Synthesis of Marinoquinoline A, Aplidiopsamine A, Chlorizidine A and Their Congeners for Structure-activity Relationship Studies

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By

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Synopsis of the Thesis to be Submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry

Name of the Candidate	Jyoti Pankaj Mahajan
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Abstract:

Natural products play a vital role in the development of new chemical entities for drug discovery. Nearly, 40% drugs are either natural products or derived from natural products. Hence, their potential contribution makes them an attractive target. The present thesis mainly deals with the synthesis of bioactive natural products and their rational analogues for structure-activity relationship studies in search of novel drug candidates. The first chapter describes the synthesis of Marinoquinoline A and first total synthesis of antimalarial marine natural product Aplidiopsamine A utilizing Pd-catalyzed imine cyclization as a key step. The generalization of this method was demonstrated by synthesizing various interesting heterocyclic scaffolds. The second chapter deals with the QSAR based rational design and synthesis of a library of Marinoquinoline A analogues taking different amines as reacting partners. The screening of these analogues for their antimalarial activity against *P. falciparum* 3D7 strain provided potent candidates for further investigation. The third chapter portrays the first total synthesis of methyl protected (±)-Chlorizidine A. The synthesis has been achieved in ten steps utilizing Pd-catalyzed decarboxylative coupling, samarium (II) iodide mediated reformatsky reaction, intramolecular Mitsunobu reaction, and late-stage oxidation as key transformations.

Chapter 1: Diversity-oriented Synthesis of Antimalarial Marine Natural Products Marinoquinoline A and Aplidiopsamine A.

This chapter describes the synthesis of antimalarial natural products Marinoquinoline A and Aplidiopsamine A.

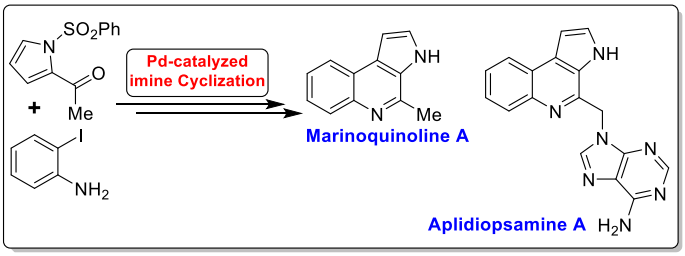


Figure 1: Synthesis of antimalarial natural products Marinoquinoline A and Aplidiopsamine A

Marinoquinoine A was isolated from the novel marine gliding bacterium *Rapidithrix thailandica* by Plubrukarn *et al.* in 2008 and again in 2011 from gliding bacterium *Ohtaekwangia Kribbensis* together with Marinoquinolines B-F by Muller *et al.*

Aplidiopsamine A was isolated from temperate Australian ascidian *Aplidiopsis confluata* by Carroll *et al.* in 2010. Taking advantage of their common 3H-pyrrolo[2,3-c]quinoline core skeleton, we developed a diversity-oriented synthetic approach for their synthesis using Pd-catalyzed imine cyclization protocol as a novel key-step (Figure 1).

The synthesis of marinoquinoline A was carried out in three steps with 71% overall yields and the first total synthesis of aplidiopsamine A was achieved in five steps with 27% overall yields. To show the broadness and utility of the developed Pd-catalyzed imine cyclization protocol synthesis of various marinoquinloline analogues as well as interesting scaffolds have been achieved (Figure 2).[1] Thus, we have demonstrated a novel and general approach for synthesis of rare 3H-pyrrolo[2,3-c]quinoline core, which can be applied in the synthesis of other Marinoquinoline natural products and quinoline alkaloids by taking respective ketone as starting material.

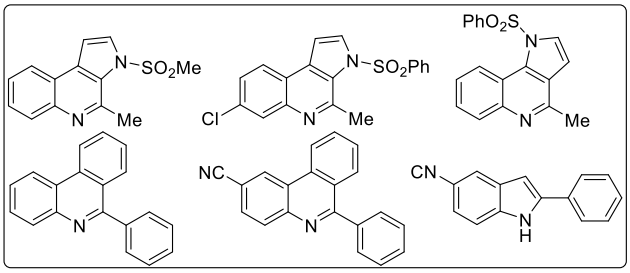


Figure 2: Generalization of imine cyclization protocol

Chapter 2: Amine Incorporated Novel Marinoquinolines: Design, Synthesis and Antimalarial Study

The chapter deals with the design and synthesis of derivatives of the antimalarial marine natural product Marinoquinoline A. The natural product marinoquinoline A showed promising antimalarial activity against the most lethal species *Plasmodium falciparum*. In view of the potency of the marinoquinoline A, its rational analogues have been designed based on QSAR analysis and synthesized using various aliphatic/aromatic amines as reacting partners, and screened for their antimalarial activity against *P. falciparum* 3D7 strain (Figure 3).

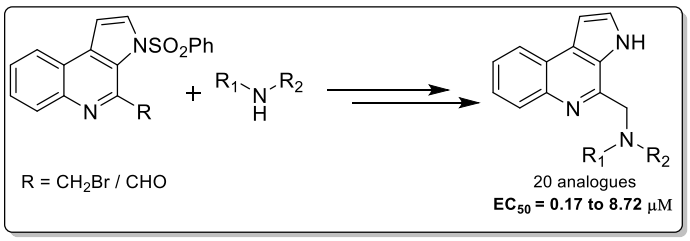


Figure 3: Synthesis of various analogues

Accordingly, we planned the synthesis of new analogues utilizing marinoquinoline A core as a fixed skeleton by changing the side chain with various aromatic and aliphatic amines as coupling partners. Taking aliphatic amines as coupling partners four analogues have been synthesized (Figure 4).

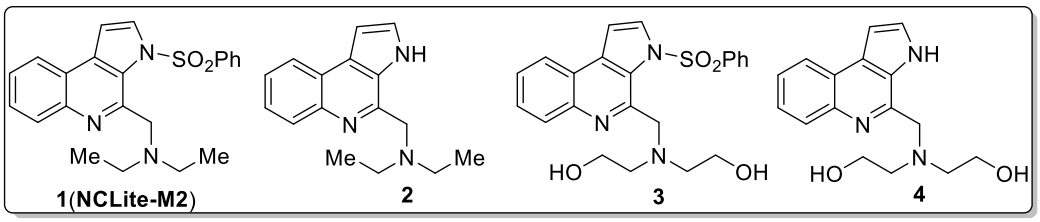


Figure 4. Synthesis of analogues using aliphatic amine as a coupling partner

Eight analogues were synthesized taking secondary aromatic amine as coupling partners. Aromatic amines *n*-methyl aniline, 4-methoxy-*n*-methyl aniline and cyclic aliphatic amine morpholine reacted smoothly. Interestingly, when aniline was used as a coupling partner, dimerized product formation was observed (Figure 5). Analogues using primary amine as coupling partners were found to be unstable.

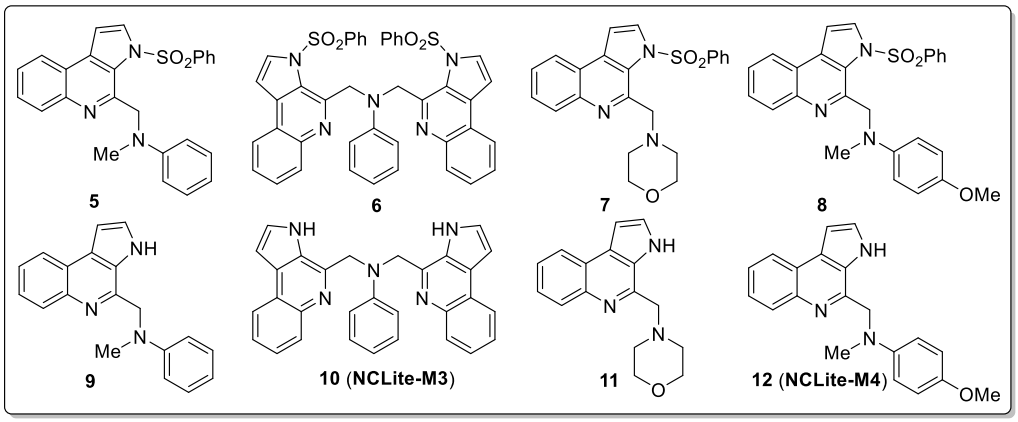


Figure 5. Synthesis of analogues using aromatic amine as a coupling partner

The analogue using chloroquine side chain amine as coupling partner was synthesized in four steps, and the natural product hybrid analogue **18** (NCLite-M5) was synthesized by reacting quinazolin-4(*3H*)-one in anticipation to get enhanced antimalarial activity. The remaining analogues were obtained using our previous protocol (Figure 6). Most of the compounds displayed good to excellent EC_{50} values and ≥ 80% growth inhibition. Our findings show that compound **1** (**NCLite-M2**), **10** (**NCLite-M3**), **12** (**NCLite-M4**) and **13** (**NCLite-M5**) are potential leads for malaria.[2] These analogues may provide an important starting point for the development of new antimalarial drug candidate. This study also confirms that natural products and their rational modification is a key tool in the development of a new drug.

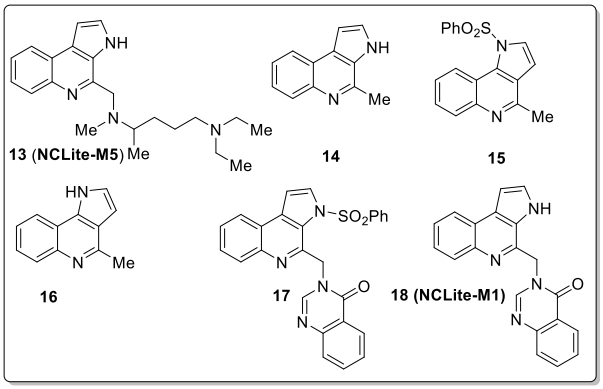
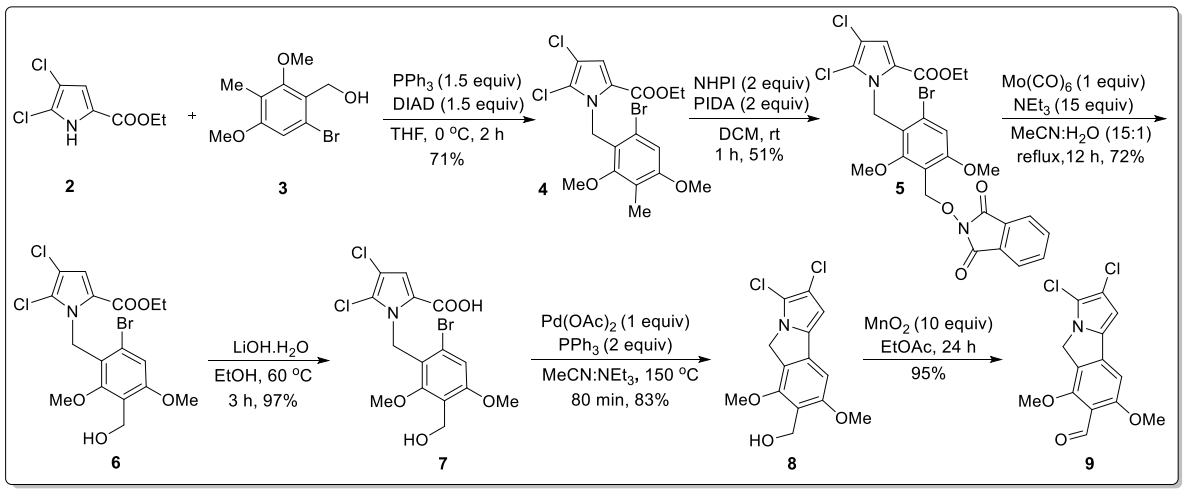


Figure 6. Synthesis of other analogues

Chapter 3: Studies Towards the Synthesis of Anticancer Natural Product Chlorizidine A

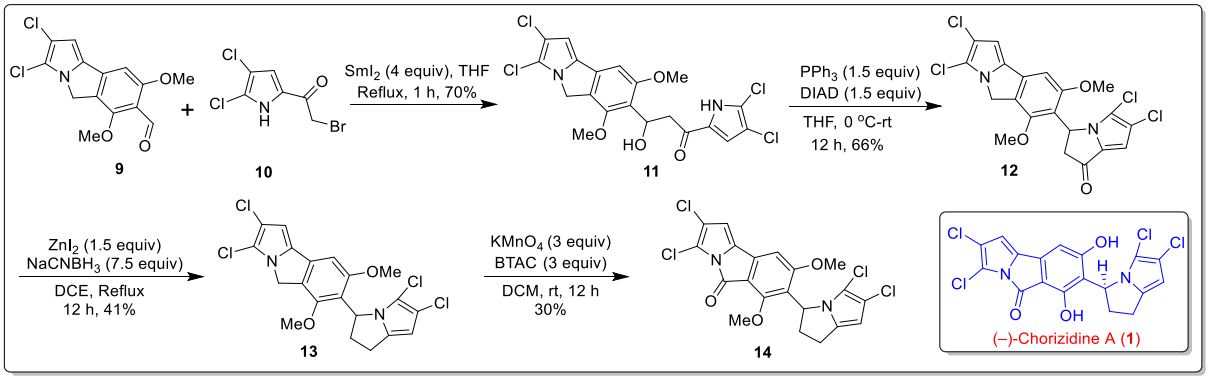
The natural product (–)-Chlorizidine A (**1**) was isolated from the cultivation of obligate marine *Streptomyces* sp. strain CNH-287 by Hughes and co-workers in 2013. This natural product is not stable, but displays remarkable cytotoxicity against HCT-116 adenocarcinoma cell lines with IC_{50} value 3.2-4.9 µM.



Scheme 1: Synthesis of aldehyde **9**

Its stable derivatives also exhibit good potency against various cancer cell lines. In spite of fascinating structure and good biological activity, there is no report for its chemical synthesis. We envisioned that 2,3-dihydropyrrolizine ring could be installed at a later stage and 5H-pyrrolo [2, 1-a] isoindol-5-one ring system could be obtained using *N*-alkylation and decarboxylative coupling reactions.

Aldehyde **9** was synthesized over six linear steps using ester **2** and alcohol **3** as starting materials. The Mitsunobu reaction worked well to deliver compound **4** followed by synthesis of phthalimide adduct **5** in moderate yield. Reductive cleavage of phthalimide adduct provided the ester **6** which on hydrolysis provided the acid **7**. Decarboxylative coupling of the acid **7** followed by benzylic oxidation of **8** delivered required aldehyde **9** in good yields (Scheme 1).



Scheme 2: Completion of synthesis

Aldehyde **9** and bromoketone **10** were treated under SmI_2 mediated Reformatsky reaction condition to provide the β-hydroxy ketone **11**. Further intramolecular Mitsunobu reaction of **11** and ketone reduction provided **13**. Final benzylic oxidation of **13** using $KMnO_4$-BTAC delivered methyl protected (±)-Chlorizidine A **14** in moderate yield (Scheme 2). Thus, the first total synthesis of methyl protected (±)-Chlorizidine A was achieved in ten steps.[3] Other potential analogues could be accessed using the designed synthetic route for further SAR study.

In summary, present desertion describes the synthesis of important natural products and their potential analogues for biological studies.

References:

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