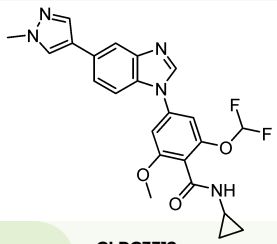
Small Molecule Highlights

Snapshots from Recent Literature in Target-oriented Drug Design

DALRIADA TURN-KEY™ DRUG DISCOVERY



pan-SIK(1/2/3)

GLPG3312
Inflammation

Target: **S**alt-**i**nducible **k**inase (**SIK**) **1/2/3**
Indication: Inflammatory diseases (ex. IBD)
Inhibitor design: HTS screen followed by SAR studies
Activity: SIK1/2/3 IC_{50} = 2/0.7/0.6 nM for SIK1, SIK2, and SIK3, respectively (biochemical); TNFα IC_{50} = 17/34 nM in human monocytes/human MdM cells (cellular).
ADME/PK: Clearance (L/hr/kg) = 0.945 in mouse; F(%) = 60/41.4/45.5 in mouse/rat/dog; $T_{1/2}$ (hr) = 0.58 in mouse.
In vivo: Dose-dependent decrease in serum TNFα concentrations and increasing IL-10 levels (77% decrease in TNFα and 3.1-fold increase in IL-10) observed at 3 mg/kg (p.o.)

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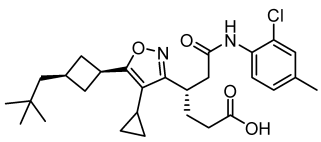
Galapagos , France/Belgium



RORγ

JTE-151
Inflammation

Target: **R**etinoic acid receptor-related **o**rphan **r**eceptor (**ROR**) **γ**
Indication: Inflammatory diseases (ex. Lupus, MS, Rheumatoid Arthritis, etc.)
Inhibitor design: HTS screen followed by SAR directed by drug-like indices.
Activity: Luciferase EC_{50} = 13 nM (cellular); >100-fold selectivityagainst closely related nuclear factors (15 in total).
ADME/PK: Clearance (L/hr/kg) = 0.11 in rat; F(%) = 98/64 in rat/dog; $T_{1/2}$ (hr) = 3.8/5.5 in rat/dog.
In vivo: Dose-dependent decrease in the severity of paralysis in a mouse model of experimental autoimmune encephalomyelitis (EAE). Dose-dependent increase in plasma exposure (30 – 1600 mg) in healthy humans with no severe adverse events observed at the highest dose.

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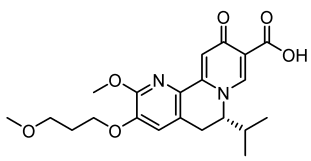
Takatsuki Research Center, Japan



PAPD5/7

AB-452
Hepatitis B

Target: **P**oly(**A**) RNA **p**olymerase associated **d**omain (**PAPD**) **5/7**
Indication: **H**epatitis **B** **v**irus (**HBV**) infection
Inhibitor design: Scaffold Hopping followed by SAR.
Activity: HBsAg EC_{50} = 13 nM (cellular); Cytotoxicity CC_{50} > 50 μM (cellular).
ADME/PK: Clearance (mL/min/kg) = 30/9.6/5.4 in mouse/rat/dog; F(%) = 99/80/98 in mouse/rat/dog; $T_{1/2}$ (hr) = 5.8/3.4/2.8 in mouse/rat/dog; Cardiotoxicity IC_{50} > 10 μM (rabbit Langendorff model).
In vivo: Dose-dependent decrease in serum/liver HBsAg and Liver HBV RNA. Signs of peripheral neuropathy in preclinical safety study.

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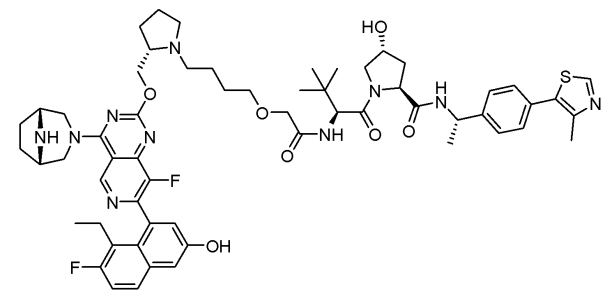
Arbutus Biopharma, USA



KRAS (G12D)

8o
Oncology

Target: **K**irsten **r**at **s**arcoma virus (**KRAS**) **G12D**
Indication: **P**ancreatic **d**uctal **a**deno**c**arcinoma (**PDAC**), **n**on**s**mall-**c**ell **l**ung **c**ancer (**NSCLC**), and **c**olo**r**ectal **c**ancer (**CRC**)
Inhibitor design: SAR commencing from established pharmacophore.
Activity: KRAS G12D DC_{50} = 38/20/53/7/88 nM in AsPC-1/SNU-1/HPAF-II/AGS/PANC 04.03 (cellular); D_{max} = 98.9/97.5/97.3/96.5/99.3 % in AsPC-1/SNU-1/HPAF-II/AGS/PANC 04.03 (cellular); IC_{50} = 60/44/45/31/52 in AsPC-1/SNU-1/HPAF-II/AGS/PANC 04.03 (cellular).
ADME/PK: $T_{1/2}$ (hr) = 8.7 in mouse; $AUC_{0-\infty}$ (h·ng/mL) = 5057; MRT (hr) = 9.33.
In vivo: 68% tumor growth inhibition by over 22-day chronic dosing (50 mg/kg, QD, s.c.) regime with no signs of toxicity. Demonstrated KRAS G12D degradation and down-regulation of pERK.

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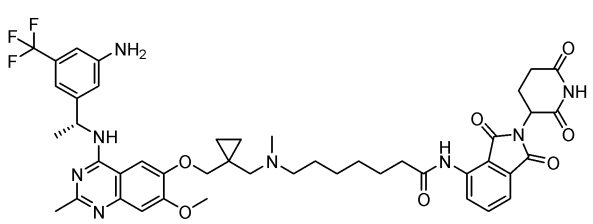
Multiple Institutions, China



SOS1

Compound 4
Oncology

Target: **S**on **o**f **S**evenless (**SOS1**) 1
Indication: **P**ancreatic **d**uctal **a**deno**c**arcinoma (**PDAC**), **n**on**s**mall-**c**ell **l**ung **c**ancer (**NSCLC**), and **c**olo**r**ectal **c**ancer (**CRC**)
Inhibitor design: SAR commencing from established pharmacophore.
Activity: Cell proliferation IC_{50} = 5/2151/43/63 nM in NCI-H358 (G12C)/GP2D (G12D)/NCI-H441 (G12V)/DLD-1 (G13D) (cellular); SOS1 DC_{50} = 13 nM (cellular).
ADME/PK: $T_{1/2}$ (hr) = 4.05 in mouse; $AUC_{0-\infty}$ (h·ng/mL) = 4738; C_{max} (ng/mL) = 1868.
In vivo: 60% tumor growth inhibition in BALB/c H358 xenograft model (30 mg/kg, i.p., 21-days). Outperformed BI3406 (30 mg/kg, p.o.) in the same model by nearly 2-fold

J. Med. Chem.
Shanghai Zelgen Pharma-Tech and the East China University of Science and Technology , China

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