New ChemDiv Library "Beyond Flatland"

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ChemDiv, Inc.

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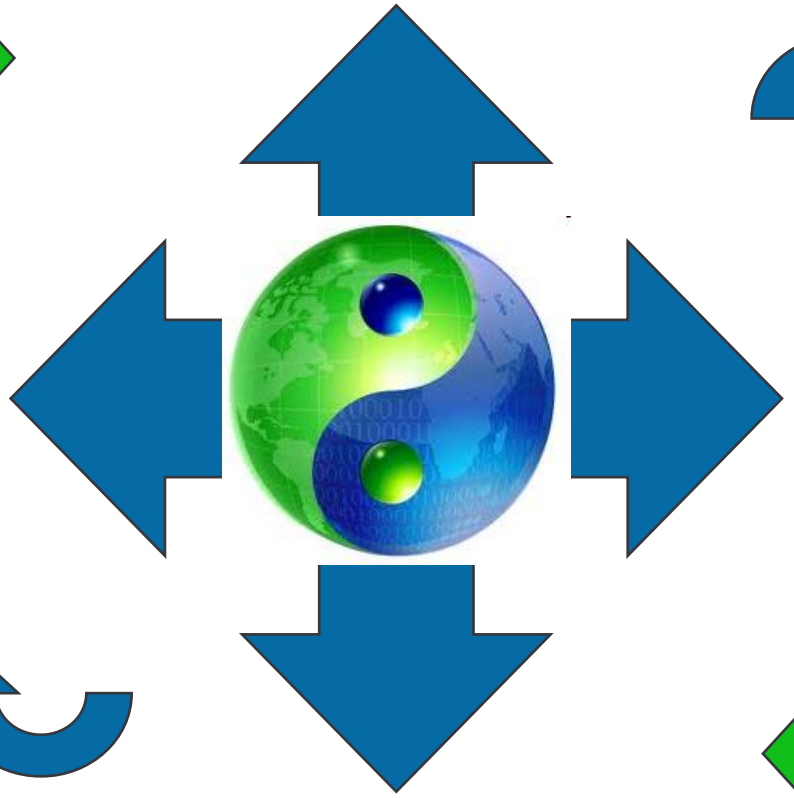
Union of Efficiency and Innovation

Yin & Yang Algorithm

New Literature & Screening Data Knowledge Database

Chemotype & Compounds Evaluation

Discovery and Development of New Reactions



Available Compound libraries

New Scaffolds Generation

High Throughput Synthesis of New Compounds

Diversity Oriented Synthesis; Effective Synthetic Tools

New Focused Libraries

“Escape from Flatland” – New Approach for Scaffold & Library Design

Inspired by: Frank Lovering, et.al. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. J. Med. Chem. 2009, 52, 6752–6756

Fsp3 = number of sp3-hybridized carbons/ total carbon count

- **The increase of scaffold/molecule saturation leads to:**
  - **More diverse set of compounds**
  - **More highly complex molecules**
  - **Natural product-likeness**
  - **Access to greater chemical space**
  - **Better complement to the spatial subtleties of target proteins**
  - **3D-dimensionality may result in greater selectivity**
  - **Higher water solubility**
  - **Better phys-chemical parameters (logP and PSA)**
  - **Very low increase of MW**
  - **New stereo-centers**
- **As result: Faster transition of compound from discovery to drugs**

One difficulty: more complex scaffold/molecules require new perfect synthetic approaches.
Diversity oriented synthesis!!!

3D-Shape
Why do we need to escape the Flatland?

Nature "sees" and "recognizes" molecules as 3D surfaces of chemical information. Therefore, the biological activity of any given molecule strongly depends on its 3D shape.

In contrast to planar molecules, 3D-molecules with developed 3D shape have more chances to be recognized by nature

The molecular shape diversity of a small molecule library is fingerprints of overall functional diversity

Fsp^3 parameter as a measure of saturation has become one of the most important criterion of scaffold/molecule value

Diversity

The term “diversity” is somewhat subjective and needs to be specified.

We recognize six key components of structural diversity that have been consistently identified in the literature

- **Scaffold diversity - presence of a range of distinct molecular scaffolds;**
- **Functional groups diversity - variation in the functional groups present;**
- **Appendage diversity (substituent or building-block diversity) - variation in structural moieties around a common scaffold;**
- **Stereochemical diversity - variation in the orientation of potential macromolecule-interacting elements;**
- **Conformational diversity - variation of possible conformers of molecules;**
- **Chain diversity – presence of different distinct chains (especially if scaffold is not determined uniquely)**

Fsp3 of Small Molecules in Clinical Trials

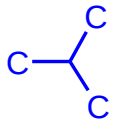
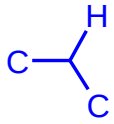
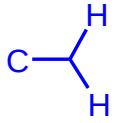
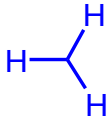
Phase	#compounds	Fsp3%
Launched	1719	45.4
Phase 2&3	2315	42.7
Discontinued& Withdrawn	2146	42.4
Phase 1	1223	41.1
Preclinical	21204	37.7

(compounds with MW>650 were excluded)

Fsp3 is important drug-like parameter

Comparison of Drug-like vs Natural Libraries 1

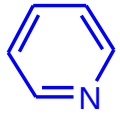
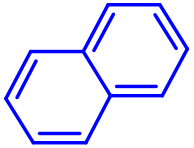
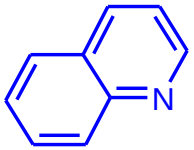
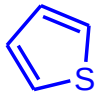
Content of sp3 carbons (frequency of occurrence)

Type of sp3 carbons	Content in Kinase Targeted library	Content in Natural Product library
	**23.2%**	**68.1%**
	**59.8%**	**92.3%**
	**87.5%**	**95.6%**
	**69.3%**	**87.8%**

Drug-like library – Kinase database (Integrity) ~25K compounds
Natural Product library – combined sources ~ 25K compounds
(compounds with MW>650 were excluded)

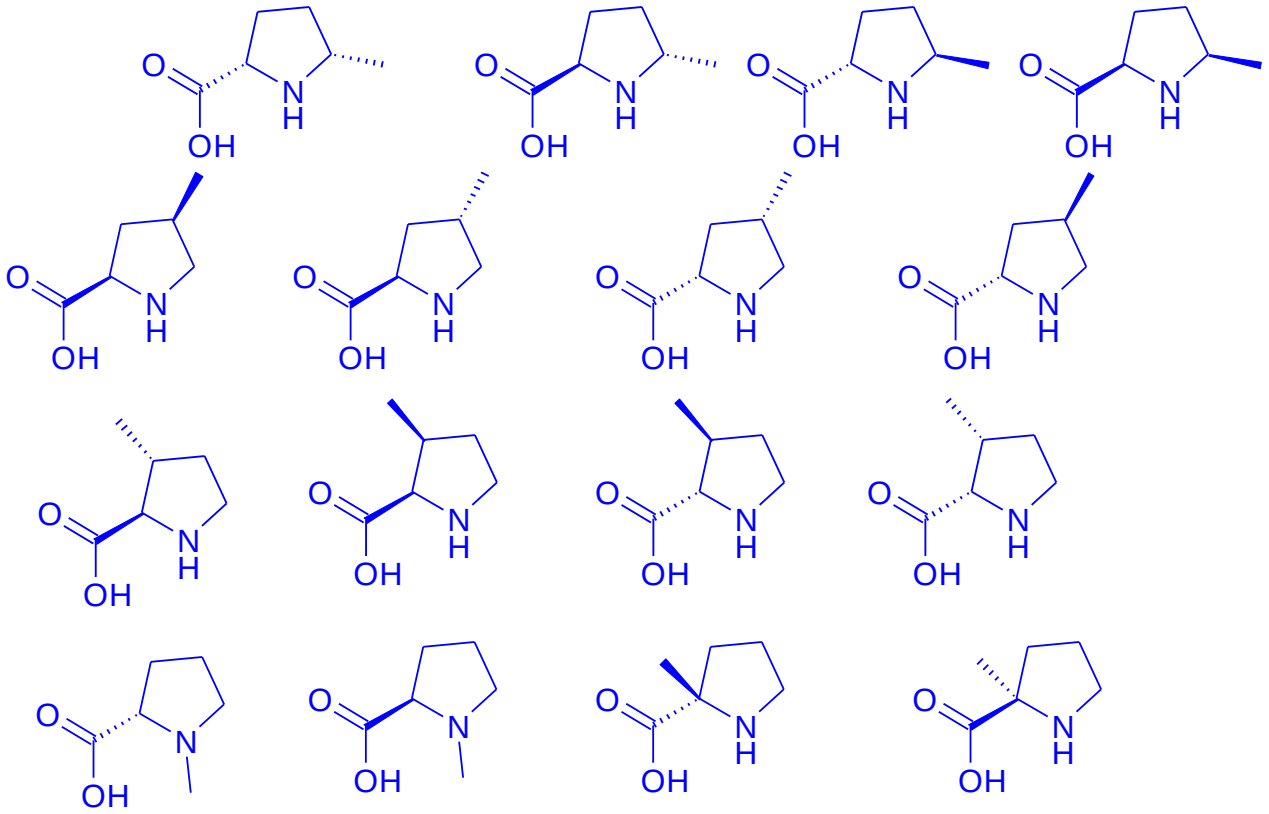
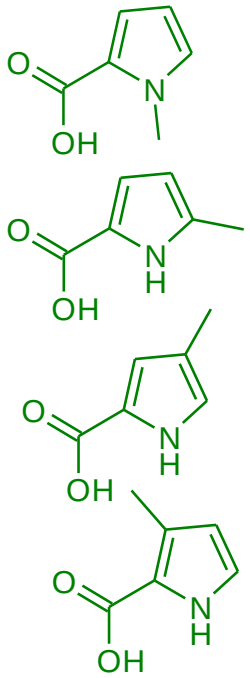
Comparison of Drug-like vs Natural Libraries 2

Content of flat fragments (frequency of occurrence)

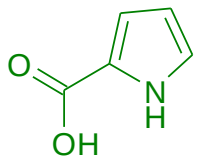
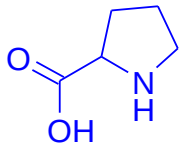
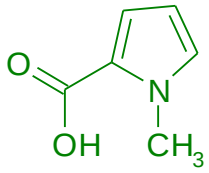
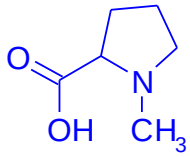
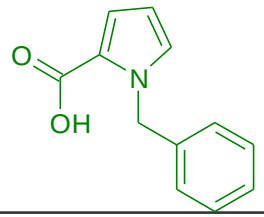
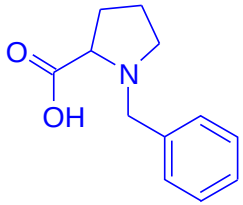
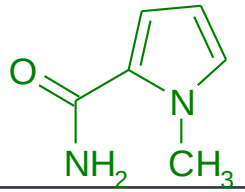
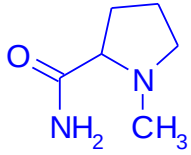
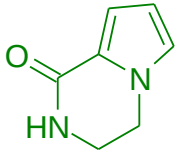
Type of flat fragment	Content in Kinase Targeted library	Content in Natural Product library
	91.9%	59.7%
	34.8%	7.80%
	2.03%	2.53%
	4.48%	2.51%
	5.09%	1.04%

Drug-like library – Kinase database (Integrity) ~25K compounds
Natural Product library – combined sources ~ 25K compounds
(compounds with MW>650 were excluded)

Increased 3D-Diversity of Flexible vs Flat Structures Example: Proline-like compounds

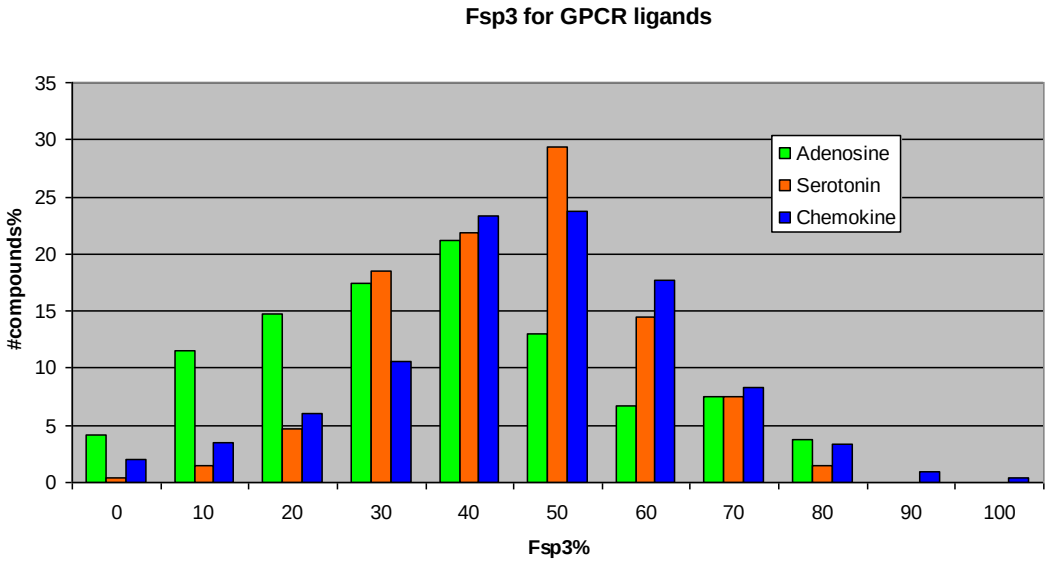
16 Isomers of Methyl-proline	4 Isomers of flat analogs
	

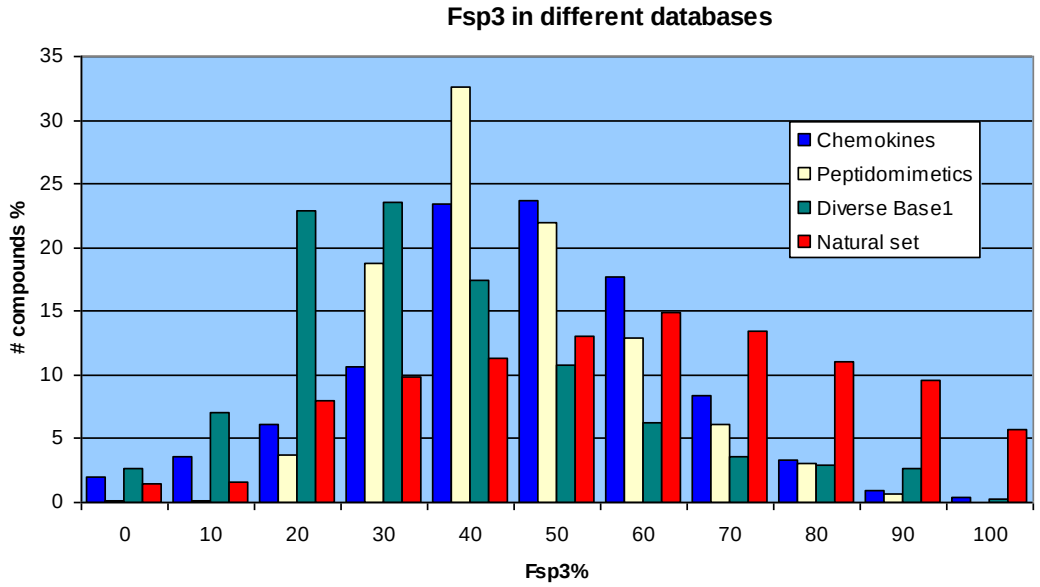
Proline-like compounds 2

Structure Flat compounds	Phys-chemical properties	Structure Flexible	Phys-chemical properties
	Fsp^3=0.0000 logP=0.980 logSW=-3.44 PSA=53.09		Fsp^3=0.8000 logP=-2.330 logSW=-0.890 PSA=49.33
	Fsp^3=0.167 logP=1.180 logSW=-2.25 PSA=42.23		Fsp^3=0.833 logP=-0.840 logSW=-0.826 PSA=40.54
	Fsp^3=0.083 logP=2.81 logSW=-4.17 PSA=42.23		Fsp^3=0.417 logP=1.540 logSW=-1.445 PSA=40.54
	Fsp^3=0.167 logP=0.680 logSW=-2.15 PSA=48.02		Fsp^3=0.833 logP=-1.00 logSW=-0.784 PSA=46.33
	Fsp^3=0.286 logP=1.13 logSW=-3.71 PSA=34.03		Fsp^3=0.857 logP=0.100 logSW=-0.454 PSA=32.34

Flexibility improves phys-chemical properties (logSW, ClogP, PSA) of scaffolds or building blocks

Fsp3 Difference of Different GPCR Ligands and Libraries





Virtual database from Integrity & MedChem sources:

- **Chemokine - 4.2K ligands**
- **Serotonin - 8.6K ligands**
- **Adenosine - 2.4K ligands**
- **Natural set - 25K compounds**

Available collection of compounds:

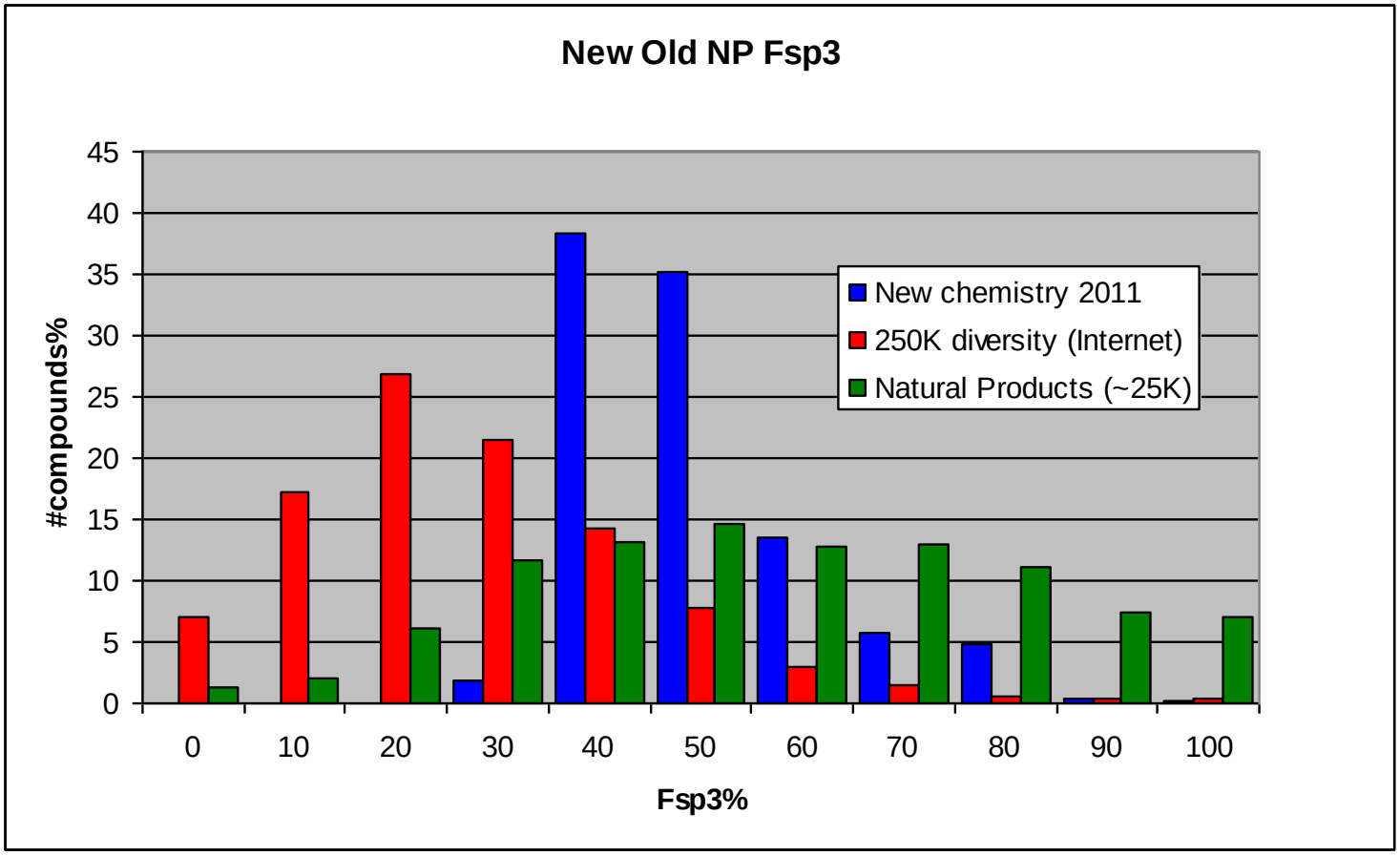
- **Peptidomimetic Library ~ 20K compounds**
- **Diverse set - 250K compounds**

Chemokines Set and Peptidomimetic Library have a similar distribution of the Fsp3 Chemokines are very different from diverse and natural sets

Criteria to be Considered for Novel Scaffold/Molecule Design

Parameter	Scaffold	Molecule
No undesirable functionalities (MedChem filters)		
No undesirable chemotypes (MedChem filters)		
Amide bonds	No more 2 amide bonds (cyclic or linear)	No more 2 amide bonds (cyclic or linear)
Aromatic rings	No more 2 aromatic rings	No more 3 aromatic rings
MW	100<MW<350	150<MW<450
Fsp3	>0.30	>0.30
ClogP	-1.0 <ClogP< 3.5	0 <ClogP<5.0
PSA	10<PSA<60	40<PSA<90
HBA/HBD	<6/2	<8/3
Rotatable bonds	<6	<8

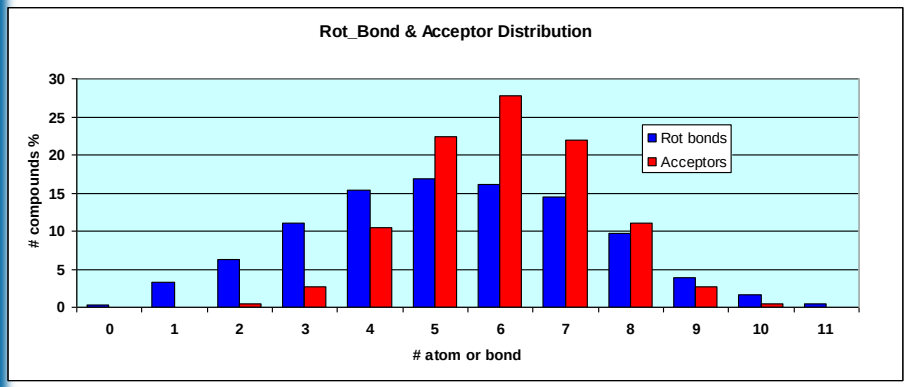
Comparison of Newest Chemdiv's Library (~25K), Available Diversity Set (Internet, 250K) and Natural Products (~25K)

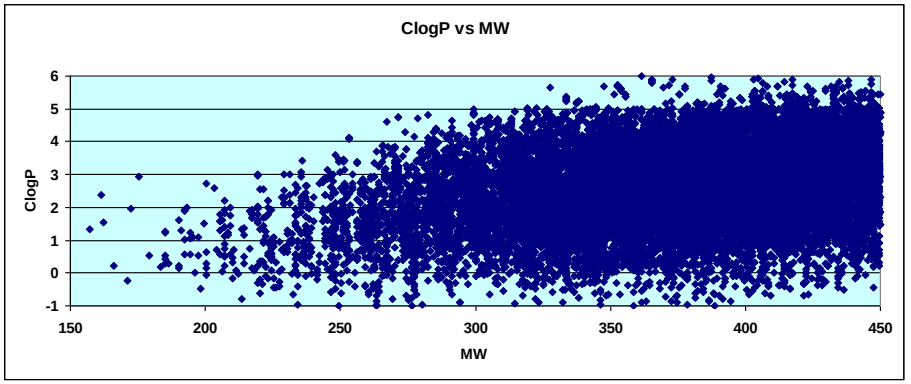


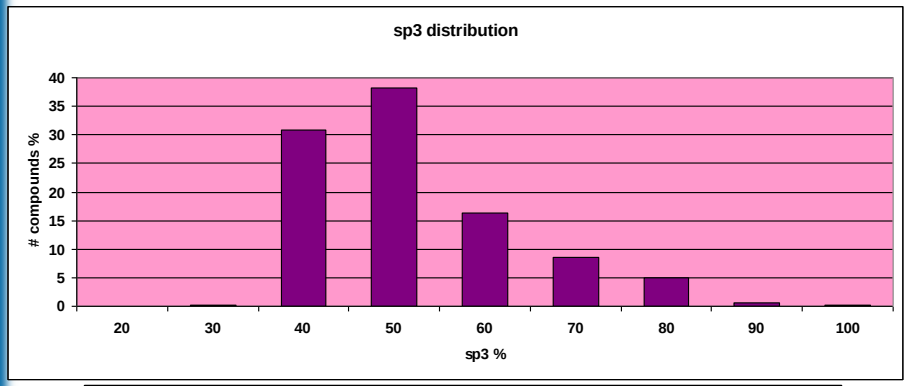
Our chemistry is becoming more similar to natural products

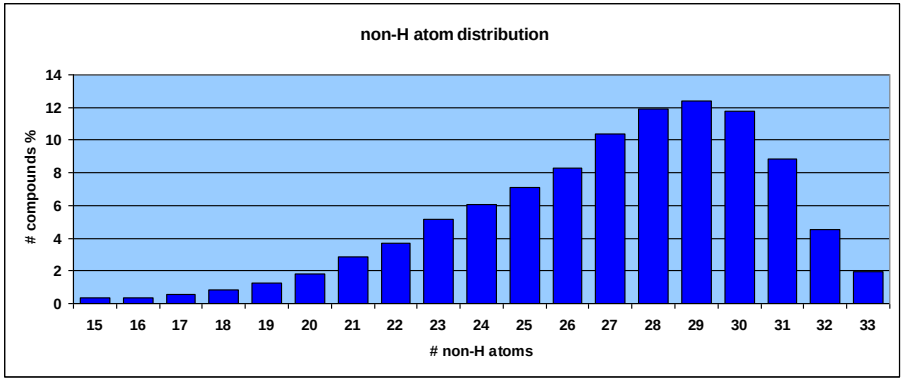
Available Library “Beyond Flatland”

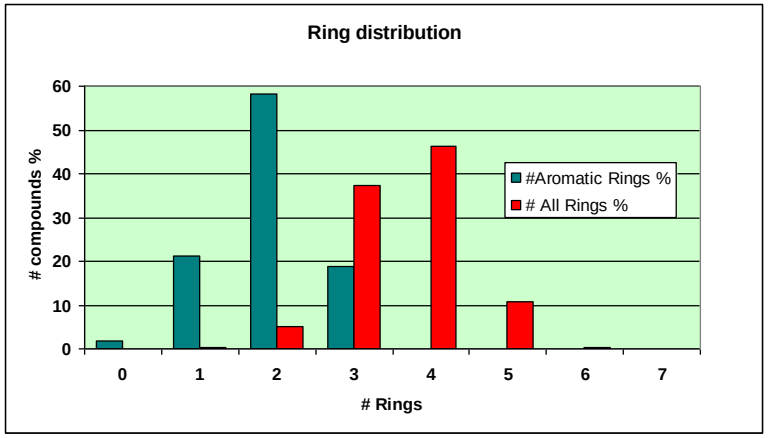
Library (Edition March 2012) contains 26267 compounds









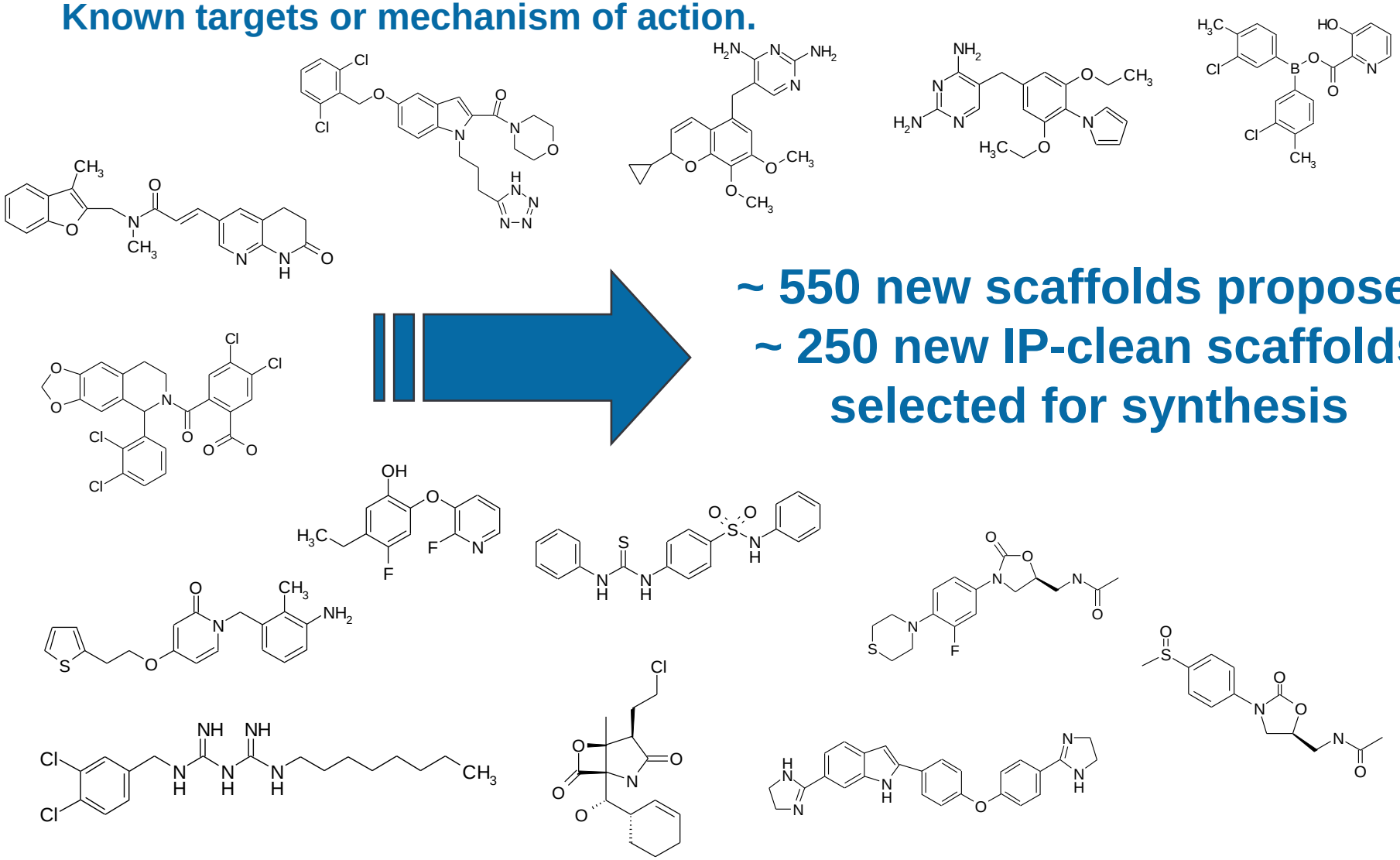


- ❖New drug-like compounds
- ❖Natural-like compounds
- ❖Unique scaffolds
- ❖3D diversity
- ❖Enrichment of unique structures
- ❖(spiro ~7%)

Scaffold Selection

From Prototypes to Scaffolds

Prototypes: more 1,500 antibacterial small molecules (from new patents, preclinical, phase I-III, under active development, natural, natural-like, etc.). Known targets or mechanism of action.



~ 550 new scaffolds proposed

~ 250 new IP-clean scaffolds selected for synthesis

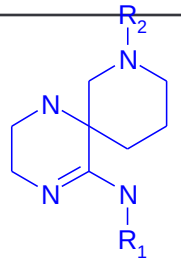
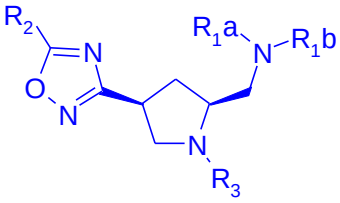
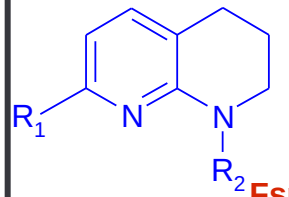
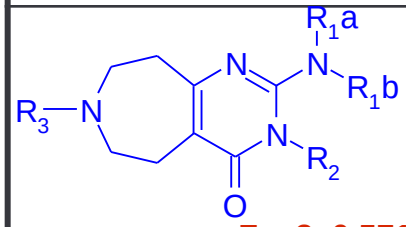
“Beyond the Flatland” Template Design Criteria: at least one of the following:

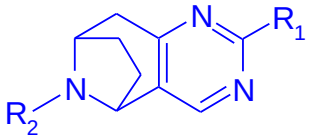
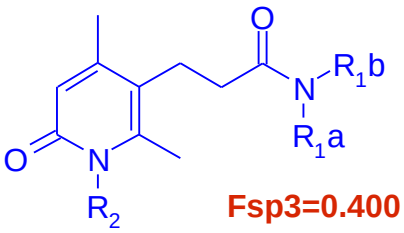
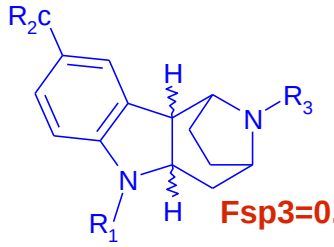
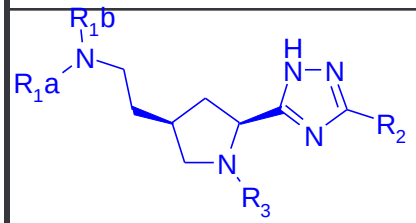
- High degree of (hetero-)cycle saturation (Preferable Fsp^3= 0.3 - 1)
- One or more stereogenic centers
- Bridged or spiro-fused ring systems
- Structural fragments of naturally occurring compounds possessing interesting biological activity
- 7 (or more) membered (hetero-)cyclic rings
- Rare or unique combinations of privileged heterocycles
  - *widely distributed in nature, e.g. indole, isoquinoline, etc.*
  - *preferably with at least one stereogenic center*

&

- **(if possible) biological annotation**

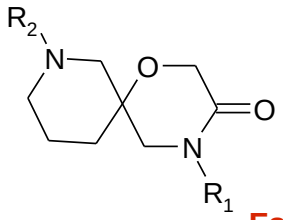
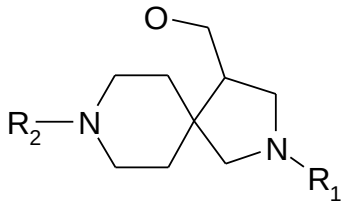
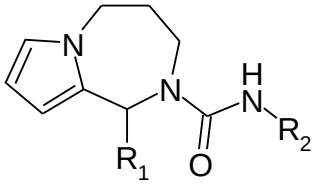
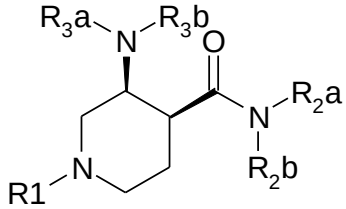
New Anti-bacterial Scaffolds (Examples)

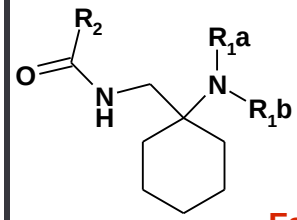
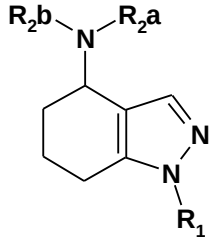
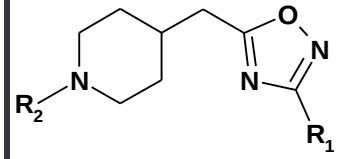
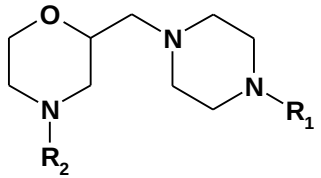
Scaffold	Possible Targets
 Fsp3=0.875	Bacterial Efflux Pump Toll-Like Receptors Ligase dltA
 Fsp3=0.714	Bacterial transcriptional regulatory repressor protein EthR
 Fsp3=0.375	Enoyl-(acyl-carrier protein) Reductase FabI
 Fsp3=0.571	FtsZ Polymerization

Scaffold	Possible Targets
 Fsp3=0.555	Cell Wall Biosynthesis MurF Synthetase
 Fsp3=0.400	Undecaprenyl pyrophosphate synthase (UPPS)
 Fsp3=0.538	Phosphopantetheine Adenylyltransferase (PPAT)
 Fsp3=0.750	Histidine protein kinase

Scaffolds with high Fsp3 and good phys-chemical properties

New Metabolic Scaffolds (Examples)

Scaffold	Possible Targets
 Fsp3=0.875	Histamine H3 Receptor Antagonists
 Fsp3=1.00	Somatostatin SRIF1B (sst5) Antagonists
 Fsp3=0.444	Bile Acid Responsive TGR5 Receptors (AXOR 109, GPCR19) Agonists
 Fsp3=0.833	Triacylglycerol Lipase (Hormone-Sensitive Lipase) Inhibitors

Scaffold	Possible Targets
 Fsp3=0.875	Melanocortin MC4 Agonists
 Fsp3=0.571	5-HT2C Receptor Ligands
 Fsp3=0.750	Orexin OX-1 Antagonists
 Fsp3=1.00	Acetyl-CoA Carboxylase (ACC) Inhibitors

Scaffolds with high Fsp3 and good phys-chemical properties

Chemistry

Synthetic Tools for Framework Assembly

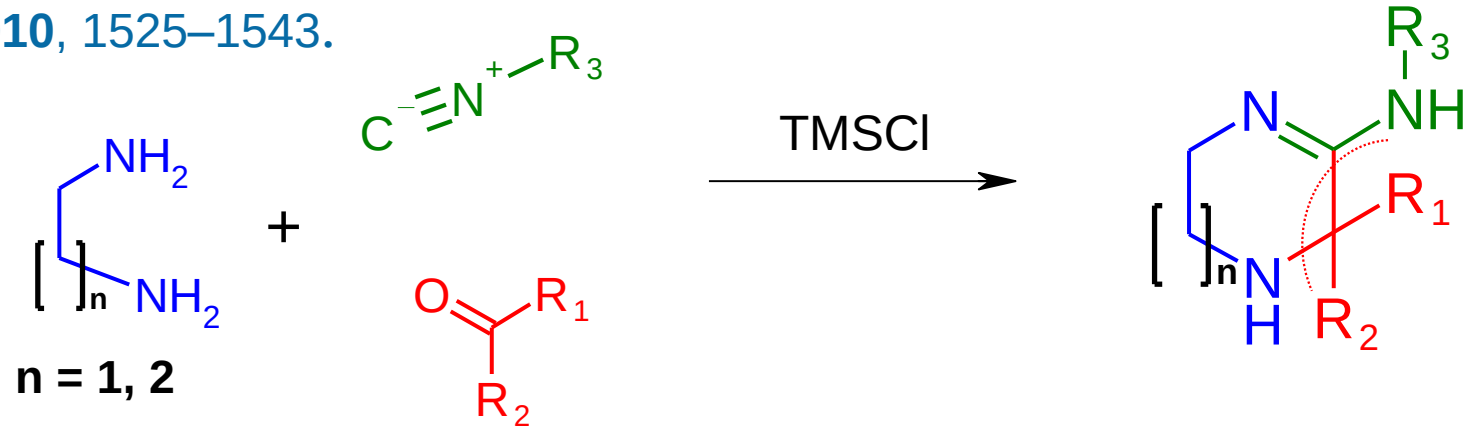
- Reaction Types:
  - ***multicomponent reactions (MCR), intramolecular and post-MCR modifications;***
  - ***new MCRs;***
  - ***azomethine dipolar cycloaddition;***
  - ***Halocyclizatons;***
  - ***"classic" (hetero-)cyclization, but in new sequences (e.g. Michael addition followed by cyclization);***
  - ***ring closure metathesis (RCM);***
  - ***Unique unions of known and recently developed reactions (e.g., Ugi-MCR – Diels-Alder-skeletal rearrangement; intramolecular Ugi-MCR – selective reduction etc.);***
  - ***and more…***

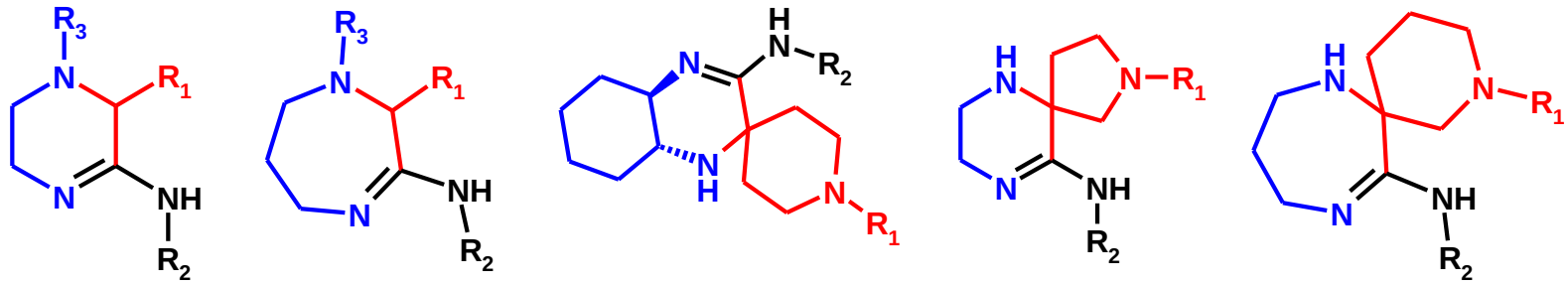
The chemistry should meet DOS (Diversity Oriented Synthesis) criteria!

Multicomponent Reactions (MCR)

New MCR: unique tool for functionally enriched pyrazines and 1,4-diazepines synthesis developed at ChemDiv

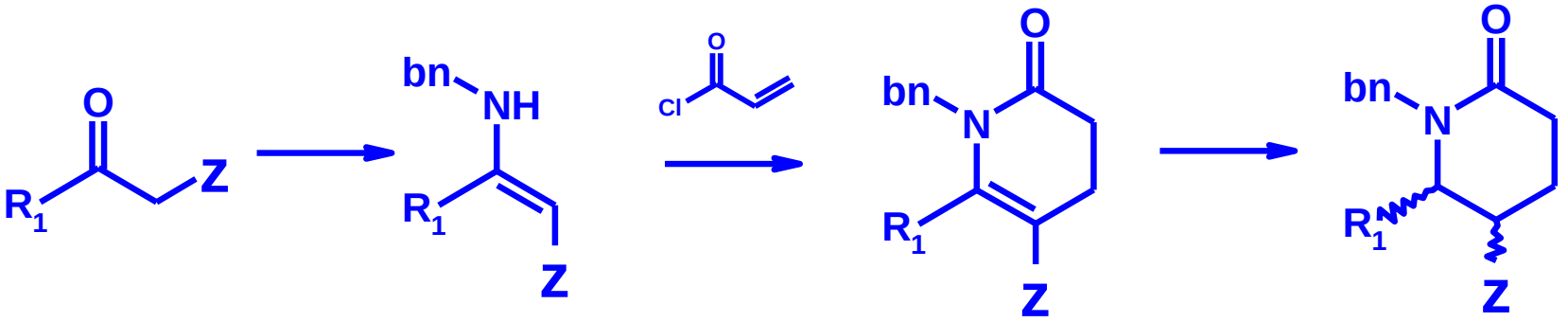
TL **2007**,*48*, 6239-6244;
TL **2009**, *50*, 2854–2856;
Eur. JOC **2010**, 1525–1543.





Michael-type Azaanulation

Acylation of N-Bn-enamines based on activated ketones with acryloyl chloride followed by Michael-type cyclization has been reported by Paulvannan and Stille [*JOC* **1994**, *59*, 1613-1620].

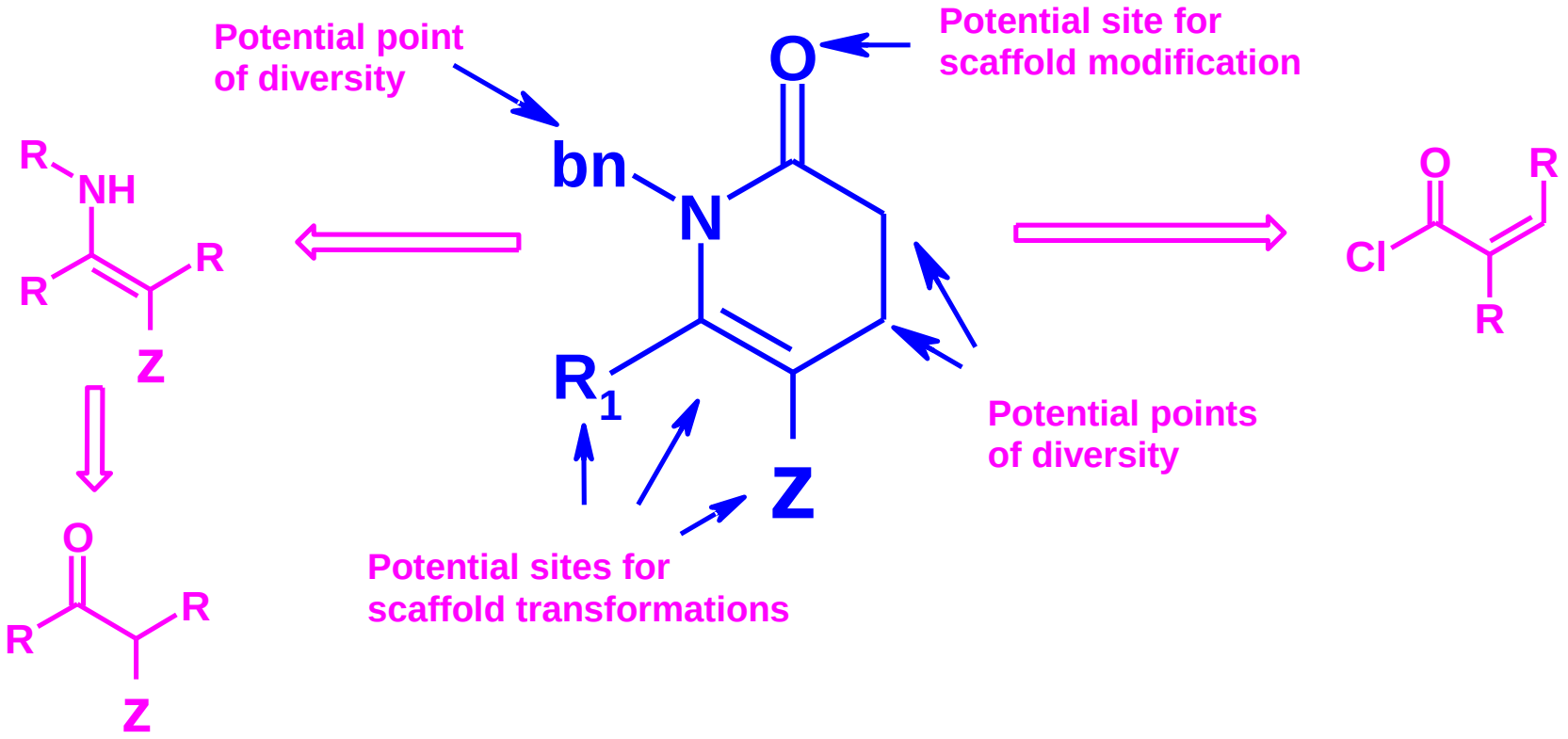


Z = CO_2Et, COR, CONHPh, SO_2R, CN; R1 = Alk.

How can we use this chemistry for unique scaffolds generation?

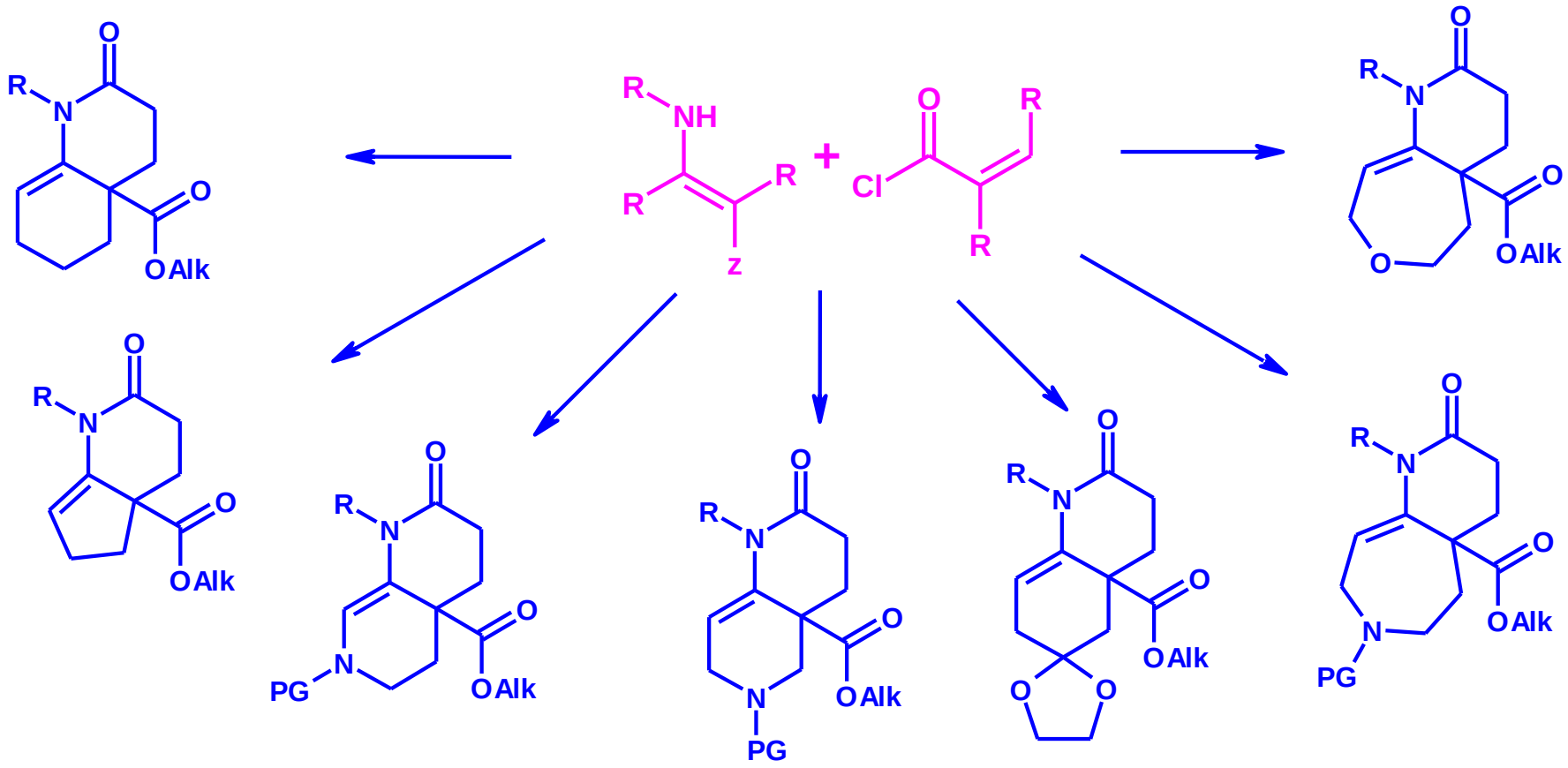
Michael-type Azaanulation

Study of the scope of the reaction and/or reactivity of functional groups that could be incorporated into the core might provide a great number of unique scaffolds



Michael-type Azaanulation

Structural variety of activated ketones ensures cores variety



Our Expertise in Novel Library/Compound Design

❖Tsaloev A., Ilyin A., Tkachenko S., Ivachtchenko A., Kravchenko D., Krasavin M. Cyclic products of the Ugi reaction of aldehydo and keto carboxylic acids: chemoselective modification. ***Tetrahedron Letters***. **2011**, ***52***: 1800–1803.

❖Kysil V., Khvat A., Tsirulnikov S., Tkachenko S, Williams C., Churakova M., Ivachtchenko A. General Multicomponent Strategy for the Synthesis of 2-Amino-1,4-diazaheterocycles: Scope, Limitations, and Utility. ***European Journal of Organic Chemistry***. **2010**; 1525–1543.

❖Kysil V.M., Khvat A., Tsirulnikov S., Tkachenko S., Ivachtchenko A. Multicomponent approach to unique 1,4-diazepine-2-amines. ***Tetrahedron Letters***. **2009**; ***50(24)***: 2854-2856.

❖Balakin K.V., Ivanenkov Y.A., Tkachenko S.E., Kiselyov A.S., Ivachtchenko A.V. Regulators of chemokine receptor activity as promising anticancer therapeutics. ***Current Cancer Drug Targets***. **2008**; ***8(4)***: 299-34.

❖Kiselyov A.S., Tkachenko S.E., Balakin K.V., Ivachtchenko A.V. Small-molecule modulators of Hh and Wnt signaling pathways. ***Expert Opinion on Therapeutic Targets***. **2007**; ***11(8)***: 1087-1101.

❖ Savchuk N.P., Tkachenko S.E., Balakin K.V. Design of pGPCR-targeted Libraries. In Rognan D., ed. ***Ligand Design for G Protein-coupled Receptors.*** Methods and Principles in Medicinal Chemistry (Volume 30). Weinheim: Wiley VCH. **2006**, pp. 137-164.

❖ Kysil V., Tkachenko S., Khvat A., Williams C., Tsirulnikov S., Churakova M., Ivachtchenko A. TMSCl-Promoted Isocyanide-Based MCR of Ethylenediamines: an Efficient Assembling of 2-Aminopyrazine Core. ***Tetrahedron Letters***, **2007**; ***48(36)***: 6239-6244.

Thank You