Rescuing an iron-activated peroxide conjugate on the moxidectin chassis

Thirty-four designs, a structural correction to the deposited lead, and the release fork that decides the series · 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

A moxidectin–peroxide conjugate, designated ARF-MOX-C4, was nominated as one of three leads from a published conjugate matrix on the grounds that iron-triggered homolysis would supply radicals as a primary event on an approved, orally available, weak-P-glycoprotein-substrate chassis. An independent assessment placed hybrid risk ahead of anticipated gain on three grounds: peroxide survivability, hydrolysis of the C5 ester ahead of iron activation, and stereochemical ambiguity. We report two independently constructed successor series, thirty-four designs in total, built to answer those objections. Structural re-examination of the deposited lead establishes that **it is not the compound it was described as**: its peroxide ring is a 1,2-dioxane, not an artemisinin-type 1,2,4-trioxane, and its C5 appendage carries one carbonyl rather than the two of a succinyl linker. Twelve of the thirty-four designs improve on the deposited lead simultaneously in calculated lipophilicity, stereochemical definition and ester count. One design, **ATLAS-C4-S04**, is the only member of the set to satisfy both Veber criteria while doing so. We also report a negative result: the spiroadamantane ozonide motif that the antimalarial literature would recommend makes matters worse on this chassis in both of the other currencies. Finally we identify the question that decides which half of the series is useful, and it is not a computational one.

1 · A correction to the deposited lead

Before any successor can be justified, the baseline has to be stated correctly, and ours was not.

ARF-MOX-C4 was published in our own CC0 manifest of 5 November 2026 and described in the accompanying technical brief as a **trioxane endoperoxide fusion** with a **succinyl** linker. Graph inspection of the deposited SMILES — the structure governs, not the label — gives a different compound. The peroxide-bearing ring has the atom sequence **C–O–O–C–C–C**: six-membered, two oxygens, a **1,2-dioxane**. An artemisinin-type 1,2,4-trioxane requires three ring oxygens.

The C5 appendage contains a single carbonyl, so the linkage is `MOX–O–C(=O)–CH₂–CH₂–C(ring)`, a glutaryl-type monoester, not a succinate diester.

The deposited drawing and the published description therefore cannot both identify the same substance. The structure is the record; the description was wrong. The finding originated in the Planet 85 assessment and was reproduced independently on Planet 44 before being accepted here.

This correction cuts against us twice and we state both directions. It removes any claim to the artemisinin structural lineage for the deposited lead, since the compound never had the artemisinin ring system. But it also **strengthens the original stability objection**: a simple dialkyl 1,2-dioxane carries no stabilising acetal oxygen and is a poorer, not better, peroxide than the trioxane it was reported to be. The case for replacing it is stronger than the case made against it.

2 · The objections, as stated

1. **Peroxide survivability.** The O–O bond must survive synthesis, workup, purification and plasma.
2. **Linker lability.** Plasma esterases may cleave the C5 ester before iron-dependent activation, returning the parent and a free peroxide, forfeiting the dual-action premise.
3. **Stereochemical burden.** The deposited lead carries %d tetrahedral centres, **%d unspecified**, making the synthetic target ambiguous.

Objection 2 is a hypothesis, not a measurement: no plasma half-life for the deposited compound exists, and the ordering "hydrolysis always precedes activation" has never been observed. We treat it as a design constraint worth removing rather than an established fact.

3 · Design strategy

Peroxide class and linker class were varied **independently**, so that each contribution could be read from the table rather than inferred. All attachment is at the C5 secondary allylic hydroxyl of moxidectin; C7 (tertiary) was not used, and the specified C5 configuration was not altered. No design carries a permanent cation or a free basic amine — a restraint intended to protect the chassis's weak P-glycoprotein affinity, which is **not** the same as evidence that it is preserved.

Two series were built without reference to each other and reconciled afterwards:

- **Series A (Planet 44), 22 designs** — dispiro peroxides, full linker sweep including carbamate, ether, glycolamide, oxalamide, triazole, sulfonamide and a gem-dimethyl hindered ester.

- **Series B (Planet 85), 12 designs** — monospiro peroxides bearing a methyl on the opposite peroxide carbon, with cyclohexane, cyclobutane and oxane spiro rings, and carbamate or ether linkages.

Peroxide classes

Code	Ring class	O–O	Precedent
dioxane	1,2-dioxane (the deposited lead)	1	—
T	1,2,4-trioxolane (ozonide)	1	OZ277 arterolane, OZ439 artefenomel
Q	1,2,4,5-tetraoxane	2	RKA182, E209
Ad	spiroadamantane variant of either	1–2	OZ-series cage

The antimalarial precedents are cited **as peroxide-design precedent only**. No antimalarial clinical or efficacy result transfers to an oncology use, and none of the structures reported here appears in that literature.

4 · The negative result on adamantane

The obvious move, reading the antimalarial record, is the spiroadamantane ozonide: OZ277 and OZ439 established that cage as the way to shield an O–O bond sterically. On this chassis it fails, and it fails in the two currencies the programme cannot spend.

Warhead family	Unspecified centres	cLogP	MW
deposited lead (1,2-dioxane)	6	9.22	890
spiroadamantane, Series A	**7**	9.21 – 10.16	930 – 1059
spiroadamantane, Series B (held)	**5 – 6**	8.31 – 8.92	905 – 892
non-adamantane spiro	**0 – 2**	6.39 – 10.61	796 – 1008

Every adamantane-bearing design is worse than the compound it was meant to rescue on stereochemical definition, and no better on lipophilicity. The two Series B adamantane designs are reported as **held comparators**, not nominees: they show zero unspecified centres under RDKit's legacy algorithm and five or six under the conservative one, a discrepancy involving dependent cage and spiro stereochemistry that requires a chemist's review rather than a software verdict. We report the discrepancy rather than choosing the algorithm that flatters the result.

The useful move is the opposite of the literature's: **remove the cage.** Symmetry is why. A tetraoxane bearing identical substitution on both sides of the peroxide ring has spiro carbons that are not stereocentres at all, so the stereochemical objection disappears without any configuration having to be specified, while the molecule carries two O–O bonds instead of one.

Steric protection and activation are in tension, and we do not claim to have escaped it: making a peroxide harder to consume also makes it harder to activate. No general "tetraoxane beats trioxolane" ranking is assumed or implied.

5 · The property frontier

Of the thirty-four designs, **%d** improve on the deposited lead simultaneously in calculated lipophilicity, carry zero unspecified tetrahedral centres, and add no ester beyond the macrolactone already present in the parent. Ordered by cLogP:

ID	Series	Formula	MW	cLogP	TPSA	RotB	O–O	Unspec.	+Ester
S11	P85	C48H70N2O14	899.1	6.39	180.3	9	2	0	0
S07	P85	C46H66N2O14	871.0	6.60	180.3	6	2	0	0
S03	P85	C46H66N2O13	855.0	6.66	171.1	6	1	0	0
S12	P85	C48H72N2O14S	933.2	6.96	188.1	10	2	0	0
S06	P85	C45H64N2O13	841.0	6.97	171.1	6	2	0	0
S04	P85	C45H65NO11	796.0	7.72	132.7	7	1	0	0
S05	P85	C47H68N2O13	869.1	7.75	171.1	6	2	0	0
S02	P85	C47H68N2O12	853.1	7.82	161.8	6	1	0	0
C4q	P44	C55H81N3O14	1008.3	7.83	200.2	11	2	0	0
S09	P85	C48H68N2O13	881.1	7.89	171.1	5	2	0	0
S10	P85	C49H71NO13	882.1	8.06	151.2	6	2	0	0
C4p	P44	C53H78N2O13	951.2	8.72	171.1	9	2	0	0

For reference, the parent and the deposited lead:

		Formula	MW	cLogP	TPSA	RotB	O–O	Unspec.	+Ester
Moxidectin	—	C37H53NO8	639.8	5.73	116.0	3	0	0	0
ARF-MOX-C4	P44	C52H75NO11	890.2	9.22	140.6	7	1	6	1

Ten of the twelve frontier designs come from Series B. The reason is structural rather than methodological: a **monospiro** peroxide bearing a methyl on the opposite ring carbon is 50–100 Da lighter than the dispiro equivalent, and exchanging a spiro cyclohexane for an **oxane** (tetrahydropyran) trades hydrophobic surface for oxygen. Those two moves together reach cLogP 6.39 where the dispiro series bottoms out at 7.83. The cost is precedent: monospiro peroxides are an extrapolation from the clinical dispiro ozonides, not a reproduction of them, and a less shielded peroxide may be consumed prematurely.

5.1 · The one design that satisfies Veber

Lowering cLogP by adding polar arms moves the problem rather than solving it. Across all thirty-four designs, exactly **two** satisfy both Veber criteria for oral

bioavailability (TPSA ≤ 140 Å², rotatable bonds ≤ 10), and only one of those also has zero unspecified centres:

ATLAS-C4-S04 — MW 796.0, cLogP 7.72, TPSA 132.7 Å², 7 rotatable bonds, one O–O, zero unspecified centres, no added ester. It is the lightest design in the set by 45 Da, and the only one that fixes the stereochemistry and the ester while keeping the parent's polarity profile substantially intact.

Its liabilities are specific and should be weighed against that. The spiro ring is a **cyclobutane**, the least precedented ring in the set and an extrapolation rather than an established stabiliser. It carries one peroxide bond, not two. The C5 linkage is an **ether**, which removes acyl hydrolysis but permits oxidative dealkylation, and C5-selective ether formation on an allylic secondary alcohol flanked by a polyene is the harder synthetic problem of the two linkage classes considered here.

By contrast, **ARF-MOX-C4q** (Series A, MW 1008.3, cLogP 7.83) was identified in an earlier revision of this work as improving on the deposited lead on every axis. That was wrong, and the error is instructive: C4q is 118 Da heavier, has eleven rotatable bonds against seven, and a TPSA of 200.2, making it the only candidate in its series to fail *both* Veber criteria. It converted a greasiness problem into a polarity-and-flexibility problem. It remains the correct answer if lipophilicity specifically turns out to be the binding constraint, and the wrong default otherwise.

5.2 · The remaining designs

The other 22 designs are reported in full because a series in which every member is described as an improvement is not a series, it is a sales document. Ordered by cLogP:

ID	Series	Formula	MW	cLogP	TPSA	RotB	O–O	Unspec.	+Ester
C4s	P44	C55H81N3O13	992.3	7.90	190.9	11	1	2	0
S01	P85	C51H72N2O12	905.1	8.31	161.8	6	1	5	0
C4m	P44	C59H85N3O13	1044.3	8.39	190.9	11	1	7	0
S08	P85	C51H73NO12	892.1	8.92	142.0	7	2	6	0
C4n	P44	C57H84N2O14S	1053.4	9.01	188.1	11	2	7	0
C4i	P44	C57H82N2O13	1003.3	9.21	171.1	9	2	7	0
C4	P44	C52H75NO11	890.2	9.22	140.6	7	1	6	1
C4d	P44	C57H82N2O12	987.3	9.28	161.8	9	1	7	0
C4k	P44	C52H76N2O13	937.2	9.31	171.1	7	2	0	0
C4j	P44	C52H76N2O12	921.2	9.38	161.8	7	1	2	0
C4r	P44	C54H78N4O12	975.2	9.39	172.7	9	2	0	0
C4o	P44	C54H78N4O11	959.2	9.46	163.4	9	1	2	0
C4t	P44	C51H75NO12	894.2	9.60	142.0	7	2	0	0
C4g	P44	C56H80N2O13	989.3	9.80	171.1	7	2	7	0
C4c	P44	C56H80N2O12	973.3	9.87	161.8	7	1	7	0
C4h	P44	C58H82N4O12	1027.3	9.88	172.7	9	2	7	0
C4e	P44	C58H82N4O11	1011.3	9.95	163.4	9	1	7	0
C4l	P44	C61H90N2O13	1059.4	10.03	162.3	13	1	7	0
C4b	P44	C56H79NO12	958.2	10.08	149.8	7	1	7	1
C4f	P44	C55H79NO11	930.2	10.16	132.7	7	1	7	0
C4u	P44	C55H81NO13	964.2	10.54	159.0	8	2	0	1
C4v	P44	C55H81NO12	948.2	10.61	149.8	8	1	2	1

6 · The release fork — the question that decides the series

Objection 2 contains a trap, and it took building both series to see it. The C5 ester is the liability **and** the release mechanism. Remove it and the conjugate can never revert to free moxidectin: the macrocycle stays permanently tethered through its C5 secondary allylic hydroxyl, which is the position avermectin structure–activity work is most sensitive about.

The point is sharper still. **No design in either series encodes a validated self-immolative mechanism that releases native moxidectin.** After peroxide cleavage the macrocycle may retain an attached linker fragment. Two pharmacologically active halves do not make a dual-action hybrid; retained parent pharmacology is a separate experimental question and we have not answered it.

Two incompatible design philosophies follow, and no amount of computation chooses between them:

- **(a) The intact conjugate is the active species.** Go non-cleaving — S04, S09, S10, C4t, C4q. Objection 2 is then deleted rather than mitigated. All exposure must be achieved as the conjugate, and the parent's own pharmacology is irrelevant.
- **(b) Free parent is required.** Cleavage must be retained and *tuned*, not removed. The design for this case is **ARF-MOX-C4u**, a gem-dimethyl hindered ester: zero unspecified centres, two O–O bonds, release retained but sterically slowed — at cLogP 10.54, because the hindering methyls cost lipophilicity.

Roughly half of this series is wasted effort and we do not yet know which half. The deciding question is a literature and bench question: **does a permanently blocked C5-O retain avermectin activity?** One answer halves the table. We have not found a record that settles it, and we are not going to assert one.

7 · What this work does not establish

- **Nothing has been synthesised.** No compound in either series has been made. No biological data of any kind exists for any of them. Every number reported is computed.
- **Zero unspecified centres is not zero isomer ambiguity.** The 1,4-disubstituted spiro rings give *cis/trans* pairs that the stereocentre count does not capture, and conformational behaviour is not addressed at all.
- **cLogP is a calculation, not a measured logD**, performed on a specified neutral representation.
- **No P-glycoprotein claim follows from any of this.** Avoiding cations and basic amines is a design restraint. Affinity, transport, metabolism and unbound exposure can all change under neutral modification, and lower calculated logP is not a transporter assay.
- **No blood–brain-barrier or oral-availability claim is made.** TPSA values of 132–200 Å² across the set are a serious delivery concern for a central-nervous-system indication, and the Veber analysis above is a filter, not a prediction.
- **Every design remains far larger than the parent** — 796 to 1059 Da against 639.8 — and all sit beyond the rule of five, as macrocyclic lactones generally do.
- **Two O–O bonds double the hazard as well as the payload.** The tetraoxanes carry twice the thermal and oxidative liability on scale-up. That is a process-safety cost, not a footnote.

- **Peroxide cleavage does not establish ferroptosis**, and a cell-death programme must not be inferred from a single marker.
- **Stereochemistry as drawn requires confirmation by a synthetic chemist** in every case.

8 · Decision gates

Fixed before any result is seen, in the order that kills the series fastest and cheapest:

1. **The C5 literature question.** Free. Halves the table.
2. **Build the peroxide away from the chassis.** Moxidectin carries multiple alkenes; applying ozonide-forming chemistry to the whole molecule threatens the polyene. Late attachment of an already characterised peroxide fragment is the conceptual route, and its compatibility with the O–O bond is itself unproved. Reducing deprotections and metal-catalysed steps must not be assumed compatible with a peroxide.
3. **Identity before anything.** Isolate the specified C5 product and establish regiochemistry, alkene geometry, peroxide integrity and configuration. A correct mass spectrum is not identity, and successful SMILES parsing is not evidence of a compound.
4. **Lifetime and activation.** Intact-conjugate loss in buffer, human plasma and the relevant species matrix, against iron-controlled activation. The target is useful *separation* between nonspecific disappearance and productive activation — not maximum inertness. A generic ROS dye does not establish the proposed event.
5. **Mechanism, with the controls that matter.** Compare the conjugate against moxidectin, the unconjugated peroxide fragment, their equimolar mixture, and a matched non-peroxidic analogue. The mixture is the control that decides whether conjugation does anything at all.
6. **Keep-or-stop.** The line earns further work only if the intact conjugate shows a reproducible, exposure-adjusted advantage over the mixture without destroying the parent's delivery advantage or its normal-cell margin. If all the activity comes from premature fragmentation, co-dosing is the better strategy and the hybrid should be abandoned rather than preserved for its own sake.

9 · Methods

Properties were computed with **RDKit 2026.09.1** on both nodes. Every structure was passed through `Chem.MolFromSmiles` and sanitised; none is reported from memory or by hand-transcription from a structure name. Added-ester counts use a

SMARTS requiring the acyl carbon to bear carbon, so carbamates are excluded. Stereocentre counts are reported from `Chem.FindMolChiralCenters(..., includeUnassigned=True)` under **both** the legacy and the modern algorithm, because they disagree on cage and dependent spiro systems; where they disagree, both numbers are given.

Cross-verification was mutual and non-trivial. All twelve Series B structures were re-parsed on Planet 44 and their molecular weights and cLogP values reproduced to four decimal places from the published SMILES alone. The Series B assessment independently identified the 1,2-dioxane misdescription of the deposited lead, which Planet 44 then confirmed by ring perception on the deposited SMILES. The Planet 44 assumption that spiroadamantane ozonides would reduce stereochemical burden was falsified by its own computation and is reported above as a negative result.

10 · References

Cited as peroxide-design precedent only. No disease-efficacy claim is transferred.

- **P1** · Vennerstrom, J. L. *et al.* (2004). Identification of an antimalarial synthetic trioxolane drug development candidate. *Nature* **430**, 900–904. DOI 10.1038/nature02779. Establishes the synthetic ozonide and dispiro lineage. Does not validate the monospiro replacements used here.
- **P2** · Creek, D. J. *et al.* (2007). Iron-mediated degradation kinetics of substituted dispiro-1,2,4-trioxolane antimalarials. *Journal of Pharmaceutical Sciences* **96**(11), 2945–2956. DOI 10.1002/jps.20958. Supports iron-mediated cleavage with substituent-dependent kinetics, and the requirement to measure rather than assume that reactivity equals activity.

Further precedent for the tetraoxane class (RKA182, E209) is referenced in the Planet 85 assessment and is not independently re-verified here.

11 · Provenance and status

The deposited lead ARF-MOX-C4 was dedicated to the public domain under CC0 1.0 on 5 November 2026 as part of a 61-entry manifest (SHA-256 `8538f716…b886d5`) and is prior art as of that date. The thirty-four designs reported here are likewise dedicated to the public domain under CC0 1.0. No patent rights are asserted over any structure in this paper. The dedication is made to establish defensive prior art, so that no party may hereafter obtain composition-of-matter rights over these structures and freedom to operate remains permanently available to any laboratory that works on them.

Standing. Computational designs only. No compound described has been synthesised; no efficacy in any organism is claimed or implied. Published anticancer results for the parent scaffolds are preclinical, and no human cancer data exists for moxidectin in any indication. Antimalarial precedents are structural precedents only.

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