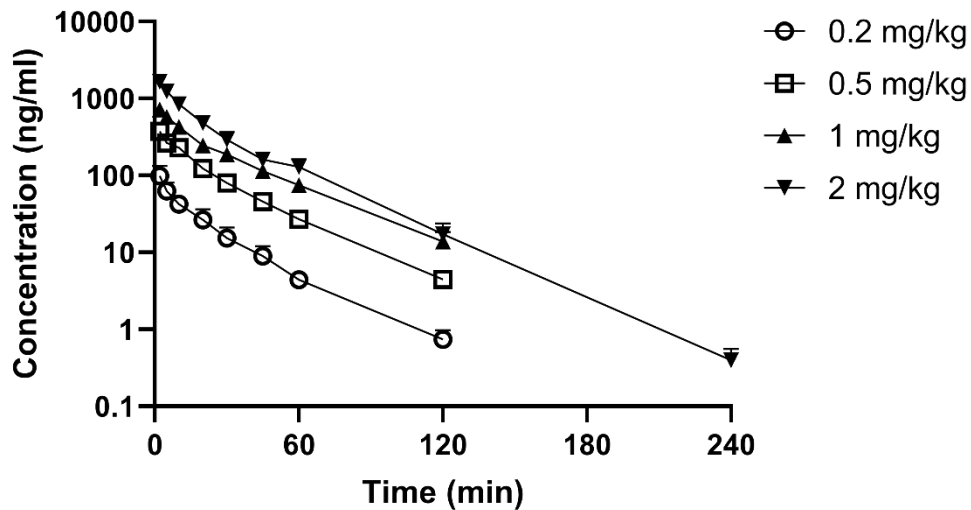


Figure S4. The pharmacokinetic profiles in systemic plasma of MDZ after intravenous administration of 0.2, 0.5, 1, and 2 mg/kg MDZ in SD rats

Table S1 MDZ Compartment model pharmacokinetics parameter estimates

	0.2 mg/kg	0.5 mg/kg	1 mg/kg	2 mg/kg
V1 (mL/kg)	654.84	100.03	3035.97	2149.36
CL (mL/min/kg)	199.59	50.01	137.88	103.34
V2 (mL/kg)	1476.54	1245.10	1038.23	1300.16
CLD2 (mL/min/kg)	129.94	36.21	42.30	204.67
V3 (mL/kg)	9289.02	/	/	/
CLD3 (mL/min/kg)	130.03	/	/	/
K10_HL (min)	2.27	1.39	15.26	14.42

The parameters of 0.2 mg/kg are estimated from 3-compartment model; the parameters of 0.5, 1, and 2 mg/kg are estimated from 2-compartment model

Table S2 The ratios of the calculated AUCs of MDZ coming from extrapolation in different plasma with different administration routes

AUC_Extrap (%) in	0.2 mg/kg		0.5 mg/kg		1 mg/kg		2 mg/kg	
systemic plasma								
Administration route	mean	S.D.	mean	S.D.	mean	S.D.	mean	S.D.
IV	0.95	0.29	0.45	0.88	0.05	0.02	0.03	0.01
PV	8.88	3.69	4.61	2.74	0.05	0.03	0.11	0.07
AUC_Extrap (%) of oral administration	2mg/kg		5mg/kg		10mg/kg		20mg/kg	
Systemic plasma	2.53	1.97	1.26	1.06	0.76	0.62	1.01	0.17
Portal plasma	8.64	7.63	6.25	2.20	8.10	7.75	7.37	5.64