RTI Treatment Of Pandemic Diseases: Admetlab 2.0 StudyReport On 5- Substituted Norfloxacin Derivatives

Seema Garg[1] & Vandana Sharma[2]

Associate Professor in Chemistry, SPC Government College, Ajmer[1]

Research scholar, Jodhpur[2]

ABSTRACT

Fluoroquinolones are among the pharmacological agents being investigated for potentialanti-SARS-COV-2 activities. The antibiotics are used either to resolve bacterial infections co-existing with COVID-19 infections or exploitation of their potential antiviral activities. The heavy use of antibiotics during the COVID-19 pandemic would likely worsen antibiotic resistance crisis. So, the present research is focused on the modification of existing norfloxacin at its C-5 position for increasing its antibacterial pharmacokinetic properties and biological activity and for this a detailed in study is reported using ADMET lab 2.0 ADMET lab 2.0 is used for the designing, systematical evaluation of ADMET properties and physicochemical properties of the modified drug. The norfloxacin derivative is showing lesser respiratory toxicity value and increased potency as compared to the existing drug norfloxacin.

INTRODUCTION

The heavy use of antibiotics during the COVID-19 pandemic would likely worsen antibiotic resistance crisis. Hence, antibiotic stewardship should be strengthened in order to prevent the impacts of COVID-19 on the antibiotic resistance crisis (Yacouba A et al.,2021). Norfloxacinis chosen as the model drug for a common empirical treatment of pneumonia caused by Gram-negative bacteria such as *H. influenza* as well as Gram-positive bacteria such as *S. pneumoniae* (Kays et al.,2012)

Respiratory fluoroquinolones are characterized by advantageous pharmacokinetic properties; higher concentrations in the lungs; and an excellent safety profile comparable to otherantibiotics used to treat respiratory infections, such as macrolides and b-lactams. Based on their potential antiviral activity and immunomodulatory properties, the favorable pharmacokinetics and safety profile, we propose the use of respiratory fluoroquinolones as adjuncts in the treatment of SARS-CoV-2 associated pneumonia (Irene K et al.,2020). It is evident that norfloxacin resistance is one of the main reasons behind treatment failure of pneumonia (Endimiani et al., 2005)Therefore, public awareness about low quality medicine can be created through the reported resistant susceptibility and quality of levofloxacin (Talan et al., 2016). The poor quality of norfloxacin tablets could be an important factor causing resistance of norfloxacin. Clinical efficacy of this broad spectrum antibiotic relies on the quality of the levofloxacin tablet in terms of in vivo release and dissolution inside thegastrointestinal tract. As poor performances of quality control tests of norfloxacin tabletshave been reported in developing countries, more PMS to ensure quality of levofloxacin tablets are required to prevent therapy failure and antibiotic resistance (Ensieh Izadi etal.,2019). SAR and QSAR studies of fluoroquinolone drugs revealed that C-5 has hydrogen atoms which could be replaced by amine moiety. Some types of bulky (5- or 6- membered rings) nitrogen heterocycle e.g. morpholine offers the best enhancement of activity. Literaturereveals that morpholine relieves pain and produces euphorbia. There are receptors to which morpholine binds in the brain, spinal cord and gastrointestinal tract (Vandana et al.,2012).

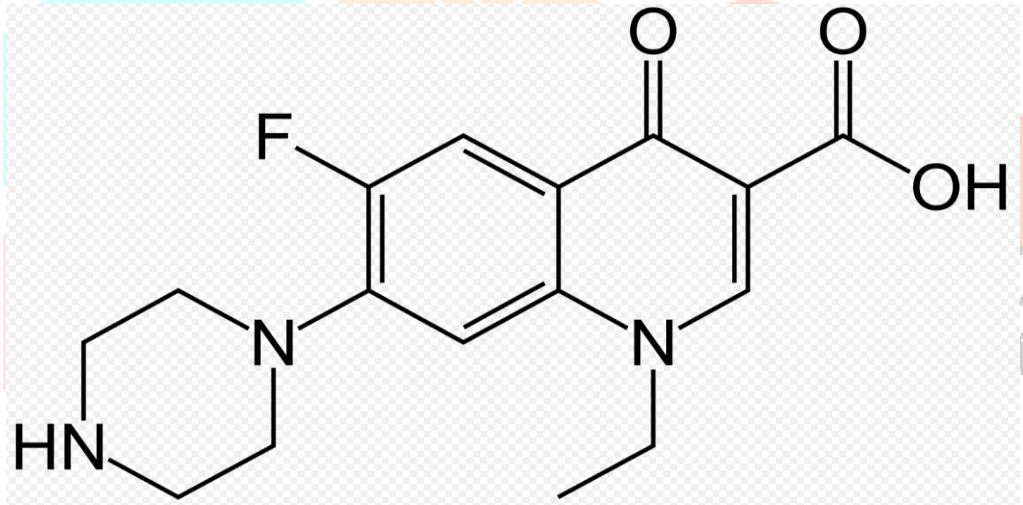
ADMETlab 2.0 is an integrated online platform for accurate and comprehensive predictions of ADMET properties (Guoli Xiong et al.,2021)

Methodology

Undesirable pharmacokinetics and toxicity of candidate compounds are the main reasons for the failure of drug development, and it has been widely recognized that absorption, distribution, metabolism, excretion and toxicity (ADMET) of chemicals should be evaluated as early as possible. ADMETlab 2.0 is an enhanced version of the widely used ADMETlabfor systematic evaluation of ADMET properties, as well as some physicochemical properties and medicinal chemistry friendliness. With significant updates to functional modules, predictive models, explanations, and the user interface, ADMETlab 2.0 has greater capacity to assist medicinal chemists in accelerating the drug research and development process.

Norfloxacin

Formula- $C_{16}H_{18}FN_3O_3$



Norfloxacin has oxo group at C-4 position, it is essential for antibacterial activity, C-5position has a hydrogen atom which could be replaced by amine moiety for increasing the antibacterial activity as well as solubility. So, a 5-substituted morpholine derivative of norfloxacin can be formed via chlorination of norfloxacin.

Pharmacokinetics and Toxicity

Drug-likeness is a prediction that determines whether a particular pharmacological agent has properties consistent with being an orally active drug. The chemical structure of the compounds was converted to their canonical simplified molecular input line entry (SMILE) system and submitted to ADMET lab 2.0 tool to estimate *in vivo* pharmacokinetic parameters. ADMET lab 2.0 predictor provides information on the numbers of hydrogen donors, hydrogen acceptors, rotatable bonds and total polar surface area of a compound. The compounds were also subjected to Lipinski et al., screened using physicochemical property and medicinal chemistry predictors.

RESULTS & DISCUSSION

Comparative studies on the properties of Norfloxacin (A) and Norfloxacin Derivative (B):

1. Physicochemical Properties:

a) The molecular weight of compound A is $319.336\ g{\cdot}mol^{-1}$ while the molecular weight ofcompound B is increased to 404.35 after the addition of morpholine at C-5 position. Hence both the compounds are showing optimal molecular weight value i.e 100~600. The properties like volume, density, nHA, nHD, nRot, MaxRing are showing optimal values for compound A and B.

b) The number of heteroatoms (nHet) is 8 for A while 10 for B. Similarly, the number ofrigid bonds is 23 for A while it is 29 for B, both are within optimal range i.e 0~30.The flexibility, stereo centers, topological polar surface area (TPSA), logS, logP, and log D are optimal for both the compounds.

2. Medicinal Chemistry:

a) The results showing QED (drug likeness), SA score (Synthetic Accessibility score) and MCE-18 (Medicinal chemistry evolution) are the same for both the compounds Aand B.

b) NPscore, Lipinski Rule, Pfizer Rule are showing acceptability of both the drugs A and B. GSK Rule is showing rejection to both the compounds. Golden Triangle rule is accepting both the compounds A and B which means original drug as well as its derivative compound have a more favourable ADMET profile.

3. Absorption:

The properties e.g. CaCO-2 permeability, Human Intestinal Absorption, Bioavailability etc. are showing similar values for both A and B which is indicating good absorption of these drugs.

4. Distribution: The properties responsible for the distribution of drugs e.g. Plasma Protein Binding (PPB), Volume Distribution (VD), Blood-Brain Barrier Penetration and the fraction unbound in plasma are also showing very optimal values for compound A and B.

5. Metabolism:

The output values for CYPIA2 inhibitor, CYP1A2 substrate, CYP2C19 inhibitor, CYP2C19 substrate etc. are showing optimal values for the probability of beinginhibitor or substrate for A and B both.

6. Excretion:

The excretion of a drug compound is shown by its Clearance (CL) and its half-life ($T_{1/2}$). The output CL values are showing low clearance for A and B. The $T_{1/2}$ value for compound A and its derivative B are almost the same and indicate the probability of having long half-life.

7. Toxicity:

a) According to property named hERG Blockers the output values are indicating the probability of being active for A as well as B. The Human Hepatotoxicity (H-HT) values for compound A and B are indicating the probability of being toxic.

b) Drug Induced Liver Injury (DILI) value for A is 0.972 while for B is 0.987. So, both the compounds are showing probability of being toxic. The output values obtained from AMES toxicity test and Rat Oral Acute Toxicity test are showing the probability of being toxic for both A and B.

c) The FDA MDD (Maximum Recommended Daily Dose) test and Carcinogenicity test are also showing the probability of being toxic for both A and B. The output value of Skin Sensitization test is showing the probability of being sensitizer for both A and B.

d) The Eye Corrosion test is showing the probability of being corrosive for A and B. The Eye Irritation test has shown the probability of being irritants for both the compounds.

e) The **Respiratory toxicity** value for compound A is 0.713 which indicates the probability of being toxic. While compound B is showing comparatively lesser output value i.e 0.33 and hence is less toxic than compound A. So the levofloxacinderivative is more effective over the parent norfloxacin drug for the treatment of Respiratory Tract Infection (RTI).

8. Environmental toxicity:

The properties like Bioconcentration Factors, IGC_{50}, $LC_{50}FM$ and $LC_{50}DM$ are showing acceptable output values for both the compounds.

9. Tox21 pathway:
   The properties named NR-AR (Androgen receptor), NR-AR-LBD (Androgen receptor ligand-binding domain), NR-AhR (Aryl hydrocarbon receptor) etc. are showing acceptable output values and the results for both the compounds are indicating the probability of being active.
10. Toxicophore Rules:
    The Acute Toxicity Rule, Genotoxic Carcinogenicity Rule etc. are showing few alerts for both A and B.

CONCLUSION

Since the beginning of the COVID-19 pandemic, researchers have focused on repurposing existing antibiotics, antivirals and anti-inflammatory drugs to find an effective therapy. Norfloxacin is a respiratory fluoroquinolone as it constitutes the first line therapeutic agentfor the management of severe community-acquired pneumonia and is used for the treatment of respiratory tract infection (RTI). So, to increase the potency of the parent norfloxacin drugwe have modified it by adding morpholine at its C-5 position. ADMET lab 2.0 tool had been used for estimating *in vivo* pharmacokinetic parameters of norfloxacin (Compound A) and norfloxacin derivative (Compound B). The compounds were also subjected to Lipinski et al., screened using physicochemical property and medicinal chemistry predictors.

A comparative study report indicates that the modification of norfloxacin at its C-5 position by morpholine has increased its potency and decreased its respiratory toxicity value. **Respiratory toxicity** test is a very important test as the drug levofloxacin is a very widely used drug against respiratory tract infection (**RTI**) in COVID-19.

So, based on the favourable pharmacokinetics and safety profile we propose the use oflevofloxacin derivative as adjunct in the treatment of SARS-CoV-2 associated pneumonia.

Tables

ADMETlab 2.0

CC1COc2c(N3CCN(C)CC3)c(F)cc3c(=O)c(C(=O)O)cn1c23

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	361.14	Contain hydrogen atoms. Optimal:100~600
Volume	344.058	Van der Waals volume
Density	1.05	Density = MW / Volume
nHA	7	Number of hydrogen bond acceptors. Optimal:0~12
nHD	1	Number of hydrogen bond donors. Optimal:0~7
nRot	2	Number of rotatable bonds. Optimal:0~11
nRing	4	Number of rings. Optimal:0~6
MaxRing	12	Number of atoms in the biggest ring. Optimal:0~18
nHet	8	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4

nRig	23	Number of rigid bonds. Optimal:0~30
Flexibility	0.087	Flexibility = nRot /nRig
Stereo Centers	1	Optimal: ≤ 2
TPSA	75.01	Topological Polar Surface Area. Optimal:0~140
logS	-4.121	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	-0.283	Log of the octanol/water partition coefficient. Optimal:0~3
logD	0.762	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	**Value**	**Decision**	**Comment**
QED	0.875	•	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	3.098	•	■ 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	0.444	•	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. Fsp^3≥0.42 is considered a suitable value.
MCE-18	83.077	•	MCE-18 stands for medicinal chemistry evolution. MCE-18≥45 is considered a suitable value.

NPscore	-0.212	-	Natural product-likeness score. ■ This score is typically in the range from −5 to 5. Thehigher the score is, the higher the probability is that themolecule is a NP.
Lipinski Rule	Accepted	•	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption orpermeability is possible, one is acceptable.
PfizerRule	Accepted	•	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75)are likely to be toxic.
GSK Rule	Accepted	•	MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile

Golden Triangle	Accepted	●	200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule mayhave a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters,Alpha-screen artifacts and reactive compound.
ALARM NMR	1 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	-4.778	●	Optimal: higher than -5.15 Log unit
MDCK Permeability	1.2e-05	E•	low permeability: < 2 × 10−6 cm/s medium permeability: 2–20 × 10^{-6} cm/s high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.001	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is theprobability of being Pgp-inhibitor
Pgp-substrat e	0.994	•	Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of beingPgp-substrate
HIA	0.005	●	Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0:HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.003	●	20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); Theoutput value is the probability of being $F_{20\%}$+
$F_{30\%}$	0.001	●	30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	39.49%	●	Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-boundmay have a low therapeutic index.
VD	2.074	●	Volume Distribution Optimal: 0.04-20L/kg
BBB Penetration	0.211	●	Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	70.42%	●	The fraction unbound in plasma Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.05	▪ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.417	▪ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.021	▪ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.733	▪ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.065	▪ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.228	▪ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.014	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ Theoutput value is the probability of being inhibitor.
CYP2D6 substrate	0.203	■ Category 1: Substrate; Category 0: Non-substrate; ■ Theoutput value is the probability of being substrate.
CYP3A4 inhibitor	0.008	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ Theoutput value is the probability of being inhibitor.
CYP3A4 substrate	0.694	■ Category 1: Substrate; Category 0: Non-substrate; ■ Theoutput value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	2.326	●	Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg;low: <5 mL/min/kg
$T_{1/2}$	0.058	-	■ Category 1: long half-life ; Category 0: shorthalf-life; long half-life: >3h; short half-life: <3h ■ The output value is the probability of having a longhalf-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.209	●	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.894	●	Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0:H-HT negative(-); The output value is the probability of being toxic.
DILI	0.972	●	Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The outputvalue is the probability of being toxic.
AMES Toxicity	0.052	●	Category 1: Ames positive(+); Category 0: Ames negative(-); The output value is the probability of being toxic.
Rat OralAcute Toxicity	0.084	●	Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of beinghighly toxic.
FDAMDD	0.545	•	Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0:FDAMDD (-) ■ The output value is the probability ofbeing positive.
Skin Sensitization	0.231		■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is theprobability of being sensitizer.
Carcinogencity	0.372	●	■ Category 1: carcinogens; Category 0:non-carcinogens; The output value is the probability of being toxic.
Eye Corrosion		●	■ Category 1: corrosives ; Category 0: non corrosives ■ The output value is the probability ofbeing corrosives.

Eye Irritation	0.009	●	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.713	●	■ Category 1: respiratory toxicants; Category 0: respiratory intoxicants The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	0.327	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks tohuman health via the food chain. The unit is −log10[(mg/L)/(1000*MW)]
IGC_{50}	2.299	■ Tetrahymena pyriformis 50 percent growthinhibition concentration The unit is −log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	2.802	■ 96-hour fathead minnow 50 percent lethalconcentration ■ The unit is −log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	3.957	■ 48-hour daphnia magna 50 percent lethalconcentration ■ The unit is −log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.86	●	Androgen receptor ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
NR-AR-LBD	0.012	●	Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
NR-AhR	0.087	●	$_T$I■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
Aromatase	0.002	●	■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
NR-ER	0.547		Estrogen receptor ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
NR-ER-LBD	0.012		■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: in actives; ■ Theoutput value is the probability of being active.

NR-PPAR Gamma	0.013	●	Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
SR-ARE	0.465	●	Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.014	●	ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
SR-HSE	0.006	●	Heat shock factor response element ■ Category 1: actives ; Category 0: in actives; ■ The outputvalue is the probability of being active.
SR-MMP	0.014	●	Mitochondrial membrane potential ■ Category 1: actives ; Category 0: in actives; ■ The outputvalue is the probability of being active.
SR-p53	0.013	●	■ Category 1: actives ; Category 0: in actives; ■ The outputvalue is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	1 alerts	20 substructures acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	4 alerts	117 substructures carcinogenicity or mutagenicity
NonGenotoxic CarcinogenicityRule	3 alerts	■ 23 substructures ■ carcinogenicity throughnongenotoxic mechanisms
Skin SensitizationRule	0 alerts	155 substructures skin irritation
Aquatic ToxicityRule	1 alerts	99 substructures toxicity to liquid(water)
NonBiodegradableRule	2 alerts	19 substructures non-biodegradable
SureChEMBL Rule	0 alerts	164 substructures MedChem unfriendly status

ADMETlab 2.0

C[C@H]1COc2c(N3CCN(C)CC3)c(F)c(N3CCOCC3)c3c(=O)c(C(=O)O)cn1c23

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	446.2	Contain hydrogen atoms. Optimal:100~600
Volume	424.473	Van der Waals volume
Density	1.051	Density = MW / Volume
nHA	9	Number of hydrogen bond acceptors. Optimal:0~12
nHD	1	Number of hydrogen bond donors. Optimal:0~7
nRot	3	Number of rotatable bonds. Optimal:0~11
nRing	5	Number of rings. Optimal:0~6
MaxRing	12	Number of atoms in the biggest ring. Optimal:0~18
nHet	10	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	29	Number of rigid bonds. Optimal:0~30
Flexibility	0.103	Flexibility = nRot /nRig
Stereo Centers	1	Optimal: ≤ 2
TPSA	87.48	Topological Polar Surface Area. Optimal:0~140
logS	-4.008	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	-0.242	Log of the octanol/water partition coefficient. Optimal:0~3
logD	0.559	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.757	●	■ A measure of drug-likeness based on the conceptof desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	3.466	●	■ 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	0.545	●	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. Fsp^3≥0.42 is considered a suitable value.

MCE-18	104.059	●	MCE-18 stands for medicinal chemistry evolution. MCE-18≥45 is considered a suitable value.

NPscore	-0.444	-	Natural product-likeness score. ■ This score is typically in the range from −5 to 5. Thehigher the score is, the higher the probability is that themolecule is a NP.
Lipinski Rule	Accepted	●	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption orpermeability is possible, one is acceptable.
PfizerRule	Accepted	●	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75)are likely to be toxic.
GSK Rule	Rejected	●	MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Accepted	●	200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule mayhave a more favorable ADMET profile.
PAINS	1 alerts	-	Pan Assay Interference Compounds, frequent hitters,Alpha-screen artifacts and reactive compound.
ALARM NMR	3 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	-5.052	●	Optimal: higher than -5.15 Log unit
MDCK Permeability	8e-06	●	low permeability: < 2 × 10−6 cm/s medium permeability: 2–20 × 10−6 cm/s high passive permeability: > 20 × 10−6 cm/s
Pgp-inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is theprobability of being Pgp-inhibitor
Pgp-substrat e	0.943	●	Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of beingPgp-substrate

HIA	.002	●	Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0:HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.262	●	20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); Theoutput value is the probability of being $F_{20\%}$+

$F_{30\%}$	0.002	●	30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being$F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	46.66%	●	Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-boundmay have a low therapeutic index.
VD	2.021	●	Volume Distribution Optimal: 0.04-20L/kg
BBB Penetration	0.218	●	Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	47.41%	●	The fraction unbound in plasma Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.037	▪ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.134	▪ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.018	▪ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.772	▪ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.099	▪ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9	0.25	: Substrate; Category 0: Non-substrate;
substrate		ut value is the probability of being substrate.

CYP2D6 inhibitor	0.014	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ Theoutput value is the probability of being inhibitor.
CYP2D6 substrate	0.211	■ Category 1: Substrate; Category 0: Non-substrate; ■ Theoutput value is the probability of being substrate.
CYP3A4 inhibitor	0.016	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ Theoutput value is the probability of being inhibitor.
CYP3A4 substrate	0.403	■ Category 1: Substrate; Category 0: Non-substrate; ■ Theoutput value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	2.122	●	Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg;low: <5 mL/min/kg
$T_{1/2}$	0.054	-	■ Category 1: long half-life ; Category 0: shorthalf-life; long half-life: >3h; short half-life: <3h ■ The output value is the probability of having a longhalf-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.198	●	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.857	●	Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0:H-HT negative(-); The output value is the probability of being toxic.
DILI	0.987	●	Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The outputvalue is the probability of being toxic.
AMES Toxicity	0.165	●	Category 1: Ames positive(+); Category 0: Ames negative(-); The output value is the probability of being toxic.
Rat OralAcute Toxicity	0.024	●	Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of beinghighly toxic.
FDAMDD	0.022	●	Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0:FDAMDD (-) ■ The output value is the probability ofbeing positive.

Skin Sensitization	0.425	●	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is theprobability of being sensitized.
Carcinogencity	0.615	●	■ Category 1: carcinogens; Category 0:non-carcinogens; The output value is the probability of being toxic.
Eye Corrosion		●	■ Category 1: corrosives ; Category 0: non corrosives ■ The output value is the probability ofbeing corrosives.
Eye Irritation	0.009	●	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.33	●	■ Category 1: respiratory toxicants; Category 0: respiratory intoxicants The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	0.417	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks tohuman health via the food chain. The unit is −log10[(mg/L)/(1000*MW)]
IGC_{50}	2.838	■ Tetrahymena pyriformis 50 percent growthinhibition concentration The unit is −log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	2.942	■ 96-hour fathead minnow 50 percent lethalconcentration ■ The unit is −log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	3.909	■ 48-hour daphnia magna 50 percent lethalconcentration ■ The unit is −log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.88	●	Androgen receptor ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
NR-AR-LBD	0.063	●	Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
NR-AhR	0.114	●	Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.

Aromatase	0.002	●	■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
NR-ER	0.551	●	Estrogen receptor ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
NR-ER-LBD	0.092		■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: in actives; ■ Theoutput value is the probability of being active.
NR-PPAR Gamma	0.063	●	Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
SR-ARE	0.693	●	Antioxidant response element ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.
SR-ATAD5	0.007	●	ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: in actives; ■ The output value is the probability of being active.

SR-HSE	0.004	●	Heat shock factor response element ■ Category 1: actives ; Category 0: in actives; ■ The outputvalue is the probability of being active.
SR-MMP	0.048	●	Mitochondrial membrane potential ■ Category 1: actives ; Category 0: in actives; ■ The outputvalue is the probability of being active.
SR-p53	0.029	●	■ Category 1: actives ; Category 0: in actives; ■ The outputvalue is the probability of being active.

10. Toxicophore Rules

Property	**Value**	**Comment**
Acute Toxicity Rule	1 alerts	20 substructures acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	5 alerts	117 substructures carcinogenicity or mutagenicity
NonGenotoxic CarcinogenicityRule	3 alerts	23 substructures ■ carcinogenicity through nongenotoxicmechanisms
Skin SensitizationRule	0 alerts	155 substructures skin irritation
Aquatic ToxicityRule	1 alerts	99 substructures toxicity to liquid(water)
NonBiodegradableRule	3 alerts	19 substructures non-biodegradable

SureChEMBL Rule	0 alerts	164 substructures MedChem unfriendly status

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