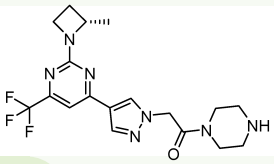
Small Molecule Highlights

Snapshots from Recent Literature in Target-oriented Drug Design

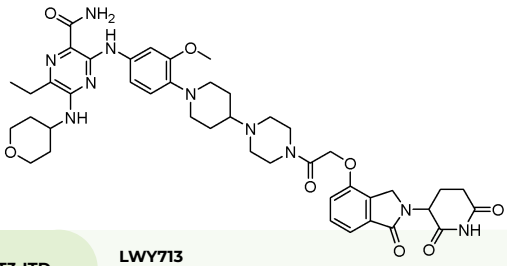
DALRIADA TURN-KEY™ DRUG DISCOVERY



Ketohexokinase A&C | **LY3522348** | **Diabetes**

Target: **K**eto**h**exo**k**inase (**KHK**) **A&C**
Indication: Diabetes and related comorbidities
Inhibitor design: Rational design from a potent lead
Activity: KHK-A IC_{50} = 20 nM (biochemical); KHK-C IC_{50} = 24 nM (biochemical): F1P IC_{50} = 41 nM (cellular).
ADME/PK: Microsome Clearance (mL/hr/kg) = 6/3 in rat/dog; F(%) = 83/87 in rat/dog; $T_{1/2}$ (hr) = 17/37 in rat/dog.
In vivo: Dose dependant increase in serum fructose in treated mice (30 and 100 mg/kg, p.o.), with compound being distributed to key organs (kidney, liver, and heart).

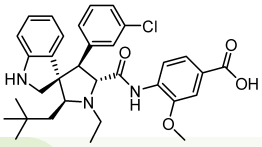
J. Med. Chem.
Eli Lilly , USA



FLT3/FLT3-ITD | **LWY713** | **Leukemia**

Target: **F**ms-**L**ike **T**yrosine Kinase **3 (FLT3)**
Indication: **A**cute **M**yeloid **L**eukemia **(AML)**
Inhibitor design: SDR study originating from Gilteritinib
Activity: FLT3 DC_{50} = 0.64 nM (cellular); FLT3 DC_{max} = 94.8% (cellular); Cytotoxicity IC_{50} = 1.5 nM (cellular).
In vivo: No increase in tumor volume observed over 21 days in an MV4-11 xenograft model (NOD/SCID mice, female, 6 mg/kg, QD, i.p.). No toxicity observed in treated mice as evidenced by body weight measurements.

Eur. J. Med. Chem.
State Key Laboratory of Chemical Biology, Shanghai, China



MDM2 | **JN122** | **Oncology**

Target: **M**ouse **D**ouble **M**inute **2** (**MDM2**)
Indication: Oncology
Inhibitor design: SAR
Activity: MDM2 K_i = 0.7 nM (biochemical); MDM4 K_i = 527 nM (biochemical); HCT-116 IC_{50} < 1 nM (cellular); RKO IC_{50} = 43.2 nM (cellular); U2-OS IC_{50} = 10.8 nM (cellular).
ADME/PK: $T_{1/2}$ (hr) = 5.35/7.42 i.v./p.o. in mouse; C_{max} (ng/mL) = 23760/4151 i.v./p.o. in mouse; F(%) = 30.3 in mouse.
In vivo: Median survival increased by 11 days 31 days (100 mg/kg, p.o., once daily, 21 days); no signs of toxicity.

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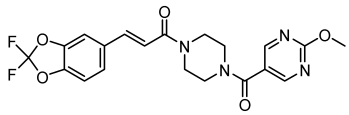

GPR183 | **Compound 32** | **Rheumatoid Arthritis**

Target: **G-p**rotein-coupled **r**eceptor (**GPR**) 183
Indication: Rheumatoid Arthritis (RA)
Inhibitor design: SAR optimization from a potent lead
Activity: Chemotaxis of U937 IC_{50} = 5.5 nM (cellular; transwell assay); Chemotaxis of Th17 IC_{50} = 3.8 nM (cellular; transwell assay); Calcium mobilization IC_{50} = 31.3 nM (cellular).
ADME/PK: Microsome $T_{1/2}$ (min) > 186 in human/mouse/rat/dog/monkey; hERG IC_{50} = 7.9 μM; F(%) = 119 in mouse; $T_{1/2}$ (hr) = 2.97 in mouse.
In vivo: Dose dependant decrease in the swelling of paws and joints, decreased levels of proinflammatory cytokines and inflammatory cell infiltrate, decreased cartilage damage and bone erosion in affected joints (mouse collagen induced arthritis model).

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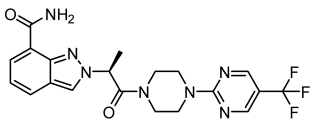
Immunophage Biotech Co., Ltd., China



PARP7 | ***(S)*-XY-05** | **Immunooncology**

Target: **P**oly (**A**DP-**R**ibose) **P**olymerase **7** (**PARP7**)
Indication: Oncology
Inhibitor design: Scaffold-hop/rigidification and SAR
Activity: PARP7 IC_{50} = 4.5 nM (biochemical); PARP1 IC_{50} > 1300 nM (biochemical); PARP2 IC_{50} = 302.8 nM (biochemical).
ADME/PK: $T_{1/2}$ (hr) = 1.22 (i.v.) in mouse; Clearance (mL/hr/kg) = 577 (i.v.); F(%) = 94.6 in mouse.
In vivo: 83% tumor growth inhibition (25 mg/kg, 14 days, p.o.); no signs of toxicity; pronounced $CD8^+$T cell infiltrate in resected tumors.

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State Key Laboratory of Natural Medicines, Nanjing, China

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