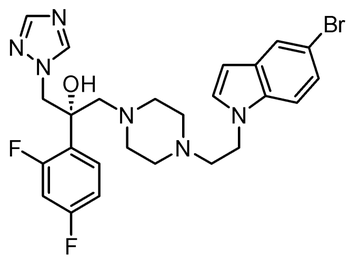
Small Molecule Highlights

Snapshots from Recent Literature in Target-oriented Drug Design



S-F24 **CYP51** **Anti-fungal**

Triazole-based fluconazole-core inhibitor of CYP51 (*Candida albicans*)
Inhibitor design: Scaffold-hopping + structure-based strategies (PDB 5TZ1)
MIC_{80} (μg/mL) C. gui, C.par, C. tro, C. alb = 0.015, 0.008, 0.156, 0.015
Efficacy: ICR model of *C. albicans* infection (5 mg/kg, low resistance susceptibility)
In vivo anti-fungal efficacy in skin models of *C. albicans* (+ histological analysis)

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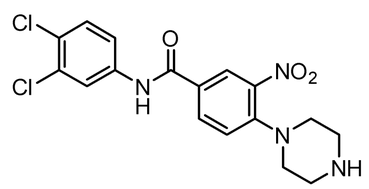
China Pharmaceutical University, China



Compound 79 ***L. mexicana*** **Anti-parasitic**

2,4,5-trisubstituted benzamide as anti-leishmanial scaffold (piperazine-handle)
Inhibitor design: Scaffold-hopping, solubility/bioavailability-focused, phenotypic
L. mexicana EC_{50} = 0.66 μM, LipE = 3.72, Aq. Sol. = 45 μM, $T_{1/2}$ MLM = 114.8 mins
BJ cells EC_{50} = 15.0 μM, $Cl_{int.}$ = 12 mL/min/kg, *F* % (10 mg/kg, p.o.) = 80%
In vivo efficacy in Balb/c mice models (infected with *L. mexicana*) (50 mg/kg, p.o.)

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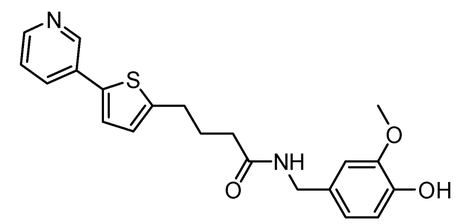

Compound 3a **TRPV1** **Anti-nociceptive**

4-(thiophen-2-yl) based transient receptor potential vanilloid Type-1 agonist
TRPV1: Target for pain, inflammation, pathophysiology via sensory neurons (nociception)
Inhibitor-design: *In silico*-guided structure-based strategy (MM, GBSA, MIFs)
MM/GBSA ΔG_{bind} = -67.72 kcal/mol (key π-π interactions + H-bond networks)
TRPV1 EC_{50} = 76.4 nM, IC_{50} = 145 nM, TRPV1 Efficacy = 90 %, TRPA1 Efficacy < 10%
Efficacy in formalin test in mice (nociceptive response, 0.15 μg/paw, 30 μL)

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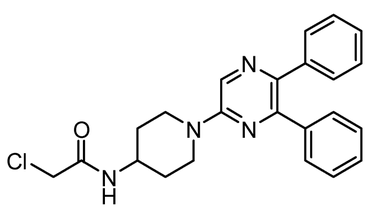

Compound 14i **Skp2** **Oncology**

1,3-Diphenylpyrazine S-phase kinase-associated protein 2 inhibitor
Skp2: Cullin-RING ligases (Ubiquitin-proteosome system, oncogenesis)
Inhibitor design: 2K HTS via HTRF screens + structure-based strategies
Skp2-Cks1 binding IC_{50} = 2.8 μM (Chloroacetamide E+, potential covalent)
MGC-803, MCF-7, EC-1, PC-3, NCI-H1299 IC_{50} = 7.0, 4.4, 7.0, 4.8, 7.1 μM
In vivo efficacy PC-3 xenograft model (50 mg/kg, i.g.) (rel. to paclitaxel)

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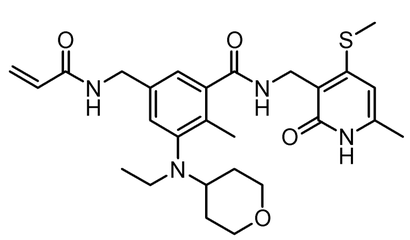

BBDDL2059 **EZH2** **Oncology**

Pyridone-based non-competitive enhancer of zeste homologue 2 inhibitor
EZH2: Cat. Subunit of PRC2 (SAM $–CH_3$ to H3K27) – transcription/cancer progression
Inhibitor design: Scaffold-hopping + structure-based strategy (Acrylamide E+ Cys663)
EZH2 (Y641F) IC_{50} = 1.5 nM, KARPAS422 IC_{50} = 64 nM, HLM $T_{1/2}$ = 33.8 mins
Covalency: IP-MS (Cys modification), Western-blots (+ wash-outs), CADD analysis
Kinetic binding experiments: Non-competitive with cofactor S-adenosylmethionine
Lymphoma cell lines (potent): Pfeiffer, KARPAS422, SU-DHL-10, RL, HT (IC_{50} < 1 μM)

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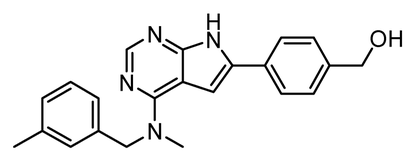

Compound 23 **CSF1R** **Oncology**

Pyrrolo[2,3-d]pyrimidine-based Colony-stimulating factor-1 receptor inhibitor
CSF1R: Receptor tyrosine kinase (tissue-resident macrophages + cancer progression)
Inhibitor design: Ligand-based strategies + co-crystal analysis (CSF1R, PDB 8CGC)
CSF1R IC_{50} = 0.5 nM, CSF1R LANCE (ATP 25 μM) IC_{50} < 3 nM, EGFR IC_{50} = 133 nM
Non-autoinhibited CSF1R K_d = 320 nM, autoinhibited CSF1R K_d = 26 nM
HLM/MLM Cl_{int} = 15.5/40 μL/min/mg, Plasma % remaining at 5.0 μM = 69%

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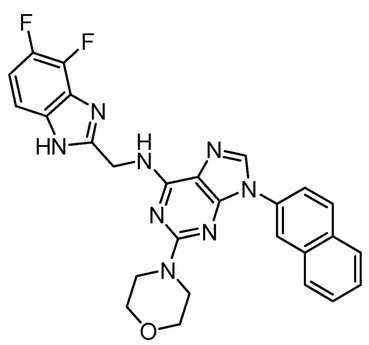

SR-4133 **CK1** **Oncology**

Pyrimidine-based Casein kinase 1 inhibitor (CK1δ vs. CK1ε, 97% sequence identity)
CK1: Ser/Thr kinases, signaling pathways (Wnt/β-catenin + more) (cancer progression)
Inhibitor Design: Structure-based strategy + scaffold hopping (CK1δ–SR-3029 6RCG)
CK1δ IC_{50} >1000 nM, CK1ε IC_{50} = 58 nM (>172-fold selectivity), activity in UM-UC-3/T24
Bladder cancer lines T24, 5637, UM-C-3 EC_{50} = 265, 314, 540 nM (+Western-blot analysis)

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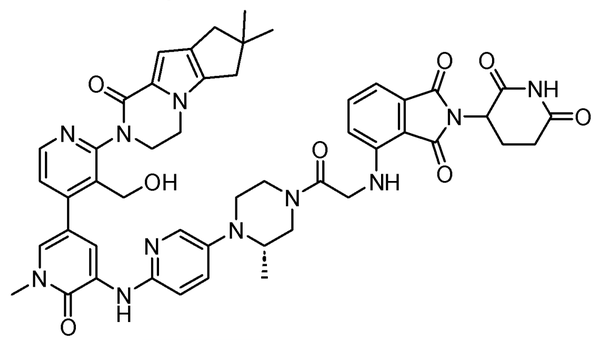

PTD10 **BTK** **Oncology**

Proteolysis targeting chimera (PROTAC) degrader of Bruton's tyrosine kinase
BTK: Nonreceptor tyrosine kinase (Tec, BCR) in B-cell malignancies (CLL, MCL, DLBCL)
PROTAC design: Scaffold-hopping (Fenebrutinib) + linker opt. + Pomalidomide (CRBN)
BTK Ramos cells DC_{50} = 0.5 nM, JeKo-1 cells DC_{50} = 0.6 nM (+ Western-blot analysis)
BTK K_d = 2.28 nM, BTK IC_{50} = 97 nM, CRBN IC_{50} = 107 nM (+ live cell target engagement)
Induction of apoptosis (BTK degradation), BTK-selective vs. CSK, SYK, HCK, and LYN

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