Synthesizing Modified Quinoline Imidazole Analogues

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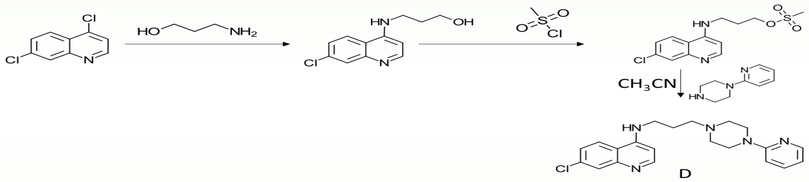
Abstract:

Malaria is a parasitic disease that continues to be a significant public health concern for developing countries where transmission regularly occurs. Antimalarial drug resistance is one of the most significant challenges to malaria control that has arisen within the 21st century. Synthesizing new compounds that are not subject to said resistance is critical to solving this problem. The work presented here involves a one-step process to attach an imidazole head group to a quinoline ring. This work is a continuation of Jacqueline Ballay's work on an honors project. Prior work to synthesize simplified versions of reversed chloroquine analogues involved several steps and included a modified version of a known pharmacophore, that helped reverse chloroquine resistance. This work involves nucleophilic aromatic substitution via a benzyne intermediate, which should help the process be more efficient. Attaching a library of different head groups to the same imidazole ring will allow the deployment of many different synthesis reactions. IR was used to analyze the compounds, and product purity was checked using TLC.

Background:

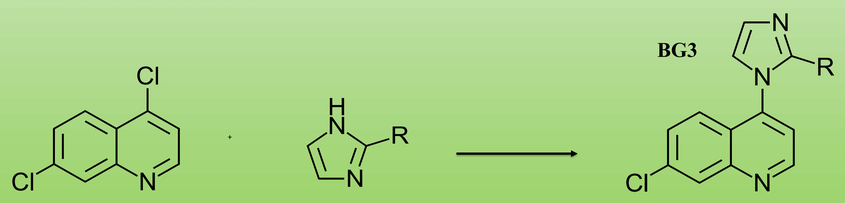
Antimalarial drug resistance in malaria is now so widespread that nearly all currently available antimalarial drugs have lost efficacy in many parts of the world. Several analogues which have the quinoline ring moiety have been used to fight malaria. These analogues have the ability to accumulate in the digestive vacuole of *P.falciform*, causing toxic heme to build up in the organism, resulting in death. Evidence suggests that the cause of resistance of interest could likely be the inhibition of the accumulation of these quinoline Imidazole analogues in the digestive vacuole of the parasite[1]. The synthesized compound combats this inhibiting mechanism by acting as a reversal agent while still delivering a drug moiety that prevents the toxic form of heme from being polymerized into a less toxic version known as hemozoin. Prior synthesis done by Dr. Gunsaru was a three step process to create a reversed chloroquine as shown in figure 1 below.



Scheme 1. Schematic of the synthesis of simplified reversed chloroquines. The synthesis being proposed is a one step process as shown in scheme 2 below.

Method:

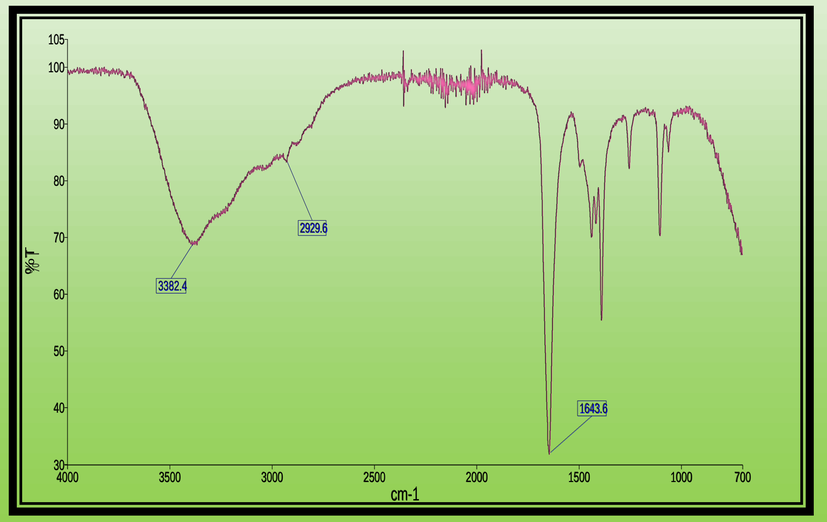
To synthesize BG3, 0.96 grams (0.024 moles) of NaH (60% dispersion in mineral oil) was added in portions to a stirred solution of 1.46 grams (0.00999 moles) of 2-Phenyl-2-imidazoline in 30 milliliters of DMF at 0ºC in a three-necked round-bottom flask. The mixture was stirred for 30 minutes at 0ºC and 1.98 grams (0.00999 moles) of 4,7-Dichloroquinoline was added to the mixture. The mixture was heated to 130ºC and was stirred overnight. The reaction was then poured into a 30-milliliter saturated solution of ammonium chloride. The reaction mixture was extracted with four, 15 milliliter portions of ethyl acetate. The resulting organic phases were dried over sodium sulfate. The dried phase was filtered and evaporated under reduced pressure to remove volatile materials (Zhao, et al., 2018). The synthesized compound was then recrystallized using ethanol as the solvent. After recrystallization for purity of the sample, TLC and IR spectroscopy were used to characterize the compound to affirm the reaction and recrystallization was successful. It is important to note that the imidazole ring is common for all synthesis reactions mentioned above.



Scheme 2. Schematic illustrating the synthesis of head group BG3. The imidozoline ring is common for all synthesis reactions mentioned. The R group is what predominantly changes according to what head group is attached.

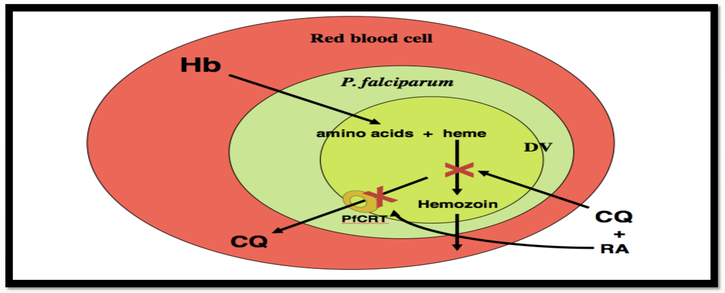
Results and Discussion:

Test	Observation
Weight (crude)	 6.50 g
Weight (recrystallized)	 4.23 g
Melting Point	Compound sublimed between 285 – 290ºC
TLC [30% ethyl acetate to 70% hexane]	Rf value = 0.5



We expect that the 1643.6 peak is the aromatic C=C peak. It is visibly strong which is to be expected because a quinoline and benzene ring is in our product. The IR was visibly different from the two starting materials used to synthesize the compound BG3. Characterization of the compound will be performed at Portland State University. Additionally, antimalarial testing against sensitive and resistant strains will be done at OHSU.

Cholorquine is known to inhibit the polymerization of heme into hemozoin. This is likely due to the quinoline ring. These compounds retain the quinoline ring, so we expect the synthesized compound to behave in a similar fashion as shown below:



Future Work:

The next steps would include trying to synthesize other modified quinoline imidazole analogue compounds (Fig.1) and sending them to Dr. Jane Xu Kelly's lab at PDX for antimalarial testing. If these compounds are found to be potential drug candidates, a one step synthesis process could be theoretically easier to scale up and deployed among populations that are most in need. The development of new antimalarial compounds is always desirable because they may not be recognized by the resistant parasite.

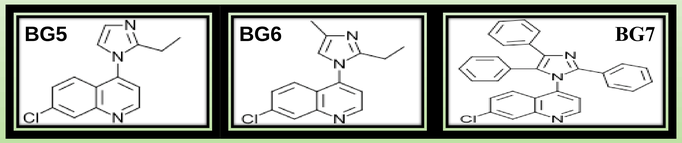


Figure 1. Future work with three additional imidazoline head groups

References:

1. Simplified Reversed Chloroquines to Overcome Malaria Resistance to Quinoline-based Drugs" by Bornface Gunsaru, Steven Burgess, Westin Morrill, Jane Kelly, Shawheen Shomloo, Martin Smilkstein, Katherine Leibmann, and David Peyton (2017). Antimicrobial Agents and Chemotherapy, 61(4):
2. Bhattacharjee, A. K.; Kyle, D. E.; Vennerstrom, J. L.; Milhous, W. K. *J. Chem. Inf. Comput. Sci.*, 2002, **42**, 1212-1220

Acknowledgements:

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