

Experiment Number: K12006

Toxicokinetics Data Summary

Request Date: 3/12/2021

Route: Intravenous, Oral Gavage

Compound & Analyte: 2-(2H-Benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)phenol

Request Time: 2:30:16

Species/Strain: Rat/Harlan Sprague-Dawley

CAS Number: 25973-55-1

Lab: BAT

Male

Treatment Group (mg/kg)

2.25 IV^a Blood

30 Gav^b Blood

300 Gav^b Blood

C ₀ min_pred (ng/mL)	37400 ± 2700		
C _{max} _pred (ng/mL)		7090 ± 3280	11100 ± 4400
T _{max} _pred (hour)		2.96 ± 1.10	6.29 ± 1.69
C _{max} _obs (ng/mL)	37900	10400	17000
T _{max} _obs (hour)		2.00	4.00
Alpha_Half-life (hour)	0.313 ± 0.048	2.67 ± 8.82	6.72 ± 41.2
Beta_Half-life (hour)	1.46 ± 0.16	13.4 ± 7.2	17.1 ± 53.3
Gamma_Half-life (hour)	22.4 ± 1.8		
k ₀₁ (hour ⁻¹)		0.541 ± 1.35	0.284 ± 0.592
k ₀₁ _Half-life (hour)		1.28 ± 3.20	2.44 ± 5.10
k ₁₀ (hour ⁻¹)	1.02 ± 0.07	0.134 ± 0.298	0.0674 ± 0.134
k ₁₀ _Half-life (hour)	0.678 ± 0.047	5.19 ± 11.6	10.3 ± 20.5
k ₁₂ (hour ⁻¹)	0.602 ± 0.171	0.0775 ± 0.438	0.0142 ± 0.181
k ₂₁ (hour ⁻¹)	0.840 ± 0.174	0.100 ± 0.177	0.0621 ± 0.457
k ₁₃ (hour ⁻¹)	0.221 ± 0.023		
k ₃₁ (hour ⁻¹)	0.0379 ± 0.0032		
Cl ₁ (mL/hr/kg)	61.6 ± 1.9		
Cl ₂ (mL/hr/kg)	36.2 ± 8.8		
Cl ₃ (mL/hr/kg)	13.3 ± 1.2		
Cl ₁ _F (mL/hr/kg)		314 ± 87	1110 ± 280
Cl ₂ _F (mL/hr/kg)		182 ± 643	235 ± 2550
V ₁ (mL/kg)	60.2 ± 4.3		
V ₂ (mL/kg)	43.1 ± 6.3		
V ₃ (mL/kg)	350 ± 34		
V ₁ _F (mL/kg)		2350 ± 5480	16500 ± 32600
V ₂ _F (mL/kg)		1810 ± 3590	3790 ± 17100

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300 Gav^b Blood

MRT (hour) 7.37 ± 0.52

AUC_{0-T} (ng/mL·hr)

37700

83800

290000

AUC_{inf} (ng/mL·hr)

36500 ± 1100

95400 ± 26600

269000 ± 67000

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LEGEND

MODELING METHOD & BEST FIT MODEL

^a WinNonlin three-compartment model with bolus input, first order output, and $1/Y_{\text{hat}}^2$ 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 $1/Y_{\text{hat}}^2$ weighting (model #13).

ANALYTE

2-(2H-Benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)phenol

TK PARAMETERS

C_{0min_pred} = Fitted plasma concentration at time zero (IV only)

C_{max_obs} = Observed maximum plasma concentration

C_{max_pred} = Predicted maximum plasma concentration

T_{max_obs} = Time at which observed C_{max} occurs

T_{max_pred} = Time at which predicted C_{max} 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, k_a

k_{01_Half-life} = Half-life of the absorption process to the central compartment

k₁₀ = Elimination rate constant from the central compartment also k_e or k_{elim}

k_{10_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 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)phenol (DitPe-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. Parent (free) was analyzed by LC-MS/MS with a lower limit of quantitation (LLOQ) of 5.0 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 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)phenol (DitPe-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. Parent (free) was analyzed by LC-MS/MS with a lower limit of quantitation (LLOQ) of 5.0 ng/mL. Parameter estimates are reported to three significant figures with standard error (SE). Observed values do not have a reported SE.