**Supplementary Table 1:** Medicinal chemistry properties for the most active compounds.

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| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Compounds** | | | | **Comment** |
| **6** | **7** | **15** | **16** |
| QED | 0.133 | 0.123 | 0.438\* | 0.618 | A measure of drug-likeness based on the concept of desirability; Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34 |
| Synth | 3.164 | 3.24 | 3.755 | 3.647 | Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. SAscore > 6, difficult to synthesize; SAscore <6, easy to synthesize |
| Fsp3 | 0.133 | 0.133 | 0.217 | 0.217 | The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. Fsp3 ≥0.42 is considered a suitable value. |
| MCE-18 | 33 | 34 | 78.571 | 75.429 | MCE-18 stands for medicinal chemistry evolution. MCE-18≥45 is considered a suitable value. |
| Natural Product-likeness | -0.835 | -0.896 | -1.366 | -1.177 | Natural product-likeness score.  This score is typically in the range from -5 to 5. The higher the score is, the higher the probability is that the molecule is a NP. |
| Lipinski | Rejected | Rejected | Accepted | Accepted | MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5. If two properties are out of range, a poor absorption or permeability is possible, one is acceptable. |
| Pfizer | Accepted | Accepted | Accepted | Accepted | logP > 3; TPSA < 75, Compounds with a high log P (>3) and low TPSA  (<75) are likely to be toxic. |
| Golden Triangle | Rejected | Rejected | Accepted | Accepted | 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5  Compounds satisfying the Golden Triangle rule may have a more favourable ADMET profile. |

**\***: underline value indicates good property.

**Supplementary Table 2**: Absorption profile for the most active compounds.

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| **Parameter** | **Compounds** | | | | **Comment** |
| **6** | **7** | **15** | **16** |
| HIA | 0.92 | 0.961 | 0.004 | 0.003 | Human Intestinal Absorption. Category 1: HIA+( HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+ |
| F(20%) | 0.007 | 0.002 | 0.005 | 0.003 | 20% Bioavailability.  Category 1: F20%+ (bioavailability < 20%); Category 0: F20%- (bioavailability ³20%); The output value is the probability of being F20%+ |
| F(30%) | 0.004 | 0.002 | 0.001 | 0.001 | 30% Bioavailability  Category 1: F30%+ (bioavailability < 30%); Category 0: F30%- (bioavailability ³30%); The output value is the probability of being F30%+ |
| Caco-2 permeability | -5.567 | -5.544 | -4.882 | 4.833 | Optimal: higher than -5.15 Log unit |
| MDCK permeability | 6.84-5 | 4.78-5 | 0.000252 | 4.69-5 | low permeability: < 2 × 106 cm/s  medium permeability: 2–20× 106 cm/s  high passive permeability: > 20 ×106 cm/s |

**\***: underline value indicates good property.

**Supplementary Table 3:** Distribution property for the most active compounds.

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| **Parameter** | **Compounds** | | | | **Comment** |
| **6** | **7** | **15** | **16** |
| BBB | 0.015 | 0.018 | 0.488 | 0.22 | Blood-Brain Barrier Penetration  Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+. |
| PPB | 99.88% | 100.21% | 83.87% | 86.99% | Plasma Protein Binding  Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index. |
| VDss | 0.298 | 0.271 | 0.562 | 0.701 | Volume Distribution  Optimal: 0.04-20L/kg |
| Fu | 0.90% | 0.85% | 6.07% | 3.48% | The fraction unbound in plasma  Low: <5%; Middle: 5~20%; High: > 20% |

**\***: underline value indicates good property.

**Supplementary Table 4**: Metabolism profile for the most active compounds.

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| **Parameter** | **Compounds** | | | | **Comment** |
| **6** | **7** | **15** | **16** |
| CYP1A2-inh | 0.211 | 0.331 | 0.142 | 0.198 | Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor. |
| CYP1A2-sub | 0.141 | 0.362 | 0.111 | 0.315 | Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate. |
| CYP2C19-inh | 0.83 | 0.88 | 0.787 | 0.841 | Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor. |
| CYP2C19-sub | 0.041 | 0.044 | 0.063 | 0.07 | Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate. |
| CYP2C9-inh | 0.948 | 0.95 | 0.924 | 0.935 | Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor. |
| CYP2C9-sub | 0.044 | 0.052 | 0.746 | 0.853 | Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate. |
| CYP2D6-inh | 0.699 | 0.841 | 0.058 | 0.077 | Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor. |
| CYP2D6-sub | 0.1 | 0.107 | 0.076 | 0.05 | Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate. |
| CYP3A4-inh | 0.962 | 0.966 | 0.919 | 0.862 | Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being inhibitor. |
| CYP3A4-sub | 0.108 | 0.111 | 0.757 | 0.865 | Category 1: Substrate; Category 0: Non-substrate; The output value is the probability of being substrate. |

**Supplementary Table 5**: Excretion for the most active compounds.

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| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Compounds** | | | | **Comment** |
| **6** | **7** | **15** | **16** |
| CL | 6.014 | 5.125 | 5.092 | 4.499 | Clearance, High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 L/min/kg |
| T12 | 0.141 | 0.063 | 0.138 | 0.073 | 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. |

**Supplementary Table 6**: Toxicity for the most active compounds.

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| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Compounds** | | | | **Comment** |
| **6** | **7** | **15** | **16** |
| H-HT | 0.687 | 0.579 | 0.66 | 0.556 | Human Hepatotoxicity.  Category 1: H-HT positive (+); Category 0: H-HT negative (-); The output value is the probability of being toxic. |
| Ames | 0.043 | 0.026 | 0.966 | 0.87 | Category 1: Ames positive (+); Category 0: Ames negative(-);  The output value is the probability of being toxic. |
| ROA | 0.005 | 0.01 | 0.139 | 0.164 | Rat Oral Acute Toxicity  Category 0: low-toxicity; Category 1: high-toxicity; The output value is the probability of being highly toxic. |
| FDAMDD | 0.024 | 0.039 | 0.883 | 0.878 | Maximum Recommended Daily Dose. Category 1: FDAMDD (+); Category 0: FDAMDD (-). The output value is the probability of being positive |
| SkinSen | 0.08 | 0.048 | 0.504 | 0.121 | Category 1: Sensitizer; Category 0: Non-sensitizer; The output value is the probability of being sensitizer. |
| Carcinogenicity | 0.113 | 0.237 | 0.524 | 0.337 | Category 1: carcinogens; Category 0: non-carcinogens; |
| EC | 0.003 | 0.003 | 0.003 | 0.003 | Eye corrosion  Category 1: corrosives; Category 0: noncorrosives. The output value is the probability of being corrosives |
| EI | 0.011 | 0.011 | 0.018 | 0.014 | Eye irritation  Category 1: irritants; Category 0: nonirritants. The output value is the probability of being irritants |