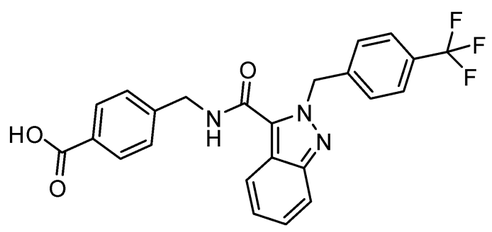
Small Molecule Highlights

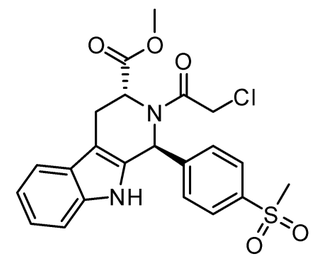
Snapshots from Recent Literature in Target-oriented Drug Design



Compound 14 **EP4** **Oncology**

2H-Indazole-3-carboxamide EP4 antagonist (immunotherapy, CRC)
EP4: Gα_s-GPCR, c-AMP pathways (PGE_2 immunosuppressive response)
hEP_4 IC_{50} (cAMP assay) = 1.1 nM, *h*EP1/EP2/EP3 IC_{50} > 10 μM
hEP_4 IC_{50} Ca^{2+} Flux, β-arrestin, CRE assays = 2.1 nM, 0.9 nM, 4.1 nM
HLM $T_{1/2}$ > 145 mins, CYPi > 50 μM, *F* % = 46.8% (5 mg/kg, p.o.)
In vivo efficacy in CT26 syngeneic tumor model (100 mg/kg, p.o.) (TGI = 76%)

J. Med. Chem.
ECNU, China



Compound 24 **GPX4** **Oncology**

Covalent glutathione peroxidase 4 (GPX4) inhibitor (Ferroptosis)
GPX4: Role in PLOOH (via Selenocysteine active site)/ROS generation
Chloroacetamide electrophile, targeting active site selenocysteine (Se)
Cell viability EC_{50} = 117 nM, *h*Plasma $T_{1/2}$ = 14 hrs, GSH $T_{1/2}$ = 1.3 hrs
PK (100 mg/kg): C_{Max} = 5.31 μg/mL, PAMPA = 3.1, Aq. Sol. = 13.8 μM (pH 7)
Engagement of kidney GPX4 and induction of PD markers in SCID/beige mice

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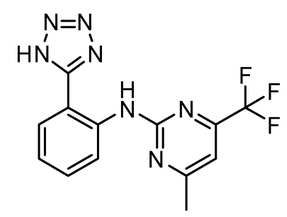

Compound 28.1 **TAS2R** **Neurology**

2-aminopyrimidine bitter taste receptor (TAS2R14) agonist
TAS2R14: GPCR with roles in bronchodilation (target for asthma/COPD)
Scaffold-hopping: Structural analogs of Flufenamic acid (NSAID Std.)
TAS2R14 activation, EC_{50} = 72 nM, E_{Max} = 129% (relative to Std.)
Molecular docking studies: Phe186, Phe243, Trp89 (Tetrazole, stacking)
Selectivity for TAS2R14: Relative to 24 relevant non-bitter taste receptors

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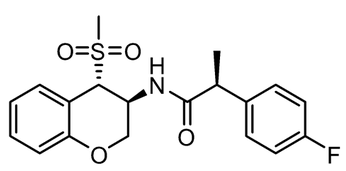
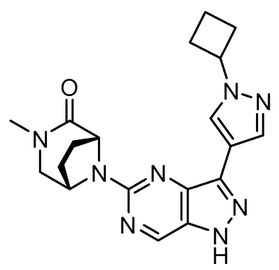


CVN636 **mGluR$_7$** **Neurology**

Chromane metabotropic glutamate receptor allosteric agonist
mGluR$_7$: CNS (pre-synapse of Glutamatergic/GABAergic terminals)
HTS of 650K = 3 rounds optimization = CVN636 EC_{50} = 7 nM (CNS-penetrant)
mGluR$_7$ EC_{50} = 7 nM (cAMP assay), PSA/MW = 72.5/377, cLogP = 2.06
PK (3 mg/kg, p.o.): $T_{1/2}$, T_{Max} , C_{Max} = 2.25 hrs, 0.67 hrs, 1.24 μM, *F* = 24 %
CVN636: Reduced ethanol self-administration in msP rats (*In vivo*)

ACS. Med. Chem. Lett.
Cerevance/Takeda, UK



Compound 19 **FGFR2/FGFR3** **Oncology**

Pyrazolo[4,3-d]pyrimidine fibroblast growth factor receptor inhibitor
FGFR Tyr kinase: Roles in PLCγ, PI3K-AKT, and RAS-MAPK signaling (oncology)
Repurposing ALKi: From IC_{50} = 0.98 nM to > 500 nM), *Hit*ID FGFR3 IC_{50} = 266 nM
FGFR1,2,3,4 IC_{50} = 27, 1.8, 2.0, 157 nM (FGFR2/3 selective, FS = 14-79x)
FGFR2 KATOIII IC_{50} = 24 nM, FGFR3 BaF3/V555L IC_{50} = 16/1.5 nM (cellular)
PK (cyno, 3 mg/kg, p.o.): $T_{1/2}$, C_{Max} , *F* % = 3.2 hrs, 825 nM, 20% (FaSSIF 557 μg/mL)

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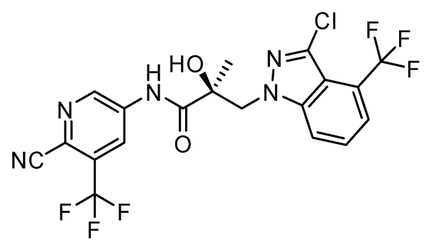
Incyte, US



Compound 35i **AR** **Oncology**

3-substituted indazole androgen receptor antagonist (prostate cancer)
Strategy: Improve metabolic stability of first-in-class *Indole* AR antagonist
Focus: 2,3-indole positions (as metabolic soft spots), use blocking groups
AR antagonist IC_{50} = 21 nM, no binding to AR LBD K_i > 100 μM, weak degrader
In vitro MLM $T_{1/2}$ = 120.6 mins (~10x better), CL_{int} = 0.6 mL/min/kg (~9x better)
3-substituted indazole analogs: *In vivo* AR antagonism (Hershberger assay)

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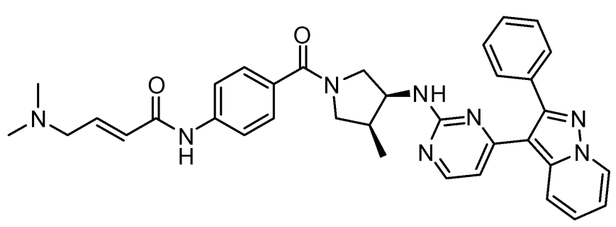
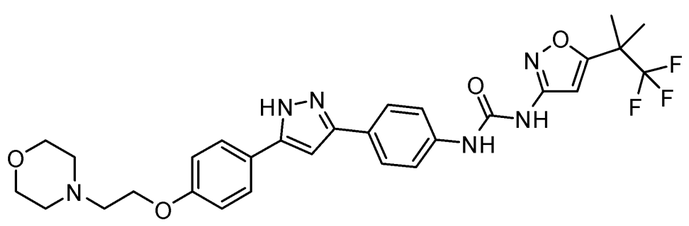


YL5084 **JNK2/JNK3** **Oncology**

Covalent c-Jun N-terminal protein kinase inhibitor (Cys116)
Electrophile: 1,4-conjugated acrylamide (+dimethylamino-handle)
JNK (MAPK pathway): JNK1 (apoptosis), JNK2 (cell survival), JNK3 (CNS)
JNK1, JNK2, JNK3 IC_{50} = 2173, 70, 84 nM (30x FS for JNK2 over JNK1)
JNK1, JNK2 k_{inact}/K_i = 335 M^{-1} s^{-1}, 7166 M^{-1} s^{-1} (Selective covalent potency)
Anti-proliferation, and Induction of apoptosis in MM cells (JNK2-dependent manner)

J. Med. Chem.
Stanford University, USA



Compound 17b **RET** **Oncology**

3,5-diaryl-1H-pyrazol-urea based RET kinase inhibitor (broad anti-tumor)
Ligand-based design strategy: Scaffold-hopping FLTi to RET K_d = 6.5 nM
BaF3, BaF3-CCD6, V804M, G810C RET IC_{50} = 3870, 13.6, 12.1 84.6 nM
468 Kinome screen (1 μM): RET, DDR1, KIT, PDGFRB (IC_{50} < 100 nM)
Cellular target engagement: RET-signalling (BaF3-CCD6-RET cells)
In vivo PK (25 mg/kg, p.o.): $T_{1/2}$, T_{Max} , *F* % = 12.4 hrs, 6.7 hrs, 21.1%

Eur. J. Med. Chem.
Jinan University, China

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