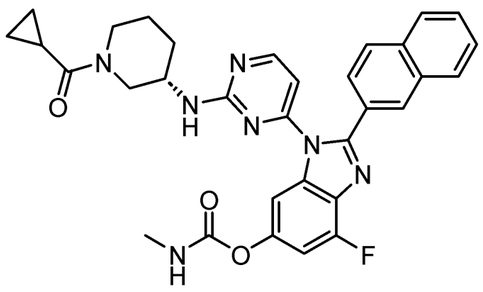
Small Molecule Highlights

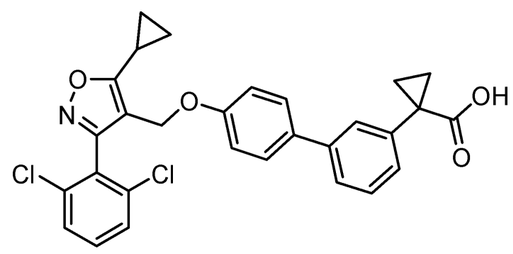
Snapshots from Recent Literature in Target-oriented Drug Design



Compound 3h **JNK3** **Neurology**

N-monomethyl carbamate c-Jun N-terminal kinase 3 inhibitor (JNK3)
JNK3/Alzheimer's (AD) via APP, $A\beta_{42}$, AMPK, Tau = Neuronal cell death
Inhibitor design: Pharmacodynamic-focused structure optimizations
In vitro kinase activity JNK1, JNK2, JNK3 IC_{50} = >10,000, 2202, 21 nM
Induced fit docking (H-bonds): Lys68, Met149, Gln155, H_2O (PDB 4KKH)
Neuroprotection in cells, Efficacy in 3xTg mice (restore cognitive function)

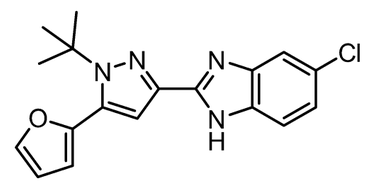
J. Med. Chem.
CPHU/Samjin Pharma, South Korea



ZLY28 **FXR/FABP1** **Metabolism**

First-in-Class intestinal restricted FXR/FABP1 dual modulator
FXR/FABP1: Drug targets for nonalcoholic steatohepatitis (NASH)
Inhibitor design: Comprehensive multi-parameter optimizations
FXR FRET IC_{50} = 143 nM, Cell-based IC_{50} = 491 nM, FABP1 IC_{50} = 2.7 μM
LM % rem. mouse, rat, beagle, human (at 1 hr) = 64.3, 68.6, 57.4, 71.6 %
Efficacy in histological, and *in vivo* NASH models/liver lipid metabolism

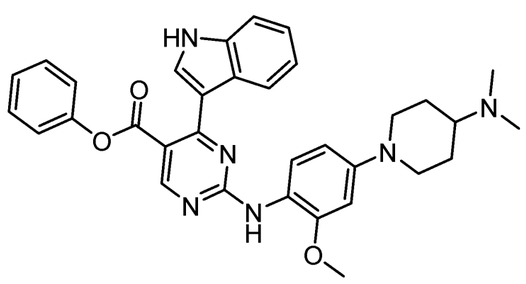
J. Med. Chem.
GPU, China



Compound 50 **$P2Y_6R$** **Inflammation**

Pyrazole benzimidazole-based selective $P2Y_6R$ antagonist
$P2Y_6R$: Inflammatory disease (Ulcerative colitis/Acute lung injury)
Inhibitor design: MD, virtual screen (50K), SBDD towards HitID
$P2Y_6R$ % Inh. (1 μM) = 132.71%, IC_{50} = 5.91 nM (5x Improv. MRS2578)
Docking Interactions: Asp179, Leu180, Pro183, Tyr262, Leu263, Tyr283
In vivo efficacy in DSS-induced ulcerative colitis/LPS-induced ALI models

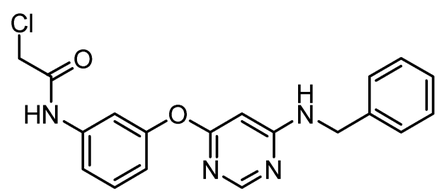
J. Med. Chem.
SU/CPU, China



Compound 13 **EGFR** **Oncology**

Reversible aminopyrimidine as double-mutant $EGFR^{L858R/C797S}$ inhibitor
Rationale: Address Osimertinib resistance due to $EGFR^{L858R/C797S}$ mutations
Inhibitor design: Structure-based strategy (targeting hydrophobic back pocket)
HTRF $EGFR^{WT}$, $EGFR^{L858R/C797S}$, $EGFR^{L858R/C797S/T790M}$ IC_{50} = 0.008, 0.020, 0.64 nM
Cell activity $EGFR^{WT}$ A431 IC_{50} = 1837 nM, $EGFR^{L858R/C797S}$ Ba/F3 IC_{50} = 7.1 nM
Co-crystal $EGFR^{T790M/V948R}$ PDB 7ZYQ: Gln791, Met793, hydrophobic interactions

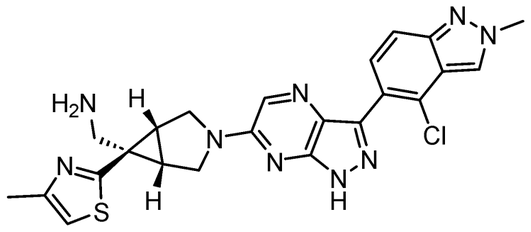
J. Med. Chem.
DDHD/ZIW, Germany



DK-2403 **MAP2K7** **Oncology**

Covalent, selective MAP2K7 inhibitor (chloroacetamide E+)
MAP2K7: Pediatric T-cell acute lymphoblastic leukemia (T-ALL)
Inhibitor design: Structure-based , One-pot synthesis, Cys218
MAP2K7 ADP Glo-assay IC_{50} = 10 nM (no pre-incubation, IC_{50} = 93 nM)
Selectivity across 90 kinases (wild-type), 1 off-target: EGFR (at 1 μM)
Cell activity KOPT-K1, ALL-SIL IC_{50} = 2.8, 1.1 μM (persisted post wash-out)

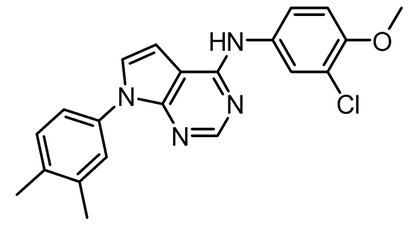
ACS Med. Chem. Lett.
Northwestern University, USA



Compound 25 **SHP2** **Oncology**

Allosteric SH2-protein tyrosine phosphatase inhibitor (bicyclo[3.1.0]hexane)
SHP2: Nonreceptor PTPase, roles in Ras/MAPK, JAK/STAT, PI3K/AKT (oncology)
Inhibitor design: Ligand-based strategies (pyrazopyrazines conformational analysis)
In vitro SHP2 IC_{50} = 5 nM, pERK SHP2 IC_{50} = 25 nM, hERG (Tox.) IC_{50} >30 μM
In vivo PK (SD rats, 1 mg/kg, p.o.): $T_{1/2}$, *F* % , C_{Max} = 1.9 hrs, 1.2%, 0.01 μM
P-gp substrate (in rats), likely responsible for poor oral bioavailability

ACS Med. Chem. Lett.
IRBM/Promidis, Italy



ARUK2002821 **PI5P4Kα** **Oncology**

Pyrrolopyrimidine phosphatidylinositol 5-phosphate 4-kinase inhibitor
PI5P4K: Roles in cancer, neurodegeneration, immunology (+ PIP/PIP_2)
Inhibitor design: Virtual screen/Scaffold-hopping strategy (known PI5P4Ki)
ADP-glo assay PI5P4Kα pIC_{50} = 8.0, PI5P4Kγ+ pIC_{50} <4.7 (XlogP = 5.8)
InCELL Pulse (Cell Target Eng.) PI5P4Kα pIC_{50} = 6.6, MLM $T_{1/2}$ = 11 mins
Co-crystal structure with PI5P4Kα (PDB 8C8C) + conformational analysis

RSC Med. Chem.
University of Cambridge, UK

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