Targeted SL: Antimalarial Agents-1

Challenge:

Novel starting points in Malaria drug discoverty [1].

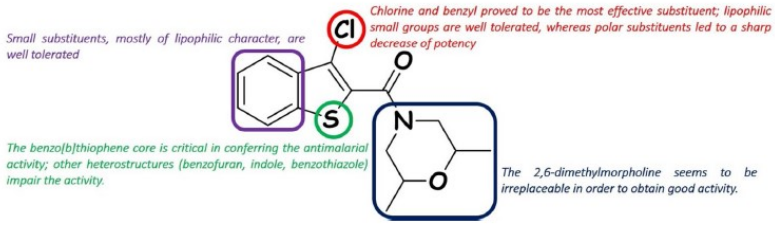
Design Rationale:

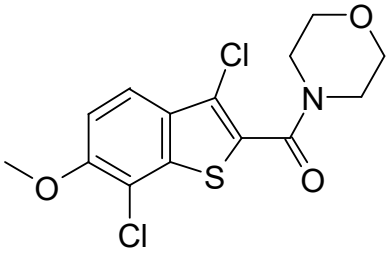
Analogs of known antimalarial agents [1-2] form Asinex lead-like collections.

Library Size: 80 compounds

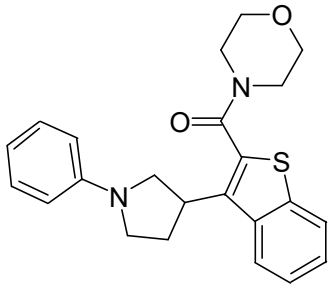
Scaffold: benzo[*b]thiophene-2*-carboxamides

SDF: SL#61_Malaria-1.sdf

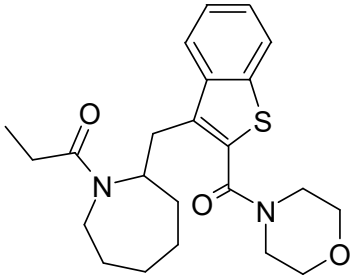




LAS 00336460



LAS 27573234



LAS 24035304

Reference:
• An Invitation to Open Innovation in Malaria Drug Discovery: 47 Quality Starting Points from the TCAMS. ACS Med. Chem. Lett. 2011, 2, 741–746. 10.1021/ml200135p.
• Accepting the Invitation to Open Innovation in Malaria Drug Discovery: Synthesis, Biological Evaluation and Investigation on the Structure Activity Relationships of Benzo[b]thiophene-2-carboxamides as Antimalarial Agents. J. Med. Chem., 2017. 10.1021/acs.jmedchem.6b01685.

Targeted SL: Microbial b-glucuronidase inhibitors

Challenge:

Inhibitors of bacterial b-glucuronidases for controlling drug-induced gastrointestinal toxicity.

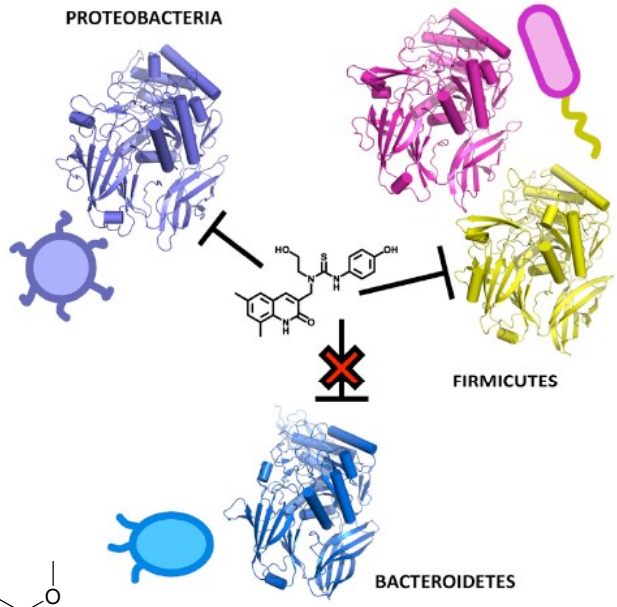
Design Rationale:

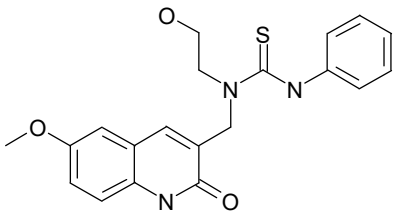
Analog search around published inhibitors [1].

Library Size: 80 compounds

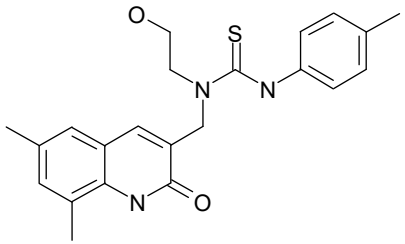
Scaffold: 3-aminomethylquinol-2-one aryl-thiocarbamates

SDF: SL#62_Mic_bGluc.sdf

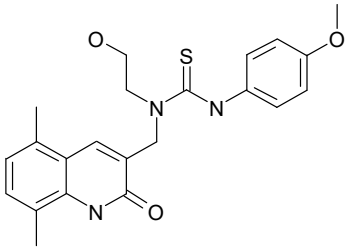




LAS 03367093



LAS 03273358



LAS 03364961

Reference:

- Structure and Inhibition of Microbiome b-Glucuronidases Essential to the Alleviation of Cancer Drug Toxicity Chemistry & Biology 22, (2015), 1238–1249. 10.1016/j.chembiol.2015.08.005

Chemocentric SL: Preferred RNA-binding motif: 2-phenyl benzimidazole

Challenge:

Novel ncRNA-binding small molecule scaffolds for drug discovery.

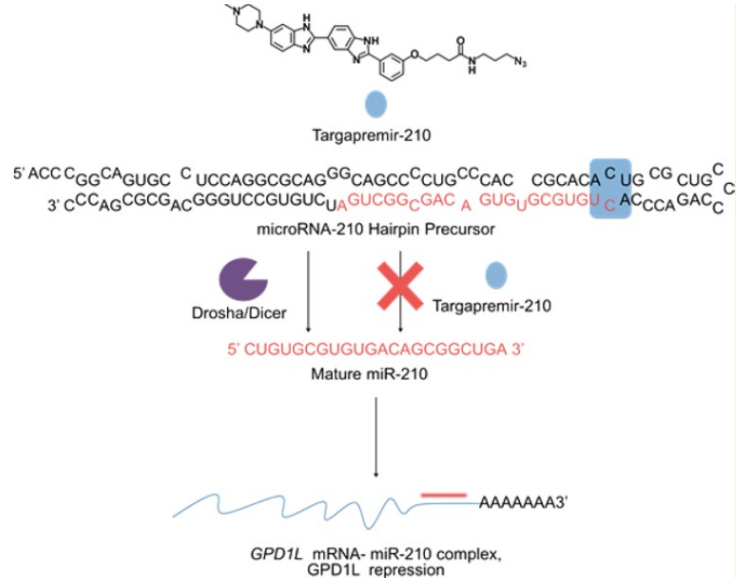
Design Rationale:

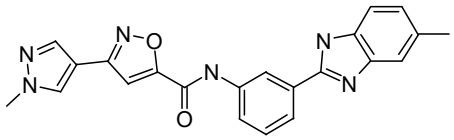
Analogs of published microRNA-binding ligands [1-3].

Library Size: 80 compounds

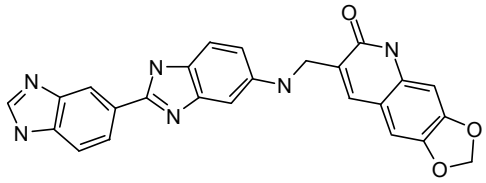
Scaffold: 2-phenyl benzimidazole

SDF: SL#63_BenzImidaz_miR.sdf

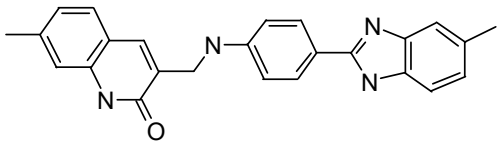




LAS 23011230



LAS 07407958



LAS 07407793

Reference:
- Identifying the preferred RNA motifs and chemotypes that interact by probing millions of combinations. NATURE COMMUNICATIONS (2012). 10.1038/ncomms2119.
- Small Molecule Inhibition of microRNA-210 Reprograms an Oncogenic Hypoxic Circuit. J. Am. Chem. Soc. (2017). 10.1021/jacs.6b11273.
- Approaches for the Discovery of Small Molecule Ligands Targeting microRNAs. Top Med Chem. 2017. 10.1007/7355_2017_3.

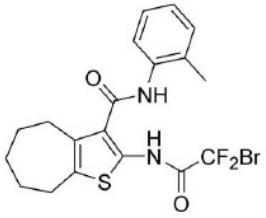
Targeted SL: TMEM16A Channel Modulators

Challenge:

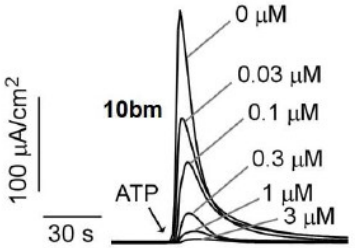
Novel drug-like molecules targeting calcium-activated chloride channels.

Design Rationale:

Analogs of published small molecule TMEM16A modulators [1].



10bm IC_{50} = 30 nM

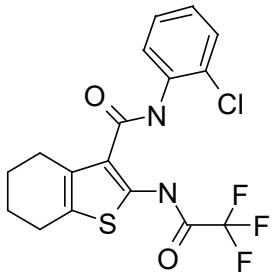


TMEM16A short-circuit current

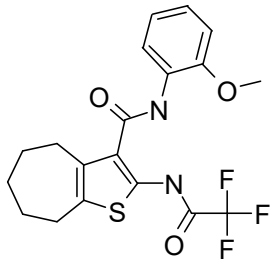
Library Size: 80 compounds

Scaffold: 2-acylamino-cycloalkylthiophene-3-carboxylic acid arylamides

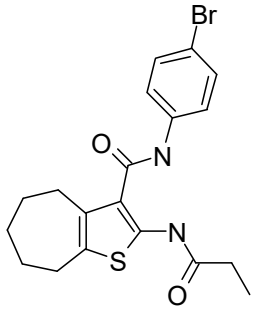
SDF: SL#64_TMEM16A_ICh.sdf



LAS 00832372



LAS 00832131



LAS 00832089

Reference:
• Substituted 2-acylamino-cycloalkylthiophene-3-carboxylic acid arylamides as inhibitors of the calcium-activated chloride channel transmembrane protein 16A (TMEM16A).
Journal of Medicinal Chemistry (2017). 10.1021/acs.jmedchem.7b00020

Targeted SL: Antileishmaniasis Agents

Challenge:

Novel starting points in Leishmania drug discovery.

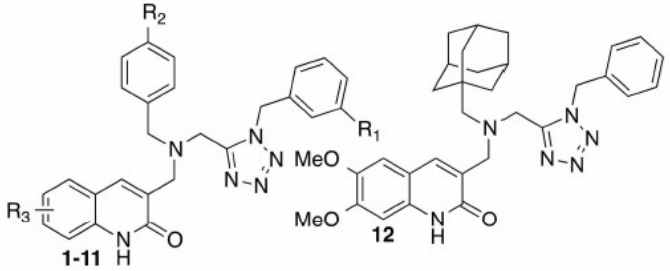
Design Rationale:

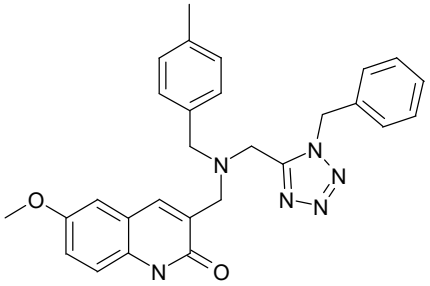
Analogs of published inhibitors of Leishmania major tryparedoxin peroxidase (LmTXNPx) [1].

Library Size: 80 compounds

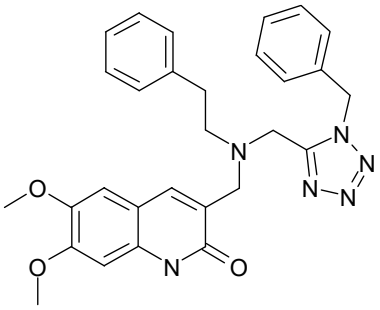
Scaffold: N,N-disubstituted 3-aminomethyl quinolone

SDF: SL#65_Leishmaniasis.sdf

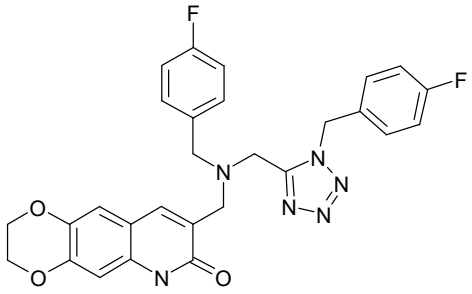




LAS 05298441



LAS 05298743



LAS 05299027

Reference:
• Structure-based discovery of the first non-covalent inhibitors of Leishmania major tryparedoxin peroxidase by high throughput docking.. Sci. Rep. 5, 9705; DOI:10.1038/srep09705 (2015).

Targeted SL: miR-21 inhibitors

Challenge:

Novel microRNA-binding molecules the treatment for microRNA-associated pathologies [1].

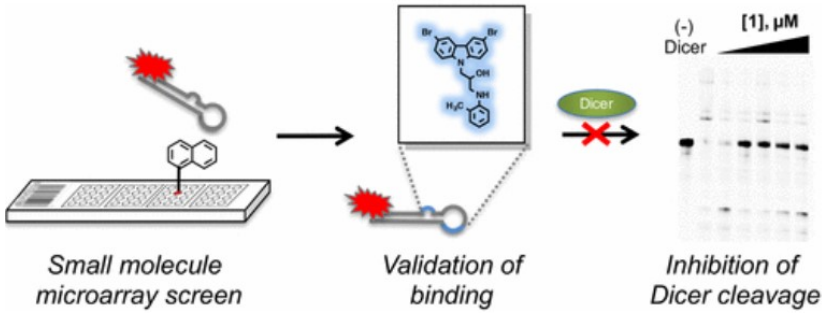
Design Rationale:

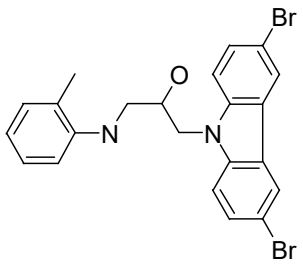
Analogs of published small molecules targeting miR-21 [2].

Library Size: 80 compounds

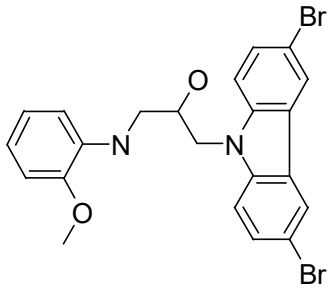
Scaffold: amino - 3 - (carbazol - 9 - yl)propan - 2 -

SDF: SL#66_miR-21.sdf

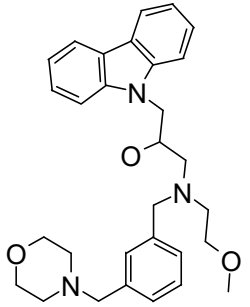




LAS 00340464



LAS 00340482



LAS 52133541

Reference:
• Neuroprotection of microRNA in neurological disorders. BIOMEDICAL REPORTS (2014), 611-619. 10.3892/br.2014.297.
• Discovery of Inhibitors of MicroRNA-21 Processing Using Small Molecule Microarrays. ACS Chemical Biology. (2016). 1021/acschembio.6b00945.

Targeted SL: miR-29 inhibitors

Challenge:

Novel microRNA-binding molecules the treatment for microRNA-associated pathologies [1].

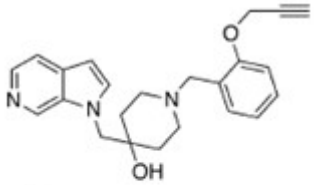
Design Rationale:

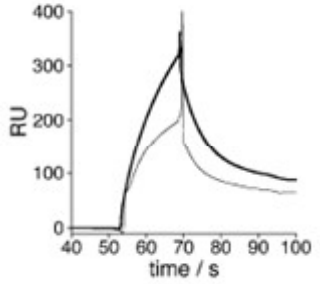
Analogs of published small molecules targeting miR-29.

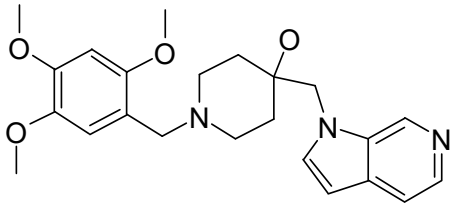
Library Size: 80 compounds

Scaffold: 4-(azaindolyl)methyl-4-hydroxy-piperidine

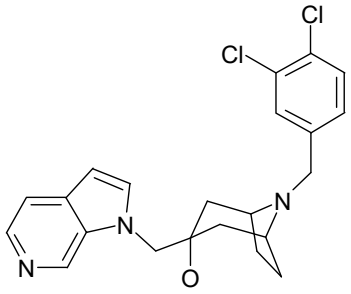
SDF: SL#67_miR-29.sdf



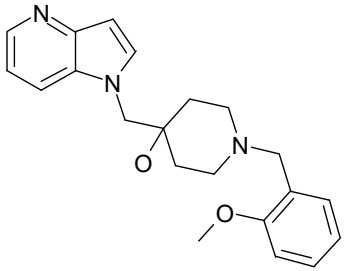




LAS 17111600



LAS 18105751



LAS 18687451

Reference:
• Exploratory Study on the RNA-Binding Structural Motifs by Library Screening Targeting pre-miRNA-29a. Chem. Eur. J. 2015, 21, 16859 – 16867. 10.1002/chem.201502913.

Targeted SL: Bacterial riboswitch inhibitors

Challenge:

Novel bacterial RNA-interacting small molecules for the treatment of microbial-associated pathologies.

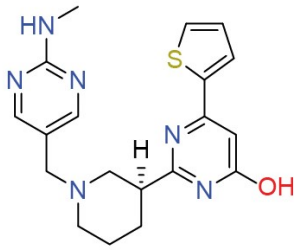
Design Rationale:

Analogs of Ribocil [1,2].

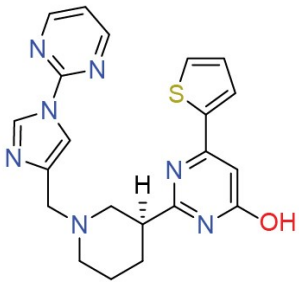
Library Size: 80 compounds

Scaffolds: Asinex BioDesign Scaffolds

SDF: SL#68_FMN_riboswitch.sdf



Ribocil-B

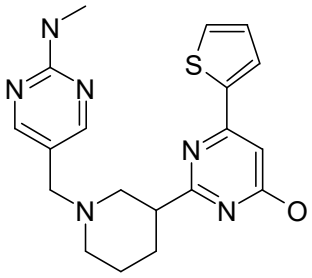


Ribocil-C

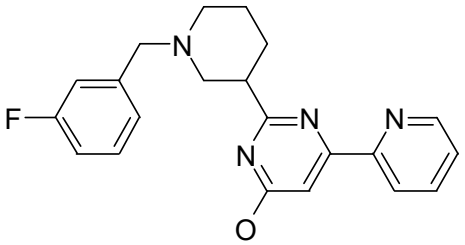
MIC *E. coli* MB5746 (µg/mL)

1

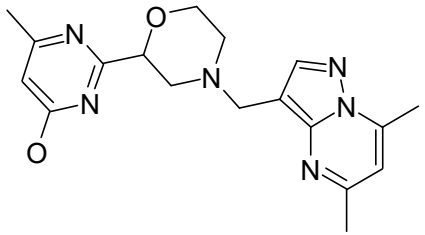
0.25



LAS 19562546



LAS 17848165



LAS 33057040

Reference:

- Selective small-molecule inhibition of an RNA structural element. Nature (2015). 10.1038/nature15542.
- Atomic resolution mechanistic studies of ribocil: A highly selective unnatural ligand mimic of the E. coli FMN riboswitch. RNA BIOLOGY (2016), VOL. 13, NO. 10, 946–954. 10.1080/15476286.2016.1216304.

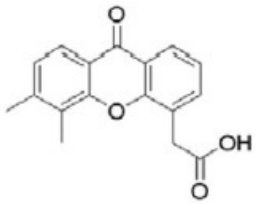
Chemocentric SL: Interferon (IFN) inducers

Challenge:

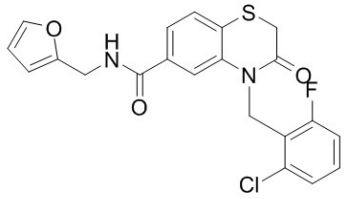
Novel small molecule agents that can effectively modulate innate immune signaling pathways.

Design Rationale:

Analogs of published small molecule modulators of IFN activation [1,2].



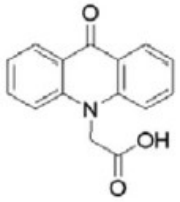
DMXAA



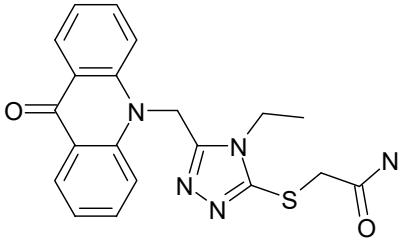
STING agonist-1 (G10)

Library Size: 80 compounds

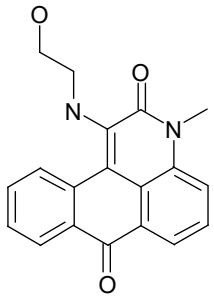
SDF: SL#69_IFN_inducer.sdf



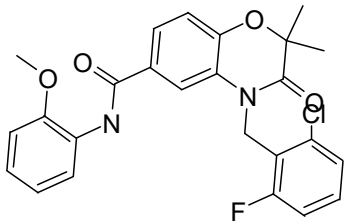
CMA



LAS 12777229



LAS 05532733



LAS 06577425

Reference:

• Species-specific detection of the antiviral small-molecule compound CMA by STING. The EMBO Journal (2013) 32, 1440–1450. 10.1038/emboj.2013.86.

• Characterization of a Novel Human-Specific STING Agonist that Elicits Antiviral Activity Against Emerging Alphaviruses. PLOS Pathogens (2015). 10.1371/journal.ppat.1005324.

Targeted SL: HIV TAR RNA small molecule binders

Challenge:

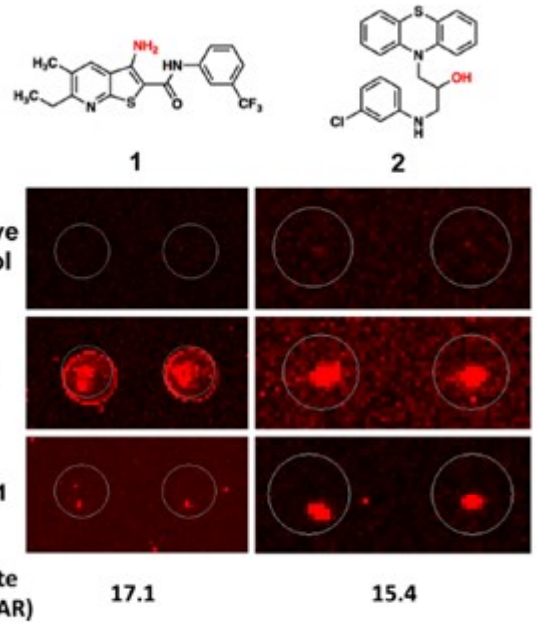
Novel RNA-interacting small molecules for the treatment of viral infections.

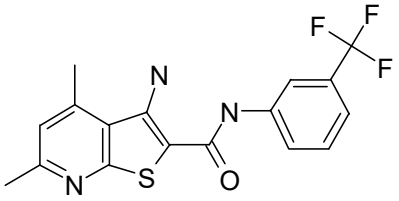
Design Rationale:

Analogs of published molecules interacting with HIV transactivation response (TAR) RNA hairpin [1].

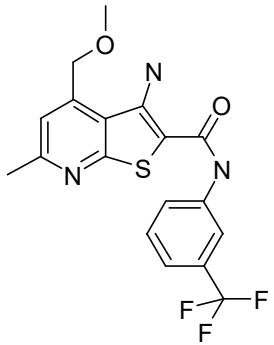
Library Size: 80 compounds

SDF: SL#70_HIV_TAR_binder.sdf

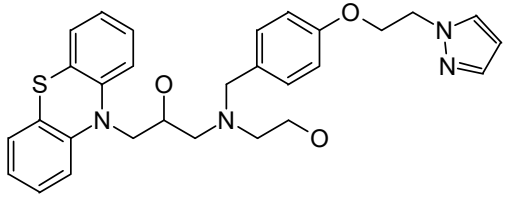




LAS 02054032



LAS 13120244



LAS 52118989

Reference:

• Identification of Biologically Active, HIV TAR RNA-Binding Small Molecules Using Small Molecule Microarrays. J. Am. Chem. Soc. 2014, 136, 8402−8410. 10.1021/ja502754f

Chemocentric SL: Taxol mimetics

Challenge:

Drug-like small molecule Taxol mimetics that display a Taxol-like mechanism of action (microtubule polymerization).

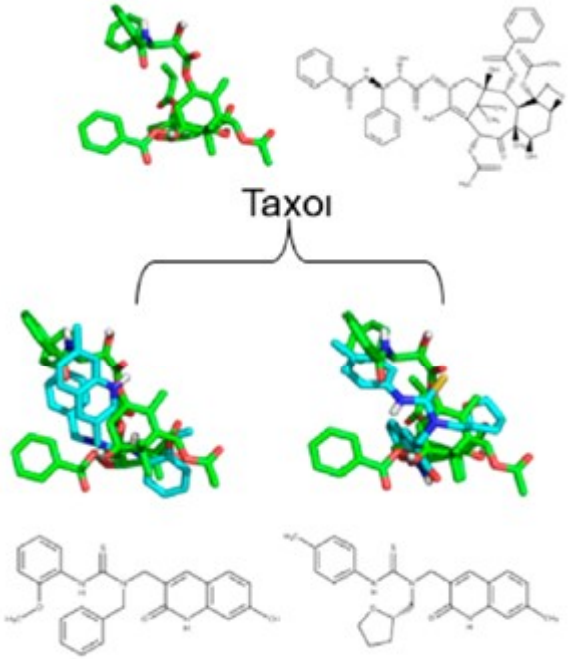
Design Rationale:

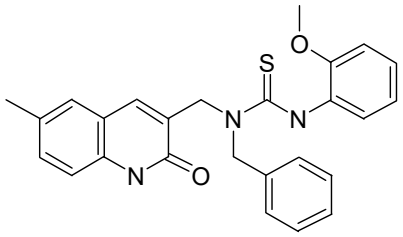
Analog search based on published small molecule Taxol mimetics [1].

Library Size: 80 compounds

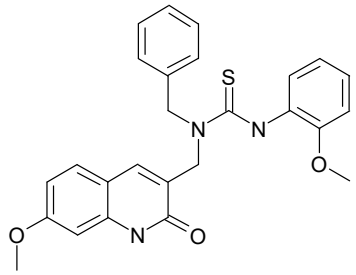
Scaffolds: 3-aminomethylquinol-2-one aryl-thiocarbamates

SDF: SL#71_Taxol-like.sdf





LAS 03069755



LAS 03366822

Reference:
• 3D Chemical Similarity Networks for Structure-Based Target Prediction and Scaffold Hopping. ACS Chem. Biol (2016). 10.1021/acschembio.6b00253.

Targeted SL: Cystic fibrosis

Challenge:

Novel small molecules for Cystic Fibrosis drug discovery.

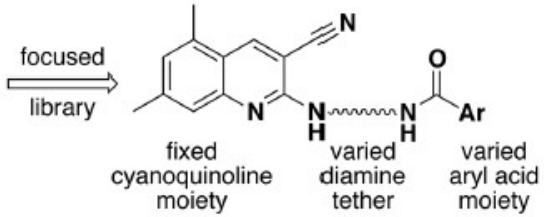
Design Rationale:

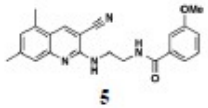
Analogs of published correctors of ΔF508-CFTR channels [1].

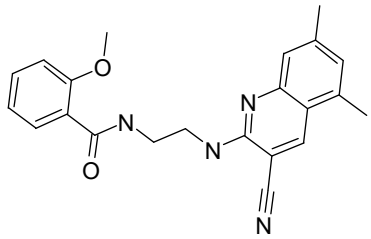
Library Size: 80 compounds

Scaffolds: 2-amino-3-cyanoquinolines

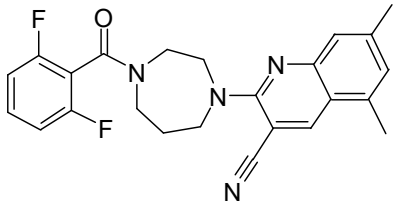
SDF: SL#72_CFTR.sdf



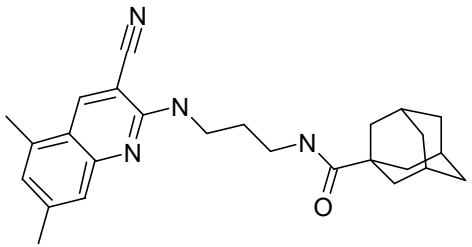
CoPo	Corrector		Potentiator	
	EC_{50} (μM)	V_{max} (μM/S)	EC_{50} (μM)	V_{max} (μM/s)
 5	2.2 ±0.3	300	5.9 ± 0.5	216



LAS 06540480



LAS 06541401



LAS 06540921

Reference:
• Structure-Activity Relationships of Cyanoquinolines with Corrector-Potentiator Activity in *delta-F508-Cystic Fibrosis* Transmembrane Conductance Regulator Protein. J Med Chem. 2012 February 9; 55(3): 1242–1251. doi:10.1021/jm201372q

Targeted SL: DLK (MAP3K12) kinase inhibitors for CNS

Challenge:

Small molecule inhibitors of DLK (MAP3K12) kinase for CNS-related drug discovery [1].

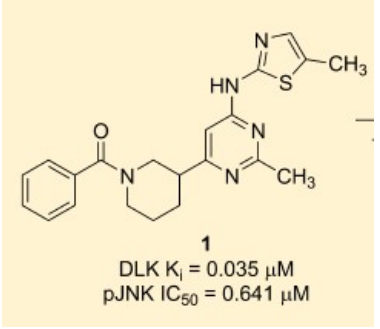
Design Rationale:

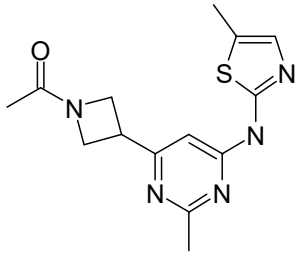
Analogs of published small molecule DLK kinase inhibitors [2].

Library Size: 80 compounds

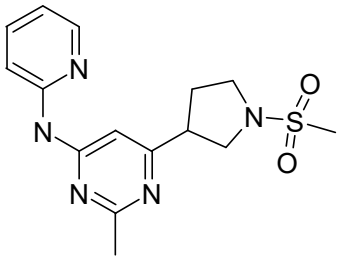
Scaffold: Asinex BioDesign

SDF: SL#73_DLK_inh.sdf

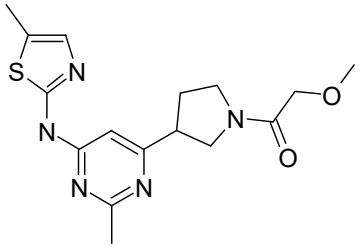




LAS 28291789



LAS 28294592



LAS 28296678

Reference:
- Dual leucine zipper kinase (MAP3K12) modulators: a patent review (2010–2015) Conductance Regulator Protein. EXPERT OPINION ON THERAPEUTIC PATENTS, 2016. 10.1517/13543776.2016.1170810
- Discovery of Dual Leucine Zipper Kinase (DLK, MAP3K12) Inhibitors with Activity in Neurodegeneration Models J. Med. Chem. 2015, 58, 401−418. 10.1021/jm5013984.

Targeted SL: Inhibitors of PKCε/RACK2 interaction

Challenge:

Non-peptidic, non-ATP binding small molecule regulators of PKCε signaling.

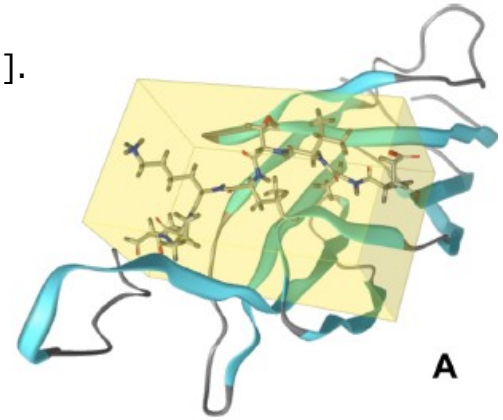
Design Rationale:

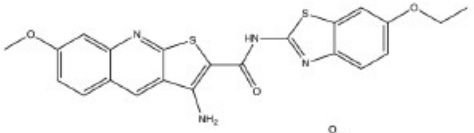
Analogs of published cell-permeable inhibitors of PKCε/RACK2 interaction [1].

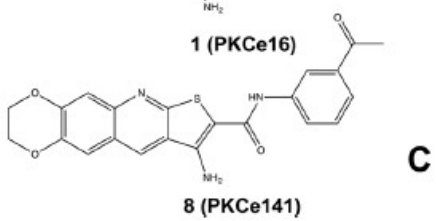
Library Size: 80 compounds

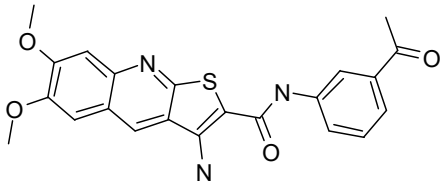
Scaffold: 3-amino-2-carboxy-thienoquinoline amides

SDF: SL#74_PKCε_RACK2.sdf

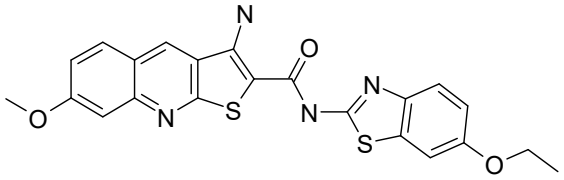








LAS 05545456



LAS 02538754

Reference:

• Thienoquinolines as Novel Disruptors of the PKCε/RACK2 Protein−Protein Interaction. J.Med.Chem. **57**, 3235. 10.1021/jm401605c

Targeted SL: Wnt pathway inhibitors

Challenge:

Small molecules capable of modulating the Wnt/β-catenin signaling pathway.

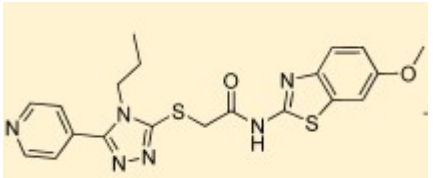
Design Rationale:

Analog of published inhibitors of Porcupine - a membrane bound O-acyl transferase [1].

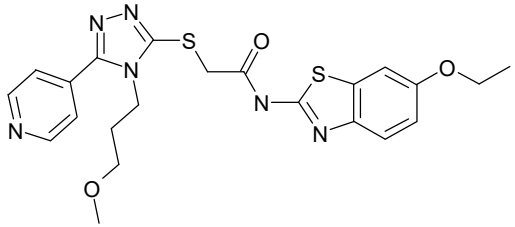
Library Size: 80 compounds

Scaffold: 2-aminobenzothiazole amides

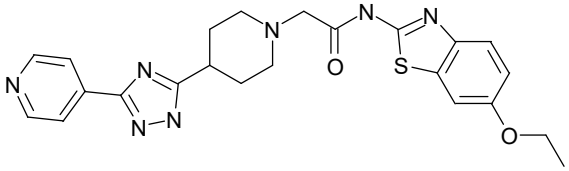
SDF: SL#75_WNT_PORCN.sdf



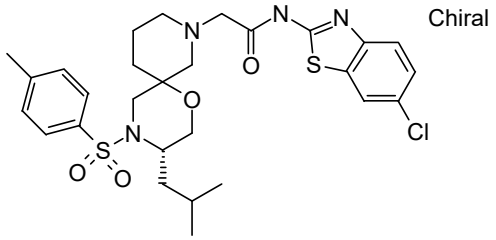
GNF-1331 (HTS hit)
IC_{50} = 12 nM



LAS 03221732



LAS 10371130



LAS 51217050

Reference:
• Discovery of Pyridinyl Acetamide Derivatives as Potent, Selective, and Orally Bioavailable Porcupine Inhibitors. ACS Med. Chem. Lett. **2016**. 10.1021/acsmedchemlett.6b00038.

Chemocentric SL: OxyTerpenoids for CNS drug discovery

Challenge:

Novel skeletally diverse, Natural Product-like molecules for CNS drug discovery.

Design Rationale:

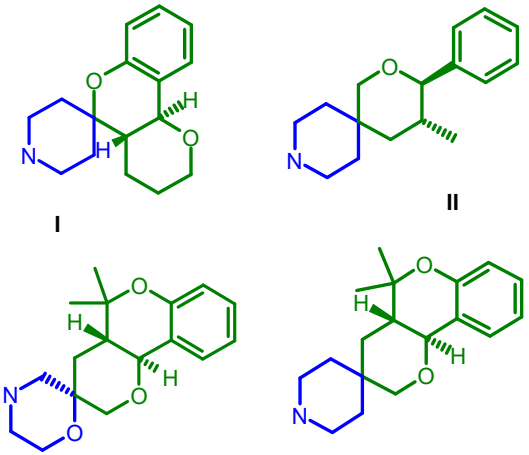
CNS MPO score-based selection of terpenoid-like small molecules with good PAMPA and PAMPA-BBB permeability [1-2].

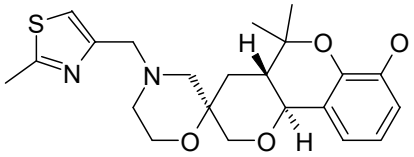
Library Size: 80 compounds

Scaffold: polycyclic oxygenated terpenoid-like

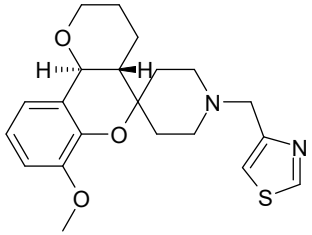
SDF: SL#76_OxyTerpenoid_for_CNS.sdf

Scaffolds¥Cores

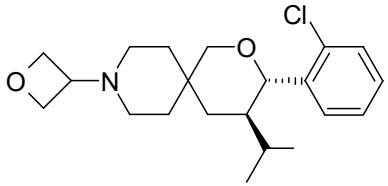




LAS 73704969
CNS MPO 4.8
PAMPA BBB 8*10-6 cm/s



LAS 33900206
CNS MPO 5.1
PAMPA BBB 9.9*10-6 cm/s



LAS 73708654
CNS MPO 4.9
PAMPA BBB 7.9*10-6 cm/s

Reference:
• CNS Drug Design: Balancing Physicochemical Properties for Optimal Brain Exposure.
J. Med. Chem., **2015**, *58* (6), pp 2584–2608. 10.1021/jm501535r.
• Central Nervous System Multi-Parameter Optimization (CNS MPO) Desirability: Application in Drug Discovery.
ACS Chem. Neurosci., **2016**, *7* (6), pp 767–775. 10.1021/acschemneuro.6b00029.

Chemocentric SL: Morpholines for CNS

Challenge:

Novel lead-like molecules for CNS drug discovery.

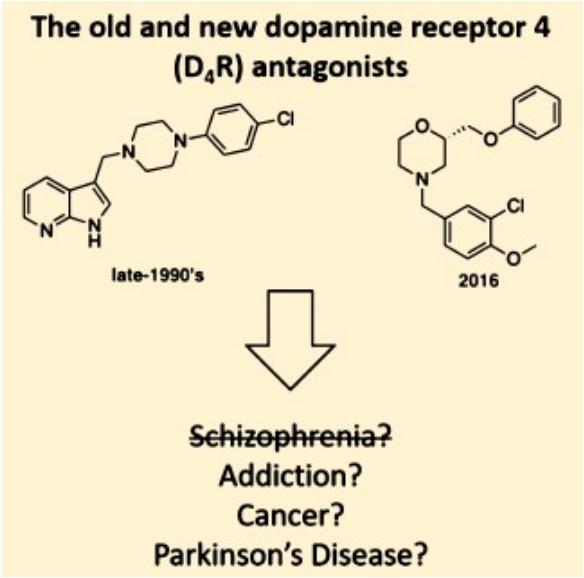
Design Rationale:

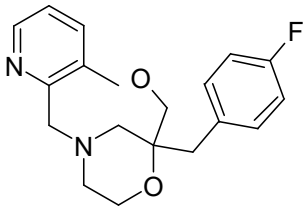
CNS MPO score-based selection of morpholine-containing small molecules with good PAMPA and PAMPA-BBB permeability [1-2].

Library Size: 80 compounds

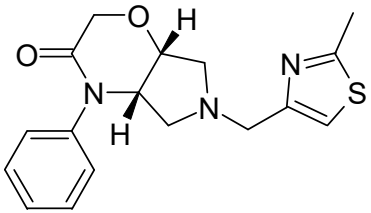
Scaffold: morpholine-containing, N-basic

SDF: SL#77_Morpholines_for_CNS

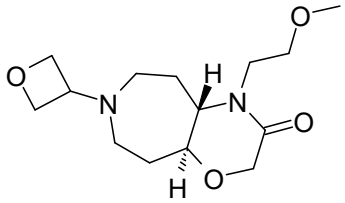




LAS 51753386
CNS MPO 5.8



LAS 73701293
CNS MPO 5.8



LAS 73708666
CNS MPO 6.0

Reference:
- Innovative solutions to novel drug development in mental health. Neuroscience and Biobehavioral Reviews 37 (2013) 2438–2444. 10.1016/j.neubiorev.2013.03.022
- Return of D4 Dopamine Receptor Antagonists in Drug Discovery. J. Med. Chem., Article ASAP (2017). 10.1021/acs.jmedchem.7b00151

Chemocentric SL: Sympathomimetics

Challenge:

Novel lead-like small molecules mimicking the effects of endogenous agonists of the sympathetic nervous system.

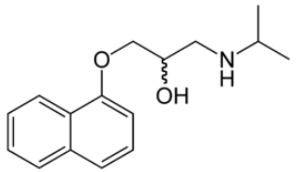
Design Rationale:

Sympathomimetic scaffolds containing skeletaly diverse 3-amino-2-hydroxypropanol fragments [1-3].

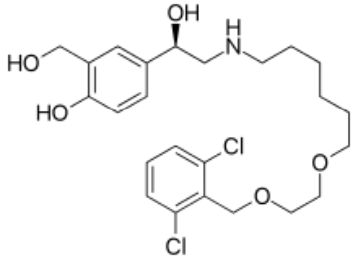
Library Size: 80 compounds

Scaffold: 3-amino-2-hydroxypropanol

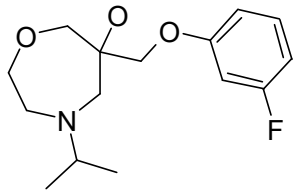
SDF: SL#78_Sympathomimetics-1.sdf



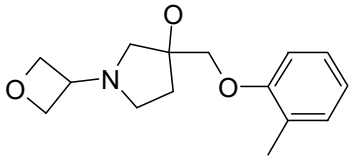
The first clinically successful beta blocker - **Propranolol**



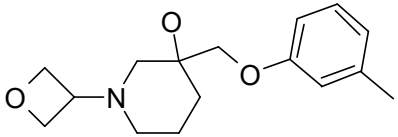
Vilanterol (GSK)
Ultra-long-acting β_2 adrenergic receptor agonists.
Approved in May 2013.
Chronic obstructive pulmonary disease (COPD) treatment.



LAS 51737785



LAS 73700556



LAS 73700446

Reference:
- Beta-Adrenergic Receptors, from Their Discovery and Characterization through Their Manipulation to Beneficial Clinical Application. Cardiology 2012;122:104–112. 10.1159/000339271
- Basic and Clinical Pharmacology of Autonomic Drugs. Anesth Prog 59:159–169 2012. 10.2344/0003-3006-59.4.159
- Beta-adrenergic blocking drugs in breast cancer: a perspective review. Therapeutic Advances in Medical Oncology 2012; 4(3):113-125.

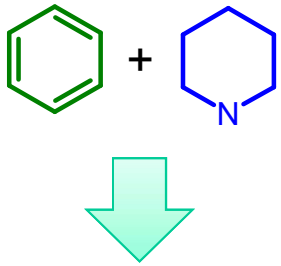
Chemocentric SL: Piperidines for CNS - 1

Challenge:

Novel stating points for CNS drug discovery.

Design Rationale:

CNS MPO score-based selection form 3-benzylpiperidine-containing scaffolds, demonstrating good PAMPA, PAMPA-BBB permeability.

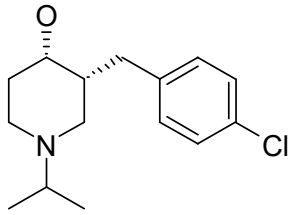


Library Size: 80 compounds

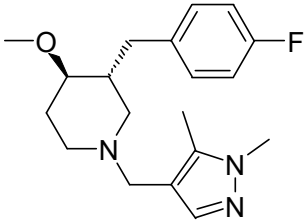
Scaffolds: 3-benzylpiperidine

SDF: SL#79_Piperidine_for_CNS_1.sdf

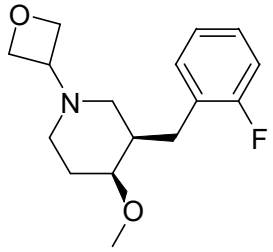
>100 Approved Drugs
for CNS-related Disorders
(www.drugbank.ca)



LAS 51737914



LAS 51758855



LAS 73700598

Reference:
• BioCores: identification of a drug/natural product-based privileged structural motif for small-molecule lead discovery. Mol Divers (2010) 14:193–200. 10.1007/s11030-009-9157-5.

Chemocentric SL: Analgesics

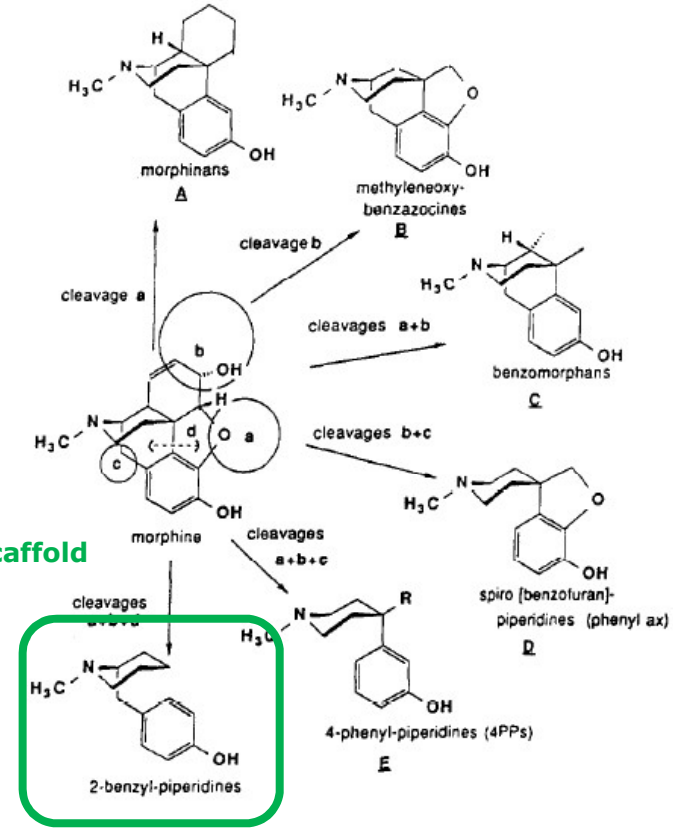
Challenge:

Lead-like starting points for discovery of novel analgesics.

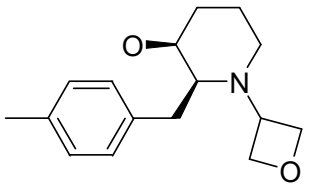
Design Rationale:

Privileged scaffold derivatives selected by CNS MPO scoring and PAMPA /PAMPA-BBB permeability profiling [1-3].

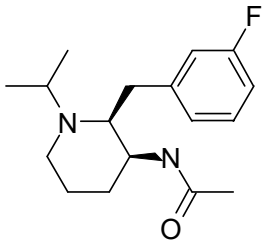
Library Size:	80 compounds
Scaffold:	2-benzylpiperidine
SDF:	SL#80_Analgesic_for_CNS-1.sdf



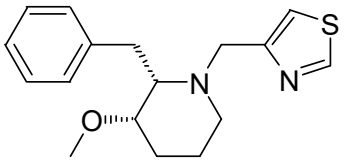
Schematic representation of the reduction of morphine into various substructures retaining opiate activity [3].



LAS 73700634



LAS 52207105



LAS 51749203

Reference:

- Breaking barriers to novel analgesic drug development. Nature Reviews Drug Discovery (2017). 10.1038/nrd.2017.87
- Structure–based discovery of opioid analgesics with reduced side effects. Nature. 2016 September 08; 537(7619): 185–190. doi:10.1038/nature19112
- Structure-activity studies of morphine fragments. III. Synthesis, opiate receptor binding, analgetic activity and conformational studies of Spiro [tetralin-1,4'-piperidines]. Eur J Med Chem (1991) 26,775-785.