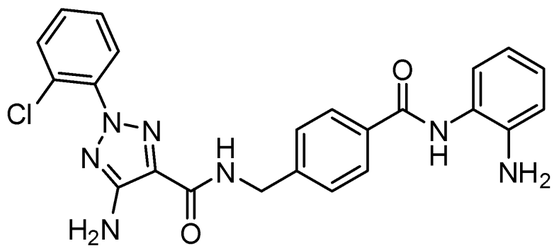
Small Molecule Highlights

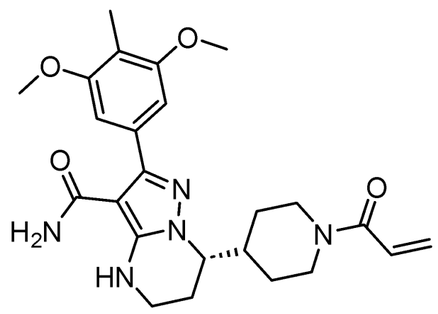
Snapshots from Recent Literature in Target-oriented Drug Design



Compound 19h **HDAC** **Oncology**

Triazole-based histone deacetylase (HDAC) inhibitor (Class I selective)
Inhibitor Design: Structural screen of various surface cap groups
HDAC1, HDAC2, HDAC3 IC_{50} = 47, 125, 450 nM, HDAC4-11 IC_{50} > 10 μM
Anti-proliferative activity: MC38, HCT116, A549, PC-9, ES-2, DoHH2
MOA: HDACi results in cell cycle arrest, and induces apoptosis (FACS)
In vivo efficacy in both MC38, and HCT116 Xenograft models (TGI > 80%)

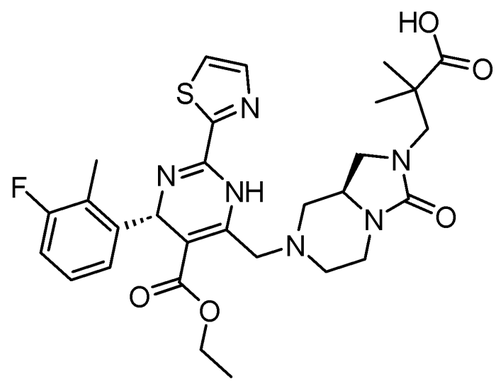
J. Med. Chem.
SIAIS/XMU, China



BGB-8035 **BTK** **Oncology**

Covalent inhibitor of Bruton's Tyrosine Kinase (BTK)
Structural optimization of Zanubrutinib (Selectivity, Kinase DFG-out)
Covalent mechanism: Standard acrylamide electrophile (Cys481, BTK)
BTK, EGFR, TEC IC_{50} = 1.1, 621, 99 nM (Off-targets: TXK, NLK, BMX)
Cellular p223-BTK IC_{50} = 14 nM, pEGFR IC_{50} > 10 μM, pTEC IC_{50} = 223 nM
In vivo efficacy in REC-1 Xenografts (TGI = 79%) and a CIA rat model

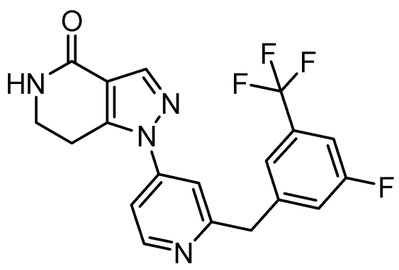
J. Med. Chem.
BeiGene, China



RG7907 **HBV** **Antiviral**

Hepatitis B Virus (HBV) core protein allosteric modulator (anti-viral)
Structural core: Hetero-aryldihydropyrimidine (Derivatization of HAP_R01)
HBV DNA (HepG.2.2.15) EC_{50} = 6 nM, HepDE19 cells CC_{50} > 100 μM, LogD = 1.75
Co-crystal structural determination of Cp149 Y132A: PDB 8I71 (Trp125, H_2O)
In vivo PK characterization: Rat, monkey, minipig (oral bioavailability observed)
In vivo Efficacy in adeno-associated virus-HBV mouse model (20 mg/kg, q.d.)

J. Med. Chem.
CICoR, Roche, China



HTL0041178 **GPR52** **Neurology**

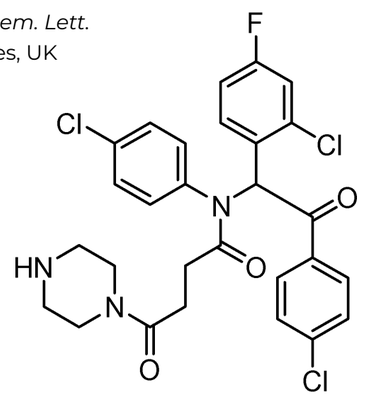
GPR52 agonist (Lactam-pyrrolo core), identified via FBDD
GPR52: orphan G-αs G protein-coupled receptor, GPCR (D1/D2)
cLogP, tPSA, GPR52 pEC_{50}, Chrom. LLE = 3.1, 60 $Å^2$, 7.5, 3.6
Molecular docking studies: Superposition with c17 control analog
In vivo PK (3 mg/kg, p.o.): C_{Max} , *F*, F_{abs} % = 486 ng/mL, 95, 80%
Efficacy in *d*-amphetamine-induced hyperactivity/locomotion in rats

ACS. Med. Chem. Lett.
Sosei Heptares, UK

Compound 11 **DA/5-HT** **Neurology**

Multi-target arylpiperazine-based binder of aminergic GPCRs (anti-psychotic)
Polypharmacology: Antagonist of D2/5-HT2A, Agonist of 5-HT1A receptor
Structural optimization of D2AAK3 analog (Linker, aryl group derivatization)
D2, 5-HT1A, 5-HT2A K_i (Competitive-radio ligand binding) = 596, 56.6, 66.7 nM
5-HT2C, H1 K_i (Competitive-radio ligand binding) = 552, 1141 nM
5-HT1A Agonism (cAMP) EC_{50} = 160 nM, 5-HT2A Antagonism (IP) K_b = 96.4 nM

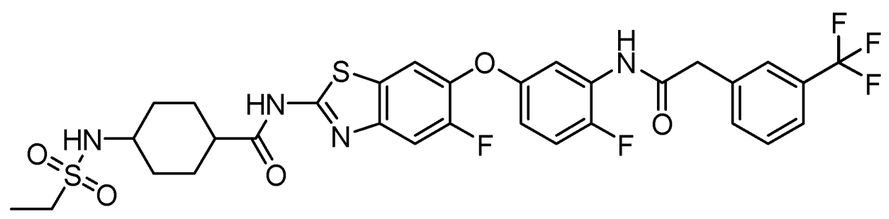
Eur. J. Med. Chem.
Medical University of Lublin, Poland



Compound C16 **p53-MDM2/MDMX** **Oncology**

α-aminoketone 4-ring dual inhibitor of p53-MDM2/MDMX
p53-MDM2/MDMX: Regulates p53 transcriptional response
Structural optimization: MDM2/MDMX K_i = 0.23/2.45 μM
Antiproliferative activity: HCT116/SH-SY5Y IC_{50} = 0.68/0.54 μM
MM/GBSA calculations of binding hot-spot residues of MDM2/MDMX
Inhibition of HCT116 migration/invasion + reactivation of p53 activity

Eur. J. Med. Chem.
NUCM/SUCM, China



SZM-1209 **RIPK1** **Respiratory**

Benzothiazole Receptor-Interacting Protein Kinase 1 (RIPK1) inhibitor
RIPK1: Target for Acute lung injury/acute respiratory distress syndrome (ALI/ARDS)
Inhibitor Design: Ligand based scaffold hopping (related necroptosis inhibitors)
Antinecroptosis EC_{50} = 22 nM, Cytotoxicity CC_{50} > 100 μM (Improve. TAK-632)
RIPK1 K_d = 85 nM, RIPK3 K_d > 10 μM (Recombinant protein) (>100x FS for RIPK1)
In vivo Anti-inflammatory effects of SZM-1209 in an NNK-induced ALI model

J. Med. Chem.
SMMU, China

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