

Design of Combinatorial Libraries for the Rapid Lead Optimization of Glucagon Antagonists

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Outline

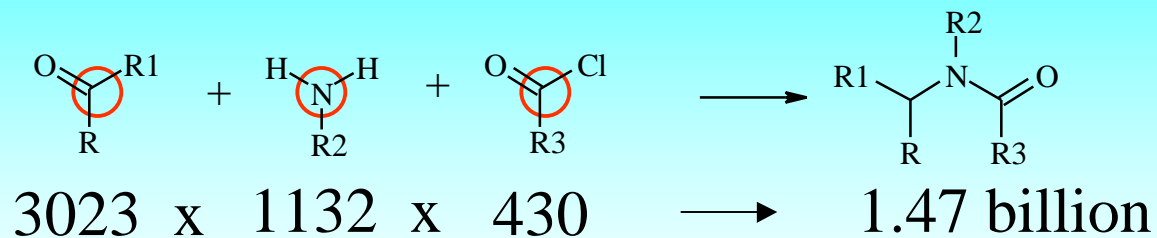
- **Description of some unique features of LiBrain TM, an in-house developed software system, for combinatorial library design ;**
- **The strategies of combinatorial library design for lead optimization and its application in Glucagon antagonist project ;**

LiBrain™-Intelligent system for Combinatorial Library Design

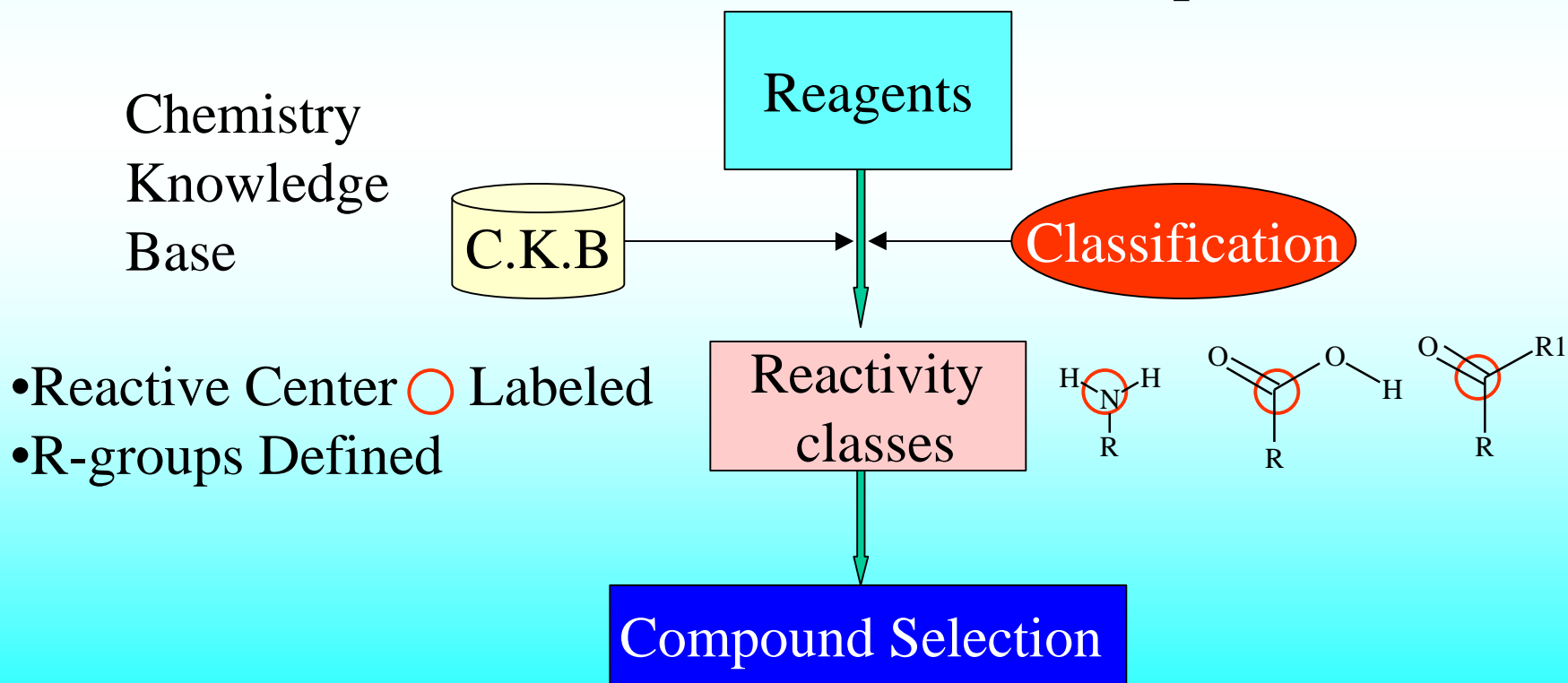
Unique Features for Combinatorial Library Design

- **Reactant-Based Selection;**
- **R-Group-Based Comparison;**
- **Affinity-Generating Element, AE-Based Perception.**

Reactant-Based Selection

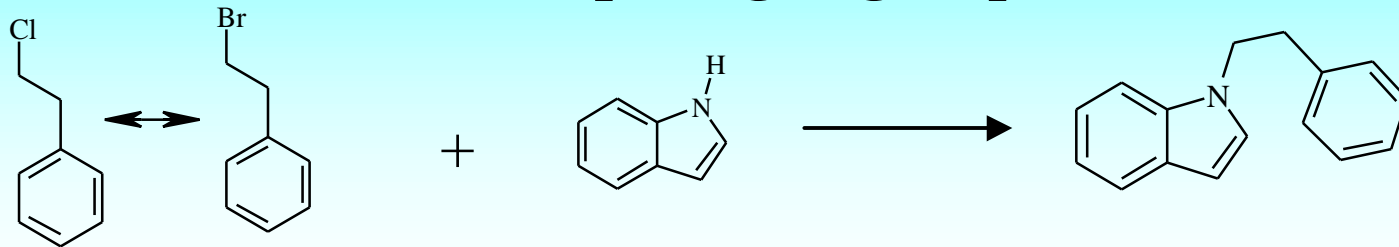


Number of reactants \lll number of products



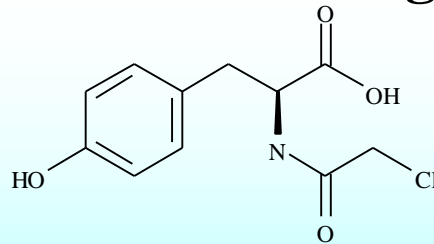
R-group-Based Comparison

Comparing their R-groups of Reactants rather than Comparing reactants themselves = Comparing R-groups of Products



As alkyl-halides they are identical

The same compound has **different R-groups** in different **reactivity classes**



Reactivity Classes	Alkyl_halide	Carboxylic Acid	Phenol
R-groups			

Affinity-Generating Element, AE- Based Perception

Chemistry-Perception, characterization of molecules, which determines the mathematical representation of molecules, is the most important issue in the design of libraries for activity

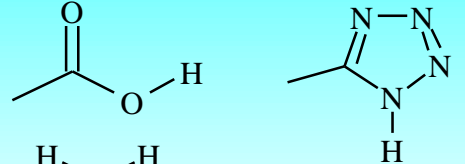
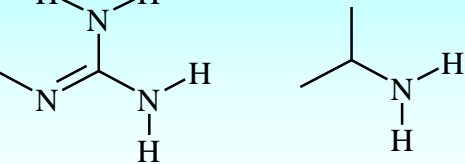
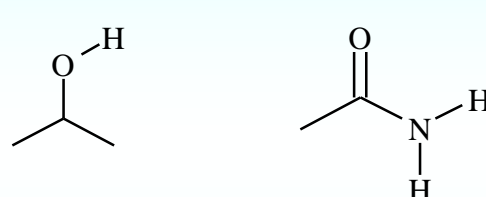



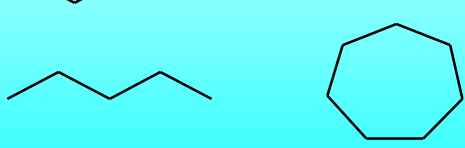
- Different characterizations of molecules lead to different molecular representation spaces;
- The same set of molecules could have vastly different distributions in its various representation spaces;

AE-Based Perception

Characterization of molecules should be based on bio-chemistry-knowledge, the understanding of interaction of ligands with proteins

**Affinity-generating structure-Elements, AE,
-- substructures involved in interaction with target proteins**

Affinity-generating Elements

Interaction	AE	Examples
Charge-charge Electrostatic	Acids Bases	 
Hydrogen Bonding	HBD HBA	
Electric Dipole	Polar	 
Hydrophobic	Aromatic Aliphatic	 

AE Features of R-groups

- **Number of AE's in an AE class**
- **Bond-distance of AE to the Connection Atom**
- **Property-value of AE:**

AE	Property
Acid	pKa
Base	pKa
HBD	pKa
HBA	pKa
Polar	Dipole
Aromatic	Ring size
Aliphatic	Size of connected group

R-group AE Feature Vector Space

21-Dimensional

R-group AE Feature Vector, RAEFV

Default	Acid	Base	HBD	HBA	Polar	Aromatic	Aliphatic
	N	N	N	N	N	N	N
3	$\langle Bd^2 \rangle$	$\langle Bd^2 \rangle$	$\langle Bd^2 \rangle$	$\langle Bd^2 \rangle$	$\langle Bd^2 \rangle$	$\langle Bd^2 \rangle$	$\langle Bd^2 \rangle$
	$\langle Pr \rangle$	$\langle Pr \rangle$	$\langle Pr \rangle$	$\langle Pr \rangle$	$\langle Pr \rangle$	$\langle Pr \rangle$	$\langle Pr \rangle$

- **N**: the number of AE's in an AE class
- $\langle Bd^2 \rangle$: the average value of the square of the bond distances
- $\langle Pr \rangle$: the average value of the property values

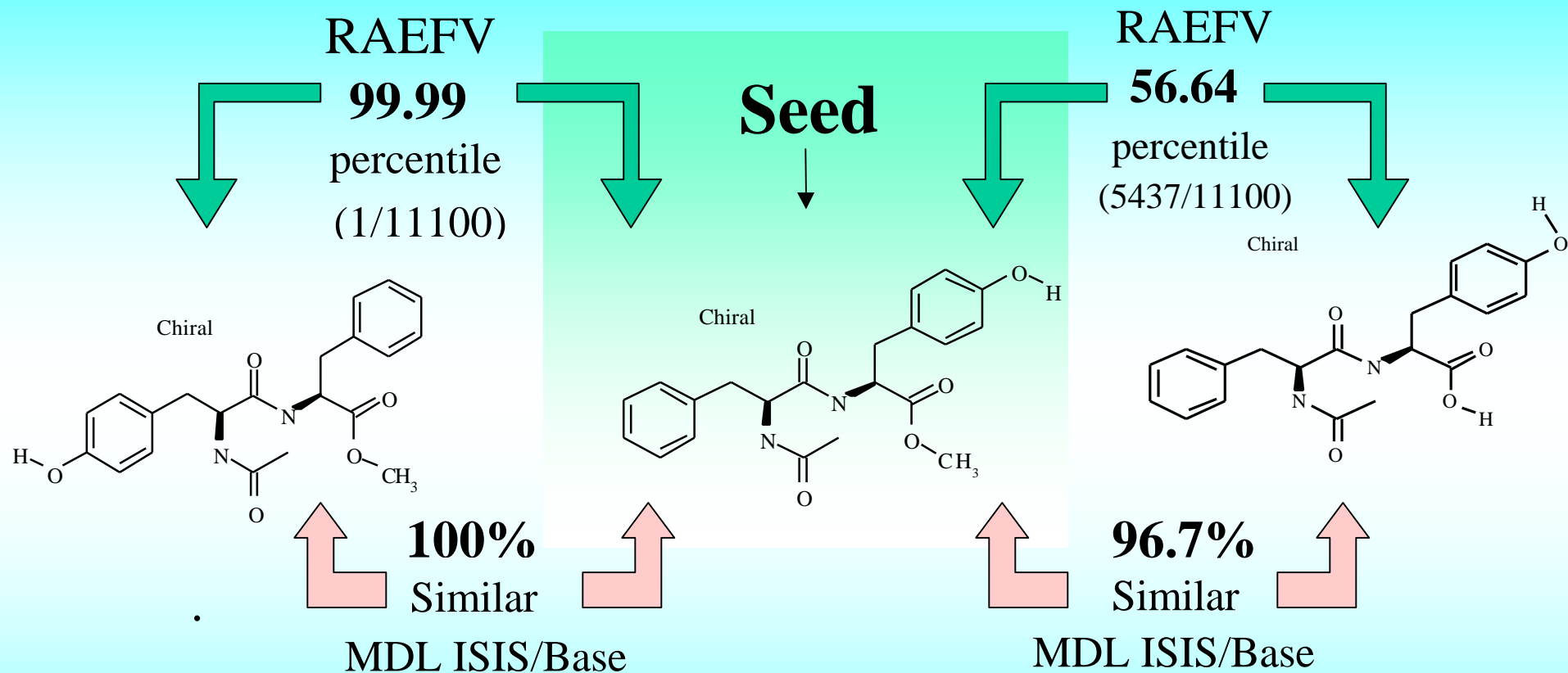
Distance Measure for Quantitative Comparison

Euclidean distance $d_{i,j}$

$$d_{ij} \equiv \sum_{k=1}^n |R_k^i - R_k^j|$$

R_k^i and R_k^j are the R-group AE feature vectors of R-group k of reactants, i and j in a reactivity class with n non-equivalent R-groups.

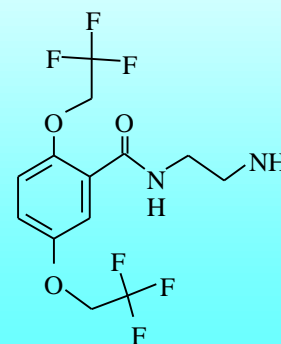
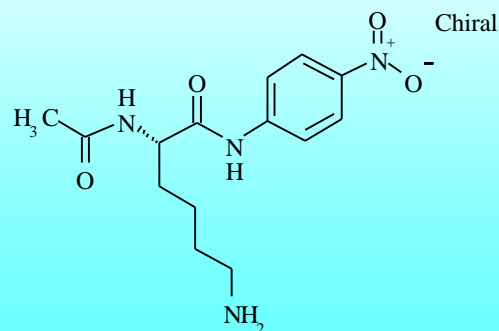
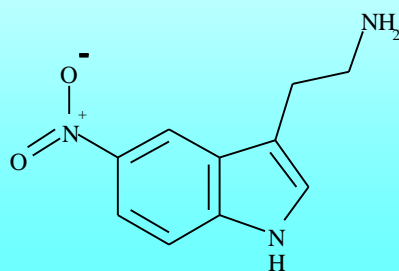
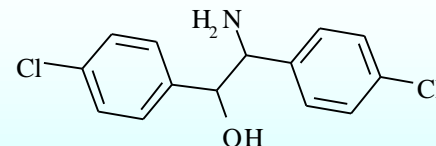
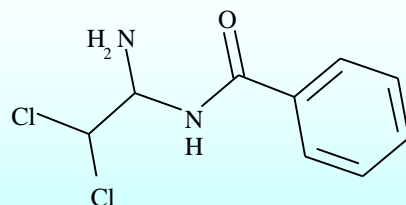
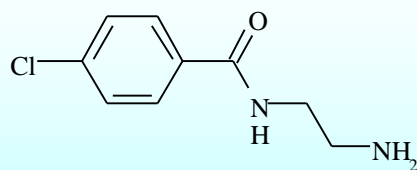
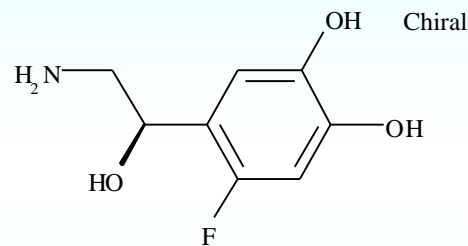
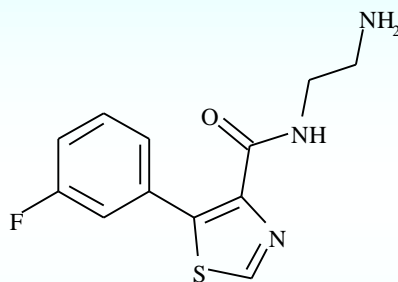
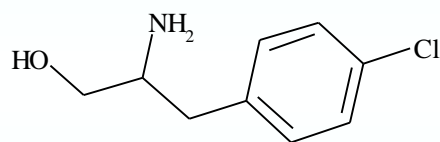
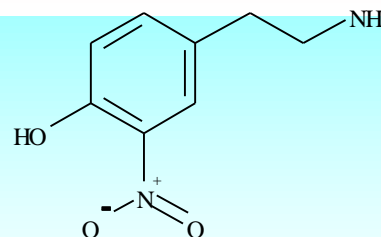
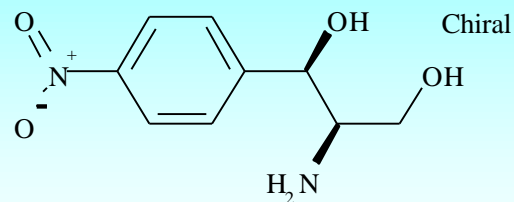
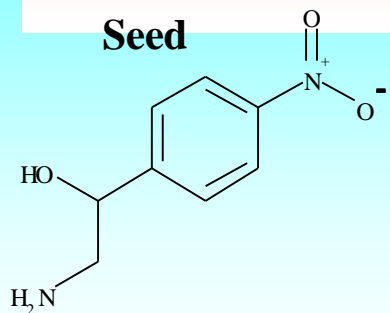
R-group AE Feature Vector Based Similarity



**In Phenol Reactivity Class From
MDL ACD Database**

Similarity Selection in RAEFV Space For Primary-amines

Seed



Maximin-Algorithm-Based Maximum Diversity Trajectory

Assume: a subset, G , of $N > 0$ compounds in the domain set, Q , of M compounds has been selected;

Define the distance of a compound i in $W = Q - G$ to the set G as

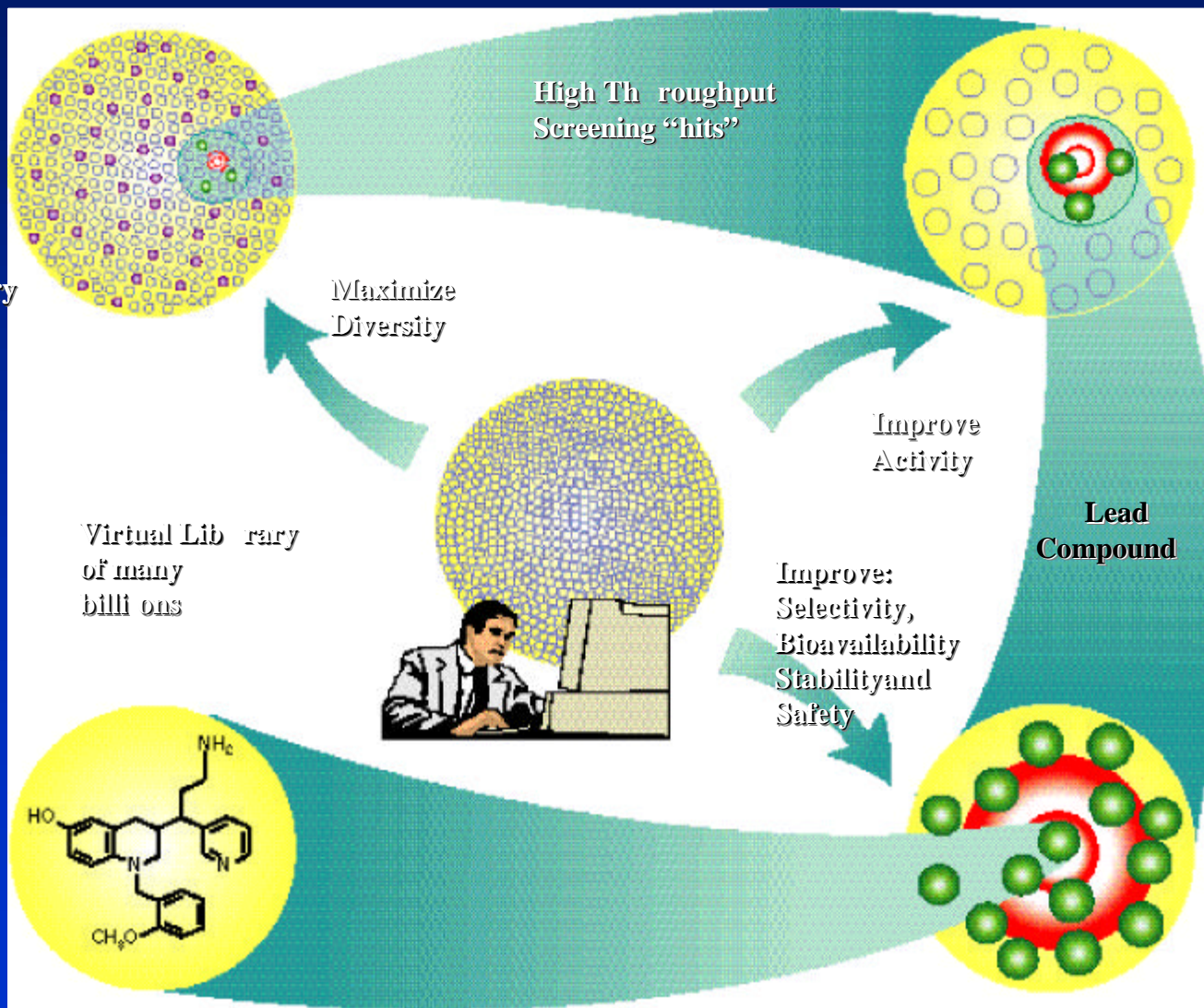
$$\Delta_i(\Gamma) \equiv \text{Min} \{d_{ij}\}, j = 1, \dots, N \text{ in } \Gamma.$$

For maximum diversity, the $(N+1)$ th compound should have a maximum of the distance to the subset G for all the compounds i in the remaining subset W

$$\begin{aligned} D_{(N+1)}(\Gamma) &= \text{Max} \{\Delta_i(\Gamma)\}, i = 1, \dots, M - N \text{ in } \Omega \\ &\equiv \text{Max}_i \text{Min}_j \{d_{ij}\}, i = 1, \dots, M - N \text{ in } \Omega \text{ and } j = 1, \dots, N \text{ in } \Gamma \end{aligned}$$

General Strategies of Targeted Library Design for Lead Optimization

Exploratory Library



Targeted Library by Analogy (Similarity)

Medicinal Chemistry, Analog Libraries

nM Initial hit

↕
~ one good fit to
the binding site

?



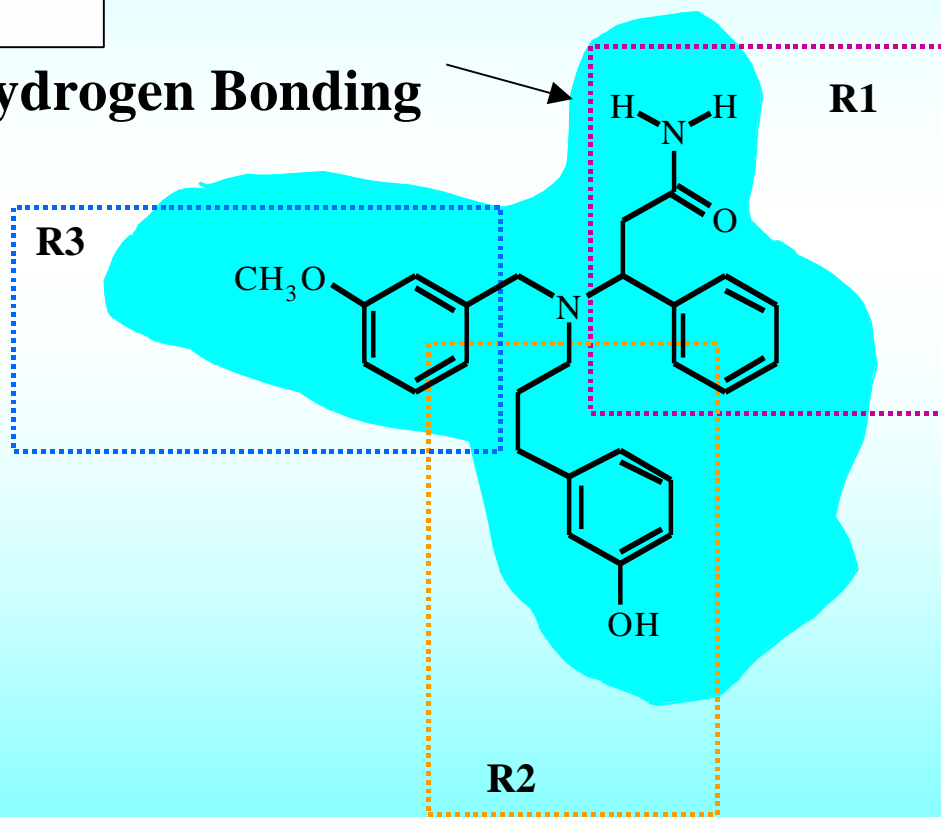
Design Library of Analogs by

- Whole Molecule Similarity
- R-group by R-group Control

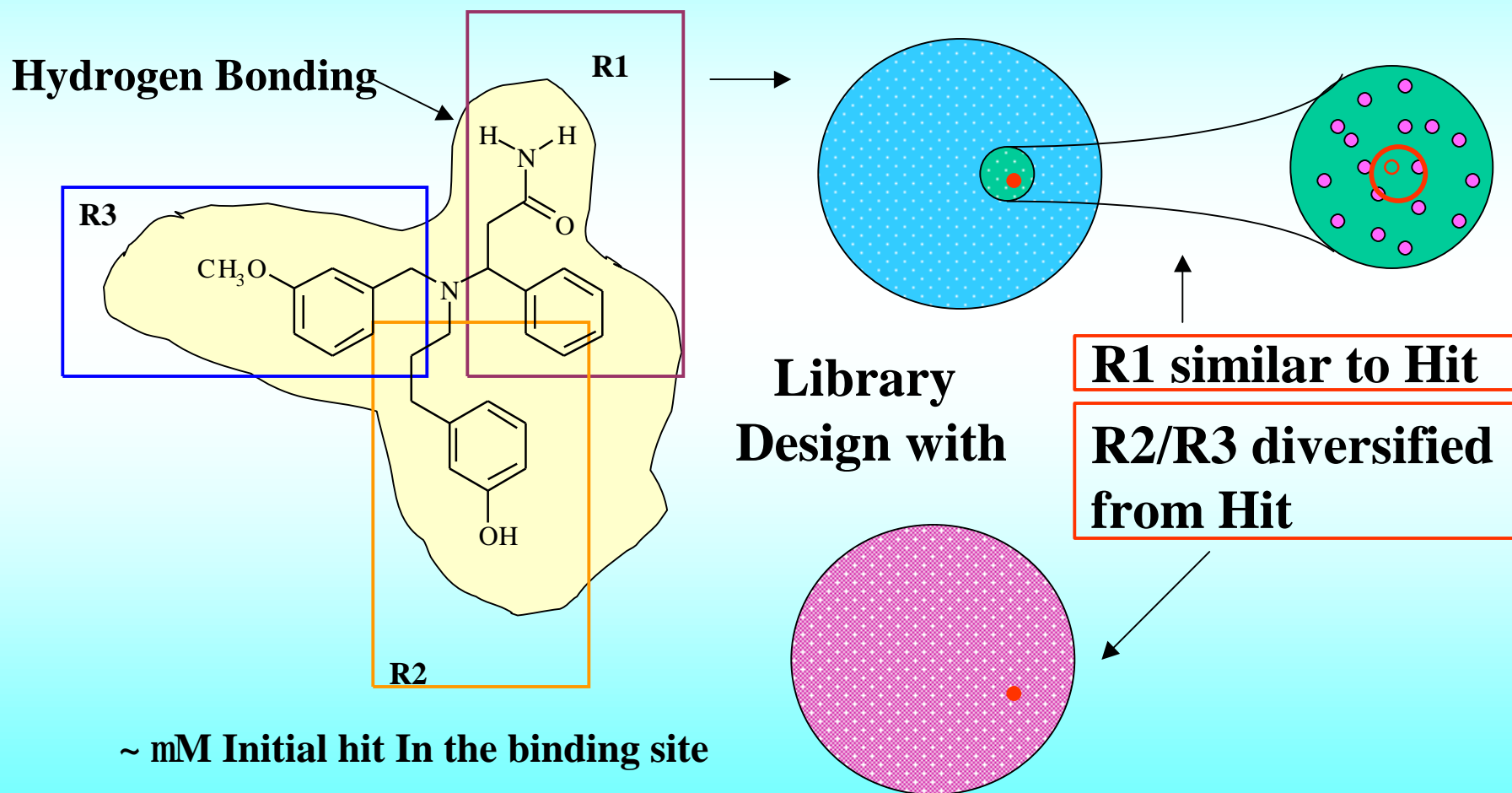
nM Lead

↕
~three good
fits to the
binding sites

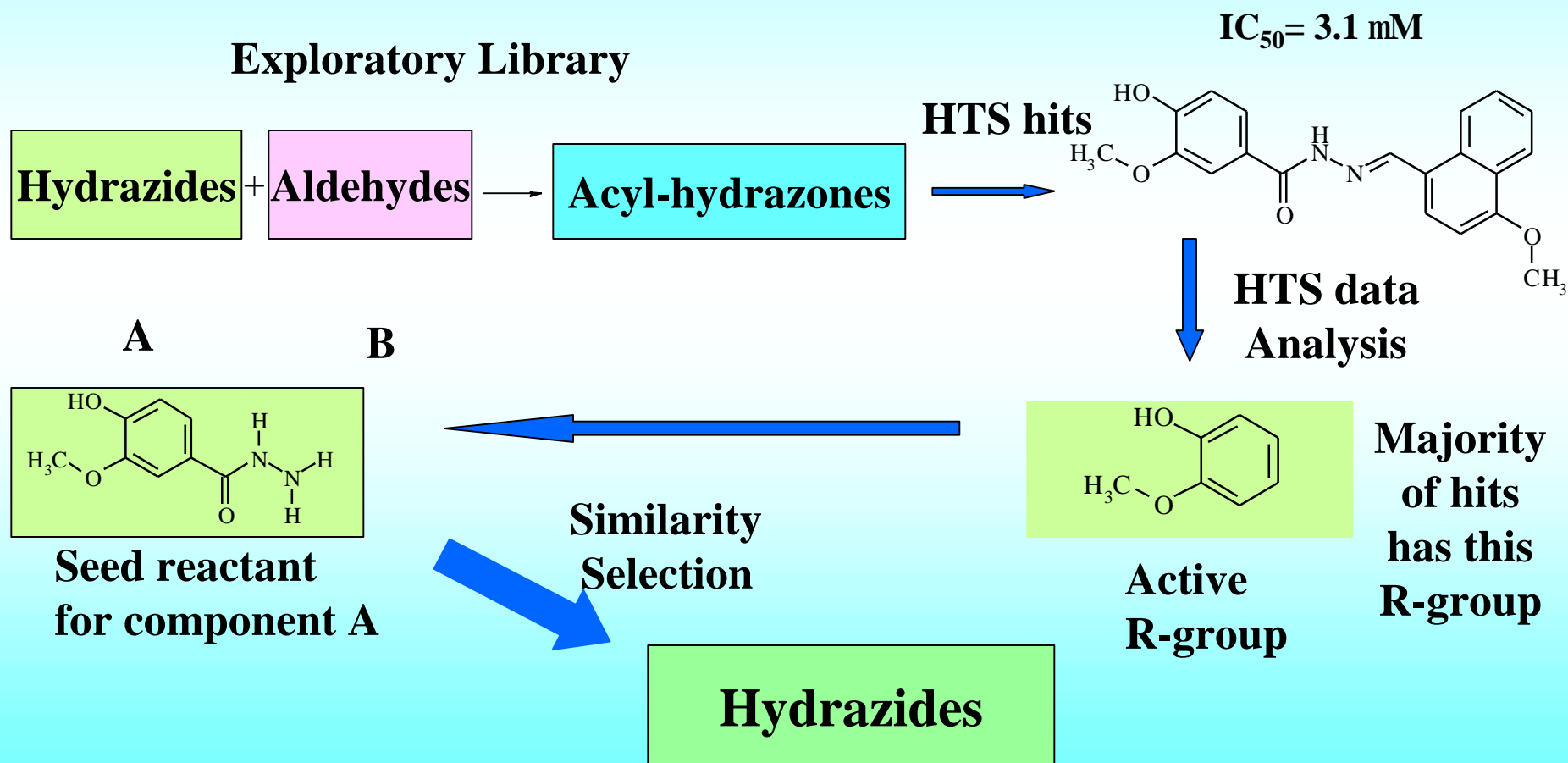
Hydrogen Bonding



R-group-based Strategies of Targeted Library Design for Lead Optimization

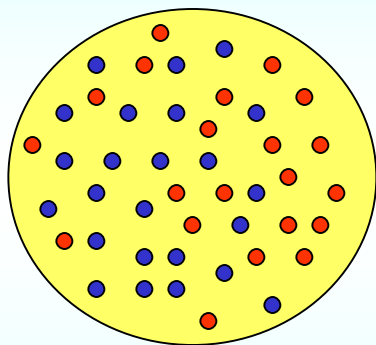


Example-Targeted Library design for Glucagon Antagonist Project



First Round Targeted Library for Glucagon Antagonist

- aldehydes for component B
Selected by Maximum
Diversity Trajectory with
• as seeds



+

Hydrazides

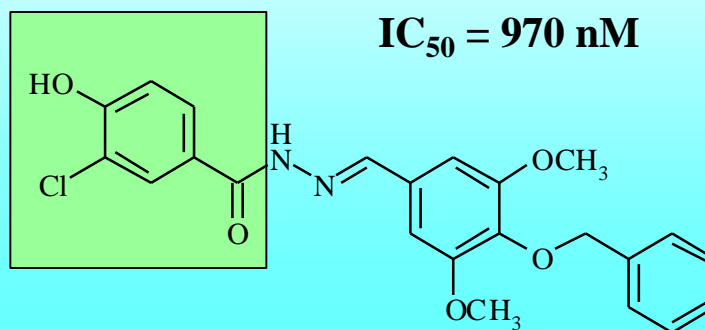
Targeted Library

- Aldehydes for component B
Used in HTS

HTS hits

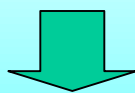
From HTS data identified
3-chloro-4-hydroxy-benzoyl
moiety

IC₅₀ = 970 nM



Remarks

- **Low dimensional RAEFV captures main features of molecules important in binding. Analogs in RAEFV space have similar interaction with target proteins;**
- **R-group-based comparison makes it possible to optimize the different parts of the lead with different strategies (similarity /diversity);**
- **Reactant-based selection scales as $S N_i$ rather than $P N_i$ of product-based selection**



Efficient and Effective Lead Optimization

Acknowledgements

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