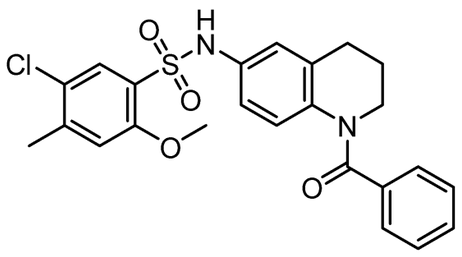
Small Molecule Highlights

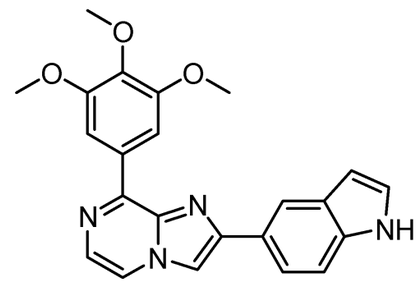
Snapshots from Recent Literature in Target-oriented Drug Design



B53 **SGRM** **Immunology**

Selective glucocorticoid receptor modulator (SGRM)
Extensive SAR of sulfonamide tetrahydroquinolines (62 analogs)
Potent transrepression ($IC_{50\ NF\text{-}\kappa B}$ = 9 nM) (No transactivation)
Reduces expression of inflammatory biomarkers: IL-6, IL-1β, TNF-α
Efficacy in DNCB-induced atopic dermatitis model (20 mg/kg)$_{p.o.}$

J. Med. Chem.
Zhejiang University, China



TB-25 **Tubulin** **Oncology**

Imidazo[1,2-a]pyrazine tubulin inhibitor (Ring-fusion towards CBSI)
HepG-2/HCT-116/A459/MDA-MB-231 IC_{50} = 146/23/154/74 nM
Induction of apoptosis (HCT-116 cells) = 50.1% (at 120 nM)
Cell cycle arrest (G2/M phase) observed = 79.6% (at 120 nM)
Cell migration (wound-healing assay): $\%_{inh}$ = 60.5% (at 80 nM)

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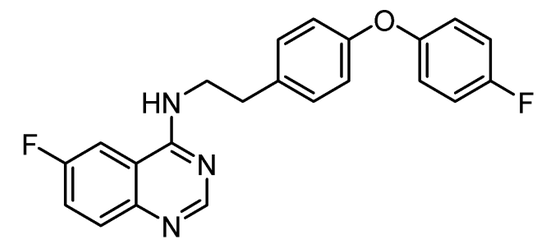
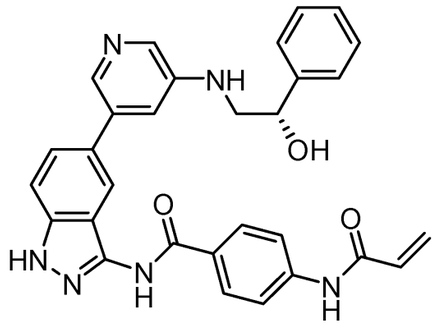
SMU/SCU, China



Compound 15B **EGFR** **Oncology**

Spautin-1 derived EGFR^{mut} inhibitor (Ex19Del, L858R/T790M)
Original hit (5 μM potency) to 15B (NSCLC PC-9 IC_{50} = 4 nM)
Quinazoline core: Formamide coupling with 2-carboxyanilines
Limited toxicity BEAS-2B (non-cancer): Cell viability >95%
CovEGFRi Afatinib co-incubation = 2x potency improv. (additive)

Bioorg. Med. Chem. Lett.
VUB, Belgium



B2 **CDK7** **Kidney Disease (PKD)**

Covalent CDK inhibitor for AD polycystic kidney disease (PKD)
Lead optimization of identified CDK7 hit THZ1 (6XD3)
CDK7 IC_{50} = 4 nM, CDK1, 2, 3, 5, 6, 9, 12 IC_{50} = 0.5 – 10 μM
Off-targets at 1 μM: GSK3β, AMPKα1, TAK1, PKCθ, JAK2
PK (5 mg/kg)$_{s.c.}$: $t_{1/2}$/T_{max}/F = 3.4 hrs/0.5 hrs/64.2%
Efficacy in MDCK cyst model/ADPKD mouse model (5 mg/kg)$_{s.c.}$

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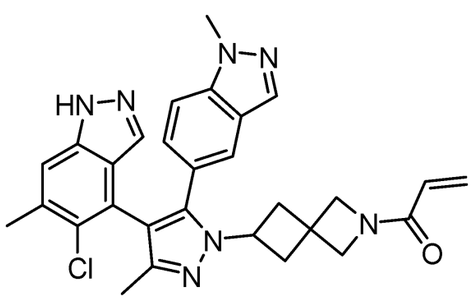
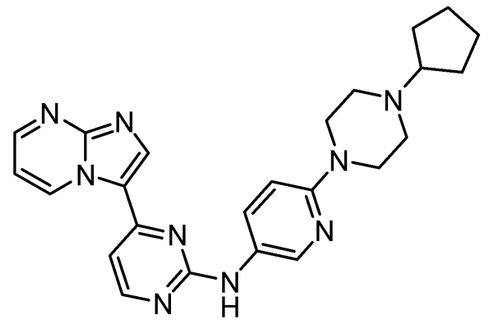
UCAS/CAS, China



JDQ443 **KRAS^{G12C}** **Oncology**

Covalent KRAS^{G12C} inhibitor, stable atropisomer (unique pyrazole core)
SBDD, *de novo* HitID, reactivity optimization (spiro-azetidine linker)
k_{inact}/K_i = 141 $mM^{-1}s^{-1}$, pERK IC_{50} = 20nM (NCI-H358^{mut}), $LogD_{7.4}$ = 4.1
Co-crystal structure (7R0M) (Novel non-His95 interactions)
GSH $t_{1/2}$ = 254 mins, Caco-2 P_{app} (10^{-6} cm s^{-1}) = 6.78, WBS $t_{1/2}$ > 240 mins
Efficacy in MIA Paca-2 tumor models (-87% MTV, day 20) (30 mg/kg)$_{p.o./q.d.}$

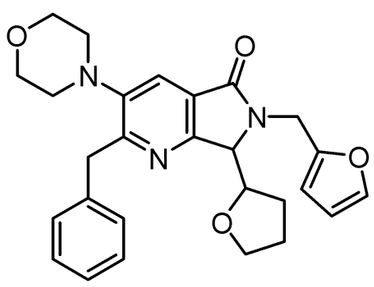
J. Med. Chem.
Novartis (NIBR), Switzerland



Compound 9Q **CDK7/9** **Oncology**

N-pyridinylpyrimid-2-amine dual CDK7/9 inhibitor
Percent inhibition (%) of CDK7H/CDK9T1 (1 μM) = 87/90 %
Apparent K_i (CDK7H/CDK9T1) = 55/38 nM, [ATP] = K_m
MCF-7/A2780/H460/MV4;11 GI_{50} = 0.41/0.15/0.55/0.21 μM
Induction of apoptosis (MV4;11): FACS Annexin V^+/PI^+

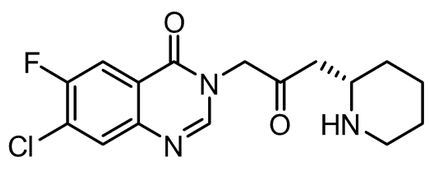
Chem. Med. Chem
University of South Australia, Australia



Compound 1F **SARS-CoV2** **Antiviral**

bis-furyl-pyrrolo[3,4-*b*]pyridin5-ones as SARS-CoV2 inhibitor
Ugi-Zhu 3-component reaction (UZ-3CR) via $Yb(OTf)_3$ catalyst
SARS-CoV2 Infection Vero-E6: $\%_{inh}$ EC1/EC2 = 31.9/15 %
Inhibitor displayed both prophylactic/therapeutic effects
Docking: M^{pro}/NSP3/Spike-Glyco = -5.71/-4.72/-4.49 kcal mol^{-1}

RSC Med. Chem.
UAM/UGto, Mexico



Compound 3 **ProRS** **Antibacterial**

Staphylococcus aureus prolyl-tRNA synthetase (*Sa*ProRS) inhibitor
Co-crystal of *Sa*ProRS:3:AMPPNP complex (5ZNK) – ATP-aided MOA
*Sa*ProRS K_d (-ATP) = 376 μM, K_d (+ATP) = 30 nM (~10^4-fold increase)
E. coli (GPB)/*MRSA252* (GNB) MIC = 1 μg/mL, *Sa*ProRS IC_{50} = 0.15 μM
*Sa*ProRS/*Ec*ProRS ΔT_m (°C) = 10.2/20.4 (fluorescence-thermal shift assay)

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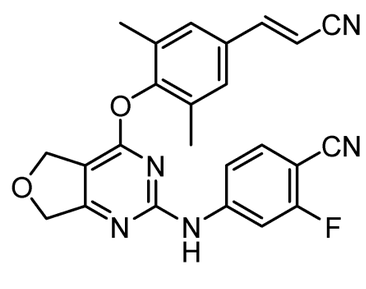
SYSU, China



Compound 36A **NNRT** **Antiviral**

Non-nucleoside reverse transcriptase (NNRT) inhibitor (HIV-1)
Co-crystal structure-based design strategy/molecular docking
HIV-1 WT/L100I/K103N/RES056 EC_{50} = 2.2/3.0/2.8/53.3 nM
HIV-1 K_d (SPR) = 2.50 μM (comparable to Etravirine clinical std.)
PK of 36A.HCl (10 mg/kg)$_{p.o.}$ $t_{1/2}$/T_{max}/*F* (%) = 5.12 hrs/0.25 hrs/12

J. Med. Chem.
Shandong University/Rega Institute, China/Belgium

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