

Analytix

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Analytical

Riedel-deHaën

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HYDRANAL® reagents

30



- Microbiological Food Tests
- CRMs for ICP
- CRMs for Herbal Drugs
- Chiral Derivatisation of Amino Acids
- Ion Exchange Media

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Andrea Felgner
Product Manager
Analytical Reagents

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With kind regards,

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Product Manager Analytical Reagents
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Celebrating 30 years of HYDRANAL® reagents

Outstanding Performance and Excellent Quality for Karl Fischer Titration

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When Riedel-de Haën researchers Eugen Scholz and Helga Hoffmann began their investigations of the Karl Fischer (KF) reagents in 1979, this method for water determination was already a widely used technique. However, there was clearly room for development. Safety, water and buffer capacity, reaction rate and sample solution were only some of the reagent characteristics that needed improvement. Ground-breaking efforts were required to address persistent issues that prevented widespread implementation. Thus, the HYDRANAL product family was founded, and today HYDRANAL is used around the globe in every industry sector, from foods to semi-conductors, from pharmaceuticals to petrochemicals.

Water content is an important parameter, primarily for production processes, chemical processes and reactions, product stability, shelf life, and microbiological growth. The constant need for a defined reliable and feasible method for water determination had led German chemist Karl Fischer to his research and finally to the publication of his manuscript "New procedure for the determination of the water content in liquids and solids" in 1935 [1].

The water determination procedure documented by Karl Fischer became a widely used analytical method. However, performing this analysis was neither safe nor pleasant for laboratory employees at the time. Malodorous, toxic ingre-

dients in the KF reagents, as well as slow reactions and unclear endpoints, called for improvement of Karl Fischer's original formulation.

In 1979, researchers Eugen Scholz and Helga Hoffmann at Riedel-de Haën started their research in the field of KF titration, aiming to improve reagents' safety, yield more accurate results, simplify use and handling, and extend utilisation of KF methodology to a wider range of substances through elimination of unwanted side reactions and enhancement of sample solubility. As a result, the first members of the HYDRANAL product family were launched in 1980: HYDRANAL Solvent, Titrant and Composite, the first pyridine-free HYDRANAL KF reagents.

Ongoing research led to improvements in reagent characteristics such as safety, buffering capacity, and water capacity, and pressed beyond towards the development of an innovative product line of HYDRANAL reagents, including:

- Coulometric reagents free of halogenated hydrocarbons
- Reference standards for water content
- Methanol-free K-reagents for elimination of side reactions caused by aldehydes and ketones
- Ethanol-based non-toxic E-type reagents
- Reagents containing solubilisers for increased sample solubility





Based upon the results of Dr. Scholz and his team's investigations, patents were received for many of the new HYDRANAL® reagents and their use. So far, more than fifty patents have been issued or are pending in Europe, the US, Japan and other countries. Dr. Scholz's results have also been published in several journals and a book about KF titration [2].

Advantages and chemical characteristics of HYDRANAL KF reagents include:

- Broad variety: volumetric and coulometric reagents, water standards and auxiliary reagents
- Safety: all HYDRANAL products are free of pyridine, carbon tetrachloride, and 2-methoxyethanol
- Highest quality: large water capacity, high reaction speed, stable end points, excellent reproducibility, accurate results
- Extensive storage stability and extensive shelf-life
- Ethanol-based non-toxic products available
- Products without halogenated hydrocarbons available
- No crystallisation (patented formulation)
- Universal applicability: suitable for water content determination in a very wide range of samples
- Production and expiry date on the bottle
- Poly-coated bottles available for USA & Canada



Over the years, we have advanced research efforts in the utilisation of KF titration and established a solid knowledge base. Sigma-Aldrich's HYDRANAL service labs in Germany and in the USA provide constant customer support in the use of HYDRANAL reagents and KF techniques for sample as well as analytical requirements.

This technical help includes solving technical problems such as sample solubility or side reactions, selecting the appropriate KF reagent for specific needs, and providing assistance for the analysis of challenging samples; application reports for over 600 different samples are available. We also offer extensive literature support such as our HYDRANAL manual, a CD guide for KF titration, videos of KF titration techniques and a selection of brochures, as well as regular KF seminars for interested customers.

References

- [1] K. Fischer, "Neues Verfahren zur Bestimmung des Wassergehaltes in Flüssigkeiten und Feststoffen." *Angew. Chemie* 1935, 48, 394.
- [2] E. Scholz, "Karl-Fischer-Titration. Methoden zur Wasserbestimmung." Springer Verlag, Berlin, Heidelberg, New York, Tokyo, 1984 (ISBN 3-540-12846-8 German Edition, ISBN 3-540-13734-3 English Edition).

For more details about HYDRANAL reagents, please visit our website sigma-aldrich.com/hydranal

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Microbiological Control of Spices and Herbs

Cultures around the world rely on herbs and spices to add flavour and zest to food. Many spices, however, contain very high numbers of bacteria, making them a potent source for food spoilage and pathogens.

To study the microbiological status of herbs and spices, E. de Boer et al. [1] tested 150 samples collected from 54 different spices, spice mixtures and herbs. They reported at least 1,000 organisms per gram, with most spices containing 10^5 - 10^6 cells per gram. A high number of psychotropic bacteria, yeasts and Enterobacteriaceae was detected mainly on herbal spices originating in moderate climate areas. The study also reported high mould counts, identifying *Aspergillus niger*, *A. flavus*, *A. tamarii*, *Penicillium citrinium*, *P. chrysogenum*, and *Absidia corymbifera* as the most frequent isolated species. Since *A. flavus* may produce aflatoxins, one of the most potent naturally occurring toxins, its presence should be a matter of concern and monitored closely by the spice industry. Another serious potential public health risk may involve the presence of pathogenic bacteria; frequently reported species are *Clostridium perfringens*, *Bacillus cereus* and *Salmonella*.

Several issues present a challenge in the microbiological study of dried herbs and spices. Dryness, inhibiting substances, high osmotic pressure, and other adverse conditions heavily stress the cells. Long stress periods can eventually lead the cells to a "viable but not culturable" (VNC) state. In a VNC state, the microbes cannot grow on conventional laboratory plating media but may revive in vivo and cause disease. However, with the addition of certain growth factors, traditional media can be upgraded and VNC organisms can be resuscitated.

Organisms	ng/mL
<i>Salmonella</i>	75
<i>Cronobacter</i> spp. (<i>Enterobacter sakazakii</i>)	150
<i>Yersinia enterocolitica</i>	100

Table 1 Recommended end concentration of ferrioxamine E

One of these growth factors is ferrioxamine E, which significantly improves the recovery of *Salmonella*, *Cronobacter* spp., *Staphylococcus aureus* and *Yersinia enterocolitica* from contaminated foods [2-4]. A concentration of ferrioxamine E (available from Fluka, see **Table 2**) in the range of 5-200 ng/mL supports reproducible growth (see **Table 1**). Ferrioxamine E provides the essential bio-available form of micro-nutrient iron (III) to the organisms (see **Figure 2**). This leads

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Did you know?



The combination of garlic and clove is able to kill 99% of *E. coli* in Salami. (Source Institute of Food Technologists 1998)

Figure 1 Spices of plant origin

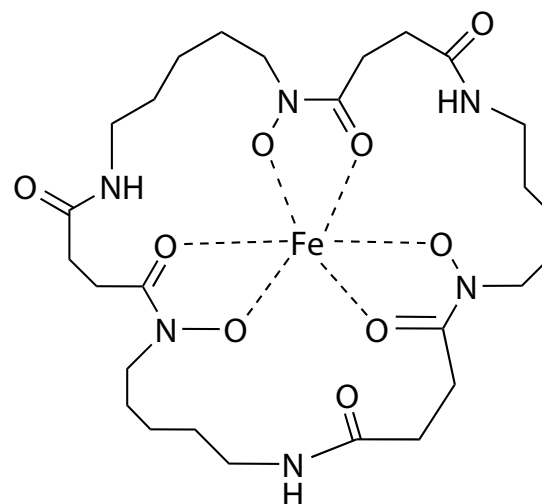


Figure 2 Structure of ferrioxamine E

to a reduced lag-phase in the medium and reactivates damaged bacteria, leading to optimal microbial analyses.

Product	Brand	Cat. No.
Ferrioxamine E	Fluka	38266
NEW Peptone Water, phosphate-buffered with Ferrioxamine E	Fluka	67331

Table 2 Ferrioxamine E products

In addition, Sigma-Aldrich offers an extensive product line of classical nutritional media for the detection, isolation and identification of organisms. These media are officially used for the microbiological control of spices and herbs. The most important media are listed in **Table 3**.

Specificity	Name	Brand	Cat. No.
<i>B. cereus</i>	Cereus Selective Agar	FLUKA	22310
	HiCrome™ Bacillus Agar	FLUKA	92325
<i>B. cereus</i> /Enterobacteriaceae	Glucose Bromcresol Purple Agar	FLUKA	16447
<i>C. perfringens</i>	Lactose Gelatin Medium (Base)	FLUKA	61348
	Liver Broth	FLUKA	61724
	Motility Nitrate Medium	FLUKA	14305
	TSC Agar	FLUKA	93745
Coliform/E.coli	Brilliant Green Bile Lactose Broth	FLUKA	16025
	EC Broth	FLUKA	44653
	Lauryl sulfate Broth	FLUKA	17349
	m-Lauryl Sulfate Broth	FLUKA	07348
	VRB MUG Agar	FLUKA	95273
Enterobacteriaceae	China Blue Lactose Agar	FLUKA	22520
	Levine EMB Agar	FLUKA	62087
	Lysine Iron Agar	FLUKA	62915
	Methyl Red Voges Proskauer Saline Broth	FLUKA	69150
	Triple Sugar Iron Agar	FLUKA	44940
	Violet Red Bile Agar	FLUKA	70188
Enterococci	Bile Esculin Agar	FLUKA	48300
	KF-Streptococcus Agar	FLUKA	60641
Lactobacilli	Rogosa Agar	FLUKA	83920
<i>Salmonella</i>	SS-Agar	FLUKA	85640
	Bismuth sulfite Agar	FLUKA	95388
	Tetrathionate Enrichment Broth according to Muller-Kauffmann	FLUKA	88148
<i>S. aureus</i>	Baird Parker Agar	FLUKA	11705
Total Count	Vogel-Johnson Agar	FLUKA	70195
	Brain Heart Infusion Broth	FLUKA	53286
Yeasts	Czapek Dox Agar	FLUKA	70185
	Plate Count Agar	FLUKA	70152
	Plate Count Agar according to Buchbinder et al.	FLUKA	88588
	Plate Count MUG Agar	FLUKA	51413
	Wort Agar	FLUKA	70196

Table 3 Media used for the microbiological control of spices



Figure 3 HiCrome™ Bacillus Agar

References:

- [1] E. de Boer et al., Microbiology of spices and herbs, Antonie van Leeuwenhoek, Volume 51, Number 4, 435–438, Springer Netherlands (1985).
- [2] S. Makino, et al., Does Enterohemorrhagic *Escherichia coli* O157:H7 Enter the Viable but Nonculturable State in Salted Salmon Roe?, Appl. Environ. Microbiol., 66 (12): 5536–5539 (2000).
- [3] I. Barcina, P. Lebaron, J. Vives-Rego, Survival of allochthonous bacteria in aquatic systems: a biological approach, FEMS Microbiol. Ecol., 23:1–9 (1997).
- [4] J.C. Choa, S.J. Kim, Viable, but non-culturable, state of a green fluorescence protein-tagged environmental isolate of *Salmonella typhi* in groundwater and pond water, FEMS Microbiol. Lett., 170:257–264 (1999).

Are your Reference Materials up to Standard?



Laboratory technical managers recognise that reference materials are critical supplies that underpin the validity of method validation, equipment calibration, and the traceability of all measurements made by the laboratory. In these laboratories, ISO 9001 certification held by reference material producers (RMPs) has historically been regarded as a reliable demonstration of the competence and suitability of the supplied reference materials. This has been particularly true of analytical laboratories in the chemical analysis sector. Because of the critical role that reference materials hold, it has become increasingly imperative that laboratory technical managers establish the quality of reference materials beyond the inferences made from only the ISO 9001 certification of the RMPs.

The United Kingdom Accreditation Service (UKAS) has recognised this need and is proactive in providing guidelines in support of increased quality efforts. UKAS stands apart as the sole accreditation body recognised by the United Kingdom. UKAS embodies over 40 years of experience in accreditation, and during that time the principles of accreditation have been maintained while adapted to changes in technology, markets and regulations. The core accreditation principle mandates that businesses demonstrate competence, reliability and accuracy, and this directive has endured at UKAS. Accreditation offers reference material producers many commercial benefits including the opportunity to be able to compete in an ever-increasing and evolving marketplace.

Following the publication of TPS 57 in 2006, UKAS has required laboratories to conduct more in-depth evaluations of the producers of their reference materials, and to provide UKAS with justifications as to why they have deemed the producer competent. As such, RMPs have been coming under increased scrutiny from their customers who are seeking assurance as to the RMPs' competence to produce reference materials and the suitability of these materials.

Jeff Ruddle, Accreditation Manager jr@ukas.com

As a result, many RMPs are now looking to accreditation as a meaningful demonstration of their competence. In 2006, UKAS accredited several RMPs to ISO Guide 34 "General requirements for the competence of reference material producers". Prior to this, UKAS has been accrediting RMPs to ISO/IEC 17025 (calibration). In addition, many other accreditation bodies have seen an increase in applications from RMPs as the demand for confidence in their products grows. In particular, RMPs increasingly see accreditation to ISO Guide 34 as the most relevant accreditation standard for their business.



Laboratories have now begun to recognise that in order to have confidence in these critical reference materials – materials that underpin the day-to-day measurements they perform – it is necessary to have confidence in the competence of the RMP that produced the reference material. This refers not only to the confidence that the RMP makes accurate measurements (as would be assured by ISO/IEC 17025 calibration accreditation) but also in their ability to both determine the stability and homogeneity of the material and store and distribute it in a way that does not affect its validity. Accreditation of an RMP to ISO Guide 34 provides this level of confidence.

However, the process of evaluating suppliers can be challenging for many laboratories. Some of these challenges result from the broad use of the term 'Reference Materials' which encompasses Matrix Reference Materials, Pure Materials, Certified Reference Materials, Calibration Standards and Quality Control Reference Materials.

Once the relevant terminology is understood, laboratories must determine the suitability of each of these different types of reference materials in their respective applications. This exercise can be successfully approached by first asking, "What is the reference material being used for, and therefore what are our requirements that the reference material will need to meet?" Once these questions have been answered, the laboratory should be in a position to evaluate the RMP that will be providing the reference material.

There are many uses for reference materials within analytical laboratories and therefore the criteria for their selection vary. Some of the key criteria and questions that need to be considered when determining the suitability of a reference material and its producer are:

- **Traceability** – Is the reference material being purchased going to be used for calibration? If yes, then the traceability of the material needs to be linked to a higher standard (preferably national or international).
- **Homogeneity** – Is there a potential for heterogeneity within the reference material, and if so, how homogenous does the reference material need to be for the proposed application?
- **Stability** – How long does the reference material need to be stable, and has its stability in use and transit been checked?

Purchasers of reference materials can be confident when engaging the services of an RMP accredited to ISO Guide 34 that these issues will have been addressed and statements relating to the above issues will have been robustly determined.

However, if the purchaser has engaged an organisation that holds a different kind of third-party verification, then further investigation will be required. Examples include:

- ISO/IEC 17025 calibration accreditation provides confidence in the traceability of the assigned values, though the purchaser will still need to confirm any issues relating to the stability and homogeneity of the reference material.
- ISO/IEC 17025 testing accreditation may provide confidence in the traceability of the assigned values, though the purchaser will still need to confirm this and any issues relating to the stability and homogeneity of the reference material.
- ISO 9001 certification from an accredited certification body provides confidence in the quality system of the RMP. However, confidence in the technical competence of the RMP is not assured and further investigations are required.

If you wish to discuss the requirements for selection of reference materials or want to discuss becoming accredited as a reference material producer, please contact your National Accreditation Body or Jeff Ruddle on +44 (0)208 917 8519 or jr@ukas.com

New 10g/L TraceCERT® Single Element Standards for ICP

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Our Fluka-branded TraceCERT standards are developed and produced according to ISO/IEC 17025 and ISO Guide 34 [1, 2]. This is the highest achievable quality standard for producers of certified reference materials (CRM). For the production, we use very well characterised highest-purity starting materials. TraceCERT CRM are traceable to at least two independent references (i.e. NIST, BAM or SI unit kg) and are delivered together with a comprehensive documentation including a proper uncertainty calculation, expiry date and storing/handling instructions.

The portfolio of 1 g/L single-element standard solutions for ICP as well as for AAS includes standards for more than 40 different elements so far, and is continually expanded. For the most commonly used single-element standards, we now also offer concentrated solutions at 10 g/L for ICP. Equal to the 1 g/L ICP solutions, these products are supplied in 100 mL HDPE bottles sealed in an aluminium bag. Owing to this sophisticated packaging, the standards have low uncertainties and a shelf life of four years. The printed certificates are delivered with the product and list up to 70 trace impurities.

In the table below, the new ICP concentrates are listed. For the complete TraceCERT product portfolio and for further information on the TraceCERT line, please visit sigma-aldrich.com/tracecert or order our new TraceCERT brochure.

References:

[1] TraceCERT Traceable Certified Reference Materials, Analytix, Vol 5, 2006; Analytix Vol 1–4, 2007.

[2] "Double Accreditation brings a new class of CRMs" Analytix, Vol 2, 2008.

Element (10 g/L)	Composition	Cat. No.	Pack Size
Aluminum	Al(NO ₃) ₃ x 9H ₂ O in 5% HNO ₃	41377	100 mL
Calcium	CaCO ₃ in 5% HNO ₃	94458	100 mL
Copper	Cu metal in 5% HNO ₃	94459	100 mL
Iron	Fe metal in 5% HNO ₃	56209	100 mL
Magnesium	Mg metal in 5% HNO ₃	80759	100 mL
Nickel	Ni metal in 5% HNO ₃	19013	100 mL
Phosphorous	H ₃ PO ₄ in H ₂ O	19916	100 mL
Potassium	KNO ₃ in 5% HNO ₃	68371	100 mL
Silicon	Si metal in 5% HNO ₃ and 0.1%HF	04713	100 mL
Sodium	NaNO ₃ in 5% HNO ₃	39924	100 mL
Sulfur	H ₂ SO ₄ in H ₂ O	94430	100 mL
Zinc	Zn metal in 5% HNO ₃	68961	100 mL



TraceCERT®
Inorganic CRMs

- Certified Reference Materials for **AAS**, **ICP** and **IC**
- Production in accordance with **ISO/IEC 17025** and **ISO Guide 34**
- Highest accuracy and reliability of certified concentrations
- Traceability to at least two independent references (i.e. NIST, BAM or SI unit kg)

For more information, please visit our website at sigma-aldrich.com/tracecert or order the brand new TraceCERT brochure using the BRC of this issue.

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Application of Reference Standards in the Analysis of Herbal Medicinal Products

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Figure 1 Hawthorn (*Crataegus monogyna*)

In collaboration with HWI ANALYTIK, Sigma-Aldrich is launching a new product line of primary reference standards for use in the quality control, in-process control and stability testing of herbal medicinal products.

These standards are produced and qualified by HWI ANALYTIK in Ruelzheim (Germany), and are exclusively distributed by Sigma-Aldrich. A first series of 23 standards is listed in **Table 1**. The unique and novel certification concept of these reference standards is based on the quantitative NMR technique (qNMR) for content assignment. The application of qNMR, a relative primary method of measurement, is advantageous compared to the usual combination of two chromatographic methods, Karl Fischer titration and residual solvent determination due to higher reliability of the certified content value. The analytical report delivered with these products contains two identity proofs, the content by qNMR and the chromatographic purity. Comprehensive documentation on further parameters, detailed method descriptions and validation data can be ordered on request directly from HWI ANALYTIK.

While the following article in this issue (page 14 f) focuses on the content assignment of these standards by quantitative NMR, this article addresses the applications of reference standards in the analysis of herbal medicinal products.

Reference standards used for pharmaceutical analysis in a GMP environment are standards for qualitative and/or quantitative determinations within the scope of in-process controls, batch release analyses and stability studies of herbal drugs, herbal preparations and finished products. In case of herbal medicinal products, the reference standard may be a standard specimen of the drug, the drug preparation (e. g. extract or tincture) or a chemically defined substance. Regarding the latter case, only a limited number of herbal substances and herbal preparations possess constituents which are generally accepted to contribute substantially to their therapeutic activity. These are defined as 'constituents with known therapeutic activity', e. g. sennosides in preparations from senna leaves or fruits. However, for the majority of herbal substances and herbal preparations, the constituents or groups of constituents responsible for the therapeutic activity are not yet known. In some cases, certain constituents or groups of constituents may be generally accepted to contribute to the therapeutic activity but are not responsible for the full therapeutic effect. Such constituents or groups of constituents are useful for control purposes and are defined as 'active markers'. Distinct from them, analytical markers are constituents or groups of constituents that serve solely for analytical purposes [1].

(continued on page 12)



Figure 2 Lemon balm (*Melissa officinalis*)

Markers are used for both quantitative and qualitative purposes. For all kinds of analytes – constituents with known therapeutic activity, active and analytical markers – there is a need to establish reference standards for quality control and stability testing of herbal preparations and herbal medicinal products.

In the pharmaceutical environment, a primary reference standard initially needs to be established and certified. Its content should be assigned without requiring comparison to another chemical substance. Primary reference standards in pharmaceutical analysis are of a defined purity. A comprehensive documentation needs to be filed for the marketing authorisation dossier. The process of establishment, certification and content of documentation to be filed has recently been described by Veit and Wissel [2, 3].

For routine analysis, working standards may be used. Working standards are secondary standards serving as ready-to-use reference standards for the testing. They are derived from primary reference standards by intercalibration. The extent of characterisation and testing of a secondary chemical reference substance is less than that of a primary chemical reference substance.

Great difficulties may arise when it comes to establishing natural product standards for use in identity testing and assays by the application of constituents with known therapeutic activities or (active) markers. Substances of natural origin usually display a complex molecular structure, which is why they are hardly accessible synthetically and quite frequently have to be isolated from the natural sources. Hence, establishing primary standards for the quality analysis of herbal medicinal products is often very complex and requires special know-how. Additional problems then arise due to the small amounts accessible this way, thus requiring an elaborate concept for the storage and employment of such standards. Special suppliers have therefore started to establish, store and manage the primary standards at a central site and supply their customers with qualified working standards that are ready to use.

Product Name	Prod. No.	Pack Size
Bisabolol oxide A, primary reference standard	00630590	25 mg
Chlorogenic acid, primary reference standard	00500590	10 mg
Coumarin, primary reference standard	01260595	25 mg
Ginkgolide A, primary reference standard	00770590	10 mg
* Ginkgolic acid C15:1, primary reference standard	02580185	10 mg
Ginkgolic acid C17:1, primary reference standard	01390590	10 mg
Ginsenoside Rb1, primary reference standard	00170580	10 mg
Ginsenoside Rg1, primary reference standard	00370580	10 mg
Harpagoside, primary reference standard	00420580	10 mg
Hulupinic acid, primary reference standard	01090595	10 mg
* Hypericin, primary reference standard	00190180	10 mg
Hyperoside, primary reference standard	00180585	10 mg
Isoquercitrin, primary reference standard	00140585	10 mg
Quercetin dihydrate, primary reference standard	00200595	50 mg
Quercitrin, primary reference standard	00740580	10 mg
Rosmarinic acid, primary reference standard	00390580	10 mg
Rutin trihydrate, primary reference standard	00300590	50 mg
Sennoside A, primary reference standard	01870575	10 mg
Sennoside B, primary reference standard	00530580	10 mg
Silibinin, primary reference standard	02000585	10 mg
Valerenic acid, primary reference standard	02010595	10 mg
Vitexin-2"-O-rhamnoside, primary reference standard	00660585	10 mg
Xanthohumol, primary reference standard	01130595	10 mg

Table 1 Primary Reference Standards from HWI ANALYTIK exclusively available at Sigma-Aldrich

* for Ginkgolic acid C15:1 and Hypericin, the content determination by qNMR was not applicable due to overlapping signals. For these two products, the content has been assigned by the usual mode combining two chromatographic methods, water content by Karl Fischer and determination of residual solvents and of inorganic compounds.

Batch-specific control of a herbal medicinal product containing extracts of lemon balm and hawthorn

In herbal medicinal products containing more than one herbal preparation, the choice of appropriate reference standards becomes far more challenging, because substances usually used as reference standards for a dedicated plant may occur in the other component of the combination drug, too. Due to this challenge, reference standards for a combination product should be selected in such a way that they are characteristic for each individual herbal preparation in the product. In the following example, the batch-specific control of a herbal medicinal product with the two main components, lemon balm and hawthorn, is presented.

For the quantification of hawthorn, the constituent vitexin-2"-O-rhamnoside is used as an analytical marker (chromatogram and the structure of the reference standard vitexin-2"-O-rhamnoside are shown in **Figure 3a**). The chromatogram of an extract of hawthorn (**Figure 3b**), due to its complexity, highlights the need for an appropriate reference standard in the analysis of herbal medicinal products.

One main component of the extract of lemon balm is rosmarinic acid, which is used as an active marker (a chromatogram and the structure of rosmarinic acid are shown in **Figure 3c**; a chromatogram of an extract of lemon balm is shown in **Figure 3d**).

In **Figure 3e**, the chromatogram of the final herbal medicinal product is presented. The content of hawthorn and lemon balm extract in the final medicinal product is determined by the use of the reference standards vitexin-2"-O-rhamnoside and rosmarinic acid. This chromatogram highlights the challenge of the analysis of herbal medicinal products due to their complex composition.

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Chromatographic conditions for Fig. 3a-e:

HPLC: Alliance 2695, Waters
 Detector: DAD @ 330 nm for rosmarinic acid
 DAD @ 340 nm for vitexin-2"-O-rhamnoside
 Column: Synergi Polar RP; 250 x 4,6 mm (4 µm) with guard column
 Temperature: 25 °C
 Mobile Phase: Gradient: Water/TFA (pH 2,0)/acetonitrile
 Flow rate: 1,0 ml/min
 Injection volume: 20 µl

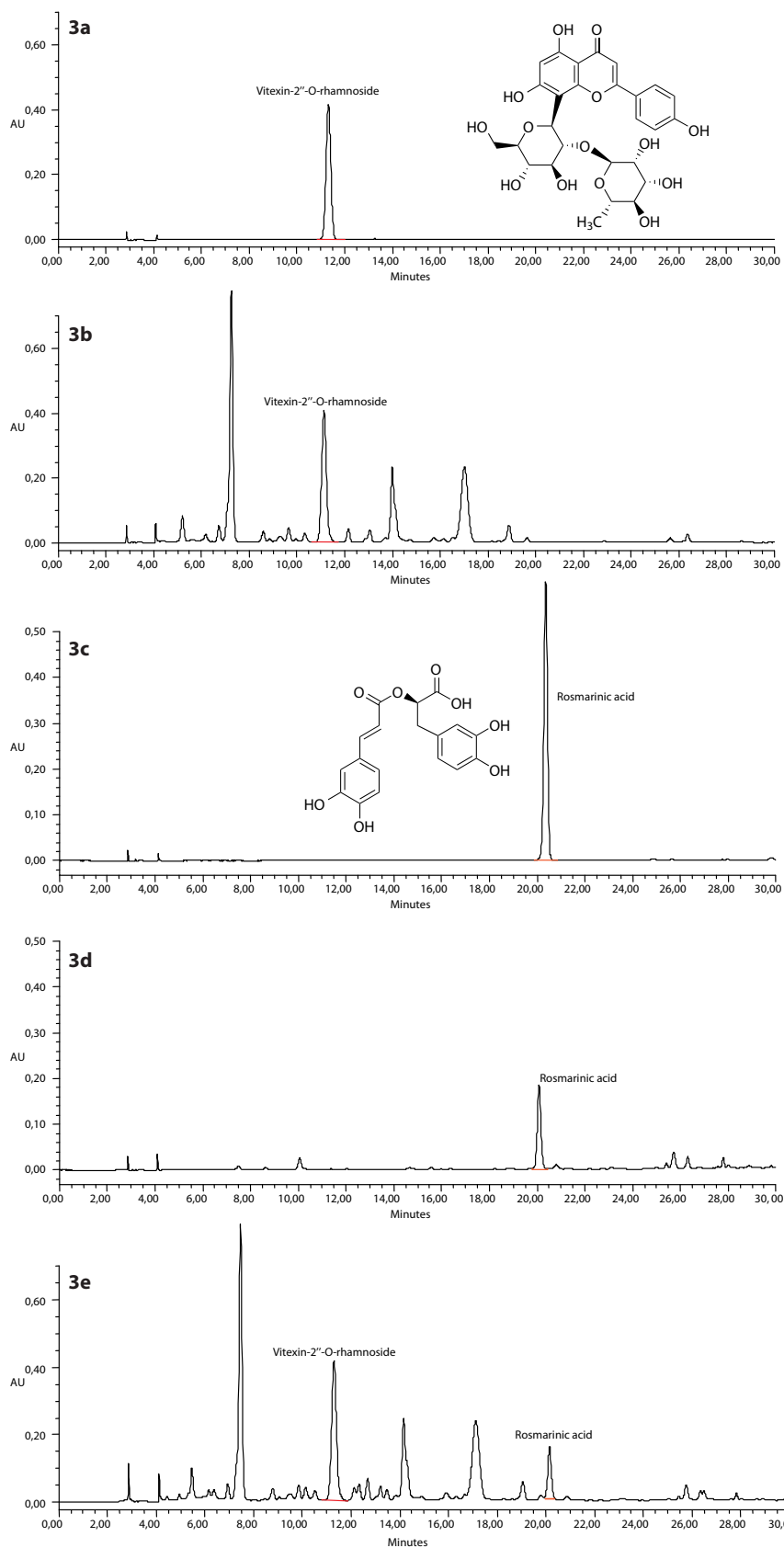


Figure 3a) Reference standard vitexin-2"-O-rhamnoside, $c = 0,15 \text{ mg/ml}$; **3b)** Sample solution of an extract of hawthorn leaves, flowers and fruits; **3c)** Reference standard rosmarinic acid, $c = 0,1 \text{ mg/ml}$; **3d)** Sample solution of an extract of lemon balm leaves; **3e)** Sample solution of the herbal medicinal product, exemplary recorded at 340 nm.

Quantitative NMR Used for Content Assignment of Reference Standards for Quality Control of Herbal Medicinal Products

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Within the scope of a marketing authorisation procedure for herbal medicinal products, a comprehensive dossier and a certificate of analysis must be compiled for all reference standards used. In this dossier, information on identity (NMR, MS, IR, UV, and others), purity (water content, residual solvents, inorganic impurities, and organic impurities), and the content of the reference standard must be provided. Currently, assay is performed using two methods which preferably are independent from each other. For this purpose, chromatographic methods are usually applied. Content assignment is then performed based on the results obtained from the purity tests and the respective area percentage of the analyte in the chromatographic separation systems. However, this procedure is only applicable for sufficiently pure (>99.5%) reference standards.

Reference standards of natural origin usually have a complex molecular structure, which is why they are rarely accessible synthetically and thus must be isolated from natural sources. When isolating the substances from plants, however, a purity exceeding 99.5% can only be achieved with considerable effort. In addition, the scope of isolation purification is performed via chromatographic methods, thus the same methods are usually applied for content and for purity analysis within the framework of certification. This redundancy results in the risk that impurities that could not be separated during purification may also be overlooked during certification. Such impurities are frequently biogenetically related to the analyte and display very similar structures, which makes analytical separation even more difficult. Hence, the selectivity (or specificity) of the method applied for purity testing plays a central role, especially with respect to reference standards isolated and purified from natural sources. As a result, reference standards isolated from natural sources can only rarely be certified according to the relevant guidelines by using the established procedure.

Avoiding all problems described, “direct” or “relative” primary methods of measurement that convey a direct traceability to the SI units ensure a higher metrological quality [1]. These methods are increasingly applied for content assignment of natural products used as pharmaceutical reference standards.

Quantitative NMR spectroscopy (qNMR) is a potential relative primary method [2]. Employment of qNMR simplifies and increases the reliability of the establishment of reference standards and their certification. The most important basis of quantitative NMR spectroscopy is the direct proportionality of the signal intensity with the number of nuclei contributing to the resonance line.

In general, there are two possibilities of content analysis: that of direct analysis via the principal component and that of indirect analysis via the impurities. Since content assignment plays a central role in the certification of reference standards, the direct method is applied here. In doing

so, the principal component, i. e. the reference standard, is evaluated against an internal standard. The advantage of this method lies in the fact that only the unequivocal assignment of an optimally integrable signal of the principal component is required. In this context, knowledge about the composition and/or qualitative assignment of the other signals is usually not necessary. For determination of the content of the principal component, the internal standard and analyte must be weighed together into one NMR tube. Intensities of appropriate selective signals of the principal component and the internal standard are used for calculation. Based on the ratio of intensities, the relative content of the analyte can be calculated as m/m%.

As an example, the spectrum of vitexin-2"-O-rhamnoside containing 2-hydroxy-3,5-dinitro benzoic acid as an internal standard is shown in **Figure 1**.

Ultimately, not only content assignment could be performed using the method described, but also the proof of identity in one step using the NMR method in the classical way for structural analysis. Hence, the supplied substance requiring certification, for instance the very expensive natural products, could essentially be decreased, thus reducing the high costs associated with the extensive effort in connection with isolation and purification.

The European CCQM (Comité Consultatif pour la Quantité de Matière) ensures the harmonisation of physical parameters as well as accurately describing and improving the accuracy and precision of measurement methods in analytical chemistry. From CCQM directives, the German Federal Institute for Materials Research and Testing (BAM) has been charged with defining the capabilities of quantitative NMR spectroscopy and proving its effectiveness in international interlaboratory tests [3]. In this respect, BAM acts as a national metrology institute for Germany. Within a public-funded project in Germany, comprehensive validation results for the certification of reference standards could be established, which are largely publicly available now [4]. Since NMR spectroscopy has the character of a primary method, as demonstrated in publications for the CCQM [3,4], all requirements are satisfied to perform metrologically top-quality, SI-based certifications for pharmaceutical reference materials. In Ph. Eur. the monograph on NMR spectroscopy was revised based on the results of the research project, now permitting the use of qNMR as an official method in pharmaceutical analysis.

During realisation of this project, qNMR could be proven to be basically appropriate as a potential primary analytical method for the certification of natural products as reference standards for quality control of herbal medicinal products. Using a total of 14 samples of selected reference materials relevant for the analysis of herbal medicinal products, the metrological quality of the quantitative ¹H-NMR, and hence its suitability for pharmaceutical analysis, were investigated.

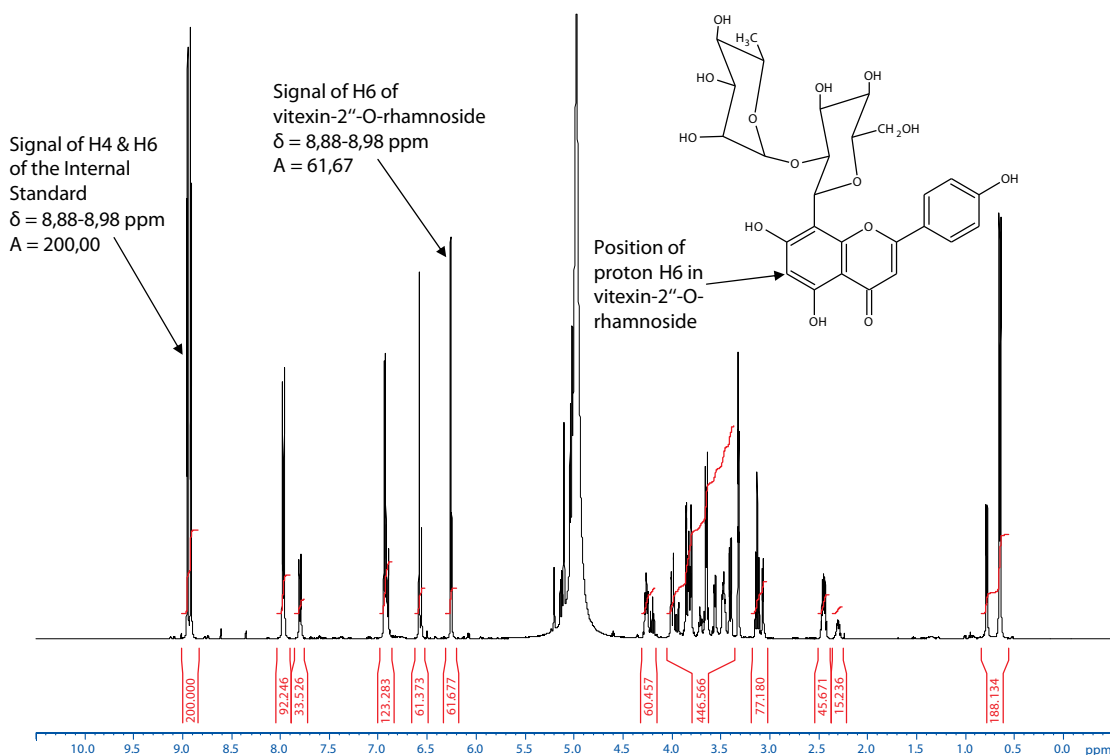


Figure 1 NMR spectrum of vitexin-2''-O-rhamnoside and the Internal Standard 2-hydroxy-3,5-dinitro benzoic acid. For quantification of the content of the principal component the signals of proton H6 of the vitexin-2''-O-rhamnoside and of the aromatic protons (H4 and H6) of the 2-hydroxy-3,5-dinitro benzoic acid are used.

The qualitative assignment of signals in the spectrum (specificity and selectivity) was shown to be the most important part of the quantitative analysis. The larger and more complex the molecule, the more difficult this evaluation became. Additionally aggravating was the fact that, in the case of complex compounds, impurities with a very similar structure differed just slightly in the spectrum and/or only at a few frequencies. This problem, however, is not NMR-specific but can be transferred to all spectroscopic and chromatographic methods. Nevertheless, where other methods fail because the analyte cannot be selectively quantified, qNMR provided accurate results in such cases by evaluation via further signals in the spectrum. Furthermore, for some substances, additional impurities not detected using chromatographic methods could be detected and even partially identified and quantified by qNMR. For each target analyte, selectivity of the signals used for analysis was established by means of ^1H -NMR (partly using ^{13}C decoupling) and ^1H , ^{13}C hetero correlated 2D NMR techniques (HMQC, HMBC), and for assignment of signals originating from impurities by H,H correlated 2D NMR techniques (COSY).

As a result, a standard operating procedure is now available for the recording, processing and evaluation of qNMR measurements for the certification of reference standards.

To confirm the acceptance of qNMR results by the German national regulatory authority (BfArM) and the European

EMA, these studies were conducted according to the ICH guidelines [5]. By means of an organised and evaluated national interlaboratory test with 22 participants from industry, research and university facilities, the generalisation of laboratory internal validation was proved unequivocally on the basis of one substance.

In order to determine the metrological quality (accuracy and precision), the complete uncertainty budget according to ISO guidelines was established for assay using qNMR spectroscopy. Generally, an expanded uncertainty of measurement ($k = 2$) of $\leq 1\text{g/g}\%$ was determined for all substances investigated.

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Simple, Rapid and Inexpensive Determinations of Enantiomeric Purities: Oxiranes, Amino Acids and Pharmaceuticals

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Introduction

Analytical methods for the determination of enantiomeric purities should go beyond high-quality standards to include important additional features: simple, rapid and inexpensive. Attractive alternatives to high-cost, so-called *chiral columns* (chiral stationary phases) are inexpensive reversed-phase (RP) columns in combination with suitable derivatisation reagents. In this series of articles, we describe applications of such systems involving suitably substituted monosaccharide-based isothiocyanates for the determination of enantiomeric purities of the title compounds (**Figure 1**).

All derivatisations are based on the simple transformations of these reagents into the corresponding diastereomeric thioureas by reaction with (primary and secondary) amino groups (**Figure 2**). These transformations can either be created by reaction of the oxiranes under consideration with amines (leading to the corresponding β -amino alcohols, see *Oxiranes* below) or are already part of the molecule to be analysed (amino acids, pharmaceuticals such as β -blockers etc.).

As derivatives of natural mono-saccharides all of these reagents are optically pure, and the ratios of diastereoisomers thus produced directly reflect the enantiomeric composition of the amino compound in question. The first examples for such applications [using the tetra acetate, GITC Aldrich T5783 and the triacetate of α -D-arabinose AITC Fluka 90245] were introduced between 1980–1984 by Kinoshita et al. [1]; in the meantime both performance and UV-detection were considerably improved by the introduction of benzoyl groups (BGITC Aldrich 335622) [2] and naphthoyl groups (NGallTC Fluka 04669) [3]. Also, the introduction of pivaloyl groups (PGallTC, Fluka 88102) led in many cases to improved separations [2].

This series of articles consists of three parts, each addressing one group of the title compounds: oxiranes, amino acids (proteinogenic, non-proteinogenic, β -amino- and α,α' -disubstituted-), and pharmaceuticals carrying amino functions.

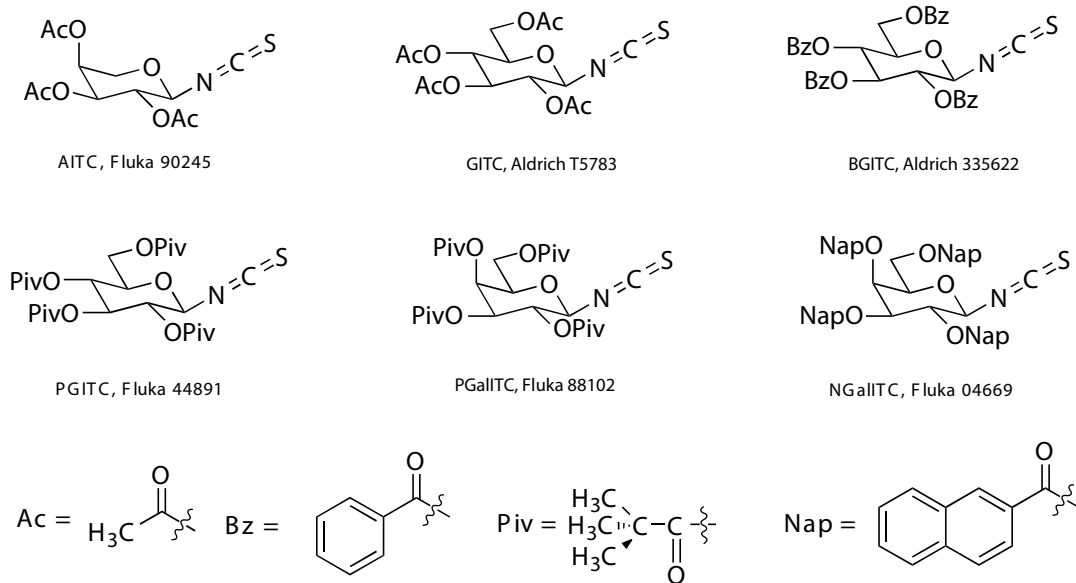


Figure 1 Structure formulas of monosaccharide-based isothiocyanates

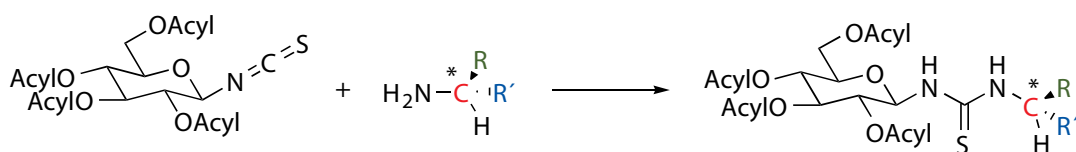


Figure 2 Formation of diastereomeric thioureas (schematic) [* denotes centre of chirality]

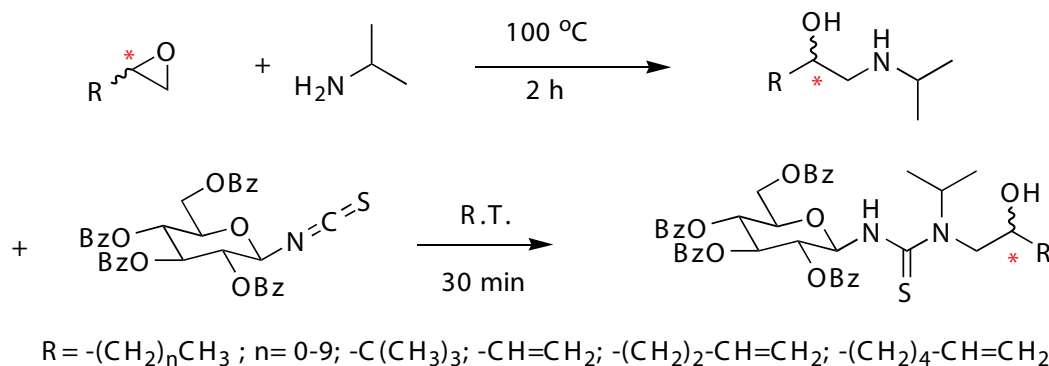


Figure 3 Conversion of alkyl oxiranes into diastereomeric thiureas using a two-step strategy [* denotes centre of chirality]

Oxiranes

Enantiomerically pure, mono-substituted alkyloxiranes (compare **Figure 3**) are important chiral building blocks [4] for the syntheses of numerous natural products, including (*inter alia*) pheromones [5], γ - and δ -Lactones [6], various natural products [7], and ferroelectric liquid crystals [8]. The enantiomeric purity levels of these materials can be determined by numerous methods. For low molecular weight alkyl oxiranes, the analyst can utilise complexation gas-liquid chromatography employing chiral metal complexes (Ni, Mn, Co, Zn) as stationary phases [9]. However, this method may not be applicable to molecules of higher molecular weight, in which case decompositions are occasionally observed. Also, low-separation factors are frequently observed. Modified cyclodextrins can also be employed as chiral stationary phases for this purpose [10]. Yet, none of these methods seems to be generally applicable for enantiomeric purity determinations irrespective of structure and molecular weight. Since so-called *chiral columns* may not be commercially available for specific cases or are expensive, reversed phase columns can provide an alternative approach when employed in combination with suitable derivatisation reagents. With this methodology, the best and most generally applicable separations are achieved

using a two-step strategy involving a) regioselective ring opening of the oxirane moiety using a simple sterically demanding amine leading to the corresponding β -amino alcohols, followed by b) derivatisations of the resulting β -amino alcohols with the above reagents. Based on earlier results by Gal [11], this procedure was further optimised by employing 2-propylamine for step a), thereby considerably shortening the time required for the sample preparation, and for step b), employing BGITC for improved UV detection [2] (**Figure 3**).

In using PGallITC (Fluka 88102) and GITC (Aldrich T5783) only partial or no separations are achieved. Clearly the very best results were obtained using BGITC (Aldrich 335622). Base-line separations are achieved in all cases ($\alpha=1.15-1.23$; $R_s = 2.14-2.29$) and all retention times are within a reasonable time-range (**Table 1**).

In view of the mild separation conditions (quite in contrast to the high temperatures required in GC separations), no decompositions are observed. Both enantiomers were converted completely and with the same rate. The analytically determined ratios (integrations) are thus a true reflection of the enantiomeric compositions. In **Table 1** the separation

R	Mobile Phase MeOH:H ₂ O	k'_R	k'_S	α	R_s	Mobile Phase MeOH:H ₂ O	k'_R	k'_S	α	R_s
(CH ₂) ₉ -CH ₃	90:10	9.38	11.35	1.12	4.34	95:5	3.16	3.62	1.15	4.70
(CH ₂) ₇ -CH ₃	90:10	5.58	6.71	1.20	3.51	95:5	1.91	2.17	1.14	2.70
(CH ₂) ₆ -CH ₃	90:10	4.17	5.00	1.20	3.66					
(CH ₂) ₅ -CH ₃	90:10	3.06	3.63	1.19	2.92					
(CH ₂) ₄ -CH=CH ₂	90:10	2.52	2.95	1.17	2.66	85:15	6.99	8.77	1.26	4.62
(CH ₂) ₄ -CH ₃	90:10	2.62	3.06	1.17	2.30	85:15	7.10	8.88	1.25	4.26
(CH ₂) ₃ -CH ₃	90:10	2.19	2.54	1.16	2.16	85:15	5.53	6.83	1.24	4.03
C(CH ₃) ₃	90:10	2.77	2.43	1.14	1.75	85:15	2.29	4.45	1.17	3.01
(CH ₂) ₂ -CH=CH ₂	90:10	1.92	2.23	1.16	1.58	85:15	4.47	5.53	1.24	3.64
(CH ₂) ₂ -CH ₃	90:10	1.96	2.27	1.16	1.58	85:15	3.71	4.50	1.21	3.27
CH ₂ -CH ₃	90:10	1.60	1.82	1.14	1.36	85:15	3.46	4.16	1.20	2.73
CH=CH ₂	90:10	1.55	1.78	1.15	1.73	85:15	3.14	3.78	1.20	2.86
CH ₃	90:10	1.45	1.65	1.14	1.55	85:15	2.57	3.06	1.19	2.55

Table 1 Separation of diastereomeric BGITC – derivatives obtained from oxirane – derived β -amino alcohols. Column: Li Chrospher 100 RP-18 (5 μ m); flow rate = 0.5 ml min⁻¹; t_0 = 3.1 min; wavelength of detection = 231 nm; R = substituents as shown in Figure 3.

k' = capacity factors; α = separation factor; R_s = resolution.

(continued on page 18)

parameters for 13 different alkyl oxiranes are summarised together with the separation conditions. Owing to their different retention times, it was also possible to separate a mixture of 10 oxirane-derived β -amino alcohols (derived from 5 racemic oxiranes of different substitution patterns) in one single experiment (Figure 4).

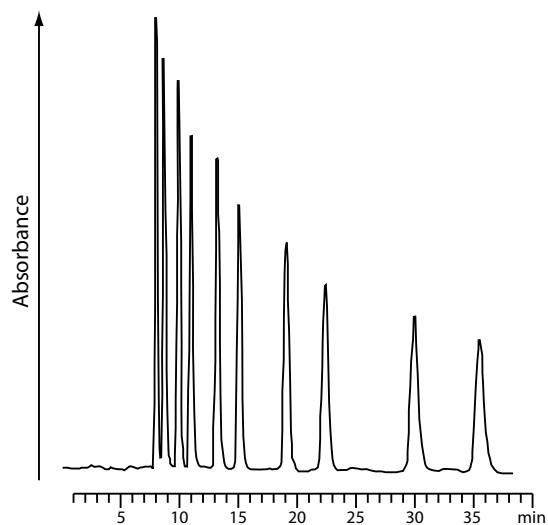


Figure 4 Separation of ten oxirane-derived β -amino alcohols as diastereomeric thiourea derivatives in a single experiment. Mobile phase, methanol-water (90:10); flow rate, 0.5 ml min⁻¹; 0.7 nmol of each derivative are injected. Components were eluted in the following order: always (R) - before (S) for R = C₂, C₄, C₆, C₈, C₁₀.

Summary

The method described above allows the rapid and inexpensive determination of enantiomeric purities in a wide variety of structurally varied alkyl oxiranes. Base-line separations are observed in all cases and the determined ratios are a true reflection of the enantiomeric purities. The method is clearly adaptable to automation using reaction batteries and auto-samplers. The method is thus applicable both on a laboratory scale and in on-line quality control. It is thus highly suitable for monitoring asymmetric syntheses of oxiranes [4] as well as enzyme-catalysed transformations.

Experimental

50 μ L of the corresponding alkyl oxirane is mixed with 200 μ L of 2-propylamine in a 1 mL vial (having a tightly sealed, Teflon-lined cap) and heated at 100 °C for 2 hours. Excess 2-propylamine is evaporated in a slow stream of N₂ after which 950 μ L of acetonitrile are added. 50 μ L aliquots of this solution are mixed with 0.66% (w/v) BGITC in acetonitrile

and the mixtures are allowed to react for 30 min at room temperature. After dilution with CH₃CN to a final volume of 1 mL, 7 μ L aliquots are injected into the HPLC (RP-18, mobile phase MeOH: H₂O = 85:15 up to 95:5, depending on the case, flow rate 0.5 mL/min, compare table).

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Brand	Prod. No.	Description	Abbr.	Pack Size
Fluka	90245	2,3,4-Tri- <i>O</i> -acetyl- α -D-arabinopyranosyl-isothiocyanate	AITC	100 mg, 500 mg
Sigma	T5783	2,3,4,6-Tetra- <i>O</i> -acetyl- β -D-glucopyranosyl-isothiocyanate	GITC	100 mg, 1 g
Aldrich	335622	2,3,4,6-Tetra- <i>O</i> -benzoyl- β -D-glucopyranosyl-isothiocyanate	BGITC	500 mg
Fluka	44891	2,3,4,6-Tetra- <i>O</i> -pivaloyl- β -D-glucopyranosyl-isothiocyanate	PGITC	100 mg
Fluka	88102	2,3,4,6-Tetra- <i>O</i> -pivaloyl- β -D-galactopyranosyl-isothiocyanate	PGallTC	100 mg
Fluka	04669	2,3,4,6-Tetra- <i>O</i> -(2-naphthoyl)- β -D-galactopyranosyl-isothiocyanate	NGallTC	25 mg, 100 mg

Table 2 Product information

Ion Exchange Media

For Diverse Separation Applications

Shyam Verma, Market Segment Manager, Reagents & Chemicals shyam.verma@sial.com



Ion exchange resins allow exchange of specific ions on the resin surface with ions in a solution in contact. The exchange takes place without any physical alteration to the resin. These resins are highly ionic, covalently cross-linked polymeric media. They are commonly prepared from styrene mixed with different levels of a cross-linking agent divinyl benzene (DVB) that controls the porosity of the particles. Other base polymeric materials are also selectively used in manufacturing these resins.

These insoluble polyelectrolyte matrices, supplied as beads, have either a dense internal structure without any discrete pores (gel resins, also called microporous resins) or a porous multi-channelled structure (macroreticular or macroporous resins). High effective surface area of the **macroporous resins** facilitates the ion exchange process by allowing easy access to the charged (exchange) sites for larger ions. These resins are rigid beads, clean and easy to handle. **Microporous resins**, on the other hand, allow diffusion of the solute ions through the particle for interaction with the exchange sites. Despite diffusional limitations on reaction rates, these resins demonstrate faster reaction, higher loading capacities, and low fragility in handling.

Ion exchange resin classification: Based on the charges on the exchangeable counter-ion (cation or anion exchanger) and the ionic strength of the bound ion (strong or weak exchanger), there are four primary types of ion exchange resins:

- 1. Strong anion exchange resins** contain quarternary ammonium groups. These resins are highly ionised and can be used over the entire pH range.
 - Type I** of these resins contain trialkyl ammonium chloride or hydroxide
 - Type II** resins contain dialkyl 2-hydroxyethyl ammonium chloride or hydroxide quarternary ammonium group
- 2. Weak anion exchange resins** contain ammonium chloride or hydroxide. The degree of ionisation for these resins is strongly influenced by pH and they exhibit minimum exchange capacity above pH of 7.0.
- 3. Strong cation exchange resins** contain sulphonic acid groups or the corresponding salts. These resins are highly ionised in both the acid and salt forms. The exchangeable Na^+ and H^+ ions of the resin are readily available for exchange over the entire pH range. The exchange capacity is, therefore, independent of solution pH.

(continued on page 20)

4. Weak cation exchange resins contain carboxylic acid as the ionisable group and exhibit stronger affinity for hydrogen ions. Consequently, these resins need less acid for regeneration to hydrogen form. The degree of dissociation of these resins is dependent on solution pH.

Other resins: Mixed bed resins are a blend of cation and anion exchange resins. Few other application-specific resins are also available.

Guidelines for selecting a resin: Resin functionality and its porosity (or degree of cross-linking) plays a significant role in its suitability for a specific application. Particle size distribution is important for many column applications. The following basic guidelines are suggested for resin selection for an application:

- Generally, strongly acidic cation exchange resins or strongly basic anion exchange resins can be used for adsorbing all ionic species. For biological materials where regeneration efficiency or stability of materials is required, a weakly charged resin is usually preferred.
- A high porosity (low cross-linking) resin allows rapid diffusion of ions and faster kinetics. On the other hand, a resin with low porosity (high cross-linking) shows greater selectivity and can exclude larger molecules.
- Small resin beads adsorb and release compounds more quickly than larger beads due to shorter diffusion path lengths.

Applications: Ion exchange resins are widely used in chromatography, separation and purification, decontamination and many other processes. Water softening, purification of water and juices, manufacturing sugars, high-purity water production for electronic and nuclear industries, and pharmaceuticals are among many separation and purification processes where ion exchange media is used. In pharmaceutical manufacturing, ion exchange resins are used for catalysing certain reactions, isolating and purification of active ingredients, and also as an excipient in pharmaceutical formulations. Other applications include: separation of charged molecules such as, proteins, extraction and purification of biologically produced materials such as: amino acids and proteins, food & beverage, enrichment and purification of precious metals, metal finishing, and similar applications in many industries.

Sigma-Aldrich offers a variety of resins including *Dow, Rom & Haas and GE resins:*

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Mixed Bed Ion Exchange Media:

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Chelating Ion Exchange media:

Amberlite, Diaion, Dow, Duolite, Dowex, Lewatit

Nuclear Ion Exchange media:

Amberlite, Dowex

Other Ion Exchange Resins:

Sephadex®, Toyopearl®

Advantages of ion exchange media: Ion exchange resins are easy to handle and can be easily removed from the reaction medium by filtration. Use of resins greatly reduces corrosion problems and unwanted by-products peculiar to the use of homogeneous liquid catalysts. With resins, neutralisation, precipitation, distillation and extraction steps associated with homogenous catalysts are also eliminated.

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- Color-coded buffer solutions for pH 4 (red), 7 (green), 9 (blue) and 10 (violet); ideal for instrument calibration
- High-precision buffer solutions according to DIN 19266 for high-precision measurements

More information and complete product listings are available on our website

sigma-aldrich.com/titration

The following FIXANAL® pH buffer concentrates are available with HUGE SAVINGS OF 35% OFF until end March 2010:

Cat. No.	Brand	Description
38740	Fluka	Buffer concentrate pH 1.00 for 500 ml buffer solution
38741	Fluka	Buffer concentrate pH 2.00 for 500 ml buffer solution
38742	Fluka	Buffer concentrate pH 3.00 for 500 ml buffer solution
38743	Fluka	Buffer concentrate pH 4.00 for 500 ml buffer solution
38744	Fluka	Buffer concentrate pH 5.00 for 500 ml buffer solution
38745	Fluka	Buffer concentrate pH 6.00 for 500 ml buffer solution
38746	Fluka	Buffer concentrate pH 7.00 for 500 ml buffer solution
38747	Fluka	Buffer concentrate pH 8.00 for 500 ml buffer solution
38748	Fluka	Buffer concentrate pH 9.00 for 500 ml buffer solution
38749	Fluka	Buffer concentrate pH 10.00 for 500 ml buffer solution
38750	Fluka	Buffer concentrate pH 11.00 for 500 ml buffer solution
38751	Fluka	Buffer concentrate pH 12.00 for 500 ml buffer solution
38752	Fluka	Buffer concentrate pH 13.00 for 500 ml buffer solution
32048	Fluka	Potassium sodium phosphate buffer solution, (for 1 L buffer solution), according to Weise, pH 7.20

To take advantage of this offer, please use promotion code 960. Offer valid until March 31, 2010.

sigma-aldrich.com/titration

New High-Purity Standards for Pesticide Residue Analysis

Matthias Nold, Product Manager Analytical Standards matthias.nold@sial.com



Through our PESTANAL® line we offer a wide portfolio of over 1200 high-purity pesticide and metabolite standards for food and environmental analysis. We are continually expanding our portfolio by adding new standards. Below you will find the most recent additions to our offering of

pesticide and pesticide metabolite standards, including isotope-labelled compounds.

Please visit our website and our on-line catalogue to find the appropriate standard for your application:

Brand	Cat. No.	Description	Pack Size
Fluka	32527	Acequinocyl	50 mg
Fluka	32521	Azimsulfuron	25 mg
Fluka	32866	Beflubutamid	100 mg
Fluka	32504	Bifenazate	50 mg
Fluka	32505	Cadusafos	50 mg
Fluka	32510	Chlorantraniliprole	25 mg
Fluka	32743	Cyclosulfamuron	100 mg
Fluka	32753	Cyhalofop-butyl	50 mg
Fluka	32522	Cyprosulfamide	100 mg
Fluka	32677	Difenacoum	25 mg
Fluka	32506	Etoxazole	50 mg
Fluka	32509	Fonicamid	25 mL
Fluka	32529	Flucycloxiuron	25 mg
Fluka	32525	Flumioxazin	100 mg
Fluka	32523	Flurprimidol	100 mg

Brand	Cat. No.	Description	Pack Size
Fluka	32532	Isopyrazam	100 mg
Fluka	32524	Isotianil	100 mg
Fluka	32507	Methoxyfenozide	50 mg
Fluka	32668	Nabam-d4 hexahydrate	10 mg
Fluka	32613	NaDMTC-d6 dihydrate	10 mg
Fluka	32528	Pethoxamid	50 mg
Fluka	32508	Proquinazid	50 mg
Fluka	32538	Pyridaphenthion	100 mg
Fluka	32682	Tembotrion metabolite AE 1417268 solution	2 mL
Fluka	32766	Tembotrione	100 mg
Fluka	32531	Tralomethrin	50 mg
Fluka	32611	Triflumizole	100 mg
Fluka	32501	Zoxamide	50 mg

New Mycotoxin Standards

Matthias Nold, Product Manager Analytical Standards matthias.nold@sial.com



Fungal infection of crops can lead to mycotoxin contamination of human food, either directly or through their use as livestock feed. Our OEKANAL® product line comprises a comprehensive range of analytical standards of mycotoxins

and isotope-labelled mycotoxins for food residue analysis. The table below lists the most recent additions to this portfolio. For a complete list of mycotoxin standards, please visit our website.

Brand	Cat. No.	Description	Pack Size
Fluka	32754	Aflatoxin B1	5 mg
Fluka	32764	Aflatoxin B1- ¹³ C ₁₇ solution	1 mL
Fluka	32755	Aflatoxin B2	5 mg
Fluka	32771	Aflatoxin B2- ¹³ C ₁₇ solution	1 mL
Fluka	32756	Aflatoxin G1	5 mg
Fluka	32772	Aflatoxin G1- ¹³ C ₁₇ solution	1 mL
Fluka	32757	Aflatoxin G2	5 mg
Fluka	32777	Aflatoxin G2- ¹³ C ₁₇ solution	1 mL
Fluka	32606	Fumonisin B3 solution	1 mL

Brand	Cat. No.	Description	Pack Size
Fluka	32541	[D-Asp3, (E)-Dhb7]-Microcystin-RR solution	1 mL
Fluka	32773	Mycophenolic acid- ¹³ C ₁₇ solution	1 mL
Fluka	32539	Nodularin solution	1 mL
Fluka	32763	Ochratoxin A in wheat flour	100 g
Fluka	32759	Patulin	5 mg
Fluka	32609	Sterigmatocystin	5 mg
Fluka	32758	Zearalenone- ¹³ C ₁₈ solution	1 mL

New Veterinary Drug Standards

Matthias Nold, Product Manager Analytical Standards matthias.nold@sial.com



The use of drugs for the prevention or cure of infections, parasites or diseases in animals plays a very important role in modern agriculture. As a consequence, foodstuffs of animal origin may contain residues of medicinal products and their metabolites.

Our VETRANAL® product line includes over 200 high-purity standards of the active ingredients of veterinary drugs, including isotope-labelled compounds for use as internal standards in residue analysis. The table below lists the most recent product additions of the VETRANAL line.

Brand	Cat. No.	Description	Pack Size
Fluka	32733	5-Amino-2-methyl-3-nitrobenzamide	10 mg
Fluka	32731	3-Amino-2-methyl-5-nitrobenzamide	10 mg
Fluka	32738	Azaperol	10 mg
Fluka	32671	Carnidazole	10 mg
Fluka	32736	Carprofen-d3	10 mg
Fluka	32554	Chlorpromazine-d6 hydrochloride	10 mg
Fluka	32568	Cimaterol	10 mg
Fluka	32569	Cimaterol-d7	10 mg
Fluka	32576	Cimbuterol	10 mg
Fluka	32580	Clenhexerol	10 mg
Fluka	32571	Clorprenaline	10 mg
Fluka	32552	Decoquinat-d5	10 mg
Fluka	32582	Diflovidazin	25 mg
Fluka	32526	Eprinomectin	100 mg
Fluka	32749	beta-Estradiol-3-methylether-solution	2 mL
Fluka	32729	Febantel-d6	10 mg
Fluka	32544	Fenbendazole sulfone	10 mg
Fluka	32545	Fenbendazole sulfone-d3	10 mg
Fluka	32567	Fenbendazole-d3	10 mg
Fluka	32511	Furazolidone-d4	10 mg
Fluka	32673	Ketoprofen-d3	10 mg
Fluka	32573	Mabuterol hydrochloride	10 mg
Fluka	32542	Menidazol	10 mg
Fluka	32744	Metronidazole-13C2,15N2	10 mg
Fluka	32549	Miloxacin-d3	10 mg
Fluka	32513	Nitrofurantoin-13C3	10 mg
Fluka	32512	Nitrofurazon-13C,15N2	10 mg
Fluka	32543	Oxfendazole-d3	10 mg
Fluka	32737	Oxibendazole-d7	10 mg
Fluka	32551	Pefloxacin-d5	10 mg
Fluka	32548	Sulfachloropyridazine-phenyl-13C6	10 mg
Fluka	32518	Sulfadiazine-phenyl-13C6	10 mg
Fluka	32517	Sulfamerazine-phenyl-13C6	10 mg
Fluka	32519	Sulfamethazine-phenyl-13C6 hemihydrate	10 mg
Fluka	32514	Sulfamethoxazole-phenyl-13C6	10 mg
Fluka	32516	Sulfanilamide-13C6	10 mg
Fluka	32547	Sulfapyridine-phenyl-13C6	10 mg
Fluka	32546	Sulfaquinoxaline-phenyl-13C6	10 mg
Fluka	32515	Sulfathiazole-phenyl-13C6	10 mg
Fluka	32676	Testosterone acetate solution	2 mL
Fluka	32553	Tinidazole	10 mg
Fluka	32533	Vedaprofen (Racemat)	10 mg
Fluka	32534	Vedaprofen-d3 (Racemat)	10 mg
Fluka	32555	Xylazine-d6	10 mg

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