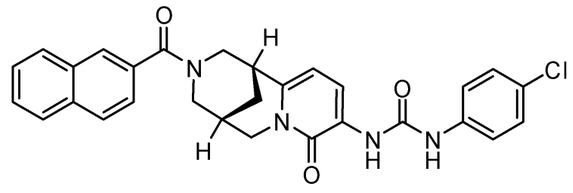
Small Molecule Highlights

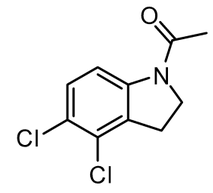
Snapshots from Recent Literature in Target-oriented Drug Design



C2 | **Proteosome β5** | **Oncology**

Naphthyl-azo-tricyclic-urea-based proteosome inhibitor
Ubiquitin-proteasome: Oncology, autoimmune, neurology
VS of natural product ZINC library (*N* = 5000) + SBDD strategy
β5c IC_{50} = 3.43 μM, K_i = 1.15 μM (purified enzymatic assay)
Docking: β5c (Tyr169) and β5i (Phe124, Tyr130): pi-pi stacking

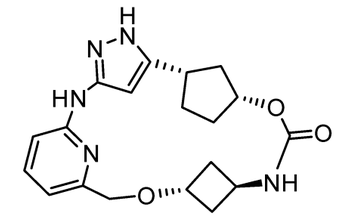
RSC Med. Chem.
Middlesex University, UK



Compound 4W | **CES** | **Oncology**

N-acyl-indoline carboxylesterase Notum inhibitor
CES Notum: Implicated in Wnt signalling (Oncology)
SBDD strategy starting with covalent *hit* (Ester E+)
Analog XRD (8BT8): Phe268 (stack) + H_2O bridge (H-bond)
Notum-OPTS IC_{50} = 4.9 nM, Cell TCF-LEF EC_{50} = 22 nM
$LogD_{7.4}$ = 3.1, PBS Sol. = 0.4 μg/mL, Plasma $T_{1/2}$ > 4 hrs

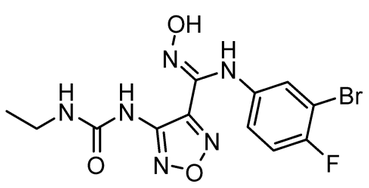
Eur. J. Med. Chem.
UCL/University of Oxford, UK



QR-6401 | **CDK2** | **Oncology**

Macrocyclic Cyclin-dependent kinase 2 (CKD2) inhibitor
Utility in CDK2-dependent cancers, and CCNE1 resistance
SBDD/Macrocycle generation models: Accelerated H2L
CDK2/E1 IC_{50} = 0.37 nM, CDK1/A2 IC_{50} = 22 nM (59x FS)
OVCAR3 cellular IC_{50} = 34 nM, HLM $T_{1/2}$ = 150 mins
OVCAR3 xenografts: 50 mg/kg (BID) (TGI = 78%) (o.g.)

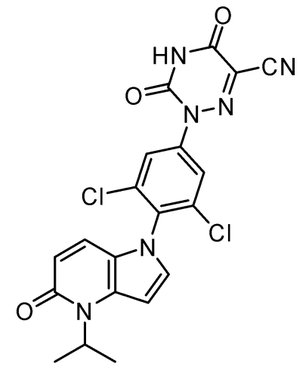
ACS Med. Chem. Lett.
Tencent AI/Regor Therapeutics, China



Compound 3 | **IDO1** | **Oncology**

Oxadiazole carboximidamides indoleamine dioxygenase inhibitor
IDO1: Heme-enzyme (Trp/Kyn metabolism) implicated in oncology
SBDD strategy: Analogs of Epacadostat drug standard (PDB 5WN8)
Biochemical hIDO1 IC_{50} = 67.4 nM, Cell HeLa IDO1 IC_{50} = 17.6 nM
Cellular activity: HeLa, HCT116, CT26 IC_{50} = 46.1, 19.6, 34.9 μM
In vivo efficacy LLC xenografts: 200 mg/kg (BID) (TGI = 53.07%) (p.o.)

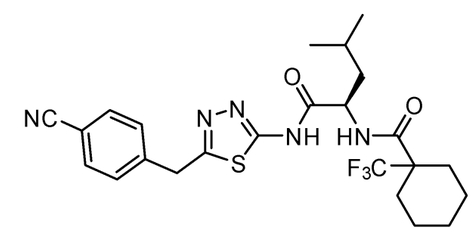
Eur. J. Med. Chem.
CPU, China



Compound 15 | **THR-β** | **Inflammation**

Pyrrolopyridin-5-one thyroid hormone receptor β agonist
THR-β implicated in Nonalcoholic steatohepatitis (NASH)
SBDD strategy of related structural analog (PDB 1N46)
THR-α EC_{50} = 220 nM, THR-β EC_{50} = 30 nM (11.2x FS)
$T_{1/2}$, T_{Max}, C_{Max} = 8.7 hrs, 8 hrs, 2830 ng/mL (30 mg/kg) (p.o.)
In vivo cholesterol reducing activity = 33.5% (30 mg/kg) (o.g.)

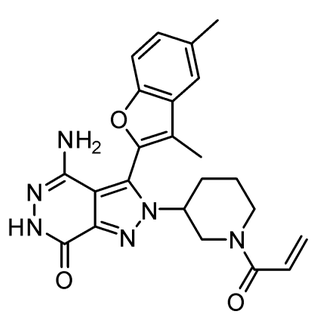
J. Med. Chem.
UCAS, China



BAY-805 | **USP21** | **Oncology**

1,3,4-thiadiazol-based ubiquitin-specific protease inhibitor
USP21, deubiquitinating enzyme (DUBs): Oncology target
Cascade: 5M HTS, 10K primary hits, 2.5K secondary hits (H2L)
Screening *hit* hUSP21 HTRF IC_{50} = 11.8 μM, BAY-805 = 6 nM
SPR K_d = 2.2 nM, hUSP21 (Ub-Rhod) IC_{50} = 2 nM
LogD/LLE = 3.6/4.6, NF-κB reporter assay EC_{50} = 16.6 nM

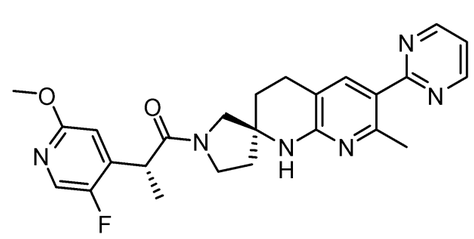
J. Med. Chem.
Bayer & ICB, Germany/SGC, Canada



Compound 2E | **FGFR** | **Oncology**

Covalent pyrazolo[3,4-*d*]pyridazinone FGFR inhibitor
FGFR: FGFR1-4, FGFRL1 (Validated clinical oncology target)
Lead Op. via SBDD/Molecular Docking: PDB 3TT0 (Model)
FGFR1, FGFR2, FGFR3 IC_{50} = 24.1, 13.6, 52.6 nM (Cys488)
FGFR2-N549H IC_{50} = 16 nM, SNU-16/H716 IC_{50} = 1.2/3.2 nM
In 3 FGFR xenograft models: 200 mg/kg (p.o.) (TGI = 68-83%)

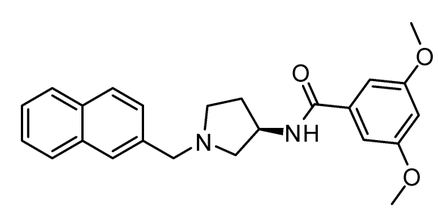
J. Med. Chem.
UCAS, China



PF-07258669 | **MC4R** | **Neurology**

Spirocyclic melanocortin-4 receptor (MC4R) antagonist
MC4R: GPCR implicated in hyperphagia, anorexia, cachexia
28K screen + structural migration: 1-acylaminopyrrolidine series
*h*MC4R IC_{50} = 13 nM, K_i = 0.46 nM, Hep. CL = 12 μL/min/10^6 cells
In vivo PK_{rat} (5 mg/kg) (p.o.): $T_{1/2}$, T_{Max}, % *F* = 0.98 hrs, 0.5 hrs, 28%
Rat models of anorexia/cachexia: 10 mg/kg (BID) (+111% food intake)

J. Med. Chem.
Pfizer, USA



MH3 | **MCH** | **Neurology**

R-3-aminopyrrolidine Melanin Concentrating Hormone inhibitor
MCH-R1: GPCR implicated in food intake/weight loss/appetite
SBDD strategy/Docking: Key int. Phe282, Trp248, Asp192, Gln196
BBB+ via predicted SWISS ADME Boiled-egg model: Yellow region
Radio-ligand binding assay CHO (I^{125}-MCH-R1) K_i = 7 nM

Bioorg. Med. Chem. Lett.
UST, Egypt/University of Mississippi, USA

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