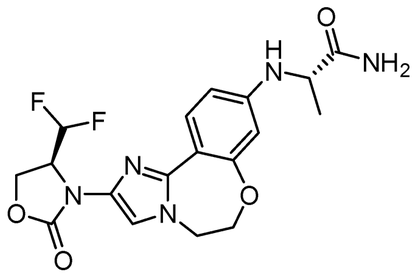
Small Molecule Highlights

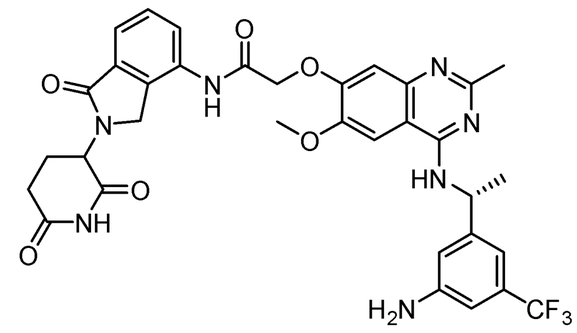
Snapshots from Recent Literature in Target-oriented Drug Design



GDC-0077 **p110α/PI3Kα** **Oncology**

Phosphatidylinositol 3-kinase (PI3K) inhibitor/p110*α* degrader
p110*α*: Catalytic unit of PI3K, ATP-competitive benzoxazepine
PI3K K_i α/β/γ/δ = 0.034/99.7/18.2/12.2 nM (>300-fold), LLE = 7.4
Crystal with p110*α* (8EXV), Novel H-bonds (-CHF_2- Ser774)
HCC1954 pPRAS40 EC_{50} = 19 nM, Mouse $(F)_{p.o.}$ = 58% (50 mg/kg)
Active in HCC1954 *PIK3CA*-mut BC xenograft (TGI = 149%)

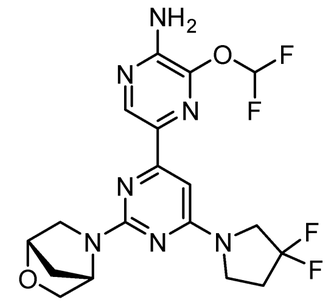
J. Med. Chem.
Genentech/Charles River, USA



P7 **SOS1** **Oncology**

Son of sevenless homolog 1 (SOS1) degrader (*KRAS*^{mut} CRC)
SBDD: Cereblon/SOS1 co-crystal, Lenalidomide E3 ligase
SOS1 $\%_{Deg}$ (1 μM, 6 hrs) SW620 (CRC) = 64% (to 92%, 48 hrs)
SW620 Proteomics (1 μM, 24 hrs): ABCG1 (up) SOS1 (down)
SOS1 degradation in PDO (1 μM, 24 hrs) (Improv. to BI3406)
No cytotoxicity in HPNE cells (healthy cells) (up to 100 μM)

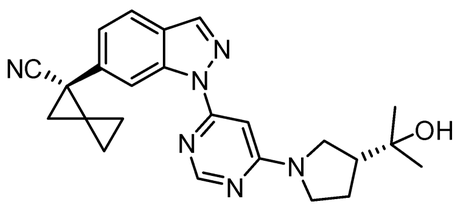
J. Med. Chem.
UCF/HLMCC, USA



DN-1289 **DLK/LZK** **Neurology**

Dual leucine zipper kinase/Leucine zipper-bearing kinase inhibitor
Role: neuronal degeneration/amyotrophic lateral sclerosis (ALS)
DLK/LZK IC_{50} = 17/40 nM, DLK p-c-Jun/LZK p-c-Jun EC_{50} = 88/711 nM
Co-crystal of analog shows interactions with hinge/P-loop (8DEG)
In vivo PK_{rat}: $T_{1/2}$/% *F* (p.o., 3 mg/kg) = 4.6 hrs/52%, PK in mouse/cyno
Efficacy in an acute ONC model, and SOD-1 model of ALS

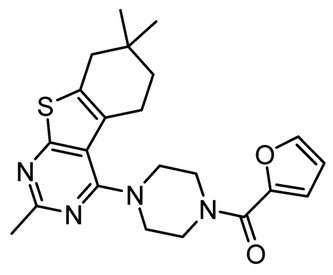
J. Med. Chem.
Denali Therapeutics, USA



Compound 25 **LRRK2** **Neurology**

Leucine-rich repeat kinase 2 (LRRK2) inhibitor (Parkinson's)
1-heteroaryl-1H-indazole (ATP-competitive), spiro[2.2]pentane motif
Crystal with LRRK2-CHK1 chimera (8E81): Spiro-nitrile (hydrophobic)
LRRK2 IC_{50} = 0.9 nM (kinase inhibition assay), $Cell_u$ IC_{50} = 0.3 nM
Acute PK/PD study, decrease in LRRK2 pS935 (EC_{50} = 0.18 nM)
Negative AMES (5 strains), project human dose (45 mgs, $T_{1/2}$ = 16 hrs)

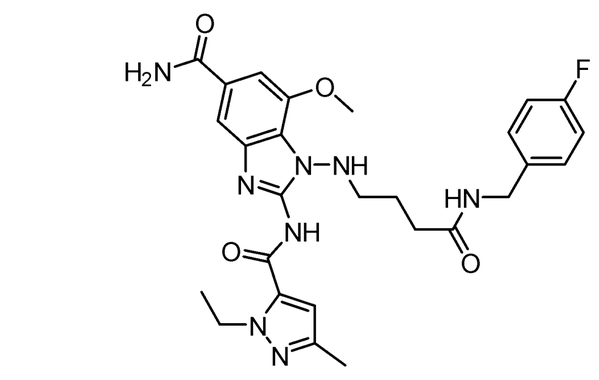
J. Med. Chem.
Merck, USA



Compound 24 **GPR55** **Oncology/Neurology**

G-protein coupled receptor 55 (GPR55) inhibitor (orphan GPCR)
Thienopyrimidine (based on GPR55 antagonist ML192 via HTS)
β-arrestin recruitment assay (CHO cells) IC_{50} = 0.28 μM
Molecular docking suggest hydrophobic interactions (di-Me)
Limited affinity against CB1/CB2 (at 4 μM) in comp. binding assay
Weak GPR55 inverse agonist (SRE assay)/GPR55 antagonist (+LPI)

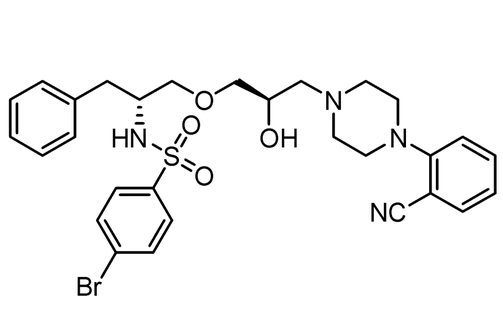
ACS Med. Chem. Lett.
CSIC/UNC, Spain/USA



Compound 72 **STING** **Oncology**

Stimulator of interferon genes (STING) agonist
THP1 STING EC_{50} = 1.58 μM, THP1 STING-KO EC_{50} > 100 μM
THP1-Dual STING MTS, THP1-Dual STING-KO MTS > 100 μM
Rat blood plasma stability, % rem: 78.7% (1 hr), 60.5% (2 hr)
STING-TBK1-IRF3 signaling: pSTING (Ser366), Increased IFN-β
High selectivity for *h*STING vs. *m*STING (secreted luciferase reporter)

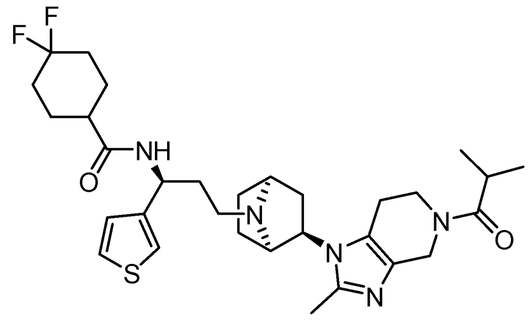
Eur. J. Med. Chem.
CAMS/PUMC, China



B1a **CatL/CatS** **Oncology**

Cathepsin L (CatL)/Cathepsin S (CatS) dual inhibitor
Dual strategy: Anti-metastatic effects in BxPC-3/PANC-1 cells
Design via scaffold-hopping (24 analogs) vs. ASPER-29
CatL/CatS/CatK IC_{50} = 4.10/1.79/100 μM, B1a stereochem (*R, R*)
Anti-metastasis: Wound-healing/transwell chamber assays

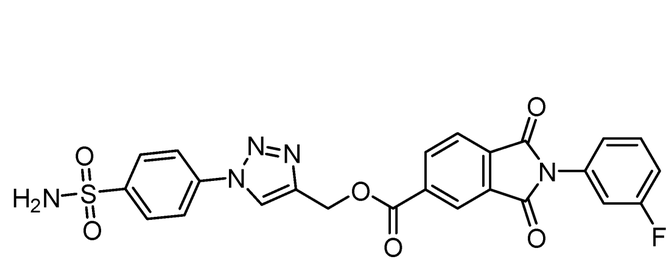
Bioorg. Med. Chem. Lett.
SPU, China



Compound 25 **CCR5** **Anti-viral**

C-C chemokine receptor 5 (CCR5) antagonist (Tropane linker)
CCR5 antagonism: Anti-HIV-1 strategy (Maraviroc, FDA approved Std.)
CCR5 binding activity (HEK293) IC_{50} = 8.34 nM (Equipotent Maraviroc)
HIV-1 Ba-L/YU-2/SF162/KIZ001/KIZ006 EC_{50} = 16.9/8.7/15.9/7.8/12.6 nM
CCR5-Tropic Integrase resistant strain HIV-$1_{YU-2\ (G140S/Q148H)}$ EC_{50} = 4.34 nM
PK SD rats (10 mg/kg)$_{P.o.}$ = $T_{1/2}$/T_{max}/MRT/% *F* = 10.3 hrs/2.0 hrs/13.2 hrs/15.7 %

J. Med. Chem.
CAMS, China



Compound 7e ***h*CA** **Oncology**

α-carbonic anhydrase (*hCA)* inhibitor (1,2,3-triazole benzenesulfonamide)
Inhibitor design: Hybridization with 1,3-dioxoisoindoline-5-carboxylate
*h*CA I/II/IV/IX/XII K_i IC_{50} = 48.1/9.72/18.28/22.85/19.72 nM (improve. vs. AAZ)
Modelling with *h*CA II (PDB 3HS4): H-bonds, pi-pi stacking (Thr, Gly, Phe, Zn^{2+})

Bioorg. Med. Chem.
Sakarya/Anadolu University, Turkey

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