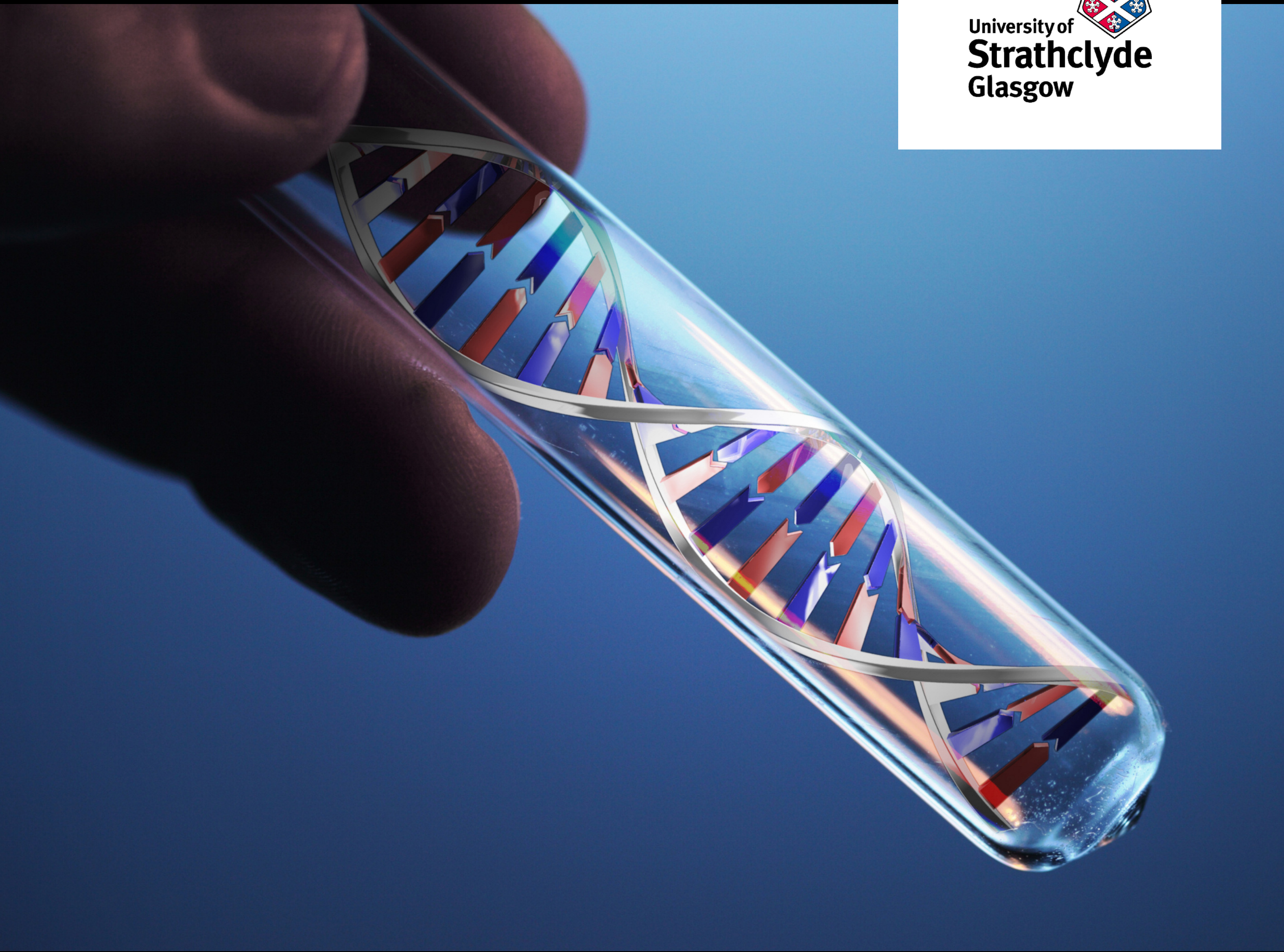

Why does heterocyclic chemistry matter?

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Why does heterocyclic chemistry matter?

'The world is all that is the case' wrote the philosopher, Ludwig Wittgenstein, to begin his Tractatus Logico-philosophicus in the early 20th century. With admitted exaggeration, I'm tempted to begin this e-book about the field of science known as Heterocyclic Chemistry by asserting 'The world is all that is heterocyclic chemistry'! I'd better justify this assertion initially with a definitional retreat. Atmospheric gases and minerals, of course, are not heterocyclic compounds but pretty much everything else we see, manufacture, and use contains heterocyclic compounds. When I look out of my office window I see objects from both nature and technology: trees, flowers, painted objects, dyed banners, for example. I've picked or implied colours because colour is the visible manifestation of one of the most important branches of chemistry; scientists call it heterocyclic chemistry. Basically, it's defined as the chemistry of compounds containing atoms joined in rings, mostly with 5 or 6 atoms, most of which are carbon but others are nitrogen especially, oxygen, sulfur, or phosphorus and sometimes metals and other elements. I've worked in heterocyclic chemistry all of my research career from PhD onwards and for me heterocyclic compounds make things happen.

Figure 1. Most of the colours in nature we see around us are due to heterocyclic compounds, the green of leaves and stems (chlorophylls), the petals of plants (anthocyanidins). The rhododendrons in this picture were originally planted at Ross Priory (University of Strathclyde) as a potential source of plant dyes for the nearby cotton thread industry in Paisley.

Heterocyclic chemistry is intrinsically interesting to scientists like me but easily intimidating to the lay person. However these days, probably more important than the science itself, is the context in which heterocyclic chemistry works. There's an enormous number of possible heterocyclic compounds taking account of the possible combinations of ring size, ring combination, and the nature and number of the heteroatoms (atoms other than carbon). In fact there are more conceivable compounds than could possibly be made by synthetic chemistry. But it's the huge variety of compounds with their widely different properties that makes heterocyclic chemistry so significant. With the chemists' understanding of how the molecules behave and how to make them, we can obtain compounds to carry out all sorts of valuable, useful, and beneficial tasks in applications ranging from drugs to TV screens.

Life itself depends exquisitely on heterocyclic chemistry. Indeed biology as we know it just would not exist without heterocyclic compounds. It's enough

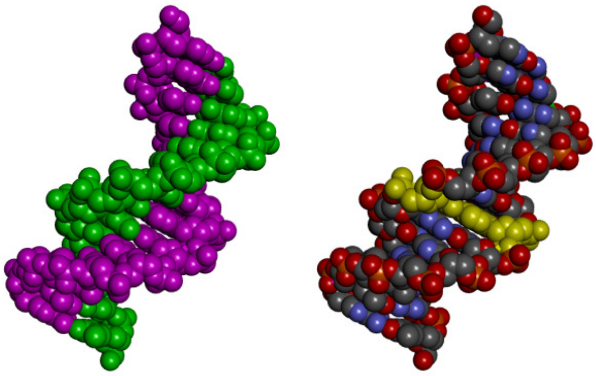

Figure 2. (Left) A representation of a section of the double helix of DNA; the two strands can be seen in green and purple winding round each other.

(Right) The same section of the double helix with most of the atoms coloured according to their type but two of the heterocyclic bases and their connected deoxy ribose heterocycles coloured yellow.

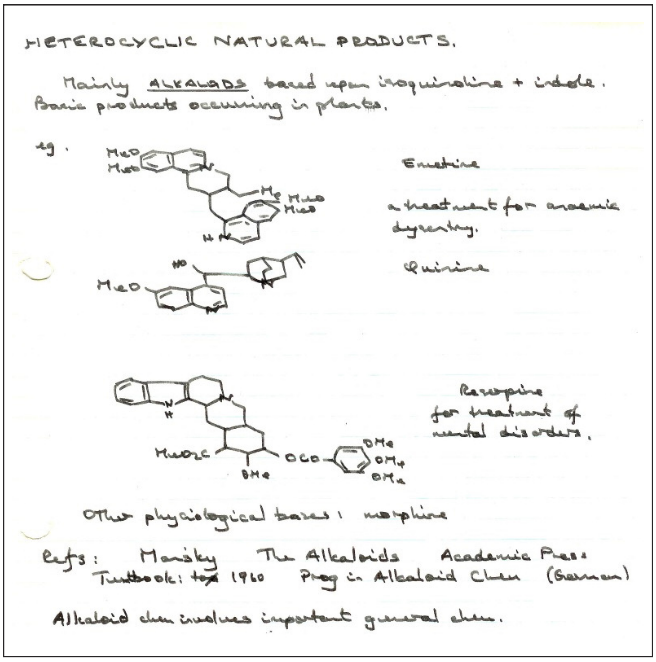

Figure 3. An extract from my lecture notes, University of Liverpool, 1967, all taken down live by hand. It's noticeable that the compounds selected by the lecturer, Professor Alan Battersby FRS, were all naturally occurring compounds with medicinal applications. Of the three, quinine, which was used to treat malaria, is probably the best known to most people.

to make this point to say that DNA is a giant molecule made up of thousands of heterocyclic compounds linked together. The so-called heterocyclic bases that code the information in DNA are linked through a sugar, deoxyribose, which in DNA is also a heterocycle also. Many of the working components of living cells are also heterocyclic compounds; for us, vitamins are very good examples, such as folic acid to name but one that is well known. We'll return to DNA at the end of this article.

It would take much more than the available space to explain adequately how heterocyclic chemistry works; my e-book published by Adjacent Government, does this with reference to the field of drug discovery and the basic concepts are equally appropriate to other fields of application.

http://www.adjacentgovernment.co.uk/ebooks/professor-colin-j-suckling-university-strathclyde/22964/

To my mind, however, the most significant general points about heterocyclic compounds themselves are the following.

1. Variety of structure, which makes the extraordinary range of both naturally occurring and synthetic compounds possible.

2. Tunable properties available from the variety of structure, which allow for the effective functioning of life and for the design of new synthetic compounds for specific purposes.

3. Synthesisable and manufacturable, which make available new compounds for technological applications especially in electronics and medicine.

It's probably more for these reasons than for the novelty of the science that we still teach heterocyclic chemistry today. Like other core components of chemistry, thermodynamics, kinetics, functional group chemistry, and the chemistry of the elements, heterocyclic chemistry fundamental heterocyclic chemistry has not changed in the last 50 years, or longer even. I checked and looked at my old lecture notes, which I still have. For example, although now presented in a modern teaching environment instead of with chalk and blackboard, the basic material of heterocyclic chemistry that I learned would still be appropriate today.

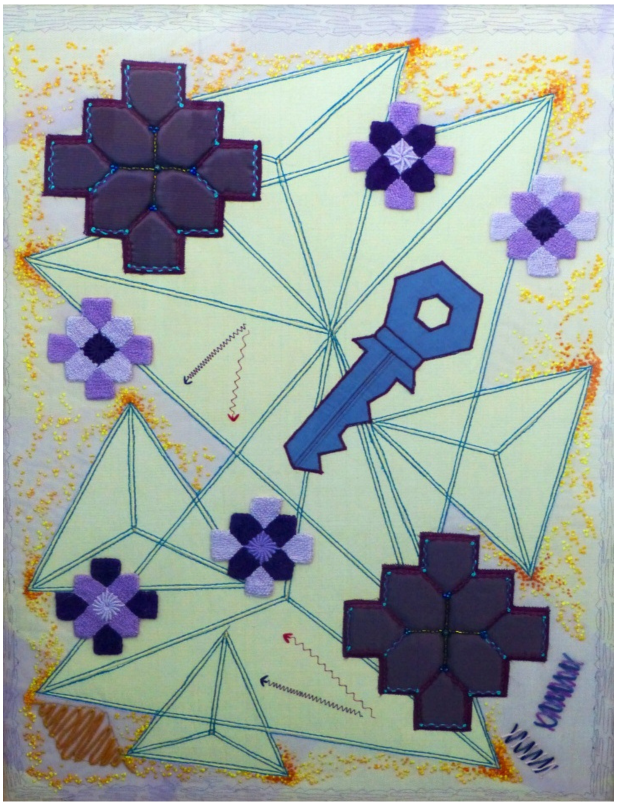

Figure 4. Heterocyclic Chemistry as imagined in an embroidery by the author's mother, Margaret Suckling. The components represent organic chemistry (the tetrahedra) porphyrins (purple structures) , quanta of light, DNA helices, and molecular recognition chemistry (the key, to drug discovery).

An illustration of tunability – indigo and Tyrian purple dyes

It's probably easiest to illustrate tuning properties by choice of structure using something coloured, dyestuffs, in this case, ancient dyes derived from naturally occurring materials. Celtic tribes of 2000 years ago are well known for using woad. Today the same dye is extensively used in denim products.

In the competing and conquering Roman civilisation, Tyrian purple was the colour of royalty and was obtained from a Mediterranean snail at great cost; the pigment is a close chemical relation of indigo and the addition of the bromine atoms (Br) is responsible for the change of colour.

An illustration of manufacture

The heterocyclic chemistry based industries rely heavily upon the provision of many compounds as building blocks from which the variety of new

Figure 5. Colour tenability in heterocyclic compounds – indigo and Tyrian purple. The ovals show the respective colours. The chemical formulae shows the structure of the pigments; the introduction of bromine (Br) into the otherwise identical compounds causes the change of colour.

compounds can be developed. Diversification of structure is an important concept in synthesis for new drug discovery. It's easy to imagine in terms of a building block kit of heterocyclic rings, with different attachments decorating them, being linked together by chemical reactions to give the compounds with the properties you want. Fine adjustments can also be made once the linking process is complete. Although widely used in the synthesis of new pharmaceuticals, a good example of this approach, keeping it simple to appreciate by staying within the field of dyestuffs, concerns a technology developed in the 1950s known as Fibre Reactive Dyes. The technology is still in use today (Figure 6). There are more than 3,500 patents on reactive dyes alone in the EUPO database of world patents. Their benefit is that they provide colour fastness because the colour is chemically bonded permanently to the fibre, not simply absorbed as is the case with indigo and related compounds. Of course fashion jeans should fade; that's part of their appeal but every material is not intended to look washed out!

Similar chemistry involving cyanuric chloride was once used for the production of herbicides such as atrazine and simazine but these are no longer licensed in the EU. The use for reactive dyes and optical brighteners, however, remains worldwide. The global market for cyanuric chloride is in excess of 200,000 tons, which at a typical price of $2000 per ton indicates a market worth at least $40M.

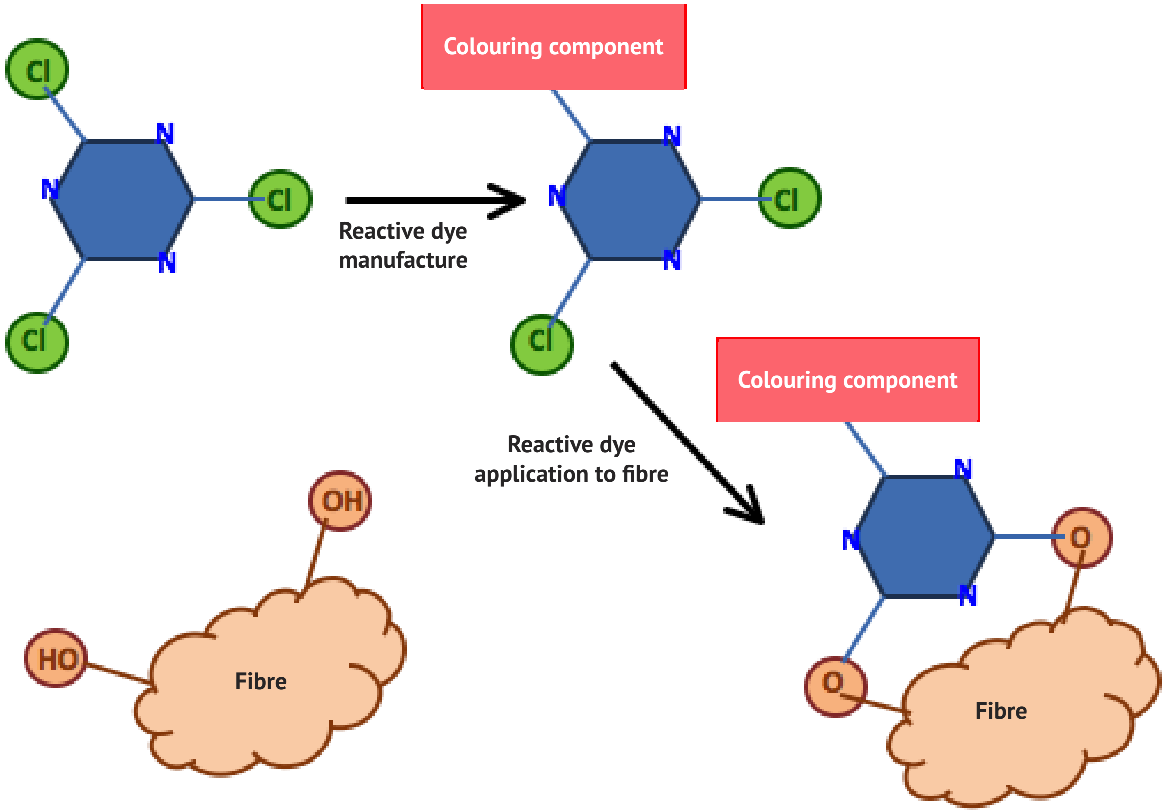

Figure 6. The manufacture and use of fibre reactive dyes. The precursor heterocyclic compound, cyanuric chloride (blue, top left) has three sequentially replaceable chloride atoms (green). In the manufacture of the fibre reactive dye the molecule that gives the colour (red in this case) is attached displacing one of the chlorine atoms and forming a stable chemical bond to cyanuric chloride (top centre). The fibre (bottom left), bearing atoms that can displace the chlorine under suitable conditions, in this case oxygen in a cellulose, is then immersed in a solution of the fibre reactive dye and heated until the dye is fixed to the fibre.

New heterocyclic chemistry around the world today

Despite its age as a branch of science there is no doubt that heterocyclic chemistry remains an active and important area for research and technology. One source of evidence for this assertion is the publication of patents. Last year I looked at the international patent offices' databases that provide information on published applications. Using the subject code 'C07D' for Heterocyclic Chemistry we can see from the European Patent Office database that between 50,000 and 60,000 patent applications concerning heterocyclic chemistry have been published each year for the past 10 years. The World Intellectual Property Organization database lists those applications that have been taken forward to the international stage (PCT as it is known). The numbers are smaller, 2,000 to 3,000, which is not surprising considering the cost at the PCT stage, but in the context of the ubiquity of heterocyclic chemistry it is interesting to note the specific topics for which international applications have been published.

Here are what the patents are intended to provide from the database:

Organic optical materials:

- A novel organic compound and alternatively provide an organic compound that can be used as an electron-transport material of a light-emitting element; from Japan

- A material for organic electroluminescent devices which has a high efficiency and a long life, and an organic electroluminescent device using the material; from Korea

Figure 7. Drums containing fibre reactive dyes. http://www.openpr.com/news/531638/Global-Dyes-Market-2017-Sumitomo-Everlight-Chemical-Kyung-In-Atul-Bodal-Chemical.html

Chemical synthesis and process chemistry (typically to provide compounds for use as drugs):

- A synthesis method for a spiro-oxy indole compound; from Canada

- A process for making modulators of cystic fibrosis transmembrane conductance regulator (CFTR); from the USA.

Drugs and medicines:

- Novel compounds for use in the treatment or prophylaxis of cancers and other proliferative conditions; from Scotland

- A compound as a glucokinase activator useful for treatment of metabolic diseases and disorders, preferably diabetes and more preferably Type II diabetes; from Switzerland

- Compounds and methods for treating tuberculosis; from India.

This list suggests two major current fields of research, namely optical materials and medicinal chemistry, both of which are strongly represented at the University of Strathclyde as part of the WestCHEM research school in Glasgow.

Some real current examples from the WestCHEM Research School, Glasgow

Optical materials and plastic semiconductors

My colleague, Professor Peter Skabara, is expert in the design, synthesis and application of new organic semiconductors with widespread applications (Figure 9). Interestingly, unlike most pharmaceuticals, which contain nitrogen and oxygen heterocycles, Peter's compounds contain sulfur and selenium. Again it's the building block and decoration strategy to construct and tune the heterocyclic compounds to do what you want that is important. He writes: "Whereas inorganic semiconductors are well established and of exceptional value to society and industry (e.g. silicon based chips, low power solid state lighting), the versatility of organic chemistry allows the characteristics of organic or 'plastic' semiconductors to be tuned in terms of properties and functionality, allowing them to be applied in more sophisticated, multi-purpose applications. Tuning of organic materials is achieved through structural design at the molecular level and it is therefore a facet that inorganic bulk semiconductors lack. The field of plastic electronics is new and promises cheap and easily adaptable devices. Potential applications are far-reaching and include biocompatible sensors, printable solar cells and ultra-efficient large panel lighting. Organic light emitting diodes (OLEDs) are already commercialised in the display market in large OLED TVs and Samsung Galaxy smartphones … The future of plastic electronics has huge potential benefits – experts have predicted that organic light emitting diodes alone will represent a $12 billion industry by 2020."

Heterocyclic compounds as drugs

It's a curious fact that synthetic drugs in the pharmaceuticals industry actually emerged from the

Figure 8. WestCHEM is the joint chemistry research school of the Universities of Glasgow and Strathclyde.

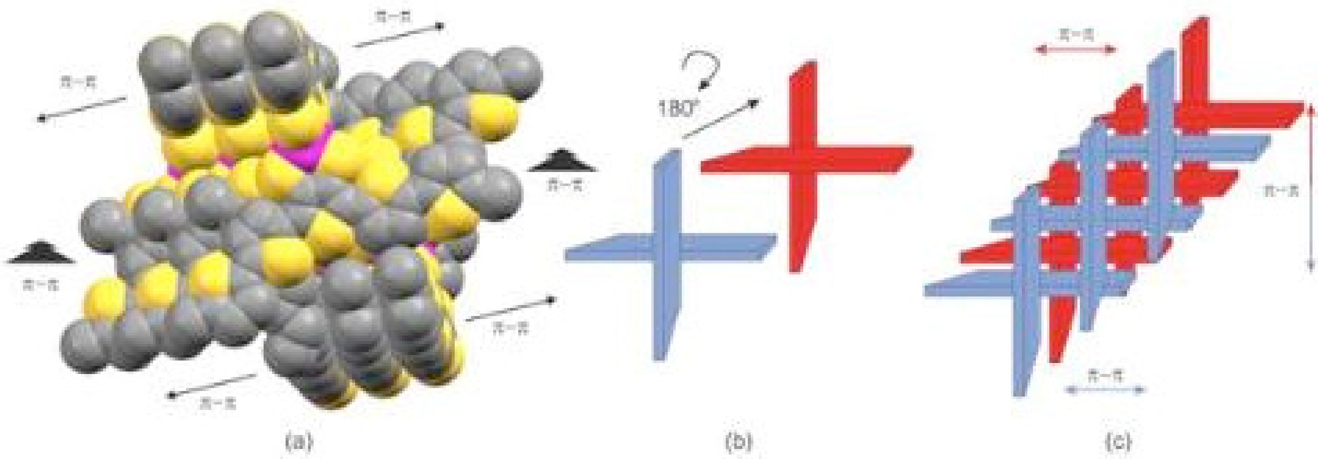

Figure 9. Images of some of the beautiful star-shaped molecules invented by Peter Skabara and his team for applications in the plastic electronics field.

use of dyes to assist the study of microorganisms under the microscope. It was found that not only did the dyes absorb in the membranes of some microorganisms, thereby revealing their shape and structure, but they also killed some of them too. Little by little this led to the discovery of sulphonamide drugs, the first effective synthetic antibacterial compounds some of which, sulfadiazine, for example, are still in use today. Further generations of antibiotics including penicillins are also heterocyclic compounds. The variety of structures available in heterocyclic compounds is what makes it possible to obtain compounds that will act selectively in medicines to treat all kinds of diseases. To learn more about how this is done, please visit the following website for an e-book that explains more.

http://www.adjacentgovernment.co.uk/ebooks/professor-colin-j-suckling-university-strathclyde/22964

Drug discovery at Strathclyde

Several teams at the University of Strathclyde are actively developing new drugs using heterocyclic compounds. More details of all of these projects can be found in the profiles listed at the end of this article. We're interested in compounds to treat infectious diseases, including those caused by bacteria, fungi, and various parasites for human and animal medicine. A major field is that of minor groove binders for DNA. These compounds, called Strathclyde-MGBs (S-MGBs) bind to DNA in the target infectious organism thereby causing major and fatal changes in its biochemistry. One of our compounds has successfully completed a Phase 1 clinical trial for the treatment of Clostridium difficile infections; the trial was conducted by our commercial partner, MGB Biopharma. Others are on the cusp of selection in the next year for development as treatments for fungal diseases and for the parasitic disease, African Animal Trypanosomiasis, the latter in collaboration with the University of Glasgow. Using specially designed S-MGBs we can observe their direct interaction with the target DNA-containing organelles of the cells of the parasite (Figure 10).

http://www.gla.ac.uk/researchinstitutes/iii/research/researchareas/parasitology/aat/#/

In another project led by my colleague, Professor Simon Mackay, we've recently published a new approach to the treatment of challenging cancers, including prostate and pancreatic cancer, by describing the first compounds (heterocycles, of course) that have the necessary selectivity for the new drug target that has not been exploited before. Building on the work in this paper, we now have compounds with the required property profiles for development but until the patents have been filed, we're not able to disclose details.

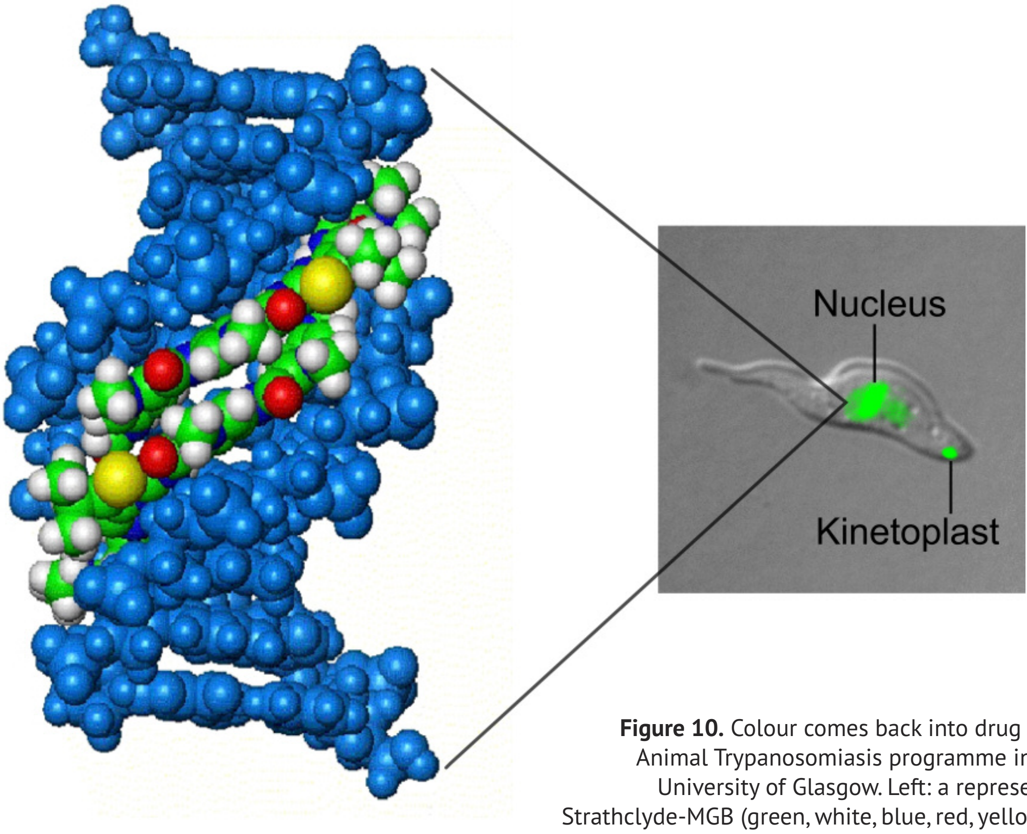

Figure 10. Colour comes back into drug discovery in our African Animal Trypanosomiasis programme in collaboration with the University of Glasgow. Left: a representation of a model of a Strathclyde-MGB (green, white, blue, red, yellow) bound to DNA (blue) in the minor groove. Right: image of a Trypanosoma congolense treated with a fluorescent S-MGB, which localises in the parasite's DNA-containing organelles (nucleus and kinetoplast). Image produced by Dr Federica Giordani of the University of Glasgow.

Thirdly, in a project in which the biology has been led by Professor Billy Harnett of this University and Professor Maggie Harnett of the University of Glasgow, we have been able to derive new compounds, some of which are heterocycles, for the treatment of inflammatory disease from the properties of a parasitic worm. The Harnetts identified compounds from a specially synthesised collection that stimulated or depressed the immune response or did nothing at all. In the very first set of compounds that we tested, two were found that had strong immunomodulatory properties. That success was just lucky, but still more surprising was that when these compounds were tested in animal models for the treatment of inflammatory diseases including asthma, rheumatoid arthritis, and lupus they were found to be safe (non-toxic) and effective both curatively and prophylactically. A partnership with Jubilant Biosystems (India) has now produced results to show beneficial effects in fibrosis. Discussions are progressing for the commercialisation of these discoveries.

In all of these projects, the key to success is being able to design the structures of the heterocyclic compounds using the building block approach so that we can optimise the biological and physicochemical properties for a given therapeutic application. It's the variety and tunability of compounds that we can make in our laboratory that makes such progress possible. In other words what we do comes from the very heart of heterocyclic chemistry not just with an academic interest in synthesising new compounds but with a powerful drive to see the benefit of our research in health care worldwide. I know of no field of chemistry that has the same broad scope and powerful impact in many functions and walks of life as heterocyclic chemistry.

End note

In compiling this article I have drawn on material presented in previous contributions to Adjacent Government together with some new illustrations of heterocyclic chemistry. There are short **special reports** on various aspects of heterocyclic chemistry which are available on the Adjacent Government website. The most recent are:

Do we need to think more broadly about what makes a drug candidate? (February 2016)
Heterocyclic chemistry challenges the Antibiotic Apocalypse: Smart Diagnosis (May 2016)
Should we bother to teach chemistry any more? (August 2016)
Pushing the limits of heterocyclic chemistry (February 2017)
There's life in the old science (literally) (June 2017)

There are also some **profiles** that describe in more detail specific projects at Strathclyde. The most recent are:

The antibiotic apocalypse – can heterocyclic chemistry help? (April 2016)
An international approach to the anti-infectives challenge. (December 2016)
Animal health matters too. (July 2017)

Other **e-books** I have contributed that may be of interest are:

Blue sky research – is it worth it? (January 2017)
It's a question of balance – broadening concepts in drug discovery (June 2016)

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