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Original Research Paper

EVALUATION OF PHARMACOKINETIC DRUG INTERACTION BETWEEN PDE 5 INHIBITOR, SILDENAFIL AND HDAC INHIBITORS, SAHA AND MS275 IN SCID MICE

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ABSTRACT

Combining a cytotoxic drug with a non-cytotoxic drug to reduce adverse effects associated with cytotoxic drugs, without compromising efficacy, is one of the widely pursued approach in cancer research. In order to optimize the dose or prevent adverse effects, it is important to understand the potential drug-drug interaction that may occur between such combinations. In the present study we have evaluated pharmacokinetic drug interaction between phosphodiesterase (PDE) inhibitor Sildenafil (SDFL) and histone deacetylase inhibitors (HDACi, SAHA and MS-275) in mice. SDFL (50 mg/kg i.p.) was administered alone or in combination with SAHA (50 mg/kg i.p.) and MS-275 (35 mg/kg p.o.) to separate set of animals. At predetermined time points, blood samples were collected and plasma was separated and analysed for SDFL, SAHA and MS-275 concentrations using HPLC. Co-administration of SAHA significantly (*$p<0.05$) enhanced the systemic exposures of SDFL in mice. Mean time to reach peak SDFL plasma concentrations (T_{max}) increased by 2 fold. The mean SDFL AUC_{0-24} when administered in combination with SAHA (15,620 ng*h/mL) was approximately 50% greater than the mean AUC_{0-24} when SDFL was administered alone (10,630 ng*hr/mL). Further, in presence of SAHA, SDFL was eliminated slowly with mean $t_{1/2}$ value of 1.74 h in comparison to 0.95 h when administered alone. Accordingly, the SDFL oral clearance was found to be increased (~3 fold) significantly (*$p<0.05$) when co-administered with SAHA than when given alone. Similarly, Mean plasma clearance of SDFL was ~3 fold higher and $t_{1/2}$ increased by ~2 fold when administered with MS-275 than alone. Further, mean plasma AUC_{0-24} of SDFL increased by ~70% in presence of MS-275 than when given alone, thereby, clearly demonstrating the pharmacokinetic drug-drug interaction between HDAC inhibitors and PDE inhibitor. In conclusion Coadministration of SDFL with SAHA/MS-275 resulted into pharmacokinetic drug-drug interactions that lead to altered pharmacokinetic of SDFL in SCID mice. Whereas SAHA and MS275 pharmacokinetics remained unchanged when coadministered with SDFL. To the best of our knowledge, this is the first study to document an *in vivo* drug interaction between these drugs in mice.

Keywords: Drug interaction, HDAC inhibitor, MS-275, PDE5 inhibitor, Pharmacokinetics, SAHA, Sildenafil.

INTRODUCTION

As a disease, cancer is becoming a major threat to the human population and the heterogeneity of the tumors made anti cancer drug discovery a highly challenging endeavor.[1,2] The conventional

chemotherapeutic approaches to cancer treatment have clear limitation due to the adverse side effects and the extended toxicity.[3] In the last decade there has been a tremendous increase in the knowledge of molecular mechanism and pathophysiology of human cancers and many of them have been exploited in the development of targeted cancer therapies.[4,5] However the requirement for anti cancer drugs with promising efficacy and limited toxicity remains elusive. HDAC have been considered as one of the most promising targets for cancer therapy.[6] Recent years have seen a great upsurge in development of HDAC inhibitors (HDACi).[7] Many HDACi have entered pre-clinical or clinical studies. Recently, Vorinostat (suberoylanilide hydroxamic acid, SAHA) a predominant class I and II HDACi, and Entinostat (MS-275), a class I HDACi have been approved by the Food and Drug Administration (FDA) for the treatment of relapsed and refractory cutaneous T-cell lymphoma (CTCL).[8] Although complete inhibition of HDACs has shown to be beneficial for the treatment of certain cancers still it is accompanied by many un-desirable side effects such as thrombocytopenia, neutropenia, fatigue, diarrhea and. Nausea.[9] In order to achieve optimum efficacy and minimal or no adverse effects while treating cancer, multiple strategies have been tried by researchers.[10] Combination therapy involving a cytotoxic and a non-cytotoxic drug is one such approach which provides an opportunity to reduce the dose of cytotoxic drug and minimize the associated adverse effects.[11] Cyclic nucleotide phosphodiesterases (PDEs) are a family of related phosphohydrolases that selectively catalyze the hydrolysis of the 3' cyclic phosphate bonds of cAMP and cGMP, second messengers in the cell.[12] The PDE enzymes, of at least 11 types, are ubiquitous through out the body, and perform a variety of functions. PDE-5 is the primary enzyme in the corpus cavernosum, and plays a crucial role in vascular smooth muscle contraction.[13] Recently, role of PDE-5 Inhibitors in Prostate Cancer degradation of cGMP (Bender and Beavo, 2006) was studied.[13] Emerging evidence indicates that SDFL and other PDE-5 inhibitors may enhance the sensitivity of certain types of cancer to standard chemotherapeutic drugs.[14,20,21] In a recent study, SDFL used SDFL along with other anticancer agents to enhance the anti cancer property of the combining drug were observed in lung (A549) colon (HCT116) cancer cell lines.[15]

In the light of above findings, we evaluated the efficacy of a combination of HDACi (SAHA and MS-275) and PDE-5 inhibitor (SDFL) in animal models of cancer, at reduced dose levels. The combination therapy showed synergistic efficacy both in in vitro and in vivo studies (data not shown). To further decipher, if the observed synergism is due to pharmacokinetic and/or pharmacodynamic drug-drug interaction between HDACi and PDE-5 inhibitors, we investigated pharmacokinetic drug-drug interaction between above mentioned drugs. Studies were conducted in severe combined immunodeficiency (SCID) mice at the doses similar to those used in efficacy studies.

MATERIALS AND METHODS

Chemicals

All solvents and reagents used were of HPLC grade or higher. SAHA, MS-275 celecoxib, are synthesized by OCPL (Orchid Chemicals and Pharmaceuticals Ltd.,), Chennai, INDIA. SDFL was obtained as a gift from Zydus Scadila Ahemadabad Chemicals of reagent grade (for chemical synthesis) was obtained from standard sources.

Animals

SCID mice were selected as a suitable animal for this project since the efficacy studies have been carried out in the same strain of mice. All animals will be handled similarly and with due regard for their welfare. Care of animals will comply with the regulations of Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. The study design was reviewed and approved by the Institutional Animal Ethics Committee. (IAEC) (Protocol No. 02/IAEC-01/CAN/2012). Six-eight week-old SCID mice were taken from in-house breeding facility of OCPL, Chennai (India). Animals will be maintained in individually

ventilated cage system with a controlled environment of temperature 22±3° C, humidity of 50±20%, a light/dark cycle of ~12 h and minimum 50 fresh air changes per hour. Mice were allowed to acclimate to their new environment at least 7 days before study initiation.

In Vivo Pharmacokinetic Interaction Study

PDE5 Selective inhibitor SDFL, was administered in combination with HDACi SAHA and MS-275. SDFL, was dissolved in Saline and SAHA was formulated in 2% 1M NaOH, 98 % HPβCD (20%) whereas MS-275 in 5% DMSO, 45% PEG, 50 PVP (5%) as solutions daily. SDFL at 50 mg/kg i.p, were the dose been selected for administered in combination with SAHA at 50 mg/kg i.p and MS-275 at 35 mg/kg p.o. Selected doses of HDACi were half of ED_{max} dose in xenograft animal models. The above said inhibitors were administered in combination to three sets of three animals each at the mentioned doses. Sample collection was staggered such that each time point resulted in an n=3 to allow for minimal sampling volumes from each animal. Heparinized blood was collected at 0.08, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h time points post dosing using retro orbital bleeding method. Plasma was separated from blood by centrifugation at 9,000 g for five minutes and immediately stored at 80 °C until later analysis. The plasma samples were thawed down and processed by protein precipitation method using organic solvent (acetonitrile). The processed samples were analyzed by HPLC method as described below.

Sample Extraction

Plasma samples (0.1ml) were spiked with celecoxib (internal standard) 1000 ng/ml then extracted with 100% ACN vortexed for 5 min and centrifuged at 14000 rpm for 10 min. The supernatant was evaporated to dryness under a gentle stream of nitrogen at 45 °C for 20 minutes at 5 psi and reconstituted the extract with 100 µl of 10 mM potassium di hydrogen phosphate buffer (pH 7.4) containing ACN(70:30). The mixture was vortexed and centrifuged at 14000g for 5 minutes and the aliquot (100 µl) was injected onto the HPLC system. Samples for standard curve were prepared in parallel using known concentration of SAHA (200 µg/ml - 0.2 µg/ml), MS-275 (200 µg/ml - 0.2 µg/ml), SDFL (200 µg/ml - 0.2 µg/ml) and internal standard (1000 ng/ml). Mobile phase was selected as the diluent for preparing stock solutions.

Bioanalysis of SDFL, SAHA and MS-275 in Plasma

The HPLC system consisted of a Beckman pump (114M solvent Delivery Module), Hewlett-Packard 1050 auto sampler (Hewlett-Packard Co., Wilmington, DE), Spectroflow 757 UV detector (ABI Analytical Kratos Division), and a C_{18} reversed phase column (Agilent Zorbax 80A C18 column (150*4.6 mm, 5µm).The mobile phase was 10mm potassium dihydrogen phosphate and Acetonitrile (HPLC gradient), at 70:30 delivered at a flow rate of 1 ml/min. PDA detection at wavelength range from 210-400nm. The quantitation was done for each compound at their respective λmax. The retention times and λmax for SDFL, SAHA and MS-275 were, ~6.1 and 240 nm, ~6.8 and 233 nm, and ~11.2 and 230 nm respectively. The limit of detection for SDFL was 10 nm.

Data Analysis

Plasma concentrations and time profiles of SDFL, SAHA and MS-275 were subjected to non-compartmental analysis and pharmacokinetic parameters were estimated using Phoenix Win Nonlin (Pharsight Corp., Mountain View, CA, USA). Statistical significance was determined by Student's 't' test wherever applicable using Graph pad prism 4. For statistical tests, a value of $p<0.05$ was considered to be statistically significant.

RESULTS

In Vivo Pharmacokinetics of PDE Inhibitor in Presence of HDAC Inhibitor

The mean pharmacokinetic parameters of SDFL alone and in presence of SAHA are summarized in Table 1. Co-administration of SAHA significantly ($p<0.05$) enhanced the systemic exposures of SDFL in mice. Mean time to reach

peak SDFL plasma concentrations (T_{max}) increased by 2 fold however the mean C_{max} remained unchanged, indicating that SAHA failed to influence the SDFL peak plasma concentrations (Table 1). SDFL median T_{max} values were 0.5 h following dosing alone and 1 h following dosing in combination with SAHA. The mean SDFL AUC_{0-24} when administered in combination with SAHA (15,620 ng*h/mL) was approximately 50% greater than the mean AUC_{0-24} when SDFL was administered alone (10,630 ng*hr/mL). Further, SAHA was found to be significantly ($p<0.05$) affecting the elimination half-life of SDFL. In presence of SAHA, SDFL was eliminated slowly with mean $t_{1/2}$ value of 1.74 h in comparison to 0.95 h when administered alone as reflected in plasma concentrations-time profile of SDFL with and without SAHA (Figure 2). Accordingly, the SDFL clearance was found to be increased significantly (~3 fold) when co-administered with SAHA than when given alone. Similarly, as shown in figure 3, SDFL pharmacokinetics was found to be influenced significantly when co-administered with MS-275. As summarized in table 2, although the median T_{max} and mean C_{max} of SDFL remained fairly unchanged in presence of MS-275, systemic clearance and elimination $t_{1/2}$ were found to be significantly ($p<0.05$) higher in presence of MS-275 than when given alone. Mean plasma clearance of SDFL was ~3 fold higher and $t_{1/2}$ increased by ~2 fold when administered with MS-275 than alone. Further, AUC_{0-24} of SDFL increased by ~70% ($p<0.01$) in presence of MS-275 than when given alone, thereby, clearly demonstrating the pharmacokinetic drug-drug interaction between HDAC inhibitors SAHA and MS-275 and PDE inhibitor SDFL.

In Vivo Pharmacokinetics of HDAC Inhibitor in Presence of PDE Inhibitor

We also evaluated the influence of PDE inhibitor SDFL on plasma pharmacokinetics of SAHA and MS-275 in mice. As shown in table 1 and table 2, the mean plasma pharmacokinetics of SAHA and MS-275 when co-administered with SDFL remained unchanged. This data clearly demonstrated lack of pharmacokinetic drug-drug interaction between SDFL with SAHA and MS-275 in mice (Figure 1).

DISCUSSION

Recently, a new school of thought has emerged for treating different types of cancers with the major objective to overcome the resistance and/or to reduce the dose of cytotoxic drug(s) by combining it with a non-cytotoxic drug that is capable of complimenting the anticancer activity of the cytotoxic drug by virtue of its unique pharmacological action against tumors.[3,5,6] In the last decade much of the focus has been on PDE inhibitors, which are known to control cyclic nucleotide action including cGMP, and researchers in various studies have demonstrated potential therapeutic application of PDE inhibitors in cancer.[11, 12, 17, 18] In the light of above findings we intended to evaluate the combined efficacy of PDE inhibitors and HDAC inhibitors in the xenograft mouse model of breast cancer. Results showed improved efficacy with combination therapy in comparison to monotherapy (data not shown). Hence, we intended to investigate if the improved efficacy observed in our study is due to pharmacodynamic and/or pharmacokinetic interaction between PDE and HDAC inhibitors.

In the present investigation, pharmacokinetic drug-drug interaction between SDFL with SAHA and MS-275 was evaluated. Co administration of SDFL and SAHA was well tolerated by the animals with no obvious clinical signs. There was a statistically significant pharmacokinetic drug-drug interaction when therapeutic dose of SDFL was administered in combination with the efficacy dose of SAHA where as no alterations was observed in the SDFL combination with MS-275. Consistent with historical data, SDFL and SAHA plasma concentrations exhibited monoexponential decay with time.[19] Co-administration of SDFL with SAHA showed no effect on the extent of absorption of SDFL, however, the mean T_{max} of SDFL was delayed by ~50% the peak plasma concentrations remained unchanged in both the combinations. However, elimination profile of SDFL was found to be

significantly altered by SAHA. The mean plasma $t_{1/2}$ of SDFL increased by 2 fold and accordingly clearance was also found to be increased by ~3 fold in presence of SAHA. The altered clearance resulted into significant increase (50%) in plasma exposures of SDFL in presence of SAHA in comparison to SDFL alone.

SAHA showed linear decay in plasma concentrations with time. Mean plasma pharmacokinetics of SAHA in presence of SDFL remained fairly unchanged, with an exception of peak plasma concentrations which increased by almost 50%. This finding clearly demonstrates the absence of influence of SDFL on plasma pharmacokinetics of SAHA in the current study.

Metabolic pathway represents the major route of elimination of SDFL, SAHA and MS-275; however, the drugs are metabolized by different enzymes. SDFL primarily undergoes phase-1 metabolism via CYP3A4 whereas SAHA is metabolized (minor) by phase-2 metabolism by UDPG enzyme and MS-275 by CYP1A2 enzyme.[22] Further, SAHA and MS-275 are known to be predominantly eliminated renally.[23] Thus, SDFL does not share a common metabolic pathway with SAHA and MS-275, therefore, a hepatic isozyme interaction is not likely to account for the pharmacokinetic drug interaction observed in the present study.

There could be more than one mechanism that could have contributed to the altered pharmacokinetics of SDFL in presence of SAHA or MS-275. The increased ($p<0.01$) (580%) volume of distribution of SDFL in presence of SAHA appears to be one of those contributing factor. SDFL per se has very low logP (0.29) value which suggests that SDFL is less permeable through biological membranes and into the tissues. However, in presence of SAHA the dramatic increase in volume of distribution of SDFL points at the interaction that could have resulted into the enhanced paracellular/trancellular transport of SDFL into the tissues in presence of SAHA. The ~6 fold increase in SDFL volume of distribution appears to be contributing to the longer plasma $t_{1/2}$ and hence lower plasma clearance and increased AUC_{0-24} observed in presence of SAHA. Further detailed work to investigate the mechanistic aspects of involvement of transporters in pharmacokinetic drug-drug interaction between SDFL with SAHA is warranted.

CONCLUSION

The clinical relevance of the pharmacokinetic interaction observed between SDFL and SAHA was not assessed in the current study. The improved pharmacokinetic profile of SDFL when co-administered with SAHA may predict greater efficacy for the combination than standard dosing with either drug alone. Additionally, SAHA could hypothetically speed the onset of action of SDFL by shortening SDFL T_{max} and slowing down its elimination from the body. Further, the enhanced efficacy that we have observed in our prostrate xenograft model (data not shown) can be attributed to the pharmacokinetic as well as pharmacodynamic drug-drug interaction between SDFL and SAHA. Pharmacodynamic drug interaction was further confirmed when tested in an in vivo study, the combination of SDFL and SAHA showed superior inhibition of prostrate cancer xenograft in comparison to either drug alone (data not shown) and SDFL by virtue of its unique and different mechanism of action further appears to be contributing to the observed pharmacodynamic drug interaction.

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Table 1: Mean pharmacokinetic parameters of SDFL and SAHA when administered alone and in combination

Parameters	Units	SDFL (50 mg/kg i.p.)		SAHA (50 mg/kg i.p.)	
		Alone	With SAHA	Alone	With SDFL
Dose	mg/kg	50	50	50	50
C_{max}	ng/mL	6,104	6,606	836	1,445
T_{max}	H	0.5	1	0.5	0.5
AUC_{0-24}	ng*h/mL	10,630	*15,620	1,120	1,310
$t_{1/2}$	h	0.95	*1.74	0.78	0.29
Vz_F	L/kg	1.20	**7.03	48.17	15.69
CL_F	L/h/kg	0.88	*2.81	42.74	36.90

*p<0.05, **p<0.01 when compared to alone treatment student's 't' test was performed

Table 2: Mean pharmacokinetic parameters of SDFL and MS-275 when administered alone and in combination

Parameters	Units	SDFL (50 mg/kg i.p.)		MS-275 (35 mg/kg p.o.)	
		Alone	With MS-275	Alone	With SDFL
Dose	mg/kg	50	50	35	35
C_{max}	ng/mL	6,104	9,663	11,526	13,429
T_{max}	H	0.5	0.5	0.5	0.5
AUC_{0-24}	ng*h/mL	10,630	*17,880	21,210	23,910
$t_{1/2}$	h	0.95	0.83	1.35	1.12
Vz_F	L/kg	1.20	**3.17	3.14	2.34
CL_F	L/h/kg	0.88	*2.64	1.61	1.44

*p<0.05, **p<0.01 when compared to alone treatment student's 't' test was performed

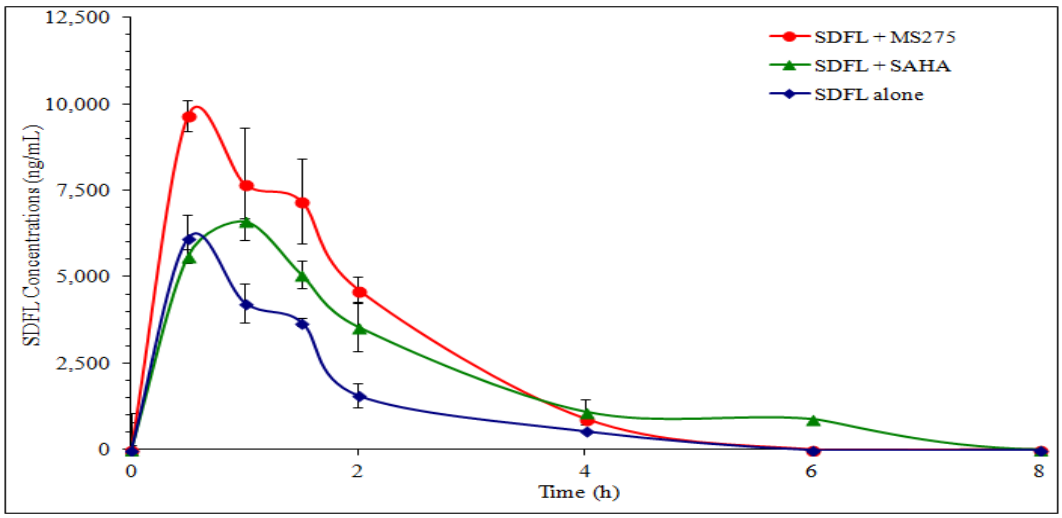

Figure 1: Mean (±SEM) plasma concentrations-time profiles of SDFL (50 mg/kg i.p.) with and without SAHA (50 mg/kg/i.p.) or MS-275 (35 mg/kg/p.o.) administration in SCID mice.

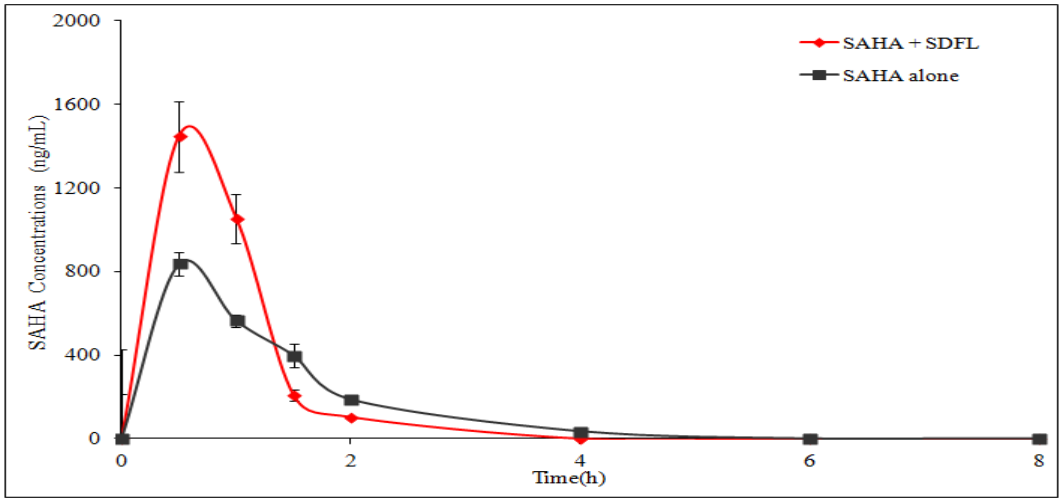

Figure 2: Mean (±SEM) plasma concentrations-time profiles of SAHA (50 mg/kg i.p.) with and without SDFL (50 mg/kg/i.p.) administration in SCID mice.

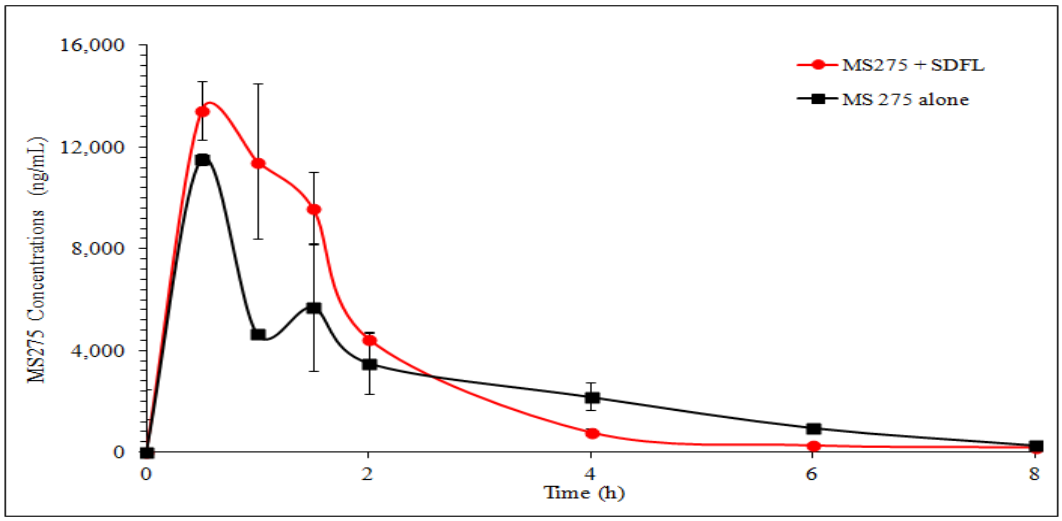

Figure 3: Mean (±SEM) plasma concentrations-time profiles of MS-275(35 mg/kg p.o.) with and without SDFL (50 mg/kg/i.p.) administration in SCID mice.

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