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RESEARCH ARTICLE

Design, synthesis, in vitro cytotoxicity evaluation and structure–activity relationship of Goniothalamin analogs

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Abstract A series of six/five member (*E*/*Z*)-Goniothalamin analogs were synthesized from commercially available (3,4-dihydro-2*H*-pyran-2-yl)methanol/5-(hydroxymethyl) dihydrofuran-2(3*H*)-one in three steps with good to moderate overall yields and their cytotoxicity against lymphoblastic leukemic T cell line (Jurkat E6.1) have been evaluated. Among the synthesized analogs, (*Z*)-Goniothalamin appeared to be the most active in cytotoxicity ($IC_{50} = 12$ μM). Structure–activity relationship study indicates that introducing substituent in phenyl ring or replacing phenyl ring by pyridine/naphthalene, or decreasing the ring size of lactones (from six to five member) do not increase the cytotoxicity.

Keywords *E*-Goniothalamin · *Z*-Goniothalamin · Cytotoxicity · Jurkat E6.1

Introduction

Goniothalamin (**1**) is natural styryllactone was first isolated in 1967 by Hlubucek from *Cryptocarya caloneura* (Hlubucek and Robertson 1967). Since then, it has been isolated from various sources like *Goniothalamus amuyon* (Lan et al. 2003). *G. andersonni* (Jewers et al. 1972), *G. borneensis* (Cao et al. 1998), *G. dolichocarpus* (Goh et al. 1995), *G. giganteus* (El-Zayat et al. 1985), *G. malayanus* (Jewers et al. 1972), *G. macrophyllus* (Jewers et al. 1972; Sam et al. 1987), *G. uvaroides* (Ahmad et al. 1991), *G. sesquipedalis* (Hasan et al. 1995), *G. velutinus* (Annonaceae) (Jewers et al. 1972), *Cryptocarya latifolia* (Drewes et al. 1995), *C. moschata C.* (Cavalheiro and Yoshida 2000), *wyliei* (Lauraceae) (Drewes et al. 1995), and *Bryonopsis laciniosa* (Cucurbitaceae) (Mosaddik et al. 2000; Kabir et al. 2003).

Goniothalamin had been showing to induce endocrine activities, including anti-inflammatory (Tanaka et al. 2001), anti-estrogenic (Zauyah et al. 1997), anti-progestogenic (Kabir et al. 2003) and anti-fertility (Azimahtol Hawariah et al. 1994) activities. Moreover, it had also demonstrated toxicity against many living organisms, it was shown to be antibacterial (El-Sharkawy et al. 1996; Mosaddik and Haque 2003), antifungal (Jewers et al. 1972; El-Sharkawy et al. 1996), insecticidal (Kabir et al. 2003) and mosquito larvicide (Jewers et al. 1972; El-Sharkawy et al. 1996; Mosaddik and Haque 2003), as well as cytotoxic on various mammal cell lines (Ali et al. 1997; Azimahtol Hawariah and Stanslas 1998; Inayat-Hussain et al. 1999; Teoh and Azimahtol Hawariah 1999; Meenakshii et al. 2000; Mereyala and Joe 2001; Chien and Azimahtol Hawariah 2003; de Fátima and Pilli 2003b; Inayat-Hussain et al. 2003; de Fátima et al. 2005, 2006a; Zhou et al. 2005;). More specifically, Goniothalamin showed to be as potent as tamoxifen, on both MCF-7 and T47-D cell lines (Zauyah et al. 1997). It displayed anti-proliferative activity against the following murine cancer cell lines: P-388 (leukemia), WEHI164 (fibro sarcoma), and human cancer cell lines: NCI-ADR (breast expressing a multidrug resistance phenotype), NCI-460

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(lung, non-small cells), UACC62 (melanoma), 786-0 (kidney), OVCAR03 (ovarian), PCO 3 (prostate), and HT-29 (colon), U937 (leukemia), Hep3B (hepatoma), HepG2 (hepatocellular carcinoma), and MDA-MB-231 (estrogen receptor negative breast cancer) (Mu et al. 2003; de Fátima et al. 2006b) with IC_{50} ranging between 1.6 and 9 μM. In contrast, Azimahtol and coworkers demonstrated that Goniothalamin has no significant cytotoxicity toward non-malignant cells (Azimahtol Hawariah and Stanslas 1998), implying that it acts mainly on malignant cells (HL-60 and CEM-SS cells) (Rajab et al. 2005).

The mechanism of action of Goniothalamin had been studied by a number of groups, it was reported that Goniothalamin can cause DNA damage in vascular smooth muscle cells leading to growth inhibition and apoptosis (Chan et al. 2006), naturally-occurring (*R*)-Goniothalamin causes cell death primarily by apoptosis as opposed to synthetic (S)-Goniothalamin, which induces autophagy (de Fátima et al. 2008), (*R*)-Goniothalamin provokes apoptosis in Jurkat T cell and MCF-7 cells by activating caspases 3 and 7 with consequent release of cytochrome *c* (Inayat-Hussain et al. 1999; Lee et al. 2003; Inayat-Hussain et al. 2010). This results from a mitochondrial pathway leading to the activation of the apical caspase-9 with loss of mitochondrial membrane potential ($\Delta\psi m$) in HL-60 leukemia cells (Inayat-Hussain et al. 2003), over-expression of full-length receptor for activated protein C-kinase 1 (RACK-1) and pc3n3, which up regulates the endogenous RACK-1 and protects against Goniothalamin-induced cell death leading to increase cell survival (Inayat-Hussain et al. 2009). Goniothalamin also induces the generation of reactive oxygen species and DNA damage in Jurkat T cells leading to the activation of an intrinsic apoptotic pathway that is independent of caspase-2 and Bcl-2 regulation (Inayat-Hussain et al. 2010). (*R*)-Goniothalamin has shown to cause rapid decrease in the intracellular thiol levels in human breast cancer cells (MDA-MB-231) in a concentration- and time-dependent manner (Chen et al. 2005). Treatment of human breast cancer cells (MDA-MB-231) with (*R*)-Goniothalamin caused down regulation of tyrosine phosphatase (cdc25) inducing G2/M phase arrest (Chen et al. 2005).

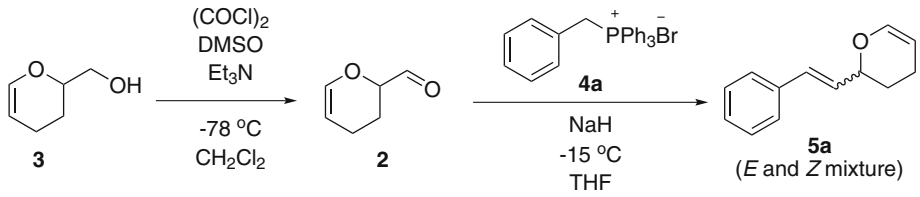
Because of its apparent simple structure and the broad spectrum of activities, Goniothalamin has attracted the attention of several synthetic groups in recent years. In 1986, Just and Connor reported the first enantioselective synthesis of (+)-Goniothalamin from diacetone-D-glucose in 15 steps (O'Connor and Just 1986; Mondon and Gesson 2006). Simultaneously, Riehl and coworkers (1988) described a similar synthesis of (+)-Goniothalamin from the same intermediate in 11 steps. Very recently, Goniothalamin was synthesized through various methods: (i) enantioselective Maruoka allylation followed by ring-closing metathesis (Ramachandran et al. 2000; Ram Reddy et al. 2001; de Fátima and Pilli 2003a, b; de Fátima et al. 2006a), using expensive Grubbs' catalyst (Grubbs 2004); (ii) asymmetric hetero Diels–Alder reactions (Quitschalle et al. 2001), where benzyl alcohol was used as starting material with 21 % overall yield; (iii) diastereoselective [2+2]-cycloaddition reaction (Fournier et al. 2004); (iv) sulfoxide-modified Julia olefination (Pospíšil and Markó 2006); (v) Cosford cross-coupling protocol (Sabitha et al. 2006); and (vi) olefin ring-closing metathesis reaction (Harsh and O'Doherty 2009). Lipase (Sundby et al. 2004) and PS-C Amano II (Gruttadauria et al. 2004) have also been used as catalysts for the synthesis of Goniothalamin. Finally, solid phase enantioselective oxa Diels–Alder reaction was introduced by Torben Leßmann in 2004 (Leßmann et al. 2007). Nevertheless, up to this point the development of procedures for the synthesis of Goniothalamin relied on the use of expensive reagents and/or many steps, which led continuing interests to develop an efficient procedure and/or catalyst to future development of the cytotoxic agents. In this article, we therefore developed a simple and efficient procedure for the synthesis of Goniothalamin and its analogs in three steps with good to moderate overall yields from (3,4-dihydro-2*H*-pyran-2-yl)methanol/5-(hydroxymethyl)dihydrofuran-2(3*H*)-one followed by evaluating their cytotoxicity against lymphoblastic leukemic T cell line (Jurkat E6.1) for continuously searching for new cytotoxic agents with Structure–activity relationship (SAR) study.

Results and discussions

Synthesis of 6-styryl-5,6-dihydro-2*H*-pyran-2-one (*E*/*Z*)-Goniothalamin

The starting 3,4-dihydro-2*H*-pyran-2-carbaldehyde (**2**) (Jagtap et al. 2009) (aldehyde 2 is unstable, presence of aldehyde group was confirmed by proton nuclear magnetic spectroscopy, which was showing δ at 9.64 ppm for aldehyde functionality) was prepared via previously reported Swern oxidation method using commercially available inexpensive 3,4-dihydro-2*H*-pyran-2-methanol (**3**). On the other hand, benzyltriphenylphosphonium bromide (**4a**) was prepared using microwave irradiation for 30 min at 60 °C in tetrahydrofuran (THF) from triphenylphosphine and benzyl bromide. Subsequently, Wittig reaction of aldehyde **2** with phosphonium salt **4a** was performed in presence of NaH at low temperature (−15 °C) in THF solution, yielded 2-styryl-3,4-dihydro-2*H*-pyran (**5a**) (Schmidt 2004) as a mixture of *E* and *Z* isomer (1:4) with 55 % yield (Scheme 1). Isomers of **5a** (***E*-5a** and ***Z*-5a**) were separated by flash column chromatography and characterized by

Scheme 1 Synthesis of 2-styryl-3,4-dihydro-2*H*-pyran (**5a**)

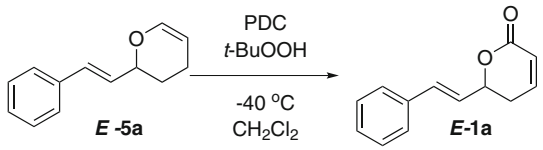


proton nuclear magnetic resonance spectra [*E*/*Z*-isomers were purified by column chromatography using *n*-hexane. The first fraction (approximately, $R_f = 0.75$ *n*-hexane) gave *Z*-isomers and later fraction (approximately, $R_f = 0.40$ *n*-hexane) obtained *E*-isomers]. In ***E*-5a**, olefinic proton shows a coupling constant of 15.5–16.0 Hz, while in ***Z*-5a** it was 11.5–12.0 Hz. In addition to confirm the structures of two isomers, resonances of all protons of ***E*-5a** and ***Z*-5a** were assigned by double-quantum filtered COSY experiments and were in agreement with reported data (Schmidt 2004).

After successful separation of the two isomers, *E*-isomer (***E*-5a**) was oxidized by PDC/*t*-BuOOH (Chidambaram et al. 1989) in CH_2Cl_2 at 0 °C and only trace amount of (*E*)-Goniothalamin (***E*-1a**) was obtained. Therefore, we optimized the conditions of the previously reported method (Chidambaram et al. 1989) by decreasing the reaction temperature until −78 °C to obtain the higher yields. To our delight, when the temperature was −20 °C we obtained 25 % of ***E*-1a**; at −40 °C, the yield increased to 78 % (Scheme 2), however, we could not obtain higher than 78 % yield with lower/higher temperature and we obtained only 10 % product at −60 °C and 0 % at −78 °C. The structures of the compounds were confirmed by ^{1}H, ^{13}C and COSY NMR, mass spectrometer and reported melting point (de Fátima et al. 2005).

On the other hand, ***Z*-5a** gave 36 % of (*Z*)-Goniothalamin (***Z*-1a**) (de Fátima and Pilli 2003a) with 38 % of (*Z*)-6-(*tert*-butylperoxy)-2-styryl-3,6-dihydro-2*H*-pyran (***Z*-6a**) as a by-product at 0 °C. Then we optimized the conditions adopted for *E*-isomer (***E*-5a**) and obtained 84 % of ***Z*-1a** with 6 % of unexpected by-product (*Z*)-Styryl-2,3-dihydro-4*H*-pyran-4-one (***Z*-7a**) along with 3 % pyran ***Z*-6a**, the by-product of *E*-isomers ***Z*-7a** is known (Schaus et al. 1998; Du et al. 2002). The by-product pyran ***Z*-6a** was then treated with triethylamine to obtain ***Z*-1a** at 80 °C for 1 h using a previously reported method (Chidambaram et al. 1989) (Scheme 3).

The experimental data and results for various temperatures are summarized in Table 1. The structures of (*Z*)-Goniothalamin and by-products were confirmed by ^{1}H, ^{13}C and COSY NMR as well as mass spectroscopy and were in agreement with those reported values



Scheme 2 Oxidation of (*E*)-2-styryl-3,4-dihydro-2*H*-pyran (***E*-5a**)

(Chidambaram et al. 1989; Pospíšil and Markó 2006; Sabitha et al. 2006).

After successfully obtaining (*E*)-and (*Z*)-Goniothalamin, we used various Wittig reagents (**4b–k**) to synthesize Goniothalamin analogs (**1b–k**) via the precursors **5b–k** (Scheme 4) using the same condition adopted for (*E*)-and (*Z*)-Goniothalamin.

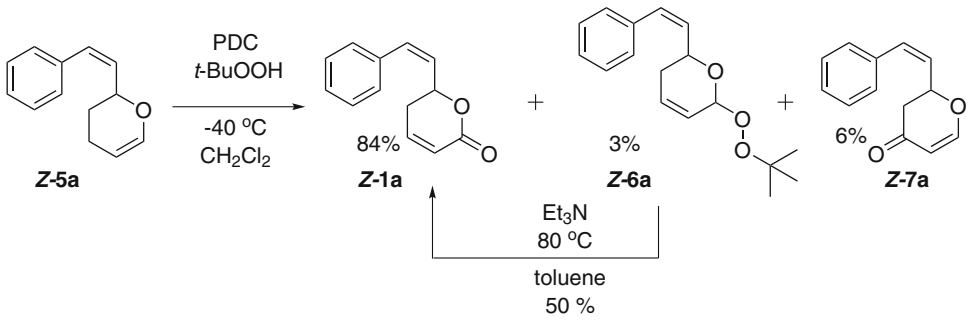
It should be noted that, reaction of **2** with **4c**, **4g–k** gives only *Z* isomers (**5c** and **5g–k**). In addition, one of the pyridine analogs ***E*-5f** gives two by-products in the similar pattern as ***Z*-5a–k**. Isolated yields for all the *E*/*Z* isomers of pyrans (**5a–k**), lactones (**1a–k**), peroxides (**6a–k**) and pyranones (**7a–k**) are depicted in Table 2.

Cytotoxicity of 6-styryl-5,6-dihydro-2*H*-pyran-2-one (*E*/*Z*)-Goniothalamin analogs

Cytotoxicity of the prepared compounds (**5**, **1**, **6** and **7**) was screened by the previously reported method (Chan et al. 2006) against lymphoblastic leukemic T cell (Jurkat E6.1) cancer line. As shown in Table 3, IC_{50} values of compounds **1a–k** were higher than any other by-products (**6** or **7**) as well as precursor (**5**) against Jurkat E6.1 cancer cell line.

In our finding, IC_{50} values of compound ***Z*-1a** was 12 μM, and ***Z*-1k** was 15 μM against Jurkat E6.1 cell line, while the natural (*E*)-(+)-Goniothalamin was having the IC_{50} value of 22 μM as positive control. Also for the compounds ***Z*-1c** and ***Z*-1e**, the IC_{50} values were 24 and 32 μM, respectively, which indicate that, these 4 compounds would be a potential anticancer candidates compared with natural (*E*)-(+)-Goniothalamin. Unfortunately, synthetic *E*-isomer of Goniothalamin (***E*-1a**) shows the IC_{50} value of 87 μM. On the other hand, precursor of Goniothalamin (*E*/*Z*-isomer of pyran, **5**), peroxide (**6**) and Pyranone (**7**) did not show the cytotoxicity.

Scheme 3 Synthesis of (*Z*)-Goniothalamin (***Z*-5a**)



Synthesis of 5-styryldihydrofuran-2(3*H*)-one

To extend our interest in continuously searching for the new cytotoxic agents, we then designed to synthesize new five-member Goniothalamin analogs using the same method to see whether these analogs will be a potent cytotoxic agents or not. In this regard, commercially available 5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (**8**) was used for the preparation of aldehyde **9** followed by Wittig reaction with various Wittig reagents (**4a–b**, **4g–h** and **4l–n**) to obtain Goniothalamin analogs (**10a–g**) (Scheme 5) in presence of NaH in THF solution at −15 °C.

Isolated yields for all the five-member Goniothalamin analogs (**10a–g**) are depicted in Table 4.

Cytotoxicity of five-member Goniothalamin analogs (**10a–g**)

IC_{50} values of five-member Goniothalamin analogs (**10a–g**) were evaluated and found ranging from 62 to 100 μM for **10a–f**, and no cytotoxicity was shown for **10g** ($IC_{50} \geq 100$ μM) against Jurkat E6.1 cell line (Table 5).

SAR study of Goniothalamin analogs

The results of the cytotoxicity of analogs **1** and **10** (Chart 1) against Jurkat E6.1 cell line screening lead to the following assumptions about the structural activity relationship (SAR).

Synthetic *E*-Goniothalamin (***E*-1a**) shows the value of IC_{50} is 87 μM. Introducing substituents (***E*-1e,** methoxy groups in 11 and 13 positions) in the phenyl ring of ***E*-1a** or replacing a carbon of ***E*-1a** by nitrogen ***(E*-1f**) decreased the cytotoxicity. Interestingly, while phenyl ring was replaced by naphthalene ring ***(E*-1b**), the cytotoxicity was improved in relation to that of ***E*-1a**.

Z-Goniothalamin (***Z*-1a**) is much more potent (IC_{50} = 12 μM) than synthetic *E*-Goniothalamin (***E*-1a**) as well as the natural (*E*)-(+)-Goniothalamin (IC_{50} = 22 μM). Introducing substituent in phenyl ring of ***Z*-1a** at 11-position with methoxy group (***Z*-1c**, IC_{50} = 24 μM); or 11, 13 positions with methoxy groups (***Z*-1e**, IC_{50} = 32 μM); or 12-position with trifluoromethoxy (–OCF_3) group (***Z*-1k**, IC_{50} = 15 μM) decrease the activity comparing to *Z*-Goniothalamin (***Z*-1a,** IC_{50} = 12 μM), but still significantly higher or similar comparing with natural (*E*)-(+)-Goniothalamin (IC_{50} = 22 μM) in cytotoxicity. Introducing methoxy group in phenyl ring of ***Z*-1a** at 12-position; Iodo group at 12-position; Fluoro group at 11-position, 10/11-positions or 11/12 positions did not increase the activity of ***Z*-1a**.

Replacing phenyl ring of ***Z*-1a** with naphthalene ring (***Z*-1b**) or pyridine ring (***Z*-1f**) almost did not show activity, where replacing 6-member lactone ring by 5-member lactone ring (**10a–g**) of (*E*/*Z*)-Goniothalamin shows moderate activities compare to ***E*-1a** but still very less than ***Z*-1a**.

Effects of *Z*-Goniothalamin (***Z*-1a**) on the viability of Jurkat E6.1 cell line

Z-Goniothalamin (***Z*-1a**) induced a dose-dependent decrease in cell viability following a 24-h treatment are shown in Fig. 1. The IC_{50} value of *Z*-Goniothalamin (***Z*-1a**) was 12 μM which indicate that this compound is efficient as a cytotoxic agent and in inducing cell death in Jurkat E6.1 cancer cell line.

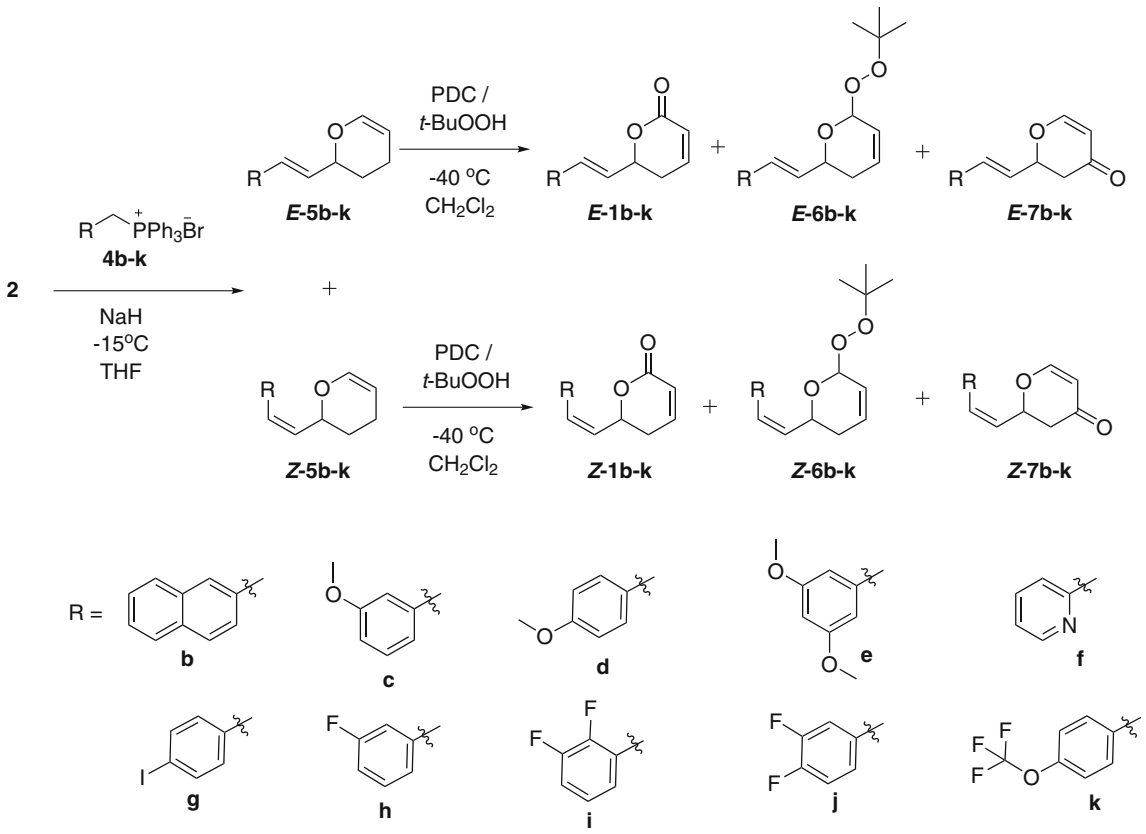
Experimental section

General

(3,4-dihydro-2*H*-pyran-2-yl) methanol and all the chemicals were purchased from Aldrich Chemicals. Organic solvents

Table 1 Oxidation of ***Z*-5a** by PDC in the presence of *t*-BuOOH in CH_2Cl_2

Temperature (°C)	Yields (%) of the oxidation products		
	***Z*-1a**	***Z*-6a**	***Z*-7a**
0	36	38	0
−20	50	2	6
−40	84	3	6
−60	29	0	Trace
−78	0	0	0



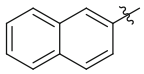
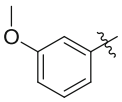
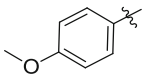
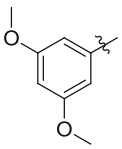
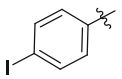
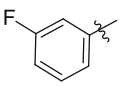
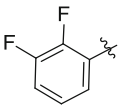
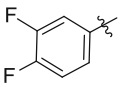
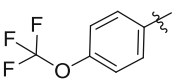
Scheme 4 Synthesis of Goniothalamin derivatives/analogs

were dried and purified by distillation (wherever appropriate) prior to their use. THF and diethyl ether were freshly distilled over sodium/benzophenone under nitrogen gas. Dichloromethane was freshly distilled over calcium hydride under nitrogen gas. All reactions were carried out under an atmosphere of nitrogen gas inside the fume hood by using a flame-dried apparatus with magnetic stirrer, unless otherwise indicated. TLC analysis was carried out on glass-backed TLC silica plates (silica gel 60 F_{254}, 0.25 mm) impregnated with fluorescence indicator (Merck art. 1.05554). The detection of UV-active substances was visualized using Ultra-Violet light ($\lambda_{max} = 254$ nm) and for non UV active substances $KMnO_4$/PMA/*p*-anisaldehyde stains were used. For all chromatographic purification steps, silica gel (Kieselgel 60, particle size range 0.040–0.063 mm) from Merck was used. ^{1}H- and ^{13}C-NMR spectrum was recorded on a Bruker 500 AVANCE III spectrometer. Chemical shift for ^{1}H- and ^{13}C-NMR (δ) are reported in ppm. The working frequency for ^{1}H- and ^{13}C- were 500 MHz and 125 MHz, respectively. $CDCl_3$, CD_3OD and Acetone-d_6 were used as internal standard in ^{1}H- as 7.24, 3.31 and 2.05 ppm, while in ^{13}C- as 77, 49, 29.84 and 206.26 ppm respectively. The coupling constants *J* are reported in Hertz (Hz). Peaks were described as broad signals (br), singlet (s), doublets (d), doublets of doublets (dd), doublets of doublets of doublets (ddd), triplets (t) and multiplets (m), doublets of triplets (dt), triplets of doublets (td). Occasionally, two-dimensional NMR experiments such as COSY-45, HMBC, and HSQC have been taken. MS-TOF spectra were recorded on an Agilent Technologies 6224 TOF LC/MS. Results are reported by presenting the mass of the fragments (*m*/*z*) as a proportion of intensity compared to the base peak (100 %) in percentage. Only signals presenting a high intensity ($\geq$10 %) or characteristics signals (generally $[M+H]^+$ are reported. Melting points were determined in open capillary tubes with a Büchi Melting Point B-545 apparatus and are uncorrected. Microwave-heated reactions were performed in a monomode reactor MicroSYNTH Plus.

General procedure for the preparation of Wittig reagents

A mixture of (substituted)-benzyl halide (bromide/chloride, **4**, 1.0 mmol) with triphenylphosphine (1.0 mmol) in THF (30 mL) was homogenized by stirring and shaking. The reaction mixture was exposed to microwave irradiation (MW) for the appropriate times (30 min) and temperatures (60 °C). Once the heating cycle is completed, the reaction mixture was then cooled to ambient temperature, the precipitated salt was filtered off, washed with cold THF and

Table 2 Synthesis of (*E*)- and (*Z*)-Goniothalamin (***E*-1a** and ***Z*-1b**) and their analogs

Entry	Substrate (R)	Yields (%) of *E*/*Z* pyran (**5**)		Yields (%) of *E* and *Z*-isomer of products		
				Lactones (**1**)	Peroxide (**6**)	Pyranone (**7**)
a		*E*	(14)	78	0	0
		Z	(56)	84	10	6
b		*E*	(40)	26	0	0
		Z	(40)	45	5	0
c[a]		*Z*	(37)	51	0	0
d		*E*	(1)	0	0	0
		Z	(32)	31	10	8
e		*E*	(19)	13	0	0
		Z	(19)	37	7	3
f		*E*	(26)	18	3	4
		Z	(26)	56	2	1
g[a]		*Z*	(52)	62	6	3
h[a]		*Z*	(46)	68	12	5
i[a]		*Z*	(70)	58	14	0
j[a]		*Z*	(68)	53	8	6
k[a]		*Z*	(46)	46	8	5

[a] No *E*-isomers were obtained

dried at 50 °C for overnight and obtained pure (substituted)-triphenylphosphonium halide (bromide/chloride) with excellent yields. The compounds were characterized by NMR and mass spectroscopic data as well as physical properties such as melting point.

*Benzyltriphenylphosphonium bromide (**4a**)*

White crystal, mp. 296.4 °C (CAS: 1449-46-3). ^{1}H-NMR (500 MHz, Acetone-d_6): δ 7.94 (td, J = 7.5, 2.0 Hz, 3H), 7.85 (m, 6H), 7.77 (m, 6H), 7.32 (m, 1H), 7.23 (t, J = 7.7 Hz, 2H), 7.17 (m, 2H), 5.37 (d, J_{HP} = 15.1 Hz, 2H, –CH_2) ppm.

*Naphthalene-2-yl-methyltriphenylphosphonium bromide (**4b**)*

White powder, mp. 253.8 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.73–7.67 (m, 9H), 7.64 (d, J = 8.0 Hz, 1H), 7.58–7.53 (m, 6H), 7.49 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H),

Table 3 In vitro cytotoxicity of compounds **5**, **1**, **6** and **7** on Jurkat E6.1 cell line

Entry[a]	IC_{50} (μM)							
	5		**1**		**6**		**7**	
	E	***Z***	***E***	***Z***	***E***	***Z***	***E***	***Z***
a	N/D[b]	N/D[b]	87	12	–[c]	>100	–[c]	>100
b	>100	>100	52	90	–[c]	–[c]	–[c]	–[c]
c	–[c]	>100	–[c]	24	–[c]	–[c]	–[c]	–[c]
d	>100	>100	–[c]	92	–[c]	>100	–[c]	>100
e	>100	>100	90	32	–[c]	>100	–[c]	>100
f	>100	>100	>100	>100	>100	>100	>100	>100
g	–[c]	>100	–[c]	42	–[c]	>100	–[c]	>100
h	–[c]	>100	–[c]	68	–[c]	>100	–[c]	>100
i	–[c]	>100	–[c]	44	–[c]	>100	–[c]	>100
j	–[c]	>100	–[c]	48	–[c]	>100	–[c]	>100
k	–[c]	>100	–[c]	15	–[c]	>100	–[c]	>100

[a] Natural (*E*)-(+)-Goniothalamin used as positive control having IC_{50} = 22 μM

[b] Not detected

[c] No compound were evaluated

7.40–7.31 (m, 2H), 7.11 (dt, J = 8.0, 1.5 Hz, 1H), 5.49 (d, J_{HP} = 14.5 Hz, 2H, $–CH_2$) ppm.

*3-Methoxybenzyltriphenylphosphonium bromide (**4c**)*

White powder, mp. 261.7 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.67 (m, 9H), 7.56 (td, J = 7.8, 3.5 Hz, 6H), 6.94 (t, J = 8.1 Hz, 1H), 6.69 (m, 2H), 6.57 (m, 1H), 5.22 (d, J_{HP} = 14.4 Hz, 2H, $–CH_2$), 3.45 (s, 3H, $–OCH_3$) ppm.

*4-Methoxybenzyltriphenylphosphonium bromide (**4d**)*

White powder, mp. 248.3 °C (234–235 °C, Zhang and Go 2007). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.76–7.66 (m, 9H), 7.60 (td, J = 7.8, 3.5 Hz, 6H), 6.98 (dd, J = 8.7, 2.5 Hz, 2H), 6.62 (d, J = 8.7 Hz, 2H), 5.25 (d, J_{HP} = 14.0 Hz, 2H, $–CH_2$), 3.69 (s, 3H, $–OCH_3$) ppm.

*3,5-Dimethoxybenzyltriphenylphosphonium bromide (**4e**)*

White powder, mp. 267.3 °C (264–265.3 °C, Sun et al. 2010), ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.75–7.67 (m, 9H), 7.61–7.56 (m, 6H), 6.28 (t, J = 2.4 Hz, 2H), 6.24 (q, J = 2.3 Hz, 1H), 5.22 (d, J_{HP} = 14.4 Hz, 2H, $–CH_2$), 3.47 (s, 6H, 2 × $–OCH_3$) ppm.

*Pyridine-2-yl-methyltriphenylphosphonium bromide (**4f**)*

Light yellow powder, mp. 116.2 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.65 (d, J = 5.8 Hz, 1H), 8.34 (d, J = 6.2 Hz, 2H), 8.32 (d, J = 1.6 Hz, 1H), 8.22 (d, J = 7.4 Hz, 1H), 8.09 (t, J = 7.4 Hz, 1H), 7.90–7.75 (m, 6H), 7.71 (d, J = 8.1 Hz, 1H), 7.64 (td, J = 7.8, 3.6 Hz, 6H), 6.13 (d, J_{HP} = 15.0 Hz, 2H, $–CH_2$) ppm.

*4-Iodobenzyltriphenylphosphonium bromide (**4g**)*

White powder, mp. 269.7 °C (255–256 °C, Rodríguez et al. 2003), ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.78–7.71 (m, 9H), 7.62–7.57 (m, 6H), 7.39 (dd, J = 9.0, 1.0 Hz, 2H), 6.95 (dd, J = 8.5, 2.5 Hz, 2H), 5.67 (d, J_{HP} = 15 Hz, 2H).

*3-Fluorobenzyltriphenylphosphonium bromide (**4h**)*

White powder, mp. 315 °C (290–292 °C, Wyatt et al. 2006; 290–292 °C, Zhou and Keana 1999), ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.78–7.73 (m, 9H), 7.64–7.59 (m, 6H), 7.08 (q, J = 8.0 Hz, 1H), 7.04 (d, J = 1.0 Hz, 1H), 6.88 (t, J = 8.5 Hz, 1H), 6.72 (dd, J = 9.5, 1.5 Hz, 1H), 5.56 (d, J_{HP} = 14.5 Hz, 2H).

*2,3-Difluorobenzyltriphenylphosphonium bromide (**4i**)*

White powder, mp. 292.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.78–7.71 (m, 9H), 7.64–7.58 (m, 6H), 7.29 (t, J = 6.0, 2.0 Hz, 1H), 7.05–6.97 (m, 1H), 6.92–6.86 (m, 1H), 5.52 (d, J_{HP} = 14.5 Hz, 2H).

Scheme 5 Synthesis of styryldihydrofuran-2(3*H*)-one (**10a–g**)

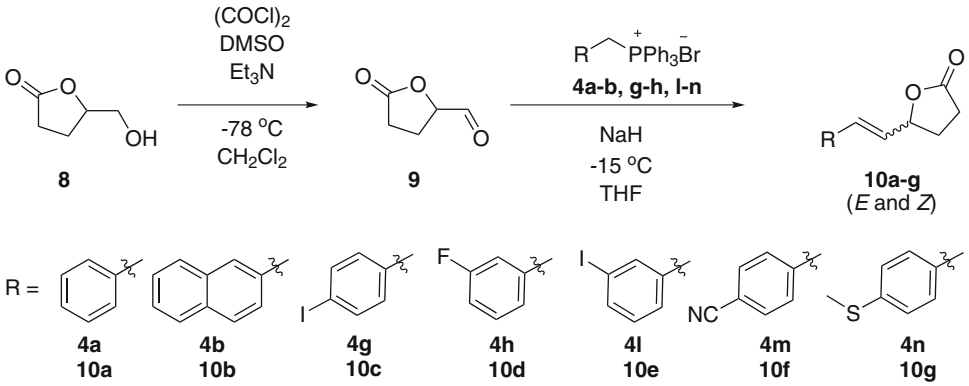
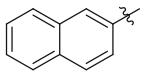
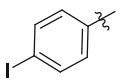
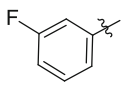
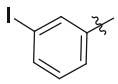
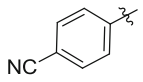
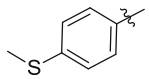


Table 4 Synthesis of five-member Goniothalamin analogs (**10a–g**) from aldehyde (**9**)

Entry	Substrate (R)	Yields (%) of lactones (**10**)	
		***E*-10**	***Z*-10**
a		35	16
b		30	15
c		21	22
d		18	16
e		18	20
f		28	15
g		15	30

*3,4-Difluorobenzyltriphenylphosphonium bromide (**4j**)*

White powder, mp. 315.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.80–7.69 (m, 9H), 7.60–7.54 (m, 6H), 7.05–6.01 (m, 1H), 6.98–6.92 (q, $J = 9.5$ Hz, 1H), 6.82–6.75 (q, $J = 9.5$ Hz, 1H), 5.67 (d, $J_{HP} = 15.0$ Hz, 2H).

*4-Trifluoromethoxybenzyltriphenylphosphonium bromide (**4k**)*

White powder, mp. 314.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.81–7.73 (m, 9H), 7.63–7.58 (m, 6H) 7.26 (dd, $J = 8.5$, 3.0 Hz, 2H), 6.94 (d, $J = 9.0$ Hz, 2H), 5.67 (d, $J_{HP} = 14.5$ Hz, 2H).

*3-Iodobenzyltriphenylphosphonium bromide (**4l**)*

White powder, mp. 291.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.89–7.72 (m, 9H), 7.65–7.58 (m, 6H), 7.48 (d, 1H), 7.37 (d, 1H), 7.04 (s, 1H), 6.86–6.83 (t, $J = 8$ Hz, 1H), 5.46 (d, $J = 15$ Hz, 2H $-CH_2$).

*4-Cyanobenzyltriphenylphosphonium bromide (**4m**)*

White powder, mp. 328.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.76–7.71 (m, 3H), 7.64–7.53 (m, 12H) 7.35 (d, $J = 8.0$ Hz, 2H), 7.16 (dd, $J = 8.5$, 2.5 Hz, 2H), 5.67 (d, $J_{HP} = 15$ Hz, 2H).

Table 5 In vitro cytotoxicity of compounds **10a–g** on Jurkat E6.1 cell line

Entry[a]	IC_{50} (μM)	
	***E*-10**	***Z*-10**
a	66	60
b	70	100
c	75	70
d	68	77
e	72	70
f	65	60
g	>100	>100

[a] Natural (*E*)-(+)-Goniothalamin used as positive control having $IC_{50} = 22$ μM

*4-Methylthiobenzyltriphenylphosphonium bromide (**4n**)*

White powder, mp. 232.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.74–7.68 (m, 9H), 7.61–7.56 (m, 6H), 7.02–6.99 (dd, 2H), 6.92 (d, 2H), 5.34 (d, $J = 14.5$ Hz, 2H $-CH_2$), 2.36 (s, 3H).

General procedure for the preparation of pyran **5**

(Substituted)-benzyl triphenylphosphonium halide (bromide/chloride **4**, 0.3 mmol) was added slowly to a stirrer suspension of NaH (60 % in mineral oil, 0.3 mmol) in dry THF (5 mL) at −15 °C. The solution was stirred for 30 min, freshly prepared 3,4-dihydro-2*H*-pyran-2-carbaldehyde (**2**, 0.45 mmol) in dry THF (1 mL) was added slowly, stirring was continued for 3–4 h at the same temperature and 1 h at room temperature. The reaction mixture was then diluted with ether, the ether layer were collected, washed with brine, dried and purified by column chromatography using *n*-hexane. The earlier fraction gave *Z*-isomer and the later fraction obtained *E*-isomer. The compounds were characterized by NMR and mass spectroscopic data as well as physical properties such as melting point.

*(E)-2-Styryl-3,4-dihydro-2H-pyran (**E-5a**)*

Yellow oil ($R_f = 0.68$, *n*-hexane). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38 (dd, $J = 8.1$, 0.9 Hz, 2H, H11/H13), 7.29 (m, 2H, H10/H14), 7.21 (m, 1H, H12), 6.62 (m, 1H, H8), 6.42 (m, 1H, H2), 6.25 (dd, J = 16.0, 6.2 Hz, 1H, H7), 4.70 (m, 1H, H6), 4.48 (m, 1H, H3), 2.05 (m, 3H, H4/H5), 1.78 (m, 1H, H4) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 143.55, 130.88, 129.06, 128.78, 128.54, 127.36, 126.51, 100.58, 75.29, 29.70, 19.40 ppm.

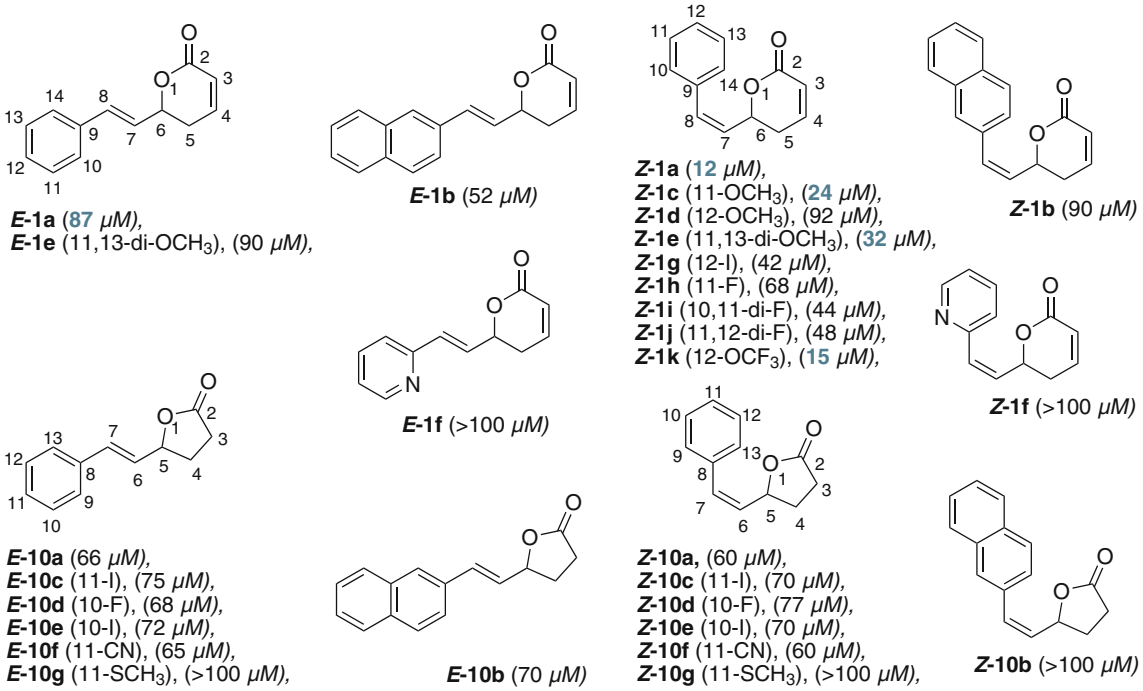


Chart 1 Structures of Goniothlamin analogs

*(Z)-2-Styryl-3,4-dihydro-2H-pyran (**Z-5a**)*

Low melting white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29 (m, 5H, –Ph), 6.62 (d, $J = 11.5$ Hz, 1H, H8), 6.41 (d, $J = 6.2$ Hz, 1H, H2), 5.75 (dd, $J = 11.5$, 9. Hz, 1H, H7), 4.70 (m, 2H, H3, H6), 2.15–2.05 (m, 1H, H4/H5), 2.04–1.96 (m, 1H, H4/H5), 1.94–1.88 (m, 1H, H4/H5), 1.82–1.72 (m, 1H, H4) ppm.

*(E)-2-(2-(Naphthalen-2-yl)vinyl)-3,4-dihydro-2H-pyran (**E-5b**)*

Light yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.78 (d, $J = 6$ Hz, 2H, H11), 7.76 (d, $J = 8$ Hz, 1H, H13/H16), 7.73 (s, 1H, H18), 7.59 (dd, $J = 9.5$, 1 Hz, 1H, H10), 7.43 (m, 2H, H14/H15), 6.79 (d, $J = 16.0$ Hz, 1H, H8), 6.45 (dt, $J = 6.5$, 1.0 Hz, 1H, H2), 6.38 (dd, $J = 16.0$, 6.5 Hz, 1H, H7), 4.73 (m, 1H, H6), 4.54 (m, 1H, H3), 2.18–2.10 (m, 1H, H4/H5), 2.08–1.98 (m, 2H, H4/H5), 1.87–1.77 (m, 1H, H4/H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 143.51, 130.99, 128.18, 127.98, 127.65, 126.53, 126.24, 125.88, 123.61, 100.60, 75.37, 28.36, 19.42 ppm.

*(Z)-2-(2-(Naphthalen-2-yl)vinyl)-3,4-dihydro-2H-pyran (**Z-5b**)*

Light yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.81 (d, $J = 9.0$ Hz, 1H, H11), 7.80 (d, $J = 8.5$ Hz, overlap, 1H), 7.78 (d, $J = 8.5$ Hz, 1H, H13/H16), 7.74 (s, 1H, H18), 7.47–7.44 (m, 2H, H10), 7.42 (dd, $J = 8.5$, 1.7 Hz, 1H, H14/H15), 6.77 (d, $J = 11.7$ Hz, 1H, H8), 6.44 (dt, $J = 6.4$, 1.0 Hz, 1H, H2), 5.83 (dd, $J = 11.6$, 9.1 Hz, 1H, H7), 4.79 (td, $J = 9.5$, 2.5 Hz, 1H, H6), 4.72–4.69 (m, 1H, H3), 2.14–1.93 (m, 3H, H4/H5), 1.89–1.81 (m, 1H, H4) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 143.64, 134.05, 132.56, 132.30, 131.53, 128.13, 127.83, 127.60, 126.87, 126.14, 100.52, 71.47, 28.27, 19.37 ppm.

*(Z)-2-(3-Methoxystyryl)-3,4-dihydro-2H-pyran (**Z-5c**)*

Light yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24 (t, $J = 8.0$ Hz, 1H, H13), 6.87 (dd, $J = 8.0$, 1.5 Hz, 2H, H10/H14), 6.81 (m, 1H, H12), 6.59 (d, $J = 11.5$ Hz, 1H, H8), 6.49 (dt, $J = 6.5$ Hz, 1H, H2), 5.74 (dd, $J = 11.5$, 9.0 Hz,

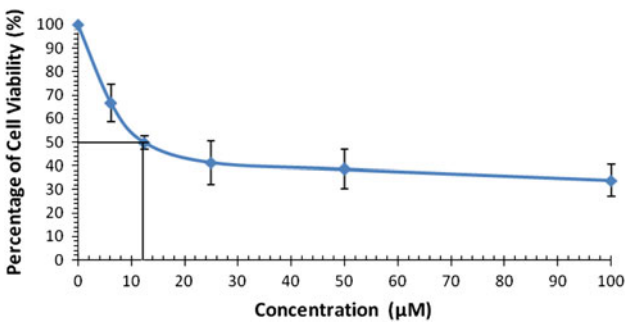


Fig. 1 Effects of *Z*-Goniothalamin (**Z-1a**) on the viability of Jurkat E6.1 cell as measured by MTT assay (data were given as mean ± SD of three independent experiments)

1H, H7), 4.70 (m, 2H, H6/H3), 3.84 (s, 3H, –OCH_3), 2.15–2.05 (m, 1H, H4/H5), 2.03–1.96 (m, 1H, H4/H5), 1.93–1.88 (m, 1H, H4/H5), 1.85–1.75 (m, 1H, H4/H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 143.60, 137.86, 132.24, 131.32, 129.30, 121.26, 114.14, 113.20, 100.52, 71.40, 55.18, 28.21, 19.38 ppm.

*(E)-2-(4-Methoxystyryl)-3,4-dihydro-2H-pyran (**E-5d**)*

Light yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35 (d, $J = 9.0$ Hz, 2H, H10/H14), 6.87 (d, $J = 8.5$ Hz, 2H, H10/H14), 6.61 (d, $J = 15.9$ Hz, 1H, H8), 6.46 (dd, $J = 6.5$, 2.6 Hz, 1H, H2), 6.15 (dd, $J = 16.0$, 6.5 Hz, 1H, H7), 4.74 (m, 1H, H6), 4.48 (m, 1H, H3), 3.83 (s, 3H, –OCH_3), 2.20–2.10 (m, 1H, H4/H5), 2.09–1.96 (m, 2H, H4/H5), 1.75–1.65 (m, 1H, H4/H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 143.54, 130.54, 127.70, 126.88, 113.99, 100.50, 75.53, 55.29, 37.10, 31.92, 30.03, 29.67, 28.42, 19.46 ppm.

*(Z)-2-(4-Methoxystyryl)-3,4-dihydro-2H-pyran (**Z-5d**)*

Light yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.27 (d, $J = 9.5$ Hz, 2H, H10/14), 6.91 (d, $J = 8.5$ Hz, 2H, H11/H13), 6.59 (d, $J = 11.6$ Hz, 1H, H8), 6.46 (d, $J = 6.2$ Hz, 1H, H2), 5.69 (dd, $J = 11.6$, 9.1 Hz, 1H, H7), 4.74 (m, 2H, H6/H3), 3.84 (s, 3H, –OCH_3), 2.20–2.10 (m, 1H, H4/H5), 2.09–2.00 (m, 1H, H4/H5), 1.98–1.92 (m, 1H, H4/H5), 1.90–1.80 (m, 1H, H4/H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 158.97, 143.68, 131.89, 130.11, 129.53, 129.15, 113.78, 100.44, 71.42, 55.26, 29.69, 28.25, 19.41 ppm.

*(E)-2-(3,5-Dimethoxystyryl)-3,4-dihydro-2H-pyran (**E-5e**)*

Light yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.57 (d, $J = 15.5$ Hz, 1H, H8), 6.55 (s, 2H, H2), 6.44 (dt, $J = 9.0$, 1.8 Hz, 1H, H10/H14), 6.37 (d, $J = 2.2$ Hz, 1H, H12), 6.24 (dd, $J = 16.0$, 6.1 Hz, 1H, H7), 4.73 (m, 1H, H6), 4.48 (m, 1H, H3), 3.79 (s, 6H, 2 × –OCH_3), 2.17–2.10 (m, 1H, H4/H5), 2.07–1.97 (m, 2H, H4/H5), 1.82–1.75 (m, 1H, H4/H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 160.94, 143.46, 138.81, 130.80, 129.64, 104.65, 100.58, 100.09, 75.15, 55.28, 29.69, 28.30, 19.39 ppm.

*(Z)-2-(3,5-Dimethoxystyryl)-3,4-dihydro-2H-pyran (**Z-5e**)*

Light yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.56 (d, $J = 11.5$ Hz, 1H, H8), 6.46 (d, $J = 2.2$ Hz, 1H, H2), 6.41 (d, $J = 6.2$ Hz, 1H, H14/H10), 6.38 (t, $J = 2.2$ Hz, 1H, H12), 5.73 (dd, $J = 11.6$, 9.1 Hz, 1H, H7), 4.70 (m, 1H, H6/H3), 3.77 (s, 6H, 2 × –OCH_3), 2.13–2.03 (m, 1H, H4/H5), 2.02–1.95 (m, 1H, H4/H5), 1.93–1.88 (m, 1H, H4/H5), 1.85–1.75 (m, 1H, H4/H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 160.65, 143.59, 138.38, 132.43, 131.46, 106.79, 100.58, 99.82, 71.46, 55.31, 28.22, 19.43 ppm.

*(E)-2-(2-(3,4-Dihydro-2H-pyran-2-yl)vinyl)pyridine (**E-5f**)*

Light yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.54 (dt, $J = 4.5$, 1.0 Hz 1H, H11), 7.61 (td, $J = 8.0$, 2.0 Hz, 1H, H13), 7.26 (d, $J = 7.9$ Hz, 1H, H14), 7.11 (ddd, $J = 7.5$, 5.0, 0.5 Hz, 1H, H12), 6.77 (dd, $J = 15.8$, 5.0 Hz, 1H, H7), 6.70 (d, $J = 15.5$ Hz, 1H, H8), 6.43 (d, $J = 6.5$ Hz, 1H, H2), 4.74–4.70 (m, 1H, H6), 4.58–4.53 (m, 1H, H3), 2.17–2.07 (m, 1H, H4/H5), 2.05–1.97 (m, 2H, H4/H5), 1.82–1.75 (m, 1H, H4/H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): 155.20, 149.54, 143.35, 136.49, 133.56, 129.97, 122.18, 121.91, 100.65, 74.63, 28.05, 19.29 ppm.

*(Z)-2-(2-(3,4-Dihydro-2H-pyran-2-yl)vinyl)pyridine (**Z-5f**)*

Light yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.57 (dt, $J = 4.5$, 1.0 Hz 1H, H11), 7.61 (td, $J = 7.5$, 1.5 Hz, 1H, H13), 7.22 (d, $J = 8.0$ Hz, 1H, H14), 7.09 (ddd, $J = 7.5$, 5.0, 0.5 Hz, 1H, H12), 6.48 (dd, $J = 12.0$, 1.1 Hz, 1H, H8) 6.40 (dt, $J = 6.5$, 2.0 Hz, 1H, H2), 5.95 (dd, $J = 12.0$, 8.5 Hz, 1H, H7), 5.45 (tdd, $J = 9.0$, 2.0, 1.0 Hz, 1H, H6), 4.72–4.69 (m, 1H, H3), 2.20–2.12 (m, 1H, H4/H5), 2.11–2.05 (m, 1H, H4/H5), 2.03–1.96 (m, 1H, H4/H5), 1.82–1.78 (m, 1H, H4/H5) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 155.68, 149.33, 143.42, 136.11, 129.14, 124.18, 121.56, 100.67, 72.31, 27.34, 19.40 ppm.

*(Z)-2-(4-Iodostyryl)-3,4-dihydro-2H-pyran (**Z-5g**)*

Light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.65 (dt, $J = 8.5$, 1.5 Hz, 2H), 7.02 (dt, $J = 8.5$, 1.5 Hz, 2H), 6.52 (d, $J = 11.5$ Hz, 1H), 6.39 (dt, $J = 6.0$, 1.0 Hz, 1H), 5.76 (dd, $J = 11.5$, 9.0 Hz, 1H), 4.71–4.67 (m, 1H), 4.60 (td, $J = 8.5$, 2.0 Hz, 1H), 2.12–2.04 (m, 1H, H4/H5), 2.031–1.955 (m, 1H, H4/H5), 1.97–1.85 (m, 1H, H4/H5), 1.83–1.75 (m, 1H, H4/H5) ppm.

*(Z)-2-(3-Fluorostyryl)-3,4-dihydro-2H-pyran (**Z-5h**)*

Light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.31–7.26 (m, 1H), 7.05 (d, $J = 7.5$ Hz, 1H), 7.02–6.92 (m, 2H), 6.57 (d, $J = 11.5$ Hz, 1H), 6.41 (d, $J = 6.0$ Hz, 1H), 5.78 (dd, $J = 11.5$, 9.0 Hz, 1H), 4.72–4.68 (m, 1H), 4.68–4.62 (m, 1H), 2.15–1.76 (m, 4H).

*(Z)-2-(2,3-Difluorostyryl)-3,4-dihydro-2H-pyran (**Z-5i**)*

Light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.15–7.02 (m, 3H), 6.65 (d, $J = 11.5$ Hz, 1H), 6.42 (d,

$J = 6.0$ Hz, 1H), 5.76 (dd, $J = 11.5$, 9.5 Hz, 1H), 4.75–4.71 (m, 1H), 4.61–4.55 (m, 1H), 2.15–1.78 (m, 4H).

*(Z)-2-(3,4-Difluorostyryl)-3,4-dihydro-2H-pyran (**Z-5j**)*

Light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.15–7.07 (m, 2H), 7.03–6.98 (m, 1H), 6.51 (d, $J = 11.5$ Hz, 1H), 6.41 (d, $J = 6.5$ Hz, 1H), 5.76 (dd, $J = 11.5$, 9.0 Hz, 1H), 4.73–4.68 (m, 1H), 4.62–4.56 (m, 1H), 2.14–1.76 (m, 4H).

*(Z)-2-(4-(Trifluoromethoxy)styryl)-3,4-dihydro-2H-pyran (**Z-5k**)*

Light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.31 (d, $J = 8.5$ Hz, 2H), 7.17 (d, $J = 8.0$ Hz, 2H), 6.59 (d, $J = 12.0$ Hz, 1H), 6.41 (d, $J = 6.0$ Hz, 1H), 5.78 (dd, $J = 11.75$, 9.5, 9.0 Hz, 1H), 4.73–4.68 (m, 1H), 4.65–4.59 (m, 1H), 2.15–1.76 (m, 4H).

General procedure for the preparation of Goniothalamin Analogs **1a–k**

t-Butyl hydroperoxide (55 %) (50 μL, 0.3 mmol) was added to a stirring mixture of pyridinium dichromate (PDC) (75 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) at 0 °C and the stirring was continued for 15 min. The resulting solution was quickly filtered over a cotton plug and the filtrate was placed at −40 °C. To this solution, ***E*-5** or ***Z*-5** (0.11 mmol) in CH_2Cl_2 (1 mL) was added drop wise and the reaction mixture was stirred at the same temperature for 2 h. A precipitate was formed, CH_2Cl_2 was evaporated under reduced pressure and the solid residue was washed with ether (5 mL). The crude products were purified by flash chromatography on silica gel (EtOAc:*n*-hexane, 1:4) to obtain compounds ***E*-1a–k** or ***Z*-1a–k.** The compounds were characterized by NMR and mass spectroscopic data as well as physical properties such as melting point.

*(E)-6-Styryl-5,6-dihydro-2H-pyran-2-one (E-Goniothalamin, **E-1a**)*

Yellow solid (78 %), mp. = 81 °C (80–82 °C, Schaus et al. 1998), $R_f = 0.33$, EtOAc:*n*-hexane (1:4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, $J = 8$ Hz, 2H, H10/H14) 7.32 (t, $J = 7.5$ Hz, 2H, H11/H13), 7.26 (t, $J = 6.5$ Hz, 1H, H12), 6.91 (ddd, $J = 9.8$, 6.3, 2.4 Hz, 1H, H4), 6.71 (d, $J = 16.1$ Hz, 1H, H8), 6.26 (dd, $J = 16.0$, 6.3 Hz, 1H, H7), 6.08 (dt, $J = 10$, 1.5 Hz, 1H, H3), 5.09 (m, 1H, H6), 2.53 (m, 2H, H5) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.77, 144.43, 135.81, 133.16, 128.69, 128.36, 126.71, 125.69, 121.77, 77.90, 29.91 ppm. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{13}H_{12}O_2$: 223.0761; measured: 223.10.

*(E)-6-(2-(Naphthalen-2-yl)vinyl)-5,6-dihydro-2H-pyran-2-one (**E-1b**)*

Light yellow oil (26 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (m, 3H, H13, H16, H18), 7.73 (d, $J = 5.5$ Hz 1H, H11), 7.57 (ddd $J = 4.8$, 2.7, 1.6 Hz, 1H, H10), 7.45 (m, 2H, H14/H15), 6.87 (d, $J = 16.0$ Hz, 1H), 6.41 (dd, $J = 15.9$, 6.4 Hz, 1H, H7), 6.34 (dd, $J = 15.9$, 6.0 Hz, 1H, H7), 6.10 (m, 1H, H3), 5.10 (m, 1H, H6), 2.61 (m, 2H, H5) ppm. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{17}H_{14}O_2$: 273.0894; measured: 273.91.

*(E)-6-(3,5-Dimethoxystyryl)-5,6-dihydro-2H-pyran-2-one (**E-1e**)*

Light yellow oil (13 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (dq, $J = 9.5$, 6, 3 Hz, 1H, H4), 6.68 (d, $J = 15.0$ Hz, 1H, H8), 6.57 (d, $J = 2.2$ Hz, 2H, H10/H14), 6.43 (dd, $J = 2.9$, 1.6 Hz, 1H, H12), 6.28 (ddd, $J = 15.8$, 6.0, 1.4 Hz, 1H, H7), 6.12 (d, $J = 9.0$ Hz, 1H, H3), 5.13 (m, 1H, H6), 3.83 (s, 6H, 2 × –OCH_3), 2.56 (m, 2H, H5) ppm. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{15}H_{16}O_4$: 283.0946; measured: 283.0950.

*(E)-6-(2-(Pyridin-2-yl)vinyl)-5,6-dihydro-2H-pyran-2-one (**E-1f**)*

Light yellow oil (18 %), $R_f = 0.33$, EtOAc:*n*-hexane (1:4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (dt, $J = 4.5$, 1.0 Hz, 1H, H11), 7.61 (td, $J = 7.7$, 1.8 Hz, 1H, H13), 7.29 (d, $J = 7.9$ Hz, 1H, H14), 7.12 (dq, $J = 7.5$, 4.8, 1.0 Hz, 1H, H12), 6.82 (q, $J = 15.8$, 3H, H4/H7/H8), 6.41 (dt, $J = 6.3$, 1.8 Hz, 1H, H3), 4.82 (m, 1H, H6), 2.14 (m, 2H, H5) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 154.97, 149.59, 141.24, 136.43, 132.75, 131.57, 122.37, 122.31, 101.07, 100.92, 80.31, 29.68 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{12}H_{11}NO_2$: 202.0790; measured: 202.09.

*(E)-2-(2-(6-(Tert-butylperoxy)-3,6-dihydro-2H-pyran-2-yl)vinyl)pyridine (**E-6f**)*

White crystals (3 %), $R_f = 0.55$, EtOAc:*n*-hexane (1:4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (dt, $J = 4.5$, 1.0 Hz, 1H, H11), 7.61 (td, $J = 8.0$, 1.1 Hz, 1H, H13), 7.30 (d, $J = 8.0$ Hz, 1H, H14), 7.11 (ddd, $J = 8.0$, 4.5, 1.5 Hz, 1H, H12), 6.78 (d (overlaped), $J = 3.7$ Hz, 2H, H7/H8), 6.17 (m, 1H, H4), 5.72 (dm, 1H, H3), 5.54 (brs, 1H, H2), 4.68 (dt, $J = 10$, 4.0, 1H, H6), 2.19 (m, 2H, H5), 1.25 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 155.63, 149.25, 136.03, 135.79, 132.37, 129.71, 128.25, 124.28, 121.55, 121.07, 99.41, 97.58, 80.57, 68.97, 84.85, 60.36, 53.38, 29.69, 26.0 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{16}H_{21}NO_3$: 276.1521; measured: 276.15.

*(E)-2-(2-(Pyridin-2-yl)vinyl)-2H-pyran-4(3H)-one (**E-7f**)*

Light yellow solid (4 %), $R_f = 0.40$, EtOAc:*n*-hexane (1:4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (d, $J = 4.8$ Hz, 1H, H11), 7.66 (td, $J = 7.5$, 2 Hz, 1H, H13), 7.46 (dd, $J = 7.9$, 0.9 Hz, 1H, H14), 7.30–7.22 (m, 1H, H7/H8), 7.15 (dq, $J = 7.4$, 4.9, 1.1 Hz, 1H, H12), 6.39 (m, 1H, H4), 5.99 (d, $J = 9.1$ Hz, 1H, H2), 4.88 (m, 1H, H3) 4.65 (dd, $J = 9.1$, 0.7 Hz, 1H, H6), 2.43 (m, 2H, H5) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 152.97, 141.59, 136.42, 122.33, 121.87, 102.71, 101.92, 80.53, 29.67 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{12}H_{11}NO_2$: 202.0790; measured: 202.0866.

*(Z)-6-Styryl-5,6-dihydro-2H-pyran-2-one (Z-Goniothalamin, **Z-1a**)*

Light yellow solid (84 %), $R_f = 0.36$, EtOAc:*n*-hexane (1:4). 83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (t, $J = 8$ Hz, 2H, –Ph) 7.27(m, 3H, –Ph), 6.85 (ddd, $J = 9.8$, 5.6, 2.9 Hz, 1H, H4), 6.75 (d, $J = 11.5$ Hz, 1H, H8), 6.03 (ddd, $J = 9.8$, 2.4, 1.2 Hz, 1H, H3), 5.81 (dd, $J = 11.5$, 9.3 Hz, 1H, H7), 5.28 (td, $J = 9.9$, 4.6 Hz, 1H, H6), 2.47 (m, 2H, H5) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.81, 144.43, 135.69, 134.81, 128.61, 128.55, 121.70, 74.14, 29.79 ppm. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{13}H_{12}O_2$: 223.0735; measured: 223.0734.

*(Z)-6-(Tert-butylperoxy)-2-styryl-3,6-dihydro-2H-pyran (**Z-6a**)*

White crystal (10 %), mp. 70 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, $J = 7.7$ Hz, 2H, H10/H14) 7.31 (t, $J = 7.6$ Hz, 2H, H11/H13), 7.3 (m, $J = 1$H, H12) 6.62 (d, $J = 11.6$ Hz, 1H, H8), 6.12 (m, 1H, H4), 5.68 (m, $J = 11.5$, 9.0 2H, H7), 5.49 (brs, 1H, H2), 4.94 (td, $J = 10.5$, 3.4 Hz, 1H, H3), 2.19 (m, 1H, H6), 2.06 (m, 1H, H5), 1.20 (s, 9H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.56, 132.64, 131.69, 131.13, 128.99, 128.18, 127.26, 121.36, 97.65, 80.51, 63.74, 30.63, 29.69, 26.45 ppm. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{17}H_{22}O_3$: 297.1467; measured: 297.1484.

*(Z)-Styryl-2,3-dihydro-4H-pyran-4-one (**Z-7a**)*

$R_f = 0.43$, EtOAc/*n*-hexane (1:4), (5 mg, 6 %), low melting solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, $J = 6$ Hz, 1 H H4), 7.36–7.18 (m, 5 H, Ph), 6.78 (d, $J = 11.5$ 1 H, H2′), 5.83 (dd, $J = 11.5$, 9.5 Hz, 1 H, H1′), 5.41 (dd, $J = 6.0$, 1.0 Hz, 1 H, H3), 5.32–5.24 (m, 1 H, H6), 2.71 (dd, $J = 17.0$, 12.5 Hz, 1 H, H5), 2.53 (ddd, $J = 17.0$, 4.0, 1.0 Hz, 1 H, H5) ppm. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{13}H_{12}O_2$: 223.0837; measured: 223.0734.

*(Z)-6-(2-(Naphthalen-2-yl)vinyl)-5,6-dihydro-2H-pyran-2-one (**Z-1b**)*

Light yellow solid. (45 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (dd, $J = 9.3$, 4.6 Hz, 3H, H13/H16/H18), 7.74 (s, 1H, H11), 7.47 (m, 2H, H10), 7.38 (dd, $J = 8.5$ Hz, 1.7 Hz, 1H, H14/H15), 6.90 (d, $J = 11.5$ Hz, 1H, H8), 6.85 (ddd, $J = 9.8$, 5.6, 2.9 Hz, 1H, H4), 6.04 (ddd, $J = 9.8$, 2.5, 1.2 Hz, 1H, H3), 5.90 (dd, $J = 11.5$, 9.3 Hz, 1H, H7), 5.36 (m, 1H, H6), 2.49 (m, 2H, H5) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.96, 144.48, 134.90, 133.19, 132.74, 128.24, 128.21, 128.16, 127.74, 127.65, 126.47, 126.40, 121.70, 74.27, 29.82, 29.69 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{17}H_{14}O_2$: 251.0994; measured: 251.1070.

*(Z)-6-(Tert-butylperoxy)-2-(2-(naphthalen-2-yl)vinyl)-3,6-dihydro-2H-pyran (**Z-6b**)*

Low melting white crystal (5 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ δ 7.70 (m, 2H, H11/H13/H16/H18), 7.43 (ddd, $J = 14.2$, 8.3, 4.9, 2H, H10/H14/H15), 6.75 (m, 1H, 1H, H8), 6.18 (m, 1H, H4), 6.12 (m, 1H, H4), 5.73 (dd, $J = 11.5$, 9.0 Hz, 1H, H7), 5.70–5.66 (m, 1H, H7), 5.54 (d, $J = 10.2$ Hz, 1H, H2), 5.33 (brs, 1H, H2), 5.03 (m, 1H, H3), 4.67 (m, 1H, H6), 2.16 (m, 1H, H5), 1.73 (m, 1H, H5), 1.23 (d, 9H) ppm.

*(Z)-6-(3-Methoxystyryl)-5,6-dihydro-2H-pyran-2-one (**Z-1c**)*

Light yellow oil (51 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (t, $J = 7.7$ Hz, 1H, H13), 6.84 (m, 4H, H10/H12/H14), 6.72 (d, $J = 11.6$ Hz, 1H, H8), 6.03 (dd, $J = 9.8$, 4.0 Hz, 1H, H4), 5.81 (dd, $J = 11.5$, 9.3 Hz, 1H, H7), 5.29 (m, 1H, H3/H6), 3.79 (s, 3H, $–OCH_3$), 2.45 (m, 2H, H5) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.69, 144.46, 137.05, 134.74, 129.56, 128.12, 121.68, 120.97, 114.07, 113.61, 74.17, 55.27, 29.77, 29.68, 14.07 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{14}H_{14}O_3$: 231.0943; measured: 231.1018.

*(Z)-6-(4-Methoxystyryl)-5,6-dihydro-2H-pyran-2-one (**Z-1d**)*

Light yellow solid (31 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, $J = 9.5$ Hz, 2H, H10/H14), 6.86 (d, $J = 9.5$ Hz, 2H, H11/H13), 6.86 (overlaped, 1H), 6.68 (d, $J = 11.3$ Hz, 1H, H8), 6.04 (dq, $J = 9.8$, 4.0, 2.4, Hz, 1H, H4), 5.71 (dd, $J = 11.5$, 9.3 Hz, 1H, H7), 5.29 (m, 1H, H3/H6), 3.80 (s, 3H, $–OCH_3$), 2.46 (m, 2H, H5) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.53, 144.54, 134.59, 130.03, 126.35, 121.71, 113.99, 74.28, 55.29, 29.85, 29.69 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{14}H_{14}O_3$: 231.043; measured: 231.1020.

*(Z)-6-(Tert-butylperoxy)-2-(4-methoxystyryl)-3,6-dihydro-2H-pyran (**Z-6d**)*

White crystals (10 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, $J = 8.7$ Hz, 2H, H10/H14), 6.89 (d, $J = 8.7$ Hz, 2H, H11/H13), 6.59 (d, $J = 11.6$ Hz, 1H, H8), 6.16 (m, 1H, H4), 5.72 (m, 1H, H3), 5.63 (dd, $J = 11.6$, 8.9 Hz, 1H, H7), 5.54 (brs, 1H, H2), 4.97 (m, 1H, H6), 3.83 (s, 3H, $–OCH_3$), 2.22 (m, 1H, H5), 2.10 (m, 1H, H5), 1.27 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 158.11, 131.81, 130.41, 129.48, 121.31, 113.64, 97.86, 80.55, 55.20, 30.73, 29.68, 29.34, 26.54 ppm. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{18}H_{24}O_4$: 327.1572; measured: 327.1465.

*(Z)-2-(4-Methoxystyryl)-2H-pyran-4(3H)-one (**Z-7d**)*

Light yellow solid (8 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (dd, $J = 6.0$, 0.5 Hz, 1H, H2), 7.16 (d, $J = 8.5$ Hz, 2H, H10/H14), 6.87 (d, $J = 8.5$ Hz, 2H, H11/H13), 6.87 (overlaped, 1H), 6.71 (d, $J = 11.6$ Hz, 1H, H8), 5.73 (dd, $J = 11.5$, 9.2 Hz, 1H, H7), 5.42 (dd, $J = 6.1$, 1.1 Hz, 1H, H3), 3.80 (s, 3H, $–OCH_3$), 2.71 (dd, $J = 16.9$, 13.2 Hz, 1H, H5), 2.53 (dq, $J = 8.8$, 4.4, 3.3, 1 Hz, 1H, H5), ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.10, 134.81, 129.97, 125.68, 114.06, 107.21, 75.88, 55.31, 42.09, 29.69, 14.09 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{14}H_{14}O_3$: 231.0943; measured: 231.0977.

*(Z)-6-(3,5-Dimethoxystyryl)-5,6-dihydro-2H-pyran-2-one (**Z-1e**)*

Light yellow solid (37 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.89 (ddd, $J = 9.8$, 5.6, 2.9 Hz, 1H, H4), 6.74 (d, $J = 11.5$ Hz, 1H, H12), 6.46 (overlaped, 1H), 6.46 (d, $J = 2.2$ Hz, 2H, H10), 6.06 (ddd, $J = 9.8$, 2.5, 1.2 Hz, 1H, H8), 5.84 (dd, $J = 11.4$, 9.2 Hz, 1H, H7), 5.33 (m, 1H, H3/H6), 3.83 (s, 6H, 2 × $–OCH_3$), 2.50 (m, 2H, H5) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.85, 144.57, 137.61, 134.91, 128.25, 121.64, 106.60, 100.08, 74.20, 55.40, 29.77, 29.69 ppm. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{15}H_{16}O_4$: 283.0948; measured: 283.0946.

*(Z)-6-(Tert-butylperoxy)-2-(3,5-dimethoxystyryl)-3,6-dihydro-2H-pyran (**Z-6e**)*

White crystal (7 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (d, $J = 11.5$ Hz, 1H, H12), 6.52 (d, $J = 2.2$ Hz, 1H, H10), 6.43 (s, 1H), 6.38 (d, $J = 2.0$ Hz, 1H, H12), 6.11 (m, 1H, H3), 5.68 (dd, $J = 11.7$, 8.9 Hz, 2H, H7), 5.46 (brs, 1H, H2), 4.95 (m, 1H, H6), 3.77 (s, 6H, 2 × $–OCH_3$), 2.10 (m, 2H, H5), 1.23 (s, 9H) ppm.

*(Z)-2-(3,5-Dimethoxystyryl)-2H-pyran-4(3H)-one (**Z-7e**)*

Light yellow solid (3 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, $J = 6$ Hz, 1H, H2), 6.77 (d, $J = 12$ Hz, 1H, H8), 6.50 (d, $J = 2$ Hz, 1H, H12), 6.44 (m, 2H, H10/H14), 5.86 (dd, $J = 9.5$, 1.5 Hz, 1H, H7), 5.63 (m, 1H), 5.45 (m, 1H, H3), 3.81 (s, 6H, 2 × $–OCH_3$), 2.74 (dd, $J = 16.5$, 12.5 Hz, 1H, H5), 2.54 (m, 1H, H5) ppm.

*(Z)-6-(2-(Pyridin-2-yl)vinyl)-5,6-dihydro-2H-pyran-2-one (**Z-1f**)*

Light yellow solid (56 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (d, $J = 4.8$ Hz, 1H, H11), 7.64 (td, $J = 7.7$, 1.9 Hz, 1H, H13), 7.20 (d, $J = 2.6$ Hz, 1H, H14), 7.12 (dd, $J = 7.6$, 4.9 Hz, 1H, H12), 6.93 (dq, $J = 9.8$, 5.9, 2.5 Hz, 1H, H4), 6.48 (dd, $J = 11.9$, 1.4 Hz, 1H, H7/H8), 6.27 (m, 1H, H6), 6.02 (ddd, $J = 4.3$, 2.7, 1.1 Hz, 2H, H3), 2.90 (m, 1H, H5), 2.41 (m, 1H, H5) ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{12}H_{11}NO_2$: 202.0790; measured: 202.0864.

*(Z)-2-(2-(6-(Tert-butylperoxy)-3,6-dihydro-2H-pyran-2-yl)vinyl)pyridine (**Z-6f**)*

White crystals (2 %). ^{1}H (NMR (500 MHz, $CDCl_3$): δ 8.55 (d, $J = 4.8$ Hz, 1H, H11), 7.60 (td, $J = 8.0$, 2.0 Hz, 1H, H13), 7.38 (d, $J = 7.9$ Hz, 1H, H14), 7.08 (m, 1H, H12), 6.51 (d, $J = 11.9$ Hz, 1H, H8), 6.17 (m, 1H, H4), 5.92 (dd, $J = 11.9$, 8.1 Hz, 1H, H7), 5.69 (m, 1H, H3), 5.49 (brs, 1H, H2), 5.45 (m, 1H, H6), 2.43 (m, 1H, H5), 2.13 (m, 1H, H5), 1.23 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.63, 149.25, 136.03, 132.37, 129.71, 124.28, 121.55, 121.07, 97.58, 80.57, 29.55, 26.47 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{16}H_{21}NO_3$ 276.1521; measured: 276.1601.

*(Z)-2-(2-(Pyridin-2-yl)vinyl)-2H-pyran-4(3H)-one (**Z-7f**)*

Light yellow solid (1 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (d, $J = 4.8$ Hz, 1H, H11), 7.63 (td, $J = 7.7$, 1.8 Hz, 1H, H13), 7.37 (d, $J = 6.0$ Hz, 1H, H14), 7.18 (d, $J = 7.9$ Hz, 1H, H2), 7.12 (dq, $J = 7.5$, 4.8, 0.9 Hz, 1H, H12), 6.50 (d, $J = 11.9$ Hz, 1H, H8), 6.37 (m, 1H, H4), 6.03 (dd, $J = 11.9$, 7.5 Hz, 1H, H7), 5.44 (m, 1H, H3/H6), 2.91 (dd, $J = 16.5$, 4 Hz, 1H, H5), 2.61 (dd, $J = 16.8$, 13.1 Hz, 1H, H5) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 162.94, 149.52, 136.34, 132.36, 129.81, 124.56, 122.02, 107.34, 60.36, 53.37, 40.59, 29.69, 14.18 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{12}H_{11}NO_2$: 202.0790; measured: 202.0883.

*(Z)-6-(4-Iodostyryl)-5,6-dihydro-2H-pyran-2-one (**Z-1g**)*

Light yellow solid (62 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.67 (d, $J = 8.0$ Hz, 2H), 7.00 (d, $J = 8.5$ Hz, 2H), 6.87–6.84 (ddd, $J = 9.5$, 5.5, 2.5 Hz, 1H), 6.65 (d, $J = 11.5$ Hz, 1H), 6.03 (ddd, $J = 9.5$, 1.5, 1.0 Hz, 1H), 5.82 (dd, $J = 11.5$, 9.5 Hz, 1H), 5.22–5.16 (m, 1H), 2.52–2.36 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 163.60, 144.43, 137.71, 135.07, 133.85, 130.40, 128.63, 121.66, 93.71, 73.86 and 29.68. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{13}H_{11}IO_2$: 326.9804; measured: 326.9883.

*(Z)-6-(Tert-butylperoxy)-2-(4-iodostyryl)-3,6-dihydro-2H-pyran (**Z-6g**)*

White powder (6 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.63 (d, $J = 8.5$ Hz, 2H), 7.23 (dd, $J = 8.0$, 1.5 Hz, 1H), 7.18 (dd, $J = 8.0$, 1.5 Hz, 1H), 6.49 (d, $J = 12.0$ Hz, 1H), 6.14–6.09 (m, 1H), 5.74–5.65 (m, 2H), 5.49 (s, 1H), 4.88–4.82 (m, 1H), 2.21–2.13 (m, 1H), 2.06–1.98 (m, 1H), 1.23 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 137.35, 135.95, 131.89, 131.56, 130.94, 121.29, 97.85, 93.00, 80.66, 63.51, 30.61, 29.67, 26.47. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{17}H_{21}IO_3$: 423.0433; measured: 423.0434.

*(Z)-2-(4-Iodostyryl)-2H-pyran-4(3H)-one (**Z-7g**)*

Light yellow liquid (3 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.68 (d, $J = 8.0$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 1H), 6.96 (d, $J = 8.0$ Hz, 2H), 6.69 (d, $J = 11.5$ Hz, 1H), 5.85 (dd, $J = 11.5$, 9.0 Hz, 1H), 5.42 (dd, $J = 6.0$, 1.0 Hz, 1H), 5.23–5.16 (m, 1H), 2.70 (dd, $J = 16.8$, 13.5, 13.0 Hz, 1H), 2.50 (dq, $J = 16.9$, 1.5, 1.0 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 191.29, 162.83, 137.77, 134.90, 134.13, 130.28, 128.02, 107.33, 93.85, 75.44, 41.90, 29.68. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{13}H_{11}IO_2$: 348.9701; measured: 348.9728.

*(Z)-6-(3-Fluorostyryl)-5,6-dihydro-2H-pyran-2-one (**Z-1h**)*

Light yellow solid (68 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.33–7.28 (m, 1H), 7.05 (d, $J = 8.0$ Hz, 1H), 7.01–6.92 (m, 2H), 6.89–6.84 (m, 1H), 6.70 (d, $J = 11.5$ Hz, 1H), 6.03 (ddd, $J = 10.0$, 1.5, 1.0 Hz, 1H), 5.85 (dd, $J = 11.5$, 9.5 Hz, 1H), 5.28–5.21 (m, 1H), 2.53–2.39 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 163.68, 161.76, 144.49, 137.73, 133.54, 130.16, 128.95, 124.37, 121.63, 115.43, 114.88, 73.86, 29.64. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{13}H_{11}FO_2$: 219.0743; measured: 219.0829.

*(Z)-6-(Tert-butylperoxy)-2-(3-fluorostyryl)-3,6-dihydro-2H-pyran (**Z-6h**)*

White powder (12 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.35–7.28 (m, 1H), 7.23 (d, $J = 7.5$ Hz, 1H), 7.17 (d, $J = 10.0$ Hz, 1H), 6.98 (dt, $J = 8.5$, 2.5 Hz, 1H), 6.62 (d, $J = 11.5$ Hz, 1H), 6.20–6.14 (m, 1H), 5.78 (dd, $J = 11.5$, 9.0 Hz, 1H), 5.75–5.70 (m, 1H), 5.53 (s, 1H), 4.98–4.91 (m, 1H), 2.27–2.19 (m, 1H), 2.13–2.05 (m, 1H), 1.26 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 163.77, 161.81, 138.62, 132.13, 131.62, 129.65, 124.82, 121.29, 115.70, 114.23, 97.67, 80.73, 63.47, 30.57, 26.37. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{17}H_{21}FO_3$: 315.1372; measured: 315.1377.

*(Z)-2-(3-Fluorostyryl)-2H-pyran-4(3H)-one (**Z-7h**)*

Light yellow liquid (5 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.38 (d, $J = 6.5$ Hz, 1H), 7.34–7.28 (m, 1H), 7.02–6.97 (m, 2H), 6.94 (d, $J = 9.5$ Hz, 1H), 6.74 (d, $J = 11.5$ Hz, 1H), 5.87 (dd, $J = 11.5$, 9.5 Hz, 1H), 5.43 (dd, $J = 6.3$, 1.0, 0.5 Hz, 1H), 5.26–5.19 (m, 1H), 2.71 (dd, $J = 16.8$, 13.5, 13.0 Hz, 1H), 2.54–2.48 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 191.32, 163.76, 162.86, 161.79, 137.57, 134.00, 130.19, 128.33, 124.26, 115.24, 107.33, 75.42, 41.88. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{13}H_{11}FO_2$: 219.0743; measured: 219.0843.

*(Z)-6-(2,3-Difluorostyryl)-5,6-dihydro-2H-pyran-2-one (**Z-1i**)*

Light yellow solid (58 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.13–7.01 (m, 3H), 6.88–6.83 (d, $J = 8.0$ Hz, 1H), 6.68 (d, $J = 11.5$ Hz, 1H), 6.03–5.94 (m, 2H), 5.14–5.07 (m, 1H), 2.53–2.39 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 163.59, 148.84, 148.82, 144.36, 134.26, 133.59, 130.10, 128.68, 121.71, 121.46, 120.98, 73.78, 29.69. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{13}H_{20}F_2O_3$: 259.0547; measured: 259.0611.

*(Z)-6-(Tert-butylperoxy)-2-(2,3-difluorostyryl)-3,6-dihydro-2H-pyran (**Z-6i**)*

White powder (14 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.41–7.36 (m, 1H), 7.10–6.99 (m, 2H), 6.64 (d, $J = 11.5$ Hz, 1H), 6.14–6.09 (m, 1H), 5.89–5.83 (dd, $J = 11.75$, 9.5, 9.0 Hz,1H), 5.69–5.64 (m, 1H), 5.48 (s, 1H), 4.80–4.74 (m, 1H), 2.23–2.15 (m, 1H), 2.07–2.00 (m, 1H), 1.24 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 151.52, 149.35, 147.16, 133.98, 131.59, 126.46, 125.93,

124.34, 123.64, 121.24, 116.3, 97.61, 80.58, 63.79, 30.35, 26.42. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{17}H_{20}F_2O_3$: 333.1278; measured: 333.1277.

*(Z)-6-(3,4-Difluorostyryl)-5,6-dihydro-2H-pyran-2-one (**Z-1j**)*

Light yellow solid (53 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.17–7.05 (m, 2H), 7.04–6.99 (m, 1H), 6.89–6.84 (m, 1H), 6.65 (d, $J = 11.5$ Hz, 1H), 6.07–6.03 (m, 1H), 5.84 (dd, $J = 11.3$, 9.5, 9.0 Hz, 1H), 5.22–5.16 (m, 1H), 2.54–2.39 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 163.52, 151.12, 149.13, 144.35, 132.74, 132.48, 128.86, 124.95, 121.72, 117.54, 73.64, 29.67. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{13}H_{10}F_2O_2$: 237.0649; measured: 237.0729.

*(Z)-6-(Tert-butylperoxy)-2-(3,4-difluorostyryl)-3,6-dihydro-2H-pyran (**Z-6j**)*

White powder (8 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.36–7.30 (m, 1H), 7.20–7.15 (m, 1H), 7-12-7.05 (m, 1H), 6.53 (d, $J = 11.5$ Hz, 1H), 6.15–6.10 (m, 1H), 5.72–5.66 (m, 2H), 5.49 (s, 1H), 4.87–4.81 (m, 1H), 2.23–2.14 (m, 1H), 2.06–1.99 (m, 1H), 1.24 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 150.95, 148.98, 133.36, 131.59, 125.47, 121.19, 117.90, 116.91, 97.97, 80.93, 63.19, 30.67, 26.36. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{17}H_{20}F_2O_3$: 333.1278; measured: 333.1318.

*(Z)-2-(3,4-Difluorostyryl)-2H-pyran-4(3H)-one (**Z-7j**)*

Light yellow liquid (6 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.38 (d, $J = 6.0$ Hz, 1H), 7.17–7.10 (m, 1H), 7.09–7.03 (m, 1H), 6.97–6.92 (m, 1H), 6.68 (d, $J = 11.5$ Hz, 1H), 5.85 (dd, $J = 11.5$, 9.0 Hz, 1H), 5.43 (dd, $J = 6.0$, 1.0 Hz, 1H), 5.21–5.14 (m, 1H), 2.74–2.66 (dd, $J = 17.0$, 13.0 Hz, 1H), 2.51 (dq, $J = 16.8$, 4.0, 3.5 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 191.14, 162.73, 151.18, 149.19, 133.29, 132.38, 128.29, 124.84, 117.55, 107.40, 75.20, 41.86. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{13}H_{10}F_2O_2$: 259.0547; measured: 259.0612.

*(Z)-6-(4-(Trifluoromethoxy)styryl)-5,6-dihydro-2H-pyran-2-one (**Z-1k**)*

Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.30 (d, $J = 8.5$ Hz, 2H), 7.19 (d, $J = 8.5$ Hz, 2H), 6.88–6.83 (m, 1H), 6.72 (d, $J = 11.5$ Hz, 1H), 6.06–6.02 (m, 1H), 5.85 (dd, $J = 11.5$, 9.0 Hz, 1H), 5.24–5.18 (m, 1H), 2.54–2.39 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 163.59, 148.83, 144.36, 134.26, 133.59, 130.10, 128.68, 121.71, 121.46, 120.98, 73.78, 29.28. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{14}H_{11}F_3O_3$: 285.0660; measured: 285.0733.

*(Z)-6-(Tert-butylperoxy)-2-(4-(trifluoromethoxy)styryl)-3,6-dihydro-2H-pyran (**Z-6k**)*

White powder (8 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.53 (d, $J = 8.5$ Hz, 2H), 7.20 (d, $J = 8.5$ Hz, 2H), 6.65 (d, $J = 11.5$ Hz, 1H), 6.18 (m, 1H), 5.76 (dd, $J = 11.5$, 9.0 Hz, 1H), 5.73 (m, 1H), 5.55 (s, 1H), 4.91 (m, 1H), 2.25 (m, 1H), 2.09 (m, 1H), 1.28 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 148.44, 135.09, 131.93, 131.67, 130.59, 121.52, 121.22, 120.68, 97.91, 80.71, 63.36, 30.68, 26.41. MS-TOF: *m/z* $[M+Na]^+$; Calculated for $C_{18}H_{21}F_3O_4$: 381.1290; measured: 381.1289.

*(Z)-2-(4-(Trifluoromethoxy)styryl)-2H-pyran-4(3H)-one (**Z-7k**)*

Light yellow liquid (5 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.42 (d, $J = 6.0$ Hz, 1H), 7.30 (d, $J = 8.5$ Hz, 2H) 7.24 (d, $J = 8.5$ Hz, 2H), 6.80 (d, $J = 11.5$ Hz, 1H), 5.92 (dd, $J = 11.5$, 9.0 Hz, 1H), 5.48 (dd, $J = 6.3$, 1.0, 0.5 Hz, 1H), 5.29–5.22 (m, 1H), 2.77 (dd, $J = 17.0$, 13.0 Hz, 1H), 2.56 (dq, $J = 19.5$, 6.5, 5.3, 3.8, 3.0, 1.0, 0.5 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 191.39, 162.91, 148.89, 134.09, 133.84, 130.03, 128.08, 121.44, 121.06, 107.34, 75.37, 39.28. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{14}H_{11}F_3O_3$: 285.0660; measured: 285.0734.

General procedure for the preparation of **10a–g**

In a stirrer suspension of sodium hydride (NaH) in dry THF at −40 °C was added Phosphonium salt **4** under nitrogen atmosphere, stirrer were continue for 30 min, a solution of aldehyde **9** (aldehyde **9** is unstable, conversion of alcohol to aldehyde was confirmed by ^{1}HNMR spectroscopy, which was showing δ at 9.58 ppm for aldehyde functionality) in dry THF (5 mL) was added drop wise. The reaction mixture was stirred for 6 h at the same temperature and was continued overnight at room temperature. Brine was added to the reaction mixture followed by addition of Et_2O. The ether layers were collected and aqueous layer were washed three time with ether, the combined organic phases were dried over anhydrous $MgSO_4$, evaporated, residue was subjected to flash chromatography on silica gel (EtOAc:*n*-hexane, 1:4, V/V) to afford *E-*/*Z*-isomer of **10**.

*(E)-5-Styryldihydrofuran-2(3H)-one (**E-10a**)*

Colorless powder (35 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, $J = 8.5$ Hz, 2H), 7.32 (t, $J = 7.5$ Hz, 2H), 7.28–2.26 (m, 1H), 6.67 (d, $J = 16.0$ Hz, 1H), 6.23 (dd,

J = 16.0, 6.5 Hz, 1H), 5.13–5.08 (m, 1H), 2.60–2.56 (m, 2H), 2.50–2.42 (m, 1H), 2.12–2.05 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.81, 135.68, 132.89, 128.71, 128.39, 126.72, 126.42, 80.63, 28.97, 28.53 ppm. MS-TOF: m/z $[M+H]^+$; Calculated for $C_{12}H_{13}O_2$: 189.09; measured: 189.09.

*(Z)-5-Styryldihydrofuran-2(3H)-one (**Z-10a**)*

Colorless powder (16 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (t, J = 7.5 Hz, 2H) ppm, 7. 34 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 11.5 Hz, 1H), 5.71 (dd, J = 11.5, 9.0 Hz, 1H), 5.31 (m, 1H), 2.69–2.53 (m, 2H), 2.51–2.44 (m, 1H), 2.25–2.15 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.85, 135.64, 134.81, 128.85, 128.69, 128.48, 127.92, 77.90, 28.75, 28.43 ppm. MS-TOF: m/z $[M+H]^+$; Calculated for $C_{12}H_{13}O_2$: 189.0916; measured: 189.0922.

*(E)-5-(2-(Naphthalen-2-yl)vinyl)dihydrofuran-2(3H)-one (**E-10b**)*

White solid (30 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 8.5 Hz, 3H), 7.74 (s, 1H), 7.57 (dd, J = 8.5 Hz, 1H), 7.50–7.42 (m, 2H), 6.83 (d, J = 16.0 Hz, 1H,), 6.31 (dd, J = 16.0, 6.5 Hz, 1H) 5.20–5.14 (m, 1H), 2.64–2.58 (m, 2H), 2.55–2.45 (m, 1H), 2.16–2.09 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.84, 133.48.133.32, 133.11, 133.01, 128.44, 128.11, 127.71, 127.18, 126.72, 126.48, 126.32, 123.36, 80.74, 28.94, 28.58 ppm. MS-TOF: m/z $[M+H]^+$; Calculated for $C_{16}H_{15}O_2$: 239.0994; measured: 239.1070.

*(Z)-5-(2-(Naphthalen-2-yl)vinyl)dihydrofuran-2(3H)-one (**Z-10b**)*

White solid (15 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 8.5 Hz, 3H), 7.71 (s, 1H), 7.48 (m, 2H), 7.37 (dd, J = 8.5, 2.5 Hz, 2H), 6.91 (d, J = 11.5 Hz, 1H,), 5.79 (dt, J = 11.5, 9.0 Hz, 1H) 5.40–4.31 (m, 1H), δ 2.65–2.50 (m, 2H), 2.50–2.40 (m, 1H), 2.12–2.04 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.89, 134.92, 133.16, 133.14, 132.75, 129.20, 128.15, 128.12, 127.81, 127.67, 126.50, 126.43, 76.84, 29.94, 28.98 ppm. MS-TOF: m/z $[M+H]^+$; Calculated for $C_{16}H_{15}O_2$: 239.0994; measured: 239.1088.

*(E)-5-(4-Iodostyryl)dihydrofuran-2(3H)-one (**E-10c**)*

White solid (21 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H), 6.62 (d, J = 16.0 Hz, 1H), 6.23 (dd, J = 16.0, 6.5 Hz, 1H), 5.17–5.12 (m, 1H), 2.66–2.61 (m, 2H), 2.55–2.48 (m, 1H), 2.16–2.07 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.65, 137.83, 135.20, 131.69, 128.40, 127.31, 93.85, 80.26, 28.75, 28.43 ppm. MS-TOF: m/z $[M+H]^+$; Calculated for $C_{12}H_{12}O_2$ I: 314.9837; measured: 314.9879.

*(Z)-5-(4-Iodostyryl)dihydrofuran-2(3H)-one (**Z-10c**)*

White powder (22 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.71 (d, J = 11.5 Hz, 1H), 5.77 (dd, J = 11.5, 9.0 Hz, 1H), 5.25–5.22 (m, 1H), 2.69–2.55 (m, 2H), 2.49–2.42 (m, 1H), 2.13–2.05 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.70, 137.66, 135.02, 133.90, 130.47, 129.58, 93.71, 76.38, 29.30, 28.88 ppm. MS-TOF: m/z $[M+H]^+$; Calculated for $C_{12}H_{12}O_2$ I: 314.9837; measured: 314.9880.

*(E)-5-(3-Fluorostyryl)dihydrofuran-2(3H)-one (**E-10d**)*

White solid (18 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (tdd, J = 7.8, 6.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.07 (dt, J = 10.0, 2.0 Hz, 1H), 6.96 (td, J = 8.5, 2.5 Hz, 1H), 6.64 (d, J = 15.8 Hz, 1H), 6.19 (dd, J = 15.8, 6.0 Hz, 1H), 5.10 (q, J = 6.0 Hz, 1H), 2.61–2.52 (m, 2H), 2.51–2.44 (m, 1H), 2.14–2.01 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.64, 164.06, 138.04, 131.55, 130.24, 127.84, 122.66, 115.30, 113.24, 80.13, 28.77, 28.41. MS-TOF: m/z $[M+H]^+$; Calculated for $C_{12}H_{12}O_2F$: 207.0777; measured: 207.0831.

*(Z)-5-(3-Fluorostyryl)dihydrofuran-2(3H)-one (**Z-10d**)*

White solid (16 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (tdd, J = 7.8, 6.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.99 (td, J = 10.0, 2.0 Hz, 1H), 6.94 (dt, J = 9.0, 2.0 Hz, 1H), 6.70 (d, J = 11.5 Hz, 1H), 6.75 (dd, J = 11.5, 9.0 Hz, 1H), 5.27–5.21 (m, 1H), 2.63–2.52 (m, 2H), 2.47–2.39 (m, 1H), 2.10–2.00 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.66, 163.06, 137.68, 133.54, 130.09, 130.02, 124.46, 115.59, 114.96, 76.34, 29.27, 28.86. MS-TOF: m/z $[M+H]^+$; Calculated for $C_{12}H_{12}O_2F$: 207.0777; measured: 207.0821.

*(E)-5-(3-Iodostyryl)dihydrofuran-2(3H)-one (**E-10e**)*

Colorless oil (18 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (t, J = 2.0 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.95 (t, J = 7.5 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.22 (dd, J = 16.0, 6.5 Hz, 1H), 5.13 (m, 1H),), 2.64–2.58 (m, 2H), 2.54–2.49 (m, 1H), 2.14–2.07 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.63, 137.90, 137.19, 135.53, 131.10, 130.35, 127.91, 126.01, 94.64, 80.11, 28.77, 28.40 ppm. MS-TOF: m/z $[M+H]^+$; Calculated for $C_{12}H_{12}O_2$ I: 314.9837; measured: 314.9888.

*(Z)-5-(3-Iodostyryl)dihydrofuran-2(3H)-one (**Z-10e**)*

White powder (20 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, $J = 8.0$ Hz, 1H), 7.62 (s, 1H), 7.27 (dd, $J = 8.0$, 2.5 Hz, 1H), 7.23 (t, $J = 8.0$ Hz, 1H), 6.69 (d, $J = 11.9$ Hz, 1H), 5.78 (dd, $J = 11.5$, 7.0 Hz, 1H), 5.25 (m, 1H),), 2.68–2.58 (m, 2H), 2.50–2.42 (m, 1H), 2.12–2.05 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.55, 137.74, 137.43, 136.89, 133.07, 130.16, 130.13, 127.82, 94.50, 76.26, 29.24, 28.82 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{12}H_{12}O_2$ I: 314.9837; measured: 314.9877.

*(E)-5-(4-Cyanostyryl)dihydrofuran-2(3H)-one (**E-10f**)*

White solid (28 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, $J = 8.5$ Hz, 2H), 7.45 (d, $J = 8.0$ Hz, 2H), 6.69 (d, $J = 16.0$ Hz, 1H), 5.31 (dd, $J = 16.0$, 6.0 Hz, 1H), 5.15–5.10 (m, 1H), 2.62–2.57 (m, 2H), 2.53–2.47 (m, 1H), 2.13–2.04 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.38, 140.13, 132.54, 130.61, 130.34, 127.19, 118.64, 111.72, 79.61, 28.65, 28.27 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{13}H_{12}O_2$ N: 214.0790; measured: 214.0877.

*(Z)-5-(4-Cyanostyryl)dihydrofuran-2(3H)-one (**Z-10f**)*

White solid (15 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, $J = 8.5$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 6.75 (d, $J = 11.5$ Hz, 1H), 5.85 (dd, $J = 11.5$, 9.5 Hz, 1H), 5.18–5.11 (m, 1H), 2.66–2.52 (m, 2H), 2.47–2.38 (m, 1H), 2.12–2.01 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.34, 140.11, 133.21, 132.29, 131.52, 129.35, 118.47, 111.76, 75.87, 29.18, 28.70 ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{13}H_{12}O_2$ N: 214.0790; measured: 214.0827.

*(E)-5-(4-Methylthiostyryl)dihydrofuran-2(3H)-one (**E-10g**)*

White solid (15 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, $J = 8.5$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 6.65 (d, $J = 15.5$ Hz, 1H), 6.18 (dd, $J = 15.5$, 6.5 Hz, 1H), 5.13 (q, $J = 7.0$ Hz, 1H),), 2.65–2.59 (m, 2H), 2.52–2.46 (m, 1H), 2.50 (s, $–SCH_3$, 3H), 2.16–2.08 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.78, 139.03, 132.50, 132.35, 127.11, 126.53, 125.71, 80.07, 28.90, 28.56, 15.64 ($–S–CH_3$) ppm. MS-TOF: *m/z* $[M+H]^+$; Calculated for $C_{13}H_{15}O_2$ S: 235.0793; measured: 235.0785.

*(Z)-5-(4-(Methylthiostyryl)dihydrofuran-2(3H)-one (**Z-10g**)*

White solid (30 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, $J = 8.5$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 6.61 (d, $J = 11.5$ Hz, 1H), 6.13 (dd, $J = 11.5$, 9.0 Hz, 1H), 5.08 (m, 1H),), 2.62–2.55 (m, 2H), 2.49–2.42 (m, 1H), 2.46 (s, $–SCH_3$, 3H) 2.12–2.035 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.79, 139.02, 132.50, 132.35, 127.10, 126.53, 125.72, 80.70, 28.89, 28.56, 15.64 ($–S–CH_3$) ppm. MS-TOF; *m/z* $[M+H]^+$; Calculated for $C_{13}H_{15}O_2$ S: 235.0748; measured: 235.0790.

Cytotoxicity assay

Each compound was tested in vitro against lymphoblastic leukemic T cell Jurkat E6.1 cell. Cells were prepared at 2×10^6 cells/mL. A twofold dilution of compound [100 mM stock in phosphate-buffered saline (PBS), penicillin/streptomycin] was prepared in a 96-well plate in a series of concentration from 0 to 200 μM (100 μL per well). Compounds were dissolved in dimethyl sulfoxide (DMSO), filter sterilized, diluted at the appropriate concentrations with the culture medium. In all wells, 1 % DMSO concentration was fixed. Dilutions of compounds were freshly prepared before each experiment. Then, 100 μL of 2×10^6 cells/mL was added to each well (final volume 200 μL of cells at 1×10^6 cells/mL treated with 0, 6.25, 12.5, 25, 50 and 100 μM compound). Cells were treated with the extracts for 48 h and cytotoxic effects were determined by 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-*2H*-tetrazolium bromide based colorimetric assay. This method depends on the cleavage of tetrazolium salt to purple formazan crystals by mitochondrial enzymes of metabolically active cells. After treatment incubation, 20 μL, 5 mg/mL MTT (in PBS) was added to each well in dark. Briefly, before the end of incubation period, medium of the cells was removed and wells were washed by pre-warmed PBS to remove any trace of compounds and to prevent color interference while optical density determination. MTT stock solution (5 mg/mL) were diluted to 1:10 ratio into complete culture media, 150 μL of MTT dilution were added into each well and incubated for 4 h at 37 °C. After 3.5 h, plates were centrifuged at 1800 rpm for 15 min at 37 °C to avoid accidental removal of formazan crystals. Crystals were dissolved with 100 μL DMSO. The absorbance was determined at 570 nm using microtiter plate reader. Results were represented as percentage of cell viability and calculated by the following formula.

$$\%\text{viability} = [(OD_S - OD_B/OD_C - OD_B) \times 100]$$

OD_B indicated the optical density of blank, OD_S indicated the optical density of sample and OD_C indicated the optical density of control. Assays were performed in triplicate on three independent experiments.

Conclusion

In conclusion, in contrast with the use of expensive reagents and/or many steps, we have applied a short and an efficient procedure for the synthesis of Goniothalamin analogs. Commercially available inexpensive 3,4-dihydro-*2H*-pyran-2-methanol/5-(hydroxymethyl)dihydrofuran-2(3*H*)-one were used as starting materials for the preparation of aldehydes. Easy accessible reagents/catalysts/solvents were used for the Wittig reaction. *E*/*Z*-isomers of the precursor of Goniothalamin were easily separated by flash column chromatography. A large number of Goniothalamin analogs have been synthesized and evaluated for their cytotoxicity against lymphoblastic leukemic T cell line (Jurkat E6.1), and *Z*-Goniothalamin and *Z*-(4-trifluoromethoxy)-Goniothalamin were found the most potent in cytotoxicity, whereas *Z*-(3-methoxy)-Goniothalamin and *Z*-(3,5-dimethoxy)-Goniothalamin showed excellent cytotoxicity, compare with natural (*E*)-(+)-Goniothalamin.

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References

Ahmad, F.B., W.A. Tukol, S. Omar, and A.M. Sharif. 1991. 5-Acetyl goniothalamin, a styryl dihydropyrone from *Goniothalamus uvaroides*. *Phytochemistry* 30(7): 2430–2431.

Ali, A.M., M.M. Mckeen, M. Hamid, Q.B. Aun, Y. Zauyah, H.L.P. Azimahtol, and K. Kawazu. 1997. Cytotoxicity and electron microscopy of cell death induced by goniothalamin. *Planta Medica* 63(01): 81–83.

Azimahtol Hawariah, L.P., M. Munawer, and L.B. Din. 1994. Antifertility effect of goniothalamin: A styrylpyrone isolated from *Goniothalamus tapis* miq. *Asia Pacific journal of pharmacology* 9(273–277): 273.

Azimahtol Hawariah, L.P., and J. Stanslas. 1998. Antagonistic effects of styrylpyrone derivative (spd) on 7, 12, dimethylbenzanthracene-induced rat mammary tumors. *In vivo* 12(4): 403–410.

Cao, S.-G., X.-H. Wu, K.-Y. Sim, B.K.H. Tan, J.T. Pereira, and S.-H. Goh. 1998. Styryl-lactone derivatives and alkaloids from *Goniothalamus borneensis* (Annonaceae). *Tetrahedron* 54(10): 2143–2148.

Cavalheiro, A.J., and M. Yoshida. 2000. 6-[ω-Arylalkenyl]-5,6-dihydro-α-pyrones from *Cryptocarya moschata* (Lauraceae). *Phytochemistry* 53(7): 811–819.

Chan, K.M., N.F. Rajab, M.H.A. Ishak, A.M. Ali, K. Yusoff, L.B. Din, and S.H. Inayat-Hussain. 2006. Goniothalamin induces apoptosis in vascular smooth muscle cells. *Chemico-Biological Interactions* 159(2): 129–140.

Chen, W.-Y., C.-C. Wu, Y.-H. Lan, F.-R. Chang, C.-M. Teng, and Y.-C. Wu. 2005. Goniothalamin induces cell cycle-specific apoptosis by modulating the redox status in MDA-MB-231 cells. *European Journal of Pharmacology* 522(1–3): 20–29.

Chidambaram, N., K. Satyanarayana, and S. Chandrasekaran. 1989. A general approach to the synthesis of 5,6-dihydro-2(2*H*)pyranones; simple synthesis of α-pyrone, (±)-argentilactone and (±)-goniothalamin. *Tetrahedron Letters* 30(18): 2429–2432.

Chien, A.L.T., and L.P. Azimahtol Hawariah. 2003. Styrylpyrone derivative induces apoptosis through the up-regulation of bax in the human breast cancer cell line MCF-7. *Journal of Biochemistry and Molecular Biology* 36: 269–274.

De Fátima, Â., L.K. Kohn, M.A. Antônio, J.E. De Carvalho, and R.A. Pilli. 2005. (*R*)-Goniothalamin: Total syntheses and cytotoxic activity against cancer cell lines. *Bioorganic & Medicinal Chemistry* 13(8): 2927–2933.

De Fátima, Â., L.K. Kohn, J.E. De Carvalho, and R.A. Pilli. 2006a. Cytotoxic activity of (*S*)-goniothalamin and analogues against human cancer cells. *Bioorganic & Medicinal Chemistry* 14(3): 622–631.

De Fátima, Â., L.V. Modolo, L.S. Conegero, R.A. Pilli, C.V. Ferreira, L.K. Kohn, and J.E. De Carvalho. 2006b. Styryl lactones and their derivatives: Biological activities, mechanisms of action and potential leads for drug design. *Current Medicinal Chemistry* 13(28): 3371–3384.

De Fátima, Â., and R.A. Pilli. 2003a. Enantioselective approach to the asymmetric synthesis of (6*R*)-hydroxymethyl-5,6-dihydro-2*H*-pyran-2-one. A formal synthesis of (*R*)-argentilactone and total synthesis of (*R*)-goniothalamin (RR-820CP). *Arkivoc* 2003(10): 118–126.

De Fátima, Â., and R.A. Pilli. 2003b. Total syntheses of (*R*)-argentilactone and (*R*)-goniothalamin via catalytic enantioselective allylation of aldehydes. *Tetrahedron Letters* 44(48): 8721–8724.

De Fátima, Â., W.F. Zambuzzi, L.V. Modolo, C.A.B. Tarsitano, F.R. Gadelha, S. Hyslop, J.E.D. Carvalho, I. Salgado, C.V. Ferreira, and R.A. Pilli. 2008. Cytotoxicity of goniothalamin enantiomers in renal cancer cells: Involvement of nitric oxide, apoptosis and autophagy. *Chemico-Biological Interactions* 176(2–3): 143–150.

Drewes, S.E., M.M. Horn, and R.S. Shaw. 1995. A-pyrones and their derivatives from two cryptocarya species. *Phytochemistry* 40(1): 321–323.

Du, H., J. Long, J. Hu, X. Li, and K. Ding. 2002. 3,3′-Br2-BINOL-Zn complex: A highly efficient catalyst for the enantioselective hetero-Diels–Alder reaction. *Organic Letters* 4(24): 4349–4352.

El-Sharkawy, S., Z. Yusuf, L.P. Azimahtol Hawariah, and A.M. Ali. 1996. Metabolism of goniothalamin in animal and microbial system. *Bollettino Chimico Farmaceutico* 135(1): 35–40.

El-Zayat, A.A.E., N.R. Ferrigni, T.G. Mccloud, A.T. Mckenzie, S.R. Byrn, J.M. Cassady, C.-J. Chang, and J.L. Mclaughlin. 1985. Goniothalenol: A novel, bioactive, tetrahydrofurano-2-pyrone from *Goniothalamus giganteus* (Annonaceae). *Tetrahedron Letters* 26(8): 955–956.

Fournier, L., P. Kocienski, and J.-M. Pons. 2004. The β-lactone route to α,β-unsaturated δ-lactones. Total syntheses of (±)-goniothalamin and (−)-massoialactone. *Tetrahedron* 60(7): 1659–1663.

Gillard, F., D. Heissler, and J.-J. Riehl. 1988. Synthesis of the 5,6-dihydro-2-pyrone moiety of (+)-anamarin. *Journal of the Chemical Society, Perkin Transactions* 10(8): 2291–2295.

Goh, S.H., G.C.L. Ee, C.H. Chuah, and C. Wei. 1995. Styrylpyrone derivatives from *Goniothalamus dolichocarpus*. *Australian Journal of Chemistry* 48(2): 199–205.

Grubbs, R.H. 2004. Olefin metathesis. *Tetrahedron* 60(34): 7117–7140.

Gruttadauria, M., P. Lo Meo, and R. Noto. 2004. Short and efficient chemoenzymatic synthesis of goniothalamin. *Tetrahedron Letters* 45(1): 83–85.

Harsh, P., and G.A. O'doherty. 2009. De novo asymmetric syntheses of (+)-goniothalamin, (+)-goniothalamin oxide, and 7,8-bis-epi-goniothalamin using asymmetric allylations. *Tetrahedron* 65(26): 5051–5055.

Hasan, C.M., M.A. Hussain, M.Y. Mia, and M.A. Rashid. 1995. Goniothalamin from *Goniothalamus sesquipedalis*. *Fitoterapia* 4: 378–379.

Hlubucek, J.R., and A.V. Robertson. 1967. (+)-(5*S*)-δ-Lactone of 5-hydroxy-7-phenylhepta-2,6-dienoic acid, a natural product from *Cryptocarya caloneura* (Scheff.) Kostermans. *Australian Journal of Chemistry* 20(10): 2199–2206.

Inayat-Hussain, S.H., B.O. Annuar, L.B. Din, A.M. Ali, and D. Ross. 2003. Loss of mitochondrial transmembrane potential and caspase-9 activation during apoptosis induced by the novel styryl-lactone goniothalamin in HL-60 leukemia cells. *Toxicology in Vitro* 17(4): 433–439.

Inayat-Hussain, S.H., K.M. Chan, N.F. Rajab, L.B. Din, S.C. Chow, A. Kizilors, F. Farzaneh, and G.T. Williams. 2010. Goniothalamin-induced oxidative stress, DNA damage and apoptosis via caspase-2 independent and Bcl-2 independent pathways in jurkat T-cells. *Toxicology Letters* 193(1): 108–114.

Inayat-Hussain, S.H., A.B. Osman, L.B. Din, A.M. Ali, R.T. Snowden, M. Macfarlane, and K. Cain. 1999. Caspases-3 and -7 are activated in goniothalamin-induced apoptosis in human jurkat T-cells. *FEBS Letters* 456(3): 379–383.

Inayat-Hussain, S.H., L.T. Wong, K.M. Chan, N.F. Rajab, L.B. Din, R. Harun, A. Kizilors, N. Saxena, M. Mourtada-Maarabouni, F. Farzaneh, and G.T. Williams. 2009. RACK-1 overexpression protects against goniothalamin-induced cell death. *Toxicology Letters* 191(2–3): 118–122.

Jagtap, P.G., Z. Chen, K. Koppetsch, E. Piro, P. Fronce, G.J. Southan, and K.-N. Klotz. 2009. Synthesis of (*R*)-3,4-dihydro-2*H*-pyran-2-carboxaldehyde: Application to the synthesis of potent adenosine A2A and A3 receptor agonist. *Tetrahedron Letters* 50(22): 2693–2696.

Jewers, K., J.B. Davis, J. Dougan, A.H. Manchanda, G. Blunden, A. Kyi, and S. Wetchapinan. 1972. Goniothalamin and its distribution in four goniothalamus species. *Phytochemistry* 11(6): 2025–2030.

Kabir, K.E., A.R. Khan, and M.A. Mosaddik. 2003. Goniothalamin—a potent mosquito larvicide from *Bryonopsis laciniosa* L. *Journal of Applied Entomology* 127(2): 112–115.

Lan, Y.-H., F.-R. Chang, J.-H. Yu, Y.-L. Yang, Y.-L. Chang, S.-J. Lee, and Y.-C. Wu. 2003. Cytotoxic styrylpyrones from *Goniothalamus amuyon* L. *Journal of Natural Products* 66(4): 487–490.

Lee, A.T., L.P. Azimahtol Hawariah, H.L. Azimahtol, and A.N. Tan. 2003. Styrylpyrone derivative (SPD) induces apoptosis in a caspase-7-dependent manner in the human breast cancer cell line MCF-7. *Cancer Cell International* 3: 1–8.

Leßmann, T., M.G. Leuenberger, S. Menninger, M. Lopez-Canet, O. Müller, S. Hümmer, J. Bormann, K. Korn, E. Fava, M. Zerial, Thomas U. Mayer, and H. Waldmann. 2007. Natural product-derived modulators of cell cycle progression and viral entry by enantioselective oxa Diels–Alder reactions on the solid phase. *Chemistry & Biology* 14(4): 443–451.

Meenakshii, N., A. Lee, H.L.P. Azimahtol, and S. Hasidah. 2000. Increased levels of apoptosis correlate with p53 protein accumulation in response to styrylpyrone derivative (SPD) treatment of the "Huggins Tumor". *Malaysian Applied Biology* 29(1 & 2): 121–126.

Mereyala, H.B., and M. Joe. 2001. Cytotoxic activity of styryl lactones and their derivatives. *Current Medicinal Chemistry—Anti-Cancer Agents* 1(3): 293–300.

Mondon, M., and J.-P. Gesson. 2006. Asymmetric synthesis of styryllactones. *Current Organic Synthesis* 3(1): 41–75.

Mosaddik, M.A., M. Ekramul Haque, and M. Abdur Rashid. 2000. Goniothalamin from *Bryonopsis laciniosa* linn (cucurbiataceae). *Biochemical Systematics and Ecology* 28(10): 1039–1040.

Mosaddik, M.A., and M.E. Haque. 2003. Cytotoxicity and antimicrobial activity of goniothalamin isolated from *Bryonopsis laciniosa*. *Phytotherapy Research* 17(10): 1155–1157.

Mu, Q., W.D. Tang, R.Y. Liu, C.M. Li, L.G. Lou, H.D. Sun, and C.Q. Hu. 2003. Constituents from the stems of *Goniothalamus griffithii*. *Planta Medica* 69(09): 826–830.

O'connor, B., and G. Just. 1986. Syntheses of argentilactone 11 and goniothalamin 15. *Tetrahedron Letters* 27(43): 5201–5202.

Pospíšil, J., and I.E. Markó. 2006. Total synthesis of (*R*)-(+)-goniothalamin and (*R*)-(+)-goniothalamin oxide: First application of the sulfoxide-modified Julia olefination in total synthesis. *Tetrahedron Letters* 47(33): 5933–5937.

Quitschalle, M., M. Christmann, U. Bhatt, and M. Kalesse. 2001. Synthesis of unsaturated lactone moieties by asymmetric hetero Diels–Alder reactions with binaphthol–titanium complexes. *Tetrahedron Letters* 42(7): 1263–1265.

Rajab, N.F., Z.A. Hamid, H. Hassan, A.M. Ali, L.B. Din, and S.H. Inayat-Hussain. 2005. Evaluation of the cytotoxic and genotoxic effects of goniothalamin in leukemic cell lines. *Environmental Mutagen Research* 27(3): 161–164.

Ram Reddy, M.V., H.C. Brown, and P.V. Ramachandran. 2001. Asymmetric allylboration for the synthesis of β-hydroxy-δ-lactone unit of statin drug analogs. *Journal of Organometallic Chemistry* 624(1–2): 239–243.

Ramachandran, P.V., M.V.R. Reddy, and H.C. Brown. 2000. Asymmetric synthesis of goniothalamin, hexadecanolide, massoia lactone, and parasorbic acid via sequential allylboration–esterification ring-closing metathesis reactions. *Tetrahedron Letters* 41(5): 583–586.

RodríGuez, J.G., R. Martín-Villamil, and A. Lafuente. 2003. Π-Extended conjugate phenylacetylenes Synthesis of 4-[(*E*) and (*Z*)-2-(4-ethenylphenyl)ethenyl]pyridine. Dimerization, quaternation and formation of charge–transfer complexes. *Tetrahedron* 59(7): 1021–1032.

Sabitha, G., K. Sudhakar, and J.S. Yadav. 2006. Application of the cosford cross-coupling protocol for the stereoselective synthesis of (*R*)-(+)-goniothalamin, (*R*)-(+)-kavain and (*S*)-(+)-7,8-dihydrokavain. *Tetrahedron Letters* 47(48): 8599–8602.

Sam, T.W., C. Sew-Yeu, S. Matsjeh, E.K. Gan, D. Razak, and A.L. Mohamed. 1987. Goniothalamin oxide: An embryotoxic compound from *Goniothalamus macrophyllus* (Annonaceae). *Tetrahedron Letters* 28(22): 2541–2544.

Schaus, S.E., J. Brånalt, and E.N. Jacobsen. 1998. Asymmetric hetero-Diels–Alder reactions catalyzed by chiral (salen)chromium(III) complexes. *The Journal of Organic Chemistry* 63(2): 403–405.

Schmidt, B. 2004. Ruthenium-catalyzed olefin metathesis double-bond isomerization sequence. *The Journal of Organic Chemistry* 69(22): 7672–7687.

Sun, B., J. Hoshino, K. Jermihov, L. Marler, J.M. Pezzuto, A.D. Mesecar, and M. Cushman. 2010. Design, synthesis, and biological evaluation of resveratrol analogues as aromatase and quinone reductase 2 inhibitors for chemoprevention of cancer. *Bioorganic & Medicinal Chemistry* 18(14): 5352–5366.

Sundby, E., L. Perk, T. Anthonsen, A. Jørgen Aasen, and T. Vidar Hansen. 2004. Synthesis of (+)-goniothalamin and its enantiomer by combination of lipase catalyzed resolution and alkene metathesis. *Tetrahedron* 60(3): 521–524.

Tanaka, S., S. Yoichi, L. Ao, M. Matumoto, K. Morimoto, N. Akimoto, G. Honda, M. Tabata, T. Oshima, T. Masuda, M. Zaini Bin Asmawi, Z. Ismail, S.M. Yusof, L.B. Din, and I.M. Said. 2001. Potential immunosuppressive and antiinflammatory activities of Malaysian medicinal plants characterized by reduced cell surface expression of cell adhesion molecules. *Phytotherapy Research* 15(8): 681–686.

Teoh, P.L., and L.P. Azimahtol Hawariah. 1999. Effects of styrylpyrne derivative (SPD) on expression of Bcl-2 and box genes in human ovarian carcinoma cell line, Caov-3. *Malaysian Applied Biology* 28(1 & 2): 107–111.

Wyatt, P., A. Hudson, J. Charmant, A.G. Orpen, and H. Phetmung. 2006. Synthesis and chemistry of enantiomerically pure 10,11-dihydrodibenzo[b,f]thiepines. *Organic & Biomolecular Chemistry* 4(11): 2218–2232.

Zauyah, Y., A.H. Lope Pihie, R.M. Noah, and J. Stanslas. 1997. Cytotoxicity of goniothalamin on hormone-dependent breast cancer cells. *Malaysian Journal of Biochemistry and Molecular Biology* 2: 29–32.

Zhang, W., and M.L. Go. 2007. Quinone reductase induction activity of methoxylated analogues of resveratrol. *European Journal of Medicinal Chemistry* 42(6): 841–850.

Zhou, F.S., W.D. Tang, Q. Mu, G.X. Yang, Y. Wang, G.L. Liang, and L.G. Lou. 2005. Semisynthesis and antitumor activities of new styryl-lactone derivatives. *Chemical & Pharmaceutical Bulletin* 53(11): 1387–1391.

Zhou, Z.-L., and J.F.W. Keana. 1999. A practical synthesis of 4-(substituted-benzyl)piperidines and (±)-3-(substituted-benzyl)pyrrolidines via a wittig reaction. *The Journal of Organic Chemistry* 64(10): 3763–3766.