



ChiroSolve Screen Kits

Achieve Chiral Resolution Early

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Common Methods for Chiral Separation

Chiral technologies

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graph TD; A[Chiral technologies] --> B[Industry Standard]; A --> C[Asymmetric]; A --> D[Biological]; B --> E[Diastereomeric crystallization]; B --> F[Chiral pool]; B --> G[Chromatographic resolution]; C --> H[Asymmetric synthesis]; C --> I[Asymmetric Catalysis]; D --> J[Kinetic resolution]; D --> K[Biocatalysis];
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Industry
Standard

Asymmetric

Biological

Chiral pool

Asymmetric
synthesis

Asymmetric
Catalysis

Kinetic
resolution

Biocatalysis

**Diastereomeric
crystallization**

Chromatographic
resolution

Chirosolve products and services are based on Diastereomeric Crystallization (most common technique used for Commercial Manufacturing)

Diastereomeric crystallization challenges

- **Optimal Separation Condition:** Choosing the right set of resolving agents and solvents out of 1000s of combinations is impossible
- **Manual Screening:** Time consuming, monotonous, and error-prone
- **Project risks:** Unbiased screening under same experimental conditions is essential to ensure optimum results

ChiroSolve Kits - Features/Benefits

- **Quick Results:** 384 reactions done in parallel, results within 24 hours
- **Consistent results:** Elimination of human errors through full automation
- **Exhaustive screening** of most commercially viable resolution conditions
- **Standardized kits** can be used for robotic manipulation, vials and rack made of polypropylene; chemically inert and withstand extreme temperature

ChiroSolve Kits - Features/Benefits

- **Applicability:** Designed to screen any racemate against reagents and solvents within 24 hours for optimum resolution
 - Racemate can be acid, base, alcohol, aldehyde, ketone or amino acid
- **“Commercializability”:** Criteria for choosing reagents and solvents:
 - Literature precedent for optimum crystallisation
 - Compliance/traceability
 - Availability and cost
 - Environmental/FDA regulations (i.e. no acetone due to shipping issues)
- **“Robotizability”:** Conveniently designed for easy robotic manipulations for high throughput labs
 - Kits come with pierceable seal or cap-mat to accommodate direct injection of racemate by liquid dispensers

Types of Kits

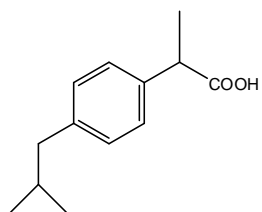
- **Standard Kits**: Need 3 mmol of racemate per kit; 4 kits per racemate
- **Strong Acid Kits**: Additional kits for weakly base racemates: 2 kits
- **Glass Vial Kits**: For use with HPLC; need only 0.1 mmol racemate per kit; 4 kits per racemate

Kits have 2 components:

- 96-vial kit containing chiral resolving agents
- 96-well plate containing Chirosolve solvents

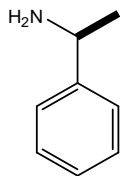
Diastereomeric Crystallization

(+/-)Ibuprofen



+

(-) phenethyl amine

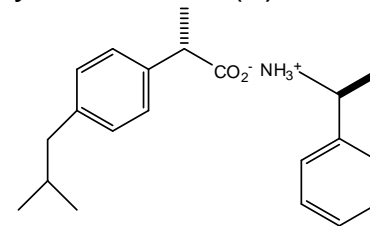


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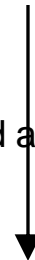
2-propanol

=

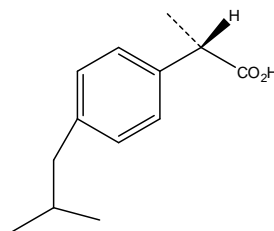
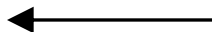
Diastereomeric salt
(-) crystalline and (+) filtrate



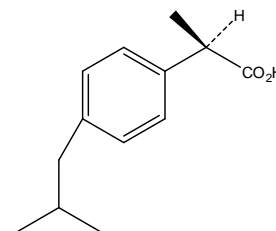
Treat with strong acid and separate out



Scale-up to identify
of re-crystallizations
needed to get target purity



(-)isomer (crystalline)



(+)isomer (filtrate)

How to use ChiroSolve Kits

Reaction Flow of Solid Racemate Kit

ChiroSolve, Inc. 



1 Use the ChiroSolv kit for solid racemate



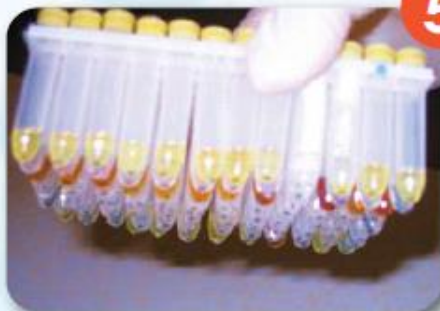
2 Add racemate and remove the "Transfer" solvent



3 Add ChiroSolv solvents



4 Heat the kit until vials contain homogeneous solution



5 Cool the homogeneous content until crystals form



6 Identify vials with crystals for further analysis

ChiroSolve Screen can be used

- **To obtain higher purity when other chiral separation methods are used during development stage**
 - **Citalopram** for treatment of depression, is a racemic mixture whose entire inhibitory activity resides in the S (+)-enantiomer. The key intermediate was purified by using (+)-di-p-toluoyl tartaric acid and recrystallizing salt twice in medium polar solvent
- **During pilot studies; proof of concept stage**
 - **Lyrica** by Pfizer, the initial route used equimolar quantity of S-Mandelic acid to resolve the desired enantiomer to obtain multi-kilo quantities of Lyrica; before enzymatic route was developed
- **To identify crystallization conditions during manufacturing**
 - **Paroxetine** by Novo Nordisk's subsidiary, Ferrosan
 - **Clopidogrel or Plavix** is marketed by sanofi-synthlebo and BMS

Success stories

- **Discovery group** from **big pharma** unable to separate out enantiomers; ChiroSolve Screening services were able to give them 4 combinations of resolving agents and solvents that gave good crystals. As a result, they were able to complete the project successfully.
- **Discovery startup** needed a very quick turn-around to explore different separation methods for IP prosecution. Using ChiroSolv kits, they were able to quickly explore the methods without having to compromise quality, leading to patentable results.
- **Process chemistry** group from **major Bio-pharma** used ChiroSolv kits to identify higher purity, and in the process, found a better method that reduced re-crystallization steps from 4 to 3.
- **CRO firm** was able to choose the best derivatisation route that would give optimum end results in terms of enantiomeric purity and yield



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