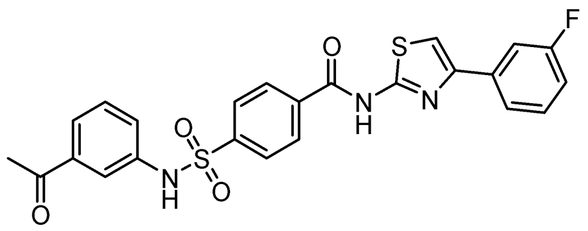
Small Molecule Highlights

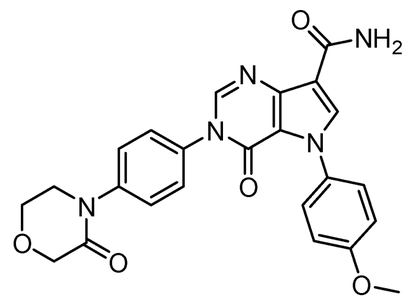
Snapshots from Recent Literature in Target-oriented Drug Design



D8 **PHGDH** **Oncology**

Phosphoglycerate dehydrogenase (PHGDH) inhibitor
Disruption of *de novo* serine biosynthesis (anti-cancer)
PHGDH IC_{50} = 2.80 μM, K_d (MST assay/SPR) = 2.33/2.48 μM
MDA-MB-468/MCF10A IC_{50} = 5.30/52.9 μM, Co-crystal (7VA1)
$T_{1/2}/T_{max}/F$ (%) (3 mg/kg, p.o.) = 4.74 hrs/3.33 hrs/82% (ICR mice)
Anti-cancer in vivo efficacy in PC-9 tumors (25 mg/kg, TGI = 68.9%)

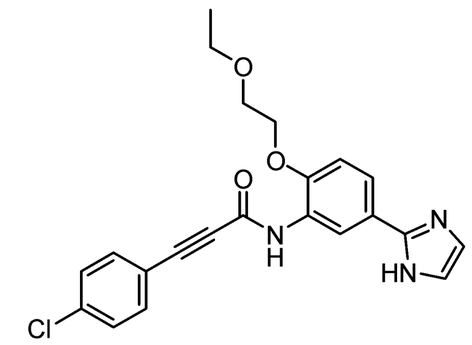
J. Med. Chem.
SHUTCM, China



Compound 17A **FXa** **Anti-coagulant**

Pyrrolo[3,2-d]pyrimidinone as coagulation factor Xa (FXa) inhibitor
FXa IC_{50} = 1.57 nM, Clinical Std. Rivaroxaban FXa IC_{50} = 14.38 nM
Enzymatic activity FXa = 46.7% at 20 nM inhibitor (as in Rivaroxaban)
Prothrombin time (PT %) rises in concentration-dependent manner
Docking analysis: pyrimidinone C=O---NH of G216 (as in Apixaban)
Thrombus inhibition rate: (1 mg/kg) = 68%, Rivaroxaban = 75%

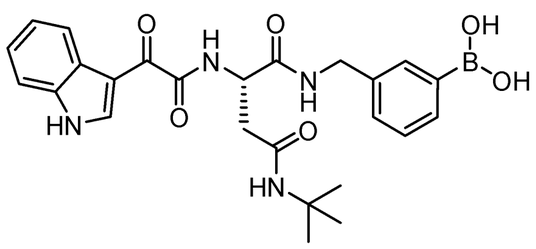
Bioorg. Med. Chem. Lett.
Nanjing Zhongrui Pharmaceutical Co./Xuchang University, China



Compound 19F **VCP/p97 ATPase** **Oncology**

Covalent Valosin-containing protein (VCP)/p97 ATPase inhibitor
p97 homohexamer: AAA+ ATPase implicated in various cancers
SAR identified most p97 inhibitor: Propiolamide E+ (Cys522, D2)
Docking suggests useful H-bond (Gln473 --- imidazole) + hydrophobics
p97 IC_{50} (activity assay) = 13.86 nM, U87MG (GBM) IC_{50} = 19.06 nM
ABPP pull-down/Western blots confirmed p97 engagement *in cellulo*

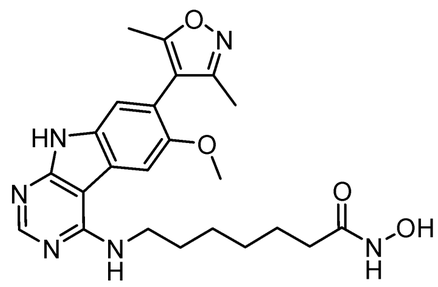
Eur. J. Med. Chem.
CAMS/PUM, China



WZ-1831 **β5c** **Oncology**

Constitutive proteasome chymotryptic activity (β5c) inhibitor
β5c (20S proteosome/Ub proteosome): Implicated in Multiple Myeloma
Asparagine-EDA core to WZ-1831 via core-hopping/docking strategies
β5c IC_{50} = 10 nM, β5i IC_{50} = 7.10 μM (>700-fold selective for β5c)
1H-indole-ketoamide-Asn-*tert*-butyl-Ar-$B(OH)_2$: critical for β5c selectivity
HepG2/MM.1S/RPMI8226 IC_{50} = 3.2 μM/60 nM/2.3 μM (MM1.S potency)
Synergy with β5i-selective PKS21265 in MM1.S/RPMI8226, IC_{50} < 10 nM

J. Med. Chem.
WCM/MSK/HMS, USA



Compound 13C **BET/HDAC** **Oncology/Anti-fungal**

Bromodomain and extra-terminal (BET)/histone deacetylase (HDAC) inhibitor
Dual-mode inhibition of breast cancer/resistant *C. albicans* infections (fungal)
HDAC1 IC_{50} = 10 nM, BRD4 IC_{50} = 35 nM, Azole-resistant *C. albicans* FICI 0.070
HDAC1/HDAC2/HDAC6 IC_{50} = 10/152/9 nM, BRD2/BRD3 IC_{50} = 174/113 nM
K562/HEL/HL60/MDA-MB-231 IC_{50} = 2.5/3.9/1.2/0.5 μM (anti-proliferative)
Induction of MDA-MB-231 apoptosis (FACS), *C. albicans* conversion block (+FLC)

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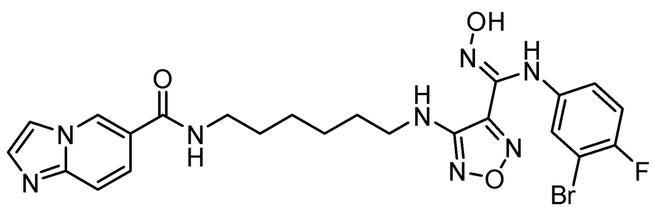
SMMU, China



Compound 10E **NAMPT/IDO1** **Oncology**

NAM Phosphoribosyltransferase (PT)/Indoleamine Dioxygenase (IDO1) inhibitor
Dual inhibition strategy: anti-cancer utility against NSCLC (NAD^+ blockage)
In vitro NAMPT IC_{50} = 57.7 nM, IDO1 IC_{50} = 160 nM, A549/R cells IC_{50} = 5.35 μM
A549/R colony inhibition + NAD^+ depletion + ROS accumulation (5.0-15.0 μM)
Anti-tumor efficacy *in vivo* (A549/R): 100 mg/kg (p.o.)(b.i.d.) + Synergy with Taxol

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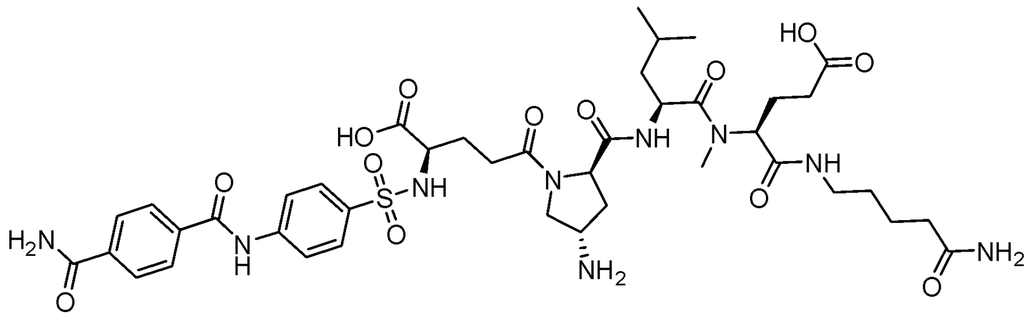
CPU, China



TP0597850 **MMP2** **Oncology**

Matrix metalloproteinase-2 (MMP2) inhibitor: Anti-cancer/anti-fibrosis
Benzamide (S1' pocket), γ-D-Glu (Zn^{2+} chelation), 4*S*-amino-Pro (stability)
MMP2 IC_{50}/K_i = 0.22/0.034 nM, >2000-fold subtype selectivity for MMP2
Extended chemical stability (pH 7.4, 37 °C, >14 days): >99% residual rate
Co-crystal with MMP2 catalytic domain (8H78): Zn^{2+} chelation confirmed

J. Med. Chem.
Taisho Pharmaceutical Co., Japan

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