

Discovering a Green Pesticide Candidate for Controlling Bac-terial Plant Disease: 1,2,3,4-Tetrahydro- β -carboline as a Poten-tial 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 |

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|----------------|--------|--|
| 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 | ● | <ul style="list-style-type: none"> ■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34 |
| SAscore | 3.196 | ● | <ul style="list-style-type: none"> ■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore \square 6, difficult to synthesize; SAscore <6, easy to synthesize |
| Fsp3 | 0.455 | ● | <ul style="list-style-type: none"> ■ The number of sp³ hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp³ \square 0.42 is considered a suitable value. |
| MCE-18 | 47.125 | ● | <ul style="list-style-type: none"> ■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18 \square 45 is considered a suitable value. |
| NPscore | 0.653 | - | <ul style="list-style-type: none"> ■ Natural product-likeness score. ■ 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. |
| Lipinski Rule | Accepted | ● | <ul style="list-style-type: none"> ■ MW \square 500; logP \square 5; Hacc \square 10; Hdon \square 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable. |
| Pfizer Rule | Accepted | ● | <ul style="list-style-type: none"> logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic. |
| GSK Rule | Accepted | ● | <ul style="list-style-type: none"> ■ MW \square 400; logP \square 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile |
| Golden Triangle | Rejected | ● | <ul style="list-style-type: none"> ■ 200 \square MW \square 50; -2 \square logD \square 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile. |

| | | | |
|---------------|----------|---|---|
| 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 \geq 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 \geq 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 plasmas ■ Low: <5%; Middle: 5-20%; High: > 20% |

5. Metabolism

| Property | Value | Comment |
|-------------------|-------|--|
| CYP1A2 inhibitor | 0.103 | <ul style="list-style-type: none"> ■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor. |
| CYP1A2 substrate | 0.219 | <ul style="list-style-type: none"> ■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate. |
| CYP2C19 inhibitor | 0.065 | <ul style="list-style-type: none"> ■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor. |
| CYP2C19 substrate | 0.884 | <ul style="list-style-type: none"> ■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate. |
| CYP2C9 inhibitor | 0.011 | <ul style="list-style-type: none"> ■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor. |
| CYP2C9 substrate | 0.192 | <ul style="list-style-type: none"> ■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate. |
| CYP2D6 inhibitor | 0.422 | <ul style="list-style-type: none"> ■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor. |
| CYP2D6 substrate | 0.871 | <ul style="list-style-type: none"> ■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate. |
| CYP3A4 inhibitor | 0.068 | <ul style="list-style-type: none"> ■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor. |
| CYP3A4 substrate | 0.367 | <ul style="list-style-type: none"> ■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate. |

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. |
| FDAMDD | 0.854 | ● | <ul style="list-style-type: none"> ■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ 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. |

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8. Environmental toxicity

| Property | Value | Comment |
|--------------------------|-------|---|
| Bioconcentration Factors | 0.511 | <ul style="list-style-type: none"> ■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is $\log_{10}[(\text{mg/L})/(1000*\text{MW})]$ |
| IGC ₅₀ | 2.987 | <ul style="list-style-type: none"> ■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is $\log_{10}[(\text{mg/L})/(1000*\text{MW})]$ |
| LC ₅₀ FM | 3.056 | <ul style="list-style-type: none"> ■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is $\log_{10}[(\text{mg/L})/(1000*\text{MW})]$ |
| LC ₅₀ DM | 4.875 | <ul style="list-style-type: none"> ■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is $\log_{10}[(\text{mg/L})/(1000*\text{MW})]$ |

9. Tox21 pathway

| Property | Value | Decision | Comment |
|---------------|-------|----------|--|
| NR-AR | 0.004 | • | <ul style="list-style-type: none"> ■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active. |
| NR-AR-LBD | 0.002 | • | <ul style="list-style-type: none"> ■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active. |
| NR-AhR | 0.224 | • | <ul style="list-style-type: none"> ■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active. |
| NR-Aromatase | 0.004 | • | <ul style="list-style-type: none"> ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active. |
| NR-ER | 0.081 | • | <ul style="list-style-type: none"> ■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active. |
| NR-ER-LBD | 0.007 | • | <ul style="list-style-type: none"> ■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active. |
| NR-PPAR-gamma | 0.002 | • | <ul style="list-style-type: none"> ■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active. |
| SR-ARE | 0.067 | • | <ul style="list-style-type: none"> ■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active. |
| SR-ATAD5 | 0.017 | • | <ul style="list-style-type: none"> ■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active. |
| SR-HSE | 0.241 | • | <ul style="list-style-type: none"> ■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active. |
| SR-MMP | 0.02 | • | <ul style="list-style-type: none"> ■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active. |

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| SR-p53 | 0.012 | ● | ■ 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 | ■ 20 substructures ■ acute toxicity during oral administration |
| Genotoxic Carcinogenicity Rule | 1 alerts | ■ 117 substructures ■ carcinogenicity or mutagenicity |
| NonGenotoxic Carcinogenicity Rule | 0 alerts | ■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms |
| Skin Sensitization Rule | 3 alerts | ■ 155 substructures ■ skin irritation |
| Aquatic Toxicity Rule | 1 alerts | ■ 99 substructures ■ toxicity to liquid(water) |
| NonBiodegradable Rule | 0 alerts | ■ 19 substructures ■ non-biodegradable |
| SureChEMBL Rule | 0 alerts | ■ 164 substructures ■ MedChem unfriendly status |

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

