

2019 Cresset User Group Meeting Cambridge

A Tale of Hide and Seek: Hit to Drug Candidate

June 20, 2019

Inhee Choi, RPh, PhD

Institut Pasteur Korea

We are Pasteurians fighting disease in Korea for all mankind

Institut Pasteur International Network

Institut Pasteur Korea Mission

Institut Pasteur Korea
Discovery Approach

Driving convergence of BT, IT and Chemistry in the pursuit of Innovative drug discovery

Discovery Biology

Institut Pasteur Korea has been fighting infectious and neglected diseases.

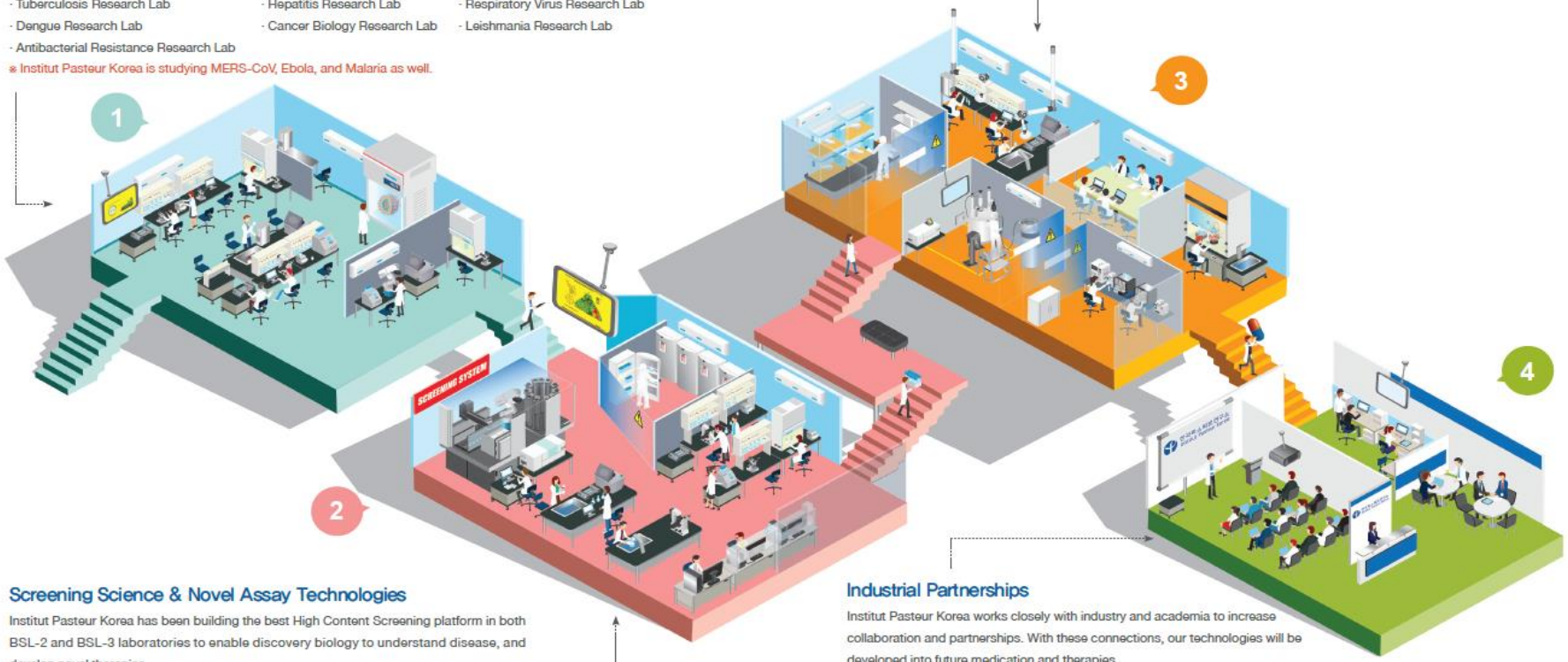
- Tuberculosis Research Lab
- Hepatitis Research Lab
- Respiratory Virus Research Lab
- Dengue Research Lab
- Cancer Biology Research Lab
- Leishmania Research Lab
- Antibacterial Resistance Research Lab

※ Institut Pasteur Korea is studying MERS-CoV, Ebola, and Malaria as well.

Discovery Chemistry

Once Institut Pasteur Korea has identified promising molecules, our chemists turn them into more effective drug candidates.

- Lead Optimization
- Early Safety Profiling
- Testing in Animal Models



Screening Science & Novel Assay Technologies

Institut Pasteur Korea has been building the best High Content Screening platform in both BSL-2 and BSL-3 laboratories to enable discovery biology to understand disease, and develop novel therapies.

- Technology Development Platform
- Computational Biology
- Assay Development & Screening
- Sample Management & Automation
- Lab Support Operation

Industrial Partnerships

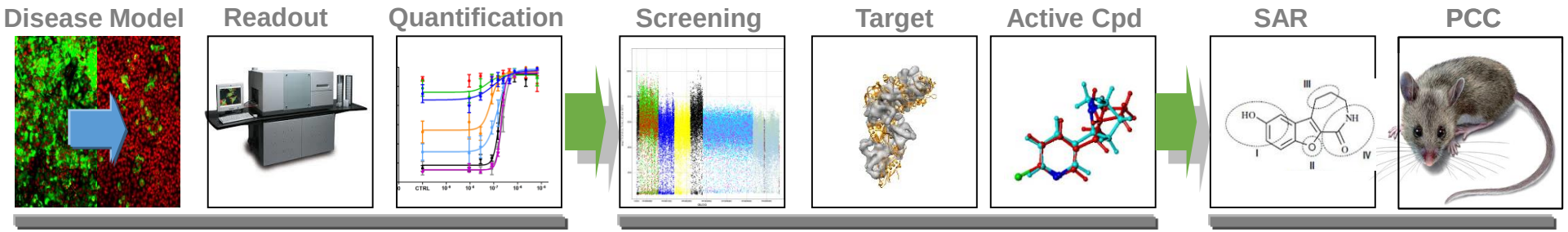
Institut Pasteur Korea works closely with industry and academia to increase collaboration and partnerships. With these connections, our technologies will be developed into future medication and therapies.

- Invention Disclosure
- Patent
- Consulting
- R&D Collaboration
- Intellectual Property
- Licensing
- Knowledge and Practice
- Material Transfer Agreement

※ Please visit our website to see more on our institute's inventions and technologies.

Institut Pasteur Korea RND Infrastructure

General workflow



Outline

I. Strategic procurement of HTS chemical library

II. Success story of development of antitubercular drug

III. DFRS virtual libraries

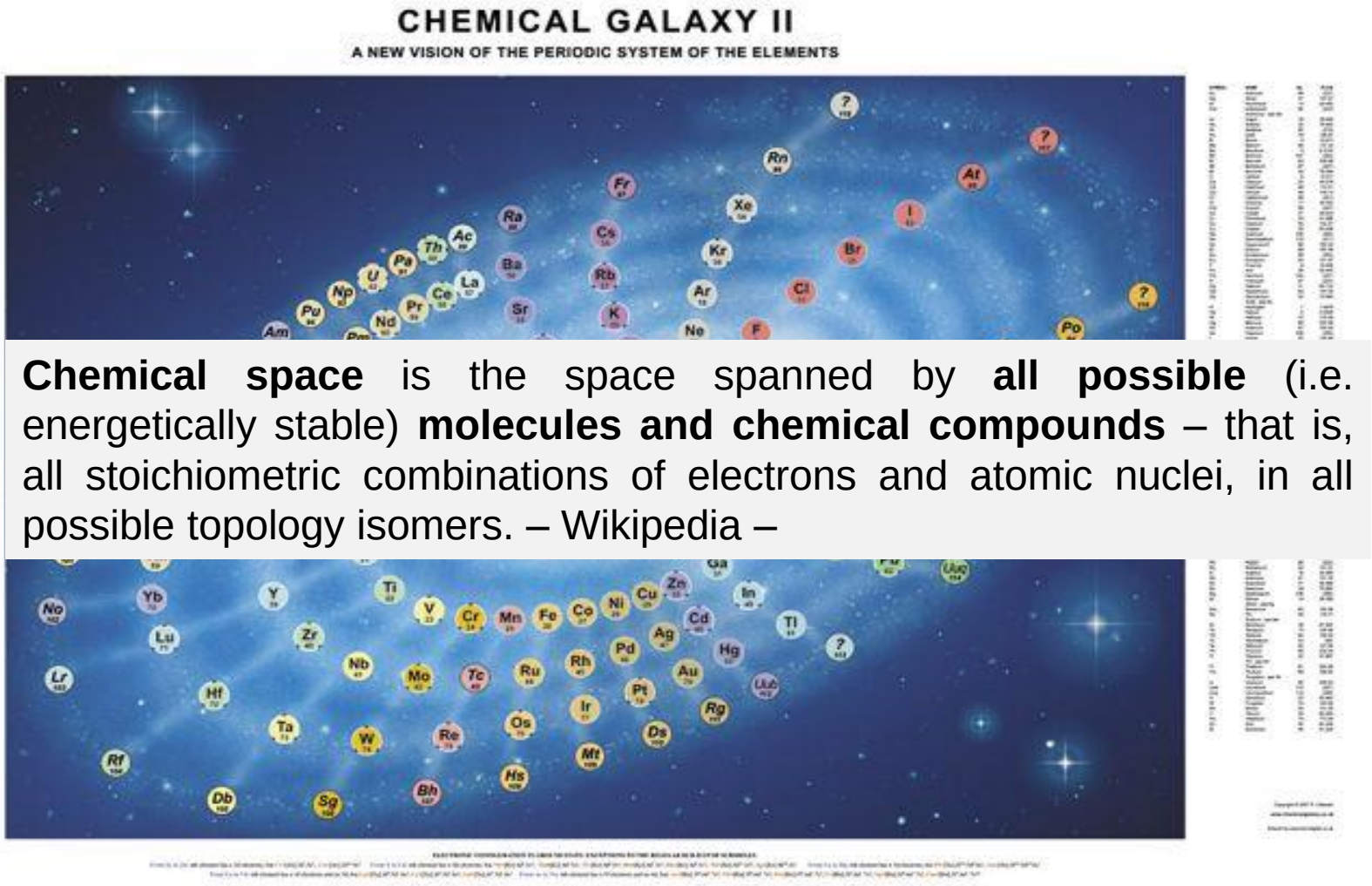
Outline

I. **Strategic procurement of HTS chemical library**

II. Success story of development of antitubercular drug

III. DFRS virtual libraries

What is “Chemical” Space?



Chemical space is the space spanned by **all possible** (i.e. energetically stable) **molecules and chemical compounds** – that is, all stoichiometric combinations of electrons and atomic nuclei, in all possible topology isomers. – Wikipedia –

Image - http://www.chemicalgalaxy.co.uk/

What is the Size of Chemical Space?

A typical pharma corporate compound set
~ 10^{6-7}

Publicly disclosed molecules
~ 10^{8}

Possible molecules with < 30 Heavy Atoms and MW < 500

Virtual molecules claimed by patent Markush structures
> 10^{12}

~ 10^{63}

Synthetic feasible Combi. Chem. Libraries
~ 10^{13}

Virtual compound space defined by other means
10^{10} ~ 10^{30}

Peng Z, Drug Discovery Today: Technologies, 2013

How many FDA approved drugs today?

1827 Morphine (Merck)

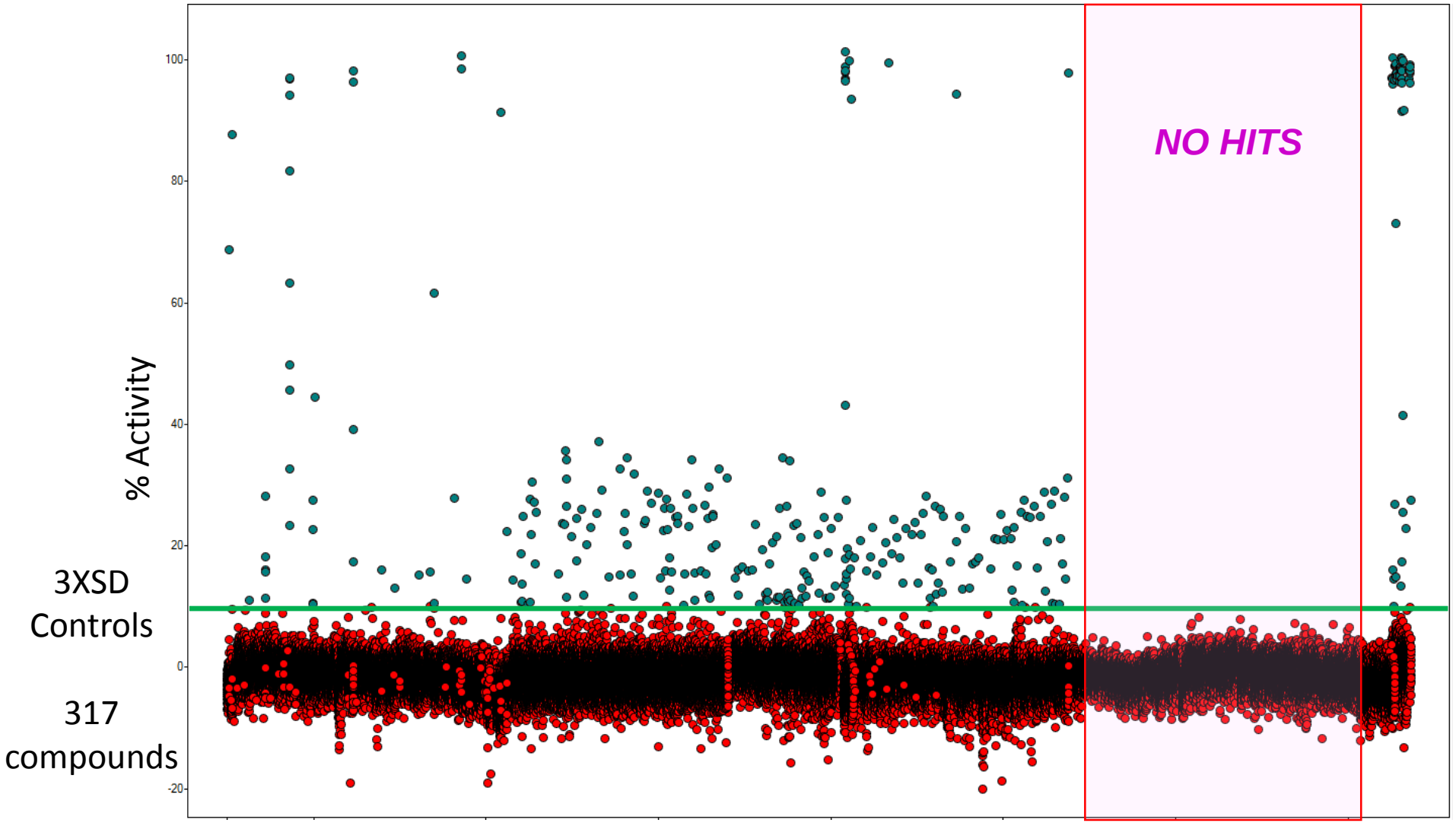
1899 Aspirin (Bayer)

1906

2019

1815 Approved Active Ingredients
- 1736 **chemical drugs**
- 79 **biotech drugs**

Case study: Hits from HTS



Compound Procurement Workflow

Selection of chemical vendors

- Validated 11 chemical vendors for quality and diversity of compounds based on major pharmaceutical companies collaborations as well as publications

Comprehensive Assessment of the Structural and Property Diversity

Physicochemical property analysis

- Physicochemical property from whole molecule

Scaffold diversity analysis

- Analysis of scaffolds in legacy library: Bemis-Murcko framework
- Selection of compounds with different scaffolds

Cherry picking by fingerprints

- Diverse compounds selection using molecular fingerprints, functional connectivity (FCFP), extended connectivity (ECFP)

Choi I *et al.*, Bull. Korean. Chem. Soc., 2018

Chemical Vendors

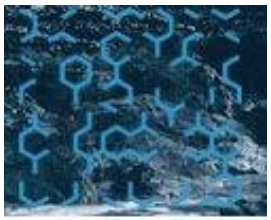
- **Validated chemical vendors for quality and diversity of compounds based on major pharmaceutical companies collaborations as well as publications**

ChemBridge

ChemDiv

Enamine

Life Chemicals



Maybridge

InterBioScreen

Princeton

Otava

TimTec

Specs

Vitas-M

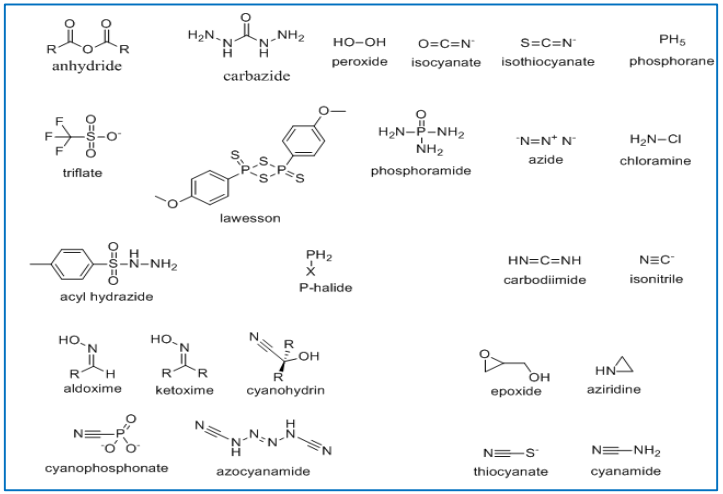
Filtering Criteria 1: Drug-like Rules

❖In order to discriminate between drug-like compounds and non-drug compounds, a combination of Lipinski's, Veber's and Oprea's rules were applied

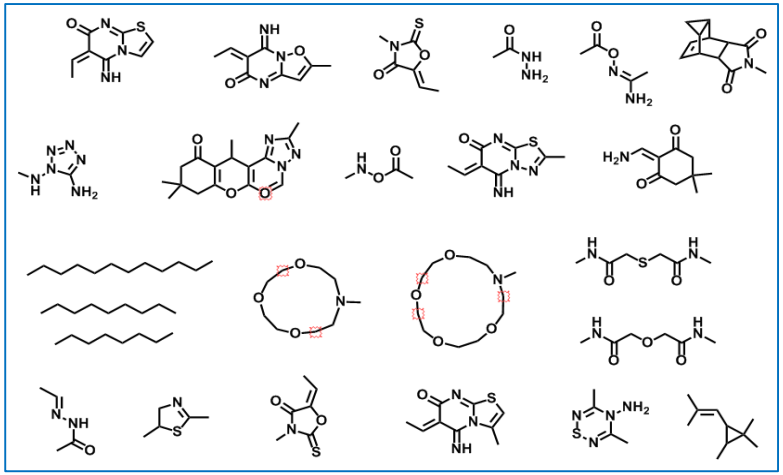
Lipinski Rule of 5	Vebers' Rule	Oprea's Rules (MDDR-like)
MW 250-500 LogP 0-5 H-bond donor ≤ 5 H-bond acceptor ≤ 10	Polar Surface Area ≤ 140 Å No. Rotatable Bonds 0-10	<u>Drug-like</u> No. Rings ≥ 3 No. Rotatable bonds ≥ 6 <u>Nondrug-like</u> No. Rings ≤ 2 No. Rotatable bonds ≤ 5

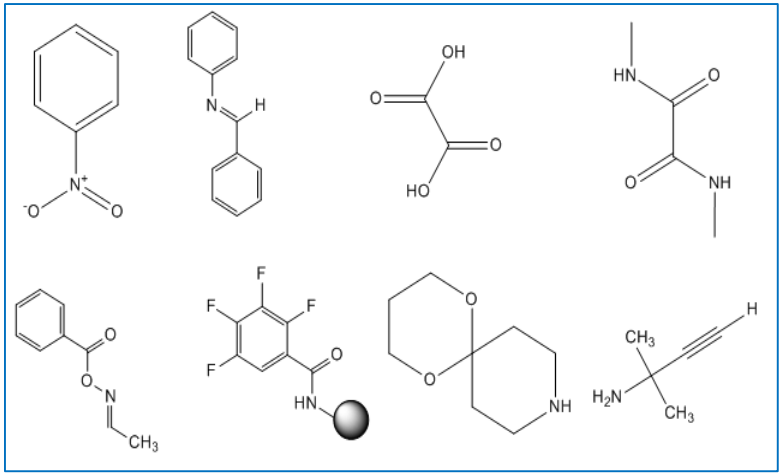
Filtering Criteria 2: Fragments

- **Oprea's Filter: Non-drug like fragments & toxicophore filter**



- **Chemically not interesting fragments**

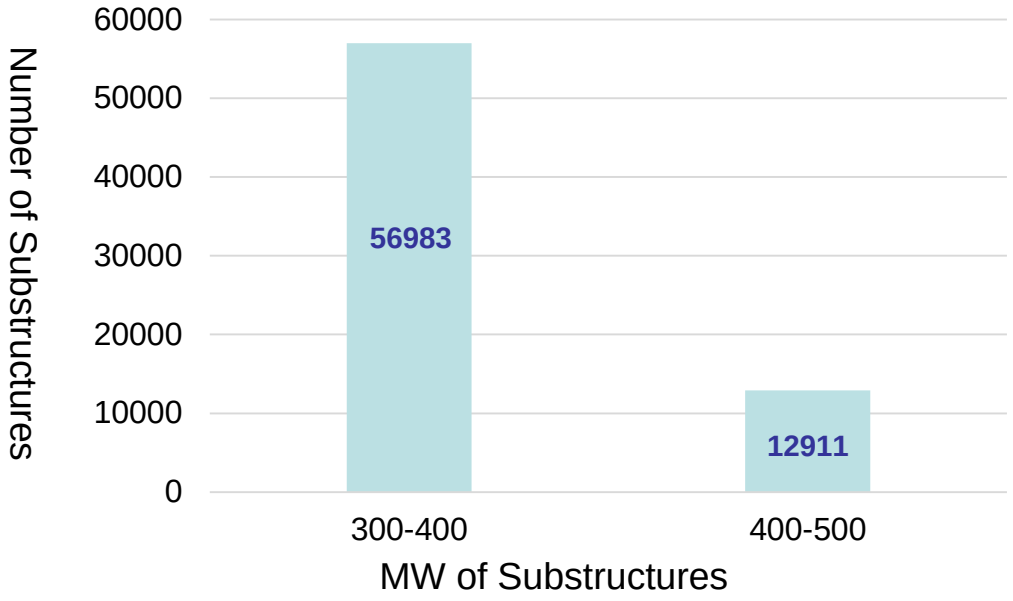




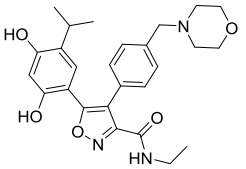
Oprea,T.I. J. Comput. Aid. Mol. Des., 2000

Filtering Criteria 3: Scaffold Diversity Analysis

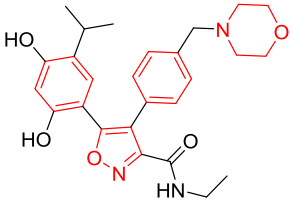
- **Bemis-Murcko scaffolds (BMS) were generated and used as filter to achieve lead-likeness of a compound library**



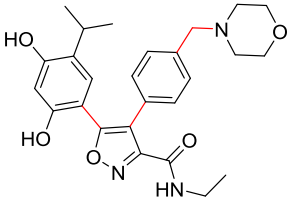
Scaffold Representations



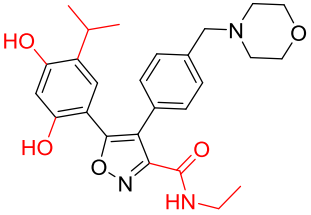
NVY-AUY922



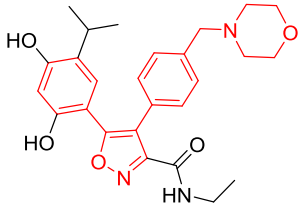
Ring systems



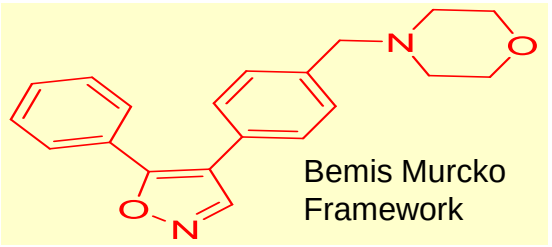
Linkers



Side Chains



Framework

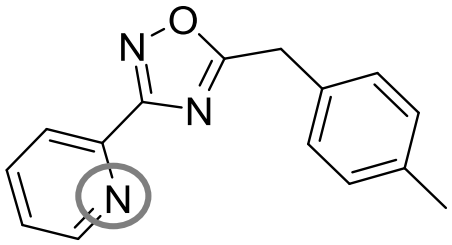


Bemis Murcko Framework

- ✓ **Compounds similar to "Lead-like" Bemis-Murcko scaffolds were selected**
  - **Excluding compounds with MW ≥ 400 Bemis-Murcko scaffolds**

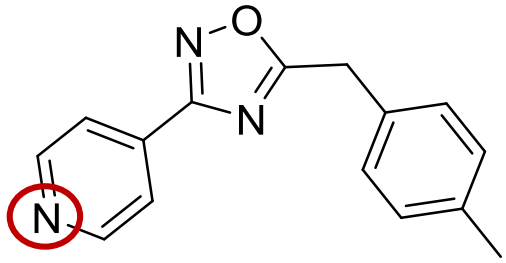
Langdon *et al.*, J. Chem. Inf. Model., 2011

Deception of Similarity Prediction



PubChem CID: 2195520

Structural Descriptor Similarity Score 1.0



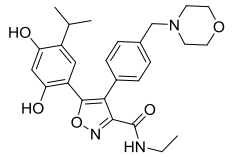
PubChem CID: 895193

- **BioAssay AID: 1321**
- **BioAssay Name: Primary Cell-based High Throughput Screening Assay for Inhibitors of Wee1 Degradation**
- **Target Protein: WEE1**

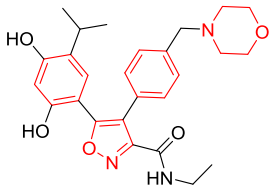
Scaffold Diversity Analysis

❖**Bemis-Murcko scaffolds (BMS) were generated and used as filter to achieve scaffold diversity of a compound library**

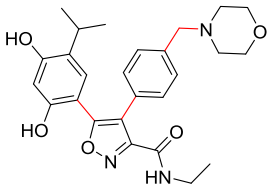
Scaffold Representations



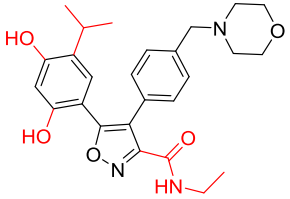
NVY-AUY922



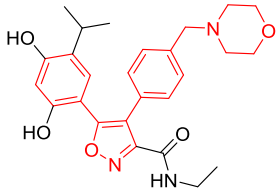
Ring systems



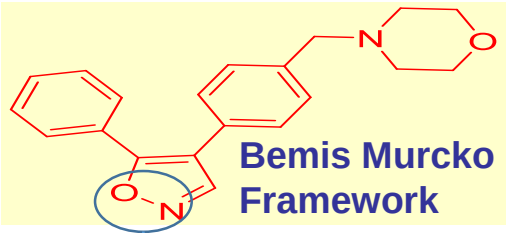
Linkers



Side Chains



Framework

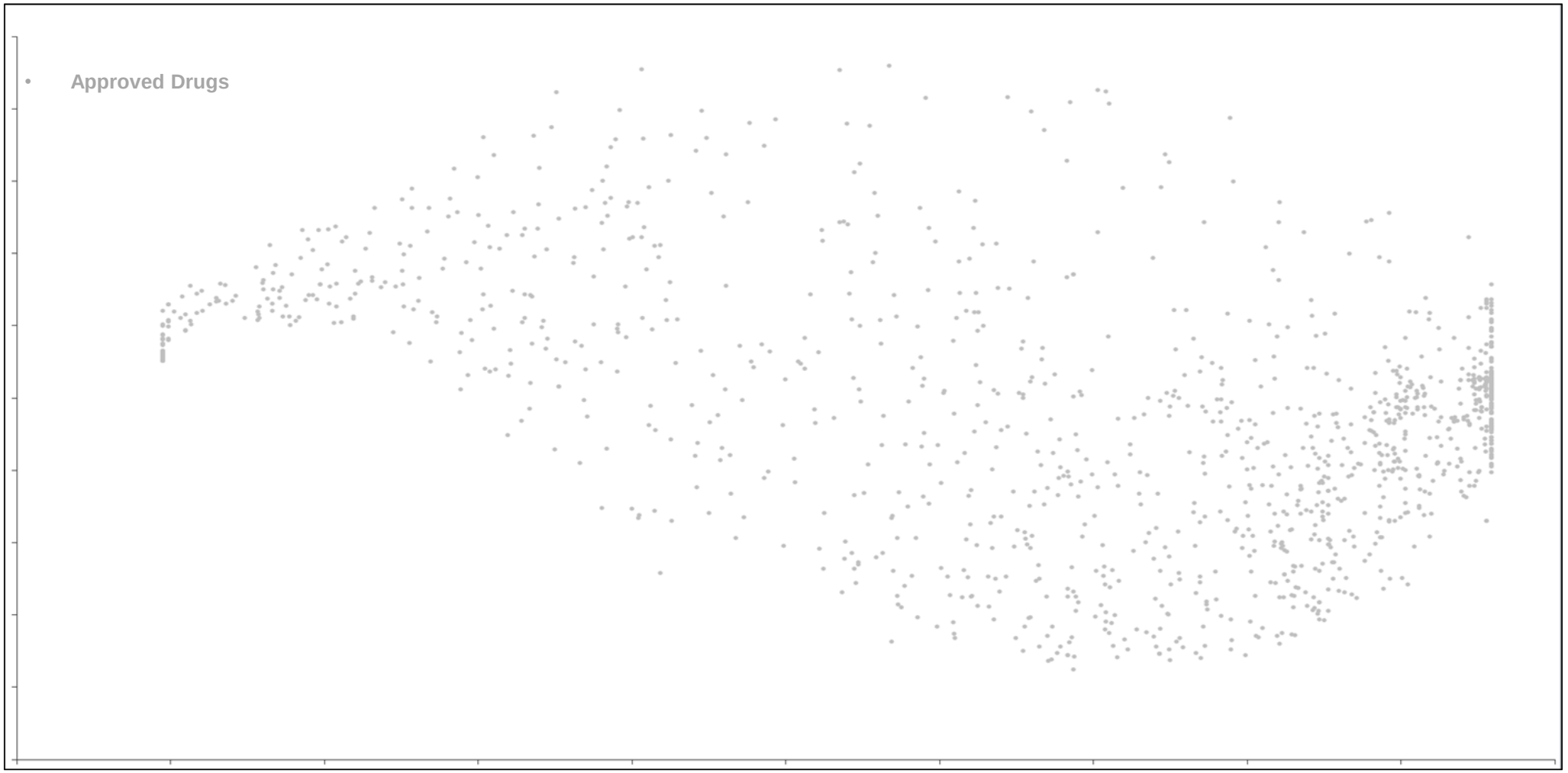


Framework atoms

- ✓ **Ring systems and linkers are identified for potential use in a combinatorial-type approach to compound library generation.**
- ✓ **Consideration of atom properties (atom type, hybridization, and bond order) for framework atoms.**
- ✓ **Compound libraries may be evaluated for their relationship to the shapes of compounds. In other words, we can evaluate how well the diversity space of a library is.**

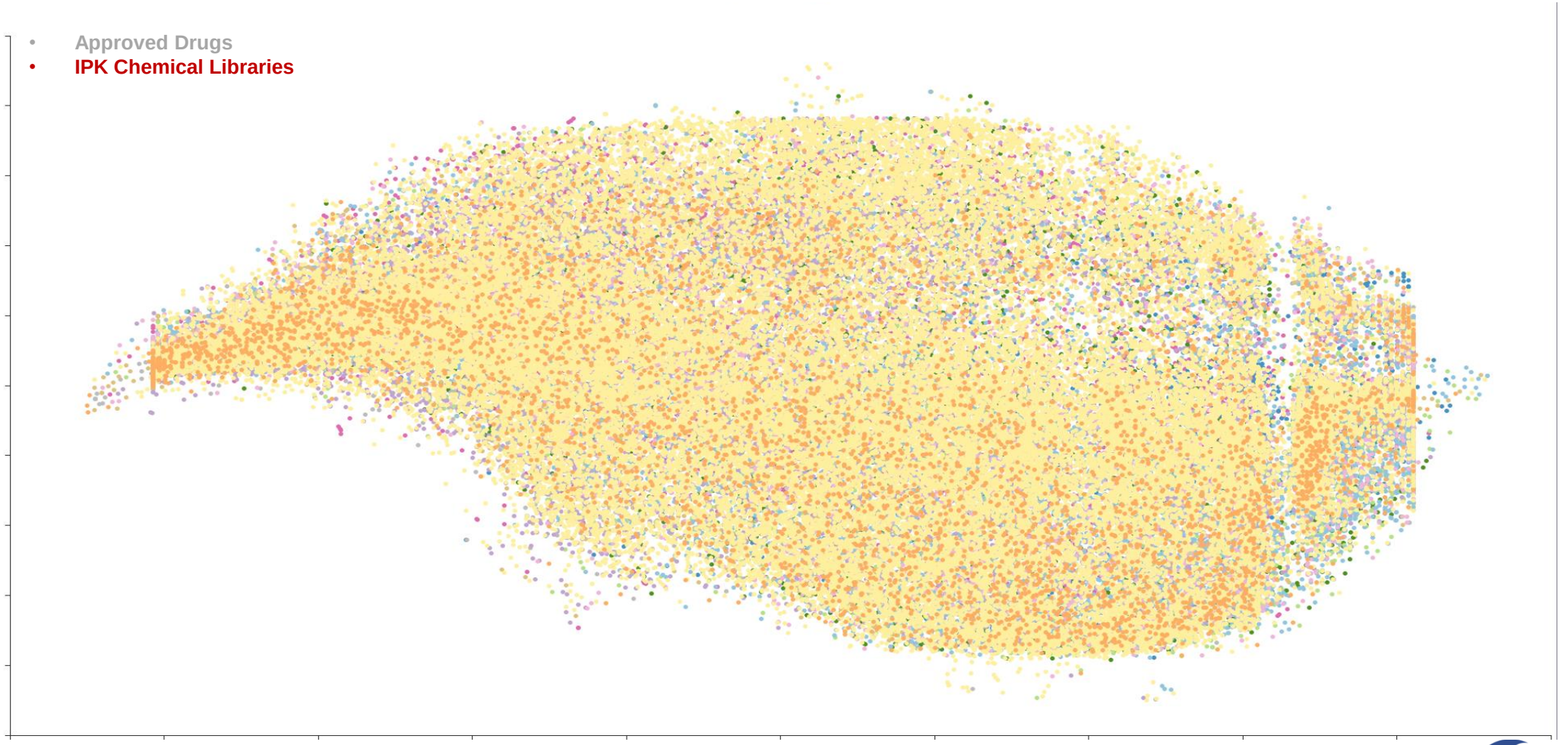
Diversity: BMS Chemical Space

❖ **Bemis-Murcko scaffolds of approved drugs**



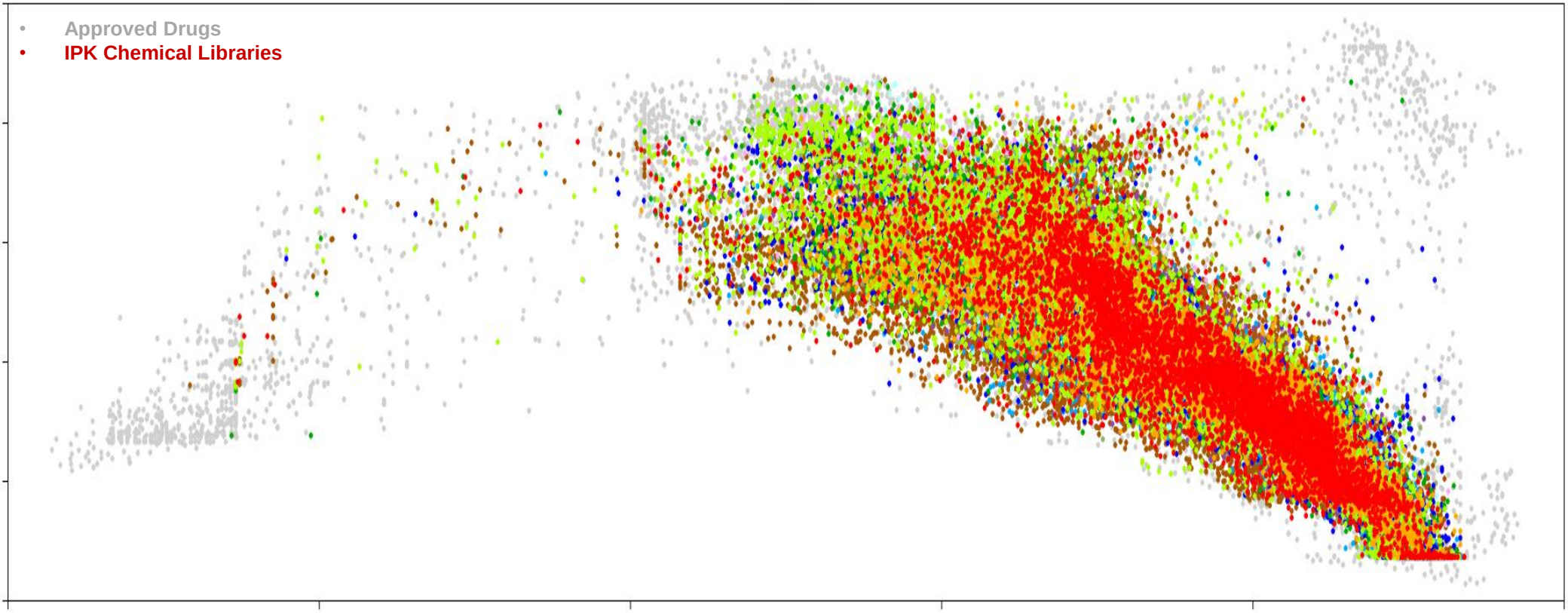
Diversity: BMS Chemical Space

- **Bemis-Murcko scaffolds in IPK library are diversely distributed and covering the realm of FDA approved drugs.**



Diversity: Whole Compounds' Chemical Space

- **Compounds in IPK library are diversely distributed and covering the realm of FDA approved drugs.**



Analysis of IPK Chemical Libraries

Number of compounds in IPK collection

❖ Four major chemical libraries from IPK collection

IPK Collection	Total number of compounds*	Number of Bemis-Murcko Scaffolds
IPK Legacy	~122,300	~68,600
IPK Bioactives	~7,500	~1,800
IPK Chemistry	~8,000	~3,400
IPK 2015	~100,200	~35,700
	238K	**110K**

* Duplicates and salt forms have been removed

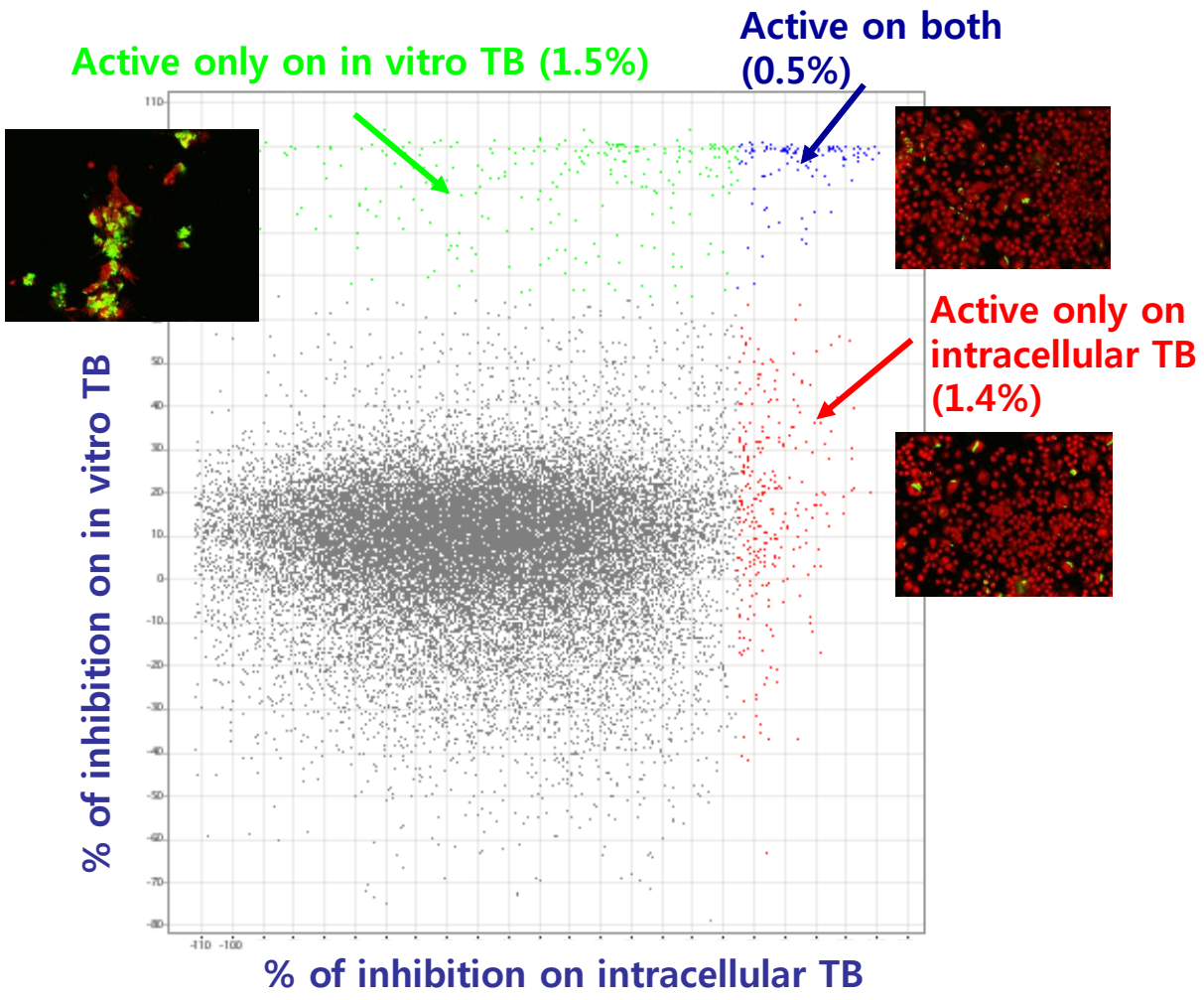
Outline

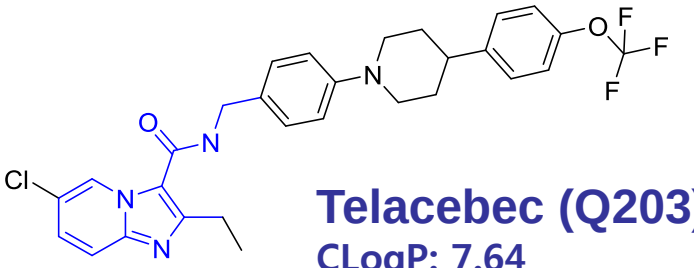
I. Strategic procurement of HTS chemical library

II. Success story of development of antitubercular drug

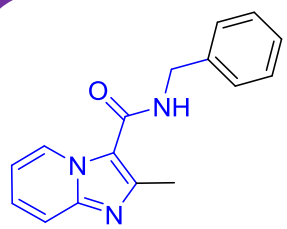
III. DFRS virtual libraries

Success @ IPK: Hit to Lead

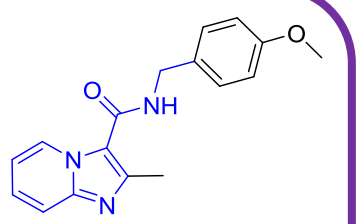




Telacebec (Q203)
CLogP: 7.64
MW: 557



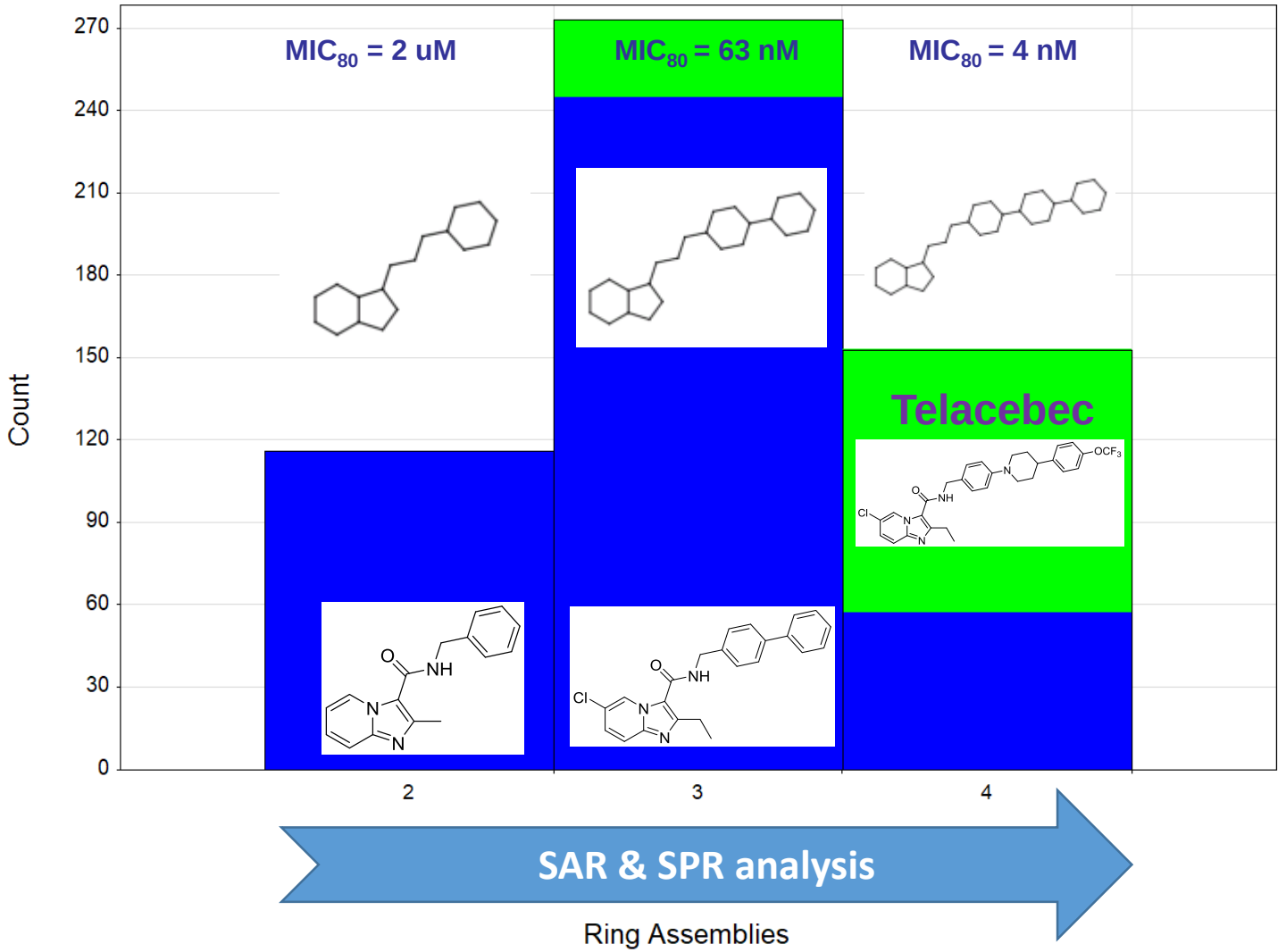
IPA1: Active
CLogP: 3.1
MW: 265.32



IPA2: Inactive
CLogP: 3.02
MW: 295.15

PMID: 24870926 | PMID: 23913123

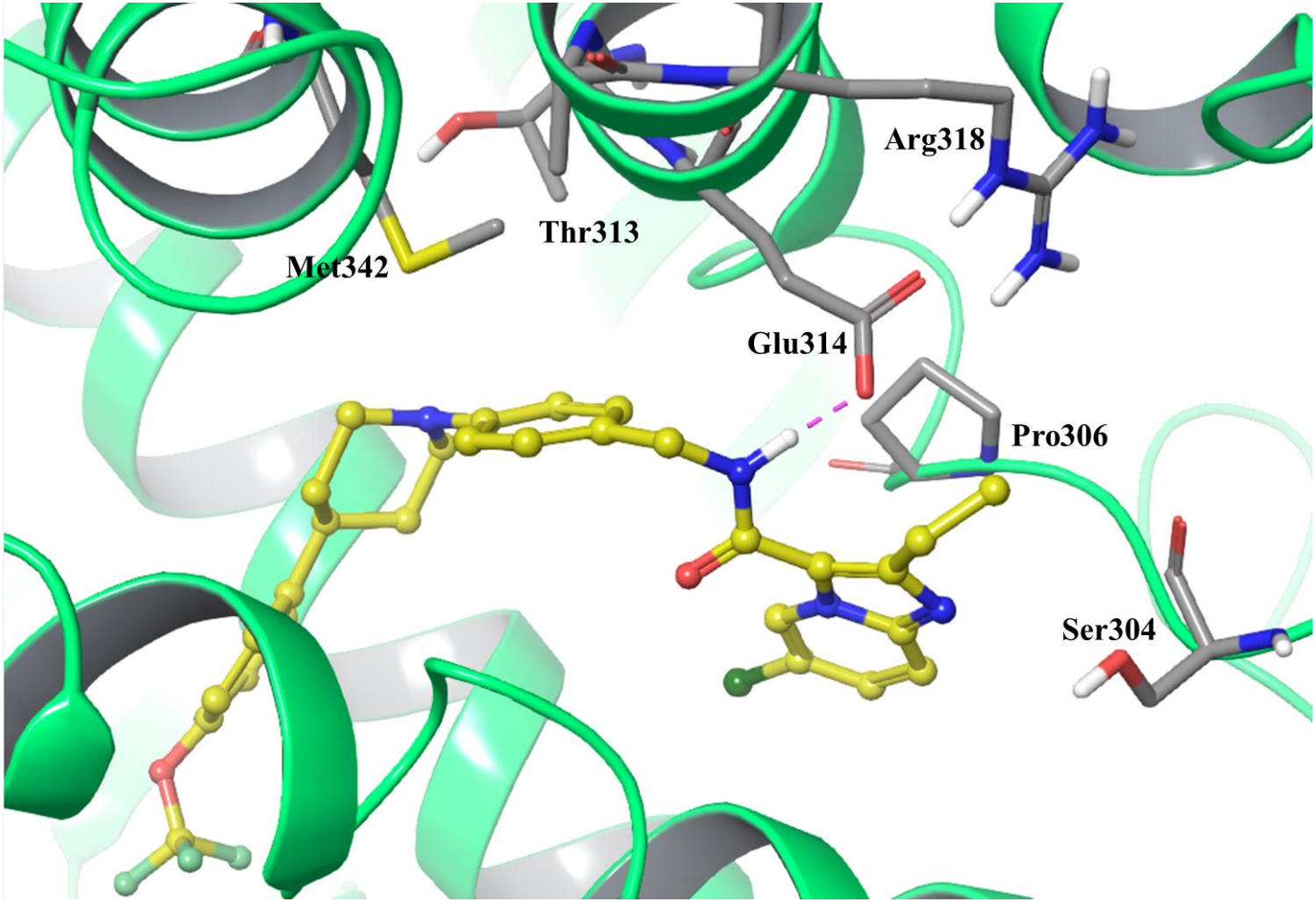
IPA series: Bemis Murcko Scaffolds



Blue: Lipinski pass
Green: Lipinski fail

PMID: 24870926 | PMID: 23913123

Target of Telacebec: QcrB



Choi I *et al.*, Bull. Korean. Chem. Soc., 2016

Outline

I. Strategic procurement of HTS chemical library

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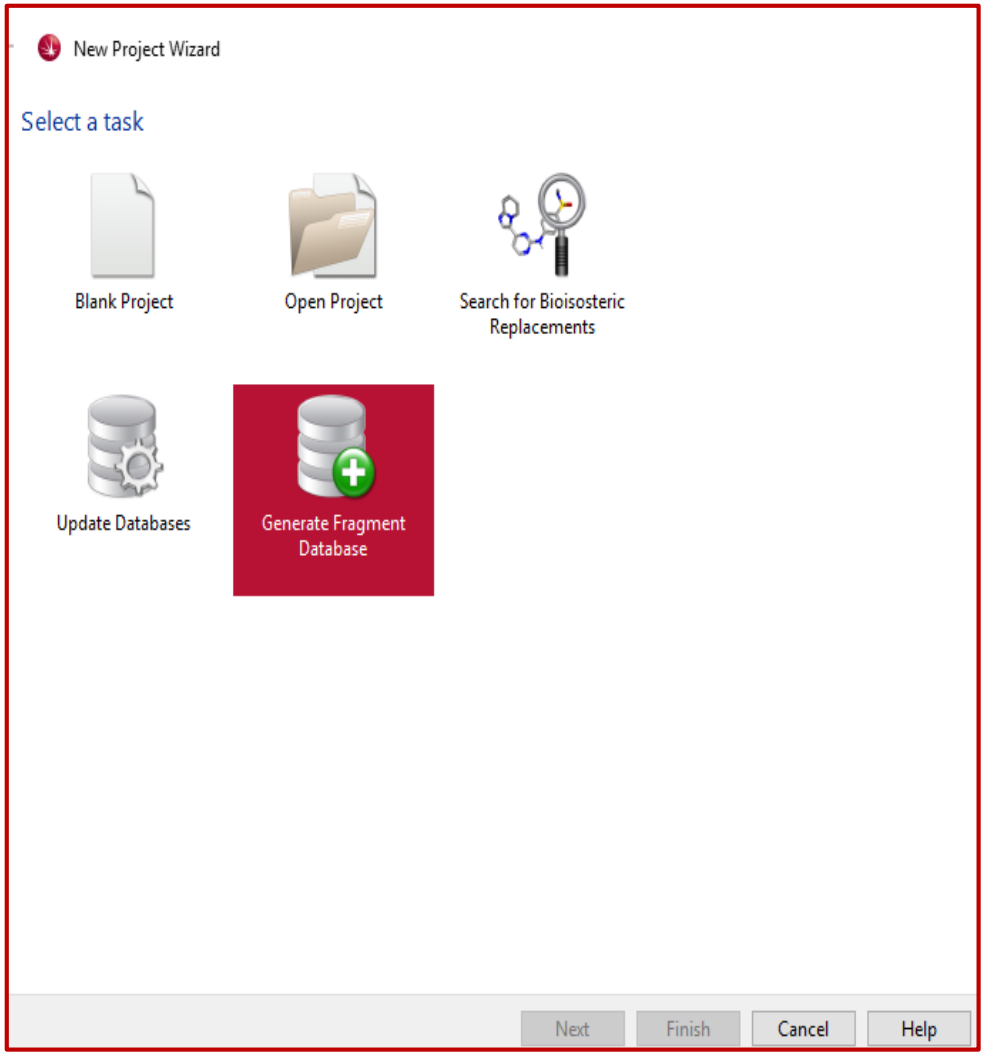
Combinatorial Virtual Chemical Libraries

Deconstructed
Fragment
Recombined
Scaffold

spark

1. Generate Fragment Databases

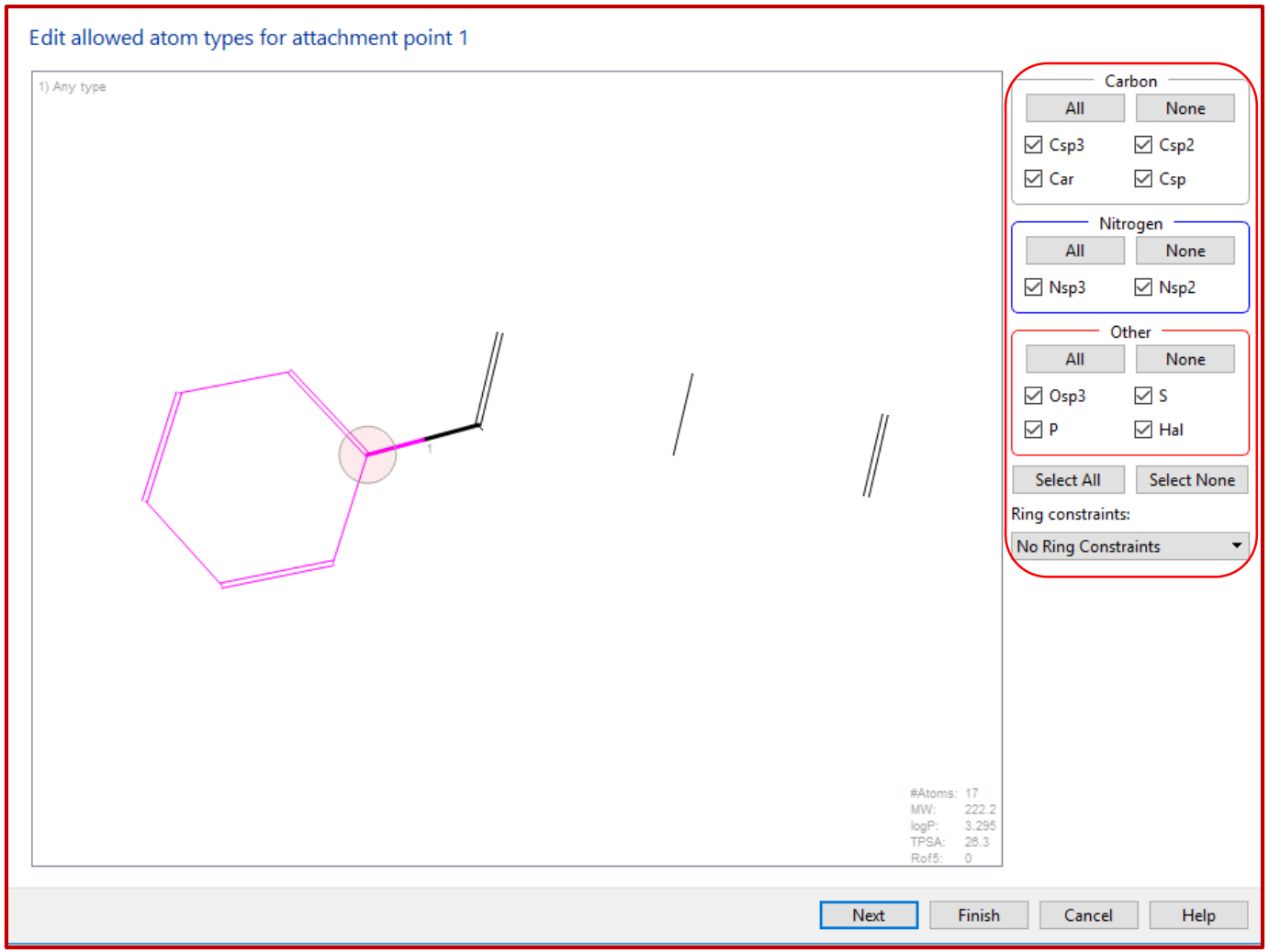


STRATEGY

***Deconstruction* of fragment library from APPROVED drugs**

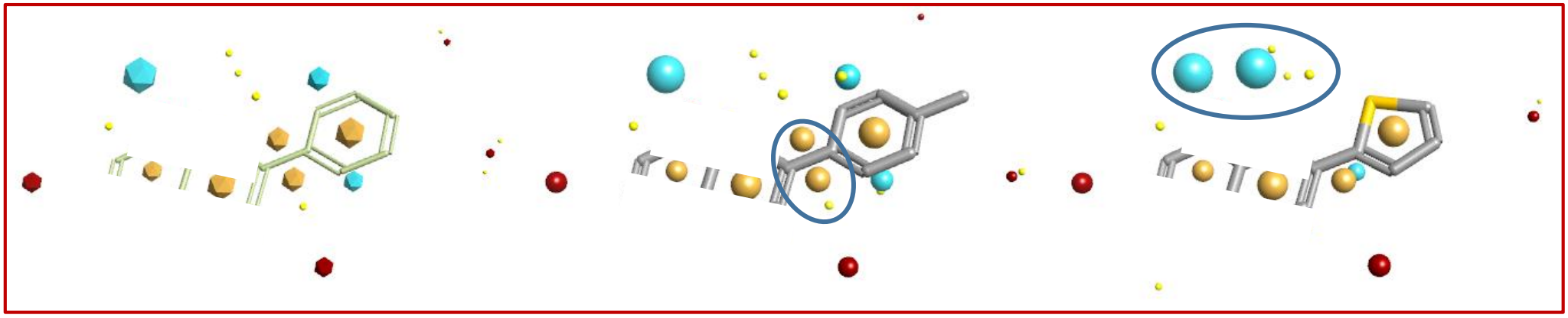
- **ChEMBL Drugs**
- **PW DRUG-FRAGMENT LIBRARY**

2. Selection and Edit Attachment Points



3. Search Fragments

- **Results Interpretation: Field points, Bio-Isostere Factor (BIF%), Score (Field score + Shape score)**

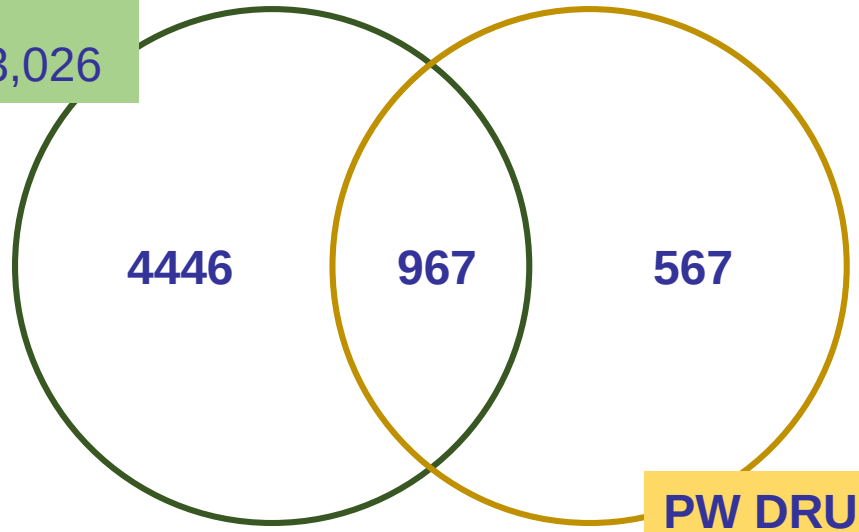


Tile Results

0.610 Rank: 1 Fav: BIF%: 100 Score: 0.999	0.610 Rank: 2 Fav: BIF%: 100 Score: 0.999	0.727 Rank: 3 Fav: BIF%: 92 Score: 0.982	0.727 Rank: 4 Fav: BIF%: 92 Score: 0.982	0.644 Rank: 5 Fav: BIF%: 89 Score: 0.977	0.644 Rank: 6 Fav: BIF%: 89 Score: 0.976
0.587 Rank: 7 Fav: BIF%: 88 Score: 0.974	0.587 Rank: 8 Fav: BIF%: 88 Score: 0.974	0.727 Rank: 9 Fav: BIF%: 88 Score: 0.973	0.727 Rank: 10 Fav: BIF%: 88 Score: 0.973	0.644 Rank: 11 Fav: BIF%: 87 Score: 0.971	0.644 Rank: 12 Fav: BIF%: 87 Score: 0.971
0.587 Rank: 13 Fav: BIF%: 86 Score: 0.969	0.587 Rank: 14 Fav: BIF%: 86 Score: 0.969	0.790 Rank: 15 Fav: BIF%: 85 Score: 0.967	0.790 Rank: 16 Fav: BIF%: 85 Score: 0.967	0.604 Rank: 17 Fav: BIF%: 84 Score: 0.966	0.604 Rank: 18 Fav: BIF%: 85 Score: 0.966
0.830 Rank: 19 Fav: BIF%: 83 Score: 0.963	0.830 Rank: 20 Fav: BIF%: 83 Score: 0.963	0.807 Rank: 21 Fav: BIF%: 83 Score: 0.963	0.807 Rank: 22 Fav: BIF%: 83 Score: 0.963	0.577 Rank: 23 Fav: BIF%: 83 Score: 0.962	0.577 Rank: 24 Fav: BIF%: 83 Score: 0.962
0.807 Rank: 25 Fav: BIF%: 83 Score: 0.962	0.807 Rank: 26 Fav: BIF%: 83 Score: 0.962	0.666 Rank: 27 Fav: BIF%: 81 Score: 0.959	0.666 Rank: 28 Fav: BIF%: 81 Score: 0.959	0.717 Rank: 29 Fav: BIF%: 81 Score: 0.958	0.717 Rank: 30 Fav: BIF%: 81 Score: 0.958
0.787 Rank: 31 Fav: BIF%: 81 Score: 0.958	0.787 Rank: 32 Fav: BIF%: 81 Score: 0.958	0.577 Rank: 33 Fav: BIF%: 80 Score: 0.957	0.577 Rank: 34 Fav: BIF%: 80 Score: 0.957	0.824 Rank: 35 Fav: BIF%: 80 Score: 0.956	0.824 Rank: 36 Fav: BIF%: 80 Score: 0.956

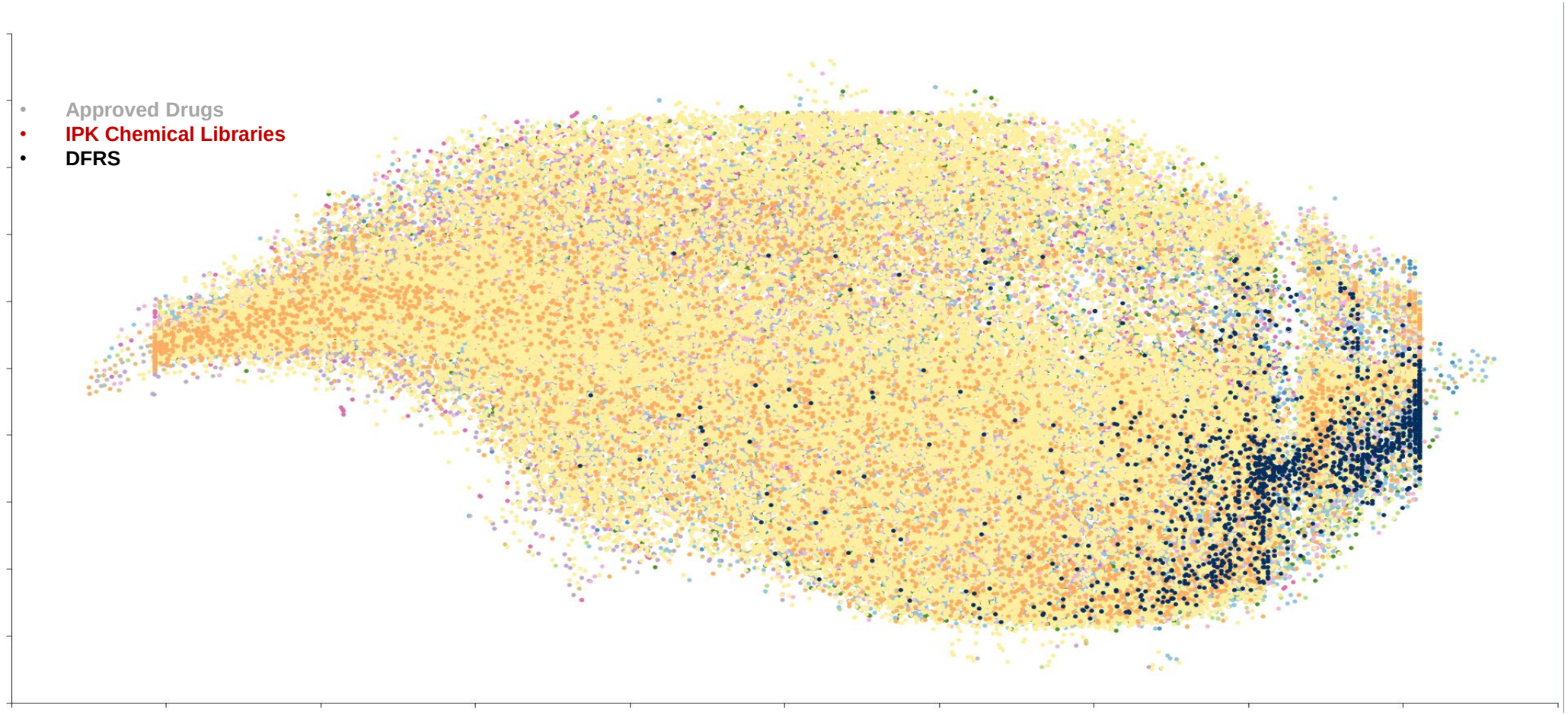
Generated DFRS Virtual Chemical Libraries

ChEMBL DRUGS
SDF: 11,542
Fragments: 13,026

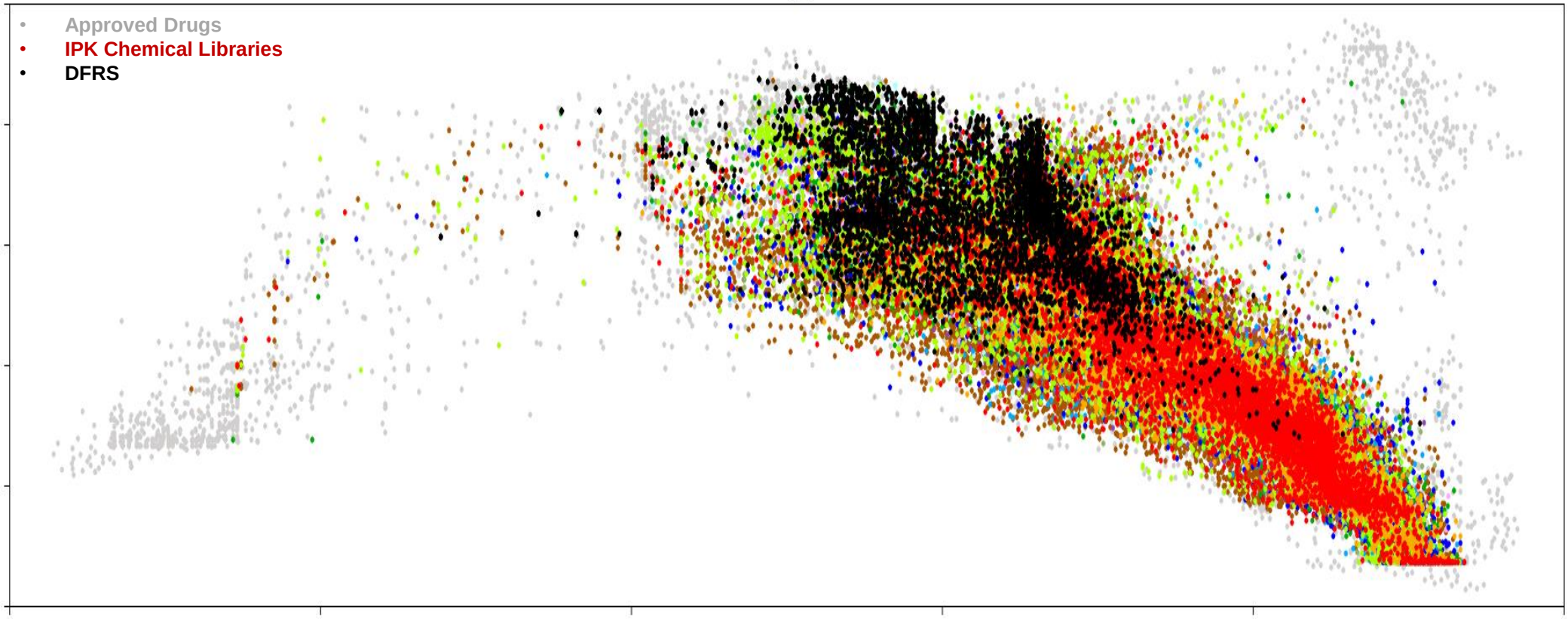


PW DRUG-FRAGMENT LIBRARY
SDF: 1,454
Fragments: 2,862

DFRS Virtual Chemical Libraries: BMS Chemical Space

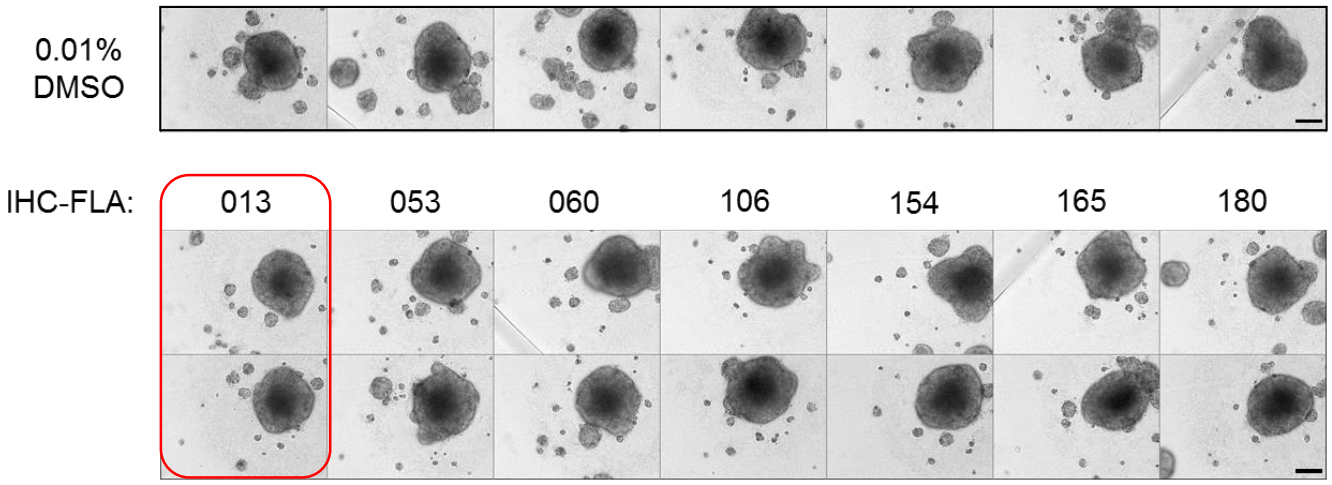


DFRS Virtual Chemical Libraries
Whole Compounds' Chemical Space



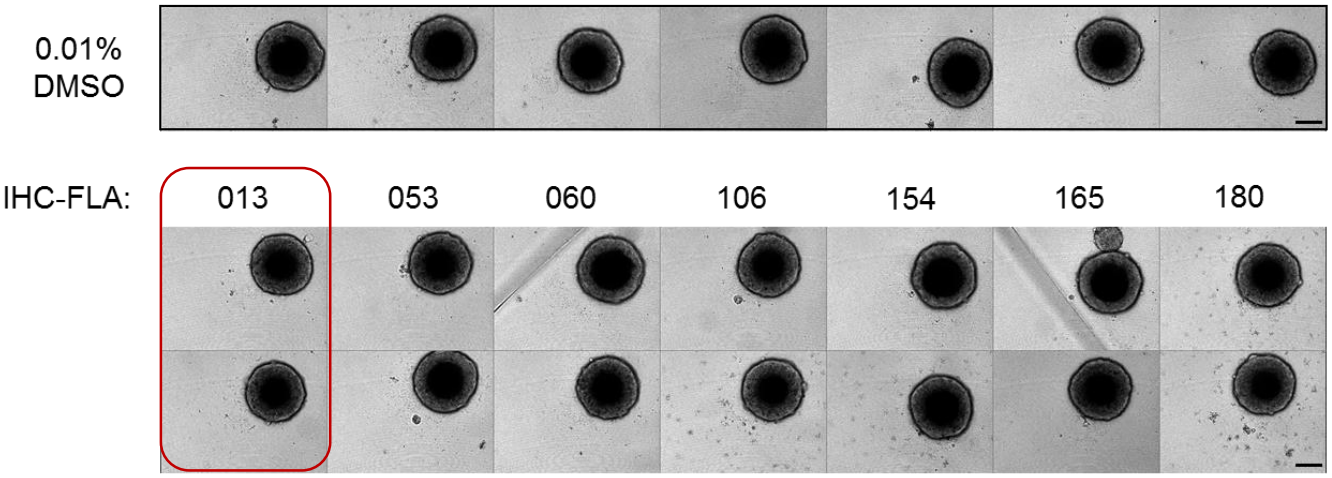
Biological activities of SPARK designed compounds: Liver cancer

Huh7.5 Spheroids



Scale bar=200μm

Hep3B spheroids



Scale bar=200μm

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