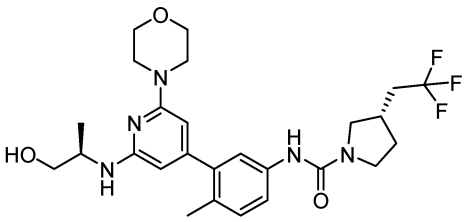
# Small Molecule Highlights

Snapshots from Recent Literature in Target-oriented Drug Design

DALRIADA TURN-KEY™ DRUG DISCOVERY

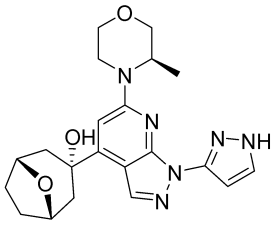


**BRAF**

**KIN-2787 (Exarafenib)**
**Oncology**

*Target:* **BRAF**
*Indication*: Various oncology indications
*Inhibitor design:* SAR optimization using naporafenib as a starting point.
*Activity*: pERK $EC_{50}$ = 62/103/10/51/26/9/18 nM in A375/Colo800/NCI-H2405/BxPC-3/OV-90/ WM3629/CAL-12T (cellular); RAF A/B/C $IC_{50}$ = 2.4/3.5/1.4 nM (biochemical).
*ADME/PK*: Hepatocyte Stability (% remaining after 60 min) = 85/72/69/62 in human/rat/dog/mouse in mouse; F(%) = 44/82/96 in mouse/rat/dog.
*In vivo*: Dose-dependent tumor growth inhibition in BxPC-3, WM3629, and A375 xenograft bearing mice with no overt signs of toxicity.

*J. Med. Chem.*
Kinnate Biopharma, USA

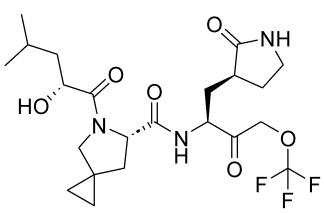


**ATR**

**RP-3500 (Camonsertib)**
**Oncology**

*Target:* **A**taxia **t**elangiectasia and **R**ad3-related (**ATR**) kinase
*Indication*: Various oncology targets
*Inhibitor design:* Optimization of lead pharmacophore via SAR studies
*Activity*: ATR in HeLa $IC_{50}$ = 0.9 nM (cellular); LoVo $IC_{50}$ = 28 nM (cellular); Selectivity ratio in LoVo cells (ATR $IC_{50}$ = 0.22 nM) 30x/2200x/>20000x/>20000x for mTOR, PI3Ka/ATM/DNA-PKcs (cellular).
*ADME/PK*: Hepatocyte Clearance (µL/min/$10^6$ cells) = 11/17/<1/3.6/1.5 in mouse/rat/dog/monkey/human; F(%) = 72/45/113/56 in mouse/rat/dog/monkey.
*In vivo*: Effective control of tumor growth in Granta-519 tumor-bearing mice without severe implications on erythroid cells.

*J. Med. Chem.*
Repare Therapeutics , Canada

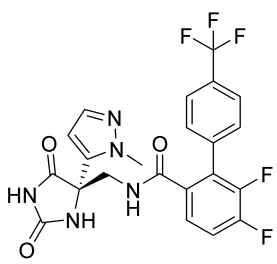


**$CL^{pro}$**

**CMX990**
**SARS-CoV-2 infection**

*Target:* SARS-CoV-2 3C-like protease ($CL^{pro}$)
*Indication:* SARS-CoV-2 infection
*Inhibitor design:* Drug repurposing library screen followed by SAR studies
*Activity*: HeLa SARS-CoV-2 $EC_{90}$ = 63/35/37 nM in SARS-CoV-2 alpha/delta/omicron (cellular); SARS-CoV-2 $CL^{pro}$ $IC_{50}$ = 23.4 nM (biochemical).
*ADME/PK*: Human Microsomal Clearance (µL/min/mg) = 7.5, Human Hepatocyte Clearance (µL/min/$10^6$) = 0.2; F(%) = 14.5/12.2/52.8/1.1 in mouse/rat/dog/monkey.
*In vivo*: No sustained adverse effects in CD-1 mice and beagles in MTD studies after 5 days– meets NOAELs criteria.

*J. Med. Chem.*
Calibr at Scripps Research Institute, USA

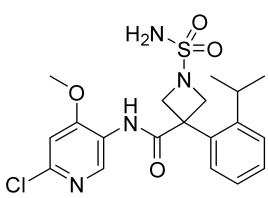


**ADAMTS7**

**BAY-9835**
**Coronary Artery Disease**

*Target:* **A d**isintegrin **a**nd **m**etalloproteinase with **t**hrombo**s**pondin motifs **7** (**ADAMTS7**)
*Indication*: **C**oronary **A**rtery **D**isease (**CAD**)
*Inhibitor design: In silico* design and SAR
*Activity*: ADAMTS7 $IC_{50}$ = 6 nM (biochemical); 1121x/1654x/375x/5467x/962x/17316x/5x selectivity against ADAMTS4/ ADAMTS5/ADAM8/ADAM10/ADAM17/MMP2/ADAMTS12 (biochemical).
*ADME/PK*: $CL_{Hep}$ (L/h/kg) = 0.32/0.17/0.06/0.0001 in mouse/rat/dog/human; $CL_{blood}$ (L/kg/h) = 1.1/0.55/0.02 in mouse/rat/dog (*in vivo*); F(%) = 100/96/77 in mouse/rat/dog.
*In vivo*: Well tolerated in a two-week chronic dosing study in rats (50 mg/kg/day, p.o.) with no observable signs of toxicity.

*J. Med. Chem.*
Bayer AG, Germany



**LPAR1**

**ACT-1016-0707**
**Fibrotic Disease**

*Target:* **L**yso**p**hosphatidic **a**cid **r**eceptor subtype **1** (**LPAR1**)
*Indication*: Fibrotic Disease
*Inhibitor design:* Lead optimization/SAR
*Activity*: LPAR1 $IC_{50}$ = 2.9 nM (cellular), LPAR2 $IC_{50}$ > 10 µM (cellular), LPAR3 $IC_{50}$ > 10 µM (cellular).
*ADME/PK*: $CL_{LM}$ (µL/min/mg) = 26/21/13 in rat/mouse/dog; $CL_{Hep}$ (µL/min/$10^6$) = 7.4/n.d./<2 in rat/mouse/dog; F(%) = 49/79/52 in rat/mouse/dog.
*In vivo*: Significant reduction in LPA induced vascular leakage observed at 30 mg/kg (p.o., mice)

*J. Med. Chem.*
Idorsia Pharmaceuticals, Ltd., Switzerland



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