TelesisPharma

rijksuniversiteit groningen

Drug Discovery at the Speed of Sound

The Chemical Space of Multicomponent Reactions

Dr Constantinos Neochoritis

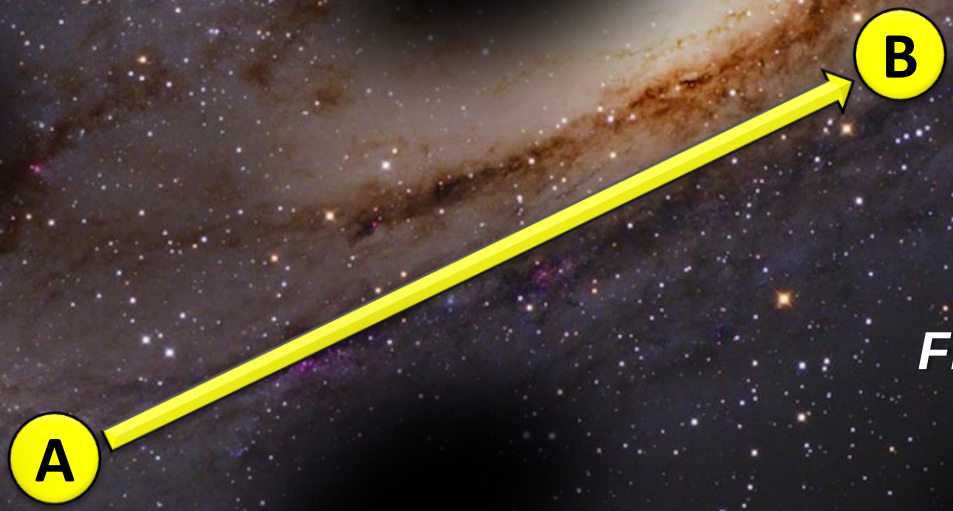
GRONINGEN 2018

10^{60} *might exhibit drug activity (C, N, O, S / 500 da / 4 rings)*

7×10^{6} *PubChem*

10^{60} *might exhibit drug activity (C, N, O, S / 500 da / 4 rings)*

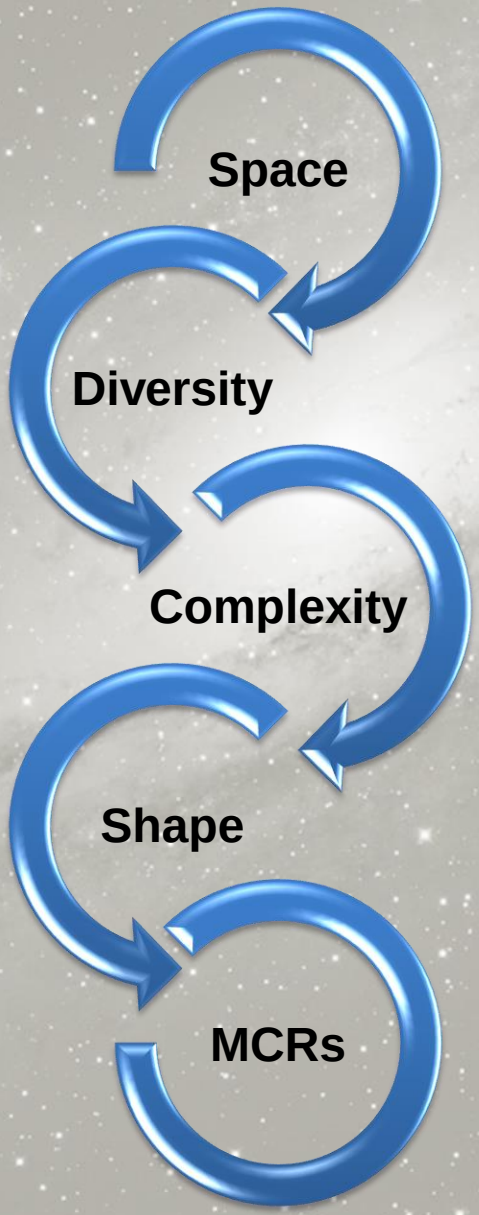
7×10^{6} *PubChem*



MCRs

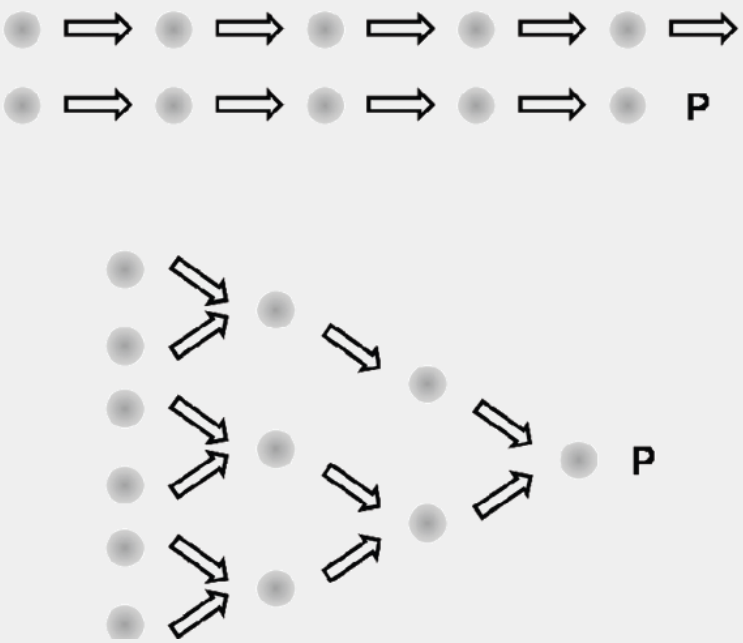
Finest tool of exploring

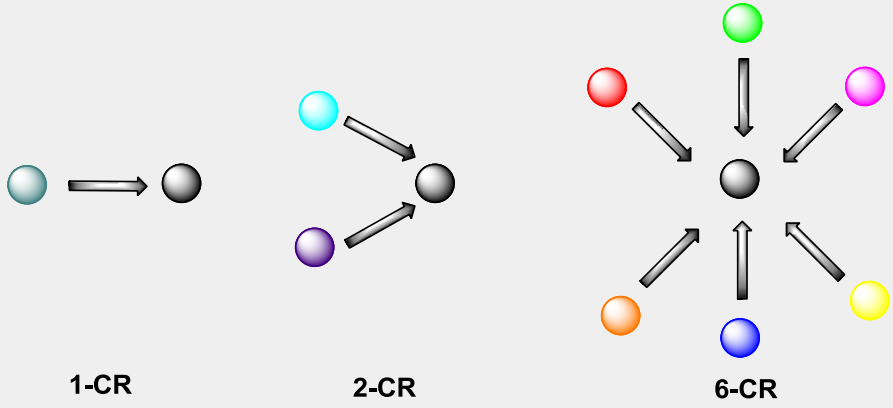
Multi-Component Reactions



MCRs-*intro*

- One-pot reactions
- More than two starting materials
- Most of the atoms of the starting materials are incorporated in the final product

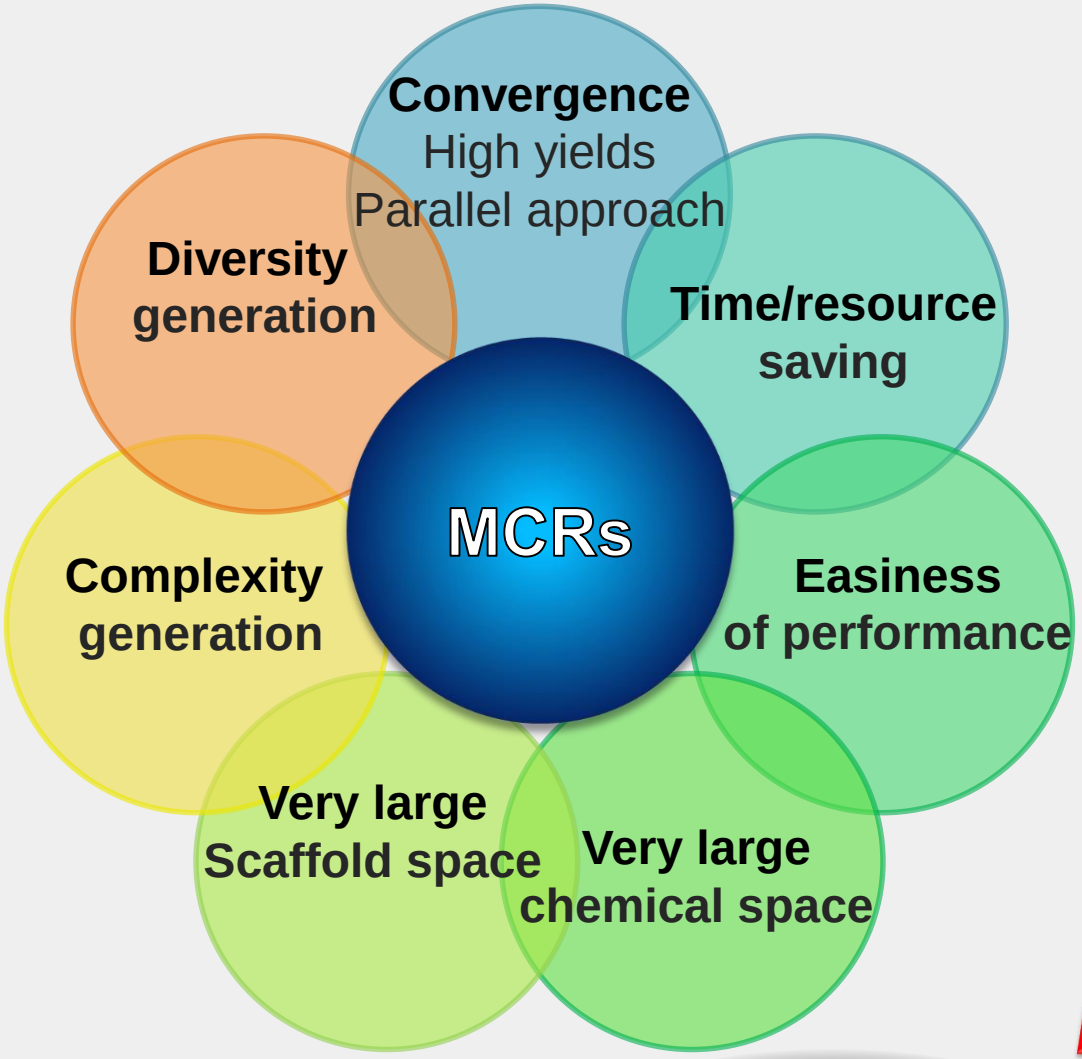




A. Dömling, *Chem. Rev.* **2006**, *106*, 17;
A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083

Ugi-4 component
40 each of the different components
40^4= 2,560,000 reaction products

MCRs-*characteristics*

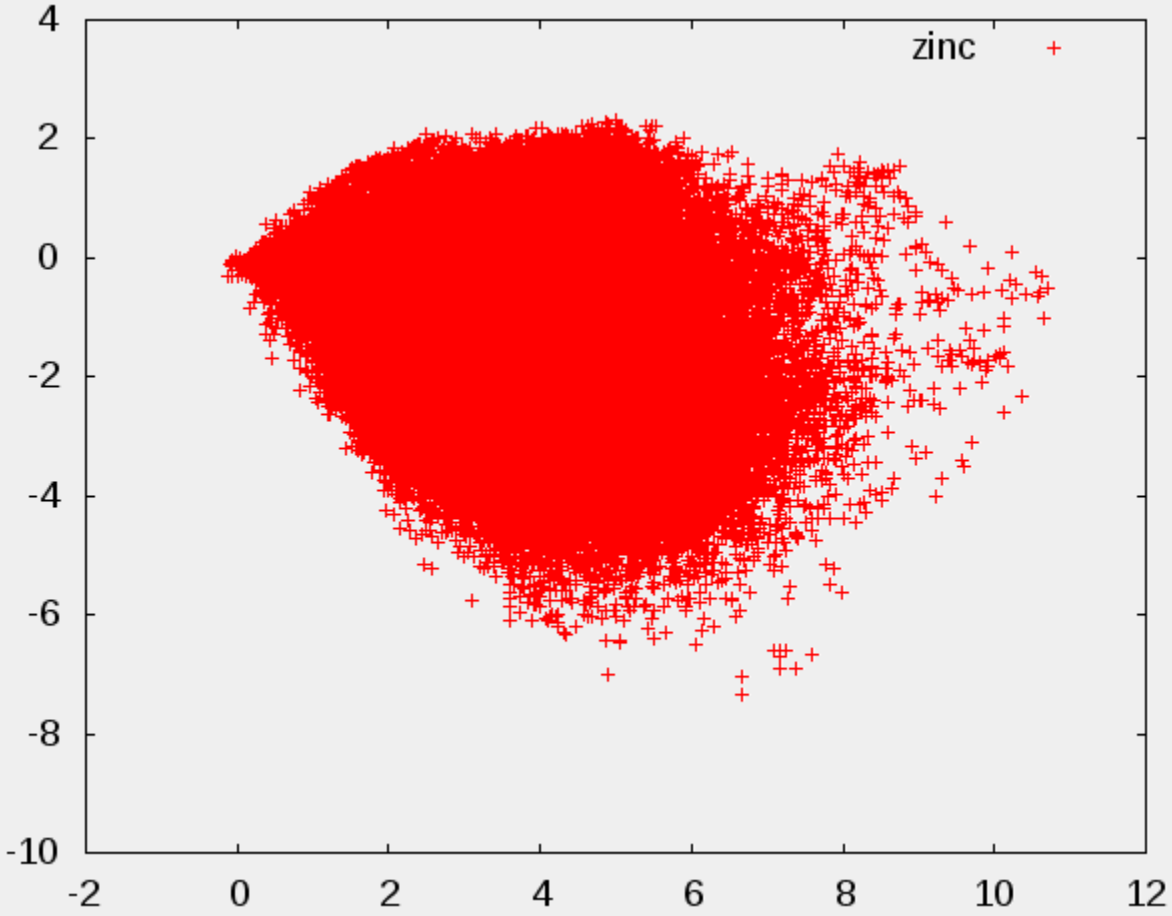


Primary classical MCRs (e.g. Ugi, *Hantzsch*, Mannich, Passerini…)

Secondary scaffolds based on *bifunctional* starting materials and/or secondary reactions

The diversity of MCRs

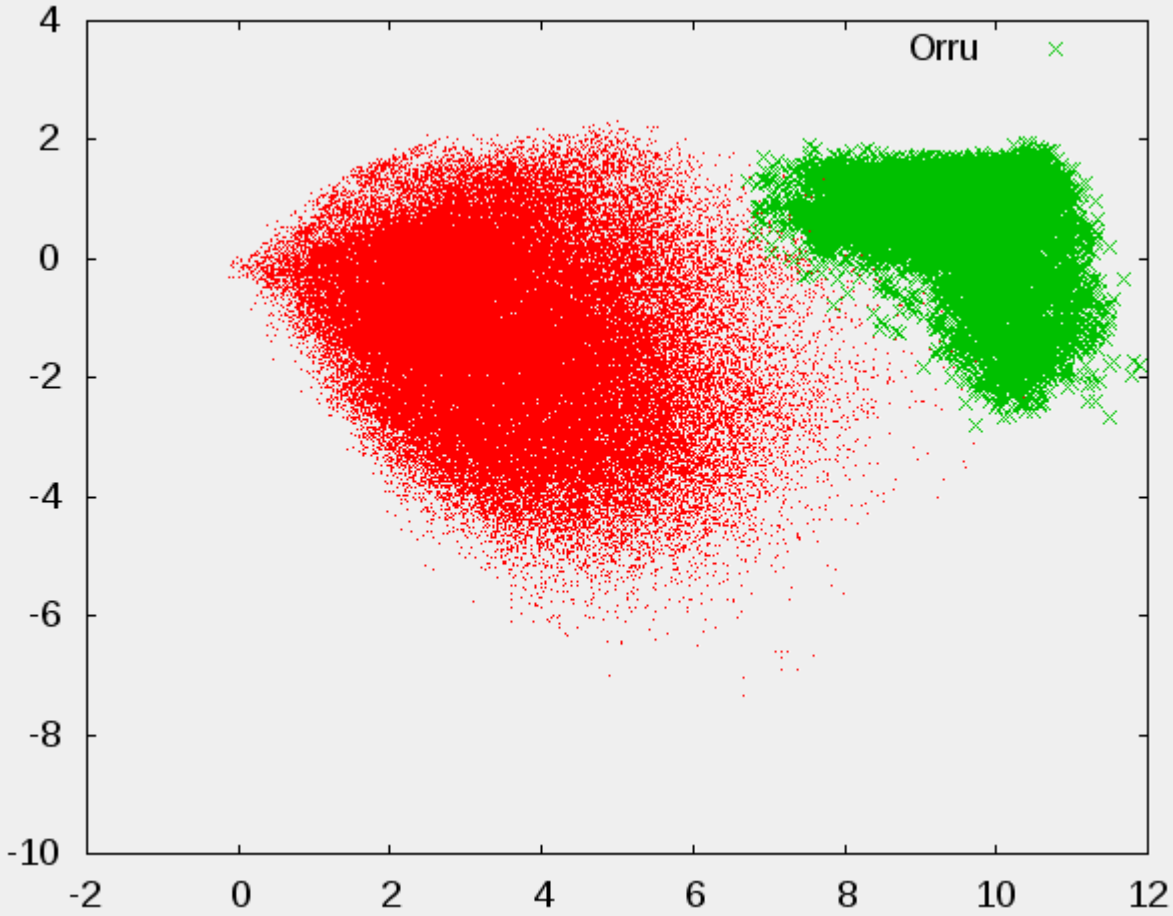
- Principle compound analysis (PCA)

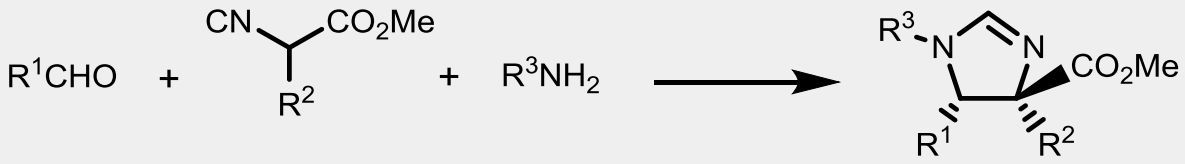


- ✓ ZINC contains over 100 million purchasable compounds in ready-to-dock, 3D formats

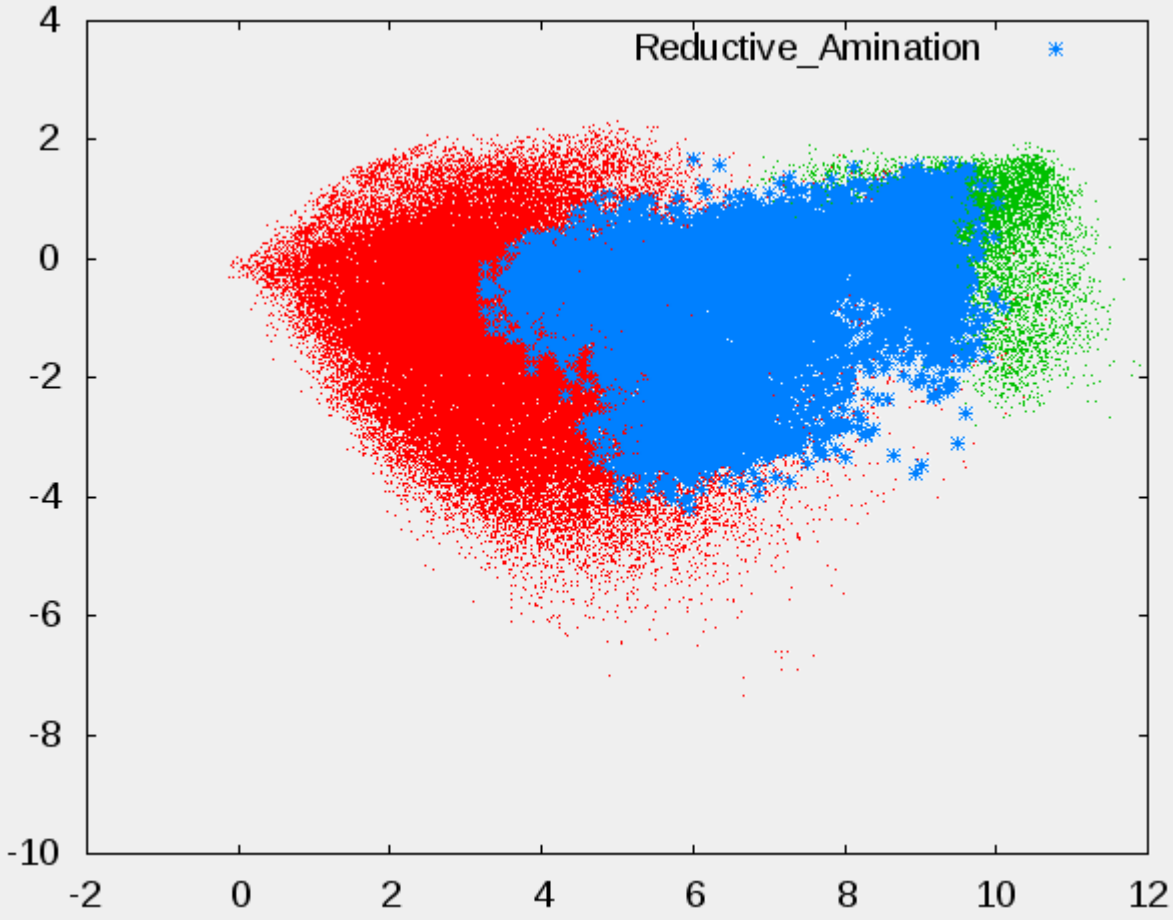
T. Sterling, J.J. Irwin, *J. Chem. Inf. Model.*, **2015**, *55*, 2324

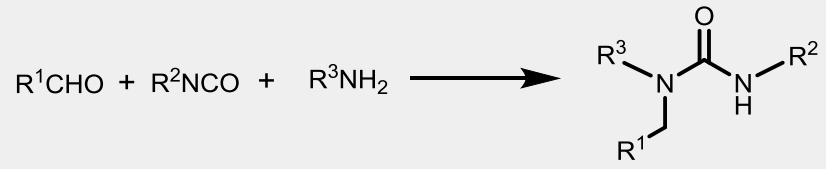
The diversity of MCRs

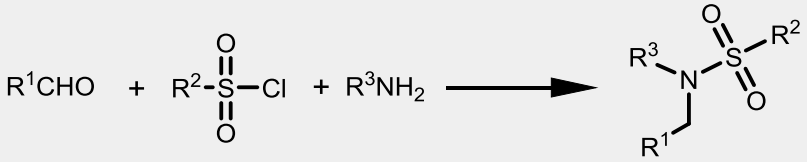




The diversity of MCRs

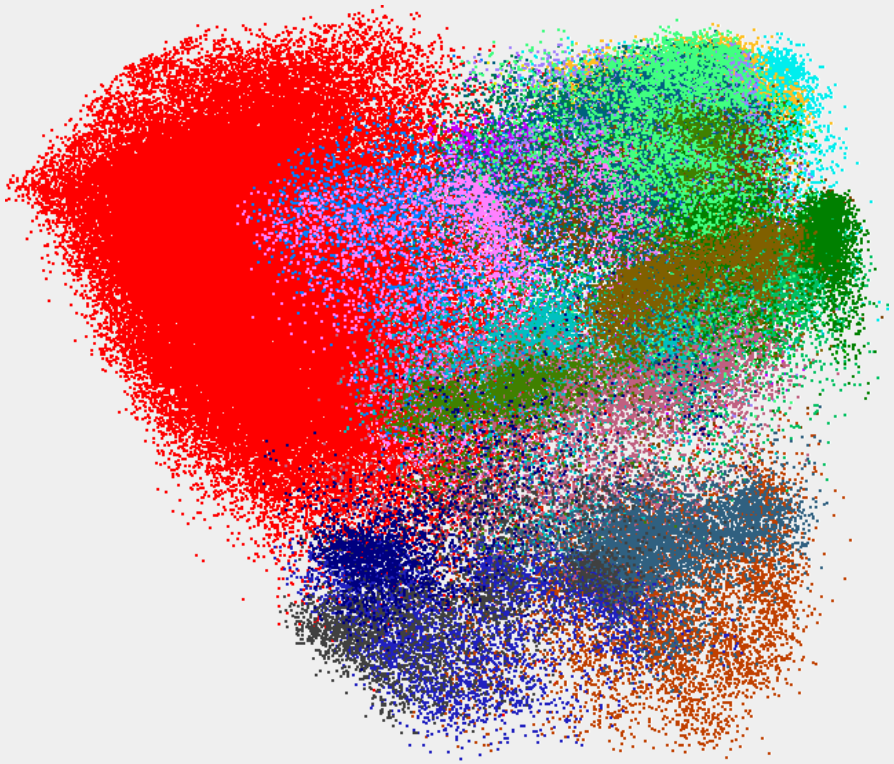






The diversity of MCRs-chemical space

- Doebner
- Gewald
- Groebcke
- Hydantoin
- Zhu
- PZQ
- UDC
- Tetrazole
- U4C-5CR
- Thiazole
- Sulfonamide
- Beta lactam
- U-4C
- Schollkopf_amidation
- Thienodiazepine
- Van Leusen
- Imidazole
- Orru+amidation
- Homophthalic acid
- Reductive amination
- Orru
- DKP



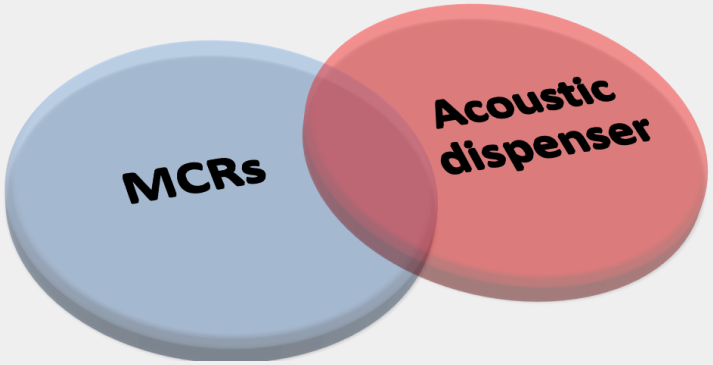
Diversity analysis is created using the full FP2 (Daylight) path-descriptor-based fingerprint

✓ Comparison with ZINC library: Diversity analysis shows **very low overlap** with and not just a subset of ZINC

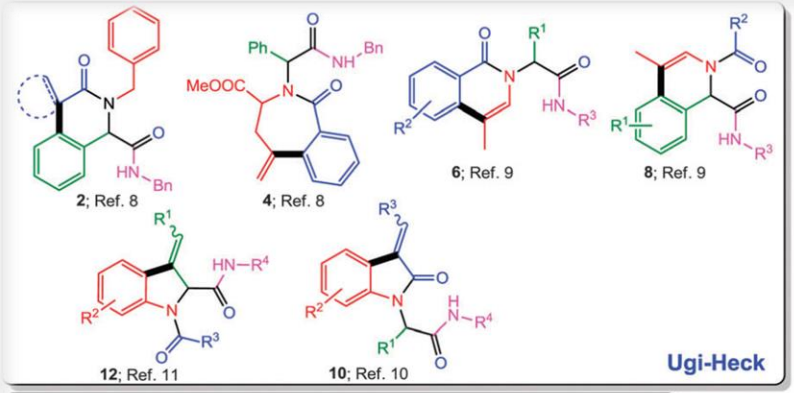
MCRs *(space, diversity, complexity, shape)*

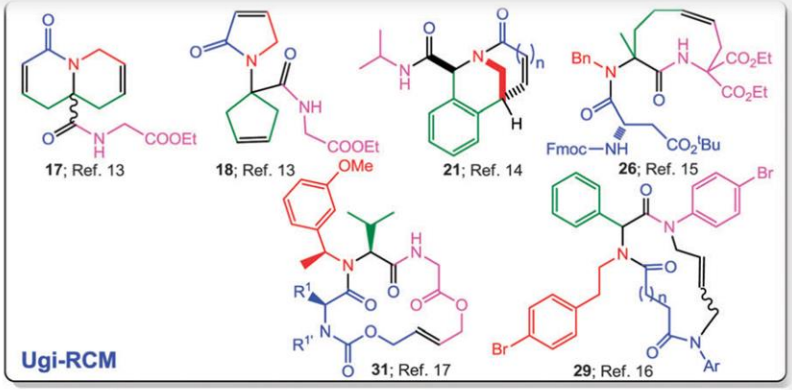
TelesisPharma

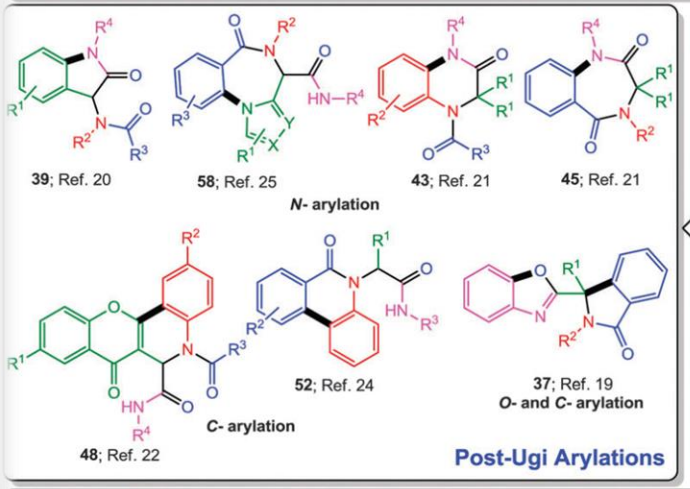
- Currently **>525 scaffolds** based on various MCRs (~500 million cpds)
  - MCR starting materials **easily accessible**
  - Hits based around MCR scaffold = **faster SAR**
  - Resynthesis of hits in an easy, fast manner (immediately)
  - Reactions based on MCR, ***and*** classical organic reactions (**≤4 steps**)
- **Easily modified** compounds = **greater control** over physiochemical properties
- Scaffolds are more **3D like** than traditional libraries

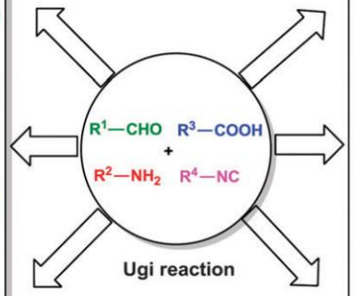


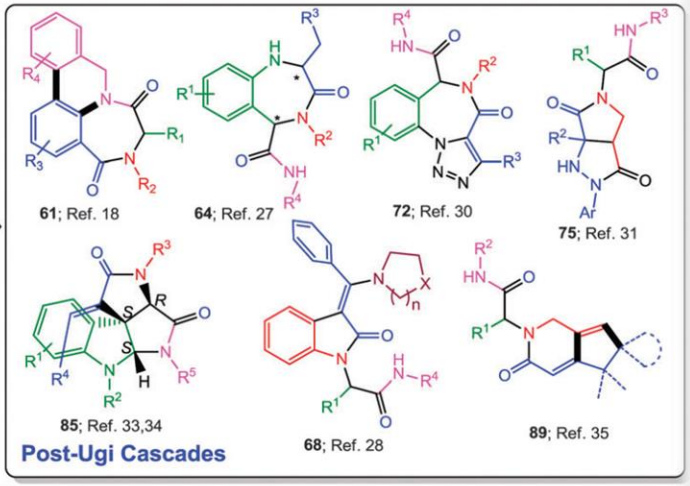
MCRs-*complexity/couplings*

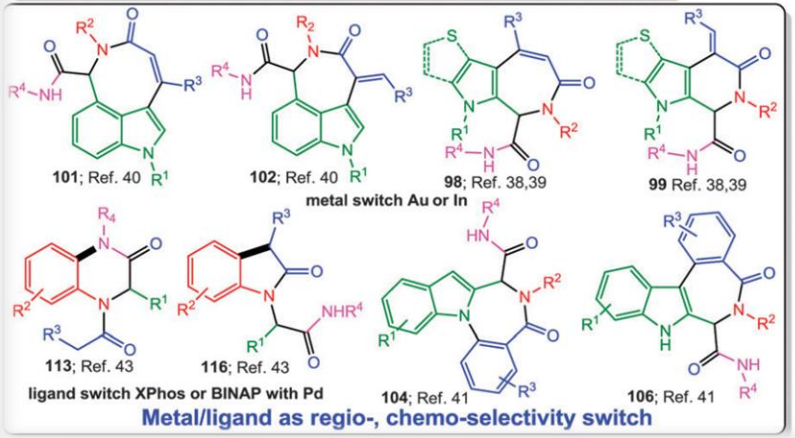


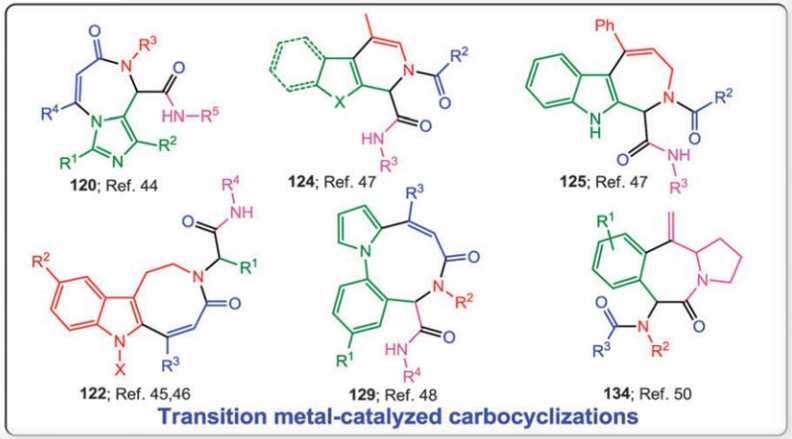








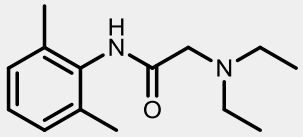




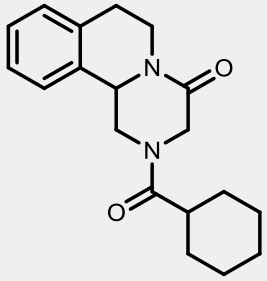
How relevant are MCR scaffolds to “real drugs”?

MCRs and drugs

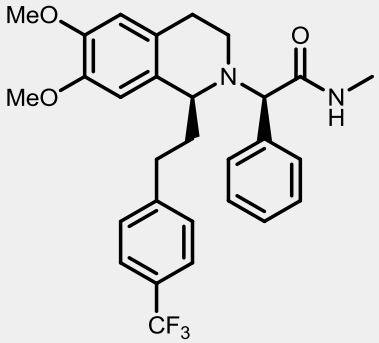
Marketed or late-stage clinical trial



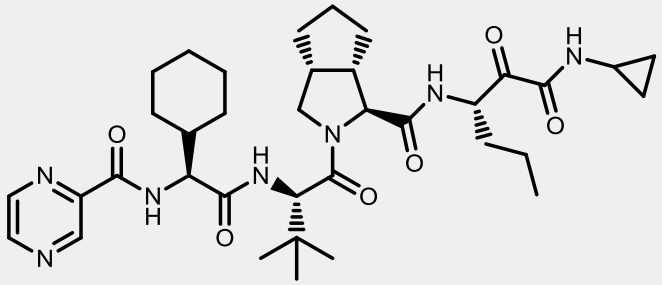
Lidocaine



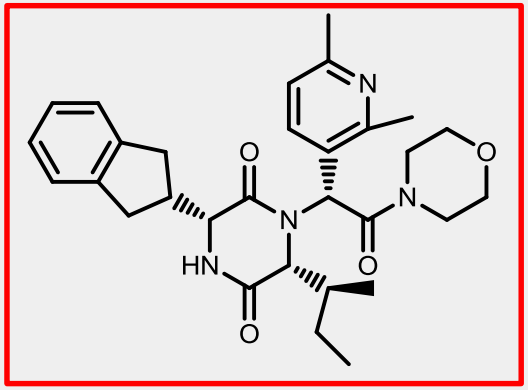
Praziquantel
Biltricide®



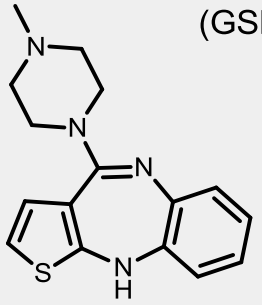
Almorexant
(GSK, Actelion)



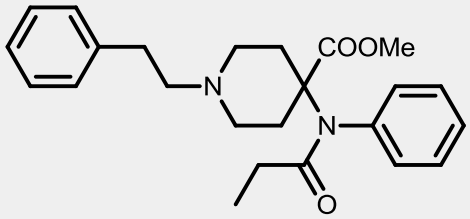
Telaprevir
Incivek® (Vertex/J&J)



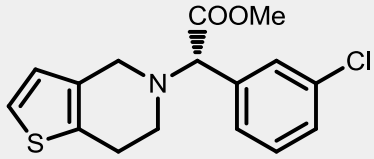
Epelsiban
(GSK)



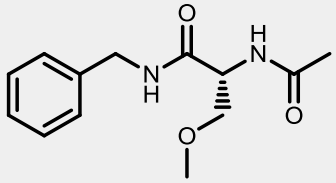
Olanzepine
Zyprexa®



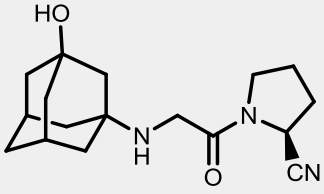
Carfentanil



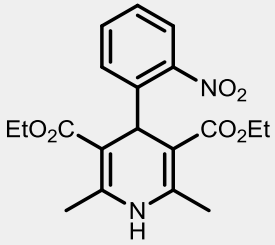
Clopidogrel
Plavix®



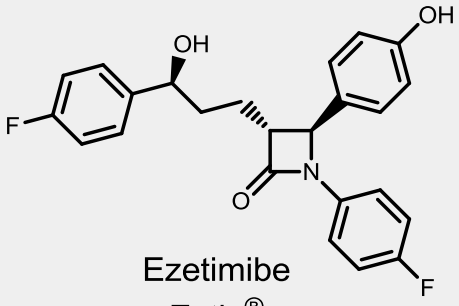
Lacosamide
Vimpat® (UCB)



Vildagliptin
Galvus®, Zomelis®

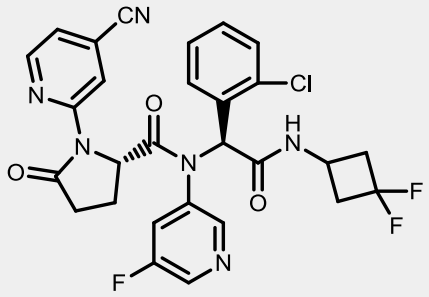


Nifedipin
Adalat®

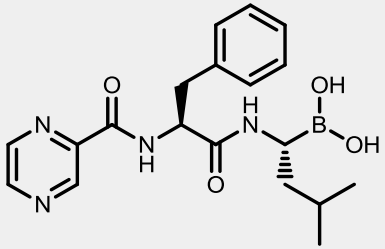


Ezetimibe
Zetia®

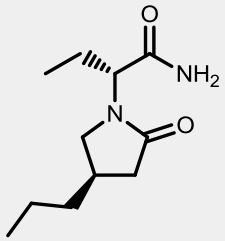
Marketed or late-stage clinical trial



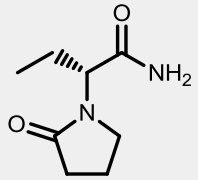
Ivosidenib
(Agios)



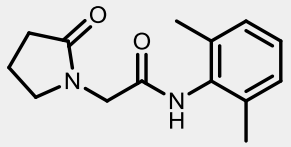
Bortezomib
Velcade®



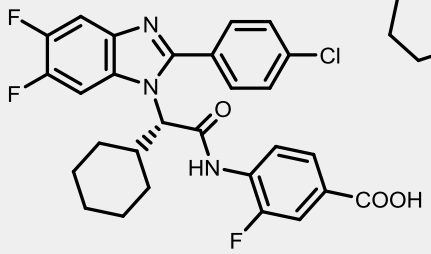
Brivaracetam
Briviact® (UCB)



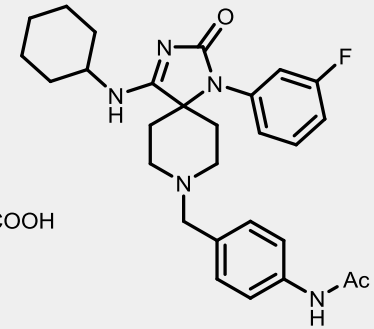
Levetiracetam
Keppra® (UCB)



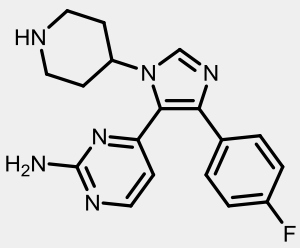
Nefiracetam



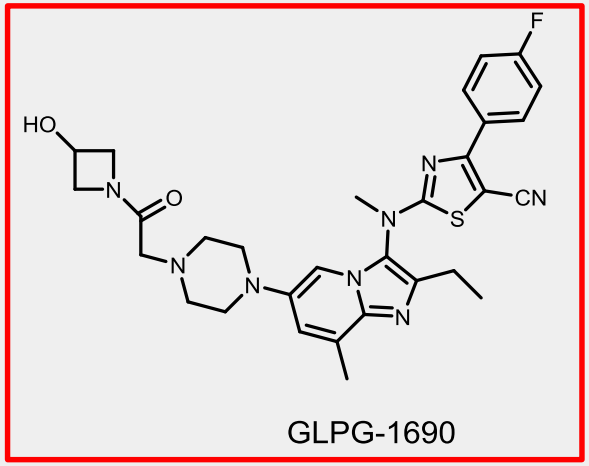
FXR
(Roche, Phase I)



BACE



p38
(GSK, Phase III)



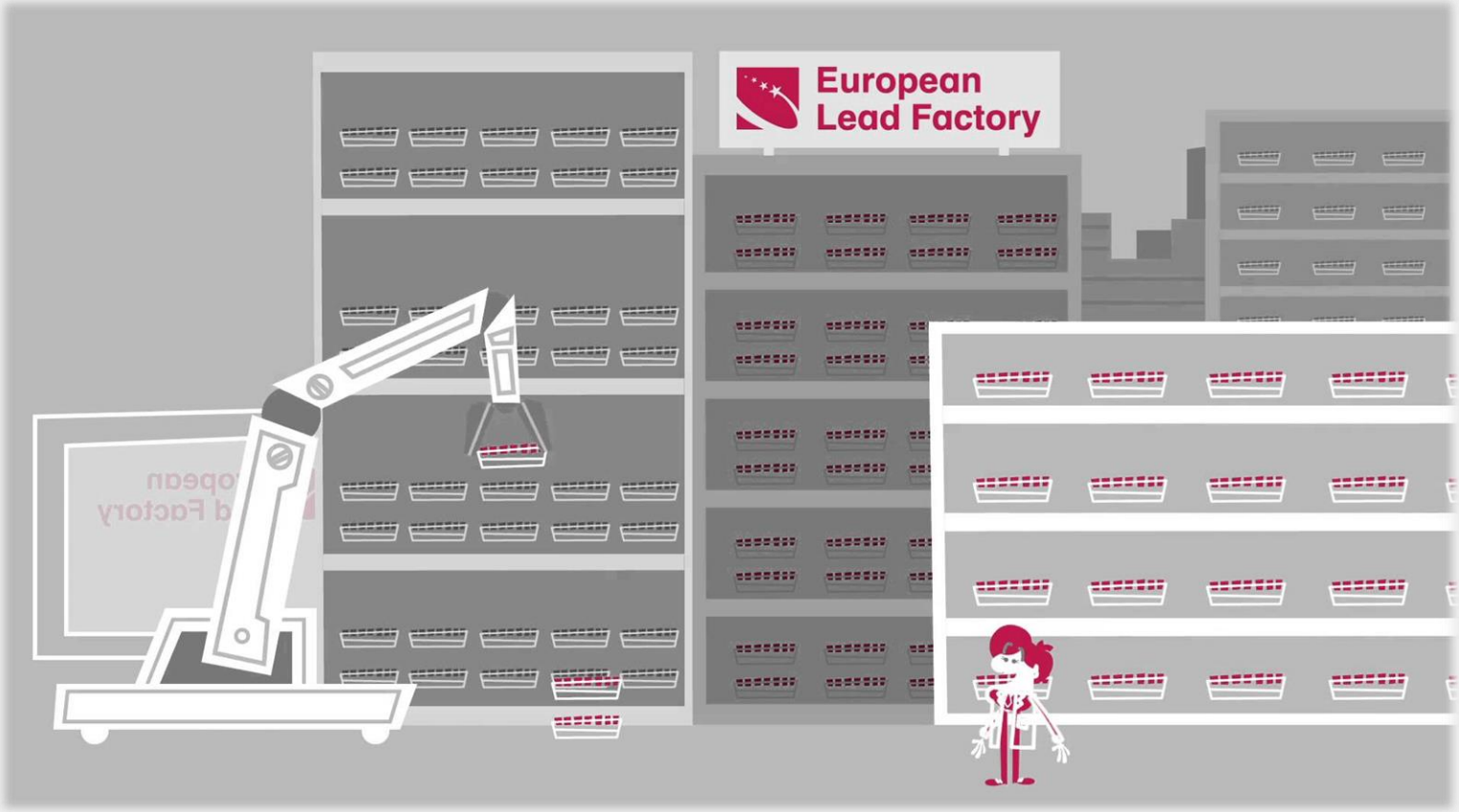
GLPG-1690

- **MCR chemistry for production**
- **Hit validation time** (“hit to lead transition”) often dramatically **shortened**
- 7-8 steps in average for an API
- **10% of drugs can be produced by MCR**

European Lead Factory

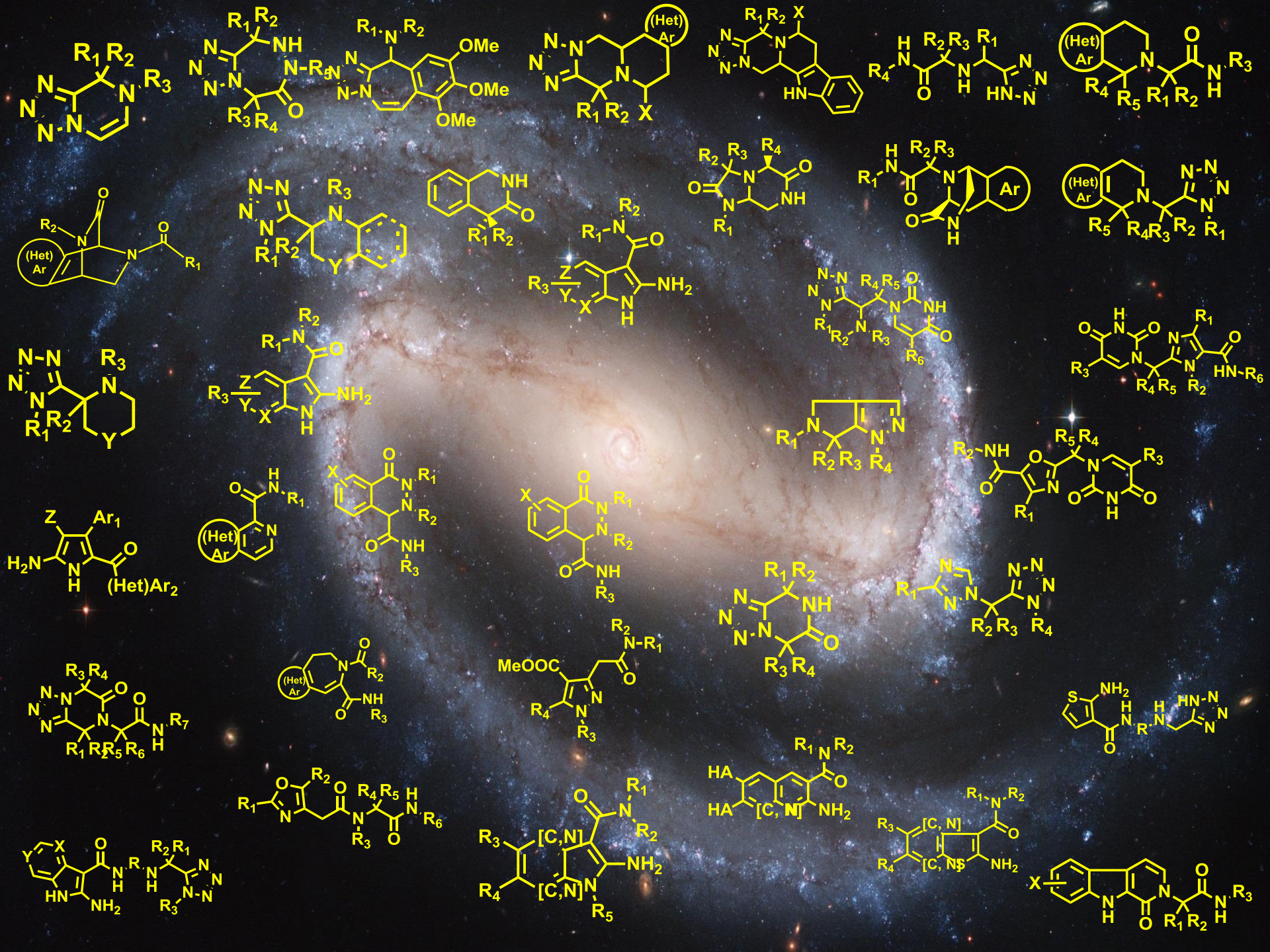
Innovative Medicines Initiative

rijksuniversiteit groningen



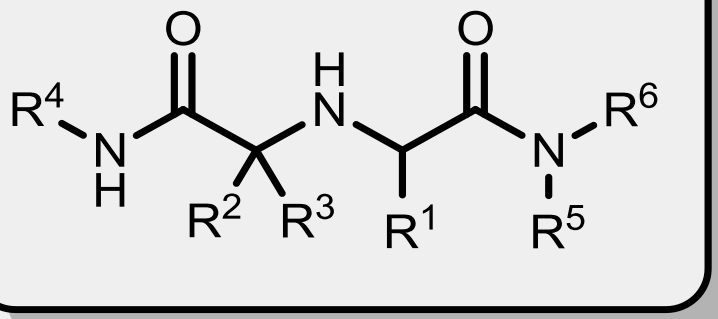
- ✓ Public-private partnership that aims to accelerate early drug discovery in Europe
- ✓ Major contribution with drug-like MCR-based libraries

MCRs-scaffolds

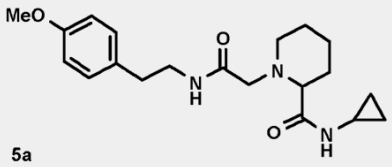


MCRs-*scaffolds*

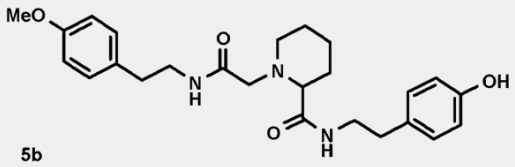
Peptidomimetics



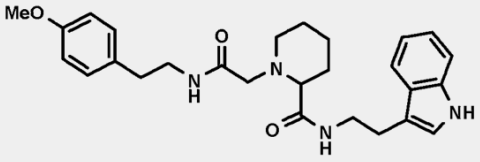
- Versatile and broad scope reaction
- Stereoselective



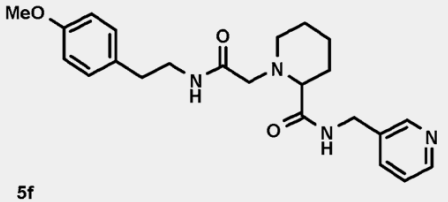
5a



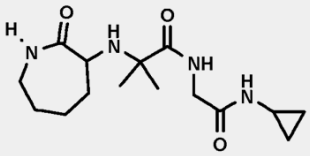
5b



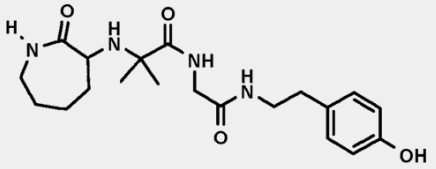
5e



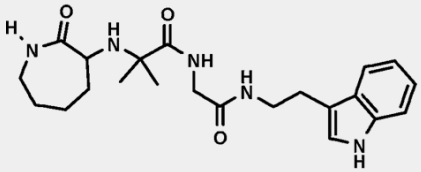
5f



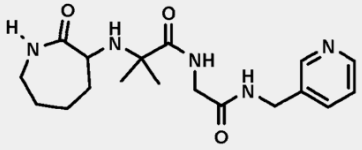
5i



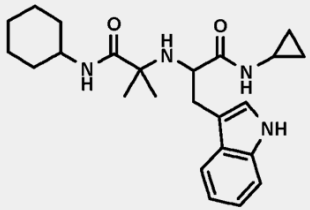
5j



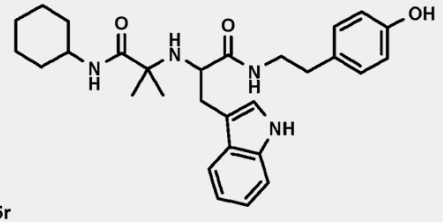
5m



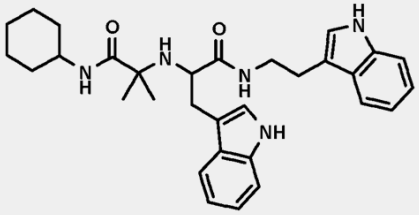
5n



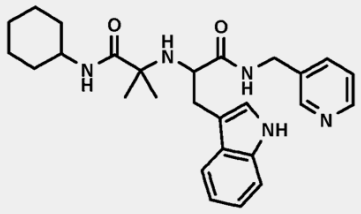
5q



5r



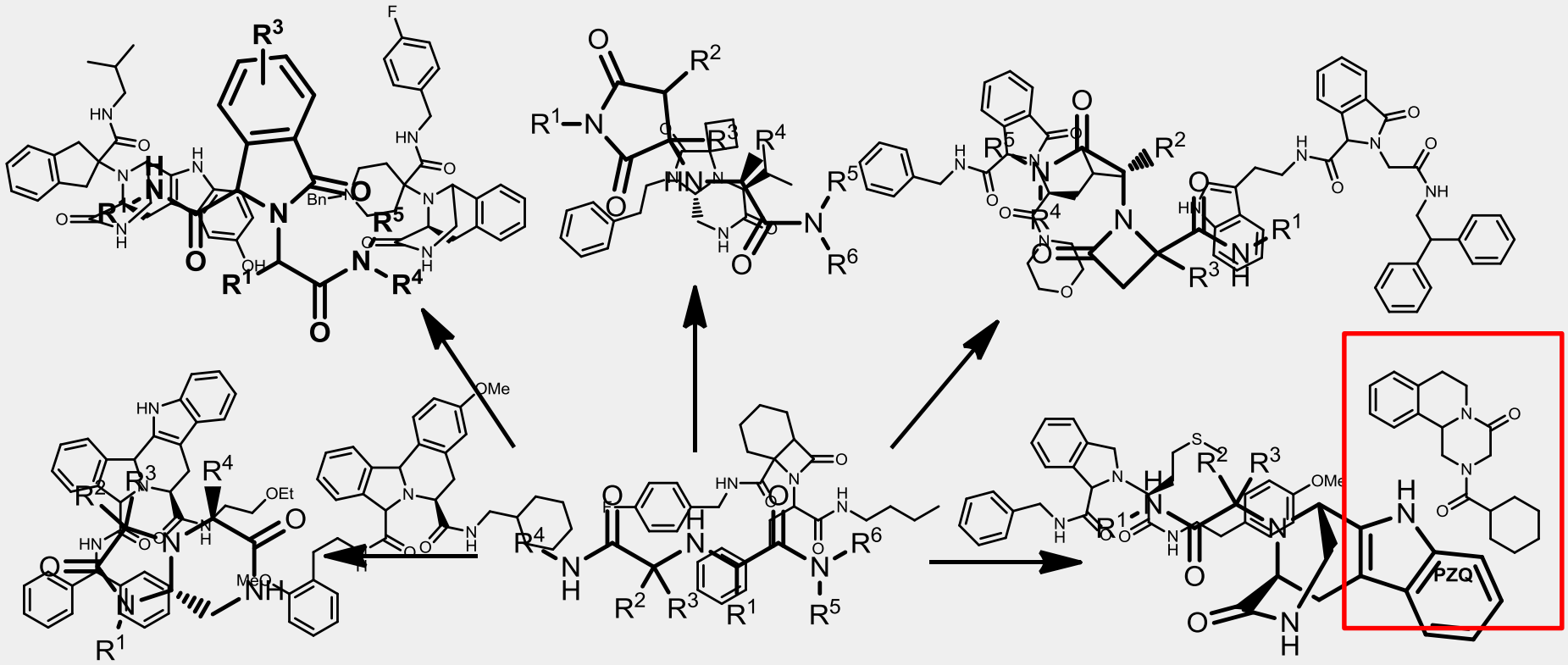
5u



5v

Dömling *et al., Angew.Chem.* **2012,** *124,* 10426

Polycyclic scaffolds

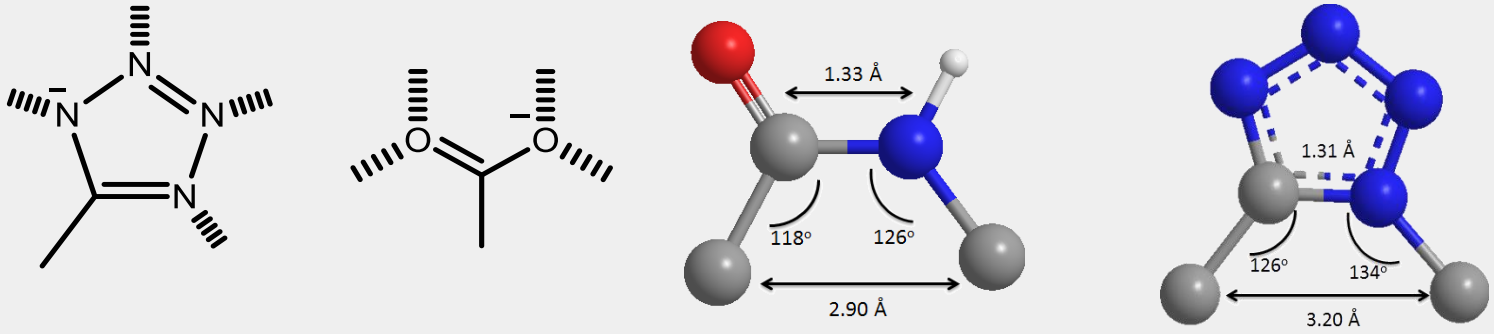


- Easy access to complex and diverse polycyclic compounds
- Defined 3D conformations
- Drug-like compounds
- Low number of rotatable bonds

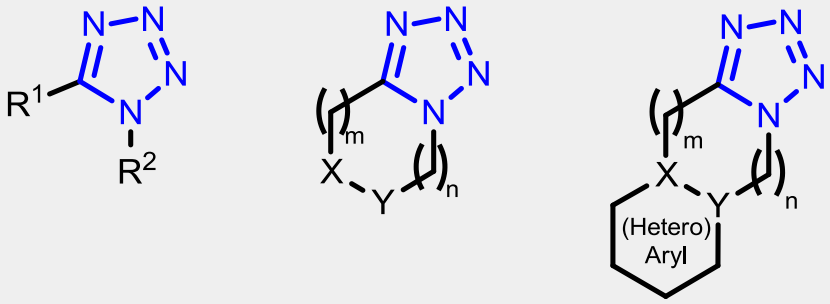
Tetrazole-based compounds

- **43** drugs that contain 1*H*- or 2*H*-tetrazole substituents, **23** of them FDA approved
- Carboxylic acid/ *cis*-amide bonds in peptidomimetics bioisosters

Drug Bank



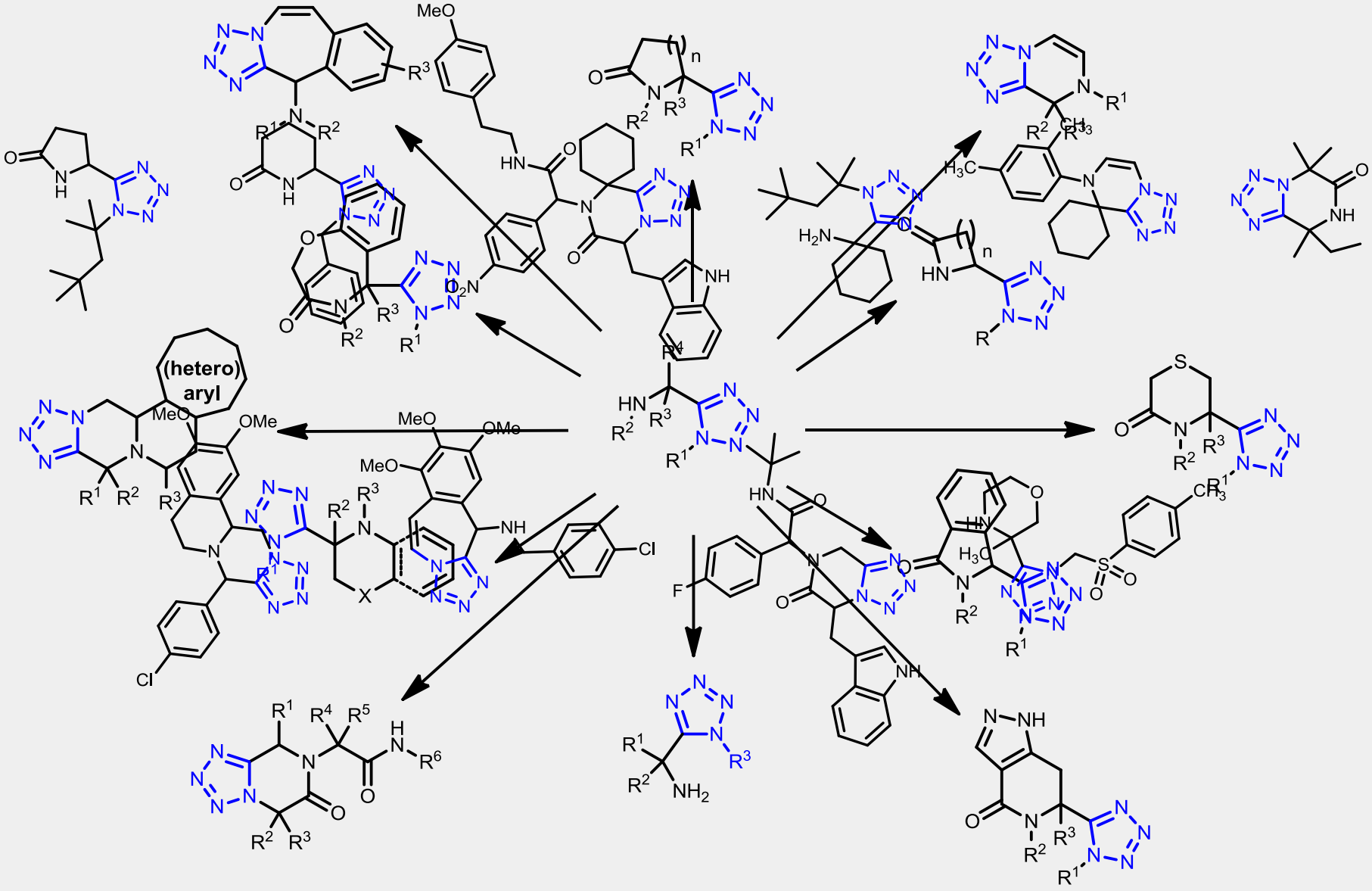
- Enhanced metabolic stability ⟶ prolonged half-life
- Increased lipophilicity ⟶ better membrane penetration

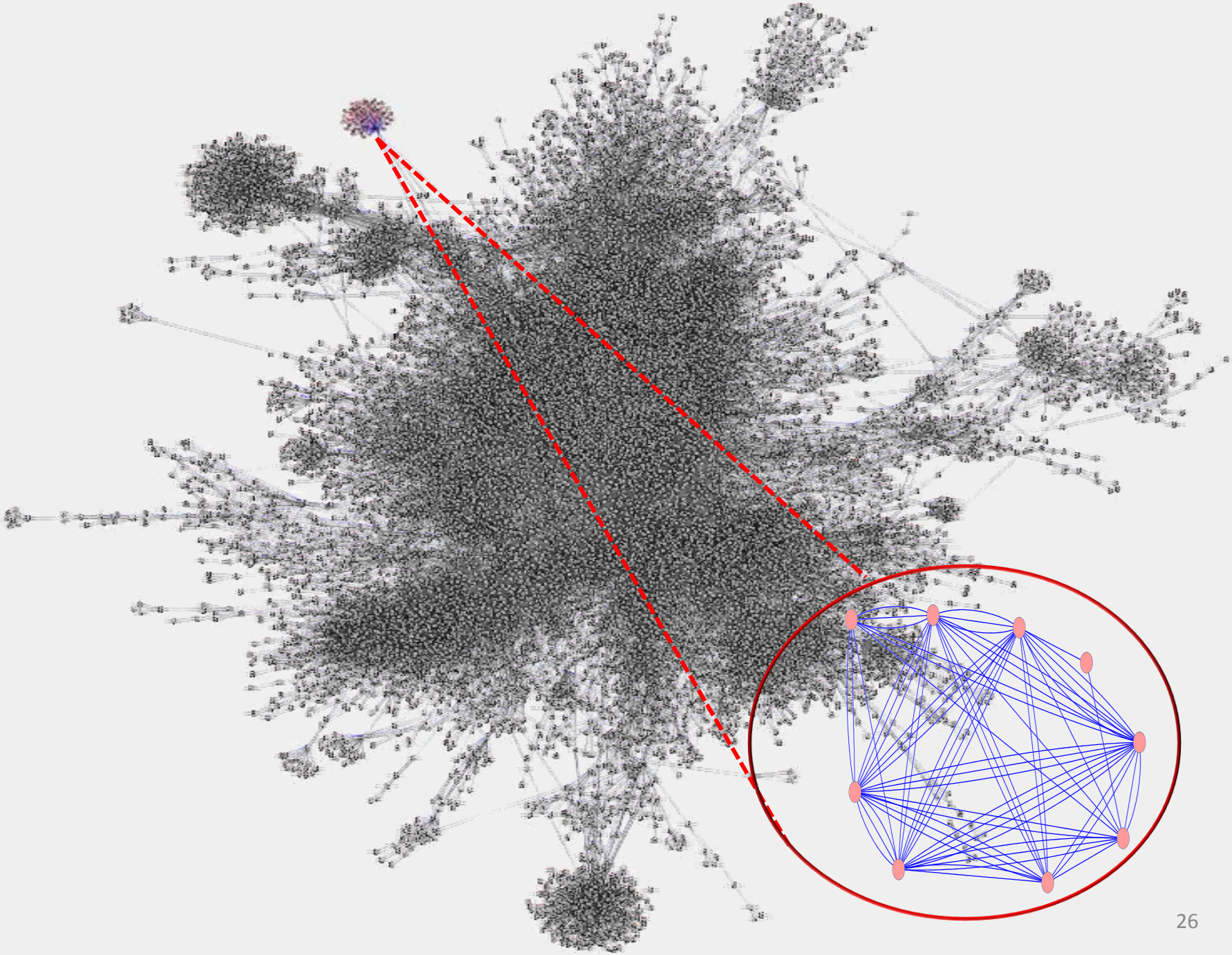


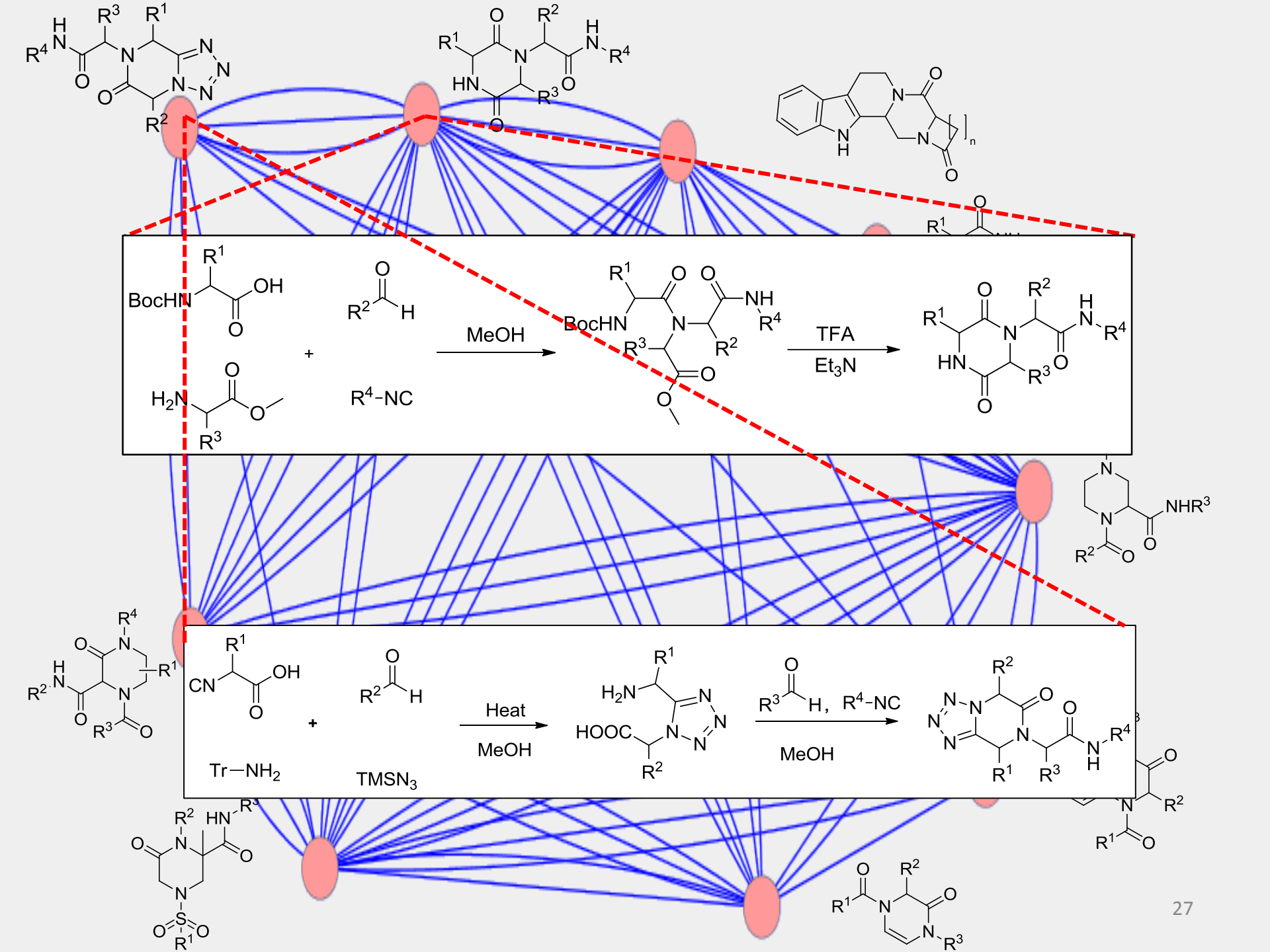
monocyclic *bicyclic* *tricyclic or polycyclic*

Tetrazole-based compounds

MCR tetrazole platform






BocHN
OH
MeOH
TFA
Et3N
R4-NC
CN
Heat
MeOH
Tr—NH2
TMSN3
HOOC
H2N
NHR3

Druggable space beyond the Ro5

Covalent inhibitors

- Reassessment of covalent inhibitors
- Design and synthesis of covalent binders based on unique and yet unexplored scaffolds equipped with a variety of electrophilic warheads, to target electrophiles in (mutant) proteins

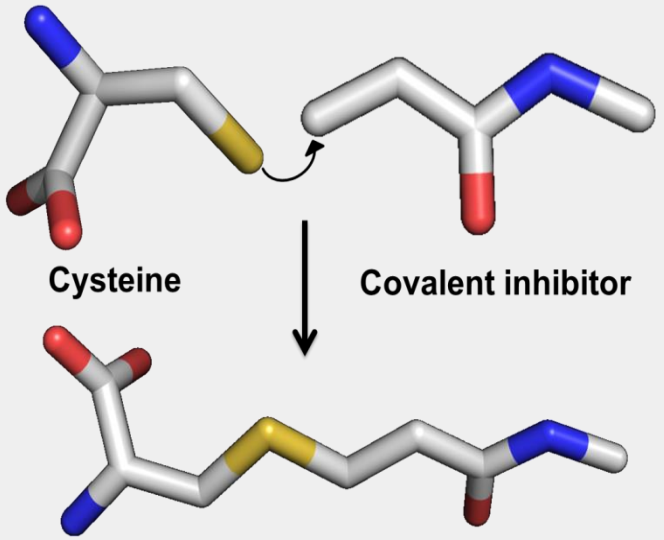
Covalent inhibitors
(unique and novel scaffolds)

↓

Variety of electrophilic warheads

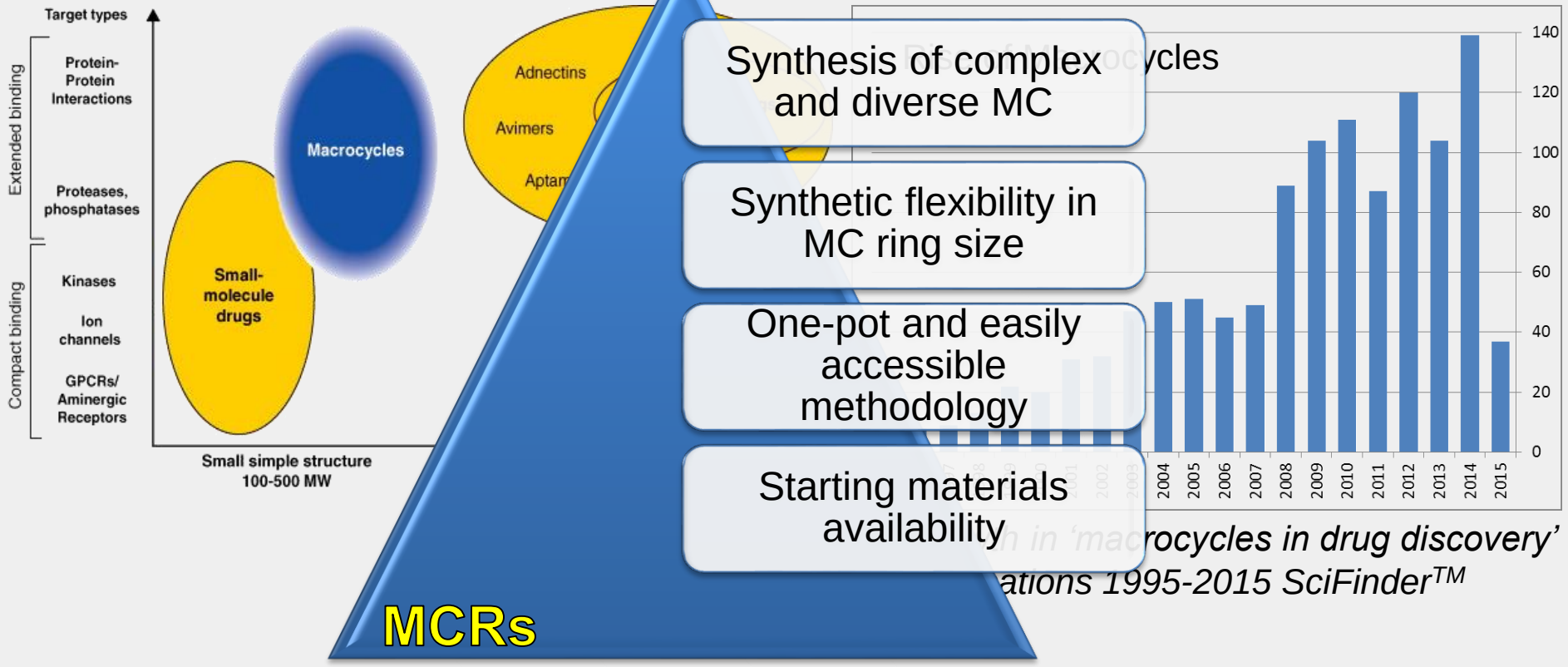
↓

target mutant proteins
(KRAS (G12/13C), p53 (Y220C), IDH1 (R132C) or DNMT3a (R882C)



Macrocycles (MCs)

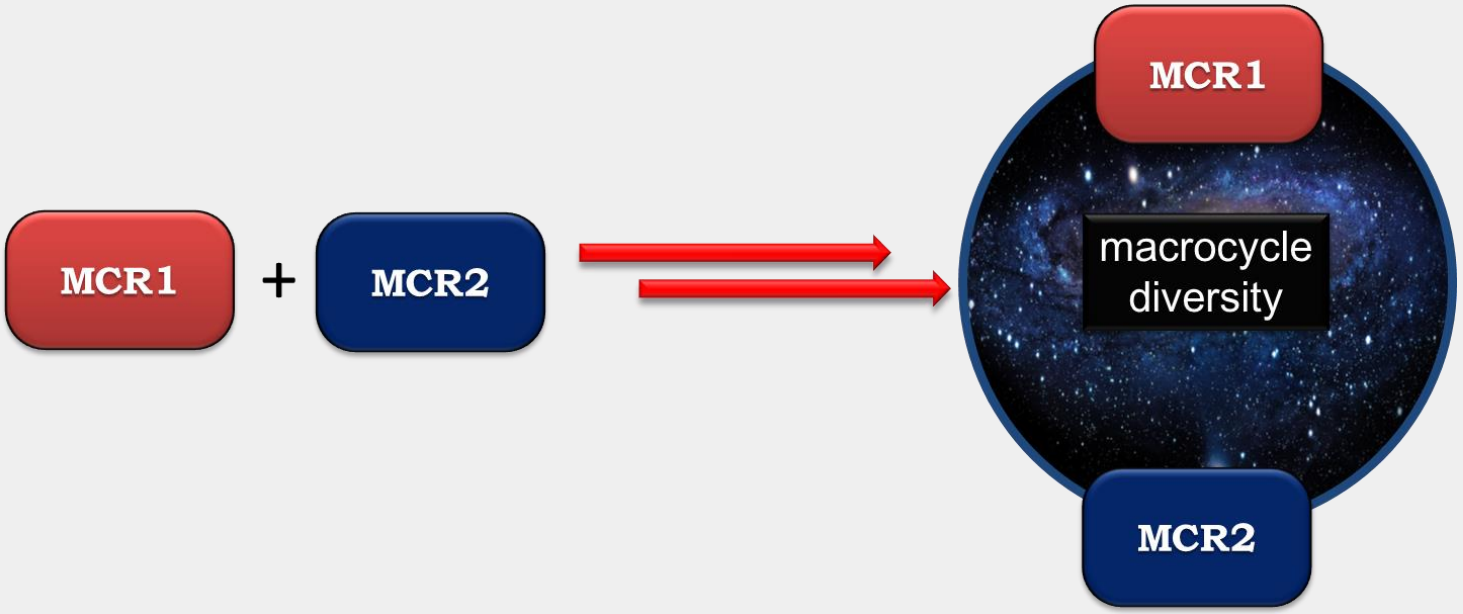
- Improved binding ⟶ Higher surface area for flat protein surfaces & ΔS advantage
- Improved transport properties ⟶ Chameleon behavior in lipophilic as well as hydrophilic media



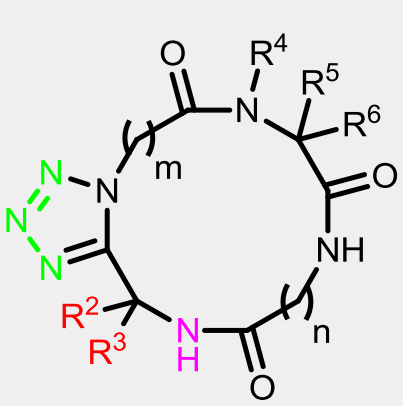
rocycles in drug discovery'
ations 1995-2015 SciFinder™

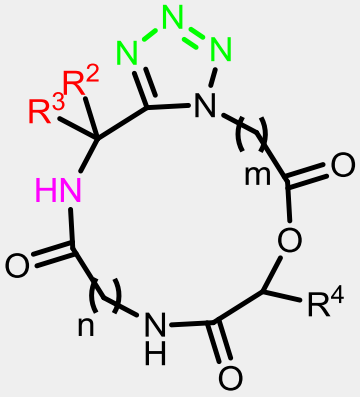
Artificial macrocycles by MCRs

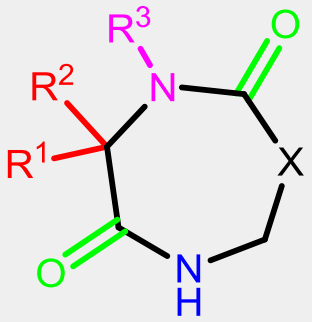
➢ Strategy I



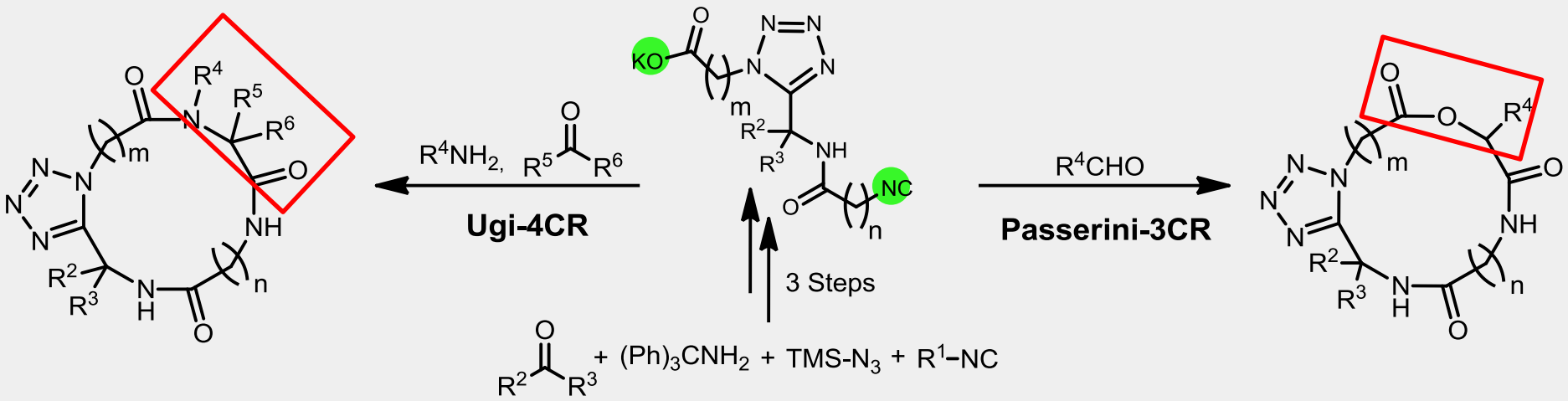
e.g.

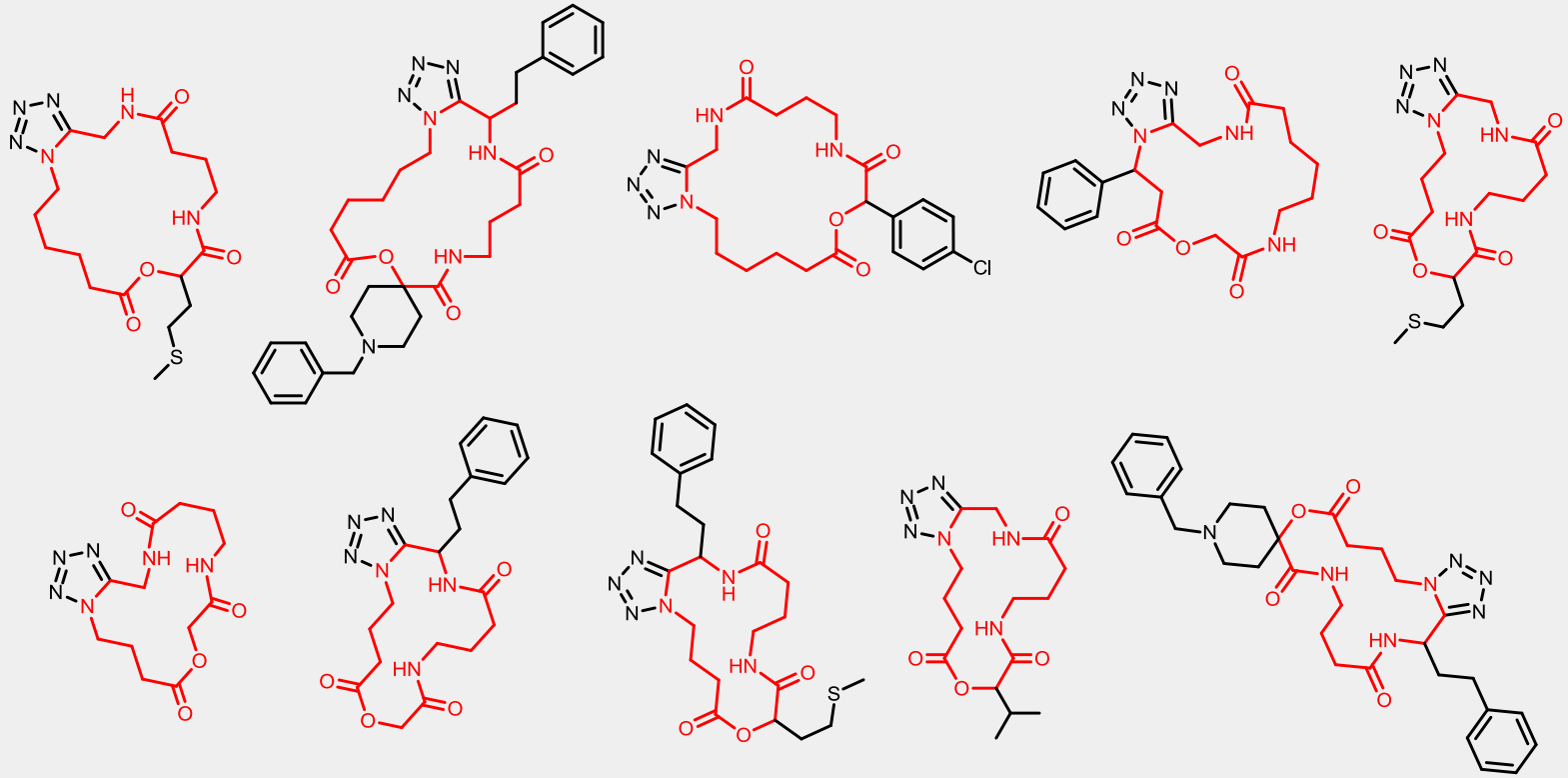




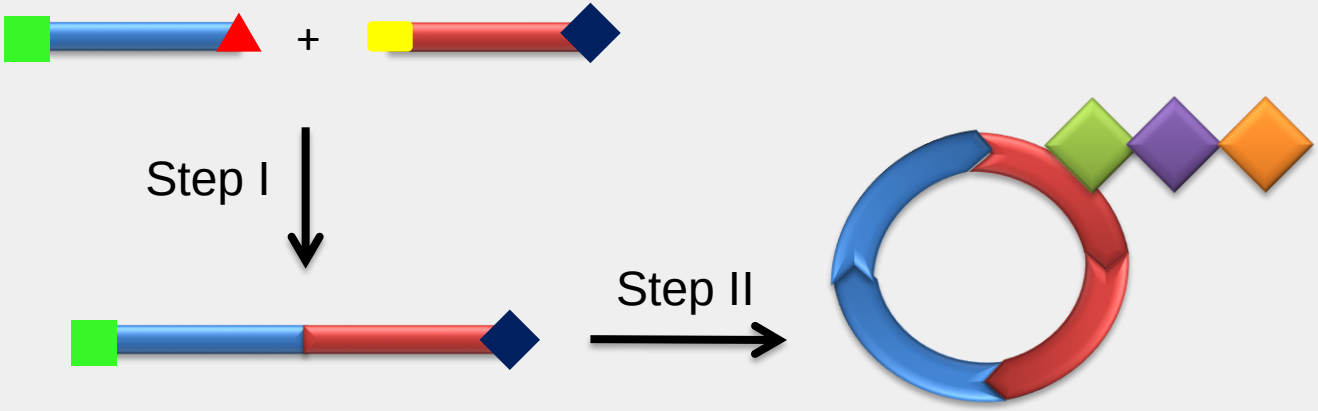


Dömling *et al*, *Org.* Lett. **2015**, *17*, 4980


R4NH2, R5 R6
Ugi-4CR
3 Steps
R4CHO
Passerini-3CR
+ (Ph)3CNH2 + TMS-N3 + R1–NC

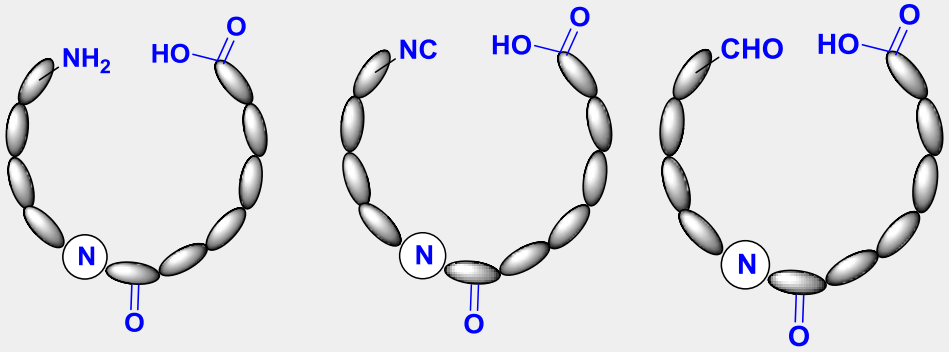


➢ Strategy II



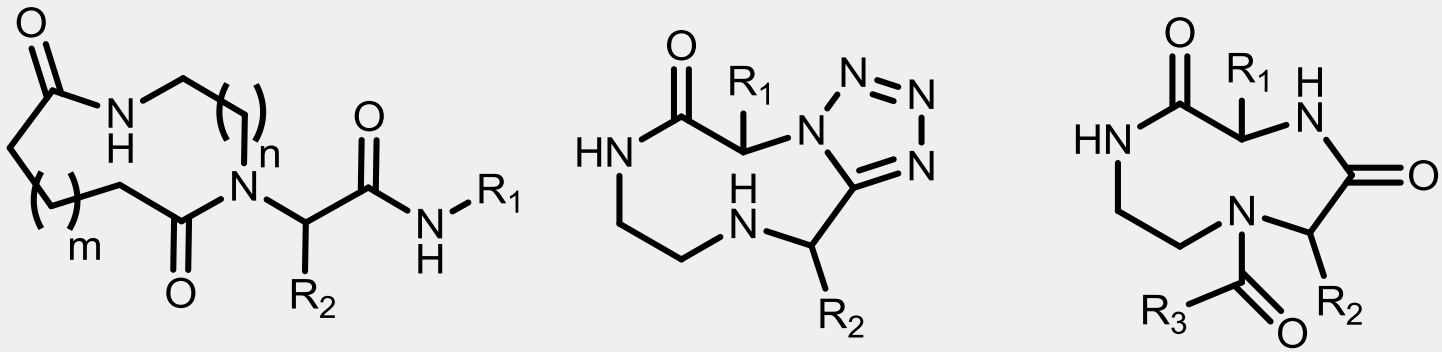
Linear diversification

Exponential diversification

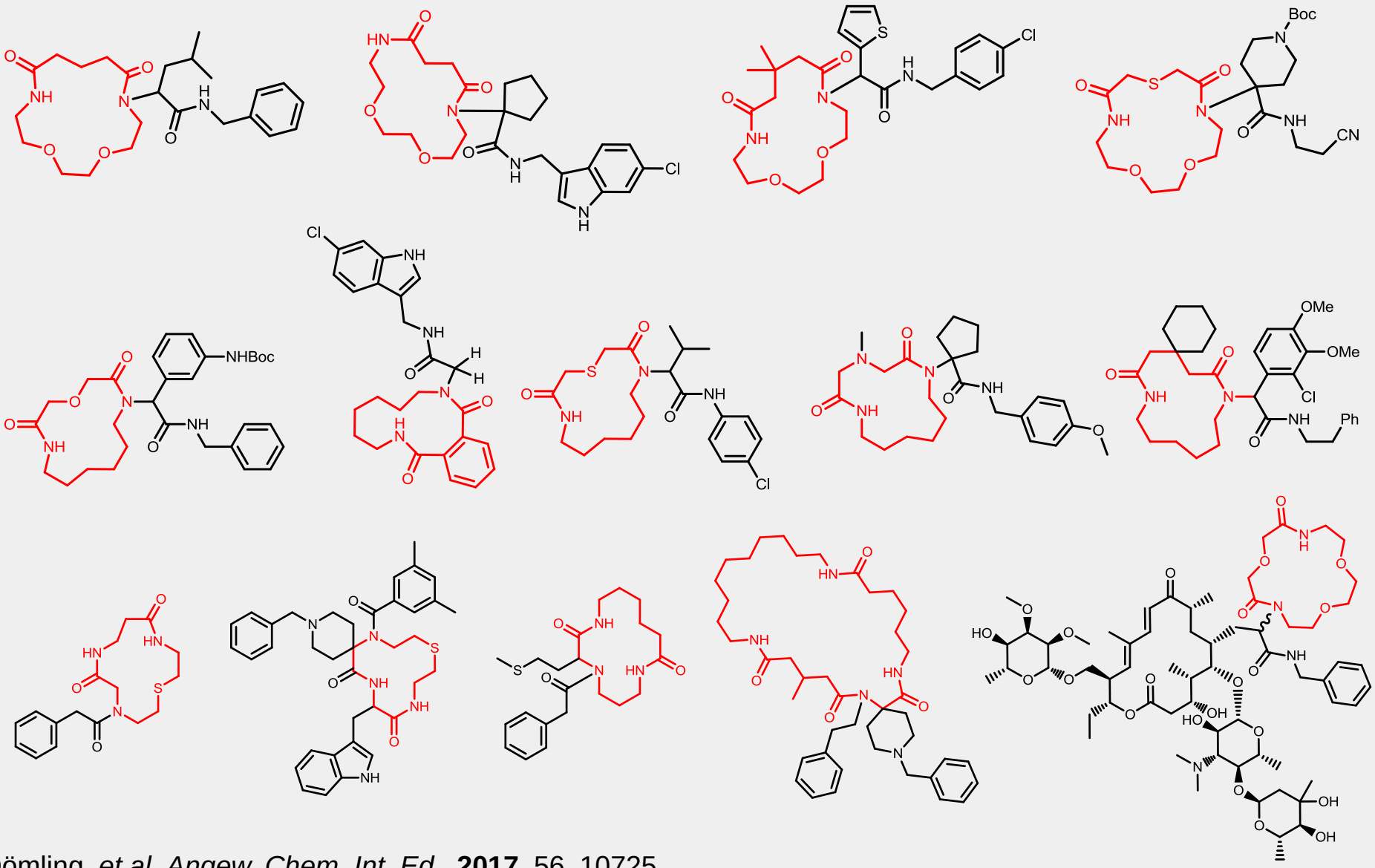


- Solubilizing (transporter) elements
- Stiffening elements (flexibility)

e.g.



✓ More than 200 different macrocycles



Dömling *et al*, *Angew. Chem. Int. Ed.*, **2017**, 56, 10725
Dömling *et al*, *J. Org. Chem.* **2016**, *81*, 8789
Dömling *et al*, *Org.* Lett. **2017**, *19*, 6176

- MCRs *(building blocks)*

Simple: combine, filter, wash

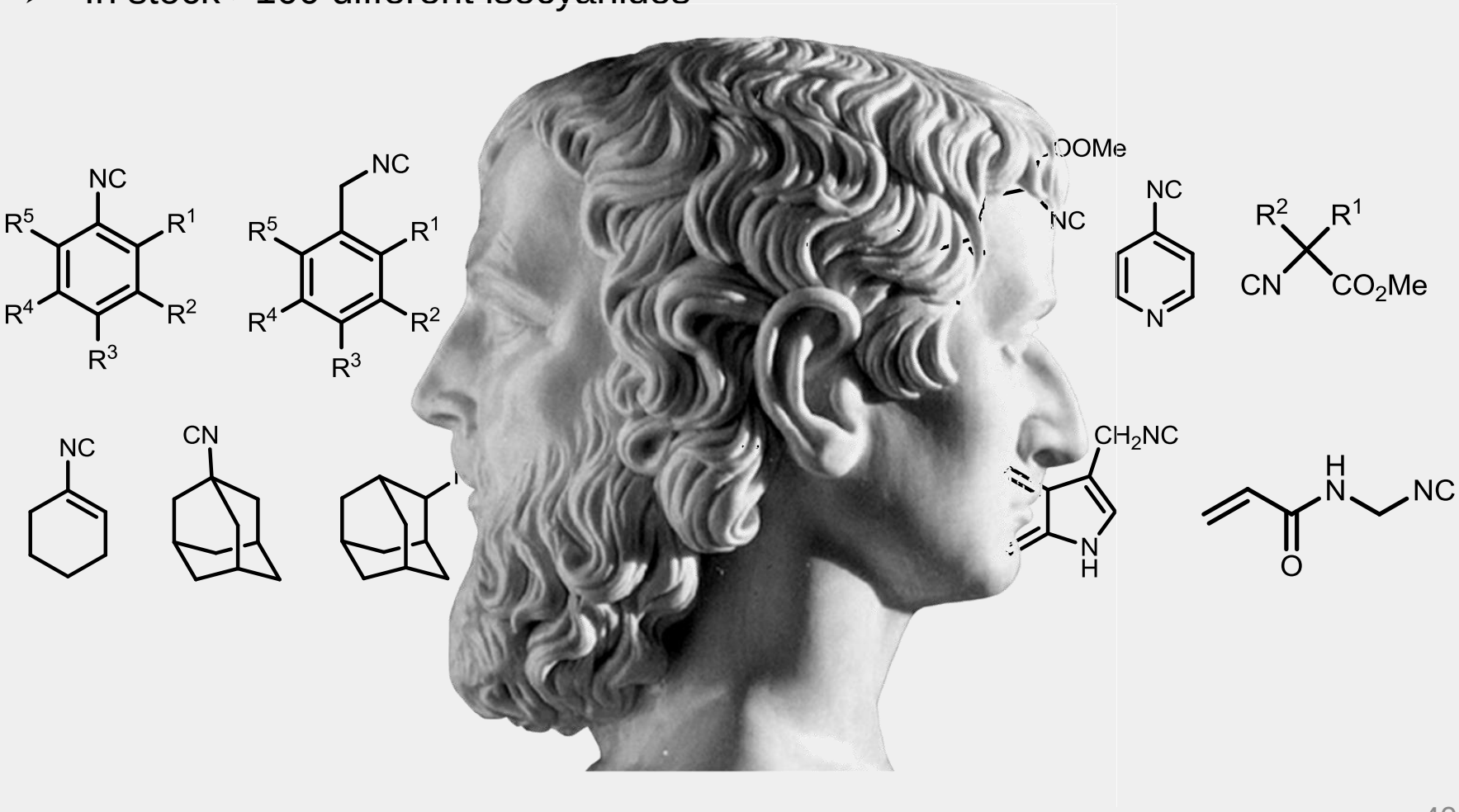
Cheap & abundant starting materials

Rich Chemistry

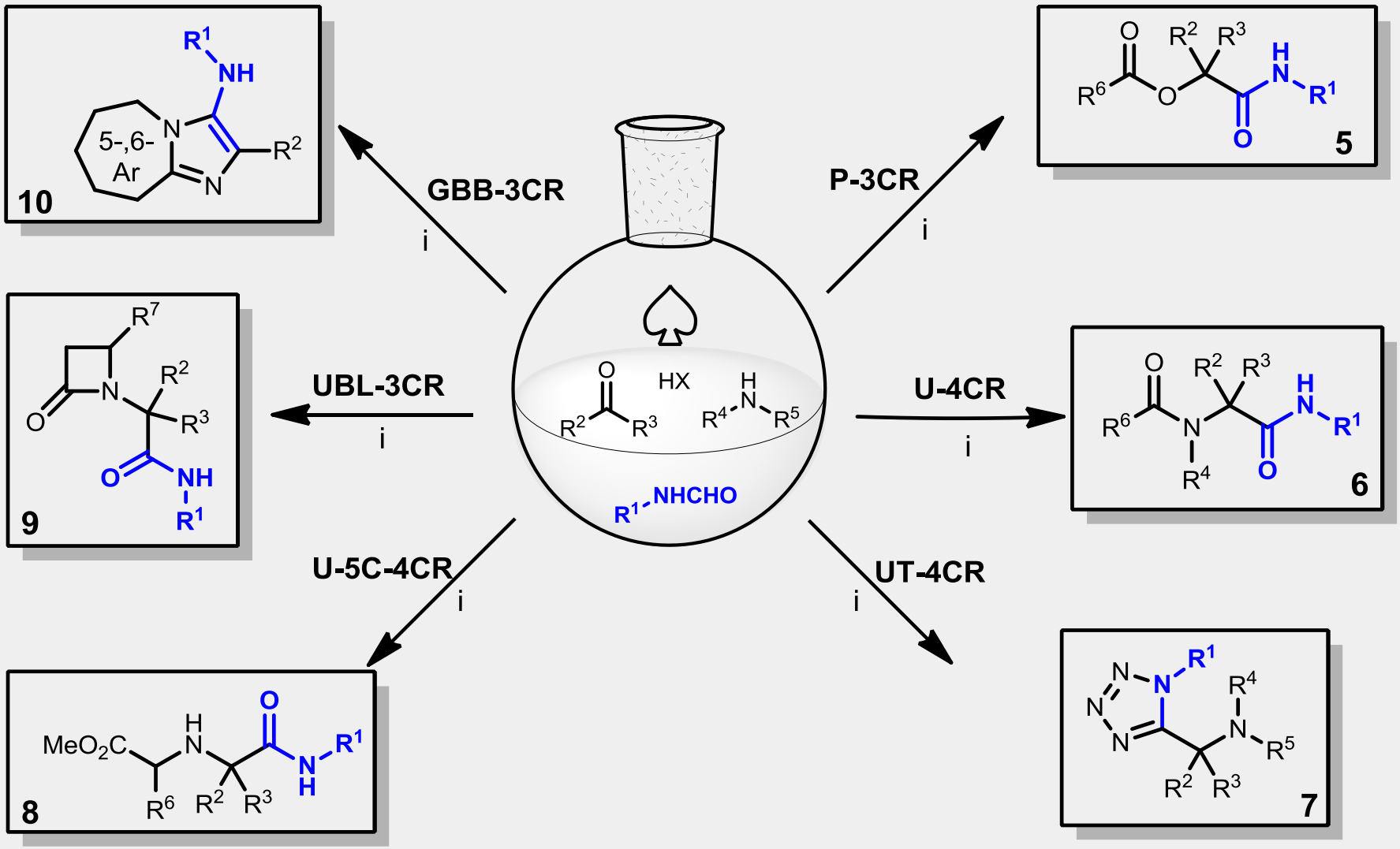
Scalable to multi gram

Isocyanides

- Worldwide experts in isocyanide chemistry
- Access from primary amines or carbonyl compounds
- In stock >100 different isocyanides



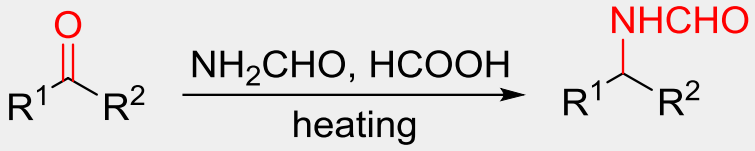
Efficient Isocyanide -less Isocyanide- based MCR



(i): **1**. Triphosgene/Et_3N in DCM at 0 °C
2. Amine/aldehyde/acid component in MeOH at rt for 24-48 h

C. Neochoritis, S. Stotani, B. Mishra, A. Dömling, *Org. Lett.* **2015**, *17*, 2002

- Access to isocyanides from carbonyls

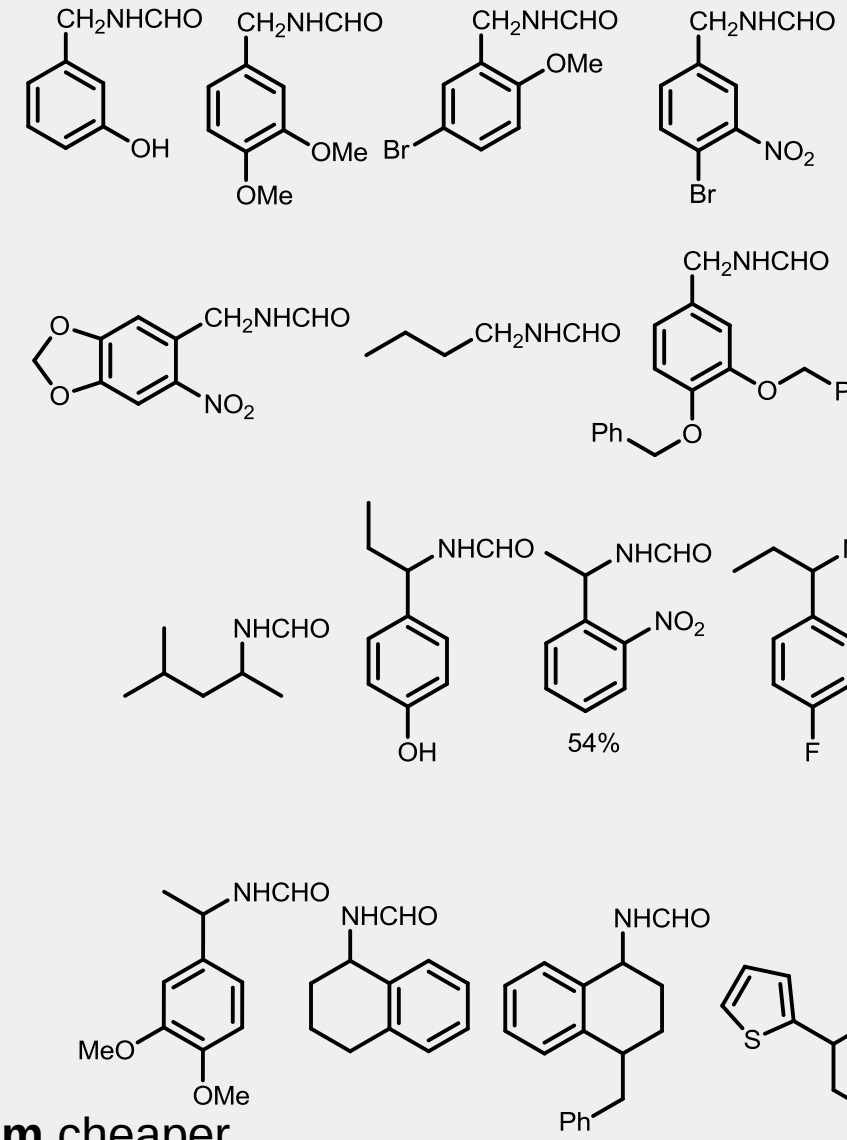


1 {1-40}

2 {1-15}

3 {1-40}

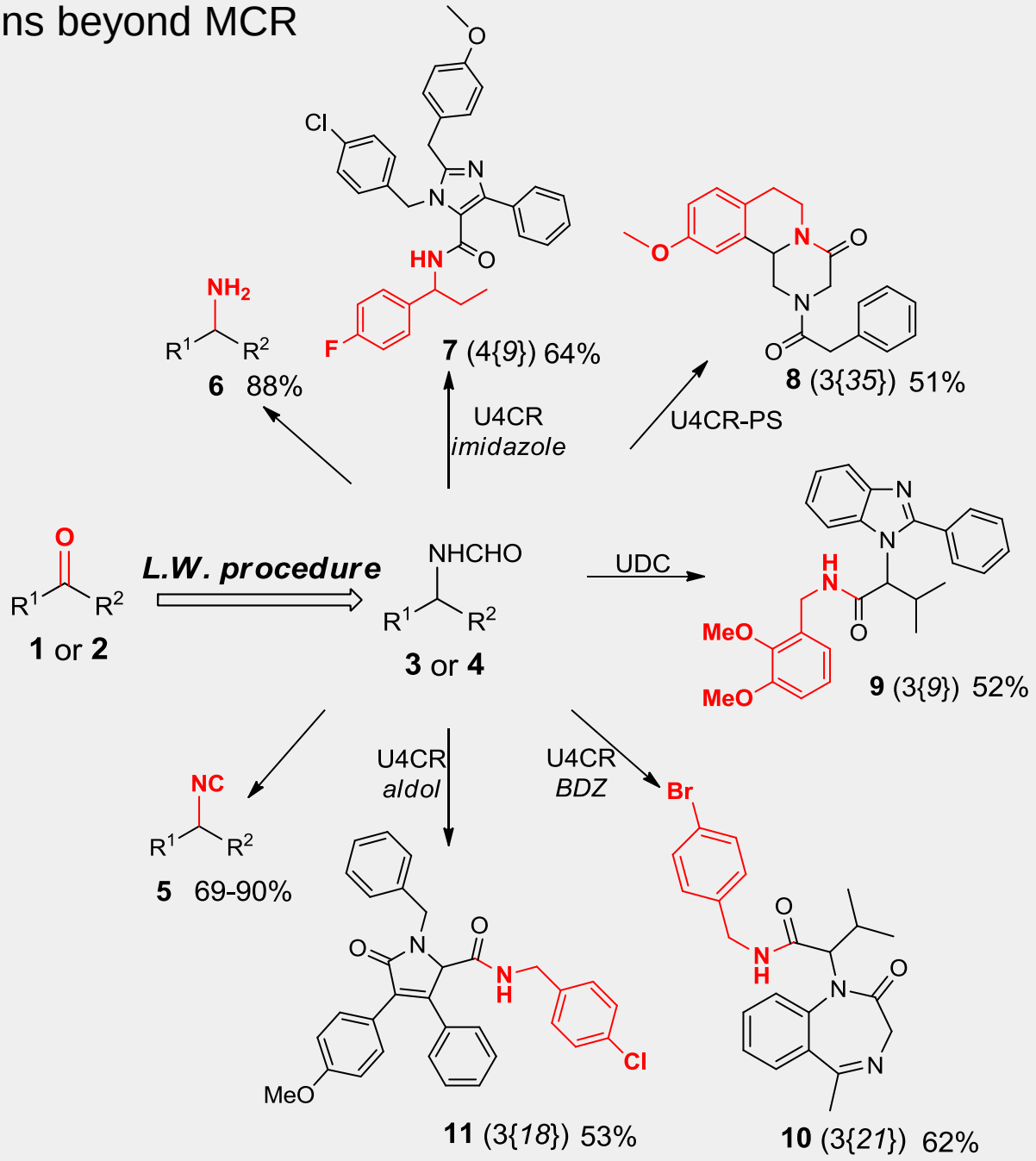
4 {1-15}



- ✓ Oxo compounds are on average **$75/gram** cheaper
- ✓ Scaling up improves yields
- ✓ Ketones create stereogenic center

C. Neochoritis *et al*., *ACS Comb.Sci*. **2015**, *17*, 493-499

➢ Post-modifications beyond MCR

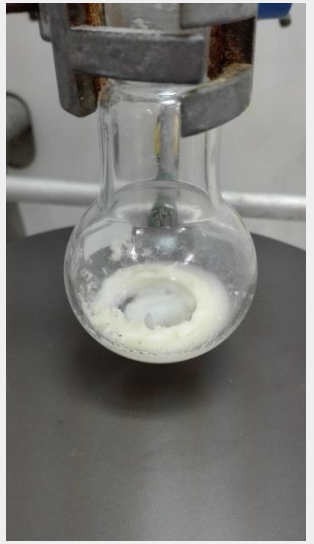


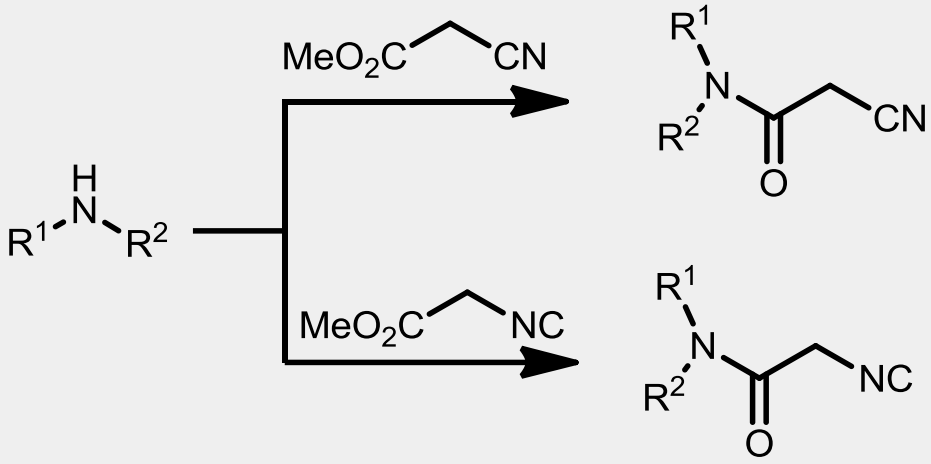
C. Neochoritis *et al*., *ACS Comb.Sci*. **2015**, *17*, 493-499

43

Cyanoacetamides/Isocyanoacetamides

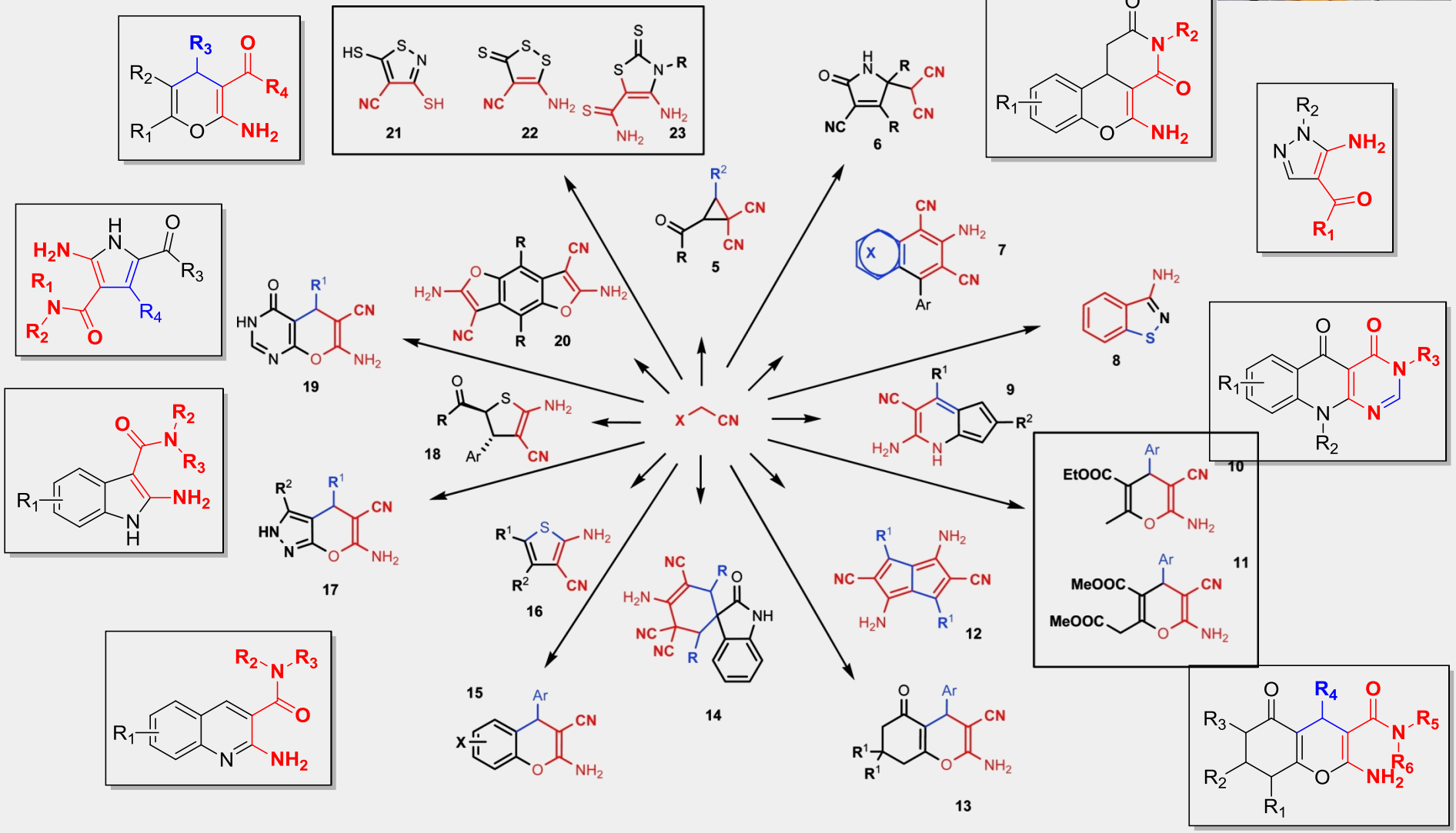
- Replacement of cyanoacetic acids
- Cheap, easy and scalable synthesis
- Access to different substituted heterocycles





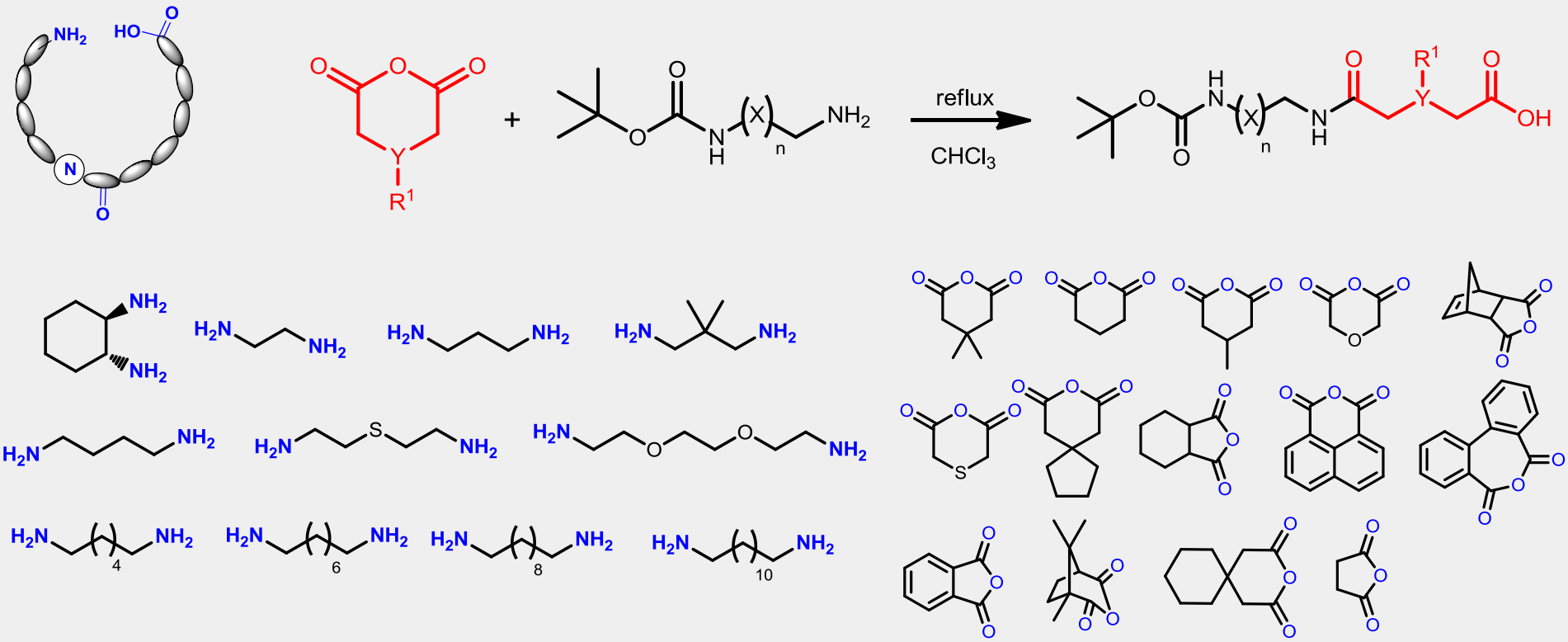
Dömling *et al*, *J. Comb. Chem.* **2009,** *11,* 920
A. Dömling; B. Beck; T. Fuchs; A. Yazbak; *J. Comb. Chem.* **2006,** 8, 872

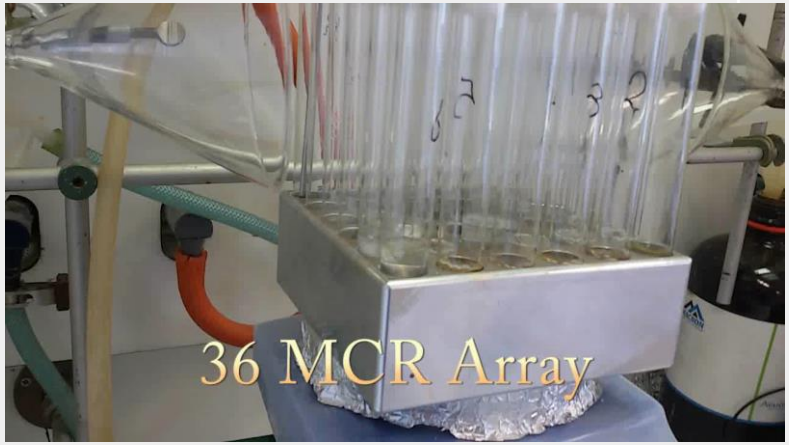
Scaffold Diversity of cyanoacetamides

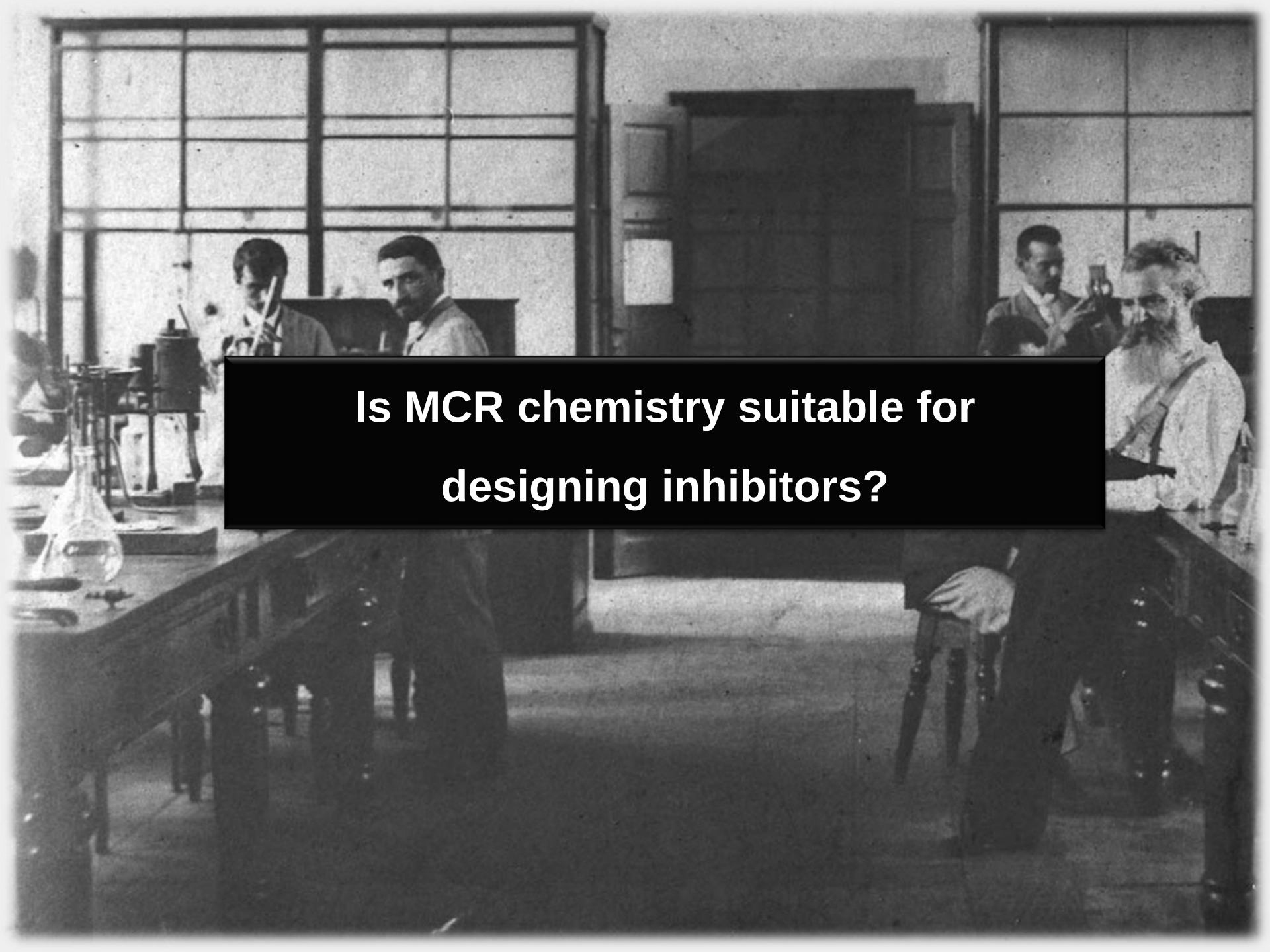


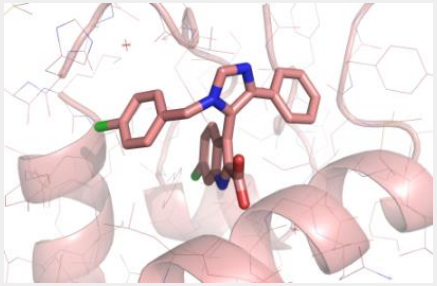
Dömling *et al*, *J. Comb. Chem.* **2009,** *11,* 920

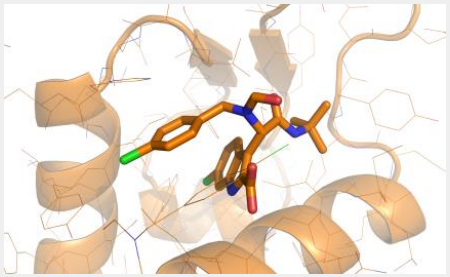
α-Amino-ω-carboxylic acids

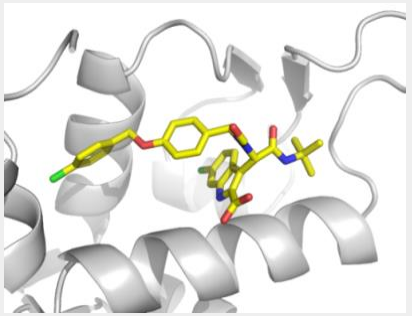


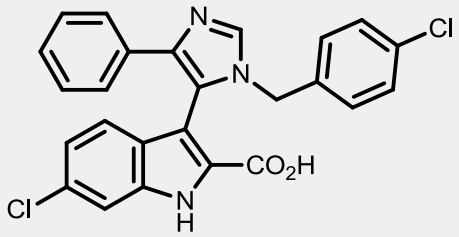



Is MCR chemistry suitable for
designing inhibitors?

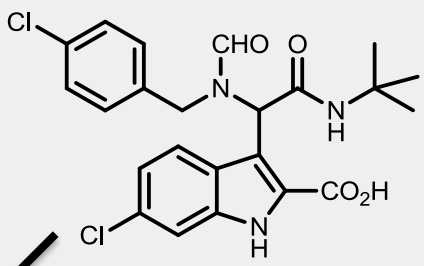


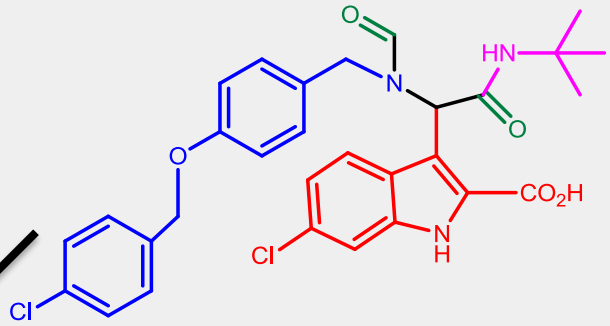




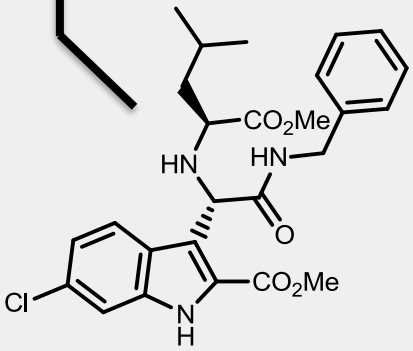


WK1

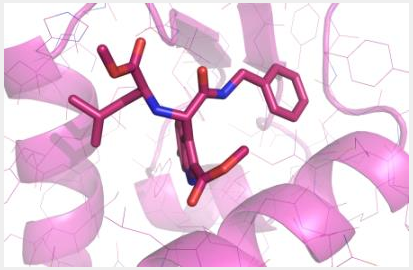




past

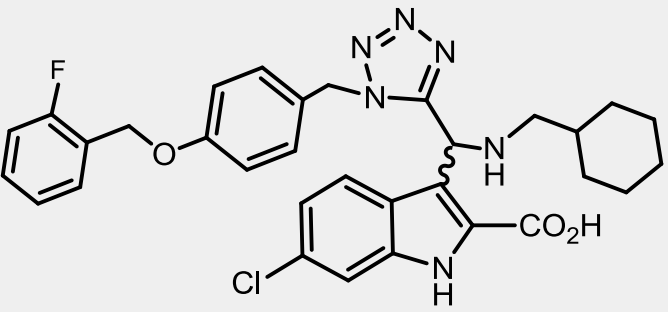


KK268

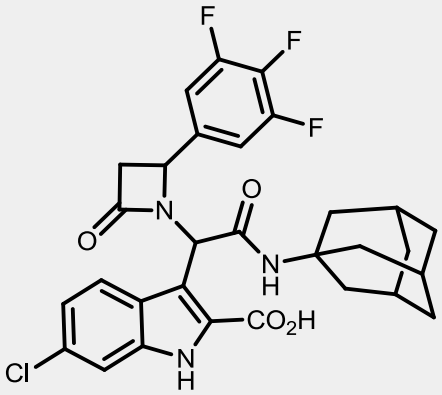


N. Estrada-Ortiz, C. Neochoritis, A. Dömling, *Chem. Med. Chem*. **2016**, *8*, 757-772

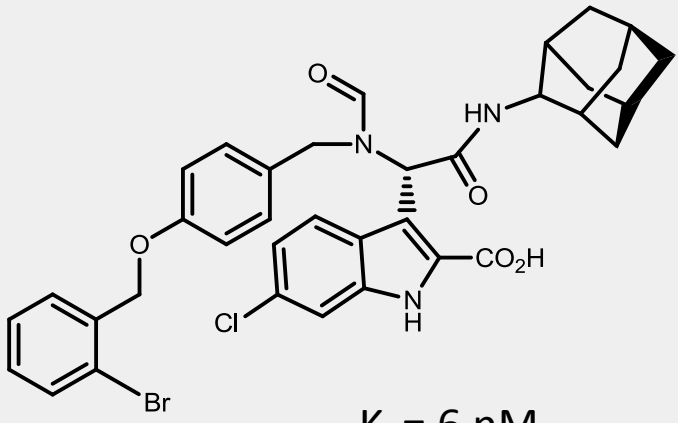
Scaffold hopping via ANCHOR.QUERY™



K_i = 200 nM

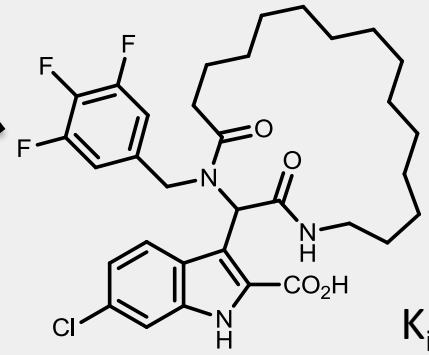


K_i = 20 nM



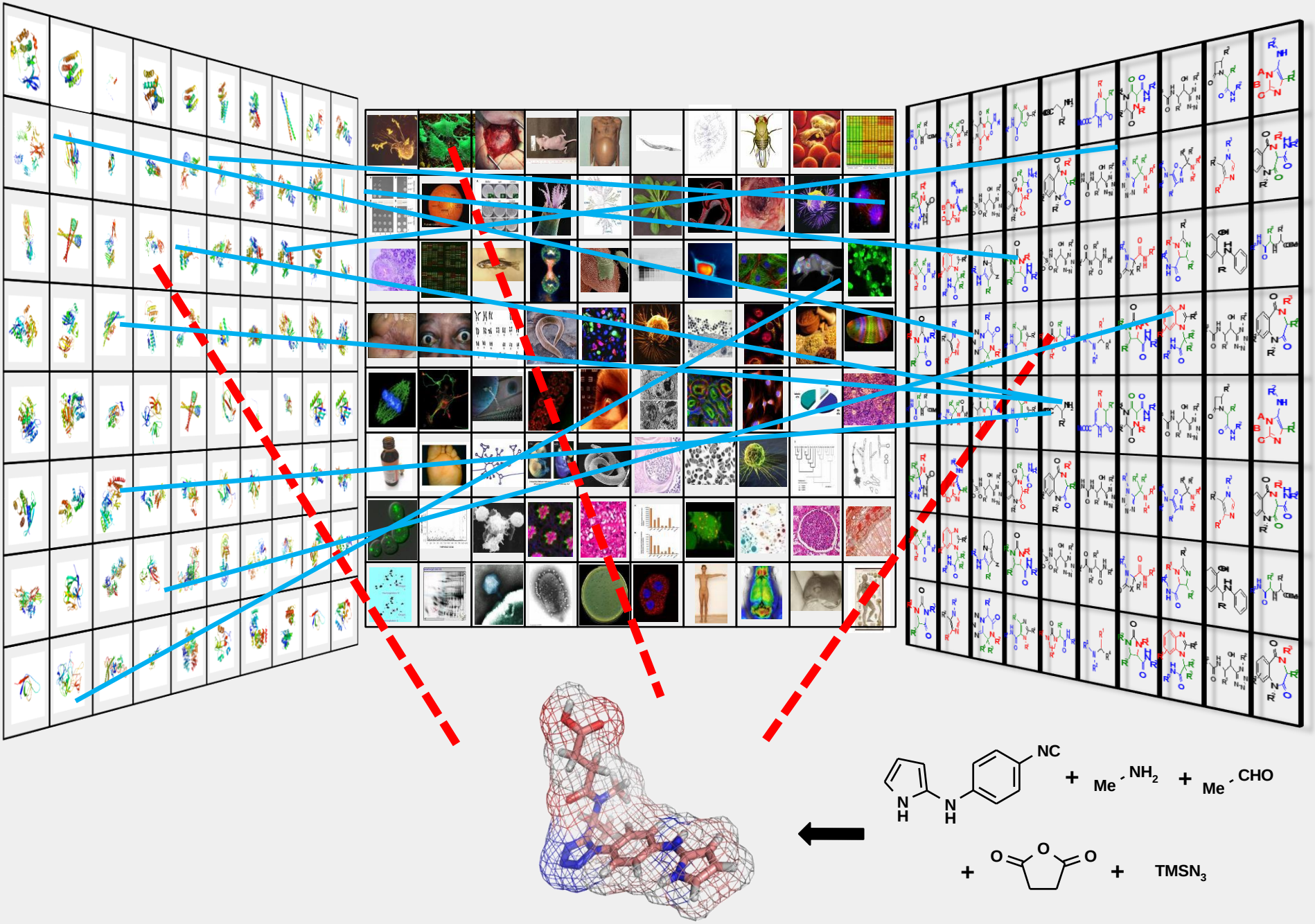
K_i = 6 nM

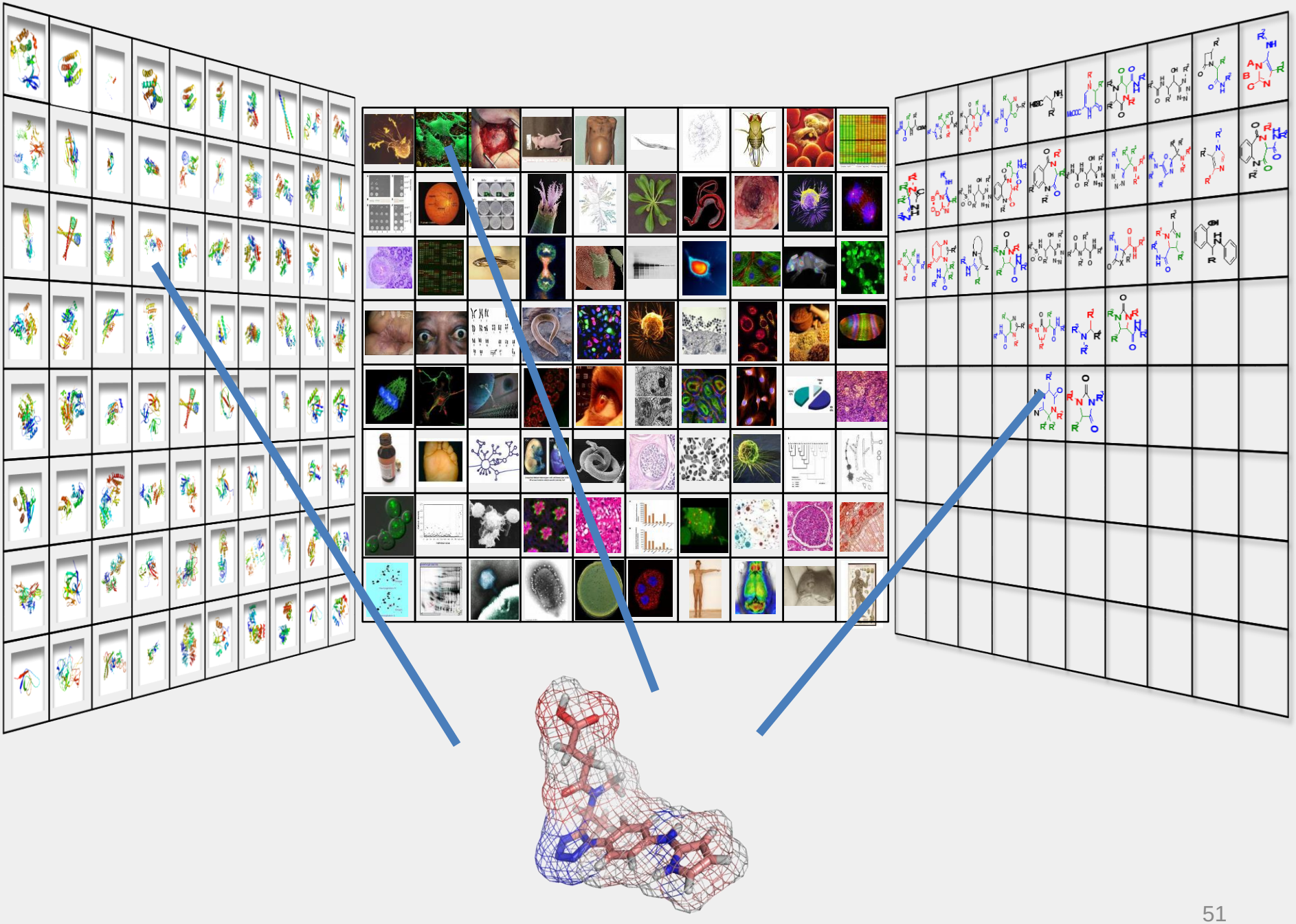
future

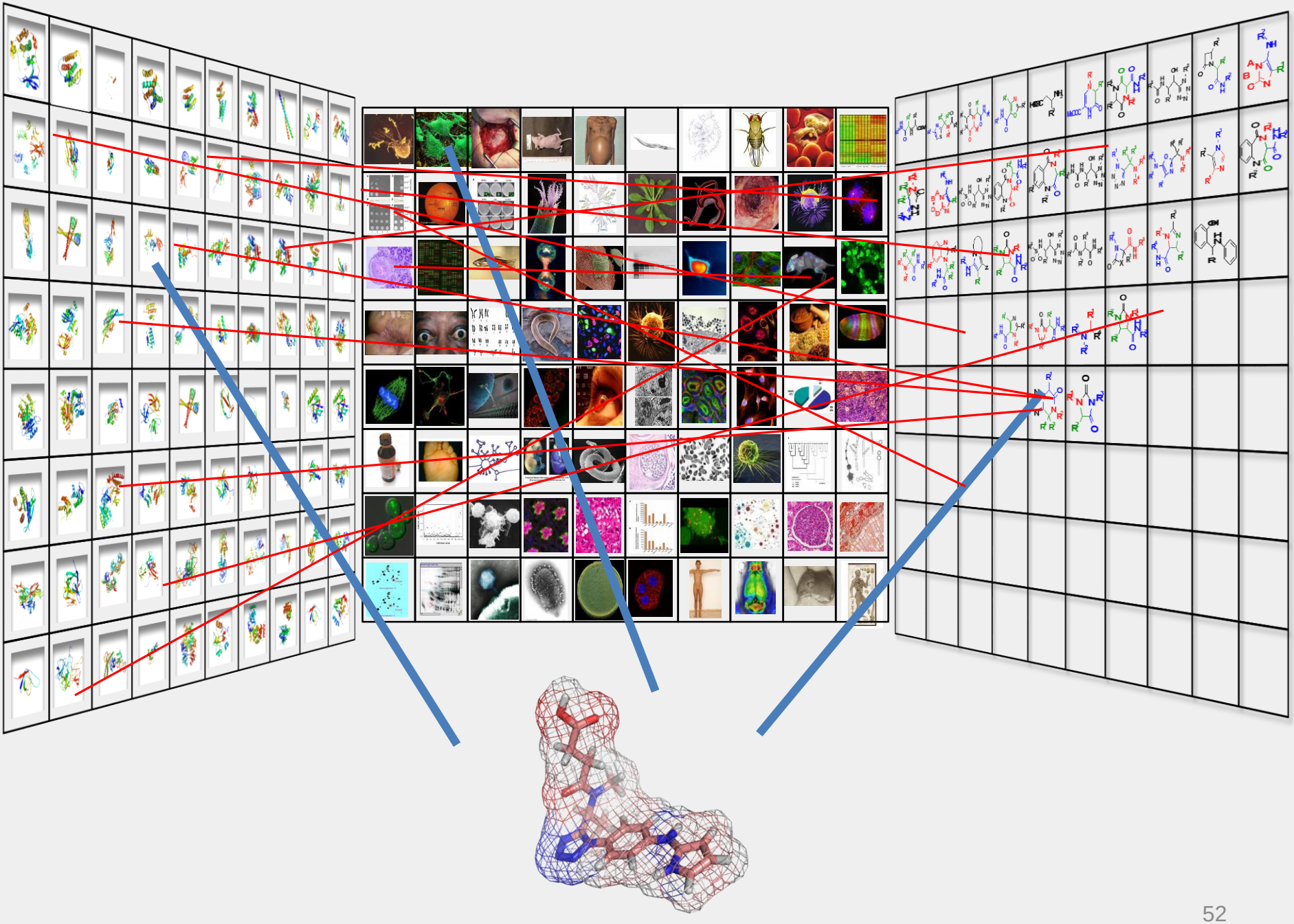


K_i = 60 nM

49


NC
+
Me
NH2
+
Me
CHO
+
+
TMSN3





Miniaturizing the MCR chemistry

Sealstone, 3500 B.C.