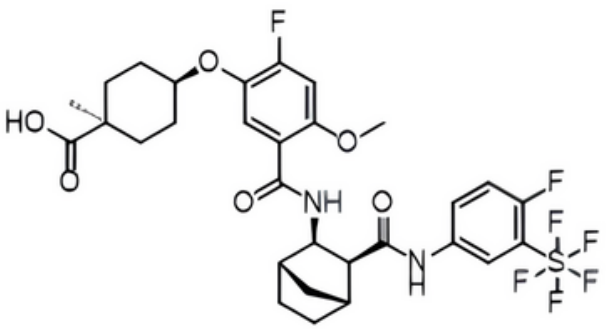
# Small Molecule Highlights

Snapshots from Recent Literature in Target-oriented Drug Design

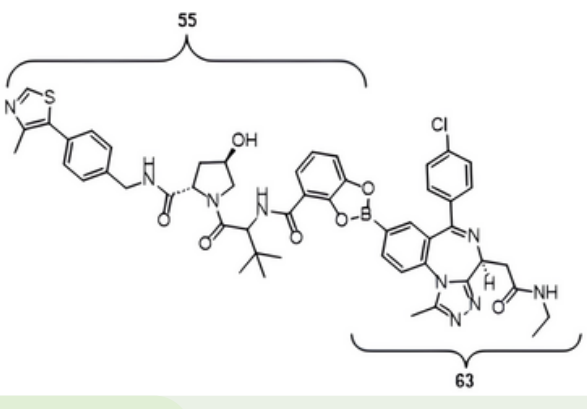
DALRIADA TURN-KEY™ DRUG DISCOVERY



## RXFP1 — AZ7976 (Heart)

Target: Relaxin family peptide receptor 1 (RXFP1)
Indication: Heart failure
Inhibitor design: SAR optimization from known small molecule agonist.
Activity: cAMP pEC50 = 9.4 (cellular); RXFP1 selectivity >5000-fold (Eurofins selectivity panel)
ADME/PK: CLHep(mL/min/106 cells) = 23 in rat; F(%) = 11 in rat; T1/2(h) = 2.9 in rat.
In vivo: Increased heart rate and mean blood pressure in anesthetized rats (1.5 + 9 mg/kg, i.v.).

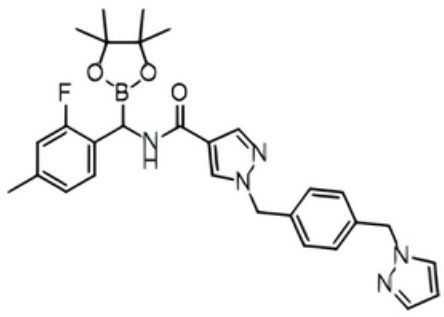
J. Med. Chem.
AstraZeneca and the Mitsubishi Tanabe Pharma , Sweden/Japan




## BRD4 — CURE-PRO 55+63 (Oncology)

Target: Bromodomain-containing protein 4 (BRD4)
Indication: Oncology
Inhibitor design: Combinatorial screening.
Activity: BRD4 EC50 = 358 nM (cellular); Real-time kinetic degradation observed in HiBiT-BRD4 KI HEK293 (LgBiT) cells.
ADME/PK: Microsome stability T1/2 >60 min/29 min for 63/55 in mouse liver microsomes; T1/2 >60 for 63 & 55 in human liver microsomes; In vivo T1/2 = 6.3 h for 63 & 55 (mouse, 10 mg/kg, i.p.), Tmax = 0.5 h for 63 & 55 (mouse, 10 mg/kg, i.p.), AUClast = 2340/1890 h*ng/mL for 55/63, respectively.
In vivo: BRD4 degradation was demonstrated in an MV4-11 mouse xenograft model. Time-course results were in line with in vitro results.

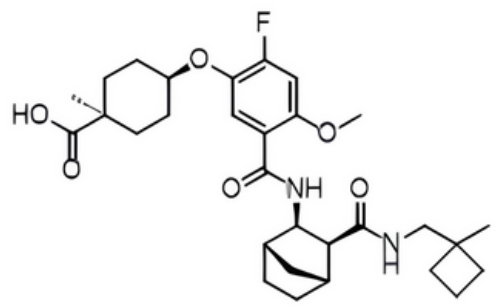
J. Med. Chem.
Cornell University, USA



## PKa — Compound 20 (Cardiovascular)

Target: Plasma kallikrein (PKa)
Indication: Hereditary angioedema (HAE)
Inhibitor design: Structure-based drug design and SAR.
Activity: PKa IC50 = 66/6.9/0.3/0.07 nM @ 1/10/60/1440 min (biochemical); Selectivity >1000-fold against FXIa, thrombin, trypsin, and Plasmin (biochemical); No dissociation observed in a jump dilution assay (biochemical).

Med. Chem. Lett
KalVista Pharmaceuticals and the University of Nottingham , USA



## RXFP1 — AZD5462 (Heart)

Target: Relaxin family peptide receptor 1 (RXFP1)
Indication: Heart failure
Inhibitor design: SAR, lead optimization.
Activity: cAMP pEC50 = 7.8 (cellular); cGMP pEC50 = 7.3 (cellular); ERK pEC50 = 8.2 (cellular).
ADME/PK: CLHep(mL/min/106 cells) = 11 in rat; F(%) = 47 in rat; T1/2(h) = 4.6 in rat.
In vivo: Increased heart rate and mean blood pressure in anesthetized rats (11 + 45 mg/kg, i.v.). Sustained increase in left ventricle ejection fraction in a monkey model of heart failure (1 mg/kg, s.c., b.i.d.; 10 mg/kg, s.c., b.i.d.)

J. Med. Chem.
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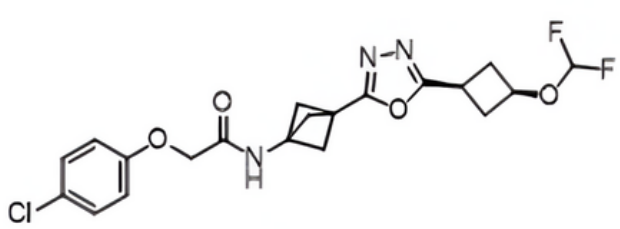

## eIF2B — DNL343 (Neurodegenerative)

Target: Eukaryotic translation initiation factor 2B (eIF2B)
Indication: Vanishing white matter (VWM) disease and amyotrophic lateral sclerosis (ALS)
Inhibitor design: Structure-based drug design, HTS screening, and SAR.
Activity: ATF4 IC50 = 9.8 nM (cellular); stress granule IC50 = 13 nM (cellular) .
ADME/PK: F(%) = 65/>99/>99 in rat/dog/monkey; In vivo T1/2(h)= 12.5/7.4/7.6 in rat/dog/monkey; Bu/Pu Ratio = 0.8/0.9 in rat/monkey.
In vivo: Observed decrease in ISR transcript markers in the brain 4-7 hours post after last dose in Eif2b5 R191H homozygous mice (50 mg/kg, q.d., 2-day study)

J. Med. Chem.
Denali Therapeutics, USA



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