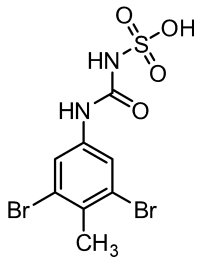
Small Molecule Highlights

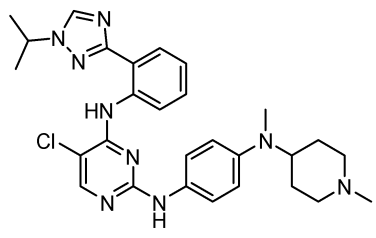
Snapshots from Recent Literature in Target-oriented Drug Design



SPAA-52 **LMW-PTP** **Oncology**

LMW tyrosine phosphatase inhibitor
SBDD from 2.1 μM hit (7UW6)
K_i = 1.2 nM (enzyme inhibition assay)
>8000x selective (vs. 24 PTPs)
$F\ (\%)_{mouse}$ = 34%, No CYPi (10 μM)

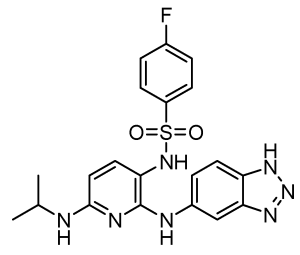
J. Med. Chem.
Eli Lilly/Indiana University, USA



Compound M16 **AXL** **Oncology**

Axl receptor tyrosine kinase inhibitor
SBDD/Molecular docking (5U6B)
KinaseProfiler® IC_{50} = 5 nM
HLM $T_{1/2}$ = 60.6 mins, $F\ (\%)_{rat}$ = 56.1%
Axl, Mer, Aur A, Flt3 (vs. 75 kinases)

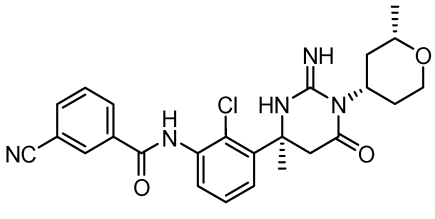
RSC Med. Chem.
Hunan Normal University, China



Compound 43 **BET** **Oncology**

BRD4-BD1 bromodomain inhibitor
AlphaScreen® assay (HTS 200K)
Inhibitor BD1 IC_{50} = 0.24 μM
Fragment co-crystal resolved (7W3D)
Novel H-bonds: Asn, Gln, Pro (SO_2Ar)

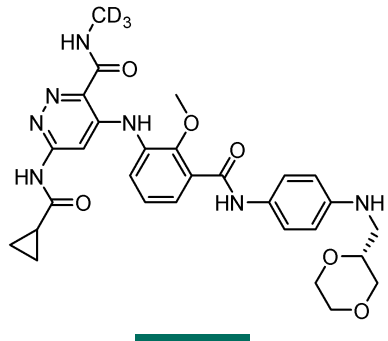
Bioorg. Med. Chem.
KRICT/UST, South Korea



UCB7362 **PMX** **Malaria**

Plasmepsin X protease inhibitor
PMX: Multistage roles in Malaria
FRET-PMX IC_{50} = 7 nM
$F\ (\%)_{cyno/dog}$ = 39/100%
Efficacy *Pf* human mouse model

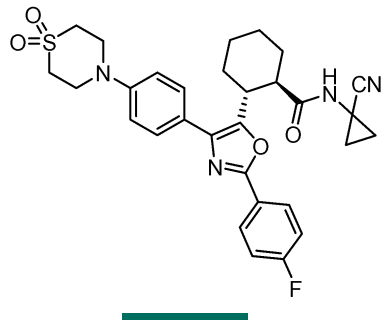
J. Med. Chem.
UCB Pharma, Belgium/UK



Compound 30 **TYK2** **Immunology**

Tyrosine kinase 2 (TYK2) inhibitor
MOA: IL-12, IL-23, IFNα (autoimmune)
IFNα-pSTAT3 (Jurkat) IC_{50} = 1.90 nM
$F\ (\%)_{rat}$ >100% (rapid clearance)
Efficacy in colitis/acanthosis models

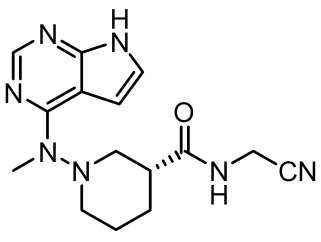
ACS. Med. Chem. Lett.
NJUST, China



Compound 23 **Cat K** **Osteoarthritis**

Cathepsin K inhibitor (osteoarthritis)
In vitro Cat K IC_{50} = 0.5 nM
>1460x selective vs Cat V (most-to-date)
$F\ (\%)_{dog}$ = 38% *In vivo* PD via uCTX-1 (mature dogs) $PO_{q.d.}$ = 0.3 mg/kg

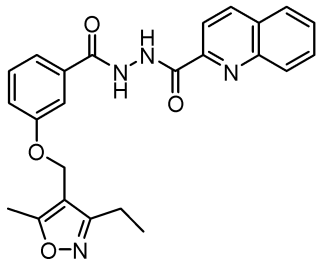
Bioorg. Med. Chem. Lett.
Merck & Co., USA



Compound 8O **JAK1** **R. Arthritis**

Janus kinase 1 (JAK1) inhibitor
MOA: JAK-STAT (rheumatoid arthritis)
In vitro JAK1/JAK2 IC_{50} = 0.3/3.6 nM
PO $F\ (\%)_{rat}$ /$T_{1/2}$ (hrs) = 82.3%/1.5 hrs
Efficacy in CIA mouse model (RA)

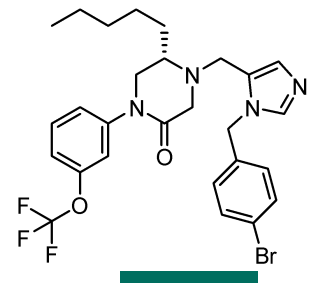
Bioorg. Med. Chem. Lett.
Wuxi AppTec, China



Compound 17 **PRMT5:MEP50** **Oncology**

Protein:Protein Interaction (PPI) inhibitor
ZINC library virtual screen (*N* = 30 million)
BiFC PPI % inhibition at 250 nM = 50-60%
Efficacy in prostate cancer cells (LNCaP)
RNA-Seq. revealed >100 DEGs (vs. DMSO)

J. Med. Chem.
Purdue & Pittsburgh University, USA



Compound 2F **Ftase** **Anti-fungal**

Farnesyltransferase Inhibitor
Disrupt. *Ras* signalling in *C. neoformans*
Enzymatic assays (+PO_4^{2-}) *K* = 3 nM
>8x improv. vs. Fluconazole (Diflucan®)
FTase co-crystal resolved (7T0A)

J. Med. Chem.
Duke University, USA

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