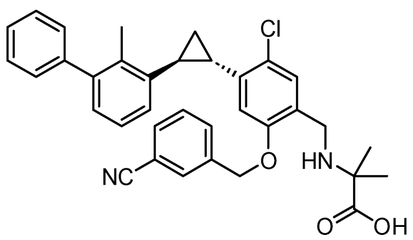
Small Molecule Highlights

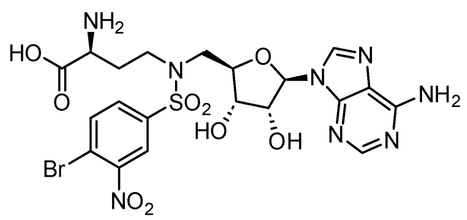
Snapshots from Recent Literature in Target-oriented Drug Design



A25 **PD-1/PD-L1** **Oncology**

Biphenyl-based Programmed Cell Death/Ligand 1 (PD-1/PD-L1) inhibitor
Inhibitor design: Optimized stereochemistry (1*S*, 2*S*) via critical -cPr motif
Inhibition of PD-1/PD-L1 interaction (HTRF) IC_{50} = 29 nM, (SPR) K_D = 155 nM
In vivo pharmacokinetics (10 mg/kg, p.o.): $T_{1/2}$, T_{Max}, % *F* = 3.45 hrs, 3.00 hrs, 21.58%
In vivo efficacy (LLC1 lung carcinoma mouse model, 30 m/kg, i.p.), TGI = 56.91%

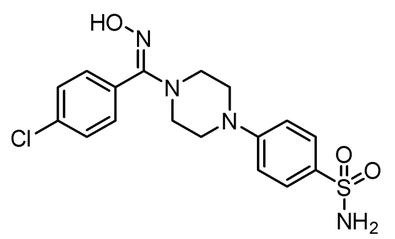
J. Med. Chem.
SYSU, China



Compound 80 **DNMT2** **Oncology**

Covalent S-Adenosylhomocysteine-Based DNA Methyltransferase 2 Inhibitor
DNMT2: RNA modifying enzyme (implicated in metabolic disease, cancer)
Inhibitor design: Ligand-based strategy (*Topliss scheme*) + non-covalent std.
MST K_D^{app} = 2.3 µM, ITC K_D^{app} = 4.9 µM, ^{3}H assay IC_{50} = 1.2 µM (Cys79 – Aryl-Br E+)
Intact-mass : hDNMT2Δ + RNA methyltransferase inhibition, >99% Inh. (100 µM)

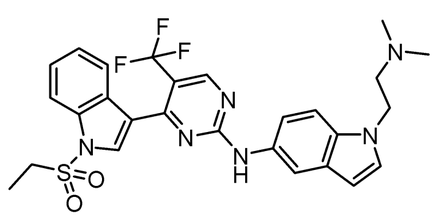
J. Med. Chem.
JGU, Germany



Compound 30 **hCA IX/XII** **Oncology**

Piperazine-based benzenesulfonamide human Carbonic Anhydrase IX/XII inhibitor
hCA (EC 4.2.1.1): Implicated in epilepsy, edema, glaucoma, obesity, and cancer
Inhibitor design: SBDD/Scaffold-hopping (SLC-0111 + hydroxyimino of Psammaplin C)
hCA I, II, IX, XII K_i = 3.5, 9.4, 43, 8.2 nM, SI vs. hCA XI/I = 12.3x, IX/II = 4.6x, XII/I = 2.3x
Physicochemical scores: MW, MlogP, HBD, HBA, BBB = 394.88, 2.11, 2, 5, No (0.55 BS)

ACS Med. Chem. Lett.
University of Florence, Italy



D51 **EGFR** **Oncology**

4th generation pyrimidine-based triple-mutant $EGFR^{L858R/T790M/C797S}$ inhibitor
Inhibitor design: LBDD/SBDD (overcoming Osimertinib-EGFR mutant resistance)
$EGFR^{WT}$ IC_{50} > 5 µM, $EGFR^{L858R/T790M/C797S}$ IC_{50} = 14 nM, $EGFR^{del19}$ IC_{50} = 19 nM
BaF_3, H1975, BaF_3 ^{TM}, $H1975^{TM}$ IC_{50} = 641 nM, 96 nM, 26 nM, 14 nM (+FACS apoptosis)
In vivo efficacy in a $H1975^{L858R/T790M/C797S}$ mouse model (100 mg/kg, p.o.) TGI = 80%

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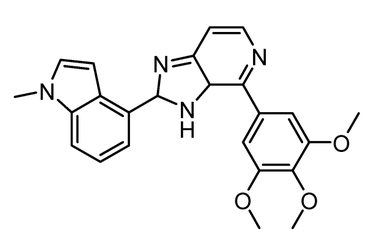

Compound 3a **Tubulin** **Oncology**

Bi-aryl Indole-based tubulin-targeting Colchicine-Binding Site Inhibitor (CBSI)
α/βTubulin: Cytoskeleton, cell motility, cell growth, oncogenesis, metastasis
Inhibitor design: structure-based (XRC PDB: 7DBA), scaffold-hopping/bioisosterism
MCF-7, B16-F10, HeLa, HePG-2 IC_{50} = 6 nM, 2 nM, 9 nM, 1 nM (Better than Colchicine)
Mechanistic studies: XRC (PDB 8HUH), FACS, Cell-cycle arrest (HepG-2), SPR K_D = 18.3 µM
In vivo inhibition B16-F10 melanoma growth (3a + PD-1/PD-L1i NP19, 5 mg/kg), TGI = 77.85%

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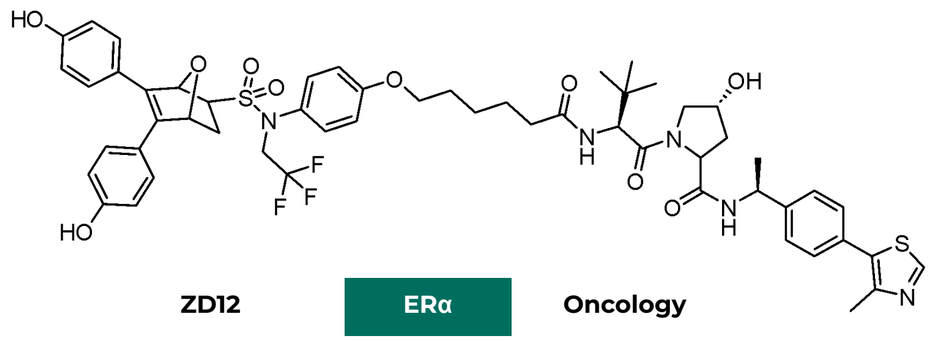

ZD12 **ERα** **Oncology**

Oxabicycloheptane sulfonamide-based PROTAC targeting Estrogen Receptor α
ERα: Estrogen-receptor positive breast cancer (ER^+ BC) (vs. endocrine resistance)
PROTAC design: Scaffold-hopping (SERDs, Elacestrant) + VHL E3 ligase + Linker opt.
RBA % ERα = 0.04 %, ERβ = 0.03 %, ERα K_i = 5.08 µM, Erβ K_i = 26.20 µM
Degradation of WT/Mutant ERα in ER^+ BC cell lines: MCF-7 (Ful as positive control)
Inhibition of nascent RNA synthesis of several ERα target genes: IGFBP4, GREB1

J. Med. Chem.
Wuhan University, China

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