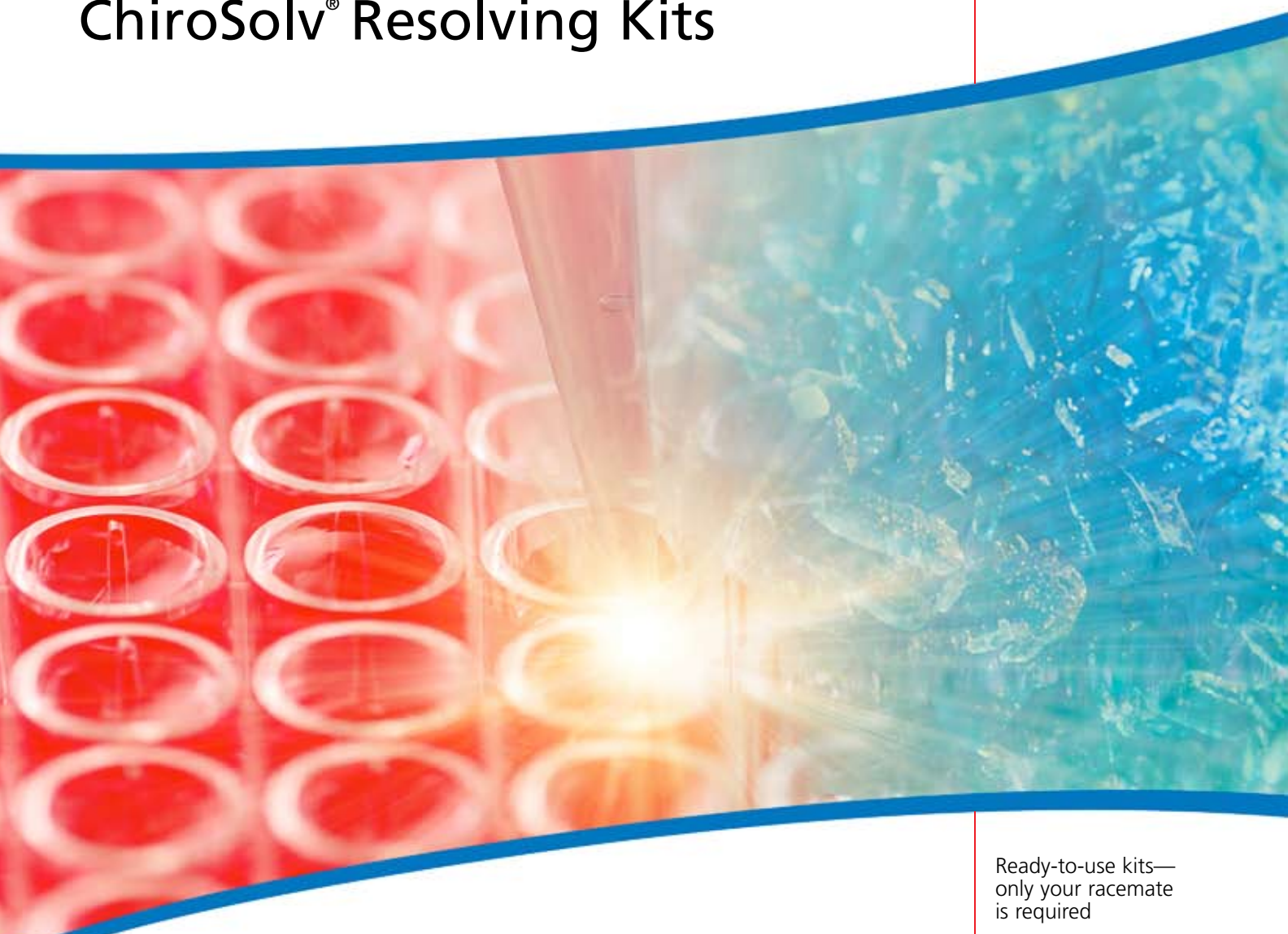


ChemFiles

Supplement I, 2008



ChiroSolv[®] Resolving Kits



Sigma-Aldrich and ChiroSolve, Inc. are partnering to bring facile and rapid chiral resolution to you.

Ready-to-use kits—
only your racemate
is required

Accurate and
consistent results

Increased likelihood of
project success

Tremendous time and
money savings

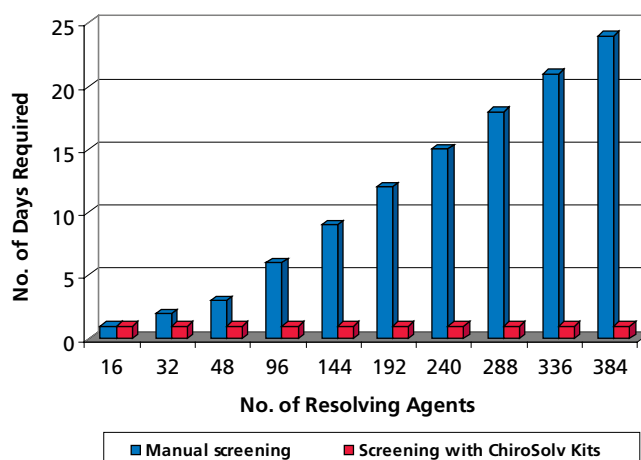
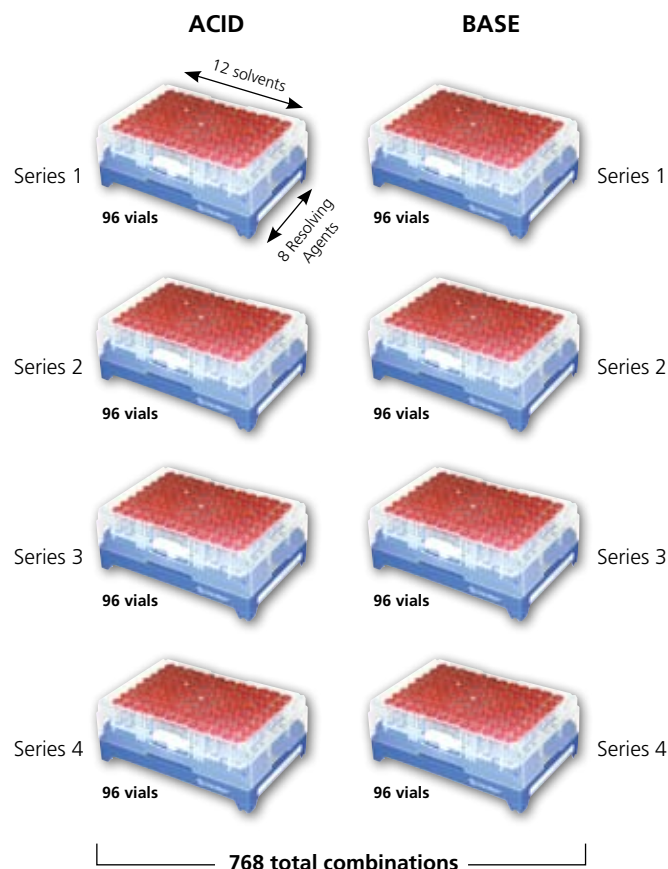
Facile and Rapid Chiral Resolution with ChiroSolv® Kits

Sigma-Aldrich® is pleased to partner with ChiroSolve, Inc. to offer, through an exclusive distribution agreement, a series of ready-to-use kits for chiral resolution of racemates. These kits allow scientists to quickly screen resolving agents and solvents against a racemate to find the optimum combination, as well as to optimize reaction conditions in order to separate a racemic mixture into its constituent enantiomers. They can be used for racemic acids, bases, alcohols, amino acids, aldehydes, and ketones.

There are four Acid Series kits and four Base Series kits, available individually or as the complete acid or base set. Each individual kit is in a ready-to-use, 96-vial, high-throughput format that allows the entire analysis to be performed inside the kit without removing any vials. The kit is made of polypropylene material that can withstand extreme temperatures (-20 to 120 °C), allowing the entire kit to be placed in an oven or ice bath without damage.

The kits can be supplied in two different formats, either as kits for solid racemates or kits for liquid racemates. The kits for liquid racemates provide calibrated quantities of a unique resolving agent and solvent combination in each vial. The racemate can then simply be added to start the screening process. The kits for solid racemates allow the researcher to dissolve the racemate into a volatile solvent and then dispense the resultant solution into each vial containing a resolving agent. The volatile solvent is evaporated and the prepared screening solvents are then dispensed from a separate plate into each vial.

Resolving agents are chosen with manufacturing use in mind; they are relatively inexpensive and recoverable in high yield after the resolution is complete. Using all four kits in an acid or base series, 384 resolving agent-solvent combinations can be explored for a single racemate. The high-throughput format allows scientists to identify within 24 hours the optimum resolution process which might otherwise take over 2 months.



Types of Kits

Acid

Acid Series 1, 2, 3 and 4 include a distinct group of chirally pure acids and are used to resolve racemic bases and amino acids (some pre-processing is required for amino acids). Examples of resolving agents in the acid kits are:

- (-)-Camphoric acid
- (+)- and (-)-Camphorsulphonic acid
- (+)- and (-)-Dibenzoyltartaric acid
- (-)-Malic acid
- (+)- and (-)-Mandelic acid
- (+)-Lactic acid
- (+)- and (-)-Tartaric acid

Base

Base Series 1, 2, 3 and 4 include a distinct group of chirally pure bases or amines and are used to resolve racemic acids, alcohols, aldehydes, and ketones (some pre-processing is required for the latter three). Examples of resolving agents in the base kits are:

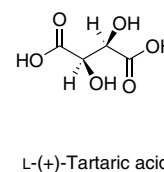
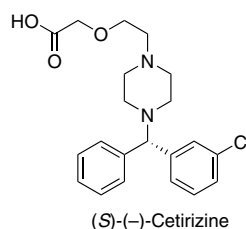
- (-)-2-Aminobutanol
- (-)-Brucine
- (-)-Cinchonidine
- (+)-Cinchonine
- (+)-Dehydroabietylamine
- (+)- and (-)-Methylbenzylamine
- (+)-Quinidine
- (-)-Quinine

Case Studies with ChiroSolv® Kits

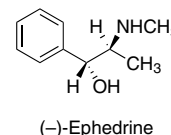
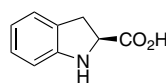
ChiroSolv Kits have been used by several pharmaceutical, fine chemical, and contract R&D companies to reduce their product development time and increase speed to market. Two examples of the application of this technology for determining the ideal solvent/resolving agent combination for the resolution of key compounds are shown.

In the first case, a key advanced intermediate in the synthesis of (*S*)-(-)-cetirizine, a non-sedative histamine H-1 receptor antagonist used for the treatment of allergies, was screened against the kits in the Acid Series. The combination of L-(+)-tartaric acid in methanol was determined to provide the maximum optical purity after its chiral resolution.

In the second example, (-)-ephedrine in isobutanol was determined to be the ideal combination for resolving indoline-2-carboxylic acid to yield the (*S*)-(-)-enantiomer, which is an intermediate for ACE inhibitors such as trandolapril and perindopril. For this compound, the racemic mixture was screened against the three ChiroSolv Kits in the Base Series.



Case Study 1



Case Study 2

How Do ChiroSolv® Kits Work?

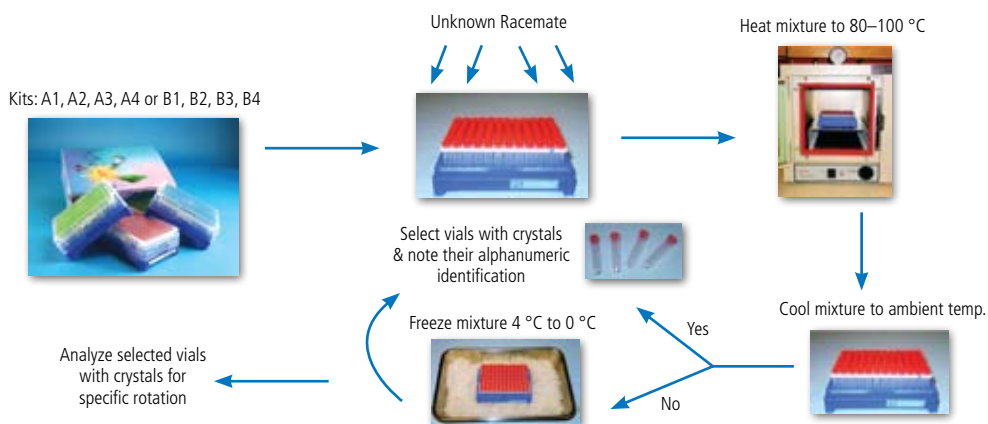
ChiroSolv Kits use the method of diastereomeric crystallization, a process that chemically separates enantiomers in a racemic mixture by complexation with an enantiopure acid or base, resulting in a mixture of diastereomeric salts. These salts have different chemical and physical properties, which allow their separation. This well-established technology competes favorably with newer techniques such as asymmetric synthesis, biocatalysis, enzyme resolution, kinetic resolution, or chiral chromatography.

One major advantage of diastereomeric crystallization is that the procedure scales up easily for manufacturing purposes. Today around 65% of chiral products are made using this technique. Examples:

- Paroxetine is a selective serotonin reuptake inhibitor developed by Novo Nordisk's subsidiary, Ferrosan, and licensed to GlaxoSmithKline. It is sold as the hydrochloride salt under the name Paxil® for the treatment of depression,

anxiety, and obsessive-compulsive disorder. It is prepared by resolution using (–)-di-*p*-toluoyl-L-tartaric acid.

- Setraline is an antidepressant that inhibits the uptake of serotonin in the central nervous system and is sold by Pfizer under the name Zoloft®. Diastereomeric crystallization of the racemate by (*R*)-mandelic acid is used in its preparation.
- 2-Amino-5-methoxytetralin is an intermediate in the synthesis of N-0923 (Nagase & Co., Ltd., Japan), a potent dopamine D₂ agonist, effective against Parkinson's disease (currently in clinical trial). This intermediate is resolved by diastereomeric salt formation with (*S*)-mandelic acid. The undesired isomer is then racemized and reused in an iterative process.
- In the synthesis of AG-7404 (Pfizer), a key intermediate was resolved by (–)-norephedrine. The final compound was obtained by the combination of diastereomeric and enzymatic resolution.

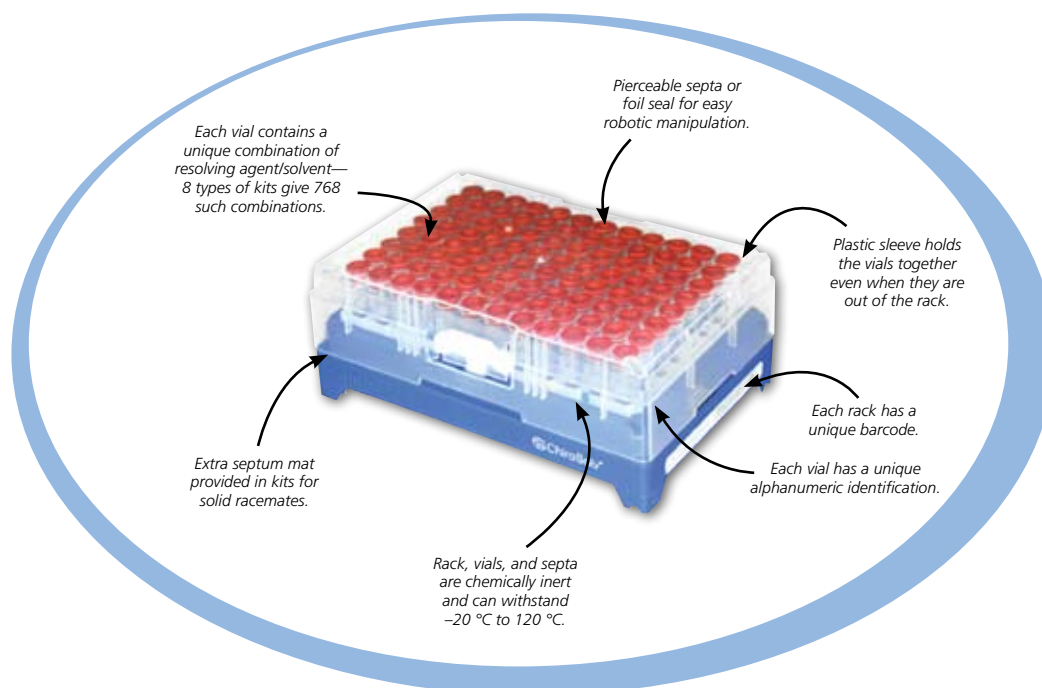


How to Use ChiroSolv Kits

1. Choose the right type of kit (Acid Series 1, 2, 3, 4 or Base Series 1, 2, 3, 4) depending on the identity of the racemate.
2. If the racemate is an alcohol, amino acid, aldehyde or ketone, you may need to pre-process the racemate (refer to chirosolve.com/typesofkit.html for details).
3. Add 0.03 mmol of your racemate to each of the 96 vials. Depending on the availability of the dispensing autostation and the racemate type (liquid or powder), you may need to remove the seal on the vials. Note that the seal is pierceable to accommodate direct injection of racemate by liquid dispensers.
4. In an oven or water bath, heat the rack along with its vials to 80 °C (optimum temperature for most of these experiments) or until the mixture becomes homogeneous.
5. Allow the kit to cool to ambient temperature. If required, further cool it to 4 °C or 0 °C to observe crystallization. Vials with crystals are considered positive results and should be examined further.
6. Often, more vials with positive results can be obtained using standard crystal initiation techniques. Vials with no crystals even after this effort are considered negative results.
7. Separate out the positive test results and note down their alphanumeric identification.
8. Liberate the enantiomers from their diastereomeric salts and analyze by optical rotation. Typically, only one or two vials will show maximum optical purity.

Features

- Eight types of ready-to-use disposable kits providing a total of 768 resolving agent–solvent combinations.
- Very little amount of racemate required (less than 3 mmol per kit).
- Concentrations of the resolving agents are calibrated to give accurate results and optimal crystallization.
- Pierceable seal allows easy racemate dispensing; vials held together by a plastic ring so that vials can be picked up and inspected together for crystal formation.
- Easy to follow, step-by-step instructions and results charts.
- Conveniently designed for easy robotic manipulations.
- Kits and vials have unique identification (barcode or alphanumeric) for cross-referencing.
- Long shelf life at room temperature (2 years).



Product Information for Liquid Racemates

Prod. No.	Prod. Name/Description
681431	ChiroSolv Resolving Kit, Acid Series 1
681423	ChiroSolv Resolving Kit, Acid Series 2
681415	ChiroSolv Resolving Kit, Acid Series 3
699217	ChiroSolv Resolving Kit, Acid Series 4
700363	ChiroSolv Resolving Kit, Complete Acid Series
681407	ChiroSolv Resolving Kit, Base Series 1
681393	ChiroSolv Resolving Kit, Base Series 2
681377	ChiroSolv Resolving Kit, Base Series 3
699241	ChiroSolv Resolving Kit, Base Series 4
700371	ChiroSolv Resolving Kit, Complete Base Series

Product Information for Solid Racemates

Prod. No.	Prod. Name/Description
698881	ChiroSolv Resolving Kit, Acid Series 1
699527	ChiroSolv Resolving Kit, Acid Series 2
698873	ChiroSolv Resolving Kit, Acid Series 3
699225	ChiroSolv Resolving Kit, Acid Series 4
700398	ChiroSolv Resolving Kit, Complete Acid Series
699233	ChiroSolv Resolving Kit, Base Series 1
698938	ChiroSolv Resolving Kit, Base Series 2
698946	ChiroSolv Resolving Kit, Base Series 3
698954	ChiroSolv Resolving Kit, Base Series 4
700401	ChiroSolv Resolving Kit, Complete Base Series

For more information, please visit sigma-aldrich.com/chirosolv

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