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Experimental logP and pKa reveal ABX464 as a nonspecific, insoluble, mass action membrane toxicant.

Meyer-Overton signature in C. elegans predicts mass action cytotoxicity across species.
BRlogP (reversed-phase HPLC), potentiometric Sirius T3 titration, and analog correlation
ABX464 (obefazimod), 8-chloro-N-[4-(trifluoromethoxy)phenyl]quinolin-2-amine

Abstract

We report the measured logP and pKa of ABX464 (obefazimod) and a lipophilicity-potency analysis that demonstrates mass action narcosis of ABX464. We have been unable to locate previously published or disclosed experimental values, and thus believe this to be the first time that they are reported.

Rationale

The only physical parameter we could find for ABX464 was a crystalline melting point, disclosed in two formulation patents as 120.5 °C for crystalline Form I. The in silico logP estimates ranged from 5.7 to 6.2, but we found no measured value. These estimates indicate extremely limited aqueous solubility, yet we found no solubility measurement, and the Selleck product sheet lists ABX464 as insoluble in water. The drug carries an ionizable nitrogen and is a weak base, therefore its pKa determines whether it is trapped in the acidic lysosomal compartment, but we found no measured pKa. Every value we found was an in silico estimate from a non-Abivax source. As of this report, dated November 20, 2026, Abivax to the best of our knowledge had disclosed no measured values for these parameters. We measured them experimentally in this study.

Materials and methods

Partition coefficient (logP): BRlogP by reversed-phase HPLC

- Method: We measured the logP of ABX464 using a chromatographic method designed for high logP compounds, the BRlogP method[1]; LogP was read from a log k′60 retention time and a 36-compound reference set ($R^2 = 0.93$).
- Result: The measured partition coefficient was 6.35 ± 0.07 (BRlogP; n = 3 separate runs, 6.31, 6.32, and 6.43), a value just above the calculated 5.7 to 6.2 window. Our calculated logP indicates that ABX464 will prefer lipids 2.2 million-times over water.

Basic pKa by potentiometric titration (Sirius T3)

- Method: The pKa of ABX464 was determined by potentiometric titration on a Sirius T3 instrument (Pion Inc.) with a silver chloride pH electrode and a turbidity-sensing capability. Titrations were run in 0.15 M KCl under nitrogen at 25 ± 1 °C with 0.5 M KOH/0.5 M HCl gradients. Assays were conducted in a 30% to 50% cosolvent (20% acetonitrile, 20% dioxane, 20% methanol) and pure aqueous values were extrapolated by the Yasuda-Shedlovsky method (Avdeef et al., 1993).

[1] Ermondi et al., 2019

- Result: ABX464 had no measurable pKa between pH 2 and 12. ABX464 will be uncharged in all physiological compartments. Ionization will not rescue its aqueous insolubility. Thus, logP equals logD, allowing an accurate solubility estimate from the general solubility equation (GSE, 0.16 µM).

Lipophilicity-potency correlation across the analog series (original reanalysis in C. elegans)

- Method: To test whether the biological potency of ABX464 tracked lipophilicity or chemical structure, we took the eight ABX464 analog structures and their C. elegans activities from Shanley et al. (2024) and calculated the logP of each analog. The analogs shared ABX464's quinoline scaffold and differed only in the para substituent on the N-linked phenyl ring. We estimated the partition coefficients by fragment-based additive calculation[2]. We included ABX464 at its equivalent calculated logP of 5.9. We log-transformed the EC50 values to match the predicted log-linear (Meyer-Overton) relationship and plotted the log10(EC50) vs calculated logP.
- Result: The relationship was linear by least squares analysis, slope −0.587, $R^2 = 0.834$, p = 0.0015, n = 8. Potency increased linearly with logP across all eight analogs. This indicated that ABX464 activity was mediated by mass-action narcosis not receptor engagement. Receptor engagement would change with molecular shape.

Conclusions

Solubility

ABX464 is a non-ionizable (neutral), planar, stackable ultra-high lipophile (logP of 6.35), with a crystalline melting point of 120.5 °C and an aqueous solubility threshold of 0.16 µM. We measured the logP and pKa and the crystalline melting point was disclosed in 2 Abivax patents. We estimated the aqueous solubility using 2 measured parameters, the crystalline melting point and the measured logP that we determined experimentally. For a neutral logP 6.35 drug the GSE generally agrees closely with the solvent dilution measured values. Our DLS study demonstrated the drug was completely aggregated and, on the assay well floor at 1 µM, consistent with our GSE calculation showing the soluble fraction of drug is limited to 0.16 µM.

None of the Abivax patents reported a logP, a pKa, or a solubility for ABX464 in water or in simple buffer without added bile salts, polymer, or surfactant. The preparation-method patent dissolves the crystalline free base only in a cationic surfactant with 0.1 M hydrochloric acid, conditions present in no body compartment, and still reports no aqueous or buffer solubility for crystalline Form I, the free base that constitutes the drug product. The intrinsic aqueous solubility is absent from the patent record. We disclose it here for the first time as 0.16 µM, calculated from the general solubility equation (GSE) using the measured logP of 6.35 and the 120.5 °C melting point of Form I. Potentiometric titration found ABX464 neutral across pH 2 to 12, therefore the GSE limit is pH independent and the same across that range, from the small intestine to plasma.

The measured logP of 6.35 is a membrane-to-water partition of 2.2 million to one ($1x10^{6.35}$), therefore ABX464 partitions almost entirely into lipid over water. From this partition we calculated two concentrations that characterize the molecule in a lipid bilayer. A free aqueous concentration of 0.039 µM loads the membrane to the mass-action narcosis threshold of 2.7 mol%. For ABX464, the maximal loading concentration, reached when the free aqueous phase is at the 0.16 µM solubility limit, is 11 mol%, 4-fold above the narcosis threshold.

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[2] ChemAxon; Hansch-Leo and Crippen-type atom and fragment contributions; Hansch and Leo, 1979; Wildman and Crippen, 1999

The free concentration in a biological system is not known. We found no disclosed blood-to-plasma partitioning or plasma protein binding studies, which are standard IND-enabling measurements for a first-in-human drug with a logP of 6.35. We can, however, estimate the membrane concentrations in the gastrointestinal tract from the simulated intestinal fluid solubilities Abivax disclosed in the amorphous solid dispersion patent (WO2021/152129; US 2023/0218605 A1).

A single 25 mg dose saturates the gut

GI cell membrane concentrations were estimated from the chemical activity of ABX464 in intestinal fluid, defined as the dissolved concentration divided by the biorelevant solubility (WO2021/152129; US 2023/0218605 A1). The saturation mole fraction is 11 mole percent, fixed by the 120.5 °C melting point of crystalline Form I, and the mass-action narcotic threshold is a constant at 2.7 mol% for all drugs. A saturated membrane, therefore, will be 4.1-fold above the narcotic threshold, above the concentration where mass action membrane narcosis occurs. Biorelevant solubilities were taken from the Abivax patent[3]: 207 µM in fasted-state simulated intestinal fluid and 1500 µM in fed-state fluid, for crystalline ABX464. A 25 mg dose is 73.8 µmol, which in a 250 mL luminal volume is 295 µM as shown in Table 1.

Table 1. Simulated fasted/fed GI membrane concentrations relative to the narcotic membrane mole percent of 2.7.

Dose	Luminal (µM)	Fasted membrane (mol%)	Fasted × narcotic	Fed membrane (mol%)	Fed × narcotic
25 mg	295	11	4.1	2.2	0.8
50 mg	590	11	4.1	4.3	1.6
100 mg	1181	11	4.1	8.7	3.2

Fasted membrane is at the 11 mol% saturation ceiling at all three doses; the narcotic threshold is 2.7 mol%.

In the fasted state the luminal concentration of 295 µM exceeds the solubility of 207 µM. The resident GI cells and enterocyte apical membranes reach saturation at 11 mol%, 4.1 times the narcotic threshold. The 25, 50, and 100 mg doses produce the same saturated membrane, which we believe to account for the absence of a dose-response in the gastrointestinal endpoints. In the fed state the gut will be 80% saturated following a single dose and fully saturated after the second.

The trial protocol specifies the investigational medicinal product as a hard gelatin, powder-filled capsule containing ABX464 drug substance. The drug substance is therefore the crystalline Form I, which Abivax describes as the naturally occurring, stable crystal form. The fasted and fed biorelevant solubilities of 207 µM and 1500 µM for crystalline ABX464 that we used in the simulations are therefore applicable.

Membrane narcosis in the GI

Any drug that reaches the narcotic concentration in cell membranes causes narcosis. The mass-action effect is therefore predictable from the mechanism itself, independent of the drug scaffold, and the narcotic concentration is the same across mass-action drugs. ABX464 is predicted to partition into the membranes of gut cells, including enterocytes, goblet cells, resident macrophages, and neutrophils, and into the organelle membranes, including the mitochondria and the nuclear envelope. Membrane loading shifts the bilayer from a fluid, liquid-disordered state to an ordered, gel-like state. Mass-action narcosis

[3] Biorelevant solubilities for crystalline ABX464 are from the amorphous solid dispersion patent (WO2021/152129; US 2023/0218605 A1), Example 3, a two-step dissolution-precipitation measurement read at the final timepoint for the crystalline drug: 0.070 mg/mL in FaSSIF (fasted-state simulated intestinal fluid) and 0.508 mg/mL in FeSSIF (fed-state simulated intestinal fluid). Converted with the molecular weight of 338.71 g/mol, these are 207 µM and 1500 µM.

impairs signal transduction, lets ions leak across the bilayer, and disrupts protein-protein and protein-lipid interactions, glucose transporter function, and mitochondrial ATP synthesis. Mass-action drugs are cytotoxic to cells regardless of type, and the most affected are the metabolically active cells, such as the dividing stem cells that renew the gut, and the cells with a large surface-to-volume ratio, such as small-fiber neurons and macrophages.

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In connection with our scientific research, we retained and compensated third-party scientists and laboratories, including researchers affiliated with academic institutions that we believe to be reputable, to conduct experiments and analyses. Although we exercised reasonable efforts to oversee their work and assess its quality, and believe their methods and procedures to be consistent with accepted scientific standards, we have not independently verified every aspect of their work and cannot and do not make any representations or warranties regarding the accuracy, completeness, reliability, or reproducibility of their instruments, calibrations, protocols, data, results, or adherence to our specifications; furthermore, although compensation was agreed upon in advance and was not contingent upon any particular findings or outcomes, such third parties may have financial or other conflicts of interest, biases, or incentives that could influence their work or reporting.

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The principal individual responsible for the research, analysis, and preparation of this report is Gurkirat Kahlon, Founder and Chief Investment Officer of Scorpion Capital LLC.