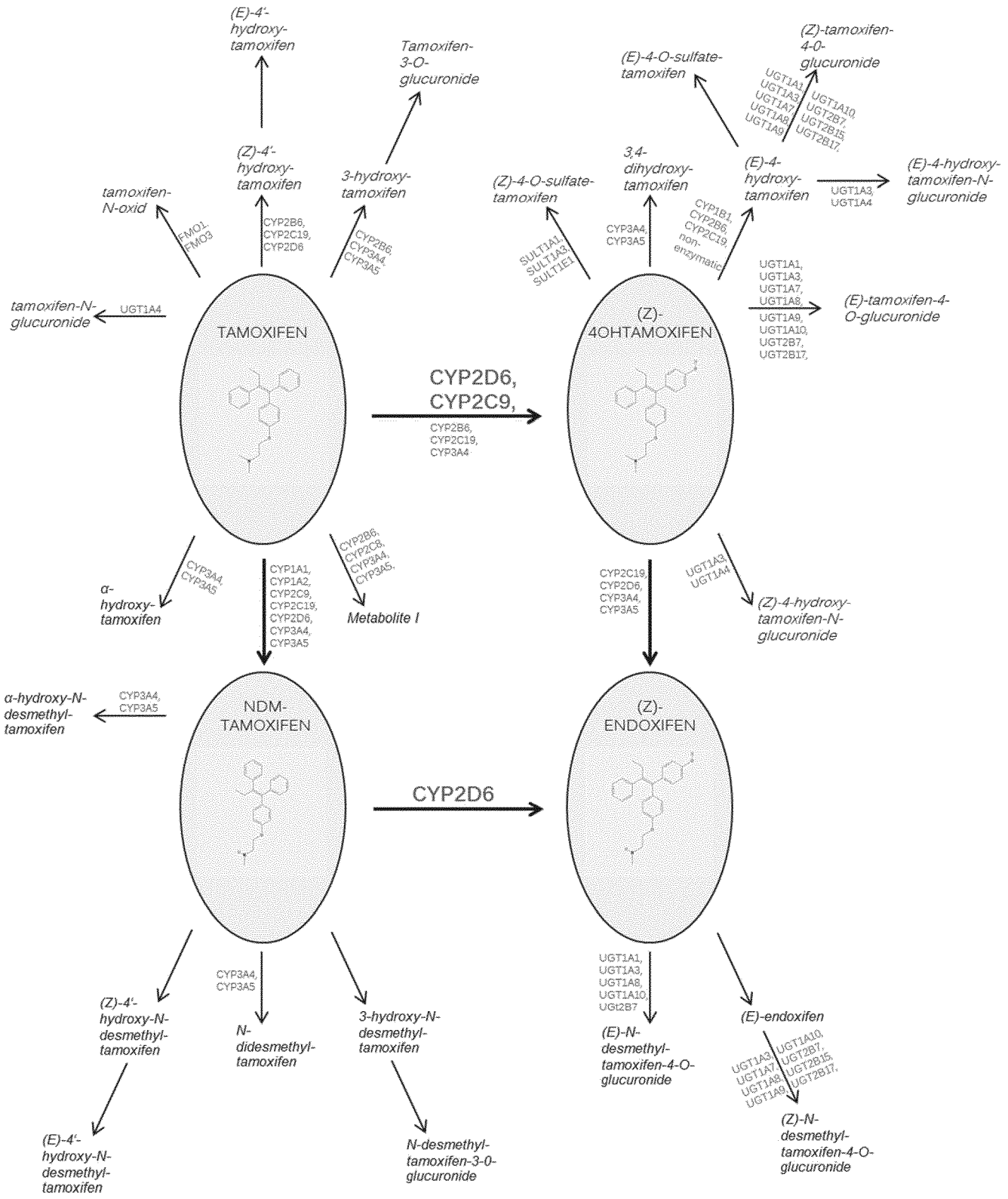

(E)-4'-hydroxy-tamoxifen
Tamoxifen-3-O-glucuronide
(Z)-4'-hydroxy-tamoxifen
3-hydroxy-tamoxifen
tamoxifen-N-oxid
FMO1-FMO3
CYP2B6, CYP2C19, CYP2D6
CYP2B6, CYP3A4, CYP3A5
tamoxifen-N-glucuronide
UGT1A4
TAMOXIFEN
CYP2D6, CYP2C9,
CYP2B6, CYP2C19, CYP3A4
CYP3A4, CYP3A5
α-hydroxy-tamoxifen
CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5
CYP2B6, CYP2C8, CYP3A4, CYP3A5
Metabolite I
α-hydroxy-N-desmethyl-tamoxifen
CYP3A4, CYP3A5
NDM-TAMOXIFEN
CYP2D6
(Z)-4'-hydroxy-N-desmethyl-tamoxifen
CYP3A4, CYP3A5
N-didesmethyl-tamoxifen
3-hydroxy-N-desmethyl-tamoxifen
(E)-4'-hydroxy-N-desmethyl-tamoxifen
N-desmethyl-tamoxifen-3-0-glucuronide
(E)-4-O-sulfate-tamoxifen
(Z)-tamoxifen-4-0-glucuronide
UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9
UGT1A10, UGT2B7, UGT2B15, UGT2B17,
(Z)-4-O-sulfate-tamoxifen
3,4-dihydroxy-tamoxifen
(E)-4-hydroxy-tamoxifen
(E)-4-hydroxy-tamoxifen-N-glucuronide
UGT1A3, UGT1A4
SULT1A1, SULT1A3, SULT1E1
CYP3A4, CYP3A5
CYP1B1, CYP2B6, CYP2C19, non-enzymatic
UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, UGT2B17,
(E)-tamoxifen-4-O-glucuronide
(Z)-4OHTAMOXIFEN
CYP2C19, CYP2D6, CYP3A4, CYP3A5
UGT1A3, UGT1A4
(Z)-4-hydroxy-tamoxifen-N-glucuronide
(Z)-ENDOXIFEN
UGT1A1, UGT1A3, UGT1A8, UGT1A10, UGt2B7
(E)-N-desmethyl-tamoxifen-4-O-glucuronide
(E)-endoxifen
UGT1A3, UGT1A7, UGT1A8, UGT1A9
UGT1A10, UGT2B7, UGT2B15, UGT2B17,
(Z)-N-desmethyl-tamoxifen-4-O-glucuronide

Abbildung 1

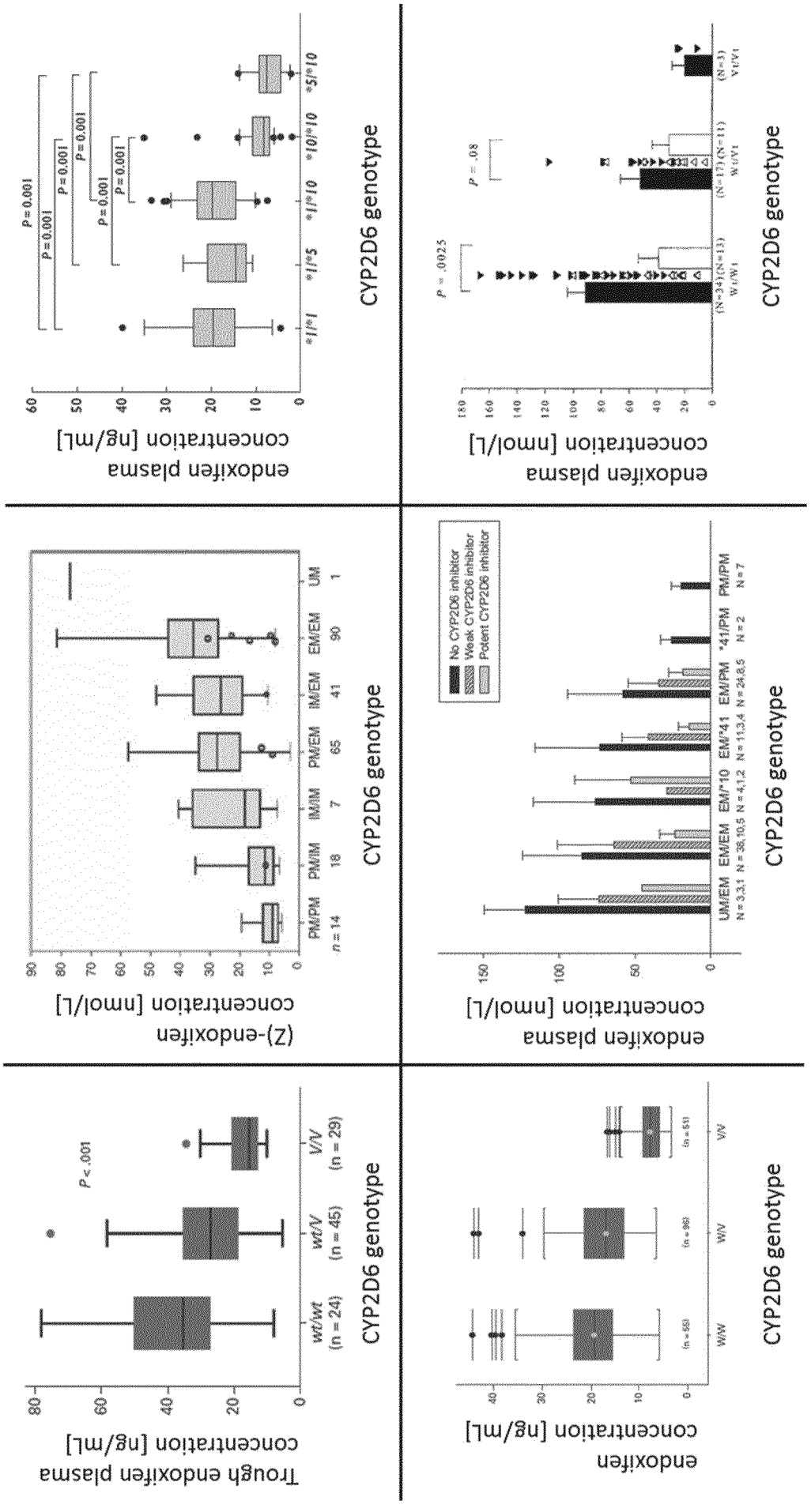

Trough endoxifen plasma concentration [ng/mL]
P < .001
wt/wt (n = 24)
wt/V (n = 45)
V/V (n = 29)
CYP2D6 genotype
(Z)-endoxifen concentration [nmol/L]
PM/PM n = 14
PM/IM 18
IM/IM 7
PM/EM 65
IM/EM 41
EM/EM 90
UM 1
CYP2D6 genotype
endoxifen concentration [ng/mL]
W/W (n = 69)
W/V (n = 96)
V/V (n = 51)
CYP2D6 genotype
endoxifen plasma concentration [nmol/L]
No CYP2D6 inhibitor
Weak CYP2D6 inhibitor
Potent CYP2D6 inhibitor
UM/EM N = 3,3,1
EM/EM N = 38,10,5
EM/*10 N = 4,1,2
EM/*41 N = 11,3,4
EM/PM N = 24,8,5
*41/PM N = 2
PM/PM N = 7
CYP2D6 genotype
endoxifen plasma concentration [nmol/L]
P = .0025
P = .08
(N=34)(N=13) Wt/Wt
(N=17)(N=11) Wt/Vt
(N=3) Vt/Vt
CYP2D6 genotype
endoxifen plasma concentration [ng/mL]
P = 0.001
P = 0.001
P = 0.001
P = 0.001
P = 0.001
P = 0.001
*1/*1
*1/*5
*1/*10
*10/*10
*5/*10
CYP2D6 genotype

Abbildung 2

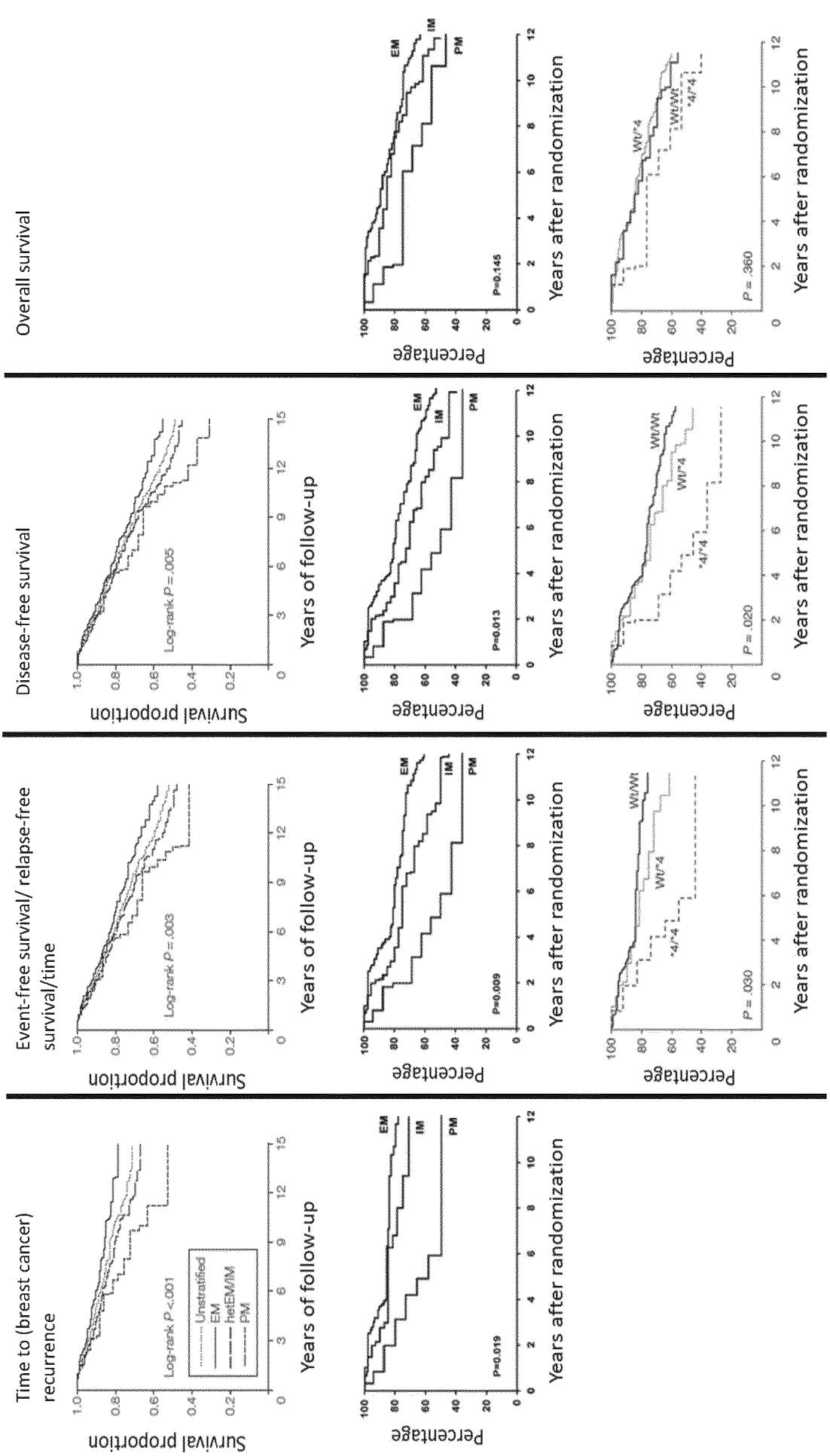
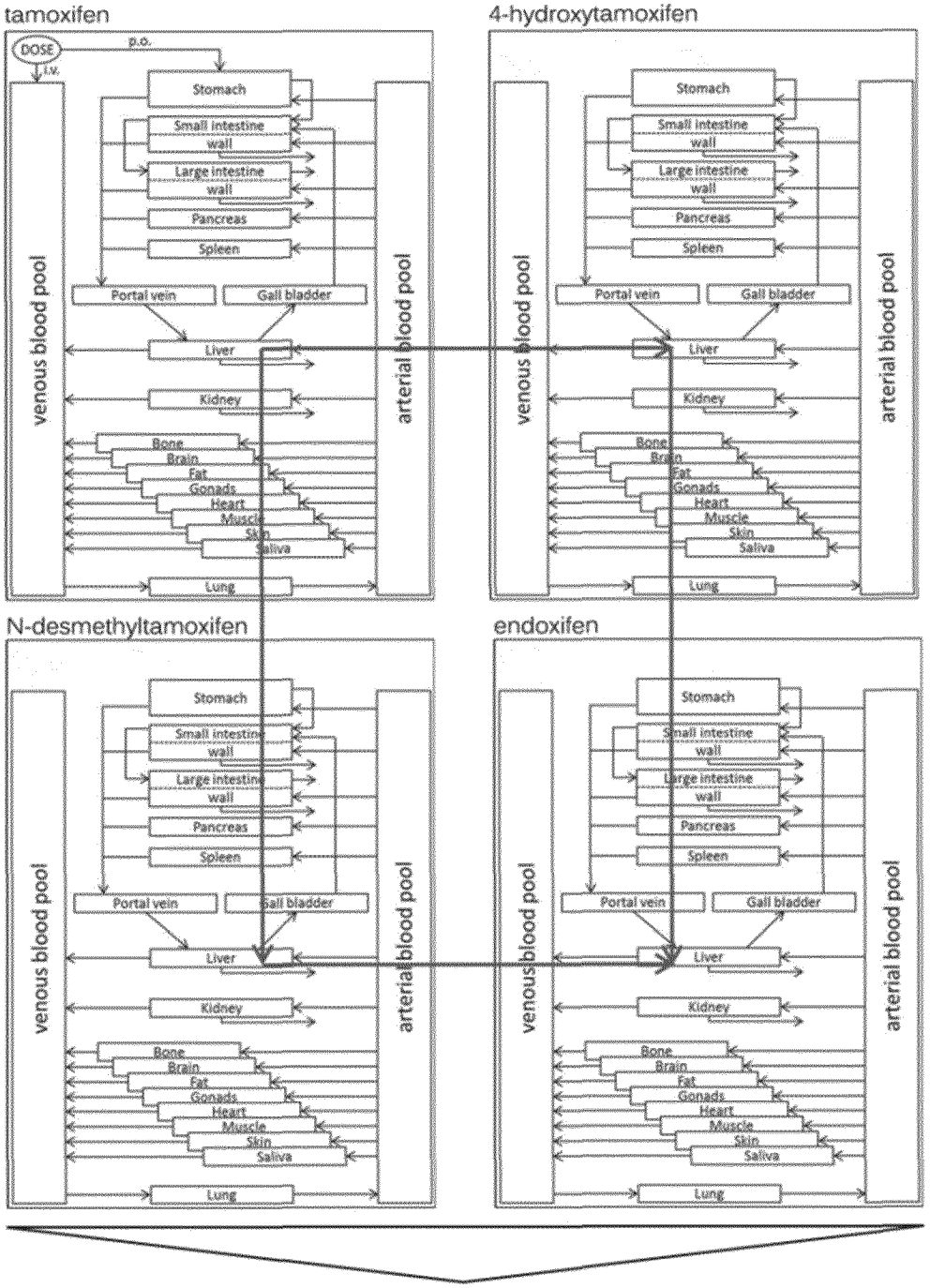

Time to (breast cancer) recurrence
Event-free survival/ relapse-free survival/time
Disease-free survival
Overall survival
Survival proportion
Years of follow-up
Unstratified
EM
hetEM/IM
PM
Log-rank P <.001
Log-rank P = .003
Log-rank P = .005
Percentage
Years after randomization
EM
IM
PM
P=0.019
P=0.009
P=0.013
P=0.145
Wt/Wt
Wt/*4
*4/*4
P = .030
P = .020
P = .360

Abbildung 3


tamoxifen
DOSE
p.o.
i.v.
Stomach
Small intestine wall
Large intestine wall
Pancreas
Spleen
Portal vein
Gall bladder
Liver
Kidney
Bone
Brain
Fat
Gonads
Heart
Muscle
Skin
Saliva
Lung
venous blood pool
arterial blood pool
4-hydroxytamoxifen
N-desmethyltamoxifen
endoxifen

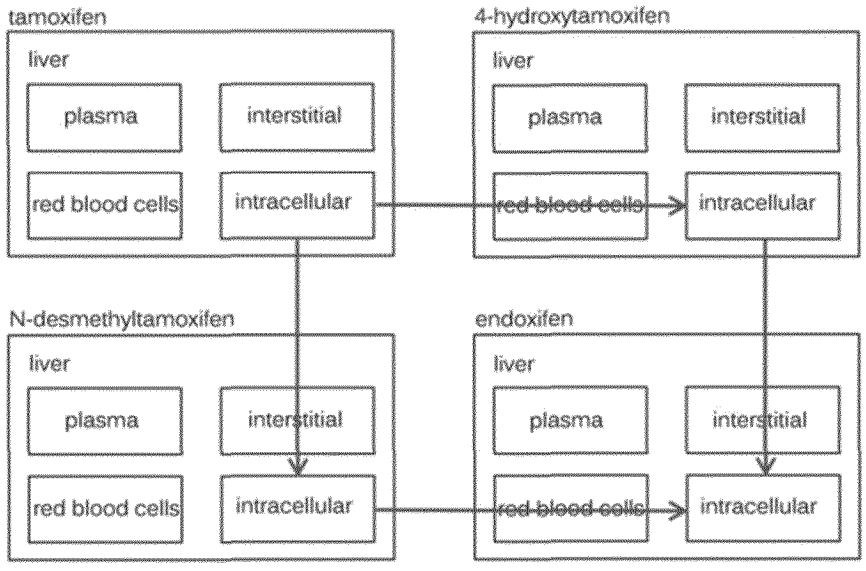

tamoxifen
liver
plasma
interstitial
red blood cells
intracellular
4-hydroxytamoxifen
N-desmethyltamoxifen
endoxifen

Abbildung 4

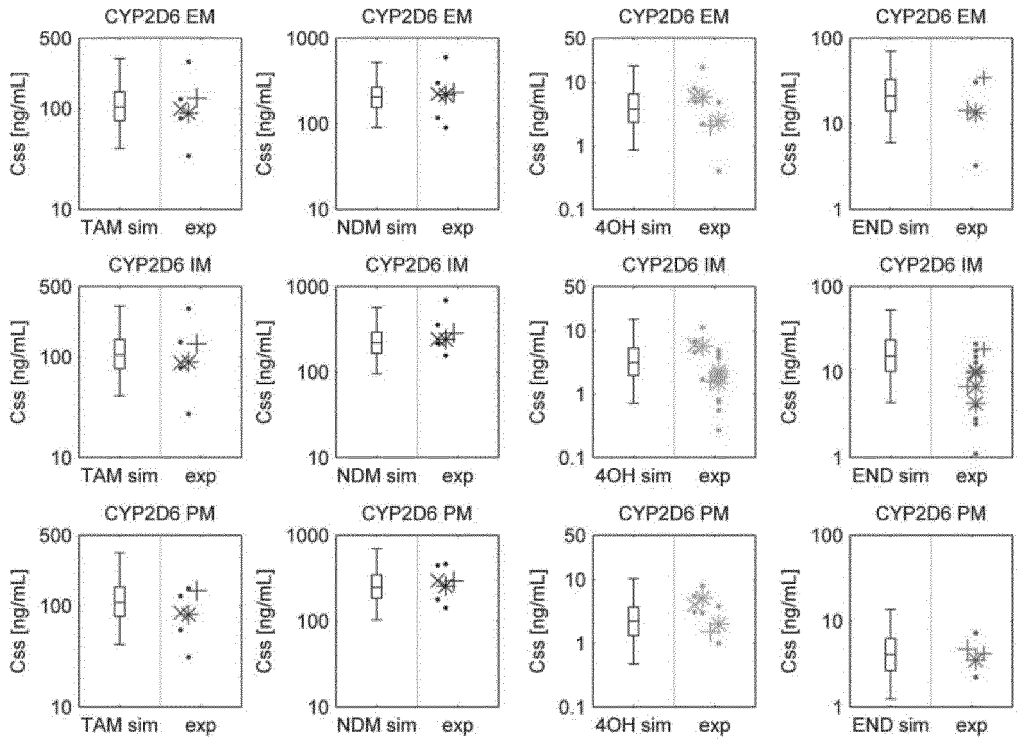


Abbildung 5A

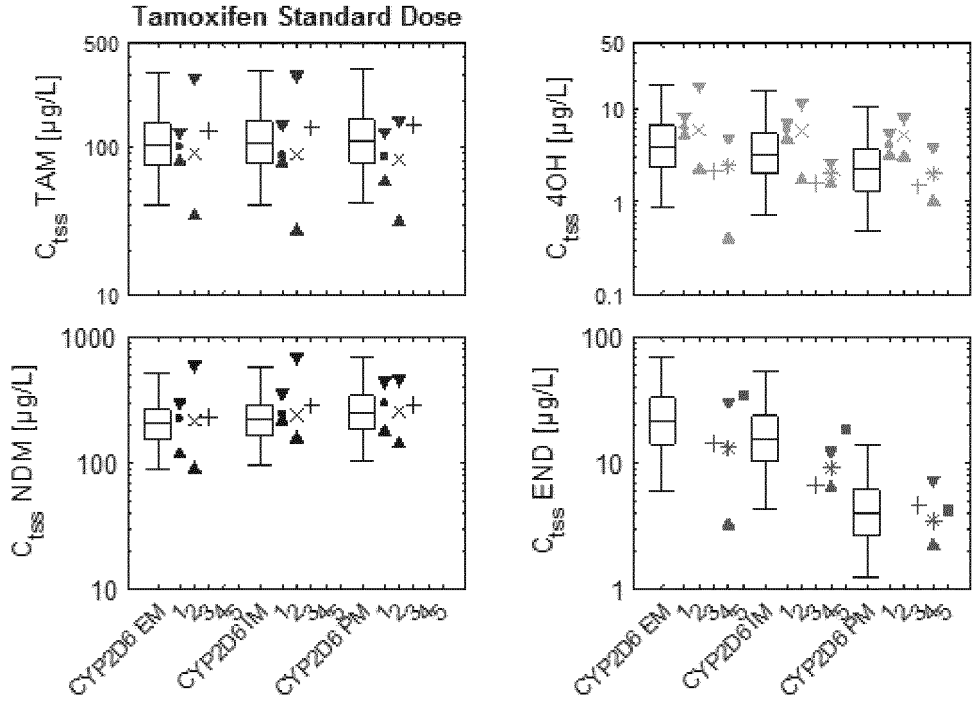


Abbildung 5B

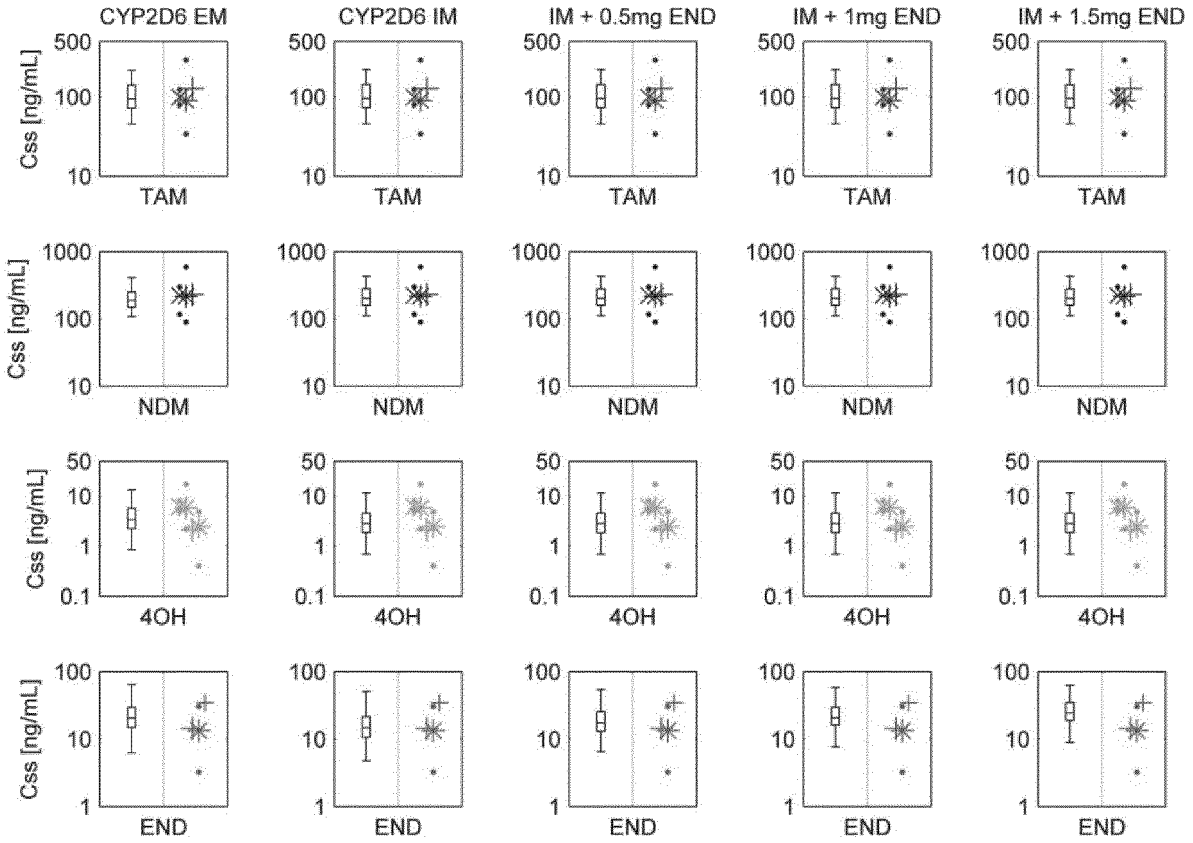


Abbildung 6A

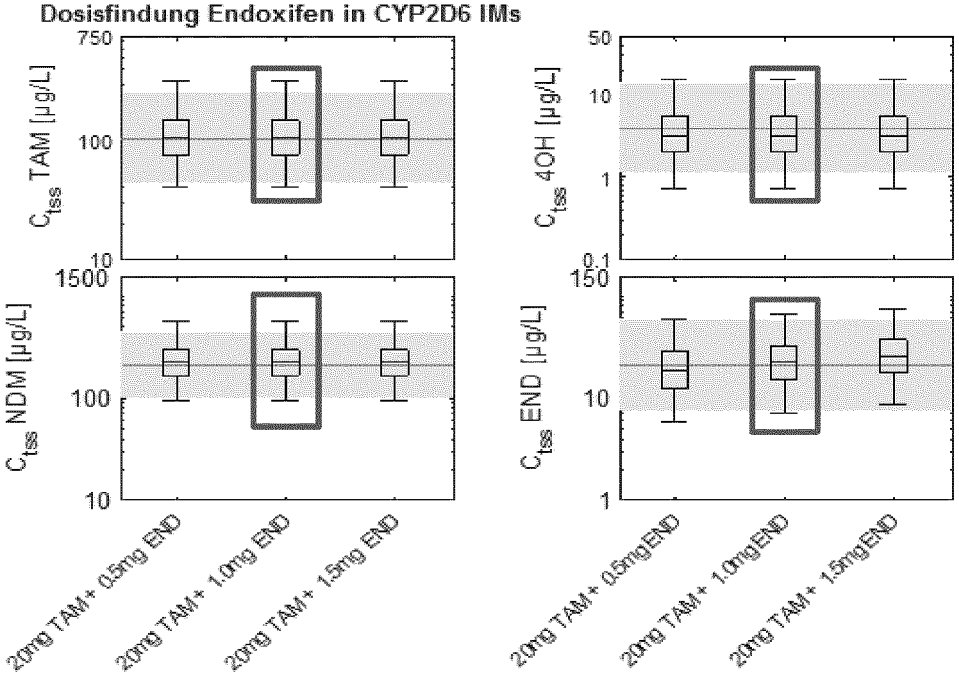


Abbildung 6B

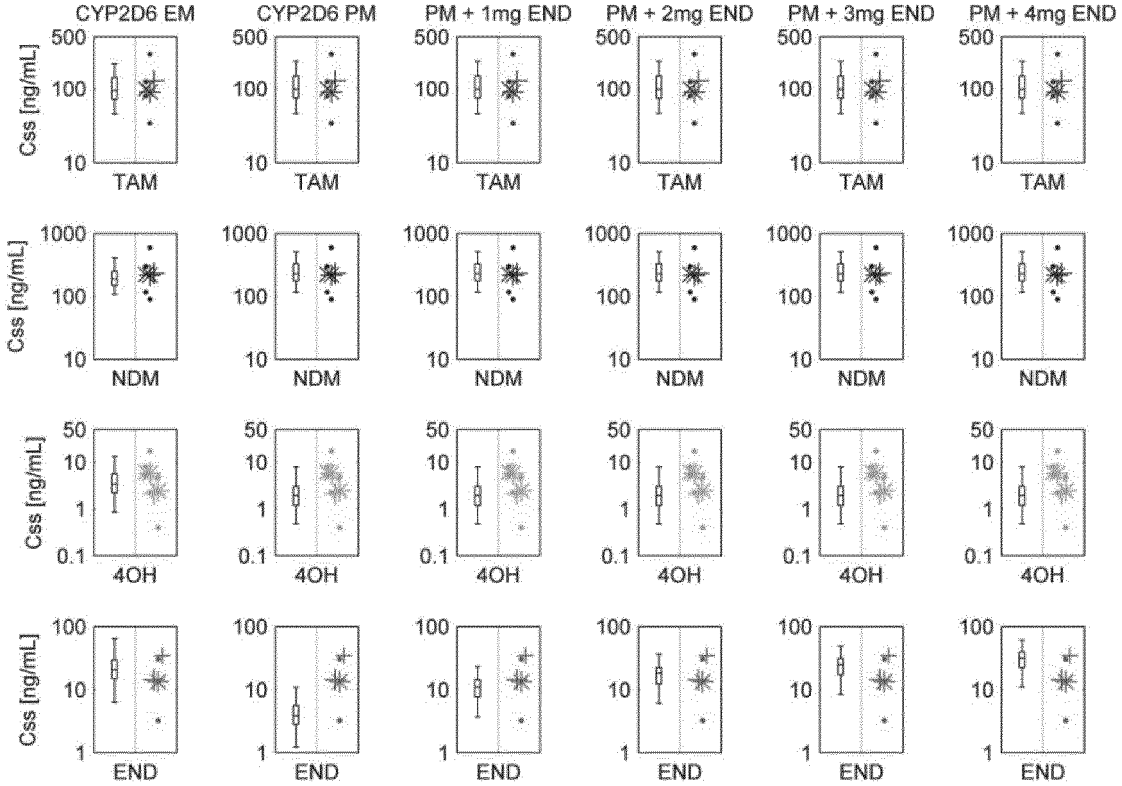


Abbildung 7A

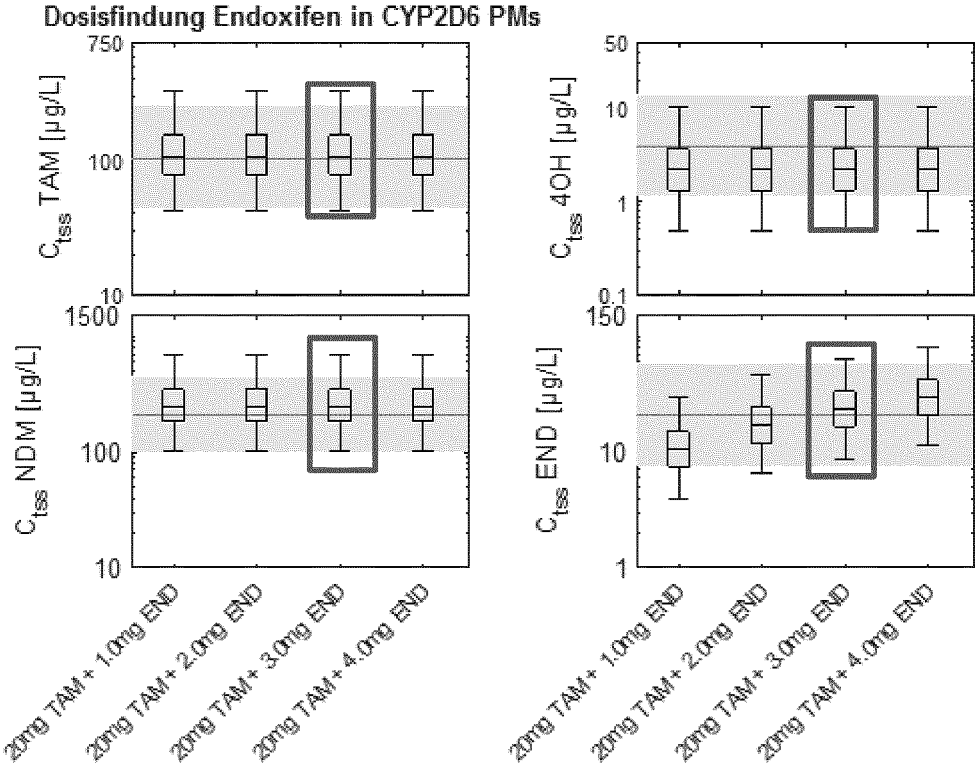


Abbildung 7B

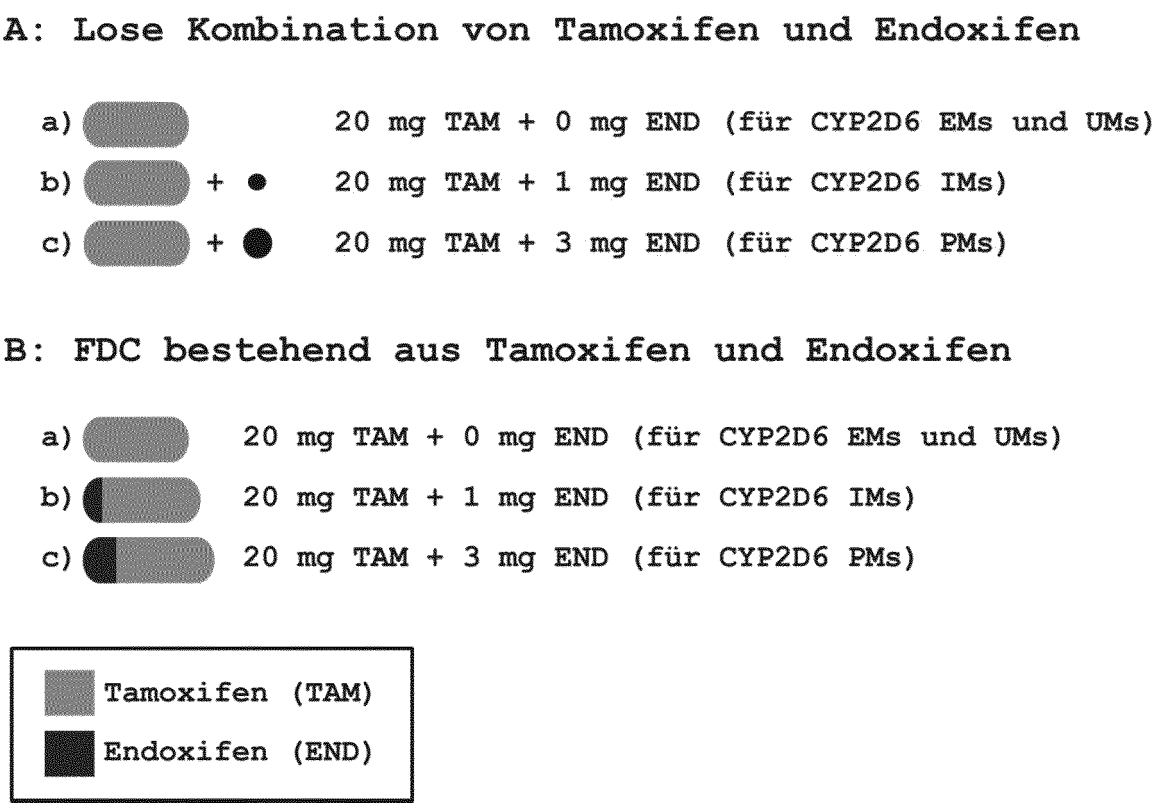

A: Lose Kombination von Tamoxifen und Endoxifen
a) 20 mg TAM + 0 mg END (für CYP2D6 EMs und UMs)
b) + 20 mg TAM + 1 mg END (für CYP2D6 IMs)
c) + 20 mg TAM + 3 mg END (für CYP2D6 PMs)
B: FDC bestehend aus Tamoxifen und Endoxifen
a) 20 mg TAM + 0 mg END (für CYP2D6 EMs und UMs)
b) 20 mg TAM + 1 mg END (für CYP2D6 IMs)
c) 20 mg TAM + 3 mg END (für CYP2D6 PMs)
Tamoxifen (TAM)
Endoxifen (END)

Abbildung 8

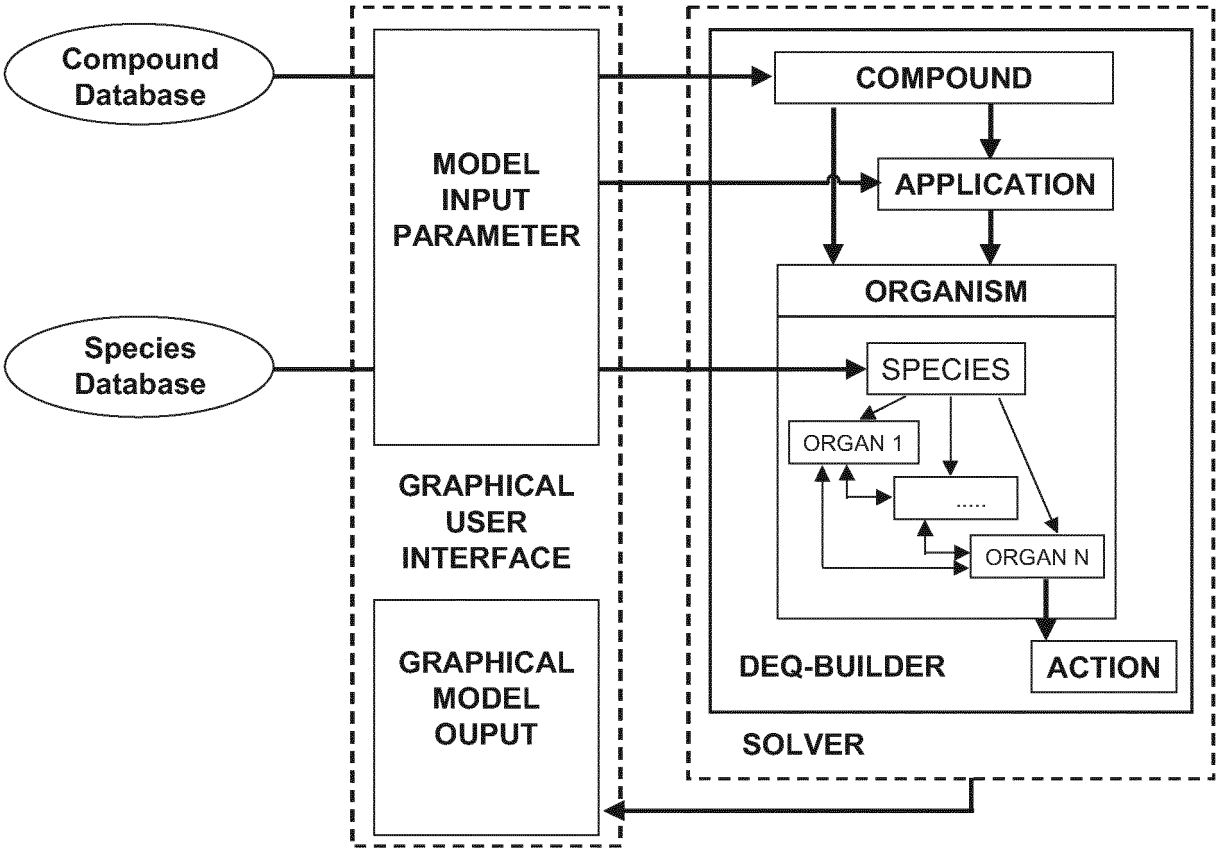

Compound Database
Species Database
MODEL INPUT PARAMETER
GRAPHICAL USER INTERFACE
GRAPHICAL MODEL OUPUT
COMPOUND
APPLICATION
ORGANISM
SPECIES
ORGAN 1
.....
ORGAN N
DEQ-BUILDER
ACTION
SOLVER

Abbildung 9

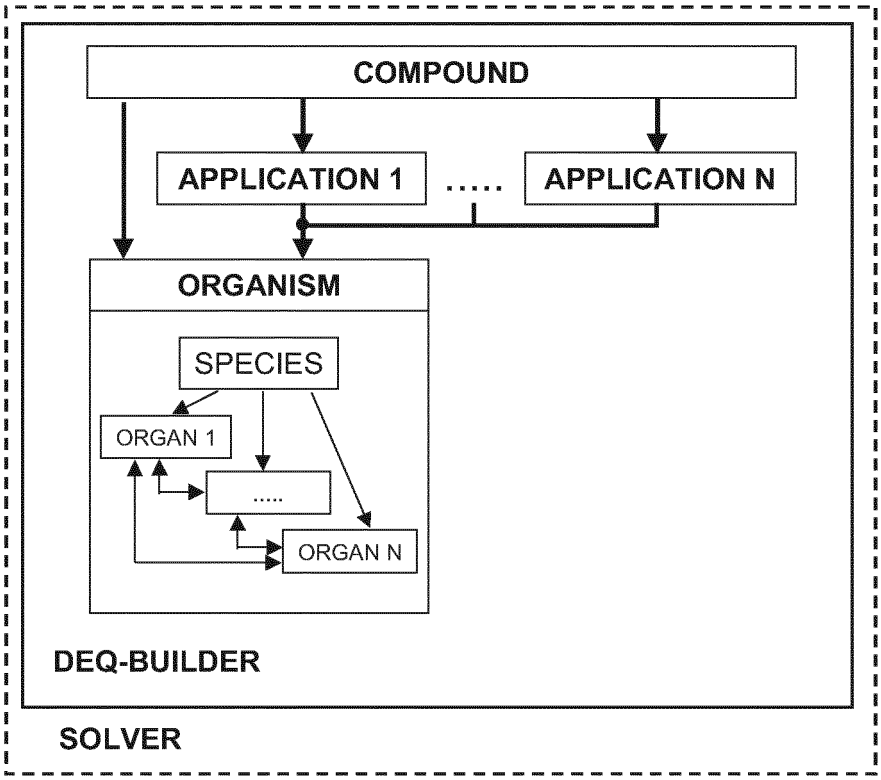


Abbildung 10

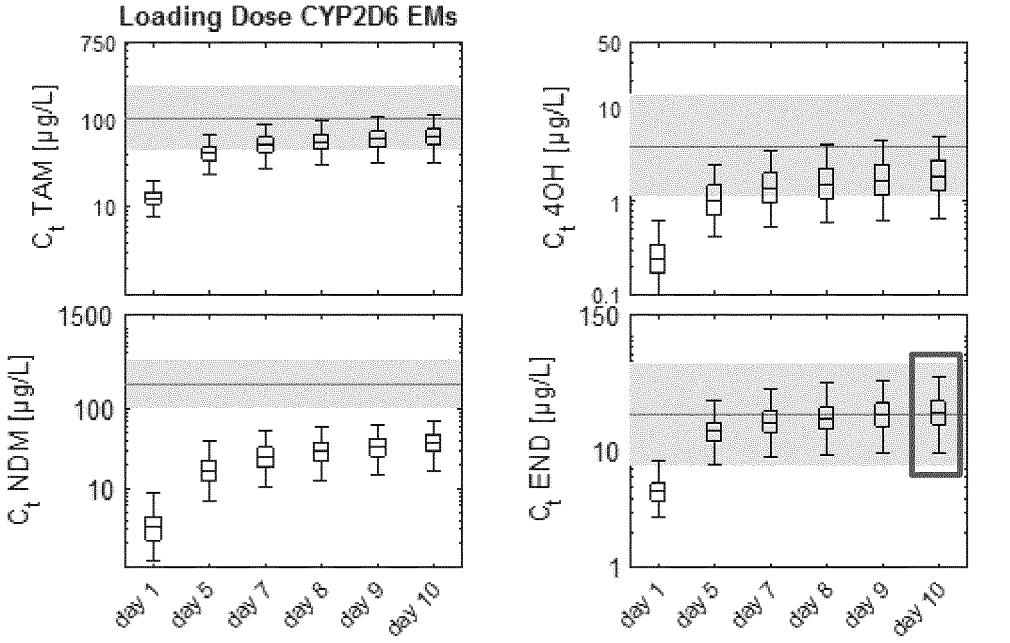


Abbildung 11

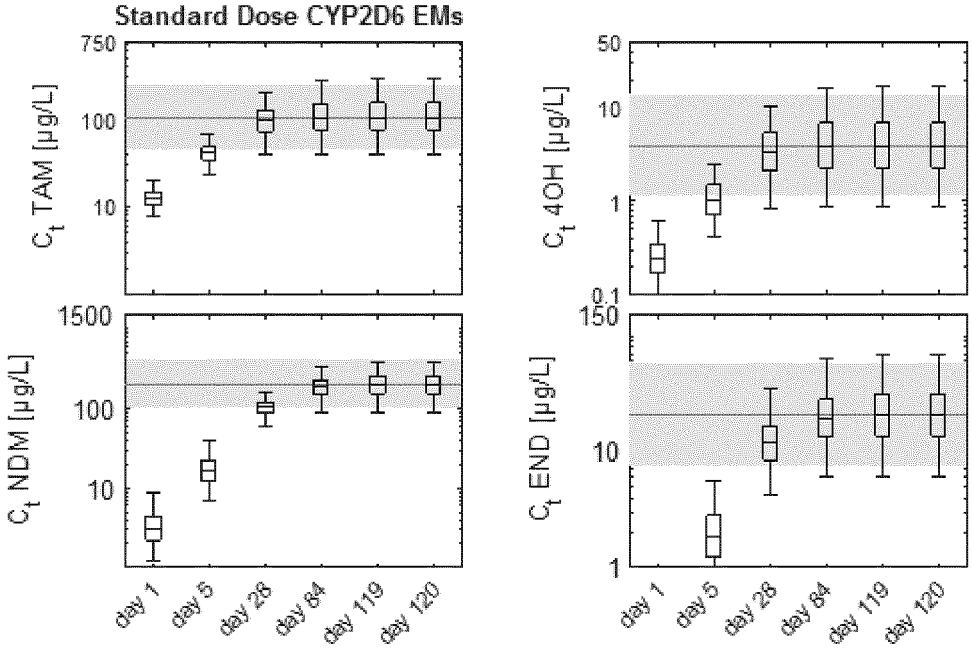


Abbildung 12

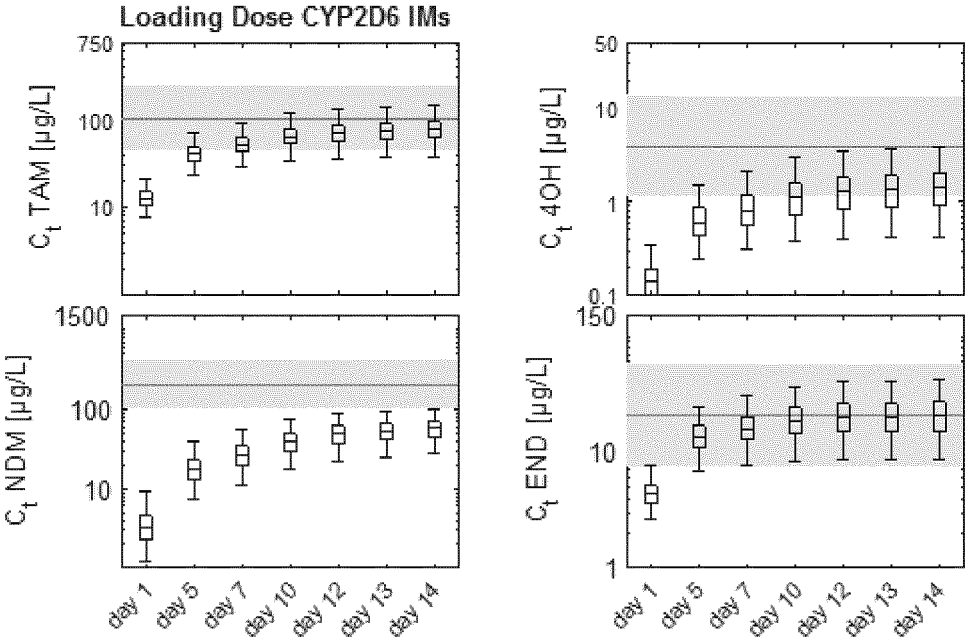


Abbildung 13

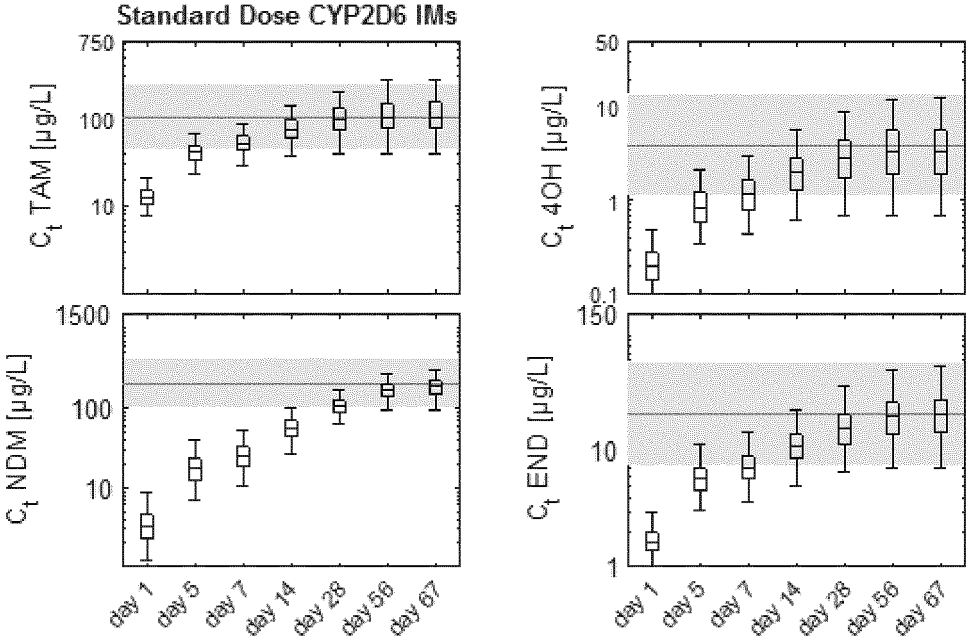


Abbildung 14

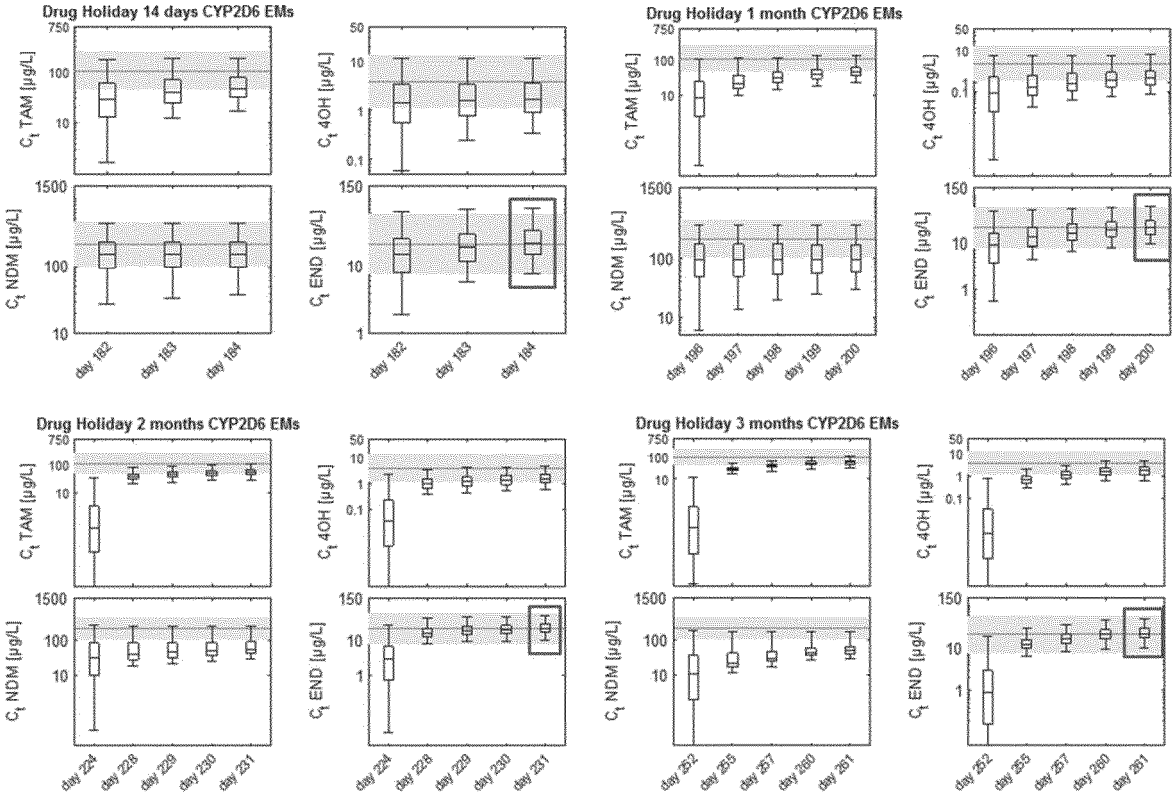


Abbildung 15

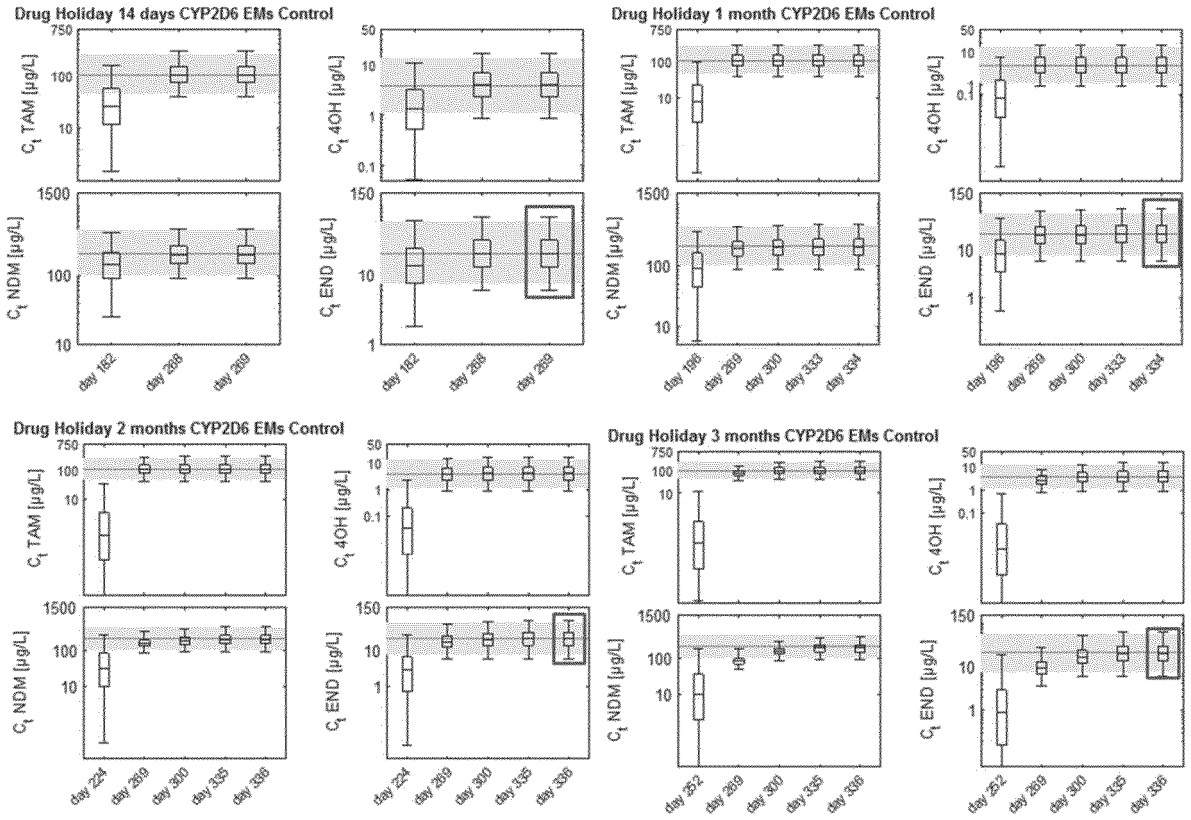


Abbildung 16

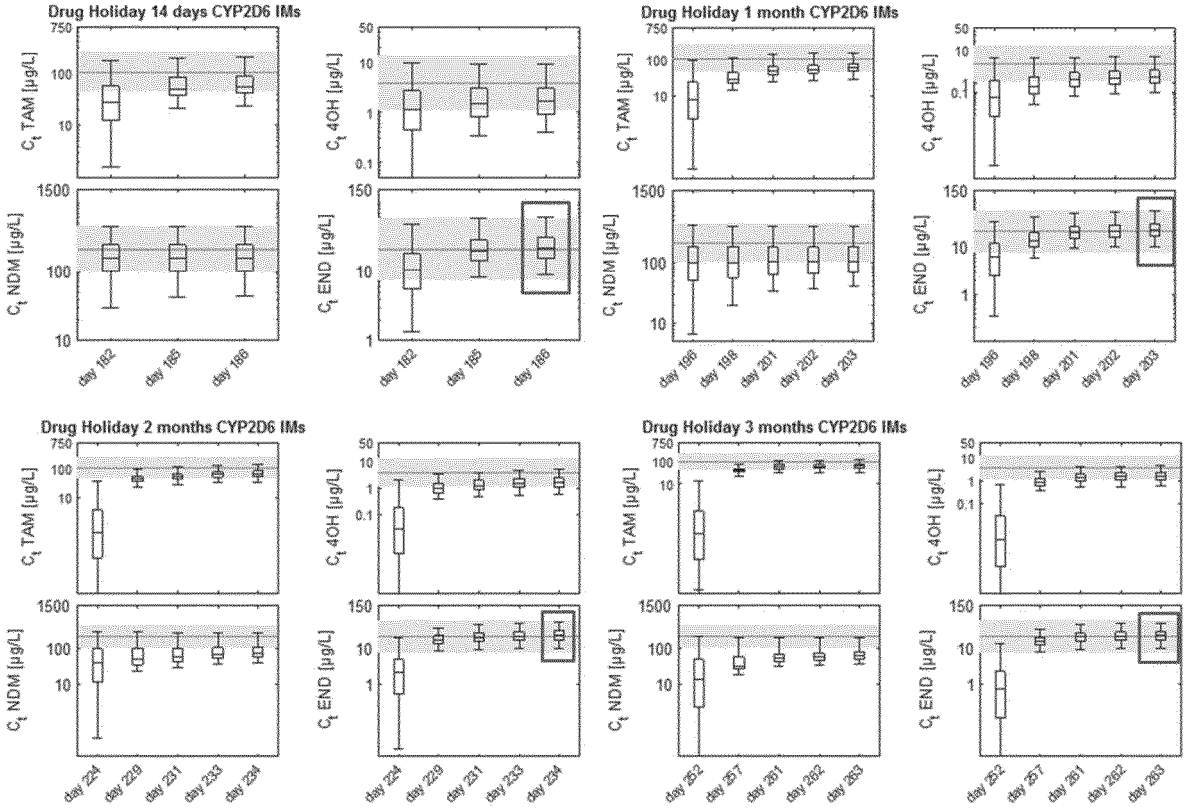


Abbildung 17

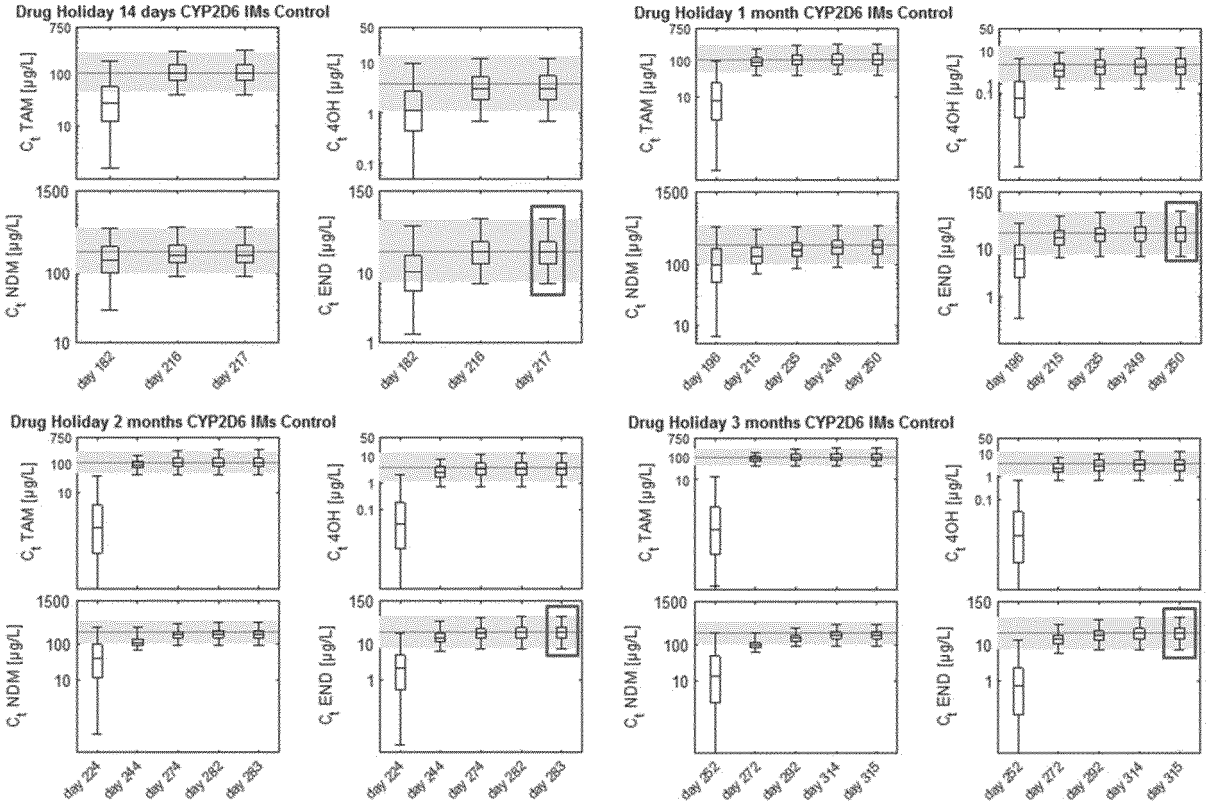


Abbildung 18