Supplemental material to "Population pharmacokinetics and exposure-response analysis of tribendimidine to improve treatment for children with hookworm infection"

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Table S1. Patient and study characteristics.

	All	Placebo (children)	100 mg (children)	200 mg (children)	400 mg (children)	400 mg (adolescents)
N	155	32	34	36	34	19
Samples	2347	0	679	660	640	368
Sex (M/F)	108/47	21/11	21/13	27/9	25/9	14/5
Tablets	50/200 mg	placebo	2x 50 mg	1x 200 mg	2x 200 mg	2x 200 mg + placebo
Age (y)*	10 (6-18)	9 (6-12)	9 (6-12)	9 (6-13)	8.5 (6-12)	15 (15-18)
Weight (kg)*	26 (12-65)	27 (12-40)	26 (18-42)	24.5 (14-38)	23 (14-36)	48.5 (30-65)
Height (cm)*	130 (95-167)	131 (106-149)	128 (95-155)	129 (105-147)	123.5 (96-152)	159 (131-167)
BMI (kg/m^2)*	15.4 (9.6-26.6)	15.9 (9.8-24.9)	15.1 (12.5-26.6)	14.9 (9.6-22.3)	14.7 (12.0-26.0)	18.9 (14.8-24.0)
Malaria (y/n)	57/79	13/19	17/17	14/22	13/21	NA
Temperature (°C)*	36.7 (35.5-38.3)	36.7 (35.5-37.4)	36.6 (35.7-37.2)	36.7 (35.5-38.3)	36.7 (35.6-37.5)	36.9 (36.5-37.3)
Heart rate*	97 (55-152)	98 (60-126)	92 (63-140)	97 (55-138)	100 (67-152)	NA
Creatinine (mg/L)*	32 (1-56)	31 (3-45)	34 (1-56)	30.5 (2-55)	34.5 (2-53)	NA
Urea (g/L)*	43.5 (34-71)	41 (34-64)	41.5 (36-68)	46 (35-71)	48 (34-70)	NA
Azotemia (g/L)*	5 (1-19)	4 (1-15)	6 (1-19)	4 (1-14)	4 (1-18)	NA
AST (UI/L)*	41 (16-59)	41 (19-53)	40.5 (16-56)	42 (23-57)	42 (16-59)	NA
ALT (UI/L)*	33 (11-61)	34.5 (12-48)	32.5 (11-57)	32.5 (14-53)	33.5 (15-61)	NA
Bilirubin (mg/L)*	31.5 (1-56)	34.5 (3-51)	28 (1-55)	32 (7-53)	30 (5-56)	NA
Infection intensity	Light-Moderate	Light	Light	Light	Light	Light-Moderate
Egg reduction (%)	-	34	39	49	68	74
Cured (%)	-	22	21	36	50	53

*median (range). BMI: body mass index. M/F: male/female. NA not available.

Table S2. Model development history

Model description	Study population	OFV	ΔOFV
dADT: first-order absorption, two compartment distribution, linear elimination, no covariates	School-aged children	7804	X
As previous + allometric scaling (correlating body weight to all clearance and volume parameters with exponents of 0.75 and 1, respectively)	School-aged children	7786	-18
As previous + 4 transit compartments for delayed absorption	School-aged children	7602	-184
As previous + tablet formulation as covariate on absorption rate constant	School-aged children	7575	-211
As previous + addition of adADT data, assumption of 65% formation, two-compartments for distribution, linear elimination. Best model so far: - First-order absorption with four transit compartments, - Two compartments for distribution of dADT, - Linear elimination of dADT, of which 65% formation of adADT, - Two compartment for distribution of adADT, - linear elimination of adADT - allometric scaling.	School-aged children	11755	X
Model as above with re-estimation of all PK parameters based on PK data of school-aged children and adolescents	School-aged children and adolescents	30124	X
Addition of Sterling approximation estimating the number of transit compartments	School-aged children and adolescents	30070	-54
Removal of IIV parameter for $V_{central,adADT}$ (to increase model stability)	School-aged children and adolescents	30069	-1
Volume of adADT peripheral compartment equalized to volume of its central compartment (to increase model stability)	School-aged children and adolescents	30210	+140
Addition of IIV parameter for bioavailability	School-aged children and adolescents	30170	-40
Addition of tablet formulation as covariate on absorption rate constant	School-aged children and adolescents	30089	-81

OFV: Objective function value.

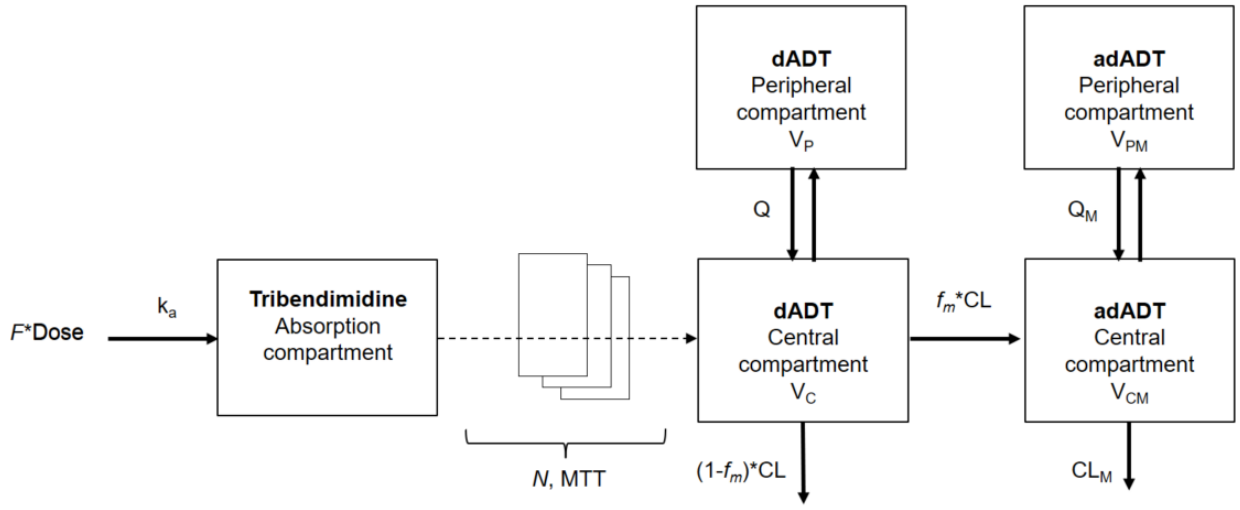


Figure S1. Schematic presentation of the model structure. F: bioavailability, k_a: absorption rate constant, N: estimated number of transit compartments, MTT: mean transit time, dADT: primary metabolite, V_C and V_P: volume of distribution of the central and peripheral compartment, Q: inter-compartmental clearance, CL: clearance, f_m: fraction metabolized into adADT (secondary metabolite). All PK parameters describing the secondary metabolite adADT are indicated with the subscript M.

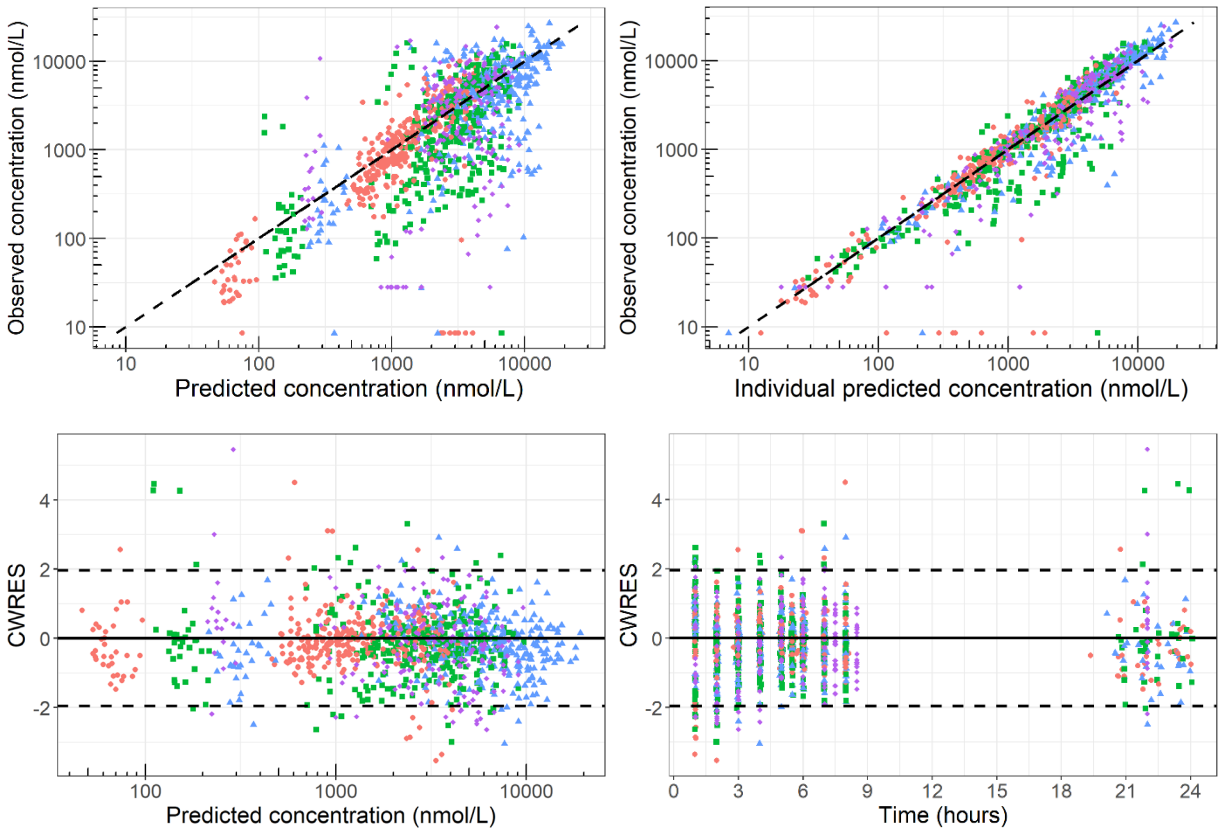


Figure S2. Goodness-of-fit plots of primary metabolite dADT, with population and individual predicted concentrations versus observed concentrations (top row) and conditionally weighted residuals (CWRES) versus predicted concentration and time after dose (bottom row). Colors and shape indicate different dose levels: 100 mg (red circle), 200 mg (green square), and 400 mg in school-aged children (blue triangle) and 400 mg in adolescents (purple diamond).

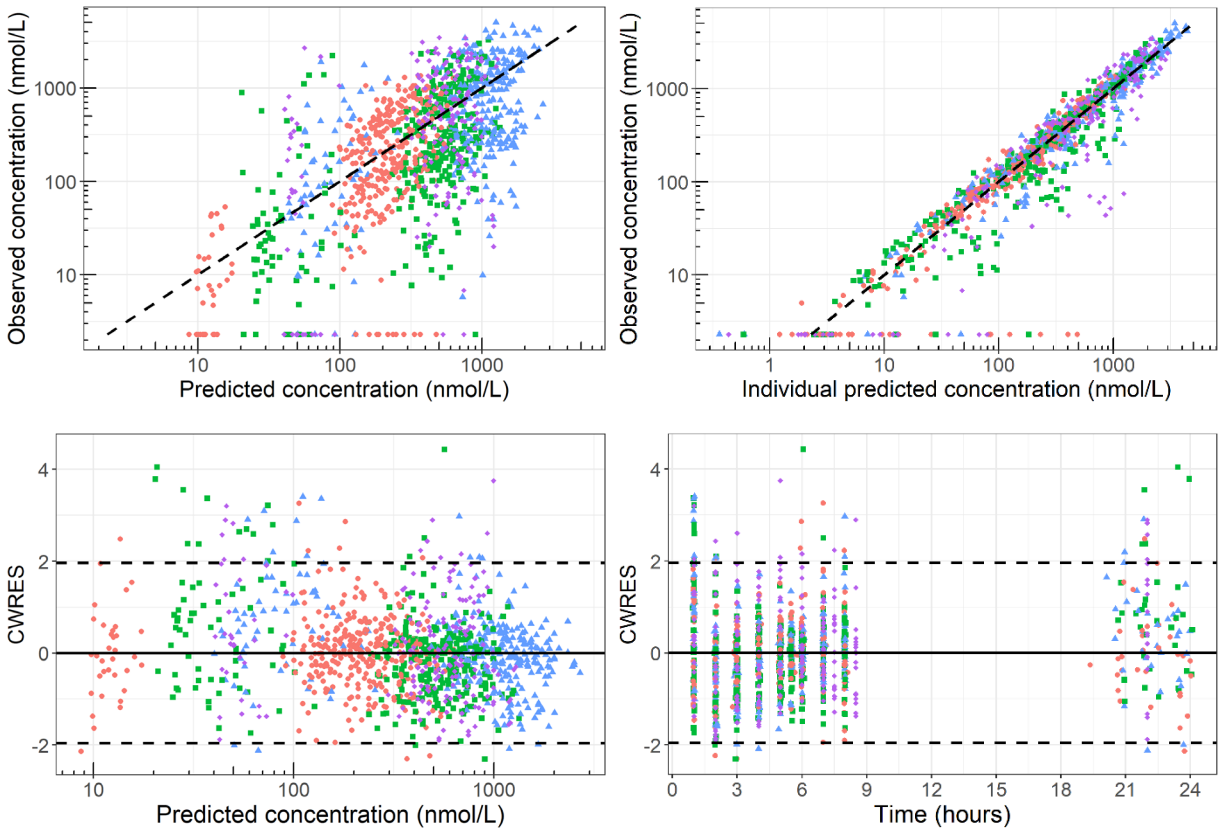


Figure S3. Goodness-of-fit plots of secondary metabolite adADT, with population and individual predicted concentrations versus observed concentrations (top row) and conditionally weighted residuals (CWRES) versus predicted concentration and time after dose (bottom row). Colors and shape indicate different dose levels: 100 mg (red circle), 200 mg (green square), and 400 mg in school-aged children (blue triangle) and 400 mg in adolescents (purple diamond).

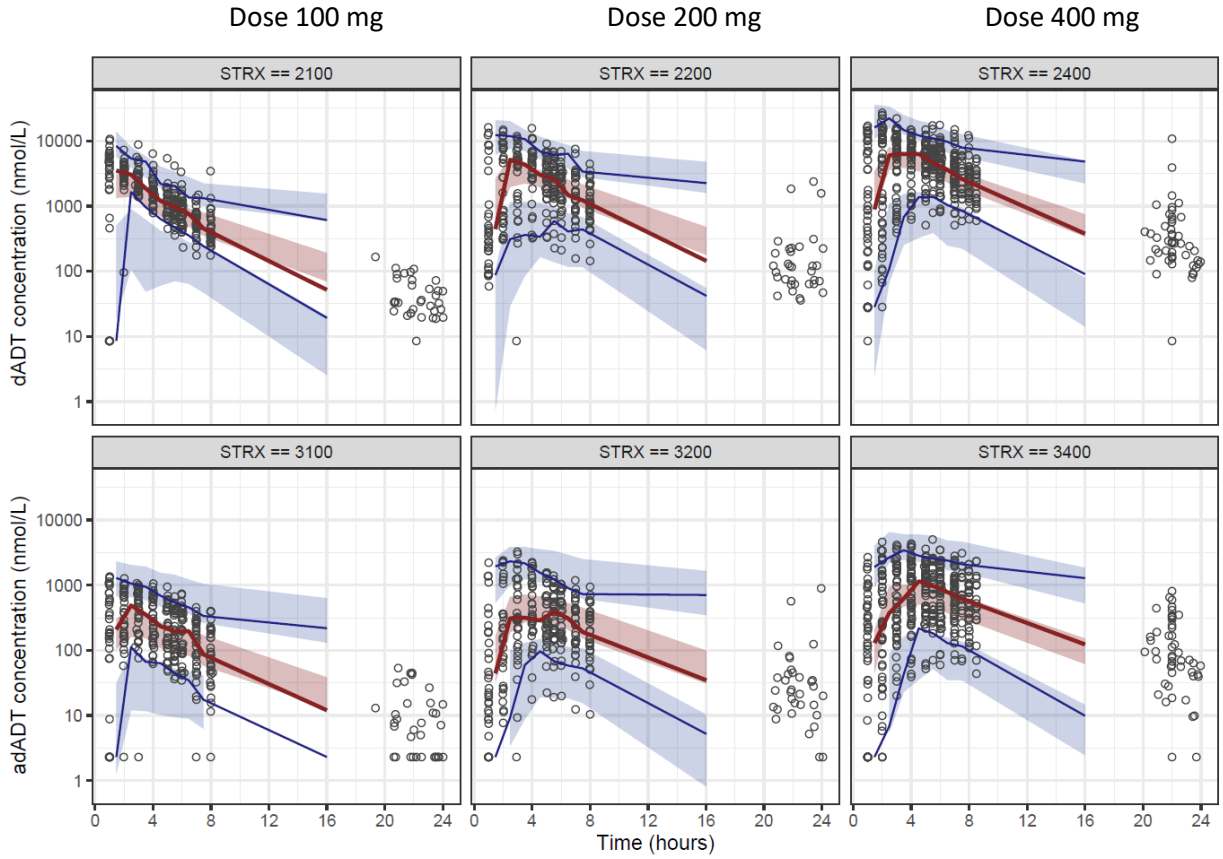


Figure S4. Visual predictive check (VPC) for dADT (top row) and adADT (bottom row), with observed (points and summarized in lines) and simulated (shaded areas, n=500) concentration over time in children and adolescents. Plots are stratified per dose level, with left: 100 mg (STRX 2100, 3100), middle: 200 mg (STRX 2200, 3200), right: 400 mg (STRX 2400, 3400).

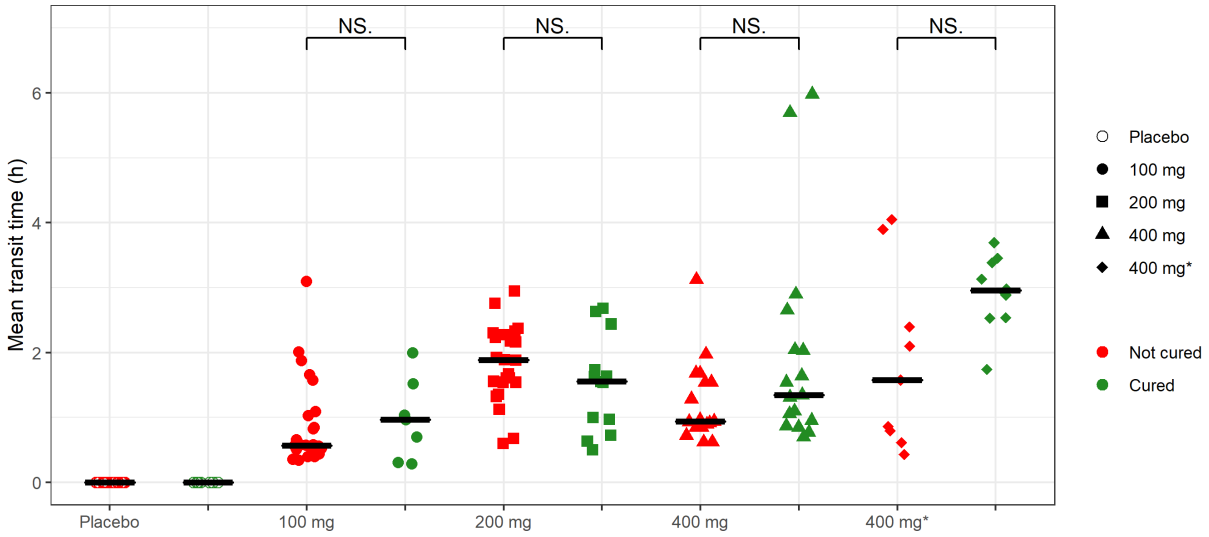


Figure S5. Intestinal residence time (reflected by mean transit time) *versus* response. Symbols represent different dose arms (open circle: placebo, closed circle: 100 mg, square: 200 mg, triangle: 400 mg in school-aged children, diamond: 400 mg in adolescents), and colors indicate study participants who are cured (green), and who are not cured (red). *Two groups of subjects received a 400 mg dose: school-aged children "400 mg", and adolescents who are indicated with an asterisk: "400 mg*". NS indicates no significant group differences were observed in the independent 2-group Wilcoxon-Mann-Whitney test ($p > 0.05$).

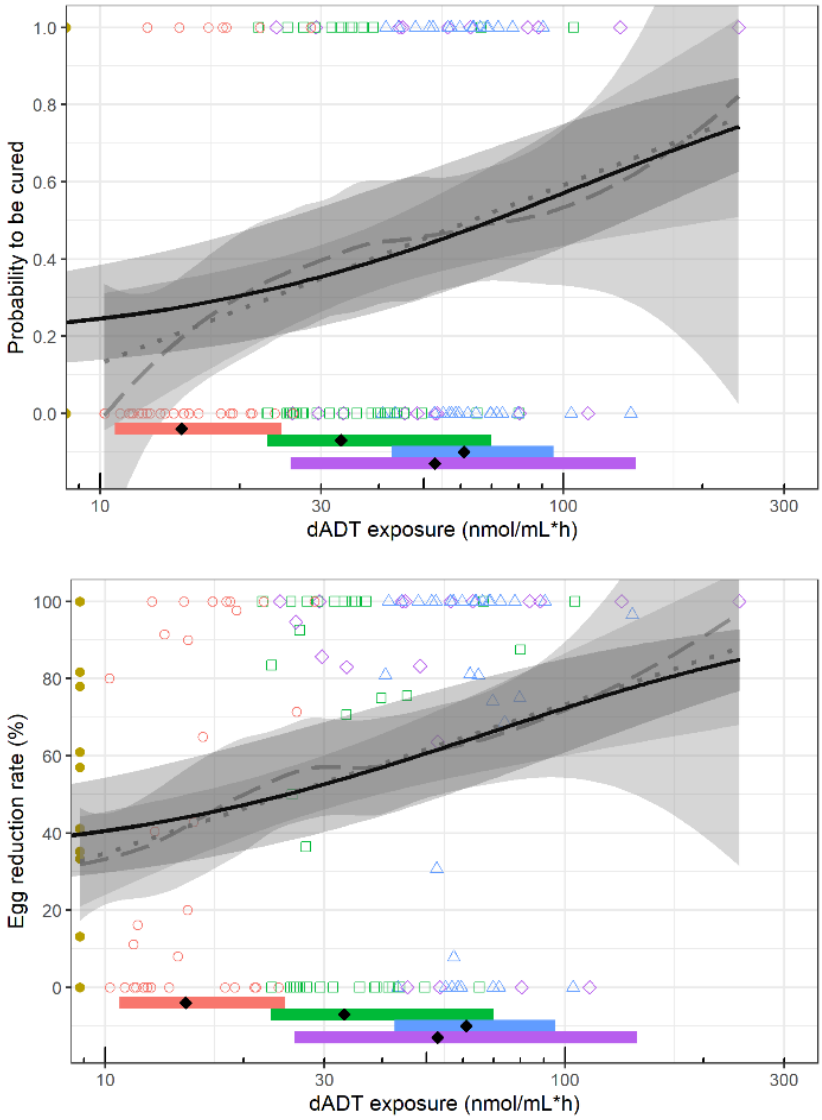
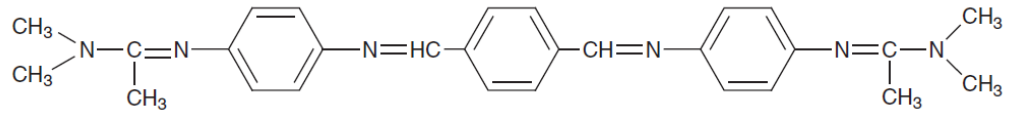
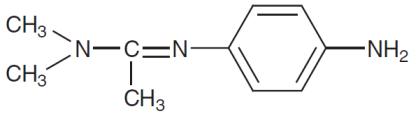


Figure S6. Evaluation of the exposure-response analysis. (A) dADT exposure versus probability to be cured. (B) dADT exposure versus egg reduction rate. Colored symbols indicate individuals receiving different dose levels, with yellow for placebo arm, red for 100 mg, green for 200 mg, blue for 400 mg in school-aged children, and purple for 400 mg in adolescents. Black solid line: predicted model, with 80% confidence interval (shaded area). The horizontal colored bars show the 90% confidence interval of exposure per dose group with the black diamond indicating the median exposure per arm. The grey dashed (--) and dotted (···) lines are smoothing functions, summarizing the data using a loess function and a linear model, respectively.

Tribendimidine



dADT



adADT

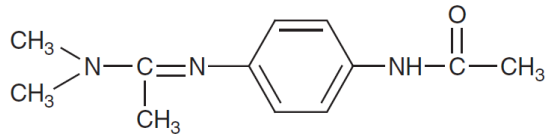


Figure S7. Molecular structures of the prodrug Tribendimidine, the active primary metabolite deacetylated amidantel (dADT) and the secondary metabolite, acetylated derivative of amidantel (adADT).