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Teaser Drug discovery research is a stimulating, viable and worthwhile endeavour for the undergraduate preparing for a career in industry.

Passing on the medicinal chemistry baton: training undergraduates to be industry-ready through research projects between the University of Nottingham and GlaxoSmithKline

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In this article we describe a radically different industry–academia collaboration between the School of Chemistry, University of Nottingham, and GlaxoSmithKline (GSK), aiming to train students in research and give them an insight into medicinal chemistry as practiced in industry. The project concerns the discovery of potent and selective $\alpha_v\beta_6$ integrin antagonists to treat idiopathic pulmonary fibrosis; the synthetic chemistry is performed by a group of ten final-year undergraduates and the biological and physicochemical screening data are generated by GSK. The project planning, organisation and operation are discussed, together with some of the challenges and rewards of working with undergraduates.

Introduction

The state of the pharmaceutical industry has changed dramatically over the past decade. Through a combination of factors such as increased attrition during drug development owing to higher safety hurdles and the need for differentiation over existing therapies, mergers and acquisitions, competition from generics, drug pricing pressures and the sheer cost of drug discovery and development, have all meant maintaining the delivery of new medicines has been challenging [1]. Yet, many diseases – neurodegeneration, some cancers and fibrotic diseases to name just a few – lack effective treatments, and threats like drug-resistant bacterial infections are only just materialising. Alongside the pharmaceutical industry, there is hope that an emerging drug discovery sector based in universities (particularly in partnership with industry) will help fill the gap, but there is considerable debate about how effective it can be, given the significant costs and expertise required to deliver a clinical candidate and hence a marketed drug [1–7]. There are a few notable successes [8–11], but academic institutions are unlikely to achieve a critical mass of projects and expertise individually for self-sustainability and success [12].

What can a university realistically contribute, particularly at the undergraduate level [13]? We recently reported on a practical drug discovery project aimed at teaching students who are in the third year of a four-year master's (MSci) degree course how new medicines are discovered [14]. The

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http://dx.doi.org/10.1016/j.drudis.2016.01.015

objectives are: to give an appreciation of the role of the chemist in drug discovery; to give students practice in compound design and data interpretation; to use industry-standard equipment and methods in the laboratory; and to develop communication, team-working and interpersonal skills. The participation of scientists from GlaxoSmithKline (GSK) as lecturers and workshop mentors is a very important feature. Although the project achieves its aims very well, the biological target and synthetic chemistry are carefully chosen to ensure that students successfully complete a set of target compounds and receive limited screening data (pIC_{50}, log *D* and aqueous solubility) to analyse. The practical part of the project concerns phosphatidylinositol-3-kinase inhibitors (pi3kδ) for the treatment of severe asthma [15,16], and is based upon the work published by the Piramed-Genentech-Roche groups [17–20]. The project is choreographed to ensure that most (but not quite all) of the outcomes are predictable. In this article we will discuss how we are setting realistic goals for and addressing the challenges and limitations of a more ambitious drug discovery project with fourth-year undergraduate chemists – namely the discovery of integrin antagonists to treat idiopathic pulmonary fibrosis (IPF).

Project description and aims

First and foremost, the purpose of the research project is educational, and it has been designed to meet the course requirements of the School of Chemistry at the University of Nottingham and the need to prepare 'industry-ready' graduates. Thus, the 120 or so students taking the MSci degree courses spend about half of their time during the autumn and spring semesters (20 weeks in all, around 17 h per week laboratory time) on a research project, chosen from a list covering the whole range of research interests within the School of Chemistry. The remainder of their course consists of lectures on advanced chemistry topics (a choice of six from nine topics). The assessment of all the MSci projects is the same, consisting of a report (up to 60 pages long), an oral presentation, a *viva voce* examination and a lab mark based on the level of engagement. What sets this project apart from most other chemistry-based projects is the close collaboration between the university and GSK, and the unique perspective obtained by working on an industrially relevant project that is live at GSK. The project is taught exclusively by industrial or ex-industrial[a] medicinal chemists and benefits from considerable support from GSK, especially contributions to the research direction, planning and delivery of medicinal chemistry teaching, for which GSK staff make regular visits to Nottingham. In addition, one of the authors of this review (T.M.) supervises the students in the laboratory in contrast to many undergraduate projects where guidance for day-to-day activities is provided by a PhD student.

The project started in September 2011 with the intention of focusing on selective antagonists of the $\alpha_v\beta_6$ integrin with oral activity. Once diagnosed, IPF is usually fatal within 30–42 months, making a prognosis worse than many cancers [21–23]. It is a disease where, for unknown reasons, the microstructure of the lung progressively thickens, thereby losing its usual respiratory function. However, there is now reasonable evidence that the RGD (arginine-glycine-aspartic acid) integrin receptor $\alpha_v\beta_6$ could play an important part in the initiation and progression of IPF [24,25]. This receptor is predominantly expressed in injured lung tissue, and inhibition of the receptor with $\alpha_v\beta_6$ antibodies or its absence in knockout mice leads to substantial protection from the development of fibrosis in bleomycin- [26] and radiation-induced [27] animal models. Selective $\alpha_v\beta_6$ antibodies (e.g. Biogen's STX-100, Phase II) are in development for fibrotic diseases. The mechanism by which the $\alpha_v\beta_6$ integrin causes fibrosis is believed to be by binding to the latency-associated peptide (LAP), the role of which is to regulate the activity of transforming growth factor-β (TGF-β), which in turn promotes fibrosis, among other functions. Thus, antagonism of $\alpha_v\beta_6$ should maintain complexation of LAP to TGF-β, attenuate the fibrotic response and so arrest progression of the disease.

The nature of the research is that of an inquiry-based project: the outcome is undetermined and the approach is inductive [28] (i.e. the students derive understanding of the science through hypothesis generation and, in the case of a medicinal chemistry project, test these hypotheses through compound design, synthesis and biological screening) [29,30]. Ideally the following objectives should be met during a project [31]:

- Training in 'the scientific method' [i.e. an opportunity to contribute to the discovery of new scientific information (which could be publishable)].
- To provide challenges relating to a valid scientific problem: assimilation of scientific background; problem-solving.
- To develop skills in experimental design and execution.
- To provide training and practice in experimental and analytical techniques.
- To develop critical skills in the interpretation of experimental data.
- To develop skills in reporting and presenting findings.
- To develop self-awareness (strengths and weaknesses), self-confidence and independence, particularly in team situations.
- To develop self-management skills (e.g. time management, dealing with disappointments).
- To engage in scientific debate with others; to examine from literature reading how others might be tackling the same (or similar) problems.
- There is an agreed strategy to deal with any intellectual property arising (see below).

On average, half the students taking the integrin research project had previously taken the third-year medicinal chemistry module, and some, on the Chemistry with a Year in Industry course, had experience within a pharmaceutical company. However, to expect undergraduates to devise and execute a successful small molecule drug design programme unaided is completely unrealistic [32]. Consequently, during the first week of the academic year, the students attend a seminar entitled 'medicinal chemistry in a nutshell', which covers the following topics in a couple of hours:

- The role of chemists in drug discovery.
- The design–synthesis–screen–analyse cycle.
- Drug binding.
- Agonists and antagonists: measurement of drug potency, IC_{50} and selectivity.

[a] M.J.F. was employed by Pfizer Global Research and Development 1986–2010 and T.M. was employed by Fisons (latterly Astra and then AstraZeneca) 1977–2011.

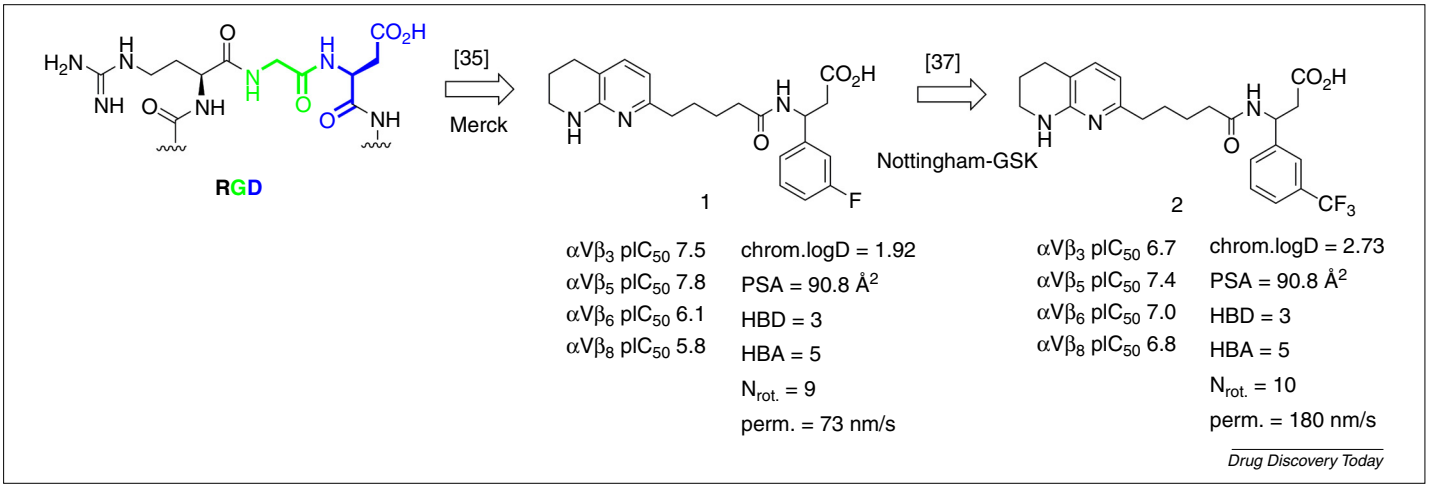

FIGURE 1

Rational design of α_v integrin antagonists starting from the RGD amino acid triad motif of the endogenous ligand LAP. Experimental data generated by James Rowedder (biological cell adhesion assays) and Alan Hill (physicochemical) at GSK, see [38]. Abbreviations: HBD, hydrogen-bond donor; HBA, hydrogen-bond acceptor; LAP, latency-associated peptide; N_{rot}, number of rotatable bonds; perm, high-throughput permeability; PSA, polar surface area.

- Pharmacophores.
- Shape of molecules.
- Bio-isosteres.
- Physicochemical properties.
- Lipophilicity, Lipinski's Rule of Five and Veber's Rules.
- Pharmacokinetics and drug metabolism.

This seminar acts as a refresher for students who have already taken a medicinal chemistry lecture course, and covers the main topics for those who have had no such exposure. Particular emphasis is placed on drug design that produces compounds with balanced properties (e.g. potency and selectivity have to be achieved within certain boundary conditions for lipophilicity, solubility, membrane permeability, etc.). Next, there are workshops (run jointly between university and GSK staff) in which the students are introduced to the project (the disease and the therapeutic approach) and the way in which novel integrin antagonists can be designed in a rational way by starting from the structure of the endogenous ligand (i.e. the RGD amino acid sequence of the LAP). A case history of how scientists at Merck approached the design of $\alpha_v\beta_3$ antagonists points to a general strategy for developing integrin antagonists (compounds **1**,**2**; Fig. 1) [33–36].

The students then discuss the screening results from previous years [37] and, with help, start to develop ideas about which target compounds to make next. Synthetic routes are discussed; for example, which analogues can be made by an established route (and would therefore be readily accessible) and which would require more ambitious methodology. The other aspect of compound design is to enumerate the properties of the target compounds, so that due consideration is given to molecular weight, numbers of H-bond donors and acceptors, calculated lipophilicity (*c*log *P*), polar surface area and number of rotatable bonds [38–41]. Attention is also paid to ensuring the absence of obvious toxicophores and metabolically vulnerable groups [5]. The students also familiarise themselves with the laboratory in which they will be working and receive briefings regarding safety, waste disposal and where to find apparatus and consumables. A check is also made that they have personal protective equipment and laboratory notebooks. During the year the students use standard university spectroscopic facilities such as infrared (which they will have used before) and high-field NMR and high-resolution mass spectrometry (for which they receive training). They also have access to LCMS and two microwave reactors.

Discussion: project philosophy, challenges and findings

Which factors should be considered when deciding the subject for an undergraduate medicinal chemistry project? The choice was made to study IPF and integrin antagonists because (i) IPF is a disease with high unmet need and (ii) a parallel project had been running at GSK for some time and all the necessary assays were available and reliable.[b] Furthermore, the University of Nottingham Faculty of Medicine and Health Sciences employs Gisli Jenkins, a world expert in interstitial lung diseases, of which IPF is one such disease [42]. His group is also able to run some of the more advanced assays and *in vivo* efficacy models if required.

The project is chiefly about medicinal chemistry, not synthesis. Consequently, success (at least at a scientific level) is measured by the screening results from the compounds made and what they tell us about the SAR, where the ultimate goal is to identify a development candidate (Box 1). However, the tractability of the target compounds is very important, especially given the limited laboratory experience of the students and the time available. For example, in the first year of the project, a student successfully prepared only a single analogue during her 20 weeks – it was a 12-step synthesis. Even though this compound made a valuable addition to the SAR, it was felt that it was more important (at least from the point of view of medicinal chemistry learning) that each group of students should complete at least two design–synthesis–data–analysis cycles, so they had a chance to modify the target compound design by responding to SAR for initial targets. We suspect that one of the most important learning points of inflexion occurs when students receive the data for the compounds they have designed

[b] There is nothing more dispiriting to the medicinal chemist than to have the project's biological assays deemed 'unreliable', thereby causing a hiatus that could last several months before screening can resume.

BOX 1

Who owns any arising intellectual property?

Given GSK has an active programme running concurrently with the students' project, various questions arise concerning who owns the intellectual property (IP) that might be generated during the research. Or should the project target a pre-competitive area to avoid the question? Is the objective to teach and train while discovering a development candidate, a tool compound or to just carry out some good quality science? Should both partners in the project see all the data generated for the project?

We regard the *goal* of identifying a development candidate as being essential for teaching crucial components of industrial medicinal chemistry, but the goal itself is likely to remain an aspiration. Thus, for teaching purposes, synthesising compounds with the appropriate physicochemical properties and structural features is more important than reaching the goal itself.

To simplify the IP arrangements, we decided to ring-fence GSK's IP around their proprietary compounds and that the university would own the IP for any discoveries made by the students in their series. The structures from the series owned by Nottingham are not displayed in the GSK corporate database and are thus not seen by the GSK medicinal chemists who actively work on the proprietary GSK series. This seeks to minimise any 'contamination' of GSK IP by Nottingham students or employees and *vice versa*.

However, this arrangement also means that, should an exciting compound be synthesised by the students that requires extensive and/or expensive screening, large-scale synthesis or patent protection, then the University will have to find the necessary funding for it. To reap the benefits of discovering a patentable asset, and certainly once the patent clock starts ticking after patent filing, one must make rapid progress and collect sufficient data to justify the patent filing. For example, additional screening and more expert synthetic resource *inter alia* would be essential.

Several referees raised the question that it is difficult for the external observer to judge how GSK benefit from the research carried out by the students. Of course GSK is in pole position to benefit from any discoveries and there is a mutual understanding that GSK has first refusal of any emerging lead or asset. But, in reality, while providing personal development opportunities for GSK staff, the company's sponsorship of this module is almost completely philanthropic in intent with the predominant aim of contributing towards the training of the next generation. Indeed, to the industrial medicinal chemist, pursuing a lead optimisation programme with ten inexperienced undergraduates who are only able to work for six months of the year and synthesise ~20 compounds per year - sometimes selected predominantly because they are synthetically accessible - is simply uncompetitive, with progress being too slow and too restrictive. If the value of GSK's cash and in-kind contributions to the fourth-year module at Nottingham were spent on fully trained chemists at CRO's, much faster progress could be made. In addition, the compounds currently being synthesised [37] are derived from literature leads and are covered by or close to IP filed by institutions other than GSK, which would is a non-optimal starting point where the end point is commercial exploitation.

and made (particularly if the data are disappointing), and then determine what to make next. In subsequent years, therefore, we have taken steps to ensure that the first synthesis attempted is as straightforward and short as possible [i.e. 3–5 steps to target **3**; Fig. 2; and, to facilitate this, key intermediates e.g. **4** (R = 3-Br) and **5** have been purchased or made by contract research organisations].

Projects where there are no obvious lead compounds are much more problematic to initiate, although a number of screening libraries (in addition to commercial ones) are now available [43–45]. A project in the hit-to-lead phase might well be frustrated by the low number of active compounds synthesised, thereby making it difficult to guide students to make rationally designed targets. By contrast, projects with highly developed lead matter could produce sparse SAR improvements owing to challenging and/or lengthy synthetic routes.

The difficulty and hazards of the synthesis must also be assessed carefully owing to the students' inexperience. However, depending on the students' progress, more ambitious and challenging chemistry can be introduced in the second semester. For example, the latest cohort of students found exploiting bromophenyl- or iodophenyl-substituted analogues by using Suzuki–Miyaura reactions and copper-catalysed arylation of nitrogen heterocycles problematic and challenging.[c] A further feature of medicinal chemistry projects is that the SAR tends to drive the chemistry strategy. What if this direction makes it very difficult for the undergraduates to complete any target compounds? If the chemistry is too mundane and repetitive, there could be a criticism that the students are not being challenged enough or are experiencing too narrow a range of chemistry. At the moment we feel that the balance is about right,[d] but will it remain so as the project evolves?

The project mimics real-life medicinal chemistry as carried out in the pharmaceutical industry in that it teaches the students about the need to submit pure compounds for testing with accurate associated data. In contrast to a typical academic project, target compounds are likely to contain irritating but essential functionality (as demanded by the SARs) and there are cut-off dates for compound delivery (so that screening results can be returned in time). In contrast to many academic research projects where the emphasis is on the individual, here the emphasis is on the team (Box 2). An industrial approach is also reflected in having a carefully defined goal, and a sense of urgency and clarity.

Another challenge of running a project over several years with undergraduates is to maintain progress and continuity. Inevitably, a new group of students takes a while to settle in and, having worked from September to April, disappears to the examination hall, graduates and progress halts until the next group arrives at the start of the next academic year. A project with up to ten students needs more organisation because the research must be coordinated. A significant amount of time must be invested in deciding the overall strategy for the coming year and developing presentations to set up the medicinal chemistry questions we would like the students to address. However, this effort is greatly appreciated by the students who, from the outset, gain a very clear understanding of the background to the project, the ultimate goal

[c] In some cases we have been able to anticipate synthetic challenges and develop solutions through summer internships at GSK, Stevenage. These internships are invaluable at providing students with direct experience in an industrial environment, but there is a significant challenge in finding scientists at GSK with enough time to act as trainers and supervisors.

[d] If anything, the delivery of compounds is weighted more heavily than the desirability of compounds. However, a comparison with traditional fourth-year projects revealed little difference in the range of chemistry experienced.

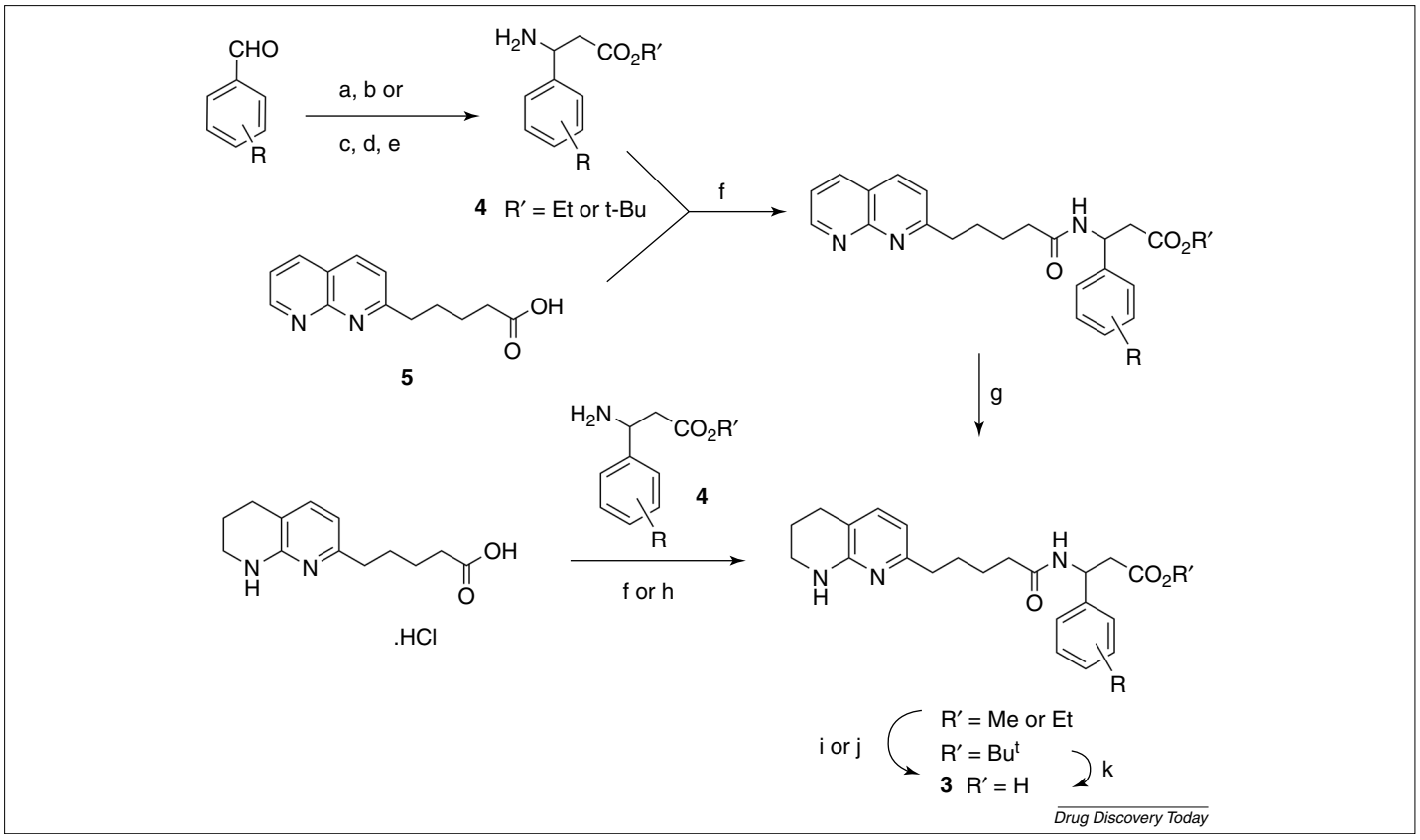

FIGURE 2

General synthetic route to integrin antagonists starting from substituted 3-amino-3-arylpropanoate esters and 5-(1,8-naphthyridin-2-yl)pentanoic and 5-(5,6,7,8-tetrahydronaphthyridin-2-yl)pentanoic acids. Reagents and conditions: **(a)** malonic acid, ammonium acetate, MeOH or EtOH or ^{i}PrOH, reflux. **(b)** $SOCl_2$, EtOH, −15 °C then reflux. **(c)** Bu^tSONH_2, $Ti(OPr^i)_4$, THF, 60 °C. **(d)** $BrCH_2CO_2Bu^t$, Zn dust, THF, 50 °C, then add product from step (c), 0–20 °C. **(e)** $HCl_{(g)}$, Et_2O, 0 °C. **(f)** *N*-ethyl-*N*?-3-(dimethylaminoprop-1-yl)carbodiimide, *N*-methylmorpholine, 1-hydroxybenzotriazole, MeCN or CH_2Cl_2, 20 °C. **(g)** H_2 (1 bar), 10% Pd/C, EtOH, 20 °C. **(h)** *N*-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU), Et_3N, CH_2Cl_2, room temperature. **(i)** $NaOH_{(aq.)}$, EtOH, 20 °C. **(j)** LiOH, THF/H_2O, 20 °C. **(k)** CF_3CO_2H, CH_2Cl_2 or $HCl_{(g)}$, dioxane, 20 °C.

and what they are to do (at least for the first semester). Each student also chooses the part of the project to which they want to contribute. We have been fortunate that the project is a popular choice and we have had no shortage of students, but it is a key part of the fourth year at Nottingham that the students choose their research supervisors, not the other way around. Therefore, if we get it wrong, the students will seek projects elsewhere in the department. At the end of the year we usually ask the students for feedback (Box 3; and see the Supplementary material online) so we continually try to improve the experience of future cohorts of students. Several themes recur:

- The students like the applied nature of the project, working towards a clear goal of an unmet medical need. They see their energies and ideas might ultimately result in a medicine that might prove useful.
- The students (in the main) enjoy working in a team environment.
- The students appreciate the contact with industry.

Inevitably the cost of running undergraduate research projects is an important factor. In medicinal chemistry, a wide range of reagents and molecular building blocks is available commercially. This facilitates rapid exploration of SAR but some reagents are prohibitively expensive (e.g. >£100 per mmole). The university is very fortunate that GSK provides money for equipment and consumables (~£2000 per student) and more than ten pieces of data for most compounds – pIC_{50}s in fluorescence polarization and cell-based adhesion assays for most RGD integrins ($n = 2$) measured by an expert professional [46], $\log D_{7.4}$ measured by the chromatographic method [47], high-throughput membrane permeability and protein binding to human serum albumin. *In vitro* assays to measure drug metabolism and pharmacokinetic potential are also available if required. GSK also funds a Teaching Fellowship (for M.J.F.).

The authors perceive several benefits. Firstly, the project is a great challenge and tremendous fun. It is very satisfying to be able to carry out some science of publishable quality and work towards the discovery of a clinical candidate. By having relatively large resources (numbers of students, funding and screening) we can feasibly make reasonable progress towards our goals. In the past four years we have completed the synthesis of over 80 target compounds (**3**) and have also been able to explore a second structural series (data not shown). During the past year we have also improved the profile of our lead compound from the published series (Fig. 1) [37], improving potency and selectivity for $\alpha_v\beta_6$ [48], and these results will be published elsewhere shortly. For the scientists from GSK the ability to pursue some interesting but

BOX 2

Teamwork skills for undergraduates: preparation for employment or a distraction from education?

In essence GSK's involvement in these MSci projects is to contribute towards the students' education and their preparation for employment with a naturally greater tendency to enhance the latter. Central to most employment – and certainly that in the pharmaceutical industry – is for the employee to have some kind of ability to work in a team. Most tasks are either too complex, too urgent or a combination of both to be left to a single individual to accomplish. Individuals who are unwilling to work in a team sharing and adjusting their own work to common goals usually find career progression is slower and move into an environment that is more suited to their outlook.

As part of the brief to prepare 'industry-ready' graduates, the MSci projects require the students to work in teams and to exhibit behaviours conducive to the team goal. There is, however, an undercurrent of tension between this and the predominant experience of the undergraduate, who is more used to progressing almost exclusively on the basis of their own academic ability. Some points and questions raised have been:

- how/should teamwork be assessed (teamwork is not assessed in the MSci projects at Nottingham);
- I don't want to jeopardise my marks by having to rely on another – and potentially weaker – student;
- this is my degree, my education in chemistry – how does teamwork fit into that?

Of course some, if not most, of the students really enjoy working as part of the team and quickly appreciate faster progress can be made by doing so and willingly carry out tasks that benefit other team members as much as themselves. The peer support provided by a team is transformational for less self-confident students. Opportunities emerge for the student's leadership and team working skills to become apparent and be expressed. Some groups gelled quickly and became particularly effective. Behaviours from team members that built the team (such as making cakes for their fellow students to share during tea-break) or enhanced the team's capability (analysis and visualisation of structure–activity relationships) have been observed. In an attempt to catalyse and promote communication between team members which underpins such behaviours, students are encouraged to learn more about each other in the first week of the semester (almost in a speed-dating style), set tasks that require team interactions and they are even given a small budget for team building activities. As with the third-year undergraduate module described previously [13], the students complete the Belbin questionnaire to determine their preferred roles when working in teams and the questionnaires are then used to assemble the teams [51]. Finally, a team skills workshop takes place [52], where the students identify some of their own work styles and approaches to consider when working with colleagues who are task or people focused and are self or team focused.

BOX 3

Student feedback

Brief testimonies from two students are provided (others are provided in the Supplementary material online). In summary, the students appreciated:

- the applied nature and goal;
- the link and connections to industry;
- learning and being supervised by industrialists or ex-industrialists (as opposed to PhD students);
- that the organisation and focus on achieving various goals to a deadline was a real reflection of medicinal chemistry in industry;
- receiving data on the compounds they had designed and made;
- working in a team environment.

Student 4 (2012–2013) – currently a scientist and study director at Medpharm

"I thought the project was a fantastic experience. It boasts a wealth of day to day activities with depth of work and knowledge. I certainly learnt more doing that project than I did during any other aspect of my degree. It has set me in good stead for a career in the pharma industry (still at it!) and definitely pushed me towards working in pharma. The lab environment and work was excellent along with generous support and guidance that really helped draw out the strengths of each character in the team. There were great opportunities to see behind the closed doors of industry leaders and to meet some key characters in the industry which certainly helped moving into the career afterwards feel a little less alien. End of the day, I don't regret doing the project for a second."

Student 5 (2013–2014) – currently a scientist at Evotech

"The project provided an enjoyable and valuable insight into the 'real life' application of organic chemistry in a medicinal chemistry setting which could not be gained from lectures alone. Undertaking the project after returning from a 12 month industrial placement in a pharmaceutical company, I can say the work was truly reflective of the work carried out in pharma. The project set-up was equivalent to industry, where we reported updates back to the team regularly, held meetings to discuss synthetic obstacles and held discussions to re-evaluate targets after receiving biological data. The project enabled us to carry out a large number of reactions using a wide variety of techniques, and the access to resources available in industry allowed for more efficient synthesis of the targets, ultimately allowing us to do more than those students on traditional projects. We gained the same experimental and analytical report writing skills gained from traditional projects, but our med chem and industry knowledge was unrivalled by traditional project students. We had the added benefit of support and guidance from experienced industrial minds. I attribute landing my job in a pharmaceutical company immediately after graduating to the experience I gained on this project, which I believe gave me the edge over other graduates at interview. I would recommend this to anyone looking for a career in the pharma industry as it gives you a great head start on all other chemistry graduates!"

noncritical scientific ideas is a refreshing and complementary contrast from the industrial requirements for prioritisation of critical path activities delivering to business deadlines. This has extended to new research projects allied to the main project (Box 4) and has been facilitated by the appointment of S.J.F.M. as a visiting professor at the university.

One of the limitations of the project has been that we have not been able to exploit structure-based drug design. Although the X-ray crystal structures of $\alpha_v\beta_3$ and $\alpha_v\beta_6$ integrins have been published [49,50], they are very challenging to generate and exploit. It is unrealistic for GSK to prioritise work for the university over its own; certain members of the School of Chemistry also have the expertise but need to be persuaded of the value of the work compared with other computational projects in progress, particularly given the challenges involved.

BOX 4

Spinout projects

At the core of the MSci projects is medicinal chemistry (i.e. the iterative design, synthesis and testing of compounds with activity as integrin inhibitors). However various other fourth-year MSci projects have unexpectedly emerged. In the first example of this, one student had just completed a year in industry in analytical chemistry and wished to use his experience in the GSK sponsored MSci projects. This led to a new project at the interface of mass spectrometry, biology and chemistry where the activity of the compounds made by the medicinal chemistry students was determined by mass spectrometry using equilibrium dialysis. This work represents a novel way of determining biological activity against integrins and has recently been published [53].

Other spinout projects relate to identifying asymmetric synthetic routes to target compounds while another is exploring QSAR from the large number of compounds and associated biological data now available from the various cohorts of medicinal chemistry MSci students.

What have we learnt from these spinout projects?

- The academics we have approached in the university have been impressively collegiate and open to collaboration. The sheer range of expertise available in the university is vast even in comparison with a large pharmaceutical company.
- A productive approach is to identify aspects of the research that overlap strongly with academics' existing expertise or ongoing work in their laboratories. Perhaps, unsurprisingly, exploration of a new area of research – particularly with an inexperienced fourth-year student – is substantially more challenging.
- Identifying or articulating the value that could emerge from a potential spinout project can be more open-ended but usually value does emerge sometimes in an unanticipated way.
- In industry, where resource is remorselessly focused on business-critical activities, the opportunity to explore novel areas and run less focused experiments is refreshing and has proved to be highly stimulating.

Concluding remarks

Over the past four years we have trained 40 students in experimental techniques, data analysis and medicinal chemistry principles through a lead optimisation programme. We have published one paper already [40] and two more are planned. Eighty-four aryl analogues have been prepared and screened, from which we have identified potent but modestly selective leads, not unexpected for RGD integrins. It is becoming apparent, however, that achieving membrane permeability commensurate with good oral absorption could be difficult to achieve without the log *D* becoming too high. Should we be fortunate enough to identify a quality compound with development potential, it is evident that a significant increase in resources will be necessary to progress it into a marketable entity (i.e. available for licensing for progression to clinical trials). We foresee that such further work, in essence a lead optimisation programme, might be more effectively pursued outside the university. In this case, the university might apply for external funding and/or work with a CRO to exploit any potential lead or asset.

For someone else contemplating running a similar project, we would advise choosing the disease and biological target with a great deal of care. Which resources do you have and which do you lack? For example, you cannot run a medicinal chemistry project if the necessary screening is unavailable or too slow to feed back data for the next round of compound design. Projects at a relatively early stage of lead identification or optimisation are probably better than those near candidate selection owing to the smaller number and cheaper cost of screens. There might also be more flexibility regarding the selection of lead structure and synthetic route, because the latter must not be too long, complex or hazardous. Ideally you should be able to access some key intermediates that can be exploited quickly with straightforward chemistry, at least at the beginning. Target structures should be selected based on an appreciation of their predicted properties, including the presence or absence of toxicophores and metabolic liability; all are crucial for teaching industry-focused medicinal chemistry because they underpin real-life lead optimisation towards a clinical candidate, which is different and often more difficult than identifying a biological tool or probe. Students find their first foray into real research to be daunting. They need considerable support in the laboratory, from practical techniques to developing problem-solving skills, and from spectroscopic data analysis to oral or written presentation skills. In addition to the usual scientific activities, we have taught the students about the importance of team skills in industry.

Has the collaboration successfully delivered 'industry-ready' graduates? It is a little early to tell, but the prospects look good. Not surprisingly, many of the students who gained first or upper second class degrees have decided to pursue further academic study (57% going on to PhDs as well as one student studying medicine). A pleasing 18% is now employed in the pharmaceutical industry and 12% in other industrial positions. Three students have decided to become school teachers.

Conflicts of interest

The authors declare no conflicts of interest. M.J.F. held a Teaching Fellowship in Organic and Medicinal Chemistry funded by GSK between 2010 and 2015. S.J.F.M. is a shareholder in GSK and is a nonstipendiary visiting professor at the School of Chemistry, University of Nottingham.

Acknowledgements

The authors wish to thank James Rowedder and Alan Hill for their expertise in providing quality biological and physicochemical screening data, respectively; Stephen Swanson and Simon Peace for presenting workshops on various medicinal chemistry topics and discussing emerging SARs; Marius Kausas for molecular modelling; the analytical services team in the School of Chemistry; and last, but by no means least, the students – James Adams, Edward C. Anderson, Blake Baker, Thomas Barlow, Emma E. Blackham, Akono O. Brathwaite, Thomas Bridges, Christine L. Butcher, Yin Wa Ryan Chiu, Thomas Clarke, Stephanie L. Dickinson, Adam Eason, Natasha Eccles, Adam Fearnley, Aimie E. Garces, Luke A. Gill, Joshua J. Haye, Harvey T. Haywood, Nick A. Herbert, Christian R. Hoenig, Dominic M. Howgego, Alice E.H. Johnson, S. Paul Jones, Georgia F. Pigott, William J. Restorick, Hannah L. Russell, Thomas J. Sanderson, Imandeep S. Sehmbi, Christopher Smedley, Frances R. Smith, Jack O. Sorrell, Nichola J. Starr, Robert N. Straker, Claire Sycamore, William J. Tipping, Tom Tongue, Peter Walters, Charlotte C. Wood, Jason Yeung and Max Ziemann.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drudis.2016.01.015.

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