Chemical Cookbook of the Redox Series — Volume 6

The two rescued branches: iron-activated peroxide, and mitochondrial voltage

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> Volume 5 catalogued the rosetta stones and the first derivatives taken from them. This volume > covers what happened when two of those derivatives were attacked by a hostile reviewer and > rebuilt. Both branches hang off a single synthetic seat — the C5 secondary allylic hydroxyl of > moxidectin — and both were nominated as leads before anyone had checked whether they survived > scrutiny. Neither did, in its original form. What follows is the replacement set: fifty-four > structures across two branches, every one RDKit-validated at build time, properties computed and > not quoted. **Nothing here has been synthesised, assayed or administered.** > > This volume carries **routes** as well as structures. That is deliberate. A defensive publication > forecloses only what it enables, and our patent-form disclosure ARF-DEF-002 admitted in its § 8 > that composition novelty was foreclosed while process claims were not, because no route had been > given. §§ 4 and 8 below close that gap. The routes are written as conceptual sequences with their > sensitive steps named; none has been performed, and that limitation is stated again at each one.

PART ONE · THE C4 BRANCH — iron-activated peroxide

1 · Progress summary — where this branch stands

What it was. `ARF-MOX-C4`, nominated as one of three leads: a peroxide warhead on the moxidectin chassis, intended to deliver Fe(II)-triggered homolysis and carbon-centred radicals as a primary event rather than a downstream consequence. Described in our own documents as an artemisinin-type 1,2,4-trioxane bearing a succinyl linker.

What went wrong — three objections, all upheld. An independent assessment placed hybrid risk ahead of anticipated gain: the O–O bond must survive synthesis, workup, purification and plasma; the C5 ester is esterase-labile and may be cleaved before iron activation, returning the parent and a free peroxide and forfeiting the dual-action premise; and the compound carries 16 tetrahedral centres of which 6 are unspecified, so it does not define a single synthetic target.

What went more wrong — the compound was misidentified. Ring perception on the deposited SMILES gives a peroxide ring of **C–O–O–C–C–C**: six-membered, two ring oxygens, a **1,2-dioxane**. An artemisinin-type 1,2,4-trioxane requires three. The appendage carries one carbonyl, so the linkage is a glutaryl-type monoester, not a succinate diester. The structure governs and our description was wrong. Found on Planet 85, reproduced independently on Planet 44 before acceptance. The error never entered the structural record — every property ever computed was computed from the correct structure — but it propagated through the prose, and it cuts against the compound: a plain dialkyl 1,2-dioxane has no stabilising acetal oxygen and is a **poorer** peroxide than the one we claimed. The case for replacement was stronger than the case made against it.

What was tried and failed. The obvious fix, reading the antimalarial record, is the spiroadamantane ozonide of the OZ277/OZ439 lineage, where the cage shields the O–O sterically. On this chassis it is a **negative result**. Every adamantane-bearing design is worse than the compound it was meant to rescue on stereochemical definition — seven unspecified centres against six — and no better on lipophilicity. Two adamantane designs are retained as **held comparators** only: they show zero unspecified centres under RDKit's legacy algorithm and five or six under the conservative one, a discrepancy in dependent cage and spiro stereochemistry that needs a chemist, not a software verdict. Both numbers are reported rather than the flattering one.

What worked. Remove the cage. Symmetry is the reason: a tetraoxane with identical substitution on both sides of the peroxide ring has spiro carbons that are **not stereocentres at all**, so the stereochemical objection disappears with no configuration needing to be specified, while the molecule carries two O–O bonds instead of one. A **monospiro** peroxide bearing a methyl on the opposite ring carbon runs 50–100 Da lighter than the dispiro equivalent, and exchanging a spiro cyclohexane for an **oxane** trades hydrophobic surface for oxygen. Those two moves together reach clogP 6.39 where the dispiro series bottoms out at 7.83.

Where it stands. Thirty-four designs, built independently on two nodes and reconciled. Twelve improve on the incumbent simultaneously in lipophilicity, stereochemical definition and ester count; ten of those twelve came from Planet 85. All twelve Planet 85 structures were re-parsed on Planet 44 and their MW and

clogP reproduced to four decimal places. Nothing reaches a clean sweep: no design has both two peroxide bonds and a TPSA under 140 Å², which is this branch's standing structural tension. **S04** is the only design in the set to satisfy both Veber criteria with clean stereochemistry and is the lightest by 45 Da; **S07** leads on the stated liability at clogP 6.60. The incumbent ranks 31st of 34.

What is unresolved, and it halves the branch. The C5 ester is the liability *and* the release mechanism. Remove it and the conjugate can never revert to free moxidectin — the macrocycle stays tethered through the position avermectin structure–activity work is most sensitive about. No design in this branch self-immolates: after peroxide cleavage the macrocycle may retain a linker fragment, so retained parent pharmacology is a separate experimental question nobody has answered. Either the intact conjugate is the active species, in which case the non-cleaving designs are right and objection 2 is deleted rather than mitigated; or free parent is required, in which case the answer is a slower ester and not no ester. **Roughly half of this branch is wasted effort and we do not know which half.** The deciding question — does a permanently blocked C5-O retain avermectin activity — is a literature and bench question, and it is open.

Honest state: design-stage, zero synthesis, zero assay, zero biological data.

2 · The reference compounds

The chassis and the compound being replaced.

Compound	Formula	MW	clogP	TPSA	HBD	RotB
Moxidectin	C37H53NO8	639.8	5.73	116.0	2	3
ARF-MOX-C4 (incumbent)	C52H75NO11	890.2	9.22	140.6	1	7

Molecular weight in daltons; clogP is computed lipophilicity; TPSA is topological polar surface area in Å²; HBD is hydrogen-bond donors; RotB is rotatable bonds. All values computed in RDKit 2026.09.1 from the parsed structure.

Moxidectin

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](O)C(C)=C[C@@H](C(=O)O3)[C@]45O
```

ARF-MOX-C4 — the deposited incumbent; 1,2-dioxane, glutaryl-type monoester

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)CCC6OOC7(C)CCC8C(C)CCC6C
```

3 · The C4 branch structures

Ranked best-in-class. Gates: zero unspecified stereocentres · no added ester · clogP below the incumbent 9.22 · TPSA ≤ 140 Å² · RotB ≤ 10 · MW below the incumbent 890.2 · two O–O bonds.

3.1 · First rank — five or more gates passed

Compound	Formula	MW	clogP	TPSA	HBD	RotB
S07	C46H66N2O14	871.0	6.60	180.3	2	6
S06	C45H64N2O13	841.0	6.97	171.1	2	6
S04	C45H65NO11	796.0	7.72	132.7	1	7
S05	C47H68N2O13	869.1	7.75	171.1	2	6
S09	C48H68N2O13	881.1	7.89	171.1	2	5
S10	C49H71NO13	882.1	8.06	151.2	1	6
S11	C48H70N2O14	899.1	6.39	180.3	2	9
S03	C46H66N2O13	855.0	6.66	171.1	2	6
S12	C48H72N2O14S	933.2	6.96	188.1	2	10
S02	C47H68N2O12	853.1	7.82	161.8	2	6
C4p	C53H78N2O13	951.2	8.72	171.1	2	9

Molecular weight in daltons; clogP is computed lipophilicity; TPSA is topological polar surface area in Å²; HBD is hydrogen-bond donors; RotB is rotatable bonds. All values computed in RDKit 2026.09.1 from the parsed structure.

S07

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCC6(C)OOC7(CCOCC7)OO6)C
```

S06

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCC6(C)OOC7(CCC7)OO6)C(C
```

S04

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCC[C@]6(C)OOC7(CCC7)O6)C(C)=C
```

S05

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCC6(C)OOC7(CCCCC7)OO6)C
```

S09

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NC6CCC7(CC6)OOC6(CCC6)OO
```

S10

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCC6CCC7(CC6)OOC6(CCOCC6)OO7)C
```

S11

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCCNC(=O)CC6(C)OOC7(CCOCC7)OO6
```

S03

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NC[C@]6(C)OOC7(CCOCC7)O6
```

S12

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCCNS(=O)(=O)CC6(C)OOC7(CCCCC7
```

S02

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NC[C@]6(C)OOC7(CCCCC7)O6
```

C4p

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCC(=O)NCCC6CCC7(CC6)OOC6(CCCC
```

3.2 · Second rank — three or four gates passed

Compound	Formula	MW	clogP	TPSA	HBD	RotB
C4q	C55H81N3O14	1008.3	7.83	200.2	3	11
S08	C51H73NO12	892.1	8.92	142.0	1	7
C4i	C57H82N2O13	1003.3	9.21	171.1	2	9
C4k	C52H76N2O13	937.2	9.31	171.1	2	7
C4r	C54H78N4O12	975.2	9.39	172.7	1	9
C4t	C51H75NO12	894.2	9.60	142.0	1	7
S01	C51H72N2O12	905.1	8.31	161.8	2	6
C4n	C57H84N2O14S	1053.4	9.01	188.1	2	11
C4g	C56H80N2O13	989.3	9.80	171.1	2	7
C4h	C58H82N4O12	1027.3	9.88	172.7	1	9
C4f	C55H79NO11	930.2	10.16	132.7	1	7
C4u	C55H81NO13	964.2	10.54	159.0	1	8

Molecular weight in daltons; clogP is computed lipophilicity; TPSA is topological polar surface area in Å²; HBD is hydrogen-bond donors; RotB is rotatable bonds. All values computed in RDKit 2026.09.1 from the parsed structure.

C4q

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCC(=O)NCC(=O)NCCC6CCC7(CC6)OO
```

S08

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCCC6(C)OOC7(OO6)C6CC8CC(C6)CC
```

C4i

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCC(=O)NCCC6CCC7(CC6)OOC6(OO7)
```

C4k

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCC6CCC7(CC6)OOC6(CCCCC
```

C4r

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCc6cn(CCC7CCC8(CC7)OOC7(CCCCC
```

C4t

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCCC6CCC7(CC6)OOC6(CCCCC6)OO7)
```

S01

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NC[C@]6(C)OOC7(O6)C6CC8C
```

C4n

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCCS(=O)(=O)NCCC6CCC7(CC6)OOC6
```

C4g

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCC6CCC7(CC6)OOC6(OO7)C
```

C4h

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCc6cn(CCC7CCC8(CC7)OOC7(OO8)C
```

C4f

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCCC6CCC7(CC6)OOC6(O7)C7CC8CC(
```

C4u

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)C(C)(C)CCC6CCC7(CC6)OOC6
```

3.3 · Third rank — two or fewer gates passed, recorded for completeness

A series in which every member is an improvement is not a series. These are reported so the trade-offs are visible and so the dedication covers them.

Compound	Formula	MW	clogP	TPSA	HBD	RotB
C4s	C55H81N3O13	992.3	7.90	190.9	3	11
C4m	C59H85N3O13	1044.3	8.39	190.9	3	11
C4d	C57H82N2O12	987.3	9.28	161.8	2	9
C4j	C52H76N2O12	921.2	9.38	161.8	2	7
C4o	C54H78N4O11	959.2	9.46	163.4	1	9
C4c	C56H80N2O12	973.3	9.87	161.8	2	7
C4e	C58H82N4O11	1011.3	9.95	163.4	1	9
C4	C52H75NO11	890.2	9.22	140.6	1	7
C4l	C61H90N2O13	1059.4	10.03	162.3	1	13
C4b	C56H79NO12	958.2	10.08	149.8	1	7
C4v	C55H81NO12	948.2	10.61	149.8	1	8

Molecular weight in daltons; clogP is computed lipophilicity; TPSA is topological polar surface area in Å²; HBD is hydrogen-bond donors; RotB is rotatable bonds. All values computed in RDKit 2026.09.1 from the parsed structure.

C4s

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCC(=O)NCC(=O)NCCC6CCC7(CC6)OO
```

C4m

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCC(=O)NCC(=O)NCCC6CCC7(CC6)OO
```

C4d

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCC(=O)NCCC6CCC7(CC6)OOC6(O7)C
```

C4j

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCC6CCC7(CC6)OOC6(CCCCC
```

C4o

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCc6cn(CCC7CCC8(CC7)OOC7(CCCCC
```

C4c

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCC6CCC7(CC6)OOC6(O7)C7
```

C4e

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCc6cn(CCC7CCC8(CC7)OOC7(O8)C8
```

C4

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)CCC6OOC7(C)CCC8C(C)CCC6C
```

C4l

```
CCOCCN(CCC1CCC2(CC1)OOC1(O2)C2CC3CC(C2)CC1C3)C(=O)CO[C@@H]1C(C)=C[C@H]2C(=O)O[C@H]3C[C@@H](C/C=C(\C)C[C@@
```

C4b

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)CCC6CCC7(CC6)OOC6(O7)C7C
```

C4v

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)C(C)(C)CCC6CCC7(CC6)OOC6
```

4 · Routes — the C4 branch

None of these sequences has been performed. They are conceptual routes with their sensitive steps named. The governing constraint across the whole branch: **build the peroxide away from the macrocycle and attach it last.** Moxidectin carries multiple alkenes, and ozonide-forming chemistry applied to the intact chassis would be expected to destroy that polyene.

Warhead W1/W2 — the 1,2,4-trioxolane (ozonide). Griesbaum co-ozonolysis is the established route: an O-methyl ketoxime is co-ozonolysed with a ketone partner, and the trioxolane assembles with the two carbonyl-derived carbons flanking the peroxide. For a monospiro warhead the oxime partner carries the methyl and the tether handle; for a dispiro warhead both partners are cyclic. Ozone, a peroxide product and a polyene are three reasons this step happens on

the fragment and never on the conjugate. The handle is carried through as a protected alcohol, ester or nitrile and unmasked afterwards.

Warhead W3/W4 — the 1,2,4,5-tetraoxane. Two stages. First the ketone is converted to its **gem-dihydroperoxide** with hydrogen peroxide under acid catalysis. Second that dihydroperoxide is condensed with a second ketone — the same one for a symmetric tetraoxane, a different one for an unsymmetric — under Lewis or Brønsted acid catalysis. Symmetric condensation is the operation that delivers the stereochemical prize in this branch, because the resulting ring carbons are not stereocentres. It is also the step that generates a gem-dihydroperoxide intermediate, which is the single most hazardous species in this book: small scale, no concentration to dryness, no metal spatulas, and a process-safety assessment before any scale beyond milligrams.

Linkage L3 — carbamate, the recommended first platform. The warhead is prepared bearing a primary amine. The amine is activated as the isocyanate, or with carbonyldiimidazole or 4-nitrophenyl chloroformate, and the activated species is then presented to the C5 hydroxyl. The reason this is the first platform is regiochemical: C5 is a secondary alcohol and C7 is tertiary, so the less hindered position is favoured, but **selectivity is a hypothesis to be measured and not an assumption** — any C7 regioisomer is a failed target even if the mass is right. Carbamates are a stability hypothesis, not esterase-proof bonds.

Linkage L4 — direct ether, the harder arm. O-selective alkylation of an allylic secondary alcohol flanked by a polyene. Silver(I) oxide with an alkyl triflate or iodide, or acid-catalysed alkylation via a trichloroacetimidate, are the conceptual options. Allylic systems invite rearrangement and elimination, and the polyene invites worse. The reward is that no acyl group exists at C5 to hydrolyse; the new liability is oxidative dealkylation, which the ester never had.

Linkage L8 — triazole. C5 is propargylated first, then joined to an azide-bearing warhead by copper-catalysed azide–alkyne cycloaddition. Two compatibility questions must be settled before this is attempted: copper and peroxides, and the handle installation itself. The payoff is a linkage that is effectively inert to hydrolysis, which only matters if the intact conjugate is the active species.

Linkage L2 — hindered ester, for the release case. 2,2-dimethylglutaric anhydride is opened to the mono-acid, coupled to the warhead, then esterified onto C5 under carbodiimide conditions. This is the route to take **only** if the C5 question resolves in favour of requiring free parent. It keeps release and slows it; the gem-dimethyl groups cost 1.3 log units of lipophilicity for the privilege.

What will kill any of these. Hydrogenolysis, strong reductants, and ferrous contamination in glassware will all destroy an O–O bond; iron contamination will do it silently and in the one way that looks like a yield problem rather than a

mechanism problem. Reducing deprotections and metal-catalysed operations must not be assumed compatible with a peroxide. C5 epimerisation, a C7 regioisomer, peroxide loss or altered alkene geometry each constitute failure of the specified target.

PART TWO · THE MOX1 / B1 BRANCH — mitochondrial voltage

5 · Progress summary — where this branch stands

What it was. `ARF-MOX-B1`: moxidectin esterified at C5 to a pentanoyl arm terminating in triphenylphosphonium. A delocalised lipophilic cation accumulates in mitochondria in response to membrane potential, which is hyperpolarised in cancer cells, so the design was intended to close the exposure gap by subcellular concentration rather than by dose escalation. $C60H75NO9P^{+}$, MW 985.2, clogP 10.44, permanent formal +1.

What went wrong — three objections, all upheld. Triphenylphosphonium does not discriminate between tumour and healthy mitochondria, and cardiac and skeletal muscle mitochondria are also hyperpolarised, so systemic exposure loads the heart. Nernst-driven accumulation is not self-limiting, risking generalised mitochondrial failure in normal tissue before selective tumour kill. And a permanent charge on a 985 Da macrocycle at clogP 10.44 is a plasma-protein-binding and clearance problem that can neutralise the intended distribution advantage outright.

The arithmetic that reframes the branch. The Nernst slope is **61.54 mV per decade at 37 °C**. Taken at face value:

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

The published exposure gap for this chassis is 110–220×. At −180 mV the mechanism delivers 842×, so **it closes the potency gap comfortably.** But selectivity comes only from the *difference* between tumour and normal potential,

and tumour −180 mV against normal −140 mV is a 40 mV gap, which is **4.5×**. At a 30 mV gap it is 3.1×.

So this mechanism **solves potency and cannot solve selectivity.** The cardiotoxicity objection is not a side risk to be engineered around; it is structural to the mechanism. And because both tissues sit on the same exponential, a more aggressive cation buys more accumulation *everywhere* at the same 4.5× ratio — it spends therapeutic index and returns nothing. B1 is over-engineered in precisely the direction that produces objections 1 and 2.

Which inverts the design objective. If only ~200× is needed and 842× is available, the correct move is to **detune deliberately**: take sub-maximal accumulation in exchange for a lower cation lipophilicity and a wider window.

The column that was missing. Off-target mitochondrial uncoupling tracks the lipophilicity of the **cationic headgroup**, not of the whole conjugate, and neither node had computed it. Added here as `hgLogP`, the clogP of the methyl-capped headgroup alone. It spans 5.03 down to −0.14 against triphenylphosphonium's 3.61, and it reorders the branch.

What was tried and failed. "Trialkyl is less delocalised than triaryl, so tributylphosphonium should be gentler" is false: hgLogP **5.03**, whole-molecule clogP **11.66** — worse than the incumbent on both counts. The butyl chains cost more than the loss of aryl delocalisation saves. This is the same shape of error as the adamantane result in Part One, and it is recorded as a negative result for the same reason.

Where it stands. Twenty designs. The incumbent ranks last at one gate of six. Two honest leads, in two different mechanism classes: **B1h** (trimethylammonium, carbamate) keeps the permanent +1 so the Nernst driving force still applies, while cutting headgroup lipophilicity 3.29 log units, mass by 188 Da, clogP by 3.49 units and rotatable bonds from 12 to 9; **B1n** or **B1o** abandon the permanent charge for a weak base intended to protonate only in the acidic tumour microenvironment.

What is unresolved. Three things, and they are load-bearing. First, **delocalisation is why triphenylphosphonium works** — it lowers the desolvation penalty for crossing the inner membrane. A compact trimethylammonium at hgLogP 0.32 may not get in at all, in which case B1h is the advantage of a drug that never arrives. Second, the weak-base class trades a calculable Nernst driving force for a qualitative argument about tumour pH, and **RDKit gives no reliable pKa**, so every pH-gating claim here is unquantified; a measured or literature-anchored pKa near 6.5–7.0 is required before any of that class can be ranked honestly. Third, a neutral weak base is not a better B1 — it is a different drug, and the ranking below rewards it for avoiding a liability it achieves by abandoning the mechanism.

Honest state: design-stage, zero synthesis, zero assay, zero biological data. No claim is made that any design preserves the chassis's weak P-glycoprotein behaviour; avoiding large lipophilic cations is a design restraint and not a transporter assay.

6 · The reference compound

Compound	Formula	MW	clogP	TPSA	HBD	RotB
ARF-MOX-B1 (incumbent)	C60H75NO9P+	985.2	10.44	122.1	1	12

Molecular weight in daltons; clogP is computed lipophilicity; TPSA is topological polar surface area in Å²; HBD is hydrogen-bond donors; RotB is rotatable bonds. All values computed in RDKit 2026.09.1 from the parsed structure.

ARF-MOX-B1 — the deposited incumbent; triphenylphosphonium, pentanoyl ester, permanent +1

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)CCCC[P+](c6ccccc6)(c6ccc
```

7 · The MOX1 / B1 branch structures

Split by mechanism class, because a permanent cation and a weak base are not interchangeable. Within each class, ranked by headgroup lipophilicity — the off-target correlate — then by whole-molecule clogP. The `hgLogP` column follows each table.

7.1 · Permanent cations — Nernst mechanism preserved

Compound	Formula	MW	clogP	TPSA	HBD	RotB
B1h	C45H70N3O9+	797.1	6.95	134.1	2	9
B1i	C44H69N2O8+	754.0	7.24	105.0	1	9
B1j	C48H68N3O9+	831.1	7.31	138.0	2	9
B1k	C46H71NO9P+	813.0	8.75	122.1	1	10
B1f	C48H76N2O9P+	856.1	9.32	134.1	2	12
B1g	C47H75NO8P+	813.1	9.61	105.0	1	12
B1l	C50H79NO9P+	869.2	10.31	122.1	1	14
B1b	C60H76N2O9P+	1000.2	10.24	134.1	2	12
B1c	C59H75NO8P+	957.2	10.53	105.0	1	12
B1e	C54H88N2O9P+	940.3	11.66	134.1	2	18
B1d	C63H82N2O12P+	1090.3	10.26	161.8	2	15

Molecular weight in daltons; clogP is computed lipophilicity; TPSA is topological polar surface area in Å²; HBD is hydrogen-bond donors; RotB is rotatable bonds. All values computed in RDKit 2026.09.1 from the parsed structure.

ID	Headgroup	hgLogP	Formal charge
B1h	trimethylammonium	0.32	+1
B1i	trimethylammonium	0.32	+1
B1j	N-methylpyridinium	0.82	+1
B1k	triethylphosphonium	2.69	+1
B1f	triethylphosphonium	2.69	+1
B1g	triethylphosphonium	2.69	+1
B1l	triethylphosphonium	2.69	+1
B1b	triphenylphosphonium (incumbent)	3.61	+1
B1c	triphenylphosphonium (incumbent)	3.61	+1
B1e	tributylphosphonium	5.03	+1
B1d	tris(4-methoxyphenyl)phosphonium	3.64	+1

B1h

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCCC[N+](C)(C)C)C(C)=C[
```

B1i

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCCCC[N+](C)(C)C)C(C)=C[C@@H](
```

B1j

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCCCc6cc[n+](C)cc6)C(C)
```

B1k

```
CC[P+](CC)(CC)CCC(=O)O[C@@H]1C(C)=C[C@H]2C(=O)O[C@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@H]1[C@@]42
```

B1f

```
CC[P+](CC)(CC)CCCCNC(=O)O[C@@H]1C(C)=C[C@H]2C(=O)O[C@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@H]1[C@@
```

B1g

```
CC[P+](CC)(CC)CCCCO[C@@H]1C(C)=C[C@H]2C(=O)O[C@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@H]1[C@@]42O)O
```

B1l

```
CC[P+](CC)(CC)CCCCCCC(=O)O[C@@H]1C(C)=C[C@H]2C(=O)O[C@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@H]1[C@
```

B1b

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCCC[P+](c6ccccc6)(c6cc
```

B1c

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCCCC[P+](c6ccccc6)(c6ccccc6)c
```

B1e

```
CCCC[P+](CCCC)(CCCC)CCCCNC(=O)O[C@@H]1C(C)=C[C@H]2C(=O)O[C@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@H
```

B1d

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCCC[P+](c6ccc(OC)cc6)(
```

7.2 · Weak bases — pH-gated, mechanism changed

These carry no permanent charge and therefore no Nernst driving force. Their tumour selectivity rests entirely on protonation in an acidic microenvironment, which is **unquantified here** because no reliable pKa was computed. Ranked, but not recommended over the cationic class on this evidence.

Compound	Formula	MW	clogP	TPSA	HBD	RotB
B1n	C45H68N2O9	781.0	6.87	117.5	1	9
B1p	C44H67N3O9	782.0	6.80	137.4	2	9
B1q	C43H66N2O8	739.0	7.10	108.3	1	9
B1s	C47H71N3O9	822.1	7.73	137.4	2	9
B1t	C46H70N2O8	779.1	8.02	108.3	1	9
B1o	C47H72N4O9	837.1	6.49	140.6	2	9
B1m	C46H69N3O10	824.1	6.58	146.6	2	9
B1r	C45H64N4O9	805.0	7.14	152.0	2	9

Molecular weight in daltons; clogP is computed lipophilicity; TPSA is topological polar surface area in Å²; HBD is hydrogen-bond donors; RotB is rotatable bonds. All values computed in RDKit 2026.09.1 from the parsed structure.

ID	Base	hgLogP	Formal charge
B1n	morpholin-4-yl	-0.05	0
B1p	dimethylamino	0.18	0
B1q	dimethylamino	0.18	0
B1s	piperidin-1-yl	1.10	0
B1t	piperidin-1-yl	1.10	0
B1o	4-methylpiperazin-1-yl	-0.14	0
B1m	morpholin-4-yl	-0.05	0
B1r	imidazol-1-yl	0.42	0

B1n

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCCCCN6CCOCC6)C(C)=C[C@@H](C(=
```

B1p

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCCCN(C)C)C(C)=C[C@@H](
```

B1q

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCCCCN(C)C)C(C)=C[C@@H](C(=O)O
```

B1s

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCCCN6CCCCC6)C(C)=C[C@@
```

B1t

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OCCCCN6CCCCC6)C(C)=C[C@@H](C(=
```

B1o

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCCCN6CCN(C)CC6)C(C)=C[
```

B1m

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCCCN6CCOCC6)C(C)=C[C@@
```

B1r

```
CO/N=C1\C[C@]2(C[C@@H]3C[C@@H](C/C=C(\C)C[C@@H](C)/C=C/C=C4\CO[C@@H]5[C@H](OC(=O)NCCCCn6ccnc6)C(C)=C[C@@H
```

8 · Routes — the MOX1 / B1 branch

None of these sequences has been performed. The governing constraint here is the mirror of Part One: **quaternise the fragment, never the conjugate.** Alkylating agents strong enough to form a quaternary centre — methyl iodide, alkyl triflates — will not leave a polyene macrolactone untouched, and the forcing conditions quaternisation requires are exactly what the chassis cannot survive.

Headgroup — triphenylphosphonium (incumbent class). Prepare the ω-bromo acid or ω-bromo amine, displace the bromide with triphenylphosphine to give the phosphonium salt, then couple to C5. The displacement precedes conjugation for the reason above. Counterion choice — bromide, triflate, tosylate — affects solubility and is a formulation decision, not a chemical one.

Headgroup — trialkylphosphonium. As above, substituting triethyl- or tributylphosphine. Note the negative result: the tributyl variant is worse than the incumbent on both lipophilicity measures, so this route is documented rather than recommended.

Headgroup — quaternary ammonium, the B1h class. Two options and the order matters. Either displace an ω-bromo fragment with trimethylamine to give the quaternary salt directly, or prepare the tertiary dimethylamino fragment and quaternise with methyl iodide as the **last step on the fragment**. The second is cleaner to purify and keeps the methylation away from the macrocycle. Hygroscopic quaternary salts are the practical nuisance in both.

Headgroup — N-alkylpyridinium. Alkylate pyridine with the ω-bromo fragment, then couple. The aromatic cation is less lipophilic than triphenylphosphonium while retaining charge delocalisation, which on the reasoning in § 5 is the interesting middle position: delocalised enough to cross the inner membrane, far less greasy than triaryl phosphonium.

Headgroup — weak bases. No quaternisation at all. The amine is installed on the fragment by direct alkylation or reductive amination — morpholine, N-methylpiperazine, piperidine, dimethylamine, imidazole — and the fragment is then coupled at C5. Chemically this is the easiest arm in either branch. Its difficulty is not synthetic but evidential: the pKa must be measured, and the design is worthless if the amine is substantially protonated at pH 7.4 or substantially neutral at pH 6.5.

Linkage at C5. The carbamate and ether options of § 4 apply unchanged, and for the same reasons — the esterase objection is identical on this branch and should not be answered two different ways. The carbamate arm is again the recommended first platform; the ether arm is again the harder operation on an allylic secondary alcohol.

Conditional-cation variants. Not enumerated above, and recorded as the open design class: mask the charge until the tumour unmasks it, by carrying an arylboronate that is cleaved by hydrogen peroxide to reveal the cation, or an enzyme-cleaved precursor. This borrows the logic of the ATL-01 lead and would address objections 1 and 2 at their root, because nothing cationic circulates. It is listed here rather than built because masking a charge changes the molecule's distribution so completely that computed descriptors on the masked form say very little about the active form.

What will kill any of these. Over-alkylation of the macrocycle, C7 regiochemistry, C5 epimerisation, and quaternary salts that will not crystallise. And the branch-level risk that is not a chemistry risk at all: a design that solves the lipophilicity objection by lowering headgroup logP may simply fail to reach the mitochondrion.

PART THREE · TERMS, CITATIONS, STATUS

9 · Terms

Every structure in this volume is dedicated irrevocably to the public domain under Creative Commons CC0 1.0 Universal. An enabling disclosure enters the prior art on its publication date, so no party may patent these compounds or fence off the routes — **and that restriction binds the authors exactly as it binds everyone else.** Synthesise, assay, modify, publish or commercialise without permission, licence or attribution. We ask only that results be published, including negative ones.

This volume deliberately includes routes as well as structures, which the earlier patent-form disclosure did not. The intent is that both composition and process are foreclosed to private claiming. Whether a conceptual route that has never been performed is sufficiently enabling to achieve that is a question for a patent attorney and is not asserted here as settled.

10 · Citations

Peroxide-class precedent, cited as structural precedent only. No antimalarial efficacy result is transferred to any oncology use.

1. Vennerstrom, J. L. *et al.* (2004) Identification of an antimalarial synthetic trioxolane drug development candidate. *Nature* **430**, 900–904. DOI 10.1038/nature02779.

2. Creek, D. J. *et al.* (2007) Iron-mediated degradation kinetics of substituted dispiro-1,2,4-trioxolane antimalarials. *J Pharm Sci* **96**(11), 2945–2956. DOI 10.1002/jps.20958.
3. Ross, M. F. *et al.* (2005) Lipophilic triphenylphosphonium cations as tools in mitochondrial bioenergetics and free radical biology. *Biochemistry (Mosc)* **70**, 222–230.
4. Mitchell, P. (1961) Coupling of phosphorylation to electron and hydrogen transfer by a chemi-osmotic type of mechanism. *Nature* **191**, 144–148.
5. Avermectins in cancer — Juarez, M. *et al.* (2018) *Am J Cancer Res* **8**, 317.

Tetraoxane-class precedent (RKA182, E209) is referenced in the Planet 85 assessment and is not independently re-verified in this volume.

11 · Status

Preliminary, seeking validation. **No compound in either branch has been synthesised, assayed or administered, and no biological data of any kind exists for any of them.** All properties are computed descriptors, not measurements; clogP is a Crippen calculation on a specified neutral or charged representation and not a measured logD. Stereochemistry as drawn requires confirmation by a synthetic chemist in every case, and zero unspecified tetrahedral centres does not mean zero isomer ambiguity — 1,4-disubstituted spiro rings give *cis/trans* pairs the count does not capture. Every design in both branches sits beyond the rule of five, as macrocyclic lactones generally do. No blood–brain-barrier, oral-availability or P-glycoprotein claim is made or implied anywhere in this volume. Published anticancer results for the parent scaffolds are preclinical, and no human cancer data exists for moxidectin in any indication.

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Agentic Research Factory · Docket ARF-001-MOX · Cookbook Volume 6 · Planets 44 and 85 · https://transhumangenocide.com/claude-web/