University of Strathclyde Glasgow

New and effective drugs?

Yes, please, but where from?

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Heterocyclic Chemistry in Drug Discovery at the University of Strathclyde

Where can we begin?

Disease will always be with us although the critical diseases will differ from place to place and time to time. There will therefore always be a demand for new and effective drugs but it has become much more difficult to bring them to market in recent decades. There's been a lot written about the slow-down in the marketing of new drugs in the last 20 years from the point of view of the international pharmaceutical industry establishment. But if you asked an Indian physician what is needed to discover a new drug he or she might say, "Very little, actually. We've have plenty of good drugs from Mother Nature in our traditional Ayurvedic medicine". Nevertheless from industrial pharma the slow-down is a fact and various reasons have been noted as contributors including an increasingly challenging regulatory environment, a lack of good druggable targets (all the easy ones having been done), increasingly demanding disease states associated with aging populations, a lack of good quality new chemical entities, and so on. Overall an intrinsically risky business has become riskier. What's to be done? It's entirely appropriate and understandable that companies should take serious steps to mitigate the risks and thereby increase profitability. It's also very clear that companies have to make choices about what to develop from the many opportunities arising from their own research. Nevertheless, the demand remains and scientific research, much of it academic, has the responsibility to create opportunities to satisfy the demand.

This E-Book is about how we have approached meeting this responsibility at the University of Strathclyde in Glasgow, Scotland. To expand on the background to what we do it is worth recalling that some of the most outstanding achievements in drug discovery have been recognized by the award of Nobel Prizes. Nobel Prizes normally go to scientists whose fundamental discoveries have had a major impact over a number of years in the particular field of scientific research. Just occasionally a Nobel Prize recognizes a discovery that has come directly to the consumer. From the point of view of a medicinal chemist it's notable that two good examples of this concern the Nobel Prize for Physiology or Medicine, not for chemistry, and are associated with drug discovery.

In 1988 the Nobel Prize was awarded jointly to Sir James Black, and Drs Gertrude Elion, and George Hitchings for their establishing 'important principles for drug treatment', which in practice meant the discovery of ß-blockers (Black) and antibacterial agents (Elion and Hitchings). The important principles here were to do with the scientific approaches that can lead to effective medicines. These scientists were outstanding in demonstrating the connection between a biological mechanism and a successful drug, in this way bringing chemistry and biology closer together than ever before to the benefit of millions of people.

As I write the news has come through that this year the Nobel Prize for Physiology or Medicine has been awarded to William C. Campbell and Satoshi Omura for their discovery of the antiparasitic drug, avermectin, and to Youyou Tu for her discovery of the antimalarial drug, artemisinin. Avermectin was isolated by Omura from a soil bacterium, *Streptomyces avermitilis*. Tu discovered her active compound in a plant that figures in Chinese traditional medicine, *Artemesia annua*. In both cases, the clinically used products today are derivatives of the naturally occurring compounds that

the Nobel Laureates discovered. They are telling examples of a tradition of drug discovery based upon compounds isolated from plants and microorganisms that has been one of the main sources of drugs for centuries.

Translating this to the range of opportunities for chemistry available today in drug discovery there is the combination of chemical and biological mechanisms (following Black, Elion, and Hitchings) on the one hand, and the identification and modification of naturally occurring compounds (following Campbell, Omura, and Tu) on the other. Drug discovery is intrinsically multidisciplinary but chemistry is always at its heart because chemistry creates the vast majority molecules that become drugs. Another Nobel Laureate, the Lord Todd of Trumpington, a man of many honours including Nobel Laureate, Order of Merit, Past President of the Royal Society, had strong views on the importance of chemistry. He declared in an after dinner speech at a meeting I had organised, "Chemistry is the Queen of Sciences. Get your chemistry right and everything else follows." Lord Todd's scientific contribution that led to his great distinction was at the border of chemistry and biology, in his time, as now, an area of science with great intrinsic interest and potential for useful, translatable discoveries and inventions. He was an organic chemist who laid the chemical foundations upon which much of the chemistry of the components of DNA was built. And derived from this we have the synthesis of genes (first demonstrated by Ghobind Khorana) and ultimately much of modern chemical biology. In the following pages I want to show how several of our drug discovery projects at the University of Strathclyde have learned from these outstanding contributions.

The Special Properties of the compounds we call Heterocycles

Todd worked in the field of compounds known as nucleosides and nucleotides, which are components of DNA and many other compounds of biological machinery, referred to as cofactors or coenzymes. All of these compounds contain heterocycles which are, simply stated, compounds with rings of atoms built from carbon together with other elements, nitrogen, oxygen, and sulfur, being the most relevant to biological chemistry. Whilst not always the most challenging class of compounds for academic organic chemical synthesis, heterocyclic compounds are especially rich in their biological importance, a fact that has a lot to do with their ability to interact with each other. A very large part of the molecular machinery of biology involves one heterocyclic compound bonding with another. So it is no surprise that when we want to manipulate biology, to treat disease, for example, the compounds that we commonly use are also heterocyclic compounds.

Before introducing my topics let's consider the essentials of how heterocyclic chemistry works in a very conceptual way. Whatever application we're interested in it's the sheer diversity of compounds that can be made in the laboratory that makes heterocyclic chemistry so important. As chemists, we have our detailed structural formulae to represent compounds and the ways in which they react; it's a very powerful means of international communication and very arcane to the non-chemist. But if we leave the synthetic chemistry on one side and assume that we can make the compounds we want (an assumption) it is possible to understand why heterocyclic compounds have such interesting and diverse applications using a few simple ideas.

Most applications of heterocyclic compounds in medicinal chemistry or in materials chemistry do not depend upon reactions of the compounds but upon the way in which molecules stick together or associate. Association can be strong or weak, long or short lived but whatever its type, the fundamental interactions are based upon the same three things, molecular size, shape, and electrostatic charge. It's not necessary to understand the detail of how charges arise but Figure 1 shows the consequences step by step. The basic rules of electrostatics apply to atoms and molecules: like charges repel and opposite

charges attract (Figure 1A). All this assumes that the interacting parts of molecules can actually get together, in other words that their shapes match. Even if there are attracting charges, if the molecules can't get close together because there are other atoms in the way, we won't see any chemical interaction and won't be able to create a useful application, particularly in medicinal chemistry (Figure 1B). Given the right charge, shape, and size, some molecules are able to associate in stacks or rods or other arrangements. Such multimolecular aggregates are the basis of materials that are important in many electronic applications (Figure 1C).

So in discovering new drugs, we're chiefly concerned with finding compounds that act in a specific way in a biological system. If there's an infection, we want to kill the infectious agent but not the patient. If there's an imbalance in a person's function, such as high blood pressure or a psychiatric problem, we want a medicine that will restore the balance to normal. In all these things we require selective action to minimise side effects and we need subtle and selective chemistry to provide it. That's where the refined application of heterocyclic chemistry comes in. Using heterocyclic compounds we can find compounds that engage through their charge and shape with a specific component of biology, typically a protein or DNA molecule, and modify the biological function which, if taken through to a medicine, will benefit the patient. In fact all of the medicines deriving from the Nobel Prize winning work mentioned in the introduction contain heterocyclic components.

New Drugs from Academic Research

It's not uncommon for people to ask why academic scientists should be involved in medicinal chemistry when globally we have such a well-developed pharmaceutical industry. The pharmaceutical industry itself has made it clear for many years that despite its size it cannot do everything worth doing or interesting. It has a challenging regulatory and commercial framework in which to work and these challenges have led to systematisation of research processes and decision-making. All of this is understandable in their context but, if I am being critical, it has industrialised thinking and thereby circumscribed creativity. Both for reasons of coverage and creativity, therefore, there is a real place for academic teams in drug discovery. It boils down simply to the academic sector fulfilling one of its prime roles, namely to create opportunity.

Well if the industry cannot do it all, in what fields of chemistry should one choose to work? These days industry is replete with highly skilled synthetic chemists so it is not in synthetic chemistry itself that new things are most wanted. Anyway, from my point of view, other people do specialised organic synthesis better than me. The need that my colleagues and I have tried to satisfy is to create new compounds with specific biological effects, either to treat disease (which is medicinal chemistry) or to investigate how biology works (which is chemical biology). In my view and experience, medicinal chemistry and chemical biology go hand in hand. To make a significant contribution, we've had to make choices about what to study but we've also been able to take opportunities as they have arisen; then with the flexibility that good academic teamwork can bring, one thing leads creatively to another. Chemical and biological mechanisms and naturally occurring compounds all take part and we can look to all of the Nobel Laureates mentioned above for inspiration.

I'll present three examples of our projects. The first begins with the chemistry of a class of heterocyclic compound known as *pteridines*, so called because they were first discovered as pigments in the wings of butterflies. It leads little by little to a new class of compound discovered by our teams at Strathclyde primarily for the treatment of challenging cancers such as prostate and pancreatic cancer. The second concerns an opportunity brought to us by colleague biologists based upon some intriguing properties of a protein secreted by a parasitic worm that affects some Asian rodents. Following this line of research, we have obtained new compounds with proven

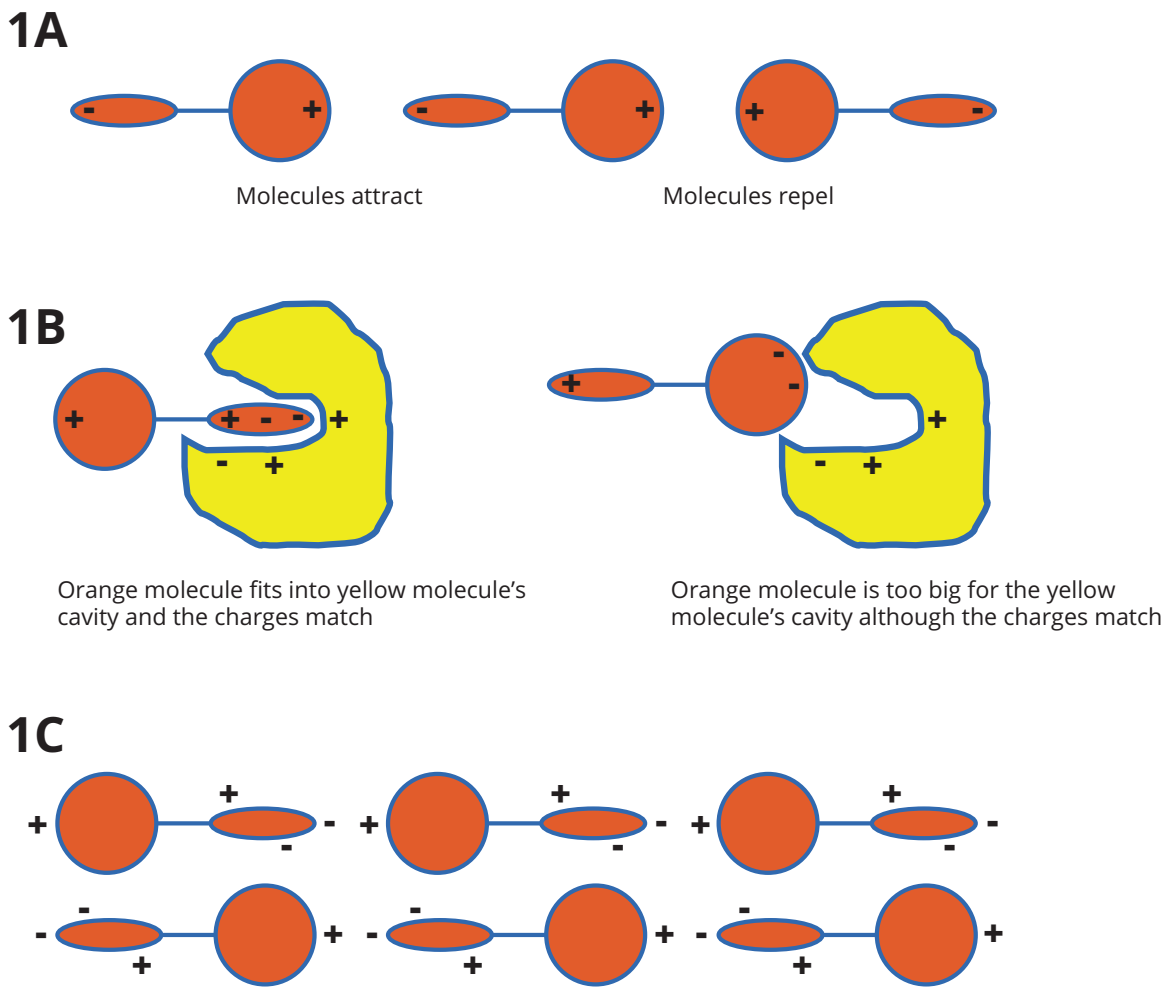
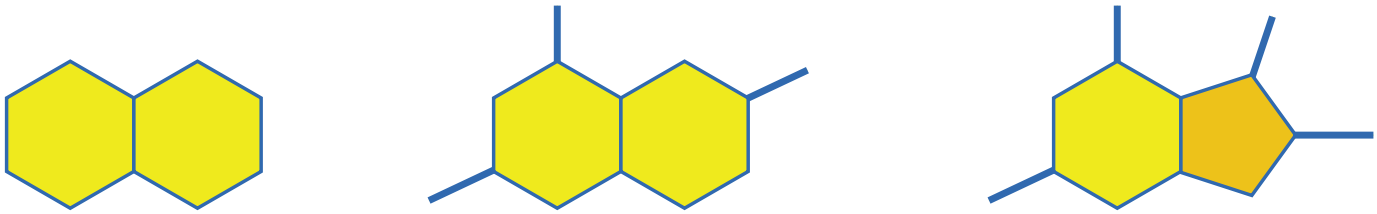


Figure 1A. Cartoon of two heterocyclic molecules with opposite charges at each end showing how they interact with each other as charges approach. **B.** A cartoon of how a drug molecule can be understood to fit its biological target molecule by having the right charge and shape. If the molecule is too big, it will not bind and have an effect, even if the charges attract. **C.** An illustration of how charge and shape in heterocyclic molecules can lead to association of molecules in rows and in stacks. Such structures occur in molecular materials.

potential for treating inflammatory diseases such as asthma and rheumatoid arthritis; we call it '*The Worms Project*'. Finally, I shall describe our most advanced project, which concerns a group of compounds known as *minor groove binders* because they bind to a part of the structure of DNA known as the minor groove. Most, but not all of the applications of these compounds, are as treatments for infectious diseases. One compound has entered clinical trials for the treatment of *Clostridium difficile* infections and we have good evidence that others can be developed to treat parasitic diseases such as sleeping sickness and Leishmaniasis.

Now we in this Department can't do it all either and each of these projects has required contributions from willing colleagues and effective collaborators in other institutions. What I am about to describe is a team effort. There's a lot of chemistry and I'm going to try to deal with it without using detailed chemical structures. Instead, I've drawn abstracted cartoons with which I can show not only the essential shape of our molecules but also how they work to control biology beneficially. Even getting one compound to clinical trials is good going for an academic laboratory. We hope and that more will progress and we're working hard at it with our partners.



A. Parent
Pteridine

B. Add substituents
Muscle relaxants

C. Change ring size
New synthesis

Figure 2. A. Cartoon representation of a pteridine, two fused six membered rings. **B.** In nature, pteridines have additional atoms of groups of atoms attached (substituents). The naturally occurring pattern of substituents is fixed but we can vary them using synthetic chemistry to obtain compounds with different properties such as artery relaxation. **C.** We can also create families of related compounds by changing the shape a little, for example changing a six to a five-membered ring. To do this and include a variety of substituents we had to develop new synthetic methods.

From pteridine chemistry to anticancer drugs

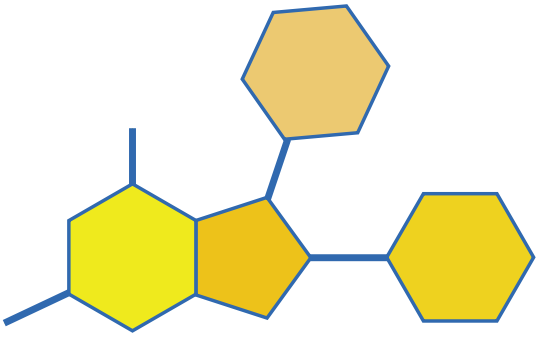
Looking back, choosing to continue a tradition of work in pteridine chemistry was an important strategic decision. My late colleague, Professor Hamish Wood, introduced me to the field and it has been taken forward working closely with my current colleague, Dr Colin Gibson. Pteridines are significant in biology because as parts of biological synthetic processes in vivo they contribute to the availability of essential components for life, in particular the heterocyclic components of nucleic acids including DNA and certain essential amino acids. Therefore there was a good chance that we would find some interesting biology and useful chemical compounds in this field.

Some of the secrets of medicinal chemists: How we come up with new compounds

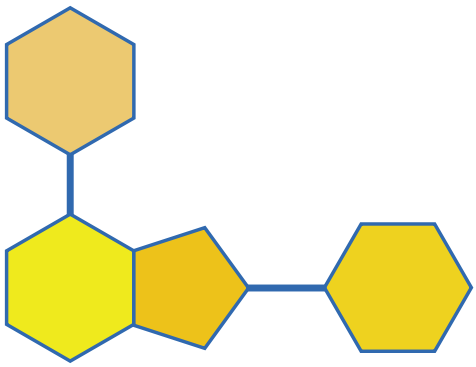
Pteridines consist of two six-membered rings composed of carbon and nitrogen fused together along one side (Figure 2). Whilst the rings themselves are significant in the chemical and biological properties, the atoms and groups of atoms attached to the rings provide the diversity, interest, and significance in their chemistry. As suggested by Figure 2, if a new molecule is invented with a different structure on the right, it should still bind to the biological machinery, most commonly enzymes, but might do different things from the naturally occurring pteridine. The differences could in principle be either to block a naturally occurring reaction (an inhibitor or antagonist) or to promote it (an activator or agonist). Depending upon the application and desired outcome one or the other might be required. This logically simple concept of modifying part of a molecule to control its function in the desired way is at the heart of much medicinal chemistry design as will be seen below. Whilst it is a simple concept, the challenge is converting the concept into new chemistry and useful applications. In the case of our work with pteridines and their relatives, we have been interested in both activators and inhibitors.

If we just take our starting pteridine template, we've been able to vary and add substituents to obtain compounds that stimulate the production one of the smallest naturally synthesised molecules, nitric oxide (Figure 2B). Nitric oxide acts as a signalling agent in several biological systems including stimulating the relaxation of muscle in arteries and our new compounds can indeed promote such muscle relaxation. This could have benefit for example in treating the symptoms of high blood pressure such as occurs in diabetes.

Modification of the pteridine can become more complex (Figure 2C). We can change size of one ring whilst keeping much of the rest of the compound, including the substituents on the 6-membered ring, the same. To do this flexibly we had to design and



D. Add substituents
Target sleeping sickness



E. Different substituents,
Different places
Anti-cancer drugs

D. Adding substituents to this new structure, we obtained potential compounds to treat sleeping sickness. **E.** Adding different substituents in different places, we obtained compounds effective in models of prostate cancer; these compounds are being further developed.

develop new synthetic methods. When the new compounds became available, with the help of colleagues, they were screened to find significant biological activity. In fact two new substantial projects were seeded in this way, the first to treat sleeping sickness, a disease caused by parasites known as *Trypanosomes*, and the second to treat cancers such as prostate and pancreatic cancer. Different modifications (Figure 2D and E) were required for the two different diseases. Every project at this stage is not taken forward. In these cases, the compounds designed to treat sleeping sickness were too toxic. On the other hand, the anti-cancer compounds are actively being refined and developed in a project led by my colleague, Professor Simon Mackay.

We have sophisticated tools to help design our compounds. Figure 3 shows the fit of one of our more active anti-trypanosomal compounds to its molecular target, an enzyme known as pteridine reductase 1. The connection between the green framework structure and the cartoon 2D is clear. In red is shown a piece of the molecular machinery, the cofactor, NAD, which is one of the compounds that Todd worked on leading to his Nobel Prize. The largely grey surface with patches of blue and red represents the surface of the target enzyme itself with red showing regions of positive electrostatic potential and blue negative potential. The interpretation of the surfaces and charges allows us to understand how our compounds bind to their target and hence to design new candidates for synthesis and evaluation. Such so-called structure based design is a common feature of many medicinal chemistry projects. This study was made possible by collaboration with Prof Mike Barrett, a parasitologist at the University of Glasgow, and Prof Bill Hunter, a crystallographer and enzymologist at the University of Dundee.

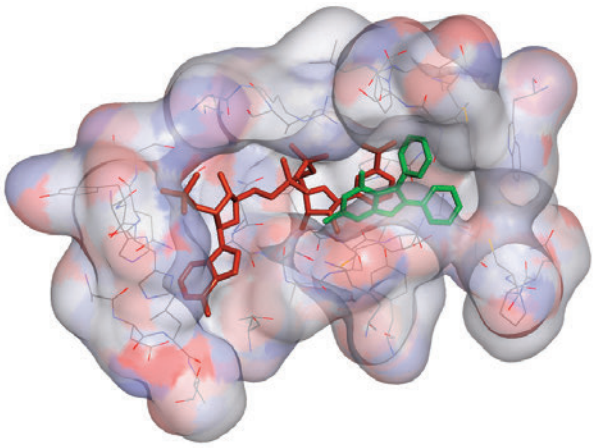


Figure 3. A representation of the molecular target of the antitrypanosome compounds derived from X-ray crystallography. Interpretation of the image allows us to understand how the inhibitor binds to its target and to design new structures for synthesis and evaluation. The 'drug' is shown in green. The red framework shows one of the compounds that Todd worked on, the coenzyme NAD, which is also a heterocyclic compound.

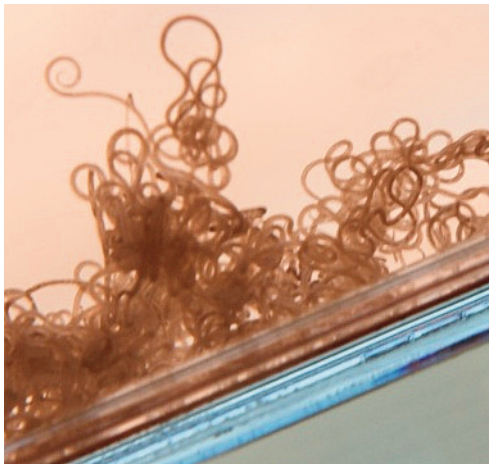


Figure 4. The parasite *Acanthocheilonema viteae* that secretes ES-62 to maintain its balance with its gerbil host.

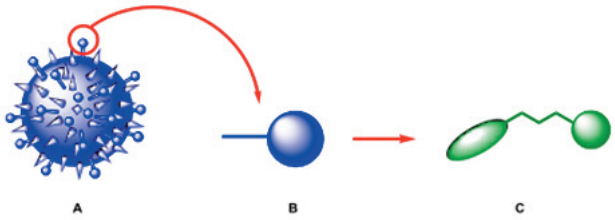


Figure 5. A cartoon representation of the design of the small molecule analogues (SMAs) of ES-62. **A.** A representation of the ES-62 protein with many surface groups. **B.** The phosphorylcholine (PC) component to be mimicked. **C.** Cartoon of the SMA in which there is a carrier part of the molecule (oval) linked by a flexible chain to the PC-like head group. The heterocyclic chemistry component is found in the positively charged head group of the SMA or in the carrier component.

The Worms Project

Parasites that cause sleeping sickness, a largely untreatable disease, were a target one of the pteridine-related projects. But in the Worms Project, a parasite has suggested to us how to create compounds that modulate the immune system beneficially. This is a good example of a drug intended to restore the balance that has been disturbed in a disease. A husband and wife team of professors from the University of Strathclyde and the University of Glasgow, respectively Billy and Maggie Harnett, have made their careers from the study of a protein known as ES-62, which is secreted by a worm *Acanthocheilonema viteae* (Figure 4) that is a parasite of gerbils. Billy and Maggie isolated and purified ES-62 and showed that it lowered the activity of the immune system so that the parasite was not attacked by its host but not so much that the host was killed by bacterial or viral infections. Obviously the parasite needs its host to reproduce and survive so the immunomodulation by ES-62 was very important. Billy and Maggie were convinced that there could be a useful drug somewhere related to this biology. However the protein itself was not suitable: it was too big a molecule to be formulated easily as a medicine. Moreover, because it is not a human protein, the human immune system would most probably be stimulated and ES-62 destroyed. Lastly, if given orally, it would be destroyed by digestion. What was needed was a small, drug-like molecule that could reproduce the potentially beneficial immunomodulatory properties of ES-62. An interesting ethnological and philosophical aspect of this opportunity is that it considers the immunological balance in a person to be important for their health and the success of their treatment. It thus connects with eastern medicinal traditions, including the Ayurvedic medicine of India.

Transforming biology into manageable chemistry

In the pteridine-related projects we had somewhere obvious to start designing compounds, namely the structures of the naturally occurring pteridines. Here, however, there were no such templates. Moreover in a further contrast to the pteridine projects, we had no idea what the molecular target or targets for ES-62 were. To put it another way, we did not know the chemistry by which ES-62 worked. And to make it even more challenging, there was no crystal structure of ES-62 available from which we could build a model; there still isn't. So none of the usual starting points for a medicinal chemistry project was present; we're working from a naturally occurring compound but we don't have any information about its detailed structure. In this situation, we fell back on the basic principles of chemical structure and reactivity applying them to the biological context.

Fortunately, one small aspect of the structure of ES-62 that was important to its function had been identified by the biologists. Attached to the surface of ES-62 were many small molecules known as phosphoryl choline (PC) and through a number of experiments it had been shown that these PC components were important in the biological activity of ES-62. That gives a starting point but PC is so common in biology that simple analogues of it as potential drugs would be unlikely to be selective enough to be developed as medicines. However with one or two other clues from PC-containing molecules that the Harnetts had studied, it was possible to design some compounds that would be worth testing. Figure 5 illustrates how this was done.

If you look at a chemical structure with the eyes of a chemist, you can identify those parts of the molecule most likely to be important in determining the chemical and biological properties of the compound represented. In the case of the PC component of ES-62, the most important feature was electrostatic charge, one positive and one negative. To create a small molecule analogue (SMA) of ES-62 we needed to include positive and negative charge in the right relative positions to each other and with the right shape. In this way we should obtain a compound that will interact with the biological systems that lead to immunomodulation in a manner similar to that of ES-62. We can also build into the design features of chemical stability and variability so that an optimised drug can be obtained in due course from the same molecular template.

Having solved the conceptual chemistry design problem we had to test the compounds that we made to see if they could replicate the functions of ES-62. This relied upon the skill of the biologists, Billy and Maggie Harnett, and their teams to devise assays that would lead us in the right direction. By carrying out a wide range of assays using cultured cells important in the immune system, the Harnetts identified compounds that stimulated or depressed the immune response or did nothing at all. From the very first set of compounds that we tested two were found that had strong and similar effects to those of ES-62. 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.

So from this project we have compounds with the potential to be beneficial in a wide range of diseases in which the balance of the immune system is important. The task now is to fund an optimisation and development programme. This is proving difficult because despite the demonstrated efficacy of the SMAs, industry is reluctant to form a partnership with us because the biological mechanism of action of the SMAs has not been established. We understand as academics the wish of industry to minimise risks but wonder whether it is appropriate to expect the academic world both to discover new drugs and opportunities and to undertake their initial development. The pharmaceutical industry is no charity nor does it sometimes appear to be philanthropic but is the balance right now?

Anti-infective drugs from DNA minor groove binders

Turning now to our most advance project area in which one compound has reached clinical trials. As I said earlier, we could not do it on our own but before I come to the commercial development partnership, I'll explain how we came to discover a class of compounds with wide ranging biological activities, especially in infectious diseases. When choosing a field of study, it's a good idea to consider its potential impact as well as its intrinsic scientific interest. The field of DNA binding compounds passed both of these tests because there were some interesting challenges to design novel, tight-binding compounds together with the expectation of significant exploitable biological activity if new compounds could be discovered. There is, however, a really critical

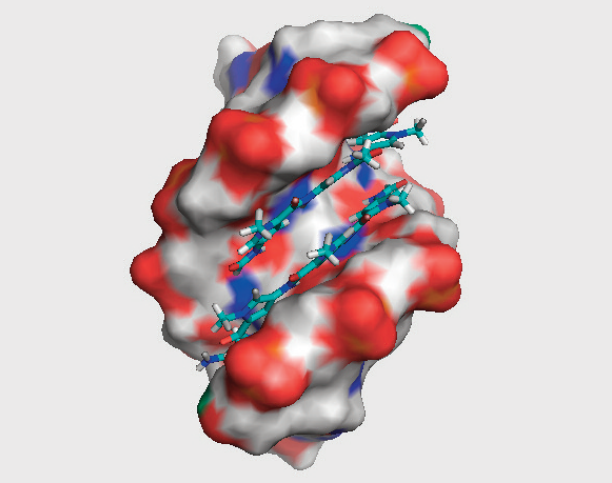


Figure 6. A minor groove binder (MGB) fitting into DNA. With the Strathclyde drugs and related compounds, two molecules of MGB bind side by side into the minor groove which is forced to expand a little. This changes the shape of DNA sufficiently to prevent its normal biological operation, a situation that can lead to many functional changes, including ultimately cell death.

challenge for the development of new drugs from this field which arises as follows. Our compounds will be designed to bind tightly to DNA which will lead to some sort of biological activity. But all living organisms use DNA to contain their basic biological information so that they can function and reproduce effectively. So how can we arrange for our new compounds to be selective and affect only pathological conditions such as cancer and infections but not do any damage to healthy cells and healthy people?
To be honest, we did not know. When this project began, Roger Waigh and I, who led the team, believed that it was sufficiently important to look for new opportunities in this field that we would deal with this question later. What guided us were the results from biological assay in which we compared the behaviour of our compounds in bacterial cells and human cells; we followed the trail shown by toxicity to bacterial cells but lack of effect on human cells.

As everyone knows, the DNA molecule exists principally as a double helix. What's less well known is that the two chains wind round each other such that the grooves created are different sizes. The larger, the major groove, is principally where proteins bind to control the operation of DNA and the smaller, the minor groove, is the molecular target for our drugs. Figure 6 shows how our compounds fit into the minor groove. Two molecules of our compounds bind side by side causing the minor groove to expand. This in turn changes the shape of DNA preventing its proper biological function ultimately leading to cell death. Roger Waigh and I thought that if we could increase the strength of binding of our MGBs to DNA by strengthening the interactions between the MGB and the non-charged patches on the DNA surface (grey in figure 6) we would increase binding and potentially selectivity in a way that no-one else had yet investigated. We had a starting point for chemical design in the form of a compound made by *Streptomyces* spp called distamycin. Distamycin was known to be an MGB but it was non-selective in its biological activity and also too toxic to be a useful drug.
By 'thinking out of the box' Roger and I designed a family of compounds that were apparently non-toxic to cells but very toxic (at least 1,000 fold greater) to the cells of one of the major classes of bacteria, Gram-positive bacteria. This class includes organisms well known for causing infections that are difficult to treat, typically hospital acquired infections such as cause by *Staphylococcus aureus* and *Clostridium difficile*. So we were on the track to deal with a major therapeutic need. I'll describe the development leading to clinical trial in a moment.

The design of Minor Groove Binders

The key characteristic of a minor groove binder for DNA is that its structure matches the curvature of the helix of DNA so that it can fit to the minor groove. There are several classes of compound that do this including some dyestuffs, known in the field as Hoechst after the company that discovered them, and some naturally occurring compounds, the so-called anthramycins, that have been developed as anticancer drugs at the School of Pharmacy, University of London. These are all heterocyclic compounds with a curve. The prototype for our discoveries, distamycin, was discovered by Arcamone in Italy in the 1960s. It

has the necessary curved structure and the beauty of it from the point of view of drug discovery is that it is made up of a series of heterocycles called pyrroles that are linked in a chain in the same way that amino acids are linked in proteins. This gives a very variable starting structure into which we can incorporate an enormous range of different heterocycles so that we can obtain the required selectivity for a drug and the required properties for a medicine. To achieve this we have to be able to synthesise the necessary building blocks and to have reliable methods of linking them. All of this is solid, standard synthetic heterocyclic chemistry, some of which is necessary for every project. Figure 7 shows the architecture of the molecules.

A wide range of therapeutic opportunities

Dr Abedawn Khalaf was the main contributor to the early synthesis of minor groove binders and in fact to all of the subsequent work. With some contributions from others he made about 300 compounds in the same family but with substantial detailed variations. From this library we selected a subset that included all the major characteristic details of structure and worked with further biologists to investigate their activity. This research team included Mike Barrett from the University of Glasgow to look at trypanosomiasis in animals. This disease, the animal equivalent of human sleeping sickness, is a serious economic problem in sub-Saharan Africa affecting the cattle upon which the human populations depend. Mike's group has found that one of our MGBs is curative in an animal model of trypanosomiasis. A further study in antiparasitic activity is led by Dr Chris Carter here at Strathclyde; she has found that a different group of our compounds is affective against Leishmania spp., parasites that cause both skin and visceral disease. Again, we have proof of concept that such compounds might be developed as medicines through in vivo activity in an animal model. Lastly in our survey of possible applications to infectious diseases, collaborating with Dr Arvind Patel of the University of Glasgow, yet another sub-class of compounds has shown up with significant activity against virally infected cells (hepatitis C virus) but this project has

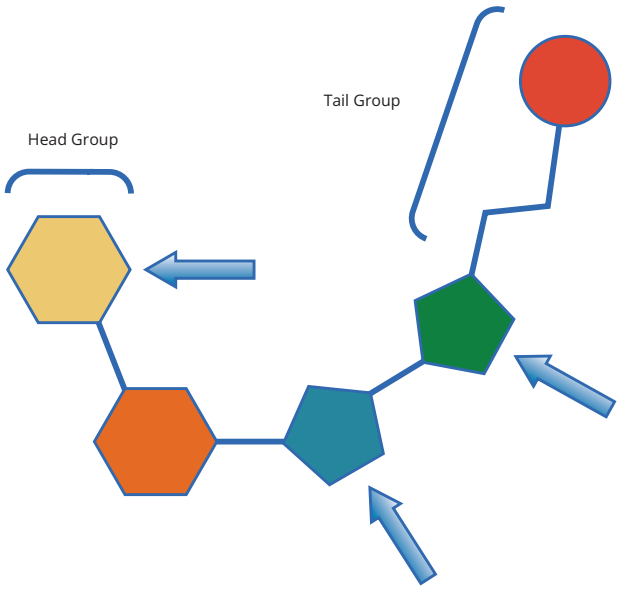
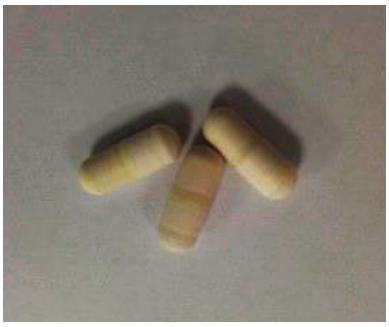


Figure 7. Components of a typical Strathclyde MGB. The filled circle, hexagons and pentagons represent different heterocyclic building blocks and the precise choice of heterocycle and its position in the molecule determines that MGBs chemical and biological properties. The arrows indicate positions at which the MGBs contact the grey parts of the DNA molecule (Figure 6); these are points of structural variety also. Biological selectivity so far seems to be principally determined by the nature of the head group and tail group; details of this selectivity are a topic of active research.

really only reached the screening stage. So far, at least in discovery terms, Roger's and my hunch has paid off: we have found compounds with substantial and selective activity. What now has to be done is to develop the optimised compounds ready for the clinic and to optimise the others ready for development.

The development of MGB BP3

I've mentioned several times that there is a real problem in translating a good drug opportunity, new compounds with new mechanism of action, into a medicine ready for clinical trial. The way in which the multinational pharmaceutical industry has developed essentially precludes the large companies (so-called 'big pharma') from taking up such opportunities. Smaller companies often lack the resource to research and manage a development project. So it was necessary to find a way to bring our antibacterial compounds



Left: Capsules of MGB-BP-3 formulated for use in the treatment of Clostridium difficile infections.

Right: A freeze-dried sample of MGB-BP-3 formulated after reconstitution for intravenous administration.

through to clinical trials and it took some time to work out. This part of the story is not heterocyclic chemistry itself but belongs very much to the theme of this article because it deals with the important steps in translating a discovery into a medicine. The solution has involved teamwork but in a different way from the scientific teams that I have mentioned already.

In a traditional big-pharma company there would be research and development arms that could interact. In our development of MGB BP3 a new model has been developed around a new Scottish company, MGB Biopharma. The initiative to form this company came from Dr Miroslav Ravic, who is medically qualified and has great experience in the development of compounds and of clinical trials. Together with others, he worked with the Scottish financial community to raise funds to carry out the necessary development work to GLP standards acceptable to international medicines regulators. A key player in the financial arrangements is John Waddell who is Chief Executive of Archangels, the syndicate that has played the major role in supporting the development of MGB Biopharma. It is notable in what he says that getting involved in a drug development project was not an easy decision. John writes:

"Chief Medical Officer for England Prof Dame Sally Davies recently described the threat of antimicrobial resistance as a "ticking time bomb" and said the dangers it posed should be ranked along with terrorism. New antibiotics made by the biotech and pharmaceutical industry will be central to resolving this crisis, but there has been a market failure; no new classes of antibiotics have been identified for more than twenty-five years. The issue is now high on the government and global agenda and as a result there is a growing focus on the opportunities and challenges of funding biotech and drug development. Archangels had to face these challenges when the possibility of investing in MGB Biopharma came up in 2009. Archangels is a long-established Edinburgh-based, business angel syndicate with a track record of successful investments in life science companies but it took some time to get comfortable with the scenario of backing a drug development project."

As a company, MGB Biopharma describes the opportunity and the development like this:

"Drug development opportunities for new antibiotics have improved dramatically in the past few years, with antimicrobal drug resistance increasingly being recognised as a serious global public health concern. Nevertheless, the number of new classes of antibacterial drugs under development remains very small…

MGB Biopharma Limited, a biotechnology company with headquarters in Glasgow, is developing a truly novel class of antibiotics based on the minor-groove binder (MGB) platform technology developed by the University of Strathclyde…

MGB-BP-3 has a truly novel mechanism of action, and is the first of an entirely new class of antibacterials. MGB-BP-3 is being developed against a broad range of Gram-positive hospital acquired infections."

In this development project, MGB Biopharma actively manages the project and recruits contributions from suitably skilled, qualified, and equipped contract research organizations to undertake specific components of the work plan. The University, with its

expertise in heterocyclic chemistry, medicinal chemistry, and microbiology provides underpinning research and consultancy. The scientific and intellectual standing of the University of Strathclyde adds greatly to the strength of MGB Biopharma as has been shown by the recent award of over £1M in competitive public funding from the UK's Technology Strategy Board to support the Phase 1 clinical trial of MGB BP3 for the treatment of Clostridium difficile infections. Further applications for approval for clinical trial using other formulations of our most advanced compound will follow in the next year. Moreover, we are able to pursue in partnership a number of the other compounds for anti-infective indications that I have described above some of which are particularly important in developing countries.

Where heterocyclic chemistry has taken us.

In addition to quoting Lord Todd's remark 'Chemistry is the Queen of Sciences', two of the most important learned societies in the world have promoted similar views: 'Chemistry is central to everything' (American Chemical Society), and 'Better living through chemistry' (Royal Society of Chemistry). One of the satisfactions for me looking back at the research in heterocyclic chemistry carried out at the University of Strathclyde over the past 40 years is that we've been able to justify within our research and its applications these grand statements of an august person and of major international scientific societies. I think it fortunate that my University and I were in tune with each other in the balance of research and development. In particular, the systems and internal workings of the University's administration actively supported scientific creativity and translational research. Key members of this team have included Dr David McBeth and Dr Catherine Breslin; Catherine has been most important in getting all of the teams to function and to link the research outcomes to the commercial external environment. We think we've been able to do something special at Strathclyde in recent years and we're working hard to get the best possible chances for outcomes that will benefit health care for millions of people world-wide.

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