https://doi.org/10.31925/farmacia.2022.1.5 **ORIGINAL ARTICLE**

SYNTHESIS OF 4-BENZYLSULFANYL AND 4-BENZYLSULFONYL CHALCONES. BIOLOGICAL EVALUATION AS ANTIMALARIAL AGENTS

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Abstract

Malaria management has been complicated in recent times, perhaps, by increasing the *Plasmodium* spp. resistance to the drugs of clinical use for its treatment. The study describes the synthesis of a new series of chalcones **7 - 40** and their antimalarial efficacy against a chloroquine-susceptible strain of *Plasmodium berghei*. Furthermore, we carried out hemin-dependent studies to unfold the mechanism of action of these synthesized hybrid molecules. Twenty compounds showed inhibitory activity on the formation of β-hematin higher than 75%, compared to chloroquine. The compounds **9**, **21**, **33** and **37** showed enhanced antimalarial activity *in vivo* and may reduce malaria progression in this model through a mechanism related to the inhibition of hemozoin formation. Critical aspects of the structure-activity relationship (SAR) are also discussed to better understand the effect shown by these compounds.

Rezumat

Controlul malariei a devenit o provocare în ultimii ani, în urma creșterii rezistenței paraziților malariei la medicamente. Studiul descrie sinteza unei noi serii de chalcone și eficacitatea lor terapeutică asupra unei tulpini de *Plasmodium berghei* sensibilă la clorochină. În plus, am efectuat studii hemin-dependente pentru a evidenția mecanismul de acțiune al acestor molecule hibride sintetizate. Douăzeci de compuși au prezentat activitate inhibitoare asupra formării de β-hematine, mai mare cu 75% comparativ cu clorochina. Compușii **9**, **21**, **33** și **37** au prezentat activitate antimalarică *in vivo* și pot inhiba progresia malariei printr-un mecanism de acțiune inhibitor asupra formării hemozoinei.

Keywords: antimalarial, chalcones, β-haematin, *Plasmodium berghei*

Introduction

Human malaria, a tropical, re-emerging infectious disease caused by several types of protozoan parasites of the genus *Plasmodium*, has been a primary concern to humanity for centuries and is now extended to more than 40% of the world's population. It is a disease primarily of the tropics but is also found in many temperate regions. The disease is responsible for 229 million cases resulting in 409000 deaths in 2019 [1]. Humans are affected by six species of the genus *Plasmodium*: *falciparum*, *vivax*, *ovale curtisi*, *ovale wallikeri*, *malariae*, and occasionally *knowlesi*. Of these, *P. falciparum* and *P. vivax* are the most aggressive species worldwide, often fatal to humans [2]. Several factors contribute to the increasing spread of malaria. Besides climatic and environmental factors, the *Anopheles* mosquito has become increasingly resistant to insecticides and has adapted to avoid insecticide-treated surfaces. The other cause for the re-emergence of malaria is the development of parasite resistance to antimalarial drugs, in particular, some of the commonly used synthetic quinolines such as chloroquine (CQ), antifolates. Resistance even to the artemisinin derivatives has been recently reported [3, 4].

Vaccine development has been an imperative for decades. Still, today it seems unlikely because of the extreme degree of antigenic variation exhibited by these parasites and the lack of resources for translational work and large vaccine trials. In October 2019, WHO announced the phase 3 trial results for malaria vaccine RTS,S/AS01 in Africa [5]. Therefore, chemotherapy remains the only treatment option for controlling infection once acquired, but none of the different chemotherapeutic strategies used in the past has proven consistently successful.

To overcome the drug resistance issue, extensive modification of existing antimalarial chemotypes and the search for novel targets (and new chemotypes interacting with them) have been undertaken and are currently being pursued. Thus, many interesting compounds have been selected for use in monotherapy or, even better, in combination chemotherapies able to improve efficacy and delay the onset of resistance [6-11].

Since the antimalarial activity of licochalcone A, a natural product isolated from Chinese liquorice roots, has been reported, several research groups around the world have isolated from natural sources and synthesized a wide variety of chalcone derivatives to study their chemotherapeutic activities and modify their pharmacokinetic properties [12-25].

Chalcone compounds have a common chemical scaffold of 1,3-diaryl-2-propen-1-one, that exists as *trans* and *cis* isomers, with the trans isomer being thermodynamically more stable (Figure 1) [26].

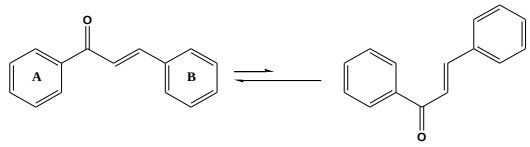


Figure 1.
Structures of chalcone *trans* and *cis* isomers

Reports indicate that the chalcones can exert the antimalarial activity through their action on several targets, namely: by inhibition of falciparum-2 [27-29], sorbitol-induced hemolysis [30], protein kinases (Pfmrk and PfPK5) [31], topoisomerase-II [32], β-hematin [18, 21, 33, 34], plasmepsin-II [35].

As part of our ongoing drug discovery program in developing potential antimalarial agents, we recently designed and synthesized a series of potent novel quinolinylbenzocycloalcanones, 2-(2´-Chloro-3´-quinolinylmethylidene)-5,7-dimethoxy-indanones, [(7-chloroquinolin-4-yl)amino]chalcones, chloro-vinyl sulfones, sulfonamide chalcones, and 7-chloro-quinolinyl-chalcones [18-21, 34, 36]. Inspired by these encouraging results, and because of their simple synthetic procedure, herein, we report, design and synthesis of 4-benzylsulfanyl and 4-benzylsulfonyl chalcone derivatives and their antimalarial evaluation *in vitro* and *in vivo* against a sensible strain of *P. berghei*.

Materials and Methods

Chemistry

General: The synthesis of intermediate (**4 - 6**) and target compounds (**7 - 40**) was performed as outlined in Figure 2.

All moisture and oxygen-sensitive reactions were carried out in flame-dried glassware under N_2. All solvents were dried and distilled under a nitrogen atmosphere. Evaporations were conducted under reduced pressure at temperatures less than 40°C unless otherwise noted. Thin-layer chromatography (TLC) was carried out on Merck silica F254 0.255-mm plates, and spots were visualized by UV fluorescence at 254 nm, using ethyl acetate: hexane (1:1 v/v) as eluent. At final compounds the impurities were removed by recrystallization. Melting points were measured in open capillary tubes in a Thomas Hoover™ apparatus and are uncorrected. IR spectra were determined as KBr pellets on a Shimadzu™ model 470 spectrophotometer and are expressed in cm^{-1}. NMR spectres were obtained using a JEOL Eclipse™ 270 MHz for ^{1}H-NMR and at 67.9 MHz for ^{13}C-NMR using $CDCl_3$ and are reported in parts *per* million (ppm) downfield from the residual $CHCl_3$ (δ 7.25 for ^{1}H-NMR and 77.0 for ^{13}C-NMR, respectively). Coupling constants (*J*) are expressed in Hz. Abbreviations for multiplicities and descriptors of signals in ^{1}H-NMR spectra are as follows: singlet (s), doublet (d), doublet doublets (dd), triplet (t) and multiplet (m). A Perkin Elmer™ 2400 CHN elemental analyser was used to obtain the elemental analyses, and the results were within ± 0.4% of the predicted values.

*General procedure for the synthesis of 4-(Benzylsulfanyl)benzaldehyde and 4-(Benzylsulfanyl)acetophenone **4, 5***

A mixture of Benzylmercaptan 1 (2.73 g, 22 mmol) and potassium hydroxide (1.23 g, 22 mmol) was dissolved in ethanol 95%. The resulting solution was heated to reflux until KOH had dissolved entirely and was cooled to room temperature. 4-Chlorobenzaldehyde 2 (2.81 g, 20 mmol) or 4-Chloroacetophenone 3 (3.09 g, 20 mmol) was dissolved in ethanol 95% was then added dropwise. The solution was heated to reflux for 24 hours. When cooled, a yellow solid precipitate formed, filtered and washed with ethanol 95% and water. The solid was dissolved in ether, washed with water and 1 N NaOH aqueous solution, dried with $MgSO_4$, and the solvent removed to yield a white solid; the solid was recrystallized from ethanol.

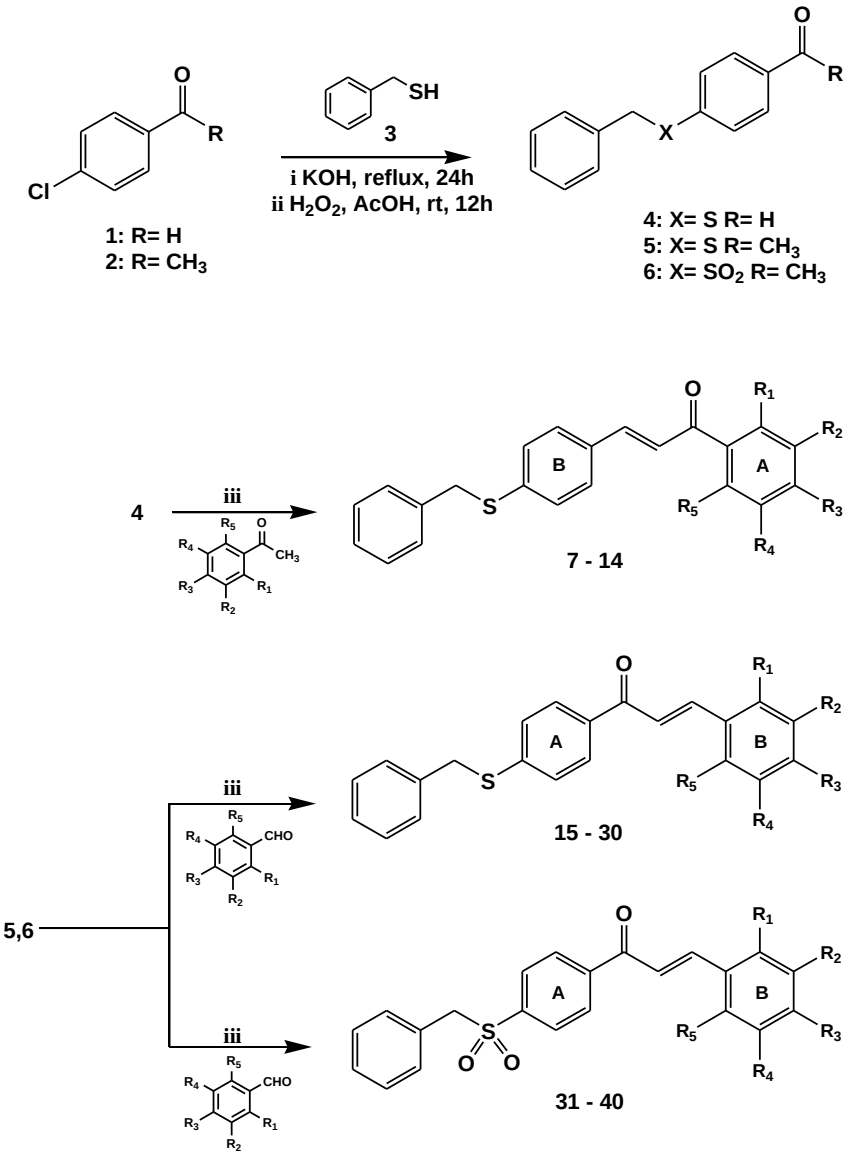
*4-(Benzylsulfanyl)benzaldehyde **4***

White amorphous powder. Yield: 60%; mp: 80 - 81°C [37]; IR KBr (cm^{-1}): 1696, 1581, 1555, 1552; ^{1}H-NMR ($CDCl_3$, 270 MHz) δppm: 4.23 (s, 2H, CH_2), 7.28 - 7.36 (m, 5H, Ar), 7.36 (d, 2H, $H_{3,5}$, J = 8.4 Hz), 7.73 (d, 2H, $H_{2,6}$, J = 8.4 Hz), 9.89 (s, 1H, CHO); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 37.1, 126.9, 127.7, 128.8, 130.1, 133.9, 136.2, 145.0, 191.3. Anal. Calcd for $C_{14}H_{12}OS$: % C 73.65, H 5.30. Found: % C 73.67, H 5.31.

*4-(Benzylsulfanyl)acetophenone **5***

White amorphous powder. Yield: 80%; mp: 110 - 112°C (110 - 112°C) [38]; IR KBr (cm^{-1}): 2935, 1689, 1570, 1370, 1344; ^{1}H-NMR ($CDCl_3$, 270 MHz) δppm: 2.54 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 7.26 - 7.38 (m, 5H, Ar), 7.33 (d, 2H, $H_{3,5}$, J = 8.6 Hz), 7.82 (d, 2H, $H_{2,6}$, J = 8.6 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 26.4, 37.4,

127.1, 127.6, 128.7, 128.8, 134.4, 136.4, 144.2, 197.1. % C 74.33, H 5.85.
Anal. Calcd for $C_{15}H_{14}OS$: % C 74.34, H 5.82. Found



No	R_1	R_2	R_3	R_4	R_5
7	H	H	H	H	H
8	NH_2	H	H	H	H
9	H	H	F	H	H
10	OCH_3	H	OCH_3	H	H
11	OCH_3	H	H	OCH_3	H
12	H	OCH_3	OCH_3	H	H
13	H	OCH_2O		H	H
14	OCH_3	OCH_3	OCH_3	H	H
15	CH_3	H	H	H	H
16	H	CH_3	H	H	H
17	H	H	CH_3	H	H
18	H	OCH_3	H	H	H
19	H	H	F	H	H
20	H	H	Cl	H	H
21	OCH_3	H	OCH_3	H	H
22	F	H	F	H	H
23	OCH_3	H	H	OCH_3	H

No	R_1	R_2	R_3	R_4	R_5
24	H	Cl	Cl	H	H
25	OCH_3	OCH_3	H	H	H
26	H	OCH_3	OCH_3	H	H
27	OCH_3	H	OCH_3	H	H
28	F	H	F	H	H
29	OCH_3	H	OCH_3	H	OCH_3
30	CH_3	H	CH_3	CH_3	H
31	CH_3	H	H	H	H
32	H	CH_3	H	H	H
33	H	H	CH_3	H	H
34	H	OCH_3	H	H	H
35	H	H	F	H	H
36	F	H	F	H	H
37	OCH_3	H	OCH_3	H	H
38	OCH_3	H	H	OCH_3	H
39	OCH_3	OCH_3	OCH_3	H	H
40	OCH_3	H	OCH_3	H	OCH_3

Figure 2.
Synthesis of 4-benzylsulfanyl chalcones **7 - 30** and 4-benzylsulfonyl chalcones **31 - 40**

*4-(Benzylsulfonyl)acetophenone **6***

1.94 g (8 mmol) of 4-(Benzylsulfanyl)acetophenone **5** was dissolved in 20 mL of acetic acid. To this solution was added 20 mL of 30% aqueous hydrogen peroxide dropwise while stirring. The reaction was stirring by 12 hours and a white precipitate had formed. The reaction mixture was poured into 20 mL of ice water, and then the solid was filtered and washed with cold water, the solid was recrystallized from ethanol to give a white powder. Yield: 70%; mp: 170 - 172°C; (170 - 172°C) [39]; IR KBr (cm^{-1}): 3069, 2982, 2930, 1690, 1320, 1292, 1140; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 2.62 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 7.06 (d, 2H, $H_{2',6'}$, J = 6.7 Hz), 7.27 - 7.34 (m, 3H, Ar), 7.69 (d, 2H, $H_{3,5}$, J = 6.9 Hz), 7.97 (d, 2H, $H_{2,6}$, J = 6.9 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 26.9, 62.9, 127.8, 128.6, 128.8, 129.0, 129.1, 130.9, 140.9, 141.8, 196.7. Anal. Calcd for $C_{15}H_{14}O_3S$: % C 65.67, H 5.14, S 11.69. Found % C 65.66, H 5.14, S 11.73.

*General procedure for the synthesis of 4-(benzylsulfanyl)chalcones and 4-(benzylsulfonyl)chalcones derivatives **7 - 40***

A mixture of 4-(Benzylsulfanyl)benzaldehyde **4**, or 4-(Benzylsulfanyl)acetophenone **5**, or 4-(benzylsulfonyl)acetophenone **6** (0.25 mmol) with the respective substituted acetophenones or benzaldehydes (0.25 mmol) and sodium hydroxide (0.1 mmol) in ethanol 95% (5 mL) was stirred at room temperature by 12 h. The resulting precipitate was collected by filtration, washed with cold water, sodium bi-sulphite 10% aqueous solution and diethyl ether, and re-crystallized from ethanol-water (9:1).

*(2E)-3-[4-(Benzylsulfanyl)phenyl]-1-phenylprop-2-en-1-one **7***

Yellow powder. Yield: 51%; mp: 102 - 104°C; IR KBr (cm^{-1}): 1680, 1550, 1400, 1331, 1305; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 4.18 (s, 2H, CH_2), 7.22 - 7.40 (m, 10H, Ar), 7.52 (d, 2H, $H_{3,5}$, J = 8.4 Hz), 7.56 (d, 1H, H_β, J = 15.8 Hz), 7.74 (d, 1H, H_α, J = 15.8 Hz), 7.99 (d, 2H, $H_{2,6}$, J = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 38.1, 121.7, 127.5, 128.2, 128.5, 128.6, 128.8, 130.4, 132.5, 132.7, 133.1, 137.1, 138.4, 140.5, 144.1, 190.4. Anal. Calcd for $C_{22}H_{18}OS$: % C 79.96, H 5.49, S 9.70 Found % C 79.97, H 5.51, S 9.79.

*(2E)-1-(2-Aminophenyl)-3-[4-(benzylsulfanyl)-phenyl]prop-2-en-1-one **8***

Yellow powder. Yield: 48%; mp: 105 - 107°C; IR KBr (cm^{-1}): 3472, 1642, 1613, 1578, 1533, 1491, 1331; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 4.17 (s, 2H, CH_2), 6.69 (m, 2H, Ar), 7.22 - 7.34 (m, 8H, Ar, NH_2), 7.49 (d, 2H, $H_{2,6}$, J = 8.4 Hz), 7.52 (d, 1H, H_β, J = 15.6 Hz), 7.67 (d, 1H, H_α, J = 15.6 Hz), 7.82 (dd, 1H, $H_{6'}$, J = 8.4, 1.5 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 38.3, 116.0, 117.4, 119.3, 122.8, 127.4, 128.7, 128.8, 128.9, 131.0, 133.1, 134.3, 137.0, 139.8, 142.3, 151.0, 191.6. Anal. Calcd for $C_{22}H_{19}NOS$: % C 76.49, H 5.54, N 4.05, S 9.28. Found C 76.50, H 5.56, N 4.22, S 9.35.

*(2E)-3-[4-(Benzylsulfanyl)phenyl]-1-(4-fluorophenyl)-prop-2-en-1-one **9***

Yellow amorphous powder. Yield: 72%; mp: 116 - 118°C; IR KBr (cm^{-1}): 1661, 1600, 1581, 1549, 1488, 1405, 1334; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 4.18 (s, 2H, CH_2), 7.16 (t, 2H, $H_{3',5'}$, J = 8.6 Hz), 7.25 - 7.36 (m, 7H, Ar), 7.43 (d, 1H, H_β, J = 15.6 Hz), 7.51 (d, 2H, $H_{2,6}$, J = 8.4 Hz), 7.74 (d, 1H, H_α, J = 15.6 Hz), 8.03 (dd, 2H, $H_{2',6'}$, J = 8.6; 6.9 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 38.1, 115.6, 115.9, 121.1, 127.5, 128.6, 128.7, 128.8, 131.0, 131.1, 132.4, 134.7, 136.8, 140.7, 144.3, 188.7. Anal. Calcd for $C_{22}H_{17}FOS$: % C 75.84, H 4.92, S 9.20. Found % C 75.81, H 4.92, S 9.33.

*(2E)-3-[4-(Benzylsulfanyl)phenyl]-1-(2,4-di-methoxyphenyl)prop-2-en-1-one **10***

Yellow powder. Yield: 70%; mp: 138 - 140°C; IR KBr (cm^{-1}): 1645, 1610, 1574, 1488, 1418, 1325; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2), 6.48 (d, 1H, H_3, J = 2.2 Hz), 6.55 (dd, 1H, $H_{5'}$, J = 8.7, 2.2 Hz), 7.24 - 7.31 (m, 7H, Ar), 7.39 (d, 1H, H_β, J = 15.8 Hz), 7.46 (d, 2H, $H_{2,6}$, J = 9.1 Hz), 7.61 (d, 1H, H_α, J = 15.8 Hz), 7.74 (d, 1H, $H_{6'}$, J = 8.6 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 38.3, 55.5, 55.9, 98.8, 105.4, 126.9, 127.4, 128.6, 128.7, 128.8, 132.9, 133.3, 137.0, 139.5, 141.3, 160.5, 164.3, 190.4. Anal. Calcd for $C_{24}H_{22}O_3S$: % C 73.82, H 5.68, S 8.21. Found % C 73.84, H 5.69, S 8.30.

*(2E)-3-[4-(Benzylsulfanyl)phenyl]-1-(2,5-di-methoxyphenyl)prop-2-en-1-one **11***

Yellow powder. Yield: 80%; mp: 111 - 113°C; IR KBr (cm^{-1}): 1654, 1581, 1491, 1424, 1325; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.17 (s, 2H, CH_2), 6.92 (d, 1H, $H_{3'}$, J = 8.9 Hz), 7.02 (dd, 1H, $H_{4'}$, J = 8.9; 2.9 Hz), 7.16 (d, 1H, $H_{6'}$, J = 2.9 Hz), 7.23 - 7.30 (m, 7H, Ar), 7.35 (d, 1H, H_β, J = 15.8 Hz), 7.46 (d, 2H, $H_{2,6}$, J = 8.2 Hz), 7.57 (d, 1H, H_α, J = 15.8 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 38.2, 55.9, 56.7, 113.7, 114.6, 119.2, 126.6, 127.4, 128.6, 128.7, 128.8, 129.9, 132.9, 136.9, 140.0, 142.5, 152.7, 153.8, 192.2. Anal. Calcd for $C_{24}H_{22}O_3S$: % C 73.82, H 5.68, S 8.21. Found % C 73,79, H 5.67, S 8.26.

*(2E)-3-[4-(Benzylsulfanyl)phenyl]-1-(3,4-di-methoxyphenyl)prop-2-en-1-one **12***

Yellow powder. Yield: 55%; mp: 136 - 138°C; IR KBr (cm^{-1}): 1648, 1581, 1418; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.95 (s, 6H, 2 x OCH_3), 4.17 (s, 2H, CH_2), 6.91 (d, 1H, $H_{5'}$, J = 8.4 Hz), 7.24 - 7.35 (m, 7H, Ar), 7.49 (d, 1H, H_β, J = 15.6 Hz), 7.51 (d, 2H, $H_{2,6}$, J = 8.2 Hz), 7.60 (d, 1H, $H_{2'}$, J = 1.9 Hz), 7.66 (dd, 1H, $H_{6'}$, J = 8.4, 1.9 Hz), 7.74 (d, 1H, H_α, J = 15.6 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 38.2, 56.1,

110.2, 111.1, 121.3, 123.0, 127.4, 128.6, 128.7, 128.8, 131.5, 132.8, 136.9, 140.2, 143.2, 149.4, 153.4, 188.5. Anal. Calcd for $C_{24}H_{22}O_3S$: % C 73.82, H 5.68, S 8.21. Found % C 73,80, H 5.71, S 8.29.

(2E)-1-(2H-1,3-Benzodioxol-5-yl)-3-[4-(benzylsulfanyl)phenyl]prop-2-en-1-one ***13***

Yellow powder. Yield: 61%; mp: 126 - 128°C; IR KBr (cm^{-1}): 1648, 1581, 1488, 1443, 1328; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 4.17 (s, 2H, CH_2), 6.05 (s, 2H, CH_2), 6.88 (d, 1H, $H_{5'}$, J = 8.2 Hz), 7.24 - 7.36 (m, 7H, Ar), 7.42 (d, 1H, H_β, J = 15.6 Hz), 7.48 - 7.51 (m, 3H, Ar, H_β), 7.62 (dd, 1H, $H_{6'}$, J = 8.2; 1.8 Hz), 7.72 (d, 1H, H_α, J = 15.6 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 38.2, 101.9, 107.9, 108.5, 121.4, 124.6, 127.4, 128.7, 128.8, 132.7, 133.2, 136.9, 140.2, 143.5, 148.4, 151.7, 188.2. Anal. Calcd for $C_{23}H_{18}O_3S$: % C 73.77, H 4.85, S 8.56. Found % C 73.77, H 4.83, S 8.72.

(2E)-3-[4-(Benzylsulfanyl)phenyl]-1-(2,3,4-trimethoxyphenyl)prop-2-en-1-one ***14***

Yellow powder. Yield: 48%; mp: 131 - 133°C; IR KBr (cm^{-1}): 1660, 1580, 1488, 1400, 1312; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.17 (s, 2H, CH_2), 6.74 (d, 1H, $H_{5'}$, J = 8.6 Hz), 7.24 - 7.31 (m, 9H, Ar), 7.37 (d, 1H, H_β, J = 15.7 Hz), 7.47 (d, 1H, $H_{6'}$, J = 8.2 Hz), 7.61 (d, 1H, H_α, J = 15.8 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 38.2, 56.2, 61.1, 62.1, 107.5, 125.7, 126.3, 127.0, 127.4, 128.6, 128.7, 128.8, 133.0, 136.9, 139.9, 142.3, 142.4, 153.8, 157.1, 190.7. Anal. Calcd for $C_{25}H_{24}O_4S$: % C 71.40, H 5.75, S 7.63. Found % C 71.45, H 5.79, S 7.59.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(2-methylphenyl)prop-2-en-1-one ***15***

Yellow powder. Yield: 67%; mp: 108 - 110°C; IR KBr (cm^{-1}): 1654, 1590, 1398, 1334, 1315; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 2.46 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 7.23 - 7.36 (m, 9H, Ar), 7.41 (d, 1H, H_β, J = 15.6 Hz), 7.67 (d, 2H, $H_{2'',6''}$, J = 7.4 Hz), 7.91 (d, 2H, $H_{2,6}$, J = 6.7 Hz), 8.09 (d, 1H, H_α, J = 15.6 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 19.8, 37.5, 122.9, 126.4, 126.5, 127.4, 127.5, 128.7, 128.8, 129.0, 130.2, 131.0, 134.0, 135.4, 136.5, 138.4, 142.4, 143.9, 189.3. Anal. Calcd for $C_{23}H_{20}OS$: % C 80.19, H 5.85, S 9.31. Found % C 80.23, H 5.84, S 9.42.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(3-methylphenyl)prop-2-en-1-one ***16***

Yellow powder. Yield: 77%; mp: 98 - 100°C; IR KBr (cm^{-1}): 1654, 1594, 1318; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 2.39 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 7.19 - 7.44 (m, 11H, Ar), 7.47 (d, 1H, H_β, J = 15.8 Hz), 7.77 (d, 1H, H_α, J = 15.6 Hz), 7.91 (d, 2H, $H_{2,6}$, J = 8.7 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 21.3, 37.5, 121.7, 125.7, 127.4, 127.5, 128.7, 128.8, 128.9, 129.0, 129.1, 131.4, 135.0, 135.5, 136.5, 138.7, 143.9, 144.9, 189.3. Anal. Calcd for $C_{23}H_{20}OS$: % C 80.19, H 5.85, S 9.31. Found % C 80.20, H 5.86, S 9.38.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(4-methylphenyl)prop-2-en-1-one ***17***

Yellow powder. Yield: 83%; mp: 100 - 102°C; IR KBr (cm^{-1}): 1648, 1594, 1507, 1398, 1331; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 2.38 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 7.21 (d, 2H, $H_{3',5'}$, J = 7.9 Hz), 7.27 - 7.38 (m, 7H, Ar), 7.45 (d, 1H, H_β, J = 15.8 Hz), 7.52 (d, 2H, $H_{2',6'}$, J = 8.1 Hz), 7.78 (d, 1H, H_α, J = 15.6 Hz), 7.91 (d, 2H, $H_{2,6}$, J = 8.2 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 21.5, 37.6, 120.9, 127.4, 127.5, 128.5, 128.7, 128.8, 128.9, 129.7, 132.3, 135.6, 136.5, 141.0, 143.7, 144.7, 189.4. Anal. Calcd for $C_{23}H_{20}OS$: % C 80.19, H 5.85, S 9.31. Found % C 80.19, H 5.84, S 9.33.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(3-methoxyphenyl)prop-2-en-1-one ***18***

Yellow powder. Yield: 52%; mp: 120 - 122°C; IR KBr (cm^{-1}): 1654, 1597, 1488, 1312; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.84 (s, 3H, OCH_3), 4.22 (s, 2H, CH_2), 6.95 (dd, 1H, $H_{6'}$, J = 8.2; 2.5 Hz), 7.13 (s, 1H, $H_{2'}$), 7.22 - 7.38 (m, 9H, Ar), 7.46 (d, 1H, H_β, J = 15.6 Hz), 7.75 (d, 1H, H_α, J = 15.6 Hz), 7.90 (d, 2H, $H_{2,6}$, J = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 37.5, 55.4, 113.6, 116.3, 121.1, 122.3, 127.4, 127.6, 128.7, 128.8, 129.0, 129.9, 135.4, 136.4, 143.9, 144.6, 160.1, 189.3. Anal. Calcd for $C_{23}H_{20}O_2S$: % C 76.64, H 5.59, S 8.90. Found % C 76.67, H 5.60, S 9.05.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(4-fluorophenyl)prop-2-en-1-one ***19***

Yellow powder. Yield: 67%; mp: 147 - 149°C; IR KBr (cm^{-1}): 1654, 1590, 1507, 1427, 1336; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 4.22 (s, 2H, CH_2), 7.09 (t, 2H, $H_{3',5'}$, J = 8.6 Hz), 7.27 - 7.35 (m, 7H, Ar), 7.41 (d, 1H, H_β, J = 15.3 Hz), 7.61 (dd, 2H, $H_{2',6'}$, J = 8.6, 5.4 Hz), 7.75 (d, 1H, H_α, J = 15.6 Hz), 7.89 (d, 2H, $H_{2,6}$, J = 8.6 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 37.5, 116.0, 116.3, 121.6, 127.3, 127.6, 128.7, 128.8, 128.9, 130.2, 130.4, 131.3, 131.4, 135.3, 136.4, 143.3, 144.0, 189.1. Anal. Calcd for $C_{22}H_{17}FOS$: % C 75.84, H 4.92, S 9.20. Found % C 75.85, H 4.95, S 9.27.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(4-chlorophenyl)prop-2-en-1-one ***20***

Yellow powder. Yield: 90%; mp: 172 - 174°C; IR KBr (cm^{-1}): 1654, 1587, 1488, 1405, 1334, 1318; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 4.22 (s, 2H, CH_2), 7.28 - 7.39 (m, 9H, Ar), 7.46 (d, 1H, H_β, J = 15.8 Hz), 7.55 (d, 2H, $H_{2',6'}$, J = 8.4 Hz), 7.74 (d, 1H, H_α, J = 15.8 Hz), 7.90 (d, 2H, $H_{2,6}$, J = 8.7 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 37.5, 122.4, 127.3, 127.6, 128.7, 128.8, 128.9, 129.3, 129.6, 133.6, 135.2, 136.4, 136.5, 143.1, 144.2, 188.9. Anal. Calcd for $C_{22}H_{17}ClOS$: % C 72.42, H 4.70, S 8.79. Found % C 72.47, H 4.73, S 8.91.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(2,4-dimethoxyphenyl)prop-2-en-1-one ***21***

Yellow powder. Yield: 41%; mp: 98 - 100°C; IR KBr (cm^{-1}): 1648, 1590, 1501, 1453, 1341; ^{1}H-NMR

($CDCl_3$, 270 MHz) δ ppm: 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.21 (s, 2H, CH_2), 6.46 (d, 1H, $H_{3'}$, J = 2.2 Hz), 6.52 (dd, 1H, $H_{5'}$, J = 8.4, 2.2 Hz), 7.27 - 7.37 (m, 7H, Ar), 7.49 (d, 1H, H_β, J = 15.8 Hz), 7.55 (d, 1H, $H_{6'}$, J = 8.4 Hz), 7.89 (d, 2H, $H_{2,6}$, J = 8.4 Hz), 8.02 (d, 1H, H_α, J = 15.8 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 38.3, 55.6, 98.7, 105.5, 117.4, 120.3, 127.5, 128.7, 128.8, 128.9, 130.8, 136.7, 140.5, 143.0, 150.0, 160.5, 163.2, 188.3. Anal. Calcd for $C_{24}H_{22}O_3S$: % C 73.82, H 5.68, S 8.21. Found % C 73.89, H 5.67, S 8.30.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(2,4-difluorophenyl)prop-2-en-1-one ***22***

Yellow powder. Yield: 48%; mp: 105 - 107°C; IR KBr (cm^{-1}): 1654, 1587, 1498, 1430, 1334; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 4.23 (s, 2H, CH_2), 6.84 - 6.97 (m, 3H, Ar), 7.27 - 7.39 (m, 7H, Ar), 7.54 (d, 1H, H_β, J = 15.8 Hz), 7.82 (d, 1H, H_α, J = 15.8 Hz), 7.91 (d, 2H, $H_{2,6}$, J = 6.9 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 37.4, 104.3, 104.8, 112.0, 112.3, 123.9, 127.3, 127.6, 128.7, 128.8, 129.0, 131.0, 135.1, 136.3, 136.4, 144.2, 189.0. Anal. Calcd for $C_{22}H_{16}F_2OS$: % C 72.11, H 4.40, S 8.75. Found % C 72.15, H 4.43, S 8.83.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(2,5-dimethoxyphenyl)prop-2-en-1-one ***23***

Yellow powder. Yield: 78%; mp: 118 - 120°C; IR KBr (cm^{-1}): 1654, 1600, 1584, 1539, 1494, 1456, 1392; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.22 (s, 2H, CH_2), 6.86 (d, 1H, $H_{3'}$, J = 8.9 Hz), 6.93 (dd, 1H, $H_{4'}$, J = 8.9; 2.9 Hz), 7.14 (d, 1H, $H_{6'}$, J = 2.9 Hz), 7.27 - 7.37 (m, 7H, Ar), 7.53 (d, 1H, H_β, J = 15.8 Hz), 7.89 (d, 2H, $H_{2,6}$, J = 8.6 Hz), 8.05 (d, 1H, H_α, J = 15.8 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 37.6, 55.9, 56.3, 112.7, 114.0, 117.3, 123.1, 124.8, 127.4, 127.5, 128.7, 128.8, 129.0, 135.7, 136.5, 140.0, 143.5, 153.5, 153.7, 189.9. Anal. Calcd for $C_{24}H_{22}O_3S$: % C 73.82, H 5.68, S 8.21. Found % C 73.86, H 5.73, S 8.33.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(3,4-dichlorophenyl)prop-2-en-1-one ***24***

Yellow powder. Yield: 65%; mp: 154 - 156°C; IR KBr (cm^{-1}): 1654, 1600, 1581, 1552, 1469, 1398, 1331; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 4.23 (s, 2H, CH_2), 7.25 - 7.41 (m, 10H, Ar), 7.46 (d, 1H, H_β, J = 15.6 Hz), 7.67 (d, 1H, H_α, J = 15.6 Hz), 7.90 (d, 2H, $H_{2,6}$, J = 8.7 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 37.4, 123.4, 127.2, 127.5, 127.6, 128.7, 129.0, 129.7, 131.0, 133.4, 134.4, 134.9, 135.1, 136.3, 141.7, 144.5, 188.6. Anal. Calcd for $C_{22}H_{16}Cl_2OS$: % C 66.17, H 4.04, S 8.03. Found % C 66.14, H 3.98, S 8.17.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(2,3-dimethoxyphenyl)prop-2-en-1-one ***25***

Yellow powder. Yield: 72%; mp: 161 - 163°C; IR KBr (cm^{-1}): 1654, 1594, 1472, 1398, 1338; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.22 (s, 2H, CH_2), 6.95 (dd, 1H, $H_{4'}$, J = 8.2; 1.5 Hz), 7.08 (t, 1H, $H_{5'}$, J = 7.9 Hz), 7.23 - 7.36 (m, 8H, Ar), 7.55 (d, 1H, H_β, J = 15.5 Hz), 7.91 (d, 2H, $H_{2,6}$, J = 8.4 Hz), 8.07 (d, 1H, H_α, J = 15.6 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 37.6, 56.0, 61.3, 114.4, 119.9, 123.6, 124.2, 127.4, 127.5, 128.7, 128.8, 129.0, 129.3, 135.5, 136.5, 139.6, 143.7, 149.1, 153.3, 189.7. Anal. Calcd for $C_{24}H_{22}O_3S$: % C 73.82, H 5.68, S 8.21. Found % C 73.80, H 5.68, S 8.29.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(3,4-dimethoxyphenyl)prop-2-en-1-one ***26***

Yellow powder. Yield: 66%; mp: 158 - 160°C; IR KBr (cm^{-1}): 1669, 1580, 1441, 1400, 1380, 1132; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.22 (s, 2H, CH_2), 6.88 (d, 1H, $H_{5'}$, J = 8.6 Hz), 7.13 (d, 1H, $H_{2'}$, J = 1.9 Hz), 7.21 (dd, 1H, $H_{6'}$, J = 8.6, 2.0 Hz), 7.27 - 7.37 (m, 8H, Ar), 7.74 (d, 1H, H_α, J = 15.6 Hz), 7.90 (d, 2H, $H_{2,6}$, J = 8.7 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 37.1, 56.0, 56.1, 112.8, 114.5, 120.5, 123.8, 127.4, 127.5, 128.7, 128.8, 129.0, 129.3, 135.5, 136.5, 140.6, 143.7, 149.7, 151.6, 188.9. Anal. Calcd for $C_{24}H_{22}O_3S$: % C 73.82, H 5.68, S 8.21. Found % C 73.82, H 5.70, S 8.25.

(2E)-1-[4-Benzylsulfanyl)phenyl]-3-(3,5-dimethoxyphenyl)prop-2-en-1-one ***27***

Yellow powder. Yield: 85%; mp: 114 - 116°C; IR KBr (cm^{-1}): 1661, 1590, 1453, 1421; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.82 (s, 6H, 2 x OCH_3), 4.22 (s, 2H, CH_2), 6.51 (d, 1H, $H_{4'}$, J = 2.2 Hz), 6.75 (d, 2H, $H_{2',6'}$, J = 2.2 Hz), 7.25 - 7.38 (m, 7H, Ar), 7.42 (d, 1H, H_β, J = 15.6 Hz), 7.69 (d, 1H, H_α, J = 15.6 Hz), 7.89 (d, 2H, $H_{2,6}$, J = 8.6 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 37.5, 55.5, 102.9, 106.5, 122.5, 127.4, 127.5, 128.7, 128.8, 129.0, 135.4, 136.5, 137.0, 144.0, 144.7, 161.2, 189.2. Anal. Calcd for $C_{24}H_{22}O_3S$: % C 73.82, H 5.68, S 8.21. Found % C 73.81, H 5.73, S 8.32.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one ***28***

Yellow powder. Yield: 42%; mp: 130 - 132°C; IR KBr (cm^{-1}): 1648, 1594, 1491, 1459, 1405, 1331; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.21 (s, 2H, CH_2), 6.74 (d, 1H, $H_{5'}$, J = 8.6 Hz), 7.26 - 7.32 (m, 7H, Ar), 7.43 (d, 1H, H_β, J = 15.6 Hz), 7.46 - 7.49 (m, 3H, Ar), 7.61 (d, 1H, H_α, J = 15.6 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 38.2, 56.2, 61.1, 62.1, 107.5, 125.7, 126.3, 127.0, 127.4, 128.6, 128.7, 128.8, 132.9, 136.9, 139.9, 142.3, 142.4, 153.8, 157.1, 190.7. Anal. Calcd for $C_{25}H_{24}O_4S$: % C 71.40, H 5.75, S 7.63. Found % C 71.44, H 5.79, S 7.70.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(2,4,6-trimethoxyphenyl)prop-2-en-1-one ***29***

Yellow powder. Yield: 35%; mp: 136 - 138°C; IR KBr (cm^{-1}): 1645, 1590, 1562, 1466, 1453, 1331; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.84 (s, 3H, OCH_3), 3.89 (s, 6H, 2 x OCH_3), 4.20 (s, 2H, CH_2), 6.12 (s, 2H, $H_{3',5'}$), 7.26 - 7.37 (m, 7H, Ar), 7.83 (d, 1H, H_β,

J = 16.0 Hz), 7.89 (d, 2H, $H_{2,6}$, *J* = 8.4 Hz), 8.23 (d, 1H, H_α, *J* = 15.8 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 37.8, 55.4, 55.9, 90.8, 106.9, 122.0, 127.4, 127.5, 128.7, 128.8, 128.9, 135.9, 136.8, 142.5, 161.8, 163.2, 191.0. Anal. Calcd for $C_{25}H_{24}O_4S$: % C 71.40, H 5.75, S 7.63. Found % C 71.39, H 5.75, S 7.67.

(2E)-1-[4-(Benzylsulfanyl)phenyl]-3-(2,4,5-trimethylphenyl)prop-2-en-1-one ***30***

Yellow powder. Yield: 60%; mp: 159 - 161°C; IR KBr (cm^{-1}): 1654, 1594, 1491, 1341, 1315; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 2.25 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 6.99 (s, 1H, $H_{3'}$), 7.27 - 7.36 (m, 7H, Ar), 7.42 (s, 1H, $H_{6'}$), 7.46 (d, 1H, H_β, *J* = 15.3 Hz), 7.92 (d, 2H, $H_{2,6}$, *J* = 8.4 Hz), 8.07 (d, 1H, H_α, *J* = 15.3 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 19.2, 19.3, 19.6, 37.6, 121.6, 127.4, 127.5, 128.7, 128.8, 128.9, 131.4, 132.4, 134.5, 135.7, 136.0, 136.5, 139.5, 142.5, 143.6, 188.9. Anal. Calcd for $C_{25}H_{24}OS$: % C 80.60, H 6.49, S 8.61. Found % C 80.59, H 6.50, S 8.75.

(2E)-1-[4-(Benzylsulfonyl)phenyl]-3-(2-methylphenyl)prop-2-en-1-one ***31***

Yellow powder. Yield: 38%; mp: 140 - 142°C; IR KBr (cm^{-1}): 1680, 1580, 1391 1310; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 2.46 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 7.08 (t, 2H, $H_{5'}$, *J* = 6.7 Hz), 7.23 - 7.32 (m, 8H, Ar), 7.36 (d, 1H, H_β, *J* = 15.6 Hz), 7.71 (t, 1H, $H_{4'}$, *J* = 8.6 Hz), 8.02 (d, 2H, $H_{2,6}$, *J* = 8.6 Hz), 8.12 (d, 1H, H_α, *J* = 15.6 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 19.9, 62.9, 123.2, 125.9, 126.8, 127.5, 127.7, 128.7, 128.8, 128.9, 130.0, 131.0, 134.2, 135.7, 136.5, 138.2, 142.8, 145.9, 190.6. Anal. Calcd for $C_{23}H_{20}O_3S$: % C 73.38, H 5.35, S 8.52. Found % C 73.40, H 5.38, S 8.67.

(2E)-1-[4-(Benzylsulfonyl)phenyl]-3-(3-methylphenyl)prop-2-en-1-one ***32***

Yellow powder. Yield: 70%; mp: 170 - 172°C; IR KBr (cm^{-1}): 1678, 1580, 1510, 1390, 1330: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 2.39 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 7.07 (t, 1H, $H_{5'}$, *J* = 6.4 Hz), 7.34 - 7.34 (m, 8H, Ar), 7.42 (d, 1H, H_β, *J* = 15.6 Hz), 7.80 (d, 1H, H_α, *J* = 15.6 Hz), 8.01 (d, 2H, $H_{3,5}$, *J* = 8.7 Hz), 7.97 (d, 2H, $H_{2,6}$, *J* = 8.7 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 21.3, 62.9, 123.2, 127.4, 127.5, 128.1, 128.7, 128.8, 128.9, 129.0, 129.1, 131.4, 137.0, 138.8, 143.9, 144.9, 146.3, 189.3. Anal. Calcd for $C_{23}H_{20}O_3S$: % C 73.38, H 5.35, S 8.52. Found % C 73.43, H 5.32, S 8.61.

(2E)-1-[4-(Benzylsulfonyl)phenyl]-3-(4-methylphenyl)prop-2-en-1-one ***33***

Yellow powder. Yield: 82%; mp: 202 - 204°C; IR KBr (cm^{-1}): 1669, 1650, 1577, 1331, 1312; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 2.39 (s, 3H, CH_3), 4.34 (s, 2H, CH_2), 7.08 (d, 2H, $H_{3',5'}$, *J* = 6.7 Hz), 7.21 - 7.29 (m, 5H, Ar), 7.38 (d, 1H, H_β, *J* = 15.8 Hz), 7.52 (d, 2H, $H_{2',6'}$, *J* = 8.1 Hz), 7.72 (d, 2H, $H_{3,5}$, *J* = 8.2 Hz), 7.77 (d, 1H, H_α, *J* = 15.8 Hz), 7.99 (d, 2H, $H_{2,6}$, *J* = 8.2 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 21.5, 63.1, 120.1, 125.6, 127.3, 128.1, 128.8, 128.8, 128.9, 129.9, 133.0, 135.1, 136.1, 141.0, 145.4, 144.7, 190.2. Anal. Calcd for $C_{23}H_{20}O_3S$: % C 73.38, H 5.35, S 8.52. Found % C 73.39, H 5.35, S 8.56.

(2E)-1-[4-(Benzylsulfonyl)phenyl]-3-(3-methoxyphenyl)prop-2-en-1-one ***34***

Yellow powder. Yield: 75%; mp: 185 - 187°C; IR KBr (cm^{-1}): 1654, 1597, 1558, 1488, 1405, 1312; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.84 (s, 3H, OCH_3), 4.32 (s, 2H, CH_2), 6.98 (dd, 1H, $H_{6'}$, *J* = 8.4, 2.2 Hz), 7.11 (d, 1H, $H_{2'}$, *J* = 2.2 Hz), 7.21 - 7.31 (m, 7H, Ar), 7.39 (d, 1H, H_β, *J* = 15.6 Hz), 7.55 (d, 1H, H_α, *J* = 15.6 Hz), 7.72 (d, 2H, $H_{3,5}$, *J* = 8.4 Hz), 8.01 (d, 2H, $H_{2,6}$, *J* = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 56.0, 61.5, 113.0, 116.0, 122.1, 122.7, 127.5, 127.6, 128.6, 128.8, 128.9, 130.0, 135.9, 137.2, 140.9, 143.1, 159.9, 190.1. Anal. Calcd for $C_{23}H_{20}O_4S$: % C 70.39, H 5.14, S 8.17. Found % C 70.37, H 5.18, S 8.25.

(2E)-1-[4-(benzylsulfonyl)phenyl]-3-(4-fluorophenyl)prop-2-en-1-one ***35***

Yellow powder. Yield: 52%; mp: 192 - 194°C; IR KBr (cm^{-1}): 1654, 1597, 1581, 1453, 1414, 1309; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 4.34 (s, 2H, CH_2), 7.11 (t, 2H, $H_{3',5'}$, *J* = 8.6 Hz), 7.22 - 7.29 (m, 5H, Ar), 7.35 (d, 1H, H_β, *J* = 15.8 Hz), 7.63 (dd, 2H, $H_{2',6'}$, *J* = 8.6, 5.4 Hz), 7.73 (d, 2H, $H_{3,5}$, *J* = 8.6 Hz), 7.77 (d, 1H, H_α, *J* = 15.6 Hz), 8.00 (d, 2H, $H_{2,6}$, *J* = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 62.9, 116.2, 116.5, 121.3, 127.8, 128.7, 128.8, 129.0, 129.1, 130.6, 130.7, 130.9, 141.4, 142.3, 145.2, 189.1. Anal. Calcd for $C_{22}H_{17}FO_3S$: % C 69.46, H 4.50, S 8.43. Found % C 69.45, H 4.48, S 8.50.

(2E)-1-[4-(Benzylsulfonyl)phenyl]-3-(2,4-difluorophenyl)prop-2-en-1-one ***36***

Yellow powder. Yield: 47%; mp: 205 - 207°C; IR KBr (cm^{-1}): 1658, 1603, 1584, 1501, 1430, 1398, 1312; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 4.35 (s, 2H, CH_2), 6.84 - 6.97 (m, 3H, Ar), 7.27 - 7.39 (m, 5H, Ar), 7.48 (d, 1H, H_β, *J* = 15.8 Hz), 7.86 (d, 1H, H_α, *J* = 15.8 Hz), 7.91 (d, 2H, $H_{3,5}$, *J* = 8.4 Hz), 7.99 (d, 2H, $H_{2,6}$, *J* = 6.9 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 62.9, 104.6, 105.0, 112.2, 112.7, 119.1, 123.7, 127.8, 128.8, 129.0, 129.1, 130.8, 131.1, 131.3, 131.4, 138.2, 141.5, 142.1, 189.3. Anal. Calcd for $C_{22}H_{16}F_2O_3S$: % C 66.32, H 4.05, S 8.05. Found % C 66.30, H 4.06, S 7.98.

(2E)-1-[4-(Benzylsulfonyl)phenyl]-3-(2,4-dimethoxyphenyl)prop-2-en-1-one ***37***

Yellow powder. Yield: 58%; mp: 129 - 131°C; IR KBr (cm^{-1}): 1660, 1581, 1500, 1331; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.33 (s, 2H, CH_2), 6.41 (d, 1H, $H_{3'}$, *J* = 2.2 Hz), 6.48 (dd, 1H, $H_{5'}$, *J* = 8.4, 2.2 Hz), 7.21 - 7.29 (m, 5H, Ar), 7.38 (d, 1H, H_β, *J* = 15.8 Hz), 7.51 (d, 1H, $H_{6'}$, *J* = 8.4 Hz), 7.77 (d, 2H, $H_{3,5}$, *J* = 8.6 Hz), 7.82

(d, 2H, $H_{2,6}$, J = 8.6 Hz), 7.99 (d, 1H, H_{α}, J = 15.8 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 55.0, 55.1, 63.1, 98.9, 105.1, 116.9, 122.0, 127.5, 128.7, 128.8, 129.0, 130.9, 137.2, 142.5, 143.4, 149.2, 161.5, 163.9, 189.4. Anal. Calcd for $C_{24}H_{22}O_5S$: % C 68.23, H 5.25, S 7.59. Found % C 68.24, H 5.27, S 7.65.

(2E)-1-[4-(benzylsulfonyl)phenyl]-3-(2,5-dimethoxyphenyl)prop-2-en-1-one ***38***

Yellow powder. Yield: 72%; mp: 176 - 178°C; IR KBr (cm^{-1}): 1681, 1610, 1530, 1488, 1432, 1390; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.32 (s, 2H, CH_2), 6.83 (d, 1H, $H_{3'}$, J = 8.6 Hz), 6.94 (dd, 1H, $H_{4'}$, J = 8.6, 2.2 Hz), 7.11 (d, 1H, $H_{6'}$, J = 2.2 Hz), 7.21 - 7.31 (m, 5H, Ar), 7.41 (d, 1H, H_{β}, J = 15.8 Hz), 7.68 (d, 2H, $H_{3,5}$, J = 8.4 Hz), 7.81 (d, 2H, $H_{2,6}$, J = 8.4 Hz), 8.00 (d, 1H, H_{α}, J = 15.8 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 55.8, 56.1, 62.9, 112.6, 114.2, 117.1, 123.5, 124.8, 127.4, 127.6, 128.7, 128.8, 128.9, 135.1, 136.0, 141.4, 144.5, 153.6, 153.7, 189.8. Anal. Calcd for $C_{24}H_{22}O_5S$: % C 68.23, H 5.25, S 7.59. Found % C 68.19, H 5.25, S 7.67.

(2E)-1-[4-(benzylsulfonyl)phenyl]-3-(3,5-dimethoxyphenyl)prop-2-en-1-one ***39***

Yellow powder. Yield: 90%; mp: 135 - 137°C; IR KBr (cm^{-1}): 1680, 1591, 1500, 1441, 1312; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.84 (s, 6H, 2 x OCH_3), 4.32 (s, 2H, CH_2), 6.49 (t, 1H, $H_{4'}$, J = 2.2 Hz), 6.77 (d, 2H, $H_{2',6'}$, J = 2.1 Hz), 7.19 - 7.25 (m, 5H, Ar), 7.39 (d, 1H, H_{β}, J = 15.6 Hz), 7.58 (d, 1H, H_{α}, J = 15.6 Hz), 7.88 (d, 2H, $H_{3,5}$, J = 8.6 Hz), 8.01 (d, 2H, $H_{2,6}$, J = 8.6 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 56.0, 63.2, 102.7, 106.1, 123.5, 127.0, 127.3, 128.7, 128.8, 128.9, 135.0, 136.1, 137.3, 145.1, 144.7, 161.5, 189.0. Anal. Calcd for $C_{24}H_{22}O_5S$: % C 68.23, H 5.25, S 7.59. Found % C 68.25, H 5.29, S 7.71.

(2E)-1-[4-(Benzylsulfonyl)phenyl]-3-(2,4,6-trimethoxyphenyl)prop-2-en-1-one ***40***

Yellow powder. Yield: 51%; mp: 184 - 186°C; IR KBr (cm^{-1}): 1651, 1600, 1555, 1466, 1318; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ ppm: 3.85 (s, 3H, OCH_3), 3.88 (s, 6H, 2x OCH_3), 4.33 (s, 2H, CH_2), 6.12 (s, 2H, $H_{3',5'}$), 7.08 (d, 2H, $H_{2'',6''}$, J = 7.9 Hz), 7.21 - 7.30 (m, 3H, Ar), 7.69 (d, 2H, $H_{3,5}$, J = 8.2 Hz), 7.75 (d, 1H, H_{β}, J = 15.8 Hz), 7.97 (d, 2H, $H_{2,6}$, J = 8.7 Hz), 8.24 (d, 1H, H_{α}, J = 15.8 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ ppm: 55.5, 55.9, 63.0, 90.7, 106.5, 121.6, 127.9, 128.7, 128.8, 128.9, 130.9, 138.0, 140.4, 143.7, 162.1, 163.9, 191.3. Anal. Calcd for $C_{25}H_{24}O_6S$: % C 66.35, H 5.35, S 7.09. Found % C 66.36, H 5.35, S 7.18.

Biological activity

Inhibition of β-haematin formation in vitro: The assay was performed according to previously reported protocols [40-42]. Hemin chloride (50 mL, 4 mM) in DMSO (5.2 mg/mL) was pipetted in to 96-well microplates. Different concentrations (5 - 100 mM) of the compounds in DMSO were added in triplicate (50 mL). Water (50 mL) or DMSO (50 mL) were used as controls. Acetate buffer (100 mL, 0.2 M, pH 4.4) initiated the formation of β-hematin. Next, the plates were incubated at 37ºC for 48 hours and subsequently centrifuged (4000 rpm x 15 min). The supernatant was washed twice with DMSO (200 mL) and re-suspended in NaOH (200 mL, 0.2 N). The solubilized products were diluted (1:2) with NaOH (0.1 N), and the plates were read in an ELISA reader at 405 nm (Microplate Reader, BIORAD-550). The results are expressed as % βIHF.

Parasite, the experimental host and strain maintenance: Male Balb-C mice, weight 18 - 22 g, were fed with a commercial diet *ad libitum* under standard animal care procedures following the aforementioned method approved by the Ethics Committee of the Institute of Immunology, Caracas, Venezuela. The animals were infected with a rodent malaria strain of *Plasmodium berghei* ANKA. A million infected erythrocytes, in phosphate-buffered saline solution (PBS, 10 mM, pH 7.4, 0.1 mL), were inoculated IP to infect the animal. The parasitemia was inspected by continuous microscopic examination of Giemsa-stained smears [40, 41, 43].

Four-day suppressive test: One million *P. berghei*, injected in the caudal vein i.v, were used to infect the mice (18 - 22 g, n = 6). After two hours of inoculation, the compounds that were active *in vitro* were dissolved in DMSO (0.1 M) and subsequently diluted with Saline-Tween 20 solution (2%) and administered i.p. for 4 days (20 mg/kg). The parasite load was evaluated on day four by examining Giemsa-stained smears. The positive control was chloroquine (20 mg/kg), and the negative control was a saline solution. Non-treated mice were used as a baseline control for survival times [40, 41, 44]. The survival days and percentage of parasitaemia were used to express the results.

Statistical analysis: One-way ANOVA and T-tests for specific group comparisons were used for data analysis. Significance was only considered when $p < 0.05$ for all analyses. Data were expressed as mean SD. The software used was Graph Pad Prism 4.02 [45].

Results and Discussion

Chemistry

We prepared 34 chalcone derivatives through a facile synthesis of two and three steps. The most important change in the design of these derivatives is the addition of benzyl mercaptan moiety to 4-chloro-benzaldehyde or 4-chloroacetophenone (Figure 2) [38]. We designed this inclusion because we wanted to evaluate the antimalarial activity of these compounds with a sulphur atom and possible changes when sulphur is oxidized to sulfone (Figure 2) [39]. The final compounds **7 - 40** were synthesized through

aldol condensation of Claisen-Schmidt between **4** and several substituted acetophenones and compounds **5** and **6** with several substituted benzaldehydes, using sodium hydroxide as a catalyst in ethanol at room temperature. These conditions were found to be satisfactory for the synthesis in good yields. Only (*E*) isomers were obtained, which were confirmed by the doublets in the ^{1}H-NMR spectra between 7.35 - 7.83 and 7.55 - 8.24 ppm, with coupling constants around (15 - 16 Hz), assigned to the two protons in the Hβ and Hα position, respectively, and confirmed by COSY (Correlated Spectroscopy) experiment. The ^{13}C-NMR spectrum of the same compounds exhibit signals between 120 - 127 ppm for Cβ, 135 - 145 ppm for Cα, and 188 - 192 ppm for C=O, which were also confirmed by DEPT 135° (Distortionless Enhancement by Polarization Transfer) and 2D NMR experiments as HECTOR (Heteronuclear Correlation Spectroscopy) and FLOCK (Multiple Bird long Range Correlation Spectroscopy). The compounds' infrared (IR) spectra show one characteristic intense stretching band between 1642 - 1680 cm^{-1}, confirming the presence of α,β unsaturated C=O. A characteristic signal is observed for compounds where the sulphur atom was oxidized to sulfone (SO_2) for this functional group between 1310 -1390 cm^{-1}.

Biological activity

Antimalarial activity: The novel synthesized compounds **4 - 40** were tested *in vitro* as inhibitors of β-hematin formation and *in vivo* in a murine model (Table I) [40-42]. Intermediates **4**, **5** and **6** reduced heme crystallization to 68.98 ± 0.014%, 76.76 ± 0.021%, 85.89 ± 0.001% respectively, with an IC50 > 10 μM. Most of the compounds evaluated (**9**, **10**, **16**, **17**, **19 - 21**, **23 - 25**, **27**, **30**, **32 - 35** and **37 - 39**) exhibited inhibition percentages higher than 73% with an IC50 less than 10 μM. The values are comparable to CQ 94.39 ± 0.01% with an IC50 value of 0.18 ± 0.03.

Table I

The half maximal inhibitory concentrations (IC_{50}) of chalcone derivatives for the formation of β-hematin (βHF), and the effect on *P. berghei* infected mice (20 mg/kg)

No.	R	IC_{50}[a] (μM)	%IβHF (± SEM)[d]	Sd[b] (± SEM)[e]	%P[c] (± SEM)[d]
9	4-F	9.10 ± 0.41	86.92 ± 0.016	25.77 ± 2.45 *	3.81 ± 0.83*
10	2,4-OMe	7.06 ± 0.36	80.60 ± 0.022	11.20 ± 0.80	22.74 ± 0.96
16	3-Me	8.12 ± 0.27	82.36 ± 0.030	9.11 ± 1.50	18.77 ± 2.95
17	4-Me	9.03 ± 1.02	75.00 ± 0.107	11.28 ± 2.40	16.28 ± 3.46
19	4-F	9.70 ± 0.83	87.34 ± 0.013	13.60 ± 0.51	11.07 ± 0.80
20	4-Cl	9.01 ± 0.79	82.78 ± 0.017	17.20 ± 0.66	5.54 ± 0.56
21	2,3-OMe	5.14 ± 0.45	79.87 ± 0.668	23.59 ± 3.21*	5.62 ± 1.50
23	2,5-OMe	6.29 ± 0.93	79.04 ± 0.086	9.01 ± 1.68	21.09 ± 2.74
24	3,4-Cl	9.44 ± 1.19	87.34 ± 0.006	9.40 ± 0.24	22.14 ± 0.94
25	2,3-OMe	7.08 ± 0.87	81.43 ± 0.012	11.33 ± 2.39	19.82 ± 3.62
27	3,5-OMe	7.45 ± 1.09	77.38 ± 0.027	12.35 ± 1.50	20.18 ± 3.37
30	2,4,5-Me	9.84 ± 0.76	88.07 ± 0.011	12.20 ± 0.37	22.05 ± 0.78
32	3-Me	9.27 ± 1.10	87.65 ± 0.016	12.38 ± 1.73	16.30 ± 2.84
33	4-Me	6.79 ± 0.83	75.20 ± 0.008	25.48 ± 2.79*	4.52 ± 0.96*
34	3-OMe	7.41 ± 0.67	89.83 ± 0.012	7.21 ± 1.67	21.32 ± 4.55
35	4-F	8.75 ± 1.24	86.72 ± 0.005	12.00 ± 0.84	20.71 ± 1.03
37	2,4-OMe	5.01 ± 0.32	74.89 ± 0.045	23.75 ± 1.46*	4.65 ± 1.06*
38	2,5-OMe	7.22 ± 1.17	88.69 ± 0.020	10.26 ± 2.06	20.51 ± 3.09
39	3,5-OMe	7.85 ± 0.89	88.07 ± 0.011	8.54 ± 1.63	17.63 ± 3.78
CQ		0.18 ± 0.03	98.52 ± 0.01	30	1.40 ± 0.2
CiSS		--	--	6.31 ± 0.8	22.1 ± 1.4

No. **11** - **15**, **18**, **22**, **26**, **28**, **29**, **31**, **36** and **40**: %IβHF < 75. [a]IC_{50}: Inhibitory concentration 50 (βHF) (n = 3). [b]Sd: Survival days. [c]%P: Percentage of parasitemias. [d]SEM: Standard error of the mean. CiSS = Control infected and treated with saline solution. CQ = chloroquine. $^{*}p < 0.001$ compared to CiSS. n = 6.

Compounds with a percentage higher than 75% inhibition of β-hematin formation *in vitro* were tested *in vivo* in mice infected with P.berghei ANKA, a chloroquine-susceptible strain of murine malaria. The antimalarial potential of these compounds was assessed by their ability to reduce parasitemia and increase survival at the fourth-day post-infection compared to the untreated control group. Mice were treated, i.p. once daily, with the test compounds (20 mg/kg) or CQ (20 mg/kg) for consecutive days (days 1 - 4 post-infection). The survival times and percentage of parasitemia on day four were compared with those of control mice receiving only saline [36, 44]. The Institute of Immunology Bioethical Committee approved the study according to universal guidelines of the National Research Council's Institute for Laboratory Animal Research (ILAR) and the ethical principles for medical research by the World Medical Association Declaration of Helsinki.

Structures **9**, **21**, **33** and **37** used as a single therapy extended the average survival time of infected mice to 25.77 ± 2.45, 23.59 ± 3.21, 25.48 ± 2.79 and

23.75 ± 1.46 days, respectively; however, they were not able to decrease or delay the evolution of malaria (3.81 ± 0.83, 5.62 ± 1.50, 4.52 ± 0.96 and 4.65 ± 1.06%). CQ prolonged the mouse survival time to 30 days and decreased the development of malaria to 1.86 ± 0.35%.

We can see that the type of substituent on the phenyl rings (A and B) had a significant effect on the potential antimalarial activity of the target compounds. When the phenyl group (A) had a withdrawing electron substituent group at position 4, the corresponding compound exhibited excellent activity as an inhibitor of β-hematin formation and an antimalarial *in vivo*. In the compounds **15 - 40**, when group phenyl (B) was mono-substituted in position 2 with group Me or F, but with an S in position 4 of the ring (A), the activity was marginal, however with these same substituents in positions 2, 3 or 4, but with a functional group SO_2 in position 4 of the ring (A) the activity was increased. Compounds di-substituted with F in (B) are showing marginal activity as inhibitors of β-hematin formation. It was found that when the phenyl group (B) was substituted with OMe in position 2, 3 and 4 or 2, 4 and 6 the antimalarial activity was marginal; however, di-substituted with the OMe group in position 2 and 3, 2 and 4 or 2 and 5 the corresponding compounds were able to inhibit very well the β-hematin formation *in vitro*, but the compounds 2,4-OMe (B) with an S or SO_2 group in position 4 of (A) exhibited an excellent activity *in vivo*. Our studies have demonstrated that compounds **9**, **21**, **33** and **37** may inhibit malaria progression in this model through a mechanism of action related to the inhibition of the hemozoin formation.

Three types of interactions for these compounds are possible: hydrogen bonding, π-π stacking and coordination. These interactions have been proposed for quinidine, quinine, chloroquine and mefloquine [14, 46-48].

Conclusions

We synthesized 34 compounds derived from chalcones using synthetic strategies that were very useful and feasible since they allowed us to obtain moderate to very good yields. Nineteen compounds showed inhibitory activity on the formation of β-hematin greater than 75%. Concerning the *in vivo* antimalarial evaluation, we observed that the derivatives **9**, **21**, **33** and **37** decreased the parasitaemia on the fourth day after infection and increased the survival days in a more significant way of the mice. The results reported allowed us to infer and propose some characteristics that must possess the different functional groups present in both rings A and B to achieve that activity, however, noting that none of the compounds eliminates the parasites, we propose that this could be due to low bioavailability. Our results are still in the introductory phase and need further experiments with chloroquine-susceptible and resistant *Plasmodium falciparum* strains and studies to improve bioavailability.

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Conflict of interest

The authors declare no conflict of interest.

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