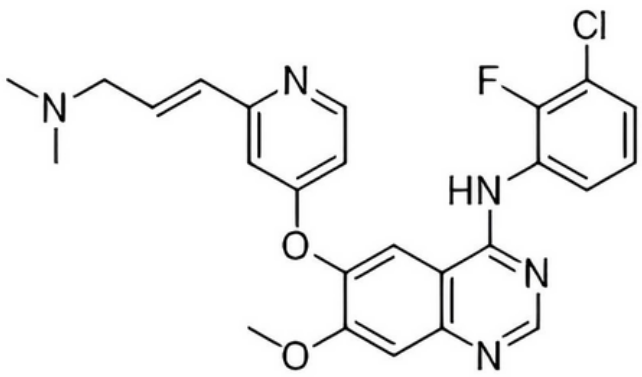
Small Molecule Highlights

Snapshots from Recent Literature in Target-oriented Drug Design



12 EGFR () (Oncology)

Target: Epidermal growth factor receptor EGFR
Indication: Oncology
Inhibitor design: Structure-based drug design, SAR
Activity: EGFR (enzyme) pIC50 = 9.4, EGFR (cell) pIC50 = 8.4, covalent MOA confirmed by mass spectrometry
ADME: logD pH 7.4, = 3.4, solubility, pH 7.4 = 122 µM, CLint rat hepatocytes = 12 µL/min/106 cells, HLM CLint = 28 µL/min/mg, glutathione t1/2 pH 7.4 37 °C= 404 min

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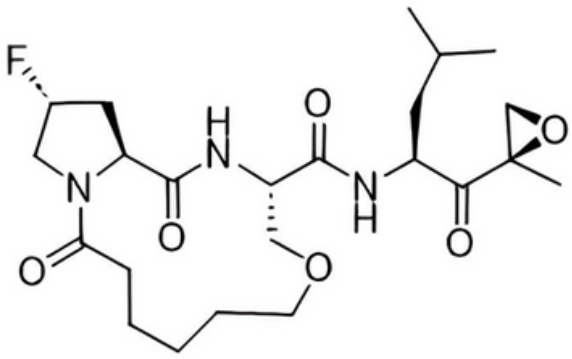

5 LMP2 (Alzheimer's Disease)

Target: Low molecular mass polypeptide LMP2 subunit of immunoproteasome (iP)
Indication: Alzheimer's disease (AD)
Inhibitor design: SAR
Activity: LMP2 IC50 = 87 nM, BV2 cells > 20% remaining LMP2 activity at 1 mM of 5
ADME/PK: HLM CLint = 32.4 mL/min/kg, in silico logP = 0.75, Papp = 17.3 (10-6 cm/s) ER = 2.62, in silico TPSA = 117.34 Å, mouse, 150 mg/kg, p.o., AUCinf = 3571, h*ng/mL, Cmax = 3630 ng/L, T1/2(h) = 0.79, F = 9.8%.
In vivo: healthy mice, 40 mg/kg i.v. , 100% inhibition blood LMP2, 39% inhibition brain LMP2 at 24 h postdose, 150 mg/kg p.o. ~90% inhibition blood LMP2, 21% inhibition brain LMP2 at 6 h postdose

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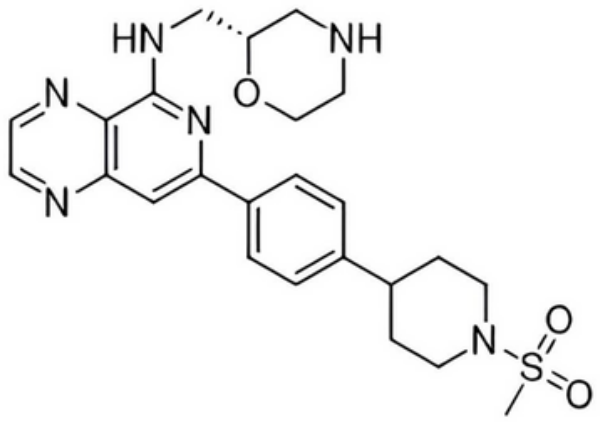

Sovleplenib 41 SyK (Autoimmune, Oncology)

Target: Spleen Tyrosine Kinase Syk
Indication: Autoimmune diseases (e.g. rheumatoid arthritis, immune thrombocytopenic purpura), oncology
Inhibitor design: SAR, SBDD
Activity: Syk enzymeIC50 = 25 nM, Syk degranulation IC50 = 51 nM, KDR enzyme IC50 = 390 nM, KDR cell IC50 = 5051 nM
ADME/PK: Papp (10-6 cm/s) A-B = 5, RLM percent remaining = 75%, MLM 81%, hERG >50 µM, PPB H 83% bound, M 93% bound, logP = 2.49
PK: mouse, 10 mg/kg, p.o., AUC0-t = 7761, h*ng/mL, Cmax = 1587 ng/mL, T1/2(h, i.v.) = 1.4, F = 94.1 %.
In vivo: Mouse collagen II-induced arthritis (CIA) model, 30 mg/kg dose reduced arthritis score of paws by 159.3%. Improved weight loss at 10 and 30 mg/kg doses

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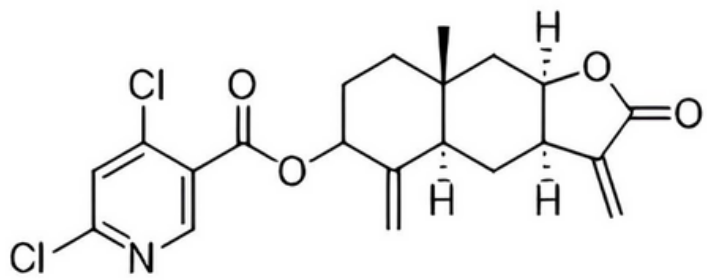

49 NLRP3 (Inflammatory Diseases)

Target: NLRP3 inflammasome
Indication: Ulcerative colitis
Inhibitor design: SBDD and SAR
Activity: IL-1b IC50 = 290 nM, 94% inhibition of nigericin-induced IL-1b release in THP-1 cells, PBMC IL-1b production IC50 = 45 nM
ADME/PK: HLM T1/2 = 182 min, H Clint = 7.5 mL/min /g protein, MLM T1/2 = 65 min, M Clint = 21.2 mL/min/g protein, hERG = 10.6 mM
PK: Mouse 30 mg/kg, i.p. AUC0-t = 16.75, h*ng/mL, Cmax = 1.57 ng/mL, T1/2(h) = 6.83, CLz/F 637.4 (L/h/kg) (clearance)
In vivo: DSS induced acute ulcerative colitis mouse model, significant effects on body weight loss, disease activity index, colon length shortening at 15 and 30 mg/kg. Improvements in colonic tissue (histology). Significant reduction in IL-1 β and TNF-α in colonic tissues demonstrated

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