Learn Chemistry

Molecules against Malaria: Design of a Structure Activity Relationship Study of Antimalarial 4-Aminoquinolines

Tutor Guide

Developed by Dr. Claire McDonnell and Dr. Sarah Rawe, Dublin Institute of Technology

This resource was produced as part of the National HE STEM Programme

National HE STEM Programme

RSC | Advancing the Chemical Sciences

www.rsc.org/learn-chemistry

Registered Charity Number 207890

Acknowledgements

The authors would like to thank the people who contributed to this work: Dr. Brigid Lanigan, Mr. Damien Coman, Dr Michael Seery and Dr. Christine O'Connor of the DIT Chemistry Education Research Team for their input and for many useful discussions. We would also like to thank the people who trialled this resource for their very valuable input: Dr. Graham Patrick and Dr. Morag Dagen, University of The West of Scotland, Dr. Trinidad Velasco-Torrijos and Orla Fenelon, National University of Ireland (NUI) Maynooth, and Dr. Julie Dunne, Dublin Institute of Technology. We would also like to thank our external reviewer who provided valuable feedback for the development of the final resource.

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Context/Problem-Based Learning (C/PBL)

A C/PBL approach aims to increase students' engagement with a subject by designing courses based upon real-life applications of the principles, techniques and experiments that they encounter during their undergraduate careers. These real world contexts are presented in the form of problem scenarios which are ill-defined and have a number of satisfactory solutions. Learners work collaboratively to solve problems and acquire new knowledge and then present the outcomes or product. This approach encourages students to take control of their learning, gain a deeper understanding and provides the opportunity to develop valuable transferable skills such as communication, team work and problem solving. Academic staff adopt the role of facilitator or guide during the process. The following review on C/PBL can be consulted for further information: T. L. Overton, Context and Problem-Based Learning, *New Directions*, Issue 3, Oct 2007, pages 7-12.

http://www.heacademy.ac.uk/assets/ps/documents/new_directions/new_directions/newdir3_link.pdf

About This Resource

This resource is designed to introduce students to the activities that make up the early stages of drug discovery and development. It focuses on antimalarial 4-aminoquinolines (4-AQs) and involves an introduction to malaria, its causes, societal impact and the need for new drugs. It then presents an overview of 4-AQs, their mode of action, structure activity relationships (SARs) and pharmacokinetics. The resource differs from a traditional lecture course by employing Context/Problem-Based Learning (C/PBL) as a teaching methodology. The context of the resource asks the students to adopt the role of a medicinal chemist working for the GHO (Global Health Organisation) in the Tropical Diseases Research Centre. The students are asked to prepare a research proposal of not more than 2000 words to seek funding for a SAR study which aims to find new and much needed antimalarial 4-AQs. The students will work in groups of 3-5 and the overall task will be achieved in a stepwise manner over a number of Workshops.

The resource is designed to map onto the Human Health theme of the RSC Roadmap. The development and use of drugs and therapies to improve human health is a key challenge that the RSC have chosen to promote as part of their Chemistry for Tomorrow's World initiatives. Through this, they aim to demonstrate how harnessing the basic sciences can help transform drug discovery, development and the human healthcare landscape.

An Overview of the Resource

This Tutor Guide accompanies the resource "*Molecules against Malaria: Design of a Structure Activity Relationship Study of Antimalarial 4-Aminoquinolines*", a C/PBL resource developed for the Royal Society of Chemistry in 2012 as part of the HE-STEM programme. It is intended to be part of a pharmaceutical/medicinal chemistry curriculum for students in the last 2 years of an undergraduate chemistry (or related) degree although it could be adapted for more advanced groups (see 'Flexibility within the Resource', below). The resource is composed of:

- A Student Guide.
- This Tutor Guide.
- PowerPoint presentations for each Workshop.
- An optional supporting resource "Hybrid Workshops to Support: *Molecules against Malaria: Design of a Structure Activity Relationship Study of Antimalarial 4-Aminoquinolines*" is also available (see below, 'Navigating the Resource' for more information).

In writing this resource, the authors' intention was to move away from the traditional approach used to deliver their 'Introduction to Medicinal Chemistry' module, which generally required students to rote learn a large volume of material in order to pass an examination, and towards a module that requires students to apply knowledge. It is not envisioned that tutors delivering this module have to be medicinal chemists. Medicinal chemistry can be described as the application of the general principles of organic and physical organic chemistry to the interaction of a small molecule (a drug) with a large biomolecule (drug target e.g. an enzyme). Some specialist terminology is required (e.g. the intermolecular interactions between a drug and its target are referred to as binding interactions). Some knowledge of biomolecules, and the cell and its organelles, would also be useful but is not essential. The authors recommend any one of the two introductory texts listed below (Text Books and Reference Materials) both to students and to tutors delivering this material for the first time.

It should be noted that the biological target of the 4-aminoquinoline antimalarials is unusual in that it is *not* a protein or other macromolecular biomolecule. This has the advantage that no prior knowledge of the structure and function of biomolecules is required prior to undertaking the Antimalarial Workshops described herein, thus allowing students to focus on many of the fundamental principles of drug design and development from a chemist's perspective. However the authors acknowledge that for this reason it may not be suitable as a stand-alone module for those wishing to expose students to a broader pharmacologically based medicinal chemistry syllabus.

Students participating in these Workshops should have some prior knowledge of the fundamental concepts of medicinal chemistry (drugs, drug targets, binding, phases of drug action, stages of drug discovery and development, etc). However, if the student cohort has not had any previous instruction in medicinal chemistry it would be appropriate to provide a further 10 contact hours in which these concepts are introduced. In order to facilitate this learning, the authors of this Guide have developed a number of learning activities that can be adopted as part of a hybrid approach to C/PBL (Hybrid Workshops 1-5). A hybrid approach refers to short periods of traditional lecture activity interspersed frequently with problem solving. The learning outcomes associated with the Hybrid Workshops are given in the Appendices to this Guide and summarise the prior knowledge required for students undertaking the Antimalarial Workshops. Please refer to the accompanying Guide "Hybrid Workshops to Support: *Molecules against Malaria: Design of a Structure Activity Relationship Study of Antimalarial 4-Aminoquinolines*" if appropriate for your student group.

It was assumed when writing this resource that students participating in this module have access to and can use a chemical drawing programme. If not, it may be appropriate to schedule appropriate training in advance. Versions of Accelrys Draw (which has replaced ISIS/Draw) or ChemSketch can be downloaded and used by academic institutions and students for free. In addition, several online tutorials on the use of the software are available.

- http://accelrys.com/products/informatics/cheminformatics/draw/no-fee.php
- http://www.acdlabs.com/resources/freeware/chemsketch/

Navigating the Resource

This Guide describes a classroom-based case study involving seven Workshops (Antimalarial Workshops, Table 1) that require 14 contact hours divided into 7 x 2 hour or 14 x 1 hour sessions. A schedule for the delivery of the Antimalarial Workshops is outlined in Table 1, which also summarises tutor and student activities, what the tutor should do between Workshops, deadlines and learning outcomes. A simplified version of Table 1 can be found in the Student Guide (also Table 1) and tutors should consult the tables for an overview of the resource.

The Appendices to this Guide contain student handouts (Appendix 1) which are organised according to the Workshops with which they are associated. Appendix 2 contains the 'Tutor Notes for Workshops 1-5' (organised according to Workshop) and provides the specialist knowledge concerning the medicinal chemistry of antimalarial 4-AQs – it can also serve as a sample answer when marking the final proposals submitted by the students. A 'Making It Work' section is also provided in the Appendix 10 and gives some tips and advice gained from the authors' and the trial teams' experiences of implementing this and similar resources.

Table 1 and associated Appendices may provide sufficient information for many experienced tutors planning to adopt the resource. However, the Table was obtained by summarising a detailed task-by-task breakdown (for both tutors and students) of the content of every Workshop and so the authors have included detailed descriptions of each Workshop in this Guide (Workshop Content) that can be used for further clarification.

How is the Resource Delivered?

The resource is designed to be delivered to students as a continuously assessed module. Together with the Hybrid Workshops (10 hours of contact time), independent study and writing-up time, it is intended that this resource requires a total of 50 learning hours (a total of 24 contact hours plus 26 hours of self study). As such it represents approximately 2.5 European Transfer Credit System (ECTS) or 5 UK credits of work or 1.5 US credits.

Flexibility within the Resource

The resource can be adapted to suit students at various levels, with varying knowledge and experience of C/PBL. For this reason, the Guides and accompanying materials are provided in a format that can be modified by the tutor. The Student Guide and associated PowerPoint presentations contain stepwise instructions for the students to help them complete the tasks associated with each Workshop. Some tutors will feel that these instructions are too comprehensive / leading for their student group, preferring to let the students find their own way and can edit the Guide as appropriate.

A number of texts, articles and weblinks are listed throughout the Guides and it is up to the tutor to decide which of these are suitable for their students and, again, he /she can amend the Student Guide to suit the student group. For second year undergraduates, it is likely that the recommended text books and a small number of articles and weblinks, along with the student handouts would be sufficient to allow them to engage with the resource at an appropriate level. For final year undergraduates with previous experience of C/PBL and medicinal chemistry, the review articles may be made available as an alternative to much of the information contained within the student handouts (Report: Parts A to C, see Appendices). For very advanced groups (e.g. postgraduates), a more student driven approach may be taken in which the students are required to search the literature in order to find all of the appropriate information for themselves.

The authors have designed the resource as a whole to be delivered as 10 hours of Hybrid Workshops followed by 14 hours of Antimalarial Workshops, but have suggested alternative modes of delivery in the Appendices to this Guide. Tutors with groups who have already completed pharmacology or medicinal chemistry modules should consult this section. It is also envisaged that the Hybrid Workshops could stand-alone as part of an introductory module. Moreover, one or more Workshops could be employed in place of a laboratory in a larger medicinal chemistry module.

In summary, tutors are invited to adapt this resource to suit the needs of their student cohort.

Table 1: Content and Recommended Schedule for Delivery of Antimalarial Workshops 1 to 7

Session Title, Time Allocation	Tutor Aims	Activities	Learning Outcomes On completion of this session, the student should be able to:
Workshop 1: • Introduction to Workshops and the context. • Abstract writing. 2 hours or two 1 hour sessions	**Module induction** • Assign groups, give an introduction to the context, problem and outline the learning outcomes and assessment of the module. Look over the Student Guide. **Introduction to the Context** Introduce the following topics that will need to be researched further by the student: • What is malaria? • What is the impact of malaria in a global context? • The malaria parasite and its lifecycle. • Chloroquine and its mode of action. • Problems with the use of chloroquine and the need for new drugs. • Drug resistance. **Preparing Abstracts** To introduce and discuss the following topics: • What is an abstract? • How is an abstract prepared? • Differences between scientific and lay abstracts. **If you are asking students to peer assess individual contributions to group work as part of this module, you should inform and brief them accordingly.** **In advance of Workshop 2:** **Obtain student emails and invite them to join the group wikis.**	**Hour 1** Tutor presentation of introductory material: Includes a schedule of Workshops, assessment criteria and learning outcomes. Students are provided with a Chemistry World article which reviews aspects of the context (Malaria No More, V.Gill, Chemistry World, April 2008, 50-55). They are given time to read it, to discuss it in their groups and then as a class. **Hour 2** Using the Chemistry World article students are required to work in groups to: • Select information that they think should be in an abstract of the article. • Feed back and prepare a class abstract (agreed key points and order). • Compare the content of a sample abstract provided to that decided above. • Read newspaper articles concerning malaria. • Compare and contrast the style used in the popular press to that used in Chemistry World and suggest changes to be made to the abstract if it was aimed at a lay audience.	• Gain an awareness of the global impact of malaria. • Identify the malaria parasite as the cause of malaria, to note its lifecycle and importance of this to developing new antimalarial drugs. • Identify chloroquine; explain its mode of action and the need for new therapies to replace chloroquine. • Explain what is meant by the term 'drug resistance' and why this problem is significant. • Construct an abstract and assess the relevance of information provided in articles. • Gain an awareness of the need for scientists to communicate with a lay audience and consider how this can be best achieved.

Session Title and Time Allocation	Tutor Aims	Activities	Learning Outcomes On completion of this session, the student should be able to:
Workshop 2: • Tools to support the project - using a wiki (requires a computer lab if available).	**Using a Wiki (in computer lab if available)** To introduce and discuss the following topics: • What is a wiki? • How to use a wiki. • It's role in group assessment and in production of final report. • Demonstration of how individual contributions to a wiki can be monitored and assessed by the tutor.	Students are shown how to use a wiki and how it can be used to assess their contribution to group work. They will: • Set up the wiki according to the guidelines. • Begin generating group wikis by uploading content researched over the previous week. • Use this content to begin preparing the research proposal including a bibliography and continue it on an ongoing basis.	Use and contribute to a wiki to organise and facilitate collaborative work and understand how this activity contributes to the assessment.
• The relationship between chemical structure and biological activity. 2 hours or two 1 hour sessions	**Identifying the relationship between the chemical structure and antimalarial activity** To guide learners through the following processes, using relevant data (student handout): • Recognising the chemical structure of 4-aminoquinolines (4-AQs). • Using IC_{50} data to determine the relationship between the chemical structure and potency. • Identifying a likely pharmacophore. • Suggesting likely drug target interactions. • Explaining the probable mode of action of 4-AQ antimalarials. **Between Workshops:** **Review student wikis and provide feedback (brief comment). Ensure wikis are set up correctly (correct pages / headings, Appendix 3) to produce the final research proposal.**	From the information provided in the student handout for the Workshop, students will be asked to: • Determine how changes in the structure of compounds affect the activity and therefore identify a likely/probable pharmacophore of 4-AQs. • Describe the mode of action of chloroquine, identifying the drug target and suggest likely drug target interactions. • Determine groups that can be varied in order to investigate the SAR of 4-aminoquinolines with a view to developing more potent analogues. • The tutor will lead a class discussion that aims to critically evaluate the data provided in Report Part A (particularly Table A1).	• Give an overview of the structures and mode of action of clinically useful antimalarial 4-AQs. • Identify a likely pharmacophore. • Explain the mode of action of chloroquine and related antimalarials identifying the drug target and relevant binding interactions. • Explain the outcome of previous SAR studies and recognise the potential to design new antimalarial 4-aminoquinolines. • Critically evaluate biological data obtained from the literature.

Session Title and Time Allocation	Tutor Aims	Activities	Learning Outcomes On completion of this session, the student should be able to:
Workshop 3: **Designing and Planning a SAR Study** **Including:** • Selection of a lead compound. • Design of a structure activity relationship study, including synthetic route(s). • Selection of appropriate bioassay(s). 2 hours or two 1 hour sessions	**Designing and Planning a SAR Study** To guide learners through the following processes, using the information provided in the student handout: • Selection of a lead compound and / or recognition of the desired properties of a lead compound. • Design of a small SAR study (3-5 analogues which are referred to as the target compounds) by proposing molecular modifications of a lead compound and the synthetic route(s) and bioassay(s) to be used. • Use of online chemical catalogues/databases to source commercially available materials for SAR studies. Stepwise nature of experimental design should be emphasised. **Between Workshops:** **Review student wikis and provide feedback in the form of a brief comment.** **Direct students to appropriate section in text book (or other) concerning pharmacokinetics.**	Students will be asked to: Design a SAR study, to suggest the synthetic route(s) to target compounds from commercially available materials and to recommend the appropriate bioassay(s).	• Design a logical SAR study taking into account the pharmacophore and previous SAR studies. • Design the synthetic route(s) to the target compounds. • Use a chemical catalogue to source commercially available materials for the synthesis of target compounds. • Be aware of the criteria for the selection of a biological assay and select the appropriate bioassay(s) for the SAR study.

Session Title and Time Allocation	Tutor Aims	Activities	Learning Outcomes On completion of this session, the student should be able to:
Workshop 4: • Pharmacokinetics. • Timelines. 2 hours or two 1 hour sessions	To guide learners through the following problems, using information provided in the student handout and from their own reading: **Examining the relationship between the chemical structure, drug metabolism and oral availability** • Prediction of the route by which the target compounds could be metabolised. • Analysis of oral availability of the target compounds (designed in Workshop 3). • Evaluation of the importance of the above in early stages of the drug discovery process. **Timelines** • The use of a Gantt chart to plan a small scale SAR study. To ensure learners have an awareness of subsequent steps and the time required for drug development. **Set a deadline for submission of memo and drug-likeness sheets.** **Between Workshops:** • **Review and provide feedback on memo and drug-likeness sheets (see PowerPoint presentation).** • **Review wiki, ensure memo and Gantt chart uploaded.** • **Remind students draft proposal due after Workshop 6.**	Students will be asked to: • Research relevant information about drug metabolism (objectives and the transformations that may take place). • Predict metabolism of the new 4-aminoquinolines and note how this will impact on the design of the SAR study. • Consider how the physiochemical properties of compounds affect oral availability. • Prepare a memo summarising the above and complete drug-likeness sheets for target compounds. • Plan the time that it will take to carry out the proposed SAR study and show graphically in the form of a Gantt chart. • Estimate the time involved in taking a lead compound from the bench to clinical use.	• Describe the metabolism of antimalarial 4-AQs. • Predict oral availability of drugs. • Explain why it is important to consider pharmacokinetics when designing new drugs. • Be aware of the time that it takes to execute a small scale SAR study. • Use a Gantt chart to show a timeline graphically. • Demonstrate awareness of the stages of the drug discovery process and the time involved in developing a new drug to clinical approval stage from a promising lead.

Session Title and Time Allocation	Tutor Aims	Activities	Learning Outcomes On completion of this session, the student should be able to:
Workshop 5: Parallel synthesis and high throughput screening (HTS). 2 hours or two 1 hour sessions	To guide learners through the following problem, using information provided in the student handout and from their own reading: Evaluation of the impact of parallel synthesis and HTS on the proposed SAR study, both positive and negative. There should be time to help learners review progress to date, and to identify areas of the final proposal that require more work before a draft version is submitted in advance of Workshop 6. **Set deadlines for: Submission of memo, draft proposal and work-in-progress summary.** **Between Workshops:** **Review draft proposals and provide feedback.**	Students will be asked to: • Research relevant information about the tools available to a medicinal chemist. • Critically assess how the use of these tools will impact on their proposed SAR arriving at a recommendation for the use (or not) of these tools. • Prepare a memo summarising the above and incorporate information into the wiki. • Assess progress to date, identifying sections of the proposal that require work. • Consult with tutor if there are any issues / problems that need to be addressed / clarified.	• Explain and critically evaluate the application, advantages and any disadvantages involved in the use of parallel synthesis and HTS in the drug discovery process. • Identify any other appropriate tools for the SAR study. • Work effectively as a group to assess progress to date, identify areas of the proposal that require work and plan the final stages of the project.
Workshop 6: Clinic for Formative Feedback. 2 hours or two 1 hour sessions	• To provide learners with formative feedback on the areas of the proposal requiring more attention and those that have been addressed satisfactorily. • To provide clarification on any student queries, review assessment criteria for module and to promote discussion as appropriate among the learners and encourage peer learning. **If you wish students to peer assess presentations, brief students and circulate forms.**	'Clinic' where each group; • Has submitted a draft 'work in progress' report in advance on which they will receive feedback. • Will discuss any queries or problems that they have encountered.	• Work effectively as a group. • Listen to and act on constructive feedback provided as required. • Identify problems and questions that relate to the assignment and related activities.

Session Title and Time Allocation	Tutor Aims	Activities	Learning Outcomes On completion of this session, the student should be able to:
Workshop 7: Group presentations. 2 hours or two 1 hour sessions.	• To provide feedback to the learners on their presentation skills and the content of their proposal. • To allow students to learn from each other's presentations and to ask each other questions. • To allow students to peer assess presentations (optional). • To arrange /allow students to peer assess individual contributions to group work (optional). • To ask students to complete module evaluation forms (optional). • To review the assessment criteria in detail ahead of the final submission. **Set deadlines for:** **Submission of reflective piece.** **Submission of final research proposal.** **Advise students of format (PDF from wiki or Word® document).**	Students will be asked to: • Give a presentation to peers summarising the proposal followed by questions from the tutor and other students. • Peer-assess presentations (optional). • Peer-assess individual contributions (optional). • Provide feedback to tutor on module (optional). The tutor will: • Give general oral and/or written feedback on each presentation. • Give a deadline for submission of the reflective piece and final proposal.	• Produce a clear and legible PowerPoint (or other) presentation and present findings in a professional manner. • Work effectively as a group, develop oral and written communication skills. • Listen to and act on constructive feedback provided as required. • Reflect on participation in a group project, and the knowledge and skills acquired. • Peer-assess presentations and individual contributions to group work (optional). • Provide constructive feedback about the module (optional).

Assessment

The assessment components (Table 2) will mean that each group maintains and contributes to a wiki, gives a group presentation and submits a final group report in the form of a research proposal in keeping with the context. An individual reflective piece is also required. Therefore the assessment focuses on:

1. Contribution to the group project (most conveniently monitored using a wiki).
2. The group presentation.
3. The group research proposal (generated from the wiki).
4. An individual reflective piece.

Assessment components and a guideline for the weighting of the assessment are suggested in Table 2. These are suggestions only and should be adapted to suit the group and tutor. Note that any changes made should also be made to the equivalent tables in the Student Guide and accompanying PowerPoint presentations (Intro to Molecules against Malaria Tutor Presentation, and Molecules against Malaria_Antimalarial Workshops 1-7 Tutor Presentation- slides in Workshops 6 and 7).

Table 2: Assessment components and suggested weightings

Activity	Basis of Delivery	% Marks Allocation
Participation during Workshops (and to group work)[##]	Individual	15
Contribution to wiki[##]	Individual	30
Presentation[#]	Group	10
Research proposal (Generated directly from the wiki. Criteria- content, accuracy, structure, clarity, reasoning.)	Group	35
Reflective piece	Individual	10

[#]*You may choose a component of this mark (e.g. 5 %) to be awarded by peer assessment by other class members. More information is given in Workshop 6, below and Presentation Evaluation Forms can be found in the Appendices to this Guide.*

[##]*If incorporating a peer assessment element, Table 2 should be amended (in Guides and PowerPoint Presentations) to include the phrase in parenthesis. In this case, students will be asked to peer-assess contributions of other group members both inside and outside of the classroom, online and face-to-face. Clear guidelines must be provided to the students (see Implementation: Peer Assessment and Evaluation of the Resource, below).*

A Word about Wikis

A wiki is an excellent tool to facilitate group learning and the final research proposal is generated directly from it (by converting it to PDF or printing). It is useful to remind students of this throughout the project. The main benefit to a tutor is that the quality and quantity of contributions made by an individual student can be tracked relatively easily and that the process as well as the product can be assessed.

Advice on monitoring and correcting wikis is provided in the Appendices to this Guide, but briefly, the tutor should log into each group's wiki once per week (assuming 2 hours contact per week), providing feedback on the execution of tasks associated with each Workshop and the extent of individual contributions. Feedback is also provided on the students' draft reports (research proposals), with the remaining correction

time spent on the completed reports (research proposals), presentations and individual reflective pieces. In this manner, students receive feedback as a group and as individuals at various stages throughout the project.

Although it is recommended that a wiki be used as a component of this C/PBL activity, an alternative can be adopted if preferred. Some type of online interaction among a group such as a discussion board or online group is very useful and, if this has been set up by the tutor, there is the advantage that they will be able to monitor progress being made. If this option is not used, the minutes of the weekly group meeting summaries should be submitted regularly and can be used to monitor progress and to check that all members are making a contribution. To provide a facility similar to the wiki for organisation of the work being undertaken, it would be useful for groups to use a ring binder / file with sections that correspond to the main parts of the proposal in which hard copies of useful documents and draft work can be kept. Under these circumstances, it is recommended that this draft work and supporting information is submitted as an appendix to the final proposal.

Implementation: Class Organisation

Whenever possible, the tutor should take a back seat and direct the students to the Student Guide and recommended resources to obtain relevant information. This encourages learners to read and engage fully with the materials provided. The distribution of the workload associated with the tasks should be assigned by the students in their groups.

The resource is designed so that students work together in small groups to complete the tasks associated with each Workshop. The authors recommend groups of 3-5 students, but this will depend on the class size, ability and prior learning. It is recommended that these groups be assigned at (or before) the start of the first class and that the classroom used is a flexible space that allows students to sit near to each other and allow conversation without the need for raised voices. Students should then be asked to sit in their groups for each class. If at all possible, each group should have access to a laptop with internet access so that the wiki can be updated during each Workshop, but this is not a requirement. A computer lab is required for the first part of Workshop 2 and student access to nearby computer facilities is strongly recommended for all Workshops.

Groups must be allocated at the start of Workshop 1. It is a good idea to ask the groups to choose a name and design a logo for their team as, in practice, this has been found to work as a good ice-breaker. Advise the students that there are 3 roles that must be assigned to group members each week on a rotating basis: Chair, Reporter and Editor. The Chair will prepare the agenda for meetings, will lead/run the group meeting/discussions, listen with an open mind to all group members, and ensure that everyone in the group has the opportunity to contribute. The Reporter should prepare a summary of the action items arising from discussions and meetings and must post these on the group wiki before the next Workshop. The Editor will review the wiki content to ensure a consistent style, coherency and an overall structure; he / she will also liaise with authors when changes to content are required. Each student should adopt each role at least once during the Workshops (an Editor is not required for Workshop 1). Remind the students to nominate these roles at the start of each new Workshop.

Students' email addresses should be collected at the outset of the module and used to set up each group wiki. At the latest, the each student must be invited to join his or her group wiki before the beginning of Workshop 2.

Once the Workshops are underway, it is recommended that you ask the students to stop what they are doing 20 minutes before the end of each 2 hour Workshop or 10 minutes before the end of a 1 hour Workshop. Ask the students to identify all tasks that need completing before the next Workshop, to review the description of the following Workshop and to arrange a date and time to meet outside of the class contact

time. It may be a good idea to ask a spokesperson from each group to very briefly summarise the progress of the group to the class (if there are a large number of groups, each group can take turns to feed back over the course of the module).

Experience in delivering these and similar workshops has demonstrated that a ratio of one tutor to 15 students (5 groups of 3) is most effective. Even so, it is not easy to ensure that equal time is spent with each group due to the nature of the C/PBL approach and tutors must do their best to ensure this is the case. If involved in a particularly interesting discussion with one group that merits more time, it may be a good idea to open up this discussion up to the entire class and in that way include all students. If a group has a problem that requires a significant proportion of your attention (e.g. the group is not functioning as a team, the students do not understand the tasks), it may be wise to meet with that group outside of normal contact time.

Implementation: Tools to Support the Resource

In addition to the group wikis that the students will produce, it is strongly recommended that a Virtual Learning Environment (or a 'central' wiki to which all students are invited) is used to support this module. This will allow the tutor to host the Student Guide, supplementary material (presentations, student handouts, weblinks) and any other information that is deemed appropriate, on a central resource that all the students can access. It also provides a discussion board that may be useful in implementing the resource (providing reminders of tasks to be completed and deadlines, etc).

In addition to the Appendices to this Guide (which contain student handouts, notes for the tutor, tips and advice, etc), PowerPoint presentations are available to help structure each Workshop. The presentations contain an introduction/overview, a description of associated learning outcomes and a checklist of tasks. They can be adapted to meet the individual needs of the tutor and group (slides can be added, removed or amended). It is recommended that the tutor review all supporting information, the slides and the slide notes in advance of each Workshop.

Implementation: Peer Assessment and Evaluation of the Resource

In Table 2 (Assessment components and suggested weightings), the authors have suggested that a component of the marks for some elements can be awarded by peer assessment. If the tutor decides that this is appropriate, the students should be informed at the start of the module. When peer assessing group work, students can be asked to complete a form in which they rate the frequency and quality of contributions of each individual to the group. However, the authors recommend automation of the process by using peer review software such as CATME (Comprehensive Assessment of Team Member Effectiveness) which is available to download for free at https://engineering.purdue.edu/CATME. This software has been developed with support from the National Science Foundation and a range of statements can be selected for use with a given group. In the description of Workshop 6, a note is included about peer-assessment of presentations and Presentation Evaluation Forms are provided in the Appendices to this Guide.

If the tutor wishes to evaluate the implementation of the resource in his / her own institution, a Resource Evaluation Form is included in the Appendices to this Guide and can be distributed and completed by students at the end of Workshop 7. Useful feedback will also be obtained from the students' individual reflective pieces (see Assessment, below, Workshop 7 and Appendix 8).

Learning Outcomes

The learning outcomes associated with each Workshop are presented in Table 1 and are specific to the context described. In general, on completion of the resource the learner will be able to do the following, within the context provided:

- To explain the principles of drug action.
- To identify drug targets and drug-target interactions.
- To discuss how the structure of a drug can be altered (by chemical modification of a lead compound or de novo synthesis of analogues) and explain how such changes may affect activity.
- To differentiate between various compounds in terms of the possible effect of functional groups on binding interactions and physiochemical properties.
- To explain the importance of considering drug metabolism and the physicochemical properties of drugs in the early stages of drug design, including the use of Lipinski's rule of 5 and alternatives to predict oral availability.
- To propose synthetic routes (by chemical modification of a lead compound or de novo synthesis of analogues) to a new drug.
- To interpret IC_{50} data in order to determine the effectiveness of a compound in the context of SAR studies and to critically evaluate the use of data reported in the literature.
- To be aware of the need for and types of assays used for the biological evaluation of compounds in the context of SAR studies.
- To describe the stages of drug discovery and development, and be aware of the timelines involved.
- To critically evaluate the use of high throughput screening and parallel synthesis as tools in the development of new drugs.
- To be aware of the issues of drug resistance and the problems it causes.
- To gain an appreciation of the importance of the study of medicinal chemistry and how it impacts on everyday lives.

Transferable Skills Development

Students will be asked to reflect on the development of the following skills at the end of the project:

- Problem solving: Learners work in groups to address the brief presented in the context scenario.
- Team work: Learners work in teams to complete the tasks assigned, using a wiki to facilitate collaboration and meeting between Workshops to review progress.
- Information technology skills: learners use a wiki to collaborate and develop their ability to use word-processing, presentation, chemical drawing and database software.
- Professional skills: Learners adopt a professional role and construct a report in the form of a 'research proposal' in keeping with the context. This requires adherence to a strict word limit and incorporation of relevant information only. Learners are also required to adhere to deadlines.
- Independent learning: Learners can justify decisions, assumptions and conclusions made with reference to supporting documents and literature in order to produce a logical and clearly reasoned scientific proposal.
- Communication: Learners will be able to produce an abstract for a scientific and lay audience and grant proposal and be aware of the requirements to use the appropriate language and terminology in each case.
- Information retrieval and literacy: Learners must find and use relevant information in order to complete the research proposal.
- Metacognition: Learners reflect on the process involved in preparing the group proposal, the extent to which the stated learning outcomes were met and to which their transferable skills were developed.

Recommended Texts and Reference Materials:

In this section a number of texts, articles and weblinks are listed. A similar list is presented in the Student Guide and can be edited as appropriate. Note that other useful references and weblinks are given throughout the resource (under relevant sections of the Tutor Guide and in the slide notes of the accompanying PowerPoint presentations).

One or more of the following two text books are suitable introductory texts and can be recommended to the students at the start of the project and were used by the authors in compiling this resource. They provide a good introduction to medicinal chemistry:

- An Introduction to Medicinal Chemistry, G. Patrick, 4th edition, Oxford University Press, Oxford, England (2009).

  This text is aimed at undergraduates and graduates with a basic grounding in chemistry. It builds on the history of drug development, but does not assume much background knowledge. Section A covers the basic principles and techniques of medicinal chemistry, while section B focuses on a selection of specific topic areas such as antibacterial agents and opium analgesics.

- Medicinal Chemistry: An Introduction, G. Thomas, 2nd edition, Wiley and Sons, Chichester, England (2007).

  This introduction to medicinal chemistry focuses on the interdisciplinary nature of rational drug discovery, organising the chapters by biochemical and pharmaceutical fields rather than by drug classes. Topics covered include physicochemical considerations regarding drug candidate bioavailability, approaches to identifying lead compounds, quantitative structure−activity relationships in drug design, combinatorial syntheses and high-throughput screening, membrane theory, receptors and messengers, enzymes as targets, and pharmacokinetic modelling/metabolism.

Additional text books that may be useful include:

- In Quest of Tomorrow's Medicines, Drews, J., Springer Verlag, New York (2003).
- The Rise and Fall of Modern Medicine, Le Fanu, J., Carol and Graf Publishing (2001).
- Foye's Principles of Medicinal Chemistry, 6th edition, Lemke, T.L., Williams, D.A., Lippincott, Williams and Wilkins, Philadelphia (2007).
- The Organic Chemistry of Drug Design and Action, 2nd edition, Silverman, R.B., Academic press, San Diego (2004).
- Drug Discovery: Past, Present and Future, Sneader, W., John Wiley and Sons, Chichester (2004).
- The Practice of Medicinal Chemistry, 3rd edition, Wermuth, C.G. Academic Press London (2008).

Detailed notes about the medicinal chemistry of 4-AQ are provided for the tutor (Notes for Tutor) in the Appendices to this Guide organised according to Workshop. Three reviews (listed below) were the main source of the information used to compile the core resource and the tutor notes. It is not anticipated that these reviews would be given directly to students since most of the information required to design the SAR study is provided in the student handouts.

- Quinoline Antimalarials, Timothy J Egan, Expert Opinion on Therapeutic Patents, Vol. 11, No. 2 , 2001, Pages 185-209

  This review discusses the relevant patents and scientific literature concerning quinoline antimalarial treatments, their mechanism of action, mechanism of resistance and structure-function relationships. It provides a brief history of current antimalarial drugs and describes some features about their use, occurrence of drug resistance, their metabolism and known adverse effects. Recent advances in our

understanding of the mechanism of action of 4-aminoquinolines, quinoline methanols and 8-aminoquinolines are discussed as is the current state of knowledge regarding the mechanisms of drug resistance. The review emphasises advances made between 1997 and 2001.

- Quinolines and structurally related heterocycles as antimalarials. K. Kaur, M. Jain, Meenakshi, R. P. Ravi, R. Jain, European Journal of Medicinal Chemistry, Vol. 45, No. 8, 2010, Pages3245-3264

  This review provides an overview of the study of quinolines and also other heterocycles, structurally similar to the quinolines, of interest for the treatment of malaria. It consists of discussion on the biological activities, structure–activity relationships, and potential biochemical pathways of 4-aminoquinolines, 4-anilinoquinolines, 8-aminoquinolines, quinolines from nature, quinolones, isoquinolines and tetrahydroquinolines, ring-modified quinolines, and miscellaneous quinolines.

- A Medicinal Chemistry Perspective on 4-Aminoquinoline Antimalarial Drugs, P. M. O' Neill, S. A. Ward, N. G. Berry, J. P. Jeyadevan, G. A. Biagini, E. Asadollaly, B. K. Park and P. G. Bray; Current Topics in Medicinal Chemistry, Vol 6, No. 5, 2006, Pages 479-507.

  A broad overview is presented describing the current knowledge and the ongoing research concerning the 4-aminoquinolines (4-AQs) as chemotherapeutic antimalarial agents. Discussions cover the mechanism of action, structure activity relationships (SAR), chemistry, metabolism and toxicity and parasite resistance mechanisms. Current development of new lead compounds is described along with an overview of physicochemical properties of chloroquine and amodiaquine analogues.

Online resources that can be made available to students via a VLE or central wiki include:

- Medicines for Malaria Venture website: http://www.mmv.org/

  MMV, is a not-for-public-private partnership, established in 1999 with the mission to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating delivery of new, effective and affordable antimalarial drugs. The website's "information for scientists" section provides useful background information for students on the drug development process

- Roll Back Malaria Partnership website: http://www.rbm.who.int/

  The RBM Partnership is the global framework to implement coordinated action against malaria. It was launched in 1998 by WHO, UNICEF, UNDP and the World Bank, in an effort to provide a coordinated global response to the disease. RBM's overall strategy aims to reduce malaria morbidity and mortality by reaching universal coverage and strengthening health systems. The website provides access to a number of publications, photos, audio public service announcements and video clips about malaria, produced by its partners.

- World Health Organisation website: http://www.who.int/topics/malaria/en/

  The WHO malaria topic area provides an overview of the disease, including its symptoms, treatment and impact on society, and access to more detailed resources for research purposes.

- World Health Organisation website, World Malaria Report 2011, http://www.who.int/malaria/world_malaria_report_2011/en/index.html

  The *World Malaria Report 2011* summarizes information received from 106 malaria-endemic countries and a range of other sources.

- YouTube video about the AntiMal Consortium: http://youtu.be/RWST6Iq4VcI

AntiMal (http://www.antimal.eu/) is an integrated project comprising leading groups of malaria researchers with expertise in malaria biology, chemotherapy and drug development. The aim is to exploit new scientific and political opportunities to secure the development of a portfolio of viable novel antimalarial drugs. The video provides an overview of the history of malaria treatment, the lifecycle of the disease and the challenges of research into new treatments.

- Malaria Atlas Project: http://www.map.ox.ac.uk/

  The Malaria Atlas Project aims to disseminate free, accurate and up-to-date information on malaria and associated topics, organised on a geographical basis. This should give students a clear image of the areas most affected by malaria.

- ChemSpider, The free chemical database: http://www.chemspider.com/

  This database provides access to over 26 million structures, properties and associated information.

- DrugBank, Open Data Drug and Drug Target Database: http://www.drugbank.ca/

  The DrugBank is a bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information. The database contains 6711 drug entries including 1447 FDA-approved small molecule drugs, 131 FDA-approved biotech (protein/peptide) drugs, 85 nutraceuticals and 5080 experimental drugs.

- New Scientist 'Why we mustn't let malaria defences crumble', 22/06/09, http://www.newscientist.com/article/mg20227136.200-why-we-mustnt-let-malaria-defences-crumble.html (requires subscription to access full content)

  The article discusses issues surrounding the evolving resistance of malaria parasites to drugs and the importance of combinatorial treatment methods to prevent this occurring.

Workshop Content

In this section, a detailed description of the content of each Workshop (tutor and student tasks) is provided, including a list of supporting materials. This amount of detail may seem a little daunting at first and tutors are advised to have a stepwise (i.e. week by week) approach to implementing these Workshops for the first time. Table 1 provides a summary of the detail contained within this section.

Workshop 1: Introduction to the Context and Abstract Writing

Duration: All Workshops will take approximately. 2 hours to complete

Part 1: Introduction to the Context and Problem (Allow 40 minutes)

This will allow time to introduce the context and problem. The introduction will give an outline of the overall student activity, protocols for assessment, module timeline, desired learning outcomes, and will allow group allocation and distribution of the Student Guide and handouts.

The following supplementary material is available and should be of use in running this part of the Workshop:

- PowerPoint presentation: Intro to Molecules against Malaria Tutor Presentation (contains quick interactive quiz 'What do you know about malaria?' and slide notes accompany each slide and should be read in advance).
- Tutor notes (Useful Information and Historical Perspective on the Development of 4-AQs, Background Information).
- See Table 1 for summary of aims, activities and learning outcomes.

Part 2: Writing an Abstract (Allow 1 hour)

Students will be required to read a Chemistry World article which is accessible online (Malaria No More, V. Gill, Chemistry World, April 2008, 50-55, see http://www.rsc.org/images/MALARIA_tcm18-116487.pdf or http://www.rsc.org/chemistryworld/Issues/2008/April/MalariaNoMore.asp). This article expands on many aspects of the context introduced above, discussing malaria in terms of cause, global impact and the efforts to eliminate it, an overview of the life cycle of the parasite, the stage in this life cycle where antimalarial 4-AQs (such as chloroquine) are effective, an overview of the mode of action of chloroquine, and the problem of chloroquine resistance.

In part 2 of this introductory session, the importance of an effective abstract will be examined. This is to ensure that students have a clear understanding of how to prepare an abstract in preparation for the research proposal. Guidelines for preparing abstracts are provided in the Student Guide, Appendix 1 and a PowerPoint presentation on this topic is available.

In summary, students will use the Chemistry World article provided (Malaria No More, V. Gill, Chemistry World, April 2008, 50-55) to discuss and determine the important information that should be included in an abstract. The key points and the order in which they should appear will be discussed by the class and the planned abstract can then be compared to a sample abstract provided in the Appendices to this Guide. As a class, the students then suggest amendments to the abstract to suit a predetermined audience (a lay audience instead of an audience with a science education). Amendments should be justified and discussed.

Students can be asked to read the article before they come to the class so that they are prepared for this Workshop.

The following supplementary material is available and should be of use in running this part of the Workshop:

- PowerPoint presentation: Molecules against Malaria_Antimalarial Workshops 1-7 Tutor Presentation.
- Sample abstract (given in the Appendices to this Guide).
- It is useful to have a dictionary available so that students can look up unfamiliar terms.
- Some links to newspaper articles (broadsheet and tabloid) are provided here.

  http://seattletimes.nwsource.com/html/health/2004261357_malaria05m.html
  http://www.telegraph.co.uk/health/7878524/Why-cant-we-rid-the-world-of-malaria.html
  http://www.mirror.co.uk/3am/celebrity-news/cheryl-cole-has-malaria-dr-miriam-233475
  http://www.dailymail.co.uk/tvshowbiz/article-1293071/Nadine-Coyle-urges-prayers-Cheryl-Cole-spends-fifth-day-hospital-battling-malaria.html

Tasks for Tutor:

Part 1

- Allocate groups, request student email addresses and explain the roles of Chair, Reporter and Editor. Ask students to nominate the roles for Week 1 (Editor not needed until Week 2).
- Distribute the Student Guide, Internal Memo #1 and Molecules against Malaria Call for Proposals.
- Use the PowerPoint presentation to introduce the context and explain the student activity, assessment protocols, timeline and desired learning outcomes of resource.
- Distribute the Chemistry World article. The students should be given time to read the article if it was not circulated in advance of the Workshop.

Part 2

- PowerPoint presentation on preparing abstracts is provided and should be discussed with students.
- Ask students to highlight the information in the article that they think will be relevant to produce an abstract.
- Ask the students (in their groups) to discuss and highlight the key points from the article that they believe should be included in the abstract.
- Ask for feedback from each group (several points should be requested from each group, depending on class size, until approximately 15 have been collected). Record the points on the board and discuss their relevance with the class.
- The class must then decide if any points should be excluded, if any are missing and the order in which they should be presented in an abstract. It is useful to point out that the order will be similar but not necessarily the same as in the article as it is important to structure the abstract so that it is a "stand-alone" piece.
- Distribute the sample abstract provided and note the length of the abstract. You should check to see which points from the abstract plan prepared by the class are included. Also, note any differences.
- Discuss the vocabulary and terminology used in this article. Ask students to suggest amendments to the abstract to suit a lay audience instead of an audience with a science education.
- If there is time, some sample newspaper articles about malaria may be provided. Discuss how they vary in style from each other and from the original article.
- Before the end of the Workshop, ask students to read the learning outcomes associated with the Workshop in the Student Guide and PowerPoint presentation. Students should use these as a checklist to ensure that they have identified the appropriate information from the article, and are in a position to begin their research.
- Before the next Workshop: Invite the students to join the appropriate group wikis and update the VLE/central wiki.

Tasks for Students to Complete During Workshop 1:

- Start group work: Move to sit close to other group members, select a name and logo (if required), and nominate the Chair and Reporter.
- Read and understand the article on malaria provided. Discuss any new terms with group members and the tutor. The tutor may direct students to the appropriate reference source.
- Highlight or prepare a list of the main points to be included in the abstract.
- As a group, feed back to the class some of the highlighted points. Once all the points have been recorded on the board, decide if any points should be excluded, if any are missing and the order in which they should be presented in an abstract.
- Critique the sample abstract provided, comparing it to the one planned by the class. Note its length.
- If time, read the newspaper articles provided and discuss the differences in the style of writing between the articles.

- As a class, consider how the abstract could be modified to suit a lay audience.
- Provide an e-mail address to the tutor so that the wiki for your group can be set up before Workshop 2.
- Arrange a time when the group will have a short meeting to review progress before the next Workshop.

Tasks for Students to Complete Before Workshop 2

- Review all the material distributed in Workshop 1 including the Student Guide and in particular the assessment criteria and activity schedule provided. Review Memo (#1) and the Call for Funding provided and ensure that the overall brief is understood.
- Meet as a group to review progress and assign tasks.
- Carry out research as part of a group on areas relevant to the grant proposal.
- Save a typed summary of the research carried out (approximately half a page) in advance of the next Workshop and have it available to add to the group wiki.

It is suggested that students can consult the library website for guidelines on carrying out a search of the relevant literature or read Section 4 on Information Retrieval in Key Skills for Scientists, Royal Society of Chemistry, 2009 (http://www.rsc.org/images/Updated_Skills_2010_tcm18-193493.pdf) and Chapter 5 of "Study and Communication Skills for the Chemical Sciences"; Overton, T., Johnson, S., Scott, J.; Oxford University Press (2011).

Desired Learning Outcomes from Workshop 1:

On completion of this Workshop the students will able to:

- Understand the context based scenario and be aware of how the module will be assessed.
- Gain an awareness of the global impact of malaria and empathise with populations that live with the threat of this disease.
- Recall the life cycle of the malaria parasite that causes the disease and the relevance of this to developing new antimalarial drugs.
- Identify chloroquine and its proposed mode of action.
- Be aware of the issue of chloroquine resistance and the problems it causes.
- Construct an abstract and assess the relevance of information within articles.
- Gain an awareness of the need for scientists to communicate with a lay audience and discuss how this may be achieved.

Workshop 2: Tools to Support the Project (and to Monitor Group Work) and the Relationship Between Chemical Structure and Biological Activity.

Part 1: Introduction to Using a Wiki as a Tool to Support and Assess the Workshops (Allow 30-40 mins)

A computer lab is recommended for the first part of this session and student access to nearby computer facilities throughout would be ideal for all Workshops. Some students may be encouraged to bring their laptops to class (particularly where wireless internet is available), but this is obviously at the discretion of both students and tutors concerned.

This Workshop will explore the uses and versatility of wikis and sets out protocols for the wiki based project. All members of each group will have received invitations to their wiki by e-mail. Uploading files and editing page details can be practiced at this stage. Guidelines on using a wiki are provided in Appendices of both this Guide and the Student Guide.

Most wikis allow conversion of the document to PDF form. In this manner, the students' wikis can form their final proposal and they may not be required to produce another, separate document. You may prefer students to copy and paste the relevant sections of the proposal into a Word® document, allowing a word count if your wiki software cannot provide one. It is important that during, or very soon after, this Workshop each group set up their wiki appropriately, correctly identifying the page headings in line with the required content of their final proposal. They can then begin to populate it over the next few Workshops.

NOTE: An alternative approach is to arrange wiki training for the tutor and students by a third party through the Learning and Teaching centre at your institution.

Part 2: The Relationship between Structure and Activity (Allow 1 hour)

Students will be provided with the appropriate information (in the form of Report Part A: 4-AQ and Related Antimalarials and Internal Memo #2) to allow them to become familiar with the structures of 4-aminoquinolines and to interpret the outcome of previous SAR studies of 4-aminoquinolines. From the information provided they will be required to:

- Identify a possible pharmacophore.
- Suggest likely drug target and binding interactions.
- Give a detailed description of the mode of action of 4-aminoquinolines.
- Suggest how 4-aminoquinolines could be chemically modified in a SAR study while still retaining the pharmacophore.
- Discuss the nature and reliability of the biological data provided.

The following supplementary material is provided and should be of use while running this Workshop:

- PowerPoint presentation: Molecules against Malaria_Antimalarial Workshops 1-7 Tutor Presentation (and slide notes).
- Guidelines concerning the use of wikis are in the Appendices to both Guides.
- Tutor notes.
- See Table 1 for summary of aims, activities and learning outcomes.

Tasks for Tutor

Part 1

- Remind the students to select a Chair, Recorder and Editor.
- Remind the students to read the guidelines provided for using a wiki, particularly the section on 'netiquette'.

- Ensure that students are using the proposal guidelines provided (Workshop 1, Call for Funding) to identify headings for the pages of the wiki and are able to set it up correctly (i.e. when adding pages to the wiki it is important they remember that they should be aligned with the sections of the final proposal that they have been asked to produce – refer to screenshot in the Appendix 3). Make sure that they include a wiki page for Group Planning and Communication with sub-headings / links to pages for submitted work, project planning & meetings, and a bibliography (see screenshot in Appendix 3).
- Remind the students that the wiki will become the final proposal and so the content should reflect that of the final proposal. Note that most wiki software allows wikis to be converted to a PDF format, but you should check this is the case with the wiki software that you are using. However, you may request that the final proposal be submitted in the form of a Word® document by cutting and pasting the appropriate sections from the wiki (allowing a word count if your wiki software does not, for example).
- Ensure the students are able to upload files and to link them to the appropriate wiki pages where necessary.
- Ensure that students write a brief comment on every document or item that they upload stating what it is and why it is relevant, so that other members of the group can keep track of each individual contribution and group progress.
- Demonstrate how you can use 'Page History' to monitor individual contributions.

Part 2

- Distribute 'Internal Memo #2' and 'Report Part A: 4-Aminoquinolines and Related Antimalarials'. Ensure that they read the documents carefully since important information is also contained within legends for schemes and figures.
- Ensure that the students use the Student Guide to identify the tasks that need to be completed within the Workshop using the information provided.
- At a suitable point in the Workshop, pause group discussions and lead a whole class discussion (approximately. 10 mins) about the nature and reliability of the biological data provided in Table A1. See Tutor Notes.
- Before the end of the Workshop, pause activities and ask each group to review tasks completed and those that need to be addressed before the next Workshop. Ask the groups to feed back to class.
- **Before the next Workshop,** you will need to review each wiki and provide feedback to ensure that students have correctly identified the areas that need to be addressed for their final proposal. We recommend that you post a comment on each wiki providing brief feedback to the students and allowing you to keep a record of the level of guidance required. See the Appendices to this Guide for suggestions on reviewing the wikis and examples of comments.
- **Before the next Workshop,** update the supporting VLE/central wiki with student handouts, presentations and any other supporting information.

Tasks for Students to Complete During Workshop 2:

- Use the proposal guidelines provided in Workshop 1 to identify headings for the pages of the wiki and set it up accordingly. When adding pages to the wiki it is important that they remember that they should be aligned with the sections of the final proposal that they have been asked to produce.
- Upload files and link them to the appropriate wiki pages where necessary. Begin compiling a bibliography and continue to add to it throughout the project (see wiki guidelines). The wiki should include a brief comment on everything that uploaded stating what it is and why it is relevant so that other members of the group can keep track of each individual contribution and group progress.
- Identify a likely pharmacophore of 4-aminoquinoline antimalarials based on the structures and activities of existing drugs and analogues.

- Identify the part or parts of the compounds that could be altered while still retaining the pharmacophore.
- Identify and describe the proposed mode of action of 4-aminoquinoline antimalarials, identifying the drug target.
- Suggest likely drug target interactions.
- Incorporate this information into the appropriate section of the wiki (if possible during class time).
- Compile a list of actions, people responsible for each action and the dates due in order to complete all of the tasks associated with this Workshop.
- Arrange a time when the group will have a short meeting to review progress before the next Workshop.

Tasks for Students to Complete Before Workshop 3:

- Meet as a group and review progress on the actions assigned. Post a short summary of the meeting (date, time, those present and action items resulting).
- Continue to carry out research as part of the group on areas relevant to the grant proposal.
- Continue to update and edit the wiki by uploading files, posting summaries and responding to contributions from other group members.

Desired Learning Outcomes from Workshop 2:

On completion of this session the student will able to:

- Log in and edit a wiki page, upload files and add comments.
- Collaborate with other members of a group using the wiki and organise a list of actions for the group's activity.
- Explain how the wiki will contribute to the overall assessment of the project.
- Give an overview of the structures and mode of action of clinically useful 4-aminoquinoline antimalarial drugs.
- Identify attributes of a pharmacophore and explain how chloroquine and related antimalarials interact with their target, identifying relevant binding interactions.
- Explain the outcome of previous SAR studies.
- Critically evaluate the reliability/limitations of biological data used.

Workshop 3: Designing and Planning a SAR Study

Selection of a lead compound, appropriate biological assay(s) and the synthetic routes to new compounds.

Overview:

In this Workshop, Report Part B: 4-AQ and Related Antimalarials and Internal Memo #3 will be presented to the students. The report contains information about the synthetic routes to known and clinically useful 4-aminoquinolines and on the biological assays that could be employed for a SAR study. The students will also be provided with information that will allow them to determine the time required for each synthetic step and each assay which will be required in Workshop 4.

From the information provided in this and previous Workshops students will be required to:

- Select a lead compound and justify the selection.[#]
- Propose chemical modifications of the lead compound to afford new 4-AQs.
- Suggest a synthetic route to the new 4-AQs and identify commercially available starting materials.
- Propose a method or methods for biological evaluation of the new 4-AQs.

The following supplementary material is provided and should be of use while running this Workshop:

- PowerPoint presentation: Molecules against Malaria_Antimalarial Workshops 1-7 Tutor Presentation (and slide notes).
- Tutor Notes.
- See Table 1 for summary of aims, activities and learning outcomes.

[#]See Tasks for Tutor, below, for more information about lead selection.

Note that this is a very demanding Workshop and students will need to be organised and work hard to complete all the tasks associated with it. It may be necessary to remind students that later Workshops have fewer tasks associated with them (particularly Workshops 5 and 6). There will be time to review and amend work in these later Workshops.

Tasks for Tutor:

- Remind the groups to select the Chair, Recorder and Editor for the week and to refer to the appropriate section of the Student Guide.
- Demonstrate the use of an online chemical catalogue, including any advanced and structure-based search features.
- Distribute the Internal Memo #3 and Report Part B: 4-Aminoquinolines and Related Antimalarials.
- Refer to the Student Guide and ask students to identify the tasks that need to be completed within the Workshop and to briefly review those that need to be done before the next Workshop.
- Selection of a lead compound, this can be done in a number of ways but we propose 4 options:
    1. Allow each group to select their own lead compound from those provided asking them to explain their selection **(preferred by the authors)**.
    2. Assign each group a different lead compound from those provided in Antimalarial Workshop 2.
    3. Ask the entire class to use a short chain chloroquine analogue as the lead compound.
    4. Assign groups either a short chain chloroquine analogue or amodiaquine as lead compounds.

  If using methods 2-4, a class discussion arriving at the definition of the term ‘lead compound’ and the reasons for the selection of the lead may be appropriate to ensure the learning outcomes are met. See Tutor Notes.

- Assign each group the number of target compounds that you wish them to propose for the SAR study. One target compound per group member is advised by the authors, but the tutor may wish to change this in line with the prior knowledge and experience of the class concerned.
- Before the end of the Workshop, pause activities and ask each group to review tasks completed and those that need to be addressed before the next Workshop. Ask the groups to feed back to the class.
- At the end of this Workshop and in advance of Workshop 4, you will need to recommend a textbook or section of an appropriate text giving a broad overview/introduction to pharmacokinetics.
- **Before the next Workshop,** you will need to review each wiki and provide feedback to ensure that students have correctly identified the areas that need to be addressed for their final proposal. We recommend that you post a comment on each wiki providing brief feedback to the students and allowing you to keep a record of the level of guidance required. See the Appendices to this Guide for suggestions on reviewing the wikis and examples of comments.
- **Before the next Workshop,** update the supporting VLE/central wiki with student handouts, presentations and any other supporting information.

Tasks for Students to Complete During Workshop 3:

- Read Internal Memo #3 and Part B of the report.
- If students have not been assigned a lead compound by the tutor, the first task is to select a lead compound and provide reasons for the selection. If possible, the structure of the lead compound and a justification for the selection should be uploaded onto the wiki during the Workshop.
- In Workshop 2, students identified the part or parts of 4-AQs that could be altered while still retaining the pharmacophore. Using this information and Part B of the report provided, students should discuss possible chemical modifications that they can make to the lead compound in order to produce 'novel' 4-AQs.
- Propose structures of target compounds for the SAR study and discuss these with the tutor.
- Suggest synthetic route(s) to the target compounds ensuring, where possible, that they begin from commercially available starting materials.
- Discuss the biological assays described and select one or more. Amongst other things, students should consider time and cost. Students must justify the selection.
- Incorporate this information into the appropriate section of the wiki (if possible during class time).
- Compile a list of actions, people responsible for each action and the dates due in order to complete all the tasks associated with this Workshop.
- Arrange a time when the group will have a short meeting to review progress before the next Workshop.

Tasks for Students to Complete Before Workshop 4:

- Read the pharmacokinetics section of the recommended text(s).
- Meet as a group and review progress on the actions assigned. Post a short summary of the meeting (date, time, those present and action items resulting).
- Continue to carry out research as part of the group on areas relevant to the grant proposal.
- Continue to update and edit the wiki by uploading files, posting summaries drafting sections of the proposal and responding to contributions from other group members. Remembering to add comments to explain why particular files and links that they uploaded are relevant.

Desired Learning Outcomes from Workshop 3:

On completion of this session the student will able to:

- Recall the mode of action of the lead compound.
- Explain what is meant by the term ‘SAR’ and describe the steps involved in carrying out an SAR study.
- Explain what is meant by the term ‘lead compound’.
- Suggest suitable molecular modifications of the lead compound and propose synthetic route(s) for achieving these.
- Discuss the importance of selecting a suitable bioassay for a SAR study.
- Use a chemical catalogue to source commercially available materials.

Workshop 4: Pharmacokinetics and Timelines for the Drug Discovery and Development Process.

Part 1: Pharmacokinetics (Allow 1 hour)

This Workshop asks students to consider the impact of the study of drug pharmacokinetics on the early stages of the drug discovery and the development of successful pharmaceutical agents. Students will be provided with Part C of the Report summarising the pharmacokinetics of known 4-AQ antimalarials (in particular chloroquine and amodiaquine) and asked to analyse the target compounds in light of this and information obtained from their own reading.

Students will then be asked to:

- Analyse the structures of the target compounds using Lipinski's rule of 5.
- Estimate the Polar Surface Area (PSA) using appropriate software and determine the number of rotatable bonds.
- Predict whether the target compounds would be orally available drugs.
- Predict how the target compounds would be metabolised.

The information concerning the pharmacokinetics of the target compounds should be summarised in the form of an internal memo and emailed or delivered in hardcopy to the tutor(s) with the completed worksheets for each compound. Relevant material should also be incorporated into the appropriate section of the group wiki.

Part 2: Timelines (Allow 40 mins)

Students will also be asked to produce a Gantt chart as a tool for planning and presenting the timeline for the SAR study. The information required to produce the chart can be obtained from Report Part B (Antimalarial Workshop 3). Finally, students are also asked to estimate the time it would take to bring a successful target compound from 'bench to bedside'.

Students will be asked to:

- Produce a Gantt chart.
- Estimate time to take target compound to clinical use.

The following supplementary material is provided and should be of use while running this Workshop:

- PowerPoint presentation: Molecules against Malaria_Antimalarial Workshops 1-7 Tutor Presentation (and slide notes).
- Tutor Notes.
- Template for drug-likeness analysis and sample Gantt chart (Appendices of this Guide and Student Guide).
- See Table 1 for summary of aims, activities and learning outcomes.
- Weblinks for free access, online drug-likeness calculators if no in-house software available:

Drug-Likeness Calculators (free online, for PSA and c Log P):

- http://www.molsoft.com/mprop/
- http://www.organic-chemistry.org/prog/peo/ (OSIRIS Property Explorer)

Note that the next Workshop (Antimalarial Workshop 5) has fewer tasks associated with it and, therefore, time should be available in Workshop 5 to address any tasks not completed in Workshops 2-4.

Tasks for Tutor:

- Remind the groups to select the Chair, Recorder and Editor for the week and to refer to the appropriate section of the Student Guide.

- Direct students to freeware for drug-likeness calculation if no in-house version available.
- Distribute the Internal Memo #4, Report Part C: Pharmacokinetics of 4-Aminoquinoline Antimalarials and templates for drug-likeness analyses (several to each group, print template from PowerPoint presentation).
- Let the students know if you wish them to re-evaluate their SAR studies.
- Optional: Provide electronic version of Gantt chart as a template.
- If the students do not submit during the Workshop, a deadline and format (hard copy, via VLE, etc) for submission of the internal memo and drug-likeness analyses worksheets should be stated.
- Before the end of the Workshop, pause activities and ask each group to review the tasks completed and those that need to be addressed before the next Workshop. Ask the groups to feed back to class.
- At the end of this Workshop and in advance of Workshop 5, you will need to recommend a textbook or section of an appropriate text explaining the terms and use of parallel synthesis and high throughput screening in the drug discovery process.
- **By the start of Workshop 5,** provide feedback on the groups' memos and drug-like analyses.
- **Before the next Workshop,** update the supporting VLE/central wiki with student handouts, presentations and any other supporting information.

Tasks for Students to Complete During Workshop 4:

- Read the report provided.
- Complete the template provided for 'Analysis of Drug-Likeness' for each target compound. Students should identify the functional groups, HBD, HBA (hydrogen bond donors and acceptors) and rotatable bonds in the structures.
- Apply Lipinski's rule of 5 to the target compounds identifying any violations. Use the online (or other) drug-likeness calculator to obtain c Log P.
- Use an online calculator to determine the PSA of the target compounds.
- Predict the oral availability of the target compounds based on the above analyses.
- Using the information provided in the report and that obtained from students' own reading, suggest the route by which the target compounds will be metabolised.
- Prepare a memo (no more than one page) summarising the predicted pharmacokinetics and any additional information that is relevant and submit it to the tutor with the completed 'Analysis of Drug-Likeness' sheets.
- ***This stage should only be carried out if there is time (at the tutor's discretion):*** Students may wish to modify the proposed SAR study on the basis of the findings. If possible, students must also propose associated changes to the synthetic route. Proposed changes and justifications must be made by the beginning of Workshop 7.
- Produce a Gantt chart to show the time that it will take to carry out the proposed SAR study. An example of a Gantt chart is provided in the Appendices to the Guides.
- Estimate the time that it would take to take for one of the target compounds to enter clinical use assuming it was successful in all steps of the drug development process. Provide a brief explanation for the answer and cite references used.
- Assign tasks to group members ensuring that all of the information and decisions from this Workshop will be uploaded to and recorded accurately on the wiki in the appropriate section before the next Workshop (bearing in mind that this information will form a large part of the final research proposal).

Tasks for Students to Complete Before Workshop 5:

- Meet as a group and review progress on the actions assigned. Post a short summary of the meeting (date, time, those present and action items resulting).

- Complete the pharmacokinetics section of the wiki/proposal and upload the Gantt chart to the wiki.
- Continue to carry out research as part of the group on areas relevant to the grant proposal.
- Continue to update and edit the wiki by uploading files, posting summaries and responding to contributions from other group members.
- Read the appropriate sections of the recommended text in advance of the next Workshop concerning the use of parallel synthesis and high throughput screening in the drug discovery process (your tutor will advise).

Students should note that the first draft of the proposal should be nearing completion. While there will be an additional task in Workshop 5, there will also be time to review the wiki/first draft of the proposal and address any areas of concern. The deadline for submission of the draft should be during or shortly after Workshop 5.

Desired Learning Outcomes from Workshop 4:

On completion of this session the student will able to:

- Discuss the effect of the study of pharmacokinetics on the early stages of the drug discovery.
- Apply Lipinski's Rule of 5 and the use of PSA/no. of rotatable bond to estimate oral availability of a drug.
- Explain what is meant by the term drug metabolism and describe how 4-aminoquinoline antimalarials are metabolised.
- Plan the time required for a small scale SAR study using a Gantt chart to show the timeline.
- Be aware of the typical stages of the drug discovery and development process and the time that it takes to develop a new drug.

Workshop 5: Parallel Synthesis and High Throughput Screening

Part 1: Parallel Synthesis and High Throughput Screening Evaluation (Allow 1 hour)

The students will be asked to consider the impacts (both positive and negative) that parallel synthesis and high throughput screening (HTS) could have on the proposed SAR study. Students will be provided with sufficient information about a high throughput method reported to be suitable for screening antimalarial 4-AQs in the form of a letter from Inspired Pharmaceuticals Ltd. but otherwise will have to research the topics for themselves. Students will be asked to produce a memo indicating whether they wish to use these tools and to explain their decision. For example, if they choose to avail of these techniques they should describe the impact that they expect them to have and indicate any problems or difficulties that may need to be addressed. If they decide that they do not wish to take advantage of these tools, they must justify their decision in the memo.

Part 2: Student Teams Reviewing Progress and Completing Tasks (Allow 40 mins)

The remainder of this Workshop should be used for consultation with the tutor, review of progress to date, identification of any weaknesses or tasks that are not yet complete and for addressing feedback.

If you allow students to go to the library or computer room, remind them to return 20 minutes before the end of the 2 hour Workshop or 10 minutes before the end of a one hour Workshop.

The deadline for submission of the draft proposal should be during or shortly after this Workshop.

The following supplementary material is provided and should be of use while running this Workshop:

- PowerPoint presentation: Molecules against Malaria_Antimalarial Workshops 1-7 Tutor Presentation (and slide notes).
- Tutor Notes.
- See Table 1 for summary of aims, activities and learning outcomes.

Tasks for Tutor:

- Distribute Internal Memo #5 and attached letter from Inspired Pharmaceuticals Ltd. either at or in advance of the Workshop.
- Students should complete a memo during the first part of the Workshop. If they have found other tools that would be of use in an SAR study (molecular modelling, combinatorial chemistry, QSARs) access to these may be requested in the memo. A brief justification for their use must also be given.
- Remind students that this is the last task and that they should now have all the information required to complete their wiki and research proposal. Ask them to review the guidelines for the proposal and their progress and identify any areas that need further attention.
- Before the end of the Workshop, pause activities and ask each group to review tasks completed and those that need to be addressed before the next Workshop. Ask the groups to feed back to the class.
- **By Workshop 6,** you will be required to provide formal feedback on each group's proposal in the next Workshop and so you should set a deadline for submission of a draft proposal that will give you adequate time to review them. It is recommended that a hard copy (i.e. a PDF version of the wiki) is submitted so that students can continue to update the wiki and so that students have practised conversion of the wiki to a hard copy.
- **Before the next Workshop,** update the supporting VLE/central wiki with student handouts, presentations and any other supporting information.

Tasks for the Students to Complete During Workshop 5:

- Read the information provided.
- Using the information provided and that from the recommended text(s), critically evaluate the impact of parallel synthesis and HTS on the SAR study. In order to do this, they must consider both the positive and negative aspects of their application.
- Write a memo (no more than one page) stating whether or not these tools will be employed in the study, ensuring that a brief summary of the discussions and a justification is given (i.e. stating both advantages and disadvantages regardless of their final decision). Upload the memo onto the wiki during the class, if possible.
- If there are other tools that would be of use in the current study, access to these may be requested in the memo. A brief justification for their use must also be given.
- As a group, review the work to date and identify any weaknesses or areas that need further work. Use the checklist provided in the Appendices to the Student Guide.
- Act on feedback provided from previous Workshops.
- Take a note of the submission date and format for the draft research proposal.
- Compile a list of actions, people responsible for each action and the dates due in order to complete all of the tasks associated with this Workshop and with completion of the draft of the proposal.
- Arrange a time when the group will have a short meeting to review progress before the next Workshop.
- Assign tasks to group members ensuring that the memo is uploaded onto the wiki and that the appropriate sections of the wiki are updated.

Tasks for Students to Complete Before Workshop 6:

- Submit a work in progress summary (maximum one page) listing the areas of the research proposal addressed and which are not complete with details on who is responsible and due dates. Any clarifications required or queries that students have should also be noted. Upload a copy onto your wiki.
- Submit a draft proposal by the deadline in the format requested. It is important that students meet this deadline to allow sufficient time to review the draft and provide feedback.
- Meet as a group and review progress on the actions assigned. Post a short summary of the meeting (date, time, those present and action items resulting).
- Continue to carry out research as part of the group on areas relevant to the grant proposal.
- Continue to update and edit the wiki by uploading files, posting summaries and responding to contributions from other group members.

Desired Learning Outcomes from Workshop 5:

On completion of this session the students will able to:

- Describe what is meant by HTS and parallel synthesis.
- Critically evaluate, by discussing the advantages and disadvantages, the use of HTS and parallel synthesis in SAR studies.
- Identify any other appropriate tools for a SAR study.
- Work effectively as a group to assess progress to date, identify areas of the proposal that require work and plan the final stages of the project.

Workshop 6: Clinic for Formative Feedback

Overview:

This clinic is designed to allow the students to obtain feedback from the tutor on their work to date. Clarification on delivery aspects and protocols for assessment will be reiterated. Question time will be assigned to each group to ensure students are up to date with the work load and expectations. A brief discussion about presentations (and peer assessment if appropriate) should take place. If there is sufficient time, students should begin preparations for their presentation for Workshop 7.

The main aims of this Workshop are:

1. To answer any student queries on the assignment and activities, and to discuss any issues raised.
2. To provide learners with formative feedback (as an entire class and to each group) on which areas of the report they need to work on and which ones have been addressed satisfactorily.
3. Identify the tasks remaining and plan for when they will be achieved.

The following supplementary material is provided and should be of use while running this Workshop:

- PowerPoint presentation: Molecules against Malaria_Antimalarial Workshops 1-7 Tutor Presentation (and slide notes).
- Tutor Notes.
- Checklist for Submission of Final Proposal (Appendices to the Guides).
- Guidelines for oral presentations (Appendices to the Student Guide).
- Information concerning peer evaluation of presentations (see below).
- See Table 1 for summary of aims, activities and learning outcomes.

Tasks for Tutor:

- Provide formal feedback to each group on their draft proposal.
- Remind students of overall aim and the assessment criteria.
- Direct students to the PowerPoint presentation guidelines in the Appendices to the Student Guide. Note that you may allow them to present directly from their wiki instead of creating a PowerPoint presentation, giving them more time to act on feedback and produce their final proposal. You will need to instruct them accordingly. Briefly discuss what is expected (e.g. format and timing of presentation) and remind students that each group member should participate.
- If peer evaluation of presentations is to be used, the students should be briefed at the end of this Workshop and see below.
- Remind students that now the main body of the proposal has been prepared, they should focus on ensuring a good structure, coherence and consistency of style and formatting of the final proposal. If the abstracts were not submitted with the draft, they now need attention. A checklist for submission of the final proposal is provided in the Appendices to the Guides).
- If you have not done so already, give a deadline for submission of the final proposal and the reflective piece.

Tasks for Students to Complete During Workshop 6:

- Act on feedback provided and ask questions if anything is not clear.
- Review work as a group and identify any tasks that need to be completed.
- Complete any outstanding tasks.
- Plan and begin preparations for the presentation.

Tasks for Students to Complete Before Workshop 7:

- Meet as a group to finalise and practice the final presentation. Practise it several times as a "dry run" and ensure it meets the time requirement. Students do not need to post full minutes, but should post a list on the wiki stating who attended the meeting and the tasks completed at the meeting.
- Continue to update and edit the wiki by uploading files, posting summaries, redrafting sections of the proposal and responding to contributions from other group members ensuring that they meet the deadline given by the tutor.

- The structure, coherence, consistency of style and formatting of the final proposal are important considerations at this stage.
- If the abstracts were not submitted with the draft proposal, they now need attention.

Desired Learning Outcomes from Workshop 6:

On completion of this session and the related independent learning hours the students will able to:

- Clarify the expectations for the final Workshop.
- Communicate effectively when receiving formative feedback to ensure that the maximum benefit is obtained.
- Work effectively as a group to:
    - Discuss their thoughts in relation to completion of the assignment.
    - Act on constructive criticism and suggestions.
    - Prioritise the remaining work to be done.
    - Prepare an informative and visually engaging presentation.
    - Identify problems and questions that relate to the assignment and related activities.

Advance Information for Workshop 7: Peer Assessment of Presentations

If using peer assessment students should be briefed a week in advance and shown the forms to be used. Students should be asked to identify strengths as well as weaknesses when peer assessing colleagues and it should be explained that any criticism should be constructive.

Presentation Skills Assessment Forms can be found in the Appendices to this Guide and can be printed two to a page. Both tutor and students can use this form to provide written feedback. Each student should be given one of the forms and should write his or her name in the Speaker/Group position and on the back of the sheet. Students should then be asked to swap forms with a person from another group so that each student will be providing feedback to one other person. The system can be kept anonymous if preferred. In this case, the tutor should collect the forms once the student has inserted his or her name (this is probably best done at the end of Workshop 6 to save time in Workshop 7). The tutor can distribute the forms at the start of Workshop 7, and will collect them following the presentations and pass the completed forms to the student concerned.

Workshop 7: Final Presentations and Feedback

Overview:

This Workshop is designed to allow each group of students to present their research proposals to the class. Each group should be allocated an identical time period to complete the oral presentation and to answer questions from the class and the tutor. Time will be allocated at the end for closing feedback/debriefing from the tutor and students.

The following supplementary material is provided and should be of use while running this Workshop:

- PowerPoint presentation: Molecules against Malaria_Antimalarial Workshops 1-7 Tutor Presentation (and slide notes).
- Checklist for Submission of Final Proposal (Appendices to the Guides).
- Information concerning peer evaluation of group work.
- Resource Evaluation Forms (Appendices to this Guide).
- See Table 1 for summary of aims, activities and learning outcomes.

Tasks for Tutor:

- Remind students of how to behave during the presentations in order to provide a supportive environment.
- Instruct/remind students on the form and purpose of peer assessment, if necessary.
- Provide formal feedback to each group on their presentation (verbally and/or in writing).
- Discuss the purpose of the reflective piece (Guidelines are provided in the Appendices to the Guides).
- Give the deadlines for the submission of the final proposal and the reflective piece.
- Optional: Handout and collect Resource Evaluation Forms (Appendices of this Guide).
- Optional: Request peer assessment of group work (students should have been informed at the start of the module if this is to take place). Prepare forms or set up peer assessment software for each group.

Tasks for Students to Complete During Workshop 5:

- Give an oral presentation.
- Peer-assess the oral presentations of the other groups in the class, if required.
- Ensure that they have discussed and arranged submission of final proposal including the abstracts.
- Complete resource evaluation forms (optional).

Remaining Tasks for Students to Complete for the Module:

- Incorporation of feedback from the presentation into the group report.
- Final editing and completion of group's grant proposal.
- Print out and submit the final proposal. Your tutor may require you to produce the final report as a Microsoft Word document to allow page numbering and a word count check.
- Produce and submit your individual reflective piece (Guidelines are given in the Appendix to this Guide).
- Peer assessment of the other students in your group based on frequency and quality of contributions to the group (optional).

Desired Learning Outcomes from Workshop 7:

On completion of this session the students will able to:

- Present findings in a professional manner.
- Produce a clear and legible PowerPoint (or other) presentation.
- Reflect on the process involved in preparing the group proposal, the extent to which the stated learning outcomes were met and to which the listed transferable skills were developed.
- Work effectively as a group to:
    - Act on constructive criticism and suggestions.
    - Prioritise the remaining work to be done.
    - Identify problems and questions that relate to the assignment and related activities.

Appendices

Appendix 1: Student Handouts for Workshops 1-5

List of Handouts:

Workshop 1:

- Internal Memo #1
- Call for Funding & Proposal Guidelines

Workshop 2:

- Internal Memo #2
- Report Part A: 4-Aminoquinolines and Related Antimalarials

Workshop 3:

- Internal Memo #3
- Report Part B: Synthesis and Biological Evaluation of 4-Aminoquinolines and Related Antimalarials

Workshop 4:

- Internal Memo #4
- Report Part C: Pharmacokinetics of 4-Aminoquinoline Antimalarials

Workshop 5:

- Internal Memo #5
- Letter from Inspired Pharmaceuticals Ltd

Handouts for Workshop 1:

- Internal Memo #1
- Call for Funding & Proposal Guidelines
- Sample Abstract

INTERNAL MEMO #1

Global Health Organisation,
Tropical Diseases Research Centre,
Wainwright House, West Street, Castletown.

Dear All,

We have just been made aware of a funding call for a new research programme entitled “Molecules against Malaria”. The Tropical Diseases Research Centre has been invited to submit an application and the proposal guidelines are attached. This initiative focuses on the development of new quinoline antimalarial drugs, thus I have recommended that the Medicinal Chemistry Research and Development Group be primarily responsible for our application for funding. I have requested that the other departments in the centre provide them with the support required to ensure that all elements of the proposal can be addressed effectively.

I would like to draw your attention to an exciting new element to this programme, in that a major pharmaceutical company, Inspired Pharmaceuticals Ltd., have offered consultation with their drug discovery and design team, and access to state-of-the-art equipment and computer facilities for the teams that are awarded funding.

This is a very exciting opportunity for the centre and I look forward to a progress update on the proposal prepared by the group in due course. In the interim, please report to your group manager if you have any queries.

Yours sincerely,

Rebecca Woodward

Prof. R. Woodward,
Centre Director.

Call for Funding

According to the World Malaria Report, there were 216 million cases of malaria in 2010, resulting in an estimated 655 000 deaths in 2010. Treating and preventing malaria puts a huge burden on those countries least able to shoulder it.

The Molecules against Malaria research programme has just been established with funding from several not-for-profit organisations and government agencies. We are seeking proposals urgently from research and development groups in relation to the development of new 4-aminoquinoline antimalarials to address the development of parasite resistance to existing quinoline drugs.

The applications received will be reviewed by our advisory committee made up of several drug discovery and design experts. Funding will be provided for a three year period, but is subject to satisfactory evaluation on a yearly basis.

The Molecules against Malaria research programme is also supported by Inspired Pharmaceuticals Ltd., as part of their corporate responsibility plan. As a result, groups that submit successful applications will be offered the opportunity of consultation with the Inspired Pharmaceuticals drug discovery and design team, and access to their state-of-the-art equipment and computer hardware and software.

Proposal Guidelines

Each proposal should be a maximum of 2,000 words and should contain the following elements:

- Title of the proposed research project and applicant names.
- A scientific abstract (maximum 200 words).
- A project abstract (aimed at a lay audience, maximum 200 words).
- Project significance; a short summary that addresses why the problem is significant, the benefit of the proposed work to society in the UK / Ireland and in a country of the applicant's choice in which malaria is endemic (maximum 200 words).
- The main body of proposal to include:
    - Aims and objectives
    - Background information (including mode of action, pharmacophore and binding interactions of 4-aminoquinolines).
    - Identification of a suitable lead compound and proposed Structure Activity Relationship (SAR) study.
    - Synthetic route to the target compounds.
    - Consideration of metabolism and oral availability of target compounds.
- References should be formatted according to the Royal Society of Chemistry Publishing author guidelines format. (See page eleven of the document at this link: http://www.rsc.org/images/Guidelines_tcm18-186308.pdf).
- A timeline or Gantt chart for the proposed work, and an estimate of the time it would take for any successful compounds to be brought from the bench to clinical use.

Sample Abstract

Sample abstract of Chemistry World article, "Malaria No More"
(April 2008, pages 50 – 55)

Malaria kills over one million each year, and the battle to eliminate it has been a long one. Recently, there have been some important developments, many of which are linked to the Roll Back Malaria Partnership.

A significant problem that occurred previously was the development of resistance to drugs by the parasite responsible for the disease. To address this, combination drug therapies are now used and more are being developed. As several modes of drug action are involved, resistance is unlikely to emerge. Many of these therapies are the result of public-private partnerships which involve resources and staff contributed from pharmaceutical companies in conjunction with public funding. These partnerships are also active in developing new anti-malarial drugs.

From the perspective of prevention, a big breakthrough is that a malaria vaccine developed by a partnership is about to enter phase III clinical trials. In addition, work is ongoing to monitor the extent of resistance to insecticides of the mosquitoes that carry the parasite and to discover new insecticides.

Other important activities are the provision of kits that will diagnose quickly and easily if someone has the disease, publishing a list indicating which kits are effective, and making available washable insecticide-treated bed nets and approved indoor insect sprays. A new research focus is the investigation of how well treatment and prevention methods fit in with people's lives.

It is hoped that the well-funded, coordinated approach currently in place will result in significant reductions in death rates by 2015.

(246 words)

(Original article: Malaria No More, V. Gill, Chemistry World, April 2008, pages 50-55)

Handouts for Workshop 2:

- Internal Memo #2
- Report Part A: 4-Aminoquinolines and Related Antimalarials

This Workshop requires students to interpret data, which is presented in a similar form to that found in the literature, in order to draw conclusions about the nature of the pharmacophore and the outcome of previous SAR studies. Using the information provided within Report Part A and the Chemistry World article, Malaria No More, the students should be able to propose a reasonable mechanism of action for chloroquine and related 4-aminoquinoline antimalarials.

INTERNAL MEMO #2

Global Health Organisation,

Tropical Diseases Research Centre,

Wainwright House, West Street, Castletown.

Global Health Organisation
Library Information Services

To: Medicinal Chemistry Research and Development Group

Re: Preliminary Research Report Part A: 4-Aminoquinolines and Related Antimalarials

As requested, we have done a preliminary review of the literature and attach a report (Part A) of our findings. Contained within the report is information about how the malaria parasite breaks down host haemoglobin and the acidic nature of the parasite's food vacuole in which this process takes place. We believe that this information will allow you to propose a mechanism of action for 4-aminoquinolines including identification of the drug target, likely binding interactions and to propose an explanation as to why these compounds have been shown to accumulate within the parasite's food vacuole.

The outcome of the biological evaluations that are reported in the literature are given in Table A1 and were obtained from several sources. No single SAR study of this class of compounds was available to us in preparing the report. During our search of the literature, we discovered that many well known 4-aminoquinoline antimalarial drugs, including chloroquine, sontoquine, quinacrine and amodiaquine, were developed in the period from the late 1920s to 1950s and were evaluated directly *in vivo,* however, only more recent *in vitro* data is included in Table 1. While there has always been interest in developing new antimalarial drugs, it was not until chloroquine resistance emerged in the 1960s that the search became urgent. Systematic SAR studies become more prominent in the literature from the early 1980s.

We hope that the information contained within the report will be of use to you in preparing your research proposal. Please contact us with any specific questions that arise during your work and we shall do our best to answer them. Part B of this report will follow shortly.

Yours Faithfully,

Samuel Southern

Dr. S. Southern,

Library Information Services.

Report Part A: 4-Aminoquinolines and Related Antimalarials

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List of Figures

List of Tables

The Malaria Parasite: *Plasmodium*

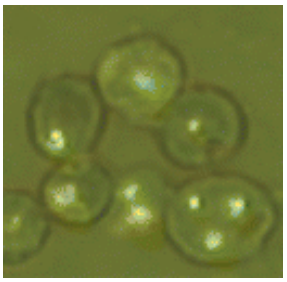


Figure A1: Visible micrograph image showing haemozoin deposits in several parasite infected cells (illuminated by the partial dark-field effect). The infected erythrocyte towards the bottom right corner is triply infected. (From B. R. Wood, A. Hermelink, P. Lasch, K. R. Bambery, G. T. Webster, M. A. Khiavi, B. M. Cooke, S. Deed, D. Naumann and D. McNaughton, *Analyst*, 2009, 134, 1119-1125).

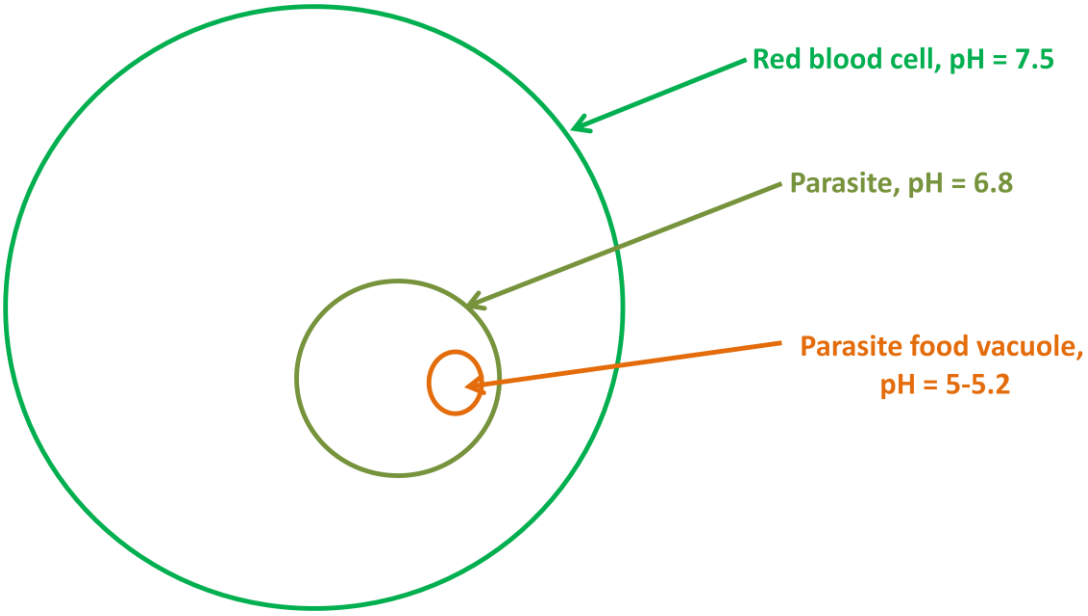
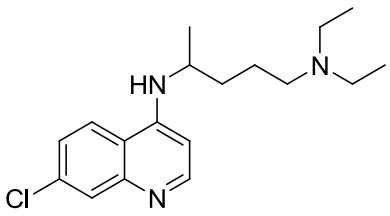


Figure A2: Diagram showing the relative pH values of the compartments of a parasite infected red blood cell. Note the acidic food vacuole within the malaria parasite which is where digestion of haemoglobin takes place. Note the pH gradient.



Chloroquine (CQ)

Figure A3: The structure of chloroquine (CQ), a well known and clinically used antimalarial 4-aminoquinoline which is known to accumulate in the food vacuole of the parasite. The pK_{aH} of the quinolinium cation is 8.55 and the pK_{aH} of the tertiary ammonium is 9.11

The malaria parasite breaks down host haemoglobin to obtain amino acids that it uses for growth. A by-product of this process is haem which is toxic to the parasite and so the parasite polymerises haem to non-toxic crystalline haemozoin. An overview of this process is shown in Figure A4. The synthetic form of haemozoin is called β-haematin (it is structurally identical to haemozoin). The formation of β-haematin from haematin (or a similar precursor) can be observed and measured by UV/vis spectroscopy.

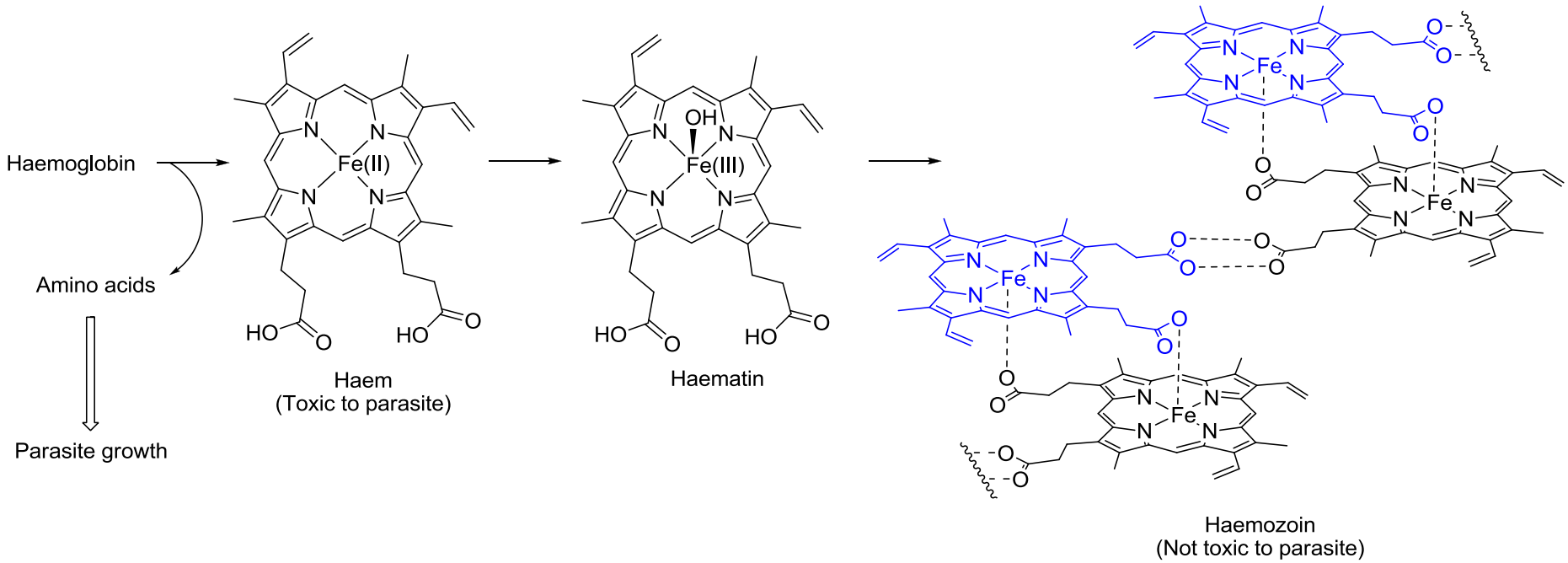


Figure A4: Overview of the breakdown of host haemoglobin by the malaria parasite (*Plasmodium*) to afford amino acids used for parasite growth and non-toxic haemozoin.

Structures of Antimalarial 4-Aminoquinolines (4-AQs) and Related Acridines

All of the compounds shown have been or are currently used clinically to treat malaria.

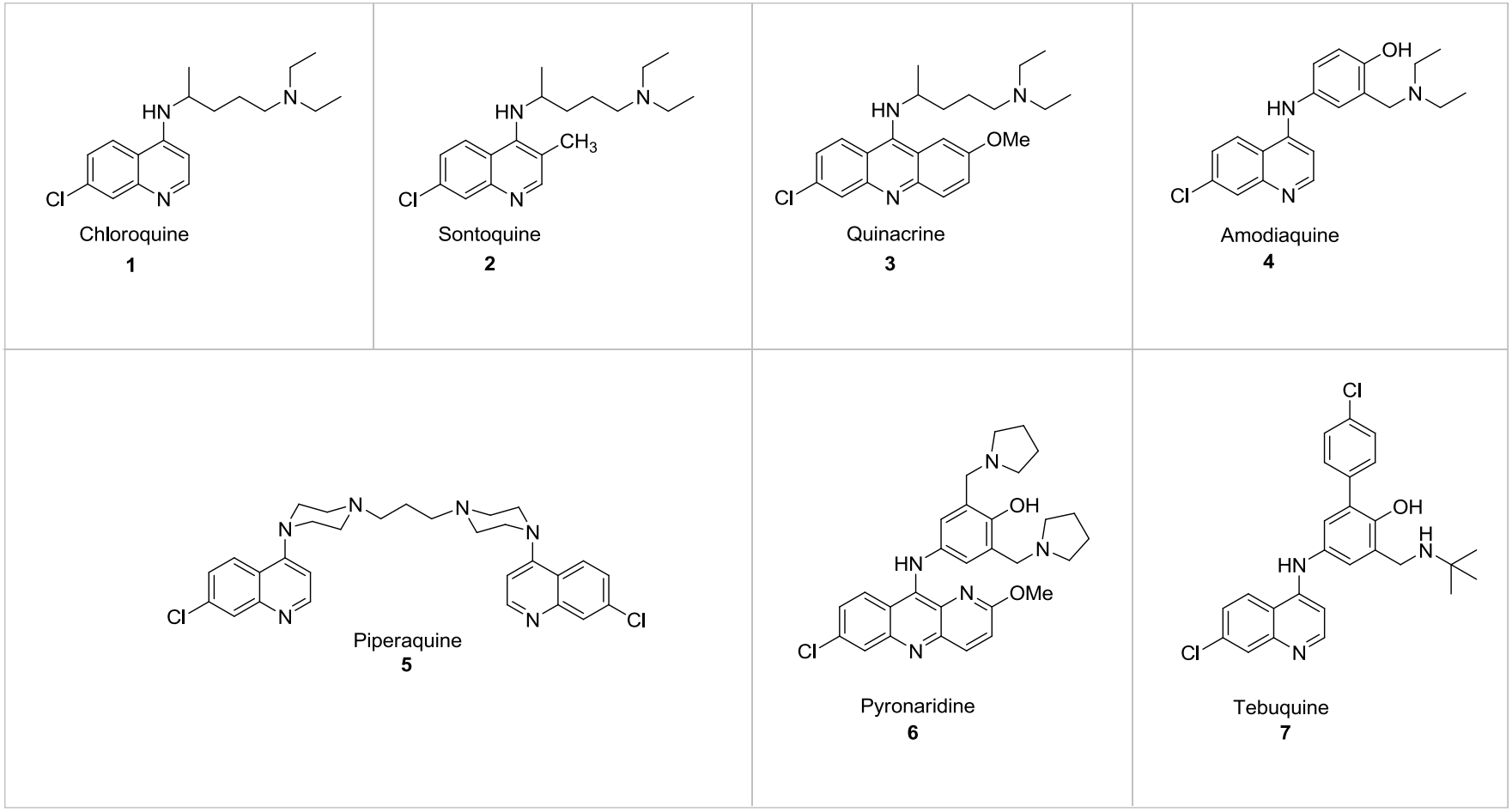


Figure A5: Structures of antimalarial 4-aminoquinolines (4-AQs) and related acridines.

Structures of 4-AQs and Related Compounds

The following compounds have been reported in the literature. They are taken from a number of sources. Each has received some attention as part of ongoing investigations to develop new 4-AQ antimalarials.

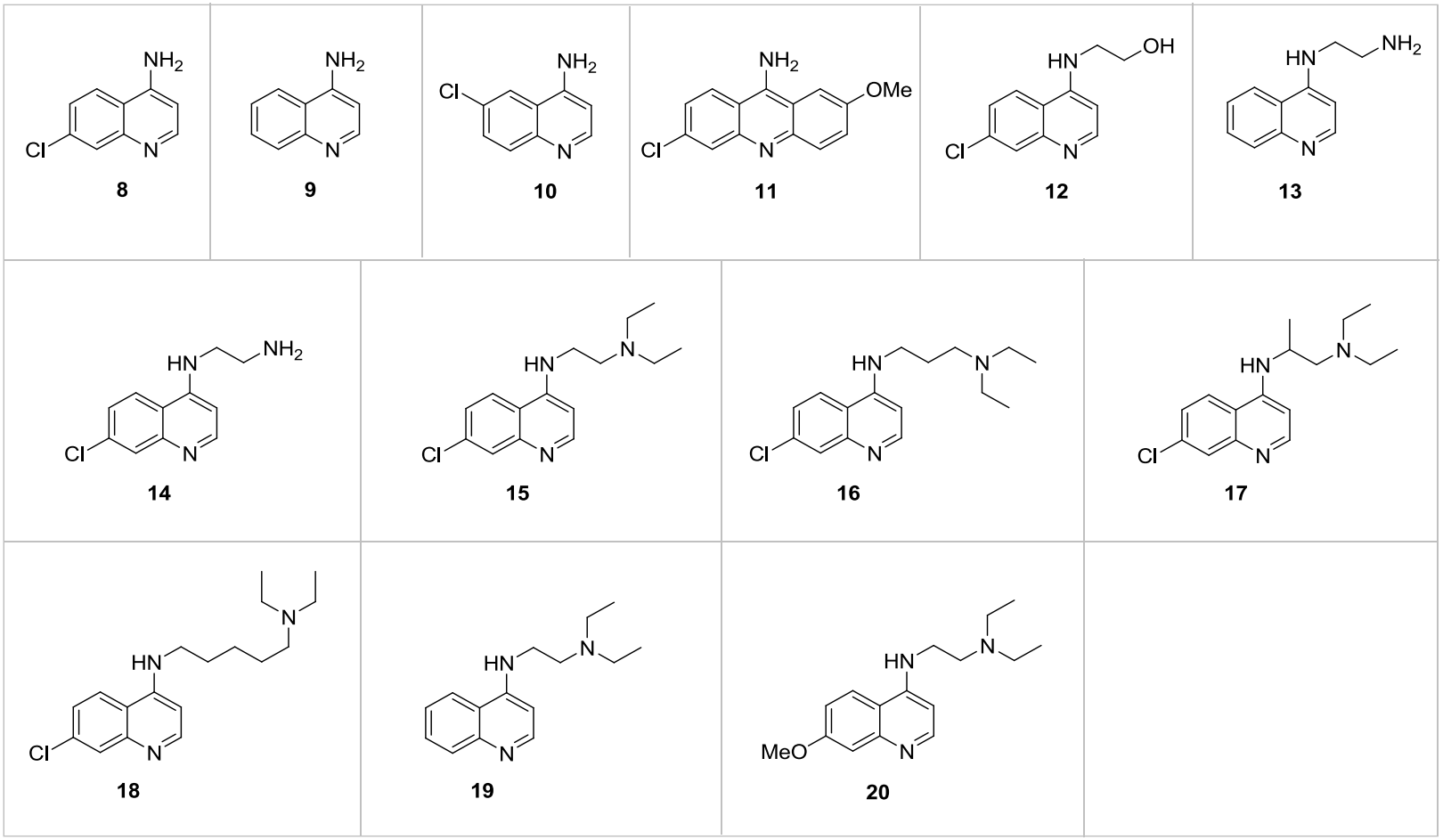


Figure A6: Structures of 4-AQ employed in SAR studies.

Biological Activity of 4-AQ and Related Compounds 1-20

Table A1 shows the reported *in vitro* activity of compounds **1-20** against chloroquine resistant and chloroquine sensitive clones of the malaria parasite (*Plasmodium falciparum*) as determined by the hypoxanthine incorporation assay which measures the inhibition of parasite growth. It also shows the ability of the compounds to inhibit β-haematin formation obtained from the β-haematin inhibitory assay (BHIA) as either '+', indicating that inhibition was observed, or '-', indicating that the compound does not inhibit β-haematin formation. The clones used for each of the *in vitro* assays are shown in brackets. The data was obtained from a number of sources as indicated.

Table A1: *In vitro* activity of 1-20 against chloroquine resistant and chloroquine sensitive clones of *P. falciparum* and the outcome (positive or negative) of the BHIA. NA means that data is not available.

Compound	BHIA	IC_{50}/nM Against chloroquine sensitive clone	IC_{50}/nM Against chloroquine resistant clone
1[a]	+	38 ± 14 ((D10)	315 ± 82 (K1)
2	+	Active	NA
3[b]	+	8 (NF54)	31 (K1)
4[c]	+	3.7 ± 0.8 (HB3)	27.2 ± 4.3 (K1)
5[d]	+		
6[e]	+	NA	0.8-17.9 (strains)
7[c]	+	0.9 ± 0.3 (HB3)	20.8 ± 1.4 (K1)
8[a]	+	3800 ± 500 (D10)	NA
9[a]	-	>10000 (D10)	NA
10[a]	-	NA	NA
11[a]	+	NA	NA
12[a]	+	5070 ± 80 (D10)	NA
13[a]	-	4700 ± 800 (D10)	NA
14[a]	+	92 ± 12 (D10)	NA
15[f]	+	24 ± 6 (NF54)	49 ± 14 (K1)
16[f]	+	18 ± 5 (NF54)	59 ± 15 (K1)
17[f]	+	25 ± 5 (NF54)	61 ± 15 (K1)
18[g]	+	6	58
19[h]	-	1060 ± 103 (D10)	NA
20[h]	-	448 40 (D10)	NA

a) Timothy J Egan, Expert Opinion on Therapeutic Patents, 11, *2*, **2001**, 185-209, b) C. Chong, Biochem. Pharmacol. 66, *11*, **2003**, 2201-2212 c) P. M. O'Neill *et al*, J. Med. Chem, 40, *4*, **1997**, 437-48, d) still need to find, e) M. Schlitzer, ChemMedChem, 2, *7*, **2007**, 944-986, f) R. Ridley *et al*, Antimicrob. Agents Chemother., 40, *8*, **1996**, 1846-1854, g) D. De et al, J. Med. Chem, 41, *25*, **1998**, 4918-4926, h) C. Kaschula *et al*, J. Med. Chem, 45, *16*, **2002**, 3531-3539.

Handouts for Workshop 3:

- Internal Memo #3
- Report Part B: Synthesis and Biological Evaluation of 4-Aminoquinolines and Related Antimalarials

In this Workshop, students should recognise that the simplest solution to the problem is to recognise which of the reagents in Schemes B1-6 can be changed in order to arrive at new 4-AQ analogues while still retaining the pharmacophore. Having sourced the reagents from a chemical catalogue, they should be able to give the synthetic routes. Students should then decide on the appropriate biological assay or assays for a SAR study. Tutors should emphasise the importance of the stepwise nature of experimental design and the need for a small scale SAR study such as the one proposed to allow pairwise comparison of compounds.

Schemes B1 and 2 are best presented to students in colour as shown.

INTERNAL MEMO #3

Global Health Organisation,

Tropical Diseases Research Centre,

Wainwright House, West Street, Castletown.

Global Health Organisation
Library Information Services

To: Medicinal Chemistry Research and Development Group

Re: Report Part B: Synthesis and Biological Evaluation of 4-Aminoquinolines and Related Antimalarials

Further to the request made by your team, we have now investigated the synthetic routes commonly used to prepare a number of 4-aminoquinoline and related antimalarial drugs. Please find the report (Part B) attached. We hope that the information provided can be used to help to identify how your lead compound can be modified as part of a SAR study, and will help you to deduce how the modifications could be made. We also recommend that you research the chemistry of amines and the various methods that can be used for the synthesis of amines.

We have also investigated and outlined three biological assays that may be suitable for assessing the activity of your compounds. We have access to the expertise and facilities to carry out each of these assays if they are required.

In our opinion, when planning the time it will take you to prepare each target compound, you should allow one week for the preparation, purification and characterisation of sufficient quantities of each target compound. The time needed to carry out each assay can be determined from the overview of the procedures provided.

Please do not hesitate to contact us if you require further assistance or clarification on anything contained within the report.

Yours Faithfully,

Samuel Southern

Dr. S. Southern,

Library Information Services.

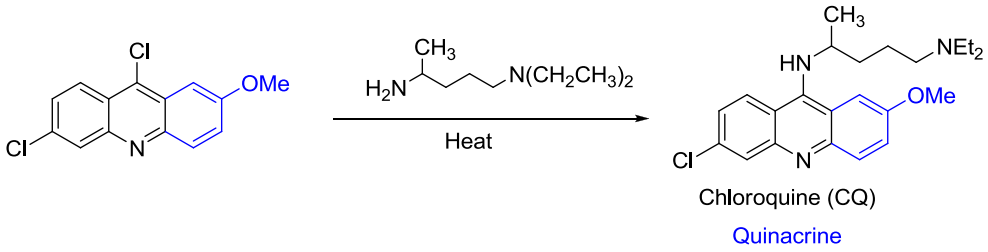
Report Part B: Synthesis and Biological Evaluation of 4-Aminoquinolines and Related Antimalarials

Contents:

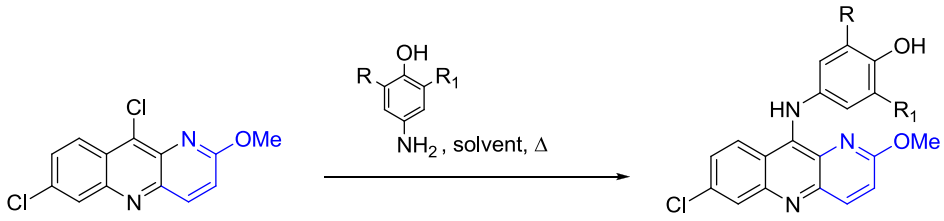
List of Schemes:

List of Figures:

Synthetic Routes to 4-Aminoquinolines Antimalarials



Scheme B1: The synthesis of CQ and quinacrine (Nucleophilic aromatic substitution).



Amodiaquine (ADQ): R = H, $R_1 = CH_2N(CH_2CH_3)_2$

Tebuquine (TQ): R = 4-ClC_6H_4, $R_1 = CH_2NH(C(CH_3)_3)$

Pyronaridine (PA): $R = R_1 = CH_2N(CH_2)_4$,

Scheme B2: The synthesis of ADQ, TQ and PA (Nucleophilic aromatic substitution).

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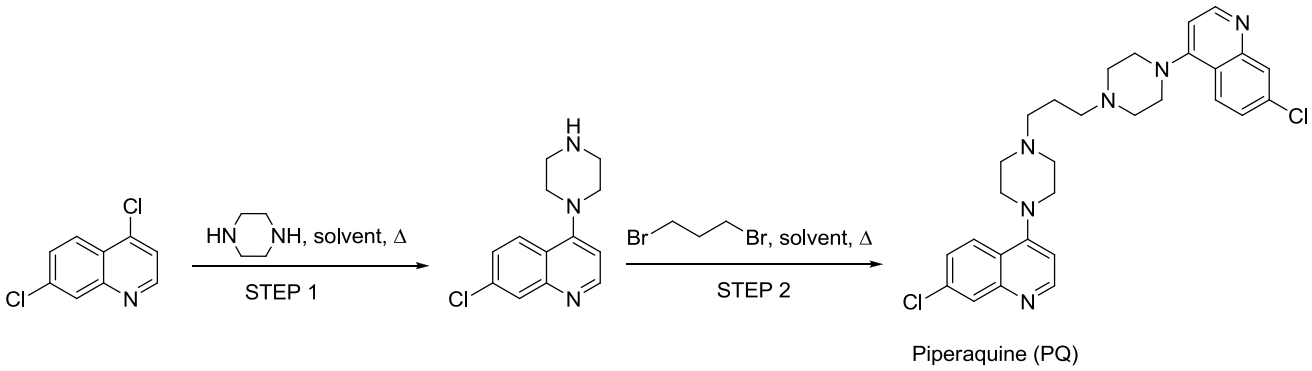
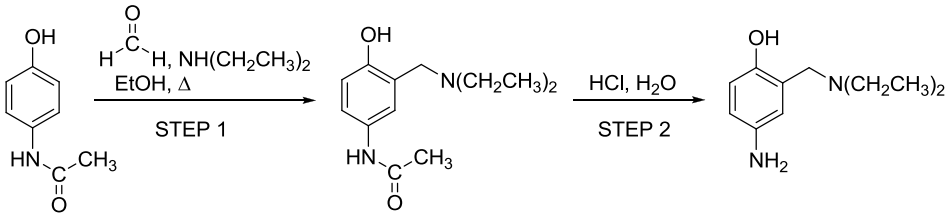


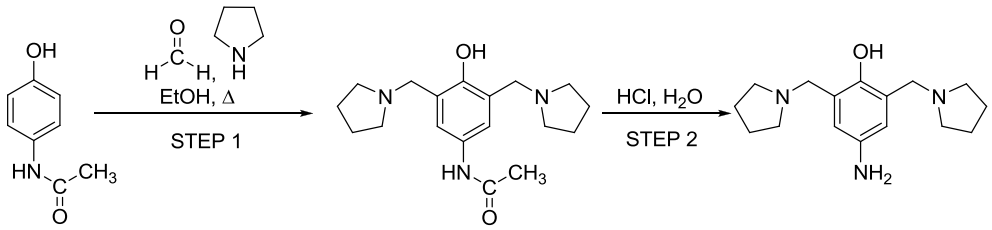
Piperaquine (PQ)

Scheme B3: The synthesis of PQ (Step 1: Nucleophilic aromatic substitution, Step 2: Nucleophilic substitution of a haloalkane).

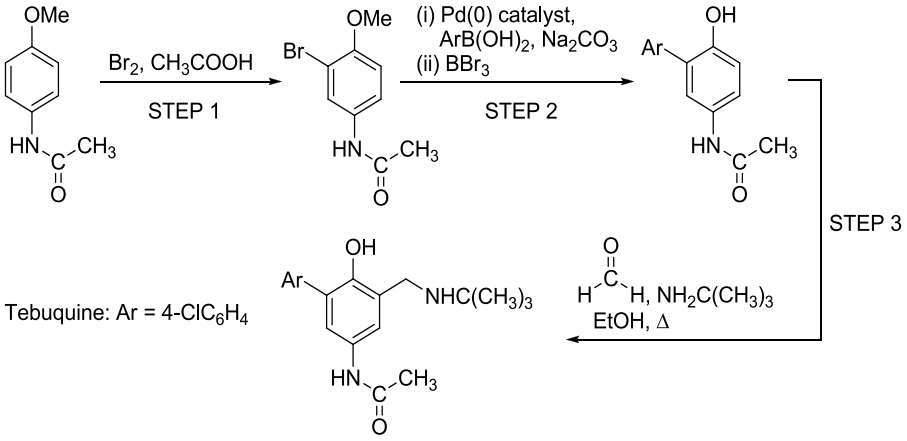
Synthesis of Aromatic Anilines Required to Prepare ADQ, TQ and PA



Scheme B4a: The synthesis of the aromatic side chains of ADQ (Step 1: Mannich Reaction, Step 2: Hydrolysis of an amide).

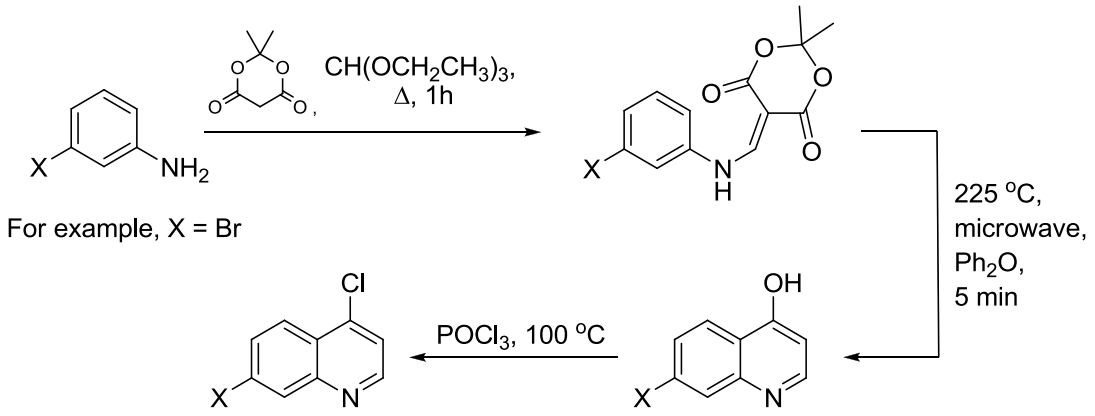


Scheme B4b: The synthesis of the aromatic side chains of PA (Step 1: Mannich Reaction, Step 2: Hydrolysis of an amide).



Scheme B5: The synthesis of the aromatic side chain of TQ (Step 1: Bromination, Step 2: (i) Suzuki coupling, (ii) Demethylation, Step 3: Mannich reaction).

Synthesis of 7-Substituted 4-Chloroquinolines



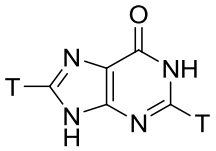
Scheme B6: The synthesis of the 7-substituted 4-chloroquinolines.

Biological Evaluation of 4-AQ and Related Compounds

A brief description of three biological assays that you may wish to use is provided below. The description of the assays, and the procedures that are outlined, are taken from information obtained from a number of literature sources.

1. *In Vitro* Assay: [^{3}H]Hypoxanthine Incorporation Assay [1-3]

The assay measures the viability of parasites after treatment with a known concentration of a drug. It is a radioactivity-based method in which parasites cultured in human serum and human red blood cells under sterile conditions are incubated with [^{3}H]hypoxanthine (tritium labelled hypoxanthine). Viable parasites incorporate the radiolabelled purine into parasitic nucleic acids and the degree of incorporation can be measured quantitatively by measuring radioactivity following incubation with [^{3}H]hypoxanthine.



[3H]Hypoxanthine

Figure B1: The structure of hypoxanthine

Parasites that have not been treated with a drug are used as a control and the level of radioactivity following incubation with [^{3}H]hypoxanthine is measured and quantified as 100 % viability. Parasites incubated with the radiolabel under the same conditions but that are also treated with an active drug will not incorporate the radiolabel to the same extent as the untreated parasites (the control). Quantitative detection of radioactivity following treatment with the drug allows calculation of % viability relative to the controls. The % viability will be proportional to the potency and concentration of the active drug.

This assay is performed on a 96 well plate. Each plate must be prepared in triplicate and the mean of the triplicate results determined and used to calculate the % inhibition. Only 60 wells are used to evaluate compounds or accommodate the necessary controls. The outer most wells are not used. Malaria infected erythrocytes are applied to each well of the plates at 0.2 % parasitemia.

Controls must be performed and include 2 wells of uninfected red blood cells (which allow collection of a background), 4 wells contain untreated infected red blood cells (negative control), 4 wells contain parasite infected red blood cells treated with a known antimalarial agent at two concentrations (for example, 100 and 5 nM); often chloroquine is used and these wells are the positive controls.

The remaining 50 wells can be used to evaluate new compounds, and therefore can accommodate 5 compounds at 10 different concentrations. If the compounds are applied in an organic solvent (such as DMSO) the concentration of the solvent must be low (< 1 %) and the controls must contain the same volume of solvent (and have the same volume overall).

DAY 0: The plates are prepared without drugs and are incubated at 37 ^{o}C for 24 hours.

DAY 1: The appropriate drug compounds are then applied and the plates are incubated at 37 ^{o}C for a further 24 hours.

DAY 2: The radiolabelled hypoxanthine is added to each well and the plates are incubated for a further 18 hours.

DAY 3: The cells are harvested and the count per minute measured and used to determine % inhibition of radiolabelled hypoxanthine incorporation in drug treated cells.

When the % viability of parasites (as determined by the degree of [^{3}H]hypoxanthine incorporation) is plotted as a function of drug concentration the result is a dose-response curve which is sigmoidal, see Figure B2 below. From this curve the IC_{50} can be determined. The IC_{50} is the concentration of drug required to reduce viability by 50 %; the lower the value the more potent the drug. Good candidates for further study should have IC_{50} values in the nanomolar range.

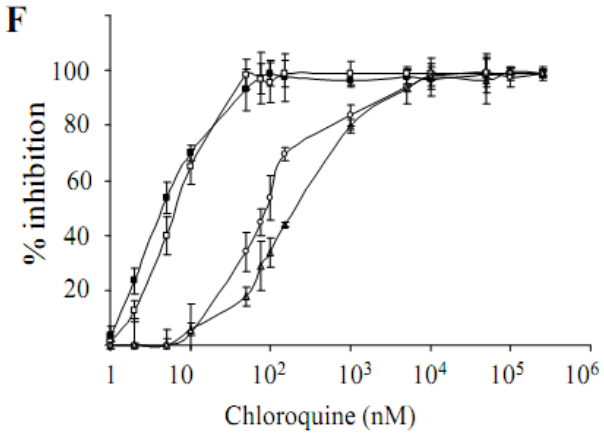


Figure B2: Dose-response curves showing the inhibition of [^{3}H]hypoxanthine incorporation as a function of chloroquine concentration in 4 clones of *P.falciparum*: 3D7 (closed squares), HB3 (open squares), W2 (open circles), and Dd2 (open triangles). (Figure 1F, Reynolds, J. et al., BMC Clinical Pharmacology, 2007, 7:13).

Note:

$$\% \text{ Inhibition} = 100\ \% - \frac{(\text{mean of cpm of control}^* - \text{mean of sample with drug})}{\text{mean of cpm of control}^*} \times 100$$

*negative control, i.e. the untreated infected red blood cells

cpm = counts per minutes

2. *In Vivo* Assay[3]

Initial *in vivo* methods evaluate drugs against a rodent strain of the malaria parasite (e.g. *Plasmodium berghei*) since parasites that cause the primate disease do not infect non-primate species. The assay is called the '4 day suppression test'. Mice used must be free from infections known to accelerate the disease or to help survival. The mice must be maintained under strictly controlled environmental conditions and fed a specific diet. Mice are divided into 3 groups with 5 mice in each group. These groups are 'the control group' who will not receive a drug, 'the reference drug group' that will be treated with a known antimalarial (often chloroquine) and 'the test group' that will receive the drug being evaluated.

Day 0: Mice in all 3 groups are infected with a specific dose of parasitised red blood cells. 2-4 hours after infection, the mice are treated with the drugs (or blank for the control group). The drugs are administered by the appropriate route.

Days1-3: Mice receive the same dose of the drug each day administered by the same route.

Day 4: 24 hours after the last dose of drug is administered, blood smears are taken and the % parasitemia (parasite density) relative to the control group is calculated.

If the drug is slow acting, further smears are taken on days 5 and 6.

Untreated mice (the control group) usually die one week after infection. The mean survival time is recorded for the treated mice and compared with the control. Mice surviving on day 30 are considered cured.

If drugs are successful at this stage, the amount of drug needed to reduce the parasitaemia by 50 % compared to untreated control infected mice is determined (the ED_{50} value, recorded in mg/kg). To obtain the ED_{50} the infected mice are exposed to the drug at a range of concentrations and the % reduction of parasitemia compared to the control (untreated mice) is plotted as a function of the drug concentration. A sigmoidal dose response curve is normally generated. For a drug to have potential for further *in vivo* evaluation an ED_{50} below 20 mg/kg is generally required. Various routes of administration may be investigated.

Drugs successful in the mouse model will then be tested in primate models before entering Phase I clinical evaluations in humans.

Note:

$$\% \text{ Reduction} = 100\ \% - \left(\frac{\text{mean parasitemia of treated group}}{\text{mean parasitemia of control group}} \times 100 \right)$$

3. β-Haematin Inhibitory Activity (BHIA) Assay [5,6]

This assay determines whether the compound under investigation is able to inhibit the formation of β-haematin from haematin or haemin (Figure B3). There are two forms of this assay, the non-quantitative IR assay which dates back to the early 1990s or the quantitative version of the assay developed and standardised for the screening of antimalarial compounds much more recently (and discussed in detail below).

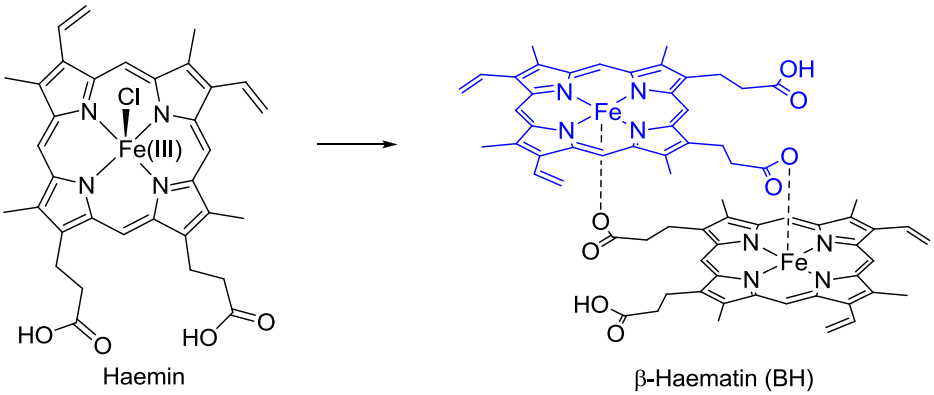


Figure B3: Formation of β-haematin from haemin

When performed in a non-quantitative manner, the results of this assay are presented as either positive (+, the compound in question does inhibit the formation of β-haematin) or negative (-, the compound does not inhibit the formation of β-haematin). In this procedure, 4 molar equivalents of the drug or compound under investigation are incubated with a solution of 1 molar equivalent of haematin. Following incubation at 37 ^{o}C for 18 hours, the sample is analysed by IR spectroscopy. If the compound inhibits the formation of β-haematin, the strong absorbance bands at 1660 cm^{-1} and 1210 cm^{-1} which are characteristic of β-haematin will not be present in the IR spectrum collected.

The quantitative version of this assay can be used to determine an IC_{50} value for each compound investigated. While several versions of this assay are found in the literature, the one reported herein was published in 2000 and represents a version that has been standardised for the screening of antimalarial compounds. In this assay, the quantity of β-haematin formed following treatment of haemin (Figure B3) with the compound under investigation is determined spectrophotometrically using UV/vis spectroscopy, and the concentration of β-haematin determined from a standard curve of known concentrations of β-haematin.

The compound under investigation is incubated at 37 ^{o}C for 18 hours at a range of concentrations with a known quantity of haemin. During this time, polymerisation of haemin to β-haematin will occur to a more or lesser extent depending on the potency and concentration of the compound. After this time, the solid β-haematin formed is collected and re-dissolved in a basic solution for quantitative analysis by UV/vis spectroscopy of the absorbance band at 405 nm. The lower the absorbance observed at this wavelength, the lower the concentration of the β-haematin present, and therefore the more effective the compound at inhibiting β-haematin formation.

96 well plates are used and a negative and positive control are also applied. Untreated haemin solution is used as a negative control (i.e. no drug present) and a known 4-AQ antimalarial at relevant concentrations (often chloroquine) is used as the positive control. Each plate must be prepared in triplicate, and the mean of the triplicate results used to determine the % BHI (β-haematin inhibition). Only 60 wells are used to evaluate compounds or accommodate the necessary controls (2 wells for negative control, for example 2 wells for chloroquine applied at two known concentrations. The outer

most wells are not used. The remaining 56 wells can be used to analyse 7 compounds at 8 different concentrations.

A known concentration of haemin in DMSO is distributed to each well (except the outside wells) of the plate. A known concentration of the compounds (from 1 to 20 molar equivalents relative to haemin) is applied as appropriate as a solution in water or DMSO (ensuring the volume of DMSO used is constant in each well). Addition of pH 5 acetate buffer initiates β-haematin formation and the plates are then incubated as described above.

On removal from the incubator, the plates are centrifuged and the solid β-haematin pellet collected. The pellet is re-suspended in DMSO and centrifuged once more to ensure all of the soluble haemin is removed. Once again, the solid β-haematin pellet is collected and this time the solid material is dissolved in 0.1 M sodium hydroxide for spectroscopic analysis (β-haematin forms soluble haematin in strongly basic conditions allowing spectrophotometric determination of β-haematin concentration).

A known volume of the β-haematin in sodium hydroxide solution is added via a pipette onto a clean 96 well plate and serial dilutions are made. The plate is analysed at 405 nm using a plate reader.

A standard curve of haematin in 0.1 M sodium hydroxide is used to calculate the amount of haematin present in each well and therefore the amount of β-haematin formed in the presence of the drug at each concentration. From this, the percentage inhibition of β-haematin formation can be plotted as a function of drug concentration to determine the IC_{50} value of each compound analysed (i.e. the concentration of compound required to inhibit formation of β-haematin by 50 % relative to the negative control). A sigmoidal dose response curve is normally generated.

Note: It is important that you note that the IC_{50} values obtained using this method for BHI do not correlate well with *in vitro* antimalarial activity of known antimalarials. However, one report has shown that if IC_{50} values for BHI are normalised to account for accumulation of a compound in the parasitic food vacuole a good correlation with *in vitro* IC_{50} values can be observed.[1]

$$\% \text{ Inhibition} = 100\ \% - \left(\frac{\text{mean [BH] of sample with drug}}{\text{mean [BH] of sample without drug (control)}} \right) \times 100$$

References

1. J. D. Chulay, J. D. Haynes and C. L. Diggs, *Experimental Parasitology*, 1983, **55**, 138-146.
2. R. E. Desjardins, C. J. Canfield, J. D. Haynes and J. D. Chulay, *Antimicrobial Agents and Chemotherapy*, 1979, **16**, 710-718.
3. J. M. Reynolds, K. El Bissati, J. Brandenburg, A. Günzl and C. B. Mamoun, *BMC Clinical Pharmacology*, 2007, **7**, 13.
4. B. Kalra, S. Chawla, P. Gupta and Valecha, *Indian Journal of Pharmacology*, 2006, **38**, 5-12.
5. S. Parapini, N. Basilico, E. Pasini, T. J. Egan, P. Olliaro, D. Taramelli and D. Monti, *Experimental Parasitology*, 2000, **96**, 249-256.
6. C. H. Kaschula, T. J. Egan, R. Hunter, N. Basilico, S. Parapini, D. Taramelli, E. Pasini and D. Monti, *Journal of Medicinal Chemistry*, 2002, **45**, 3531-3539

Handouts for Workshop 4:

- Internal Memo #4
- Report Part C: Pharmacokinetics of 4-Aminoquinoline Antimalarials

In this Workshop, students will be asked to use Lipinski's Rule of 5 and PSA / rotatable bonds to predict oral availability of the target compounds. In addition, students will apply the general transformations listed in Part C of the Report to their target compounds in order to predict how they will be metabolised. They should consider how these factors will impact on their SAR study and on the further development of the compounds as drugs.

This workshop should also present the tutor with the opportunity to discuss the preference for orally administered drugs, particularly in the context described, and the need for multi-property optimisation of lead compounds in the early stages of drug development to reduce attrition (see below).

INTERNAL MEMO #4

Global Health Organisation,

Tropical Diseases Research Centre,

Wainwright House, West Street, Castletown.

To: Medicinal Chemistry Research and Development Group

Re: Meeting with GHO Pharmacology Team

Please find attached Part C of the report concerning the pharmacokinetics of 4-AQs. In addition to the information contained in the report, you should use the results of your own research to complete the relevant section of the proposal (metabolism and oral availability). Your own research will be particularly important if your target molecules contain functional groups that are not present in CQ and ADQ.

The GHO Pharmacology Team have been briefed on the proposed research project and will play an important role in the research if your team is awarded the funding. They have also received a copy of this part of the report. The GHO Pharmacology Team have requested that you complete the attached template for 'Drug-Likeness Analysis' of each target molecule and return them along with an internal memo summarising your analyses which will include:

- Structures of the target compounds clearly identifying the functional groups,
- Analysis of the target compounds using (i) Lipinski's Rule of 5 (including number of violations) and (ii) by calculation of PSA and the number of rotatable bonds. HBD, HBA and rotatable bonds must be clearly identified in the structures of the target compounds.
- A prediction of whether the target compounds are likely to be orally available, based on the analyses above,
- Suggested possible route(s) by which the target compounds will be metabolised.

In addition, if there are other measurements of physicochemical or pharmacokinetic properties of the target compounds that will need to be made during the SAR study, please identify these in your memo providing a brief justification for their inclusion.

The Pharmacology Team will use the information that you provide to plan for further drug development of any active compounds. The information that you provide in your memo can also be included in the relevant section of your proposal where appropriate.

Yours Faithfully,

Rebecca Woodward

Prof. R. Woodward,
Centre Director.

Report Part C: 4-Aminoquinolines and Related Antimalarials (Pharmacokinetics)

Contents:

List of Schemes

List of Figures

Pharmacokinetics of 4-Aminoquinolines

The literature contains detailed information concerning the pharmacokinetics of CQ and ADQ, but information about many other 4-aminoquinolines is harder to find. In part, this is because several of the compounds that have been used clinically were discovered before the study of pharmacokinetics was established. This report focuses on CQ and ADQ but is relevant to structurally related 4-AQs.

Overview of the pharmacokinetics of CQ and ADQ

CQ and ADQ are usually administered orally. They are absorbed rapidly from the GI tract and have good bioavailability (e.g. the bioavailability (F) of CQ is reported to be 70 %). 4-AQs are widely distributed through the body although they accumulate in the blood (volume of distribution for CQ is reported to be V_d = 13000 L). The half life ($t_{1/2}$) of CQ is very long (reported value varies between studies from 7-56 days) however ADQ is subject to rapid first pass metabolism in which it is *N*-dealkylated (Scheme C1) to give mono desethyl ADQ which is the active drug. CQ is excreted in the urine mainly as mono desethyl CQ but also as bis-desethyl CQ; a very small amount of minor metabolites resulting from oxidative deamination of the terminal amino group and loss of the 4-amino side chain by *N*-dealkylation have also been reported. In contrast, ADQ is excreted predominantly in the bile as mono desethyl ADQ. Figure C1 shows the structures of the major desethyl metabolites of CQ and ADQ.

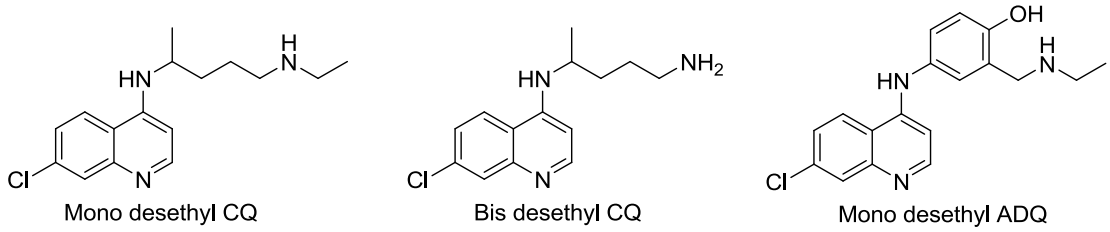
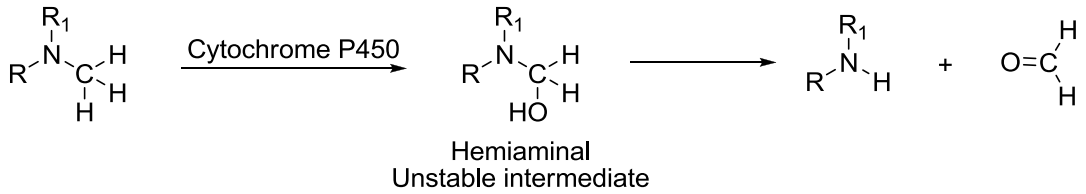


Figure C1: Structures of the major desethyl metabolites of CQ and ADQ.

N-Dealkylation: A key reaction in 4-AQ metabolism

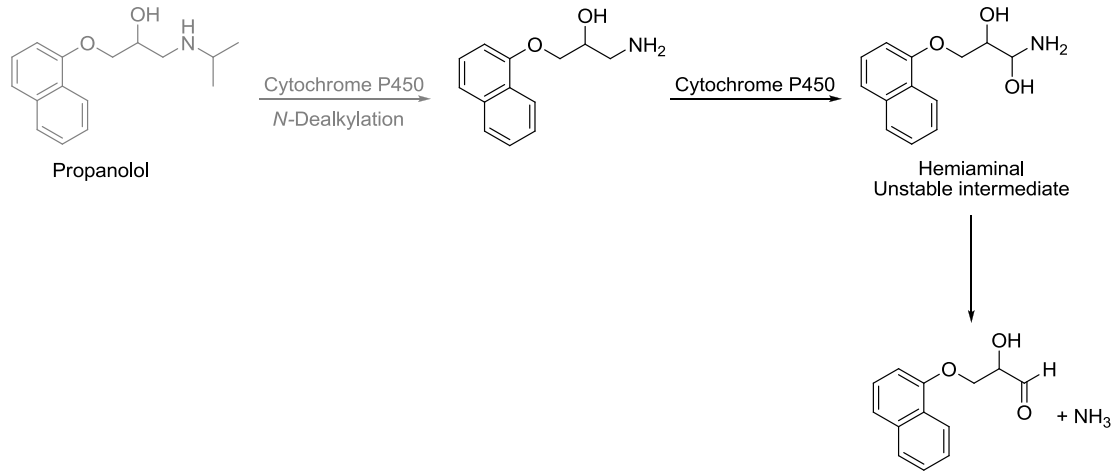
P450-mediated *N*-dealkylation of the amino groups in drugs is common for primary and secondary amines and proceeds via α-hydroxylation (Scheme C1). However, tertiary alkyl groups cannot be metabolised in this way. This type of metabolism is fastest for unbranched (unhindered), short chain alkyl groups but is significantly slower for longer chains and particularly slow for branched (hindered) alkyl groups.



Scheme C1: *N*-Dealkylation via α-hydroxylation.

Oxidative deamination results in formation of the minor metabolites of CQ

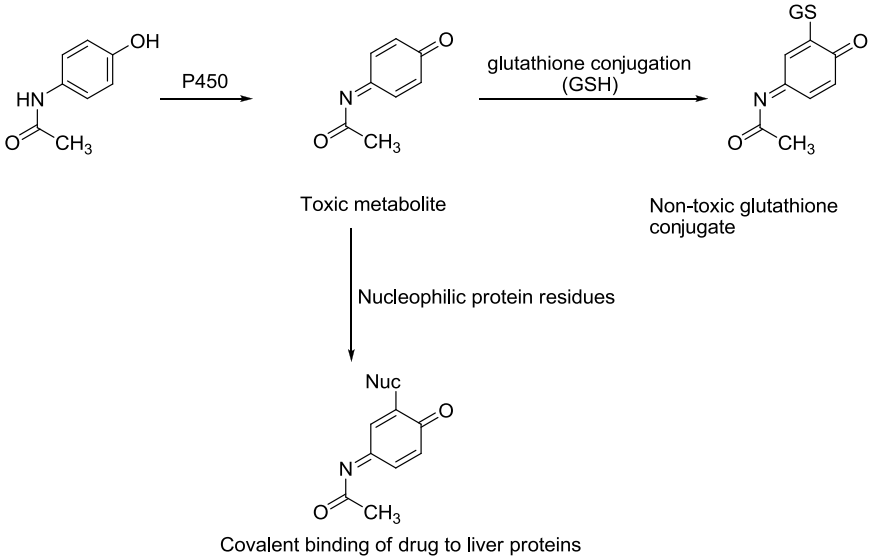
Primary amines can undergo oxidative loss of the amino group by deamination. This type of transformation is also mediated by P450 and is essentially via the same mechanism (i.e. α-hydroxylation) as that shown in Scheme C1. This is shown for propanolol (a β-blocker) in Scheme C2. The resulting aldehydes are then subject to further oxidation to the carboxylic acid derivatives (also P450 mediated).



Scheme C2: Oxidative deamination of propanolol.

Toxicity of ADQ and related compounds

ADQ is no longer used clinically due to issues associated with its dose-dependent liver toxicity. Like phenacetin (the first marketed NSAID), ADQ undergoes P450-mediated oxidation to form a quinone-imine intermediate. Formation of this intermediate is only possible because there is a 1,4-relationship between the amido/amino and phenolic groups of the aromatic substituent. In low doses, conjugation of this intermediate with glutathione gives a non-toxic metabolite that is excreted. However, at high doses, there are insufficient quantities of glutathione for conjugation of the quinone-imine and the intermediate will react with nucleophilic residues of proteins in the liver, covalently binding to them and causing irreversible liver damage. The metabolism of phenacetin by this route is given in Scheme C3. Phenacetin was withdrawn from the market in the 1970s.



Scheme C3: P450 oxidation of phenacetin to form a toxic metabolite.

Handouts for Workshop 5:

- Internal Memo #5
- Letter from Inspired Pharmaceuticals Ltd

The authors have found that by taking a traditional lecture approach to teaching about the various tools available to a medicinal chemist, often students will learn the material but do not really appreciate the real potential or limitations of these techniques. It is hoped that this will be avoided by asking them to find out about the techniques for themselves and to critically evaluate their application in their own SAR study in this Workshop.

INTERNAL MEMO #5

Global Health Organisation,

Tropical Diseases Research Centre,

Wainwright House, West Street, Castletown.

To: Medicinal Chemistry Research and Development Group

Re: Inspired Pharmaceuticals Ltd: Parallel Synthesis and HTS

I am delighted to inform you that Inspired Pharmaceuticals Ltd. are very happy with the progress that your team has made on the proposal to date. They have offered access to their facilities so that you can conduct your SAR study using parallel synthesis and high throughput screening (HTS). Details of the synthesiser and biological assay that Inspired Pharmaceuticals propose to use are given in the attached letter that I received this morning.

I would like you to avail of this offer where possible and therefore request that you critically assess how these facilities could be used to enhance your SAR study, highlighting any changes to your current proposal that will be needed and the advantages and disadvantages of employing this methodology.

Yours Faithfully,

Rebecca Woodward

Prof. R. Woodward,
Centre Director.

Inspired Pharmaceuticals Ltd
Quinnstown Industrial Estate
North Road
Castletown

Prof. R. Woodward, Centre Director
Tropical Diseases Research Centre
Global Health Organisation
West Street
Castletown

Dear Prof. Woodward,

As you are aware, our company is very committed to the Molecules against Malaria Research Programme, and in addition to providing research funding we are also offering access to our facilities. We are very impressed by the recent progress reports made by your Medicinal Chemistry Research and Development Group, and are keen to work closely with the Global Health Organisation in developing much needed antimalarial 4-aminoquinolines.

We would like to offer you the opportunity to avail of our parallel synthesiser. The synthesiser is able to perform up to 24 stirred reactions at one temperature from -70 to +150 ^{o}C at any one time. It is also suitable for solid-supported reagent based chemistry if required.

In order to maximise the outputs of your research, we would also like to offer you the opportunity to use our recently validated bioassay for high throughput screening of compounds that are known to inhibit the formation of β-haematin. This assay has been developed from similar assays reported in the literature but does not require centrifugation or changing of plates making it much faster and more convenient

The assay involves treating haemin with known concentrations of a compound and determining the extent of β-haematin formation by measuring the absorbance of the remaining unpolymerised free haemin at 400 nm (rather than requiring the collection, solubilisation and quantitative analysis of polymerised β-haematin). In contrast to other assays it is performed in sodium bicarbonate at pH = 9.1 (rather than 0.1 M sodium hydroxide solution) since free haemin is soluble in these conditions while β-haematin is not. As with previously reported assays, 60 wells of a 96 well plate are used. Appropriate controls are required and average absorbance values are obtained from triplicate experiments. Each compound should be evaluated at 8 concentrations from 500 nM to 20 mM.

We hope that you will be able to take up this opportunity and that your teams will integrate this technology into their research proposals.

Yours Sincerely,

Dr. T. Velasco,

Head of Drug Discovery, Inspired Pharmaceuticals Ltd.

END OF STUDENT HANDOUTS

Appendix 2: Tutor Notes for Workshops 1-5

Useful information for the tutor and historical perspective on the development of 4-AQs:

There are 3 classes of quinoline antimalarials, and this resource focuses only on 4-aminoquinolines and the closely related acridines (which also contain the 4-aminoquinoline nucleus). The other two classes are the quinoline methanols (quinine, mefloquine (lariam)) and the 8-aminoquinolines (primaquine, pamaquine).

- 4-Aminoquinolines: Of the 3 classes, the structure activity relationships and mode of action of these drugs is best understood and has been more extensively investigated than for other quinoline containing antimalarials.
- 8-aminoquinolines are active against the liver phase of the disease and their molecular mechanism of action is different from other aminoquinolines. This class of antimalarials have been less studied and their precise mechanism of action has not been fully elucidated and so is beyond the scope of this resource.
- Quinoline methanols are known to inhibit β-haematin formation and so their mechanism of action may be similar to that of the 4-aminoquinolines. However, their association with β-haematin *in vitro* is significantly weaker and, since the first pK_{aH} of these compounds (the quinolonium ion) is much lower than for the 4-AQ, the accumulation / pH trapping within the acidic food vacuole of the parasite is less than for the 4-aminoquinolines. Therefore, these drugs are not considered within the resource.

Found in the bark of the Cinchona tree, quinine and its isomers were used by indigenous populations for the treatment of fever for centuries. Once brought to the attention of western medicine (purportedly by the Countess of Chinchon in the 1640s), it was the most common treatment for malaria in Europe until WWI.

If tutors feel the content of the video found at the link below is appropriate, it can be made available to students and is loosely related to the context. In this video, Prof. David K. Smith from York University makes a gin and tonic and discusses the origins of the drink and ingredients used. Of relevance to this resource is the quinine in the tonic water and its use by British colonials in Africa and India: http://www.youtube.com/watch?v=Eni5sc4xebk

As a consequence of the naval blockade of Germany during WWI, the Germans began a search for new antimalarials which lead to the first synthetic 4-AQ antimalarials. This effort culminated in the synthesis of sontoquine which fell into US hands during WWII. Subsequent research efforts in the US led to the identification of chloroquine, amodiaquine and other synthetic quinolines. Chloroquine had been discovered in Germany in 1934, but development was abandoned due to observed high toxicity (therapeutic index of CQ = 2). Chloroquine entered clinical use in 1947.

Workshop 1

Background information

Malaria is caused by a protozoan of the genus *Plasmodium*. There are four species of *Plasmodium* that infect humans and these are *malariae*, *ovale*, *vivax* and *falciparum*. *P.falciparum* and *P.vivax* are the most prevalent and *P.falciparam* the most likely to lead to complicated clinical cases and patient death (it can lead to cerebral malaria and patient coma).

When the malaria parasite infects a mammalian host (as sporozoites, via the saliva of the female *Anopholes* mosquito following a mosquito bite) it travels to the liver where it multiplies during the asymptomatic, liver stage of the disease. Note that *P.vivax* and *P.ovale* parasites may lie dormant in the liver (as hypnozoites) and cause recurrent infection). In the next stage of the lifecycle, parasites enter the blood stream (as merozoites) and infect red blood cells causing the symptomatic, blood stage of the disease. While in the red blood cells, parasites will grow and divide (into a ring stage and then develop into trophozoites) before bursting from these cells (as blood schizonts) and infecting more red blood cells. Since the malaria parasite uses host haemoglobin as a source of amino acids for growth, patients will often exhibit symptoms of anaemia. Note that this is the asexual phase of the parasite's lifecycle although during the blood phase of the disease some parasites will form sexual stages (gametocytes) which will infect a mosquito when it takes a blood meal.

As a consequence of haemoglobin catabolism, which takes place within the parasite in an acidic compartment called the food vacuole, free haem is released. Free haem is rapidly oxidised to haematin which is toxic to the parasite and is rapidly converted to haemozoin, an insoluble polymeric material also known as the malaria pigment. Haemozoin is excreted from the parasite. Note that detection of haemazoin / the malaria pigment in blood smears of patients as a brown-black pigment can be used to diagnose the disease. 4-Aminoquinolines inhibit the formation of haemazoin.

The structures of haem (Fe(II)), haematin (ferrriprotoporphyrin XI OH, Fe(III)) and haemozoin (Fe(III)) are given in Figure A4 of Report Part A. The crystal structure of the synthetic form of haemozoin (which is called β-haematin) has been published: The structure of the malaria pigment β-haematin, Silvina Pagola *et al*, Nature, **2000**, *404*, pp 307-310.

Workshop 2

The following summarises an accepted mode of action of chloroquine:

In the article (Malaria No More), the mode of action of chloroquine is described as follows: “As the parasite feeds, it breaks down the oxygen-carrying molecule haemoglobin, releasing the iron-based haem unit. This is toxic to the parasite, which normally polymerises it into harmless haemozoin chains. But chloroquine enters the digestive vacuole of the malaria parasite and caps the haemozoin chains, preventing further polymerisation and causing a build-up of toxic haem that eventually kills the parasite.”, which implies that the target is polymeric haemozoin. This is acceptable within the context of the resource, and allows the students to identify an iron-centred porphyrin as the drug target. However, there is considerable evidence that free haematin is actually the target of 4-AQ antimalarials and that interaction with free haematin prevents its incorporation into haemozoin ultimately causing the parasite’s death, perhaps by an oxidative mechanism. More advanced students may come across this and other mechanisms from their own reading.

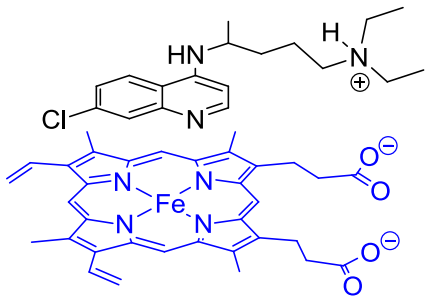
In addition, the **ion / pH trapping** or accumulation of CQ within parasitic food vacuole is important in explaining the observed activity of these compounds. Therefore, students are provided with a diagram that illustrates the differences in pH values of the red blood cell (RBC), parasite cytoplasm and parasitic food vacuole (FV) showing a pH gradient. They are also provided with the pK_{aH} values of the quinolinium and tertiary ammonium ions. From the information provided, it is hoped that students will recognise that the un-ionised form of the drug can enter the parasitic FV by diffusion across the membrane, but once inside the FV it becomes diprotonated and cannot exit. This results in accumulation of the drug in the FV (i.e. at the site of action) by ion trapping. The tutor may need to point out that the other amino group in the side chain of CQ (the 4-amino group) is not sufficiently basic to be protonated (compare 4-AQ amino group to 4-aminopyridine).

In our experience, students struggle to understand how the pH affects the distribution of drugs with ionisable groups and the equilibrium nature of this process. Learning activity 15 in the supporting resource, “Hybrid Workshops to Support: *Molecules against Malaria: Design of a Structure Activity Relationship Study of Antimalarial 4-Aminoquinolines*”, concerns the effect of pH on the absorption of ionisable drugs. Tutors may also wish to consult Chapters 1 and 2 of ‘Essentials of Pharmaceutical Chemistry’ by Donald Cairns (Pharmaceutical Press, 2000) and Chapter 2 of ‘Basic Pharmacology’ by Maria Hernandez and Apu Rathinavelu (CRC Press, 2006) for further examples and explanation of the effect of pH on drug absorption and distribution.

The drug target interactions can be described as follows:

The most significant/principal interaction between 4-AQ and their target, haematin, is a hydrophobic π–π stacking between the quinoline ring and planar porphyrin ring of haematin.

A second electrostatic interaction between the carboxyl groups of haematin and the quaternary ammonium ion of the side chain is also possible where the distance between these groups is optimal (in CQ, TQ, ADQ for example). However, analogues with shorter (2C) and longer side chains (5C) have good activity, so this interaction is much less significant for drug action.



Note that students could suggest an interaction between a lone pair of the quinoline ring and the Fe(III) centre of haematin. This is not unreasonable.

Identification of the pharmacophore:

Nanomolar activity is desired in order for these compounds to be considered active *in vitro*. This is due to the low therapeutic index/high toxicity associated with them. For example, the TI of CQ = 2 (10 mg kg^{-1}/20 mg kg^{-1}).

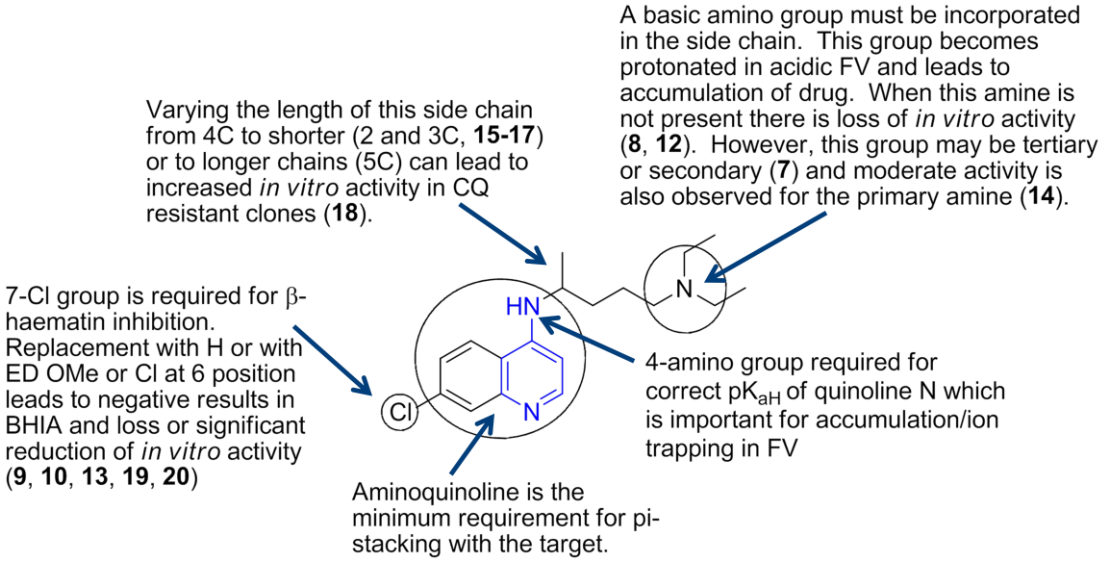
From the information provided the students should be able to draw the following conclusions about the pharmacophore of these compounds:

- All compounds contain a quinoline ring (minimum requirement for π–π stacking).
- All compounds have a 4-amino on the quinoline ring (important in determining the pK_{aH} of the quinoline N, important for pH trapping in FV).
- All compounds have a second amino group in their side chains (protonated in FV, required for pH trapping).
- A Cl atom at the 7 position of the quinoline ring is essential for activity in the BHIA (β-haematin inhibitory assay, see Workshop 3) and therefore for activity (see SAR notes below for qualification of this statement).

The tutor should note the following, which will be discussed in more detail in the tutor notes for Antimalarial Workshop 3:

- While the chain length of 4C is optimal for allowing the ionic interaction with carboxyl side chains of the porphyrin, this interaction is not essential for activity. Students should note that chain lengths less than and greater than 4C lead to enhanced activity against resistant strains. (For tutor only: A proposed reason for this is that analogues with different length side chains are not recognised by the CRT (chloroquine resistance transporter, see note on CQ resistance below). Note that the inter N distance in amodiaquine (ADQ) **4**, pyronaridine (PY) **6** and tebuquine (TQ) **7** is very similar to that in CQ (~8.3 Å).
- Students should note that while tertiary amino groups seem to be preferred in the side chain, that they are not a requirement for activity. In a later workshop (Antimalarial Workshop 4) the physicochemical properties of these compounds will be considered and students may then consider the implications of varying the amino substituents.
- While replacement of the 7-Cl group with an electron donating (ED) methoxy group leads to inactive compounds (in both the BHIA and hypoxanthine incorporation assay) replacement of this group with one of similar EW capacity (as indicated by the Hammett constant (F, Br, I, CF_3, NO_2)) and with lipophilic groups does result in analogues with activity in both assays and so students should not be discouraged from proposing such a change.

Summary of the SAR studies:



SAR study of quinoline antimalarials. Numbers given refer to structures listed in Figures A5 and A6 in Report A. Adapted from Figure 2, Quinoline Antimalarials, T. J. Egan, Expert Opinion on Therapeutic Patents, 2001, Pages 185-209 (Figure 2).

Possible modifications of these compounds:

It is hoped that students will propose that some/all of the following modifications could be investigated as part of an SAR study, while still retaining the pharmacophore:

- Variation of the side chain (length, branching) of CQ while retaining the basic amino group (or other basic group) and noting that chains shorter or longer than 4C are likely to be of more interest for finding analogues with activity against resistant strains.
- Variation of the side chain in analogues of ADQ, TQ and PY is possible providing the basic group in the side chain is retained.
- Variation of the substituents on the terminal N of the amino group.
- Variation of the 7-position substituent within the limits discussed above.
- Variation/extension of the aromatic ring system as long as the 4-aminoquinoline nucleus is retained (i.e. acridine analogues and others).
- Dimeric compounds such as piperaquine (PQ) could be investigated with varying linkers but ensuring that the linker contains a basic group.
- It would not be unreasonable for students to suggest that substituents at other positions of the quinoline nucleus as in sontoquine (SQ) would be tolerated.

A note on CQ resistance for tutor information only:

The reason or mechanism for CQ resistance is not yet fully understood, but it seems likely that it involves the chloroquine resistance transporter (CRT), a protein in the membrane of the parasitic FV. CRT is believed to be responsible for efflux of the diprotonated form of CQ from the FV, although the precise mechanism by which it does this is also not known. However, the result is a reduction in concentration of CQ in the FV and thus a reduction in binding to haematin. It has been proposed that, in sensitive strains, a basic lysine residue in the channel of CRT repels the dication whereas in resistant parasites a mutation results in replacement of this residue with a threonine (or other) residue allowing efflux of the dication down a steep concentration gradient.

Notes to consider when critically evaluating biological data:

Tutors may wish to lead class discussions on, or simply highlight, some or all of the following as students analyse the information provided in Part A of the Report.

- Nanomolar activity is desired in order for these compounds to be considered active *in vitro*. This is due to the low therapeutic index/high toxicity associated with them. For example, the TI of CQ = 2 (10 mg kg^{-1}/20 mg kg^{-1}).
- Students should be reminded that a SAR study typically involves pairwise comparison of compounds. This is possible for some of the compounds **1-20** but not for others. Students are asked to consider the information provided in paragraph 2 of internal memo #2. Research into 4-AQs predates formalised methods used in modern SAR studies; moreover, in early work, compounds were tested *in vivo* since reliable techniques for cloning parasites and/or other *in vitro* assays were not available.
- The BHIA (β-haematin inhibitory assay) - having proposed a mechanism of action, students should understand the significance of this assay. Compounds that are not active in this assay do not associate sufficiently strongly with haematin, and therefore cannot inhibit the incorporation of β-haematin into non-toxic haemozoin (or, as phrased in article cannot 'cap' haemozoin chains – see Tutor Notes for Workshop 2) and so will not be active against the parasite.
- Students should also appreciate the significance of the inclusion of the outcome of the hypoxanthine incorporation assay against both CQ sensitive and resistant clones, in that their brief is to design a SAR study to find analogues with activity against resistant strains.

Critical Evaluation of Biological Data:
• The data provided in Table A1 is not available from a single SAR study and therefore was obtained from a number of sources. As a result, while data for activity against resistant and sensitive clones is included, the actual clones that were employed in biological evaluations were not the same for each study, i.e. experiments were not performed in the same laboratories. • In cell culture, parasites are cloned and a code used to identify the clone (given in brackets in Table A1). The clone employed should be reported with any biological data of this nature since clones are obtained from different geographical locations, and therefore have been exposed to different chemotherapies and environmental factors. This affects their sensitivity to particular chemotherapies arising from variations/mutations of the genome (with mutations resulting in CQ resistance being the best known due to the huge impact of this type of mutation). • Chemists need to understand that biologists deal with complex systems that can vary depending on conditions and limits of any data collected by biologists must be clearly communicated to allow work to progress. See: A Pharmacology Primer, Theory, Application and Method, T. Kenakin, 2nd Edition, Elsevier (2006), page 2, http://thiqaruni.org/pharmacy/2.pdf • The first part of the following short article mentions the difficulties reproducing biological results and goes on to talk about communication problems between chemists and biologists: http://www.rsc.org/chemistryworld/2012/05/peace-love-and-understanding

Workshop 3

This Workshop provides students with the opportunity to be creative in applying their knowledge of organic chemistry. To a large extent, there are no right or wrong answers – the problem has a large number of possible solutions providing the pharmacophore is retained. Students are *not* expected to search the scientific literature but to use the information provided, a text book and prior knowledge.

The easiest way for students to approach the problem is to identify which reagents in Schemes B1-6 could be replaced to generate a 'novel' compound. They must then source the replacement reagent in a chemical catalogue. Advanced students may be able to extend this and suggest using alternative chemistry. See the examples of changes to reagents listed at the bottom of the page and a brief summary of a number of SAR studies reported in the literature below.

It would be appropriate for tutors to discuss the stepwise nature of experimental design and emphasise that a logical SAR study of this scale (i.e. of only a small number of analogues) will allow pairwise comparison of compounds.

Selection of a Lead Compound: If the tutor has not assigned a lead compound, it is hoped that students will select a lead from those that are active against resistant strains of the parasite and that they will state this as the reason for the selection. Compounds **3-7** and **15-18** would be suitable leads in this respect (Report Part A, Antimalarial Workshop 2).

Selection of a Biological Assay: It is hoped that students will select the *in vitro* assays as more appropriate for SAR studies. The BHIA is useful as a preliminary screen allowing elimination of compounds that are not active in this assay early on in the SAR study. In comparison to the tritium-labelled hypoxanthine incorporation assay, it is very cheap, and it can be performed in the chemistry laboratory. It would be appropriate for students to select this assay as a first method of evaluating the target compounds. Target compounds active in this assay can then go forward to the more expensive tritium-labelled hypoxanthine incorporation assay. *In vivo* testing would not be appropriate for this type of SAR study but would be used at a later date once a promising target compound had been identified by the *in vitro* assays and the pharmacokinetics of that compound have been given appropriate consideration.

Chemical Modification: In proposing chemical modifications (*de novo* synthesis is likely to be required), it may be necessary to remind students that a well designed SAR study will ideally allow pairwise comparison of the lead and the target compounds. However, it is noted by the authors that there are many reports in the literature where more extensive changes have been made to a structure and so some flexibility may be permitted in this respect if the tutor deems it appropriate.

The synthetic routes provided are to give a starting point for group discussions. It is hoped that from these, even less experienced/less advanced students will be able to identify how one or more of the starting materials for each step could be substituted with another and therefore result in a new/target compound. Students are directed by the internal memo to the appropriate section of an organic chemistry text book (the synthesis of amines) from where they may gain additional inspiration. More experienced/advanced students may be able to draw on knowledge from other modules or will have done their own research to arrive at other solutions/target compounds.

Examples of some straightforward changes of the reagents in Schemes B1-6 that could result in 'novel' / target compounds (students should of course be mindful of the pharmacophore and/or be able to explain why a modification is of interest):

- From Schemes B1 and B2: Variation of the diamine or aniline (also see Scheme B4a and b).
- From Scheme B3: In step 1, use of a different diamine and/or in step 2, use of a different dihaloalkane will afford analogues of PQ.

- From Scheme B4a and B4b: Use of different amines in the Mannich reaction (step 1) and formation of either mono- or disubstituted Mannich products.
- From Scheme B5: Step 2, variation of the boronic acid used in the Suzuki coupling or use of an alternative palladium coupling. Step 3, variation of the Mannich reaction as described for Scheme B4.
- From Scheme B6: Variation of the X group of the aniline moiety (an EW group would be most appropriate, however see SAR studies listed below).

Other suitable changes that may be proposed: Replacement of the aniline group with a saturated equivalent in ADQ/TQ/PA series, investigation of the use of secondary amines and variation of the amino substituents at the terminal position, trimers or other repeat units of CQ (PQ series), use of another nitrogen in the quinoline nucleus (aza analogues), introduction of other substituents (in addition to 7-Cl and 4-amino) to the quinoline nucleus.

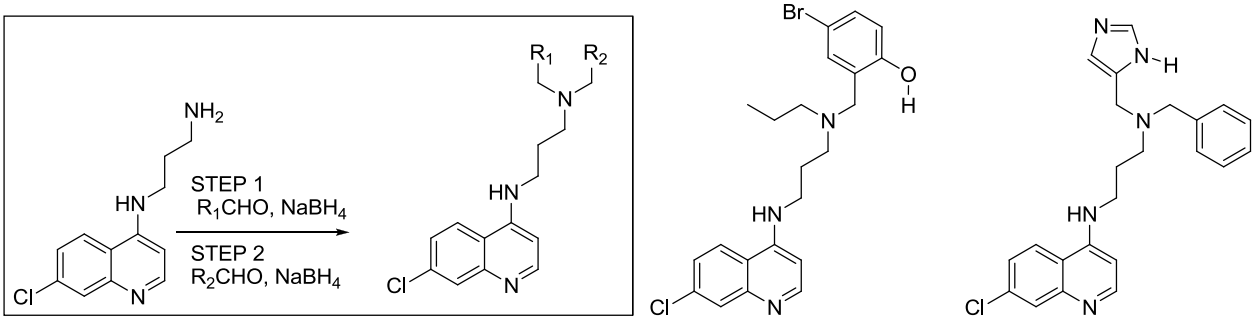
Examples of compounds from SAR studies described in the literature are provided below. The students may not require guidance from the tutor, but if they do, the following may be useful in providing direction/inspiration.

Examples of modifications in SAR studies of CQ-type analogues

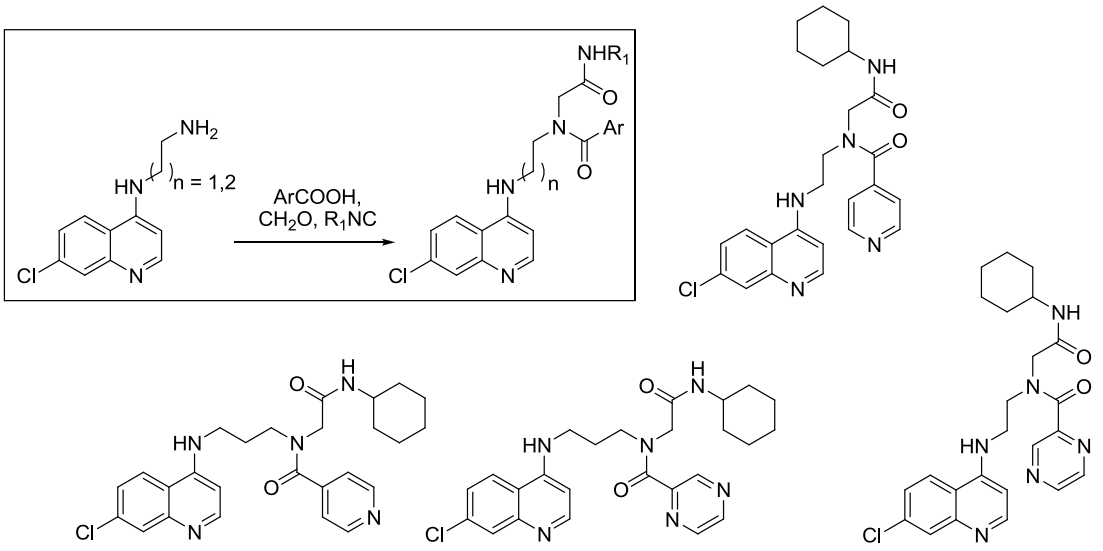
Those groups who have investigated variations of the 7-position and the groups on the terminal amine usually did so using shortened chains (2 or 3C) to overcome CQ resistance due to the CRT.

- Substitution of the terminal amino group:

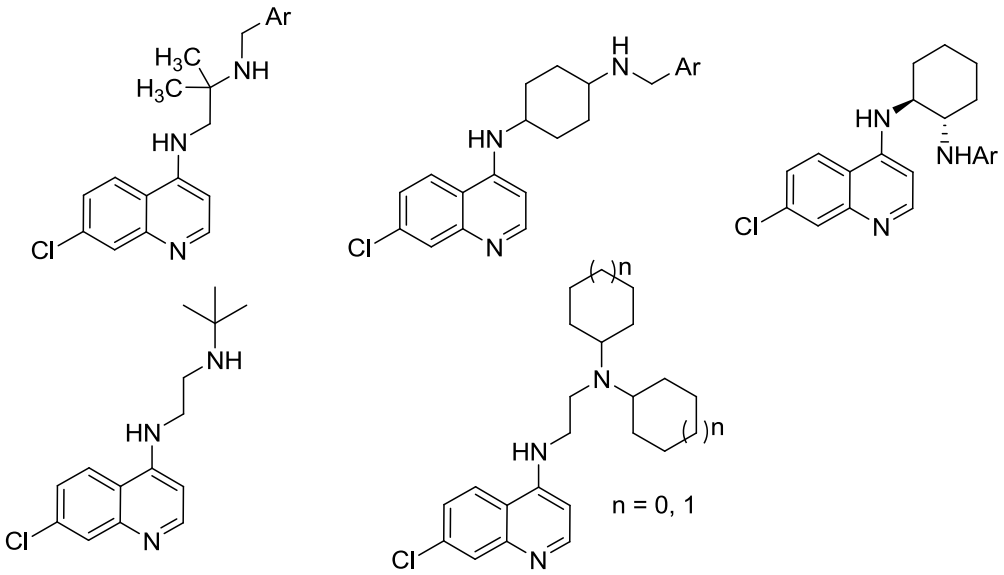
Madrid and co-workers (J. Combinat. Chem., 6, *3*, **2004**, 437-442) used successive reductive aminations to prepare 24 analogues by parallel synthesis. They identified 4 compounds with activity against resistant strains including the two shown below.



The Ugi reaction was used to introduce diversity at the terminal amino position (Musonda et al, Bioorg. Med. Chem. Lett., *14*, **2004**, 3901-3905). Analogues with protonable N atoms incorporated into the Ar substituent of the side chain were shown to have activity versus resistant strains:

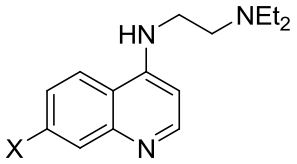


- Other analogues with activity against resistant strains (Roche group):



- Substitution at the 7-position:

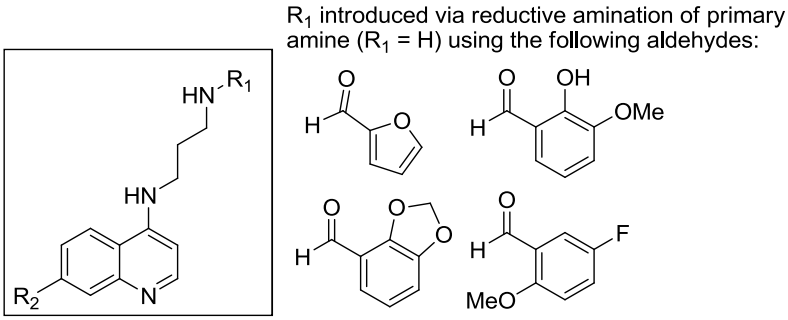
Replacement of the 7-Cl group with an electron withdrawing group (as determined by the Hammett constant σ_m) gave the following analogues with good activity versus resistant strains (Kaschula *et al*, J. Med. Chem., 45, *16*, **2002**, 3531-3539):



X = F, Br, I, CF_3

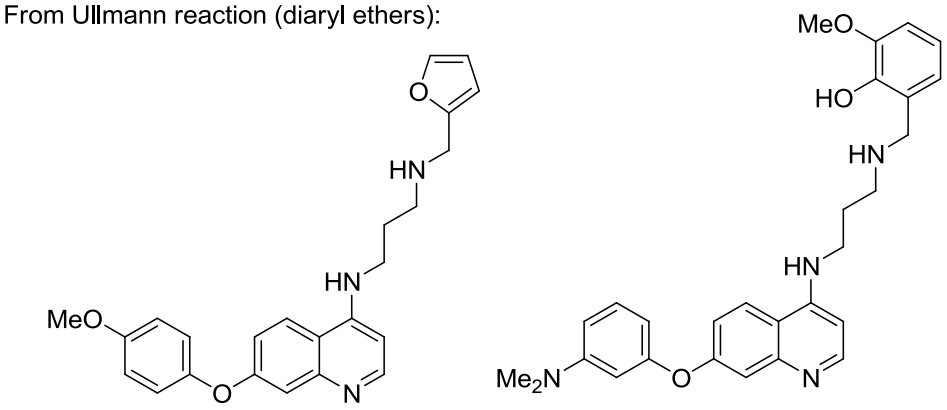
- Substitution of both side chain and the 7-position:

Hwang and co-workers (*J. Med. Chem.*, 54, *20*, **2011**, 7084-7093) employed a combinatorial approach to prepare a library of more than 100 compounds using one of the 4 aldehydes shown (introduced by reductive amination) on the terminal N and a large number of lipophilic substituents at the 7-position. 7-Substituted compounds were prepared by the appropriate coupling of the 7-Br derivative and were introduced via the Ullmann reaction (to afford 7-substituted diaryl ethers, Series 1), Suzuki coupling (to afford 7-substituted diaryl compounds, Series 2) and Negishi reagents (to afford 7-substituted alkyl or benzyl aryls, Series 3). Series 3 (the alkyl/benzyl aryl series) did not have activity versus resistant strains.

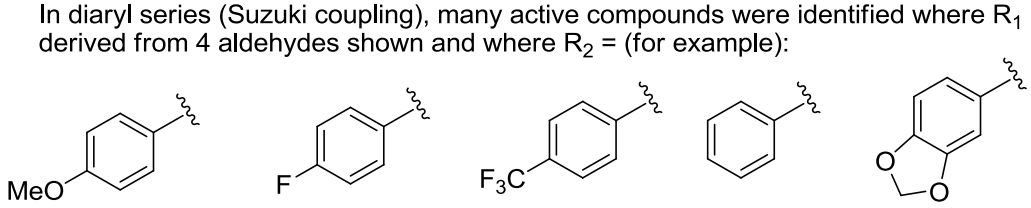


Series 1-3 were prepared from the 7-Br (R_2 = Br) derivative:
Series 1: R_2 = OAr, diaryl ethers, introduced via Ullman reaction from corresponding phenols
Series 2: = Ar, biaryl compounds, introduced by Suzuki coupling using corresponding boronic acids
Series 3: = CH_2Ar, alkyl/benzylaryl series, introduced Negishi coupling from corresponding alkyl or benzyl zincs

From Series 1, the following compounds were found to be the most active against resistant strains:

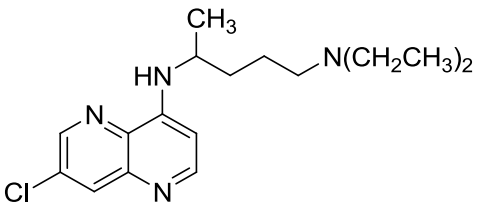


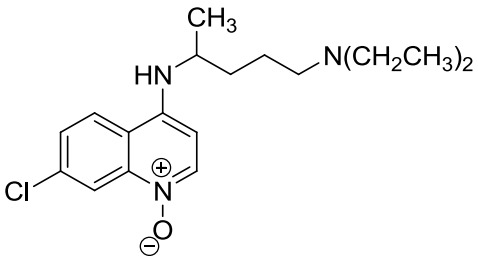
From Series 2:



- Other modifications:

The following compounds have been reported to have in vivo activity in a mouse model:

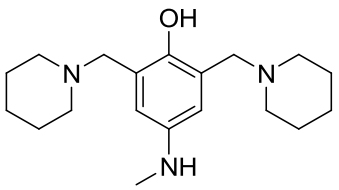


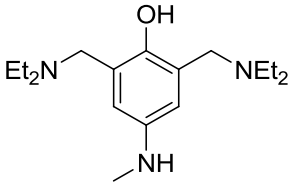


Examples of modifications in SAR studies of 4-anilino analogues (ADQ, TQ, PA)

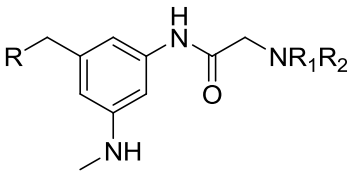
For these compounds, much of the focus has been on the removal of the 4'-hydroxy group since it ultimately leads to paracetamol-like toxicity (see Tutor Notes, Workshop 4). This group has been removed and replaced (with F) to afford analogues with activity against resistant strains. Variation of the side chain amino group has also been investigated. Examples of these types of modifications are given below.

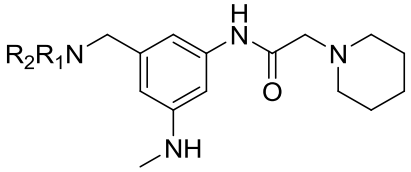
Side chains in the ADQ series:

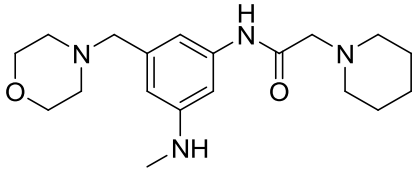


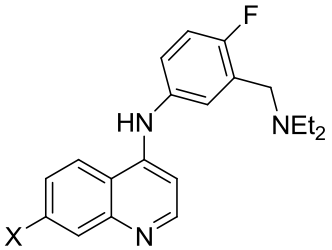


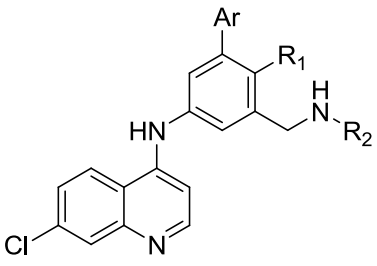
4' dehydroxy analogues





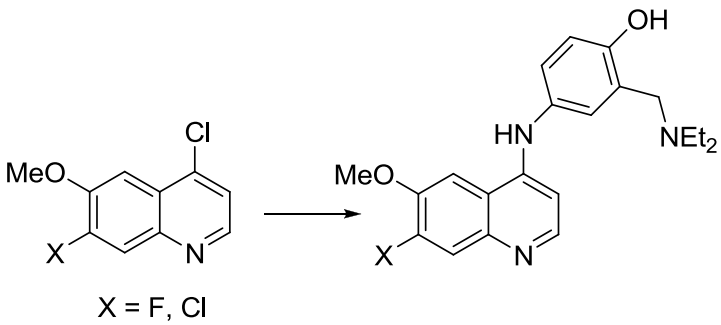






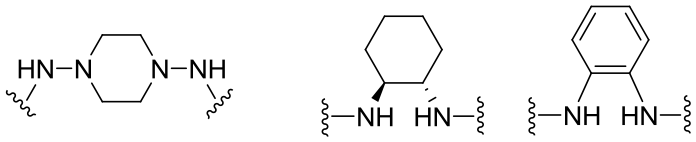
R_1 = OH or F
Ar = Introduced via Suzuki coupling from corresponding boronic acid and Ar-Br
R_2 = Mannich reaction for primary amine

One SAR study reports active compounds following modification of the quinoline nucleus:



Examples of modifications in SAR studies of PQ series

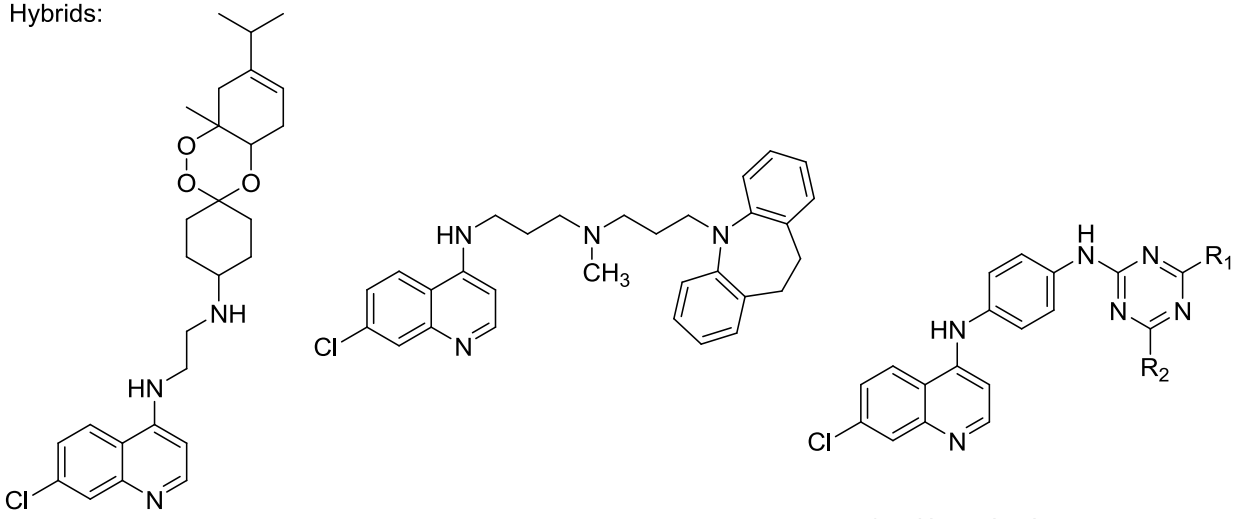
For these dimers of CQ (PQ series), SAR studies have focused mainly on variation of the linker. Some modifications of the linker that have resulted in compounds with activity against resistant strains are shown. Note that trimers have also been reported.



Miscellaneous

More recently, the literature has included examples of hybrid drugs containing a 4-aminoquinoline linked to a second antimalarial/functional compound. Examples include artemisinin-quinoline hybrids, DHFR inhibitor-quinoline hybrids (e.g. the triazine hybrid shown below), ferrocene-chloroquine hybrids and others.

Hybrids:



Workshop 4

In this section, an overview of the metabolism of CQ and ADQ and some guidance on other aspects of the Workshop that may be of use in assessing the students progress are provided.

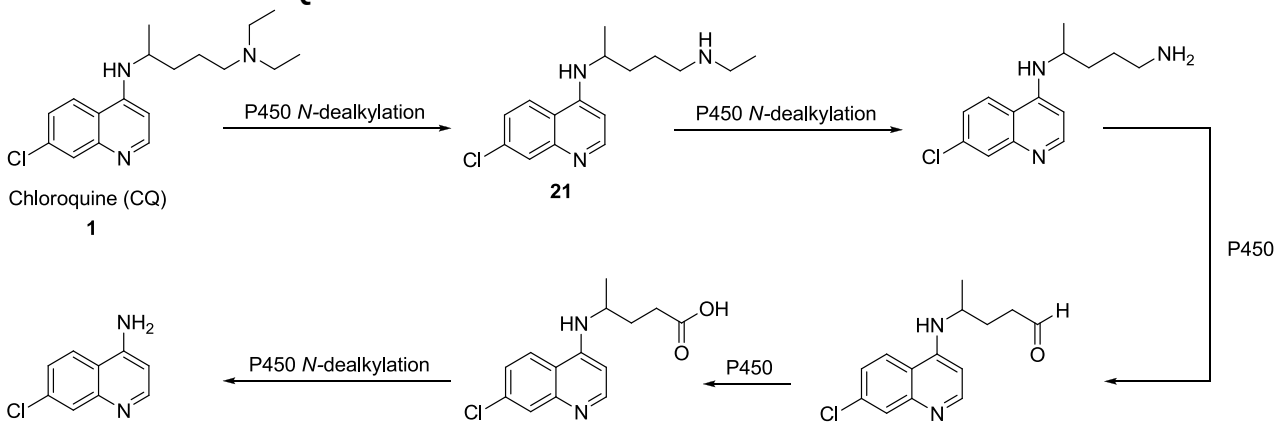
In addition to the reviews listed previously, the following review was used to compile Tutor Notes for this section: Antimalarial 4-Aminoquinolines: Mode of Action and Pharmacokinetics, E. Pussard and F. Verdier, Fundamental and Clinical Pharmacology, Vol 8, No. 1, Pages 1-17.

Rule of 5 and PSA:

Students should use the template provided for drug-likeness analyses (note that it is very similar to the template used for Learning Activity 17 in the supporting resource, "Hybrid Workshops to Support: *Molecules against Malaria: Design of a Structure Activity Relationship Study of Antimalarial 4-Aminoquinolines*"). Online drug-likeness calculators may be required to provide an estimated value of Log P and PSA (polar surface area). Note that these calculators also list the number of HBD, HBA, number of violations and rotatable bonds but students are asked to clearly identify these features in their structures for themselves. It is also of note that the quality and methods used to determine the various parameters vary greatly between versions of online calculators and tutors may wish to evaluate a number before asking students to use them.

Students are asked to identify other physicochemical and pharmacokinetic properties that will be important for the SAR study. Based on the information provided in previous Workshops, it is hoped that students may wish to determine the pK_{aH} values of the quinolonium and ammonium ions (if present) in the target structures. Credit can be awarded for other appropriate answers (log D (advanced students), for example).

The metabolism of CQ:

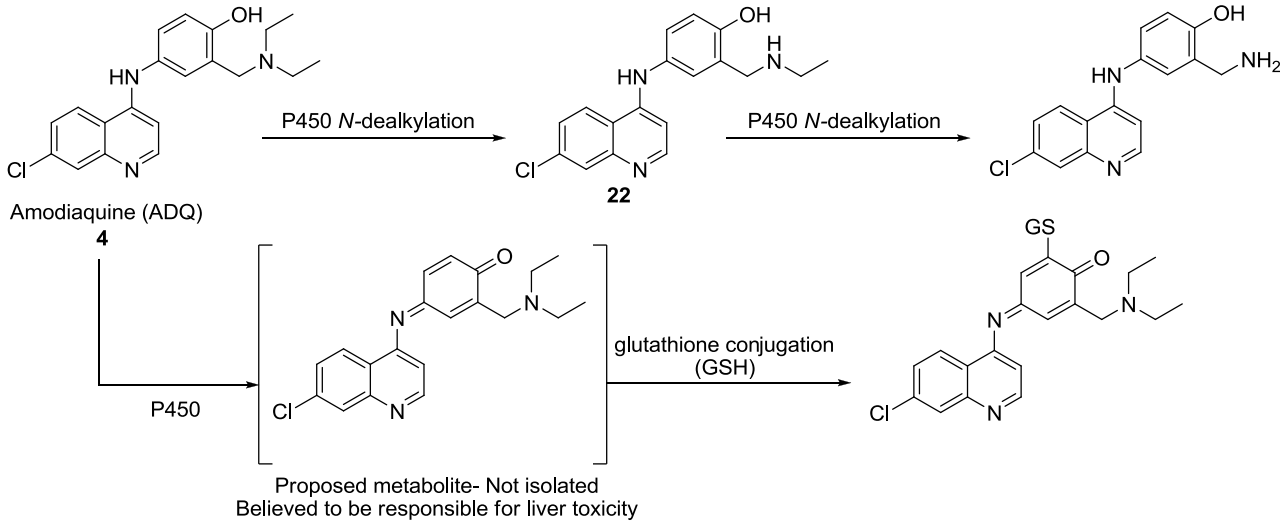


The major metabolite of CQ (detected in the urine) is the mono-desethylated compound (**21**). In rats, the subsequent oxidative deamination, oxidation and *N*-dealkylation to afford 4-amino-7-chloroquinoline was observed, however it has been suggested that metabolism is less extensive in humans. Note that CQ itself was also excreted unchanged in the urine.

The major metabolite (desethylCQ) is also active against the parasite (vs. sensitive strains) though it is much less active against resistant strains. This is true of other desalkyl analogues (and applies to ADQ, below), which are more water soluble than the parent drug and the pK_{aH} values of the secondary ammonium ions are higher than those of the corresponding tertiary ammonium ions.

The metabolism of ADQ:

ADQ undergoes rapid first pass metabolism to afford desethyl ADQ, **22**. This metabolism is so extensive that the desethyl analogue is the active drug and therefore ADQ itself can be considered to be a prodrug. While this is the major route by which ADQ is metabolised, note the second pathway in which a quinone-imine is formed (via N-OH) resulting in dose-dependent toxicity (described in the Report Part C).



Discussion of Drug-Like Properties:

A review that contains a discussion of the necessity to develop drug-like properties in lead compounds very early in the drug discovery process is:

'Hit and Lead Generation: Beyond High-Throughput Screening', Bleicher, K. H. et al., Nature Reviews Drug Discovery, **2003**, Vol 2, 369-378.

Timelines:

The tutor may wish to make the Gantt chart provided in the Student Guide available to the students in electronic format so that it can be used as a template to save time. The following information was provided in Antimalarial Workshop 4 and should be considered when preparing Gantt charts:

- Allow one week for the preparation, purification and characterisation of sufficient quantities of each target compound.
- [^{3}H] Hypoxanthine incorporation assay, day 0-day 4, 96 hours. 5 compounds per 96 well plate.
- BHIA: 36 hours of for incubation plus time to prepare plates and analyse (perhaps allow 48 hours). 7 compounds per 96 well plate.

The in vivo assay should not be used as part of the proposed SAR study but the information provided may be useful for considering the time it will take for the next stage of the drug development process: Up to 7 days (168 hours) for slow acting compounds.

Timelines from discovery to market launch:

Students are expected to indicate the main stages involved in drug discovery and development and to provide some estimates of the timeframe involved with supporting references. It would be expected that they will conclude that it is only possible to provide a very rough estimate of the time required and

that the further along the development path a project progresses, the greater the potential loss if the drug does not successfully reach the market place (this is a particular difficulty for smaller companies and organisations).
The main stages involved are summarised in the relevant chapters in Medicinal Chemistry textbooks (see also Hybrid workshop 2, Learning Activity 4, the Drug Discovery Process). Some information on timelines is available in the core textbooks recommended. For example, in Chapter 16 of Medicinal Chemistry: An Introduction, G. Thomas, 2nd edition, Wiley and Sons, Chichester, England (2007), seven to ten years is the timeframe quoted and information on the critical path for the development of a drug and the stages involved is provided.
Another text that can be consulted is:
Pharmaceutical Process Development – Current Chemical and Engineering Challenges, A.J.Blacker and M.T. Williams, Royal Society of Chemistry, Cambridge (2011). Chapter 1 in this book estimates a timeline of 12 to 15 years and considers each stage during development as well as the quantities of a potential drug required for each phase.

Details of two very useful references that students can be directed to;

- An article from Nature Reviews Drug Discovery on trends in drug development cycles – the timeline quoted is 12 – 15 years.

  B.M. Bolten and T. DeGregorio, Trends in Development Cycles, *Nature Reviews Drug Discovery*, 2002, 1, 335-336. (accessed at http://www.nature.com/nrd/journal/v1/n5/full/nrd805.html)

- A PowerPoint presentation prepared by Dr Steve Carney of Drug Discovery Today in April 2011 provides a comprehensive treatment of the main issues in relation to drug discovery and development. From slide 29 on, timelines are discussed and an estimate of 9-16 years is given.

  S. Carney, Drug Discovery: an Industrial Process. How are drugs discovered and developed? 06 April 2011, presentation (accessed at http://www.drugdiscoverytoday.com/download/494/)

Re-evaluation of Target Compounds and Synthetic Routes:

This step should only be encouraged where there is plenty of time available. It is probably sufficient that students recognise any possible problems with the pharmacokinetics of the target compounds at this stage and are able to highlight them (e.g. possible liver toxicity if quinone-imines are present).

Workshop 5

Students are *not* expected to search the scientific literature but to use the information provided, the text book and prior knowledge.

In their memo, each group is expected to summarise the advantages and disadvantages of applying parallel synthesis and high-throughput screening to their SAR study. A summary of the main points based on information from the textbook references indicated follows.

Suggested textbook references on parallel synthesis and high throughput screening:

- Medicinal Chemistry: An Introduction, G. Thomas, 2nd edition, Wiley and Sons, Chichester, England, 2007. Section 5.6, pages 170-174 on high throughput screening and Sections 5.2.2 (solid phase parallel synthesis) and 5.4.1 (solution phase parallel synthesis).
- An Introduction to Medicinal Chemistry, G. Patrick, 4th edition, Oxford University Press, Oxford, England (2009). Section 16.9, pages 324-330 on parallel synthesis and Section 12.3.5, page 194 on high throughput screening.

Parallel Synthesis

Advantages:

- As parallel synthesis involves the small scale synthesis of many compounds at the same time, it facilitates the preparation of many structurally related compounds (analogues) quickly.
- This removes a common “bottleneck” in the drug discovery and development process and is especially effective when combined with high-throughput screening (automated biological testing) which addresses the other main “bottleneck”.
- Automated systems can be applied in parallel synthesis which means that reproducibility is easy to achieve.
- There is the potential to use microwave irradiation instead of thermal methods which allows for faster reaction rates (up to 1000-fold) and improved yields are often also observed due to less side reactions occurring.

Limitations:

- The synthetic steps involved should be clean and reproducible, have high yields and involve reagents and techniques that are suitable for automation. Many advances have been made in this regard as solid supported reagents can be used and can be easily removed at the end of a reaction and solid phase extraction can be applied for work-ups.
- Data management is a very important aspect of this approach and systems need to be in place to uniquely identify and track each analogue prepared.
- As many compounds can be prepared, there can be a tendency to focus on the quantity of analogues synthesised instead of the likelihood that a given compound will provide information that is useful in the SAR study.

High throughput screening

Advantages:

- As high throughput screening allows rapid, automated primary screening of compounds for biological activity on a very small scale, once a suitable assay has been validated, many compounds can be tested in a short amount of time.

- It is particularly effective when combined with parallel synthesis which generates many analogues to be tested.

Limitations:

- Further testing is required before a compound that is shown to be active (a hit) is adopted as a lead compound.
- As with any *in vitro* test methods, information on pharmacokinetic effects cannot be obtained.
- False positives and negatives can sometimes occur.
- If the target in the assay is a protein, compounds that are known alkylating or acylating reagents should not be included as they can bind irreversibly and result in a false hit.

Application of these methods to the SAR study

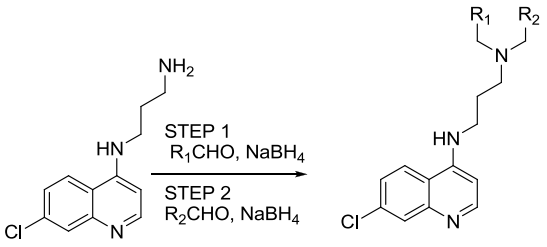
Students should comment that in using these methods, they would have the potential to make many more analogues in the time that it would take to conduct the short SAR study proposed. However, this would depend on the proposed chemistry. If the chemistry is likely to meet the criteria described it might be suitable for adaptation to parallel synthesis. However, good students may note that some time would be required for optimisation of procedures.

Any information available on conditions such as temperatures outside the parameters stated in the reference material, long heating times, use of a reagent in significant excess and extraction and purification steps that would require modification should be noted. If these details are not accessible, students should indicate that they would need to be assessed before a decision on using parallel synthesis techniques was reached and that clean, high yielding, reproducible reactions are required.

The high throughput screening bioassay has been validated and is much faster than the other *in vitro* methods presented in Report Part B in Workshop 3. This would allow elimination of compounds that are not active in this assay early on in the SAR study. Compounds active in this assay could then go forward to the more expensive tritium-labelled hypoxanthine incorporation assay. *In vivo* testing would not be appropriate for this type of SAR study, but would be used at a later date once a promising target compound had been identified by the *in vitro* assays and the pharmacokinetics of that compound had been given appropriate consideration. The possibility of obtaining a false negative in the HTS bioassay should be considered and, if it had been strongly suspected that an analogue would show activity, but it did not do so in preliminary screening, it could be considered whether to put it forward for the tritium-labelled hypoxanthine incorporation assay.

You may wish to consult or refer to the following reference which provides an example of parallel synthesis being applied in the context of antimalarials (also referred to in the notes for Workshop 3):

> Madrid *et al.,* Journal of Combinatorial Chemistry, **2004**, 6, 437-442.
>
> A three step synthesis was developed and purification was by means of an automated HPLC system. 48 compounds in which the alkyl groups on the terminal nitrogen (R_1 and R_2 in Figure X below) were modified were then prepared in 5 days by parallel synthesis using robotics. The average yield was 29% and average purity was 91%. Four compounds showed activity against drug resistant parasite strains.



Additional tools

Since the parallel synthesis workstation being made available is also suitable for solid supported reagents, combinatorial synthesis is possible (although not included as part of this task). If time allows, the tutor may like to refer to the term, and ask if students have come across it in their reading on parallel synthesis. A definition of combinatorial synthesis that may be useful is; "the preparation of a large group of related compounds ("library") by covalently bonding sets of building blocks that possess varying substituents."

An example of a combinatorial approach being applied in the context of antimalarials is described by Hwang and co-workers (*J. Med. Chem.*, 54, *20*, 2011, 7084-7093) who employed a combinatorial approach to prepare a library of more than 100 compounds (See Tutor Notes for Workshop 3).

If some students have identified additional tools that they would like to be made available, they can also be discussed briefly. They may mention molecular modelling and Quantitative Structure Activity Relationships (including 3D-QSAR) and should justify why these approaches would be appropriate. It may be useful to emphasise that all of these techniques are intended to be used only when appropriate, and often in combination with each other, and should be applied along with more traditional approaches to drug design.

The following references provide examples of these approaches being applied in the context of antimalarials:

- Molecular modelling - O'Neill, P.M. *et al.*, *Journal of Medicinal Chemistry*, **1997**, 40(9), 437-448.
  In this article, molecular modelling of chloroquine, amodiaquine and a new analogue, tebuquine, of the isolated drug and of the haem-drug complex was performed. Further modelling studies on the interaction of these 4-AQs with haem, the proposed cellular receptor, showed that favourable interaction energies resulted.
- 3D QSAR - Maurice, H. B., *Tanzania Journal of Natural and Applied Sciences*, **2010**, 1 (2), 182-195.
  This article describes "virtual" screening by 3D QSAR methods to identify molecules that can inhibit an enzyme specific to the Plasmodium parasite (initiates the breakdown of haemoglobin in red blood cells). Protease inhibitors used to treat HIV were the lead compounds used and software was used to "dock" these to the target enzyme and then 3D-QSAR methods were applied to calculate the 3D pharmacophore. 16 compounds were identified and *in vitro* and *in vivo* evaluation is now underway.

Suggested further reading

- Macarron, R. *et al.*, Impact of High-throughput screening in biomedical research, *Nature Reviews Drug Discovery* 10, 188-195 (March 2011).
- Colombo, M., Peretto, I., Chemistry strategies in early drug discovery: an over view of recent trends, *Drug Discovery Today*, **2008**, 13 (15-16), 677-84.
- Presentation on 'Drug Discovery: An Industrial Process' by S. Kearney, editor, *Drug Discovery Today*, 2011, accessed at http://www.drugdiscoverytoday.com/download/494/

Appendix 3: Notes on Using Wikis for the Tutor

A wiki is "a collaborative website consisting of one or more pages that allow authorized users to contribute to or edit page content." (source: http://usermanual.pbworks.com/Glossary)

Note that although many wikis are open access, those described for this project are secure and only those invited to join the group / wiki by the tutor administrator will have access.

Why use a wiki?

Wiki software is very easy to use and allows students to work and to write collaboratively to produce a report / presentation / webpage. The wiki is a means of generating a very useful archive of all of the information that is relevant to the assignment as the project proceeds. It provides the added flexibility of being able to work anywhere where a PC or laptop and internet connection are available at any time.

All previous versions of each page can be accessed using the Page History function which means that no work can be permanently overwritten or deleted. Contributions made by each member can be easily tracked to assess their quality, quantity and whether they were made across the entire timeframe of the assignment. Peer feedback and review is facilitated by the comments and page editing option. The assignments and the feedback provided can be accessed easily and stored indefinitely for future reference and are available in a flexible format (pages can usually be saved as PDF). Wikis are regularly used in organisations to allow groups to collaborate on projects and documents and to share knowledge and the ability to use one is a valuable transferable skill (see the references at end of this section).

Available software

The authors have experience of using PBworks, but there are several other products and most virtual learning environments now have a built-in wiki.
PBworks has a basic version that is free to use (see https://plans.pbworks.com/academic to sign up and http://usermanual.pbworks.com/w/page/11632089/Home for help)

What do academic staff need to be able to do?

In advance:

The common tasks tutors perform initially are creating new wikis, adding group members to them and adding a message to the front page. You may decide to add some of the wiki pages the group will need by adding new pages and naming them appropriately (e.g. Abstracts and Project Significance, Aims and Objectives, Identification of Lead Compound and Proposed SAR etc.). However, it is less time consuming if the students are asked to add the pages themselves – they should refer to the proposal guidelines provided to establish what pages should be added to their main Table of Contents page. It may also be helpful to create one central wiki that all groups have access to where assignment details and general feedback can be posted and all technical / academic queries can be dealt with. This will avoid duplication. Video files (e.g. tutorials on software) and audio files can also be added if you wish to do so.

On an ongoing basis:

You may have to deal with some technical queries. It is recommended that students are required to confirm that they already asked a peer about their technical problem and that they checked any guidelines they already have before they post a query to the tutor. Posting the answer in a central location accessible to all students saves considerable time and builds up a "Frequently Asked Questions" page.

You should aim to provide some feedback on progress each week if possible. This would usually be posted as a comment on each group's page although general feedback on a central wiki can also be used if similar issues are cropping up or if time is an issue. **The first week is particularly important** as students may be reticent about being the first to write on a page and often need encouragement. Students may find that adding files with their draft work in advance of their weekly group meeting and then deciding what will be added to the page at their meeting is a good way of getting started. A selection of tutor comments from previous wiki assignments assessed by the authors have been added at the end of this section and you may want to cut and paste some of these and/or begin to save some of your own to a Microsoft Word file to make this process easier. Each group is required to post a short summary of their weekly meeting (decisions made and resulting actions, people responsible and dates to be completed) and, in this way, work undertaken that may not otherwise be apparent from the wiki is captured.

What do students need to be able to do?

The common tasks students will perform are adding and editing wiki pages, adding comments and links to pages and inserting tables and chemical schemes / structures. Note that most chemical drawing software allows for structures to be saved as images and the format required by the wiki for embedding an image directly will be specified in the help menu (for PBworks wikis, images need to be in a PNG, JPEG, or GIF format). If students have not used wikis before, it is recommended that time be booked in a computer lab to allow them to practice these tasks on the wiki you have set up for each group if possible.

This should only take 30-40 minutes maximum and requires you to have obtained student e-mail addresses in advance to set up the wikis.

Some issues with wikis

Netiquette and group interaction:

The concept of "netiquette" is discussed in the student guide and is important to highlight at the outset because of the lack of visual cues when not communicating face-to-face. Students should be respectful to each other and be conscious of not offending or insulting anyone. You may want to ask the students to suggest some ground rules about working in their groups such as remaining respectful towards a group member who is not contributing, providing constructive feedback to peers (e.g. posting a comment first before making changes to someone else's work) and consulting with the group in relation to important decisions.

Plagiarism

Students may need to be reminded of the importance of providing references for information (and acknowledging the source of images) and of the need to use their own words to incorporate the ideas and information from the sources used into their report / presentation. Students can be asked to sign a declaration such as the one below (see also "A Handbook for Deterring Plagiarism in Higher

Education", Jude Carroll, Oxford Centre for Staff and Learning Development, Oxford, 2002). Alternatively, they can be asked to convert their wiki pages to PDF files and submit them to plagiarism detection software.

Example of a statement of originality;

We hereby affirm that

(1) the research and writing of this proposal/presentation is entirely our work;

(2) we have not intentionally plagiarised any portion of the proposal/presentation and have included quotation marks or references where required;

Signature: _____ Date: _____

Signature: _____ Date: _____

Signature: _____ Date: _____

Signature: _____ Date: _____

Suggested assessment criteria

Peer assessment criteria that can be used are the frequency and quality of contributions. Tutor assessment criteria that can be used for individual students are effort and collaboration (see this video of two staff from Swinburne University of Technology discussing using wikis in education for more details http://www.youtube.com/watch?v=gRj5ABJ-IPY&feature=related).

A detailed rubric for assessing contributions to a group wiki is provided on page 3 of the following reference and it is recommended that this rubric be modified as required and used: Learning to Teach Online, Case Study. Using wikis for student collaboration, Simon McIntyre, accessed 12 January 2012 at http://online.cofa.unsw.edu.au/sites/default/files/episode-pdf/CS_Wikis_LTTO.pdf.

Suggested aspects to consider for wiki assessment are provided below.

Contribution to Group (based on wiki, summaries of meetings and workshop participation)
Effort (based on wiki, summaries of meetings and workshop participation)
Peer Assessment (frequency and quality of contributions, both online and face-to-face)

Further Reading / Viewing:

A video showing how to set up a PBworks wiki for educational use:
http://www.youtube.com/watch?v=SZ5OV14v4xU

References on use of wikis in organisations:

- "Corporate Wiki Users: Results of a Survey", A. Majchrzak, C. Wagner & D. Yates, *WikiSym'06, Proceedings of the 2006 international symposium on Wikis*, D. Riehle, J. Noble, Eds. (ACM Press, 2006), vol. Odense, De, pp. 99-104, accessed 18 October 2011 at https://blog.itu.dk/MVOL-F2010/files/2010/02/corporate-wiki-users-results-of-a-survey.pdf
- A wiki to develop policy in the area of green chemistry in California is available here: http://cagreenchem.wikidot.com/start and here: http://cagreenchem.wikidot.com/welcome ;

http://eponline.com/articles/2009/02/09/calif-launches-wiki-to-develop-green-chemistry-regulations.aspx

- Ganfyd wiki is a medical database that can be edited by registered medical practitioners and viewed by anyone: http://www.ganfyd.org/index.php?title=Main_Page
- Drug Discovery Today article on use of an in-house wiki by Hoffman La Roche to share medicinal chemistry knowledge: Mayweg, A., Hofer, U., Schnider, P., Agnetti, F., Galley, G., Mattei, P., Lucas, M., Boehm, H. J.; ROCK: the Roche medicinal chemistry knowledge application - design, use and impact. *Drug Discovery Today* **2011,** *16* (15-16), 691-696.

Use of wikis in teaching and learning chemistry

- Chemistry Education Research and Practice paper that discusses using wikis to support PBL in **chemistry** (see page 26): Williams, D. P., Woodward, J. R., Symons, S. L., Davies, D. L.; A Tiny Adventure: the introduction of problem based learning in an undergraduate chemistry course. *Chemistry Education Research and Practice* **2010,** *11* (1), 33-42.
- J Chem Ed article on using wikis to promote collaboration on online lab reports: Elliott, E. W., Fraiman, A.; Using Chem-Wiki To Increase Student Collaboration through Online Lab Reporting. *Journal of Chemical Education* **2010,** *87* (1), 54-56.
- Evans, M. J.; Moore, J. S., A Collaborative, Wiki-Based Organic Chemistry Project Incorporating Free Chemistry Software on the Web. *Journal of Chemical Education* **2011,** *88* (6), 764-768.

Some useful assessment and evaluation guidelines, learning factors and project design information:

- Tsai, W. T.; Li, W.; Elston, J.; Chen, Y. N., Collaborative Learning Using Wiki Web Sites for Computer Science Undergraduate Education: A Case Study. *Transactions on Education* **2011,** *54* (1), 114-124.

Sample Front page of Wiki (input from tutor needed where highlighted)

Welcome to your Medicinal Chemistry Group Assignment Wiki (Link to Index page)

Dear Group X,
Welcome to your wiki. You can begin to add relevant links and files on background material and your group meetings and draft your proposal / presentation for your context/problem based learning assignment here. Please take advantage of the **Help** link above to the right and the links provided below by the software providers to ensure that you are using the wiki effectively. There are also some videos available on YouTube that show you how to carry out particular tasks.

Each group member can edit any wiki page or add a comment. The **Page History** link allows you to see previous versions of each page and recall portions of it if you want to do so. It also provides a permanent record of which group member did what. The **Pages & Files** tab on the top left has a number of existing templates that you can edit that you may find useful (e.g. meeting agenda). You can also create new pages with the formatting of your choice. Please use folders, link related pages and name files and pages in a logical and structured way so that you can find information here easily. To help with this, your group should select names that will be used for the pages that will make up the main body of your proposal / presentation. **There is a space limit on each wiki page. If you find that a page is no longer accepting edits, you have probably reached this limit. You will need to add a new page and link to this new page from the end of the existing one to continue that section.**

You should receive notification by e-mail on a daily basis of changes made to each page, but you can change that to a different interval if you wish to do so by altering the Notification Preferences settings at the bottom of your log-in page.

Please make sure that all members of your group have access to this wiki. If there is a problem, ask the person who has not received an invitation to the wiki to e-mail me at tutorname@xxx to request access.

Also, remember that this wiki is for academic use only, that all changes are saved and traceable and all entries made by a student are used to determine the grade obtained.

I'm looking forward to seeing the work that your group produces,

Tutor name.

Welcome to PBworks

Need Help? We're here for you:

- **The PBworks Manual** can help show you how to edit, add videos and invite users.
- The best way to get your support questions answered is to **click the help link** at the top of this page. Our support gurus will get back to you asap.

Sample feedback comments from wikis used previously

The purpose of the weekly reviews is to identify the most significant misunderstandings or errors made and not to give detailed feedback on the wiki content. Common errors include plagiarism of large sections of material and not including the references of source material, for example. You may also find that a group has not understood an aspect of the proposal or has failed to address a task or topic and you can correct this error at an early stage. You will find that feedback comments often apply to several groups and therefore we recommend saving your comments in a Word document and re-using them as appropriate.

We recommend that you spend no more than 15 minutes reviewing each wiki.

Initial comments

- This is a reminder to start to use this wiki to plan your group assignment. Please make sure that you discuss it as a group (face to face or in an online chat) and post some minutes with a summary of group decisions as soon as possible. It is recommended to assign two roles in meetings that rotate each week - a "chair" (organises meetings, decides on agenda and running order and deals with any differences of opinion) and a "recorder" (records a summary of the decisions made and resulting actions, people responsible and dates to be completed meetings). Good luck with your assignment.
- You've made a good start here. Hopefully the other people in your group will also begin to contribute soon.
- This looks good so far. Can you add the reference numbers in below the relevant images though, and add them into the text where relevant too.
- Your page is coming along very well. You've done a lot of research so far and found some interesting information.

Positive comments

- The pages are well researched and referenced in general.
- Relevant schemes and images have been used and they have been referred to.
- Well done on preparing a well researched and clearly structured report/presentation with relevant schemes and images that all team members contributed too.
- Your work has been carefully checked and proofread and the wiki page history shows that you were all contributing.

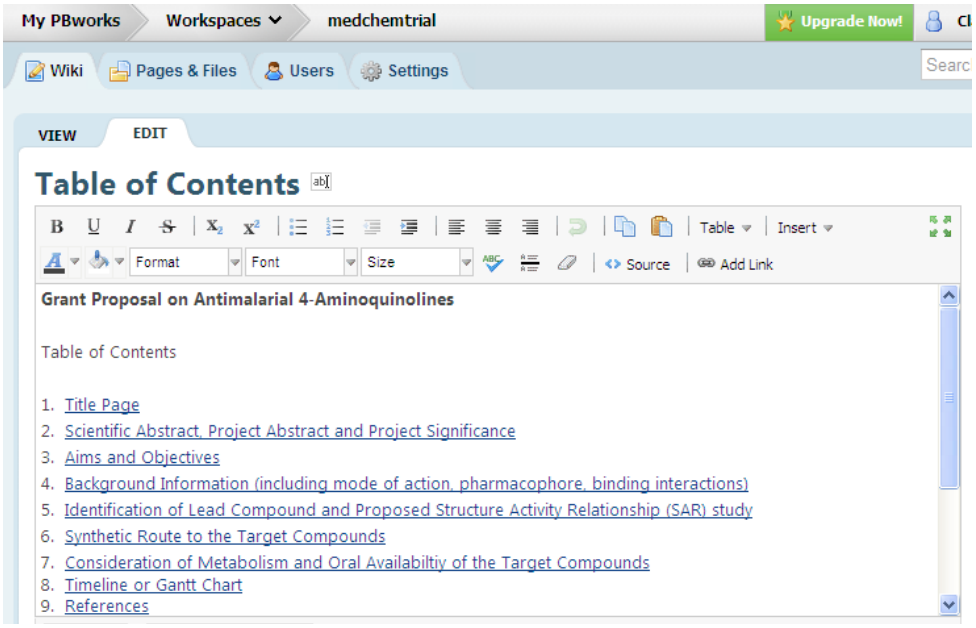
Room for improvement

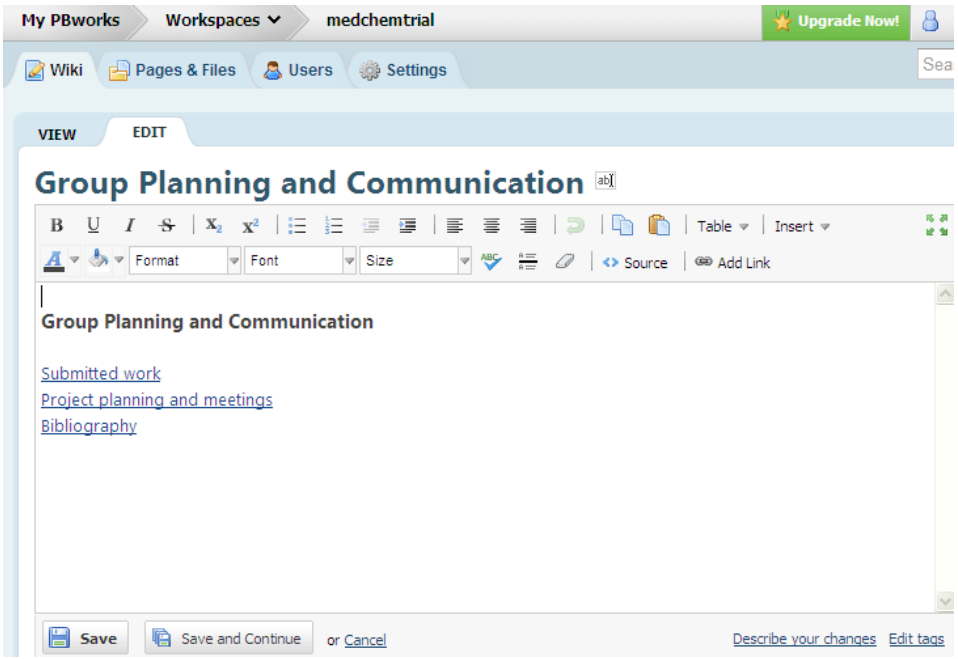
As far as possible, any comment on an improvement that could be made was prefaced by a positive comment on another aspect of the wiki.

- There is some repetition of information - particularly about xxxxx.
- The overall report/presentation is quite long and is in need of a final edit - for structure and content and language errors.
- It is important that a group make sure they have time to review their work together towards the end and edit it to make sure that there is no repetition and that all information can be clearly understood.
- Only include information that you understand yourself and explain all scientific and technical terms which would be unfamiliar to your peers.
- More textbook references instead of websites would have been nice to see.
- Add references for information you have given where appropriate.
- Be careful that you have put all information in your own words and haven't plagiarised.

- A diagram/table/scheme in the section on xxxxxx would be helpful.
- Information on xxxxx was not included. Please add this before submission of the final version.
- Include a few more chemical structures.
- Look over where xxxxx is discussed. It could be made clearer.
- Make sure that one or two people edit the whole report/presentation at the end to make sure that there is a "flow" between the sections and a similar style is used all the way through.
- Give the information required in the correct format in the references e.g. article authors / journal name / place published for a text book.

Screenshots of a Sample Wiki Showing the pages Linked to the Two Main Pages





Appendix 4: Learning Outcomes of Hybrid Workshops 1-5 (Principles and Concepts)

The following learning outcomes summarise the prior learning that the authors believe is required for students participating in the Antimalarial Workshops. A supporting resource "Hybrid Workshops to Support: *Molecules against Malaria: Design of a Structure Activity Relationship Study of Antimalarial 4-Aminoquinolines*" is available and is designed to take approximately 10 hours of contact time.

Students should be able to:

- Provide a definition of the term 'drug' suitable for use by a medicinal chemist.
- Provide a definition of the 'therapeutic index', use the therapeutic index to assess drug safety and describe the limitations of the application of the therapeutic index.
- Classify drugs by a number of methods and discuss the reasons for attempting classification and the possible advantages or disadvantages of these methods.
- Describe the drug discovery and development process, be aware of all the stages involved and be able to identify those that require input from a medicinal chemist.
- Describe the stages of drug action and duration, and explain what takes place during each stage and the objectives of the stages.
- Explain what is meant by the term 'pharmacodynamics' and, from the structure of a drug and binding site, identify binding interactions.
- Describe the stages involved in a SAR study.
- Use IC_{50} data to compare the biological activity of drugs.
- Explain what is meant by the term 'pharmacokinetics' and describe the processes that a drug will undergo on entering the body (ADME).
- Describe how the physicochemical properties (i.e. log P, pK_a) of a drug affect drug action and oral availability (i.e. application of Lipinski's Rule of 5, use of PSA and rotatable bonds).
- Explain how pharmacokinetic parameters can be obtained from experimental data and use of these parameters.

In addition to the learning outcomes above, the Hybrid Workshops are also used to introduce students to a PBL approach and allows them to practise other transferable skills that will be developed further in the Antimalarial Workshops.

- Problem solving: Learners work in groups to address the brief presented in the context / scenarios provided.
- Team work: Learners work in teams to complete the problems.
- Independent learning: Learners are required to read about many of the topics in order to solve the problems and must be able to explain their answers in full.
- Communication: Learners will be asked to feed back their answers to the class and to give a short presentation.

Appendix 5: Sample Gantt Chart

Work package	Day X-Y	Day X-Y	Day X-Y	Day X-Y	Day X-Y	Day X-Y
WP1						
WP2						

The work packages must be named and described.

Appendix 6: Checklist for Submission of Final Research Proposal

Have they included the following in their final research proposal?

- A scientific abstract (maximum 200 words).
- A project abstract (aimed at a lay audience, maximum 200 words).
- A short summary that addresses why the problem is significant, the benefit of the proposed work to society in the UK / Ireland and in a country of the applicant's choice in which malaria is endemic (maximum 200 words).
- Have references been included in the correct format?
- Have all sources of information and any diagrams, schemes, tables etc that are not their own been correctly referenced?
- Is proposal within the word limit of 2000 words?

Student should cover the following in the main body of the proposal:

- A section / paragraph outlining the aims and objectives of the SAR study in the main body.
- A section / paragraph providing appropriate background information including the mode of action of quinoline antimalarials (including the drug target and -interactions between the drug and the drug target).
- Has a lead compound been clearly identified and a justification provided for the selection?
- Have structures been proposed for 3-5 new analogues, giving the synthetic route that the group intend to use and the method or methods that they will use to assess their antimalarial activity?
- Have they explained why the lead compound was selected and modified in the ways suggested?
- Have they explained why they have used the method or methods selected for biological evaluation?
- Have they included a section about the possible route of metabolism of their new analogues, proposing structures of the metabolites and applied Lipinski's rule of 5 and / or PSA /rotatable bonds to each of their analogues, explaining the impact of these factors on the overall 'drug-likeness' and oral availability of the compounds?
- Have they provided definitions for all of the terminology used?
- Have they included a Gantt chart for the proposed work and an estimate of the time for taking any successful compounds from bench to clinical use, with a brief explanation?

Appendix 7: Presentation Skills Evaluation Form

Presentation Skills Evaluation Form

Speaker/ Group:

Topic:

What I liked:

Suggestions:

Date **Signed (Optional):**

Presentation Skills Evaluation Form

Speaker/ Group:

Topic:

What I liked:

Suggestions:

Date **Signed (Optional):**

Appendix 8: Guidelines for the Reflective Piece

In this short report (500 to 800 words approximately), students should:

1. Briefly describe his / her role in the project and the contribution he /she made.
2. Discuss how he / she experienced working in a team (consideration of both the positive and negative aspects).
3. Discuss any changes that he / she would make to how he / she and the group as a whole went about the project if they were to repeat it.
4. Summarise what he / she found to be most the interesting aspect of the project as well as the most challenging aspect.
5. Consider whether he / she thinks the project was useful to his / her learning and whether all of the learning outcomes (see page 13) were met.
6. Assess whether he / she has developed the transferable skills listed as a result of this project. Highlight any that he / she thinks are particularly important or that he / she has gained confidence in.
7. Consider whether he / she has found that writing a reflective piece like this helps to review what was learnt over the course of the project.

This reflective piece is assessed based on:

- **Content** (60% - there are no right or wrong opinions but you must make sure that you discuss **all** of the topics listed above)
- **Presentation** (10%) and
- **Coherence, accuracy and structure** (30%).

Appendix 9: Resource Evaluation Forms

Questionnaire On Context/Problem Based Learning Antimalarial Case Study and Medicinal Chemistry Learning Activities

The questionnaire is completely confidential and will be made anonymous.
Please answer all questions to the best of your ability and with reference to your workshops on Medicinal Chemistry this semester.

It will take approximately 15 to 20 minutes to complete this survey.

Course/ProgrammeTitle: _____

Year of Course: Year _____ of _____ (e.g. Year 2 of 3)

Module Title: _____

Have you signed the consent form? Yes ☐ No ☐

Attitudes and Views on Learning Medicinal Chemistry

A number of paired statements are presented below which may or may not reflect your views on learning about medicinal chemistry and your experience of this to date. Please tick the box which best reflects your opinion / feeling about each pair of statements.

If you don't understand a statement, please leave it blank. If you have no strong opinion, choose neutral.

	Strongly Agree	Agree	Neutral	Agree	Strongly Agree	
1) I am enjoying medicinal chemistry						I am not enjoying medicinal chemistry
2) I feel I am coping well with medicinal chemistry so far						I feel I am not coping well with medicinal chemistry so far
3) I have found medicinal chemistry easy so far						I have found medicinal chemistry difficult so far
4) I work well as a member of a group						I do not work well as a member of a group
5) I feel that working on the learning activities has improved my overall confidence in medicinal chemistry						I do not feel that working on the learning activities has improved my overall confidence in medicinal chemistry
6) I feel that working on the antimalarial case study has improved my overall confidence in medicinal chemistry						I do not feel that working on the antimalarial case study has improved my overall confidence in medicinal chemistry
7) It is important to know how a topic relates to the "real world"						It is not important to know how a topic relates to the "real world"
8) It is important to know how a new medicinal chemistry topic relates to what I already know						It is not important to know how a new medicinal chemistry topic relates to what I already know

	Strongly Agree	Agree	Neutral	Agree	Strongly Agree	
9) Sometimes I find I learn more about a subject by discussing it with other students than I do by sitting and revising at home						I never find I learn more about a subject by discussing it with other students than I do by sitting and revising at home
10) A lot of the material in medicinal chemistry does not make sense to me so I just memorise the information.						A lot of the material in medicinal chemistry makes sense to me so I do not just memorise the information.
11) When I am answering medicinal chemistry questions and problems, I often do not really understand what I'm doing.						When I am answering medicinal chemistry questions and problems, I usually understand what I'm doing.

Learning Outcomes

A number of statements are presented below that relate to the expected learning outcomes for your medicinal chemistry module. Please tick the box which best reflects your evaluation on whether these outcomes have been met.

If you don't understand a statement, please leave it blank. If you have no strong opinion, choose neutral.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
I can describe the phases of drug activity.					
I can identify binding groups and binding interactions (pharmacodynamics).					
I can explain the importance of adsorption, distribution, metabolism and excretion for drug action: (pharmacokinetics).					
I can suggest how the structure of a drug can be altered & explain how the changes may affect activity.					
I can differentiate between various compounds in terms of the possible effect of functional groups on binding interactions and physiochemical properties.					
I can propose synthetic routes (by chemical modification of a lead compound or de novo synthesis of analogues) to a new drug.					
I can interpret IC_{50} data and therefore determine the effectiveness of a compound in the context of SAR studies.					
I am aware of the need for and types of assays that are used for the biological evaluation of compounds in the context of SAR studies.					

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
I can describe the drug development and drug discovery process from 'bench to bedside', and am aware of the timelines involved.					
I am aware of the issues of drug resistance and the problems it causes.					
I can critically evaluate the use of high throughput screening and parallel synthesis as tools in the development of new drugs.					
I appreciate the importance of the study of medicinal chemistry and how it impacts on everyday life.					

Development of Transferable Skills

A number of statements are presented below that relate to the development of transferable skills in your medicinal chemistry module. Please tick the box which best reflects your evaluation on whether these skills have been developed.

If you don't understand a statement, please leave it blank. If you have no strong opinion, choose neutral.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
My team work skills have improved.					
My ability to adopt a professional role has developed.					
My ability to draw conclusions and recommendations from data has improved.					
My written communication skills have improved.					
My oral communication skills have improved.					
My problem solving skills have improved.					
My ability to use information technology has improved. (wiki, word-processing and presentation software and library databases).					
My ability to reflect on my work has improved (evaluating the extent to which the stated learning outcomes were met and transferable skills were developed.)					

1. Prior to this series of lectures, were you regularly involved in group work during lectures for your other modules?

   Yes (regularly) ☐ Yes (sometimes) ☐ No ☐

   If Yes, please give details (module name): _____

   _____

2. Would you feel more comfortable discussing a solution to a learning activity with another student or with a small group of your class mates now?

More than at the beginning of this module ☐ Unchanged from the beginning of this module ☐

If you would like to comment further, please do so here:

_____

3. Would you feel more comfortable presenting a solution to a learning activity to the entire class group now?

More than at the beginning of this module ☐ Unchanged from the beginning of this module ☐

If you would like to comment further, please do so here:

_____

4. In relation to the examples of drugs provided during the workshops, do you think that using real life examples made the topics easier to understand?

Yes ☐ No ☐ Unsure ☐

If you would like to comment further, please do so here:

_____

5. In relation to the antimalarial case study, do you think that using the grant proposal scenario;

(i) helped you to understand the topics?

Yes ☐ No ☐ Unsure ☐

(ii) made the applications of medicinal chemistry more obvious to you?

Yes ☐ No ☐ Unsure ☐

If you would like to comment further, please do so here:

_____

6. Do you prefer the active learning / group work approach used in this module to the more traditional teaching approaches you have encountered in other modules?

Yes ☐ No ☐ Unsure ☐

If you would like to comment further, please do so here:

_____

_____

7. Did you notice any difference during this module in your interaction with your lecturers as a result of the active learning activities and case study used?

   Yes ☐ No ☐ Unsure ☐

   If you would like to comment further, please do so here:

   _____

   _____

8. Do you have any suggestions for changes or improvements to the medicinal chemistry learning activities or to the case study on antimalarial drugs?

_____

_____

_____

Thank you for taking the time to complete this questionnaire.

Appendix 10: Making It Work

Keeping the Project on Track

In order to relieve the cognitive workload in each Workshop, some of the trial teams recommended that the student handouts should be circulated at least 24 hours (and up to a week) in advance to give students time to read the new material before each class.

Tutors should give lots of verbal reminders to the students throughout the Workshops to ensure that each group is keeping up with the tasks assigned.

Identify groups that are struggling early on. With this type of project work, when students fall behind they can easily become overwhelmed and often respond by failing to engage with subsequent tasks and activities. It may be useful to remind students that while they may struggle with one aspect of the Workshops, they will find other tasks easier.

Workload

The nature of the C/PBL approach generally means that there is often a heavier workload for tutor and students during the term time and this was noted by the trial teams. However, there is no end-of-module exam to sit or mark. It is often very rewarding for the tutor as it involves a more personal and interactive approach (and misunderstandings can be identified and corrected immediately, etc). Placing the problem in context makes it 'come alive' for the students who are generally more engaged and enthusiastic. In addition, the students and tutors involved in the trial felt that transferable skills gained were very valuable.

If the students are struggling with the workload, we recommend that you can change the resources in the following manner:

- Omit Workshop 5 and replace with an additional work-in-progress clinic.
- Ask students to present directly from the wiki rather than prepare a PowerPoint presentation.
- Decide to assess the project either by a presentation or a proposal (and the wiki).

Note that one of the trial teams felt that designing the synthetic routes to new compounds was inappropriate for the group concerned as they had relatively little experience of synthetic organic chemistry. Cleverly, an internal memo was used as a device to inform the students that the synthesis was to be outsourced to Inspired Pharmaceuticals Ltd.

Group Work

Students with little or no experience of group work will often find this aspect of the module challenging. It is useful to remind students that group work is representative of the challenges that exist in the workplace and is a valuable learning experience and a vital part of their professional development - it is important that you emphasise that this aspect of the project is important.

Tutors and students with no experience of group work are directed to the following text;
Chapter 3 in "Study and Communication Skills for the Chemical Sciences"; Overton, T., Johnson, S., Scott, J.; Oxford University Press (2011).

The tutor should pre-assign the student groups so that; there are a range of abilities and skills, international students are fully integrated with domestic students and, if possible, that students get an opportunity to work with people they may not know very well. One other important consideration is that

each member of a group should have similar class contact timetables so that it is easy for them to arrange to meet.

It is important that the groups get off to a good start. For example, we have suggested that allowing students to choose a group name and design a logo is a good ice-breaker and gives them a team identity. In addition, the assignment and rotation of roles (Chair, Recorder and Editor), regular group meetings and the assignment of tasks are also designed to ensure that the groups will work together.

If some tensions become apparent in a group over the weeks that follow, it is likely to be as a result of one member not contributing, a personality clash or one person working on their own and not collaboratively. The tutor should review the wiki and the minutes from group meetings as early as possible in the project (every week is recommended). You don't need to spend more than 10-15 minutes per group to do this, but the extent of collaborative group work should be apparent from these. It is important that you identify and address problems as soon as possible.

Student who are not contributing:

At the first instance, at the start of the next Workshop, you should remind the group as a whole that the method of assessment (monitoring of the group wiki and weekly minutes) ensures that those not contributing or collaborating effectively will lose marks. If using peer assessment, remind the students that they themselves will be able to penalise students that are not contributing. If this does not work, the tutor will need to address the individual concerned - try to ascertain whether there are external issues that are preventing the student from participating fully in the project. If not, inform the student that you will apply a penalty and then inform the group as a whole – once the appropriate penalty has been applied, groups are often happy to take back the offender.

Students who are dominating group work:

While it may be easy to spot someone who is not contributing, sometimes one person may be working alone and not collaboratively. In this case, you may notice that one personality is dominating the wiki (minutes to meetings may also reflect this) either by posting large volumes of material or substantially editing other students' work without adhering to netiquette (e.g. failing to post a comment before making changes to someone else's work).

Remind students that the group work and group product is assessed - working alone will result in a lower mark. Also point out that the tutor can observe individual intellectual contributions from the wiki and minutes of group meetings. There is no need to withhold ideas from other members of the group: An effective team needs to take into account the skills of its individuals, recognising strengths and weaknesses and assigning tasks accordingly - while one person may have a lot of good ideas, another individual may be good at executing those ideas to produce a good product.

The group breaks up:

In some cases, tensions within a group may escalate and the group may fracture. This type of problem cannot be addressed easily within the Workshops themselves and at this stage it will be necessary to ask all of the group members to meet with you outside of the Workshops to discuss the problem. One of the trial teams faced a group of 4 that had divided into 2 groups which sat on opposite sides of the classroom. The group met with the tutor and they were informed that they could continue in their smaller groups but that they should recognise each group would have half the labour

and double the workload of the original larger group. This group went on to resolve their differences and made it to the end of a module as a single cohesive unit.

Misunderstanding Concepts and Principles

The Pharmacophore

Workshop 2, Report Part A: Students did not recognise that the pharmacophore of the 4-AQs should be obtained by considering only the active compounds (and particularly focusing on those with activity versus resistant strains). The tutor may need to ensure that students know the definition of the term 'pharmacophore' (perhaps via a PowerPoint slide).

The acid-base properties of drugs

Workshop 2, Report Part A: Students are required to explain why 4-AQs accumulate within the parasitic food vacuole by recognising a pH gradient and ionisable groups in the pharmacophore. Within the 'Notes for Tutor' for this Workshop, we have recommended a learning activity within the Hybrid Workshops and two texts that may be of use in explaining and addressing students' understanding of the acid-base properties of drugs and how these affect absorption and distribution (and in this case, accumulation).

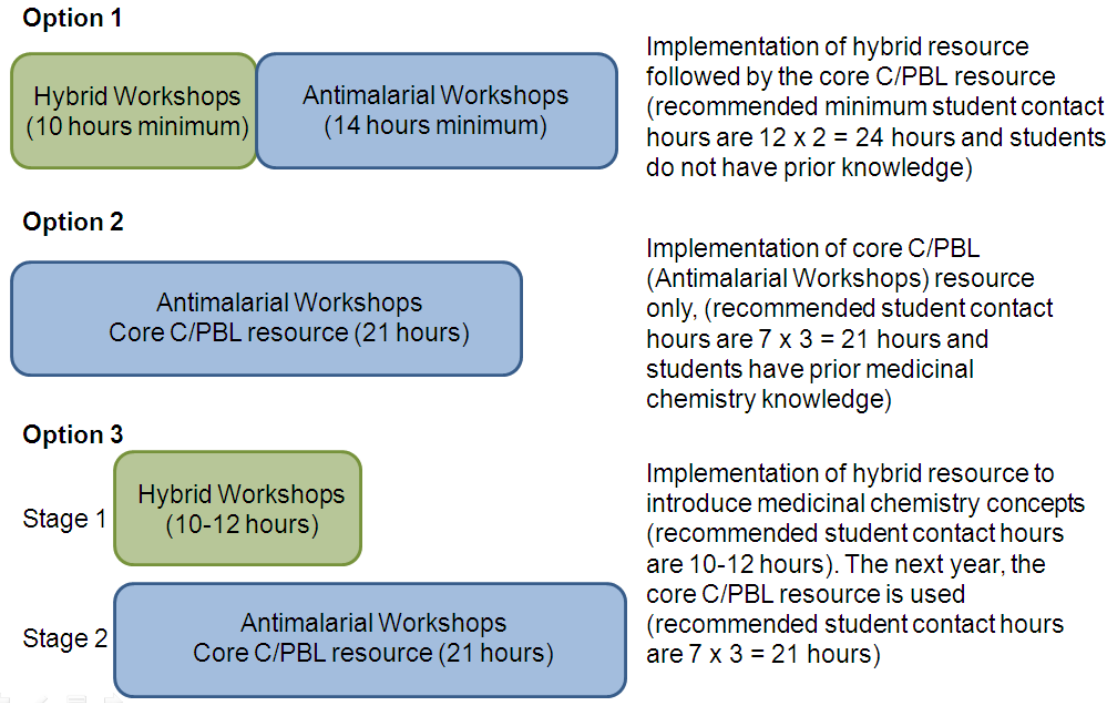
IC_{50} values

Workshop 2, Table A1 (Report Part A): The IC_{50} values presented are for inhibition of parasite growth. Tutors are advised to direct students to the text (underlined) 'Table A1 shows the reported *in vitro* activity of compounds **1-20** against chloroquine resistant and chloroquine sensitive clones of the malaria parasite (*Plasmodium falciparum*) as determined by the hypoxanthine incorporation assay which measures the inhibition of parasite growth.'

Nomenclature:

- Haem is a Fe(II) centred porphyrin that is a product of haemoglobin breakdown.
- Haematin is the Fe(III) centred hydroxide of haem (Fe(III) protoporphyrin IX).
- Haemozoin is also known as the malaria pigment. It is composed of strands of Fe(III) porphyrin dimers units linked by propionate oxygen-iron bonds and into the polymer by hydrogen bonds between the remaining propionic acid group on each porphyrin (Silvina Pagola *et al*, Nature, **2000**, *404*, pp 307-310).
- β-Haematin is the synthetic form of haemozoin and has been shown to be spectroscopically and crystallographically identical (Silvina Pagola *et al*, Nature, **2000**, *404*, pp 307-310).

Appendix 11: Alternative Modes of Delivery



The resource has been written to facilitate **Option 1** and the timings indicated throughout the tutor guide reflect that.

Option 2: If the core resource (the Antimalarial Workshops) is being used on its own and the students have not been introduced to C/PBL, working in their groups and using a wiki, it is recommended that 21 contact hours would be allocated for Antimalarial Workshops 1-7 (7 x 3 hour sessions or 7 x 2 hour sessions plus a one hour tutorial per Workshop). With an additional 29 hours for independent learning and self-study, this would equate to 2.5 European Transfer Credit System (ECTS) or 5 UK credits of work or 1.5 US credits.

If students already have experience of C/PBL, group work and / or using a wiki, or if less contact time is available, 18 hours is thought to be a feasible time allocation for option 2. In this case, 3 hours should be given to Antimalarial Workshops 1-5 and only 2 hours to Workshops 5-8. Alternatively, Workshop 5 could be omitted (see Make It Work, Appendix 10, Workload for suggestions about stream-lining the workload).

Where timings have been indicated in the guide, they refer to a two hour workshop. If a three hour timeframe is available, an activity that is timed for 40 minutes can be extended to 1 hour and an activity scheduled for an hour can be extended to an hour and a half.

Option 3 suggests that the hybrid workshops are implemented in one year (which could be the first year of a chemistry degree, for example) and are allocated 2.5 UK credits and the core resource is used the following year. It would be expected that the core resource would require 18-21 hours of contact time as described for option 2 above.

One of the trial teams suggested a **4th option.** This involves full integration of the Hybrid and Antimalarial Workshops, thus delivering the material contained within the Hybrid Workshops as needed to 'solve' the Antimalarial Workshops. If following this option for delivery, Antimalarial Workshop 1 and the use of wikis should be delivered first, followed by Hybrid Workshops 1-3, Antimalarial Workshops 2 & 3, Hybrid Workshops 4 & 5 and finally Antimalarial Workshops 4-7.