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Original article

Syntheses, antiproliferative activity and theoretical characterization of acitretin-type retinoids with changes in the lipophilic part

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ABSTRACT

Acitretin analogs, incorporating changes in the lipophilic part, were efficiently synthesized from commercially available aromatic aldehydes or methyl ketones using the Wittig or Horner–Wadsworth–Emmons reaction. Their antiproliferative activity was evaluated against human breast MCF-7 epithelial cells. Analogs **3**, **4**, **8** and **11** exhibited strong, dose-dependent, antiproliferative activity on the tested cell line. Analog **3**, incorporating three methoxy groups in the aromatic ring, exhibited the strongest inhibitory effect at 10 μM. High-level all electron conventional ab initio and density functional theory quantum chemical calculations were performed to obtain the molecular structure, electron charge distribution and polarization properties of all compounds of interest in this work. The most active analogs were planar and were characterized by larger dipole moments than the other synthesized molecules. Another factor of importance to the analysis of the activity of these molecules is the dipole polarizability.

1. Introduction

Retinoids, a large family of natural and synthetic compounds structurally related to vitamin A, play an important role in a variety of biological functions including vision, development, reproduction and cell differentiation and have been applied successfully to the management of severe skin disorders and more recently to cancer prevention and therapy [1]. For example, the synthetic analogs of *all-trans*-retinoic acid (ATRA, **1**) 13-*cis*-retinoic acid (isotretinoin) and acitretin (**2**) (Fig. 1) are presently regarded as the drugs of choice for the treatment of several dermatological disorders. However, retinoids are toxic compounds in large doses as well as teratogenic. Retinoids exert their effects through their interaction with the nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs) which act as ligand-activated transcription regulators for specific genes [2]. ATRA, together with its 9-*cis* isomer, have been identified as the principal activators of the afore mentioned receptors. ATRA binds selectively with high affinity to RARs. ATRA homeostasis is very important in the cell as shortage or excess of it might cause malfunctioning of the retinoid-mediated signaling pathways. ATRA concentration in the cell cytoplasm is controlled by the so-called retinoid-binding proteins, two of which are the cellular retinoic acid binding proteins CRABP I and CRABP II [3]. ATRA has also high affinity for these proteins and in particular for CRABP I [3,4]. It has been proposed that this protein removes ATRA from RARs and that it might enhance the metabolism of ATRA to inactive derivatives, thus rendering ATRA unavailable to nuclear receptors [5]. On the other hand, the CRABP II-RAR complex is believed to mediate channeling of ATRA from the binding protein to its receptors and thus facilitate ATRA's ligation and potentiaton of its transcriptional activity [2].

Due to their significance in dermatology and human cancer, a huge array of ATRA analogs have been already synthesized in order to improve the therapeutic efficacy to toxicity index as well as to secure better selectivities for various therapeutic applications. These analogs involve changes in the lipophilic or the hydrophilic part or the spacer or a combination of changes in the parent compound ATRA. Changes in the lipophilic part, of relevance to the present work, are directed towards altering the steric bulk or

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influencing the torsion angle between the ring and the spacer. Acitretin in particular, a second generation monoaromatic retinoid, is the drug of choice for the systemic treatment of certain types of psoriasis [6–8]. However, acitretin is a potent teratogen and is also associated with various other, dose dependent, side effects, which can prevent use of higher, more efficacious, therapeutic doses in some patients [7]. The mechanism by which acitretin acts seems not to be through binding with the retinoid receptors (it has low affinity for RARs) but through the displacement of ATRA from CRABPs (it has high affinity for CRABPs) and therefore by increasing the ATRA occupancy of the nuclear receptors [4,9]. Acitretin shows a better biological profile than ATRA in various systems [10–12]. For example, it was recently reported that acitretin is a more potent inhibitor of RNase P activity than ATRA and this was attributed to the higher lipophilicity of the aromatic ring imposed by the methoxy group on the aromatic ring [12].

Several studies indicate that retinoids can serve as potential chemotherapeutic agents in the treatment of breast cancer. Retinoids are known to cause changes in the expression of genes in target cells. The RAR*b* gene may act as a tumor suppressor and loss of RAR*b*2 messenger RNA (mRNA) expression may be an important event in tumorigenesis. Reduced RAR*b*2 mRNA expression has been observed in a number of solid tumor cells, including lung carcinoma, squamous cell carcinoma of the head and neck, and breast cancer. RAR*b* transcription has been shown to be downregulated in breast cancer cell lines and tumors and upregulated in normal mammary epithelial cells [13]. Growth inhibition induced by ATRA in breast cancer cells has been correlated with its ability to decrease expression of cyclin D1 and D3, the activity of cdk2 and cdk4, and the expression and phosphorylation of pRb. Cdk inhibitors may also be a target of ATRA. ATRA increased also p21 levels, which were associated with decreased cdk2 activity in normal breast epithelial cells. Thus, ATRA appears to induce its antiproliferative effects predominantly by blocking the transition from G1 to S phase [14]. Bexarotene, ATRA, 9-*cis*-retinoic acid and *N*-(4-hydroxyphenyl) retinamide (4-HPR, fenretinide) possess antiproliferative and proapoptotic properties, making them a promising class of chemopreventive agents against breast cancer. 4-HPR effectively inhibits the proliferation of breast cancer cells that do not express RARs [15]. Furthermore, a novel synthetic retinoid 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (AHPN) could directly induce p21WAF1/CIP1 and cause apoptosis of breast cancer MCF-7 cells and MDA-MB-231 cells independent of p53 [16]. Acitretin has been reported to induce *in vitro* more significant apoptosis, than ATRA and tazarotene on melanoma A375 cells [17]. *In vitro* studies indicate that ATRA inhibits the growth of estrogen receptor (ER)-positive but not ER-negative human breast cancer cells. The main mechanism by which ATRA inhibits the proliferation of breast cancer cells is by inducing G1 cell cycle arrest. ER-positive breast cancer cells like MCF-7 are sensitive to the growth inhibitory effects of ATRA, while the majority of ER-negative cells are resistant. ER-positive cells respond to ATRA because they express the RAR*a* gene [18]. The antitumor activity of retinoids could be mediated by inhibition of proliferation. It has been mentioned that acitretin inhibits proliferation in a series of transformed cell lines (HL-60, SCC4, SCC15, MCF-7 and A431) [19] and glucuronide conjugates of acitretin have been studied for their antiproliferative activity in MCF-7 cells [20].

We now considered of interest to synthesize a series of acitretin analogs, suitable for structure–activity relationship studies, and study initially their potential antiproliferative activity against breast cancer MCF-7 cells. These analogs were designed to present variable electron density, lipophilicity and steric bulk in the aromatic ring as well as variable dihedral angle between the aromatic ring and the spacer. The desired changes were thought of being imposed by the use of appropriate electron donating by resonance (OMe, NMe_2) or inductively electron withdrawing (F, CF_3) groups (analogs **3**–**7**), the presence of additional aromatic rings (analogs **8** and **9**) and/or the incorporation of the C8–C9 double bond within a benzene ring as exemplified with acitretin analogs **10**–**12** (Fig. 1).

We have completed our synthetic work by adding an extensive theoretical investigation of the molecular structure and properties of all compounds involved in this study. Computational quantum chemistry methods have emerged as a powerful tool with significant contributions to chemical synthesis in recent years [21]. Important fields include the identification of new chemical species [22], pharmacological studies and medicinal chemistry [23] and the directed synthesis of molecules with specific properties for materials science applications [24]. In the present work we relied on the widely used density functional theory (DFT) B3LYP method to obtain molecular geometries. It was ensured that the determined structures represent true minima on the potential energy surface by calculating the relevant harmonic frequencies. We obtained atomic charges for all most stable molecular structures via a natural bond orbital (NBO) analysis [25]. In addition to the molecular geometries and the charge distribution, we calculated the electric dipole moment (μ), polarizability (α) and first hyperpolarizability (β). These properties are now recognized as powerful molecular descriptors for quantitative structure–property (QSPR) or structure–activity (QSAR) relationships [26]. From a physico-chemical point of view, the electric properties are of primary importance in modeling solvation properties [27,28] or in the determination of the lipophilicity [29]. In-depth discussions of the importance of the polarizability and the hyperpolarizability may be found in standard monographs [30] or comprehensive reviews [31,32]. The role of electric polarizability in chemical–biological interactions has been recently examined by Hansch et al [33]. We placed particular emphasis on the determination of the polarizability as this property is of universal importance to molecular science. It is extensively used to model intermolecular interactions [34]. It is also associated to basic molecular characteristics as the ionization

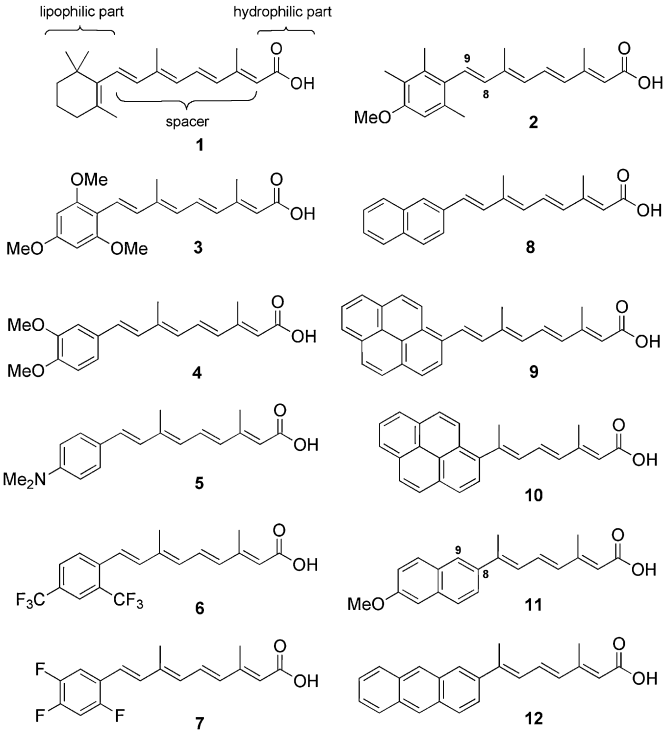
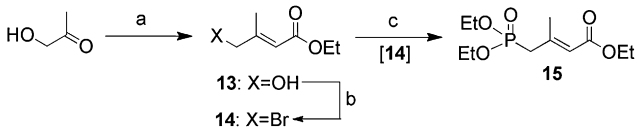


Fig. 1. Structures of retinoids referred to in the present work.



Scheme 1. *Reagents and reaction conditions*: (a) $Ph_3P{=}CHCO_2Et$, MeCN, 12 h, 82 °C, 85%; (b) CBr_4, Ph_3P, MeCN, 1h, 25 °C, 89%; (c) $(EtO)_3P$, 1 h, 120 °C, 73%.

potential [35], acidity and basicity [36], hardness and softness [37], hypersoftness [38], stiffness [39] and compressibility [40]. There is currently active interest in the theoretical determination of the electric (hyper)polarizability and the extension of the applicability of quantum chemical methods to large molecules [41–43].

2. Results and discussion

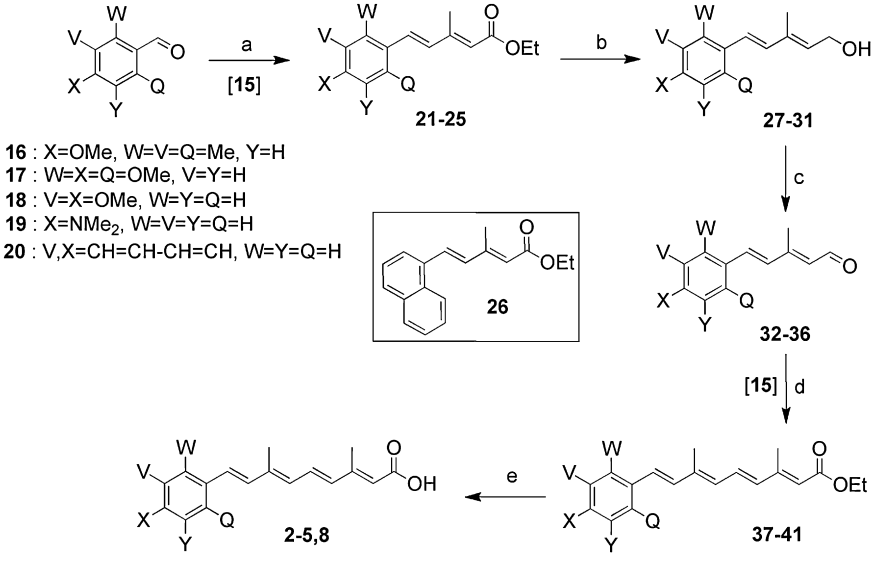
2.1. Chemistry

Various synthetic protocols have been published for the total synthesis of acitretin and analogs involving as the key-step for the assembly of the spacer at the tetraene level the Wittig reaction [10] or a Stobbe-type condensation [11]. These protocols assemble the molecule in either the $C_{10} + C_{10}$ or the $C_{13} + C_7$ or the $C_{15} + C_5$ mode. For the assembly of the tetraene chain of acitretin (**2**) and its analogs **3**–**9** we initially decided to use the alternative $C_{10} + C_5 + C_5$ strategy. This should involve the condensation of suitably substituted, commercially available, aromatic aldehydes with ethyl *E*-4-(diethylphosphono)-3-methyl-2-butenoate (**15**) (Scheme 1) through a Horner–Wadsworth–Emmons (HWE) reaction.

Phosphonate esters like **15** have been often used, in the assembly of retinoid spacers, as mixtures of their *E*- and *Z*-isomers [44]. These esters are prepared through a Michaelis–Arbusov reaction between $(EtO)_3P$ and the required allyl bromide, which in turn is obtained as a mixture of *E*- and *Z*-isomers through allylic bromination of methyl or ethyl 3-methyl-2-butenoate (senecioate) [44a,45]. In an effort to obtain configurational pure *E*-ester **15**, which might be advantageous to the synthesis of the projected retinoids, we decided to develop an alternative methodology for the preparation of 4-halo-3-methyl-2-butenoates.

This initially involved the Wittig reaction of commercially available hydroxyacetone with the stabilized phosphorane $Ph_3P{=}CHCO_2Et$. This reaction proceeded stereoselectively, leading to the isolation of pure allylic alcohol **13** in 85% yield (Scheme 1) [46]. The configuration of the double bond of alcohol **13** was determined by 2D NMR experiments (see Supplementary data). This alcohol was then converted to the corresponding *E*-chloride in 63% yield, using the system Ph_3P/CCl_4 [47]. The latter was reacted with $(EtO)_3P$ for 2.5 h at 150 °C to effect complete conversion, but unfortunately the anticipated *E*-phosphonate ester **15** was obtained in mixture with its *Z*-isomer, in the ratio 70:30 (based on the chemical shift of methylene protons at 2.69 and 3.47 ppm, for the *E* and *Z* isomers, respectively). We reasoned that replacement of the chlorine by the better leaving group bromine would allow the reaction to proceed under milder reaction conditions and thus produce pure *E*-**15**. Indeed, alcohol **13** was converted to the corresponding *E*-bromide **14** (Scheme 1) in 89% yield, using the bromination system Ph_3P/CBr_4. It is worth noting that the chemical shifts for the protons of the acid part of this compound are essentially identical to those reported for the corresponding pure methyl *E*-4-bromo-3-methyl-2-butenoate [11]. Treatment of this bromide with $(EtO)_3P$ for 1 h at 120 °C, produced exclusively isomer *E*-**15**, which was obtained pure in 73% yield by distillation under reduced pressure.

The applicability of *E*-phosphonate **15** was initially tested towards the total synthesis of acitretin (**2**) itself (Scheme 2). Accordingly, HWE condensation of 4-methoxy-2,3,6-trimethylbenzaldehyde (**16**) [11] with *E*-**15** in THF, in the presence of *n*-BuLi and DMPU [48] at −78 °C for 3 h, afforded ester **21** in 83%, as a mixture of 2*E*,4*E* and 2*Z*,4*E* isomers in the ratio of 90:10 (only the *E*,*E* isomer is drawn). To our surprise, the consequent $LiAlH_4$-mediated reduction of ester **21** led to an unacceptably low yield (47%) of the corresponding allylic alcohol **27** and we therefore decided to use alternatively AlH_3 [49] for this conversion. Indeed, reduction of **21** with AlH_3 in THF, at 0 °C for 1 h, gave the anticipated alcohol **27** (83% yield), as a mixture of 2*E*,4*E* and 2*Z*,4*E* isomers in the ratio of 90:10 (only the *E*,*E* isomer is drawn). Oxidation of alcohol **27** with activated MnO_2 in DCM, in the presence of Na_2CO_3 [50], took place at ambient temperature for 1 h and afforded aldehyde **32** in 90% yield as the mixture of geometric isomers 2*E*,4*E* *and* 2*Z*,4*E* (only the *E*,*E* isomer is drawn) in the ratio 90:10, as determined by ^1H NMR. The latter, was subjected to an HWE



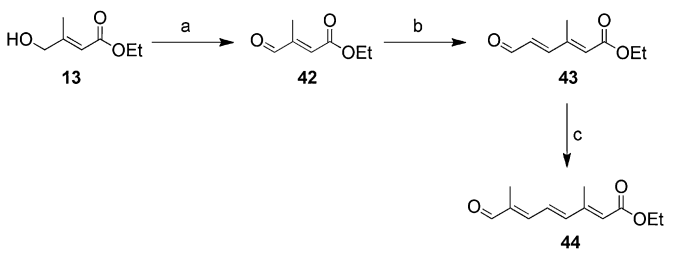
Scheme 2. *Reagents and reaction conditions*: (a) *n*-BuLi, DMPU, THF, 2–3 h, −78 °C–25 °C (**21**, 83%; **22**, 74%; **23**, 83%; **24**, 85%; **25**, 77% and **26**, 15%); (b) $LiAlH_4$, $AlCl_3$, THF, 1 h, 0 °C–25 °C (**27**, 83%; **28**, 80%; **29**, 84%; **30**, 87%; **31**, 82%); (c) MnO_2, Na_2CO_3, DCM, 1 h, 25 °C (**32**, 90%; **33**, 86%; **34**, 85%; **35**, 81%; **36**, 80%); (d) *n*-BuLi, DMPU, THF, 2–3 h, −78 °C–25 °C (**37**, 74%; **38**, 80%; **39**, 75%; **40**, 81%; **41**, 72%); (e) i) 8 M aq. NaOH, MeOH, DMSO, 1–2 h, 65 °C, ii) crystallization from EtOAc (**2**, 48%; **3**, 54%; **4**, 70%; **5**, 61%; **8**, 81%).

reaction with *E*-**15** in THF for 2 h, from −78 °C to ambient temperature, to give the desired ester **37** as a mixture of three stereoisomers (as indicated by HPLC) in 74% yield (only the *all-E* isomer is drawn). Finally, ester **37** was saponified, with an aqueous 8 M solution of NaOH in DMSO/MeOH for 2 h at 65 °C, and crystallized from EtOAc [51] to give pure acitretin (**2**) in 48% yield.

Identical methodology was employed for the preparation of acitretin analogs **3**–**5** and **8**. The syntheses were realized initially through an HWE reaction of ester *E*-**15** with the commercially available 2,4,6-trimethoxy(**17**)-, 3,4-dimethoxy(**18**)- and 4-dimethylamino(**19**)-benzaldehyde and 2-naphthaldehyde (**20**) to afford the anticipated esters **22**–**25** as mixture of isomers (only the *E,E* isomers are drawn) in 74–85% yields (Scheme 2). It is worth mentioning here that the coupling of the commercially available 2-naphthaldehyde (**20** of ca. 98% purity) with the ester *E*-**15** gave, apart from ester **25**, its unexpected regioisomer **26**. These esters (**25** and **26**) could be separated by FCC in the ratio ca. 5:1 and both had the 2*E*,4*E* configuration, as shown by ^{1}H NMR. No other double bond isomers of these compounds were observed. It should be noted that the use of NaOMe in MeOH as the base to obtain esters **21**–**25** led, in general, to lower yields and increased quantities of the undesirable isomer [45].

The thus obtained esters were subjected to reduction with AlH_3 to give the corresponding alcohols **28**–**31** in 80–87% yields as mixture of isomers. AlH_3-mediated reduction of pure **25** gave without isomerization (as shown by ^{1}H NMR) the corresponding alcohol **31** in 82% yield. MnO_2-mediated oxidation of alcohols **28**–**31** in the presence of Na_2CO_3 afforded the corresponding dienals **33**–**36** in 80–86% yield, as mixtures of isomers (only the *E,E* isomers are drawn) with the exception of alcohol **31**. These dienals were then condensed with ester *E*-**15** and gave a mixture of three geometric isomers of esters **38**–**40** and of two geometric isomers of ester **41** (seen by HPLC) in 72–81% yield (only the all-*E* isomers are drawn). Finally, these esters were saponified with an aqueous 8 M solution of NaOH in DMSO/MeOH for 1–2 h at 65 °C, followed by crystallization from EtOAc to give a*ll-trans* acids **3**–**5** and **8**, in a 54–81% yield.

On the other hand, we decided to use convergent methodologies toward the synthesis of the remaining projected analogs, which involved the condensation of appropriate phosphonium salts with suitable *all-E* unsaturated aldehydes, such as **42**–**44**, which have been extensively used in the past for the assembly of the retinoid spacer [10,52]. We envisaged an alternative methodology for their preparation which would secure the retention of the desirable *all-E* configuration. The latter would be an advantage in the total synthesis of the projected retinoids. Thus, oxidation of allylic alcohol **13** with activated MnO_2 in DCM, at ambient temperature for 1 h, resulted in *E*-aldehyde **42** (92% yield), which was further coupled with the stabilized phosphorane $Ph_3P{=}CHCHO$ (Trippett's reagent) [53b] in DCM, at ambient temperature for 14 h, to afford the *E,E*-aldehyde **43**, as the only product, in 68% yield [53a]. The latter, was subjected to another Wittig reaction, with stabilized phosphorane $Ph_3P{=}C(CH_3)CHO$ in PhMe, at 70 °C for 6 h, to give exclusively the *all-E*-aldehyde **44** in 82% yield (Scheme 3).



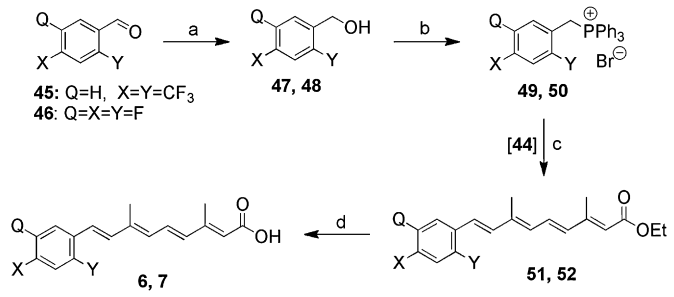
Scheme 3. *Reagents and reaction conditions*: (a) MnO_2, DCM, 1h, 25 °C, 92%; (b) $Ph_3P{=}CHCHO$, DCM, 14 h, 25 °C, 68%; (c) $Ph_3P{=}C(CH_3)CHO$, PhMe, 6 h, 70 °C, 82%.

The required primary phosphonium salts **49** and **50** were obtained in 69–77% overall yield, through $NaBH_4$-mediated reduction of the commercially available 2,4-bistrifluoromethyl(**45**)- and 2,4,5-trifluoro(**46**)-benzaldehyde in MeOH, followed by treatment of the thus obtained alcohols **47** and **48** with $Ph_3P{\cdot}HBr$ in MeCN/THF at 80 °C for 5–6 h. Condensation of **49** and **50** with the trienal **44** in DMF, using 1,2-butylene oxide as a base, at 60 °C for 4–8 h, gave a mixture of two geometric isomers (as indicated by HPLC) of esters **51** and **52** in 74–79% yield (only the *all-E* isomers are drawn). These esters were finally saponified, with an aqueous 8 M solution of NaOH in DMSO/MeOH for 2–3 h at 65 °C, and the obtained acids were crystallized from EtOAc to give a*ll-trans* acids **6** and **7** in 40–42% yield (Scheme 4).

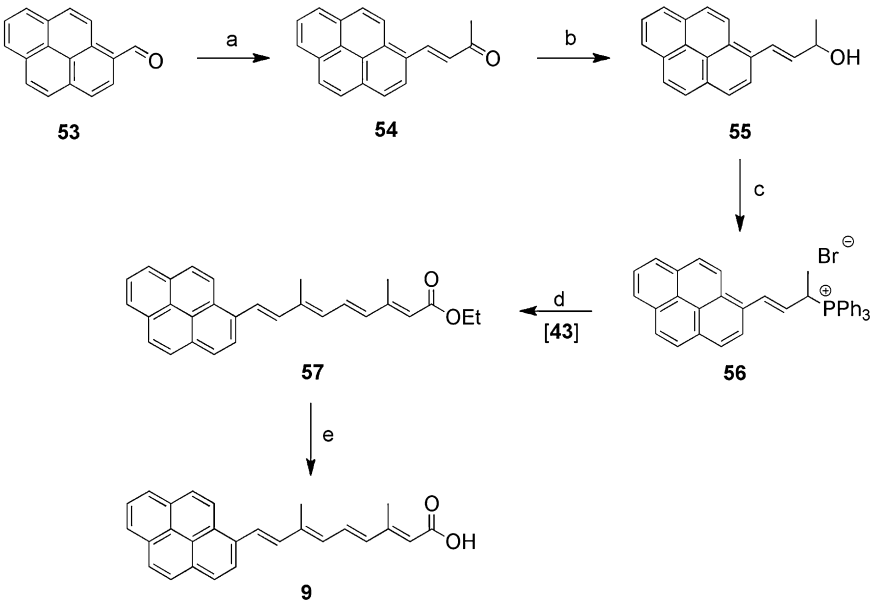
On the other hand, pyrene-1-carboxaldehyde (**53**) was condensed with the commercially available reagent $(EtO)_2P(O)CH_2C(CH_3){=}O$ in PhMe, in the presence of a 2 N solution of MeONa in MeOH, at ambient temperature for 10 h, to afford the *E*-unsaturated methyl ketone **54** in 66% yield, as the only isomer. The latter was reduced with $NaBH_4$ in MeOH to give alcohol **55** in 65% yield, which was furthermore converted to the secondary unsaturated *E*-phosphonium salt **56** in 98% yield, using $Ph_3P{\cdot}HBr$ in MeOH/diglyme at ambient temperature for 3 h (Scheme 5). The latter was reacted with aldehyde **43** in THF, using *n*-BuLi as the base, from −78 °C to ambient temperature (2.5 h), giving a mixture of two geometric isomers (as indicated by HPLC) of ester **57** in 81% yield (only the all-*E* isomer is drawn). Finally, ester **57** was saponified, with an aqueous 8 M solution of NaOH in DMSO/MeOH for 2.5 h at 65 °C, followed by crystallization from EtOAc to give *all*-trans acid **9** in 45% yield.

Finally, acitretin analogs **10**, **11** and **12**, were synthesized as follows. HWE reaction of the commercially available $(EtO)_2P(O)CH_2CO_2Et$ with the also commercially available 1-acetylpyrene (**58**), 2-acetyl-6-methoxynaphthalene (**59**) and 2-acetylanthracene (**60**), in DMF and in the presence of a 2 N solution of MeONa in MeOH, at ambient temperature (**58**, **59**) or heated at 80 °C (**60**), for 5–20 h, afforded the unsaturated *E*-esters **61**–**63**, as the only isomers in 70–96% yields. It is worth mentioning that attempted preparation of esters **62** and **63** through the condensation of the corresponding aromatic methyl ketones with the stabilized phosphorane $Ph_3P{=}CHCO_2Et$ produced a mixture of the geometric isomers in the ratio 70:30.

Esters **61**–**63** were reduced with AlH_3 to give the corresponding *E*-alcohols **64**–**66** in 65–80% yields, as the only isomer. The latter, were converted to the corresponding unsaturated primary phosphonium salts **67**–**69**, using $Ph_3P.HBr$ in MeOH/THF or MeOH/diglyme at ambient temperature, in 85–98% yield. These salts were then condensed with aldehyde **42** in DMF, using 1,2-butylene oxide as the base, at 60 °C for 2–10 h, affording a mixture of two geometric isomers of esters **70**–**72** (as indicated by ^{1}H NMR and/or



Scheme 4. *Reagents and reaction conditions*: (a) $NaBH_4$, MeOH, 0.5 h, 0 °C–25 °C, 96%; (b) $Ph_3P{\cdot}HBr$, MeCN/THF 1:1, 5–6 h, 80 °C (**49**, 72%; **50**, 80%); (c) 1,2-butylene oxide, DMF, 4–8 h, 60 °C (**51**, 74%; **52**, 79%); (d) i) 8 M aq. NaOH, MeOH, DMSO, 1–2 h, 65 °C, ii) crystallization from EtOAc (**6**, 40%; **7**, 42%).



Scheme 5. *Reagents and reaction conditions*: (a) $(EtO)_2P(O)CH_2C(CH_3)$=O, MeONa/MeOH, PhMe, 10 h, 25 °C, 66%; (b) $NaBH_4$, MeOH, 0.5 h, 0 °C–25 °C, 65%; (c) Ph_3P.HBr, MeCN/diglyme 1:1, 3h, 25 °C, 98%; (d) *n*-BuLi, THF, 2.5 h, −78 °C–25 °C, 81%); (e) i) 8 M aq. NaOH, MeOH, DMSO, 2.5 h, 65 °C, ii) crystallization from EtOAc, 45%.

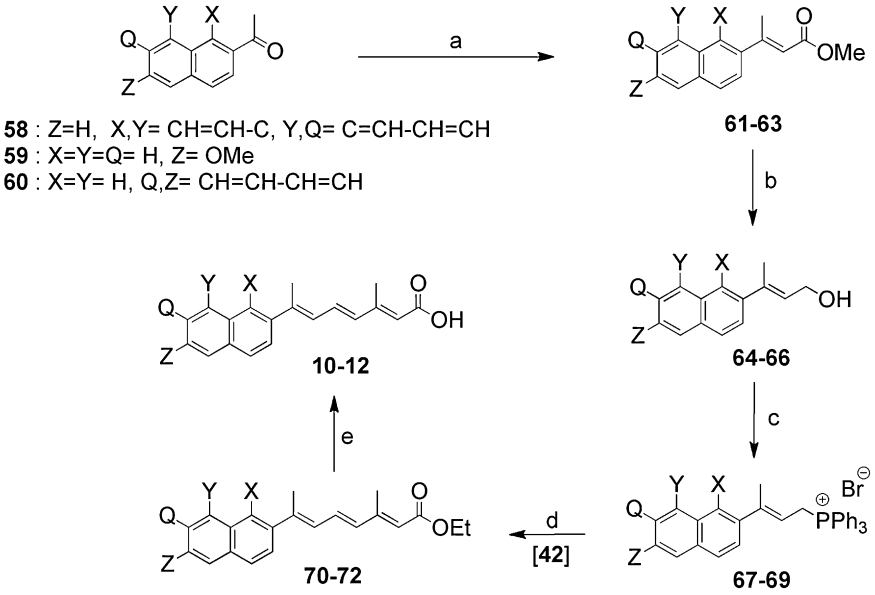
HPLC) in 54–77% yield (only the *all-E* isomers are drawn). Finally, these esters were saponified, with an aqueous 8 M solution of NaOH in DMSO/MeOH for 2–5 h at 65 °C and the thus obtained acids were crystallized from EtOAc to give *all-trans* acids **10**–**12**, in 45–52% yield (Scheme 6).

2.2. Antiproliferative activity

Acitretin and its new synthetic analogs were studied for their antiproliferative activity on the MCF-7 breast cancer cells, cultured in serum-containing medium in order to achieve as close as possible *in vivo* conditions. Initially, acitretin was screened in a wide range of concentrations (10^{-7}, 5×10^{-7}, 10^{-6}, 5×10^{-6} and 10^{-5} M). As showed in Fig. 2, acitretin presented a significant, dose-dependent, inhibition of cell growth.

In order to evaluate the antiproliferative effects of the new synthetic acitretin analogs, three concentrations were tested (10^{-5}, 5×10^{-6} and 10^{-6} M). ATRA, which was also used as reference compound, exerted antiproliferative effect in MCF-7 breast cancer cells to almost the same extent as acitretin. The effects of the above analogs on cell growth are shown in Figs. 3 and 4.

Analogs **10** and **12** incorporating condensed aromatic systems and the C8–C9 double bond within a benzene ring did not show a significant inhibitory activity. Analogs **6** and **7** which were



Scheme 6. *Reagents and reaction conditions*: (a) $(EtO)_2P(O)CH_2CO_2Et$, MeONa/MeOH, DMF, 5–20 h, 0 °C–25 °C (**58**, **59**) or 80 °C (**60**) (**61**, 75%; **62**, 96%; **63**, 70%); (b) $LiAlH_4$, $AlCl_3$, THF, 1 h, 0 °C–25 °C (**64**, 80%; **65**, 65%; **66**, 73%); (c) $Ph_3P{\cdot}HBr$, MeOH/diglyme or MeOH/THF (1:1), 10–24 h, 25 °C (**67**, 85%; **68**, 98%; **69**, 88%); (d) 1,2-butylene oxide, DMF, 2–16 h, 60 °C (**70**, 77%; **71**, 77%; **72**, 54%); (e) i) 8 M aq. NaOH, MeOH, DMSO, 2–5 h, 65 °C, ii) crystallization from EtOAc (**10**, 51%; **11**, 45%; **12**, 52%).

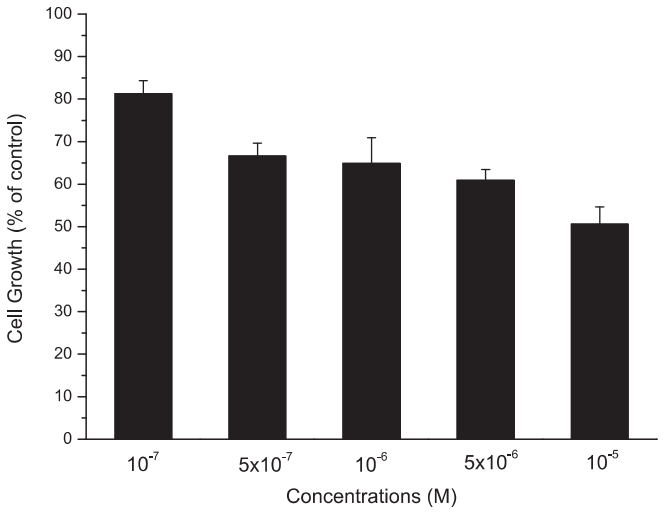


Fig. 2. Study of antiproliferative effect of acitretin on ER-positive breast cancer MCF-7 cell line. The cells were incubated in serum-containing medium for 72 h in the presence of increasing concentrations (10^{-7}, 5×10^{-7}, 10^{-6}, 5×10^{-6} and 10^{-5} M). Cell proliferation was assessed by the WST-1 assay. The results are presented as percentage of growth in respect to control cells. Each point represents the average ± standard deviation of three individual experiments, performed in three replicates.

characterized by the presence of lipophilic but inductively electron withdrawing groups (F, CF_3) presented in general similar biological behavior and their antiproliferative activity was comparable to acitretin at the higher concentrations tested. Only derivative **6**, bearing two trifluoromethyl substituents on the aromatic ring, caused a small inhibition at the concentration of 5 μM.

The presence of four condensed benzene rings (pyrene ring-system) in the lipophilic part of the molecule (analog **9**) seemed to offer no advantage over acitretin. On the contrary analog **8**, which incorporates the naphtalene ring system (only two condensed benzene rings) in the lipophilic part, showed a significant inhibitory effect (approximately 10–25%, compared to acitretin treated cells). This inhibition was further enhanced upon substituting

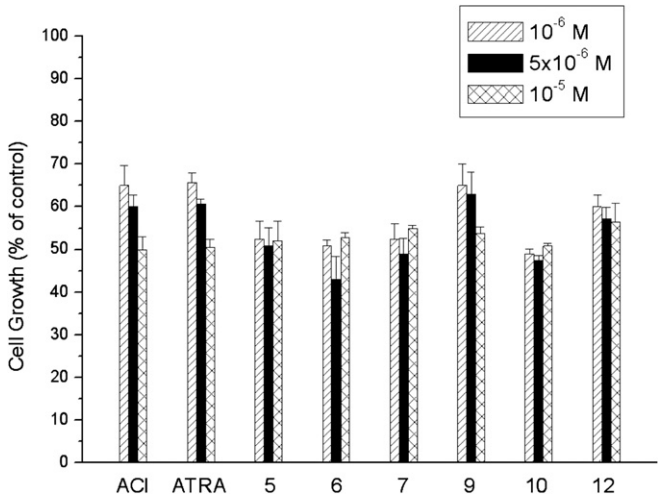


Fig. 3. Inhibitory effects of acitretin analogs **5**, **6**, **7**, **9**, **10** and **12** on human breast cancer MCF-7 cell line. The cells were incubated in serum-containing medium for 72 h in the presence of increasing concentrations of ATRA and acitretin analogs. Cell proliferation was determined by measuring the absorbance at 450 nm (WST-1 method). Data are expressed as % of growth as compared to control untreated cells. Results are expressed as average ± SD of three individual experiments, performed in triplicate.

one of the benzene rings of the naphtalene ring-system with the electron-donating through resonance methoxy group and incorporating the C8–C9 double bond within the other benzene ring (analog **11**), but only at the highest concentration tested (10 μM).

As concerns the remaining three acitretin analogs, bearing the electron-donating methoxy and dimethylamino groups, analog **5** (one dimethylamino group in the benzene ring) possessed a similar inhibitory effect at all concentrations tested. However, the antiproliferative effect was significantly higher for the acitretin analog **4** which was substituted with two methoxy groups. On the other hand, the most potent compound of all tested was analog **3** with three methoxy groups on the benzene ring. A dose-dependent inhibitory effect on cell growth was observed and, at the concentration of 10 μM, maximum inhibition (52% as compared to acitretin treated cells and ca. 77% as compared to control untreated cells) was obtained. The results of the inhibitory effect of analog **3** on MCF-7 cells found with the WST-1 assay were also verified with an MTT assay (data not shown).

Having found that analog **3** inhibits the growth of MCF-7 cultures with the WST-1 and MTT assays, we investigated the possibility that this compound could induce apoptosis and/or growth arrest in this cancer cell line. To this end, we have first collected control and cells treated with analog **3** for 4 h and then tested the status of PARP, whose fragmentation is a downstream effect in the apoptotic pathway. As a positive control, cells treated with staurosporine, a classical apoptosis inducer, were also used. As can be seen in Fig. 5, while staurosporine clearly provokes PARP fragmentation, this cannot be seen in analog **3**-treated cells. Similar results were observed with samples collected 9 h after treatment (not shown). This indicates that analog **3** at this concentration does not provoke apoptosis in MCF-7 cells.

Consequently, we looked for alterations in cell cycle regulation. In Fig. 6, it can be seen that analog **3** (10^{-5} M) does not alter cell cycle distribution at 9, 24 and 48 h after addition. Finally, we tested the activation of Akt, a major signaling molecule involved in both apoptosis and cell cycle progression and in accordance to the above, no change in its activation was found after 4 h of incubation (Fig. 7). Similar results were found also 9 h after treatment (not shown). Accordingly, the mechanism underlying the inhibitory effect of analog **3** on MCF-7 growth needs further investigation.

2.3. Computational chemistry

All molecular geometry calculations have been performed with the widely used B3LYP [54,55] density functional theory method and the 6-31G* basis set, as implemented in the GAUSSIAN 03 program [56]. The Cartesian coordinates of the optimal molecular geometries are given in the Supplementary data. In addition to the geometrical parameters, we give the atomic charges calculated via an NBO analysis with the second-order Møller-Plesset perturbation method (MP2) [57] with the 6-31G* basis set. Furthermore, we have calculated basic electric properties for all molecules. We rely exclusively on Buckingham's notation and definitions in this work [58]. We calculated the Cartesian components of the dipole moment (μ_α), dipole polarizability ($\alpha_{\alpha\beta}$) and hyperpolarizability ($\beta_{\alpha\beta\gamma}$) tensors. Subsequently, we calculated the total dipole moment (μ), the mean ($\overline{\alpha}$) and the anisotropy ($\Delta\alpha$) of the dipole polarizability and the total first hyperpolarizability (β). The above quantities are defined as

$$\mu = \sqrt{\mu_x^2 + \mu_y^2 + \mu_z^2} \quad (1)$$

$$\overline{\alpha} = (\alpha_{xx} + \alpha_{yy} + \alpha_{zz})/3 \quad (2)$$

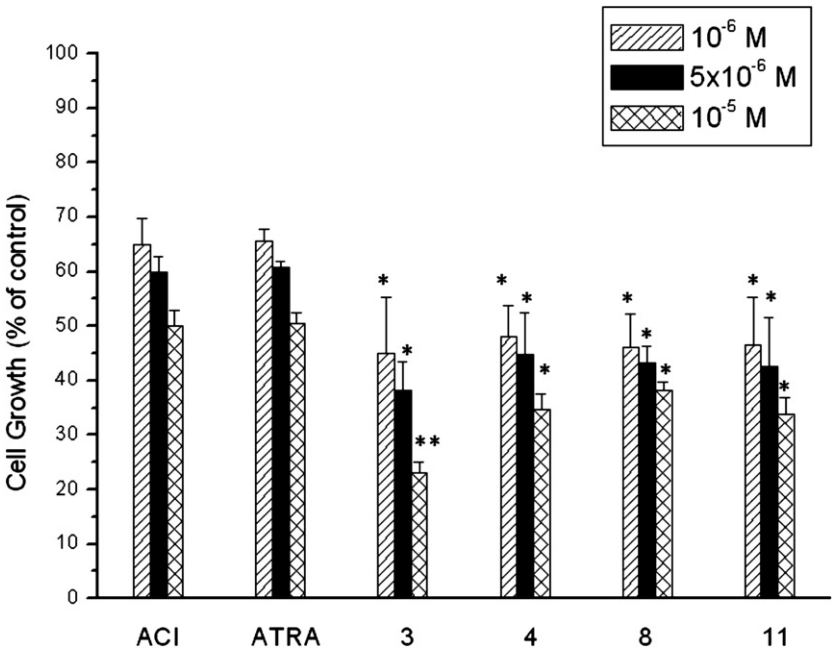


Fig. 4. Study of antiproliferative effects of acitretin analogs **3**, **4**, **8** and **11** on human breast cancer MCF-7 cell line. The cells were incubated in serum-containing medium for 72 h in the presence of increasing concentrations of ATRA and acitretin analogs. Cell proliferation was determined by measuring the absorbance at 450 nm (WST-1 method). Data are expressed as % of growth as compared to control untreated cells. Results are expressed as average ± SD of three individual experiments, performed in triplicate. Asterisks indicate the statistically significant changes of cells treated with analogs as compared to those treated with the respective concentrations of acitretin at the levels of (*, $p \leq 0.05$ and **, $p \leq 0.01$).

$$\Delta\alpha = \sqrt{\frac{(\alpha_{xx}-\alpha_{yy})^2+(\alpha_{yy}-\alpha_{zz})^2+(\alpha_{zz}-\alpha_{xx})^2+6\alpha_{xz}^2+6\alpha_{yz}^2+6\alpha_{zx}^2}{2}} \quad (3)$$

$$\beta = \sqrt{(\beta_{xxx}+\beta_{xyy}+\beta_{xzz})^2+(\beta_{yyy}+\beta_{yxx}+\beta_{yzz})^2+(\beta_{zzz}+\beta_{zxx}+\beta_{zyy})^2} \quad (4)$$

The calculated values, obtained at the B3LYP/6-31G* level of theory, are collected in Table 1 together with torsional angles, lipophilicities and biological data for the sake of comparison. Based on previous experience [59–61] and findings of other authors [62] we do not claim that the (hyper)polarizability values calculated with the 6-31G* basis set are fully converged. Nevertheless, the present values should offer a reasonable representation of the trends in the evolution of the (hyper)polarizability within the group of molecules studied in this work. The HOMO and LUMO as well as the charge distribution on the molecular frame for all compounds (**1**–**12**) are provided in the Supplementary data.

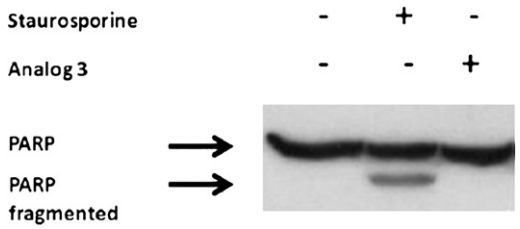


Fig. 5. Treatment of MCF-7 with analog **3** does not lead to PARP fragmentation. Cells were treated with staurosporine (2×10^{-6} M) or with analog **3** (10^{-5} M). After 4 h, cellular protein was collected and subjected to western analysis, as described in the experimental data. A representative experiment out of two similar experiments is presented here.

The results of the antiproliferative activity tests described above show that the four most active analogs are, in decreasing order, **3** > **11** ≈ **4** > **8**. A first examination of the molecular geometry of the above analogs reveals that the dihedral angle between the aromatic ring and the tetraene chain is 0° whereas the analogs **3**, **4** and **8**, with a single aromatic ring in the lipophilic part, have as a whole a planar geometry (see Supplementary data). In analog **11**, where the C8–C9 double bond is restricted within a benzene ring, the dihedral angle between the plane of the naphthalene nucleus and the conjugated triene chain is 23.46°. For comparison, the calculated values for the dihedral angles for ATRA and ACI are 11.03° and 40.21°, respectively. It is interesting here to note that the crystal structure of ATRA bound on its RAR receptor shows that the dihedral angle between the β-ionone ring and the tetraene chain is 43° [63]. Similarly, the crystal structure of Ro12-7310, an inactive metabolite of the antipsoriatic drug tigason (acitretin ethyl ester) which, compared to acitretin, lacks the *O*-methyl group, bound on CRABP II showed the dihedral angle between the plane aromatic ring and the tetraene chain to be 56° [3]. On the other hand, acitretin itself has been crystallized in three polymorphic forms I, II and III and their structures have been recently determined [64]. Indeed, the aromatic ring is out of the plane of the tetraene chain by

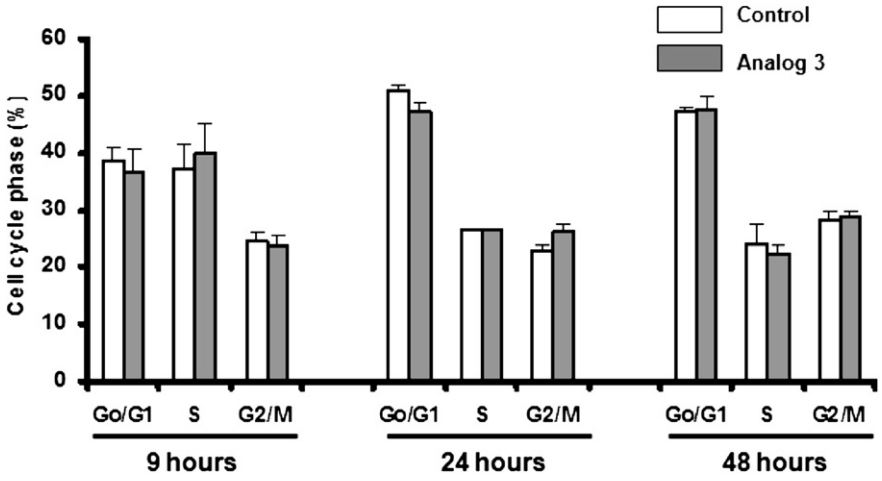


Fig. 6. Cell cycle analysis of MCF-7 cells in the presence of analog **3**. Subconfluent cultures of MCF-7 cells were treated with analog **3** at a concentration of 10^{-5} M and they were collected at the indicated time points and were subjected to FACS analysis. A representative experiment out of two similar ones, performed in duplicates, is presented here.

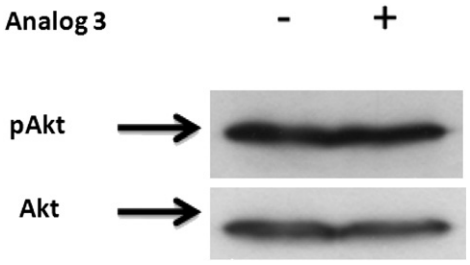


Fig. 7. Treatment of MCF-7 with analog **3** does not affect Akt activation. MCF-7 cells were treated with analog **3** (10^{-5} M). After 4 h cellular protein was collected and subjected to western analysis by using an antibody against phosphorylated Akt. Total Akt served as a loading control. A representative experiment out of two similar experiments is presented here.

14.7° (form II), 29.8–38.4° (form I, molecules A–D) and in one case (form III) by 60.8°. Quite recently, the crystal structure of acitretin analog **10** was determined by single crystal X-ray crystallography. Accordingly, the dihedral angle between the plane of the aromatic rings and the spacer for the two independent molecules (A and B) of the asymmetric unit was found to be 52.8° and 42.2°, respectively [65], with the former value being closer to the herein theoretically calculated one (65.93°, Table 1). It is apparent that there is a significant conformational freedom in this part of the molecule. Accordingly, it would be interesting to calculate in a subsequent study the potential energies required for the variation of the dihedral angle under consideration.

Another important observation from our theoretical studies is that the most active inhibitor (analog **3**) possesses the largest dipole moment $\mu = 3.3054$ ea_0. This is highly significant as from an intermolecular interactions point of view, the dipole–dipole contribution to the interaction energy of two polar molecules is very important (a R^{-3} term) [34]. For comparison, the dipole moments of ATRA and acitretin are $\mu/ea_0 = 2.1289$ and 1.8988, respectively. It is also worth noticing that the ordering of the most active analogs (**3** > **11** ≈ **4** > **8**) is roughly that of the respective dipole moments as well: $\mu/ea_0 = 3.3054$ (**3**) > 1.8302 (**4**) > 1.6611 (**11**) > 1.2908 (**8**).

In addition, analog **3** is characterized by a larger mean and anisotropy of the dipole polarizability: $\overline{\alpha}/e^2a_0^2E_h^{-1} = 331.203$ (**ATRA**), 352.526 (**acitretin**), 374.753 (**3**) and $\Delta\alpha/e^2a_0^2E_h^{-1} = 495.312$ (**ATRA**), 516.409 (**acitretin**), 610.804 (**3**). A similar trend is easily verified for the first hyperpolarizability as β (**ATRA**) < β (**acitretin**) < β (**3**). Furthermore, it is worth noting that the most active compounds in the present study, that is compounds **3**, **4** and **11**, are characterized by lower calculated lipophilicity (cLogP) values (4.699, 4.357 and 5.188, respectively) than acitretin (6.065) and ATRA (6.744). Finally, although the presence of at least one OMe group in the ring seems to be beneficial to the antiproliferative activity of the

Table 1
Electric properties of all molecules studied, in atomic units.[a] The properties of the most active inhibitor (analog **3**) are given in bold italics.

Molecule	Dihedral angle	μ	$\overline{\alpha}$	$\Delta\alpha$	β	Lipophilicity (cLogP)[c]	% Inhibition (−) or induction (+) ± SD of **ACI** at 10^{-5} M
1	11.03°	2.1289	331.203	495.312	12165.59	6.744	+3.1 ± 1.1699
2	40.21°	1.8988	352.526	516.409	18656.48	6.065	–
3	***0°***	***3.3054***	***374.753***	***610.804***	***20577.13***	***4.699***	***−53 ± 1.9457***
4	0°	1.8302	352.380	584.785	21544.67	4.357	−30 ± 2.8205
5	0.32°	3.0011	375.197	661.847	32720.13	4.864	+5 ± 1.1678
6	23.56°	0.5918	319.061	500.524	1295.07	6.465	+6 ± 0.7362 [d]
7	0°	0.5169	297.509	505.927	7430.82	5.085	+10 ± 1.6439 [d]
8	0°	1.2908	363.414	594.293	12267.71	5.873	−25 ± 1.5217
9	36.53°	1.2635	446.205	610.867	18020.77	6.161	+4 ± 0.6796[d]
10	0°[b]	1.2017	345.074	404.059	6260.54	5.557	+8 ± 2.9767
11	0°[b]	1.6611	319.475	495.772	13333.50	5.188	−32 ± 3.2233
12	0°[b]	1.2802	372.466	622.968	10825.48	6.443	+15 ± 1.2103

[a] Conversion factors to SI are: dipole moment, 1 $ea_0 = 8.478358 \times 10^{-30}$ cm, dipole polarizability, 1 $e^2a_0^2E_h^{-1} = 1.648778 \times 10^{-41}$ C^2 m^2 J^{-1} and first dipole hyperpolarizability, 1 $e^3a_0^3E_h^{-2} = 3.206361 \times 10^{-53}$ C^3 m^3 J^{-2}.
[b] For compounds **10**, **11** and **12** the dihedral angles between the plane of the rings and triene chain are 65.93°, 23.46° and 21.37°, respectively.
[c] cLogP values were obtained with the aid of ChemOffice Ultra 2006 (CambridgeSoft).
[d] For compounds **6**, **7** and **9** inhibition at 5×10^{-6} M was observed which had the following absolute values 13.9 ± 5.3547, 2 ± 3.6510 and 5.2 ± 1.1964, respectively.

present set of compounds (the most active inhibitor has actually three such groups), substitution of the *p* methoxy group by the more efficient electron-donating but basic dimethylamino group has the opposite effect even though the resulting molecule is essentially planar and has a relatively high dipole moment (3.0011 ea_0).

3. Conclusions

The present studies are referred to analogs of the aromatic retinoid acitretin with changes in the lipophilic part of the molecule which include the introduction of electron-releasing (OMe or NMe_2) or electron-withdrawing (F or CF_3) groups with variable lipophilicity or of additional aromatic rings and/or the restriction of the C8–C9 double bond within a benzene ring. These analogs were readily obtained using commercially available aromatic aldehydes and methyl ketones as starting materials and linear or convergent methodologies and the Wittig or the Horner–Wadsworth–Emmons reaction for the assembly of the polyene chain. Key-building blocks in the assembly of the tetraene chain were the phosphonate ester *E*-**15**, the *E*-aldehyde **42**, the *E,E*-aldehyde **43** and the *E,E,E*-aldehyde **44**, all prepared stereoselectively through new methodologies.

Preliminary evaluation of these analogs concerning their ability to inhibit the proliferation of human breast cancer MCF-7 cells, revealed that certain analogs (**3**, **4**, **8** and **11**) are stronger inhibitors compared to acitretin. In particular analog **3**, with three methoxy groups on the ring, is more than twice stronger than acitretin. Analog **3** does not exert its antiproliferative effect through apoptosis or by affecting cell cycle progression and does not activate Akt. Theoretical ab initio calculations of this set of compounds indicated that the most active inhibitor **3** is characterized by an extended planar geometry and has a larger dipole moment, mean polarizability, anisotropy of dipole polarizability and first hyperpolarizability than ATRA and acitretin.

Further studies are now in progress in order to determine the actual mechanism(s) through which analog **3** exerts its potent antiproliferative effect, as well as the synthesis, the theoretical calculation and the antiproliferative study of a larger set of acitretin analogs with changes in the lipophilic part in order to be able to correlate more clearly particular molecular descriptors with the observed biological activity.

4. Experimental section

4.1. Chemistry

4.1.1. General

Melting points were determined with a Buchi SMP-20 apparatus and are uncorrected. IR spectra were recorded for KBr pellets unless otherwise stated on a Perkin Elmer 16 PC FT-IR spectrophotometer. ^{1}H NMR spectra were obtained at 400.13 MHz, ^{13}C NMR spectra at 100.62 MHz and ^{19}F NMR spectra at 376.50 MHz, using a Bruker DPX spectrometer. Chemical shifts (δ) are in parts per million (ppm) downfield from TMS or 0.05% triflurotoluene (in case of ^{19}F NMR) used as the internal standard. The assignments of the ^{1}H NMR spectra (see Supplementary data) were based on chemical shift arguments, analysis of coupling patterns and signal intensities. Electron-spray ionization (ESI) mass spectra were on a WATERS Micromass ZQ spectrometer, equipped with a quantropole detector, using MeOH as solvent. Analytical RP-HPLC was performed on a Waters system (2695 Alliance). Elution of the compounds was determined from the absorbance at 254 nm (Waters 2996 Diode array detector). Compound purity was assessed using a XBridge™ C18 column (3.5 μm, 150 × 4.6 mm) and a linear gradient of 40%–100% or 70%–100% acetonitrile (containing 0.08% TFA) in water (containing 0.08% TFA) over 30 min at a flow rate of 1 mL/min. GC analyses were performed on an Agilent Technologies 6890 N gas chromatograph fitted with a capillary column (30.0 m; 250 μm; 0.25 μm nominal) having as stationary phase HP-5MS 5% Phenyl Methyl Siloxane. Carrier gas flow-rate: 26.4 mL min^{-1} He; injection port temperature 300 °C; program: 70–300 °C at 14.45 min. Electron Impact mass spectra were recorded at 20 eV on an Agilent Technologies 5975B instrument, tandem to the above mentioned GC spectrometer. Microanalyses were performed on a Carlo Erba EA 1108 CHNS elemental analyzer in the Laboratory of Instrumental Analysis of the University of Patras. Flash column chromatography (FCC) was performed on Merck silica gel 60 (230–400 mesh) and TLC on 60 Merck $60F_{254}$ films (0.2 mm) precoated on aluminium foil. Spots were visualized with UV light at 254 nm and charring agents. Unless otherwise stated, the solvent systems used for the FCC purifications are identical to those indicated in the R_f values of the purified compounds. The eluant systems used were: (A) PhMe/Hexane (7:3), (B) PhMe/Hexane (9:1), (C) PhMe, (D) PhMe/EtOAc (95:5), (E) PhMe/EtOAc (9:1), (F) PhMe/EtOAc (8:2), (G) PhMe/EtOAc (7:3), (H) PhMe/EtOAc (1:1). All solvents (Merck) were dried and/or purified according to standard procedures prior to use. Anhydrous Na_2SO_4 was used for drying solutions and subsequently solvents were routinely removed at ca. 40 °C under reduced pressure (water aspirator). All reagents employed in the present work were purchased from either Aldrich or Fluka and used without further purification, with the exception of 4-methoxy-2,3,6-trimethylbenzaldehyde (**16**), which synthesized according to a literature procedure [11]. All reactions described below were conducted under dim light.

4.1.2. Syntheses of key-compounds *13–15* and *42–44*

*4.1.2.1. Ethyl E-4-hydroxy-3-methyl-2-butenoate (**13**).* A suspension of hydroxyacetone (16.43 mL, 240 mmol) and stabilized phosphorane $Ph_3P{=}CHCO_2Et$ (100.5 g, 288 mmol) in MeCN (525 mL) was refluxed for 12 h. The reaction mixture was evaporated to dryness, triturated with Et_2O and cooled overnight. The precipitated $Ph_3P{=}O$ and excess phosphorane were filtered off and discarded. The filtrate was evaporated and the residue was subjected to FCC using as eluant the solvent system *E* to afford pure **13**. Yield: 29.4 g (85%), yellow oil; R_f (*E*): 0.13; IR (neat, cm^{-1}): 3442, 1716, 1698, 1656; GC–MS (EI, 20 eV): $t_R = 6.14$ min, m/z (%) = 144 (8, [M]), 126 (14, [M − H_2O]), 115 (29, [M − CH_2CH_3]), 99 (68, [M − OCH_2CH_3]), 98 (100, [M − CH_3CH_2OH]), 87 (35, [115-CO]), 71 (38, [115-CO_2]); ^{1}H NMR ($CDCl_3$, δ): 5.97 (m, 1H), 4.15 (q, 2H, $J = 7.2$ Hz), 4.12 (m, 2H), 2.15 (s, 1H), 2.07 (unresolved d, 3H), 1.27 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$, δ): 167.1, 157.5, 113.8, 67.2, 59.9, 15.8, 14.5.

*4.1.2.2. E-4-Bromo-3-methyl-2-butenoate (**14**).* To an ice-cold solution of alcohol **13** (18.74 g, 130 mmol) and Ph_3P (34 g, 130 mmol) in MeCN (32 mL), CBr_4 (43 g, 130 mmol) was added carefully and the resulting solution was stirred at ambient temperature for 1 h. The reaction mixture was evaporated to dryness and the residue was subjected directly to FCC, using C as eluant, to afford pure bromide **14**. Yield: 23.96 g (89%), colorless oil; R_f (C): 0.48; IR (neat, cm^{-1}): 1710, 1651; GC–MS (EI, 20 eV): $t_R = 6.23$ min, m/z (%) = 206 and 208 (54 and 52, [M]), 178 and 180 (92 and 89, [M − $CH_2{=}CH_2$]), 161 and 163 (100 and 97, [M − OCH_2CH_3]), 99 (69, [M − Br−$CH_2{=}CH_2$]), 82 (56, M − Br−OCH_2CH_3]); ^{1}H NMR ($CDCl_3$, δ): 5.96 (s, 1H), 4.17 (q, 2H, $J = 7.2$ Hz), 3.94 (s, 2H), 2.28 (s, 3H), 1.28 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$, δ): 166.1, 152.5, 119.7, 60.3, 38.5, 17.4, 14.4.

*4.1.2.3. Ethyl E-4-(diethylphosphono)-3-methyl-2-butenoate (**15**).* To neat $(EtO)_3P$ (49.28 mL, 288 mmol) kept at 100 °C, bromide **14** (115 mmol, 23.80 g) was added dropwise. The temperature was then raised to 150 °C and kept at that temperature for further 30 min. Pure **15** was then obtained by high vacuo fractional distillation (102 °C/10^{-2} mmHg). Yield: 17.35 g (73%), colorless oil; R_f (H): 0.27;

IR (neat, cm^{-1}): 1713, 1649, 1250; GC–MS (EI, 20 eV): t_R = 8.70 min, *m/z* (%): 264 (10, [M]), 218 (100, [M − CH_3CH_2OH]), 190 (94, [218-CO or 218-CH_2=CH_2]), 162 (94, [190-CH_2=CH_2]), 134 (94, [162-CH_2=CH_2]); ^{1}H NMR ($CDCl_3$, δ): 5.76 (δ, 1H, J_{PH} = 4.8 Hz), 4.15–4.06 (three q, 6H, *J* = 7.2 Hz), 2.66 (d, 2H, J_{PH} = 23.6 Hz), 2.28 (dd, 3H, J_{PH} = 3.6 and J_{HH} = 0.8 Hz), 1.30 (t, 6H, *J* = 7.2), 1.25 (t, 3H, *J* = 7.2); ^{13}C NMR ($CDCl_3$, δ): 166.2 (d, J_{PC} = 3.6 Hz), 149.6 (d, J_{PC} = 10.9 Hz), 120.3 (d, J_{PC} = 11.8 Hz), 62.6 (d, 2C, J_{PC} = 6.7 Hz), 60.0, 38.6 (d, J_{PC} = 134.6 Hz), 20.2 (d, J_{PC} = 2.6 Hz), 16.6 (d, 2C, J_{PC} = 6.0 Hz), 14.4

*4.1.2.4. Ethyl E-4-formyl-3-methyl-2-butenoate (**42**).* To a vigorously stirred solution of alcohol **13** (9.37 g, 65 mmol) in CH_2Cl_2 (1.3 L), activated MnO_2 powder (56.5 g, 650 mmol) was added. The resulting suspension was stirred at ambient temperature for 1 h and subsequently passed through a celite pad. Evaporation of the filtrate resulted in pure **42** as a yellow oil. Yield: 7.66 g (92%); R_f (D): 0.35; IR (neat, cm^{-1}): 2829, 2740, 1718, 1660; GC–MS (EI, 20 eV): t_R = 4.82 min, *m/z* (%): 142 (4, [M]), 114 (15, [M − CO]), 97 (100, [M − OCH_2CH_3]), 96 (100, [M − CH_3CH_2OH]); ^{1}H NMR ($CDCl_3$, δ): 9.54 (s, 1H), 6.49 (unresolved q, 1H), 4.26 (q, 2H, *J* = 6.8 Hz), 2.15 (d, 3H, *J* = 1.2 Hz), 1.33 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, δ): δ 194.8, 165.7, 150.6, 135.8, 61.3, 14.4, 11.0

*4.1.2.5. Ethyl (2E,4E)-5-formyl-3-methylpenta-2,4-dienoate (**43**).* To a solution of aldehyde **42** (5.69 g, 40 mmol) in DCM (40 mL) phosphorane Ph_3P=CHCHO (13.39 g, 44 mmol) was added. The resulting suspension was stirred at ambient temperature for 14 h. The reaction mixture was evaporated to dryness, triturated with Et_2O and cooled overnight. The precipitated Ph_3P=O and excess phosphorane were filtered off and discarded. The filtrate was evaporated and the residue was subjected to FCC to afford pure **43**. Yield: 4.44 g (68%), yellow solid; R_f (D): 0.25; mp 58–60 °C; IR (KBr, cm^{-1}): 2834, 2748, 1714, 1678, 1600; GC–MS (EI, 20 eV): t_R = 7.08 min, *m/z* (%), 168 (5, [M]), 139 (22, [M − HCO]), 123 (57, [M − OCH_2CH_3]), 111 (66, [139-CH_2=CH_2]), 95 (100, [123-CO]); ^{1}H NMR ($CDCl_3$, δ): 9.67 (d, 1H, *J* = 7.6 Hz), 7.10 (d, 1H, *J* = 15.6 Hz), 6.45 (dd, 1H, *J* = 7.6 and 15.6 Hz), 6.12 (unresolved q, 1H), 4.22 (q, 2H, *J* = 7.2 Hz), 2.31 (d, 3H, *J* = 0.8 Hz), 1.31 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, δ): 193.4, 165.9, 154.3, 148.7, 132.9, 127.1, 60.7, 14.4, 14.0; Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.41; H, 7.05.

*4.1.2.6. Ethyl (2E,4E,6E)-3,7-dimethyl-8-oxoocta-2,4,6-trienoate (**44**).* To a solution of aldehyde **43** (3.36 g, 20 mmol) in PhMe (20 mL), phosphorane Ph_3P=C(CH_3)CHO (7.0 g, 22 mmol) was added. The resulting suspension was heated at 70 °C for 6 h (GC–MS was used to monitor the progress of the reaction). The reaction mixture was evaporated to dryness, triturated with Et_2O and cooled overnight. The precipitated Ph_3P=O and excess phosphorane were filtered off and discarded. The filtrate was evaporated and the residue was subjected to FCC to afford pure **44**. Yield: 3.42 g (82%), yellow solid; R_f (D): 0.25; mp 82–84 °C; IR (KBr, cm^{-1}): 2832, 2740, 1711, 1670, 1600; GC–MS (EI, 20 eV): t_R = 8.93 min, *m/z* (%), 208 (12, [M]), 179 (95, [M − HCO]), 163 (32, [M − OCH_2CH_3]), 162 (53, [M − CH_3CH_2OH]), 134 (45, [162-CO]), 91 (72, [$C_7H_7^+$]); ^{1}H NMR ($CDCl_3$, δ): 9.51 (s, 1H), 7.00 (dd, 1H, *J* = 11.2 and 14.8 Hz), 6.69 (d, 1H, *J* = 11.2 Hz), 6.66 (d, 1H, *J* = 14.8 Hz), 5.95 (s, 1H), 4.20 (q, 2H, *J* = 6.8 Hz), 2.37 (s, 3H), 1.93 (s, 3H), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, δ): 194.8, 166.7, 150.7, 147.3, 143.8, 140.1, 128.5, 123.6, 60.4, 14.5, 13.9, 10.1 ppm; Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.04; H, 7.98.

4.1.3. General procedure for the Horner–Emmons reactions

*4.1.3.1. With ethyl E-4-(diethylphosphono)-3-methyl-2-butenoate (**15**).* To a solution of phosphonate **15** (2 equiv.) in THF (concentration: 0.6 M) kept at 0 °C, were added sequentially DMPU (4 equiv.) and *n*-BuLi (1.6 M in Hexanes, 2.2 equiv.). The resulting mixture was stirred at 0 °C for additional 40 min and then cooled to −78 °C. Aromatic (**16**–**20**, 5 mmol) or allylic (**32**–**36**, 1.7 mmol) aldehydes were added portionwise over 20 min and the reaction mixture was stirred at −78 °C for additional 1 h and then left to attain 0 °C to complete the reaction (monitored by TLC). Excess *n*-BuLi was destroyed by the careful addition of a 5% aqueous solution of NH_4Cl to pH 7–8 and then the reaction mixture was extracted with EtOAc (twice). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4 and evaporated to dryness. The residues were subjected to FCC affording the corresponding esters **21**–**25** and **37**–**41**. NMR spectra are provided only for the most abundant *all-E* isomer.

*4.1.3.1.1. Ethyl-5-(4-methoxy-2,3,6-trimethylphenyl)-3-methylpenta-2,4-dienoate (**21**).* Reaction time: 3 h; Isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 90:10. Yield: 1.04 g (83%), yellow solid; R_f (C): 0.22; IR (KBr, cm^{-1}): 1704, 1596; MS (ESI, 30 eV): *m/z* 274.38 [MH − CH_3]; ^{1}H NMR ($CDCl_3$, δ): 6.99 (d, 1H, *J* = 16.0 Hz), 6.60 (s, 1H), 6.21 (d, 1H, *J* = 16.0 Hz), 5.80 (s, 1H), 4.20 (q, 2H, *J* = 7.2 Hz), 3.82 (s, 3H), 2.44, 2.29, 2.22 and 2.15 (4 s, 12H), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, δ): 167.2, 156.5, 152.4, 137.1, 133.5, 129.1, 128.2, 125.3, 118.9, 117.1, 110.0, 59.7, 55.5, 21.5, 17.4, 14.4, 13.7, 11.8.

*4.1.3.1.2. Ethyl-5-(2,4,6-trimethoxyphenyl)-3-methylpenta-2,4-dienoate (**22**).* Reaction time: 3 h; Isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 75:25. Yield: 1.13 g (74%), yellow solid; R_f (E): 0.21; IR (KBr, cm^{-1}): 1698, 1592; MS (ESI, 30 eV): *m/z* 292.74 [MH − CH_3]; ^{1}H NMR ($CDCl_3$, δ): 7.28 (s, 2H), 6.16 (s, 2H), 5.86 (s, 1H), 4.20 (q, 2H, *J* = 7.2 Hz), 3.88 (s, 6H), 3.86 (s, 3H), 2.44 (s, 3H), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, δ): 167.1, 161.5, 159.9 (2C), 154.6, 131.8, 126.0, 116.8, 106.2, 91.2 (2C), 61.2, 56.0 (2C), 55.6, 15.9, 13.2.

*4.1.3.1.3. Ethyl-5-(3,4-dimethoxyphenyl)-3-methylpenta-2,4-dienoate (**23**).* Reaction time: 2 h; Isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 90:10. Yield: 1.15 g (83%), yellow solid; R_f (E): 0.35; IR (KBr, cm^{-1}): 1713, 1594; MS (ESI, 30 eV): *m/z* 262.59 [MH − CH_3], 230.56 [M − CH_3CH_2OH]; ^{1}H NMR ($CDCl_3$, δ): 7.03 (d, 1H, *J* 8.4 Hz), 7.01 (s, 1H), 6.88 (d, 1H, d, *J* 16.0 Hz), 6.85 (1H, d, *J* 8.4 Hz), 6.69 (1H, d, *J* 16.0 Hz), 5.89 (1H, s), 4.19 (2H, q, *J* 7.2 Hz), 3.92 (3H, s), 3.90 (3H, s), 2.40 (3H, s), 1.30 (3H, t, *J* 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 167.5, 152.6, 149.8, 149.2, 134.1, 129.9, 129.4, 120.8, 118.5, 110.8, 109.2, 61.3, 55.9, 55.8, 15.7, 13.7.

*4.1.3.1.4. Ethyl-5-(4-(dimethylamino)phenyl)-3-methylpenta-2,4-dienoate (**24**).* Reaction time: 3 h; Isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 85:15. Yield: 1.10 g (85%), yellow solid; R_f (C): 0.32; IR (KBr, cm^{-1}): 1700, 1595; ESI-MS (30 eV): *m/z* 245.69 (MH − CH_3); ^{1}H NMR ($CDCl_3$, δ): 7.37 (d, 2H, *J* = 8.4 Hz), 6.88 (d, 1H, *J* = 16.0 Hz), 6.70 (d, 2H, *J* = 8.4 Hz), 6.65 (d, 1H, *J* = 16.0 Hz), 5.83 (s, 1H), 4.18 (q, 2H, *J* = 7.2 Hz), 3.00 (s, 6H), 2.40 (s, 3H), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, δ): 167.7, 153.5, 150.7, 134.6, 128.3 (2C), 127.3, 124.5, 116.9. 112.2 (2C), 61.2, 40.2 (2C), 15.6, 13.8.

*4.1.3.1.5. Ethyl (2E,4E)-3-methyl-5-(naphthalen-2-yl)penta-2,4-dienoate (**25**).* Reaction time: 3 h; Ester **25** was separated, as the 2*E*,4*E*-isomer (1.03 g, 77%) from its regioisomer **26**; yellow solid; mp: 100–102 °C; R_f (G): 0.18; IR (KBr, cm^{-1}): 1707, 1609; MS (ESI, 30 eV): *m/z* 252.75 [MH − CH_3]; ^{1}H NMR ($CDCl_3$, δ): 7.86–7.78 (m, 4H), 7.66 (dd, 1H, *J* = 1.6 and 8.4 Hz), 7.49 and 7.47 (two dt, 2H, *J* = 1.6 and 7.6 Hz), 7.11 (d, 1H, *J* = 16.0 Hz), 6.94 (d, 1H, *J* = 16.0 Hz), 5.96 (s, 1H), 4.21 (q, 2H, *J* = 7.2 Hz), 2.46 (s, 3H), 1.32 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, δ): 167.2, 152.1, 134.1, 133.6, 133.3, 133.2, 131.9, 128.2, 127.9, 127.6, 127.5, 126.2, 126.1, 123.2, 119.2, 61.3, 15.4, 13.5; Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.39; H, 6.54.

*4.1.3.1.6. Ethyl (2E,4E)-3-methyl-5-(naphthalen-1-yl)penta-2,4-dienoate (**26**).* Yield: 0.2 g (15%), yellow oil; R_f (G): 0.20; IR (neat, cm^{-1}): 1712, 1611; ^{1}H NMR ($CDCl_3$, δ): 8.54 (d, 1H, *J* = 16.0 Hz),

7.85–7.77 (m, 5H), 7.47–7.45 (two dt, 2H, J = 1.2 and 5.2 Hz), 7.08 (d, 1H, J = 16.0 Hz), 5.78 (s, 1H), 4.20 (q, 2H, J = 7.2 Hz), 2.17 (s, 3H), 1.32 (t, 3H, J = 7.2 Hz).

*4.1.3.1.7. Ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyln ona-2,4,6,8-tetraenoate (**37**).* Reaction time: 2 h; Isolated, through FCC using as eluant the solvent system G, as an inseparable mixture of three isomers as indicated by HPLC (70% MeCN/H_2O to 100% MeCN), t_{R1} = 16.364 min, t_{R2} = 16.694 min (main peak), t_{R3} = 17.324 min; Yield: 0.45 g (74%), yellow solid; R_f(G): 0.20; IR (KBr, cm^{-1}): 1701, 1610, 1568; MS (ESI, 30 eV): m/z 355.76 [MH], 309.41 [MH − CH_3CH_2OH].

*4.1.3.1.8. Methyl 9-(2,4,6-trimethoxyphenyl)-3,7-dimethylnona-2,4, 6,8-tetraenoate (**38**).* Reaction time: 2 h; Isolated, through FCC using as eluant the solvent system D, as an inseparable mixture of three isomers as indicated by HPLC (70% MeCN/H_2O to 100% MeCN), t_{R1} = 13.055 min (main peak), t_{R2} = 13.508 min, t_{R3} = 15.164 min; Yield: 0.51 g (80%), yellow solid; R_f (D): 0.35; IR (KBr, cm^{-1}): 1706, 1606, 1582, 1561; MS (ESI, 30 eV): m/z 358.82 [MH − CH_3].

*4.1.3.1.9. Methyl 9-(3,4-dimethoxyphenyl)-3,7-dimethylnona-2,4, 6,8-tetraenoate (**39**).* Reaction time: 2 h; Isolated, through FCC using as eluant the solvent system D, as an inseparable mixture of three isomers as indicated by HPLC (70% MeCN/H_2O to 100% MeCN), t_{R1} = 8.658 min (main peak), t_{R2} = 9.198 min, t_{R3} = 9.683 min; Yield: 0.44 g (75%), yellow solid; R_f (D): 0.24; IR (KBr, cm^{-1}): 1696, 1604, 1568; MS (ESI, 30 eV): m/z 328.56 [MH − CH_3].

*4.1.3.1.10. Methyl 9-(4-(dimethylamino)phenyl)-3,7-dimethylnona-2,4,6,8-tetraenoate (**40**).* Reaction time: 2 h; Isolated, through FCC using as eluant the solvent system C, as an inseparable mixture of three isomers as indicated by HPLC (70% MeCN/H_2O to 100% MeCN), t_{R1} = 10.168 min (main peak), t_{R2} = 10.618 min, t_{R3} = 11.195 min; Yield: 0.45 g (81%), yellow solid; R_f (C): 0.23; IR (KBr, cm^{-1}): 1702, 1607, 1565; MS (ESI, 30 eV): m/z 311.91 [MH − CH_3].

*4.1.3.1.11. Methyl 3,7-dimethyl-9-(naphthalen-3-yl)nona-2,4,6,8-tetraenoate (**41**).* Reaction time: 2 h; Isolated, through FCC using as eluant the solvent system G, as an inseparable mixture of two isomers as indicated by HPLC (70% MeCN/H_2O to 100% MeCN) t_{R1} = 14.485 min, t_{R2} = 15.109 min (main peak); Yield: 0.41 g (72%), yellow solid; R_f (G): 0.26; IR (KBr, cm^{-1}): 1702, 1610, 1576; MS (ESI, 30 eV): m/z 318.84 [MH − CH_3].

4.1.3.2. With diethyl ethoxycarbonylmethylphosphonate. To an ice-cold solution of aromatic methyl ketones **58**–**60** (5 mmol) and diethyl ethoxycarbonylmethylphosphonate (10 mmol, 1.98 mL) in DMF (2.5 mL), a 2 M solution of MeONa in MeOH (10 mmol, 5 mL) was added dropwise over 30 min. The resulting reaction mixture was stirred at ambient temperature (**58**, **59**) or heated at 80 °C (**60**) to complete the reaction (monitored by TLC). The reaction mixture was diluted with EtOAc, washed twice with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residues were subjected to FCC, affording the corresponding *E*-esters (**61**–**63**).

*4.1.3.2.1. Methyl (E)-3-(pyren-1-yl)but-2-enoate (**61**).* Reaction time: 12 h; Yield: 1.13 g (75%), pale yellow solid; mp 101–103 °C; R_f (B): 0.34; IR (KBr, cm^{-1}): 1722, 1634; MS (ESI, 30 eV): m/z 323.39 [M + Na], 301.31 [MH], 300.41 [M], 270.30 [MH − OCH_3], 269.29 [M − OCH_3]; ^{1}H NMR ($CDCl_3$, δ): 8.22–8.13 (m, 4H), 8.11–8.06 (m, 3H), 8.02 (t, 1H, J = 7.6 Hz), 7.83 (d, 1H, J = 7.6 Hz), 6.11 (q, 1H, J = 1.2 Hz), 3.84 (s, 3H), 2.78 (d, 3H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, δ): 166.9, 157.4, 139.3, 131.4, 130.9, 130.8, 127.8, 127.6, 127.3, 127.2, 126.1, 125.3, 125.1, 124.9, 124.8, 124.7, 124.5, 124.4, 121.0, 51.1, 22.1; Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.75; H, 5.60.

*4.1.3.2.2. Methyl (E)-3-(6-methoxynaphthalen-2-yl)but-2-enoate (**62**).* Reaction time: 20 h; Yield: 1.23 g (96%), white solid; mp 102–104 °C; R_f (C): 0.27; IR (KBr, cm^{-1}): 1716, 1618, 1600; MS (ESI, 30 eV): m/z 279.37 [M + Na], 225.27 [MH − CH_3OH]; ^{1}H NMR ($CDCl_3$, δ): 7.89 (δ, 1H, J = 2.0 Hz), 7.77 (d, 1H, J = 8.8 Hz), 7.73 (d, 1H, J = 9.0 Hz), 7.59 (dd, 1H, J = 2.0 and 8.8 Hz) 7.18 (dd, 1H, J = 2.6 and 9.0 Hz), 7.14 (d, 1H, J = 2.6 Hz), 6.29 (q, 1H, J = 1.2 Hz), 3.94 (s, 3H), 3.78 (s, 3H), 2.69 (d, 3H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, δ): 167.4, 158.4, 155.6, 137.0, 134.9, 130.0, 128.6, 127.0, 125.8, 124.4, 119.3, 116.7, 105.6, 55.3, 51.1, 17.0; Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.12; H, 6.22.

*4.1.3.2.3. Methyl (E)-3-(anthracen-2-yl)but-2-enoate (**63**).* Reaction time: 5 h; Yield: 0.97 g (70%), yellow solid; mp 137–139 °C; R_f (C): 0.31; IR (KBr, cm^{-1}): 1710, 1634, 1614; MS (ESI, 30 eV): m/z 299.27 [M + Na]; ^{1}H NMR ($CDCl_3$, δ): 8.46 (s, 1H), 8.41 (s, 1H), 8.13 (s, 1H), 8.02 (ddd, 1H, J = 2.0, 3.6 and 8.8 Hz), 7.99 (d, 2H, J = 8.8 Hz), 7.60 (ddd, 1H, J = 2.0, 3.6 and 8.8 Hz), 7.49 (dt, 2H, J = 3.6 and 8.8 Hz), 6.36 (q, 1H, J = 1.2 Hz), 3.80 (s, 3H), 2.74 (d, 3H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, δ): 166.9, 155.2, 138.4, 132.3, 132.1, 131.4, 131.2, 128.5, 128.2, 127.3, 126.4, 126.0, 125.9, 125.7, 123.5, 117.5, 117.0, 51.1, 17.7; Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.80; H, 5.66.

4.1.3.3. With diethyl (2-oxopropyl)phosphonate. To an ice-cold solution of pyrene-1-carboxaldehyde (**53**, 1.15 g, 5 mmol) and diethyl (2-oxopropyl)phosphonate (1.44 mL, 7.5 mmol) in PhMe (2.5 mL), a 2 M solution of MeONa in MeOH (3.75 mL, 7.5 mmol) was added dropwise over 30 min. The resulting reaction mixture was stirred at ambient temperature for 10 h and then diluted with EtOAc. The organic phase was washed twice with H_2O, dried over Na_2SO_4 and evaporated to dryness. The oily residue was subjected to FCC, using as eluant the solvent system E, to afford pure methyl ketone **54**.

*4.1.3.3.1. (E)-4-(Pyren-1-yl)but-3-en-2-one (**54**).* Yield: 0.90 g (66%), reddish solid; mp 81–83 °C; R_f(E): 0.29, IR (KBr, cm^{-1}): 1664, 1638, 1592; MS (ESI, 30 eV): m/z 563.31 [2M + Na], 293.15 [M + Na], 271.08 [MH]; ^{1}H NMR ($CDCl_3$, δ): 8.66 (d, 1H, J = 16.0 Hz), 8.44 (d, 1H, J = 9.6 Hz), 8.27 (d, 1H, J = 8.4 Hz), 8.22 (d, 2H, J = 8.1 Hz), 8.17 (d, 1H, J = 9.6 Hz), 8.14 (d, 1H, J = 8.1 Hz), 8.12 (d, 1H, J = 8.1 Hz), 8.04 (d, 1H, J = 8.4 Hz), 8.03 (t, 1H, J = 8.4 Hz), 7.00 (d, 1H, J = 16.0 Hz), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 198.2, 139.8, 132.9, 131.3, 130.7, 130.0, 128.9, 128.7 (2C), 128.1, 127.3, 126.3, 126.1, 125.9, 125.1, 127.9, 124.6, 124.2, 122.3, 28.2; Anal. Calcd for $C_{20}H_{14}O$: C, 88.86; H, 5.22. Found: C, C, 89.01; H, 5.05.

4.1.4. General procedure for the AlH_3-mediated ester reductions

To an ice-cold suspension of $LiAlH_4$ (0.24 g, 6.3 mmol) in THF (11 mL), $AlCl_3$ (0.3 g, 2.25 mmol) was added portionwise over 30 min and the resulting mixture was stirred for additional 20 min. Then, the unsaturated esters **21**–**25**, **61** and **62** (3 mmol) were added portionwise over 30 min and the resulting suspension was stirred at ambient temperature to complete the reaction (monitored by TLC). Excess of the reducing agent was destroyed by the careful addition of a saturated aqueous solution of Na_2SO_4, followed by filtration. The filtrate was evaporated and the residue was taken up with EtOAc and washed twice with H_2O, dried over Na_2SO_4 and evaporated to dryness. The anticipated alcohols (**27**–**31**, **64** and **65**, only the *all-E* isomer are drawn) were obtained pure after FCC purification.

*4.1.4.1. 5-(4-Methoxy-2,3,6-trimethylphenyl)-3-methylpenta-2,4-dien-1-ol (**27**).* Reaction time: 1 h; Isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 85:15. Yield: 0.61 g (83%), yellow solid; R_f(E): 0.18; IR (KBr, cm^{-1}): 3229, 1626, 1609; MS (ESI, 30 eV): m/z 247.08 [MH], 228.40 [M − H_2O]; ^{1}H NMR ($CDCl_3$, δ): 6.53 (s, 1H), 6.49 (d, 1H, J = 16.0 Hz), 6.09 (d, 1H, J = 16.0 Hz), 5.61 (t, 1H, J = 6.8 Hz), 4.27 (d, 2H, J = 6.8 Hz), 3.74 (s, 3H), 2.21, 2.15, 2.07 and 1.89 (4 s, 12H); ^{13}C NMR ($CDCl_3$, δ): 156.0, 137.9, 136.7, 135.9, 133.8, 130.0, 129.5, 127.2, 122.6, 109.9, 59.4, 55.4, 21.3, 17.4, 12.6, 11.9.

*4.1.4.2. 5-(2,4,6-trimethoxyphenyl)-3-methylpenta-2,4-dien-1-ol (**28**).* Reaction time: 1 h; Isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 70:30. Yield: 0.63 g (80%), yellow

solid; R_f (F): 0.18; IR (KBr, cm^{-1}): 3390, 1603; MS (ESI, 30 eV): *m/z* 511.06 [2M + H − H_2O], 246.77 [M − H_2O]; ^1H NMR ($CDCl_3$, δ): 7.18 (d, 1H, *J* = 16.0 Hz), 6.84 (d, 1H, *J* = 16.0 Hz), 6.16 (s, 2H), 5.75 (t, 1H, *J* = 6.8 Hz), 4.34 (d, 2H, *J* = 6.8 Hz), 3.86 (2 s, 6H), 3.84 (s, 3H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 160.0, 159.2 (2C), 138.3, 134.4, 128.8, 119.2, 108.1, 90.8 (2C), 59.6, 55.7 (2C), 55.3, 12.2.

*4.1.4.3. 5-(3,4-Dimethoxyphenyl)-3-methylpenta-2,4-dien-1-ol (**29**).* Reaction time: 1 h; Isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 80:20. Yield: 0.59 g (84%), yellow solid; R_f (G): 0.16; IR (KBr, cm^{-1}): 3259, 1626, 1596, 1580; MS (ESI, 30 eV): *m/z* 490.98 [2M + Na], 216.55 [M − H_2O]; ^1H NMR ($CDCl_3$, δ): 6.99 (s, 1H), 6.98 (d, 1H, *J* = 8.6 Hz), 6.84 (d, 1H, *J* = 8.6 Hz), 6.70 (d, 1H, *J* = 16.0 Hz), 6.53 (d, 1H, *J* = 16.0 Hz), 5.80 (t, 1H, *J* = 6.8 Hz), 4.35 (d, 2H, *J* = 6.8 Hz), 3.93 and 3.90 (2 s, 6H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 149.0, 148.7, 136.4, 131.1, 130.5, 130.1, 127.9, 119.6, 111.2, 108.8, 59.4, 55.9, 55.8, 12.6.

*4.1.4.4. 5-(4-(Dimethylamino)phenyl)-3-methylpenta-2,4-dien-1-ol (**30**).* Reaction time: 1 h; Isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 65:35. Yield: 0.57 g (87%), yellow solid; R_f (E): 0.16; IR (KBr, cm^{-1}): 3309, 1605; MS (ESI, 30 eV): *m/z* 218.57 [MH], 217.56 [M], 199.65 [M − H_2O]; ^1H NMR ($CDCl_3$, δ): 7.32 (d, 2H, *J* = 8.8 Hz), 6.70 (d, 2H, *J* = 8.8 Hz), 6.66 (d, 1H, *J* = 16.0 Hz), 6.52 (d, 1H, *J* = 16.0 Hz), 5.73 (t, 1H, *J* = 6.8 Hz), 4.32 (d, 2H, *J* = 6.8 Hz), 2.97 (s, 6H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 150.0, 137.3, 133.4, 130.7, 128.5, 127.7 (2C), 122.8, 112.8 (2C), 59.7, 40.7 (2C), 12.8.

*4.1.4.5. 3-Methyl-5-(naphthalen-2-yl)penta-2,4-dien-1-ol (**31**).* Reaction time: 1 h; isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 90:10. Yield: 0.55 g (82%), pale yellow solid; R_f (E): 0.15; IR (KBr, cm^{-1}): 3306, 2213, 1624, 1590; MS (ESI, 30 eV): *m/z* 448.21 [2M], 206.59 [M − H_2O]; ^1H NMR ($CDCl_3$, δ): 7.82–7.77 (m, 4H), 7.64 (dd, 1H, *J* = 1.2 and 9.6 Hz), 7.46 and 7.42 (two dt, 2H, *J* = 1.2 and 6.8 Hz), 6.94 (d, 1H, *J* = 16.0 Hz), 6.74 (d, 1H, *J* = 16.0 Hz), 5.86 (t, 1H, *J* = 6.8 Hz), 4.37 (d, 2H, *J* = 6.8 Hz), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 136.4, 134.9, 133.7, 133.2, 131.1, 128.3, 128.2, 127.9, 127.7 (2C), 126.4, 126.3, 125.8, 123.5, 59.5, 12.7.

*4.1.4.6. (E)-3-(Pyren-1-yl)but-2-en-1-ol (**64**).* Reaction time: 1 h; Yield: 0.66 g (80%), pale green solid; mp 115–117 °C; R_f (F): 0.26; IR (KBr, cm^{-1}): 3234, 1654; MS (ESI, 30 eV): *m/z* 567.43 [2M + Na], 295.14 [M + Na], 273.13 [MH], 255.06 [MH − H_2O]; ^1H NMR ($CDCl_3$, δ): 8.14 (d, 1H, *J* = 9.0 Hz), 8.09 (d, 1H, *J* = 7.4 Hz), 8.08 (d, 1H, *J* = 7.4 Hz), 8.06 (d, 1H, *J* = 8.0 Hz), 7.98 (d, 1H, *J* = 9.0 Hz), 7.97 (br.s, 2H), 7.92 (t, 1H, *J* = 7.4 Hz), 7.74 (d, 1H, *J* = 8.0 Hz), 5.79 (tq, 1H, *J* = 1.2 and 6.8 Hz), 4.47 (d, 2H, *J* = 6.8 Hz), 2.21 (d, 3H, *J* = 1.2 Hz); ^{13}C NMR ($CDCl_3$, δ): 140.6, 138.9, 131.6, 131.2, 130.5, 130.4, 128.0, 127.5, 127.4, 127.3, 126.1, 125.8, 125.2, 125.1 (three C), 125.0, 124.7, 60.0, 19.8; Anal. Calcd for $C_{20}H_{16}O_2$: C, 88.20; H, 5.92. Found: C, 88.02; H, 6.11.

*4.1.4.7. (E)-3-(6-methoxynaphthalen-2-yl)but-2-en-1-ol (**65**).* Reaction time: 1 h; Yield: 0.45 g (65%), white solid; mp 118–120 °C; R_f (F): 0.21; IR (KBr, cm^{-1}): 3260, 1626, 1600; MS (ESI, 30 eV): *m/z* 211.29 [MH − H_2O], 158.15 [211.29-C_4H_5]; ^1H NMR ($CDCl_3$, δ): 7.76 (br.s, 1H), 7.72 (d, 1H, *J* = 8.8 Hz), 7.68 (d, 1H, *J* = 8.6 Hz), 7.57 (dd, 1H, *J* = 1.6 and 8.6 Hz), 7.14 (dd, 1H, *J* = 2.4 and 8.8 Hz), 7.12 (br.s, 1H), 6.11 (t, 1H, *J* = 6.8 Hz), 4.42 (d, 2H, *J* = 6.8 Hz), 3.92 (s, 3H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 157.8, 137.9, 137.7, 133.9, 129.6, 128.8, 126.6, 126.3, 124.6, 124.3, 118.9, 105.7, 60.00, 55.3, 15.9; Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.12; H, 6.88.

*4.1.4.8. (E)-3-(Anthracen-2-yl)but-2-en-1-ol (**66**).* The unsaturated ester **63** (2.5 mmol) was reduced by using $LiAlH_4$ (0.29 g, 7.5 mmol) in THF (11 mL) and $AlCl_3$ (0.36 g, 2.7 mmol), to obtain alcohol **66** following the procedure described above. Reaction time: 1 h; Yield: 0.5 g (73%), yellow solid; mp 152–154 °C; R_f (E): 0.14; IR (KBr, cm^{-1}): 3256, 1654; MS (ESI, 30 eV): *m/z* 231.32 [MH − H_2O]; ^1H NMR ($CDCl_3$, δ): 8.41 (s, 1H), 8.38 (s, 1H), 8.00–7.94 (m, 4H), 7.63 (dd, 1H, *J* = 1.6 and 8.8 Hz), 7.45 (dt, 2H, *J* = 3.2 and 9.6 Hz), 6.23 (t, 1H, *J* = 6.8 Hz), 4.47 (d, 2H, *J* = 6.8 Hz), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 139.2, 137.6, 132.2, 132.0, 131.8, 131.2, 131.1, 128.3, 128.2, 127.4, 126.6, 126.0, 125.5, 125.4, 124.5, 124.2, 60.2, 15.9; Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 87.24; H, 6.26.

4.1.5. General procedure for the MnO_2-mediated oxidations of allylic alcohols

To a vigorously stirred solution of alcohols **27**–**31** (2.2 mmol) in CH_2Cl_2 (45 mL), Na_2CO_3 (4.77 g, 45 mmol) and activated MnO_2 powder (3.91 g, 45 mmol) were added. The resulting suspension was stirred at ambient temperature to complete the reaction (monitored by TLC) and then passed through a celite pad. The filtrate was evaporated to dryness to leave a residue. Allylic aldehydes **32**–**36** (only the 2*E*,4*E*-isomer is drawn) were obtained from this residue through FCC purification.

*4.1.5.1. 5-(4-Methoxy-2,3,6-trimethylphenyl)-3-methylpenta-2,4-dienal (**32**).* Reaction time: 1 h; Isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 85:15. Yield: 0.48 g (90%), yellow solid; R_f (C): 0.28; IR (KBr, cm^{-1}): 2855, 2770, 1684, 1610; MS (ESI, 30 eV): *m/z* 267.61 [M + Na], 245.12 [MH]; ^1H NMR ($CDCl_3$, δ): 10.17 (d, 1H, *J* = 8.0 Hz), 7.16 (d, 1H, *J* = 16.0 Hz), 6.60 (s, 1H), 6.32 (d, 1H, *J* = 16.0 Hz), 5.99 (d, 1H, *J* = 8.0 Hz), 3.82 (s, 3H), 2.42, 2.30, 2.23 and 2.14 (4 s, 12H); ^{13}C NMR ($CDCl_3$, δ): 191.4, 156.9, 154.6, 136.6, 136.1, 135.3, 134.2, 129.3, 128.7, 128.4, 110.1, 55.5, 21.4, 17.5, 13.3, 11.7.

*4.1.5.2. 5-(2,4,6-Trimethoxyphenyl)-3-methylpenta-2,4-dienal (**33**).* Reaction time: 1 h; Isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 70:30. Yield: 0.50 g (86%), yellow solid; R_f (E): 0.24; IR (KBr, cm^{-1}): 2860, 2778, 1653, 1598; MS (ESI, 30 eV): *m/z* 285.14 [M + Na], 263.10 [MH]; ^1H NMR ($CDCl_3$, δ): 10.12 (d, 1H, *J* = 8.4 Hz), 7.45 (d, 1H, *J* = 16.0 Hz), 7.30 (d, 1H, *J* = 16.0 Hz), 6.13 (s, 2H), 6.04 (d, 1H, *J* = 8.4 Hz), 3.80 (s, 6H), 3.77 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 191.2, 161.8, 160.4 (2C), 157.4, 132.0, 128.3, 127.3, 107.2, 90.7 (2C), 55.7 (2C), 55.3, 12.7.

*4.1.5.3. 5-(3,4-Dimethoxyphenyl)-3-methylpenta-2,4-dienal (**34**).* Reaction time: 1 h; isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 80:20. Yield: 0.43 g (85%), yellow solid; R_f (E): 0.21; IR (KBr, cm^{-1}): 2841, 2754, 1685, 1604; MS (ESI, 30 eV): *m/z* 233.80 [MH]; ^1H NMR ($CDCl_3$, δ): 10.14 (d, 1H, *J* = 8.0 Hz), 7.07 (d, 1H, *J* = 8.2 Hz), 7.03 (s, 1H), 7.02 (d, 1H, *J* = 16.0 Hz), 6.87 (d, 1H, *J* = 8.2 Hz), 6.77 (d, 1H, *J* = 16.0 Hz), 6.07 (d, 1H, *J* = 8.0 Hz), 3.95 (s, 3H), 3.93 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 191.2, 154.6, 150.3, 149.2, 135.6, 129.4, 129.3, 128.9, 124.5, 111.2, 109.2, 55.9 (2C), 13.1.

*4.1.5.4. 5-(4-(Dimethylamino)phenyl)-3-methylpenta-2,4-dienal (**35**).* Reaction time: 1 h; Isolated as a mixture of two geometric isomers in the ratio 2*E*,4*E*/2*Z*,4*E* = 70:30. Yield: 0.38 g (81%), yellow solid; R_f (D): 0.24; IR (KBr, cm^{-1}): 2836, 2777, 1650, 1595; MS (ESI, 30 eV): *m/z* 216.68 [MH]; ^1H NMR ($CDCl_3$, δ): 10.17 (d, 1H, *J* = 8.0 Hz), 7.41 (d, 2H, *J* = 8.8 Hz), 7.03 (d, 1H, *J* = 16.0 Hz), 6.72 (d, 1H, *J* 16.0 Hz), 6.70 (d, 2H, *J* = 8.8 Hz), 6.03 (d, 1H, *J* = 8.0 Hz), 3.03 (s, 6H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 191.1, 155.7, 151.1, 136.4, 128.9 (2C), 128.2, 126.5, 123.8, 112.1 (2C), 40.2 (2C), 13.0.

*4.1.5.5. 3-Methyl-5-(naphthalen-3-yl)penta-2,4-dienal (**36**).* Reaction time: 1 h; Isolated as a mixture of two geometric isomers in the 2*E*,4*E*/2*Z*,4*E* = 90:10. Yield: 0.39 g (80%), yellow

solid; R_f (D): 0.19; IR (KBr, cm^{-1}): 2862, 2784, 1647, 1608; MS (ESI, 30 eV): m/z 222.61 [M]; ^1H NMR ($CDCl_3$, δ): 10.19 (d, 1H, $J = 8.0$ Hz), 7.89 (br. s, 1H), 7.85–7.81 (m, 3H), 7.68 (dd, 1H, $J = 1.6$ and 8.8 Hz), 7.52–7.48 (m, 2H), 7.24 (d, 1H, $J = 16.0$ Hz), 7.02 (d, 1H, $J = 16.0$ Hz), 6.13 (d, 1H, $J = 8.0$ Hz), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 191.2, 154.2, 135.8, 133.7, 133.5, 133.4, 131.6, 130.1, 128.6, 128.5, 128.3, 127.8, 126.8, 126.6, 123.4, 13.1.

4.1.6. General procedure for the $NaBH_4$-mediated reductions

*4.1.6.1. 2,4-Bis(trifluoromethyl)benzyl alcohol (**47**) and 2,4,5-trifluorobenzyl alcohol (**48**).* To an ice-cold solution of aldehydes **45** and **46** (5 mmol) in MeOH (10 mL), $NaBH_4$ (0.28 g, 7.5 mmol) was added portionwise over 20 min. The resulting reaction mixture was stirred at ambient temperature for 30 min. Excess $NaBH_4$ was destroyed by the addition of ice chips. The reaction mixture was evaporated and a residue was taken up in EtOAc and washed twice with H_2O. Drying over Na_2SO_4 and evaporation gave the corresponding alcohols **47** and **48** in 96% yield as colorless oils. The spectroscopic data of these compounds were identical to those of samples of the same compounds from commercial sources.

*4.1.6.2. (E)-4-(Pyren-1-yl)but-3-en-2-ol (**55**).* Methyl ketone **54** (1.35 g, 5 mmol) was reduced with $NaBH_4$ (0.47 g, 12.5 mmol) in MeOH (5.8 mL) and THF (8.7 mL), following the procedure described above. The anticipated alcohol **55** was obtained after FCC purification as a yellow solid. Reaction time: 30 min; Yield 0.89 g (65%); mp 108–110 °C; R_f (E): 0.17; IR (KBr, cm^{-1}): 3276, 1654; MS (ESI, 30 eV): m/z 567.43 [2M + Na], 295.14 [M + Na], 255.06 [MH − H_2O]; ^1H NMR ($CDCl_3$, δ): 8.35 (d, 1H, $J = 9.2$ Hz), 8.16 (d, 1H, $J = 7.6$ Hz), 8.12 (d, 1H, $J = 7.6$ Hz), 8.06 (d, 1H, $J = 9.2$ Hz), 8.04 (ABq, 2H, $J = 8.4$ Hz), 8.02 (ABq, 2H, $J = 9.2$ Hz), 7.98 (t, 1H, $J = 7.6$ Hz), 7.61 (d, 1H, $J = 16.0$ Hz), 6.48 (dd, 1H, $J = 6.4$ and 16.0 Hz), 4.70 (quint, 1H, $J = 6.4$ Hz), 1.51 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR ($CDCl_3$, δ): 137.0, 131.5, 131.3, 130.9, 130.8, 128.2, 127.6, 127.4, 127.3, 126.5, 126.0, 125.3, 125.0 (2C), 124.9 (2C), 124.0, 123.0, 67.4, 23.7; Anal. Calcd for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.40; H, 5.78.

4.1.7. General procedure for the preparation of triphenylphosphonium bromide salts

Triphenylphosphonium salts **49** and **50** were obtained by treating alcohols **47** and **48** (4.5 mmol) in MeCN/THF (1:1, 10 mL) with $Ph_3P.HBr$ (3.12 g, 9 mmol). The resulting reaction mixture was heated at 80 °C to complete the reaction (as indicated by TLC). The solvents were evaporated and the oily residues were triturated with Et_2O. After overnight refrigeration and filtration of the precipitates, the corresponding salts were obtained and used without further purification.

*4.1.7.1. Triphenyl(2,4-bis(trifluoromethyl)benzyl)phosphonium bromide (**49**).* Reaction time: 5 h; Yield: 1.84 g (72%), white solid; IR (KBr, cm^{-1}): 1584, 1436, 1110, 996, 754, 722, 690; MS (ESI, 30 eV): m/z 489.41 [M − Br].

*4.1.7.2. Triphenyl(2,4,5-trifluorobenzyl)phosphonium bromide (**50**).* Reaction time: 6 h; Yield: 1.75 g (80%), white solid; IR (KBr, cm^{-1}): 1586, 1436, 1110, 996, 864, 756, 722, 690; MS (ESI, 30 eV): m/z 407.18 [M − Br].

The triphenylphosphonium salts **56** and **67**–**69** were synthesized by treating alcohols **55** and **64** (4.5 mmol) in MeOH/diglyme (1:1, 10 mL) or **65** and **66** (4.5 mmol) in MeOH/THF (1:1, 10 mL) with $Ph_3P{\cdot}HBr$ (1.87 g, 5.4 mmol) at ambient temperature. When the reaction was complete (indicated by TLC, 3–24 h), volatile solvents were evaporated and the residues were triturated with Et_2O. After overnight refrigeration and filtration of the thus obtained precipitates, the corresponding salts were obtained and used as such without further purification.

*4.1.7.3. (E)-Triphenyl(4-(pyren-1-yl)but-3-en-2-yl)phosphonium bromide (**56**).* Reaction time: 3 h; Yield: 2.64 g (98%), yellow solid; IR (KBr, cm^{-1}): 1630, 1585, 1560, 1436, 1106, 994, 848, 722, 690; MS (ESI, 30 eV): m/z 517.25 [M − Br].

*4.1.7.4. (E)-Triphenyl(3-(pyren-1-yl)but-2-enyl)phosphonium bromide (**67**).* Reaction time: 24 h; Yield: 2.29 g (85%), yellow solid; IR (KBr, cm^{-1}): 1622, 1584, 1436, 1112, 994, 852, 744, 720, 688; MS (ESI, 30 eV): m/z 517.23 [M − Br].

*4.1.7.5. (E)-(3-(6-Methoxynaphthalen-2-yl)but-2-enyl)triphenylphosphonium bromide (**68**).* Reaction time: 10 h; Yield: 2.44 g (98%), white solid; IR (KBr, cm^{-1}): 1622, 1598, 1438, 1112, 886, 758, 726, 688; MS (ESI, 30 eV): m/z 473.07 [M − Br].

*4.1.7.6. (E)-(3-(Anthracen-2-yl)but-2-enyl)triphenylphosphonium (**69**).* Reaction time: 24 h; Yield: 2.27 g (88%), pale yellow solid; IR (KBr, cm^{-1}): 1624, 1584, 1438, 1112, 900, 858, 754, 722, 684; MS (ESI, 30 eV): m/z 493.25 [M − Br].

4.1.8. General procedure for the Wittig reactions

*4.1.8.1. With ethyl E-3-formylbut-2-enoate (**42**).* To a solution of salts **67**–**69** (3 mmol) and aldehyde **42** (0.36 g, 2.5 mmol) in DMF (3 mL), 1,2-butylene oxide (6 mmol, 0.52 mL) was added and the resulting solution was heated at 60 °C. When reaction was complete (monitored by TLC), the resulting mixture was diluted in EtOAc, the resulting mixture was washed twice with H_2O, dried over Na_2SO_4 and evaporated to dryness to leave a residue. The corresponding unsaturated esters **70**–**72** (only the *all-E* isomer is drawn) were obtained pure from this residue with the aid of FCC.

*4.1.8.1.1. Ethyl 3-methyl-7-(pyren-1-yl)octa-2,4,6-trienoate (**70**).* Reaction time: 16 h; Compound **70** was obtained as an inseparable mixture of 2 isomers in the ratio 2*E*,4*E*,6*E*:2*E*,4*Z*,6*E* = 80:20 as indicated by HPLC (70% MeCN/H_2O to 100% MeCN), $t_{R1} = 24.167$ min, $t_{R2} = 26.088$ min; Yield: 0.74 g (77%), orange solid; R_f(A): 0.29; IR (KBr, cm^{-1}): 1708, 1630, 1600; MS (ESI, 30 eV): m/z 761.55 [2M + H], 381.25 [MH].

*4.1.8.1.2. Ethyl 7-(6-methoxynaphthalen-2-yl)-3-methylocta-2,4,6-trienoate (**71**).* Reaction time: 3 h; Compound **71** was obtained as an inseparable mixture of 2 isomers in the ratio 2*E*,4*E*,6*E*:2*E*,4*Z*,6*E* = 55:45 as indicated by HPLC (70% MeCN/H_2O to 100% MeCN), $t_{R1} = 26.281$ min, $t_{R2} = 26.902$ min; Yield: 0.65 g (77%), orange solid; R_f (B): 0.28; IR (KBr, cm^{-1}): 1708, 1626, 1602; MS (ESI, 30 eV): m/z 337.13 [MH].

*4.1.8.1.3. Ethyl (E)-7-(anthracen-2-yl)-3-methylocta-2,4,6-trienoate (**72**).* Reaction time: 2 h; The *all-trans*-**72** was isolated through FCC from its 4*Z* isomer (0.22 g, 25%), using the solvent system C as eluant; Yield: 0.98 g (54%), yellow solid; R_f (C): 0.29; mp 160–162 °C; IR (KBr, cm^{-1}): 1708, 1654, 1616; MS (ESI, 30 eV): m/z 357.13 [MH], 311.36 [MH − CH_3CH_2OH]; ^1H NMR ($CDCl_3$, δ): 8.41 (s, 1H), 8.37 (s, 1H), 8.05 (br.s, 1H), 8.00–7.98 (m, 2H), 7.96 (d, 1H, $J = 9.2$ Hz), 7.69 (dd, 1H, $J = 1.6$ and 9.2 Hz), 7.47 (dt, 2H, $J = 3.8$ and 9.6 Hz), 7.12 (dd, 1H, $J = 11.2$ and 15.2 Hz), 6.83 (d, 1H, $J = 11.2$ Hz), 6.45 (d, 1H, $J = 15.2$ Hz), 5.85 (s, 1H), 4.18 (q, 2H, $J = 7.2$ Hz), 2.42 (d, 3H, $J = 0.8$ Hz), 2.41 (s, 3H), 1.32 (t, 3H, $J = 7.2$ Hz).

For the sake of comparison, the 4*Z*-isomer showed the protons: H-2 as a singlet (5.85 ppm), H-4 as a doublet (5.94 ppm, $J = 11.6$ Hz), H-5 as a triplet (6.67 ppm, $J = 11.6$ Hz) and H-6 as a doublet (7.19 ppm, $J = 12.0$ Hz).

*4.1.8.2. With ethyl (2E,4E)-5-formyl-3-methylpenta-2,4-dienoate (**43**).* To a cooled (−78 °C) suspension of salt **56** (1.8 g, 3 mmol) in

THF (7 mL), a 1.6 M solution of *n*-BuLi in hexanes (1.92 mL) was added dropwise and the resulting mixture was vigorously stirred for additional 30 min, at this temperature. Then, aldehyde **43** (0.39 g, 2.3 mmol) was added and the resulting reaction mixture was further stirred at −78 °C for 30 min and then left to attain room temperature where it remained for 1.5 h. Excess *n*-BuLi was then destroyed by the careful addition of a 5% aqueous solution of NH_4Cl. The resulting mixture was extracted with EtOAc, washed twice with H_2O, dried over Na_2SO_4 and evaporated to dryness. The unsaturated ester **57** was obtained pure after FCC.

*4.1.8.2.1. Ethyl 3,7-dimethyl-9-(pyren-1-yl)nona-2,4,6,8-tetraenoate (**57**).* Ester **57** was obtained as an inseparable mixture of 2 isomers in the ratio 2*E*,4*E*,6*E*,8*E*:2*E*,4*E*,6*Z*,8*E* = 60:40 as indicated by HPLC (70% MeCN/H_2O to 100% MeCN), t_{R1} = 21.163 min, t_{R2} = 21.476 min; Yield: 0.72 g (81%), orange solid; R_f (A): 0.18; IR (KBr, cm^{-1}): 1718, 1708, 1654, 1604; MS (ESI, 30 eV): *m*/*z* 429.55 [M + Na].

*4.1.8.3. With ethyl (2E,4E,6E)-7-formyl-3-methylocta-2,4,6-trienoate (**44**).* To a solution of phosphonium salts **49** or **50** (3 mmol) and aldehyde **44** (0.31 g, 1.5 mmol) in DMF (5 mL), 1,2-butylene oxide (0.31 mL, 3.6 mmol) was added and the resulting solution was heated at 60 °C for 4–8 h. When the reaction was complete, the resulting mixture was diluted with EtOAc and the resulting organic phase was washed twice with H_2O, dried over Na_2SO_4 and evaporated to dryness to leave a residue. The corresponding unsaturated esters **51** and **52** were obtained from this residue after FCC purification.

*4.1.8.3.1. Ethyl 9-(2,4-bis(trifluoromethyl)phenyl)-3,7-dimethylnona-2,4,6,8-tetraenoate (**51**).* Ester **51** was obtained as an inseparable mixture of 2 isomers in the ratio 2*E*,4*E*,6*E*,8*E*:2*E*,4*E*,6*E*,8*Z* = 1:1 as indicated by HPLC (70% MeCN/H_2O to 100% MeCN), t_{R1} = 22.281 min, t_{R2} = 24.177 min; Reaction time: 4 h; Yield: 0.46 g (74%), yellow solid; R_f (B): 0.30; IR (KBr, cm^{-1}): 1706, 1630, 1602; MS (ESI, 30 eV): *m*/*z* 859.91 [2M + Na], 441.21 [M + Na].

*4.1.8.3.2. Ethyl 3,7-dimethyl-9-(2,4,5-trifluorophenyl)nona-2,4,6,8-tetraenoate (**52**).* Ester **52** was obtained as an inseparable mixture of 2 isomers in the ratio 2*E*,4*E*,6*E*,8*E*:2*E*,4*E*,6*E*,8*Z* = 60:40 as indicated by HPLC (70% MeCN/H_2O to 100% MeCN), t_{R1} = 24.922 min, t_{R2} = 25.989 min; Reaction time: 8 h; Yield: 0.40 g (79%), yellow solid; R_f (B): 0.36; IR (KBr, cm^{-1}): 1706, 1635, 1600; MS (ESI, 30 eV): *m*/*z* 337.94 [M + H], 291.85 [MH − CH_3CH_2OH].

4.1.9. General procedure for the saponification of tri- or tetraene esters

To a suspension of crude esters **37**–**41**, **51**, **52**, **57**, **70**, **71** and ***E*-72** (0.9 mmol) in MeOH (1.8 mL) and DMSO (0.25 mL), an 8 N aqueous solution of NaOH (0.31 mL) was added. The resulting reaction mixture was heated at 65 °C until completion of the reaction (as indicated by TLC). After evaporation of MeOH, the oily residue was diluted with H_2O (5 mL), cooled to 0 °C and acidified with a 5% aqueous solution of citric acid to pH 5. The resulting mixture was extracted twice with EtOAc. The organic layers were combined and washed once with a saturated aqueous solution of NaCl and twice with H_2O, dried over Na_2SO_4 and evaporated to dryness to obtain the corresponding acids **2**–**12**. Acitretin (**2**) and analogs **3**–**12** were obtained as *all-E* acids after crystallization from EtOAc.

*4.1.9.1. (2E,4E,6E,8E)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid (**2**).* Reaction time: 2 h; Yield: 0.14 g (48%), yellow solid; mp 228–230 °C; IR (KBr, cm^{-1}): 3300–2500, 1700, 1608, 1576; HPLC (40% MeCN/H_2O to 100% MeCN): t_R = 18.629 min; MS (ESI, 30 eV): *m*/*z* 327.49 [MH], 309.41 [MH − H_2O]; ^{1}H NMR (DMSO-d_6, δ): 7.05 (d, 1H, *J* = 11.6 and 15.2 Hz), 6.71 (d, 1H, *J* = 15.2 Hz), 6.69 (s, 1H), 6.42 (d, 1H, *J* = 15.2 Hz), 6.29 (d, 1H, *J* = 11.6 Hz), 6.28 (d, 1H, *J* = 15.2 Hz), 5.79 (s, 1H), 3.75 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (DMSO-d_6, δ): 167.8, 155.6, 151.6, 138.9, 137.6, 135.8, 135.2, 133.5, 130.7, 130.5, 129.2, 128.1, 121.5, 119.7, 110.1, 55.3, 21.2, 17.2, 13.4, 12.7, 11.8.

*4.1.9.2. (2E,4E,6E,8E)-3,7-Dimethyl-9-(2,4,6-trimethoxyphenyl) nona-2,4,6,8-tetraenoic acid (**3**).* Reaction time: 2 h; Yield: 0.17 g (54%), reddish solid; mp 241–243 °C; IR (KBr, cm^{-1}): 3300–2500, 1674, 1607, 1555; HPLC (40% MeCN/H_2O to 100% MeCN): t_R = 12.086 min; MS (ESI, 30 eV): *m*/*z* 688.12 [2 M], 687.17 [2M − H], 345.44 [MH], 327.42 [MH − H_2O]; ^{1}H NMR (DMSO-d_6, δ): 7.22 (d, 1H, d, *J* = 16.4 Hz), 7.05 (dd, 1H, *J* = 11.6 and 15.2 Hz), 6.89 (d, 1H, *J* = 16.4 Hz), 6.41 (d, 1H, *J* = 15.2 Hz), 6.27 (d, 1H, *J* = 11.6 Hz), 6.26 (s, 2H), 5.76 (s, 1H), 3.83 (s, 6H), 3.80 (s, 3H), 2.28 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (DMSO-d_6, δ): 167.8, 160.3, 159.1 (2C), 151.7, 140.6, 134.8, 133.5, 131.1, 129.7, 120.5, 119.1, 106.9, 91.0 (2C), 55.8 (2C), 55.3, 13.4, 12.4; Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.55; H, 7.19.

*4.1.9.3. (2E,4E,6E,8E)-9-(3,4-dimethoxyphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid (**4**).* Reaction time: 2 h; Yield: 0.2 g (70%), yellow solid; mp 235–237 °C; IR (KBr, cm^{-1}): 3200–2500, 1670, 1604, 1574; HPLC (40% MeCN/H_2O to 100% MeCN): t_R = 10.250 min; MS (ESI, 30 eV): *m*/*z* 666.96 [2M + K], 628.11 [2M], 627.28 [2M − H], 353.37 [M + K], 315.40 [MH], 297.38 [MH − H_2O]; ^{1}H NMR (DMSO-d_6, δ): 7.17 (s, 1H), 7.05 (dd, 1H, *J* = 11.6 and 15.2 Hz), 7.04 (d, 1H, *J* = 8.0 Hz), 6.95 (d, 1H, *J* = 16.0 Hz), 6.92 (d, 1H, *J* = 8.0 Hz), 6.69 (d, 1H, *J* = 16.0 Hz), 6.43 (d, 1H, *J* = 15.2 Hz), 6.40 (d, 1H, *J* = 11.6 Hz), 5.81 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 2.29 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (DMSO-d_6, δ): 167.8, 151.6, 148.9, 148.8, 137.4, 135.1, 130.7, 130.0, 129.2, 123.3, 120.0, 119.4, 111.8, 110.5, 109.3, 55.5, 55.4, 13.4, 12.8; Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.70; H, 6.87.

*4.1.9.4. (2E,4E,6E,8E)-9-(4-(Dimethylamino)phenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid (**5**).* Reaction time: 1 h; Yield: 0.16 g (61%), yellow solid; mp 249–251 °C; IR (KBr, cm^{-1}): 3200–2500, 1674, 1604, 1556; HPLC (40% MeCN/H_2O to 100% MeCN): t_R = 4.217 min; MS (ESI, 30 eV): *m*/*z* 594.34 [2M], 593.33 [2M − H], 298.45 [MH], 280.44 [MH − H_2O]; ^{1}H NMR (DMSO-d_6, δ): 7.36 (d, 2H, *J* = 8.4 Hz), 7.05 (dd, 1H, *J* = 12.0 and 15.2 Hz), 6.80 (d, 1H, *J* = 16.0 Hz), 6.69 (d, 2H, *J* = 8.4 Hz), 6.64 (d, 1H, *J* = 16.0 Hz), 6.40 (d, 1H, *J* = 15.2 Hz), 6.33 (d, 1H, *J* = 12.0 Hz), 5.78 (s, 1H), 2.92 (s, 6H), 2.28 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (DMSO-d_6, δ): 167.9, 151.9, 149.9, 139.6, 134.7, 131.15 (2C), 129.7, 129.5, 128.3, 128.2, 127.7 (2C), 125.0, 119.1, 112.2 (2C), 13.4, 12.8 ppm; Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.90; H, 7.54; N, 4.60.

*4.1.9.5. (2E,4E,6E,8E)-9-(2,4-bis(Trifluoromethyl)phenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid (**6**).* Reaction time: 2 h; Yield: 0.13 g (40%), yellow solid; mp 235–237 °C; IR (KBr, cm^{-1}): 3200–2500, 1694, 1604, 1574; HPLC (40% MeCN/H_2O to 100% MeCN): t_R = 19.908 min; MS (ESI, 30 eV): *m*/*z* 391.35 [MH], 373.34 [MH − H_2O]; ^{1}H NMR (DMSO-d_6, δ): 8.18 (d, 1H, *J* = 8.4 Hz), 8.03 (d, 1H, *J* = 8.4 Hz), 7.98 (s, 1H), 7.32 (d, 1H, *J* = 16.0 Hz), 7.08 (dd, 1H, *J* = 11.6 and 15.2 Hz), 6.88 (d, 1H, *J* = 15.2 Hz), 6.61 (d, 1H, *J* = 11.6 Hz), 6.57 (d, 1H, *J* = 16.0 Hz), 5.89 (s, 1H), 2.29 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (DMSO-d_6, δ): 167.7, 151.0, 140.0, 139.8, 138.3, 137.6, 135.4, 130.1, 129.4 (unresolved m), 128.1, 127.5 (q, J_{FC} = 37.7 Hz), 126.1 (q, J_{FC} = 35.6 Hz), 123.6 (q, J_{FC} = 270.9 Hz), 123.4 (q, J_{FC} = 288.4 Hz), 123.0 (unresolved m), 121.4, 121.1, 13.4, 12.5; ^{19}F NMR (DMSO-d_6, δ): −58.78 (3F), −61.21 (3F); Anal. Calcd for $C_{19}H_{16}F_6O_2$: C, 58.47; H, 4.13; Found: C, 58.30; H, 4.32.

*4.1.9.6. (2E,4E,6E,8E)-3,7-Dimethyl-9-(2,4,5-trifluorophenyl)nona-2,4,6,8-tetraenoic acid (**7**).* Reaction time: 1 h; Yield: 0.12 g (42%), yellow solid; mp 220–222 °C; IR (KBr, cm^{-1}): 3200–2500, 1676, 1602; HPLC (40% MeCN/H_2O to 100% MeCN): t_R = 15.238 min; MS (ESI, 30 eV): *m/z* 309.41 [MH], 291.40 [MH − H_2O]; ^{1}H NMR (DMSO-d_6, δ): 12.20 (br.s, 1H), 7.89 (unresolved dt, 1H), 7.55 (unresolved dt, 1H), 7.15 (d, 1H, *J* = 16.0 Hz), 7.05 (dd, 1H, *J* = 12.0 and 15.2 Hz), 6.66 (d, 1H, *J* = 16.0 Hz), 6.51 (d, 1H, *J* = 15.2 Hz), 6.29 (d, 1H, *J* = 12 Hz), 5.86 (s, 1H), 2.28 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (DMSO-d_6, δ): 167.8, 154.7 (dd, J_{FC} = 7.2 and 250.6 Hz), 151.3, 148.4 (dd, J_{FC} = 19.3 and 240.9 Hz), 146.6 (dd, J_{FC} = 11.4 and 240.4 Hz), 138.2, 137.3, 136.5, 133.5, 130.4, 122.2 (unresolved m), 120.6, 118.2, 114.4 (dd, J_{FC} = 4.4 and 19.6 Hz), 106.1 (dt, J_{FC} = 7.8 and 29 Hz), 13.4, 12.6; ^{19}F NMR (DMSO-d_6, δ) −114.88, −119.44, −135.19; Anal. Calcd for $C_{17}H_{15}F_3O_2$: C, 66.23; H, 4.90. Found: 66.05; H, 4.98.

*4.1.9.7. (2E,4E,6E,8E)-3,7-dimethyl-9-(naphthalen-2-yl)nona-2,4,6,8-tetraenoic acid (**8**).* Reaction time: 1 h; Yield: 0.22 g (81%), yellow solid; mp 231–233 °C; IR (KBr, cm^{-1}): 3200–2500, 1670, 1604, 1570; HPLC (40% MeCN/H_2O to 100% MeCN): t_R = 18.177 min; MS (ESI, 30 eV): *m/z* 305.83 [MH], 287.79 [MH − H_2O]; ^{1}H NMR (DMSO-d_6, δ): 12.08 (br.s, 1H), 7.96 (s, 1H), 7.87 (d, 2H, *J* = 6.8 Hz), 7.87 (d, 1H, *J* = 8.4 Hz), 7.80 (d, 1H, *J* = 8.4 Hz), 7.50 (t, 1H, *J* = 6.4 Hz), 7.47 (t, 1H, *J* = 6.4 Hz), 7.21 (d, 1H, *J* = 16.0 Hz), 7.09 (t, 1H, *J* = 13.4 Hz), 6.92 (d, 1H, *J* = 16.0 Hz), 6.49 (d, 2H, *J* = 13.4 Hz), 5.85 (s, 1H), 2.30 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (DMSO-d_6, δ): 167.8, 151.4, 138.9, 136.3, 134.8, 133.5, 133.3, 132.5, 132.0, 130.7, 129.1, 128.2, 127.9, 127.6, 126.5, 126.4, 126.0, 123.7, 120.1, 13.4, 12.8 ppm; Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 83.00; H, 6.48.

*4.1.9.8. (2E,4E,6E,8E)-3,7-dimethyl-9-(pyren-1-yl)nona-2,4,6,8-tetraenoic acid (**9**).* Reaction time: 2.5 h; Yield: 0.16 g (45%), orange solid; mp 252–254 °C; IR (KBr, cm^{-1}): 3200–2500, 1690, 1594, 1556; HPLC (40% MeCN/H_2O to 100% MeCN): t_R = 25.231 min; MS (ESI, 30 eV): *m/z* 417.30 [M + K], 379.32 [MH], 361.43 [MH − H_2O]; ^{1}H NMR (DMSO-d_6, δ) 8.65 (d, 1H, *J* = 9.6 Hz), 8.44 (d, 1H, *J* = 8.0 Hz), 8.31–8.23 (m, 4H), 8.16 (s, 2H), 8.07 (t, 1H, *J* = 8.0 Hz), 7.85 (d, 1H, *J* = 15.6 Hz), 7.37 (d, 1H, *J* = 15.6 Hz), 7.15 (dd, 1H, *J* = 11.2 and 15.2 Hz), 6.60 (d, 1H, *J* = 11.2 Hz), 6.53 (d, 1H, *J* = 15.2 Hz), 5.86 (s, 1H), 2.33 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (DMSO-d_6, δ): 167.9, 151.5, 139.6, 136.6, 136.1, 132.6, 131.5, 131.1, 130.9, 130.5, 130.3, 127.7, 127.6, 127.5, 127.3, 126.4, 125.5, 125.4, 125.2 (2C), 124.4, 124.1, 123.4, 123.1, 120.1, 13.5, 13.1; Anal. Calcd for $C_{27}H_{22}O_2$: C, 85.69; H, 5.86. Found: C, 85.89 H, 5.65.

*4.1.9.9. (2E,4E,6E)-3-Methyl-7-(pyren-1-yl)octa-2,4,6-trienoic acid (**10**).* Reaction time: 2.5 h; Yield: 0.16 g (51%), orange solid; mp 244–245 °C; IR (KBr, cm^{-1}): 3200–2500, 1700, 1590, 1574; HPLC (40% MeCN/H_2O to 100% MeCN): t_R = 21.073 min; MS (ESI, 30 eV): *m/z* 704.21 [2M], 703.23 [2M − H], 353.37 [MH], 335.36 [MH − H_2O]; ^{1}H NMR (DMSO-d_6, δ): 12.12 (br.s, 1H), 8.30 (d, 1H, *J* = 9.6 Hz), 8.29 (d, 1H, *J* = 7.6 Hz), 8.26 (d, 1H, *J* = 9.6 Hz), 8.18 (br.s, 2H), 8.17 (br.s, 2H), 8.08 (t, 1H, *J* = 7.6 Hz), 7.95 (d, 1H, *J* = 7.6 Hz), 7.23 (dd, 1H, *J* = 11.2 and 15.2 Hz), 6.53 (d, 1H, *J* = 15.2 Hz), 6.39 (d, 1H, *J* = 11.2 Hz), 5.83 (s, 1H), 2.47 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (DMSO-d_6, δ): 167.8, 151.5, 140.5, 140.2, 136.4, 131.1, 130.9, 130.5, 130.4, 129.0, 127.5, 127.3, 127.2, 127.1, 124.4, 125.6, 125.3, 125.0, 124.8, 124.7, 124.2, 124.1, 120.0, 20.0, 13.5 ppm; Anal. Calcd for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72. Found: C, 85.01; H, 5.94.

*4.1.9.10. (2E,4E,6E)-7-(6-methoxynaphthalen-2-yl)-3-methylocta-2,4,6-trienoic acid (**11**).* Reaction time: 2 h; Yield: 0.13 g (45%), yellow solid; mp 241–243 °C; IR (KBr, cm^{-1}): 3200–2500, 1674, 1594, 1575; HPLC (40% MeCN/H_2O to 100% MeCN): t_R = 13.831 min; MS (ESI, 30 eV): *m/z* 616.19 [2M], 615.19 [2M − H], 309.41 [MH], 291.40 [MH − H_2O]; ^{1}H NMR (DMSO-d_6, δ): 12.03 (br. s, 1H), 7.98 (s, 1H), 7.85 (d, 1H, *J* = 9.2 Hz), 7.79 (d, 1H, *J* = 8.8 Hz), 7.73 (d, 1H, *J* = 8.8 Hz), 7.30 (br. s, 1H), 7.16 (d, 1H, *J* = 9.2 Hz), 7.14 (dd, 1H, *J* = 11.2 and 15.2 Hz), 6.86 (d, 1H, *J* = 11.2 Hz), 6.57 (d, 1H, *J* = 15.2 Hz), 5.82 (s, 1H), 3.87 (s, 3H), 2.33 (s, 6H); ^{13}C NMR (DMSO-d_6, δ): 167.7, 157.5, 151.6, 138.9, 136.6, 136.1, 133.8, 131.2, 129.8, 128.4, 126.7, 126.2, 124.4, 124.0, 119.5, 118.7, 105.8, 55.2, 15.7, 13.4 ppm; Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 78.03; H, 6.35.

*4.1.9.11. (2E,4E,6E)-7-(Anthracen-2-yl)-3-methylocta-2,4,6-trienoic acid (**12**).* Reaction time: 5 h; Yield: 0.15 g (52%), yellow solid; mp 251–253 °C; IR (KBr, cm^{-1}): 3200–2500, 1676, 1610, 1590; HPLC (40% MeCN/H_2O to 100% MeCN): t_R = 20.185 min; MS (ESI, 30 eV): *m/z* 656.20 [2M], 655.30 [2M − H], 329.44 [MH], 311.43 [MH − H_2O]; ^{1}H NMR (DMSO-d_6, δ): 8.58 (s, 1H), 8.52 (s, 1H), 8.19 (s, 1H), 8.12–7.98 (m, 3H), 7.83 (d, 1H, *J* = 8.8 Hz), 7.52 (m, 2H), 7.18 (unresolved dd, 1H), 6.99 (d, 1H, *J* = 11.2 Hz), 6.64 (d, 1H, *J* = 14.8 Hz), 5.85 (s, 1H), 2.39 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (DMSO-d_6, δ) 167.8, 151.6, 138.6, 138.1, 136.9, 131.6, 131.5, 131.3, 131.2, 130.6, 128.1 (2C), 128.0, 127.4, 126.7, 125.8 (2C), 125.7, 124.6, 123.5, 120.0, 15.6, 13.5; Anal. Calcd for $C_{23}H_{20}O_2$: C, 84.12; H, 6.14. Found: C, 84.40; H, 5.94.

4.2. Biological studies

4.2.1. Materials

Eagle's minimal essential medium (EMEM), fetal bovine serum (FBS), sodium pyruvate, sodium bicarbonate, nonessential amino acids, penicillin, streptomycin, amphoterecin B, gentamycin and L-glutamine were all obtained from Biochrom KG (Berlin, Germany). Insulin was obtained from Sigma Chemicals (Steinhelm, Germany). All other chemicals used were of the best commercially available grade.

4.2.2. Cell culture conditions

MCF-7 (ATCC: HTB 22; human breast adenocarcinoma, ER-positive) was obtained from the American Type Culture Collection (ATCC) and cultured as monolayers at 37 °C in a humidified atmosphere of 5% (v/v) CO_2 and 95% air. Cells were seeded in 75-cm^2 plastic tissue culture flasks and cultured in EMEM supplemented with 10% FBS, 2 mM L-glutamine, 0.8 mM sodium pyruvate, 1.5 g/L sodium bicarbonate, 0.1 mM nonessential amino acids, 0.01 mg/mL of insulin and a cocktail of antimicrobial agents (100 IU/mL penicillin, 100 μg/mL streptomycin, 2.5 μg/mL amphotericin B and 10 μg/mL gentamicin sulphate) [66]. According to pilot experiments with respect to growth rate and doubling time, the medium was changed every three days. Confluent cultures, after being washed with phosphate buffered saline (PBS), were harvested by trypsinization with 0.05% (w/v) trypsin in PBS containing 0.02% (w/v) Na_2EDTA.

4.2.3. Cell proliferation

In order to evaluate the effects of the new acitretin derivatives on cell proliferation, cells were seeded in the presence of serum into 48-well plates at a density of 1.5×10^4 cells/well. Twenty-four hours after plating, new medium supplemented with the compounds to be tested was added. The compounds were diluted in DMSO as a stock reagent and remained stored at −20 °C. To achieve the desirable concentrations for the experiments, the stock reagents were diluted to appropriate final concentrations in the culture media [67]. After 72 h incubation, WST-1 (water-soluble tetrazolium salt) was added at a ratio 1:10. Cells were incubated for 1 h and the quantification of the formazan dye in the microplate was measured with an ELISA plate reader at 450 nm (reference wavelength at 650 nm).

4.2.4. Cell cycle analysis

Cell cycle analysis was performed by flow cytometry as previously described [68], that is cells were plated at a density of 104 cells/cm^2 in DMEM containing 10% FBS and after 24 h analog **3** at a concentration of 10^{-5} M was added. After 9, 24 and 48 h the cells were trypsinized, washed with PBS, fixed in 70% (v/v) ice-cold ethanol, and stained with propidium iodide (50 μg/mL), in the presence of $MgCl_2$ (5 mM) and RNAse A (10 μg/mL) in Tris–HCl pH 7.5 (10 mM). DNA content was analyzed on a FACS Calibur flow cytometer (Becton–Dickinson, San Jose, CA) using the Modfit software.

4.2.5. Western immunoblot analysis

MCF-7 cells were treated with analog **3** at a concentration of 10^{-5} M and after treatment they were washed with ice-cold tris buffered saline (TBS: 10 mM Tris–HCl pH 7.4, 150 mM NaCl) and scraped immediately in hot 2× SDS-PAGE sample buffer [125 mM Tris–HCl pH 6.8, 5% (w/v) SDS, 20% (v/v) glycerol, 125 mM β-mercaptoethanol, 0.02% (w/v) bromophenol blue], supplemented with protease- and phosphatase-inhibitor cocktails (Sigma). Cell-lysates were sonicated for 15 s, boiled for 5 min, clarified by centrifugation, aliquoted and stored at −80 °C until use. The samples were separated on SDS-PAGE and the proteins were transferred to PVDF membranes (Amersham Biosciences, Buckinghamshire, UK). The membranes were blocked with 5% (w/v) non-fat milk in 10 mM Tris–HCl pH 7.4, 150 mM NaCl, 0.05% Tween-20 (TBS-T) buffer and incubated overnight at 4 °C with the appropriate primary antibodies. After washing with 5% non-fat milk, the membranes were incubated with the respective second antibody for 1.5 h, washed again with 5% non-fat milk and TBS-T, and the immunoreactive bands were visualized on Kodak-X-OMAT AR film by chemiluminescence (ECL kit) according to the manufacturer's (Amersham Biosciences, Buckinghamshire, UK) instructions.

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Appendix. Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.ejmech.2010.12.008.

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