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Application of multicomponent reactions to antimalarial drug discovery. Part 3: Discovery of aminoxazole 4-aminoquinolines with potent antiplasmodial activity in vitro

Chitalu C. Musonda,[a] Susan Little,[b] Vanessa Yardley[b] and Kelly Chibale[a,c,*]

[a]*Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa*
[b]*Department of Infectious & Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK*
[c]*Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Rondebosch 7701, South Africa*

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Abstract—The synthesis and antimalarial activity of a novel series of first generation 4-aminoquinoline-containing 2,4,5-trisubstituted aminoxazoles against two strains of the *Plasmodium falciparum* parasite in vitro is described. A number of compounds significantly more potent than the standard drug chloroquine were identified.

The problem of endemic malaria continues unabated globally. Malaria affects 40% of the global population, causing an estimated annual mortality of 1.5–2.7 million people.[1,2] The World Health Organisation (WHO) estimates that 90% of these deaths occur in sub-Saharan Africa among infants under the age of five. There are four species of *Plasmodium* that cause malaria in humans, namely *P. falciparum*, *P. malariae*, *P. ovale* and *P. vivax*. Of these *P. falciparum* is the most virulent and causes the majority of deaths. While a vaccine against malaria continues to be elusive, chemotherapy remains the most viable alternative towards treatment of the disease. With the malaria parasite having developed multiple drug resistance to clinically established drugs, there is a compelling need to introduce new chemical entities that can overcome the resistance (Fig. 1).

In the context of our ongoing research towards the discovery of new antimalarial compounds, we have been successfully employing the isocyanide-based multicomponent reaction (MCR) strategy to synthesize new compounds in which diversity is introduced in a single step. To this end, we have synthesized varying classes of compounds based on the quinoline substructure, a pharmacophore found present in a number of antimalarial drugs including chloroquine (CQ) **1** and quinine **2**.[3,4]

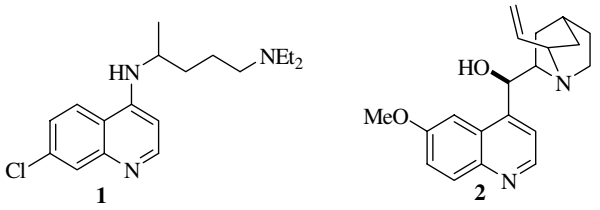

Figure 1. Chemical structures of chloroquine (**1**) and quinine (**2**).

In this communication, we wish to report on the synthesis and antiplasmodial activity of a novel class of 4-aminoquinolines that contain a heterocyclic 2,4,5-trisubstituted aminoxazole unit in the lateral side chain. The synthesis was based on the 3-component condensation domino reaction reported by Zhu et al.,[5,6] wherein an amine, aldehyde and isocyanoacetamide react to afford 2,4,5-trisubstituted aminoxazoles. We were attracted to this reaction owing to its simplicity and amenability to parallel synthesis and rapid library generation.

Chemistry. We intended to incorporate the 4-aminoquinoline substructural motif into the amine inputs required for the MCR. As such, the requisite amines **9**–**12** were synthesized according to Scheme 1,[7] whereby

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* Corresponding author. E-mail: Chibale@uct.ac.za

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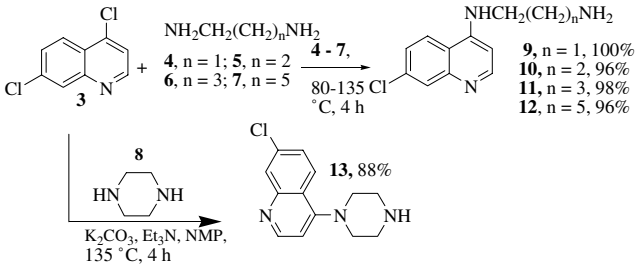
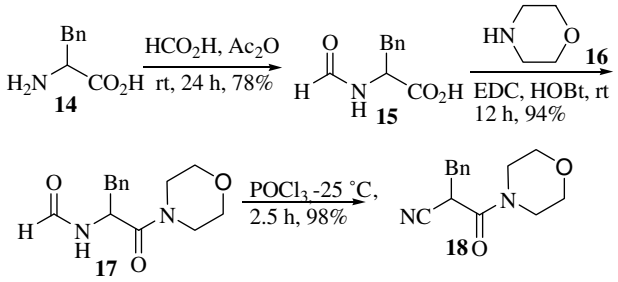


Scheme 1. Synthesis of 4-aminoquinoline amines **9**–**13**.



Scheme 2. Synthesis of isocyanoacetamide **18**.

commercially available 4,7-dichloroquinoline **3** was treated with an excess of the dialkyl amines **4**–**7**, initially at 80 °C and then at 135 °C for 3 h. On the other hand, treatment of 4,7-dichloroquinoline with excess piperazine[7] afforded the monosubstituted amine **13**, Scheme 1.[8] The five amines **9**–**13** were obtained in excellent yields (88–100%), the results of which are shown in Scheme 1.

The next step was to generate the isocyanoacetamide required for the multicomponent reaction, and this was realised from L-phenylalanine **14** according to Scheme 2 under standard conditions.[9]

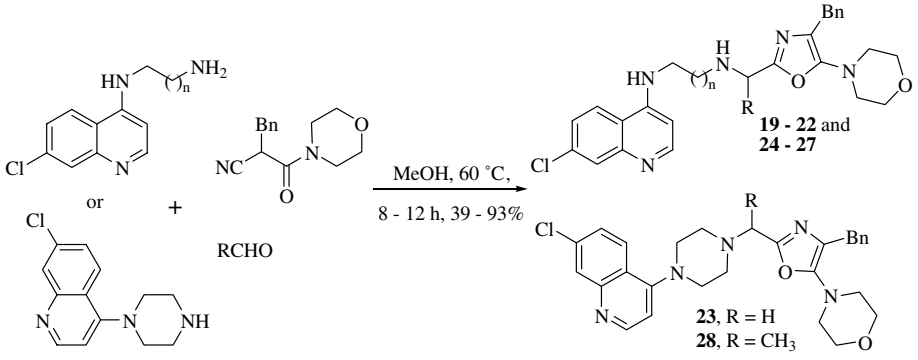
Treatment of L-phenylalanine with a mixture of formic acid (HCOOH) and Ac_2O at sub-zero temperature for 20 min, followed by stirring at room temperature, afforded the formamide **15** in 78% yield.

Subsequent coupling of **15** with morpholine **16**, mediated by EDC and HOBt in DCM at room temperature, gave the formamide **17** in 94% yield. Finally, dehydration of **17** to the isocyanoacetamide **18** was achieved in 98% yield by treatment with $POCl_3$ in DCM at −25 °C.[10] Finally, the multicomponent reactions were conducted in parallel array format in MeOH at 60 °C according to Scheme 3.

Following pre-treatment of the amines **9**–**13** with either *para*-formaldehyde or acetaldehyde for 30 min, isocyanoacetamide **18** was added to each of the reaction mixtures. The initial choice of *para*-formaldehyde and acetaldehyde as the aldehyde inputs was governed by our desire to obtain low molecular weight compounds.[11] Isolation of the compounds was achieved by means of chromatography on silica (SiO_2) gel. Table 1 shows the isolated yields and purities of the compounds obtained.

Biological results. Compounds **19**–**28** were evaluated against two different strains of *P. falciparum*, namely a chloroquine-sensitive (CQS) 3D7 strain and a chloroquine-resistant

(CQR) K1 strain. Results of these assays are shown in Table 2. From the results in Table 2, compound **26** was the most active in the chloroquine-sensitive 3D7 strain which, with an IC_{50} = 0.0038 μM, was 5 times more efficacious than chloroquine (IC_{50} = 0.02 μM). Also of note was **19** (IC_{50} = 0.0084 μM) which was also active in the low nanomolar range. On the other hand, **20** exhibited slightly weaker potency at IC_{50} = 0.041 μM than chloroquine although not significantly so, while **25** (IC_{50} = 0.079 μM), **22** (IC_{50} = 0.15 μM), **23** (IC_{50} = 0.52 μM) and **28** (IC_{50} = 0.14 μM) exhibited weakened antiplasmodial activities in comparison to chloroquine. Interestingly, the introduction of a methyl substituent into the side chains of compounds **19** and **20** caused reductions in the activities of the corresponding derivatives **24** and **25**, respectively. In contrast, the introduction of a methyl substituent into the side chains of **21** and **22** resulted in significant improvements in the efficacies of the resulting compounds **26** and **27**. With IC_{50}s of 0.0038 and 0.018 μM, respectively, **26** and **27** exhibited the best potencies, showing 21-fold and eightfold improvements in efficacy against the chloroquine-sensitive strain.



Scheme 3. Multicomponent synthesis of compounds **19**–**28**.