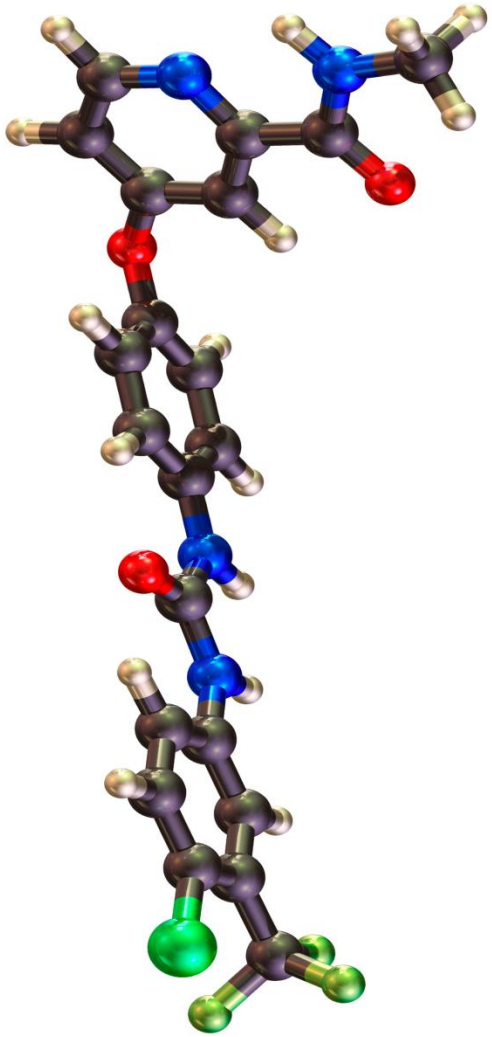
ChemDiv
The chemistry of cures℠



Antiviral Library

ChemDiv Inc.

2015

Discovery™ outSource

Target to Lead
Lead to Candidate
Candidate to POC
POC to Market

Knowledge Mining Sources

PubChem Database

Thomson Integrity

SciFinder

ChEMBL

Pocketom

BindingDB

Protein Data Bank

MOAD

Scientific publication & Patents (2010-2015)

Knowledge Progression & Selection

Learning → Analysis → CADD → Selection → Screening

Reference Compounds

- isosteric & bioisosteric transformations
- hot-spots & crucial binding points
- scaffold hopping
- 2D topological & 3D similarity
- 2D & 3D fingerprints
- scaffold & target priority/profiling

- 2D Similarity
- 3D Molecular Docking
- 2D/3D Topological analogues
- 3D Pharmacophore modeling

- >25K Templates Design
- Focus on novel chemistry
- Targeted Diversity
- Scaffold prioritization
- MedChem Filters

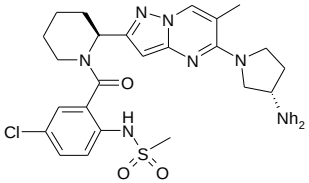
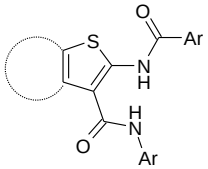
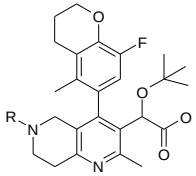
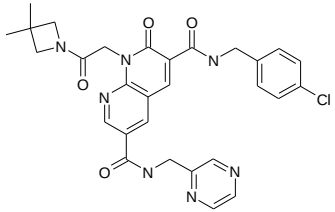
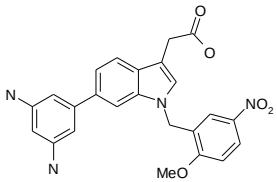
Antiviral Library

Comprehensive Evaluation

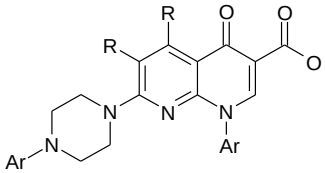
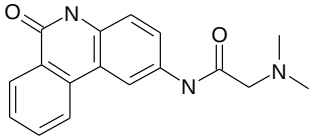
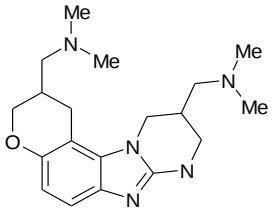
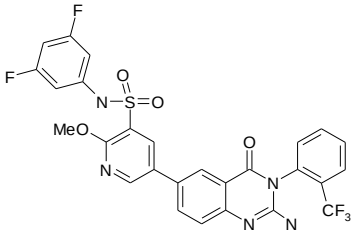
Reference Set Selection

Virus	Viral Targets & Assays
HCV	NS3 Helicase, NS3/4A protease, NS5A, NS5B, other
HIV	NL4-3, Fusion, Integrases, Trascriptase, Capsid Protein p24, Nucleocapsid, CCR5, other
Influenza	Neuraminidase, NS1, NS1A, phenotypical assay
Coronavirus	Phenotypical assay
Marburg	Entry, phenotypical assay
RSV	Fusion, non-fusion, phenotypical assay
Varicella zoster virus	Phenotypical assay
HSV	Phenotypical assay
Other viral targets	Over 50 targets evaluated

Reference Compounds (Examples)

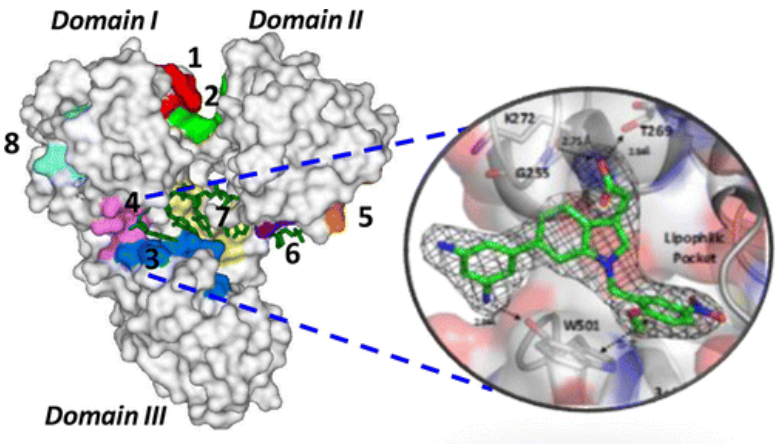
Structure	MOA	Activity	References
	RSV fusion inhibitor	RSV remission/reduction, in vitro, IC_{50}=0.430 nM	New Engl J Med **2014**, 371(8): 711
	RdRP inhibitors PB1/2/PA Influenzavirus A antiviral activity	IC_{50}=20-90 μM (ELISA assay)	J Med Chem **2013**, 56(24): 10118
	NL4-3 inhibitor Anti-HIV Agents	EC_{50}~0.001 μM	WO **2013**123148
	DNA Polymerase Inhibitor	IC_{50}=22 nM, HCMV polymerase (UL54) activity in vitro inhibition, TR-FRET LANCE assays	WO **2013**152063
	NS3 Protease Inhibitor Anti-Hepatitis C Virus Drug	IC_{50}=3.00 μM, Hepacivirin (helicase domain) inhibition, Fluorescent assay	J Med Chem **2014**, 57(5): 2074

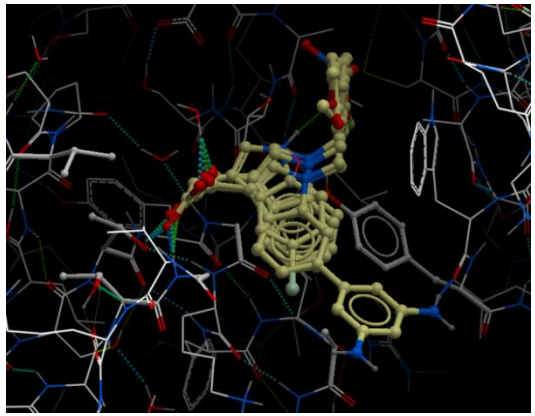
Reference Compounds (Examples)

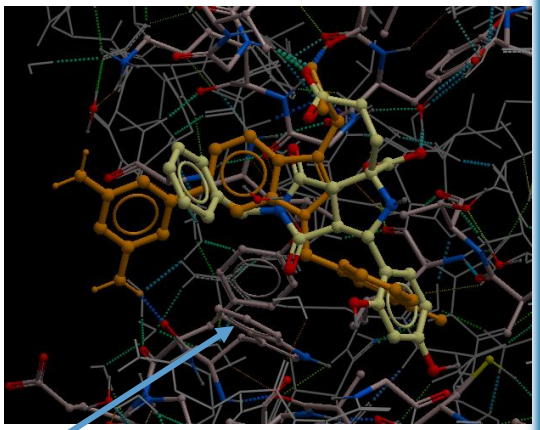
Structure	MOA	Activity	References
	human cytomegalovirus immediate-early 2 protein inhibitor/ E6 and E7 oncogene expression inhibitor	IC_{50}=0.260 μM, Luciferine/luciferase assay, Gene (HPV-16 E6/E7) transcription, inhibition	ChemMedChem **2013**, 8: 1403 J Med Chem 2014, 57(13): 5649
 **PJ-34**	CoVs N protein inhibitor		J Med Chem. **2014** Mar 27;57(6):2247-57
 **IBIS-00560146**	Internal Ribosomal Entry Site (IRES) Inhibitor Anti HCV Drug	IC_{50}=0.600 μM, Fluorescent assay	Nat Chem Biol **2009**, 5(11): 823
	PI4Ka Inhibitor Anti HCV Drug	pIC_{50}=8.60, Luciferine/luciferase assay, Recombinant enzyme	J Med Chem **2014**, 57(5): 2091

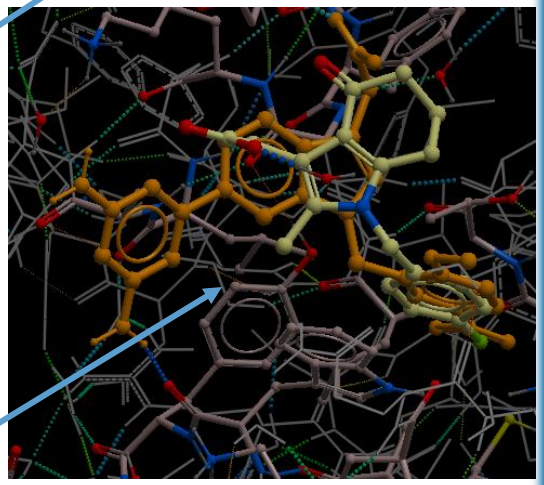
Methodology for Compound Selection

Modeling and *in silico* Evaluation (Example, NS3 Helicase)

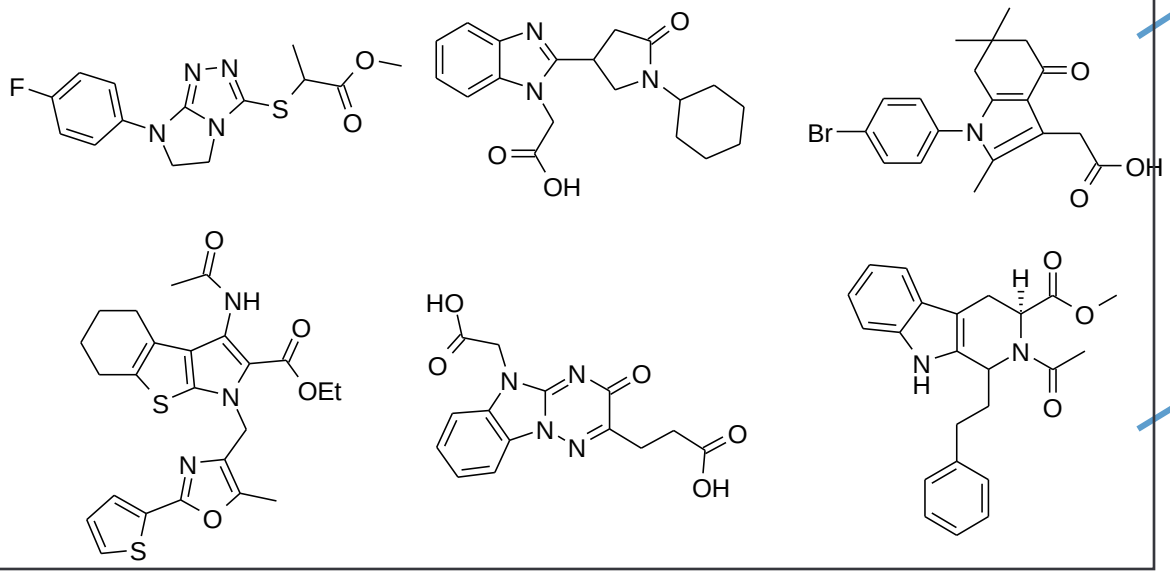








Library Examples



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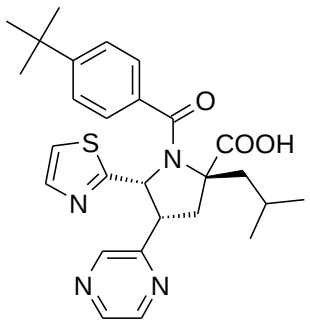
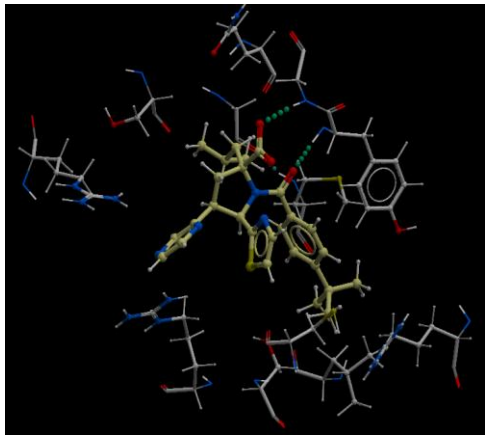
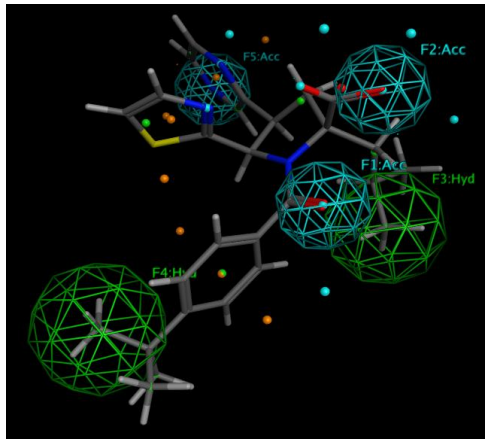
The chemistry of cures℠

Methodology for Compound Selection

Modeling and *in silico* Evaluation (Example, NS5B Pharmacophores)







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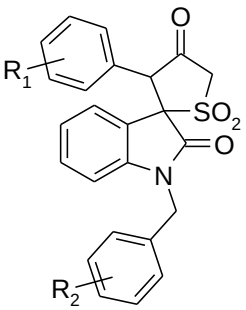
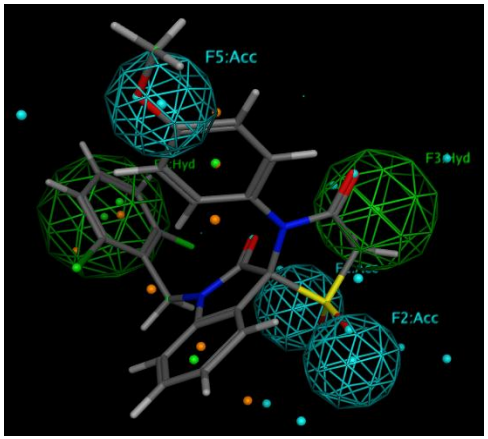
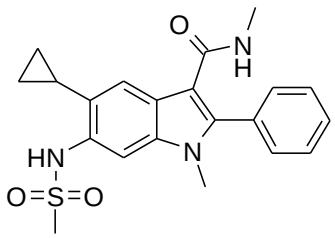
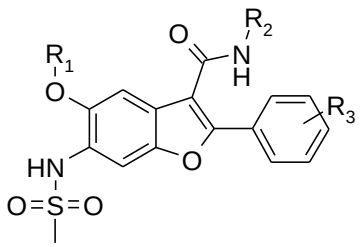


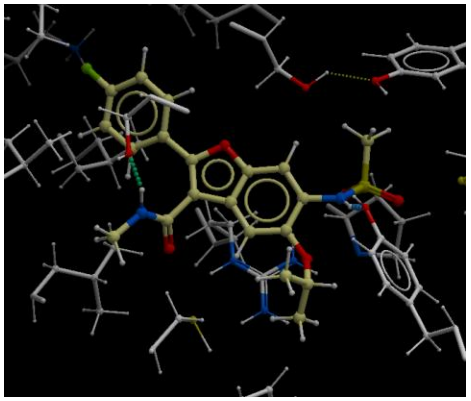


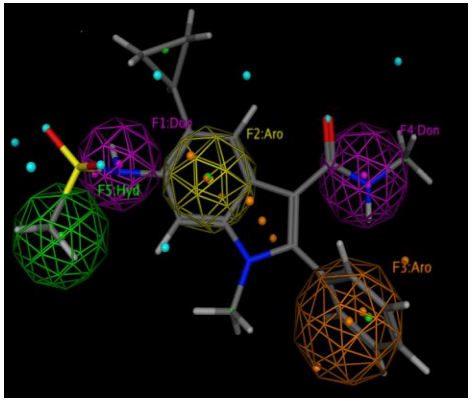
Methodology for Compound Selection

Modeling and *in silico* Evaluation (Example, NS5B Pharmacophores)





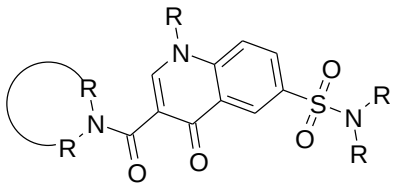




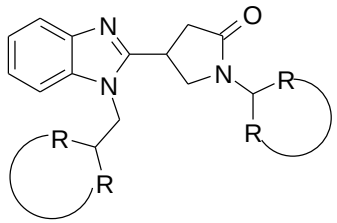
J.Med.Chem. **2014, 57:** 1855-1879

Validation of Antiviral Library

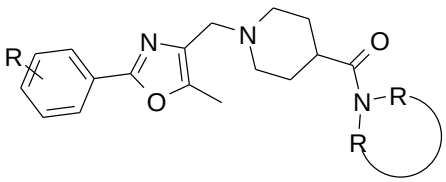
ChemDiv's Design & Activity (PubMed Examples)



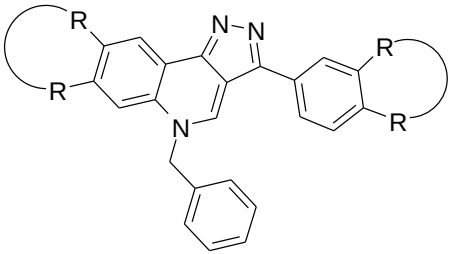
Hepatitis C Virus (HCV)
RNA polymerase binding and polymerization activities
Hck-Nef inhibitors



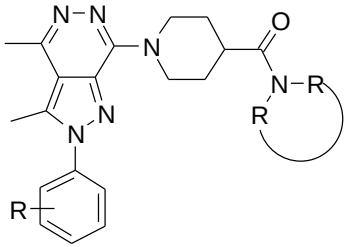
Respiratory Syncytial Virus (RSV)
Epstein-Barr Virus



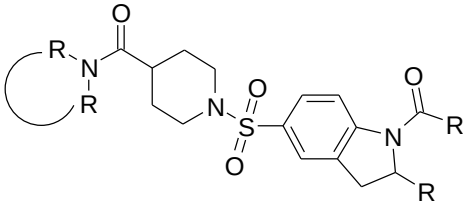
West Nile Virus
HCV NS3 helicase inhibitors
Vaccinia Orthopoxvirus
Marburg Virus
VEEV (TC-83 strain)



VIF Inhibitors
inhibitors of HIV-1
LEDGF/p75 DNA Integration



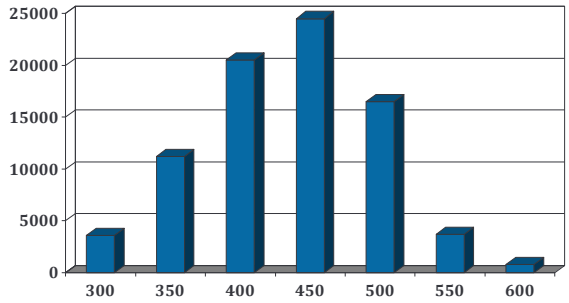
Inhibitors of Vif-A3F interactions
Vaccinia Orthopoxvirus
Respiratory Syncytial Virus (RSV)
Lassa Virus
HCV NS3 helicase inhibitors



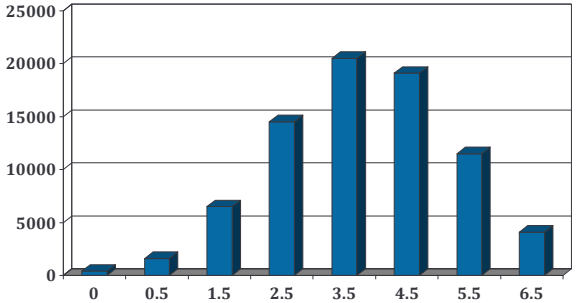
Agonists of NR2E3 (Herpes Virus)
HCV NS3 protein helicase inhibitorsMarburg Virus

Antiviral Library Statistics

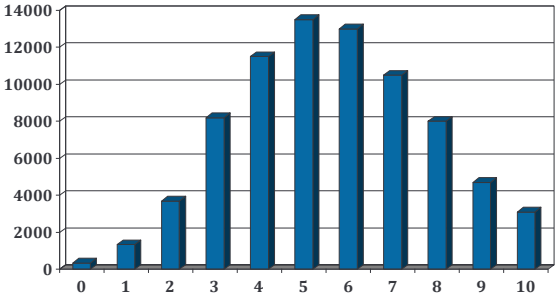
Library Parameter	Value
# of Compounds	80000
# of Scaffolds	3000
Unique Heterocycles	1150
Diversity Coefficient	0.8319



MW Distribution



LogP Distribution



Rotational bonds Distribution

Expertise in Antiviral Research

Hoffmann-La Roche – Viriom program

Pre-Clinical and Clinical development of NNRTIs for treatment of HIV/AIDS

Status: *Phase 2b and Drug-Drug Interaction studies ongoing*

iDialog – Abbott program

Discovery, pre-clinical and clinical development novel HCV entry inhibitor

Status: *Clinical POC achieved*

Expertise in Antiviral Research

Avivir

Pre-clinical and clinical development of Influenza inhibitors

Status: *POC in vivo achieved, pre-clinical studies completed, Phase I First-in-Man clinical study begins Q1 2015*

Merck

Discovery program in discovery of non-nucleoside NS5B inhibitors

Status: *Program completed, novel lead series discovered*

MERCK
Be well

Expertise in Antiviral Research

Big Pharma collaboration 1

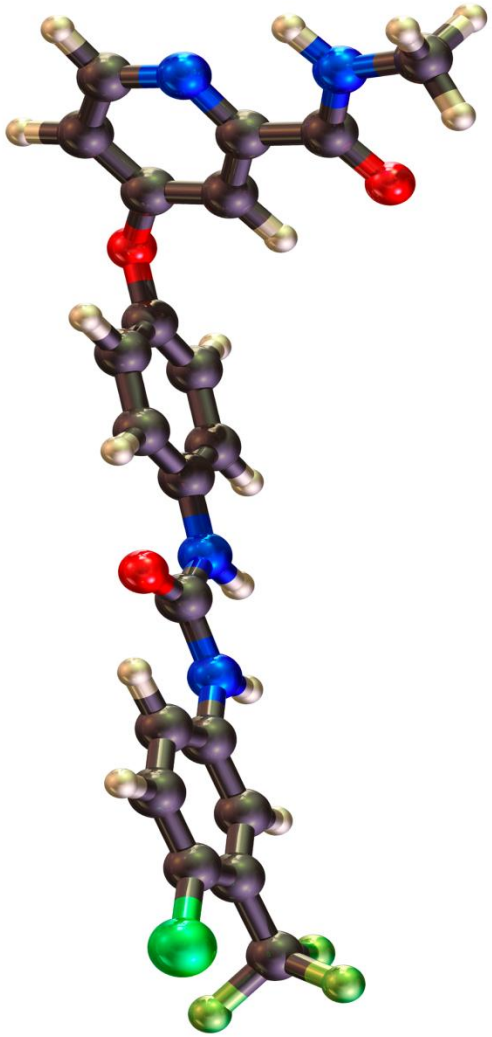
Integrated program on discovery and pre-clinical development of a small molecule human flavivirus inhibitor

Status: *Program completed, novel class of inhibitors discovered*

Big Pharma collaboration 2

Integrated program on discovery and pre-clinical development of a small molecule human paramyxovirus inhibitor

Status: *HTS completed, hit to lead expansion completed, novel class of inhibitors discovered, POC in vivo achieved*



Thank you