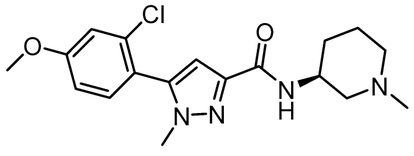
Small Molecule Highlights

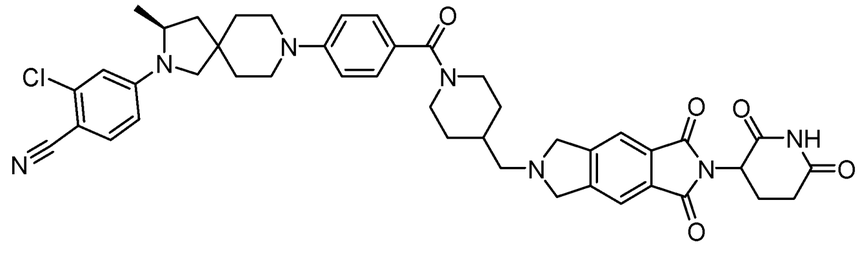
Snapshots from Recent Literature in Target-oriented Drug Design



CVN417 | **α6-nAchR** | **CNS**

Target: **α6-N**icotinic **a**cetyl**ch**oline **r**eceptors (**nAChr**)
Indication: Parkinson's disease and Huntington's chorea
Inhibitor design: High-throughput screening (650 K compounds) and SAR to develop lead.
Activity: = α6-nAChr IC_{50} = 0.086 μM, α3-nAChr IC_{50} = 2.56 μM , α4-nAChr IC_{50} = 0.66 μM (cellular)
ADME/PK: Microsome Stability (mL/min/kg) = 2.8/31.2/33.3/27.7 for human/rat/mouse/dog; $K_{p,uu}$ = 1.4 (rat); F(%) = 11/43.8 for rat/dog
In vivo: Dramatic decrease of evoked tremor duration in a rat resting tremor model (>70% decrease @ 25 mg/kg p.o.)

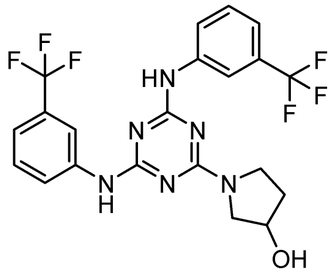
J. Med. Chem.
Cerevance Ltd., USA



ARD-1676 | **AR** | **Oncology (Prostate)**

Target: **A**ndrogen **R**eceptor (**AR**)
Indication: Prostate Cancer
Inhibitor design: Rational design and SAR (linker and E3 ligase ligand)
In vitro Activity: VCaP: DC_{50} = 0.1 nM, D_{max} = 99% (cellular); LNCaP: DC_{50} = 1.1 nM, D_{max} = 98% (cellular).
ADME/PK: Liver Microsome Stability: $T_{1/2}$= >60 min in mouse, human, rat, dog, and monkey; Oral bioavailability: F(%) = 67/44/31/99 in mouse/rat/beagle/monkey; hERG Inhibition: IC_{50} > 30 μM.
In vivo: 85% tumor growth inhibition in a mouse VCap xenograft model (40 mg/kg; po, 44 days)

J. Med. Chem.
University of Michigan, USA



Compound 36 | **IDH2** | **Oncology**

Target: **I**socitrate **D**e**h**ydrogenase **2 (IDH2)**
Indication: Acute Myeloid Leukemia **(CD38)**
Inhibitor design: structure-based drug design (SBDD) and SAR
Activity: $IDH2^{R140Q}$ IC_{50} = 29 nM and 204 nM @ 1 hr (biochemical); $IDH2^{WT}$ IC50 > 100 μM @ 1 hr. D2HG IC_{50} = 10 nM (cellular).
ADME/PK: liver Microsomes $T_{1/2}$ = >180/137.1 min for human/mouse; F(%) = 90.3% in mouse; hERG IC_{50} = >30 μM
In vivo: Decreased d2HG levels (68%) in TF-1/$IDH2^{R140Q}$ xenograft mice (25 mg/kg, p.o., 1 dose per day)

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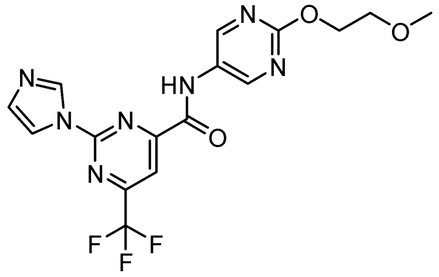
Jiangsu Provincial Medical Innovation Center , China



Compound 1 | **CD38** | **Mitochondrial Disorder**

Target: **C**luster of **D**ifferentiation **38 (CD38)**
Indication: Mitochondrial Myopathy
Inhibitor design: Scaffold hopping and SAR
Activity: hCD38 IC_{50} = 11 nM (biochemical); mCD38 IC_{50} = 9.8 nM (biochemical)
ADME/PK: Hepatocyte Stability $T_{1/2}$ = >180 min for human/mouse; F(%) = 61/55/127/247% for mouse/rat/dog/monkey; hERG IC_{50} = >30 μM
In vivo: Increased NAD^+ and exercise capacity with decreased lactic acid buildup in Pus1 KO mice (1 mg/kg, p.o., 1 dose per day for 58 days)

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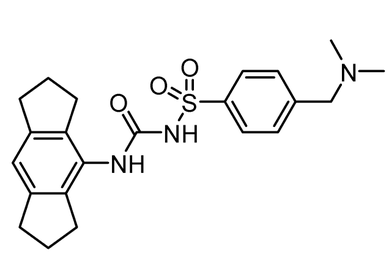

N14 | **NLRP3** | **Inflammation**

Target: **N**OD-, **LR**R-, and **p**yrin domain-containing protein **3 (NLRP3)**
Indication: **N**on-**a**lcoholic **s**teato**h**epatitis (**NASH**), septic shock, and colitis.
Inhibitor design: Rational design and SAR
Activity:IL-1β IC_{50} = 25 nM (cellular)
ADME/PK: $T_{1/2}$ = 4.01 h/3.50 h (in mouse; i.v./p.o.); F(%) = 85.21% in mouse.
In vivo: 70% survival in toxic shock model (40 mg/kg, p.o., 1 dose, 72 hrs); No reduction in colonic length in a murine ulcerative colitis model (10 mg/kg, p.o., 1 dose per day, 9 days); Decreased liver/body ratio and improved liver morphology in a murine NASH model (40 mg/kg, p.o.)

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Key Laboratory of Marine Drugs , China

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