Indexing and searching chemical structures and reactions with stereo-selectivity

Andrew Lemon PhD
• Binding is shape dependant
• Chiral Drugs
• IDBS Stereochemical descriptors
• Searching
• Reactions and Schemes
• Future Developments

IDBS provide Cheminformatics solutions
Receptor mapping is shape dependant
The rise of the Chiral Drug Industry

- “Combined US demand for chiral chemicals -- including the value of merchant sales and captive and contract production will rise 9.4 percent annually to $15.1 billion in 2005, with real demand advancing six percent per year.”
- “Pharmaceutical applications will lead growth as regulatory requirements and competitive advantages promote the development of new and re-formulated drugs containing single isomer active ingredients.”
Advantages of Chiral Drugs

• Single Isomer Compounds are more active and require lower doses and exhibit fewer side effects than racemic drugs
• Extending Patent Lifetimes – Marketing chiral versions of racemic drugs to extend patent times
The importance of tracking stereochemistry

FDA'S POLICY STATEMENT FOR THE DEVELOPMENT OF NEW STEREOISOMERIC DRUGS

- “Geometric Isomers and diastereoisomers should with the rare exception of cases where *in vivo* interconversion occurs be treated as separate drugs”
- “The stereoisomeric composition of a drug with a chiral center should be known and the quantitative isomeric composition of the material used in pharmacologic, toxicologic, and clinical studies known. Specifications for the final product should assure identity; strength, quality, and purity from a stereochemical viewpoint”
Why is this important?

- Different isomers can have very different activity

Thalidomide

Potential anti-morning sickness treatment

Note: Still racemates under physio pH

Teratogenic
Challenge to cheminformatics

• Track the chemical structures of compounds down to the enantiomeric level
• Store and represent both single enantiomers and mixtures of different diastereoisomers
• Resolve stereoisomers into different chemical entities
IDBS Chemical Representation

• Stereochemical descriptors
  – Stereocentres
    • R
    • S
    • R*S
  – Bond stereochemistry
    • E (Trans)
    • Z (Cis)
    • E*Z
Specification of stereochemistry

Carvone

Spearmint

Caraway

- Calculated from Bond Markings using CIP Rules
- Calculated from 3D Coordinates
- Assigned to stereogenic atoms
- Chiral Flag Trigger
Specification of stereochemistry

Bombykol

Sex Pheromone of Codling Moth
(E,Z)-10,12-Hexadecadien-1-ol

- Calculated from Bond arrangements
- Assigned to stereogenic bonds
- Chiral Flag Trigger
Representation of Diastereoisomers

SSSS Tetracycline

SRRS Tetracycline
Representation of mixtures of diastereoisomers

- Synthesis may generate specific mixtures of diastereoisomers
- \( n \) stereogenic centers generates \( 2^n \) stereoisomers

![Tetracycline](image)

- 16 possible enantiomers of Tetracycline RRRR to SSSS
Representation of mixtures of diastereoisomers

- Advanced stereochemical descriptors
  - R/S coupled descriptors
  - S/R coupled descriptors
  - R*S
- R/S R/S S S represents 2 diastereoisomers RRSS and SSSS
- R*S R*S R/S S/R represents 8 possible diastereoisomers
Searching

- Three level searching capability
  - Ignore
  - Relative (Bond Marks only)
  - Stereochemical
- All stereochemical descriptors can be used for searching
- Look for specific enantiomers or ranges of diastereoisomers
- Exact Match
- Substructure Searching
- SuperStructure Searching
Deployment

- IDBS Chemical Technology
  - Oracle DataCartridge (NT/2K, Solaris7,8, Linux, SGI)
- IDBS Chemistry Client API
- StructureBase
- ReactionBase
Indexing and Searching Reactions

• Stereoselective Reactions

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• Stereo descriptors available for describing reactions
  • Describe mixtures of possible products
Indexing and Searching Reaction Schemes

- Stereoselective Reaction Schemes

1. ![Reaction Scheme 1]

2. ![Reaction Scheme 2]

3. ![Reaction Scheme 3]

4. ![Reaction Scheme 4]

- Search across multiple reactions in a reaction scheme
  - With stereoselectivity and transformation mapping
Summary

• Use of stereochemical descriptors
• Representation of diastereoisomers
• Searching with stereoselectivity
• Deployment
• IDBS Offer Cheminformatics Solutions
Future Developments

• Stereoselective Combinatorial Libraries
• Stereoselective Enumeration Services

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