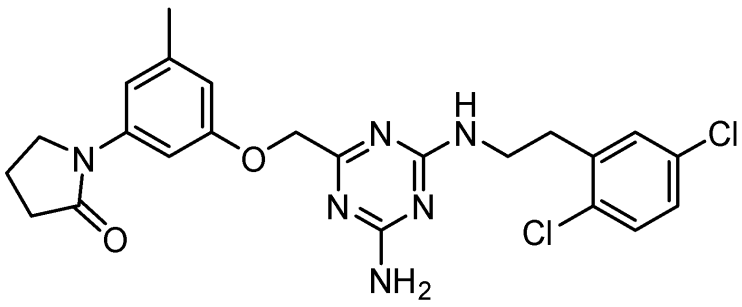
Small Molecule Highlights

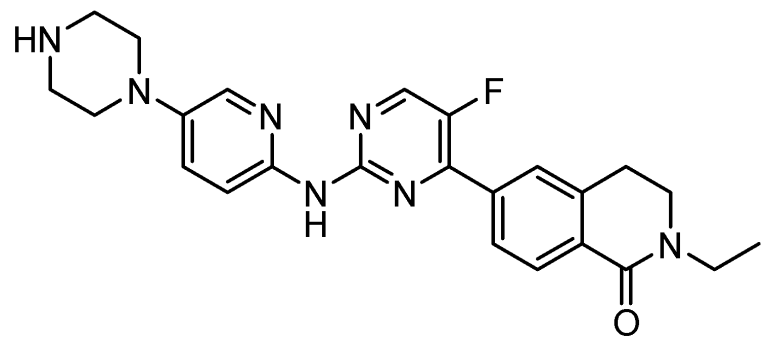
Snapshots from Recent Literature in Target-oriented Drug Design



Compound 83 **FFAR1/4** **Metabolism**

First-in-class dual FFAR1/4 allosteric agonist
FFARs are GPCRs: Roles in T2DM/Inflammation
FFAR1 EC_{50} = 1 nM, FFAR2 EC_{50} = 2 nM
Efficacy/potency improved over lit. std. TAK-875
PBS Sol. = 19 μM, LogD =3.46, $S9_{t1/2}$ = 1.9 mins

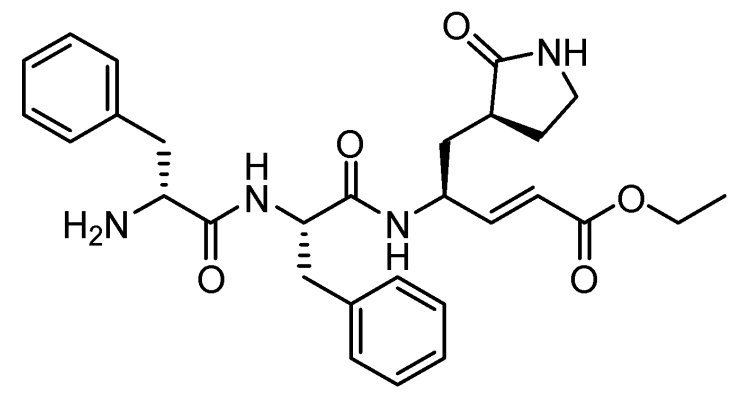
ACS. Med. Chem. Lett.
University of Copenhagen, Denmark



Compound 42 **CDK4/6** **Oncology**

Cyclin-dependent kinase (CDK) inhibitor
SBDD/Pharmacophore model (*N* > 200K)
CDK4/6 IC_{50} = 10/16 nM (200x from HitID)
$F_{p.o.}(\%)_{rats}$ = 43%, $T_{1/2}$ = 3.5 hr, T_{max} = 6.0 hr
Efficacy: MCF7 Xenografts (150 mg/kg, p.o.)

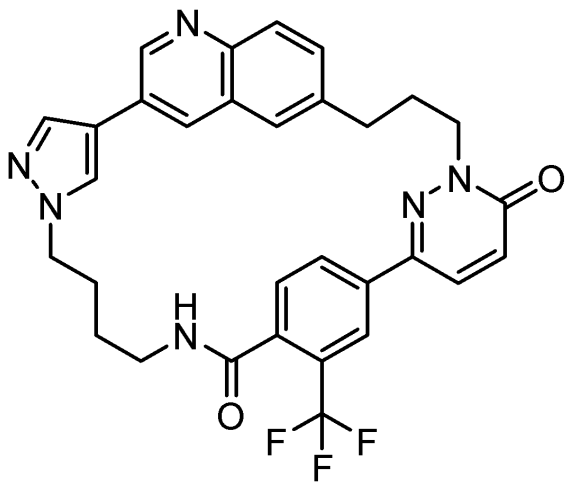
J. Med. Chem.
CPU/CAMS, China



SM141 **M^{Pro}/CatL** **Anti-viral**

SARS-CoV2-M^{pro} /Cathepsin L dual inhibitor
Covalent Cys145 M^{pro} bond (Acrylate E+)
M^{pro} IC_{50} = 900 nM, CatL IC_{50} = 60 nM
Anti-viral A549 hACE2 EC_{50} = 8.2 nM
NAS: Improved survival (SARS-CoV2 mice)

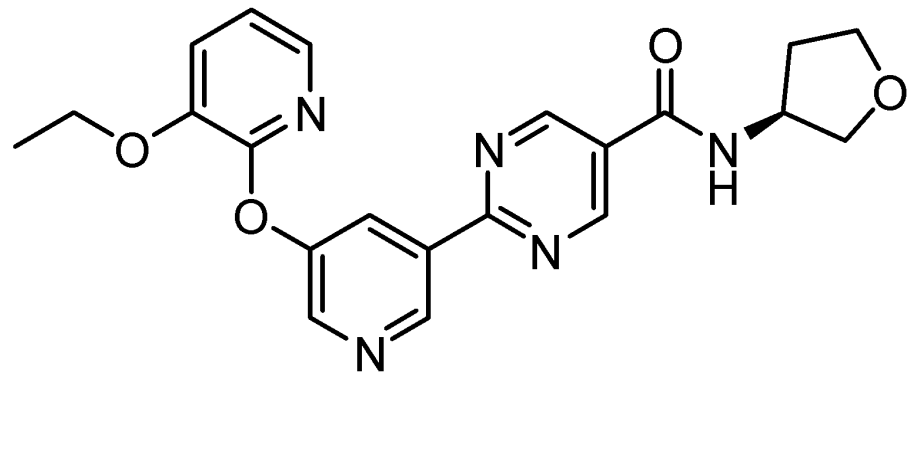
J. Am. Chem. Soc.
University of Massachusetts, USA



D6808 **cMET** **Oncology**

Macrocyclic cMET inhibitor (Gastric cancers)
Cyclization via FDPP-mediated amide-bond
$cMET_{(ATP\ at\ 50uM)}$/$Hs746T_{cell}$ IC_{50} = 2.9/0.7 nM
Macrocycle lowers ΔS_{bind} (Improves affinity)
Selectivity (373 kinases), off-targets (Axl, Trk)

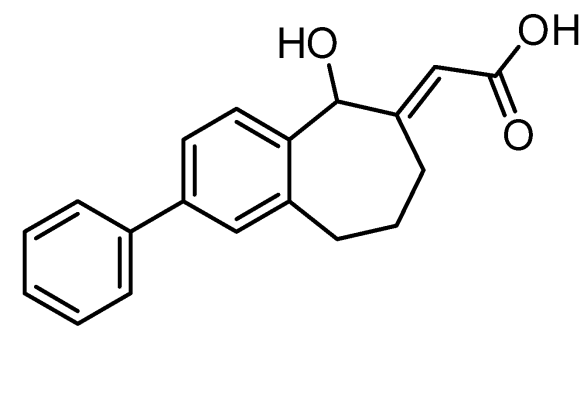
J. Med. Chem.
CSU/JNU, China



PF-06865571 **DGAT2** **Steatohepatitis**

Diacylglycerol acyltransferase (DGAT) inhibitor
DGAT2 IC_{50} (activity assay) = 17.2 nM
MW/LogD/TPSA/$F_{p.o.}(\%)_{rat}$ = 407/1.9/108/31%
Decreased HHEP $CL_{int,app}$ = 3.9 μL/min/10^6 cells
In vivo reduction of TG levels (0.3-90 mg/kg, p.o.)

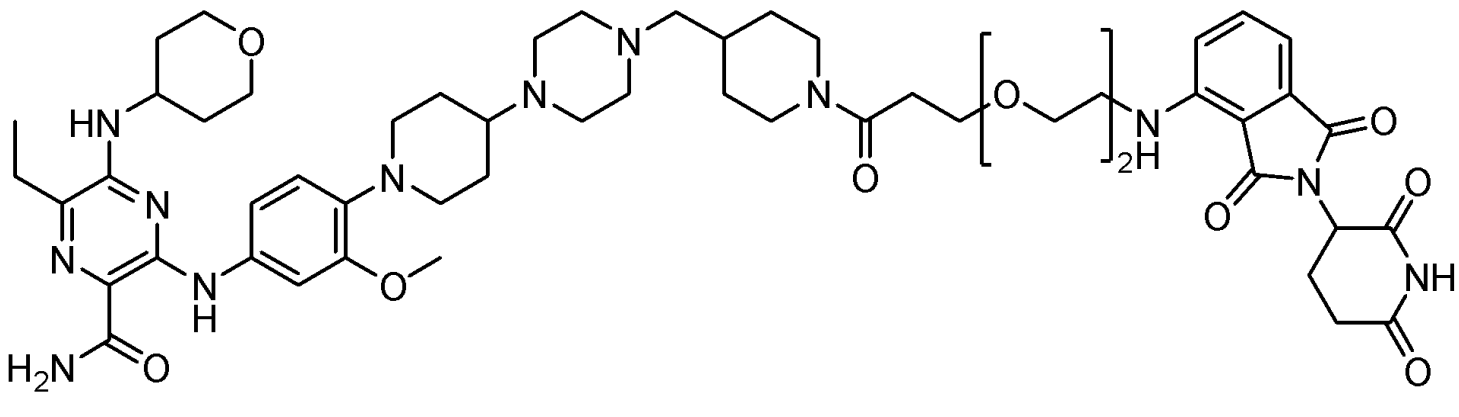
J. Med. Chem.
Pfizer, USA



PH-HTBA **CaMKIIα** **Neurology**

Ca^{2+}/calmodulin-dep. kinase IIα inhibitor
CaMKIIα K_i (binding assay) = 78 nM
CaMKIIα hub-domain K_D (SPR) = 757 nM
ΔT_m (DSF) = +19.02 °C (at >100 μM)
HEP Cl_i(H/M) = 8.6/65 μL/min/10^6 cells

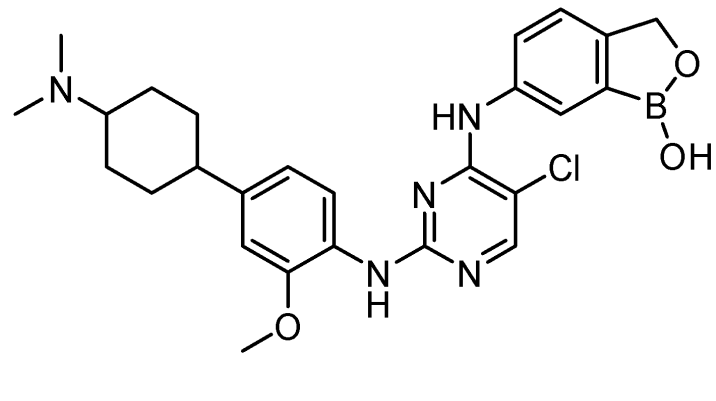
J. Med. Chem.
University of Copenhagen, Denmark



CRBN (FLT3)-8 **FLT3-ITD** **Oncology**

Gilteritinib-based FLT3-ITD PROTAC (CRBN E3 ligase)
FLT3-ITD: most common driver mutation in AML (~25%)
Decrease of FLT3 levels in MV4-11/MOLM-14 cells (PEG2)
FLT3 down-regulation supressed by UPSi (UPS-dep. MOA)
$AML^{FLT3\text{-}ITD}$ MV4-11/MOLM-14 cells, IC_{50} = 0.9/2.8 nM

ACS. Med. Chem. Lett.
NIHS/DSI, Japan



Compound 10K **ALK** **Oncology**

Anaplastic lymphoma kinase (ALK) inhibitor
First report of boronic-acid based ALKi ($Asn^{H\text{-}bond}$)
SBDD/isosterism, ALK^{L1196M} IC_{50} = 8.4 nM
$NCI\text{-}H2228_{cell}$ IC_{50} = 520 nM, HLM $T_{1/2}$ = 4.0 hr
Lung cancer xenografts, (50 mgs/kg, i.g.) TGI = 52%

Bioorg. Med. Chem.
CTTQ/Nanjing University, China

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