Design and Synthesis of New Phosphoramidates Chloroquine Analogs

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Keywords: Antimalarial, chloroquine, phosphoramidate.

INTRODUCTION

About 3.3 billion people - half of the world's population - are at risk of malaria. Every year, this leads to about 250 million malaria cases and nearly one million deaths.[1]

Therefore, there is urgency to develop new affordable, safe, and efficacious antimalarilas. Although the resistance to chloroquine (CQ) and related 4-aminoquinoline antimalarial drugs has emerged; designing new antimalarial based on the quinoline pharmacophore has distinct advantages due to unique pharmacological effect of 4-aminoquinoline drugs.[2]

Several studies demonstrated that various structurally diverse modifications in the side chain of CQ were well tolerated for the antimalarial activity. Systematic variation of the branching and basicity of the side chain of CQ yielded the new 4-aminoquinoline derivatives exhibiting excellent potency against CQ-sensitive and CQ-resistant strains.[3]

A new class of Chloroquine analogs containing phosphoramidate group and different alkyl spacer (***Figure 1***) was structurally planned by modification of side-chain based on the previously described.

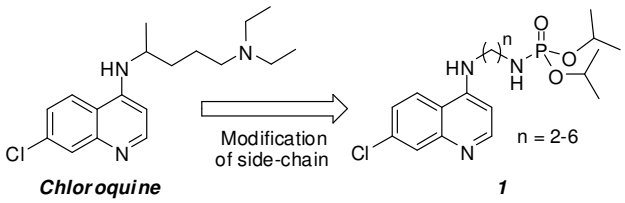


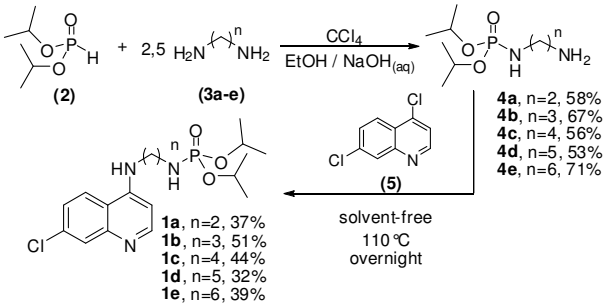
Figure 1. Design strategy for Chloroquine analogs (**1**).

RESULTS AND DISCUSSION

The phosphoramidates chloroquine analogs (**1a-e**) used in the present study were prepared by nucleophilic aromatic substitution on 4,7-dichloroquinoline (**5**) with excess of aminoalkyl phosphoramidates (**4a-e**) in solvent-free at 110ºC overnight as outlined in **Scheme 1**.

The starting aminoalkyl phosphoramidates (**4a-e**) are easily prepared from selective monophosphorylation of aliphatic diamines (**3a-e**) with diisopropyl phosphonate (**2**).[4]

All the synthesized compounds were well characterized by IR, 1H, 13C and 31P NMR spectroscopy.



Scheme 1. Synthetic route of new phosphoramidates chloroquine analogs (**1a,b**).

CONCLUSION

Five new phosphoramidates derivatives, closely mimicking the antimalarial drug chloroquine, have been prepared.

The compounds were obtained in satisfactory yields by nucleophilic aromatic substitution of the chloro atom in 4-position of the 4,7-dichloroquinoline (**5**) with aminoalkyl phosphoramidates (**4a-e**).

Studies on the properties antimalarial of these new derivatives are currently under investigation in our laboratories.

ACKNOWLEDGEMENTS

UFF, FAPERJ, CAPES and CNPq.

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