

Experiment Number: K12013

Toxicokinetics Data Summary

Request Date: 3/12/2021

Route: Intravenous, Oral Gavage Compound & Analyte: 2-(5-Chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)phenol Request Time: 2:30:16

Species/Strain: Rat/Harlan Sprague-Dawley

CAS Number: 3864-99-1

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)	36400 ± 1600		
C _{max} _pred (ng/mL)		3560 ± 7800	6810 ± 2420
T _{max} _pred (hour)		4.32 ± 4.15	4.53 ± 1.38
C _{max} _obs (ng/mL)	35600	4940	9980
T _{max} _obs (hour)		4.00	4.00
Alpha_Half-life (hour)	0.199 ± 0.016	1.16 ± 8640	4.01 ± 11.5
Beta_Half-life (hour)	1.60 ± 0.10	14.1 ± 4.3	14.0 ± 13.3
Gamma_Half-life (hour)	17.3 ± 0.6		
k ₀₁ (hour ⁻¹)		0.613 ± 2820	0.330 ± 0.701
k ₀₁ _Half-life (hour)		1.13 ± 5190	2.10 ± 4.46
k ₁₀ (hour ⁻¹)	1.04 ± 0.04	0.0517 ± 237	0.114 ± 0.216
k ₁₀ _Half-life (hour)	0.666 ± 0.028	13.4 ± 61500	6.06 ± 11.4
k ₁₂ (hour ⁻¹)	1.45 ± 0.17	0.0258 ± 2570	0.0331 ± 0.191
k ₂₁ (hour ⁻¹)	1.03 ± 0.11	0.569 ± 1640	0.0747 ± 0.156
k ₁₃ (hour ⁻¹)	0.387 ± 0.026		
k ₃₁ (hour ⁻¹)	0.0565 ± 0.0024		
Cl ₁ (mL/hr/kg)	64.3 ± 1.0		
Cl ₂ (mL/hr/kg)	89.6 ± 8.2		
Cl ₃ (mL/hr/kg)	23.9 ± 1.3		
Cl ₁ _F (mL/hr/kg)		336 ± 134	2660 ± 650
Cl ₂ _F (mL/hr/kg)		168 ± 15900000	768 ± 3070
V ₁ (mL/kg)	61.8 ± 2.7		
V ₂ (mL/kg)	87.1 ± 5.7		
V ₃ (mL/kg)	423 ± 18		
V ₁ _F (mL/kg)		6500 ± 29800000	23200 ± 46000
V ₂ _F (mL/kg)		295 ± 27300000	10300 ± 22600

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Treatment Group (mg/kg)

2.25 IV^a Blood

30 Gav^b Blood

300 Gav^b Blood

MRT (hour) 8.90 ± 0.23

AUC_{0-T} (ng/mL·hr)

35900

73200

126000

AUC_{inf} (ng/mL·hr)

35000 ± 600

89400 ± 40700

113000 ± 28000

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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-(5-Chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)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-(5-chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)phenol (ditBu-CIBZT). 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 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 2-(5-chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)phenol (ditBu-CIBZT). 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 1.0 ng/mL. Parameter estimates are reported to three significant figures with standard error (SE). Observed values do not have a reported SE.