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Research paper

Synthesis and antiplasmodial activity of novel indoleamide derivatives bearing sulfonamide and triazole pharmacophores

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ABSTRACT

Due to the recent reports of growing parasite resistance to artemisinins and other antimalarial drugs, development of new antimalarial chemotypes is an urgent priority. Here in, we report a novel series of adamantyl/cycloheptyl indoleamide derivatives bearing sulfonamide and triazole pharmacophores adopting different chemical modifications and evaluated them for antiplasmodial activity *in vitro*. Among all the indoleamides, compounds **22**, **24**, **26** and **30** with sulfonamide pharmacophore showed promising activity with IC_{50} of 1.87, 1.93, 2.00, 2.17 μM against CQ sensitive *Pf*3D7 strain and 1.69, 2.12, 1.60, 2.19 μM against CQ resistant *Pf*K1 strain, respectively.

1. Introduction

Malaria, caused mainly by *P. falciparum* is one of the major causes of morbidity and mortality globally, especially in young children and pregnant women. WHO has reported 214 million malaria incidences and 438,000 deaths worldwide in 2015, among that 306,000 deaths occurred only in children under age 5 years [1]. Despite the progress in reduction of malaria cases, parasite resurgence and developing resistance to classical antimalarial drugs such as chloroquine, artemisinin and its derivatives and absence of any viable vaccine are alarming the researchers to develop new antimalarial chemotypes with novel mechanisms to curb malaria effectively [1,2]. However, despite significant advances in our insight about the plasmodium genome, the identification and validation of new drug targets have been challenging [3,4].

It has been proved beyond doubt that genes related to ubiquitin-proteasomal degradation are up regulated during parasite transformation from late trophozoite to schizont stage and are very important for survival and growth of the parasite [5,6]. In support of this hypothesis, several reports indicated that proteasome of *Plasmodium* is likely to serve as an excellent drug target as the parasite is susceptible to chemicals that inhibit proteasome function [7,8]. Many inhibitors of ubiquitin-proteasome system are known to possess potent antiplasmodial activity [9,10]. Melatonin (**B**, Fig. 1), an indole based carboxamide and many of its derivative regulate the life cycle of blood stage of *P. falciparum* as they block the human malaria parasite *P. falciparum* cell cycle from trophozoite to schizont stage acting on the signalling molecules [11–14].

To the best of our knowledge, only few reports exist on antimalarial activity of indole based molecules [2,11,15–17,33]. NITD609 (**A**, Fig. 1), a spiroindolone class antimalarial compound is currently under phase-I clinical trial and exhibited potent *in vitro* blood stage antimalarial activity with IC_{50} of <10 nM against all *P. vivax* and *P. falciparum* isolates [2]. Besides this, many other indole based molecules exhibit antimalarial activity in the range of 39 to 0.65 μM [15,16]. Violacein (**C**, Fig. 1), an indole based violet pigment isolated from *Chromobacterium violaceum* showed potent antimalarial activity with IC_{50} of 0.65 μM [16]. Recently, Garcia C.R.S group has reported novel indole based molecules with antiplasmodial activity with the IC_{50} range of 19 to 2.9 μM [11]. Where, they have described that presence of carboxamide group at 3rd position of indole was crucial for activity and also the insignificant effect of methoxy group present on benzene ring of melatonin. Very

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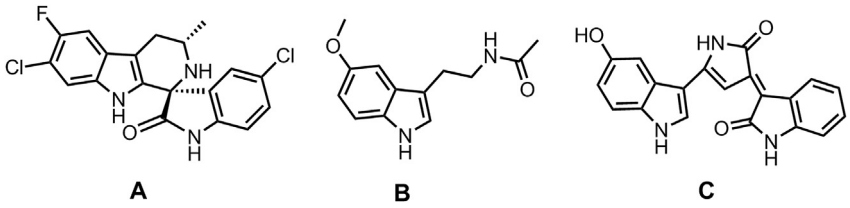
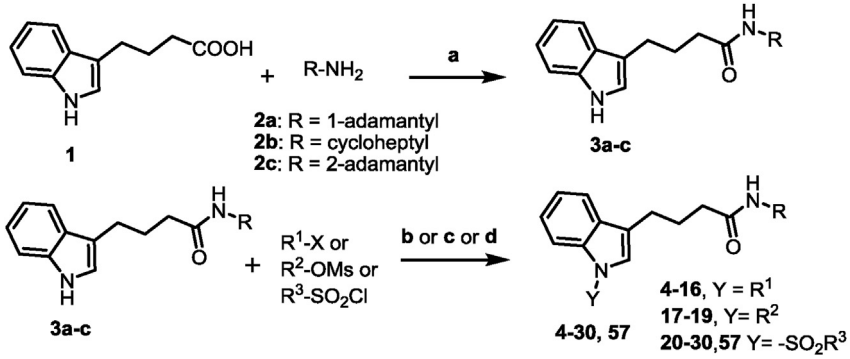


Fig. 1. Reported indole based molecules with potent antimalarial activity.



Scheme 1. Synthesis of adamantyl/cycloheptyl indoleamide derivatives.
Reagent and Conditions: a) EDCI, HOBt, TEA, DCM, rt, 8–10 h, 90–92% **b**) for R^1-X: aq. KOH, TBAB, DCM, rt, 12–15 h, **c**) for R^2-OMs: NaH, DMF, 0 °C-rt, 80–89% **d**) for R^3-SO_2Cl: KOH, DCM, TBAHS, rt, 2–3 h, 75–86%.

recently, we have reported antimalarial activity in a series of β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles and postulated that these potent compounds boost p53 protein levels to exhibit this activity [18]. Moreover, several 1,2,3-triazole as well as sulfonamide based molecules have been reported with potent antimalarial, anticancer, antidiabetic, antitubercular, antifungal and antiinflammatory activities [19–25]. Keeping in mind the above facts, we were prompted to synthesise few indole carboxamide derivatives bearing additional pharmacophores at 1- and 3-positions of indole in an anticipation that they will act on dual targets and exhibit antimalarial activity.

2. Results and discussion

2.1. Chemistry

The synthetic protocols for the targeted compounds are depicted in Scheme 1,2 and 3. Acid-amine coupling reaction of indole-3-butyric acid **1** and adamantyl-1-amine **2a** or cycloheptylamine **2b** with the 1-ethyl-3-(3-dimethylamino propyl)carbodiimide (EDCI) as a coupling reagent in the presence of anhydrous dichloromethane gave the corresponding amides **3a** and **3b** in 90–92% yield [26]. Alkylation of these amides **3a** and **3b** separately with various alkyl halides using aq. KOH and mesylation using NaH as a base gave the target alkylated compounds **4-19** in 80–89**%** yield [26–28]. On the other hand, sulfonylation with various aromatic sulfonylchlorides using KOH as a base resulted the sulfonated indoleamides **20-30** in 75–86% yield as shown in Scheme 1 [29].

Propargylation of amides **3a** and **3b** was carried out separately with propargyl bromide using NaH as a base in the presence of dimethylformamide to give the alkyne derivatives **31a** and **31b** respectively in good yields as shown in Scheme 2. These intermediates **31a** and **31b** on Cu catalysed alkyne-azide cycloaddition reaction (CuAAC) separately with the various azides **32a-g** and **33** afforded regioselectively the respective 1,4-disubstituted 1,2,3-triazole derivatives **34-45** and **46, 47** in 80–94% yield [30]. Regioselectivity in these 1,4-disubstituted 1,2,3-triazoles was confirmed by their NMR spectroscopy. To synthesise compounds with more lipophilic nature, we have designed the prototype as shown in Scheme 3. Acid-amine coupling of indole-3-acetic acid **48** with propargylamine resulted the intermediate **49** in 84% yield. CuAAC reaction of the latter separately with different azides gave the respective 1,4-disubstituted 1,2,3-triazoles **50-56** in 75–86% yield. Compounds **57**, **60** and **61** were synthesised in good yields according to the above mentioned procedures as shown in Schemes 1 and 4 to study structure-activity relationships of most active compounds **22** and **26**. All of these synthesised compounds were purified by silica gel column chromatography, characterised by their ^{1}H, ^{13}C and HRMS data and further evaluated for their *in vitro* antiplasmodial activity against CQ sensitive (3D7) and resistant (K1) strains of *P. falciparum*.

2.2. Antiplasmodial activity

All of the above synthesised targeted compounds (**3a-c**, **4-30**, **34-47**, **50-57, 59a-b, 60, 61**) were evaluated for *in vitro* antiplasmodial activity against CQ sensitive (3D7) and CQ resistant (K1) strains of *P. falciparum* by using chloroquine as a reference drug (Table 1). First we performed biological screening of the initially synthesised indole NH-free compounds **3a** and **3b** containing 1-adamantyl and cycloheptyl as R group respectively, and both the compounds were found to be inactive against both of the strains(IC_{50} = >10 μM). Next, we have modified these two compounds **3a** and **3b** to have additional pharmacophores such as sulfonamide and triazole attached to N1 position of indole and also with the simple alkylating agents. Alkylated compounds **4-16** displayed antiplasmodial activity only at high concentrations with the IC_{50} range of 2.20–9.73 μM except compound **9**. Compound **9** with n-heptyl chain was found to be active with IC_{50} of 1.91 μM against sensitive strain. Compounds **17-19** were synthesised with the aim of incorporation of biologically significant pyrrolidine, piperidine and morpholine moieties [31,32] respectively at N1 position of