Bioorganic & Medicinal Chemistry 20 (2012) 3635–3651

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis of methoxylated goniothalamin, aza-goniothalamin and γ-pyrones and their in vitro evaluation against human cancer cells

Rosimeire Coura Barcelos [a], Julio Cezar Pastre [a], Vanessa Caixeta [a], Débora Barbosa Vendramini-Costa [b,c], João Ernesto de Carvalho [b,c], Ronaldo Aloise Pilli [a,b,*]

[a] Departamento de Química Orgânica, Instituto de Química, UNICAMP, CP 6154, 13083-970 Campinas, SP, Brazil
[b] Programa de Pós-graduação em Biologia Celular e Estrutural, Instituto de Biologia, UNICAMP, CP 6109, 13083-970 Campinas, SP, Brazil
[c] Divisão de Farmacologia e Toxicologia, Centro Pluridisciplinar de Pesquisas Químicas, Biológicas e Agrícolas (CPQBA), UNICAMP, CP 6171, 13083-970 Campinas, SP, Brazil

ARTICLE INFO

Article history:
Received 18 January 2012
Revised 16 March 2012
Accepted 23 March 2012
Available online 1 April 2012

Keywords:
Goniothalamin
Cancer cells
Antiproliferative activity
γ-Pyrones
Dihydro-γ-pyrones
Aza-goniothalamin

ABSTRACT

The present work describes the preparation of three novel series of compounds based on the structure of goniothalamin, a natural styryl lactone which has been found to display cytotoxic and antiproliferative activities against a variety of cancer cell lines. A focused library of 29 novel goniothalamin analogues was prepared and evaluated against seven human cancer cell lines. While the γ-pyrones and the aza-goniothalamin analogues were less potent than the lead compound, 2,4-dimethoxy analogue **88** has shown to be more potent in vitro than goniothalamin against all cancer cell lines evaluated. Furthermore, it was more potent than doxorubicin against NCI-ADR/RES, OVCAR-03 and HT-29 while being less toxic to human keratinocytes (HaCat). The 3,5-dimethoxy analogue **90** and 2,4,5-trimethoxy analogue **92** also displayed promising antiproliferative activity when compared to goniothalamin (**1**). These results provide new elements for the design and synthesis of novel representatives of this family of natural compounds.

1. Introduction

Cancer treatment includes many strategies and chemotherapy plays a central role in curing the disease or considerably prolonging and improving the patient's quality of life. However, resistance of tumor cells to multiple structurally unrelated cytotoxic drugs (multidrug resistance) is nowadays the major limitation to the successful chemotherapeutic treatment of disseminated neoplasms. In this regard, natural products remain a privileged source for the discovery and the development of new compounds for cancer treatment.[1]

During an ongoing program to identify new candidates for cancer treatment, goniothalamin (**1**) (Fig. 1) was recognized as a good lead compound with significant cytotoxic and antiproliferative activities against a variety of cancer cell lines, including kidney, prostate, breast carcinoma, leukemia, lung and liver.[2,3] Originally isolated from various species of the genus *Goniothalamus*,[4] this styryl lactone also presents other important biological activities including antimicrobial,[5] antifungal,[6] larvicidal,[7] insecticidal[8] and trypanocidal.[9]

Several efforts have been made in an attempt to elucidate the mechanism responsible for the cytotoxic and antiproliferative properties displayed by goniothalamin and analogues. Some studies indicate the apoptotic activity of goniothalamin in cancer cell lines through different pathways, including the increase in the expression of caspases 3, 7 and 9,[10] increase in the expression of pro-apoptotic protein Bax,[11] inhibition of constitutive NOS[12] and inhibition of nucleus-cytoplasm transport mediated by CRM1.[13] Recently, in vivo studies performed by our group with goniothalamin in a solid tumor experimental model in mice confirmed its low acute toxicity and suggested a relationship between anticancer and anti-inflammatory activities, with the anti-inflammatory activity favoring the antiproliferative activity itself.[14]

In order to fine tune the cytotoxic activity and to better understand its mode of action, the synthesis of new goniothalamin derivatives continues to attract interest. Such analogues could be useful for the elucidation of structure–activity relationships (SARs) and could result in the development of compounds with higher activity and selectivity.

A limited number of structure–activity relationship studies of goniothalamin and synthetic analogues established some of the relevant structural requirements for the cytotoxic activity (Fig. 2).[15]

Mu and co-workers described the semi-synthesis of 19 derivatives of the natural isomer (*R*)-goniothalamin (only most active compounds were shown) and found that 2- and 4-nitro analogues **2** and **3**, respectively, were the most active against promyelocytic leukemia (HL-60) and human lung carcinoma (A549) cells. On

* Corresponding author. Tel.: +55 19 3521 4739; fax: +55 19 3521 4892.
E-mail address: pilli@iqm.unicamp.br (R.A. Pilli).

0968-0896/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2012.03.059

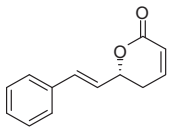


Figure 1. Chemical structure of (*R*)-goniothalamin (**1**).

the other hand, most of the amino acid derivatives of goniothalamin expressed poor antitumor activities.[16]

Later, Pilli and co-workers prepared both enantiomers of goniothalamin and it was found that (*S*)-goniothalamin (**15**) was 1,600-fold more potent than (*R*)-goniothalamin (**1**) against kidney cancer cells (786-0), possessing IC_{50} in the nanomolar range. Synthesis of analogues **16**–**23** also allowed the identification of the pharmacophoric groups responsible for the high antiproliferative activity and selectivity displayed by (*S*)-goniothalamin against the cancer cell line 786-0. Analogues **21**–**23** lacking one or two double bonds were marginally active or inactive, showing that the *endo* and *exo* double bond related to the pyrone ring are essential for the activity against kidney cancer (786-0) cell line.[2] From this study and others performed with fostriecin and cytostatin,[17] the α,β-unsaturated δ-lactone moiety seems to be a key feature for activity as a result of its ability to act as a Michael acceptor in the presence of biomolecules containing nucleophilic amino acid (e.g. cysteine, lysine, serine and threonine) or guanine residues.

In the same study, goniothalamin analogue **14** displaying *Z*-configured double bond in the styryl moiety, was 2-fold less active against most of the cell lines evaluated. Having this in mind, Çağır and co-workers prepared and evaluated a series of 2-naphtyl and 3-quinolyl derivatives in order to better understand the role of the *exo* double bond in the antiproliferative activity.[18] It was observed that analogues **24** and **25** had slightly better antiproliferative activities against prostate (PC-3) and breast (MCF-7) cancer cell lines compared to goniothalamin (**1**), which may be related to higher conformational restriction or steric hindrance due to the 2-naphtyl and 3-quinolyl substituents. Interestingly, 1-naphthyl substitution in the lactone ring dramatically enhanced the cytotoxic activity, especially when it posses a methyl group in the 2 or 3 position. For example, analogue **31** was 80- and 40-fold more potent against PC-3 and MCF-7 cells, respectively, in comparison with goniothalamin (**1**).

Gademann and co-workers designed a series of goniothalamin analogues aiming to evaluate the impact of the distance of the phenyl group to the lactone in the biological activity.[13] In the event, truncated goniothalamin analogues **32**, **34** and **35** were prepared. Additionally, extended analogues containing a phenyl **36** or a triple bond **33** spacer were obtained. These compounds were investigated in the inhibition of CRM1-dependente nuclear export of the protein kinase Rio2 in HeLa cells, which could be associated to potent antiproliferative effects. Of all the analogues tested, only **32** showed activity similar to goniothalamin and analogues **33**–**36** did not display significant inhibition of nuclear export.

Recently, Pilli et al. evaluated racemic goniothalamin against several human cancer cell lines and it was observed that the racemate exhibited similar antiproliferative activity profile compared to both enantiomers against glioma (U251), breast expressing the multidrug resistance phenotype (NCI-ADR/RES), kidney (786-0), lung (NCI-H460) and prostate (PC-3) cancer cells. However, in analogy to (*R*)-goniothalamin (**1**), the racemic form displayed higher potency against melanoma (UACC-62), breast (MCF-7), ovarian (OVCAR-03) and colon (HT-29) cancer cells than (S)-goniothalamin.[14]

In our previus work, 4-methoxy substitution afforded the highly active and selective derivative **18** against breast cancer cells expressing the multidrug resistance phenotype (NCI-ADR/RES), with IC_{50} in the nanomolar range. In addition, a recent work performed to evaluate the bioactivity of stilbenes demonstrated that those having methoxy groups exhibited stronger inhibition of tumor growth in roundworms when compared to the hydroxylated ones.[19] Methoxylation can increase bioactivity in vivo since stilb-

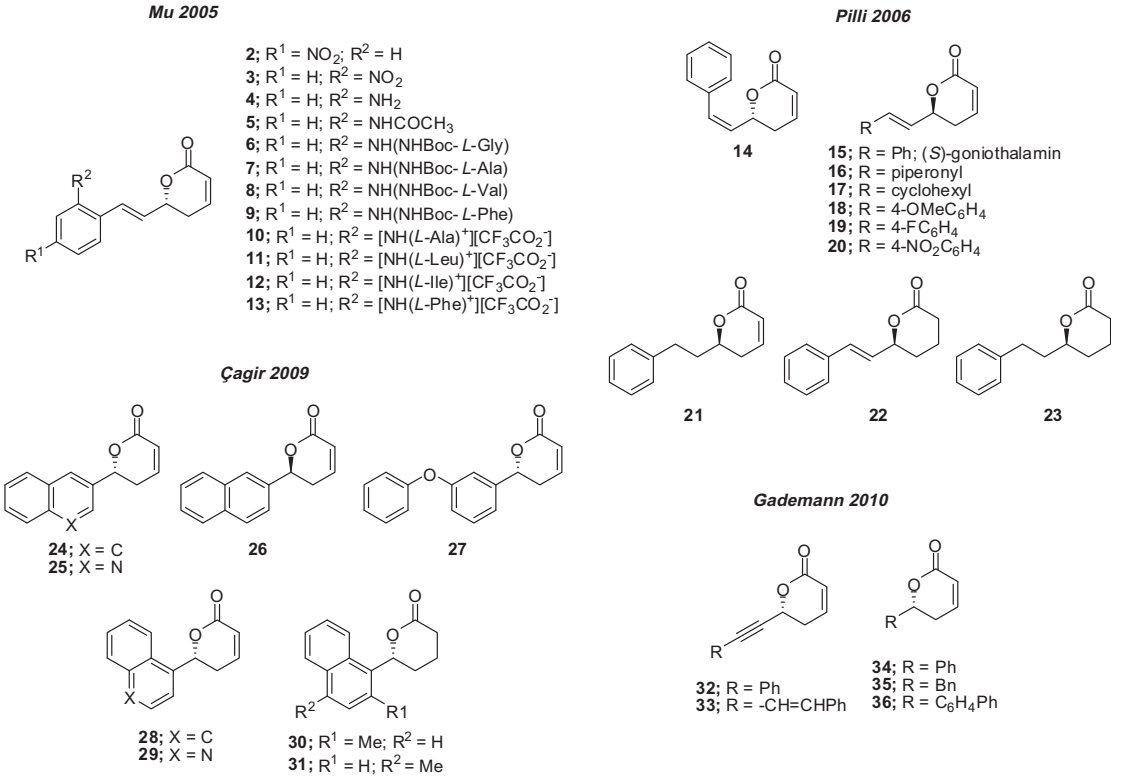
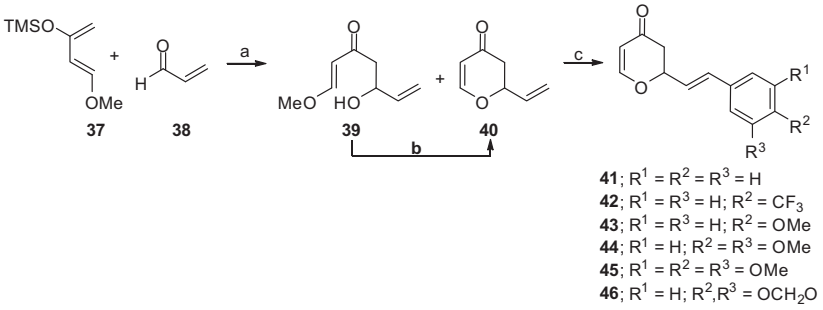
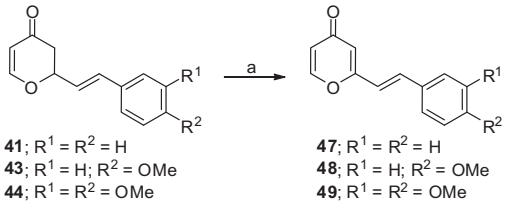


Figure 2. Analogues of goniothalamin (**1**) reported in the literature.



Scheme 1. Synthesis of compounds **40**–**46**. Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, Et_2O, −78 °C, 3 h; (b) TFA (1.3 equiv), CH_2Cl_2, 0 °C to rt, 40 min (59–70%, over 2 steps); (c) Styrene (3–5 equiv), Grubbs' second generation catalyst (2 mol %), CuI (3 mol %), CH_2Cl_2, reflux, 3–6 h (56–79%).



Scheme 2. Synthesis of compounds **47**–**49**. Reagents and conditions: (a) DDQ (1.7 equiv), benzene, reflux, 3 h (78–85% yield).

enes that have methoxyl groups are metabolized and excreted slower than those with hydroxyl groups. Therefore, the synthesis of poly-methoxylated goniothalamin analogues stands as a promising approach to improve the potency and selectivity of this family of compounds as well as the incorporation of fluorine into the structure of the lead compound which has become a common tool in medicinal chemistry for improving the pharmacological profile of bioactive compounds.[20]

Additionally, the synthesis of aza-analogues is another strategy employed to prepare compounds with better bioavailability. Several reports in the literature have validated this approach,[21] the most representative case being ixabepilone, an epothilone B analogue with increased stability due to isosteric replacement of the lactone ring by a lactam one,[22] which has been approved by U.S. Food and Drug Administration (FDA) for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane.[23] The synthesis of aza-analogues of goniothalamin would also enable further evaluation of the importance of the Michael acceptor site for the cytotoxic and antiproliferative activities of this family of compounds since α,β-unsaturated δ-lactams are less electron deficient than α,β-unsaturated δ-lactones thus impacting their biological profile.

Along this line of reasoning, the synthesis of dihydro-γ-pyrones analogues of goniothalamin seemed to be of interest as vinylogous lactones are expected to display electron acceptor properties in the range of α,β-unsaturated δ-lactones and α,β-unsaturated δ-lactams as changing the oxygen atom from alpha (lactones) to gamma position (γ-pyrones) is expected to change the electron deficiency of the α,β-unsaturated system. γ-Pyrones are considered to be an important class of natural products isolated mainly from marine organisms and displaying structural diversity.[24] Most biological studies with γ-pyrones were performed in marine ecosystem and less attention has been devoted to their potential as prototypes for the development of new drug candidates. Furthermore, despite the considerable number of synthetic methodologies, to our knowledge no evaluation of the cytotoxic activity of simple dihydro-γ-pyrones against cancer cell lines have been reported.

Herein, we report the design and synthesis of a focused library of goniothalamin analogues displaying the δ-lactone, δ-lactam and γ-pyrone structural motifs and their in vitro evaluation against seven human cancer cell lines: U251 (glioma), MCF-7 (breast), NCI-ADR/RES (breast expressing the multidrug resistance phenotype), 786-0 (kidney), NCI-H460 (lung non-small cells), OVCAR-03 (ovarian) and HT-29 (colon).

2. Results and discussion

2.1. Chemistry

The synthetic strategy aiming the preparation of dihydro-γ-pyrones is outlined in Scheme 1. Olefin **40** was prepared using optimized conditions of the reported procedure.[25] The boron trifluoride catalyzed hetero Diels–Alder reaction (HDA) of Danishefskýs diene **37** with acrolein **38** afforded a mixture of **39**/**40** (1:2 molar ratio), due to the competitive Mukaiyama aldol reaction. Adduct **39** was cyclized after treatment with trifluoroacetic acid, allowing to obtain dihydro-γ-pyrone **40** in 59–70% yield, over two steps. Next, an olefin cross metathesis reaction with various styrenes in the presence of Grubbs' second generation catalyst (2 mol %) and CuI (3 mol %) as additive, in refluxing CH_2Cl_2, afforded the desired dihydro-γ-pyrones **41**–**46** in moderate to good yields (56–79%). The exclusive formation of the *E* isomer (>95:05 by ^1H NMR) was confirmed by NMR analysis of the coupling constants of the double bond (J = 16.0 Hz).

The synthesis of γ-pyrones **47**–**49** was performed using oxidation of the corresponding dihydro-γ-pyrones **41**, **43** and **44** with DDQ in refluxing benzene as shown in Scheme 2 (78–85% yield).

In order to evaluate the importance of the styryl moiety of the dihydro-γ-pyrones to the antiproliferative activity, aryl derivative **50** was prepared according to the methodology described by Rawal and Huang.[26] Next, the synthesis of the γ-pyrone **51** was performed using the previously reported DDQ oxidation (Scheme 3), albeit in longer reaction time (15 h), in 87% yield. Finally, the α-bromo and α-iodo-dihydro-γ-pyrones **52** and **53**, respectively, were prepared according to the protocol developed by Evans et al.[27] Thus, treatment of compound **50** with iodosobenzene diacetate and trimethylsilyl bromide, in the presence of pyridine, furnished the α-bromo-dihydro-γ-pyrone **52** in 81% yield, as shown in Scheme 3. Iodination of the dihydro-γ-pyrone **50** was performed using molecular iodine under essentially identical reaction conditions, giving α-iodo-dihydro-γ-pyrone **53** in excellent yield (92%).

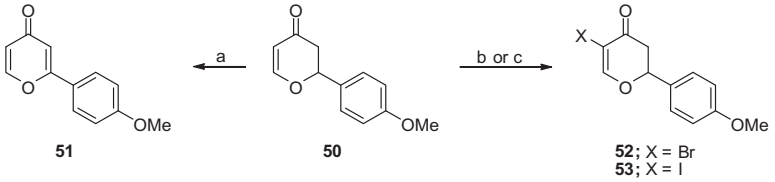
The synthesis of the racemic form of the trifluoromethylated and methoxylated analogues of goniothalamin (compounds **85**–**92**) was carried out using the reaction sequence depicted below (Scheme 4). Triethyl phosphonoacetate was used to homologate commercially available aldehydes **54**–**60** by the Horner–Wadsworth–Emmons reaction, followed by reduction with DIBAL-H and oxidation with IBX, leading to the corresponding α,β-unsaturated aldehydes **61**–**62**, **64**–**68** in 50–90% yields. The final steps in

the preparation of goniothalamin analogues **85**–**92** involved the addition of the allyl Grignard reagent to the corresponding aldehyde, followed by esterification of the resulting alcohol with acryloyl chloride and ring-closing metathesis reaction employing Grubbs' first generation catalyst. Overall yields ranged from 15–70% and the goniothalamin analogues **85**–**92**, as well as the corresponding intermediates, were purified by column chromatography on silica gel and characterized by IR, NMR and HRMS analyses.

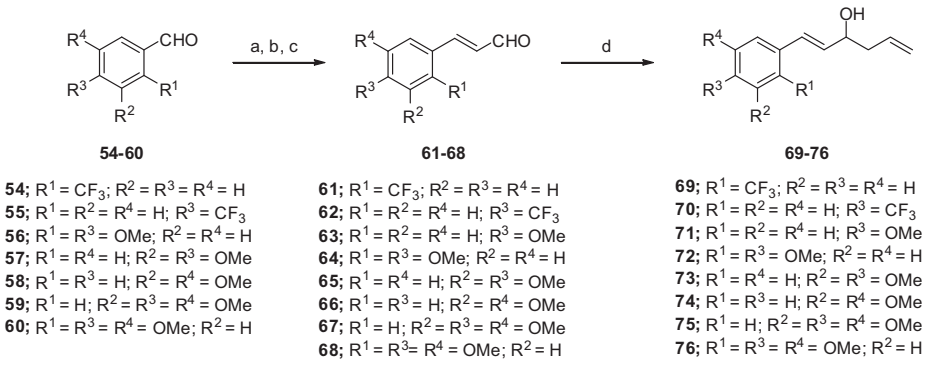
The aza-goniothalamin series (compounds **103**–**111**) were achieved from the corresponding amides (Scheme 5) obtained according to the methodology described by Hart et al.[28] This scaffold was derived from reaction between the unsaturated aldehyde and a solution of lithium hexamethyldisilazide (LHMDS) in THF at 0 °C, followed by the addition of an allylmagnesium bromide solution leading to a primary amine. This crude product was dissolved in dichloromethane and treated with acryloyl chloride in the presence of triethylamine to afford amides **94**–**102**, in 50–87% yields. Finally, the aza-goniothalamin analogues **103**–**111** were achieved by reacting the amides **94**–**102** with Grubbs' second generation catalyst (2 mol %). Overall yields for **103**–**111** ranged from 20–70%. The aza-goniothalamin derivatives, as well as the corresponding intermediates, were purified by column chromatography on silica gel and characterized by IR, NMR and HRMS analyses.

2.2. Biological activities

Considering that different cell lines display different sensitivities toward the same cytotoxic compound, the antiproliferative activity of all the goniothalamin analogues were evaluated in vitro against seven different human cancer cell lines (U251—glioma; MCF-7—breast; NCI-ADR/RES—breast expressing the multidrug resistance phenotype; 786-0—kidney; NCI-H460—lung non-small cells; OVCAR-03—ovary and HT-29—colon). The cytotoxic activity of each compound was also evaluated in vitro against spontaneously transformed keratinocytes from histologically



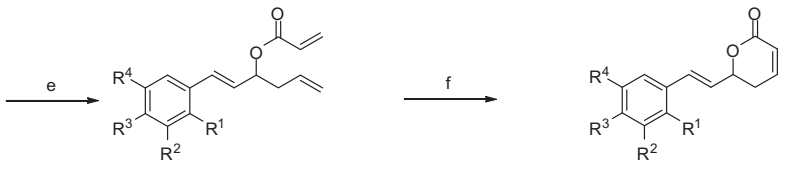
Scheme 3. Synthesis of compounds **51**–**53**. Reagents and conditions: (a) DDQ (1.7 equiv), benzene, reflux, 15 h (87% yield). (b) Iodosobenzene diacetate (2.2 equiv), trimethylsilyl bromide (4.4 equiv), pyridine (5.0 equiv), CH_2Cl_2, 0 °C, 30 min (81% yield). (c) Molecular iodine (2.25 equiv), pyridine (5.0 equiv), CH_2Cl_2, 0 °C, 30 min, then rt, 2.5 h (92% yield).



54; $R^1 = CF_3$; $R^2 = R^3 = R^4 = H$
55; $R^1 = R^2 = R^4 = H$; $R^3 = CF_3$
56; $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
57; $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
58; $R^1 = R^3 = H$; $R^2 = R^4 = OMe$
59; $R^1 = H$; $R^2 = R^3 = R^4 = OMe$
60; $R^1 = R^3 = R^4 = OMe$; $R^2 = H$

61; $R^1 = CF_3$; $R^2 = R^3 = R^4 = H$
62; $R^1 = R^2 = R^4 = H$; $R^3 = CF_3$
63; $R^1 = R^2 = R^4 = H$; $R^3 = OMe$
64; $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
65; $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
66; $R^1 = R^3 = H$; $R^2 = R^4 = OMe$
67; $R^1 = H$; $R^2 = R^3 = R^4 = OMe$
68; $R^1 = R^3 = R^4 = OMe$; $R^2 = H$

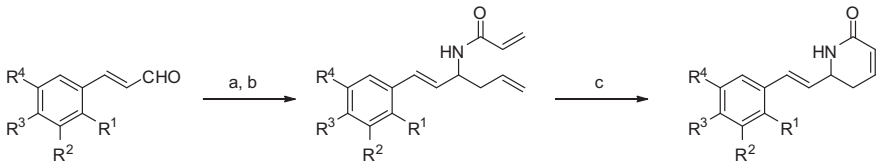
69; $R^1 = CF_3$; $R^2 = R^3 = R^4 = H$
70; $R^1 = R^2 = R^4 = H$; $R^3 = CF_3$
71; $R^1 = R^2 = R^4 = H$; $R^3 = OMe$
72; $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
73; $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
74; $R^1 = R^3 = H$; $R^2 = R^4 = OMe$
75; $R^1 = H$; $R^2 = R^3 = R^4 = OMe$
76; $R^1 = R^3 = R^4 = OMe$; $R^2 = H$



77; $R^1 = CF_3$; $R^2 = R^3 = R^4 = H$
78; $R^1 = R^2 = R^4 = H$; $R^3 = CF_3$
79; $R^1 = R^2 = R^4 = H$; $R^3 = OMe$
80; $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
81; $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
82; $R^1 = R^3 = H$; $R^2 = R^4 = OMe$
83; $R^1 = H$; $R^2 = R^3 = R^4 = OMe$
84; $R^1 = R^3 = R^4 = OMe$; $R^2 = H$

85; $R^1 = CF_3$; $R^2 = R^3 = R^4 = H$
86; $R^1 = R^2 = R^4 = H$; $R^3 = CF_3$
87; $R^1 = R^2 = R^4 = H$; $R^3 = OMe$
88; $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
89; $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
90; $R^1 = R^3 = H$; $R^2 = R^4 = OMe$
91; $R^1 = H$; $R^2 = R^3 = R^4 = OMe$
92; $R^1 = R^3 = R^4 = OMe$; $R^2 = H$

Scheme 4. Synthesis of compounds **85**–**92**. Reagents and conditions: (a) NaH (1.5 equiv), THF, DMF, 0 °C, triethyl phosphonoacetate (1.3 equiv), 15 min, then rt, aldehydes **54**–**60**, (b) CH_2Cl_2, −78 °C, DIBAL-H (2.5 equiv), 30 min, (c) IBX (3.0 equiv), 80 °C, 3.5 h, (d) aldehydes **61**–**68**, THF, −78 °C, allylmagnesium bromide (1.2 equiv), 30 min, (e) alcohols **69**–**76**, CH_2Cl_2, 0 °C, Et_3N (2.0 equiv), acryloyl chloride (1.5 equiv), then rt, 1 h. (f) esters **77**–**84**, CH_2Cl_2, reflux, Grubbs' first generation catalyst (10 mol %), 8 h.



93; $R^1 = R^2 = R^3 = R^4 = H$
61; $R^1 = CF_3$; $R^2 = R^3 = R^4 = H$
62; $R^1 = R^2 = R^4 = H$; $R^3 = CF_3$
63; $R^1 = R^2 = R^4 = H$; $R^3 = OMe$
64; $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
65; $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
66; $R^1 = R^3 = H$; $R^2 = R^4 = OMe$
67; $R^1 = H$; $R^2 = R^3 = R^4 = OMe$
68; $R^1 = R^3 = R^4 = OMe$; $R^2 = H$

94; $R^1 = R^2 = R^3 = R^4 = H$
95; $R^1 = CF_3$; $R^2 = R^3 = R^4 = H$
96; $R^1 = R^2 = R^4 = H$; $R^3 = CF_3$
97; $R^1 = R^2 = R^4 = H$; $R^3 = OMe$
98; $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
99; $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
100; $R^1 = R^3 = H$; $R^2 = R^4 = OMe$
101; $R^1 = H$; $R^2 = R^3 = R^4 = OMe$
102; $R^1 = R^3 = R^4 = OMe$; $R^2 = H$

103; $R^1 = R^2 = R^3 = R^4 = H$
104; $R^1 = CF_3$; $R^2 = R^3 = R^4 = H$
105; $R^1 = R^2 = R^4 = H$; $R^3 = CF_3$
106; $R^1 = R^2 = R^4 = H$; $R^3 = OMe$
107; $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
108; $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
109; $R^1 = R^3 = H$; $R^2 = R^4 = OMe$
110; $R^1 = H$; $R^2 = R^3 = R^4 = OMe$
111; $R^1 = R^3 = R^4 = OMe$; $R^2 = H$

Scheme 5. Synthesis of compounds **103**–**111**. Reagents and conditions: (a) LHMDS (1.2 equiv), THF, 0 °C, aldehydes **61**–**68**, **93**, then allylmagnesium bromide (1.2 equiv), 30 min, (b) CH_2Cl_2, 0 °C, Et_3N (2.0 equiv), acryloyl chloride (1.5 equiv), then rt, 1 h, (c) amides **94**–**102**, CH_2Cl_2, reflux, Grubbs' second generation catalyst (2 mol %), 6 h.

normal skin (HaCat cells). Doxorubicin was employed as the positive control and goniothalamin was included as the reference compound.

Cell proliferation was determined spectrophotometrically using sulforhodamine B (SRB) as protein-binding dye and analyses were based on the U.S. National Cancer Institute (NCI) 60 human tumour cell line anticancer drug screen (NCI60).[29] Differently from other methods, in the SRB assay measurement of the cell population density at time zero (the time at which drugs are added) is possible, which allows the calculation of the cellular responses for total growth inhibition. The drug concentration resulting in total growth inhibition (TGI) is calculated from T = T0, where the amount of protein at the end of drug incubation (T) is equal to the amount at the beginning (T0).[29a]

Goniothalamin (**1**) and its analogues were employed at concentrations between 0.25 and 250 μg/mL and doxorubicin at 0.025–25 μg/mL. Concentration that elicits total growth inhibition (TGI) was determined after 48 h of cell treatment. The initial in vitro screening evaluations were planned to select the best candidates for anticancer drug development in animal models and, eventually, in clinical trials. To identify compounds with growth-inhibitory or toxic effects on particular tumour types, it is important to characterize the disease-oriented concept.[29b]

The biological evaluation of dihydro-γ-pyrones **41**–**46**, **50**, **52** and **53** and γ-pyrones **47**–**49** and **51** (Fig. 3) are summarized in Table 1, which displays the total growth inhibition concentration (TGI) value for each compound.

In general, the dihydro-γ-pyrones and γ-pyrones evaluated were shown to be less potent than goniothalamin (**1**) with γ-pyrones being less cytotoxic than the corresponding dihydro-γ-pyrones. In particular, γ-pyrone **51** did not display any cytotoxic effect against the cancer cell lines over the range of concentration employed and γ-pyrones **47**–**49** displayed a clear correlation between their total growth inhibition (TGI) values and the degree of methoxylation of the aromatic ring with the dimethoxylated derivative **49** being the less cytotoxic in this series of compounds. For the dihydro-γ-pyrones series (**43**–**46**), there is no clearcut correlation between the degree of oxygenation of the aromatic ring and the antiproliferative potency of these compounds, the 4-methoxy derivative **43** displaying the largest TGI value in this series.

The reduced antiproliferative activity of dihydro-γ-pyrones and γ-pyrones as compared to goniothalamin (**1**) can be correlated to the diminished electron acceptor nature of the vinylogous lactone moiety present in these goniothalamin analogues while the lack of potency of γ-pyrones can be ascribed to the extensive electronic conjugation with the aromatic ring which is expected to reduce the Michael acceptor nature of the heterocyclic ring, particularly when the aromatic ring is substituted with electron donating methoxyl groups.

On the other hand, noteworthy are the superior antiproliferative properties of the halogenated dihydro-γ-pyrones **42**, **52** and **53** when compared to the other representatives in this series, a behavior which is in line with the reasoning that electron withdrawing groups are beneficial to the antiproliferative activities of goniothalamin analogues, a pattern that may be worthy to explore further.

Table 2 features the total growth inhibition values for goniothalamin (**1**), aza-goniothalamin (**103**) and their analogues **85**–**92** and **104**–**111** (Fig. 4), as well as for doxorubicin.

It is evident from the data shown that the introduction of the lactam ring significantly reduces the antiproliferative activity for all cancer cell lines evaluated. In fact, aza-goniothalamin (**103**) did not display any cytotoxic activity against several cancer cell lines and human keratinocytes (HaCat) cells. This pattern is even more pronounced when we compare the cytotoxic activity of the methoxy derivatives in both series: all aza-goniothalamin analogues investigated were not cytotoxic against the cell lines evaluated except for the 3,5-dimethoxy derivative **109** which only displayed cytotoxic activity at the largest concentration employed in the assay. The only aza-goniothalamin derivative deserving further investigation seems to be the trifluoromethylated analogue **104** wihich displayed promising TGI values for breast cancer expressing the multidrug resistance phenotype (NCI-ADR/RES) and glioma (U251) cells (40.6 and 69.9 μM, respectively).

In contrast to the aza-goniothalamin series, the methoxylation of the aromatic ring proved to be beneficial for the in vitro antiproliferative activity of the goniothalamin analogues. While the 3,4,5-trimethoxy goniothalamin **91** was less potent than goniothalamin (**1**) for all the cell lines evaluated, the 3,5-dimethoxy and the 2,4,5-trimethoxy analogues **90** and **92**, respectively, displayed lower TGI values for most of the cell lines tested while 2,4-dimethoxy goniothalamin **88** proved to be more potent than goniothalamin against all cancer cell lines. Lower TGI values than doxorubicin were observed for 2,4-dimethoxy goniothalamin **88** against breast cancer expressing the multidrug resistance phenotype (NCI-ADR/RES), ovary (OVCAR-03) and colon (HT-29) in addition to be less toxic to human keratinocytes (HaCat).

3. Conclusions

As compared to our previous study,[2b] the present work shed new light on the SAR for goniothalamin analogues regarding the

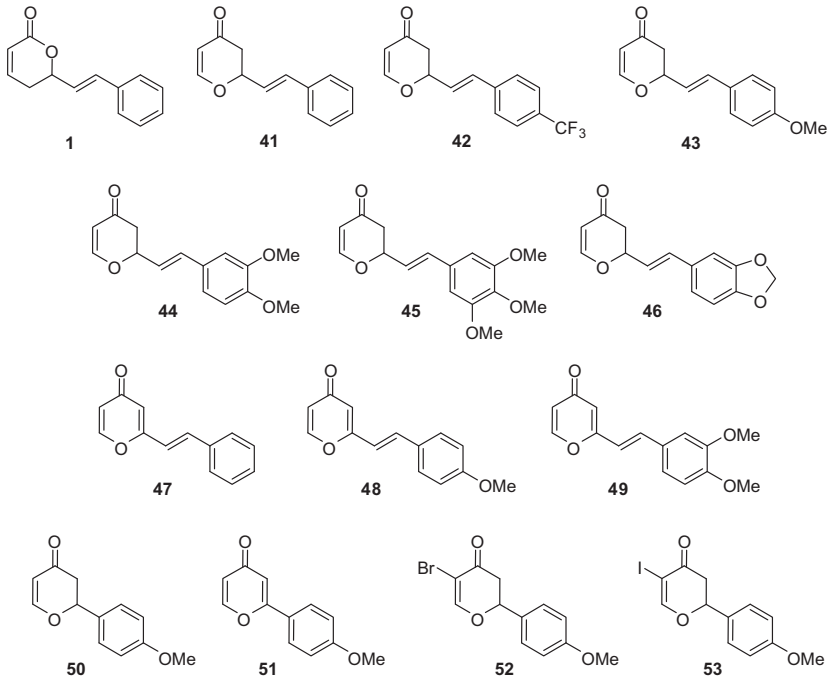


Figure 3. Structures of dihydro-γ-pyrones **41**–**46**, **50**, **52** and **53**, γ-pyrones **47**–**49** and **51** and the lead compound goniothalamin (**1**).

Table 1
TGI values, given in μM, for compounds **1**, **41**–**53** and doxorubicin (DOX) necessary for total inhibition of tumor cell proliferation[a]

TGI	U251	MCF7	NCI-ADR	786-0	NCI-H460	OVCAR-03	HT-29	HaCat
DOX[b]	2.4	3.7	13.5	2.1	1.3	6.3	7.1	0.8
1	13.7	12.7	8.0	14.8	13.6	14.2	13.9	27.7
41	121.8	152.6	105.3	138.2	82.4	58.2	123.6	126.5
42	38.6	41.2	51.6	39.6	95.6	58.2	33.3	122.8
43	151.9	155.5	239.3	191.5	149.4	87.4	203.9	144.5
44	86.9	130.2	145.8	145.1	89.6	74.3	123.2	133.5
45	101.8	149.4	223.2	125.0	127.3	85.4	134.5	154.7
46	77.0	81.4	186.8	104.1	147.4	101.7	126.9	144.9
47	285.4	691.1	514.2	409.9	508.5	545.5	344.1	710.8
48	278.4	395.9	309.9	376.8	606.1	327.9	379.2	710.0
49	338.9	953.6	407.9	635.4	545.5	540.2	806.7	689.7
50	226.1	172.9	419.6	197.0	192.8	248.6	203.4	264.4
51	>1236.3	>1236.3	>1236.3	>1236.3	>1236.3	>1236.3	>1236.3	>1236.3
52	46.4	42.2	52.9	33.4	117.7	113.5	69.0	164.0
53	24.4	43.2	39.7	27.0	74.6	38.2	24.4	53.3

[a] Concentration that elicits total growth inhibition (TGI) was determined from non-linear regression analysis using the ORIGIN 7.5® (OriginLab Corporation).
[b] Doxorubicin (DOX) was the positive control.

prevalence of the α,β-unsaturated δ-lactone ring as the pharmacophoric motif for the in vitro antiproliferative activity as compared to the α,β-unsaturated δ-lactam, dihydro-γ-pyrone and the γ-pyrone motifs.

When compared to the 4-methoxy analogue **87**, the 2,4-dimethoxy derivative **88** displayed higher potency against all the seven human cancer cell lines investigated, as well as the 3,5-dimethoxy analogue **90**. As to the trimethoxylated series of compounds, the 2,4,5-trimethoxy analogue **92** proved to be more potent than the monosubstituted derivative **87** and displayed higher antiproliferative activity than the 3,4,5-trimethoxy analogue **91**. Additionally, the 2,4-dimethoxy goniothalamin **88** was shown to be more potent than goniothalamin (**1**) against all cancer cell lines evaluated and more potent than doxorubicin against NCI-ADR/RES, OVCAR-03 and HT-29 while being less toxic to human keratinocytes (HaCat). The 3,5-dimethoxy and the 2,4,5-trimethoxy analogues **90** and **92** also displayed promising antiproliferative activity when compared to goniothalamin (**1**).

It seems that the beneficial effect of the methoxy groups attached to the aromatic ring in goniothalamin derivatives investigated could be judiciously explored in the future design of novel series of analogues as well it can be coupled to the effect of halogen substituents at C-α of the α,β-unsaturated δ-lactone ring, following the results observed for dihydro-γ-pyrones **52** and **53**, in the design of novel and more potent analogues for further studies.

4. General procedures

Reagents and solvents were commercial grade and were used as supplied, except when specified in the experimental procedure. Grubbs' first generation catalyst (Lot#MKBF1581 V) and Grubbs' second generation catalyst (Lot#MKBG2090 V) were purchased from Aldrich. Doxorubicin was purchased from Europharma. Racemic goniothalamin (**1**) was prepared according to previously described methodology, except for the utilization of allylmagnesium bromide in substitution to the enantioselective allylation

Table 2
TGI values, given in μM, for compounds **1**, **85–92**, **104–111** and doxorubicin (DOX) necessary for total inhibition of tumor cell proliferation[a]

TGI	U251	MCF7	NCI-ADR	786-0	NCI-H460	OVCAR-03	HT-29	HaCat
Dox[b]	2.4	3.7	13.5	2.1	1.3	6.3	7.1	0.8
1	13.7	12.7	8.0	14.8	13.6	14.2	13.9	27.7
103	797.6	607.4	966.6	>1254.8	928.5	>1254.8	1195.8	>1254.8
85	43.4	50.4	75.5	52.3	241.5	295.6	71.7	82.7
104	69.9	120.2	40.6	123.4	194.7	329.3	195.4	249.1
86	36.8	51.0	54.8	44.5	476.9	167.2	36.2	69.7
105	130.3	149.5	71.8	127.8	150.4	126.0	139.2	173.7
87	20.6	25.5	17.3	21.6	28.3	61.5	33.7	58.8
106	981.3	>1090.4	841.7	>1090.4	>1090.4	786.8	>1090.4	>1090.4
88	4.6	5.4	8.8	4.1	6.0	5.6	6.6	15.8
107	>964.1	>964.1	>964.1	>964.1	>964.1	>964.1	>964.1	>964.1
89	23.9	7.8	11.6	10.9	14.6	16.8	17.2	63.0
108	>964.1	>964.1	>964.1	>964.1	>964.1	>964.1	>964.1	>964.1
90	8.1	9.5	8.9	10.6	9.0	19.1	8.2	8.8
109	169.9	146.4	203.2	173.4	145.5	232.1	196.6	211.9
91	25.1	15.3	35.1	18.5	28.8	44.9	18.8	21.6
110	>864.1	>864.1	>864.1	>864.1	>864.1	>864.1	>864.1	>864.1
92	11.5	3.8	9.4	6.0	9.8	7.2	15.9	46.9
111	>864.1	>864.1	>864.1	>864.1	>864.1	>864.1	>864.1	>864.1

[a] Concentration that elicits total growth inhibition (TGI) was determined from non-linear regression analysis using the ORIGIN 7.5® (OriginLab Corporation).
[b] Doxorubicin (DOX) was the positive control.

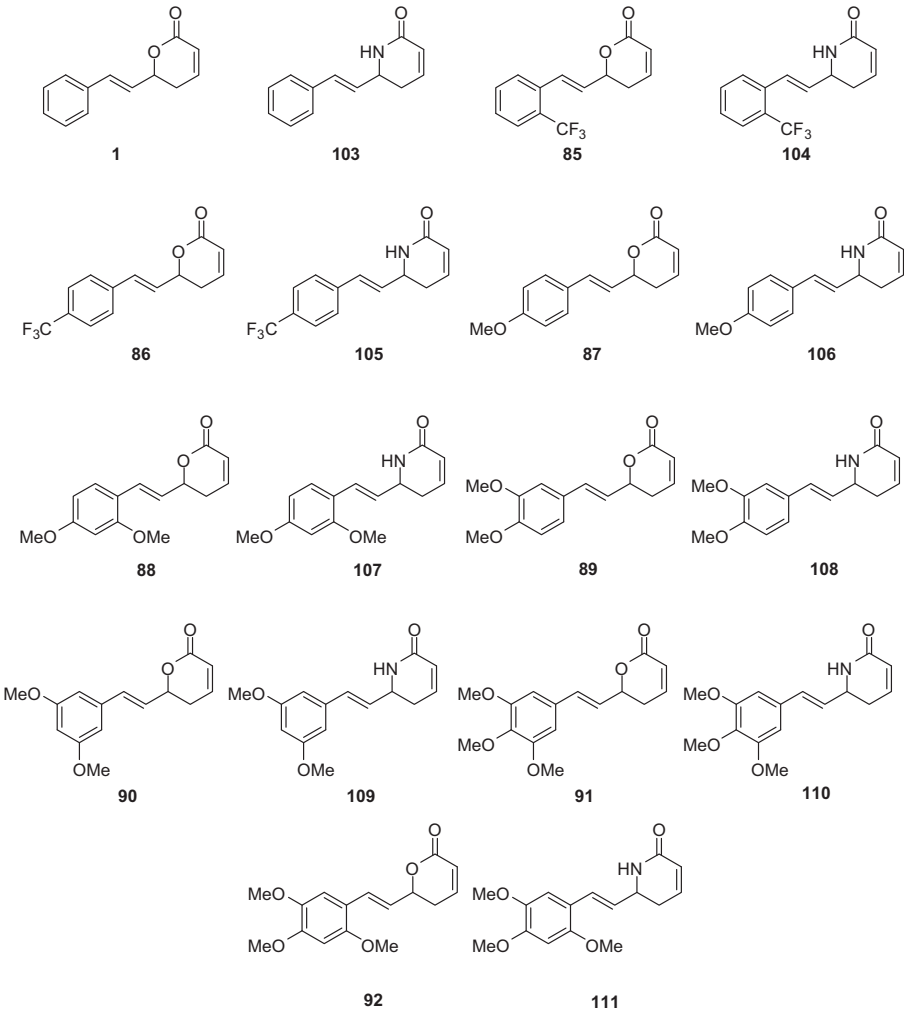


Figure 4. Structures of methoxylated and trifluoromethylated goniothalamin **85–92** and aza-goniothalamin **104–111** analogues.

step.[2a,b] Et_3N and CH_2Cl_2 were distilled from calcium hydride and THF, ether and benzene were distilled from Na/benzophenone. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Acros silica gel 60, 0.040–0.063 mm. ^1H NMR and ^{13}C NMR data were recorded on a Varian Inova (500 MHz for ^1H and

125 MHz for ^{13}C NMR) or Bruker Avance (250 MHz for ^{1}H and 62.5 MHz for ^{13}C NMR) spectrometer using as internal standard the residual nondeuterated solvent ($CHCl_3$) or TMS (^{1}H NMR). Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad signal, app = apparent signal), coupling constant (Hz), integration. High resolution mass spectra (HRMS) for novel compounds were measured on a Waters XEVO Q-TOF spectrometer (ESI) or in a Waters GCT Premier (EI). Infrared spectra (IR) were obtained on a ABB Bomem MB Series B102, Thermo-Nicolet IR-200 or iS5 spectrometer and absorptions are reported in reciprocal centimeters. Melting points were recorded on an Electrothermal 9100 melting point apparatus and were uncorrected.

4.1. Experimental procedures

4.1.1. 2-Vinyl-*2H*-pyran-4(*3H*)-one (40)

To a solution of acrolein (**38**, 42.4 mmol, 2.83 mL) in anhydrous diethyl ether (160 mL) under nitrogen atmosphere at −78 °C was added *trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene (**37**, 15.3 mmol, 2.64 g), followed by 1.3 equiv of boron trifluoride etherate (20.3 mmol; 2.51 mL). After 3.0 h, a saturated aqueous solution of sodium bicarbonate (100 mL) was added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (250 mL) and the resulting solution was cooled to 0 °C. Trifluoroacetic acid (22.0 mmol; 1.7 mL; 1.3 equiv) was added and the resulting solution was maintained under magnetic stirring and at room temperature for 40 min. The solvent was removed under reduced pressure and the residue was dissolved in diethyl ether (100 mL) and washed with a saturated aqueous solution of sodium hydrogen carbonate (100 mL). The aqueous layer was extracted with diethyl ether (2 × 100 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by flash column chromatography (hexanes/ethyl acetate 2:1 v/v) giving the desired dihydro-γ-pyrone **40** in 70% yield (1.33 g), as a light yellow oil. IR (cm^{-1}, thin film): 1678, 1594, 1405, 1273, 1225, 1039, 993, 937, 895, 795; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38 (d, J = 6.0 Hz, 1H), 5.95 (ddd, J = 16.6, 10.6 and 5.8 Hz, 1H), 5.45 (s, 1H), 5.38 (dd, J = 16.6 and 12.2 Hz, 2H), 4.98–4.85 (m, 1H), 2.71–2.49 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 191.3 (C_0), 162.5 (CH), 134.1 (CH), 117.9 (CH_2), 106.9 (CH), 79.1 (CH), 41.1 (CH_2).

4.1.2. General procedure for the olefin cross-metathesis reaction

A typical procedure for the preparation of dihydro-γ-pyrones **41**–**46** follows: to a solution of dihydro-γ-pyrone **40** (0.5 mmol; 62.0 mg) in anhydrous CH_2Cl_2 (9 mL) was added the corresponding styrene (3–5 equiv), Grubbs' second generation catalyst (8.5 mg; 2 mol %) and copper iodide (2.9 mg; 3 mol %), under nitrogen atmosphere. The reaction mixture was immersed in an oil bath and heated at reflux until TLC analysis indicated complete consumption of the starting material (3–6 h). After cooling to room temperature, 50 equiv of DMSO (relative to the catalyst) were added and the mixture was maintained under magnetic stirring overnight. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography (using the eluent indicated) to afford the corresponding cross-metathesis adducts **41**–**46**.

4.1.2.1. (*E*)-2-Styryl-*2H*-pyran-4(*3H*)-one (41). Prepared according to the general procedure for the olefin cross-metathesis reaction in 79% yield (light brown viscous oil). Eluent: hexanes/ethyl acetate 2:1, 1:1 v/v. IR (cm^{-1}, thin film): 2925, 2855, 1676, 1594, 1452, 1406, 1268, 1219, 1038, 969, 741; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.47–7.25 (m, 6H), 6.73 (d, J = 16.0 Hz, 1H), 6.31 (dd, J = 16.0 and 6.5 Hz, 1H), 5.46 (d, J = 6.0 Hz, 1H), 5.11–5.02 (m, 1H), 2.73 (dd, J = 16.8 and 12.4 Hz, 1H), 2.60 (dd, J = 16.8 and 4.4 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 191.8 (C_0), 162.9 (CH), 135.5 (C_0), 133.7 (CH), 128.6 (2 × CH), 128.5 (CH), 126.7 (2 × CH), 125.0 (CH), 107.2 (CH), 79.6 (CH), 41.9 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{13}H_{13}O_2$ [M+H$^+$] 201.0916, found 201.0903.

4.1.2.2. (*E*)-2-(4-(Trifluoromethyl)styryl)-*2H*-pyran-4(*3H*)-one (42). Prepared according to the general procedure for the olefin cross-metathesis reaction in 58% yield (light yellow solid). Eluent: hexanes/ethyl acetate 1:1 v/v. Mp: 43.0–44.4 °C; IR (cm^{-1}, thin film): 1678, 1596, 1408, 1325, 1269, 1220, 1165, 1121, 1067, 1039, 973; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.60 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 6.0 Hz, 1H), 6.76 (d, J = 16.0 Hz, 1H), 6.39 (dd, J = 16.0 and 6.1 Hz, 1H), 5.49 (dd, J = 6.0 and 0.6 Hz, 1H), 5.15–5.06 (m, 1H), 2.81–2.56 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 191.4 (C_0), 162.7 (CH), 139.1 (C_0), 131.9 (CH), 130.2 (q, J = 32.4 Hz, C_0), 127.7 (CH), 126.9 (2 × CH), 125.7 (q, J = 15.1 Hz, 2 × CH), 124.0 (q, J = 270.0 Hz, C_0), 107.5 (CH), 79.1 (CH), 41.7 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{14}H_{12}F_3O_2$ [M+H$^+$] 269.0789, found 269.0838.

4.1.2.3. (*E*)-2-(4-Methoxystyryl)-*2H*-pyran-4(*3H*)-one (43). Prepared according to the general procedure for the olefin cross-metathesis reaction in 73% yield (light yellow solid). Eluent: hexanes/ethyl acetate 2:1 v/v. Mp: 79.0–80.0 °C; IR (cm^{-1}, thin film): 2928, 1673, 1594, 1513, 1463, 1405, 1251, 1219, 1177, 1034, 970, 835, 792; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.39 (d, J = 6.0 Hz, 1H), 7.34 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 16.0 Hz, 1H), 6.15 (dd, J = 16.0 and 6.8 Hz, 1H), 5.45 (d, J = 6.0 Hz, 1H), 5.08–4.98 (m, 1H), 3.80 (s, 3H), 2.72 (dd, J = 16.8 and 12.6 Hz, 1H), 2.59 (dd, J = 16.8 and 4.1 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 192.0 (C_0), 163.0 (CH), 159.9 (C_0), 133.5 (CH), 128.2 (C_0), 128.0 (2 × CH), 122.7 (CH), 114.1 (2 × CH), 107.2 (CH), 80.0 (CH), 55.2 (OCH_3), 42.0 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{14}H_{15}O_3$ [M+H$^+$] 231.1021, found 231.1062.

4.1.2.4. (*E*)-2-(3,4-Dimethoxystyryl)-*2H*-pyran-4(*3H*)-one (44). Prepared according to the general procedure for the olefin cross-metathesis reaction in 56% yield (light yellow viscous oil). Eluent: CH_2Cl_2/ethyl acetate 95:05 v/v, then hexanes/ethyl acetate 1:1 v/v. IR (cm^{-1}, thin film): 1671, 1593, 1515, 1463, 1406, 1263, 1140, 1027, 970, 794; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40 (d, J = 6.0 Hz, 1H), 6.95–6.81 (m, 3H), 6.65 (d, J = 15.9 Hz, 1H), 6.16 (dd, J = 15.9 and 6.8 Hz, 1H), 5.46 (d, J = 6.0 Hz, 1H), 5.09–5.00 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.74 (dd, J = 16.7 and 12.5 Hz, 1H), 2.59 (dd, J = 16.7 and 4.2 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 191.9 (C_0), 162.9 (CH), 149.5 (C_0), 149.1 (C_0), 133.7 (CH), 128.5 (C_0), 122.9 (CH), 120.3 (CH), 111.0 (CH), 108.9 (CH), 107.2 (CH), 79.8 (CH), 55.8 (2 × OCH_3), 42.0 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{17}O_4$ [M+H$^+$] 261.1127, found 261.1207.

4.1.2.5. (*E*)-2-(3,4,5-Trimethoxystyryl)-*2H*-pyran-4(*3H*)-one (45). Prepared according to the general procedure for the olefin cross-metathesis reaction in 67% yield (light yellow solid). Eluent: CH_2Cl_2/ethyl acetate 95:05 v/v, then hexanes/ethyl acetate 1:1 v/v. Mp: 128.0–130.0 °C; IR (cm^{-1}, thin film): 2928, 1663, 1592, 1507, 1423, 1402, 1334, 1248, 1237, 1124, 1038, 1008, 982, 795; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 6.0 Hz, 1H), 6.65 (d, J = 15.7 Hz, 1H), 6.64 (s, 2H), 6.22 (dd, J = 15.9 and 6.5 Hz, 1H), 5.47 (d, J = 6.0 Hz, 1H), 5.12–5.02 (m, 1H), 3.88 (s, 6H), 3.86 (s, 3H), 2.75 (dd, J = 16.8 and 12.2 Hz, 1H), 2.62 (dd, J = 16.8 and 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.7 (C_0), 162.8 (CH), 153.3 (C_0), 138.5 (C_0), 133.7 (2 × CH), 131.2 (C_0), 124.4 (CH),

107.2 (CH), 103.8 (CH), 79.5 (CH), 60.8 (OCH_3), 56.1 (2 × OCH_3), 41.9 (CH_2); HRMS (ESI+) *m*/*z*: Calcd for $C_{16}H_{19}O_5$ [M+H$^+$] 291.1232, found 291.1327.

4.1.2.6. (*E*)-2-(2-(Benzo[*d*][1,3]dioxol-5-yl)vinyl)-*2H*-pyran-4(*3H*)-one (46). Prepared according to the general procedure for the olefin cross-metathesis reaction in 64% yield (light yellow solid). Eluent: CH_2Cl_2/ethyl acetate 95:05 v/v, then hexanes/ethyl acetate 1:1 v/v. Mp: 111.2–112.2 °C; IR (cm^{-1}, thin film): 2917, 1666, 1592, 1503, 1449, 1257, 1225, 1191, 1037, 974, 927, 906, 791; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40 (d, *J* = 6.0 Hz, 1H), 6.94 (d, *J* = 1.5 Hz, 1H), 6.85 (dd, *J* = 8.0 and 1.5 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.12 (dd, *J* = 15.9 and 6.7 Hz, 1H), 5.97 (s, 2H), 5.46 (d, *J* = 6.0 Hz, 1H), 5.09–4.97 (m, 1H), 2.72 (dd, *J* = 16.8 and 12.5 Hz, 1H), 2.59 (dd, *J* = 16.8 and 4.4 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 191.8 (C_0), 162.9 (CH), 148.1 (C_0), 148.0 (C_0), 133.5 (CH), 129.9 (C_0), 123.1 (CH), 121.8 (CH), 108.3 (CH), 107.2 (CH), 105.8 (CH), 101.2 (CH_2), 79.8 (CH), 42.0 (CH_2); HRMS (ESI+) *m*/*z*: Calcd for $C_{14}H_{13}O_4$ [M+H$^+$] 245.0808, found 245.0817.

4.1.3. General procedure for the DDQ oxidation of dihydro-γ-pyrones

To a solution of the dihydro-γ-pyrone **41**, **43**, **44** or **50** (0.25 mmol) in dry benzene (3.0 mL), under nitrogen atmosphere and magnetic stirring, was added DDQ (1.7 equiv; 0.43 mmol; 96.5 mg) and the reaction mixture was heated to reflux for 3–15 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with a saturated aqueous solution of sodium hydrogen carbonate (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (using the eluent indicated) to provide the corresponding γ-pyrones **47**–**49** or **51** .

4.1.3.1. (*E*)-2-Styryl-*4H*-pyran-4-one (47). Prepared according to the general procedure for oxidation with DDQ in 85% yield (white solid). Eluent: hexanes/ethyl acetate 2:1, 1:1, 1:3 v/v. Mp: 83.8–85.0 °C; IR (cm^{-1}, thin film): 2927, 1646, 1596, 1411, 1381, 1260, 1171, 973, 945, 874, 851, 759, 695; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 3.0 Hz, 1H), 6.66 (dd, *J* = 4.1 and 0.8 Hz, 2H), 7.42–7.33 (m, 4H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.31–6.27 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 179.2 (C_0), 162.2 (C_0), 154.4 (CH), 136.2 (CH), 134.8 (C_0), 129.7 (CH), 128.9 (2 × CH), 127.5 (2 × CH), 119.4 (CH), 116.8 (CH), 114.9 (CH); HRMS (ESI+) *m*/*z*: Calcd for $C_{13}H_{11}O_2$ [M+H$^+$] 199.0759, found 199.0820.

4.1.3.2. (*E*)-2-(4-Methoxystyryl)-*4H*-pyran-4-one (48). Prepared according to the general procedure for oxidation with DDQ in 78% yield (off-white solid). Eluent: ethyl acetate. Mp: 123.4–124.0 °C; IR (cm^{-1}, thin film): 3060, 2919, 2848, 1652, 1599, 1515, 1411, 1383, 1264, 1252, 1165, 1018, 970, 949, 859, 847, 810; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.70 (d, *J* = 5.7 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 16.0 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.31–6.19 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 179.2 (C_0), 162.6 (C_0), 160.9 (C_0), 154.2 (CH), 135.8 (CH), 129.0 (2 × CH), 127.5 (C_0), 117.0 (CH), 116.6 (CH), 114.3 (2 × CH), 114.1 (CH), 55.3 (OCH_3); HRMS (ESI+) *m*/*z*: Calcd for $C_{14}H_{13}O_3$ [M+H$^+$] 229.0865, found 229.0879.

4.1.3.3. (*E*)-2-(3,4-Dimethoxystyryl)-*4H*-pyran-4-one (49). Prepared according to the general procedure for oxidation with DDQ in 85% yield (off-white solid). Eluent: ethyl acetate + 2% MeOH v/v. Mp: 133.5–134.6 °C; IR (cm^{-1}, thin film): 2918, 1647, 1596, 1508, 1412, 1380, 1263, 1156, 1140, 1019, 966, 942, 862, 800, 769; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.71 (d, *J* = 5.5 Hz, 1H), 7.32 (d, *J* = 16.0 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 7.03 (s, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.30–6.20 (m, 2H), 3.92 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 179.2 (C_0), 162.5 (C_0), 154.2 (CH), 150.7 (C_0), 149.2 (C_0), 136.1 (CH), 127.8 (C_0), 121.9 (CH), 117.2 (CH), 116.6 (CH), 114.2 (CH), 111.2 (CH), 109.2 (CH), 55.9 (2 × OCH_3); HRMS (ESI+) *m*/*z*: Calcd for $C_{15}H_{15}O_4$ [M+H$^+$] 259.0970, found 259.1017.

4.1.3.4. 2-(4-Methoxyphenyl)-*4H*-pyran-4-one (51). Prepared according to the general procedure for oxidation with DDQ in 87% yield (light yellow solid). Eluent: CH_2Cl_2/ethyl acetate 1:2 v/v). Mp: 123.0–125.0 °C; IR (cm^{-1}, thin film): 2919, 2838, 1644, 1594, 1512, 1430, 1365, 1307, 1262, 1233, 1181, 1017, 930, 815, 645; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.78 (d, *J* = 5.8 Hz, 1H), 7.67 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.31 (dd, *J* = 5.8 and 2.4 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 179.1 (C_0), 163.9 (C_0), 162.1 (C_0), 154.5 (CH), 127.3 (2 × CH), 123.3 (C_0), 116.7 (CH), 114.3 (2 × CH), 110.7 (CH), 55.3 (OCH_3); HRMS (ESI+) *m*/*z*: Calcd for $C_{12}H_{11}O_3$ [M+H$^+$] 203.0708, found 203.0797.

4.1.4. 5-Bromo-2-(4-methoxyphenyl)-*2H*-pyran-4(*3H*)-one (52)

Iodosobenzene diacetate (2.2 equiv; 1.14 mmol; 368 mg) was suspended in anhydrous CH_2Cl_2 (2.6 mL) and cooled under magnetic stirring to 0 °C, under nitrogen atmosphere. Trimethylsilyl bromide (4.4 equiv; 2.29 mmol; 302 μL) was then added dropwise and the resulting orange colored solution stirred at this temperature for 45 min. Freshly distilled pyridine (5.0 equiv; 2.6 mmol; 210 μL) was added, followed by a solution of dihydro-γ-pyrone **50** (0.52 mmol; 106 mg) in anhydrous CH_2Cl_2 (2.6 mL). The resultant reaction mixture was maintained under these conditions for ca. 30 min. After this period, the reaction was quenched with a saturated aqueous solution of sodium thiosulfate (2.0 mL) and partitioned between a saturated solution of aqueous sodium hydrogen carbonate (20 mL) and CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/ethyl acetate 4:1, 3:1 v/v) to afford the desired 3-bromo-dihydro-γ-pyrone **52** in 81% yield (119 mg), as a light yellow solid. Mp: 108.2–108.9 °C; IR (cm^{-1}, thin film): 3039, 2919, 1667, 1617, 1567, 1519, 1357, 1260, 1181, 1128, 1029, 996, 818; ^{1}H NMR (250 MHz, $CDCl_3$, δ): 7.79 (s, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 5.49 (dd, *J* = 14.1 and 3.6 Hz, 1H), 3.84 (s, 3H), 3.09 (dd, *J* = 16.9 and 14.1 Hz, 1H), 2.90 (dd, *J* = 16.9 and 3.6 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 185.0 (C_0), 161.9 (CH), 160.3 (C_0), 128.6 (C_0), 127.8 (2 × CH), 114.2 (2 × CH), 102.4 (C_0), 81.7 (CH), 55.3 (OCH_3), 43.0 (CH_2); HRMS (ESI+) *m*/*z*: Calcd for $C_{12}H_{12}BrO_3$ [M+H$^+$] 282.9964, found 283.0009.

4.1.5. 5-Iodo-2-(4-methoxyphenyl)-*2H*-pyran-4(*3H*)-one (53)

To a solution of molecular iodine (2.25 equiv; 4.73 mmol; 1.2 g) in anhydrous CH_2Cl_2 (11 mL) at 0 °C, under magnetic stirring and nitrogen atmosphere, was added freshly distilled pyridine (5.0 equiv; 23.7 mmol; 0.8 mL). A solution of dihydro-γ-pyrone **50** (2.10 mmol; 430 mg) in anhydrous CH_2Cl_2 (11 mL) was then added dropwise. The resultant reaction mixture was maintained under magnetic stirring at 0 °C for 30 min and then at room temperature for ca. 2.5 h. After this period, the reaction was quenched with a saturated aqueous solution of sodium thiosulfate (20 mL) and partitioned between a saturated solution of aqueous sodium hydrogen carbonate (50 mL) and CH_2Cl_2 (3 × 70 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/ethyl acetate 2:1 v/v)

to afford the desired 3-iodo-dihydro-γ-pyrone **53** in 92% yield (0.64 g), as a light yellow solid. Mp: 113.6–114.2 °C; IR (cm^{-1}, thin film): 1660, 1612, 1552, 1516, 1342, 1273, 1250, 1175, 1119, 1102, 1022, 987, 951, 815; ^1H NMR (250 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.32 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 5.51 (dd, J = 13.7 and 4.0 Hz, 1H), 3.83 (s, 3H), 3.11 (dd, J = 16.8 and 13.7 Hz, 1H), 2.97 (dd, J = 16.8 and 4.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 186.2 (C_0), 166.0 (CH), 160.3 (C_0), 128.7 (C_0), 127.8 (2 × CH), 114.3 (2 × CH), 81.7 (CH), 76.8 (C_0), 55.3 (OCH_3), 42.5 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{12}H_{12}IO_3$ [M+H$^+$] 330.9826, found 330.9882.

4.1.6. General procedure for the aldehyde homologations

To a suspension of sodium hydride 60% in mineral oil (1.5 equiv; 18.1 mmol) in a mixture of anhydrous THF (50 mL) and anhydrous DMF (4 mL), under nitrogen atmosphere and cooled at 0 °C, was added triethyl phosphonoacetate (1.3 equiv; 15.6 mmol). The reaction mixture was maintained under magnetic stirring under these conditions for 15 min. A solution of aldehyde **54**–**60** (12.0 mmol) in anhydrous THF (10 mL) was then added dropwise and the cooling bath was removed. After total consumption of the starting material (TLC analysis), the reaction mixture was filtered on silica under reduced pressure and the filter cake washed with ethyl acetate. The solution was concentrated to dryness under vacuum and the residue was subjected to flash column chromatography (hexanes/ethyl acetate 2:1, 1:1 v/v or 10:1 v/v in the case of the CF_3-derivatives). The ester intermediate obtained (10.7 mmol) was dissolved in anhydrous CH_2Cl_2 (107 mL) and the resulting solution was cooled to −78 °C, under nitrogen atmosphere and magnetic stirring. DIBAL-H (2.5 equiv; 26.8 mmol) was added dropwise and the reaction mixture was maintained under these conditions until completion, ca. 30 min. After this period, the temperature was raised to 0 °C and ethyl acetate (15 mL) was added carefully, followed by 1 M HCl (90 mL). The emulsion remained under strong stirring until complete phase separation. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (hexanes/ethyl acetate 1:1 v/v or 2:1 v/v in the case of the CF_3-derivatives) and the allylic alcohol obtained (10.7 mmol) was dissolved in ethyl acetate (77 mL). Next, IBX was added (3.0 equiv; 32.1 mmol) and the resulting suspension was immersed in an oil bath at 80 °C. After, vigorous stirring under open atmosphere for approximately 3.5 h, the reaction mixture was cooled to room temperature, filtered over Celite under vacuum and the filter cake washed with ethyl acetate (3 × 20 mL). The filtrates were combined and the solvent was removed under reduced pressure. The residue obtained was purified by flash column chromatography (hexanes/ethyl acetate 2:1, 1:1 v/v or 3:1 v/v in the case of the CF_3-derivatives) to give the homologated aldehydes **61**–**62**, **64**–**68**.

4.1.6.1. (E)-3-(2-(Trifluoromethyl)phenyl)acrylaldehyde (61). Prepared according to the general procedure for the aldehyde homologations in 61% yield (yellow solid). Mp: 39.0–41.0 °C; IR (cm^{-1}, thin film): 3079, 1689, 1631, 1603, 1577, 1489, 1315, 1166, 1122, 1061, 1037, 974, 768; ^1H NMR (250 MHz, $CDCl_3$): δ 9.68 (d, J = 7.6 Hz, 1H), 7.80 (dd, J = 15.8 and 1.8 Hz, 1H), 7.68 (t, J = 7.5 Hz, 2H), 7.60–7.40 (m, 2H), 6.62 (dd, J = 15.8 and 7.6 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.0 (CH), 147.1 (q, J = 2.0 Hz, CH), 132.5 (q, J = 1.4 Hz, C_0), 132.1 (CH), 131.8 (CH), 130.3 (CH), 128.6 (q, J = 30.4 Hz, C_0), 127.8 (CH), 126.1 (q, J = 5.7 Hz, CH), 123.7 (q, J = 274.2 Hz, C_0); HRMS (ESI+) m/z: Calcd for $C_{10}H_8F_3O$ [M+H$^+$] 201.0527, found 201.0619.

4.1.6.2. (*E*)-3-(4-(Trifluoromethyl)phenyl)acrylaldehyde (62). Prepared according to the general procedure for the aldehyde homologations in 80% yield (yellow solid). Mp: 59.0–61.0 °C; IR (cm^{-1}, thin film): 2819, 2721, 1680, 1629, 1574, 1421, 1322, 1171, 1122, 1065, 981, 821, 760; ^1H NMR (250 MHz, $CDCl_3$): δ 9.75 (d, J = 7.6 Hz, 1H), 7.70–7.67 (m, 4H), 7.51 (d, J = 16.0 Hz, 1H), 6.77 (dd, J = 16.0 and 7.6 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.0 (CH), 150.0 (CH), 137.2 (C_0), 132.0 (q, J = 32.9 Hz, C_0), 130.2 (CH), 128.3 (2 × CH), 125.7 (q, J = 3.9 Hz, 2 × CH), 123.5 (q, J = 272.5 Hz, C_0); HRMS (ESI+) m/z: Calcd for $C_{10}H_8F_3O$ [M+H$^+$] 201.0527, found 201.0619.

4.1.6.3. (*E*)-3-(2,4-Dimethoxyphenyl)acrylaldehyde (64). Prepared according to the general procedure for the aldehyde homologations in 61% yield (yellow solid). Mp: 99.0–100.0 °C; IR (cm^{-1}, thin film): 2970, 2922, 2845, 2767, 1668, 1610, 1573, 1503, 1469, 1455, 1427, 1327, 1278, 1168, 1110, 971, 843, 785; ^1H NMR (250 MHz, $CDCl_3$): δ 9.59 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 15.9 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 6.67 (dd, J = 15.9 and 7.9 Hz, 1H), 6.51 (dd, J = 8.6 and 2.3 Hz, 1H), 6.44 (d, J = 2.3 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 194.5 (CH), 163.7 (C_0), 159.9 (C_0), 148.3 (CH), 130.4 (CH), 126.7 (CH), 116.1 (C_0), 105.6 (CH), 98.3 (CH), 55.5 (OCH_3), 55.4 (OCH_3); HRMS (ESI+) m/z: Calcd for $C_{11}H_{13}O_3$ [M+H$^+$] 193.0865, found 193.0950.

4.1.6.4. (*E*)-3-(3,4-Dimethoxyphenyl)acrylaldehyde (65). Prepared according to the general procedure for the aldehyde homologations in 81% yield (yellow solid). Mp: 80.0–81.5 °C; IR (cm^{-1}, thin film): 3014, 2974, 2923, 2841, 2806, 2749, 1673, 1621, 1596, 1513, 1421, 1266, 1226, 1138, 1131, 1017, 878, 800, 742; ^1H NMR (250 MHz, $CDCl_3$): δ 9.66 (d, J = 7.7 Hz, 1H), 7.41 (d, J = 15.8 Hz, 1H), 7.16 (dd, J = 8.3 and 1.8 Hz, 1H), 7.08 (d, J = 1.8 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.61 (dd, J = 15.8 and 7.7 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.3 (CH), 152.7 (CH), 151.8 (C_0), 149.2 (C_0), 126.9 (C_0), 126.5 (CH), 123.3 (CH), 111.0 (CH), 109.8 (CH), 55.8 (OCH_3), 55.7 (OCH_3); HRMS (ESI+) m/z: Calcd for $C_{11}H_{13}O_3$ [M+H$^+$] 193.0865, found 193.0866.

4.1.6.5. (*E*)-3-(3,5-Dimethoxyphenyl)acrylaldehyde (66). Prepared according to the general procedure for the aldehyde homologations in 87% yield (yellow solid). Mp: 78.5–80.0 °C; IR (cm^{-1}, thin film): 3090, 2994, 2968, 2846, 2814, 2730, 1674, 1590, 1446, 1424, 1349, 1299, 1264, 1209, 1193, 1152, 1126, 1058, 970, 832, 819; ^1H NMR (250 MHz, $CDCl_3$): δ 9.67 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 15.9 Hz, 1H), 6.68 (d, J = 2.2 Hz, 2H), 6.65 (dd, J = 15.9 and 7.7 Hz, 1H), 6.53 (t, J = 2.2 Hz, 1H), 3.80 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.5 (CH), 161.1 (2 × C_0), 152.6 (CH), 135.8 (C_0), 128.9 (CH), 106.3 (2 × CH), 103.3 (CH), 55.4 (2 × OCH_3); HRMS (ESI+) m/z: Calcd for $C_{11}H_{13}O_3$ [M+H$^+$] 193.0865, found 193.0950.

4.1.6.6. (*E*)-3-(3,4,5-Trimethoxyphenyl)acrylaldehyde (67). Prepared according to the general procedure for the aldehyde homologations in 90% yield (yellow solid). Mp: 110.0–111.0 °C; IR (cm^{-1}, thin film): 3013, 3002, 2979, 2948, 2840, 2749, 1699, 1677, 1621, 1581, 1504, 1470, 1422, 1335, 1123, 998, 973, 817, 736; ^1H NMR (250 MHz, $CDCl_3$): δ 9.66 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 15.8 Hz, 1H), 6.78 (s, 2H), 6.61 (dd, J = 15.8 and 7.7 Hz, 1H), 3.88 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.3 (CH), 153.5 (2 × C_0), 152.6 (CH), 140.9 (C_0), 129.4 (C_0), 127.9 (CH), 105.7 (2 × CH), 60.9 (OCH_3), 56.1 (2 × OCH_3); HRMS (ESI+) m/z: Calcd for $C_{12}H_{15}O_4$ [M+H$^+$] 223.0970, found 223.0979.

4.1.6.7. (*E*)-3-(2,4,5-Trimethoxyphenyl)acrylaldehyde (68). Prepared according to the general procedure for the aldehyde homologations in 50% yield (yellow solid). Mp: 129.0–130.5 °C;

IR (cm^{-1}, thin film): 3056, 2989, 2934, 2843, 1658, 1604, 1505, 1468, 1310, 1277, 1210, 1120, 1025, 876, 828, 751; ^1H NMR (250 MHz, $CDCl_3$): δ 9.43 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 15.9 Hz, 1H), 6.82 (s, 1H), 6.44 (dd, J = 15.9 and 7.8 Hz, 1H), 6.33 (s, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.6 (CH), 153.7 (C_0), 152.9 (C_0), 147.3 (CH), 142.8 (C_0), 125.7 (CH), 113.9 (C_0), 110.2 (CH), 96.0 (CH), 55.9 (OCH_3), 55.7 (OCH_3), 55.5 (OCH_3); HRMS (ESI+) m/z: Calcd for $C_{12}H_{15}O_4$ [M+H$^+$] 223.0970, found 223.1012.

4.1.7. General procedure for the allylation reactions

To a stirred solution of the homologated aldehyde **61**–**68** (4.94 mmol) in anhydrous THF (25 mL), at −78 °C under nitrogen atmosphere, was added dropwise a solution of allylmagnesium bromide in diethyl ether (1.2 equiv; 5.93 mmol). The reaction mixture was maintained under these conditions for 30 min. After this period, a saturated aqueous solution of ammonium chloride (10 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (using the eluent indicated) to give the corresponding homoallylic alcohols **69**–**76**.

4.1.7.1. (E)-1-(2-(Trifluoromethyl)phenyl)hexa-1,5-dien-3-ol (69). Prepared according to the general procedure for the allylation reactions in 90% yield (yellow oil). Eluent: hexanes/ethyl acetate 4:1 v/v. IR (cm^{-1}, thin film): 3418, 3078, 2931, 1640, 1614, 1576, 1488, 1455, 1315, 1165, 1123, 1036, 974, 921, 768; ^1H NMR (250 MHz, $CDCl_3$): δ 7.66–7.57 (m, 2H), 7.50 (t, J = 7.5 Hz, 1H), 7.39–7.29 (m, 1H), 6.99 (d, J = 15.7 Hz, 1H), 6.21 (dd, J = 15.7 and 6.5 Hz, 1H), 5.95–5.77 (m, 1H), 5.26–5.13 (m, 2H), 4.46–4.35 (m, 1H), 2.54–2.32 (m, 2H), 1.83 (d, J = 4.1 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 136.0 (CH), 135.9 (C_0), 133.7 (CH), 131.8 (CH), 127.5 (CH), 127.4 (q, J = 30.0 Hz, C_0), 127.3 (CH), 126.3 (q, J = 1.8 Hz, CH), 125.7 (q, J = 5.7 Hz, CH), 124.3 (q, J = 273.9 Hz, C_0), 118.7 (CH_2), 71.5 (CH), 41.8 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{13}H_{12}F_3$ [M+H$^+$−18] 225.0891, found 225.0911.

4.1.7.2. (E)-1-(4-(Trifluoromethyl)phenyl)hexa-1,5-dien-3-ol (70). Prepared according to the general procedure for the allylation reactions in 99% yield (yellow oil). Eluent: hexanes/ethyl acetate 4:1 v/v. IR (cm^{-1}, thin film): 3411, 3079, 2981, 2933, 1642, 1616, 1579, 1514, 1415, 1326, 1166, 1125, 1067, 1017, 971, 921, 863, 838, 819; ^1H NMR (250 MHz, $CDCl_3$,): δ 7.54 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 15.9 Hz, 1H), 6.33 (dd, J = 15.9 and 5.9 Hz, 1H), 5.95–5.75 (m, 1H), 5.25–5.11 (m, 2H), 4.38 (q, J = 5.9 Hz, 1H), 2.52–2.31 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 140.2 (C_0), 134.3 (CH), 133.7 (CH), 129.3 (q, J = 32.3 Hz, C_0), 128.7 (CH), 126.6 (2 × CH), 125.5 (q, J = 3.9 Hz, 2 × CH), 124.2 (q, J = 271.3 Hz, C_0), 118.6 (CH_2), 71.3 (CH), 41.9 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{13}H_{12}F_3$ [M+H$^+$−18] 225.0891, found 225.0962.

4.1.7.3. (E)-1-(4-Methoxyphenyl)hexa-1,5-dien-3-ol (71). Prepared according to the general procedure for the allylation reactions in quantitative yield (yellow oil). Eluent: hexanes/ethyl acetate 3:2 v/v. IR (cm^{-1}, thin film): 3409, 3075, 3004, 2934, 2904, 2837, 1641, 1607, 1578, 1512, 1465, 1302, 1250, 1175, 1033, 969, 917, 816; ^1H NMR (250 MHz, $CDCl_3$): δ 7.26 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.50 (d, J = 15.9 Hz, 1H), 6.09 (dd, J = 15.9 and 6.6 Hz, 1H), 5.87 (dtd, J = 17.2, 10.2, 6.6 and 6.6 Hz, 1H), 5.20–5.07 (m, 2H), 4.29 (q, J = 6.6 Hz, 1H), 3.72 (s, 3H), 3.26 (br s, 1H), 2.39 (t, J = 6.6 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 158.7 (C_0), 134.1 (CH), 129.3 (2 × CH), 129.1 (C_0), 127.2 (2 × CH), 117.2 (CH_2), 113.5 (2 × CH), 71.6 (CH), 54.7 (OCH_3), 41.6 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{13}H_{15}O$ [M+H$^+$−18] 187.1123, found 187.1203.

4.1.7.4. (E)-1-(2,4-Dimethoxyphenyl)hexa-1,5-dien-3-ol (72). Prepared according to the general procedure for the allylation reactions in quantitative yield (yellow oil). Eluent: hexanes/ethyl acetate 2:1 v/v. IR (cm^{-1}, thin film): 3442, 3072, 3002, 2938, 2838, 1638, 1609, 1505, 1465, 1209, 1159, 1034, 921, 834; ^1H NMR (250 MHz, $CDCl_3$): δ 7.33 (d, J = 8.2 Hz, 1H), 6.81 (d, J = 16.0 Hz, 1H), 6.47 (d, J = 2.3 Hz, 1H), 6.45–6.41 (m, 1H), 6.13 (dd, J = 16.0 and 6.8 Hz, 1H), 5.87 (dtd, J = 17.2, 10.2, 6.8 and 6.8 Hz, 1H), 5.21–5.08 (m, 2H), 4.32 (q, J = 6.8 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.40 (app t, J = 6.8 Hz, 2H), 2.06 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 160.4 (C_0), 157.8 (C_0), 134.4 (CH), 130.1 (CH), 127.5 (CH), 125.0 (CH), 118.6 (C_0), 117.8 (CH_2), 104.7 (CH), 98.3 (CH), 72.4 (CH), 55.3 (OCH_3), 55.2 (OCH_3), 42.0 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{14}H_{17}O_2$ [M+H$^+$−18] 217.1228, found 217.1205.

4.1.7.5. (E)-1-(3,4-Dimethoxyphenyl)hexa-1,5-dien-3-ol (73). Prepared according to the general procedure for the allylation reactions in 94% yield (yellow oil). Eluent: hexanes/ethyl acetate 1:1 v/v. IR (cm^{-1}, thin film): 3479, 3075, 3002, 2936, 2909, 2837, 1678, 1641, 1600, 1586, 1515, 1464, 1265, 1139, 1026, 969, 918, 863; ^1H NMR (250 MHz, $CDCl_3$): δ 6.95–6.87 (m, 2H), 6.79 (app d, J = 8.0 Hz, 1H), 6.52 (d, J = 15.9 Hz, 1H), 6.09 (dd, J = 15.9 and 6.5 Hz, 1H), 5.85 (dtd, J = 17.2, 10.2, 6.5 and 6.5 Hz, 1H), 5.22–5.10 (m, 2H), 4.32 (q, J = 6.5 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.44–2.34 (m, 2H), 1.92 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 149.0 (C_0), 148.8 (C_0), 134.1 (CH), 130.1 (CH), 129.7 (C_0), 129.6 (CH), 119.6 (CH), 118.2 (CH_2), 111.1 (CH), 108.9 (CH), 71.8 (CH), 55.8 (2 × OCH_3), 42.0 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{14}H_{17}O_2$ [M+H$^+$−18] 217.1228, found 217.1205.

4.1.7.6. (E)-1-(3,5-Dimethoxyphenyl)hexa-1,5-dien-3-ol (74). Prepared according to the general procedure for the allylation reactions in quantitative yield (light brown viscous oil). Eluent: hexanes/ethyl acetate 1:1 v/v. IR (cm^{-1}, thin film): 3418, 3076, 3002, 2937, 2838, 1640, 1593, 1459, 1427, 1205, 1154, 1064, 969, 923, 828; ^1H NMR (250 MHz, $CDCl_3$): δ 6.52 (d, J = 2.1 Hz, 2H), 6.49 (d, J = 15.9 Hz, 1H), 6.36 (t, J = 2.1 Hz, 1H), 6.20 (dd, J = 15.9 and 6.3 Hz, 1H), 5.84 (dtd, J = 17.2, 10.2, 6.3 and 6.3 Hz, 1H), 5.20–5.07 (m, 2H), 4.30 (q, J = 6.3 Hz, 1H), 3.75 (s, 6H), 2.45 (br s, 1H), 2.38 (app t, J = 6.3 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 160.7 (2 × C_0), 138.6 (C_0), 134.0 (CH), 132.1 (CH), 129.9 (CH), 118.0 (CH_2), 104.4 (2 × CH), 99.7 (CH), 71.4 (CH), 55.1 (2 × OCH_3), 41.7 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{14}H_{19}O_3$ [M+H$^+$] 235.1334, found 235.1407.

4.1.7.7. (E)-1-(3,4,5-Trimethoxyphenyl)hexa-1,5-dien-3-ol (75). Prepared according to the general procedure for the allylation reactions in 92% yield (yellow oil). Eluent: hexanes/ethyl acetate 3:2 v/v. IR (cm^{-1}, thin film): 3439, 3074, 2999, 2938, 2838, 1640, 1584, 1507, 1463, 1420, 1329, 1241, 1127, 1004, 969, 919, 814; ^1H NMR (250 MHz, $CDCl_3$): δ 6.55 (s, 2H), 6.47 (d, J = 15.9 Hz, 1H), 6.11 (dd, J = 15.9 and 6.5 Hz, 1H), 5.82 (dtd, J = 17.2, 10.2, 6.5 and 6.5 Hz, 1H), 5.18–5.06 (m, 2H), 4.30 (q, J = 6.5 Hz, 1H), 3.82 (s, 6H), 3.80 (s, 3H), 2.42–2.32 (m, 2H), 2.23 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 153.1 (2 × C_0), 137.7 (C_0), 134.0 (CH), 132.3 (C_0), 131.0 (CH), 130.0 (CH), 118.1 (CH_2), 103.5 (2 × CH), 71.5 (CH), 60.7 (OCH_3), 55.9 (2 × OCH_3), 41.8 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{21}O_4$ [M+H$^+$] 265.1440, found 265.1553.

4.1.7.8. (E)-1-(2,4,5-Trimethoxyphenyl)hexa-1,5-dien-3-ol (76). Prepared according to the general procedure for the allylation reactions in 80% yield (yellow oil). Eluent: hexanes/ethyl acetate 1:1 v/

v. IR (cm^{-1}, thin film): 3422, 3074, 3000, 2936, 2834, 1641, 1609, 1511, 1466, 1208, 1034, 973, 916, 874, 732; ^1H NMR (250 MHz, $CDCl_3$): δ 6.83 (s, 1H), 6.17 (d, J = 16.0 Hz, 1H), 6.34 (s, 1H), 5.99 (dd, J = 16.0 and 6.7 Hz, 1H), 5.86–5.64 (m, 1H), 5.12–4.91 (m, 2H), 4.26–4.11 (m, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H), 2.67 (br s, 1H), 2.28 (t, J = 6.7 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 151.3 (C_0), 149.4 (C_0), 143.2 (C_0), 134.3 (CH), 129.9 (CH), 124.7 (CH), 117.8 (CH_2), 117.3 (C_0), 109.9 (CH), 97.6 (CH), 72.3 (CH), 56.4 (2 × OCH_3), 55.9 (OCH_3), 41.9 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{19}O_3$ [M+H$^+$−18] 247.1334, found 247.1358.

4.1.8. General procedure for the esterification reactions

To a solution of the homoallylic alcohols **69**–**76** (3.40 mmol) in anhydrous CH_2Cl_2 (70 mL), at 0 °C under magnetic stirring and nitrogen atmosphere, was added triethylamine (2.0 equiv; 6.80 mmol), followed by acryloyl chloride (1.5 equiv; 5.10 mmol). The cooling bath was removed and the reaction mixture was stirred for 1 h at room temperature. After this period, the volatiles were removed under reduced pressure and the crude was purified by flash column chromatography (using the eluent indicated) to afford the corresponding esters **77**–**84**.

4.1.8.1. (E)-1-(2-(Trifluoromethyl)phenyl)hexa-1,5-dien-3-yl acrylate (77). Prepared according to the general procedure for the esterification reactions in 61% yield (yellow oil). Eluent: hexanes/ethyl acetate 9:1 v/v. IR (cm^{-1}, thin film): 3078, 2928, 2855, 1726, 1638, 1576, 1406, 1315, 1189, 1165, 1124, 1036, 967, 809, 765; ^1H NMR (250 MHz, $CDCl_3$): δ 7.65–7.55 (m, 2H), 7.48 (t, J = 7.6 Hz, 1H), 7.38–7.29 (m, 1H), 7.02 (d, J = 16.0 Hz, 1H), 6.46 (dd, J = 17.3 and 1.3 Hz, 1H), 6.23–6.10 (m, 2H), 5.91–5.72 (m, 2H), 5.60 (q, J = 6.5 Hz, 1H), 5.22–5.07 (m, 2H), 2.55 (t, J = 6.5 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.2 (C_0), 135.5 (q, J = 1.8 Hz, C_0), 132.7 (CH), 131.8 (CH), 131.4 (CH), 130.9 (CH_2), 128.5 (CH), 128.1 (q, J = 1.8 Hz, CH), 127.6 (q, J = 29.9 Hz, C_0), 127.5 (2 × CH), 125.7 (q, J = 5.8 Hz, CH), 124.2 (q, J = 274.0 Hz, C_0), 118.4 (CH_2), 73.2 (CH), 38.9 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{16}H_{16}F_3O_2$ [M+H$^+$] 297.1102, found 297.1135.

4.1.8.2. (E)-1-(4-(Trifluoromethyl)phenyl)hexa-1,5-dien-3-yl acrylate (78). Prepared according to the general procedure for the esterification reactions in 41% yield (yellow oil). Eluent: hexanes/ethyl acetate 9:1 v/v. IR (cm^{-1}, thin film): 3081, 2927, 2855, 1727, 1640, 1617, 1407, 1326, 1189, 1167, 1125, 1068, 970, 810; ^1H NMR (250 MHz, $CDCl_3$): δ 7.56 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 16.0 Hz, 1H), 6.45 (dd, J = 17.3 and 1.5 Hz, 1H), 6.28 (dd, J = 16.0 and 7.0 Hz, 1H), 6.16 (dd, J = 17.3 and 10.4 Hz, 1H), 5.86 (dd, J = 10.4 and 1.5 Hz, 1H), 5.81 (dtd, J = 17.4, 10.2, 7.0 and 7.0 Hz, 1H), 5.58 (q, J = 7.0 Hz, 1H), 5.19–5.08 (m, 2H), 2.55 (t, J = 7.0 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.3 (C_0), 139.7 (C_0), 132.7 (CH), 131.1 (CH), 131.0 (CH_2), 129.7 (q, J = 32.3 Hz, C_0), 129.7 (CH), 128.5 (CH), 126.7 (2 × CH), 125.5 (q, J = 3.9 Hz, 2 × CH), 124.3 (q, J = 272.2 Hz, C_0), 118.4 (CH_2), 73.5 (CH), 38.9 (CH_2); HRMS (EI) m/z: Calcd for $C_{16}H_{15}F_3O_2$ [M$^+$] 296.1024, found 296.1039.

4.1.8.3. (E)-1-(4-methoxyphenyl)hexa-1,5-dien-3-yl acrylate (79). Prepared according to the general procedure for the esterification reactions in 86% yield (yellow oil). Eluent: hexanes/ethyl acetate 2:1 v/v. IR (cm^{-1}, thin film): 3077, 3036, 3005, 2959, 2934, 2837, 1722, 1638, 1608, 1513, 1405, 1250, 1190, 1176, 1036, 966, 808; ^1H NMR (250 MHz, $CDCl_3$): δ 7.27 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.58 (d, J = 15.9 Hz, 1H), 6.40 (dd, J = 17.3 and 1.3 Hz, 1H), 6.12 (dd, J = 17.3 and 10.3 Hz, 1H), 6.03 (dd, J = 15.9 and 6.7 Hz, 1H), 5.88–5.69 (m, 1H), 5.75 (dd, J = 10.3 and 1.3 Hz, 1H), 5.54 (q, J = 6.7 Hz, 1H), 5.18–5.02 (m, 2H), 3.69 (s, 3H), 2.49 (t, J = 6.7 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.8 (C_0), 159.2 (C_0), 132.8 (CH), 132.0 (CH), 130.1 (CH_2), 128.5 (C_0), 128.4 (CH), 127.4 (2 × CH), 124.3 (CH), 117.6 (CH_2), 113.6 (2 × CH), 73.7 (CH), 54.6 (OCH_3), 38.7 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{13}H_{15}O$ [M+H$^+$−72] 187.1123, found 187.1203.

4.1.8.4. (E)-1-(2,4-Dimethoxyphenyl)hexa-1,5-dien-3-yl acrylate (80). Prepared according to the general procedure for the esterification reactions in 60% yield (yellow oil). Eluent: hexanes/ethyl acetate 3:1 v/v. IR (cm^{-1}, thin film): 3004, 2936, 2837, 1723, 1609, 1580, 1505, 1465, 1289, 1264, 1208, 1159, 1036, 974, 834; ^1H NMR (250 MHz, $CDCl_3$,): δ 7.33 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 16.0 Hz, 1H), 6.51–6.35 (m, 3H), 6.22–6.04 (m, 2H), 5.90–5.70 (m, 2H), 5.54 (q, J = 6.8 Hz, 1H), 5.18–5.04 (m, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 2.52 (t, J = 6.8 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.5 (C_0), 160.7 (C_0), 158.1 (C_0), 133.4 (CH), 130.4 (CH_2), 128.9 (CH), 127.9 (CH), 127.7 (CH), 125.2 (CH), 118.3 (C_0), 117.9 (CH_2), 104.8 (CH), 98.4 (CH), 74.8 (CH), 55.4 (2 × OCH_3), 39.3 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{14}H_{17}O_2$ [M+H$^+$−72] 217.1228, found 217.1308.

4.1.8.5. (E)-1-(3,4-Dimethoxyphenyl)hexa-1,5-dien-3-yl acrylate (81). Prepared according to the general procedure for the esterification reactions in 60% yield (yellow oil). Eluent: hexanes/ethyl acetate 2:1 v/v. IR (cm^{-1}, thin film): 3077, 3002, 2956, 2937, 2837, 1722, 1639, 1602, 1586, 1515, 1465, 1406, 1266, 1192, 1027, 967, 809; ^1H NMR (250 MHz, $CDCl_3$): δ 6.93–6.84 (m, 2H), 6.76 (d, J = 8.7 Hz, 1H), 6.55 (d, J = 15.9 Hz, 1H), 6.39 (d, J = 17.3 Hz, 1H), 6.11 (dd, J = 17.3 and 10.3 Hz, 1H), 6.02 (dd, J = 15.9 and 6.7 Hz, 1H), 5.87–5.67 (m, 1H), 5.78 (d, J = 10.3 Hz, 1H), 5.51 (q, J = 6.7 Hz, 1H), 5.17–5.01 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 2.50 (t, J = 6.7 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.2 (C_0), 149.0 (C_0), 148.8 (C_0), 132.9 (CH), 132.5 (CH), 130.5 (CH_2), 129.1 (C_0), 128.5 (CH), 124.7 (CH), 119.7 (CH), 117.9 (CH_2), 110.9 (CH), 108.9 (CH), 73.9 (CH), 55.7 (OCH_3), 55.6 (OCH_3), 38.9 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{17}H_{21}O_4$ [M+H$^+$] 289.1440, found 289.1489.

4.1.8.6. (E)-1-(3,5-Dimethoxyphenyl)hexa-1,5-dien-3-yl acrylate (82). Prepared according to the general procedure for the esterification reactions in 92% yield (yellow oil). Eluent: hexanes/ethyl acetate 2:1 v/v. IR (cm^{-1}, thin film): 3078, 3002, 2939, 2838, 1723, 1636, 1593, 1457, 1428, 1405, 1295, 1268, 1205, 1193, 1154, 1066, 967, 809; ^1H NMR (250 MHz, $CDCl_3$): δ 6.62–6.35 (m, 5H), 6.24–6.06 (m, 2H), 5.90–5.70 (m, 2H), 5.55 (q, J = 6.6 Hz, 1H), 5.19–5.06 (m, 2H), 3.77 (s, 6H), 2.52 (t, J = 6.6 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.1 (C_0), 160.8 (2 × C_0), 138.1 (C_0), 132.8 (CH), 132.6 (CH), 130.6 (CH_2), 128.5 (CH), 127.4 (CH), 118.1 (CH_2), 104.5 (2 × CH), 100.2 (CH), 73.6 (CH), 55.1 (2 × OCH_3), 38.9 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{17}H_{21}O_4$ [M+H$^+$] 289.1440, found 289.1381.

4.1.8.7. (E)-1-(3,4,5-Trimethoxyphenyl)hexa-1,5-dien-3-yl acrylate (83). Prepared according to the general procedure for the esterification reactions in 82% yield (yellow oil). Eluent: hexanes/ethyl acetate 2:1 v/v. IR (cm^{-1}, thin film): 3077, 2998, 2940, 2840, 1722, 1638, 1619, 1583, 1507, 1463, 1455, 1420, 1405, 1330, 1241, 1190, 1127, 967, 810; ^1H NMR (250 MHz, $CDCl_3$): δ 6.61–6.56 (m, 2H), 6.56 (d, J = 16.0 Hz, 1H), 6.43 (d, J = 17.3 Hz, 1H), 6.20–6.00 (m, 2H), 5.89–5.69 (m, 2H), 5.53 (q, J = 6.6 Hz, 1H), 5.19–5.09 (m, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 2.52 (t, J = 6.6 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.3 (C_0), 153.2 (2 × C_0), 138.1 (C_0), 132.9 (CH), 132.8 (CH), 131.8 (C_0), 130.7 (CH_2), 128.6 (CH), 126.3 (CH), 118.1 (CH_2), 103.7 (2 × CH), 73.8 (CH), 60.8 (OCH_3), 56.0 (2 × OCH_3), 39.0 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{19}O_3$ [M+H$^+$−72] 247.1334, found 247.1389.

4.1.8.8. (E)-1-(2,4,5-Trimethoxyphenyl)hexa-1,5-dien-3-yl acrylate (84). Prepared according to the general procedure for the esterification reactions in 83% yield (yellow oil). Eluent: hexanes/ethyl acetate 2:1 v/v. IR (cm^{-1}, thin film): 2995, 2922, 2831, 1724, 1607, 1511, 1464, 1402, 1206, 1123, 1033, 985, 869; ^1H NMR (250 MHz, $CDCl_3$): δ 6.96–6.83 (m, 2H), 6.50–6.32 (m, 2H), 6.19–5.98 (m, 2H), 5.89–5.68 (m, 2H), 5.53 (q, J = 6.4 Hz, 1H), 5.17–5.00 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 2.51 (t, J = 6.4 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.3 (C_0), 151.6 (C_0), 149.7 (C_0), 143.1 (C_0), 133.2 (CH), 130.4 (CH_2), 128.7 (CH), 127.3 (CH), 124.9 (CH), 117.8 (CH_2), 116.8 (C_0), 110.0 (CH), 97.5 (CH), 74.6 (CH), 56.4 (2 × OCH_3), 55.9 (OCH_3), 39.1 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{19}O_3$ [M+H$^+$−72] 247.1334, found 247.1389.

4.1.9. General Procedure for the Preparation of Lactones

To a solution of esters **77**–**84** (1.80 mmol) in CH_2Cl_2 (180 mL), under reflux and magnetic stirring, was added Grubbs' first generation catalyst (10 mol %; 0.18 mmol). After 8.0 h under these conditions, the reaction was allowed to cool to room temperature, DMSO (50 equiv relative to the catalyst) was added and the mixture was maintained under magnetic stirring overnight. After this period, the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (using the eluent indicated) to afford the corresponding lactones **85**–**92**.

4.1.9.1. (E)-6-(2-(Trifluoromethyl)styryl)-5,6-dihydro-2H-pyran-2-one (85). Prepared according to the general procedure for the preparation of lactones in 70% yield (yellow oil). Eluent: hexanes/ethyl acetate 2:1 v/v. IR (cm^{-1}, thin film): 3074, 2925, 1725, 1605, 1577, 1488, 1384, 1314, 1246, 1164, 1120, 1058, 1036, 968, 832, 815, 743; ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.08 (d, J = 15.9 Hz, 1H), 6.94 (ddd, J = 9.7, 4.8 and 3.8 Hz, 1H), 6.28 (dd, J = 15.9 and 6.5 Hz, 1H), 6.11 (dt, J = 9.7 and 1.7 Hz, 1H), 5.17–5.12 (m, 1H), 2.60–2.56 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.6 (C_0), 144.5 (CH), 134.9 (q, J = 1.5 Hz, C_0), 132.0 (CH), 130.2 (CH), 129.2 (q, J = 1.6 Hz, CH), 128.0 (CH), 127.7 (q, J = 30.0 Hz, C_0), 127.6 (CH), 125.8 (q, J = 5.7 Hz, CH), 124.1 (q, J = 273.7 Hz, C_0), 121.6 (CH), 77.7 (CH), 29.6 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{14}H_{12}F_3O_2$ [M+H$^+$] 269.0789, found 269.0835.

4.1.9.2. (E)-6-(4-(Trifluoromethyl)styryl)-5,6-dihydro-2H-pyran-2-one (86). Prepared according to the general procedure for the preparation of lactones in 73% yield (yellow solid). Eluent: hexanes/ethyl acetate 2:1 v/v. Mp: 72.3–74.2 °C; IR (cm^{-1}, thin film): 2922, 1714, 1615, 1428, 1418, 1384, 1328, 1245, 1162, 1120, 1069, 1017, 971, 861, 814; ^1H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H), 6.93 (ddd, J = 9.7, 5.3 and 3.2 Hz, 1H), 6.78 (d, J = 16.0 Hz, 1H), 6.36 (dd, J = 16.0 and 5.9 Hz, 1H), 6.11 (ddd, J = 9.7, 2.3 and 1.3 Hz, 1H), 5.16–5.11 (m, 1H), 2.63–2.50 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.6 (C_0), 144.7 (CH), 139.3 (C_0), 131.4 (CH), 130.0 (q, J = 32.3 Hz, C_0), 128.3 (CH), 126.9 (2 × CH), 125.6 (q, J = 3.8 Hz, 2 × CH), 124.0 (q, J = 271.9 Hz, C_0), 121.5 (CH), 77.4 (CH), 29.7 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{14}H_{12}F_3O_2$ [M+H$^+$] 269.0789, found 269.0730.

4.1.9.3. (E)-6-(4-Methoxystyryl)-5,6-dihydro-2H-pyran-2-one (87). Prepared according to the general procedure for the preparation of lactones in 74% yield (white solid). Eluent: hexanes/ethyl acetate 1:1 v/v. Mp: 110.6–112.5 °C; IR (cm^{-1}, thin film): 3045, 2936, 2839, 1712, 1651, 1605, 1513, 1455, 1420, 1245, 1145, 1025, 968, 849, 809, 771; ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, J = 8.7 Hz, 2H), 6.90 (dt, J = 9.7 and 4.3 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 6.64 (d, J = 15.9 Hz, 1H), 6.12 (dd, J = 15.9 and 6.6 Hz, 1H), 6.06 (dt, J = 9.7 and 1.8 Hz, 1H), 5.08–5.02 (m, 1H), 3.79 (s, 3H), 2.53–2.49 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.9 (C_0), 159.6 (C_0), 144.7 (CH), 132.6 (CH), 128.3 (C_0), 127.8 (2 × CH), 123.3 (CH), 121.3 (CH), 113.9 (2 × CH), 78.1 (CH), 55.1 (OCH_3), 29.8 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{14}H_{15}O_3$ [M+H$^+$] 231.1021, found 231.1013.

4.1.9.4. (E)-6-(2,4-Dimethoxystyryl)-5,6-dihydro-2H-pyran-2-one (88). Prepared according to the general procedure for the preparation of lactones in 50% yield (yellow solid). Eluent: hexanes/ethyl acetate 1:1 v/v. Mp: 72.4–74.6 °C; IR (cm^{-1}, thin film): 3003, 2940, 2838, 1719, 1608, 1505, 1465, 1384, 1247, 1209, 1160, 1031, 972, 815, 734; ^1H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, J = 8.5 Hz, 1H), 6.91 (d, J = 16.0 Hz, 1H), 6.90 (dt, J = 9.8 and 4.5 Hz, 1H), 6.47 (dd, J = 8.5 and 2.4 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 6.21 (dd, J = 16.0 and 6.9 Hz, 1H), 6.06 (dt, J = 9.8 and 1.8 Hz, 1H), 5.08–5.02 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 2.55–2.50 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.0 (C_0), 160.7 (C_0), 157.9 (C_0), 144.9 (CH), 128.0 (CH), 127.8 (CH), 123.7 (CH), 121.0 (CH), 117.4 (C_0), 104.7 (CH), 98.0 (CH), 78.8 (CH), 55.1 (2 × OCH_3), 29.7 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{17}O_4$ [M+H$^+$] 261.1127, found 261.1112.

4.1.9.5. (E)-6-(3,4-Dimethoxystyryl)-5,6-dihydro-2H-pyran-2-one (89). Prepared according to the general procedure for the preparation of lactones in 45% yield (yellow solid). Eluent: hexanes/ethyl acetate 1:1 v/v. Mp: 116.0–118.0 °C; IR (cm^{-1}, thin film): 3001, 2934, 2843, 1715, 1602, 1585, 1515, 1464, 1421, 1383, 1266, 1251, 1141, 1023, 968, 817; ^1H NMR (500 MHz, $CDCl_3$): δ 6.95–6.89 (m, 3H), 6.82 (d, J = 8.5 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 6.13 (dd, J = 15.9 and 6.5 Hz, 1H), 6.07 (dt, J = 9.8 and 1.6 Hz, 1H), 5.10–5.04 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.57–2.50 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.7 (C_0), 149.1 (C_0), 148.8 (C_0), 144.7 (CH), 132.7 (CH), 128.5 (C_0), 123.4 (CH), 121.2 (CH), 119.9 (CH), 110.9 (CH), 108.7 (CH), 77.9 (CH), 55.6 (2 × OCH_3), 29.6 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{17}O_4$ [M+H$^+$] 261.1127, found 261.1207.

4.1.9.6. (E)-6-(3,5-Dimethoxystyryl)-5,6-dihydro-2H-pyran-2-one (90). Prepared according to the general procedure for the preparation of lactones in 88% yield (yellow oil). Eluent: hexanes/ethyl acetate 1:1 v/v. IR (cm^{-1}, thin film): 3002, 2940, 2840, 1721, 1661, 1592, 1459, 1428, 1383, 1246, 1205, 1154, 1060, 967, 818, 734; ^1H NMR (500 MHz, $CDCl_3$): δ 6.91 (ddd, J = 9.7, 5.0 and 3.5 Hz, 1H), 6.64 (d, J = 15.8 Hz, 1H), 6.53 (d, J = 2.2 Hz, 2H), 6.39 (t, J = 2.2 Hz, 1H), 6.24 (dd, J = 15.9 and 6.3 Hz, 1H), 6.07 (dt, J = 9.7 and 1.4 Hz, 1H), 5.11–5.05 (m, 1H), 3.79 (s, 6H), 2.58–2.47 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.4 (C_0), 160.5 (2 × C_0), 144.8 (CH), 137.4 (C_0), 132.4 (CH), 125.9 (CH), 120.8 (CH), 104.3 (2 × CH), 100.0 (CH), 77.4 (CH), 54.8 (2 × OCH_3), 29.3 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{17}O_4$ [M+H$^+$] 261.1127, found 261.1112.

4.1.9.7. (E)-6-(3,4,5-Trimethoxystyryl)-5,6-dihydro-2H-pyran-2-one (91). Prepared according to the general procedure for the preparation of lactones in 70% yield (yellow solid). Eluent: hexanes/ethyl acetate 1:2 v/v. Mp: 117.6–119.0 °C; IR (cm^{-1}, thin film): 2940, 2840, 1721, 1658, 1583, 1508, 1463, 1455, 1421, 1244, 1125, 1018, 967, 817; ^1H NMR (500 MHz, $CDCl_3$): δ 6.91 (ddd, J = 13.3, 4.9 and 3.5 Hz, 1H), 6.62 (d, J = 15.9 Hz, 1H), 6.64–6.62 (m, 2H), 6.17 (dd, J = 15.9 and 6.3 Hz, 1H), 6.06 (dt, J = 9.8 and 1.5 Hz, 1H), 5.14–5.06 (m, 1H), 3.85 (s, 6H), 3.82 (s, 3H), 2.62–2.50 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.3 (C_0), 152.8 (2 × C_0), 144.7 (CH), 137.8 (C_0), 132.4 (CH), 131.0 (C_0), 124.8 (CH), 120.7 (CH), 103.3 (2 × CH), 77.4 (CH), 60.3 (OCH_3), 55.5 (2 × OCH_3), 29.2 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{16}H_{19}O_5$ [M+H$^+$] 291.1233, found 291.1263.

4.1.9.8. (E)-6-(2,4,5-Trimethoxystyryl)-5,6-dihydro-2H-pyran-2-one (92). Prepared according to the general procedure for the preparation of lactones in 45% yield (yellow solid). Eluent: hexanes/ethyl acetate 1:1 v/v. Mp: 101.4–102.8 °C; IR (cm^{-1}, thin film): 2995, 2934, 2825, 1714, 1586, 1513, 1464, 1404, 1208, 1030, 873, 816; ^1H NMR (250 MHz, $CDCl_3$): δ 7.00–6.86 (m, 3H), 6.49 (s, 1H), 6.18 (dd, J = 16.1 and 6.9 Hz, 1H), 6.07 (dt, J = 9.7 and 1.7 Hz, 1H), 5.13–5.02 (m, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 2.58–2.50 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.9 (C_0), 151.7 (C_0), 150.0 (C_0), 144.8 (CH), 143.1 (C_0), 127.8 (CH), 123.7 (CH), 121.3 (CH), 116.1 (C_0), 109.9 (CH), 97.2 (CH), 78.7 (CH), 56.3 (2 × OCH_3), 55.9 (OCH_3), 29.8 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{16}H_{19}O_5$ [M+H$^+$] 291.1233, found 291.1232.

4.1.10. General Procedure for the Preparation of the Amides

To a stirred solution of lithium hexamethyldisilazide (1.2 equiv; 5.93 mmol) in anhydrous THF (20 mL), at 0 °C under nitrogen atmosphere, was added a solution of the homologated aldehyde **61**–**68**, **93** (4,94 mmol) in anhydrous THF (5 mL). After 15 min under these conditions, a solution of allylmagnesium bromide in diethyl ether (1.2 equiv; 5.93 mmol) was added dropwise and the resulting solution was stirred at room temperature for 30 min. After this period, a saturated aqueous solution of ammonium chloride (35 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was dissolved in anhydrous CH_2Cl_2 (50 mL), triethylamine (2.0 equiv; 9.88 mmol) was added and the resulting solution was cooled to 0 °C. Acryloyl chloride (1.5 equiv; 7.41 mmol) was then added dropwise and the reaction mixture was stirred for 1 h at room temperature. After completion (indicated by TLC analysis), the volatiles were removed under reduced pressure and the crude was purified by flash column chromatography (using the eluent indicated), giving the corresponding amides **94**–**102**.

4.1.10.1. (E)-N-(1-Phenylhexa-1,5-dien-3-yl)acrylamide (94). Prepared according to the general procedure for the preparation of the amides in 85% yield (white solid). Eluent: hexanes/ethyl acetate 1:2 v/v. Mp: 94.2–96.0 °C; IR (cm^{-1}, thin film): 3277, 3079, 3028, 2979, 2927, 1657, 1627, 1553, 1406, 1250, 1070, 992, 967, 926, 745; ^1H NMR (250 MHz, $CDCl_3$): δ 7.38–7.18 (m, 5H), 6.53 (d, J = 16.1 Hz, 1H), 6.31 (dd, J = 17.0 and 1.6 Hz, 1H), 6.22–6.08 (m, 2H), 5.93 (br s, 1H), 5.81 (dtd, J = 17.0, 10.0, 7.0 and 7.0 Hz, 1H), 5.65 (dd, J = 10.0 and 1.6 Hz, 1H), 5.20–5.08 (m, 2H), 4.90–4.76 (m, 1H), 2.45 (t, J = 7.0 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.8 (C_0), 136.5 (C_0), 133.7 (CH), 130.9 (CH), 130.7 (CH), 128.9 (CH), 128.5 (2 × CH), 127.6 (CH), 126.6 (CH_2), 126.4 (2 × CH), 118.4 (CH_2), 50.1 (CH), 39.3 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{18}NO$ [M+H$^+$] 228.1388, found 228.1422.

4.1.10.2. (E)-N-(1-(2-(Trifluoromethyl)phenyl)hexa-1,5-dien-3-yl)acrylamide (95). Prepared according to the general procedure for the preparation of the amides in 60% yield (yellow oil). Eluent: hexanes/ethyl acetate 2:1 v/v. IR (cm^{-1}, thin film): 3271, 3075, 2982, 2933, 1658, 1628, 1544, 1488, 1409, 1315, 1164, 1124, 1060, 1036, 966, 921, 765; ^1H NMR (250 MHz, $CDCl_3$): δ 7.61 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.51–7.42 (m, 1H), 7.38–7.28 (m, 1H), 6.88 (d, J = 15.8 Hz, 1H), 6.31 (dd, J = 17.0 and 1.6 Hz, 1H), 6.22–6.07 (m, 2H), 5.90–5.70 (m, 2H), 5.67 (dd, J = 10.0 and 1.6 Hz, 1H), 5.22–5.10 (m, 2H), 4.92–4.78 (m, 1H), 2.45 (t, J = 6.4 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.9 (C_0), 135.8 (C_0), 133.5 (CH), 133.4 (CH), 131.8 (CH), 130.7 (CH), 127.6 (CH), 127.4 (q, J = 29.9 Hz, C_0), 127.3 (CH), 126.7 (CH_2), 126.5 (q, J = 1.6 Hz, CH), 125.7 (q, J = 5.7 Hz, CH), 124.3 (q, J = 273.4 Hz, C_0), 118.7 (CH_2), 49.9 (CH), 39.0 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{16}H_{17}F_3NO$ [M+H$^+$] 296.1262, found 296.1331.

4.1.10.3. (E)-N-(1-(4-(Trifluoromethyl)phenyl)hexa-1,5-dien-3-yl)acrylamide (96). Prepared according to the general procedure for the preparation of the amides in 50% yield (white solid). Eluent: hexanes/ethyl acetate 2:1 v/v. Mp: 113.6–115.3 °C; IR (cm^{-1}, thin film): 3280, 3069, 2981, 2934, 1660, 1631, 1548, 1409, 1330, 1245, 1164, 1122, 1069, 958, 925, 811; ^1H NMR (250 MHz, $CDCl_3$): δ 7.54 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 6.55 (d, J = 16.1 Hz, 1H), 6.32 (dd, J = 17.0 and 1.6 Hz, 1H), 6.25 (dd, J = 16.1 and 6.5 Hz, 1H), 6.15 (dd, J = 17.0 and 10.0 Hz, 1H), 5.90–5.70 (m, 2H), 5.67 (dd, J = 10.0 and 1.6 Hz, 1H), 5.21–5.10 (m, 2H), 4.84 (quint, J = 6.5 Hz, 1H), 2.46 (t, J = 6.5 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.2 (C_0), 140.1 (C_0), 133.5 (CH), 131.9 (CH), 130.9 (CH), 129.3 (q, J = 32.7 Hz, C_0), 129.2 (CH), 126.7 (CH_2), 126.5 (2 × CH), 125.4 (q, J = 3.8 Hz, 2 × CH), 124.1 (q, J = 271.6 Hz, C_0), 118.5 (CH_2), 50.3 (CH), 39.2 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{16}H_{17}F_3NO$ [M+H$^+$] 296.1262, found 296.1364.

4.1.10.4. (E)-N-(1-(4-Methoxyphenyl)hexa-1,5-dien-3-yl)acrylamide (97). Prepared according to the general procedure for the preparation of the amides in 84% yield (white solid). Eluent: hexanes/ethyl acetate 2:1 v/v. Mp: 128.0–130.0 °C; IR (cm^{-1}, thin film): 3276, 3075, 3005, 2979, 2954, 2932, 2905, 2834, 1658, 1627, 1606, 1545, 1512, 1248, 1178, 1033, 971, 915, 803; ^1H NMR (250 MHz, $CDCl_3$): δ 7.25 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 6.46 (d, J = 15.9 Hz, 1H), 6.29 (dd, J = 16.9 and 1.9 Hz, 1H), 6.22–6.08 (m, 2H), 6.00 (dd, J = 15.9 and 6.2 Hz, 1H), 5.79 (dtd, J = 17.2, 10.2, 6.2 and 6.2 Hz, 1H), 5.61 (dd, J = 9.8 and 1.9 Hz, 1H), 5.18–5.04 (m, 2H), 4.78 (quint, J = 6.2 Hz, 1H), 3.77 (s, 3H), 2.42 (t, J = 6.2 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.8 (C_0), 159.1 (C_0), 133.8 (CH), 130.9 (CH), 130.1 (CH), 129.3 (C_0), 127.5 (2 × CH), 126.7 (CH), 126.4 (CH_2), 118.1 (CH_2), 113.8 (2 × CH), 55.2 (OCH_3), 50.2 (CH), 39.4 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{16}H_{20}NO_2$ [M+H$^+$] 258.1494, found 258.1542.

4.1.10.5. (E)-N-(1-(2,4-Dimethoxyphenyl)hexa-1,5-dien-3-yl)-acrylamide (98). Prepared according to the general procedure for the preparation of the amides in 50% yield (yellow solid). Eluent: hexanes/ethyl acetate 2:1 v/v. Mp: 79.1–81.0 °C; IR (cm^{-1}, thin film): 3276, 3074, 3002, 2938, 2837, 1658, 1609, 1504, 1465, 1439, 1209, 1159, 1035, 972, 835; ^1H NMR (250 MHz, $CDCl_3$, δ): 7.25 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 16.0 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 6.42–6.35 (m, 2H), 6.27 (dd, J = 17.0 and 2.6 Hz, 1H), 6.16 (dd, J = 17.0 and 9.2 Hz, 1H), 6.04 (dd, J = 16.0 and 7.0 Hz, 1H), 5.78 (dtd, J = 17.2, 10.2, 7.0 and 7.0 Hz, 1H), 5.55 (dd, J = 9.2 and 2.6 Hz, 1H), 5.13–5.00 (m, 2H), 4.83–4.68 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 2.40 (t, J = 7.0 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.7 (C_0), 160.2 (C_0), 157.6 (C_0), 134.0 (CH), 131.0 (CH), 127.4 (CH), 127.1 (CH), 126.0 (CH_2), 125.1 (CH), 118.5 (C_0), 117.7 (CH_2), 104.6 (CH), 98.1 (CH), 55.2 (OCH_3), 55.1 (OCH_3), 50.7 (CH), 39.4 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{17}H_{22}NO_3$ [M+H$^+$] 288.1600, found 288.1629.

4.1.10.6. (E)-N-(1-(3,4-Dimethoxyphenyl)hexa-1,5-dien-3-yl)acrylamide (99). Prepared according to the general procedure for the preparation of the amides in 60% yield (yellow oil). Eluent: hexanes/ethyl acetate 2:1 v/v. IR (cm^{-1}, thin film): 3280, 3074, 3002, 2936, 2911, 2836, 1659, 1627, 1603, 1515, 1464, 1264, 1238, 1139, 1026, 965, 803; ^1H NMR (250 MHz, $CDCl_3$): δ 7.14 (d, J = 8.5 Hz, 1H), 6.75–6.58 (m, 3H), 6.33 (d, J = 16.0 Hz, 1H), 6.22–6.16 (m, 2H), 5.90 (dd, J = 16.0 and 6.4 Hz, 1H), 5.77–5.57 (m, 1H), 5.51–5.41 (m, 1H), 5.05–4.88 (m, 2H), 4.73–4.58 (m, 1H), 3.68 (s, 6H), 2.40 (t, J = 6.4 Hz, 2H); ^{13}C NMR (62.5 MHz,

$CDCl_3$): δ 164.7 (C_0), 148.5 (C_0), 148.3 (C_0), 133.7 (CH), 130.8 (CH), 130.0 (CH), 129.4 (C_0), 126.8 (CH), 126.0 (CH_2), 119.1 (CH), 117.5 (CH_2), 110.8 (CH), 108.6 (CH), 55.4 (OCH_3), 55.3 (OCH_3), 50.2 (CH), 39.0 (CH_2); HRMS (ESI+) *m*/*z*: Calcd for $C_{17}H_{22}NO_3$ [M+H$^+$] 288.1600, found 288.1629.

4.1.10.7. (E)-N-(1-(3,5-Dimethoxyphenyl)hexa-1,5-dien-3-yl)acrylamide (100). Prepared according to the general procedure for the preparation of the amides in 50% yield (yellow oil). Eluent: hexanes/ethyl acetate 2:1 v/v. IR (cm^{-1}, thin film): 3283, 3075, 3002, 2938, 2838, 1659, 1627, 1593, 1538, 1461, 1427, 1205, 1154, 1064, 967, 923, 828; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.67 (d, *J* = 8.5 Hz, 1H), 6.44 (d, *J* = 2.2 Hz, 2H), 6.39–6.18 (m, 4H), 6.10 (dd, *J* = 15.9 and 6.5 Hz, 1H), 5.75 (dtd, *J* = 17.1, 10.3, 6.5 and 6.5 Hz, 1H), 5.57 (dd, *J* = 8.9 and 2.9 Hz, 1H), 5.13–5.00 (m, 2H), 4.75 (quint, *J* = 6.5 Hz, 1H), 3.71 (s, 6H), 2.37 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.8 (C_0), 160.6 (2 × C_0), 138.5 (C_0), 133.7 (CH), 130.8 (CH), 130.3 (CH), 129.4 (CH), 126.2 (CH_2), 117.9 (CH_2), 104.3 (2 × CH), 99.6 (CH), 55.0 (2 × OCH_3), 50.1 (CH), 39.0 (CH_2); HRMS (ESI+) *m*/*z*: Calcd for $C_{17}H_{22}NO_3$ [M+H$^+$] 288.1600, found 288.1629.

4.1.10.8. (E)-N-(1-(3,4,5-Trimethoxyphenyl)hexa-1,5-dien-3-yl)acrylamide (101). Prepared according to the general procedure for the preparation of the amides in 75% yield (yellow solid). Eluent: hexanes/ethyl acetate 2:1 v/v. Mp: 104.2–106.0 °C; IR (cm^{-1}, thin film): 3284, 2938, 2839, 1658, 1627, 1583, 1508, 1420, 1240, 1127, 1004, 964, 920, 807; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.58–6.45 (m, 3H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.30–6.09 (m, 2H), 6.00 (dd, *J* = 15.8 and 6.5 Hz, 1H), 5.73 (dtd, *J* = 17.2, 10.2, 6.5 and 6.5 Hz, 1H), 5.55 (dd, *J* = 9.0 and 2.8 Hz, 1H), 5.12–4.98 (m, 2H), 4.72 (quint, *J* = 6.5 Hz, 1H), 3.76 (s, 9H), 2.37 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.7 (C_0), 152.8 (2 × C_0), 137.3 (C_0), 133.7 (CH), 132.2 (C_0), 130.8 (CH), 130.2 (CH), 128.4 (CH), 126.0 (CH_2), 117.6 (CH_2), 103.1 (2 × CH), 60.4 (OCH_3), 55.6 (2 × OCH_3), 50.1 (CH), 38.9 (CH_2); HRMS (ESI+) *m*/*z*: Calcd for $C_{18}H_{24}NO_4$ [M+H$^+$] 318.1705, found 318.1799.

4.1.10.9. (E)-N-(1-(2,4,5-Trimethoxyphenyl)hexa-1,5-dien-3-yl)acrylamide (102). Prepared according to the general procedure for the preparation of the amides in 87% yield (yellow solid). Eluent: hexanes/ethyl acetate 1:5 v/v. Mp: 103.0–105.0 °C; IR (cm^{-1}, thin film): 3259, 3070, 2999, 2956, 2935, 2836, 1655, 1627, 1514, 1463, 1210, 1063, 1044, 1031, 968, 869, 734; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.77 (d, *J* = 16.1 Hz, 1H), 6.46 (s, 1H), 6.29–5.97 (m, 3H), 5.91–5.70 (m, 2H), 5.61 (d, *J* = 9.8 Hz, 1H), 5.18–5.03 (m, 2H), 4.87–4.72 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 2.50–2.39 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.7 (C_0), 151.4 (C_0), 149.5 (C_0), 143.2 (C_0), 134.0 (CH), 130.9 (CH), 127.2 (CH), 126.3 (CH_2), 125.0 (CH), 118.1 (CH_2), 117.3 (C_0), 110.0 (CH), 97.6 (CH), 56.5 (2 × OCH_3), 56.0 (OCH_3), 50.5 (CH), 39.4 (CH_2); HRMS (ESI+) *m*/*z*: Calcd for $C_{18}H_{24}NO_4$ [M+H$^+$] 318.1705, found 318.1635.

4.1.11. General procedure for the preparation of lactams

To a solution of the amides **94**–**102** (1.52 mmol) in CH_2Cl_2 (152 mL), under reflux and magnetic stirring, was added second generation Grubbs catalyst (2 mol %; 0.03 mmol). After 6.0 h under these conditions, the reaction was allowed to cool to room temperature, DMSO (50 equiv relative to the catalyst) was added and the mixture was maintained overnight under magnetic stirring. After this period, the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (using the eluent indicated) to afford the corresponding lactams **103**–**111**.

4.1.11.1. (E)-6-Styryl-5,6-dihydropyridin-2(1H)-one (103). Prepared according to the general procedure for the preparation of lactams in 82% yield (white solid). Eluent: hexanes/ethyl acetate 1:1, 1:2 v/v. Mp: 152.8–154.2 °C; IR (cm^{-1}, thin film): 3211, 1676, 1610, 1415, 1327, 1275, 1126, 965, 816, 754; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.21 (m, 5H), 6.64–6.53 (m, 2H), 6.19 (dd, *J* = 15.8 and 7.3 Hz, 1H), 6.03 (br s, 1H), 5.95 (dd, *J* = 9.9 and 2.0 Hz, 1H), 4.36–4.24 (m, 1H), 2.54 (dt, *J* = 17.8 and 5.3 Hz, 1H), 2.36 (dddd, *J* = 17.8, 9.5, 3.4 and 2.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.2 (C_0), 139.9 (CH), 135.9 (C_0), 131.8 (CH), 128.5 (2 × CH), 128.4 (CH), 127.9 (CH), 126.4 (2 × CH), 124.4 (CH), 53.1 (CH), 30.2 (CH_2); HRMS (ESI+) *m*/*z*: Calcd for $C_{13}H_{14}NO$ [M+H$^+$] 200.1075, found 200.1077.

4.1.11.2. (E)-6-(2-(Trifluoromethyl)styryl)-5,6-dihydropyridin-2(1H)-one (104). Prepared according to the general procedure for the preparation of lactams in 64% yield (white solid). Eluent: hexanes/ethyl acetate 1:1, 1:2 v/v. Mp: 98.1–100.0 °C; IR (cm^{-1}, thin film): 3384, 3044, 1681, 1609, 1429, 1316, 1158, 1117, 1105, 1036, 967, 809, 766; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 6.97 (dd, *J* = 15.7 and 1.7 Hz, 1H), 6.63 (ddd, *J* = 10.0, 5.0 and 3.5 Hz, 1H), 6.18 (dd, *J* = 15.7 and 7.7 Hz, 1H), 5.97 (dq, *J* = 10.0 and 2.0 Hz, 1H), 5.50 (br s, 1H), 4.39–4.33 (m, 1H), 2.59 (dt, *J* = 17.8 and 5.0 Hz, 1H), 2.41 (dddd, *J* = 17.8, 9.7, 3.5 and 2.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.0 (C_0), 139.9 (CH), 135.1 (q, *J* = 1.6 Hz, C_0), 132.8 (CH), 131.9 (CH), 128.5 (q, *J* = 1.7 Hz, CH), 127.8 (CH), 127.6 (q, *J* = 30.0 Hz, C_0), 127.6 (CH), 125.8 (q, *J* = 5.7 Hz, CH), 124.6 (CH), 124.2 (q, *J* = 274.0 Hz, C_0), 53.5 (CH), 30.3 (CH_2); HRMS (ESI+) *m*/*z*: Calcd for $C_{14}H_{13}F_3NO$ [M+H$^+$] 268.0949, found 268.1034.

4.1.11.3. (E)-6-(4-(Trifluoromethyl)styryl)-5,6-dihydropyridin-2(1H)-one (105). Prepared according to the general procedure for the preparation of lactams in 60% yield (white solid). Eluent: hexanes/ethyl acetate 1:1, 1:2 v/v. Mp: 129.6–131.0 °C; IR (cm^{-1}, thin film): 3218, 3053, 1681, 1611, 1415, 1324, 1172, 1117, 1067, 1016, 973, 818, 734; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 6.65–6.60 (m, 2H), 6.30 (dd, *J* = 15.9 and 7.2 Hz, 1H), 5.98 (dq, *J* = 10.0 and 2.0 Hz, 1H), 5.53 (br s, 1H), 4.38–4.32 (m, 1H), 2.61 (dt, *J* = 17.8 and 5.3 Hz, 1H), 2.41 (dddd, *J* = 17.8, 9.3, 3.5 and 2.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.3 (C_0), 139.8 (CH), 139.5 (C_0), 131.3 (CH), 130.5 (CH), 129.8 (q, *J* = 32.4 Hz, C_0), 126.7 (2 × CH), 125.6 (q, *J* = 4.0 Hz, 2 × CH), 124.6 (CH), 124.1 (q, *J* = 272.1 Hz, C_0), 53.0 (CH), 30.1 (CH_2); HRMS (ESI+) *m*/*z*: Calcd for $C_{14}H_{13}F_3NO$ [M+H$^+$] 268.0949, found 268.1065.

4.1.11.4. (E)-6-(4-Methoxystyryl)-5,6-dihydropyridin-2(1H)-one (106). Prepared according to the general procedure for the preparation of lactams in 76% yield (white solid). Eluent: hexanes/ethyl acetate 1:2 v/v. Mp: 157.0–158.0 °C; IR (cm^{-1}, thin film): 3184, 2928, 2835, 1673, 1655, 1608, 1514, 1306, 1241, 1177, 1031, 969, 850, 822, 811; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.60 (ddd, *J* = 9.9, 5.0 and 3.0 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.04 (dd, *J* = 15.8 and 7.4 Hz, 1H), 5.94 (dd, *J* = 9.9 and 1.4 Hz, 1H), 5.80 (br s, 1H), 4.30–4.23 (m, 1H), 3.80 (s, 3H), 2.51 (dt, *J* = 17.8 and 5.0 Hz, 1H), 2.35 (ddt, *J* = 17.8, 9.9 and 3.0 Hz, 1H); **^{13}C NMR** (62.5 MHz, $CDCl_3$): δ 166.2 (C_0), 159.4 (C_0), 140.0 (CH), 131.3 (CH), 128.6 (C_0), 127.6 (2 × CH), 126.1 (CH), 124.3 (CH), 113.9 (2 × CH), 55.1 (OCH_3), 53.3 (CH), 30.4 (CH_2); HRMS (ESI+) *m*/*z*: Calcd for $C_{14}H_{17}NO_2$ [M+H$^+$] 230.1181, found 230.1200.

4.1.11.5. (E)-6-(2,4-Dimethoxystyryl)-5,6-dihydropyridin-2(1H)-one (107). Prepared according to the general procedure for the preparation of lactams in 64% yield (white solid). Eluent: hexanes/ethyl acetate 1:1, 1:5, 1:10 v/v. Mp: 165.6–166.7 °C; IR (cm^{-1}, thin film): 3193, 3104, 3049, 2964, 2846, 1673, 1607, 1504, 1417, 1308, 1282, 1208, 1026, 975, 825, 813; ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 15.9 Hz, 1H), 6.60 (ddd, J = 9.8, 5.1 and 3.0 Hz, 1H), 6.46 (dd, J = 8.5 and 2.3 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H), 6.08 (dd, J = 15.9 and 7.7 Hz, 1H), 5.93 (d, J = 9.9 Hz, 1H), 5.64 (br s, 1H), 4.30–4.22 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.49 (dt, J = 17.8 and 5.1 Hz, 1H), 2.35 (ddt, J = 17.8, 10.5 and 3.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.1 (C_0), 160.8 (C_0), 157.8 (C_0), 140.2 (CH), 127.7 (CH), 126.8 (CH), 126.5 (CH), 124.3 (CH), 117.7 (C_0), 104.8 (CH), 98.3 (CH), 55.3 (OCH_3), 55.2 (OCH_3), 54.1 (CH), 30.7 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{18}NO_3$ [M+H$^+$] 260.1287, found 260.1298.

4.1.11.6. (E)-6-(3,4-Dimethoxystyryl)-5,6-dihydropyridin-2(1H)-one (108). Prepared according to the general procedure for the preparation of lactams in 60% yield (white solid). Eluent: hexanes/ethyl acetate 1:1, 1:5, 1:10 v/v. Mp: 162.7–164.3 °C; IR (cm^{-1}, thin film): 3187, 3045, 2929, 2846, 1674, 1609, 1517, 1417, 1265, 1141, 1017, 965, 822, 807; ^1H NMR (500 MHz, $CDCl_3$): δ 6.92–6.88 (m, 2H), 6.81 (d, J = 8.8 Hz, 1H), 6.60 (ddd, J = 9.9, 4.9 and 3.0 Hz, 1H), 6.50 (d, J = 15.8 Hz, 1H), 6.05 (dd, J = 15.8 and 7.5 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 5.77 (br s, 1H), 4.31–4.24 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.54 (dt, J = 17.8 and 4.9 Hz, 1H), 2.37 (ddt, J = 17.8, 9.7 and 3.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.1 (C_0), 148.9 (C_0), 148.8 (C_0), 139.9 (CH), 131.5 (CH), 128.9 (C_0), 126.3 (CH), 124.3 (CH), 119.6 (CH), 110.9 (CH), 108.7 (CH), 55.7 (OCH_3), 55.6 (OCH_3), 53.1 (CH), 30.3 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{18}NO_3$ [M+H$^+$] 260.1287, found 260.1298.

4.1.11.7. (E)-6-(3,5-Dimethoxystyryl)-5,6-dihydropyridin-2(1H)-one (109). Prepared according to the general procedure for the preparation of lactams in 70% yield (white solid). Eluent: hexanes/ethyl acetate 1:1, 1:5, 1:10 v/v. Mp: 101.9–103.6 °C; IR (cm^{-1}, thin film): 3227, 2939, 2839, 1677, 1592, 1457, 1427, 1205, 1153, 1064, 969, 814; ^1H NMR (250 MHz, $CDCl_3$): δ 6.60 (ddd, J = 9.9, 5.0 and 3.6 Hz, 1H), 6.61 (d, J = 2.2 Hz, 2H), 6.50 (d, J = 15.7 Hz, 1H), 6.38 (app t, J = 2.2 Hz, 1H), 6.16 (dd, J = 15.7 and 7.3 Hz, 1H), 5.95 (dd, J = 9.9 and 2.0 Hz, 1H), 5.81 (br s, 1H), 4.36–4.22 (m, 1H), 3.79 (s, 6H), 2.56 (dt, J = 17.7 and 5.0 Hz, 1H), 2.36 (dddd, J = 17.7, 9.4, 3.6 and 2.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$,): δ 166.1 (C_0), 160.6 (2 × C_0), 139.8 (CH), 137.8 (C_0), 131.5 (CH), 128.9 (CH), 124.3 (CH), 104.4 (2 × CH), 100.0 (CH), 55.0 (2 × OCH_3), 52.8 (CH), 30.0 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{15}H_{18}NO_3$ [M+H$^+$] 260.1287, found 260.1298.

4.1.11.8. (E)-6-(3,4,5-Trimethoxystyryl)-5,6-dihydropyridin-2(1H)-one (110). Prepared according to the general procedure for the preparation of lactams in 97% yield (white solid). Eluent: hexanes/ethyl acetate 1:1, 1:5, 1:10 v/v. Mp: 138.2–139.2 °C; IR (cm^{-1}, thin film): 3219, 3012, 2996, 2968, 2934, 2839, 1673, 1608, 1583, 1462, 1423, 1127, 1006, 971, 815, 736; ^1H NMR (500 MHz, $CDCl_3$): δ 6.64–6, 65 (m, 3H), 6.49 (d, J = 15.7 Hz, 1H), 6.10 (dd, J = 15.7 and 7.3 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 6.80 (br s, 1H), 4.29 (q, J = 7.3 Hz, 1H), 3.86 (s, 6H), 3.83 (s, 3H), 2.56 (dt, J = 17.8 and 5.4 Hz, 1H), 2.43–2.34 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.0 (C_0), 153.0 (2 × C_0), 139.7 (CH), 137.7 (C_0), 131.5 (CH), 131.4 (C_0), 127.8 (CH), 124.2 (CH), 103.4 (2 × CH), 60.5 (OCH_3), 55.8 (2 × OCH_3), 52.7 (CH), 30.0 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{16}H_{20}NO_4$ [M+H$^+$] 290.1392, found 290.1408.

4.1.11.9. (E)-6-(2,4,5-Trimethoxystyryl)-5,6-dihydropyridin-2(1H)-one (111). Prepared according to the general procedure for the preparation of lactams in 60% yield white solid). Eluent: hexanes/ethyl acetate 1:1, 1:5, 1:10 v/v. Mp: 136.8–138.6 °C; IR (cm^{-1}, thin film): 3238, 3001, 2938, 2835, 1673, 1608, 1513, 1464, 1440, 1208, 1125, 1031, 973, 813; ^1H NMR (500 MHz, $CDCl_3$): δ 6.91 (s, 1H), 6.83 (d, J = 15.9 Hz, 1H), 6.60 (ddd, J = 9.9, 5.0 and 3.0 Hz, 1H), 6.47 (s, 1H), 6.06 (dd, J = 15.9 and 7.7 Hz, 1H), 5.93 (dd, J = 9.9 and 1.1 Hz, 1H), 5.71 (br s, 1H), 4.31–4.24 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 2.51 (dt, J = 17.7 and 5.0 Hz, 1H), 2.36 (ddt, J = 17.7, 10.3 and 3.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.0 (C_0), 151.3 (C_0), 149.7 (C_0), 143.0 (C_0), 140.0 (CH), 126.4 (CH), 126.2 (CH), 124.2 (CH), 116.3 (C_0), 109.8 (CH), 97.3 (CH), 56.3 (OCH_3), 56.2 (OCH_3), 55.8 (OCH_3), 53.8 (CH), 30.5 (CH_2); HRMS (ESI+) m/z: Calcd for $C_{16}H_{20}NO_4$ [M+H$^+$] 290.1392, found 290.1404.

4.2. In vitro antiproliferative assay

4.2.1. Cell lines

Human tumor cell lines U251 (glioma), MCF-7 (breast), NCI-H460 (lung, non-small cells), OVCAR-03 (ovarian), HT-29 (colon), 786-0 (kidney), and NCI-ADR/RES (ovarian expressing phenotype multiple drugs resistance) were obtained from National Cancer Institute at Frederick MA-USA.

4.2.2. Cell culture

Stock cultures were grown in medium containing 5 mL RPMI 1640 (GIBCO BRL) supplemented with 5% fetal bovine serum (FBS, GIBCO) at 37 °C with 5% CO_2. Penicillin: streptomicyne (1000 μg/L:1000 U/L, 1 mL/L) were added to the experimental cultures.

4.2.3. Antiproliferative assay

Cells in 96 well plates (100 μL cells/well) were exposed to goniothalamin and its analogues in concentrations 0.25, 2.5, 25 and 250 μg/mL in DMSO (Merck)/RPMI at 37 °C, 5% of CO2 in air for 48 h. Doxorubicin was used as positive control (0.025, 0.25, 2.5 and 25 μg/mL). Final DMSO concentration did not affect cell viability. Afterwards cells were fixed with 50% trichloroacetic acid (Merck) and cell proliferation determined by spectrophotometric quantification (540 nm) of cellular protein content using sulforhodamine B assay.[30a] Using the concentration-response curve for each cell line, the TGI (concentration that produces total growth inhibition or cytostatic effect) were determined through non-linear regression analysis (Table 1 and 2) using software ORIGIN 7.5® (OriginLab Corporation).[30b]

Acknowledgments

The authors thank FAPESP (10/16990–1 and 2009/51602–5), CNPq and Capes for financial support and the National Cancer Institute-Frederick, MA, USA for granting the human tumor cell lines.

Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra and concentration–response curve) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.03.059.

References and notes

1. (a) Newman, D. J.; Cragg, G. M. J. *Nat. Prod.* **2012**, *75*, 311; (b) Harvey, A. L. *Drug Discovery Today* **2008**, *13*, 894.
2. (a) de Fátima, A.; Kohn, L. K.; Antonio, M. A.; de Carvalho, J. E.; Pilli, R. A. *Bioorg. Med. Chem.* **2005**, *13*, 2927; (b) de Fátima, A.; Kohn, L. K.; de Carvalho, J. E.; Pilli, R. A. *Bioorg. Med. Chem.* **2006**, *14*, 622.

3. For antiproliferative activities against lung and liver cell lines, see: (a) Chiu, C.-C.; Liu, P.-L.; Huang, K.-J.; Wang, H.-M.; Chang, K.-F.; Chou, C.-K.; Chang, F.-R.; Chong, I.-W.; Fang, K.; Chen, J.-S.; Chang, H.-W.; Wu, Y.-C. *Agric. J. Food Chem.* **2011**, *59*, 4288; (b) Al-Qubaisi, M.; Rozita, R.; Yeap, S.-K.; Omar, A.-R.; Ali, A.-M.; Alitheen, N. B. *Molecules* **2011**, *16*, 2944.
4. Ali, A.; Mackeen, M. M.; Hamid, M.; Aun, Q. B.; Zauyah, Y.; Azimahtol, H. L. P.; Kawazu, K. *Planta Med.* **1997**, *63*, 81.
5. (a) Khan, M. R.; Komine, K.; Omoloso, A. D. *Phar. Biol.* **1999**, *37*, 340; (b) Mosaddik, M. A.; Haque, M. E. *Phytother. Res.* **2003**, *17*, 1157; (c) Martins, C. V. B.; de Resende, M. A.; da Silva, D. L.; Magalhães, T. F. F.; Modolo, L. V.; Pilli, R. A.; de Fátima, A. *J. Appl. Microb.* **2009**, *107*, 1279.
6. Martins, C. V. B.; de Resende, M. A.; Magalhães, T. F. F.; Santiago, B. H. S.; Watanabe, G. A.; Ruiz, A. L. T. G.; de Carvalho, J. E.; Pilli, R. A.; de Fátima, A. *Lett. Drug Design Discov.* **2008**, *5*, 74.
7. Kabir, K. E.; Khan, A. R.; Mosaddik, M. A. *JEN* **2003**, 112.
8. (a) Senthil-Nathan, S.; Choi, M.; Paik, C.; Kalaivani, K. *Chemosphere* **2008**, *72*, 1393; (b) Rajab, N. F.; Hamid, Z. A.; Hassan, H.; Ali, A. M.; Din, L. B.; Inayat-Hussain, S. H. *Environ. Mutagen. Res.* **2005**, *27*, 161; (c) Lan, Y.; Chang, F.; Yu, J.; Yang, Y.; Chang, Y.; Lee, S.; Wu, Y. *J. Nat. Prod.* **2003**, *66*, 487.
9. de Fátima, A.; Marquissolo, C.; Albuquerque, S.; Carraro-Abrahão, A. A.; Pilli, R. A. *Eur. J. Med. Chem.* **2006**, *41*, 1210.
10. (a) Inayata-Hussain, S.; Annuar, B. O.; Din, L. B.; Ali, A. M.; Ross, D. *Toxicol. In vitro* **2003**, *17*, 433; (b) Inayat-Hussain, S. H.; Osman, A. B.; Din, L. B.; Ali, A. M.; Snowden, R. T.; MacFarlane, M.; Cain, K. *FEBS Lett.* **1999**, *456*, 379.
11. Pihie, A. H. L.; Stanlsas, J.; Bin Din, L. *Anticancer Res.* **1998**, *18*, 1739.
12. DeFátima, A.; Zambuzzi, W. F.; Modolo, L. V.; Tarsitano, C. A. B.; Gadelha, F. R.; Hylsop, S.; de Carvalho, J. E.; Salgado, I.; Ferreira, C. V.; Pilli, R. A. *Chemico-Biol. Inter.* **2008**, *176*, 143.
13. Wach, J.-Y.; Güttinger, S.; Kutay, U.; Gademann, K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2843.
14. Pilli, R. A.; de Carvalho, J. E.; Vendramini-Costa, D.; de Castro, I. D. B.; Ruiz, A. L. T.; Marquissolo, C. *Bioorg. Med. Chem.* **2010**, *18*, 6742.
15. de Fátima, A.; Modolo, L. V.; Conegero, L. S.; Pilli, R. A.; Ferreira, C. V.; Kohn, L. K.; de Carvalho, J. E. *Curr. Med. Chem.* **2006**, *13*, 3371.
16. Zhou, F. S.; Tang, W. D.; Mu, Q.; Yang, G. X.; Wang, Y.; Liang, G. L.; Lou, L. G. *Chem. Pharm. Bull.* **2005**, *11*, 1387.
17. (a) Bialy, L.; Waldmann, H. *Chem. Commun.* **1872**, *2003*, 15; (b) Buck, S. B.; Hardouin, C.; Ichikawa, S.; Soenen, D. R.; Gauss, C.-M.; Hwang, I.; Swingle, M. R.; Bonness, K. M.; Honkanen, R. E.; Boger, D. L. *J. Am. Chem. Soc.* **2003**, *125*, 15694.
18. Kasaplar, P.; Yılmazer, O.; Çağır, A. *Bioorg. Med. Chem.* **2009**, *17*, 311.
19. Wilson, M. A.; Rimando, A. M.; Wolkow, C. A. *BMC Pharmacol.* **2008**, *8*, 15.
20. (a) Zhang, S.; Zhang, Y.; Ji, Y.; Li, H.; Wang, W. *Chem. Commun.* **2009**, 4886; (b) Hao, L.; Yafei, L.; Shilei, Z.; ChenGuang, Y.; Wei, W. *Sci. China Chem.* **2010**, *53*, 135; (c) Dumitrescu, L.; Huong, D. T. M.; Hung, N. V.; Crousse, B. *Eur. J. Med. Chem.* **2010**, *45*, 3213.
21. (a) Chandrasekhar, S.; Babu, G. S. K.; Reddy, C. R. *Tetrahedron: Asymmetry* **2009**, *20*, 2216; (b) Förster, S.; Persch, E.; Tverskoy, O.; Rominger, F.; Helmchen, G.; Klein, C.; Gönen, B.; Brügger, B. *Eur. J. Org. Chem.* **2011**, *5*, 878.
22. (a) Stachel, S. J.; Lee, C. B.; Spassova, M.; Chappell, M. D.; Bornmann, W. G.; Danishefsky, S. J.; Chou, T.-C.; Guan, Y. *J. Org. Chem.* **2001**, *66*, 4369; (b) Mulzer, J.; Altmann, K.-H.; Höfle, G.; Müller, R.; Prantz, K. C. R. *Chimica* **2008**, *11*, 1336.
23. http://www.cancer.gov/cancertopics/druginfo/fda-ixabepilone (accessed on January 13, 2012).
24. Wilk, W.; Waldmann, H.; Kaiser, M. *Bioorg. Med. Chem.* **2009**, *17*, 2304.
25. Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 3183.
26. Huang, Y.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 3321.
27. Evans, P. A.; Nelson, J. D.; Manangan, T. *Synlett* **1997**, 968.
28. (a) Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555; (b) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 298.
29. (a) Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Nat. Cancer Inst.* **1991**, *83*, 757; (b) Shoemaker, R. *Nat. Rev.* **2006**, *6*, 813.