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Synthesis and *In-vitro* Antimalarial Activity of Estrone based Carbohydrazide

Mistry S*, Singh AK

Department of Applied Science, Parul University, Gujarat, India

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ABSTRACT

A new series of estrone base carbohydrazide has been designed and synthesized. Characterization and in vitro antimalarial evaluation of the newly synthesized compounds are discussed. Estrone and 4'-bromomethyl-2-cyanobiphenyl reacted in presence of potassium carbonate and potassium iodide in anhydrous acetone leads ether 4'-(3-yloxymethyl)-estrone-biphenyl-2-carbonitrile formation, which on sequential condensation with hydrazine hydrate and acid chloride give steroidal carbohydrazide in quantitative yield. Their structures were confirmed by Mass spectra, IR spectra and 1H, 13C NMR spectroscopy. The formation of carbohydrazide linkage with different acid chlorides had an excellent effect on the activity of the compounds. The newly synthesized steroidal carbohydrazide are screened for antimalarial activity against the P. Falciparum.

Keywords: Estrone;4'-bromomethyl-2-cyanobiphenyl;Acid chloride;Steroidal carbohydrazide; Antimalarial activity

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INTRODUCTION

Malaria is one of the major health diseases caused by a parasite. The parasite is transmitted to humans through the bites of infected mosquitoes. The World Health Organization (WHO) estimate shows that approximately 3.3 billion people are living at risk places of malaria. Nearly 80% of cases and 90% of deaths are reported from sub-Saharan Africa and children under the age of 5 years and pregnant women are severely affected [1,2]. In 2016, it was estimated that there were 216 million cases of malaria globally and 445,000 deaths due to malaria. Moreover, exterior Africa, it is the profusely populated Southeast Asia where 30% of the total population is approximated to be at risk of malaria, of which India contributes (80%) most of the cases. The development of resistance to mainstay drugs like chloroquine, and controlled use of new artemisinin analogs have created an urgent need to discover new antimalarial agents in Figure 1.

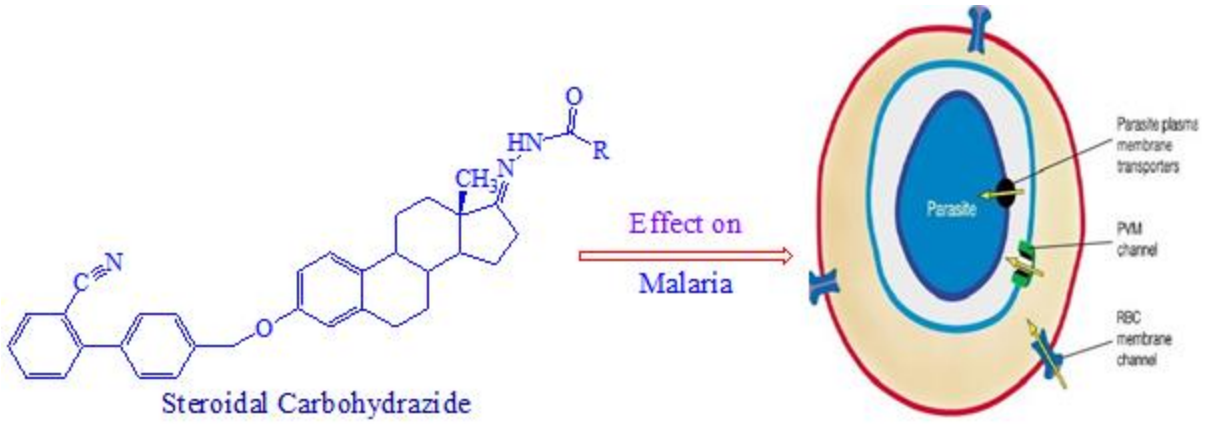

Figure 1: Steroidal carbohydrazide tested for antimalarial activity

Steroids play a very important role in human. Steroids, an important family of polycyclic molecules with various structures, have drawn extensive attention due to their diverse bio-activities and highly bioavailable [3]. Steroids are naturally occurring compounds with broad spectrum of biological activities such as anti-microbial, anti-inflammatory, anti-cancer, Anti-inflammatory, Anti tuberculosis and antimalarial. Steroidal ring modification and incorporation of heteroatom, heterocycle, amides or replacing one or more carbon atoms in steroidal molecule may improves its biological activities have been researched and reported [4-6].

Many steroid-based drugs have been applied in clinical treatments and become one of the highest marketed classes of pharmaceuticals [7]. Estrone is extensively distributed in many steroidal drugs, such as contraceptive pills (Ethinyl estradiol and Estradiol). So the modification of estrone structure is important for developing a new therapeutic agent. Rational modification of steroid molecule with improved biological activities has been reported. Alkaloids having steroidal nucleus have also been isolated and shown to possess antimalarial activity. Dua, et al. investigated the *in vitro* antimalarial and cytotoxic effects of the known compound, conessine [8-10].

Carbohydrazide is an attractive and versatile scaffold with relevant application in several areas, including asymmetric catalysis, coordination chemistry, agrochemicals and pharmacology [11]. A number of carbohydrazide derivatives possess interesting bioactivity such as antifungal, anti-inflammatory, antiplatelets, antimalarial and anticancer activities [12].

A survey of the literature reveals that many researchers have synthesized carbohydrazide by condensation of aldehyde and hydrazide. Carbohydrazide derivative of 3-O-ether-estrone-17-hydrazone with acid chloride is still not reported. This encourages to synthesize steroidal carbohydrazide by the condensation of acid chloride with hydrazide and evaluated their antimalarial activity against *P. falciparum* strain. In the search of new antimalarial agents, a series of steroidal carbohydrazide containing -NHCO- group attached to steroidal 17-hydrazone were synthesized from estrone as starting material [13]. The structural modification of estrone building block is carried out on C-3 and C-17 in ring-A and D respectively. As per our knowledge, estrone based carbohydrazide with antimalarial activity have not been reported.

MATERIALS AND METHODS

All the chemicals were used as received from commercial sources. All reaction progress was monitored by thin-layer chromatography (TLC) analysis using silica gel 60 F254 TLC plates.

IR spectra were recorded using potassium bromide discs on a Bruker Optics with software Opus (4.2). 1H and 13C NMR spectra were recorded on Varian spectrometer 200 MHz and 50 MHz respectively; the chemical shifts δ were measured in ppm with respect to the solvent. High resolution mass spectra were recorded on Waters make Acquity model and UPLC connected with SQ detector (Single Quadra pole) with Software Mass Lynx (401). Measurements were performed in positive (MS+) ion mode [14].

Synthesis

Our prime focused on the preparation and evaluation of steroidal carbohydrazide, the title compounds (5-5 g) were synthesized as depicted in Figures 2 and 3.

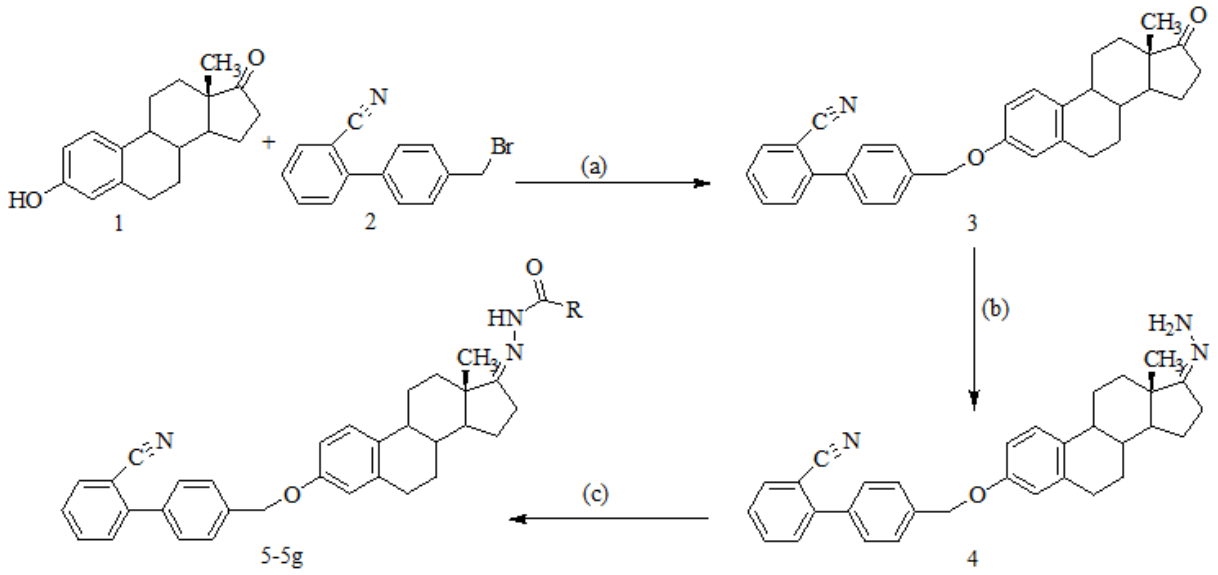

Figure 2: Synthesis Carbohydrazide (a) K_2CO_3 (previously dry at 105°C), KI, TBAB, Acetone, 50°C-55°C, 16 h; (b) Hydrazine hydrate (80%), glacial acetic acid, methanol, reflux; (c) Methylene chloride, Triethylamine, Acid chloride

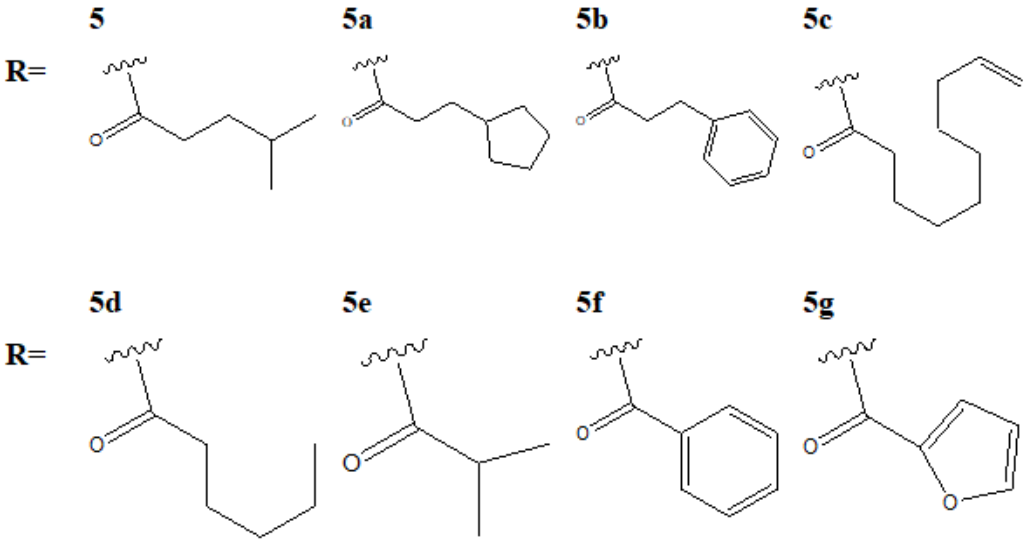

Figure 3: R=Acid chloride. General procedure for the synthesis 5-5i (Steroidal carbohydrazide)

Synthesis of 4'-(3yloxymethyl)-1,3,5(10)-estratriene-biphenyl-2-carbonitrile 3: A suspension of Estrone 1 (15 g, 55 mmol), potassium carbonate (K_2CO_3) (11.4 g, 82 mmol) (previously dried at 105°C), potassium iodide (KI) (10% mol), Tetra Butyl Ammonium Bromide (TBAB) (10% mol) in a mixture of acetone (150 ml) and DMF (Dimethyl formamide) (15 ml) was stirred for 10-15 minutes at 25°C-30°C. Charged 4'-bromomethyl-2-cyanobiphenyl 2 (16.5 g, 60 mmol) in to reaction mass at 25°C-30°C. The reaction went to completion within 16 h at 50°C-55°C. Progress of reaction was monitored by TLC [mobile phase: Chloroform/Acetone (7/3) (v/v)]. Distilled out solvent under vacuum at about 60°C and replaced with water (250 ml). The mass was agitated for 30 minutes at 25°C-30°C. The solid was removed by filtration, washed with water till neutral pH, sequentially washed with chilled (5°C-10°C) methanol (25 ml × 2). Dried under vacuum at 45°C-50°C resulted in a white solid of 3 (20 g, 80%) [15].

Synthesis of 4'-[17-(hydrazone)-3yloxymethyl-1,3,5(10)-estratriene]-biphenyl-2-carbonitrile 4: The intermediate 3 (10 g, 21 mmol) was reflux with hydrazine hydrate (80%) (20 ml) in methanol (100 ml) using 2-3 drops of glacial acetic acid as catalyst. Progress of reaction was monitored by TLC [mobile phase: Chloroform/Acetone (7/3) (v/v)]. TLC indicated that reaction was complete (about 3 h). The mixture was cooled to 25°C-30°C and resulting white solid was filtered and washed with Methanol (20 ml). The wet solid dried under vacuum at about 50°C to provide 7.5 g (75%) of 4.

Synthesis of carbohydrazide 5-5 g: A solution of compound 4 (1.0 mmol), in dry methylene dichloride (25 ml) with triethylamine (3 ml) was stirred and cooled to 5°C to 10°C. Then solution of acid chloride (1.5 mmol) in methylene dichloride (10 ml) were added and the reaction mass was warmed to 25°C-30°C. Progress of reaction was monitored by TLC. [Mobile phase: Toluene/Ethyl acetate (8/2) (v/v)]. TLC indicated that reaction was completed (about 30 minutes). The reaction mass was diluted with water (5 ml), settled and separated the lower organic layer which was washed with sodium carbonate solution and then wash with dil. HCl solution, finally adjusted neutral pH

by water washing. Solid isolated by filtration from methanol. The wet solid dried under vacuum at about 50°C. The yield of desired compound 5-5 g is 70% ± 5%.

4'-{17-[-(Isocaproic)-hydrazide]-3-yloxymethyl-1,3,5(10)-estratriene}-biphenyl-2-carbonitrile (5): White solid, 0.6 g, Yield 66%; m.p. 190-192°C; IR (KBr, νmax, cm $^{-1}$): 1251, 1496, 1605(C=N), 1662(C=O), 2223(C≡N), 2930, 3060, 3165; 1H NMR (200 MHz $CDCl_3$, δ, ppm) : 0.98(s,3H,-CH_3), 1.1(d,6H J=6.9,-CH_3), 5.18(s,2H,-OCH_2-), 6.44-7.67(m,11H,Ar-H); 13C NMR (50 MHz $CDCl_3$): 16.9(-CH_3), 22.1, 26.4, 28.4, 30.2, 31.5, 33.5, 34.7, 35.4, 36.2, 39.2, 42.4, 44.2, 53.4(-OCH_2), 69.9, 111.5, 112.3, 114.8, 118.7(C≡N), 126.4, 127.6, 127.7, 129.0, 130.0, 132.7, 132.8, 133.8, 137.6, 137.9, 145.1, 157.3(C3), 161.0(C=N), 177.0(C=O); M/S m/z: 574.32[M+K]+; Anal. Calcd. for $C_{39}H_{37}N_{3O}$.

4'-{17-[-(3-Cyclopentyl propionic)-hydrazide]-3-yloxymethyl-1,3,5(10)-estratriene}-biphenyl-2-carbonitrile (5a): White solid, 0.61 g,Yield 71%; m.p. 170°C-172°C; IR (KBr, νmax, cm^{-1}) 1253, 1498, 1610(C=N), 1665(C=O), 2224(C≡N), 2934, 3063, 3176; 1H NMR (200 MHz CDCl3, δ, ppm) : 0.94(s,3H,-CH3), 5.13 (s,2H,-OCH2-), 6.77-7.91(m,11H,Ar-H); 13C NMR (50 MHz $CDCl_3$): 17.1(-CH_3), 23.2, 25.1, 25.2, 26.2, 27.1, 29.7, 31.1, 31.9, 32.5, 34.1, 38.1, 39.9, 44.1, 44.8, 52.4 (-OCH_2), 69.5, 111.2, 112.3, 114.8, 118.7(C≡N), 126.4, 127.6, 127.7, 129.0, 130.0, 132.7, 132.8, 133.8, 137.6, 137.9, 145.1, 156.7(C_3), 165.0(C=N), 176.0(C=O); M/S m/z: 601.31[M+H]+.; Anal. Calcd. for $C_{40}H_{90}N_3O_2$.

4'-{17-[-(3-Phenyl propionic)-hydrazide]-3-yloxymethyl-1,3,5(10)-estratriene}-biphenyl-2-carbonitrile (5b): White solid, 0.64 g, Yield 70%; m.p. 173°C-175°C; IR (KBr, νmax, cm – 1): 1257, 1496, 1609(C=N), 1667(C=O), 2223(C≡N), 2931, 3065, 3159; 1H NMR (200 MHz $CDCl_3$, δ, ppm): 1.1(s,3H,-CH_3), 2.35(s,3H,-CH_3), 5.14(s,2H,-OCH_2-), 6.44-7.66(m,15H,Ar-H), 8.42(s,1H,-CH=N); 13C NMR (0 M5Hz CDCl3): 16.1, 25.4, 26.2, 27.4, 29.7, 31.0, 33.2, 38.2, 42.6, 45.1, 52.9(-OCH_2), 70.1, 110.9, 112.1, 114.2, 118.6, 125.7, 127.1, 127.3, 127.9, 128.4, 129.1, 130.2, 132.8, 137.6, 141.2, 145.1, 154.5(C3), 160.4(C=N), 175(C=O); M/S m/z : 608.118.6[M+H]+; Anal. Calcd. for $C_{40}H_{39}N_{3O}$.

4'-{17-[-(10-Undecanoic)-hydrazide]-3-yloxymethyl-1,3,5(10)-estratriene}-biphenyl-2-carbonitrile (5c): White solid, 0.66 g, Yield 70%; m.p. 148°C-150°C; IR (KBr, νmax, cm^{-1}): 1253, 1495, 1608(C=N), 1660 (C=O), 2222(C≡N), 2925, 3060, 3164; 1H NMR (200 MHz $CDCl_3$, δ, ppm): 1.04(s,3H,-CH_3), 4.80(dd, J=17, 10, 2H,=CH_2), 5.16(s,2H,-OCH_2-), 5.61(m,1H,-CH), 6.64-7.75(m,11H,Ar-H); 13C NMR (50 MHz $CDCl_3$): 24.2(-CH_3), 23.2, 25.1, 25.2, 26.2, 27.1, 29.7, 31.1, 31.9, 32.5, 34.1, 38.1, 39.9, 44.1, 44.8, 52.4(-OCH_2), 69.8, 111.2, 112.3, 114.8, 115.4(=CH_2), 118.6(C≡N), 126.4, 127.6, 127.7, 129.0, 130.0, 132.7, 132.8, 133.8, 137.6, 137.9, 140.1, 145.1, 154.7(C_3), 157.2(C=N), 168.1(C=O); M/S m/z: 628.21[M+H]+; Anal. Calcd. for $C_{42}H_{49}N_3O_2$.

4'-{17-[-(Hexanoic)-hydrazide]-3-yloxymethyl-1,3,5(10)-estratriene}-biphenyl-2-carbonitrile (5d): White solid, 0.8 g, Yield 66.6%; m.p. 178°C-180°C; IR (KBr, νmax, cm^{-1}): 1252, 1497, 1606(C=N), 1666(C=O), 2222(C≡N), 2928, 3061, 3168; 1H NMR (200 MHz $CDCl_3$, δ, ppm): 0.98(s,6H,-CH_3(estrone) & -CH_3 (Hexanoyl chloride), 5.13(s,2H,-OCH_2-), 6.77-7.92(m,11H,Ar-H); 13C NMR (50 MHz $CDCl_3$): 14.01[-CH3(terminal methyl group of Hexanoyl chloride)], 17.1(-CH_3), 22.4, 23.2, 24.4, 25.2, 26.1, 27.1, 29.7, 31.6, 32.5, 34.1, 38.1, 44.1, 44.7, 52.4,

69.5(-OCH_2), 111.2, 112.3, 114.8, 118.7(C≡N), 126.4, 127.6, 127.7, 129.9, 130.0, 132.7, 132.8, 133.8, 137.6, 137.9, 145.1, 156.7(C3), 165.0(C=N), 175.8(C=O); M/S m/z: 574.3[M+H]+; Anal. Calcd. for $C_{40}H_{39}N_3O_2$.

4'-{17-[-(Isobutyric)-hydrazide]-3-yloxymethyl-1,3,5(10)-estratriene}-biphenyl-2-carbonitrile (5e): Off white solid, 0.67 g, Yield 75%; m.p. >200°C; IR (KBr, νmax, cm^{-1}): 1244, 1491,1609(C=N), 1664(C=O), 2222(C≡N), 2939, 3061, 3170; 1H NMR (200 MHz $CDCl_3$, δ, ppm): 0.99(s,3H,-CH_3), 1.19(d,6H J=6.9,-CH_3), 5.13(s,2H,-OCH_2-), 6.55-7.95(m,11H,Ar-H); 13C NMR (50 MHz $CDCl_3$): 18.9, 25.4, 26.4, 27.4, 28.3, 29.5, 33.6, 38.7, 42.9, 43.6, 45.1, 52.4(-OCH_2), 69.7, 111.2, 112.3, 114.8, 118.6(C≡N), 126.6, 127.3, 127.5, 129.5, 130.1, 132.7, 132.8, 133.8, 135.6, 137.6, 138.1, 145.1, 157.7(C_3), 163.0(C=N), 170.0(C=O); M/S m/z : 546.34 [M+H]+; Anal. Calcd. for $C_{36}H_{39}N_3O_2$ [16].

4'-{17-[-(Benzoic)-hydrazide]-3-yloxymethyl-1,3,5(10)-estratriene}-biphenyl-2-carbonitrile (5f): Off white solid, 0.67 g, Yield 75%; m.p. 227°C-229°C; IR (KBr, νmax, cm^{-1}): 1249, 1498, 1607(C=N), 1663(C=O), 2224(C≡N), 2933, 3064, 3173; 1H NMR (200 MHz $CDCl_3$, δ, ppm): 1.04(s,3H,-CH_3), 5.14(s,2H,-OCH_2-), 6.55-7.95(m,16H,Ar-H); 13C NMR (50 MHz $CDCl_3$): 23.1(-CH_3), 25.5, 26.4, 27.2, 28.3, 29.4, 33.6, 38.7, 42.4, 44.3, 53.3(-OCH_2), 69.6, 111.2, 112.3, 114.8, 118.6(C≡N), 126.6, 127.4, 127.6, 128.3, 128.6, 132.5, 133.3, 135.6, 138.6, 145.1, 155.7(C_3), 159.9(C=N), 169.0(C=O) M/S m/z : 580.51[M+H]+; Anal. Calcd. for $C_{39}H_{37}N_3O_2$.

4'-{17-[-(Furan-2-carboxylic)-hydrazide]-3-yloxymethyl-1,3,5(10)-estratriene}-biphenyl-2-carbonitrile (5g): Off white solid, 0.55 g, Yield 65%; m.p. 178°-180°C; IR (KBr, νmax, cm-1):1246, 1496, 1608(C=N), 1666 (C=O), 2222(C≡N) , 2931, 3066, 3174; 1H NMR (200 MHz $CDCl_3$, δ, ppm): 1.0(s, 3H, -CH_3), 5.12(s,2H,-OCH_2-), 6.55-7.80(m,14H,Ar-H & Furan-H); 13C NMR (50 MHz $CDCl_3$): 23.2(-CH_3), 25.7, 25.9, 26.0, 26.5, 27.0, 27.3, 29.2, 29.6, 29.8, 30.2, 31.5, 35.9, 38.3, 38.6, 44.0, 48.0, 50.4, 51.3(-OCH_2), 69.4, 111.2, 111.6, 111.7, 111.9, 112.2, 112.3, 112.4, 113.0, 113.8, 114.4, 114.6, 114.7, 114.8, 116.4, 118.7(C≡N), 119.4, 119.5, 126.3, 126.4, 127.6, 127.7, 128.9, 130.0, 132.8, 133.8, 137.6, 137.9, 138.0, 144.9, 145.1, 145.3, 145.4, 145.5, 145.7, 146.3(C_3), 156.6(C=N), 156.7(C=O); M/S m/z: 571.22$[M+H]^+$; Anal. Calcd. for $C_{37}H_{35}N_3O_3$.

In vitro Antimalarial Screening

The *in vitro* antimalarial assay was carried out in 96 well microtitre plates according to the micro assay protocol of Rieckmann and co-workers with minor modifications. The cultures of *P. falciparum* strain were maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasites of *P. falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, an initial ring stage parasitemia of 0.8% to 1.5% at 3% haematocrit in a total volume of 200 µ l of medium RPMI-1640 was determined by Jaswant Singh Bhattacharya (JSB) staining to assess the percent parasitemia (rings) and uniformly maintained with 50% RBCs (O^+) [17].

A stock solution of 5 mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. The diluted samples in 20 µl volume were added to the test wells so as to obtain final concentrations (at fivefold dilutions) ranging between 0.4 µg/ml to 100 µg/ml in duplicate well containing parasitized cell preparation. The culture plates were incubated at 37°C in a candle jar. After 36 to 40 hours incubation, thin blood smears from each well were prepared and stained with JSB stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in presence of

different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentrations (MIC) [18-20].

Observation of the *in vitro* Anti-malarial Screening

The mean number of rings, trophozoites and schizonts recorded per 100 parasites from duplicate wells after incubation for 38 hours, and percent maturation inhibition with respect to control group [21-24] (Table 1).

Table: 1 Anti-malarial activity

MIC (Minimal Inhibition Concentration)		
Sr. No.	**Compound ID**	**Mean IC 50 Values a**
1	5	0.55 µg/ml
2	5a	1.12 µg/ml
3	5b	0.36 µg/ml
4	5d	0.48 µg/ml
5	5f	0.72 µg/ml
6	5g	0.63 µg/ml
STD	Chloroquine	0.020 µg/ml
	Quinine	0.268 µg/ml

Mean values in representative assay. All experiments were performed in duplicate.

RESULTS AND DISCUSSION

The hydrazide group present in the compound 4 is capable of carbohydrazide formation. Compound 4 is reacted with different acid chloride in presence of base such as triethyl amine in dichloromethane as solvent to give carbohydrazide derivatives (scheme-1) [25]. Eight compounds were successfully synthesized as per general procedure. Compound 5a was isolated as white solid, gave a [M+H]+ion peak at m/z 601.31 ESI-MS match with the molecular formula $C_{40}H_{45}N_3O_2$. On other hand compound 5 g, obtained as white solid, gave a [M+H]+ion peak at m/z 571.22 ESI-MS match with the molecular formula $C_{37}H_{35}N_3O_3$. The IR spectrum of steroidal carbohydrazide

recorded using KBr pellet, showed strong band at around 1666 cm-1 and 3470-3380 cm^{-1} region are due to carbonyl and NH of CONH group respectively [26]. 13C NMR spectra of compound 5a and 5d revealed the presence of $–OCH_2-$ (estrone-3-O-ether) at around δ 52, and two signals at δ 175-177 and δ161-165 corresponding to CO and C=N groups.

The test result showed that the IC50 value of compound 5, 5a, 5b, 5d, 5f and 5g as much as 0.55, 1.12, 0.36, 0.48, 0.72 and 0.63 µg/mL respectively. Chloroquine and Quinine were used as the reference drug with as much as 0.002 and 0.268 µg/mL IC50 (Table 1). Among the six compounds, compound 5b displayed equivalent antimalarial activity with a MIC of 0.36 µg/mL as compared to the reference drug Quinine (MIC 0.268 µg/mL). This may be due to the compound contain phenyl ring with propionyl substitution [27]. All other derivatives, 5, 5a, 5d, 5f and 5g exhibited moderate MIC values at 0.55 µg/mL-1.12 µg/mL. Furthermore, the synthesized compounds are considered as lacking the ability to fight against the chloroquine so it may not be promoted as an antimalarial agent.

CONCLUSION

Best of our knowledge Estronic carbohydrazide with biphenyl moiety has not yet been synthesized and its antimalarial, cytotoxic, and antitumor activities not studied. This result provides a new way for modification of Estronic steroidal derivatives for the development of new antimalarial agents.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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