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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.

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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

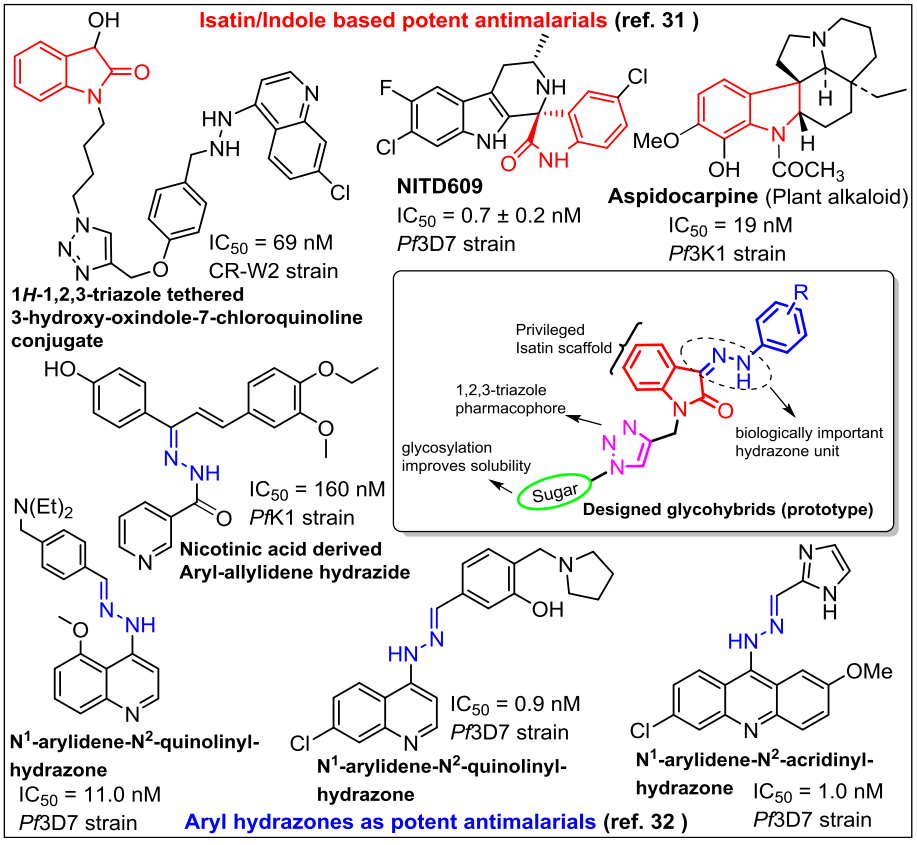
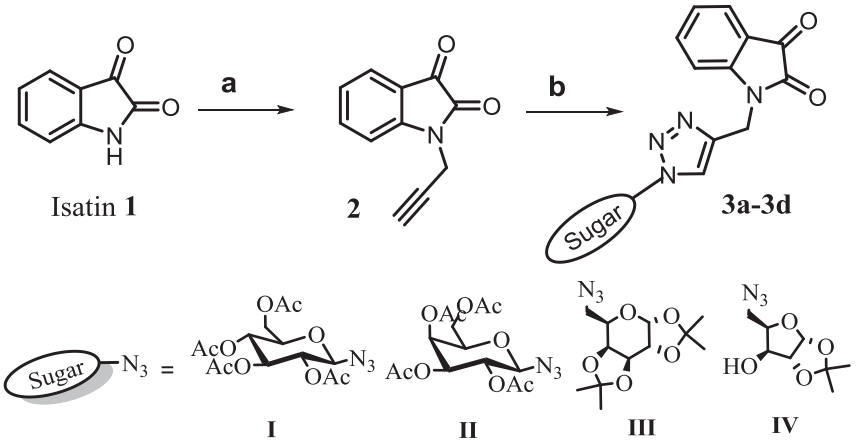
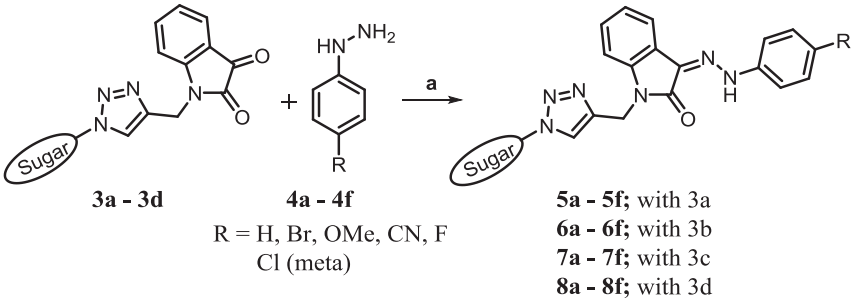


Fig. 1. Design of glycohybrids of phenylhydrazono indolinones based on reported potent antimalarials having an isatin/indole core or hydrazones.



Scheme 1. Synthesis of glycosylated 1,2,3-triazolyl-methyl-indoline-2,3-diones. **Reagent and Conditions**: **a**) Propargyl bromide, K_2CO_3, DMF, rt, 6 h, 72% **b**) respective Sugar Azide (**I-IV**), $CuSO_4.5H_2O$, Na-Ascorbate, THF:H_2O (1:1 v/v), rt, 4 h, 90–95%.



Scheme 2. Synthesis of glycohybrids of phenylhydrazono indolinones from glycosylated-1,2,3-triazolyl-methyl-indoline-2,3-diones. **Reagent and Conditions: a**) Glacial acetic acid (0.5 mL), Ethanol, 80 °C, 1 h, 85–95%.

NH, which suggests that it exists as *Z* conformation in solution. Moreover, the chemichal shift value of hydrazone NH (NH-2‴) at δ 12.71 ppm is in good agreement with previous reported value for hydrazone NH in case of *Z* conformation, which further supported that it exists as *Z* conformation.

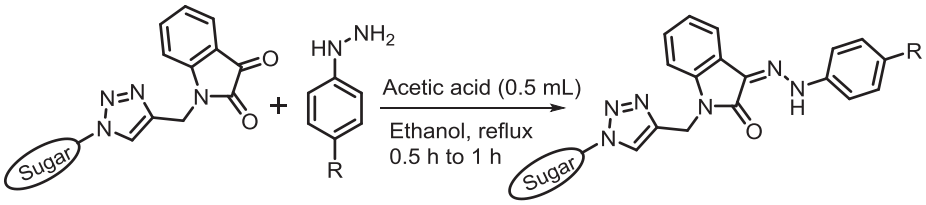
Further, we have synthesized deacetylated glycohybrids of phenylhydrazono indolinones from respective acetylated analogues. The deacetylation was performed by treating the corresponding acetylated compound (**5** or **6**) in MeOH with methanolic NaOMe at room temperature, to give the desired deacetylated analogues (**9** or **10**) in good yields (75–85%) (Scheme 3, Table 2). All the synthesized deacetylated analogues were characterized by their spectroscopic data ^1H, ^{13}C and mass.

2.2. Biology

The glycohybrids of phenylhydrazono indolinones (**5, 6, 7, 8, 9** and **10**) were screened *in vitro* against Chloroquine-susceptible (3D7) and Chloroquine-resistant (K1) strains of *P. falciparum* for their antiplasmodial activity. The cytotoxic concentrations 50% (CC_{50} in μM) and selectivity indices (SI) against both *Pf* strains are enlisted in Table 3.

As evident from the activity results, on *in vitro* screening of the intermediates glycosylated 1,2,3-triazolyl-methyl-indoline-2,3-diones **3a**-**3d** against *P. falciparum* 3D7 strain, compounds **3a** and **3d** showed moderate to less activity with IC_{50} values of 3.54 μM and 4.33 μM, respectively. Compounds **3b** and **3c** were found inactive at higher concentration with IC_{50} values in 7.51–8.41 μM range against both 3D7 and K1 strains. Compounds **6c** and **7c** having 4-methoxy group in the phenyl ring of hydrazone moiety, exhibited good activity against the sensitive strain 3D7 with IC_{50} 1.27 and 1.64 μM respectively, while **7b** with 4-bromo and **6f** with 3-chloro substitution on the phenyl ring of hydrazone showed good activity against the resistant strain K1 with IC_{50} 1.61 and 1.93 μM, respectively. The above compound **7b** and another compound **6b** with 4-bromo substitution, showed good to moderate activity against the sensitive strain 3D7 with IC_{50} 1.96 and 2.09 μM, respectively. It is also evident from the results that antiplasmodial activity enhanced in different phenylhydrazono indolinones as compared to intermediates **3a**-**3d**. The effect of substituents in the sugar moiety and nature of sugar in the targeted compounds was also studied in displaying the antiplasmodial activity. Compounds **5a-f** with an acetylated glucose unit showed moderate to less antiplasmodial activities with IC_{50} values in 2.25–4.13 μM range against both 3D7 and K1 strains, except compounds **5a**, **5d** and **5f** which were found inactive at higher concentration with IC_{50} values in 5.72–8.67 μM range against K1 strain. On the other hand, compounds **6a-f** with an acetylated galactose unit and compounds **7a-f** having a diacetonide protected galactose unit, displayed comparatively very good results with IC_{50} values in good to moderate range of 1.2–2.5 μM against 3D7 and K1 strains. Compounds **8a-f** with acetonide protected xylose sugar unit showed moderate to less activity against both the strains with IC_{50} values in 3.08–4.79 μM range. Based on the observation of antiplasmodial activities of the acetylated analogues **6**, compounds **5** and **6** were deacetylated to give the respective deacetylated analogues **9** and **10** (Scheme 3, Table 3). These deacetylated analogues also showed moderate to less activity against both strains, but displayed poor results as compared to acetylated analogues. Most of the compounds among **9a-f**, with a glucose unit were found inactive at higher concentration with IC_{50}

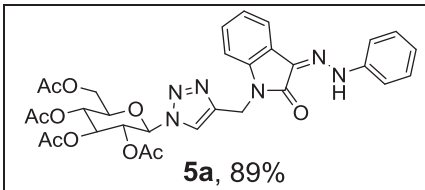
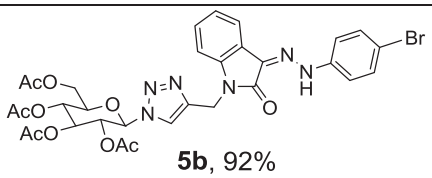
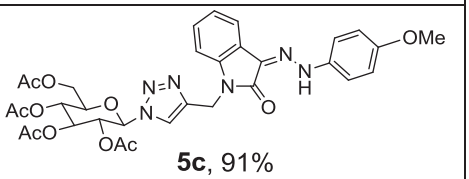
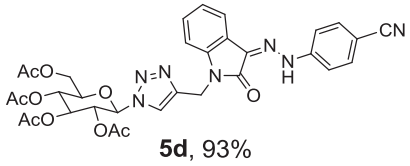
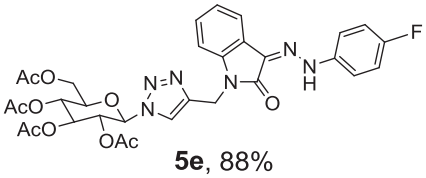
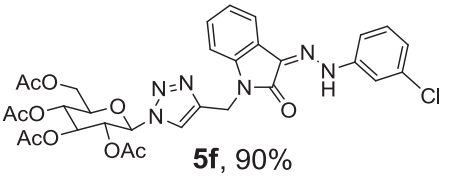
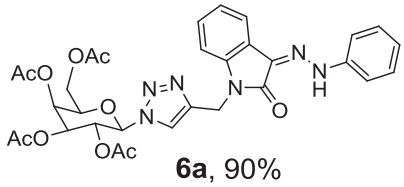
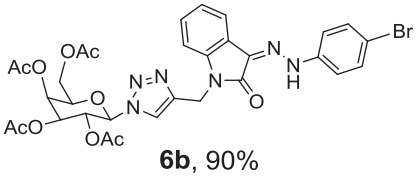
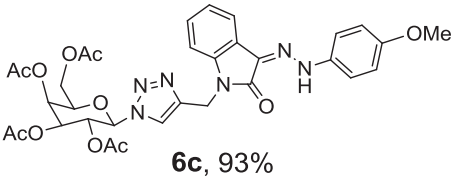
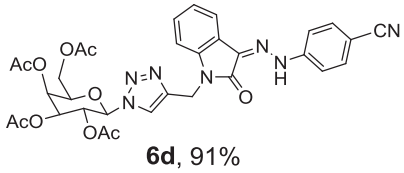
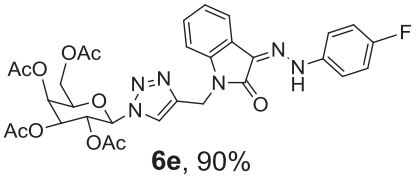
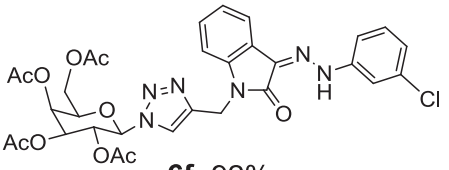
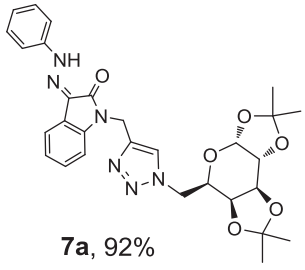
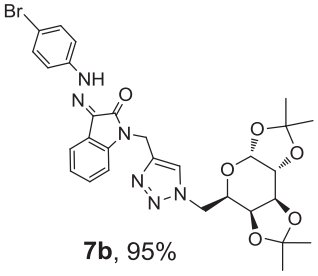
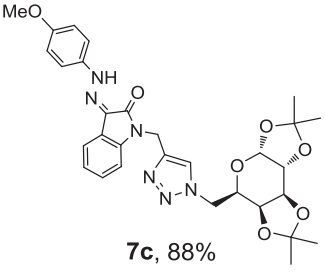
Table 1
Synthesis of glycohybrids of phenylhydrazono indolinones (**5**–**8**) by the reaction of glycosylated 1,2,3-triazolyl-methyl-indoline-2,3-diones (**3a**-**3d**) and different phenyl hydrazine hydrochlorides (**4a**-**4f**).

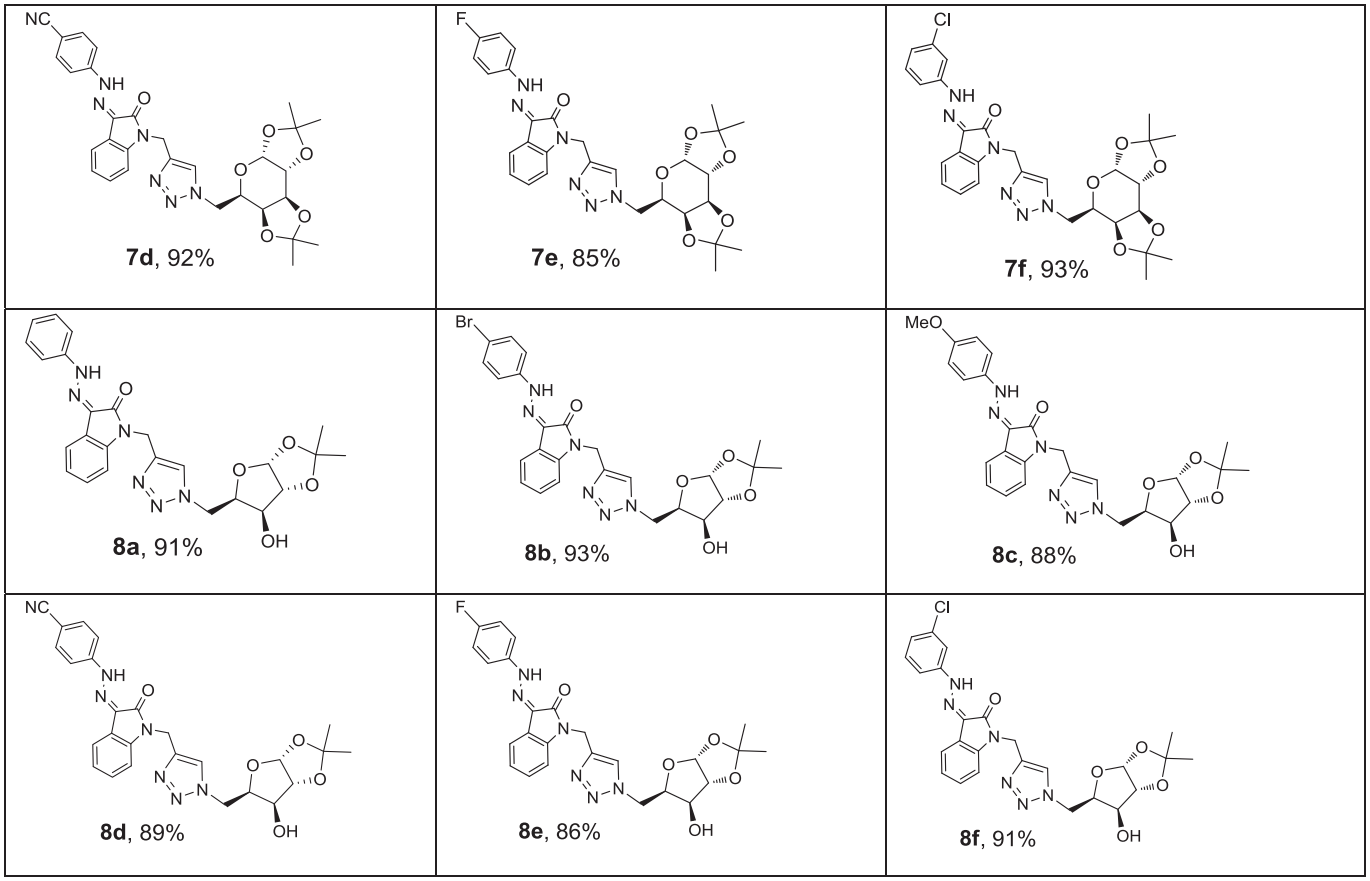


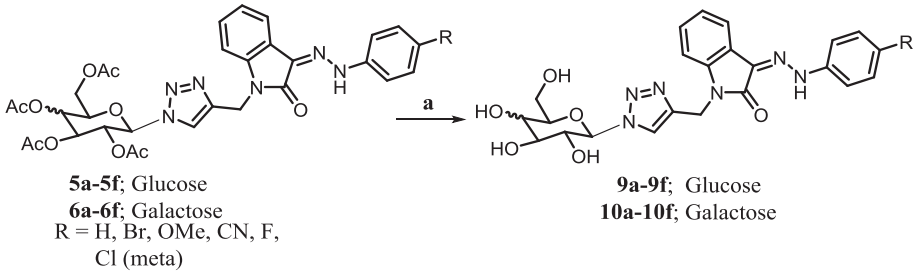
3a - 3d **4a - 4f**

R = H, Br, OMe, CN, F
Cl (meta)

5a - 5f; with 3a
6a - 6f; with 3b
7a - 7f; with 3c
8a - 8f; with 3d

 **5a**, 89%	 **5b**, 92%	 **5c**, 91%
 **5d**, 93%	 **5e**, 88%	 **5f**, 90%
 **6a**, 90%	 **6b**, 90%	 **6c**, 93%
 **6d**, 91%	 **6e**, 90%	 **6f**, 92%
 **7a**, 92%	 **7b**, 95%	 **7c**, 88%





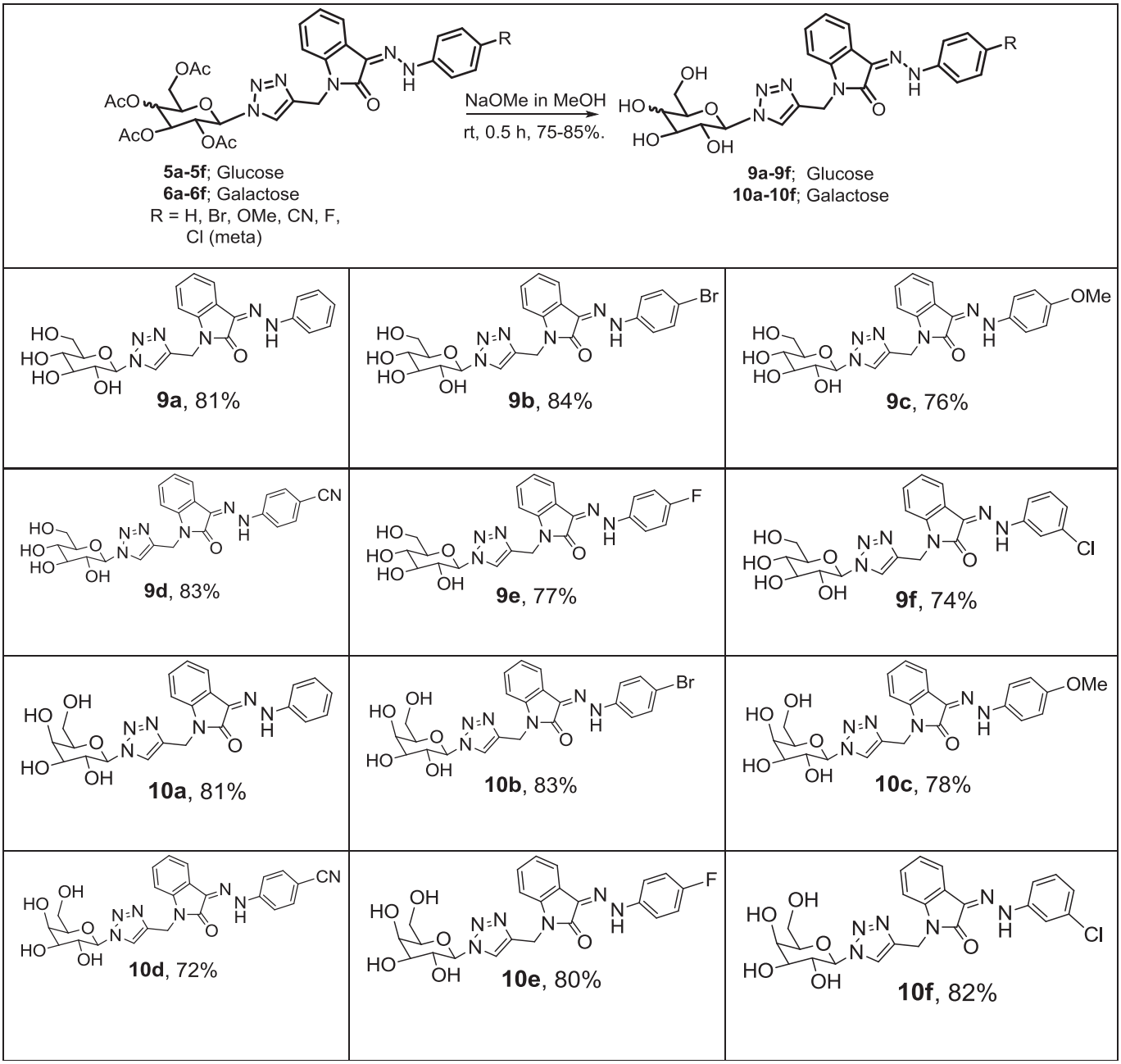
Scheme 3. Deacetylation of the synthesized acetylated analogues (**5** and **6**). **Reagent and Conditions: a**) NaOMe, Methanol, rt, 0.5 h, 75–85%.

values in 6.73–9.34 μM range against both strains, except compound **9c** which showed moderate activity with IC_{50} of 3.27 μM against 3D7 strain. The deacetylated analogues **10a-f**, with a galactose unit showed comparatively better results with some moderate to less activities having IC_{50} values in 2.62–5.20 μM range against both strains and few of them were found inactive at higher concentration with IC_{50} values in 6.64–8.68 μM range. Thus, the acetylated analogues **5**–**6** exhibited better activity than their respective deacetylated analogues **9**–**10**, similar to our previous report [37]. The compounds with $IC_{50} < 5$ μM in either of the *Pf* strains, were also evaluated for their cytotoxicity against a monkey kidney cell line (VERO) and these compounds have SI values greater than the desired one. The most active compounds **6c**, **7b** and **7c** with IC_{50} values < 2 μM against *Pf*3D7 strain, have shown high CC_{50} values as 62.52, 118.96 and 105.25 μM, respectively. These values clearly indicate that our active compounds have very good CC_{50} values and their safety is also reflected by their high SI values 49.22, 60.69 and 64.17 μM, respectively for *Pf*3D7 strain. The compounds **6f** and **7b** with good activity against *Pf*K1 resistant strain have also exhibited high SI values as 45.51 and 73.88 μM, respectively. Therefore, our active compounds have no cytotoxicity and can be persuaded for further development.

3. Conclusion

In conclusion, a small library of glycohybrids of phenylhydrazono-indolinones (**5**–**8, 9** and **10**) were prepared as possible antiplasmodial agents with a view to develop them as antimalarials. Out of all the compounds screened againt both Chloroquine-sensitive 3D7 and Chloroquine-resistant K1 strains of *P. falciparum*, 6c, 6f, 7b and 7c have displayed considerably good activity with IC_{50} values < 2 μM against either of the strains. The

Table 2
Synthesis of deacetylated glycohybrids of phenylhydrazono indolinones (9 and 10) from the respective acetylated analogues (5 and 6).



SAR study revealed that compounds with acetylated or diacetonide galactose units showed better activity against both strains than those with acetylated glucose or acetonide xylose units. Also, the acetylated compounds are more active than their respective deacetylated compounds.

4. Materials & methods

4.1. In vitro cultivation of P. falciparum

The CQ sensitive (3D7) and resistant (K1) strains of *P. falciparum* were cultured *in vitro* as per Trager and Jensen (1976) method with some modifications [42]. Cultures were maintained in fresh human erythrocytes at 5% hematocrit in complete medium. RPMI-1640 (HEPES modified) medium (Sigma) supplemented with 0.5% AlbuMaxII, 0.2% glucose, sodium bicarbonate and 15 μM hypoxanthine and incubated at 37 °C in CO_2 incubator. Parasite growth rate and stage was determined by the test of Giemsa's stained thin smears of the RBCs. All the above mentioned final compounds were tested over a concentration range of 150 nM to 10 μM. *P. falciparum* drug susceptibility test was carried out by determining fifty percent inhibitory concentration (IC_{50}) according to the method of Johnson et al. (2007) with some modifications [43]. Briefly, two fold serial dilutions of compounds and chloroquine were prepared in 96 well plates and then 50 μL asynchronous cultures of infected erythrocytes with 0.8–1% parasitaemia and 1% hematocrit was added to

Table 3
In vitro antiplasmodial activity and cytotoxicity of compounds **(3, 5–10).**

Com. Code	IC_{50} (μM)[a,b]		CC_{50} (μM)[b,d]	SI(μM)[c]		Com. Code	IC_{50} (μM)[a,b]		CC_{50} (μM)[b,d]	SI(μM)[c]	
	*Pf*3D7	*Pf*K1		*Pf*3D7	*Pf*K1		*Pf*3D7	*Pf*K1		*Pf*3D7	*Pf*K1
3a	3.54	>10	136.60	38.58	13.66	**7e**	3.07	2.64	122.41	39.87	46.36
3b	8.40	8.07	ND	NA	NA	**7f**	3.23	2.49	117.05	36.23	47.00
3c	8.41	7.51	ND	NA	NA	**8a**	4.67	4.66	82.14	17.58	17.62
3d	4.33	3.40	>200	46.18	58.82	**8b**	4.05	3.52	72.92	18.00	20.71
5a	3.73	7.11	107.62	28.85	15.13	**8c**	3.80	3.28	74.46	19.59	22.70
5b	3.79	3.84	116.21	30.66	30.26	**8d**	4.79	3.40	104.62	21.84	30.77
5c	3.05	4.13	95.27	31.23	23.06	**8e**	3.08	3.99	83.78	21.20	20.99
5d	3.33	5.72	75.37	22.63	13.17	**8f**	4.47	3.42	70.00	15.65	20.46
5e	2.25	3.80	68.73	30.54	18.08	**9a**	4.70	8.11	88.45	18.81	10.91
5f	3.96	8.67	116.55	29.43	13.44	**9b**	9.34	7.95	ND	NA	NA
6a	3.50	4.13	65.17	18.62	15.77	**9c**	3.27	4.89	79.64	24.35	16.28
6b	**2.09**	2.91	83.39	39.89	28.65	**9d**	7.78	7.01	ND	NA	NA
6c	**1.27**	3.12	62.52	49.22	20.03	**9e**	8.00	8.53	ND	NA	NA
6d	3.67	4.28	75.52	20.57	17.64	**9f**	6.73	7.62	ND	NA	NA
6e	2.44	3.00	78.62	32.22	26.20	**10a**	4.8	8.68	83.37	17.36	9.60
6f	2.47	**1.93**	87.85	35.56	45.51	**10b**	3.59	4.68	91.48	25.84	19.54
7a	3.87	2.62	105.27	27.20	40.17	**10c**	3.46	5.20	76.21	22.02	14.65
7b	**1.96**	**1.61**	118.96	60.69	73.88	**10d**	7.65	3.30	93.70	12.24	28.39
7c	**1.64**	2.29	105.25	64.17	45.96	**10e**	6.64	3.23	92.08	13.86	28.50
7d	3.59	2.77	125.63	34.94	147.80	**10f**	6.74	2.62	84.49	12.53	32.24
				Chloroquine			**0.007**	**0.5**	**>500**	**>71428.6**	**>1000**

[a] 50% Inhibitory concentration against chloroquine sensitive (3D7) and resistant (K1) strains of *P. falciparum*.
[b] Values are represented as average of at least duplicate determinations.
[c] Selectivity index (SI) = CC_{50}/IC_{50}.
[d] 50% Cytotoxic concentrations. NA = Not applicable. ND = Not done.

each well (100 μL-final volume). Eight wells were treated as positive control (without drug) and 4 wells as negative control (without parasite and drug). These plates were incubated in CO_2 incubator maintained at 37 °C for 72 h. Then 100 μL lytic buffer containing SYBR Green 1x final concentration was added to each well and incubated for 2 h at room temperature in a dark place. Plates were read under fluorescence reader at Ex. 485 nm, Em. 535 nm. Fifty percent inhibitory concentration (IC_{50}) was determined by quantifying DNA in treated and control cultures of parasites in human erythrocytes according to the SYBR Green I (Sigma Aldrich) fluorescence based method.

4.2. Cytotoxicity assay

Cytotoxic level of compounds was determined according to O'Brien et al. (2000) method with few modifications [44]. The monkey kidney cell line (VERO) was maintained *in vitro* in MEM medium (Sigma) supplied with 15% fetal bovine serum (FBS) and 5% CO_2 at 37 °C. An appropriate serial drug dilution was prepared in culture plates and the cells were exposed to the concentrations of particular compounds for three days, 10% resazurin, a cell viability marker, was added and read under fluorescent reader at excitation of 530 ± 25 nm and emission of 590 ± 25 nm wavelength for calculation of the median cytotoxic concentration (CC_{50}).

Author contributions

The manuscript was written through contributions from all authors. All authors have given approval to the final version of the manuscript. R.K.T. and P.J. contributed equally to this work.

Conflicts of interest

The authors declare that they have no conflicts of interest with the contents of this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejmech.2018.06.042.

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