

Experiment Number: K02825
Route: IV, Gavage
Species/Strain: Rats/ Fischer 344

Toxicokinetics Data Summary
Compound: 2-Methylimidazole/ Analyte: 2-Methylimidazole
CAS Number: 693-98-1

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: Battelle Columbus

Male

Treatment Group (mg/kg)

10 IV Plasma^{a,c}

25 Gavage Plasma^{b,d}

50 Gavage Plasma^{b,e}

100 Gavage Plasma^{b,e}

	10 IV Plasma ^{a,c}	25 Gavage Plasma ^{b,d}	50 Gavage Plasma ^{b,e}	100 Gavage Plasma ^{b,e}
Cmax_pred (ug/mL)	8.48 ± 1.31	6.29 ± 0.69	14.2 ± 1.5	28.1 ± 2.7
Tmax_pred(hour)		0.756 ± 0.106	0.757 ± 0.100	0.757 ± 0.099
Alpha (hour ⁻¹)	2.96 ± 1.52			
Alpha Half-life (hour)	0.234 ± 0.120			
Beta (hour ⁻¹)	0.788 ± 0.102			
Beta Half-life (hour)	0.879 ± 0.114			
k01 (hour ⁻¹)		2.32 ± 0.69	2.28 ± 0.65	2.74 ± 0.70
k01 Half-life (hour)		0.299 ± 0.089	0.304 ± 0.086	0.253 ± 0.064
k10 (hour ⁻¹)	1.34 ± 0.19	0.663 ± 0.083	0.679 ± 0.081	0.504 ± 0.059
k10 Half-life (hour)	0.516 ± 0.074	1.04 ± 0.13	1.02 ± 0.12	1.38 ± 0.16
k12 (hour ⁻¹)	0.667 ± 0.587			
k21 (hour ⁻¹)	1.74 ± 0.90			
Cl (mL/hr/kg)	1590 ± 80			
Cl _{1_F} (mL/hr/kg)		1600 ± 180	1430 ± 150	1230 ± 110
V1 (mL/kg)	1180 ± 180			
Vss (mL/kg)	1630 ± 130			
MRT (hour)	1.03 ± 0.06			
AUCinf_pred (ug/ml*hr)	6.31 ± 0.30	15.7 ± 1.7	35.1 ± 3.7	81.6 ± 7.0
F (percent)		94.8	109	126

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Female

Treatment Group (mg/kg)

10 IV Plasma^{a,c}

25 Gavage Plasma^{b,d}

50 Gavage Plasma^{b,e}

100 Gavage Plasma^{b,e}

	10 IV Plasma ^{a,c}	25 Gavage Plasma ^{b,d}	50 Gavage Plasma ^{b,e}	100 Gavage Plasma ^{b,e}
Cmax_pred (ug/mL)	9.60 ± 1.56	6.26 ± 0.71	14.8 ± 2.0	30.4 ± 3.7
Tmax_pred(hour)		0.519 ± 0.092	0.671 ± 0.128	0.612 ± 0.113
Alpha (hour ⁻¹)	5.36 ± 1.63			
Alpha Half-life (hour)	0.129 ± 0.039			
Beta (hour ⁻¹)	0.803 ± 0.046			
Beta Half-life (hour)	0.863 ± 0.049			
k01 (hour ⁻¹)		4.23 ± 1.32	3.18 ± 1.13	4.11 ± 1.31
k01 Half-life (hour)		0.164 ± 0.051	0.218 ± 0.078	0.169 ± 0.054
k10 (hour ⁻¹)	1.81 ± 0.27	0.664 ± 0.063	0.540 ± 0.079	0.433 ± 0.061
k10 Half-life (hour)	0.383 ± 0.058	1.04 ± 0.10	1.28 ± 0.19	1.60 ± 0.22
k12 (hour ⁻¹)	1.97 ± 0.94			
k21 (hour ⁻¹)	2.38 ± 0.54			
Cl (mL/hr/kg)	1890 ± 70			
Cl _{1_F} (mL/hr/kg)		1880 ± 210	1270 ± 160	1090 ± 110
V1 (mL/kg)	1040 ± 170			
Vss (mL/kg)	1910 ± 110			
MRT (hour)	1.01 ± 0.04			
AUCinf_pred (ug/ml*hr)	5.30 ± 0.19	13.3 ± 1.5	39.5 ± 4.8	91.5 ± 9.2
F (percent)		98.5	144	162

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LEGEND

MODELING SOFTWARE

WinNonlin V01.5A,

MODELING METHOD & BEST FIT MODEL

^aWinNonlin V01.5A, using Gauss-Newton (Levenberg and Hartley) method, one-compartment model with first order elimination. The concentration values were weighted $1/y^2$.

^bWinNonlin V01.5A, using Gauss-Newton (Levenberg and Hartley) method, one-compartment model with no lag phase and first order absorption and elimination. The concentration values were weighted $1/y^2$ (predicted).

EXCEPTION

^cThe observed AUC T is equal to 4 hours. V1 represents Volume.

^dThe observed AUC T is equal to 4 hours

^eBioavailability numbers are considered unreliable due to non-linear kinetics at 50 and 100 mg/kg doses which meant clearance values were not constant. The

ANALYTE

2-Methylimidazole

TK PARAMETERS

Cmax_pred = Observed or Predicted Maximum plasma (or tissue) concentration

Tmax_pred = Time at which Cmax predicted or observed occurs'

Alpha = Hybrid rate constant of the alpha phase

Alpha Half-life = Half-life for the alpha phase

Beta = Hybrid rate constant of the beta phase

Beta Half-life = Half-life for the beta 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

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TK PARAMETERS (cont'd)

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

Cl = Clearance, includes total clearance

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

V1 = Volume of distribution of the central compartment, includes Vd and V volume of distribution, Vz apparent volume of distribution NCA, Vapp apparent volume of distribution for intravenous studies

Vss = Volume of distribution at steady state

MRT = Mean residence time Mean residence time

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

F = Bioavailability, absolute bioavailability

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Single bolus intravenous administration into the femoral vein through an indwelling catheter 15 rats/sex. Blood was collected at 10 timepoints (5, 10, 15, 30, 45, 60, 90, 120, 240, and 480 minutes n=3 rats/sex/dose level bled at each timepoint.) Each rat/sex sampled twice (at two different time points). Blood collected by retro-orbital puncture. Plasma samples were analyzed using a validated gas chromatography method using an internal standard and extracted with ethyl acetate. Plasma method's Limit of Quantitation (LOQ) was 0.1 ug/mL. those values below the LOQ were not used to fit the profile to a model.

TK_INTRAVENOUS PLASMA

10 mg/kg Male

Bodyweights given are for 25 animals in the study and replacement animal IV female mouse group. Only 15 animals were used for this dose level.

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TK PARAMETERS PROTOCOL (cont'd)

TK_INTRAVENTOUS PLASMA

10 mg/kg Female

Bodyweights given are for 25 animals in the study and replacement animal IV female mouse group. Only 15 animals were used for this dose level.

ANALYSIS METHOD

Single bolus oral gavage administration to 14 (25 and 50 mg/kg dose)or 15 (100 mg/kg dose) rats/sex. Blood was collected at 9-10 timepoints (blood collection time points were 5, 10, 15, 30, 60, 120, 240, 360 720, and 1440 (100 mg/kg group only) minutes (n=3 rats/sex/dose level bled at each timepoint.) Each rat/sex sampled twice (at two different time points). Blood collected by retro-orbital puncture. Plasma samples were analyzed using a validated gas chromatography method using an internal standard and extracted with ethyl acetate. Plasma method's Limit of Quantitation (LOQ) was 0.1 ug/mL. those values below the LOQ were not used to fit the profile to a model.

TK_GAVAGE PLASMA

25 mg/kg Male

Bodyweights given are for the 55 total number of male gavage rats-study animals, replacements, all dose levels combined. Only 14 animals from this group were used for this dose level.

25 mg/kg Female

Bodyweights given are for the 55 total number of female gavage rats-study animals, replacements, all dose levels combined. Only 14 animals from this group were used for this dose level.

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TK PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Single bolus oral gavage administration 15 rats/sex. Blood was collected at 9-10 timepoints (blood collection time points will be 5, 10, 15, 30, 60, 120, 240, 360 720, and 1440 (100 mg/kg group only) minutes (n=3 rats/sex/dose level bled at each timepoint.) Each rat/sex sampled twice (at two different time points). Blood collected by retro-orbital puncture. Plasma samples were analyzed using a validated gas chromatography method using an internal standard and extracted with ethyl acetate. Plasma method's Limit of Quantitation (LOQ) was 0.1 ug/mL. those values below the LOQ were not used to fit the profile to a model.

TK_GAVAGE PLASMA

50 mg/kg Male

Bodyweights given are for the 55 total number of male gavage rats-study animals, replacements, all dose levels combined. Only 14 animals from this group were used for this dose level.

25 mg/kg, 50 mg/kg Female

Bodyweights given are for the 55 total number of female gavage rats-study animals, replacements, all dose levels combined. Only 14 animals from this group were used for this dose level.

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TK PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Single bolus oral gavage administration 15 rats/sex. Blood was collected at 9-10 timepoints (blood collection time points will be 5, 10, 15, 30, 60, 120, 240, 360 720, and 1440 (100 mg/kg group only) minutes (n=3 rats/sex/dose level bled at each timepoint.) Each rat/sex sampled twice (at two different time points). Blood collected by retro-orbital puncture. Plasma samples were analyzed using a validated gas chromatography method using an internal standard and extracted with ethyl acetate. Plasma method's Limit of Quantitation (LOQ) was 0.1 ug/mL. those values below the LOQ were not used to fit the profile to a model.

100 mg/kg Male

Bodyweights given are for the 55 total number of male gavage rats-study animals, replacements, all dose levels combined. Only 15 animals from this group were used for this dose level.

100 mg/kg Female

Bodyweights given are for the 55 total number of male gavage rats-study animals, replacements, all dose levels combined. Only 15 animals from this group were used for this dose level.