OPEN DISCLOSURE
C5-Functionalised Moxidectin Conjugates Targeting the Bioelectric and Redox State of Tumour Cells

A defensive publication of fourteen compounds, their design rationale and their syntheses

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1. Field

Chemical compounds: C5-*O*-functionalised conjugates of moxidectin, compositions containing them, and their proposed use in proliferative disease. The compounds are designed to engage a *cell-state* target — transmembrane and mitochondrial membrane potential, cellular redox tone and proteostatic load — rather than a single receptor, and to overcome the exposure limitation of existing macrocyclic lactones.

2. Background and the problem addressed

Four chemically unrelated, off-patent drug classes — avermectins, benzimidazoles, HIV protease inhibitors and artemisinin endoperoxides — report antiproliferative activity across many tumour lines while sharing no pharmacophore. We take that convergence to indicate a shared *target state* rather than a shared key: the cell's bioelectric and redox field.

Four problems follow for any agent intended to engage that state.

(i) Insufficient intratumoural exposure. Ivermectin's active *in-vitro* concentrations exceed plasma levels at tolerated antiparasitic doses. **(ii) No targeting of the proposed site of action.** If the target is the most polarised structure in the cell — the mitochondrial membrane — an untargeted lipophile distributes everywhere except preferentially where it is needed. **(iii) Single-axis pharmacology.** Existing agents engage voltage *or* redox *or* proteostasis; we predict super-additivity when two are engaged by one molecule. **(iv) Multidrug resistance.** P-glycoprotein efflux clamps intracellular ivermectin.

Why moxidectin is the scaffold

Moxidectin is human-approved (2018), has a terminal half-life of approximately 18–23 days against ivermectin's ~18 hours, a higher log P (5.4 vs 4.3), and is a *poor* P-glycoprotein substrate — so the efflux escape route that limits ivermectin is largely closed. It carries exactly two free hydroxyls, a tertiary C7-OH and a secondary allylic **C5-OH**; the latter is the

classical synthetic handle of the macrocyclic-lactone class. All compounds disclosed herein are C5-*O*-acyl conjugates, leaving the spiroketal, the C23-methoxime and the macrocycle intact.

3. Summary — Formula I

MOX–O–C(=O)–L–T

where **MOX–O–** is the moxidectin residue bonded through the C5 oxygen (C7-OH free or acylated); **L** is absent or a linker; and **T** is a targeting or pharmacophore moiety from one of four families, each corresponding to one mechanistic door:

Family A — the metabolic door. T is a saccharide residue, for uptake by GLUT1/GLUT3 transporters over-expressed in glycolytic tumours, with intracellular esterase release.
Family B — the voltage door. T is a delocalised lipophilic cation, which accumulates across the inner mitochondrial membrane in proportion to its potential; the target state is itself the delivery mechanism.
Family C — two doors in one key. T is a quinone or endoperoxide, engaging the voltage and redox axes simultaneously with guaranteed co-delivery and shared pharmacokinetics.
Family D — delivery. Solubilising and transporter-directed promoieties addressing the polarity and molecular-weight liabilities the other families incur.

4. The fourteen compounds

Code	Conjugate at moxidectin C5-O	Door / intent
A1	glucosyl succinate	GLUT import; lead glycoconjugate
A2	2-deoxyglucosyl succinate	Non-metabolisable sugar; traps conjugate
A3	GlcNAc succinate	Hexosamine route; evades GLUT downregulation
A4	glucuronyl carbamate	Carbamate linker; slower release
B1	triphenylphosphonium pentanoate	$\Delta\psi_m$-driven; lead mitochondriotropic
B2	triphenylphosphonium propanoate	Short linker; tether-length probe
B3	*N*-methylpyridinium butanoate	Lower-MW cation
B4	guanidinium hexanoate	Cell-penetrating cation
C1	menadione glycolate	Voltage + redox; lead hybrid
C2	plumbagin-type glycolate	Distinct redox potential
C3	juglone-type glycolate	ROS-forward hydroxynaphthoquinone
C4	trioxane (artemisinin-like) ester	Fe-triggered; fuses two drug classes in one molecule
D1	PEG_3 solubilising ester	Offsets series polarity liability
D2	valine prodrug	PepT1 peptide-transporter route

Computed properties (RDKit 2026.09.1): A1 $C_{47}H_{67}NO_{16}$, MW 902.0, clogP 3.40, TPSA 238.6, HBD/HBA 5/17, RotB 9. B1 $C_{60}H_{75}NO_9P^+$, MW 985.2, clogP 10.44, TPSA 122.1, HBD/HBA 1/10, RotB 12. C1 $C_{50}H_{61}NO_{12}$, MW 868.0, clogP 7.65, TPSA 165.5, HBD/HBA 1/13, RotB 7. High MW and TPSA are acknowledged liabilities and are precisely why a transporter/prodrug strategy is specified rather than passive uptake. Stereochemistry as generated; to be re-drawn and confirmed by a synthetic chemist before any bench work.

5. Structures — isomeric SMILES, in full

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> A1 — glucosyl succinate (GLUT import)

```
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)CCC(=O)OC[C@H]6O[C@@H](O)[C@H](O)[C@@H](O)[C@@H]6O)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

A2 — 2-deoxyglucosyl succinate

```
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)CCC(=O)OC[C@H]6O[C@@H](O)C[C@@H](O)[C@@H]6O)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

A3 — GlcNAc succinate

```
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)CCC(=O)OC[C@H]6O[C@@H](O)[C@H](NC(C)=O)[C@@H](O)[C@@H]6O)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

A4 — glucuronyl carbamate

```
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@H]6O[C@@H](O)[C@H](O)[C@@H](O)[C@@H]6C(=O)O)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

B1 — TPP pentanoate

```
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)(c6ccccc6)c6ccccc6)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

B2 — TPP propanoate (short linker)

```
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)CC[P+](c6ccccc6)(c6ccccc6)c6ccccc6)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

B3 — N-methylpyridinium butanoate

```
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)CCC[n+]6ccccc6C)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

B4 — guanidinium hexanoate

```
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)CCCCCNC(N)=[NH2+])C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

C1 — menadione glycolate

```
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)COC6=C(C)C(=O)c7ccccc7C6=O)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

C2 — plumbagin-type glycolate

```
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)COC6=CC(=O)c7c(O)cccc7C6=O)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

C3 — juglone-type glycolate

```
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)COC6=CC(=O)c7c(O)cccc7C6=O)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

C4 — trioxane (artemisinin-like) ester

```
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)CCC6C87)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

D1 — PEG3 solubilising ester

```
COCCOCCOCCC(=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@@]42O)O[C@@]1(C/C(=N\OC)[C@H](C)[C@@H](/C(C)=C/C(C)C)O1)C3
```

D2 — valine prodrug (PepT1)

```
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@@H](N)C(C)C)C(C)=C[C@@H](C(=O)O3)[C@]45O)O2)O[C@H](/C(C)=C/C(C)C)[C@H]1C
```

6. Preparation

General route: acylate the C5 hydroxyl of moxidectin with an activated acid of formula HO_2C–L–T, or a protected precursor thereof, and deprotect. Standard activation (carbodiimide with DMAP, or the acid chloride/anhydride) in an aprotic solvent at 0 °C to ambient; the C7 tertiary hydroxyl is markedly less reactive and in most cases needs no protection. For Family A the saccharide hydroxyls are protected (acetate or benzyl) during coupling and removed under Zemplén or hydrogenolytic conditions. For Family B the phosphonium or pyridinium salt is formed by quaternisation of

the ω-halo-ester with triphenylphosphine or the pyridine, prior to coupling. For Family C the quinone is introduced as its O-glycolic acid; the endoperoxide of C4 requires mild, non-reducing conditions throughout and must not be exposed to Fe(II). Purify by reverse-phase chromatography; confirm by HRMS and $^{1}H/^{13}C/^{31}P$ NMR.

7. Disclosed subject matter (published, unclaimed)

The following are disclosed so that they cannot be claimed by another. The numbering mirrors the form of claims for clarity only; **no right is asserted in any of them**.

1. A compound of Formula I, MOX–O–C(=O)–L–T, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein MOX–O– is the moxidectin residue bonded through the C5 oxygen, the C7 hydroxyl being free or substituted with C_1–C_6 acyl; L is absent or is C_1–C_{10} alkylene, C_2–C_{10} alkenylene, $–(CH_2)_n–O–(CH_2)_m–$, $–(CH_2)_n–C(=O)O–(CH_2)_m–$, $–(CH_2)_n–NH–C(=O)–(CH_2)_m–$, $–(CH_2CH_2O)_p–$, or an amino-acid or dipeptide residue (n, m = 0–6; p = 1–8); and T is a saccharide residue, a delocalised lipophilic cation, or a redox-active quinone or endoperoxide moiety as further specified below.

2. The compound of 1 wherein T is a saccharide selected from D-glucose, 2-deoxy-D-glucose, D-mannose, D-galactose, *N*-acetyl-D-glucosamine, D-glucuronic acid, or a disaccharide thereof, and L comprises an ester or carbamate linkage cleavable by intracellular esterase.

3. The compound of 1 wherein T is a delocalised lipophilic cation selected from tri(C_6–C_{10} aryl)phosphonium, tri(C_1–C_6 alkyl)phosphonium, *N*-(C_1–C_6 alkyl)pyridinium, quinolinium, rhodamine-19-yl and guanidinium, with a pharmaceutically acceptable counterion.

4. The compound of 1 wherein T is a redox-active moiety selected from 1,4-naphthoquinon-2-yl, 3-methyl-1,4-naphthoquinon-2-yl, 1,2-naphthoquinonyl, 5-hydroxy-1,4-naphthoquinon-2-yl, a β-lapachone residue, and a 1,2,4-trioxane or 1,2,4,5-tetraoxane endoperoxide residue.

5. The specific compounds A1, A2, A3, A4, B1, B2, B3, B4, C1, C2, C3, C4, D1 and D2 as drawn in §5.

6. A pharmaceutical composition comprising any compound above and a carrier; optionally liposomal, nanoparticle, cyclodextrin-complexed or lipid-nanoparticle; optionally formulated for intratumoural, intraperitoneal, intravenous or depot administration.

7. Such a composition further comprising a benzimidazole (mebendazole, albendazole, flubendazole or fenbendazole), a protease or proteasome inhibitor (nelfinavir, ritonavir, bortezomib), an artemisinin derivative, or a glycolysis inhibitor (2-deoxy-D-glucose, dichloroacetate).

8. Use of any compound above in the treatment of a proliferative disorder, optionally glioma, glioblastoma, triple-negative breast cancer, colorectal carcinoma, melanoma, multiple myeloma or a paediatric central-nervous-system tumour.

9. Such use wherein administration is **intermittent** — a dosing period of 1–4 days followed by a non-dosing period of 3–10 days, repeated — on the rationale that an adaptive target re-tunes to a constant perturbation.

10. Such use further comprising selecting the subject by measuring mitochondrial membrane potential, transmembrane potential or a redox marker in a tumour sample, and administering where the measured value differs from matched normal tissue by a predetermined threshold.

11. A process for preparing any compound above comprising acylating the C5 hydroxyl of moxidectin with an activated acid $HO_2C–L–T$ or a protected precursor, and deprotecting.

12. The corresponding C5-*O*-conjugates of nemadectin, selamectin, milbemycin oxime and doramectin, prepared by the same process with the same T groups.

8. What would disprove this

The design rests on testable predictions and we publish them with the structures. If accumulation of B1–B4 does not collapse when $\Delta\psi_m$ is dissipated; if GLUT knockdown does not abolish the A-family advantage; if C1 does not exceed an equimolar physical mixture of moxidectin and menadione under Bliss and Loewe; or if potency across the series fails to track baseline membrane potential and redox tone rather than ordinary molecular descriptors — then the rationale is wrong and these compounds are merely heavy esters. We would rather that be found out quickly by someone else than slowly by us.

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