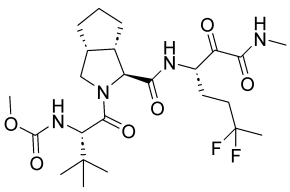
Small Molecule Highlights

Snapshots from Recent Literature in Target-oriented Drug Design

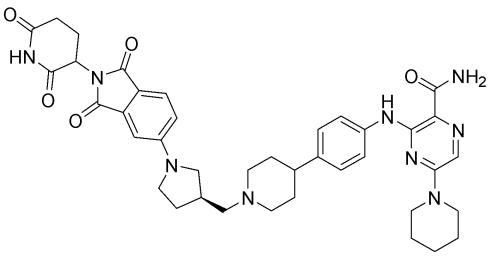
DALRIADA TURN-KEY™ DRUG DISCOVERY



CL^{pro} | **MK-7845** | **Antiviral**

Target: SARS-CoV-2 3**C**-**l**ike **pro**tease (**CL^{pro}**)
Indication: SARS-CoV-2 infection
Inhibitor design: Structure based design and SAR optimization.
Activity: 3CL^{pro} WT IC_{50} = 8.7 nM (biochemical), 3CL^{pro} P132H IC_{50} = 15 nM (biochemical); A549 cell replicon IC_{50} = 15 nM (cellular); Cytopathic effect A549-ACE2-TMPRSS2 EC_{50} = 444/351/215 nM in WA1/2020/Delta AY.2/Omicron B.1.1.529+R346K (cellular).
ADME/PK: *In vivo* $T_{1/2}$ = 9.1/2.7/1.3 h in rat/dog/monkey; F(%) = 90/70 in rat/dog; CYP2B6 inhibition = 7 – 12% @ 20 μM; CYP3A4 inhibition = 22 – 48% @ 20 μM; CYP3A (K_I/k_{inact} = 110 μM/0.03 min^{-1}.
In vivo: Outperformed nirmatrelvir in a mouse model of SARS-CoV-2 infection.

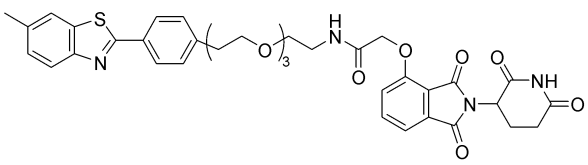
J. Med. Chem.
Merck, USA



BTK & IKZF1/3 | **NX-2127** | **Oncology**

Target: **B**urton's **T**yrosine **K**inase (**BTK**) and **Ik**aros family **z**inc **f**inger protein **1/3** (**IKZF1/3**)
Indication: Various B-cell malignancies
Inhibitor design: SBDD and SAR.
Activity: BTK WT DC_{50} = 4.5 nM (cellular); BTK C481S DC_{50} = 31 nM (cellular); IKZF1 DC_{50} = 57 nM (cellular); IKZF3 DC_{50} = 36 nM (cellular).
ADMET/PK: F(%) = 36/7.1/1/1.2 in mouse/rat/dog/monkey; hERG IC_{50} >30 μM; CYP IC_{50} >30 μM (CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2)
In vivo: Near total TGI in BTK WT TMB8 xenograft mice (90 mg/kg, 5 day, QD, p.o., 25-day trial).

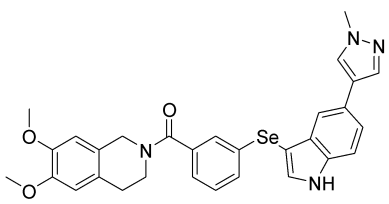
J. Med. Chem.
Nurix Therapeutics, USA



α-Syn & tau | **T3** | **Neurodegenerative Disease**

Target: **α-Syn**uclein (**α-Syn**) and tau
Indication: Alzheimer's disease and Parkinson's disease.
Inhibitor design: SAR for optimization of the linker and E3 requiting ligand.
Activity: Tau DC_{50} = 4.09 μM (cellular); α-Syn DC_{50} = 1.57 μM (cellular); Cytoprotective effect @ 5 μM in SH-SY5Y cells (cellular).
ADME/PK: *In vivo* Plasma $T_{1/2}$ = 3.24/3.78 in mouse/rat; Brain $T_{1/2}$ = 4.21 h in mouse; CL_{plasma} = 0.1/0.12 L/h/kg in mouse/rat.
In vivo: Effectively decreased levels of α-Syn and tau protein aggregates and protected dopaminergic neurons from injury in an MPTP induced model of neurotoxic protein aggregation (8 mg/kg, i.v., mouse).

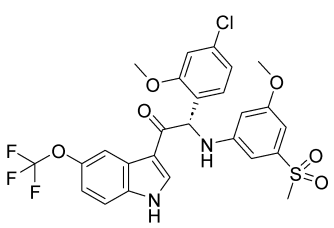
J. Med. Chem.
Sun Yat-sen University, China



P-gp | **H27** | **Oncology**

Target: **P-g**lyco**p**rotein (**P-gp**)
Indication: Various oncology indications
Inhibitor design: SAR optimization of previous scaffold.
Activity: Cytotoxicity - %inhibition = 21.1/33.7 in MCF7/MCF7/ADR (cellular); Combination with doxorubicin - IC_{50} = 46.6 nM in MCF7/ARD (cellular).

Eur. J. Med. Chem
Zhejiang University, China



NS4B | **JNJ-1802** | **Antiviral**

Target: **NS4B**
Indication: Dengue Virus
Inhibitor design: SAR optimization from lead scaffold.
Activity: EC_{50} = 0.24/0.057/2.1/11 nM against DENV-1/DENV-2/DENV-3/DENV-4 (cellular).
ADMET/PK: F(%) = 108/58/51/50 in mouse/rat/dog/monkey; CL (mL/min/kg) = 4.97/4.9/6.4/2.45 in mouse/rat/dog/monkey; hERG IC_{50} > 30 μM; Ames II was negative
In vivo: Dose-dependant decrease in viral RNA after 3 days in a murine model of DENV-2 infection. Viral RNA was undetectable in four of the seven mice treated with the highest dose (60 mg/kg, b.i.d.).

J. Med. Chem.
Janssen, Belgium

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