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| RESEARCH ARTICLE

The Theoretical Synthesis and *in silico* Modelling of Lysergic Acid Biscinnamylidene Amide from the Adduct Formation of d-Lysergic Acid Amide and Cinnamaldehyde

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| ABSTRACT
Here is a theoretical synthesis for a cinnamaldehyde adduct formation of a hypothetically proposed lysergamide derivative named cinnamylidene-bislysergamide or lysergic acid biscinnamylidene amide (LSBC). This lysergamide name and abbreviation is in keeping with names of other lysergamide derivatives, such as d-lysergic acid amine (LSA), lysergic acid 2-butyl amide (LSB), lysergic acid diethylamide (LSD), d-lysergic acid α-hydroxyethylamide (LSH), lysergic acid methylisopropylamide (LSMIP), and lysergic acid 3-pentyl amide (LSP). Lysergamides are generally psychedelic in nature. The evidence for LSBC adduct formation is plausible, but the evidence supporting its psychedelic effects is weak.

| KEYWORDS
Cinnamylidene-bislysergamide, cinnamylidene-bislysergic acid amide, CBLSA, LSC, LSBC, adduct, LSA, LSH, d-lysergic acid amide

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1. Introduction

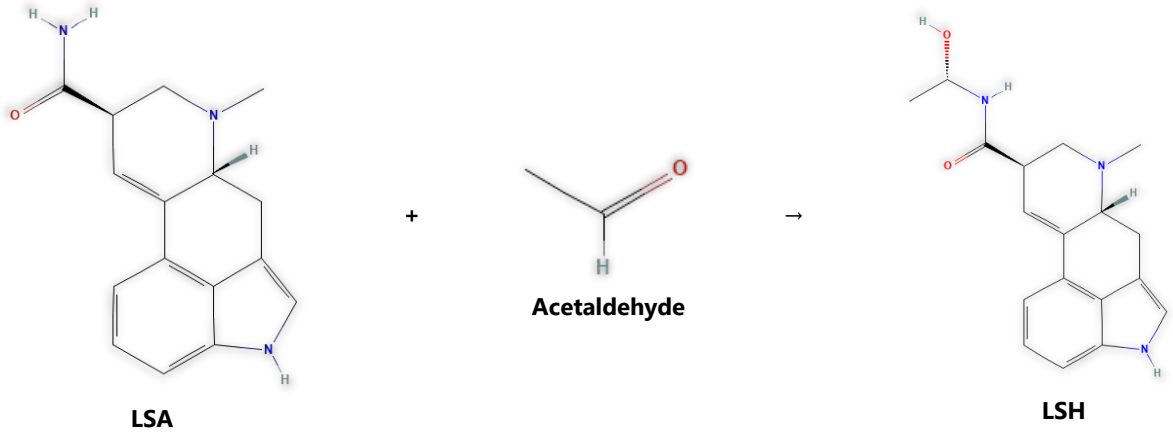
LSA commonly known as ergine is a naturally occurring ergoline alkaloid found in the seeds of *Ipomoea spp.* (morning glories), *Argyeria nervosa* (Hawaiian baby wood rose), and the ergot fungus *Claviceps paspali*. The LSA constituent of *Claviceps paspali* forms LSH when submerged into fermented liquor [Arcamone, 1961]. LSH is the chemical adduct formed from the reaction of LSA and acetaldehyde. Fermented liquor, such as some wines, contain acetaldehyde. Thus, a probable explanation for the formation of LSH from *Claviceps paspali* and fermented alcohol, is the adduct formation of LSA and acetaldehyde, depicted in Figure 1. This adduct formation is supported by anecdotal evidence of co-administering LSA with fresh peppermint leaves on forums as individuals search to exploit legal systems in search for a 'legal high'. Fresh peppermint leaves are high in acetaldehyde; thus, it is probable that individuals are forming LSH through the adduct formation of LSA and acetaldehyde.

2. The Theory

Individuals on online forums have hypothesised that if LSA can form an adduct with acetaldehyde, it should be able to form adducts with other aldehydes. Anecdotal evidence found on online forums, states that, individuals who have ingested LSA and cinnamon essential oil have experienced a psychoactive effect that differs from LSA and is more like LSD. Cinnamon essential oil contains approximately 90% cinnamaldehyde [Wong, 2014]. This paper will provide scientific authentication to propose a theory for the adduct formation between LSA and cinnamaldehyde.

LSBC is a theoretical adduct of LSA and cinnamaldehyde. LSBC is composed of two molecules of LSA and one molecule of cinnamaldehyde. It is theorised that the LSCB adduct forms a 2:1 ratio based on other amine and amide cinnamaldehyde adducts such as cinnamylidene-bisacetamide and cinnamylidene-bisphenylacetamide, which are proven to form without the need for a catalyst. See Table 1 and Table 2.

Figure 1. LSH adduct formation by LSA and acetaldehyde



3. Aldehyde Adduct Formations

Aldehydes are a chemical group of highly volatile aromatic compounds. Some aldehydes can form adducts with amides or amines without the need for a catalyst at standard ambient temperatures. Below are some examples of aldehyde adduct formations.

Table 1. Adduct formations of cinnamaldeyhe and amines

Amine	Aldehyde	Adduct formation	Reference
Phenylethylamine	Benzaldehyde	*N*-Benzylideme-*N*-phenethylamine	[3]
Dapsone	Cinnamaldehyde	4-(Cinnamylideneamino)phenyl sulfone	[4]
Glutathione	Cinnamaldehyde	1'-(Glutathion-S-yl)-dihydrocinnnamaldehyde	[5]

Table 2. Adduct formations of cinnamaldeyhe and amides

Amide	Aldehyde	Adduct formation	Reference
2-Phenylacetamide	Cinnamaldehyde	Cinnamylidene-bisphenylacetamide	[6]
Acetamide	Cinnamaldehyde	*N*,*N*'-cinnamylidenediacetamide	[6]
LSA	Acetaldehyde	LSH	

4. Theoretical LSA and Cinnamaldehyde Adduct Formation

Theoretically, one molecule of LSA would form an adduct with one molecule of cinnamaldehyde similarly as LSA and acetaldehyde in a 1:1 molar ratio. This compound is named on online forums as cinnamylidene-lysergamide. But, in keeping with lysergamide derivatives the name lysergic acid cinnamylidene amide (LSC) is more appropriate. The reaction is represented in Figure 2. However, the amides phenylacetamide, acetamide, and the amine dapsone form an adduct with cinnamaldehyde at a 2:1 molar ratio of two molecules of amide or amine to one molecule of cinnamaldehyde, shown in Figure 5.

Following other aldehyde adduct formations of cinnamaldehyde with amines or amides, a more likely theoretical adduct of LSA and cinnamaldehyde is cinnammylidene-bislysergamide. Cinnammylidene-bislysergamide is composed of two molecules of LSA and one molecule of cinnamaldehyde in a 2:1 molar ratio. An appropriate abbreviation for cinnammylidene-bislysergamide would be CLSA or CDLSA. However, to keep in line with the abbreviations of the other lysergic ergolines LSD, LSA, LSP, and LSH, the synonym lysergic acid biscinnamylidene amide is used, and abbreviation LSBC is appropriate in this context.

Figure 2. LSC formation by the adduct of LSA and cinnamaldehyde at a 1:1 molar ratio

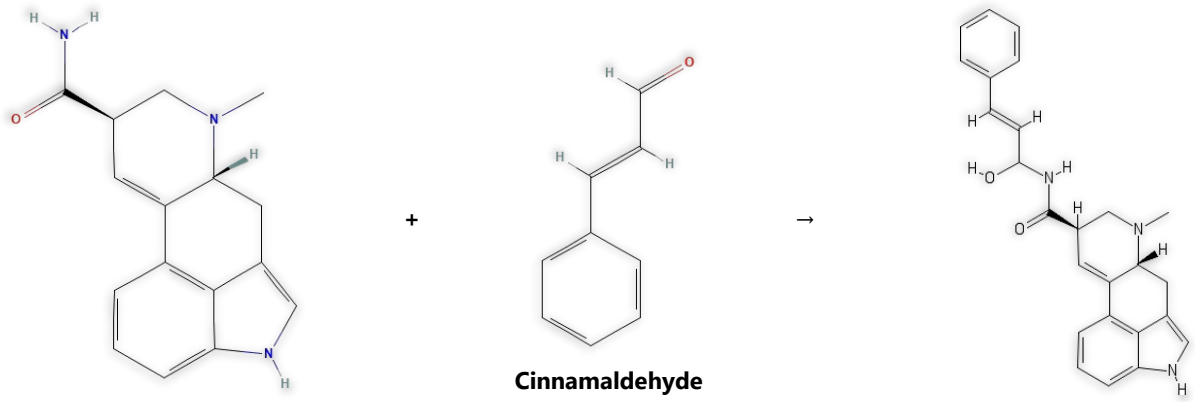
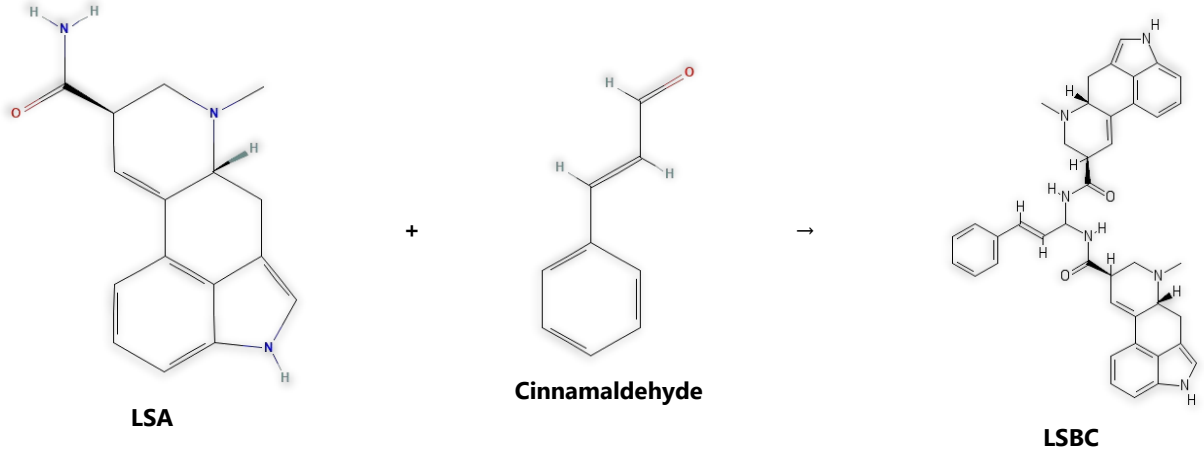


Figure 3. LSBC formation by the adduct of LSA and cinnamaldehyde at a 2:1 molar ratio



5. LSBC Molecular Properties

The cheminformatic web tool molinspiration (mi) was employed to draw the LSC molecule, at www.molinspiration.com. The mi web tool automatically generates Simplified Molecular Input Line Entry System (SMILES) for the respectively drawn molecule. The miSMILES generated was:

CN7C[C@H](C(=O)NC(C=Cc1ccccc1)NC(=O)[C@@H]3C=C2c4cccc5[nH]cc(C[C@H]2N(C)C3)c45)C=C6c8cccc9[nH]cc(C[C@H]67)c89.

From here molecular properties and *in silico* bioactivity can be predicted. Figure 4 depicts the drawing of the LSBC molecule in the mi web tool. Table 3 contains the molecular properties and Table 4 the *in silico* bioactivity.

Figure 4. Molinspiration SMILES-input of LSBC

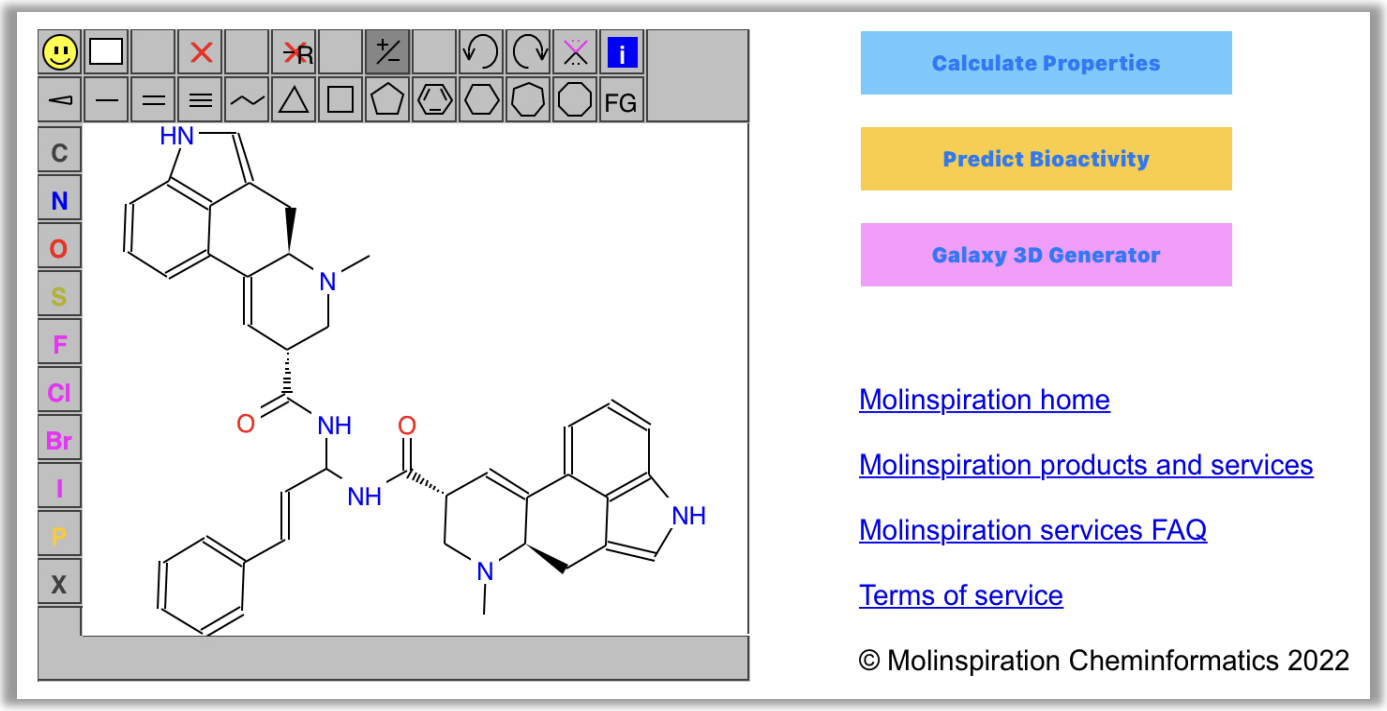


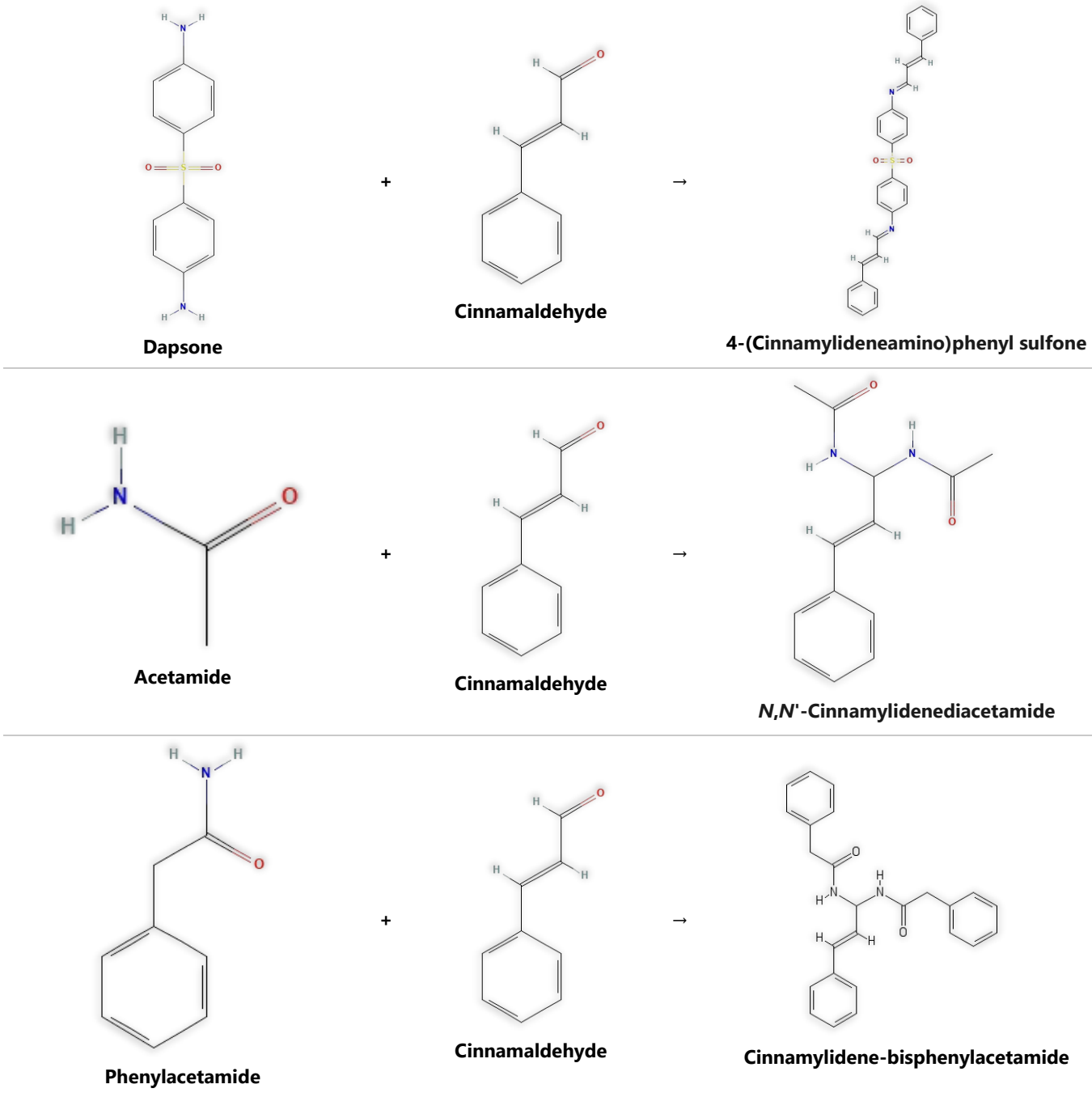
Table 3. Molinspiration molecular property *in silico* predictions for LSBC

Property	Description	Value
miLogP	Octanol/water partition coefficient	5.34
TPSA	Topological polar surface area	96.25
natoms	Number of atoms	49
MW	Molecular weight	648.81
nON	Number of hydrogen bond acceptors	8
nOHNH	Number of hydrogen bond donors	4
nviolations	Number of Lipinski violations	2
nrotb	Number of rotatable bonds	T
volume	Molecular volume	596.51

Table 4. Molinspiration molecular bioactivity *in silico* predictions for LSBC

Property	Value
GPCR ligand	-0.06
Ion channel modulator	-1.12
Kinase inhibitor	-0.83
Nuclear receptor ligand	-1.16
Protease inhibitor	-0.24
Enzyme inhibitor	-0.67

Figure 5. Cinnamaldehyde adduct formations in a 2:1 molar ratio with amides and amines



6. Discussion

If LSBC is synthesised as an adduct formation, the molecular properties in Table 3 should predict its bioavailability using Lipinski's Rule of Five. Lipinski's Rule of Five states that generally an oral drug must satisfy four criteria to be orally active [Lipinski, 2004]. The drug candidate must have a molecular mass of less than or equal to 500 daltons, a log *P* that does not exceed five, no more than five hydrogen donors, and no more than 10 hydrogen acceptors. Table 5 below compares Lipinski's Rule of Five with the *in silico* molecular property predictions for LSBC.

Table 5. Lipinski's Rule of Five with the in silico molecular property predictions for LSCB

Property	Lipinski	LSBC
miLogP	≤ 5	5.34
MW	≤ 500	648.81
nON	≤ 10	8
nOHNH	≤ 5	4

Lipinski's Rule of Five states, in general, an orally active drug has no more than one violation of the rules [Lipinski, 2001]. LSBC has two violations of the rule, in molecular weight and Log *P*.

Molinspiration predicts a G-protein coupled receptor (GPCR) ligand activity score of -0.06. A bioactivity score of under 0.50 is presumed to be inactive [Agwon, 2019]. The main serotonin psychedelic receptor is the serotonin subtype-2A (5-HT_{2A}) receptor [10]. The 5-HT_{2A} is a GPCR.

The evidence for LSBC adduct formation is plausible, however, the evidence of LSBC being bioavailable or agonising 5-HT_{2A} is weak. An explanation for individuals experiencing a subjectively LSD-like experience may be explained by LSBC metabolism by enzymes in the gastrointestinal tract, first-pass metabolism in the liver, or fermentation by human microflora into a different compound. Alternatively, the Molinspiration predictions may be incorrect, a placebo effect may be felt, or the cinnamaldehyde could be interacting with the LSA through P450 isozyme induction or inhibition.

7. Conclusion

It is anecdotally hypothesised that the LSBC adduct forms a 2:1 molar ratio of LSA to cinnamaldehyde based on other amide and amine cinnamaldehyde adducts, such as *N*,*N*'-cinnamylidenediacetamide, cinnamylidene-bisphenylacetamide, and 4-(cinnamylideneamino)phenyl sulfone. Here is the scientific justification to turn this hypothesis into a theory. Although the adduct formation is plausible, the evidence purporting LSBC to have psychedelic effects is weak. Research is needed in analytical testing of potential LSBC synthesis.

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Conflicts of Interest: The author declares no conflict of interest.

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