Drug Metabolism and Disposition

DMD-AR-2022-001096

Supplementary data

Absorption, Metabolism, and Excretion of Taselisib (GDC-0032), a Potent β-sparing PI3K Inhibitor, in Rats, Dogs, and Humans

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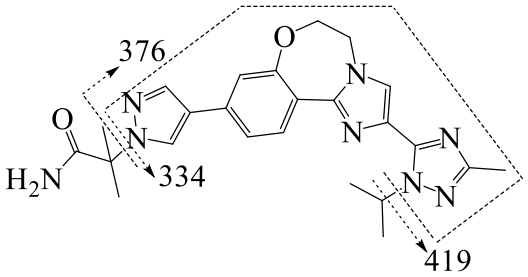
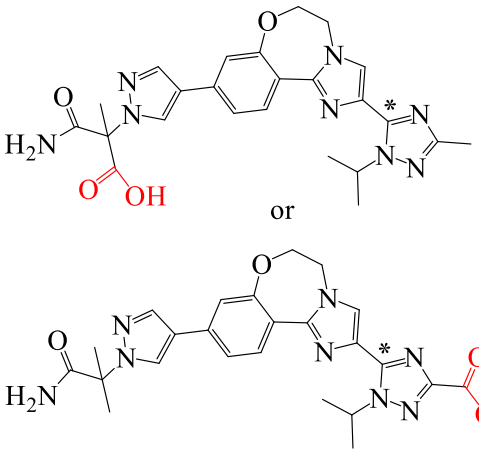
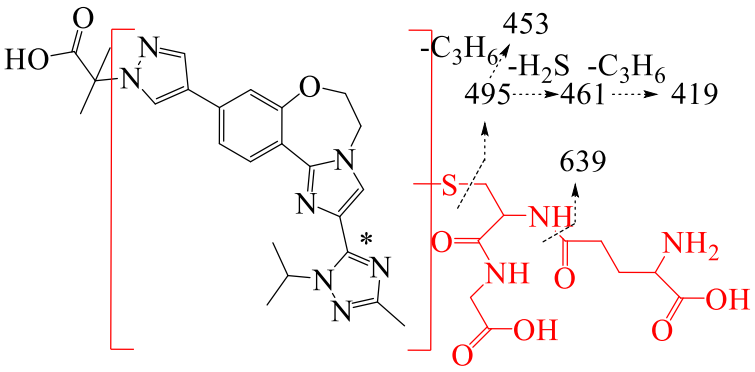
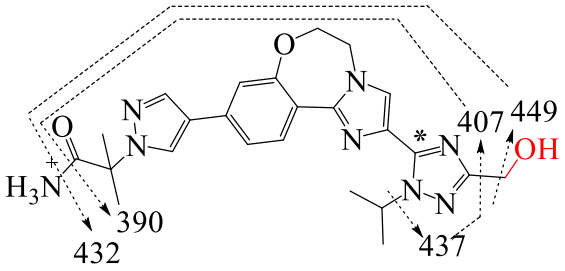
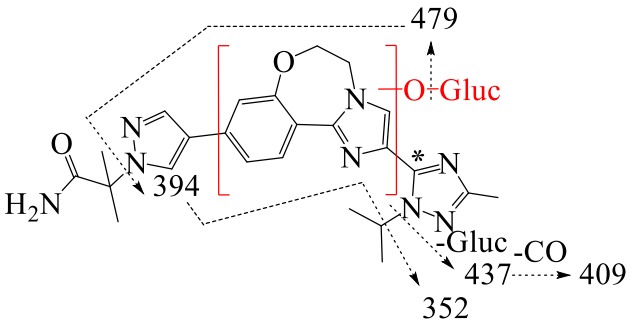
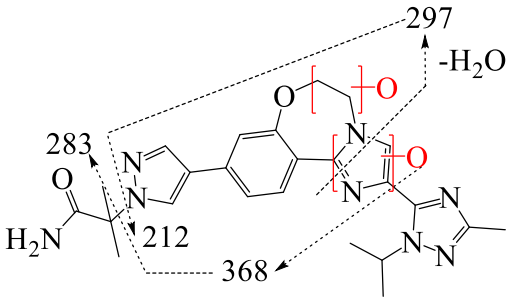
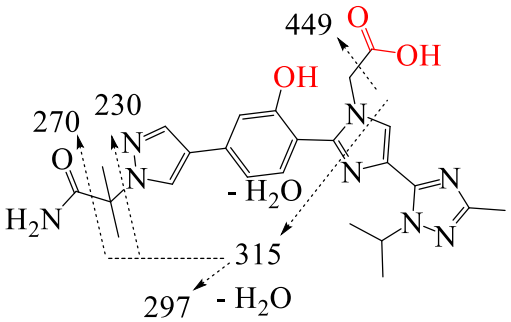
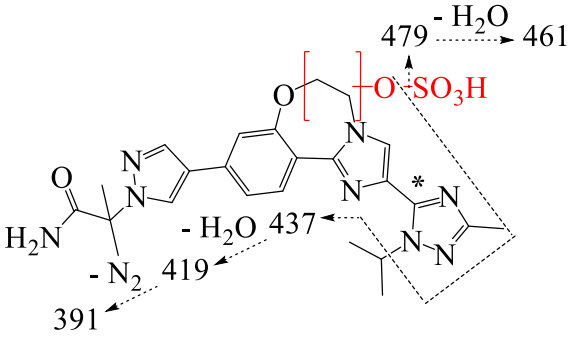
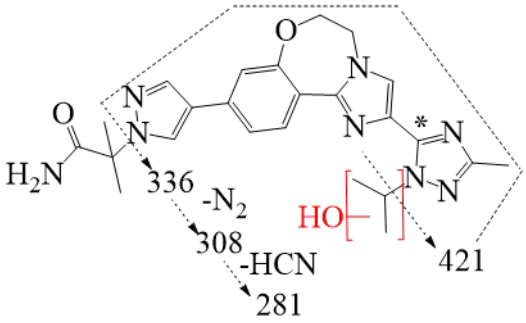
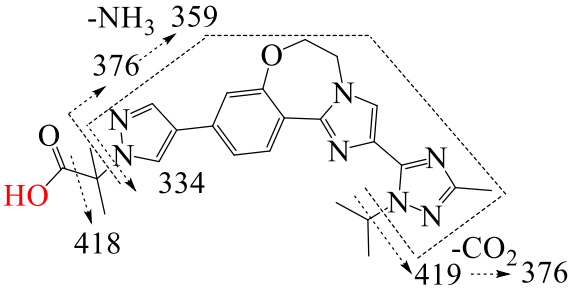
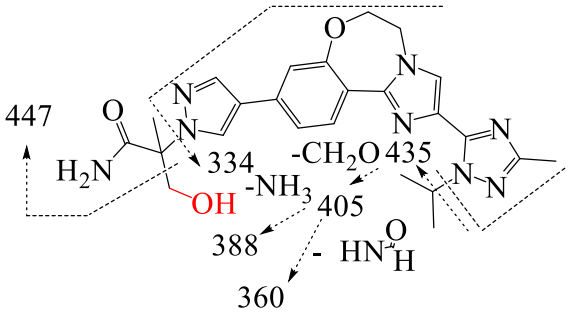
Supplementary Table S1. Summary of structures and mass fragmentation for metabolites of Taselisib in rats, dogs and humans.

Analyte	Observed MH+ (Chemical formula	Source	Structure
Taselisib	461.2408 ($C_{24}H_{29}N_8O_2^+$)	Rat: P, U, F, B Dog: P, U, F, B Human: P, U, F	
M1 (Oxidation to carboxylic acid)	*493.2182 ($^{14}CC_{23}H_{27}N_8O_4^+$)	Rat: B	 $[M+H]^+$=493 491-H_2O= 473 493-CO_2=449 449-NH_3=432 449-C_3H_6=407 432-CO=404 449-NH_3-C_3H_6=39
M2 (Glutathione conjugation	*768.3123 ($^{14}CC_{33}H_{44}N_{11}O_8S^+$)	Rat: B	

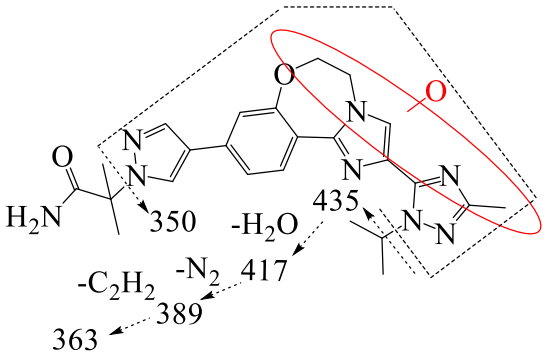
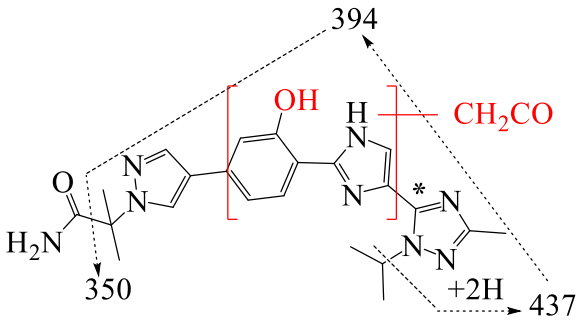
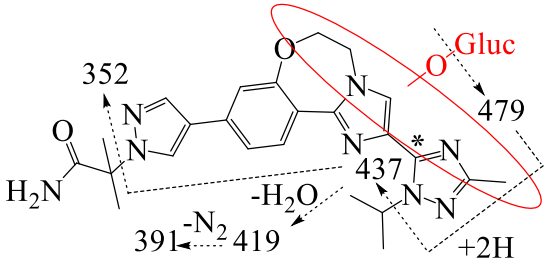
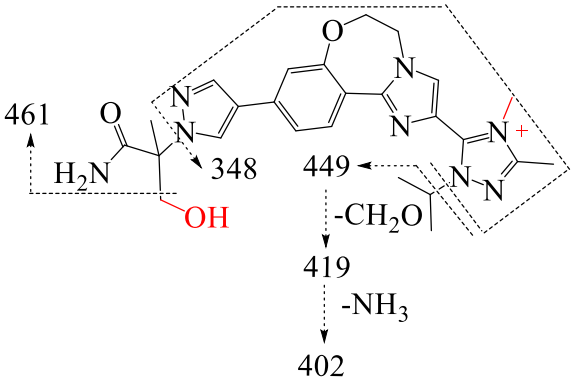
Supplementary Table S1 (continued). Summary of structures and mass fragmentation for metabolites of Taselisib in rats, dogs and humans.

Analyte	Observed MH+ (Chemical formula	Source	Structure
M3 (oxidation)	*479.2389 ($^{14}CC_{23}H_{29}N_8O_3^+$)	Rat: B	
M4 (oxidation & glucuronidation)	*655.2713 ($^{14}CC_{29}H_{37}N_8O_9^+$)	Rat: B	
M5 (Di-oxidation)	493.2306 ($C_{24}H_{29}N_8O_4^+$)	Rat: F, B Human: F	
M6 (Oxidative ring opening)	493.2306 ($C_{24}H_{29}N_8O_4^+$)	Rat: B Human: F	

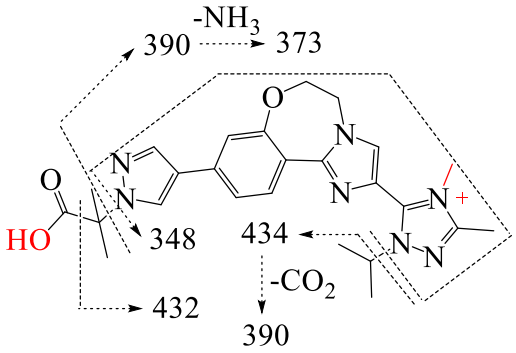
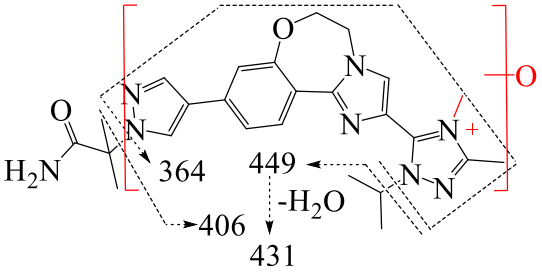
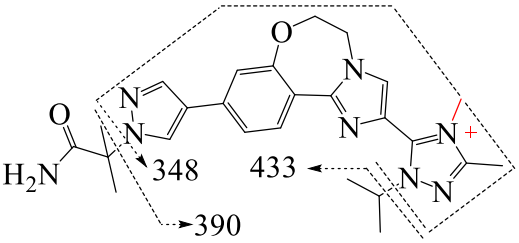
Supplementary Table S1. Summary of structures and mass fragmentation for metabolites of Taselisib in rats, dogs and humans.

Analyte	Observed MH+ (Chemical formula	Source	Structure
M7 (Oxidation & sulfation)	*559.1958 ($^{14}CC_{23}H_{29}N_8O_6S^+$)	Rat: B	
M8 (Oxidation)	*479.2390 ($^{14}CC_{23}H_{29}N_8O_3^+$)	Rat: U	
M9 (Amide hydrolysis)	*462.2248 ($C_{24}H_{28}N_7O_3^+$)	Rat: F, B Dog: P, U, F, B Human: U, F	
M10 (Oxidation)	477.2370 ($C_{24}H_{29}N_8O_3^+$)	Rat: P, U, F, B Dog: P, U, F, B Human: U, F	

Supplementary Table S1 (continued). Summary of structures and mass fragmentation for metabolites of Taselisib in rats, dogs and humans.

Analyte	Observed MH+ (Chemical formula	Source	Structure
M11 (Oxidation)	477.2359 ($C_{24}H_{29}N_8O_3^+$)	Rat: U, F, B Dog: P, U, F, B Human: U, F	
M12 (Acetylation & ring opening)	*479.2392 ($^{14}CC_{23}H_{29}N_8O_3^+$)	Rat: B	
M13 (Oxidation & glucuronidation)	*655.2710 ($^{14}CC_{29}H_{37}N_8O_9^+$)	Rat: U, F, B	
M14 (Methylation & Oxidation)	491.2526 ($C_{25}H_{31}N_8O_3^+$)	Dog: P, U, F, B	

Supplementary Table S1 (continued). Summary of structures and mass fragmentation for metabolites of Taselisib in rats, dogs and humans.

Analyte	Observed MH+ (Chemical formula	Source	Structure
M15 (Methylation & hydrolysis)	476.2416 ($C_{25}H_{30}N_7O_3^+$)	Dog: P, U, F, B	
M16 (Methylation & oxidation)	491.2525 ($C_{25}H_{31}N_8O_3^+$)	Dog: P, U, F, B	
M17 (Methylation)	475.2571 ($C_{25}H_{31}N_8O_2^+$)	Dog: P, U, F, B	

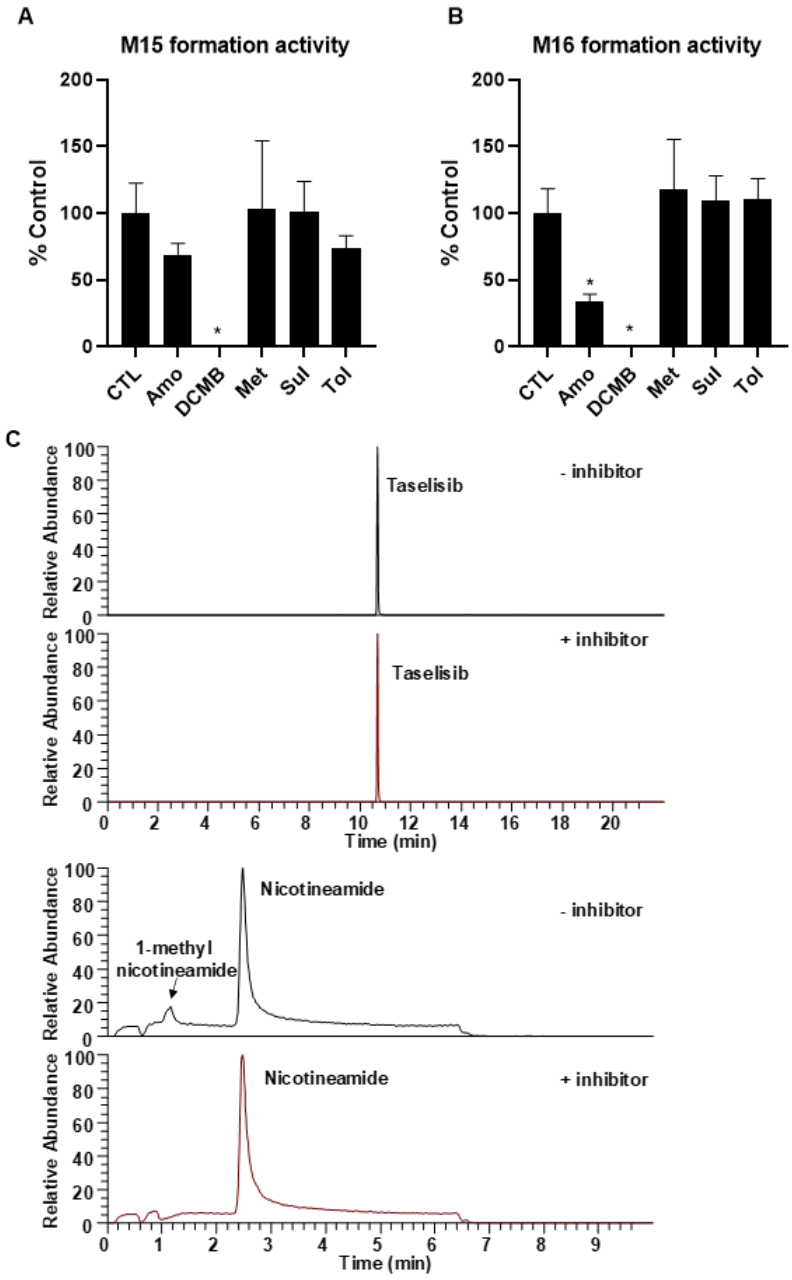
*; **m/z values of an analyte and its fragments were based on [^{14}C] compounds.**

Supplementary Table S2. ^{1}H and ^{13}C NMR Data for GDC-0032 and M17 (δ in ppm)

Position	GDC-0032[a]		M17[a]	
	^{13}C	^{1}H, multiplicity (J in Hz)	^{13}C	^{1}H, multiplicity (J in Hz)
1	131.8	8.41, d (8.4)	131.8	8.43, d (8.4)
2	121.0	7.37, dd (1.8,8.4)	120.8	7.41, dd (1.8,8.4)
3	117.3	---	116.2	---
4	118.1	7.30, d (1.8)	118.0	7.36, d (1.8)
5	158.0	---	158.3	---
6	136.4	---	137.1	---
7	146.8	---	148.8	---
9	131.3	---	122.2	---
10	124.8	7.71, s	128.9	8.19, s
12	51.5	4.52, m	51.7	4.64, m
13	70.0	4.52, m	69.5	4.59, m
14	123.2	---	122.8	---
15	138.8	7.97, brs	138.6	7.99, brs
18	127.5	8.27, d (0.5)	127.3	8.29, d (0.5)
19	66.6	---	66.2	---
20	177.9	---	177.7	---
21	26.4	1.86, s	26.0	1.87, s
22	26.4	1.86, s	26.0	1.87, s
23	149.5	---	146.4	---
26	160.3	---	154.7	---
28	52.4	5.91, sep (6.6)	55.4	5.52, sep (6.6)
29	22.7	1.54, d (6.6)	21.8	1.62, d (6.6)
30	22.7	1.54, d (6.6)	21.8	1.62, d (6.6)
31	13.7	2.36, s	10.6	2.64, s
32			33.6	3.95, s

[a] Measured in methanol-d_4 with ^{1}H at 500 MHz, and ^{13}C at 125 MHz. The ^{13}C NMR signals for M17 were indirect from HSQC and/or HMBC spectra.

d: doublet; dd: double doublet; s: singlet; brs: broad singlet; sep: septet; m: multiplet.



Supplementary Figure S1. Chracterization of methyltransferase involved in inavolisib metabolism in dogs. (A & B) Taselisib was incubated with dog hepatocytes in the presence of various human methyltransferase inhibitors for 3 h: Amo; amodiaquine (HNMT inhibitor), DCMB; 2,3-dichloromethylbenzylamine (TMT inhibitor), Met; 1-methyl nicotinamide (NNMT inhibitor), Sul; sulfasalazine (TPMT inhibitor), Tol; tolcapone (COMT inhibitor). (C) Recombinant NNMT was incubated with taselisib or nicotine amide for 1 hours in the presence of 5-amino-1-methylquinolin-1-ium iodide (NNMT inhibitor). *; $p<0.05$ compared to CTL from student t-test.