

Discovering a Green Pesticide Candidate for Controlling Bacterial Plant Disease: 1,2,3,4-Tetrahydro- β -carboline as a Potential Biofilm Inhibitor

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Table S1. ADMETlab assessment.

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	174.12	Contain hydrogen atoms. Optimal:100~600
Volume	187.227	Van der Waals volume
Density	0.93	Density = MW / Volume
nHA	2	Number of hydrogen bond acceptors. Optimal:0~12
nHD	2	Number of hydrogen bond donors. Optimal:0~7
nRot	0	Number of rotatable bonds. Optimal:0~11

nRing	3	Number of rings. Optimal:0~6
MaxRing	13	Number of atoms in the biggest ring. Optimal:0~18
nHet	2	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	15	Number of rigid bonds. Optimal:0~30
Flexibility	0.0	Flexibility = nRot /nRig
Stereo Centers	2	Optimal: \square 2
TPSA	24.06	Topological Polar Surface Area. Optimal:0~140
logS	-1.673	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	1.226	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	1.414	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.623	●	<p>■ A measure of drug-likeness based on the concept of desirability;</p> <p>■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34</p>
SAscore	3.196	●	<p>■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules.</p> <p>■ SAscore \square 6, difficult to synthesize; SAscore <6, easy to synthesize</p>
Fsp3	0.455	●	<p>■ The number of sp³ hybridized carbons / total carbon count, correlating with melting point and solubility.</p> <p>■ Fsp³ \square 0.42 is considered a suitable value.</p>
MCE-18	47.125	●	<p>■ MCE-18 stands for medicinal chemistry evolution.</p> <p>■ MCE-18 \square 45 is considered a suitable value.</p>
NPscore	0.653	-	<p>■ Natural product-likeness score.</p> <p>■ This score is typically in the range from \square 5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.</p>
Lipinski Rule	Accepted	●	<p>■ MW \square 500; logP \square 5; Hacc \square 10; Hdon \square 5</p> <p>■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.</p>
Pfizer Rule	Accepted	●	<p>logP > 3; TPSA < 75</p> <p>Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.</p>
GSK Rule	Accepted	●	<p>■ MW \square 400; logP \square 4</p> <p>■ Compounds satisfying the GSK rule may have a more favorable ADMET profile</p>
Golden Triangle	Rejected	●	<p>■ 200 \square MW \square 50; -2 \square logD \square 5</p> <p>■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.</p>

PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALAR M NMR	0 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.987	●	Optimal: higher than -5.15 Log unit
MDCK Permeability	6e-06	●	■ low permeability: $< 2 \times 10^{-6}$ cm/s ■ medium permeability: $2-20 \times 10^{-6}$ cm/s ■ high passive permeability: $> 20 \times 10^{-6}$ cm/s
Pgp-inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.293	●	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.012	●	■ Human Intestinal Absorption ■ Category 1: HIA+ (HIA $< 30\%$); Category 0: HIA- (HIA $< 30\%$); The output value is the probability of being HIA+
F _{20%}	0.027	●	■ 20% Bioavailability ■ Category 1: F _{20%} ⁺ (bioavailability $< 20\%$); Category 0: F _{20%} ⁻ (bioavailability $\square 20\%$); The output value is the probability of being F _{20%} ⁺
F _{30%}	0.024	●	■ 30% Bioavailability ■ Category 1: F _{30%} ⁺ (bioavailability $< 30\%$); Category 0: F _{30%} ⁻ (bioavailability $\square 30\%$); The output value is the probability of being F _{30%} ⁺

4. Distribution

Property	Value	Decision	Comment
PPB	21.79%	●	■ Plasma Protein Binding ■ Optimal: $< 90\%$. Drugs with high protein-bound may have a low therapeutic index.
VD	3.381	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.868	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	66.67%	●	■ The fraction unbound in plasms ■ Low: $< 5\%$; Middle: 5~20%; High: $> 20\%$

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.103	<p>■ Category 1: Inhibitor; Category 0: Non-inhibitor;</p> <p>■ The output value is the probability of being inhibitor.</p>
CYP1A2 substrate	0.219	<p>■ Category 1: Substrate; Category 0: Non-substrate;</p> <p>■ The output value is the probability of being substrate.</p>
CYP2C19 inhibitor	0.065	<p>■ Category 1: Inhibitor; Category 0: Non-inhibitor;</p> <p>■ The output value is the probability of being inhibitor.</p>
CYP2C19 substrate	0.884	<p>■ Category 1: Substrate; Category 0: Non-substrate;</p> <p>■ The output value is the probability of being substrate.</p>
CYP2C9 inhibitor	0.011	<p>■ Category 1: Inhibitor; Category 0: Non-inhibitor;</p> <p>■ The output value is the probability of being inhibitor.</p>
CYP2C9 substrate	0.192	<p>■ Category 1: Substrate; Category 0: Non-substrate;</p> <p>■ The output value is the probability of being substrate.</p>
CYP2D6 inhibitor	0.422	<p>■ Category 1: Inhibitor; Category 0: Non-inhibitor;</p> <p>■ The output value is the probability of being inhibitor.</p>
CYP2D6 substrate	0.871	<p>■ Category 1: Substrate; Category 0: Non-substrate;</p> <p>■ The output value is the probability of being substrate.</p>
CYP3A4 inhibitor	0.068	<p>■ Category 1: Inhibitor; Category 0: Non-inhibitor;</p> <p>■ The output value is the probability of being inhibitor.</p>
CYP3A4 substrate	0.367	<p>■ Category 1: Substrate; Category 0: Non-substrate;</p> <p>■ The output value is the probability of being substrate.</p>

6. Excretion

Property	Value	Decision	Comment
CL	9.98	●	<ul style="list-style-type: none"> ■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
T _{1/2}	0.386	-	<ul style="list-style-type: none"> ■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.177	●	<ul style="list-style-type: none"> ■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.652	●	<ul style="list-style-type: none"> ■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.044	●	<ul style="list-style-type: none"> ■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.918	●	<ul style="list-style-type: none"> ■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.825	●	<ul style="list-style-type: none"> ■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FEAMDD	0.654	●	<ul style="list-style-type: none"> ■ Maximum Recommended Daily Dose ■ Category 1: FEAMDD (+); Category 0: FEAMDD (-) ■ The output value is the probability of being positive.
Skin Sensitization	0.618	●	<ul style="list-style-type: none"> ■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogenicity	0.09	●	<ul style="list-style-type: none"> ■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.005	●	<ul style="list-style-type: none"> ■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.
Eye Irritation	0.037	●	<ul style="list-style-type: none"> ■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.
Respiratory Toxicity	0.975	●	<ul style="list-style-type: none"> ■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	0.511	<p>■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain.</p> <p>■ The unit is $\square \log_{10}[(\text{mg/L})/(1000 \cdot \text{MW})]$</p>
IGC ₅₀	2.987	<p>■ Tetrahymena pyriformis 50 percent growth inhibition concentration</p> <p>■ The unit is $\square \log_{10}[(\text{mg/L})/(1000 \cdot \text{MW})]$</p>
LC ₅₀ ^{FM}	3.056	<p>■ 96-hour fathead minnow 50 percent lethal concentration</p> <p>■ The unit is $\square \log_{10}[(\text{mg/L})/(1000 \cdot \text{MW})]$</p>
LC ₅₀ ^{DM}	4.875	<p>■ 48-hour daphnia magna 50 percent lethal concentration</p> <p>■ The unit is $\square \log_{10}[(\text{mg/L})/(1000 \cdot \text{MW})]$</p>

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.004	●	<p>■ Androgen receptor</p> <p>■ Category 1: actives ; Category 0: inactives;</p> <p>■ The output value is the probability of being active.</p>
NR-AR-LBD	0.002	●	<p>■ Androgen receptor ligand-binding domain</p> <p>■ Category 1: actives ; Category 0: inactives;</p> <p>■ The output value is the probability of being active.</p>
NR-AhR	0.224	●	<p>■ Aryl hydrocarbon receptor</p> <p>■ Category 1: actives ; Category 0: inactives;</p> <p>■ The output value is the probability of being active.</p>
NR-Aromatase	0.004	●	<p>■ Category 1: actives ; Category 0: inactives;</p> <p>■ The output value is the probability of being active.</p>
NR-ER	0.081	●	<p>■ Estrogen receptor</p> <p>■ Category 1: actives ; Category 0: inactives;</p> <p>■ The output value is the probability of being active.</p>
NR-ER-LBD	0.007	●	<p>■ Estrogen receptor ligand-binding domain</p> <p>■ Category 1: actives ; Category 0: inactives;</p> <p>■ The output value is the probability of being active.</p>
NR-PPAR-gamma	0.002	●	<p>■ Peroxisome proliferator-activated receptor gamma</p> <p>■ Category 1: actives ; Category 0: inactives;</p> <p>■ The output value is the probability of being active.</p>
SR-ARE	0.067	●	<p>■ Antioxidant response element</p> <p>■ Category 1: actives ; Category 0: inactives;</p> <p>■ The output value is the probability of being active.</p>
SR-ATAD5	0.017	●	<p>■ ATPase family AAA domain-containing protein 5</p> <p>■ Category 1: actives ; Category 0: inactives;</p> <p>■ The output value is the probability of being active.</p>
SR-HSE	0.241	●	<p>■ Heat shock factor response element</p> <p>■ Category 1: actives ; Category 0: inactives;</p> <p>■ The output value is the probability of being active.</p>
SR-MMP	0.02	●	<p>■ Mitochondrial membrane potential</p> <p>■ Category 1: actives ; Category 0: inactives;</p> <p>■ The output value is the probability of being active.</p>

SR-p53	0.012	●	<ul style="list-style-type: none"> ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
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10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	<ul style="list-style-type: none"> ■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	1 alerts	<ul style="list-style-type: none"> ■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	<ul style="list-style-type: none"> ■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	3 alerts	<ul style="list-style-type: none"> ■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	1 alerts	<ul style="list-style-type: none"> ■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	<ul style="list-style-type: none"> ■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	<ul style="list-style-type: none"> ■ 164 substructures ■ MedChem unfriendly status

Figure S1. The antibacterial activity of four THC analogues and thiodiazole-copper against Xoo.

