Study Notes — Lysergamides

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Substances discussed on this site are controlled in many jurisdictions (in the United Kingdom: Class A under the Misuse of Drugs Act 1971, with many analogues captured by the Act or by the Psychoactive Substances Act 2016). This material distinguishes human data, animal data and in-silico predictions throughout, and cites peer-reviewed sources. It contains no instructions on acquiring, preparing or consuming any substance.

Available documents

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CHAPTER 01

Basic chemistry & structure–activity relationships

The tetracyclic ergoline core of LSD, the positions that matter (N1, N6, the core itself), and what the systematic deconstruction of the molecule revealed.

1.1 — The tetracyclic ergoline core

LSD (lysergic acid diethylamide) possesses a **tetracyclic ergoline core**: four fused rings (conventionally A, B, C and D) that form its molecular scaffold. Rings A and B make up the indole portion — with the indole nitrogen at position **N1** — ring C is an unsaturated six-membered ring, and ring D is a piperidine-type ring containing the tertiary amine nitrogen at position **N6**. At C8 sits the amide side chain — in LSD, a **diethylamide** — which is crucial for receptor recognition (Basargin et al. 2026, DOI 10.1073/pnas.2603412123).

This architecture, which combines structural features of both the tryptamine and phenethylamine psychedelic families, has historically limited structure–activity relationship (SAR) studies: the number of accessible modifications is small and synthesising simplified analogues is far from trivial (DOI 10.1073/pnas.2603412123).

1.2 — The positions that count: N1, N6 and the ergoline core

Position	Structural feature	Pharmacological relevance
N1	Indole nitrogen of rings A/B; free N–H in LSD	Blocking it with acyl groups (acetyl, propionyl, butyryl…) suppresses 5-HT2A affinity in vitro; in vivo hydrolysis removes the acyl group and regenerates LSD (Ch. 2)
N6	Tertiary amine nitrogen of ring D	Allyl (AL-LAD) or ethyl (ETH-LAD) substitution yields analogues that are active per se, not prodrugs (Ch. 3)
Ergoline core	The tetracyclic scaffold as a whole	Systematic deconstruction (function-oriented synthesis) identified the minimal pharmacophore for maximal 5-HT2A agonism and hallucinogenic-like behavioural effects (DOI 10.1073/pnas.2603412123)

1.3 — Deconstructing LSD: the PNAS contribution

The study "Deconstruction of lysergic acid diethylamide" (Basargin et al. 2026, DOI 10.1073/pnas.2603412123) applied the principles of function-oriented synthesis to systematically remove portions of the ergoline core, generating **nine simplified analogues** ("ergologs") evaluated in assays relevant to 5-HT2A, 5-HT2B and 5-HT2C receptor function. Key findings:

- identification of the **key molecular features** and the **minimal pharmacophore** required for maximal 5-HT2A agonism and hallucinogenic-like behavioural effects (measured as the head-twitch response, HTR, in mice — animal data);
- strategies for **reducing the hallucinogenic and cardiotoxic potential** (5-HT2B activation is associated with cardiac valvulopathy), identifying the ergologs **UCD0094** and **UCD0076** as having improved safety profiles;
- UCD0076 shows **preference for 5-HT2C** over the other 5-HT2 receptors and produced antipsychotic-like properties in mouse behavioural assays (animal data).

1.4 — Why N1 modification is "silent in vitro, active in vivo"

A paradigmatic SAR result: acylating the indole nitrogen N1 **abolishes 5-HT2A affinity in vitro**, because the bulky acyl group and the loss of the indolic N–H compromise key interactions with the receptor pocket. Yet the N1-acyl compounds **are active in vivo**: after administration, the acyl group is removed by **hydrolysis (chemical and hepatic)**, liberating intact LSD — the true active agent (Ch. 2; DOI 10.1073/pnas.2603412123). They are therefore **prodrugs**, not autonomous agonists.

> **Remember**
>
> The tetracyclic ergoline core is the scaffold of every lysergamide. The two "historical" modifiable positions are N1 (indole nitrogen: modifications → prodrugs) and N6 (amine nitrogen: modifications → active-per-se analogues). Systematic deconstruction of the core (PNAS 2026) identified the minimal 5-HT2A pharmacophore and simplified analogues with improved safety profiles.

REFERENCES

• Basargin AG, Domokos A, Hennessey JJ, et al. Deconstruction of lysergic acid diethylamide. PNAS 123(38): e2603412123 (2026). DOI 10.1073/pnas.2603412123

• Halberstadt AL, et al. Neuropharmacology 172: 107856 (2020). DOI 10.1016/j.neuropharm.2019.107856

CHAPTER 02

The N1-acyl series: prodrugs of LSD

ALD-52, 1P-LSD, 1B-LSD, 1V-LSD and 1cP-LSD — compounds whose indole nitrogen is blocked by an acyl group, and which release LSD through hydrolysis in vivo.

2.1 — The compounds of the series

Substance	N1 acyl group
ALD-52	Acetyl — the oldest of the series, described in the 1950s
1P-LSD	Propionyl
1B-LSD	Butyryl
1V-LSD	Valeroyl (pentanoyl)
1cP-LSD	Cyclopropanecarbonyl
1S-LSD	3-(Trimethylsilyl)propanoyl — silicon-containing acyl group

In every member of the series the indole nitrogen N1 is blocked by an acyl group of different length or shape. This single change defines the pharmacology of the whole family.

2.2 — Mechanism: hydrolysis → LSD

All N1-acyl compounds behave as **prodrugs**: the acyl bond at N1 is labile and is cleaved both by **chemical hydrolysis** (non-enzymatic, favoured at physiological pH) and by **hepatic hydrolysis** via esterases, liberating intact LSD. The parent molecule itself has negligible 5-HT2A affinity in vitro — 1–2 orders of magnitude below LSD (DOI 10.1016/j.neuropharm.2019.107856; DOI 10.1073/pnas.2603412123).

2.3 — Key data, by evidence tier

- **1P-LSD** — human data (n = 2): oral bioavailability of LSD close to **100%**; only LSD — never the parent compound — detected in serum after oral administration (DOI 10.1002/dta.2821; PMID 32415750).
- **1B-LSD** — animal data: murine HTR potency only **14% of LSD** (ED50 976.7 vs 132.8 nmol/kg; DOI 10.1002/dta.2613; PMID 31083768), consistent with a prodrug whose activation depends on hydrolysis efficiency.
- **1V-LSD** — in-silico only: predicted pulmonary risk **92%** and hERG inhibition IC50 **1.4 µM** (Percepta; DOI 10.1007/s00204-025-04255-1) — a potential proarrhythmic signal that has never been verified experimentally.
- **1cP-LSD** — in-silico: predicted pulmonary risk **81%** and genotoxicity alerts up to 90% probability, unverified (DOI 10.1007/s00204-025-04255-1).
- **1S-LSD** — in-vitro metabolism: early formation of LSD in human liver microsomes, confirming the prodrug behaviour of the silicon-containing acyl series (in-vitro data; PMID 40730742).

Box — "Weak in vitro, active in vivo": why

In 5-HT2A binding assays performed in vitro (receptor preparation, no metabolism), N1-acyl compounds do not bind the receptor: the N1 acyl group abolishes affinity. In vivo, however, the organism hydrolyses the acyl group (chemically + via hepatic esterases) and releases LSD, which reaches the CNS and produces the effect. The observed behavioural phenotype — including the potency of the administered compound — is therefore entirely attributable to liberated LSD, not to the prodrug. Consequences: (a) these are not "new substances with new effects" but delivery routes for LSD; (b) differences in in-vivo potency reflect hydrolysis efficiency and pharmacokinetics, not intrinsic receptor action.

Remember

N1-acyl series = prodrugs. Hydrolysis (chemical + hepatic) → LSD. 1P-LSD: oral bioavailability ~100%, only LSD in serum (human data, PMID 32415750). 1B-LSD: HTR potency 14% of LSD (animal data, PMID 31083768). 1V-LSD: pulmonary risk 92% and hERG IC50 1.4 µM (in silico, DOI 10.1007/s00204-025-04255-1).

REFERENCES

- Grumann C, et al. Drug Test Anal 12(8): 1144–1153 (2020). DOI 10.1002/dta.2821; PMID 32415750 — human data (n = 2)
- Brandt SD, et al. Drug Test Anal 11(8): 1122–1133 (2019). DOI 10.1002/dta.2613; PMID 31083768 — animal data
- Halberstadt AL, et al. Neuropharmacology 172: 107856 (2020). DOI 10.1016/j.neuropharm.2019.107856; PMID 31756337 — prodrug mechanism
- Jurowski K, et al. Arch Toxicol 100: 3091–3110 (2026). DOI 10.1007/s00204-025-04255-1 — in-silico predictions

CHAPTER 03

The N6-substituted series: active per se

AL-LAD (N6-allyl) and ETH-LAD (N6-ethyl) — analogues modified on the amine nitrogen that are pharmacologically active molecules in their own right, not prodrugs.

3.1 — The compounds of the series

In the N6-substituted series the modification targets the tertiary amine nitrogen of ring D:

- **AL-LAD** — 6-allyl-6-nor-LSD (allyl group at N6);
- **ETH-LAD** — 6-ethyl-6-nor-LSD (ethyl group at N6).
- **PRO-LAD** — 6-propyl-6-nor-LSD (propyl group at N6).

3.2 — Not prodrugs, but autonomous agonists

Unlike the N1-acyl series, the N6-substituted analogues **do not convert to LSD** in the body: substitution on a tertiary amine is not hydrolysable. They are therefore **active per se**, with a receptor profile of their own. This has two important consequences:

- their effect is not pharmacokinetically reducible to LSD: potency data must be interpreted as the intrinsic activity of each individual molecule;
- their safety and metabolic profiles are **independent** of LSD's and cannot be inferred from it.

3.3 — Potency and safety data

- **AL-LAD** — animal data: in the murine HTR assay its potency is about **76% of LSD's** (ED50 174.9 vs 132.8 nmol/kg; DOI 10.1002/dta.1985; PMID 27265891), indicating 5-HT2A agonism only moderately reduced relative to the parent molecule.
- **ETH-LAD** — no controlled human data. Available information comes from preclinical models and non-controlled reports; the precautionary principle requires treating every estimate of human potency and safety as uncertain.
- **PRO-LAD** — animal data: in rat drug-discrimination studies it fully substitutes for LSD (~100% of LSD potency, reported); no murine HTR value is consolidated in the literature.

> **Remember**
>
> N6-substituted series = active-per-se analogues, not prodrugs; they do not convert to LSD. AL-LAD: HTR potency ~76% of LSD (animal data). ETH-LAD: no human data → maximum caution in any claim.

REFERENCES

• Brandt SD, et al. Return of the lysergamides. Part II. Drug Test Anal 9(1): 38–50 (2016). DOI 10.1002/dta.1985; PMID 27265891 — animal data

• Basargin AG, et al. PNAS 123(38): e2603412123 (2026). DOI 10.1073/pnas.2603412123 — SAR context

CHAPTER 04

Human safety data

The largest controlled human dataset for LSD — and the near-total evidence vacuum for every analogue discussed on this wiki.

4.1 — LSD: the pooled study in 83 healthy subjects

The most solid human safety picture for LSD comes from a pooled analysis of four double-blind, randomized, placebo-controlled crossover studies in **83 healthy subjects** (131 single-dose administrations) at **25, 50, 100 and 200 µg** of LSD base (Holze et al. 2021, DOI 10.1007/s00213-021-05978-6 — human data, in a controlled clinical setting). Key results:

Parameter	Result
Common adverse effects	Headache, anxiety, nausea, dizziness
200 µg — peak heart rate >100 bpm	25% of subjects
200 µg — peak body temperature >38 °C	34% of subjects
Liver and kidney function	No clinically relevant alterations

The overall picture — within a monitored clinical setting — indicates that adverse effects are predominantly **acute sympathomimetic** (tachycardia, hyperthermia) and **psychic** (anxiety), with no signs of renal or hepatic organ toxicity at the doses studied (human data).

4.2 — The analogues: an evidence vacuum

- **No controlled human clinical data** exist for ALD-52, 1B-LSD, 1V-LSD, 1cP-LSD, AL-LAD or ETH-LAD.
- For **1P-LSD** only extremely limited human data exist (**n = 2**), concerning analytical confirmation that LSD is what appears in serum (PMID 32415750) — not a safety study.
- The **toxicity of the analogues** (hERG cardiotoxicity, pulmonary risk, haematotoxicity, genotoxicity) is currently assessed almost exclusively through **in-silico predictions**, which are hypothetical and cannot replace experimental data (DOI 10.1007/s00204-025-04255-1).

> **Remember**
>
> LSD: the only compound in this wiki with a genuine human safety study (83 subjects, 25–200 µg; acute sympathomimetic and psychic adverse effects; no renal/hepatic alterations). For all the analogues: no controlled clinical data (1P-LSD only n = 2); toxicity estimated in silico only.

REFERENCES

• Holze F, Caluori TV, Vizeli P, Liechti ME. Psychopharmacology (2021). DOI 10.1007/s00213-021-05978-6 — human data

• Grumann C, et al. Drug Test Anal 12(8): 1144–1153 (2020). DOI 10.1002/dta.2821; PMID 32415750 — limited human data (n = 2)

• Jurowski K, et al. Arch Toxicol 100: 3091–3110 (2026). DOI 10.1007/s00204-025-04255-1 — in-silico predictions

CHAPTER 05

Analytical methods

Why cheap field tests cannot tell lysergamides apart — and what LC-MS/MS and NMR can do.

5.1 — Immunochromatographic and colorimetric tests

Field tests (immunochromatographic strips; colorimetric reagents such as Ehrlich's) rely on recognising the **indole structure** shared by all lysergamides. Direct consequence: **they detect indoles but cannot distinguish LSD from 1P-LSD, 1V-LSD or the other analogues**. A "positive" result signals generically the presence of a lysergamide, without identifying it.

5.2 — LC-MS/MS: the reference standard

Liquid chromatography coupled to tandem mass spectrometry (**LC-MS/MS**) is the reference method: it **separates and simultaneously identifies all the analogues** (LSD, 1P-LSD, 1B-LSD, 1V-LSD, 1cP-LSD, AL-LAD, ETH-LAD and metabolites) by combining retention time, precursor ions and fragmentation transitions. It is the method used in clinical and toxicological studies (e.g. DOI 10.1002/dta.2821; PMID 32415750).

5.3 — NMR: complete structural characterization

Nuclear magnetic resonance spectroscopy (**NMR**) provides the **complete structural characterization** of a new analogue: assignment of all proton and carbon resonances, confirmation of the substitution position (N1 vs N6), stereochemistry and purity. It is the method by which new compounds such as **1B-LSD** were first characterised in the literature (DOI 10.1002/dta.2613; PMID 31083768).

5.4 — Limitations of inexpensive tests

- **Not specific**: they respond to the chemical class (indoles), not to the individual substance;
- **not quantitative**: they cannot distinguish doses;
- **prone to false positives/negatives** depending on matrix and interferents;
- **they do not say which substance** is actually present — information that is crucial both in clinical toxicology and for harm-reduction purposes.

> **Remember**
>
> Rapid tests (immunochromatographic/colorimetric) = detect the indole class, cannot distinguish analogues. LC-MS/MS = separates and identifies all analogues simultaneously (reference method). NMR = complete structural characterization (e.g. 1B-LSD). Inexpensive tests have specificity and quantification limits.

REFERENCES

• Grumann C, et al. Drug Test Anal 12(8): 1144–1153 (2020). DOI 10.1002/dta.2821; PMID 32415750 — LC-MS/MS application

• Brandt SD, et al. Drug Test Anal 11(8): 1122–1133 (2019). DOI 10.1002/dta.2613; PMID 31083768 — NMR characterization of 1B-LSD