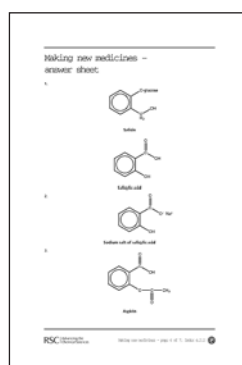
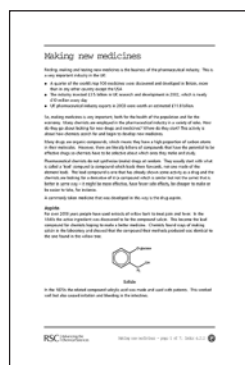


Making new medicines – combinatorial chemistry



Index 4.2.1

1 sheet

Index 4.2.2

7 sheets

Making medicines and drugs is a topic of interest to many students as virtually all will have taken some kind of medicine at some point in their lives. The pharmaceutical industry is also a major contributor to the UK economy and employs a large number of chemists. Pharmaceutical companies carry out nearly a quarter of all industrial research and development in the UK. However, medicinal chemistry rarely features in pre-16 chemistry courses because the organic chemistry involved in a lot of the processes is too complex.

This activity looks at some cutting edge industrial chemistry – the development of combinatorial chemistry. It does not require students to have an understanding of organic chemistry beyond the simple addition reactions that feature in many pre-16 courses. Students will be guided to:

- Notice differences between the structures of given molecules
- Predict the products of a reaction when given the reactants and products of a similar reaction
- Calculate the number of possible products of a combinatorial synthesis when given appropriate information.

While this activity can stand on its own, it is probably best used alongside the resource **Making medicines** on the RSC's CDROM *Alchemy?* This resource includes a five minute video clip which will be accessible to the majority of 14–16 year olds. The question sheets provided on the CDROM are more suited to post-16s, but alternative questions are suggested here. The video clip will help students understand the written material provided here. It would fit well after the section on aspirin. If the question sheet is used, the film should be shown at least twice. Alternatively, students could be given individual access to the clip and allowed to pause it when required.

This activity could be introduced using the history of medicine timeline available on the Association of the British Pharmaceutical Industry's website:

<http://www.abpischools.org.uk/resources04/history/index.asp> (accessed November 2005).

It may be worth explaining to students the use of the terms 'drug' and 'medicine.' A drug is a substance that affects how the body works – either for better or for worse. A medicine improves health. A medicine contains beneficial drugs as the active

ingredients (or a precursor which forms the active ingredient once inside the body) as well as other substances that make it easy or convenient to take.

Make sure students appreciate that chemists are required to design the synthetic methods and routes used in combinatorial chemistry. The involvement of a robot does not mean that chemists are not required. The syntheses must be designed to be general methods which can be used to make several members of a class of compounds. Once a particular molecule has been selected for further work, an alternative synthesis may be developed that produces the specific compound of interest more efficiently.

Once combinatorial synthesis is complete, mass spectrometry and NMR (nuclear magnetic resonance) spectroscopy are used to confirm the identity of the compounds that have been made, although this is often only attempted for the substances which have shown evidence of the required activity.

References and further information

T. Lister, *Cutting Edge Chemistry*, London: Royal Society of Chemistry, 2000.

Alchemy? CDROM from the Royal Society of Chemistry, sections entitled Making medicines and Combinatorial chemistry. For further information, see <http://www.chemsoc.org/networks/learnnet/alchemy.htm>.

Chemistry Now – Combinatorial Chemistry leaflet from the Royal Society of Chemistry which can be downloaded free from http://www.chemsoc.org/networks/learnnet/chemnow_combi.htm

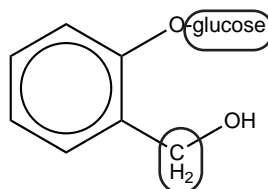
Answers

Video questions

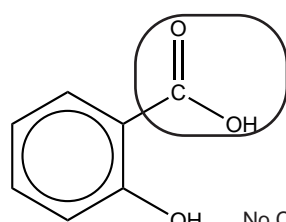
1. A pharmaceutical company makes around 10 000 new chemicals in the process of developing each new medicine.
2. The three main reasons for failure are that the compound is not effective, produces side effects and/or is toxic.
3. About 1 g of a compound is generally made by traditional methods.
4. A few micrograms are required for biological activity testing.
5. The types of chemical used as a starting point are:
 - A chemical found in the body
 - An existing drug
 - A chemical that chemists think might react with an enzyme (they decide by looking at the structure of the compound).
6. An acid (usually trifluoroethanoic acid) is used to detach new compounds from resin beads.
7. Up to 100 kg can be made at a pilot plant.
8. It takes around 10 years to develop a drug.

Making new medicines

1.



Salicin

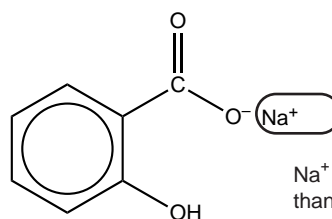


This group is different

No CH₂ group

Salicylic acid

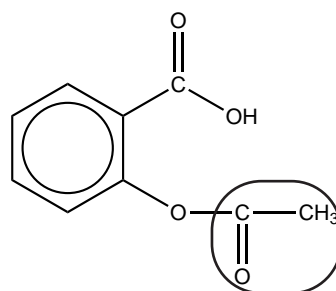
2.



Na⁺ and O⁻ rather than OH group

Sodium salt of salicylic acid

3.

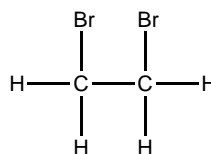


This group instead of just an H atom

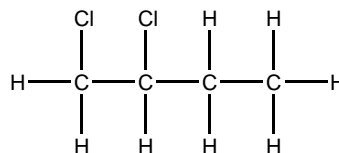
Aspirin

4. 12 products can be made.

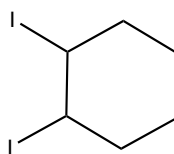
5. The product from bromine and ethene would be:



The product from chlorine and butene would be:



The product from iodine and cyclohexene would be:



6. 96 compounds would be made in a 12 x 8 synthesis.
7. Reaction vessel 3 will contain the following at stage 2:
 - Bead + ●■
 - Bead + ▲■
 - Bead + ■■
8. $3^4 = 3 \times 3 \times 3 \times 3 = 81$.
9. $4^3 = 4 \times 4 \times 4 = 64$.

Making new medicines – video questions

These questions are to be used with the video clip on the RSC CDROM Alchemy?.

1. For every new drug which reaches the market, how many new chemicals does a pharmaceutical company make?

.....

2. What are the three main reasons why most compounds fail?

.....
.....
.....

3. How much compound is usually made using traditional methods?

.....

4. How much compound is required for testing for biological activity?

.....

5. What three types of chemical might be used as the starting point of a synthesis?

.....
.....
.....

6. What is used to break a new compound off the resin bead?

.....

7. A pilot plant is the last stage before full scale production. What quantity of product is made at a pilot plant?

.....

8. About how long does it usually take to develop a new drug, from the initial idea to the marketing of the product?

.....
.....

Making new medicines

Finding, making and testing new medicines is the business of the pharmaceutical industry. This is a very important industry in the UK:

- A quarter of the world's top 100 medicines were discovered and developed in Britain, more than in any other country except the USA
- The industry invested £3.5 billion in UK research and development in 2002, which is nearly £10 million every day
- UK pharmaceutical industry exports in 2003 were worth an estimated £11.8 billion.

So, making medicines is very important, both for the health of the population and for the economy. Many chemists are employed in the pharmaceutical industry in a variety of roles. How do they go about looking for new drugs and medicines? Where do they start? This activity is about how chemists search for and begin to develop new medicines.

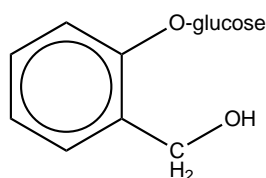
Many drugs are organic compounds, which means they have a high proportion of carbon atoms in their molecules. However, there are literally billions of compounds that have the potential to be effective drugs so chemists have to be selective about which ones they make and study.

Pharmaceutical chemists do not synthesise (make) drugs at random. They usually start with what is called a 'lead' compound (a compound which leads them forwards, not one made of the element lead). The lead compound is one that has already shown some activity as a drug and the chemists are looking for a derivative of it (a compound which is similar but not the same) that is better in some way – it might be more effective, have fewer side effects, be cheaper to make or be easier to take, for instance.

A commonly taken medicine that was developed in this way is the drug aspirin.

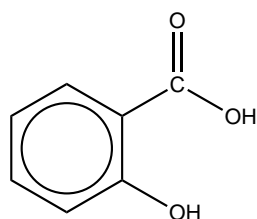
Aspirin

For over 2000 years people have used extracts of willow bark to treat pain and fever. In the 1840s the active ingredient was discovered to be the compound salicin. This became the lead compound for chemists hoping to make a better medicine. Chemists found ways of making salicin in the laboratory and showed that the compound their methods produced was identical to the one found in the willow tree.



Salicin

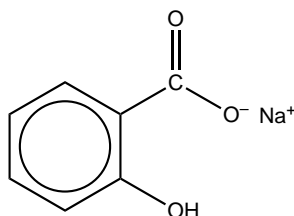
In the 1870s the related compound salicylic acid was made and used with patients. This worked well but also caused irritation and bleeding in the intestines.



Salicylic acid

1. Look at the diagrams of salicylic acid and salicin on the separate answer sheet. Circle the parts of the molecules where the two compounds are different.

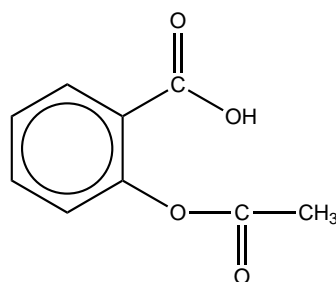
The sodium salt of salicylic acid was tried next. This also worked but it caused vomiting and tasted dreadful.



Sodium salt of salicylic acid

2. What is the difference between this compound and salicylic acid? Circle the difference on the diagram of the sodium salt on your answer sheet.

In the 1890s another derivative of salicin was made. It was shown to be just as effective as the other compounds that had been tried but it caused far less stomach irritation and tasted less unpleasant. This is the drug we still use today – aspirin.



Aspirin

3. What is the difference between this compound and salicylic acid? Circle the difference on the diagram of aspirin on your answer sheet.

The development of aspirin did not stop there. Throughout the twentieth century new uses have been found for it. Low doses are used to help prevent heart attacks and strokes and to help prevent blood clots in vulnerable people.

This method of drug development is effective, but very time consuming. The potential new drugs must be synthesised one at a time, purified, their structures confirmed and then tested for effectiveness. As about 10 000 new chemicals are made for each new drug which reaches the

market, this a very slow process. Using traditional methods of synthesis, a chemist can make about 50–100 new compounds every year. Until recently, this is what they did. Now, however, faster methods are being developed that use robots to help speed the process up. These faster methods are developed using ‘combinatorial chemistry.’

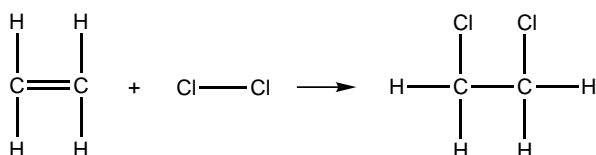
Combinatorial chemistry

Over the past few years several techniques have been developed that enable chemists to produce thousands of related compounds quickly. These techniques use computer-controlled syringes to carry out repetitive chemical tasks such as adding chemicals. The two most common combinatorial methods are called parallel synthesis and solid phase reactions (also known as ‘mix and split’).

Parallel synthesis

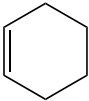
This method can be used for a huge variety of reactions but the principle can be shown by the following example.

Alkenes, which contain a double bond, can be reacted with a halogen as shown below:



The double bond in the alkene breaks open and the chlorine atoms join on to the carbon atoms.

Parallel synthesis could be used to react (for example) three different halogens with four different alkenes:

	Chlorine	Bromine	Iodine
Ethene $\begin{array}{c} \text{H} & \text{H} \\ & \\ \text{C} & = & \text{C} \\ & \\ \text{H} & \text{H} \end{array}$			
Propene $\begin{array}{c} \text{H} & \text{H} \\ & \\ \text{C} & = & \text{C}-\text{CH}_3 \\ \\ \text{H} \end{array}$			
Butene $\begin{array}{c} \text{H} & \text{H} \\ & \\ \text{C} & = & \text{C}-\text{CH}_2-\text{CH}_3 \\ \\ \text{H} \end{array}$			
Cyclohexene 			

Write in the answers to questions 4–9 on your answer sheet.

- How many different compounds can be made from the seven starting compounds shown in the table?
- Fill in the shaded boxes of the table by drawing the structures of the compounds that would be made by reacting the pairs of starting compounds shown.
- This is a 4 x 3 parallel synthesis. In the pharmaceutical industry a 12 x 8 arrangement is common. How many different compounds would be made at once in a 12 x 8 synthesis?

Solid phase reactions ('mix and split')

In solid phase reactions the starting material is attached to a bead of plastic – usually polystyrene. This method was developed for the synthesis of polypeptides. (Polypeptides are short pieces of protein made by joining amino acids together.) These days, the method is used to make a large number of different sorts of polymer-type compounds.

The following example shows how the process could be used to link three different monomers together. To keep things simple, the monomers are represented by a triangle, a square and a circle.

Step 1: Split the beads into three portions and attach a different monomer to each one.



Step 2: Mix all the beads together and then split them up into three portions again. Now there will be some of each monomer in each portion of beads. Attach a second monomer to the first one on every bead. This gives nine different compounds.

Step 3: Mix the beads up and split them into three portions again. Add a third monomer. This gives 27 different compounds.

Stage	Reaction vessel 1	Reaction vessel 2	Reaction vessel 3	No. of compounds
1	Bead + ●	Bead + ▲	Bead + ■	3
MIX				
2.	Bead + ●● Bead + ▲● Bead + ■●	Bead + ●▲ Bead + ■▲ Bead + ■▲		9
MIX				
3.	Bead + ●●● Bead + ▲●● Bead + ■●● Bead + ●▲● Bead + ▲▲● Bead + ■▲● Bead + ●■● Bead + ▲■● Bead + ■■●	Bead + ●●▲ Bead + ▲●▲ Bead + ■●▲ Bead + ●▲▲ Bead + ▲▲▲ Bead + ■▲▲ Bead + ●■▲ Bead + ▲■▲ Bead + ■■▲	Bead + ●●■ Bead + ▲●■ Bead + ■●■ Bead + ●▲■ Bead + ▲▲■ Bead + ■▲■ Bead + ●■■ Bead + ▲■■ Bead + ■■■	27
MIX				

7. What will reaction vessel 3 contain during stage 2?

When the required number of steps have been completed, the bead mixtures are filtered and thoroughly washed to get rid of any remaining chemicals. The plastic bead is then removed from the polymer by a chemical reaction.

This process can very quickly generate a vast 'library' of compounds. The size of the library is X^n where X is the number of monomers and n is the number of steps in the reaction. In this example, $X = 3$ (three monomers) and $n = 3$ (three steps). So, $3^3 = 3 \times 3 \times 3 = 27$ different compounds were made.

8. If a fourth step were added to this sequence, how many different polymers (each with four monomers linked together) would be made?
9. If you used four monomers and three steps, how many polymers would be made?

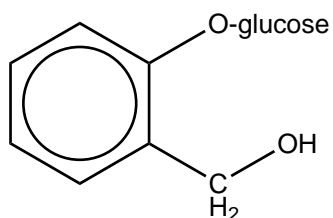
Testing for activity

One of the main reasons why these synthesis techniques have been developed is that there have been improvements in methods for rapidly screening large numbers of compounds to see if they have potential activity as drugs. There is no point making huge numbers of compounds at once if it takes years to screen them all.

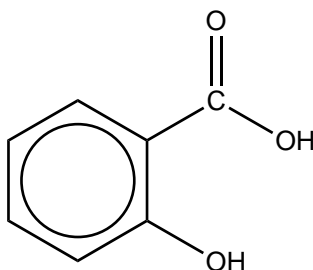
The compounds are initially tested by measuring their ability to affect enzymes or other components of cells. This is done in a test-tube ('in vitro' testing) and not on living things. Only compounds which show activity are developed further. They are made in larger quantities and subjected to more and more tests. To develop a new drug from the initial idea to a product that is available for use takes about 10 years and £450 million.

Making new medicines – answer sheet

1.

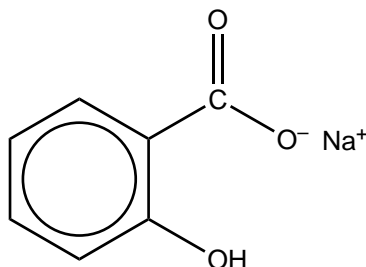


Salicin



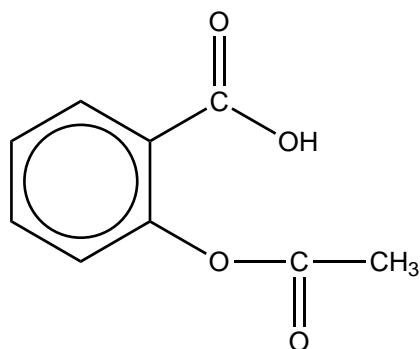
Salicylic acid

2.



Sodium salt of salicylic acid

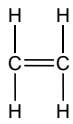
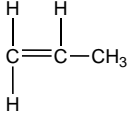
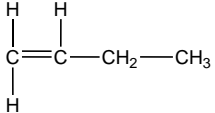
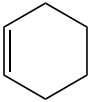
3.



Aspirin

4. _____ products could be made.

5.

	Chlorine	Bromine	Iodine
Ethene 			
Propene 			
Butene 			
Cyclohexene 			

6. _____ compounds can be made in a 12 x 8 parallel synthesis.

7. Reaction vessel 3 contains:

Bead + _____

Bead + _____

Bead + _____

8. Three monomers and four steps give _____ compounds.

9. Four monomers and three steps give _____ compounds.