Alan Scientific Inc

ADMET Report

A Comprehensive ADMET Prediction Report

Cepharanthine · CEP

A Comprehensive Assessment of the Absorption, Distribution, Metabolism, Excretion, and Toxicity of a Bisbenzylisoquinoline Alkaloid

CAS 481-49-2 ◆ $C_{37}H_{38}N_2O_6$ ◆ MW 606.71 Da

Bisbenzylisoquinoline Alkaloid

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ABSTRACT

Cepharanthine (CEP) is a naturally occurring bisbenzylisoquinoline alkaloid isolated from the roots of *Stephania cepharantha* Hayata (Menispermaceae). It has been used clinically in Japan for more than half a century for the treatment of leukopenia, idiopathic thrombocytopenic purpura, alopecia areata, and snake venom poisoning. During the post-COVID-19 era, CEP has regained considerable attention owing to its potent **in vitro** inhibitory activity against SARS-CoV-2.

This report integrates computational predictions from major in silico ADMET platforms, including **SwissADME**, **ADMETlab 2.0**, and **pkCSM**, together with published **in vitro** (human liver microsomes) and **in vivo** (rat pharmacokinetic) experimental data to provide a comprehensive evaluation of the ADMET characteristics of CEP.

Overall, CEP is characterized by **high lipophilicity** (cLogP ≈ 6.4) and a **large molecular weight** (606.71 Da), resulting in two violations of Lipinski's Rule of Five. Oral bioavailability is poor (approximately **5.65% in rats**). CEP acts as a **potent time-dependent inhibitor of CYP3A4** (Ki = 8.12 μM), suggesting a clinically relevant risk of drug-drug interactions (DDIs). In addition, **a moderate-to-high risk of hERG channel inhibition** is predicted.

*Table **1.0** · Executive Summary of ADMET Properties*

A · Absorption	D · Distribution	M · Metabolism	E · Excretion	T · Toxicity
C Poor	**B** Extensive tissue distribution	**C** High metabolic interaction risk	**B** Moderate	**B** Safety concerns requiring monitoring

I. Compound Identity & Structure

***Table 1.1** · Compound Information*

Compound Name	Cepharanthine
IUPAC Description	Bisbenzylisoquinoline macrocyclic ether (cepharanthine type)
CAS Registry Number	481-49-2

PubChem CID	10206
DrugBank ID	DB16824
Molecular Formula	C37H38N2O6
Molecular Weight	606.71 g/mol
Structural Class	Bisbenzylisoquinoline alkaloid (macrocyclic diaryl ether type)
Botanical Source	*Stephania cepharantha* Hayata (Menispermaceae)
SMILES	COc1ccc(C[C@@H]2N(C)CCc3cc(OC)c(OC)c(Oc4cc5c(cc4)C[C@H]4N(C)CCc6cc(OC)c(Oc7ccc1cc7)c-6C4)c-23)cc1

Structurally, cepharanthine consists of two 1-benzylisoquinoline units linked head-to-tail by two diaryl ether bridges, forming a rigid 16-membered macrocyclic framework. This unique elliptical macrocycle confers both **cationic amphiphilicity** and pronounced **lipophilicity**, providing the structural basis for many of its pharmacokinetic and pharmacodynamic properties. The molecule contains four methoxy groups, one methylenedioxy bridge, and two N-methyl tertiary amine nitrogen atoms capable of protonation under physiological conditions. Together, these structural features largely determine CEP's membrane permeability, tissue distribution, lysosomal accumulation, metabolic behavior, and potential toxicity.

II. *Physicochemical Properties*

Physicochemical descriptors serve as the critical link between molecular structure and pharmacokinetic behavior. The principal challenge associated with cepharanthine (CEP) lies in its combination of **high molecular weight** and **pronounced lipophilicity**, both of which extend beyond the conventional drug-like chemical space. Nevertheless, its **topological polar surface area (TPSA)** and **molecular flexibility** remain within acceptable ranges.

Table 2.1 *· Key Physicochemical Properties of Cepharanthine*

(Calculated using SwissADME and ADMETlab 2.0)

Parameter	Value	Recommended Range	Verdict
MW	606.71 g/mol	≤ 500	Above threshold; unavoidable due to the rigid macrocyclic scaffold
cLogP (XLogP3)	6.42	≤ 5	Highly lipophilic; adversely affects aqueous solubility and free drug fraction
cLogP (iLOGP, SwissADME)	5.18	—	Highly lipophilic (slightly lower estimate)
Topological Polar Surface Area (TPSA)	61.86 Å²	< 140 Å²	Acceptable; favorable for membrane permeability
Hydrogen Bond Donors (HBD)	0	≤ 5	Acceptable
Hydrogen Bond Acceptors (HBA)	8	≤ 10	Acceptable
Rotatable Bonds (RotB)	4	≤ 10	Acceptable; macrocyclization substantially limits conformational flexibility
Molar Refractivity (MR)	181.0	40–130	Above the recommended range
Predicted Water Solubility (LogS, ESOL)	−7.2	> −4	Practically insoluble in water
Number of Aromatic Rings	4	≤ 3 (preferred)	Slightly excessive
Predicted pKa (Most Basic Nitrogen)	≈ 8.4	—	Partially protonated under physiological conditions
Net Charge (pH 7.4)	+1 (Weakly cationic)	—	Weakly cationic; cationic amphiphilic compound

Bioavailability Radar Interpretation

The **SwissADME Bioavailability Radar** graphically illustrates the optimal physicochemical space for orally administered small-molecule drugs using six descriptors.

• LIPO（Lipophilicity）：cLogP = 6.4，substantially exceeding the recommended range and representing a major limitation.

• SIZE（Molecular Size）：MW = 606，Molecular weight of **606.71 Da**, considerably larger than the preferred drug-like space.

• INSOLU（INSOLU）：LogS = −7.2，Predicted LogS of **−7.2**, indicating extremely poor aqueous solubility.

• POLAR / FLEX / INSATU：Within the optimal range.

Conclusion：CEP simultaneously deviates from the optimal drug-like region with respect to **lipophilicity**, **molecular size**, and **aqueous solubility**, suggesting a significant limitation for oral absorption. This prediction is highly consistent with experimental pharmacokinetic data demonstrating an oral bioavailability of only **approximately 5.65% in rats**.

III. Absorption *Membrane Permeability & Oral Absorption*

The absorption profile of cepharanthine exemplifies a classic **"lipophilicity paradox."** Although its physicochemical properties predict efficient passive membrane permeation, its actual oral bioavailability remains remarkably low. This discrepancy is primarily attributable to extremely poor aqueous solubility leading to dissolution-limited absorption, active efflux mediated by **P-glycoprotein (P-gp)**, and extensive intestinal and hepatic first-pass metabolism, predominantly via **CYP3A4**.

Table 3.1 *· Absorption Parameters: Predicted Versus Experimental Data*

Parameter	Predicted / Experimental Value	Data Type	Interpretation
Human Intestinal Absorption (HIA)	High (> 75%)	Prediction	Passive intestinal permeability is expected to be favorable based on TPSA and lipophilicity
Caco-2 Permeability	−4.78 cm/s	Prediction	Borderline permeability (values < −5 indicate poor permeability)
MDCK Permeability	2.1×10^{-6} cm/s	Prediction	Moderate membrane permeability
P-glycoprotein Substrate	Yes（Strong）	Experimental	CEP has been experimentally confirmed as a P-gp substrate

Parameter	Predicted / Experimental Value	Data Type	Interpretation
P-glycoprotein Inhibitor	Yes	Experimental	CEP functions as both a substrate and an inhibitor of P-gp
Water Solubility	Very low	Experimental	Practically insoluble in water; readily soluble in DMSO, ethanol, and methanol
Oral Bioavailability (Rat)	5.65 ± 0.35 %	Experimental	10 mg/kg p.o. vs 1 mg/kg i.v.
Tmax (Rat, Oral)	≈ 2.67 h	Experimental	Relatively slow absorption
Cmax (Rat, Oral, 10 mg/kg)	46.89 ± 5.25 ng/mL	Experimental	—
Cmax (Rat, Intravenous, 1 mg/kg)	153.17 ± 16.18 ng/mL	Experimental	—

▲ *Mechanistic Analysis of the Absorption Limitation*

The limited oral bioavailability of cepharanthine (CEP) is primarily driven by the synergistic interplay of dissolution-limited absorption, P-glycoprotein (P-gp)-mediated efflux, and extensive CYP3A4-dependent first-pass metabolism in both the intestine and liver, rather than by insufficient membrane permeability. Accordingly, formulation-based approaches—including nanocrystals, lipid-based nanocarriers, solid dispersions, and self-emulsifying drug delivery systems (SEDDS)—have demonstrated considerable potential for enhancing its oral exposure.

IV. Distribution *Tissue Distribution & Plasma Binding*

The high lipophilicity and cationic amphiphilic nature of CEP predispose it to accumulate in lipid-rich or negatively charged organelles (e.g., mitochondria and lysosomes) and facilitate its penetration across the blood–brain barrier. These properties constitute the structural basis for its antiviral and antitumor activities, while also contributing to its potential central nervous system adverse effects.

***Table 4.1** · Predicted Distribution Parameters*

Parameter	Predicted Value	Data Type	Interpretation
Plasma Protein Binding (PPB)	>95%	Prediction	High LogP results in strong binding to human serum albumin
Plasma Free Fraction (fu, plasma)	<0.05	Prediction	High susceptibility to pharmacokinetic drug interactions
Volume of Distribution (Vdss)	~8–15 L/kg	Prediction	Extensive tissue distribution (> total body water)
Blood–Brain Barrier Permeability (BBB)	Yes (Permeable)	Prediction	TPSA <90 Å² and high LogP
LogBB	+0.32	Prediction	Brain-to-plasma concentration ratio ≈ 2:1
CNS Permeability (LogPS)	−2.1	Prediction	Moderate-to-high CNS penetration
Lysosomal Tropism	High	Prediction	Weak base + high lipophilicity → lysosomal accumulation
Phospholipidosis Risk	Probable	Prediction	Typical cationic amphiphilic drug (CAD) structure

> ◇ ***Characteristics of Cationic Amphiphilic Drugs (CADs)***
>
> CEP fulfills the two defining criteria of a typical CAD compound: (i) the presence of at least one protonatable amine, and (ii) a hydrophobic moiety with LogP >4. CAD compounds are susceptible to lysosomal ion trapping, leading to the formation of drug–phospholipid complexes. Long-term administration may induce drug-induced phospholipidosis (DIPL), although this phenomenon may also partially explain the antiviral mechanism of CEP through disruption of the endocytic–lysosomal pathway.

V. Metabolism *CYP450 Interactions & Biotransformation*

Metabolism represents the principal risk dimension of CEP. Chang et al. (2020) systematically evaluated the inhibitory effects of CEP on eight human hepatic CYP isoforms using human liver microsomes (HLMs). The results demonstrated that CEP is a clinically relevant multi-CYP inhibitor, with particularly pronounced time-dependent inactivation of CYP3A4 (mechanism-based inhibition, MBI).

***Table 5.1** · Inhibitory Effects of CEP on Human Hepatic CYP450 Isoforms (Chang et al., 2020, in vitro)*

CYP Isoform	IC50 (μM)	Ki (μM)	Inhibition Type	Clinical / Mechanistic Significance
CYP3A4	16.29	8.12	Noncompetitive + Time-dependent (KI/kinact = 10.84/0.058 min/μM)	High risk — irreversible MBI; involved in the metabolism of approximately 50% of clinically used drugs
CYP2C9	24.57	13.06	Competitive	Moderate-to-high risk — warfarin, NSAIDs, sulfonylureas
CYP2E1	25.62	11.78	Competitive	Moderate risk — ethanol and acetaminophen bioactivation
CYP1A2	>100 (NS)	—	No significant inhibition	Low risk
CYP2A6	>100 (NS)	—	No significant inhibition	Low risk
CYP2D6	>100 (NS)	—	No significant inhibition	Low risk
CYP2C19	>100 (NS)	—	No significant inhibition	Low risk
CYP2C8	>100 (NS)	—	No significant inhibition	Low risk

5.2 · *Predicted Metabolic Pathways*

Based on site-of-metabolism (SoM) prediction, the primary metabolic transformation sites of CEP are as follows:

***Table 5.2** · Predicted Phase I Metabolic Pathways*

Reaction Type	Major Enzyme(s)	Predicted Site / Metabolite
O-Demethylation	CYP3A4 / CYP2D6	Any of the four methoxy groups; formation of corresponding phenolic metabolites (cepharanoline-type metabolites)
N-Demethylation	CYP3A4	N-methyl isoquinoline nitrogen → secondary amine; increased polarity and reduced lipophilicity
Aromatic Hydroxylation	CYP3A4 / CYP1A2	Ortho- or para-position of the aromatic ring; potential formation of catechol metabolites (reactive metabolites)
Phase II Conjugation	UGT1A1, UGT1A3, SULT	Glucuronidation or sulfation of phenolic hydroxyl groups generated during Phase I metabolism

▲ ***Clinically Relevant DDI Warning***

1. Time-dependent inactivation of CYP3A4 (MBI) is the most clinically significant metabolic characteristic of CEP. MBI implies that even after CEP has been eliminated, inactivated CYP3A4 enzymes must be regenerated through de novo protein synthesis (human recovery half-life: approximately 70–100 h).

2. Concomitant administration with narrow therapeutic index CYP3A4 substrates—including tacrolimus, cyclosporine, midazolam, simvastatin, verapamil, imatinib, rivaroxaban, and olaparib—is expected to result in a substantial increase in systemic exposure (AUC).

3. Combined inhibition of CYP2C9 may further increase the risk of drug interactions. Close monitoring of the international normalized ratio (INR) is recommended when CEP is co-administered with warfarin.

5.3 · *Metabolic Stability*

Parameter	Predicted Value	Interpretation
HLM Microsomal Stability	Low–Moderate · t1/2 ≈ 25–40 min	Significant CYP3A4-mediated metabolic clearance
Intrinsic Hepatocellular Clearance (CLint)	~40 μL/min/10^6 cells	Moderate metabolic clearance
CYP3A4 Auto-inhibition	Yes (KI = 10.84 μM)	Repeated dosing may result in nonlinear pharmacokinetics

VI. Excretion *Clearance & Elimination Kinetics*

The excretion profile of CEP reflects its large volume of distribution and moderate metabolic clearance, characterized by a relatively long terminal half-life and a low fraction of renal excretion. These findings indicate that the risk of accumulation is driven primarily by metabolism rather than renal function.

***Table 6.1** · Excretion-Related Parameters*

Parameter	Value	Data Type	Interpretation
Terminal Half-life, t1/2 (i.v., rat)	6.76 ± 1.21 h	Experimental	Rat, 1 mg/kg intravenous administration
Terminal Half-life, t1/2 (p.o., rat)	11.02 ± 1.32 h	Experimental	"Flip-flop" phenomenon: absorption rate-limited
Predicted Human t1/2	~15–24 h	Extrapolation	Allometric scaling supports once-daily dosing
Hepatic Clearance (CLH, predicted)	~8–14 mL/min/kg	Prediction	Moderate metabolic clearance
Fraction Excreted Unchanged in Urine (fe)	<5%	Prediction	Predominantly eliminated via the hepatobiliary route
OCT2 Substrate	Possible	Prediction	The cationic structure may undergo uptake by renal proximal tubular cells

Parameter	Value	Data Type	Interpretation
Biliary Excretion	Major route (predicted)	Prediction	Consistent with high molecular weight, high LogP, and P-gp substrate characteristics

VII. Toxicity *Predicted Safety Liabilities*

CEP has been used clinically in Japan for more than 70 years (1–60 mg/day), and is generally recognized as having a relatively wide safety margin. Nevertheless, *in silico* toxicity predictions indicate several safety liabilities that warrant attention, particularly hERG blockade and phospholipidosis.

***Table 7.1** · Predicted Toxicity Endpoints*

Toxicity Endpoint	Prediction	Risk Level	Comments
hERG Blockade	Likely · pIC50 ≈ 5.8	Moderate–High	Basic nitrogen + two aromatic rings + high LogP, a typical hERG pharmacophore
Ames Mutagenicity	Negative	Low	No typical mutagenic structural alerts
In Vitro Micronucleus Test	Negative	Low	—
Hepatotoxicity (DILI)	Moderate	Moderate	Catechol-type metabolites may form reactive intermediates
Skin Sensitization	Low	Low	—
Acute Oral LD50 in Rats	~1000–1500 mg/kg	Low (GHS Category 5)	Historical data: actual safety margin is relatively wide
Drug-Induced Phospholipidosis (DIPL)	Probable	Moderate	Typical liability of CAD compounds

Toxicity Endpoint	Prediction	Risk Level	Comments
Reproductive Toxicity / Teratogenicity	Limited data	To be determined	BBB penetration suggests caution during pregnancy
Immunosuppression-Related Risk	Potential	Moderate	Known immunomodulatory activity; monitoring is required during long-term high-dose administration

> **▲ *hERG Blockade Warning***
>
> CEP contains two protonatable tertiary amines with an appropriate geometric distribution relative to distal aromatic rings—this is a typical pharmacophore of hERG channel blockers (a basic center + hydrophobic aromatic surface separated by 6–10 Å). In clinical use, particularly when co-administered with other QT-prolonging drugs (such as certain macrolides, fluoroquinolones, antipsychotics, and 5-HT3 inhibitors), electrocardiographic monitoring is recommended. However, it should be noted that no significant QT prolongation has been reported during previous clinical use in Japan, possibly because, at conventional doses (1–60 mg/day), the unbound plasma concentration remains substantially below the hERG IC50.

VIII. *Drug-likeness Rules*

Across multiple classical drug-likeness rules, CEP is generally classified as a "non-drug-like oral compound." However, it should be noted that bisbenzylisoquinoline natural products inherently lie outside the classical drug-like chemical space, as is also observed with other macrocyclic natural products such as rapamycin and paclitaxel. The successful development of such compounds into marketed drugs depends more heavily on formulation engineering than on the molecular structure itself.

***Table 8.1** · Drug-Likeness Rule Screening*

Rule	Criteria	CEP Assessment
Lipinski's Rule of Five	MW ≤ 500 · LogP ≤ 5 · HBD ≤ 5 · HBA ≤ 10	2 violations — MW = 606, cLogP = 6.42
Veber's Rule	RotB ≤ 10 · TPSA ≤ 140 Å²	Pass — RotB = 4; TPSA = 61.86

Rule	Criteria	CEP Assessment
Ghose Filter	160 ≤ MW ≤ 480 · −0.4 ≤ LogP ≤ 5.6 · 40 ≤ MR ≤ 130	Fail — MW/LogP/MR all exceed the limits
Egan's Rule	WLogP ≤ 5.88 · TPSA ≤ 131.6 Å²	Borderline — TPSA passes; LogP is borderline-violating
Muegge Filter	200 ≤ MW ≤ 600 · −2 ≤ XLogP ≤ 5 · and other criteria	Fail — LogP exceeds the limit
PAINS / Brenk Alerts	Broad-spectrum interference and toxic/active structural fragments	No alerts — structurally clean

***Table 8.2** · Overall Drugability Scores*

Score	Value	Interpretation
SwissADME Bioavailability Score	0.17	Low (<0.55 indicates poor oral absorption)
Synthetic Accessibility (SA) Score	6.4 / 10	Relatively difficult to synthesize (challenging total synthesis of the natural product)
QED Drug-Likeness Index	~0.28	Low (<0.5 indicates deviation from drug-like chemical space)

IX. *Integrated Assessment & Development Strategy*

9.1 SWOT *· SWOT Summary · Profile Summary*

Dimension	Key Findings
Strengths	① Multitarget pharmacological activity (antiviral, anti-inflammatory, antitumor, and immunomodulatory); ② Good long-term human safety record; ③ TPSA, HBD, HBA, and RotB are all within reasonable ranges; ④ No PAINS/Brenk alerts; ⑤ BBB penetration provides potential for CNS applications.

Dimension	Key Findings
Weaknesses	① Both MW and LogP exceed the recommended limits, resulting in two violations of Lipinski's rule; ② Extremely poor aqueous solubility, with oral F <6%; ③ Time-dependent CYP3A4 inhibitor—significant clinical DDI risk; ④ Potential hERG blockade and cardiotoxicity; ⑤ CAD structure → phospholipidosis risk.
Opportunities	① Nanocrystals/SEDDS/liposomes and other formulations may substantially improve bioavailability; ② Injectable formulations can bypass the oral absorption bottleneck; ③ Appropriate co-administration with CYP3A4 substrates may enable "repurposing" as a bioavailability-enhancing agent; ④ Expansion into new indications such as COVID-19.
Threats	① Interactions with narrow-therapeutic-index CYP3A4 substrates should be carefully considered in clinical use; ② ECG monitoring is required when co-administered with QT-prolonging drugs; ③ Long-term high-dose administration requires evaluation of phospholipidosis and immunosuppression risks.

9.2 · *Recommendations*

◇ *Route of Administration and Formulation Strategy*

1. Prioritize the development of intravenous/intramuscular or nanocrystal suspension formulations to bypass the oral absorption bottleneck;

2. Oral formulations should employ SEDDS, SMEDDS, solid dispersions, phospholipid complexes, or PLGA nanoparticles;

3. Inhaled administration for pulmonary antiviral applications warrants exploration (COVID-19 and ARDS indications).

◆ *Clinical Medication Warnings*

Monitoring required： Plasma drug concentrations when co-administered with CYP3A4 substrates; electrocardiography when co-administered with QT-prolonging drugs; liver function and phospholipidosis markers during long-term use.

Avoid concomitant use： Tacrolimus, cyclosporine, quinidine, terfenadine, itraconazole, and other sensitive CYP3A4 substrates or potent hERG blockers.

Dose adjustment： Dose reduction is required in patients with hepatic impairment; conservative starting doses are recommended for elderly patients and those receiving multiple concomitant medications.

▲ *Research Gaps*

① Systematic human PK/PD data remain relatively limited, with most evidence derived from rat or mouse models; ② The activity and toxicity profiles of the major metabolites of CEP have not yet been adequately characterized; ③ Further *in vivo* evidence is required to evaluate the effects of long-term administration on lysosomal function; ④ Potential synergistic or antagonistic effects in combination with emerging modalities such as PROTACs and molecular glues have not been investigated.

Data Sources & References

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Disclaimer

This report integrates experimental data from publicly available literature with prediction results from mainstream computational platforms. All “predicted values” are subject to methodological uncertainty and cannot replace rigorous in vivo or clinical studies. The contents of this report are intended solely for scientific discussion and educational purposes and do not constitute any clinical medication recommendations.