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One-pot synthesis and negative ion mass spectrometric investigation of a densely functionalized cinnoline.

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ABSTRACT

Known, densely substituted 3-amino-5,7,8-trichloro-6-hydroxycinnoline-4-carbonitrile was synthesized using a one pot synthetic protocol under base-mediated conditions in a polar medium. Condensation of excess malononitrile with chloranil in ethanol at reflux gave quinone methide - 2-(2,4,5-trichloro-3-hydroxy-6-oxocyclohexa-2,4-dien-1-ylidene) malononitrile which was isolated as the triethylamine salt). This represents an atom efficient, simple and effective procedure for the preparation of a highly substituted cinnolines that may serve as relay materials for antimalarial prototypes.

An impressive range of bicyclic heterocyclic compounds have been studied as prototypes for antimalarial drugs of which only a handful have made the arduous and costly transition to clinically useful chemotherapeutic agents (Fig. 1).[1] Historically, they have been based on their natural product counterparts and among these, quinolines, such as quinine **1**, have continued to feature prominently in antimalarial drug research.[2] Additionally, there are acridine drugs, such as quinacrine **2**, originating from unnatural vat dyes which were themselves used to stain and quantify parasites within mammalian cells.[3] As part of our ongoing antimalarial program aimed at uncovering undiscovered or neglected chemo-types, we noted that cinnolines were under-represented within natural products (an exception is the symmetrical compound 4849F **3**.[4] It was of interest to study whether lead substances incorporating such heterocycles (**4** where X= N) could act as surrogates for the quinoline ring system, especially for drugs such as chloroquine (**4** where X= CH) and, more importantly, could evade induction and persistence of drug resistance.[5]

Cinnolines, in general, have been rarely studied in terms of their pharmacokinetic (ADMET) properties (especially pK_a values) whereas pharmacodynamic investigations, especially against our ~~malaria r~~eceptor of interest, heme, are unknown.[2,6] Our studies have focused on understanding how additional nitrogen groups decorating *bi-* and *tri*-cycles modulate the lipophilicity, pharmacokinetics and drug receptor binding, [7] especially in the 1,5-naphthyridine ring system, which is present in pyronaridine **5** (Fig. 1**)**, a Chinese drug currently being fast tracked for global dissemination by MMV/WHO.[8]

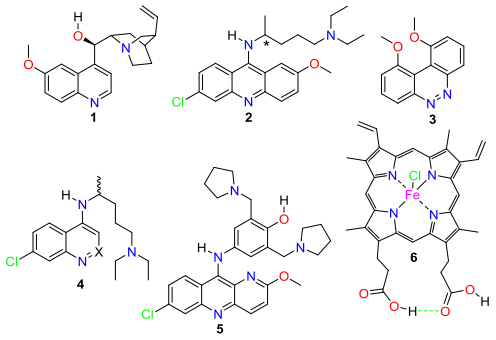

Figure 1. quinine **1**, mepacrine (quinacrine) **2**, 4849F **3**, X = N **4a**, chloroquine (X = CH) **4b**, pyronaridine **5**, hemin chloride **6**.

The criteria for selecting drugs according to a generalized pharmacophore have been published[2,6,9] and subsequently, we

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