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Research paper

Exploring the 3-piperidin-4-yl-1*H*-indole scaffold as a novel antimalarial chemotype

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ABSTRACT

A series of 3-piperidin-4-yl-1*H*-indoles with building block diversity was synthesized based on a hit derived from an HTS whole-cell screen against *Plasmodium falciparum*. Thirty-eight compounds were obtained following a three-step synthetic approach and evaluated for anti-parasitic activity. The SAR shows that 3-piperidin-4-yl-1*H*-indole is intolerant to most *N*-piperidinyl modifications. Nevertheless, we were able to identify a new compound (**10d**) with lead-like properties (MW = 305; cLogP = 2.42), showing antimalarial activity against drug-resistant and sensitive strains (EC_{50} values ~ 3 μM), selectivity for malaria parasite and no cross-resistance with chloroquine, thus representing a potential new chemotype for further optimization towards novel and affordable antimalarial drugs.

1. Introduction

Malaria is one of the most life-threatening diseases, with almost one-third of the world's population at risk it represents a major public health problem due to its morbidity and mortality [1,2]. An estimated 198 million cases led to nearly 584,000 deaths in 2013, 90% of which were reported in sub-Saharan Africa [1]. Malaria has a broad impact throughout tropical and subtropical areas of the globe, affecting indigenous populations as well as an increasing number of travelers [3–5]. According to the 2014 World Health Organization (WHO) Malaria Report, about 78% of deaths attributed to malaria occur in African children under age of 5 [1]. In addition to the human cost of malaria, the economic burden of the disease is significant with a huge impact upon individual households due to lost wages and healthcare costs as well as detrimental affect on the national scale with about 40% of African health budgets spent on malaria every year [6].

Five *Plasmodium* species are known to infect humans and cause malaria: *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, *Plasmodium knowlesi* and *Plasmodium falciparum* [7]. Of these species, *P. falciparum* is the most widespread in nearly all malaria endemic countries and is responsible for the majority of malaria mortality [8]. The parasite has a complex life cycle, which involves alternate developmental stages within the human host and the female *Anopheles* mosquito [2,9]. Within the human host, the asexual erythrocytic stage of the infection accounts for the clinical symptoms and constitutes the target for most chemotherapeutics used in the clinic, such as chloroquine (**1**) (Fig. 1) and artemisin combination therapies (ACTs) [9–11].

The emergence of drug resistance has already rendered once-effective malaria treatments less reliable. Today, ACTs are the front line therapies for treatment of symptomatic malaria, however, we are at risk of losing their utility due to the emergence and spread of resistance [12–14]. The *Plasmodium* parasite has demonstrated an ability to evolve and adapt to every drug introduced thus far, and with this in mind, it is crucial that efforts are made to develop new analogues active against resistant strains, to identify new drugs, or even identify new therapeutic targets in the parasite [11,15].

The strategies currently used for the development of novel antimalarial drugs include many approaches such as: the discovery

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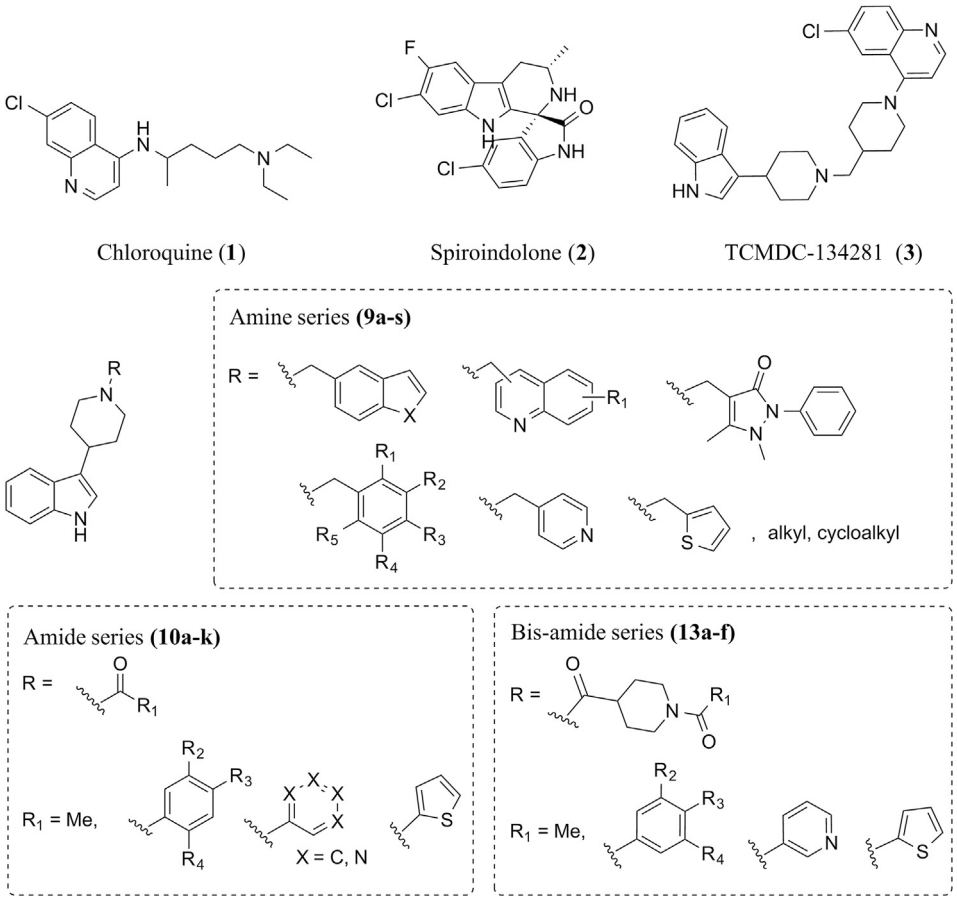

Fig. 1. Structures of (**1**), (**2**), TCMDC-134281 (**3**) and the indole-based explored scaffold.

of new active molecules from natural sources [16–23], repurposing of commercially available drugs, the development of hybrid compounds [24], and rational drug design with chemical modifications of existing antimalarials and hits [25–27], amongst others. Also, a great number of drug discovery and development programs from both public and private institutions, and public-private partnerships, using phenotypic screening with sensitive and resistant strains of *P. falciparum* have been pursued in the past recent years. Among them were large libraries from Novartis, St. Jude Children's Research Hospital and GlaxoSmithKline (GSK) [28,29].

Joining these international efforts, we analyzed the recently disclosed Tres Cantos Antimalarial Set (TCAMS) from GSK to identify novel indole-based antimalarials as starting points for the development of next generation antimalarial drugs. Indoles are an emerging antimalarial fragment present in several lead drug candidates with new mechanisms of action, such as the spiroindolone (**2**) [30–34] and aminoindoles classes [33,35]. We were intrigued by TCMDC-134281 (**3**) (Fig. 1), which emerged as a very potent antiplasmodial compound, with a reported EC_{50} of 34 nM against the chloroquine-sensitive *P. falciparum* 3D7 strain. Additionally, compound **3** did not demonstrate measurable cytotoxicity as its EC_{50} against the human HepG2 hepatoma cell line was greater than 10 μM [28].

However, this compound showed poor drug-like properties and cross-resistance with chloroquine, possibly due to the presence of the 4-aminoquinolinyl fragment, which is the essential pharmacophore of chloroquine (CQ). To address these liabilities, we decided to remove one of the piperidin-4-yl fragments and to replace the 4-aminoquinoline fragment. This resulted in an overall reduction of the compound's LogP and MW and chemically differentiates the molecule from the 4-aminoquinoline antimalarials, which we hypothesized would overcome the observed cross-resistance with CQ. We herein report a structure-activity study aiming to explore the antimalarial potential of the 3-piperidin-4-yl-1*H*-indole scaffold (Fig. 1). We synthesized three series of derivatives following a reagent-based diversity approach, in a total of 38 compounds, and assayed them against the multidrug resistant *P. falciparum* Dd2 strain at a fixed 5 μM concentration. The most potent derivatives were further profiled in dose–response against both *P. falciparum* drug-resistant (Dd2) and sensitive (3D7) strains to determine activity and parasite selectivity.

2. Results and discussion

2.1. Chemistry

We first resynthesized the original hit compound **3**, following a six-step synthesis, as shown in Scheme 1. Starting with the condensation of the indole with N-benzyl-4-piperidone in the presence of a base, compound **4** was obtained in high yield (98%). Subsequent debenzylation with concurrent olefin reduction afforded the common intermediate 3-piperidin-4-yl-1*H*-indole (**5**) with 96% yield. Compound **5** was coupled with 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid to give the amide intermediate **6** in moderate yield (60%). Reduction of the carbonyl group afforded compound 7, followed by Boc-deprotection to yield the amine compound **8**. Compound **3** was obtained by nucleophilic aromatic substitution of 4,6-dichloroquinoline with the amine intermediate **8** (Scheme 1).