University of Strathclyde Glasgow

We'd be in poor health without heterocyclic chemistry – vitamins and drugs

www.strath.ac.uk/chemistry

Heterocyclic chemistry is all around us – and in us!

As I noted at the beginning of my last e-book for Adjacent Government, the philospopher, Ludwig Wittgenstein, wrote 'The world is all that is the case' to begin his Tractatus Logico-philosophicus in the early 20th century. With admitted exaggeration, I began that e-book about the field of science known as Heterocyclic Chemistry by asserting 'The world is all that is heterocyclic chemistry' before backing off with a definitional retreat. 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. In this e-book, I'm writing about heterocyclic chemistry, vitamins, and new medicines.

Life itself depends exquisitely on heterocyclic chemistry. Indeed biology as we know it just would not exist without heterocyclic compounds. It's enough to make this point to say that DNA is a giant

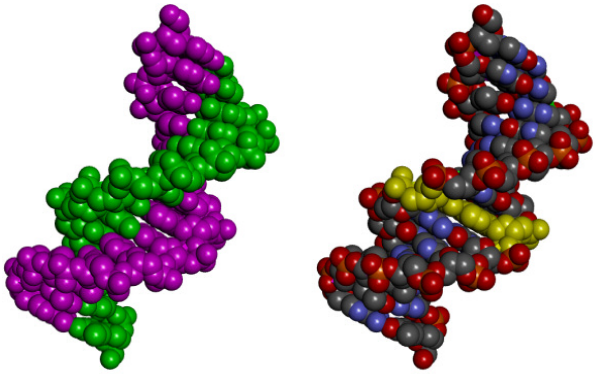


Figure 2. (Left) A representation of a section of the double helix of DNA; the two strands can be seen in green and purple winding round each other.

(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.

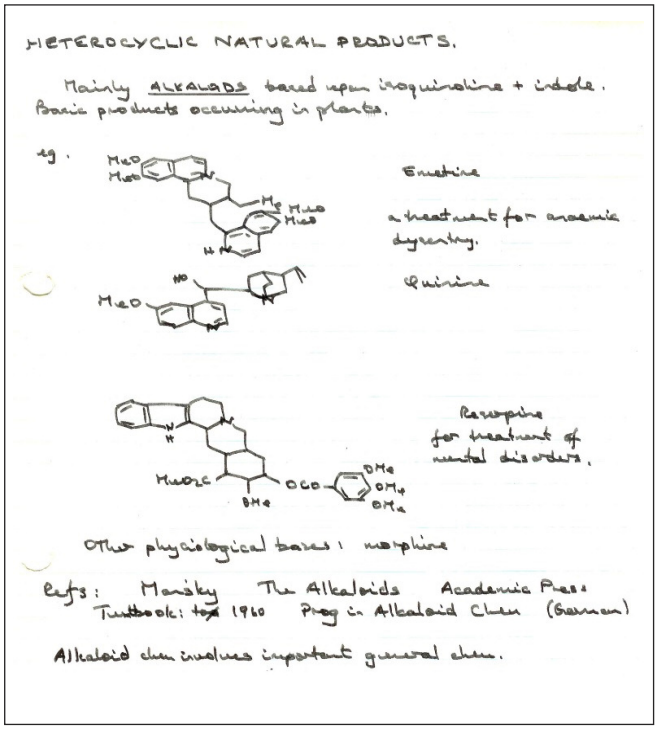


Figure 3. An extract from my lecture notes, University of Liverpool, 1967, all taken down live by hand. It's noticeable that the compounds selected by the lecturer, Professor Alan Battersby FRS, were all naturally occurring compounds with medicinal applications. Of the three, quinine, which was used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

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. 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.

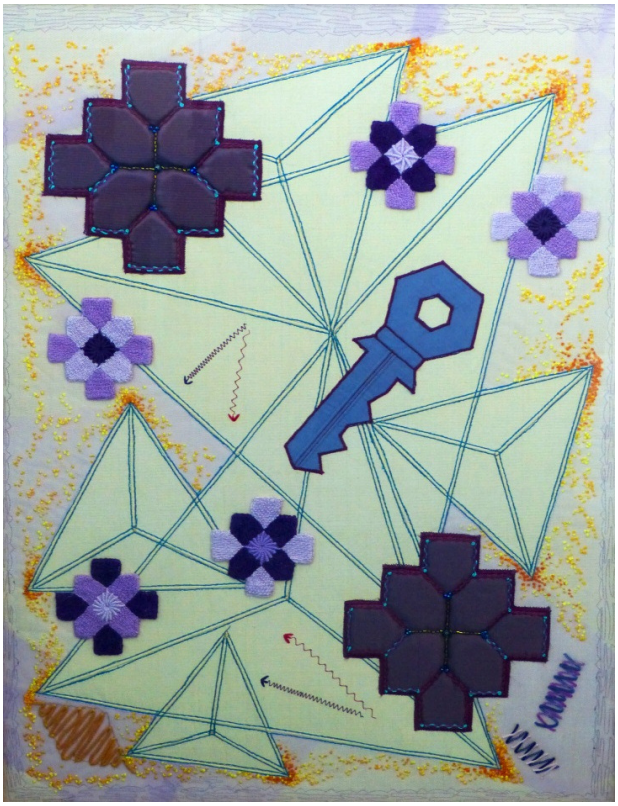


Figure 4. Heterocyclic Chemistry as imagined in an embroidery by the author's mother, Margaret Suckling. The components represent organic chemistry (the tetrahedra) porphyrins (purple structures) , quanta of light, DNA helices, and molecular recognition chemistry (the key, to drug discovery).

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.

Figure 5. Colour tunability 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.

Vitamins

The way our biology as humans has evolved means that there are some essential compounds and elements that we need for our bodies to work and that have to be obtained from food; we cannot make them for ourselves using our own biochemistry. These compounds and elements are vitamins. Many of the best known are heterocyclic compounds. Typical vitamins in a branded breakfast cereal include vitamins B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B9 (folic acid), B12 (cobalamin), and C (ascorbic acid). It is well known that vitamin deficiency can lead to many diseases, of which scurvy, due to shortage of vitamin C was the first to be identified. Perhaps more frequently encountered these days is anaemia due to folic acid deficiency. The interest here is not in tunability because, of course, the chemical structures of vitamins and our need for them are the result of evolution. What I find remarkable is that the chemical structures have evolved to be exquisitely suited to promote the reactions that they mediate, chemical reactions in nature that proteins or nucleic acids alone cannot carry out. The effectiveness of the chemistry of many vitamins is such that scientists have sought successfully to use the same mechanisms of action to carry out synthetic chemistry in the laboratory typically using simpler

compounds related to the vitamins themselves. Scientific interest notwithstanding, the greater significance of vitamins as chemical compounds is their economic value.

Because they are essential for health a substantial industry world-wide has grown up for the manufacture, packaging, and distribution of vitamins. The world market for vitamins and vitamin-based food supplements has almost doubled in value since 2007 reaching US$B 106.2 in 2017. Specialist shops charge high prices for nicely packaged vitamin supplements which are basically cheap heterocyclic compounds. I write 'cheap' because the manufacture of vitamins is a large scale industrial process. For example vitamin C is manufactured from the sugar, sorbitol, obtained from corn syrup using either fermentation processes or a mixture of chemical reactions and fermentation processes (https://vitamincinformation.weebly.com/manufacturing-process.html). New products containing one or more vitamins continue to be devised and approved for sale (see , for example, http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con769970.pdf). Such products are under the same good manufacturing practice regulations as medicines and there should therefore be no anxiety that a manufactured vitamin additive is intrinsically hazardous. Large scale manufacture takes place all round the world with recent substantial growth in India and China. There's little doubt that the heterocyclic compounds belonging to the class of vitamins make a substantial contribution both to the medical and economic well-being of much of our world.

Tunability and effective medicines

Heterocyclic compounds as drugs

It's a curious fact that synthetic drugs in the pharmaceuticals industry actually emerged from the 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 and cephalosporins are also heterocyclic compounds. In fact more than half of the drugs on the WHO list of essential medicines for a basic health care system are 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 read the following e-book. Here, however, I want to expand briefly upon one of the most significant challenges for new drugs of modern times, namely antimicrobial resistance.

Selective anti-infective agents and antimicrobial resistance

Media features, scientific papers, and official government sponsored reports all paint the same picture in different ways and with appropriately differing emphasis. For most of us most of the time an Antibiotic Apocalypse is as remote as a universal apocalypse but for many people, especially those otherwise ill and with weakened immune systems, it is real and immediately life-threatening. Every time I talk to my clinical colleague, Dr Stephanie Dancer, who is a consultant clinical microbiologist at an NHS District General Hospital in central Scotland, her frustration at being unable to help patients with life-threatening infections because of the lack of effective antibiotics is both challenging and moving. When you get closer to people afflicted by incurable infections the Antibiotic Apocalypse transforms from a media feature, scientific discourse, or an official pronouncement to an imperative for action. We are all vulnerable. A world without antibiotics is a public health issue.

When we come to discovering new and effective drugs, however, it's the tunability and variety of structure in heterocyclic compounds that gives them their value and importance. A good example is the continuing development of antibacterial drugs of several distinct classes. In figure 6 I illustrate this point with respect to the cephalosporins, structural

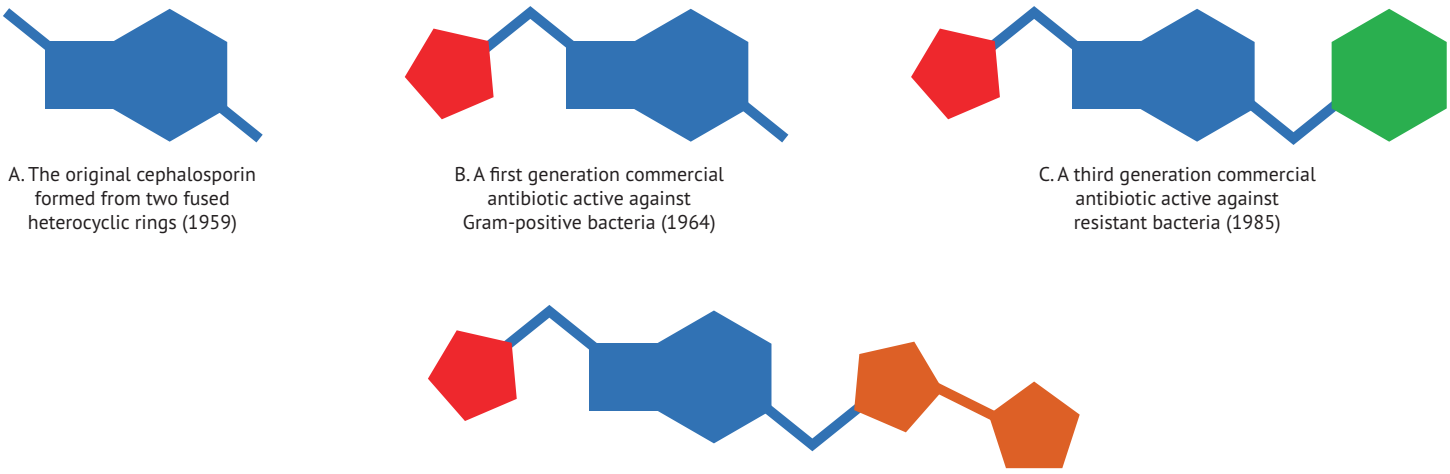


Figure 6. Diagrammatic representation of the evolution of improved cephalosporin antibacterial drugs. The originally discovered compound is illustrated by the four and six-membered rings fused together (A. blue) to which additional components can be attached by chemical synthesis at the bonds leading away from the rings. In the first generation commercial products a new heterocyclic ring (B. red) was added together with some smaller modifications that are not represented. After twenty years substantial resistance had been developed but a third generation had been discovered in which an additional heterocyclic ring was added on the other side of the molecule (C. green). Nearly thirty years later still we have now reached the best cephalosporins currently available in terms of range of activity and absence of resistance. These fifth generation compounds are still more elaborate with two additional heterocyclic rings added (D. brown). It is unlikely that this will be the last generation to evolve. Similar evolutionary pathways for other classes of heterocyclic antibacterial drug such as the quinolones and oxazolidinones have been followed.

relatives of penicillins, that were discovered in the mid-1940s and eventually brought into widespread clinical use in the mid-1960s. Resistance to the treatment of infections with penicillins was already a clinically significant problem and the availability of a related but more effective antibiotic was of great value. Within a very short time, however, resistant strains of bacteria emerged and ever since there has been a race between scientists and the bacteria, the former to maintain antibacterial activity and the latter to survive. This is not the place to go into details about the mechanisms in play here but it is valuable to note that it is the very variety and tunability of heterocyclic compounds that have made it possible for scientists and clinicians at least to remain in the race (figure 6).

What chemists have done essentially is to introduce new components, mostly additional heterocyclic rings (red, green, and orange in figure 6), to the basic core structure of the cephalosporin (blue). Although shown diagrammatically, the details of the chemical structure changes are actually quite complex and subtle requiring a substantial research effort to optimise. For a time each change was enough to give rise to a new and active subclass of antibacterial drug. But even the fifth generation cephalosporins (2013) are not active against all strongly infecting bacteria that have mechanisms (specific enzymes) capable of damaging the structure of the drug so that its activity is lost. There is more to do. How we at Strathclyde have tackled the problem using heterocyclic chemistry is outlined in the following paragraphs.

Figure 7. WestCHEM is the joint chemistry research school of the Universities of Glasgow and Strathclyde.

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 8).
http://www.gla.ac.uk/researchinstitutes/iii/research/researchareas/parasitology/aat/#/

A particularly important property of S-MGBs is that they seem to be very good at minimising the development of resistance. This is because their mechanism of action involves multiple biological targets. My biology colleagues in both antibacterial and antitrypanosomal fields have tried hard to generate resistance in the laboratory but so far have failed. Of course this does not mean that resistance will not evolve at all. It simply points to a greater challenge to microbial adaptation and evolution than has been posed by antibiotics so far. We can imagine a mechanism by which resistance might arise and in due course if any of these compounds reach the market eventually their target organisms will adapt to find it. This is inevitable. Meanwhile we must ride the wave and make it as difficult as possible for the microorganism.

In another project in heterocyclic chemistry 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.

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.

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

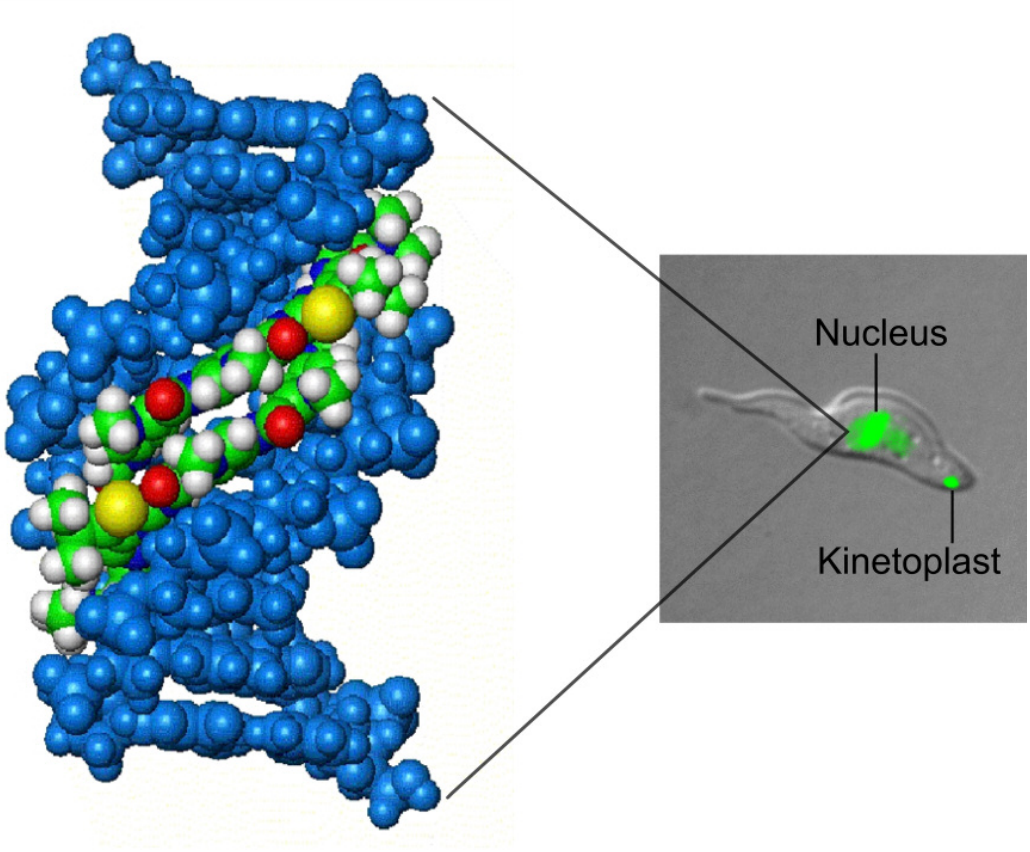


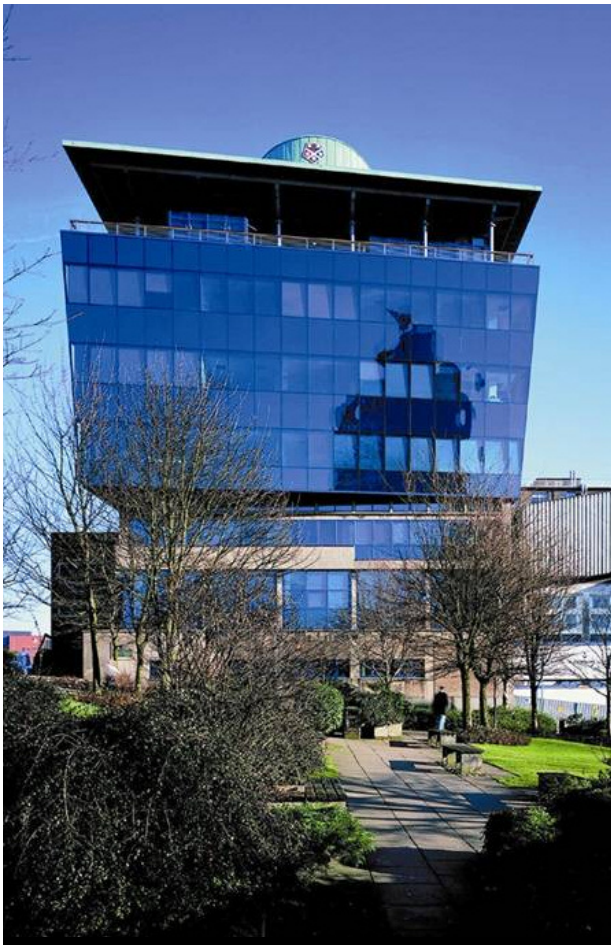
Figure 8. Colour comes back into drug discovery in our African Animal Trypanosomiasis programme in collaboration with the University of Glasgow. Left: a representation of a model of a Strathclyde-MGB (green, white, blue, red, yellow) bound to DNA (blue) in the minor groove. Right: image of a Trypanosoma 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.

physicochemical properties for a given therapeutic application. It's the variety and tunability of heterocyclic 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)



Department of Pure & Applied Chemistry,
University of Strathclyde

Professor Colin J Suckling
Research Professor of Chemistry

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:

- **Why does heterocyclic chemistry matter?** (October 2017)
- **Blue sky research – is it worth it?** (January 2017)
- **It's a question of balance – broadening concepts in drug discovery** (June 2016

Department of Pure & Applied Chemistry, University of Strathclyde

University of Strathclyde Glasgow

University of Strathclyde Glasgow

Professor Colin J Suckling OBE DSc FRSE
Research Professor of Chemistry
Department of Pure & Applied Chemistry
University of Strathclyde
295 Cathedral Street
Glasgow G1 1XL

Tel: 0141 548 2271
Fax: 0141 548 5743

www.strath.ac.uk/chemistry