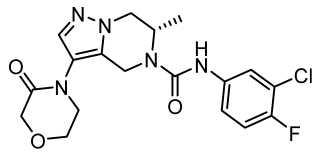
Small Molecule Highlights

Snapshots from Recent Literature in Target-oriented Drug Design

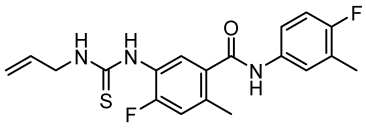
DALRIADA TURN-KEY™ DRUG DISCOVERY



HBV Core Protein | **Lead 45** | **HBV/Liver**

Target: **H**epatitis **B V**irus (**HBV**) Core Protein
Indication: liver cirrhosis and **h**epatocellular **c**ar**c**inoma (**HCC**)
Inhibitor design: SAR
Activity: Anti HBV DNA EC_{50} = 27 nM (cellular)
ADME/PK: Microsome Clearance (mL/min/kg) = 7.1/39 for human/mouse; F(%) = 48 for mouse; $T_{1/2}$ = 2 hr; Cl (mL/min/kg) = 10.
In vivo: Moderate but not durable efficacy in a mouse model of HBV replication.

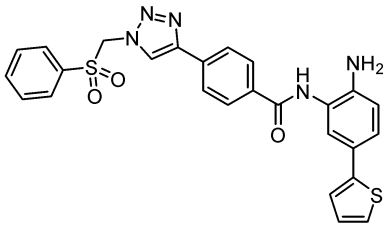
J. Med. Chem.
China Innovation Center of Roche , China



HBV Core Protein | **Compound 17i** | **HBV/Liver**

Target: **H**epatitis **B V**irus (**HBV**) Core Protein
Indication: liver cirrhosis and **h**epatocellular **c**ar**c**inoma (**HCC**)
Inhibitor design: Bioisostere incorporation and SAR.
Activity: Anti HBV DNA EC_{50} = 12 nM (cellular); CC50 = 26.6 μM
ADME/PK: Microsome $T_{1/2}$ (min.) =38.1 min in humans; Plasma $T_{1/2}$ (min.) =54 min in humans; CL (mL/min/kg) = 10.3 in rat; F(%) = 67.7 in rat.
In vivo: Significant reduction in serum HBV DNA after 18 days in an HBV carrier mouse model (daily dosing; 25 mg/kg; p.o.)

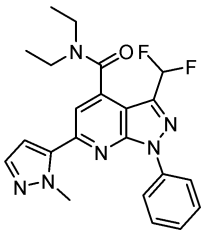
J. Med. Chem.
Weifang Medical University, China



HDAC1/2 | **KPZ560** | **Oncology/Neuorology**

Target: **H**istone **De**a**c**etylase **1** and **2** (**HDAC1/2**)
Indication: Breast Cancer
Inhibitor design: Diversity oriented synthesis.
Activity: MCF-7 GI_{50} = 43 nM (cellular); HMEC IC_{50} = 9.85 μM (cellular); HDAC2 T_R = 417 min.
In vivo: Increased neurite outgrowth and density in a BALB/c mice (osmotic pump; 1 μM)

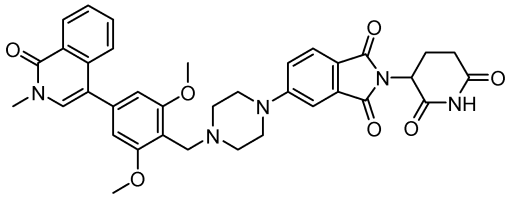
J. Med. Chem.
SANKAN, Japan



PDE114A | **23b** | **CNS**

Target: **P**hospho**die**sterase **11A4 (PDE11A4)**
Indication: Age-related Cognitive Decline
Inhibitor design: High-throughput screening and SAR to develop lead.
Activity: = PDE11A4 IC_{50} = 12 nM (biochemical); HT-22 EC_{50} = 2.5 μM (cAMP) and 2.5 μM (cGMP) (cellular)
ADME/PK: $Solubility_{pH\ 7.4\ PBS}$ = 42 μM; Microsome $T_{1/2}$ = 4.3 min/3.6 min in human/mouse; Cyp IC_{50} = 5.8 μM/>10 μM/5.6 μM for CYP3A4/CYP2D6/CYP2C9.

J. Med. Chem.
Sokol Institute of Pharmaceutical Life Sciences , USA



BRD9 | **C6** | **Leukemia**

Target: **Br**omo**d**omain-containing protein 9 (**BRD9**)
Indication: **A**cute **M**yeloid **L**eukemia (**AML**)
Inhibitor design: Rational design and SAR.
Activity: = MV4-11 IC_{50} = 3.69 nM (cellular); BRD9 DC_{90} = 10 nM
ADME/PK: $T_{1/2}$ = 8.8 hrs, C_{max} = 3436.95 ng/mL, AUC_{0-t} = 17749.45 h·ng/mL in mouse (20 mg/kg, p.o.)

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