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Synthesis and biological activity of new diarylalkenes

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Condensation of 5-nitro-, 3-chloro-, and 5-chlorosalicylic acid with formaldehyde afforded dimeric disalicylmethanes which were O-methylated with dimethyl sulfate and oxidized with chromium(VI) oxide to give the diarylketones **10**, **11**, **12**. Wittig reaction with ylides obtained by deprotonation of alkyltriphenylphosphonium salts with sodium bis (trimethylsilyl)amide yielded a series of diarylalkenes. Some of the obtained compounds showed high antimicrobial activity *in vitro* against *Bacillus subtilis* and *Mycobacterium smegmatis.*

1. Introduction

Recently we have discovered a new class of antiviral compounds. Two groups of symmetrical diaryl alkenes showed high activity particularly against HIV viruses [1–6]. A first major group **1** contained ammonium salts of disalicylethylenes with a large lipophilic, aliphatic or alicylic substituent. The biological activity correlated positively with chain length and lipophilicity of the alkenes. The most active compound was a derivative with 3-(5α) cholestanyl substituent (EC_{50} 3 μM). The mechanism of action of these compounds involves insertion of a lipophilic moiety in the lipid bilayer of the cell membrane and the viral envelope. A protruding disalicylmethylene fragment may interfere with the binding of lymphocytes to the virus envelope and inhibits the fusion of the viral envelope with the cell membrane.

To the second minor group **2** of active compounds belong aromatic neutral disalicylethylenes with a short side chain, penetrating the white cell membranes and HIV envelope, and inhibiting HIV-1 reverse transcriptase.

Diarylalkenes are also active against human cytomegalovirus, herpex simplex viruses, against Junin and Tacaribe viruses as well as against influence viruses.

Dichlorodiphenylethylens **3** with *N*,*N*-diarylurea substituents show insecticidal properties [7].

This biological activity has induced us to prepare new derivatives of diarylalkenes and examine their biological activity.

2. Investigations, results and discussion

2.1. Synthesis of diarylalkenes

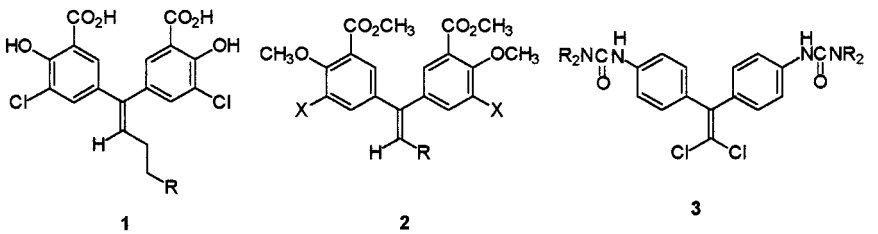
Several series of diarylalkenes have been prepared by Wittig reaction of the substituted benzophenones with the phosphonium salts (Schemes 1, 2).

The starting compound 5-nitrosalicylic acid (**4**) was isolated by fractional crystallization of a mixture of 3- and 5-nitrosalicylic acids obtained by nitration of salicylic acid with 8% nitric acid [8]. Condensation with paraformaldehyde in the presence of sulfuric acid was carried out by modification of the known reaction [9]. Following the original procedure a mixture of compounds was obtained from which the expected diphenylmethane **6** was obtained with only 20% yield.

However, consideration of plausible reaction mechanism [10] led us to conclude that a solvent of low dielectric constant would favour the process. In the intermediate state of this reaction scattering of the positive charge in comparison with the substrates occurs. Dilution of sulfuric acid (dielectric constant = 100) with *p*-dioxane (dielectric

Table 1: Physical and analytical data of phosphonium salts 3a–i

Compd.	R'_5	Molcular formula (weight)	M.P. (°C)	Yield (%)
13a	CH_3	$C_{19}H_{18}IP$ 404.2	184–186	97.0
13b	C_2H_5	$C_{20}H_{20}BrP$ 371.3	205–206	96.8
13c	n-C_3H_7	$C_{21}H_{22}BrP$ 385.3	234–236	95.1
13d	n-C_4H_9	$C_{22}H_{24}BrP$ 399.3	237	94.4
13e	n-C_5H_{11}	$C_{23}H_{26}BrP$ 413.4	166–167	92.8
13f	n-C_6H_{13}	$C_{23}H_{28}BrP$ 427.4	203–204	95.6
13g	n-$C_{11}H_{23}$	$C_{29}H_{38}BrP$ 497.5	63	69.2
13h	n-$C_{14}H_{29}$	$C_{32}H_{44}BrP$ 539.6	82	78.6
13i	n-$C_{20}H_{41}$	$C_{38}H_{56}Br^-$ 623.8	93–95	87.3



1 **2** **3**

X=Cl, Br; R=C_6H_{14}
X=Cl, R=C_2H_4Br

R=C_2H_5 - $C_{12}H_{25}$

Scheme 1

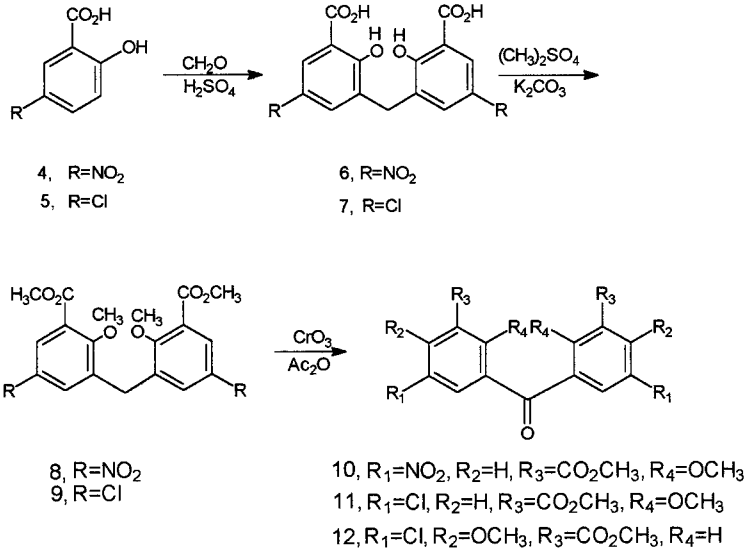


Table 2: Physical and analytical data of diarylalkenes 14–32

Compd.	R_1	R_2	R_3	R_4	R_5	Molecular formula (weight)	M.P. (°C) solvent	Yield (%)
14	NO_2	H	CO_2CH_3	OCH_3	CH_3	$C_{21}H_{20}N_2O_{10}$ 460.4	137–139 EtOH	69.4
15	NO_2	H	CO_2CH_3	OCH_3	n-C_3H_7	$C_{23}H_{24}N_2O_{10}$ 488.4	84–85 EtOH	70.6
16	NO_2	H	CO_2CH_3	OCH_3	n-C_5H_{11}	$C_{25}H_{28}N_2O_{10}$ 516.4	–	97.0
16a	NO_2	H	CO_2H	OCH_3	n-C_5H_{11}	$C_{23}H_{24}N_2O_{10}$ 488.4	183 $CHCl_3$-hexane	
17	NO_2	H	CO_2CH_3	OCH_3	n-$C_{10}H_{21}$	$C_{30}H_{38}N_2O_{10}$ 586.6	68 EtOH	79.3
18	NO_2	H	CO_2CH_3	OCH_3	n-$C_{13}H_{27}$	$C_{33}H_{44}N_2O_{10}$ 628.7	63–65 EtOH	72.7
19	Cl	H	CO_2CH_3	OCH_3	H	$C_{20}H_{18}Cl_2O_6$ 425.2	62–64	78.3
20	Cl	H	CO_2CH_3	OCH_3	CH_3	$C_{21}H_{20}Cl_2O_6$ 439.3	90–91 MeOH	89.2
21	Cl	H	CO_2CH_3	OCH_3	C_2H_5	$C_{22}H_{22}Cl_2O_6$ 453.3	–	58.9
21a	Cl	H	CO_2H	OH	C_2H_5	$C_{18}H_{14}Cl_2O_6$ 397.2	240–245 CH_2Cl_2	
22	Cl	H	CO_2CH_3	OCH_3	n-C_3H_7	$C_{23}H_{24}Cl_2O_6$ 467.3	–	68.7
23	Cl	H	CO_2CH_3	OCH_3	n-C_4H_9	$C_{24}H_{26}Cl_2O_6$ 481.1	–	71.4
24	Cl	H	CO_2CH_3	OCH_3	n-C_5H_{11}	$C_{25}H_{28}Cl_2O_6$ 495.4	–	66
25	Cl	H	CO_2CH_3	OCH_3	n-$C_{10}H_{21}$	$C_{30}H_{38}Cl_2O_6$ 565.5	–	65.1
26	Cl	H	CO_2CH_3	OCH_3	n-$C_{13}H_{27}$	$C_{33}H_{44}Cl_2O_6$ 607.6	–	60.0
27	Cl	H	CO_2CH_3	OCH_3	n-$C_{19}H_{39}$	$C_{39}H_{56}Cl_2O_6$ 691.8	–	62.0
28	Cl	OCH_3	CO_2CH_3	H	n-C_3H_7	$C_{23}H_{24}Cl_2O_6$ 467.3	83–85 EtOH	48.5
29	Cl	OCH_3	CO_2CH_3	H	n-$C_{10}H_{21}$	$C_{30}H_{38}Cl_2O_6$ 565.5	70–71 EtOH	56.7
30	H	Cl	H	H	n-$C_{10}H_{21}$	$C_{24}H_{30}Cl_2$ 389.4	–	91.2
31	H	Cl	H	H	n-C_3H_7	$C_{17}H_{16}Cl_2$ 291.2	–	83.2
32	H	F	H	H	n-$C_{10}H_{21}$	$C_{24}H_{30}F_2$ 356.5	–	96.0

constant = 2.2) resulted in an unexpectedly big increase in yield to 78%.

Condensation of 5-chlorosalicylic acid with formaldehyde proceeded much faster and more efficiently than the reaction of the corresponding nitroacid, and cooling of the reaction mixture was necessary. In the dimeric products **6** and **7** the two carboxylic and two phenolic groups were methylated with dimethyl sulfate using potassium carbonate as a base. The methylene unit of **8** and **9** was oxidized with chromic trioxide in acetic anhydride to afford benzophenes **10** and **11**. The benzophenone **12** was similarly prepared [2] from 3-chlorosalicylic acid. 4,4′-Dichloro- and 4,4′-difluorobenzophenones were purchased from Aldrich. The obtained substituted benzophenones underwent reaction with ylides obtained by deprotonation of the corresponding phosphonium salts (Table 1) with sodium bis(trimethylsilyl)amide in THF to yield a series of olefins with good (60–98%) yield (Table 2). Character of the base was essential, since in several cases where sodium hydride was used instead, a useless alkyldiphenylphosphine oxide was obtained (Scheme 2).

To study further a structure-activity relationship some functional groups transformations were carried out. First, ester groups in nitro compound **16** were saponified to afford the dimethoxy diacid **16a**. Then two methoxy and two ester groups were demethylated with boron tribromide-dimethyl sulfide complex [6] to get the phenol acid **21a**. The double bond in chloroester **20** was selectively reduced by catalytic hydrogenation with platinum oxide in ethyl acetate to yield the dihydro compound **20a** (Scheme 2).

2.2. Discussion of antimicrobial screening results

Results of the antimicrobial tests are presented in Table 3. The highest activity was shown by chlorodiarylalkenes with a short C_3–C_4 side chain reaching a MIC of 1 μg/ml for compound **22** against *Bacillus subtilis* and *Mycobacterium smegmatis*. Interestingly an isomer of this alkene, compound **28** differing only in the substitution pattern of aromatic rings was devoid of activity. (MIC > 100 μg/cm^3). Alkene **31** with 4,4′-chlorosubstitution of the aromatic rings showed a much smaller activity than alkene **22** of the same side-chain length. Saponification of ester groups did not affect the activity (compare data for compounds **16** and **16a**), but full demethylation resulted in a small increase of antimicrobial potency (alkenes **21** and **21a**). Saturation of the alkene function led to lowering of activity (compare data for compounds **20** and **20a**). These results indicate that the chlorodisalicyl moiety is a toxicophore in this type of compounds.

Table 3: Antimicrobial activity (MIC) of diarylalkenes (μg/ml)

Compd.	*Bacillus subtilis*	*Mycobacterium smegmatis*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*
14	>100	100	>100	>100
15	>100	>100	>100	>100
16	>100	100	>100	>100
16a	>100	100	>100	>100
17	>100	>100	>100	>100
18	100	>100	100	>100
19	>100	>100	>100	>100
20	>100	50	>100	>100
20a[1]	>100	100	>100	>100
21	>100	>100	>100	>100
21a	100	50	>100	>100
22	1	1	>100	>100
23	>100	5	>100	>100
24	>100	100	>100	>100
25	>100	100	>100	>100
26	>100	>100	>100	>100
27	>100	100	>100	>100
28	>100	>100	>100	>100
29	>100	100	100	>100
30	>100	>100	>100	>100
31	>100	10	100	>100
32	>100	>100	>100	>100

[1] Compound **20a** is a diarylalkane obtained by hydrogenation of alkene **20** (Scheme 3)

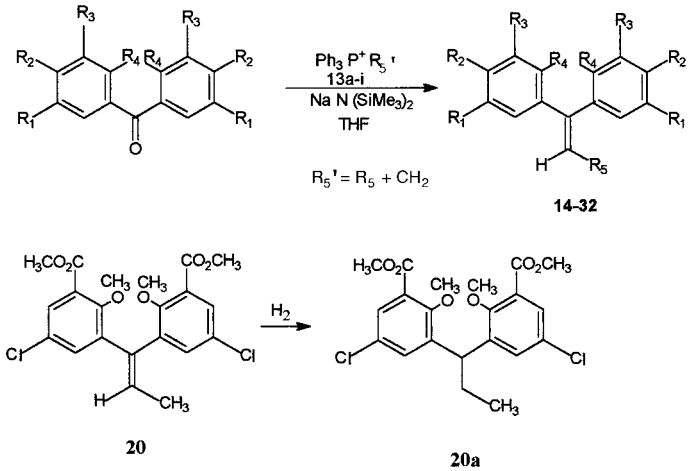
3. Experimental

Melting points were determined in capillary tubes and are uncorrected. Spectra were obtained as follows: IR spectra on JASCO FTIR-420 spectrometer, ^{1}H NMR spectra on Varian 500 UNITY plus-500 and Varian 200 UNITY plus 200 spectrometers, EI MS on an AMD M-40 spectrometer. Elemental analyses were performed at the Microanalysis Laboratory of the Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, and all values were within ±0.4% of the calculated compositions. Flash-chromatography was carried out using silica gel S 230-400 (Riedel-de Haen).

3.1. 3,3′-Dicarboxy-2,2′-dihydro-5,5′-dinitrodiphenylmethane **(6)**

Conc. H_2SO_4 acid (95 ml) was added dropwise to a suspension of 5-nitrosalicylic acid (**4**, 20 g, 0.109 mol) in 1,4-dioxane (31 ml) with H_2O cooling. Paraformaldehyde (3.30 g) was added and the mixture was vigorously stirred at 65 °C for 9 h. It was poured on crushed ice (ca. 600 g) and the precipitate was filtered off and dried at RT for 2 d. The product was crystallized from 1,4-dioxane to afford pure compound **6** (11.93 g, 75.7%), m.p. > 260 °C; IR (KBr): 3450–2600 (OH), 1680 (C=O), 1624 (C=C), 1532, 1346 (NO_2) cm^{-1}; ^{1}H NMR (DMSO d_6): δ 8.50 (d, J = 2.7 Hz, 2 H, H-4.4′), 8.21 (d, J = 2.7 Hz, 2 H, H-6, -6′), 4.94 (s, 2 H).

Scheme 2



3.2. 3,3′-Dicarbomethoxy-2.2′-dimethoxy-5,5′-dinitrophenylmethane (**8**)

Compound **8** was obtained from **6** by methylation with $(CH_3)_2SO_4$ [2] and recrystallized from a CH_2Cl_2/*n*-hexane mixture, yield 7.6 g (55.5%), m.p. 131 °C; IR (KBr): 3020, 810 (H−C=), 1730 (C=O), 1613, 1590 (C=C), 1527, 1350 (NO_2), 1297, 1262, 1205, 1163, (C−O−C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.61 (d, J = 3 Hz, 2 H, H-4, -4′), 8.17 (d, J = 3 Hz, 2 H, H-6, -6′), 4.17 (s, 2 H), 3.98 (s, 6 H), 3.90 (s, 6 H); MS-GC m/z (%) 434 (M^+, 12), 417 (M^+-OH, 100), 403 (M^+-OCH_3, 67).

3.3. 3,3′-Dicarbomethoxy-2.2′-dimethoxy-5,5′-dinitrobenzophenone (**10**)

Ketone **10** was prepared from **8** by chromic anhydride oxidation [2] and recrystallized from a CH_2Cl_2/*n*-hexane mixture, yield 2.2 g (71%), m.p. 153–153.5 °C; IR (KBr): 1742 (C=O), 1732 (O−C=O), 1612, 1596 (C=C), 1532, 1352 (NO_2), 1268, 1240, 1166 (C−O−C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.83 (d, J = 2.9 Hz, 2 H), 8.61 (d, J = 2.9 Hz, 2 H), 3.98 (s, 6 H), 3.68 (s, 6 H); MS-GC m/z (%) 448 (M^+, 4), 431 (M^+-OH, 41), 417 (M^+-OCH_3, 5).

3.4. 5.5′-Dichloro-3.3′-dicarbomethoxy-2,2′-dimethoxydiphenylmethane (**9**)

Conc. H_2SO_4 (360 ml) was added dropwise to a mixture of 5-chlorosalicylic acid (**5**, 30 g) and H_2O (18 ml). The mixture was cooled in dry ice bath at such a rate to keep the temperature below 5 °C. The reaction mixture was stirred at ice bath for 1 h and then cooled in dry ice again. A solution of 37% aqueous formaldehyde (85 ml) in MeOH (85 ml) was added at such a rate to keep the temperature below 5 °C. The mixture was stirred at 0 °C for 4 h and left overnight. It was poured on crushed ice (1.5 kg), and the precipitate was filtered and dried. The product **7** (29.55 g) was methylated with $(CH_3)_2SO_4$ [2], recrystallized from a CH_2Cl_2/*n*-hexane mixture, yield 17.75 g (47.2% for the two steps), m.p. 85–86 °C; IR KBr): 1728 (C=O), 1650 (C=C), 1108 (C−Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.70 (d, J = 3 Hz, 2 H, H-4, 4′), 7.19 (d, J = 3 Hz, 2 H, H-6, 6′), 4.02 (s, 2 H), 3.93 (s, 6 H), 3.78 (s, 6 H).

3.5. 5.5′-Dichloro-3.3′-dicarbomethoxy-2,2′-dimethoxybenzophenone (**11**)

Compound **11** was prepared similarly to ketone **10** [2], recrystallized from CH_2Cl_2-*n*-hexane mixture, m.p. 137–138 °C; IR (KBr): 1748 (C=O), 1732 (C−O−C), 1650 (C=C), 1265, 1232, 1193, 1167 (C−O−C), 1100 (C−Cl), 898 (HC=C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.93 (d, J = 2.9 Hz, 2 H), 7.66 (d, J = 2.9 Hz, 2 H), 3.91 (s, 6 H); MS-GC m/z (%) 427 (M^+, 35), 397 (MH^+-OCH_3, 100), 338 (MH^+-OCH_3, $-CO_3CH_3$, 42).

3.6. n-Alkyltriphenylphosphonium salts **13a–i.** *General procedure*

The physical and analytical data are shown in Table 2.

n-Hexyltriphenyl phophonium bromide (**13f**): A solution of *n*-hexyl bromide (23.5 g, 0.142 mol) and triphenylphosphine (37.4 g, 0.142 mol) in CH_3CN (40 ml) was heated under reflux for 16 h. The solvent was removed in vacuo, the solid residue was triturated with *n*-heptane (50 ml), filtered off and washed with *n*-hexane (3 × 25 ml). The product was dried in a vacuum desiccator over P_4O_{10}, yield 58.0 g (95.6%), m.p. 203–204 °C, (lit. [11] m.p. 198–200 °C). In case of higher analogues it was necessary to repeat trituration and decantation of heptane several times to get solid products.

3.7. 1,1-Bis(3′-Dicarbomethoxy-2′-dimethoxy-5′-dinitrophenyl)-1-alkenes **14–***18. General procedure*

The physical and analytical data are shown in Table 1.

3.7.1. 1,1-Bis(3′-Dicarbomethoxy-2′-dimethoxy-5′-dinitrophenyl)-1-propene (**14**)

Ethyltriphenylphosphonium bromide (**13b**) (1.76 g, 4.74 mmol) was suspended in THF (36 ml, freshly distilled from sodium-benzophenone) under dry N_2 atmosphere. The mixture was cooled in an ice bath, and sodium bis (trimethylsilyl) amide (1 M solution in THF, 4.5 ml) was added dropwise. The mixture was stirred for 30 min, and a solution of nitrobenzophenone **7** (1.60 g, 3.57 mmol) in THF (20 ml) was added dropwise. The reaction mixture was stirred at 60 °C for 1 h and for 20 h at RT. The reaction was quenched with NH_4Cl solution, the THF phase was separated, and the aqueous phase was extracted with $(C_2H_5)_2O$. The combined organic extracts were dried (Na_2SO_4) and evapourated in vacuo. Flash chromatography of the residue on silica gel (95 g, *n*-hexane/ethyl acetate 2 : 1) yielded yellow product which was crystallized from the corresponding solvent. IR (KBr): 3063, 810, 801 (H−C=), 1713 (C=O), 1592, 1569 (C=C), 1513, 1326 (NO_2), 1256 (C−O−C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.65 (d, J = 2.9 Hz, 1 H′), 8.60 (d, J = 2.9 Hz, 1 H), 8.35 (d, J = 2.9 Hz, 1 H), 8.33 (d, J = 2.9 Hz, 1 H), 6.30 (q, J = 7.3 Hz, 1 H, H-2), 3.94 (s, 3 H), 3.92 (s, 3 H), 3.66 (s, 3 H), 3.59 (s, 3 H), 1.86 (d, J = 7.3 Hz, 3 H, H-3); EIMS m/z (%) 461 (MH^+, 3), 443 (11), 429 (MH^+-MeOH, 29), 411 (M^+-CO_2Me, 52).

3.7.2. Compound **15**

IR KBr): 3064, 801 (H−C=), 1727 (C=O), 1600 (C=C), 1515, 1341 (NO_2), 1253 (C−O−C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.65 (d, J = 3 Hz, 1 H), 8.60 (d, J = 3 Hz, 1 H), 8.34 (d, J = 3 Hz, 1 H), 8.32 (d, J = 3 Hz, 1 H), 6.20 (t, J = 7.8 Hz, 1 H, H-2), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.65 (s, 3 H), 3.60 (s, 3 H), 2.16 (m, 2 H, H-3), 1.56 (m, 2 H, H-4), 0.97 (t, J = 7.4 Hz, 3 H).

3.7.3. Compound **16**

This compound was obtained as an oil after CC (*n*-hexane/ethyl acetate 4 : 1). IR (neat): 3073, 802 (H−C=), 1728 (C=O), 1600, 1573 (C=C), 1517, 1340 (NO_2), 1257 (C−O−C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.64 (d, J = 2.9 Hz, 1 H), 8.58 (d, J = 2.9 Hz, 1 H), 8.33 (d, J = 2.9 Hz, 1 H), 8.31 (d, J = 2.9 Hz, 1 H), 6.20 (t, J = 7.6 Hz, 1 H), 3.93 (s, 3 H), 3.93 (s, 3 H, CO_2CH_3−C-3, or C-3′), 3.92 (s, 3 H), 3.65 (s, 3 H, OCH_3−C-2, or -C-2′), 3.60 (s, 3 H), 2.16 (m, 2 H), 1.51 (m, 2 H), 1.33 (m, 4 H), 0.89 (t, J = 6.9 Hz, 3 H); GC-MS m/z (%) 517 (MH^+, 2), 485 (MH^+-MeOH, 17), 468 (17).

3.7.4. 1,1-Bis(3′-carboxy-2′-methoxy-5′-nitrophenyl)-1-heptene (**16a**)

Compounds **16a** was obtained by heating of nitroester **16** with an excess of aqueous-methanolic KOH for 1 h, followed by acidifiction and $CHCl_3$ extraction. IR (KBr) 3600–2500 (OH), 3073, 798 (H−C=), 1700 (C=O) 1600, 1568 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz): δ 3.73 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3); EIMS m/z (%) 488 (M^+-H_2O, 22), 453 (26).

3.7.5. Compound **17**

IR (KBr): 3076, 800 (H−C=), 1725 (C=O), 1599, 1580 (C=C), 1527, 1340 (NO_2), 1261 (C−O−C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.65 (d, J = 2.8 Hz, 1 H), 8.59 (d, J = 2.8 Hz, 1 H, 8.33 (d, J = 2.8 Hz, 1 H), 8.31 (d, J = 2.8 Hz, 1 H), 6.20 (t, J = 7.4 Hz, 1 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.65 (s, 3 H), 360 (s, 3 H), 2.16 (m, 2 H), 1.51 (m, 2 H), 1.25 (m, 14 H), 0.87 (t, J = 6.6 H, 3 H).

3.7.6. Compound **18**

IR (KBr): 3072, 813, 800 (H−C=), 1727, (C=O), 1520, 1339 (NO_2), 1253, 981 cm^{-1}; ^1H NMR ($CDCl_3$, δ 500 MHz): 8.65 (J = 3 Hz, 1 H), 8.59 (d, J = 3 Hz, 1 H), 8.33 (d, J = 3 H, 1 H), 8.31 (d, J = 3 Hz, 1 H), 6.19 (t, J = 7.4 Hz, 1 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.65 (s, 3 H), 3.60 (s, 3 H), 2.16 (m, 2 H), 1.51 (m, 2 H), 1.31 (m, 2 H), 1.25 (m, 18 H), 0.88 (t, J = 7 Hz, 3 H).

3.8. 1,1-Bis-(3′-dicarbomethoxy-5′-dichloro-2′-dimethoxyphenyl)-1-alkenes **19–27**

The alkenes **19–27** have been prepared by Wittig reaction of chlorobenzophenone **11** with *n*-alkyltriphenylphosphonium salts under similar conditions as described above for the synthesis of nitroalkenes, with the difference that the reaction mixture after addition of the ketone **11** was not heated.

3.8.1. 1.1-Bis(3′-dicarbomethoxy-5′-dichloro-2′-dimethoxyphenyl)-ethylene (**19**)

IR (KBr): 3067, 880, 867, 800 (H−C=), 1728 (C=O), 1610, 1571 (C=C), 1253, 1226, 1195 (C−O−C), 1087 (C−Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.73 (d, J = 2.3 Hz, 2 H, H-4′), 7.45 (d, J = 2.3 Hz, 2 H, H-6′), 5.66 (s, 2 H, H-2), 3.88 (s, 3 H), 3.50 (s, 3 H).

3.8.2. Compound **20**

IR (KBr): 3057, 886, 853, 800 (H−C=), 1727 (C=O), 1704, 1569 (C=C), 1095 (C−Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.75 (d, J = 2.4 Hz, 1 H), 7.66 (d, J = 3 Hz, 1 H), 7.41 (d, J = 2.4 Hz, 1 H), 7.38 (d, J = 3 Hz, 1 H), 6.18 (q, J = 7.0 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.53 (s, 3 H), 3.48 (s, 3 H), 1.77 (d, J = 7.0 Hz, 3 H).

3.8.3. 1,1-Bis-(5′-chloro-3′-carbomethoxy-2′-methoxyphenyl)propane (**20a**)

A solution of alkene **20** (123 mg) in ethyl acetate (6 ml) was stirred with Adams catalyst (35 mg) in hydrogen atmosphere for 3.5 h. Usual work-up yielded product as a colourless oil; IR (neat) 3080, 887, 872, 805 (H−C=), 1734 (C=O), 1580, 1110 (C−Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.68 (d, J = 2.8 Hz, 2 H, H-4′), 7.27 (d, J = 2.8 Hz, 2 H, H-6′), 4.64 (t, J = 7.2 Hz, 1 H, H-1), 3.91 (s, 6 H, CO_2CH_3), 3.70 (s, 6 H, OCH_3), 1.92 (m, 2 H, H-2), 0.93 (t, J = 7.2 Hz, H-3); EIMS m/z (%) 440 (M^+, 5), 408 (M^+-CH_3OH, 12).

3.8.4. Compound **21**

IR (neat): 3067, 880, 860, 800 (H−C=), 1569 (C=O), 1240, 1187 (C−O−C), 1061 (C−Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.74 (d,

J = 3 Hz, 1 H), 7.65 (d, J = 3 Hz, 1 H), 7.41 (d, J = 2.5 Hz, 1 H), 7.36 (d, J = 2.5 Hz, 1 H), 6.07 (t, 8.0 Hz, 1 H, H-2), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.53 (s, 3 H), 3.50 (s, 3 H), 2.13 (s, 2 H, 3-H), 1.06 (t, J = 8.0 Hz, 3 H, H-4).

3.8.5. 1,1-Bis(3′-carboxy-5′-chloro-2′-hydroxyphenyl)-1-butene (**21a**)

Compound **21a** was prepared by demethylation of methoxyester **21** with boron tribromide/dimethyl sulfide complex [6]; IR (KBr) 3500–2800 (OH), 1661 (C=O), 1605 (C=C), 1100 (C–Cl), 886, 802 (H–C=) cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz): δ 11.45 (s, 1 H, OH), 11.33 (s, 1 H, OH), 7.83 (d, J = 3 Hz, 1 H), 7.77 (d, J = 2.4 Hz, 1 H), 7.48 (d, J = 2.4 Hz, 1 H), 7.47 (d, J = 3.0 Hz, 1 H), 6.15 (t, J = 7.2 Hz, 1 H, H-2), 2.10 (m, 2 H, H-3), 1.05 (t, J = 7.4 Hz, 3 H, H-4); EIMS m/z (%) 396 (M+, 18), 378 (M^+-H_2O, 45), 332 (100).

3.8.6. Compound **22**

Compound **22** was eluted from a silica gel column with hexane/ethyl acetate 6 : 1. IR (neat): 3068, 880, 863, 800 (H–C=), 1732 (C=O), 1573 (C=C), 1251, 1180 (C–O–C), 1096 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.75 (d, J = 2.5 Hz, 1 H), 7.65 (d, J = 2.5 Hz, 1 H), 7.41 (d, J = 3 Hz, 1 H), 7.36 (d, J = 3 Hz, 1 H), 6.09 (t, J = 7 Hz, 1 H, H = 2), (3.89 (s, 3 H), 3.88 (s, 3 H), 3.52 (s, 3 H), 3.50 (s, 3 H), 2.11 (m, 2 H, H-3), 1.49 (m, 2 H, H-3), 0.94 (t, J = 7.5 Hz, 3 H, H-5). EIMS m/z (%) 466 (M^+, 3), 403 (10), 152 (63).

3.8.7. Compound **23**

IR (neat): 3064, 883, 863, 800 (H–C=), 1733 (C=O), 1572 (C=C), 1247, 1189, 1096 (C–Cl), (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.74 (d, J = 2 Hz, 1 H), 7.65 (d, J = 2 Hz, 1 H), 7.41 (d, J = 2 Hz, 1 H), 7.35 (d, J = 2 Hz, 1 H), 6.09 (t, J = 7 Hz, 1 H, H-2), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.52 (s, 3 H), 3.50 (s, 3 H), 2.12 (m, 2 H, H-3), 1.44 (m, 2 H, H-4), 1.34 (m, 2 H, H-5), 0.89 (t, J = 7 Hz, 3 H, H-6); EIMS m/z (%) 481 (M^+, 10), 441 (M^+-OCH_3, 30), 418 (M^+-2 × OCH_3, 16).

3.8.8. Compound **24**

IR (neat): 3067, 880, 867, 800 (H–C=), 1727 (C=O), 1567 (C=C), 1256 (C–O–C), 1096 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.75 (d, J = 2.4 Hz, 1 H), 7.65 (d, J = 3 Hz, 1 H), 7.41 (d, J = 3 Hz, 1 H), 7.35 (d, J = 2.4 Hz, 1 H), 6.09 (t, J = 7.4 Hz, 1 H, H-2), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.52 (s, 3 H), 3.50 (s, 3 H), 2.11 (m, 2 H), 1.46 (m, 2 H), 1.30 (m, 4 H), 0.88 (t, J = 6.8 Hz, 3 H); EIMS m/z (%) 494 (M^+, 4), 462 (M^+-CH_3OH, 14), 431 (M^+-CH_3OH, $-OCH_3$, 7).

3.8.9. Compound **25**

Compounds **25** was eluted with *n*-hexane/ethyl acetate 12 : 1; IR (neat): 3065, 880, 864, 800 (H–C=), 1732 (C=O), 1240 (C–O–C), 1093 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.74 (d, J = 2.4 Hz, 1 H), 7.65 (d, J = 3 Hz, 1 H), 7.41 (d, J = 3 Hz, 1 H), 7.35 (d, J = 2.4 Hz, 1 H), 6.09 (t, J = 7.4 Hz, 1 H), 3.88 (s, 6 H), 3.88 (s, 6 H), 3.52 (s, 3 H), 3.50 (s, 3 H), 2.11 (m, 2 H), 1.45 (m, 2 H), 1.25 (m, 14 H), 0.88 (t, J = 6.8 Hz, 3 H).

3.8.10. Compound **26**

IR (neat): 3067, 880, 863, 800 (H–C=), 1733 (C=O), 1223, 1181 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.74 (d, J = 2.7 Hz, 1 H), 7.65 (d, J = 2.8 Hz, 1 H), 7.41 (d, J = 2.8 Hz, 1 H), 7.35 (d, J = 2.7 Hz, 1 H), 6.09 (t, J = 7.5 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.52 (s, 3 H), 3.49 (s, 3 H), 2.10 (m, 2 H), 1.41 (m, 2 H), 1.25 (m, 20 H), 0.88 (t, J = 6.2 Hz, 3 H).

3.8.11. Compound **27**

IR (neat): 3000, 882, 864, 800 (H–C=), 1713 (C=O), 1573 (C=C), 1247 (C–O–C), 1095 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.74 (d, J = 3 Hz, 1 H), 7.60 (d, J = 3 HZ, 1 H), 7.41 (d, J = 3 Hz, 1 H), 7.35 (d, J = 3 Hz, 1 H), 6.09 (t, J = 7 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.52 (s, 3 H), 3.49 (s, 3 H), 2.10 (m, 2 H), 1.41 (m, 2 H), 1.25 (m, 20 H), 0.88 (t, J = 6.2 Hz, 3 H).

3.9. 1,1-Bis(3′-carbomethoxy-5′-chloro-4′-methoxyphenyl)-1-alkenes **28–29**

3.9.1. 1,1-Bis(3′-carbomethoxy-5′-chloro-4′-methoxyphenyl)-1-n-pentene (**28**)

Compound **28** was prepared by Wittig reaction of 3,3′-dicarbomethoxy-5,5′-dichloro-4,4′-dimethoxybenzophenone [2] with *n*-butyltriphenylphosphonium bromide as described for alkene **22**.
IR (neat): 3049, 887, 802 (H–C=), 1735 (C=O), 1252 (C–O–C), 1095 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.50 (d, J = 2.6 Hz, 1 H), 7.48 (d, J = 2.2 Hz, 1 H), 7.32 (d, J = 2.2 Hz, 1 H), 7.30 (d, J = 2.6 Hz, 1 H), 6.07 (t, J = 7.6 Hz, 1 H), 3.40 (s, 3 H), 3.93 (s, 3 H), 3.91 (s, 3 H), 2.07 (m, 2 H), 1.48 (m, 2 H), 0.92 (t, J = 7.4 Hz, 3 H); EIMS: m/z (%) 4.66 (M^+, 52), 431 (M^+-Cl, 16), 407 (M^+-CO_2CH_3, 40), 59 (100).

3.9.2. 1,1-Bis(3′carbomethoxy-5′-chloro-4′-methoxyphenyl)-1-n-dodecene (**29**)

IR (KBr): 3050, 886, 838, 804 (H–C=), 1734 (C=O), 1595 (C=C), 1250 (C–O–C), 1091 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.49 (d, J = 2.6 Hz, 1 H), 7.48 (d, J = 2.2 Hz, 1 H), 7.32 (d, J = 2.2 Hz, 1 H), 7.30 (d, J = 2.6 Hz, 1 H), 6.07 (t, J = 7.4 Hz, 1 H), 4.00 (s, 3 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 2.09 (m, 2 H), 1.44 (m, 2 H), 1.25 (m, 14 H), 0.88 (t, J = 6.2 Hz, 3 H); EIMS: m/z (%) 564 (M^+, 41), 529 (M^+-Cl, 7), 505 (M^+-CO_2CH_3, 13), 424 (24).

3.10. 1,1-Bis(4′-halophenyl)-l-alkenes **30–32**

3.10.1. 1,1-Bis(4′-chlorophenyl)-1-dodecene (**30**)

IR (neat): 3080, 3029, 831 (H–C=), 1591, 1493, (C=C), 1091 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.35 (d, J = 8.5; 2.5 Hz, 2 H), 7.22 (dt, J = 8.5; 2.5 Hz, 2 H), 7.11 (dt, J = 8.5; 2.5 Hz, 2 H), 7.08 (dt, J = 8.5; 2.5 Hz, 2 H), 6.06 (t, J = 7.5 Hz, 1 H), 2.07 (m, 2 H), 1.40 (m, 2 H), 1.23 (m, 14 H), 0.88 (t, 7 Hz, 3 H); EIMS: m/z (%) 388 (M^+, 29), 353 (M^+-Cl, 18), 261 (M^+-C_9H_{19}, 42), 213 (5), 178 (10), 149 (23), 125 (25).

3.10.2. 1,1-Bis(4′-chlorophenyl)-1-n-pentene (**31**)

IR (neat): 3027, 827 (HC=), 1591, 1486 (C=C), 1086 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.26 (m, 8 H), 6.07 (t, J = 7.4 Hz, 1 H), 2.06 (m, 2 H, H-3), 1.45 (m, 2 H), 0.89 (t, J = 7.4 Hz, 3 H); EIMS: m/z (%) 290 (M^+, 25), 261 (65), 255 (40), 226 (48), 191 (59), 149 (100).

3.10.3. 1,1-Bis(4′-fluorophenyl)-1-n-dodecene (**32**)

IR (neat): 3040, 840, 800 (H–C=), 1604, 1509 (C=C), 1235 (C–F), 1153 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.13 (m, 4 H), 7.05 (tt, J = 9; 2.5 Hz, 2 H), 6.94 (tt, J = 9; 2 Hz, 2 H), 6.00 (t, J = 7.5 Hz, 1 H), 2.07 (m, 2 H), 1.40 (m, 2 H), 1.24 (m, 14 H), 0.88 (t, J = 7 Hz, 3 H); EIMS: m/z (%) 356 (M^+, 32), 229 (100), 261 (67), 203 (21), 133 (34).

3.11. Antimicrobial testing

The antimicrobial activities of the synthesized compounds were assayed by the agar plate dilution method [12]. Test compounds were applied at specific concentrations to a nutrient agar medium on Petri plates where tested bacterial strains were next seeded. After incubation at 25–27 °C for 48 h the minimal inhibitory concentrations (MIC) were determined. Stock solutions of the tested compounds were prepared in acetone. All experiments were performed in triplicate.

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