Medicinal Chemistry Research (2019) 28:300–319
https://doi.org/10.1007/s00044-018-02285-2

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Novel fluorinated quaternary ammonium salts and their in vitro activity as trypanocidal agents

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Received: 18 September 2018 / Accepted: 24 December 2018 / Published online: 2 January 2019

Abstract

As the impact of aromatic rings and fluorine substituents in commercial drugs is attributed to their electronic distribution and structure rigidity that determine metabolic stability and toxicity, 30 quaternary ammonium salts (QAS) of the form $[X\text{-}CH_2N(CH_3)_2(CH_2)_nCH=C(Ar_2)]^+I^-$ (where X=H, Cl or I, $n=2$ or 3, and Ar = *m*-$C_6H_4CF_3$, *p*-$C_6H_4CF_3$, *m*-C_6H_4F, *p*-C_6H_4F or C_6H_5) were tested as potential trypanocidal agents and assessed their cytotoxicity on U-937 cells. CF_3-substituted QASs exhibited LC_{50} values in the range of 0.5 to 6.4 µg/mL and trypanocidal EC_{50} values between 0.6 and 7.0 µg/mL, while the LC_{50} values for F-substituted analogs are between 7.0 and 207 µg/mL and EC_{50} values range from 3.8 to 40.9 µg/mL. As a general trend, the more effective are those bearing an *N*-iodomethyl moiety or having a longer tether, and *para*-substituted ones. Few drugs therapies are in use for Chagas disease, so this study becomes a promising contribution.

Keywords Trifluoromethylated quaternary ammonium salts · Fluorinated quaternary ammonium salts · *Trypanosoma cruzi* · Cytotoxicity · Anti-trypanosomal activity

Introduction

Aromatic rings are key scaffold components of pharmacologically active molecules. Different studies established the biologic role exerted by rings (Gibson et al. 1996; Meyer et al. 2003; Dalvie et al. 2010), their presence in the vast list of commercial drugs available (Hann et al. 2001), and their statistical correlation with the number of rings or ring systems (Wang and Hou 2010; Taylor et al. 2014). The impact of aromatic rings in commercial drugs is attributed in part to their electronic distribution and structure rigidity that determine molecular properties such as lipophilicity enhancement (Lipinski 2000; Ran et al. 2001), improvement of the ligand-receptor properties, and/or alterations in the molecular reactivity, metabolic stability and toxicity (Meyer et al. 2003). The aromatic rings count becomes the second molecular descriptor, after hydrophobicity, in assessing the potential for a molecule to be developed as a drug (Young et al. 2011).

On the other hand, there is an increasing trend of using halogenated substituents in synthetic biologically active molecules, often giving rise to modifications of their pharmacological potential, due in part to the role of halogen-bond in substrate selectivity (Metrangolo et al. 2005; Scholfield et al. 2013) and molecular recognition (Jiang et al. 2016; Mendez et al. 2017), or changing membrane binding ability and permeability (Gerebtzoff et al. 2004). Special attention has focused on the use of fluorinated substituents (Isanbor and O'Hagan 2006; Kirk 2006; Gillis et al. 2015; Reddy 2015; Shi et al. 2017), taking advantage of the unique properties of fluorine such as its high electronegativity and small size such that it is only 20% bigger than hydrogen. The short C–F bond distance and its bond

Supplementary information The online version of this article (https://doi.org/10.1007/s00044-018-02285-2) contains supplementary material, which is available to authorized users.

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energy, that is about 5 Kcal mol^{-1} higher than C–H, enhances metabolic stability of fluorinated molecules. Also, very often enzymes do not recognize the difference between a natural metabolite and a fluorinated analog, and these effects give rise to enzyme inhibition and mimetic effects (Ojima 2009). In addition, as a general trend, fluorination or polyfluorination of aromatic rings or π systems enhances lipophilicity of bioactive compounds, and this property determines the absorptivity, transport and binding substrate-receptor affinity and interactions (Gillis et al. 2015; Shi et al. 2017). Additionally, fluorine or trifluoromethyl groups can modify intrinsic potency, membrane permeability, metabolic pathways, pharmacokinetic properties, and pKa values of vicinal groups (Shi et al. 2017). In particular, the CF_3 group confers to molecules a steric demand similar to the isopropyl group (Reddy 2015) and, if incorporated on to an aromatic ring, increases the lipophilicity and the bioavailability of a compound. This group also reduces the electron density of the ring, rendering less reactive and less prone to oxidative metabolism (Reddy 2015).

Also important for consideration, quaternary ammonium salts (QASs), some of those being also called ionic liquids, are widely used or investigated by the pharmaceutical industry (Egorova et al. 2017) for their recognized activity against tumor cells, bacteria, fungi, viruses, and parasites, although these salts may also be highly toxic agents. The toxicity of ionic liquids is not distinguishable only by their structure because cell type and other external factors exert influence on the activity, and this would be expected also for biological behavior in general, which is reported to be strongly dependent on the organism (Avlonitis et al. 2003; Pérez-Victoria et al. 2003; Pham et al. 2010; Egorova et al. 2017). Thus, every kind of QASs or every structural modification or different scaffolds are worthy to be explored for a variety of pharmaceutical purposes. While a lot more attention has focused on QASs as anticancer, antimicrobial or antifungal activity (Egorova et al. 2017; Ng et al. 2006; Obłąk et al. 2016), much less attention has been paid to them as anti-parasitic agents. Nevertheless, there are some reports on antimalarial (Basilico et al. 2015), anti-leishmanial (Avlonitis et al. 2003; Pérez-Victoria et al. 2003) or anti-trypanosomal (de Castro et al. 2004) activity of QASs. In fact, some of the current commercially available drugs for treatment of leishmaniasis are QASs structurally related to choline, classified as alkyl-lysophospholipids (de Castro et al. 2004; Pachioni et al. 2013), such as miltefosine, ildefosine or edelfosine, presumably operating as inhibitors of phosphocholine kinases (Rakotomanga et al. 2007; Tischer et al. 2012) or disrupting parasites cell membrane (Palermo et al. 2011).

Since *Leishmania* spp. and *Trypanosoma cruzi* parasites are kinetoplastid organisms that share biochemical metabolism profiles (El-Sayed et al. 2015; Khare et al. 2016), it is expected that antiparasitic agents would be functional both as anti-leishmanials and anti-trypanosomals. In fact, some alkyl-lysophospholipids have been shown to be effective in vitro and in vivo against *T. cruzi* and other trypanosomatids (de Castro et al. 2004). Searching for new drugs against Chagas disease is very challenging (WHO 2015, 2016). Only two drugs, with serious side effects, benznidazole and nifurtimox are currently commercially available, whereas about 6–7 million people are infected overseas and it is estimated that nearly 13% of the Latin American population is currently under risk (WHO 2015).

In our efforts to look for therapeutic alternatives against neglected parasitic diseases, particularly antileishmanials, we evaluated QASs with a terminal two phenyl ring-scaffold which exhibited in vitro and in vivo activity against amastigotes of *Leishmania panamensis* (Ríos et al. 2015; Duque-Benítez et al. 2016; Fernández et al. 2018). We have now extended that work to assess if these QASs behave as anti-trypanosomal agents as well, and if the presence of CF_3 or F substituents in the ring system modify effectiveness or cytotoxicity. In this work, we studied 24 unknown fluorinated QASs of the form $\{X\text{-}CH_2N(Me)_2[(CH_2)_nCH=CAr_2]\}^+ I^-$ and six non-fluorinated, known analogs, against *T. cruzi* amastigotes and their cytotoxicity in U-937 macrophages. A preliminary structure-activity relationship is also presented.

Materials and methods

General information for chemistry

The progress of most reactions was monitored by TLC, using TLC Silica gel 60 F_{254}. Compounds were visualized by irradiation with UV light, and exposure to I_2 vapor. Column chromatography was performed on silica gel 60, 63–200 microns. Melting points (m.p.) were determined in a KRÜSS melting point meter KSP1N.

Structural characterization of compounds was carried out by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, infrared spectroscopy (FTIR), elemental analysis, and mass spectrometry. ^{1}H NMR and ^{13}C NMR spectra were obtained at 400 MHz and 101 MHz, respectively, on a Bruker AV-II 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as solvent. ^{19}F NMR spectra were obtained at 500 MHz on a Bruker AV-III 500 MHz spectrometer and were referenced relative to external $CFCl_3$. The chemical shifts are reported in ppm from TMS (δ scale) but were measured against the solvent signal; coupling constants *J*, are measured in Hz. IR spectra were recorded with Thermo Scientific Nicolet iS5 FTIR Spectrometer. Elemental analyses of carbon, hydrogen, and nitrogen were conducted in a Perkin Elmer 2400 Series II Analyzer at the microanalysis laboratory at the University

of Illinois (Urbana-Champaign, IL, USA). Mass spectra were obtained on a Bruker QTOF Impact II MS (ESI+) at Universidad de Antioquia (Colombia).

Solvents and reagents were obtained from different commercial sources; the dry ethyl ether was further dried with molecular sieves.

Chemistry

General procedure for the in situ preparation of Grignard reagents from 6 (a, b, c or d)

The methodology was used according to the literature (Chen et al. 2011; Huang et al. 2014; Li et al. 2014) with modifications. Prior to each reaction, all glassware was flamed and purged with nitrogen. The reactions were carried out under a dry nitrogen atmosphere and with protection from light. The assemblage for the reaction consisted of a three-necked flask with an addition funnel and a vertical condenser. A suspension of magnesium turnings (2.4 eq), a tiny crystal of iodine and dry ethyl ether (1 mL per mmol) was prepared inside the flask, and then 2.5 eq. of the respective fluorinated bromoaryl precursors **6** (**a**, **b**, **c** or **d**) dissolved in dry ethyl ether (1 mL per mmol of **6**) were added dropwise from the addition funnel. At the beginning, about a quarter of the solution of **6** was used until the iodine color disappeared, and then the reaction mixture was kept stirring for 1 h. After this time, the remaining solution of **6** was added dropwise while the reaction mixture was kept under magnetic stirring. Once the magnesium was consumed, the reaction mixture was stirred for an additional 2.5 h. Grignard reagents from **6a**, **6c** or **6d** were cannulated out from the reactant mixture to another assemblage for the subsequent reaction with esters **5**, while the very sticky Grignard reagent from **6b** was used immediately in the same reaction flask.

General procedure for the preparation of ω-bromo-α,α-bis-(aryl) alcohols 7 and 8

To a three-necked flask, equipped with a vertical condenser and an addition funnel, and containing the respective Grignard reagents prepared from **6**, was added dropwise the corresponding ω-bromoester **5** (1 eq) in dry ethyl ether (0.8 mL per mmol) from the funnel, during a period of 30 to 60 min avoiding reflux. The reaction mixture was kept stirring (between 2 and 12 h). After the reaction was complete, an aqueous solution of 1 M HCl was added at 0 °C, followed by the respective phase separation. The organic layer was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by rotary evaporation under reduced pressure. When necessary, it was subjected to trituration with hexane, and the solvent was again removed by rotary evaporation under reduced pressure. The products were purified by column chromatography. Pure alcohols were obtained as yellow or colorless oils.

5-Bromo-1,1-*bis*-(3-trifluoromethylphenyl)pentan-1-ol (7a) Starting from ethyl 5-bromovalerate **5a**, product **7a** was obtained as yellow oil (43% yield) and purified by column chromatography eluting with hexane/ethyl acetate/methanol 90:7:3 (*Rf* 0.36). IR (KBr) ν_{max} (cm^{-1}): 3463 (O–H), 3077 (C–H_{Ar}), 1128 (C–F, CF_3), 563 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74 (2H, s, Ar-H2′), 7.54 (4H, m, Ar–H4′, Ar-H6′), 7.45 (2H, m, Ar–H5′), 3.38 (2H, t, *J* = 6.7 Hz, H-5), 2.34 (2H, t, *J* = 7.8 Hz, H-2), 2.18 (br s, OH), 1.91 (2H, quintet, *J* = 7.0, H-4), 1.43 (2H, m, H-3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 147.2 (C-1′$_{Ar}$), 131.0 (q, *J* = 32.2 Hz, C-3′$_{Ar}$), 129.6 (C-5′$_{Ar}$), 129.1 (C-6′$_{Ar}$), 124.4 (m, C-2′$_{Ar}$), 124.2 (q, *J* = 272.4 Hz, CF_3), 122.7 (q, *J* = 3.5 Hz, C-4′$_{Ar}$), 77.8 (C-1), 41.0 (C-2), 33.2 (C-5), 32.8 (C-4), 22.3 (C-3).

5-Bromo-1,1-*bis*-(4-trifluoromethylphenyl)pentan-1-ol (7b) Starting from ethyl 5-bromovalerate **5a**, product **7b** was obtained as a yellow oil (47% yield), and purified by trituration with hexane and column chromatography eluting with hexane/ethyl acetate 50:50 and corrected with column chromatography eluting with hexane/ethyl acetate/methanol 90:5:5 (*Rf* 0.3). IR (KBr) ν_{max} (cm^{-1}): 3473 (O–H), 3067 (C–HAr), 1131 (C–F, CF_3), 563 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.59 (4H, d, *J* = 8.4 Hz, Ar–H3′), 7.54 (4H, d, *J* = 8.3 Hz, Ar–H2′), 3.38 (2H, t, *J* = 6.7 Hz, H-5), 2.32 (2H, m, H-2), 1.90 (2H, m, H-4), 1.45 (2H, m, H-3), 1.26 (br s, OH); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 150.0 (C-1′$_{Ar}$), 129.7 (q, *J* = 32.5 Hz, (C-4′$_{Ar}$), 126.4 (C-2′$_{Ar}$), 125.6 (q, *J* = 3.6 Hz, C-3′$_{Ar}$), 124.2 (q, *J* = 272.1 Hz, CF_3), 77.8 (C-1), 40.9 (C-2), 33.3 (C-5), 32.8 (C-4), 22.4 (C-3).

5-Bromo-1,1-*bis*-(3-fluorophenyl)pentan-1-ol (7c) Starting from ethyl 5-bromovalerate **5a**, product **7c** was obtained as transparent oil (65% yield) and it was purified by column chromatography eluting with hexane/ethyl acetate 90:10 (*Rf* 0.36). IR (KBr) ν_{max} (cm^{-1}): 3471 (O–H), 3073 (C–H_{Ar}), 1236 (C–F), 559 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32 (2H, m, Ar–H5′), 7.19 (4H, m, Ar–H2′, Ar–H6′), 6.97 (2H, m, Ar–H4′), 3.40 (2H, t, *J* = 6.8 Hz, H-5), 2.29 (2H, m, H-2), 2.07 (br s, OH), 1.92 (2H, quintet, *J* = 7.1 Hz, H-4), 1.47 (2H, m, H-3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 163.0 (d, *J* = 245.9 Hz, C–F), 149.1 (d, *J* = 6.5 Hz, C-1′$_{Ar}$), 130.0 (d, *J* = 8.1 Hz, C-5′$_{Ar}$), 121.6 (d, *J* = 2.5 Hz, C-6′$_{Ar}$), 114.2 (d, *J* = 21.1 Hz, C-4′$_{Ar}$), 113.3 (d, *J* = 22.7 Hz, C-2′$_{Ar}$), 77.6 (C-1$_{vinyl}$), 41.0 (C-2$_{vinyl}$), 33.4 (C-5), 33.0 (C-4), 22.5 (C-3).

5-Bromo-1,1-*bis*-(4-fluorophenyl)pentan-1-ol (7d) Starting from ethyl 5-bromovalerate **5a**, product **7d** was obtained as a white solid (54% yield), and it was triturated with hexane and purified by column chromatography eluting with hexane/ethyl acetate 90:10 (*Rf* 0.29); m.p. 63.5–64.3 °C. IR (KBr) ν_{max} (cm^{-1}): 3488 (O–H), 3046 (C–H_{Ar}), 1227 (C–F), 587 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34 (4H, m, Ar–H2′), 7.00 (4H, m, Ar–H3′), 3.37 (2H, t, *J* = 6.8 Hz, H-5), 2.55 (2H, m, H-2), 1.87 (2H, m, H-4), 1.70 (s, OH), 1.49–1.32 (2H, m, H-3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 161.9 (d, *J* = 246.0 Hz, C–F), 142.6 (d, *J* = 3.1 Hz, C-1′$_{Ar}$), 127.9 (d, *J* = 8.0 Hz, C-2′$_{Ar}$), 115.2 (d, *J* = 21.3 Hz, C-3′$_{Ar}$), 77.6 (C-1$_{vinyl}$), 41.4 (C-2$_{vinyl}$), 33.4 (C-4), 33.0 (C-5), 22.6 (C-3).

6-Bromo-1,1-*bis*-(3-trifluoromethylphenyl)hexan-1-ol (8a) Starting from ethyl 6-bromohexanoate **5b**, product **8a** was obtained as a colorless oil (55% yield) and purified by column chromatography eluting with hexane/ethyl acetate 90:10 (*Rf* 0.46). IR (KBr) ν_{max} (cm^{-1}): 3479 (O–H), 3077 (C–H_{Ar}), 1129 (C–F, CF_3), 562 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74 (2H, s, Ar–H2′), 7.54 (4H, m, Ar–H4′, Ar–H6′), 7.44 (2H, t, *J* = 7.8 Hz, Ar–H5′), 3.36 (2H, t, *J* = 6.7 Hz, H-6), 2.32 (2H, m, H-2), 1.83 (2H, quintet, *J* = 6.8, H-5), 1.50 (2H, m, H-4), 1.30 (2H, m, H-3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 147.9 (C-1′$_{Ar}$), 130.9 (q, *J* = 32.2 Hz, C-3′$_{Ar}$), 129.6 (C-5′$_{Ar}$), 129.1 (C-6′$_{Ar}$), 124.3 (q, *J* = 3.7 Hz, C-2′$_{Ar}$), 124.2 (q, *J* = 272.5 Hz, CF_3), 122.7 (q, *J* = 3.8 Hz, C-4′$_{Ar}$), 77.8 (C-1), 41.8 (C-2), 33.7 (C-6), 32.6 (C-5), 28.5 (C-4), 22.9 (C-3).

6-Bromo-1,1-*bis*-(4-trifluoromethylphenyl)hexan-1-ol (8b) Starting from **5b**, product **8b** was obtained as a yellow oil (38% yield), and it was triturated with hexane and purified by column chromatography eluting with hexane/ethyl acetate 90:10 (*Rf* 0.28). IR (KBr) ν_{max} (cm^{-1}): 3479 (O–H), 3067 (C–H_{Ar}), 1124 (C–F, CF_3), 562 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.59 (4H, d, *J* = 8.4 Hz, Ar–H4′), 7.53 (4H, d, *J* = 8.5 Hz, Ar–H2′), 3.37 (2H, t, *J* = 6.7 Hz, H-6), 2.32 (2H, m, H-2), 1.83 (2H, quintet, *J* = 6.8, H-5), 1.50 (2H, m, H-3), 1.30 (2H, m, H-4); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.2 (C-1′$_{Ar}$), 129.6 (q, *J* = 32.6 Hz, C-4′$_{Ar}$), 126.4 (C-2′$_{Ar}$), 125.5 (q, *J* = 3.8 Hz, C-3′$_{Ar}$), 124.2 (q, *J* = 272.1 Hz, CF_3), 77.9 (C-1), 41.7 (C-2), 33.7 (C-6), 32.7 (C-5), 28.5 (C-4), 22.9 (C-3).

6-Bromo-1,1-*bis*-(3-fluorophenyl)hexan-1-ol (8c) Starting from ethyl 6-bromohexanoate **5b**, product **8c** was obtained as colorless oil (44% yield) and it was purified by column chromatography eluting with hexane/ethyl acetate 90:10 (*Rf* 0.29). IR (KBr) ν_{max} (cm^{-1}): 3479 (O–H), 3038 (C–H_{Ar}), 1236 (C–F), 565 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.21 (4H, m, Ar–H2′, Ar–H6′), 7.06 (2H, m, Ar–H5′), 6.86 (2H, m, Ar–H4′), 3.29 (2H, t, *J* = 6.7 Hz, H-6), 2.16 (2H, m, H-2), 2.07 (s, OH) 1.78 (2H, m, H-5), 1.40 (2H, m, H-3), 1.22 (2H, m, H-4); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 163.0 (d, *J* = 245.8 Hz, C–F), 149.3 (d, *J* = 6.4 Hz, C-1′$_{Ar}$), 130.0 (d, *J* = 8.1 Hz, C-5′$_{Ar}$), 121.6 (d, *J* = 2.8 Hz, C-6′$_{Ar}$), 114.1 (d, *J* = 21.2 Hz, C-4′$_{Ar}$), 113.3 (d, *J* = 22.7 Hz, C-2′$_{Ar}$), 77.7 (t, *J* = 1.6 Hz, C-1$_{vinyl}$), 41.8 (C-2$_{vinyl}$), 33.8 (C-6), 32.7 (C-5), 28.6 (C-4), 22.9 (C-3).

6-Bromo-1,1-*bis*-(4-fluorophenyl)hexan-1-ol (8d) Starting from ethyl 6-bromohexanoate **5b**, product **8d** was obtained as a white solid (62% yield) and it was triturated with hexane and purified by column chromatography eluting with hexane/ethyl acetate 90:10 (*Rf* 0.31), m.p. 53.1–54.3 °C. IR (KBr) ν_{max} (cm^{-1}): 3404 (O–H), 3064 (C–H_{Ar}), 1229 (C–F), 587 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (4H, m, Ar–H3′), 6.99 (4H, m, Ar–H2′), 3.36 (2H, t, *J* = 6.7 Hz, H-6), 2.24 (2H, m, H-2), 1.82 (2H, m, H-5), 1.46 (2H, m, H-3), 1.30 (2H, m, H-4); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 161.9 (d, *J* = 245.9 Hz, C–F), 142.8 (d, *J* = 3.1, C-1′$_{Ar}$), 127.9 (d, *J* = 8.0 Hz, C-2′$_{Ar}$), 115.2 (d, *J* = 21.3 Hz, C-3′$_{Ar}$), 77.7 (C-1$_{vinyl}$), 42.2 (C-2$_{vinyl}$), 33.8 (C-6), 32.7 (C-5), 28.6 (C-4), 23.1 (C-3).

General procedure for the preparation of fluorinated or trifluoromethylated ω-bromo-α,α-diaryl olefins 9 and 10

Products **9** and **10** were prepared according to the literature (Duque-Benítez et al. 2016; Ríos et al. 1996) with modifications. A round-bottomed flask was equipped with a Dean-Stark trap and a vertical condenser. Alcohols **7** or **8** (**a** or **b**) and *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) in a molar ratio of about 60:1 were dissolved in benzene (4.8 mL per mmol of alcohol) and refluxed during 8 h. After cooling down, the crude mixture was neutralized with an oversaturated $NaHCO_3$ aqueous solution, and then the organic layer was washed with brine solution, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed by rotary evaporation under reduced pressure. The products were purified by column chromatography eluting with hexane. Colorless oils were obtained.

5-Bromo-1,1-*bis*-(3-trifluoromethylphenyl)pent-1-ene (9a) Starting from **7a**, product **9a** was obtained as colorless oil (61% yield), *Rf* 0.45 (hexane). IR (KBr) ν_{max} (cm^{-1}): 3076 (C–H_{Ar}), 3040 (=C–H_{vinyl}), 1129 (C–F, CF_3), 563 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.63 (1H, d, *J* = 7.8 Hz, $Ar_{a\ or\ b}$–H4′), 7.54 (2H, m, $Ar_{a\ or\ b}$–H5′), 7.49 (1H, s, $Ar_{a\ or\ b}$–H2′), 7.44 (1H, s, $Ar_{a\ or\ b}$–H2′), 7.38 (2H, m, $Ar_{a\ or\ b}$–H5′), 7.29 (1H, d, *J* = 7.8 Hz, $Ar_{a\ or\ b}$–H6′), 6.16 (1H, t, *J* = 7.5 Hz, = CH$_{vinyl}$), 3.39 (2H, t, *J* = 6.6 Hz, H-5a, H-5b), 2.28 (2H, m, H-3a, H-3b), 2.03 (2H, quintet, *J* = 6.8, H-4a, H-4b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 142.6 (C-1′$Ar_{a\ or\ b}$), 140.9 (C-1′$Ar_{a\ or}$

$_b$), 139.9 (C-1$_{vinyl}$), 133.3 (C-6′ Ar$_{a\ or\ b}$), 131.1 (m, C-3′Ar$_a$, C-3′Ar$_b$), 130.7 (C-2$_{vinyl}$, C-6′Ar$_{a\ or\ b}$), 129.2 (C-5′Ar$_{a\ or\ b}$), 129.0 (C-5′Ar$_{a\ or\ b}$), 126.5 (m, C-2′ Ar$_{a\ or\ b}$), 124.6 (m, C-4′ Ar$_{a\ or\ b}$), 124.3 (q, $J = 3.9$ Hz, C-4′ Ar$_{a\ or\ b}$), 124.2 (q, $J = 275.0$ Hz, CF_3), 124.2 (q, $J = 276.7$ Hz, CF_3), 123.7 (q, $J = 4.0$ Hz, C-2′ Ar$_{a\ or\ b}$), 32.8 (C-5), 32.7 (C-4), 28.5 (C-3).

5-Bromo-1,1-*bis*-(4-trifluoromethylphenyl)pent-1-ene (9b) Starting from **7b**, product **9b** was obtained as colorless oil (47% yield), *Rf* 0.42 (hexane). IR (KBr) ν (cm^{-1}): 3049 (=C–H$_{vinyl}$), 1128 (C–F, CF_3), 564 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.67 (2H, d, $J = 8.1$ Hz, Ar$_{a\ or\ b}$–H3′), 7.53 (2H, d, $J = 8.3$ Hz, Ar$_a$ or b-H3′), 7.28 (4H, m, Ar$_a$–H2′, Ar$_b$–H2′), 6.19 (1H, t, $J = 7.5$ Hz, = CH$_{vinyl}$), 3.39 (2H, t, $J = 6.6$ Hz, H-5a, H-5b), 2.29 (2H, m, H-3a, H-3b), 2.03 (2H, quintet, $J =$ 6.8, H-4a, H-4b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 145.0 (C-1′Ar$_{a\ or\ b}$), 142.8 (C-1′Ar$_{a\ or\ b}$), 140.9 (C-1$_{vinyl}$), 130.9 (C-2$_{vinyl}$), 132.3 (m, C-4′Ar$_{a\ or\ b}$), 130.1 (C-2′Ar$_{a\ or\ b}$), 127.4 (C-2′Ar$_{a\ or\ b}$), 125.5 (q, $J = 3.7$ Hz, C-3′Ar$_{a\ or\ b}$), 125.3 (q, $J = 3.6$ Hz, (C-3′Ar$_{a\ or\ b}$), 32.7 (C-5), 32.6 (C-4), 28.5 (C-3), Ar**C**F_3 not seen.

5-Bromo-1,1-*bis*-(3-fluorophenyl)pent-1-ene (9c) Starting from **7c**, product **9c** was obtained as colorless oil (55% yield) and it was purified by column chromatography eluting with hexane (*Rf* 0.29). IR (KBr) ν_{max} (cm^{-1}): 3070 (C–H$_{Ar}$), 3023 (=C–H$_{vinyl}$), 1233 (C–F), 562 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.40 (1H, td, $J = 7.9$, 6.0 Hz, Ar$_{a\ or\ b}$–H5′), 7.27 (1H, td, $J = 7.7$, 5.9 Hz, Ar$_{a\ or\ b}$–H5′), 7.01 (6H, m, Ar–H2′, Ar–H4′, Ar–H-6′), 6.13 (1H, t, $J =$ 7.5 Hz, =C–H$_{vinyl}$), 3.42 (2H, t, $J = 6.7$ Hz, H-5a, H-5b), 2.32 (2H, m, H-3a, H-3b), 2.05 (2H, m, H-4a, H-4b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 162.9 (d, $J = 245.9$ Hz, C–F), 144.2 (d, $J = 7.4$ Hz, C-1′Ar$_{a\ or\ b}$), 141.6 (d, $J = 7.6$ Hz, C-1′Ar$_{a\ or\ b}$), 141.1 (C-1$_{vinyl}$), 130.1 (d, $J = 8.3$ Hz, C-5′Ar$_{a\ or\ b}$), 129.7 (d, $J = 8.3$ Hz, C-5′Ar$_{a\ or\ b}$), 129.4 (C-2$_{vinyl}$), 125.6 (d, $J = 2.1$ Hz, C-6′Ar$_{a\ or\ b}$), 122.9 (d, $J = 1.9$ Hz, C-6′Ar$_{a\ or\ b}$), 116.8 (d, $J = 21.2$ Hz, C-4′Ar$_{a\ or\ b}$), 114.5 (d, $J = 21.1$ Hz, C-4′Ar$_{a\ or\ b}$), 114.2 (d, $J = 21.3$ Hz, C-2′Ar$_{a\ or\ b}$), 114.1 (d, $J = 22.1$ Hz, C-2′Ar$_{a\ or\ b}$), 32.9 (C-4), 32.9 (C-5), 28.5 (C-3).

5-Bromo-1,1-*bis*-(4-fluorophenyl)pent-1-ene (9d) Starting from **7d**, product **9d** was obtained as colorless oil (70% yield) and it was purified by column chromatography eluting with hexane (*Rf* 0.42). IR (KBr) ν_{max} (cm^{-1}): 3076 (C–H$_{Ar}$), 3046 (=C–H$_{vinyl}$), 1233 (C–F), 577 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.06 (8H, m, Ar–H2′, Ar–H3′), 5.98 (1H, t, $J = 7.5$ Hz, =CH$_{vinyl}$), 3.39 (2H, t, $J =$ 6.8 Hz, H-5a, H-5b), 2.26 (2H, m, H-3a, H-3b), 2.00 (2H, m, H-4a, H-4b); ^{13}C NMR (101 MHz, CDCl3): δ = 162.4 (d, $J = 246.8$ Hz, C–F), 162.2 (d, $J = 246.3$ Hz, C–F), 141.3 (C-1$_{vinyl}$), 138.6 (d, $J = 3.2$ Hz, C-1′Ar$_{a\ or\ b}$), 135.7 (d, $J =$ 3.5 Hz, C-1′Ar$_{a\ or\ b}$), 131.5 (d, $J = 7.9$ Hz, C-2′Ar$_{a\ or\ b}$), 128.9 (d, $J = 7.9$ Hz, C-2′Ar$_{a\ or\ b}$), 127.9 (C-2$_{vinyl}$), 115.5 (d, $J = 21.3$ Hz, C-3′Ar$_{a\ or\ b}$), 115.2 (d, $J = 21.5$ Hz, C-3′Ar$_{a\ or\ b}$), 33.1 (C-5), 33.0 (C-4), 28.5 (C-3). Data are in agreement with those reported in the literature (Li et al. 2014).

6-Bromo-1,1-*bis*-(3-trifluoromethylphenyl)hex-1-ene (10a) Starting from **8a**, product **10a** was obtained as colorless oil (63% yield), *Rf* 0.48 (hexane). IR (KBr) ν_{max} (cm^{-1}): 3070 (C–H$_{Ar}$), 3040 (=C–H$_{vinyl}$), 1127 (C–F, CF_3), 562 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (1H, d, $J = 7.8$ Hz, Ar$_{a\ or\ b}$–H4′), 7.52 (3H, m, Ar$_{a\ or\ b}$–H5′, Ar$_{a\ or\ b}$–H2′), 7.43 (1H, s, Ar$_{a\ or\ b}$–H2′), 7.37 (2H, m, Ar$_{a\ or\ b}$–H5′), 7.29 (1H, d, $J = 7.9$ Hz, Ar$_{a\ or\ b}$–H6′), 6.19 (1H, t, $J = 7.5$ Hz, = CH$_{vinyl}$), 3.37 (2H, t, $J = 6.7$ Hz, H-6a, H-6b), 2.15 (2H, q, $J = 7.5$ Hz,), 1.86 (2H, m, H-5a, H-5b), 1.64 (2H, m, H-4a, H-4b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 142.7 (C-1′ Ar$_{a\ or\ b}$), 140.1 (C-1′ Ar$_{a\ or\ b}$, C-1$_{vinyl}$), 133.3 (C-6′ Ar$_{a\ or\ b}$), 132.1 (C-6′ Ar$_{a\ or\ b}$), 130.0 (m, C-3′Ar$_a$, C-3′Ar$_b$), 130.7 (C-5′ Ar$_{a\ or\ b}$), 129.2 (C-2$_{vinyl}$), 128.9 (C-5′ Ar$_{a\ or\ b}$), 126.6 (q, $J = 3.8$ Hz, C-2′ Ar$_{a\ or\ b}$), 124.5 (q, $J = 3.7$ Hz, C-4′ Ar$_{a\ or\ b}$), 124.2 (q, $J = 272.3$ Hz, CF_3), 124.2 (q, $J = 272.3$ Hz, CF_3), 124.1 (q, $J = 3.8$ Hz, C-4′ Ar$_{a\ or\ b}$), 123.7 (q, $J = 3.8$ Hz, C-2′ Ar$_{a\ or\ b}$), 33.4 (C-6), 32.4 (C-5), 29.1 (C-4), 28.3 (C-3).

6-Bromo-1,1-*bis*-(4-trifluoromethylphenyl)hex-1-ene (10b) Starting from **8b**, product **10b** was obtained as colorless oil (92% yield), *Rf* 0.26 (hexane). IR (KBr) ν_{max} (cm^{-1}): 3049 (=C–H$_{vinyl}$), 1128 (C–F, CF_3), 563 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.66 (2H, d, $J = 8.0$ Hz, Ar$_{a\ or\ b}$–H3′), 7.53 (2H, d, $J = 8.2$ Hz, Ar$_{a\ or\ b}$–H3′), 7.28 (4H, d, $J = 8.4$ Hz, Ar$_a$–H2′, Ar$_b$–H2′), 6.21 (1H, t, $J = 7.5$ Hz, =CH$_{vinyl}$), 3.37 (2H, t, $J = 6.7$ Hz, H-6a, H-6b), 2.15 (2H, q, $J = 7.5$ Hz, H-3a, H-3b), 1.87 (2H, m, H-5a, H-5b), 1.64 (2H, m, H-4a, H-4b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 145.3 (C-1′ Ar$_{a\ or\ b}$), 143.1 (C-1′ Ar$_{a\ or\ b}$), 140.3 (C-1$_{vinyl}$), 132.4 (C-2$_{vinyl}$), 130.4 (C-2′ Ar$_{a\ or\ b}$), 129.8 (m, C-4′ Ar$_{a\ or\ b}$), 127.5 (C-2′ Ar$_{a\ or\ b}$), 125.6 (q, $J = 3.7$ Hz, C-3′ Ar$_{a\ or\ b}$), 125.4 (q, $J = 3.7$ Hz, C-3′ Ar$_{a\ or\ b}$), 33.5 (C-6), 32.4 (C-5), 29.1 (C-4), 28.3 (C-3), Ar**C**F_3 not seen.

6-Bromo-1,1-*bis*-(3-fluorophenyl)hex-1-ene (10c) Starting from **8c**, product **10c** was obtained as colorless oil (60% yield) and it was purified by column chromatography eluting with hexane (*Rf* 0.4). IR (KBr) ν_{max} (cm^{-1}): 3073 (C–H$_{Ar}$), 3023 (=C–H$_{vinyl}$), 1230 (C–F), 592 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36 (1H, td, $J = 7.9$, 6.0 Hz, Ar$_{a\ or\ b}$–H5′), 7.22 (1H, td, $J = 8.0$, 6.2 Hz, Ar$_{a\ or\ b}$–H5′), 6.96 (6H, m, Ar$_{a\ or\ b}$–H2′, Ar$_{a\ or\ b}$–H-4′, Ar$_{a\ or\ b}$–H6′), 6.11 (1H, t, $J = 7.5$ Hz, =CH$_{vinyl}$), 3.36 (2H, t, $J = 6.7$ Hz, H-6a, H-6b), 2.14 (2H, q, $J = 7.5$ Hz, H-3a, H-3b), 1.86 (2H, m,

H-5a, H-5b), 1.60 (2H, m, H-4a, H-4b); ^{13}C NMR ($CDCl_3$,101 MHz): δ = 163.0 (d, J = 245.0 Hz, C–F), 144.3 (d, J = 7.4 Hz, C-1′ $Ar_{a\ or\ b}$), 141.8 (d, J = 7.6 Hz, C-1′ $Ar_{a\ or\ b}$), 140.4 (C-1_{vinyl}), 130.9 (C-2_{vinyl}), 130.1 (d, J = 8.3 Hz, C-5′$Ar_{a\ or\ b}$), 129.7 (d, J = 8.3 Hz, C-5′$Ar_{a\ or\ b}$), 125.7 (d, J = 2.5 Hz, C-6′$Ar_{a\ or\ b}$), 122.9 (d, J = 2.0 Hz, C-6′$Ar_{a\ or\ b}$), 116.8 (d, J = 21.0 Hz, C-4′$Ar_{a\ or\ b}$), 114.4 (d, J = 21.0 Hz, C-2′$Ar_{a\ or\ b}$), 114.1 (d, J = 21.6 Hz, C-2′$Ar_{a\ or\ b}$), 33.6 (C-6), 32.4 (C-5), 28.9 (C-4), 28.3 (C-3).

6-Bromo-1,1-*bis*-(4-fluorophenyl)hex-1-ene (10d) Starting from **8d**, product **10d** was obtained as colorless oil (72% yield) and it was purified by column chromatography eluting with hexane (*Rf* 0.41). FT-IR (KBr) ν_{max} (cm^{-1}): 3117 (C–H_{Ar}), 3046 (=C–H_{vinyl}), 1227 (C–F), 580 (C–Br); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.06 (8H, m, $Ar_{a\ or\ b}$H2′, $Ar_{a\ or\ b}$H3′), 6.01 (1H, t, J = 7.4 Hz, =C–H$_{vinyl}$), 3.49 (2H, t, J = 6.6 Hz, H-6a, H-6b), 2.14 (2H, q, J = 7.4 Hz, H-3a, H-3b), 1.78 (2H, m, H-5a, H-5b), 1.60 (2H, m, H-4a, H-4b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 162.2 (d, J = 246.4 Hz, C–F), 162.1 (d, J = 246.4 Hz, C–F), 140.4 (C-1_{vinyl}), 138.7 (d, J = 3.1 Hz, C-1′$Ar_{a\ or\ b}$), 135.9 (d, J = 3.2 Hz, C-1′$Ar_{a\ or\ b}$), 131.5 (d, J = 7.9 Hz, C-2′$Ar_{a\ or\ b}$), 129.4 (C-2_{vinyl}), 128.8 (d, J = 7.9 Hz, C-2′$Ar_{a\ or\ b}$), 115.4 (d, J = 21.3 Hz, C-3′$Ar_{a\ or\ b}$), 115.1 (d, J = 21.4 Hz, C-3’$Ar_{a\ or\ b}$), 33.7 (C-6), 32.4 (C-5), 28.9 (C-4), 28.5 (C-3).

General procedure for the preparation of fluorinated or trifluoromethylated ω-(*N,N*-dimethylamino)-α,α-diaryl olefins 11 and 12

The methodology was carried out according to the literature (Ríos et al. 1996; Duque-Benítez et al. 2016) with modifications. The reaction of fluorinated or trifluoromethylated ω-bromo-α,α-diaryl olefins **9** and **10** with a 40% aqueous dimethylamine solution was carried out using the appropriate volume for a molar ratio amine/olefin 30:1. The aqueous dimethylamine solution was poured slowly into a round-bottomed flask immersed in an ice bath containing a THF solution of **9** (**a** or **b**) or **10** (**a** or **b**) (3.5 mL per mmol of olefin **9** or **10**) while stirring. The mixture was properly closed and stirred at 30 °C during 52 h. After this time, the excess of dimethylamine was removed under reduced pressure. Then it was transferred to a separatory funnel and extracted with ethyl ether. The organic layer was separated and extracted with aqueous 30% HCl. The aqueous extract was neutralized with aqueous 30% NaOH, and it was extracted again with ethyl ether. The ethereal amine extract was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed by rotary evaporation under reduced pressure. After that, it was triturated with hexane. The products were purified by column chromatography, yielding the expected amines as yellow oils.

***N,N*-dimethyl-5,5-*bis*-(3-trifluoromethylphenyl)pent-4-en-1-amine (11a)** Starting from **9a**, product **11a** was obtained as yellow oil (60% yield), *Rf* 0.50 (dichloromethane/methanol 91:9). IR (KBr) ν_{max} (cm^{-1}): 3073 (C–H_{Ar}), 3043 (=C–H_{vinyl}), 2818, 2770 (N–CH_3, N–CH_2), 1127 (C–F, CF_3), 1042 (N–$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.60 (1H, d, J = 7.8 Hz, $Ar_{a\ or\ b}$-H4’), 7.51 (2H, m, $Ar_{a\ or\ b}$-H5’), 7.48 (1H, s, $Ar_{a\ or\ b}$-H2’), 7.45 (1H, s, $Ar_{a\ or\ b}$–H2’), 7.37 (2H, m, $Ar_{a\ or\ b}$–H5′), 7.29 (1H, d, J = 7.9 Hz, $Ar_{a\ or\ b}$–H6’), 6.21 (1H, t, J = 7.6 Hz, =CH$_{vinyl}$), 2.26 (2H, m, H-5a, H-5b), 2.20 (6H, s, NCH$_3$), 2.13 (2H, q, J = 7.6 Hz, H-3a, H-3b), 1.63 (2H, m, H-4a, H-4b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 142.9 (C-1′$Ar_{a\ or\ b}$), 140.2 (C-1′$Ar_{a\ or\ b}$), 139.7 (C-1_{vinyl}), 133.4 (C-6′$Ar_{a\ or\ b}$), 132.6 (C-6′$Ar_{a\ or\ b}$), 131.0 (m, C-3′Ar_a, C-3′Ar_b), 130.7 (C-2_{vinyl}), 129.1 (C-5′$Ar_{a\ or\ b}$), 128.9 (C-5′$Ar_{a\ or\ b}$), 126.6 (q, J = 3.6 Hz, C-2′$Ar_{a\ or\ b}$), 124.4 (q, J = 3.5 Hz, C-4′$Ar_{a\ or\ b}$), 124.2 (q, J = 272.4 Hz, CF_3), 124.2 (q, J = 272.6 Hz, CF_3), 124.0 (q, J = 3.3 Hz, C-4′$Ar_{a\ or\ b}$), 123.7 (q, J = 3.8 Hz, C-2′$Ar_{a\ or\ b}$), 59.3 (C-5), 45.4 (NCH$_3$), 27.9 (C-3, C-4).

***N,N*-dimethyl-5,5-*bis*-(4-trifluoromethylphenyl)pent-4-en-1-amine (11b)** Starting from **9b**, product **11b** was obtained as yellow oil (89% yield) and purified by column chromatography eluting with dichloromethane/methanol 91:9 (*Rf* 0.53). IR (KBr) ν_{max} (cm^{-1}): 3073 (C–H_{Ar}), 3043 (=C–H_{vinyl}), 2818, 2770 (N–CH_3, N–CH_2), 1125 (C–F, CF_3), 1042 (N–$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (2H, d, J = 8.2 Hz, $Ar_{a\ or\ b}$–H3′), 7.51 (2H, d, J = 8.3 Hz, $Ar_{a\ or\ b}$–H3′), 7.28 (4H, m, Ar_a–H2′, Ar_b–H2′), 6.23 (1H, t, J = 7.5 Hz, = CH$_{vinyl}$), 2.34 (2H, m, H-5a, H-5b), 2.28 (6H, s, NCH$_3$), 2.14 (2H, q, J = 7.5 Hz, H-3a, H-3b), 1.68 (2H, m, H-4a, H-4b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 145.3 (C-1′$Ar_{a\ or\ b}$), 143.2 (C-1′$Ar_{a\ or\ b}$), 140.1 (C-1_{vinyl}), 132.5 (C-2_{vinyl}), 130.3 (C-2′$Ar_{a\ or\ b}$), 130.0 (m, C-4′$Ar_{a\ or\ b}$), 127.5 (C-2’$Ar_{a\ or\ b}$), 125.6 (q, J = 3.7 Hz, C-3’$Ar_{a\ or\ b}$), 125.4 (q, J = 3.7 Hz, C-3′$Ar_{a\ or\ b}$), 124.3 (q, J = 271.8 Hz, CF_3), 124.3 (q, J = 271.9 Hz, CF_3), 59.1 (C-5), 45.2 (NCH$_3$), 27.8 (C-3), 27.5 (C-4).

***N,N*-dimethyl-5,5-*bis*-(3-fluorophenyl)pent-4-en-1-amine (11c)** Starting from **9c**, product **11c** was obtained as yellow oil (68% yield), and purified by column chromatography eluting with dichloromethane/methanol 10:1 (*Rf 0.5*). IR (KBr) ν_{max} (cm^{-1}): 3073 (C–H_{Ar}), 3026 (=C–H_{vinyl}), 2820, 2767 (CH_3–N, CH_2–N), 1233 (C–F), 1042 (N–$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34 (1H, m, $Ar_{a\ or\ b}$H5′), 7.21 (1H, m, $Ar_{a\ or\ b}$H-5′), 6.95 (6H, m, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$–H4′, $Ar_{a\ or\ b}$–H6′), 6.17 (1H, t, J = 7.5 Hz, =C–H$_{vinyl}$), 2.25 (2H, m, H-1a, H-1b), 2.20 (6H, s, NCH$_3$), 2.12 (2H, q, J = 7.5 Hz, H-3a, H-3b), 1.62 (2H, m, H-2a, H-2b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 162.9 (d, J = 245.2 Hz, C–F), 162.9 (d, J = 246.4 Hz, C–F), 144.5 (d, J = 7.4 Hz,

C-1′$Ar_{a\ or\ b}$), 141.9 (d, $J = 7.5$ Hz, C-1′$Ar_{a\ or\ b}$), 140.0 (C-5_{vinyl}), 131.3 (C-4_{vinyl}), 130.0 (d, $J = 8.3$ Hz, C-5′$Ar_{a\ or\ b}$), 129.7 (d, $J = 8.4$ Hz, C-5′$Ar_{a\ or\ b}$), 125.7 (d, $J = 2.1$ Hz, C-6′$Ar_{a\ or\ b}$), 122.8 (d, $J = 2.0$ Hz, C-6′$Ar_{a\ or\ b}$), 116.9 (d, $J =$ 21.1 Hz, C-4′$Ar_{a\ or\ b}$), 114.3 (d, $J = 21.6$ Hz, C-4′$Ar_{a\ or\ b}$), 114.0 (d, $J = 23.2$ Hz, C-2′$Ar_{a\ or\ b}$), 114.0 (d, $J = 21.3$ Hz, C-2′$Ar_{a\ or\ b}$), 59.4 (C-1), 45.5 (N$\underline{C}H_3$), 28.0 (C-3), 27.8 (C-2).

***N,N*-dimethyl-5,5-*bis*-(4-fluorophenyl)pent-4-en-1-amine (11d)** Starting from **9d**, product **11d** was obtained as colorless oil (57% yield) and purified by column chromatography eluting with dichloromethane/methanol 10:1 (*Rf 0.47*). IR (KBr) ν_{max} (cm^{-1}): 3067 (C–H_{Ar}), 2817, 2767 (CH_3–N, CH_2-N), 1227 (C–F), 1045 (N–$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.05 (8H, m, $Ar_{a\ or\ b}$$\underline{H}$2′, $Ar_{a\ or\ b}$$\underline{H}$3′), 6.01 (1H, t, $J = 7.4$ Hz, =C–$\underline{H}_{vinyl}$), 2.26 (8H, m, H-1a, H-1b, N$\underline{C}H_3$), 2.11 (2H, m, H-3a, H-3b), 1.62 (2H, m, H-2a, H-2b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 162.2 (d, $J = 246.1$ Hz, C–F), 162.1 (d, $J = 246.1$ Hz, C–F), 140.1 (C–5_{vinyl}), 138.8 (d, $J = 3.2$ Hz, C-1′$Ar_{a\ or\ b}$), 135.9 (d, $J = 3.5$ Hz, C-1′$Ar_{a\ or\ b}$), 131.5 (d, $J = 7.9$ Hz, C-2′$Ar_{a\ or\ b}$), 129.7 (C-4_{vinyl}), 128.8 (d, $J = 7.8$ Hz, C–2′$Ar_{a\ or\ b}$), 115.4 (d, $J = 21.3$ Hz, C–3′$Ar_{a\ or\ b}$), 115.1 (d, $J = 21.3$ Hz, C-3′$Ar_{a\ or\ b}$), 59.4 (C-1), 45.4 (N$\underline{C}H_3$), 28.0 (C-3), 27.8 (C-2).

***N,N*-dimethyl-6,6-*bis*-(3-trifluoromethylphenyl)hex-5-en-1-amine (12a)** Starting from **10a**, product **12a** was obtained as yellow oil (75% yield), *Rf* 0.52 (dichloromethane/methanol 91:9). IR (KBr) ν_{max} (cm^{-1}): 3073 (C–H_{Ar}), 3043 (=C–H_{vinyl}), 2817, 2769 (N–CH_3, N–CH_2), 1127 (C–F, CF_3), 1041 (N–$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.60 (1H, d, $J =$ 7.8 Hz, $Ar_{a\ or\ b}$–$\underline{H}$4′), 7.50 (3H, m, $Ar_{a\ or\ b}$–$\underline{H}$5′, $Ar_{a\ or\ b}$–$\underline{H}$2′), 7.43 (1H, s, $Ar_{a\ or\ b}$–$\underline{H}$2′), 7.36 (2H, m, $Ar_{a\ or\ b}$–$\underline{H}$5′), 7.28 (1H, d, $J = 7.8$ Hz, $Ar_{a\ or\ b}$–$\underline{H}$6′), 6.19 (1H, t, $J = 7.5$ Hz,=C$\underline{H}_{vinyl}$), 2.24 (2H, m, H-6a, H-6b), 2.20 (6H, s, N$\underline{C}H_3$), 2.13 (2H, q, J = 7.1 Hz, H-3a, H-3b), 1.49 (4H, m, H-4a, H-4b, H-5a, H-5b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 142.9 (C-1′$Ar_{a\ or\ b}$), 140.3 (C-1′$Ar_{a\ or\ b}$), 139.6 (C-1_{vinyl}), 133.4 (C-6′$Ar_{a\ or\ b}$), 132.9 (C-6′$Ar_{a\ or\ b}$), 131.0 (m, C-3′Ar_a, C-3′Ar_b), 130.7 (C-2_{vinyl}), 129.1 (C-5′$Ar_{a\ or\ b}$), 128.9 (C-5′$Ar_{a\ or\ b}$), 126.7 (q, $J = 3.8$ Hz, C-2′$Ar_{a\ or\ b}$), 124.2 (q, $J = 275.9$ Hz, CF_3), 124.2 (q, $J =$ 272.3 Hz, CF_3), 124.4 (q, $J = 3.6$ Hz, C-4′$Ar_{a\ or\ b}$), 124.0(m, C-4′$Ar_{a\ or\ b}$), 123.8 (q, $J = 3.8$ Hz, C-2′$Ar_{a\ or\ b}$), 59.6 (C-6), 45.5 (N$\underline{C}H_3$), 29.8 (C-3), 27.6 (C-4), 27.4 (C-5).

***N,N*-dimethyl-6,6-*bis*-(4-trifluoromethylphenyl)hex-5-en-1-amine (12b)** Starting from **10b**, product **12b** was obtained as yellow oil (53% yield). Eluted with dichloromethane/methanol/acetonitrile (80:20:5) with *Rf* 0.66. IR (KBr) ν_{max} (cm^{-1}): 3073 (C–H_{Ar}), 3043 (=C–H_{vinyl}), 2818, 2768 (N–CH_3, N–CH_2), 1126 (C–F, CF_3), 1042 (N–$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (2H, d, $J = 8.1$ Hz, $Ar_{a\ or\ b}$–$\underline{H}$3′), 7.51 (2H, d, $J = 8.2$ Hz, $Ar_{a\ or\ b}$–$\underline{H}$3′), 7.28 (4H, m, Ar_a–$\underline{H}$2′, Ar_b–$\underline{H}$2′), 6.21 (1H, t, $J = 7.5$ Hz, =C$\underline{H}_{vinyl}$), 2.26 (2H, m, H-6a, H-6b), 2.23 (6H, s, N$\underline{C}H_3$), 2.13 (2H, m, H-3a, H-3b), 1.47 (4H, m, H-4a, H-4b, H-5a, H-5b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 145.5 (C-1′$Ar_{a\ or\ b}$), 143.3 (C-1′$Ar_{a\ or\ b}$), 139.8 (C-1_{vinyl}), 133.1 (C-2_{vinyl}), 130.4 (C-2′$Ar_{a\ or\ b}$), 129.5 (m, C-4′$Ar_{a\ or\ b}$), 127.5 (C-2′$Ar_{a\ or\ b}$), 125.5 (q, $J = 3.5$ Hz, C-3′$Ar_{a\ or\ b}$), 125.3 (m, C-3′$Ar_{a\ or\ b}$), 124.3 (q, J = 272.0 Hz, CF_3), 124.3 (q, $J = 272.1$ Hz, CF_3), 59.5 (C-6), 45.4 (N$\underline{C}H_3$), 29.8 (C-3), 27.6 (C-4), 27.2 (C-5).

***N,N*-dimethyl-6,6-*bis*-(3-fluorophenyl)hex-5-en-1-amine (12c)** Starting from **10c**, product **12c** was obtained as yellow oil (75% yield) and purified by column chromatography eluting with dichloromethane/methanol 10:1 (*Rf* 0.48). IR (KBr) ν_{max} (cm^{-1}): 3073 (C–H_{Ar}), 3029 (=C–H_{vinyl}), 2823, 2770 (CH_3–N, CH_2–N), 1230 (C–F), 1042 (N–$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (1H, td, $J = 7.9$, 6.0 Hz, $Ar_{a\ or\ b}$$\underline{H}$5′), 7.21 (1H, td, $J = 7.9$, 6.2 Hz, $Ar_{a\ or\ b}$$\underline{H}$-5′), 6.95 (6H, m, $Ar_{a\ or\ b}$$\underline{H}$-2′, $Ar_{a\ or\ b}$ $\underline{H}$-4′, $Ar_{a\ or\ b}$$\underline{H}$-6′), 6.11 (1H, t, $J = 7.5$ Hz, =C$\underline{H}_{vinyl}$), 2.20 (6H, 6, N$\underline{C}H_3$), 2.11 (2H, q, $J = 7.0$, H-4a, H-4b), 1.46 (4H, m, H-2a, H-2b, H-3a, H-3b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 162.9 (d, $J = 245.1$ Hz, C–F), 162.9 (d, $J = 246.3$ Hz, C–F), 144.6 (d, $J = 7.5$ Hz, C-1′$Ar_{a\ or\ b}$), 142.0 (d, $J = 7.4$ Hz, C-1′$Ar_{a\ or\ b}$), 139.8 (t, $J = 2.0$ Hz, C-6_{vinyl}), 131.7 (C-5_{vinyl}), 129.9 (d, $J = 8.3$ Hz, C-5′$Ar_{a\ or\ b}$), 129.6 (d, $J = 8.2$ Hz, C-5′$Ar_{a\ or\ b}$), 125.7 (d, $J = 2.9$ Hz, C-6′$Ar_{a\ or\ b}$), 122.8 (d, $J = 2.7$ Hz, C-6′$Ar_{a\ or\ b}$), 116.9 (d, $J = 21.1$ Hz, C-4′$Ar_{a\ or\ b}$), 114.2 (d, $J = 21.1$ Hz, C-4'$Ar_{a\ or\ b}$), 114.1 (d, $J = 22.0$ Hz, C-2′$Ar_{a\ or\ b}$), 113.9 (d, $J = 21.3$ Hz, C-2′$Ar_{a\ or\ b}$), 59.7 (C-1), 45.6 (N$\underline{C}H_3$), 29.7 (C-4), 27.7 (C-3), 27.5 (C-2).

***N,N*-dimethyl-6,6-*bis*-(4-fluorophenyl)hex-5-en-1-amine (12d)** Starting from **10d**, product **12d** was obtained as yellow oil (63% yield) and purified by column chromatography eluting with dichloromethane/methanol 10:1 (*Rf* 0.47). IR (KBr) ν_{max} (cm^{-1}): 3046 (=C–H_{vinyl}), 2817, 2767 (CH_3–N, CH_2–N), 1227 (C–F), 1042 (N–$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.03 (8H, m, $Ar_{a\ or\ b}$$\underline{H}$2′, $Ar_{a\ or\ b}$$\underline{H}$3′), 6.00 (1H, t, $J = 7.5$ Hz, =C$\underline{H}_{vinyl}$), 2.21 (2H, m, H-3a, H-3b), 2.18 (6H, s, N$\underline{C}H_3$), 2.11 (2H, q, $J = 7.0$ Hz, H-4a, H-4b), 1.49 (4H, m, H-2a, H-2b, H-3a, H-3b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 162.1 (d, $J = 246.1$ Hz, C–F), 162.0 (d, $J = 245.9$ Hz, C–F), 139.9 (C-6_{vinyl}), 138.9 (d, $J = 3.2$ Hz, C-1′$Ar_{a\ or\ b}$), 136.0 (d, $J = 3.3$ Hz, C-1′$Ar_{a\ or\ b}$), 131.6 (d, $J = 7.9$ Hz, C-2′$Ar_{a\ or\ b}$), 130.2 (C-5_{vinyl}), 128.8 (d, $J = 7.8$ Hz, C-2′$Ar_{a\ or\ b}$), 115.3 (d, $J = 21.3$ Hz, C-3′$Ar_{a\ or\ b}$), 115.0 (d, $J = 21.4$ Hz, C-3′$Ar_{a\ or\ b}$), 59.7 (C-1), 45.6 (N$\underline{C}H_3$), 29.7 (C-4), 27.8 (C-3), 27.4 (C-2).

General procedure for the preparation of fluorinated or trifluorimethylated QASs 1-4

Synthesis of QASs was according to the literature (Ríos et al. 1996; Duque-Benítez et al. 2016) with modifications. To a round-bottomed flask containing a 50% w/w acetonitrile solution of CH_2I_2 or $ClCH_2I$ (3 equivalents) or CH_3I (1 equivalent), 1.0 equivalent of the ω-(*N,N*-dimethylamino)-α,α-diphenyl olefins **11** (**a** or **b**) or **12** (**a** or **b**) was added dropwise, and the mixture was stirred at room temperature between 22 and 123 h. The precipitated salts were washed with ethyl ether or hexane, and then recrystallized from water/isopropyl alcohol (except for salt **3a**, which was recrystallized from ether/acetone). Pure trifluoromethylated QASs were obtained as white solids.

***N*-chloromethyl-*N*-[5,5-*bis*-(3-trifluoromethylphenyl)pent-4-en-1-yl]-N,N-dimethylammonium iodide (1a)** Starting from **11a** and $ClCH_2I$, product **1a** was obtained (56% yield) as a white solid: m.p. 119–121 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3070 (C–H_{Ar}), 3004 (=C–H_{vinyl}), 2884 ($^+$N–CH_2), 1115 (C–F, CF_3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.64 (1H, d, *J* = 7.8 Hz, $Ar_{a\ or\ b}$–H4′), 7.59 (1H, t, *J* = 7.6 Hz, $Ar_{a\ or\ b}$–H5′), 7.51 (1H, m, $Ar_{a\ or\ b}$–H4′), 7.44 (1 H, s, $Ar_{a\ or\ b}$–H2′), 7.40 (4H, m, $Ar_{a\ or\ b}$–H5′, $Ar_{a\ or\ b}$–H6′, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$–H6′), 6.21 (1H, t, *J* = 7.2 Hz, =CH_{vinyl}), 5.70 (2H, s, $^+$NCH_2Cl), 3.61 (2H, m, $^+$NCH_2), 3.54 (6H, s, H-1a, H-1b), 2.25 (2H, q, *J* = 7.3 Hz, H-3a, H-3b), 2.01 (2H, m, H-2a, H-2b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 141.9 (C-1′$Ar_{a\ or\ b}$), 141.9 (C-1′$Ar_{a\ or\ b}$), 139.5 (C-5_{vinyl}), 133.3 (C-6′$Ar_{a\ or\ b}$), 131.1 (m, C-3′Ar_a, C-3′Ar_b), 131.0 (C-6′$Ar_{a\ or}$), 129.7 (C-5′ $Ar_{a\ or\ b}$),129.1 (C-4_{vinyl}), 128.7 (C-5′$Ar_{a\ or\ b}$), 126.2 (q, *J* = 3.6 Hz, C-2′$Ar_{a\ or\ b}$), 124.9 (q, *J* = 3.5 Hz, C-4′$Ar_{a\ or\ b}$), 124.5 (q, *J* = 3.7 Hz, C-4′$Ar_{a\ or\ b}$), 124.1 (q, *J* = 272.8 Hz, CF_3), 124.1 (q, *J* = 272.2 Hz, CF_3), 123.9 (q, *J* = 3.6 Hz, C-2′ $Ar_{a\ or\ b}$), 69.0 ($^+$NCH_2Cl), 62.8 (C-1), 50.4 ($^+$NCH_3), 26.4 (C-3), 23.0 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −64.11 (s), −64.25 (s); HRESIMS *m/z* (pos) $[C_{22}H_{23}ClF_6N]^+$: 450.1400 (calcd. 450.1423); Anal. Calcd. for $C_{22}H_{23}ClF_6IN$: C, 45.73%; H, 4.01%; N, 2.42%; found: C, 45.38%; H, 3.83%; N, 2.25%.

***N*-[5,5-*bis*-(3-trifluoromethylphenyl)pent-4-en-1-yl]-*N*-iodomethyl-*N,N*-dimethylammonium iodide (1b)** Starting from **11a** and CH_2I_2, **1b** was obtained (82% yield) as a white solid: m.p. 130–132 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3058 (C–H_{Ar}), 3011 (=C–H_{vinyl}), 2843 ($^+$N–CH_2), 1116 (C–F, CF_3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (2H, m, $Ar_{a\ or\ b}$–H4′, $Ar_{a\ or\ b}$–H5′), 7.51 (1H, m, $Ar_{a\ or\ b}$–H4′), 7.41 (5H, m, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$–H5′, $Ar_{a\ or\ b}$–H6′, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$–H6′), 6.22 (1H, t, *J* = 7.2 Hz, =CH_{vinyl}), 5.63 (2H, s, $^+$NCH_2I), 3.61–3.55 (2H, m, H-1a, H-1b), 3.54 (6H, s, $^+$NCH_3), 2.25 (2H, q, *J* = 7.3 Hz, H-3a, H-3b), 1.99 (2H, m, H-2a, H-2b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 142.0 (C-1′$Ar_{a\ or\ b}$), 141.8 (C-1′$Ar_{a\ or\ b}$), 139.5 (C-5_{vinyl}), 133.4 (C-6′ $Ar_{a\ or\ b}$), 131.0 (m, C-3′Ar_a, C-3′Ar_b), 131.0 (C-6′ $Ar_{a\ or\ b}$), 129.7 (C-5′ $Ar_{a\ or\ b}$), 129.2 (C-4_{vinyl}), 128.9 (C-6′ $Ar_{a\ or\ b}$), 126.3 (q, *J* = 3.9 Hz, C-2′$Ar_{a\ or\ b}$), 124.9 (q, *J* = 3.6 Hz, C-4′$Ar_{a\ or\ b}$), 124.5 (m, C-4′$Ar_{a\ or\ b}$), 124.1 (q, *J* = 272.3 Hz, CF_3), 124.1 (q, *J* = 272.2 Hz, CF_3), 123.9 (q, *J* = 3.9 Hz, C-2′ $Ar_{a\ or\ b}$), 65.6 (C-1), 52.7 ($^+$NCH_3), 36.0 ($^+$NCH_2I), 26.3 (C-3), 23.6 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −64.09 (s), −64.26 (s); HRESIMS *m/z* (pos) $[C_{22}H_{23}F_6I_2N]^+$: 542.0762 (calcd. 542.0779); Anal. Calcd. for $C_{22}H_{23}F_6I_2N$: C, 39.48%; H, 3.46%; N, 2.09%; found: C, 39.30%; H, 3.38%; N, 1.92%.

***N*-[5,5-*bis*-(3-trifluoromethylphenyl)pent-4-en-1-yl]-*N,N,N*-trimethylammonium iodide (1c)** Starting from **11a** and CH_3I, **1c** was obtained (61% yield) as a white solid: m.p. 158.0–158.6 °C. IR (KBr) ν_{max} (cm^{-1}): 3076 (C–H_{Ar}), 3002 (=C–H_{vinyl}), 2843 ($^+$N–CH_2), 1117 (C–F, CF_3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.61 (2H, m, $Ar_{a\ or\ b}$–H4′, $Ar_{a\ or\ b}$–H5′), 7.51 (1H, m, $Ar_{a\ or\ b}$-H4′), 7.40 (5H, m, $Ar_{a\ or\ b}$-H2′, $Ar_{a\ or\ b}$–H5′, $Ar_{a\ or\ b}$–H6′, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$–H6′), 6.22 (1H, t, *J* = 7.3 Hz, = CH_{vinyl}), 3.59 (2H, m, H-1a, H-1b), 3.43 (9H, s, $^+$NCH_3), 2.25 (2H, q, *J* = 7.4 Hz, H-3a, H-3b), 1.97 (2H, m, H-2a, H-2b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 142.0 (C-1′$Ar_{a\ or\ b}$), 141.5 (C-1′$Ar_{a\ or\ b}$), 139.5 (C-5_{vinyl}), 133.3 (C-6′$Ar_{a\ or\ b}$), 131.0 (C-6′$Ar_{a\ or}$), 130.9 (m, C-3′Ar_a, C-3'Ar_b), 129.7 (C-5′ $Ar_{a\ or\ b}$), 129.1 (C-4_{vinyl}), 128.1 (C-5′$Ar_{a\ or\ b}$), 126.2 (q, *J* = 3.6 Hz, C-2′$Ar_{a\ or\ b}$), 124.8 (q, *J* = 3.6 Hz, C-4′$Ar_{a\ or\ b}$), 124.4 (q, *J* = 3.9 Hz, C-4′$Ar_{a\ or\ b}$), 124.1 (q, *J* = 272.9 Hz, CF_3), 124.1 (q, *J* = 272.6 Hz, CF_3), 123.8 (q, *J* = 3.5 Hz, C-2′ $Ar_{a\ or\ b}$), 66.6 (C-1), 54.0 ($^+$NCH_3), 26.4 (C-3), 23.4 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −64.14 (s), −64.26 (s); HRESIMS *m/z* (pos) $[C_{22}H_{24}F_6N]^+$: 416.1810 (calcd. 416.1813); Anal. Calcd. for $C_{22}H_{24}F_6IN{\cdot}^1/_2H_2O$: C, 47.84%; H, 4.56%; N, 2.54%; found: C, 47.73%; H, 4.20%; N, 2.33%.

***N*-chloromethyl-*N*-[5,5-*bis*-(3-fluorophenyl)pent-4-en-1-yl]-*N,N*-dimethylammonium iodide (1d)** Starting from **11c** and $ClCH_2I$, product **1d** was obtained (77% yield) as a white solid: m.p. 122.7–124.4 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3061 (C–H_{Ar}), 3020 (C–H_{vinyl}), 2873 ($^+$N–CH_2), 1233 (C–F); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.39 (1H, m, $Ar_{a\ or\ b}$–H5′), 7.23 (1H, m, $Ar_{a\ or\ b}$ H5′), 6.94 (6H, m, $Ar_{a\ or\ b}$H2′, $Ar_{a\ or\ b}$–H4′, $Ar_{a\ or\ b}$–H6′), 6.13 (1H, t, *J* = 7.2 Hz, = CH_{vinyl}), 5.69 (2H, s, $^+$NCH_2Cl), 3.61 (2H, m, H-1a, H-1b), 3.53 (6H, s, $^+$NCH_3), 2.24 (2H, q, *J* = 7.3 Hz, H-3a, H-3b), 1.98 (2H, m, H-2a, H-2b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 162.9 (d, *J* = 247.1 Hz, C–F′$_{Ar}$), 162.8 (d, *J* = 245.1 Hz, C–F′$_{Ar}$), 143.5 (d, *J* = 7.4 Hz, C–1′$Ar_{a\ or\ b}$), 141.9 (t, *J* = 1.7 Hz, C-5_{vinyl}), 141.0 (d, *J* = 7.4 Hz, C-1′$Ar_{a\ or\ b}$), 130.5 (d, *J* = 8.4 Hz, C-5′$Ar_{a\ or\ b}$), 129.8 (d, *J* = 8.5 Hz, C-5′$Ar_{a\ or\ b}$), 127.6 (C-4_{vinyl}), 125.5 (d, *J* = 2.8 Hz, C-6′$Ar_{a\ or\ b}$), 123.1 (d, *J* = 2.7 Hz, C-

5′$Ar_{a\ or\ b}$), 116.6 (d, $J = 21.2$ Hz, C-4′$Ar_{a\ or\ b}$), 114.7 (d, $J =$ 20.9 Hz, C-4′$Ar_{a\ or\ b}$), 114.4 (d, $J = 21.7$ Hz, C-2′$Ar_{a\ or\ b}$), 114.2 (d, $J = 22.5$ Hz, C–$Ar_{a\ or\ b}$), 69.0 ($^{+}$N<u>C</u>H_2Cl), 62.8 (C-1), 50.3 ($^{+}$N<u>C</u>H_3), 26.2 (C-3), 23.0 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): $\delta = -114.66$ (s), -115.53.(s); HRESIMS *m/z* (pos) $[C_{20}H_{23}F_2NCl]^+$: 350.1476 (calcd. 350.1487); Anal. Calcd. $C_{20}H_{23}ClF_2IN$: C, 50.28%; H, 4.85%; N, 2.93%; found C, 50.04%; H, 4.71%; N, 2.94%.

***N*-[5,5-*bis*-(3-fluorophenyl)pent-4-en-1-yl]-*N*-iodomethyl-*N*,*N*-dimethylammonium iodide (1e)** Starting from **11c** and CH_2I_2, product **1e** was obtained (83% yield) as a white solid: m.p. 155.6–155.9 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3070 (C–H_{Ar}), 3049 (C–H_{vinyl}), 2849 ($^{+}$N–CH_2), 1239 (C–F); ^{1}H NMR (DMSO, 400 MHz): $\delta = 7.51$ (1H, m, $Ar_{a\ or\ b}$-<u>H</u>5'), 7.36 (1H, m, $Ar_{a\ or\ b}$–<u>H</u>5′), 6.94 (6H, m, $Ar_{a\ or\ b}$<u>H</u>2′, $Ar_{a\ or\ b}$–<u>H</u>4′, $Ar_{a\ or\ b}$–<u>H</u>6′), 6.26 (1H, t, $J = 7.3$ Hz, = C<u>H</u>$_{vinyl}$), 5.17 (2H, s, $^{+}$NC<u>H</u>$_2$I), 3.35 (2H, m, H-1a, H-1b), 3.13 (6H, s, $^{+}$NC<u>H</u>$_3$), 2.11 (2H, q, $J = 7.0$ Hz, H-3a, H-3b), 1.86 (2H, m, H-2a, H-2b); ^{13}C NMR (DMSO, 101 MHz): $\delta = 162.2$ (d, $J = 245.4$ Hz, <u>C</u>–F′$_{Ar}$), 143.5 (d, $J = 7.4$ Hz, C-2′$_{Ar}$), 141.0 (d, $J = 7.6$ Hz, C-2′$_{Ar}$), 139.9 (C-5_{vinyl}), 130.7 (d, $J = 8.3$ Hz, C-5'$Ar_{a\ or\ b}$), 130.3 (d, $J = 8.3$ Hz, C-5′$Ar_{a\ or\ b}$), 129.5 (C-4_{vinyl}), 125.6 (d, $J = 2.4$ Hz, C-6′$Ar_{a\ or\ b}$), 123.0 (d, $J = 2.2$ Hz, C-6′$Ar_{a\ or\ b}$), 116.2 (d, $J = 21.0$ Hz, C-4′$Ar_{a\ or\ b}$), 114.5 (d, $J = 20.8$ Hz, C-4′$Ar_{a\ or\ b}$), 114.1 (d, $J = 21.4$ Hz, C-2′$Ar_{a\ or\ b}$), 113.2 (d, $J = 22.1$ Hz, C-2′$Ar_{a\ or\ b}$), 63.8 (C-1), 51.2 ($^{+}$N<u>C</u>H_3), 32.6 ($^{+}$N<u>C</u>H_2I), 25.9 (C-3), 22.0 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): $\delta = -114.59$ (s), -115.50 (s); HRESIMS *m/z* (pos) $[C_{20}H_{23}F_2NI]^+$: 442.0834 (calcd. 442.0843); Anal. Calcd. for $C_{20}H_{23}F_2I_2N$: C, 42.20%; H, 4.07%; N, 2.46%; found C, 41.95%; H, 3.75%; N, 2.49%.

***N*-[5,5-*bis*-(3-fluorophenyl)pent-4-en-1-yl]-*N*,*N*,*N*-trimethylammonium iodide (1f)** Starting from **11c** and CH_3I, product **1f** was obtained (85% yield) as a white solid: m.p. 177.7–178.8 °C. IR (KBr) ν_{max} (cm^{-1}): 3058 (C–H_{Ar}), 3038 (C–H_{vinyl}), 2835 ($^{+}$N–CH_2), 1233 (C–F); ^{1}H NMR (DMSO, 400 MHz): $\delta = 7.50$ (1H, m, $Ar_{a\ or\ b}$–<u>H</u>5′), 7.36 (1H, m, $Ar_{a\ or\ b}$–<u>H</u>5′), 7.23 (1H, m, $Ar_{a\ or\ b}$–<u>H</u>6′), 7.05 (5H, m, $Ar_{a\ or\ b}$–<u>H</u>2′, $Ar_{a\ or\ b}$–<u>H</u>4′, $Ar_{a\ or\ b}$–<u>H</u>6′), 6.27 (1H, t, $J = 7.2$ Hz, =C<u>H</u>$_{vinyl}$), 3.30–3.22 (2H, m, H-1a, H-1b), 3.04 (9H, s, $^{+}$NC<u>H</u>$_3$), 2.09 (2H, q, $J = 7.1$ Hz, H-3a, H-3b), 1.86 (2H, m, H-2a, H-2b); ^{13}C NMR (DMSO, 101 MHz): $\delta = 162.2$ (d, $J = 243.3$ Hz, C–F), 162.2 (d, $J = 244.5$ Hz, C–F), 143.5 (d, $J = 7.4$ Hz, C-1′$Ar_{a\ or\ b}$), 141.1 (d, $J = 7.7$ Hz, C-1′$Ar_{a\ or\ b}$), 139.7 (t, $J = 1.9$ Hz, C-5_{vinyl}), 130.7 (d, $J = 8.6$ Hz, C-5′$Ar_{a\ or\ b}$), 130.3 (d, $J = 8.6$ Hz, C-5′$Ar_{a\ or\ b}$), 129.7 (C-4_{vinyl}), 125.6 (d, $J = 2.7$ Hz, C-6′$Ar_{a\ or\ b}$), 123.0 (d, $J = 2.6$ Hz, C-6′$Ar_{a\ or\ b}$), 116.2 (d, $J = 21.2$ Hz, C-4′$Ar_{a\ or\ b}$), 114.4 (d, $J = 20.7$ Hz, C-4′$Ar_{a\ or\ b}$), 114.0 (d, $J = 21.1$ Hz, C-2′$Ar_{a\ or\ b}$), 113.2 (d, $J = 22.0$ Hz, C-2′$Ar_{a\ or\ b}$), 64.8 (C-1), 52.2 ($^{+}$N<u>C</u>H_3), 26.2 (C-3), 22.0 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): $\delta = -114.70$ (s), -115.54 (s); HRESIMS *m/z* (pos) $[C_{20}H_{24}F_2NI]^+$: 316.1865 (Calcd. 316.1877); Anal. Calcd. for $C_{20}H_{24}F_2IN$: C, 54.19%; H, 5.45%; N, 3.16%; found C, 53.97%; H, 5.31%; N, 2.99%.

***N*-chloromethyl-*N*-[5,5-*bis*-(4-trifluoromethylphenyl)pent-4-en-1-yl]-*N*,*N*-dimethylammonium iodide (2a)** Starting from **11b** and $ClCH_2I$, **2a** was obtained (78% yield) as a white solid: m.p. 143–145 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3073 (C–H_{Ar}), 3042 (=C–H_{vinyl}), 2878 ($^{+}$N–CH_2), 1125 (C–F, CF_3); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.69$ (2H, d, $J =$ 8.0 Hz, $Ar_{a\ or\ b}$–<u>H</u>3′), 7.53 (2H, d, $J = 8.3$ Hz, $Ar_{a\ or\ b}$–<u>H</u>3′), 7.35 (2H, d, $J = 8.2$ Hz, $Ar_{a\ or\ b}$–<u>H</u>2′), 7.30 (2H, d, $J = 8.0$ Hz, $Ar_{a\ or\ b}$–<u>H</u>2′), 6.26 (1H, t, $J = 7.2$ Hz, =C<u>H</u>$_{vinyl}$), 5.70 (2H, s, $^{+}$NC<u>H</u>$_2$Cl), 3.65 (2H, m, H-1a, H-1b), 3.52 (6H, s, $^{+}$NC<u>H</u>$_3$), 2.28 (2H, q, $J = 7.2$ Hz, H-3a, H-3b), 2.01 (2H, m, H-2a, H-2b); ^{13}C NMR ($CDCl_3$, 101 MHz): $\delta = 144.5$ (C-1′$Ar_{a\ or\ b}$), 142.5 (C-1′$Ar_{a\ or\ b}$), 142.0 (C-5_{vinyl}), 130.2 (C-2′ $Ar_{a\ or\ b}$), 130.0 (m, C-4′Ar_a, C-4′Ar_b), 129.0 (C-4_{vinyl}), 127.8 (C-2′ $Ar_{a\ or\ b}$), 125.9 (q, $J = 3.7$ Hz, C-3′ $Ar_{a\ or\ b}$), 125.4 (q, $J = 3.6$ Hz, C-3′ $Ar_{a\ or\ b}$), 124.2 (q, $J = 274.4$ Hz, CF_3), 124.2 (q, $J = 272.2$ Hz, CF_3), 69.1 ($^{+}$N<u>C</u>H_2I), 62.9 (C-1), 50.3($^{+}$N<u>C</u>H_3), 26.3 (C-3), 23.0 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): $\delta = -64.07$ (s), -64.11 (s). HRESIMS *m/z* (pos) $[C_{22}H_{23}ClF_6N]^+$: 450.1421 (calcd. 450.1423); Anal. Calcd. for $C_{22}H_{23}ClF_6IN$: C, 45.73%; H, 4.01%; N, 2.42%; found C, 45.50%; H, 3.92%; N, 2.27%.

***N*-[5,5-*bis*-(4-trifluoromethylphenyl)pent-4-en-1-yl]-*N*-iodomethyl-*N*,*N*-dimethylammonium iodide (2b)** Starting from **11b** and CH_2I_2, **2b** was obtained (79% yield) as a white solid: m.p. 138–140 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3064 (C–H_{Ar}), 3043 (=C–H_{vinyl}), 1113 (C–F, CF_3); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.69$ (2H, d, $J = 8.0$ Hz, $Ar_{a\ or\ b}$–<u>H</u>3′), 7.53 (2H, d, $J = 8.3$ Hz, $Ar_{a\ or\ b}$–<u>H</u>3′), 7.36 (2H, d, $J = 8.2$ Hz, $Ar_{a\ or\ b}$–<u>H</u>2′), 7.31 (2H, d, $J = 8.0$ Hz, $Ar_{a\ or\ b}$–<u>H</u>2′), 6.27 (1H, t, $J = 7.2$ Hz, = C<u>H</u>$_{vinyl}$), 5.63 (2H, s, $^{+}$NC<u>H</u>$_2$I), 3.61 (2H, m, H-1a, H-1b), 3.51 (6H, s, $^{+}$NC<u>H</u>$_3$), 2.27 (2H, q, $J = 7.2$ Hz, H-3a, H-3b), 1.99 (2H, m, H-2a, H-2b); ^{13}C NMR ($CDCl_3$, 101 MHz): $\delta = 144.6$ (C-1′$Ar_{a\ or\ b}$), 142.5 (C-1′$Ar_{a\ or\ b}$), 142.0 (C-6_{vinyl}), 130.2 (m, C-4′Ar_a, C-4′Ar_b) 130.3 (C-2′ $Ar_{a\ or\ b}$), 129.1 (C-5_{vinyl}), 127.9 (C-2′ $Ar_{a\ or\ b}$), 125.8 (q, $J = 3.5$ Hz, C-3′ $Ar_{a\ or\ b}$), 125.4 (q, $J = 3.3$ Hz, C-5′ $Ar_{a\ or\ b}$), 65.6 (C-1), 52.7 ($^{+}$N<u>C</u>H_3), 36.2 ($^{+}$N<u>C</u>H_2I), 26.3 (C-3), 23.5 (C-2), Ar**C**F_3 not seen; ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): $\delta = -64.07$ (s), -64.09 (s). HRESIMS *m/z* (pos) $[C_{22}H_{23}F_6IN]^+$: 542.0775 (calcd. 542.0779); Anal. Calcd. for $C_{22}H_{23}F_6I_2N$: C, 39.48%; H, 3.46%; N, 2.09%; found: C, 39.36%; H, 3.26%; N, 2.12%.

***N*-[5,5-*bis*-(4-trifluoromethylphenyl)pent-4-en-1-yl]-*N,N,N*-trimethylammonium iodide (2c)** Starting from **11b** and CH_3I, **2c** was obtained (73% yield) as a white solid: m.p. 210.5–212.1 °C. IR (KBr) ν_{max} (cm^{-1}): 3495 (OH, H_2O), 3046 (C–H_{Ar}), 3004 (=C–H_{vinyl}), 2878 ($^+$N–CH_2), 1116 (C–F, CF_3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.69 (2H, d, J = 8.0 Hz, $Ar_{a\ or\ b}$–H3′), 7.53 (2H, d, J = 8.2 Hz, $Ar_{a\ or\ b}$–H3′), 7.36 (2H, d, J = 8.2 Hz, $Ar_{a\ or\ b}$–H2′), 7.30 (2H, d, J = 8.0 Hz, $Ar_{a\ or\ b}$–H2′), 6.27 (1H, t, J = 7.2 Hz, = CH_{vinyl}), 3.64 (2H, m, H-1a, H-1b), 3.42 (9H, s, $^+$NCH_3), 2.27 (2H, q, J = 7.3 Hz, H-3a, H-3b), 1.98 (2H, m, H-2a, H-2b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 144.6 (C-1′$Ar_{a\ or\ b}$), 142.5 (C-1′$Ar_{a\ or\ b}$), 141.6 (C-5_{vinyl}), 130.3 (C-2′ $Ar_{a\ or\ b}$), 130.5–129.0 (m, C-4′Ar_a, C-4'Ar_b), 129.4 (C-4_{vinyl}), 127.9 (C-2′ $Ar_{a\ or\ b}$), 125.9 (q, J = 3.6 Hz, C-3′ $Ar_{a\ or\ b}$), 125.4 (q, J = 3.6 Hz, C-3′ $Ar_{a\ or\ b}$), 124.1 (q, J = 272.0 Hz, CF_3), 124.1 (q, J = 272.20 Hz, CF_3), 66.5 (C-1), 54.0 ($^+$NCH_3), 26.4 (C-3), 23.3 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −64.07 (s), −64.11 (s); HRESIMS *m/z* (pos) $[C_{22}H_{24}F_6N]^+$: 416.1817 (calcd. 416.1813); Anal. Calcd. for $C_{22}H_{24}F_6IN \cdot {}^1/_2H_2O$: C, 47.84%; H, 4.56%; N, 2.54%; found: C, 47.82%; H, 4.41%; N, 2.35%.

***N*-chloromethyl-*N*-[5,5-*bis*-(4-fluorophenyl)pent-4-en-1-yl]-*N,N*-dimethylammonium iodide (2d)** Starting from **11d** and $ClCH_2I$, product **2d** was obtained (77% yield) as a white solid: m.p. 110.7–112.7 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3061 (C–H_{Ar}), 3023 (C–H_{vinyl}), 2881 ($^+$N–CH_2), 1215 (C–F); ^{1}H NMR (DMSO, 400 MHz): δ = 7.21 (8H, m, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$–H3′), 6.11 (1H, t, J = 7.3 Hz, =CH_{vinyl}), 5.33 (2H, s, $^+$NCH_2Cl), 3.35 (2H, m, H-1a, H-1b), 3.12 (6H, s, $^+$NCH_3), 2.09 (2H, q, J = 7.1 Hz, H-3a, H-3b), 1.86 (2H, m, H-2a, H-2b); ^{13}C NMR (DMSO, 101 MHz): δ 161.5 (d, J = 244.6 Hz, C–F), 161.3 (d, J = 244.2 Hz, C–F), 140.2 (C-5_{vinyl}), 138.0 (d, J = 3.0 Hz, C-1′$Ar_{a\ or\ b}$), 135.2 (d, J = 3.1 Hz,C-1′$Ar_{a\ or\ b}$), 131.4 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 128.7 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 127.7 (C-4_{vinyl}), 115.4 (d, J = 21.3 Hz, C-3′$Ar_{a\ or\ b}$), 115.1 (d, J = 21.4 Hz, C-3$Ar_{a\ or\ b}$), 68.3 ($^+$NCH_2Cl), 61.7 (C-1), 49.0 ($^+$NCH_3), 26.0 (C-3), 21.8(C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ −116.70 (s), −117.32 (s); HRESIMS *m/z* (pos) $[C_{20}H_{23}F_2ClN]^+$: 350.1474 (calcd. 350.1487); Anal. Calcd. for $C_{20}H_{23}F_2ClNI$: C, 50.28%; H, 4.85%; N, 2.93%; found C, 49.99%; H, 4.75%; N, 2.79%.

***N*-[5,5-*bis*-(4-fluorophenyl)pent-4-en-1-yl]-*N*-iodomethyl-*N,N*-dimethylammonium iodide (2e)** Starting from **11d** and CH_2I_2, product **2e** was obtained (75% yield) as a white solid: m.p. 149.5–149.9 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3067 (C–H_{Ar}), 3046 (C–H_{vinyl}), 2852 ($^+$N–CH_2), 1236 (C–F); ^{1}H NMR (DMSO, 400 MHz): δ = 7.22 (8H, m, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$–H3′), 6.11 (1H, t, J = 7.3 Hz, =CH_{vinyl}), 5.16 (2H, s, $^+$NCH_2I), 3.35 (2H, m, H-1a, H-1b), 3.13 (6H, s, $^+$NCH_3), 2.09 (2H, q, J = 7.1 Hz, H-3a, H-3b), 1.83 (2H, m, H-2a, H-2b); ^{13}C NMR (DMSO, 101 MHz): δ 161.5 (d, J = 244.3 Hz, C–F), 161.3 (d, J = 244.1 Hz, C–F), 140.2 (C-5_{vinyl}), 138.0 (d, J = 3.0 Hz, C-1′$Ar_{a\ or\ b}$), 135.2 (d, J = 3.1 Hz, C-1′$Ar_{a\ or\ b}$), 131.4 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 128.7 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 127.8 (C-4_{vinyl}), 115.5 (d, J = 21.3 Hz, C-3′$Ar_{a\ or\ b}$), 115.1 (d, J = 21.3 Hz, C-3′$Ar_{a\ or\ b}$), 63.8 (C-1), 51.2 ($^+$NCH_3), 32.8 ($^+$NCH_2I); 25.9 (C-3), 22.2 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ −116.98 (s), −117.69 (s); HRESIMS *m/z* (pos) $[C_{20}H_{23}F_2IN]^+$: 442.0840 (calcd. 442.0843); Anal. Calcd. for $C_{20}H_{23}F_2I_2N$: C, 42.20%; H, 4.07%; N, 2.46%; found C, 42.06%; H, 3.71%; N, 2.49%.

***N*-[5,5-*bis*-(4-fluorophenyl)pent-4-en-1-yl]-*N,N,N*-trimethylammonium iodide (2f)** Starting from **11d** and CH_3I, product **2f** was obtained (76% yield) as a white solid: m.p. 170.4–171.1 °C. IR (KBr) ν_{max} (cm^{-1}): 3046 (C–H_{vinyl}), 2845 ($^+$N–CH_2), 1223 (C–F); ^{1}H NMR (DMSO, 400 MHz): δ = 7.19 (8H, m, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$-H3'), 6.11 (1H, t, J = 7.3 Hz, = CH_{vinyl}), 3.25 (2H, m, H-1a, H-1b), 3.03 (9H, s, $^+$NCH_3), 2.07 (2H, q, J = 7.2 Hz, H-3a, H-3b), 1.85 (2H, m, H-2a, H-2b); ^{13}C NMR (DMSO, 101 MHz): δ = 161.45 (d, J = 244.3 Hz, C–F), 161.33 (d, J = 244.1 Hz, C–F), 140.0 (C-5_{vinyl}), 138.1 (d, J = 3.0 Hz, C-1′$Ar_{a\ or\ b}$), 135.3 (d, J = 3.1 Hz, C-1′$Ar_{a\ or\ b}$), 131.4 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 128.73 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 128.0 (C-4_{vinyl}), 115.43 (d, J = 21.3 Hz, C-3′$Ar_{a\ or\ b}$), 115.07 (d, J = 21.3 Hz, C-3′$Ar_{a\ or\ b}$), 64.7 (C-1), 52.2 ($^+$NCH_3), 26.1 (C-3), 22.2 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ −116.80 (s), −117.43 (s); HRESIMS *m/z* (pos) $[C_{20}H_{24}F_2N]^+$: 316.1863 (calcd. 316.1877); Anal. Calcd. for $C_{20}H_{24}F_2IN$: C, 54.19%; H, 5.45%; N, 3.16%; found C, 54.08%; H, 5.41%; N, 3.27%.

***N*-chloromethyl-*N*-[6,6-*bis*-(3-trifluoromethylphenyl)hex-5-en-1-yl]-*N,N*-dimethylammonium iodide (3a)** Starting from **12a** and $ClCH_2I$, **3a** was obtained (59% yield) as a white solid: m.p. 108–110 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3055 (C–H_{Ar}), 3007 (=C–H_{vinyl}), 2864 ($^+$N–CH_2), 1108 (C–F, CF_3); ^{1}H NMR (DMSO, 400 MHz): δ = 7.79 (1H, d, J = 7.9 Hz, $Ar_{a\ or\ b}$–H4′), 7.72 (1H, t, J = 7.8 Hz, $Ar_{a\ or\ b}$–H5′), 7.65 (1H, d, J = 7.8 Hz, $Ar_{a\ or\ b}$–H4′), 7.58 (1H, t, J = 7.8 Hz, $Ar_{a\ or\ b}$–H2′), 7.53 (2H, m, $Ar_{a\ or\ b}$–H2′), 7.50 (1H, s, $Ar_{a\ or\ b}$–H2′), 7.45 (1H, d, J = 7.9 Hz, $Ar_{a\ or\ b}$–H6′), 6.40 (1H, t, J = 7.4 Hz, =CH_{vinyl}), 5.32 (2H, s, $^+$NCH_2Cl), 3.37 (2H, m,, H-1a, H-1b), 3.11 (6H, s, $^+$NCH_3), 2.11 (2H, q, J = 7.3 Hz, H-4a, H-4b), 1.69 (2H, m, H-2a, H-2b), 1.47 (2H, m, H-3a, H-3b); ^{13}C NMR ($CDCl_3$,101 MHz): δ = 142.4 (C-1′$Ar_{a\ or\ b}$), 140.8 (C-1′$Ar_{a\ or\ b}$), 139.85 (C-6_{vinyl}), 133.4 (C-6′$Ar_{a\ or\ b}$), 131.1 (m, C-3′Ar_a, C-3′Ar_b), 130.8 (C-6′$Ar_{a\ or}$), 130.7 (C-6_{vinyl}), 129.5 (C-5′ $Ar_{a\ or\ b}$), 129.1 (C-5′$Ar_{a\ or\ b}$), 126.4 (q, J = 3.9 Hz, C-2′$Ar_{a\ or\ b}$), 124.7 (q, J = 3.6 Hz, C-

4′$Ar_{a\ or\ b}$), 124.3 (m, C-4′$Ar_{a\ or\ b}$), 124.2 (q, $J = 274.3$ Hz, CF_3), 124.2 (q, $J = 276.1$ Hz, CF_3), 123.8 (q, $J = 3.8$ Hz, C-2′ $Ar_{a\ or\ b}$) 69.0 ($^+$N<u>C</u>H_2Cl), 63.3 (C-1), 50.1 ($^+$N<u>C</u>H_3), 29.4 (C-4), 26.3 (C-3), 22.6 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −64.10 (s), −64.26 (s); HRESIMS *m/z* (pos) $[C_{23}H_{25}ClF_6N]^+$: 464.1581 (calcd. 464.1580); Anal. Calcd. for $C_{23}H_{25}ClF_6IN$: C, 46.68%; H, 4.26%; N, 2.37%; found: C, 46.32%; H, 4.08%; N, 2.23%.

***N*-[6,6-*bis*-(3-trifluoromethylphenyl)hex-5-en-1-yl]-*N*-iodomethyl-*N,N*-dimethylammonium iodide (3b)** Starting from **12a** and CH_2I_2, **3b** was obtained (71% yield) as a white solid: m.p. 100–102 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3049 (C–H_{Ar}), 3001 (=C–H_{vinyl}), 2858 ($^+$N–CH_2), 1125 (C–F, CF_3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (1H, d, $J = 7.6$ Hz, $Ar_{a\ or\ b}$–<u>H</u>4′), 7.57 (1H, t, $J = 7.6$ Hz, $Ar_{a\ or\ b}$–<u>H</u>5′), 7.50 (1H, d, $J = 7.5$ Hz, $Ar_{a\ or\ b}$–<u>H</u>4′), 7.45 (1H, s, $Ar_{a\ or\ b}$–<u>H</u>2′), 7.39 (3H, m, $Ar_{a\ or\ b}$–<u>H</u>5′, $Ar_{a\ or\ b}$–<u>H</u>6′, $Ar_{a\ or\ b}$–<u>H</u>2′), 7.33 (1H, d, $J = 7.8$ Hz, $Ar_{a\ or\ b}$–<u>H</u>6′), 6.18 (1H, t, $J = 7.4$ Hz, =C<u>H</u>$_{vinyl}$), 5.58 (2H, s, $^+$NC<u>H</u>$_2$I), 3.76 (2H, m, H-1a, H-1b), 3.50 (6H, s, $^+$NC<u>H</u>$_3$), 2.21 (2H, q, $J = 7.3$ Hz, H-4a, H-4b), 1.77 (2H, m, H-2a, H-2b), 1.58 (2H, m, H-3a, H-3b); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 142.4 (C-6_{vinyl}), 140.7 (C-1′$Ar_{a\ or\ b}$), 139.8 (C-1′$Ar_{a\ or\ b}$), 133.4 (C-6′ $Ar_{a\ or\ b}$), 131.0 (m, C-3′Ar_a, C-3′Ar_b), 130.9 (C-6′ $Ar_{a\ or\ b}$, C-5_{vinyl}), 129.5 (C-5′ $Ar_{a\ or\ b}$), 129.0 (C-5′ $Ar_{a\ or\ b}$), 126.4 (m, C-2′$Ar_{a\ or\ b}$), 124.6 (q, $J = 3.4$ Hz, C-4′$Ar_{a\ or\ b}$), 124.3 (m, C-4′$Ar_{a\ or\ b}$), 124.1 (q, $J = 272.6$ Hz, CF_3), 124.1 (q, $J = 272.1$ Hz, CF_3), 123.3 (m, C-2′ $Ar_{a\ or\ b}$). 65.8 (C-1), 52.5 ($^+$N<u>C</u>H_3), 35.7 ($^+$N<u>C</u>H_2I), 29.4 (C-4), 26.3 (C-3), 23.2 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −64.07 (s), −64.24 (s); HRESIMS *m/z* (pos) $[C_{23}H_{25}F_6IN]^+$: 556.0938 (calcd. 556.0979); Anal. Calcd. for $C_{23}H_{25}F_6I_2N$: C, 40.43%; H, 3.69%; N, 2.05%; found: C, 40.10%; H, 3.38%; N, 2.06%.

***N*-[6,6-*bis*-(3-trifluoromethylphenyl)hex-5-en-1-yl]-*N,N,N*-trimethylammonium iodide (3c)** Starting from **12a** and CH_3I, **3c** was obtained (41% yield) as a white solid: m.p. 127.5–128.3 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3073 (C–H_{Ar}), 3021 (=C–H_{vinyl}), 2851 ($^+$N–CH_2), 1128 (C–F, CF_3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.77 (1H, d, $J = 7.8$ Hz, $Ar_{a\ or\ b}$–<u>H</u>4′), 7.71 (1H, t, $J = 7.6$ Hz, $Ar_{a\ or\ b}$–<u>H</u>5′), 7.63 (1H, d, $J = 7.7$ Hz, $Ar_{a\ or\ b}$–<u>H</u>4′), 7.54 (3H, m, $Ar_{a\ or\ b}$–<u>H</u>2′, $Ar_{a\ or\ b}$–<u>H</u>5′, $Ar_{a\ or\ b}$–<u>H</u>6′), 7.47 (2H, m,), 6.40 (1H, t, $J = 7.3$ Hz, = C<u>H</u>$_{vinyl}$), 3.26 (2H, m, H-1a, H-1b), 3.04 (9H, s, $^+$NC<u>H</u>$_3$), 2.10 (2H, q, $J = 7.3$ Hz, H-4a, H-4b), 1.69 (2H, m, H-2a, H-2b), 1.45 (2H, m, H-3a, H-3b); ^{13}C NMR (DMSO, 101 MHz): δ = 142.2 (C-6_{vinyl}), 139.8 (C-1′$Ar_{a\ or\ b}$), 138.6 (C-1′$Ar_{a\ or\ b}$), 133.8 (C-6'$Ar_{a\ or\ b}$), 132.2 (C-5_{vinyl}), 130.8 (C-6′$Ar_{a\ or\ b}$), 129.9 (C-5′ $Ar_{a\ or\ b}$), 129.6 (C-5′ $Ar_{a\ or\ b}$), 129.3 (m, C-3′Ar_a, C-3'Ar_b), 125.8 (q, $J = 3.5$ Hz, C-2′$Ar_{a\ or\ b}$), 124.4 (q, $J = 3.6$ Hz, C-4′$Ar_{a\ or\ b}$), 124.1 (q, $J = 272.4$ Hz, CF_3), 123.8 (m, C-4′$Ar_{a\ or\ b}$), 122.8 (q, $J = 3.7$ Hz, C-2′ $Ar_{a\ or\ b}$), 65.1 (C-1), 52.2 ($^+$N<u>C</u>H_3), 29.0 (C-4), 25.7 (C-3), 21.9(C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −64.10 (s), −64.25 (s); HRESIMS *m/z* (pos) $[C_{23}H_{26}F_6N]^+$: 430.1968 (calcd. 430.1969); Anal. Calcd. for $C_{23}H_{26}F_6IN$: C, 49.56%; H, 4.70%; N, 2.51%; found: C, 49.35%; H, 4.68%; N, 2.41%.

***N*-chloromethyl-*N*-[6,6-*bis*-(3-fluorophenyl)hex-5-en-1-yl]-*N,N*-dimethylammonium iodide (3d)** Starting from **12c** and $ClCH_2I$, product **3d** was obtained (85% yield) as a white solid: m.p. 130.2–131.0 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3061 (C–HAr), 2855 ($^+$N–CH_2), 1233 (C–F); ^{1}H NMR (DMSO, 400 MHz): δ = 7.49 (1H, m, $Ar_{a\ or\ b}$<u>H</u>5′), 7.35 (1H, m, $Ar_{a\ or\ b}$<u>H</u>5′), 7.22 (1H, m, $Ar_{a\ or\ b}$<u>H</u>6′), 7.10 (1H, m, $Ar_{a\ or\ b}$<u>H</u>6'), 6.96 (4H, m, $Ar_{a\ or\ b}$<u>H</u>2′, $Ar_{a\ or\ b}$<u>H</u>4′), 6.28 (1H, t, $J = 7.3$ Hz, =C<u>H</u>$_{vinyl}$), 5.32 (2H, s, $^+$NC<u>H</u>$_2$Cl), 3.39 (2H, m, H-1a, H-1b), 3.11 (6H, s, $^+$NC<u>H</u>$_3$), 2.10 (2H, q, $J = 7.4$ Hz, H-4a, H-4b), 1.69 (2H, m, H-2a, H-2b), 1.43 (2H, m, H-3a, H-3b); ^{13}C NMR (DMSO, 101 MHz): δ 162.2 (d, $J = 243.1$ Hz, C–F), 162.2 (d, $J = 244.4$ Hz, C–F), 143.7 (d, $J = 7.4$ Hz, C-1′$Ar_{a\ or\ b}$), 141.31 (d, $J = 7.9$ Hz, C-1′$Ar_{a\ or\ b}$), 139.4 (s, C-6_{vinyl}), 130.8 (s, C-5_{vinyl}), 130.6 (d, $J = 8.6$ Hz, C-5′$Ar_{a\ or\ b}$), 130.2 (d, $J = 8.7$ Hz, C-5′$Ar_{a\ or\ b}$), 125.7 (d, $J = 2.7$ Hz, C-6′$Ar_{a\ or\ b}$), 122.9 (d, $J = 2.4$ Hz, C-6′$Ar_{a\ or\ b}$), 116.16 (d, $J = 20.9$ Hz, C-4′$Ar_{a\ or\ b}$), 114.29 (d, $J = 20.9$ Hz, C-4′$Ar_{a\ or\ b}$), 113.89 (d, $J = 21.2$ Hz, C-2′$Ar_{a\ or\ b}$), 113.10 (d, $J = 22.1$ Hz, C-2′$Ar_{a\ or\ b}$), 68.3 ($^+$N<u>C</u>H_2Cl), 62.1 (C-1), 48.9 ($^+$N<u>C</u>H_3), 28.8 (C-4), 25.6 (C-3), 21.3 (C-2); ^{19}F NMR (CD_3OD, 500 MHz): δ −114.90 (s), −115.64 (s); HRESIMS *m/z* (pos) $[C_{21}H_{25}F_2NCl]^+$: 364.1643 (calcd. 364.1644); Anal. Calcd. for $C_{21}H_{25}ClF_2IN$: C, 51.29%; H, 5.12%; N, 2.85%; found C, 51.15%; H, 5.00%; N, 2.88%.

***N*-[6,6-*bis*-(3-fluorophenyl)hex-5-en-1-yl]-*N*-iodomethyl-*N,N*-dimethylammonium iodide (3e)** Starting from **12c** and CH_2I_2, product **3e** was obtained (76% yield) as a white solid: m.p. 149.3–149.6 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3061 (C–H_{Ar}), 2858 ($^+$N–CH_2), 1234 (C–F); ^{1}H NMR (DMSO, 400 MHz): δ = 7.50 (1H, m, $Ar_{a\ or\ b}$<u>H</u>5′), 7.35 (1H, td, $J = 8.0$, 6.5 Hz, $Ar_{a\ or\ b}$<u>H</u>5′), 7.22 (1H, m, $Ar_{a\ or\ b}$<u>H</u>6′), 7.09 (1H, m, $Ar_{a\ or\ b}$<u>H</u>6′), 7.01 (4H, m, $Ar_{a\ or\ b}$<u>H</u>2′, $Ar_{a\ or\ b}$<u>H</u>4′), 6.29 (1H, t, $J = 7.3$ Hz, = C<u>H</u>$_{vinyl}$), 5.15 (2H, s, $^+$NC<u>H</u>$_2$I), 3.35 (2H, m, H-1a, H-1b), 3.12 (6H, s, $^+$NC<u>H</u>$_3$), 2.10 (2H, q, $J = 7.4$ Hz, H-4a, H-4b), 1.67 (2H, m, H-2a, H-2b), 1.44 (2H, m, H-3a, H-3b); ^{13}C NMR (DMSO, 101 MHz): δ = 162.2 (d, $J = 243.3$ Hz, C–F), 162.2 (d, $J = 244.8$ Hz, C–F), 143.7 (d, $J = 7.3$ Hz, C-1′$Ar_{a\ or\ b}$), 141.32 (d, $J = 7.5$ Hz, C-1′$Ar_{a\ or\ b}$), 139.1 (C-6_{vinyl}), 130.8 (C-5_{vinyl}), 130.6 (d, $J = 8.6$ Hz, C-5′$Ar_{a\ or\ b}$), 130.2 (d, $J = 8.7$ Hz, C-5'$Ar_{a\ or\ b}$), 125.7 (d, $J = 2.8$ Hz, C-6′$Ar_{a\ or\ b}$), 122.9 (d, $J = 1.9$ Hz, C-6′$Ar_{a\ or\ b}$), 116.2 (d, $J = 21.1$ Hz, C-4′$Ar_{a\ or\ b}$), 114.3 (d, $J = 20.5$ Hz, C-4'$Ar_{a\ or\ b}$), 113.9 (d, $J =$

21.5 Hz, C-2′$Ar_{a\ or\ b}$), 113.1 (d, $J = 22.6$ Hz, C-2′$Ar_{a\ or\ b}$), 64.2 (C-1), 51.2 ($^{+}$N$\underline{C}H_3$), 32.7 ($^{+}$N$\underline{C}H_2$I), 28.8 (C-4), 25.6 (C-3), 21.8 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −114.87 (s), −115.62 (s); HRESIMS *m/z* (pos) $[C_{21}H_{25}F_2NI]^+$: 456.0986 (calcd. 456.1000); Anal. Calcd. for $C_{21}H_{25}F_2I_2N$: C, 43.25%; H, 4.32%; N, 2.40%; found C, 43.18%; H, 4.03%; N, 2.46%.

***N*-[6,6-*bis*-(3-fluorophenyl)hex-5-en-1-yl]-*N,N,N*-trimethylammonium iodide (3f)** Starting from **12c** and CH_3I, product **3f** was obtained (89% yield) as a white solid: m.p. 196.5–197.2 °C. IR (KBr) ν_{max} (cm^{-1}): 3061 (C–H_{Ar}), 3022.9 (C–H_{vinyl}), 2855 ($^{+}$N–CH_2), 1230 (C–F); ^{1}H NMR (DMSO, 400 MHz): δ = 7.49 (1H, m, $Ar_{a\ or\ b}$H5′), 7.34 (1H, m, $Ar_{a\ or\ b}$H5′), 7.21 (1H, m, $Ar_{a\ or\ b}$H6′), 7.04 (5H, m, $Ar_{a\ or\ b}$H2′, $Ar_{a\ or\ b}$–H4′, $Ar_{a\ or\ b}$–H6′), 6.29 (1H, t, $J = 7.3$ Hz, = C$\underline{H}_{vinyl}$), 3.25 (2H, m, H-1a, H-1b), 3.03 (9H, s, $^{+}$N$\underline{C}H_3$), 2.09 (2H, q, $J = 7.3$ Hz, H-4a, H-4b), 1.67 (2H, m,, H-2a, H-2b), 1.42 (2H, m,, H-3a, H-3b); ^{13}C NMR (DMSO, 101 MHz): δ 162.2 (d, $J = 243.3$ Hz, C–F), 162.2 (d, $J = 244.5$ Hz, C–F), 143.7 (d, $J = 7.4$ Hz, C-1′$Ar_{a\ or\ b}$), 141.3 (d, $J = 7.6$ Hz, C-1′$Ar_{a\ or\ b}$), 139.0 (C-6_{vinyl}), 130.8 (C-5_{vinyl}), 130.6 (d, $J = 8.5$ Hz, C-5′$Ar_{a\ or\ b}$), 130.2 (d, $J = 8.7$ Hz, C-5′$Ar_{a\ or\ b}$), 125.6 (d, $J = 2.6$ Hz, C-6′$Ar_{a\ or\ b}$), 122.9 (d, $J = 2.4$ Hz, C-6′$Ar_{a\ or\ b}$), 116.1 (d, $J = 20.9$ Hz, C-4′$Ar_{a\ or\ b}$), 114.3 (d, $J = 20.7$ Hz, C-4′$Ar_{a\ or\ b}$), 113.9 (d, $J = 21.2$ Hz, C-2′$Ar_{a\ or\ b}$), 113.1 (d, $J = 22.1$ Hz, C-2′$Ar_{a\ or\ b}$), 65.1 (C-1), 52.19 ($^{+}$N$\underline{C}H_3$), 28.9 (C-4), 25.7 (C-3), 21.9 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −114.93 (s), −115.64 (s); HRESIMS *m/z* (pos) $[C_{21}H_{26}F_2N]^+$: 330.2022 (calcd. 330.2033); Anal. Calcd. for $C_{21}H_{26}F_2IN$: C, 55.15%; H, 5.72%; N, 3.06%; found C, 54.92%; H, 5.63%; N, 3.17%.

***N*-chloromethyl-*N*-[6,6-*bis*-(4-trifluoromethylphenyl)hex-5-en-1-yl]-*N,N*-dimethylammonium iodide (4a)** Starting from **12b** and $ClCH_2I$, **4a** was obtained (85% yield) as a white solid: m.p. 137–139 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3052 (C–H_{Ar}), 3003 (=C–H_{vinyl}), 2863 ($^{+}$N–CH_2), 1113 (C–F, CF_3); ^{1}H NMR (DMSO, 400 MHz): δ = 7.82 (2H, d, $J = 8.0$ Hz, $Ar_{a\ or\ b}$–H3′), 7.68 (2H, d, $J = 8.2$ Hz, $Ar_{a\ or\ b}$–H3′), 7.41 (4H, m, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$–H2′), 6.40 (1H, t, $J = 7.3$ Hz, = C$\underline{H}_{vinyl}$), 5.31 (2H, s, $^{+}$N$\underline{C}H_2$Cl), 3.38 (2H, m, H-1a, H-1b), 3.11 (6H, s, $^{+}$N$\underline{C}H_3$), 2.13 (2H, q, $J = 7.3$ Hz, H-4a, H-4b), 1.70 (2H, m, H-2a, H-2b), 1.49 (2H, m, H-3a, H-3b); ^{13}C NMR (101 MHz, DMSO) δ = 145.6 (C-1′$Ar_{a\ or\ b}$), 143.6 (C-1′$Ar_{a\ or\ b}$), 139.6 (C-6_{vinyl}), 133.0 (C-5_{vinyl}), 131.0 (C-2′ $Ar_{a\ or\ b}$), 128.3 (m, C-4′Ar_a, C-4'Ar_b), 128.0 (C-2′ $Ar_{a\ or\ b}$), 126.1 (q, $J = 3.5$ Hz, C-3′ $Ar_{a\ or\ b}$), 125.8 (q, $J = 3.5$ Hz, C-3′ $Ar_{a\ or\ b}$), 68.8 ($^{+}$N$\underline{C}H_2$I), 62.6 (C-1), 49.4 ($^{+}$N$\underline{C}H_3$), 29.4 (C-4), 26.1 (C-3), 21.8 (C-2), Ar**C**F_3 are non-visible overlapped signals; ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −64.03 (s), −64.04 (s); HRESIMS *m/z* (pos) $[C_{23}H_{25}ClF_6N]^+$: 464.1570 (calcd. 464.1580); Anal. Calcd. for $C_{23}H_{25}ClF_6IN$: C, 46.68%; H, 4.26%; N, 2.37%; found: C, 46.25%; H, 4.11%; N, 2.21%.

***N*-[6,6-*bis*-(3-trifluoromethylphenyl)hex-5-en-1-yl]-*N*-iodomethyl-*N,N*-dimethylammonium iodide (4b)** Starting from **12b** and CH_2I_2, **4b** was obtained (80% yield) as a white solid: m.p. 143–146 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3055 (C–H_{Ar}), 3002 (=C–H_{vinyl}), 2862 ($^{+}$N–CH_2), 1113 (C–F, CF_3); ^{1}H NMR (DMSO, 400 MHz): δ = 7.82 (2H, d, $J = 8.0$ Hz, $Ar_{a\ or\ b}$–H3′), 7.68 (2H, d, $J = 8.2$ Hz, $Ar_{a\ or\ b}$–H3′), 7.42 (4H, m, Ar_a –H2′, Ar_b–H2′), 6.40 (1H, t, $J = 7.3$ Hz, =C$\underline{H}_{vinyl}$), 5.15 (2H, s, $^{+}$N$\underline{C}H_2$I), 3.36 (2H, m, H-1a, H-1b), 3.12 (6H, s, $^{+}$N$\underline{C}H_3$), 2.13 (2H, q, $J = 7.3$ Hz, H-4a, H-4b), 1.68 (2H, m, H-2a, H-2b), 1.46 (2H, m, H-3a, H-3b); ^{13}C NMR (DMSO, 101 MHz) δ = 145.1 (C-1′$Ar_{a\ or\ b}$), 143.1 (C-1′$Ar_{a\ or\ b}$), 139.1 (C-5_{vinyl}), 132.5 (C-5_{vinyl}), 130.5 (C-2′ $Ar_{a\ or\ b}$), 128.0 (m, C-4′Ar_a, C-4′Ar_b), 127.5 (C-2′ $Ar_{a\ or\ b}$), 125.6 (q, $J = 3.4$ Hz, C-3′ $Ar_{a\ or\ b}$), 125.3 (q, $J = 3.7$ Hz, C-3′ $Ar_{a\ or\ b}$), 64.2 (C-1), 51.2 ($^{+}$N$\underline{C}H_3$), 32.6 ($^{+}$N$\underline{C}H_2$I), 28.9 (C-4), 25.5 (C-3), 21.8 (C-2), Ar**C**F_3 are non-visible overlapped signals; ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −64.04 (s) ($2CF_3$); HRESIMS *m/z* (pos) $[C_{23}H_{25}F_6IN]^+$: 556.0928 (calcd. 556.0979); Anal. Calcd. for $C_{23}H_{25}F_6I_2N$: C, 40.43%; H, 3.69%; N, 2.05%; found: C, 40.17%; H, 3.46%; N, 1.88%.

***N*-[6,6-*bis*-(4-trifluoromethylphenyl)hex-5-en-1-yl]-*N,N,N*-trimethylammonium iodide (4c)** Starting from **12b** and CH_3I, **4c** was obtained (86% yield) as a white solid: m.p. 189.7–190.7 °C. IR (KBr) ν_{max} (cm^{-1}): 3473 (OH, H_2O), 3051 (C–H_{Ar}), 3012 (=C–H_{vinyl}), 2863 ($^{+}$N–CH_2), 1113 (C–F, CF_3); ^{1}H NMR (DMSO, 400 MHz): δ = 7.82 (2H, d, $J = 8.0$ Hz, $Ar_{a\ or\ b}$–H3′), 7.68 (2H, d, $J = 8.3$ Hz, $Ar_{a\ or\ b}$–H3′), 7.41 (4H, t, $J = 8.8$ Hz, Ar_a –H2′, Ar_b–H2′), 6.41 (1H, t, $J = 7.4$ Hz, =C$\underline{H}_{vinyl}$), 3.24 (2H, m, H-1a, H-1b), 3.02 (9H, s, $^{+}$N$\underline{C}H_3$), 2.13 (2H, q, $J = 7.4$ Hz, H-4a, H-4b), 1.78 (2H, m, H-2a, H-2b), 1.45 (2H, m, H-3a, H-3b); ^{13}C NMR (DMSO, 101 MHz): δ = 145.1 (C-1′$Ar_{a\ or\ b}$), 143.1 (C-1′$Ar_{a\ or\ b}$), 139.0 (C-6_{vinyl}), 132.6 (C-5_{vinyl}), 130.5 (C-2′ $Ar_{a\ or\ b}$), 127.5 (C-2′ $Ar_{a\ or\ b}$), 126.7 (m, C-4′Ar_a, C-4′Ar_b), 125.6 (q, $J = 3.6$ Hz, C-3′ $Ar_{a\ or\ b}$), 125.3 (q, $J = 3.2$ Hz, C-3′ $Ar_{a\ or\ b}$), 65.1 (C-1), 52.2 ($^{+}$N$\underline{C}H_3$), 29.0 (C-4), 25.7 (C-3), 21.9 (C-2), Ar**C**F_3 are non-visible overlapped signals; ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −64.04 (s), −64.06 (s); HRESIMS *m/z* (pos) $[C_{23}H_{26}F_6N]^+$: 430.1970 (calcd 430.1969); Anal. Calcd. for $C_{23}H_{26}F_6IN$. H_2O: C, 48.01%; H, 4.91%; N, 2.43%; found: C, 47.90%; H, 4.73%; N, 2.26%.

***N*-chloromethyl-*N*-[6,6-*bis*-(4-fluorophenyl)hex-5-en-1-yl]-*N,N*-dimethylammonium iodide (4d)** Starting from **12d** and $ClCH_2I$, product **4d** was obtained (89% yield) as a white solid: m.p. 132.7–133.7 °C. IR (KBr) ν_{max} (cm^{-1}): 3020 (C–

H_{vinyl}), 2870 ($^{+}N–CH_2$), 1233 (C–F; ^1H NMR (DMSO, 400 MHz): δ = 7.20 (8H, m, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$–H3′), 6.12 (1H, t, J = 7.3 Hz, $=CH_{vinyl}$), 5.31 (2H, s, $^{+}NCH_2Cl$), 3.36 (2H, m, H-1a, H-1b), 3.10 (6H, s, $^{+}NCH_3$), 2.09 (2H, q, J = 7.4 Hz, H-4a, H-4b), 1.69 (2H, m, H-2a, H-2b), 1.43 (2H, m, H-3a, H-3b); ^{13}C NMR (DMSO, 101 MHz): δ 161.37 (d, J = 244.2 Hz, C–F), 161.26 (d, J = 243.8 Hz, C–F), 139.4 (C-6_{vinyl}), 138.2 (d, J = 3.0 Hz, C-1′$Ar_{a\ or\ b}$), 135.5 (d, J = 3.1 Hz, C-1′$Ar_{a\ or\ b}$), 131.4 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 129.1 (C-5_{vinyl}), 128.7 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 115.4 (d, J = 21.2 Hz, C-3′$Ar_{a\ or\ b}$), 115.0 (d, J = 21.3 Hz, C-′$Ar_{a\ or\ b}$), 68.2 ($^{+}NCH_2Cl$), 62.1 (C-1), 48.9 ($^{+}NCH_3$), 28.8 (C-4), 25.8 (C-3), 21.3 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ −116.99 (s), −117.69 (s); HRESIMS *m/z* (pos) $[C_{21}H_{25}F_2NCl]^+$: 364.1634 (calcd. 364.1644); Anal. Calcd. for $C_{21}H_{25}F_2ClNI$: C, 51.29%; H, 5.12%; N, 2.85%; found C, 51.07%; H, 5.16%; N, 2.93%.

N-[6,6-bis-(4-fluorophenyl)hex-5-en-1-yl]-N-iodomethyl-N, N-dimethylammonium iodide (4e) Starting from **12d** and CH_2I_2, product **4e** was obtained (76% yield) as a white solid: m.p. 149.3–149.6 °C (dec). IR (KBr) ν_{max} (cm^{-1}): 3061 (C–H_{Ar}), 2858.0 ($^{+}N–CH_2$), 1234 (C–F); ^1H NMR (DMSO, 400 MHz): δ = 7.19 (8H, m, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$–H3′), 6.12 (1H, t, J = 7.3 Hz, $=CH_{vinyl}$), 5.15 (2H, s, $^{+}NCH_2I$), 3.35 (2H, m, H-1a, H-1b), 3.11 (6H, s, $^{+}NCH_3$), 2.09 (2H, q, J = 7.3 Hz, H-4a, H-4b), 1.68 (2H, m, H-2a, H-2b), 1.41 (2H, m, H-3a, H-3b); ^{13}C NMR (DMSO, 101 MHz): δ 161.4 (d, J = 244.2 Hz, C–F), 161.3 (d, J = 243.8 Hz, C–F), 139.4 (C-6_{vinyl}), 138.3 (d, J = 3.0 Hz, C-1′$Ar_{a\ or\ b}$), 135.5 (d, J = 3.1 Hz, C-1′$Ar_{a\ or\ b}$), 131.4 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 129.1 (C-5_{vinyl}), 128.7 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 115.4 (d, J = 21.2 Hz, C-3′$Ar_{a\ or\ b}$), 115.1 (d, J = 21.3 Hz, C-3′$Ar_{a\ or\ b}$), 64.2 (C-1), 51.2 ($^{+}NCH_3$), 32.7 ($^{+}NCH_2I$), 28.8 (C-4), 25.8 (C-3), 21.8 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ −114.87 (s), −115.62 (s); HRESIMS *m/z* (pos) $[C_{21}H_{25}F_2NI]^+$: 456.0987 (calcd. 456.1000); Anal. Calcd. $C_{21}H_{25}F_2I_2N$: C, 43.25%; H, 4.32%; N, 2.40%; found C, 43.18%; H, 4.03%; N, 2.46%.

***N*-[6,6-*bis*-(4-fluorophenyl)hex-5-en-1-yl]-*N,N,N*-trimethylammonium iodide (4f)** Starting from **12d** and CH_3I, product **4f** was obtained (80% yield) as a white solid: m.p. 172.0–173.4 °C. IR (KBr) ν_{max} (cm^{-1}): 3076 (C–H_{Ar}), 3046.3 (C–H_{vinyl}), 2855 ($^{+}N–CH_2$), 1224 (C–F); ^1H NMR (DMSO, 400 MHz): δ = 7.20 (8H, m, $Ar_{a\ or\ b}$–H2′, $Ar_{a\ or\ b}$–H3′), 6.13 (1H, t, J = 7.3 Hz, = CH_{vinyl}), 3.24 (2H, m, H-1a, H-1b), 3.02 (9H, s, $^{+}NCH_3$), 2.08 (2H, q, J = 7.4 Hz, H-4a, H-4b), 1.67 (2H, m, H-2a, H-2b), 1.41 (2H, m, H-3a, H-3b); ^{13}C NMR (101 MHz, DMSO): δ = 161.4 (d, J = 244.2 Hz, C–F), 161.3 (d, J = 244.1 Hz, C–F), 139.3 (C-6_{vinyl}), 138.2 (d, J = 3.0 Hz, C-1′$Ar_{a\ or\ b}$), 135.6 (d, J = 3.4 Hz, C-1′$Ar_{a\ or\ b}$), 131.4 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 129.2 (C-5_{vinyl}), 128.6 (d, J = 8.1 Hz, C-2′$Ar_{a\ or\ b}$), 115.0 (d, J = 21.3 Hz, C-3′$Ar_{a\ or\ b}$), 115.0 (d, J = 21.4 Hz, C-3′$Ar_{a\ or\ b}$), 65.1 (C-1), 52.2 ($^{+}NCH_3$), 29.4 (C-4), 26.5 (C-3), 22.4 (C-2); ^{19}F NMR (CD_3OD, 500 MHz, ref. $CFCl_3$): δ = −117.03 (s), −117.74 (s); HRESIMS *m/z* (pos) $[C_{21}H_{26}F_2N]^+$: 330.2019 (calcd. 330.2033); Anal. Calcd. for $C_{21}H_{26}F_2IN$: C, 55.15%; H, 5.72%; N, 3.06%; found C, 54.90%; H, 5.55%; N, 3.13%.

Biological study

Cells and culture conditions

U-937 promonocytes (CRL1593.2™) were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA), cultured in suspension in complete RPMI-1640 medium (Sigma) supplemented with 10% fetal bovine serum (FBS) (Gibco, Life Technologies, Grand Island, NY, USA) and 1% antibiotics (100 U/mL penicillin and 0.1 mg/mL streptomycin) (Sigma). Cells were maintained in standard conditions at 37 °C, 5% CO_2 with change of medium every three days until use.

Trypanosoma strain and cultivation of parasites

Compounds were tested on intracellular amastigotes of *T. cruzi*, Tulahuen strain transfected with β-galactosidase gene (Buckner et al. 1996) donated by Dr. F. S. Buckner, University of Washington. Intracellular amastigotes were obtained after infection of U-937 cells with trypomastigotes as described elsewhere (Valencia et al. 2011). Briefly, 100,000 U-937 cells/mL were seeded in RPMI-1640 medium and 100 ng/mL of phorbol 12-myristate 13-acetate (PMA). For adhesion, 1 mL of cells in suspension were incubated for 48 h at 37 °C and 5% CO_2, in 24 plates, with fresh medium change without PMA at 24 h. The adhered cells were infected with trypomastigotes of *T. cruzi* at a ratio of 1:10 cell/parasite and incubated for 24 h, at 37 °C, with 5% CO_2 in RPMI medium enriched with 5% fetal bovine serum. After 24 h of infection, cells were ready to be used in anti-trypanosomal testing assay as described below.

In vitro cytotoxicity using U-937 cells

The cytotoxic activity of the compounds was assessed based on the viability of the human promonocytic cell line U-937 evaluated by the MTT [3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide] enzymatic micromethod, following a previously described methodology (Duque-Benítez et al. 2016). Briefly, into each well of the 96-well cell-culture plates, a concentration of 100,000 cells/mL were dispensed in RPMI-1640 supplemented with 10% FBS

and 100 µL of the corresponding concentration of the compound using a serial dilution. Six double-serial concentrations for each compound (from 200 to 6.25 µg/mL) were evaluated. Cells were incubated at 37 °C with 5% CO_2 for 72 h in the presence of compounds, and then the toxic effect was determined by measuring the activity of the mitochondrial dehydrogenase by adding 20 µL of MTT reagent (0.5 mg/mL) and subsequently incubated at 37 °C for 3 h. The reaction was stopped and the cell viability was determined based on the quantity of formazan produced according to the intensity of color (absorbance) registered as optical densities (OD) obtained at 570 nm in a spectrophotometer (Varioskan™ Flash Multimode Reader-Thermo Scientific, USA). Cells cultured in the absence of the compounds but maintained under the same conditions were used as a negative control; doxorubicin or benznidazole addition were used as the positive controls. All determinations were performed in triplicate in two isolated experiments.

In vitro anti-trypanosomal activity

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 (Coa et al. 2017). The anti-trypanosomal activity was initially screened at a single concentration of 20 µg/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 a 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, and 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. This was done by adding, to each well, 100 µM chlorophenolred-β-D-galactopyranoside (CPRG) and 0.1% nonidet P-40. 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 OD. 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 benznidazole 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 OD of the blank. Determinations were done by triplicate in at least two independent experiments.

Data analysis

Cytotoxicity was determined according to the percentages of viability registered to each tested compound and culture medium alone. Percentage of mortality was calculated by Eq. 1, where the OD of control cells, corresponds to 100% of viability.

$$\%\,\text{mortality} = 100 - \left[\left(\text{OD}_{\text{exposed}}/\text{OD}_{\text{control cells}}\right) \times 100\right] \quad (1)$$

Results were expressed as LC_{50} values that correspond to the concentration of drug that gives the half-maximal inhibitory concentration that reduce the cell growth using the Probit analysis (Finney 1978). On the other hand, anti-trypanosomal activity was determined according to the percentage of infected cells and parasite load, obtained for each experimental condition by colorimetry. The parasite inhibition was calculated by Eq. 2, where the OD of control cells corresponds to 100% of parasites.

$$\%\,\text{parasite inhibition} = 100 - \left[\left(\text{OD}_{\text{exposed parasites}}/\text{OD}_{\text{control parasites}}\right) \times 100\right] \quad (2)$$

Results of anti-trypanosomal activity were also expressed as EC_{50} values that correspond to the concentration of drug that gives the half-maximal reduction of the parasites in infected cells determined by the Probit method (Finney 1978). The selectivity index (SI), was calculated by dividing the cytotoxic activity by the anti-trypanosomal activity using Eq. 3.

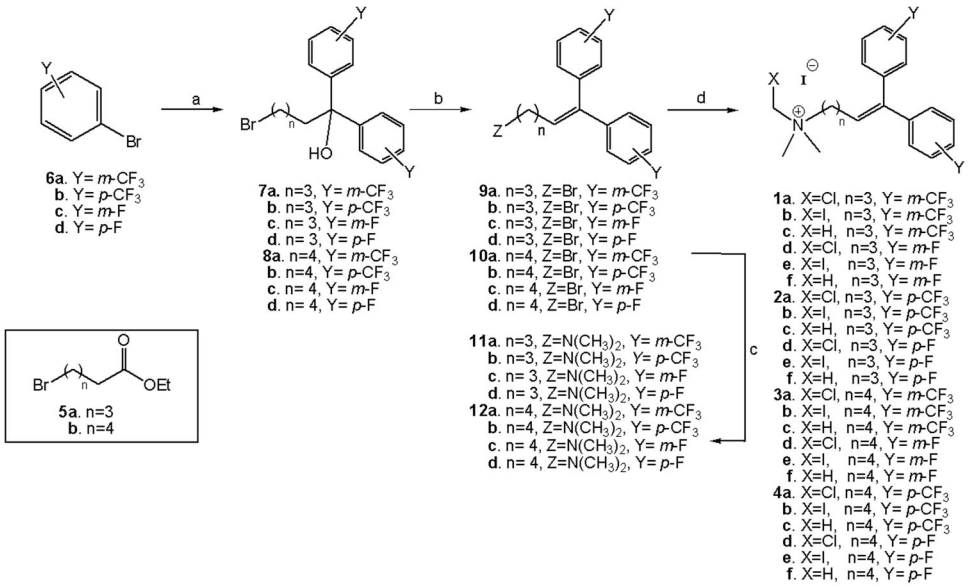
$$\text{SI} = \text{LC}_{50}/\text{EC}_{50} \quad (3)$$

Results and discussion

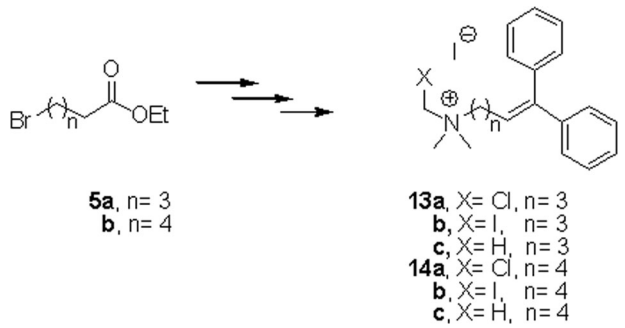
Chemistry

As mentioned before, aromatic rings are important components of pharmacologically active molecules (Gibson et al. 1996; Meyer et al. 2003; Dalvie et al. 2010) and may influence the development of successful oral drugs (Ritchie and Macdonald 2009). Indeed, the presence of two aromatic rings in the structure increases the likelihood of success (Hann et al. 2001). From a synthetic point of view, an advantage is that assemblage of aromatic rings in the scaffold is available through a variety of well-established methodologies (Zhao 2017). With this in mind, as well as the ability of fluorinated substituents to enhance pharmacological effects (Isanbor and O'Hagan 2006; Kirk 2006; Gillis et al. 2015; Reddy 2015; Shi et al. 2017), we decided

Scheme 1 Synthesis of target QASs **1–4**



Reagents and conditions: a. [i] Mg / dry ether; [2] **5** ; b.TsOH.H_2O 1.5% molar, benzene; c. 40% aq. $(CH_3)_2NH$ (30 eq); d. XCH_2I where X= Cl, I or H (3.0 eq), CH_3CN.



Scheme 2 Synthesis of non-fluorinated QAS **13–14** (Duque-Benítez et al. 2016)

to look for new anti-trypanosomal agents with a terminal system of two fluorinated aromatic rings. Thus we selected a group of QASs **1–4** of the form $\{X\text{-}CH_2N(Me)_2[(CH_2)_nCH{=}CAr_2]\}^+ I^-$, characterized by either a *m*-F, *p*-F, *m*-CF_3 or *p*-CF_3 substitution pattern and a short tether of $n = 3$ or 4 methylene groups. These structural features resemble non-fluorinated molecules which have already been studied as anti-leishmanial agents (Ríos et al. 2015; Duque-Benítez et al. 2016; Pulido et al. 2017; Fernández et al. 2018). Starting from ω-bromoacyl esters **5**, twenty four novel fluorinated QASs (**1a–f**, **2a–f**, **3a–f**, and **4a–f**) were prepared through a known four-step sequence (Duque-Benítez et al. 2016) depicted in Scheme 1, with appropriate modifications when required.

For comparison of their biological activity, non-fluorinated analog QASs **13–14** were also prepared according to literature (Scheme 2), and their spectroscopic properties matched the reported signals (Duque-Benítez et al. 2016).

For the synthesis of fluorinated target QASs **1–4** (Scheme 1), Grignard reagents from **6a** and **6c** were prepared with a stoichiometric 1:1 molar ratio of magnesium under dilute conditions (0.5–0.6 M) to prevent eventual explosions (Zhao 2017; Waymouth and Moore 1997; Tang et al. 2009) and cannulated to another reaction flask, while the one from **6d** is a commercially available Grignard precursor and used as such. When starting from **6b** and a strict stoichiometric ratio 1:1 of magnesium, a very sticky dark reagent was formed, and it was used in situ for the Grignard reaction. The resulting ω-bromo-α,α-diphenyl alcohols **7–8** were obtained with isolated yields ranging from 38 to 65%, suggesting that the handling method of the Grignard reagent did not change the outcome of the reaction. In the second step (Scheme 1), acid-catalyzed dehydration of alcohols **7–8** under benzene gave rise to the corresponding ω-bromo-α,α-diphenyl olefins **9–10** with isolated yields between 47 and 92%. Next, displacement of bromide by dimethylamine generated ω-(*N,N*-dimethylamino)-α,α-diphenyl olefins **11–12** with isolated yields ranging from 53 to 89%. Finally amines **11–12** were converted into the target QASs **1–4** by displacement of an iodide anion from either iodomethane, chloroiodomethane or diiodomethane, with isolated yields between 41 and 89%. Overall isolated yields from starting materials ranged between 9 and 25%.

While synthetic intermediate alcohols **7–8**, bromoolefins **9–10**, and aminoolefins **11–12** were characterized by ^1H and ^{13}C NMR and FTIR, target QASs **1–4** were fully characterized by ^1H, ^{19}F and ^{13}C NMR, FTIR, HR-MS and elemental C, H, N analysis, confirming their identity and purity. Fluorinated and trifluoromethylated QASs are white

Table 1 In vitro anti-trypanosomal activity and U-937 macrophages cytotoxicity of trifluoromethylated and fluorinated QASs (**1a–f**, **2a–f**, **3a–f**, and **4a–f**) and their non-fluorinated QASs analogs (**13a–c**, **14a–c**)

Compound	LC_{50}		EC_{50}		SI
	μg/mL	μM	μg/mL	μM	LC_{50}/EC_{50}
1a	0.7 ± 0.1	1.2 ± 0.2	1.4 ± 0.2	2.4 ± 0.3	0.5
1b	0.9 ± 0.1	1.3 ± 0.2	1.1 ± 0.1	1.6 ± 0.2	0.8
1c	2.9 ± 0.1	5.3 ± 0.2	2.8 ± 0.4	5.2 ± 0.7	1.0
1d	16.8 ± 2.2	35.2 ± 4.6	18.5 ± 3.6	38.7 ± 7.5	0.9
1e	21.2 ± 4.5	37.2 ± 7.9	30.2 ± 2.6	53.1 ± 4.6	0.7
1f	9.1 ± 0.2	20.5 ± 0.5	8.8 ± 1.30	19.9 ± 2.9	1.0
2a	2.7 ± 0.1	4.7 ± 0.2	3.7 ± 0.1	6.4 ± 0.2	0.7
2b	2.3 ± 0.3	3.4 ± 0.5	2.0 ± 0.2	3.0 ± 0.3	1.2
2c	3.6 ± 0.4	6.6 ± 0.7	3.2 ± 0.2	5.9 ± 0.4	1.1
2d	135 ± 9.5	282.6 ± 19.9	34.3 ± 3.6	71.8 ± 7.5	3.9
2e	111.1 ± 2.3	195.2 ± 4.0	16.4 ± 3.9	28.8 ± 6.9	6.8
2f	112.9 ± 18.1	254.7 ± 40.7	40.9 ± 5.7	92.2 ± 12.9	2.8
3a	5.6 ± 0.1	9.5 ± 0.2	4.1 ± 0.2	6.9 ± 0.3	1.4
3b	0.5 ± 0.1	0.7 ± 0.1	0.6 ± 0.1	0.9 ± 0.1	0.8
3c	5.7 ± 0.1	10.2 ± 0.2	2.3 ± 0.1	4.1 ± 0.2	2.6
3d	7.6 ± 0.2	15.5 ± 0.4	3.8 ± 0.3	7.7 ± 0.6	2.0
3e	14.6 ± 2.3	25.0 ± 3.9	8.1 ± 1.7	13.9 ± 2.9	1.8
3f	7.0 ± 0.5	15.2 ± 1.0	27.7 ± 2.7	60.6 ± 5.8	0.3
4a	5.3 ± 0.2	9.0 ± 0.3	2.7 ± 0.7	4.6 ± 1.2	2.0
4b	6.4 ± 0.1	9.4 ± 0.1	1.9 ± 0.3	2.8 ± 0.4	3.3
4c	5.4 ± 0.1	9.7 ± 0.2	7.0 ± 0.2	12.6 ± 0.4	0.8
4d	26.2 ± 0.3	53.3 ± 0.6	5.2 ± 0.4	10.5 ± 0.7	5.0
4e	207 ± 8.7	354.9 ± 14.9	6.8 ± 1.3	11.7 ± 2.2	30.4
4f	47.6 ± 2.0	104.2 ± 4.5	28.5 ± 2.8	62.3 ± 6.2	1.7
13a	15.3 ± 6.1	34.6 ± 13.8	5.9 ± 0.4	13.4 ± 0.9	2.6
13b	19.6 ± 1.1	36.7 ± 2.1	18.6 ± 1.1	34.9 ± 2.1	1.1
13c	8.6 ± 0.6	21.1 ± 1.5	5.9 ± 0.2	14.5 ± 0.5	1.4
14a	13.4 ± 3.2	29.4 ± 7.0	6.5 ± 0.2	14.3 ± 0.4	2.1
14b	6.5 ± 0.2	11.9 ± 0.4	3.6 ± 0.2	6.6 ± 0.4	1.8
14c	9.9 ± 1.4	23.5 ± 3.3	7.3 ± 0.5	17.3 ± 1.2	1.4
Benznidazole	>128	>492	14.3 ± 3.3	55.0 ± 12.7	
Doxorubicin	0.21 ± 0.1	0.4 ± 0.2	NA	NA	

Results reported as the mean value ± standard deviation; cytotoxicity as lethal concentration 50 (LC_{50}) and anti-trypanosomal activity as effective concentration 50 (EC_{50}); the selectivity index (SI) = LC_{50}/EC_{50}

solids, non-moisture sensitive compounds, and those bearing an *N*-iodomethyl- or *N*-chloromethyl moiety decompose at their melting point temperature. Non *N*-halomethylated QASs of our study bearing fluorine or the CF_3 group in the terminal aromatic rings are stable at their melting point temperature.

Biological study

Both cytotoxicity and anti-trypanosomal activity of the selected QASs were tested in vitro, as shown in Table 1. Target compounds included trifluoromethylated and fluorinated QASs (**1a–f**, **2a–f**, **3a–f**, and **4a–f**) and non-fluorinated analogs (**13a–c**, **14a–c**).

The effect of target compounds on cell viability was tested first for toxicity on U-937 human macrophages that are the host cells for *T. cruzi* parasites. Their LC_{50} values were determined in comparison to the highly toxic reference compound doxorubicin and to the current trypanocidal drug benznidazole. The extent of toxicity was graded according to the LC_{50} value using the following scale: high cytotoxicity ($LC_{50} < 100$ μg/mL), moderate cytotoxicity (100 μg/mL < $LC_{50} > 200$ μg/mL) or potentially non-cytotoxicity ($LC_{50} > 200$ μg/mL). On the other hand, anti-

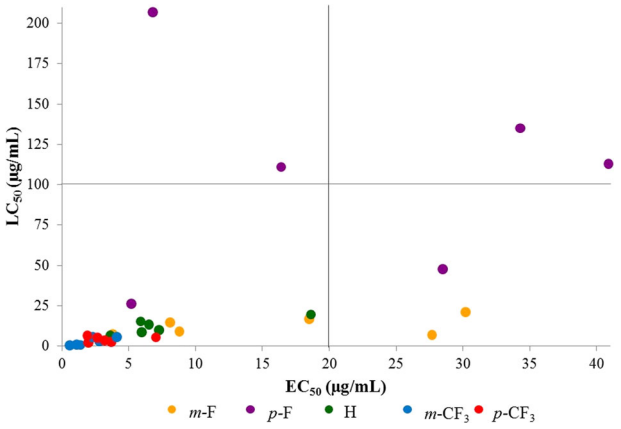


Fig. 1 Scatter diagram of EC_{50} vs LC_{50} values for thirty QASs **1–4** and **13–14**

trypanosomal activity was graded according to the EC_{50} value using the following scale: high activity ($EC_{50} < 20$ µg/mL), moderate activity (20 µg/mL < $EC_{50} < 50$ µg/mL) or low activity ($EC_{50} > 50$ µg/mL).

As illustrated in Table 1, all tested trifluoromethyl-substituted QASs (Y = *p*-CF_3 and *m*-CF_3) showed $LC_{50} < 7$ µg/mL and were therefore classified as highly cytotoxic, with **3b** being the most cytotoxic with a $LC_{50} = 0.5 \pm 0.1$ µg/mL (0.7 ± 0.1 µM) and being **4b** the least cytotoxic with a $LC_{50} = 6.4 \pm 0.1$ µg/mL (9.4 ± 0.1 µM). In contrast, the non-fluorinated analogs were less cytotoxic, with LC_{50} values ranging from 6.5 ± 0.2 µg/mL (11.9 ± 0.4 µM) and 19.6 ± 1.1 µg/mL (36.7 ± 2.1 µM). Eight fluorinated QASs (Y = *p*-F and *m*-F, i.e., **1d–f**, **3d–f**, **4d**, and **4f**) showed $LC_{50} \leq 48$ µg/mL and were therefore classified as highly cytotoxic, with **3f** being the most cytotoxic ($LC_{50} = 7.0 \pm 0.5$ µg/mL; 15.2 ± 1.0 µM).

Additionally, the *para*-fluorinated QASs **2d-f** were classified as moderated cytotoxic compounds, with LC_{50} values ranging from 111.1 ± 2.3 µg/mL (195.2 ± 4.0 µM) to 135 ± 9.5 µg/mL (282.6 ± 19.9 µM), while the *para*-fluorinated QAS **4e** was a non-cytotoxic species, with $LC_{50} = 207 \pm 8.7$ µg/mL (354.9 ± 0.2 µM). In contrast, the non-fluorinated analogs were classified as highly cytotoxic compared with all fluorinated QASs. As expected, doxorubicin showed a very high cytotoxicity, with $LC_{50} = 0.21 \pm 0.1$ µg/mL.

Also, shown in Table 1, dose-response relationship suggested that all trifluoromethyl-substituted QASs were highly active against intracellular *T. cruzi* parasites, with EC_{50} values ≤ 7 µg/mL. Compound **3b** showed the highest activity with an $EC_{50} = 0.6 \pm 0.1$ µg/mL (0.9 ± 0.1 µM) and **4c** exhibited the least activity with an $EC_{50} = 7.0 \pm 0.2$ µg/mL (12.6 ± 0.4 µM). These results contrasted with the non-fluorinated analogs, which were less active on average, with EC_{50} values ranging from 3.6 ± 0.2 µg/mL (6.6 ± 0.4 µM) and 18.6 ± 1.1 µg/mL (34.9 ± 2.1 µM).

On the other hand, fluorinated QASs (Y = *p*-F or *m*-F) presented a range of EC_{50} values between 3.8 and 40.9 µg/mL and were therefore considered highly or moderately active against intracellular *T. cruzi* parasites, being **1d**, **1f**, **2e**, **3d**, **3e**, **4d**, and **4e** classified as highly active with $EC_{50} < 19$ µg/mL. Compound **3d** showed the highest activity with an $EC_{50} = 3.8 \pm 0.3$ µg/mL (7.7 ± 0.6 µM), while **1e**, **2d**, **2f**, **3f**, and **4f** were classified as moderately active with EC_{50} values ranging from 27.7 ± 2.7 µg/mL (60.6 ± 5.8 µM) to 40.9 ± 5.7 µg/mL (92.2 ± 12.9 µM). The non-fluorinated analogs exhibited comparable activity values ($EC_{50} < 19$ µg/mL) with respect to fluorinated QASs. As expected, the trypanocidal reference compound benznidazole exhibited a high anti-parasitic activity ($EC_{50} = 14.3 \pm 3.3$ µg/mL; 55.0 ± 12.7 µM).

As a preliminary approximation to a study of the structure-activity relationship of all the tested compounds, a dispersion chart (Fig. 1) was prepared using the results obtained from cytoxicity (LC_{50}) and anti-trypanosomal activity (EC_{50}).

All trifluoromethyl-substituted compounds (**1a–c**, **2a–c**, **3a–c**, **4a–c**), all non-fluorinated compounds (**13a–c** and **14a–c** such that Y=H), four *meta*-fluorinated compounds (**1d**, **1f**, **3d**, **3e**) and the *para*-fluorinated compound **4d** were grouped in the lower left quadrant of the graph. Thus they exhibit high anti-trypanosomal effectiveness but are highly cytotoxic as well. On the other hand, in the right lower quadrant are located two *meta*-fluorinated compounds (**1e** and **3f**) and the *para*-fluorinated compound **4f**, so these three compounds are classified as highly cytotoxic and moderately effective. In the right upper quadrant are located two *para*-fluorinated compounds (**2d** and **2f**) which are considered effective and moderately cytotoxic. Finally, in the left upper quadrant are located two *para*-fluorinated compounds (**2e** and **4e**), with **2e** being highly effective and moderately cytotoxic, and **4e** highly effective with $EC_{50} = 6.8$ µg/mL ± 1.3 (11.7 ± 2.2 µM) and potentially non-toxic with $LC_{50} = 207$ µg/mL ± 8.7 (354.9 ± 14.9 µM).

Another graphical analysis of the results is depicted in Fig. 2, where LC_{50} values are represented by vertical bars while EC_{50} values are connected by a line overlapping LC_{50} bars. High bars correspond to low-toxicity values, while the most effective anti-trypanosomal compounds lay on minimum points of the EC_{50} values-line.

There is a clear trend of CF_3-substituted QASs being highly cytotoxic compounds (falling right bound in Fig. 2) and F-substituted QASs being the lower cytotoxic ones (falling left bound). Furthermore, in the series of CF_3-derived QASs, *para*-substituted ones tend to be a little less cytotoxic, with the exception of **3b** which was shown to be the most cytotoxic. The same trend was observed in the series of F-substituted QASs, with *para*-substituted being less cytotoxic than *meta*-substituted ones. Also, in Fig. 2,

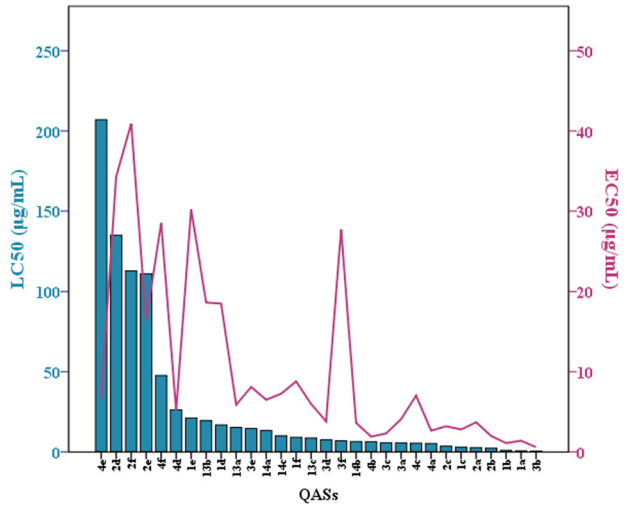


Fig. 2 Combined graph LC_{50} and EC_{50} for the thirty QASs (**1**–**4** and **13**–**14**) evaluated in this study

for CF_3-substituted QASs, the shorter tether ($n = 2$) render them more cytotoxic than $n = 3$. However, this effect behaved randomly with F-substituted or non-fluorinated QASs, and no clear effect of the nature of the covalently attached halogen (or no halogen) in the ammonium head was observed.

Although a more random behavior was observed when analyzing EC_{50} values (line over bars on Fig. 2), the observed general trend favors CF_3-substituted QASs as the more effective ones although they are more cytotoxic as well. The F-substituted QASs are the more promising ones because they are reasonably effective and moderately or low toxic agents. Although not being a definite trend, on average *N*-iodomethyl containing QASs tend to be more anti-parasite agents in comparison to chloro- or non-halogen containing compounds.

Taking into consideration that the SI is a measure of the balance between the cytotoxicity and anti-parasite activity, this allows the identification of promising compounds as those with SI values >1.0. As suggested by Table 1 and Fig. 2, QAS **4e** is the most promising with a SI of 30.4, followed by **2e** (SI = 6.8), **4d** (SI = 5.0) and **2d** (SI = 3.9). In Fig. 2, they are recognized by high bars (low toxicity) matching minimum points in the EC_{50}-line (high effectiveness). Also, regarding SI values for *meta*- or *para*-trifluoromethyl-substituted QASs or non-fluorinated ones, **4b** was the most promising compound (SI = 3.3), followed by **1d** and **3c** (SI = 2.6 for both). Third place in this analysis is **3d** and **4a** (SI = 2.1 and 2.0, respectively) as depicted in Fig. 2. The opposite trend was observed for QASs **1a**, **1b**, **2a**, **3b**, and **4c**, which were not considered promising targets because their SI values are lower than 1.0.

Conclusion

Twenty four novel and six known QASs of the form [X-$CH_2N(CH_3)_2(CH_2)_nCH = C(Ar_2)]^+ I^-$ (where X=H, Cl or I, $n = 2$ or 3, and Ar = *m*-$C_6H_4CF_3$, *p*-$C_6H_4CF_3$, *m*-C_6H_4F, *p*-C_6H_4F or C_6H_5) were synthesized and tested against in vitro anti-*T. cruzi* activity and cytotoxicity using the U-937 human cell line. Based on in vitro EC_{50} values against *T. cruzi*, it was determined that QAS **3b**, (X = I, $n = 3$, Ar = *m*-$C_6H_4CF_3$) was the most effective one but the most toxic as well, while QAS **4e** (X = I, $n = 3$, Ar = *p*-C_6H_4F) was the least cytotoxic compound and the most promising compound exhibiting the best SI (30.4). Thus, monofluoro substitution in the aromatic rings gives rise to better profiles than CF_3-substitution in terms of less cytotoxicity and higher SI values. As a general trend, the salts bearing an *N*-iodomethyl moiety or a longer tether ($n = 3 > n = 2$) are more effective against *T. cruzi* parasites than those bearing a *N*-chloromethyl group. Also, on average, *para*-substitution in the aromatic rings tends to render QASs better anti-trypanosomal compounds. These results have encouraged us to approach an in vivo study on experimental animals and to probe more in deep into a QSAR study in order to have a more comprehensive understanding of how these promising agents represent the very best anti-trypanosomal candidates. These studies are in due course.

Acknowledgements The authors are grateful to Departamento Administrativo de Ciencia, Tecnología e Innovación - COLCIENCIAS and Universidad de Caldas for the financial support through the Grant No. 112765843017.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Avlonitis N, Lekka E, Detsi A, Koufaki M, Calogeropoulou T, Scoulica E, Siapi E, Kyrikou I, Mavromoustakos T, Tsotinis A, Makriyannis A (2003) Antileishmanial ring-substituted ether phospholipids. J Med Chem 46:755–767

Basilico N, Migotto M, Ilboudo DP, Taramelli D, Stradi R, Pini E (2015) Modified quaternary ammonium salts as potential anti-malarial agents. Bioorg Med Chem 23:4681–4687

Buckner FS, Verlinde CL, La Flamme AC, Van Voorhis WC (1996) Efficient technique for screening drugs for activity against *Trypanosoma cruzi* using parasites expressing beta-galactosidase. Antimicrob Agents Chemother 40:2592–2597

Chen G, Xia H, Cai Y, Ma D, Yuan J, Yuan C (2011) Synthesis and SAR study of diphenylbutylpiperidines as cell autophagy inducers. Bioorg Med Chem Lett 21:234–239

Coa JC, García E, Carda M, Agut R, Vélez ID, Muñoz JA, Yepes LM, Robledo SM, Cardona WI (2017) Synthesis, leishmanicidal, trypanocidal and cytotoxic activities of quinoline-chalcone and quinoline-chromone hybrids. Med Chem Res 26:1405–1414

Dalvie D, Sajiv N, Kang P, Loi CM (2010) Influence of aromatic rings on ADME properties of drugs. In: Smith DA (ed) Metabolism, Pharmacokinetics and Toxicity of Functional Groups: impact of chemical building blocks on ADMET. Drug Discovery. Royal Society of Chemistry, Cambridge, pp 275–327

de Castro SL, Santa-Rita RM, Urbina JA, Croft SL (2004) Anti-protozoal lysophospholipid analogues: a comparison of their activity against trypanosomatid parasites and tumor cells. Mini-Rev Med Chem 4:141–151

Duque-Benítez SM, Ríos-Vásquez LA, Ocampo-Cardona R, Cedeño DL, Jones MA, Vélez ID, Robledo SM (2016) Synthesis of novel quaternary ammonium salts and their in vitro antileishmanial activity and U-937 cell cytotoxicity. Molecules 21:281–296

Egorova KS, Gordeev EG, Ananikov VP (2017) Biological activity of ionic liquids and their application in pharmaceutics and medicine. Chem Rev 117:7132–7189

El-Sayed NM, Myler PJ, Blandin G, Berriman M, Crabtree J, Aggarwal G, Caler E, Renauld H, Worthey EA, Hertz-Fowler C, Ghedin E, Peacock C, Bartholomeu DC, Haas BJ, Tran AN, Wortman JR, Alsmark UCM, Angiuoli S, Anupama A, Badger J, Bringaud F, Cadag E, Carlton J, Cerqueira G, Creasy T, Delcher AL, Djikeng A, Embley TM, Hauser C, Ivens AC, Kummerfield SK, Pereira-Leal JB, Nilsson D, Peterson J, Salzberg S, Shallom J, Silva JC, Sundaram J, Westenberger S, White O, Melville S, Donelson JE, Andersson B, Stuart KD, Hall N (2015) Comparative genomics of trypanosomatid parasitic protozoa. Science 309:404–409

Fernández M, Murillo J, Ríos-Vásquez LA, Ocampo-Cardona R, Cedeño DL, Jones MA, Vélez ID, Robledo SM (2018) In vivo studies of the effectiveness of novel N-halomethylated and non-halomethylated quaternary ammonium salts in the topical treatment of cutaneous leishmaniasis. Parasitol Res 117:273–286

Finney DJ (1978) Statistical Method in Biological Assay. Charles Griffin, London

Gerebtzoff G, Li-Blatter X, Fischer H, Frentzel A, Seelig A (2004) Halogenation of drugs enhances membrane binding and permeation. ChemBioChem 5:676–684

Gibson S, McGuire R, Rees DC (1996) Principal components describing biological activities and molecular diversity of heterocyclic aromatic ring fragments. J Med Chem 39:4065–4072

Gillis EP, Eastman KJ, Hill MD, Donnelly DJ, Meanwell NA (2015) Applications of fluorine in medicinal chemistry. J Med Chem 58:8315–8359

Hann MM, Leach AR, Harper G (2001) Molecular complexity and its impact on the probability of finding leads for drug discovery. J Chem Inf Comput Sci 41:856–864

Huang MT, Wu HY, Chein RJ (2014) Enantioselective synthesis of diaryl aziridines using tetrahydrothiophene-based chiral sulfides as organocatalysts. Chem Commun 50:1101–1103

Isanbor C, O'Hagan D (2006) Fluorine in medicinal chemistry: a review of anti-cancer agents. J Fluor Chem 127:303–319

Jiang S, Zhang L, Cui D, Yao Z, Gao B, Lin J, Wei D (2016) The Important role of halogen bond in substrate selectivity of enzymatic catalysis. Sci Rep 6:34750

Khare S, Nagle AS, Biggart A, Lai YH, Liang F, Davis LC, Barnes SW, Mathison CJN, Myburgh E, Gao MY, Gillespie JR, Liu X, Tan JL, Stinson M, Rivera IC, Ballard J, Yeh V, Groessl T, Federe G, Koh HX, Venable JD, Bursulaya B, Shapiro M, Mishra PK, Spraggon G, Brock A, Mottram JC, Buckner FS, Rao SP, Wen BG, Walker JR, Tuntland T, Molteni V, Glynne RJ, Supek F (2016) Proteasome inhibition for treatment of leishmaniasis, Chagas disease and sleeping sickness. Nature 537:229–233

Kirk KL (2006) Fluorine in medicinal chemistry: recent therapeutic applications of fluorinated small molecules. J Fluor Chem 127:1013–1029

Li J, Zhou H, Weng J, Wang M, Ge C, Tu W (2014) Concise synthesis of chiral *N*-benzyl-α,α-diarylprolinols through Shi asymmetric epoxidation. Synlett 25:805–808

Lipinski CA (2000) Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods 44:235–249

Mendez L, Henriquez G, Sirimulla S, Narayan M (2017) Looking back, looking forward at halogen bonding in drug discovery. Molecules 22:1397

Metrangolo P, Neukirch H, Pilati T, Resnati G (2005) Halogen bonding based recognition processes: a world parallel to hydrogen bonding. Acc Chem Res 38:386–395

Meyer EA, Castellano RK, Diederich F (2003) Interactions with aromatic rings in chemical and biological recognition. Angew Chem Int Ed 42:1210–1250

Ng CKL, Obando D, Widmer F, Wright LC, Sorrell TC, Jolliffe KA (2006) Correlation of antifungal activity with fungal phospholipase inhibition using a series of bisquaternary ammonium salts. J Med Chem 49:811–816

Obłąk E, Piecuch A, Maciaszczyk-Dziubińska E, Wawrzycka D (2016) Quaternary ammonium salt *N*-(dodecyloxycarboxymethyl)-*N*,*N*,*N*-trimethylammonium chloride induced alterations in saccharomyces cerevisiae physiology. J Biosci 41:601–614

Ojima I (2009) Fluorine in Medicinal Chemistry and Chemical Biology. John Wiley & Sons, Chichester, UK

Pachioni J, de A, Magalhães JG, Lima EJC, de Moura Bueno L, Barbosa JF, de Sá MM, Rangel-Yagui C, de O (2013) Alkylphospholipids - a promising class of chemotherapeutic agents with a broad pharmacological spectrum. J Pharm Pharm Sci 16:742–759

Palermo EF, Lee DK, Ramamoorthy A, Kuroda K (2011) Role of cationic group structure in membrane binding and disruption by amphiphilic copolymers. J Phys Chem B 115:366–375

Pérez-Victoria FJ, Castanys S, Gamarro F (2003) *Leishmania donovani* resistance to miltefosine involves a defective inward translocation of the drug. Antimicrob Agents Chemother 47:2397–2403

Pham TPT, Cho CW, Yun YS (2010) Environmental fate and toxicity of ionic liquids: a review. Water Res 44:352–372

Pulido SA, Nguyen VH, Alzate JF, Cedeño DL, Makurath MA, Ríos-Vásquez A, Duque-Benítez SM, Jones MA, Robledo SM, Friesen JA (2017) Insights into the phosphatidylcholine and phosphatidylethanolamine biosynthetic pathways in *Leishmania* parasites and characterization of a choline kinase from *Leishmania infantum*. Comp Biochem Physiol B 213:45–54

Rakotomanga M, Blanc S, Gaudin K, Chaminade P, Loiseau PM (2007) Miltefosine affects lipid metabolism in leishmania donovani promastigotes. Antimicrob Agents Chemother 51:1425–1430

Ran Y, Jain N, Yalkowsky SH (2001) Prediction of aqueous solubility of organic compounds by the general solubility equation (GSE). J Chem Inf Comput Sci 41:1208–1217

Reddy VP (2015) Organofluorine Compounds in Biology and Medicine. Elsevier, Amsterdam, The Netherlands

Ríos LA, Dolbier WR, Paredes R, Lusztyk J, Ingold KU, Jonsson M (1996) Generation and study of the reactivity of α-ammonium distonic radical cations in solution. J Am Chem Soc 118:11313–11314

Ríos LA, Ocampo R, Duque SM, Robledo SM, Vélez ID, Cedeño DL, Jones MA (2015) Quaternary N-(halomethyl)ammonium salts as therapeutic agents. U.S. Patent 9,145,352 B2, Sept 29

Ritchie TJ, Macdonald SJF (2009) The impact of aromatic ring count on compound developability - are too many aromatic rings a liability in drug design? Drug Discov Today 14:1011–1020

Scholfield MR, Vander Zanden CM, Carter M, Ho PS (2013) Halogen bonding (X-bonding): a biological perspective. Protein Sci 22:139–152

Shi DY, Wang BC, Wang LJ, Jiang B, Wang SY, Wu N, Li XQ (2017) Application of fluorine in drug design during 2010-2015 years: a mini-review. Mini-Rev Med Chem 17:683–692

Tang W, Sarvestani M, Wei X, Nummy LJ, Patel N, Narayanan B, Byrne D, Lee H, Yee NK, Senanayake CH (2009) Formation of 2-trifluoromethylphenyl Grignard reagent via magnesium - halogen exchange: process safety evaluation and concentration effect. Org Process Res Dev 13:1426–1430

Taylor RD, Maccoss M, Lawson ADG (2014) Rings in drugs. J Med Chem 57:5845–5859

Tischer M, Pradel G, Ohlsen K, Holzgrabe U (2012) Quaternary ammonium salts and their antimicrobial potential: targets or nonspecific interactions? ChemMedChem 7:22–31

Valencia L, Muñoz DL, Robledo SM, Echeverri F (2011) Actividad tripanocida y citotóxica de extractos de plantas colombianas. Biomédica 31:552–559

Wang J, Hou T (2010) Drug and drug candidate building block analysis. J Chem Inf Model 50:55–67

Waymouth R, Moore EJ (1997) Metal fluoride stability. Chem Eng News 75:6

World Health Organization (2015) Investing to Overcome the Global Impact of Neglected Tropical Diseases: Third WHO Report on Neglected Tropical Diseases, Vol. 3

World Health Organization (2016). World Health Statistics. Monitoring Health for the SDGs, Sustainable Development Goals

Young RJ, Green DVS, Luscombe CN, Hill AP (2011) Getting physical in drug discovery II: the impact of chromatographic hydrophobicity measurements and aromaticity. Drug Discov Today 16:822–830

Zhao W (2017) Handbook for Chemical Process Research and Development. CRC Press Ed