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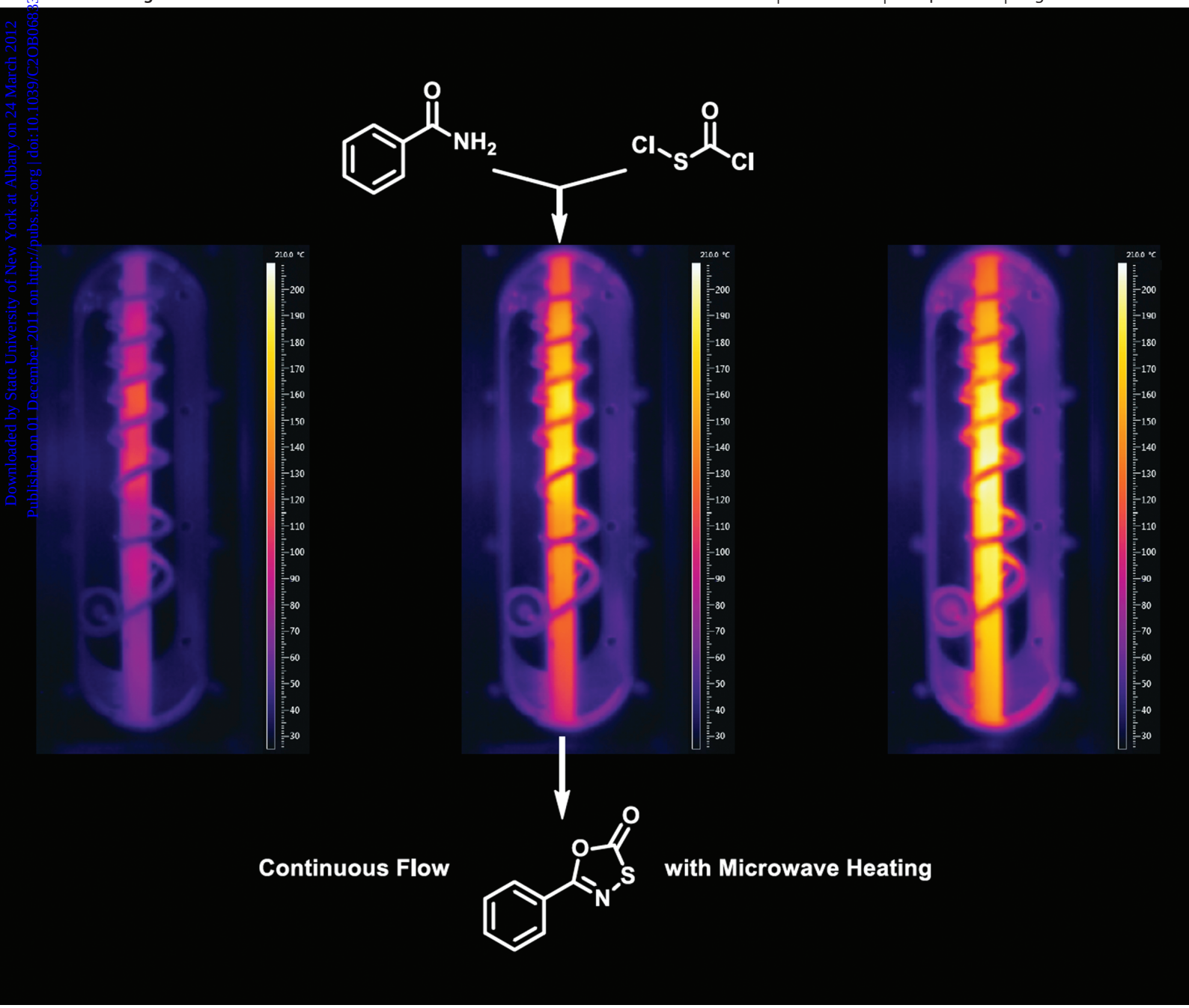

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PERSPECTIVE

Microwave-assisted synthesis of small molecules targeting the infectious diseases tuberculosis, HIV/AIDS, malaria and hepatitis C

Johan Gising, Luke R. Odell and Mats Larhed*

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The unique properties of microwave *in situ* heating offer unparalleled opportunities for medicinal chemists to speed up lead optimisation processes in early drug discovery. The technology is ideal for small-scale discovery chemistry because it allows full reaction control, short reaction times, high safety and rapid feedback. To illustrate these advantages, we herein describe applications and approaches in the synthesis of small molecules to combat four of the most prevalent infectious diseases; tuberculosis, HIV/AIDS, malaria and hepatitis C, using dedicated microwave instrumentation.

1. Introduction

Microwave ovens were introduced into analytical chemistry in the late 1970s and the first articles reporting that microwaves could be used to accelerate organic reactions appeared in 1986.[1,2] The uptake of this new heating technology in the synthetic chemistry community was initially slow due to problems with reproducibility, controllability, and safety aspects, together with a generally low degree of understanding of the basic principles of microwave (MW) heating (the fact that all polar solvents can be heated with microwaves and not only water was not generally recognised).[3–7] However, it has gained in popularity, and sophisticated microwave systems can today be found in most well-equipped organic and medicinal chemistry laboratories in industry and academia.[8] The reason behind its popularity lies in the user friendly instrumentation and its outstanding ability to reduce reaction times by superheating of organic reactions in sealed vessels.

All domestic microwave ovens, as well as the commercial reactors found in chemistry laboratories, operate at 2.45 GHz in order not to interfere with the wavelengths used for radar or telecommunication. This frequency corresponds to a wavelength of 12.2 cm and is located between the infrared and radiowave wavelengths in the electromagnetic spectrum. Dipolar polarisation is

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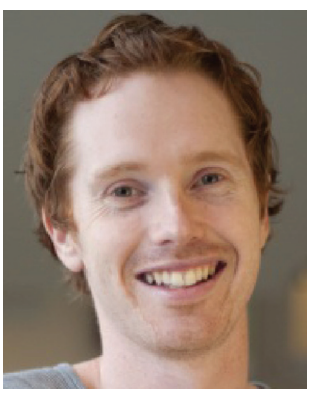
Johan Gising

Johan Gising was born in 1981 in Falun, Sweden. In 2001, he commenced undergraduate studies at Uppsala University and, in 2006, he received a master degree in pharmaceutical chemistry. In the same year he began his PhD studies under Professor Mats Larhed and Professor Anders Karlén and he will defend his thesis during the spring of 2012. His research focus has been the design, synthesis and physiochemical properties of new inhibitors targeting enzymes for the potential treatment of tuberculosis, hepatitis C and HIV.



Luke Odell

Luke Odell was born in Tamworth, Australia in 1981. He graduated with an Honours BSc in Forensic Science from the University of Newcastle, Australia in 2002. He completed his PhD studies at the same university under the guidance of Professor Adam McCluskey in 2006 working on the synthesis of enzyme inhibitors. In 2006, he took up a postdoctoral position with Professor Mats Larhed at Uppsala University. Since 2009, he has been an Associate Professor at Uppsala University and his research interests include microwave-assisted metal catalysis, heterocyclic chemistry and medicinal chemistry.

the main mechanism accounting for microwave heating in polar systems although in materials containing ions, ionic conduction starts to prevail.[3] In contrast to classical heating, microwaves generate heat inside the bulk of the sample (*in situ* heating) and will be distributed from inside and out (no wall heating) causing the sample to heat up evenly and rapidly. It is important to realise that, in principle, all reactions that are driven by heat can be performed with microwave heating. In theory, the use of non-polar microwave-transparent solvents should give poor heating but in reality the presence of polar or ionic starting materials, reagents, catalysts and additives in the reaction system enables satisfactory heating of most laboratory-scale organic reactions. By using sealed reaction vessels it is thus possible to rapidly and safely heat nearly all reaction systems and to maintain the temperature much above the atmospheric reflux temperature.[9]

Most of the examples of microwave-assisted organic synthesis before 2002 were carried out using domestic microwave ovens.[4] These ovens produce a non-continuous heating pattern within the microwave cavity due to an on–off cycle of the power supply, leading to problems associated with reproducibility and the accuracy of (or lack of) temperature measurements. Furthermore, domestic microwave ovens are not constructed to withstand an explosion and are also associated with other safety hazards. To solve the problems mentioned above, modern, scientific microwave reactors for organic chemistry applications were developed in the mid to late 1990s and today there are several models available on the market.

Two general classes of dedicated microwave reactors are currently available, multimode and single-mode.[4,5] In the multimode instruments, microwaves are randomly distributed within the large cavity and less defined regions of high and low intensity are produced. These instruments often rely on continuous rotation of the samples in the cavity to ensure an even energy distribution. This is a design suitable for parallel or large-scale (<1000 mL) processing. On the other hand, in a single-mode microwave cavity a continuous standing wave is generated with well-defined regions of maxima and minima field strengths.[10] The single-mode equipment is more energy efficient and allows the placement of the reaction vessel at a fixed position with high energy density. The temperature level is varied by software-controlled modulation of the continuous-wave output using an IR-sensor or a fibre-optic probe. As IR sensors actually measure the temperature of the reaction vessel walls, they will not always reflect the temperature inside the vessel. Therefore multiple fibre-optic sensors immersed in the reaction mixture should be used if a correct temperature measurement is required.[11] Importantly, the difficulties concerning correct temperature measurements are also true for multimode reactors and especially in case of parallel processing of different reaction mixtures.[12]

The use of single-mode cavities is of particular importance in the acceleration of sealed small-scale (0.2–20 mL) reactions requiring high temperature, pressure monitoring and safe processing, making the equipment ideal for reaction scouting and chemical optimisation.[13] Further, automated, sequential single-mode reactors with disposable reaction vials are of huge importance for compound production in discovery projects.[14]

While the commercially available microwave equipment of today is very useful in lead generation and lead optimisation, it is necessary to obtain larger quantities of compound at the later stages of development. However, the invention of microwave flow reactors,[3,15–19] or the use of high quality large-scale multimode batch reactors[20] may provide attractive microwave solutions to the problem of scalability.

2. Infectious diseases

Infectious diseases are a major cause of death worldwide claiming the lives of as many as 15 million people each year and, to make matters worse, people carrying one infectious disease become more susceptible to other diseases.[21] Accordingly, significant effort has been put into identifying new and effective ways to combat these diseases. Moreover, many of the pathogens exhibit extremely fast mutation rates, leading to the emergence of drug resistance and in some cases, extreme drug resistance. This has resulted in the need for the continuous development of new therapeutic agents and effective combination therapies. This perspective will focus on the use of single-mode microwave irradiation for the synthesis of small molecules in laboratory scale for the potential treatment of tuberculosis, HIV/AIDS, malaria and hepatitis C; four of the most dangerous and prevalent infectious diseases.

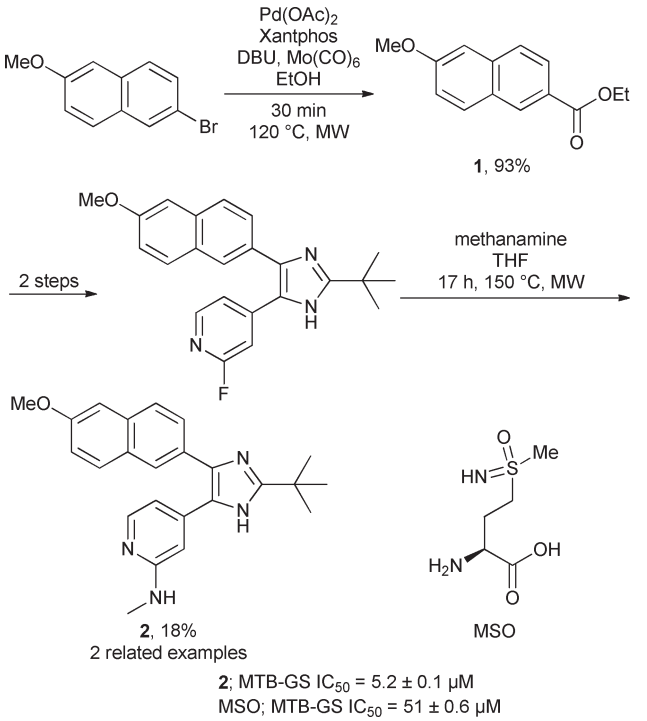
2.1 Tuberculosis

One of the world's deadliest diseases is tuberculosis (TB) which is caused by infection with *Mycobacterium tuberculosis* (MTB). Today, 2 billion people or one third of the world's population are infected with the TB bacillus and each year over 9 million new TB cases are discovered.[22] In 2009, 1.7 million people died from TB which equates to over 4600 deaths a day.[22] The emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) confirms the urgent need for development of new TB specific drugs.[23,24]

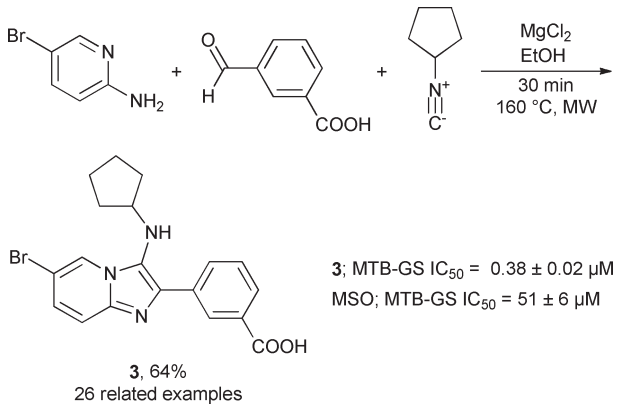
MTB glutamine synthethase (MTB-GS) is believed to be involved in cell wall biosynthesis[25] and the pathogens ability to

Mats Larhed

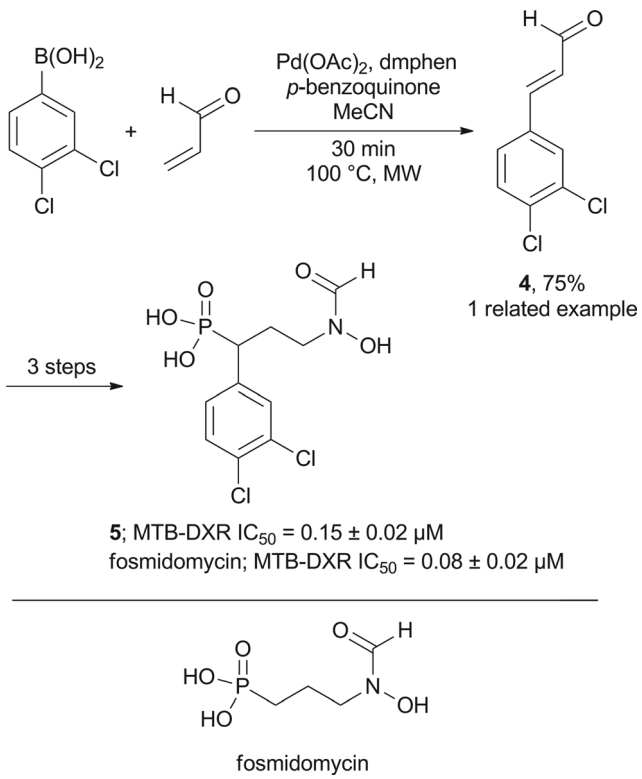
Mats Larhed received his PhD in 1997 and became a full professor in 2007. He holds the position as Chair of the Division of Organic Pharmaceutical Chemistry and as Head of Preclinical PET at Uppsala University. Dr Larhed's main research focus has been towards the development of fast, selective and robust synthetic methods for use in preparative medicinal chemistry. His work in microwave-assisted metal-catalysis covers different types of palladium-catalyzed coupling reactions, gas-free carbonylations and the development of environmentally benign chemical transformations. During the last ten years he has been increasingly engaged in the development of enzyme inhibitors for potential treatment of HIV, malaria, Alzheimer's disease and tuberculosis.



Scheme 1 Synthesis of MTB-GS inhibitors *via* a microwave-assisted palladium-catalysed alkoxycarbonylation.



Scheme 2 Microwave-assisted synthesis of MTB-GS inhibitors *via* multi-component heterocyclisation.



Scheme 3 Synthesis of MTB-DXR inhibitors *via* a microwave promoted oxidative Heck reaction.

inhibit phagosome-lysosome fusion and phagosome acidification.[26,27] An inhibitor of the enzyme, L-methionine-(*SR*)-sulfoximine (MSO, see Scheme 1), has been shown to hinder bacterial growth both *in vitro*[28] and *in vivo*[29] confirming MTB-GS as a promising and druggable target.

Recently Gising and co-workers reported the synthesis and biological evaluation of tri-substituted imidazoles as a new class of MTB-GS inhibitors (Scheme 1).[30] Through a palladium-catalysed alkoxycarbonylation, 2-bromo-6-methoxynaphthalene was coupled with ethanol utilising single-mode microwave irradiation as heating source to give the ethyl ester **1** in excellent yield (93%). A sluggish S_NAr substitution of the fluorine with methanamine gave the final inhibitor **2**. Compound **2** was 10 fold more active towards MTB-GS than MSO. In addition, an analogue to **2** was the most potent compound in the series (IC_{50} = 0.049 μM).

In 2009, Odell *et al.* investigated functionalised 3-amino-imidazo[1,2-*a*]pyridines as MTB-GS inhibitors derived from a HTS.[31] The target compounds were synthesised in moderate to good yields *via* an Ugi-type, multi-component heterocylisation from a 2-aminopyridine, an aldehyde and an isocyanate (Scheme 2). Compound **3** displayed considerable better activity *in vitro* than MSO (MTB-GS IC_{50} = 0.38 μM *vs.* 51 μM).

For an additional multi-component, microwave-assisted, heterocylisation in the synthesis of isoniazid analogues see the recent report by Manjashetty *et al.*[32]

Isopentyl diphosphate, the precursor to a group of essential isoprenoids for the TB bacilli is synthesised through the non-mevalonate pathway.[33] In eukaryotes however, isopentyl diphosphate is instead produced in the classical mevalonate pathway. As the routes differ from man to bacilli, the non-mevalonate pathway enzymes are suitable targets for drug discovery. MTB 1-deoxy-D-xylulose 5-phosphate reductoisomerase (MTB-DXR, also referred to as IspC) is involved in the non-mevalonate pathway[34] and fosmidomycin[35] (see Scheme 3) is a known inhibitor of the enzyme. Furthermore, knockouts of the DXR gene in *E. coli.* are lethal promoting DXR as promising target for drug development.[36,37]

In the exploration of fosmidomycin analogues for MTB-DXR inihibition, Andaloussi *et al.* introduced various aromatic groups α to the phosphonic acid (Scheme 3).[38] An oxidative Heck reaction under single-mode microwave heating was employed to

substitute the boronic acid for an acrylaldehyde using palladium(II) acetate and 2,9-dimethyl-1,10-phenanthroline (dmphen) as the catalytic system.[39,40] The cinnamalaldehyde **4** allowed easy access to the final compounds, exemplified by **5**, one of the most active compounds. Compound **5** displayed a comparable anti-TB activity to fosmidomycin.

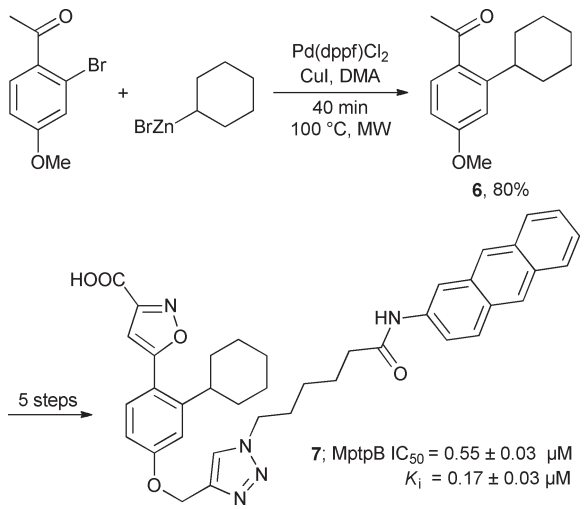
In related studies, the same group explored the aromatic substituents further[40] and also investigated bioisosteres to the phosphonic and hydroxamic acid groups.[41]

MTB protein tyrosine phosphatase (MptpB) is an important signalling enzyme in the bacteria. A mutant strain of MTB with disrupted MptpB activity impairs the bacterial survival in a guinea pig model.[42] The complete function of the enzyme is not yet fully understood and therefore the discovery of inhibitors of the enzyme would be of great value. Finding selective inhibitors is a challenge as the active site is highly conserved by most members in the protein tyrosine phosphatase family.[43]

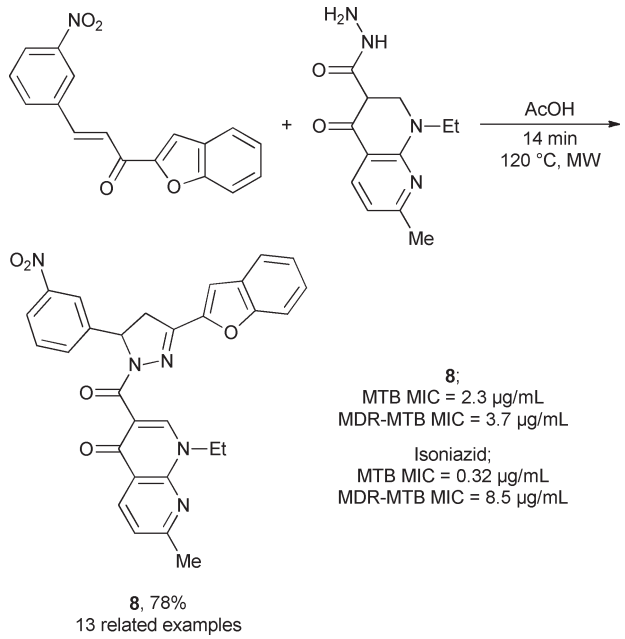
In an effort to identify selective MptpB inhibitors, a library of ~3500 bidentate compounds was designed by Tan and co-workers (Scheme 4).[44] In the search for additional interactions to an allosteric site, a linker was incorporated between the acidic active site binder and the anthracene moiety. In the synthesis of one of the active site binders, a palladium-catalysed Negishi cross-coupling was performed under temperature controlled microwave heating giving **6** in good yield. In the final step, 11 alkynes containing active site binders were reacted with numerous azide linkers to form triazoles.[45,46] Compound **7** displayed submicromolar activity towards MptpB and was one of the most promising entities in the 3500 compound library.

For the microwave promoted synthesis of other MTB inhibitors through metal catalysis see Kim *et al.*[47] and Lagerlund *et al.*[48]

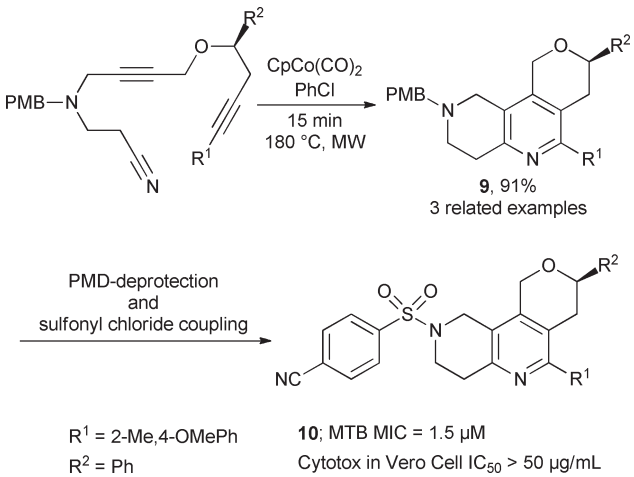
In a report from 2010, Manna *et al.* described the synthesis of MTB and MDR-TB inhibitors through heterocyclisation to give 1,3,5-trisubstituted-4,5-dihydro-1*H*-pyrazoles.[49] The yield for the cyclisation was improved by applying single-mode microwave heating in sealed vessels and reaction times could be decreased to 12–22 min instead of reflux for 6–10 h. A set of 14 α,β-unsaturated ketones were reacted with two hydrazides to



Scheme 4 Synthesis of MptpB inhibitors using a microwave-assisted Negishi cross-coupling.



Scheme 5 Synthesis of MTB inhibitors *via* a microwave heated 5-membered heterocyclisation.

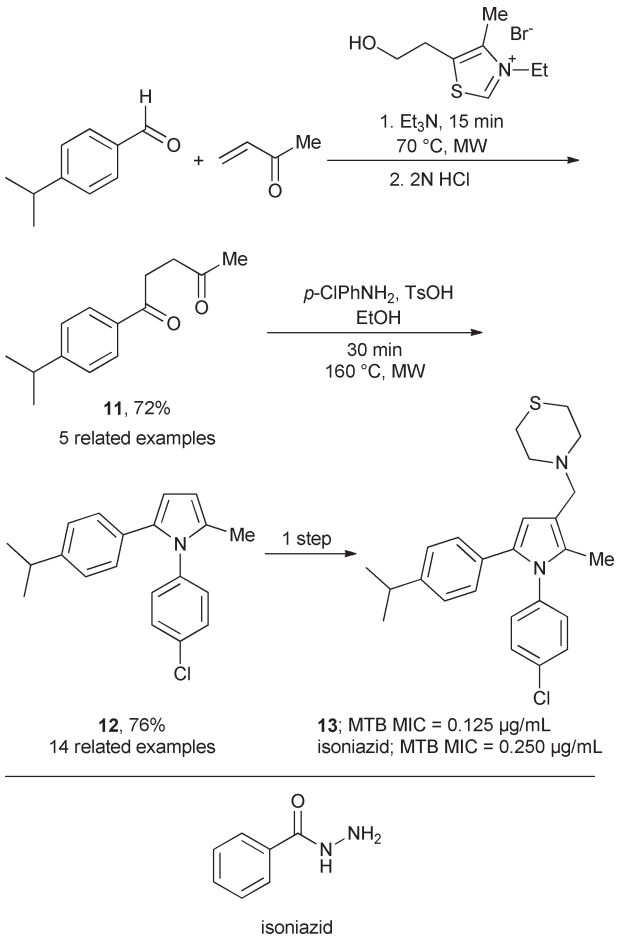


Scheme 6 Synthesis of MTB inhibitors *via* a microwave-assisted 6-membered heterocyclisation.

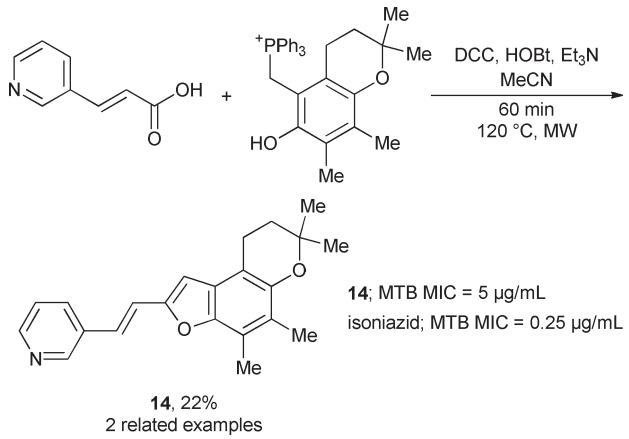
yield the final products in good yields (Scheme 5). Of the 28 1,3,5-trisubstituted-4,5-dihydro-1*H*-pyrazoles synthesised, inhibitor **8** was amongst the most active compounds and it was twice as active against MDR-TB than isoniazid. Furthermore, compound **8** was reported to lower the *Mycobacterium tuberculosis* count in lung and spleen two log units further than isoniazid in a mouse model.

A number of related examples of microwave-assisted, 5-membered heterocyclisations towards MTB inhibitor synthesis have also been reported.[31,50–55]

Zhou *et al.* synthesised a library of pyrano-annulated 5,6,7,8-tetrahydro-1,6-naphthyridines, exemplified by **9** (Scheme 6), in the search for active compounds towards MTB.[56] The



Scheme 7 Microwave-assisted synthesis of MTB inhibitors *via* a condensation reaction.



Scheme 8 Synthesis of MTB inhibitors *via* a microwave promoted Wittig reaction.

intramolecular cobalt-catalysed [2 + 2 + 2] cyclisation gave **9** in excellent yield under microwave irradiation for 30 min at 180 °C. For diversity, four variants of **9** were synthesised where R^1 and R^2 were altered with alkyls and aryls. After PMB-deprotection the four resulting secondary amines were coupled with a diverse set of 8 isocyanates, acyl chlorides and sulfonyl chlorides to yield ureas, amides and sulphonamides, respectively. In the constructed library of 96 compounds, the scaffold with R^1 = 2-methyl-4-methoxyphenyl and R^2 = phenyl was shown to be most promising as low micromolar inhibitors were found in all three N-2 derivatised classes, exemplified by **10** in Scheme 6. The sulfonamide **10** was the most promising compound in the library with a low micromolar MIC (minimum inhibitory concentration) and a good cytotoxicity profile.

Synthesis of other microwave-assisted 6-membered heterocyclisations towards MTB inhibitors have been reported by Balamurugan *et al.*,[57] Kim *et al.*[58] and Manjashetty *et al.*[32]

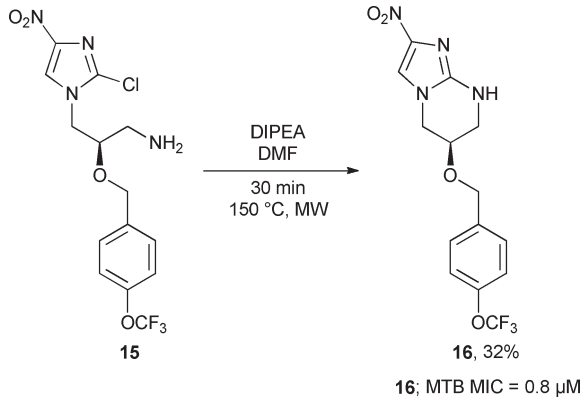
In 2008, Biava and co-workers described the optimisation of 1,5-diarylpyrrole derivatives toward MTB inhibition.[53] In the synthetic route, a Stetter reaction was employed between cuminaldehyde and methyl vinyl ketone (Scheme 7). The reaction was performed under microwave irradiation and driven by the addition of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide which gave the 1,4-diketone **11** in good yield. In the next step, the diketone **11** was cyclised under Paal–Knorr conditions with 4-chloroaniline yielding the tri-substituted pyrrole **12**. By the use of a dedicated microwave reactor and septa-sealed reaction vials, the temperature could safely be raised to 160 °C, double the boiling point of the solvent (EtOH), reaching full conversion within 30 min. One of the most active compounds **13** was twice as effective as isoniazid on wild type MTB. The inhibitor **13** was also active towards isoniazid- and rifampicin resistant MTB (MIC = 8.0 and 0.125 μg mL^{-1} respectively). Recently, the group presented further exploration of the 1,5-diarylpyrrole derivatives.[52,59]

For further condensation reactions under microwave heating in the synthesis of MTB inhibitors see the following reports by Bairwa *et al.*,[60] Torres *et al.* [61] and Casagnolo *et al.*[62]

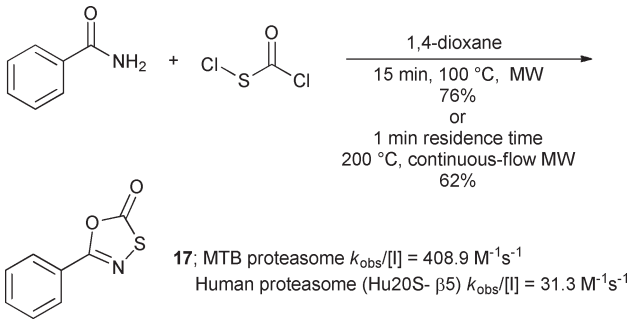
A Wittig type cyclisation to afford benzofurans was exploited by Alvety *et al.* in the synthesis of MTB inhibitors (Scheme 8).[54] It was found that isolation of phosphonium salt increased the yields and furthermore, the reaction times could be shortened from 88 h to 1 h with the use of microwave irradiation compared to traditional reflux. In the one-pot two-step synthesis, the hydroxyl was first coupled with acids or acyl chlorides. In the second step, the esters were then cyclised in a Wittig reaction affording the benzofurans exemplified by **14** (Scheme 8). Compound **14** was also one of the most active compounds which displayed moderate activity in the whole bacterial assay compared to isoniazid.

A structure–activity relationship study of antitubercular nitroimidazoles was carried out by Kim and co-workers in 2009.[58] In one of the synthetic routes an intramolecular S_NAr reaction was conducted under single-mode microwave irradiation (Scheme 9). By heating a DMF solution of the amino-functionalised 2-chloroimidazole **15** in the presence of a mild base, at a temperature of 150 °C for 30 min, compound **16** was prepared in modest yield. Inhibitor **16** was evaluated in a whole bacterial assay and displayed a low MIC and furthermore, a related structure in the study was 20 times more potent (MTB, MIC = 0.039 μM).

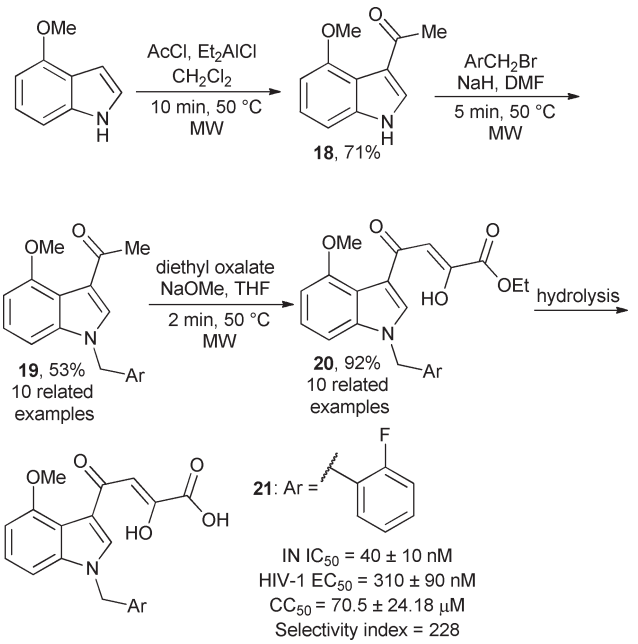
Proteasomes are involved in the degradation of proteins and have been exploited as targets in a number of human deseases.[63] As the proteasomal enzymes are structurally conserved in both eukaryotes and prokaryotes, selectivity is crucial to avoid



Scheme 9 Synthesis of MTB inhibitors *via* a microwave-assisted intramolecular S_NAr reaction.



Scheme 10 Synthesis of a MTB proteasome inhibitor by a single-mode batch reactor or by a continuous flow non-resonant microwave apparatus.



Scheme 11 Microwave-assisted synthesis of diketo acid HIV-1 integrase inhibitors.

cytotoxicity. The resolved crystal structure of MTB proteasome[64] in 2006 improves the prospect for designing MTB specific inhibitors.

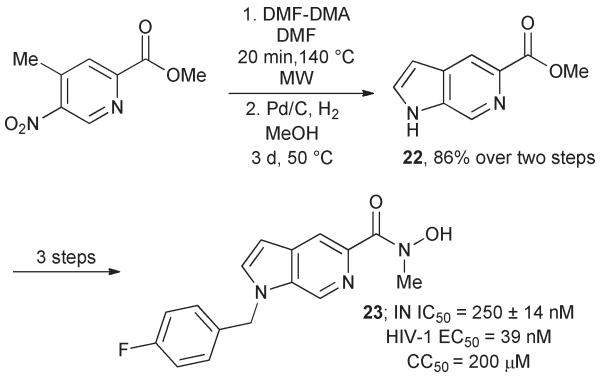
In 2009, Lin *et al.* reported the results and exploration of the hits from a HTS targeting the MTB proteasome.[65] The active compounds comprised an oxathiazol-2-one ring that was found to react covalently but reversibly with the enzyme. In the cyclisation an aryl/heteroaryl-amide was reacted with chlorocarbonylsulfenyl chloride at ambient temperature for 16 h, affording the 5-substituted oxathiazol-2-one in good yield. With the help of a dedicated microwave reactor, the reaction times could be shortened to only 15 min at 100 °C with comparable yields. The 5-phenyl-oxathiazol-2-one **17** was synthesised by the single-mode microwave-assisted method (Scheme 10) and was one of most active compounds towards MTB proteasome displaying a 13-fold selectivity ratio for the rate of inactivation (k_{obs}) over the human proteasome.

Öhrngren and co-workers have evaluated a novel non-resonant microwave reactor for continuous-flow chemistry applications.[18] The non-resonant irradiation heats the entire reactor vessel without pronounced hot or cold spots. The instrument allows high level of safety thanks to a limited reaction zone and fast access to optimised protocols, ready to scale-out. One of the reported applications was the synthesis of the 5-substituted 1,3,4-oxathiazol-2-one **17** (Scheme 10). The reaction was performed with two stock solutions of benzamide and chlorocarbonylsulfenyl chloride that were pumped through a mixer before reaching the microwave applicator. With the optimised conditions; flow rate of 353 μL min^{-1}, residence time 1 min and a temperature of 200 °C, the product **17** was isolated in 62% yield with a throughput of 3.3 mol h^{-1}.

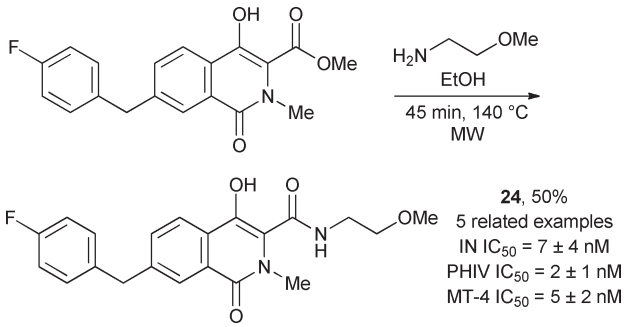
2.2 HIV/AIDS

Human immune deficiency virus (HIV) was identified 30 years ago and since then acquired immune deficiency syndrome (AIDS) has claimed more than 25 million lives. Today, more than 7000 people, including 100 children, are newly infected with the virus each day.[66] The current treatment consists of highly active antiretroviral therapy (HAART) where patients are given combinations consisting of three or more drugs belonging to two or more classes. These classes include the nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, CCR5 antagonists and integrase inhibitors.

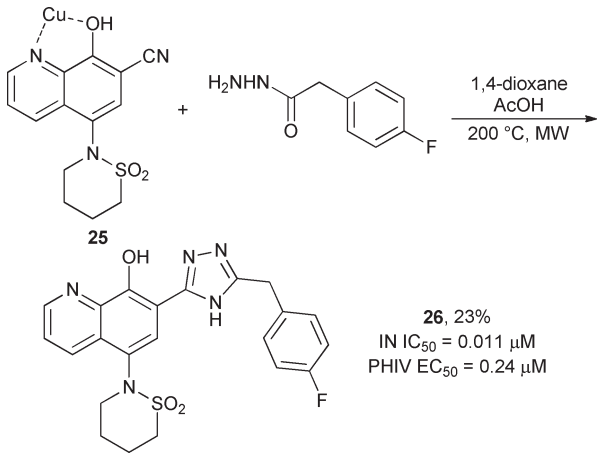
The integrase enzyme (IN) is used by the virus to insert the pro-viral DNA into the host celluar DNA and thus plays a critical role in the virus life-cycle. Today, raltegravir is the only IN inhibitor approved for clinical use. Chimiri and co-workers have described the synthesis of 1*H*-benzylindole IN inhibitors where microwave irradiation was employed in three of the four steps in the reaction pathway (Scheme 11).[67,68] The synthesis commenced with the treatment of commercially available 4-methoxyindole with acetyl chloride in the presence of diethylaluminum chloride. The 3-acylated derivative **18** was obtained after only 10 min of microwave heating at 50 °C compared to 2 h under conventional conditions. Intermediate **18** was then N-alkylated with various benzyl bromides and microwave irradiation was shown to again reduce reaction times (5 min *vs.* 30 min) and



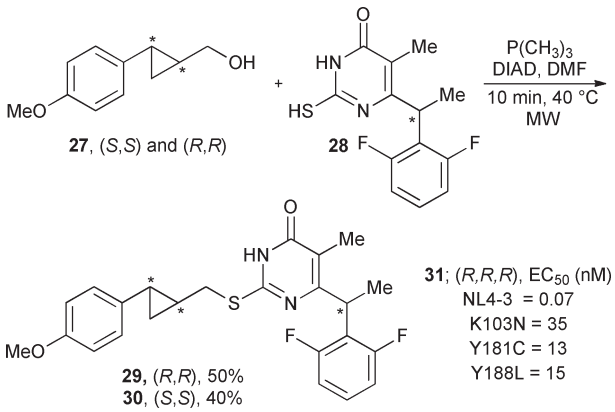
Scheme 12 Microwave-assisted Leimgruber–Batcho synthesis.



Scheme 13 Microwave-assisted synthesis of HIV IN inhibitor **24** *via* an ester aminolysis.



Scheme 14 Microwave-assisted triazole formation from a nitrile and an acyl hydrazide.



Scheme 15 The synthesis of *S*-DABO derivatives using a microwave-assisted Mitsunobu reaction.

also allow the use of less solvent. The 1-benzyl-1*H*-indoles **19** were then effectively coupled with diethyl oxalate after only 2 min of microwave heating at 50 °C. Finally, the chelating diketo acid group was unmasked under basic conditions to provide the free inhibitor. One of the best compounds **21** showed nanomolar inhibition of the integrase enzyme and HIV-1 replication and had a selectivity index of 228 (Scheme 11).

For additional examples of microwave-assisted S_N2 N-alkylation reactions in the preparation of anti-HIV compounds see Tang *et al.*[69] Monforte *et al.*[70] and De Luca *et al.*[71]

The Leimgruber–Batcho synthesis[72,73] is a widely used strategy for the formation of indoles from *ortho*-nitrotoluenes. This approach was recently utilised in the synthesis of azaindole hyroxamic acid inhibitors of HIV-1 IN (Scheme 12).[74] The azaindole ring system was assembled by the microwave-assisted reaction of nitropicoline with dimethylformamide dimethyl acetate at 140 °C for 20 min followed by a palladium-catalysed reduction/cyclisation of the enamine intermediate. Subsequent N-alkylation of **22** and installation of the hydroxamic acid moiety gave the final test compounds. The most promising inhibitor **23** exhibited nanomolar enzymatic and anitiviral activity, however the compound series displayed low metabolic stability due to rapid clearance through phase 2 glucuronidation pathways.

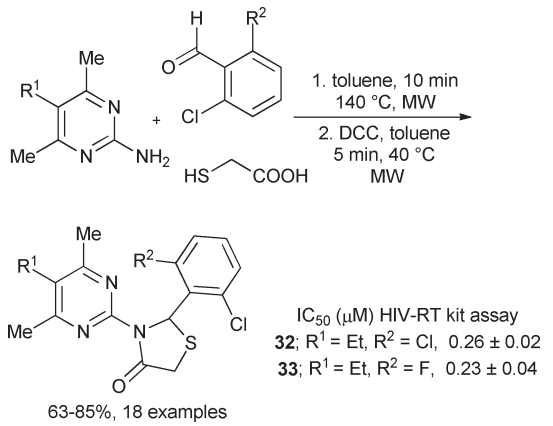
In 2009, Yoshinaga and co-workers disclosed a series of 7-benzyl-4-hydroxyisoquinolin-2(1*H*)-one IN inhibitors where a microwave-assisted ester aminolysis approach was used to introduce various carboxamides into the C-3 position.[75] Compound **24** (Scheme 13) displayed single-digit nanomolar activity in both enzymatic (HIV integrase) and cellular antiviral assays and was also found to possess reasonable bioavailability (20–25%) and acceptable *in vivo* clearance (11.8 mL min^{-1} kg^{-1}).

A microwave-assisted triazole formation was employed by Johns *et al.* in the preparation of **26**, a potent IN inhibitor and anti-HIV agent (Scheme 14).[76] Compound **26** was synthesised in moderate yield by the condensation of nitrile **25** with 4-fluorophenylacetic hydrazide at 200 °C.

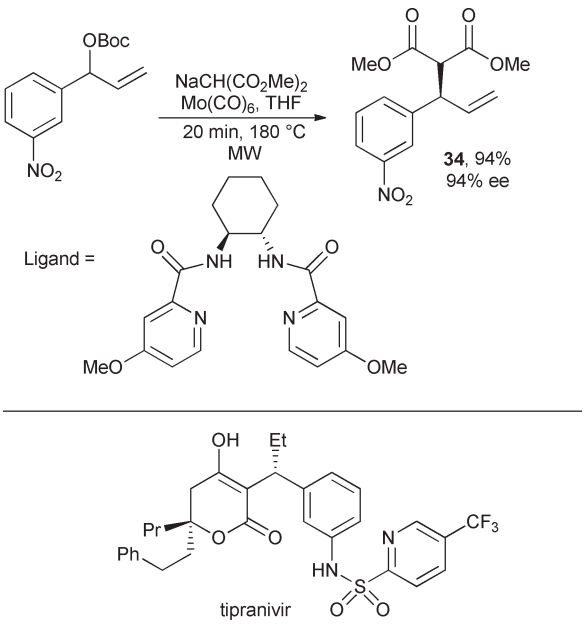
For additional examples of microwave-assisted heterocyclisations in the synthesis of anti-HIV compounds, see Mehta *et al.*,[77] Zhao *et al.*,[78] Pace *et al.* [79] and Fisher *et al.*[80]

The reverse transcriptase (RT) of HIV-1 plays an essential role in the synthesis of viral DNA and is the target of sixteen FDA approved drugs. Despite the large number of drugs already on the market, the emergence of resistant virus strains has catalysed the continued search for new RT inhibitors.

In 2009, the Botta group reported the synthesis and anti-HIV activity of a number of chiral cyclopropyl *S*-DABO (dihydroalkylthio-benzyl-oxopyrimidine) derivatives.[81] The inhibitors were synthesised *via* a microwave-assisted Mitsunobu reaction between enantiopure cylcopropyl derivatives **27** and 2-thiouracil **28** (Scheme 15). The pure diastereomers were then separated by



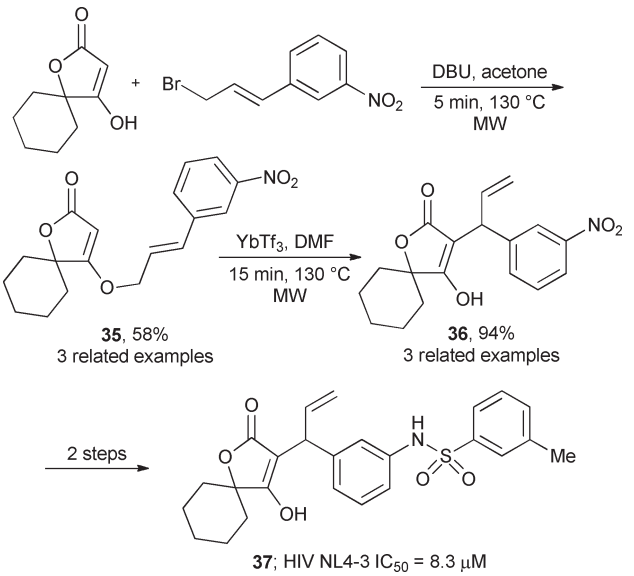
Scheme 16 A microwave-assisted three-component synthesis of thiazolidin-4-one derivatives.



Scheme 17 Microwave-assisted asymmetric molybdenum-catalysed alkylation in the synthesis of the HIV-1 protease inhibitor tipranivir.

HPLC and tested for their anti-HIV activity in MT-4 cells. The (*R*,*R*,*R*) isomer **31** was the most potent derivative with picomolar activity against wildtype virus strain and nanomolar activity against three tested mutant strains. The Corelli group has also described the synthesis of *S*-aryl-*S*-DABO based HIV-1 inhibitors, synthesised through a microwave-assisted Ullmann type reaction of 2-thiouracils and various arylboronic acids.[82]

A microwave-assisted three component reaction has been used in the synthesis of 2,3-diaryl-1,3-thiozolidin-4-ones possessing HIV-RT inhibitory activity.[83] The inhibitors were prepared by heating various 2-aminopyridines, benzaldehydes and mercaptoacetic acid in the presence of DCC. The two most potent inhibitors **32** and **33** (Scheme 16) displayed submicromolar inhibitory activity in a HIV-RT kit assay. The same group has also reported the synthesis of dinucleoside substituted



Scheme 18 Microwave-assisted synthesis of tetronic acid analogues of tipranivir.

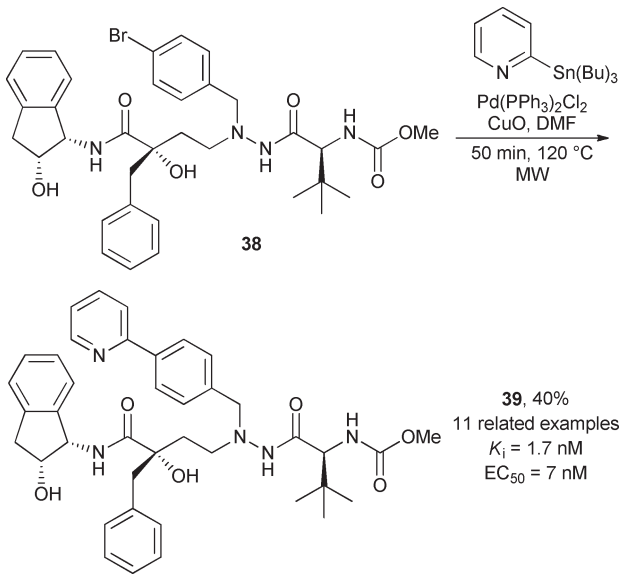
thiazolidin-4-ones *via* a microwave-assisted one-pot Staudinger/aza-Wittig/cyclisation sequence.[84,85]

Inhibition of the HIV protease enzyme has been a successful strategy in the fight against HIV/AIDS and today there are 10 HIV-1 protease inhibitors on the market. The enzyme is responsible for cleavage of the viral polyprotein into functional enzymes and structural proteins in the final stages of viral replication and is essential for the production of new mature virions.

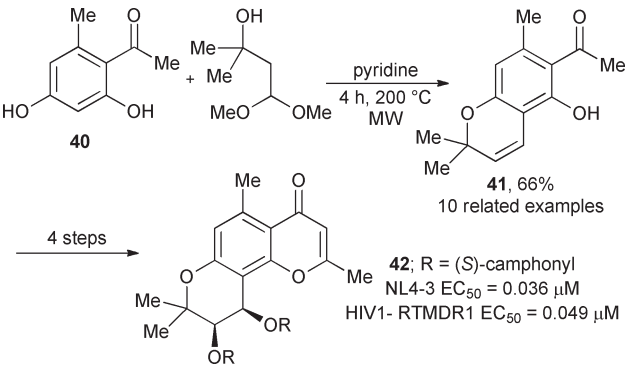
In work directed towards a stereoselective synthetic route to the HIV-1 protease inhibitor tipranavir, Trost and Andersen used a microwave-assisted molybdenum-catalysed allylic alkylation to prepare one of the key intermediates **34** (Scheme 17). The reaction time was reduced from 24 h at 67 °C to 20 min at 180 °C with only a small reduction in ee (from 96% ee to 94% ee).[86] In addition, more convenient $Mo(CO)_6$[87,88] could be used as the molybdenum source instead of the sensitive pre-catalyst complex $Mo(CO)_3(C_7H_8)$.

A microwave-assisted S_N2 alkylation/Claisen rearrangement sequence has been utilised by Schobert *et al.* in the synthesis of tetronic acid analogues of tipranavir.[89] The most active derivative **37** displayed low micromolar activity against the protease-sensitive virus strain HIV-NL4-3 (Scheme 18).

Hallberg, Larhed and co-workers have, over the past decade, published a number of studies on the microwave-assisted synthesis of HIV-1 protease inhibitors.[14,90] In general, these have involved the metal-catalysed functionalisation of a target scaffold, with the aid of microwave heating. A range of different scaffolds containing linear and cyclic 1,2-dihydoxyethylene[91–99] and tertiary alcohol[100–104] transition-state mimicking groups and various palladium-catalysed transformations, including Suzuki–Miyaura, Mizoroki–Heck, Negishi, Stille, Sonogashira, cyanation and aminocarbonylation reactions, have all been explored using this strategy. In a recent example, a microwave-accelerated Stille-coupling was used to prepare **39**, a compound possessing potent antiviral activity (Scheme 19, EC_{50} = 7 nM).[103] Compound **39** was synthesised in a moderate yield (40%) by treating



Scheme 19 Microwave-assisted synthesis of HIV-1 protease inhibitor **39** *via* a Stille cross-coupling.

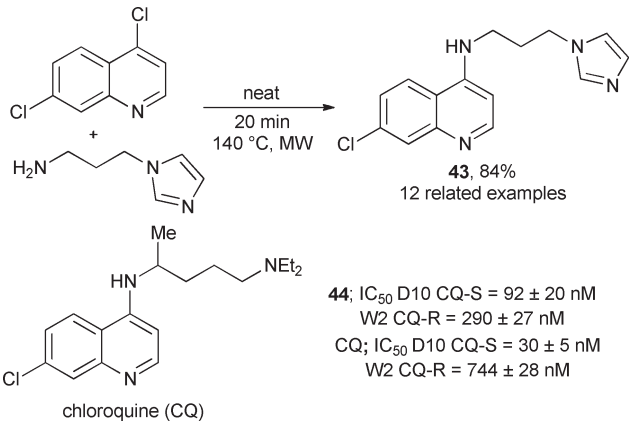


Scheme 20 Microwave-assisted preparation of an anti-HIV DCP analogue.

aryl bromide **38** with 2-pyridyl tributyltin, $Pd(PPh_3)_2Cl_2$ and CuO at 120 °C for 50 min. Importantly, **39** was only slowly degraded by metabolic enzymes and also retained potency against several resistant HIV-1 isolates.

Microwave-assisted metal-catalysed coupling-reactions have also been utilised by Wiscount *et al.*[105] and Williams *et al.*[106] in the preparation of HIV inhibitors.

A microwave-assisted one-pot alkylation/cyclisation protocol for the synthesis of 2′-2′-dimethyldihydropyranochromone (DCP) containing compounds has recently been developed by the Lee group (Scheme 20).[107,108] This method was subsequently applied to the synthesis of a library of anti-HIV agents, from which **42** was identified as the most promising drug candidate. Compound **41** was synthesised by treating the resorcinol derivate **40** with 4,4-dimethoxy-2-methyl-2-butanol in the presence of pyridine at 220 °C for 4 h. Further synthetic manipulations led to **42**, which showed potent anti-HIV activity against both non-drug-resistant ($HIV\text{-}1_{NL4\text{-}3}$) and drug-resistant (HIV-RTMDR1) viral strains.



Scheme 21 Synthesis of a CQ analogue *via* a microwave-assisted S_NAr reaction.

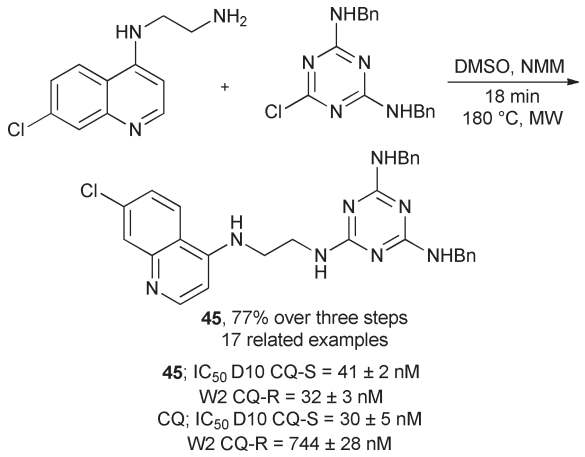
2.3 Malaria

According to the WHO, over 3 billion people worldwide live under the threat of malaria infection and in 2009, nearly 800,000 people lost their lives to the disease.[109,110] Malaria is caused by infection with four species of the family *Plasmodium*; *Plasmodium falciparum* (*Pf*), *Plasmodium malariae* (*Pm*), *Plasmodium ovale* (*Po*) and *Plasmodium vivax* (*Pv*) of which *Pf* is responsible for the most severe and fatal form of the disease.† Most of the drugs currently used in the treatment of malaria target either the haem detoxification system (*e.g.* chloroquine and mefloquine) or the biosynthesis of nucleotide bases by inhibiting dihydrofolate reductase (DHFR) or dihydropteroate reductase (DHPR) (*e.g.* pyrimethamine/sulfadoxine). The mode of action of artimisenin and its derivitives is still the subject of considerable debate.[111]

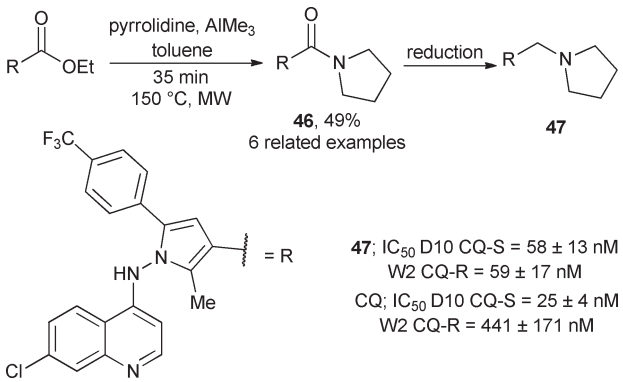
Chloroquine (CQ) has been the anti-malaria drug of choice for many decades, however the emergence of CQ-resistance has significantly reduced its efficacy. Thus, the synthesis of CQ analogues with increased activity against CQ-resistant parasite strains has been investigated by a number of research groups. In 2007, Monti and co-workers reported the synthesis of a library of 4-aminoquinolines *via* microwave-assisted S_NAr reactions of commercially available 4,7-dichloroquinoline with various amines (Scheme 21).[112] The use of sealed vials and single-mode microwave irradiation was found to decrease reaction times and allowed the reaction to be carried out with aromatic amine nucleophiles. The most promising compound **44** was more active than CQ on a W2 (CQ-resistant) strain of *Pf* (Scheme 21).

The following year, the same group used microwave-assisted S_NAr reactions to construct a library of triamino-substituted triazines as analogues of both CQ and cycloguanil (Scheme 22).[113] The target compounds were prepared from cyanuric chloride by three consecutive S_NAr reactions, the first two conducted at 0 °C and room temperature, respectively, and the final reaction at 180 °C using high density microwave irradiation. The most active compound **45** displayed similar CQ-sensitive (CQ-S) activity and higher CQ-resistant (CQ-R) activity compared to CQ.

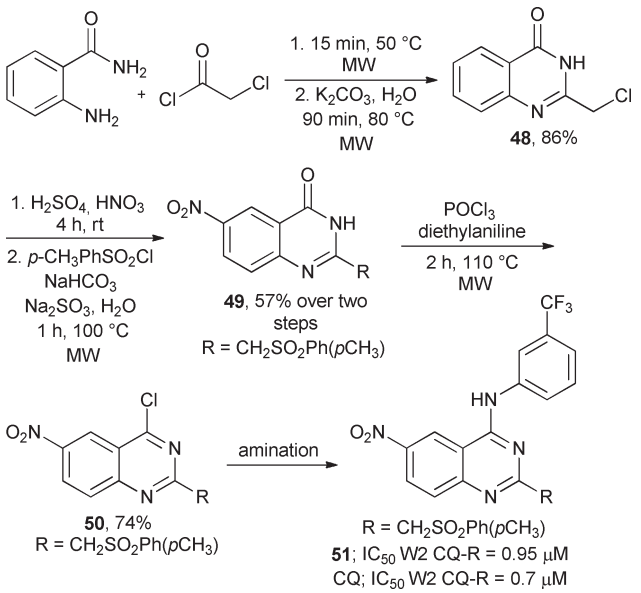
Microwave-assisted S_NAr reactions have also been utilised by a number of other groups in the synthesis of antimalarial agents.[114–117]



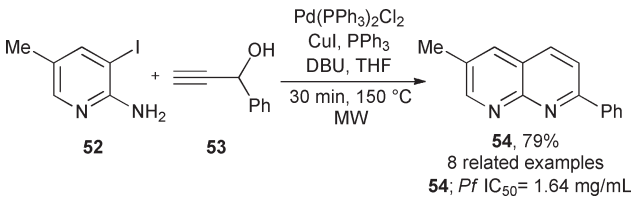
Scheme 22 Synthesis of anti malarial triamino-substituted triazines *via* a microwave heated sequential S_NAr reactions.



Scheme 23 Synthesis of CQ analogues *via* a microwave enhanced trimethylaluminium-mediated amide bond formation.



Scheme 24 Synthesis of 4-aminoquinazoline **51** *via* a multistep microwave-assisted reaction sequence.



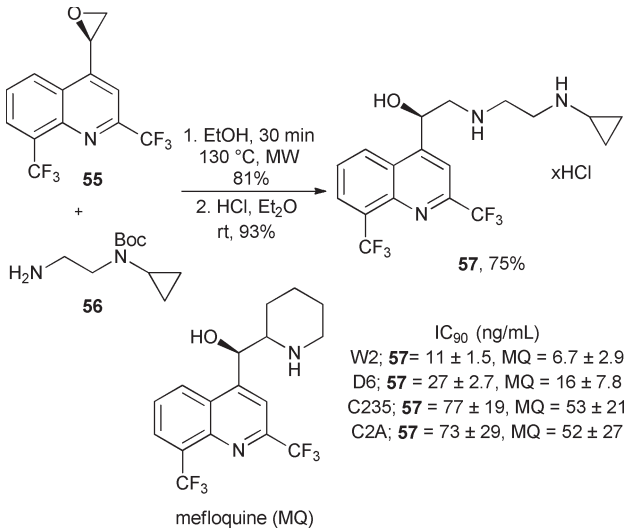
Scheme 25 Synthesis of 4-aminoquinazoline **54** *via* a microwave-assisted coupling-isomerisation reaction.

Recently, Sparatore and co-workers described the synthesis and evaluation of CQ and amodiaquine analogues, where a pyrrole ring was introduced into the linker between the 7-chloro-4-aminoquinoline moiety and the basic amine head group.[118,119] A microwave-assisted trimethylaluminium-mediated amide bond formation was used to install the key basic head group in a number of derivatives, including **47**, one of the most active compounds (Scheme 23).[119] The use of single-mode microwave heating allowed the reaction time to be reduced from 24 h to 35 min and also improved the yield (<10% *vs.* 49%) when compared to classical heating conditions. Compound **47** displayed comparable activity to CQ against the D-10 (CQ-S) strain and better activity than CQ on the W2 (CQ-R) parasite strain of *Pf*. In addition, a microwave-assisted DCC mediated amide coupling was used to attach the basic head group in a number of less potent compounds.

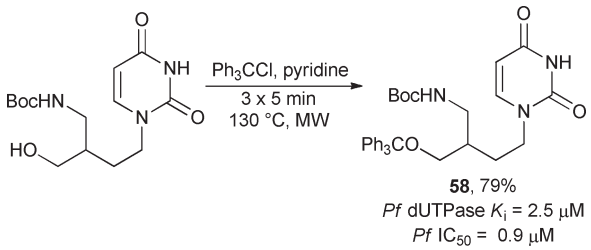
In 2010, Kabri *et al.* reported the preparation of 4-anilinoquinazoline derivatives where the majority of the synthetic steps employed microwave heating.[120] The synthesis of the most active series began with the treatment of 2-aminobenzamide with an excess of chloroacetylchloride (Scheme 24). The intermediate chloroacetamide was then directly cyclised upon reaction with K_2CO_3 in water. This two-step microwave-assisted procedure afforded 2-chloromethylquinazolin-4(3*H*)-one (**48**) in excellent yield (86% over two steps).[121] Following a standard nitration, treatment with 4-methylbenzenesulfonyl chloride, under microwave conditions, led to the *S*-alkylated intermediate **49**.[122] Microwave-assisted chlorination and a nucleophilic substitution of the chlorine with various anilines furnished the target library. The most potent member of the series **51** was marginally less active than CQ on the W2 CQ-R parasite strain.

Naphthyridine **54** (Scheme 25), a compound with modest antiplasmodial activity (*Pf* IC_{50} = 1.64 mg mL^{-1}), was prepared by a microwave-assisted coupling-isomerisation reaction (MACIR).[123] Mechanistically, the reaction is believed to occur *via* an initial Sonogashira coupling of iodide **52** and propargylic alcohol **53** followed by a base-catalysed propargyl alcohol-enone isomerisation to afford a chalcone intermediate. Finally, a base-mediated *trans–cis* isomerisation and subsequent intramolecular cyclisation generates the naphthyridine ring system.

Very recently, Milner *et al.* have utilised microwave-assisted nucleophilic epoxide ring opening reactions to prepare a library of diamine quinoline methanol derivatives, based on the mefloquine (MQ) scaffold (Scheme 26).[124] The most promising candidate **57** was prepared by reacting the enantiopure epoxide **55** with amine **56** under microwave conditions, followed by an acid mediated deprotection of the Boc group. Compound **57** exhibited similar potency to MQ across a range of drug resistant *Pf* strains and after single dose administration in mice, cured 4 out of



Scheme 26 Synthesis of MQ analogue **57** *via* a microwave-assisted epoxide ring opening.



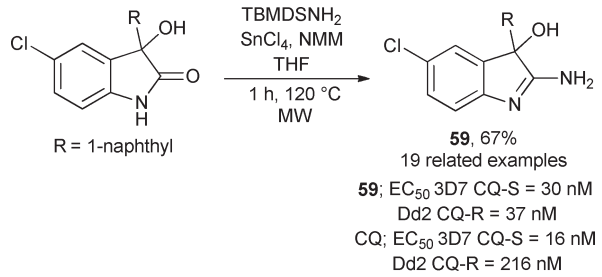
Scheme 27 Synthesis of a *Pf* dUTPase inhibitor *via* microwave-assisted S_N1 reaction.

5 mice at an orally administrated dose of 320 mg kg^{-1} without evidence of toxicity.

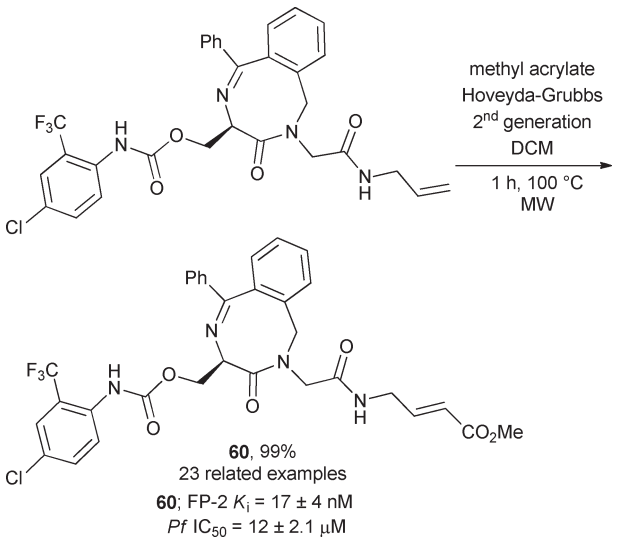
For additional examples of microwave promoted nucleophilic ring opening reactions see Robin *et al.* (epoxide opening)[125] and D'hooghe *et al.* (aziridine opening).[126]

Gilbert and co-workers have reported the discovery of acyclic uracil-based inhibitors of the *Pf* enzyme deoxyuridine nucleotidohydrolyase (dUTPase).[127] A microwave-assisted nucleophilic substitution was used to produce the tritylated compound **58** (Scheme 27) and interestingly, attempts to conduct the reaction under classical heating conditions failed. Compound **58** was found to selectively inhibit *Pf* dUTPase (K_i = 2.5 μM *vs.* human dUTPase K_i > 1000 μM) and inhibit the growth of *Pf in vitro* (IC_{50} = 0.9 μM).

As part of a screening campaign aimed at identifying small-molecules with whole-cell antimalarial activity, Mazitshek and co-workers discovered a 2-amino-3-hydroxyindole derivative with good *in vivo* efficacy (Scheme 28).[128] To facilitate rapid analogue generation, the authors sought to develop a short and robust synthetic method for the preparation of the unusual core structure. The target compounds were accessed in only two steps starting with a Grignard addition to commercially available isatins. The oxindole intermediate was then treated with *tert*-butyldimethylsilyl amine ($TBDMSNH_2$) and $SnCl_4$ under microwave irradiation, in a one-pot amidine formation/deprotection reaction, to afford the desired 2-amino-3-hydroxyindoles in



Scheme 28 Microwave-assisted synthesis of a anti malarial 2-amino-3-hydroxyindole derivative.

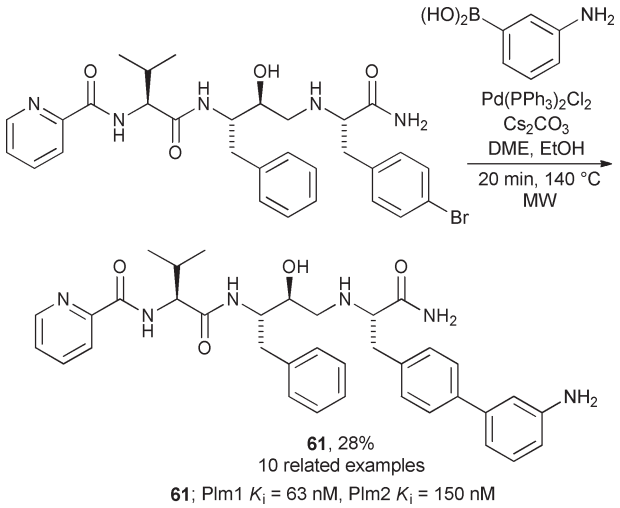


Scheme 29 Microwave-assisted cross metathesis in the synthesis of a Falcipain-2 inhibitor.

reasonable yields. Notably, this was the first reported use of $TBDMSNH_2$ as an ammonia equivalent and no loss of enantiomeric excess was detected when the reaction was carried out with an enantioenriched oxindole. The most active compound **59** (Scheme 28) was more active than CQ on a drug-resistant parasite strain and slightly less potent than CQ on a drug-sensitive strain.

Falcipain-2 (FP-2) is a cysteine protease involved in haemoglobin degradation, a process that provides essential nutrients for parasite growth[129] and cleavage of host cytoskeleton proteins, leading to cell rupture and merozoite release.[130] The Zappalà group have utilised microwave-assisted cross metathesis reactions as a key step in the synthesis of peptidomimetic inhibitors of FP-2.[131–133] The cross-metathesis reaction was used to introduce various α,β-unsaturated electrophilic groups onto a 1,4-benzodiazepine scaffold and the synthesis of one of the most potent compounds **60** (FP-2 K_i = 17 nM and *Pf* IC_{50} = 12 μM) is depicted in Scheme 29.

The plasmepsins are a group of 10 aspartic acid proteases encoded in the Pf genome and four of these, plasmepsin I (Plm1), plasmepsin II (Plm2), plasmepsin IV (Plm4) and histoaspartic protease (HAP or Plm3), are involved in haemoglobin degradation. In 2003, Hallberg and co-workers presented the first[134] of a series papers describing the single-mode microwave-

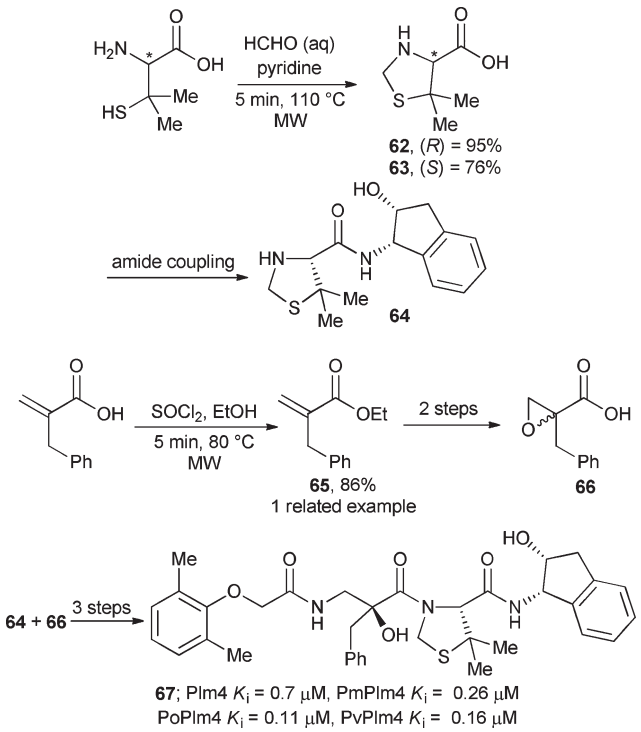


Scheme 30 Synthesis of a plasmepsin I and II inhibitor *via* a microwave induced Suzuki–Miyaura reaction.

assisted synthesis of plasmepsin inhibitors.[13,135–137] In this work, a hydroxyethylamine transition-state isostere was utilised and different P1 side chains were evaluated *via* the decoration of the benzylic side chains (Scheme 30). Inhibitors containing either a *para*-bromo or a *meta*-triflate group in the P1-position served as starting materials for microwave-assisted Suzuki–Miyaura reactions with four different arylboronic acids. In total, eight inhibitors were produced after 20 min of irradiation, however the isolated yields were only moderate. The most potent inhibitor of the series (**61**) displayed a K_i value of 63 nM for Plm I and 150 nM for Plm II, with moderate selectivity *versus* Cat D (Scheme 30).

For additional examples of microwave-asssisted metal-catalysed coupling reactions in the synthesis of antimalarial agents see Choi *et al.* (cyanation)[138] Bulbule *et al.* (cyanation)[139] Bouloc *et al.* (Suzuki–Miyaura)[140]

In 2009, Orrling *et al.* described the synthesis of Plm4 inhibitors containing an α-substituted norstatine transition-state isostere.[141] The inhibitors were prepared by a convergent sequence where two key intermediates (**64** and **66**) were assembled with the aid of microwave heating (Scheme 31). The 5,5-dimethylthiazolidine moiety (**62** and **63**) was generated by treating penicillamine with formaldehyde at 110 °C, which resulted in a reduction of the reaction time from 16 h to 5 min when compared to the previously reported room temperature procedure.[142] The α-substituted norstatine core **66** was derived from a substituted acrylic acid ester **65**, prepared in a one-pot esterification of the corresponding acid using $SOCl_2$ and ethanol. The best compound in the series (**67**) displayed nanomolar K_i values against Plm4 from all four disease causing parasite species.



Scheme 31 Microwave-assisted synthesis of a plasmepsin IV inhibitor.

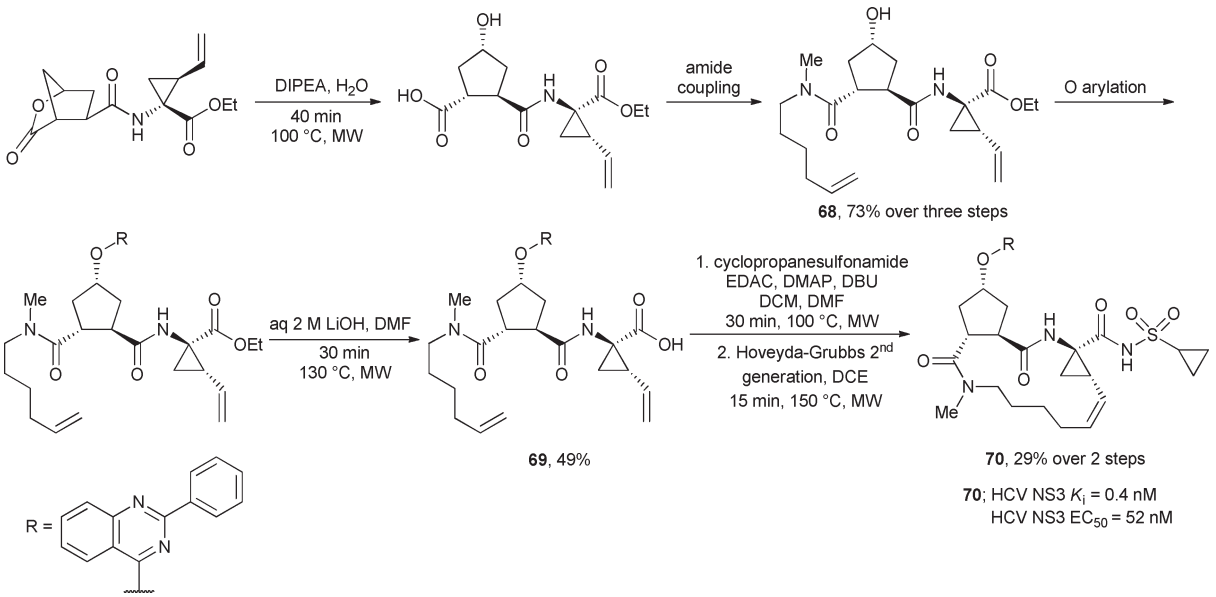
2.4 Hepatitis C

In 2009, it was estimated that 130–170 million people or 2.2–3% of the world's population were infected with hepatitis C (HCV).[143] One in every forty deaths is related to HCV and the virus accounts for 27% of all cirrhosis deaths and 25% of all hepatocellular carcinoma deaths worldwide.[144] The current HCV-treatment is a combination therapy with pegylated interferon alfa and ribavirin together with one of the newly FDA approved drugs, boceprevir or telaprevir, which also are the first HCV specific drugs that have reached the market. Boceprevir and telaprevir target the HCV NS3 protease which is involved in viral polyprotein processing that releases the essential structural proteins and viral enzymes required for viral replication.[145]

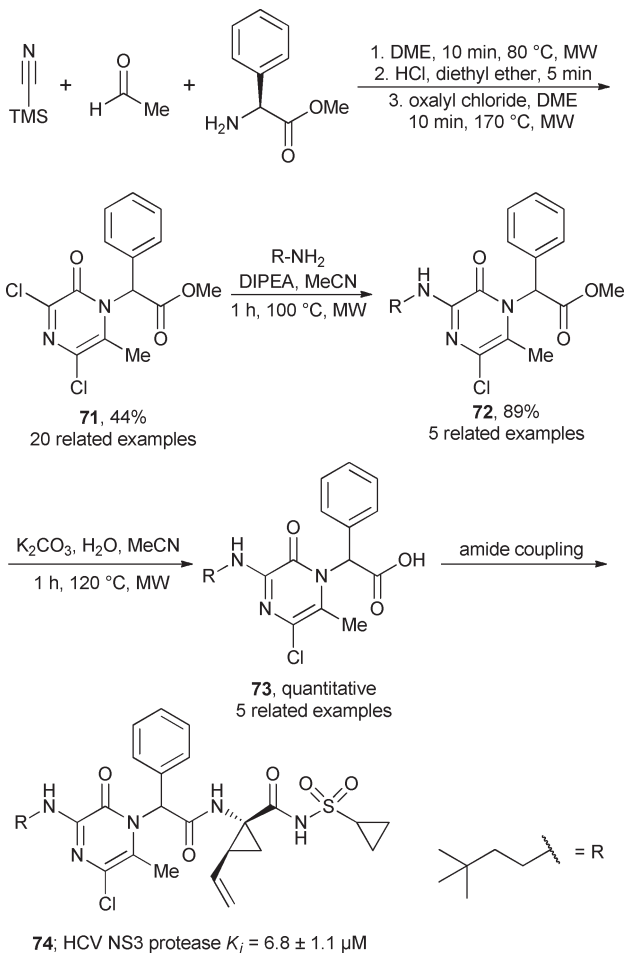
Nilsson and co-workers explored a series of HCV NS3 inhibitors that were cyclised between the P1 and P3 residue (Scheme 32).[146] A microwave-assisted ring opening of the tricyclic lactone followed by amide coupling gave the key intermediate **68** in good yield over three steps with retained stereochemistry. After O-arylation, the ethyl ester was hydrolysed under basic conditions using microwave heating. A two-step microwave-assisted protocol was then applied to couple the resulting acid with cyclopropanesulfonamide followed by macrocyclic ring closing metathesis to yield **70**. The macrocyclic inhibitor **70** showed subnanomolar affinity to the HCV NS3 protease.

There are additional examples of NS3 protease inhibitors synthesised *via* microwave accelerated metathesis macrocyclisations between P2–P1′[147] and between P2–P4[148] in the literature.

In 2009, Gising *et al.* developed a microwave-assisted one-pot two-step protocol to afford N-1 and C-6 functionalised 3,5-dichloro-2(1*H*)-pyrazinones with an application towards HCV NS3 protease inhibition (Scheme 33).[149] The products were isolated in comparable yields with the literature and the reaction time was shortened to 2 times 10 min instead of several hours with traditional heating. In the one-pot two-step sequence an amine, an aldehyde and trimethylsilyl cyanide were cyclised together with oxalyl chloride to afford a set of 3,5-dichloro-2



Scheme 32 Microwave-assisted synthesis of HCV NS3 protease inhibitors *via* metathesis.



Scheme 33 Synthesis of HCV NS3 protease inhibitors *via* microwave mediated multi-component heterocyclisation and S_NAr substitution.

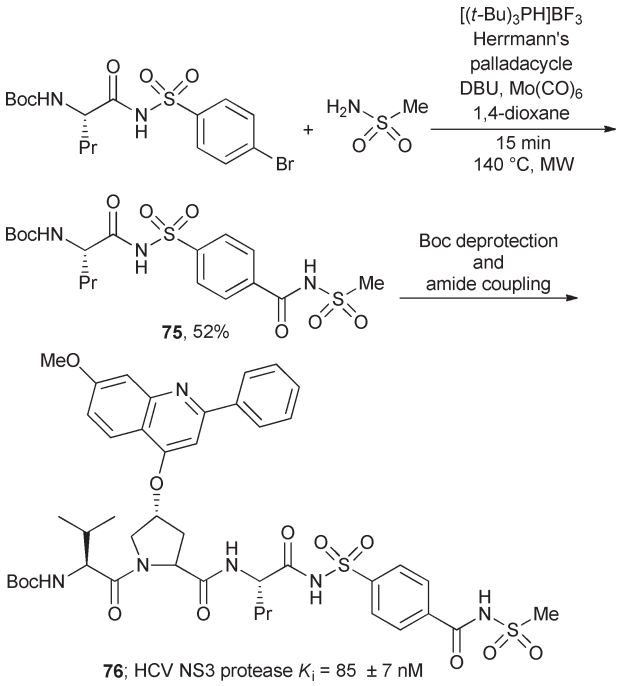
(1*H*)-pyrazinones exemplified by **71** in Scheme 33.[149] The following year Örtqvist and co-workers reported a number of 2 (1*H*)-pyrazinone based HCV NS3 protease inhibitors.[150] Single-mode microwave heating was utilised to selectively substitute the C-3 chlorine with 3,3-dimethylbutanamine yielding **72** and hydrolysis under controlled microwave irradiation gave **73** quantitatively. The final inhibitor **74** was reached after peptide coupling and showed moderate affinity to the NS3 protease.

In 2005, Wu *et* al. explored palladium-catalysed amidocarbonylation reactions using septa-sealed microwave vials and $Mo(CO)_6$ as a solid source of carbon monoxide. The developed protocol was also employed in the synthesis of a NS3 protease inhibitor **76** (Scheme 34).[151] The scope of the reaction was further investigated by Rönn and co-workers in 2008, exploiting more complex aryl bromides as NS3 protease inhibitor precursors in 11 related examples.[152]

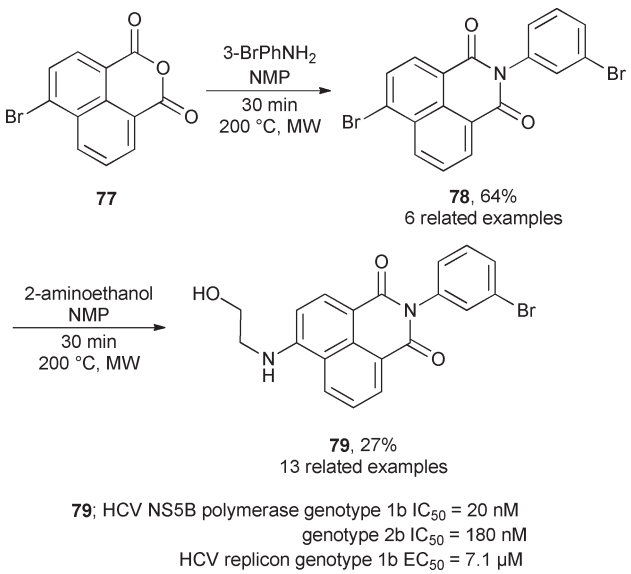
Another viral target under investigation is the NS5B polymerase that catalyzes RNA synthesis during replication. NS5B is a validated target and is crucial for viral infectivity.[153]

A recent article from Ontoria *et al.* described the results from a HTS targeting the NS5B polymerase and the further exploration of the resulting hits.[154] The re-synthesis and exploration of the hits started with a condensation between the cyclic anhydride **77** and 3-bromoaniline. The reaction required heating in NMP for 24 h at 145 °C to reach full conversion giving the product in moderate yield. The use of microwave heating of sealed reactions increased the yield and decreased the reaction time to 30 min at 200 °C. A subsequent S_NAr substitution of **78** with various amines produced a set of NS5B polymerase inhibitors and the most promising compound **79** (Scheme 35) was more potent towards HCV genotype 1 than to genotype 2.

Recently, Lazerwith co-workers described the pharmacokinetic optimisation of a HCV replicon inhibitor.[155] One of the most promising compounds was synthesised through a



Scheme 34 Microwave-assisted synthesis of HCV NS3 protease inhibitors *via* a palladium-catalysed amidocarbonylation.

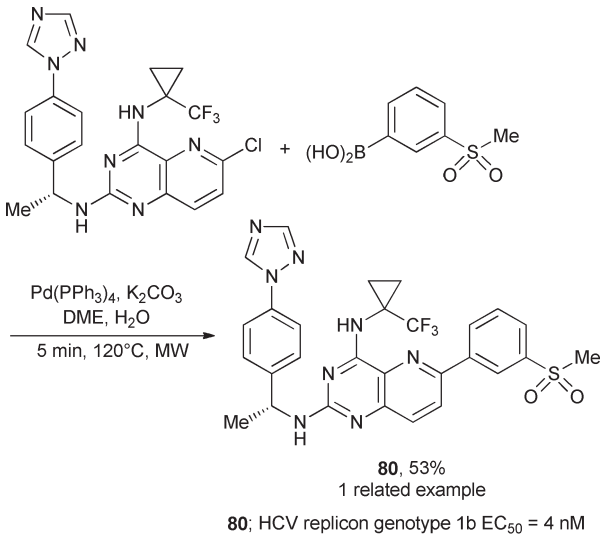


Scheme 35 Synthesis of HCV NS5B polymerase inhibitors *via* a microwave promoted condensation reaction.

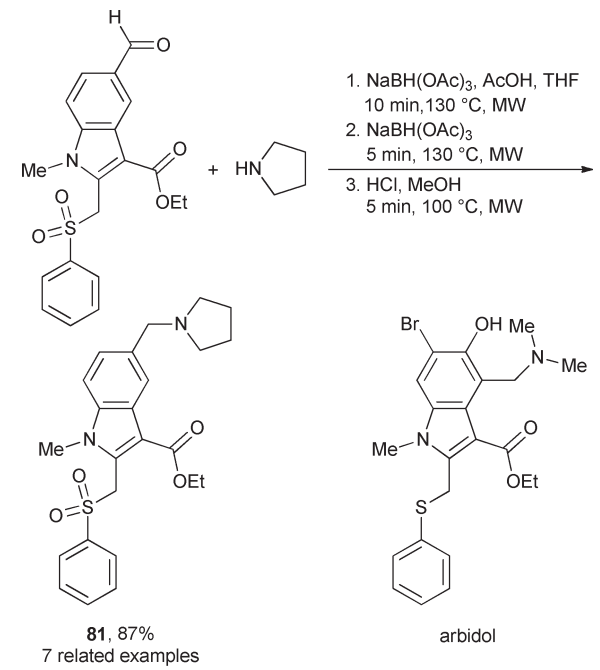
palladium-catalysed, microwave mediated Suzuki–Miyaura cross-coupling[156] (Scheme 36). Compound **80** displayed improved bioavailability (F = 88% *vs.* 2%) and prolonged mean residence time (MRT = 3.5 h *vs.* 0.4 h) in rat.

Other successful microwave-assisted metal-catalysed cross-couplings for the synthesis of HCV inhibitors have been reported by several groups and include; Suzuki–Miyaura cross-couplings,[157,158] Sonogashira couplings,[159,160] Negishi cross-coupling[161] and Cu-mediated cyanation.[162]

Arbidol (see Scheme 37) is a broad spectrum antibiotic and a known HCV entry inhibitor.[163] In a report from 2010, Selitto and



Scheme 36 Synthesis of HCV replicon inhibitors *via* a microwave heated Suzuki–Miyaura cross-coupling.



Scheme 37 Synthesis of HCV entry inhibitors *via* a microwave promoted reductive amination.

co-workers described the synthesis and evaluation of arbidol analogues.[164] In the final synthetic step, a set of amines was introduced by reductive amination in sealed vials under controlled microwave irradiation (Scheme 37). One of the most active compounds **81**, showed comparable anti HCV entry inhibition to arbidol and a better cytotoxicity profile (TC_{50}>50 μM *vs.* arbidol, TC_{50} = 12 μM).

3. Conclusions

Controlled and automated single-mode microwave heating is one constituent of the collection of novel techniques that provide medicinal chemists with new and powerful production tools. In this perspective we have summarised a number of diverse microwave-assisted synthetic protocols that have been useful in discovery projects towards the development of new antibiotics and antiviral compounds. In many of the depicted examples, the main chemical effort was directed towards fast, smooth and reliable small-scale procedures avoiding complicated handling of inert conditions and reactive gases. Furthermore, the microwave methodology helped establish the structure–activity relationships in a uniquely rapid fashion. Thus, the field of organic synthesis is evolving and controlled microwave heating will continue to change the way we perform both target and diversity driven medicinal chemistry. Today, microwave chemistry accelerates and increases the opportunities to develop not only new antibiotics and antiviral drugs but all kinds of new medicines.

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Notes and references

† All biological data refers to *Pf* unless otherwise stated.

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