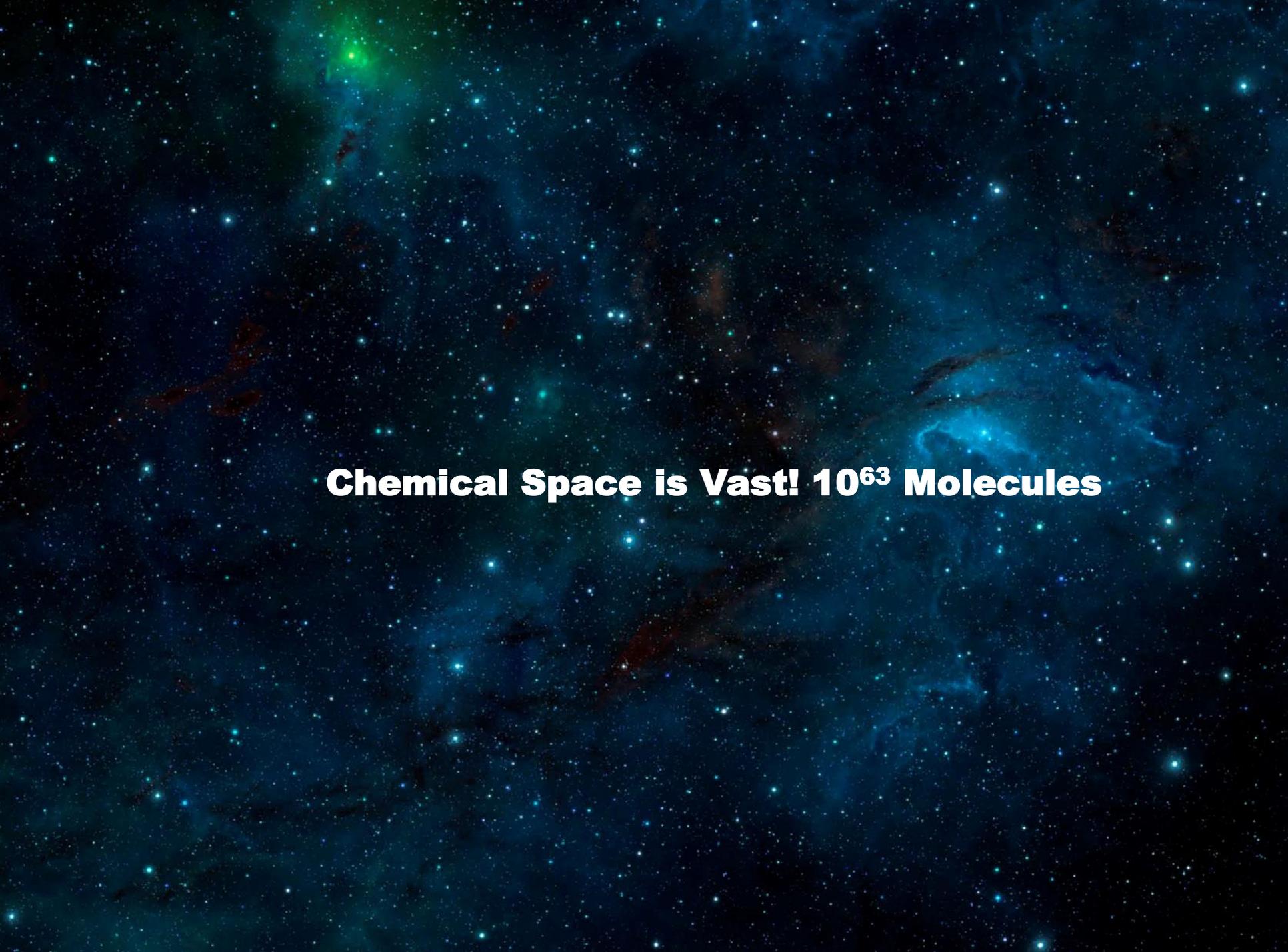




Making Virtual *REAL*: an Approach to Access Billions of Make-on-Demand Compounds

Yurii Moroz, PhD
CEO at Chemspace, Scientific Advisor at Enamine

July 2020

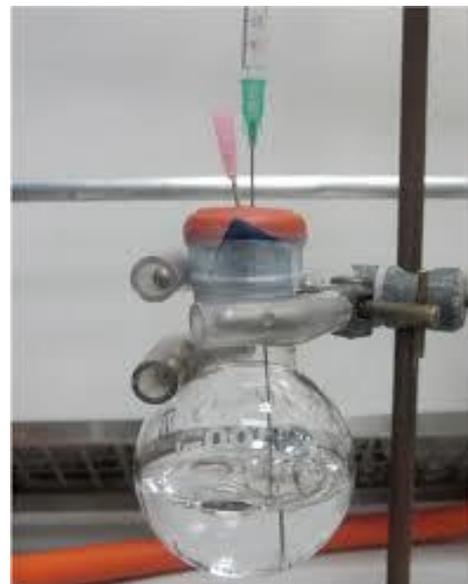


Chemical Space is Vast! 10^{63} Molecules

Commercially accessible chemical space



8 Million in-stock items



Billions of Virtual Compounds

Virtual compounds are alternative to overused stock



Chemistry is a bottleneck of virtual compounds

Reagents/building blocks are unavailable,

Synthetic procedures have to be developed

⇒ **Low Deliverability**



Low deliverability makes us unhappy



Virtual compounds are seen as pollutants



Virtual compounds are provided mostly by non-experts



Compound libraries made easy

The screenshot displays the JChem software interface, which is used for managing chemical libraries. The interface includes a menu bar with options like File, Home, Insert, Page Layout, Formulas, Data, Review, View, and JChem. Below the menu bar is a toolbar with various icons for file operations, editing, and data management. The main workspace is a grid with columns labeled A through I and rows numbered 1 through 7. Each cell in the grid contains a chemical structure in the first column and its corresponding SMILES string in the subsequent columns. The structures shown include various organic molecules such as amines, alcohols, and heterocycles.

	A	B	C	D	E	F	G	H	I
1									
2									
3									
4									
5									
6									
7									

Experimental synthetic expertise is needed!



Dr. Sci Pavel Mykhailiuk

CSO Enamine

135 publications

organic and medicinal chemistry

nature

Letter | Published: 09 September 2019

Hindered dialkyl ether synthesis with electrogenerated carbocations

Jinbao Xiang, Ming Shang, Yu Kawamata, Helena Lundberg, Solomon H. Reisberg, Miao Chen, Pavel Mykhailiuk, Gregory Beutner, Michael R. Collins, Alyn Davies, Matthew Del Bel, Gary M. Gallego, Jillian E. Spangler, Jeremy Starr, Shouliang Yang, Donna G. Blackmond & Phil S. Baran 

Nature 573, 398–402(2019) | [Cite this article](#)

Enamine: operating since 1991



Expertise as a good red wine – it gets better with time

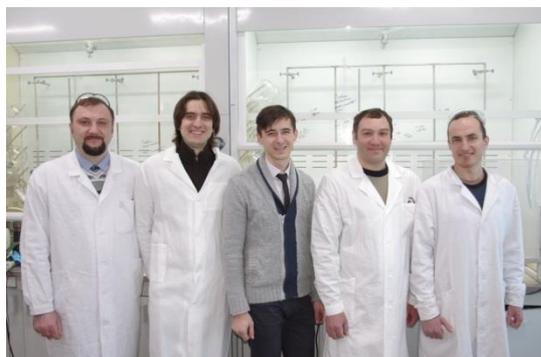
Synthetic experience: 3 Mio compounds synthesized



Enamine: over 1,000 scientists



Catalog business allows sharing chemical knowledge

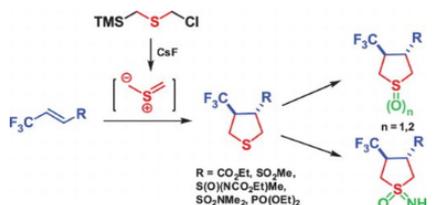


Over 50 scientific publications yearly

Building Blocks
 Library Synthesis
 Hit Finding
 Fragments
 Discovery

Home > Research > Publications > Additions and Corrections: 3-Benzyl-3-azabicyclo[3.1.1]heptan-6-one: a promising building block for medicinal chemistry

PUBLICATIONS



3-Functional substituted 4-trifluoromethyl tetrahydrothiophenes via [3+2]-cycloaddition reactions

J. Sulfur Chem. 2019, in press
DOI: 10.1080/17415993.2019.1633326

Markitanov Y.; Timoshenko V.; Rudenko T.; Rusanov E.; Shermolovich Y.

Hindered dialkyl ether synthesis with electrogenerated carbocations

Nature 2019, 573 (7774), 398-402
DOI: 10.1038/s41586-019-1539-y

Xiang J.; Shang M.; Kawamata Y.; Lundberg H.; Reisberg S.; Chen M.; Mykhailiuk P.; Beutner G.; Collins M.; Davies A.; Del Bel M.; Gallego G.; Spangler J.; Starr J.; Yang S.; Blackmond D.; Baran P.

SAR by space: Enriching hit sets from the chemical space

Molecules 2019, 24 (17), 3096
DOI: 10.3390/molecules24173096

Klingler F.; Gastreich M.; Grygorenko O.; Savych O.; Borysko P.; Griniukova A.; Gubina K.; Lemmen C.; Moroz Y.

Synthesis of Isomeric 6-Trifluoromethyl-3-azabicyclo[3.1.0]hexanes:
 Confor...
 Open Access...
 Eur J Org Chem...
 DOI: 10.1002/ejoc.201900121

Synthesis and Characterization of β -Trifluoromethyl-Substituted Pyrrolidines
 Vladimir S. Yuravichuk,^{1,2} Olga V. Shakhin,^{1,3} Viktoria S. Starova,^{1,4} Olga A. Zaporozhets,^{1,4} Olga Kravchuk,^{1,4} Sergey Zaitsev,^{1,4} Igor V. Komarov,^{1,4} and Pavel K. Mykhailiuk^{1,4*}
 Keywords: Synthetic methods / Medicinal chemistry / Drug design / Drug discovery / Nitrogen heterocycles / Amino / Fluorine
 A practical synthetic approach to the construction of a library of these nitrogen heterocycles...
 Introduction

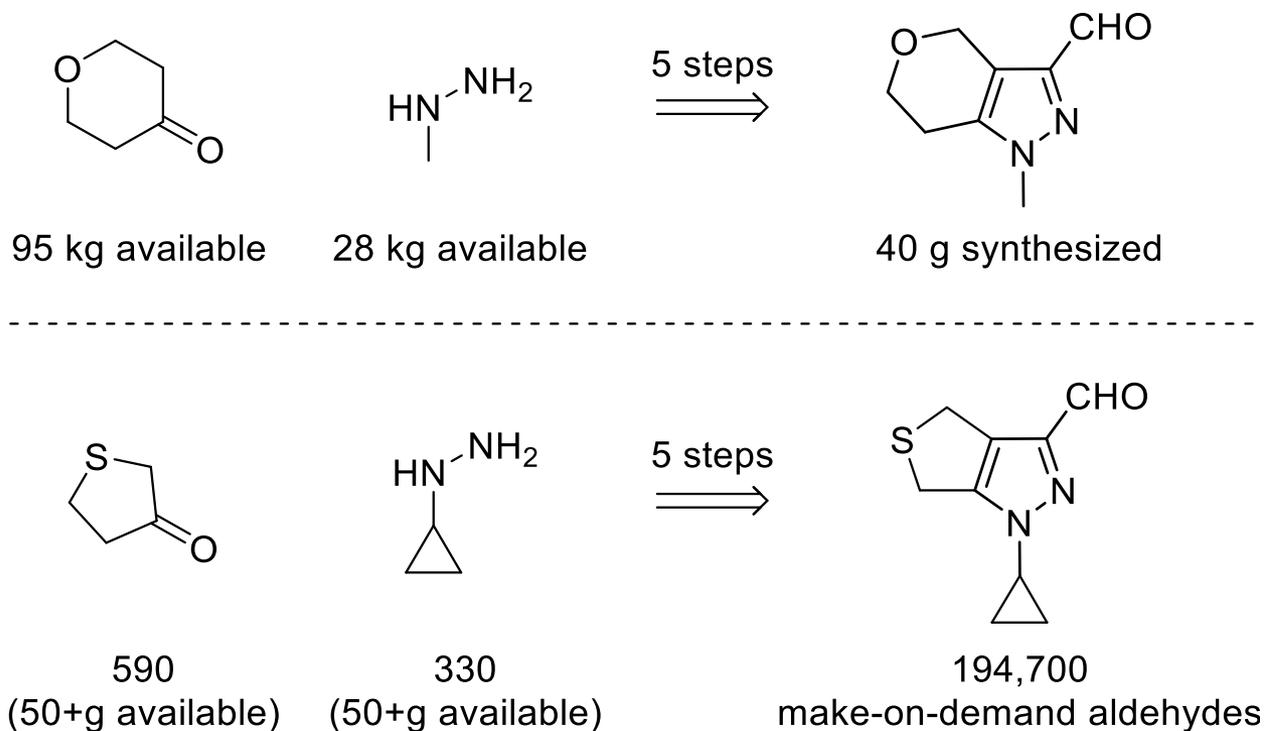
Tetrahedron Letters
 Contents lists available at ScienceDirect
 Elsevier
 www.elsevier.com/locate/tetlet

An easy synthesis of α -trifluoromethyl-amines from aldehydes or ketones using the Ruppert-Prakash reagent
 Dmytro S. Radchenko^{1,2}, Oleg M. Michurin^{1,3}, Anton V. Chernykh^{1,2}, Oleg Lugin^{1,4}, Pavel K. Mykhailiuk^{1,4*}
 Abstract...
 Eur J Org Chem...
 DOI: 10.1002/ejoc.201900121

Controlling Biological Activity with Light: Diarylethene-Containing Cyclic Peptidomimetics[®]
 Oleg Babi, Sergei Afonin, Marina Berdnik, Sabine Reifer, Pavel K. Mykhailiuk, Vladimir S. Kubyshkin, Thomas Steinbrecher, Anne S. Ulrich, and Igor V. Komarov¹
 Abstract: Photochemical processes in nature are easily triggered by uncomplex chromophores or by modified acid chromophores...
 Figure 1. General structure of photochromic fluorogenic amino acid derivatives...
 Figure 2. Synthesis of diarylethene-containing cyclic peptidomimetics...
 Figure 3. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 4. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 5. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 6. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 7. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 8. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 9. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 10. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 11. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 12. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 13. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 14. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 15. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 16. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
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 Figure 18. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 19. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 20. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 21. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 22. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
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 Figure 34. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
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 Figure 57. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 58. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...
 Figure 59. Fluorescence resonance energy transfer (FRET) between the photochromic fluorogenic amino acid derivatives...

Chemical knowledge is a key to a make-on-demand concept

Validated synthetic procedures



In-stock starting reagents

Make-on-demand concept: price and lead time are known

chem-space.com/search/sub/O%253DCc1nn%2528C2CC2%2529c2CSCc12/828836a5d1b28938b05bceab7ad9dd58

CHEM SPACE
Delivering Discovery Solutions®

Search by name, CAS, MFCD, ID

Register Sign in

Home Products Services Companies Information

0 USD

Refine Query

New Search

Select All Compounds Export to file

Show 12 Items per page

Make-On-Demand Building Blocks (8)

Supplier	Ships within	Price, \$	Pack	
MADE Compounds	Up to 1 month	985	1g	Add to cart
For a custom pack size or bulk please drop us a line.				
Enquire				
MADE Compounds	Up to 1 month	971	1g	Add to cart
For a custom pack size or bulk please drop us a line.				
Enquire				

Sort

- Price
- Mol. Weight
- Ships within

Filter

- Filter suppliers
- Filter by properties
- Remove all filters

CSMB00052977033

CSMB00021265251

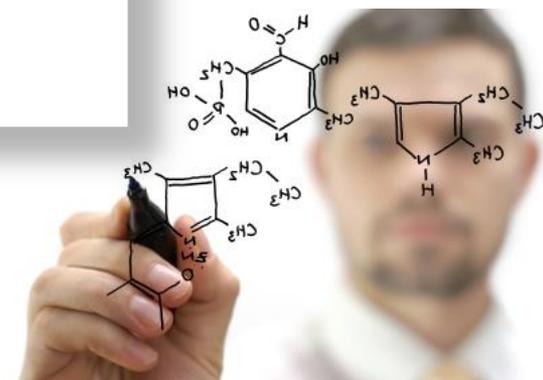
Make-on-demand: in-between

Make-on-demand

The screenshot shows the CHEMSPACE website interface. At the top, there is a search bar and navigation links for Home, Products, Services, Companies, and Information. Below the search bar, there are filters for 'Refine Query' and 'New Search'. The main content area displays two search results for 'Make-On-Demand Building Blocks'. Each result includes a chemical structure, a product ID (CSMB00052977033 and CSMB00021265251), and a table of details: Supplier, Ships within, Price, and Pack. Each entry also has an 'Add to cart' button and an 'Engage' button.



In-stock items



Custom Synthesis

Shades of make-on-demand

***MADE* Building blocks, 240 Mio**

***REAL* database, 1.36 Bn**

***REAL* Space, 15.5 Bn**

MADE building blocks



**Flask chemistry,
up to 5 steps, gram scale**

MADE building blocks

[Home](#) / [Chimica Oggi-Chemistry Today](#) / [Vol. 28\(1\)](#) / [World largest collection ...](#)

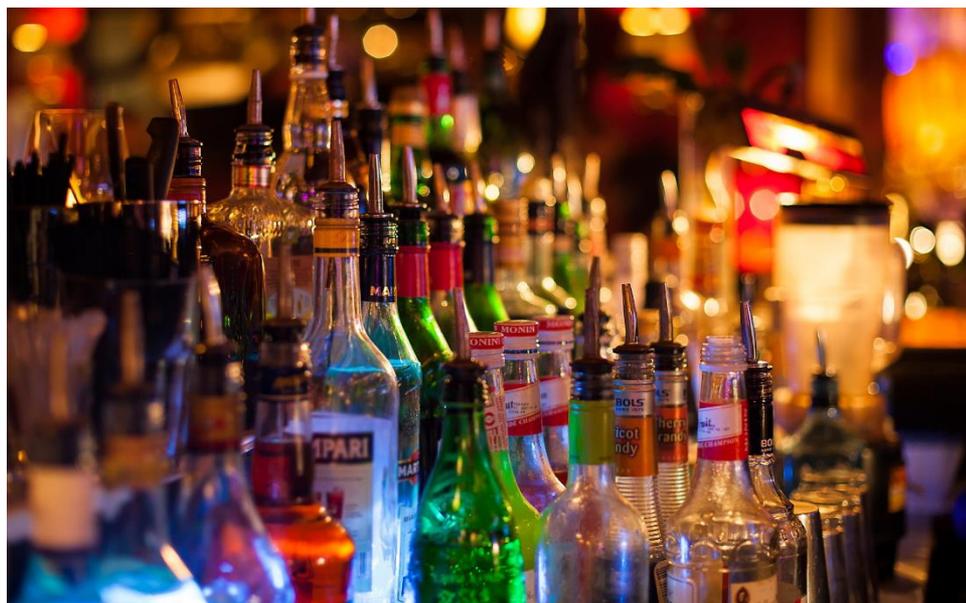
P. 12-13 / PRODUCT FOCUS

WORLD LARGEST COLLECTION OF TANGIBLE BUILDING BLOCKS AND FRAGMENTS FOR DRUG DISCOVERY

Keywords: Enamine, Uorsy

Synthesis of small organic molecules lies at the hard of modern drug discovery (1). Highthroughput biological screening (2) requires large diverse libraries of organic compounds whose structures and physical properties (molecular weight, clogP, logS, number of hydrogen bond donors and acceptors) obey certain rules such as rule of 5 (3) that increase the probability of biological activity. In silico designed focused libraries of small molecules are synthesized through attaching various functional groups to molecular cores (scaffolds) in a fashion predicted to maximize ligand – target interactions (4).

MADE Building blocks are not reagents



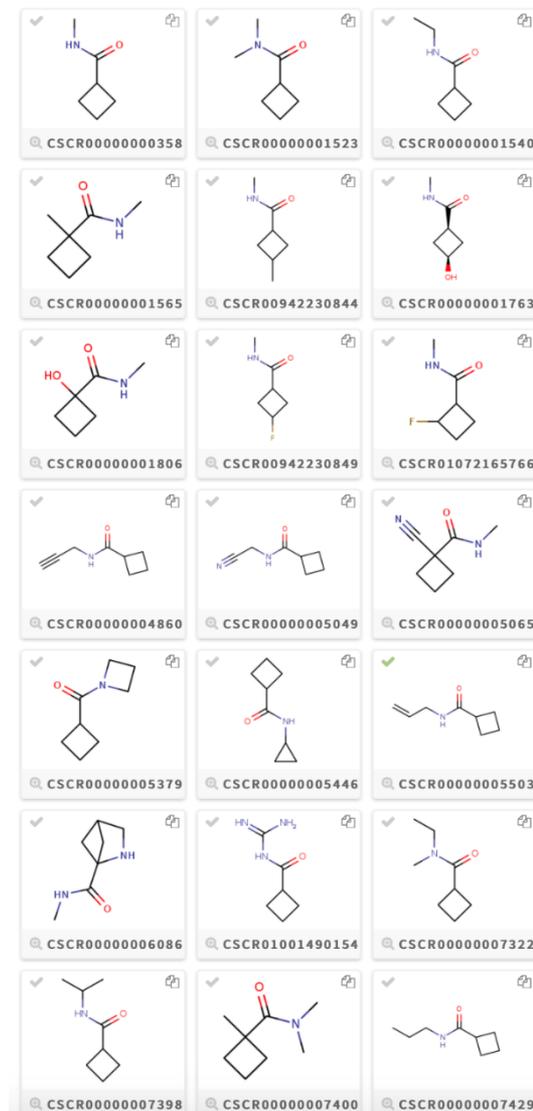
MADE Building blocks are advanced reagents



REAL compounds



One-pot parallel chemistry
1-3 steps, mg scale



REAL compounds

iScience

Volume 23, Issue 11, 20 November 2020, 101681



Article

Generating Multibillion Chemical Space of Readily Accessible Screening Compounds

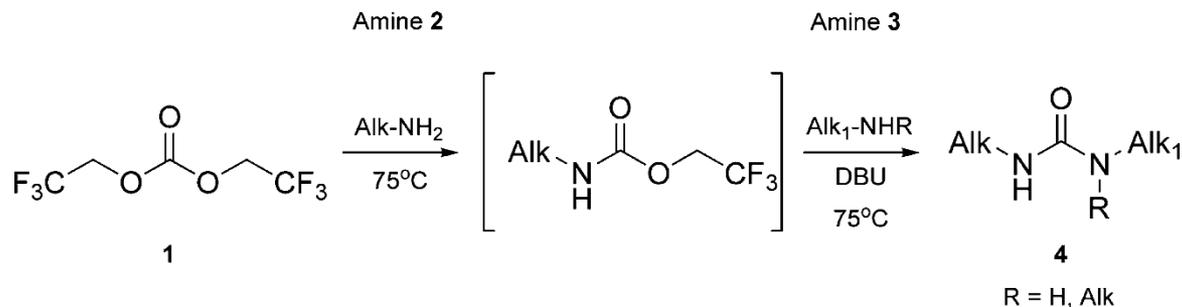
Oleksandr O. Grygorenko^{1,2}  , Dmytro S. Radchenko^{1,2}, Igor Dziuba³, Alexander Chuprina⁴, Kateryna E. Gubina², Yurii S. Moroz^{2,3,5}  

***REAL* compounds, billions to taste test**



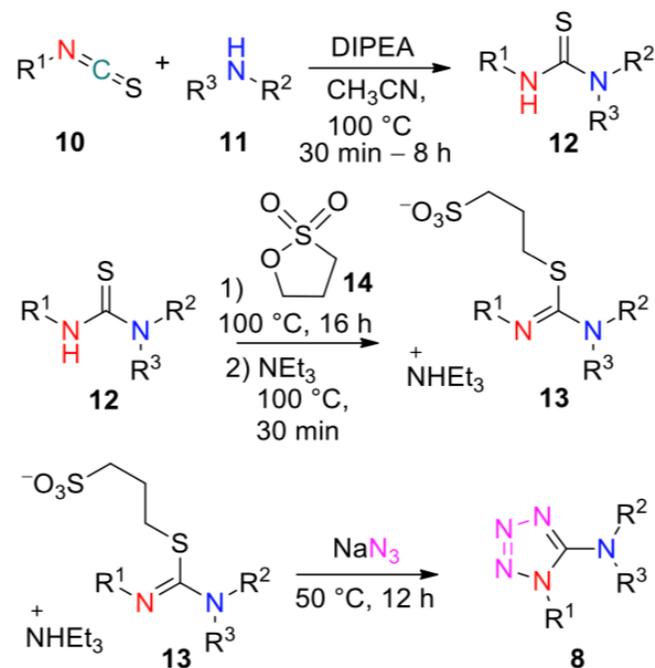
REAL compounds: 195 validated procedures

Simple one-pot! chemistry, **S REAL** compounds



REAL compounds: 195 validated procedures

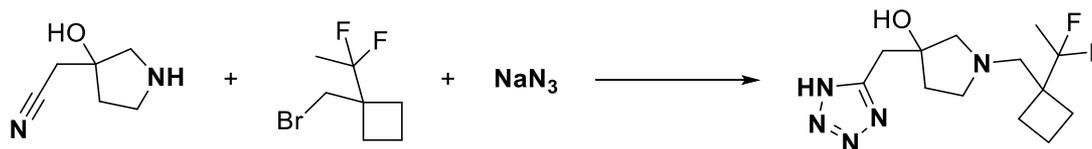
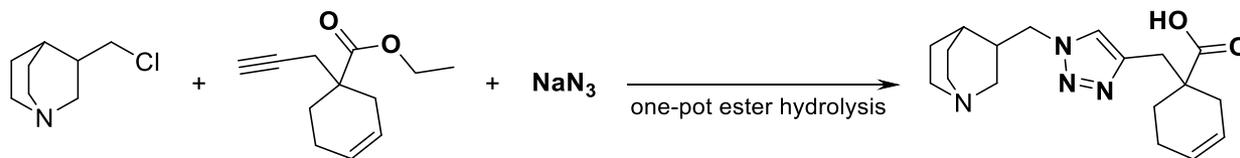
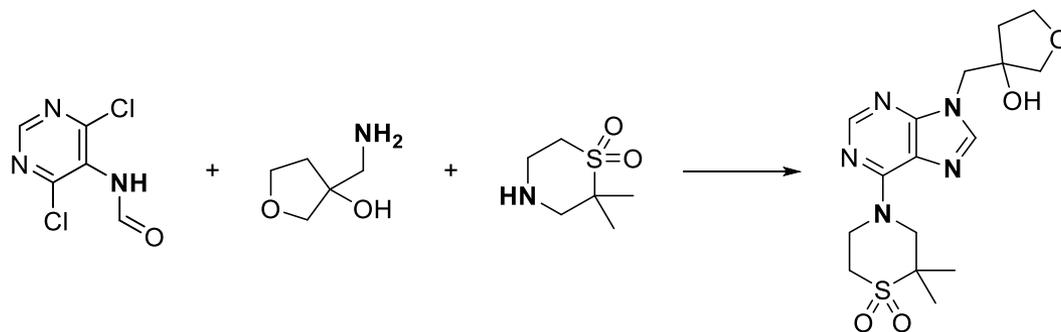
Advanced, Not Simple, one-pot! chemistry, **M REAL** compounds



One-Pot Parallel Synthesis of 5-(Dialkylamino)tetrazoles

Olena Savych,^{†,‡} Yuliya O. Kuchkovska,^{†,§} Andrey V. Bogolyubsky,[†] Anzhelika I. Konovets,[†] Kateryna E. Gubina,[§] Sergey E. Pipko,^{||} Anton V. Zhemera,[†] Alexander V. Grishchenko,[†] Dmytro N. Khomenko,[§] Volodymyr S. Brovarets,^{‡,⊙} Roman Doroshchuk,[§] Yurii S. Moroz,^{§,||} and Oleksandr O. Grygorenko^{*,†,§,⊙}

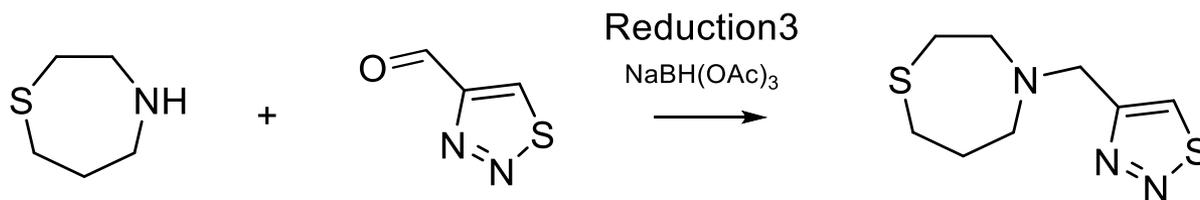
q1-2 2020 *REAL* update: 10 new validated procedures



REAL compounds: 130,000 building blocks in use

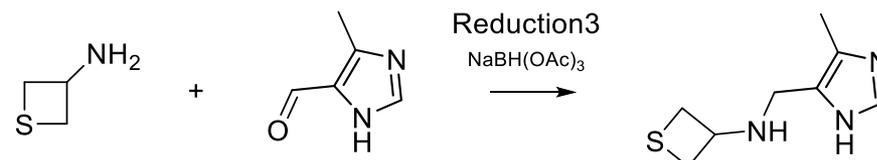


REAL compounds: qualified building blocks only



High-score aldehyde

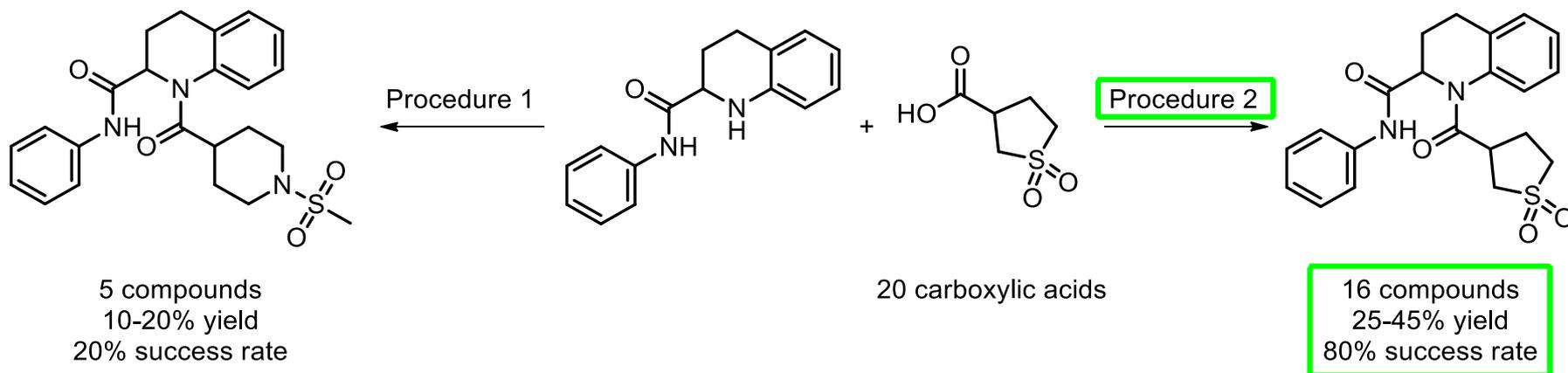
293 reductive aminations set
81% succeeded



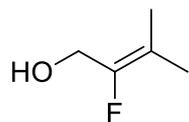
Low-score aldehyde

54 reductive aminations set
4% succeeded

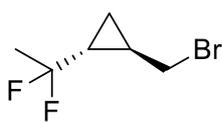
REAL compounds: fight for each building block



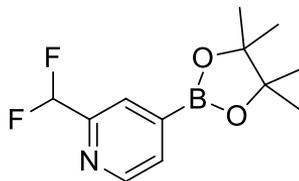
q1-2 2020 REAL update: 10,000 new building blocks



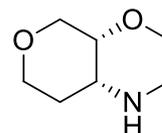
EN300-7183630



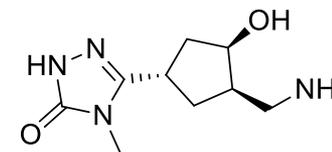
EN300-7182324



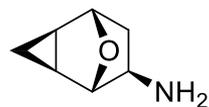
EN300-7182871



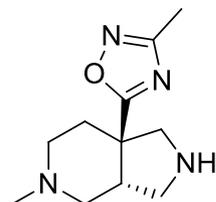
EN300-719522



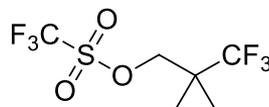
EN300-724808



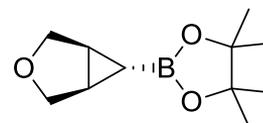
EN300-725095



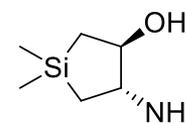
EN300-726367



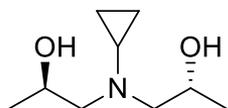
EN300-7296674



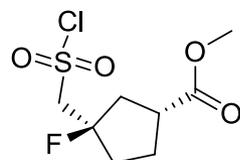
EN300-7537541



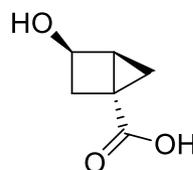
EN300-7354885



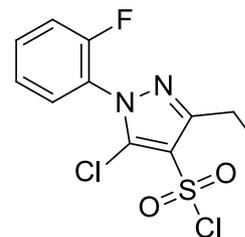
EN300-7354104



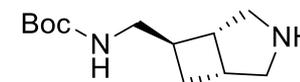
EN300-7430019



EN300-7433125

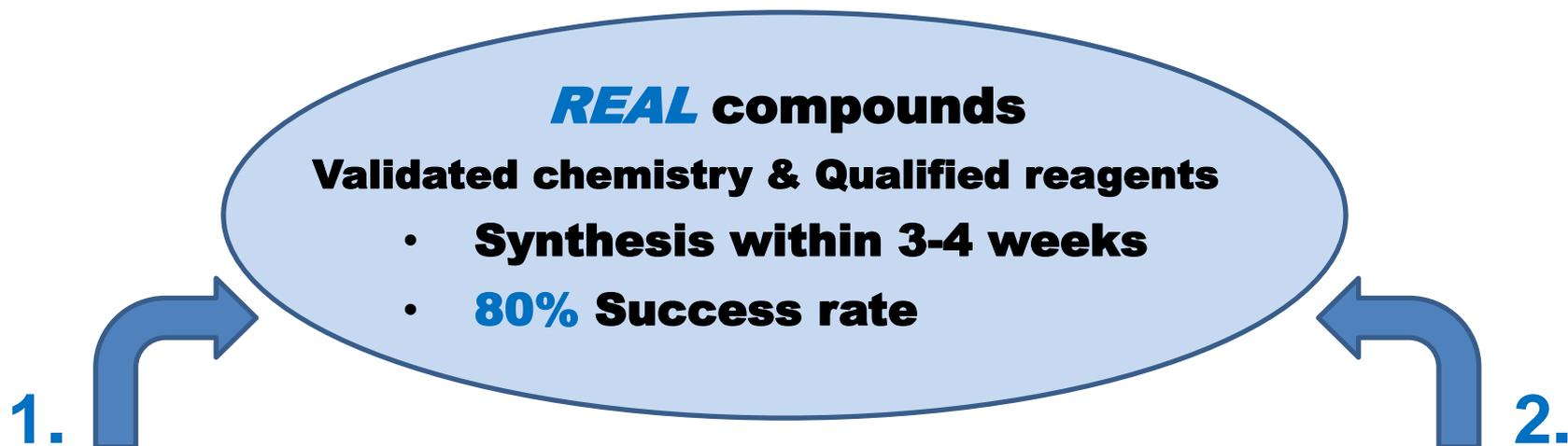


EN300-7504218



EN300-7355116

Surfing in the *REAL*



***REAL* database**

2020q1-2, 1.36 Bn

**a subset of the *REAL* Space
database with enumerated structures**

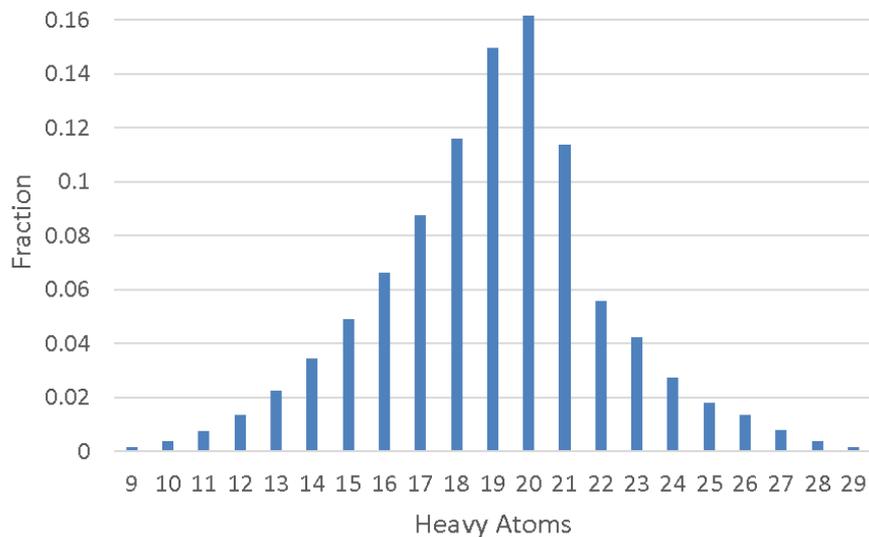
***REAL* Space with FTrees**

Nov 2020, 15.5 Bn

**software tool
collaboration with BioSolveIT**



Surfing in the *REAL*

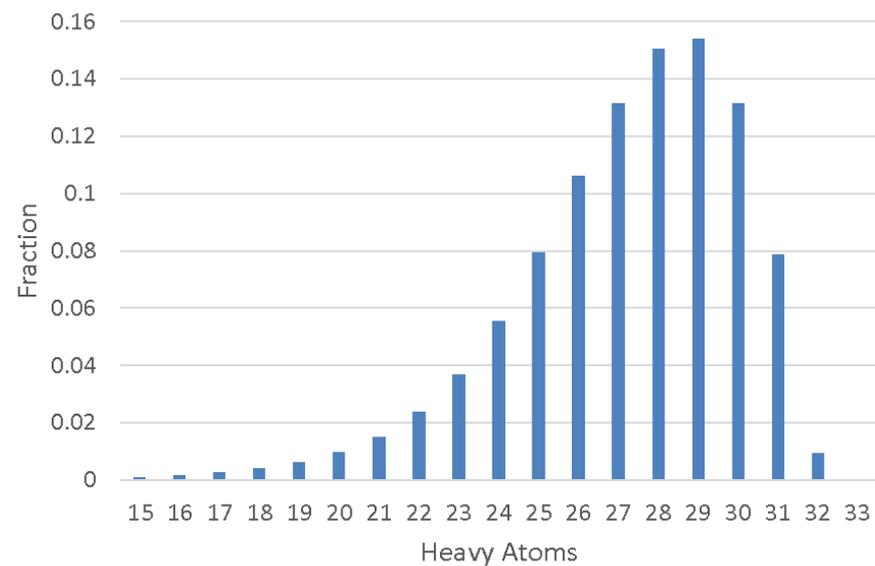


***REAL* database**

2020q1-2, 1.36 Bn

a subset of the *REAL* Space

database with enumerated structures



***REAL* Space with FTrees**

Nov 2020, 15.5 Bn

software tool

collaboration with BioSolveIT



REAL database: enumerated molecules

SMILES	REAGENT1 SMILES	REAGENT2 SMILES
<chem>CC(N(C)C(=O)c1cc2OCCn2n1)c3ccc(cc3)n4cnc5ccccc45</chem>	<chem>CNC(C)c1ccc(cc1)n2cnc3ccccc23</chem>	<chem>OC(=O)c1cc2OCCn2n1</chem>
<chem>O=C(NCCCC1CCCC1)C2CC32CCc4cc(ccc43)c5cccn5</chem>	<chem>NCCCC1CCCC1</chem>	<chem>OC(=O)C1CC21CCc3cc(ccc32)c4cccn4</chem>
<chem>O=C(NCCCC1CCCC1)[C@@H]2CCCN2C(=O)c3cccs3</chem>	<chem>NCCCC1CCCC1</chem>	<chem>OC(=O)C1CCCN1C(=O)c2cccs2</chem>
<chem>CN(Cc1nccn1C(F)F)C(=O)CC2(COC2)N3CCc4ncccc4C3</chem>	<chem>CNCc1nccn1C(F)F</chem>	<chem>[Na+].[O-]C(=O)CC1(COC1)N2CCc3ncccc3C2</chem>
<chem>CN(Cc1nccn1C(F)F)C(=O)CC2(COC2)N3CCc4ncccc4C3</chem>	<chem>CNCc1nccn1C(F)F</chem>	<chem>[Na+].[O-]C(=O)CC1(COC1)N2CCc3ncccc3C2</chem>
<chem>CN(Cc1nccn1C(F)F)C(=O)C2C(Si)(C)(C)CN2Cc3ccccc3</chem>	<chem>CNCc1nccn1C(F)F</chem>	<chem>Cl.C(Si)1(C)CC(N(Cc2ccccc2)C1)C(=O)O</chem>
<chem>CN(Cc1nccn1C(F)F)C(=O)C2C(Si)(C)(C)CN2Cc3ccccc3</chem>	<chem>CNCc1nccn1C(F)F</chem>	<chem>Cl.C(Si)1(C)CC(N(Cc2ccccc2)C1)C(=O)O</chem>
<chem>CN(Cc1nccn1C(F)F)C(=O)c2cc(Cl)c3CCN(CCO)Cc3n2</chem>	<chem>CNCc1nccn1C(F)F</chem>	<chem>OCCN1CCc2c(Cl)cc(nc2C1)C(=O)O</chem>
<chem>CN(Cc1nccn1C(F)F)C(=O)c2cc(Cl)c3CCN(CCO)Cc3n2</chem>	<chem>CNCc1nccn1C(F)F</chem>	<chem>Cl.OCCN1CCc2c(Cl)cc(nc2C1)C(=O)O</chem>
<chem>CN(Cc1nccn1C(F)F)C(=O)c2cc(Cl)c3CCN(CC4CC4)Cc3n2</chem>	<chem>CNCc1nccn1C(F)F</chem>	<chem>OC(=O)c1cc(Cl)c2CCN(CC3CC3)Cc2n1</chem>
<chem>CN(Cc1nccn1C(F)F)C(=O)c2cc(Cl)c3CCN(CC4CC4)Cc3n2</chem>	<chem>CNCc1nccn1C(F)F</chem>	<chem>OC(=O)c1cc(Cl)c2CCN(CC3CC3)Cc2n1</chem>
<chem>CN(Cc1nccn1C(F)F)C(=O)Cc2ccc3OCCCc3c2</chem>	<chem>CNCc1nccn1C(F)F</chem>	<chem>OC(=O)Cc1ccc2OCCCc2c1</chem>
<chem>CCn1cc(C(=O)N(C)Cc2nccn2C(F)F)c(n1)C3CCOCC3</chem>	<chem>CNCc1nccn1C(F)F</chem>	<chem>CCn1cc(C(=O)O)c(n1)C2CCOCC2</chem>
<chem>CN(Cc1nccn1C(F)F)C(=O)c2ccc(C)nc2C3CC3</chem>	<chem>CNCc1nccn1C(F)F</chem>	<chem>Cc1ccc(C(=O)O)c(n1)C2CC2</chem>

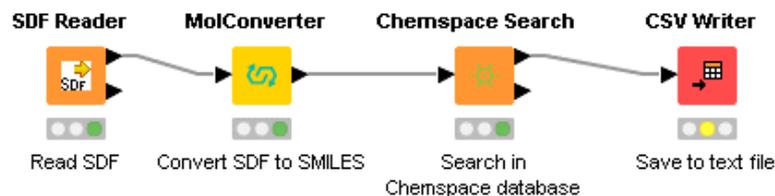
REAL database: 1.36 Bn drug-like molecules

		%
S REAL compounds	932.6 Mio	69%
M REAL compounds	428.6 Mio	31%
Average MW	370	
Average SlogP	2.6	
Average QED	0.75	
Drug-Like molecules	1.36 Bn	100%
Lead-Like molecules	967 Mio	71%
Fragment-Like molecules	13.7 Mio	1%
Passed PAINS filters	1.35 Bn	99%
Passed LILLY rules	1.22 Bn	90%

REAL database: searchable online, via API, and KNIME

enaminestore.com/search

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REAL compounds: use cases

nature

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Ultra-large library docking for discovering new chemotypes

Jiankun Lyu, Sheng Wang, Trent E. Balius, Isha Singh, Anat Levit, Yurii S. Moroz, Matthew J. O'Meara, Tao Che, Enkhjargal Alгаа, Kateryna Tolmacheva, Andrey A. Tolmachev, Brian K. Shoichet , Bryan L. Roth  & John J. Irwin 

Nature 566, 224–229 (2019) | [Download Citation](#) 

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REAL Space exploration: the FTrees-based similarity

Drug Discovery Today • Volume 00, Number 00 • March 2019

REVIEWS



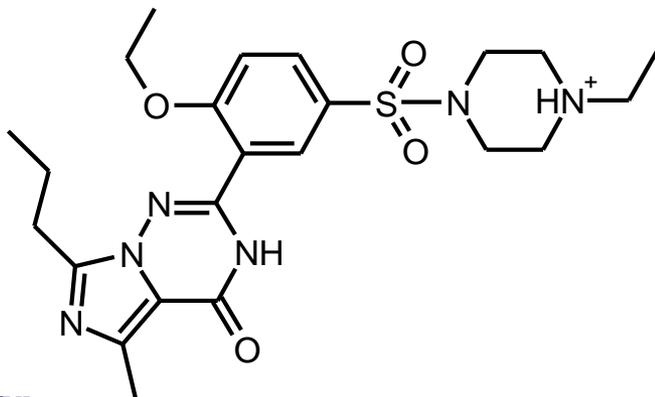
The next level in chemical space navigation: going far beyond enumerable compound libraries

Torsten Hoffmann¹ and Marcus Gastreich²

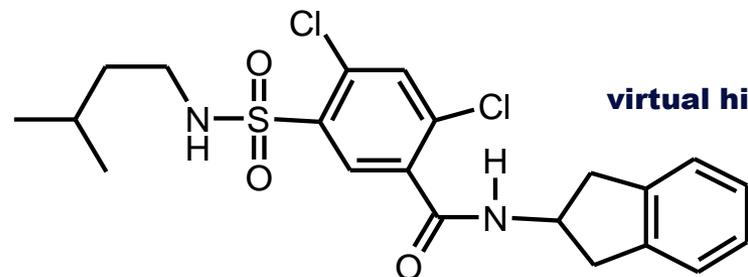
¹Taros Chemicals GmbH & Co. KG, Emil-Figge-Str. 76a, 44227 Dortmund, Germany

²BioSolveIT GmbH, An der Ziegelei 79, 53757 Sankt Augustin, Germany

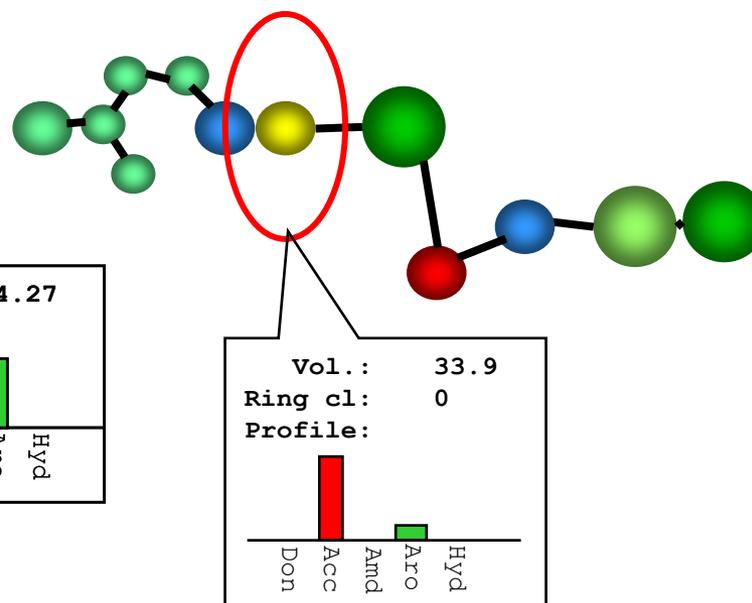
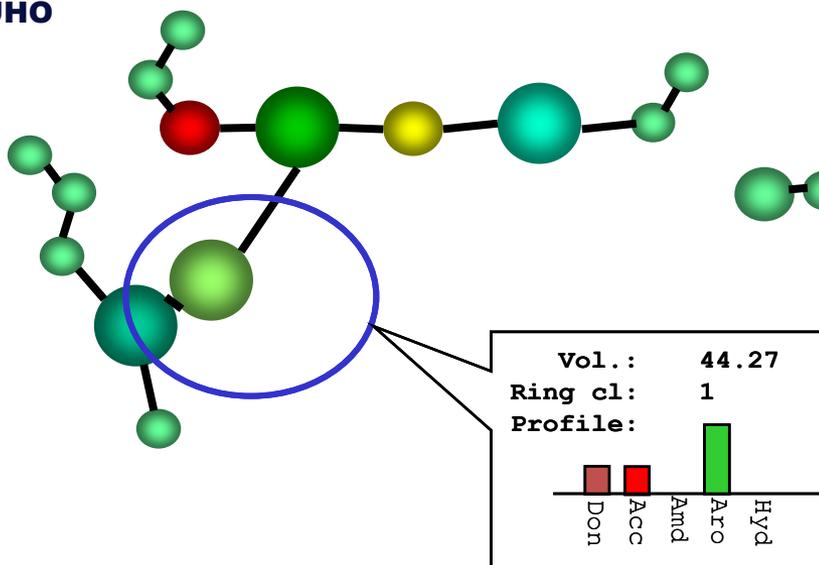
REAL Space exploration: the FTrees-based similarity



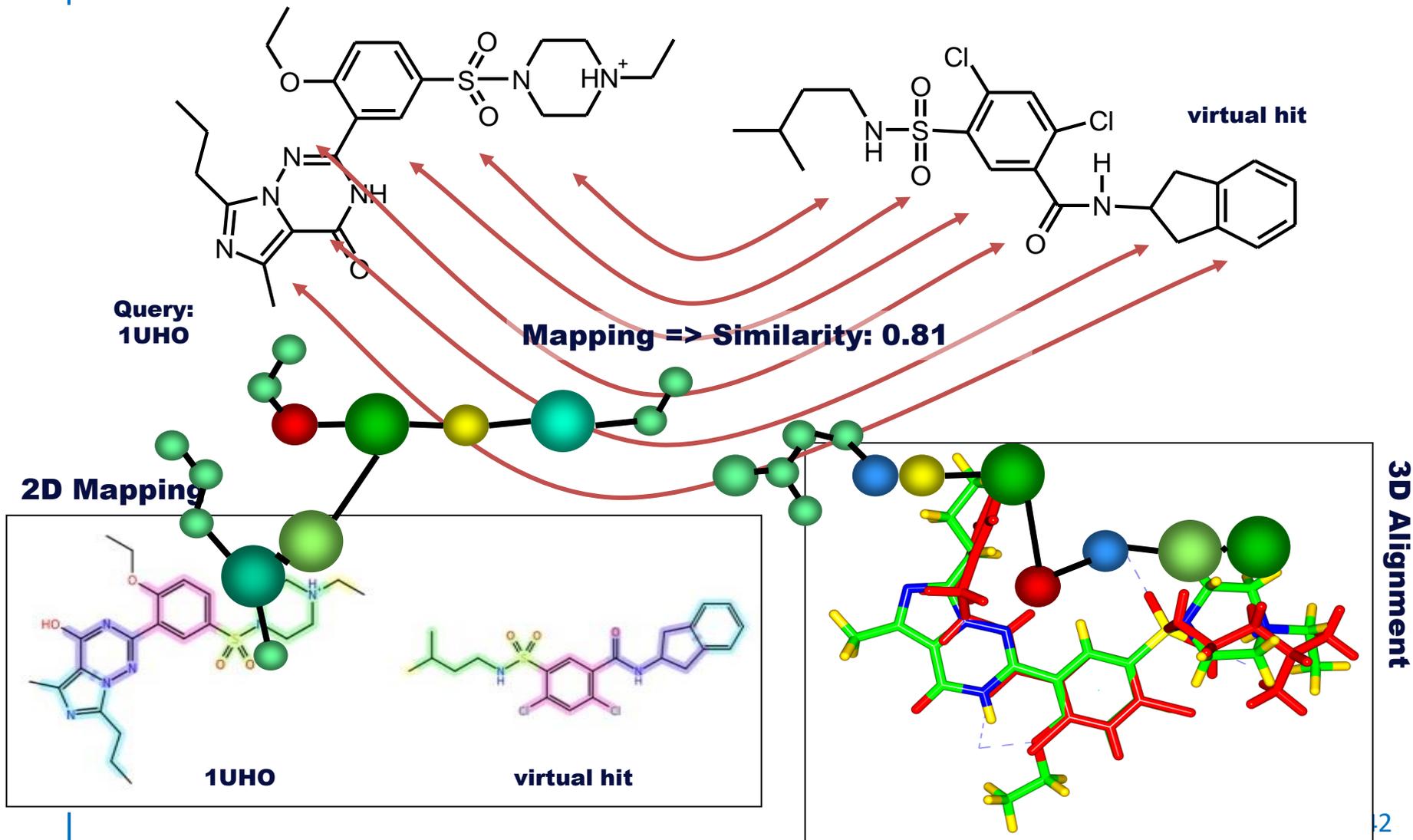
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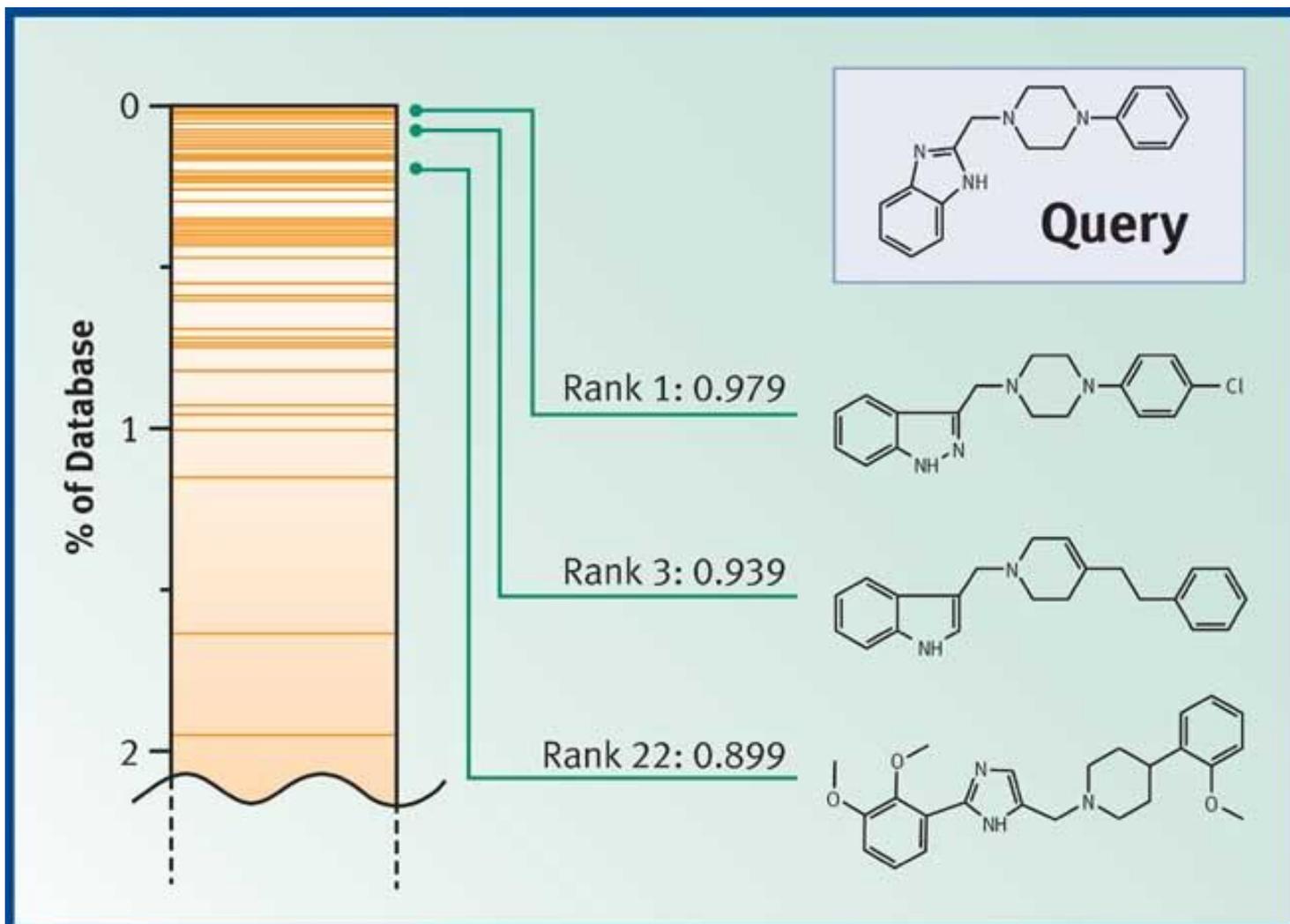
virtual hit



REAL Space exploration: the FTrees-based similarity



FTrees' strength: scaffold hopping



REAL Space exploration with FTrees: use case



Article

SAR by Space: Enriching Hit Sets from the Chemical Space

Franca-Maria Klingler ^{1,*}, Marcus Gastreich ¹, Oleksandr O. Grygorenko ^{2,3}, Olena Savych ², Petro Borysko ⁴, Anastasia Griniukova ⁴, Kateryna E. Gubina ³, Christian Lemmen ¹ and Yurii S. Moroz ^{3,5,*}

REAL Space exploration: options

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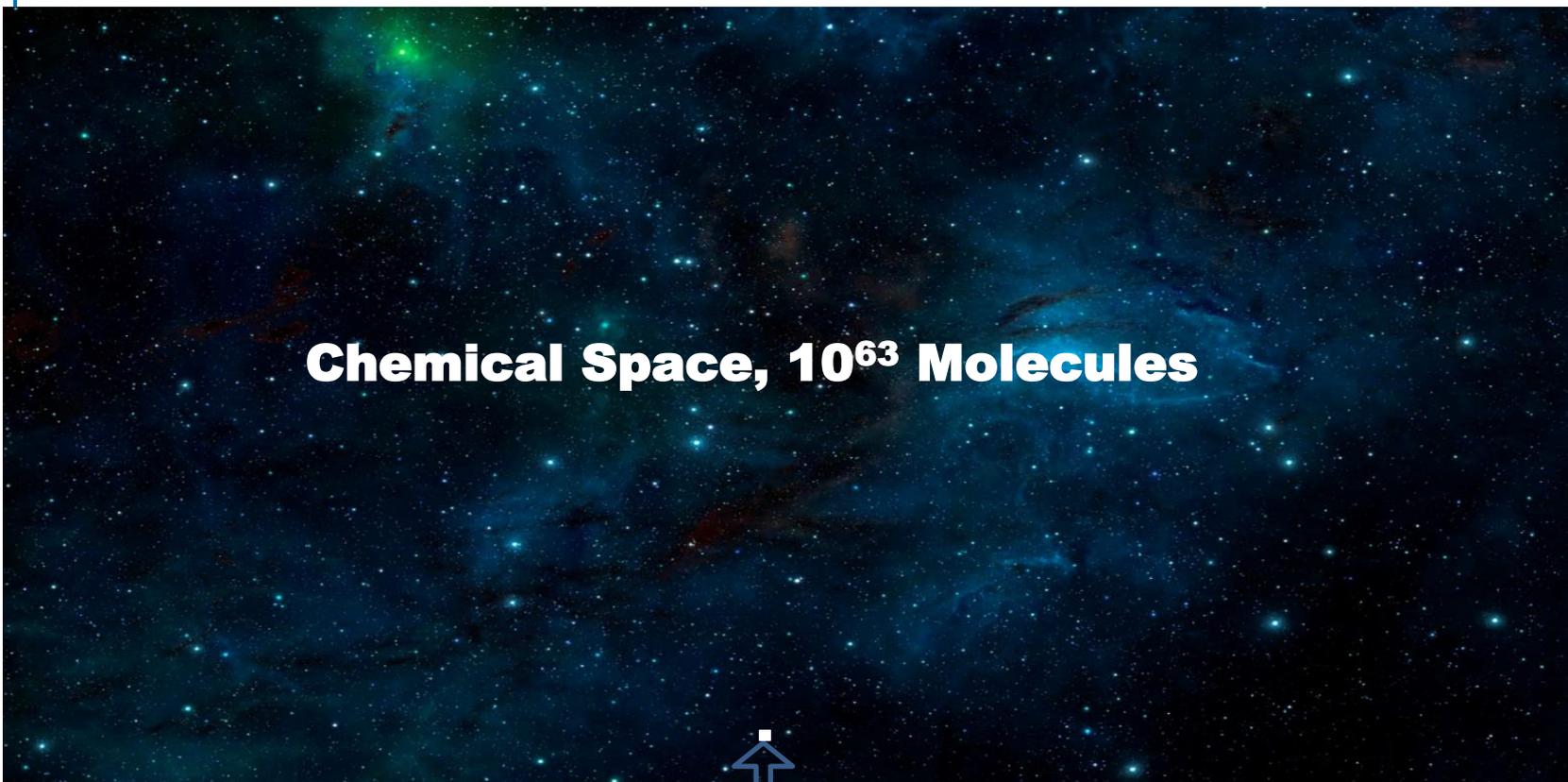
<https://chem-space.com/real-space>



infiniSee



<https://www.biosolveit.de/infiniSee>

A large, dark blue and black image of a starry night sky with various colored nebulae and stars.

Chemical Space, 10^{63} Molecules

A white arrow pointing upwards from the box below to the text above.

To Procure 10^{10} Molecules





Acknowledgements

Enamine
Chemspace
BioSolveIT

UCSF
HMS
CMU

and **thank you** to everyone who trusts in **Make-on-Demand**