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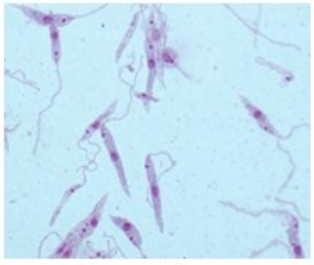
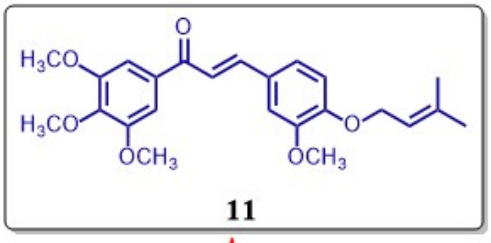


L. mexicana

11 SI 80.94
17 SI 1.24



11

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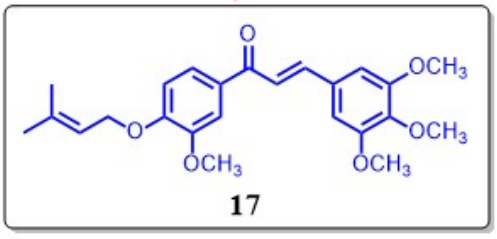
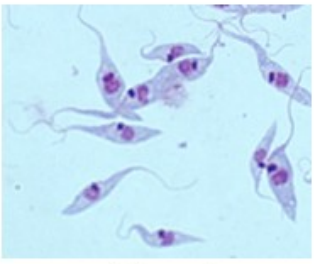


17



T. cruzi

11 SI 75.11
17 SI 1.43

Novel Prenyloxy Chalcones as Potential Leishmanicidal and Trypanocidal Agents: Design, Synthesis and Evaluation

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[§] Equivalent contribution

Abstract

The available drugs for treating Leishmaniasis and American trypanosomiasis have high toxicity and multiple side effects, among other problems. More effective and less toxic treatments are urgently needed. A series of chalcones that contained a prenyloxy or geranyloxy substituent was synthesized and characterized. Each substituent was attached to the A ring in some compounds and to the B ring in others, with additional substituents placed on the chalcone moiety. The present aim was to evaluate the effect of the substitution pattern on leishmanicidal and trypanocidal activity. When tested at a single concentration, the compounds exerting a metabolic inhibition close to or exceeding 50% for *Leishmania mexicana* were **11**, **17** and **12**, and for *Trypanosoma cruzi* were **11**, **17**, **15** and **26**. Upon determining the selectivity index (SI =IC_{50}/CC_{50}), the values were 80.9, 1.24 and 55.12 for **11**, **17** and **12** (respectively) versus *L. mexicana*, and 75.1, 1.43, 27.36 and 33.52 for **11**, **17**, **15** and **26** (respectively) versus *T. cruzi*. Structural isomers **11** and **17** showed activity for both the *L. mexicana* and *T. cruzi* strains, though the greater cytotoxic activity of **17** led to a lower SI. Compounds **12**, **15** and **26** were species specific. For *T. cruzi*, the SI was higher for **11**, **15** and **26** than for the reference drugs nifurtimox and benznidazole. The examination of promastigote morphology after exposing *L. mexicana* and *T. cruzi* to **11**

revealed a decrease in cell density. The current findings suggest that **11** could be a useful lead compound for further SAR studies.

Keywords: Chalcones, *Leishmania*, *Trypanosoma cruzi*, structure-activity relationship, metabolic inhibition, selectivity index.

1. Introduction

Leishmaniasis and American trypanosomiasis are among the neglected tropical diseases (NTDs), which are overlooked because the world pharmaceutical industry does not consider it profitable to invest in the development of new medicines for their treatment [1]. NTDs prevail in regions with a tropical and subtropical climate where most of the affected population is living in extreme poverty.

Leishmaniasis consists of a variety of diseases resulting from infection by flagellated protozoan parasites of the *Leishmania* genus. This disease is transmitted to humans by the bite of *Lutzomiya* or *Phlebotomus* mosquitoes carrying the protozoa [2]. According to the World Health Organization (WHO) estimate, there are between 700,000 and 1,000,000 new cases each year [3]. Depending on the species of *Leishmania* involved, the disease can be manifested as cutaneous leishmaniasis (with cutaneous ulcers), mucocutaneous leishmaniasis (with massive destruction of nasopharyngeal mucosa), and visceral leishmaniasis (involving organs such as the liver, leading to a high mortality rate if not properly treated). Whereas the most prevalent condition is cutaneous leishmaniasis in America, itis visceral leishmaniasis in India and Africa [2, 3].

The first line treatments for leishmaniasis usually involve drugs derived from pentavalent antimonium, including meglumine antimoniate (Glucantime) and sodium stibogluconate (Pentostam). Some alternative treatments are amphotericin B (Amph B), pentamidine and paromomycin. All currently available drugs require prolonged periods of administration and produce high toxicity with several side effects, which limits their clinical use [4].

On the other hand, the potentially lethal American trypanosomiasis (Chagas disease) is caused by the protozoan parasite *Trypanosoma cruzi*. It is transmitted to humans when an infected hematophagous triatomine vector deposits its feces after a blood meal. The

parasite-infected feces enter the organism through lesions or mucous membranes [1b, 5]. Additionally, *T. cruzi* can be transmitted through transfusions with infected blood, during pregnancy or orally. The WHO estimates that more than 8 million people are infected worldwide, resulting in a death rate of around 12,000 people per year in Latin America [1b]. The pharmacological treatment for Chagas disease is based on the only medications available for this purpose: nifurtimox (Nfx) and benznidazole (Bnz). These drugs not only show limited activity during the acute stage of Chagas disease, but also have high toxicity and multiple side effects [6].

Thus, novel treatments for leishmaniasis and American trypanosomiasis are urgently needed [7, 8]. The WHO and the Special Program for Research and Training in Tropical Diseases (TDR) have prioritized the search for new drugs that have cost-effective benefits for combatting the causal agents of NTDs [9]. In the effort of scientists to develop potential agents for treating *Leishmania spp* and *T. cruzi*, novel compounds have been synthesized and natural products isolated [8, 10-13].

Substituted phenols are commonly studied in order to develop novel antileishmanial agents [14]. Among these compounds are chalcones, the structural framework of which is a 1,3-diphenyl-2-propen-1-one with one or more free hydroxyl groups or an ether function (Figure 1) [15].

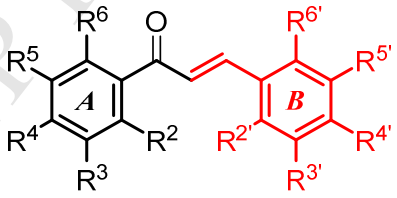


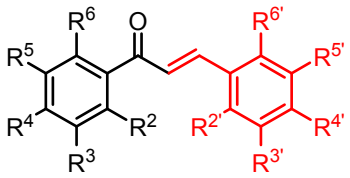
Figure 1. General structure of the chalcone system.

Natural chalcones are ubiquitous substances existing in various plant species (e.g., *Angelica*, *Glycyrrhiza*, *Piper* and *Ruscus*) [15-17]. They are considered precursors to diverse compounds, especially polyphenols such as flavonoids [16]. The numerous natural chalcones contain different substituents in their phenyl rings, especially hydroxyl and ether groups. A wide spectrum of activity has been found for some of these compounds,

including antibacterial, antiviral, cytotoxic, antifungal and antiprotozoal [17, 18]. The structural unit of chalcones is easily synthesized by several procedures, especially by Claisen-Schmidt condensation between properly substituted aromatic aldehydes and acetophenones [15]. The combination of diverse biological activity, relatively simple synthesis and readily available precursors has made chalcones a target for the development of novel compounds that can potentially act as medicinal drugs [19-23].

Among naturally occurring chalcones, those with a prenyl derivative attached to either an oxygen (*O*-prenyl) or carbon (*C*-prenyl) atom are reported to display interesting biological activity (e.g., anti-inflammatory, antioxidant, antifungal, antimicrobial and cytotoxic) [23, 24]. The synthesis of all these chalcones is based on a common metabolic pathway involving the isoprene route [25]. For the *O*-prenyl substituted compounds, the type of derivative depends on the size of the prenyl group, which can be the C-5 (prenyl), C-10 (geranyl) or C-15 (farnesyl) unit.

Licochalcone A (**1**), one of the most widely studied *C*-prenyl substituted chalcones, is known for its antileishmanial activity [26]. This compound produces growth inhibition of the promastigote form of *L. donovani* by damaging the ultrastructure of its mitochondria [26]. It also blocks the promastigote respiratory chain by inhibiting the activity of the fumarate reductase enzyme in the mitochondria [27, 28]. Also exhibiting antileishmanial activity are *O*-allyl-containing chalcones, such as substituted chalcones with a 4-allyloxy group on ring A and dimethoxy groups on ring B (**2** and **3**, respectively; Figure 3). The latter compounds have demonstrated strong antileishmanial activity (IC_{50} 1.4 – 88.8 µM) both *in vitro* and *in vivo* in *L. major* and *L. donovani* amastigotes, apparently by interfering with mitochondrial function [29]. In addition, the geranyloxy chalcone **4** (Figure 2) at a 50 mg/kg dose administered for 10 days showed over 80% inhibition of the *L. donovani* parasite *in vivo* [26]. Another study synthesized and evaluated some chalcones substituted with prenyloxy on the B ring, of the same type as **5**-**10** in the present work (Figure 2). The prenyl groups increased inhibitory activity compared to the unsubstituted chalcones when tested against *L. amazonensis* and *L. infantum* promastigotes. Overall, these results suggest that lipophilicity and structural changes may be an important factor in the development of novel antileishmanial agents [30].



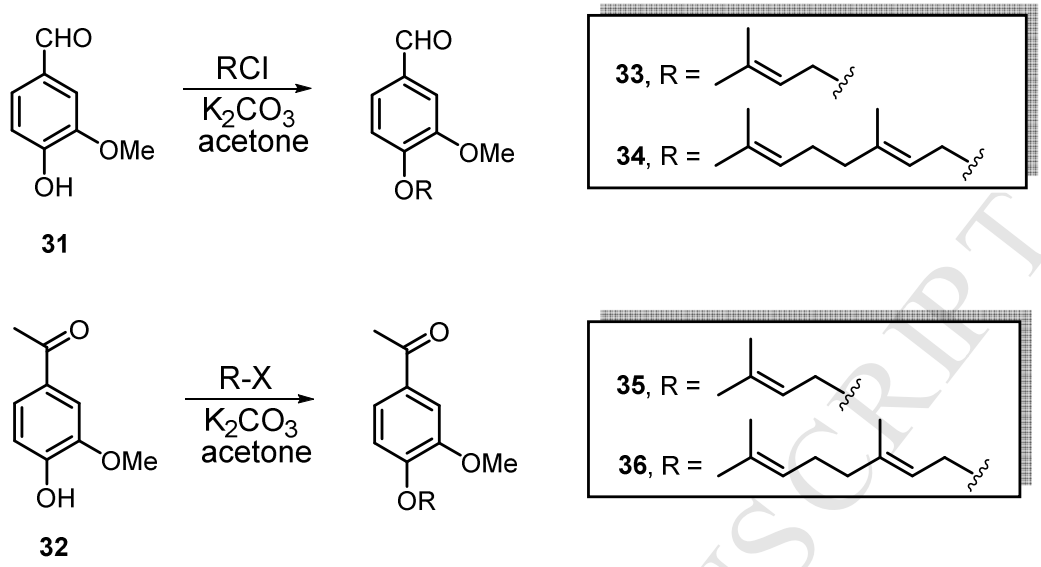
1, $R^2 = R^3 = R^5 = R^6 = R^{3'} = R^{6'} = H$, $R^4 = OH$, $R^{2'} = OCH_3$, $R^{4'} = OH$, $R^{5'} = -C(CH_3)_2CH{=}CH_2$
2, $R^2 = R^3 = R^5 = R^6 = R^{2'} = R^{3'} = R^{5'} = R^{6'} = H$, $R^4 = OCH_2CH{=}CH_2$, $R^{4'} = OCH_3$
3, $R^2 = R^3 = R^5 = R^6 = R^{2'} = R^{4'} = R^{6'} = H$, $R^4 = OCH_2CH{=}CH_2$, $R^{3'} = R^{5'} = OCH_3$
4, $R^2 = R^3 = R^5 = R^6 = R^{2'} = R^{3'} = R^{5'} = R^{6'} = H$, R^4 = geranyl, $R^{4'} = OCH_3$
5, $R^2 = R^3 = R^4 = R^5 = R^6 = H$, $R^{2'} = O$-prenyl, $R^{3'} = R^{4'} = R^{5'} = R^{6'} = H$
6, $R^2 = R^3 = R^4 = R^5 = R^6 = R^{2'} = H$, $R^{3'} = O$-prenyl, $R^{4'} = R^{5'} = R^{6'} = H$
7, $R^2 = R^3 = R^4 = R^5 = R^6 = H$, $R^{2'} = O$-geranyl, $R^{3'} = R^{4'} = R^{5'} = R^{6'} = H$
8, $R^2 = R^3 = R^4 = R^5 = R^6 = R^{2'} = H$, $R^{3'} = O$-geranyl, $R^{4'} = R^{5'} = R^{6'} = H$
9, $R^2 = R^3 = R^4 = R^5 = R^6 = H$, $R^{2'} = O$-farnesyl, $R^{3'} = R^{4'} = R^{5'} = R^{6'} = H$
10, $R^2 = R^3 = R^4 = R^5 = R^6 = H$, $R^{2'} = H$, $R^{3'} = O$-farnesyl, $R^{4'} = R^{5'} = R^{6'} = H$

Figure 2. Structures of diversely substituted prenyloxy chalcones here in examined for their antileishmanial activity.

Since chalcones containing *O*-prenyl groups are a proven source of new antileishmanial drugs, the present effort was based on synthesizing chalcones with an *O*-5 (prenyl) or an *O*-10 (geranyl) unit on the A ring, and in another compound the same unit on the B ring. Other substituents were added to the chalcone moiety. The aim of this study was to evaluate the activity of these compounds against *L. mexicana* and *T. cruzi.*

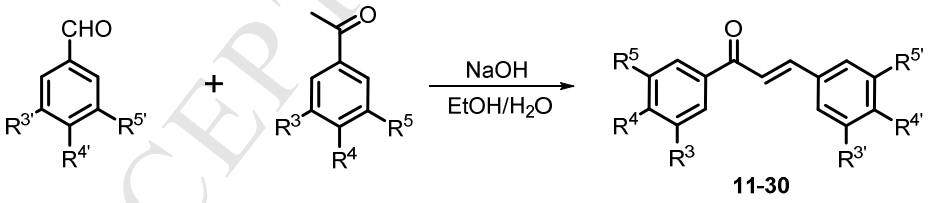
2. Chemistry

For the preparation of a series of substituted chalcones, a substituent was attached to the A ring in one compound and to the B ring in another. This procedure was carried out for various substituents to determine whether their respective position has an effect on biological activity. The structures of the synthesized chalcones and their antileishmanial activity are summarized in Table 1. The key precursors used herein were vanillin (**31**) and acetovanillone (**32**), which were prenylated by reaction with geranyl chloride or prenyl bromide, respectively (Scheme 1).



Scheme 1. Synthesis of *O*-prenyl and *O*-geranyl precursors **33**-**36**.

Additional hydroxyl- and methoxy-substituted aldehydes and ketones are commercially available. The prenylated chalcones, with substituents on either the A or B ring, were synthesized by Claisen-Schmidt condensation between the appropriately substituted aromatic aldehydes **33**, **34**, **37**-**40** and acetophenones **35**, **36**, **41**-**44**. The 20 chalcones obtained (Scheme 2, Table 1) were all appropriately characterized by spectral data (NMR, IR and HRMS).



Scheme 2. Claisen-Schmidt condensation between substituted benzaldehydes and acetophenones.

3. Biological Assays

3.1. Chemical compounds

The synthesized chalcones were evaluated for their *in vitro* leishmanicidal and trypanocidal effects, as well as for cytotoxic effects on mammalian cells, as described previously [13a-b, 31]. For each compound, a known amount (50-100 mg) was dissolved in dimethyl sulfoxide (DMSO; Sigma-Aldrich, St. Louis, MO, USA) to reach a concentration of 10 mg/mL. From this stock solution, the corresponding dilutions were prepared for biological assays in phosphate-buffered saline (PBS).

3.2. Evaluation of the compound-induced metabolic inhibition in parasites

L. mexicana promastigotes (MNYC-BZ/62/M379 ATCC) and *T. cruzi* INC-5 epimastigotes (MHOM/MX/1994/INC5) were examined by using the MTT colorimetric method. In each case, parasites where used in stationary phase (7-day culture). For *L. mexicana*, 5 x 10^5 metacyclic promastigotes were culture in 100 µL supplemented RPMI 1640 medium (Gibco, Carlsbad, CA, USA) containing 10% heat-inactivated fetal bovine serum (FBS; Gibco, Grand Island, NY, USA) and 100 U/mL penicillin-streptomycin (In vitro S.A., Mexico City, Mexico) and seed in a sterile 96-well microplate. All compounds were assayed in triplicate at a 10 µg/mL concentration. Amphotericin B (Amph B) was employed as the reference compound and untreated parasites as the positive viability control [32, 13b].

For *T. cruzi*, 1 x 10^6 epimastigotes were seeded in a 96-well plate in 100 µL of Brain Heart Infusion (BHI) medium (Becton Dickinson; Heidelberg, Germany) supplemented with 10% heat-inactivated FBS and 100 U/mL penicillin-streptomycin. Each compound was assayed in triplicate at a 10 µg/mL concentration. The reference drugs, Nfx and Bnz, served as the negative viability control and untreated parasites as the positive viability control [13a].

Microplates were incubated at 27°C in the dark for 24 h. Subsequently, 10 µL of 5 mg/mL MTT were added to each well and incubated for another 24 h under the same conditions. Upon completion of this time, 100 µL of a solution of SDS (10%) and HCl (0.01N) were added to each well to dissolve the formazan salts. The plates were read on a

spectrophotometer (Spectramax Plus 384; Molecular Devices Corp., Sunnyvale, CA, USA) at 570 nm. The absorbance of each treated well was compared to that of the blank and is expressed as a percentage of metabolic inhibition [13a].

Compounds inhibiting the metabolic activity of the parasite by at least 50% were assessed at different concentrations. The same methodology was employed, obtaining the concentrations by serial dilutions starting from 20 µg/mL. Finally, the 50% inhibitory concentration (IC_{50}) for the active compounds was determined with Probit [13a-b].

3.3. Evaluation of compound-induced cytotoxic activity on murine macrophages

From the murine macrophage cell line J774A.1 (TIB-61 ATCC), $5x10^4$ cells were placed in each well of a 96-well microplate, with a final volume of 100 µL. The plates were incubated at 37 °C in a 5% CO_2 atmosphere for 24 h. Each compound was tested at distinct concentrations (in triplicate), utilizing untreated cells as the negative cytotoxicity control. After adding the corresponding compound, incubation was carried out for another 20 h under the same conditions. Then10 µL of MTT (5 mg/mL) were added and the plates were incubated for an additional 4 h before a solution (100 µL) of 10% SDS and 0.01N HCl was added to each well to dissolve the formazan crystals. The concentration-response analysis was conducted as described in the previous section to determine the 50% cytotoxic concentration (CC_{50}) for each compound [33].

3.4. Selectivity Index (SI)

The SI was calculated as the ratio between the CC_{50} for mammalian cells and the CI_{50} for parasites (CC_{50}/ CI_{50}). A good biological activity is considered when the SI $\geq$ 10 [34, 35].

3.5. Morphological analysis

The morphology of *L. mexicana* promastigotes and *T. cruzi* epimastigotes was analyzed with light microscopy. Parasites treated under different conditions were washed and resuspended in PBS, then embedded on a slide using cystopin (LaboFuge 400, Thermo Scientific, USA). Following the staining of the samples with Giemsa (dilution 1:10; Merck,

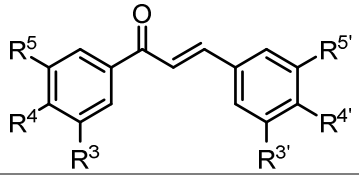
Darmstadt, Germany) during 30 min, the slides were examined on a light microscope at 100x (Primo Star, Zeiss). Images were captured with an Axiocam ER 5s camera [13b].

4. Results and discussion

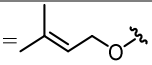
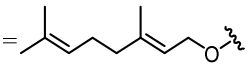
The synthesis of the targeted chalcones was performed by Claisen-Schmidt condensation between the appropriately substituted benzaldehydes and benzophenones to afford the corresponding chalcones in fair to good yields (11-92 %). There was a preliminary evaluation of the compound-induced metabolic inhibition on *L. mexicana* promastigotes and *T. cruzi* epimastigotes at a concentration of 10 µg/mL (Table 1). The most active compounds, those producing metabolic inhibition near to or exceeding 50%, were subjected to further testing at various concentrations.

The most active compounds for *L. mexicana* were **11** and **17**, giving rise to 71.3% and 59.1% inhibition, respectively, while compound **12** showed close to 50% inhibition. None of the test compounds exceeded the inhibition produced by Amph B, the reference drug. Compounds **11** and **17** were also the most active for *T. cruzi*, with 84% and 80.3% inhibition, respectively. Both exceeded the activity of Bnz, the reference drug. The inhibition afforded by compounds **15** (43.9%) and **26** (45%) evidenced a lesser degree of trypanocidal activity. Interestingly, compounds possessing medium-level activity (**12**, **15** and **26**) were species-specific.

Table 1. Structures of the synthesized chalcones and a preliminary *in vitro* biological evaluation.



Cpd.	µM equivalent to 10µg/mL	R^3	R^4	R^5	$R^{3'}$	$R^{4'}$	$R^{5'}$	% Metabolic inhibition	
								L. mexicana	*T. cruzi*
11	24.2 **µM**	OCH_3	OCH_3	OCH_3	H	*O*-pre	OCH_3	**71.3** ± 0.8	**84.0** ± 1.1
12	26.1 **µM**	H	OCH_3	OCH_3	H	*O*-pre	OCH_3	**48.3** ± 0.8	**11.8** ± 1.9
13	28.4 **µM**	H	OCH_3	H	H	*O*-pre	OCH_3	**25.5** ± 4.7	**2.6** ± 1.8
14	29.6 **µM**	H	OH	H	H	*O*-pre	OCH_3	**17.7** ± 1.0	**23.8** ± 2.7
15	19.8 **µM**	H	*O*-ger	OCH_3	H	*O*-pre	OCH_3	**-8.0** ± 3.8	**43.9** ± 3.4
16	22.9 **µM**	H	*O*-pre	OCH_3	H	*O*-pre	OCH_3	**3.9** ± 4.4	**20.0** ± 4.5
17	24.2 **µM**	H	*O*-pre	OCH_3	OCH_3	OCH_3	OCH_3	**59.1** ± 0.5	**80.3** ± 1.2
18	20.7 **µM**	H	*O*-pre	OCH_3	H	OCH_3	OCH_3	**15.6** ± 1.7	**25.3** ± 4.7
19	28.4 **µM**	H	*O*-pre	OCH_3	H	OCH_3	H	**1.0** ± 2.6	**7.9** ± 0.7
20	29.6 **µM**	H	*O*-pre	OCH_3	H	OH	H	**4.6** ± 2.0	**16.3** ± 1.3
21	19.8 **µM**	H	*O*-pre	OCH_3	H	*O*-ger	OCH_3	**-3.2** ± 1.4	**33.2** ± 5.2
22	20.8 **µM**	OCH_3	OCH_3	OCH_3	H	*O*-ger	OCH_3	**11.3** ± 0.6	**31.6** ± 3.0
23	22.2 **µM**	H	OCH_3	OCH_3	H	*O*-ger	OCH_3	**13.5** ± 1.7	**22.0** ± 0.7
24	23.8 **µM**	H	OCH_3	H	H	*O*-ger	OCH_3	**0.70** ± 1.9	**13.7** ± 3.1
25	24.6 **µM**	H	OH	H	H	*O*-ger	OCH_3	**17.6** ± 0.4	**20.4** ± 1.7
26	17.5 **µM**	H	*O*-ger	OCH_3	H	*O*-ger	OCH_3	**1.0** ± 1.7	**45.0** ± 3.3
27	20.8 **µM**	H	*O*-ger	OCH_3	OCH_3	OCH_3	OCH_3	**2.1** ± 3.6	**-0.8** ± 7.1
28	22.2 **µM**	H	*O*-ger	OCH_3	H	OCH_3	OCH_3	**27.3** ± 0.7	**28.3** ± 1.6
29	23.8 **µM**	H	*O*-ger	OCH_3	H	OCH_3	H	**0.0** ± 2.8	**-11.6** ± 3.2
30	24.6 **µM**	H	*O*-ger	OCH_3	H	OH	H	**4.9** ± 3.7	**-5.5** ± 4.0
Bnz	38.42 **µM**	-	-	-	-	-	-	-	**77.4** ± **3.8**
Amph B (0.5 µg/mL)	0.54 **µM**	-	-	-	-	-	-	**99.0** ± 1.2	-

Bnz= Benznidazole; Amph B = Amphotericn *O*-pre =  *O*-ger = 

Compounds exhibiting medium and high inhibitory activity were selected for evaluation at various concentrations to determine their IC_{50} for *L. mexicana* promastigotes and *T. cruzi* epimastigotes. Additionally, the CC_{50} for murine macrophages was ascertained to calculate the selectivity index (SI). As previously mentioned [35, 36], selectivity is considered for compounds with an SI ≥10 (Table 2).

Table 2. IC_{50} and CC_{50} for the most active compounds.

	L. mexicana	***T. cruzi* INC-5**	**Macrophages J774**	**SI**	
	IC_{50} (µM)	**IC_{50} (µM)**	**CC_{50} (µM)**	***L. mexicana***	***T. cruzi***
11	16.2 (13.4-19.2)	17.5 (13.5-20.6)	1312.9 (1080.4-1544.8)	80.94	75.11
12	31.8 (23.4-40.2)	Nd	1752.6 (1638.7-1866.5)	55.12	Nd
15	Nd	30.1 (23.9-36.3)	824.8 (718.7-931.1)	Nd	27.36
17	20.7 (13.4-32.5)	17.8 (14.9-20.7)	25.6 (11.5-45.3)	1.24	1.43
26	Nd	30.4 (22.9-37.9)	1018.4 (875.5-1161.2)	Nd	33.52
Amph B	0.28 (0.26-0.29)	Nd	60.7 (52.6-68.9)	215.84	Nd
Bnz	Nd	42.3 (36.6-48.1)	352.2 (334.9-369.1)	Nd	8.31
Nfx	Nd	8.7 (4.8-12.5)	201.1 (188.6-213.5)	Nd	23.10

Nd = Not determined
The values in parentheses represent the confidence interval determined by the Probit method with 95% confidence

Interestingly, there was a lower cytotoxic effect (CC_{50}) produced by compounds **11**, **12**, **15** and **26** than by the reference drugs. When applied to the *L. mexicana* strain, compounds **11** and **12** showed a high SI (80.94 and 55.12, respectively), though they were below the value for Amph B. The lower cytotoxic activity of **11** and **12** than Amph B makes them candidates for lead compounds. Compound **17** exhibited a good IC_{50} value, but generated cytotoxic activity against mammalian macrophages at reduced concentrations, resulting in an SI value below that of **11** (Table 2).

For the *T. cruzi* epimastigotes, compound **11** also displayed the highest SI (75.11), followed by compounds **15** (27.36) and **26** (33.52). The SI of these three chalcones was better than

reference drugs, Bnz (8.31) and Nfx (23.10). As found with *L. mexicana*, compound **17** displayed a low SI value with *T. cruzi* (Table 2).

Since compound **11** showed the best SI for both trypanosomatids, its effect on parasite cell morphology was examined at concentrations higher and lower than the IC_{50} value. Typical promastigote morphology was found when *Leishmania* parasites were incubated without treatment (0 µg/mL), being elongated, thin, flagellated, and with a defined nucleus and kinetoplast. When **11** was added in increasing concentrations, its leishmanicidal activity was evidenced by the corresponding decrease in parasite cell density (Figure 3). At the highest concentration (equivalent to three times the IC_{50}), only a few promastigotes were observed, which were rounded, dead and with a short flagella.

There was also a dose-dependent effect on the cell density of *T. cruzi* epimastigotes induced by **11** as of 2.5 µg/mL (Figure 4). Although a clear parasiticidal activity was evident for compound **11** at concentrations near its IC_{50} (5 and 10 µg/mL), judging by the metabolic inhibition and reduced cell density, the parasites maintained their general structure (Table 2), indicating that light microscopy is not enough sensitive for detecting modifications induced by the compound.

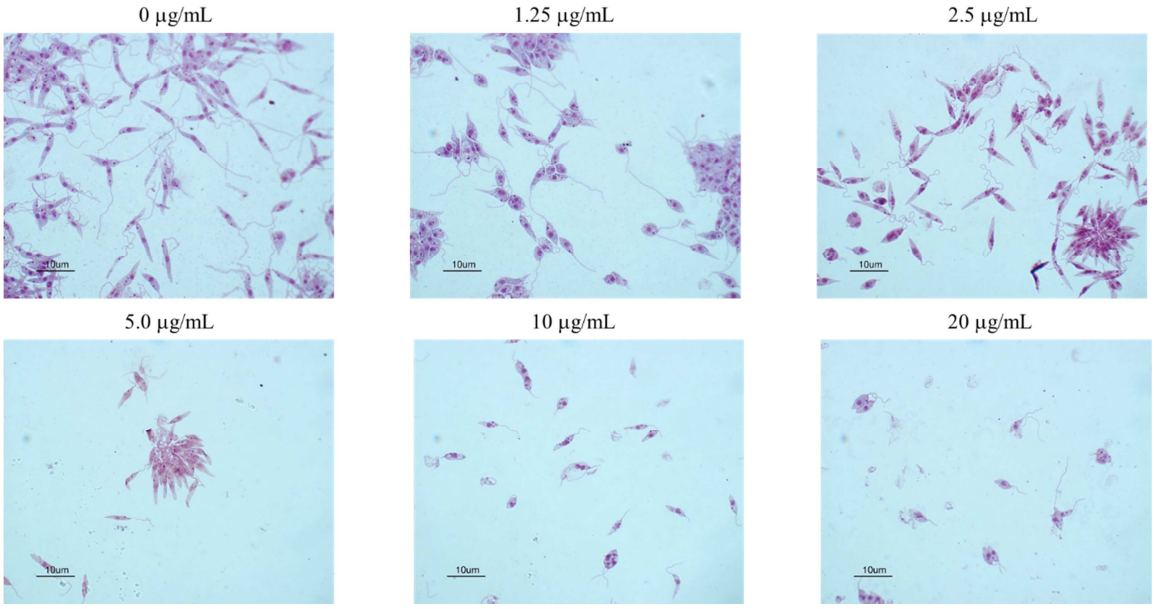


Figure 3. Effect of compound **11** on the morphology of *L. mexicana* promastigotes. Parasites were exposed to different concentrations of compound **11** for 24 h, stained with Giemsa and analyzed by light microscopy at 100x.

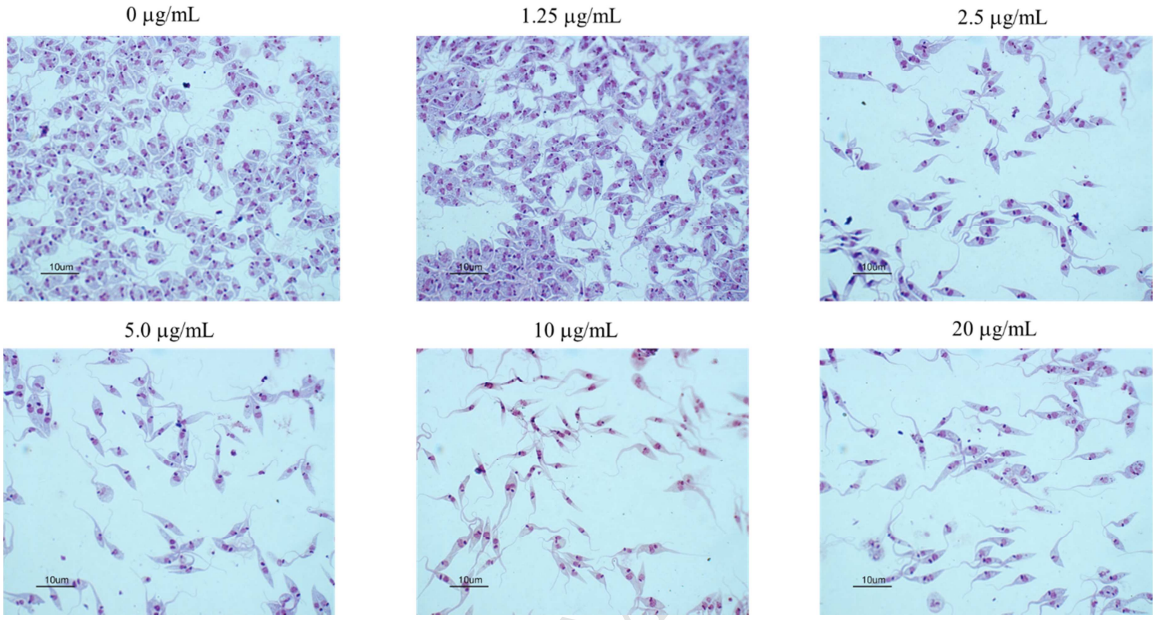


Figure 4. Effect of compound **11** on the morphology of *T. cruzi* epimastigotes. Parasites were exposed to different concentrations of compound **11** for 24 h, stained with Giemsa and examined by light microscopy at 100x.

According to the analysis of the structure-activity relationship (SAR) of chalcones for *L. mexicana*, the greatest inhibition corresponded to compounds containing the 3,4,5-trimethoxyphenyl and 3,4-dimethoxyphenyl groups as substituents. Contrarily, the compounds with geranyloxy groups were not active. For *T. cruzi*, the 3,4-dimethoxyphenyl group did not show activity, but inhibition was produced by the geranyloxy and prenyloxy groups when located on either side of the chalcone ring system.

The inhibitory effects were compared for two distinct positions of each substituent, on the A ring and on the B ring. Two structural isomers, compounds **11** and **17**, showed very similar IC_{50} values when tested on both *L. mexicana* and *T. cruzi*. However, significantly greater cytotoxic activity against macrophages was caused by **17** than **11**. The only difference between the two molecules is that the prenyloxy group is attached to the A ring

of **17** and to the B ring of **11**. Hence, **17** is characterized by a lower selectivity (Figure 5, Table 2). This highlights the importance of structural modifications on the A and B rings of the chalcone scaffold, suggesting that the nature and position of the substituents probably influences biological activity by an electronic and/or steric interaction with the parasite. In particular, the lipophilicity of the chain length (prenyl *vs.* geranyl) may affect the absorption of the compound into the parasite and therefore its biological activity.

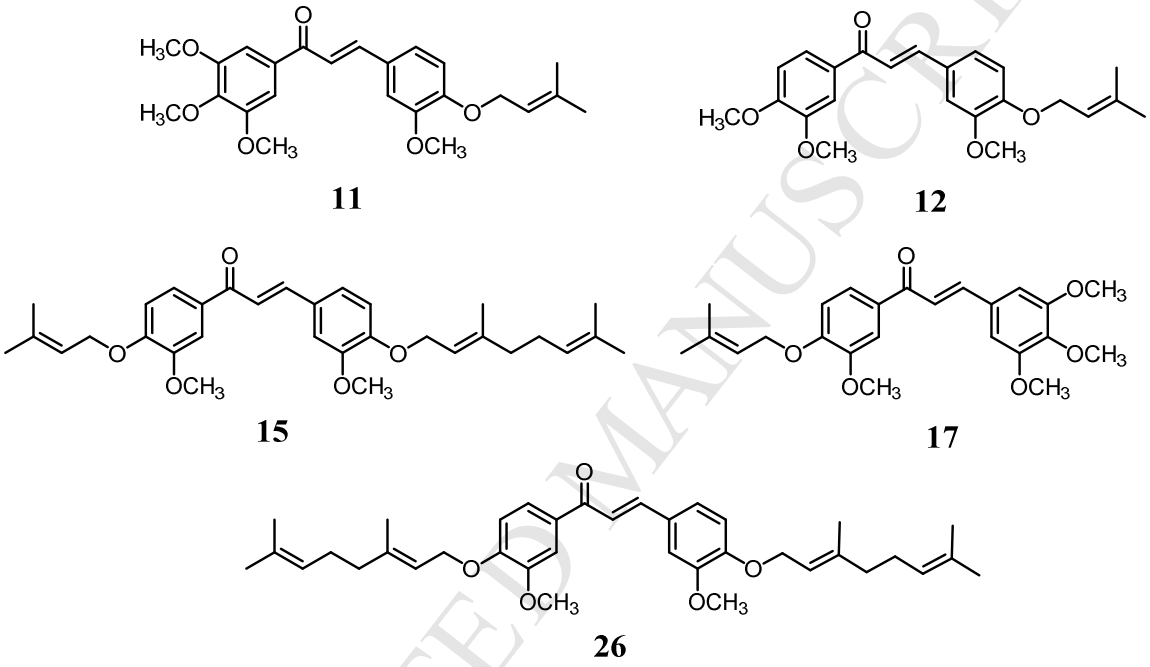
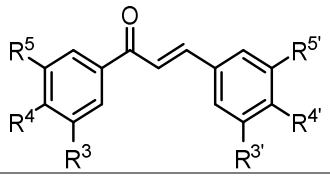


Figure 5. Chemical structures of the most active synthetized analogs.

In addition, an *in silico* analysis was carried out to gain further insights into the drug likeness properties of the synthesized compounds (Table 3).

Table 3. *In silico* results of the synthesized chalcones.



Comp	R^3	R^4	R^5	$R^{3`}$	$R^{4`}$	$R^{5`}$	Molecular Properties						
							MW	**cLogP**	**cLogS**	**TPSA**	**HBA**	**HBD**	**$logS_w$**
11	OCH_3	OCH_3	OCH_3	H	*O*-pre	OCH_3	412.48	4.47	-6.12	63.22	6	0	-4.69
12	H	OCH_3	OCH_3	H	*O*-pre	OCH_3	382.45	4.49	-5.95	53.99	5	0	-4.79
13	H	OCH_3	H	H	*O*-pre	OCH_3	352.42	4.51	-5.78	44.76	4	0	-4.74
14	H	OH	H	H	*O*-pre	OCH_3	338.4	4.11	-5.68	55.76	4	1	-4.67
15	H	*O*-ger	OCH_3	H	*O*-pre	OCH_3	504.66	7.12	-9.43	53.99	5	0	-7.24
16	H	*O*-pre	OCH_3	H	*O*-pre	OCH_3	436.54	5.64	-7.5	53.99	5	0	-5.7
17	H	*O*-pre	OCH_3	OCH_3	OCH_3	OCH_3	412.48	4.47	-6.12	63.22	6	0	Nd
18	H	*O*-pre	OCH_3	H	OCH_3	OCH_3	382.45	4.48	-5.95	53.99	5	0	Nd
19	H	*O*-pre	OCH_3	H	OCH_3	H	352.42	4.51	-5.78	44.76	4	0	-4.56
20	H	*O*-pre	OCH_3	H	OH	H	338.4	4.1	-5.68	55.76	4	1	Nd
21	H	*O*-pre	OCH_3	H	*O*-ger	OCH_3	504.66	7.08	-9.43	53.99	5	0	Nd
22	OCH_3	OCH_3	OCH_3	H	*O*-ger	OCH_3	480.59	5.95	-8.04	63.22	6	0	-5.87
23	H	OCH_3	OCH_3	H	*O*-ger	OCH_3	450.57	5.93	-7.88	53.99	5	0	-5.67
24	H	OCH_3	H	H	*O*-ger	OCH_3	420.54	5.97	-7.71	44.76	4	0	Nd
25	H	OH	H	H	*O*-ger	OCH_3	406.51	5.57	-7.6	55.76	4	1	Nd
26	H	*O*-ger	OCH_3	H	*O*-ger	OCH_3	572.77	8.51	-11.36	53.99	5	0	-8.31
27	H	*O*-ger	OCH_3	OCH_3	OCH_3	OCH_3	480.59	5.92	-8.04	63.22	6	0	Nd
28	H	*O*-ger	OCH_3	H	OCH_3	OCH_3	450.57	5.96	-7.88	53.99	5	0	Nd
29	H	*O*-ger	OCH_3	H	OCH_3	H	420.54	5.97	-7.71	44.76	4	0	-6.07
30	H	*O*-ger	OCH_3	H	OH	H	406.51	5.53	-7.6	55.76	4	1	-5.61

Predictions were made by using the web tool SwissADME [36]. MW, molecular weight; cLogP, average predicted octanol/water partition coefficient; cLogS, predicted aqueous solubility; TPSA, calculated topological surface polar area; HBA, number of H-Bond acceptors; HBD, number of H-Bond donors. Prediction of Log S_w were made using the general solubility equation reported in [37].

The biological activity of **15** and **26** was specific to *T. cruzi*. These compounds have some physicochemical characteristics that violate L+6ipinski's rule of five, which could possibly be reflected in their pharmacokinetic and pharmacodynamic properties, such as limited drug availability.

According to the *in silico* results, all the synthesized compounds show lipophilicity and low water solubility. These properties may be advantageous for the delivery of the active

compounds in topical form, specifically as an ointment for the treatment of cutaneous leishmaniasis. However, further structural analysis is required in order to develop analogs with more equilibrated cLogP and cLogS properties for application in other drug delivery forms.

5. Conclusions

In summary, a series of chalcones containing a prenyloxy or geranyloxy unit were synthesized and characterized. Compounds **11** and **17** displayed the greatest parasiticidal activity against both trypanosomatids herein tested (*L. mexicana* and *T. cruzi*). For chalcone **12** and derivatives **15** and **26**, a selective activity was found for *L. mexicana* and *T. cruzi*, respectively. The highest SI against *L. mexicana* and *T. cruzi* corresponded to compound **11**, owing itself to lower cytotoxic activity on mammalian macrophages than that found with its structural isomer **17**.

The SAR study demonstrated that the position of the substituents in the molecule, being either on the A or B ring of the chalcone system, has an influence on the biological activity and the selectivity index of these compounds. Although the mechanism of action of the compounds on each parasite is still unclear, the present biological results justify further research on chalcone derivatives, especially by using **11** as a lead compound. The synthesis of chalcones with attracting and donating functional groups other than prenyloxy or geranyloxy substituents is currently underway and will be reported in due time.

6. Experimental section

General: Melting points (uncorrected) were determined on a capillary melting point apparatus. The NMR spectra were recorded on a Varian (at 300 MHz) or Bruker (at 400 MHz) spectrophotometer, using TMS as internal standard. High-resolution mass spectra were obtained in the electron impact (EI) mode (70 eV) (Jeol JSM-GCMate-II). Infrared spectra were recorded by the ATR technique from 4000 to 400 cm^{-1} (Agilent Cary-600-Series-FTIR).

3-Methoxy-4-((3-methylbut-2-en-1-yl)oxy)benzaldehyde (**33**). A mixture of 2.28 g (15.0 mmol) vanillin (**31**), 3.04 g (22.0 mmol) potassium carbonate and 30 mL acetone was

stirred at room temperature for 10 minutes. Subsequently, 1.88 g (18.0 mmol) prenyl chloride were added dropwise and then the mixture was stirred at reflux for 24 hours. Upon completion of this time, the mixture was filtered and diluted with EtOAc (25 mL), the organic layer washed with NaOH 3N (2x25 mL), and finally the solvent removed under vacuum and purified by column chromatography over silica gel (10 g/g crude, hexane/EtOAc, 9:1) to give 1.58 g (48%) as a whitish-lemon solid. R_f 0.40 (hexane/EtOAc, 8:2); mp47-49 °C. IR (film) $\overline{\nu}$ 2935, 1679, 1583, 1506, 1464, 1424, 1260, 1232, 1134, 1032, 979, 865, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.76 (s, 3H, CH=C(CH_3)$_2$), 1.79 (s, 3H, CH=C(CH_3)$_2$), 3.93 (s, 3H, OCH_3), 4.68 (d, *J* = 6.7 Hz, 2H, H-1''),5.52 (dddt, *J* = 6.7, 5.6, 2.8, 1.4 Hz, 1H, H-2''), 6.98 (d, *J* = 8.1 Hz, 1H, H-5'), 7.41 (d, *J* = 1.8 Hz, 1H, H-2'), 7.44 (dd, *J* = 8.1, 1.9 Hz, 1H, H-6'), 9.84 (s, 1H, C*H*O). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 18.3 (CH=C(*C*H_3)$_2$), 25.9 (CH=C(*C*H_3)$_2$), 56.0 (O*C*H_3), 65.9 (C-1''), 108.9 (C-2'), 111.5 (C-5'), 118.9 (C-2''), 126.8 (C-6'), 129.8 (C-1'), 138.8 (C-3''), 149.8 (C-3'), 153.8 (C-4'), 191.0 (*C*HO). HRMS (EI) *m*/*z* [M^+] calculated for $C_{13}H_{16}O_3$: 220.1100. Found: 220.1105.

1-(3-Methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)ethan-1-one (**35**). To a mixture of 2.50 g (15.0 mmol) acetovanillone (**32**) in 30 mL acetone was added 3.04 g (22.0 mmol) of K_2CO_3 and the mixture was stirred at room temperature for 10 minutes. Afterwards, 1.88 g (18.0 mmol) prenyl bromide was added dropwise and the mixture stirred at reflux for 24 hours. The crude was filtered and the solvent removed under vacuum and dissolved in 25 mL of EtOAc, followed by washing the organic layer with NaOH 3N (2x25 mL). The solvent was removed under vacuum and dissolved in hexane/EtOAc (9:1), the insoluble solid removed by filtration and crystalized to afford 1.58 g (40%) of **35** as a whitish-lemon solid. R_f 0.35 (hexane/EtOAc, 8:2); mp 42-43 °C. IR (film) $\overline{\nu}$ 2935, 1679, 1583, 1506, 1464, 1424, 1260, 1232, 1134, 1032, 979, 865, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.76 (s, 3H, CH=C(CH_3)$_2$), 1.79 (s, 3H, CH=C(CH_3)$_2$), 2.57 (s, 3H, C=OCH_3), 3.93 (s, 3H, OCH_3), 4.66 (d, *J* = 6.7 Hz, 2H, H-1''), 5.51 (dddt, *J* = 6.7, 5.6, 2.8, 1.4 Hz, 1H, H-2''), 6.89 (d, *J* = 8.3 Hz, 1H, H-5'), 7.53 (d, *J* = 2.0 Hz, 1H, H-2'), 7.56 (dd, *J* = 8.3, 2.0 Hz, 1H, H-6'). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 18.4 (CH=C(*C*H_3)$_2$), 26.0 (CH=C(*C*H_3)$_2$), 26.3 (C=O*C*H_3), 56.0 (O*C*H_3), 65.9 (C-1''), 110.1 (C-2'), 111.2 (H-5'), 119.2 (C-2''), 123.3 (C-

6'), 130.3 (C-1'), 138.6 (C-3''), 149.3 (C-3'), 152.7 (C-4'), 197.0 (*C*=O). HRMS (EI) *m/z* [M^+] calculated for $C_{14}H_{18}O_3$: 234.1256. Found: 234.1258.

4-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-3-methoxybenzaldehyde (**34**). A mixture of 2.28 g (15.0 mmol) vanillin (**31**) and 3.04 g (22.0 mmol) potassium carbonate in 30 mL acetone was stirred at room temperature for 10 minutes. Subsequently, 3.11 g (18.0 mmol) geranyl chloride was added dropwise and the mixture stirred at reflux for 24 hours. It was then filtered and diluted with EtOAc (25 mL) and the organic layer washed with 2 x 25 mL NaOH 3N. The solvent was removed under vacuum and purified by column chromatography over silica gel (10 g/g crude, hexane/EtOAc, 9:1) to furnish 0.21 g (33%) of **34** as a pale-yellow oil. R_f 0.56 (hexane/EtOAc, 8:2). IR (film) $\bar{\nu}$ 2968, 2915, 1683, 1682, 1541, 1503, 1440, 1377, 1303, 1264, 1175, 1028, 847, 791, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.60 (s, 3H, CH=C(CH_3)$_2$), 1.66 (s, 3H, CH=C(CH_3)$_2$), 1.76 (s, 3H, CH=C(CH_3)$_2$), 2.03 – 2.17 (m, 4H, H-4'' and H-5''), 3.94 (s, 3H, OCH_3), 4.72 (d, *J* = 6.5 Hz, 2H, H-1''), 5.07 (t, *J* = 6.0 Hz, 1H, H-6''), 5.51 (t, *J* = 6.4 Hz, 1H, H-2''), 6.97 (d, *J* = 8.1 Hz, 1H, H-5'), 7.41 (d, *J* = 1.7 Hz, 1H, H-2'), 7.44 (dd, *J* = 8.2, 1.7 Hz, 1H, H-6'), 9.85 (s, 1H, C*H*O). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 16.9 (CH=C(*C*H_3)$_2$), 17.8 (CH=C(*C*H_3)$_2$), 25.8 (CH=C(*C*H_3)$_2$), 26.3 (C-4'' or C-5''), 39.6 (C-4'' or C-5''), 56.1 (O*C*H_3), 66.1 (C-1''), 109.0 (C-2'), 111.7 (C-5'), 118.8 (C-2''), 123.7 (C-6''), 126.9 (C-6'), 129.9 (C-1'), 132.0 (C-7''), 141.8 (C-3''), 149.9 (C-3'), 153.9 (C-4'), 191.1 (*C*HO). HRMS (EI) *m/z* [M^+] calculated for $C_{18}H_{24}O_3$: 288.1726. Found: 288.1723.

1-(4-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)ethan-1-one (**36**). A mixture of 2.50 g (15.0 mmol) acetovanillone (**32**) and 3.04 g (22.0 mmol) potassium carbonate were stirred in 30 mL of acetone at room temperature for 10 minutes. Afterwards, 3.11 gr (18.0 mmol) geranyl chloride was added dropwise and the mixture stirred at reflux for 24 hours before filtration followed by dilution with 25 mL EtOAc. The solution was washed with 2 x 25 mL 3N NaOH, the organic layer dried, and the solvent removed under vacuum and purified by column chromatography over silica gel (10 g/g crude, hexane/EtOAc, 9:1) to provide 1.78 g (40%) of **36** as a pale-yellow oil. R_f 0.49 (hexane/EtOAc, 8:2). IR (film) $\bar{\nu}$ 2924, 1674, 1586, 1509, 1417, 1356, 1267, 1218, 1148, 1033, 987, 876, 807, 642, 576 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.59 (s, 3H,

CH=C(CH_3)$_2$), 1.66 (s, 3H, CH=C(CH_3)$_2$), 1.75 (s, 3H, CH=C(CH_3)$_2$), 2.05 – 2.17 (m, 4H, H-4'' and H-5''), 2.56 (s, 3H, C=OCH_3), 3.91 (s, 3H, OCH_3), 4.69 (d, *J* = 6.4 Hz, 2H, H-1''), 5.02 – 5.11 (m, 1H, H-6''), 5.50 (tt, *J* = 5.2, 2.7 Hz, 1H, H-2''), 6.88 (d, *J* = 8.2 Hz, 1H, H-5'), 7.52 (d, *J* = 1.9 Hz, 1H, H-2'), 7.45 (dd, *J* = 8.1, 2.1 Hz, 1H, H-6'). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 16.6 (CH=C(*C*H_3)$_2$), 17.6 (CH=C(*C*H_3)$_2$), 25.6 (CH=C(*C*H_3)$_2$), 26.1 (C=O*C*H_3 and C-4'' or C-5''), 39.4 (C-4'' or C-5''), 55.8 (O*C*H_3), 65.8 (C-1''), 110.0 (C-2'), 111.2 (C-5'), 118.9 (C-2''), 123.1 (C-6''), 123.6 (C-6'), 130.1 (C-1'), 131.7 (C-7''), 141.3 (C-3''), 149.1 (C-3'), 152.5 (C-4'), 196.7 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{19}H_{26}O_3$: 302.1882. Found: 302.1881.

General procedure for the preparation of chalcones 11–30. **(*E*)-3-(3-Methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one** (**11**). A mixture of 0.220 g (1.00 mmol) **33**, 0.210 g (1.00 mmol) 3,4,5-trimethoxyacetophenone (**41**) and 0.680 g (17.0 mmol) NaOH in 40 mL H_2O/EtOH (2:1) was stirred at room temperature for 48 hours. Upon completion of this time, the solvent was removed under vacuum and the residue purified by column chromatography over silica gel (10 g/g of crude, hexane/EtOAc, 9:1) to yield 0.050 g (12%) of **11** as a yellow powder. R_f 0.10 (hexane/EtOAc, 8:2); mp 96-98 °C. IR (film) $\bar{\nu}$ 2936, 1732, 1655, 1578, 1505, 1463, 1414, 1337, 1253, 1127, 1001, 808, 702, 573 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.76 (s, 3H, CH=C(CH_3)$_2$), 1.79 (s, 3H, CH=C(CH_3)$_2$), 3.94 (s, 6H, OCH_3), 3.95 (s, 6H, OCH_3), 4.65 (d, *J* = 6.7 Hz, 2H, OCH_2CH=C), 5.48 – 5.58 (m, 1H, OCH$_2$C*H*=C), 6.91 (d, *J* = 8.3 Hz, 1H, H-5''), 7.15 (d, *J* = 1.8 Hz, 1H, H-2''), 7.24 (dd, *J* = 8.3, 1.8 Hz, 1H, H-6''), 7.27 (s, 2H, H-2' and H-6'), 7.33 (d, *J* = 15.6 Hz, 1H, H-2), 7.77 (d, *J* = 15.6 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 18.4 (CH=C(*C*H_3)$_2$), 26.0 (CH=C(*C*H_3)$_2$), 56.1 (O*C*H_3), 56.5 (O*C*H_3), 61.1 (O*C*H_3), 65.9 (C-1'''), 106.1 (C-6' and C-2'), 110.7 (C-2''), 112.6 (C-5''), 119.4 (C-2'''), 119.8 (C-2), 122.9 (C-6''), 127.8 (C-1''), 134.0 (C-1'), 138.4 (C-3'''), 142.3 (C-4'), 145.2 (C-3), 149.6 (C-3''), 150.9 (C-4''), 153.2 (C-3' and C-5'), 189.6 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{24}H_{28}O_6$: 412.1886. Found: 412.1896.

(*E*)-1-(3,4-Dimethoxyphenyl)-3-(3-methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)prop-2-en-1-one (**12**). Following the general procedure for the preparation of chalcones, a mixture of 0.220 g (1.00 mmol) **33**, 0.180 g (1.00 mmol) **42** and 0.680 g

(17.0 mmol) NaOH produced 0.15 g (39%) of **12** as a yellow powder. R_f 0.07 (hexane/EtOAc, 8:2); mp 104-106 °C. IR (film) $\bar{\nu}$ 2934, 1651, 1594, 1509, 1420, 1259, 1199, 1140, 1025, 982, 804, 766 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.75 (s, 3H, CH=C(CH_3)$_2$), 1.78 (s, 3H, CH=C(CH_3)$_2$), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.64 (d, *J* = 6.7 Hz, 2H, OCH_2CH=C), 5.48 – 5.57 (m, 1H, OCH$_2$C*H*=C), 6.91 (t, *J* = 8.8 Hz, 2H, H-5' and H-5''), 7.17 (d, *J* = 1.6 Hz, 1H, H-2''), 7.22 (dd, *J* = 8.3, 1.6 Hz, 1H, H-6''), 7.43 (d, *J* = 15.5 Hz, 1H, H-2), 7.63 (d, *J* = 1.5 Hz, 1H, H-2'), 7.66 – 7.72 (dd, *J* = 8.4, 1.2 Hz, 1H, H-6'), 7.77 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 18.4 (CH=C(*C*H$_3$)$_2$), 25.9 (CH=C(*C*H$_3$)$_2$), 56.0 (OCH$_3$), 56.1 (OCH$_3$), 56.1 (OCH$_3$), 65.8 (C-2'''), 109.9 (C-5''), 110.4 (C-2''), 110.8 (C-2'), 112.6 (C-5'), 119.4 (C-2'''), 119.5 (C-2), 122.9 (C-6''), 122.9 (C-6'), 127.9 (C-1''), 131.6 (C-1'), 138.3 (C-3'''), 144.3 (C-3), 149.2 (C-3'), 149.6 (C-3''), 150.7 (C-4''), 153.1 (C-4'), 188.7 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{23}H_{26}O_5$: 382.1780. Found: 382.1771.

(*E*)-3-(3-Methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**13**). Following the general procedure for the preparation of chalcones, a mixture of 0.220 g (1.00 mmol) **33**, 0.150 g (1.00 mmol) **43** and 0.680 g (17.0 mmol) NaOH generated 0.14 g (39%) of **13** as a yellow powder. R_f 0.20 (hexane/EtOAc, 8:2); mp 97-98 °C. IR (film) $\bar{\nu}$ 2929, 1734, 1655, 1599, 1508, 1255, 1167, 1024, 983, 833, 596 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.75 (s, 3H, CH=C(CH_3)$_2$), 1.79 (s, 3H, CH=C(CH_3)$_2$), 3.89 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.64 (d, *J* = 6.7 Hz, 2H, OCH_2CH=C), 5.48 – 5.56 (m, 1H, OCH$_2$C*H*=C), 6.90 (d, *J* = 8.3 Hz, 1H, H-5''), 6.95 – 7.02 (m, 2H, H-3' and H-5'), 7.16 (d, *J* = 1.7 Hz, 1H, H-2''), 7.21 (dd, *J* = 8.3, 1.8 Hz, 1H, H-6''), 7.41 (d, *J* = 15.5 Hz, 1H, H-2), 7.76 (d, *J* = 15.5 Hz, 1H, H-3), 8.01 – 8.07 (m, 2H, H-2' and H-6'). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 18.4 (CH=C(*C*H$_3$)$_2$), 26.0 (CH=C(*C*H$_3$)$_2$), 55.6 (OCH$_3$), 56.1 (OCH$_3$), 65.9 (C-1'''), 110.3 (C-2''), 112.6 (C-5''), 113.9 (C-3' and C-5'), 119.5 (C-2'''), 119.7 (C-2), 123.0 (C-6''), 128.0 (C-1''), 130.8 (C-2' and C-6'), 131.4 (C-1'), 138.3 (C-3'''), 144.4 (C-3), 149.6 (C-3''), 150.7 (C-4''), 163.4 (C-4'), 188.9 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{22}H_{24}O_4$: 352.1675. Found: 352.1668.

(*E*)-1-(4-Hydroxyphenyl)-3-(3-methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)prop-2-en-1-one (**14**). Following the general procedure for the preparation of chalcones, a mixture

of 0.220 g (1.00 mmol) **33**, 0.136 g (1.00 mmol) **44** and 0.680 g (17.0 mmol) NaOH resulted in 0.14 g (40%) of **14** as a yellow powder. R_f 0.23 (hexane/EtOAc, 8:2); mp 130-131 °C. IR (film) $\overline{\nu}$ 2939, 1733, 1655, 1599, 1508, 1421, 1251, 1166, 1035, 957, 918, 835, 804 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.75 (s, 3H, CH=C(CH_3)$_2$), 1.78 (s, 3H, CH=C(CH_3)$_2$), 3.93 (s, 3H, OCH_3), 4.64 (d, *J* = 6.7 Hz, 2H, OCH_2CH=C), 5.51 (td, *J* = 6.1, 5.4, 3.4 Hz, 1H, OCH$_2$C*H*=C), 6.90 (d, *J* = 8.3 Hz, 1H, H-5''), 6.95 – 7.00 (m, 2H, H-3' and H-5'), 7.15 (d, *J* = 1.8 Hz, 1H, H-2''), 7.21 (dd, *J* = 8.3, 1.9 Hz, 1H, H-6''), 7.41 (d, *J* = 15.5 Hz, 1H, H-2), 7.77 (d, *J* = 15.5 Hz, 1H, H-3), 7.98 - 8.00 (m, 2H, H-2' and H-6'). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 18.4 (CH=C(*C*H$_3$)$_2$), 26.0 (CH=C(*C*H$_3$)$_2$), 56.1 (O*C*H$_3$), 65.9 (C-1'''), 110.4 (C-2''), 112.7 (C-5''), 115.7 (C-3' and C-5'), 119.4 (C-2'''), 119.7 (C-2), 123.2 (C-6''), 127.9 (C-1''), 131.1 (C-1'), 131.3 (C-2' and C-6'), 138.5 (C-3'''), 144.9 (C-3), 149.6 (C-3''), 150.8 (C-4''), 160.6 (C-4'), 189.5 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{21}H_{22}O_4$: 338.1518. Found: 338.1520.

(*E*)-1-(4-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)-3-(3-methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)prop-2-en-1-one (**15**). Following the general procedure for the preparation of chalcones, a mixture of 0.220 g (1.00 mmol) **33**, 0.302 g (1.00 mmol) **36** and 0.680 g (17.0 mmol) NaOH promoted the formation of 0.25 g (50%) of **15** as a yellow powder. R_f 0.27 (hexane/EtOAc, 8:2); mp 86-87 °C. IR (film) $\overline{\nu}$ 2929, 1653, 1594, 1509, 1258, 1141, 983, 803, 615 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.60 (s, 3H, CH=C(CH_3)$_2$), 1.67 (s, 3H, CH=C(CH_3)$_2$), 1.76 (s, 6H, CH=C(CH_3)$_2$), 1.79 (s, 3H, CH=C(CH_3)$_2$), 2.04 – 2.17 (m, 4H, H-4''' and H-5'''), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.64 (d, *J* = 6.7 Hz, 2H, H-1''''), 4.72 (d, *J* = 6.4 Hz, 2H, H-1'''), 5.04 – 5.12 (m, 1H, H-6'''), 5.53 (dt, *J* = 6.6, 3.2 Hz, 2H, H-2''' and H-2''''), 6.91 (t, *J* = 8.6 Hz, 2H, H-5' and H-5''), 7.16 (d, *J* = 1.8 Hz, 1H, H-2''), 7.22 (dd, *J* = 8.3 Hz, 1.8, 1H, H-6''), 7.42 (d, *J* = 15.5 Hz, 1H, H-2), 7.63 (d, *J* = 1.9 Hz, 1H, H-2'), 7.66 (dd, *J* = 8.4, 1.9 Hz, 1H, H-6'), 7.77 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 16.9 (CH=C(*C*H$_3$)$_2$), 17.8 (CH=C(*C*H$_3$)$_2$), 18.4 (CH=C(*C*H$_3$)$_2$), 25.8 (CH=C(*C*H$_3$)$_2$), 26.0 (CH=C(*C*H$_3$)$_2$), 26.3 (C-4''' or C-5'''), 39.6 (C-4''' or C-5'''), 56.1 (O*C*H$_3$), 56.2 (O*C*H$_3$), 65.8 (C-1''' or C-1''''), 66.0 (C-1''' or C-1''''), 110.4 (C-2''), 111.0 (C-2'), 111.4 (C-5''), 112.6 (C-5'), 119.2 (C-2'''), 119.5 (C-2), 119.6 (C-2''''), 122.9 (C-6'), 122.9 (C-6''), 123.8 (C-6'''), 128.0 (C-1''), 131.4 (C-1'), 132.0 (C-7'''), 138.3 (C-3''''), 141.4 (C-3'''), 144.3 (C-3), 149.6 (C-

3’’), 149.6 (C-3’), 150.7 (C-4’’), 152.5 (C-4’), 188.8 (C-1). HRMS (EI) *m/z* [M^+] calculated for $C_{32}H_{40}O_5$: 504.2876. Found: 504.2869.

(*E*)-1,3-Bis(3-methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)prop-2-en-1-one (**16**). Following the general procedure for the preparation of chalcones, a mixture of 0.220 g (1.00 mmol) **33**, 0.234 g (1.00 mmol) **35** and 0.680 g (17.0 mmol) NaOH delivered 0.188 g (43%) of **16** as a yellow powder. R_f 0.18 (hexane/EtOAc, 8:2); mp 76-78 °C. IR (film) $\overline{\nu}$ 2933, 1736, 1652, 1593, 1508, 1420, 1257, 1140, 982, 804 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.77 (s, 3H, CH=C(CH_3)$_2$), 1.78 (s, 3H, CH=C(CH_3)$_2$), 1.81 (s, 6H, CH=C(CH_3)$_2$), 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.66 (d, *J* = 6.7 Hz, 2H, H-1’’’’), 4.70 (d, *J* = 6.7 Hz, 2H, H-1’’’), 5.50 – 5.59 (m, 2H, H2’’’ and H-2’’’’), 6.93 (dd, *J* = 10.2, 8.4 Hz, 2H, H-5’ and H-5’’), 7.18 (d, *J* = 1.8 Hz, 1H, H-2’’), 7.24 (dd, *J* = 8.3, 1.8 Hz, 1H, H-6’’), 7.44 (d, *J* = 15.5 Hz, 1H, H-2), 7.64 (d, *J* = 1.9 Hz, 1H, H-2’), 7.68 (dd, *J* = 8.4, 1.9 Hz, 1H, H-6’), 7.78 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 18.4 (CH=C(*C*H_3)$_2$), 18.4 (CH=C(*C*H_3)$_2$), 26.0 (CH=C(*C*H_3)$_2$), 56.1 (O*C*H_3), 56.2 (O*C*H_3), 65.9 (C-1’’’ or C-1’’’’), 65.9 (C-1’’’ or C-1’’’’), 110.4 (C-2’’), 111.0 (C-2’), 111.3 (C-5’), 112.6 (C-5’’), 119.3 (C-2’’’ or C-2’’’’), 119.5 (C-2), 119.6 (C-2’’’ or C-2’’’’), 122.9 (C-6’ or C-6’’), 122.9 (C-6’ or C-6’’), 128.0 (C-1’’), 131.5 (C-1’), 138.3 (C-3’’’ or C-3’’’), 138.5 (C-3’’’ or C-3’’’), 144.3 (C-3), 149.6 (C-3’ or C-3’’), 149.6 (C-3’ or C-3’’), 150.7 (C-4’’), 152.6 (C-4’), 188.8 (C-1). HRMS (EI) *m/z* [M^+] calculated for $C_{27}H_{32}O_5$: 436.2250. Found: 436.2252.

(*E*)-1-(3-Methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**17**). Following the general procedure for the preparation of chalcones, with a mixture of 0.234 g (1.00 mmol) **35**, 0.196 g (1.00 mmol) **37** and 0.680 g (17.0 mmol) NaOH, 0.272 g (66%) of **13** were obtained as a yellow oil. R_f 0.07 (hexane/EtOAc, 8:2). IR (film) $\overline{\nu}$ 2937, 1716, 1655, 1579, 1504, 1419, 1317, 1271, 1166, 1126, 1092, 980, 812, 615 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.77 (s, 3H, CH=C(CH_3)$_2$), 1.79 (s, 3H, CH=C(CH_3)$_2$), 3.90 (s, 3H, OCH_3), 3.93 (s, 6H, OCH_3), 3.96 (s, 3H, OCH_3), 4.68 (d, *J* = 6.6 Hz, 2H, H-1’’’), 5.44 – 5.61 (m, 1H, H-2’’’), 6.88 (s, 2H, H2’’ and H-6’’), 6.93 (d, *J* = 8.4 Hz, 1H, H-5’), 7.45 (d, *J* = 15.5 Hz, 1H, H-2), 7.62 (d, *J* = 1.8, 1H, H-2’), 7.67 (dd, *J* = 8.4, 1.9 Hz, 1H, H-6’), 7.73 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR

(101 MHz, $CDCl_3$) δ = 18.4 (CH=C(CH_3)$_2$), 26.0 (CH=C(CH_3)$_2$), 56.2 (OCH_3), 56.3 (OCH_3), 61.1 (OCH_3), 65.9 (C-1'''), 105.6 (C-2'' and C-6''), 111.0 (C-2'), 111.3 (C-5'), 119.2 (C-2'''), 121.2 (C-2), 123.0 (C-6'), 130.7 (C-1''), 131.2 (C-1'), 138.6 (C-3'''), 140.3 (C-4''), 144.1 (C-3), 149.6 (C-3'), 152.7 (C-4'), 153.5 (C-3'' and C-5''), 188.7 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{24}H_{28}O_6$: 412.1886. Found: 412.1886.

(*E*)-3-(3,4-Dimethoxyphenyl)-1-(3-methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)prop-2-en-1-one (**18**). Following the general procedure for the preparation of chalcones, a mixture of 0.234 g (1.00 mmol) **35**, 0.166 g (1.00 mmol) **38** and 0.680 g (17.0 mmol) NaOH gave 0.25 g (52%) of **18** as a yellow oil. R_f 0.06 (hexane/EtOAc, 8:2). IR (film) $\bar{\nu}$ 2935, 1716, 1651, 1593, 1578, 1509, 1420, 1309, 1259, 1142, 1025, 981, 805, 615 cm^{-1}. ^{1}H NMR (400 MHz,$CDCl_3$) δ = 1.77 (s, 3H, CH=C(CH_3)$_2$), 1.79 (s, 3H, CH=C(CH_3)$_2$), 3.94 (s, 3H, OCH_3), 3.96 (s, 6H, OCH_3), 4.68 (d, *J* = 6.7 Hz, 2H, H-1'''), 5.53 (dt, *J* = 6.6, 3.3 Hz, 1H, H-2'''), 6.90 (d, *J* = 8.4 Hz, 1H, H-5''), 6.92 (d, *J* = 8.4 Hz, 1H, H-5') 7.17 (d, *J* = 1.8 Hz, 1H, H-2''), 7.25 (dd, *J* = 8.3, 1.8 Hz, 1H, H-6''), 7.43 (d, *J* = 15.5 Hz, 1H, H-2), 7.62 (d, *J* = 1.9 Hz, 1H, H-2'), 7.67 (dd, *J* = 8.4, 1.9 Hz, 1H, H-6'), 7.77 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 18.4 (CH=C(CH_3)$_2$), 26.0 (CH=C(CH_3)$_2$), 31.1 (OCH_3), 56.1 (OCH_3), 56.1 (OCH_3), 56.2 (OCH_3), 65.9 (C-1'''), 110.2 (C-2''), 111.0 (C-2'), 111.2 (C-5' or C-5''), 111.3 (C-5' or C-5''), 119.3 (C-2'''), 119.8 (C-2), 122.9 (C-6' or C-6''), 123.0 (C-6' or C-6''), 128.2 (C-1''), 131.4 (C-1'), 138.6 (C-3'''), 144.2 (C-3), 149.3 (C-3''), 149.6 (C-3'), 151.3 (C-4''), 152.6 (C-4'), 188.9 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{23}H_{26}O_5$: 382.1780. Found: 382.1790.

(*E*)-1-(3-Methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**19**). Following the general procedure for the preparation of chalcones, a mixture of 0.234 g (1.00 mmol) **35**, 0.136 g (1.00 mmol) **39** and 0.680 g (17.0 mmol) NaOH afforded 0.324 g (92%) of **19** as a yellow powder. R_f 0.18 (hexane/EtOAc, 8:2); mp 82-83 °C. IR (film) $\bar{\nu}$ 2933, 1735, 1652, 1595, 1572, 1509, 1422, 1252, 1172, 1148, 1030, 982, 829, 799 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.78 (s, 3H, CH=C(CH_3)$_2$), 1.80 (s, 3H, CH=C(CH_3)$_2$), 3.86 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.69 (d, *J* = 6.8 Hz, 2H, H-1'''), 5.54 (t, *J* = 6.6 Hz, 1H, H-2'''), 6.91 – 6.99 (m, 3H, H-5' and H-3''), 7.47 (d, *J* = 15.5 Hz, 1H, H-2), 7.59 – 7.70 (m, 4H, H-2', H-6' and H-2''), 7.80 (d, *J* = 15.6 Hz, 1H, H-3). ^{13}C

NMR (101 MHz, $CDCl_3$) δ = 18.4 (CH=C(CH_3)$_2$), 26.0 (CH=C(CH_3)$_2$), 55.5 (OCH_3), 56.1 (OCH_3), 65.9 (C-1’’’), 110.9 (C-2’), 111.3 (C-5’), 114.5 (C-3’’), 119.3 (C-2’’’), 119.4 (C-2), 122.8 (C-6’), 127.9 (C-1’’), 130.2 (C-2’’), 131.4 (C-1’), 138.5 (C-3’’’), 143.8 (C-3), 149.5 (C-3’), 152.5 (C-4’), 161.6 (C-4’’), 188.7 (C-1). HRMS (EI) *m/z* [M^+] calculated for $C_{22}H_{24}O_4$: 352.1675. Found: 352.1675.

(*E*)-3-(4-Hydroxyphenyl)-1-(3-methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)prop-2-en-1-one (**20**). Following the general procedure for the preparation of chalcones, a mixture of 0.234 g (1.00 mmol) **35**, 0.122 g (1.00 mmol) **40** and 0.680 g (17.0 mmol) NaOH furnished 0.149 g (44%) of **20** as a yellow oil. R_f 0.20 (hexane/EtOAc, 8:2). IR (film) $\bar{\nu}$ 2938, 1716, 1654, 1595, 1508, 1423, 1243, 1171, 1035, 960, 918, 830, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.76 (s, 3H, CH=C(CH_3)$_2$), 1.78 (s, 3H, CH=C(CH_3)$_2$), 3.94 (s, 3H, OCH_3), 4.68 (d, *J* = 6.7 Hz, 2H, H-1’’’), 5.52 (ddd, *J* = 6.7, 5.4, 1.3 Hz, 1H, H-2’’’), 6.89 – 6.96 (m, 3H, H-5’ and H-3’’), 7.44 (d, *J* = 15.6 Hz, 1H, H-2), 7.52 – 7.57 (m, 2H, H-2’’), 7.62 (d, *J* = 1.9 Hz, 1H, H-2’), 7.67 (dd, *J* = 8.4, 2.0 Hz, 1H, H-6’), 7.79 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 18.4 (CH=C(CH_3)$_2$), 26.0 (CH=C(CH_3)$_2$), 56.1 (OCH_3), 66.0 (C-1’’’), 111.1 (C-2’), 111.4 (C-5’), 116.2 (C-3’’), 119.1 (C-2), 123.1 (C-6’), 127.5 (C-1’’), 130.6 (C-2’’), 131.3 (C-1’), 138.7 (C-3’’’), 144.6 (C-3), 149.6 (C-3’), 152.7 (C-4’), 158.8 (C-4’’), 189.5 (C-1). HRMS (EI) *m/z* [M^+] calculated for $C_{21}H_{22}O_4$: 338.1518. Found: 338.1518.

(*E*)-3-(4-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)-1-(3-methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)prop-2-en-1-one (**21**). Following the general procedure for the preparation of chalcones, a mixture of 0.234 g (1.00 mmol) **35**, 0.288 g (1.00 mmol) **34** and 0.680 g (17.0 mmol) NaOH provided 0.242 g (48%) of **21** as a yellow oil. R_f 0.21 (hexane/EtOAc, 8:2). IR (film) $\bar{\nu}$ 2931, 1716, 1653, 1593, 1508, 1420, 1340, 1258, 1140, 1031, 983, 844, 803, 612 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.59 (s, 3H, CH=C(CH_3)$_2$), 1.66 (s, 3H, CH=C(CH_3)$_2$), 1.73 (s, 3H, CH=C(CH_3)$_2$), 1.74 (s, 3H, CH=C(CH_3)$_2$), 1.77 (s, 3H, CH=C(CH_3)$_2$), 1.99 – 2.19 (m, 4H, H-4’’’’ and H-5’’’’), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.61 – 4.69 (m, 4H, H-1’’’ and H-1’’’’), 4.99 – 5.11 (m, 1H, H-6’’’’), 5.50 (dt, *J* = 5.2, 2.7 Hz, 2H, H-2’’’ and H-2’’’’), 6.89 (t, *J* = 8.1 Hz, 2H, H-5’ and H-5’’), 7.17 (d, *J* = 1.8 Hz, 1H), 7.20 (dd, *J* = 8.3, 1.9 Hz, 1H, H-6’’), 7.43 (d, *J* = 15.5 Hz, 1H, H-2), 7.61 (d,

J = 1.9 Hz, 1H, H-2'), 7.66 (dd, *J* = 8.4, 2.0 Hz, 1H, H-6'), 7.76 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 16.7 (CH=C(*C*H_3)$_2$), 17.7 (CH=C(*C*H_3)$_2$), 18.3 (CH=C(*C*H_3)$_2$), 25.7 (CH=C(*C*H_3)$_2$), 25.8 (CH=C(*C*H_3)$_2$), 26.2 (C-4'''' or C-5''''), 39.5 (C-4'''' or C-5''''), 55.9 (OC*H*$_3$), 56.0 (OC*H*$_3$), 65.8 (C-1''' or C-1''''), 65.8 (C-1''' or C-1''''), 110.3 (C-2''), 110.8 (C-2'), 111.2 (C-5'), 112.6 (C-5''), 119.2 (C-2''' and C-3''''), 119.4 (C-2), 122.8 (C-6' or C-6''), 122.8 (C-6' or C-6''), 123.7 (C-6''''), 127.9 (C-1''), 131.3 (C-1'), 131.7 (C-7''''), 138.4 (C-3'''), 141.1 (C-3''''), 144.1 (C-3), 149.5 (C-3' and C-3''), 150.5 (C-4''), 152.4 (C-4'), 188.6 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{32}H_{40}O_5$: 504.2876. Found: 504.2884.

(*E*)-3-(4-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**22**). Following the general procedure for the preparation of chalcones, a mixture of 0.288 g (1.00 mmol) **34**, 0.210 g (1.00 mmol) **41** and 0.680 g (17.0 mmol) NaOH yielded 0.159 g (33%) of **22** as a yellow powder. R_f 0.15 (hexane/EtOAc, 8:2); mp 66-67 °C. IR (film) $\overline{\nu}$ 2937, 1655, 1578, 1505, 1463, 1414, 1334, 1253, 1231, 1157, 1127, 1001, 840, 766 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.60 (s, 3H, CH=C(C*H*$_3$)$_2$), 1.67 (s, 3H, CH=C(C*H*$_3$)$_2$), 1.75 (s, 3H, CH=C(C*H*$_3$)$_2$), 2.03 – 2.16 (m, 4H, H-4''' and H-5'''), 3.94 (s, 3H, OC*H*$_3$), 3.94 (s, 3H, OC*H*$_3$), 3.95 (s, 6H, OC*H*$_3$), 4.69 (d, *J* = 6.4 Hz, 2H, H-1'''), 5.08 (td, *J* = 6.7, 6.0, 3.3 Hz, 1H, H-6'''), 5.51 (dt, *J* = 6.3, 3.2 Hz, 1H, H-2'''), 6.91 (d, *J* = 8.3 Hz, 1H, H-5''), 7.16 (d, *J* = 1.9 Hz, 1H, H-2''), 7.23 (dd, *J* = 8.5, 2.0 Hz, 1H, H-6''), 7.27 (d, *J* = 2.2 Hz, 2H, H-2' and H-6'), 7.33 (d, *J* = 15.6 Hz, 1H, H-2), 7.77 (d, *J* = 15.6 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 16.9 (CH=C(*C*H_3)$_2$), 17.8 (CH=C(*C*H_3)$_2$), 25.8 (CH=C(*C*H_3)$_2$), 26.3 (C-4''' or C-5'''), 39.7 (C-4''' or C-5'''), 56.2 (O*C*H_3), 56.5 (O*C*H_3), 61.1 (O*C*H_3), 66.0 (C-1'''), 106.2 (C-2' and C-6'), 110.8 (C-2''), 112.8 (C-5''), 119.3 (C-2'''), 119.8 (C-2), 122.9 (C-6''), 123.8 (C-6'''), 127.8 (C-1''), 132.0 (C-7'''), 134.0 (C-1'), 141.4 (C-3'''), 142.4 (C-4'), 145.2 (C-3), 149.7 (C-3''), 150.9 (C-4''), 153.2 (C-3' and C-5'), 189.6 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{29}H_{36}O_6$: 480.2512. Found: 480.2510.

(*E*)-1-(3,4-Dimethoxyphenyl)-3-(4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)prop-2-en-1-one (**23**). Following the general procedure for the preparation of chalcones, a mixture of 0.288 g (1.00 mmol) **34**, 0.180 g (1.00 mmol) **42** and

0.680 g (17.0 mmol) NaOH produced 0.167 g (37%) of **23** as a yellow powder. R_f 0.10 (hexane/EtOAc, 8:2); mp 48-49 °C. IR (film) $\bar{\nu}$ 2933, 1652, 1594, 1578, 1509, 1463, 1420, 1259, 1160, 1139, 1024, 984, 803, 766 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.60 (s, 3H, CH=C(CH_3)$_2$), 1.67 (s, 3H, CH=C(CH_3)$_2$), 1.75 (s, 3H, CH=C(CH_3)$_2$), 2.02 – 2.19 (m, 4H, H-4''' and H-5'''), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.68 (d, *J* = 6.4 Hz, 2H, H-1'''), 5.08 (t, *J* = 6.0 Hz, 1H, H-6'''), 5.45 – 5.59 (m, 1H, H-2'''), 6.90 (d, *J* = 8.3 Hz, 1H, H-5''), 6.94 (d, *J* = 8.4 Hz, 1H, H-5'), 7.17 (d, *J* = 1.7 Hz, 1H, H-2''), 7.22 (dd, *J* = 8.3, 1.7 Hz, 1H, H-6''), 7.42 (d, *J* = 15.5 Hz, 1H, H-2), 7.63 (d, *J* = 1.8 Hz, 1H, H-2'), 7.69 (dd, *J* = 8.4, 1.9 Hz, 1H, H-6'), 7.77 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 16.9 (CH=C(*C*H_3)$_2$), 17.8 (CH=C(*C*H_3)$_2$), 25.8 (CH=C(*C*H_3)$_2$), 26.3 (C-4''' or C-5'''), 39.7 (C-4''' or C-5'''), 56.1 (O*C*H_3), 56.2 (O*C*H_3), 56.2 (O*C*H_3), 66.0 (C-1'''), 110.0 (C-5'), 110.5 (C-2''), 110.9 (C-2'), 112.8 (C-5''), 119.4 (C-2'''), 119.6 (C-2), 122.9 (C-6' and C-6''), 123.9 (C-6'''), 128.0 (C-1''), 131.7 (C-1'), 132.0 (C-7'''), 141.3 (C-3'''), 144.4 (C-3), 149.3 (C-3'), 149.6 (C-3''), 150.7 (C-4''), 153.2 (C-4'), 188.8 (C-1). HRMS (EI) *m/z* [M^+] calculated for $C_{28}H_{34}O_5$: 450.2406. Found: 450.2406.

(*E*)-3-(4-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**24**). Following the general procedure for the preparation of chalcones, a mixture of 0.288 g (1.00 mmol) **34**, 0.150 g (1.00 mmol) **43** and 0.680 g (17.0 mmol) NaOH generated 0.130 g (31%) of **24** as a yellow oil. R_f 0.25 (hexane/EtOAc, 8:2). IR (film) $\bar{\nu}$ 2930, 1736, 1655, 1599, 1508, 1463, 1421, 1308, 1252, 1212, 1165, 1138, 983 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.60 (s, 3H, CH=C(CH_3)$_2$), 1.67 (s, 3H, CH=C(CH_3)$_2$), 1.74 (s, 3H, CH=C(CH_3)$_2$), 2.03 – 2.15 (m, 4H, H-4''' and H-5'''), 3.87 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.67 (d, *J* = 6.4 Hz, 2H, H-1'''), 5.04 – 5.12 (m, 1H, H-6'''), 5.47 – 5.55 (m, 1H, H-2'''), 6.89 (d, *J* = 8.3 Hz, 1H, H-5''), 6.94 – 7.01 (m, 2H, H-3'), 7.17 (d, *J* = 1.8 Hz, 1H, H-2''), 7.20 (dd, *J* = 8.3, 1.9 Hz, 1H, H-6''), 7.41 (d, *J* = 15.5 Hz, 1H, H-2), 7.76 (d, *J* = 15.5 Hz, 1H, H-3), 8.01 – 8.08 (m, 2H, H-2'). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.8 (CH=C(*C*H_3)$_2$), 17.8 (CH=C(*C*H_3)$_2$), 25.8 (CH=C(*C*H_3)$_2$), 26.3 (C-4''' or C-5'''), 39.6 (C-4''' or C-5'''), 55.5 (O*C*H_3), 56.0 (O*C*H_3), 65.9 (C-1'''), 110.3 (C-2''), 112.7 (C-5''), 113.8 (C-3'), 119.3 (C-2'''), 119.6 (C-2), 123.0 (C-6''), 123.8 (C-6'''), 127.9 (C-1'), 130.8 (C-2'), 131.4 (C-1''), 131.9 (C-7'''), 141.2 (C-3'''), 144.3 (C-

3), 149.6 (C-3''), 150.6 (C-4''), 163.3 (C-4'), 188.8 (C-1). HRMS (EI) *m/z* [M^+] calculated for $C_{27}H_{32}O_4$: 420.2301. Found: 420.2305.

(*E*)-3-(4-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (**25**). Following the general procedure for the preparation of chalcones, a mixture of 0.288 g (1.00 mmol) **34**, 0.136 g (1.00 mmol) **44** and 0.680 g (17.0 mmol) NaOH resulted in 0.126 g (31%) of **25** as a yellow oil. R_f 0.29 (hexane/EtOAc, 8:2). IR (film) $\overline{\nu}$ 2938, 1655, 1599, 1508, 1421, 1308, 1252, 1212, 1166, 1035, 957, 918, 803 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.59 (s, 3H, CH=C(CH_3)$_2$), 1.66 (s, 3H, CH=C(CH_3)$_2$), 1.74 (s, 3H, CH=C(CH_3)$_2$), 2.02 – 2.16 (m, 4H, H-4''' and H-5'''), 3.93 (s, 3H, OCH_3), 4.67 (d, *J* = 6.4 Hz, 2H, H-1'''), 5.02 – 5.11 (m, 1H, H-6'''), 5.46 – 5.57 (m, 1H, H-2'''), 6.89 (d, *J* = 8.3 Hz, 1H, H-5''), 6.97 (d, *J* = 8.7 Hz, 2H, H-3'), 7.15 (d, *J* = 1.8 Hz, 1H, H-2''), 7.20 (dd, *J* = 8.3, 1.8 Hz, 1H, H-6''), 7.42 (d, *J* = 15.5 Hz, 1H, H-2), 7.77 (d, *J* = 15.5 Hz, 1H, H-3), 7.99 (d, *J* = 8.8 Hz, 2H, H-2'). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 16.9 (CH=C(*C*H$_3$)$_2$), 17.8 (CH=C(*C*H$_3$)$_2$), 25.8 (CH=C(*C*H$_3$)$_2$), 26.3 (C-4''' or C-5'''), 39.6 (C-4''' or C-5'''), 56.1 (O*C*H$_3$), 66.0 (C-1'''), 110.4 (C-2''), 112.7 (C-5''), 115.7 (C-3'), 119.2 (C-2'''), 119.7 (C-2), 123.2 (C-6''), 123.9 (C-6'''), 127.9 (C-1''), 130.8 (C-1'), 131.3 (C-2'), 132.0 (C-7'''), 141.4 (C-3'''), 144.9 (C-3), 149.6 (C-3'), 150.8 (C-4''), 161.1 (C-4'), 189.6 (C-1). HRMS (EI) *m/z* [M^+] calculated for $C_{26}H_{30}O_4$: 406.2144. Found: 406.2148.

(*E*)-1,3-Bis(4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)prop-2-en-1-one (**26**). Following the general procedure for the preparation of chalcones, a mixture of 0.288 g (1.00 mmol) **34**, 0.302 g (1.00 mmol) **36** and 0.680 g (17.0 mmol) NaOH promoted the formation of 0.309 g (54%) of **26** as a yellow powder. R_f 0.47 (hexane/EtOAc, 8:2); mp 54-55 °C. IR (film) $\overline{\nu}$ 2916, 1654, 1594, 1509, 1420, 1259, 1141, 1032, 985, 801 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.60 (s, 6H, CH=C(CH_3)$_2$), 1.67 (s, 6H, CH=C(CH_3)$_2$), 1.75 (d, *J* = 4.1 Hz, 6H, CH=C(CH_3)$_2$), 2.03 – 2.16 (m, 8H, H-4''', H-5''', H-4'''' and H-5''''), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.68 (d, *J* = 6.4 Hz, 2H, H-1''''), 4.72 (d, *J* = 6.4 Hz, 2H, H-1'''), 5.02 – 5.15 (m, 2H, H-6''' and H-6''''), 5.52 (q, *J* = 5.0 Hz, 2H, H-2''' and H-2''''), 6.91 (dd, *J* = 10.5, 8.4 Hz, 2H, H-5' and H-5''), 7.17 (d, *J* = 1.8 Hz, 1H, H-2''), 7.22 (dd, *J* = 8.3, 1.8 Hz, 1H, H-6''), 7.42 (d, *J* = 15.5 Hz, 1H, H-2), 7.63 (d, *J* = 1.9

Hz, 1H, H-2'), 7.66 (dd, *J* = 8.4, 1.9 Hz, 1H, H-6'), 7.77 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 16.9 (CH=C(*C*H_3)$_2$), 17.8 (CH=C(*C*H_3)$_2$), 25.8 (CH=C(*C*H_3)$_2$), 26.3 (C-4''' or C-5''' and C-4'''' or C-5''''), 39.6 (C-4''' or C-5''' and C-4'''' or C-5''''), 56.1 (O*C*H_3), 56.2 (O*C*H_3), 66.0 (C-1''' or C-1''''), 66.0 (C-1''' or C-1''''), 110.4 (C-2''), 111.0 (C-2'), 111.4 (C-5'), 112.7 (C-5''), 119.2 (C-2''' or C-2''''), 119.3 (C-2''' or C-2''''), 119.6 (C-2), 122.8 (C-6' or C-6''), 122.9 (C-6' or C-6''), 123.8 (C-6''' or C-6''''), 123.8 (C-6''' or C-6''''), 128.0 (C-1''), 131.4 (C-1'), 131.9 (C-7''' or C-7''''), 131.9 (C-7''' or C-7''''), 141.3 (C-3''' or C-3''''), 141.4 (C-3''' or C-3''''), 144.3 (C-3), 149.6 (C-3' or C-3''), 149.6 (C-3' or C-3''), 150.7 (C-4''), 152.5 (C-4'), 188.8 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{37}H_{48}O_5$: 572.3502. Found: 572.3493.

(*E*)-1-(4-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**27**). Following the general procedure for the preparation of chalcones, a mixture of 0.302 g (1.00 mmol) **36**, 0.196 g (1.00 mmol) **37** and 0.680 g (17.0 mmol) NaOH delivered 0.187 g (39%) of **27** as a yellow oil. R_f 0.11 (hexane/EtOAc, 8:2). IR (film) $\bar{\nu}$ 2933, 1653, 1594, 1578, 1463, 1420, 1341, 1309, 1259, 1196, 1143, 1025, 982, 913 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.59 (s, 3H, CH=C(C*H*$_3$)$_2$), 1.66 (s, 3H, CH=C(C*H*$_3$)$_2$), 1.75 (s, 3H, CH=C(C*H*$_3$)$_2$), 2.02 – 2.20 (m, 4H, H-4''' and H-5'''), 3.90 (s, 3H, OC*H*$_3$), 3.92 (s, 6H, OC$\underline{H}_3$), 3.96 (s, 3H, OC*H*$_3$), 4.71 (d, *J* = 6.4 Hz, 2H, H-1'''), 5.07 (ddd, *J* = 6.7, 4.0, 1.3 Hz, 1H, H-6'''), 5.46 – 5.56 (m, 1H, H-2'''), 6.87 (s, 2H, H-2'' and H-6''), 6.92 (d, *J* = 8.4 Hz, 1H, H-5'), 7.45 (d, *J* = 15.5 Hz, 1H, H-2), 7.62 (d, *J* = 1.9 Hz, 1H, H-2'), 7.67 (dd, *J* = 8.4, 2.0 Hz, 1H, H-6'), 7.72 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 16.8 (CH=C(*C*H_3)$_2$), 17.8 (CH=C(*C*H_3)$_2$), 25.7 (CH=C(*C*H_3)$_2$), 26.2 (C-4''' or C-5'''), 39.6 (C-4''' or C-5'''), 56.1 (O*C*H_3), 56.2 (O*C*H_3), 61.0 (O*C*H_3), 66.0 (C-1'''), 105.5 (C-2'' and C-6''), 110.9 (C-2'), 111.3 (C-5'), 119.0 (C-2'''), 121.1 (C-2), 123.0 (C-6'), 123.7 (C-6'''), 130.7 (C-1''), 131.1 (C-1'), 131.9 (C-7'''), 140.2 (C-4''), 141.5 (C-3'''), 144.1 (C-3), 149.6 (C-3'), 152.6 (C-4'), 153.5 (C-3'' and C-5''), 188.6 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{29}H_{36}O_6$: 480.2512. Found: 480.2505.

(*E*)-3-(3,4-Dimethoxyphenyl)-1-(4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)prop-2-en-1-one (**28**). Following the general procedure for the

preparation of chalcones and with a mixture of 0.302 g (1.00 mmol) **36**, 0.166 g (1.00 mmol) **38** and 0.680 g (17.0 mmol) NaOH, 0.284 g (63%) of **13** were obtained as a yellow oil. R_f 0.10 (hexane/EtOAc, 8:2). IR (film) $\bar{\nu}$ 2935, 2840, 1655, 1593, 1579, 1419, 1315, 1259, 1197, 1146, 1127, 1027, 982, 807 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.60 (s, 3H, CH=C(CH_3)$_2$), 1.67 (s, 3H, CH=C(CH_3)$_2$), 1.76 (s, 3H, CH=C(CH_3)$_2$), 2.03 – 2.17 (m, 4H, H-4''' and H-5'''), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.71 (d, *J* = 6.5 Hz, 2H, H-1'''), 5.04 – 5.12 (m, 1H, H-6'''), 5.52 (t, *J* = 6.0 Hz, 1H, H-2'''), 6.91 (dd, *J* = 9.7, 8.5 Hz, 2H, H-5' and H-5''), 7.17 (d, *J* = 1.8 Hz, 1H, H-2''), 7.24 (dd, *J* = 8.3, 1.8 Hz, 1H, H-6''), 7.44 (d, *J* = 15.5 Hz, 1H, H-2), 7.63 (d, *J* = 1.9 Hz, 1H, H-2'), 7.67 (dd, *J* = 8.4, 1.9 Hz, 1H, H-6''), 7.77 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (101 MHz, CDCl3) δ = 16.8 (CH=C(*C*H_3)$_2$), 17.7 (CH=C(*C*H_3)$_2$), 25.7 (CH=C(*C*H_3)$_2$), 26.2 (C-4''' or C-5'''), 39.6 (C-4''' or C-5'''), 56.0 (O*C*H_3), 56.0 (O*C*H_3), 56.1 (O*C*H_3), 66.0 (C-1'''), 110.1 (C-2''), 110.9 (C-2'), 111.1 (C-5''), 111.3 (C-5'), 119.1 (C-2'''), 119.6 (C-2), 122.8 (C-6'), 122.9 (C-6''), 123.7 (C-6'''), 128.1 (C-1''), 131.3 (C-1'), 131.8 (C-7'''), 141.4 (C-3'''), 144.0 (C-3), 149.2 (C-3''), 149.5 (C-3'), 151.2 (C-4''), 152.5 (C-4'), 188.6 (C-1). HRMS (EI) *m*/*z* [M^+] calculated for $C_{28}H_{34}O_5$: 450.2406. Found: 450.2416.

(*E*)-1-(4-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**29**). Following the general procedure for the preparation of chalcones, a mixture of 0.302 g (1.00 mmol) **36**, 0.136 g (1.00 mmol) **39** and 0.680 g (17.0 mmol) NaOH gave 0.185 g (44%) of **29** as a yellow powder. R_f 0.26 (hexane/EtOAc, 8:2); mp 84-85 °C. IR (film) $\bar{\nu}$ 2928, 1654, 1596, 1572, 1509, 1463, 1422, 1328, 1294, 1253, 1172, 1031, 984, 828 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.60 (s, 3H, CH=C(CH_3)$_2$), 1.67 (s, 3H, CH=C(CH_3)$_2$), 1.76 (s, 3H, CH=C(CH_3)$_2$), 2.03 – 2.17 (m, 4H, H-4''' and H-5'''), 3.86 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.72 (d, *J* = 6.4 Hz, 2H, H-1'''), 5.08 (t, *J* = 6.0, 1H, H-6'''), 5.52 (t, *J* = 6.1 Hz, 1H, H-2'''), 6.88 – 6.97 (m, 3H, H-5' and H-3''), 7.45 (d, *J* = 15.6 Hz, 1H, H-2), 7.57 – 7.65 (m, 3H, H-2'' and H-2'), 7.66 (dd, *J* = 8.4, 1.9 Hz, 1H, H-6'), 7.79 (d, *J* = 15.6 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 16.9 (CH=C(*C*H_3)$_2$), 17.8 (CH=C(*C*H_3)$_2$), 25.8 (CH=C(*C*H_3)$_2$), 26.3 (C-4''' or C-5'''), 39.7 (C-4''' or C-5'''), 55.5 (O*C*H_3), 56.2 (O*C*H_3), 66.1 (C-1'''), 111.0 (C-2''), 111.4 (C-5''), 114.5 (C-3''), 119.2 (C-2'''), 119.5 (C-2), 122.8 (C-6''), 123.8 (C-6'''), 127.9 (C-1''), 130.2 (C-2''), 131.5 (C-1'), 132.0 (C-7'''), 141.5 (C-3'''), 143.8 (C-3),

149.6 (C-3'), 152.5 (C-4'), 161.6 (C-4''), 188.8 (C-1). HRMS (EI) *m/z* [M^+] calculated for $C_{27}H_{32}O_4$: 420.2301. Found: 420.2304.

(*E*)-1-(4-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-3-methoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (**30**). Following the general procedure for the preparation of chalcones, a mixture of 0.302 g (1.00 mmol) **36**, 0.122 g (1.00 mmol) **40** and 0.680 g (17.0 mmol) NaOH afforded 0.118 g (29%) of **30** as a yellow powder. R_f 0.31 (hexane/EtOAc, 8:2); mp 82-83 °C. IR (film) $\bar{\nu}$ 2936, 1655, 1596, 1573, 1463, 1422, 1324, 1258, 1171, 1147, 1122, 1035, 960 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.59 (s, 3H, CH=C(CH_3)$_2$), 1.66 (s, 3H, CH=C(CH_3)$_2$), 1.75 (s, 3H, CH=C(CH_3)$_2$), 2.02 – 2.16 (m, 4H, H-4''' and H-5'''), 3.93 (s, 3H, OCH_3), 4.71 (d, *J* = 6.4 Hz, 2H, H-1'''), 5.01 – 5.12 (m, 1H, H-6'''), 5.43 – 5.59 (m, 1H, H-2'''), 6.88 – 6.98 (m, 3H, H-5' and H-3''), 7.44 (d, *J* = 15.5 Hz, 1H, H-2), 7.51 – 7.56 (m, 2H, H-2''), 7.62 (d, *J* = 1.9 Hz, 1H, H-2'), 7.67 (dd, *J* = 8.5, 1.9 Hz, 1H, H-6'), 7.80 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 16.9 (CH=C(*C*H$_3$)$_2$), 17.8 (CH=C(*C*H$_3$)$_2$), 25.8 (CH=C(*C*H$_3$)$_2$), 26.3 (C-4''' or C-5'''), 39.6 (C-4''' or C-5'''), 56.1 (O*C*H$_3$), 66.1 (C-1'''), 111.0 (C-2'), 111.5 (C-5'), 116.3 (C-3''), 118.9 (C-2), 119.0 (C-2'''), 123.2 (C-6'), 123.8 (C-6'''), 127.3 (C-1''), 130.6 (C-2''), 131.2 (C-1'), 132.0 (C-7'''), 141.7 (C-3'''), 144.9 (C-3), 149.5 (C-3'), 152.8 (C-4'), 159.0 (C-4''), 189.7 (C-1). HRMS (EI) *m/z* [M^+] calculated for $C_{26}H_{30}O_4$: 406.2144. Found: 406.2150.

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Highlights for review

- Prenyloxylated chalcones display metabolic inhibition against *Leishmania mexicana* and *Trypanosoma cruzi*.
- Prenyloxy groups attached to A-ring display less cytotoxicity against macrophages.
- Structural isomers of chalcones display different selectivity indexes.
- Three of the synthesized chalcones shown better selectivity index than reference drugs for *Trypanosoma cruzi*.