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2005 Product CATALOG

Synthesis Solutions and Optimization

Initiator™ Microwave Synthesis Systems

Advancer

Biotage Microwave Vials

Biotage PathFinder

Applications Corner

Flash Purification Solutions and Optimization

FLASH™, Syntage™ and Samplet™ Cartridges

Discovery-scale FLASH Systems and Modules

SP™ Flash Purification Systems

Quad™ Parallel Purification Systems

Development-scale FLASH Chromatography Systems

Parallex Flex® HPLC Systems

FLASH-AC™ Activated-Carbon Cartridges

Production-scale FLASH Systems

Kiloprep® Preparative HPLC Systems

Biotage



Biotage

2005 Product Catalog

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Blending Technology



Working together—Today pharmaceutical chemists throughout the world rely on Biotage products as part of their daily workflow. Data shows that chemists have performed more than 900,000 microwave syntheses and 1.7 million flash purifications using Biotage products. As the innovators of microwave synthesis technology and cartridge based flash purification, we have set the industry standard for speed, safety and ease of use.

The new Initiator™ microwave synthesizer and SP1™ flash purification systems from Biotage each perform significant roles in the drug discovery process. Small enough to fit side-by-side in a fume hood, these instruments work together to reduce drug discovery cycle-times and improve success rates.

The Biotage consumable line includes microwave vials and flash chromatography cartridges custom engineered to deliver maximum performance.

Four optimum microwave vial sizes allow chemists to migrate from milligrams to grams without re-optimization. Durable and safe these vials are manufactured from contaminant free glass capable of withstanding pressures of 20 bars (ca 300 psi). Biotage FLASH+ cartridges are available in a variety of sizes and medias to provide selectivity choices for optimal purifications. Patented design accommodates five different loading techniques and withstands pressures up to 100 psi for faster flow rates and increased throughput.

Biotage products range from discovery through clinical trials and large-scale production. We offer application expertise and personal customer support, customizing solutions to meet the needs of customers. Biotage will continue providing new and innovative tools to meet today's research and development challenges.



Customer Support and Service

1-Point Support™, The Answer to All Your Questions

Support and Service

1-Point Support™

The answer to all your questions

Biotage is ready to assist you through specialists with years of preparative chromatography and synthesis experience. Our experts frequently visit customers and attend conferences to expand the Biotage knowledge base. This gives us the ability to offer customized solutions in the following areas.

The Biotage 1-Point Support Philosophy

Our service and support mission is to offer our customers a superior quality of service through our broad support superstructure, which is reached through a single point of customer contact, our 1-Point Support team. This approach goes beyond simply providing product repair or replacement service. It is a customer-centered philosophy that provides the answer to all your questions. In fact, each member of our support team is capable of supplying comprehensive solutions for your questions concerning software, hardware and applications issues; when you contact our 1-Point Support Team your inquiries are resolved swiftly and efficiently, saving you valuable time. If we cannot answer your question immediately, let us find solutions and quickly bring them to you. Most importantly, we are dedicated to building long-term relationships with customers through quality service and timely customer support.

Scale-up

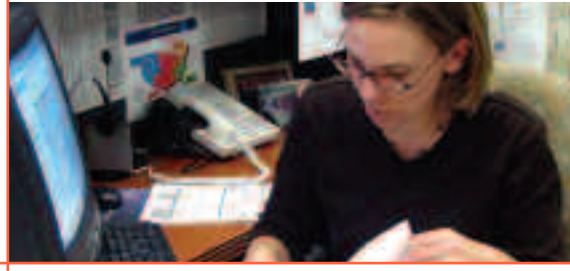
Our products and knowledge base support your progression from research to production scale.

Training and Workshops

Courses on improving purification and synthesis with Biotage systems and products are offered for new or advanced users and include hands-on training with user-supplied samples.

Instrument Training Plans

Part Number	Description	Instrument
SER-FLEX-TRAIN	3-day training course	Parallex Flex systems
SER-FLEX-INSTL	Installation and Start-up	Parallex Flex systems
SER-QUAD3-INSTL	Installation/Training	Quad 3
SER-QUADUV-INSTL	Installation/Training	Quad UV
INTR-INT-000	Installation/Training	Initiator/EXP
INTR-INT-0060	Installation/Training	Initiator 60/60 EXP
INTR-INT-1060	Installation	Upgrade from Initiator 1 to Initiator 60
INTR-SP1-0000	Installation/Training	SP1
353997	EWM Training	Microwave Instrumentation



1-Point Support™

THE ANSWER TO ALL YOUR QUESTIONS

Problem-solving Techniques

We can assist you in solving tough purification and synthesis problems to help you maximize your productivity. Our customer-support mission at Biotage is to offer superior service. Our broad support superstructure is available through a single point of contact, our 1-Point Support team.

Products and Plan Coverage

Biotage 1-Point Support plans offer various levels of support for our purification and synthesis product lines. In addition to the standard 1-Point Support provided to all Biotage customers, as described in detail below, you can purchase extended warranty plans for each product, or broad support plans for your entire array of Biotage systems. The types of coverage range from standard maintenance and spare parts to advanced training, applications support, and frequent visits by our field engineers.

The 1-Point Support Standard Plan

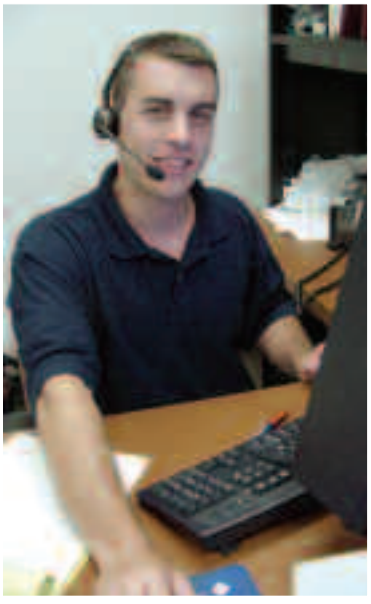
With every system purchase from Biotage, the 1-POINT SUPPORT standard plan is automatically included. This provides customers unlimited access to:

- our dedicated technical support line
- all published Biotage material
- tips and procedures for all of our products
- our 1-POINT SUPPORT Web site www.biotage.com, which gives customers exclusive access to:
  - our user manuals
  - spare-parts lists linked to system diagrams
  - special application notes
  - technical bulletins

The 1-Point Support Instrument Plan

The aim of our individual products support plans is to supply different levels of coverage for travel, labor, and permanent parts required to maintain a system in "like-new" condition and to enable 100% utilization of the system capabilities. Our individual Platinum plans also include:

- all service and maintenance covered in the standard warranty
- product software patches for the software written by Biotage
- preventative maintenance visit(s), scheduled at the customer's request during the coverage period



Instrument Plans

Part Number	Type	Instrument	Labor	Travel	Parts	PMs
354292	Gold	Liberator	N	N	N	1
353075	Gold	Synthesizer	N	N	N	1
354266	Gold	Optimizer	N	N	N	1
SER-100-OEXP	Gold	Optimizer EXP	N	N	N	1
353083	Gold	Creator	N	N	N	1
SER-100-CEXP	Gold	Creator EXP	N	N	N	1
SER-100-QUAD	Gold	Quad 3	N	N	N	1
SER-100-QDUV	Gold	Quad UV	N	N	N	1
SER-100-PIONR	Gold	Pioneer	N	N	N	1
SER-100-HRZN	Gold	Horizon	N	N	N	1
SER-100-SP4	Gold	SP4	N	N	N	1
SER-102-FLEX	Gold	2 Channel Flex	N	N	N	1
SER-104-FLEX	Gold	4 Channel Flex	N	N	N	1
SER-MUX-FLEX	Gold	4 Channel Flex MUX	N	N	N	1
SER-PXSC-0110	Gold	Parallex	N	N	N	1
SER-100-PLLXMUX	Gold	Parallex MUX	N	N	N	1
355478	Gold	Initiator and Initiator EXP	N	N	N	1
355480	Gold	Initiator 60 and Initiator 60 EXP	N	N	N	1
SER-100-SP1	Gold	New SP1	N	N	N	1
SER-100-SP4	Gold	New SP4	N	N	N	1
353074	Platinum	Synthesizer	Y	Y	Y	2
354264	Platinum	Optimizer	Y	Y	Y	2
SER-200-O EXP	Platinum	Optimizer EXP	Y	Y	Y	2
353076	Platinum	Creator	Y	Y	Y	2
SER-200-CEXP	Platinum	Creator EXP	Y	Y	Y	2
SER-101-QUAD	Platinum	Quad 3	Y	Y	Y	1
SER-101-QUADUV	Platinum	Quad UV	Y	Y	Y	1
SER-200-PIONR	Platinum	Pioneer	Y	Y	Y	1
SER-200-HRZN	Platinum	Horzon	Y	Y	Y	1
SER-200-SP4	Platinum	SP4	Y	Y	Y	1
SER-FLEX-SC02	Platinum	2 Channel Flex	Y	Y	Y	1
SER-FLEX-SC04	Platinum	4 Channel Flex	Y	Y	Y	1
SER-300-FLEX4MUX	Platinum	4 Channel Flex MUX	Y	Y	Y	1
SER-400-PLLX	Platinum	Parallex	Y	Y	Y	1
SER-400-PLLXMUX	Platinum	Parallex MUX	Y	Y	Y	1
354921	Platinum	Liberator	Y	Y	Y	2
355479	Platinum	Initiator and Initiator EXP	Y	Y	Y	2
355481	Platinum	Initiator 60 and Initiator 60 EXP	Y	Y	Y	2
SER-200-SP1	Platinum	SP1	Y	Y	Y	1



Support and Service Tiers

1-Point Support™

THE ANSWER TO ALL YOUR QUESTIONS

Broad Support for Customers with Multiple Biotage Systems

In addition to the standard 1-Point Support™ plan automatically supplied with each Biotage system, we offer you the option of further support designed to match the increased requirements at sites with numerous system and application demands.

We have created Bronze through Platinum 1-Point Support Site Plans to provide our customers with the exact level of service and support required. As your business grows, so too can the support you receive from Biotage.

Optimize the productivity of your group by allowing our dedicated team of more than 15 technical-support engineers, who have a combined total of over 100 years of support experience, help you obtain the most from your equipment. Learn more about our various extended 1-Point Support plans.

THE BRONZE 1-Point Support Site Plan

For customers with up to 20 FLASH and/or Quad products

- Standard 1-Point Support
- Spare parts
- A bimonthly visit from our field engineers, who service the products and offer application support

THE SILVER 1-Point Support Site Plan

For customers with up to 50 FLASH and/or Quad products and one Parallex Flex™ and/or Microwave Synthesis system

- Standard 1-Point Support
- Spare parts
- A Visit one day per week from our field engineers, who service the products and offer application support

THE GOLD 1-Point Support Site Plan

For customers with up to 75 FLASH and/or Quad products and up to three Parallex Flex and/or three Microwave Synthesis systems

- Standard 1-Point Support
- Spare parts
- Visits three days per week from our field engineers, who service the products and offer application support

THE PLATINUM 1-Point Support Site Plan

For customers with up to 75 FLASH and/or Quad products, up to three Parallex Flex systems, and/or five Microwave Synthesis systems

- Standard 1-Point Support
- Spare parts
- Visits five days per week from our field engineers, who service the products and offer application support

Support and Service

Repair and Return Policy

Before Calling Us

A 1-Point Support™ team member will be able to serve you more efficiently if you have the following information:

- Serial number and model number of each device involved
- Concise list of symptoms
- List of operating procedures and conditions you were using when the problem arose
- List of other devices connected to the unit
- List of other electrical connections in the room

Warranty Repair

Units covered under warranty will be repaired and returned to you at no charge. If you have any questions about the applicability, please contact your local 1-Point Support team.

Non-Warranty Repair

For out-of-warranty repairs, contact your local 1-Point Support team. A team member will discuss service options with you and assist in arranging the return of the equipment for repair, if necessary.

Biotage may utilize refurbished components when repairing units.

Return Procedure

Contact your local Biotage 1-Point Support team (see page 11) to obtain a Return Material Authorization (RMA) number before returning any Biotage system.

Carefully pack the system to prevent damage in transit. Check with Biotage regarding proper method of shipment. Indicate the RMA number on the carton and on the packing slip. Biotage assumes no responsibility for damage caused by improperly packaged units.

Always insure for the replacement value of the system.

Include a description of symptoms, your name, address, and telephone number, and a purchase order to cover repair costs, return and shipping charges, if your company requires it.

In the U.S. and Canada, ship to:
Biotage AB
RMA Number:
1725 Discovery Drive
Charlottesville, VA 22911

In Europe ship to:
Please contact your local 1-Point Support representative for the correct return address.
(see contact information on page 11)

In Japan, ship to:
Biotage Japan, Ltd.
RMA Number:
Medi Coop BLDG. 8 5F
2-4-14 Kichijojihoncho,
Musashinoshi
Tokyo, Japan 180-0004

How to Place Your Order

How to Use this Catalog

Product information is displayed with easy-to-follow text and diagrams highlighting the system operation and application. Sections are color-coded. Ordering information is found following each product listing.

How to Order

Europe

+46 18 56 57 10
Fax: +46 18 56 57 05
E-mail: ordermailbox@eu.biotage.com

US or Canada

1 800 446 4752 (8:30 a.m. and 5:30 p.m. EST)
Fax: 1 434 979 4743
E-mail: ordermailbox@biotage.com

Japan

+81 (422) 28-1233
Fax: +81 (422) 28-1236
E-mail: order@biotage.co.jp

When placing your order please have available:

- Your purchase order number
- Biotage part number(s)
- Product description(s)
- Shipping address
- Billing address
- Contact person, including telephone number
- Product user name and department

Orders can also be placed using your VISA, Mastercard or American Express account IN THE US ONLY.

Prices and Specifications

Prices in the accompanying Biotage Price Book are suggested list prices and are current at the time of the book's printing. Specifications not listed in this catalog can be obtained by contacting Biotage Customer Support and Service or your local distributor.

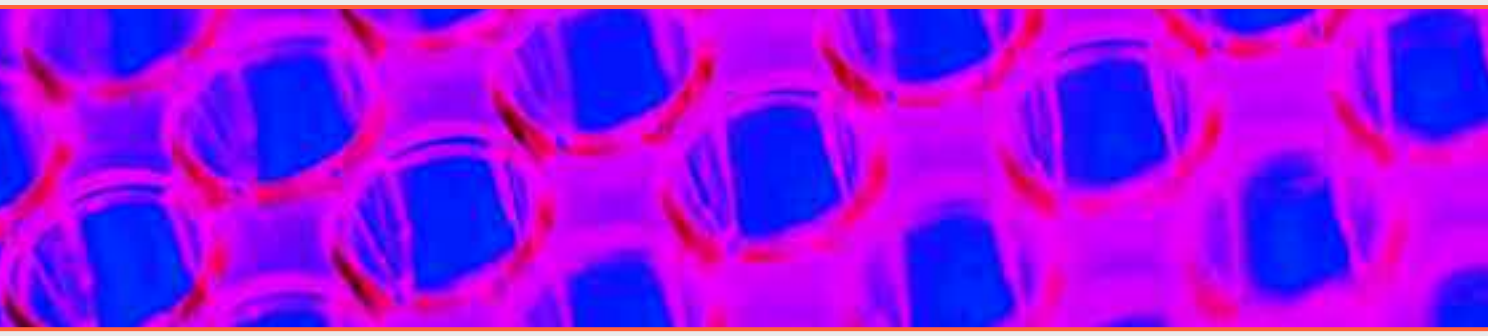
Contact Biotage 1-Point Support

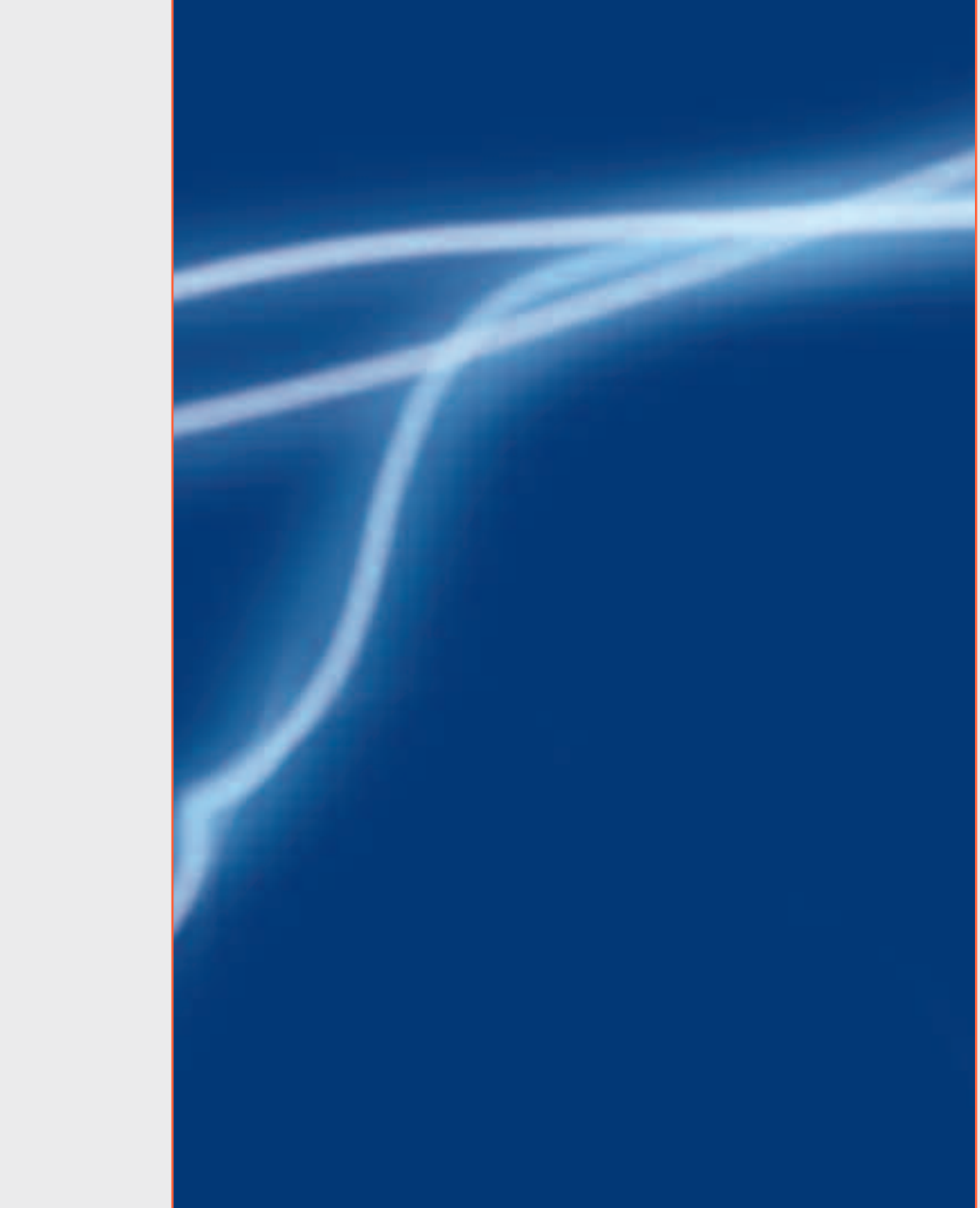
www.biotage.com
The Biotage Web site offers our customers easy access to current information on new products, applications, and events.

Europe
Service and Support
Telephone: +46 18 56 59 11
E-mail: 1-PointSupport@eu.biotage.com

United States
Service and Support
Telephone: 1 800 446 4752
press (3) at the auto attendant
E-mail: 1-pointsupport@biotage.com

Japan
Service and Support
Telephone: +81 422 28 1233
E-mail: 1-pointsupport@biotage.co.jp





Synthesis Solutions and Optimization

Microwave Synthesis Solutions

Biotage Microwave Vials

Biotage exclusively designed microwave vials support microwave synthesis from mg to grams, without the need for re-optimization. Biotage microwave vials are uniquely designed to fit into all Biotage Initiator microwave synthesis systems. These vials allow safe convenient, and reproducible syntheses from 0.2 mL to 20 mL. Methods that are synthesized at a lower volume are directly transferable across the entire volume range.

Initiator™ Microwave Synthesis System

The Initiator microwave synthesizer enables medicinal chemists to quickly synthesize compounds using microwave heating. Through superior heating features, the Initiator is able to quickly achieve temperatures and pressures beyond the traditional reflux heating. The base system is easily upgradable to an 8 or 60-position sample bed that supports the production of focused libraries, multiuser environments and scale-out. The Initiator 8 and 60 provide flexible operation that enables the use of both large and small vials in combination at any time and in any order without manual intervention.

Advancer™

Advancer is designed for reliable and reproducible scale-up of microwave-assisted synthesis, handling reaction volumes from 50 mL to 300 mL at temperatures from 60-250 ºC and pressures of up to 20 bar. Synthesis methods developed in other Biotage microwave synthesis systems can be directly transferred to the Advancer. The product purities and yields are comparable or even improved. This unique scalability enables the user to safely and rapidly translate optimized reactions to the larger scale. With its 350 mL reaction vessel, the Advancer serves all the chemist's needs for scaffolds and intermediates or substance for early toxicological and formulation tests.



Optimizing Microwave Synthesis

Understanding Microwaves

Microwave is a collective name for electro magnetic irradiation with frequencies in the range of 0.3-300 GHz. To avoid interferences between the different applications, it has been agreed that appliances for heating purposes will operate at 2.45 GHz corresponding to a wavelength of 12.2 cm.

Energy in the form of microwaves can be transferred to substances that are present in the beam line of the microwave radiation. Absorption of the energy occurs when dipolar molecules rotate to align themselves with the fluctuating electric field component of the irradiation or when ions move back and forth by the same phenomenon; Figure 1.

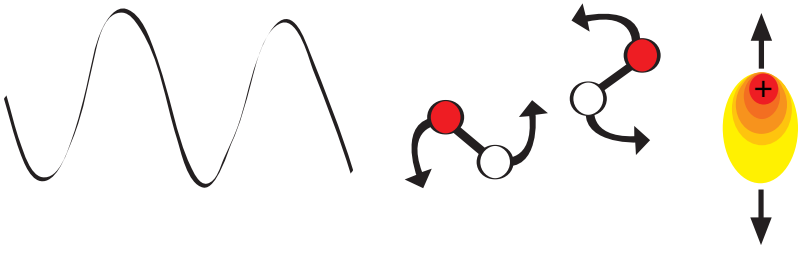


Figure 1. *Dipolar molecules and ions, which try to move with an oscillating electric field.*

It should be pointed out that the energy-quantum of the microwave irradiation is totally inadequate for interacting directly with atom-atom bonds or for exciting specific molecules. When molecules rotate or move back and forth in a matrix, they generate heat by friction. The amount of heat generated by a given reaction mixture is a complex function of its dielectric property, volume, geometry, concentration, viscosity and temperature.[1] Thus, two samples irradiated at the same power level for the same period of time will most likely end up with rather different final temperatures.

Essentially, the ability of a substance to heat in a microwave field is dependent upon two factors: (1) the efficiency with which the substance adsorbs the microwave energy, normally described by its dielectric properties, ε' and (2) the efficiency with which the adsorbed energy can be converted to heat, described by the loss factor, ε''.

A convenient way to evaluate the ability of two closely related substances to convert microwave energy into heat is to compare their respective "loss tangent" values, where the loss tangent is defined as the tangent of the ratio of the loss factor and the dielectric properties, Eqn. 1. For a deeper insight into the mechanism of microwave dielectric heating the review by Mingos et al.[2] is recommended.

$$\tan \delta = \varepsilon''/\varepsilon' \qquad \textbf{Eqn. 1}$$

Synthesis Optimization

However, with any Biotage microwave synthesizer, the problems of selecting the appropriate matrix is more or less invisible to the end user since these machines are capable of reliably heating a wide variety of substances and have both variable power output and temperature control.

Multimode vs. Single Mode

Despite several subcategories there are two fundamentally different constructs of microwave-heating devices namely multimode or single mode. The main difference between the two is in the build-up of the energy field within the systems. In both cases microwaves are generated by a magnetron and led into the reaction chamber, the cavity, through a wave-guide. When the microwaves in a multimode apparatus enter the cavity, they are reflected by the walls generating a three-dimensional stationary pattern of standing waves within the cavity, called modes. Multimode microwaves are optimized to give high efficiency for 200-1000g loads and, consequently, they operate less reliably for smaller loads. However, for chemistries required on larger scales the multimode device is appropriate since single mode devices would be inefficient, therefore, this is what is used for our large-scale microwave, Advancer.

Ideally, to obtain a well-defined heating pattern for small loads, a microwave apparatus utilizing a single mode cavity is preferred. This type of cavity allows only one single mode to be present. Much higher field strengths can be obtained, giving rise to more rapid heating. A properly designed cavity also prevents the formation of hot and cold spots within the sample, resulting in a uniform heating pattern. This is very important when microwave technology is used in organic chemistry, since the heating pattern for small samples can be well controlled. This allows for higher reproducibility and predictability of results as well as optimization of yields, which are usually more difficult when using a domestic microwave oven. All research-scale microwaves from Biotage are equipped with single-mode resonators.

Why Does Microwave Irradiation Speed Up Chemical Reactions?

Chemical reactions, performed using microwave synthesis techniques, are rapid mainly because microwaves are able to quickly achieve higher temperatures and pressures. All Biotage microwave synthesizers can achieve temperatures of up to 250 °C and pressures of up to 20 bars allowing reactions to be carried out much faster than traditional reflux heating.

In early literature, there were many claims of a specific microwave effect responsible for the observed rate accelerations.[3,4,5] Later experiments show some of these early reports to be artifacts[6], while others are debatable or difficult to explain.[7] An attempt to rationalize a possible specific microwave effect has been published by Perreux *et al.*[8] Most of the reports on specific effects, however, can be rapidly dismissed due to poor temperature control. These inaccuracies in temperature measurements often occur when performing the reactions in domestic ovens, with microtitre plates or on solid supports, where there are inherent difficulties in



measuring the temperature accurately.[2,5] Even with today's specialized equipment, it is very difficult to capture the true temperature of a reaction performed on a dry, solid support or in a continuous-flow system.

When trying to understand these questions, the introduction of the so-called "cooling while heating technique"[9] is very misleading. This technology proposes the reaction mixture is heated as the outside of the vessel is simultaneously cooled, hypothetically increasing the energy input. However, since the temperature is normally read on the surface of the vial, the accuracy of the temperature measurement is lost along with reproducibility, controllability and predictability.

The temperature difference of measured and actual temperature is strongly dependent on the microwave-absorbing properties of the sample, the temperature of the cooling gas, the velocity of the cooling gas, the thickness of the vial-wall etc., and can easily be as much as 50 °C, Figure 2.

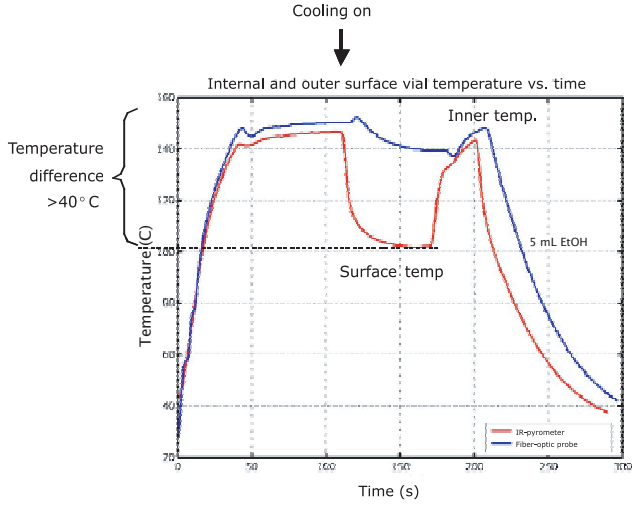


Figure 2. *Difference of measured and actual temperature in 5 mL of ethanol. The actual temperature is measured via a fiber-optic probe inserted directly into the solvent.*

Under some circumstances, the rapid rate of microwave heating can produce heat profiles that are not easily accessible using traditional heating techniques. In such cases, experiments performed using microwave synthesis may well result in a different outcome to conventionally heated reactions, even if the final reaction temperature is the same.[10]

Another phenomenon that might account for some of the claims of specific effects, for reactions run under atmospheric pressure, is the superheating effect.[2,11] Under microwave irradiation at atmospheric pressure, the boiling point of solvents can be raised up to 26 °C above their conventional values. The enhanced boiling point can be maintained in pure solvents for as long as the microwave radiation is applied. Substrates or ions

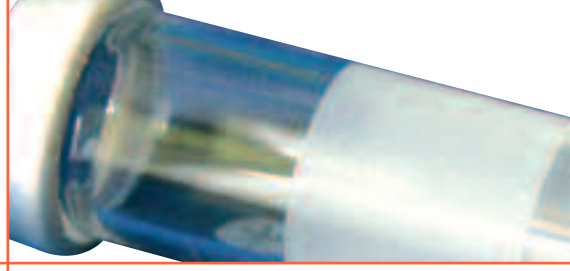
present in the solvent aid in the formation of a boiling nuclei, and the rate at which the temperature of the mixture returns back to the normal boiling point is solvent dependent. It is now accepted that the major part of rate enhancements observed with microwave synthesis is strictly due to thermal effects, even though the unique temperature profiles accessible by microwave radiation may result in novel outcomes. While the existence of a specific microwave effect cannot be completely ruled out, the effect appears to be a rarity of marginal synthetic importance.

Where to Start with Microwave Synthesis?

Microwave synthesis is normally conducted under conditions that vary considerably from what is conventionally used in today's chemistry laboratories. Biotage microwave systems support a wide variety of different reaction conditions, accommodating different solvents, volumes, concentrations and phases, and are characterized by reproducible results. Because microwave synthesis occasionally uses uncommon methods, the novel user might feel unsure of what conditions to use, therefore Biotage has developed a database, Biotage PathFinder, which rapidly gives even novice users in the field a flying start toward the productivity increases inherent in microwave synthesis.

Biotage PathFinder is a Web-based service featuring a unique microwave synthesis database including more than 3,800 carefully selected microwave reactions. It gives chemists direct access to years of experience in microwave synthesis, conducted on Biotage microwave systems delivered in a detailed, easy-to-use and accessible format. More information can be found in the Biotage PathFinder section on page 48 of this catalog or online at www.biotagepathfinder.com.

With more experience in microwave chemistry, it is possible to translate conventional methods into microwave methods. As previously mentioned, reactions proceed faster using microwave synthesis simply because they are conducted at higher temperatures. As a basic rule of thumb, using the Arrhenius equation, a 10-degree increase in reaction temperature doubles the reaction speed. For example, if your reaction took four hours at 60 °C, it will take approximately two hours at 70 °C. However, keep in mind, this new reaction temperature must be evaluated according to substrate and reagent stabilities as in all chemistry. The reaction temperature and time can be easily converted using the prediction chart provided below in Table 1.



Prediction Chart

Table 1: Time Prediction chart

Change in field color represents change in unit (hour/minutes/seconds) relevant to your starting unit. For example, if your reaction took 6 hours at 100 °C (in this instance, white=hours), it will take approximately 5 minutes at 160 °C (blue=minutes), see red numbers in the table above.

Temp (°C)	Times - change in field color represents change in unit									
20	1	2	4	6	8	12	24	48	96	172
30	30	1	2	3	4	6	12	24	48	86
40	15	30	1	1.5	2	3	6	12	24	43
50	8	15	30	45	1	1.5	3	6	12	22
60	4	8	15	23	30	45	1.5	3	6	11
70	2	4	8	11	15	23	45	1.5	3	5
80	56	2	4	6	8	11	23	45	1.5	3
90	28	56	2	3	4	6	11	23	45	1
100	14	28	56	1	2	3	6	11	23	40
110	7	14	28	42	56	1	3	6	11	20
120	4	7	14	21	28	42	1	3	6	10
130	2	4	7	11	14	21	42	1	3	5
140	53	2	4	5	7	11	21	42	1	3
150	26	53	2	3	4	5	11	21	42	1
160	13	26	53	1	2	3	5	11	21	38
170	7	13	26	40	53	1	3	5	11	19
180	3	7	13	20	26	40	1	3	5	9
190	2	3	7	10	13	20	40	1	3	5
200	1	2	3	5	7	10	20	40	1	2
210		1	2	2	3	5	10	20	40	1
220			1	1	2	2	5	10	20	35
230					1	1	2	5	10	18
240						1	1	2	5	9
250								1	2	4

With courtesy of David Rudge, AstraZeneca, Macclesfield, UK

Synthesis Optimization

Practical Tips and Tricks When Performing Microwave Synthesis

Solvent

- Different solvents interact very differently with microwaves because of their diverse polar and ionic properties.
- Acetonitrile, DMF and alcohols are often used for microwave-assisted organic synthesis.
- You might not need to change from the solvent that is specified for the reaction under traditional chemistry conditions. First, try using the solvent that you would normally use.
- Polar solvents (e.g., DMF, NMP, DMSO, methanol, ethanol and acetic acid) couple well with microwaves due to their polarity, i.e., the temperature will rise substantially with these solvents.
- Non-polar solvents (e.g., toluene, dioxane, THF) can be heated only if other components in the reaction mixture respond to microwave energy, i.e., if the reaction mixture contains either polar reactants or ions. When using less polar solvents, more concentrated reaction mixtures are preferred. Under such circumstances, very high temperatures can be achieved.
- Ionic liquids are reported as new, environmentally friendly, recyclable alternatives to dipolar aprotic solvents for organic synthesis. The dielectric properties of ionic liquids make them highly suitable for use as solvents or additives in microwave-assisted organic synthesis. Ionic liquids absorb microwave irradiation extremely efficiently and they have a low vapor pressure, enhancing the heating process. Despite ionic liquids being salts, they dissolve easily in a wide range of organic solvents, and can be used to increase the microwave absorption of low absorbing reaction mixtures.
- Solvents can behave differently at elevated temperatures and most solvents become less polar with increased temperature. Water is the most interesting case. At elevated temperatures, the bond angle in water widens and its dielectric properties approach those of organic solvents. Water at 250 °C actually has similar dielectric properties as acetonitrile at room temperature. Thus, water can be used as a pseudo-organic solvent at elevated temperatures where organic molecules will dissolve, not only because of the temperature, but also because of the change in dielectric properties. This makes some reactions that normally would not run in water perfectly feasible.
- Solvents with low boiling points (e.g., methanol, dichloromethane and acetone), give lower achievable temperatures due to the pressure build-up in the vessel. If a higher absolute temperature is desirable to achieve a fast reaction, it is advisable to change to a closely related solvent with a higher boiling point, e.g., dichloroethane instead of dichloromethane.

Solvent Table

Table 2: Solvent table

To show the responses of various solvents to microwave irradiation, we measured the temperature and pressure of pure solvents after 100 seconds of microwave irradiation. "Fixed Hold Time" was set to "Off," "Absorption Level" was set to "Normal" and the temperature was set to 250°C.

Solvent (Volume=2.5 mL)	Boiling Point (1 atm) (°C)	Attained Temp (°C)	Attained Pressure (bar)
1-Methyl-2-pyrrolidinone (NMP)	202	250	1
1,2-Dichloroethane	83	180	5
1,2-Dimethoxyethane (DME)*	85	130	3
1,4-Dioxane*	100	56	0
Acetone	56	150	7
Acetonitrile	81	180	13
Dichloromethane	40	110	5
Dimethylsulfoxide (DMSO)	189	250	1
Ethanol	78	155	13
Methanol	65	145	17
N,N-Dimethylformamide (DMF)	153	250	4
o-Dichlorobenzene	180	250	2
Tetrahydrofuran (THF)*	65	110	3
Water*	100	165	10
Xylenes*	137	50	0

* *Some solvents can reach higher temperatures if they contain microwave-absorbing material and are heated for a longer time. For the very poorly microwave-absorbing solvents, much higher temperatures have been observed in various reactions, for example: xylene (150 °C), 1,4-dioxane (200 °C), water (220 °C), 1,2-dimethoxyethane (200 °C), and tetrahydrofuran (180 °C).*

Volume

Do not exceed or fall below the vial's specified volumes. Too low a volume will give an incorrect temperature measurement; while too high a volume does not leave sufficient head space for pressure build-up. Since microwave heating is strongly dependent upon geometry and volume, Biotage provides four different vial sizes to ensure similar performance and scalability throughout the entire volume range, Figure 3.



Figure 3. *Biotage Microwave Vials.* *For more information on Biotage's Microwave Vials, go to page 44.*

Synthesis Optimization

Concentration

The concentration depends on the type of chemistry that is performed. A unimolecular reaction is independent of concentration and can be performed in very diluted solutions. Bi- or tri-molecular reactions, on the other hand, are highly dependent on the concentration; a higher concentration gives a faster reaction. The maximum obtainable concentration is dependent on the properties of the substrates and reagents as well as the properties of the solvent(s).

Phase

In a Biotage microwave synthesizer, all different phases can be used, i.e., solution phase, solid phase, solid-supported reagents, solvent-free and scavenger resins. Please consider the difficulties in correctly measuring the temperature when solvent free techniques are used.

Stirring

Always add a magnetic stirring bar to the process vial. Stirring improves mass transport, avoids tearing of solid materials and is beneficial for rapid heat distribution.

Inert atmosphere

In general, inert atmosphere is not initially employed in microwave chemistry, and is often not needed even if the reaction is carried out in this way conventionally. If needed, flush the vial with an inert gas before capping.

Time

As expected, the reaction time will be a function of the reaction temperature and the thermal stability of substrates, reagents and products. A typical reaction normally requires two to 15 minutes of irradiation. When trying out a new reaction for the first time, three to five minutes of reaction time is normally used, provided the required temperature is compatible with all of the ingredients.

Temperature

All synthesis systems from Biotage work in a temperature range between 60 °C and 250 °C. Optimally, the reaction temperature should be as high as substrates and products allow before they start decomposing or as high as the reaction solvent allows, whichever is lowest.

Pressure

The reactions can safely be performed at pressures of up to 20 bar. If the pressure in a vial becomes higher, the heating is automatically stopped and cooling begins. For an indication of the expected pressure of a reaction, please use the solvent table or the vapor pressure calculator at www.biotagepathfinder.com.

Optimize Your Reaction

With the speed and simplicity offered by microwave synthesis in general and Biotage microwave synthesizers in particular, optimization has never been easier.

Optimizing a microwave synthesis is very similar to optimizing a conventional synthesis. If your first reaction was not a success, changing the target temperature and reaction time can cause significant improvement. All remaining parameters (e.g., concentration, solvent, reagent, etc.) should be varied when applicable.

If the reaction is not proceeding at all or not going to completion:

- Increase the temperature. As long as the reactants/reagents can withstand the higher temperature, the only limit is the pressure build-up in the vial and the security limit of 250 °C.
- Extend the reaction time.
- Increase the concentration(s) of reagent(s).
- Change the solvent. Some solvents, e.g., water, will behave differently at high temperatures as they become less polar. This makes some reactions that normally would not work in polar solvents perfectly feasible.
- Change the reagent(s). Due to the high temperatures that can be reached, sometimes a less reactive, but more temperature-stable, reagent can be used.

If you see decomposition of reactants/reagents/products:

- Lower the temperature.
- Shorten the reaction time. It may be that the desired product is actually formed, but then decomposes rapidly at elevated temperatures. In some cases it is therefore possible to "trap" the product by using a shorter reaction time.
- Decrease the concentration(s) of reagent(s).
- Change to a more temperature stable reagent.

How Microwave Synthesis Impacts Chemistry Research and Development

Microwave synthesis can have a significant impact on chemistry research and development if its strengths, namely speed and simplicity, are capitalized upon.

Speed

The main benefit of microwave synthesis is shorter reaction times through an increase in reaction temperature. Herein we describe how this affects chemistry development.

Chemistry, like all sciences, consists of never-ending iterations of hypotheses and experiments with results

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Synthesis Optimization

guiding the progress and development of projects. The shorter reaction times that microwave synthesis provides make it ideal for rapid reaction scouting and optimization, allowing chemists to proceed very rapidly through the hypotheses-experiment-result iterations, resulting in more decision points per time unit; Figure 4.

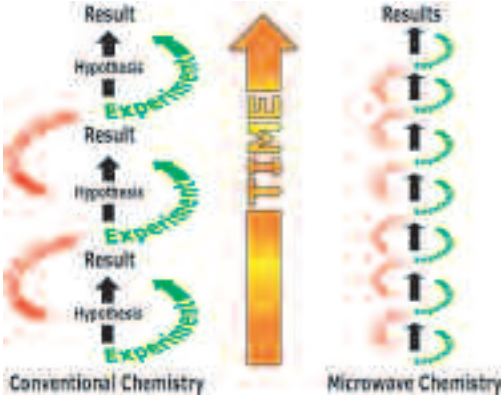


Figure 4. *Microwave-assisted organic chemistry can be used to speed up the chemistry development by allowing more experiments to be conducted per time unit.*

The only prerequisite for this approach to be productive is that reactions need to be successful enough times to make it worthwhile, (i.e., the molecules have to withstand the extreme thermal conditions for the short time that the reaction proceeds). At a time when the trend in organic synthesis is moving toward using ambient conditions, it may seem incredulous to heat reactions above 200 °C, nevertheless, most reagents, catalysts and substrates have been shown to survive extreme temperatures for short periods of time.

In order to fully benefit from this technique, chemists have to be ready to risk trying reactions at high temperatures and be prepared to fail or succeed. While failure could cost a few minutes, success would gain many hours or even days. To gain the most from microwave synthesis, it needs to be regularly used as the preferred technique for synthesis.

Simplicity

Simplicity is one of the assets of modern microwave equipment. Reactions are performed in glass vials sealed with crimp caps; the vials are subsequently heated in the microwave cavity at a constant temperature for a set period of time. The reaction can be analyzed by sampling through the septa. With the availability of proper analytical facilities, the time from the genesis of an idea to the result can be a matter of minutes enabling the chemist to rapidly test the feasibility of novel synthetic routes.

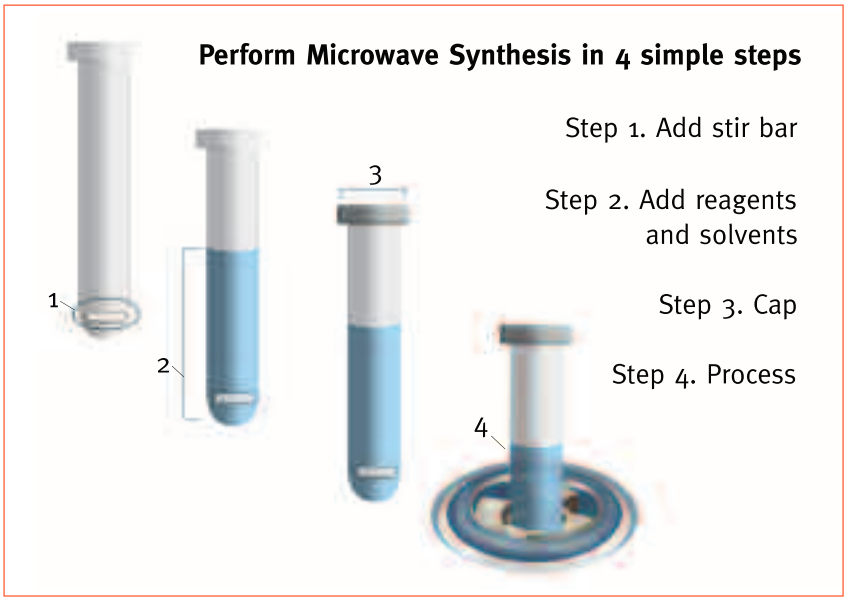


Figure 5. *The simple preparations needed to perform microwave synthesis on a Biotage system.*

Productivity

Successful chemistry development relies on two basic foundations: (1) the level of synthetic complexity and (2) the likelihood of a positive outcome.

Thus, a synthetic procedure with a greater likelihood of success with the least possible effort usually becomes established and widely used. As mentioned previously, the synthetic procedure with microwave synthesis is generally of very low complexity. Until recently, there has been an uncertainty about the likelihood of success using microwave synthesis. However, during the past couple of years, there has been a real breakthrough in this area as indicated by the vast number of reviews published,[12] showing the utility of this technique. The extreme simplicity, the proven likelihood of good results and the wide reaction range that can be easily performed has made microwave synthesis one of the most valuable tools for the chemist during the past few years.

This simple dogma can have enormous effects on the chemistry development as shown by Chris Sarko and his colleagues[13] at the second Coherent Synthesis conference in San Diego, April 2002. The same group showed that the technology-enhanced chemistry development by over 1000% in individual optimization cycles and that an overall productivity enhancement of 200 - 400% was achieved in their library syntheses.

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Initiator
Biotage



Initiator™ Microwave Synthesis Systems

Fast, Safe and Scalable Microwave Synthesis

INITIATOR™

The Initiator™ microwave synthesizer enables medicinal chemists to quickly synthesize compounds using microwave heating. In addition to speed, microwave synthesis offers other advantages such as simplicity and broader exploration. Through superior heating features, the Initiator is able to quickly achieve temperatures and pressures beyond the traditional reflux heating. This allows chemists to perform complex reactions formerly not possible and is, therefore, the fastest growing technology in the pharmaceutical research laboratory.

Features and Benefits

Compact footprint
The Initiator is 45% smaller than its predecessor, fitting easily into any standard fume-hood space.

Touch Logic control
Load and run your samples using a touch-screen monitor for simple and intuitive navigation without the need for an external computer, keyboard or mouse.

0.2 to 20 mL without system modifications
With the EXP function, use four different vial sizes in any order or combination at any time without system modifications for greater flexibility and direct scale-up of milligrams to grams.

Modular design
Easily upgrade from a single-sample manual format to an automated 8 or 60-position system.

Enhanced heating performance
The new single-mode applicator with the proven Dynamic Field Tuning™ feature offers faster heating of a broader range of solvents.

Best-in-class safety
All Biotage microwave synthesizers are designed for safe operation at elevated temperatures and pressures. The Initiator triple tier safety-lock feature ensures maximum operator safety at all times.

1-Point Support™
Biotage's world-class field-service organization serves customers on site to provide the highest quality personalized support.

Upgrade to Initiator 8 or 60



Initiator™ Eight

The 8-position sample bed provides automation to medicinal chemists for rapid optimization of reaction conditions and analog synthesis. The ability to use both large and small vials, in combination at any time and in any order without manual intervention, provides the medicinal chemist flexibility and the ability to rapidly scale-up compounds of interest.

Initiator™ Sixty

The 60-position sample bed supports the production of focused libraries, multiuser environments and scale-up by scale-out. Flexible operation enables the use of both large and small vials in combination at any time and in any order without manual intervention.

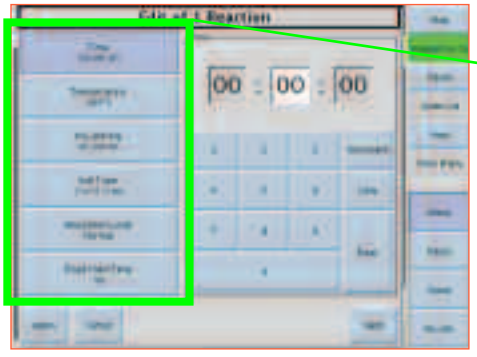
Intuitive Touch Logic Control™—as simple as 1-2-3



Step 1

Experiment Editor

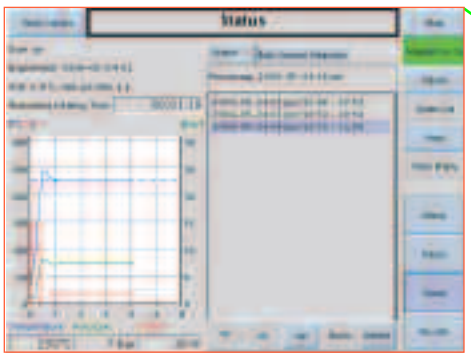
Select Rack type. Select the number of reactions and vial position(s) to load. Enter conditions for each vial (step 2). View experiment, select user and run.



Step 2

Edit Your Method

Specify reaction time, temperature, vial size and select absorption properties of your sample. Select to use fixed hold time if needed.



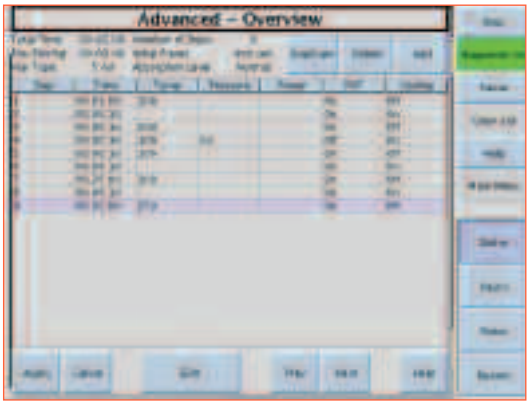
Step 3

Status

Check run status, remaining processing time and queue status. View temperature, pressure and power profile for the reaction being processed. Edit the run on-the-fly, change parameters as needed.

Advanced Edit

Control pressure and power. Set individual pressure and power thresholds for each reaction. Build step or pulse sequences of up to 99 steps using all available control parameters; time, temperature, pressure, power, fixed hold time and cooling.



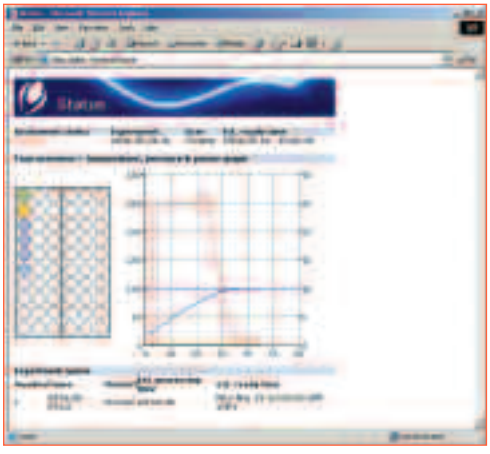
Racks with Track Overlay—Vial Type

Check the specific parameters used and find the result for any given reaction on the tray. Display the parameter of choice for all reactions and remove performed experiments.

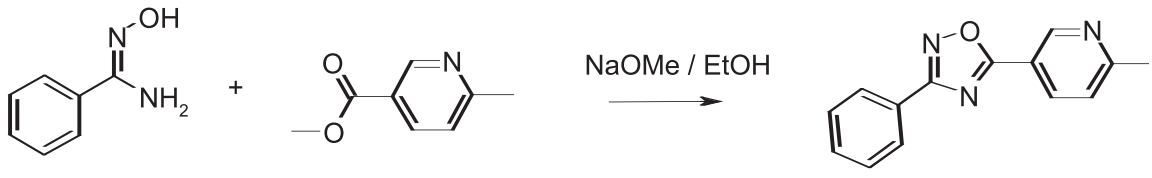


Remote Viewer

View the status of the instrument and the progress of your reaction from a remote location (your office). View, save and print results.



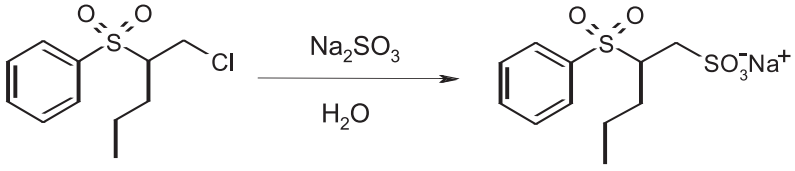
Faster reactions and higher yields for Synthesis of 1,2,4 oxadiazoles



	Temp	Time	Yield
Conventional	78 ºC	18 to 24 hours	7% to 63%
Microwave	160 ºC	5 minutes	80%

An early example from our in-house work illustrates how reaction times can be shortened while improving yields: Conventionally, the condensation of aldoximes with esters required 18 to 24 hours at reflux to provide the 1,2,4-oxadiazoles in yields of 7 - 63% (depending on what substrates were used). Using microwaves, it took 5 minutes at 160 °C to provide the product at 80% yield.

Broader exploration using unconventional solvents



	Temp	Time	Yield
Conventional	reflux	16 hours	<10%
Microwave	185 ºC	6 minutes	99%

Data courtesy of: Michael H. Howard, DuPont® Crop Protection Products

Using microwave synthesis, uncommon solvents such as water can be used. When water is heated to a very high temperature the dielectric constant decreases as the temperature increases. Water has a dielectric constant, which decreases from 78 at 25 °C to 20 at 300 °C, this latter value is comparable to that of solvents such as acetone at ambient temperature. This molecular mutation promotes the solubility of organic substances in water not only because of the elevated temperatures but also due to the change in dielectric properties. Therefore, water acts as a pseudo-organic solvent in the microwave synthesis process.

This example was performed at DuPont Crop Protection. The product was used as a key intermediate in the synthesis of potential metallo-enzyme inhibitors. While reflux in water gave <10% yield, the microwave technique provided the desired product in 99% yield.

Specifications

INITIATOR™
SPECIFICATIONS

Heating Process

Temperature	60-250 °C (140-482 °F)
Temperature increase	2-5 °C/sec (36-41 °F/sec)
Pressure range	0-20 bar (2 MPa, 290 PSI)
Power range	0-300 W at 2.45 GHz
Reaction vials	2 or 4 vial sizes (mL): 0.5-2, 2-5, (0.2-0.5 and 10-20 with EXP function)
Reaction volumes	0.5-5 mL, (0.2-20 mL with EXP function)
Agitation	Magnetic stirrer

System Requirements

Temperature	18-32 °C (64-90 °F)
Humidity	20-95% RH
Electrical supply	EU: 220-240 V, 50 Hz (5 Å) US: 120 V, 60 Hz (10 Å) JP: 100V, 50/60 Hz (10 Å)
Maximum power consumed	1100 VA
Cooling	Pressurized air supply >60 L/min (2.1 cubic feet/min), 2.5–4 bar (0.25-0.4 MPa, 36-58 PSI)
Weight	48.9 lb (22.2 kg)
Dimensions	14.4 x 15.9 x 16.3” W x D x H (365 x 405 x 415 mm)

Interfaces

Touch screen	6.4”
Ethernet LAN	complies with IEEE 802.3 (ANSI 8802.3) MII
Archiving and back-up	Via the LAN

Upgrade Path

The Initiator system can be automated with Robot 8 or Robot 60.

Initiator Eight

Rack capacity	4 vials in rack for 0.2-5 mL vials 2 vials in rack for 10-20 mL vials
Dimensions	15.7 x 19.7 x 22.8” W x D x H (400 x 500 x 580 mm)
Weight	64 lb (29 kg)

Initiator Sixty

Rack Capacity	30 vials in rack for 0.2-0.5, 0.5-2 and 2-5 mL vials 12 vials in rack for 10-20 mL vials
Dimensions	24.6 x 15.9 x 18.5” W x D x H (625 x 405 x 470 mm)
Weight	77 lb (34.9 kg)



Initiator Ordering Information

Part Number	System	Country
Systems		
355230	Initiator	EU
355286	Initiator	US
355287	Initiator	JPN
355301	Initiator EXP	EU
355302	Initiator EXP	US
355303	Initiator EXP	JPN
355522	Initiator Eight	EU
355524	Initiator Eight	US
355526	Initiator Eight	JPN
355521	Initiator Eight EXP	EU
355523	Initiator Eight EXP	US
355525	Initiator Eight EXP	JPN
355435	Initiator Sixty	EU
355437	Initiator Sixty	US
355439	Initiator Sixty	JPN
355434	Initiator Sixty EXP	EU
355436	Initiator Sixty EXP	US
355438	Initiator Sixty EXP	JPN
Upgrade Modules		
Initiator Robot Eight		355380
Initiator Robot Sixty		355381
Initiator EXP Upgrade		355420
Emrys™ PathFinder		355239
Web Subscription		
Accessories		
Initiator Waste Tray Inserts		355366
Biotage Microwave Vials	0.2-0.5 mL, Qty 100	355458
Biotage Microwave Vials	0.5-2 mL, Qty 100	352016
Biotage Microwave Vials	0.5-2 mL, Qty 3x100	354625
Biotage Microwave Vials	2-5 mL, Qty 100	351521
Biotage Microwave Vials	2-5 mL, Qty 3x100	354624
Biotage Microwave Vials	10-20 mL, Qty 50	354833
Microwave Vial Caps		352298
Crimper		353671
Decapper		353913
Vial Adapters	0.2-0.5 mL, Qty 10	355459
Vial Adapters	10-20 mL, Qty 12	355367
O-rings for Vial Adapters	10-20 mL, Qty 10	354838
Initiator Cavity Air Guide		354974
Vial Rack (Initiator 8)	Vial 4-rack (0.2-5 mL)	355391
Vial Rack (Initiator 8)	Vial 2-rack (10-20 mL	355390
Vial Rack (Initiator 60)	Vial 30-rack (0.2-5 mL)	353478
Vial Rack (Initiator 60)	Vial 12-rack (10-20 mL)	354836
Magnetic Stir Bars	10-20 mL, Qty 5	353930
Screwdriver Insex		354107
Screwdriver Torx TX20		355415
Venting Screw Replacement		354878

Installation and Training

See page 6 in the Customer Support and Service Section for installation and training information.





Advancer™

The batch microwave synthesizer for scale-up of organic synthesis

The batch microwave synthesizer for the scale-up of organic synthesis.

The Advancer system is designed for reliable and reproducible batch scale-up of microwave-assisted synthesis, handling reaction volumes from 50 to 300 mL at temperatures from 60 to 250 ºC and pressures of up to 20 bar. Synthesis methods developed using other Biotage microwave synthesis systems can be directly transferred to the Advancer. Purities and yields are comparable or even improved, enabling chemists to safely and quickly translate optimized reactions to a larger scale. With its 350 mL reaction vessel, the Advancer serves the chemist's needs for scaffolds and intermediates or substance for early toxicological and formulation tests.

Features and Benefits

Batch format microwave synthesizer
Specifically designed so that methods developed in Biotage lab-scale systems can be safely and predictably transferred to a larger scale without re-optimization.

Powerful mechanical stirring (up to 1000 rpm)
In addition to homogeneous reactions, the system also supports heterogeneous reactions and the use of solid catalysts, heavy slurries and crystallizing products.

Flash cooling
The patent pending, "instant", adiabatic cooling promotes high purity and yield.
For example, 200 mL of EtOH can be cooled from 180 °C to 65 °C in just 30 seconds.

Efficient heating
Powerful (0-1200 W) focused magnetron rapidly heats large volumes.
Dynamic Field Tuning™ minimizes reflected microwave energy.

Extra vessel entry ports
Allows in-situ sampling during run, addition of reagents (better control of exothermals), or the creation of inert atmospheric conditions. Adaptable for real-time reaction monitoring through e.g. Raman spectroscopy.

Best-in-class safety features
Breech lock closure with pressure release valve and automated safety interlock, ensure maximum operator safety. System pressure control rated up to 20 bar.





Compatible with the IRORI™ X-Kan system

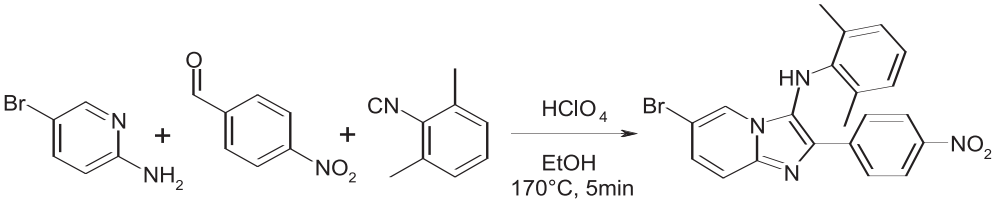
Run Array microwave assisted solid-phase chemistry in batch format using IRORI X-Kans. This technique is beneficial for the introduction of problematic diversity elements or for the rapid microwave optimization of solid-phase chemistry and validation screening of building blocks for diversity steps.

The IRORI X-Kan system with CleVap combines multiwell dispensing, cleavage, transfer, collection, formatting and evaporation. This minimizes operator intervention, improving high throughput walk-away operation by up to 1152 Kans per run at two runs per day. By pooling microreactors into common building block groups, the process is very efficient for synthesizing one discrete compound in each microreactor.

Improved Yield and Speed

Experience the same advantages achieved using microwave synthesis at discovery-scale in the scale-up laboratory. Two representative reactions illustrate improvements in speed, yield and purity.

One-step, three-component synthesis of Imidazo[1,2-a] annulated Pyridine

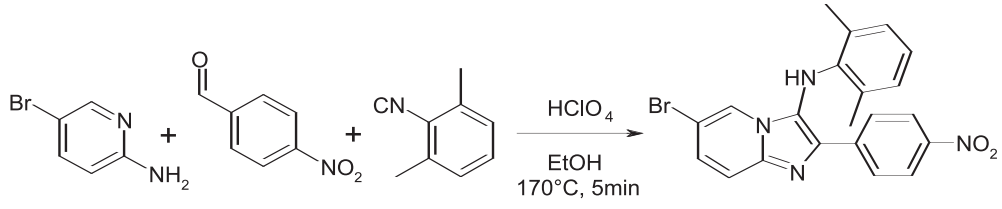


Safety. Use of Perchloric acid as catalyst.

1. Optimized on Emrys™ Liberator, 70% yield
2. Directly scaled up 30 times

- **68% yield with 5.4 g of product**
- **1HNMR showed ~100% purity**
- **Total time from discovery to 5.4 g isolated = 3 h**

Triphenylphosphine free, one-pot Wittig olefination



Solid phase supported reagent. Heterogeneous solution.

1. Developed & optimized on Emrys™ Liberator, 38% yield
2. Scaled up 30 times in Emrys™ Advancer

- **92% yield**
- **1HNMR measured purity of 95%**

System Specifications

Reaction vessel	350 mL, Teflon®
Operating temperature	60-250 °C (140-482 °F)
Pressure range	1-20 bar (2 MPa, 290 psi)
Temperature increase	0.5-4 °C/sec, solvent dependent
Power range	0-1200 W
Agitation	Overhead Stirrer
Cooling	Gas cooling, instant adiabatic flash cooling
System Control & Data Management	Windows XP® operating system, PIV 2 GHz processor, 20 GB hard disc and 256 MB primary memory. Includes 17" TFT flat screen, keyboard, mouse and Biotage Advancer 1.4 software. Prints via the LAN or USB port.
Temperature	18-32 °C (64.4-89.6 °F)
Humidity	20-95% RH
Power	220-240 VAC, 50 Hz, 1ø (EU) 208 VAC, 50/60 Hz, 2ø (US, JPN)
Air supply	> 60 lit/min, 5-10 bar
Water supply (used to cool magnetron)	1-3 lit/min
Weight	< 450 kg (985 lbs)
Dimensions	55" x 26" x 73" W x D x H (140 cm x 65 cm x 185 cm)
Three extra vessel entry ports	Two standard Upchurch Scientific® HPLC connections and one Swagelok® connection.

Ordering Information



The Biotage Advancer features several vessel entry points to facilitate in-situ sampling and the addition of reagents during a run.



The Biotage Advancer features a Teflon® 350 mL reaction vessel, insuring no cross contamination and easy clean-up.

Ordering Information

Item	Description	Part Number
Advancer Instrument	- 2 Reaction Vessels, 50-300 mL with Cap, thick-walled Teflon® vessel for repetitive usage - Infrared Temperature Probe - Temperature Probe Pocket - Pressure Sensor - Reaction Collection Package (includes an electrically driven Collection Valve, connecting Collection Tubing and Collection Vessel for receiving cooled reaction mixture) - HPLC port, consisting of fittings, tubing and a manual valve for facilitating the connection of external hardware that can aid in sampling from, or adding content to, the reaction vessel - Biotage Advancer Software 1.4, license - Pd-patent License - Advancer O-ring Kit - Overhead Propeller Stirrer - Biotage Advancer Tool Kit - Installation and training	354853

See page 11 for more information on how to request a quote or for ordering instructions.





Biotage Microwave Vials

Migrate from mg to g without reoptimization

Biotage Microwave Vials

4 exclusively designed microwave vials

support Microwave Synthesis from mg to grams, without the need for re-optimization.

Simplicity

Simplicity is one of the benefits of modern microwave equipment. Reactions are performed in glass vials sealed with caps and heated in the microwave cavity. Chemists can quickly analyze reactions by sampling through a septum.

Biotage Microwave Vials are designed to support microwave synthesis from mg to g without the need for reoptimization. With the Initiator™ EXP system, methods that are run at a lower volume are directly transferrable across the entire volume range of 0.2-20 mL.

Magnetic Stir Bars

The reaction mixture is continuously stirred by magnetic stirring during the heating process promoting even heating throughout.

Optimum Vial Sizes

Each Biotage Microwave Vial has been designed for safe and efficient heating within its specified volume range. Together, the four vial types provide full scalability within the volume range of 0.2-20 mL.

Multi-Gram Scale

Migrate directly to multi-gram scale without reoptimization using the 10-20 mL vials. These larger vials can also be used for preparation of scaffolds and intermediates or for generating larger quantities of active compounds for testing.

Choose the vial size that works best for your reaction:

Biotage recommends that reaction volumes do not fall below or exceed specified vial volumes. If the volume is too low, the temperature reading may be inaccurate, and if the volume is exceeded, insufficient space is left for pressure build-up.



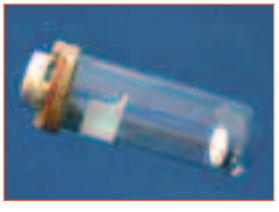
Biotage Microwave Vials 0.2-0.5 mL (only with EXP systems)



Biotage Microwave Vials 0.5-2 mL



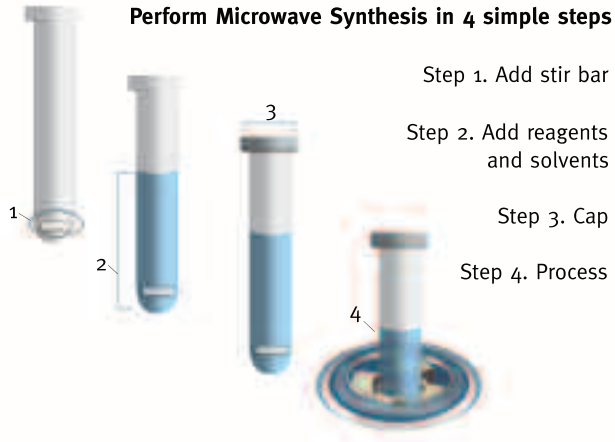
Biotage Microwave Vials 2-5 mL



Biotage Microwave Vials 10-20 mL (only with EXP systems)

Features and Benefits

- All Biotage Microwave Vials withstand pressures of 20 bars (ca 300 psi).
- With the Reseal™ design, the septum can be resealed after it has been penetrated, allowing repeated additions of reagents or insitu sampling.
- Manufactured from contaminant free microwave-safe glass.
- Magnetic stirring promotes even temperature distribution throughout the entire reaction mixture, including heterogeneous mixtures.
- Available in four sizes: 0.2-0.5 mL, 0.5-2.0 mL, 2.0-5.0 mL and 10-20 mL.



Vial Ordering information

Item	Description	Part Number
Biotage Microwave Vials	0.2-0.5 mL, Qty 100	355458
Biotage Microwave Vials	0.5-2 mL, Qty 100	352016
Biotage Microwave Vials	0.5-2 mL, Qty 3x100	354625
Biotage Microwave Vials	2-5 mL, Qty 100	351521
Biotage Microwave Vials	2-5 mL, Qty 3x100	354624
Biotage Microwave Vials	10-20 mL, Qty 50	354833
**Microwave vial caps and stir bars included with vial order*		
Accessories		
Microwave Vial Caps	Qty 107	352298
Crimper		353671
Decapper		353913
Vial Adapter	0.2-0.5 mL, Qty 10	355459
Vial Adapter	10-20 mL, Qty 12	355367
O-rings for Vial Adapters	10-20 mL, Qty 10	354838
Initiator Cavity Air Guide		354974
Vial Rack (Initiator 8)	Vial 4-rack (0.2-5 mL)	355391
Vial Rack (Initiator 8)	Vial 2-rack (10-20 mL	355390
Vial Rack (Initiator 60)	Vial 30-rack (0.2-5 mL)	353478
Vial Rack (Initiator 60)	Vial 12-rack (10-20 mL)	354836
Magnetic Stir Bars	10-20 mL, Qty 5	353930

KNOWLEDGE



Biotage PathFinder

Web-based resource for microwave synthesis methods

Maximize the Benefits of Microwave Synthesis with Biotage PathFinder Web

Biotage PathFinder

Biotage PathFinder is the world's largest database of established methods for microwave synthesis. The new Web-based format offers chemists worldwide access to more than 3,800 diverse microwave methods. More than 600 of the reactions are new. Using simple keyword and/or substructure search, it is fast and easy to find microwave conditions for your reactions of interest along with experimental details and information needed to perform the reactions.

Additional Features

Ask-a-Chemist

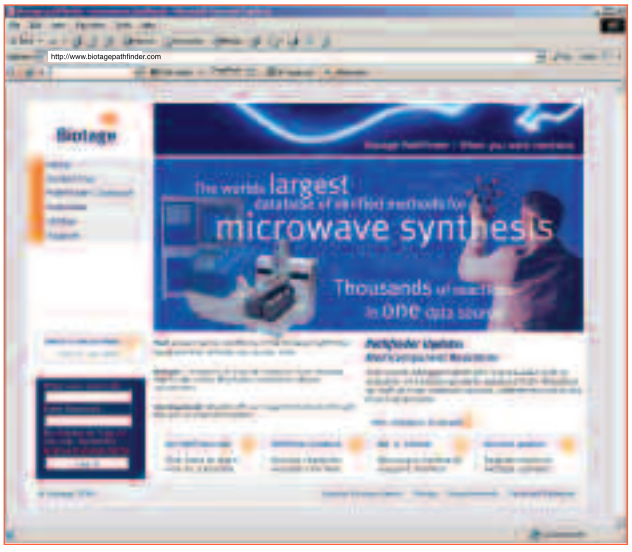
In addition to the database, Biotage Pathfinder includes an Ask-a-Chemist feature, which allows chemists to have a dialog on microwave synthesis methods and get quick answers to their questions directly from a Biotage chemist experienced in microwave synthesis.

Vapor-Pressure Calculator

This software allows chemists to automatically calculate the Vapor pressure for some common solvents at various temperatures.

Biotage Pathfinder Cookbook

A free feature that introduces all users to a sample of the valuable information available on PathFinder. Chemists may quickly browse through a selection of popular reactions and obtain reaction details.



Data Content

The data content is continually updated with new chemistries and currently contains reactions from Biotage's highly skilled internal application chemists and select contributions from our renowned Scientific Partnership Program (SPP).

To experience the benefits first hand, visit www.biotagepathfinder.com.



Figure 1. *Enter a simple substructure search.*

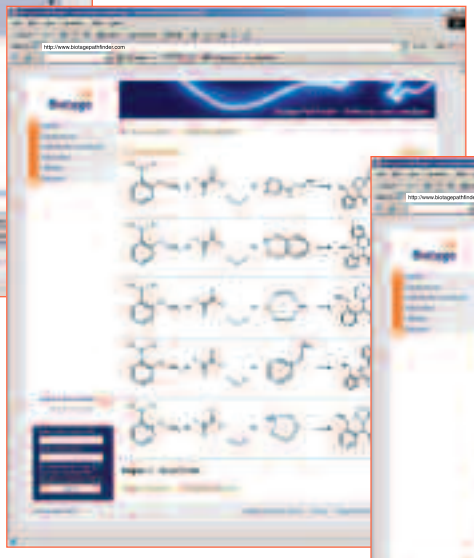


Figure 2. *Search results are displayed in an easy-to-browse format.*



Figure 3. *Reaction details needed to perform reactions are listed in an easy-to-read format.*

Ordering information

Item	Description	Part Number
Biotage Pathfinder Web	Single Seat-Annual Subscription	355239
Biotage PathFinder Web	Free 1-Month Trial of PathFinder	355241

Published Microwave Reactions

Solid-Phase Microwave Reactions...pg 52

Solid-Supported Reagents... pg 53

Polymer-Supported Microwave Reactions...pg 53

Biotage Application Notes

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Application Note 21
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Application Note 28
Performance of Parallex Flex™ HPLC...pg 56

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Continuous-Gradient Purification of Closely Related Drug Intermediates Using FLASH Chromatography...pg 57

Application Note 40
Purification of Heterocyclic Amines on a new FLASH Media—KP-NH Silica...pg 58

Application Note 41
Improving Reversed-Phase FLASH Purification Throughput...pg 59

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Using TLC to Accurately Predict FLASH Purification Results...pg 62

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Eliminating Aqueous Work-Up in Multiple Step Solution-Phase Synthesis using Flash Chromatography...pg 63

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On-Column Clean Synthesis of a Substituted Benzofuran Using TsOH Cartridges...pg 67

Application Note 45
On-Column Clean Synthesis of an Array of a-phenoxyacetophenones Using Syntage TBD Cartridges...pg 70

Application Note 46
Rapid Synthesis and Clean-up of an Array of Amines Using Pre-packed Syntage™ KP-PrSH silica-Supported Thiol Cartridges...pg 74



Applications Corner

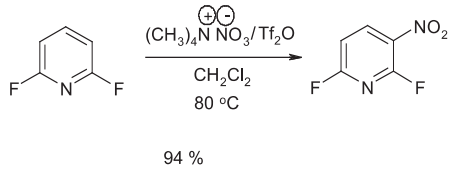
Application Notes and Index of Published Microwave Reactions

Applications Corner

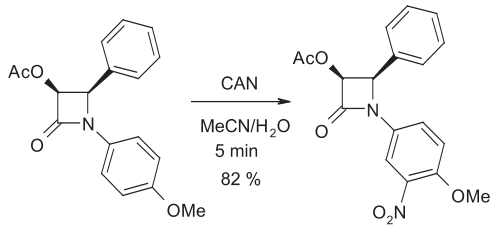
In this section, Biotage has hand selected published microwave reactions for your quick and easy reference. All chemistries listed were created using Biotage systems.

Solution-Phase Microwave Reactions

Nitration

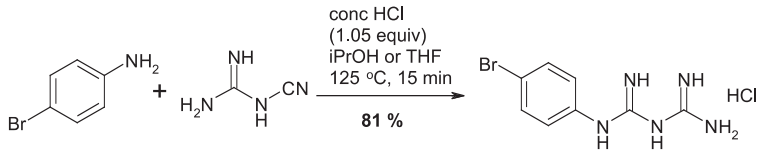


Shackelford, S. A. *et al. J. Org. Chem.* **2003**, 68, 267-275.



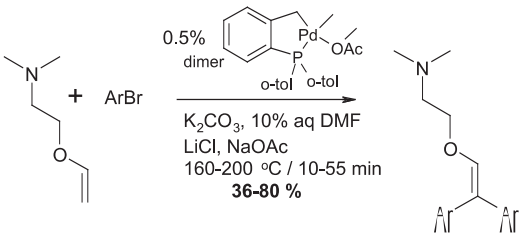
Bose, A. K. *et al. Synthesis*, **2002**, 1578-1591.

Amination

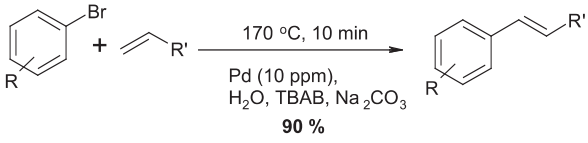


Organ, M.G. *et al. J. Combi. Chem.*, **2004**, 6, 776-782.

Coupling

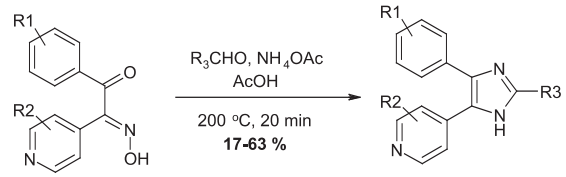


Larhed, M. *et al. J. Org. Chem.* **2004**, 69, 3345 - 3349.

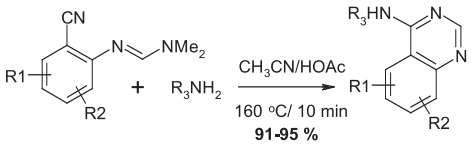


Leadbeater, *et al. J.Org. Chem.* **2005**, Article ASAP

Heterocycles

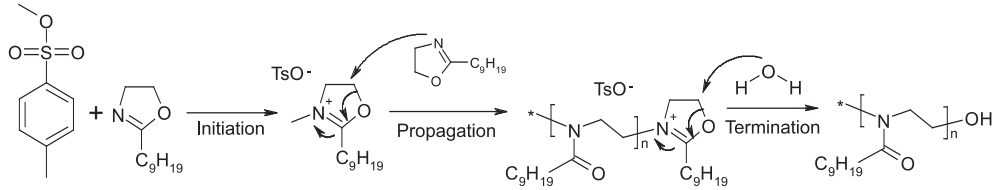


Combs, A. P.; Sparks, R. B. *Org. Lett.*; **2004**, 6 (14), 2473-2475.



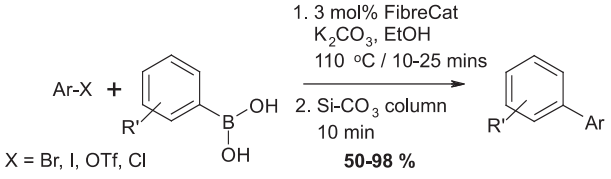
Han Y. *et al. Org. Lett.* **2004**, 6 (25), 4775-4778.

Polymerization

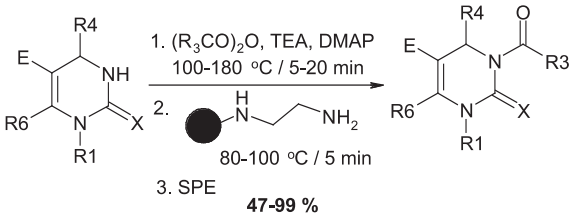


Schubert, U. S. *et al. J. Comb.Chem*. **2005**, 7, 10-13.

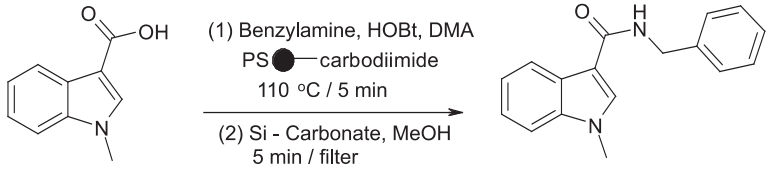
Solid-Supported Reagents



Sauer, D. R. *et al. Org. Lett.* **2004**, 6 (16), 2793-2796.

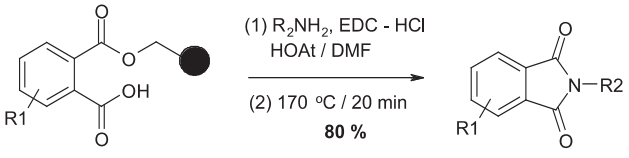


Kappe, O. C. *et al. Org. Lett.* **2003**, 5 (8), 1205-1208.

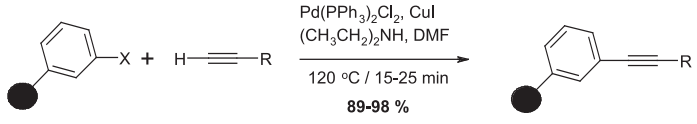


Sauer, D. R. *et al. Org. Lett.* **2003**, 5 (24), 4721-4724.

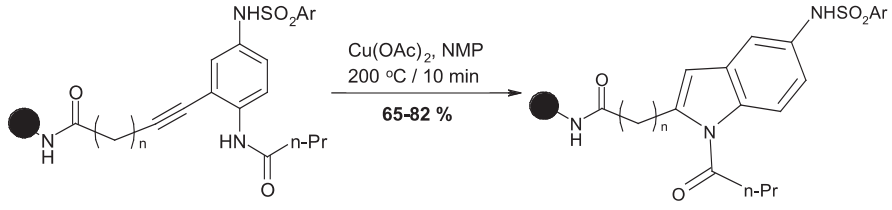
Polymer-Supported Reactions



Chassaing C. *et al. Org. Lett.* **2003**, 5 (11), 1851-1853



Gogoll, A., Erdelyi, M J. *Org. Chem.* **2003**, 68, 6431-6434



Dai, W-M. *et al. Org. Lett.* **2003**, 5 (16), 2919-2922

Review Articles:

1. Mavandadi, F.; Lidstrom, P. *Current Topics in Med. Chem.* **2004**, 4, 773-792.
2. Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, 6, 314-320.
3. Lew, A, Krutzik, P.O.; Hart, M.E.; Chamberlain, A. R. J. *Combi. Chem.* **2002**, 4, 95-105.
4. Larhed, M; Hallberg, A. *Drug Discovery Today*, **2001**, 6, 406-416.
5. Lidstrom, P.; Tierney, J. *Tetrahedron* **2001**, 57, 9225-9283.
6. Kappe, C.O. *Am. Lab.* **2001**, 33, 13-19.

Applications Corner

The applications group at Biotage uses the products we build, just as our customers do. We have a group of chemists who study the science of flash purification and apply it to synthetic organic reaction mixtures, natural product extracts, and biochemicals such as peptides and nucleotides. In this section, we highlight the most popular of the application notes published on our Web site, www.biotage.com.

Application Note 1

Purification of a Protected Peptide by FLASH Chromatography

By Shahnaz Ghassemi, Ph.D.

Product: FLASH

Abstract

Medical research involving peptides as pharmaceutical actives has increased over the last decade. Peptide synthesis requires the coupling of several different amino acids in sequential steps to obtain the desired product. The efficacy and biological activity of peptides are dependent on their final purity. Purity and yield are dramatically increased when purification is performed on smaller synthetic segments prior to segment coupling.

Historically, peptide segments have been blocked from coupling using any number of bulky, hydrophobic, removable reagents such as Fmoc (9-fluorenylmethoxycarbonyl), Boc (tert-butyloxy carbonyl), trityl, etc., which bond to the peptide N-terminus and C-terminus. The resulting protected peptides, however, are very hydrophobic and have been difficult to purify by reversed-phase techniques.

In this application, a solution containing 300 mg of a crude peptide protected with trityl and dimethylcyclopropyl amide groups was purified using normal-phase chromatography with both a Biotage FLASH 12+™ system and a self-packed glass column (containing the same silica mass) for comparison. The results in the table below clearly show higher yield and purity of the target peptide in 1/24 the time with the FLASH 12+ system.

Column	Dimensions (mm)	Separation Time (min)	Solvent Consumed (mL)	Crude Load (mg)	Peptide Mass Recovered (mg)	Peptide Yield (%)	Peptide Purity (%)
Open Glass	12 x 150	240	236	300	154	60	78
FLASH 12+	12 x 150	10	50	300	192	95	99

Application Note 21

Effects of Solvent Type and Strength in FLASH Separations

By J. Robert Bickler, M.S.

Product: Quad3™

Abstract

Isolation of desired compounds from reaction mixtures and natural products by flash chromatography is not always a straightforward process. A product and its analogs may not be separable without performing some type of method development and optimization.

Application 21 discusses the role of TLC (thin-layer chromatography) as a flash purification method-development and optimization tool, in relation to the impact of solvent choice on compound retention and selectivity. In this application, a mixture of four dyes (three hydrazine dye analogs and an anthraquinone dye) was used as an example.

TLC was used to evaluate five solvent mixtures for selectivity: ethyl acetate/heptane, acetone/heptane, isopropanol/heptane, toluene, and methylene chloride. TLC was also used to evaluate the solvent strength of these mixtures by varying the polar component percentage. A total of 12 solvent systems were transferred and simultaneously run on a 12-channel, Quad3 Parallel FLASH Purification system to show how TLC separations translate to flash separations.

TLC results show that the three hydrazine dye analogs (fat red 7B, methyl yellow, and Sudan IV) cannot be separated when an oxygen-containing solvent is used, regardless of concentration; only methylene chloride, or toluene efficiently separate all four dyes; Figures 1 and 2. Without using TLC for method development and optimization, successful FLASH purification would not have been possible.

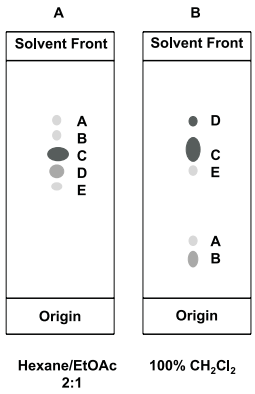


Figure 1.
TLC separations showing the effect of different solvents on elution profile (selectivity). A) A mixture of hexane (group) and ethyl acetate (group VIa), B) same sample separated with methylene chloride (group V). Note how the elution order of the five spots has changed.

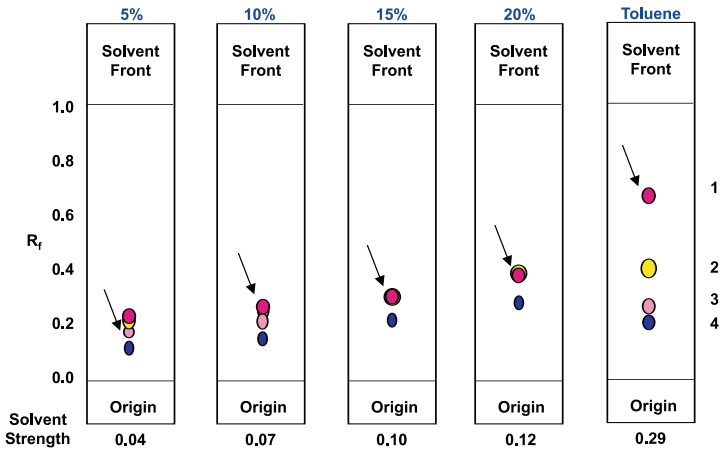


Figure 2. *TLC separation of dyes using ethyl acetate/heptane mixtures and toluene. Note the difference in selectivity (⟶) compared to toluene. Elution order. 1. fat red 7B, 2. methyl yellow, 3. Sudan IV, 4. Sudan blue.*

Application Note 28

Performance of Parallex Flex™ HPLC

By Jack Liu, Ph.D.

Product: Parallex Flex

Abstract

The Parallex Flex Flexible Purification System is a walk-up, preparative HPLC (high-performance liquid chromatography) system configured with up to four independent channels, eliminating purification-stage bottlenecks in the drug discovery process. Many drug companies choose to purify their compounds prior to biological testing. The Parallex Flex parallel purification systems make this method of prepurification efficient and effective.

The Parallex Flex uses 24-, 48-, and 96-well microtiter-plate formats for automated sample injection. Each of the four flow paths is independent; simultaneously, each can run a different gradient with a different sample on a different column. Each flow stream is monitored by a preparative dual-wavelength UV detector that allows the fraction collector to collect fractions based on slope and/or threshold settings at either wavelength. This tool minimizes mixed fractions and the total number of fractions collected. High-purity fractions are collected into 24-, 48-, or 96-well microtiter plates or test tubes.

Application 28 addresses the issues of cross-contamination and sample recovery. Cross-contamination was determined by conducting an experiment in which four samples, each containing a single paraben (methyl, ethyl, propyl or butyl) were prepared and loaded into alternate wells in two 96-well plates (methyl and ethyl in

plate one, propyl and butyl in plate two). Each plate was loaded onto a two-channel Parallex Flex and the 1-mL samples from each well of the entire plate were injected. Collected fractions were analyzed using an analytical HPLC system to determine the amount of cross-contamination. The results in Table 1 show cross-contamination levels of less than 1%.

Compound	Average(%)	Deviation (%)	Number of Samples
Methyl Paraben	0.34	0.15 – 0.68	47
Ethyl Paraben	0.70	0.05 – 1.49	47
Propyl Paraben	0.49	0.35 – 0.76	47
Butyl Paraben	0.12	0.02 – 0.29	47

Table 1. *Cross-contamination levels for Parallex Flex HPLC.*

Sample recovery was determined using a mix of ethyl and butyl parabens, with threshold and slope settings of 0.01. The samples were separated using gradient elution on a 20 x 50 mm C18 column at 20 mL/min. Collected fractions were analyzed by analytical HPLC with the results listed in Table 2. Recovery levels exceeding 96% were achieved using the Parallex Flex.

Compound	Average (%)	Standard Deviation	Number of Samples
Ethyl Paraben	96.4	0.07	24
Butyl Paraben	97.6	0.05	24

Table 2. *Fraction recovery for the Parallex Flex HPLC.*

Application Note 38

Continuous-Gradient Purification of Closely Related Drug Intermediates Using FLASH Chromatography

By Jack Liu Ph.D, Omar Mneimne M.S., J. Robert Bickler M.S., and Peter Rahn Ph.D.

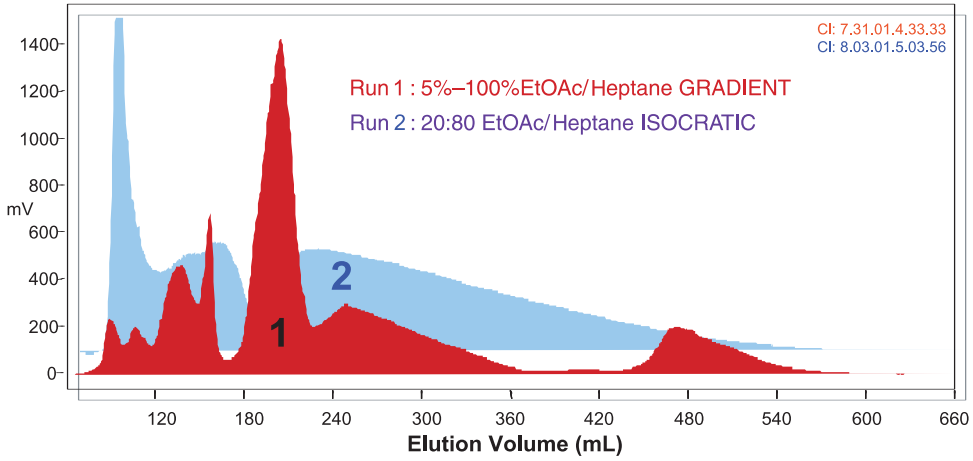
Product: Horizon™ HPFC™

Abstract

Synthetic organic chemists worldwide monitor reactions by using some type of chromatographic analysis whether it is thin-layer chromatography (TLC), gas chromatography, high-performance liquid chromatography (HPLC), or, most recently, liquid chromatography/mass spectrometry (LC/MS). By far, the simplest and most widely used analytical technique is TLC. TLC is also used to develop conditions for the purification of organic compounds, purifications typically implemented using isocratic elution with normal-phase silica columns.

Isocratic elution is effective but can be slow, requiring many column volumes of solvent to complete. Gradient elution, a chromatographic elution technique that increases the solvent strength over time, is a method of reducing purification duration.

Synthetic medicinal chemists, under pressure to increase novel lead-candidate production, need turnkey purification systems and protocols to help them achieve productivity goals. In this application, four oxazoline analogs were synthesized and purified at gram-scale using a generic gradient elution and the new Horizon high-performance FLASH chromatography (HPFC) system. The successful chromatographic results are shown in Figure 1.



Gradient Conditions

FLASH cartridge:	**FLASH 25+M 25 x 150 mm Silica**	**Waste:**	**100% A 48 mL**
Flow:	**30 mL/min**	**Gradient:**	**0% –100% B in 480 mL**
Mobile phase:	**A = Heptane**	**Detection:**	**UV @ 254 nm**
	B = Ethyl acetate		
FC format:	**16 x 150 mm test tube**		

Figure 1. *Comparison of isocratic (2) and gradient (1) elution techniques. Gradient elution provides enhanced selectivity and resolution due to gradual solvent strength change over time.*

Application Note 40

Purification of Heterocyclic Amines on a New FLASH Media—KP-NH Silica

MarthaJoy M. Spano and J. Robert Bickler

Product: Syntage KP-NH Cartridges

Abstract

Much of pharmaceutical research is centered on nitrogen heterocycle chemistry. These basic amines are difficult to purify using traditional silica chromatography because of strong interactions between acidic silica and the molecules' basic amine groups. These interactions cause band spreading and poor compound recovery.

Biotage, Inc., recently developed KP-NH, an alternative to amine-modified solvents and reversed-phase chromatography, for organic amine purification. KP-NH has a slightly alkaline nitrogenous surface chemistry that provides an "organic amine friendly" environment capable of high sample loads, improved selectivity and recovery compared to silica. This application note shows the comparison of silica to KP- NH for the purification of basic pharmaceuticals tolperisone, verapamil and nifedipine.

Results

KP-Sil strongly binds most organic amines used in this study, only nifedipine (contains a nitroaromatic ring) was recovered from silica at high yield. In Figure 1, the selectivity difference between the KP-Sil and KP-NH for sample three is shown. KP-NH separates and elutes each individual component with tolperisone eluting first, verapamil second and nifedipine third. KP-Sil binds tolperisone and does not separate verapamil from nifedipine.

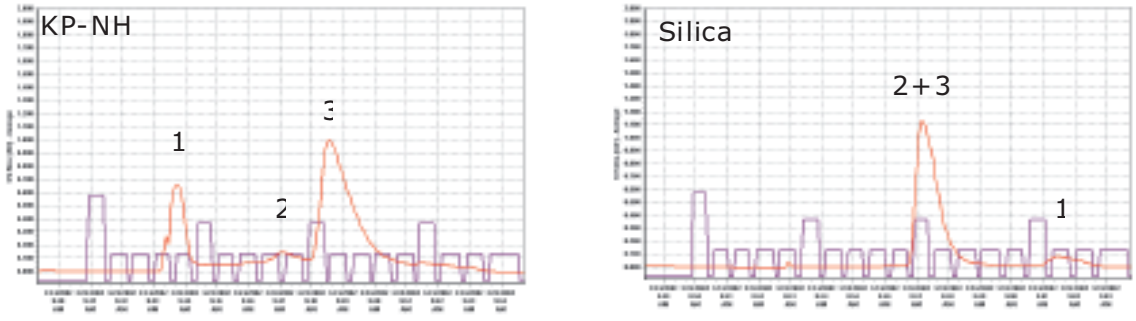


Figure 1. *Comparison of KP-NH (left) and silica purification results using a hexane – ethyl acetate (0-100%) gradient. KP-NH is able to separate and elute all three compounds, tolperisone (1), verapamil (2), and nifedipine (3). Using silica, tolperisone elutes last with lower yield, while verapamil and nifedipine co-elute. Sample load was 300 mg. Cartridge size 12 x 150 mm. Purification system, Biotage Horizon.*

Conclusion

Biotage KP-NH cartridges offer definite benefits as an alternative to plain silica in medicinal chemistry FLASH purification applications. Specifically, nitrogen heterocycles and tertiary organic amines are purified with better purity and yield on KP-NH than on plain silica using simple hexane—ethyl acetate gradients.

Application Note 41

Improving Reversed-Phase FLASH Purification Throughput

Sjaan Armentrout, John Gu, J. Robert Bickler

Abstract

Normal-phase flash purification is commonly used by organic chemists in pharmaceutical drug discovery and process development labs. However, for many synthesized products (e.g., peptides, nucleotides and basic drug

candidates) purification on standard flash silica is not an option due to irreversible adsorption, chemical interaction and/or solubility issues. Reversed-phase flash purification is an excellent solution for these applications. Yet, this technique has been used sparingly because of perceived lower loading capacity, higher operating pressures and a scarcity of publications addressing reversed-phase flash chromatography.

Samples dissolved in organic solvents, when injected into highly aqueous reversed-phase solvent systems, are typically not well retained by C-18 columns. The injection solvent competes with the sample for access to the stationary phase, causing early compound elution (breakthrough) and peak broadening. The higher operating pressures required for reversed-phase purification preclude the use of glass columns and cause leaks in many commercially available flash systems. Research shows that system backpressure (in psig) when using reversed-phased solvents is roughly four times the flow rate (in mL/min) for 50:50 methanol/water (Figure 1).

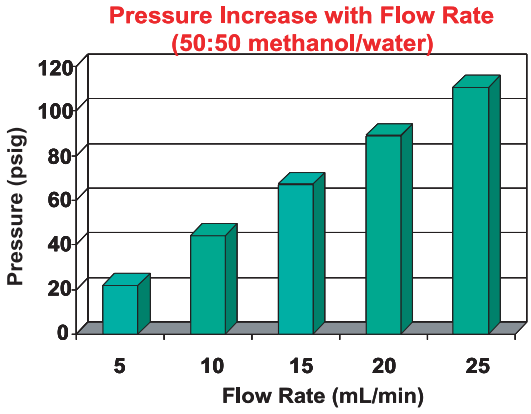


Figure 1. *Pressure increase with flow rate*

In recent years, Biotage has developed High Performance FLASH Chromatography (HPFC™) systems capable of operation at 100 mL/min and an operating pressure of up to 100 psig. HPFC systems utilize Biotage FLASH+™ cartridges and Samplets™ for sample purification. Samplets are premade sample preconcentration cartridges designed to adsorb samples dissolved in strong solvents. Once the majority of strong solvent has been removed from the Samplet, solvent effects are dramatically reduced, improving sample load and purification. Samplet-based HPFC products simplify reversed-phase FLASH purification and reduce user error.

A comparison of Samplet and direct-liquid-injection loading techniques is made in this application note. Each of these techniques is used to separate and purify several basic pharmaceutical compounds by reversed-phase HPFC. Effects of injection mass and flow rate on reversed-phase FLASH purification cartridges are shown.

Procedure

The experiments were conducted using three samples. Samples one and two consisted of a three-component equal weight mixture of 1-methylbenzimidazole, brucine and promethazine dissolved in methanol at 150 mg/mL and 300 mg/mL, respectively. Sample three contained 100 mg/mL of promethazine in methanol, which oxidized

rapidly to produce a deep blue color. Each solution was adsorbed onto C18 Samplets and air-dried in a fume hood until no solvent was organoleptically detected.

All three samples were separated on KP-C18-HS cartridges using a Horizon™ automated HPFC system. Separation performance and loading capacity were compared using a direct liquid injection (through a valve) and the Samplet injection technique. The promethazine solution was purified using a FLASH 12+S cartridge, and the three-component mixtures were separated using a FLASH 12+M cartridge. In all instances, 1 mL of sample was applied. Compound retention and peak shape were compared for each injection technique. Promethazine fractions were analyzed for peak purity by HPLC.

Results

In each case the Samplet increased compound retention and loading capacity by eliminating solvent effects. Drying the Samplets prior to purification increased compound retention (Figures 2 and 3) because the dissolution solvent, removed by evaporation, no longer competed with the compounds' interaction with the cartridge media. Also, compounds eluted with narrower peakwidth (Figure 2), higher purity (no mixed peak containing both promethazine and its degradant) and greater yield (Figure 3) when the sample was introduced onto the cartridge using the Samplet.

Higher loading capacity is also evident when using a Samplet. In figure 2, sample A (300 mg/mL) was injected using a Samplet and sample B (150 mg/mL) was directly injected using a syringe. The data shows the three components, 1-methylbenzimidazole, brucine, and promethazine, having a similar separation profile, even though twice as much sample was loaded and purified using the Samplet.

The increased pressure capability of the Horizon HPFC system enabled a separation to occur in 12 minutes at a flow rate of 13 mL/min. A similar separation would take nearly an hour to complete using glass column technology.

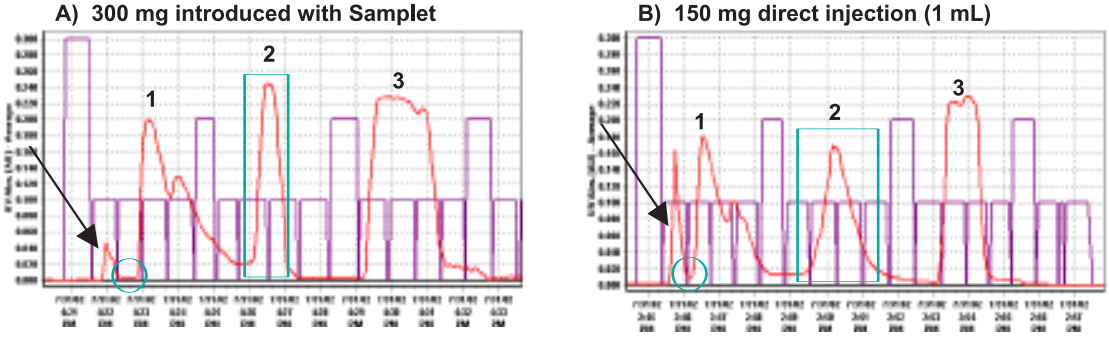
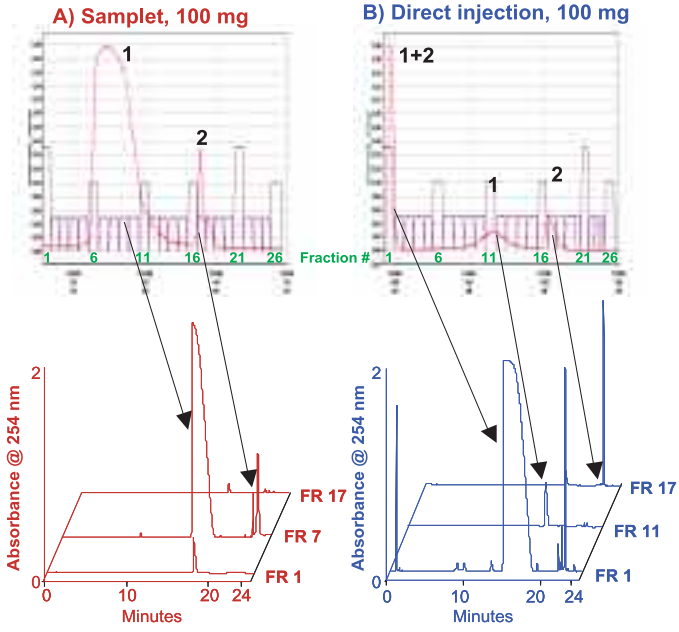


Figure 2. FLASH Elution Conditions

Cartridge:	FLASH 12+M C18
Solvents:	A = DI H2O with 0.1% NH4COOH B = 90% methanol in H2O with 0.1% NH4COOH
Gradient:	Equilibrate 12 mL at 0% B Linear gradient 0–100% B in 90 mL Hold 100% B for 24 mL, step to 0% B for 60 mL
Flow rate:	13 mL/min
Detection:	254 nm
Compounds:	1. 1-Methylbenzimidazole 2. Brucine 3. Promethazine

Conclusion

Reversed-phase purifications using KP-C18-HS cartridges with the Horizon HPFC system demonstrate high loading capacity and throughput. Because of ruggedly constructed cartridges and the Horizon's high-flow/high-pressure pump, flow-rate limitations are eliminated, reducing overall sample run time. Use of Samplet technology further increases purification throughput by increasing the loading capacity of the cartridge.



HPLC Conditions

Column:	YMC Pro C18 (4.6 x 100 mm)
Solvents:	A = Methanol/ 0.1% NH4COOH (aq) 10:90
	B = Methanol/ 0.1% NH4COOH (aq) 90:10
Gradient:	Equilibrate 2 min at 0% B
	Linear gradient 0-50% B in 20 min
	Step to 100% B, hold for 2 min
Flow rate:	2 mL/min
Injection vol.:	50 µL
Detection:	254 nm
Compounds:	1) Promethazine (100 mg/mL in methanol)
	2) Blue degradation product

Figure 3. *Samplet (A) and direct injection (B) impact on degraded promethazine purification using FLASH 12+S C18 cartridges and gradient elution. Samplet injection of promethazine sample provides complete compound (1) and degradation product (2) retention and purification while a direct liquid sample injection (1 mL) inhibits retention and purification. Collected fractions were analyzed by HPLC to verify fraction composition and compound purity.*

Samplet use greatly reduces the solvent effects seen with direct injections, increasing compound retention, purity, and yield. Additionally, co-elution or breakthrough in the void volume is reduced, elevating recovery of the compound of interest.

Application 42

Using TLC to Accurately Predict FLASH Purification Results

J. Robert Bickler

Abstract

Although many TLC and flash-grade silicas have the same physical specifications (surface area, porosity, etc.) differences in their qualities exist. These differences manifest themselves as gross errors in the calculated CV, variable selectivity, and unreliable loading capacity calculations. Because of these real method transfer problems, it is very important that the TLC silica and the flash silica be identical and from the same vendor.

When TLC and flash silicas are identical, the equation 1 / Rf = CV holds, where Rf is the retention factor of a compound separated by TLC, and CV is the number of column volumes required to elute a compound in flash. Cartridge loading capacity is based on the difference in CV (ΔCV) between two adjacent compounds.

Discussion

A test of Biotage and a competitor's TLC plates using a 5-dye test mix with identical elution conditions highlights the performance differences. Although Rf values are similar for most compounds (red, orange, black, and blue), the yellow dye shows a remarkably different Rf value, 0.18 (5.56 CV) on a Biotage TLC plate, but an Rf of 0.25 (4.00 CV) on the competitor's plate; Table 1. When this dye mix was purified on a Biotage FLASH 12+M cartridge, the yellow dye eluted in 5.50 CV, as predicted by the Biotage TLC plate; Table 1.

TLC Rf to Flash CV Correlation

	Biotage FLASH TLC Rf	Calc. CV	ΔCV	Biotage FLASH CV	% Relative Error	Comp. TLC Rf	Calc. CV	ΔCV	Biotage FLASH CV	% Relative Error
Red	0.84	1.19		1.25	4.76	0.82	1.22		1.25	2.44
Orange	0.34	2.94	1.75	3.00	1.96	0.33	3.03	1.81	3.00	-1.01
Black	0.30	3.33	0.39	3.25	-2.56	0.28	3.57	0.54	3.25	-9.89
Yellow	0.18	5.56	2.23	5.50	-1.01	0.25	4.00	0.43	5.50	27.27
Blue	0.10	10.00	4.44	9.25	-8.11	0.09	11.11	7.11	9.25	-20.12

Table 1. *Shows improved flash purification predictability when the TLC silica and flash silica are the same. Much greater reliability in calculated elution volumes (solvent consumption) is possible. In this example, the yellow dye has an Rf of 0.18 (5.56 CV) on the Biotage FLASH TLC plate but an Rf of 0.25 (4.00 CV) on the competitive plate. With more accurate CV calculations, better throughput, purity, yield, and solvent cost savings will be realized.*

Conclusion

TLC to flash method transfer accuracy is improved when TLC plates and flash cartridges made with identical silica from the same vendor are used. In the example cited above, the Biotage FLASH TLC plate Rf data correlate to flash CV with greater accuracy than a competitive plate with the same silica specifications. For synthetic chemists, the benefits of matched TLC plates and flash cartridges are better purification throughput, increased compound purity and yield, and reduced solvent cost.

Application Note 43

Eliminating Aqueous Work-Up in Multiple Step Solution-Phase Synthesis using Flash Chromatography

By Shahnaz Ghassemi, Ph.D.

Abstract

Post-reaction work-up is a major bottleneck in the synthetic process. Generally, the work-up steps of an

organic reaction take considerably longer than the actual synthesis. The major impediment with solution-phase synthesis is the multiple aqueous work-up steps often necessary to remove excess reagent and byproducts when isolating desired compounds. It is often common for some reactions to require four or five aqueous extractions followed by drying and filtration. Although these extractions are easy to perform, they require additional chemist interaction and delay the goal of obtaining pure compound for further study. In addition, the formation of emulsions during these extraction/wash steps causes lower yields and increases purification time. However, solution-phase synthetic techniques offer many advantages over solid-phase approaches including unlimited scale, easy manipulation and reduction in validation time.

By planning the solution phase synthesis to include a Flash chromatography purification step, the need for a post-reaction work-up is eliminated. To illustrate the advantages of incorporating high-performance flash chromatography (HPFC) into a solution phase synthesis reaction procedure, a polypeptide (Fmoc-Tyr(t-Bu)-Gly-Gly-Phe-Leu-NDMCP) was synthesized by an eight-step solution-phase technique using the Horizon HPFC system inline for fast product isolation. Biotage's Horizon™ HPFC system combines gradient elution capability and UV-based fraction collection in an ergonomically designed format; Figure 1.

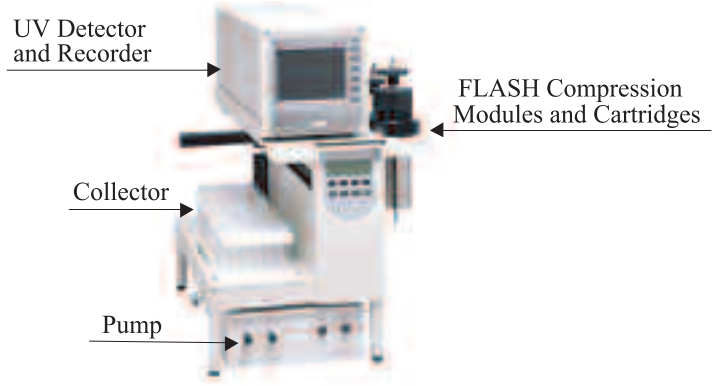


Figure 1. *The Biotage Horizon™ HPFC Purification System includes a gradient pump, UV detector and recorder. Control is accomplished via single keyboard control.*

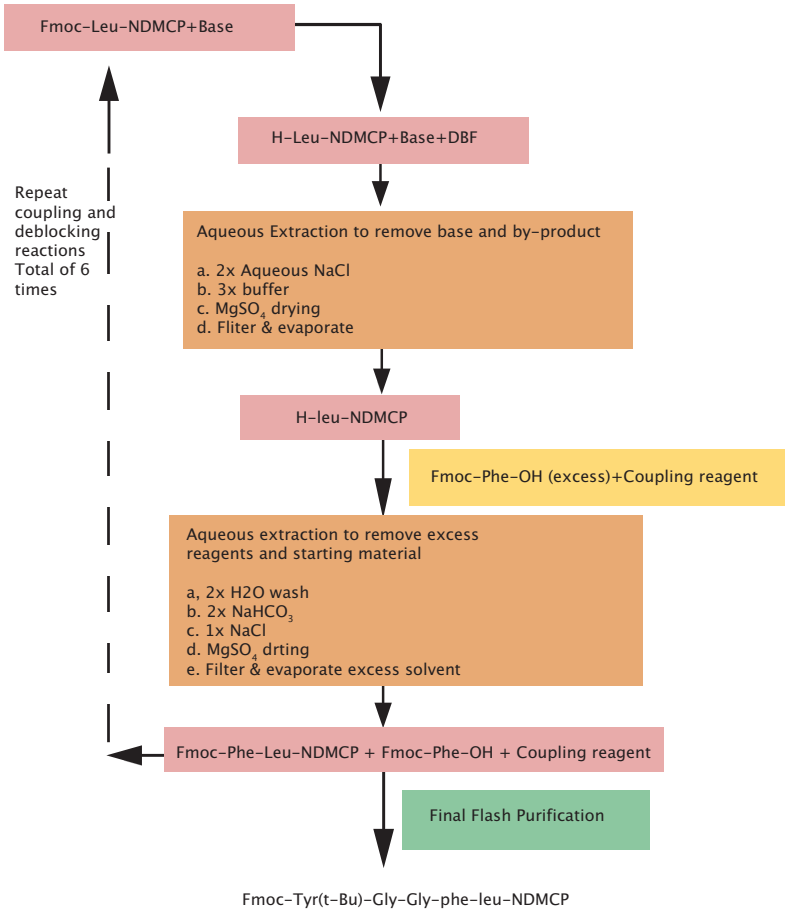
Fast Solution-Phase Synthesis of Fmoc-Tyr(t-Bu)-Gly-Gly-Phe-Leu-NDMCP

The desired polypeptide product was synthesized using the traditional solution phase synthesis technique that started with Fmoc-Leu-NDMCP. The eight steps included four amino acid coupling reactions and four Fmoc-deblocking reactions. This work compares two sample workup methods: 1) the traditional aqueous work-up 2) and the in-line HPFC technique for isolation of intermediates and final products.

Method 1: Aqueous Work-Up Technique

After reacting the Fmoc base peptide (Fmoc-Leu-NDMCP) with base and DBF (dibenzofulvene), the aqueous work up procedure requires two washes with NaCl, three washes with buffer followed by drying with magnesium sulfate and then, finally, filtering the product and evaporating the excess solvent. After the coupling reagent is added and the reaction occurs, additional aqueous extractions are required again followed by magnesium

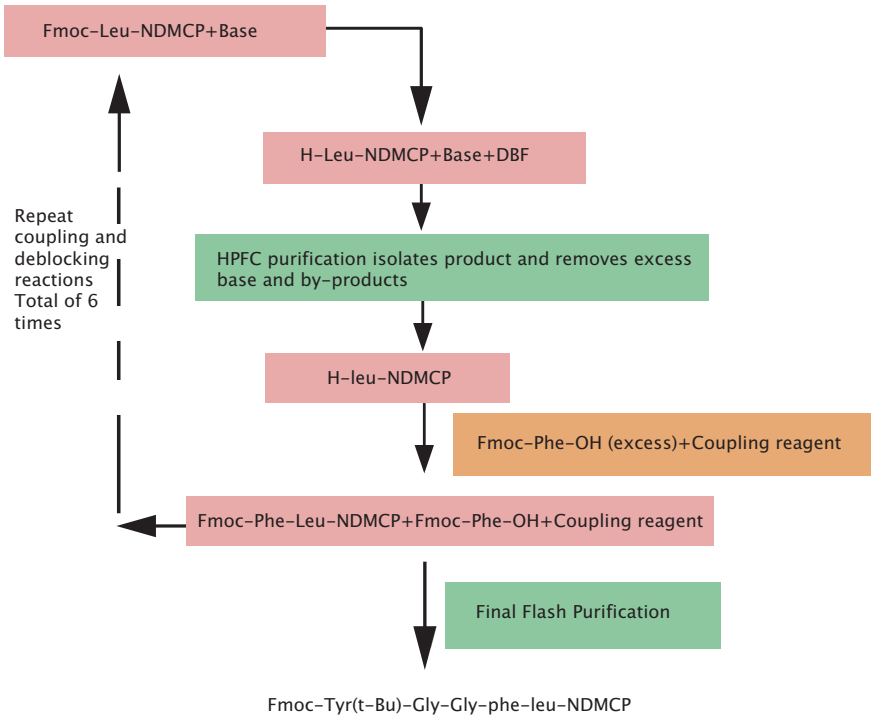
sulfate drying steps. Multiple aqueous washes with dilute acid or dilute base are utilized to remove excess reagents, byproducts or excess reagents after each synthetic step multiple aqueous washes followed by drying, filtration, and evaporation are required; Flow Chart 1.



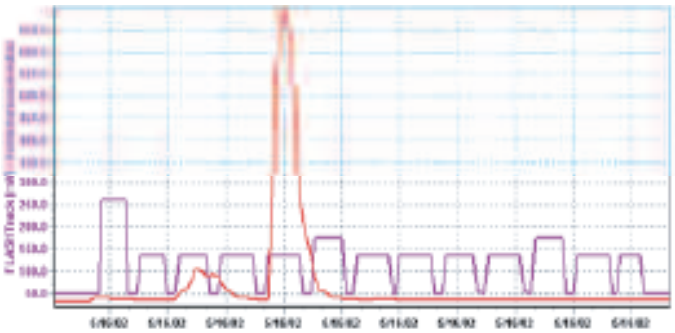
Flow Chart 1. *Aqueous work-up for removing excess reagents and byproduct.*

Method 2: In-Line HPFC Technique

The new integrated technique incorporating Flash chromatography after each Fmoc-deblocking step eliminates the aqueous wash protocol. The crude reaction mixture is directly added to a Biotage FLASH 25+ Samplet™ cartridge without any aqueous work up. Samplet cartridges allow for quick, direct loading of soluble and insoluble samples onto the FLASH cartridge. The Samplet cartridge was inserted into the FLASH 25+ cartridge and the compounds were purified using dichloromethanel/methanol (DCM/MeOH) gradients. This integrated procedure reduces sample handling, decreases the overall cycle time while providing higher yield with purer product; Flow Chart 2. The collected fractions were tested by TLC and ninhydrin test. Mass spectra (running ESI+ mode) were used to confirm identity of each isolated product after flash chromatography.



Flow Chart 2. *The new integrated technique incorporating Flash chromatography after each Fmoc-deblocking step eliminates the aqueous-wash protocol.*



Cartridge:	Biotage FLASH 25+M (25 x 150 mm)
Load:	450 mg
Detection:	254 nm
Solvent:	A: DCM
Solvent B:	MeOH
Gradient:	0-10% B in 500 mL
Flow rate:	32 mL/min.

Figure 2. *Gradient FLASH separation quickly isolates desired product from the reaction mixture after each Fmoc de-blocking step. The Horizon system was programmed with the following conditions:*

Results

This multistep solution synthesis yielded 765 mg (83.3%) of highly pure (greater than 90%) Fmoc-Tyr(t-Bu)-Gly-Gly-Phe-Leu-NDMCP in less than eight hours. Synthesis of the same compound by traditional solution phase techniques using aqueous extractions was complicated because of the formation of emulsion during the aqueous wash required at each step and the final yield was less than 40%. This synthesis required two to three days to complete this multistep synthesis.

Conclusion

Substituting aqueous work-up with FLASH™ chromatography increases the yield and purity of the final product. Because no aqueous washes are required, there is much less sample handling and no product loss due to emulsions, drying with MgSO4 and filtration. Also, using FLASH chromatography ensures up to 95% purity of isolated intermediate product at each synthetic step with very little product lost. The ability to combine Flash purification and synthesis into a single process increased the yield of the overall reaction by 100% and provided a faster process for a multiplestep synthesis that was easily completed in a single day.

Application Note 44

On-Column Clean Synthesis of a Substituted Benzofuran Using Syntage™ TsOH Cartridges

By Shahnaz Ghassemi, Ph.D.

Product: Syntage KP-TsOH cartridges

Abstract

There is a need to develop a simple, fast and flexible method to generate substituted benzofuran libraries that are utilized as potential antioxidants and drug candidates. This work illustrates an on-column synthesis of substituted benzofuran using the Syntage KP-TsOH Samplet cartridge for on-column synthesis of a heterocyclic benzofuran ring system (2) starting with α-phenoxyacetophenones (1); Figure 1.

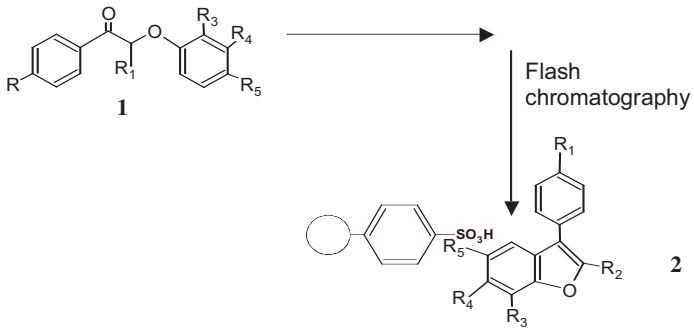


Figure 1. *Synthesis of Substituted Benzofuran using the Syntage KP-TsOH cartridge*

A Syntage KP-TsOH Samplet cartridge is a silica-bonded p-toluenesulfonic acid with a high surface area media that exhibits excellent retention of basic compounds. This reagent is useful for cyclodehydration reactions as well as scavenging amines.[1,2,3]

The Syntage KP-TsOH Samplet cartridge is sufficiently acidic to close the heterocyclic ring of organic halides[3] and for the high throughput synthesis of aryl triflates and aryl nonaflates.[4]

Silica-bound TsOH is also routinely applied in a "catch and release" protocol, whereby basic species are caught by the sulfonic acid and then subsequently released during the Flash purification step using a combination of DCM:MeOH and ammonia.

The use of solid-supported reagents combines the advantages of solution-phase synthesis, which includes easy monitoring of the reaction progress by LC-MS, TLC or NMR techniques and solid-phase chemistry, which employs excess reagent without adding additional purification steps.

The advantages of using the Syntage™ silica-supported cartridges include the following:

1. Eliminates aqueous work-up
2. Increases rate of reaction
3. Eliminates need to wash and filter solid support
4. Decreases solvent consumption
5. Facilitates easy automation for parallel solution-phase synthesis

Syntage Solid Bonded Reagent Cartridges for Synthesis

The Syntage KP-TsOH Samplet cartridge is utilized as a reagent to synthesize benzofurans by starting with ∞-phenoxyacetophenone in toluene using the following protocol:

1. 300 mg of the α-phenoxyacetophenone was dissolved in 800 mL of toluene and transferred onto a Syntage KP-TsOH Samplet cartridge; Figure 2.



Figure 2. *Syntage KP-TsOH cartridge being loaded with a-phenoxyacetophenone*

2. The Syntage KP-TsOH Samplet cartridges were placed into the heating blocks and heated for four hours at 70 °C in the oven
3. The Syntage KP-TsOH Samplet cartridge containing the starting material and product are directly placed into the FLASH+ 12™ cartridge and purified using FLASH chromatography; Figure 3.

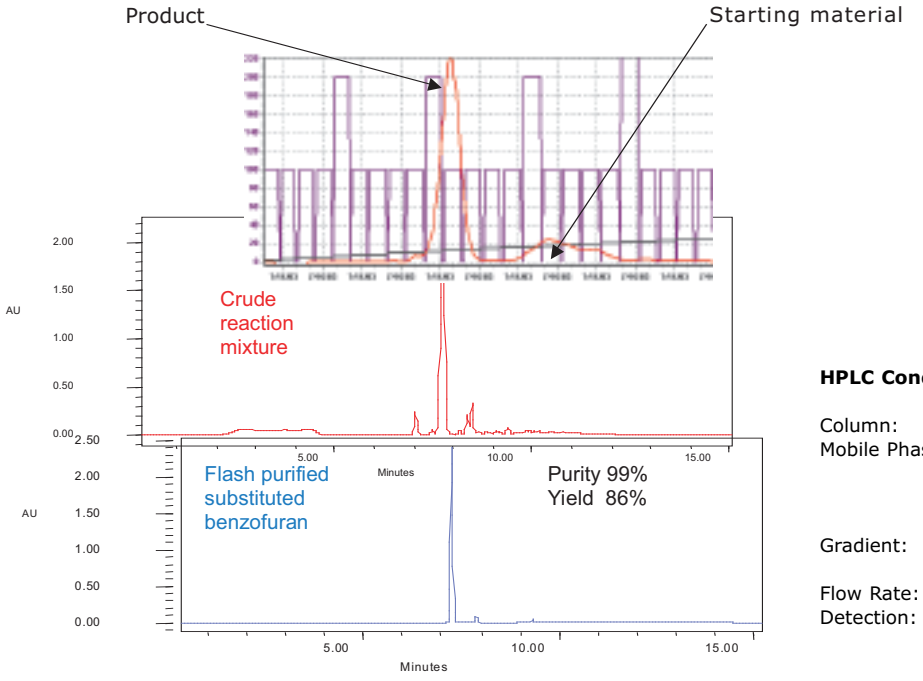


Figure 3. *After the reaction was complete, the Syntage KP-TsOH cartridge was directly inserted into FLASH cartridge eliminating the need for extra connections or sample handling. The total sample is applied to the cartridge in a plug-flow format with this sample introduction technique.*

4. The product was analyzed by HPLC and confirmed by FT-IR, H-NMR and ES-MS; Figure 4.

Figure 4 illustrates the results from the synthesis of one of the substituted benzofurans by starting with a phenoxyacetophonone that had been produced using the Syntage KP-TBD Samplet cartridge. The reaction yield was 89% and the purity of the final product was 99%.

HPLC Trace of Reaction Mixture and Final Product after Flash Purification



HPLC Conditions

Column:	C8 4.6 x 50 mm
Mobile Phase:	A: H2O:ACN (95:5) + 0.1% TFA B: ACN: H2O (95:5) + 0.1% TFA
Gradient:	5-100% B in 8 minutes, hold 2 minutes
Flow Rate:	1.5 mL/min
Detection:	254nm

Figure 4. *This is one example of the Flash purification and HPLC traces of the crude and isolated a-phenoxyacetophenone product. The Flash purification UV trace illustrates the a-phenoxyacetophenone separation from the starting materials and side products. Gradient flash conditions were used for this separation. Product purity was confirmed by HPLC.*

Conclusion

Syntage KP-TsOH Samplet cartridges easily and successfully integrate synthesis and purification. Traditional work-up steps are also eliminated when the Syntage Samplet cartridges are directly inserted into FLASH+ purification cartridges. This integrated synthesis and purification procedure eliminates solution transfers and sample manipulations, and it results in a higher yield of final product. These on-column reactions occur by solution-phase synthesis, allowing the reaction progress to be monitored at any step by TLC or HPLC eliminating a major drawback of solid-phase synthesis.

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Application Note 45

On-Column Clean Synthesis of an Array of a-phenoxyacetophenones Using Syntage™ TBD Cartridges

By Shahnaz Ghassemi, Ph.D.

Product: Syntage TBD cartridges

Introduction:

There is a need to develop a simple, fast and flexible method to generate libraries of a-phenoxyacetophenones that are precursors of substituted benzofurans. This work illustrates a new on-column synthesis of (-phenoxy-acetophenones (3) using Syntage KP-TBD Samplet cartridges by reacting (-bromoacetophenones (1) and a range of commercially available phenols (2) using the Williamson ether synthesis technique; Figure 1.

Syntage KP-TBD is a silica-supported strong hindered non-nucleophilic tertiary base that will de-protonate only moderately acidic hydrogen (e.g. phenols and activated methylenes). TBD has been used for the following:

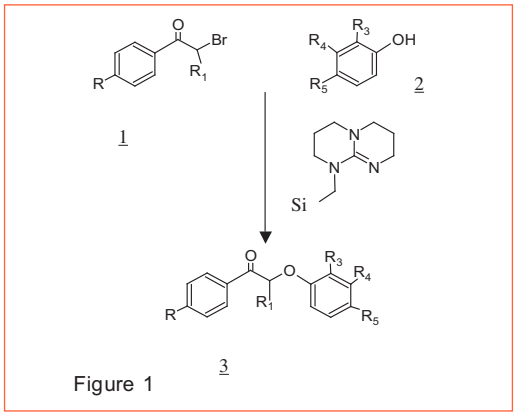


Figure 1. *Williamson ether synthesis technique*

1. Alkylation of phenols[1] and amines[2]
2. Esterification of carboxylic acids using alkyl halides
3. Alkylation of activated methylene compounds
4. De-halogenation of organic halides[3]
5. High-throughput synthesis of aryl triflates and aryl nonaflates[4]
6. Silica-bound TBD may also be applied in a "catch and release" protocol, whereby the acidic species is caught by the TBD in alkylation reactions and the addition of an electrophile results in nucleophilic substitution. The product is subsequently released into the solution.

The use of solid-supported reagents is a solution-phase synthesis technique that allows easy monitoring of the reaction progress by LC-MS, TLC or NMR techniques and employs excess reagent without adding additional purification steps.

The advantages of using the Syntage silica-supported cartridges are as follows:

1. Combining scavenging and flash purification in one step provides compounds sufficiently pure for NMR, IR and MS confirmation
2. Eliminates aqueous work-up
3. Enables real time monitoring
4. Increases the reaction rate
5. Eliminates the need to filter or remove the solid-support reagents

6. Decreases solvent consumption

7. Facilitates easy automation for parallel solution-phase synthesis

Phenol	pKa *	% Adsorption in Toluene	% Adsorption in THF	% Adsorption in DCM	% Adsorption in ACN
o-Nitrophenol	7.00	98.9	86.7	89.3	90.1
m-Nitrophenol	8.15	98.6	98.8	99.9	99.2
p-Nitophenol	6.85	99.9	95.5	99.9	99.9
o-Cresol	10.20	87.2	48.1	59.3	49.0
m-Cresol	9.70	79.6	51.2	96.7	72.5

Table 1. *Phenol loading on Syntage™ KP-TBD as a function of solvent, the maximum loading capacity was 0.3 mmole (42 mg) of 0-nitrophenol per gram.*

Solvent Effect on Capacity (Loading Levels of Phenols) of KP-TBD

As with all chemical reactions, optimizing the solvent choice is very important. The impact of the solvent type on this reaction was determined by evaluating the loading capacity of various disubstituted phenols in common reaction solvents. The contact time between KP-TBD and phenol was 15 minutes. For the phenols tested, the highest loading capacity was achieved in toluene; Table 1. After 15 minutes of contact time between the Syntage KP-TBD and the phenol, the maximum loading capacity was 1.2 mmole of o-nitrophenol per gram of Syntage KP-TBD.

For the remainder of these experiments in this application note, toluene was the solvent of choice for all of the reactions.

Synthesis procedure for x-phenoxyacetophenones

The following synthesis procedure was followed to produce the a-phenoxyacetophenone array utilizing the Syntage KP-TBD Samplet™ cartridges.

1. 1.2 mmole of each phenol was dissolved in 0.5 mL of toluene and transferred onto an individual FLASH 12+ Syntage KP-TBD Samplet cartridge; Figure 2.



Figure 2. *Syntage KP-TBD cartridge being loaded with phenol*

2. These cartridges were placed in a vacuum oven for 30 minutes and then 1.2 mmole of alkyl bromide in 0.5 mL ACN was added to each cartridge and heated in a vacuum oven for five hours at 80 °C.

3. After five hours, the Syntage KP-TBD Samplet cartridge was placed into the FLASH+™ cartridge and purified using a Biotage automated FLASH system; Figure 3.

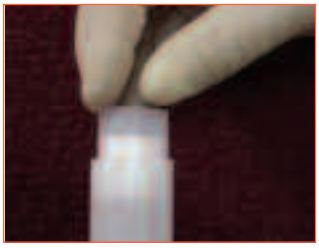


Figure 3. *After the reaction was complete, the Syntage KP-TBD Samplet cartridge was directly inserted into FLASH cartridge eliminating the need for extra hardware connections or sample handling. The total sample is applied to the cartridge in a plug-flow format with this sample introduction technique.*

Table 2 shows the a-phenoxyacetophenones synthesized in this work illustrating the broad utility of this technique. Each product was analyzed by HPLC and confirmed by FT-IR, H-NMR and ES-MS.

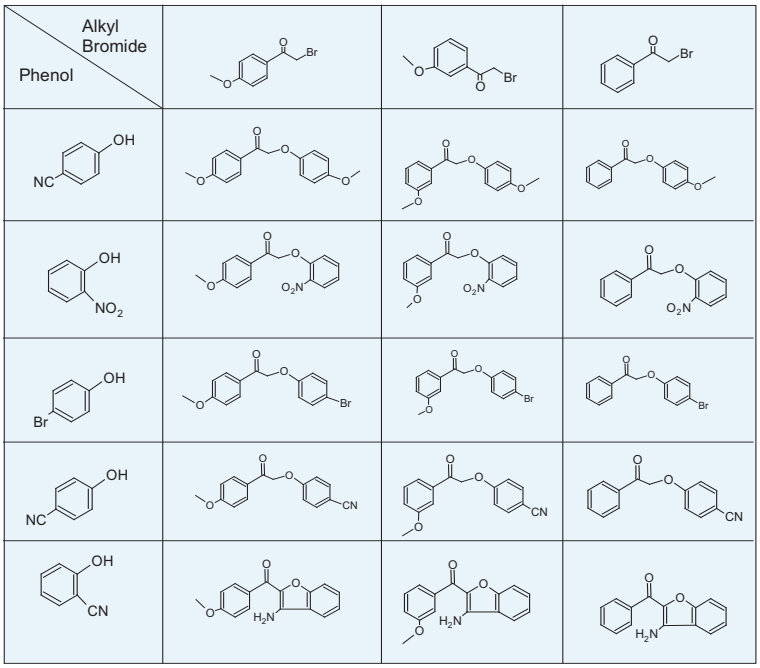
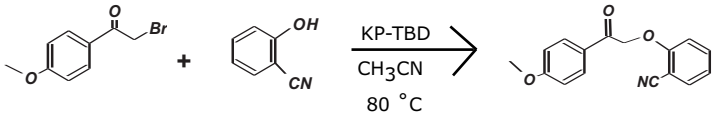
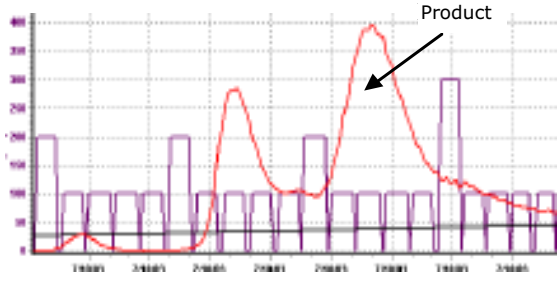
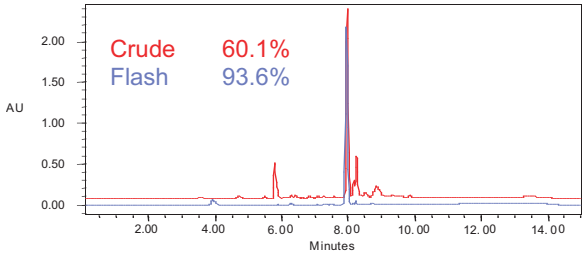


Table 2. *Twelve component a-phenoxyacetophenone array prepared using Syntage KP-TBD Samplet cartridge.*





Cartridge	FLASH 25+™M KP-Sil
Solvent	A: Hexane B: EtOAc
Gradient Program	Step 1: 0-40%B in 350 mL Step 2: 40-100%B in 300 mL
Flow Rate	25 mL/min.
Collected Fraction	25 mL/min.



HPLC Conditions

Column: YMC C8 (S-3 120 Å) 4.6 x 50 mm
Mobile Phase: A: H2O:ACN (95:5) + 0.1% TFA
B: ACN: H2O (95:5) + 0.1% TFA
Gradient: B: (5-100%) in 8 min., hold 2 min.
Flow Rate: 1.5 mL/min
Detection: 254nm

Conclusion

Syntage KP-TBD Samplet cartridges easily and successfully integrate synthesis and purification. Traditional work-up steps are eliminated when the Syntage Samplet cartridges are directly inserted into FLASH+ purification cartridges. This allows fewer solution transfers and sample manipulations, and results in a higher yield of final product. With each collected product, the purity was greater than 93% and the individual yield varied between 53 and 84%.

Since these on-column reactions occur by solution-phase synthesis, the advantage of easily monitoring the reaction progress at any step by TLC or HPLC eliminates a major drawback compared to performing solid-phase synthesis.

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Application Note 46

Rapid Synthesis and Clean-up of an Array of Amines Using Pre-packed Syntage™ KP-PrSH silica-Supported Thiol Cartridges

By Shahnaz Ghassemi, Ph.D.

Product: Syntage KP-PrSH cartridges

Abstract

Fast, efficient synthesis and purification of cyclic tertiary amines is important in drug discovery. This work illustrates a new synthesis technique that produces a high-purity array of cyclic tertiary amines using parallel solution-phase synthesis by coupling Syntage™ KP-PrSH Samplet cartridge with Flash chromatography. KP-PrSH is the silica-bonded equivalent of 1-propanethiol (Figure 1) designed to covalently scavenge alkyl, benzyl and aryl halides as well as a variety of electrophiles including acid chlorides and isocyanates. Additionally, KP-PrSH will scavenge metal catalysts used in organic synthesis including Cu, Pd and Pb.

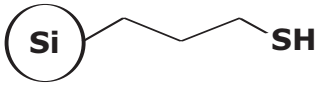


Figure 1. *Structure of Syntage KP-PrSH cartridge.*

General Synthesis and Purification procedure for solution-phase alkylation reaction

In a 5 mL vial, 0.6 mmole of amine and 1.2 mmole of alkyl halide were reacted with 1.6-mmole diisopropylamine in THF; Figure 2. The reaction mixture was stirred for 30 minutes at room temperature and then transferred onto a Syntage KP-PrSH 25 mm cartridge, dried in an oven at 80 °C for 10 minutes and then the Samplet™ cartridge was directly inserted into a FLASH 25+M™ silica cartridge; Figure 3. Products were isolated using a Biotage automated FLASH Horizon™ HPFC™ system.

Advantage of coupling KP-PrSH cartridges to flash chromatography

Figure 2 indicates the step where the Syntage™ KP-PrSH Samplet cartridge was employed in the alkylation reaction's purification step. Figure 3 chromatographically shows the TLC and HPLC chromatographic results after reacting 1,2,3,4-tetrahydroisoquinoine with 2-bromo-4'-methoxyacetophenone. When the reaction is complete, excess starting material and byproducts must be removed prior to further biological screening or use of this intermediate product.

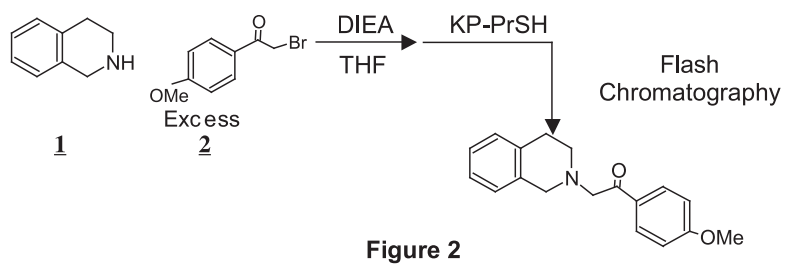


Figure 2

Figure 2.

	% Purity	Yield	Color
Reaction Mixture	42	—	Yellow Orange
Syntage KP-PrSH SPE	62	—	Yellow Orange
Flash Chromatography alone	83	85.3	None
Syntage KP-PrSH Samplet cartridge and FLASH+ Cartridge	99	93	None

Table 1. *Purity and yield comparison for three different purification techniques*

Synthesis of Small Array Using Syntage™ Samplet™ Cartridges

The general alkylation technique shown above was used to produce a small array of cyclic tertiary amines in one day. All the reaction mixtures were purified using the Horizon™ HPFC system with the Syntage KP-PrSH Samplet cartridges inserted into the head of the FLASH+ cartridge. With this new technique, all the isolated amines were produced with greater than 98% purity requiring no further workup to confirm the amines structures using high field H-NMR, FT-IR and ES-MS to calculate the purity and confirm the structures; Table 3.

Flash Purification Alone

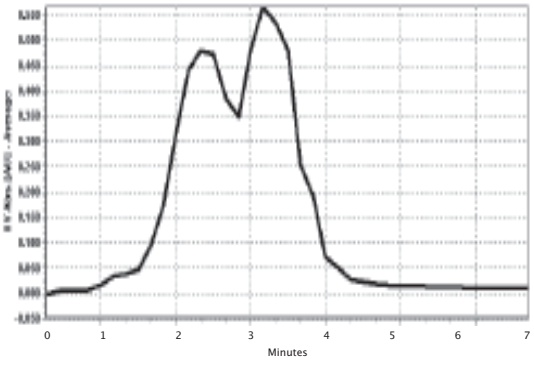
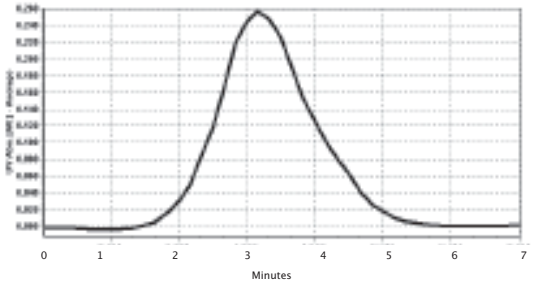


Figure 5. *Comparison of Flash separation with and without using a Syntage KP-PrSH Samplet cartridge. The Syntage KP-PrSH Samplet cartridge removes the excess alkyl halide starting material providing a higher purity product with higher yield.*

Combining Syntage KP-PrSH cartridge with Flash Purification



Flash Purification Conditions:

Eluent:	A = Hexane : EtOAc (8:2)
	B = EtOAc
Gradient:	0-35% B in 120 mL
	35-100% B in 90 mL
Fraction size:	9 mL
Flow rate:	25 mL/min

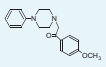
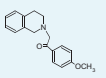
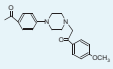
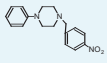
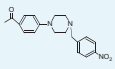
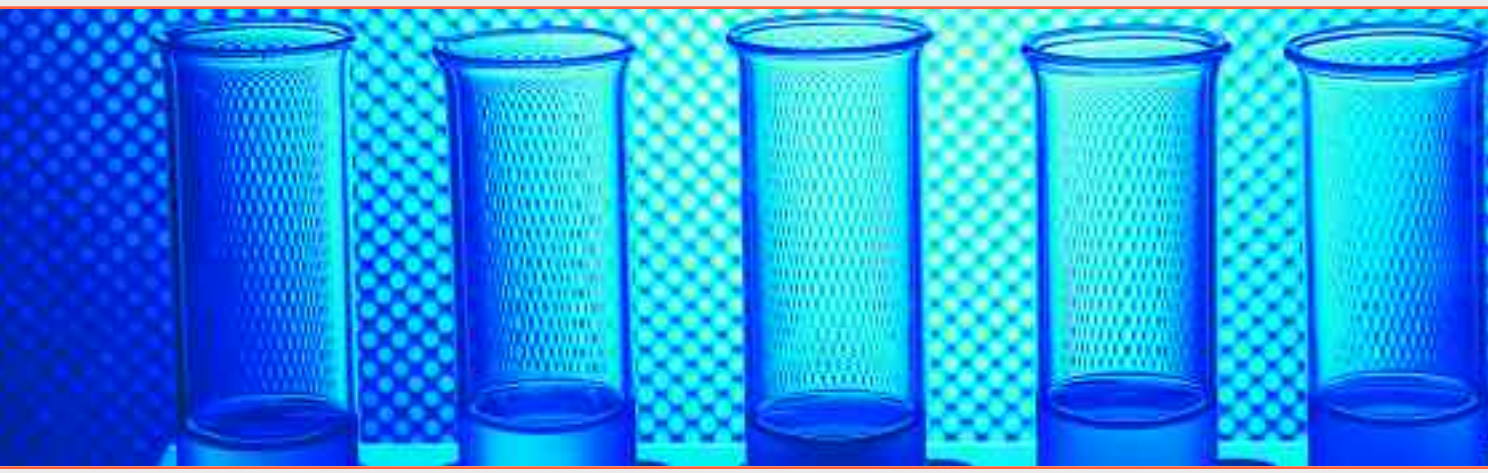
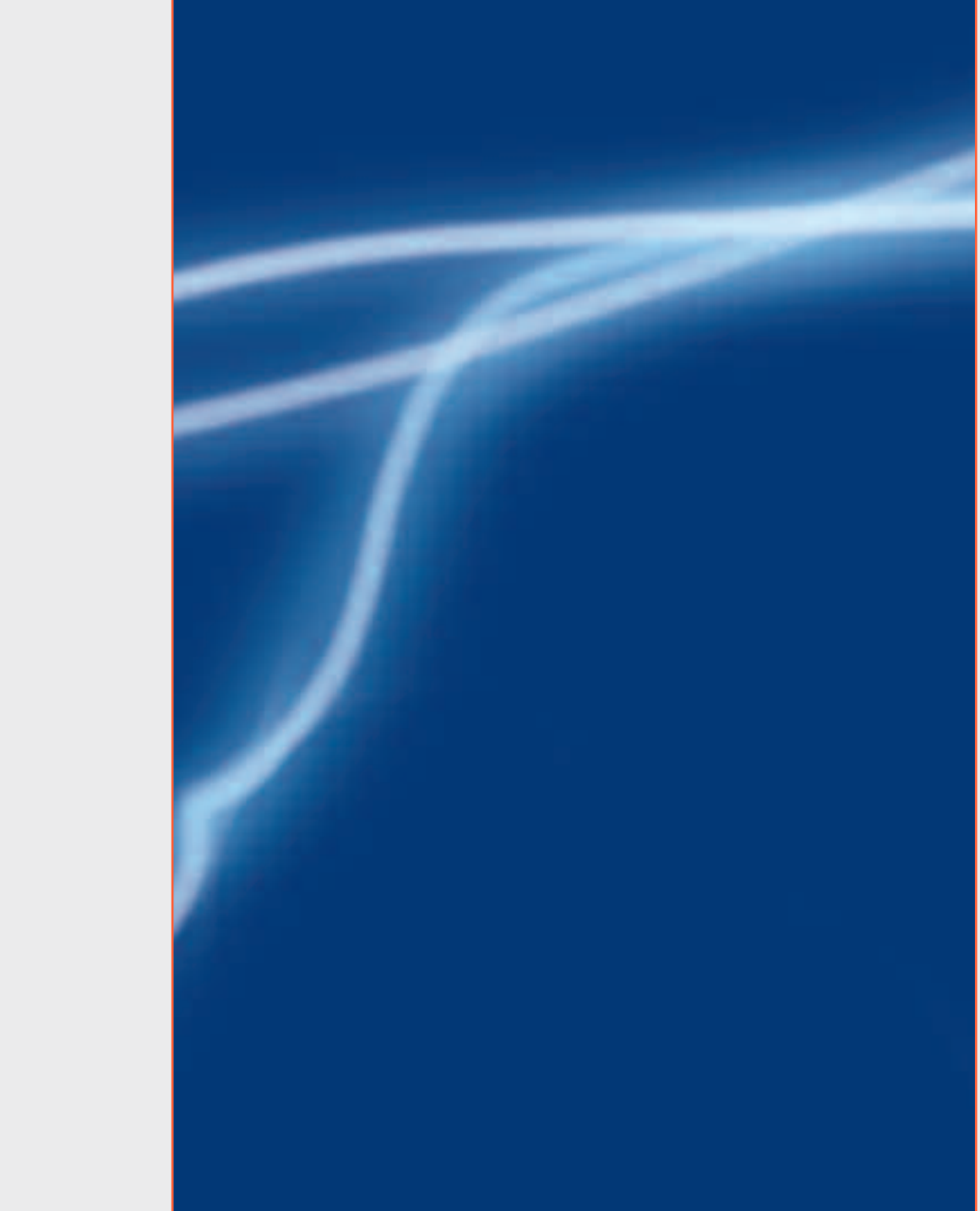
	%Purity	%Yield	ES-MS		%Purity	%Yield	ES-MS
	100	95	253.3(+)		99	95	311.3(+)
	98	63	223.1		98	93	282.3(+)
	98	74	295.2(+)		99	95	353.2(+)
	99	95	279.2(+)		98	92	298.2(+)
	99	93	250.1(+)		98	85	269.2(+)
	99	89	321.1(+)		99	88	340.2(+)

Table 2. *Summary of purity and yield achieved for small alkylation array combining the Syntage KP-Pr-SH Samplet cartridge*

Conclusion

Combining prepacked Syntage KP-PrSH Samplet cartridges with Flash chromatography represents a new technique for on-column, rapid cleanup of excess reagents. The work presented in this application note illustrates that the combination of Syntage KP-PrSH Samplet cartridges plus Flash chromatography is an efficient and easy technique amenable to parallel solution-phase synthesis of tertiary amines. This technique provides quick product recovery time by eliminating all the post-reaction filtration and washing steps. This procedure decreases the number of steps in the synthesis and purification processes since no filtration of the solid-support reagent is required. Combining scavenging and flash purification in one step provides compounds sufficiently pure for NMR, IR, and MS confirmation.





Flash Purification Solutions and Optimization

Integrated Flash Purification Solutions

From synthesis to purification, Biotage delivers innovative solutions to streamLine your work process enabling to reach your purification goals faster and easier.

Cartridges and Samplets

The Syntage™ Chemistry Samplet™ cartridges allow you to perform catalytic synthesis, catch-and-release or scavenging of your reaction sample in the Samplet format. Simply apply crude sample to the appropriate Syntage cartridge and insert it into the corresponding Biotage FLASH+™ cartridges to integrate cleanup with downstream purification.

Discovery-Scale Systems

New SP1™ automated FLASH purification system

Our revolutionary, touch-screen-operated, single-cartridge purification system automatically creates a gradient elution profile based on TLC data and will list cartridge sizes and recommended sample loads. Upgradable to the SP4 for sequential purification of up to four samples. Suitable for high throughput or multiuser needs.

FLASH 12+™, 25+™, and 40+™ reservoir-based FLASH™ purification systems

Simplify and accelerate the isolation of your discovery-scale compounds with our FLASH 12+, 25+, and 40+ reservoir-based FLASH purification systems.

Quad™ Parallel Purification systems

If you synthesize in parallel, you can purify in parallel. Available with four, eight or 12 parallel flow paths, the Quad system provides simple and efficient purification of multiple samples with the same or different solvent systems. An optional four-flow path variable wavelength UV monitor simplifies locating compounds.

Development-Scale Systems

FLASH 75i™ and 150i™ Systems

Save hours, even days, scaling-up with the FLASH 75i. Purify multigram quantities of synthetic compounds. The FLASH 150i purifies kilogram quantities of promising drug candidates. Provides capability for direct scale-up from TLC.

FLASH-AC™

Upgrade product quality by removing reaction byproducts, color and other contaminants using activated-carbon high-performance adsorption.

Production-Scale Systems

FLASH 400™ Production-scale System

Produce compounds with the highest purity, yield and throughput at the kilogram scale with the FLASH 400 system and prepacked cartridges designed for purification according to the U.S. Code of Federal Regulations' current Good Manufacturing Practices (cGMP).

MP 8000™

Automate the FLASH 400 module with an MP 8000 pumping, detection and fraction-collection system.

SIM 10000™

Increase cartridge lifetime when the crude product has limited solubility by pairing a SIM 10000 Sample Injection Module with the FLASH 400 system.

HPLC Systems for Scale-up

Parallex Flex™

The only HPLC preparative system available with one to four channels. The V3 operating software is simple to use, requiring only four clicks to load and run a sample. Ideal for multiuser environments, the Flex V3 offers reliable unattended parallel purification.

Kiloprep®

Purify grams to kilograms of peptides, oligonucleotides, enantiomers or natural products using a Kiloprep HPLC system, compression module and prepacked cartridges.



Optimizing FLASH Chromatography: Method Development Tips for Better Purification Results

This flash chromatography method development guide covers three specific types of flash purification methods—normal-phase isocratic, normal-phase gradient and reversed-phase. These guidelines address important issues related to successful flash purification:

Normal-phase:

- Converting TLC (thin-layer chromatography) Rf (retention factors) to CV (column volumes)
- Determining the best solvent selectivity using TLC
- Determining the best solvent strength using TLC
- Determining the optimum cartridge size and sample load based on TLC data

Reversed-phase:

- Converting HPLC (high-performance liquid chromatography) retention times and gradient methods to CV
- Determining the optimum cartridge size and sample load based on TLC data

Normal-phase Isocratic FLASH

1. Predicting compound retention and resolution using TLC

For successful FLASH purification, Biotage recommends method development using Biotage TLC plates. Component retention on TLC plates is measured in terms of Rf (retention factor). In FLASH purification, retention is usually measured in CV (column volumes). Methods developed using TLC are generally transferable to FLASH chromatography because the relationship between Rf and CV is reciprocal, CV=1/Rf; Figure 1.

Rf	CV
0.90	1.10
0.85	1.17
0.80	1.25
0.75	1.33
0.70	1.40
0.65	1.54
0.60	1.65
0.55	1.81
0.50	2.00
0.45	2.22
0.40	2.50
0.35	2.86
0.30	3.33
0.25	4.00
0.20	5.00
0.15	6.67
0.10	10.00

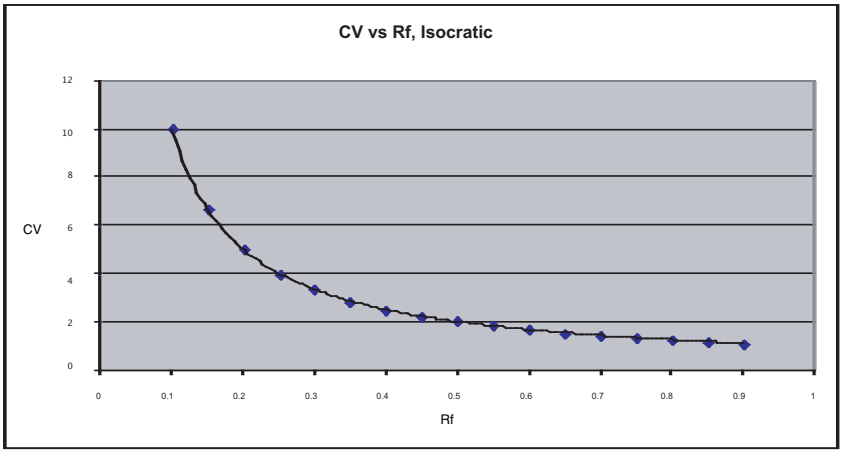


Figure 1. *Rf to CV correlation, isocratic elution.*

Flash Purification

Optimization

When scouting TLC solvent systems, it is important to realize a low Rf (0.15 – 0.35) is preferred because a lower Rf means a greater CV. Large CV's indicate increased compound-silica contact time, improving the chances of component resolution. Since CV is a measure of compound retention, then ΔCV is the measure of compound resolution, see figure 2. In FLASH purification, ΔCV dictates the sample load range possible for any given cartridge size, see table 1. For two adjacent components, a large ΔCV is desirable.

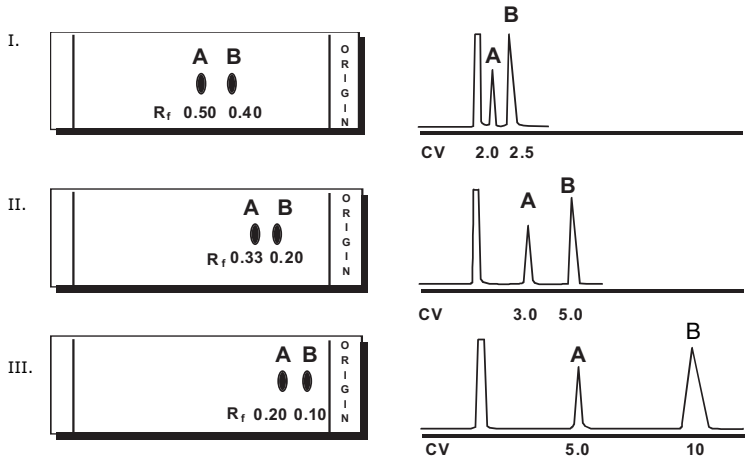


Figure 2. *The Rf – CV relationship is illustrated in this graphic. (I) Although compounds A and B are well resolved on TLC with Rf of 0.5 and 0.4, respectively, FLASH purification with the same solvent conditions provides low retention and low resolution (ΔCV = 0.5) for A and B, respectively. (II) Lowering the Rf (A = 0.33, B = 0.20) provides increased retention and resolution (ΔCV = 2). (III) Extremely high resolution (ΔCV = 5) is obtained by further reducing the compounds' Rf.*

Cartridge	Dimensions (mm x cm)	Typical Flow Rates (mL/min)	Column Volume	Silica Weight	Difficult ΔCV = 1	Typical ΔCV = 2	Easy ΔCV = 6
FLASH 12+S	12 x 7.5	2.5 – 12	6mL	4.5g	4 - 20mg	20 - 100mg	100 - 200mg
FLASH 12+M	12 x 15	2.5 – 12	12mL	9g	8 - 40mg	40 - 200mg	200 - 400mg
FLASH 25+S	12 x 7.5	10 – 25	24mL	20g	15 - 80mg	80 - 400mg	400 - 800mg
FLASH 25+M	12 x 15	10 – 25	48mL	40g	30 - 160mg	160 - 800mg	800 - 1600mg
FLASH 40+S	40 x 7.5	25 – 50	66mL	50g	40 - 200mg	200 - 1000mg	1 - 2
FLASH 40+M	40 x 15	25 – 50	132mL	100g	80-400mg	400-2000mg	2 - 5g
FLASH 65i	65 x 20	65 – 85	470mL	350g	300 - 1600mg	1.6 - 8g	8 - 20g
FLASH 75S	75 x 9	100 – 250	300mL	200g	160 - 800mg	0.8 - 4g	4 - 10g
FLASH 75M	75 x 15	100 – 250	500mL	400g	400 - 2000mg	2 - 10g	10 - 20g
FLASH 75L	75 x 30	100 – 250	1000mL	800g	800 - 4000mg	4 - 20g	20 - 40g
FLASH 150M	150 x 30	500 – 1000	4.3L	2.5kg	3 - 16g	16 - 80g	80 - 160g
FLASH 150L	150 x 60	500 – 1000	8.6L	5kg	6 - 32g	32 - 160g	160 - 320g
FLASH 400M	400 x 30	7000	38L	20kg	0.03 - 0.25kg	0.25 - 1.0kg	1 - 2kg
FLASH 400L	400 x 60	7000	76L	40kg	0.06 - 0.50kg	0.5 - 2.0kg	2 - 4kg

Table 1. *Biotage Cartridge Loading Table for Isocratic Purifications*



Optimize your Purification

2. Optimizing selectivity

The first step in successful FLASH purification is maximizing ΔCV. Accomplish this by evaluating various solvent mixtures by TLC. Look for a binary mixture that provides the largest ΔCV between the compound of interest and all the impurities.

All solvents fall into a selectivity group. Each group has a different impact on a sample component's relative retention to another compound (selectivity). In Table 2., the most frequently used flash solvents and their selectivity groups are shown.

When possible, selectivity optimization should include mixtures of hexane with ethyl acetate (VIa), methylene chloride (V), toluene (VII), tetrahydrofuran (III) and ether (I). For more polar compounds and amines, mixtures of methylene chloride (V) with methanol (II) or acetonitrile (VIb) should be evaluated. These solvent combinations provide a broad range of separation selectivity and will help define the correct solvents for a sample's purification; Figure 3. For more discussion regarding solvent selectivity in chromatography, see *Introduction to Modern Chromatography* by L.R. Snyder and J.J. Kirkland.[1]

Solvent	Selectivity Group
Ether	I
Methanol	II
Ethanol	II
Isopropanol	II
Tetrahydrofuran	III
Dichloromethane	V
Acetone	VIa
Ethyl acetate	VIa
Acetonitrile	VIb
Toluene	VII
Chloroform	VIII
Hexane	-----
Heptane	-----
Isooctane	-----

Table 2. *Solvent selectivity chart*[1]

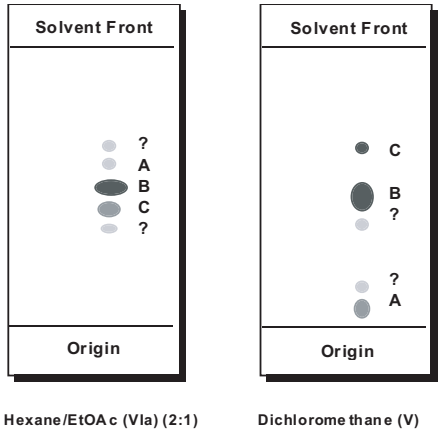


Figure 3. *Impact of solvent selectivity on a chromatographic separation. In hexane/ethyl acetate the compound of interest (B) is poorly resolved from its major impurities (A and C). In dichloromethane, the retention of impurities A and C has been dramatically altered, providing a better purification of B.*

3. Solvent strength optimization

When the correct solvents have been determined, the next step is to adjust the solvent composition (solvent strength) so the compound of interest elutes within the Rf range 0.15 – 0.35 (6.7 – 2.8 CV). By adjusting solvent strength to provide elution within this window the chances for optimal purification are greatly enhanced.

[1] L. R. Snyder and J. J. Kirkland, *Introduction to Modern Liquid Chromatography*, Wiley, 1979.

As with selectivity, each solvent has its own polarity; Table 3. Each solvent mixture or mobile phase then has its own unique solvent strength. Calculation of a solvent mixture's strength is useful for comparison to other solvent mixtures. Solvent mixtures with the same strength but different selectivity can then be evaluated.

To bring the Rf of the compound of interest into the optimal range, reduce the amount of polar solvent in the mobile phase. As an example, Figure 4, the results of a solvent selectivity study show a mobile phase of 50% hexane and 50% ethyl acetate (solvent strength = 0.30) provides adequate selectivity for a crude sample; Figure 4, top. The Rf for the compound of interest (B) is 0.4 (2.5 CV) and the Rf of the impurity (A) is 0.55 (1.8 CV), providing a ΔCV of 0.7. With a ΔCV this low, only a small sample amount can be FLASH purified before overload (resolution loss, low purity fractions) occurs. By weakening the solvent strength to 60% hexane and 40% ethyl acetate (solvent strength 0.24); Figure 4, middle; the Rf of compound B falls to 0.2 (5 CV) and impurity A's Rf is lowered to 0.3 (3.3 CV) with a resulting ΔCV of 1.7, enabling a potential five-fold increase in sample load on a FLASH cartridge; Table 1.

If you find adequate component retention with a particular solvent mixture, you can prepare other solvent mixtures of similar strength but different selectivity for comparison; Figure 4, bottom.

Solvent	Strength
Methanol	0.95
Ethanol	0.88
Isopropanol	0.82
Acetonitrile	0.65
Ethyl acetate	0.58
Tetrahydrofuran	0.57
Acetone	0.56
Dichloromethane	0.42
Chloroform	0.40
Ether	0.38
Toluene	0.29
Hexane	0.01
Heptane	0.01
Isooctane	0.01

Table 3. *A solvent mixture's strength is calculated using volume proportions and the individual solvent's strength. In the example above, diluting a solvent mixture with a less polar solvent (hexane) from 50% to 60% reduces solvent strength, increasing compound retention and resolution (ΔCV). Also, solvent combinations of similar strength but different selectivity can also be compared. Both hexane/ethyl acetate (50:50) and hexane/dichloromethane (30:70) have solvent strength of 0.3, but ethyl acetate and dichloromethane provide different selectivity.*

Formula:

$$\frac{(\text{Solvent A\% x solvent A strength})}{100} + \frac{(\text{Solvent B\% x solvent B strength})}{100}$$

Examples:

Hexane/ethyl acetate (50:50)
Solvent strength = (0.5 x 0.01) + (0.5 x 0.58) = 0.30

Hexane/ethyl acetate (60:40)
Solvent strength = (0.6 x 0.01) + (0.4 x 0.58) = 0.24

Hexane/dichloromethane (30:70)
Solvent strength = (0.3 x 0.01) + (0.7 x 0.42) = 0.30



Optimize your Purification

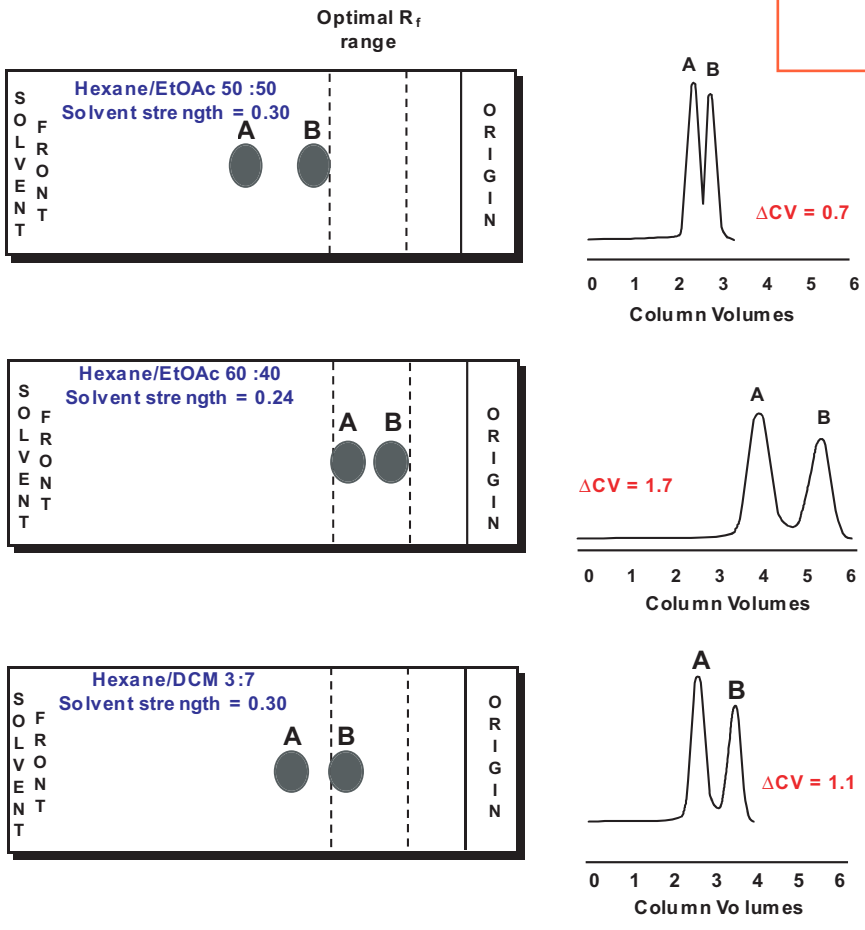


Figure 4. *Examples of solvent strength on compound retention and resolution. The top TLC shows two sample components resolved with a 50:50 hexane/ethyl acetate solvent system (ΔCV = 0.7). Neither the component of interest (B) nor the impurity (A) has an Rf value within the optimal 0.15 – 0.35 range. This leads to poor flash purification (top chromatogram). After adjusting the solvent to 60% hexane/40% ethyl acetate, the Rf values for both A and B fall into the optimal zone (middle TLC). FLASH chromatography with these conditions (middle chromatogram) shows increased compound retention and greatly improved resolution (ΔCV = 1.7). Replacing 50:50 hexane/ethyl acetate with 30:70 hexane/dichloromethane (both 0.30 solvent strength) alters both selectivity and resolution (ΔCV = 1.1).*

Once a solvent system has been selected, Rf values measured, and ΔCV values calculated, use Table 1. on page 80 to select the correct cartridge for your sample size and ΔCV. The data generated from your TLC method development efforts are applicable to any sized Biotage cartridge.

Normal-phase Gradient Flash

Gradient elution enables chemists to speed purification, improve recovery and yield and even increase fraction purity. In a gradient, the stronger eluting solvent concentration is increased over time, increasing the solubility of more highly retained components and causing them to elute sooner and in tighter bands compared to isocratic elution.

Because solvent strength is increasing during the purification, the isocratic CV=1/Rf relationship does not hold. In a gradient, compounds elute with fewer column volumes than predicted by the isocratic relationship. The exact number of elution CV depends on the gradient slope.

Biotage chemists have developed an applicable algorithm to help chemists transfer TLC Rf to gradient CV.* This algorithm is incorporated into the SP1 and SP4 graphic user interface software (Touch Logic Control). If you are using a Biotage Horizon or original SP4, a generally applicable algorithm to use is:

Segment 1:	1/4 the TLC polar solvent concentration for 1 CV
Segment 2:	Segment 1 to TLC conditions over 10 CV
Segment 3:	Hold segment 2 for 1 CV

These conditions work when your compound of interest has an Rf of ~0.4. For example, the TLC conditions are 8:2 hexane/ethyl acetate and the Rf is 0.4. Set the gradient as follows:

Segment 1:	5% ethyl acetate for 1 CV
Segment 2:	5% to 20% ethyl acetate over 10 CV
Segment 3:	hold 20% ethyl acetate for 1 CV

Using these conditions, a compound with an Rf of 0.4 is the last compound to elute. To elute more strongly retained compounds, increase the gradient's slope by decreasing the volume in segment 2 or increasing the strong solvent concentration in segments 2 and 3.

** Patent pending.*

Reversed-phase Flash

As a technique used for purification of water soluble compounds, reversed-phase flash purification method development uses an approach different than normal-phase. The recommended approach for reversed-phase includes developing and optimizing the method using HPLC and a Biotage KP-C18 scaling column (4.6 x 250 mm). The scaling column is packed with the identical C18 phase as the KP-C18 FLASH cartridges.

Begin by creating a gradient on the HPLC from 10 – 90% acetonitrile (or methanol) in water at 3 mL/min (1 CV/min) with this gradient.

Segment 1:	10% ACN (or MeOH) for 1 min.
Segment 2:	10-90% ACN (MeOH) over 10 min
Segment 3:	Hold 90% ACN for 2 CV

Continue to modify this until the compound of interest is fully separated from its impurities and has a retention time of at least five minutes. On the HPLC, the optimal load can be determined by increasing the sample amount until resolution has been lost.

To transfer the HPLC method to flash, convert compound retention time (Tr) to column volume using the following equation:

Compound CV = compound Tr/To, where To = the void time (about 1 min at 3 mL/min).

Use the same formula to convert the gradient program from time to CV:

Gradient segment length (time)/To = flash segment length (CV)

By using these formulas and the same solvents, reproducible reversed-phase flash gradients can be developed.

Flash Scale-up

Flash scale-up is based on equalizing solvent linear velocity and relative sample load for cartridges of different sizes or volumes. Flash purification performed on a small scale is easily scaled to larger cartridges using the scale-up factors in Table 4, which take into account the cartridge differences.

To successfully scale a purification, find your current FLASH cartridge in the left column. Then read across that row until you find the number closest to the scale-up factor for your larger sample. Read up to find the appropriate FLASH cartridge for that scale factor. For example, if a 1-gram purification on FLASH 25+S requires scale-up to 30-grams, the appropriate scale-up cartridge, according to the table, is a FLASH 75L.

Scale to

Scale from	12+S	12+M	25+S	25+M	40+S	40+M	65i	75S	75M	75L	150M	150L	400M	400L
12+S	1	2	4	9	11	22	78	47	78	156	625	1250	4444	8889
12+M		1	2	4	6	11	39	23	39	78	313	625	2222	4444
25+S			1	2	3	5	18	11	18	36	144	288	1024	2048
25+M				1	1	3	9	5	9	18	72	144	512	1024
40+S					1	2	7	4	7	14	56	113	400	800
40+M						1	4	2	4	7	28	56	200	400
65i							1	1	1	2	8	16	57	114
75S								1	2	3	13	27	95	190
75M									1	2	8	16	57	114
75L										1	4	8	28	57
150M											1	2	7	14
150L												1	4	7
400M													1	2
400L														1

Table 4. *Scale-up chart for Biotage FLASH cartridges.*





FLASH, Syntage™ and Samplet™ Cartridges

Integrating Purification, Work-up, Scavenging, and Synthesis Into One Process

FLASH+™ HPFC CARTRIDGES

FLASH+ HPFC cartridges were developed to meet the high performance requirements of our FLASH+ HPFC Systems. Automated cartridge packing systems efficiently pack Biotage FLASH+ cartridges to minimize performance variability. Food-grade polyethylene barrels are packed with the highest quality silica, amino, and C18 materials available. Strict ISO quality controls at Biotage and years of production experience ensure consistent performance from cartridge to cartridge.

FLASH+ cartridges are available in three diameters (12 mm, 25 mm, 40 mm) and two lengths [7.5 cm (S) and 15 cm (M)] to fulfill a broad range of sample sizes. FLASH+ cartridges are designed to utilize Samplet™ cartridges for quick and convenient sample introduction directly on top of the cartridge. Samplet cartridges simplify and improve sample preparation for multiple samples and low-solubility samples.

In a FLASH+ compression module, Biotage FLASH+ cartridges tolerate liquid pressure up to 100 psig, enabling higher flow rates, the use of higher viscosity solvents, such as those used in reversed-phase chromatography, and improved performance.

Biotage Packing Materials

Biotage KP-Sil™ Silica

Features high surface area (500 m^2/g), moderate porosity (60 Å), and a tight, uniform distribution of particles (sizes 40-63 µm). These three factors combined provide high loading capacity and efficiency.

KP-Sil TLC Plates

Biotage also offers KP-Sil on TLC (thin-layer chromatography) plates to assist in FLASH optimization and post-chromatographic analysis.

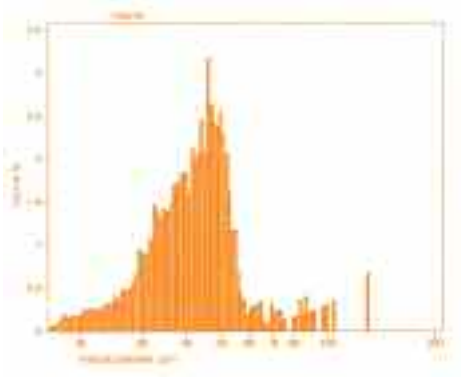


Figure 1. *Competitor's silica particle size distribution.*

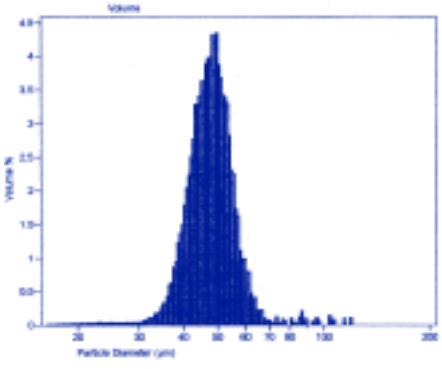


Figure 2. *Biotage's KP-Sil particle size distribution. A more narrow particle distribution ensures consistent cartridge efficiency and performance.*

FLASH+™ Cartridge Packing Material

Biotage KP-C18-HS™

Features a high surface area (450 m^2/g), moderate porosity (90 Å), and a tight, uniform distribution of particles, sizes 35-70 µm. The media contains 18% carbon by weight and is end-capped. End-capping is a silanization process designed to reduce the number of silanol sites that remain after bonding with C18, thus reducing irreversible binding interactions with polar compounds.

Biotage KP-NH™

This is an amino functionalized silica with moderate surface area (230 m^2/g), moderate porosity (100 Å), and uniform distribution of particles (sizes 40-75 µm). This unique media accepts high sample loads of polar, amine-containing samples and minimizes amine-silanol interaction.



FLASH+™ Cartridge Features and Benefits

- High surface-area silica ensures high capacity and efficiency
- Uniform particle-size distribution generates narrow elution bands
- High-pressure (100 psig) capability allows faster flow rates and provides increased throughput
- Recessed inlet provides room for Biotage Samplet™ or Syntage™ cartridge and axial compression, for higher throughput and resolution
- Three diameters accommodate purification of milligram to multigram sample loads
- Two cartridge lengths provide options for separating simple or complex mixtures
- Three standard medias provide selectivity choices for optimal purification
- FLASH silica available in TLC format improves optimization and analysis
- Polyethylene cartridge barrels reduce product cost and are disposable
- Cartridges meet 21 CFR 177.1520 regulations for extractables
- Prepacked cartridges eliminate hazards of loose silica and are safer than glass columns

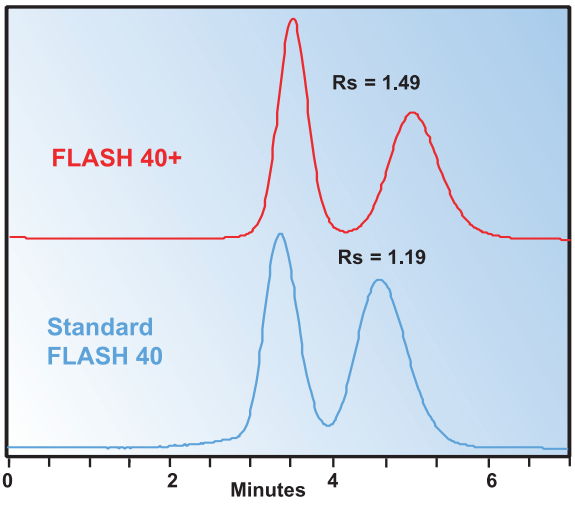


Figure 3. *The FLASH 40+™ HPFC cartridge design is more efficient (greater resolution-R_S), more retentive and delivers higher purity fractions than other cartridge designs.*

Applications

- Synthetic organic mixtures
- Natural product isolation
- Purification of highly basic compounds
- Protected peptides

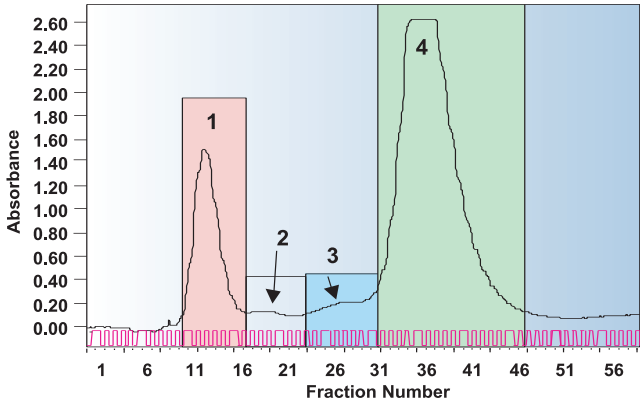


Figure 4.
FLASH 12+™M chromatogram showing purification of 90 mg of crude macrolide fermentation product. Four compounds are distinctly visible. Highlighted boxes correspond to fractions tested by TLC.

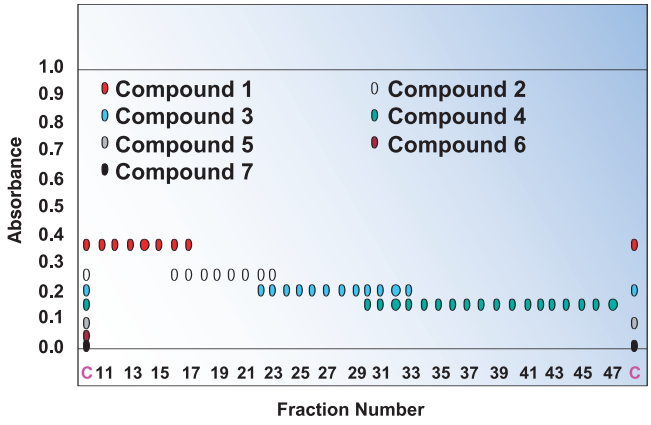
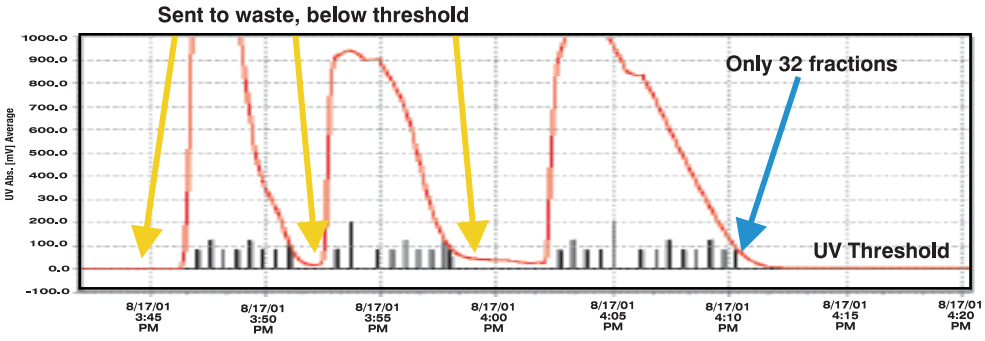


Figure 5.
TLC analysis of collected fractions. Fractions 11-15 are pure compound 1, 18-21 pure compound 2, 24-29 pure compound 3, and 34-47 pure compound 4.



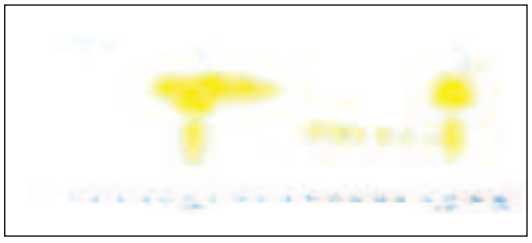


Figure 6. *Using a FLASH 65i™, a 3-component aniline mixture (10 g) was successfully separated on a Horizon™ HPFC™ system with UV collection using a FLASH 65i compression module and 65i KP-Sil™ cartridge*

		Cartridge	Dimensions	Load range (mg)
Silica Cartridge Specifications *(surface area 500 m^2/g, porosity 60 Å, particle size 40 - 63 µm)*	**KP-Sil**	FLASH 12+™S	12 x 75	4-200
		FLASH 12+M	12 x 150	8-400
		FLASH 25+™S	25 x 75	15-800
		FLASH 25+M	25 x 150	30-1600
		FLASH 40+™S	40 x 75	40-2000
		FLASH 40+M	40 x 150	80-5000
		FLASH 65i™	65 x 200	300-20000
C18 Cartridge Specifications *(surface area 450 m^2/g, porosity 90 Å, particle size 35-70 µm)*	**KP-C18**	FLASH 12+S	12 x 75	0.4-20
		FLASH 12+M	12 x 150	0.8-40
		FLASH 25+S	25 x 75	1.5-80
		FLASH 25+M	25 x 150	3-160
		FLASH 40+S	40 x 75	4-200
		FLASH 40+M	40 x 150	8-500
		FLASH 65i	65 x 200	30-2000
NH Cartridge Specifications *(surface area 230 m^2/g, porosity 100 Å, particle size 40-75 µm)*	**KP-NH**	FLASH 12+S	12 x 75	2-100
		FLASH 12+M	12 x 150	4-200
		FLASH 25+S	25 x 75	8-400
		FLASH 25+M	25 x 150	15-800
		FLASH 40+S	40 x 75	20-1000
		FLASH 40+M	40 x 150	40-3000

ORDER FLASH+™CARTRIDGES

FLASH+™Cartridge Ordering Information

Additional Packing Media Specifications

Packing	Porosity (Å)	Particle Size (µm)	Application
Mitsubishi Diaion™ HP20	300–600	250–600	fermentation capture
Mitsubishi Diaion™ HP20SS	300–600	75–150	fermentation capture
KP-C18-WP™	300	20–40	peptide purification
KP-C4-WP™	300	15–20	peptide purification

Cartridge	Description	Qty/Case	Part Number
Silica			
FLASH 12+™S	KP-Sil™, 12 x 75 mm	20	FPK0-1107-15026
FLASH 12+M	KP-Sil, 12 x 150 mm	20	FPK0-1107-15046
FLASH 25+™S	KP-Sil, 25 x 75 mm	20	FPK0-1107-16026
FLASH 25+M	KP-Sil, 25 x 150 mm	20	FPK0-1107-16046
FLASH 40+™S	KP-Sil, 40 x 75 mm	20	FPK0-1107-17026
FLASH 40+M	KP-Sil, 40 x 150 mm	20	FPK0-1107-17046

FLASH+™Cartridge Ordering Information

Cartridge	Description	Qty/Case	Part Number
C18			
FLASH 12+S	KP-C18-HS™, 12 x 75 mm	2	FPL0-1118-15025
FLASH 12+M	KP-C18-HS, 12 x 150 mm	2	FPL0-1118-15045
FLASH 25+S	KP-C18-HS, 25 x 75 mm	2	FPL0-1118-16025
FLASH 25+M	KP-C18-HS, 25 x 150 mm	2	FPL0-1118-16045
FLASH 40+S	KP-C18-HS, 40 x 75 mm	1	FPL0-1118-17020
FLASH 40+M	KP-C18-HS, 40 x 150 mm	1	FPL0-1118-17040
NH (Amine)			
FLASH 12+S	KP-NH™, 12 x 75 mm	20	FPNH-12S
FLASH 12+M	KP-NH, 12 x 150 mm	20	FPNH-12M
FLASH 25+S	KP-NH, 25 x 75 mm	10	FPNH-25S
FLASH 25+M	KP-NH, 25 x 150 mm	10	FPNH-25M
FLASH 40+S	KP-NH, 40 x 75 mm	5	FPNH-40S
FLASH 40+M	KP-NH, 40 x 150 mm	5	FPNH-40M
C18WP			
FLASH 40+S C18WP	KP-C18-WP, 40 x 75 mm	1	FPV1-0906-17020
FLASH 40+M C18WP	KP-C18-WP, 40 x 150 mm	1	FPV1-0906-17040
C4WP			
FLASH 40+S C4WP	KP-C4-WP, 40 x 75 mm	1	FPV1-1104-17020
FLASH 40+M C4WP	KP-C4-WP, 40 x 150 mm	1	FPV1-1104-17040



Order FLASH+ Samplets™

FLASH+™ Samplets™ Ordering Information

Cartridge	Description	Qty/Case	Part Number
Silica			
FLASH 12+ Silica Samplet	KP-Sil 12 mm Samplet	48	SAM-1107-1421J
FLASH 25+ Silica Samplet	KP-Sil 25 mm Samplet	20	SAM-1107-16016
FLASH 40+ Silica Samplet	KP-Sil 40 mm Samplet	20	SAM-1107-17016
C18			
FLASH 12+ C18 Samplet	KP-C18-HS 12 mm Samplet	48	SAM-1118-1421J
FLASH 25+ C18 Samplet	KP-C18-HS 25 mm Samplet	20	SAM-1118-16016
FLASH 40+ C18 Samplet	KP-C18-HS 40 mm Samplet	20	SAM-1118-17016
NH (Amine)			
FLASH 12+ NH Samplet	KP-NH 12 mm Samplet	48	SAM-NH12
FLASH 25+ NH Samplet	KP-NH 25 mm Samplet	20	SAM-NH25
FLASH 40+ NH Samplet	KP-NH 40 mm Samplet	20	SAM-NH40
C4WP			
FLASH 40+ C4WP Samplet	KP-C4-WP 40 mm Samplet	20	SAM-1104-17016
C18WP			
FLASH 40+ C18WP Samplet	KP-C18-WP 40 mm Samplet	20	SAM-0906-17016

ORDER FLASH CARTRIDGES

FLASH 12i™, 40i™ and 65i™ Cartridge Ordering Information

Cartridge	Description	Qty/case	Part number
Silica			
FLASH 12S Silica	KP-Sil, 12 mm x 75 mm	20	FK0-1107-15026
FLASH 12S Silica	KP-Sil, 12 mm x 75 mm	100	FK0-1107-15028
FLASH 12M Silica	KP-Sil, 12 mm x 150 mm	20	FK0-1107-15046
FLASH 12M Silica	KP-Sil, 12 mm x 150 mm	100	FK0-1107-15048
FLASH 40S Silica	KP-Sil, 40 mm x 75 mm	12	FK0-1107-17024
FLASH 40S Silica	KP-Sil, 40 mm x 75 mm	144	FK0-1107-17028
FLASH 40M Silica	KP-Sil, 40 mm x 150 mm	12	FK0-1107-17044
FLASH 40M Silica	KP-Sil, 40 mm x 150 mm	144	FK0-1107-17048
FLASH 40L Silica	KP-Sil, 40 mm x 200 mm	12	FK0-1107-17174
FLASH 65i Silica	KP-Sil, 65 mm x 200 mm	6	FK0-1107-1804C
C18			
FLASH 12S C18	KP-C18-HS, 12 mm x 75 mm	2	FL0-1118-15025
FLASH 12M C18	KP-C18-HS, 12 mm x 150 mm	2	FL0-1118-15045
FLASH 40S C18	KP-C18-HS, 40 mm x 75 mm	1	FL0-1118-17020
FLASH 40M C18	KP-C18-HS, 40 mm x 150 mm	1	FL0-1118-17040
FLASH 40L C18	KP-C18-HS, 40 mm x 200 mm	1	FL0-1107-17170
FLASH 65i C18	KP-C18-HS, 65 mm x 200 mm	1	FL0-1118-18040
Diaion HP20			
FLASH 40S	40 mm x 75 mm	12	FT6-2030-17024
FLASH 40M	40 mm x 150 mm	12	FT6-2030-17044
Diaion HP20SS			
FLASH 40S	40 mm x 75 mm	1	FT6-2530-17020
FLASH 40M	40 mm x 150 mm	1	FT6-2530-17040
C18 WP			
FLASH 40S	40 mm x 75 mm	1	FV1-0906-17020
FLASH 40M	40 mm x 150 mm	1	FV1-0906-17040
C4 WP			
FLASH 40S	40 mm x 75 mm	1	FV1-1104-17020
FLASH 40M	40 mm x 150 mm	1	FV1-1104-17040

Order FLASH Cartridges

FLASH 75i™ and 150i™ Cartridge Ordering Information

Cartridge	Description	Qty/Case	Part Number
Silica			
FLASH 75S Silica	KP-Sil, 75 mm x 9 cm	2	FK0-1107-19165
FLASH 75M Silica	KP-Sil, 75 mm x 15 cm	2	FK0-1107-19045
FLASH 75L Silica	KP-Sil, 75 mm x 30 cm	2	FK0-1107-19075
FLASH 75S Silica	KP-Sil, 75 mm x 9 cm	10	FK0-1107-19163
FLASH 75M Silica	KP-Sil, 75 mm x 15 cm	10	FK0-1107-19043
FLASH 75L Silica	KP-Sil, 75 mm x 30 cm	10	FK0-1107-19073
FLASH 150M Silica	KP-Sil, 150 mm x 30 cm	2	FK0-1107-25075
FLASH 150L Silica	KP-Sil, 150 mm x 60 cm	2	FK0-1107-25155
C18			
FLASH 75S	KP-C18-HS, 75 mm x 9 cm	1	FL0-1118-19160
FLASH 75M	KP-C18-HS, 75 mm x 15 cm	1	FL0-1118-19040
FLASH 75L	KP-C18-HS, 75 mm x 30 cm	1	FL0-1118-19070
FLASH 150M	KP-C18-HS, 150 mm x 30 cm	1	FL0-1118-25070
Diaion HP20			
FLASH 75S	75 mm x 9 cm	2	FT6-2030-19165
FLASH 75M	75 mm x 15 cm	2	FT6-2030-19045
FLASH 75L	75 mm x 30 cm	2	FT6-2030-19075
FLASH 75S	75 mm x 9 cm	10	FT6-2030-19163
FLASH 75M	75 mm x 15 cm	10	FT6-2030-19043
FLASH 75L	75 mm x 30 cm	10	FT6-2030-19073
FLASH 150M	150 mm x 30 cm	2	FT6-2030-25075
FLASH 150L	150 mm x 60 cm	2	FT6-2030-25155
Diaion HP20SS			
FLASH 75S	75 mm x 9 cm	1	FT6-2530-19160
FLASH 75M	75 mm x 15 cm	1	FT6-2530-19040
FLASH 75L	75 mm x 30 cm	1	FT6-2530-19070
FLASH 150M	150 mm x 30 cm	1	FT6-2530-25070
FLASH 150L	150 mm x 60 cm	1	FT6-2530-25150

ORDER FLASH CARTRIDGES

FLASH 75i™ and 150i™ Cartridges (continued)

Cartridge	Description	Qty/Case	Part Number
C18 WP			
FLASH 75S	75 mm x 9 cm	1	FV1-0906-19160
FLASH 750M	75 mm x 15 cm	1	FV1-0906-19040
FLASH 75L	75 mm x 30 cm	1	FV1-0906-19070
FLASH 150M	150 mm x 30 cm	1	FV1-0906-25070
C4 WP			
FLASH 75S	75 mm x 9 cm	1	FV1-1104-19160
FLASH 75M	75 mm x 15 cm	1	FV1-1104-19040
FLASH 75L	75 mm x 30 cm	1	FV1-1104-19070
FLASH 150M	150 mm x 30 cm	1	FV1-1104-25070



Order TLC Plates and Scaling Columns

FLASH TLC Plates Ordering Information

Cartridge	Description	Qty/Case	Part Number
KP-Sil TLC Plates, Glass	2.75 cm x 7.5 cm, glass backed	100	TLC-2575-FI
KP-Sil TLC Plates, Glass	5 cm x 10 cm, glass backed	50	TLC-0510-FI
KP-Sil TLC Plates, Glass	10 cm x 10 cm, glass backed	25	TLC-1010-FI



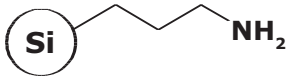
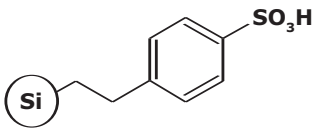
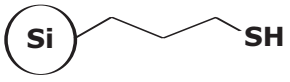
Scaling Columns

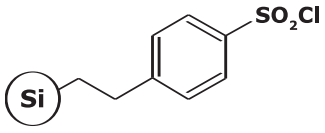
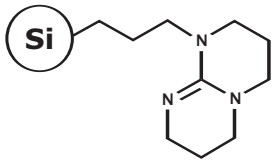
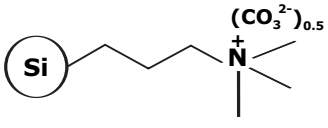
Cartridge	Description	Part Number
KP-Sil Silica		
Scaling Column	4.6 mm ID x 25 cm	S1K0-1107-93050
Scaling Column	10 mm ID x 25 cm	S1K0-1107-95050
KP-C18-HS		
Scaling Column	4.6 mm ID x 25 cm	S1L0-1118-93050
Scaling Column	10 mm ID x 25 cm	S1L0-1118-95050
Diaion HP20		
Scaling Column	4.6 mm ID x 25 cm	SFT6-2030-93050
Scaling Column	10 mm ID x 25 cm	SFT6-2030-95050
Diaion HP20SS		
Scaling Column	4.6 mm ID x 25 cm	SFT6-2530-93050
Scaling Column	10 mm ID x 25 cm	SFT6-2530-95050

The Syntage line of chemistry cartridges are preformatted sample-loading cartridges, based on Samplet cartridge technology, that contain a variety of functionalized media used for scavenging, work-up and synthesis. Unlike traditional synthesis and work-up methods, using Syntage Samplet™ cartridges with FLASH+ purification cartridges combines work-up, synthesis and purification into one process. Biotage FLASH+ and Syntage chemistry cartridges feature medium pressure (100psi) capability for faster flow rates. Syntage cartridges clean-up crude reaction mixtures while inside a FLASH+ purification cartridge and are designed to improve loading, peak shape and resolution.

Teflon® coated metal heating blocks of the corresponding sizes are also available for easy drying of solvents in the Syntage Samplet in a vacuum oven prior to FLASH chromatography.

- Samplet cartridge design improves sample-loading, peak shape, and resolution.
- Integrated technology allows chemists to purify sample loads from 5 mg - 5 g using FLASH 12+ to 40+ compression modules and cartridges.
- Compression modules have medium-pressure (100 psig) capacity allowing faster flow rates and improved resolution.

Syntage Media	Description
	**KP-PrNH** (3-propylamino silica) Samplet cartridges are the silica-bonded equivalent of n-propylamine (SAX) media, and are used for applications including scavenging organic acids, acid chlorides, isocyanates and other electrophiles.
	**KP-TsOH** (phenyl sulfonic acid silica) Samplet cartridges are the silica-bonded equivalent of p-toluenesulfonic acid (SCX) media, and are used for applications including scavenging bases or "catch-and-release" amine purification.
	**KP-PrSH** (3-mercaptopropyl silica) Samplet cartridges are the silica-bonded equivalent of 1-propanethiol media and are used for applications including scavenging of alkyl halides and removal of transition metals.

Syntage Media	Description
	**KP-TsCl** (phenylsulfonyl chloride silica) Samplet cartridges are the silica-bonded equivalent of tosyl chloride media and are used for applications including scavenging alcohols, amines, and other nucleophiles, "catch-and-release" applications, and synthesis (tertiary amines, esters and thioethers).
	**KP-TBD** (1,5,7-Triazabicyclo (4.4.0) Dec-5-ene silica) Samplet cartridges are the silica-bonded equivalent of 1,5,7-Triazabicylo (4.4.0) Dec-5-ene media and are used for applications including scavenging of phenols and alkylation of phenols and amines, and esterification of carboxylic acids using alkyl halides.
	**KP-NCO3** (trimethylpropyl ammonium silica) Samplet cartridges are silica bonded equivalent of trimethylpropyl ammonium carbonate media and can be used for applications including neutralization of amine hydrochlorides and scavenging acids and acidic phenols.
	**KP-KMNO4** (potassium permanganate silica) Samplet cartridges are silica absorbed with potassium permanganate and can be used for applications including oxidation of alcohols.

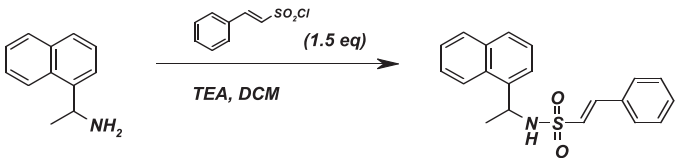
FluoroFlash* (KP-CF) cartridges are for use in the separation and purification of perfluorinated compounds. Fluorous compounds can be readily separated from nonfluorinated organic compounds or from each other (based on fluorine content) by chromatography using FluoroFlash fluorinated silica. These separations capitalize on the unique feature of fluorous stationary phases to separate molecules primarily by fluorine content.

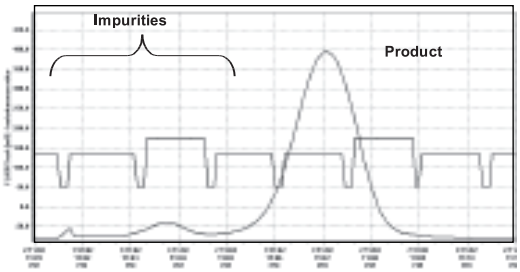
FLUOROUS
Technologies Incorporated
Fast. Pure and Simple.

** Under license from Fluorous Technologies Inc. FluoroFlash™ is a trademark of Fluorous Technologies Inc.*

Application Specifications

Figure 7. KP-PrNH Representative Scavenging Procedure. *Flash purification of a synthetic sulfonamide using Syntage™ PrNH25 Samplet™ cartridge, FLASH 25+M silica cartridge, and the following method on a Horizon™ HPFC™ system. The PrNH cartridge removes excess Tosyl chloride, simplifing the purification.*





Solvent A: EtOAc/Hexane (20:80)
Solvent B: EtOAc

Gradient: 0-100% B in 500 mL, linear
Flow Rate: 35 mL/min.

HPLC analysis of purified fractions, HPLC Purity - 98%

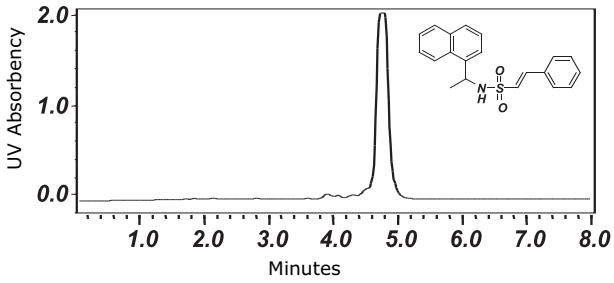
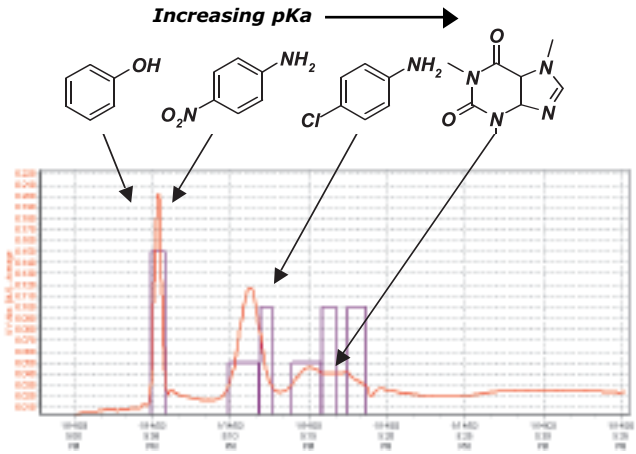
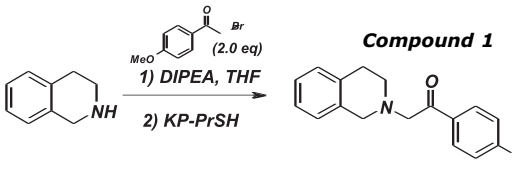


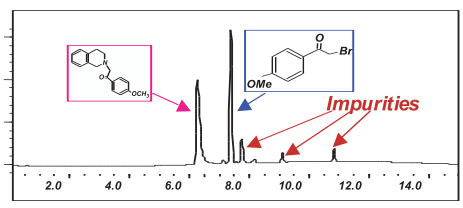
Figure 8. KP-TsOH Representative Catch and Release Procedure. *A four-component mixture of differing pKa values was dissolved in DMF and injected directly onto a TsOH12 Samplet™ and FLASH 12+M cartridge combination using the gradient method shown below. The elution order of the nitrogen containing compounds is consistent with increasing pKa values rather than polarity, phenol is not bound to TsOH.*



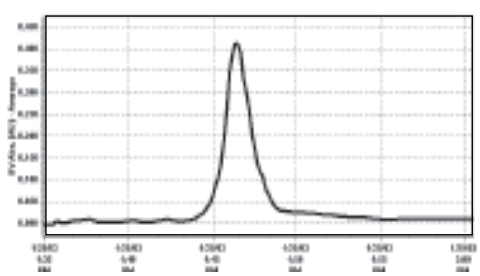
Sample: 0.25M total concentration of phenol, 4-nitroaniline, 4-chloroaniline, and caffeine dissolved in DMF
Cartridge: FLASH 12+M KP-Sil
Solvent A: Hexane
Solvent B: 1% TEA in ethyl acetate
Gradient Program: Equilibrate 2 CV (column volumes)
Step 1: 0 – 0% B for 2 CV
Step 2: 0 – 100% B for 5 CV, (linear)
Step 3: 100% B for 10 CV
Flow Rate: 12 mL/min

Figure 9. KP-PrSH Representative Scavenging Procedure. *Compound 1 was prepared on 0.1 mmol scale in the presence of excess 4 methoxyphenacyl bromide (2.0 eq) and diisopropylethylamine (3.0 eq) in THF. The solution was stirred for 30 minutes, and 0.5 mL was transferred to a PrSH12 Syntage™ Samplet™ cartridge, dried on a heating block, inserted into a FLASH 12+M silica cartridge and purified using the following method on a Horizon™ HPFC™ system. Compound 1 was isolated in 93% yield with an HPLC purity of 99%.*





Crude Reaction Mixture



Purification on Horizon System

Solvent A: EtOAc/Hexane (20:80)
Solvent B: EtOAc
Gradient: 0 – 100% B in 500 mL, linear
Flow Rate: 35 mL/min.

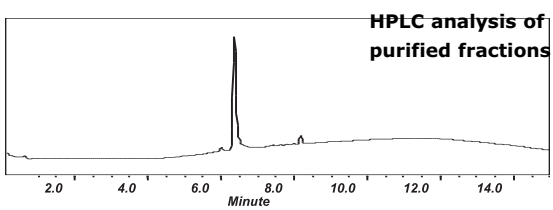
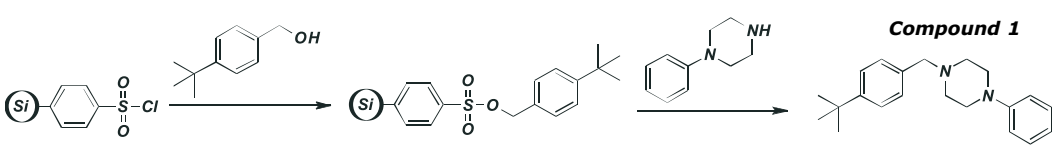
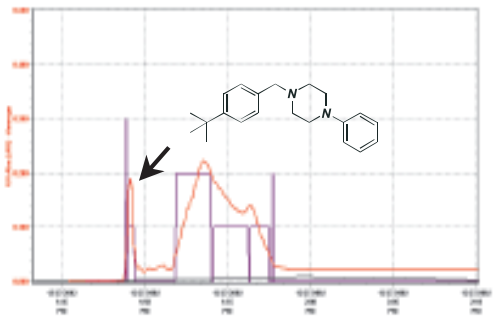


Figure 10. KP-TsCL Representative Synthesis Procedure*. Using a Tertiary Amine Synthesis Method, compound 1 was synthesized on 0.1 mmol scale using a Syntage TsCl 12 chemistry cartridge, isolated using a FLASH 12+M silica cartridge and purified using the following method on a Horizon HPFC system, resulting in 81% yield with an HPLC purity of 97%.*



Purification on Horizon System



Solvent A: Hexane (20:80)
Solvent B: 0.5% TEA/ethyl acetate
Gradient: Step 1: 25-100% B for 10 CV
Step 2: 100% B for 2 CV

HPLC analysis of purified fractions, HPLC Purity - 97%

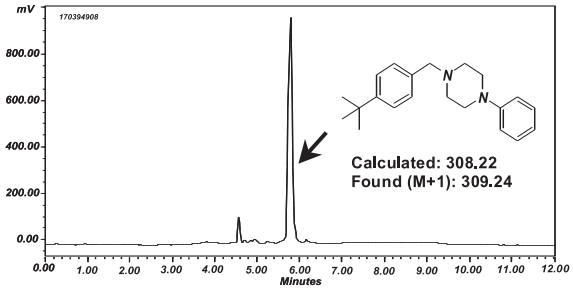
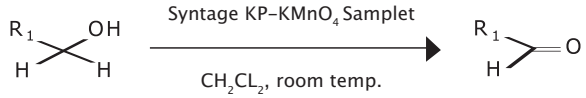
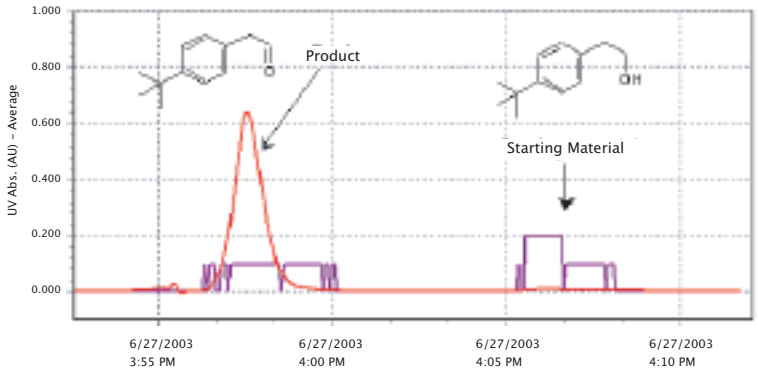


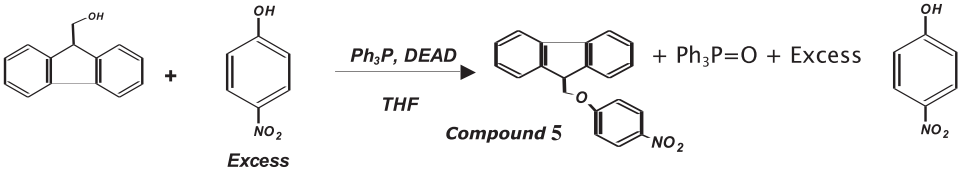
Figure 11. KMN04 Representative Oxidation Procedure. *Flash purification of a synthetic aldehyde using Syntage 12 KMnO4 Samplet cartridge, FLASH 12+ Silica cartridge and a SP4™ HPFC™ system. Oxidized products were typically purified by elution starting from 1:4 to 1:1 dichloromethane/hexane in 6 column volumes.*

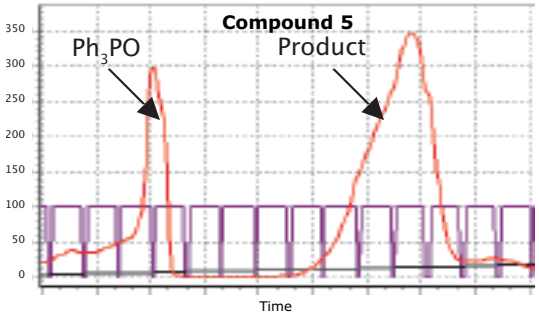




A typical purification profile of the oxidation of 4-tert-butylphenethyl alcohol using the Biotage system.

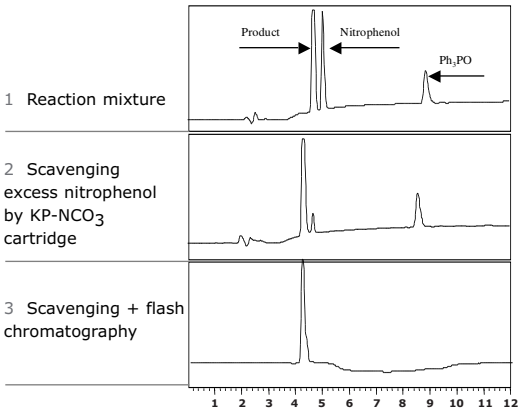
Figure 12. KP-NC03 Representative Scavenging Example*. Scavenging Nitrophenol in a Mitsunobu Reaction Compound 5 was prepared via a Mitsunobu reaction. DEAD was added to a solution of 9-fluorenemethylalcohol, nitrophenol (1.8 eq.) and triphenylphosphine (Ph_3P) in THF. The reaction mixture was stirred for three hours at room temperature and was transferred to a Syntage 12 KP-NCO3 cartridge, dried on a Syntage Samplet heating block, inserted into a FLASH 12+M silica cartridge and purified using the following method on a Horizon HPFC system:*





Flash Chromatography purification of Compound 5, with an 89% yield and HPLC purity of 98%.

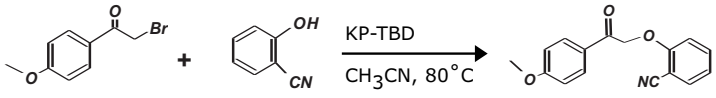
Solvent A: EtOAc/Hexane (20:80)
Condition: Isocratic
Flow Rate: 12 mL/min.

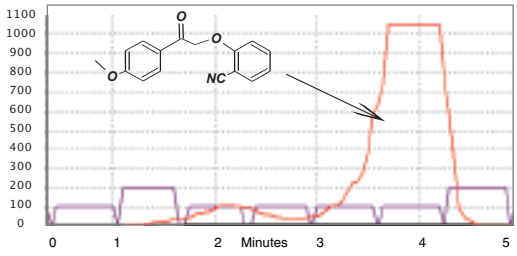


HPLC of reaction mixture and isolated product

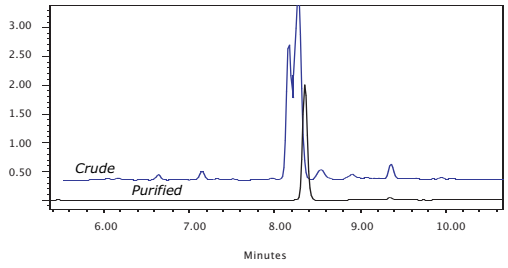
HPLC conditions
Column: PVA, 4.6 x 150
Eluent: A: EtOAc/Hexane (20:80)
B: EtOAc
Gradient: 0-100% B in 10 min
Flow Rate: 2 mL/min
Detection: UV @ 254 nm

Figure 13. KP-TBD Representative Scavenging Procedure. *Typical procedure for phenol alkylation (Williamson ether synthesis) involves choosing the appropriate Syntage cartridge size such that the phenol is 1 equivalent of the loading capacity of the cartridge. Dissolve 1 mmole of phenol in 0.5 mL toluene and transfer the dissolved phenol to the Syntage KP-TBD 25 cartridge. Apply 1 mmole of alkyhalide dissolved in 0.5 mL acetonitrile to the cartridge. Dry the Syntage Samplet™ using a Syntage heating block in a vacuum oven for five hours at 80 °C. Remove the cartridge from the oven and allow it to cool to room temperature before placing it into a FLASH 25+S KP-Sil purification cartridge. Elute the alkylated phenol using an appropriate elution profile.*





Cartridge: FLASH 25+S KP-Sil
Solvent: A: DCM
B: DCM, MeOH(9:1)
Gradient Program: Step 1:0-50%B in 10CV
Step 2: 50-100%B in 10CV
Flow Rate: 25 mL/min
Collected Fraction: 15 mL



Conditions
Column: YMC C8 (S-3 120 Å)
4.6 x 50 mm
Injection: 3 mL
Mobile Phase:
A: H2O:ACN (95:5) + 0.1% TFA
B: ACN: H2O (95:5) + 0.1% TFA
Gradient: B (5-100%) in eight minutes, hold two minutes
Flow Rate: 1.5 mL/min
Detection: 254nm

Syntage Heating Blocks™



Syntage heating blocks are designed to enhance solvent evaporation and cartridge-based reactions with Syntage Samplet chemistry cartridges. Syntage heating blocks improve heat transfer to the cartridge when used in a vacuum oven, thereby decreasing solvent evaporation time.

These modular blocks are constructed of solid anodized aluminum for maximum heat retention and to provide uniform cartridge heating. Each anodized block is Teflon® coated for added chemical resistance. Syntage heating blocks are designed for use within a standard vacuum oven or on top of a thermocouple controlled hot plate. Each heating block has one thermometer and one thermocouple well to ensure accurate temperature control and monitoring. Syntage heating blocks are machined to standard microtiter plate dimensions for easy integration with an automated liquid handler.

Features and Benefits

- Anodized and Teflon® coated solid aluminum blocks ensure uniform cartridge heating and chemical resistance
- Improved heat transfer to Syntage cartridges to decrease drying time
- Microtiter plate dimensions for easy integration with an automated liquid handler
- Available in 12, 25, and 40 sample-loading cartridges
- Protective sleeves available to minimize block contamination

Solvent	Boiling Point (°C)	Vapor Pressure (mm Hg)	Recommended Drying Temperature (°C)
Acetone	56	181	35 - 40
Acetonitrile	82	72.4	60 - 65
T-Butyl methyl ether	52	249	30 - 35
Chloroform	61	155.1	40 - 45
Cyclohexane	81	78	60 - 65
DCM	40	341.3	20 - 25
Diethyl ether	35	434.4	15 - 20
Ethanol	78	41.4	55 - 60
Ethyl acetate	77	72.4	55 - 60
Hexane	69	129.3	50 - 55
Methanol	65	93.1	45 - 50
Methyl acetate	56	173	35 - 40
THF	66	129.3	45 - 50

Recommended Drying Times

Size	Solvent A	Solvent B
12	20 min.	30 min.
25	30 min.	45 min.
40	45 min.	60 min.

Solvent A: **VP>100mm Hg**

Solvent B: **VP<10mm Hg**

Rules of thumb:

1. Make sure samples will not degrade on silica or at selected temperature
2. Gradually increase vacuum without heat
    1. No to low vacuum (760-650 mm Hg) for VP >300 mmHg
    2. Low to moderate vacuum (700-600 mm Hg) for VP >100 mm Hg
    3. Moderate to high vacuum (650–550 mm Hg) with heat for VP <100 mm Hg
3. If heating, set temp at 15 – 20 °C below solvent boiling point
4. Use Biotage heating blocks

Syntage™ Cartridge Capacity

Syntage Cartridge Capacity

Samplet™ Cartridge	Cartridge Vol. (mL)	Cartridge Loading (mmol/cartridge)	Flow Rate (mL/min)
KP-PrNH 12	1	0.26 – 0.40	10 – 15
KP-PrNH 25	5	1.3 – 2.1	20 – 50
KP-PrNH 40	10	3.1 – 4.8	30 – 100
KP-TsOH 12	1	0.26 – 0.40	5 – 10
KP-TsOH 25	5	1.3 – 2.1	15 – 25
KP-TsOH 40	10	3.1 – 4.8	30 – 50
KP-PrSH 12	1	0.21 – 0.31	5 – 10
KP-PrSH 25	5	1.1 – 1.6	15 – 25
KP-PrSH 40	10	2.5 – 3.7	30 – 50
KP-TsCL 12	1	0.26 – 0.40	5 – 10
KP-TsCL 25	5	1.3 – 2.1	15 – 25
KP-TsCL 40	10	3.1 – 4.8	30 – 50
KP-TBD 12	1	0.63-0.77	5-10
KP-TBD 25	5	3.51-4.29	15-25
KP-NC03 12	1	0.51-0.62	5-10
KP-NC03 25	5	2.81-3.63	15-25
KP-NC03 40	10	4.05-4.95	30-50
KP-KMNO4 12	1	0.82-1.0	5-10
KP-KMNO4 25	5	4.56-5.58	15-25
KP-KMNO4 40	10	10.53-12.87	30-50

** At 40 °C*

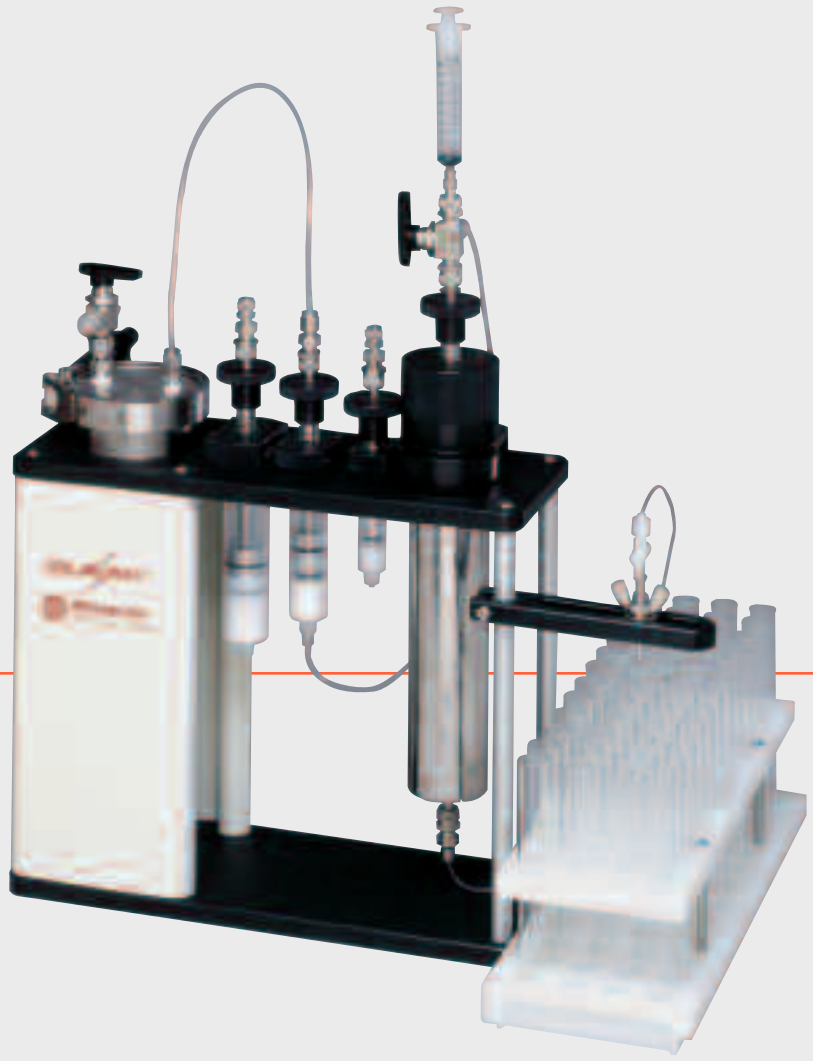
Ordering Information

Syntage Chemistry Cartridges Ordering Information

Item	Description	Part Number
KP-PrNH		
12 KP-PrNH Samplet	12 mm Syntage Samplet, 24/case	SAM-PRNH12
25 KP-PrNH Samplet	25 mm Syntage Samplet, 8/case	SAM-PRNH25
40 KP-PrNH Samplet	40 mm Syntage Samplet, 4/case	SAM-PRNH40
KP-PrSH		
12 KP-PrSH Samplet	12 mm Syntage Samplet, 24/case	SAM-PRSH12
25 KP-PrSH Samplet	25 mm Syntage Samplet, 8/case	SAM-PRSH25
40 KP-PrSH Samplet	40 mm Syntage Samplet, 4/case	SAM-PRSH40
KP-TsOH		
12 KP-TsOH Samplet	12 mm Syntage Samplet, 24/case	SAM-TSOH12
25 KP-TsOH Samplet	25 mm Syntage Samplet, 8/case	SAM-TSOH25
40 KP-TsOH Samplet	40 mm Syntage Samplet, 4/case	SAM-TSOH40
KP-TsCl		
12 KP-TsCl Samplet	12 mm Syntage Samplet, 24/case	SAM-TSCL12
25 KP-TsCl Samplet	25 mm Syntage Samplet, 8/case	SAM-TSCL25
40 KP-TsCl Samplet	40 mm Syntage Samplet, 4/case	SAM-TSCL40
KP-KMn04		
12 KP-KMn04 Samplet	12 mm Syntage Samplet, 24/case	SAM-KMNO412
25 KP-KMn04 Samplet	25 mm Syntage Samplet, 8/case	SAM-KMNO425
40 KP-KMn04 Samplet	40 mm Syntage Samplet, 4/case	SAM-KMNO440
KP-TBD		
12 KP-TBD Samplet	12 mm Syntage Samplet, 24/cse	SAM-TBD12
25 KP-TBD Samplet	25 mm Syntage Samplet, 8/case	SAM-TBD25
40 KP-TBD Samplet	40 mm Syntage Samplet, 4/case	SAM-TBD40
KP-NCO3		
12 KP-NCO3 Samplet	12 mm Syntage Samplet, 24/case	SAM-NCO312
25 KP-NCO3 Samplet	25 mm Syntage Samplet, 8/case	SAM-NCO325
40 KP-NCO3 Samplet	40 mm Syntage Samplet, 4/case	SAM-NCO340
KP-CF		
12 KP-CF Samplet	12 mm Syntage Samplet, 24/case	SAM-CF12
25 KP-CF Samplet	25 mm Syntage Samplet, 24/case	SAM-CF25
40 KP-CF Samplet	40 mm Syntage Samplet, 24/case	SAM-CF40

Syntage Heating Blocks

Item	Description	Part Number
Syntage 12 Heating Block	Solid aluminum block with Teflon coating holds 24 Syntage 12 Samplet cartridges, and Syntage 12 sleeves	09644
Syntage 12 Sleeves	Straight-side polyethylene shell for use with Syntage 12 Samplet cartridges and heating blocks, pack of 24	09641
Syntage 25 Heating Block	Solid aluminum block with Teflon coating holds 8 Syntage 25 Samplet cartridges, and Syntage 25 sleeves	09645
Syntage 25 Sleeves	Straight-side polyethylene shell for use with Syntage 25 Samplet cartridges and heating blocks, pack of 24	09642
Syntage 40 Heating Block	Solid aluminum block with Teflon coating holds 4 Syntage 40 Samplet cartridges, and Syntage 40 sleeves	09646
Syntage 40 Sleeves	Straight-side polyethylene shell for use with Syntage 40 Samplet cartridges and heating blocks, pack of 24	09643





Discovery-Scale FLASH™ Chromatography Systems and Modules

For the Manual Purification of Organic Molecules

FLASH+™ Systems

FLASH+: High-Yield, High-Performance, Milligram-to Gram-Scale Purifications

Biotage FLASH+ chromatography products incorporate all the features of our HPFC™ product line. The tools you need for efficient, effective FLASH purifications can be purchased as complete FLASH+ systems or as individual components to suit your requirements.

Easy Setup

Setting up a FLASH+ system is fast and easy. To begin your separation, simply insert a FLASH+ cartridge into the chosen compression module and attach the patented Zero Insertion Force (ZIF™) head assembly. For liquid samples, inject directly onto the head of the cartridge using a suitable sized syringe. For low-solubility samples or difficult separations, use our Samplet sample-loading cartridges (see page 88 for full description) or a Zero Insertion Force–Sample Injection Module ZIF-SIM™ (see page 118 for full description). Turn the valve to let the solvent flow and collect your fractions by placing a tube rack under the outlet line.

Applications

FLASH+ systems simplify and accelerate the isolation of organic compounds. Typical applications involve purification throughout multistep solution-phase synthesis, in which there is high probability of complex mixtures. The scale of purification ranges from milligrams to grams for simple and complex mixtures (see page 50 for more detailed application information).

Available as a Complete System or as Individual Components

FLASH+ systems include everything except the cartridges: a solvent reservoir, a stand, a ZIF-SIM, and a compression module with short and/or medium barrel(s). Other options include upgrades to larger compression modules for scale-up to gram-scale purification and a pressure regulator for controlling flow rates.



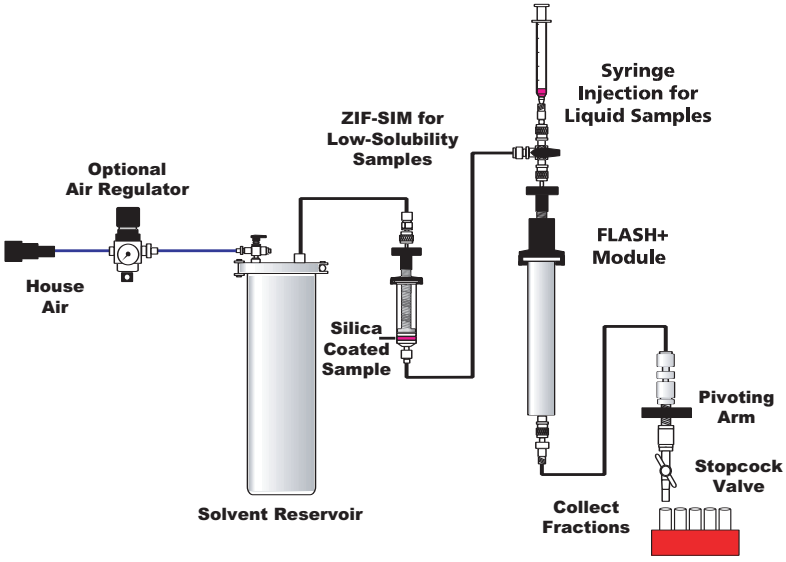


Figure 1. *FLASH+™ flow diagram.*

FLASH+ Compression Modules Incorporate ZIF™ and Samplet™ Technologies

FLASH+ compression modules use Biotage-patented FLASH+ cartridges packed with a range of normal and reversed-phase media (see page 88 for more detailed packing—media information).

The FLASH+ compression modules are designed with patented ZIF (Zero Insertion Force) head technology that improves purification of synthetic and natural products by axially compressing the FLASH+ cartridge. Axial compression of the cartridge bed minimizes void space, which improves separation efficiency and loading capacity. For simplified sample handling, the FLASH+ compression modules accept Samplet sample-loading cartridges. For low-solubility samples that cannot be dissolved in an appropriate volume for Samplet loading, a ZIF-SIM™ adds additional purification capabilities.



ZIF head assembly*, designed to distribute sample and solvent flow evenly through each cartridge.*

FLASH+™ Systems

The FLASH 12+™ Compression Module and 12-mm ID Prepacked Cartridges are Designed for Milligram-scale FLASH Separations



FLASH 12+M System with ZIF-SIM10,™ ZIF-SIM35,™ and test-tube rack



FLASH 12+S and 12+M columns, head assemblies. FLASH 12+S and 12+M cartridges and Samplets

Flash 12+ Specifications

Cartridge	Dimensions	Sample size	Flow rate	ZIF-SIM	Reservoir
FLASH 12+S	12 mm ID x 75 mm	4-200 mg	10-15 mL/min	10	1 L
FLASH 12+M	12 mm ID x 150 mm	8-400 mg	10-15 mL/min	10	1 L
FLASH 12+ Samplet™	10 mm ID x 20 mm	1 mL	----	----	----

Please refer to page 117 for all FLASH+ System ordering information.

Customize Your FLASH System

The FLASH 25™+ Compression Module and 25-mm ID Prepacked Cartridges are Designed for Milligram-to-gram Scale FLASH Separations



FLASH 25+M System with ZIF-SIM10,™ ZIF-SIM35,™ and ZIF-SIM60™ and test-tube rack



FLASH 25+S and 25+M columns head assemblies. FLASH 25+S and 25+M cartridges and Samplets

Flash 25+ Specifications

Cartridge	Dimensions	Sample size	Flow rate	ZIF-SIM	Reservoir
FLASH 25+S	25 mm ID x 75 mm	15-800 mg	20-50 mL/min	10 or 35	1 L
FLASH 25+M	25 mm ID x 150 mm	30-1600 mg	20-50 mL/min	35	1 L
FLASH 25+ Samplets™	23 mm ID x 20 mm	5 mL	----	----	----

Please refer to page 117 for all FLASH+ System ordering information.

FLASH+™ Systems

The FLASH 40+™ Compression Module



FLASH 40+™M System with ZIF-SIM10,™ ZIF-SIM35,™ and ZIF-SIM60™ and test-tube rack



FLASH 40+S and 40+M columns, head assemblies. FLASH 40+S and 40+M cartridges and Samplets

Flash 40+ Specifications

Cartridge	Dimensions	Sample size	Flow rate	ZIF-SIM	Reservoir
FLASH 40+S	40 mm ID x 75 mm	40 mg - 2 g	30-100 mL/min	60	1 L
FLASH 40+M	40 mm ID x 150 mm	80 mg -5 g	30-100 mL/min	60	1 L
FLASH 40+ Samplet™	38 mm ID x 20 mm	10 mL	----	----	----

Please refer to page 117 for all FLASH+ System ordering information.

FLASH+™ Ordering Information

Component 1	Component 2	Component 3	Options
FS1-R Any FLASH+ System and 1-Liter Reservoir	**A** FLASH 12+ S Compression Module	**0** No ZIF-SIM™	**-A** Short Barrel 12+
	B FLASH 12+M Compression Module	**1** ZIF-SIM10™	**-B** Short Barrel 25+
	C FLASH 25+ S Compression Module		
	D FLASH 25+M Compression Module	**2** ZIF-SIM35™	**-C** Short Barrel 40+
	E FLASH 40+ S Compression Module		
	F FLASH 40+M Compression Module	**3** ZIF-SIM60™	**-D** Medium Barrel 12+
	G FLASH 12+S and 25+S Compression Modules		
	H FLASH 12+M and 25+M Compression Modules	**4** ZIF-SIM10 and 35	**-E** Medium Barrel 25+
	J FLASH 12+S and 40+S Compression Modules		
	K FLASH 12+M and 40+M Compression Modules	**5** ZIF-SIM10 and 60	**-F** Medium Barrel 40
	L FLASH 25+S and 40+S Compression Modules		
	M FLASH 25+M and 40+M Compression Modules	**6** ZIF-SIM35 and 60	
	N FLASH 12, 25, 40+S Compression Modules		
	P FLASH 12, 25, 40+M Compression Modules	**7** ZIF-SIM10, 35, and 60	**-G** Air Regulator with filter

Part Number: FS1-R___-_____

Instructions: Simply choose one component from each of the component columns and then as many options as you need. Moving from left to right, fill in the spaces below the table to create a custom part number (example: FS1-RD6-BF).

FLASH+™ Components and Accessories

Item	Description	Part Number
Injection Valve	3-way vertical injection valve with Luer-Lok adapter for liquid injections	FIV-VLV-1000
1-Liter Solvent Reservoir	Stainless-steel solvent reservoir; ideal for FLASH 12+™ to 40+™ compression modules	FN-001-41201
4-Liter Solvent Reservoir	Larger stainless-steel reservoir; ideal when purifying multiple samples with the same eluent. Also ideal for the FLASH 65i™ compression module	FN-004-04000
Air Regulator	Regulates air pressure for use with all air-operated Biotage systems (0-60 psig); contains particulate filter	09350
FLASH+ Start-Up Kit	Frame and tubing	07923
FLASH 12i Compression Module	For use with FLASH 12i and Samplet™ Cartridges	FC022-15024
FLASH 12+S Compression Module	For use with FLASH 12+S and Samplet Cartridges	07857
FLASH 12+M Compression Module	For use with FLASH 12+M and Samplet Cartridges	07858
FLASH 12+S Barrel	For use with FLASH 12+S and Samplet Cartridges	07395
FLASH 12+M Barrel	For use with FLASH 12+M and Samplet Cartridges	07383
FLASH 25+™S Compression Module	For use with FLASH 25+S and Samplet Cartridges	FC-022-16024
FLASH 25+M Compression Module	For use with FLASH 25+M and Samplet Cartridges	FC-022-16044
FLASH 25+S Barrel	For use with FLASH 25+S and Samplet Cartridges	FB-022-16024
FLASH 25+M Barrel	For use with FLASH 25+M and Samplet Cartridges	FB-022-16044
FLASH 40i Compression Module	For use with FLASH 40i and Samplet Cartridges	FC022-17024
FLASH 40+S Compression Module	For use with FLASH 40+S and Samplet Cartridges	07975
FLASH 40+M Compression Module	For use with FLASH 40+M and Samplet Cartridges	07976
FLASH 40+S Barrel	For use with FLASH 40+S and Samplet Cartridges	07387
FLASH 40+M Barrel	For use with FLASH 40+M and Samplet Cartridges	07388
FLASH-Pac+	Set of 12+M, 25+M, 40+M Compression Modules and 12+S, 25+S, 40+S Barrels	08615
FLASH to ISCO	Adapters and tubing to allow use of FLASH+ or "i" style compression modules with ISCO systems	09335

FLASH 65i™ Compression Module

The FLASH 65i compression module for 65-mm cartridges now incorporates the Zero Insertion Force (ZIF™) sealing mechanism, which enables effortless insertion and removal of cartridges and reduces O-ring wear. The new ZIF head assembly improves bed stability, efficiency, and sample loading by applying axial compression to the cartridge. ZIF technology also allows increased sealing pressures up to 100 psig, providing faster flow rates and eliminating the leaks due to variations in bed heights.

The FLASH 65i compression module can be used with the Horizon™ HPFC™ system for automated purification or with our new FLASH+™ stand and a 4-liter solvent reservoir. For low-solubility samples, mixtures can be dissolved in a polar solvent, mixed with silica, concentrated, and then packed into the barrel of a ZIF-SIM60.™ The ZIF-SIM™ easily mounts between the solvent reservoir (or HPFC pump) and the FLASH 65i compression module to introduce the sample onto the cartridge.

Features and Benefits

- Easy insertion and removal of cartridges
- Low dead-volume head assembly for improved sample-injection efficiency
- All-stainless-steel flow path that simplifies cleaning between injections
- Less O-ring wear
- A ZIF sealing mechanism that allows higher operating pressures and flow rates
- Even distribution of sample and solvent flow through each cartridge



FLASH 65i *compression module and cartridge*

FLASH 65i Specifications

Cartridge	Dimensions	Weight	Flow Rate	Sample Size
KP-Sil™	65 mm x 200 mm	350 g	65-85 mL/min	0.3-13 g
KP-C18-HS™	65 mm x 200 mm	400 g	65-85 mL/min	0.03-1.3 g

Please refer to page 121 for all FLASH 65i ordering information.

ZIF-SIM™ Zero Insertion Force Sample Injection Module

Sample Injection Modules with Biotage's Patented Zero Insertion Force Design Improve Purification Performance

The new ZIF-SIM family of products is used with Biotage's FLASH 12+™, 25+™, 40+™ and 65i™ compression modules. This new design utilizes our patented Zero Insertion Force (ZIF™) technology. This simplifies sample loading and improves chromatographic performance when preadsorbed samples are loaded. The ZIF-SIM unit is designed to eliminate dead space in the barrel by applying axial compression to the silica bed. Axial compression eliminates any risk of sample dilution, cracking of the bed, and issues associated with sample remixing.

By utilizing zero insertion force technology, insertion and removal of the head assembly is greatly simplified.



ZIF-SIM10™, ZIF-SIM35™, ZIF-SIM60™

FLASH 65i™ Ordering Information

Item	Description	Part Number
Flash 65i Compression Module	Holds one 65-mm ID x 20 cm prepacked cartridge	07868
Flash 65i Compression Module Upgrade	Flash 65i head assembly, for use with older model FLASH barrel	08405
4-Liter Solvent Reservoir	SS 4-Liter, 9" (23 cm) ID x 14" (36 cm) high	FN-004-04000
Injection Valve	3-way vertical injection valve with Luer-Lok® adapter for liquid injections	FIV-VLV-1000
Air Regulator with Filter	Regulates air pressure for use with all air-operated Biotage systems (0-60 psig), contains particulate filter	09350
FLASH+™ Start-Up Kit	Frame and tubing	07923

**Biotage recommends annual replacement of Chemraz® O-rings to maintain FLASH 65i compression modules.*

ZIF-SIM™ Ordering Information

ZIF-SIM™ (Zero Insertion Force—Sample Injection Module)

Each ZIF-SIM module comes with a ZIF™ head assembly, 20 disposable sample-loading barrels (each containing a bottom frit), top frits, a frit insertion tool, tubing kit and user's manual.

Item	Description	Part Number
ZIF-SIM10™ Sample-loading Module	Holds 2.5 g (max) of silica	FZIM-0010
ZIF-SIM35™ Sample-loading Module	Holds 10 g (max) of silica	FZIM-0035
ZIF-SIM60™ Sample-loading Module	Holds 20 g (max) of silica	FZIM-0060

ZIF-SIM Consumables*

Item	Description	Part Number
ZIF-SIM10 Barrels	20 barrels with top and bottom frits	SBF-0010
ZIF-SIM35 Barrels	20 barrels with top and bottom frits	SBF-0035
ZIF-SIM60 Barrels	20 barrels with top and bottom frits	SBF-0060
ZIF-SIM Tubing Kit	Luer fitting with 1/8" tubing and 1/8" knurled nut; connects ZIF-SIM outlet to compression module	01903

**These consumables may also be used on Sample Loading Modules (SLM) for FLASH Elute Systems.*

Dry-Loading Compression Head Assembly

The Dry-Loading Compression Head Assembly allows chemists to load precoated, loose silica directly into a Biotage FLASH+™ cartridge. The new dry-loading head is compatible with all Biotage FLASH+ compression modules and FLASH+ purification cartridges. Biotage offers adapter kits to accommodate any flash system.

A counter-lock design provides a liquid-tight seal with an easy reverse-turn of the upper knob. This motion creates a tight Zero-Insertion Force (ZIF™) seal with the cartridge to prevent sample loss from leakage due to any drop in the bed level of the loose sample-coated silica.

The pre-adsorbed sample loading technique is used when the sample solubility is low or if the dissolution solvent is too strong for the purification.

This technique can be completed in four easy steps:

Step 1: The sample is adsorbed onto loose silica or another solid-support media. Biotage recommends a 1-part sample load to 2- or 3-parts silica.

Step 2: The loose sample is loaded directly into the Biotage FLASH+ purification cartridge.

Step 3: A corresponding cartridge frit is placed on top of the loose sample inside the cartridge.

Step 4: The cartridge is loaded into the barrel and sealed using the Dry-Loading Compression Head Assembly.



Features and Benefits:

- Enables easy purification of low-solubility compounds with Biotage FLASH+ purification cartridges
- Maximizes sample loading in a given cartridge
- Creates a secure, liquid-tight seal eliminating potential sample loss
- Can be adapted to other FLASH systems with our adapter kit

Cartridge Size	Maximum Silica Load/ Cartridge (g)
FLASH 12+	2
FLASH 25+	8
FLASH 40+	20

Use this table as a guide when using the Dry-Loading Compression Head Assembly.

Warning: Biotage Samplet™ cartridges are not compatible with the Dry-Loading Compression Head Assembly.

Dry-Loading Compression Head Assembly Ordering Information

Item	Description	Part Number
Dry-Loading FLASH 12+ Compression Head Assembly	For use with direct dry-loading into the FLASH 12+ cartridges	09547
Dry-Loading FLASH 25+ Compression Head Assembly	For use with direct dry-loading into the FLASH 25+ cartridges	09543
Dry-Loading FLASH 40+ Compression Head Assembly	For use with direct dry-loading into the FLASH 40+ cartridges	09535
Dry-Loading FLASH 12+S Compression Module	Compression assembly with FLASH 12+S barrel	09553
Dry-Loading FLASH 12+M Compression Module	Compression assembly with FLASH 12+M barrel	09554
Dry-Loading FLASH 25+S Compression Module	Compression assembly with FLASH 25+S barrel	09555
Dry-Loading FLASH 25+M Compression Module	Compression assembly with FLASH 25+M barrel	09556
Dry-Loading FLASH 40+S Compression Module	Compression assembly with FLASH 40+S barrel	09551
Dry-Loading FLASH 40+M Compression Module	Compression assembly with FLASH 40+M barrel	09552
Dry-Loading Frits 12+	For use with dry-loading in FLASH 12+ cartridges (20/package)	09738
Dry-Loading Frits 25+	For use with dry-loading in FLASH 25+ cartridges (20/package)	09739
Dry-Loading Frits 40+	For use with dry-loading in FLASH 40+ cartridges (20/package)	09740
FLASH to ISCO Adapter Kit	Adapter and tubing to allow use of FLASH+ or “i” style compression modules with ISCO systems	09335


Method Editor
Biotage



SP™ Flash Purification System

Fast, Intuitive, Automated Flash Purification

Fast, Intuitive, Automated Flash Purification...Reduces Bottlenecks and Increases Throughput

Today's medicinal chemists are expected to create an increasing number of new chemical entities (NCE) each year. Research shows purification to be the primary bottleneck in this drug discovery process. Therefore, chemists have turned to automated flash purification systems to purify crude samples faster using programmed elution gradients and UV fractionation. However, many of the interim steps needed to perform flash purification still remain manual and imprecise, such as determining the elution gradient using thin-layer chromatography (TLC) and choosing the right column. As instrumentation and technology become more sophisticated, they incorporate more and more of these manual steps, further reducing the purification bottleneck.



Features and Benefits

Touch Logic Control™

Load and run a sample in three simple steps using a 10.4" (26cm) touch screen, a new graphical user-interface, and a built-in Pentium® computer.

TLC-to-gradient profile

Automatically create a method and choose the optimal cartridge size based on the TLC data entered. Change the gradient and fractionation parameters "on-the-fly" (during operation).

Compact design

The SP's compact footprint fits easily into a standard fume hood and accommodates the Biotage FLASH 12–40 and 65i cartridges.

Leak sensor (optional)

Automatically detects fluid line leaks and pauses the system with a user alert.

Features and Benefits cont...

Solvent and waste monitoring

Automatically calculates the required solvent amount for a purification sequence, monitors the solvent volume used and notifies user to replenish reservoirs when needed. Accumulated waste is also measured eliminating potential overflows.

Variable dual-wavelength detector (optional)

Collect fractions using one wavelength while simultaneously monitoring the separation at a second wavelength. Flow cells available with either a 0.1 or 0.3 mm flow path.

Fraction arm positioning

Precise fraction arm positioning will not dispense fractions if misaligned, eliminating sample loss.

Fraction Finder

Locate compounds of interest faster by pressing the fraction finder button and chromatogram. The fraction position is highlighted on the chromatogram and the collection display.

Print reports

Run data and methods are automatically stored. Print results and transfer methods to another SP system or PC.

Autocontinue feature

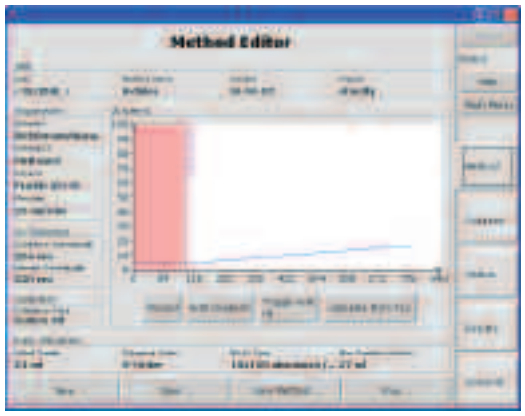
Detect UV-absorbance in the flow cell and continue pumping solvent and collecting fractions after the run, until the baseline stabilizes.

SP4™ 4-column sequential purification

Load and run up to 4 samples with just a few icon touches. Continually add samples to the queue for uninterrupted sequential purification. Flowpaths and waste streams are segregated and automatically flushed between runs eliminating sample-to-sample cross contamination.

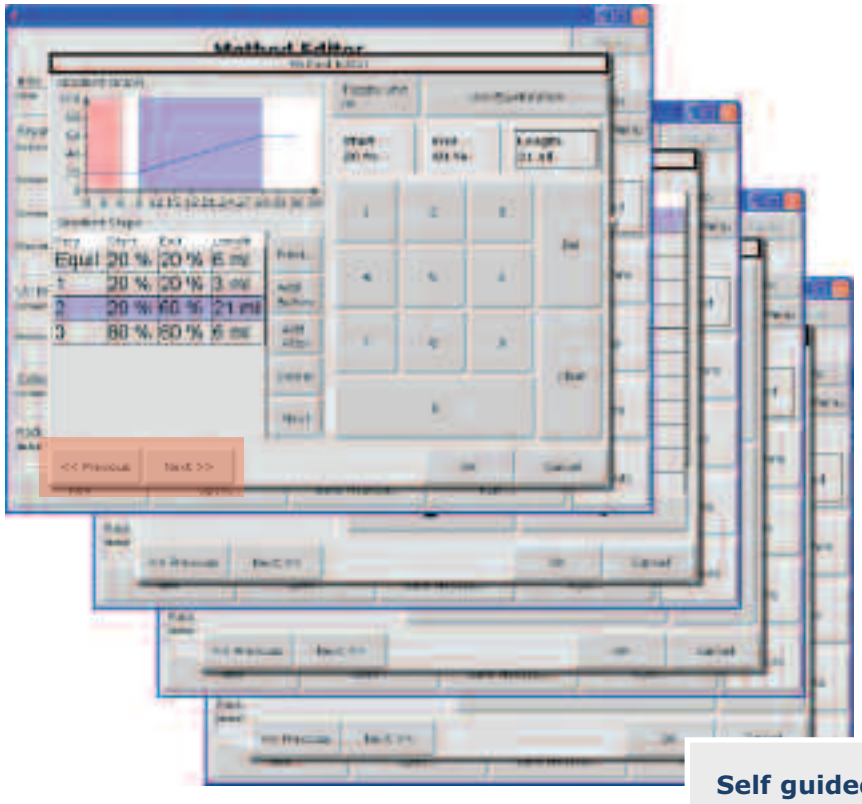
Upgradable

An SP1 system can be upgraded to an SP4 just by replacing the SP1 flow path module with an SP4 flow path module—no software changes required.



Ease of use

With Touch-Logic-Control purifications are easily programmed and executed from one single window.



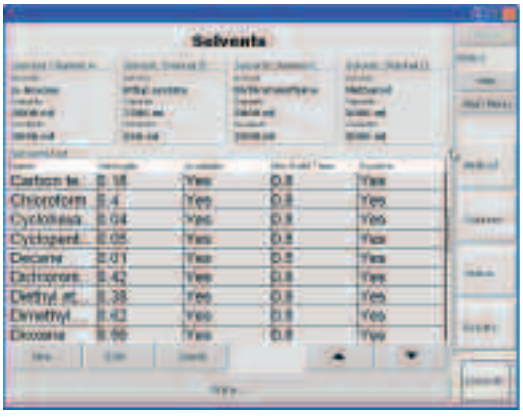
Self guided software

At any time a step-by-step wizard is available to guide users through the run setup. The Previous or Next buttons toggle between screens, allowing users to confirm that complete information has been entered.

Software Features

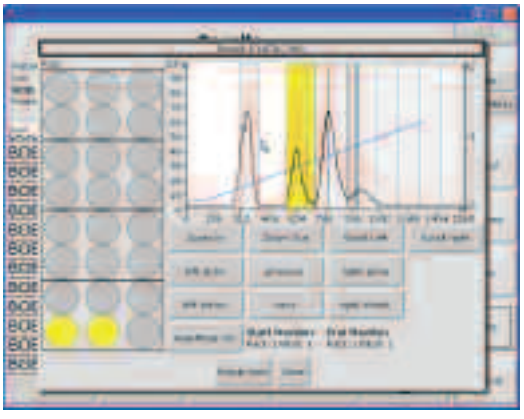
Solvent Monitoring

All solvents are entered into the system with their eluting strengths and vapor pressures to optimize ease of use and performance. The system continuously keeps track of your solvent and waste reservoirs warning when they are running low or having a risk of overflowing.



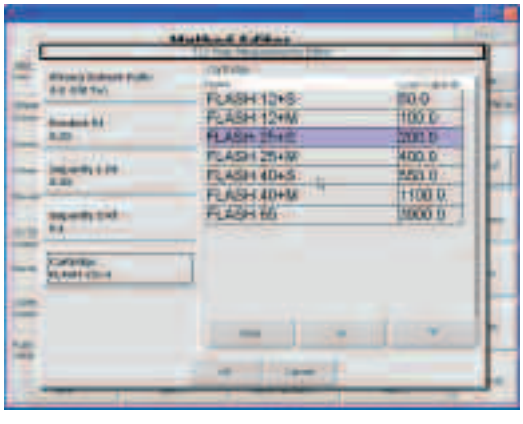
"Find a fraction"

All fractions can be easily correlated to the corresponding test tube at any time in either the status screen or the results screen. Using the Peak Mode all fractions correlating to the same peak can be identified at once.



Automated gradient creation from TLC data

Create a sample-specific gradient method by simply selecting the TLC solvents from a preprogrammed list and entering their ratio. Then, enter your compound's Rf value, choose a cartridge, collection rack, UV wavelength, and fractionation mode and the system creates a unique gradient method.



Specifications

Solvent delivery	Constant volume (3 mL) electric HPFC pump
Flow rate	1–100 mL/min
Pressure limit	100 psi (7 bar)
Liquid sample loading	Optional, 3-way liquid injection valve
Solid sample loading	Samplet™ sample loading cartridge, ZIF-SIM™
UV detection	Choice of variable dual-wavelength (200–320 nm) or fixed (254 nm) detector
Flow-cell path length	Choice of 0.1 mm or 0.3 mm
Fractionation modes	Collect all, UV threshold, UV slope
Collection vessels	Test tubes (mm): 13, 16, 17, 18, and 25, Bottles (mL): 120 and 240
Power	110–120 VAC, 60 Hz (US, Japan) 220–240 VAC, 50 Hz
System control & data management	On-board Pentium® computer with 10.4" diagonal touch-screen interface and Windows® XP-based software
Dimensions	19" x 23" x 24" W x D x H (48 cm x 58 cm x 61 cm)
Certifications	CE, CSA certified

SP System and Product Components Ordering Information

Systems

SP1™ Part Number	Base System	Country/Certification
SP1-X0A	No detector	US/CSA
SP1-X0B	No detector	UK/CE
SP1-X0C	No detector	EU/CE
SP1-A1A	Fixed Wavelength, 0.1 mm cell	US/CSA
SP1-A1B	Fixed Wavelength, 0.1 mm cell	UK/CE
SP1-A1C	Fixed Wavelength, 0.1 mm cell	EU/CE
SP1-A2A	Fixed Wavelength, 0.3 mm cell	US/CSA
SP1-A2B	Fixed Wavelength, 0.3 mm cell	UK/CE
SP1-A2C	Fixed Wavelength, 0.3 mm cell	EU/CE
SP1-B1A	Variable Wavelength, 0.1 mm cell	US/CSA
SP1-B1B	Variable Wavelength, 0.1 mm cell	UK/CE
SP1-B1C	Variable Wavelength, 0.1 mm cell	EU/CE
SP1-B2A	Variable Wavelength, 0.3 mm cell	US/CSA
SP1-B2B	Variable Wavelength, 0.3 mm cell	UK/CE
SP1-B2C	Variable Wavelength, 0.3 mm cell	EU/CE

Accessories

Item	Description	Part Number
Collection Racks		
Collection Rack	13 x 100 mm Test tube rack (120 fractions), 2/pk	HRAK-013
Collection Rack	16 x 100 mm Test tube rack (96 fractions), 2/pk	HRAK-016
Collection Rack	16 x 150 mm Test tube rack (96 fractions), 2/pk	QRAK-016
Collection Rack	17 x 130 mm Test tube rack (80 fractions), 2/pk	HRAK-017
Collection Rack	18 x 150 mm Test tube rack (48 fractions), 2/pk	QRAK-018
Collection Rack	25 x 150 mm Test tube rack (48 fractions), 2/pk	QRAK-025
Collection Rack	120 mL bottle rack (24 fractions), 1/pk	HRAK-120
Collection Rack	240 mL bottle rack (12 fractions), 1/pk	HRAK-240
Collection Rack	13 x 100 mm IsoBlock rack* (128 fractions), 4/pk	BLK-013
Collection Rack	16 x 100 mm IsoBlock rack* (128 fractions), 4/pk	BLK-016
Collection Rack	16 x 150 mm IsoBlock rack* (96 fractions), 4/pk	BLK-116
Collection Rack	18 x 150 mm IsoBlock rack* (48 fractions), 4/pk	BLK-018
Collection Rack	25 x 150 mm IsoBlock rack* (48 fractions), 4/pk	BLK-025
*IsoBlock tray	required for IsoBlock racks, 1/pk	09047
Cartridge Modules		
Compression module	FLASH 12+™S compression module, 1/pk	07857
Compression module	FLASH 12+M compression module, 1/pk	07858
Compression module	FLASH 25+™S compression module, 1/pk	FC-022-16024
Compression module	FLASH 25+M compression module, 1/pk	FC-022-16044
Compression module	FLASH 40+™S compression module, 1/pk	07975
Compression module	FLASH 40+M compression module, 1/pk	07976
Compression module	FLASH 65i™ compression module, 1/pk	07868
Compression modules	FLASHPac™ (All 12+S thru 40+M compression module components)	08615
Module Stand	FLASH 65i compression module stand (holds up to 4 compression modules)	09185
Flow path module	SP4 flow path module	09487
Leak detection kit	Contains leak collection tray and removable optical sensor	09713
3-way liquid injection valve		FLV-VLV-1000
Zif-Sim10™		FZIM-0010
Zif-Sim35™		FZIM-0035
Zif-Sim60™		FZIM-0060

Installation and Training

See page 6 in the Customer Support and Service Section for installation and training information.





Quad™ Parallel Purification Systems

Discovery-scale Parallel FLASH Chromatography

Quad™ Parallel Purification Systems

The Biotage Quad Parallel Purification Systems Were Designed by Chemists for Chemists

Quad systems address the high-throughput purification needs of medicinal chemists and are available in two configurations: the 4-channel Quad UV™ system and the 4- to 12-channel Quad3+™ system. You can customize these systems to meet your current purification requirements and upgrade them as productivity needs change.

Choose from a selection of modules and cartridge sizes, depending on the sample-load and application requirements. The Quad UV and the Quad3+ systems use the Quad FLASH Collector—which provides "no loss" fractionation. The Quad UV module has a true variable-wavelength monochromator simultaneously monitoring and recording UV absorption of up to four samples. A few simple keystrokes are all that is required to start a run.



Quad UV™ system with FLASH™ Collector, Quad UV detector, Quad 12/25™ cartridge module and Quad1™ pump

The Quad UV 4-Channel Parallel Purification System

This system simultaneously purifies up to four different reaction mixtures and collects each sample's fractions while recording the UV absorption of the compounds eluting from the FLASH+ cartridges.

Reaction mixtures from milligrams to grams can be purified by utilizing one of two cartridge modules: the Quad12/25™ or the Quad4/40™ module. The Quad 12/25 module holds up to four cartridges of either FLASH 12+™M or FLASH 25+™M. The Quad4/40+ rack holds four FLASH 40+ compression modules.

A complete 4-channel Quad UV parallel purification system includes a Quad1 pneumatic pump with four independent flow streams, a multicartridge compression module, a 4-channel variable-wavelength UV monitor, and a FLASH collector with parallel flow streams.

Quad3+ Features



The Quad3+™ includes (R. to L.) Quad3+ Pump, Quad3™ Cartridge Module and Quad FLASH Collector

The Quad3+ Parallel Purification System with up to 12 Flow Streams

The Quad3+ system performs in the same manner as the Quad UV system, except that it is available with up to 12 independent flow streams for even higher productivity.

The Quad3+ system is available in configurations of 4, 8 or 12 channels. It can be used with either a Quad3 cartridge module (takes up to 12 FLASH 12+™ cartridges) or one or two Quad4/40™ modules, which will meet growing productivity and throughput demands.

Other Options

Continuous-gradient module and an automatic step-gradient module.

Features and Benefits

- Pneumatic pump with parallel, independent flow streams delivers consistent volume, even if purified sample precipitates during purification
- Patented ZIF™ (Zero Insertion Force) head-assembly on the cartridge module pivots back for easy loading/unloading of cartridges
- Variable-wavelength UV module tunes to optimal absorption
- Multichannel UV monitoring of parallel flow streams facilitate compound location
- Milligram to multigram purifications with patented FLASH+ cartridges and Samplets
- Parallel, independent "no loss" fraction collection accommodates up to 12 samples on one fraction collector
- One-button unattended operation simplifies use

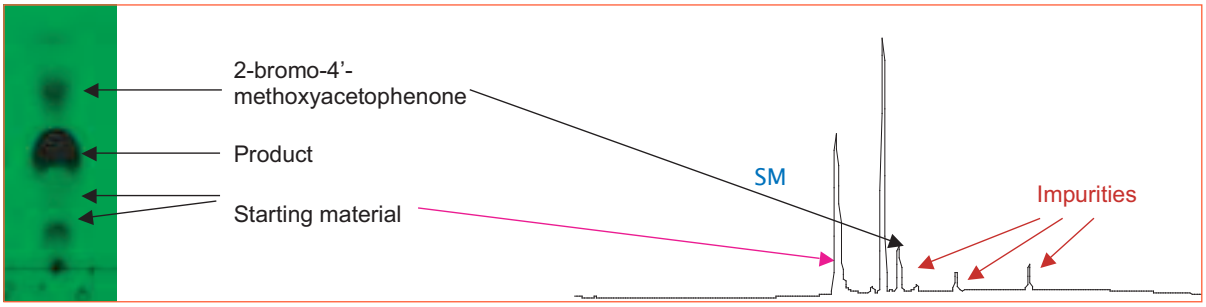


Figure 3. *TLC and RP-HPLC evaluation of the cyclic tertiary amine. The yellow color is not visible in the HPLC trace, but it is evident in the reaction mixture prior to purification.*

Comparison of different purification techniques

The alkylation reaction mixture is a yellow-colored solution that included 43% of the desired product, starting materials and some side products. The reaction mixture was then purified utilizing three separate techniques.

1. Syntage™ KP-PrSH Samplet cartridge (SPE) alone; Figure 4A.
2. Flash chromatography alone; Figure 4B.
3. Syntage™ KP-PrSH Samplet cartridge + Flash chromatography; Figure 4C.

Figure 4A indicates the SPE cartridge scavenged the excess alkyl halide starting material with an overall increase in purity to 62%, but the remainder of the impurities including the yellow color eluted along with the product as verified by HPLC.

Flash chromatography alone was also used to purify the same reaction mixture but since the alkyl halide starting material eluted close to product, the yield was sacrificed to achieve the desired purity level (Figure 4b).

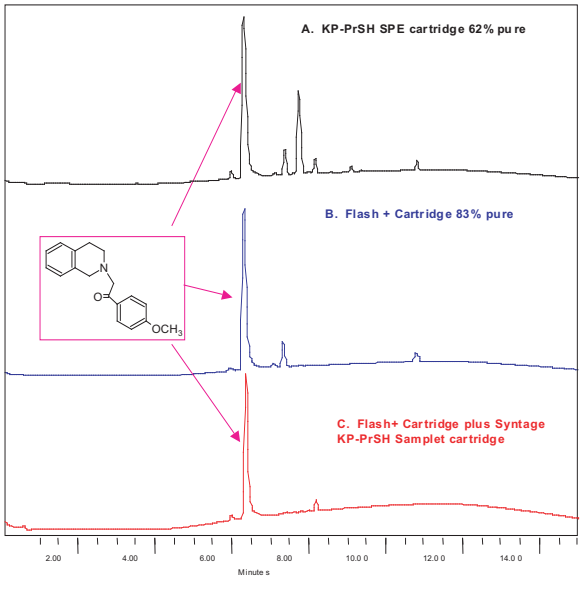


Figure 4. *Comparison of purified product by three different purification techniques. Combination of Syntage KP-PrSH cartridge and Flash+ cartridge provided the highest yield with the highest purity.*

Finally, by combining a Syntage KP-PrSH Samplet cartridge with the FLASH+ cartridge, the highest purity (99%) and the final product yield (93%) was achieved; Figure 4C. This higher purity was achieved without sacrificing yield, which is very important since the alkylation product is the starting material for additional reactions. Figure 5 shows the purification chromatogram generated by purifying the reaction mixture with and without combining it with the Syntage KP-PrSH Samplet cartridge. Flash chromatography alone provided a higher purity product (83%) compared with the SPE cartridge. The purity and yield comparison for the three different purification techniques are summarized in Table 1.

QUAD™ SPECIFICATIONS

Quad UV™ Pump and Cartridge Module Specifications

Quad1 Pump	Dimensions:	16 x 23 x 31 cm (W x D x H)
	Flow Range:	60 mL/min
	Pressure Limit:	60 psig
	Power Requirements:	30 psig compressed air or other inert gas
	Delivery Volume/Stroke:	3 mL
Quad12/25™ Cartridge Module	Dimensions:	18 x 23 x 48 cm (W x D x H)
	Flow Range:	60 mL/min
	Pressure Limit:	60 psig
	Power Requirements:	30 psig compressed air or other inert gas
	Number of Parallel Channels:	4
	Cartridge Capacity:	Up to 4 FLASH 12+™M or 25+™M with or without Samplets™
	Sample-load Range:	8 mg-1.5 g
Quad4/40+™ Rack	Dimensions:	36 x 16 x 28 cm (W x D x H)
	Number of Parallel Channels:	4
	Cartridge Capacity:	Up to 4 FLASH 40+M or S



Quad Specifications

Quad3+™ Pump and Cartridge Module Specifications

Quad3+ Pump	Flow Range:	60 mL/min
	Pressure Limit:	60 psig
	Power Requirements:	30 psig compressed air or other inert gas
	Delivery Volume/Stroke:	3 mL
Quad3™ Cartridge Module	Dimensions:	18 x 23 x 48 cm (W x D x H)
	Flow Range:	60 mL/min
	Pressure Limit:	60 psig
	Power Requirements:	30 psig compressed air or other inert gas
	Parallel Channels:	12
	Cartridge Capacity:	Up to 12 FLASH 12+™M with or without Samplets
Quad4/40+ Rack	Dimensions:	36 x 16 x 28 cm (W x D x H)
	Parallel Channels:	4
	Cartridge Capacity:	Up to 4 FLASH 40+M or S

Quad UV™Module and Quad Flash Collector Components Specifications

Quad UV Module	Dimensions:	32 x 54 x 33 cm (W x D x H)
	UV Flow-Cell Path Length:	0.1 mm (0.3 mm optional)
	Maximum Cell Pressure:	150 psig
	Power Requirements:	115-V AC, 60 Hz or 220-V AC, 50 Hz
	UV Source:	Deuterium Lamp
	UV Wavelength Range:	210-320 mm
	UV Output Voltage:	1 AU full scale
Quad FLASH Collector	Dimensions:	48 x 46 x 33 cm (W x D x H)
	Power Requirements:	115-V AC, 60 Hz or 220-V AC, 50 Hz
Quad4/40+™ Rack	Dimensions:	36 x 16 x 28 cm (WxDxH)
	Number of Parallel Channels:	4
	Cartridge Capacity:	Up to 4 FLASH 40+M or S

Quad™ Ordering Information

Component 1	Component 2	Component 3	Component 4	Component 5	Options
Q3P-Basic Quad System	For the Quad3+™ System				
	1 Quad3+ Pump Module 4-Channel	**A** Quad3™ Cartridge Module 4-Channel, 12 mm Cartridges	**0** No Collector	**A** 13-mm Test-Tube Rack 6 x 20 Fractions, 2/pk	**A** 13-mm Test-Tube Rack 6 x 20 Fractions, 2/pk
		B Quad3 Cartridge Module 8-Channel, 12 mm Cartridges		**B** 13-mm Test-Tube Rack 4 x 20 Fractions, 2/pk	**B** 13-mm Test-Tube Rack 4 x 20 Fractions, 2/pk
	2 Quad3+ Pump Module 8-Channel	**C** Quad3 Cartridge Module 12-Channel, 12 mm Cartridges		**C** 16-mm Test-Tube Rack 6 x 16 Fractions, 2/pk	**C** 16-mm Test-Tube Rack 6 x 16 Fractions, 2/pk
					D 16-mm Test-Tube Rack 4 x 16 Fractions, 2/pk
	3 Quad3+ Pump Module 12-Channel	**G** Quad 4/40+Rack, 4 40+M Compression Modules, 4 40+S Barrels and Quad Tubing kit for Channels A1,A2, A3, and A4	**1** Quad FLASH Collector™	**D** 16-mm Test-Tube Rack 4 x 16 Fractions, 2/pk	**E** 18-mm Test-Tube Rack 4 x 12 Fractions, 2/pk
					F 25-mm Test-Tube Rack 4 x 12 Fractions, 2/pk
	For the Quad UV System				**G** Scintillation-Vial Rack 4 x 10 Fractions, 2/pk*
	4 4-channel Quad1™ Pump Module 4-Channel (cannot be upgraded)	**D** Quad12/25 4-Channel, 12 and 25 mm Cartridges		**E** 18 mm Test-Tube Rack 4 x 12 Fractions, 2/pk	**H** 13-mm Microtiter Block 6 x 5 Fractions, 8/pk
					J Quad UV Module
		E Quad12/25 4-Channel, 12 mm Cartridges	**2** Quad FLASH Collector and Quad UV™ Module	**F** 25 mm Test-Tube Rack 4 x 12 Fractions, 2/pk	**K** Quad 4/40+rack, 4 40+M Compression Modules, 4 40+S Barrels and Quad Tubing Kit for channels B1,B2, B3, and B4
		F Quad12/25 4-Channel, 25 mm Cartridges		**G** Scintillation Vial Rack 4 x 10 Fractions, 2/pk	**L** Continuous Gradient Module
					M Step-Gradient Module Includes a 12-Port Manifold
		G Quad4/40+ Cartridge Module 4-Channel, 40 mm Cartridges, 4 ZIF-SIM35s™ and 4 Injection Valves		**H** 13-mm Microtiter Block 6 x 5 Fractions, 8/pk	**N** 4-Port Fraction-Collector Bracket for Scintillation-Vial Racks
					P 4-Port Fraction-Collector Bracket for Microtiter Blocks

Part Number: Q 3 P - _ _ _ _ - _ _ _ _ _ _ _ _

Instructions: Simply choose one component from each of the component columns and then as many options as you need. Moving from left to right, fill in the spaces below the table to create a custom part number. (example: Q3P-3C1A-A)

*requires Option N

Add-on Components and Accessories

Item	Description	Part Number
Quad 12/25™ Cartridge Modules		
Quad 12M Pack	Holds 4 FLASH 12+™M cartridges in parallel	QUD1-1200-0400
Quad 25M Pack	Holds 4 FLASH 25+™M cartridges	QUD1-0025-0004
Quad 12M/25M Pack	Holds 4 FLASH 12+M or 25+M cartridges	QUD1-1225-0404
Quad3™ Cartridge Modules		
Quad3 4 Pack	Holds 4 FLASH 12+M cartridges	QUAD-0004-1000
Quad3 8 Pack	Holds 8 FLASH 12+M cartridges	QUAD-0008-1000
Quad3 12 Pack	Holds 12 FLASH 12+M cartridges	QUAD-0012-1000
Quad3 Upgrade	Adds 4-cartridge capacity to existing 4- or 8-pack module	QUAD-0004-0000
Quad Pump Modules		
Quad1	Pneumatic, parallel 4-channel pump (no upgrades)	QUD1-0400-1000
Quad3 4 Pack	Pneumatic, parallel 4-channel Quad3+ pump	07675
Quad3 8 Pack	Pneumatic, parallel 8-channel Quad3+ pump	07677
Quad3 12 Pack	Pneumatic, parallel 12-channel Quad3+ pump	07346
Quad3 Upgrade	Adds 4 pump heads to existing 4- or 8-channel pump	QUAD-0400-0000B
Quad FLASH Collector™		
Quad FLASH Collector	Fraction Collector	QUD1-FRAC-2000
Fraction Tray	Holds 2 test tube racks, 4 trays/pk	TRAY-04
13-mm Test-tube Rack	6 x 20 position rack for 13 x 100 mm test-tubes, 2/pk	QRAK-013
13-mm Test-tube Rack	4 x 20 position rack for 13 x 100 mm test-tubes, 2/pk	QRUV-013
16-mm Test-tube Rack	6 x 16 position rack for 16 x 150 mm test-tubes, 2/pk	QRAK-016
16-mm Test-tube Rack	4 x 16 position rack for 16 x 150 mm test-tubes, 2/pk	QRUV-016
18-mm Test-tube Rack	4 x 12 position rack for 18 x 150 mm test-tubes, 2/pk	QRAK-018
25-mm Test-tube Rack	4 x 12 position rack for 25 x 150 mm test-tubes, 2/pk	QRAK-025
Scintillation-vial Rack	4 x 10 position rack for 20-mL scintillation vials, 2/pk	QSNT-028
13-mm Microtiter Block	6 x 5 position block for 13-mm test tubes, 8/pk	QRAK-M13
Quad UV™ Monitor		
Quad UV Monitor	4-channel UV monitor (variable wavelength, 210-320 nm)	09387
0.3-mm Path Flow Cell	Optional flow cell provides increased sensitivity 10-32 thread	07529
Quad4/40+ Rack		
Quad4/40+ Rack	Holds 4, 40+ compression modules	08238
Quad4/40+ Kit (A)	Includes a Quad 4/40+ rack, 4 40+M compression modules, 4 40+S barrels, and Quad tubing kit for channels A1, A2, A3, and A4	QPFP-440-2000A
Quad4/40+ Kit (B)	Includes a Quad 4/40+rack, 4 40+M compression modules, 4 40+S barrels, and Quad tubing kit for channels B1, B2, B3, and B4	QPFP-440-2000B
Quad Gradient Modules		
Continuous-Gradient Module	Single binary-gradient module	QCGM-1000
Step-Gradient Module	6-step automatic gradient system (requires manifold)	QSGM-1000
12-Port Manifold	Required for use with Step-Gradient Module	QMAN-1000

Installation and Training

See page 6 in the Customer Support and Service Section for installation and training information.


75
FLASH
Biotage



Development-scale FLASH™ Chromatography Systems

For the Purification of Multigram Quantities of Synthetic Compounds

FLASH 75i

Flash 75i for Reliable Scale-up Purification

Everything You Need to Begin

FLASH 75i packages include all the components necessary to begin your purification: a FLASH 75i radial-compression module, a fully integrated air manifold, a solvent reservoir, a sample-injection module, a start-up kit with all necessary tubing, a grounding kit and a user's manual.

FLASH 75i Uses Patented Radial Compression

Biotage's patented radial compression technology reduces the chance of void and channel formation, resulting in a higher bed-density. Compounds can then be collected in narrower bands for higher purity and yield.

High Flow-Rate Operation

The FLASH 75™ cartridges, available in sizes containing 200, 400 and 800 grams of media, are built to withstand operating pressures up to 100 psig.

Routinely operating at a flow rate of 250 mL/min, the FLASH 75i systems and FLASH 75 cartridges allow you to scale-up and quickly complete runs, saving hours, even days, of purification time.

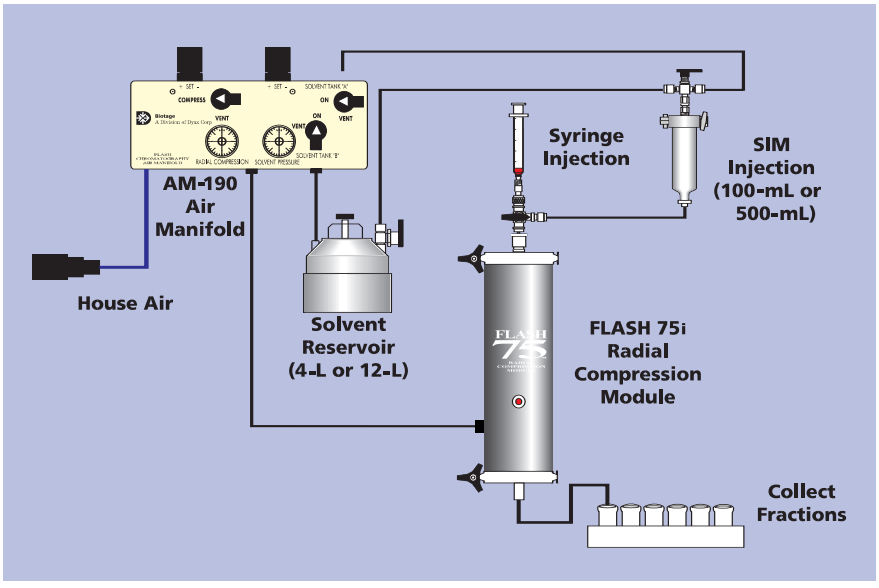


Figure 1. *Purify up to 40 grams of synthetic compound on our FLASH 75i system.*

FLASH 75 Specifications

Cartridge	Dimensions (mm ID x cm L)	Sample Size (g)	Flow RatE (mL/min)	SIM* Volume (mL)	Reservoir Volume (L)
FLASH 75™S	75 x 9	0.2 – 10	250	100	4
FLASH 75™M	75 x 15	0.4 – 20	250	500	12
FLASH 75™L	75 x 30	0.8 – 40	250	500	12

*SIM, sample-injection module for low-solubility samples or viscous oils.

Flash™ 75 Media Variety



FLASH 75S, 75M, and 75L compression modules. (See Table 1 for sample sizes.)

Safer than Glass Columns

FLASH 75™ cartridges are constructed of rugged, medium-density polyethylene and resist cracking and splitting. There is no breakable glass and all of the silica is completely self-contained, eliminating any exposure to silica dust or contaminants.

Cartridges are Available with a Variety of Media

- KP-Sil™ 40-63 µm, 60 Å, silica
- KP-C18-HS™ 40-63 µm, 90 Å, C18-bonded silica
- Mitsubishi Diaion™ HP20 and HP20SS SDVB resins
- KP-Alumina™ 40 µm, 60 Å, neutral alumina

Cartridge	Diameter (mm)	Bed Length (cm)	Packing Wt. (g) (nom)	Column Vol. (mL)	Easy ΔCV = 6	Typical ΔCV = 2	Difficult ΔCV = 1
FLASH 75S	75	9	200	320	5 - 10	1 - 5	0.2 - 1
FLASH 75M	75	15	400	535	10 - 20	2 - 10	0.4 - 2
FLASH 75L	75	30	800	1,070	20 - 40	4 - 20	0.8 - 4
							Sample Range (g)

Table 1. *Biotage FLASH 75 suggested sample sizes, based on TLC evaluation*

Faster than Glass Separations

In this comparison between a FLASH 75L prepacked cartridge and a glass column, fractions were collected in 2.5 hours using an 11- x 20-cm glass column, while a FLASH 75L 75-mm x 30-cm cartridge required just 40 minutes to complete the separation. There were fewer mixed fractions and a greater yield of pure product from the FLASH 75L.

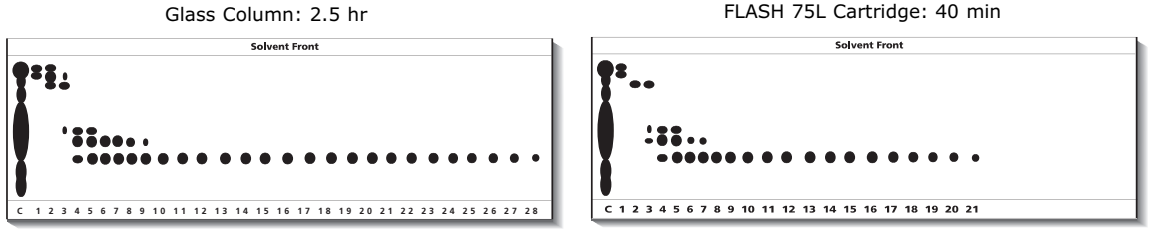


Figure 2. *Glass Column vs. FLASH 75L Cartridge.*

FLASH UV
Detector/Recorder

The Biotage FLASH UV detector/recorder module simplifies manual flash purification and improves collected compound purity and yield. The UV detector monitors, displays and records the separation in real time. Instead of collecting by volume, you can manually collect fractions using the displayed UV response as your signal to start collecting a new fraction.

The UV module comes standard with a 0.1 mm path length flow cell and monitors absorbance at 254 nm. The absorbance is displayed, recorded and saved electronically and can be downloaded to a PC for archival purposes.

This free-standing detector/recorder module can be used with any flash purification system, including Biotage FLASH 75i systems, using the provided 1/8" tubing kit. Simply attach the cartridge outlet to the flow cell inlet and connect the other tube between the flow cell outlet and the collection vessel, no tools are required for installation.



Biotage FLASH UV detector/recorder module.

Specifications

Utilities:	110 – 120 VAC, 60 Hz (US), CSA certified
	220 – 240 VAC, 50 Hz, CE certified
Fuses:	0.5 A/250 V (main 230V input power)
	0.1 A/250 V (main 100/115 V input power)
Agency certification:	CE and CSA
UV lamp:	Mercury, 254 nm
Path length:	0.1 mm (standard)
	0.3 mm (optional)
Cell pressure rating:	300 psig (20 bars)
Recorder RAM:	1MB
Size:	10" (25 cm) W x 19" (48 cm) D x 7" (18 cm) H

FLASH™ 75 Ordering Information

Item	Description	Part Number
FLASH 75 Systems		
FLASH 75S System	75S compression module, air manifold, SIM100™ 4-L solvent reservoir, tubing, grounding kit and manual	SF-022-19161
FLASH 75M System	75M compression module, air manifold, SIM500™, 12-L solvent reservoir, tubing, grounding kit and manual	SF-022-19041
FLASH 75L System	75L compression module, air manifold, SIM 500, 12-L solvent reservoir, tubing, grounding kit and manual	SF-022-19071
FLASH 75L Plus System	75L Plus compression module, interchangeable 75S barrel, air manifold, SIM 500 (including 25 frits), 12-L solvent reservoir, 10 FLASH 75L cartridges (800 g, KP-Sil™), 10 FLASH 75S cartridges (200 g, KP-Sil), tubing, grounding kit and manual	SF-222-19071
UV Detector/Recorder	Free-standing FLASH UV Detector/Recorder Module with 0.1 mm path length flow cell and start-up kit	09043

Ordering Information

Item	Description	Part Number
FLASH 75 Compression Modules		
FLASH 75S Compression Module	Powder-coated aluminum barrel with stainless-steel endcaps, V-band clamps, pressure indicator, an ASME-rated safety-relief valve and mounting bars	FC-022-19161
FLASH 75M Compression Module	Powder-coated aluminum barrel with stainless-steel endcaps, V-band clamps, pressure indicator, an ASME-rated safety-relief valve and mounting bars	FC-022-19041
FLASH 75L Compression Module	Powder-coated aluminum barrel with stainless-steel endcaps, V-band clamps, pressure indicator, an ASME-rated safety-relief valve and mounting bars	FC-022-19071
FLASH 75 Accessories		
FLASH 75S Barrel	Powder-coated aluminum barrel with pressure-relief valve and mounting bars; accepts FLASH 75S cartridges	FB-012-19160
FLASH 75M Barrel	Powder-coated aluminum barrel with pressure-relief valve and mounting bars; accepts FLASH 75M cartridges	FB-012-19040
FLASH 75L Barrel	Powder-coated aluminum barrel with pressure-relief valve and mounting bars; accepts FLASH 75L cartridges	FB-012-19070
SIM 100™ Sample Injection Module	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 100 mL	SIM-0102
SIM 500™ Sample Injection Module	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 500 mL	SIM-0502
SIM Top Frits	25 x 1.5” frits for the SIM 100 module	FTF-0125
SIM Top Frits	25 x 3” frits for the SIM 500 module	FTF-0225
SIM Bottom Frit Holder	25 stainless-steel frits and sealing rings; replaces old-style SIM bottom frits	FSS-0075
SIM Bottom Frits	25 frits and sealing rings for SIM 100 or 500; used with frit holder #FSS-0075	FBS-1025
Grounding Kit	Grounding kit includes Teflon®-coated wires and clips to dissipate static charges	FGD-15075
3-way Injection Valve	3-way vertical injection valve for direct liquid injections complete with Luer-Lok injection port	FIV-075-0000
4-L Solvent Reservoir	4 L stainless-steel solvent reservoir, ASME rated, complete with solvent shut-off and relief valves	FN-004-41201
12-L Solvent Reservoir	12 L stainless-steel solvent reservoir, ASME rated, complete with solvent shut-off and relief valves	FN-012-41201
Air Manifold	Air manifold; safely regulates the flow of air pressure and solvent(s) to FLASH 75 systems	AM-190
SIM 100 Start-up Kit	100 mL SIM, a cartridge extraction tool, tubing, user’s manual and grounding kit	SU-275-0100
SIM 500 Start-up Kit	500 mL SIM, a cartridge extraction tool, tubing, user’s manual and grounding kit	SU-275-0500
FLASH 75 Start-up Kit	Cartridge extraction tool, tubing, user’s manual and grounding kit	SU-075-2000

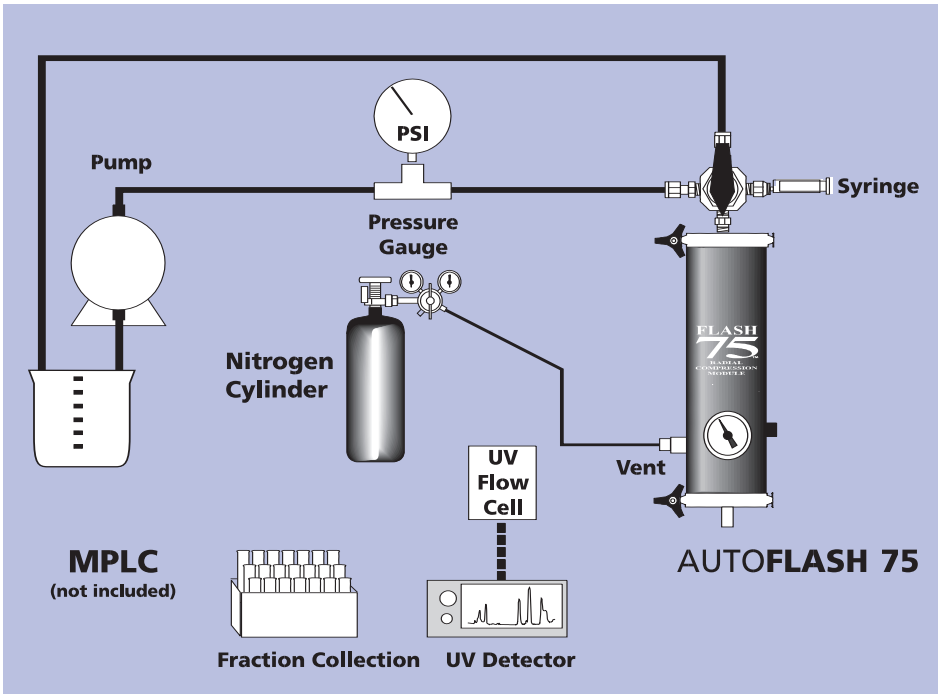


Figure 3. *The Biotage AUTOFLASH 75 kit is designed for use with medium pressure liquid chromatography (MPLC) systems.*

Medium-Pressure Liquid Chromatography with AUTOFLASH 75 Compression Modules

AUTOFLASH 75 compression modules are designed to provide FLASH 75™ capacity and performance for your medium-pressure liquid chromatography (MPLC) system. AUTOFLASH 75 compression modules come with a pressure gauge, one start-up kit with all the tubing and fittings required to connect to an MPLC system, and a four-way valve with Luer-Lok adapter for direct sample injection.

AUTOFLASH 75 compression modules use Biotage's standard FLASH 75 (75 mm ID) prepacked cartridges (see page 141).

AUTOFLASH 75 systems can utilize our patented sample-injection modules, the SIM 100™ and SIM 500.™



Autoflash 75 Ordering Information

Add-on Components and Accessories

Item	Description	Part Number
AUTOFLASH 75 Compression Modules		
AUTOFLASH 75S	75S compression module, pressure gauge, 4-way injection valve, tubing, start-up kit and manual	AF-005-19160
AUTOFLASH 75M	75M compression module, pressure gauge, 4-way injection valve, tubing, start-up kit and manual	AF-005-19040
AUTOFLASH 75L	75L compression module, pressure gauge, 4-way injection valve, tubing, start-up kit and manual.	AF-005-19070
AUTOFLASH 75™ Accessories		
AUTOFLASH 75S Barrel	Powder-coated aluminum barrel with pressure gauge and mounting bars uses FLASH 75S cartridges	03711
AUTOFLASH 75M Barrel	Powder-coated aluminum barrel with pressure gauge and mounting bars uses FLASH 75M cartridges	03710
AUTOFLASH 75L Barrel	Powder-coated aluminum barrel with pressure gauge and mounting bars uses FLASH 75L cartridges	03706
AUTOFLASH SIM 100™	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 100 mL; for use with AUTOFLASH systems	SIM-5102
AUTOFLASH SIM 500™	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 500 mL. For use with AUTOFLASH systems	SIM-5502
AUTOFLASH MPLC Start-Up Kit	Contains all required tubing, nuts and ferrules to connect an AUTOFLASH system to a MPLC pump	AFSU-1000

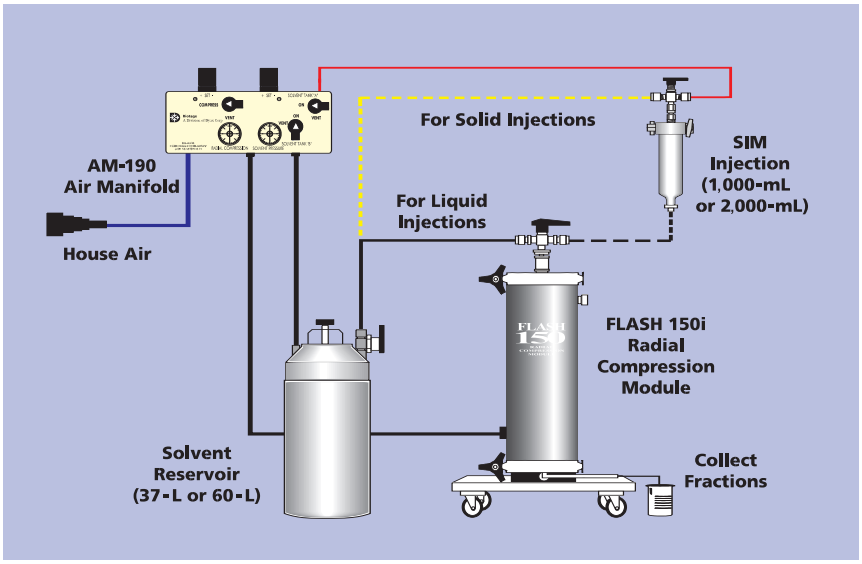


Figure 4. *Purify kilogram-per-day quantities of promising drug candidates with the Biotage 150i system and our 150-mm ID, prepacked FLASH 150 cartridges.*

Save Weeks of Separation Time

The power and performance of the FLASH 150i system is clear in this application, which saved a customer nearly four weeks of time on a 1-kilogram project.

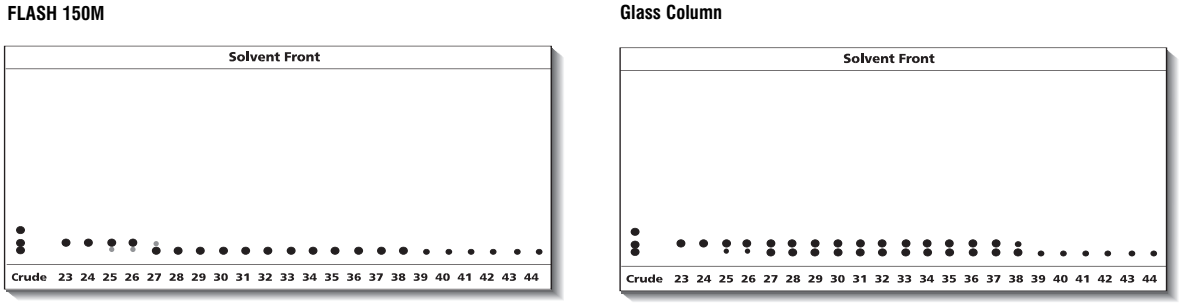


Figure 5. *FLASH 150M vs. glass column.*

	FLASH 150M	Glass Column
Column size	150 mm x 30 cm (2.5 kg)	120 mm x 66 cm (3 kg)
Sample load	180 g	450 g
Flow rate	500 mL/min	70 mL/min
No. of fractions	45	30
Purification time	90 min	430 min
Pure compound	70.5 g/run	45 g/run
Percent recovery Purification	87%	22.2%
Throughput	120 g/hr	63 g/hr

Table 2. *FLASH 150 vs. Traditional Glass Column*

FLASH 150i™ Packages

FLASH 150i packages include a radial compression module, a fully integrated air manifold, a solvent reservoir, a sample-injection module, start-up kit with all necessary tubing, a grounding kit and a user's manual. Please order your FLASH 150M (Medium) or FLASH 150L (Long) prepacked cartridges separately.

Flash 150 compression modules are mounted onto stable and robust portable bases, which are fitted with casters for easy mobility.

High Flow-rate Operation

The FLASH 150 cartridges (150-mm ID) are available in two lengths: 30 cm (2.5 kg, FLASH 150M) and 60 cm (5 kg, FLASH 150L). They are built to withstand operating pressures up to 100 psig.

With flow rates as high as 1.0 L/min these systems allow you to complete runs and scale-up faster—saving hours, even days, of separation time.

Cartridges are Available with a Variety of Media

- KP-Sil™, 40-63 µm, 60 Å, silica
- KP-C18-HS™, 40-63 µm, 90 Å, C18-bonded silica
- Mitsubishi Diaion™ HP20 & HP20SS SDVB resins

(see page 95 for more information on cartridges)



FLASH 150M, and 150L compression modules and cartridges

FLASH 150

Patented Radial Compression

Biotage's patented radial compression technology eliminates voids and channels that often occur in glass columns, resulting in a highly dense packed bed. Compounds can then be collected in narrower bands for optimum separation efficiency.

Easier and Safer to Use

Each cartridge is constructed of rugged, medium-density polyethylene to resist cracking or splitting. There's no pressurized glass and all of the silica is self-contained, eliminating any exposure to contaminated silica dust.

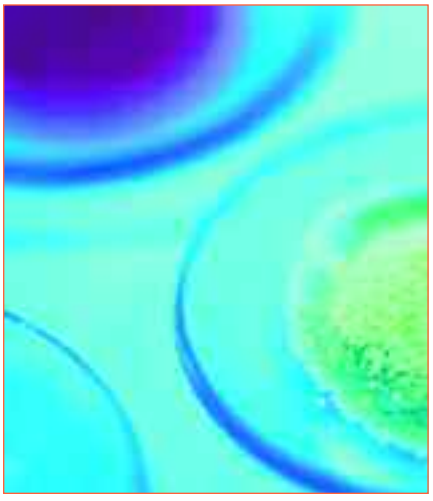
FLASH 150 Specifications

Cartridge	Dimensions (mm ID x cm L)	Sample Size (g)	Flow Rate (mL/min)	SIM* Volume (mL)	Reservoir Volume (L)
FLASH 150M™	150 x 30	3–160	500-1000	1000	37
FLASH 150L™	150 x 60	6–320	500-1000	2000	60

Cartridge (mm)	Diameter (cm)	Bed Length Wt. (kg)(nom)	Packing (L)	Column Vol. ΔCV = 6	Easy ΔCV = 2	Typical ΔCV = 1	Difficult
FLASH 150M	150	30	2.5	4.3	80-160	16-80	3-16
FLASH 150L	150	60	5	8.6	160-320	32-160	6-32

Table 3. *Biotage FLASH 150 Sample Sizes, Based on TLC Evaluation*

* *ΔCV = the difference in column volumes at which two compounds elute, calculated from the thin-layer chromatography R_f values as $1/Rf_1 - 1/Rf_2$.*



Add-on Components and Accessories

Item	Description	Part Number
FLASH 150i Systems		
FLASH 150M System	150M compression module, air manifold, SIM1000,™ 37-L solvent reservoir, tubing and manual	SF-022-25071
FLASH 150L System	150L compression module, air manifold, SIM2000,™ 60-L solvent reservoir, tubing and manual	SF-022-25151
FLASH 150M Compression Module	150M powder-coated aluminum barrel with stainless-steel endcaps, fitted on a portable base; V-band clamps; ASME-rated relief valve	FC- 022-25071
FLASH 150L Compression Module	150L powder-coated aluminum barrel with stainless-steel endcaps, fitted on a portable base; V-band clamps; ASME-rated relief valve	FC-022-25151
FLASH 150 Accessories		
FLASH 150M Barrel	Powder-coated aluminum barrel with pressure-relief valve uses FLASH 150M cartridges	FB-012-25070
FLASH 150L Barrel	Powder-coated aluminum barrel with pressure-relief valve uses FLASH 150L cartridges	FB-012-25150
SIM 1000 Sample Injection Module	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 1000 mL	SIM-1002
SIM 2000 Sample Injection Module	Stainless-steel sample-injection module, ideal for loading low-solubility samples or liquid volumes up to 2000 mL	SIM-2002
SIM Top Frits	25” x 3" frits for either the SIM1000 or SIM2000	FTF-0225
SIM Bottom Frits	25 frits and sealing rings for SIM1000 and SIM2000	FBS-1025
Grounding Kit	Grounding kit includes Teflon®-coated wires and clips to dissipate static charges.	FGD-15075
3-way Injection Valve	3-way 1/4" injection valve for direct liquid injections complete with Luer-Lok injection port	FIV-150-0000
37-L Solvent Reservoir	37-L stainless-steel solvent reservoir; ASME rated; with solvent shut-off and relief valves	FN-037-41200
60-L Solvent Reservoir	60-L stainless-steel solvent reservoir; ASME rated; with solvent shut-off and relief valves	FN-060-41200
Air Manifold	Air manifold; safely regulates the flow of air pressure and solvent(s) to FLASH 150 systems	AM-190
SIM 1000 Start-up Kit	1000-mL SIM, cartridge extraction tool, and all required tubing, user’s manual and grounding kit	SU-150-1022
SIM 2000 Start-up Kit	2000-mL SIM, cartridge extraction tool, and all required tubing, user’s manual and grounding kit	SU-150-2022
FLASH 150 Start-up Kit	Cartridge extraction tool, all required tubing, user’s manual and grounding kit	SU-150-0002





Parallex Flex™ HPLC Systems

Scalable Purification Tool for Medicinal Chemistry

Parallex Flex™

The Flex V3™ purification system is designed to meet the needs of discovery chemistry from lead discovery through lead optimization with simple software, maximum versatility and proven reliability.

Simple Software

The operating software for Flex V3 presents an intuitive graphical user-interface. This allows a chemist to load and run a sample with only four clicks of the mouse. An email notification containing a full report with chromatogram and location of the target fractions is sent upon run completion.

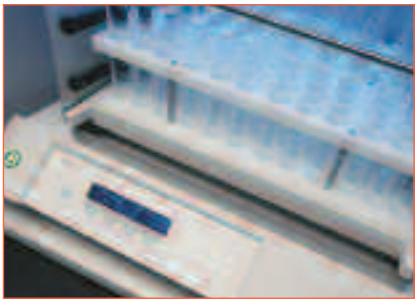
Maximum Versatility

A versatile purification tool, the Flex V3 is the only preparative HPLC system available with one to four parallel flow-streams. It is also field upgradable as throughput needs increase. A chemist can walk up with one or more vials and begin running the samples without disrupting another chemist's sequence. In addition, a core facility can load 300 samples at 5:00 p.m. and return at 8:00 a.m. with assurance of completion. The Flex V3 system can process from 1 mg to 400 mg per injection. The automated loader can handle plates, vials and tubes without reconfiguration.

Proven Reliability

The Flex V3 system constantly monitors solvent levels and fraction collection tubes, and is capable of full recovery after a power loss without losing any samples. A robust, intelligent UV-guided fraction collection system can be tailored to minimize the number of fractions or to maximize yield. Intelligent algorithms (patent pending) ensure fractionation of unresolved components, thereby yielding higher purity fractions. The Flex V3 system fully interfaces with the Water's ZQ® for on-line mass characterization.





Flex V3™ Operating Software

Simple Software

The Flex V3™ system is designed for "walk-up, walk-away" operation. The simple user-interface enables a chemist to load and run a sample in four easy steps from a single software screen; Figure 1. Simple, yet robust, this system software is suited for a multiuser environment where chemistry is the focus.

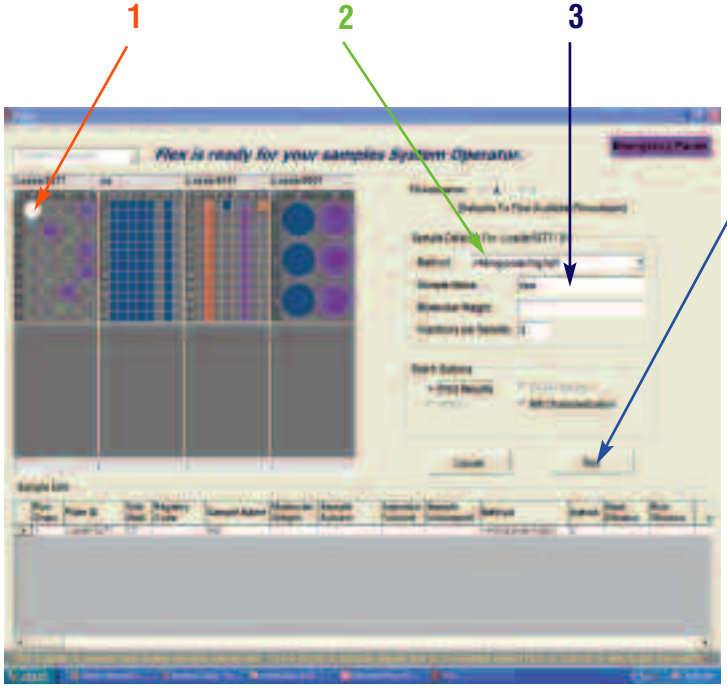


Figure 1. *Load a sample in four easy steps.*

Step 1- Click on the well

Step 2- Choose your method

Step 3- Name your sample

Step 4- Click on the run button



Figure 2. *Single-screen user-interface representing the sample injector (top left), fraction collectors (top right), and selectable sample status table (bottom) where interrupted samples can be rerun. System status is immediately visualized by intuitive color coding: samples darken on completion and fraction vessels become black as they are filled, giving an instant view of available collection capacity.*

Reliable Unattended Operation

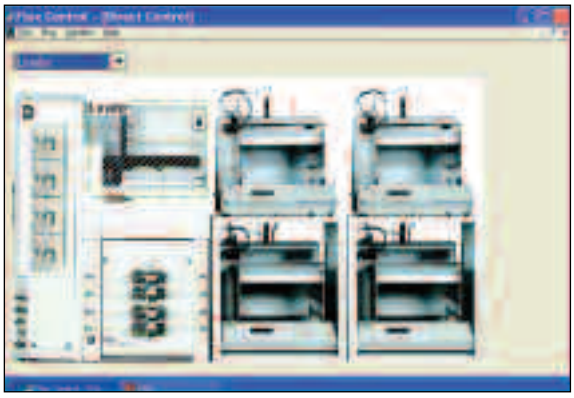
A closed-loop feedback has been incorporated into the software to compensate for occasional power loss. This feature allows the system to resume operation from the point of interruption and continue purifying active samples. Or, if necessary, samples may be rerun in the future at a more convenient time.

Solvent levels and fraction vessel capacities are monitored, causing the system to pause when a preset warning level is reached, requesting additional solvent or collector tubes be added. After the solvent is replenished or new fraction collector tubes are added, the system will resume to complete the current and queued samples.

A user-friendly manual control enables simple maintenance and troubleshooting. A system replica allows users to select a pump, loader or collect control screens for diagnostic review; Figures 3a and 3b.

Figure 3. *Interactive manual control screen (a) and pump control screen (b) allow easy column maintenance and sample recovery where necessary.*

(a)



(b)



Maximum Yield and Purity

UV-triggered fractionation is simple and reliable, giving greater than 90% yields of standard compounds; Table 1. Three standard compounds with a total load of 40 mg were separated, collected, and recovered using a fractionation trigger set at 0.2 AU (220 nm).

Patented Intelligent algorithms fractionate unresolved components into separate vessels, resulting in higher purity. This is illustrated by a separation of 100 mg crude sample on a 2.1 x 2.5 cm ABZ+ C18 column using a simple gradient method where components 1 and 2 have unresolved contaminants; Figure 4a. The expanded chromatogram shows that although components are not completely resolved, they have been collected into different tubes; Figure 4b.

	Propranolol	Verapamil	Terfenadine
Average % Recovery	97.6	91.2	92.0
SD (n=3)	2.53	2.22	2.16

Table 1. *Average percent recovery for UV-triggered fractionation.*

Figure 4a.

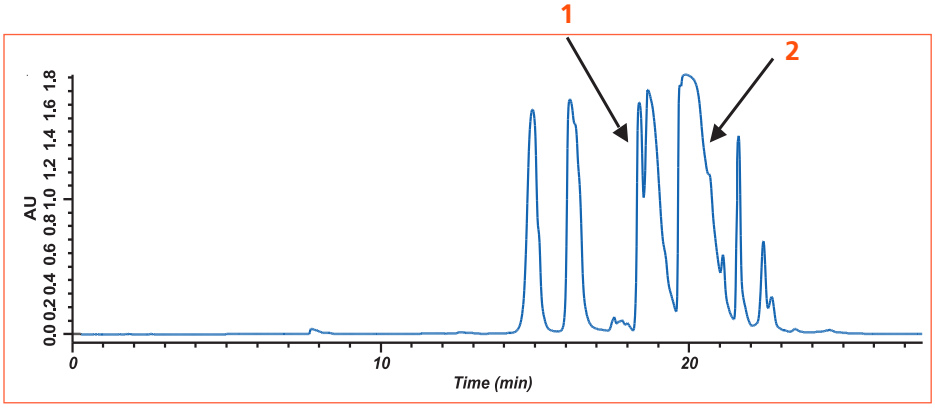
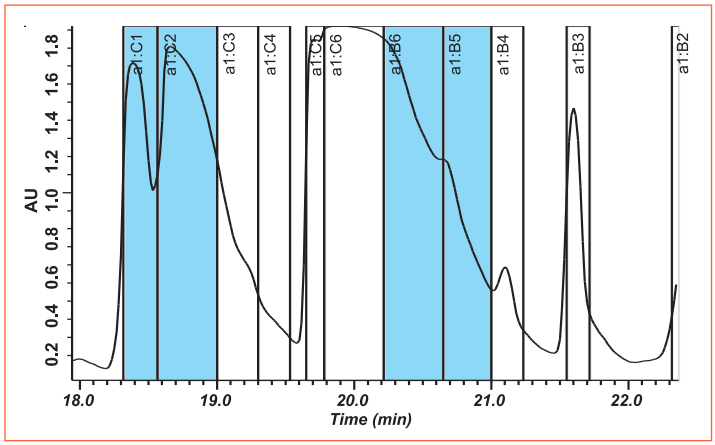


Figure 4b.



Difficult Separations

Three compounds were barely separated by analytical HPLC; Figure 5. The same three compounds were recovered with good yield and high purity using the Flex HPLC system. 26 mg of crude compound was separated with a 2.1 cm x 25 cm column. The method chosen was based on polarity and UV absorbance; Figures 6a and 6b.

Data courtesy of GSK, Harlow, UK

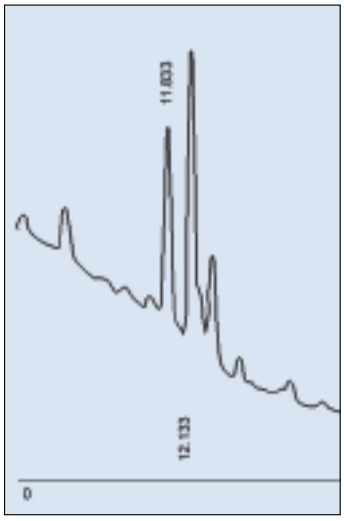


Figure 5.

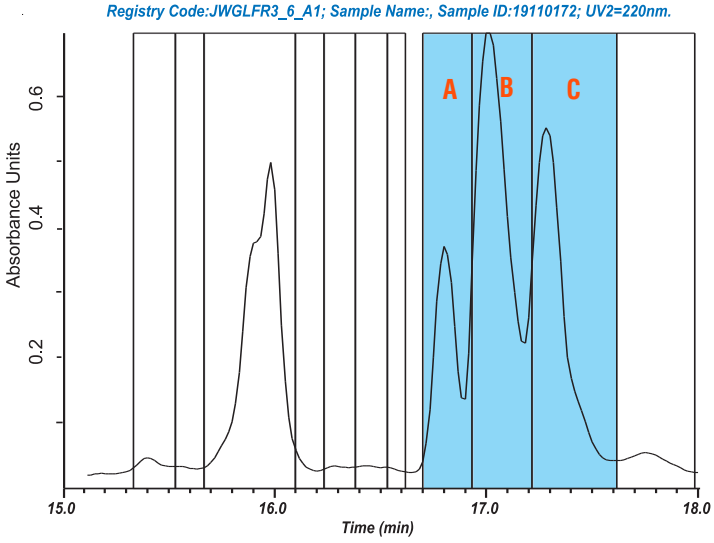


Figure 6a.



Figure 6b.

Robust Loading

Samples may be injected from individual vials or deep well plates. To minimize the risk of precipitation in the injection loop, the sample is surrounded by an air gap and a "sandwich" solvent. This prevents contact with the aqueous conditions at the start of the gradient; Figure 7. The Biotage Flex V3™ loop-loading feature facilitates the successful injection of several hundred milligrams. A 100 mg injection of synthetic sample is shown below; Figure 8. Fractionation was minimized by triggering fractionation at 0.5 AU on 254 nm. Despite poor peak shape, 77% of the target compound was recovered with a purity greater than 97%. The number of fractions can be further minimized and concentration increased by using a 0.1 mm path length flow cell.

A needle and loop wash reduces carry over to less than 0.2% even at 100 mg loads (based on studies with methyl blue, which represents a worst case).

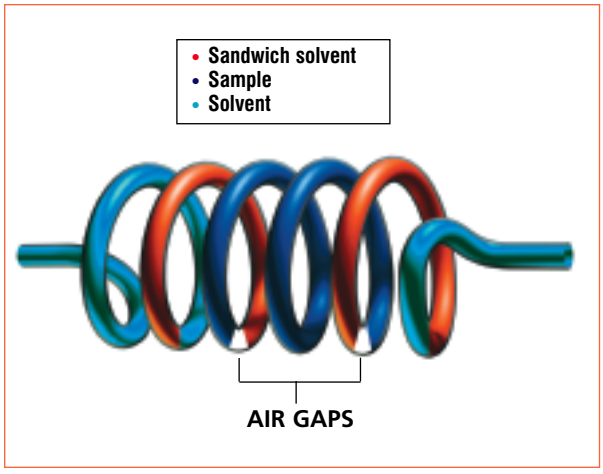


Figure 7. *Typical sample loading where the sample is separated from the solvent representing initial gradient conditions by air and a "sandwich" solvent such as DMSO, DMSO: methanol (1:1), or acetonitrile:water (1:1).*

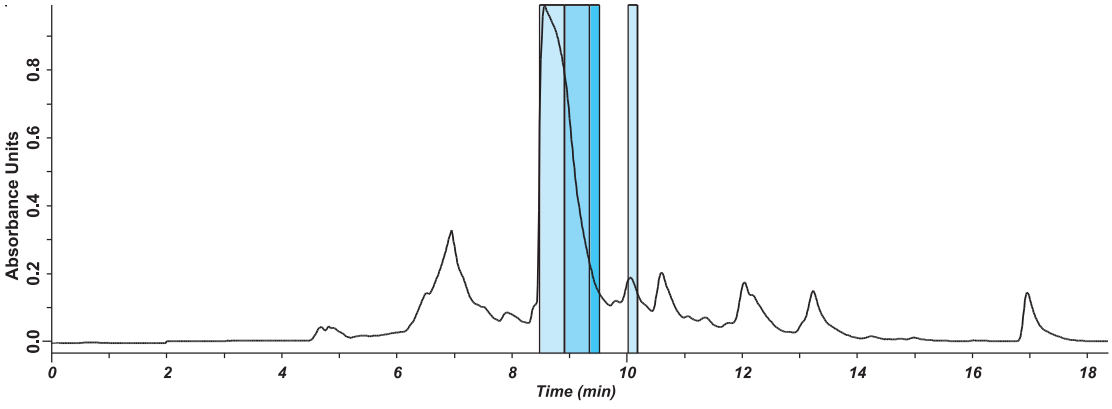


Figure 8. *100 mg/mL injection of synthetic compound separated on a 2 cm I.D. x 25 cm long C18 column. Despite poor peak shapes, a method selection containing specific fractionation decisions resulted in only four fractions being collected with three of the fractions being the target compound for a total of 20.75 mL.*

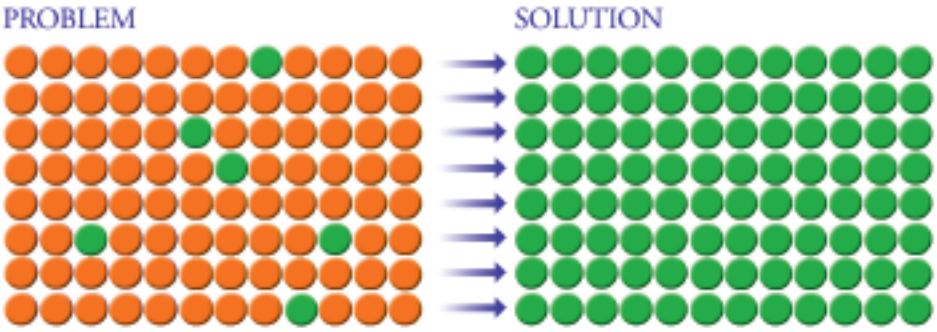


Figure 9. *Automated parallel synthesis is enabling production of arrays of single compounds to meet the demands of high throughput screening (HTS) programs. In order to obtain the most reliable data, the compounds must be purified, characterized and quantified. Flex V3 is a pivotal purification system, facilitating complete integration into a high-throughput chemistry environment providing high-quality compounds.*

High-throughput Application

The Flex V3 is a proven instrument for the purification of large numbers of compounds. Parallel flow streams allow the simultaneous purification of combinatorial arrays in a more efficient and cost-effective way than using multiple single systems. A four-channel system can purify up to 40 samples in one hour.

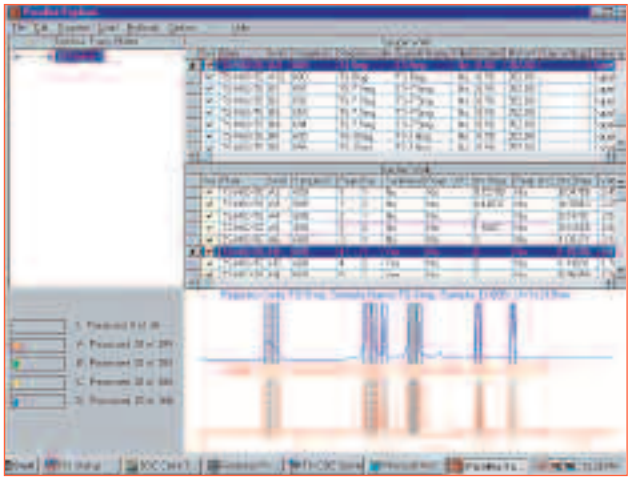
Purification, however, is only one component of the high throughput chemistry process. The Flex V3 system is designed to provide an integrated solution to the high throughput process. Data and material can be transferred easily between synthesis, characterization and quantitation systems. Its operating system is based on a Microsoft platform, enabling data transfer in the form of Excel, CSV and Access files. Fraction information can be exported from the Flex to LC-MS or MS systems and the data, confirmation of molecular weight, purity and quantity are then reimported to the Flex database. The software's superior sample-tracking features simplify data retrieval and management.

Upon completion of purification and fraction analysis, Flex Pilot™ software can be used to select target fractions and, if necessary, combine and reformat the samples to the original plate format. Fractions are selected using a simple wizard and transferred automatically using a Gilson® 215 liquid handler.

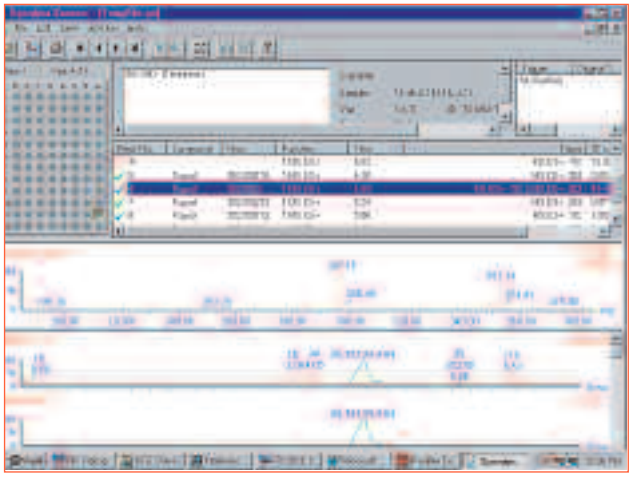


Online Characterization

The high throughput purification process can be further refined by interfacing the Flex V3™ system to a Waters® ZQ™ mass spectrometer using MUX™ technology. This interface combines robust UV-triggered collection with essential mass spectral data to enable rapid identification of target compounds; Figure 10. A single computer is used for loading samples, selecting LC and MS methods and final data review.



(a)



(b)

Figure 10. *(a) The Flex V3 database is updated with fractions containing the target mass and are confirmed "Yes." (b) The mass spectral data for each sample can be reviewed in OpenLynx browser by right-clicking on the sample information.*





FLASH-AC™

Activated-Carbon Prepacked Cartridges

For Research, Development and Production-scale Purifications

FLASH-AC Activated-Carbon Cartridges

- High-performance, easy-to-use cartridges for the purification of pharmaceuticals and fine chemicals
- Available in 12-mm, 75-mm, 150-mm and 400-mm cartridge diameters
- Provide a clean, efficient and convenient process for carbon-adsorption in a cGMP (current Good Manufacturing Practices) environment
- Engineered for optimum adsorption kinetics and fluid hydraulics for simple and effective purifications
- Custom-packing services of specific carbon media available, please inquire.

Biotage FLASH-AC cartridges are well suited for the pretreatment of compounds that will be crystallized for final purification. Pretreatment with FLASH-AC can effectively remove contaminants that cocrystallize with the product. FLASH-AC cartridges are recommended for the following applications:

- Removal of reaction byproducts, color, and other contaminants
- Removal of catalysts
- Removal of lipopolysaccharide (LPS) pyrogens
- Clean-up of degraded reagents
- Predictable scale-up from research through production

How It Works

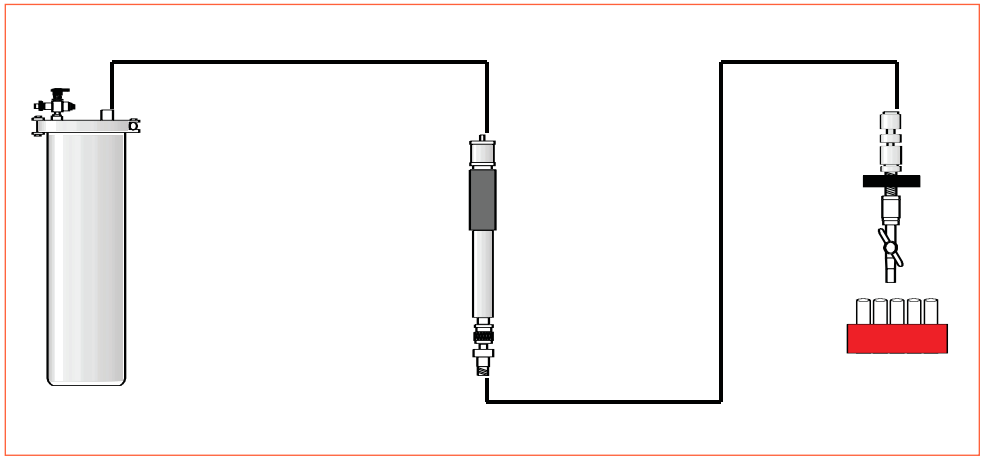


Figure 1. *The FLASH-AC 12™ cartridge (12-mm ID) fits into a standard FLASH purification system.*
See page 112 of this catalog for a complete description of FLASH 12 systems and options.

FLASH-AC Convenience and Performance

Batch vs. Cartridge Convenience

FLASH-AC™ cartridges are easier to use than batch processes

- Insert a prepacked FLASH-AC cartridge into the compression module
- Fill the pressure reservoir with solution
- Apply gas pressure
- Collect purified solution

Clean-up is even easier

- Drain and blow down the system
- Remove the top from the compression module
- Remove the spent prepacked cartridge, seal both ends, send out for disposal
- No reactors to clean
- No exposure to potentially hazardous materials

Batch vs. Cartridge Performance

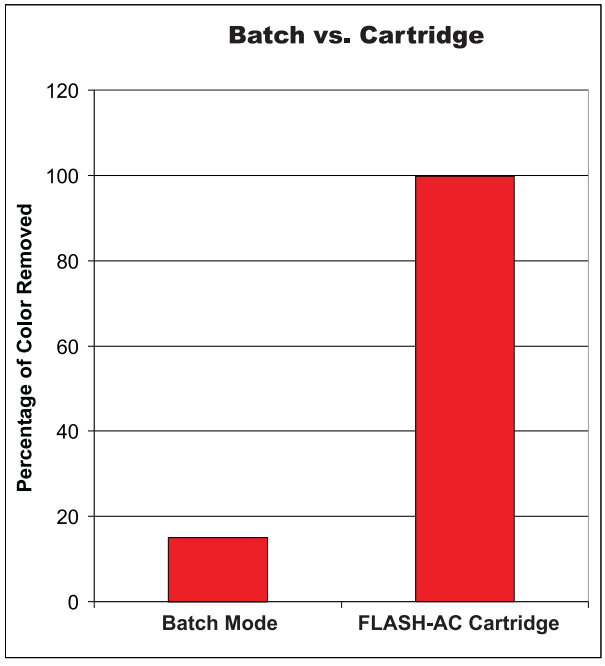


Figure 2.

The graph in Figure 2 clearly demonstrates that FLASH-AC cartridges are much more effective in removing impurities than a batch-mode process.

Even with a 24-hour contact time, the batch process removed only 18% of the contaminant. By contrast, the FLASH-AC cartridge removed 100% of the contaminant and did so in less than one-tenth the time. (For complete details about this test, please see Biotage Application Note 12 on our Web site, www.Biotage.com).

Benefits of the FLASH-AC cartridges

- Reduce process time up to 10X
- Eliminate loose carbon to reduce reactor and piping cleaning
- Eliminate the need for recrystallization and improve product yields, production rates and solvent consumption
- Simplify operation: ready-to-use cartridge reduces set-up and clean-up times

Quality Assurance

- Manufactured in an ISO 9002 certified facility
- Completely traceable materials
- Plastic components meet 21 CFR 177.1520 requirements for all components
- Certificate of compliance for activated carbon media

Superior Packing Technology

Our proprietary packing technique is critical to the high performance of the FLASH-AC cartridges. The radial compression of the cartridge eliminates early breakthrough and provides predictable scale-up.

A poorly packed column allows solution to pass through only partially treated, leading to early contaminant breakthrough and poor carbon utilization. Biotage's high-performance FLASH-AC media provides the optimum balance between adsorption kinetics and hydraulic pressure-drop for maximum performance.

FLASH-AC Specifications

Cartridge	Dimensions (mm x cm)	Typical Load (L)	Flow Rate (mL/min)
FLASH AC 12™S	12 x 7.5	0.1 - 5	20 - 15
FLASH AC 12M	12 x 15	0.1 - 5	20 - 15
FLASH AC 75™S	75 x 9	50 - 300	50 - 600
FLASH AC 75M	75 x 15	50 - 300	50 - 600
FLASH AC 75L	75 x 30	100 - 600	50 - 600
FLASH AC 150™M	150 x 30	300 - 1500	0.2 - 2.4 (L/min)
FLASH AC 150L	150 x 60	600 - 3000	0.2 - 2.4 (L/min)
FLASH AC 400™M	400 x 30	2500-1000	2 - 15 (L/min)
FLASH AC 400L	400 x 60	2500 - 10000	2 - 15 (L/min)

FLASH-AC™ Cartridges Provide Predictable Scale-up

Testing has demonstrated an excellent correlation from a lab-scale FLASH-AC purification and the actual full-scale performance. Convert existing batch and deep-bed processes to FLASH-AC cartridges with a minimal amount of process development and validation.

Contact Biotage's 1-POINT SUPPORT team for assistance with scale-up matters:

US: 1-800-446-4752 EU: +46 18 56 59 11 JP: +81 (422) 28-1233

Production Scale FLASH-AC

FLASH-AC 150-mm and 400-mm cartridges are currently in use at major pharmaceutical companies around the world. Biotage products provide standard and custom approaches to activated-carbon purifications.



FLASH-AC Ordering Information

Item	Description	Qty/Case	Part Number
Acid-Activated Carbon Cartridges			
FLASH-WAC-12S	12 mm x 7.5 cm	20	C1YR-4021-15026
FLASH-WAC-12M	12 mm x 15 cm	20	C1YR-4021-15046
FLASH-WAC-75S	75 mm x 9 cm	10	C1YR-4021-19163
FLASH-WAC-75M	75 mm x 15 cm	10	C1YR-4021-19043
FLASH-WAC-75L	75 mm x 30 cm	10	C1YR-4021-19073
FLASH-WAC-150M	150 mm x 30 cm	2	C1YR-4021-25075
FLASH-WAC-150L	150 mm x 60 cm	2	C1YR-4021-25155
FLASH-WAC-400M	400 mm x 30 cm	2	C1YR-4021-50075
FLASH-WAC-400L	400 mm x 60 cm	2	C1YR-4021-50155

The FLASH purification systems sold in this catalog readily accept FLASH-WAC acid-activated-carbon cartridges, as indicated below.

FLASH-AC Systems Ordering Information

FLASH-WAC Cartridge Model	Compatible FLASH Purification System	FLASH System Part Number
12S	FLASH 12i	SF-020-15024
12M	FLASH 12i	SF-022-15024
75S	FLASH 75S	SF-022-19161
75M	FLASH 75M	SF-022-19041
75L	FLASH 75L	SF-022-19071
75S	AUTOFLASH 75S	AF-005-19160
75M	AUTOFLASH 75M	AF-005-19040
75L	AUTOFLASH 75L	AF-005-19070
150M	FLASH 150M	SF-022-25071
150L	FLASH 150L	SF-022-25151
400M	FLASH 400M	SF-011-50070
400L	FLASH 400L	SF-011-50150

FLASH 12i: The Purification Setup FLASH-WAC-12 Cartridges

The FLASH 12i™ system includes one compression module (FLASH 12Si, 12 mm ID x 7.5 cm L), one FLASH 12M barrel (12 mm x 15 cm, interchangeable with the 12Si module), one injection valve, one solvent reservoir, one ZIF-SIM10™ sample-loading cartridge, one stand, a start-up kit and a user's manual. This system is also available without the ZIF-SIM™ (for a description of ZIF-SIMs, see page 118 of this catalog).

FLASH 12i Ordering information

Item	Description	Part Number
FLASH 12i with ZIF-SIM	Full system with ZIF-SIM	SF-022-15024
FLASH 12i	Full system, no ZIF-SIM	SF-020-15024







Production-scale FLASH™ Systems

For Large-scale Chromatography and Adsorption Processing

FLASH 400™

Production-scale FLASH Systems

FLASH 400 Systems

The Biotage FLASH 400 is a complete, skid-mounted system designed for large-scale flash chromatography and adsorption processing.

Like our smaller scale FLASH purification systems, the FLASH 400 uses prepacked cartridges (400 mm ID) and is designed for radial compression of the packing material, providing maximum performance and reliability. Biotage FLASH 400 systems are faster, safer and easier to use than traditional glass and steel columns. Built to last and engineered to perform, Biotage FLASH 400 systems are rapidly becoming the first choice of pharmaceutical companies around the world for critical adsorption purification.



FLASH 400 System Specifications

Pressure:	100 psig
Flow:	≤7 L/min @ 80 psig
Temperature:	5-80°C Wetted
Surfaces:	316 and 316L
Weight:	1000 lb (450 kg)
Dimensions:	44" x 30" x 90" (W x L x H)



FLASH 400™ systems are built with industrial-grade components that are appropriate for operations under the U.S. Food and Drug Administration regulations for current Good Manufacturing Practices (cGMP) and meet National Electrical Code® requirements for explosion proofing (CLASS I, Divisions 1 & 2, Groups C & D) .

FLASH 400 systems have interchangable barrels for use with either 400 mm x 30 cm (FLASH 400M) or 400 mm x 60 mm (FLASH 400L) cartridges. A system includes a compression module of one size, and the module of the other size can be ordered as an interchangeable option.

- 316 SS* ASME-rated compression module and radial compression tank
- 304 SS frame with industrial-style casters
- 316 SS air-operated diaphragm pump
- SS overbraided, Teflon®-lined tubing
- 316 SS valves with Teflon seats
- Calibrated pressure gauges and pressure-relief valves
- Optional frame-mounted hoist for loading and removing cartridge

**SS = stainless steel*

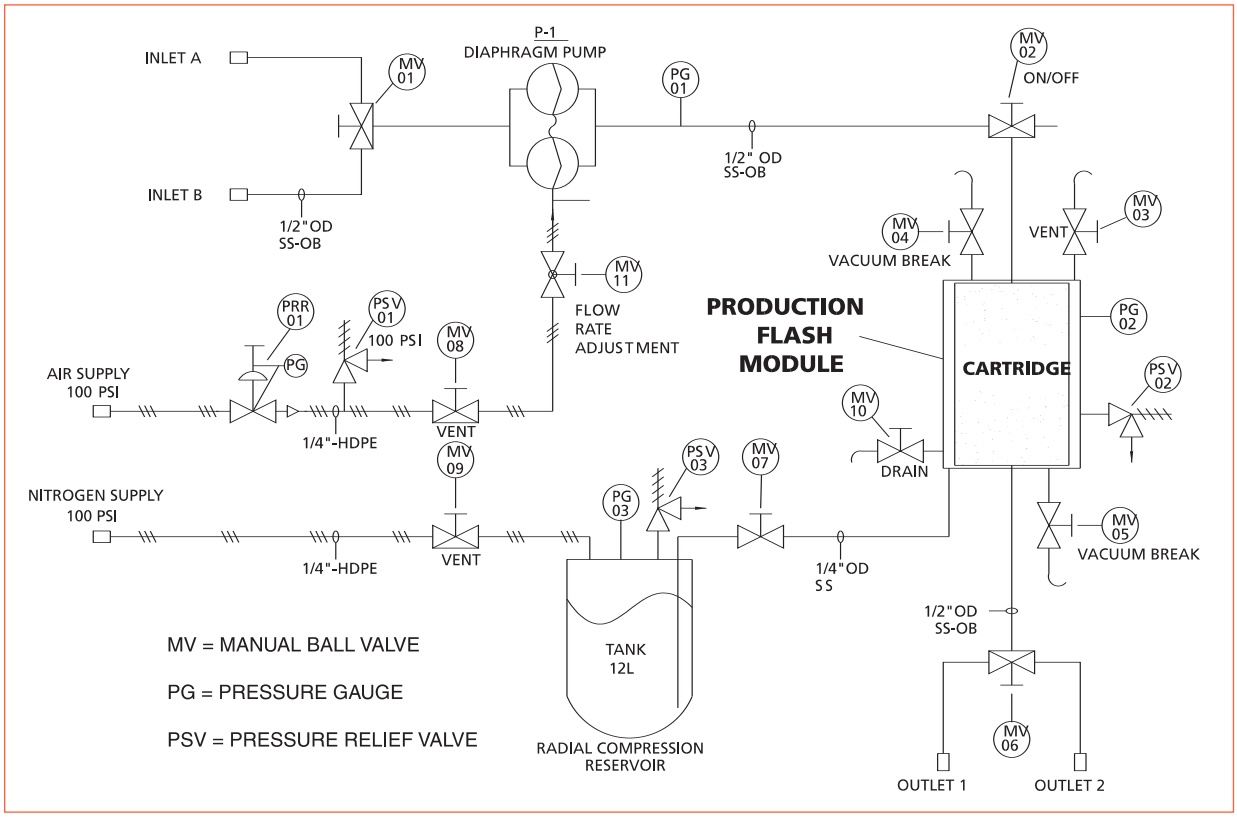


Figure 1. *FLASH 400 Process and Instrument Diagram.*

FLASH 400™

Production-scale FLASH Systems



FLASH 400 Cartridges

- FLASH 400 systems are designed for use with Biotage's family of 400-mm cartridges, which are supplied with normal and reversed-phase silica, activated carbon, polymeric adsorbents or custom-packed media
- Designed for both chromatography purification and adsorption processing of a variety of organic synthetic and natural products
- Minimum exposure to highly active or toxic compounds
- Ensure highest purity, yield and throughput

Cartridge Specifications

	FLASH 400M	FLASH 400L
Diameter (mm)	400	400
Bed Length (cm)	30	60
Flow Rate (L/min)	1-7	1-7
Column Void Volume (L)	28	56
KP-Sil™ Silica Packing Weight (kg)	20	40
FLASH-AC™ Activated Carbon Packing Weight (kg)	13	26
Mitsubishi HP20 Packing Vol (L)	38	76

FLASH 400™ Ordering Information

FLASH 400 Systems

Item	Part Number
FLASH 400M™ and FLASH 400L™ packages include a compression module with ASME "U" stamp, air-operated diaphragm pump, solvent-select valve (A or B), injection valve, collect valve (1 or 2), radial compression reservoir, 304-SS frame with casters, start-up kit, and engineering documentation package. (Can be purchased with or without hoist.)	
FLASH 400M (no hoist)*	SF-011-50070
FLASH 400L (no hoist)*	SF-011-50150
FLASH 400M (with hoist)*	SF-511-50070
FLASH 400L (with hoist)*	SF-511-50150
*Requires daily rate service (off site)	SER-001-LBR

FLASH 400 Cartridges

Item	Pkg Wt (kg)	Qty/Case	Part Number
KP-Sil™ Silica *(40-63 µm, 60 Å, nominally 500 m2/g silica) for high-capacity normal-phase purification*			
FLASH 400M	20	2	FK0-1107-50075
FLASH 400L	40	2	FK0-1107-50155
KP-C18-HS™ *(32-63 µm, 90 Å, 18% carbon, endcapped) for high-capacity reversed-phase purification*			
FLASH 400M	33	2	FL0-1118-50070
FLASH 400 Upgrades			
Cartridge Seal Adapter	With heavy-duty thread	1	07635
Cartridge Insertion Tool	Pneumatic press	1	08327
FLASH 400 Barrel Option**			
Barrel	Use with 400M		FB-012-50070
Barrel	Use with 400L		FB-012-50150
***Must be ordered with system*			
SIM [Sample Injection Module]			
SIM 10000™	Injection Module		SIM-10000
SIM 10000 Cartridge	Includes two tubes with bottom-frit assemblies and four frits for packing		FTF-10000
FLASH-WAC™ *(acid-activated carbon, classified, washed, high-efficiency adsorption)*			
FLASH-WAC-400M	13	2	C1YR-4021-50075
FLASH-WAC-400L	26	2	C1YR-4021-50155

MP 8000™

The Biotage MP 8000 is an automatic pumping and control system designed for use with the FLASH 400™ system. Biotage tailors the MP 8000 to meet individual requirements for process control and data recording.

MP 8000 System Benefits

- Fully automates the purification process, Including:
- Sample loading
- Binary gradient elution
- UV detection
- Fraction collection
- Safe operation
- Class 1, Division 2, Groups C & D, and other ratings
- Monitors multiple alarm conditions
- Explosion proof



The MP 8000™ provides monitoring and automation with the precision necessary for the purification of valuable compounds. The units are built with industrial-grade components appropriate for operations under U.S. Food and Drug Administration regulations for current Good Manufacturing Practices (cGMP). They also meet the explosion-proofing requirements of the National Electrical Code®.

MP 8000 Features

- Diaphragm pump, 0.8-8.0 L/min at 150 psig
- 316 SS* static mixer
- 304 SS* frame and NEMA X control cabinet (explosion proof)
- Dual-wavelength UV detector
- 8-port fraction collector
- 4-color touch panel and programmable logic controller
- Optional Coriolis flow meter

**SS = stainless steel*

MP 8000™ Ordering Information

Item	Description	Part Number
MP 8000	Gradient MPLC System (Automation system for FLASH 400)	Custom

Optional configurations for the MP 8000-XP include in-line monitors for pH, conductivity and/or gradient density.

To discuss your specific automation needs for FLASH or High-Pressure Liquid Chromatography, call Biotage 1-Point Support. US: 1-800-446-4752 EU: +46 18 56 59 11 JP: +81 (422) 28-1233

SIM 10000™ Production-scale Sample Injection Module

The Biotage SIM 10000 is a skid-mounted sample injection module designed for use with a FLASH 400 system. The SIM 10000 module holds disposable 10-L cartridges, to be filled with your media.

Sample injection modules are essential for the successful purification of low-purity and/or low-solubility materials. SIM 10000s are designed to ensure maximum recovery of your valuable compounds.

The SIM 10000 is built with industrial-grade components that are appropriate for operations under U.S. Food and Drug Administration regulations for current Good Manufacturing Practices (cGMP) and meet National Electrical Code® requirements (Class I, Division 1or 2, Groups C&D) for explosion-proof service.

- 316 SS* ASME-rated compression module and radial compression tank
- 304 SS frame with industrial-style casters
- SS overbraided, Teflon®-lined tubing
- 316 SS valves with Teflon seats
- Calibrated pressure gauges and pressure-relief valves

**SS = stainless steel*



SIM 10000™ Specifications 100 psig

Flow:	1 - 7 L/min
Temperature:	5 - 80° C
Weight:	440 lb (200 kg)
Dimensions:	34" x 26" x 54" (L x W x H)



SIM 10000 Cartridges and Frits

SIM 10000™ Ordering Information

Item	Description	Part number
SIM 10000	Sample Injection Module	SIM-10000
SIM 10000 Cartridge	Includes two tubes with bottom-frit assemblies and four frits for packing	FTF-10000


Kiloprep 100



Kiloprep® Preparative HPLC Systems

For Milligram-scale to Kilogram-scale HPLC Purifications

Kiloprep Preparative HPLC Systems

Kiloprep is a preparative HPLC system combined with prepacked cartridge technology to offer the highest resolution of any available preparative purification technique. Biotage offers systems and cartridges that, in a single run, will purify quantities of material ranging from milligrams to kilograms.

Customers using solid-phase synthesis to produce peptides or oligonucleotides will need this high resolution to reach their purity goals. Customers who need chiral separations or have closely related small molecules from synthesis, fermentation or natural products also can benefit from the Kiloprep technology.

Biotage Kiloprep HPLC systems are available with flow-rate ranges from 25 mL/min up to 15 L/min and pressure as high a 4,000 psig. Customers can begin with a bench-top HPLC system, the Kiloprep 100, and then move up to the pilot scale with a Kiloprep 250 and, finally to production scale, with the Kiloprep 2000, 3000 or 4000.

Features and Benefits:

- Fully integrated system, with a wide range of options
- Two system-control options
  - Desktop computer with Microsoft Windows NT; compliant with U.S. FDA regulations for electronic records and signatures (21 CFR 11)
  - PLC with touch-screen interface, offering full automation without a desktop computer
- Complete cGMP documentation package with every system
- Complete automation of loading, elution and fraction collection
- Patented gradient-control algorithm for the greatest accuracy and reproducibility
- Triple-head pumps for minimum pulsation and maximum reliability
- Explosion-proof design, with FM-approved certification
- Solvent reservoirs designed for safe operation at preparative flow rates

Kiloprep Specifications

Kiloprep Systems Specifications

Biotage Kiloprep System	Flow-rate Range (mL/min)	Maximum Pressure (psig/bar)	Suitable Column Diameters (mm ID)	Environment
KP 100 series				
KP124	25-250	4,000/270	25*-75	Lab
KP152	45-450	2,000/135	50*-100	Lab
KP192	90-900	2,000/135	75-150	Lab
KP250	100-1,000	2,000/135	75-150	Pilot
KP250EF	200-2,000	2000/135	75-200	Pilot
KP2000	450-4,500	2,000/135	150-300	Production
KP2000EF	750-7,500	1,200/80	150-400	Production
KP3000	950-9,500	1,500/100	200-600*	Production
KP3000EF	1,500-15,000	1500/100	200-800*	Production
KP4000	1,700-17,000	1,200/80	300-1,000*	Production

*Biotage Kiloprep cartridges are available from 75 mm ID to 300 mm ID

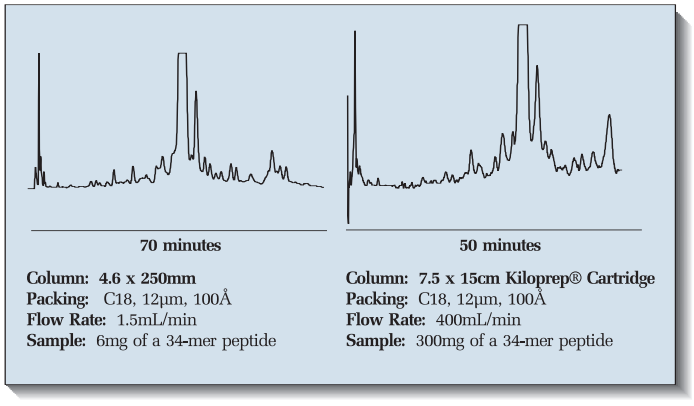


Figure 1. *High-resolution reverse-phase separation of a 34-amino acid synthetic peptide.*

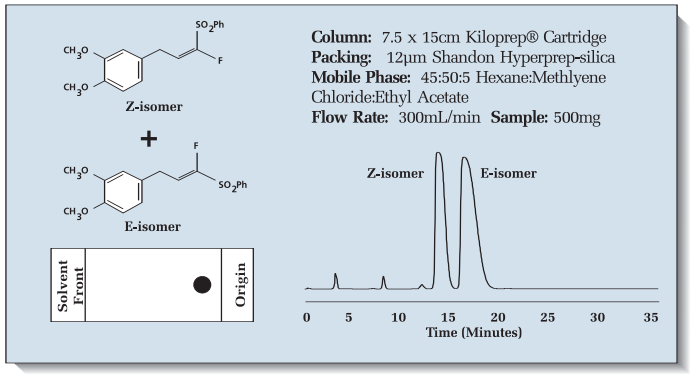
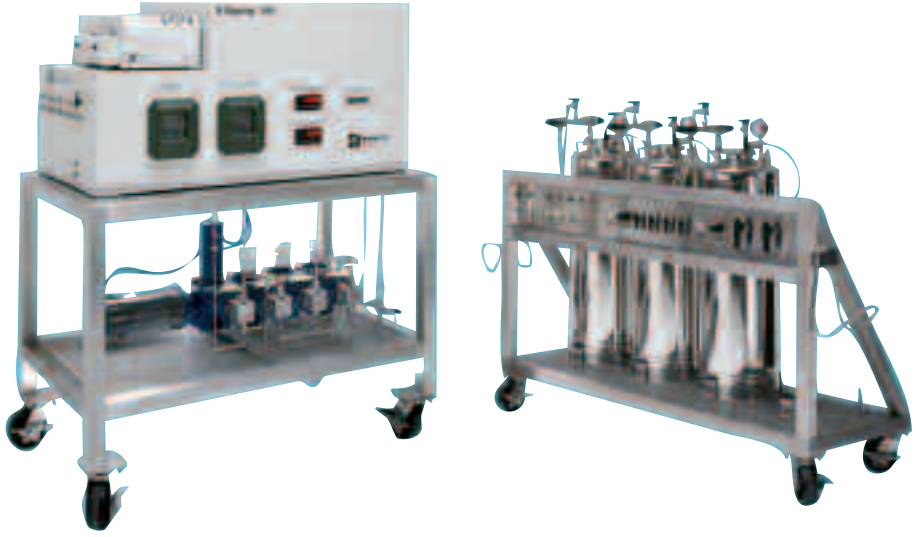


Figure 2. *High-resolution normal-phase separation of fluorosulfone Z & E isomers.*

KILOPREP® 100



Kiloprep 100

The Kiloprep 100 series are compact, bench-top HPLC systems designed for use in a laboratory environment. These systems produce milligram to multigram quantities of peptides, oligonucleotides, enantiomers or natural products. The Kiloprep 100 systems are for use in research or in process-development groups that plan to scale-up further.

Kiloprep 100 System Configuration

Component	Standard Configuration	Options
Solvent Reservoirs	(2) 37-L, ASME	(3) 60-L, ASME
Inlet Header	A + B binary gradient and separate C-inlet	Tertiary gradient (A+B+C)
Sample Loading	C-inlet on main pump	Isolated sample pump Loop injector
Instrumentation	Dual-channel, variable-wavelength UV detector Precolumn pressure transducer	pH meter Conductivity meter Densitometer Thermometer Column delta-pressure
Flow Path	3-head plunger pump Gradient mixer	Column header with forward- or reverse-flow modes Recycle valve
Fraction Collection	Waste or collect valve	12-port rotary valve Purge for high recovery
Peak-detection Mode	Time, UV threshold, UV slope Boolean combinations of parameters	

Kiloprep® 250

The Kiloprep 250 is a compact, skid-mounted HPLC system designed for use in a pilot plant or full-scale production environment. It is available for use in areas that are nonhazardous or explosion proof as defined in the National Electrical Code® Class I, Division 1, Groups C & D. Kiloprep 250 systems are used to produce multigram to kilogram quantities of peptides, oligonucleotides, chiral enantiomers, or natural products.

Kiloprep 250 System Configuration

Component	Standard Configuration	Options
Solvent Reservoirs	(2) 60-L, ASME	(3) 120-L, ASME
Inlet Header	A + B binary gradient and separate C-inlet	Tertiary gradient (A+B+C)
Sample Loading	C-inlet on main pump	Isolated sample pump
Main Pump	Three-head double diaphragm	Flow meter with feedback control
Instrumentation	Dual-channel, variable wavelength UV detector Precolumn pressure transducer	pH meter Conductivity meter Densitometer Thermometer Column delta-pressure
Flow Path	Pulse dampener Gradient mixer	Filter header with selections for • Filter or Bypass • Filter 1 or Filter 2 Column header with selections for • Forward or Reverse flow • Column 1 + Column 2 • Bypass Recycle valve Heat exchanger
Fraction Collection	Waste or collect valve	12-port rotary valve Purge for high recovery
Peak-detection Mode	Time, UV threshold, UV slope	Boolean combinations of parameters

KILOPREP®

2000, 3000, AND 4000 SKID-MOUNTED

Kiloprep 2000

The Kiloprep 2000 is a high-throughput, skid-mounted HPLC system designed for use in a pilot plant or full-scale production environment. It is available for use in areas that are nonhazardous or explosion proof as defined in the National Electrical Code Class I, Division 1, Groups C & D. These systems are used to produce multigram to kilogram quantities of peptides, oligonucleotides, chiral enantiomers or natural products.

Kiloprep 3000, 4000

The Kiloprep 3000 and 4000 are high-throughput HPLC systems with a control skid and a pump skid, designed for a full-scale production environment. They are available for use in nonhazardous or explosion proof environments as defined by the National Electrical Code Class I, Division 1, Groups C & D. These systems are used to produce multigram to kilogram quantities of peptides, oligonucleotides, chiral enantiomers or natural products.



KP 2000
KP 3000
KP 4000

Kiloprep 2000, 3000 and 4000 System Configurations

Component	Standard Configuration	Options
Inlet Header	A + B binary gradient and separate C-inlet	Tertiary gradient (A+B+C)
Sample Loading	C-inlet on main pump	Isolated sample pump
Main Pump	Three-head double diaphragm	Flow meter with feedback control
Instrumentation	Dual-channel, variable-wavelength UV monitor Precolumn pressure Transducer	pH meter Conductivity meter Densitometer Thermometer Column delta-pressure
Flow Path	Pulse dampener Gradient mixer	Filter header with selections for • Filter or Bypass • Filter 1 or Filter 2 Column header with selections for • Forward or Reverse flow • Column 1 + Column 2 • Bypass Recycle valve Heat exchanger
Fraction Collection	Waste or Collect Valve	8-port rotary valve Purge for high recovery
Peak-Detection Mode	Time, UV threshold, UV slope Boolean combinations of parameters	

The Biotage Custom Systems Group tailors each system to your specific needs. We offer the greatest range of options for flow-rate, pressure, instrumentation and flow paths. Please contact Biotage for a Kiloprep Quotation Workbook, and our technical team will help you define the optimum configuration:

US: 1 800 446 4752

EU: 001 434 979 2319



Kiloprep® Cartridges

Biotage Kiloprep cartridges are prepacked, pretested, and shipped with a certificate of compliance, so they are ready to use in high-resolution HPLC purifications. We offer media from all the leading vendors, covering the widest possible range of surface chemistries, particle sizes and pore sizes. Kiloprep cartridges are useful for all the following applications:

- Peptides
- Oligonucleotides
- Small synthetic molecules
- Enantiomers
- Natural products
- Proteins

Our cartridges offer the highest resolution and our dedicated packing facility ensures the highest possible reproducibility. Biotage purchases media in large lot sizes. We retain a sample of each lot to ensure consistency and rapid delivery, and to offer complete analytical HPLC laboratory support to our preparative-cartridge production team.

Kiloprep Cartridge Features

- Prepacked, pretested, fully documented and ready to use
- Maximum efficiency and peak symmetry
- Media fully contained in cartridge, so operators are never exposed to high-activity products or impurities
- Radial-compression technology ensures a longer column life by improving the column efficiencies
- Cartridge changeover takes only minutes
- Cartridges can be dedicated to an individual project, then cleaned and reused

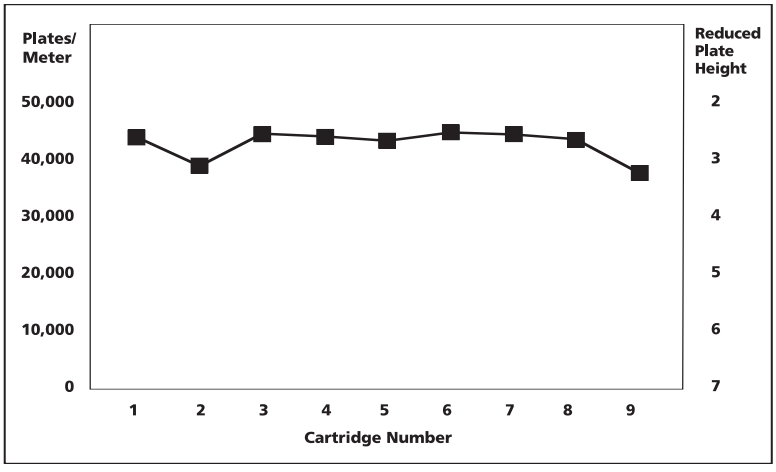


Figure 3. *This chart clearly demonstrates the consistent performance and high efficiency reported by plates per meter and reduced plate height.*



Kiloprep® Radial Compression Modules

Biotage Kiloprep Radial Compression Modules hold our prepacked cartridges and ensure that the cartridges provide the highest performance. Dynamic radial compression reduces the potential for void and channel formation, increasing cartridge lifetime. Compression modules are designed to hold cartridges of one diameter and two optional lengths (see chart below). Chemists can scale-up directly by selecting a larger compression module and increasing the cartridge diameter.

Kiloprep Compression Module	Cartridge Diameter (mm)	Cartridge Lengths (cm)	Typical Flow Rate (per min)	Typical Sample Load (g)
KPCM100	75	15 or 30	125–250 mL	0.1-50
KPCM250	100	30 or 60	250–500 mL	1-125
KPCM500	150	30 or 60	0.5–1.0 L	2-250
KPCM1000	200	30 or 60	1-2 L	5-500
KPCM3000	300	30 or 60	2-4 L	10-1,000

Preparative HPLC Scale-Up Guidelines

When scaling up a current method, a chemist can continue to use the original column and make many injections, or select a larger column that will complete the project in many fewer runs. If you have already optimized a method on an analytical or semi-prep column, Biotage can help you select a Kiloprep cartridge that will dramatically reduce the time and expense of scaling up. To determine the optimum sample size, flow rate, and gradient duration for scale-up, use the following steps:

1. Sample Size

If an initial method was developed on a 4.6-mm ID x 25-cm column with a 6-mg sample size, what is the appropriate sample size for a Biotage Kiloprep 100M cartridge, 75 mm ID x 15 cm long?

Mass (Prep) = Mass (Scaling) x dia2 (prep) x length (prep)

Preparative sample (g) = 0.006(75/4.6)2 (15/25) ~ 0.957 g

2. Flow Rate

As you scale-up a method, you will also need to adjust flow rate to keep the linear velocity constant. In many cases Biotage cartridges can be run at higher flow rates to further reduce the purification time. Therefore, this equation is a starting point for development:

Flow Rate (Prep) = Flow Rate (Scaling) x dia2 (prep)

In the same example, the chemist ran the 4.6-mm ID analytical column at 1.5 mL/min; what is the flow rate for the KP100M cartridge? Preparative flow rate (mL/min) = 1.5(75/4.6)2 ~ 400 mL/min

3. Gradient Duration

If your current method uses a linear gradient, the gradient duration must also be adjusted for the new, larger column.

Gradient Duration (Prep) = Gradient Duration (Scaling) x dia2 (prep) x length (prep) x flow rate (scaling)

In the same example, the current method used a 60-min linear gradient for 10% to 70%; what is the appropriate gradient duration for the KP100M cartridge? Preparative HPLC gradient duration (min) = 60 (75/4.6)2(15/25)(1.5/400) ~ 36 min



Spare Parts

Spare Parts: Microwave Synthesis

Accessories

Item	Description	Part Number
Crimper	Hand operated, used to crimp 20 mm caps on vials	353671
Decapper	Hand operated, used to decap 20 mm caps on vials	353913

Microwave Synthesis Miscellaneous Spare Parts

Item	Description	Part Number
Tubing kit	Interconnect tubing for syringe pump to needle	352289
Syringe	500 ul gas tight syringe	352508
Piston	500 ul Replacement piston for syringe	352509
Syringe	10 mL	352510
Piston	10 mL	352511
Rack tray	Tray for Emrys Synthesizer to hold racks	352512
Emrys grip vial tongs	Replacements for gripper	353010
GSG Booklet	Getting Started Guide Booklet	353067
GSG Poster	Getting Started Guide Poster	353068
Connection Set	Air adapters to connecting MAOS to facilities	353480
Vial Rack	Holds 12 10- 20 mL vials	354836
Cavity Air Guide	Improves cooling of vials	354974
Cavity Lid Seal	O-ring (blue) for EXP MAOS for venting on vials	354494
Vent Screw Replacement	Enables vial venting when required	354878
Cavity sleeve	Process chamber cavity sleeve	352296
Fuse kit	Set of 4, 10 A fuses	352291
Process Needles	Includes 3 needles	352024
Solvent bottles	50 mL, 6/pack	352076
Reservoir bottle	500 mL, bottle and tubing	352078
Vial Adapters	Designed to make 0.2-0.5 mL vials fit into the microwave cavity. Kit includes 10 pieces.	354459
Vial Adapters	Designed to make 10-20 mL vials fit into the microwave cavity. Kit includes 12 pieces.	354367
O-rings	Replacement O-rings for 10-20 mL adapters. Quantity 12.	354838

Initiator™ Spare Parts

Item	Description	Part Number
Initiator Software CD		355305
Initiator Sixty CD		355449
Initiator EXP Software CD		355306
Initiator Sixty EXP CD		355450
Air hose x 2m		351088
Air Control Unit		352281
Air Supply connection set		353480
Power cable (EU)		351693
Power cable (GB)		3512669
Power cable (US & JP)		3511277
Getting Started Guide		355422

Spare Parts: Purification

FLASH i-series Spare Parts

The i-series of FLASH products preceded the current FLASH+™ line.

Item	Description	Part Number
V-band Clamp	3" V-band clamp for 1-L solvent reservoirs	08526
Gasket	3" solvent reservoir gasket, polyethylene	01617
Stopcock Valve	2-way stop flow valve, polypropylene	03274
Hose Barb Adapter	Female Luer to 1/8" tube	01986
Luer-Lok® Collar	Male Luer-Lok to 1/8" tube, w/ collar	03229
Luer-Lok Kit	1 female plastimate Luer-Lok port 1 finger-tight nut 1 front 1/4" ferrule 1 back 1/4" ferrule	02838
Air Tubing	1/4" OD polyethylene tubing (6’)	03275
Air Fitting	1/4" OD 3/8" Male NPT brass bushing to 1/4" insta-tite fitting	03072
Ferrule Kit	1/4" PFA front ferrules (6) 1/4" PFA back ferrules (6)	03062
Nut and Ferrule Kit	Finger-tight nuts (2) 1/4" PFA front ferrules (2) 1/4" PFA back ferrules (2)	03061
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144

FLASH 12i™ Spare Parts

Item	Description	Part Number
O-ring kit	Chemraz® O-ring (1) Retaining ring (1) Instruction sheet	03046
Collection Tube Kit	For fraction collection, 1/16" OD tubing, FEP (12") tubing Union, 1/16" to 1/16", SS 1/16" OD tubing, SS (3.5") 1/8" to 1/16" reducing union	03071
Syringe	Disposable 2-mL polypropylene (5)	03276
Reducing Union	1/4" to 1/16" tube to tube	02979
Dip Tube	For solvent reservoir	01889
Nuts and Ferrules	1/4" and 1/8" nuts and ferrules (3 sets of each)	NF-15075
FLASH 12i Compression Module	For use with FLASH 12 Cartridges	FC-022-15024
FLASH 12i/40i Start-Up Kit	Frame and tubing	SU-242-0000
FLASH 12S Barrel	Short Barrel	02954
FLASH 12M Barrel	Medium Barrel	02942
Distribution Head	Upper flow-distribution head	02843
Distribution Head	Lower flow-distribution head	02946
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144

Spare Parts

FLASH 40i™ Spare Parts

Item	Description	Part Number
FLASH 40i Compression Module	For use with FLASH 40 Cartridges	FC-022-17024
FLASH 40S Barrel	Short Barrel	01800
FLASH 40M Barrel	Medium Barrel	01818
FLASH 40L Barrel	Long Barrel	06981
FLASH 40i Spare Parts Kit	Tubing, O-ring, gasket, V-band clamp	01985
FLASH 12i/40i Start-Up Kit	Frame and tubing	SU-242-0000
O-ring Kit	Chemraz® O-ring (1) Retaining ring (1) Instruction sheet	03216
Collection Tube Kit	For fraction collection, 1/8" tubing, FEP (3') Tube with Luer-Lok® adapter	01888
Barrel Adapter	Threaded barrel adapter connects head assembly to 40S or 40M barrel	01790
Syringe	Disposable 10-mL polypropylene	03277
Reducing Union	1/4" to 1/16"	02979
Nut and Ferrule Kit	1/4" and 1/8" nuts and ferrules (3 sets of each)	NF-15075
Head Assembly	SIM Receiver-Head Assembly	06090
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144

SIM-1040 Spare Parts

Item	Description	Part Number
O-ring	SIM Top-Head O-Ring	01963
Collar	SIM Barrel-Locking Collar	01969
Head Assembly	SIM Receiver-Head Assembly	06090
Fitting Kit	SIM Luer-Lok Kit	01984
Tubing Kit	SIM Tubing Kit	01903
Cap Kit	SIM Plastic Cap Kit, 1 SIM cap adapter and 1 retaining ring 5/8"	03251
Tool	Frit insertion tool	01965
Adapter	Male Luer to 1/8" NPT	01959
SIM Kit	35-cc barrels and frits (24)	FTF-0040

FLASH 65i™ Spare Parts

Item	Description	Part Number
O-ring	Chemraz O-ring (1)	08395
E-ring	Retainer clip needed with O-ring	03024
Barrel Retainer	Barrel	0152
Collection Tubing Kit	Adapter, Female Luer,1/16" Barb 1/8" FEP Tubing (24") 1/8" Male Luertight fitting 1/8" Knurled nut, 1/8" ferrule set, SS	08403
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144

FLASH 75i™ System Spare Parts

Item	Description	Part Number
Extraction Tool	FLASH cartridge extraction tool	02131
O-ring	Viton® O-ring	00778
V-band Clamp	4" V-Band clamp	08527
Valve	100 psi relief valve	00790
Valve	Pressure relief valve	07072
Gasket	1.5” EPDM	01644
Clamp	1.5” SS sanitary clamp	00440
Frits	Top, 1.5” frits (25)	FTF-0125
Frits	Bottom frit and sealing rings (25)	FBS-1025
Injection Valve		
Ferrule	1/4" PFA (6)	03062
Nut and Ferrule Kit	1/4" SS nut w/ PFA ferrule (2)	03061
Tube adapter	1/4" to 1/8" tube-to-tube adapter	03332
Luer-Lok® Kit	Female Luer-Lok injection kit	02838
	Sold by the foot	

FLASH 75i SIM 100™ Spare Parts

Item	Description	Part Number
Insertion Tool	Top-frit insertion tool, 1.5” diameter	01534
Gasket	1.5” polyethylene	01642
Gasket	1.5” Viton®	01643

FLASH 150i™ Compression Module Spare Parts

Item	Description	Part Number
O-ring	Viton O-ring	01420
V-band Clamp	8" V-band clamp for FLASH 150™ compression module	01419
Extraction Tool	FLASH 150 cartridge extraction tool	01428

SIM 500™, 1000™, 2000™ Spare Parts

Item	Description	Part Number
Gasket	3” polyethylene	01617
Gasket	3” Viton	01615
Gasket	3” EPDM	01616
Clamp	3” SS sanitary clamp	00444
Frits	Top, 3” frits (25)	FTF-0225
Frits	Bottom frit and sealing rings (25) for the stainless-steel frit holder	FBS-1025
Insertion Tool	Top-frit insertion tool, 3”diameter	01534
Injection Valve		
Ferrule	1/4" PFA ferrule (6)	03062
Nut and Ferrule Kit	1/4" SS nut w/ PFA ferrule (2)	03061
Luer-Lok® Kit	Female Luer-Lok injection kit	02838

Spare Parts

FLASH 400 Spare Parts

Item	Description	Part Number
O-ring	387 Viton® O-ring	03020
O-ring	387 EPDM O-ring	03019
O-ring	460 Viton O-ring	02939
O-ring	460 EPDM O-ring	03011
O-ring	223 Chemraz® O-ring	03010
O-ring	222 Chemraz O-ring	06875
O-ring	460 Chemraz™ O-ring	08648
Valve	Air Lube Free Wilden	04493
Diaphragm	Teflon® Wilden	04494
Ball	Teflon Wilden	04495
Seat	SS Wilden	04496
O-ring	119 Teflon®	04497
O-ring	120 Teflon®	04498
Diaphragm	Neoprene™ Wilden	04499

FLASH Miscellaneous Spare Parts

Item	Description	Part Number
Tubing	1/8" OD FEP tubing Sold by the foot	00088
Tubing	1/4" OD FEP tubing Sold by the foot	00089
Air Tubing	1/4" OD RED air tubing Sold by the foot	00546
Air Tubing	1/4" OD YELLOW air tubing Sold by the foot	01354
Air Tubing	1/4" OD GREEN air tubing Sold by the foot	00547
Air Tubing	1/4" OD BLUE air tubing Sold by the foot	01487

FLASH+ Spare Parts

Item	Description	Part Number
E-Clip	Retaining ring	03024
V-band Clamp	3" V-band clamp for 1-L solvent reservoirs	08526
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144

FLASH 12+™ Spare Parts

Item	Description	Part Number
Lower ZIF O-ring	Chemraz® 107 O-ring	04593
Upper ZIF O-ring	Chemraz 108 O-ring	02948
Barrel O-ring	Chemraz 108 O-ring	02948
FLASH 25+™		
Lower ZIF O-ring	Chemraz 208 O-ring	06178
Upper ZIF O-ring	Chemraz 209 O-ring	06221
Barrel O-ring	Chemraz 209 O-ring	06221
FLASH 40+™		
Lower ZIF O-ring	Chemraz 215 O-ring	08558

FLASH 12+™ Spare Parts continued...

Item	Description	Part Number
Upper ZIF O-ring	Chemraz 218 O-ring	08557
Barrel O-ring	Chemraz 218 O-ring	08557
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144

Biotage recommends annual replacement of Chemraz O-rings to maintain FLASH+ compression modules.

V1 SP4 Spare Parts *The V1 SP4 system preceded the current SP4™ system.*

Item	Description	Part Number
Lipseal	0.500 OD x .312 ID 302 SST Spring	08192
Ring Wear	.500 OD x .370 ID Quad1	06785
UV lamp	for Sp4 Detector	09427
Replacement Windows	for flow cells	08857
Valve	Solenoid 2-Way NO 24VDC 100 PSI 1/4-28 Prots	08746
Valve	Select 3 Ports	09261
Valve	Select 4 Ports	09260
UV Collect Valve	UV Collect valve for Horizon and Sp4	09341
Valve	UV Collect Valve 3-way	08091
Spring Cprsn	.0075 Wire 3/8 Long K=.22 316 SS	05461
O-Ring	014 Chemraz	05654
O-Ring	007 Chemraz	06026
Ferrule	Flangeless 1/8 Tefzel	04030
Nut	1/8 inch Flangeless Fer 5/16-24 Peek	04795
Ferrule	Flangeless, 3/16 Tubing	09312
Nut	3/16 Flangeless, 5/16-24 Peek Natural	09311
Ferrule	Flangeless 1/16 Tefzel	04009
Nut	1/6 inch Flangeless Fer 1/4-28 Peek	04794
Tubing	1/6 inch OD x .030 Inch ID x 1.83 Long Flash Collector	08173
Inlet Filters	Solvent inlet filter disks, 3/8”	01801
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144

Horizon Spare Parts

Item	Description	Part Number
Tube Assembly	Compression module outlet to fraction collector arm 1/8”	08079
Tube Assembly	Compression module outlet to UV detector inlet 1/8”	08085
Spare Parts Kit	Kit, spare tubing & fittings horizon 1/8”	08442
Tube Assembly	Flow control outlet to UV detector outlet 1/8”	08761
Tube Assembly	Flow control valve to 3-way collect valve to waste 1/8”	08762
Tube Assembly	Flow control outlet to FC arm 1/8”	08763
Valve	UV collect valve	08535
Cell	0.3 mm flow cell	08632
Valve	Stop flow control valve	08770

Horizon Spare Parts continued...

Item	Description	Part Number
Lamp	UV lamp for Horizon Detector	08771
Cell	0.1 mm flow cell	08856
Window	Replacement windows for flow cells	08857
Tubing Kit	Upgrade tubing for outlet of compression module to UV collect valve	
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144

ZIF-SIM™ Spare Parts

Item	Description	Part Number
E-Clip	Retaining ring	03024
ZIF-SIM Tubing Kit	Luer fitting with 1/8" tubing, 1/8" knurled nut, connects ZIF-SIM outlet to compression module	01903

ZIF-SIM 10™ Spare Parts

Item	Description	Part Number
Frit Insertion Tool	Polypropylene frit insertion tool	0087
Upper O-ring	Chemraz 111 O-ring	00656
Lower O-ring	Chemraz 109 O-ring	06176

ZIF-SIM 35™ Spare Parts

Item	Description	Part Number
Frit Insertion Tool	Polypropylene frit insertion tool	0088
Upper O-ring	Chemraz 208 O-ring	06178
Lower O-ring	Chemraz 206 O-ring	06177

ZIF-SIM 60™ Spare Parts

Item	Description	Part Number
Frit Insertion Tool	Polypropylene frit insertion tool	0184
Upper O-ring	Chemraz® 211 O-ring	08555
Lower O-ring	Chemraz 209 O-ring	06221

Quad™ Spare Parts

Item	Description	Part Number
Filter Kit	Replacement filters 1/4" x 1/8" reducing union (4 required per set) solvent inlet filters (12)	QFILT-0000
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144
Inlet Filter Packs	Solvent inlet filters (12)	01801
Quad Check Valve	Check disc	05516
1/8” Fitting Kit	1/8” PEEK flangeless fittings 1/8” PEEK nut 1/8” TEFZEL ferrule	QFTT-4795
1/8" PEEK Nut	1/8” PEEK nut	04795
1/8" TEFZEL Ferrule	1/8” TEFZEL ferrule	04030

Quad™ Spare Parts continued...

Item	Description	Part Number
1/16” Fitting Kit	1/16” PEEK flangeless fittings 1/16” PEEK nut 1/16” TEFZEL ferrule	QFTT-4794
1/16" PEEK Nut	1/16” PEEK nut	04794
1/16" TEFZEL Ferrule	1/16” TEFZEL ferrule	04009
Upper O-Ring Kit	Upper O-ring Kit, Chemraz 108 and 107 O-rings Retaining Clip	QUOR-001
Chemraz 108 O-ring	Chemraz 108 O-ring	02948
Chemraz 107 O-ring	Chemraz 107 O-ring	04593
Retaining Clip	Retaining clip	03024
Lower O-Ring Kit	Chemraz® 108 O-ring Retaining clip	QLOR-001

Parallex Flex™ Spare Parts

Item	Description	Part Number
Needle	Tapered-tip needle	02922
Rotor for Inject Valve	6-port rotor, 0.040" ID	03947
2-mL Loading Loop	1/16" OD x 0.040" ID, SS	02789
5-mL Syringe	Gas-tight syringe	02935
5-mL Loading Loop	1/16" OD x 0.040" ID, SS	02788
10-mL Syringe	Gas-tight syringe	02751
Labels	Labels for barcode printer	06461
Switching valve	5 port loop switching valve	02748
UV Detector		
UV Lamp	Deuterium	03945
Gasket Set	Gaskets, offset flow cell UV4	03944
Pump		
Check Valve	Check-valve assembly	06403
Plunger	Sapphire plunger w/ holder	06404
Belt	Motor belt	06407
3-way valve	Gradient 3-way proportioning valve	06408
Seal	Seal	06405
Seal	Seal	06406
Fraction Collector		
Ferrule	1/8" Tube Short Tefzel	02727
Nut	1/8" Tube x 1/4" - 28 Tefzel	02728
Ferrule	1/16" Tube Short Tefzel	02729
Nut	1/16" Tube x 1/4" - 28 Tefzel	05694
Seal Kit	Valve, Check, 25 psi, Kalrez	03451
Fuses		
Fuse	1 A	03120
Fuse	10 A	03188
Fuse	2 A	03191

Parallex Flex Miscellaneous Spare Parts

Item	Description	Part Number
Tubing		
Reservoir Pressure Tubing	1/4" OD LDPE, BLUE air line Sold by the foot	01487
PEEK Tubing	1/16" 0.020 ID Sold by the foot	03263
Teflon® Tubing		
General-Purpose	1/4" OD, 0.040" wall	00089
Waste	1/8" OD	00088
Detector-to-fraction Collector	1/16" OD connects to inlet valve Sold by the foot	02879
Unions		
Y Union	1/4" Instan-tite	01478
Tee	1/4" 316 SS* union	01049

Parallex Flex Miscellaneous Spare Parts continued...

Item	Description	Part Number
Ferrules and Nuts		
Ferrule Set	1/4" 316 SS*	01634
Nut	1/4" SS*	01635
Ferrule	1/16", SS*	02726
Nut	1/16" compression nut, SS*	02725
MVP Valve Connections		
Ferrule	1/16", w/ SS* locking ring	02445
Nut	1/16", Delrin®	02446
VICI Valve Connections		
Nut	1/16", for SS* tubing	03318
Ferrule	1/16", SS*	03319

**SS = Stainless Steel*

SP1™ Spare Parts

Item	Description	Part Number
Fraction Collector		
Guide	Needle Horizon Flash Collector	08072
UV collect valve Needle	(1/6 inch OD x .030 Inch ID x 1.83L)	08173
Nut	1/6inch Flangeless Fer 1/4-28 Peek	04794
Ferrule	Flangeless 1/16 Tefzel	04009
Valve Assembly	UV Collect 3-Way	09341
Tube Assembly	1/4 inch Trough Drain Tube Horizon Flash Collector	08432
Ferrule	Set 1/4 316 SS	01634
Nut	1/4 Tube 316 SS	01635
Tubing	1/4 OD x .040 Wall FEP Teflon	00089
Fuse	5 X 20MM 2.5A / 250V	09367
Adapter	40mm to 25mm Flash+ Module Rack	07482
Adapter	40mm to 12mm Flash+ Module Rack	07481

SP1™ Spare Parts continued...

Item	Description	Part Number
Operator's Manual	CD Sp1	09624
Software	Sp1	09702
Pump		
Valve	10 psi Max NC Collar Mount	09472
Disk	Check 3/16 inch Balls Assembly Quad3	05516
Lipseal	0.500 OD x .312 ID 302 SST Spring	08192
Ring	Wear .500 OD X .370 ID Quad1	06785
Tee	Female Branch 1/8T x 1/8 FNPT x 1/8T	9566
Nut	1/8inch Flangeless Fer 5/16-24 Peek	4795
Ferrule	Flangeless 1/8 Tefzel	4030
Valve	150 psi Max NC Collar Mount	9468
Nut	1/8 Flangeless 1/4-28 Peek	08399
Tube Assembly	Solvent Inlet 5' Color Red Sp4B/Sp1	09664-01
Tube Assembly	Solvent Inlet 5' Color Blue Sp4B/Sp1	09664-02
Tube Assembly	Solvent Inlet 5' Color Green Sp4B/Sp1	09664-03
Tube Assembly	Solvent Inlet 5' Color Gold Sp4B/Sp1	09664-04
Filter	Inlet Solvent for 3/16 In OD Tubing 20 um Porosity 316 SST	09376
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144
Tubing	3/16 OD x .125 ID Teflon FEP	09314
Nut	Flangeless 3/16T x 5/16-24 Peek Natural	09311
Ferrule	Flangeless 3/16 Tubing	09312
Tube Assembly	Compression Module Outlet to Flow Path Module Inlet, Sp4B	09665
Tube Assembly	Flow Path Module Outlet to Compression Module Inlet, Sp4B	09666
Union	1/4 T X 1/8 T W/ Knurled Nut & PFA Ferrules	04144
Tubing	1/8 OD x .062 ID FEP	00088
Nut	1/8inch Flangeless Fer 5/16-24 Peek	04795
Ferrule	Flangeless 1/8 Tefzel	04030
Tube Assembly	Collect Valve to Flow Cell Outlet & Waste Sp1	09695
Nut	1/8 T Short Flangeless, 1/4-28 PEEK	08394
Nut	1/8 Flangeless 1/4-28 Peek Blue	08372
Tubing	1/8 OD x .062 ID FEP	00088
Nut	1/8 Flangeless 1/4-28 Peek	08399
Ferrule	Flangeless 1/8 Tefzel	04030
UV Detector		
Lamp	Mercury UV Fixed Wavelength 254nm	09427
Lamp	UV Variable Wavelength	09427
0.1 mm Flow Cell	Replacement cell 0.1 mm pathlength	08856
0.3 mm Flow Cell	Replacement cell 0.3 mm pathlength	08632

SP4 Spare Parts

Item	Description	Part Number
Fraction Collector		
UV collect valve Needle	(1/6 inch OD x .030 Inch ID x 1.83L)	08173
Nut	1/6inch Flangeless Fer 1/4-28 Peek	04794
Ferrule	Flangeless 1/16 Tefzel	04009
Valve Assembly	UV Collect 3-Way	09321
Fuse	5 X 20MM 2.5A / 250V	09367
Adapter	40mm to 25mm Flash+ Module Rack	07482
Adapter	40mm to 12mm Flash+ Module Rack	07481
Operator's Manual	CD SP4	09653
Software Sp4		09701
Pump		
Valve	10 psi Max NC Collar Mount	09472
Disk	Check 3/16 inch Balls Assembly Quad3	05516
Lip seal	0.500 OD x .312 ID 302 SST Spring	08192
Ring	Wear .500 OD X .370 ID Quad1	06785
Valve	30 psi Max NC Collar Mount	09470
Valve	150 psi Max NC Collar Mount	09468
Tube Assembly	Solvent Inlet 5' Color Red Sp4B/Sp1	09664-01
Tube Assembly	Solvent Inlet 5' Color Blue Sp4B/Sp1	09664-02
Tube Assembly	Solvent Inlet 5' Color Green Sp4B/Sp1	09664-03
Tube Assembly	Solvent Inlet 5' Color Gold Sp4B/Sp1	09664-04
Filter	Inlet Solvent for 3/16 In OD Tubing 20 um Porosity 316 SST	09376
Tubing	3/16 OD x .125 ID Teflon FEP	09314
Nut	Flangeless 3/16T x 5/16-24 Peek Natural	09311
Ferrule	Flangeless 3/16 Tubing	09312
Tube Assembly	Compression Module Outlet to Flow Path Module Inlet, Sp4B	09665
Tube Assembly	Flow Path Module Outlet to Compression Module Inlet, Sp4B	09666
Union	1/4 T X 1/8 T W/ Knurled Nut & PFA Ferrules	04144
Tube Assembly	Flow Path Module UV Det Outlet to Flow Cell Inlet Sp4B	09667
Nut	1/8 Flangeless 1/4-28 Peek	08399
Tube Assembly	Waste Outlet 6' Sp4B	09668
Ferrule	Set 1/8 316 SS	01037
Tubing	1/8 OD x .062 ID FEP	00088
Nut	1/8inch Flangeless Fer 5/16-24 Peek	04795
Ferrule	Flangeless 1/8 Tefzel	04030
Tube Assembly	Collect Valve To Flow Cell Outlet & Flow Path Module Waste Inlet Sp4B	09669
Nut	1/8 T Short Flangeless, 1/4-28 PEEK	08394
Nut	1/8 Flangeless 1/4-28 Peek Blue	08372
Tubing	1/8 OD x .062 ID FEP	00088
Nut	1/8 Flangeless 1/4-28 Peek	08399
Nut	1/8inch Flangeless Fer 5/16-24 Peek	04795
Ferrule	Flangeless 1/8 Tefzel	04030

SP4 Spare Parts continued...

Item	Description	Part Number
Tube Assembly	1/4 inch Trough Drain Tube Horizon Flash Collector	08432
Ferrule,	Set 1/4 316 SS	01634
Nut	1/4 Tube 316 SS	01635
Tubing	1/4 OD x .040 Wall FEP Teflon	00089
UV Detector		
Lamp	Mercury UV Fixed Wavelength 254nm	09427
Lamp	UV Variable Wavelength	09427
0.1 mm Flow Cell		08856
0.3 mm Flow Cell		08632
Reducing Union	1/4" x 1/8" reducing union (4 required per set)	04144

Service Rates

Item	Description	Part Number
Hourly rate		
Off-Site Service	Per hour	SER-002-0001
In-House Service	Per hour	SER-002-0002
Daily rate		
Off-Site Service	Per day	SER-0001-LBR
Travel Charges		
Zone A	Local travel 1-50 miles or 1-75 km	SER-0ZA-TRVL
Zone B	Local travel 51-100 miles or 76-150 km	
Zone 1	Travel 101-200 miles or 151-300 km	SER-0Z1-TRVL
Zone 2	Travel 201-500 miles or 301-750 km	SER-0Z2-TRVL
Zone 3	Travel 501-1000 miles or 751-1500 km	SER-0Z3-TRVL
Zone 4	Travel 1001-2000 miles or 1501-3000 km	SER-0Z4-TRVL
Zone 5	Special travel	SER-0Z5-TRVL

Limited Warranty

FLASH™, QUAD™, HORIZON™, PIONEER™, Sp4™, PARALLEX™ CHROMATOGRAPHY, SYSTEMS INITIATOR™, CREATOR™, OPTIMIZER™, & ADVANCER™ SYNTHESIS SYSTEMS:

Limited Instrumentation Warranty. Biotage warrants for a period of twelve months from the date of shipment that the instrumentation products included in any FLASH, Quad, Horizon, Pioneer, Sp4, Parallex, Initiator, Emrys Creator, Emrys Optimizer, Emrys Advancer, or other Chromatography or Synthesis Systems (the "System") shall be free from defects in material and workmanship under normal use and service and when used in compliance with the applicable operating instructions. The limited instrumentation warranty is subject to the conditions set forth below.

(1) Biotage's obligation under this warranty is expressly limited at Biotage's sole discretion to the repair or replacement of the defective instrument part or item, all other damage and claims, statutory or otherwise, being hereby expressly waived by the Customer. Biotage may discharge this obligation in full either by repairing the instrument or by shipping F.O.B. to the Customer, the original site of delivery, a similar instrument part or item; provided, however, that as a condition precedent to this obligation, the Customer must have notified Biotage during the warranty period of any alleged defect, and provided further that Biotage must, after examination of the part or item, reasonably agree that the part or item is defective.

(2) This limited warranty is for the benefit of and applies only to the Customer.

(3) This warranty does not apply to any consumable items included in the System such as tubing, fittings, o-rings and gaskets, or any other part that comes in contact with the sample path.

(4) This warranty does not apply to any computer hardware delivered for use with the System, as any such computer hardware will be subject to applicable manufacturers' warranties.

(5) This warranty does not apply to failure or damage to the System incurred through neglect, lack of maintenance, misuse or accident or to improper installation, runaway microwave reactions induced by the customer, redesigning or repair by Customer or by anyone other than Biotage or its authorized agents or through any cause beyond the reasonable control of Biotage.

(6) No representative of Biotage is authorized to commit Biotage to any warranty other than the warranty contained herein.

Limited Warranty of Biotage Software Performance. Biotage warrants for a period of twelve months from the date of shipment (the "Warranty Period") that the Biotage Software will, when used in the designated operating environment, perform materially in accordance with the applicable specifications. The foregoing warranty shall apply only to the most current version of the Biotage Software that was supplied to the Customer by Biotage. The limited warranty is subject to the conditions set forth below.

(1) The Customer must give written notice to Biotage during the Warranty Period with an explanation of the circumstances of any claim that the computer programs or software fail to conform to this limited warranty.

(2) The Customer's sole and exclusive remedy in the event of any such failure is expressly limited to the correction or replacement of the defective computer program or software or the refund of the fees paid for the non-conforming computer program or software.

(3) Biotage does not warrant that the operation of the computer programs or software will be uninterrupted or error free.

(4) This limited warranty is for the benefit of and applies only to the Customer.

(5) This limited warranty does not apply to any third party operating system software included with the personal computer provided to Customer by Biotage, as any such computer software will be subject to applicable manufacturer's warranties.

(6) The limited warranty shall not apply to any Biotage Software that has been improperly installed or modified by Customer or any third party or which has been the subject of neglect, misuse, abuse, misapplication or alteration or has been used in violation of the applicable software license agreement.

(7) No representative of Biotage is authorized to commit Biotage to any warranty other than the warranty contained herein.

PURIFICATION CARTRIDGES and MICROWAVE REACTION VIALS (CONSUMABLES)

Biotage warrants that Biotage Consumables will be of good quality and workmanship, and will meet the applicable product specification. This warranty applies only to the initial test performed at the Customer’s facility upon the initial start-up of the consumables and expires at the time the user applies an actual sample to the consumable. If the cartridge is packed with media provided by the Customer, the Biotage warranty applies only to the plastic tube, frits, and labor required for packing and testing the cartridge. Biotage will not be liable for

any damage to media provided by the Customer that may be caused when Biotage packs such media in accordance with Biotage's standard operating procedures.

Should any Biotage consumable fail to meet the limited warranty above after being tested in accordance with the applicable Biotage standard operating procedures, Biotage will provide, at its sole option, either a replacement cartridge or reaction vial. If a cartridge, it will be packed with the original media, or packed with new media, at no cost to the Purchaser. If such failed cartridge is packed with media provided by the Purchaser, Biotage will make a reasonable effort to re-pack the original media, or pack a replacement cartridge with new media provided by the Purchaser.

Returns of any Consumable must be authorized in advance. Please contact Biotage for a Return Authorization (RA) number and shipping instructions. All claims must be made within thirty (30) days of shipment from Biotage, or after the initial test of the cartridge at the Customer's facility, whichever is first.

Special Request and Custom-Packed Media Cartridges

Biotage provides a limited warranty for each of its Custom-Packed Cartridges and Special Request Cartridges as is set forth in the applicable custom order quotation furnished to the Customer.

Biotage warrants that Biotage Custom-Packed cartridges and Special Request cartridges will be of good quality and workmanship. Each cartridge is packed to a density specification unique to each media and Biotage warrants the cartridge dimensions, and weight of the packed media and specifies no void exist in the media bed. Biotage does not warranty specific plate count, peak symmetry, or separation for any compounds.

For the Custom-Packed Cartridges where the cartridge is packed with media provided by the Customer, the Biotage warranty applies only to the plastic tube, frits, and labor required for packing of the cartridge. Biotage will not be liable for any damage to media provided by the Customer that may be caused when Biotage packs such media in accordance with Biotage's standard operating procedures.

If the Custom-Packed cartridge fails, Biotage will make a reasonable effort to re-pack the original media, or pack a replacement cartridge with new media provided by the Purchaser.

Should any Special Request cartridges fail, Biotage will make a reasonable effort to re-pack the original media in a replacement cartridge.

Return of the Custom-Packed or Special Request Cartridge is not permissible once the user applies a sample to the cartridge. This is in compliance to government OSHA and TOSCA regulations.

KILOPREP® CHROMATOGRAPHY SYSTEMS

Biotage provides the limited warranty for each of its Kiloprep Chromatography Systems as is set forth in the applicable System quotation furnished to the Customer.

TERMS AND CONDITIONS

1 TERMS OF SALE. Purchase of the products and services can only be made pursuant to the terms of the invoice that are set forth herein. Receipt of the products or commencement of the services shall be deemed acceptance by Customer of the terms and conditions at time of invoice.

2 PAYMENT TERMS. In addition to the prices invoiced, Customer shall pay any tax, duty, custom or other fee of any nature imposed upon the transaction by any federal, state or local government authority. In the event Biotage is required to prepay any such tax or fee, Customer will reimburse Biotage. Payment terms shall be net thirty (30) days. In addition Biotage reserves the right, in its sole discretion, to require C.O.D. payment terms from any Customer. Biotage may also refuse to sell to any Customer until all prior overdue accounts are paid in full.

3 DELIVERIES AND SHIPMENT. Unless otherwise noted on the invoice, all Products are delivered F.O.B. to Charlottesville, Virginia. Customer assumes all risk of loss or damage upon shipment. Biotage shall use commercially reasonable efforts to deliver the Products or provide the Services invoiced hereunder in accordance with the estimated delivery date, provided that Biotage shall not be liable for any losses or for general, special or consequential damages arising out of any delays.

4 WARRANTY. The Products and Services shall be provided with the applicable system standard warranty, copies of which are available upon request and will be furnished with the Products. The applicable standard warranty is in lieu of all other warranties with respect to the products and services, expressed or implied, including, but not limited to, the implied warranties of merchantability, fitness for a particular purpose and non-infringement.

5 LIMITATION OF LIABILITY. Unless otherwise prohibited by applicable law, Biotage's total liability whether for breach of warranty or contract, tort (including negligence) or otherwise shall in no event exceed the amount paid by Customer to Biotage for the product or service alleged to have caused the damage to Customer. In no event shall Biotage be liable to the Customer for any consequential or incidental damages, including but not limited to, damages due to loss of data or information or loss of use, loss of profits or loss of revenue, even if Biotage has been advised of the possibility of such damages, nor shall Biotage have any liability for any claim of any third party.

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8 EXPORT. Customer shall comply fully with all applicable provisions of the United States Export Control Laws as may be in effect for any of the Products and shall seek, whenever required and at its own expense, export licenses from the United States Department of Commerce prior to any export of the Products and shall further assure compliance with all re-export restrictions of such United States Export Control Laws.

9 GENERAL. These terms and conditions can only be modified by a written agreement duly signed by persons authorized to sign agreements on behalf of Biotage and Customer. Any variance from the terms and conditions listed in any order or other written notification from the Customer will be of no affect. If any provisions of these terms and conditions shall be held to be invalid, illegal or unenforceable, the validity, legality and enforceability of the remaining provisions shall not in any way be affected or impaired thereby. These terms and conditions will be governed by the laws of the Commonwealth of Virginia.

Returns Policy

Returns of any product must be authorized in advance. Please contact Biotage for a Return Authorization (RA) number and shipping instructions. All claims must be made within thirty (30) days of shipment from Biotage, or after the initial test at the Purchaser's facility, whichever is first.

Patent Indemnification

Biotage warrants that the Goods as delivered to Buyer do not infringe any valid claim under any issued USA or EC patent. Biotage will defend Buyer, at Biotage's expense, against any claim of infringement, provided Buyer gives Biotage sole control in the defense and any related settlement negotiations, and cooperates with Biotage in the defense of such claim. In the event that the use of the Goods is enjoined, Biotage, at its sole option will either (i) procure a license to use, (ii) or replace or modify the Goods with substantially equivalent non-enjoined Goods, (iii) or refund the full purchase price. Biotage has no other liability in the event of a patent infringement claim.

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BIOTAGE WILL NOT BE LIABLE IN ANY EVENT FOR SPECIAL, INDIRECT OR CONSEQUENTIAL DAMAGES WHETHER ARISING IN TORT, UNDER ANY WARRANTY OR OTHERWISE.

Patent Acknowledgements

U.S. Patents 4,900,537, 5,089,124, 5,112,492, 5,139,661, 5,167,822, 5,186,838, 5,200,069, 5,223,142, 5,242,586, 5,601,708, 6,019,897, 6,068,766, 6,090,278, 6,074,556, 6,117,329, 6,132,605, 6,136,157, 6,139,733, 6,149,403, 6,168,400, 6,200,113, 6,221,252, 6,294,087, 6,403,939, 6,398,953, 6,436,284, 6,551,467, 6,596,130, 6,614,010, 6,629,626, 6,630,654, 6,649,051, 6,652,746, 6,720,540 and other patents-pending.

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