Synthistat Ltd — Multi-Target HDAC Inhibitor Platform

Non-Confidential Business Development Summary

(Patent Pending)

Executive & Scientific Rationale

Executive Summary

Synthistat is developing a novel class of **multi-target epigenetic therapeutics** that unify:

- **HDAC inhibition**
- **BRD4 modulation**
- **PARP1 inhibition**
- and, in advanced embodiments, **dopamine D2 receptor (D2R) regulation**

within a **single, rationally engineered small-molecule scaffold**.

This architecture delivers coordinated control of **chromatin state, transcriptional regulation, DNA-damage response, and GPCR-mediated signalling**, establishing a new mechanistic class beyond conventional HDAC inhibitors.

Core Molecular Innovation

All compounds follow a modular pharmacophore:

Novel cap– Programmed linker – Zinc-binding group

Novel cap— Active design element
The novel proprietary cap moiety functions as a **global conformational director**, not merely a surface group:

- Prevents intramolecular folding
- Enforces extended, low-strain binding geometries
- Improves engagement of HDAC, BRD4, and PARP1
- Enhances metabolic stability and developability

Linker — target-programming domain
The linker is intentionally engineered — often **conformationally constrained** — to encode:

- exit-vector control
- three-dimensional geometry
- expansion of target scope into GPCR space (D2R)

This design allows multi-target engagement without sacrificing epigenetic pharmacology.

Integrated Multi-Target Activity

Target Class	**Functional Outcome**
HDAC2 / HDAC6	Robust zinc-coordinated inhibition with non-covalent geometry
BRD4	Stronger engagement vs panobinostat; canonical Asn140 recognition
PARP1	Enhanced binding via cap-directed conformational control
D2R (lead 8)	High-affinity **non-orthosteric negative allosteric modulation**

This produces a unified therapeutic mechanism that simultaneously disrupts:

- epigenetic control
- oncogenic transcription programs
- DNA-damage repair
- pathological dopaminergic signalling

Lead Data, Differentiation & Commercial Case

Property	Mol1	Mol2	Mol3	Mol4	Mol5	Mol6	Mol7	Mol8	Pano
BRD4 (kcal/mol)	-9.0	-8.3	-8.2	-8.3	-8.0	-8.9	-8.1 (~2.8–3.1 Å ND2–O)	-7.9 (~2.8–3.1 Å ND2–O)	-6.5
HDAC2 (kcal/mol)	-10.0	-7.8	-8.3	-8.0	-8.3	-8.3	-8.6	-8.6	-8.4
HDAC6 (kcal/mol)	-7.4	-6.8	-7.3	-7.6	-6.2	-8.6	-6.5	-6.2	-6.2
PARP1 (kcal/mol)	-11.4	-11.3	-11.4	-11.6	-10.3	-11.4	-10.3	-9.6	-8.6
D2R (kcal/mol)	—	—	—	—	—	—	—	-10.1	—
Log P	2.05	1.31	2.15	1.38	2.19	1.90	1.91	1.05	2.98
Log S (ESOL)	-3.70	-2.88	-3.75	-2.94	-3.69	-3.71	-3.54	-3.00	-3.79
BBB	No	No	No	No	No	No	No	No	Yes
CYP	2C9	—	—	—	3A4	—	3A4		1A2,2D6
Syn. Acc.	2.90	3.98	3.90	3.98	4.41	2.97	3.57	3.68	2.88
Rot. Bonds	6	6	6	6	9	6	9	8	8
Frac. Csp^3	0.18	0.43	0.45	0.43	0.50	0.18	0.50	0.48	0.19
PAINS	0	0	0	0	0	0	0	0	1
Brenk	Ani	Ani	Ani	Hyd,ON	0	Hyd,ON	0	0	3

Abbreviations: Pano = Panobinostat; Ani = Aniline; Hyd = Hydroxamate.

Table 1. Integrated ADME, Medicinal Chemistry, and Docking Comparison of Molecules 1–8 versus Panobinostat. (Newer patent series).

Docking & ADME Highlights (Molecules 1–8 vs Panobinostat)

- **All novel- capped molecules exceed panobinostat in BRD4 engagement**
- **Molecule 6**: strongest predicted HDAC6 binding (–8.6 kcal/mol)
- **Molecule 7**: validated tri-target HDAC–BRD4–PARP1 scaffold
- **Molecule 8**: unique expansion to **high-affinity D2R binding (–10.1 kcal/mol)**

Safety & Developability Advantages

- No Michael acceptors across new series
- Dramatically reduced PAINS / Brenk alerts
- Improved CYP profile
- All compounds predicted **non-BBB permeant** (peripheral safety benefit)
- 2× increase in **Fraction Csp^3** vs panobinostat (improved 3D drug-likeness)

hERG Safety
Panobinostat exhibits a high-risk U-shaped clamping pose within the hERG channel. Synthistat proprietary HDACi (notably Molecule 8) adopt **open, low-risk geometries** consistent with reduced arrhythmogenic liability.

Lead Evolution Strategy

Molecule 7 → Molecule 8
A rational lead-evolution path:

- preserve epigenetic & DNA-repair pharmacology
- reprogram linker geometry
- unlock GPCR (D2R) engagement without destabilizing HDAC / BRD4 / PARP1 binding

This is **encoded polypharmacology**, not empirical promiscuity.

Primary Oncology Applications

Strong mechanistic alignment with:

- **Acute Myeloid Leukemia (AML)**
- MYC-driven & super-enhancer-dependent cancers
- HR-deficient tumours (breast, ovarian, prostate, pancreatic, lung, glioblastoma)

Additional Commercial Application
Enhancement of **lentiviral vector production (LVV)** for:

- CAR-T
- gene therapy
- CRISPR manufacturing

Strategic Differentiation

Feature	Novel Capped Platform	Conventional HDACi
Multi-target integration	**Yes**	No
BRD4 + PARP1	**Yes**	No
D2R modulation	**Yes (select leads)**	No
Conformational control	**Engineered**	Absent
Michael acceptors	**None**	Common
hERG risk	**Low**	Elevated
Developability	**High**	Limited

Ligand Pose Verification & Structural Robustness

The multi-target activity of the platform is supported by extensive **ligand pose verification across independent docking campaigns** using multiple receptor structures, cavity definitions, and docking engines. For representative compounds (Molecules 1–8), productive and **highly reproducible binding architectures** were observed for HDAC2, HDAC6, BRD4, PARP1, and (for advanced leads) dopamine D2 receptor. Verified poses consistently display a conserved three-anchor architecture comprising **(A)** surface recognition and global conformational control, **(B)** linker-mediated directional steering through catalytic channels or vestibular pockets, and **(C)** stable zinc-binding group coordination within the HDAC active site. Zinc–ligand coordination distances (~2.0–2.6 Å) and canonical BRD4 Asn140 recognition geometries (~2.8–3.1 Å) were repeatedly reproduced, including under non-metal-aware docking conditions. The persistence of these poses across orthogonal computational conditions strongly supports that the observed interactions represent **physically meaningful, low-energy binding modes rather than scoring artifacts**, providing structural validation of the platform's encoded multi-target design.

Development & Partnering

- Provisional patent protection
- Multiple validated lead series
- Extensive structural & docking verification
- Ready for **in-vitro biology & translational development**

Synthistat welcomes partnership and collaborative development discussions.
Additional confidential data available under NDA.

Older Series, separate provisional filing.

Synthistat — HDAC/D2R Dual-Mechanism Candidate Therapeutics

Non-Confidential Scientific Summary (Patent Pending)

Synthistat is developing a new class of small-molecule therapeutic candidates designed through structure-guided computational methods to engage both histone deacetylase isoforms (HDAC2/6) and the dopamine-2 receptor (D2R), representing a mechanistically distinct direction beyond traditional pan-HDAC inhibitors. The therapeutic potential of HDAC inhibition in AML and related malignancies has long been established (San José-Enériz et al., 2019; Zhang et al., 2021).

Critically, preclinical evidence has also demonstrated that dopamine receptor antagonism — specifically via thioridazine — can selectively eliminate leukemic progenitor populations in AML that express D2R receptors, validating the relevance of dopaminergic signalling in AML pathobiology (Sachlos et al., 2012). This establishes D2R not as a hypothetical or extrapolated target, but as a demonstrated lever for AML cell vulnerability. Given the pharmacological precedent for D2R antagonism in targeting AML progenitors, the addition of rational HDAC inhibition represents a deliberate dual-modality optimisation rather than exploratory speculation.

Our novel dual action D2R/HDAC inhibitors have also been evaluated using protein docking and ADME profiling, demonstrating:

- strong predicted binding affinity to HDAC2 (down to –8.5 kcal/mol)
- additional D2R engagement (down to –6.7 kcal/mol) (potential nM potency)
- favourable solubility, polarity, and permeability indicators
- improved molecular flexibility profiles
- absence of critical toxicity-associated motifs

These findings are summarised in Table 1 comparing HDAC/D2R docking results with ADME indices.

Parameter	Panobinostat	Molecule 1	Molecule 2	Molecule 3	Advantage/Implication
HDAC2 Docking Score	-8.4	-8.0	-8.2	-8.5	Molecule 3 has the highest HDAC2 affinity.
HDAC6 Docking Score	-6.2	-8.0	-6.7	-7.7	Molecule 1 has the strongest binding to HDAC6.
D2R Docking Score	—	-6.7	-6.64	-6.499	Molecule 1 has the strongest binding to D2R.
Fsp^3 (Saturation)	0.19	0.29	0.32	0.29	Molecule 2 is the most 3D/saturated.
Log P (Lipophilicity)	2.98	2.38	2.14	2.19	All are in optimal range (1-3).
Log S (Solubility)	-3.79	-3.85	-3.90	-3.36	Molecule 3 is the most soluble.
TPSA (Polarity)	77 $Å^2$	71 $Å^2$	80 $Å^2$	88.59 $Å^2$	Molecule 1 has optimal TPSA for permeability.
Rotatable Bonds	8	6	8	5	Molecule 3 is the least flexible (best bioavailability potential).
Metabolism	CYP1A2, CYP2D6	CYP1A2, CYP2D6	Only CYP2D6	CYP1A2, CYP2D6	Molecule 2 has the simplest metabolic profile.
Michael Acceptor	Present	Absent	Absent	Absent	All molecules avoid toxicity risks of Panobinostat.

Table 1, reports comparison docking scores of our novel D2R/HDACi, alongside important ADME parameters (older patent series).

Among the current candidate set, Molecule 3 (older series) appears particularly promising, exhibiting:

- highest solubility
- lowest rotatable-bond count
- most favourable TPSA
- strong HDAC2 and D2R scores
- no reactive liabilities or Michael-acceptor features

The pursuit of combined epigenetic-and-receptor targeting reflects a trend toward multi-pathway therapeutic strategies in oncology (Grant et al., 2022). Our computational findings support continued non-clinical investigation toward in-vitro cellular assays and in-vivo feasibility studies.

Synthistat welcomes scientific feedback and exploratory discussion regarding evaluation pathways, potentially including HDAC/D2R-binding biochemical assays, AML-derived cell line testing, and future translational development considerations.

We are prepared to provide additional confidential molecular information under NDA should a collaboration or partnership with Synthistat Ltd be pursued. These structures have not been disclosed to external parties and are protected under a provisional patent filing with full priority coverage.

📚 **Updated Reference List**

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Sachlos, E., Risueno, R. M., Laronde, S., Shapovalova, Z., Lee, J.-H., Russell, J. and Bhatia, M. (2012) 'Identification of drugs including a dopamine receptor antagonist that selectively target cancer stem cells', *Cell*, 149(6), pp. 1284–1297. https://doi.org/10.1016/j.cell.2012.03.049

San José-Enériz, E., et al. (2019) 'HDAC inhibitors in acute myeloid leukemia', *Cancers*, 11(11), p. 1794. doi:10.3390/cancers11111794.

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