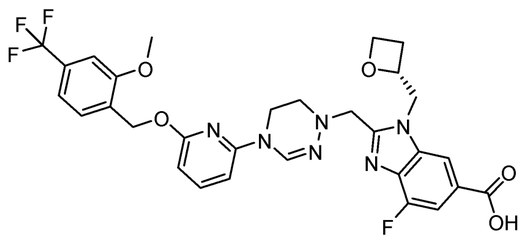
Small Molecule Highlights

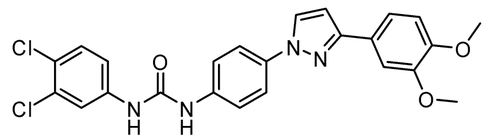
Snapshots from Recent Literature in Target-oriented Drug Design



Compound 42 **GLP-1R** **Metabolism**

Dihydro-1,2,4-triazine glucagon-like peptide-1 receptor agonist
GLP-1R: Incretin (metabolic hormone) implicated in type 2 diabetes (T2DM)
Inhibitor design: Opt. of Danuglipron (hERG liabilities) + structure-based (SBDD)
HEK293 (hGLP-1R) cAMP assay EC_{50} = 6 pM, hERG IC_{50} > 40 μM (largely inactive)
In vivo PK (5 mg/kg, p.o. rats): $T_{1/2}$, T_{Max} , C_{Max} = 1.05 hrs, 0.25 hrs, 130 ng/mL
Efficacy in OGTT study in hGLP-1R KI mice (1mg/kg, o.g.) + reduced food intake

J. Med. Chem.
CAMS, China



Compound 7a **VRSA/TB** **Anti-microbial**

Urea-based 3,4-dichlorophenyl pyrazole as *S. aureus* inhibitor
MRSA, VRSA, TB, MDR-TB, XDR-TB (*S. aureus* + *M. tuberculosis*)
Inhibitor design: Ligand-based strategies + scaffold hopping (privileged azoles)
S. Aureus ATCC 29213 MIC = 0.25 μg/mL, Mtb H37Rv ATCC 27294 = 32 μg/mL
Active against MSSA, MRSA (9 strains), VRSA (3 strains), average MIC = 0.25 μg/mL
HLM $T_{1/2}$ = 1.8 hrs, aq. solubility (phosphate buffer, pH 7.4) = 0.005 mg/mL

RSC Med. Chem.
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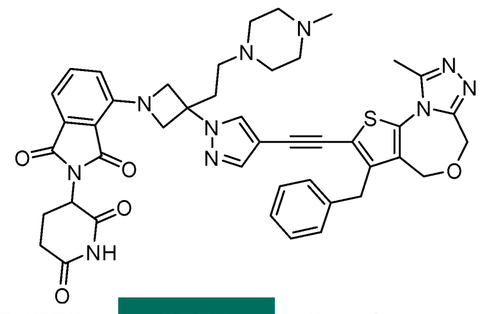

BD-9136 **BRD4** **Oncology**

Tricyclic acetylene-based BET targeting PROTAC (Pomalidomide-CRBN)
BRD4: BET domain protein (histone readers, transcription regulators)
Inhibitor design: Conformational opt. of panBETi QCA276 + Linker opt.
MV-4-11, MOLM13, HL60, RS4;11 BRD4 DC_{50} = 4.7, 1.5, 0.5, 0.7 nM
MV-4-11, MOLM13, HL60 IC_{50} = 11, 69, 5.1 nM (Protein abundance Chemoprot.)
In vivo efficacy in MV-4-11 and MD-MB-231 tumour models (TGI = 92%, 87%)

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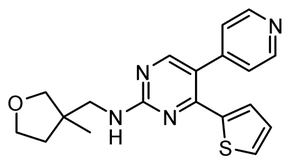

Compound 28c **A_1R** **Oncology**

3-methyl-tetrahydrofuran pyrimidine A_1 adenosine receptor inhibitor
A_1R: GPCR, signals via $G_{i/o}$ proteins (implicated in various diseases)
Inhibitor design: Virtual screen (4.6 million) + structure-based optimizations
Docking (PDB 5UEN): Interactions with His, Asn, Phe, Thr, Glu (H-bond networks)
A_1R pK_d = 8.64, A_2R pK_d = 6.76 (1.88 unit selectivity), K_d (A_1R) = 2 nM

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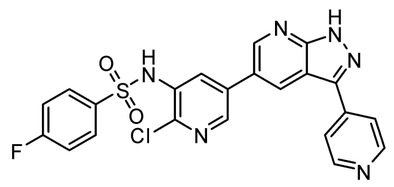

FD274 **PI3K/mTOR** **Oncology**

7-azaindole based PI3K/mTOR dual inhibitors (AML-focused molecule)
PI3K/mTOR: Strong signal transduction kinases, implicated in blood cancers
Inhibitor design: Structural opt. of FD223 + scaffold-hopping + dual-focused potency
PI3Kα, β, γ, δ IC_{50} = 0.7 nM, 1.6 nM, 0.7 nM, 0.4 nM, mTOR IC_{50} = 2 nM (10x improve.)
LLE PI3K/mTOR = 5.90/5.21, HL-60, MOLM-13, MV-4-11 IC_{50} = 84 nM, 53 nM, 92 nM
In vivo efficacy in HL-60 tumour xenografts (10 mg/kg, i.p.), TGI = 91%

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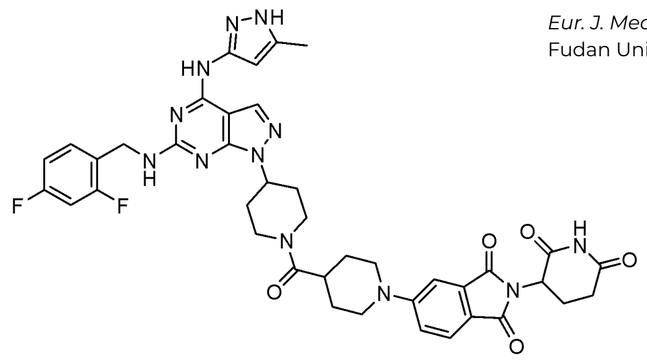
Fudan University, China



SP27 **PLK4** **Oncology**

Pyrimidine-2,4-difluorobenzylamine based Polo-like kinase 4 PROTAC (CRBN)
PLK4: Master regulator (centriole replication) + disease + *TRIM37*-Breast cancer
Inhibitor design: CZS-035 PLK4i + Linker optimization + (CRBN E3 ligase targeting group)
Affinity PLK4 IC_{50} = 8.4 nM, MCF-7 DC_{50} = 19.5 nM (IC_{50} = 73 nM) (piperidine link.)
Activity in clonogenic + FACS apoptosis assay, Wound-healing + Chemoproteomics
PK (2 mg/kg, i.v.), $T_{1/2}$, MRT, *F* = 5.34 hrs, 2.29 hrs, 149% (Inactive against CYPs)
In vivo efficacy in MCF-7 xenograft models (20 mg/kg, i.p.), TGI = 73.7%

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