Med Chem Res
DOI 10.1007/s00044-017-2076-6

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antiprotozoal activity of furanchalcone–quinoline, furanchalcone–chromone and furanchalcone–imidazole hybrids

Elisa García[1] · Juan C. Coa[1] · Elver Otero[1] · Miguel Carda[2] · Iván D. Vélez[3] · Sara M. Robledo[3] · Wilson I. Cardona[1]

Received: 24 May 2017 / Accepted: 14 September 2017

Abstract We report herein the synthesis and biological activities (cytotoxicity, leishmanicidal, and trypanocidal) of several furanchalcone–quinoline, furanchalcone–chromone, and furanchalcone–imidazole hybrids. The synthesized compounds were evaluated against amastigotes forms of *L. (V) panamensis*, which is the most prevalent *Leishmania* species in Colombia and against *Trypanosoma cruzi*, which is the major pathogenic species to humans. Cytotoxicity was evaluated against human U-937 macrophages. Compounds (**6e**, **8a–8f**, **11b**, and **11c**) were active against both *L. (V) panamensis* and *T. cruzi* being **8e** and **8f** the most active compounds with an EC_{50} of 0.78 and 2.16 μM against *L. (V) panamensis*, respectively, and 0.66 and 0.72 μM against *T. cruzi*, respectively. Seven hybrid compounds showed better activity than meglumine antimoniate and the anti-trypanosomal activity of nine compounds were higher than benznidazole. Although these compounds showed toxicity for mammalian U-937 cells, they still have the potential to be considered as candidates for antileishmanial or trypanocydal drug development. There is not a clear relationship between the antiprotozoal activity and the length of the alkyl linker. However, we obtained higher bioactivity when the alkyl linker has nine and twelve carbon atoms. Furanchalcone-imidazole hybrids were the most active of all compounds, showing that the imidazole salt moiety is important for their biological actions.

Keywords Leishmaniasis · Chagas disease · Antiprotozoal activity · Furanchalcone · Hybrids · Quinoline

Introduction

Neglected tropical diseases (NTD) are a cause of mortality in various developing countries of tropical and subtropical regions. These diseases are significant health problems in several countries, affecting more than one billion people worldwide (WHO 2013). This situation is aggravated by increasing treatment failures with available drugs (Bhutta et al. 2014). NTD include, among others, Chagas' disease (American trypanosomiasis) and leishmaniasis. These are parasitic diseases caused by the parasitic protozoan *Trypanosoma cruzi* (*T. cruzi*) and *Leishmania* species. These diseases affect more than 10 million people worldwide (Alvar et al. 2012; Nouvellet et al. 2015). *L. (V) panamensis* is one of the most prevalent *Leishmania* species involved in human cases of cutaneous leishmaniasis in Colombia (Alvar et al. 2012). Current chemotherapies are based on old drugs, such as pentavalent antimonials (meglumine antimoniate and sodium stibogluconate) to treat cutaneous leishmaniasis and

Electronic Supplementary Material The online version of this article (https://doi.org/10.1007/s00044-017-2076-6) contains supplementary material, which is available to authorized users.

✉ Sara M. Robledo
sara.robledo@udea.edu.co

✉ Wilson I. Cardona
wilson.cardona1@udea.edu.co

[1] Chemistry of Colombian Plants, Institute of Chemistry, School of Exact and Natural Sciences, University of Antioquia-UdeA, Calle 70 No. 52-21, A.A 1226, Medellín, Colombia

[2] Department of Inorganic and Organic Chemistry, Jaume I University, 12071 Castellón, Spain

[3] PECET-Medical Research Institute, School of Medicine, University of Antioquia-UdeA, Calle 70. No. 52-21, A.A1226, Medellín, Colombia

Published online: 26 September 2017

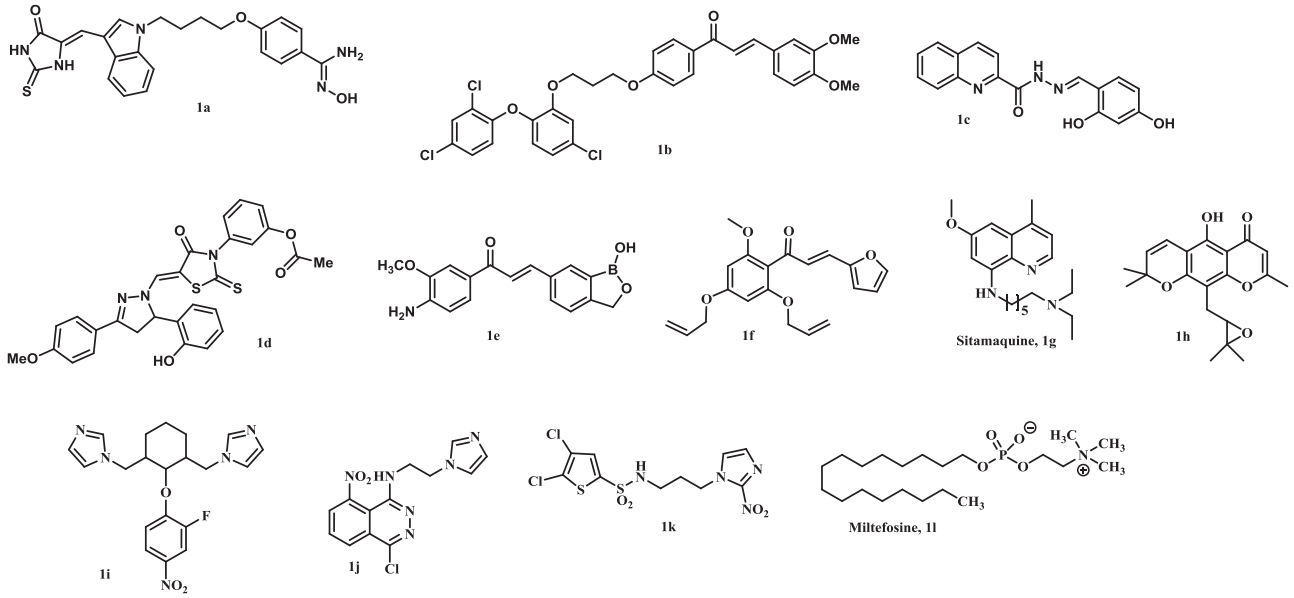


Fig. 1 Compounds with antiprotozoal activity

nitroaromatic compounds (benznidazole and nifurtimox) for treatment of Chagas disease. Unfortunately, all these drugs are not very effective in the chronic phase and have toxicity, side effects and parasite resistance (Chatelain and Ioset 2011; Den Boer et al. 2011; Keenan and Chaplin 2015).

Strategies for the discovery and development of new drugs for use in the treatment of parasitic diseases have include by decades not only natural products and synthetic derivatives, but also the development of analogs of existing agents and the design of inhibitors of target molecules of the parasite, among others (Rosenthal 2003). In recent years, a promising strategy has emerged based on hybrid molecules which bear in their structures two distinct pharmacophores having, for example, antiprotozoal, anti-inflammatory, antifungal, or anticancer activity, and thus showing a dual mode of action (Keith et al. 2005; Meunier 2008). For instance, in cell-based assays pentamidine–aplysinopsin derivative **1a** have shown anti-leishmanial activity against *L. donovani* amastigotes with ten times more activity and 401-fold less toxicity than pentamidine alone (Porwal et al. 2009) (Fig. 1). Triclosan-chalcone hybrid **1b**, was no cytotoxic against U-937 cells and active against *L. panamensis* amastigotes ($LC_{50} = >200$ µg/mL, >326.7 µM and $EC_{50} = 9.4 \pm 1.3$ µg/mL, 15.4 µM) (Otero et al. 2014) Quinoline-hydrazone hybrid **1c** showed activity against *L. panamensis* and against *T. cruzi* with EC_{50} of 0.8 ± 0.0 mg/mL (2.6 µM) and 6.6 ± 0.3 mg/mL (4.6 µM) respectively (Coa et al. 2015). Pyrazoline-thiazolidinone hybrid **1d** showed an IC_{50} value of 0.7 µM against *T. brucei* bloodstream forms and was six-times more potent and more selective than nifurtimox with a selectivity index >50 (Havrylyuk et al. 2014). Chalcone-benzoxaborole hybrid **1e** showed an IC_{50} of 0.01 µg/mL against bloodstream form of *T. brucei* and elimination of parasitemia in a murine model of infection (Qiao et al. 2012). The anti-leishmanial and anti-trypanosomal activities of chalcones, quinolines, chromones, imidazoles, and quaternary ammonium salts derivatives have been reported (Fig. 1). Some examples are: (i) Heterocycle chalcone **1f** which showed high trypanocidal activity against trypomastigotes of *T. cruzi* and low cytotoxicity with a selectivity index of 15.6 (Aponte et al. 2008). (ii) Several quinoline analogous, such as sitamaquine **1g** and imiquimod, which have been tested in vitro and in vivo over across different *Leishmania* species and have advanced to clinical phase studies (Croft and Coombs 2003). (iii) The natural derived chromone **1h** which has been isolated from *Spathelia excels* and has shown high activity against *T. cruzi* epimastigotes with IC_{50} of 11 µg/mL (Dos Santos et al. 2009). (iv) Aryloxy cyclohexane-based mono and bisimidazoles are active compounds against amastigotes of *L. donovani*, with the 2-fluoro-4-nitro aryloxy derivative **1i** displaying a 77.9% inhibition of infection in in vivo studies (Srinivas et al. 2009). (v) A nitro-phthalazine derivative with imidazole pendant **1j** were active against *T. cruzi* amastigotes (Olmo et al. 2015). (vi) The imidazole-based derivative **1k** was active against *T. cruzi* amastigotes displaying an IC_{50} of 4.75 µM a selectivity index of 16 (Papadopoulou et al. 2014). And (vii) Miltefosine (hexadecylphosphocholine) **1l** is being used for the oral treatment of both cutaneous and visceral leishmaniasis (Croft and Yardley 2002).

According to the mechanism of action of chalcones, chromones, quinolines, and imidazoles, it has been reported that chalcones may inhibit mitochondrial proteins of the

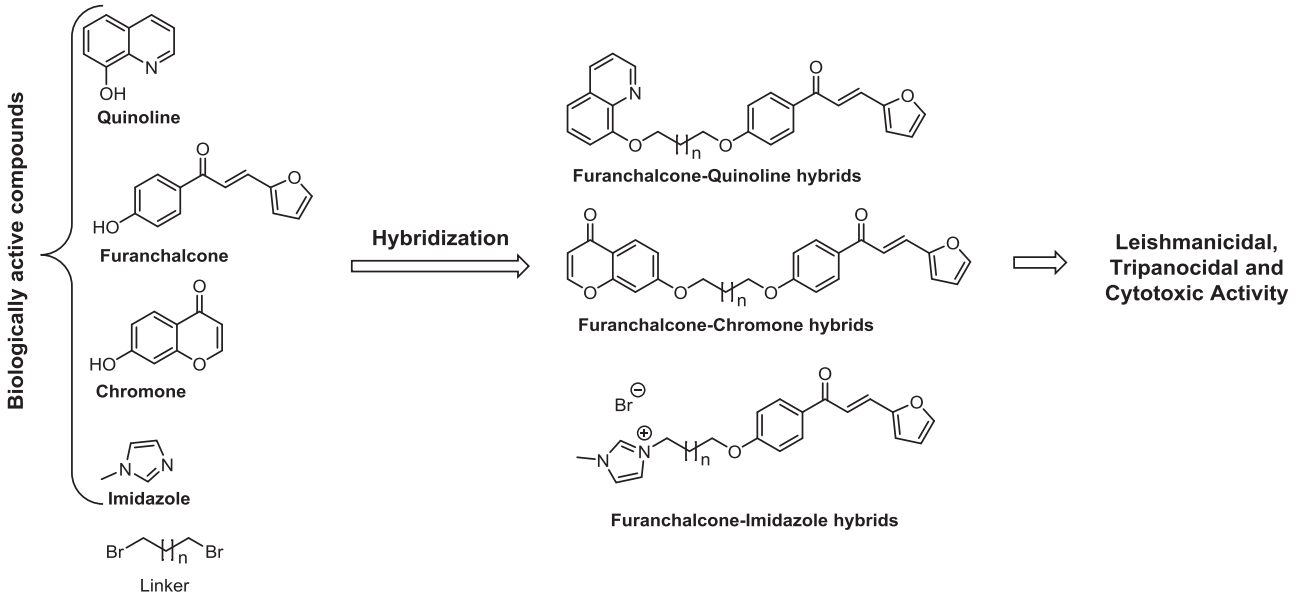


Fig. 2 Design of furanchalcone derivatives as antiprotozoal agents

Leishmania parasite, such as fumarate reductase, succinate dehydrogenase, NADH dehydrogenase, and NADH-cytochrome c reductase (Chen et al. 2001). Furthermore, chromones that are α,β-unsaturated carbonyl compounds, can react with nucleophiles such as glutathione, via conjugated addition (Aponte et al. 2008). Other compounds such as quinolines could act by stimulating nitric oxide (NO) production from macrophages (Croft and Coombs 2003) or they can mediate alterations in mitochondrial membrane potential through increase in the mitochondrial ROS production (Nakayama et al. 2005; Coimbra et al. 2016; Tempone et al. 2005). On the other hand, it has been reported that imidazoles derivatives may be potent inhibitors of iron superoxide dismutase enzyme (Fe-SOD) of promastigote forms in several species of *Leishmania* (Sánchez-Moreno et al. 2012).

In the search for new therapeutic alternatives to treat cutaneous leishmaniasis and Chagas disease, a series of furanchalcone–quinoline, furanchalcone–chromone, and furanchalcone–imidazole hybrids were designed, synthesized and evaluated in vitro their cytotoxicity, anti-leishmanial, and anti-trypanosomal activities (Fig. 2).

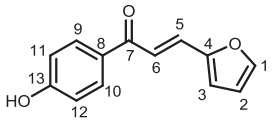
Material and methods

Chemistry

General remarks

Microwave reactions were carried out in a CEM Discover microwave reactor in sealed vessels (monowave, maximum power 300 W, temperature control by infrared (IR) sensor, fixed temperature). Furanchalcone **3** was synthesized in an ultrasonic cleaner (BRANSON). Nuclear magnetic resonance (NMR) spectra were recorded as $CDCl_3$ and dimethyl sulphoxide (DMSO)-d_6 solutions on an AMX 300 instrument (Bruker, Billerica, MA, USA) operating at 300 MHz for ^1H and 75 MHz for ^{13}C. Carbon atom types (C, CH, CH_2, CH_3) were determined by using the DEPT or APT pulse sequence. High resolution mass spectra were recorded using electrospray ionization mass spectrometry (ESI-MS). The drying and cone gas was nitrogen set to flow rates of 300 and 30 L/h, respectively. Methanol sample solutions (ca. 1×10^{-5} M) were directly introduced into the ESI spectrometer at a flow rate of 10 µL/min. A capillary voltage of 3.5 kV was used in the positive scan mode, and the cone voltage set to $Uc = 10$ V. For accurate mass measurements, a 2 mg/L standard solution of leucine enkephalin was introduced via the lock spray needle at a cone voltage set to 85 V and a flow rate of 30 µL/min. IR spectra were recorded on a Spectrum RX I Fourier transform infrared system (Perkin-Elmer, Waltham, MA, USA) in KBr disks. Silica gel 60 (0.063–0.200 mesh, Merck, Whitehouse Station, NJ, USA) was used for column chromatography, and precoated silica gel plates (Merck 60 F254 0.2 mm) were used for thin layer chromatography (TLC).

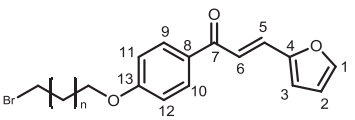
*General procedure for the synthesis of (2E)-3-(furan-2-il)-1-(4-hidroxifenil)prop-2-en-1-ona (**3**)*



This compound was prepared by the condensation of 4-hydroxyacetophenone **1** (10 mmol, 1.36 g) and furfural **2** (10 mmol, 0.96 g, 828 μL) in a solution of 20% KOH in ethanol (20 mL). The reaction mixture was sonicated for 45 min and neutralized with a solution of 10% HCl. The solid was filtered, sequentially washed with water, dried and recrystallized from ethanol to obtain the corresponding furanchalcone in 88% yield (8.8 mmol, 1.9 g). Yellow solid, M.p. 159–161 °C. IR (KBr): ν_{max} (cm^{-1}) 1647 (C=O), 1602 (C=C), 1442 (C=C_{Ar}), 819 (C-H_{Ar}). ^{1}H-NMR ($CDCl_3$-CD_3OD, 300 MHz): δ 6.49 (1H, d, $J = 3.0$ Hz, H-2), 6.70 (1H, d, $J = 3.0$ Hz, H-3), 6.88 (2H, d, $J = 7.9$ Hz, H-11, H-12), 7.27–7.58 (3H, m, H-5, H-6, H-1), 7.94 (2H, d, $J = 7.9$ Hz, H-9, H-10). ^{13}C-NMR ($CDCl_3$-CD_3OD, 75 MHz): δ 112.60 (CH, C-2), 115.40 (CH, C-6), 115.97 (CH, C-11, C-12), 119.17 (CH, C-3), 129.81 (C, C-8), 130.09 (CH, C-5), 131.08 (CH, C-9, C-10), 144.82 (CH, C-1), 151.71 (C, C-4), 161.93 (C, C-13), 188.95 (C, C=O).

General procedure for the synthesis of bromoalkyl-furanchalcones or bromoalkyl-quinolines

Furanchalcone or quinoline (1 mmol), potassium hydroxide (1.5 mmol, 84.2 mg) and acetonitrile (10 mL), were placed in a 25 mL flat-bottomed flask equipped with a magnetic stirring bar. The mixture was stirred and heated to reflux for a period of 5 min, under microwave irradiation. Then, 1,ω-dibromoalkane (1.1 mmol) was added to the reaction mixture, which was refluxed for 30 min (200 W). The crude reaction mixture was concentrated on a rotatory evaporator and the residue was purified by column chromatography over silica gel eluting with hexane and a mixture of hexane-ethyl acetate (9:1 ratio) to obtain bromoalkyl derivatives in yields ranging between 61 and 76%. Monitoring of the reaction progress and product purification was carried out by TLC.



1-{4-[(3-Bromopropyl)oxy]phenyl}−3-(furan-2-yl)propan-1-one (**4a**) It was obtained as a dark brown solid, Yield 76% (0.76 mmol, 255 mg); M.p. 61–64 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.28–2.41 (2H, m, CH_2–C$\underline{H}_2$–CH_2), 3.62 (2H, t, $J = 6.5$ Hz, C$\underline{H}_2$Br), 4.19 (2H, t, $J = 6.0$ Hz, OC$\underline{H}_2$), 6.52 (1H, dd, $J = 1.8$, 3.4 Hz, H-2), 6.72 (1H, d, $J = 3.4$ Hz, H-3), 6.99 (2H, d, $J = 8.9$ Hz, H-11, H-12), 7.48 (1H, d, $J = 15.3$ Hz, H-5), 7.54 (1H, d, $J = 1.8$ Hz, H-1), 7.60 (1H, d, $J = 15.3$ Hz, H-6), 8.06 (2H, d, $J = 8.9$ Hz, H-9, H-10). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 29.82 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 32.15 (CH_2, $\underline{C}H_2$–Br), 65.54 (CH_2, O–$\underline{C}H_2$), 112.67 (CH, C-3), 114.33 (CH, C-11, C-12), 115.93 (CH, C-2), 119.13 (CH, C-6), 130.06 (CH, C-5), 130.78 (CH, C-9, C-10), 131.23 (C, C-8), 144.78 (CH, C-1), 151.80 (C, C-4), 162.53 (C, C-13), 188.01 (C, C=O). ESI-MS: *m/z* 335.0277 $[M + H]^+$, calcd for $C_{16}H_{15}O_3Br$: 335.1970.

1-{4-[(4-Bromobutyl)oxy]phenyl}-3-(furan-2-yl)propan-1-one (**4b**) It was obtained as a yellow pale solid, yield 64% (0.64 mmol, 224 mg); M.p. 78–81 °C. ^{1}H-NMR ($CDCl_3$ 300 MHz): δ 1.95–2.05 (2H, m, CH_2–C$\underline{H}_2$–CH_2), 2.06–2.17 (2H, m, CH_2–C$\underline{H}_2$–CH_2), 3.53 (2H, t, $J = 6.7$ Hz C$\underline{H}_2$–Br), 4.10 (2H, t, $J = 6.0$ Hz, O–C$\underline{H}_2$), 6.54 (1H, dd, $J = 1.4$, 3.4 Hz, H-2), 6.73 (1H, d, $J = 3.4$ Hz, H-3), 6.99 (2H, d, $J = 8.9$ Hz, H-11, H-12), 7.50 (1H, d, $J = 15.3$ Hz, H-5), 7.56 (1H, d, $J = 1.4$ Hz, H-1), 7.62 (1H, d, $J = 15.3$ Hz, H-6), 8.07 (2H, d, $J = 8.9$ Hz, H-9, H-10). ^{13}C-NMR ($CDCl_3$ 75 MHz): δ 27.77 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.36 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 33.38 (CH_2, CH_2–Br), 67.12 (CH_2, O–CH_2), 112.66 (CH, C-3), 114.27 (CH, C-11, C-12), 115.89 (CH, C-2), 119.17 (CH, C-6), 130.03 (CH, C-5), 130.79 (CH, C-9, C-10), 131.09 (C, C-8), 144.74 (CH, C-1), 151.83 (C, C-4), 162.74 (C, C-13), 188.06 (C, C=O). ESI-MS: *m/z* 349.0434 $[M + H]^+$, calcd for $C_{17}H_{17}O_3Br$: 349.2240.

1-{4-[(5-Bromopentyl)oxy]phenyl}-3-(furan-2-yl)propan-1-one (**4c**) It was obtained as a yellow pale solid, yield 76% (0.76 mmol, 276 mg); M.p. 66–69 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.61–1.74 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 1.82–1.92 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 1.93–2.05 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 3.48 (CH_2, t, $J = 6.7$ Hz, C$\underline{H}_2$–Br), 4.08 (CH_2, t, $J = 6.3$ Hz, O–C$\underline{H}_2$), 6.54 (1H, dd, $J = 1.8$, 3.4 Hz, H-2), 6.73 (1H, d, $J = 3.4$ Hz, H-3), 6.99 (2H, d, $J = 8.8$ Hz, H-11, H-12), 7.50 (1H, d, $J = 15.4$ Hz, H-5), 7.56 (1H, d, $J = 1.8$ Hz, H-1), 7.62 (1H, d, $J = 15.4$ Hz, H-6), 8.07 (2H, d, $J = 8.8$ Hz, H-9, H-10). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 24.79 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.33 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 32.44 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 33.58 (CH_2, $\underline{C}H_2$–Br), 67.85 (CH_2, O–$\underline{C}H_2$), 112.64 (CH, C-3), 114.29 (CH, C-11, C-12), 115.85 (CH, C-2), 119.21 (CH, C-6), 130.01 (CH, C-5), 130.78 (CH, C-9, C-10), 130.99 (C, C-8), 144.75 (CH, C-1), 151.85 (C, C-4), 162.89 (C, C-13), 188.09 (C, C=O). ESI-MS: *m/z* 363.0590 $[M + H]^+$, calcd for $C_{18}H_{19}O_3Br$: 363.2510.

1-{4-[(8-Bromooctyl)oxy]phenyl}-3-(furan-2-yl)propan-1-one (**4d**) It was obtained as a yellow pale solid, yield 62% (0.62 mmol, 251 mg); M.p. 83–85 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.29–1.55 (4CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 1.75–1.95 (2CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 3.43 (CH_2, t, $J =$ 6.8 Hz, C$\underline{H}_2$–Br), 4.04 (CH_2, t, $J = 6.4$ Hz, O–C$\underline{H}_2$), 6.53 (1H, dd, $J = 1.6$, 3.4 Hz, H-2), 6.72 (1H, d, $J = 3.4$ Hz, H-3), 6.98 (2H, d, $J = 8.9$ Hz, H-11, H-12), 7.50 (1H, d, $J =$

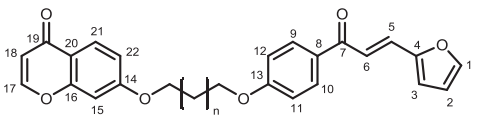
15.3 Hz, H-5), 7.54 (1H, d, $J = 1.6$ Hz, H-1), 7.61 (1H, d, $J = 15.3$ Hz, H-6), 8.06 (2H, d, $J = 8.9$ Hz, H-9, H-10). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 25.92 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.09 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.69 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.09 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.18 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 32.78 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 34.05 (CH_2, $\underline{C}H_2$–Br), 68.19 (CH_2, O–$\underline{C}H_2$), 112.64 (CH, C-3), 114.30 (CH, C-11, C-12), 115.81 (CH, C-2), 119.21 (CH, C-6), 129.93 (CH, C-5), 130.76 (CH, C-9, C-10), 130.84 (C, C-8), 144.71 (CH, C-1), 151.85 (C, C-4), 163.05 (C, C-13), 188.01 (C, C=O). ESI-MS: *m/z* 405.1060 $[M + H]^+$, calcd for $C_{21}H_{25}O_3Br$: 405.3320.

1-{4-[(9-bromononyl)oxy]phenyl}-3-(furan-2-yl)propan-1-one (**4e**) It was obtained as a yellow pale solid, yield 56% (0.56 mmol, 235 mg); 55–58 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.24–1.55 (5CH_2, m, CH_2–$C\underline{H}_2$–CH_2), 1.75–1.93 (2CH_2, m, CH_2–$C\underline{H}_2$–CH_2), 3.41 (CH_2, t, $J = 6.9$ Hz, $C\underline{H}_2$–Br), 4.03 (CH_2, t, $J = 6.3$ Hz, O–$C\underline{H}_2$), 6.51 (1H, dd, $J = 1.8$, 3.3 Hz, H-2), 6.71 (1H, d, $J = 3.3$ Hz, H-3), 6.97 (2H, d, $J = 8.9$ Hz, H-11, H-12), 7.50 (1H, d, $J = 15.2$ Hz, H-5), 7.53 (1H, d, $J = 1.8$ Hz, H-1), 7.61 (1H, d, $J = 15.2$ Hz, H-6), 8.05 (2H, d, $J = 8.9$ Hz, H-9, H-10). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 25.96 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.14 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.70 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.11 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.25 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.35 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 32.80 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 34.08 (CH_2, $\underline{C}H_2$–Br), 68.22 (CH_2, O–$\underline{C}H_2$), 112.64 (CH, C-3), 114.30 (CH, C-11, C-12), 115.79 (CH, C-2), 119.19 (CH, C-6), 129.90 (CH, C-5), 130.75 (CH, C-9, C-10), 130.81 (C, C-8), 144.71 (CH, C-1), 151.84 (C, C-4), 163.07 (C, C-13), 187.94 (C, C=O). ESI-MS: *m/z* 419.1216 $[M + H]^+$, calcd for $C_{22}H_{275}O_3Br$: 419.3990.

1-{4-[(12-bromododecyl)oxy]phenyl}-3-(furan-2-yl)propan-1-one (**4f**) It was obtained as a brown solid, yield 61% (0.61 mmol, 282 mg); 68–70 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.21–1.57 (8CH_2, m, CH_2–$C\underline{H}_2$–CH_2), 1.75–1.94 (2CH_2, m, CH_2–$C\underline{H}_2$–CH_2), 3.43 (CH_2, t, $J = 6.8$ Hz, $C\underline{H}_2$–Br), 4.05 (CH_2, t, $J = 6.6$ Hz, O–$C\underline{H}_2$), 6.53 (1H, dd, $J = 1.8$, 3.5 Hz, H-2), 6.72 (1H, d, $J = 3.5$ Hz, H-3), 6.99 (2H, d, $J = 8.9$ Hz, H-11, H-12), 7.50 (1H, d, $J = 15.4$ Hz, H-5), 7.55 (1H, d, $J = 1.8$ Hz, H-1), 7.62 (1H, d, $J = 15.4$ Hz, H-6), 8.06 (2H, d, $J = 8.9$ Hz, H-9, H-10). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 26.01 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.20 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.79 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.14 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.38 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.45 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.55 (3CH_2, CH_2–$\underline{C}H_2$–CH_2), 32.85 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 34.11 (CH_2, $\underline{C}H_2$–Br), 68.28 (CH_2, O–$\underline{C}H_2$), 112.62 (CH, C-3), 114.30 (CH, C-11, C-12), 115.77 (CH, C-2), 119.23 (CH, C-6), 129.91 (CH, C-5), 130.76 (CH, C-9, C-10), 130.82 (C, C-8), 144.69 (CH, C-1), 151.87 (C, C-4), 161.09 (C, C-13), 188.01 (C, C=O). ESI-MS: *m/z* 461.1686 $[M + H]^+$, calcd for $C_{25}H_{33}O_3Br$: 461.4400.

General procedure for the synthesis of furanchalcone–chromone and furanchalcone–quinoline hybrids

Chromone or furanchalcone (0.75 mmol), potassium hydroxide (1 mmol) and acetonitrile (10 mL), were placed in a 50 mL flat-bottomed flask equipped with a magnetic stirring bar. The mixture was stirred and heated to reflux for a period of 5 min, under microwave irradiation. Then, bromoalkyl-furanchalcone or bromoalkyl-quinoline (0.5 mmol) was added to the reaction mixture, which was then refluxed for 30 min (200 W). The crude reaction mixture was concentrated on a rotatory evaporator and the residue was purified by column chromatography over silica gel eluting with hexane-ethyl acetate (2:1 ratio) to obtain furanchalcone–chromone or furanchalcone–quinoline hybrids in yields ranging 44–65 and 34–70%, respectively. Monitoring of the reaction progress and product purification was carried out by TLC.



7-(3-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}propoxy)-4H-chromen-4-one (**6a**) It was obtained as a pale yellow solid. 59% yield (0.30 mmol, 125 mg). M.p. 146–148 °C; IR (KBr) ν_{max} (cm^{-1}) 1656 (C=O), 1627 (C=O), 1600 (C=C), 1440 (C=C_{Ar}), 1261 (C–O–C), 808 (C–H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 2.16–2.32 (CH_2, m, CH_2–$C\underline{H}_2$–CH_2), 4.27 (CH_2, t, $J = 6.2$ Hz, O–$C\underline{H}_2$), 4.31 (CH_2, t, $J = 6.2$ Hz, O–$C\underline{H}_2$), 6.26 (1H, d, $J = 6.1$ Hz, H-18), 6.68 (1H, dd, $J = 3.4$, 1.8 Hz, H-2), 7.04–7.13 (4H, m, H-5, H-6, H-15, H-21), 7.18 (1H, d, $J = 1.8$ Hz, H-3), 7.54 (2H, $s_{apparent}$, H-9, H-10), 7.90 (1H, d, $J = 1.8$, H-1), 7.93 (1H, d, $J = 8.90$, H-22), 8.06 (2H, d, $J = 8.9$ Hz, H-11, H-12), 8.22 (1H, d, $J = 6.1$ Hz, H-17). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 28.69 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 65.10 (CH_2, O–$\underline{C}H_2$), 65.65 (CH_2, O–$\underline{C}H_2$), 101.87 (CH, C-15), 112.63 (CH, C-18), 113.53 (CH, C-2), 115.02 (CH, C-11, C-12), 115.41 (CH, C-22), 117.66 (CH, C-3), 118.55 (C, C-20), 119.13 (CH, C-6), 126.89 (CH, C-21), 130.24 (CH, C-5), 130.84 (C, C-8), 131.17 (CH, C-9, C-10), 146.47 (CH, C-1), 151.69 (C, C-4), 156.97 (CH, C-17), 158.09 (C, C-16), 162.86 (C, C-13), 163.38 (C, C-14), 176.11 (C=O, C-19), 187.23 (C=O, C-7). ESI-MS: *m/z* 439.1158 $[M + Na]^+$, calcd for $C_{25}H_{20}O_6$: 439.1156.

7-(4-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}butoxy)-4H-chromen-4-one (**6b**) It was obtained as a pale yellow solid, yield 62% (0.31 mmol, 134 mg); (0.31 mmol, 134 mg); M.p. 155–157 °C; IR (KBr): ν_{max} (cm^{-1}) 1654 (C=O), 1624 (C=O), 1600 (C=C), 1440 (C=C_{Ar}), 1263 (C–O–C), 819 (C–H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.82–2.02 ($2CH_2$, m, CH_2–$C\underline{H}_2$–CH_2), 4.06–4.32 ($2CH_2$, m, O–$C\underline{H}_2$), 6.27 (1H, d, $J = 6.0$ Hz, H-18), 6.68 (1H, $s_{apparent}$, H-2), 7.01–7.18 (5H, m, H-3, H-5, H-6, H-15, H-21), 7.54 (2H, $s_{apparent}$, H-9, H-10), 7.86–7.97 (2H, m, H-1, H-22), 8.06 (2H, d, $J = 8.7$ Hz, H-11, H-12), 8.22 (1H, d, $J = 6.0$ Hz, H-17). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 25.50 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 25.64 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 67.95 (CH_2, O–$\underline{C}H_2$), 68.52 (CH_2, O–$\underline{C}H_2$), 101.80 (CH, C-15), 112.63 (CH, C-18), 113.53 (CH, C-2), 115.01 (CH, C-11, C-12), 117.02 (CH, C-22), 117.06 (CH, C-3), 118.46 (C, C-20), 119.18 (CH, C-6), 126.85 (CH, C-21), 130.21 (CH, C-5), 130.72 (C, C-8), 131.16 (CH, C-9, C-10), 146.45 (CH, C-1), 151.71 (C, C-4), 156.94 (CH, C-17), 158.25 (C, C-16), 162.97 (C, C-13), 163.58 (C, C-14), 176.13 (C=O, C-19), 187.26 (C=O, C-7). ESI-MS: *m/z* 453.1314 $[M + Na]^+$, calcd for $C_{26}H_{22}O_6$: 453.1318.

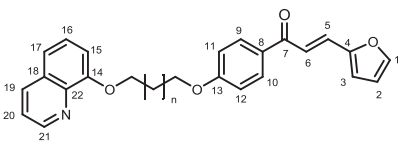
7-(3-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}pentoxy)-4H-chromen-4-one (**6c**) It was obtained as a brown solid. yield 40% (0.20 mmol, 89 mg); (0.20 mmol, 89 mg); M.p. 135–138 °C; IR (KBr): ν_{max} (cm^{-1}) 1656 (C=O), 1599 (C=O), 1566 (C=C), 1440 (C=C_{Ar}), 1265 (C–O–C), 808 (C–H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.53–1.70 ($2CH_2$, m, CH_2–$C\underline{H}_2$–CH_2), 1.75–1.89 (CH_2, m, CH_2–$C\underline{H}_2$–CH_2), 4.06–4.18 ($2CH_2$, m, O–$C\underline{H}_2$), 6.26 (1H, d, $J = 6.1$ Hz, H-18), 6.68 (1H, $s_{apparent}$, H-2), 6.97–7.17 (5H, m, H-3, H-5, H-6, H-15, H-21), 7.54 (2H, $s_{apparent}$, H-9, H-10), 7.87–7.96 (2H, m, H-1, H-22), 8.05 (2H, d, $J = 8.6$ Hz, H-11, H-12), 8.21 (1H, d, $J = 6.1$ Hz, H-17). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 22.52 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 25.05 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.53 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.65 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 68.25 (CH_2, O–$\underline{C}H_2$), 68.83 (CH_2, O–$\underline{C}H_2$), 101.74 (CH, C-15), 112.61 (CH, C-18), 113.53 (CH, C-2), 114.97 (CH, C-11, C-12), 115.42 (CH, C-22), 117.02 (CH, C-3), 118.41 (C, C-20), 119.15 (CH, C-6), 126.82 (CH, C-21), 130.19 (CH, C-5), 130.65 (C, C-8), 131.15 (CH, C-9, C-10), 146.45 (CH, C-1), 151.70 (C, C-4), 156.99 (CH, C-17), 158.25 (C, C-16), 163.10 (C, C-13), 163.61 (C, C-14), 176.11 (C=O, C-19), 187.25 (C=O, C-7). ESI-MS: *m/z* 467.1471 $[M + Na]^+$, calcd for $C_{27}H_{24}O_6$: 467.1475.

7-[(8-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}octyl)oxy]-4H-chromen-4-one (**6d**) It was obtained as a pale yellow solid. yield 63% (0.32 mmol, 156 mg); (0.32 mmol, 156 mg); M.p. 104–107 °C; IR (KBr): ν_{max} (cm^{-1}) 1654 (C=O), 1620 (C=O), 1600 (C=C), 1442 (C=C_{Ar}), 1263 (C-O-C), 817 (C–H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.25–1.50 ($4CH_2$, m, CH_2–$C\underline{H}_2$–CH_2), 1.60–1.81 ($2CH_2$, m, CH_2–$C\underline{H}_2$–CH_2), 4.00–4.13 ($2CH_2$, m, O–$C\underline{H}_2$), 6.25 (1H, d, $J = 6.2$ Hz, H-18), 6.68 (1H, $s_{apparent}$, H-2), 6.96–7.14 (5H, m, H-3, H-5, H-6, H-15, H-21), 7.53 (2H, $s_{apparent}$, H-9, H-10), 7.86–7.96 (2H, m, H-1, H-22), 8.05 (2H, d, $J = 8.4$ Hz, H-11, H-12), 8.21 (1H, d, $J = 6.2$ Hz, H-17). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 25.80 ($2CH_2$, CH_2–$\underline{C}H_2$–CH_2), 28.80 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.94 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.09 ($2CH_2$, CH_2–$\underline{C}H_2$–CH_2), 68.33 (CH_2, O–$\underline{C}H_2$), 68.90 (CH_2, O–$\underline{C}H_2$), 101.68 (CH, C-15), 112.60 (CH, C-18), 113.52 (CH, C-2), 114.94 (CH, C-11, C-12), 115.39 (CH, C-22), 117.01 (CH, C-3), 118.38 (C, C-20), 119.14 (CH, C-6), 126.81 (CH, C-21), 130.18 (CH, C-5), 130.62 (C, C-8), 131.15 (CH, C-9, C-10), 146.44 (CH, C-1), 151.70 (C, C-4), 156.92 (CH, C-17), 158.25 (C, C-16), 163.12 (C, C-13), 163.63 (C, C-14), 176.14 (C=O, C-19), 187.19 (C=O, C-7). ESI-MS: *m/z* 509.1940 $[M + Na]^+$, calcd for $C_{30}H_{30}O_6$: 509.1940.

7-[(8-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}nonyl)oxy]-4H-chromen-4-one (**6e**) It was obtained as a yellow solid. yield 51% (0.26 mmol, 130 mg); (0.26 mmol, 130 mg); M.p. 100–102 °C. IR (KBr): ν_{max} (cm^{-1}) 1654 (C=O), 1629 (C=O), 1690 (C=C), 1440 (C=C_{Ar}), 1263 (C–O–C), 812 (C-H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.18–1.48 ($5CH_2$, m, CH_2–$C\underline{H}_2$–CH_2), 1.62–1.81 ($2CH_2$, m, CH_2–$C\underline{H}_2$–CH_2), 4.00–4.13 ($2CH_2$, m, O–$C\underline{H}_2$), 6.25 (1H, d, $J = 6.1$ Hz, H-18), 6.68 (1H, dd, $J = 3.4$, 1.8 Hz, H-2), 6.97–7.13 (5H, m, H-3, H-5, H-6, H-15, H-21), 7.54 (2H, $s_{apparent}$, H-9, H-10), 7.87–7.94 (2H, m, H-1, H-22), 8.04 (2H, d, $J = 8.8$ Hz, H-11, H-12), 8.20 (1H, d, $J = 6.1$ Hz, H-17). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 25.84 ($2CH_2$, CH_2–$\underline{C}H_2$–CH_2), 28.81 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.95 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.07 ($2CH_2$, CH_2–$\underline{C}H_2$–CH_2), 29.34 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 68.33 (CH_2, O–$\underline{C}H_2$), 68.90 (CH_2, O–$\underline{C}H_2$), 101.68 (CH, C-15), 112.60 (CH, C-18), 113.52 (CH, C-2), 114.94 (CH, C-11, C-12), 115.39 (CH, C-22), 117.01 (CH, C-3), 118.37 (C, C-20), 119.14 (CH, C-6), 126.81 (CH, C-21), 130.18 (CH, C-5), 130.61 (C, C-8), 131.14 (CH, C-9, C-10), 146.44 (CH, C-1), 151.69 (C, C-4), 156.91 (CH, C-17), 158.25 (C, C-16), 163.12 (C, C-13), 163.63 (C, C-14), 176.14 (C=O, C-19), 187.19 (C=O, C-7). ESI-MS: *m/z* 523.2097 $[M + Na]^+$, calcd for $C_{31}H_{32}O_6$: 523.2100.

7-[(8-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}dodecyl)oxy]-4H-chromen-4-one (**6f**) It was obtained as a light yellow solid. yield 57% (0.29 mmol, 157 mg); (0.29 mmol, 157 mg); M.p. 120–122 °C. IR (KBr): ν_{max} (cm^{-1}) 1645 (C=O), 1622 (C=O), 1597 (C=C), 1442 (C=C_{Ar}), 1263 (C–O–-), 812 (C–H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.15–1.50 ($8CH_2$, m, CH_2–$C\underline{H}_2$–CH_2), 1.64–1.80 ($2CH_2$,

m, CH_2–C$\underline{H}_2$–CH_2), 4.06 (CH_2, t, $J = 6.6$ Hz, O–C$\underline{H}_2$), 4.09 (CH_2, t, $J = 6.6$ Hz, O-C$\underline{H}_2$), 6.26 (1H, d, $J = 6.0$ Hz, H-18), 6.68 (1H, dd, $J = 3.4$, 1.8 Hz, H-2), 6.99–7.09 (4H, m, H-5, H-6, H-15, H-21), 7.11 (1H, d, $J = 2.2$ Hz, H-3), 7.54 (2H, $s_{apparent}$, H-9, H-10), 7.88–7.96 (2H, m, H-1, H-22), 8.05 (2H, d, $J = 8.8$ Hz, H-11, H-12), 8.21 (1H, d, $J = 6.1$ Hz, H-17). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 25.84 (2CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.81 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.95 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.14 (2CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.39 (4CH_2, CH_2–C$\underline{H}_2$–CH_2), 68.33 (CH_2, O–C$\underline{H}_2$), 68.89 (CH_2, O–C$\underline{H}_2$), 101.69 (CH, C-15), 112.61 (CH, C-18), 113.52 (CH, C-2), 114.94 (CH, C-11, C-12), 115.39 (CH, C-22), 117.01 (CH, C-3), 118.38 (C, C-20), 119.15 (CH, C-6), 126.81 (CH, C-21), 130.18 (CH, C-5), 130.62 (C, C-8), 131.15 (CH, C-9, C-10), 146.44 (CH, C-1), 151.70 (C, C-4), 156.92 (CH, C-17), 158.25 (C, C-16), 163.17 (C, C-13), 163.63 (C, C-4), 176.13 (C=O, C-19), 186.99 (C=O, C-7). ESI-MS: *m/z* 565.2566 $[M + Na]^+$, calcd for $C_34H_{38}O_6$: 565.2563.



(2E)-3-(furan-2-yl)-1-{4-[4-(quinolin-8-yloxy)butoxy]phenyl}prop-2-en-1-one (**11b**) It was obtained as a yellow solid. 58% yield (0.29 mmol, 120 mg); M.p. 101–103 °C. IR (KBr): ν_{max} (cm^{-1}) 1654 (C=O), 1604 (C=C), 1564 (C=N), 1463 (C=C_{Ar}), 1259 (C–O–C), 819 (C–H_{Ar}). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.94–2.10 (2CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 4.15–4.32 (2CH_2, m, O–C$\underline{H}_2$), 6.68 (1H, dd, $J = 3.5$, 1.8 Hz, H-2), 7.08 (1H, d, $J = 3.5$ Hz, H-3), 7.10 (2H, d, $J = 8.8$ Hz, H-11, H-12), 7.16–7.25 (1H, m, H-15), 7.47–7.52 (2H, m, H-17, H-16), 7.52–7.57 (3H, m, H-20, H-5, H-6), 7.90 (1H, d, $J = 1.8$ Hz, H-1), 8.06 (2H, d, $J = 8.8$ Hz, H-9, H-10), 8.30 (1H, dd, $J = 8.3$, 1.6 Hz, H-19), 8.87 (1H, dd, $J = 4.0$, 1.6 Hz, H-21). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 25.14 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 25.77 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 68.26 (CH_2, O–C$\underline{H}_2$), 68.44 (CH_2, O–C$\underline{H}_2$), 109.76 (CH, C-15), 113.52 (CH, C-2), 115.01 (CH, C-11, C-12), 117.02 (CH, C-3), 119.18 (CH, C-6), 119.94 (CH, C-17), 122.29 (CH, C-20), 127.31 (CH, C-16), 129.49 (C, C-8), 130.19 (C, C-18), 130.65 (CH, C-5), 131.14 (CH, C-9, C-10), 136.24 (CH, C-19), 140.20 (C, C-22), 146.44 (CH, C-1), 149.43 (C, C-4), 151.70 (CH, C-21), 154.92 (C, C-14), 163.14 (C, C-13), 187.23 (C=O, C-7). ESI-MS: *m/z* 414.1705 $[M + H]^+$, calcd for $C_{26}H_{23}NO_4$: 414.1705.

(2E)-3-(furan-2-yl)-1-(4-{[5-(quinolin-8-yloxy)pentyl]oxy}phenyl)prop-2-en-1-one (**11c**) It was obtained as a dark yellow solid. 46% yield (0.23 mmol, 98 mg); M.p. 98–100 °C. IR (KBr): ν_{max} (cm^{-1}) 1656 (C=O), 1600 (C=C), 1600 (C=N), 1471 (C=C_{Ar}), 1259 (C–O–C), 819 (C–H_{Ar}). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.57–1.75 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 1.77–2.01 (2CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 4.13 (CH_2, t, $J = 6.5$ Hz, O–C$\underline{H}_2$), 4.19 (CH_2, t, $J = 6.5$ Hz, O–C$\underline{H}_2$), 6.68 (1H, dd, $J = 3.3$, 1.7 Hz, H-2), 7.07 (2H, d, $J = 9.0$ Hz, H-11, H-12), 7.08 (1H, d, $J = 3.3$ Hz, H-3), 7.14–7.23 (1H, m, H-15), 7.46–7.51 (2H, m, H-17, H-16), 7.51–7.56 (3H, m, H-5, H-6, H-20), 7.90 (1H, d, $J = 1.7$ Hz, H-1), 8.05 (2H, d, $J = 8.6$ Hz, H-9, H-10), 8.29 (1H, dd, $J = 8.3$, 1.7 Hz, H-19), 8.85 (1H, dd, $J = 4.0$, 1.2 Hz, H-21). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 22.83 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.78 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.93 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 68.36 (CH_2, O–C$\underline{H}_2$), 68.62 (CH_2, O–C$\underline{H}_2$), 109.76 (CH, C-15), 113.52 (CH, C-2), 114.98 (CH, C-11, C-12), 117.01 (CH, C-3), 119.17 (CH, C-6), 119.88 (CH, C-17), 122.25 (CH, C-20), 127.31 (CH, C-16), 129.48 (C, C-8), 130.19 (C, C-18), 130.64 (CH, C-5), 131.15 (CH, C-9, C-10), 136.21 (CH, C-19), 140.23 (C, C-22), 146.44 (CH, C-1), 149.43 (C, C-4), 151.71 (CH, C-21), 154.99 (C, C-14), 163.09 (C, C-13), 187.24 (C=O, C-7). ESI-MS: *m/z* 428.1862 $[M + H]^+$, calcd for $C_{27}H_{25}NO_4$: 428.1866.

(2E)-3-(furan-2-yl)-1-(4-{[8-(quinolin-8-yloxy)octyl]oxy}phenyl)prop-2-en-1-one (**11d**) It was obtained as a pale yellow solid, 50% yield (0.25 mmol, 117 mg); M.p. 114–115 °C. IR (KBr): ν_{max} (cm^{-1}) 1656 (C=O), 1598 (C=C), 1590 (C=N), 1471 (C=C_{Ar}), 1261 (C–O–C), 817 (C–H_{Ar}). ^{1}H-NMR ($CDCl_3$ 300 MHz): δ 1.27–1.58 (4CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 1.67–1.79 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 1.79–1.92 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 4.06 (CH_2, t, $J = 6.4$ Hz, O–C$\underline{H}_2$), 4.14 (CH_2, t, $J = 6.4$ Hz, O–C$\underline{H}_2$), 6.68 (1H, dd, $J = 3.4$, 1.8 Hz, H-2), 7.05 (2H, d, $J = 8.8$ Hz, H-11, H-12), 7.08 (1H, d, $J = 3.4$ Hz, H-3), 7.13–7.22 (1H, m, H-15), 7.44–7.52 (2H, m, H-16, H-17), 7.52–7.56 (3H, m, H-5, H-6, H-20), 7.90 (1H, d, $J = 1.7$ Hz, H-1), 8.05 (2H, d, $J = 8.8$ Hz, H-9, H-10), 8.29 (1H, dd, $J = 8.3$, 1.7 Hz, H-19), 8.84 (1H, dd, $J = 4.1$, 1.7 Hz, H-21). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 25.86 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 26.08 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.95 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.19 (3CH_2, CH_2–C$\underline{H}_2$–CH_2), 68.35 (CH_2, O–C$\underline{H}_2$), 68.64 (CH_2, O–C$\underline{H}_2$), 109.68 (CH, C-15), 113.52 (CH, C-2), 114.95 (CH, C-11, C-12), 117.01 (CH, C-3), 119.16 (CH, C-6), 119.82 (CH, C-17), 122.23 (CH, C-20), 129.48 (CH, C-16), 130.18 (C, C-8), 130.61 (C, C-18), 131.15 (CH, C-9, C-10), 131.20 (CH, C-5), 136.20 (CH, C-19), 140.19 (C, C-22), 146.44 (CH, C-1), 149.34 (C, C-4), 151.71 (CH, C-21), 155.02 (C, C-14), 163.14 (C, C-13), 187.18 (C=O, C-7). ESI-MS: *m/z* 470.2331 $[M + H]^+$, calcd for $C_{30}H_{31}NO_4$: 470.2331.

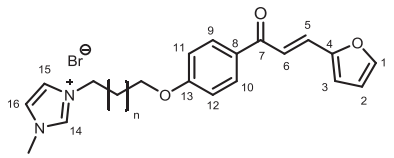
(2E)-3-(furan-2-yl)-1-(4-{[9-(quinolin-8-yloxy)nonyl]oxy}phenyl)prop-2-en-1-one (**11e**) It was obtained as a yellow solid. 54% yield (0.27 mmol, 131 mg); M.p. 109–110 °C. IR (KBr): ν_{max} (cm^{-1}) 1654 (C=O), 1600 (C=C), 1600 (C=N), 1467 (C=C_{Ar}), 1259 (C–O–C), 819 (C–H_{Ar}).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.34–1.65 ($5CH_2$, m, CH_2–C$\underline{H}_2$–CH_2), 1.75–1.97 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 2.01–2.16 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 4.07 (CH_2, t, $J = 6.6$ Hz, O–C$\underline{H}_2$), 4.28 (CH_2, t, $J = 7.2$ Hz, O–C$\underline{H}_2$), 6.55 (1H, dd, $J = 3.4$, 1.8 Hz, H-2), 6.74 (1H, d, $J = 3.4$ Hz, H-3), 7.01 (2H, d, $J = 8.9$ Hz, H-11, H-12), 7.10 (1H, dd, $J = 8.0$, 1.2 Hz, H-15), 7.41 (1H, dd, $J = 8.2$, 1.2 Hz, H-16), 7.43–7.50 (2H, m, H-6, H-20), 7.51–7.58 (2H, m, H-1, H-17), 7.63 (1H, d, $J = 15.1$ Hz, H-5), 8.08 (2H, d, $J = 8.9$ Hz, H-9, H-10), 8.16 (1H, dd, $J = 8.3$, 1.7 Hz, H-19), 8.99 (1H, dd, $J = 4.2$, 1.7 Hz, H-21). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 25.98 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 26.07 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.99 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.12 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.28 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.37 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.45 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 68.26 (CH_2, O–C$\underline{H}_2$), 68.98 (CH_2, O–C$\underline{H}_2$), 108.59 (CH, C-15), 112.61 (CH, C-2), 114.32 (CH, C-11, C-12), 115.77 (CH, C-3), 119.28 (CH, C-6), 119.38 (CH, C-17), 121.56 (CH, C-20), 126.73 (CH, C-16), 129.53 (C, C-18), 129.94 (CH, C-5), 130.78 (CH, C-9, C-10), 130.84 (C, C-8), 135.95 (CH, C-19), 140.41 (C, C-22), 146.68 (CH, C-1), 149.32 (C, C-4), 151.89 (CH, C-21), 154.89 (C, C-14), 163.11 (C, CC-13), 188.07 (C=O, C-7). ESI-MS: *m/z* 484.2488 $[M + H]^+$, calcd for $C_{31}H_{33}NO_4$: 484.2482.

(2E)-3-(furan-2-yl)-1-(4-{[12-(quinolin-8-yloxy)dodecyl] oxy}phenyl)prop-2-en-1-one (**11f**) It was obtained as a yellow solid, 57% yield (0.29 mmol, 152 mg); M.p. 90–91 °C. IR (KBr): ν_{max} (cm^{-1}) 1656 (C=O), 1598 (C=C), 1598 (C=N), 1471 (C=C_{Ar}), 1263 (C–O–C), 821 (C–H_{Ar}). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.26–1.64 ($7CH_2$, m, CH_2–C$\underline{H}_2$–CH_2), 1.70–1.91 ($2CH_2$, m, CH_2–C$\underline{H}_2$–CH_2), 2.01–2.14 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 4.07 (CH_2, t, $J = 6.5$ Hz, O–C$\underline{H}_2$), 4.28 (CH_2, t, $J = 7.1$ Hz, O–C$\underline{H}_2$), 6.55 (1H, dd, $J = 3.5$, 1.8 Hz, H-2), 6.74 (1H, d, $J = 3.5$ Hz, H-3), 7.01 (2H, d, $J = 8.9$ Hz, H-11, H-12), 7.10 (1H, dd, $J = 8.0$, 1.1 Hz, H-15), 7.41 (1H, dd, $J = 8.2$, 1.2 Hz, H-16), 7.43–7.51 (2H, m, H-6, H-20), 7.51–7.58 (2H, m, H-1-H-17), 7.63 (1H, d, $J = 15.4$ Hz, H-5), 8.08 (2H, d, $J = 8.9$ Hz, H-9, H-10), 8.16 (1H, dd, $J = 8.3$, 1.7 Hz, H-19), 8.99 (1H, dd, $J = 4.2$, 1.7 Hz, H-21). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 26.01 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 26.09 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.01 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.14 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.37 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.47 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.56 ($4CH_2$, CH_2–C$\underline{H}_2$–CH_2), 68.31 (CH_2, O–C$\underline{H}_2$), 69.03 (CH_2, O–C$\underline{H}_2$), 108.59 (CH, C-15), 112.61 (CH, C-2), 114.32 (CH, C-11, C.12), 115.76 (CH, C-3), 119.29 (CH, C-6), 119.36 (CH, C-17), 121.55 (CH, C-20), 126.73 (CH, C-16), 129.53 (C, C-8), 129.94 (C, C-18), 130.77 (CH, C-9, C-10), 130.83 (CH, C-5), 135.95 (CH, C-19), 140.41 (C, C-22), 144.68 (CH, C-1), 149.31 (C, C-4), 151.86 (CH, C-21), 154.85 (C, C-14), 163.12 (C, C-13), 188.15 (C=O, C-7). ESI-MS: *m/z* 526.2957 $[M + H]^+$, calcd for $C_{34}H_{39}NO_4$: 526.2955.

General procedure for the synthesis of furanchalcone–imidazole hybrids

Bromoalkyl–furanchalcone (**4a–f**) (0.5 mmol) and N-methylimidazole (0.5 mmol) and ethyl acetate (10 mL), were placed in a 50 mL flat-bottomed flask equipped with a magnetic stirring bar. The mixture was stirred and heated to reflux for 1 h (200 W), under microwave irradiation. Then, the reaction mixture was concentrated on a rotatory evaporator, the solid was washed several times with ethyl acetate. After dried, we obtain furanchalcone-imidazole hybrids in yields ranging 60–98%.



3-(3-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}propyl)-1-methyl-1H-imidazol-3-ium bromide (**8a**) It was obtained as a brown solid. 91% yield (0.46 mmol, 192 mg); M.p. 50–52 °C. IR (KBr): ν_{max} (cm^{-1}) 1654 (C=O), 1600 (C=C), 1600 (C=N), 1469 (C=C_{Ar}), 1259 (C–O–C), 831 (C–H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 2.24–2.36 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 3.84 (CH_3, s, N–C$\underline{H}_3$), 4.15 (CH_2, t, $J = 6.0$ Hz, N–C$\underline{H}_2$), 4.37 (CH_2, t, $J = 6.8$ Hz, O–C$\underline{H}_2$), 6.69 (1H, d, $J = 3.4$ Hz, H-2), 7.03 (2H, d, $J = 8.9$ Hz, H-11, H-12), 7.09 (1H, d, $J = 3.4$ Hz, H-3), 7.54 (2H, $s_{apparent}$, H-15, H-16), 7.72 (1H, $s_{apparent}$, H-6), 7.82 (1H, $s_{apparent}$, H-5), 7.91 (1H, d, $J = 1.4$ Hz, H-1), 8.07 (2H, d, $J = 8.9$ Hz, H-9, H-10), 9.19 (1H, s, H-14). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 29.36 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 36.22 (CH_3, N–C$\underline{H}_3$), 46.80 (CH_2, N–C$\underline{H}_2$), 65.46 (CH_2, O–C$\underline{H}_2$), 113.57 (CH, C-16), 114.96 (CH, C-11, C-12), 117.19 (CH, C-2), 119.06 (CH, C-3), 122.94 (CH, C-5), 124.07 (CH, C-15), 130.30 (CH, C-14), 130.98 (C, C-8), 131.16 (CH, C-9, C-10), 137.23 (CH, C-5), 146.51 (CH, C-1), 151.66 (C, C-4), 162.54 (C, C-13), 187.23 (C=O, C-7). ESI-MS: *m/z* $[M - Br]^+ = 337.1552$, calcd for $C_{20}H_{21}BrN_2O_3$: 337.1550.

3-(4-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}butyl)-1-methyl-1H-imidazol-3-ium bromide (**8b**) It was obtained as a brown solid. 67% yield (0.34 mmol, 147 mg); M.p. 42–45 °C. IR (KBr): ν_{max} (cm^{-1}) 1654 (C=O), 1602 (C=C), 1602 (C=N), 1471 (C=C_{Ar}), 1259 (C–O–C), 823 (C–H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.65–1.82 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 1.89–2.05 (CH_2, m, CH_2–C$\underline{H}_2$–

CH_2), 3.86 (CH_3, s, N–C$\underline{H}_3$), 4.12 (CH_2, t, $J = 6.2$ Hz, N–C$\underline{H}_2$), 4.27 (CH_2, t, $J = 7.0$ Hz, O–C$\underline{H}_2$), 6.69 (1H, d, $J =$ 3.4 Hz, H-2), 7.03–7.12 (3H, m, H-3, H-11, H-12), 7.54 (2H, s, H-16, H-16), 7.73 (1H, $s_{apparent}$, H-6), 7.82 (1H, $s_{apparent}$, H-5), 7.91 (1H, d, $J = 1.4$ Hz, H-1), 8.07 (2H, d, $J = 8.9$ Hz, H-9, H-10), 9.20 (1H, s, H-10). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 25.66 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 26.73 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 36.24 (CH_3, N–C$\underline{H}_3$), 48.90 (CH_2, N–C$\underline{H}_2$), 67.66 (CH_2, O–C$\underline{H}_2$), 113.55 (CH, C-16), 114.99 (CH, C-11,C-12), 117.11 (CH, C-2), 119.11 (CH, C-3), 122.72 (CH, C-6), 124.12 (CH, C-15), 130.25 (CH, C-14), 130.78 (C, C-8), 131.16 (CH, C-9, C-10), 137.06 (CH, C-5), 146.23 (CH, C-1), 151.67 (C, C-4), 162.89 (C, C-13), 187.01 (C=O, C-7). ESI-MS: *m/z* $[M - Br]^+ = 351.1709$, calcd for $C_{21}H_{23}BrN_2O_3$: 351.1708.

3-(5-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}pentyl)-1-methyl-1H-imidazol-3-ium bromide (**8c**) It was obtained as a brown solid, 61% yield (0.31 mmol, 138 mg); M.p. 138–139 °C. IR (KBr): ν_{max} (cm^{-1}) 1654 (C=O), 1595 (C=C), 1595 (C=N), 1471 (C=C_{Ar}), 1259 (C–O–C), 819 (C–H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.32–1.48 (CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 1.71–1.93 (2CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 3.85 (CH_3, s, N–C$\underline{H}_3$), 4.09 (CH_2, t, $J = 6.0$ Hz, N–C$\underline{H}_2$), 4.20 (CH_2, t, $J = 6.8$ Hz, O–C$\underline{H}_2$), 6.69 (1H, d, $J = 3.7$ Hz, H-2), 7.06 (2H, d, $J = 8.39$ Hz, H-11, H-12), 7.09 (1H, d, $J = 3.7$ Hz, H-3), 7.53–7.57 (2H, m, H-15, H-16), 7.72 (1H, $s_{apparent,}$ H-6), 7.79 (1H, $s_{apparent}$, H-5), 7.91 (1H, d, $J = 1.4$ Hz, H-1), 8.07 (2H, d, $J = 8.9$ Hz, H-9, H-10), 9.14 (1H, s, H-14). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 22.53 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.29 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.52 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 36.23 (CH_3, N–C$\underline{H}_3$), 49.08 (CH_2, N–C$\underline{H}_2$), 68.01 (CH_2, O–C$\underline{H}_2$), 113.56 (CH, C-16), 114.95 (CH, C-11, C-12), 117.12 (CH, C-2), 119.11 (CH, C-3), 122.76 (CH, C-6), 124.10 (CH, C-15), 130.24 (CH, C-14), 130.73 (C, C-8), 131.18 (CH, C-9, C-10), 137.01 (CH, C-5), 146.49 (CH, C-1), 151.69 (C, C-4), 162.96 (C, C-13), 187.15 (C=O, C-7). 188.74 (C=O). ESI-MS: *m/z* $[M - Br]^+ = 365.1865$, calcd for $C_{22}H_{25}BrN_2O_3$: 365.1865.

3-(8-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}octyl)-1-methyl-1H-imidazol-3-ium bromide (**8d**) It was obtained as a brown solid, 60% yield (0.30 mmol, 146 mg); M.p. 126–128 °C. IR (KBr): ν_{max} (cm^{-1}) 1654 (C=O), 1602 (C=C), 1602 (C=N), 1467 (C=C_{Ar}), 1274 (C–O–C), 833 (C–H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.11–1.47 (4CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 1.62–1.84 (2CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 3.85 (CH_3, s, N–C$\underline{H}_3$), 4.07 (CH_2, t, $J =$ 6.5 Hz, N–C$\underline{H}_2$), 4.15 (CH_2, t, $J = 6.8$ Hz, O–C$\underline{H}_2$), 6.70 (1H, dd, $J = 1.8$, 3.5 Hz, H-2), 6.90 (1H, d, $J = 3.4$, H-3), 7.05 (2H, d, H-11, H-12), 7.50–7.57 (2H, m, H-15, H-16), 7.71 (1H, $s_{apparent}$, H-6), 7.78 (1H, $s_{apparent}$, H-5), 7.91 (1H, d, $J = 1.4$ Hz, H-1), 8.06 (2H, d, $J = 8.9$ Hz, H-9, H-10), 9.14 (1H, s, H-14). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 25.56 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 25.73 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.42 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.58 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.76 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.68 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 35.09 (CH_3, N–C$\underline{H}_3$), 49.40 (CH_2, N–C$\underline{H}_2$), 68.03 (CH_2, O–C$\underline{H}_2$), 112.42 (CH, C-16), 114.13 (CH, C-11, C-12), 116.01 (CH, C-2), 118.51 (CH, C-3), 122.27 (CH, C-6), 123.57 (CH, C-15), 130.01 (CH, C-14), 130.44 (C, C-8), 130.55 (CH, C-9, C-10), 136.46 (CH, C-5), 145.34 (CH, C-1), 151.71 (C, C-4), 163.48 (C, C-13), 188.74 (C=O, C-7). ESI-MS: *m/z* $[M - Br]^+ = 407.2335$, calcd for $C_{25}H_{31}BrN_2O_3$: 407.2339.

3-(8-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}nonyl)-1-methyl-1H-imidazol-3-ium bromide (**8e**) It was obtained as a brown solid, 98% yield (0.49 mmol, 246 mg); M.p. 135–138 °C. IR (KBr): ν_{max} (cm^{-1}) 1654 (C=O), 1608 (C=C), 1608 (C=N), 1469 (C=C_{Ar}), 1276 (C–O–C), 831 (C–H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.07–1.47 (5CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 1.61–1.87 (2CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 3.85 (CH_3, s, N–C$\underline{H}_3$), 4.07 (CH_2, t, $J =$ 6.5 Hz, N–C$\underline{H}_2$), 4.15 (CH_2, t, $J = 7.0$ Hz, O–C$\underline{H}_2$), 6.69 (1H, d, $J = 3.5$ Hz, H-2), 6.98–7.12 (3H, m, H-3, H-11, H-12), 7.53–7.58 (2H, m, H-15, H-16), 7.70 (1H, $s_{apparent}$, H-6), 7.77 (1H, $s_{apparent}$, H-5), 7.91 (1H, d, $J = 1.4$ Hz, H-1), 8.06 (2H, d, $J = 8.9$ Hz, H-9, H-10), 9.14 (1H, s, H-14). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 25.87 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 25.93 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.77 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 28.96 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.10 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.20 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 29.83 (CH_2, CH_2–C$\underline{H}_2$–CH_2), 36.21 (CH_3, N–C$\underline{H}_3$), 49.20 (CH_2, N–C$\underline{H}_2$), 68.04 (CH_2, O–C$\underline{H}_2$), 113.54 (CH, C-16), 114.95 (CH, C-11, C-12), 117.06 (CH, C-2), 119.13 (CH, C-3), 122.72 (CH, C-6), 124.06 (CH, C-15), 130.21 (CH, C-14), 130.65 (C, C-8), 131.17 (CH, C-9, C-10), 136.96 (CH, C-5), 146.64 (CH, C-1), 151.73 (C, C-4), 163.11 (C, C-13), 187.61 (C=O, C-7). ESI-MS: *m/z* $[M - Br]^+ = 421.2491$, calcd for $C_{26}H_{33}BrN_2O_3$: 421.2492.

3-(8-{4-[(2E)-3-(furan-2-yl)prop-2-enoyl]phenoxy}dodecyl)-1-methyl-1H-imidazol-3-ium bromide (**8f**) It was obtained as a dark brown solid. 88% yield (0.44 mmol, 239 mg); M.p. 124–127 °C. IR (KBr): ν_{max} (cm^{-1}) 1654 (C=O), 1600 (C=C), 1600 (C=N), 1467 (C=C_{Ar}), 1259 (C–O–C), 821 (C–H_{Ar}). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.08–1.487 (8CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 1.62–1.83 (2CH_2, m, CH_2–C$\underline{H}_2$–CH_2), 3.84 (CH_3, s, N–C$\underline{H}_3$), 4.06 (CH_2, t, $J =$ 6.5 Hz, N–C$\underline{H}_2$), 4.14 (CH_2, t, $J = 7.2$ Hz, O–C$\underline{H}_2$), 6.68 (1H, d, $J = 3.5$ Hz, H-2), 7.05 (2H, d, $J = 8.9$ Hz, H-11, H-12), 7.08 (1H, d, $J = 3.5$ Hz, H-3), 7.51–7.57 (2H, m, H-15, H-16), 7.70 (1H, $s_{apparent}$, H-6), 7.77 (1H, $s_{apparent}$, H-5), 7.90 (1H, d, $J = 1.4$ Hz, H-1), 8.05 (2H, d, $J = 8.8$ Hz, H-9,

H-10), 9.13 (1H, s, H-14). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 25.87 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 25.94 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.83 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 28.95 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.17 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.27 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 29.39 ($3CH_2$, CH_2–$\underline{C}H_2$–CH_2), 29.83 (CH_2, CH_2–$\underline{C}H_2$–CH_2), 36.20 (CH_3, N–$\underline{C}H_3$), 49.21 (CH_2, N–$\underline{C}H_2$), 68.33 (CH_2, O–$\underline{C}H_2$), 113.54 (CH, C-16), 114.95 (CH, C-11, C-12), 117.66 (CH, C-2), 119.12 (CH, C-3), 122.71 (CH, C-6), 124.05 (CH, C-15), 130.20 (CH, C-14), 130.61 (C, C-8), 131.16 (CH, C-9, C-10), 136.91 (CH, C-5), 146.46 (CH, C-1), 151.68 (C, C-4), 163.12 (C, C-13), 187.21 (C=O, C-7). ESI-MS: *m/z* $[M - Br]^+ = 463.2961$, calcd for $C_{29}H_{39}BrN_2O_3$: 463.2951.

Biological activity assays

The compounds were subjected to in vitro evaluation as regards their cytotoxicity, anti-leishmanial, and anti-trypanosomal activity against U-937 human cells and intracellular amastigotes of *L. (V) panamensis* and *T. cruzi*, respectively.

In vitro cytotoxicity

The cytotoxic activity of the compounds was assessed based on the viability of the human promonocytic cell line U-937 (ATCC CRL-1593.2^{TM}) evaluated by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay following the methodology described previously (Taylor et al. 2011). Briefly, cells grown in tissue flasks were harvested and washed with phosphate buffered saline (PBS) by centrifuging. Cells were counted and adjusted at 1×10^6 cells/mL of RPMI-1640 supplemented with complete 10% fetal bovine serum (FBS) and 1% antibiotics (100 U/mL penicillin and 0.1 mg/mL streptomycin). One hundred microliter were dispensed into each well of a 96-well cell-culture plate and then 100 mL of RPMI-1640 and the corresponding concentrations of the compounds were added, starting at 200 µg/mL in duplicate. Plates were incubated at 37 °C, 5% CO_2 during 72 h in the presence of extracts. The effect of compounds was determined by measuring the activity of the mitochondrial dehydrogenase by adding 10 µL/well of MTT solution (0.5 mg/mL) and incubation at 37 °C for 3h. The reaction was stopped by adding 100 µL/well of 50% isopropanol solution with 10% sodium dodecyl sulfate and 30 min incubation. Cell viability was determined based on the quantity of formazan produced according to the intensity of color (absorbance) registered as optical densities (O.D) obtained at 570 nm in a spectrophotometer (Varioskan™ Flash Multimode Reader —Thermo Scientific, USA). Cells cultured in absence of compounds were used as control of viability (negative control), while meglumine antimoniate (Sbv) and amphotericin B (AmB) were used as control for cytotoxicity (non-cytotoxic and cytotoxic drugs, respectively). Assays were conducted in two independent runs with three replicates per each concentration tested.

In vitro leishmanicidal activity

The activity of compounds was evaluated on intracellular amastigotes of *L. (V) panamensis* transfected with the green fluorescent protein gene (MHOM/CO/87/UA140pIR-GFP) (Pulido et al. 2012). The effect of each compound was determined according to the inhibition of the infection evidenced by both, decrease of the infected cells and decrease of intracellular parasite load. Briefly, U-937 human cells at a concentration of 3×10^5 cells/mL in RPMI 1640 and 0.1 µg/mL of phorbol-12-myristate-13-acetate (PMA) were dispensed into each well of a 24-well cell culture plate and then infected with 5 days-old promastigotes in a 15:1 parasites per cell ratio. Plates were incubated at 34 °C, 5% CO_2 during 3 h and cells were washed two times with PBS to eliminate not internalized parasites. One milliliter of fresh RPMI 1640 supplemented with 10% FBS and 1% antibiotics was added into each well, cells were incubated again to guarantee multiplication of intracellular parasites. After 24 h of infection, the culture medium was replaced by a fresh culture medium containing each compound at 20 µg/mL or lower (based on the cytotoxicity showed previously by each compound) and plates were incubated at 37 °C, 5% CO_2. After 72 h, inhibition of the infection was determined. For this, cells were removed from the bottom plate with a trypsin/EDTA (250 mg) solution; recovered cells were centrifuged at 1100 rpm during 10 min at 4 °C, the supernatant was discarded and cells were washed with 1 mL of cold PBS and centrifuged at 1100 rpm during 10 min at 4 °C. The supernatant was discarded and cells were suspended in 500 µL of PBS and analyzed by flow cytometry (FC 500MPL, Cytomics, Brea, CA, US. All determinations for each compound and standard drugs were carried out in triplicate, in two independent experiments (Buckner et al. 1996; Pulido et al. 2012). Activity of tested compounds was carried out in parallel with infection progress in culture medium alone and in culture medium with AmB and Sbv as antileishmanial drugs (positive controls). Ten thousand events were counted from each well. Each concentration was assessed in triplicate in at least two independent experiments.

In vitro trypanocidal activity

Compounds were tested on intracellular amastigotes of *T. cruzi*, Tulahuen strain transfected with β-galactosidase gene (donated by Dr. F. S. Buckner, University of

Washington) (Insuasty et al. 2015). The activity was determined according to the ability of the compound to reduce the infection of U-937 cells by *T. cruzi* as described elsewhere (Taylor et al. 2011). Following the procedure described above, anti-*T. cruzi* activity was initially screened at a single concentration of 20 mg/mL. In this case, 100 µL of U-937 human cells at a concentration of 2.5×10^5 cells/mL in RPMI-1640, 10% SFB and 0.1 µg/mL of PMA were placed in each well of 96-well plates and then infected with phase growth epimastigotes in 5:1 (parasites per cell) ratio and incubated at 34 °C, 5% CO_2. After 24 h of incubation, 20 µg/mL of each compound were added to infected cells. After 72 h of incubation, the effect of all compounds on viability of intracellular amastigotes was determined by measuring the β-galactosidase activity by spectrophotometry adding 100 µM CPRG and 0.1% nonidet P-40 to each well. After 3 h of incubation, plates were read at 570 nm in a spectrophotometer (Varioskan™ Flash Multimode Reader—Thermo Scientific, USA) and intensity of color (absorbance) was registered as O.D. Compounds that showed inhibition percentages higher than 50% were evaluated again at four concentrations selected according to the LC_{50} previously obtained for each compound. Infected cells exposed to benznidazol (BNZ) were used as control for anti-trypanosomal activity (positive control) while infected cells incubated in culture medium alone were used as control for infection (negative control). Non-specific absorbance was corrected by subtracting the O.D of the blank. Determinations were done by triplicate in at least two independent experiments (Insuasty et al. 2015).

Statistical analysis

Cytotoxicity was determined according to the percentages of viability and mortality registered to each compound a concentration, including amphotericin B, meglumine antimoniate and culture medium alone. Percentage of viability was calculated by Eq. 1, where the O.D of control, corresponds to 100% of viability.

$$\%\ \text{Viability} = (\text{O.DExposedcells})/(\text{O.DControlcells}) \times 100$$

$$\text{In turn, mortality percentage corresponds to } 100 - \%\ \text{viability}. \quad (1)$$

Results were expressed as 50 lethal concentrations (LC_{50}) that corresponds to the concentration necessary to eliminate 50% of cells and calculated by Probit analysis (Finney 1978). The degree of toxicity was graded according to the LC_{50} value using the following scale: high cytotoxicity: $LC_{50} < 200$ µM; moderate cytotoxicity: $LC_{50} >$ 200 to < 600 µM and potentially non-cytotoxicity: $LC_{50} >$ 600 µM.

On the other hand, anti-leishmanial activity was determined according to the amount of parasites in the infected cells obtained for each experimental condition, determined by flow cytometry. For this, the percentage of infected cells was determined first according to the positive events in a dot plot analysis with the green fluorescence (parasites) in *y*-axis and Forward Scatte in *x*-axis. Then, the parasitic load in those infected cells was determined by a histogram of the mean fluorescence intensity (MFI) of those fluorescent parasites) (Pulido et al. 2012). Lastly, the parasite inhibition was calculated by Eq. 2, where the MFI of control corresponds to 100% of parasites.

$$\%\ \text{Parasite} = (\text{MFI Exposed parasites})/(\text{MFIControlparasites}) \times 100 \quad (2)$$

In turn, inhibition percentage corresponds to 100%–% parasites. Results of leishmanicidal activity were expressed as EC_{50} determined by the Probit analysis (Finney 1978).

Similarly, trypanocidal activity was determined according to the percentage of infection obtained for each experimental condition by colorimetry. Parasite inhibition was calculated by Eq. 3, where the O.D of control corresponds to 100% of infection.

$$\%\ \text{Infection} = (\text{O.D Exposed parasites})/(\text{O.DControlparasites}) \times 100 \quad (3)$$

In turn, percentage of inhibition of infection corresponds to 100%–% of infection.

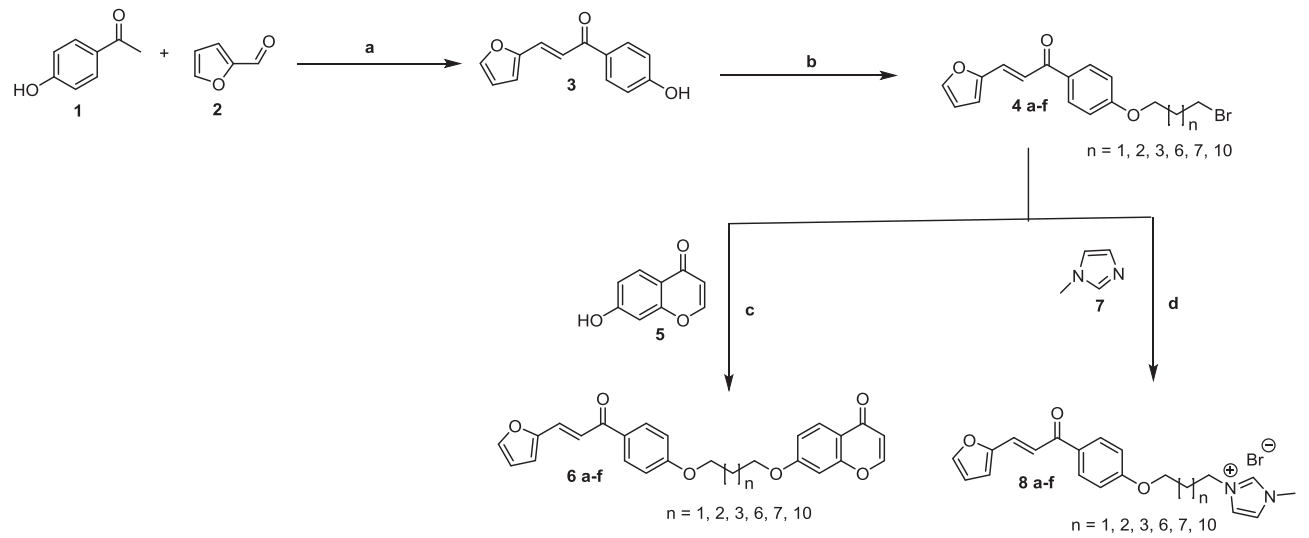
Results of anti-leishmanial and anti-trypanocidal activities were expressed as EC_{50} determined by the Probit analysis (Finney 1978). The anti-leismanial and anti-trypanosomal activities were graded according to the EC_{50} value using the following scale: High activity: $EC_{50} < 40$ µM, moderate activity: $EC_{50} >40$ to <80 µM; potentially non activity: $EC_{50} >80$ µM.

The selectivity index (SI), was calculated by dividing the cytotoxic activity and the leishmanicidal or trypanocidal activity using the following formula: $SI = LC_{50}/EC_{50}$. Cytotoxic compound: $LC_{50} < 100$ µg/mL.

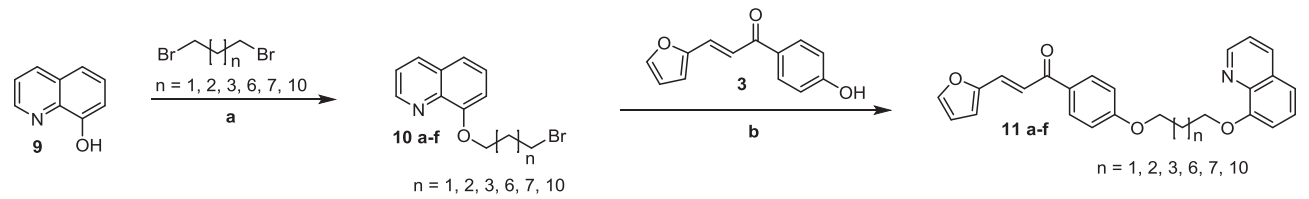
Results and discussion

Chemistry

Microwave assisted Williamson etherification of hydroxyphenyl-furylpropenone **3** with 1,ω-dibromoalkanes ($\omega = 3$, 4, 5, 8, 9, and 12) afforded bromoalkylfuranchalcone **4a–f** in yields ranging between 56 and 76% (Scheme 1) (Otero et al. 2014; Peng and Song 2002). A new



Scheme 1 Synthetic pathway to furanchalcone-chromone and furanchalcone-imidazole hybrids. Reagents and conditions: **a** KOH/MeOH/U.S, 88%; **b** 1, (ω-3,4,5,8,9 and 12), KOH/CH_3CN/MW, 55–76%; **c** KOH/CH_3CN/MW, 40–63; **d** Ethyl acetate/MW, 60–98%



Scheme 2 Synthetic pathway to furanchalcone-quinoline hybrids. Reagents and conditions: **a** 1, ω-dibromoalkane (ω-3,4,5,8,9 and 12), KOH/CH_3CN/MW, 51–80% **b** KOH/CH_3CN/MW

microwave assisted Williamson etherification of bromo-derivatives **4a–f** with 7-hydroxy-4*H*-chromen-4-one **5** gave rise to furanchalcone–chromone hybrids **6a–f** (40–63% yields). Hydroxyphenyl-furylpropenone **3** was prepared using ultrasonic irradiation assisted Claisen-Schmidt condensation between 4-hydroxyacetotophenone **1** and furfural **2** (Li et al. 2002). On the other hand, reaction of compounds **4a–f** with 1-methylimidazole **7** led to furanchalcone-imidazole hybrids **8a–f** in yields ranging between 60 and 98%.

Furanchalcone–quinoline hybrids were synthesized as indicated in Scheme 2. Thus, microwave assisted Williamson etherification of 8-hydroxyquinoline **9** with 1, ω-dibromoalkanes ($\omega = 3$, 4, 5, 8, 9, and 12) furnished bromoalkyl derivatives **10a–f**, these compounds have already been reported (Coa et al. 2017) which in turn reacted with furanchalcone **3** to produce hybrids **11b–f** in yields ranging between 46 and 58% (Scheme 2). Remarkably, low yields were obtained when bromoalkylfuranchalcone **4a–f** were used as tactical variants.

The structures of all compounds have been established by a combined study of IR, ESI-MS, ^{1}H-NMR, ^{13}C-NMR, and COSY spectra. IR spectra exhibited characteristic absorption peaks corresponding to C=O, C=C, C=C_{Ar}, C=N, C–O–C, and C–H_{Ar} groups. ESI-MS spectra showed characteristic $[M + 1]^+$ peaks corresponding to their molecular weights. The assignments of all the signals to individual H or C-atoms have been performed on the basis of typical δ-values and *J*-constants. The ^{1}H-NMR spectra of these compounds dissolved in $CDCl_3$ showed signals of –C=C–$H_{\text{furan ring}}$ (~6.64 ppm), –C=C–$H_{\text{chromone ring}}$ (~8.20 and ~6.25 ppm); –N=C–$H_{\text{quinolinic ring}}$ (~8.85 ppm) and N–$CH_{3\ \text{imidazole ring}}$ and –N–CH=N–$_{\text{imidazole ring}}$ (~3.85 and ~9.14 ppm, respectively). ^{13}C-NMR spectra showed signals around 187, 151, 163, 146, 112, 66, 46, and 36 ppm, corresponding to C=O, $CH{=}N_{\text{quinolinic ring}}$, Ar–O–, –O–$\underline{C}H{=}CH_{\text{furan ring}}$, =$\underline{C}H$–C=$O_{\text{chromone ring}}$, –$OCH_2$, –$NCH_{2-\text{imidazole ring}}$, N–$CH_{3\ \text{imidazole ring}}$, respectively.

Anti-Leishmanial, anti-trypanosomal, and cytotoxic activities

The effect of furanchalcone–quinoline, furanchalcone–chromone, and furanchalcone–imidazole hybrids on cell growth and viability was assessed in human macrophages (U-937 cells) (Taylor et al. 2011), which are the host cells

Table 1 In vitro cytotoxicity and antiprotozoal activity of furanchalcone-quinoline, furanchalcone-chromone and furanchalcone-imidazole hybrids

Compounds	Citotoxicity (U-937 cells)	Anti-Leishmanial activity		Anti-Trypanosomal activity	
	LC_{50} (Mean ± SEM) (μM)[a]	EC_{50} (Mean ± SEM) (μM)[b]	SI[c]	EC_{50} (Mean ± SEM) (μM)	SI
6a	62.24 ± 25.17	108.28 ± 7.19	0.57	92.16 ± 12.44	0.68
6b	64.32 ± 4.00	>44.23	<1.45	311.26 ± 59.90	0.21
6c	52.45 ± 21.71	125.38 ± 19.33	0.42	59.91 ± 1.87	0.92
6d	30.16 ± 2.56	44.02 ± 4.90	0.69	80.84 ± 2.99	0.37
6e	27.35 ± 5.86	46.00 ± 4.77	0.59	**25.58 ± 1.34**	1.07
6f	30.92 ± 8.83	>17.72	<1.74	126.96 ± 20.03	0.24
8a	27.42 ± 0.39	**4.65 ± 0.58**	5.90	**15.21 ± 2.86**	1.81
8b	22.71 ± 1.39	**21.78 ± 4.51**	1.05	**11.39 ± 0.63**	2.00
8c	28.78 ± 0.34	**16.43 ± 3.04**	1.76	**9.52 ± 1.24**	3.03
8d	29.18 ± 1.73	**8.39 ± 0.84**	3.48	**7.98 ± 0.43**	3.66
8e	11.02 ± 0.05	**0.78 ± 0.12**	14.17	**0.66 ± 0.04**	16.74
8f	10.60 ± 0.12	**2.12 ± 0.42**	5.01	**0.72 ± 0.04**	14.77
11b	16.16 ± 3.21	**33.64 ± 6.12**	0.48	**24.85 ± 2.32**	0.65
11c	18.15 ± 1.90	**13.78 ± 2.41**	1.32	**7.09 ± 0.42**	2.56
11d	79.58 ± 6.27	58.33 ± 3.03	1.36	50.25 ± 5.20	1.58
11e	37.23 ± 3.74	>20.69	<1.79	119.77 ± 15.21	0.31
11f	44.48 ± 11.30	207.36 ± 14.98	0.21	62.38 ± 7.52	0.71
Furanchalcone	27.07 ± 0.93	71.28 ± 13.07	0.38	124.54 ± 14.61	0.22
Quinoline	1.38 ± 0.07	2.48 ± 0.14	0.62	2.34 ± 0.48	0.66
Chromone	817.19 ± 158.50	718.45 ± 81.80	1.14	112.43 ± 16.16	7.27
Meglumine antimoniate (MA)	1137.80 ± 182.00[d]	25.68 ± 5.74	44.3	NA[e]	NA
Amphotericin B	45.60 ± 2.16	0.054 ± 0.011	842	NA	NA
Benznidazole	687.80 ± 16.14	NA	NA	40.3 ± 6.92	17.0

Data represent mean value ± standard deviation

Bold values are the most active compounds

[a] LC_{50}: Lethal concentration 50 in μM

[b] EC_{50}: Effective concentration 50 in μM

[c] SI: Selectivity index = LC_{50}/EC_{50}

[d] The molecular weight (MW) of MA is 365.98 g/mol (PubChem Compound Database, CID 64,953, National Center for Biotechnology Information) (pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=64,953)

[e] NA: Not applicable

for *L. (V) panamensis* and *T. cruzi* parasites. On the other hand, the antiparasite activity of these compounds was tested on intracellular amastigotes of *L. (V.) panamensis* (Pulido et al. 2012) and *T. cruzi* (Buckner et al. 1996; Insuasty et al. 2015), which are the form of the parasite causing the disease, assessing the ability of these compounds to reduce the amount of parasite living inside infected macrophages. Results are summarized in Table 1.

All compounds and amphotericin B were highly cytotoxic to U-937 cells showing $LC_{50} < 200$ μM (Table 1). Chromone, benznidazole and meglumine antimoniate showed no cytotoxicity ($LC_{50} > 600$ μM).

The anti-leishmanial and anti-trypanosomal activities were measured by determining the effective concentration 50 (EC_{50}) that corresponds to the concentration of drug that gives the half-maximal reduction of the amount of intracellular parasites (Table 1). Dose–response relationship showed that compounds **6d**, **6e**, **8a–8f**, and **11b–11c**, furanchalcone and quinoline were active against intracellular amastigotes of *L. (V) panamensis*.

The most active hybrids were **8e**, **8f**, **8a**, **8d**, and **11c** with an EC_{50} values of 0.78, 2.12, 4.65, 8.39, and 13.78 μM respectively, followed by **8c**, **8b**, **11b**, **6d**, and **6e** with an EC_{50} values of 16.43, 21.78, 33.64, 44.02, and 46.00 μM, respectively. As we expected, the leishmanicidal drugs amphotericin B and meglumine antimoniate showed activity with low EC_{50} values.

In turn, compounds **6e**, **8a–8f**, **11b**, **11c**, furanchalcone and quinoline were highly active against intracellular amastigotes of *T. cruzi* with EC_{50} of <30 μM. The most

active compounds were **8e**, **8f**, **11c**, **8d**, **8c**, **8b**, and **8a** with an EC_{50} values of 0.66, 0.72, 7.09, 7.98, 9.52, 11.39, and 15.21 μM, respectively. In this case, benznidazole showed activity with an EC_{50} values of 40.3 μM.

The anti-leishmanial and anti-trypanocidal activity of compounds **8a–8f**, **11c**, **11d**, and chromone were higher than their cytotoxicity. Thus, the SI (selectivity index) values calculated for these compounds were >1 (Table 1). As demonstrated elsewhere, amphotericin B and meglumine antimoniate have very high SI values, and, with the exception of compound **11d**, the other seven hybrid compounds showed better activity than this antimoniate. The anti-trypanocidal activity of nine compounds (**6e**, **8a–8f**, and **11c**) were higher than benznidazole. These results suggest that biological activity of the furanchalcone derivatives **8a**, **8d**, **8e**, and **8f** is selective, being more active against *L. (V) panamensis* than U-937 cells, while compounds **8c–8f** and **11c** were more active against *T. cruzi* parasites than U-937 cells.

There is not a clear relationship between the antiprotozoal activity and the length of the alkyl linker, as no parallel relationship between activity and the length of the chain is appreciated. However, higher bioactivity is achieved when the alkyl linker has nine and twelve carbon atoms. This could be due to an increase in lipophylicity, which facilitates the penetration of the cellular membrane (Lodish et al. 2016).

All furanchalcone–imidazole hybrids were most active than furanchalcone–quinoline and furanchalcone–chromone hybrids. This could be due to increased interactions between the polar fragment of the compounds and proteins or enzymes of the parasite, that is, acting as choline structural analogs upon reduction of the content of phosphatidylcholine and phosphatidyl ethanolamine of the parasites, metabolites that are important to synthesize and preserve the structure of the lipid membranes of eukaryotic cells (Boumann et al. 2003). This hypothesis should be confirmed in later studies.

Additionally, furanchalcone-imidazole hybrids (**8a–8f**) showed better activity against intracellular amastigotes than *N*-(halomethylated) ammonium salts and non *N*-(halomethylated) ammonium salts (<10 vs. >24.7 μg/mL) (Duque-Benítez et al. 2016). This difference could be due to the presence of the α,β-unsaturated moiety acting as a Michael acceptor for nucleophilic amino acid residues present in target enzymes of *Leishmania* (Cardona et al. 2014; Mottram et al. 2004).

Conclusions

The synthesis, anti-leishmanial, and anti-trypanosomal screening of seventeen furanchalcone derivatives are reported. Several of the synthetic compounds have potential as templates for drug development. Nine of them were active against both *L. (V) panamensis* and *T. cruzi* (**6e**, **8a–8f**, **11b**, and **11c**) being **8e** and **8f** the most active compounds with EC_{50} values of 0.78 and 2.12 μM, respectively, against *L. (V) panamensis* and 0.66 and 0.72 μM respectively, against *T. cruzi*. Seven hybrid compounds showed better activity than meglumine antimoniate and the anti-trypanosomal activity of nine compounds were higher than benznidazole. However, the SI of these compounds is affected by their high cytotoxicity. Although antiprotozoal activity levels were adequate it would still be necessary to further transform the structures of these compounds to obtain a better SI so that these derivatives can get practical use. However, these compounds still have potential to be considered as candidates for antileishmanial drug development. More studies on toxicity using other cell lines are needed to discriminate whether the toxicity shown by these compounds is specific against tumor or non-tumor cells. There is not a clear relationship between the antiprotozoal activity and the length of the alkyl linker. However, higher bioactivity was achieved when the alkyl linker has nine and twelve carbon atoms. Furanchalcone–imidazole hybrids were the most active of all compounds, showing that the imidazole salt moiety is important for their biological actions. The mechanism of action of these compounds needs to be adressed and will be the objective of further studies.

Acknowledgements The authors thank Universidad de Antioquia (grant CODI 6203 and CIDEPRO) for financial support.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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