

SYNTHESIS AND HEME DETOXIFICATION OF PYRANO[2,3-C]PYRAZOLE-AMINOQUINOLINE HYBRIDS AS ANTIMALARIAL AGENTS

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INTRODUCTION

One of the most common infectious diseases globally is malaria, which is caused by the protozoan parasite *Plasmodium* in humans [1]. The hybridization of pyrano[2,3-c]pyrazoles and 4-aminoquinoline enhances the antimalarial activity of pyrano[2,3-c]pyrazole-aminoquinoline hybrids, as both pyranopyrazole and 4-aminoquinoline derivatives have diverse therapeutic applications. Our lab has recently reported a successful cascade process for conjugating 4-aminoquinolines and pyrano[2,3-c]pyrazole derivatives as antimalarial molecule hybrids [2]. This project aims to extend a series of pyrano[2,3-c]pyrazole-aminoquinoline hybrids as potential antimalarial agents.

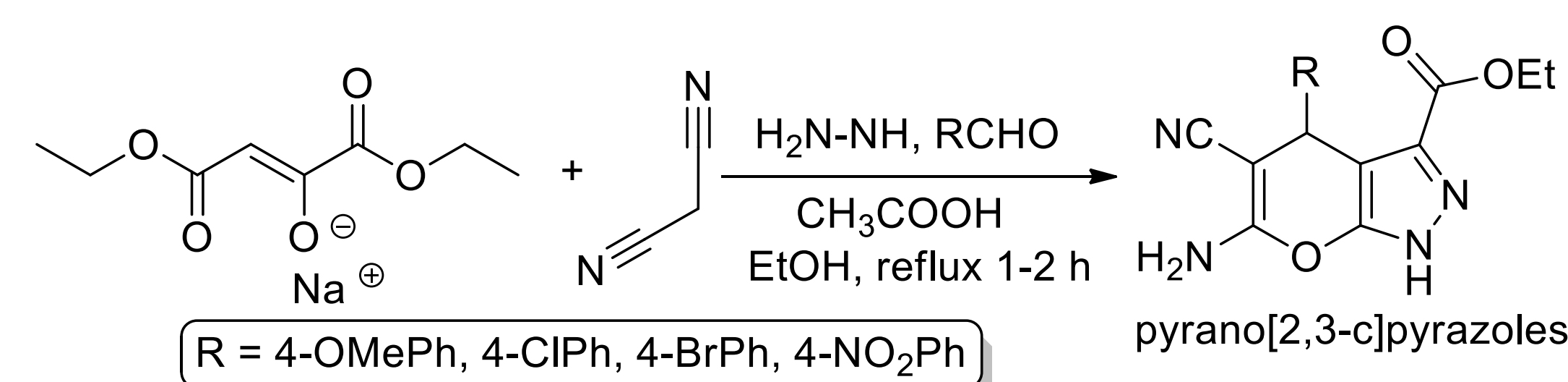
EXPERIMENTAL METHOD

Initially, the synthesis of four pyrano[2,3-c]pyrazoles proceeds via multi component reactions involving diethylmalonate, hydrazine, aldehyde, and malononitrile using ethanol as a solvent in the presence of acetic acid as a catalyst. Followed by the synthesis of 4-(bromoethylamino)-7-chloroquine through a bromination reaction and finally fusing between four pyrano[2,3-c]pyrazole derivatives and 4-aminoquinoline via nucleophilic substitution. All the synthesized hybrids were examined for inhibition of heme detoxification by using a Nano ITC (TA Instruments, New Castle, DE, USA) microcalorimeter to study the possible interaction between four hybrids and hemin at 37°C.

Fourier Transform Infrared (FT-IR), Nuclear Magnetic Resonance (NMR), and UV-Visible Spectroscopy were used to characterised all the compounds.

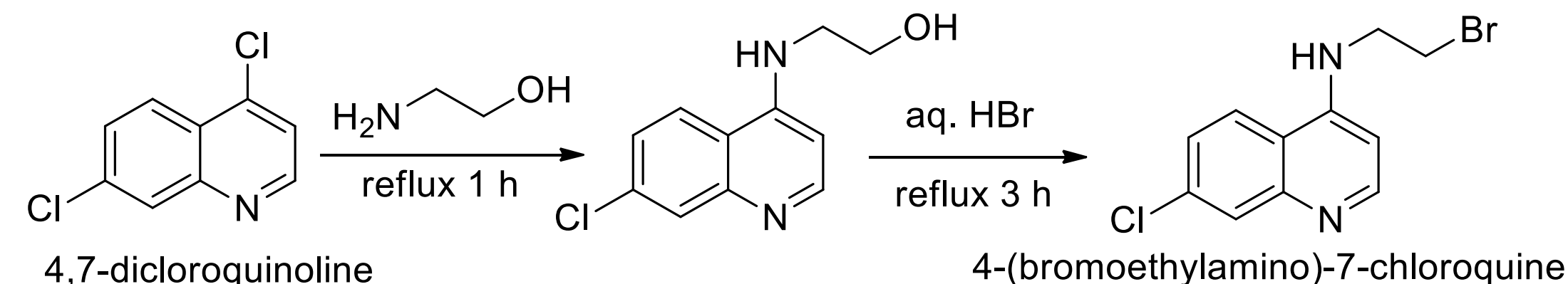
RESULTS

Syntheses of pyrano[2,3-c]pyrazoles



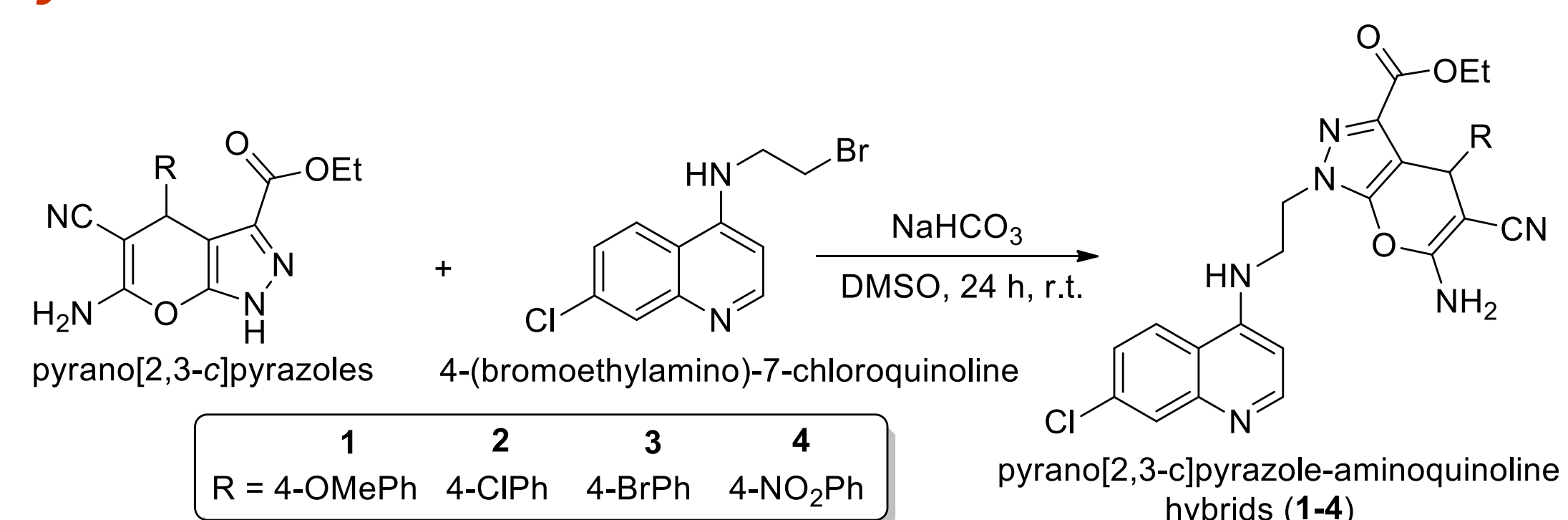
Scheme 1. Pyrano[2,3-c]pyrazoles synthesis

Syntheses of 4-(bromoethylamino)-7-chloroquinoline



Scheme 2. 4-(bromoethylamino)-7-chloroquine synthesis

Syntheses of pyrano[2,3-c]pyrazole-aminoquinoline hybrids



Scheme 3. pyrano[2,3-c]pyrazole-aminoquinoline hybrids synthesis

Affinity of hybrid compounds towards hemin

Compound	K _d (M)
Hybrid-01	4.301×10 ⁻⁷
Hybrid-02	9.925×10 ⁻⁷
Hybrid-03	1.013×10 ⁻⁵
Hybrid-04	1.137×10 ⁻⁵

Table 1. Determination of the dissociation constant (K_d) values via isothermal titration calorimetry

Titration profile of 100 μM H1 into 20 μM hemin

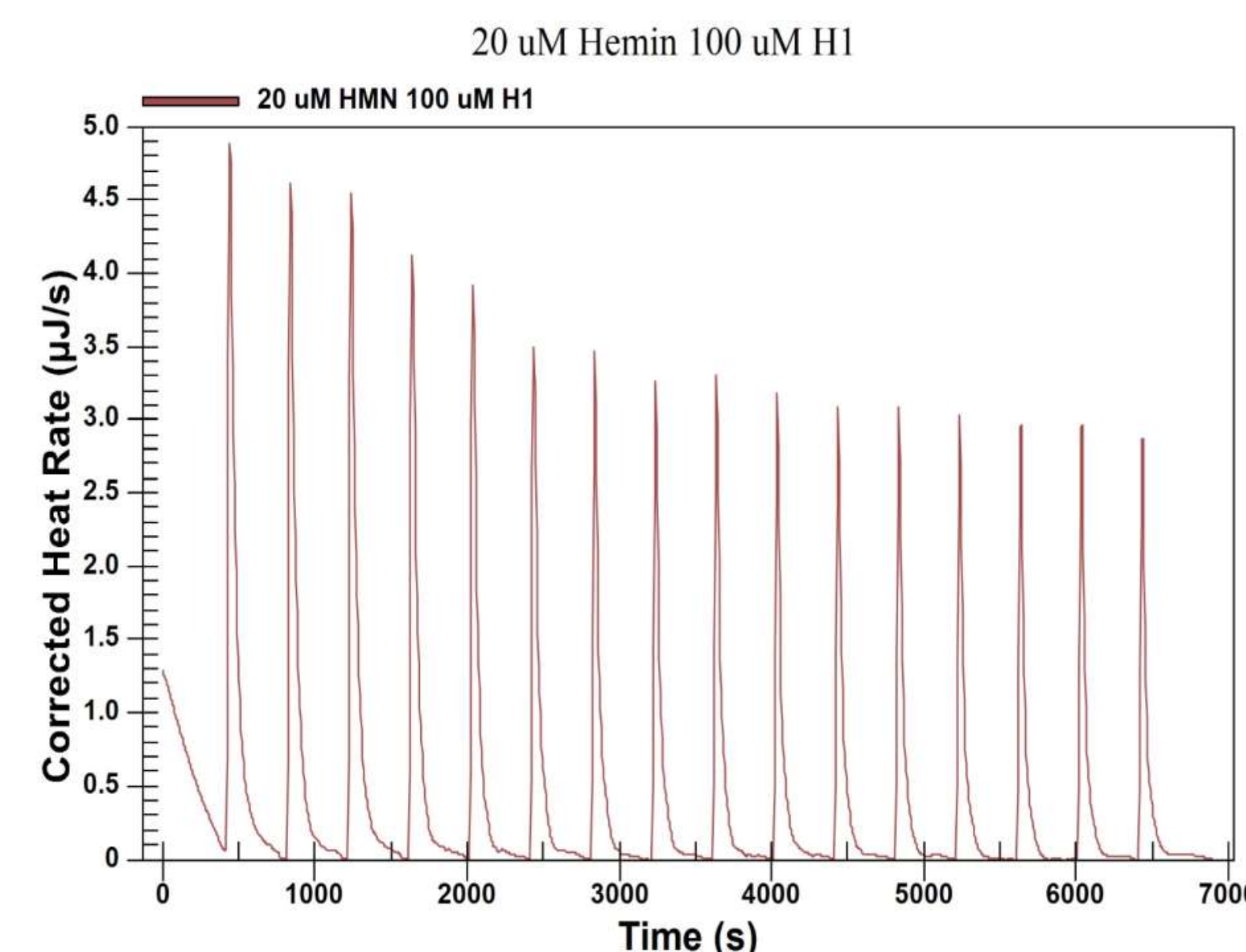


Figure 1. Thermogram of heat generation upon titration of 100 μM H1 into 20 μM hemin

CONCLUSION

•Four pyrano[2,3-c]pyrazole-aminoquinoline hybrids were successfully synthesized and characterised using spectral analysis.

•Determination of the dissociation constant (K_d) values from ITC experiments revealed varying affinities of the hybrids to hemin, reflecting the difference in their structures.

•Two of the hybrids, H1 and H2 formed more stable interactions with hemin, and thus are better antimalarial candidates compared to the other two hybrids.

REFERENCE

- 1.M. Gildenhard et al. **Mosquito microevolution drives *Plasmodium falciparum* dynamics.** *Nat. Microbiol.* 2019, 4 (6) 941.
- 2.M.A. Shamsuddin et al. **Synthesis, Molecular Docking, and Antimalarial Activity of Hybrid 4-Aminoquinoline-pyrano[2,3-c]pyrazole Derivatives.** *Pharmaceuticals*, 2021, 14 (11) 1174.

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