



## Article

# Liposomal PHD2 Inhibitors and the Enhanced Efficacy in Stabilizing HIF-1 $\alpha$

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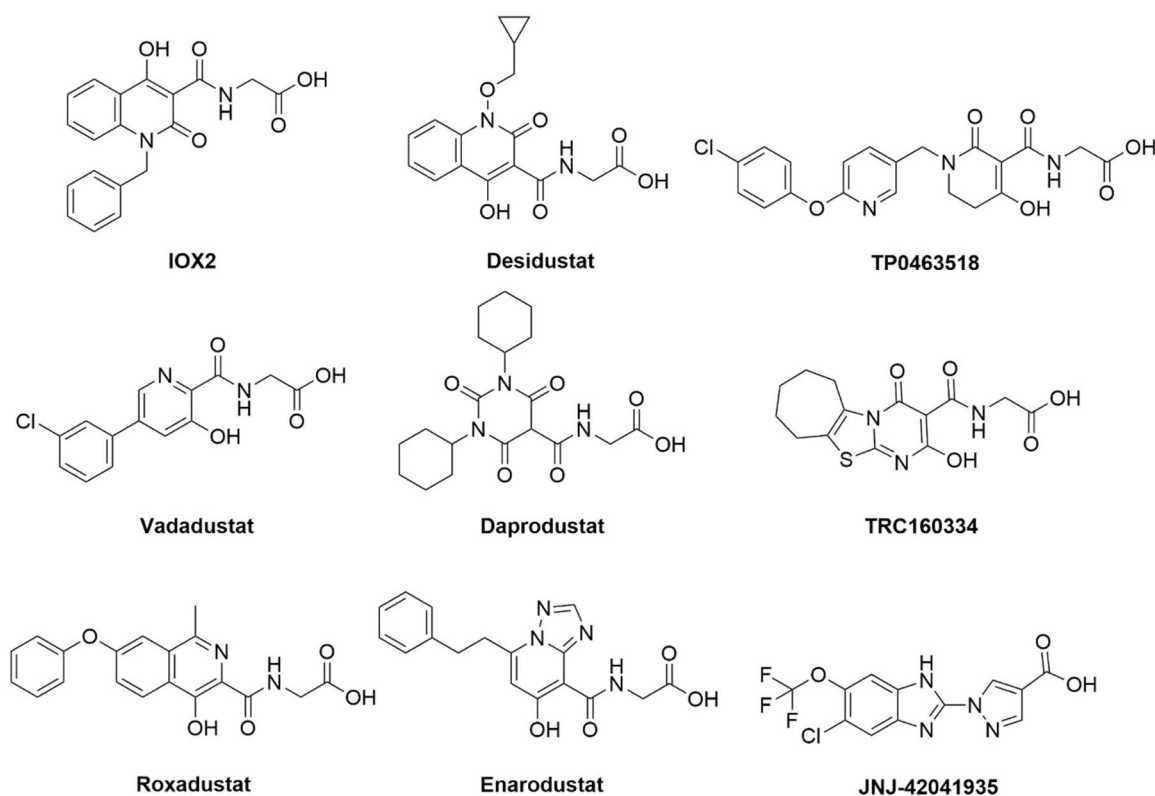


Figure S1. Examples of PHD2 inhibitors with similar pharmacophore features.

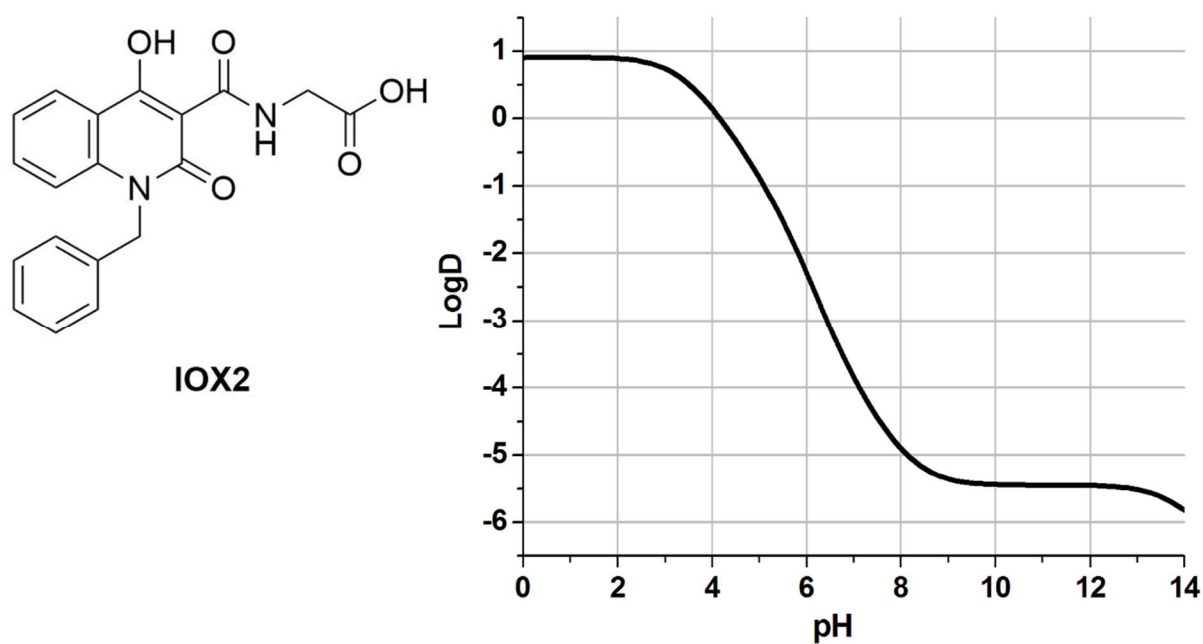


Figure S2. LogD profile for IOX2 calculated by ChemAxon software [1].

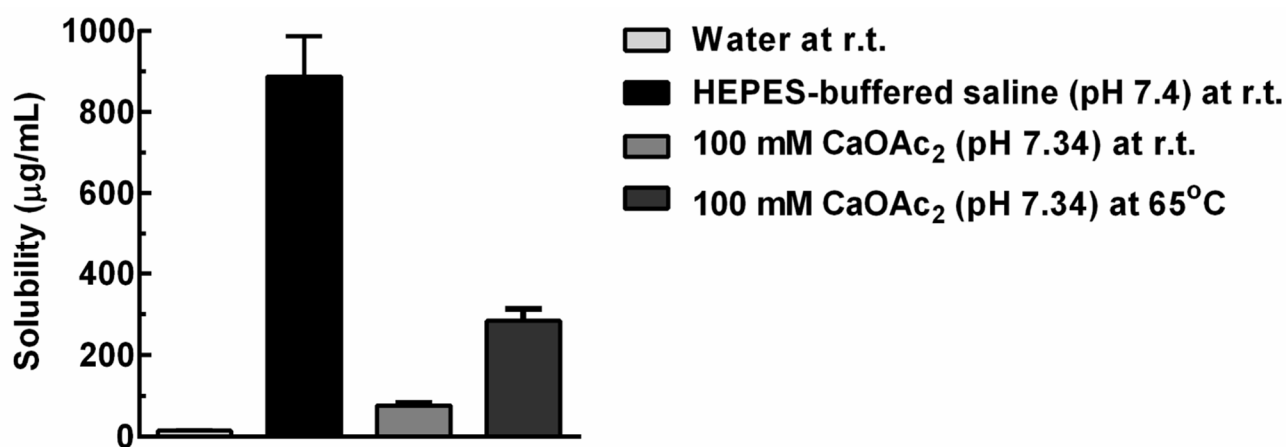
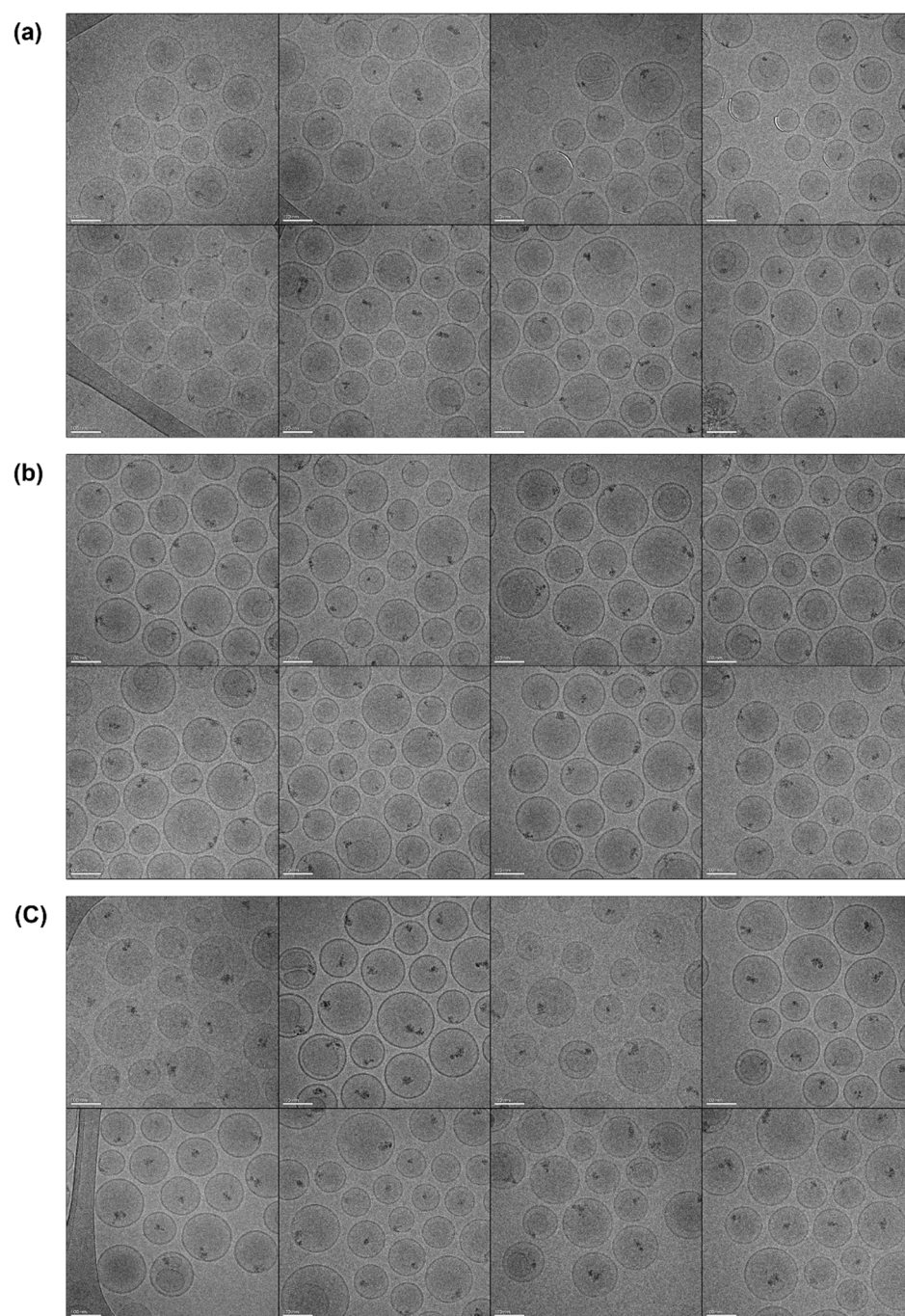
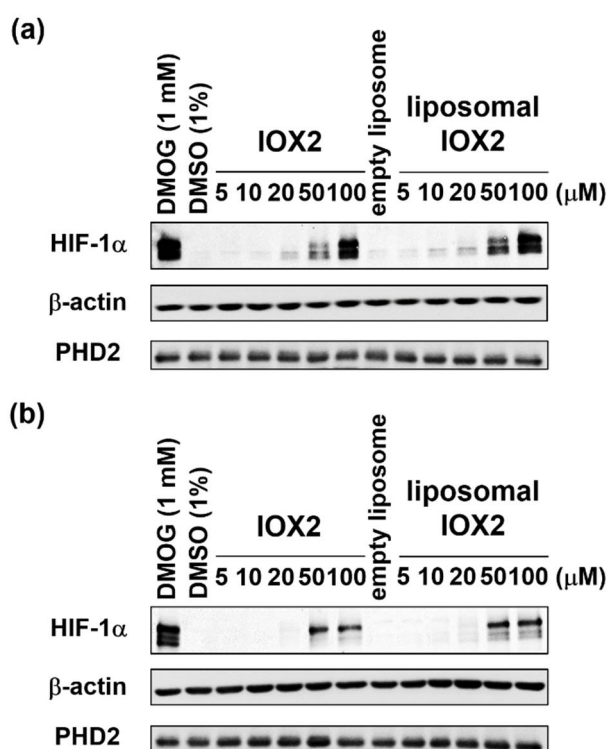


Figure S3. IOX2 solubility values in various media at room temperature (r.t.) and an elevated temperature (65 °C).



**Figure S4.** Cryo-EM images of IOX2-liposomes showing the dose-dependent Ca-IOX2 precipitate formation in the IOX2-liposomes at drug-to-lipid molar ratios of (a) 0.02, (b) 0.04, and (c) 0.08. The scale bars represent 100 nm.



**Figure S5.** HIF-1α protein levels in HeLa cells stabilized by free IOX2 and liposomal IOX2 at (a) 6 h and (b) 24 h. The time-dependent results showed the decreased drug effects in both treatment groups at 24 h, suggesting that the peak of IOX2 uptake and metabolism occurs sooner than 24 h.

**Table S1.** Particle size and ζ-potential analyses of IOX2-liposomes.

Liposome Composition		Particle Size (nm)	PDI	ζ-Potential (mV)
DSPC/cholesterol/DSPE-PEG <sub>2000</sub> =45:50:5	Before loading	116.4 ± 1.1	0.106 ± 0.028	-1.53 ± 1.12
	Blank loading	110.9 ± 2.8	0.067 ± 0.027	-1.08 ± 1.61
	IOX2 loading	109.3 ± 1.1	0.070 ± 0.011	-2.02 ± 0.88
DSPC/cholesterol/DSPE-PEG <sub>2000</sub> /DSPE-PEG <sub>2000</sub> -folate=45:50:4:1	Before loading	113.5 ± 2.2	0.188 ± 0.011	-3.08 ± 0.87
	Blank loading	100.3 ± 1.7	0.075 ± 0.018	-3.48 ± 1.50
	IOX2 loading	98.0 ± 0.7	0.072 ± 0.015	-3.07 ± 0.74

## References

1. ChemAxon, Chemicalized - Instant Cheminformatics Solutions. 2021. Available online: <https://chemicalize.com/welcome> (accessed on 3 November 2021)