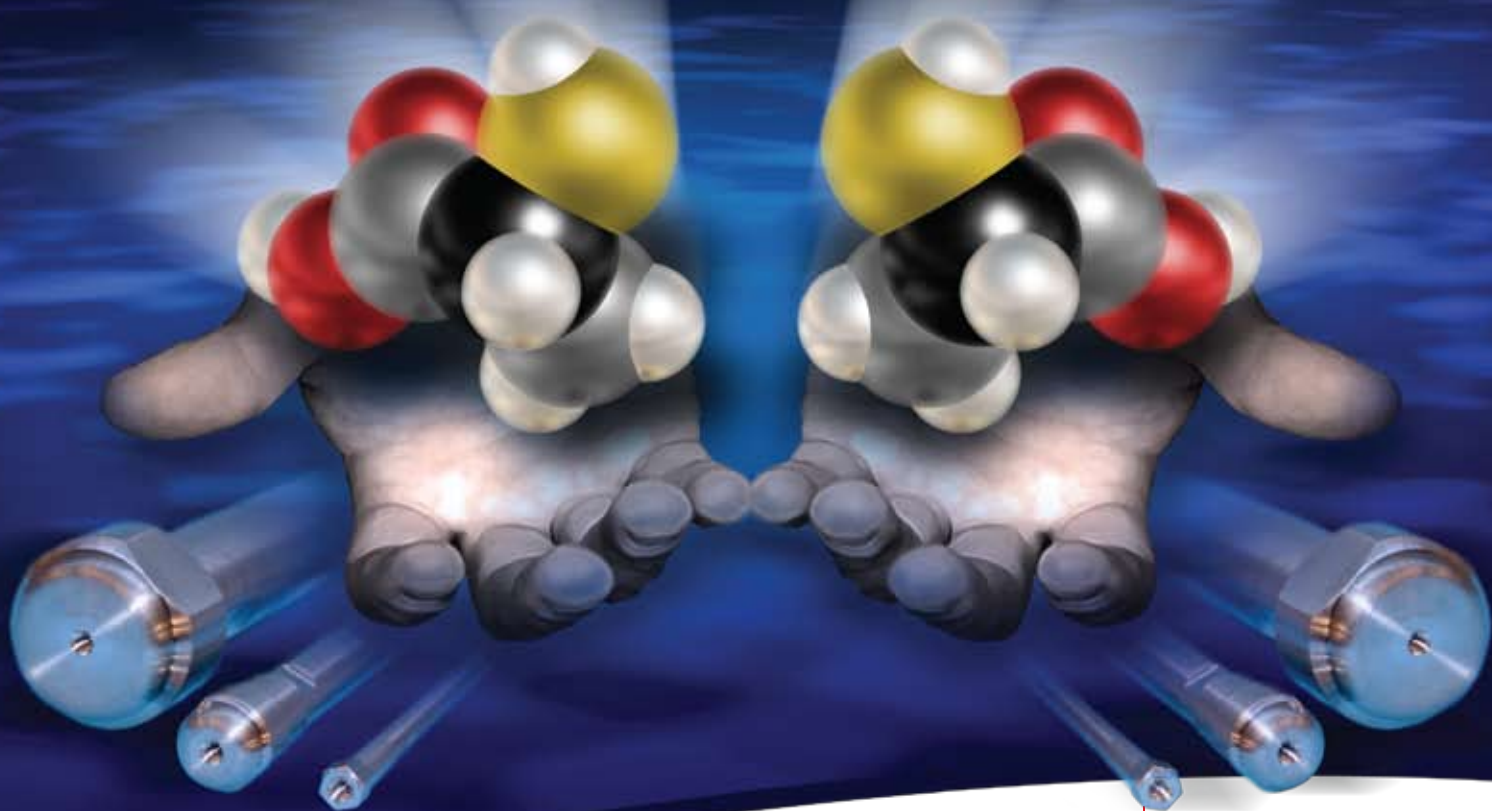


Astec CHIROBIOTIC

Macrocyclic Glycopeptide-Based Chiral
HPLC Phases



Columns for versatile,
robust chiral HPLC and
LC-MS separations

Aqueous and non-aqueous
separations on the same
column

No solvent or additive
memory effects

Wide applicability, especially
suited to polar and ionizable
compounds

Predictable scale-up from
analytical to prep



Astec CHIROBIOTIC

Versatile Chiral HPLC and LC-MS Separations of Polar, Ionizable and Neutral Compounds

Astec CHIROBIOTIC™ CSPs (chiral stationary phases) interact with polar, ionizable and neutral analytes via multiple molecular interactions. This versatility means that the same Astec CHIROBIOTIC column can be successfully used in a variety of mobile phases, a significant benefit over CSPs that operate only in a single mode, normal or reversed-phase, for example, and must be dedicated to those mobile phase systems. However, the most interesting feature of Astec CHIROBIOTIC CSPs is the presence of ionic interactions, which allows them to be used in polar ionic and reversed-phase modes for sensitive LC-MS operation.

Key application areas

- Drug Discovery – High enantioselectivity, fast screening protocols, scalability to prep, reproducibility for reliable methods, polar and non-polar analytes
- Organic Synthesis – Compatible with all HPLC solvents to optimize sample solubility, fully scalable to prep
- Bioanalytical, Drug Metabolism – High throughput, MS-compatibility, aqueous samples, short run times, rugged columns
- Amino Acid and Peptide Analysis – Resolves underivatized natural and synthetic chiral amino acids and peptides, different selectivity and higher preparative capacity than C18 for achiral amino acids

What is the Astec CHIROBIOTIC family?

Developed originally by Advanced Separations Technologies (Astec), the Astec CHIROBIOTIC family comprises highly enantioselective CSPs based on macrocyclic glycopeptides that have been bonded through multiple covalent linkages to high purity silica particles. Astec CHIROBIOTIC CSPs offer flexibility in choice of mobile phase conditions, both aqueous and non-aqueous, and are ideal for analytical and preparative separations of neutral, polar and ionic compounds.

How do Astec CHIROBIOTIC CSPs separate enantiomers?

Astec CHIROBIOTIC CSPs offer six different types of molecular interactions: ionic, H-bond, π - π , dipole, hydrophobic, and steric. They also possess multiple inclusion sites that influence selectivity based on the molecular shape of the analyte. The optimization of enantiomer resolution is achieved by changing the mobile phase to leverage the types and relative strengths of the various interactions.

What makes Astec CHIROBIOTIC CSPs unique?

The bonded macrocyclic glycopeptide itself (Figure 1), in terms of its morphology, molecular composition, and multiple covalent linkages to the silica surface, is what makes Astec CHIROBIOTIC CSPs unique and gives them significant and valuable benefits over other CSPs. The truly differentiating feature of Astec CHIROBIOTIC CSPs is the presence of ionic interactions. These interactions are unique to Astec CHIROBIOTIC CSPs and are responsible in large part for their desirable retention characteristics toward polar and ionizable analytes in aqueous and non-aqueous solvents.

How do the Astec CHIROBIOTIC CSPs differ?

The various Astec CHIROBIOTIC phases share the benefits of robustness, flexibility in mobile phase options, ionic interactions, compatibility with polar compounds and LC-MS, and preparative scalability. However, Astec CHIROBIOTIC CSPs differ in selectivity, primarily because of their differing number and types of interaction sites, and the number, type and accessibility of ionic sites in the bonded macrocyclic glycopeptide.

The Astec CHIROBIOTIC CSP Family

Astec CHIROBIOTIC CSPs are based on 5, 10 or 16 μ m, high-purity, porous silica gel. They differ in the nature of the bonded macrocyclic glycopeptide and resulting enantioselectivity.

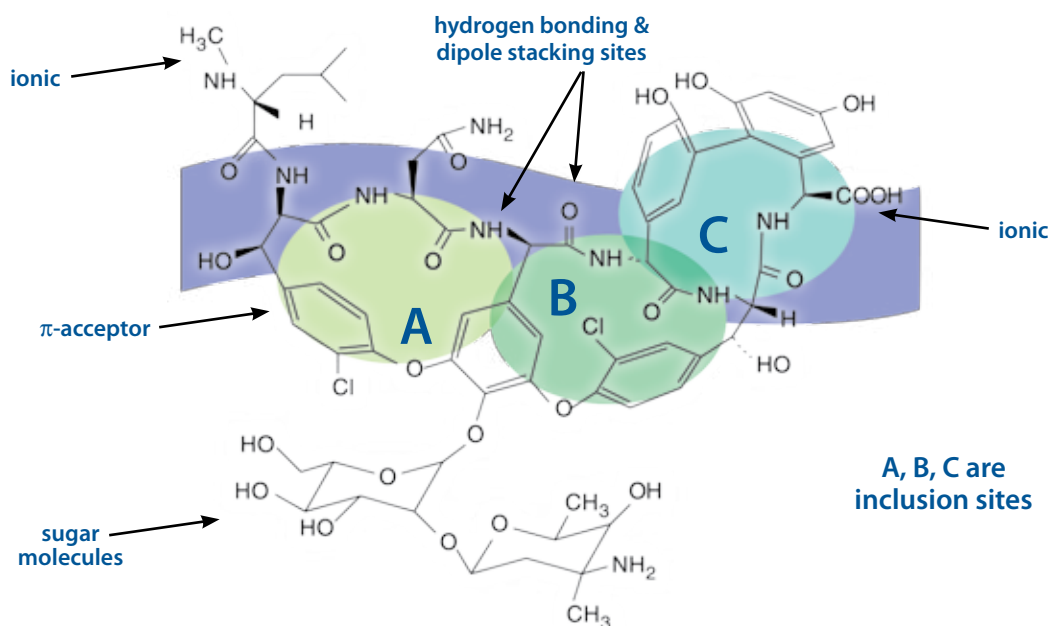
*Astec CHIROBIOTIC V and T differ from V2 and T2, respectively, in their bonding chemistry that gives them different selectivity and preparative capacity for certain classes of analytes.

- **Astec CHIROBIOTIC V and V2*** – Vancomycin
- **Astec CHIROBIOTIC T and T2*** – Teicoplanin
- **Astec CHIROBIOTIC R** – Ristocetin
- **Astec CHIROBIOTIC TAG** – Teicoplanin Aglycone

Key features of Astec CHIROBIOTIC CSPs:

- Aqueous and non-aqueous separations on the same column – Astec CHIROBIOTIC CSPs have H-bond, ionic, dispersive, π - π , dipole stacking, steric, and inclusion mechanisms, usually multiple types of interactions per analyte.
- Wide applicability – Applications cover a very broad range of compound classes, with the different Astec CHIROBIOTIC CSPs showing complementary selectivity.
- LC-MS compatibility – The wide choice of mobile phases makes Astec CHIROBIOTIC CSPs ideal for LC-MS, where analyte ionization and detection sensitivity are of critical concern.
- No solvent or additive memory effect – The same Astec CHIROBIOTIC column can be used alternately in polar, reversed-phase and normal phase solvents without damage, unlike cel-lulosic and amylosic phases that require dedicated operation.
- Robust columns with long lifetimes – Each macrocyclic glyco-peptide molecule is linked to the silica surface via four or five covalent bonds for exceptional stability and long column life. They are designed to withstand high pressure and flow rates, as well as rapid changes in mobile phase conditions.
- Solvent choices maximize sample solubility – Astec CHIROBIOTIC CSPs operate in highly-aqueous and non-aqueous polar mobile phases for polar compound solubility. They also operate in normal phase mobile phases to maximize solubility of non-polar compounds. Astec CHIROBIOTIC CSPs are compatible with all organic solvents.
- Excellent preparative scalability and capacity – From narrowbore to prep, separations on Astec CHIROBIOTIC are fully scalable, even with polar analytes. By relying on pri-marily aqueous eluents, the use and disposal of toxic organic solvents are eliminated. Additionally, preparative methods in the non-aqueous polar ionic mode are just as easy to process as normal phase solvents.
- Fast kinetics for speed and efficiency – The kinetics of the molecular interactions between the analyte and the Astec CHIROBIOTIC CSP are fast, providing efficient separations and relatively short retention times.
- Orthogonal selectivity to other CSPs – The six Astec CHIROBIOTIC CSPs are different from each other, and from other types of CSPs to offer choices in enantioselectivity, like reversal of elution order.

Figure 1. Proposed Structure of Vancomycin-based Astec CHIROBIOTIC V and V2



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Incorporating Astec CHIROBIOTIC CSPs into Your Chiral Column Screening Protocol

We recommend that you incorporate Astec CHIROBIOTIC into your routine screening protocol. Experience has shown that one or more of the Astec CHIROBIOTIC CSPs, particularly V2, T and TAG, will perform the majority of chiral separations. Even if other CSPs give adequate resolution, an Astec CHIROBIOTIC CSP may allow use of mobile phases that are better suited to your sample and detection method, or the Astec CHIROBIOTIC method may be faster, more efficient, or more robust. An Astec CHIROBIOTIC method may also have advantages from a preparative standpoint in terms of solvent selection and sample capacity.

For developing a new chiral HPLC method, we have created and use routinely in our laboratories a simple and rapid chiral column screening protocol (Table 1). It is important to keep in mind that

a single Astec CHIROBIOTIC column possesses multiple types of molecular interactions that are different in each of the four distinct modes. The same column can be exposed to all of the conditions outlined in the screening protocol shown in Table 1 without any change or loss of performance. This versatility is just one advantage that Astec CHIROBIOTIC CSPs have over other CSPs.

The four Astec CHIROBIOTIC CSPs we recommend in the screening protocol are available in 25 cm or 10 cm column kits. Also, you can further expand the screening field by incorporating Astec CYCLOBOND™ bonded cyclodextrin and Astec P-CAP™ chiral polymer CSPs into your screening protocol to accommodate other types of compounds not covered by the routine screen.

Table 1. The Astec CHIROBIOTIC Screening Protocol

columns: Astec CHIROBIOTIC V2, T, R, and TAG
procedure: Method development follows a simple strategy that tests polar ionic, polar organic, reversed-phase, and normal phase modes.

Separation Mode	Description	Types of Compound	Screening Mobile Phase	Parameters to Optimize
Polar Ionic	Polar organic solvents (CH ₃ OH or CH ₃ CN) containing small amounts of acid and base or salt	Acids, Bases, Zwitterions	(100:0.1:0.1, v:v:v) CH ₃ OH:Acetic Acid: Triethylamine	Change acid-base ratio, change the type of acid or base, add a volatile salt (test different ammonium salts)
Reversed-Phase	Typical RP eluents, water or buffers with CH ₃ OH or CH ₃ CN	Acids, Bases, Zwitterions, Neutrals	(30:70) CH ₃ CN:20mM Ammonium Acetate, pH 4.0	Change the % and type of organic modifier, adjust pH, buffer type, and ionic strength
Polar Organic	Polar organic solvents without ionic additives	Neutrals	100% Ethanol	Use other polar organic solvents or blends
Normal Phase	Non-polar organic solvents with polar solvent modifiers	Neutrals	(30:70) Ethanol:Heptane	Increase % of polar modifier, change both solvents

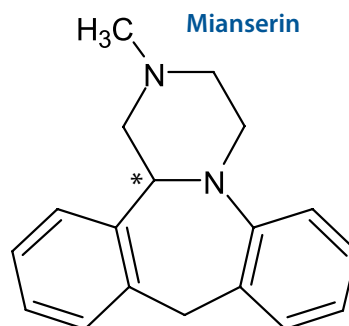
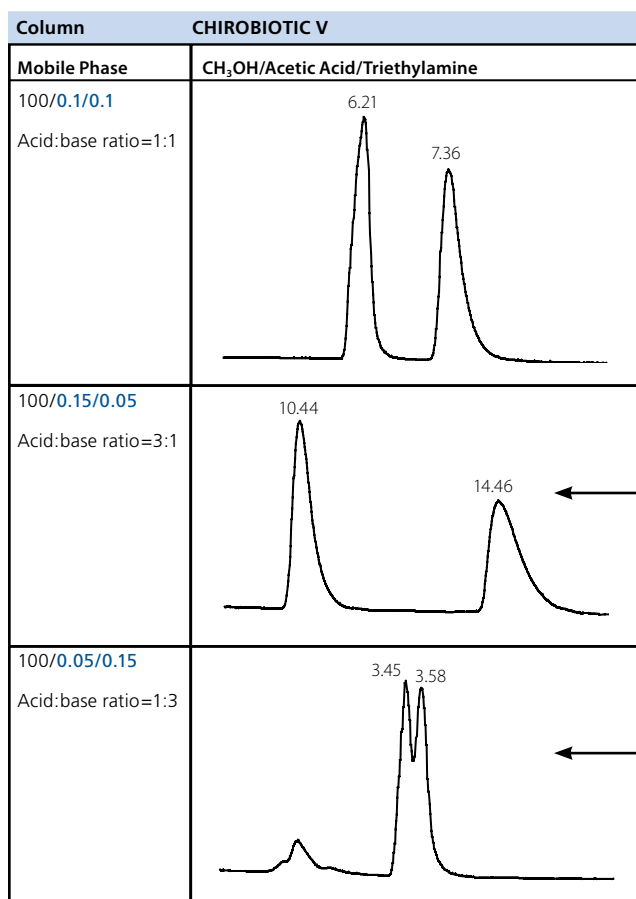
Method Optimization: Acid-Base Ratio, Temperature, and Flow Rate in Polar Ionic Mode

Using Astec CHIROBIOTIC CSPs in the polar ionic mode has the highest probability of success. Optimizing resolution usually involves changing the contribution to retention of ionic interactions between the analytes and functional groups in the macrocyclic glycopeptide structure by:

- Changing the ratio of acid to base (Figure 2)
- Adding a soluble, volatile salt (instead of the acid and base) directly to the methanol

The acid, base, or salt that is ultimately selected is based on its compatibility, with the detection method (e.g. LC-MS), sample solubility, and whether the separation will be scaled up to preparative.

Figure 2. Demonstration of Polar Ionic Mode Mechanism: Effect of Acid:Base Ratio



High acid: Nitrogen on mianserin is positively charged, while -COOH group on vancomycin is negatively charged: strong ionic interaction

High base: Nitrogen on mianserin group is free amine, but -COOH group on vancomycin is fully charged: weak ionic interaction



Astec CHIROBIOTIC: Ideally Suited for LC-MS of Polar, Ionizable and Neutral Compounds

Each of the various ionization sources has an optimal set of mobile phase conditions. Outside this set, ionization may be suppressed with resulting loss in sensitivity. Astec CHIROBIOTIC phases are uniquely able to operate across all mobile phase systems. CSPs that are limited to normal phase operation, like many cellulosic and amylosic CSPs, reduce the options in detection methods.

ESI – Operate Astec CHIROBIOTIC CSPs in reversed-phase and unique polar ionic modes.

APCI – Operate Astec CHIROBIOTIC CSPs in polar ionic mode.

APPI – Operate Astec CHIROBIOTIC CSPs in normal phase mode.

Typical polar ionic mobile phases are methanol with low concentrations (0.1 – 0.001%) of volatile salts, like ammonium acetate or ammonium formate. Figures 3 and 4 show examples of Astec CHIROBIOTIC CSPs for LC-MS in reversed-phase and polar ionic mode mobile phases, respectively.

In addition to mobile phase compatibility, the allowable high flow rates and short columns make them ideally suited to fast MS applications.

Astec CHIROBIOTIC columns can be used in conjunction with HybridSPE™-PPT plates to enhance sensitivity by completely removing endogenous proteins and phospholipids. This approach was used to resolve the enantiomers of clenbuterol on an Astec CHIROBIOTIC T column in Figure 4.

Figure 3. ESI-MS of Ketoprofen on Astec CHIROBIOTIC R in Reversed-phase Mode

column: Astec CHIROBIOTIC R, 15 cm x 2.1 mm, 5 µm particles (13019AST)
mobile phase: (30:70) CH₃OH:20 mM ammonium acetate, pH 5.6
flow rate: 0.2 mL/min.
det.: ESI(-)
temp.: 35 °C
analyte: Ketoprofen

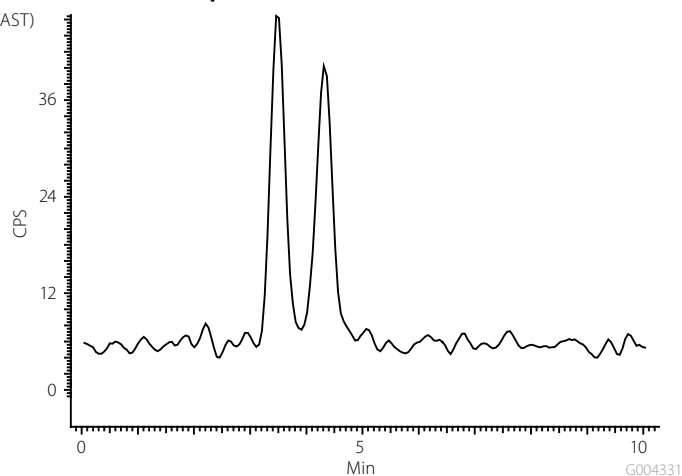
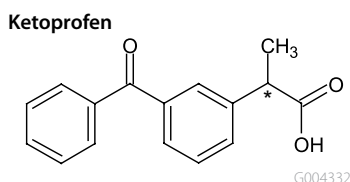
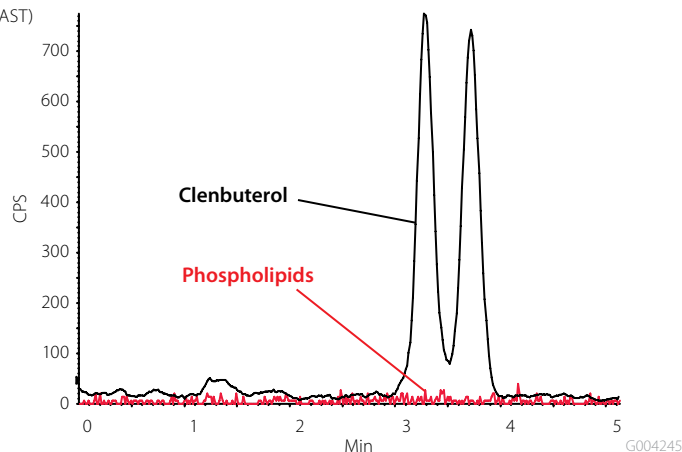
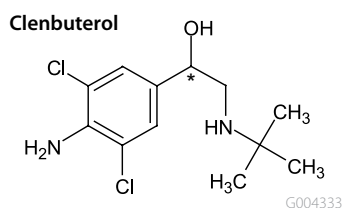


Figure 4. ESI-MS of Clenbuterol Extracted from Plasma on Astec CHIROBIOTIC T in Polar Ionic Mode

column: Astec CHIROBIOTIC T, 10 cm x 2.1 mm, 5 µm particles (12018AST)
mobile phase: 10 mM ammonium formate in CH₃OH
flow rate: 0.3 mL/min.
det.: ESI(+)
temp.: 30 °C
analyte: Clenbuterol in rat plasma (10 ng/mL)



Unique Polar Ionic Mode

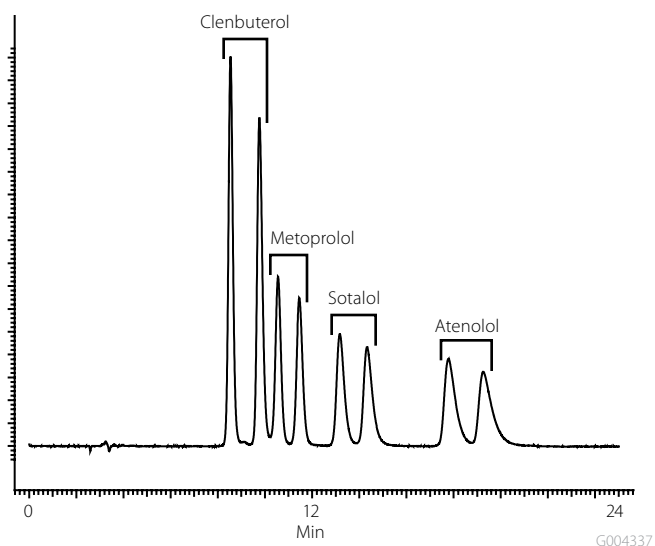
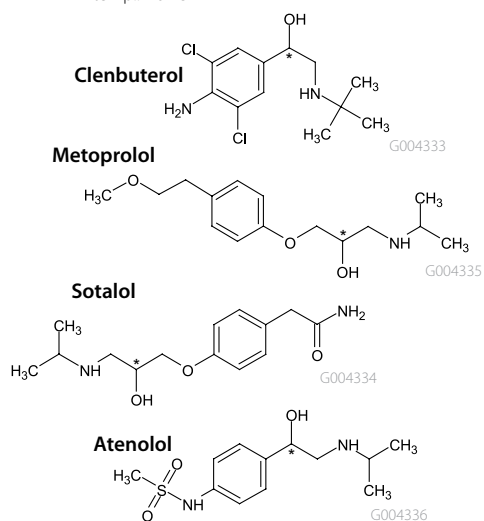
A valuable feature of Astec CHIROBIOTIC CSPs, the novel and very versatile polar ionic mode is popular because its mobile phases are polar organic solvents containing volatile additives that are ideally suited for preparative and LC-MS applications. An

example is shown in Figure 5. Additionally, compared to normal phase separations, the polar ionic mode has speed, efficiency, and sensitivity advantages, all valuable assets for LC-MS.



Figure 5. Beta-Receptors on Astec CHIROBIOTIC T in Polar Ionic Mode

column: Astec CHIROBIOTIC T, 25 cm x 4.6 mm, 5 μ m particles (12024AST)
mobile phase: 15 mM ammonium formate in CH_3OH
flow rate: 1 mL/min.
det.: UV at 220 nm
temp.: 25 $^\circ\text{C}$





Multi-modal Interactions Permit Use in Aqueous and Non-aqueous Solvents

All Astec CHIROBIOTIC CSPs possess multiple interaction sites on the same column. Changing the mobile phase affects the relative strength of specific types of interactions. The power and flexibility of multi-modal Astec CHIROBIOTIC CSPs are demonstrated in Figures 6 through 10. The vancomycin-based Astec CHIROBIOTIC CSPs were used successfully in four different modes.

Polar Ionic Mode

A valuable feature of Astec CHIROBIOTIC, the novel and very versatile polar ionic mode mobile phase system is desirable because of its high volatility and beneficial ionization effect for LC-MS (Figure 6).

Reversed-phase Mode

Also highly suitable for LC-MS and polar analytes, reversed-phase (RP) is a mode familiar to all chromatographers. Astec CHIROBIOTIC CSPs have RP character and can be used in a wide range of buffers and solvents (Figure 7).

Polar Organic Mode

Enantiomers of polar neutral analytes have been successfully separated on Astec CHIROBIOTIC in the polar organic mode where the mobile phase is typically a polar organic solvent or solvent blend. Reaction mixtures, even in pyridine, can be run on Astec CHIROBIOTIC in this mode (Figure 8).

Normal Phase Mode

Normal phase chiral separations are desirable to maintain solubility of hydrophobic compounds and when analyzing reaction mixtures in non-polar organic solvents. Astec CHIROBIOTIC CSPs have the flexibility to operate in normal phase mode. The same column can be used with normal phase and polar/aqueous solvents and additives without memory effects (Figure 9).

Figure 6. Polar Ionic Mode

column: Astec CHIROBIOTIC V2, 25 cm x 4.6 mm, 5 μ m particles (15024AST)
mobile phase: 15 mM ammonium formate in CH₃OH
flow rate: 1 mL/min.
det.: UV at 230 nm
temp.: 25 $^{\circ}$ C
analyte: Fluoxetine

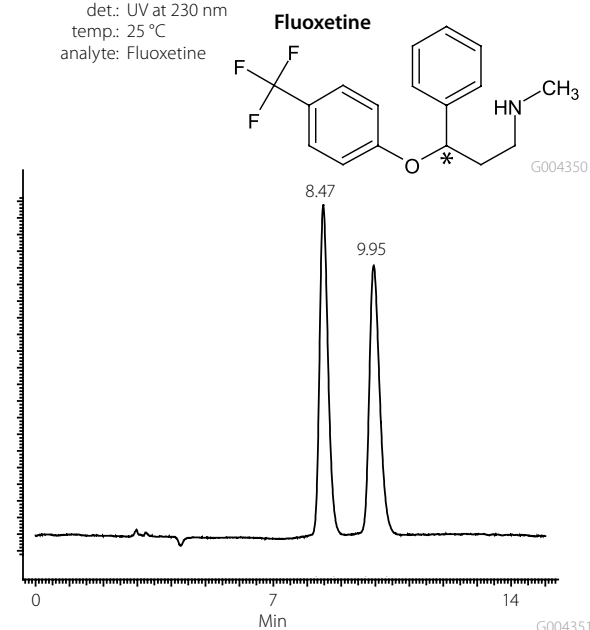


Figure 7. Reversed-phase Mode

column: Astec CHIROBIOTIC V, 25 cm x 4.6 mm, 5 μ m particles (11024AST)
mobile phase: (30:70) CH₃CN:5 mM ammonium acetate, pH 4.1
flow rate: 1 mL/min.
det.: UV at 254 nm
temp.: 25 $^{\circ}$ C
analyte: Warfarin

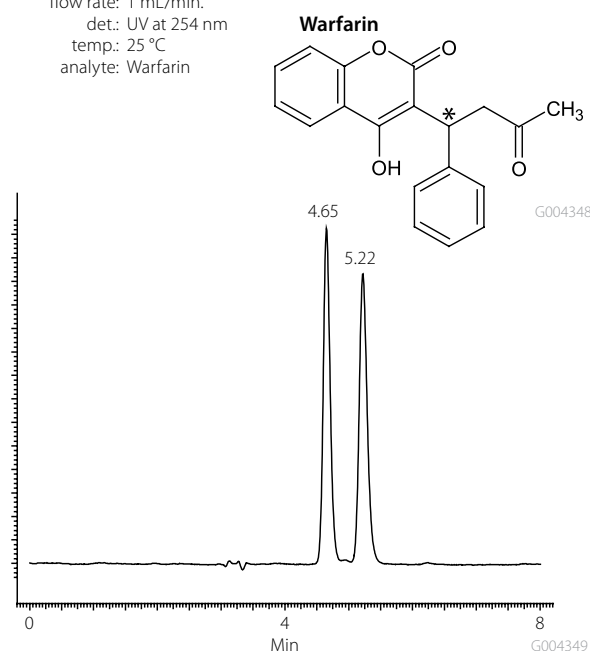


Figure 8. Polar Organic Mode

column: Astec CHIROBIOTIC V2, 25 cm x 4.6 mm, 5 μ m particles (15024AST)
mobile phase: CH₃OH
flow rate: 1 mL/min.
det.: UV at 230 nm
temp.: 25 $^{\circ}$ C
analyte: Thalidomide

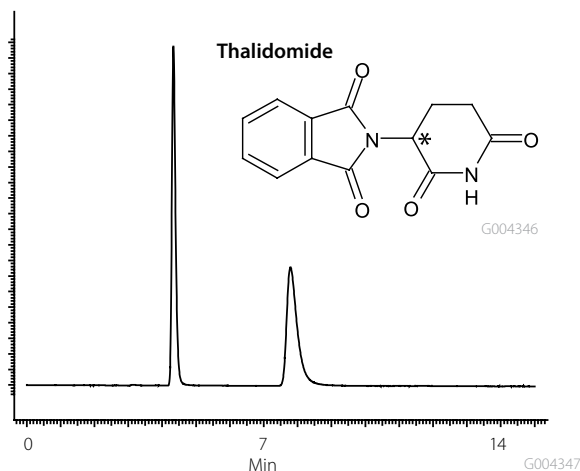
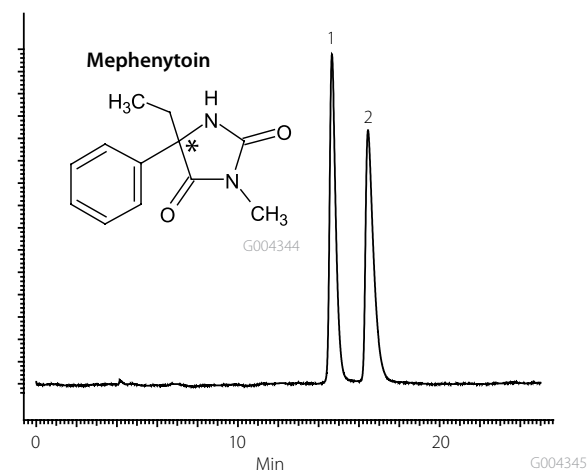


Figure 9. Normal Phase Mode

column: Astec CHIROBIOTIC V, 25 cm x 4.6 mm, 5 μ m particles (11024AST)
mobile phase: (95:5) hexane:ethanol
flow rate: 1 mL/min.
det.: UV at 205 nm
temp.: 25 $^{\circ}$ C
analyte: Mephénytoin



Preparative Applications Using Astec CHIROBIOTIC CSPs

- Scalability across all Astec CHIROBIOTIC particle sizes
- Low retention times give high throughput

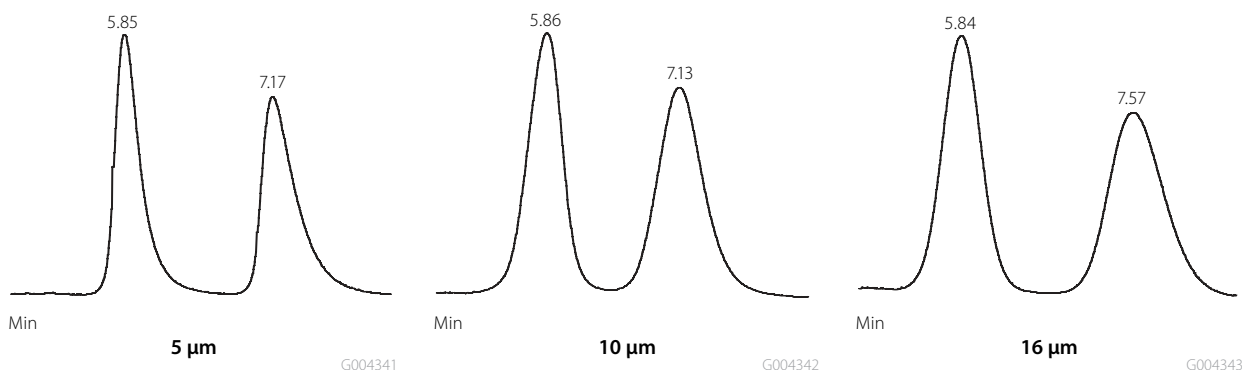
Astec CHIROBIOTIC columns can be used in all preparative HPLC techniques, including elution and recycle chromatography, mass-directed prep, SFC, and simulated moving bed (SMB). Scale-up is highly predictable because the same bonded phase chemistry is employed across all particle sizes. Multiple covalent bonds attach the Astec CHIROBIOTIC macrocyclic glycopeptides to the silica surface, meaning no CSP ligand will contaminate the product.

Preparative separations on Astec CHIROBIOTIC columns often have speed and efficiency benefits over other CSPs. In terms of loading capacity, a 25 cm x 21.2 mm column has medium to high loadings, from a few mg to over 300 mg per injection.

Preparative separations on Astec CHIROBIOTIC are reproducible and scalable. Figure 10 shows the separation of phenylalanine isomers in reversed-phase mode on columns packed with 5, 10, and 16 μ m particles of Astec CHIROBIOTIC T.

Figure 10. Scalability Across Astec CHIROBIOTIC CSP Particle Sizes

column: Astec CHIROBIOTIC T, 25 cm x 4.6 mm
mobile phase: (50:50) ethanol:water
flow rate: 0.9 mL/min.
det.: UV at 220 nm





Preparative Applications (contd.)

A significant advantage of Astec CHIROBIOTIC for preparative applications is the fact that the mobile phase can be chosen to optimize sample solubility – a critical preparative consideration. The examples here show preparative Astec CHIROBIOTIC separations in three different mobile phase systems.

Preparative Reversed-phase and Polar Ionic Modes

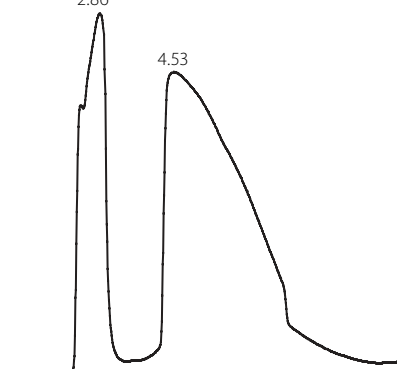
Preparative separations in reversed-phase and polar ionic mode solvents have benefits over normal phase preparative separations in terms of solvent safety and waste disposal costs. Figure 11 shows the use of Astec CHIROBIOTIC TAG in a preparative separation in polar ionic mode.

Preparative Polar Organic Mode

Figure 12 shows the analytical and preparative separations of thalidomide enantiomers on Astec CHIROBIOTIC T. The analytical scale gave an α value of 3.35 in 100% methanol and a retention time under 10 minutes. However, since thalidomide is fairly insoluble in pure methanol, it was possible to add 20% dioxane to the mobile phase to increase solubility 3.5-fold while still achieving the necessary separation.

Figure 11. Preparative Separation on Astec CHIROBIOTIC TAG in Polar Ionic Mode

column: Astec CHIROBIOTIC TAG, 25 cm x 21.2 mm, 5 μ m particles (14044AST)
mobile phase: 0.1% ammonium acetate in CH_3OH
flow rate: 35 mL/min.
det.: UV at 300 nm
throughput: 20 mg/g CSP/hr.
load: 200 mg in 6 mL
analyte: N-Acetyl Tryptophan

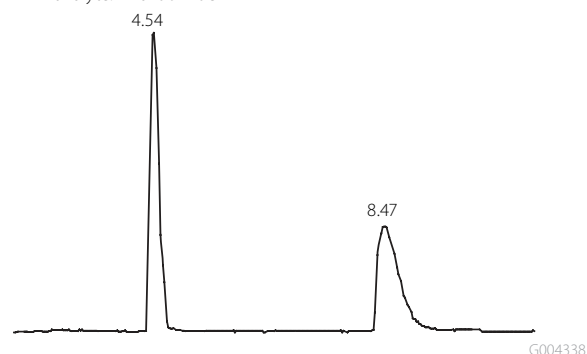


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Figure 12. Sample Solubility Considerations in Preparative

Analytical Scale

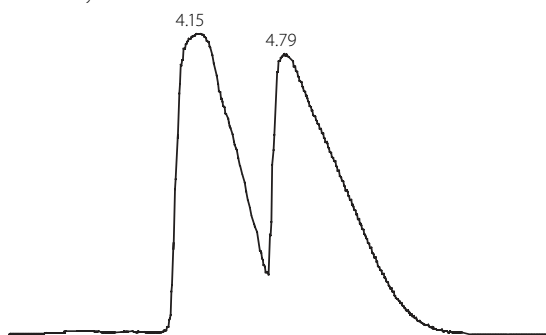
column: Astec CHIROBIOTIC V, 25 cm x 4.6 mm, 5 μ m particles (11024AST)
mobile phase: CH_3OH
det.: UV at 293 nm
flow rate: 1 mL/min.
analyte: Thalidomide



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Prep Scale

column: Astec CHIROBIOTIC V, 25 cm x 21.2 mm, 5 μ m particles (11044AST)
mobile phase: (80:20) CH_3OH :dioxane
det.: UV at 313 nm
flow rate: 20 mL/min.
load: 70 mg in 12 mL
analyte: Thalidomide



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Chiral Services: Column Screening and Small-Scale Purification

Consult Supelco to obtain a quotation for our expert services for chiral column screening (HPLC and GC), method development and optimization, as well as isolation of up to 10 grams of purified enantiomer.

The complete listing of our chiral HPLC and GC columns can be found at sigma-aldrich.com/chiral, our corporate chiral web portal, where you can view our other products for chiral chemistry, like chiral catalysts, building blocks, mobile phase additives, derivatization reagents and more.



Astec CHIROBIOTIC V and V2

Bonded Macrocylic Glycopeptide:	Vancomycin
Chiral Centers:	18
Sugar Moieties:	2
Inclusion Cavities:	3

Separates a wide variety of secondary and tertiary amines in the polar ionic mode. Have many of the separation characteristics of protein-based stationary phases but with exceptional stability and much higher sample capacity. Astec CHIROBIOTIC V2 and V differ in the chemistry used to bond the glycopeptide to the silica, which gives them differences in selectivity.

Astec CHIROBIOTIC T and T2

Bonded Macrocylic Glycopeptide:	Teicoplanin
Chiral Centers:	23
Sugar Moieties:	3
Inclusion Cavities:	4

These CSPs have resolved all of the known beta-blockers and dihydrocoumarins and many other compound classes. Generally reproduces chiral crown ether or ligand-exchange for amino acid separations. Astec CHIROBIOTIC T2 and T differ in the chemistry used to bond the glycopeptide to the silica, which gives them differences in selectivity.

Astec CHIROBIOTIC TAG

Bonded Macrocylic Glycopeptide:	Teicoplanin Aglycone
Chiral Centers:	8
Sugar Moieties:	0
Inclusion Cavities:	4

The removal of the three sugar moieties enhances resolution of many of the amino acids (alpha, beta, gamma, and cyclic). Astec CHIROBIOTIC TAG has shown remarkable selectivity for sulfur-containing molecules, such as sulfoxides and the amino acids methionine, histidine, and cysteine. Neutral molecules, like oxazolidinones, hydantoins, and diazepines, have shown enhanced resolution and, more remarkably, in single-solvent systems like methanol, ethanol, and acetonitrile. Some acidic molecules have also shown increased selectivity.

Astec CHIROBIOTIC R

Bonded Macrocylic Glycopeptide:	Ristocetin A
Chiral Centers:	38
Sugar Moieties:	6
Inclusion Cavities:	4

The presence of amines in the ristocetin structure makes it a good choice when screening acidic compounds.

Astec CHIROBIOTIC Product Listing

For more information and to review our complete offering of Astec CHIROBIOTIC columns, please visit sigma-aldrich.com/chiral

Method Development Kits

ID (mm)	Length (cm)	Cat. No.
4.6	10	10300AST - One each of Astec CHIROBIOTIC V2, T, TAG and R
4.6	25	10305AST - One each of Astec CHIROBIOTIC V2, T, TAG and R

Astec CHIROBIOTIC Columns*		V	V2	T	T2	TAG	R
ID (mm)	Length (cm)	Cat. No.	Cat. No.	Cat. No.	Cat. No.	Cat. No.	Cat. No.
5 µm							
2.1	15	11019AST	15019AST	12019AST	16019AST	14019AST	13019AST
2.1	25	11020AST	15020AST	12020AST	16020AST	14020AST	13020AST
4.6	5	11021AST	15021AST	12021AST	16021AST	14021AST	13021AST
4.6	10	11022AST	15022AST	12022AST	16022AST	14022AST	13022AST
4.6	15	11023AST	15023AST	12023AST	16023AST	14023AST	13023AST
4.6	25	11024AST	15024AST	12024AST	16024AST	14024AST	13024AST
10	25	11034AST	15034AST	12034AST	16034AST	14034AST	13034AST
10	50	11036AST	15036AST	12036AST	16036AST	14036AST	13036AST
21.2	25	11044AST	15044AST	12044AST	16044AST	14044AST	13044AST
10 µm							
4.6	25	11124AST	15124AST	12124AST	16124AST	14124AST	13124AST

*Other column dimensions, including guard columns and preparative dimensions, are found on our website or by inquiring to techservice@sial.com.

TRADEMARKS:

Astec CHIROBIOTIC, CYCLOBOND, HybridSPE, P-CAP – Sigma-Aldrich Biotechnology LP

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