



# FOCUS: ORGANIC SYNTHESIS

2023



# Welcome to the FOCUS: Organic Synthesis magazine – a place where you can discover trends, advancements and innovations.

Our second edition explores the development of key reactions and applications of organic synthesis; from traditional synthetic methods, such as oxidation reactions, to Topliss sets in drug design. We are pleased to have content from scientist contributors at our partner brands Thermo Scientific and Apollo Scientific. As well as technical discussions, we provide practical innovations in chemicals, equipment and consumables for your laboratory.

We hope you enjoy this content as we embark to set science in motion.

**Enjoy reading  
Your Organic Synthesis Team at Avantor!**

If you have any questions, feedback, or would like to be featured in future articles please reach out to us at: **[organic.synthesis@avantorsciences.com](mailto:organic.synthesis@avantorsciences.com)**

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# Synthesis reactions - chemicals

# The voice of synthesis

Researchers of synthetic chemistry endeavour to drive forward our understanding and control over the chemical world around us. We have the pleasure to provide you with highlights from key researchers, showcasing their research and demonstrating the continuing advancements in the field. Please enjoy an overview of their work, and for continued reading follow the links provided.

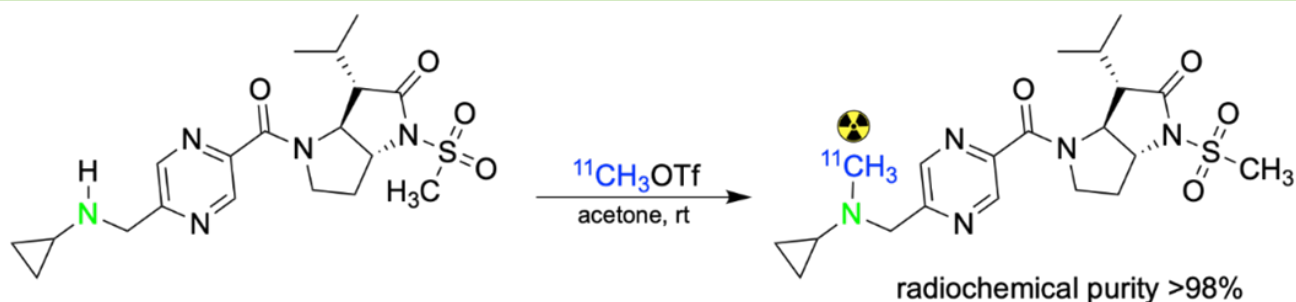
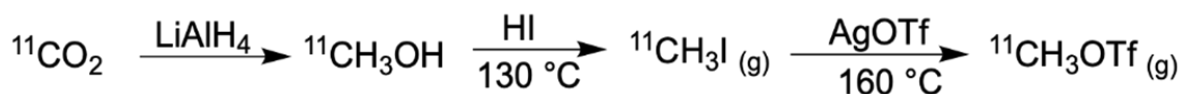
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**DR. MATHIAS ELGLAND**  
Linköping University, Sweden

Mathias received his PhD in the field of applied carbohydrate synthesis and radiochemistry in 2018 from Linköping University, Sweden. His doctoral work focused on synthesising fluorine-18 labelled glycosylated heterocycles for use as PET tracers for imaging of Alzheimer's disease.

In 2018, he took a research position at the PET centre at Uppsala University Hospital where he specialised in carbon-11 labelling of amine precursors using [11C] methyl triflate as the N-alkylating agent. His main project was the development and GMP validation of a novel carbon-11 PET ligand (11C-NES) for imaging of inflammation. 11C-NES binds specifically to neutrophil elastase, a protease, which is released by neutrophils at the site of inflammation. In 2021, the utility of 11C-NES was demonstrated in a first in-human clinical study where the inflammation in the lungs of COVID-19 patients could effectively be visualised.



In 2022, Mathias started working at the PET centre located at Linköping University Hospital where he is currently the section chief and head of research and tracer development.

His research interests now concern developing tracers for PET imaging of inflammation in cardiovascular diseases and for bacterial infection, both for which there is a tremendous clinical need for more selective and efficient PET ligands.

Below is a description of how carbon-11 labelling is realised, exemplified with the elastase PET ligand  $^{11}\text{C}$ -NES. Carbon-11 is generally formed as  $^{11}\text{C}$  carbon dioxide by irradiating a target chamber, filled with nitrogen gas and a small percentage of oxygen gas, with a beam of highly energetic protons which are produced with a cyclotron. The  $^{11}\text{C}$  carbon

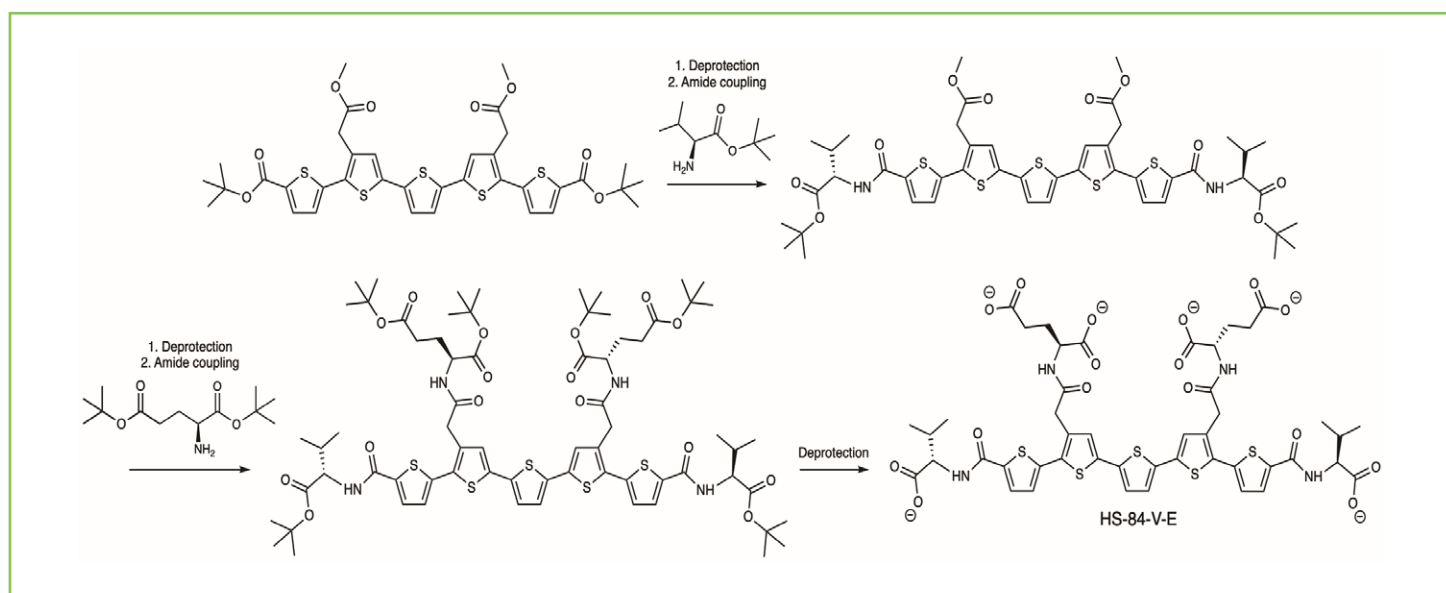
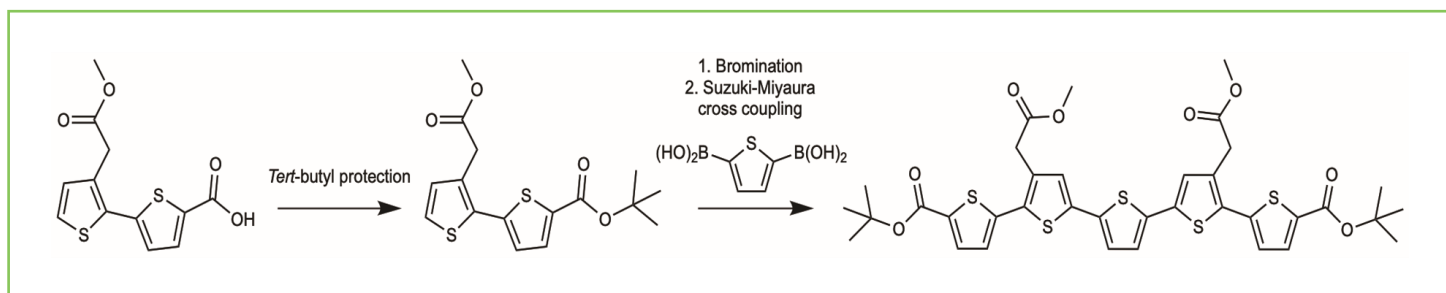
dioxide is then transferred to a vial containing a solution of lithium aluminium hydride where  $^{11}\text{C}$  carbon dioxide is reduced to  $^{11}\text{C}$  methoxide. Hydroiodic acid is then added and the solution heated at  $130\text{ }^\circ\text{C}$  thus forming volatile  $^{11}\text{C}$  methyl iodide that is evaporated and passed with a stream of nitrogen gas through a column packed with silver triflate on an activated carbon support at  $160\text{ }^\circ\text{C}$ . Fast and efficient halide displacement then lead to the formation of the highly electrophilic methylating agent,  $^{11}\text{C}$  methyl triflate.  $^{11}\text{C}$  Methyl triflate in turn is transferred into a solution of the amine precursor where an almost instantaneous reaction occurs. Subsequent preparative HPLC purification, evaporation of the eluents and reformulation in a physiological buffer for intravenous injection affords freshly prepared  $^{11}\text{C}$ -NES.



**LINNEA BJÖRK**

Linköping University, Sweden

Linnea Björk received her MSc in organic synthesis/medicinal chemistry from Linköping University in 2019, after which she received a research scholarship in Professor Peter Nilsson's research group conducting research on thiophene-based ligands as fluorescent probes for different biological targets. In October 2020, Linnea started her PhD in the same research group continuing the development and synthesis of thiophene-based ligands. Her research focuses on the development of proteophenes – amino acid functionalised thiophene-based ligands, to be used for the study of different pathological targets. Her interest in organic synthesis emerged during her undergraduate studies, and she is particularly interested in the bridge between organic chemistry and biology, where small changes in the chemical structure of molecules can have a great impact on different biological targets.

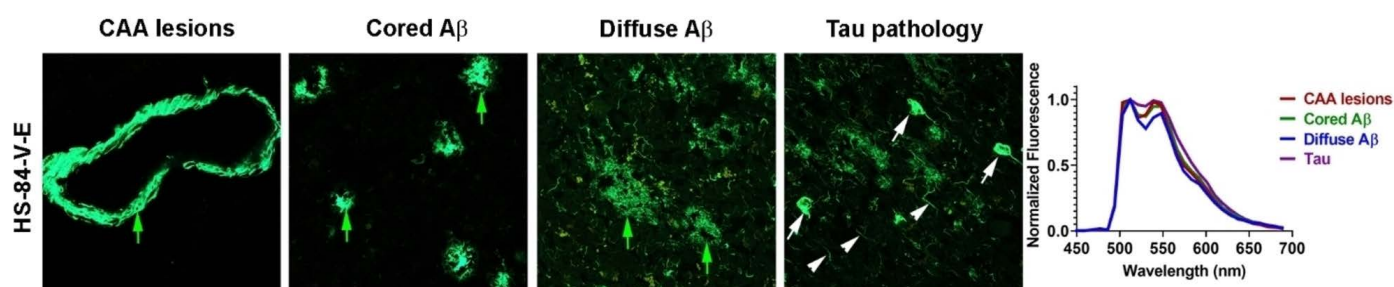




Small fluorescent probes are important tools when studying protein aggregates involved in neurodegenerative diseases, such as Alzheimer's disease (AD). Luminescent conjugated oligothiophenes (LCOs) have been shown to possess properties suitable for identification of these protein aggregates. Proteophenes – LCOs functionalised with amino acids, have interesting photophysical characteristics since the amino acids are chiral and may, thus, induce chirality to the thiophene backbone. The introduction of amino acids to the thiophene backbone may also affect the ligand's binding properties to various biological targets. To achieve pentameric proteophenes having distinct amino acids in different positions along the thiophene backbone, an orthogonally protected pentameric LCO was synthesised using repetitive protection reactions, bromination with NBS as well as palladium mediated Suzuki-Miyaura cross-coupling reactions. The orthogonally protected pentamer enabled functionalisation of distinct amino acids to

different positions along the thiophene backbone through repetitive deprotection reactions under either alkaline or acidic conditions, depending on the protecting group, followed by HATU-mediated amide coupling reactions using the methyl- or tert-butyl protected L-amino acids tyrosine (Y), glutamic acid (E), valine (V) or lysine (L). The proteophenes were used in staining experiments with human AD brain tissue and showed selectivity towards pathological hallmarks associated with AD, such as A $\beta$ - and tau aggregates, and the selectivity was highly dependent on the amino acid functionality and position. Read the full article here: <https://chemistry-europe.onlinelibrary.wiley.com/doi/epdf/10.1002/chem.202201557>

Further characterisation of the proteophenes' photophysical properties, such as induced chirality to the thiophene backbone, are ongoing.





# Click chemistry

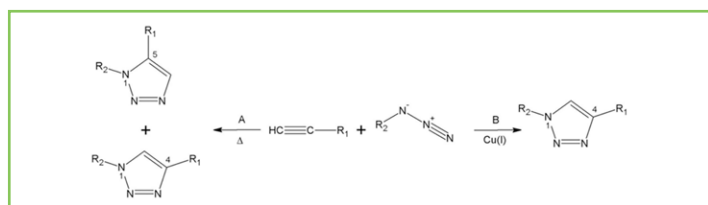
Katriann Arja

There are hundreds and hundreds of chemical reactions in organic synthesis, both rare and complicated, and everyday common straightforward reactions. These make the toolbox for a synthetic chemist to build and modify all kinds of molecules for multitudes of uses. What makes a reaction appreciated is its efficiency in form of easy 'one pot' concept, fast reaction times, high yields, and superior selectivity with a minimum number of bi-products – simply something that just clicks and is done. The term 'click chemistry' was coined by K. Barry Sharpless in 1998 for which he, together with Carolyn R. Bertozzi and Morten P. Meldal, was rewarded with the Nobel prize in chemistry in 2022.

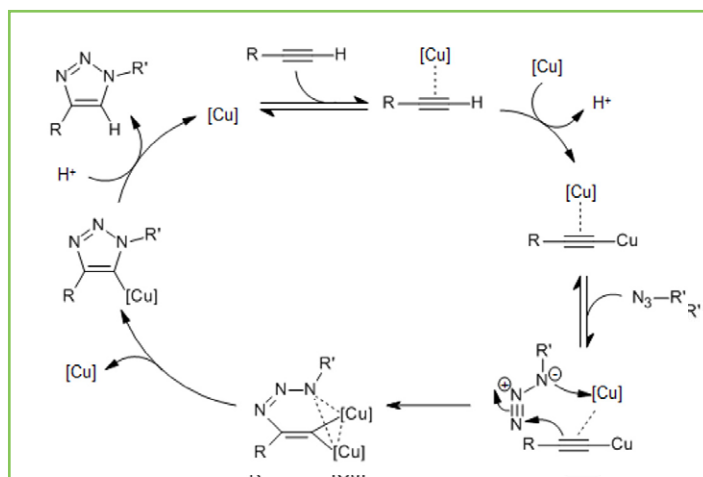
Apart from the most powerful click reaction, the Cu(I)-catalysed Huisgen 1,3-dipolar cyclo-addition between azides and terminal alkynes that has been the front runner of this chemistry for many years, there are other, less well known examples that meet the criteria of click chemistry including modularity, insensitivity to solvent parameters, high chemical yields, insensitivity towards ambient conditions, regio- and stereo-selectivity, and a large thermodynamic driving force to form a single main product. Here we summarise four major classes of click reactions.

## CYCLO-ADDITIONS

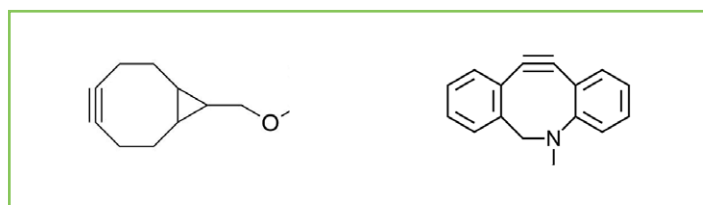
This type of click reactions primarily refers to 1,3-dipolar cycloadditions but include even hetero-Diels-Alder cyclo-additions. Cu(I)-catalysed Huisgen 1,3-dipolar cyclo-addition belongs here and is clearly one of the favourites in the field. 1,3-dipolar cyclo-additions take place between 1,3-dipoles and dipolarophiles to form five-membered rings. When copper(I)-catalysed, reaction of an azide and a terminal alkyne leads regio- and stereo-selectively to 1,4-disubstituted 1,2,3-triazoles.



The mechanism of the Cu(I)-catalysed alkyne azide cyclo-addition (CuAAC) may still be disputed over. A mechanism suggested by W.T. Worrell et al. in 2013 involves two copper ions and an unusual six-membered copper metallacycle formation as an intermediate state in the catalytic cycle.

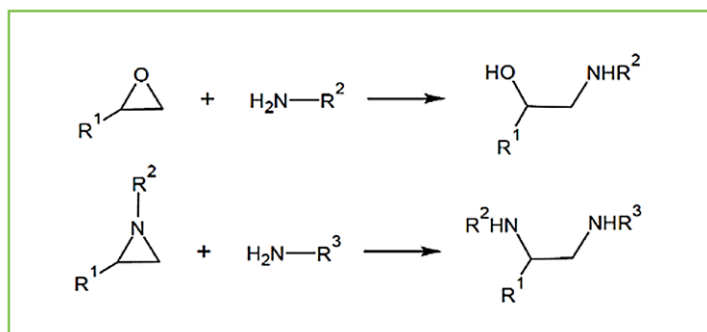


During the past decade, several alkyne substrates have evolved to make fast and efficient conjugation possible even without a copper-catalyst. Copper-free click reactions have become a versatile tool for bio orthogonal conjugation both in vitro and in vivo. In these cases, the alkyne partner is a strained cyclooctyne, such as BCN (bicyclo[6.1.0]nonyne) or DBCO (dibenzocyclooctyne), and release of the strain in the ring system plays the driving force in the reaction.



### NUCLEOPHILIC RING OPENINGS

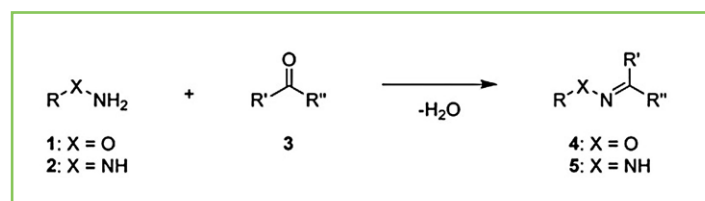
Another type of click reaction is nucleophilic ring opening of epoxides, aziridines and cyclic sulphates and similar. The strained heterocycles react with good nucleophiles in an SN1 or SN2 manner where the ring opening, and the release of the strain drives the reaction. The formed product contains an  $\alpha,\beta$ -functionalised moiety that could be further modified. Some noteworthy applications include constructing antimicrobial materials by conjugation of amine containing antimicrobial molecules on to epoxide functionalised surfaces, and in another example, using this type of click chemistry to contract protein microarrays.



### NON ALDOL CARBONYL CHEMISTRY

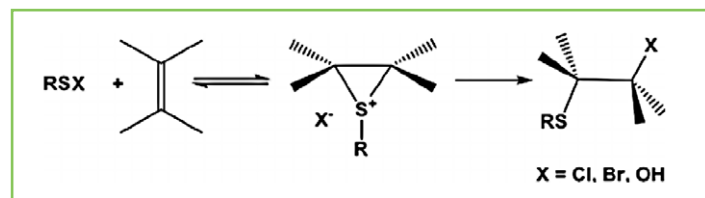
Non aldol carbonyl reactions that are classed as click chemistry include formation of ureas, thioureas, hydrazones, oxime ethers, amides and aromatic heterocycles. Reactions of hydrazine or hydrazine-containing compounds, or molecules containing oxyamine groups, with aldehydes or ketones lead to hydrozone or oxime bond formation, respectively. These reactions are employed in various scientific fields

such as a practical conjugation strategy, and possible applications are found in exploratory organic synthesis, molecular biology, and in polymer and biomaterial sciences.



### CARBON MULTIPLE BOND ADDITIONS

These types of reactions include additions to carbon-carbon multiple bonds to form various three-membered rings or open-chain addition products. Some examples are epoxidation, aziridation, dihydroxylation, sulphenyl halide addition, nitrosyl halide addition and certain Michael additions.



### CONCLUSION

Although CuAAC is the shining example of the world of click chemistry, there are plenty of other elegant reaction to be explored and further developed to make the most out of this ultimate idea of how chemistry should work to benefit us and spare the planet.

# The state of oxidation

Oxidation reactions remain one of the most common and powerful tools for synthetic chemists, allowing for the transformation of many functional groups. Although apparent in the very name 'oxidation' the addition of oxygen drives much of this chemistry, but in modern synthesis there are many methods for increasing the oxidation state of a compound. In this article we will highlight some of the key advancements in oxidation reactions, which has enabled chemists to have more efficient, selective and greener possibilities.

## BAEYER-VILLIGER OXIDATION

As one of the earliest reported oxidation reactions, A. Baeyer and V. Villiger (1899) discovered the conversion of ketones to esters and cyclic ketones to lactones. This was achieved using peracids (e.g., mCPBA, TFPAA and hydrogen peroxide). This reaction allowed for retention of the existing stereo chemistry at the migrating centre, and good regio-specificity based on the migratory ability of the substituents to stabilise the positive charge more effectively (tertiary > secondary > aryl > primary).

## OPPENAUER

As we move forward, in time there were several key advancements in the area of oxidative chemistry in the early and mid 20th century. One key reaction was 'Oppenauer Oxidation' in 1937, whereby the selective oxidation of secondary alcohols to ketones was achieved using aluminium alkoxides (reverse of the Meerwein-Ponndorf-Verley reduction of which this reaction was built from). One of the key advantages of this reaction is the high selectivity to oxidise the secondary alcohol preferentially over the primary alcohol. This high chemo selectivity and relatively mild reaction conditions means this method has been utilised in many synthetic applications to produce hormones, lactones and analgesics.



## JONES

The ability to oxidise primary and secondary alcohols using chromic acid was demonstrated by Jones in 1946. The 'Jones Reagent' is prepared by combining chromium trioxide with aqueous sulphuric acid to generate chromic acid, with acetone as the substrate solvent the oxidation can proceed. A key historical application of Jones Oxidation is found in breathalysers, whereby a green to orange colour change is seen when the chromium (VI) acid is reduced to chromium (III) sulphate. Jones Reagent has largely been replaced by more modern oxidising agents, e.g., the Collins Reagent (a pyridine, dichloromethane and chromium oxide complex) which allows for more acid-, base- and water-sensitive substrates to be oxidised.

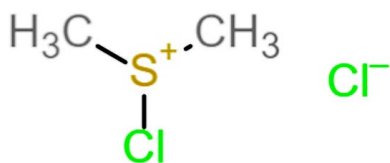
## KORNBLUM, SWERN & DMSO OXIDATION

Kornblum (1957), demonstrated the ability to oxidise alkyl halides and tosylates into carbonyl compounds using

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DMSO, a benefit of which is relatively mild conditions and lack of metal oxidants. There have been many advancements built on DMSO oxidations, mostly to improve the conditions in which the alkoxy sulphonium ion is generated which allows for the SN2 reaction mechanism to proceed (e.g.; Barton (1964), Moffatt-Pfitzner (1963) using DCC, Parikh-Doering (1967) using SO<sub>3</sub>-Pyridine Complex, and Swern (1976 and 1978) using oxalyl chloride). Initially Swern discovered the activation of DMSO could activate trifluoroacetic anhydride, however, it was later found that oxalyl chloride was a more efficient activator and is now commonly used to oxidise primary and secondary alcohols.

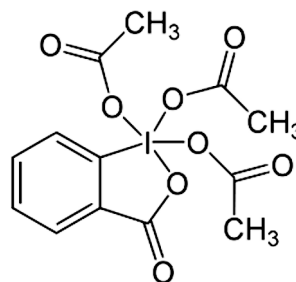
Swern alkoxy sulphonium ion:

**SHARPLESS**

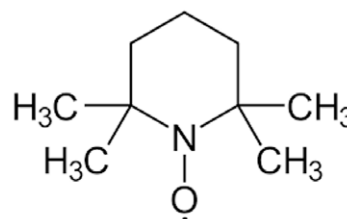
Sharpless received his Nobel prize in chemistry in 2001 for his work on asymmetric oxidations, however, his initial discoveries go back to 1980, where Sharpless and Katsuki discovered that allyl alcohols could be readily oxidised by using an optically active tartrate derivative catalyst (created by combining titanium (IV) tetra(isopropoxide), diethyl tartrate and tert-butyl hydroperoxide). Sharpless Asymmetric Epoxidation became a popular technique for the synthesis of natural products due to the low cost and availability of the reactants. Molecular sieves are commonly used to maintain the catalytic ratios required.

**DESS-MARTIN**

Dess-Martin (1983) demonstrated the use of hypervalent iodine compounds as oxidising agents. Dess-Martin Periodinane (DMP) has become a widely used oxidising reagent due to high selectivity, very mild reaction conditions, ease of work-up, and lack of toxic chromium compounds. Although other hypervalent iodine compounds were developed around the same time (e.g., 2-iodoxybenzoic acid, IBX), due to the lack of solubility in many organic solvents they did not reach the same popularity as DMP.

**DMP****TEMPO**

Initially synthesised by Lebedev and Kazarnovsky (1959), TEMPO (2, 2, 6, 6-tetramethyl-1-piperidiny-N-oxyl), became a popular chemical for many applications (e.g., catalyst, radical inhibitor and structural probe), including notably as an oxidising agent in organic synthesis. This stable radical, when combined with sodium hypochlorite, generates the active oxoammonium species which is the actual oxidant, before being re-oxidised back in a catalytic cycle. Again, the high selectivity, and lack of toxic chromium compounds, makes this a commonly used oxidising agent.

**TEMPO****SUMMARY**

Oxidation remains a key step in the synthesis of aldehydes, carboxylic acids and ketones. Over the past 100 years many contributors to this field have advanced our capability to oxidise more selectively, in milder conditions, without the use of toxic compounds, and with more readily available reagents. With Nobel prizes for oxidation chemistry being awarded as recently as 2001 (Sharpless), we can look forward to advancements in this critical area of organic synthesis.

# Five of the most useful transformations in modern organic synthesis - lessons from old and new reactions

## INTRODUCTION

The monumental efforts invested by the pharmaceutical industry since World War II into the pursuit of new biologically active molecules has undoubtedly been a major driver for the evolution of synthetic organic chemistry. Incredible creativity has gone into translating decades of chemical knowledge, allowing new discoveries from a toolbox of efficient reactions, and enabling the synthesis of very complex, multi-functional molecules.

Over the past 25 years, several scientists have been recognised with the Nobel Prize for the invention of synthetic methodologies that have changed the way chemists approach molecular design. Pd-catalysed cross-couplings, asymmetric hydrogenation, epoxidation and olefin metathesis have led to the development of completely new synthetic strategies and played a key role in the discovery and synthesis of new important drugs (e.g., L-Dopa,<sup>1</sup> Ledipasvir, Losartan<sup>2</sup>, Atorvastatin).

Despite these achievements, modern synthetic organic chemistry is often perceived as an established discipline with limited innovation. While its role remains unquestionably at the centre of new drug discovery/development, R&D efforts have progressively moved to other areas<sup>3,4,5</sup>, notoriously at the interface between biology and chemistry. From this perspective, it is interesting to look at how chemical strategies have evolved from the end of the 1900's to present days.

Brown and Boström<sup>6</sup> found that a limited number of reactions dominated the chemical landscape of modern medicinal chemistry, based on an analysis of the medicinal chemistry literature at two time points, 1984 and 2014. The most common reactions used in

1984 were still in use in 2014, with a few exceptions (increase of Suzuki–Miyaura chemistry over the years, increase in amide bond formations, and decrease in heterocyclic synthesis).

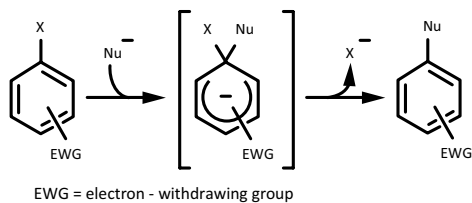
The five most widely used reaction in medicinal chemistry include a fascinating mix of 'traditional' reactions encountered by chemistry students in their first years of study and sophisticated newer transformations: aromatic nucleophilic substitution (S<sub>N</sub>Ar), amination/alkylation of amines, amine protection and deprotection, amide synthesis, and C–C cross-coupling.

## FUNCTIONALISATION OF ARYL COMPOUNDS

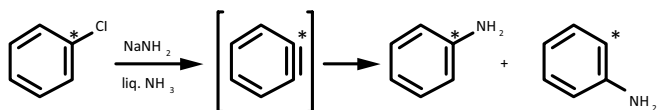
The aromatic nucleophilic substitution is an extremely useful tool for the functionalisation of aryl compounds and it has been around since the early 50's. As all substitution reactions, a nucleophile, such as an amine or an alcohol, displaces a leaving group on the aromatic ring, which is usually a halide. It typically follows three main mechanisms:

- Addition-elimination mechanism, common for substituted aryl halides
- Benzyne mechanism, relevant to unsubstituted aryl halides
- Aromatic S<sub>N</sub>1 of diazonium salts, occurring in the case of aromatic diazonium salts

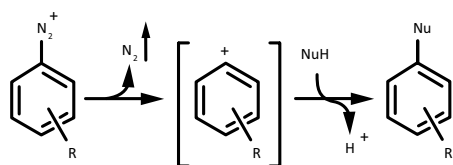
Aromatic nucleophilic substitution is the method of choice for synthesising aromatic alcohols or introducing other nucleophilic functionalities. For the synthesis of amines, however, it is being progressively abandoned in favour of milder, more robust and efficient catalytic method, the Pd-catalysed Buchwald–Hartwig C–N coupling.



Addition-elimination mechanism



Benzyne mechanism



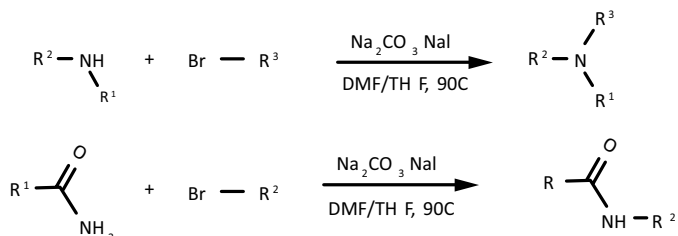
Aromatic S<sub>N</sub>1

## SYNTHESIS OF AMINES

The Buchwald-Hartwig amination of aryl halides is the first of the two main routes to adding amine functionality to organic molecules, the second one is the nucleophilic substitution of alkyl halides. A third obvious synthetic approach is the reductive amination of carbonyls, which seems however much less frequently used<sup>6</sup>.

The nucleophilic substitution of alkyl halides with aliphatic or heteroaromatic amines, often referred to as alkylation of amines, is a 'historical' organic reaction. It's simple, well established and still a primary method for the alkylation of amines with aliphatic compounds.

The reaction occurs at relatively high temperatures and often requires the use of a strong base, such as sodium bis(trimethylsilyl)amide and cryogenic conditions.

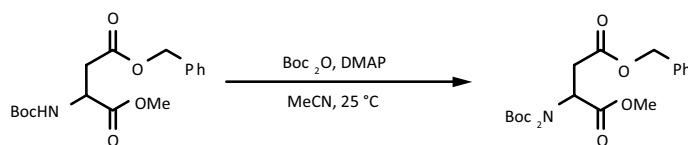


The rate of alkylation follows the order primary amine > secondary amine > tertiary amine and the reactivity of the halide derivative follows the electronegativity of the halide substituent. Bromide and iodides are the most

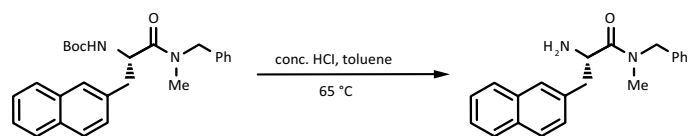
practical building blocks, while chlorides remain common for their broad commercial availability. Sodium iodide is often used to generate in-situ a more reactive alkyl iodide when the starting material is a different halide. The nucleophilic substitution of alkyl halides is not considered a green reaction as it produces a halide ion side product and it can be demanding from the calorimetric viewpoint. Big scale industrial methods for the production of simple amines tend in fact to prefer the amination of alcohols as the side product is water. Despite that, it remains an indispensable tool in the synthetic organic chemist's toolbox.

## HANDLING AMINES IN MULTIFUNCTIONAL COMPOUNDS

Given the frequency of the amine functionality in bioactive molecules, it is not surprising that amine protection and deprotection reactions are a common occurrence in synthetic chemistry. The BOC (tert-butyloxycarbonyl) protecting group, chemically a di-tert-butyl dicarbonate (Boc<sub>2</sub>O), is probably the most common amine protecting group in non peptide chemistry. The process usually achieves high yields and fast conversions under flexible and relatively mild conditions.



The deprotection of a BOC-protected amine is a simple carbamate hydrolysis in acidic conditions. The reaction is fast and happens at room temperature. Biphasic systems can be used, with the protected amine dissolved in the organic phase, mixed with the aqueous solution of the acid.

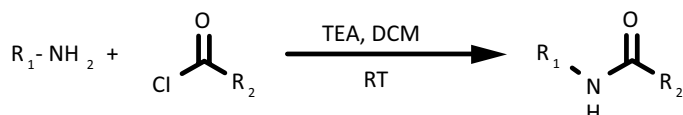


These reactions have remained unchanged over the years. Their simplicity, broad substrate scope and robustness make them extremely practical and enable flexibility in the synthesis of multi-functional compounds.



## SYNTHESIS OF AMIDES

The next class of common organic functionality, technically related to amines, are amides. The Schotten-Baumann reaction, or the acylation of amine by acyl chloride, has been the standard for a long time. The reaction proceeds rapidly at room temperature in aprotic solvents in the presence of a base, but it suffers from the instability of the acyl chlorides and some hazards related to the release of hydrochloric acid as a by-product and often other chloro-derivatives from the decomposition of the starting materials.



The coupling between the amine and an anhydride is a safer, cleaner and mechanistically related alternative, the only significant difference being the acid by-product: Hydrochloric acid in one case, a carboxylic acid in the other.

Significant progress in the synthesis of amides has been achieved in the last three decades by research in the field of peptide synthesis. These advances have de facto made the Schotten-Baumann reaction a thing of the past.

The big variety of peptide coupling reagents that are commercially available nowadays share a fundamental chemical principle: The synthesis of a highly activated ester. These activated esters can then be efficiently coupled to an amine using reaction conditions similar to the Schotten-Baumann reaction (base, aprotic solvent, RT) without its main drawbacks.

The most common reagents belong to two main groups:

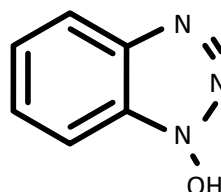
- Carbodiimides
- Hydroxybenzotriazole aminium/uronium or phosphonium salts

The two most common carbodiimides are dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC) and 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC). They react with carboxylic acids to form a highly reactive O-acylisourea that can be converted to an amide by reacting with an amine, with high yields and short reaction times.

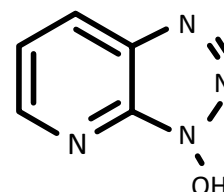
In case of chiral molecules, the reaction is often performed in the presence of a triazole to avoid

spontaneous racemisation, a common occurrence with amidation of O-acylisourea. In this case the activation step should be better described as a two-step DCC/hydroxybenzotriazole activation.

The most common triazoles are 1-hydroxy-benzotriazole (HOBt), and 1-hydroxy-7-aza-benzotriazole (HOAt).



HOBt



HOAt

A strategy to avoid the two-step acyl activation process in peptide chemistry is made possible by using ammonium/uronium or phosphonium salts of the hydroxytriazoles mentioned above. This way it is possible to avoid completely the use of DCC and the formation of the O-acylisourea intermediate.

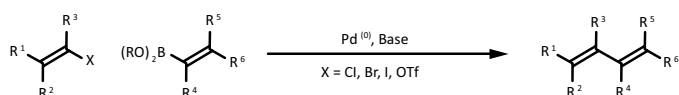
HOBt has a corresponding uronium salt called HBTU and its common phosphonium salts are called BOP and PyBOP. The corresponding uronium and phosphonium salts of HOAt are HATU and AOP/PyAOP respectively.

The history of amide chemistry over the arc of the last 25 years, inspired and driven by problems and solutions from a different field (amino acid conjugation in peptide synthesis), is a great example of how organic synthesis can evolve over time, while maintaining its fundamental principles unchanged.

## FORMATION OF C-C BONDS

The fifth and final reaction of this review addresses one of the biggest challenges in organic synthesis, the formation of C-C bonds. Carbon-Carbon cross-coupling reactions represent one of the biggest revolutions in organic chemistry and have rapidly become ubiquitous in the synthesis of fine chemicals. Their invention won Akira Suzuki, Ei-Ichi Negishi and Richard Heck the Nobel Prize for Chemistry in 2010.

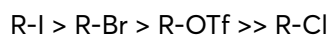
Among the various types of cross-coupling, the Suzuki-Miyaura – usually simply called “Suzuki coupling” – is arguably the one with the broadest utility and applicability. The Suzuki chemistry is based on the Pd(0) catalysed coupling of an aryl or vinyl halide with an aryl or vinyl boronic acid.



Its advantages over similar reactions reside in the mild conditions, common availability of the starting materials and their general low toxicity. Boronic acids are easily prepared, widely available on the market and reasonably cheap. As a matter of fact, they present lower environmental impact and safety hazards than organozinc or organostannane compounds, the substrates of choice for C-C bond formation until the 1990's.

Since its invention in 1979<sup>9</sup>, significant progresses have been made and the use of boronic acids, esters and trifluoroborates salts is now widely reported, while even alkyl boronic acids can be used as substrates (with the use of late generation catalysts).

The scope of the other coupling partner has also expanded over time to include pseudo-halides, such as triflates or aryl diazonium salts, and alkyl halides. The relative reactivity of the halide/pseudo-halide coupling partner can be summarised as follows:



Recent generation homogeneous Pd catalysts have reduced the catalyst loading by orders of magnitude, contributing to the economy of the reaction and enabling a growing number of commercial processes. It is possible – in fact beneficial – to screen many different catalysts, from relatively simple Pd(0) complexes, such as Pd acetate and Pd tetrakis, or various forms of Pd pre-catalysts and phosphine ligand to fully formed (pre) catalysts, often as air-stable complexes for an easier handling by the bench chemist.

## CONCLUSIONS

These 'top five reactions' tell us a fascinating story, made of tradition and a constant, sometimes subtle flow of innovation. While new inventions occasionally provide leaps forward that change profoundly the chemical landscape, innovation is driven by the sum of small steps

in the applications and reaction conditions<sup>8</sup>, often inspired by research in adjacent fields.

For example, while SNAr and BOC protection/deprotection have remained substantially unchanged, amide synthesis has benefited from progress in the field of peptide chemistry and significant progress has been made in the field of amination of aromatic substrates.

A few common traits unify all these reactions: robustness, flexibility, broad substrate and reaction conditions scope<sup>9</sup>. The importance of other, more niche transformations cannot be understated, nonetheless. They represent some incredible chemical innovations and while not as widespread as the 'top five' discussed above, they play a key role in accessing chemical space that would be otherwise inaccessible.

The research in the field of synthetic organic chemistry is focused on overcoming the historical overreliance on just a few robust synthetic transformations. Its aim is to expand the sampling of the chemical space in modern organic synthesis<sup>10</sup>, while also trying to find new solutions for unaddressed chemical problems<sup>10</sup>.

The commercial availability of starting materials, building blocks and reagents has played and will continue to play a key role in supporting the development of the field. Thermo Fisher Scientific offers a comprehensive portfolio of fine chemicals, reagents and chemical essentials through the Acros Organics and Alfa Aesar brands. All products are available in research and bulk quantities and designed to support synthetic organic chemists at all stages of their work, from early stage R&D to advanced process chemistry and production.

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# Topliss sets in drug design

## - technical notes for the medicinal chemist

### THE TOPLISS SCHEME FOR OPTIMISATION OF PHENYL RING SUBSTITUTION IN DRUG DESIGN

The drug design process, from identification of an initial hit in a biological assay to the generation of a molecule suitable for marketing as a therapeutic entity, is long, arduous and expensive. Medicinal chemists may spend years designing and synthesising thousands of analogues of an initial hit to optimise, not only the fundamental interaction of the molecule with the biological target, but also the distribution, metabolism and pharmacokinetic profiles of the drug. The length of the process ultimately has a major impact on drug development costs, and any stratagem that can help drive the design process to completion in a shorter time is highly desirable.

The optimisation process usually involves changing several characteristics of the molecule, such as its shape, functionality (often to alter H-bonding or ion-pair interactions), lipophilicity and electronic characteristics. This is a broad, multi-factorial process, and usually needs to be broken down into a step-wise approach to provide focus for synthetic activities. One such step commonly faced by the medicinal chemist during the drug design process is the identification of the optimum substitution pattern on pendant phenyl or heteroaryl rings, which are often encountered in lead compounds in new drug discovery programmes.

There are a very large number of compounds which could be explored for potency enhancement arising from substituents on a phenyl ring. Aside from the many possible substituents, numbers rapidly increase when substituent position on the ring and combinations of more than one substituent are considered. Clearly, it would be advantageous to employ approaches which have the potential to identify as quickly as possible the most promising prospects among the multitude of possibilities.

Historically, the drug design process was driven by the experience and intuition of the chemist and by the availability of starting materials. However, in the 1960s and 1970s the development of Hansch's methods for structure activity correlations brought a more rational approach and the ability to generate quantitative structure-activity relationships (QSAR) within analogue series<sup>12</sup>. Essentially, the QSAR approach aims to take a set of analogues of a biologically active molecule, identify and quantify their physicochemical properties, and determine which, if any of the properties has a significant input to the biological activity.

Commonly used property descriptors are the Substituent Hydrophobicity Constant,  $\pi$ , a measure of a substituent's hydrophobicity relative to hydrogen, the Hammett substituent constant,  $\sigma$ , a measure of the overall electron withdrawing or donating characteristics of a substituent, and Taft's steric factor,  $E_s$ . By an appropriate mathematical derivation of the relationships between these and/or other properties and the level of activity, it should then be possible to predict the biological activity of novel analogues, thereby enabling the medicinal chemist to focus synthetic activities on compounds likely to exhibit enhanced activity. Alternatively, if analogues are found which do not fit the derived relationship, this may be an indication that an as yet unidentified characteristic of the molecule is important for activity. where C is the drug concentration for a chosen biological effect and  $k_1$ -4 are regression coefficients determined by iterative curve fitting, or parabolic, for example:

$$\log \frac{1}{C} = k_1 \pi + k_2 \sigma + k_3 E_s + k_4$$

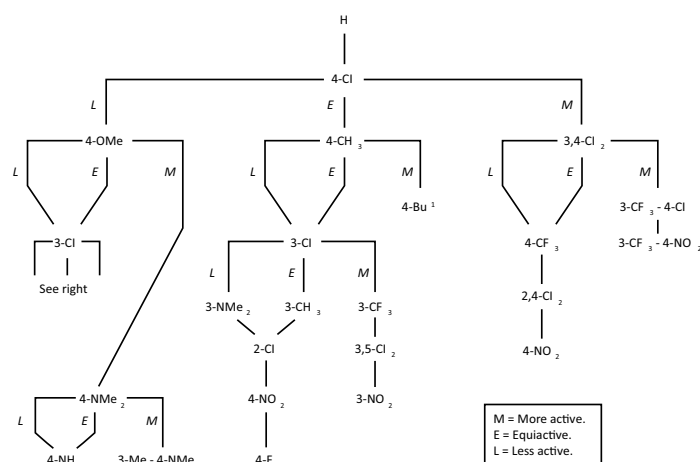
Such correlations have also been used many times in a predictive sense to direct synthesis programmes.

$$\log \frac{1}{C} = -k_1 \pi^2 + k_2 \pi + k_3 \sigma + k_4 E_s + k_5$$

However, there are a number of issues in using such approaches. To obtain a good statistical 'fit' and generate a reliable correlation, a relatively large number of compounds should be used in the initial analysis – not always a convenient approach where synthesis routes are problematic. In addition, it is not always easy to separate out the significance of different parameters. For example, if activity varies across a homologous series of compounds in which an alkyl chain is increased in size, it can be difficult to decide whether this is due to an increase in size or lipophilicity or both. Binding modes may also change across a series of compounds, thereby disrupting the continuity of the mathematical analysis. Finally, one should not underestimate the resistance of some chemists to becoming involved in this type of mathematical approach to drug design – QSAR analysis can often be seen as something "best left to the QSAR specialist".

## TOPLISS SCHEMES

In the 1970s, Professor J G Topliss addressed some of these concerns with his non mathematical operational schemes for analogue design<sup>3-5</sup>. His methods, designed for maximum simplicity of application by the medicinal chemist, were formulated to avoid the use of computers and statistical procedures and to progress as rapidly as possible to the most potent compounds in a series. The fundamental basis of the methods was the concept, pioneered by Hansch<sup>1,2</sup>, that the primary influences on activity from introduction of a substituent resulted from the lipophilic, electronic and steric properties of the substituent which could be represented in a quantitative manner by the physicochemical substituent constants,  $\pi$ ,  $\sigma$ , and  $E_s$  respectively.



**FIGURE 1:** Topliss scheme for aromatic substituents with precursor ion de-selected.

The first of these, "Utilization of Operational Schemes for Analog Synthesis in Drug Design" used a decision tree approach, which later became known as the Topliss tree<sup>3</sup>. A slightly simplified version of the scheme is summarised in Figure 1.

A step-wise procedure is used, starting with the parent unsubstituted phenyl compound and proceeding first to the 4-chloro analogue. The 4-chloro substituent is lipophilic (+ $\pi$ ) and electron withdrawing (+ $\sigma$ ). The potencies of the two compounds are then compared and the 4-chloro compound is classified as greater than, equal to, or less than the unsubstituted compound.

A potency increase can most probably be attributed to a  $+\pi$  effect, a  $+\sigma$  effect, or to a combination of  $+\pi$  and  $+\sigma$ . Then the 3,4-dichloro compound would be selected for synthesis, since whichever of these effects applies, the summed  $+\pi$  and  $+\sigma$  values would be larger with good prospects for a further potency increase.

If the 4-chloro compound was found to be 'equi' potent with the parent compound this could result from a favourable  $+\pi$  effect offset by an unfavourable  $-\sigma$  dependency. If this is the case then the 4-methyl analogue should show enhanced potency since this substituent is lipophilic and electron releasing, i.e., a  $+\pi$   $-\sigma$  type substituent.

The remaining segment of the scheme is concerned with the synthetic sequence to be followed where the 4-chloro analogue was found to be significantly less potent than the parent compound. One may conclude that either there is an unfavourable effect from any kind of 4-substitution for steric reasons, or activity is  $-\sigma$  or  $-\pi$  controlled. Assuming that the  $-\sigma$  effect is the most probable explanation, the 4-methoxy compound ought to be a favourable selection for synthesis based on the electron releasing property of this substituent and its marginally hydrophilic character.

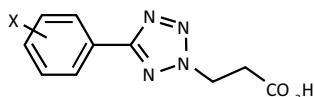
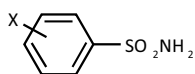
This completes a description of the top segment of the decision tree with its three branches and illustrates the type of rationale used. Note that the substituents required to follow the scheme should facilitate synthetic accessibility. Further details on the continuation of the tree are contained in the original publications<sup>3,4</sup>.

The foregoing analysis relates to a pendant phenyl ring, but with some minor modifications it could also be applied to the benzenoid portion of a heterocyclic compound e.g., indole, benzimidazole, benzthiazole, benzoxazole, quinoline or quinazoline.

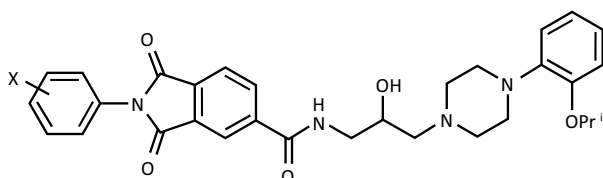
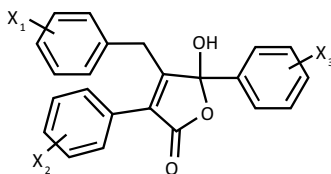
The second Topliss method<sup>5</sup>, "A manual Method for Applying the Hansch Approach to Drug Design" is a procedure in which an initial small group of compounds

is selected, tested, and ordered according to potency. These compounds, the unsubstituted parent compound, the 4-chloro, 3,4-dichloro, 4-methyl and 4-methoxy are the same as those utilised in the top portion of the operational scheme for the first method. The potency order in the compound group is then compared to the tabulated potency order calculated for various parameter dependencies relating to lipophilic, electronic and steric effects. From this activity pattern analysis probable operative parameters can be deduced and a new selection made for the synthesis of potentially more potent analogues. It differs from the previously described decision tree, the single compound, step-wise approach, in that it involves the batch-wise analysis of small groups of compounds, usually the preferred procedure for logistical reasons if the compounds are relatively easy to synthesise.

Both step-wise and batch procedures were successfully tested on a number of existing compound series as described in the initial publications, including a series of sulfonamides (Structure 1) with carbonic anhydrase inhibitory activity <sup>6</sup> and a series of antiinflammatory aryltetrazolylpropionic acids (Structure 2)<sup>7</sup>.



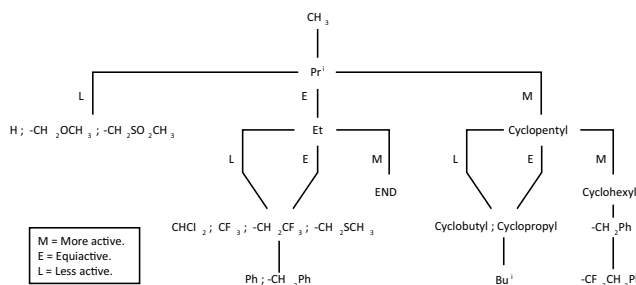
Subsequently the procedures have been widely used to advantage by medicinal chemists as evidenced by numerous literature citations over the past 30 years. Two more recent examples are a series of butenolide endothelin antagonists (Structure 3) **8** and some arylphthalimide-containing  $\alpha 1A$ -adrenergic antagonists (Structure 4)<sup>9</sup>.



The methodology has also been described in various text books of medicinal chemistry and drug design<sup>10-12</sup>.

It should be noted that if unrecognised influences other than those considered were controlling with respect to activity then the methods would not yield useful results. However, in cases such as these no disadvantage should be incurred relative to any other way of proceeding, particularly since the more accessible substituents have been emphasised. Also, situations are sometimes encountered where there is very little variation in activity in a compound series with any type of phenyl ring substitution.

Use of the procedures can be adapted to the particular circumstances faced by the medicinal chemist. This may involve, depending on the compound series at hand and the testing situation, synthesis in a more or less step-wise mode or in groups of compounds of varying size, possibly using parallel synthesis. As stated in the original publication<sup>3</sup>, it is not necessary to follow the schemes exactly as described, particularly with regard to restricting the choice of substituents to those specifically indicated in the publications. The important point is to follow the underlying concepts embodied in the procedures, i.e., ascertaining the probable key factors underlying substituent influence on potency, and following the observable trends to arrive at the most potent analogues as rapidly as possible, employing the most accessible substituents. When the most favourable type of substituent has been identified through these procedures, a detailed examination of similar substituents, including more unusual and difficultly accessible ones, could then be carried out. Whilst somewhat outside of the scope of the current discussion, it is worthy of note that Topliss schemes have also been applied to SAR development in series where the variation in substitution is applied to aliphatic side chains. The relevant scheme 3, which applies similar rationales to those described for aromatic substitution, is summarised in Figure 2.

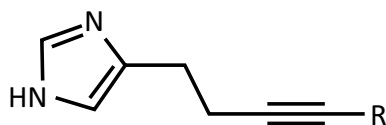


**FIGURE 2:** Topliss scheme for aliphatic side chain substituents A.

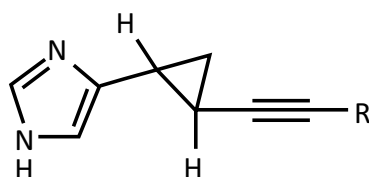
An example of this type of approach was described for some acetylene-based histamine H3 receptor ligands (Structures 5 and 6)<sup>13</sup>.



Structure 5

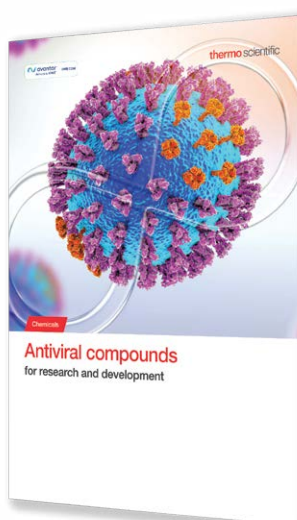
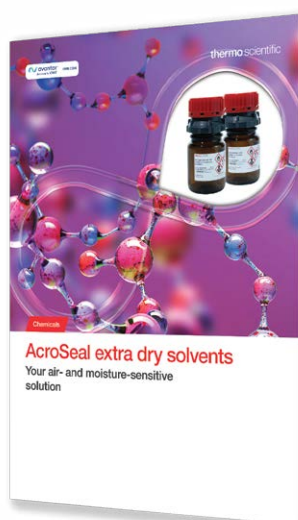


Structure 6



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# How to support a sustainable supply chain

Chemical research and innovation have a significant impact across a variety of industries. It's estimated that 96% of all manufactured goods depend on chemical manufacturers, producers and distributors to fulfil product needs. From agriculture to energy to health, chemists have a long history of applying their skills, time and expertise to provide much needed solutions. At Apollo Scientific, a leading research chemicals supplier, we understand the evolving needs of the industry and are committed to being the socially responsible partner of choice supporting discovery across the global market.

## ENABLING SCIENCE, KNOWLEDGE & DISCOVERY IN TRYING TIMES

In recent years, global mega trends such as COVID-19 and international conflicts have led to increasingly stretched supply chains. For chemists, researchers, distributors and manufacturers across the chemical industries, these disruptions impact their ability to innovate and discover.

At the same time, governing agencies and regulatory bodies have implemented robust policies, systems and procedures within the supply chain for chemicals. While these updated regulations allow customers to make informed decisions about products and suppliers, they have also placed increased pressure on an already stretched supply chain.

It's important to re-examine the modern chemical supply chain in the context of these social, economic and environmental shifts. This allows the industry to ensure it's still ready to provide chemists with the materials needed to solve the world's biggest problems. At Apollo Scientific, a trusted partner for research chemists around the world, we are committed to supporting discovery and innovation from concept to completion.

## LOCAL SUPPLIERS: GEOGRAPHICAL TRENDS IN THE SUPPLY CHAIN

Following the turbulence of the UK's exit from the EU, the COVID-19 pandemic and the conflict in Ukraine, core values driving the supply industry have changed. Supplier location is now more important than ever to the customer, ensuring that the products can be delivered consistently and at a reasonable cost. As a result of this, customers in both the US and EU markets are now more



likely to buy from suppliers based in their home region. Moreover, as customers seek to secure their supplies, more are utilising secondary suppliers to ensure there is a back-up option if their usual supplier cannot meet their requirements.

Trade barriers are also putting geographical factors at the forefront of consideration for customers. For example, the potential new costs for imports driven by Brexit or the vastly increased taxes on importing goods from China to the US. These changes are also affecting where suppliers buy their products, creating a shift in geographical manufacturing trends.

## APOLLO SCIENTIFIC IS AMONG THE TOP 1% OF COMPANIES FOR SUSTAINABILITY WITHIN OUR SECTOR

At Apollo Scientific, we have diversified our supply locations to allow us to meet the needs of customers across the globe reliably, efficiently and rapidly, while also offering the same to local customers.

To do this, we have invested in our global supply infrastructure, with warehouses in the UK and US to offer next day delivery to customers on both sides of the Atlantic. There's always room for growth though, and as such Apollo Scientific is continually expanding its partnerships with distributors in mainland Europe to ensure a quick, steady supply of its products to European customers without the complications that Brexit may cause. An Apollo Scientific warehouse in mainland Europe is also on the horizon for the near future.

The requirements of customers have changed over the past few years too, and chemical suppliers must alter

their range in line with demand. With the stresses felt by the industry in recent years, social responsibility, environmental impact and locality in supply are emerging as key drivers in making a purchasing decision.

### THE SOCIAL RESPONSIBILITIES OF THE SUPPLIER

Beyond delivering their products, suppliers have additional commitments to their customers in the scope of corporate social responsibility (CSR). Today, many suppliers have developed a code of conduct, where they screen their manufacturers and upstream suppliers to ensure that legal quality standards and human rights are being maintained and respected throughout the supply chain.

Legal requirements can only go so far, however, and suppliers must create and uphold their own internal guidelines regarding staffing, quality control and safety, with customer and stakeholder feedback as a motivator for positive change. Apollo Scientific screen parties within the supply chain, from the source to the customer, in order to maintain company standards. By visiting facilities across the world, including regions with laxer labour laws, Apollo Scientific can help ensure that robust standards are being followed across the supply chain. There are also checks carried out downstream too, ensuring potentially hazardous chemicals are only being handled by professionals.

When ordering a product, as a customer, you expect to receive exactly what you have ordered. This is especially true when working in the pharma industry where a mistake in the supply chain could potentially have fatal outcomes. This is yet another reason why upholding the highest internal guidelines and commitments is a priority for many chemical suppliers. Ensuring manufacturers and upstream suppliers are upholding these standards is an important step; however, additional safety nets can be put in place to provide customers with peace of mind. At Apollo Scientific, we have rigorous quality control and quality assurance systems to ensure that a product is of sufficient quality and is labelled correctly to avoid costly mistakes in the supply chain.

### SUPPORTING SUSTAINABILITY FOR A GREENER FUTURE

As the central science supporting critical industries, such as agriculture and pharma, chemistry and chemicals are under new pressures to meet rapidly evolving environmental needs.

The impact of sustainability pressures within the supply chain are apparent in new laws and regulations. At Apollo Scientific we believe in evolving not just to meet regulations but also to ensure our approach aligns with our values.

Being in the chemical industry, we are conscious of the impacts that our business can have on society as a whole, be it through our own activity or via third party chemical manufacturing and distribution. As such, at Apollo Scientific, we've implemented various CSR projects, to ensure our approach to business is aligned to our vision of environmental and social welfare.

Apollo Scientific has also become a member of the UN Global Compact, an initiative which calls on companies to carry out their business responsibly by aligning strategies with the UN principles surrounding labour rights, sustainability, modern slavery and anti-corruption.

### SUSTAINABLE DEVELOPMENT

In 2015, the United Nations (UN) set its 2030 agenda for sustainable development, providing an ongoing plan for peace and prosperity for everyone on Earth. At its centre are 17 Sustainable Development Goals (SDGs); a global partnership where all countries collaborate to tackle poverty, alongside improving the health of individuals and the planet, while fighting inequality and fostering economic growth.

The current SDGs are the latest of many iterations of sustainability- and development-related targets set by the UN. However, although it may seem the responsibility of governments to adhere to these goals; they can be worked on at an individual and corporate level too. We all have a part to play in making the future better, and the SDGs are our tools to make it happen.

As well as a commitment to customers, at Apollo Scientific we have made great progress in becoming a more sustainable and equitable supplier. This year, we were awarded the EcoVadis Platinum sustainability rating for a second consecutive year, further improving on our score in 2021. This puts Apollo Scientific among the top 1% of companies for sustainability within our sector. This achievement is supplemented by our commitments to a wide range of sustainability goals, such as becoming a net zero company by 2040 and using 100% sustainable packaging by 2030.

All these changes will help build a more sustainable supply chain for future generations.

Through this consultation with our suppliers and customers, we were able to switch our packaging to be more sustainable. And, by working closely with our suppliers, we can better understand the sustainability challenges within the supply chain. Allowing us to better support them in implementing greener methods.

By Chief Technical Officer, Tim Kemp and Purchasing Manager, Rory O'Donnell.

Original article published in Problem Solvers, Chemistry World on 1st December 2022 –

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The major differences are their different wavelengths and frequencies. UV rays have a higher frequency and shorter wavelength than infrared. The wavelength of IR is about 1 and 750 nm, and the ultraviolet wavelength is about 400 and 10 nm.

**UV spectroscopy:** Has a shorter wavelength compared to visible light, higher energy and frequency. It can break several organic bonds and cause skin cancer (changes in the level of electronic energy within a molecule).

**IR spectroscopy:** Has a longer wavelength compared to visible light, thus low frequency and less energy per photon (rotational and vibration movements of the molecule changes).

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Acetonitrile		84701.290	84700.320	NEW
1-Butanol		84709.290	84701.320	
tert-Butyl methyl ether		88441.290		NEW
Carbon disulphide		85971.290		
Chloroform stab.		22715.293		
Cyclohexane		23225.296		
Dichloromethane stab.	84702.260		84702.320	NEW
N,N-Dimethylformamide		84710.290		
DMSO	91258.260		84710.320	NEW
1,4-Dioxane		84715.290		
Ethanol 96%	20822.266	20822.290		
Ethanol absolute	92423.260			NEW
Ethylacetate	91259.260		91259.320	NEW
n-Heptane	84712.260			NEW
n-Hexane	140095D	84712.290		NEW
Isooctane (2,2,4-Trimethylpentane)		28776.293		
Methanol	84705.260		28776.320	NEW
n-Pentane		84714.290	84705.320	NEW
2-Propanol		84706.290	84714.320	
Tetrachloroethylene		83950.290	84706.320	
Tetrahydrofuran		84707.290	83950.320	
Toluene		84707.320	84708.290	NEW



Discover our high purity solvents for NMR and UV/Vis Spectroscopy

**DOWNLOAD**



# How your deuterated solvents for NMR spectroscopy are made

In case this has escaped your notice, all deuterated solvents contain one thing in common, deuterium! Deuterium (D) is one of two stable isotopes of hydrogen. We use it in the form of deuterium oxide ( $D_2O$ ), also called heavy water, to produce our deuterated solvents.

Heavy water is obtained from large bodies of natural water (e.g., from lakes). The natural abundance of deuterium in water (i.e., 0,015% D), is increased dramatically to the desired enrichment, for example 99,8% or 99,9% D. In theory, deuterium for heavy water could be created in a nuclear reactor, but separation from ordinary water is the cheapest bulk production process.

The most common process for producing heavy water is the dual-temperature exchange sulphide process (known as the Girdler sulphide process) developed independently and in parallel by Karl-Hermann Geib and Jerome S. Spevack in 1943. The method is an isotopic exchange process between  $H_2S$  and  $H_2O$  ('light' water), that produces heavy water over several steps. It is a highly energy intensive process. The world's leading supplier of deuterium was Atomic Energy of Canada Limited until 1997, when the last heavy water plant was shut down. The energy requirement was very large, as it is roughly the same amount of power as half a nuclear reactor at medium power requires.

In fact, it is necessary to distill 7 tons of 'light' water to obtain 1 litre of heavy water enriched to 99,9% D. This gives you an idea of the high cost associated in producing this raw material.

A fraction of the heavy water obtained is electrolysed to provide deuterium gas ( $D_2$ ). Deuterium gas is used in the synthesis of some of our deuterated solvents. Currently, we have several ways to synthesise our deuterated solvents, however, there is no standard manufacturing process for all deuterated solvents, as each solvent has specific properties (boiling point, density, etc).



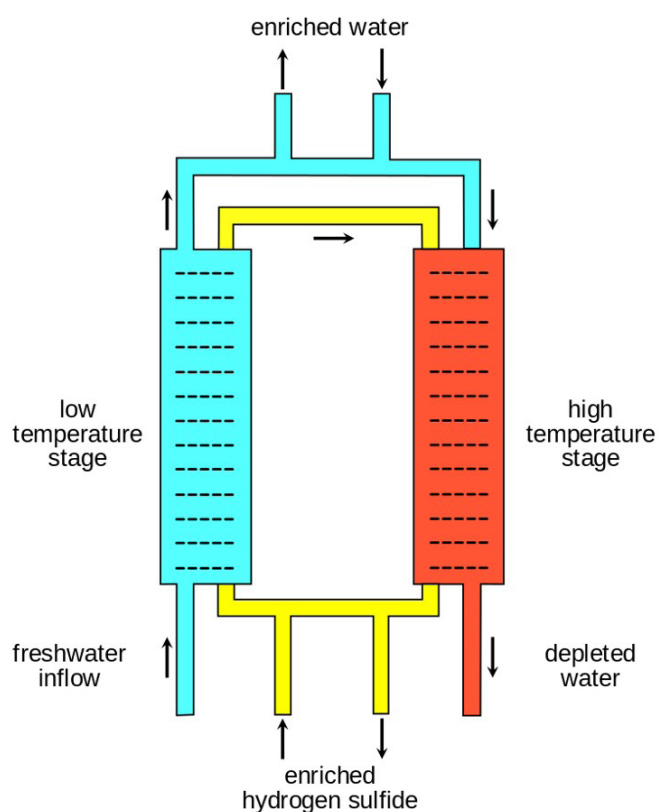
## 1. ISOTOPIC EXCHANGE

The purpose is to exchange all the hydrogen atoms of a solvent (e.g., benzene) by the deuterium atoms of  $D_2O$  under drastic conditions (often heating under pressure and elevated temperatures and basic conditions) and sometimes using a metal catalyst (platinum or nickel, for example). To bring a deuterated solvent up to 99,8 or 99,9% D, several exchanges with  $D_2O$  or  $D_2$  are often required.

## 2. TOTAL SYNTHESIS

Isotopic exchange is not possible with all solvents. Some solvents require chemical synthesis to bring the enrichment up to 99,8 or 99,9%.

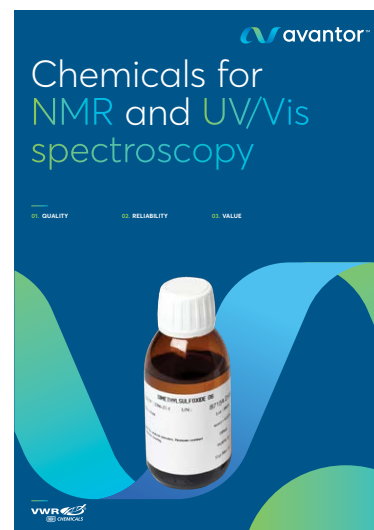
For example, deuterated chloroform ( $CDCl_3$ ) is made from hexachloroacetone ( $Cl_3C-CO-CCl_3$ ) and 'new' heavy water (two molecules of deuterated chloroform are then obtained by removing one molecule of  $CO_2$  per molecule of hexachloroacetone) under specific conditions (heating, catalyst).



Girdler sulphide process. © Roland Mattern, wikimedia common.

In this case, the desired enrichment in deuterium is achieved the first time (same as heavy water).

Once the deuterated solvent obtained, and has passed all QC testing, the material is packed for you under controlled atmospheric conditions to eliminate any contaminant.



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# High purity and yield purification of $\alpha$ -Lactalbumin from cow's milk using preparative liquid chromatography

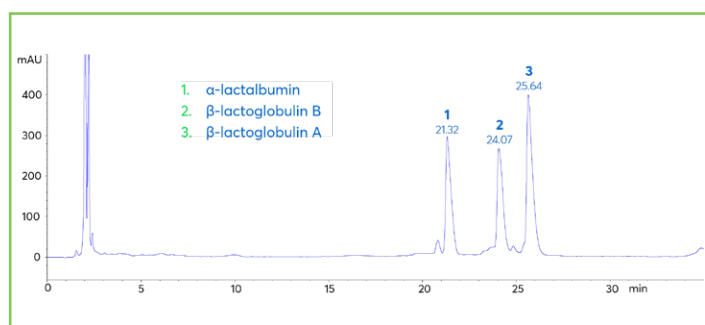
$\alpha$ -Lactalbumin is one of the main proteins in human milk<sup>1</sup>, with bovine  $\alpha$ -lactalbumin showing 72% amino acid sequence homology with human  $\alpha$ -lactalbumin<sup>2</sup>. Applications of  $\alpha$ -lactalbumin include its use in infant formula, as well as various nutraceutical and therapeutic supplements to help with dietary requirements, diseases and/or disorders<sup>3</sup>.  $\alpha$ -Lactalbumin extraction is, therefore, of high commercial value, particularly if the process is kept at a low cost<sup>4</sup>.

The extraction of targeted compound(s) from a sample is often performed using preparative scale liquid chromatography (LC) under non ideal overloaded conditions to maximise yield without compromising purity. In this knowledge note, the high yield fractionation of  $\alpha$ -Lactalbumin from cow's milk, via preparative LC using a wide pore reversed-phase column, is demonstrated. The high purity of the extracts is then confirmed by non overloaded analytical scale LC.

## IDEAL NON OVERLOADED SEPARATION CONDITIONS

The extraction of  $\alpha$ -Lactalbumin initially involves the separation of whey from bovine milk. Cow's milk (whole milk) was purchased from the local market and was curdled with the addition of a small amount of acetic acid, followed by filtration to remove the curds. A small aliquot of the filtered liquid (known as whey) was analysed by analytical LC, as shown in Figure 1. A wide pore (300 Å) C4 reversed-phase column was used to ensure good chromatographic performance for the separation of the whey proteins<sup>5,6</sup>. The use of a larger pore size ensures that the proteins have good access to the pore system within the stationary phase bead. The selection of the C4 stationary phase was based on the need for a weakly hydrophobic stationary phase, due to the hydrophobicity of the proteins. The three main whey

protein components were identified as  $\alpha$ -Lactalbumin,  $\beta$ -Lactoglobulin B and  $\beta$ -Lactoglobulin A.



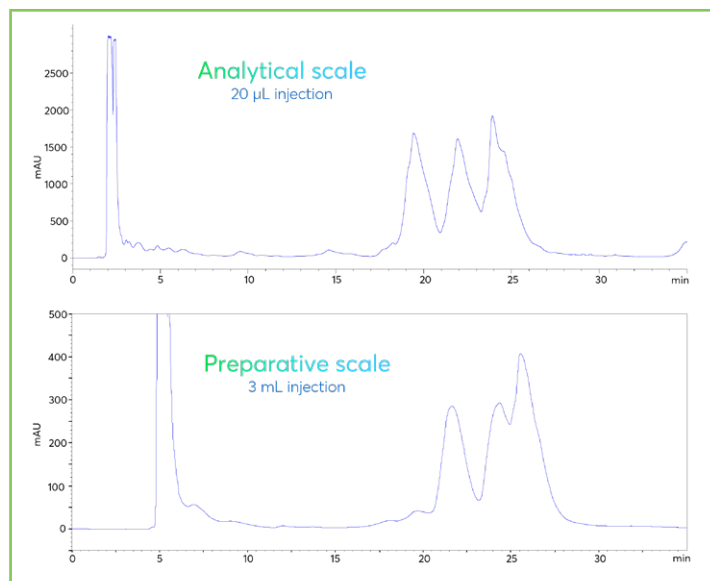
**FIGURE 1:** Separated whey proteins from cow's milk purchased at a local market. Column: Avantor® ACE® 3 C4-300, 150x2,1 mm; Mobile phase: A: 0,01% TFA (aq), B: 0,01% TFA in MeCN. Gradient: 33% B from 0 - 5 min to 43% B at 32 min. Flow rate: 0,2 ml/min; Injection volume: 1 µl; Detection: UV, 210 nm; Temperature: 45 °C; Instrument: Agilent 1290.

## HIGH YIELD EXTRACTION: NON IDEAL OVERLOADED SEPARATION CONDITIONS

The systematic increase of the whey sample loading on both an analytical (4,6 mm) and preparative (21,2 mm) scale column is shown in Figure 2. This highlights the loss of peak shape and resolution that occurs when moving to non ideal chromatographic conditions for both the analytical and preparative scale separations. In moving to non ideal, overloaded conditions, the priority is to maximise the amount of  $\alpha$ -Lactalbumin extracted from cow's milk with high purity in a particular time frame.

## HIGH PURITY CONFIRMATION

Three fractions were programmed for automated collection (green and blue bands shown in Figure 3) from the  $\alpha$ -Lactalbumin peak, using the same conditions

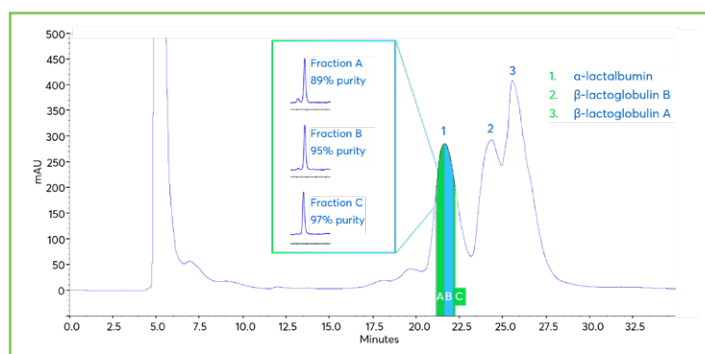


**FIGURE 2:** Analytical and preparative scale chromatograms highlighting the overloaded separation conditions of whey from cow's milk (see Figure 1 for conditions). Preparative scale separation conditions: Avantor® ACE® 5 C4-300, 150x21,2 mm; Mobile phase: A: 0,01% TFA (aq) B: 0,01% TFA in MeCN. Gradient: 33% B from 0 – 8,1 min to 43% B at 35,1 min. Flow rate: 21,2 ml/min; Injection volume: 3 ml; Detection: UV, 210 nm; Temperature: Ambient; Instrument: Knauer Azura PrepLC Premier system.

established in Figure 2 for preparative scale separation. The purity of each collected fraction was determined by taking a small aliquot from each fraction and subsequently analysing them using the analytical scale non overloaded conditions established in Figure 1. The purity of the three  $\alpha$ -Lactalbumin fractions were confirmed at 89, 95 and 97%, respectively, and shown in Figure 3's insert.

## CONCLUSION

The high yield purification of targeted compound(s) from a sample is typically performed under non ideal overloaded preparative chromatography conditions. In this knowledge note, the high yield, high purity fractionation of  $\alpha$ -Lactalbumin from cow's milk is



**FIGURE 3:** Preparative scale fractionation (conditions: See Figure 2) of  $\alpha$ -Lactalbumin with high purity analytical scale confirmation (conditions: See Figure 1). The fractions collected from the  $\alpha$ -Lactalbumin peak are highlighted in green and blue. Preparative Instrument: Knauer Azura PrepLC Premier system with Foxy fraction collector.

demonstrated. The fractionation was performed on a 21,1 mm preparative scale column to maximise the yield and amount, with purity confirmation using the analytical scale ideal chromatography conditions.

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03. D. K. Layman, B. Lönnerdal, J. D. Fernstrom Nutr. Rev. (2018) 76 444-460.
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05. Avantor® ACE® Technical Note #003 "Avantor® ACE® 300 Å Wide Pore HPLC Columns for the Separation and Purification of Proteins". (<https://av.cmd2.vwr.com/pub/apl/chrom/main?key=C-13237>)
06. Avantor® ACE® Technical Note #028 "Analysis of intact proteins using Avantor® ACE® UltraCore BIO columns". (<https://av.cmd2.vwr.com/pub/apl/chrom/main?key=C-13238>)

# New high purity HiPerSolv CHROMANORM<sup>®</sup> solvents for use in UHPLC-MS

**New**

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These **NEW** VWR Chemicals HiPerSolv CHROMANORM<sup>®</sup> UHPLC-MS solvents provide consistent, ultra-pure quality for your discovery-driving results

## For highly sensitive UHPLC-MS analyses, how do they perform?

With our high purity solvents, will reduce noise and keep additional signals to a minimum, will also raise the standard for low baseline noise and clean mass spectra.

Our new range of advanced UHPLC-MS solvents have been developed to exceed all expectations, providing rapid and reliable results in both ESI/APCI positive and negative ionisation modes, ensuring low formation of metal ion adducts and improving peak profiles

Our solvents offer real advantages when performing UHPLC-MS methods

- Suitability tested and specified for UHPLC-MS and UHPLC-UV  
**Benefit:** For analytical flexibility
- <0,1 µm ultrafiltration for demanding UHPLC-MS applications  
**Benefit:** Time and money savings - less issues due to clogging of instrument, columns and check valves
- LC-UV and LC-MS gradient suitability test  
**Benefit:** Minimal UV absorbing impurities combined with minimal MS ionising impurities, providing smooth baselines with extremely low interference, regardless of detector used
- Packed in borosilicate bottles  
**Benefit:** Significant reduction of contamination risks with metal cations (Na<sup>+</sup> and K<sup>+</sup>)
- ESI/APCI (+) <2 ppb - ESI/APCI (-) <10 ppb  
**Benefit:** Specified quality in positive and negative ESI and APCI MS for lowest detection limits and confidence in analyses in all important MS modes
- Metal content impurities <10 ppb  
**Benefit:** For minimised metal ion adduct formation - <10 ppb
- Lowest level of polyethylene glycol (PEG)- (PEG S/N signal-to-noise ratio <50)  
**Benefit:** Impurities in our entire UHPLC-MS solvent line up to give you confidence in your results.

Our advanced VWR Chemicals UHPLC-MS HiPerSolv CHROMANORM<sup>®</sup> solvents have been designed to meet the highest requirements of UHPLC-MS in research and quality control, including proteomics and metabolomics as well as environmental, clinical, food or industrial testing applications.



Description	Pk	Cat. No.
Acetonitrile HiPerSolv CHROMANORM <sup>®</sup> UHPLC-MS	1 L	83647.290
Methanol HiPerSolv CHROMANORM <sup>®</sup> UHPLC-MS	1 L	85802.290
Water HiPerSolv CHROMANORM <sup>®</sup> UHPLC-MS	1 L	83646.290



# Equipment



# Optimise your synthesis by accurate component weighing

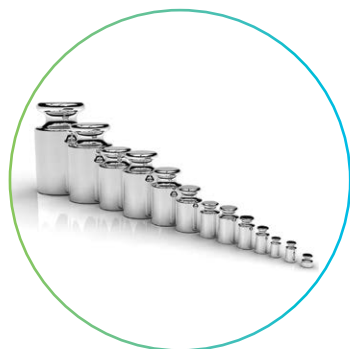
The weight of the components play an extremely important role in obtaining correct result.

All product  
info on  
calibration  
weights

## INFORMATION, CLASSIFICATION & TOLERANCES OF CALIBRATION WEIGHTS

A balance needs to be readjusted on a regular base, depending on customers regulations and wishes.

- Manual readjusting or control: You need weights
- Automatic readjusting: Just push the button
- Automatic readjusting: Depending on time and temperature



## ADVANTAGES OF BALANCES WITH INTERNAL CALIBRATION WEIGHTS

- Weights are better protected against dirt and damage
- Weights are always at the same temperature as the balance or scale
- The motorised calibration feature ensures that the weight is placed on the balance or scale in the most reproducible manner possible
- Automatic mode ultimately ensures that one of the most required tests concerning measuring equipment is fulfilled

## INFORMATION ON CALIBRATION WEIGHTS: CERTIFICATION

- Avantor offers a large range of calibration weights delivered with or without an accredited calibration certificate
- Certificate is recognised in many countries which have signed Multi-Ea and bilateral agreements

- EA: European cooperation for accreditation - <http://www.european-accreditation.org>
- Main European countries: UK (UKAS)
- Germany (DKD), France (Cofrac)

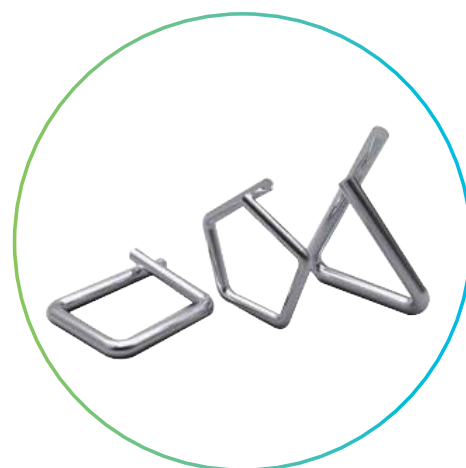
## CUSTOMER BENEFITS

- Monobloc or rectangular calibration weights
- Traceable weights with laser printing
- Delivered with or without accredited calibration certificate
- Can be recalibrated
- Complete portfolio of weights, separate or in sets

## CLASSIFICATION

The classes of weights supplied by Avantor meet the requirements described in OIML R 111-1 (2004).

- **Class E1:** Weights intended for use in the verification or calibration of Class E2 weights, and for use with weighing instruments of special accuracy Class I. Class E1 weights or weight sets will be accompanied by a calibration certificate
- **Class E2:** Weights intended for use in the verification or calibration of Class F1 weights, and for use with weighing instruments of special accuracy Class I. Class E2 weights or weight sets will be accompanied by a calibration certificate
- **Class F1:** Weights intended for use in the verification or calibration of Class F2 weights, and for use with weighing instruments of special accuracy Class I and high accuracy Class II
- **Class F2:** Weights intended for use in the verification or calibration of Class M1 and possibly Class M2 weights. Also intended for use in important commercial transactions (e.g., precious metals and stones) on weighing instruments of high accuracy Class II
- **Class M1:** Weights intended for use in the verification or calibration of Class M2 weights, and for use with weighing instruments of medium accuracy Class III
- **Class M2:** Weights intended for use in the verification or calibration of Class M3 weights, and for use in general commercial transactions, and with weighing instruments of medium accuracy Class III

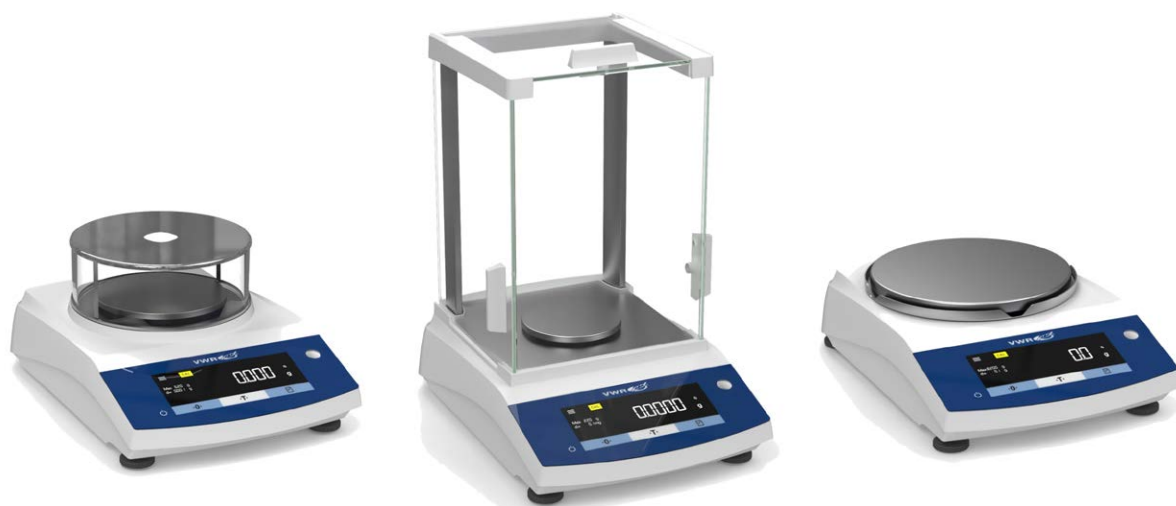


## TOLERANCE

Nominal value	± tolerance in mg						
	E1	E2	F1	F2	M1	M2	M3
1 mg	0,002	0,006	0,020	0,06	0,2	-	-
2 mg	0,002	0,006	0,020	0,06	0,2	-	-
5 mg	0,002	0,006	0,020	0,06	0,2	-	-
10 mg	0,002	0,008	0,025	0,08	0,25	-	-
20 mg	0,003	0,010	0,03	0,10	0,3	--	-
50 mg	0,004	0,012	0,04	0,12	0,4	-	-
100 mg	0,005	0,015	0,05	0,15	0,5	1,5	-
200 mg	0,006	0,020	0,06	0,20	0,6	2,0	-
500 mg	0,008	0,025	0,08	0,25	0,8	2,5	-
1 g	0,010	0,030	0,10	0,3	1,0	3	10
2 g	0,012	0,040	0,12	0,4	1,2	4	12
5 g	0,015	0,050	0,15	0,5	1,5	5	15
10 g	0,020	0,060	0,20	0,6	2,0	6	20
20 g	0,025	0,080	0,25	0,8	2,5	8	25
50 g	0,030	0,100	0,30	1,0	3,0	10	30
100 g	0,05	0,15	0,5	1,5	5	15	50
200 g	0,10	0,30	1,0	3,0	10	30	100
500 g	0,25	0,75	2,5	7,5	25	75	250
1 kg	0,5	1,5	5	15	50	150	500
2 kg	1,0	3,0	10	30	100	300	1000
5 kg	2,5	7,5	25	75	250	750	2500
10 kg	5	15	50	150	500	1500	5000
20 kg	10	30	100	300	1000	3000	10000
50 kg	25	75	250	750	2500	7500	25000

# In need of a high quality balance for basic weighing applications?

VWR® Premium Line balances and accessories: Best price/quality ratio – easy and efficient – connectivity



A selection of 44 high level balances for basic applications, with intuitive, wear resistant LED touch screen for use in research or quality control.

These high quality balances are made from polybutylene terephthalate (PBT) for the housing, which has an excellent chemical resistance. The control unit is made from glass, the glass used in the draft shields is specially coated to minimise weighing errors by electrostatically charged samples. The weighing pan is made from stainless steel.

Highly accurate results (high-end weighing technology)

- Fast stabilisation time
- Easy to clean and high chemical resistance
- Future proof USB type C interface
- Industry proof RS232 9-pin interface
- Underfloor weighing
- Six built-in applications with GLP/GMP compliant data output: Weighing and dosing – counting – percentage weighing – density determination – mass unit conversion – animal weighing
- The balance menu is available in the following seven languages: English, French, German, Italian, Polish, Portuguese and Spanish
- All models will come with one USB type C and one RS232 9-pin interface, available data transfer protocols are PC spreadsheet protocol, PC text protocol or Ascii protocols

Product  
information  
Analytical  
models

Product  
information  
Precision  
models

Balances that have an 'I' in the model's name have internal 'One Touch Calibration'.

Balances that have an FC in the model's name are delivered with a factory certificate.

Certifications: EN 61326-1:2013, EN 61010-1: 2010, EN 61010-2-010:2014, EN 50581:2012, IEC 60664-1

# Introducing the P9 double-beam precision UV/Visible spectrophotometer

With 13 years of professional spectrophotometer manufacturing experience, we have produced this precision UV/Visible spectrophotometer. The main features of the P9 are user-friendliness, high accuracy, reliability and convenience.

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HDMI, VGA, USB, RJ-45  
Connect with mouse, keyboard, printer...
- 2 Various accessories  
Wide sample room  
20 different accessories
- 3 Peltier sipper system  
Constant temperature  
High precision  
Suitable for contaminated samples
- 4 Double-beam  
High stability  
Low stray light  
Low error
- 5 New wavelength drive  
New design structure  
Fast, accurate and quiet
- 6 Built-in computer  
Windows 10 OS  
Easy to operate

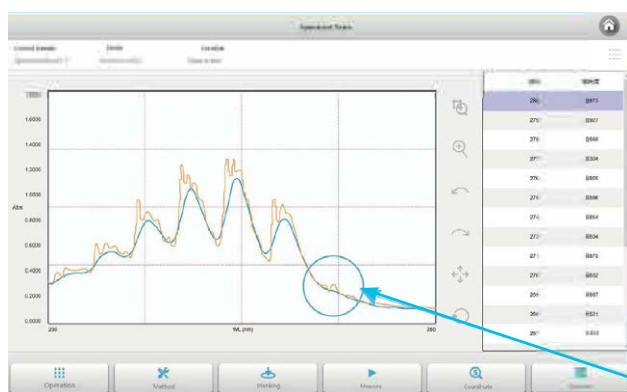
- 01. More durable with the strengthened structure
- 02. The built-in computer provides excellent display effect, simple operation and good scalability
- 03. Wide sample room, suitable for 5 to 100 mm sample holders and other accessories
- 04. The new wavelength driving mechanism greatly improves wavelength accuracy and repeatability, effectively reducing the noise (patented)
- 05. The low stray light 1200 l/mm holographic grating and optimised split beam design ensures high accuracy
- 06. With a wide variety of interfaces, you can connect keyboards, mice, projectors and printers to input and output data, and access a network for remote control and data sharing
- 07. Software design fully complies with 21CFR requirements stipulated in Pharmacopoeia. By GLP/GMP function, you can track and manage instrument performance and data
- 08. Using the open data interface protocol, users can combine with other devices through simple development and can integrate other devices into the system
- 09. A computer can be connected by USB or Bluetooth and the instrument controlled via the software
- 10. Firmware upgrades are available, USB storage
- 11. Perfect system and file management function
- 12. Self-calibration and warm-up after power on

## PRODUCT PERFORMANCE

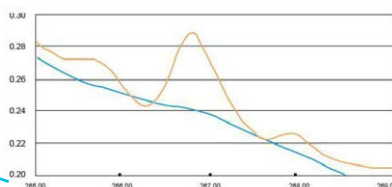
Benzene vapourisation shows an obvious absorption curve at the UV range of 230 to 280 nm. The absorption curve significantly varies with bandwidth if other conditions remain unchanged.

Use P9 to measure benzene/ethanol solution with 2 nm bandwidth and 0,5 nm bandwidth. The curves obtained are as follows (peaks will be different).

## SPECTRUM OF BENZENE/ETHANOL SOLUTION



Orange curve: Bandwidth: 0,5 nm  
Blue curve: Bandwidth: 2 nm



## PERFORMANCE VERIFICATION

- Wavelength accuracy and wavelength repeatability verification
- Photometric accuracy and photometric repeatability verification
- Stray light verification
- Resolution verification
- Noise
- Stability
- Bandwidth verification



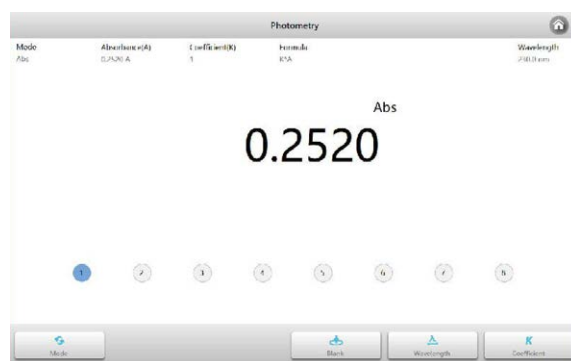
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# Product function



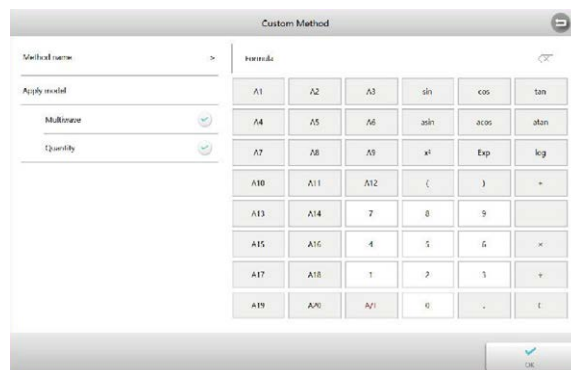
## Photometry

- One button A/T conversion
- Input coefficient K



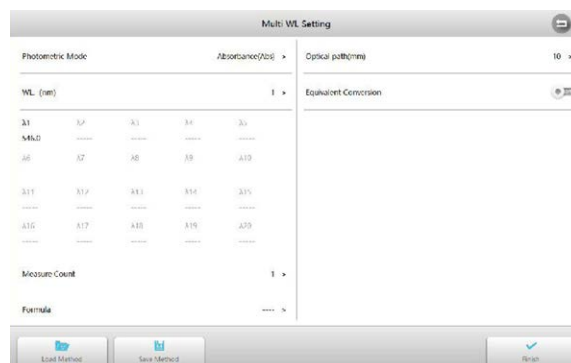
## Custom method

- Edit formulas as needed
- Formulas can be used for multiple modules



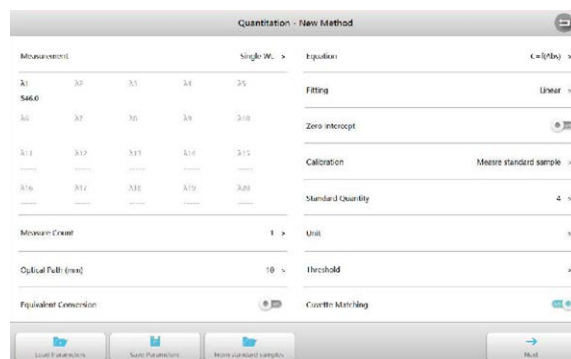
## Multi-wavelength

- Measure up to 20 wavelengths at a time
- Customise formulas for data calculation
- User-selectable one-point measurement times (1 to 50)
- Parameters can be saved and loaded
- Results can be recorded, renamed, deleted, saved, printed and exported



## Quantitation

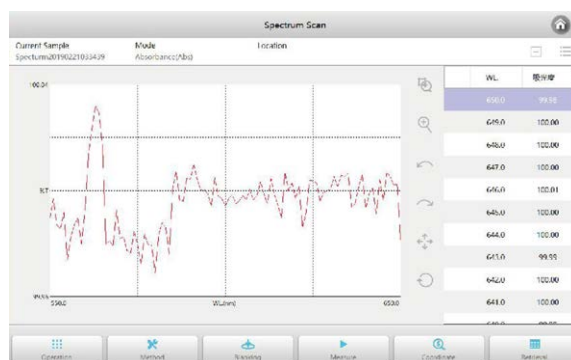
- Single-wavelength, dual-wavelength (difference, ratio), three wavelengths and custom methods
- Three ways to establish a standard curve (input coefficients, measure 2 to 20 standard samples or input absorbance and concentration values of standard samples)
- Four fitting methods (linear through zero, linear, quadratic and cubic)
- Parameters can be saved and loaded
- Standard samples can be saved and loaded
- Built-in common concentration units and user-defined units
- Diagram of measure values are displayed and results determined automatically
- Results can be recorded, named, deleted, saved, printed and exported
- Customise report layouts





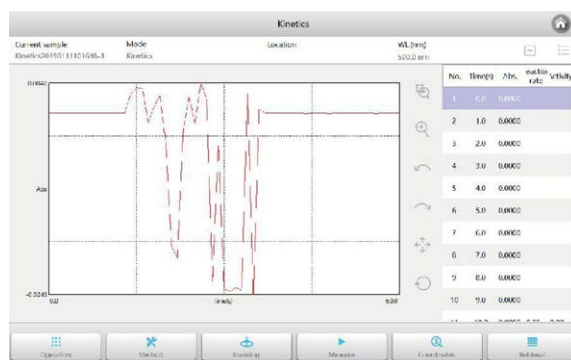
## Spectrum

- User-selectable scanning speed (low, medium and high)
- User-selectable scanning interval (0.1, 0.2 / 0.5 / 1 / 2 / 5 / 10 nm)
- A/T display mode (switchable)
- Automatic peak search
- Point by point (peak) view, mark and select
- Rich map processing functions (arithmetic operation, derivation, area and 3-D map)
- Adaptive coordinates and a variety of ways to modify coordinates
- Curves and data can be deleted, saved, printed and exported
- Curves and results can be saved and printed automatically



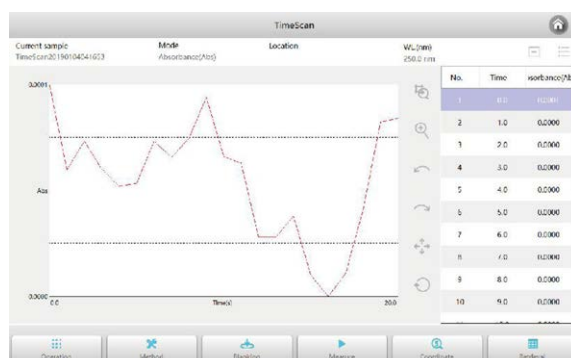
## Kinetics

- Unlimited scanning time
- Delay time and interval can be customised
- Automatically calculate kinetic rates
- Point by point (peak) view, mark and select
- Adaptive coordinates and a variety of ways to modify coordinates
- Curves and data can be deleted, saved, printed and exported
- Curves and results can be saved and printed automatically



## Time scan

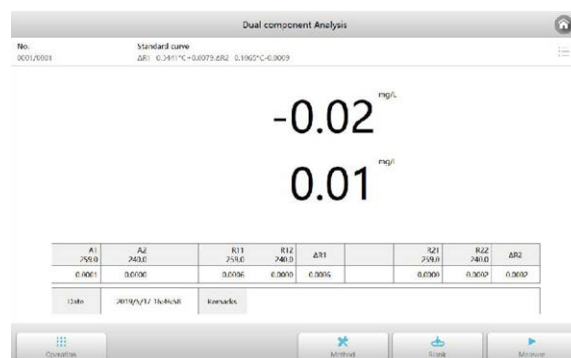
- Unlimited scanning time
- Scan interval can be customised
- Point by point (peak) view, mark and select
- Curves and data can be deleted, saved, printed and exported
- Curves and results can be saved and printed automatically





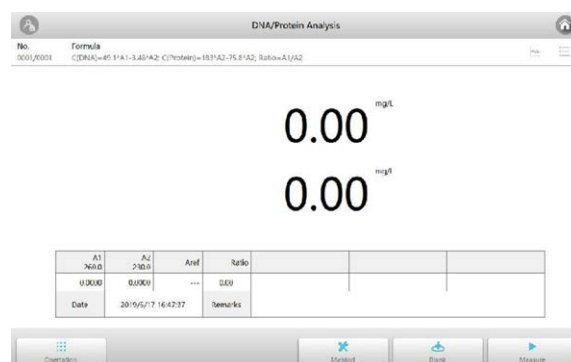
## Dual-component

- Two standard curves and their concentrations can be obtained from one measurement
- Results can be recorded, renamed, deleted and saved
- Customise printed reports



## DNA/protein

- Seven built-in methods
- 260/280, 260/320, Lowery, UV method, BCA, CBB, Biuret and custom calculation
- User-selectable one-point measurement times (1 to 50)
- Parameters can be saved and loaded
- Display a distribution map of the measured values and automatically determine the results
- Results can be recorded, named, deleted and saved
- Customise printed reports



## File manager

- Files can be deleted, renamed, and batch imported/exported

File Name	Measure type	File type	Open file	Date/Time
Spectrum20190420-443...	Data	Spectrum scan	Admin	2019/4/24 13:43:40
MultiWave-1	Data	Multi Wave length	Admin	2019/4/24 6:24:55
Spectrum201902210334...	Data	Spectrum scan	Admin	2019/2/21 15:33:32
10sample	Method	Quantitation	Guest	2019/1/19 16:25:57
1000	Method	Quantitation	Guest	2019/1/19 16:01:00
ghic	Data	Quantitation	OP	2019/1/19 14:11:17
MultiWave-1	Data	Multi Wave length	OP	2019/1/19 11:00:08
Gnetic20190111101040-1	Data	Kinetics	Admin	2019/1/11 10:15:30
Quantity-1	Data	Quantitation	Admin	2019/1/11 10:00:51
MultiMethod-1	Method	Multi Wave length	Admin	2019/1/11 9:27:01



## System

- System calibration (dark current, wavelength and system baseline)
- Light source (light switch and timing)
- Clock management
- Storage management (storage status display, formatting)
- Language (multiple languages are available)
- General setting (display resolution, system parameter, etc)
- Reset
- About (system information)

Calibration	Bandwidth	Light source	Accuracy	Language	Printer	General options
250nm	275nm/275s	0.000/0.005/0.00	English			

## GLP/GMP

### GLP/GMP COMPLIANCE

- Multi-user management
- Logging
- Binary file saving
- Quality control
- Report output

GLP/GMP options		User name	Operating time	Operating module	Operating context
Users	Select	Administrator	2019/5/17 16:43:22		login
		Guest	2019/5/17 16:43:20		Exit
		Guest	2019/5/17 16:42:18		Exit
		Guest	2019/5/17 16:42:16		Exit
		Guest	2019/5/17 16:42:09		Exit
		Guest	2019/5/17 16:42:08		Exit
		Guest	2019/5/17 16:35:19		Exit
		Guest	2019/5/17 16:35:14		Exit
		Guest	2019/5/17 16:33:29	System	Modify system language
		Guest	2019/5/17 16:33:24		Login
		Guest	2019/4/30 17:03:41		Exit
		Guest	2019/4/30 13:41:38		Login
		Admin	2019/4/30 13:35:10		Exit

### REPORT OUTPUT

Report output of measurement results  
Personalised report layouts  
Print preview

### BINARY FILE SAVING

Save measurement data in binary format  
Enhancing data confidentiality  
Saving disc space

### DATA EXPORT

Share data with other systems



### LOGGING

Automatic record of user actions  
Save log files in database format  
Administrators can look up and process logs by category

### MULTI-USER MANAGEMENT

Administrators are allowed to create users and groups with privileges  
Every user needs to enter account and password to login to the software  
Data protection for general users

### QUALITY CONTROL

Monitor measurement data according to user settings  
Abnormal data will be indicated, marked and re-measured automatically

For more information, please contact out specialists through [vwr.com](http://vwr.com)





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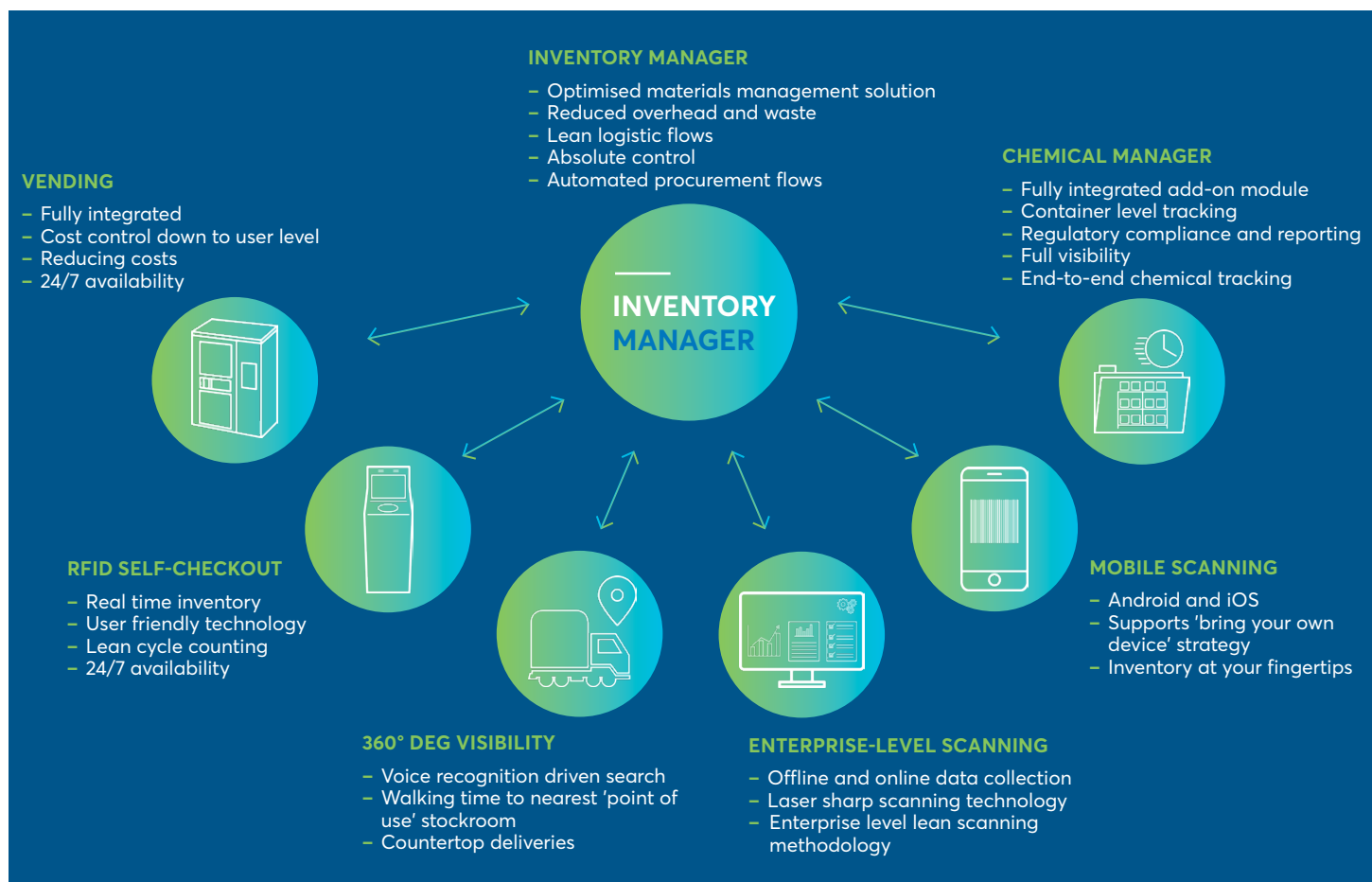
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