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Short communication

1*H*-1,2,3-triazole tethered isatin-ferrocene conjugates: Synthesis and *in vitro* antimalarial evaluation

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ABSTRACT

1*H*-1,2,3-triazole tethered isatin-ferrocene conjugates were synthesized and evaluated for their antiplasmodial activities against chloroquine-susceptible (3D7) and chloroquine-resistant (W2) strains of *Plasmodium falciparum*. The conjugates **5f** and **5h** with an optimum combination of electron-withdrawing halogen substituent at C-5 position of isatin ring and a propyl chain, introduced as linker, proved to be most potent and non-cytotoxic among the series with IC_{50} values of 3.76 and 4.58 μM against 3D7 and W2 strains, respectively.

1. Introduction

Malaria is one of the most dangerous infectious diseases transmitted through the bite of infected female Anopheles mosquito [1]. Five species of Plasmodium *viz. Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium malariae*, *Plasmodium vivax*, and *Plasmodium knowlesi* are responsible for the spread of malaria, out of which *P. falciparum* is considered as the most virulent form [1]. According to World Health Organization (WHO) factsheet 2013, out of 3.4 billion people at malarial risk, 1.2 billion are at high risk with more than one case per 1000 people, especially in tropical areas with transmission over 97 countries [2]. In 2012, more than 207 million cases were reported globally with an estimated 6,27,000 deaths; 90% of them occurred in sub-Saharan Africa in which 77% were children under the age of five [3]. Since 2006, artemisinin-based combination therapies (ACTs) have been recommended for the treatment of malaria, however, the development of resistance in the recent times to ACT in many parts of Southeast Asian regions is of great concern [4,5].

Isatin (1*H*-indole-2,3-dione) is a versatile heterocyclic scaffold with vast possibility of chemical modifications at C-3, C-5 and at *N*-1 position [6]. The endogenous molecule displays a wide range of biological and pharmacological activities such as anti-tumor [7–9], anti-HIV [10], antiviral [11], anti-angiogenic [12], antifungal [13,14], anti-Parkinson's disease therapeutic [15], anticonvulsants [16], and effective SARS coronavirus 3CL protease inhibitor [17] along with excellent tolerance in humans. Recently, Chibale and co-workers have disclosed the synthesis and antimalarial activity of a series of thiolactone–isatin conjugates and their tetracyclic by-products [18]. One of the most potent conjugate displayed an IC_{50} value of 6.92 μM against chloroquine resistant (CQ-R) W2 strain of *P. falciparum*. Further, Raval et al. described the synthesis of tetrahydropyrimidine–isatin hybrids and their *in vitro* activity against 3D7 strain of *P. falciparum* [19]. The most potent hybrid exhibited minimum inhibitory concentration (MIC) of 0.035 μg/mL which was better than the standard CQ (MIC = 0.125 μg/mL).

Last few years have witnessed a close association between the classical organometallic chemistry to medicine, biology, and

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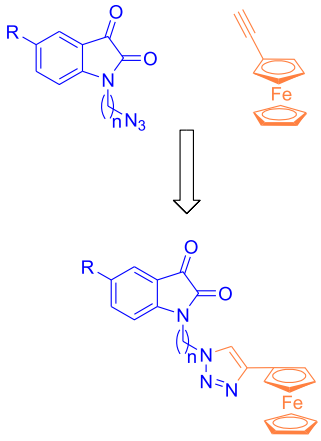


Fig. 1. Design of target hybrids.

molecular biotechnology [20]. The preparation of stable metal complexes with predictable structures, ability to tune ligand affinities along with efficient biological targeting are the major advantages associated with the synthesis of organometallics [21]. Among all the metals used, ferrocene (Fc) has played a distinctive role in the contemporary medicine because of its unique features including non-toxicity and stability under physiological conditions [22]. The replacement of the organic functionality with Fc has now been recognized as a useful strategy for the development of new and effective drugs *viz*. anti-androgen nilutamide and ferrocenyl analogs of commercial anti-estrogen tamoxifen displayed higher cytotoxicity against breast and prostate cancer cells respectively in comparison to the reference drugs [23]. Indeed, the most symbolic example of contribution of ferrocene with enhanced biological activity into a drug molecule is that of Ferroquine (FQ); derived from chloroquine (CQ) with ferrocene appended side chain which is 22 times more active than CQ against CQ-R strain of *P. falciparum* [24].

1*H*-1,2,3-triazoles are privileged class of five membered nitrogen containing heterocyclic systems which attracted the attention of both synthetic and medicinal chemists due to their synthetic applications and biological potential [25]. The systems are highly stable under the basic, acidic, reductive and oxidative conditions because of high aromatization. Moreover, high dipole moment, rigidity, stability and capability to form hydrogen bonding under *in vivo* conditions are their favorable characteristics in the binding with biological targets.

Previous reports from our group has described the synthesis and *in vitro* antimalarial potential of 1*H*-1,2,3-triazole tethered mono- and bis-ferrocenylchalcone-*β*-lactam conjugates [26] as well as 7-chloroquinoline-isatin conjugates [27] against chloroquine-susceptible (CQ-S) 3D7 and chloroquine-resistant (CQ-R) W2 strains of *P. falciparum*. In continuation with our interest, the present report describes the synthesis and *in vitro* antimalarial evaluation of 1*H*-1,2,3-triazole tethered isatin-ferrocene conjugates as depicted in Fig. 1.

2. Result and discussion

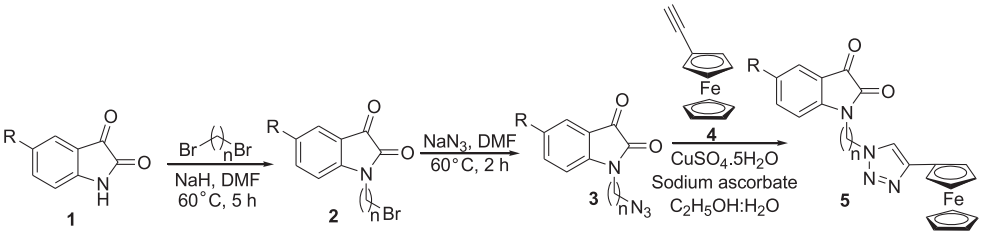
2.1. Synthetic chemistry

C-5 substituted *N*-alkylazido-isatins **3** were prepared following our previously reported protocol [28] involving an initial base-promoted alkylation of isatins **1** with dibromoalkanes at 60 °C in DMF to yield the corresponding C-5 substituted *N*-alkylbromo-isatins **2**. The subsequent treatment of **2** with sodium azide at 60 °C resulted in the formation of the desired precursors **3** as depicted in Scheme 1. The precursors' **3** and ethnylferrocene **4** were subsequently utilized in the copper promoted azide-alkyne cycloaddition reaction to yield the desired 1*H*-1,2,3-triazole tethered isatin-ferrocene conjugates **5** [29].

The structure assigned to the hybrids **5** was confirmed on the basis of spectral data and analytical evidences. Compound **5f**, for example, showed a molecular ion peak at *m/z* 458.0833 $[M]^+$ while its ^{1}H NMR spectrum exhibited a singlet at δ 4.08 corresponding to 5H (cyclopentadiene ring of ferrocene) along with singlets at δ 4.31 (2H) and δ 4.72 (2H) due to the ferrocene ring protons. The presence of a characteristic singlet at δ 7.63 corresponding to the triazole ring proton ascertained the assigned structure which was further corroborated with the number of carbon atoms in the ^{13}C NMR spectrum.

2.2. Antimalarial evaluation

The synthesized conjugates were evaluated for their antimalarial potential against chloroquine-susceptible 3D7 and chloroquine-resistant W2 strains of *P. falciparum* and the corresponding inhibitory concentration 50% (IC_{50s}) and 95% confident interval (95%CI) values are enlisted in Table 1. The synthetic precursor *viz. N*-alkylbromo-isatins were previously evaluated for their antimalarial potential against chloroquine-resistant W2 strains of *P. falciparum* and have displayed IC_{50} values >20 μM [18]. As evident from Table 1, the synthesized conjugates were not as active as standard drug chloroquine (CQ) but displayed considerable activity against both the strains. The conjugates **5a**–**d** with an ethyl chain introduced as linker failed to inhibit the growth of 3D7 even at the highest concentration tested; exception being **5a** (R = H) displaying



Entry	n	R	Entry	n	R
5a	2	H	**5e**	3	H
5b	2	F	**5f**	3	F
5c	2	CH_3	**5g**	3	CH_3
5d	2	Cl	**5h**	3	Cl

Scheme 1. Synthesis of isatin-ferrocene based conjugates.