

Experiment Number: K13115

Toxicokinetics Data Summary

Request Date: 3/12/2021

Compound & Analyte: 3-(2H-Benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid, octyl ester

Route: Intravenous, Oral Gavage

Request Time: 2:30:16

Species/Strain: Rat/Harlan Sprague-Dawley

CAS Number: 84268-23-5

Lab: BAT

Male

Treatment Group (mg/kg)

	2.25 IV ^a Blood	30 Gav ^b Blood	300 Gav ^b Blood
C _{0min} _pred (ng/mL)	22400 ± 900		
C _{max} _pred (ng/mL)		12800 ± 3100	47800 ± 13500
T _{max} _pred (hour)		1.07 ± 0.30	1.91 ± 0.56
C _{max} _obs (ng/mL)	23000	18600	65800
T _{max} _obs (hour)		0.750	1.00
Alpha_Half-life (hour)	0.386 ± 0.014	0.973 ± 0.680	2.17 ± 1.08
Beta_Half-life (hour)	1.88 ± 0.16	9.53 ± 1.73	13.6 ± 6.4
Gamma_Half-life (hour)	19.2 ± 1.1		
k ₀₁ (hour ⁻¹)		1.21 ± 1.22	0.814 ± 0.654
k ₀₁ _Half-life (hour)		0.574 ± 0.577	0.852 ± 0.684
k ₁₀ (hour ⁻¹)	1.63 ± 0.05	0.643 ± 0.446	0.296 ± 0.138
k ₁₀ _Half-life (hour)	0.426 ± 0.013	1.08 ± 0.75	2.34 ± 1.09
k ₁₂ (hour ⁻¹)	0.0989 ± 0.0142	0.0621 ± 0.0599	0.0194 ± 0.0229
k ₂₁ (hour ⁻¹)	0.396 ± 0.037	0.0807 ± 0.0174	0.0549 ± 0.0288
k ₁₃ (hour ⁻¹)	0.0397 ± 0.0028		
k ₃₁ (hour ⁻¹)	0.0370 ± 0.0021		
Cl ₁ (mL/hr/kg)	163 ± 4		
Cl ₂ (mL/hr/kg)	9.93 ± 1.34		
Cl ₃ (mL/hr/kg)	3.98 ± 0.29		
Cl ₁ _F (mL/hr/kg)		709 ± 192	1020 ± 290
Cl ₂ _F (mL/hr/kg)		68.4 ± 46.8	67.0 ± 62.9
V ₁ (mL/kg)	100 ± 4		
V ₂ (mL/kg)	25.1 ± 2.5		
V ₃ (mL/kg)	108 ± 7		
V ₁ _F (mL/kg)		1100 ± 950	3450 ± 2320
V ₂ _F (mL/kg)		848 ± 496	1220 ± 810

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Treatment Group (mg/kg)

2.25 IV^a Blood

30 Gav^b Blood

300 Gav^b Blood

MRT (hour) 1.43 ± 0.04

AUC_{0-T} (ng/mL·hr)

14600

32100

213000

AUC_{inf} (ng/mL·hr)

13800 ± 300

42300 ± 11500

294000 ± 85000

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LEGEND

MODELING METHOD & BEST FIT MODEL

^a WinNonlin three-compartment model with bolus input, first order output, and $1/Y_{hat}^2$ weighting (model #18); Cmax_pred based on the model prediction at 0 minutes.

^b WinNonlin two-compartment model with first order input, first order output, and $1/Y_{hat}^2$ weighting (model #13).

ANALYTE

3-(2H-Benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid, octyl ester

TK PARAMETERS

C_0min_pred = Fitted plasma concentration at time zero (IV only)

Cmax_obs = Observed maximum plasma concentration

Cmax_pred = Predicted maximum plasma concentration

Tmax_obs = Time at which observed Cmax occurs

Tmax_pred = Time at which predicted Cmax occurs

Alpha_Half-life = Half-life for the alpha phase

Beta_Half-life = Half-life for the beta phase

Gamma Half-life = Half-life for the gamma phase

k01 = Absorption rate constant, ka

k01_Half-life = Half-life of the absorption process to the central compartment

k10 = Elimination rate constant from the central compartment also ke or kelim

k10_Half-life = Half-life for the elimination process from the central compartment

k12 = Distribution rate constant from first to second compartment

k21 = Distribution rate constant from second to first compartment

k13 = Distribution rate constant from first to third compartment

k31 = Distribution rate constant from third to first compartment

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TK PARAMETERS (cont'd)

Cl1 = Clearance of central compartment

Cl2 = Clearance of the secondary compartment

Cl3 = Clearance of the tertiary compartment

Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model

Cl2_F = Apparent clearance of the secondary compartment

V1 = Volume of distribution of the central compartment, includes Vd and V volume of distribution

V2 = Volume of distribution for the peripheral compartment

V3 = Volume of distribution for the peripheral compartment

V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F

V2_F = Apparent volume of distribution for the peripheral compartment

MRT = Mean residence time

AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast

AUC_inf = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

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TK PARAMETERS PROTOCOL

BLOOD

IV 2.25 Rat Male

Harlan Sprague Dawley male rats were intravenously administered a single 2.25 mg/kg dose of 3-(2H-benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid, octyl ester (tBuPrOcEst-BZT). An automated blood sampling system (Culex) was used for this study. Whole blood samples were taken from n=3 animals/timepoint/per group at pre-dose and 16 timepoints at 0.0333, 0.0833, 0.167, 0.25, 0.333, 0.5, 0.75, 1, 2, 4, 8, 12, 18, 24, 48, and 72 hrs. Total analyte (free parent and conjugated parent) was analyzed using free ester and/or total acid levels with a lower limit of quantitation (LLOQ) of 1.0 ng/mL. Parameter estimates are reported to three significant figures with standard error (SE). Observed values do not have a reported SE.

BLOOD

Gavage 30 Rat Male, 300 Rat Male

Harlan Sprague Dawley male rats were administered a single gavage dose of 30 or 300 mg/kg 3-(2H-Benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid, octyl ester (tBuPrOcEst-BZT). An automated blood sampling system (Culex) was used for this study. Whole blood samples were taken from n=3 animals/timepoint/per group at pre-dose and 16 timepoints at 0.0333, 0.0833, 0.167, 0.25, 0.333, 0.5, 0.75, 1, 2, 4, 8, 12, 18, 24, 48, and 72 hrs. Total analyte (free parent and conjugated parent) was analyzed using free ester and/or total acid levels with a lower limit of quantitation (LLOQ) of 1.0 ng/mL. Parameter estimates are reported to three significant figures with standard error (SE). Observed values do not have a reported SE.