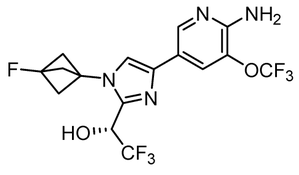
Small Molecule Highlights

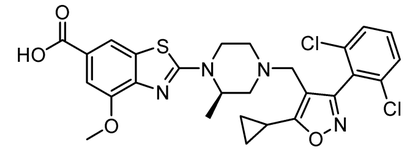
Snapshots from Recent Literature in Target-oriented Drug Design



IACS-52825 **DLK** **Neurology/Oncology**

Target: **D**ual **L**eucine Zipper **K**inase (**DLK**)
Indication: **C**hemotherapy-**i**nduced **p**eripheral **n**europathy (**CIPN**)
Inhibitor design: Optimization of CNS penetration (CNS MPO) and crystallography based rational design
Activity: DLK K_d = 1.3 nM (biochemical); p-c-Jun IC_{50} = 107 nM (cellular)
ADME/PK: Microsome Stability (mL/min/kg) = 14/16/3 for mouse/rat/human; $K_{p,uu}$ = 0.92; F(%) = >100/95/>100/>100 for mouse/rat/dog/monkey
In vivo: Near complete reversal of cisplatin-induced mechanical allodynia (model of CIPN) in mice (30 mg/kg, 1 dose per day)

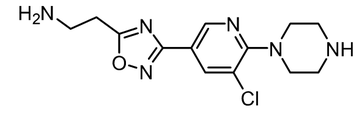
J. Med. Chem.
Institute for Applied Cancer Science (IACS), USA



HPG1860 **FXR** **Fatty Liver Disease**

Target: **F**arnesoid **X** **R**eceptor (**FXR**)
Indication: **N**on-**a**lcoholic **s**teato**h**epatitis (**NASH**), **n**on-**a**lcoholic **f**atty **l**iver **d**isease (NAFLD)
Inhibitor design: Scaffold hopping and SAR
In vitro Activity: FXR EC_{50} = 5 nM (biochemical); FXR Luciferase EC_{50} = 18 nM (cellular)
ADME/PK: Liver Microsome Stability $t_{1/2}$(min) = 447/116/237/152 for mouse/human/rat/monkey; F(%) = 77/52/59 for mouse/rat/dog
In vivo: significant impact on the transcription of FXR target genes (FGF15, SHP and BSEP) in rodent PD model. Demonstrable efficacy in CCl_4 induced NASH model.

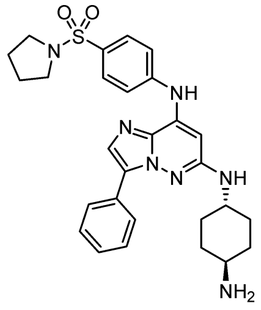
J. Med. Chem.
Hepagene Therapeutics, Inc., China



BDM91514 **AcrAB-TolC efflux pump** **Antibiotics**

Target: AcrAB-TolC efflux pump
Indication: Infection arising from **M**ulti-**d**rug **R**esistant (**MDR**) Bacteria
Inhibitor design: SAR and Rational design
In vitro Activity: MIC EC_{50} enhancement (cellular) = Chloramphenicol (4x), Oxacillin (3x), Piperacillin (>8x), Fusidic Acid (4x), Novobiocin (8x), Linezolid (8x), Erythromycin (8x), Ciproflaxin (>2x)
ADME/PK: Liver Microsome Stability $t_{1/2}$ = > 40 min (mouse), Plasma stability $t_{1/2}$ = > 6 hrs (mouse), Solubility (PBS) = >200 µ M.

Eur. J. Med. Chem.
Univ. Lille, France



Compound 34f **FLT3** **Oncology**

Target: **F**MS-**l**ike **t**yrosine kinase 3 (**FLT3**)
Indication: **A**cute **m**yeloid **l**eukemia (**AML**)
Inhibitor design: Scaffold hopping (privileged: purine) and SAR
In vitro Activity: IC_{50} (biochemical) = FLT3-ITD (4 nM), FLT3-D835Y (1 nM), CDK2 (493 nM), Kit (680 nM). EC_{50} (biological) = MV4-11 (7 nM), MOLM-13 (9 nM), SEM (140 nM), CEM (1768 nM), NOMO-1 (4275 nM), ML-2 (3030 nM).
ADME/PK: Liver Microsome Stability: CL_{int} = 18 µL/min/mg (human) 13 µL/min/mg (mouse).
In vivo: >60% tumor regression in a mouse xenograft model (mouse; 5 &10 mg/kg; ip)

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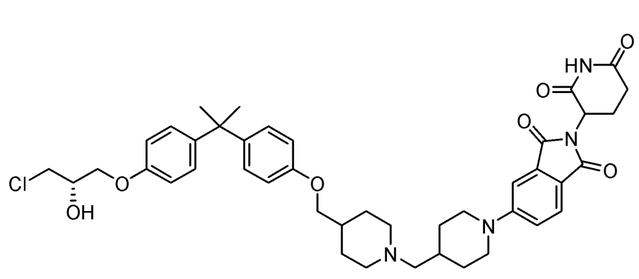

BWA-522 **AR** **Oncology (Prostate)**

Target: **A**ndrogen **R**eceptor (**AR**)
Indication: Prostate Cancer
Inhibitor design: Natural product derivative and SAR (linker and E3 ligase ligand)
In vitro Activity: DC_{50} (Cellular) = Vcap-AR-FL (730 nM), Vcap-AR-V7 (670 nM)
ADME/PK: Liver Microsome Stability: $t_{1/2}$= 187.2/187.4 min (mouse/human); Plasma: %remaining @ 60 min = 90.8/91.9 (mouse/human); Oral bioavailability: %F = 40.5/69.3% (mouse/beagle); hERG Inhibition: IC_{50} > 10 µM.
In vivo: Tumor growth inhibition in a mouse xenograft model (mouse; 60 mg/kg; po)

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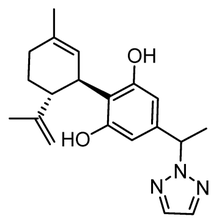
Key Laboratory of Marine Drugs, China



CIAC001 **PKM2** **Opioid Addiction**

Target: **P**yruvate **K**inase **M2** (**PKM2**)
Indication: Opioid Addiction (Morphine)
Inhibitor design: Natural product derivative and SAR
In vitro Activity: IC_{50} BV2 cells = 2.5 µM, CTX in BV2 = 57.8 µM, Therapeutic Index = 23.1, CETSA ΔTm = 3.9 ± 1.3 °C
ADME/PK: Mouse (10 mg/kg, p.o.): C_{max} = 175 ng/mg, $T_{1/2}$ = 0.8 h, MRT = 0.9 h. (in brain)
In vivo: Mouse (0.2 mg/kg, i.p.): Reduction in naloxone-precipitated morphine withdrawal behavior (80% decrease). Suppression of morphine-induced behavioral sensitization (on par with negative control).

J. Med. Chem.
Multiple Contributors, China

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