

# SYNTHESISING PHARMACEUTICALS

## Comparing manual and robotic parallel synthesis of aspirin like compounds



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### Languages available

English, Slovenian

### Summary

Imagine you have been given the task of setting up a new synthetic laboratory for a pharmaceutical company. You are putting together a plan for the first five years. The budget is fixed; you have to decide how to make best use of it. Compounds can be made by people or robots. How can you decide the balance needed in your laboratory?

### Activity type **D**

Use of scientific knowledge and understanding to solve problems

Working in teams to solve problems

Resource/budget management

### Techniques

Microscale synthesis

### Field

Pharmaceuticals

Combinatorial chemistry

### Time

Practical lessons: 180 minutes

Theory lessons: 180 minutes

Out of class time: 90 minutes

### StandardBase procedures

None

### StandardBase techniques

None

**Other resources**

GlaxoSmithKline; <http://www.gsk.com/>  
All resources are given in the text.

## Student's document

### SYNTHESISING PHARMACEUTICALS: Comparing manual and robotic parallel synthesis of aspirin like compounds

On its website (<http://www.gsk.com/research/about/about.htm>) GlaxoSmithKline says:

It takes about 12-15 years and costs over £500 million to discover and develop a new medicine, so we need to be determined and innovative to develop our molecules into medicines as fast as possible. Using the most modern technology, we can maintain a healthy product pipeline which ensures a flow of new products to people around the world.

Imagine you have been given the task of setting up a new synthetic laboratory for a pharmaceutical company. You are putting together a plan for the first five years. The budget is fixed; you have to decide how to make best use of it. Compounds can be made by people or robots. How can you decide the balance needed in your laboratory?

#### Your brief

You have three tasks to complete that will help you find out more about the techniques used in pharmaceutical companies to synthesise compounds. The tasks are:

- to carry out a microscale preparation of aspirin
- to plan a small array parallel synthesis to make a series of compounds that have structural similarities to aspirin and, therefore, may have potential as analgesics
- to compare the costs of manual one-off syntheses, manual parallel syntheses and robotic parallel syntheses.

#### *Plan and prepare*

You will work with a partner. There is quite a lot of work to do: practical work, planning a laboratory experiment, gathering information about the price of chemicals and carrying out calculations. Work out how to best share the work. You may decide that there are parts that both of you should do as this might help you check reliability. For example, each of you should make a sample of aspirin and compare your results.

There may also be occasions when you work in a group of four with another pair. Your teacher will tell you when.

#### Your investigation

##### *Practical activity*

There are three tasks to carry out.

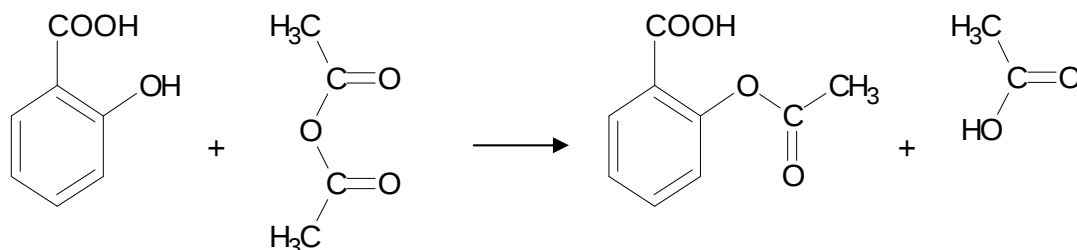
##### 1. Microscale preparation of aspirin

Follow the **procedure** *The microscale synthesis of aspirin* to make a sample of aspirin. The quantities used are small. You need to work carefully.

Record the yield of product and determine its melting point. Purify the crude product by recrystallisation and determine its melting point. Pure aspirin melts at 138-140 °C.

Investigate the purity of the crude and recrystallised products using thin layer chromatography (use the **procedure** *Thin layer chromatography of aspirin*).

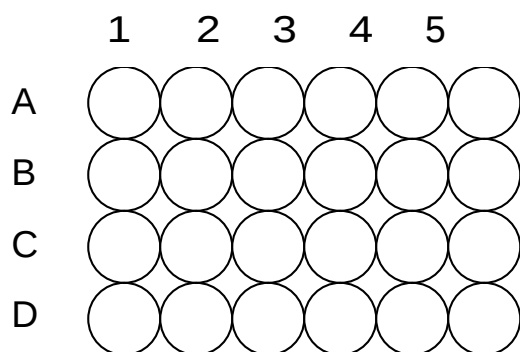
Here is the reaction you will use:



Copy this into your file or laboratory notebook and name the compounds.

## 2. Manual parallel synthesis (virtual experiment)

Pharmaceutical companies make and test tens of thousands of compounds in the search for one that shows significant therapeutic biological activity. Only small quantities are needed. For example, using plastic well plates, 10 tests for biological activity can be carried out on 1 mg of compound.



A small array, using a 6 x 4 matrix, may be used for parallel synthesis of compounds. You can make up to 24 compounds.

Each circle is the equivalent of the test tube you used in the microscale synthesis.

As little as 5 mg of a compound is synthesised. High yield is not important.

The desired compound is separated and purified by chromatography.

With your partner, plan a manual parallel synthesis of compounds that are structurally similar to aspirin, using a 6 x 4 matrix. Use these reactants:

|                       |                                                                             |                                                             |
|-----------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------|
| 2-hydroxybenzoic acid | 2-hydroxyphenylethanoic acid<br>(also called<br>2-hydroxyphenylacetic acid) | ethanoic anhydride<br>(also called<br>acetic anhydride)     |
| 3-hydroxybenzoic acid | 3-hydroxyphenylethanoic acid<br>(also called<br>3-hydroxyphenylacetic acid) | propanoic anhydride<br>(also called<br>propionic anhydride) |
| 4-hydroxybenzoic acid | 4-hydroxyphenylethanoic acid<br>(also called<br>4-hydroxyphenylacetic acid) | butanoic anhydride<br>(also called<br>butyric anhydride)    |
|                       |                                                                             | pentanoic anhydride<br>(also called<br>valeric anhydride)   |

Say which combination of reactants you would add to each reaction tube.

Write down the structural formulae of the compounds you are trying to make on the **datasheet** *Manual parallel synthesis*.

Assume that you are going to use  $2 \times 10^{-4}$  moles of each reactant. Find the cost of chemicals required to carry out the parallel synthesis. You can ignore the cost of the 85% phosphoric(V) acid. You can find prices of chemicals at this website: [http://www.sigmaaldrich.com/Area\\_of\\_Interest/Europe\\_Home/UK.html](http://www.sigmaaldrich.com/Area_of_Interest/Europe_Home/UK.html)

You should take responsibility for costing twelve of the reactions and your partner the other twelve.

Finding the data may take you some time, so plan carefully.

**Note:** This is where you might work with another pair to share the workload.

Show your calculations on the **datasheet** *Manual parallel synthesis*.

### 3. Comparing the costs of techniques

You carried out a microscale synthesis. In manual parallel synthesis, the quantities used are even smaller. In the second task, you investigated how chemists produce large numbers of compounds to test for therapeutic biological activity.

Now it is time to find out about three techniques used in pharmaceutical synthetic laboratories and understand some of the issues we started with. One example is, 'Compounds can be made by people or robots. How can you decide the balance needed in your laboratory?'

Obtain a copy of the **datasheet** *Economics of manual and robotic syntheses*. As well as data you will find some questions. Answer these on a separate piece of paper.

At the end of this task you should be able to compare the costs of the three techniques often used:

- manual one-off synthesis
- manual parallel synthesis
- robotic parallel synthesis.

Suggest situations for which each synthetic technique might be best suited.

#### *Tips for finding information*

Rather than doing a web search for the prices of chemicals, your teacher may be able to let you use a chemical supplier's catalogue.

A number of websites are recommended in this activity. For further information and ideas, use your favourite search engine.

#### *Procedures*

The information you need is on four **sheets**:

- *The microscale synthesis of aspirin*
- *Thin layer chromatography of aspirin*
- *Manual parallel synthesis*
- *Economics of manual and robotic syntheses*

## **Your findings**

Record:

- the yield and melting point of your samples of crude aspirin; the melting point of your samples of recrystallised aspirin; your chromatograms
- the cost of the manual parallel synthesis you planned
- the comparative costs of making compounds by manual one-off synthesis, manual parallel synthesis and robotic parallel synthesis.

## *Evaluating results*

Comment of the yields and purities of the aspirin samples you and your partner made.

Comment on decisions that must be made when choosing chemicals to buy for use as starting materials in syntheses.

Describe the advantages and disadvantages of the three synthetic techniques, manual one-off synthesis, manual parallel synthesis and robotic parallel synthesis.

## **Student self assessment**

This activity was about using scientific knowledge and understanding to solve problems, working in teams and understanding something about resource and budget management.

In 50- 100 words say:

- what scientific skills and knowledge you used and how effectively you used them.
- how you worked as a pair, giving examples of how you supported one another and, if appropriate, worked with another pair.
- describe what you learned about managing resources and budgets.

## Student sheet: The microscale synthesis of aspirin

This procedure is based on one found in *Microscale Chemistry*, compiled by John Skinner, published and distributed by the Royal Society of Chemistry, page 90, 1997. ISBN 1 870343 49 2

### Materials and equipment

- fume cupboard
- 2 x 50 cm<sup>3</sup> beakers (one to be used for the hot water bath)
- polystyrene drinking cup (or similar) two-thirds filled with crushed ice (the ice-bath)
- Bunsen burner, tripod and gauze (or an electric hotplate)
- 2 x test tubes with test tube rack
- 2 x dropping pipettes
- small Buchner filter funnel with filter papers
- electronic balance that weighs to 0.01 g or better
- small spatula
- watch glass
- sample tube
- distilled water wash-bottle
- 10 cm<sup>3</sup> measuring cylinder
- 2-hydroxybenzoic acid (salicylic acid)
- ethanoic anhydride
- 85% phosphoric(V) acid
- ethanol
- distilled water
- crushed ice
- apparatus for determining melting points

### Health and safety

Wear protective clothing and eye protection. A risk assessment must be carried out before starting work.

### Procedure

1. Set up a water bath by standing a beaker on a tripod and gauze and half-fill with distilled water. Warm with a non-luminous Bunsen flame (but not roaring) and maintain the temperature at about 70-80 °C.
2. Carefully weigh 0.23 g of 2-hydroxybenzoic acid into a test tube.
3. Add 25 drops of ethanoic anhydride followed by 1 drop of 85% phosphoric(V) acid to the test tube (use two clean dropping pipettes). Place the test tube with the reaction mixture in the water bath and leave it for 15 minutes.
4. Remove the test tube from the water bath and stand in a rack. Add 1.5 cm<sup>3</sup> distilled water. Leave in the rack to cool until crystals of product begin to form. Put the test tube into an ice bath and leave for several minutes until the tube and reaction mixture are ice-cold.
5. Suction filter through a small Buchner filter funnel (remember to bed the filter paper down using a squirt of distilled water). Wash with a very small quantity of ice-cold distilled water.

6. Transfer the filter paper and product to a watch glass and dry the product in an oven at about 105 °C.

7. Weigh a labelled sample tube, scrape the crude product into it and reweigh. Calculate the yield.

**If time allows:**

1. Determine the melting point of the crude product.

2. Put a small quantity of the crude product to one side (you will need it if you do the thin layer chromatography investigation). Recrystallise the remainder of the crude product using 2 cm<sup>3</sup> distilled water with 5 drops of ethanol added. Leave a small quantity for thin layer chromatography.

3. Suction filter, wash with a little ice-cold distilled water. Transfer the filter paper and product to a watch glass and dry the product in an oven at about 105 °C.

4. Scrape the recrystallised product into a labelled sample tube. You will need it for thin layer chromatography.

**Results**

For the crude product:

Yield = \_\_\_\_\_ g

Melting point = \_\_\_\_\_ °C

For the recrystallised product:

Melting point = \_\_\_\_\_ °C

## Student sheet: Thin layer chromatography of aspirin

### Equipment and materials

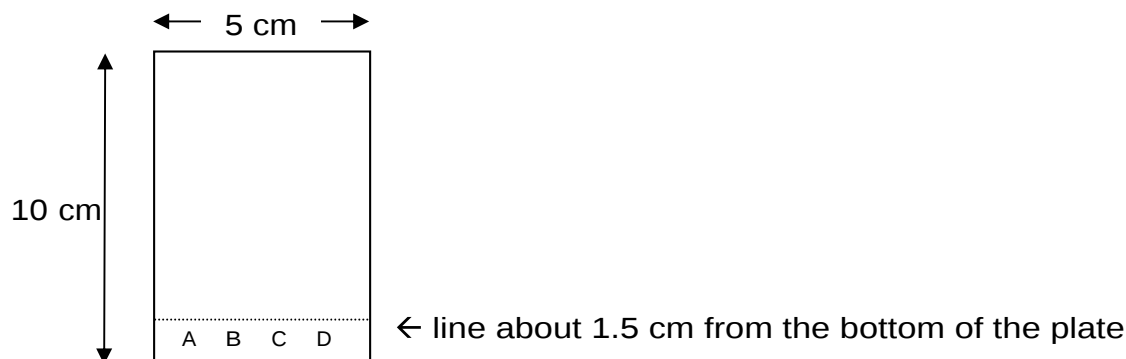
- TLC plate (coated in silica gel and containing a fluorescing agent)
- screw-capped jar or tank large enough to take the TLC plates
- finely drawn glass tubes (for spotting the plates) [CARE: fragile/break easily]
- 4 x test tubes and test tube rack
- UV lamp [CARE do not look directly at UV light]
- ethanol
- developing solvent: 95 cm<sup>3</sup> ethyl ethanoate + 5 cm<sup>3</sup> glacial ethanoic acid
- iodine crystals

### Health and safety

Wear protective clothing and eye protection. A risk assessment must be carried out before starting work.

### Procedure

1. Using a pencil, carefully mark a TLC plate as shown in the diagram. Make small crosses on the line above the letters to show where the spots will be put.



2. Put 1 cm<sup>3</sup> ethanol into each of four test tubes labelled A to D. Add small amounts of the following:

|             |                                 |
|-------------|---------------------------------|
| test tube A | pure aspirin                    |
| test tube B | crude reaction product          |
| test tube C | recrystallised reaction product |
| test tube D | 2-hydroxybenzoic acid           |

3. Spot samples from test tubes A, B, C and D on the TLC plate. Allow 2-3 minutes for the spots to dry.

4. Pour the developing solvent into the screw-capped jar to a depth of about 1 cm. Carefully put the tlc plate into the jar. Leave until the solvent has risen to about 1 cm from the top of the plate.

5. Remove the plate from the jar and in pencil (not pen), lightly mark the position of the solvent front. Leave it in a fume cupboard to dry.

6. Look at the plate under the UV lamp (DO NOT look at directly at the UV light). Alternatively, stand it in a screw-capped jar containing 2-3 iodine crystals.

### Results

Make a sketch of the chromatogram indicating the position of the spots.

## Student datasheet: Manual parallel synthesis

| Array | 1                                                                                 | 2                                                                                 | 3                                                                                 | 4                                                                                 | 5                                                                                 |
|-------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| A     |  |  |  |  |  |
| B     |  |  |  |  |  |
| C     |  |  |  |  |  |
| D     |  |  |  |  |  |

### Key to reactants:

|          |                       |          |                              |
|----------|-----------------------|----------|------------------------------|
| <b>1</b> | 2-hydroxybenzoic acid | <b>4</b> | 2-hydroxyphenylethanoic acid |
| <b>2</b> | 3-hydroxybenzoic acid | <b>5</b> | 3-hydroxyphenylethanoic acid |
| <b>3</b> | 4-hydroxybenzoic acid | <b>6</b> | 4-hydroxyphenylethanoic acid |

### A-D

|          |                     |          |                     |
|----------|---------------------|----------|---------------------|
| <b>A</b> | ethanoic anhydride  | <b>C</b> | butanoic anhydride  |
| <b>B</b> | propanoic anhydride | <b>D</b> | pentanoic anhydride |

Which starting compounds would you mix in these reaction tubes:

|    |  |  |
|----|--|--|
| A1 |  |  |
| A2 |  |  |
| A3 |  |  |
| A4 |  |  |
| A5 |  |  |
| A6 |  |  |
| B1 |  |  |
| B2 |  |  |
| B3 |  |  |
| B4 |  |  |
| B5 |  |  |
| B6 |  |  |
| C1 |  |  |
| C2 |  |  |
| C3 |  |  |
| C4 |  |  |
| C5 |  |  |
| C6 |  |  |
| D1 |  |  |
| D2 |  |  |
| D3 |  |  |
| D4 |  |  |
| D5 |  |  |
| D6 |  |  |

In the grid, draw the structural formulae of the expected reaction products.

|    |    |    |    |
|----|----|----|----|
| A1 | B1 | C1 | D1 |
| A2 | B2 | C2 | D2 |
| A3 | B3 | C3 | D3 |
| A4 | B4 | C4 | D4 |
| A5 | B5 | C5 | D5 |
| A6 | B6 | C6 | D6 |

On this sheet, record the prices you found for the chemicals to be used. Show how you calculated the cost of the 12 reactions for which you were responsible.

Write down the cost for the other 12 reactions, worked out by your partner:

Estimate the cost of the manual parallel synthesis of all 24 compounds:

Comment of factors that would affect this costing:

## **Student datasheet: Economics of manual and robotic syntheses**

Pharmaceutical companies make and test tens of thousands of compounds in the search for one that shows significant therapeutic biological activity.

Only small quantities are needed. For example, using plastic well plates, 10 tests for biological activity can be carried out on 1 mg of compound.

Compounds are prepared on a very small scale, with perhaps only 5 mg being made at a time. At this stage, efficiency (i.e. a high yield) is not important. Small quantities of the target compound may be separated from a reaction mixture using chromatography.

In a multi-stage synthesis, the yield at each stage may be low, making the overall percentage yield very low. This means that around 20-50 mg of starting materials may be needed to make just 5 mg of product.

There are three possible techniques:

- manual one-off synthesis
- manual parallel synthesis
- robotic parallel synthesis.

### **Calculating the cost**

Assumptions

- The cost of a chemist's time is £200 per day (this includes salary, National Insurance, employer's pension contribution and other benefits; it does not include building and environmental overheads).
- There are 227 working days per year.
- The same quantities of reactants and solvents are used in each synthesis.
- Starting materials cost £50 per synthesis and solvents cost £30 per synthesis. In practice the cost of starting materials varies significantly.

#### **1. Manual one-off synthesis**

One stand-alone chemist has a maximum output in a year of about 50 compounds.

- Show that the cost of making one compound is about £1000.

#### **2. Manual parallel synthesis**

Usually this is carried out in small array using a 6 x 4 matrix to make 24 compounds in parallel.

One stand-alone chemist has a maximum output in a year of about 6 small arrays.

- Show that the cost of making one compound is about £400.

#### **3. Robotic parallel synthesis**

Like manual parallel synthesis, this employs a matrix of reaction vessels. However, the fully automated process handles much larger numbers of compounds.

A high through-put robot such as Zinsser Sophas can carry out up to 764 reactions in one run. The robot costs about £100 000 and requires one full-time person to operate it. A second robot is used to purify compounds. It

costs about L150 000 and requires another full-time person to operate it. The value of both robots depreciates by 20% each year. The system has a maximum output of about 20 000 compounds in a year.

- Show that the cost of making one compound is about L90.
- Calculate the cost of making one compound if the robots only operate at 20% of their maximum capacity.
- Estimate the operating capacity at which one compound would cost L400 to make.

You can find out more about the robot at  
<http://www.zinsser-analytic.com/44.asp>

## Teacher's document

### Overview

This simulation is designed to give students insight into synthetic techniques used in research and development (R&D) laboratories. The activity makes them think about synthesising compounds in a pharmaceutical research laboratory. To be effective, they need to have appropriate scientific skills and knowledge, be able to work together as a team and understand the importance of resource and budget management.

### Developing students' skills

#### *Learning objectives*

Students learn to:

- tackle scientific problems by applying their practical skills and their knowledge
  - observe, measure and analyse data collected and to evaluate these
  - work with others and managing relationships with people
  - manage resources and budgets,
- in the context of a chemist in a laboratory synthesising pharmaceutical products.

#### *Guidance and help*

Students need to recognise the importance of taking care and pride in their work. They need to be gently reminded of this while they are working. They may need three types of help.

- Help with technical details, including manipulative skills and correct handling of chemicals and equipment.
- Help with, and vigilance over, health and safety issues.
- Help with working relationships in their group.

#### *Learning*

The "assessment for learning" approach aims to help students identify their weaknesses and work to improve them. It is not intended to be used to 'give students marks'. See: <http://www.presentingscience.com/aflchem/>

When using questioning, do not intervene too soon with 'the answer'. Give students thinking time. Use questions as prompts for students to think about what they are doing. They need to be aware of the consequences to themselves and others of actions they take. Use relevant unambiguous questions. Allow plenty of time for students to respond. Involve all members of the group.

An effective series of questions might start with a closed question, followed by open questions. For example: *What was your result? How did you arrive at that result? Where else can you use this method? How can you improve the method?*

### Organising and managing the class

It is suggested that students work in pairs.

The timing of the practical work is crucial. How it is arranged depends on lesson time. However, there are two stages at which samples need to be left to dry. It would be appropriate to fit (a) the planning task and (b) the costing task into these times.

## Notes on the tasks

### 1. Microscale preparation of aspirin

Students may not have worked on this scale before. They must be encouraged to work carefully.

While they are working on the purification of the product, they might be asked to say the smallest quantity of product they could recrystallise. This could be used to raise issues of separation and purification when working on even smaller scales, such as are used in manual parallel syntheses.

If time is short, the determination of melting point and, possibly, the TLC investigation might be omitted. If they do carry out these parts of the practical, you will need to provide guidance depending on the equipment you have available at your school/college.

### 2. Manual parallel synthesis

This task raises several issues.

Students need to be able to draw structural formulae and name organic compounds. A good approach might be to discuss the equation on their student sheet – perhaps bring two pairs together to discuss. There is also an opportunity to talk about position isomerism.

The *Sigma Aldrich* website is relatively straightforward to search. Simply type in the chemical name and search. However, there are some oddities. If 2-hydroxybenzoic acid is typed in, you are prompted to look for 2 hydroxybenzoic acid (no hyphen). This takes you to a page where the substance we want is now called salicylic acid. Clicking Salicylic acid gives ten options.

There are some important teaching points here:

- The use of common names and IUPAC names - we may teach IUPAC nomenclature but 'old' names are common in industrial laboratories and suppliers' catalogues.
- For any chemical there are invariably several options (mainly based on purity) and a closer look at each option shows a further choice – the quantity to buy; in terms of costs, both are important – the higher the purity and the smaller the quantity bought, the more it costs.

In terms of budget management students need to recognise:

- it is important to know what the minimum purity required is – there is no point in buying something of very high purity if it is not needed
- buying small quantities (especially very small quantities) is disproportionately expensive – planning ahead is imperative and if the chemical is likely to be used for further work, buy larger quantities as the price per gram is less.

Selecting a particular product gives a page with lots of useful information, including:

- synonym (which is where students will finally see 2-hydroxybenzoic acid), structural formula, molecular formula and CAS number
- prices
- properties.

It would be valuable to spend some time searching the site before the students do.

### 3. Comparing the costs of techniques

Here are some sample calculations:

#### **Manual one-off synthesis**

One stand-alone chemist has a maximum output in a year = 50

Therefore the chemist's time to make one compound =  $L45\,400 \div 50 = L908$

Cost of starting materials = L50

Cost of solvents for purification = L30

Total cost per compound (working at maximum output) = L988

So the cost of making one compound in a manual one-off synthesis is about L1000.

#### **Manual parallel synthesis**

Usually this is carried out in small array using a 6 x 4 matrix to make 24 compounds in parallel.

One stand-alone chemist has a maximum output in a year = 144 (i.e. 6 small arrays)

Therefore the chemist's time to make one compound =  $L45\,400 \div 144 = L315$

Cost of starting materials = L50

Cost of solvents (for preparation and purification) = L30

Total cost per compound (working at maximum output) = L395

So the cost of making one compound in a manual parallel synthesis is about L400.

#### **Robotic parallel synthesis**

Like manual parallel synthesis, this employs a matrix of reaction vessels. However, the fully automated process handles much larger numbers of compounds.

A high through-put robot such as Zinsser Sophas can carry out up to 764 reactions in one run. The robot costs about L100 000 and requires one full time person to operate it. A second robot is used to purify compounds. It costs about L150 000 and requires another full time person to operate it. The system has a maximum output of about 20 000 compounds in a year.

Two chemists and their robots have a maximum output in a year = 20 000

Therefore the chemists' time to make one compound =  $L(45\,400 \times 2) \div 20\,000 = L4.54$

Depreciation costs =  $L[(100\,000 + 150\,000) \times 0.2] \div 20\,000 = L2.50$

Total running costs per compound = L7.04

Cost of starting materials = L50

Cost of solvents (for preparation and purification) = L30

Total cost per compound (working at maximum output) = L87.04

So the cost of making one compound in a robotic parallel synthesis is about L90

*Calculate the cost of making one compound if the robots only operate at 20% of their maximum capacity.*

Two chemists and their robots have output in a year = 4000

Therefore the chemists' time to make one compound =  $L(45\,400 \times 2) \div 4000 = L22.70$

Depreciation costs =  $L[(100\,000 + 150\,000) \times 0.2] \div 4000 = L12.50$

Total running costs per compound = L35.20

Cost of starting materials = L50

Cost of solvents (for preparation and purification) = L30  
Total cost per compound (working at maximum output) = 115.20  
So the cost of making one compound in a robotic parallel synthesis is about L115.

*Estimate the operating capacity at which one compound would cost L400 to make.*

Cost of starting materials = L50

Cost of solvents (for preparation and purification) = L30

So total running costs would be  $L400 - 50 - 30 = L320$

Total running costs at 100% capacity (20 000 compounds) = L7.04

So, if each compound has total running cost of L320, it must be operating at 2.2%.

In other words 440 compounds, each costing L400 to make.

### **Session plan for teachers**

A suggested approach is:

- Introduction to the activity and checking prior knowledge (about 60 minutes)
- Students, arranged in pairs, discuss and allocate the work (about 30 minutes)
- Carry out the aspirin synthesis (about 90 minutes)
- Student pairs carry out the parallel synthesis planning task (about 90 minutes)
- Carry out the recrystallisation, melting point determinations and thin layer chromatography (about 90 minutes)
- Student pairs compare the costs of the three synthetic techniques (about 90 minutes)

## Technical notes

### ▪ Preparation

#### *Working environment and conditions*

Students need to work in a laboratory to prepare aspirin. Other work may be done outside the laboratory. Access to a high speed internet connection is essential if web-research is to be carried out.

### ▪ Equipment and materials

#### Materials and their CAS numbers

Common names are given in brackets

#### Preparation and purification of aspirin

|                                        |           |
|----------------------------------------|-----------|
| 2-hydroxybenzoic acid (salicylic acid) | 69-72-7   |
| ethanoic anhydride (acetic anhydride)  | 108-24-7  |
| 85% phosphoric(V) acid                 | 7664-38-2 |
| ethanol                                | 64-17-5   |

#### CAS numbers

#### Chromatography of aspirin

|                                     |         |
|-------------------------------------|---------|
| 2-ethanoyloxybenzoic acid (aspirin) | 50-78-2 |
|-------------------------------------|---------|

#### Equipment

Each student or pair of students will require:

#### The microscale synthesis of aspirin

- fume cupboard
- 2 x 50 cm<sup>3</sup> beakers (one to be used for the hot water bath)
- polystyrene drinking cup (or similar) two-thirds filled with crushed ice (for ice-bath)
- Bunsen burner, tripod and gauze (or an electric hotplate)
- 2 x test tubes with test tube rack
- 2 x dropping pipettes
- small Buchner filter funnel with filter papers
- electronic balance that weighs to 0.01 g or better
- small spatula
- watch glass
- sample tube
- distilled water wash-bottle
- 10 cm<sup>3</sup> measuring cylinder
- 2-hydroxybenzoic acid (salicylic acid)
- ethanoic anhydride
- 85% phosphoric(V) acid
- ethanol
- distilled water
- crushed ice
- apparatus for determining melting points

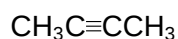
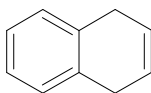
#### Thin layer chromatography of aspirin

- TLC plate (coated in silica gel and containing a fluorescing agent)
- screw-capped jar or tank large enough to take the tlc plates
- finely drawn glass tubes (for spotting the plates)
- 4 x test tubes and test tube rack
- UV lamp
- ethanol
- developing solvent: 95 cm<sup>3</sup> ethyl ethanoate + 5 cm<sup>3</sup> glacial ethanoic acid
- iodine crystals

## Testing prior knowledge

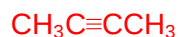
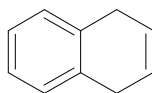
1. Match the hydrocarbon to the type it belongs with.

Hydrocarbon:



Type: alkane    alkene    alkyne    arene

Answer:



alkene

arene

alkyne

alkane

2. Match the compound group to the functional group.

Name:

primary alcohol

carboxylic acid

ester

ketone

Functional group:  $-\text{COO}-$      $>\text{C}=\text{O}$      $-\text{COOH}$      $-\text{CH}_2\text{OH}$

Answer:

primary alcohol

carboxylic acid

ester

ketone

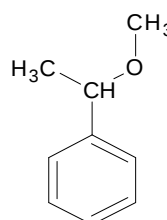
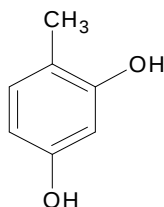
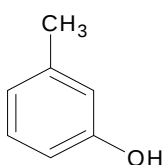
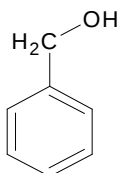
$-\text{CH}_2\text{OH}$

$-\text{COOH}$

$-\text{COO}-$

$>\text{C}=\text{O}$

3. Which of the following compounds are not phenols?



A

B

C

D

Answer: A and D

4. Draw structural formulae for these compounds:

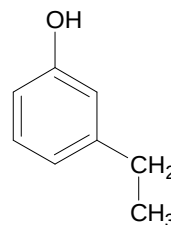
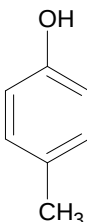
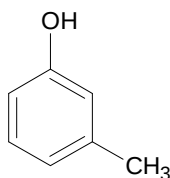
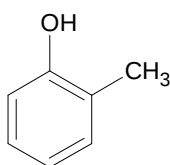
2-methylphenol

3-methylphenol

4-methylphenol

3-ethylphenol

Answer:

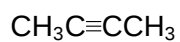
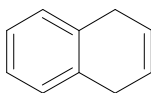


Note: Answers are given in red. These need to be removed before the test is used.

## Testing prior knowledge

1. Match the hydrocarbon to the type it belongs with.

Hydrocarbon:



Type:   alkane     alkene     alkyne     arene

2. Match the compound group to the functional group.

Name:

primary alcohol

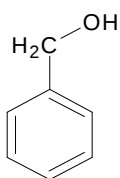
carboxylic acid

ester

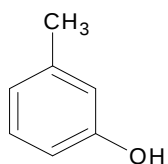
ketone

Functional group:   -COO-      $>\text{C}=\text{O}$      -COOH     -CH<sub>2</sub>OH

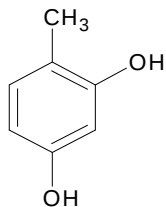
3. Which of the following compounds are not phenols?



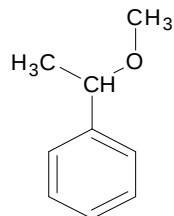
A



B



C



D

4. Draw structural formulae for these compounds:

2-methylphenol     3-methylphenol     4-methylphenol     3-ethylphenol

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