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Research paper

Synthesis and antiplasmodial activity of glyco-conjugate hybrids of phenylhydrazono-indolinones and glycosylated 1,2,3-triazolyl-methyl-indoline-2,3-diones

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ABSTRACT

A small library of 36 new glycohybrids of phenylhydrazono-indolinones was synthesized employing glycosylated 1,2,3-triazolyl-methyl-indoline-2,3-diones and different phenylhydrazines via acid catalyzed reaction. All the compounds were screened for their antiplasmodial activity *in vitro*. Compounds **6c**, **7c**, and **7b** showed significant activity with the IC_{50} values 1.27, 1.64 and 1.96 μM, respectively against CQ sensitive *Pf*3D7 strain while compounds **7b** and **6f** showed good activity with IC_{50} 1.61 and 1.93 μM, respectively against CQ resistant *Pf*K1 strain.

1. Introduction

Malaria, a parasitic disease mainly caused by *Plasmodium falciparum* claims millions of lives annually despite the availability of various drugs belonging to aminoquinolines, arylaminoalcohols, artemisinins, antifolates, antibiotics and inhibitors of the respiratory chain [1–3]. The arsenal of both prophylactic and curative antimalarial drugs are scarce in number and development of resistance to chloroquine and many other frontline antimalarial drugs including the artemisinins limits their utility [4–6]. The problems associated with the existing drugs and the absence of any viable vaccine, have triggered a massive effort to identify new antimalarial leads acting through a novel mechanism.

Several molecules possessing isatin pharmacophore are known to have a wide range of biological activities including antimalarial activity [7]. Further, the possibility of chemical modifications at C-3, C-5 and at N-1 position in the skeleton [8,9] has led to generation of library of compounds for optimization of hits to potent leads in drug design & development. Certain Schiff bases of isatin have shown different pharmaceutical properties [10] and various spirooxindoles have exhibited significant biological activities such as antimalarial [11], antiviral [12], antifungal [13,14], anti-tumour [15–17], anti-HIV [18], anticonvulsant [19], and anti-Parkinson's [20] activity. Kumar et al. have established antimalarial activity in triazole tethered isatin-ferrocene conjugates against 3D7 and W2 strains of *Plasmodium falciparum* [21]. Similarly, isatin-thiolactone conjugates have been explored as potent antimalarial agents both against chloroquine resistant (CQ-R) W2 strain of *P. falciparum* [22]. Raval et al. have also synthesized tetrahydropyrimidine-isatin hybrids as potent antiplasmodial agents against both 3D7 strain of

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P. falciparum [23]. Carbodithioate 2,3-dioxoindoline and many other derivatives of isatin have also been shown to possess good antimalarial activity against *Plasmodium falciparum* [24]. The isatin hydrazones on the other hand are endowed with diverse range of biological activities such as antimalarial [25], antimicrobial [26], anticonvulsant [27], anti-inflammatory [28], antiplatelet [29], and antitumoral [30]. Some of the reported molecules having isatin core or hydrazones with significant antiplasmodial activities are depicted in Fig. 1 [31,32].

Recently, we have explored the antitubercular and antimalarial activities in triazole derivatives [33,34]. The antimalarial activity of triazole derivatives has been shown to be due to interference with p53 protein and killing the malaria parasite [34a]. The triazole with high dipole moment, rigidity, stability and hydrogen bonding capability under in vivo conditions, has imparted significance of this pharmacophore in drug development [35].

Hybridization of active pharmacophore with sugar offers good pharmacokinetic properties and improves their solubility [36], in cases of poor solubility in DMSO. Keeping in view the above points and in continuation of our effort to develop new antimalarials [34,37], we thought to prepare molecules with two different pharmacophores exhibiting antimalarial activities and conjugate them with sugars to improve the solubility of the molecules (Fig. 1). To the best of our knowledge glycohybrids of this nature containing isatin hydrazones have not been reported previously.

2. Results and discussion

2.1. Chemistry

To start with, we have prepared glycosylated 1,2,3-triazolyl-methyl-indoline-2,3-diones (**3**) by N-alkylation of isatin (**1**) with propargyl bromide in presence of K_2CO_3 in DMF at an ambient temperature [38]. The resulting *N*-propargylated isatin (**2**) was then subjected to Cu (I) catalyzed azide-alkyne cycloaddition with different sugar azides (**I** - **IV**) prepared by the methods earlier reported [36b,39], in THF-H_2O (1:1) using equimolar quantities of the reactants, $CuSO_4.5H_2O$ (10 mol%) and sodium ascorbate (20 mol%) at room temperature. The reaction conditions were optimum and were monitored (by TLC) until the reaction was complete (Scheme 1). The respective cycloaddition products (**3a-3d**) were obtained in higher yields (90–95%). The structure elucidation of the cycloadducts was made on the basis of their spectroscopic data.

The glycohybrids of phenylhydrazono indolinones were prepared by reaction of substituted phenyl hydrazine hydrochlorides (**4a-4f**) with the glycosylated 1,2,3-triazolyl-methyl-indoline-2,3-diones (3a-3d), in ethanol in presence of acetic acid as catalyst at reflux temperature [40], to give the desired products (**5**–**8**) in good to excellent yield (85–95%) (Scheme 2, Table 1). The structure of all the synthesized compounds was established on the basis of their spectroscopic data (^{1}H, ^{13}C and mass).

The complete assignment of ^{1}H and ^{13}C NMR signals were done by utilizing various 1D (^{1}H, ^{13}C and DEPT) and 2D (COSY, TOCSY, NOESY, HSQC, HMBC) NMR experiments of one of the prototypes **5b**. HMBC correlation of H-2‴ with C-3 and C-3‴ showed their connectivity. As reported in the literature, isatin hydrazones exist predominately as the *Z* conformation in solution, presumably due to the intramolecular hydrogen bonding between the NH of the hydrazone linkage and the carbonyl group of the indolinone [41]. Confirmation of this stereochemistry was achieved by observing nOe effect (Suppl., S88), for this compound we did not observe any nOe correlations between H-4 of the isatin core and the hydrazone

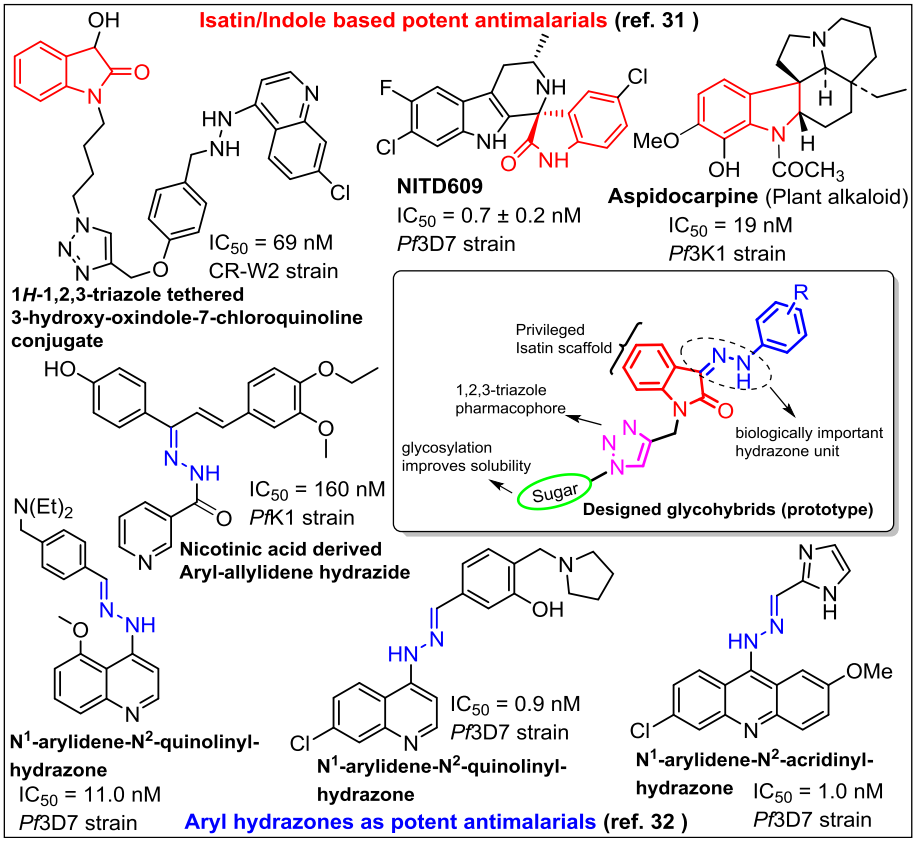

Fig. 1. Design of glycohybrids of phenylhydrazono indolinones based on reported potent antimalarials having an isatin/indole core or hydrazones.