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Short Research Article

# Microwave assisted synthesis of multiple labelled SR244870, a compound related to ferroquine (SSR97193)†

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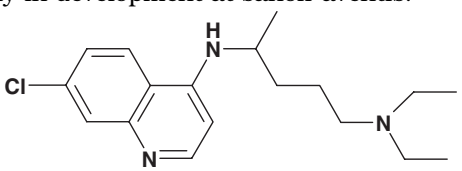
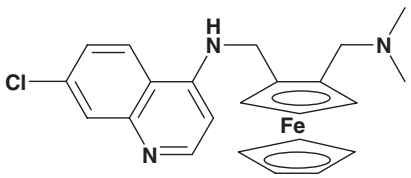
## Introduction

Malaria is caused by four species of protozoan parasites of the genus *Plasmodium* infecting human red blood cells. Of the different species, the *Plasmodium falciparum* parasite can cause death from cerebral infection, and one of the leading anti-malarial drugs is chloroquine **1**. However, increasing parasite resistance to the quinoline-based drugs has seen a gradual growth in deaths caused by the disease[1] and thus the investigation into a more potent and effective drug. One such compound is ferroquine (SSR97193) **2**, which is presently in development at sanofi-aventis.

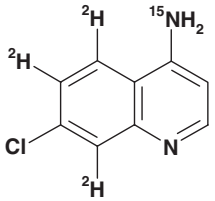



**1**




**2**

In order to support our bioanalysis studies in this area, a synthesis of a multiply stable labelled derivative of 4-amino-7-chloroquinoline (SR244870) was required. We were able to develop a route to a compound containing an additional four mass units, [$^2H_3$,$^{15}$N]SR244870 **3**. All labels were incorporated by the use of microwave-assisted reactions.




**3**

## Results and discussion

The overall synthesis (Scheme 1) was based upon our previous synthesis of [*quinoline*-3-$^{14}$C]SSR97193, recently reported by Taylor.[2] Following the reaction conditions therein, [$^2H_3$]4,7-dichloroquinoline could be derived from [2,4,5,6-$^2H_4$]3-chloroaniline and Meldrums acid.

Although [2,4,6-$^2H_3$]3-chloroaniline is commercially available it was rapidly synthesized from 3-chloroaniline *via* acid-catalysed H/$^2$H exchange, enhanced under microwave conditions.

It was found that microwave irradiation at 150°C and 150 psi was sufficient for complete exchange at the acidic positions. A natural progression of this was the incorporation of a deuterium atom at the 5-position to

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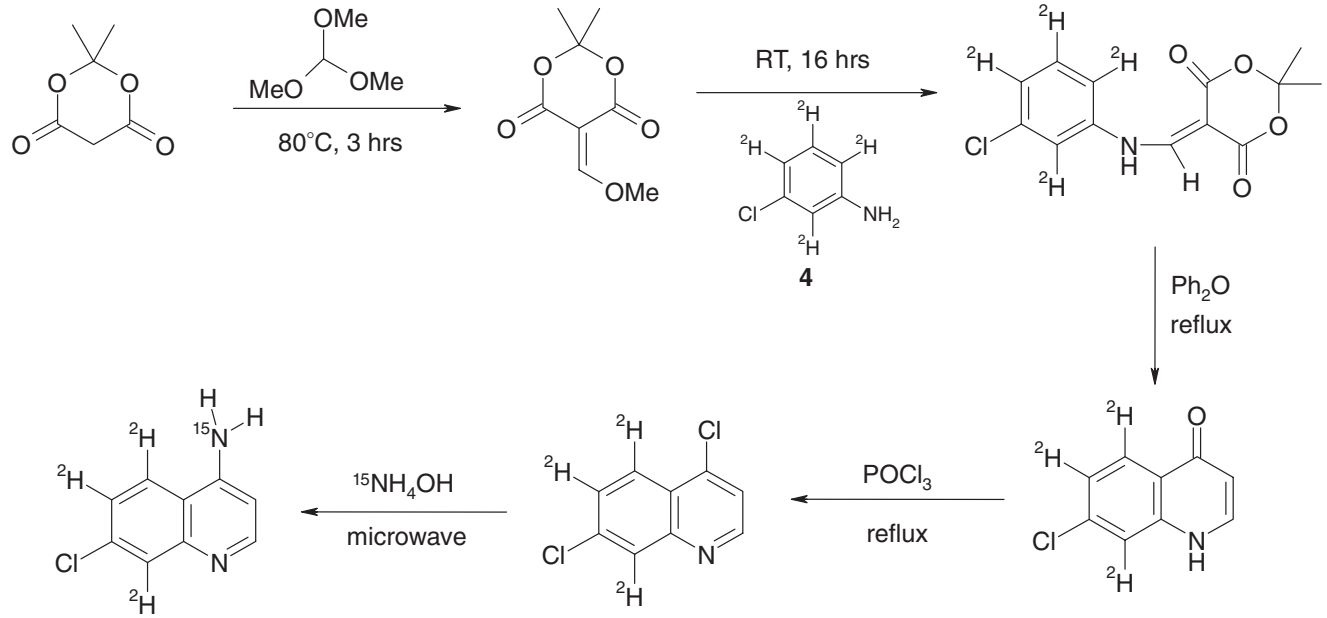


**Scheme 1**

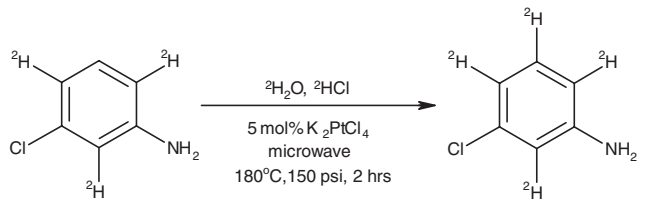


**Figure 1**

**Table 1** The ratio of residual hydrogens determined by $^{1}$HNMR at position 5 in comparison to positions 2, 4 and 6

| $^{2}$HCl[a] | Time (min)[b] | 2[c] | 4[c] | 5[c] | 6[c] |
|---|---|---|---|---|---|
| 0 | 40 | 1[d] | 1[d] | 6 | 1[d] |
| 0.2 | 40 | 1 | 1 | 3.5 | 1 |
| 0.6 | 40 | 1 | 1 | 3.5 | 1 |
| 1.1 | 40 | 1 | 1 | 2.8 | 1 |
| 2.0 | 40 | 1 | 1 | 12.5 | 1 |

[a]The number of equivalents of deuterium chloride to substrate.
[b]The irradiation time at 185°C and 150 psi.
[c]The hydrogen/deuterium exchange position on the substrate.
[d]These values are defined as the equilibrium amount of residual hydrogens.

afford the fully deuterated [2,4,5,6-$^{2}H_4$]3-chloroaniline **4**. This was achieved with the aid of a catalyst, platinum tetrachloroplatinate, *via* the homogenous H/$^{2}$H exchange reaction reported by Garnett,[3] accelerated by microwave irradiation, (see Figure 1). [2,4,5,6-$^{2}H_4$]3-chloroaniline was obtained with a yield of 60% and >97% deuterium incorporation.

The standard conditions of acetic acid in an equal ratio to deuterated water in order to increase the acidity of the mixture and aid dissolution were not necessary for our purposes. The aniline substrate was soluble in deuterated water as the deuteriochloride salt but additional deuterium chloride ($^{2}$HCl) was required to adequately lower the pH. Trials conducted varying the amount of $^{2}$HCl with a constant 5 mol% of potassium tetrachloroplatinate, indicated that 1.1 eq. of $^{2}$HCl was the optimum amount for the *meta* H/$^{2}$H exchange of [$^{2}H_3$]-3-chloroaniline, (see Table 1). These results reinforced Garnett's findings that changes in pH significantly affected the relative rates of exchange.

Further optimization, resulted in the equilibrium amount of residual hydrogens at position 5 being brought in line with positions 2, 4 and 6.

The per-deuterated 3-chloroaniline **4** was thus taken through to [$^{2}H_3$]4,7-dichloroquinoline to enable labelled trials of the amination step to be conducted. The conventional method of passing ammonia gas over the substrate in phenol was not viewed as being practical for [$^{15}$N]ammonia so the employment of other aminating reagents was explored. [$^{15}$N]Potassium pthalimide proved too unreactive even under microwave conditions. However, amination was found to proceed smoothly with [$^{15}$N]ammonium chloride in pyridine under microwave conditions to give the amine in a 49% yield. Unfortunately, none of the $^{15}$N-label was found to be incorporated into the amine produced. It is postulated that a variation of the Chichibabin reaction, which involves the attack of alkali metals with pyridine,



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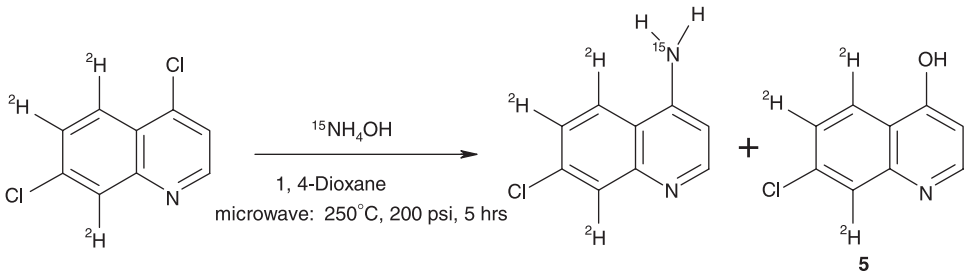


**Figure 2**

had taken place. In this case reaction between the amine and pyridine, followed by attack on the labelled 4,7-dichloroquinoline, produced exclusively the $^{14}N$-product.[4]

The desired incorporation was achieved with the use of [$^{15}N$]ammonium hydroxide solution (see Figure 2). However, the necessity to conduct the reaction at high temperature and pressure over a relatively long period of time in the microwave, led to the formation of the desired amine **3** in only 49% yield. Some hydrolysis product **5** and base-induced loss of deuterium from the 8-position were also observed. This has prompted the exploration of other methods of amine incorporation.

Success of H/$^2$H exchange on 3-chloroaniline led us to attempt direct deuteration of the 4-amino-7-chloroquinoline, in order to remove the need for synthesis. Unfortunately, deuterium exchange was only observed at the 3-position of the molecule. Attempts to promote H/$^2$H exchange in commercially available 4,7-dichloroquinoline exclusively afforded the hydrolysis product, 7-chloro-4-hydroxyquinoline, with only partial exchange at the 3, 6 and 8 positions. No exchange was observed in reaction with 7-chloro-4-hydroxyquinoline.

## Conclusion

A route to [$^2H_3$,$^{15}N$]SR244870 **3** was developed in which the stable isotopes were derived from readily available $^2H_2O$ and ammonium-$^{15}N$-hydroxide. Microwave enhanced H/$^2$H exchange promoted rapid access to the key intermediate [$^2H_4$]3-chloroaniline. The use of microwave conditions in the amination step enabled the successful incorporation of all the labels by microwave-assisted reactions.

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