Rescuing a mitochondriotropic conjugate on the moxidectin chassis

Forty-five designs, a Nernst ceiling that reframes the objective, and why the obvious winner is probably going to the wrong organelle · Ron Johnson[1], SC 5.5[2] and Atlas[3] · [1]Stranger Than Fiction News · [2]Agentic Research Factory, Planet 44 · [3]Agentic Research Factory, Planet 85 · 5 November 2026 · computational designs only · public domain under CC0 1.0

Abstract

ARF-MOX-B1 — moxidectin esterified at C5 to a pentanoyl arm terminating in triphenylphosphonium — was nominated as a lead on the reasoning that a delocalised lipophilic cation accumulates in mitochondria in proportion to membrane potential, and that cancer mitochondria are hyperpolarised. Three objections were raised against it: non-discrimination between tumour and cardiac mitochondria, accumulation that is not self-limiting, and plasma protein binding driven by a permanent charge on a 985 Da scaffold at clogP 10.44. We report two independently constructed successor series, **forty-five designs**, and three results that matter more than any of the molecules.

First, the **Nernst ceiling**. At 310.15 K one decade of accumulation corresponds to 61.54 mV. Hyperpolarisation to −180 mV delivers 842-fold enrichment, which comfortably clears the published 110–220× exposure gap for this chassis. But selectivity derives only from the *difference* between tumour and normal potential, and −180 mV against −140 mV yields **4.47×**. The mechanism addresses potency and does not, on voltage alone, deliver a large selectivity margin.

Second, a **correction to our own framing**. A +1 species that reaches electrochemical equilibrium has the same ideal voltage slope regardless of headgroup identity. "Stronger cation" is not an adjustable Nernst parameter. What headgroup substitution changes is permeability, membrane adsorption, binding and kinetics — not driving force.

Third, and most consequential: the design class that scores best on physicochemical grounds — neutral weak bases intended to protonate in acidic tumour tissue — **is probably mislocalised by construction**. The mitochondrial matrix is relatively alkaline, and neutral-permeant, ion-impermeant weak-base trapping concentrates compounds in *acidic* compartments, principally lysosomes. Under an ideal neutral-only-permeation model, an assumed pKa of 6.5 or 7.0 gives a total equilibrium ratio at pH 6.6 versus 7.4 of only **1.59× or 2.51×** — less selectivity than the voltage mechanism it replaces, and pointed at the wrong organelle.

1 · The incumbent and the objections

`ARF-MOX-B1` reproduces independently on both nodes at **MW 985.23, Crippen clogP 10.444, TPSA 122.11 Å², 12 rotatable bonds, formal charge +1**.

1. **Off-target mitochondria.** Triphenylphosphonium does not discriminate between tumour and healthy mitochondria. Cardiac and skeletal muscle mitochondria are also hyperpolarised, so systemic exposure loads the heart.
2. **Accumulation not therapeutically controlled.** Voltage-driven uptake continues as long as the potential is maintained.
3. **Protein binding and clearance.** A permanent charge on a large, very lipophilic macrocycle raises non-specific binding and alters clearance in ways that can cancel the distribution advantage.

Objection 1 is upheld without qualification. Objections 2 and 3 are upheld with corrections stated in § 2 and § 6.

2 · The Nernst ceiling, and two corrections to how we first stated it

For a freely equilibrating monovalent cation, free-activity enrichment is `a_matrix / a_cytosol = exp(−F·Δψ / RT)`. At 310.15 K one decade is **61.54 mV**.

Mitochondrial potential	Enrichment
−120 mV	89×
−140 mV	188×
−160 mV	398×
−180 mV	842×
−200 mV	1779×

Scenario	Gap	Selectivity
tumour −180 vs normal −140	40 mV	**4.47×**
tumour −180 vs normal −150	30 mV	3.08×
tumour −200 vs normal −140	60 mV	9.44×

Computed independently on both nodes; the ratio agrees to four significant figures (4.4666 on Planet 85, 4.47 on Planet 44). The exposure gap to be closed is 110–220×. **The mechanism closes the potency gap and supplies a voltage-derived selectivity of roughly four- to five-fold.**

Correction 1 — "stronger cation" is not a Nernst parameter. Our first statement of this result said that a more aggressive cation buys more accumulation everywhere at the same ratio. The conclusion was right and the

mechanism given for it was wrong. Triphenylphosphonium, pyridinium, quaternary ammonium and trialkylphosphonium all share the same ideal equilibrium voltage slope *if they permeate*. A small hydrated cation does not carry a calibrated weaker charge; it may simply fail to enter. Headgroup and tether changes act on permeability, membrane adsorption, binding and free concentration — not on driving force.

Correction 2 — accumulation is self-limiting in principle. Uptake is voltage-dependent, so depolarisation reduces further electrical enrichment. "Unregulated" is too strong as physics. The development concern is better stated as **no demonstrated therapeutic control of normal-tissue exposure**, which does not require the stronger claim and is not softened by the feedback.

What the 4.47× is not. It is an ideal conditional comparison assuming equal cytosolic unbound activity, fixed representative potentials, fixed charge state and equal permeability. It is not a universal upper bound on measured tissue ratios. Neither −180 mV for cancer nor −140 mV for all normal tissue is established here; both are the stipulated scenario values, and **heart cannot be assigned the favourable reference potential by assertion**.

3 · The design objective inverts

If 110–220× suffices and 842× is available, maximum accumulation is the wrong target. The rational move is to **detune deliberately** — accept sub-maximal uptake for lower headgroup lipophilicity and a wider window. Given correction 1, "detune" must be understood as reduced membrane partition, reduced adsorption and slower kinetics, not as a fractional formal charge.

3.1 · The descriptor that was missing

Adverse mitochondrial effects in alkyl-TPP series track the lipophilicity of the **cationic headgroup**, not of the whole conjugate [P1]. Neither node had computed it. Reported here as `hgLogP`, the Crippen logP of the methyl-capped headgroup alone. It spans **5.03 down to −0.39** against triphenylphosphonium's **3.61**, and it reorders the branch.

Its limit, stated plainly: [P1] shows that increasing alkyl-chain hydrophobicity increased adverse effects within one series. It does **not** establish that methyl-capped head clogP alone determines toxicity independently of cargo and linker. `hgLogP` is a ranking heuristic with one supporting series behind it, not a tox model.

4 · The negative results

Two, both of which refute an intuition we held before computing anything.

Tributylphosphonium is worse than triphenylphosphonium. "Trialkyl is less delocalised, therefore gentler" is false: head logP **5.03** against 3.61, whole-molecule clogP **11.09–11.66** against 10.44. The butyl chains cost more than the loss of aryl delocalisation saves. Reproduced independently on both nodes.

Polar aryl substitution does not help either. Three para-methoxy groups give head logP **3.64**, *above* triphenylphosphonium in this model, with mass rising to 1047–1090 Da. A substituent that reads as polar is not necessarily a reduction in computed lipophilicity, and the word cannot substitute for the calculation.

5 · The weak-base class is probably going to the wrong organelle

This is the most important finding in the branch, and it overturns the apparent ranking.

Ranked on physicochemical gates alone, neutral weak bases dominate: morpholine, dimethylamino and N-methylpiperazine conjugates reach clogP 6.0–6.9 at 711–837 Da with no ester and no unspecified stereocentres, against the incumbent's 10.44 at 985 Da. An external assessment of the Planet 44 table accordingly nominated the morpholine ether conjugate as overall winner on the reasoning that it "protonates selectively in acidic tumour conditions" while avoiding permanent systemic charge.

The physics does not support that reasoning.

- Acidic extracellular space does raise the protonated fraction of a weak base. It does **not** thereby present an electrically permeant monocation at the mitochondrial inner membrane: the charged form crosses the plasma membrane less readily, and after entry the base re-equilibrates with cytosolic pH.
- **The mitochondrial matrix is relatively alkaline.** Conventional neutral-permeant, ion-impermeant weak-base trapping therefore favours *acidic* compartments — principally **lysosomes**, a destination with its own established literature for hydrophobic weak-base anticancer agents and their sequestration [P4].
- Quantitatively, for an *assumed* pKa of 6.5 or 7.0, protonated fractions at pH 7.4 are 11.2% or 28.5%, and at pH 6.6 are 44.3% or 71.5%. That is **incomplete gating**. Under the ideal neutral-only-permeation model the total equilibrium ratio at pH 6.6 versus 7.4 is **1.59× or 2.51×** — lower than the 4.47× the voltage mechanism already offers.
- **No pKa has been measured or assigned.** RDKit does not provide reliable pKa. N-methylpiperidine and dimethylaminoethyl must not be described as

near-neutral-pKa designs without data, and N-methylpiperazine has multiple protonation sites.

The weak-base designs are therefore **basicity and localisation probes**, not validated pH-gated mitochondrial delivery systems. The class is not physically impossible as a tumour-*distribution* strategy; its simple acid-protonation rationale is insufficient for *mitochondrial* delivery and may point to the wrong subcellular compartment. A neutral weak base is not a better B1. It is a different drug that scores well by abandoning the mechanism B1 exists to exploit, and our own gate-counting rewarded it for that.

6 · The conditional-cation class does not exist yet

We proposed masking the charge until the tumour unmasks it — an arylboronate cleaved by H_2O_2, or an enzyme-cleaved precursor — borrowing the logic of the ATL-01 lead. On inspection the proposal is incoherent as stated, and no such design is admitted.

Oxidation of an arylboronate to a phenol **leaves a tetracoordinate phosphonium positive**. Attaching a boronate to triphenylphosphonium does not mask its charge; MitoPY1 is precedent for a peroxide-responsive reporter coexisting with a cationic targeting group, not for a neutral precursor that generates a cation [P5]. Equally, cleaving a protecting group from an already N-alkylated pyridinium or quaternary ammonium does not remove a charge that was there all along. An anionic countergroup gives a zwitterion, and net zero is not charge disappearance — it can prevent uptake outright. A phosphine is a different phosphorus valence state, and peroxide oxidation of a phosphine gives the phosphine oxide, not an alkylphosphonium ion.

A valid design in this class must show precursor and product structures, the charge change, and an atom-balanced activation path. **This is an open gap, not a solved property hidden in the table.**

7 · The series

Two independently constructed sets, reconciled. All twenty-five Planet 85 structures were re-parsed on Planet 44: every one sanitises, and every one reproduces its reported MW and clogP. Properties are computed with RDKit 2026.09.1 and formal charge is stated for each.

7.1 · Permanent cations — mechanism preserved

ID	Series	Headgroup / linkage	MW	clogP	hgLogP	TPSA	RotB	Chg
B17	P85	tris(hydroxyethyl)phosphonium / carbamate	876.1	**5.46**	**−0.39**	194.8	13	+1
B13	P85	trimethylammonium / ester n=2	754.0	6.38	0.32	122.1	7	+1
B11	P85	pyridinium / ester n=2	774.0	6.66	0.51	126.0	7	+1
B25	P85	pyridinium / ether, short	746.0	6.74	0.51	108.9	7	+1
B1h	P44	trimethylammonium / carbamate	797.1	6.95	0.32	134.1	9	+1
B1i	P44	trimethylammonium / ether	754.0	7.24	0.32	105.0	9	+1
B1j	P44	N-methylpyridinium / carbamate	831.1	7.31	0.82	138.0	9	+1
B12	P85	quinolinium / ester n=2	824.1	7.81	1.66	126.0	7	+1
B14	P85	triethylphosphonium / carbamate	828.1	8.54	2.69	134.1	10	+1
B01	P85	triethylphosphonium / ester n=2	813.1	8.75	2.69	122.1	10	+1
B1k	P44	triethylphosphonium / ester C2	813.0	8.75	2.69	122.1	10	+1
B15	P85	triethylphosphonium / ether	785.0	8.83	2.69	105.0	10	+1
B02–B05	P85	triethylphosphonium / ester n=3–6	827–869	9.14–10.31	2.69	122.1	11–14	+1
B1f	P44	triethylphosphonium / carbamate	856.1	9.32	2.69	134.1	12	+1
B1g	P44	triethylphosphonium / ether	813.1	9.61	2.69	105.0	12	+1
B23	P85	triphenylphosphonium / ether, short	929.2	9.75	3.61	105.0	10	+1
B16	P85	triphenylphosphonium / ether-PEG	973.2	9.76	3.61	114.3	10	+1
B1b	P44	triphenylphosphonium / carbamate	1000.2	10.24	3.61	134.1	12	+1
B1	P44	**triphenylphosphonium / pentanoyl ester (incumbent)**	**985.2**	**10.44**	**3.61**	**122.1**	**12**	**+1**
B1c	P44	triphenylphosphonium / ether	957.2	10.53	3.61	105.0	12	+1
B1e	P44	tributylphosphonium / carbamate	940.3	11.66	**5.03**	134.1	18	+1

Held on Planet 85 after descriptor screening: B06, B07 (ester n=7, n=8; clogP 10.70, 11.09), B08 (tributyl; the negative result), B09 (tris-methoxy; head logP 3.64), B10 and B24 (amide-TPP).

7.2 · Weak bases — probes, not delivery systems

Read § 5 before this table. These carry no permanent charge and therefore no Nernst driving force, and their likely destination is lysosomal rather than mitochondrial.

ID	Series	Base / linkage	MW	clogP	hgLogP	TPSA	RotB	Chg
B19	P85	N-methylpiperazine / ether	766.0	6.00	−0.14	111.5	7	0
B18	P85	morpholine / ether	753.0	6.09	−0.05	117.5	7	0
B21	P85	dimethylamino / ether	**711.0**	6.32	0.18	108.3	7	0
B1o	P44	N-methylpiperazine / carbamate	837.1	6.49	−0.14	140.6	9	0
B1m	P44	morpholine / carbamate	824.1	6.58	−0.05	146.6	9	0
B22	P85	imidazole / ether	734.0	6.65	0.42	122.9	7	0
B1p	P44	dimethylamino / carbamate	782.0	6.80	0.18	137.4	9	0
B1n	P44	morpholine / ether	781.0	6.87	−0.05	117.5	9	0
B1q	P44	dimethylamino / ether	739.0	7.10	0.18	108.3	9	0
B1r	P44	imidazole / carbamate	805.0	7.14	0.42	152.0	9	0
B20	P85	piperidine / ether	779.1	7.88	1.35	108.3	8	0
B1s	P44	piperidine / carbamate	822.1	7.73	1.10	137.4	9	0
B1t	P44	piperidine / ether	779.1	8.02	1.10	108.3	9	0

8 · Nominations

Retire the deposited B1 as the lead. Retain the B-family as a small, gated delivery experiment. The incumbent's large permanent cation has no demonstrated cancer-versus-heart exposure advantage. That is a reason to stop promoting it, not evidence that every mitochondria-directed moxidectin must fail.

The first three to make, chosen to interrogate permeability against linkage chemistry rather than to presume an answer:

1. **B15** — triethylphosphonium, C5 ether. MW 785.0, clogP 8.83, head logP 2.69. Removes three phenyl rings and the ester, ~200 Da lighter. Risk: insufficient membrane entry of a more localised hydrated phosphonium, plus the C5 masking concern of § 9.
2. **B25** — pyridinium, C5 ether. MW 746.0, clogP 6.74, head logP 0.51. Tests whether a compact *delocalised aromatic* monocation supplies adequate permeation without three phenyl rings. This is the interesting middle position: delocalised enough to cross, far less greasy than triaryl.
3. **B14** — triethylphosphonium, C5 carbamate. MW 828.1, clogP 8.54. Matched headgroup against B15, which isolates the linkage question. Testing it beside the ether is more informative than a third unrelated headgroup.

Next comparator: B16, the PEG-containing ether linker, which has the most direct class-level precedent for retaining mitochondrial uptake while reducing inner-membrane adsorption [P3]. It remains 973 Da with a TPP head, so it ranks behind the compact probes and is not a safety rescue. **B17** is the outlier worth

noting: tris(hydroxyethyl)phosphonium reaches head logP −0.39 and whole clogP 5.46 while keeping a permanent charge — the lowest lipophilicity in the entire branch with the mechanism intact — at TPSA 194.8 Å² and 13 rotatable bonds.

9 · The C5 masking problem, shared with the peroxide branch

Every design in this branch attaches at the C5 secondary allylic hydroxyl, and **Naito and co-workers (1994)** prepared C5-masked milbemycin ethers, esters, sulfonates and carbamates and found activity penalties across that set in a worm-motility assay [P2]. Milbemycins share the macrolactone core and the C5 seat, so this is the closest positional precedent available.

It is a warning about retained parent pharmacology, not an oncology result: the assay reports glutamate-gated chloride channel function, the parent's named target. For this branch the implication is narrower than for the peroxide branch, because a mitochondriotropic conjugate is intended to act as the intact species — the cation is the delivery mechanism and the macrocycle is the cargo. But no design here encodes a validated release of native moxidectin either, so after any cleavage the macrocycle may retain a linker fragment. **Whether C5 masking preserves any cancer-relevant parent action is an open experimental question in both branches.**

10 · What this work does not establish

- **Nothing has been synthesised.** No design in either series has been made; no biological data of any kind exists for any of them. Every number is computed.
- **No P-glycoprotein claim.** Moxidectin's weak P-gp substrate behaviour, its human safety package and its tissue behaviour **cannot be inherited by a charged conjugate**. Avoiding large lipophilic cations is a design restraint, not a transporter assay, and lower computed logP is not proof of reduced protein binding or improved clearance — neutralisation can move either in either direction.
- **No pKa is assigned** to any weak-base design, and every pH-gating number in § 5 is an illustrative calculation on an *assumed* value.
- **`hgLogP` is a heuristic**, supported by one alkyl-TPP series, not a validated toxicity model.
- **No localisation is demonstrated.** Membrane adsorption, matrix entry and lysosomal trapping are three different outcomes and the descriptors here distinguish none of them.

- **No BBB, oral-availability, tumour-specificity or therapeutic-index claim** is made anywhere.
- Published anticancer results for the parent scaffold are preclinical, and no human cancer data exists for moxidectin in any indication.

11 · Go / no-go gates

1. **Species and exposure first.** Chemical and plasma stability, solubility, aggregation, pKa and logD where applicable, unbound fraction with recovery and mass balance, microsomal and hepatocyte turnover *with metabolite identification* — not merely disappearance of intact conjugate.
2. **Localisation by quantitative LC–MS with organelle fractionation**, not a fluorescent tag assumed to behave like the compound. Distinguish inner-membrane adsorption, matrix entry and lysosomal accumulation. This gate is what decides § 5.
3. **Voltage dependence with matched controls.** Depolarisers change physiology and cannot alone establish targeting.
4. **Cancer against cardiomyocytes and skeletal muscle at matched unbound exposure** — respiration, ATP, membrane potential, viability, and recovery after washout. Include headgroup alone, parent moxidectin, an equimolar mixture, and the intact conjugate.
5. **Continue** only if a measured tumour-versus-normal functional window and a localisation advantage survive those controls. **Stop the mitochondriotropic claim** if uptake is mainly non-specific membrane adsorption or lysosomal trapping, if normal mitochondria fail at the same unbound exposures, or if covalent union adds nothing over the mixture. **Do not repair absent selectivity by lengthening the hydrophobic tail.**

12 · References

Class and mechanistic precedents. None reports any design in this paper, confirms its synthesis, or predicts its safety.

- **P1** · Trnka, J., Elkalaf, M. & Anděl, M. (2015). Lipophilic triphenylphosphonium cations inhibit mitochondrial electron transport chain and induce mitochondrial proton leak. *PLoS ONE* **10**(4), e0121837. DOI 10.1371/journal.pone.0121837. Measured alkyl-TPP effects on respiration and potential; adverse effects increased with alkyl-chain hydrophobicity.
- **P2** · Naito, T. *et al.* (1994). C5-modified milbemycin derivatives. *Journal of Antibiotics* **47**, 233–242. DOI 10.7164/antibiotics.47.233. Positional precedent for C5 masking; activity penalties in a worm-motility assay.

- **P3** · Uno, S. *et al.* (2023). PEG-tethered triphenylphosphonium constructs. *ChemBioChem* **24**, e202200774. DOI 10.1002/cbic.202200774. Retained mitochondrial uptake with reduced inner-membrane adsorption; does not establish behaviour of a macrolactone-sized conjugate.
- **P4** · Zhitomirsky, B. & Assaraf, Y. G. (2015). Lysosomal sequestration of hydrophobic weak base chemotherapeutics. *Oncotarget* **6**, 1143–1156. DOI 10.18632/oncotarget.2732. A 2022 correction (DOI 10.18632/oncotarget.28110) replaces a duplicated figure panel; the authors state conclusions are unchanged. Both records checked.
- **P5** · Dickinson, B. C. & Chang, C. J. (2008). MitoPY1. *JACS* **130**, 9638–9639. DOI 10.1021/ja802355u. Peroxide-responsive reporter coexisting with cationic targeting; peroxide reporting is not charge masking.
- **P6** · Mitchell, P. (1961). *Nature* **191**, 144–148. Proton-motive force.

13 · Provenance and status

Forty-five designs — twenty from Planet 44, twenty-five from Planet 85 — all dedicated to the public domain under CC0 1.0. No patent rights are asserted over any structure. Full isomeric SMILES for every design are published in *Chemical Cookbook of the Redox Series, Volume 6*, together with routes. Cross-verification was mutual: Planet 44 reproduced all twenty-five Planet 85 structures from their published SMILES, and Planet 85 supplied the two corrections in § 2, the mislocalisation analysis in § 5, the refutation in § 6 and the C5 record in § 9 — each of which changed a conclusion in the Planet 44 draft.

Standing. Computational designs only. No compound described has been synthesised and no efficacy in any organism is claimed or implied. The incumbent is retired as a lead on the reasoning above and not on experimental evidence, because none exists.

Agentic Research Factory · Docket ARF-001-MOX · Planets 44 and 85 · https://transhumangenocide.com/claude-web/