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Letter

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Identification of Novel Phenyl Butenonyl *C*-Glycosides with Ureidyl and Sulfonamidyl Moieties as Antimalarial Agents

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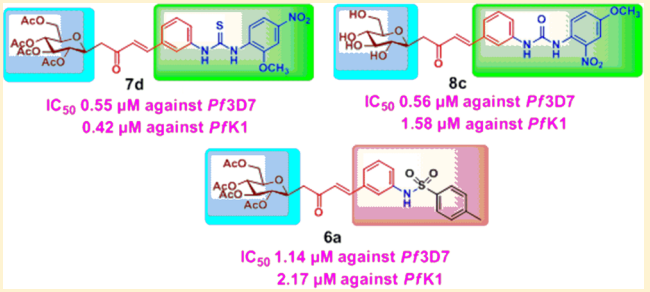
[†]Academy of Innovative Science and Research, [‡]Medicinal and Process Chemistry Division, [§]Parasitology Division, [∥]Pharmacokinetics & Metabolism Division, and [#]Molecular and Structural Biology Division, CSIR-Central Drug Research Institute (CSIR-CDRI), Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031, India

Supporting Information

ABSTRACT: A new series of *C*-linked phenyl butenonyl glycosides bearing ureidyl(thioureidyl) and sulfonamidyl moieties in the phenyl rings were designed, synthesized, and evaluated for their *in vitro* antimalarial activities against *Plasmodium falciparum* 3D7 (CQ sensitive) and K1 (CQ resistant) strains. Among all the compounds screened the *C*-linked phenyl butenonyl glycosides bearing sulfonamidyl moiety (**5a**) and ureidyl moiety in the phenyl ring (**7d** and **8c**) showed promising antimalarial activities against both 3D7 and K1 strains with IC_{50} values in micromolar range and low cytotoxicity offering new HITS for further exploration.



KEYWORDS: *Antimalarial agent, phenyl sulfonamides, diarylureides, Plasmodium falciparum*

Malaria, the most severe parasitic disease, infects more than 500 million people and continues to kill around one million children each year.[1] Most of the malarial infections and deaths are due to *Plasmodium falciparum* and *Plasmodium vivax* species. Although an arsenal of very effective antimalarial drugs have been used to control this disease, the culprit *P. falciparum* has developed resistance to nearly all available antimalarial drugs.[2] Artemisinin, the last line of defense against multidrug resistant malaria parasites in some parts of the world became resistance in present circumstance.[3,4] The recent emergence of resistance necessitates the search for new antimalarial drugs, which overcome the resistance and act through novel mechanisms.

The dihydropteroate synthase (DHPS), hemoglobin degradation enzymes, and shikimate pathway enzymes have been identified for the novel potential targets for new antimalarial drugs in the past decade.[5] Very recently a class of hemoglobin degradation enzymes, plasmepsins, has been discovered as a validated drug target and diphenyl ureas are known to inhibit this enzyme and display antimalarial activity.[6] Several other urea derivatives exhibit potent antimalarial activity.[7−10] *Plasmodium falciparum* hexose transporter (PfHT) plays a very important role in malaria parasites as a critical enzyme for glucose uptake and the survival of the parasite.[11] Simple 3-O-alkyl/alkenyl glucosides were shown to inhibit the PfHT and good antimalarial activity. Indeed, glucose is an essential energy substrate in many parasites, and they can undergo a metabolic shift *in vivo*, switching from predominately glycolytic metabolism to metabolism of alternative carbon sources through induction of gene sets combined with function of mitochondria and apicoplast.[12] Glucose delivery, however, is crucial for parasite survival and may also be critical for metabolic diversion of this key substrate from host tissues and thereby aggravating the disease processes.[13] Diphenyl propenones (chalcones), however, also exhibit antimalrial activity,[7,14−22] and malaria trophozoite cysteine protease has been proposed as possible target for this class of compound.[14,18] Phenyl urenyl chalcones also exhibit antimalrail activity via multiple mechanisms.[7]

Inspired by the above facts we thought to design and synthesize compounds based on sugars having *C*-linked phenyl propenone moiety and diphenyl urea units together to get hitherto unreported antimalarial agents (Figure 1). In order to further analyze the feature requirement of these molecules in 3D space, we analyzed the common features through HipHop algorithm.[23] The HipHop algorithm finds the common feature pharmacophore model among the set of the highly active ligands and thus referred as qualitative model without the use of the activity data representing the 3D arrangement of the essential features important for the specific activity. HypoGen on the converse deals with the development of quantitative pharmacophore model and requires biological activities with at least 3−4 orders of difference; therefore, in this work, HipHop

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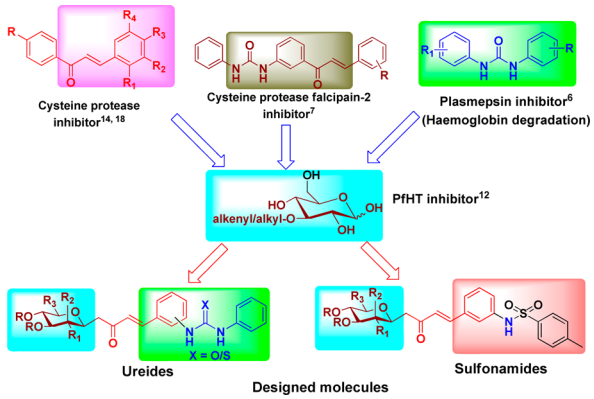
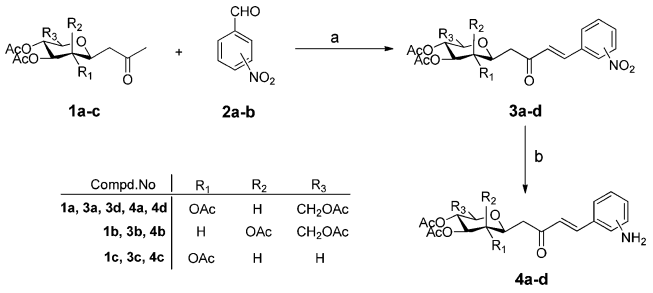


Figure 1. Known antimalarials and targeted sugar derivatives.

module is preferred over HypoGen to explain the 3D features of these compounds.

The synthetic strategy of the compounds is very simple and straightforward with no sophistication. The starting aminophenyl glycoside derivatives **4a−d** were obtained via two-step synthesis from the glycosylketones **1a−c**.[24] Thus, reaction of preformed glycosylketones **1a−d** with 3-nitro and 4-nitro benzaldehydes **2a** and **2b** in CH_2Cl_2 in the presence of pyrrolidine (20 mol %) at ambient temperature afforded the respective glycosyl butenones **3a−d** in good yields.[25−27] The chemoselective reduction of nitro group in the phenyl ring of the above nitrophenyl butenonyl glycopyranosides **3a−d** with $SnCl_2{\cdot}2H_2O$ (10.0 equiv) in ethanol under ultrasonic vibration at 30 °C afforded respective aminophenyl derivatives **4a−d** in good yields as reported earlier by us[28] (Scheme 1).

Scheme 1. Synthesis of the Aminophenyl Glycosyl Pyranosides[a]



Compd.No	R_1	R_2	R_3
1a, 3a, 3d, 4a, 4d	OAc	H	CH_2OAc
1b, 3b, 4b	H	OAc	CH_2OAc
1c, 3c, 4c	OAc	H	H

[a]Reagents and conditions: (a) pyrrolidine (20 mol %), CH_2Cl_2, RT; (b) $SnCl_2{\cdot}2H_2O$ (10eq),))))) 30 °C, EtOH.

We initially preformed bioevalution of **3a−d** and **4a−d** derivatives for their antimalarial activity against *Plasmodium falciparum* 3D7 (CQ sensitive) strain. The results depict that the nitrophenyl and aminophenyl glycosyl derivatives (**3a−d** and **4a−d**) showed very poor antimalarial activities with IC_{50} values more than 6.77 μM against *Plasmodium falciparum* 3D7 (CQ sensitive) strain (Table 1).

Next, we have targeted the amino group to pursue our investigation and further explore the SAR by carrying out modifications. The functionalization of the amine group into sulfonamides (**5** and **6**) and ureides (**7** and **8**) was thought of, using sulfonyl chloride, phenyl isocyanate, and isothiocynates by conventional methods. The reaction of 3-aminophenyl butenonyl glycopyranosides **4a−c** with *p*-toluene sulfonyl chloride in the presence of Et_3N in CH_2Cl_2 at 0−30 °C led

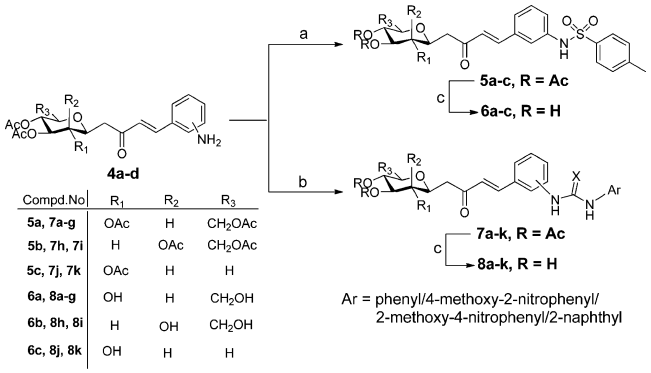
Table 1. *In Vitro* Antimalarial Activity against the *Pf* 3D7 Strain for 3a−d and 4a−d

compd	IC_{50} μM Pf3D7	compd	IC_{50} μM Pf3D7
3a	6.77	**4a**	14.05
3b	ND[a]	**4b**	ND[a]
3c	7.57	**4c**	16.77
3d	9.07	**4d**	14.39

[a]ND: Not done.

to the formation of respective peracetylated *N*-sulfonylaminophenyl glycopyranosides **5a−c** in good yields (Scheme 2).

Scheme 2. Synthesis of the *N*-Sulfonylaminophenyl, Ureido, and Thioureido Glycopyranosides[a]



Compd.No	R_1	R_2	R_3
5a, 7a-g	OAc	H	CH_2OAc
5b, 7h, 7i	H	OAc	CH_2OAc
5c, 7j, 7k	OAc	H	H
6a, 8a-g	OH	H	CH_2OH
6b, 8h, 8i	H	OH	CH_2OH
6c, 8j, 8k	OH	H	H

[a]Reagents and conditions: (a) *p*-toulene sulfonyl chloride, Et_3N, CH_2Cl_2, 0−30 °C; (b) ArNCX (X = O/S), Et_3N, CH_2Cl_2, RT; (c) NaOMe, MeOH, 10−20 min, RT.

Similar reaction of aminophenyl butenonyl glycopyranosides **4a−d** with different phenyl isocyanates and isothiocyanates separately in the presence of Et_3N in CH_2Cl_2 at ambient temperature resulted in respective peracetylated ureidophenyl and thioureidophenyl glycopyronasides (**7a−k**) in good yields (Scheme 2). The Zemplen deacetylation of the above peracetylated compounds **5a−c** and **7a−k** with NaOMe/MeOH at room temperature led to the formation of the deacetylated products **6a−c** and **8a−k**, respectively, in satisfactory yields (Scheme 2). All the synthesized compounds were fully characterized by their spectroscopic and HRMS data. In NMR (^1H and ^{13}C) spectral data of the compounds all the proton and carbon signals were observed at their usual chemical shift.

For structure−activity relationship (SAR) exploration and to find out the role of sugars on antimalrial activity, we next synthesized successively the analogues of sulfonamide and ureido derivatives without sugar moiety. The Horner−Wadsworth−Emmons (HWE) olefination of 3-nitrobenzaldehyde with triethyl phosphonoacetate in the presence of lithium hydroxide in THF at room temperature led to the formation of ethyl 3-(3-nitrophenyl)acrylate (**9**) in quantitative yield. The latter on chemoselective reduction of nitro group with $SnCl_2{\cdot}2H_2O$ (10.0 equiv) as above the respective aminophenyl derivative **10** in good yield. Compound **10** on reaction with *p*-toluene sulfonyl chlroide and phenyl isocyanates separately as reported earlier led to the formation of the desired sulfonamide (**11a**) and ureide (**11b−c**) derivatives (Scheme A, Supporting Information S2) in good yields. However, we synthesized simple phenyl sulfonamidyl (**12**), diaryl ureidyl (**13** and **14**),

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Table 2. *In Vitro* Antimalarial Activity against the *Pf* 3D7 and *Pf* K1[a]

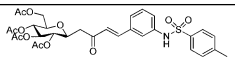
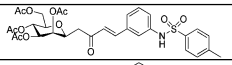
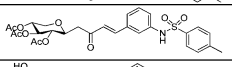
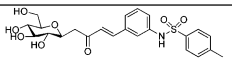
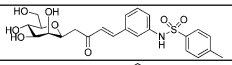
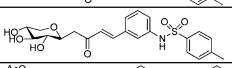
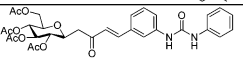
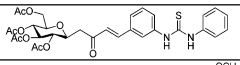
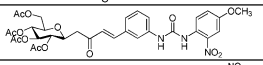
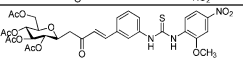
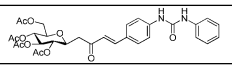
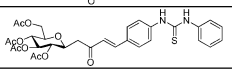
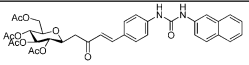
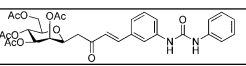
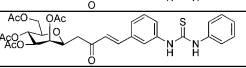
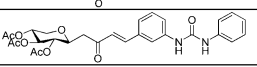
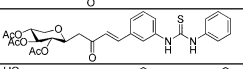
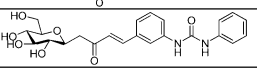
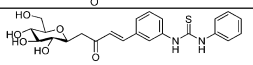
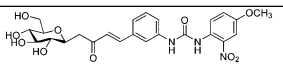
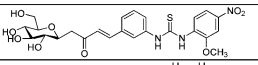
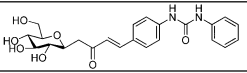
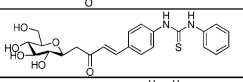
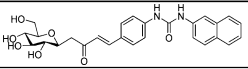
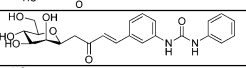
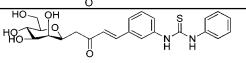
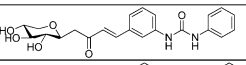
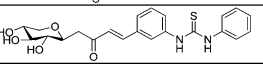
Comp. code	Compounds	IC_{50} μM		CC_{50} μM	SI	
		*Pf*3D7	*Pf*K1		*Pf*3D7	*Pf*K1
5a		**1.14**	**2.17**	**584.18**	**512.43**	**269.2**
5b		**3.96**	**5.19**	**123.25**	**31.12**	**23.73**
5c		**1.39**	**3.00**	**268.23**	**192.97**	**89.41**
6a		**2.20**	**3.87**	**380.92**	**173.14**	**98.42**
6b		**3.89**	**5.11**	**417.42**	**107.30**	**81.68**
6c		**2.93**	**6.35**	**94.74**	**32.33**	**14.91**
7a		**2.29**	**2.40**	**180.32**	**78.74**	**75.13**
7b		**1.91**	**4.48**	**336.58**	**176.21**	**75.12**
7c		**0.94**	**4.23**	**729.92**	**776.51**	**172.5**
7d		**0.55**	**0.42**	**559.20**	**1016.72**	**1331.42**
7e		5.27	5.55	819.67	155.53	147.68
7f		**1.83**	**2.30**	**663.25**	**362.43**	**288.36**
7g		2.18	5.36	481.96	221.08	89.91
7h		6.65	7.81	102.40	15.39	13.11
7i		**3.73**	**2.87**	**65.14**	**17.46**	**22.69**
7j		**3.17**	**4.92**	**101.54**	**32.03**	**20.63**
7k		4.20	5.57	58.73	13.98	10.54
8a		**3.77**	**3.39**	**373.30**	**99.01**	**110.11**
8b		9.43	7.20	371.17	39.36	51.55
8c		**0.56**	**1.58**	**708.89**	**1265.87**	**448.66**
8d		**3.35**	**2.47**	**202.62**	**60.48**	**82.03**
8e		7.51	7.66	1131.22	150.62	147.67
8f		11.85	13.79	274.45	23.16	19.90
8g		5.91	5.28	1016.26	171.95	192.47
8h		20	20	ND	ND	ND
8i		13.07	17.81	336.33	25.73	18.88
8j		**3.44**	**5.43**	**309.02**	**89.83**	**56.90**
8k		6.89	8.69	289.32	41.99	33.29

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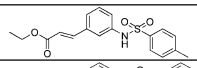
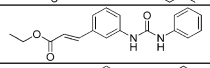
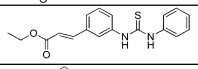
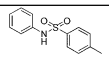
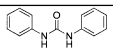
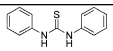
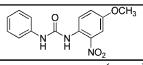
Table 2. continued

Comp. code	Compounds	IC_{50} μM		CC_{50} μM	SI	
		*Pf*3D7	*Pf*K1		*Pf*3D7	*Pf*K1
11a		16.12	16.12	77.12	4.78	4.78
11b		8.80	13.41	292.96	33.26	21.83
11c		>20	>20	279.43	<13.97	<13.97
12		>20	>20	221.32	<11.06	<11.06
13		13.79	>20	351.62	25.26	<17.58
14		>20	>20	434.52	<21.72	<21.72
15		>20	18.01	355.73	<17.78	19.78
16	Chloroquine (CQ)	0.011	1.16	684.68	58833.3	578.68

[a]IC_{50}: 50% inhibitory concentration against parasite. SI: CC_{50}/IC_{50}. ND: Not done.

and diaryl thioureidyl (**15**) moieties from aniline (Scheme B, Supporting Information S2). All the synthesized compounds were tested for their *in vitro* antimalarial activity against *Plasmodium falciparum* 3D7 (CQ sensitive) and K1 (CQ resistant). Subsequently cytotoxicities of the desired compounds against mammalian VERO cell line were also determined.

As evident from Table 2, all of the phenyl sulfonamides and most of the urea and thiourea derivatives of glycopyranosides showed better *in vitro* antimalarial activity as compared to the sulfonamido and ureido derivatives without sugar moiety. The phenyl sulfonamides with glycopyranoside moieties **5a**−**c** and **6a**−**c** displayed IC_{50} values in the range of 1.14 to 3.96 and 2.17 to 6.35 μM against the *Pf*3D7 and *Pf*K1 strains, respectively. Among the glycosides, the acetylated glucosides and xylosides bearing phenyl sulfonamides (**5a** and **5c**) displayed promising antimalarial activity with IC_{50} values of 1.14 and 1.39 μM (*Pf*3D7) and 2.17 and 3.00 μM (*Pf*K1), respectively. The deacetylated glucosides and xylosides with phenyl sulfonamides (**6a** and **6c**) did also display significant antimalarial activity with IC_{50} values 2.20 and 2.93 μM (*Pf*3D7) and 3.87 and 6.35 μM (*Pf*K1), respectively. By observing the results it is concluded that by changing the sugar with mannopyaranose in the glycopyranoside series (both peracetylated and deacetylated) having phenyl sulfonamidyl moieties **5b** and **6b** resulted in loss of antimalarial activity with IC_{50} values 3.96 and 3.89 μM (*Pf*3D7) and 5.19 and 5.11 μM (*Pf*K1), respectively.

In the case of ureide and thioureide glycoside moieties, of a total 22 compounds evaluated, 11 compounds (**7a**, **7b**, **7c**, **7d**, **7f**, **7i**, **7j**, **8a**, **8c**, **8d**, and **8j**) showed promising antimalarial activities with IC_{50} values in the range of 0.55 to 3.77 μM against *Pf*3D7 and 0.42 to 5.43 μM against *Pf*K1, respectively. In this series, acetylated thioureido glucoside (**7d**, 0.55 and 0.42 μM) exhibited the most promising activity when compared to deacetylated ureido glucoside (**8c**, 0.56 and 1.58 μM), and both have methoxy and nitro substituents in different positions on the phenyl ring. Another methoxy and nitro substituted acetylated ureido glucoside (**7c**, 0.94 and 4.23 μM) and deacetylated thioureido glucoside (**8d**, 3.35 and 2.47 μM) showed moderate activity as compared to **7d** and **8c**. Unsubstituted glucosides **7a**, **7b**, **7f**, and **8a** showed good antimalarial activity with IC_{50} values varying from 1.83 to 3.77 μM and 2.30 to 4.48 μM against *Pf*3D7 and *Pf*K1, respectively. The alteration of the glucose moiety with mannose and xylose as represented by **7i**, **7j**, and **8j** were found less active with IC_{50} values in the range of 3.17 to 3.73 μM and 2.87 to 5.43 μM against *Pf*3D7 and *Pf*K1, respectively. Therefore, it is concluded that, out of all these compounds most of the glucoside moieties displayed significant antimalarial activities as compared to the mannoside and xyloside moieties. Among this series the acetylated thioureido glucoside **7d** and deactylated ureido glucoside **8c** are very promising compounds for further optimization. All these active compounds show low cytotoxicity against VERO cell line (Monkey kidney cell line). On the basis of IC_{50} and CC_{50} values, selective index (SI) of all the compounds were calculated, and the most active compounds in these series found to have good selective indices (Figure A,B, Supporting Information S3). The two most promising antimalarial active compounds **7d** and **8c** were found to have high selective indices in this series. Furthermore, we have also screened *in vitro* antimalarial activity of phenyl sulfonamidyl (**12**), diary ureidyl (**13** and **14**), and diaryl thioureidyl (**15**) derivatives without sugar and buetenone moieties, which resulted in loss of activity as compared to their glycoside counterparts with sulfonamidyl and ureidyl derivatives.

We have investigated the inhibition of haem polymerization to the 17 most active compounds of this series. Among all the active compounds, compound **7c** exhibited the most inhibition at 92.72%, and three compounds **7a**, **7d**, and **7j** exhibited similar inhibition values of 72.47%, 72.13%, and 76.86%, respectively. Other compounds exhibited less inhibition compared to the above compounds (Table A, Supporting Information S3).

In order to find the common structural features required for this set of compounds and to further validate the SAR studies, a pharmacophore modeling was carried out using 16 training set compounds (Figure C, Supporting Information S5) and validated on 19 test set compounds (Table C, Supporting Information S6). The HipHop module was used for pharmacophore modeling using reported protocol.[23] The ten hypotheses generated had the scores ranging from 208.706 to 206.689 and four features viz. hydrogen bond acceptor lipid feature (H, 3) and hydrogen bond donor features (D, 1), common for all hypotheses (Table B, Supporting Information

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S5). Out of ten hypotheses, Hypo-3 (Figure 2A) was selected for further study as it mapped all the training set compounds

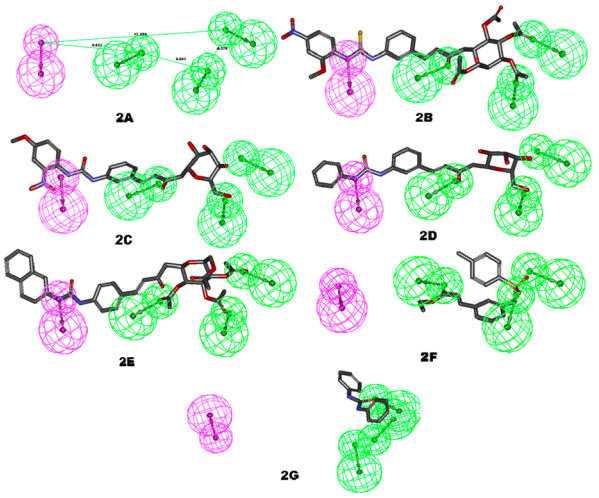

Figure 2. (A) Pharmacophore model developed using the training set compounds. (B,C) Mapping of the most active compounds (**7d** and **8c**) from the training set. (D,E) Mapping of the most active compounds from the test set (**8a** and **7g**). (F,G) Mapping of the moderately and least active compounds from the test set (**11a** and **14**).

correctly and maps all essential features of the most active compound **7d** (Figure 2B). The one N−H functionality from thioureido maps well the centroid alignment of one D feature of Hypo-3, while the one carbonyl functionality of the (*E*)-4-phenylbut-3-en-2-one part of the compound **7d** fulfills the requirement of one H functionality. The remaining two H features were supported by the C═O functionalities of 3,4-diyl diacetate. The Hypo-3 also mapped well the second most active compound **8c** satisfactorily (Figure 2C), which was predicted well in the test set compounds (Table C, Supporting Information S5) and confirms the applicability of this hypothesis. The Hypo-3 maps well the most active compounds from the test set **8a** and **7g**, respectively, into their highly active class (Figure 2D,E). The moderately active compound **11a** from this series maps well the three H features, while it is unable to map one D function of Hypo-3 (Figure 2F). Compound **14**, least active compound from this series, lacks the 2H features and one D feature (Figure 2G), therefore predicted as inactive and also observed poorly active in *in vitro* studies.

As a representative compound, the most promising glycoside with ureido phenyl butenonyl moiety (**8c**) was studied for its pharmacokinetic parameters in male Sprague−Dawley rats through intravenous administration (5 mg/kg) (Figure 3). It was quickly distributed and eliminated from the serum with terminal elimination half-life ($t_{1/2}$) of 7.1 ± 0.3 h. The volume

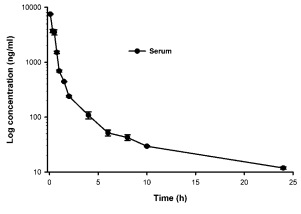

Figure 3. Concentration−time profile of **8c** after intravenous (5 mg/kg) administration in male Sprague−Dawley rats (n = 3). Bar represents SEM.

of distribution (2.8 L/kg) is higher than the total blood volume (0.054 L/kg)[29] of the rat and systemic clearance (1.02 L/h/kg) is lower than the total hepatic blood flow in rats (2.9 L/h/kg)[29] indicating extravascular distribution with negligible extrahepatic elimination (Supporting Information S7 and S8).

In conclusion, we have identified hitherto unreported novel phenyl butenonyl *C*-glycosides with ureidyl, thioureidyl, and sulfonamidyl moieties as promising antimalrials against both the 3D7 and K1 strains of *Plasmodium falciparum* with high selectivity index and low cytotoxicity. The synthesis, structure−activity relationship, and systematic bioevaluation of compounds are discussed. Compounds **7d** and **8c** exhibited the most promising activities within the series. The ureidyl and thioureidyl derivatives of the glycosides showed haem polymerization inhibition significantly. This class of compounds with good *in vitro* antimalarial activity offers a new direction to explore new antimalarials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details for synthesis and characterization of all compounds together with protocols for biological assays, pharmacokinetic parameters, and pharmacophore development. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have contributed in this study and have given their permission for communication.

Notes

The authors declare no competing financial interest.

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