The Spectrum of Computational Tools for VS routinely applied in ChemDiv

Also:
SPE,
MDS,
etc.

Neural-based Algorithms and other Non-linear Approaches, such as PCA, Genetic algorithm, Factor analysis, etc.

Correlation/regression analysis

molecular feature

compounds, %

ANN-score

Non-linear Mapping Techniques

3D-Pharmacophore modeling

3D-Molecular Docking

VIRTUAL SCREENING TECHNOLOGIES

TARGET-BASED DESIGN

STRUCTURE-BASED DESIGN

Recursive Partitioning

Structure Analysis

Chemogenomic-based Approaches

Clusterization Algorithms, «Trees»

GPCR ligands

HDSC inhibitors

Caspase inhibitors

Tyrosine Kinase inhibitors

Serine/threonine Kinase inhibitors

Drug Compounds

Nuclear Receptors/antagonists

Ca-channel blockers

2D-Similarity Methods and Bioisosteric Morphing

Histamine H1 Receptor antagonist

Dopamine D2 Receptor antagonist

3D-Structural Similarity

Histamine H1

Histamine H2

Dopamine D2

Adrenoceptor

95% similarity

15% similarity

90% similarity

GENETIC CODE
Our Experience in Computational Chemistry

The **Smart Mining**
Software developed in ChemDiv for virtual screening and QSAR analysis

Representative examples of books dedicated to computational chemistry with chapters by ChemDiv scientists

More than **120** scientific publications in the field of modern computational chemistry and QSAR modeling, including comprehensive reviews and focused full-text articles.
Software in ChemDiv

- ChemoSoft™ (CDRI)
- Smart Mining (CDRI)
- MolSoft ICM (MolSoft LLC)
- Cerius² (Accelrys)
- Discovery Studio (Accelrys)
- NeuroSolution (NeuroDimension)
- ISIS Base (MDL)
- AutoDock (Scripps)
- Surflex (Biopharmics)
- PyMOL (Biopharmics)
- MOE (Molecular operating environment)
- etc.
Substructure and Similarity Search

Bioisosteric Morphing

Example: Morphing of Quinazoline-like privileged structures

Focused Agrochemistry

**We have:**

- the reference database of more than 3K small-molecule compounds – known agrochemical agents;

- specific computational models successfully validated for the assessment of agrochemical activity and specificity (Kohonen- and Sammon-based mapping, Neural-nets (NN), recursive partitioning (RP), etc.);

- thematic library of more than 130 templates for synthesis with promising agrochemical activity (whole ChemDiv stock includes more than 1.5 mil. compounds with high diversity);

- **ALS-**, **ACS** and **ACCase**-specific models (3D-molecular docking approach & 3D-pharmacophore model) for the design of novel small-molecule ligands

**We can do:**

- synthesis of novel organic compounds comprehensively covered by our computational background and expert opinion;

- the related biological evaluation of compounds for agrochemical activity;

- development of novel structures with high IP potential;
The Main Focus is:

► considering agricultural ecology, select small-molecule compounds without a potentially toxic points, e.g. Cl, Br, I, P, etc.;

► searching for new antidotes (ppp) against herbicides – a new route to expand the field of known herbicide utilization – targeting new agricultures and weeds. As a good example - mefenpyr-diethyl, an antidote against fenoxaprop-ethyl (Puma compositions) as well as against lodosulfuron (Sekator), / high selectivity and low phytotoxicity;

► with regard to fungicides, ppp could also be effectively used for the reduction of a retardant effect;

► the privileged structures include: “amino acid” function mimetics, C-2 and C-3 amino alcohols, diamines as well as glycols, compounds with F and CF3. etc.;

► the related biological screening for ppp activity can be properly performed in Agrosintez
Examples of Novel Agrochemicals Registered in 2011-2012

- Colecalciferol rodenticide
- Oxathiapiprolin fungicide
- Pyrisonazole fungicide
- Isofetamid fungicide
- Pyflubumide acaricide
- Tolprocarbe fungicide
- Benzovindiflupyr fungicide
- Flometoquin insecticide
- Flupyradifurone insecticide
Ref. dataset

<table>
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<th>agro type</th>
<th>compounds</th>
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<tr>
<td>insecticide</td>
<td>648</td>
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<tr>
<td>fungicide</td>
<td>326</td>
</tr>
<tr>
<td>herbicide</td>
<td>576</td>
</tr>
<tr>
<td>total</td>
<td>1550</td>
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Molecular descriptors

<table>
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<tr>
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<th>definition</th>
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<tr>
<td>RotB</td>
<td>no. of rotatable bonds</td>
</tr>
<tr>
<td>H_acceptor</td>
<td>no. of H-bond acceptors</td>
</tr>
<tr>
<td>H_donor</td>
<td>no. of H-bond donors</td>
</tr>
<tr>
<td>Log_D</td>
<td>log of 1-octanol/water partition coeff. at pH 7.4</td>
</tr>
</tbody>
</table>

insecticide (in %, diff. 3D)

the average percentage of correct classification - 80%

Similar models have also been developed based on Sammon algorithm, RP as well as NN-based approach
Differences in the distribution of molecular descriptor values
Prominent Biotargets for Herbicides

**ALS inhibitors**
- ACCase inhibitors
- Auxin mimetics
- ACS inhibitors

**EPSPS inhibitors**
- Photosystem I/II inhibitors
- Inhibition of carotenoid biosynthesis
- DOXP synthase inhibitors
- Glutamine synthetase inhibitors
- DHP synthase inhibitors
- Inhibition of cell wall synthesis
- Uncoupling (membrane disruption)
- Inhibition of lipid synthesis (not ACCase inhibition)

**Herbicides**
- Inhibition of auxin transport
- Elongases inhibitors
- GGPP cyclase inhibitors
- PPO inhibitors
- GST stimulators
- 14-reductase inhibitors
- 4-HPPD inhibitors
- Weed cell cycle inhibitors
- PDS inhibitors
Examples of active compounds

**ACCase inhibitors**
- pinoxaden

**ALS inhibitors**
- chlorsulfuron
- flumetsulam
- triasulfuron

**Auxin mimetics**
- dicamba
- clopyralid
- 2,4-D
- aminopyralid

**Other examples**
- haloxyfop-R-methyl
- fluazifop-P-butyl
- imazaquin
Examples of active compounds

- aviglycine
- benzobicyclone
- cloquintocet-methyl
- mefenpir-diethyl
- spiroksamin
- fenaziquine
- fluthiacet methyle
- flufenacet
- quinmerak
- kvinoksifen
- famoksadon
- fludioksonil
- pyrimidifene
- tiadinil
- trineksapak-ethyl
- petoksamid
- isoxaflutole
- mefenpir-diethyl
- fenamidone
- fentrazamid
Representative Examples of Synthetic Agro-templates Suggested in ChemDiv Lib.
Presumably, FAD plays a purely structural role, but it can undergo reduction to FADH$_2$ as a side reaction of the catalytic cycle. Several sulfonylureas make contacts with the isoalloxazine ring, but in many cases these contacts are not required for sufficient binding.
Chlorsulfuron in the active binding sites of ALS (A); a detailed site composition and crucial binding points (B) / crystallographic data

Examples of related sulphonylureas

Metsulfuron methyl

Sulfometuron methyl

Tribenuron methyl

3D-overlapping

- Chlorimuron ethyl
- Chlorsulfuron
- Metsulfuron methyl
- Sulfometuron methyl
- Tribenuron methyl
Imazaquin and Chlorimuron ethyl in the ABS of ALS
(*crystallographic data*)

the inhibition constants for yeast ALS range from 3.25 nM for Chlorimuron ethyl to 127 nM for Chlorsulfuron

► the effect of active site tunnel mutations varies widely between these inhibitors. Thus, the G116S mutation in yeast ALS increases the inhibition constant for Chlorimuron ethyl by more than 1000-fold, while that for Chlorsulfuron is increased by less than 5-fold. These observations suggest that the interactions with the protein must differ among various sulfonylureas

Examples of novel ALS-targeted privileged scaffolds designed *in silico*

1. \[
\begin{aligned}
\text{D} &= \text{H, alkyl, alkenyl, etc.} \\
\text{R1, preferably:} &= \text{Alk} \\
\text{Alk} &= \text{Me, Et}
\end{aligned}
\]

2. \[
\begin{aligned}
\text{R1, R2: preferably OAlk, Alk, Hal}
\end{aligned}
\]

3. \[
\begin{aligned}
\text{R1} &= \text{H, Alk, OAlk, Hal} \\
\text{R2} &= \text{SO}_{2}\text{R, COOR, CONR}_{2}, \text{Hal, CF}_{3}, \text{etc.}
\end{aligned}
\]

4. \[
\begin{aligned}
\text{R1} &= \text{preferably OAlk, Alk} \\
\text{R2} &= \text{H, Alk} \\
\text{R3} &= \text{SO}_{2}\text{Ar/Het}
\end{aligned}
\]

5. \[
\begin{aligned}
\text{R} &= \text{OAlk, SO}_{2}\text{R, COOR, CONR}_{2}, \text{Hal, CF}_{3}, \text{etc.}
\end{aligned}
\]
A brief Insight into ACCase mechanism of action

- **ACCase** translocates to the carboxytransferase active site

- Provides the malonyl-CoA substrate for the biosynthesis of flavonoids, LCFAs and their elongation

- Inhibits carnitine transferase-I thereby blocking the transfer of FAs into the mitochondria

**ACCase**

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- Inhibits carnitine transferase-I thereby blocking the transfer of FAs into the mitochondria
The binding mode of pinoxaden

The electron density at 2.8-A resolution

Key interactions within the binding site

The binding site for pinoxaden

Overlay of the binding modes of pinoxaden and tepraloxydim

Overlay of the binding modes of pinoxaden and haloxyfop

3D ACCase Docking Model

**GOOD alignment**

Pinoxaden in the active binding site of ACCase (RSA data)

Tepraloxydim in the active binding site of ACCase (RSA data)

Orange – crystallographic data

Yellow – docking results (E=-60 kcal/mol)

Orange – crystallographic data

Yellow – docking results (E=-54 kcal/mol)
Examples of compounds with promising activity against ACCase

**CL2489** $E = -60$ kcal/mol

**CL3345** $E = -66$ kcal/mol

**Cl5932** $E = -52$ kcal/mol
3D ACS Docking Model

Inhibitors of transient state

aviglycine

GOOD alignment

key Aas:
R407
E47
R150
Y19

orange – crystallographic data
yellow – docking results (E=~34 kcal/mol)
Examples of compounds with promising activity against ACS

CL1161 $E = -56$ kcal/mol

CL6690 $E = -45$ kcal/mol

CL1161-1 $E = -45$ kcal/mol

CL3537 $E = -50$ kcal/mol
Examples of isosteric and topological analogues among ChemDiv Argo-templates

CL7718a

PGR
promotes pollination

CL0798

insecticide
ENT8184

CL3245

CL6690

affects cell division and
cell elongation, auxin

CL3318

fungicide
ICIA0858

CM0324

CM0325

Examples of isosteric and topological analogues among ChemDiv Argo-templates
acyclic analogues

CM1998
invert analogues

CM7718a

CL2582

ppp antidot

benoxacor

CL3410

isosteric morphing

CL9024

"next-in-class"

CL6788

spirot-analogues

CL7718a

CL3410

CL6788
CL1161

"pro-drug" moieties

N-O
C(O)alkyl
alkyl

R1a
R1b

H, alkyl

O

S

NH

O

N

O

R2a

"pro-drug" moieties

H, alkyl

R2a

R1a

R1b

R3a

O

C(O)alkyl

H, alkyl

H, alkyl

ppp aviglycine

CL2832

H, alkyl

R1a

R1b

H, alkyl

R2a

N-O

O

O

N

O

R2a

R1a

H, alkyl

R1a

R2a

H, alkyl

R1a

R2a

H, alkyl

CL2593

CL6690

CL2049

H, alkyl

H, alkyl

H, alkyl
We can offer:

► comprehensive *in silico* design of novel compounds using a range of modern computational approaches including 3D-molecular docking, Neural-Net modeling and 3D-pharmacophore searching;

► solid-phase as well as liquid-phase synthesis of novel compounds with high diversity in structure using a variety of traditional and combinatorial schemes;

► targeted library of small-molecule compounds ranged within 133 promising agrochemical templates selected in ChemDiv;

► analysis of patent landscape resulting in compounds with high IP

► HTS evaluation of novel compounds for agrochemical potency.
THANKS YOU!