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Original Article

The effect of MS-275 on CYP450 isoforms activity in rats by cocktail method

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Abstract: MS-275, is a potent, class I selective histone deacetylase inhibitor currently in clinical trials for the cure of several types of cancer. The influence of MS-275 on the activities of CYP450 isoforms CYP2B6, CYP1A2, CYP2C9, CYP2D6, CYP3A4 and CYP2C19 were evaluated by cocktail method. The rats were randomly divided into MS-275 group (Low, Medium, High) and control group. The MS-275 group rats were given 12.3, 24.5, 49 mg/kg (Low, Medium, High) MS-275 by continuous intragastric administration for 7 days. The six probe drugs were given to rats through intragastric administration, and the plasma concentration were determinated by UPLC-MS/MS. The result of MS-275 group compared to control group, there were statistical pharmacokinetics difference for bupropion, phenacetin, tolbutamide, metroprolol, midazolam and omeprazole. Continuous intragastric administration for 7 days may induce the activities of CYP2B6, CYP1A2, CYP2C9, CYP2D6, CYP3A4 and CYP2C19 of rats, and may induce the hepatocytes apoptosis. This may give advising for reasonable drug use after co-uesd with MS-275.

Keywords: CYP450, MS-275, cocktail, UPLC-MS/MS, rat, HDAC

Introduction

Entinostat, also known as SNDX-275 and MS-275, is the second generation histone deacetylase (HDAC) inhibitor with significant anti-tumor efficacy currently in clinical development [1]. It exhibits highly activities against various cancer types, including solid tumors [2], hematologic malignancies [2], breast [3] and myeloma [4] both in vitro and in vivo, and was considered as the most potent HDAC inhibitor [5]. However, there are few reports about the hepatic toxicity of MS-275, and what kind of influence would happen is still uncertain.

Cytochrome P450 (CYP450) is the most important drug-metabolizing enzymes in liver with largest number and highest abundance of CYP isoforms [6-10]. CYP1, CYP2, and CYP3 are three kinds of isoenzymes mainly involved in the metabolism of many drugs in both humans and other animals such as rats [11]. Probe drug is a kind of compound specially catalyzed by CYP isoforms, and the metabolic rate of probe drug can be used to assess the activities of CYP isoforms. In order to assess these various individual CYP450 activities, various probe drugs have been found and widely used in many clinical investigations, especially in the field of drug metabolism and pharmacogenetics [12-15].

In this paper, six probe drugs are used to evaluate the induction or inhibition effects of MS-275 on the activities of rats CYP450 isoforms such as CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6 and CYP3A4 in rats. According to the changes of pharmacokinetic parameters of six specific probe drugs, it provided the guidance for rational drug use after administration of MS-275.

Material and methods

Chemicals and animals

Bupropion, phenacetin, tolbutamide, metroprolol, midazolam, omeprazole (all >98%) and the internal standard diazepam were obtained from Sigma-Aldrich Company (St. Louis, USA).

Methanol and acetonitrile (HPLC grade) were obtained from Merck Company (Darmstadt, Germany). Ultra-pure water was prepared by Millipore Milli-Q purification system (Bedford, USA).

Sprague-Dawley rats (male, 220 ± 20 g) were purchased from Shanghai SLAC Laboratory Animal Co., Ltd. Animals were housed under a natural light-dark cycle conditions with controlled temperature (22°C). All forty rats were housed at Laboratory Animal Research Center of Wenzhou Medical University. All experimental procedures were approved ethically by the Administration Committee of Experimental Animals of Wenzhou Medical University.

UPLC-MS/MS conditions

UPLC-MS/MS with ACQUITY I-Class UPLC and a XEVO TQD triple quadrupole mass spectrometer equipped with an electrospray ionization (ESI) interface (Waters Corp., Milford, MA, USA) were used to analyze the compounds.

Bupropion, phenacetin, tolbutamide, metroprolol, midazolam, omeprazole and diazepam (IS) were separated using a BEH C18 column (2.1 mm × 100 mm, 1.7 μm) maintained at 40°C. The initial mobile phase consisted of 0.1% formic acid and acetonitrile with gradient elution at a flow rate of 0.4 mL/min and an injection volume of 2 μL. Elution was in a linear gradient, with the acetonitrile changing from 30 to 60% between 0.3 and 1.8 min and increasing up to 95% over 0.2 min. The acetonitrile content was maintained at 95% for 0.5 min and decreased to 30% within 0.1 min, and maintained at 30% for 0.4 min. The total run time of the analytes need 3 min.

The mass spectrometric detection was performed in a positive mode. Nitrogen was used as the cone gas (50 L/h) and desolvation gas (1000 L/h). The mass conditions were set as follows: source temperature 150°C; capillary voltage 2.5 kV; desolvation temperature 500°C. The multiple reaction monitoring (MRM) mode of m/z 180.1→109.9 for phenacetin, m/z 268.1→115.8 for metroprolol, m/z 326.0→291.0 for midazolam, m/z 346.1→197.8 for omeprazole, m/z 271.2→155.1 for tolbutamide, m/z 240.1→184.1 for bupropion and m/z 285.1→193.1 for IS was used as quantitative analysis.

The effect of MS-275 on CYP450 isoforms activity

The influence of MS-275 on the activities of CYP450 isoforms CYP2B6, CYP1A2, CYP2C9, CYP2D6, CYP3A4 and CYP2C19 were evaluated by cocktail method; they were responsed by the changes of pharmacokinetic parameters of bupropion, phenacetin, tolbutamide, metroprolol, midazolam and omeprazole. Forty rats (220 ± 20 g) were randomly divided to MS-275 group and control group (10 rats for each dose). MS-275 group were give MS-275 (12.3, 24.5, 49.0 mg/kg, Low, Medium, High) by continuous intragastric administration for 7 days. Control group were give saline by continuous intragastric administration for 7 days. After 8 days, the MS-275 and control group intragastric administration of mixtured six probe drugs (bupropion, phenacetin, tolbutamide, metroprolol, midazolam and omeprazole were 10, 10, 1, 10 10 and 10 mg/kg).

Blood (0.3 mL) samples were collected at 0.0833, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 h from the tail vein into heparinized 1.5 mL polythene tubes after intragastric administration of six probe drugs. The 100 μL plasma was obtained from blood sample after centrifuged at 4000 *g* for 10 min. In a 1.5 mL centrifuge tube, 100 μL of collected plasma sample followed by the addition of 200 μL of acetonitrile (containing 50 ng/mL IS). After vortex-mixed for 1.0 min, the sample was centrifuged at 13000 *g* for 15 min. Then the 2 μL supernatant was injected into the UPLC-MS/MS system for analysis.

Plasma probe drugs concentration versus time was analyzed by Version 3.0 Data Analysis System (Wenzhou Medical University, China). The main pharmacokinetic parameters of the MS-275 group and control group were analyzed by SPSS I8.0 statistical software.

Histopathology

After pharmacokinetics experiment, rats were deeply anesthetized with 10% chloral hydrate (i.p., 20 mg/kg). The liver were rapidly isolated and immersed in freshly prepared 4% w/v formaldehyde (0.1 M phosphate buffer, pH 7.2) for 48 h and then embedded in paraffin. Then 5-μm-thick histologic sections were prepared and stained with hematoxylin and eosin by routine HE method. The morphological changes were observed under light microscope.

Table 1. Pharmacokinetic parameters of bupropion and phenacetin in control-group and MS-275-group rats (mean ± SD, n = 10)

Parameters		$AUC_{(0-t)}$	$AUC_{(0-\infty)}$	$t_{1/2}$	CL	V	C_{max}
		ng/mL h*	ng/mL h*	h	L/h/kg	L/kg	ng/mL
Bupropion (CYP2B6)	Low	286.1 ± 132.7	382.8 ± 155.5	1.7 ± 0.9	31.9 ± 18.0	80.8 ± 64.9	116.0 ± 72.6
	Medium	195.4 ± 63.3	210.6 ± 68.7	1.4 ± 0.4**	54.6 ± 26.7	107.5 ± 55.6*	91.6 ± 35.9*
	High	114.8 ± 15.2**	117.2 ± 15.4**	1.0 ± 0.2	86.6 ± 11.8**	125.2 ± 25.4**	73.1 ± 24.1*
	Control	235.6 ± 67.0	238.6 ± 67.4	0.9 ± 0.2	45.2 ± 13.7	55.9 ± 23.7	149.6 ± 58.3
Phenacetin (CYP1A2)	Low	5990.4 ± 1810.1	5994.1 ± 1806.7	0.7 ± 0.5	1.8 ± 0.5	2.0 ± 1.2*	4258.2 ± 1159.4*
	Medium	4408.5 ± 1841.9*	4432.7 ± 1849.0*	0.6 ± 0.3	2.5 ± 0.6**	1.9 ± 0.8**	3187.3 ± 494.0**
	High	3949.3 ± 1438.7**	3991.7 ± 1395.5**	1.0 ±0.8*	2.8 ±1.0**	4.7 ± 2.9*	2075.2 ± 466.8**
	Control	6785.2 ± 1393.3	6787.2 ± 1393.3	0.4 ± 0.1	1.6 ± 0.5	0.8 ± 0.3	5829.5 ± 1179.7

Compared MS-275 group with the control group, *: P<0.05, **: P<0.01.

Results

Method validation

The concentration of bupropion, phenacetin, tolbutamide, metroprolol, midazolam and omeprazole in rat plasma was simultaneously determined by a sensitive and simple UPLC-MS/MS method. The LLOQ for each probe drug in plasma was 2 ng/mL. The RSD of the six probe drugs were less than 13%. The calibration plot of the probe drugs is in the range of 2-2000 ng/mL (r>0.995). The intra-day and inter-day accuracy ranged from 91% to 113%. The matrix effects were more than 84% or less than 116%. The extraction recoveries were better than 82%.

The effect of MS-275 on CYP450 isoforms activity

The main pharmacokinetic parameters of bupropion, phenacetin, tolbutamide, metroprolol, midazolam and omeprazole were summarized from non-compartment model analysis in **Tables 1-3**. The representative phenacetin, metroprolol, midazolam, omeprazole, tolbutamide and bupropion concentration vs. time profiles were presented in **Figure 1**. As could be seen from **Figure 1**, the C_{max} and AUC of bupropion, phenacetin, tolbutamide, metroprolol, midazolam and omeprazole in MS-275 group is lower than the control group.

As can be seen from **Tables 1-3**, the pharmacokinetic parameters of omeprazole and tolbutamide have changed, $AUC_{(0-t)}$ decreased (P<0.01), CL increased (P<0.01 or 0.05), C_{max} decreased (P<0.01), compared MS-275 group with the control group. It indicates that the continuous administration of MS-275 may induce the activity of CYP2C19 and CYP2C9 enzyme of rats.

While compared MS-275 group with the control group, there were no significant difference for AUC of some goup of phenacetin (medium), metroprolol (high and medium), midazolam (high) and bupropion (high and medium) (P>0.05), and here were significant difference for AUC decreased, CL increased and C_{max} decreased of phenacetin (high and low), metroprolol (low), midazolam (medium and low) and bupropion (low) (P<0.05, or 0.01), it could show that the MS-275 silghtly induce the activity of CYP1A2, CYP2D6, CYP3A4 and CYP2B6 enzyme.

Morphological changes of liver

Histopathological examination of liver shows that there was no massive degeneration changes appeared in MS-275 group. And there was no hepatocytic macrovesicular steatosis, lobular inflammatory cell infiltration and necrosis in both control group and MS-275 group (**Figure 2A**, **2B**). However, a few scattered dark and pyknotic cells group observed in MS-275 group (**Figure 2C**, **2D**). This change maybe a kind of apoptosis caused by MS-275, because MS-275 is a HDAC inhibitor and no more dark and pyknotic cells group were observed in high MS-275 dosage rats than low MS-275 dosage rats.

Discussion

The HDAC are a large family of enzymes that catalyze the removal of acetyl groups from substrate proteins and thereby regulate their function and activity [16, 17]. MS-275 is unique among HDAC inhibitors in clinical development, in that it inhibits class I HDAC (HDAC1 and 3) more than class II (HDAC4) , displays a unique

Table 2. Pharmacokinetic parameters of tolbutamide and midazolam in control-group and MS-275-group rats (mean ± SD, n = 10)

Parameters		$AUC_{(0-t)}$	$AUC_{(0-\infty)}$	$t_{1/2}$	CL	V	C_{max}
		ng/mL h*	ng/mL h*	h	L/h/kg	L/kg	ng/mL
Tolbutamide (CYP2C9)	Low	63433.0 ± 15143.5**	64600.5 ± 14541.2**	4.9 ± 1.2	0.016 ± 0.003**	0.11 ± 0.03*	5723.3 ± 1189.5**
	Medium	62062.1 ± 14665.0**	64652.5 ± 13687.3**	6.7 ± 1.8	0.016 ± 0.003**	0.15 ± 0.04**	4423.4 ± 1072.2**
	High	50095.6 ± 8644.5**	52164.7 ± 9182.5**	6.7 ± 2.9	0.020 ± 0.003**	0.18 ± 0.06**	3821.0 ± 313.2**
	Control	99947.8 ± 27778.3	100707.5 ± 29200.8	5.7 ± 2.0	0.011 ± 0.003	0.08 ± 0.02	7666.9 ± 768.9
Midazolam (CYP3A4)	Low	242.1 ± 161.5	275.3 ± 209.2	1.7 ± 0.8*	62.6 ± 52.3	163.2 ± 182.6	132.2 ± 83.2
	Medium	88.4 ± 23.1*	89.9 ± 23.7*	0.8 ± 0.4	118.6 ± 34.0**	135.4 ± 53.0**	69.5 ± 22.9*
	High	87.5 ± 45.6*	92.0 ± 45.3*	1.0 ± 0.5	134.6 ± 67.0**	193.8 ± 132.2**	59.0 ± 43.1**
	Control	319.0 ± 207.8	320.9 ± 208.4	0.7 ± 0.2*	40.8 ± 20.0	43.1 ± 26.2	257.6 ± 166.8

Compared MS-275 group with the control group, *: P<0.05, **: P<0.01.

Table 3. Pharmacokinetic parameters of metroprolol and and omeprazole in control-group and MS-275-group rats (mean ± SD, n = 10)

Parameters		$AUC_{(0-t)}$	$AUC_{(0-\infty)}$	$t_{1/2}$	CL	V	C_{max}
		ng/mL h*	ng/mL h*	h	L/h/kg	L/kg	ng/mL
Metroprolol (CYP2D6)	Low	1459.0 ± 398.5	1493.7 ± 397.8	1.9 ± 0.7	7.2 ± 2.2	20.0 ± 9.1	403.9 ± 121.7
	Medium	1016.4 ± 223.9	1025.2 ± 222.9	1.8 ± 0.9	10.2 ± 2.1	27.3 ± 19.0	374.1 ± 63.7**
	High	746.4 ± 277.1**	751.2 ± 275.9**	1.3 ± 0.2	14.4 ± 3.4**	27.9 ± 8.7	309.9 ± 71.6**
	Control	1151.8 ± 201.8	1158.3 ± 196.6	1.3 ± 0.3	8.8 ± 1.4	16.4 ± 6.4	563.1 ± 156.6
Omeprazole (CYP2C19)	Low	361.2 ± 172.8**	370.7 ± 172.0**	1.8 ± 0.5	32.3 ± 13.7**	93.3 ± 62.6**	324.2 ± 190.3**
	Medium	327.8 ± 95.8**	341.8 ± 87.0**	1.9 ± 1.0	30.9 ± 7.4**	88.6 ± 66.1	294.6 ± 129.9**
	High	367.7 ± 158.8**	455.1 ± 112.5**	10.1 ± 17.8	28.5 ± 20.0	160.4 ± 122.7**	179.9 ± 68.8**
	Control	905.9 ± 279.7	923.0 ± 295.3	1.4 ± 0.9	12.2 ± 4.9	23.2 ± 11.7	795.3 ± 229.5

Compared MS-275 group with the control group, *: P<0.05, **: P<0.01.

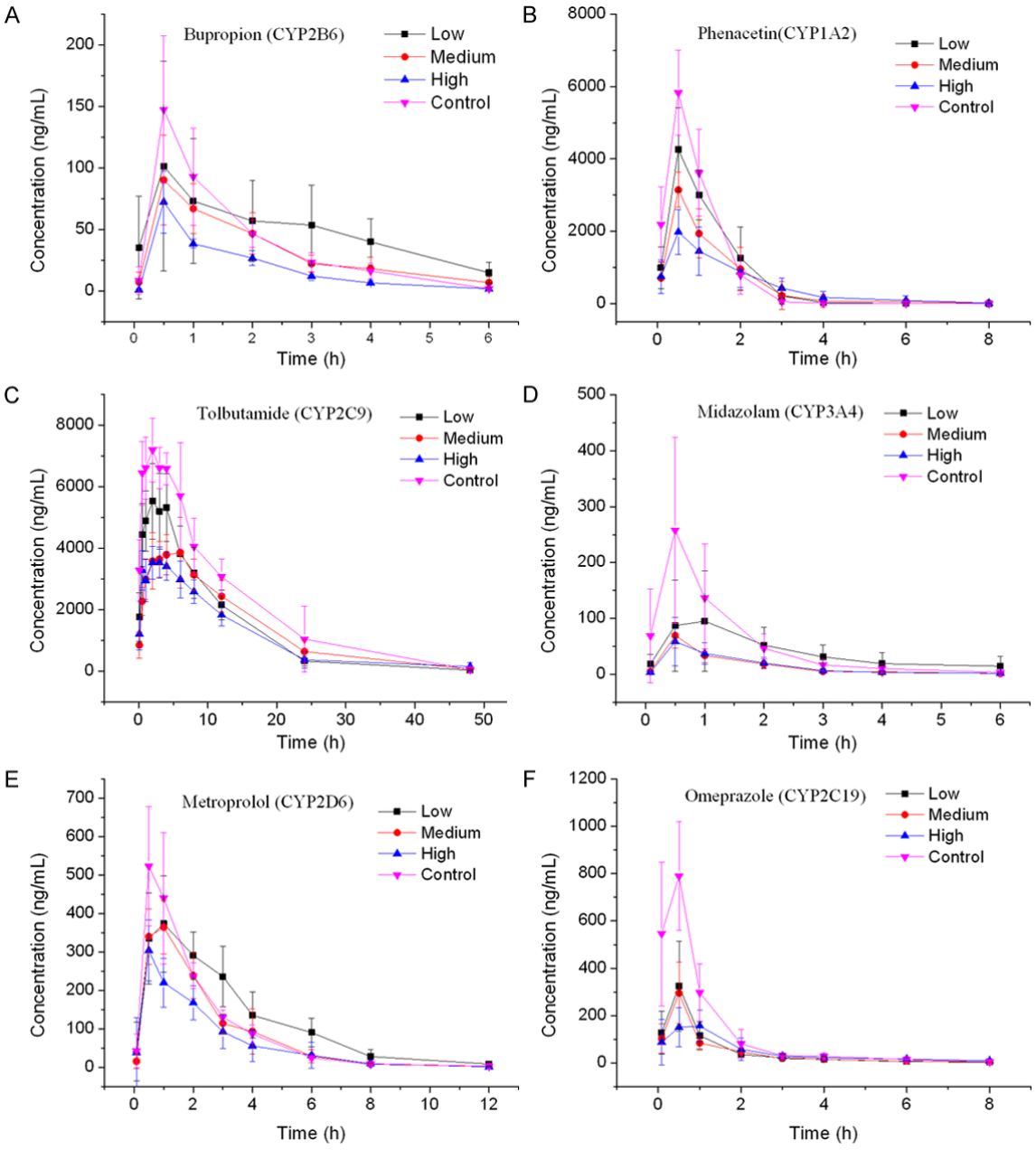

Figure 1. The pharmacokinetics profiles of bupropion (A), phenacetin (B), tolbutamide (C), midazolam (D), metoprolol (E) andomeprazole (F) in control-group and MS-275-group (low, medium, high) rats (n=10).

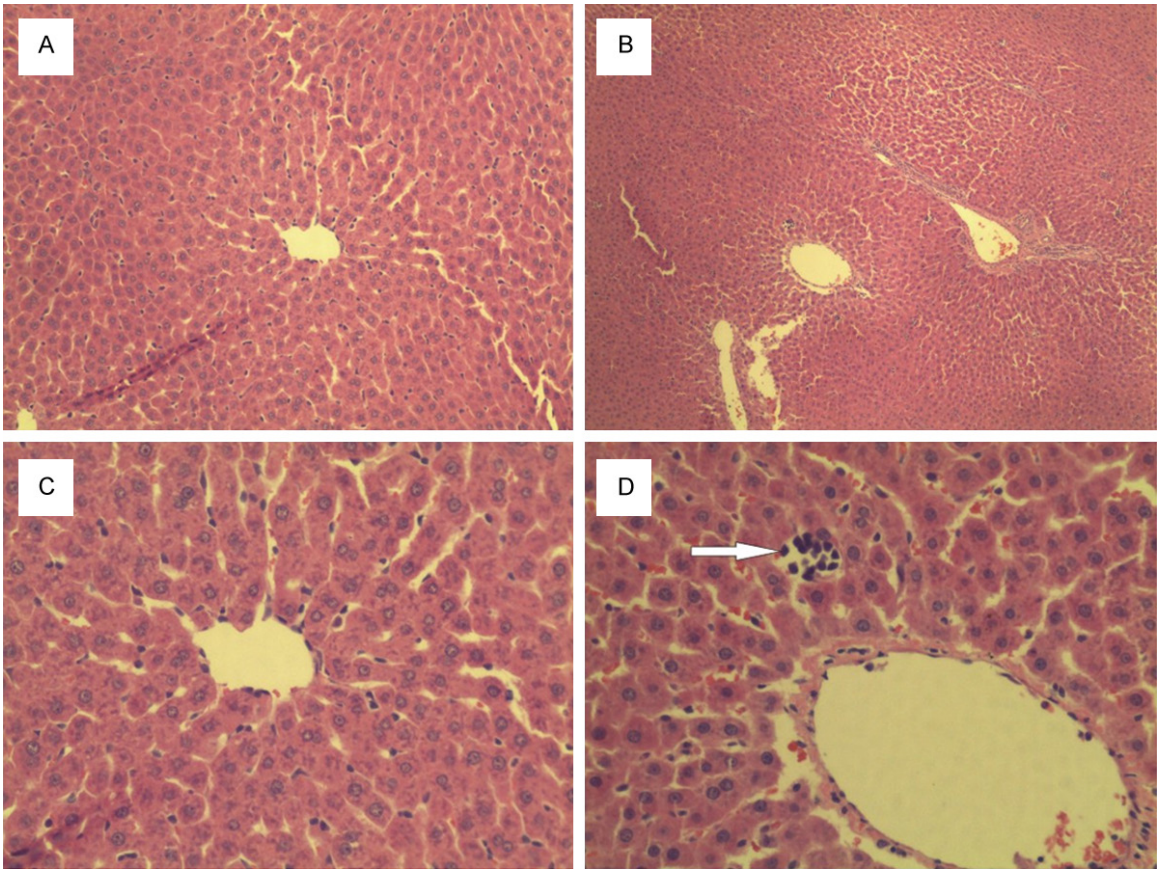

Figure 2. Morphological changes of liver in control-group (A, C) and MS-275-group at high dosage (B, D) (A, B hematoxylin-eosin, ×40; C, D hematoxylin-eosin, ×100).

in vitro cytotoxicity profile in the NCI COMPARE algorithm, inhibits tumor cell growth in nude mice comparable with or better than conventional cytotoxic agents such as 5-fluorouracil, and has relatively limited clinical toxicity, thus making it an attractive agent for development in humans [18, 19].

CYP450 mediated metabolism was found to be not a major elimination pathway for MS-275. This is not entirely bewildering due to prior work on similar agents that contain a benzamide moiety [20]. It is unlikely that CYP450-mediated oxidation is significant due to no changes in the chromatograms were paied attention and hence, the primary pathways of elimination for MS-275 remain to be elucidated [21].

As MS-275 is always used combination with other drugs, interactions between MS-275 and other drugs undertake the risk of either diminished efficacy or adverse effects. Drug-drug interactions often occur at the active site of these enzymes since CYP450 enzymes play a key role in the phase I metabolism of the majority of all marketed drugs.

In general, changes in pharmacokinetics are thought to be caused by drug-drug or drug-food interactions [22]. In pharmacokinetic interactions, approximately 65% of drug-drug interactions occur in metabolic sites, and drug metabolic enzymes are considered to be the most important interactive sites. A large number of drugs are metabolized by CYP enzymes in the liver, and more than 90% of drug-drug interactions occur at the CYP-catalyzed step [23, 24]. Similarly, supplement-drug interactions involving CYP activity are occasionally found to cause considerable adverse events. For these reasons, we evaluated the effects of intragastric administration of *MS-275* for 7 days on the

activity of CYP enzymes in *vivo*. We selected CYP isoforms CYP1A2, CYP2D6, CYP3A4, CYP2C19, CYP2C9 and CYP2B6 because more than 90% of drugs are known to be metabolized by these 6 CYP enzymes [25, 26].

Conclusion

In our study, continuous intragastric administration of MS-275 for 7 days may induce the activities of CYP450 isoforms CYP2B6, CYP1A2, CYP2C9, CYP2D6, CYP3A4 and CYP2C19 of rats, and may induce the hepatocytes apoptosis. These results would give us valuable information regarding the interactions of MS-275 with drugs, induction of drug metabolizing enzyme reduces the efficacy of drug.

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Disclosure of conflict of interest

None.

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