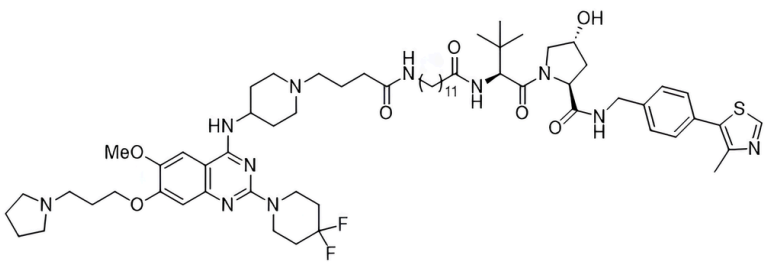
Small Molecule Highlights

Snapshots from Recent Literature in Target-oriented Drug Design

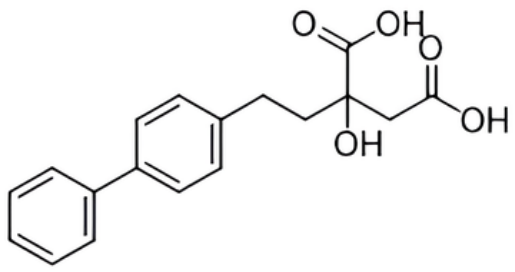
DALRIADA TURN-KEY™ DRUG DISCOVERY



G9a / GLP — MS8709 (Oncology)

Target: Lysine methyltransferases G9a / GLP
Indication: Oncology
Inhibitor design: Structure-based drug design, small molecule G9a / GLP inhibitor selection, SAR
Activity: G9a DC50 = 274 nM (cellular); GLP DC50 = 260 nM (cellular), IC50 4.1 mM 22Rv1 cell viability, selectivity, no significant inhibition (>50% at 10 mM) against a panel of 21 protein methyltransferases
ADME/PK: mouse, 50 mg/kg, i.p., Tmax 0.5 h, Cmax = 27 mM, AUClast 61 hr*mM, T1/2(h) = 1.5 (estimated)

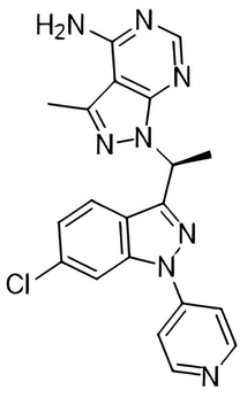
J. Med. Chem.
Mount Sinai Center for Therapeutics Discovery, United States



SLC13A5 — LBA-3 (Hyperlipidemia)

Target: Sodium-coupled citrate transporter SLC13A5
Indication: Hyperlipidemia
Inhibitor design: Structure-based drug design and SAR
Activity: HEK IC50 = 67 nM (competitive inhibitor), dose dependent significant decrease in lipid accumulation AML12 cells, NaDC1 and NaDC3 selective. Limited brain distribution (rat 5 mg / kg)
ADME/PK: HLM/RLM % remaining at 2 h > 60%, PK rat 50 mg/kg p.o., Cmax = 288262mg/L, AUC0-infin. 704570hr*mg/L, T1/2(h) = 1.09, CL 0.07 L/h/kg, F = 48.7%
In vivo: mouse hyperlipidemia model (starvation induced) 100 mg/kg resulted in significant reduction in triglycerides and nonesterified fatty acids

J. Med. Chem.
China Pharmaceutical University, China



PI3Kδ — (S)-36 (Oncology)

Target: Phosphatidylinositol-3-kinase d PI3K
Indication: Oncology (Acute myeloid leukemia, AML)
Inhibitor design: Structure based drug design & SAR
Activity: PI3Kd IC50 = 6.4 nM, PI3Ka IC50 = >10000 nM, PI3Kb IC50 = 1273 nM, PI3Kg IC50 = 8516 nM, AML cell lines, MV-4-11, IC50 = 0.74 mM, MOLM-13, IC50 = 0.23 mM
ADME/PK: rat, 20 mg/kg, p.o., AUC0-t = 22712.46, h*mg/L, Cmax = 1731 mg/L, T1/2(h) = 8.57, F = 59.6 %.
In vivo: MOLM-13 xenograft mouse model, p.o.; 5 and 10 mg/kg for 22 days; Tumour Growth Inhibition (TGI) = 67.8% (10 mg /kg)

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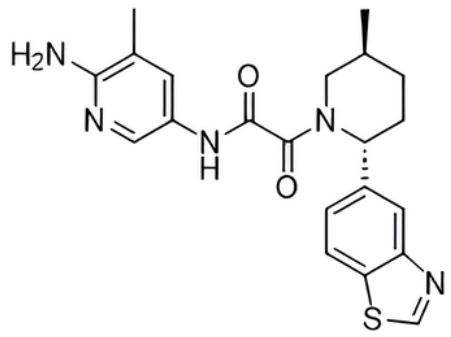
Zhejiang and Shandong Universities, China



PRMT5 — TNG908 (Oncology)

Target: Protein arginine methyltransferase 5 PRMT5
Indication: Glioblastoma, non small cell lung cancer, colorectal cancer
Inhibitor design: HTS screening, SBDD and SAR
Activity: HAP1 MTAP-null, SDMA IC50 = 9 nM, Viability GI50 = 100 nm., Viability selectivity vs MTAP WT = 15
ADME/PK: MDCKII-WT = 16 x 10−6 cm/s, efflux ratio = 3, HLM, Clint =14 mL/min/mg
PK: rat 1mg/mL i.e. / 3mg/mL p.m. CL 38.2 mL/min/kg, T1/2(h) = 2, F = > 100 %, cyno 1mg/mL i.e. / 3mg/mL p.m. CL 16.2 mL/min/kg, T1/2(h) = 1, F = 21 %, cyno p.m., Kp,uu,CSF = 0.9
In vivo: HCT116 MTAP-null xenograft model, dose dependent antitumour activity 85% Tumour Growth Inhibition, PRMT5 inhibition > 90%

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Tango Therapeutics, USA

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