Educating Chemists for Medicinal Chemistry

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Medicinal chemists for drug discovery research

Medicinal chemistry has been defined[1] as: "a chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationship."

The above definition from the Medicinal Chemistry Section of the International Union of Pure and Applied Chemistry (IUPAC) in 1998, aims to cover the many varied activities of medicinal chemists. The purpose of this article, however, is to concentrate on the major employment of practising medicinal chemists outside of academia. This is surely in the pharmaceutical industry where medicinal chemists are mainly concerned with the design and synthesis of novel organic compounds for biological evaluation in the discovery phase of researching for potential new drug therapies. They have to be excellent organic chemists, able to converse with biochemists and biologists, and able to use the tools available for relating chemical structure and properties to biological activities. This probably represents the core of their requisite abilities. It does not represent the limit of their functions, however. Medicinal chemists must be conversant with the requirements for patents in order to protect their inventions; they should appreciate the needs of chemical development to assist the scale up of their products; they ought to understand the drug development process, to communicate effectively and work efficiently in a team composed of scientists with different training and backgrounds.

This composite of abilities represents a mixture of what was imparted during the formal education in university, what has since been learned "on the job" or acquired by experience, and the chemist's own character. In terms of the latter, for example, some will hardly need to be told how to communicate whereas others may have to work very hard to learn do this. Obviously too, they must be excellent scientists. The question arises as to what should be provided as formal education and training in a university setting.

The views of pharmaceutical companies

Some years ago, the IUPAC Medicinal Chemistry Section (now part of Division VII, Chemistry and Human health) canvassed the views of industry for their preference in hiring the new employees who will become their medicinal chemists. A questionnaire was sent out in 1996 and 1997 to leading medicinal chemists and research directors in the major international pharmaceutical companies engaged in research and development. The responses were very similar and over 90% of the replies indicated a preference for well trained synthetic organic chemists rather than medicinal chemists. The results were reported in a series of publications relating to different countries[2-4].

The very strongly expressed opinion was that the most important educational background required of the new chemists was excellent training in synthetic organic chemistry.
Preferably they should possess a PhD and postdoctoral experience from laboratories of well known synthetic organic chemists. Little interest was expressed for having chemists with formal academic training in medicinal chemistry, or for chemists trained in organic synthesis but also having knowledge of biological subjects. The industrial view was that most of the medicinal chemistry aspects, other than organic synthesis, could be learned on the job or through short courses during employment. In contrast, synthesis cannot be learned effectively in a practical sense through short courses during employment although, of course, short courses are a valuable way of extending knowledge and, particularly of keeping abreast of recent developments.

It is surprising to find that such little value is attached to chemists having received some formal education in a biological topic. It seems logical to employ such chemists since it should help them to be effective as medicinal chemists form the outset, instead of having to spend quite a few years acquiring the additional understanding necessary to enable them to be effectively involved in drug design as well as in drug synthesis.

The foregoing certainly accords with my personal experience. I trained as an organic chemist and entered the pharmaceutical industry with no knowledge of medicinal chemistry or pharmacology. It took me many years to learn about these disciplines even though I had studied biology at school and for one year at university as part of my undergraduate course. The knowledge of some biology at least made me receptive to the subsequent research discussions with pharmacologists, but I had to undertake a considerable amount of private study to learn what was needed for drug discovery research.

A bachelor degree in medicinal chemistry – a proposition

The above observations are relevant to a discussion I once had when I was employed as a medicinal chemist at SmithKline & French Laboratories (SK&F) with James Black (later Sir James Black, Nobel laureate for Medicine or Physiology) seeking to define histamine H_2 receptors and to design a suitable antagonist as a useful drug (the work which led to the anti-ulcer drug, cimetidine). During this particular conversation he was very critical of some of the chemists with whom he had previously collaborated.

To him, they were hidebound in their thinking and also too ready to treat biological results as if they were precise numbers. He felt that they did not appreciate the problem of biological variation and the need to understand the statistical nature of bioassays. For him, the chemists wanted to treat values from bioassay in the manner in which they considered melting points, that is as invariant numbers. Unfortunately he felt unable to change this situation by dialogue with the chemists because, as he saw it, they were no longer flexible in their thinking. Therefore, he saw that a possible solution would be to get at the chemists in their early training, during the period in which they were undergoing mental imprinting. His solution was to have chemists study medicinal chemistry at university for their first degree.

James Black left SK&F in 1973 to take the Chair of Pharmacology at University College London (UCL), as Head of Department, from which Professor Heinz Schild had just retired. Whilst at UCL, he tried out his idea of training medicinal chemists on the Chemistry Department. He found that Professor Charles Vernon, a biological chemist, was receptive to this proposal and between them they initiated a B.Sc. in medicinal chemistry. It was an opportune time to start a new degree in chemistry because the number of students applying to study "pure" chemistry was falling and medicinal chemistry sounded attractive to some students leaving school who wished to combine their chemistry with an interest in a medicine-related subject. James Black was only at UCL for four years but, like all great men, he left his mark on the place.

Degrees in medicinal chemistry

The medicinal chemistry degree at UCL has endured and, over thirty years later, it still continues as a three-year B.Sc. or four-year M.Sci. (Master of Science). The number of students varies each year but this degree course has provided 20-30% of the annual undergraduate entrants to the Chemistry Department. The students take the same core lectures for chemistry as do the chemists except for the more advanced inorganic chemistry. Thus, they are given the same physical chemistry and organic chemistry; indeed they take the courses together.

Table 1.
The non-chemical subjects studied by students taking the medicinal chemistry degree in University College London

Year 1:	Mammalian physiology; Cellular and Molecular Biology.
Year 2:	Statistics; General and Systematic Pharmacology; Topics in Biochemistry.
Year 3:	Principles of Drug Design; Molecular Pharmacology; Receptor Mechanisms. Optional subject.

In addition to the chemistry topics, the medicinal chemists take the subjects outlined in Table 1 for the first three years, which are taught by the corresponding departments. They do this at the expense of being able to select other optional topics but this is acceptable because they have opted to take a medicinal chemistry degree course. In the fourth year, the students undertake a research project, which involves 50% of their course, and can choose to also study four optional subjects. The latter can be selected from, for example: natural products chemistry, biological chemistry, advanced spec-

troscopy, more-advanced organic synthesis, chemical computation, or a specialist biological topic. The organic chemistry content of this course is very high since, in the second and third years, 25% of the teaching time involves organic synthesis and in the fourth year, it is possible to again spend 25% of the time on organic lecture courses, and 50% of the time on a synthetic organic research project.

Table 2.
The third year course of 30 lectures (at 45 minutes each) on "the principles of drug design" for medicinal chemistry students at University College London

One lecture on:
Introduction to drug development.

Ten lectures on:
Structure-Activity Relationships:
Hammett equation, QSAR, the Hansch equation, bioisosterism, the Topliss tree, prodrugs, steric interactions, pK_a's and structure-activity analysis.

Six lectures on:
Enzyme inhibitors:
Basis of enzyme inhibition. Transition state analogues. Irreversible, active-site directed and suicide inhibitors. Pyridoxal phosphate dependent enzymes: inhibitors of aminoacid decarboxylases, transaminases, and monoamine oxidase.

Five lectures on:
Anti-bacterial and anti-fungal chemotherapy:
Bacterial infections, an historical view. Sulfa drugs. Penicillin, discovery and mechanism of action. Semi-synthetic penicillins. Other antibiotics, anti-bacterials. The development of resistance. Fungal infections and treatments. Fluconazole.

Eight lectures on:
Anti-viral and anti-cancer chemotherapy:
Viral replication. DNA-containing viruses: herpes simplex virus. Intervention in the viral life-cycle: penetration, antimetabolites, replication, and transcription inhibitors. Retroviruses: HIV. Life cycle, anti-HIV drugs. Biology of cancer: tumour suppressor and promoter genes. DNA as a target: alkylating, intercalating, and strand-cleavage agents, minor groove binders. Antimetabolites, natural products.

In the third year of the medicinal chemistry degree course, the lectures on the principles of drug design are particularly relevant to a future medicinal chemist; the stated objectives of these lectures are: "to understand how to relate chemical structure to biological activity and how to conduct a structure-activity analysis", and "to appreciate the various approaches to drug discovery and be able to exemplify them". The structure of this lecture course is given in Table 2. In the fourth year, approximately six case histories of drug discovery are also presented (generally by one of the respective inventors) by industrial lecturers.

To enhance the standing of the medicinal chemistry degree the Provost at UCL at that time (Sir James Lighthill) agreed to make a Professorial appointment at the research level. I found myself being invited for discussions. Negotiations followed and I accepted to become the SmithKline and French Professor of Medicinal Chemistry in 1986. Another lecturer was also appointed who was very active in research and this really did ensure that the Chemistry Department had a pronounced research presence in medicinal chemistry.

There are now at least fifteen other University Chemistry departments in the U.K. which offer degrees in medicinal chemistry or a closely related subject such as "Chemistry for Drug Discovery", "Biological Chemistry", or "Pharmaceutical Chemistry". Another pioneering Chemistry Department was the one at Loughborough where Professor Ken W. Bentley, initiated a medicinal chemistry degree course in the 1970's which is still active; Bentley had left Reckitt and Colman laboratories after inventing the very potent oripavine class of morphine-like anal-

gesics (Diels-Alder adducts derived from thebaine) one of which is buprenorphine.

Employment for medicinal chemists in big pharma

If bright students with first class degrees from these courses continue their studies by completing PhD's with well known outstanding and highly regarded synthetic organic chemists then they will surely be able to win employment as research medicinal chemists in the pharmaceutical industry, and they will have conformed to Sir James Black's ideal.

Of course, medicinal chemistry graduates can pursue their PhD studies in other chemical specialities such as computing, or physical-organic chemistry topics, or in drug delivery, or drug metabolism etc. The nature of the topic will generally determine the area of research in which they may seek employment.

Many medicinal chemistry graduates may choose not to continue in university for a research qualification but go into teaching or directly into industry. They will most probably not work as medicinal chemists in drug discovery. There are many other suitable types of positions for medicinal chemists available in the industry, for example: as Clinical Research Assistants or Clinical Trials Coordinators, or in Regulatory Affairs, in Information Retrieval or Patents, in Process Development, as Sales Representatives or in Marketing etc.

The highly sophisticated organisation of discovery research in big pharma depends upon the integration of many different specialities. Their greatest need for chemists is in chemical synthesis and presumably that is the reason why they seek for the best synthetic organic chemists. When it comes to the decision taking of which types of structures to synthesise, or what properties to be aiming for, however, the companies probably only need a few medicinal chemists to interface with the biochemists and biologists, and to take the main decisions about which chemical structures to pursue.

This has become even more evident with the further separation of chemist functions into library synthesis for lead generation, lead development, optimisation of drug candidate structures with respect to drug disposition and unwanted toxic or side effects, and scale-up synthesis for development. There are also many other chemists involved in various functions, for example, in the measurement of chemical properties relevant to drug discovery and development, or as computational chemists for conformational analysis and structure-activity analysis, or in information technology, spectroscopy and substance analysis and so on. With so many interconnecting specialities it is, after all, not surprising that there is only a minor proportion of medicinal chemists required to provide the leadership in drug design.

Employment for medicinal chemists in small pharma

There is a considerable contrast between big pharma as described above and the small research companies or biotech companies which do not possess large teams of chemists. In the small companies, individual scientists may have to fulfil many functions, that is they have to act as generalists rather than as specialists. Under these circumstances the medicinal chemistry

graduate is probably extremely well prepared for the interaction that must occur with the various biologically based activities.

Small biotech companies, of which there are many, often have severe limitations in the number of scientists that they can afford to employ and they require people who are able to contribute in a multifunctional manner. They are certainly not able to train their own medicinal chemists; therefore they seek personnel who have already developed medicinal chemistry skills and are capable of immediately interacting productively with scientists from other disciplines, especially from the biological sciences.

One way of getting trained medicinal chemists is to attract experienced scientists away from the big research based companies. Sometimes they become available as a consequence of a merger taking place between big companies to form even larger companies but with fewer total staff, e.g. as occurred during a decade in which GlaxoSmithKline was formed from the four large research companies, Glaxo, Wellcome, SmithKline and French, and Beecham Products. The supply of such trained professional medicinal chemists is clearly limited and, presumably, small companies cannot just wait until an appropriate merger takes place between big companies. Therefore in this sector there should be many opportunities for employment available to recently qualified medicinal chemists.

Short courses in medicinal chemistry

To assist organic chemists to appreciate what is required of a medicinal chemist, short courses have been mounted. My interest in medicinal chemistry as a scientific discipline also led me to become involved with the Royal Society of Chemistry (RSC) Summer School when I was at SK&F . My colleague, Dr AM Roe, was Chairman of the RSC Education Committee which advised the RSC on the various courses mounted for post graduate chemists on specialist topics. These were usually residential and each lasted for approximately one week. One such course had started in 1979 as a week's summer school in medicinal chemistry but it had not attracted enough chemists from the pharmaceutical industry, possibly because it appeared to be overly dependent on techniques of structure determination and chemical analysis. Anthony Roe invited me to think up a suitable syllabus.

Our aim was to provide a rapid and concentrated conversion course for recently hired postdoctoral research chemists in the pharmaceutical industry; in the main these were organic chemists who needed to know what was required to become a practising medicinal chemist. My past experience had shown me that such courses usually dealt with diseases and their test models but I decided to avoid this approach. I felt that one should aim to introduce, as well as possible, the principles of the subject. It seemed to me that the basic discipline for medicinal chemists was to understand structure-activity analysis and the interface with the other disciplines involved in drug discovery. Thus the core lectures would be on physicochemical properties (octanol-water partition, pK_a and hydrogen-bonding, conformational analysis), multiparameter correlation analysis and computation, biological targets and

Table 3.
Syllabus for a one-week school as an introduction to medicinal chemistry. The published[5] syllabus compared with the recent RSC school in Nottingham University, U.K., 4 - 8 July 2005. The lectures from the latter are asterisked.

I	Introduction:	* 1.	Research strategy
II	Biological targets:	* 2.	Lead generation/sources for drugs
		* 3.	Receptors and drug-receptor interactions
		* 4.	Enzymes and design inhibitors
		5.	Ion channels, membranes and transporters
		* 6.	Second messengers
III	Bioassay:	T 7.	Screening methods and the information that they provide
		T 8.	Determining activity: principles of pharmacological assay, biological variation (and the need for statistics), in vitro and in vivo methods
IV	Structure-activity methods:	* 9.	Physicochemical concepts, including pK_a, solvent partition, Hammett, H-bonding, steric parameters
		* 10.	QSAR, parameterization and computer assisted lead optimization, statistical methods
		* 11.	Molecular modeling, energy calculations and molecular graphics
		12.	Operational strategies in molecular modification, pharmacophore identification, conformational restriction, isosterism, lipophilicity control, solubilisation
		T 13.	Development of a lead compound (a tutorial exercise)
V	Biodisposition and implications:	* 14.	Pharmacokinetics, concepts, parameters and modeling
		* 15.	Drug metabolism
		16.	Prodrugs
		* 17.	Molecular toxicology and avoidance of toxic intermediates
VI	Case studies:	*	3 or 4 case studies of drug discovery
VII	Special topics selected from the following possibilities:		
			Bio-organic chemistry
			Chirality in drug action
			Clinical pharmacology
			Combinatorial chemistry
		*	Drug delivery
			Ethical considerations
		* †	Historical: approaches to discovering drugs
		*	Molecular biology: role in drug discovery
			Nucleotides
		*	Patents
			Peptidomimetics
			Regulatory procedures
		* †	Structure-guided drug design

T = Tutorial † new, not in ref.5

bioassay, receptors and enzymes, ion channels and transporters, drug disposition (dmpk) and the drug development process. We would also include several case histories of drug discovery (something which I had previously encountered in a Society for Drug Research Symposium). Lecturers were mainly industrial, and the number of participants was limited to around 100 to foster a more intimate and informal atmosphere.

The first "summer school" of this type was mounted in 1981 and the result was a resounding success. It has since been repeated in alternate years, always oversubscribed and with a healthy participation of delegates from continental Europe. It has received further accolade by providing the model for the annual course put on in the USA since 1987 at Drew University, Madison, N.J.

An early example[5] for a week-long syllabus is indicated in Table 3. This is compared with the most

recent RSC summer school held on Nottingham University campus, U.K. on 4-8 July 2005. Some special topics have been included (indicated by *) in place of lectures on ion channels (N°5), operational strategies (N°12), and prodrugs (N°16). Three other lecture topics (N° 7, 8 and 13) are presented as optional tutorials. The drug delivery topic was on "computational approaches to pre-formulation and formulation design". Some of the lecture subject matter or emphasis has probably changed somewhat but generally, the philosophy of the approach has been retained.

Other short courses are also available in other countries, for example: at the Leiden-Amsterdam Center for Drug Research in Noordwijkerhout in the Netherlands, the Swiss Course on Medicinal Chemistry, Leysin, Switzerland, at the Danish University of Pharmaceutical Sciences in Copenhagen Denmark, and the Italian Advanced School of Medicinal Chemistry for Ph.D. students and young researchers which is held annually in Urbino, Italy. Some of these courses tend to be "extension courses" in that they aim to extend the knowledge of medicinal chemistry students or researchers rather than being "conversion courses" aimed at non-medicinal organic chemists. Many other courses exist, run commercially or by universities, and these are usually mounted locally and focus on a specialized area of medicinal chemistry or its application. Many of the big research-based pharmaceutical companies also run their own in-house training courses of both types i.e. conversion courses and extension courses. Naturally, these are not usually open to non-employees to attend.

Schools of Pharmacy

The title of this short article "Educating Chemists for Medicinal Chemistry" is meant to convey that it is aimed at the education of real practising research oriented medicinal chemists. It has not been discussing the teaching of medicinal chemistry per se. It is an expansion of thoughts expressed earlier, e.g. in reference 6. Traditionally, the formal university teaching of medicinal chemistry takes place in the faculties or schools of pharmacy. There, medicinal chemistry is only one of a variety of subjects taught at the undergraduate level where the focus is on education of future practising pharmacists. Presumably the aim is to give pharmacists some understanding of how new medicinally useful drugs are discovered. The combined results of the responses to a questionnaire sent to schools of pharmacy have been published.[7-9]

Undergraduate medicinal chemistry is usually taught by academic staff who are practising medicinal chemists working at the research level in some aspect of drug design. These academics are usually also involved in supervising postgraduate students and/or postdoctoral researchers. The interesting question arises as to where the postgraduate students had spent their undergraduate education. Did they graduate from a pharmacy course or a chemistry course?

If students obtain both of their qualifications (i.e. bachelors degree and doctorate) from a school of pharmacy then the issue which arises for an employer seeking chemists for drug discovery is whether the prospective

employee has had sufficient exposure to chemistry and, especially, to synthetic organic chemistry. For the latter, there is a marked contrast in the organic chemistry training for a PhD degree if the student has been involved in new method development, or synthesis of a complex target molecule, in comparison with a student who has synthesized a series of structurally similar molecules using a repetitive synthesis procedure. Departments of Pharmacy vary considerably at the postgraduate level and what they teach depends very much on the specialisms of the academic teaching staff. Some Departments may specialise in drug delivery or drug formulation, others might be more involved in drug safety or biochemistry. Some are undoubtedly distinguished in chemical synthesis and new drug design and one would hope that this would be appreciated by a prospective employer. The extent of chemical training and chemical achievement demonstrated by a student will provide the basis for an employer to judge whether they wish to offer a job to a prospective employee, presenting themselves as a medicinal chemist.

Summary

This article discusses the education of medicinal chemists who will be active in drug discovery research in the pharmaceutical industry. The main theme is the combination of education in synthetic organic chemistry with other subjects relevant to medicinal chemistry. It is anticipated that such chemists will be acceptable for employment in the major R&D-active pharmaceutical companies.

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