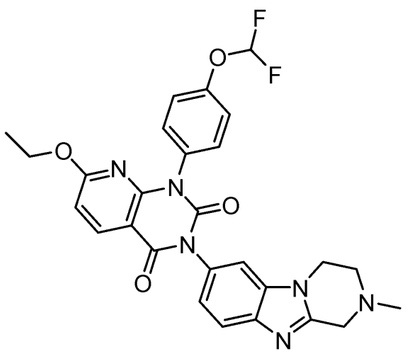
Small Molecule Highlights

Snapshots from Recent Literature in Target-oriented Drug Design



Compound 28 **MAT2A** **Oncology**

Benzoimidazopyrazine methionine adenosyltransferase 2A inhibitor
MAT2A: Metabolic enzyme, essential for cell-growth/survival (+SAM)
Inhibitor design: Follows tricyclic allosteric MAT2A inhibitors (Simcere-024)
MAT2A enzymatic inhibition IC_{50} = 26 nM, HCT-116 IC_{50} = 75 nM (MTAP -/-)
In vivo efficacy (50 mg/kg, i.g. QD), TGI = 52% (improv. clinical std. AG-270)

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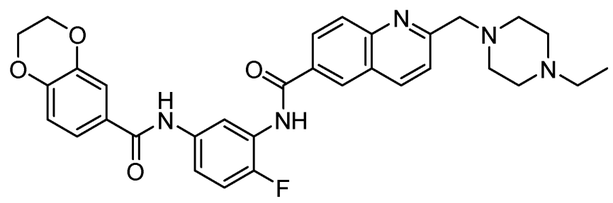
WUST/GU, China



CCT361814 **HSF1** **Oncology**

Fluoro bis-amide Heat shock transcription factor 1 (HSF1) inhibitor
HSF1: Heat-shock stress response, oncogenesis (Ovarian cancer)
Inhibitor design: Phenotypic screen towards clinical candidate
SK-OV-3 GI_{50} = 8.5 nM, pGI_{50} = 8.07, $CH1^{doxR/WT}$ = 1.8, KS = 50 μM
PK (mouse): 5 mg/kg (p.o.), T_{Max}, $T_{1/2}$, *F* % = 2.0 hrs, 4.0 hrs, 42%
In vivo efficacy (SK-OV-3, Ovarian cancer): 35 mg/kg (s.c.) (TGI = 120%)

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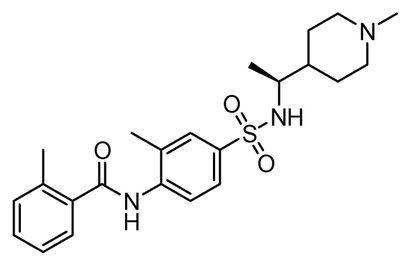

IPG7236 **CCR8** **Oncology**

Sulfonamide-based CC chemokine receptor 8 antagonist (oncology)
CCR8: Roles in T_{reg} recruitment (critical in tumor microenvironments)
Scaffold-hopping: Poor solubility/bioavailability naphthalene analog
Tango IC_{50} = 24 nM, Solubility = 254 μM, X-ray crystal of IPD obtained
MW/ClogP/tPSA = 429.58 g mol^{-1}/2.58/78.5 $Å^2$, hERG IC_{50} >30 μM
In vivo efficacy (MDA-MB-231 Xenografts): 50 mg/kg (i.v.), TGI = 55.6%

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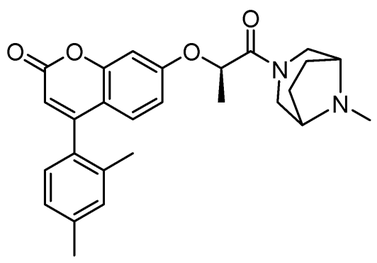

Compound D26 **POLRMT** **Oncology**

Coumarin-based human mitochondrial RNA polymerase inhibitor
POLRMT: Mitochondrial gene expression, Oxidative Phosphorylation
SBDD-based optimization of first-in-class POLMRMTi IMT1B (PK-focused)
IMT1B/D26 A2780 IC_{50} = 138/68 nM, D26 $Mitoch_{Transc}$ ND1 = 15% (at 500 nM)
D26 MDA-MB-468, DLD-1, HeLa, HepG2, A549 IC_{50} = 132, 69, 832, 152, 721 nM
In vivo efficacy A2780 tumors (50 mg/kg, p.o.), tumor weight reduced by 54.82%

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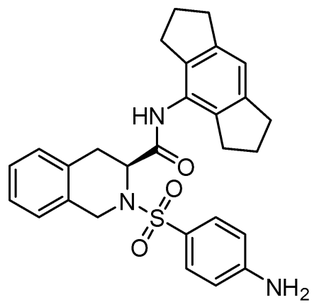

Compound 7n **NLRP3** **Oncology**

Aryl sulfonamide inhibitor of the NLRP3 inflammasome
NLRP3: Innate immunity (inflammasome-driven cancers)
Inhibitor design: Scaffold-hopping/SBDD from MCC950 (std. NLRP3i)
ELISA IL-β inhibitory rate (%) = 65.2 % (at a dose of 1 μM)
Suppression of caspase-1 activation, and IL-β secretion (THP-1 cells)
In vivo inhibition of NLRP3 inflammasome activation (C57BL/6 mice)

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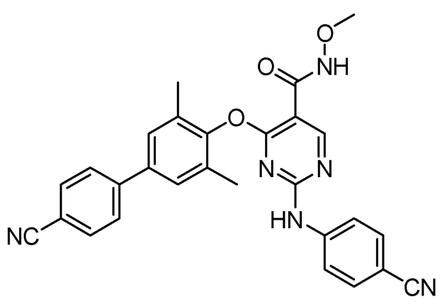

Compound 8r **NNRTI** **Anti-viral**

Biphenyl-DAPY based Non-Nucleoside Reverse Transcriptase inhibitor
NNRTI: Antiretroviral therapy, targets viral life cycle (anti-HIV/AIDS)
Inhibitor design: Carboxamide-based fragment-hopping/FBDD of previous NNRTI
MT-4 cells EC_{50} (HIV cytopathogenicity) = 2.3 nM (WT), Normal MT-4 CC_{50} > 40 μM
HIV-1 mutants L100I, K103N, Y181C, Y188L, E138K EC_{50} = 13, 8, 29, 52, 6 nM
In vivo tox.: No marked pathological damage (brain, liver, heart, spleen, lung, kidney)

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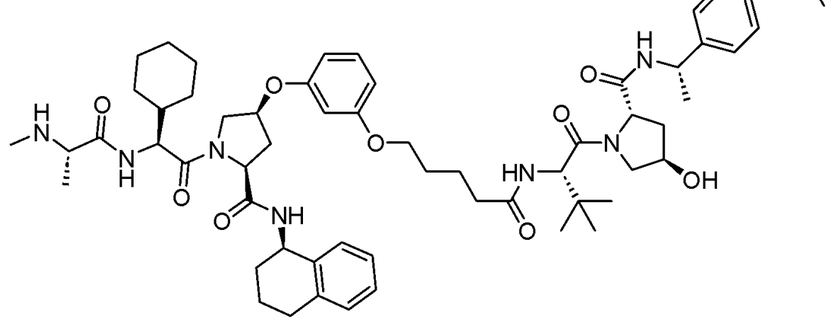

Compound 9 **IAP** **Oncology**

Bi-functional hetero-PROTAC, as pan-degrader of inhibitor of apoptosis proteins
E3 ligase cross-talk: Potent induction of pan-IAP degradation (MM.1S cells)
Degradation profile: cIAP1, cIAP2, XIAP, VHL30, CRBN, and IKZF3 levels (potent)
diaPASEF quantitative LC-MS/MS proteomics: Selectivity for cIAP1, XIAP (100 nM, 3 hrs)
NCI-H929, MOLM13, SUDHL6, DB, K562 IC_{50} = 8.5, 2.1, 1.6, 460, 420 nM (MM, AML, DLBCL)

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University of Bonn, Germany

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