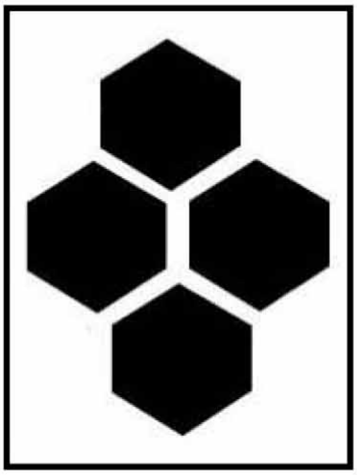
New Drugs for Old

A Problem solving case study in pharmaceutical and analytical chemistry



THE UNIVERSITY OF HULL

RSC | Advancing the Chemical Sciences

UNIVERSITY OF PLYMOUTH

New Drugs for Old

A problem solving case study in pharmaceutical and analytical chemistry

Devised by

Simon Belt
School of Environmental Sciences, University of Plymouth, Plymouth, PL4 8AA

Tina Overton
Department of Chemistry, University of Hull, Hull, HU6 7RX

Stephen Summerfield
Department of Chemistry, University of Hull, Hull, HU6 7RX

Preface

'New Drugs for Old' is one of six problem solving case studies that have been designed in order to teach analytical and applied chemistry within a 'real' life context by developing problem solving and professional skills.

Employers have long urged the Higher Education sector to produce graduates with a range of transferable skills that would make them more immediately effective in the world of work. To produce graduates who can operate in the workplace professionally, we need to go much further than just ensuring that they have a sound knowledge of chemistry, adequate practical abilities and rudimentary problem solving skills. We must ensure graduates can think critically and analytically, can interpret data and information, tackle unfamiliar open-ended problems and apply their chemical knowledge. In addition, the modern graduate must master a range of 'professional' or transferable skills including communication, team working, time management, information management, independent learning and the use of information technology.

Our approach in producing resources that address these issues in analytical chemistry has been to develop problem-solving case studies that use the contexts of forensic science, pharmaceuticals, environmental science, and industrial chemistry. These present extended problems are set in a 'real' context with incomplete or excessive data, and require independent learning, evaluation of data and information and, in some cases, do not lead to a single 'correct' answer. By tackling these cases, students are able to see the relevance of analytical chemistry and so approach the activities with enthusiasm and interest. The analytical skill developed throughout the case studies closely follow those recommended by the United Kingdom Analytical Partnership (UKAP). In addition, the transferable skills listed for each case study correlate with those identified in the RSC Undergraduate Skills Record documentation.

A Dip in the Dribble	Analytical, environmental and industrial chemistry
Launch-a-Lab	Industrial chemistry and advanced professional skills
New Drugs for Old	Pharmaceutical and analytical chemistry
Tales of the Riverbank	Analytical chemistry and environmental science
The Pale Horse	Analytical chemistry and forensic science
The Titan Project	Industrial and analytical chemistry

The case study has been extensively trialled, modified and updated. We feel that it is now in a suitable form for more widespread use. Whilst we have made every effort to ensure that this case study is free of errors and the guidelines for delivery are unambiguous, almost inevitably, we will have overlooked some detail. If users come across any errors or have any suggestions for further improvement we would be pleased to hear from you.

We thank the Royal Society of Chemistry Analytical Trust Fund for the funding of this project and the enthusiastic support of the United Kingdom Analytical Partnership (UKAP). We would like to acknowledge Pat Bailey of UMIST whose 'Hwuche Hwuche Bark' exercise provided the inspiration for this case study. We also thank Tom McCreedy and Paul Watts (University of Hull), Hywel Evans (University of Plymouth), Bob Mackison (Chemical Solutions), Jim Miller, Roger Smith and Helen Reid (Loughborough University) for their invaluable feedback and encouragement. Finally, we are indebted to all the friends, students and staff at various universities who have helped in the development of these case studies by their enthusiastic participation.

For further details contact: -

Dr. Tina Overton, Department of Chemistry, The University of Hull, Hull, HU6 7RX, UK
Telephone (01482) 465453 E-mail t.l.overton@hull.ac.uk

Dr. Simon Belt, School of Environmental Sciences, University of Plymouth, Plymouth, PL4 8AA
Telephone (01752) 233042 E-mail sbelt@plymouth.ac.uk

Contents

Aims of the Case Study

This is a problem-based case study concerned with the isolation, identification and synthesis of a pharmaceutical. The students consider the short-term experiments that would be required to isolate and identify the active ingredient in some dried leaves from Malaysia. The students then propose the longer-term experiments that would be required to bring the drug to the market place.

The students interpret the NMR, MS and FT-IR spectra to identify a series of isolated components. They then cost the synthesis of the active ingredient (salicylic acid) from cheap substrates, but realise that even this approach is likely to be financially less viable than purchasing it directly.

Aspirin is an analogue of salicylic acid and is the market leader as an analgesic. A natural conclusion of the case study is that the cost of synthesising/developing salicylic acid is probably not commercially competitive.

Who is the case study aimed at?

The case study works well with level 1 students.

How long does the case study last?

The minimum contact time required is 3-4 hours and will require the students to spend approximately 8 hours in associated independent study.

How can the activities be assessed?

The case study can be assessed in various ways including group or individual reports and oral presentations.

What are the learning outcomes?

Students must apply appropriate theory and knowledge of chemistry to tackle an extended problem set within a 'real' context. The nature of the activities involved ensure that, in order to complete the case study, students must develop a variety of scientific (table 1) and transferable skills (table 2).

Table 1: Scientific skills

Disciplines covered	Analytical chemistry, toxicology, drug design, pharmacology, marketing etc.
Scientific knowledge	Interpretation of spectra (NMR, MS, FT-IR.), drug design, and synthesis.
Handling information	Manipulation and evaluation of information and data to make realistic decisions on the evidence available.
Problem Solving	Tackling unfamiliar problems, using judgement, evaluating information, formulating hypotheses, analytical and critical thinking.

Table 2: Transferable skills

Communication skills	Oral presentations and report writing.
Improving learning and performance	Using feedback to reflect upon group and individual performance. Drawing on the experience within the group.
Information technology	Word processing reports and preparing material for presentations.
Planning and organisation	Project planning and economics. Individual judgement, decision making, time management, planning, prioritising and working to tight deadlines.
Working with others	Brainstorming, discussion, division of tasks and feeding back to the group.

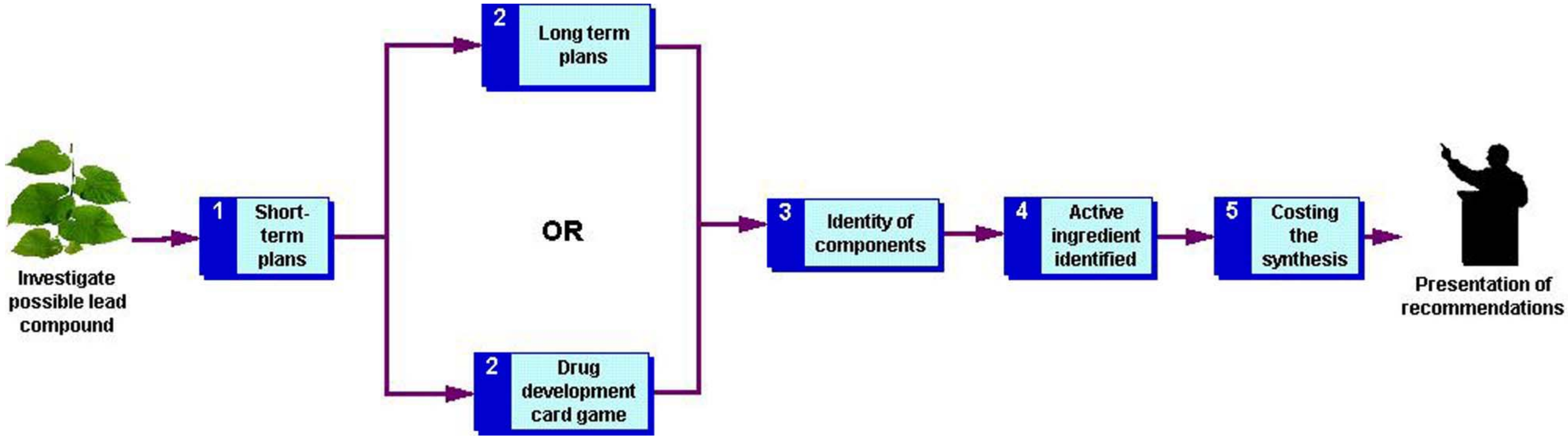


Figure 1: The case at a glance.

Making it Work

The class should be divided into groups of 3-6 students with 4 being the optimum number. It is advisable to randomise the groups so that each group has a range of abilities and skills.

Project Design

The case study is introduced by the letter from Dr. Overdone (Department of Anthropology, University of Midshire) to the Director of Research of a subsidiary of Green-Chem Inc. The letter describes a natural herbal remedy that he took in Malaysia when he was suffering from a fever. He offers to supply the company with a sample of the dried leaves if they are able to produce a credible project plan.

The importance of looking at natural products may be discussed. Students begin by considering the short term experiments that need to be carried out on receipt of the dried leaves (extract, separate and identify components, determine active ingredients.)

Longer-term plans are then made which may approximate to the simplified scheme shown in figure 2. This flow diagram from drug discovery to sale is greatly simplified. Many factors influence the development of the drug at more than one stage (e.g. economics) and occur in parallel so this should not be considered a timeline. At the end of the session, the students submit a one-page summary.

As an alternative, a drug development card game can be used to help students think about the steps involved in the development of a new drug. They are asked to create a logical sequence for the cards with an emphasis placed on a structure that has a clear rationale, rather than there being a unique correct solution. This point may be clarified by reference to a series of analogous schemes relating to the making of a mug of tea (A-7).

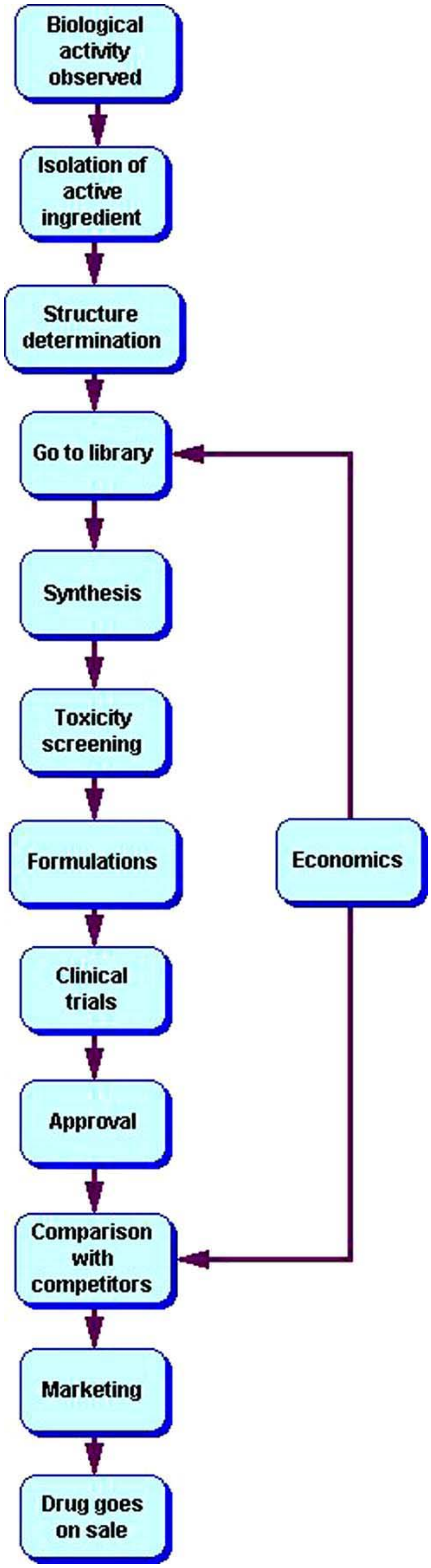
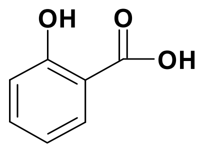
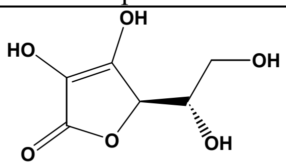
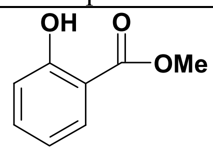
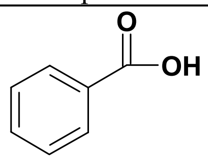


Figure 2: A possible scheme for pharmaceutical development

Identification of Isolated Compounds

The students are given spectra and other information on the 3 main components (A-C). Compound D may be used as an example of how to interpret spectra. The structures of the compounds are shown in Table 3.

Table 3: Structures of compounds A-D

 Compound A	salicylic acid
 Compound B	vitamin C (ascorbic acid)
 Compound C	methyl salicylate
 Compound D	benzoic acid

Synthesis

The students are informed that compound A (salicylic acid) is the active ingredient and they are supplied with four synthetic routes, two for phenol, and two from phenol to salicylic acid. The students cost these routes using chemical catalogues (e.g. Sigma-Aldrich, Fisher etc.).

Route I Oxidation of toluene to phenol
Route II Cumene process
Route III The Kolbe reaction
Route IV Air oxidation of salicyaldehyde

There is no model answer to this. Students are encouraged to think about the yield, temperature, pressure, the economies of scale and whether they calculate yields/efficiencies by weight or by moles. They will hopefully also compare these routes to the cost of buying phenol and/or salicylic acid directly.

Proposal

At the end of the case study, student groups are asked to present their findings. In terms of making recommendations to the company, it should be clear that performing efficient syntheses with cheap reagents may still not be competitive with purchasing the products directly. Finally, a simple comparison with a world-wide market leader (aspirin in this case) should (logically) result in a recommendation not to proceed.

Debriefing

It is recommended that at the conclusion of the case study, the tutor leads a debriefing session.

This is an opportunity to not only discuss the details of the case, but to enable students to evaluate the role of analytical science in solving this case, and help them reflect on their own development in terms of knowledge and skills.

Presentation and Assessment

Students may present their results and conclusions in several ways:-

- **One page project plan**
  Each group produces a plan of initial experiments to be carried out on the leaves, together with longer-term considerations needed for developing the pharmaceutical further (e.g. to the market place).

- **Written report (group or individual) and oral presentation**

  These should include a discussion of the project plan, identification of the active component, costing(s) of the syntheses and marketing considerations including comparison with competitive products, decisions on whether to proceed, etc

Table 4: Example assessment schemes

Project plan Group oral Presentation Final Report	25% 25% 50%
	100%

Project plan Group oral presentation	50% 50%
	100%

Any questions?

1. **Which students is this case study aimed at?**
   This case study is aimed at level 1/2 students who have some knowledge of analytical or organic chemistry.

2. **How flexible is the case study?**
   As an alternative to using the entire case study, each of the individual tasks can be used in isolation. The 'planning' sections of the case study do not require any particular in-depth knowledge of chemistry. This case study has been used on analytical chemistry, drug design and communication skills modules.

3. **Is there a definitive solution to the case study?**
   There is not a single solution to the short and long term plans section, though clearly, sound judgement must be employed. Synthetic costings will depend on sources used and estimations associated with scale-up, etc. A logical solution is described in the 'Proposal' section (vide infra).

4. **What is the function of the different reaction pathways?**
   These are given to prompt students into considering various alternatives to a target molecule, including the use of different synthetic routes to common intermediates, purchasing intermediates in situ or even purchasing products directly.

5. **Could the students be supplied with samples to do their own analysis?**
   Yes. All of A-D are readily available. Enabling students to record their own spectra can make an interesting 'practical' modification to the case study.

Session Plan for 4 One-Hour Sessions

Objective	To think critically about pharmaceutical development To consider the steps required in isolating and identifying an active ingredient.
Session 1	1. Overall aims of the case study are described. 2. Students are divided into groups. 3. Students are given the *'Letter from Dr. S. Overdone'* and use the questions to prompt their investigations. 4. Students consider a short-term experimental strategy. 5. The students consider a longer term experimental strategy. This could involve the use of the *drug development card game.*
Task 1	• Students decide the immediate short-term experiments that need to be carried out in order to isolate the chemical constituents. • Students discuss the longer-term plans after any active ingredients have been identified. • Students hand-in their conclusions or summaries. • The arrangement of the cards from the '*drug development card game*' are discussed
Objective	To identify compounds A-C.
Session 2	1. The students are given *'Identification of Components'* and the spectra required to identify the compounds A-C. 2. Compound D is benzoic acid and could be used as an example.
Task 2	• Identify the compounds A-C.
Objective	To evaluate the most cost effective method of synthesis To consider alternatives to the active ingredient.
Session 3	1. The students are given *'Synthesis of Active Component.'* 2. The students consider a synthesis of compound A and estimate the cost per kg. Chemical catalogues with prices are supplied. 3. The students are given an urgent message from Green Chem Inc.
Task 3	• Students prepare a presentation to the Director of Research outlining the potential of the project
Objective	To make recommendations to Green Chem Inc. To appreciate the important of analytical chemistry. To reflect upon group and individual work.
Session 4	1. Students give 5-minute presentations. 2. The tutor leads the debriefing.
Task 4	• Students hand in reports if required.

References

Spectra

Aldrich (1997), *The Aldrich Library of FT-IR Spectra*, 2nd Edition, Volume 1-3, Sigma Aldrich.

Mills T. and Roberson J.C. (1987), *Instrumental Data for Drug Analysis,* 2nd Edition, Volumes 1-5, Elsevier Science Publishing Co., New York

Pfleger K., Maurer H. and Weber A. (1985), *Mass spectra and GC data of drugs, poisons and their metabolites,* VCH, Germany.

Pouchert C.J. and Behnke J. (1993), *The Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra*, 1st Edition, Volume 1-3, Sigma Aldrich.
http://webbook.nist.gov/chemistry/

Interpretating Spectra

RSC 4 page guides to spectroscopy.
http://www.chemsoc.org/PDF/LearnNet/rsc/IR_txt.pdf
http://www.chemsoc.org/PDF/LearnNet/rsc/MS_txt.pdf
http://www.chemsoc.org/PDF/LearnNet/rsc/NMR_txt.pdf
http://www.chemsoc.org/PDF/LearnNet/rsc/UV_txt.pdf

Criddle W.J. and Ellis G.P. (1990), *Spectral and chemical characterisation of organic compounds*, 3rd edition, John Wiley and sons.

Dean J.R., Jones A.M., Holmes D., Reed R., Weyers J. and Jones A. (2002), *Practical skills in chemistry,* Prentice Hall, London

Harwood, L.M. and Claridge D.W. (1996), *Introduction to organic spectroscopy*, Oxford Chemistry Primer 43, Oxford University Press, Oxford

Hore, P.J. (1995), *Nuclear magnetic resonance,* Oxford University Press, Oxford.

Kemp, William, Ph.D. (1991), *Organic spectroscopy,* 3rd Edition, Macmillan, Basingstoke

Lindon J.C., Tranter G.E. and Holmes J.L. (2000), *Encyclopaedia of spectroscopy and spectrometry,* Volumes 1-3, Academic Press, London

Meyers, R.A. (Ed.), (2000), *Encyclopaedia of Analytical Chemistry: Theory and Instrumentation,* Volumes 1-15, J. Wiley and Sons Ltd., Chichester, London.

Shugar G.J. and Dean J.A. (1990), *The chemist's ready reference handbook,* McGraw-Hill, New York.

Townshend A. (1995) *Encyclopaedia of Analytical Science*, Volumes 1-10, Academic Press, London

Whittaker D. (2000), *Interpreting organic spectra,* RSC, Cambridge.

Williams D.H. and Fleming I. (1995), *Spectroscopic methods in organic chemistry,* 5th Edition, McGraw-Hill, Maidenhead.

Background Information

Barton D. and Nakanishi K. (1999), *Comprehensive natural product chemistry,* Volumes 1-9, Elsevier Science Ltd., Oxford

British Medical Association (2001), *British National Formulary,* Volume 42, British Medical Association, London

Buckingham J. and Macdonald F. (1995*), Dictionary of organic compounds,* 5th edition, CRC Press, London

Budadavari S. (1996), *The Merck Index: an encyclopaedia of chemicals, drugs and biologicals*, 12th edition, Merck and Co. Inc., New Jersey.

Cooper B., Gerlis L., Hurrell D. and Jeannet E. (1996), *A consumers guide to over the counter medicines*, Hamlyn, London.

Hansch C., Sammes P.G. and Taylor J.B. (1990), *Comprehensive medicinal chemistry: the rational design, mechanistic study and therapeutic applications of chemical compounds,* Volume 1-6, Pergamon Press, London.

Laurence D.R. and Carpenter J.R. (1994), *A dictionary of pharmacology and clinical drug evaluation,* UCL Press, London.

Ody P. (1996), *Handbook of over the counter herbal medicines,* Kyle Cathie Ltd., London

Olson K.R. (1999), *Poisoning and Drug Overdose*, 3rd Edition, a Lang Clinical Manual, Prentice Hall International, London.

Paterson D. (1998), *Aspirin: a curriculum resource for post-16 chemistry courses,* RSC, Cambridge
http://www.chemsoc.org/PDF/LearnNet/rsc/Aspirin_full.pdf

Reynolds J.E.F. (1993), *Martindale : the extra pharmacopoeia,* Pharmaceutical Press, London

Richardson M.L. and Gangolli S. (1992-1994), *The Dictionary of Substances and their Effects*, Volumes 1-7, RSC, Cambridge.