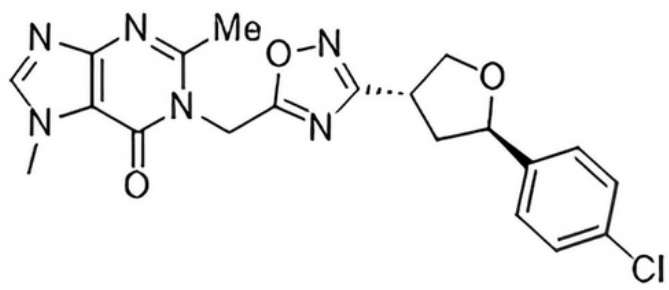
Small Molecule Highlights

Snapshots from Recent Literature in Target-oriented Drug Design

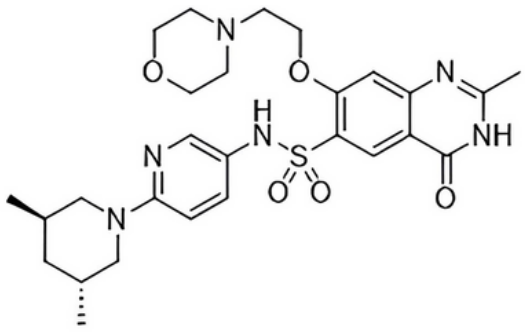
DALRIADA TURN-KEY™ DRUG DISCOVERY



TRPA1 — GDC-6599 (Respiratory)

Target: Transient receptor potential ankyrin 1 (TRPA1)
Indication: Asthma and respiratory inflammation
Inhibitor design: SAR optimization from lead scaffold.
Activity: hTRPA1 IC50 = 5.1 nM (biology).
ADME/PK: CLHep(mL/min/kg) < 4/27 in human/rat. No formation of AO metabolite in hepatocytes across species (mouse, rat, dog, monkey, and human)
In vivo: Dose-dependent control of cinnamaldehyde induced cough in guinea pig (3mg/kg max dose). Dose-dependent inhibition of AITC induced blood perfusion in guinea pig ear (3mg/kg max dose).

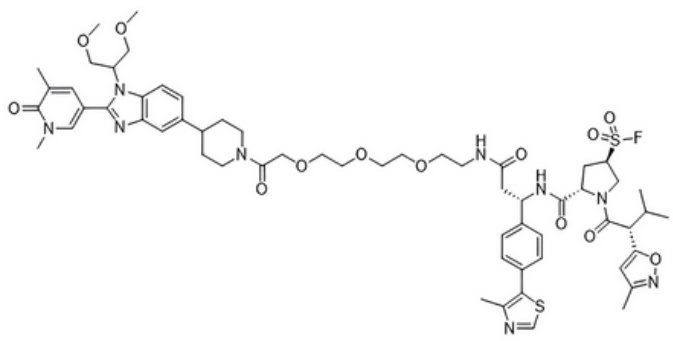
J. Med. Chem.
Genentech, USA



Troponin — CK-963 (Cardiovascular)

Target: Cardiac Troponin
Indication: Heart Failure
Inhibitor design: HTS followed by SAR optimization of hit.
Activity: Cardiac myofibrils AC50 = 0.7 μM (biochemical), Troponin Ki = 11.5 μM (ITC); PDE-3 IC50 > 40 μM (biochemical).
ADME/PK: In vivo T1/2 = 0.6 h in rat; CLrat = 7.1 mL/min/kg; PPBrat = 3.7%.
In vivo: 40% increase in left ventricle contractility in rats @ 32.8 μM plasma concentration (199 mg/kg, i.v.).

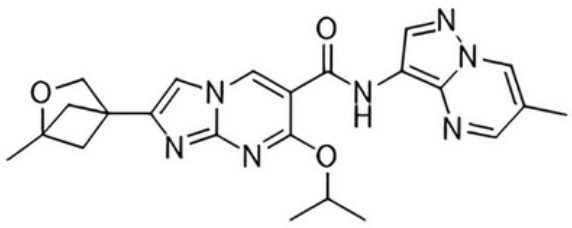
J. Med. Chem.
Cytokinetics, USA



BRD4 — BRD-SF2 (Oncology)

Target: Bromodomain-containing protein 4 (BRD4)
Indication: Oncology
Inhibitor design: Structure-guided design and SAR optimization.
Activity: BRD4 DC50 = 17.2 μM; Dmax = 60% @ 18 hrs (cellular); Degradation reduction after washout = 27% @ 24 hrs post washout.

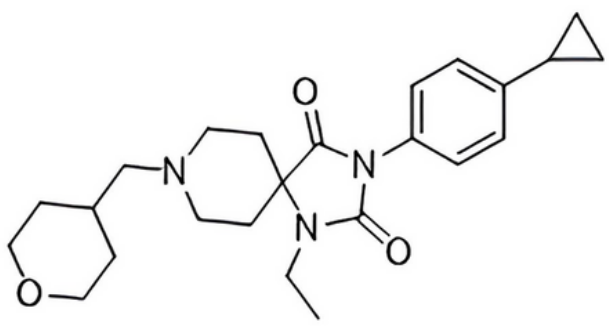
J. Med. Chem.
Molecular Sciences Research Hub at Imperial College and GSK, UK



IRAK4 — Bio-7488 (CNS)

Target: Interleukin receptor-associated kinase 4 (IRAK4)
Indication: Acute ischemic stroke (AIS)
Inhibitor design: Structure based design and SAR optimization.
Activity: IRAK4 IC50 = 0.5 nM (biochemical), IRAK4 sole hit in Eurofins Kinomescan @ 100 nM, MEK5 was observed @ 1 μM (panel of 489 kinases, biochemical).
ADME/PK: In vivo T1/2 = 12/5/8.3/10 h in rat/mouse/monkey/dog; F(%) = 91/98/95/95 in 12/5/8.3/10 h in rat/mouse/monkey/dog.
In vivo: Dose-dependent decrease in plasma cytokines (IL-1β, TNFα, and IL-6) in a murine LPS challenge model.

J. Med. Chem.
Biogen, USA



EBP — Compound 11 (MS)

Target: Emopamil binding protein (EBP)
Indication: Multiple Sclerosis (MS)
Inhibitor design: Structure based drug design (SBDD) and SAR optimization.
Activity: Zymostenol accumulation: EC50 = 6 nM (cellular; mouse OPCs), EC50 = 31 nM (cellular; human cortical organoids).
ADME/PK: F(%) = 68/42 in mouse/rat; Kp,uu = 0.77/0.74 in mouse/rat after i.v. dosing; Kp,uu = 0.72/0.50 in mouse/rat after p.o. dosing; T1/2 = 3.9/4.4 in mouse/rat after i.v. dosing; T1/2 = 5.3 in mouse p.o. dosing.

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