NewChem
TECHNOLOGIES LIMITED

newideasinchemistry

Discovery

Synthesis

Analysis

Optimisation

Our comprehensive range of synthetic chemistry services includes:

Contract Research

- Drug Discovery
- Lead Optimisation
- Route Scouting
- Process Research

Custom Synthesis

- Multi-step Synthesis
- Synthesis of Analogues
- Resolution of Chiral Compounds
- Electro-Organic Synthesis

Reference Standards

- Synthetic APIs
- Metabolites
- Impurities
- Degradation Products

Stable Isotope Labelling

- Deuterium
- Carbon-13
- Nitrogen-15
- Oxygen-17 and 18

Analytical Services

- LCMS (electrospray and APCI)
- HPLC (analytical and semi-preparative)
- NMR (up to 500 MHz)
- Karl Fischer, IR and UV

Consultancy

- Problem Solving
- Troubleshooting
- Patent Advice
- Expert Witness

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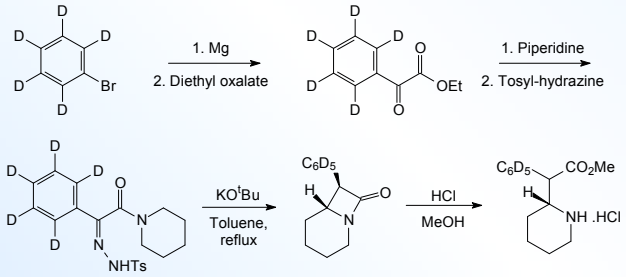
NewChem Technologies was founded in 2002 as a spin-out company from Newcastle University School of Chemistry and retains the culture of curiosity and intellectual enquiry inherited from its academic roots.

At the same time, the company has built a reputation for delivering results, meeting deadlines and paying strict regard to confidentiality. Our customers span sectors such as pharmaceuticals, diagnostics, biotechnology, veterinary science and agrochemicals and we work with leading players within these industries across the world. Below are some examples of our expertise and approach. Please contact us to explore how we can help with your synthetic and analytical needs.

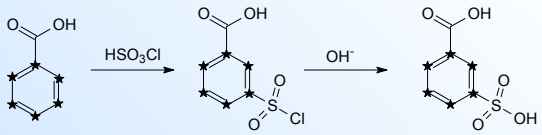
1. Stable Isotope Labelling

NewChem has expertise in the incorporation of deuterium, carbon-13, nitrogen-15 and oxygen-18 into drugs, drug metabolites, and other chemicals, with specialisation in high atom percentage isotope incorporation. Compounds can be prepared as single enantiomers where appropriate and in very high chemical purity.

An example of a deuterium labelled reference standard is the synthesis of d_5-methylphenidate.

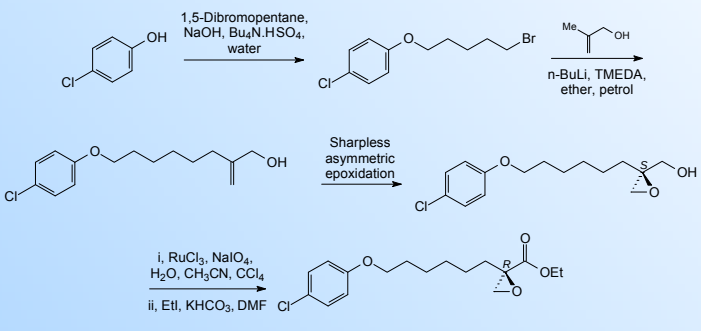


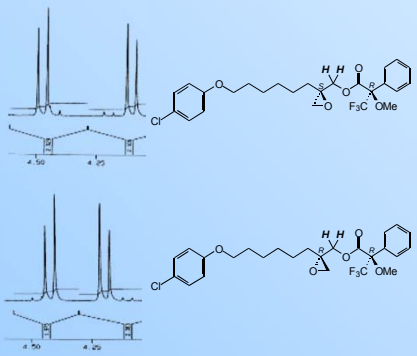
An example of a carbon-13 labelled material is [$^{13}C_6$]-3-sulfobenzoic acid, which was synthesised from [$^{13}C_6$]-3-sulfobenzoic acid (★ = ^{13}C).



3. Pharmaceutical Synthesis

The most concise chiral synthesis yet for the experimental anti-diabetic drug (*R*)-Etomoxir has been developed. The key steps in this improved synthesis are an alkylation of doubly-deprotonated methallyl alcohol, followed by a Sharpless asymmetric epoxidation.

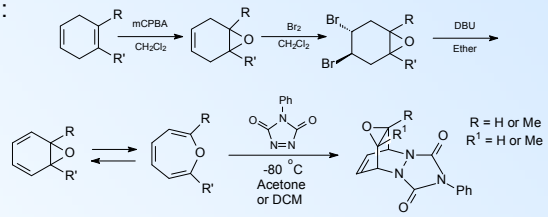




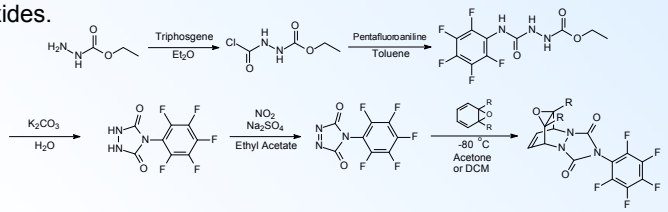
Both enantiomers were synthesised. Stereochemical purity of the epoxy alcohol products of the Sharpless epoxidation was confirmed by conversion to (*S*)-Mosher's esters and subsequent analysis by ^{1}H NMR spectroscopy.

2. Metabolites and Diagnostics

Benzene oxide (and its methyl derivatives) are metabolites/ atmospheric degradants of benzene, toluene and o-xylene, which may be readily trapped via Diels-Alder reactions with Cookson's dienophile (4-phenyl-1,2,4-triazoline-3,5-dione). Synthetic reference samples of the Diels-Alder adducts were prepared:



This methodology has been utilised in trapping arene oxides both in blood and in atmospheric chamber simulations. The corresponding pentafluorophenyl derivatives provide improved sensitivity in GC-MS analyses. 4-(Pentafluorophenyl)-1,2,4-triazoline-3,5-dione was synthesised and used to trap arene oxides.



4. Natural Products Characterisation

Various Caribbean natural product extracts, of interest in the context of gastrointestinal disorders, were separated by semi-preparative HPLC and the component compounds characterised. One of the extracts investigated ($584_{C4}E$) was from *Miconia cornifolia*, which is known to contain ellagic acid derivatives, of particular interest due to the activity of the parent compound as a prokinetic agent.

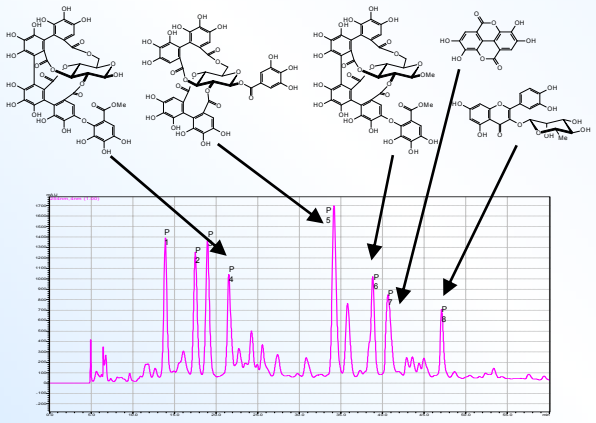


Figure 1: Optimised semi-preparative HPLC chromatogram of sample $584_{C4}E$.

Peaks 1 – 3 were relatively unstable compounds and these were not progressed for structural characterisation. **Peak 5** was identified as 1-O-galloyl-2,4:3,6-bis-hexahydroxydiphenoyl-β-D-glucose. **Peak 4** is formed from **peak 5**, and **peak 6** is the methyl glycoside of **peak 4**. **Peak 7** was identified as ellagic acid and **peak 8** was identified as quercetin 3-rhamnoside, also known as quercitrin.

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Stable Isotope Labelling

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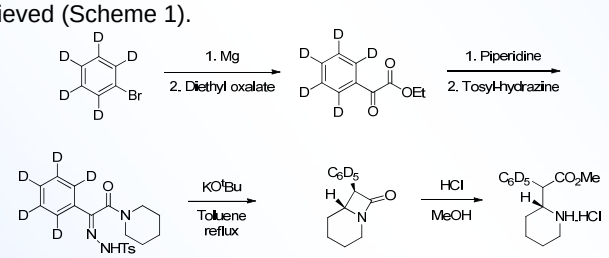
NewChem has expertise in the incorporation of deuterium, carbon-13, nitrogen-15, oxygen-17 and oxygen-18 into drugs, drug metabolites, and other chemicals, with specialisation in high atom percentage isotope incorporation. Some elegant new synthetic routes to give labelled materials have been designed and executed by NewChem, starting from commercially available labelled starting materials. Compounds can be prepared as single enantiomers where appropriate and in very high chemical purity.

Please contact Dr Alistair Henderson (0191 222 6635) with your enquiries.

Methylphenidate-d_5

Methylphenidate is a psychostimulant drug approved for treatment of attention-deficit hyperactivity disorder (ADHD), postural orthostatic tachycardia syndrome and narcolepsy. Synthesis of a deuterium labelled reference standard was achieved (Scheme 1).



Scheme 1: Synthesis of methylphenidate-d_5

3,3-Dimethylanagrelide-d_7

The anagrelide analogue 3,3-dimethylanagrelide hydrobromide (Figure 1) was synthesised by NewChem as a clinical development candidate (currently entering Phase 2) for the prevention of thrombotic complications associated with arteriovenous grafts in hemodialysis patients.

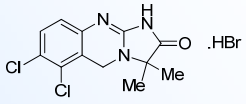
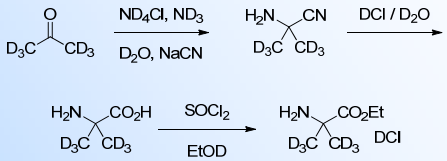


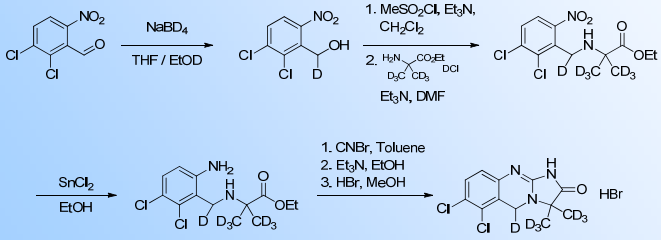
Figure 1: 3,3-Dimethylanagrelide Hydrobromide

As part of the clinical development programme, an isotopically labelled version with 7 mass units above the parent compound was required for metabolic studies using mass spectrometry. The labelled amino acid ester starting material was synthesised by NewChem starting from acetone-d_6 (Scheme 2).



Scheme 2: Synthesis of ethyl 2-amino-2-methylpropionate-d_6 deuterochloride

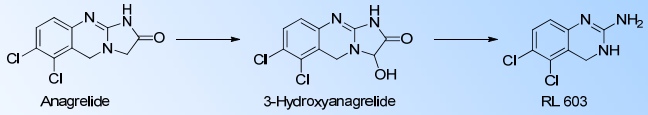
3,3-Dimethylanagrelide-d_7 hydrobromide was synthesised from 2,3-dichloro-6-nitrobenzaldehyde. Deuterium was introduced during the reduction of the aldehyde to the corresponding alcohol, which was mesylated and combined with ethyl 2-amino-2-methylpropionate-d_6 deuterochloride (Scheme 3).



Scheme 3: Synthesis of 3,3-dimethylanagrelide-d_7 hydrobromide

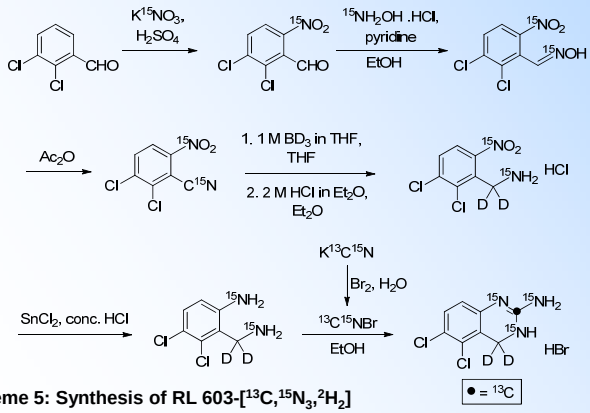
RL 603-[^{13}C,$^{15}N_3$,$^2H_2$]

Anagrelide (Agrylin, Shire Pharmaceuticals) gives rise to two metabolites: 3-hydroxyanagrelide and 2-amino-5,6-dichloro-3, 4-dihydroquinazoline (RL 603, Scheme 4).



Scheme 4: Metabolism of anagrelide

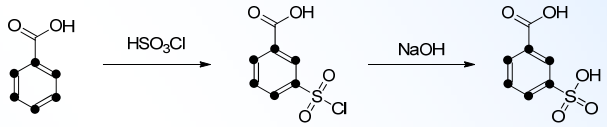
In support of the clinical development programme, synthesis was required of RL 603, isotopically labelled with 6 mass units over the parent compound. A new synthetic route was designed to enable the incorporation of 6 labelled atoms (Scheme 5).



Scheme 5: Synthesis of RL 603-[^{13}C,$^{15}N_3$,$^2H_2$]

3-Sulfobenzoic Acid-[$^{13}C_6$]

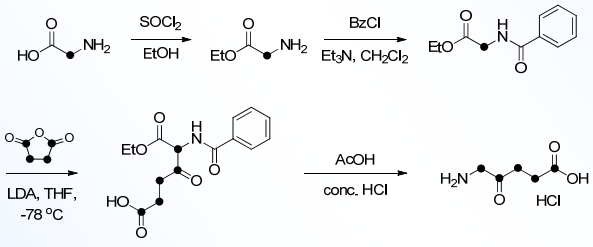
A carbon-13 labelled compound, 3-sulfobenzoic acid-[^{13}C]$_6$, was made using commercially available benzoic acid-[^{13}C]$_6$ (Scheme 2, • = ^{13}C).



Scheme 6: Synthesis of 3-sulfobenzoic acid-[$^{13}C_6$]

δ-Aminolevulinic acid-[$^{13}C_5$]

δ-Aminolevulinic acid (δ-ALA) is a building block for the biosynthesis of porphyrins, vitamin B_{12} and chlorophyll. For further studies of heme biosynthesis, δ-ALA-[$^{13}C_5$] was required (Scheme 7).



Scheme 7: Synthesis of δ-aminolevulinic acid-[$^{13}C_5$]

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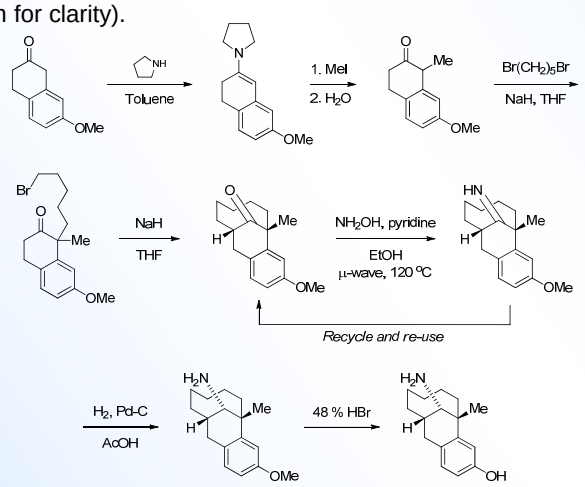
Synthetic Active Pharmaceutical Ingredients (APIs)

The total synthesis of APIs is often necessary due to the difficulties in sourcing commercially available pure compounds. NewChem is able to synthesise a wide variety of APIs using reliable chemical routes, in quantities from a few milligrams to several grams depending upon your individual needs.

Compounds can be prepared as single enantiomers as appropriate, in high chemical purity, and can be provided as a variety of salt forms as necessary. Please contact us with your enquiries.

Dezocine

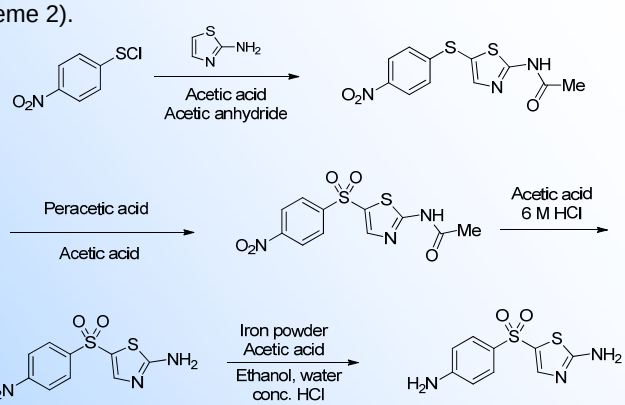
Dezocine is an opioid analgesic. The first synthesis of *rac*-dezocine developed by NewChem suffered from low yielding steps, and was subjected to extensive method development. The generation of the oxime was low-yielding, but microwave synthesis allowed easy recovery and recycling of the starting material, giving an overall high yield (Scheme 1, only one isomer shown for clarity).



Scheme 1: Synthesis of (*rac*)-Dezocine

Thiazosulfone

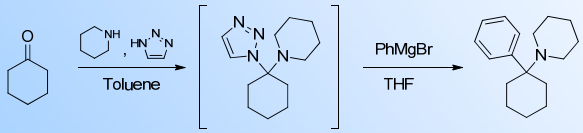
Thiazosulfone was prepared by NewChem for prodrug studies (Scheme 2).



Scheme 1: Synthesis of thiazosulfone

Phencyclidine

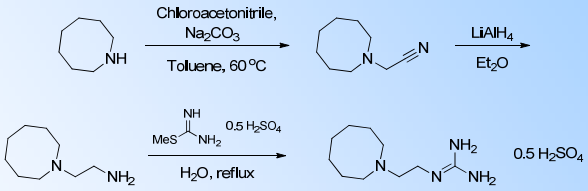
Phencyclidine (PCP), a recreational drug and anaesthetic agent, was synthesised on a 10 g scale by NewChem (Scheme 3).



Scheme 3: Synthesis of Phencyclidine

Guanethidine

Guanethidine is an antihypertensive agent, and the hemisulfate salt was synthesised by NewChem from azocane (Scheme 4).



Scheme 4: Synthesis of Guanethidine Hemisulfate

Tramadol and *O*-Desmethyltramadol

Tramadol is a centrally acting opioid analgesic drug, administered as a racemate. *O*-Desmethyltramadol is a biologically important metabolite, and contributes significantly to the complex pharmacological profile of tramadol (Figure 1, one enantiomer shown for clarity).

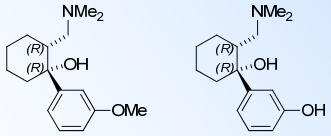
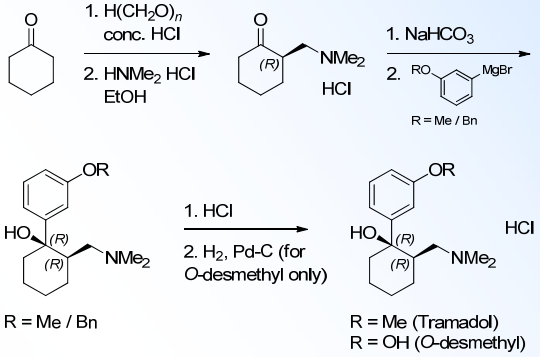


Figure 1: Tramadol (*left*) and *O*-Desmethyltramadol (*right*)

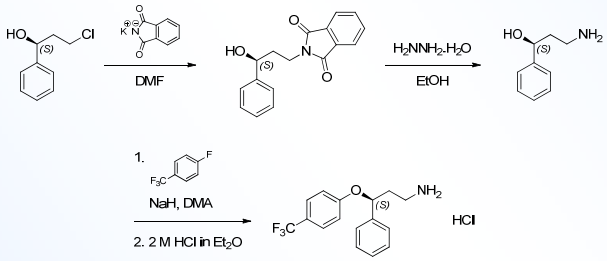
Both APIs were synthesised at NewChem, using similar routes (Scheme 5).



Scheme 5: Synthesis of Tramadol and *O*-Desmethyltramadol

Seproxetine

Seproxetine, or (*S*)-norfluoxetine, is a selective serotonin reuptake inhibitor (SSRI) and an active metabolite of fluoxetine. It was prepared by NewChem for prodrug studies (Scheme 6).



Scheme 6: Synthesis of Seproxetine Hydrochloride

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Analytical Services

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From routine analysis to purification and characterisation of complex materials, NewChem Technologies' Analytical Facility offers high quality confidential analytical expertise in all aspects of our service.

With in-house access to an array of specialist equipment, including HPLC with semi-preparative capabilities and LC-MS, plus a team of dedicated and experienced Analytical Chemists, NewChem can provide competitively priced compound-specific analysis and purification on a fast timescale in a professional environment.

Please contact Dr Alistair Henderson (0191 222 6635) for more information regarding our Analytical Services.

HPLC

We have a suite of Shimadzu LC-20A prominence HPLC systems. These machines enable a range of flow rates with variable temperature autosamplers (4 – 40 °C) and column ovens (15 – 85 °C). These factors ensure robust and reproducible analyses.

The HPLC services we offer include:

- Purity analysis of compounds either as percentage purity or by the use of internal / external standards and calibration graphs.
- Semi-preparative purification of compounds.
- Dedicated high throughput methodologies.
- Longer runtimes for separation of complex mixtures.
- Development of both generic and compound specific methodologies.
- Method validation of custom methods.
- Various detection methods – photodiode array or UV-fixed wavelength detectors; refractive index (RI) available for analytes with poor absorbing chromophores.

LC-MS

Our dedicated Shimadzu LC-MS-2010 EV system is available for analysis of both single compounds and complex mixtures. A highly sensitive detector allows for samples as small as 10 pg to be analysed and detected.

Our LC-MS services include:

- Electrospray ionisation (ESI) and atmospheric pressure chemical ionisation (APCI) probes for a range of analytes, from non-polar to highly polar compounds.
- *m/z* range of 10 – 2000 amu (ESI having a wider range than APCI).
- Development of both generic and compound specific methodologies.
- Impurity profiling – attachment of analytical HPLC columns with the use of a splitter feed to increase the resolution between compounds and allow the determination of molecular weights.
- Structure determination of unknowns.

Semi-preparative HPLC

Our semi-preparative HPLC capabilities allow the purification of compounds on milligram to gram scale to a much higher level compared to standard laboratory techniques.

In one example, a compound was prepared as a 45 : 55 mixture of diastereomers. Semi-preparative purification enabled the complete separation of the two diastereomers (Figure 1, one isomer shown).

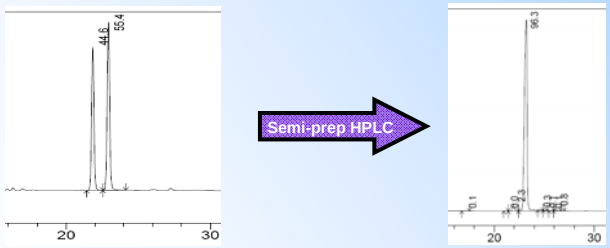

Figure 1: Semi-preparative separation of diastereomers

Natural Products Characterisation

Various Caribbean natural product extracts of interest in a medicinal chemistry project were separated by semi-preparative HPLC and the component compounds were characterised by HPLC, LC-MS and NMR analyses (Figure 2).

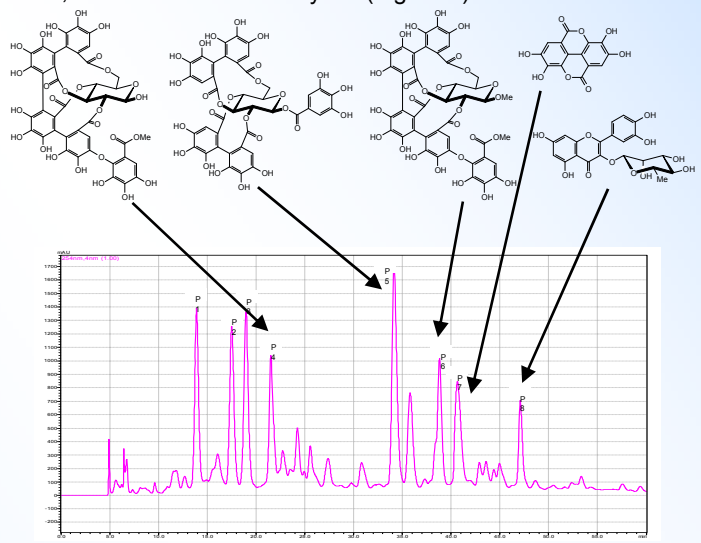

Figure 2: Optimised semi-preparative HPLC chromatogram of sample 584$_{C4}$E.

Peaks 1 – 3 were relatively unstable compounds and these were not progressed for structural characterisation. **Peak 5** was identified as 1-O-galloyl-2,4:3,6-bis-hexahydroxydiphenoyl-β-D-glucose. **Peak 4** is formed from **peak 5**, and **peak 6** is the methyl glycoside of **peak 4**. **Peak 7** was identified as ellagic acid and **peak 8** was identified as quercetin 3-rhamnoside, also known as quercitrin.

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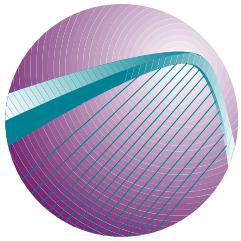
NewChem Technologies was founded in 2002 with a commitment to providing innovative solutions using our wide-ranging expertise in organic chemistry. We have built a reputation for delivering results, meeting deadlines and paying strict regard to confidentiality.

We pride ourselves in the excellence of our comprehensive range of contract chemistry services which include drug discovery, custom synthesis, process optimisation and the synthesis of reference standards.

Our customers span sectors such as pharmaceuticals, diagnostics, biotechnology, veterinary science and agrochemicals. We work with leading players within these industries from across the world.



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