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Synthesis and anti-inflammatory activity of 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid and its ester derivatives

Francesco Epifano,[a,*] Salvatore Genovese,[b] Silvio Sosa,[c] Aurelia Tubaro[c] and Massimo Curini[b]

[a]*Dipartimento di Scienze del Farmaco, Via dei Vestini 31, Università "G. D'Annunzio", Chieti-Pescara 66013 Chieti Scalo (CH), Italy*
[b]*Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica, Università degli Studi di Perugia, Via del Liceo, 06123 Perugia, Italy*
[c]*Department of Materials and Natural Resources, University of Trieste, Via A. Valerio 6, 34127 Trieste, Italy*

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Abstract—Different esters of 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid (**1**), an anti-inflammatory principle of *Acronychia baueri* Schott (Rutaceae), were synthesized. Their topical anti-inflammatory activity was evaluated using the Croton oil ear test in mice as a model of acute inflammation. The activity of the paracetamol, guaiacol and hydroquinone esters of (**1**) was higher than that of the parent compound, being similar to that exerted by indomethacin, used as reference drug.
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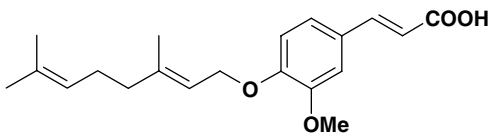
3-(4′-Geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid (**1**) is a secondary metabolite biosynthetically related to ferulic acid in which a geranyl chain is attached to the phenolic group. It has been isolated in 1966 from the bark of *Acronychia baueri* Schott, an Australian small plant belonging to the family of Rutaceae.[1] Although known for four decades, only in the last 5 years this natural compound showed valuable pharmacological properties that have been recently reviewed.[2] In particular, the ethyl ester of (**1**) showed valuable tongue and colon cancer chemopreventive and anti-inflammatory effects, the latter consisting in suppressing inducible nitric oxide synthase and the cyclooxygenase-2 promoter activity.[2]



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Since inflammation is a universal and physiological response closely related to the process of carcinogenesis, the evaluation of topical anti-inflammatory properties of novel natural and semi-synthetic derivatives of (**1**) is a field of current and growing interest, in the search of alternatives of steroids. Continuing our research aimed to better define the pharmacological profile of 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid (**1**) and its derivatives, we evaluated the topical anti-inflammatory activity of compound (**1**) and of a series of its semisynthetic esters with alcohols or phenols, already known to possess in vivo anti-inflammatory actions or related in vitro effects, such as umbelliferone (**2**),[3] 2-hydroxynaphthoquinone (**3**) (also known as lawsone,[4]) paracetamol (**4**), salicylic acid (**5**),[5] ferulic acid (**6**),[6] vanillic acid (**7**),[7] guaiacol (**8**),[8] caffeic acid (**9**),[9] hydroquinone (**10**),[10] anthraflavic acid (**11**)[11] and naringenin (**12**).[12] These esters were drawn in such a structure in order to obtain a synergism of anti-inflammatory action, once the two portions of the ester would be cleaved by exo- or endocellular esterases.

3-(4′-Geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid was synthesized in 98% yield as already reported.[13] Esters of (**1**) were synthesized in two steps by conversion of the acid into the corresponding acyl chloride by

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* Corresponding author. E-mail: fepifano@unich.it

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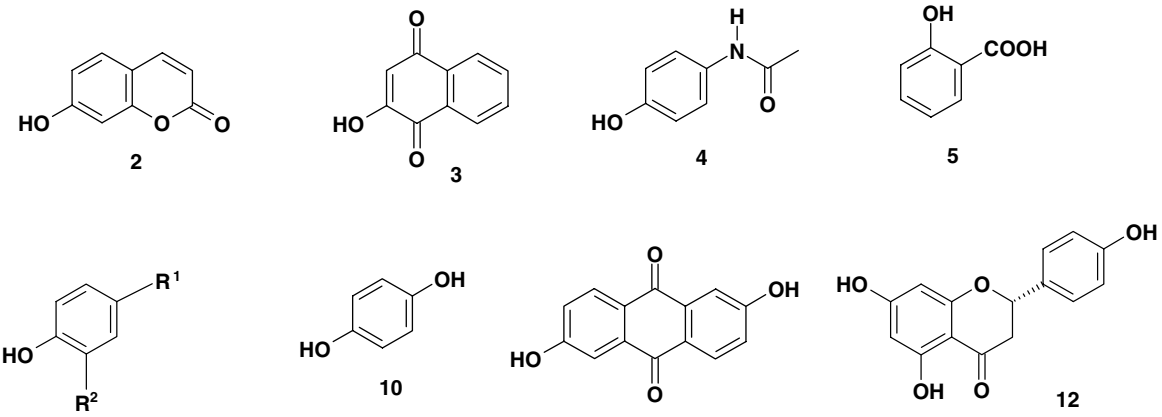


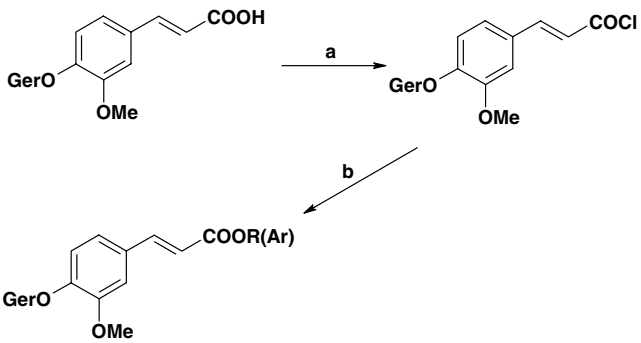
6 R^1 = -CH=CH-COOH; R^2 = -OMe
7 R^1 = -COOH; R^2 = -OMe
8 R^1 = -H; R^2 = -OMe
9 R^1 = -CH=CH-COOH; R^2 = -OH

reaction with oxalyl chloride in dry diethyl ether at rt, followed by its reaction with the alcohol or phenol and triethylamine in dry diethyl ether at rt (Scheme 1).[14]

Yields of ester derivatives are reported in Table 1.

Crucial for the success of this synthetic scheme is the reaction time to convert acid (**1**) into the corresponding chloride that had to be rigorously of 5 min, while, for longer reaction times, the acyl chloride went rapidly through decomposition. Moreover, each attempt to synthesize esters by direct condensation of the acid with alcohols or phenol in the presence of different reagents, like dicyclohexyl carbodiimide or 1,1-carbonyl diimidazole, was unsuccessful.

The topical anti-inflammatory activity of compound (**1**) and its esters was evaluated as inhibition of the Croton oil-induced ear oedema in mice.[15] The main irritant principle of Croton oil is 12-*O*-tetradecanoylphorbol-13-acetate (TPA), which induces an acute inflammatory response after single skin application. This in vivo inflammatory model possesses the advantage of using very small amounts of pure compounds under test, being particularly suitable in the biological screening



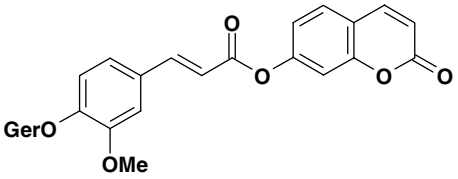
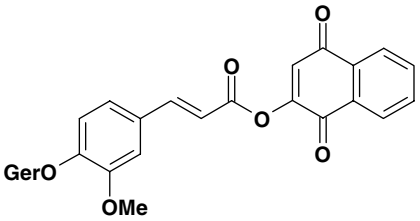
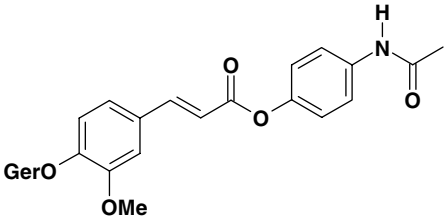
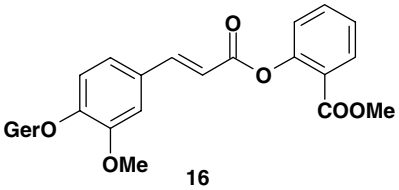
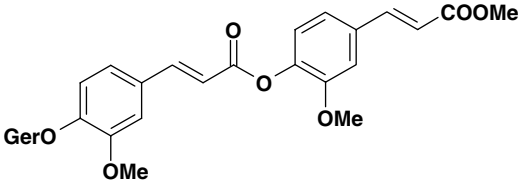
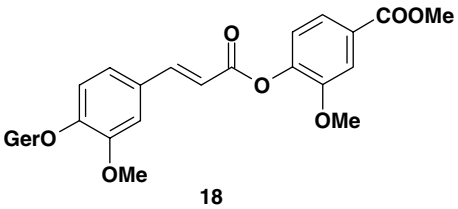
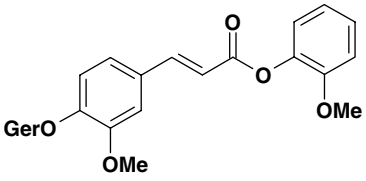
Scheme 1. Reagents and conditions: (a) $(COCl)_2$, dry Et_2O, rt 5 min; (b) ROH (ArOH), Et_3N, dry Et_2O, rt 40 min.

of natural and semi-synthetic compounds, often available only in limited amounts during their isolation or semisynthesis.

Male CD-1 mice (28–32 g, Harlan Italy, Udine, Italy) were anaesthetised with ketamine hydrochloride (145 mg/kg, intraperitoneally; Virbac, Milan, Italy). Inflammation was induced on the right ear (surface: about 1 cm^2) by application of 80 μg of Croton oil (Sigma Chemical Co., St. Louis, USA) dissolved in acetone. Control mice received only the irritant solution, whereas the others received both the irritant and the compounds under test dissolved in acetone. Six hours later, mice were sacrificed and a plug (6 mm ∅) was excised from both the treated and untreated ears to quantify oedema as weight difference between the two plugs. The anti-inflammatory activity was expressed as percent of oedema reduction in mice treated with the compounds under test with regard to control mice. Oedema values, expressed as means ± standard error of the mean, were analysed by one-way analysis of variance by Dunnett's test for multiple comparison of unpaired data. A probability level lower than 0.05 was considered as significant. Experiments complied with the Italian D.L. n. 116 of January 1992 and associated guidelines in the European Communities Council Directive of 24 November 1986.

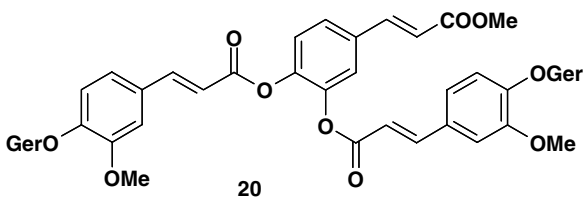
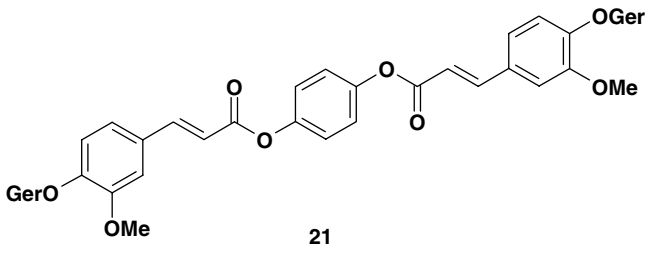
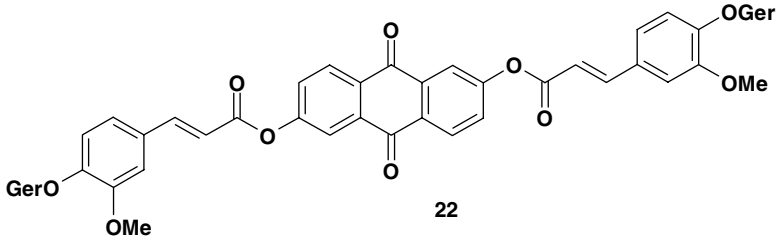
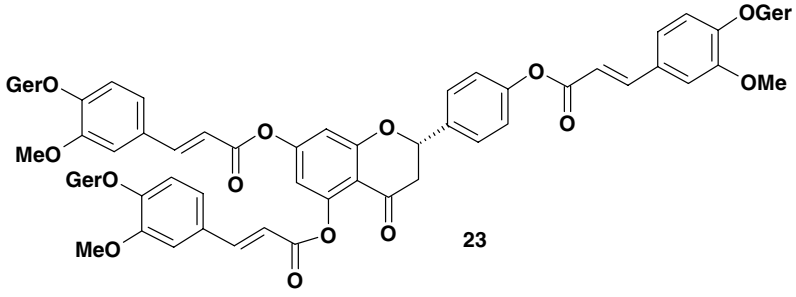
The results on the anti-inflammatory activity of compounds (**1**)–(**23**), administered at the dose of 0.3 μmol/cm^2, are reported in Table 2, in comparison to that of the same dose of the nonsteroidal anti-inflammatory drug indomethacin, used as a reference. The natural precursor 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid (**1**) induced 41% oedema inhibition, being slightly less active than indomethacin, which reduced the oedematous response by 62% at the same dose level (0.3 μmol/cm^2). It is noteworthy that, at 0.3 μmol/cm^2, the activity of (**1**) is higher than that of the well-known nonsteroidal anti-inflammatory drug

Table 1. Synthesis of ester derivatives of acid **1**

Substrate	Product	Yield[a] (%)
2	 **13**	65
3	 **14**	95
4	 **15**	90
Methyl salicylate	 **16**	81
Methyl ferulate	 **17**	63
Methyl vanillate	 **18**	80
8	 **19**	87

(*continued on next page*)

Table 1 (*continued*)

Substrate	Product	Yield[a] (%)
9	 **20**	36
10	 **21**	69
11	 **22**	44
12	 **23**	31

[a] Yields of pure isolated product fully characterized by IR, GC-MS, ^{1}H NMR and ^{13}C NMR.

paracetamol (**4**) (41% and no significant oedema reduction, respectively). Among the alcohol precursors of esters (**2**)–(**12**), only compounds (**2**)–(**7**), (**11**) and (**12**) provoked significant inhibition of oedema, which ranged from 13% to 43%, while compounds (**4**), (**8**), (**10**) and (**12**) were almost inactive in our in vivo model. Considering the semisynthetic esters, all the compounds induced a significant oedema reduction, which ranged from 29% to 57%. In particular, esters (**15**), (**19**) and (**21**), whose alcoholic portion is represented by paracetamol (**4**), guaiacol (**8**) or hydroquinone (**10**), showed an effect (49–57% oedema inhibition) significantly higher than that of the parent acid (**1**) and comparable to that of indomethacin, even though their phenol precursors (**4**), (**8**) and (**10**) were inactive, at the administered dose. The activity of the other esters was not significantly different from that of the parent acid (**1**), except that of ester (**18**), which was significantly lower (29% oedema inhibition). Nevertheless, the anti-inflammatory effect of the semisynthetic esters was slightly higher than that of the relevant alcohol precursors.

From the data reported herein it could be concluded that esterification of 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid (**1**) with the phenol derivatives paracetamol [ester (**15**)], guaiacol [ester (**19**)] or hydroquinone [ester (**21**)] slightly increases its topical anti-inflammatory effect to a level comparable to that of the nonsteroidal anti-inflammatory drug indomethacin (Fig. 1). In contrast, the anti-inflammatory activity of (**1**) is not affected by its esterification with the phenol derivative salicylic acid [ester (**16**)] or is significantly reduced by vanillic acid esterification [ester (**18**)]. Furthermore, no influence on the topical anti-inflammatory activity of (**1**) is determined by its esterification with the phenyl propanes ferulic and caffeic acids [esters (**17**) and (**20**)] as well as with the flavonoid naringenin [ester (**23**)] or the anthraquinone derivative anthraflavic acid [ester (**22**)]. It is noteworthy that the esterification of a well-established nonsteroidal anti-inflammatory drug such paracetamol, inactive at the topically administered dose, exerts an antioedematous effect similar to that of indomethacin.

Table 2. Anti-inflammatory activity of compound **1** derivatives and of their precursors (administered dose: 0.3 μmol/cm^2)

Substance	N^{**}. an.	Oedema (mg) mean ± SE	% Reduction
Controls	30	6.9 ± 0.3	—
Compound **1**	30	4.1 ± 0.2*	41
Compound **2**	10	5.3 ± 0.4*	23
Compound **13**	10	4.3 ± 0.6*	38
Compound **3**	10	5.3 ± 0.5*	23
Compound **14**	10	3.9 ± 0.3*	43
Compound **4**	10	6.0 ± 0.4	13
Compound **15**	10	3.4 ± 0.4*,**	51
Compound **5**	10	6.0 ± 0.2*	13
Compound **16**	10	4.0 ± 0.4*	42
Compound **6**	10	5.8 ± 0.2*	16
Compound **17**	10	3.9 ± 0.3*	43
Compound **7**	10	5.5 ± 0.3*	20
Compound **18**	10	4.9 ± 0.3*,**	29
Compound **8**	10	6.2 ± 0.4	10
Compound **19**	10	3.5 ± 0.3*,**	49
Compound **9**	10	6.5 ± 0.5	6
Compound **20**	10	4.3 ± 0.2*	38
Compound **10**	10	6.6 ± 0.4	4
Compound **21**	10	3.0 ± 0.3*,**	57
Compound **11**	10	5.4 ± 0.5*	22
Compound **22**	10	3.9 ± 0.5*	43
Compound **12**	10	3.9 ± 0.3*	43
Compound **23**	10	3.4 ± 0.3*	51
Indomethacin	10	2.6 ± 0.2*	62

* $p < 0.05$ at the analysis of variance, as compared with controls.
** $p < 0.05$ at the analysis of variance, as compared with compound **1**.

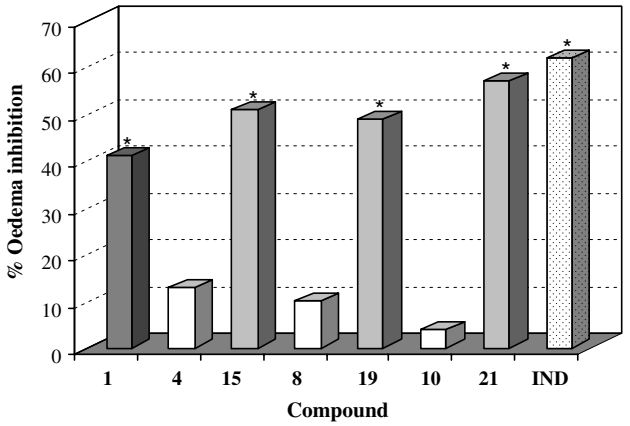


Figure 1. Improvement of the topical anti-inflammatory activity of (**1**) (0.3 μmol/cm^2) by its esterification with paracetamol [(**4**) and (**15**)], guaiacol [(**8**) and (**19**)] or hydroquinone [(**10**) and (**21**)]; IND, indomethacin (*$p < 0.05$ at the analysis of variance, as compared with controls).

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13. Curini, M.; Epifano, F.; Genovese, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5049.
14. *Experimental: Synthesis of esters of 3-(4′-geranyloxy-3′-methoxyphenyl)-2-trans propenoic acid. General procedure*. To a solution of 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid (N) (0.55 mmol) in anhydrous Et_2O (2.5 mL) oxalyl chloride (1.11 mmol) was added and the resulting solution was stirred under N_2 for 5 min at room temperature. The solvent was evaporated under vacuum, the resulting syrup was dissolved in anhydrous Et_2O (3 mL) and to this solution was added dropwise over a period of 30 min a solution of phenol derivative (0.48 mmol) and Et_3N (1.2 mmol) in anhydrous Et_2O (3 mL). The resulting mixture was stirred for 10 min and the white precipitate formed was filtered under vacuum and washed twice with Et_2O (5 mL). The filtrate was then extracted twice with a 1% solution of citric acid (10 mL), the organic phase washed twice with a 1% solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum to yield the desired ester.
Umbelliferyl (2E)-3-(4-{[(2E)-2,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoate (**13**): White solid; yield 65%; mp: 186–188 °C; IR (KBr): 1687, 1684 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$ δ): 1.62 (s, 3H), 1.69 (s, 3H), 1.75 (s, 3H), 2.09–2.20 (m, 4H), 3.95 (s, 3H), 4.69–4.72 (m, 2H), 4.97–5.13 (m, 2H), 5.47–5.56 (m, 1H), 6.48 (d, 1H, J = 9.9 Hz), 6.74 (d, 1H, J = 12.4 Hz), 6.92 (d, 1H, J = 8.1 Hz) 7.15–7.29 (m, 4H), 7.54 (d, 1H, J = 8.1 Hz), 7.73 (d, 1H, J = 9.9 Hz), 7.86 (d, 1H, J = 12.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$ δ) 16.5, 17.6, 25.4, 26.0, 39.4, 55.9, 65.9, 110.1, 111.6, 114.3, 115.3, 115.9, 116.7, 118.0, 119.4, 121.9, 123.6, 128.4, 130.1, 131.8, 141.6, 144.1, 144.4, 146.2, 150.7, 156.1, 158.0, 161.7, 165.3; Anal. Calcd for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37; O, 20.23. Found: C, 73.39, H, 6.34; O, 20.24.
1,4-Dioxo-1,4-dihydronaphthalen-2-yl (2E)-3-(4-{[(2E)-2,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoate (**14**): Yellowish solid; yield 95%; mp: 208–209 °C; IR (KBr): 1705, 1695, 1685 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$ δ): 1.62 (s, 3H), 1.69 (s, 3H), 1.73 (s, 3H), 2.08–2.21 (m, 4H), 3.97 (s, 3H), 4.71–4.73 (m, 2H), 4.98–5.11 (m, 2H), 5.51– 5.59 (m, 1H), 6.67 (d, 1H, J = 12.3 Hz) 6.94–8.17 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$ δ) 16.2, 17.4, 25.1, 25.6, 26.2, 39.5, 55.9, 65.9, 107.5, 111.6, 114.4, 119.8, 121.9, 123.9, 127.1, 127.3, 129.6, 131.2, 131.3, 132.8, 133.5, 134.1, 134.9, 141.6, 144.3, 147.4,

146.9, 150.7, 152.2, 161.8, 176.7, 183.8; Anal. Calcd for $C_{30}H_{30}O_6$: C, 74.06; H, 6.21; O, 19.73. Found: C, 74.03, H, 6.19; O, 19.70.

*4-(Acetylamino)phenyl (2E)-3-(4-{[(2E)-2,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoate (***15***)*: White solid; yield 90%; mp: 223–224 °C; IR (KBr): 1685, 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ δ): 1.59 (s, 3H), 1.66 (s, 3H), 1.74 (s, 3H), 2.09–2.23 (m, 4H), 1.59 (s, 3H), 2.18 (s, 3H), 3.92 (s, 3H), 4.66–4.69 (m, 2H), 4.99–5.12 (m, 2H), 5.48–5.57 (m, 1H), 6.47 (d, 1H, J = 12.8 Hz), 6.88 (d, 1H, J = 6.2 Hz) 7.11–7.27 (m, 4H), 7.54 (d, 1H, J = 6.2 Hz), 7.80 (d, 2H, J = 12.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$ δ) 16.1, 17.5, 25.1, 25.6, 26.2, 39.4, 55.9, 65.8, 111.8, 114.1, 116.7, 119.8, 121.9, 122.4, 122.6, 123.8, 128.4, 131.3, 134.7, 141.6, 144.4, 146.3, 146.9, 150.8, 165.7, 167.6; Anal. Calcd for $C_{28}H_{33}O_5$: C, 72.55; H, 7.18; O, 17.26. Found: C, 72.57, H, 7.17; O, 17.24.

*Methyl 2-{[(2E)-3-(4-{[(2E)-2,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoyl]oxy}benzoate (***16***)*: Yellow solid; yield 81%; mp: 182–183 °C; IR (KBr): 1698, 1695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ δ): 1.67 (s, 3H), 1.69 (s, 3H), 1.75 (s, 3H), 2.10–2.18 (m, 4H), 3.98 (s, 3H), 3.99 (s, 3H), 4.68–4.72 (m, 2H), 5.06–5.09 (m, 1H), 5.50–5.53 (m, 1H), 6.54–8.08 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$ δ) 16.4, 17.7, 25.7, 26.6, 27.5, 39.6, 51.4, 56.1, 67.9, 111.7, 114.2, 116.7, 119.4, 121.0, 121.9, 123.3, 123.9, 127.8, 128.6, 131.9, 132.1, 133.2, 135.2, 144.8, 146.2, 150.9, 155.0, 168.2, 168.5; Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94; O, 20.66. Found: C, 72.40, H, 6.93; O, 20.68.

*2-Methoxy-4-[(1E)-3-methoxy-3-oxoprop-1-enyl]phenyl (2E)-3-(4-{[(2E)-2,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoate (***17***)*: Yellowish solid; yield 63%; mp: 159–161 °C; IR (KBr): 1695, 1692 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ δ): 1.62 (s, 3H), 1.69 (s, 3H), 1.75 (s, 3H), 2.11–2.20 (m, 4H), 3.92 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.68–4.71 (m, 2H), 5.09–5.11 (m, 1H), 5.49–5.53 (m, 1H), 6.51–7.89 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$ δ) 16.2, 17.6, 25.8, 26.9, 27.2, 39.4, 55.7, 55.9, 67.9, 111.7, 112.9, 114.0, 117.7, 118.4, 121.5, 123.6, 123.8, 123.9, 127.8, 128.5, 131.5, 132.1, 132.6, 139.2, 144.2, 144.7, 146.4, 150.5, 152.9, 164.9, 169.8; Anal. Calcd for $C_{31}H_{36}O_7$: C, 71.52; H, 6.97; O, 21.51. Found: C, 71.50, H, 6.98; O, 21.50.

*Methyl 4-{[(2E)-3-(4-{[(2E)-2,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoyl]oxy}-3-methoxybenzoate (***18***)*: Yellowish solid; yield 80%; mp: 162–163 °C; IR (KBr): 1698, 1695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3\delta$): 1.62 (s, 3H), 1.69 (s, 3H), 1.74 (s, 3H), 2.11–2.19 (m, 4H), 3.94 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 4.68–4.71 (m, 2H), 5.06–5.11 (m, 1H), 5.49–5.53 (m, 1H), 6.51–7.89 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$ δ) 16.5, 17.6, 25.6, 26.9, 27.3, 39.6, 51.2, 55.9, 56.0, 67.9, 111.7, 112.8, 114.0, 117.7, 121.9, 122.3, 123.6, 126.0, 127.7, 128.8, 131.5, 132.1, 144.8, 146.0, 146.2, 149.2, 150.4, 164.8, 166.2; Anal. Calcd for $C_{29}H_{34}O_7$: C, 70.43; H, 6.93; O, 22.64. Found: C, 70.41, H, 6.92; O, 22.65.

*2-Methoxyphenyl (2E)-3-(4-{[(2E)-3,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoate (***19***)*: Orange solid; yield 87%; mp: 145–147 °C; IR (KBr): 1696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ δ): 1.62 (s, 3H), 1.69 (s, 3H), 1.72 (s, 3H), 2.11–2.20 (m, 4H), 3.91 (s, 3H), 3.94 (s, 3H), 4.68–4.71 (m, 2H), 5.07–5.12 (m, 1H), 5.50–5.53 (m, 1H), 6.53–7.86 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$ δ) 16.2, 17.5, 25.4, 26.2, 39.4, 55.8, 55.9, 65.9, 111.6, 114.4, 114.8, 117.7, 119.9, 121.9, 123.8, 123.9, 125.0, 126.6, 128.8, 131.3, 141.7, 142.5, 144.4, 146.2, 150.8, 151.2, 165.0; Anal. Calcd for $C_{27}H_{32}O_5$: C, 74.29; H, 7.39; O, 18.33. Found: C, 74.28, H, 7.37; O, 18.35.

*Methyl (2E)-3-(3,4-bis{[(2E)-3-(4-{[(2E)-3,7-dimethylocta-2,6- dienyl]oxy}-3-methoxyphenyl)prop-2-enoyl]oxy}phenyl)prop-2-enoate (***20***)*: Yellowish solid; yield 36%; mp: 208–210 °C; IR (KBr): 1699, 1695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ δ): 1.64 (s, 6H), 1.68 (s, 6H), 1.72 (s, 6H), 2.11–2.20 (m, 8H), 3.97 (s, 6H), 3.99 (s, 3H), 4.65–4.72 (m, 4H), 5.05–5.11 (m, 2H), 5.50–5.56 (m, 2H), 6.40–7.82 (m, 16H); ^{13}C NMR (50 MHz, $CDCl_3$ δ) 16.5, 17.9, 25.4, 26.0, 39.3, 51.4, 55.9, 65.9, 111.6, 114.3, 116.7, 117.8, 119.4, 121.9, 122.0, 123.7, 126.6, 128.5, 129.5, 131.8, 134.8, 136.5, 141.3, 144.4, 144.6, 146.1, 146.4, 150.7, 164.8, 164.9, 168.2; Anal. Calcd for $C_{50}H_{58}O_{10}$: C, 73.33; H, 7.14; O, 19.54. Found: C, 73.35, H, 7.11; O, 19.56.

*4-{[(2E)-3-(4-{[(2E)-3,7-Dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoyl]oxy}phenyl (2E)-3-(4-{[(2E)-3,7-dimethylocta-2,6-dienyl]oxy}-3-ethylphenyl)prop-2-enoate (***21***)*: Bright yellow solid; yield 69%; mp: 232–233 (d) °C; IR (KBr): 1693 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ δ): 1.61 (s, 6H), 1.67 (s, 6H), 1.70 (s, 6H), 2.09–2.17 (m, 8H), 3.93 (s, 6H), 4.67–4.72 (m, 4H), 5.08–5.12 (m, 4H), 5.52–5.56 (m, 2H), 6.53–7.67 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$ δ) 16.1, 17.4, 25.7, 26.3, 39.4, 55.8, 65.7, 111.8, 114.3, 116.8, 119.7, 119.8, 121.8, 123.8, 128.5, 131.5, 141.4, 144.2, 145.4, 146.2, 150.9, 165.8; Anal. Calcd for $C_{46}H_{54}O_9$: C, 77.02; H, 7.70; O, 15.28. Found: C, 77.01, H, 7.68; O,15.30.

*6-{[(2E)-3-(4-{[(2E)-2,7-Dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)-1-methyleneprop-2-enyl]oxy}-9,10-dimethylene-9,10- dihydroanthracen-2-yl (2E)-3-(4-{[(2E)-2,7-dimethylocta-2,6-dienyl]oxy}-3- methoxyphenyl)prop-2-enoate (***22***)*: Yellowish solid; yield 44%; mp: 252–255 (d) °C; IR (KBr): 1695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ δ): 1.63 (s, 6H), 1.67 (s, 6H), 1.70 (s, 6H), 2.07–2.20 (m, 8H), 3.97 (s, 6H), 4.67–4.71 (m, 4H), 5.08–5.11 (m, 2H), 5.51–5.54 (m, 2H), 6.50–8.43 (m, 16H); ^{13}C NMR (50 MHz, $CDCl_3$ δ) 16.2, 17.6, 25.6, 26.1, 39.4, 55.9, 65.8, 111.6, 114.7, 116.7, 119.8, 120.3, 121.9, 123.8, 127.6, 128.4, 129.2, 131.3, 132.0, 137.6, 141.8, 144.4, 146.9, 150.7, 157.0, 165.7, 182.9; Anal. Calcd for $C_{54}H_{56}O_{10}$: C, 74.98; H, 6.53; O, 18.50. Found: C, 74.95, H, 6.51; O, 18.46.

*4-(5,7-Bis{[(2E)-3-(4-{[(2E)-3,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoyl]oxy}-4-oxo-3,4-dihydro-2H-chromen-2-yl)phenyl (2E)-3-(4-{[(2E)-3,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoate (***23***)*: Yellowish solid; yield 31%; mp: 262–264 (d) °C; IR (KBr): 1695, 1693 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ δ): 1.64 (s, 9H), 1.68 (s, 9H), 1.75 (s, 9H), 2.09–2.26 (m, 14H), 3.95 (s, 9H), 4.69–4.75 (m, 6H), 5.08–5.56 (m, 7H), 6.53–7.82 (m, 20H); ^{13}C NMR (50 MHz, $CDCl_3$ δ) 16.3, 17.5, 25.6, 26.4, 39.3, 55.6, 65.9,78.5, 106.1 108.3, 111.7, 113.1, 114.5, 116.6, 116.7, 119.8, 121.6, 121.8, 123.9, 128.7, 130.0, 131.3, 135.9, 142.0, 144.4, 146.2, 150.1, 150.8, 153.5, 158.4, 165.2, 165.7, 169.3, 189.8; Anal. Calcd for $C_{75}H_{84}O_{14}$: C, 74.48; H, 7.00; O, 18.52. Found: C, 74.49, H, 7.02; O, 18.51.

15. Tubaro, A.; Dri, P.; Del Bello, G.; Zilli, C.; Della Loggia, R. *Agents Actions.* **1985**, *17*, 347.