## SUPPLEMENTARY TABLES

**Supplementary Table 1. The microsomal stabilities of the compounds.**

| Compound | Human liver microsomes | | Rat liver microsomes | | Mouse liver microsomes | |
|---|---|---|---|---|---|---|
| | $t_{1/2}$ (min) | $CL_{int}$ (mL/min/kg) | $t_{1/2}$ (min) | $CL_{int}$ (mL/min/kg) | $t_{1/2}$ (min) | CLint (mL/min/kg) |
| Bortezomib | 21.4 | 58.3 | 12.4 | 200.5 | 10.7 | 508.7 |
| NNU219 | 32.4 | 43 | 27.8 | 50 | 16.7 | 83 |

Note: The microsomal stabilities of bortezomib and NNU219 were determined in the presence of pooled human, rat or mouse liver microsomes. $T_{1/2}$ (min) and $CL_{int}$ (mL/min/kg) were detected by LC/MS. Antipyrine and testosterone (5 μM each) were used as positive and negative controls, respectively. Abbreviations: t = time; $CL_{int}$, intrinsic clearance.

**Supplementary Table 2. Pharmacokinetic profiles of NNU546 in mice.**

| | $t_{1/2}$ (h) | CL ($mL \cdot h^{-1} \cdot kg^{-1}$) | Vz ($mL \cdot kg^{-1}$) | $AUC_{0-t}$ ($h \cdot ng \cdot mL^{-1}$) | MRT (h) | F(%) |
|---|---|---|---|---|---|---|
| i.v. | 2.08±0.991 | 986±75.4 | 2914±1247 | 1890±73.8 | 1.55±0.133 | --- |
| i.g. | 2.41±0.420 | --- | --- | 208±26.7 | 2.35±0.221 | 11.0±1.41 |

Note: Blood samples were collected at baseline and after intravenous or oral administration of 2 mg/kg of NNU546. Each time-point represents the average value of three animals. NNU546 concentration in blood and plasma samples was determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS) in a non–good laboratory practice lab. Pharmacokinetic analysis of the blood and plasma concentration data was performed using WinNonlin version 5.2 (Pharsight Corp.). Kinetic parameters were estimated using a noncompartmental model with sparse sampling mode (model 201 for plasma and blood). Area under the concentration vs. time curve (AUC) was calculated using the linear trapezoidal rule. Abbreviations: t = time; CL, clearance; Vz, apparent volume of distribution; $AUC_{0-t}$, AUC (area under the curve) from 0 to t h; MRT, mean residence time; F%, oral bioavailability.