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Multidimensional optimization of promising antitumor xanthone derivatives

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ABSTRACT

A promising antitumor xanthone derivative was optimized following a multidimensional approach that involved the synthesis of 17 analogues, the study of their lipophilicity and solubility, and the evaluation of their growth inhibitory activity on four human tumor cell lines. A new synthetic route for the hit xanthone derivative was also developed and applied for the synthesis of its analogues. Among the used cell lines, the HL-60 showed to be in general more sensitive to the compounds tested, with the most potent compound having a GI_{50} of 5.1 μM, lower than the hit compound. Lipophilicity was evaluated by the partition coefficient (K_p) of a solute between buffer and two membrane models, namely liposomes and micelles. The compounds showed a $\log K_p$ between 3 and 5 and the two membrane models showed a good correlation ($r^2 = 0.916$) between each other. Studies concerning relationship between solubility and structure were developed for the hit compound and 5 of its analogues.

1. Introduction

Xanthones (or xanthen-9-ones) constitute a class of O-heterocycles with a dibenzo-γ-pyrone scaffold commonly found as secondary metabolites in higher plants, fungi and lichens.[1] They can also be obtained by synthesis and several strategies to achieve this goal have been described in the literature.[2] The members of the xanthone classes bear different types of substituents that are able to interact with several biological targets exerting different pharmacological activities.[3] Indeed, the xanthone core is a rigid heteroaromatic tricyclic platform which may be considered as a 'privileged structure' since it can provide potent and selective ligands through modification of functional groups, allowing them to interact with different pharmacological targets.[4] The more frequent chemical groups found in natural and synthetic xanthones are hydroxyl, methoxyl, methyl, chloro, prenyl and carboxyl.[1–3] For synthetic xanthones, other substituents have also been introduced including aminoalkyl, aminoalcohol, azido and furanyl groups.[2,3]

Prenylated xanthones are the most abundant family of naturally occurring xanthones.[5,6] This family comprises compounds that include one or more isoprenic moieties which can be found as an open chain or cyclized to give a fused furan or pyran ring. More importantly, this family of compounds has been described to possess a great variety of biological activities, in particular they have been considered as promising antitumor agents.[5–8] Representative members of prenylated xanthones with potent antitumor activity are α-mangostin (**1**) and γ-mangostin (**2**) (Fig. 1) which have been isolated from the pericarp of the mangosteen fruit.[9] These compounds have previously been shown to exert a potent growth inhibitory activity towards several tumor cell lines,[10] being capable of inducing apoptosis in leukemia cell lines through a mechanism

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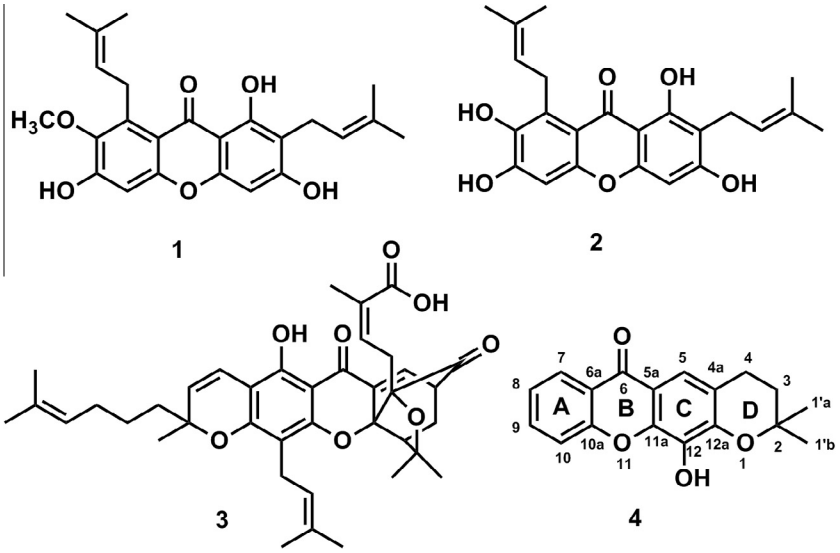


Figure 1. Prenylated xanthones with promising antitumor activity.

which involves activation of caspases-3 and -9.[11,12] Another well-known family of prenylated xanthones with promising antitumor activity are xanthones bearing a 4-oxo-tricyclo[4.3.1.0^{3,7}]dec-8-en-2-one, from which gambogic acid (**3**) is the most representative member of the so-called 'caged xanthones' (Fig. 1).[13]

In recent years, our research group has been synthesizing a small library of prenylated xanthones[14–18] and evaluating their biological activity in different cell lines. This approach was shown to be fruitful with many of the synthesized compounds presenting encouraging antitumor activity. Among them, compound **4** (12-hydroxy-2,2-dimethyl-3,4-dihydropyran[3,2*b*]xanthene-6(*2H*)-one—Fig. 1) was considered one of the most promising, exhibiting antiproliferative and pro-apoptotic activities in leukemia cell lines.[17] Interestingly, it also showed an enhancement of the anti-estrogenic effect of 4-hydroxytamoxifen in an estrogen-dependent (MCF-7) tumor cell line.[18] Therefore, this molecule has the potential to be optimized and may be used as the starting point in the search for more potent antitumor agents. To increase the likelihood of success, attention must also be paid to their pharmacokinetic behavior.[19] Consequently, it was decided to optimize this compound following a multidimensional approach looking, in parallel, at the activity and physicochemical properties, with the latter being used as a tool to predict the pharmacokinetic behavior.[20]

Compound **4** is composed of four fused rings that create a linear tetracyclic system. This structure has an unsubstituted ring A (Fig. 1) in which different groups can be introduced to increase the interactions with a putative target, and consequently, its potency. Furthermore, the introduction of substituents may also be used to improve the pharmacokinetics. The described methodology for the synthesis of compound **4** through a heterogeneous catalysis methodology has only been employed with relative success for the formation of a fused 2,2-dimethyl-3,4-dihydropyran ring in a few simple substituted xanthones,[16–18] flavonoids,[21] benzophenones[22] and phenols.[23] Moreover, low yields were generally obtained and in some cases no regioselectivity was observed. Furthermore, the scope and limitation of this reaction has not been thoroughly evaluated. In fact, for the synthesis of more complex molecules, this methodology is expected to show serious limitations. Therefore, in this paper the synthesis of compound **4** is reported by a new and more effective route and its application for the synthesis of 17 structural analogues. The targeted modifications envisaged the introduction of different functional groups on ring A and/or ring D orientation (Fig. 2). The newly synthesized analogues were evaluated for their in vitro growth inhibitory activity on four human tumor cell lines, namely MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), A375-C5 (melanoma) and HL-60 (acute myeloid leukemia).

In addition to the study of cell growth inhibitory activity, a preliminary estimation of the pharmacokinetic behavior of compound **4** analogues was made by evaluating their lipophilicity and solubility. Lipophilicity is one of the first physicochemical properties to be evaluated in the early phases of a drug discovery program[24] and has been correlated with several other physicochemical and pharmacokinetic properties, for example, solubility,[25] permeability,[26] plasma protein binding,[27] metabolism,[28] CNS penetration,[29] volume of distribution[25] and clearance.[28] Consequently, it may extensively influence the success of a drug discovery program. In fact, compounds with high lipophilicity have shown an increased risk of attrition during the clinical trials.[30] Lipophilicity is commonly evaluated by the partition coefficient of a solute in a biphasic octanol–water system which has some limitations since it fails to create the anisotropic media that is found on biomembranes and encode some important interactions that take place between the solute and the membranes.[31] Therefore, other models have been developed such as liposomes and micelles[32,33] which have proved to be advantageous when compared to octanol–water.[31] Consequently, it was decided to evaluate the lipophilicity on these two models. Solubility is emerging as one of the major issues in drug discovery and development of new chemical entities.[34] In fact, compounds with low solubility have a higher risk of attrition in the drug discovery pipeline as well as a higher cost during the drug development stage.[34] Therefore, the thermodynamic solubility in water at pH 7.4 (HEPES buffer) of compound **4** and five of its analogues (**36a–e**) was evaluated.

2. Results and discussion

2.1. Chemistry

2.1.1. Synthesis of building blocks

Pyranoxanthones are generally obtained by two classic strategies: Chemical modification of simple oxygenated xanthones or total synthesis using a benzopyran derivative as building block.[2,5,8] The former is more commonly used and was already applied for the synthesis of compound **4**.[18] However, the reaction used has some limitations and should not be applied for the synthesis of compound **4** analogues bearing substituents on ring A. As a result,

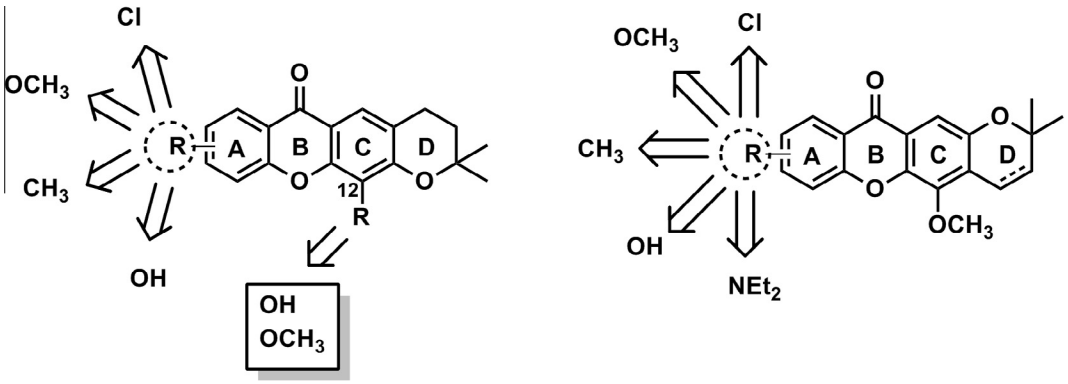


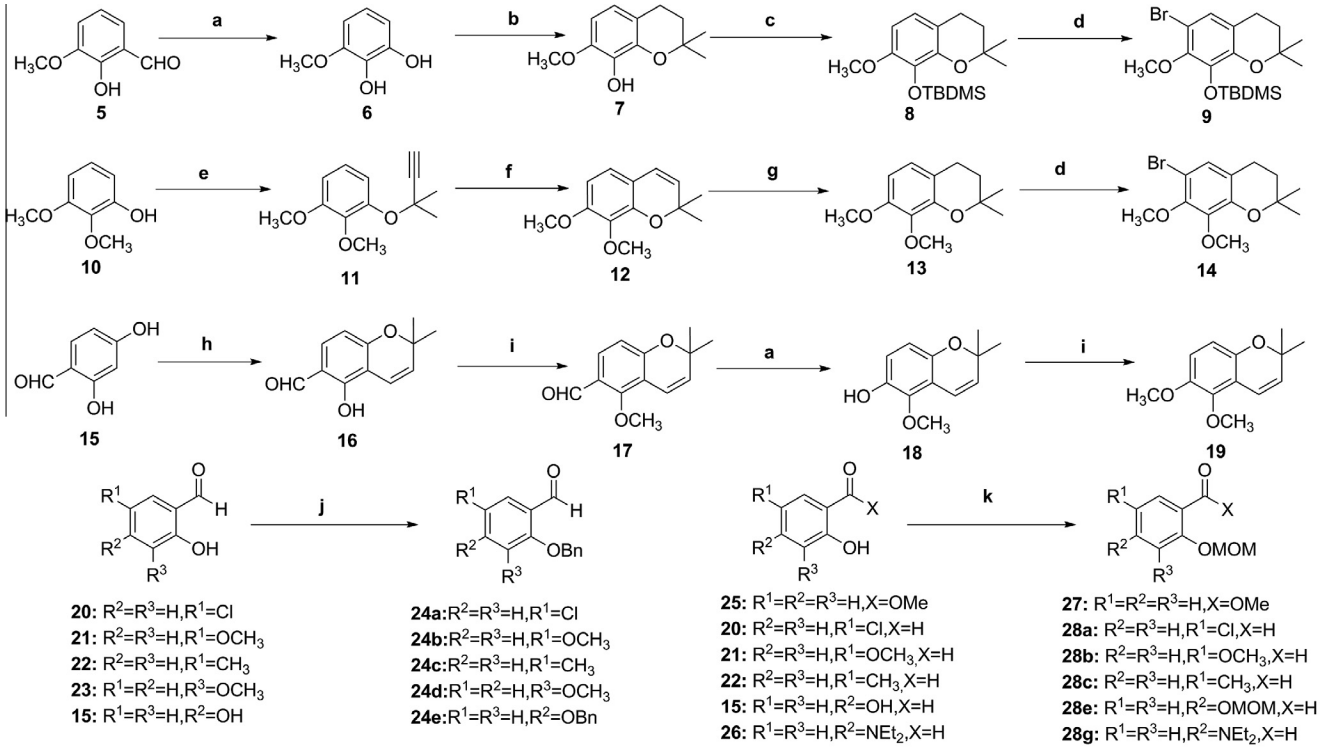
Figure 2. Targeted analogues of compound **4**.

a total synthesis approach was undertaken and the syntheses of the building blocks are represented on Scheme 1.

Benzopyran **9** was synthesized in four steps starting from *o*-vanillin (**5**). The first step was the oxidation of *o*-vanillin (**5**) to 3-methoxycatechol (**6**) using a Baeyer–Villiger-type oxidation. Formation of the benzopyran in one-step was accomplished by the reaction of 3-methoxycatechol (**6**) with a very reactive 1,1-dimethylallyl cation generated from 2-methyl-3-buten-2-ol and catalyzed by formic acid.[35] The next step was the protection of the hydroxyl with *tert*-butyldimethylsilyl (TBDMS) to yield compound **8** which was then brominated regioselectively using a NBS/NH_4OAc/CH_3CN protocol[36] to produce the desired compound **9**. Benzopyran **14** was synthesized in four steps from 2,3-dimethoxyphenol (**10**) (Scheme 1). The first part was the synthesis of the 2,2-dimethylbenzopyran moiety (**12**) which was accomplished through the cyclization of the appropriate aryl 1,1-dimethylpropargyl ether (**11**). The 2,2-dimethylbenzopyran **31** was then reduced by a transfer hydrogenation protocol[37] and brominated regioselectively to give compound **14**. Benzopyran **19** was synthesized in four steps using 2,4-dihydroxybenzaldehyde (**15**) as starting point (Scheme 1). The first step consisted of the regioselective condensation of 2,4-dihydroxybenzaldehyde (**15**) with prenal catalyzed by calcium hydroxide.[38] This compound was then O-methylated with dimethylsulfate, oxidized using a Baeyer–Villiger type oxidation and again O-methylated with dimethylsulfate to yield compound **19**. The O-protected MOM and benzyl salicylaldehydes or salicylates were either bought already protected or protected under the standard conditions (Scheme 1).

2.1.2. Synthesis of compound 4 and analogues 32, 36a–e, 41c, 41e and 41f

Scheme 2 represents the total synthesis of compound **4**. The first step involved the synthesis of the benzophenone **29** by condensation of the lithiated intermediate of compound **9** formed by



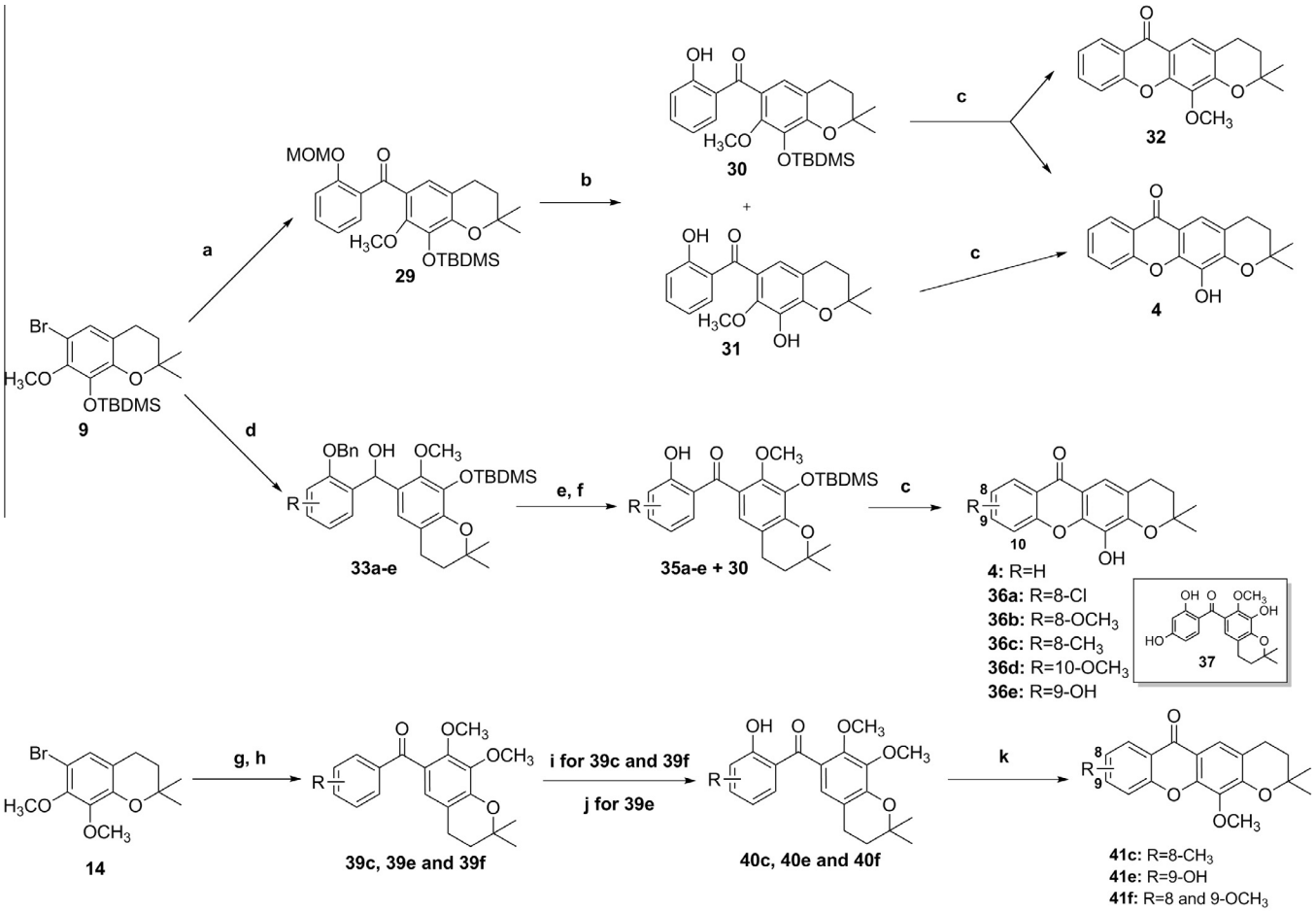
Reagents and conditions: **(a)** $KHSO_4$, H_2O_2, MeOH; **(b)** 2-methyl-3-buten-2-ol, HCOOH 80 %, 70 °C, 1h 30 min; **(c)** TBDMSCl, imidazole, DMF; **(d)** NBS, NH_4OAc, CH_3CN; **(e)** 1. 2-methyl-3-butyn-2-ol, DBU, TFAA, CH_3CN 2. **10,** DBU, $CuCl_2$, CH_3CN; **(f)** DMF, 145 °C; **(g)** Triethylsilane, Pd/C, MeOH; **(h)** Prenal, $Ca(OH)_2$, MeOH; **(i)** dimethyl sulfate, K_2CO_3, acetone; **(j)** benzyl bromide, K_2CO_3, acetone; **(k)** MOMCl, NaH, THF

Scheme 1. Synthesis of the benzopyrans **9**, **14** and **19**, O-protected salicylaldehydes and methyl salicylate.

halogen–lithium exchange and a MOM protected methyl salicylate (**27**). The MOM protective group was removed from benzophenone **29** with niobium chloride[39] which also removed the TBDMS group for part of the starting material to give benzophenones **30** and **31**. Lastly, the two benzophenones were cyclized to xanthone by an intramolecular nucleophilic aromatic substitution. The cyclization of benzophenone **31** produced compound **4** at an excellent (92%) yield while the cyclization of benzophone **30** gave rise to compound **4** and compound **32** with the formation of the latter probably being due to an unexpected methyl transfer triggered by the microwave heating and the cesium effect. In summary, compound **4** was synthesized in 7 steps at a 15% yield. The route was further applied for the synthesis of analogues bearing substituents on ring A (Scheme 2). The first step was the synthesis of the diarylmethanol derivatives **33a–e** which were then oxidized to benzophenones with IBX in DMSO and O-deprotected to give benzophenones **35a–e**. In the case of benzophenone **34a**, besides the expected compound **35a**, a hydrodechlorinated benzophenone (**30**) was also obtained. The hydrodehalogenation catalyzed by palladium on charcoal[40] has been described previously but to the best of our knowledge, no report exists in the literature of hydrodechlorination using Pd/C-triethylsilane as a transfer hydrogenation catalyst. The last step was the cyclization of benzophenones **35a–e** which led directly to the desired compounds **36a–e** and in the case of benzophenone **35e** also led to compound **37**. Compound **4** analogues bearing a methoxyl in position 12 and substituents on ring A were synthesized using the same approach described previously but instead using benzopyran **14** as building block (Scheme 2).

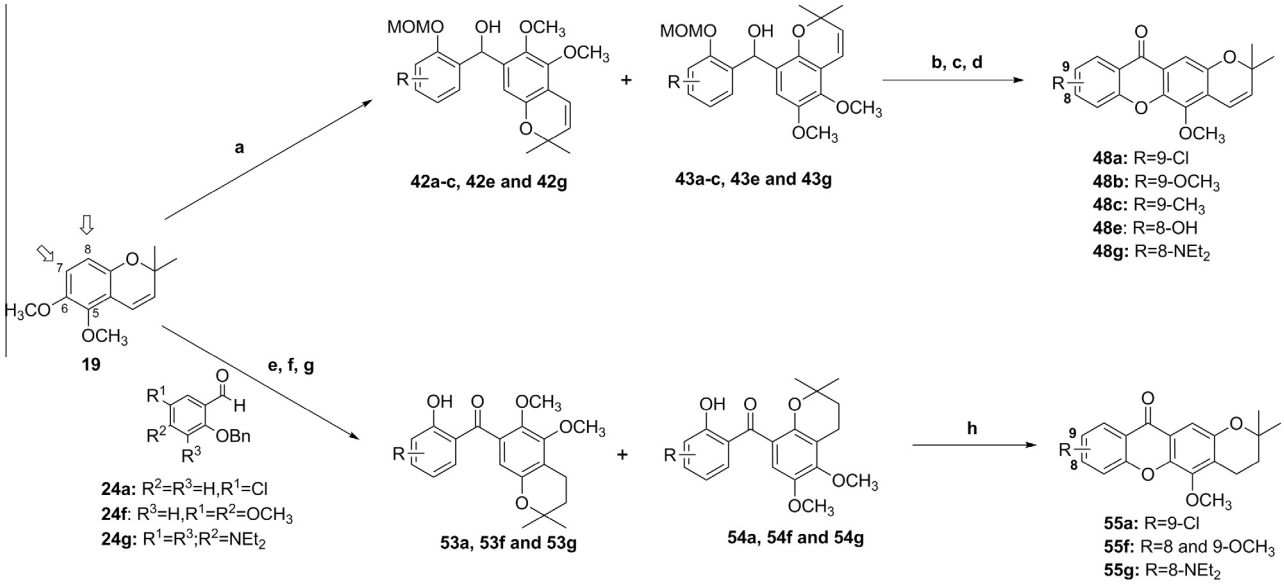
2.1.3. Synthesis of analogues 48a–c, 48e, 48g, 55a, 55f and 55g

The route for the synthesis of analogues of compound **4** with a different D ring orientation is represented in Scheme 3 and used benzopyran **19** and protected salicylaldehydes as building blocks. The *ortho*-lithiation of benzopyran **19** took place at positions 7 or 8 (highlighted in Scheme 3) since both positions are flanked by an oxygen and as a result two isomeric diaryl methanols were obtained. However, position 7 of the benzopyran **19** was favored for lithiation and diarylmethanols **42a–c**, **42e**, **42g**, **49a**, **49f** and **49g** were obtained at higher yields. This can be explained by lower steric hindrance at position 7 and the coordination effect of the two methoxyls in positions 5 and 6[41]. The two diarylmethanol isomers had a similar chromatographic behavior and were used as a mixture in the following reactions. The diarylmethanols were oxidized to benzophenones and O-deprotected. In the case of benzyl protected benzophenones, the double bond of the pyran ring was also reduced and benzophenones **53a** and **54a** also underwent hydrodehalogenation reaction. Lastly, the benzophenones with the appropriate pattern of substitution were cyclized to xanthones and separated easily from the remaining benzophenone.



Reagents and conditions: **(a)** 1. *n*BuLi, THF, -78 ºC 2. compound **27**, THF, -78 ºC to r.t.; **(b)** $NbCl_5$, CH_3CN; **(c)** Cs_2CO_3, MW, DMF; **(d)** 1. *n*BuLi, THF, -78 ºC 2. salicylaldehydes **24a-e**, THF, -78 ºC to r.t.; **(e)** IBX, DMSO to give **34a-e**; **(f)** **34a-e**, triethylsilane, Pd/C, MeOH; **(g)** 1. *n*BuLi, THF, -78 ºC 2. salicylaldehydes **24c**, **28e** and **24f**, THF, -78 ºC to r.t. to give **38c**, **38e** and **38f**; **(h)** **38c**, **38e** and **38f**, IBX, DMSO; **(i)** triethylsilane, Pd/C, MeOH; **(j)** $NbCl_5$, CH_3CN; **(k)** K_2CO_3, MW, DMF

Scheme 2. Synthesis of compound **4**, analogues **32, 36a–e**, **41c**, **41e** and **41f**.



Reagents and conditions: **(a)** 1. *n*BuLi, TMEDA, THF, 0 ºC 2. salicylaldehydes **28a-c**, **28e** and **28g**, THF; **(b) 42a-c**, **42e**, **42g**, **43a-c**, **43e** and **43g**, IBX, DMSO to give compounds **44a-c**, **44e**, **44g**, **45a-c**, **45e** and **45g**; **(c) 44a-c**, **44e**, **44g**, **45a-c**, **45e** and **45g,** $NbCl_5$, CH_3CN to give **46a-c**, **46e**, **46g**, **47a-c**, **47e** and **47g**; **(d) 46a-c**, Cs_2CO_3, DMF and **46e** and **46g,** K_2CO_3, MW, DMF; **(e)** 1. *n*BuLi, TMEDA 2. salicylaldehydes, THF to give **49a**, **49f**, **49g**, **50a**, **50f** and **50g**; **(f) 49a**, **49f**, **49g**, **50a**, **50f** and **50g**, IBX, DMSO to give compounds **51a**, **51f**, **51g**, **52a**, **52f** and **52g**; **(g) 51a**, **51f**, **51g**, **52a**, **52f** and **52g**, triethylsilane, Pd/C, MeOH to give **53a**, **53f**, **53g**, **54a**, **54f** and **54g**; **(d) 53a**, **53f**, **53g**, K_2CO_3, MW, DMF

Scheme 3. Synthesis of analogues **48a–c**, **48e**, **48g**, **55a**, **55f** and **55g**.

2.2. Biological activity

The effect of compound **4** and of its 17 analogues was evaluated in the growth of four human tumor cell lines. The cell lines used were MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), A375-C5 (melanoma) and HL-60 (acute myeloid leukemia). The drug-screening procedure used was the Sulforhodamine B (SRB) assay adopted from the National Cancer Institute (NCI, USA) which uses the protein-binding dye SRB to indirectly assess cell growth.[42,43] For all the cell lines, a dose–response curve was established for each compound studied and the concentration which caused a cell growth inhibition of 50% (GI_{50}) was determined.[44] The results obtained are summarized in Table 1.

By analyzing Table 1, it can be observed that some of the compounds studied were more active than compound **4** in the four tumor cell lines tested. Regarding the results obtained in the MCF-7 and NCI-H460 cell lines, the compound which presented higher activity (i.e., GI_{50} <20 μM) was the **55g**. In the A375-C5 cell line, the compounds that had a stronger growth inhibitory effect were the **36c** and the **55g**. Regarding the HL-60 cell line, compounds **32**, **36a**, **36c**, **41c**, **41e**, **48a**, **48e**, **48g** and **55g** presented a GI_{50} below 20 μM, with compounds **32**, **36a**, **41c**, **41e** and **48g** presenting a GI_{50} below 10 μM. In general, the synthesized compounds were more active towards the HL-60 tumor cell line. Therefore, the HL-60 cell line seems to be more sensitive to the effect of xanthones with a fused 2,2-dimethylpyran and 2,2-dimethyl-3,4-dihydropyran ring than the other cell lines tested.

The evaluation of the growth inhibitory activity on the four tumor cell lines allowed some assumptions to be made regarding structure–activity relationship of the compounds studied. In the case of the analogues of compound **4** with different substituents on ring A, it was observed that the presence of an electronegative substituent on position 8 (**36a** and **36b**) was associated with an increase in the effect in the HL-60 tumor cell line when compared to the other three cell lines studied. On the other hand, the presence of a methyl group in position 8 (**36c**) seems to have only a detrimental effect on the activity on the MCF-7 tumor cell line in comparison with the other tumor cell lines. The presence of a hydroxyl in position 9 (**36e**) or methoxyl in position 10 (**36d**) seemed to be associated with a general decrease in activity. Comparing compound **32** with compound **4**, the presence of a methoxyl instead of a hydroxyl in position 12 seemed to be associated with an increase in activity for the HL-60 tumor cell line in comparison with the other three cell lines tested. Moreover, for the compounds bearing a methoxyl in position 12, the introduction of a methyl in

Table 1
Growth inhibitory activity of the synthesized analogues in MCF-7, NCI-H460, A375-C5 and HL-60 cell lines

Compound	GI_{50} μM			
	MCF-7	NCI-H460	A375-C5	HL-60
4	39.7 ± 3.2	40.3 ± 3.3	28.9 ± 8.1	23.4 ± 1.1[a]
32	>150	>150	>150	8.8 ± 5.9
36a	>150	>150	>150	9.0 ± 1.1
36b	>150	>150	>150	23.9 ± 3.5
36c	>150	48.1 ± 13.6	17.6 ± 4.9	12.5 ± 3.2
36d	N.R.	41.1 ± 8.6	68.0 ± 4.5	27.3 ± 5.6
36e	82.5 ± 15.0	59.1 ± 14.1	40.7 ± 8.5	57.0 ± 6.8
41c	31.8 ± 5.4	30.9 ± 3.6	29.7 ± 4.7	5.14 ± 1.8
41e	>150	>150	>150	8.3 ± 2.7
41f	>100	>100	>100	72.3 ± 4.3
48a	>150	>150	>150	14.1 ± 1.4
48b	>150	>150	>150	N.R.
48c	>50	>50	>50	>50
48e	36.9 ± 4.7	34.9 ± 1.8	27.1 ± 1.7	18.8 ± 4.7
48g	34.3 ± 1.1	26.8 ± 1.6	21.9 ± 2.7	9.2 ± 4.9
55a	>75	>75	>75	48.4 ± 7.5
55f	>75	>75	>75	N.R.
55g	14.5 ± 1.0	13.7 ± 0.47	19.6 ± 4.7	14.4 ± 3.7

The values presented refer to mean ± SE of at least three independent experiments. The maximum DMSO concentration used was 0.25% for all compounds tested and did not interfere with cell growth (data not shown). Doxorubicin was used as a positive control (MCF-7: 65.4 ± 8.5 nM; NCI—H460: 64.1 ± 6.8 nM, A375-C5: 144.8 ± 9.8 nM and HL60: 28.0 ± 0.6 nM).
N.R.—non-reproducible.
[a] This compound has previously shown an IC_{50} of 6–7 μM in the HL-60 cell line and determined with the Trypan blue exclusion assay.[17]

position 8 (**41c**) or hydroxyl in position 9 (**41e**) seemed to be associated with a slight increase in the effect in the HL-60 cells and in the case of **41c** with moderate activity on the other three tumor cell lines also. Regarding the compounds bearing a different ring D orientation, the presence of an electron-donating group in position 8 of ring A (**48e**, **48g** and **55g**) seemed to be associated with a moderate to good growth inhibitory activity in the four tumor cell lines. Moreover, the presence of a 2,2-dimethyl-3,4-dihydropyran seemed to be associated with a higher growth inhibitory activity (comparing **48g** with **55g**). On the other hand, the presence of substituents on position 9 seemed to be detrimental although the presence of chlorine was associated with moderate activity for the HL-60 tumor cell line (**48a** and **55a**).

2.3. Physicochemical properties

2.3.1. Lipophilicity

The lipophilicity was determined as the partition coefficient (K_p) of the solute between buffer (pH 7.4) and micelles or liposomes, and calculated without a phase separation. The method used for the calculus considered the change in the UV–Vis spectrum produced by increasing concentrations of liposomes or micelles at constant solute concentration. This technique considers the change of an absorption parameter such as molar absorptivity (ε) or maximum wavelength (λ_{max}) of a solute when it permeates from the aqueous to a non-polar media. However, it is only possible to calculate the partition coefficient when there is a change of λ_{max} of 5–10 nm and $\varepsilon \geqslant 10\%$.[45] Moreover, in the case of liposomes, it is difficult to calculate the partition coefficient due to the light scattering at wavelengths below 300 nm which are not eliminated even with the counterbalance of the sample and reference. To overcome these limitations, it is necessary to use derivative spectrophotometry (in order of wavelength) which not only eliminates the light scattering but also leads to better resolution of overlapping bands.[45] Therefore, the K_p can be calculated using the following equation:[45]

$$D = D_w + \frac{(Dl - D_w)K_p[L]V\text{ø}}{1 + K_p[L]V\text{ø}}$$

where, [L] is the lipid concentration (mol L^{-1}), Dl the derivative of lipid absorbance, D_w the derivative of water absorbance, $V\varnothing$ the lipid molar volume (L mol^{-1}), K_p the partition coefficient (dimensionless) and:

$$D = \frac{\partial^n Abs}{\partial \lambda^n}$$

Accordingly, the partition coefficient could be calculated by fitting the derivative spectrometric data (D vs [L]) to the equation by a nonlinear regression method, with Dl and K_p being the adjustable parameters.[45]

The K_p in liposomes was determined for **4**, **32**, **36b**–**e**, **41c**, **41e**, **48c**, **55a**, **55f**, **55g** and for all compounds in micelles with the exception of compound **48g** which was obtained at low yields (Table 2). A procedure adapted from Magalhães et al.,[46] which used a 96-well plate methodology was followed and 1% of DMSO was added to each well to increase the solubility. The amount of DMSO was limited to 1% since higher concentrations could interfere with the partition between the two phases.[47] In order to calculate the K_p, several concentrations of lipid (with and without solute) needed to be prepared and a UV–Vis spectrum traced. The 96-well plate procedure made the determination of K_p quicker but could not be applied for the compounds which had a very low solubility and/or molar absorptivity (ε). In those cases, one at a time UV–Vis spectrum was traced for each in a conventional double-beam UV–Vis spectrophotometer. Contrary to micelles, liposomes have a high light scattering for wavelengths below 300 nm and even with a double-beam spectrophotometer we were unable to determine the K_p for **36a**, **41f**, **48a**, **48b** and **48e** which had both a low solubility and molar absorptivity.

Table 2
Partition coefficients in liposomes-buffer and micelle-buffer for compound **4** and16 of the analogues synthesized

Compound	$\text{Log}K_{\text{pliposomes}}$	$\text{Log}K_{\text{pmicelles}}$
4	3.35 ± 0.02	3.28 ± 0.02
32	3.60 ± 0.08	3.59 ± 0.06
36a	–	4.39 ± 0.12
36b	3.25 ± 0.08	3.35 ± 0.04
36c	3.86 ± 0.08	3.92 ± 0.01
36d	3.53 ± 0.04	3.58 ± 0.01
36e	3.32 ± 0.10	3.76 ± 0.07
41c	4.02 ± 0.03	4.01 ± 0.06
41e	3.43 ± 0.04	3.49 ± 0.06
41f	–	3.88 ± 0.03
48a	–	4.34 ± 0.04
48b	–	4.21 ± 0.04
48c	4.32 ± 0.06	4.29 ± 0.02
48e	–	3.90 ± 0.06
55a	4.48 ± 0.07	4.41 ± 0.03
55f	3.88 ± 0.08	3.83 ± 0.10
55g	4.62 ± 0.02	4.70 ± 0.04

Mean of three independent measurements.

Among the xanthones tested, **55g** was the most lipophilic and compound **4** and **36b** the less lipophilic. Considering the effect of ring A substituents on the K_p of compound **4**, it can be observed that chlorine (**36a**) and methyl (**36c**) were associated with an increase in K_p. In the case of the methoxyl, the introduction of this group in position 8 (**36b**) did not interfere with the K_p while the introduction in position 10 was associated with an increase of the K_p (**36d**). For the hydroxyl group (**36e**) an unexpected result was observed and no decrease in K_p was determined. In fact, for micelles, an increase in K_p was in fact observed. Considering the analogues of compound **4** with a methoxyl in position 12 (**32**), it can be observed that this substituent was associated with an increase in the K_p. In relation to the analogues with a different ring D orientation, it can be observed that most of the compounds had a K_p near or higher than 4 with the chlorine (**48a** and **55a**) and the diethylamine (**55g**) derivatives representing the compounds that showed a higher K_p.

For those compounds in which the partition coefficient was determined in the two models, the results obtained were compared using a linear regression analysis and the following Eq. 1 was established:

$$\begin{aligned}\text{Log}K_{\text{p liposomes}} &= -0.1614(\pm 0.382) \\ &\quad + 1.03(\pm 0.098)\text{Log}K_{\text{p micelles}}\ n \\ &= 12; r^2 = 0.916; s = 0.143; F = 109 \end{aligned} \quad (1)$$

wherein 95% confidence limits are in parentheses, n is the number of compounds, r^2 the squared correlation coefficient, s the standard deviation, and F Fisher's test. A good correlation between the two models was observed (r^2 = 0.916) and the slope of the equation is almost one (1.03), which implies that there is no clear tendency for this class of compounds to increase the affinity for either of the membrane models with an increase in hydrophobicity. The results obtained led to the observation that micelles can be used as a surrogate for liposomes for these compounds with the advantage of not having the light scattering limitation as well as a higher applicability and easier preparation.

2.3.2. Solubility

The solubility is the maximum amount of a compound that can remain in solution at a certain volume of solvent, temperature and pressure, under equilibrium conditions. The equilibrium is a result

of the net balancing of energy between the energy of the solvent and the solute interacting with themselves against the energy of solvent and solute interacting with each other.[48] The solubility of compound **4** and five ring A substituted analogues was determined by a thermodynamic assay at pH 7.4 (using HEPES as buffer) and the influence of chlorine, methoxyl, methyl and hydroxyl have on the solubility of compound **4** was evaluated.

The values of solubility for all compounds tested were low as can be depicted from Table 3. From the structure–solubility relationship for compounds **4** and **36a**–**e**, only for compound **36e** was an increase in the solubility observed when compared to **4**. The introduction of chlorine (**36a**), methyl (**36c**), and methoxyl (**36b** and **36c**) had an adverse effect on the solubility. However, the presence of a methoxyl in position 10 (compound **36d**) has a less detrimental effect on the solubility when compared to a methoxyl in position 8 (compound **36b**).

The solubility in water depends mainly on two factors: the crystallinity of the solute and its ability to interact with water and can be related to the lipophilicity and melting point.[49] Considering that compound **4** and their analogues are all linear tetracyclic systems with a high degree of planarity, this structural feature promotes high crystal packing and π–stacking interactions, corroborated by the high melting point observed for these compounds (higher than 200 °C). Moreover, all compounds showed a moderate to high lipophilicity and as a result, these structural features have a crucial impact on solubility and help to explain the low solubility found. Moreover, when compounds **36e** and **4** are compared, the introduction of a polar and ionizable hydroxyl group did not lead to a substantial increase in the solubility. This result can be explained by the increase in crystal packing caused by the phenolic group as verified by the high melting point (262–264 °C) determined for this compound.

3. Conclusion

In the present work, a new route, through a benzophenone intermediate was developed for the synthesis of compound **4** (12-hydroxy-2,2-dimethyl-3,4-dihydropyran[3,2*b*]xanthene-6(2*H*)-one). This route was further applied for the synthesis of 17 analogues bearing different substituents on ring A and different ring D orientation. Subsequently, the growth inhibitory activity of compound **4** analogues was evaluated in four human tumor cell lines, namely MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), A375-C5 (melanoma) and HL-60 (acute myeloid leukemia) and active compounds were found for all the cells lines tested. However, a higher growth inhibitory activity was generally observed for the HL-60 cells indicating that this compound may act through a mechanism/target which is of particular relevance for this cell line but not for the other cell lines tested. In addition, the results obtained in the cell lines allowed us to establish structure–activity relationship considerations for the compounds synthesized.

The lipophilicity of the 17 synthesized analogues of compound **4** was evaluated in two membrane models, namely liposomes and micelles, and all compounds showed a Log K_p higher than 3 and below 5. The two models showed a good correlation between each other and micelles could be used as a surrogate of liposomes for the determination of the partition coefficient for this type of compounds. The solubility was also evaluated for compound **4** and five analogues bearing substituents on ring A and all compounds showed a low solubility. This was explained by the high planarity and rigidity of these compounds as well as a moderate to high lipophilicity.

The scaffold of compound **4** seemed to be associated with a high potency for the HL-60 tumor cell line and a promising platform for the discovery of new antitumor compounds. The high rigidity and planarity could strongly influence the solubility. Nevertheless, this study provided an insight of the positions which seemed to be critical for activity as well as the positions where molecular modifications can be performed to decrease the lipophilicity and the planarity without significantly decreasing the activity.

Table 3
Solubility of compounds **4** and **36a**–**e**

Compound	Solubility (μM)
4	0.40 ± 0.1
36a	<0.1
36b	<0.1
36c	<0.1
36d	0.23 ± 0.02
36e	0.62 ± 0.1

Mean of three independent measurements.

4. Experimental

4.1. General methods

Microwave reactions were performed using a 100 mL closed Teflon reactor (internal reaction temperature measurement with a fiber-optic probe sensor) and were carried out using an Ethos MicroSYNTH 1600 Microwave Labstation from Milestone. Microwave reactions were also carried out on a CEM Discover BenchMate with 10-mL pressurized vials. Reactions were monitored by TLC and/or GC–MS. Melting points were obtained in a Köfler microscope and are uncorrected. IR spectra were measured on an ATI Mattson Genesis series FTIR (software: WinFirst v. 2.10) spectrophotometer in KBr microplates (cm^{-1}). ^1H and ^{13}C NMR spectra were taken in $CDCl_3$ or DMSO-d_6 at room temperature, on Bruker Avance 300 instruments and Bruker ARX-400. Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as an internal reference. ^1H NMR spectra were measured at 300.13 or 400.21 MHz and assignment abbreviations are the following: singlet (*s*), doublet (*d*), triplet (*t*), quartet (*q*), quintet (*qt*), multiplet (*m*), doublet of doublets (*dd*), double doublet of doublets (*ddd*), doublet of triplets (*dt*), triplet of doublets (*td*) and broad (*b*). ^{13}C NMR spectra were measured at 75.47 or 100.63 MHz. The EI-MS were recorded either in a Shimadzu GCMS-QP5000 or on a ThermoQuest Finnigan GC 2000 series/GCQ plus. Elemental analysis results were determined in an Analizador Elemental CarloErba 1108 at C.A.C.T.I., Vigo, Spain. HRMS spectra were recorded as ESI (electrospray ionization) mode either on an APEXQe FT-ICRMS (Bruker Daltonics), equipped with a 7T actively shielded magnet or VG Autoespec MicroTOF FOCUS (Bruker Daltonics) spectrometer at C.A.C.T.I.-University of Vigo, Spain. All reagents were purchased from Sigma Aldrich or Acros and all solvents were PA used without further purification. The anhydrous solvents were either purchased from Sigma–Aldrich or dried according to the published procedures.[50] Purifications of compounds were performed by column chromatography either by using Merck silica gel 60 (0.040–0.063 mm) (when it is referred to as flash chromatography) or using Merck silica gel 60 (0.2–0.5 mm) (when nothing is referred) or by preparative thin layer chromatography (TLC) using Merck silica gel 60 (GF_{254}) plates.

4.2. Synthesis of benzopyran 9

4.2.1. 3-Methoxycatechol (6)

o-Vanillin (**5**) (25 g/164 mmol) was solubilized in 600 mL of methanol and 22 mL of H_2O_2 30% was added. Then, $KHSO_4$ (3.3 g/24.6 mmol) was added quickly and the solution was allowed to stir at room temperature for 48 h. The reaction was quenched by the

addition 200 mL of distilled water and the methanol evaporated. The aqueous phase was extracted with 3 × 300 mL of diethyl ether. The organic phase was washed with 2 × 250 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (dichloromethane) obtaining 3-methoxycatechol (**6**) as an orange oil (20.96 g/91%)

3-Methoxycatechol (6). IR ν_{max} (cm^{-1}) (KBr): 3426, 2936, 1621, 1503, 1478, 1350, 1290, 1245, 1205, 1080, 765, 714. EIMS *m*/*z* (%): 141 (2, $[M+1]^+$), 140 (24, $[M]^+$), 125 (23), 110 (7), 107 (3), 97 (87), 79 (10), 77 (2), 68 (8), 65 (13), 63 (10), 53 (33), 52 (8), 51 (100).

4.2.2. 7-Methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-8-ol (7)

3-Methoxycatechol (**6**) (1.5 g/10.7 mmol) and 40 mL of an 80% formic acid solution were placed in a two necked round-bottom flask. The solution was heated to 80 °C and then 2-methyl-3-buten-2-ol was added dropwise (461 mg/5.35 mmol/560 μL) (over 10 min). The mixture was allowed to react for 1 h and 30 min and then cooled to room temperature. The solution was poured over 100 mL of distilled water and neutralized with a saturated solution of $NaHCO_3$ until pH 7–8. The aqueous phase was extracted with 3 × 100 mL of diethyl ether. The organic phase was washed with 2 × 100 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 9:1) and compound **7** was isolated as light orange oil (398 mg/36%).

7-Methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-8-ol (**7**). IR ν_{max} (cm^{-1}) (KBr): 3461, 2969, 2944, 2922, 2852, 2829, 1618, 1503, 1489, 1445, 1345, 1291, 1247, 1196, 1149, 1111, 1083, 962, 779, 642. ^{1}H NMR (300.13 MHz, $CDCl_3$): 6.56 (*dt*, *J* = 8.7, 0.9), 6.46 (*d*, *J* = 8.7), 3.87 (*s*, OCH_3), 2.74 (*td*, *J* = 6.7, 0.9, 2H), 1.81 (*t*, *J* = 6.7, 2 H), 1.38 (6H, *s*). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 145.3, 141.6, 134.1, 118.7, 114.5, 103.8, 75.1, 56.3, 32.9, 26.8, 21.7. EIMS *m*/*z* (%): 209 (17, $[M+1]^+$), 208 (100 $[M]^+$), 161 (15), 153 (84), 152 (17), 106 (16), 105 (27), 77 (26), 76 (23), 65 (17), 51 (18).

4.2.3. *tert*-Butyl((7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-8-yl)oxy)dimethylsilane (8)

Compound **7** (500 mg/2.4 mmol), imidazole (408.5 mg/6 mmol), and TBDMSCl (435 mg/2.9 mmol) were added to a round-bottom flask of 100 mL. The mixture was placed under nitrogen atmosphere and 5 mL of DMF anhydrous was added. The solution was allowed to react at 35 °C for 5 h. The solution was allowed to cool to room temperature and poured over 100 mL of distilled water and extracted with 3 × 50 mL of diethyl ether. The organic phase was washed with 2 × 50 mL of brine, dried over anhydrous sodium sulfate, filtered and the solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 95:5) and compound **8** was isolated as colorless oil in quantitative yield.

tert-Butyl((7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-8-yl)oxy)dimethylsilane (**8**). IR ν_{max} (cm^{-1}) (KBr): 2965, 2922, 2890, 2847, 1493, 1454, 1289, 1242, 1148, 1097, 1051, 865, 826, 773. ^{1}H NMR (300.13 MHz, $CDCl_3$): 6.60 (*d*, *J* = 8.4), 6.41 (*d*, *J* = 8.4), 3.76 (*s*, OCH_3), 2.72 (*t*, *J* = 6.7, 2H), 1.76 (*t*, *J* = 6.7, 2H), 1.34 (*s*, 6H), 1.04 (*s*, 9H), 0.16 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 150.0, 146.2, 133.7, 120.5, 114.6, 103.9, 74.1, 55.9, 32.9, 29.9, 25.9, 22.1, 18.7. EIMS *m*/*z* (%): 322 (3, $[M]^+$), 265 (10), 251 (2), 210 (17), 109 (100), 194 (16), 179 (2), 166 (7), 151 (3), 91 (2), 89 (3), 75 (6), 73 (3), 59 (2).

4.2.4. ((6-Bromo-7-methoxy-2,2-dimethyl-3,4-dihydro-8-yl)oxy)(*tert*-butyl)dimethylsilane (9)

Compound **8** (8.9 g/27.6 mmol), NH_4OAc (212 mg/2.76 mmol) and 200 mL of CH_3CN were placed in a two-necked round-bottom flask. The flask was placed at 0 °C and then NBS (5.16 g/28.9 mmol) was added in one portion. The mixture was allowed to stir for 15 min and warm to room temperature. The solution was partitioned between water and ethyl acetate. The aqueous phase was then extracted 2 × 250 mL of ethyl acetate. The organic phase was washed 2 × 250 mL with brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 99:1). Compound **9** was obtained as orange oil that solidified upon standing (10.68 g/96%).

((6-Bromo-7-methoxy-2,2-dimethyl-3,4-dihydro-8-yl)oxy)(*tert*-butyl)dimethylsilane (**9**). Mp: 41–43 °C. IR ν_{max} (cm^{-1}) (KBr): 2971, 2925, 2889, 2851, 1462, 1441, 1338, 1249, 1197, 1119, 1092, 1040, 996, 870, 831, 777. ^{1}H NMR (300.13 MHz, $CDCl_3$): 6.87 (*s*), 3.77 (*s*, OCH_3), 2.71 (*t*, *J* = 6.7, 2H), 1.75 (*t*, *J* = 6.7, 2H), 1.35 (*s*, 6H), 1.05 (*s*, 9H), 0.18 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 147.4, 146.0, 139.0, 124.2, 118.6, 106.6, 74.8, 60.2, 32.6, 26.8, 25.8, 22.1, 18.6. EIMS *m*/*z* (%): 402 (1, $[M+2]^+$), 401 (0.5, $[M+1]^+$), 400 (1, $[M]^+$), 289 (16), 288 (15), 287 (84), 174 (22), 272 (21), 265 (21), 264 (100), 249 (23),193 (36), 179 (23), 166 (23), 165 (83), 137 (34), 109 (19), 75 (56), 73 (45).

4.3. Synthesis of benzopyran 14

4.3.1. 2,4-Dimethoxy-1-((2-methylbut-3-yn-2-yl)oxy)benzene (11)

To a solution of 2-methyl-3-butyn-2-ol (4.71 g, 56 mmol) in 100 mL of anhydrous CH_3CN under nitrogen, cooled in a salt ice-bath (−5 °C) was added DBU (11.11 mL, 73 mmol) followed by trifluoroacetic anhydride dropwise (7.79 mL, 56 mmol). The reaction mixture was slowly warmed to 0 °C over 30 min. In another flask, 2,3-dimethoxyphenol (**10**) (7.5 g, 48.6 mmol) was dissolved in 100 mL of anhydrous CH_3CN and placed under nitrogen at −5 °C. To this solution was added DBU (9.62 mL, 63.2 mmol) followed by anhydrous $CuCl_2$ (6.5 mg, 0.0486 mmol, 0.1 mol %). To the later reaction mixture was added dropwise via canulla the ice-cold solution of the freshly prepared 1,1-dimethyl-2-propynyl trifluoroacetate in CH_3CN. The resulting reaction mixture was warmed to 0 °C and stirred for 7 h. The mixture was warmed to room temperature and concentrated to 100 mL. Then it was partitioned between 250 mL of distilled water and 250 mL of diethyl ether. The aqueous phase was extracted with 2 × 250 mL of diethyl ether. The organic phase was washed with 2 × 150 mL of a 5% of solution of HCl, with 2 × 150 mL of a solution of NaOH 1 M and with 1 × 150 mL of brine. The organic phase was dried over anhydrous sodium sulfate and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 9:1). Compound **11** was obtained as colorless oil (6.22 g/58%).

2,4-Dimethoxy-1-((2-methylbut-3-yn-2-yl)oxy)benzene (**11**). IR ν_{max} (cm^{-1}) (KBr): 3298, 3266, 2987, 2936, 2834, 2338, 2323, 1590, 1475, 1090, 740, 653. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.13 (*dd*, *J* = 8.3, 1.4), 6.98 (*t*, *J* = 8.2), 6.67 (*d*, *J* = 8.3, 1.4), 3.86 (*s*, OCH_3), 3.85 (*s*, OCH_3), 2.55 (*s*, 1H), 1.68 (*s*, 6H). EIMS *m*/*z* (%): 221 (8, $[M+1]^+$), 220 (19, $[M]^+$), 189 (15), 154 (100), 139 (50), 95 (21), 93 (32).

4.3.2. 7,8-Dimethoxy-2,2-dimethyl-2H-benzopyran (12)

Compound **11** (6.19 g/28.1 mmol) in anhydrous DMF (20 mL) was placed in a closed vessel. The mixture was heated 145 °C for 4 h. After cooling to room temperature, the mixture was poured into 150 g of crushed ice and extracted with 3 × 150 mL of diethyl ether. The organic phase was washed with 2 × 150 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash

chromatography (*n*-hexane/ethyl acetate 95:5). Compound **12** was obtained as colorless oil (4.11 g, 66%).

7,8-Dimethoxy-2,2-dimethyl-2H-benzopyran (**12**). IR ν_{max} (cm^{-1}) (KBr): 2973, 2934, 2933, 1605, 1496, 1455, 1098, 797, 646. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 6.69 (*d*, *J* = 8.4), 6.42 (*d*, *J* = 8.4), 6.28 (*d*, *J* = 9.8), 5.52 (*d*, *J* = 9.8), 3.87 (*s*, OCH_3), 3.85 (*s*, OCH_3), 1.48 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 153.5, 146.5, 137.5, 128.5, 122.1, 120.8, 116.3, 103.8, 76.4, 60.9, 56.0, 27.9. EIMS *m*/*z* (%): 221 (6, $[M+1]^+$), 220 (19, $[M]^+$), 205 (100), 190 (21), 161 (38), 144 (19), 91 (11).

4.3.3. 7,8-Dimethoxy-2,2-dimethyl-3,4-dihydropyran (13)

Compound **12** (2.65 g/12 mmol) and 2 mL of anhydrous methanol in nitrogen atmosphere were placed in a two-necked round-bottom flask. To the solution was added Pd/C 10% (15% weight/395 mg) in one portion. Triethylsilane (19.2 mL, 120 mmol) was then added dropwise. The mixture was allowed to stir for 15 min. The product was filtered over celite and washed 3 times with methanol. The methanol was evaporated and the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 9:1). Compound **13** was isolated as yellowish oil (2.65 g/99%).

7,8-Dimethoxy-2,2-dimethyl-3,4-dihydropyran (**13**). IR ν_{max} (cm^{-1}) (KBr): 2975, 2932, 2833, 1609, 1496, 1457, 1293, 1153, 1100, 1058, 955, 788. ^1H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 6.67 (*dt*, *J* = 8.3, 0.9), 6.37 (*d*, *J* = 8.3), 3.75 (*s*, 2×OCH_3), 2.66 (*td*, *J* = 6.7, 0.9, 2H), 1.71 (*t*, *J* = 6.7, 2H), 1.30 (*s*, 6H). EIMS *m*/*z* (%): 222 (6, $[M]^+$), 167 (100), 151 (17), 106 (12).

4.3.4. 6-Bromo-7,8-dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran (14)

Compound **13** (2.6 g/11.7 mmol), NBS (2.19 g/12.28 mmol), NH_4OAc (90 mg/1.17 mmol) and 100 mL of CH_3CN were placed in a two-necked round-bottom flask. The mixture was allowed to stir for 20 min at room temperature and then the CH_3CN was evaporated. The crude product was partitioned between water and ethyl acetate. The aqueous phase was then extracted 2 × 250 mL of ethyl acetate. The organic phase was washed 2 × 250 mL with brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 95:5). Compound **14** was isolated as colorless oil (3.4 g/96%).

6-Bromo-7,8-dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran (**14**). IR ν_{max} (cm^{-1}) (KBr): 2975, 2933, 1461, 1419, 1339, 1205, 1097, 1050, 851. ^1H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 7.01 (*t*, *J* = 1.0), 3.89 (*s*, OCH_3), 3.87 (*s*, OCH_3), 2.74 (*td*, *J* = 6.7, 1.0, 2H), 1.80 (*t*, *J* = 6.7, 2H), 1.39 (*s*, 6H). EIMS *m*/*z* (%): 302 (50, $[M+2]^+$), 300 (50, $[M]^+$), 247 (95), 245 (100), 231 (17), 229 (19).

4.4. Synthesis of benxopyran 19

4.4.1. 6-Formyl-5-hydroxy-2,2-dimethyl-2*H*-benzopyran (16)

2,4-Dihydroxybenzaldehyde (**15**) (3 g/20.17 mmol), calcium hydroxide (1.543 g/20.8 mmol) and 150 mL of methanol were place in a two-necked round-bottom flask. Then, prenal (9.135 g/108.6 mmol) was added dropwise. The mixture was allowed to stir at room temperature for 48 h. The reaction was quenched with HCl 1 M until pH 1–2. The methanol was evaporated and the aqueous phase was extracted with 3 × 150 mL of ethyl acetate. The organic phase was washed with 2 × 100 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 9:1). Compound **16** was crystallized from *n*-hexane/ethyl acetate 3:1 as a yellow solid (2.06 g/50%).

6-Formyl-5-hydroxy-2,2-dimethyl-2H-benzopyran (**16**). Mp: 68–69 °C. IR ν_{max} (cm^{-1}) (KBr): 3464, 2967, 2922, 2857, 1628, 1484, 1330, 1294, 1247, 1176, 1107, 1081, 748. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 11.65 (OH), 9.66 (*s*, CHO), 7.29 (*d*, *J* = 8.6), 6.88 (*d*, *J* = 10.0), 6.44 (*d*, *J* = 8.6), 5.61 (*d*, *J* = 10.0), 1.46 (*s*, 6H). EIMS *m*/*z* (%): 205 (5, $[M+1]^+$), 204 (10 $[M]^+$), 190 (15), 189 (100), 187 (60), 159 (12), 131 (12), 103 (10), 77 (12), 51 (6). HRMS (ESI) *m*/*z* calcd for $C_{12}H_{13}O_3$ $[M+H]^+$: 205.08570, found: 205.08592.

4.4.2. 6-Formyl-5-methoxy-2,2-dimethyl-2*H*-benzopyran (17)

Potassium carbonate (2.43 g/17.6 mmol) was placed in a round-bottom flask and under nitrogen atmosphere. Then, compound **16** (1.7976 g/8.8 mmol) solubilized in 20 mL of anhydrous acetone was added by syringe. Dimethyl sulfate (1.667/13.2 mmol) was added dropwise and the mixture was allowed to stir for 20 h at room temperature and under nitrogen atmosphere. The reaction was quenched by the addition of 20 mL of distilled water and the acetone was evaporated. The aqueous phase was acidified with HCl 1 N until pH 2–3 and extracted with 3 × 100 mL of ethyl acetate. The organic phase was washed with 2 × 50 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. Compound **17** was obtained in quantitative yield as yellow oil.

6-Formyl-5-methoxy-2,2-dimethyl-2H-benzopyran (**17**). IR ν_{max} (cm^{-1}) (KBr): 2974, 2932, 2840, 2747, 1679, 1634, 1463, 1370, 1281, 1249, 1213, 1158, 1110, 1068, 984, 736. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.18 (*s*, CHO), 7.66 (*d*, *J* = 8.6), 6.65 (*d*, *J* = 8.6), 6.60 (*dd*, *J* = 9, 9, 0.6), 5.70 (*d*, *J* = 9.9), 3.90 (*s*, OCH_3), 1.47 (*s*, 6H). EIMS *m*/*z* (%): 219 (5, $[M+1]^+$), 218 (10, $[M]^+$), 204 (18), 205 (100), 174 (10), 160 (60), 133 (16), 105 (5), 91 (8), 78 (10), 51 (6). HRMS (ESI) *m*/*z* calcd for $C_{13}H_{15}O_3$ $[M+H]^+$: 219.10177; found: 205.10157.

4.4.3. 6-Hydroxy-5-methoxy-2,2-dimethyl-2*H*-benzopyran (18)

Compound **17** (1.0139 g/4.64 mmol) was solubilized in 20 mL of methanol and H_2O_2 (540 μL of a solution of H_2O_2 30% in water). Then, $KHSO_4$ (94.7 mg/0.7 mmol) was added quickly and the solution was allowed to stir at room temperature for 8 h. The reaction was quenched by the addition 10 mL of distilled water and the methanol evaporated. The aqueous phase was extracted with 3 × 20 mL of dichloromethane. The organic phase was washed with 2 × 50 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 9:1). Compound **18** was isolated as orange oil (898 mg/4.36 mmol/94%).

6-Hydroxy-5-methoxy-2,2-dimethyl-2H-benzopyran (**18**). IR ν_{max} (cm^{-1}) (KBr): 3422, 3045, 2973, 2934, 2836, 1728, 1634, 1584, 1470, 1437, 1373, 1295, 1260, 1215, 1152, 1114, 960, 811, 731. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 6.72 (*d*, *J* = 8.6), 6.55 (*d*, *J* = 10), 6.50 (*d*, *J* = 8.6), 5.69 (*d*, *J* = 9.9), 5.15 (OH), 3.82 (*s*, OCH_3), 1.41 (*s*, 6H). EIMS *m*/*z* (%): 208 (5, $[M+2]^+$), 207 (15, $[M+1]^+$), 206 (60, $[M]^+$), 191 (100), 177 (50), 176 (30), 148 (18), 91 (10), 77 (5). HRMS (ESI) *m*/*z* calcd for $C_{12}H_{15}O_3$ $[M+H]^+$: 207.10139; found: 207.10157.

4.4.4. 5,6-Dimethoxy-2,2-dimethyl-2*H*-benzopyran (19)

Potassium carbonate (10.6 g/76.8 mmol) was placed in a round-bottom flask and under nitrogen atmosphere. Then, compound **18** (8 g/38.4 mmol) was solubilized in 100 mL of anhydrous acetone and added to the two necked round-bottom flask. Dimethyl sulfate (7.26 g/57.6 mmol) was added dropwise and the mixture was allowed to stir for 20 h at reflux and under nitrogen atmosphere. The reaction was quenched by the addition of 50 mL of distilled water and the acetone evaporated. The aqueous phase was acidified with HCl 1 N until pH 2–3 and extracted with 3 × 200 mL of ethyl ether. The organic phase was washed with 2 × 100 mL of brine, dried over sodium sulfate anhydrous, filtered and the organ-

ic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 95:5) obtaining compound **19** as light yellow oil (7.73 g/92%).

5,6-Dimethoxy-2,2-dimethyl-2H-benzopyran (**19**). IR ν_{max} (cm^{-1}) (KBr): 2974, 2932, 2831, 1576, 1474, 1215, 1063, 797. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 6.69 (*d*, *J* = 8.8), 6.65 (*d*, *J* = 9.9), 6.51 (*d*, *J* = 8.8), 5.66 (*d*, *J* = 9.9), 3.84 (*s*, OCH_3), 3.82 (*s*, OCH_3), 1.41 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 147.0, 146.7, 131.4, 131.3, 117.1, 112.7, 112.6, 111.0, 75.4, 61.3, 55.5, 27.5. EIMS *m*/*z* (%): 221 (22, $[M+1]^+$), 220 (65, $[M]^+$), 205 (100), 190 (34), 161 (34), 144 (9), 91 (14), 77 (5).

4.5. Protection of substituted salicylaldehydes with benzyl group

In a typical experiment: 5-chlorosalicylaldehyde (**20**) (1.0 g/6.4 mmol) was placed in a two-necked round-bottom flask and then it was added Cs_2CO_3 (3.13 g/9.6 mmol), benzyl bromide (1.64 g/9.6 mmol) and 50 mL of acetone. The mixture was allowed to stir at room temperature overnight. The product was then filtered and washed with acetone. The solvent was evaporated and the crude product purified by column chromatography (silica gel, *n*-hexane/ethyl acetate 95:5). Compound **24a** was obtained as white solid (1.42 g/90%).

2-(Benzyloxy)-5-chlorobenzaldehyde (**24a**) as white solid (90%). Mp: 77–78 °C. IR ν_{max} (cm^{-1}) (KBr): 2867, 2757, 1678, 1590, 1451, 1383, 1266, 1174, 1123, 1019, 819, 733, 676. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.44 (*s*, CHO), 7.75 (*d*, *J* = 2.8), 7.43–7.3 (6H, *m*), 6.97 (*d*, *J* = 8.7), 5.13 (*s*, 2H). EIMS *m*/*z* (%): 248 (0.4, $[M+2]^+$), 246 (1.5, $[M]^+$), 155 (27), 92 (11), 91 (100), 65 (34), 63 (16).

2-(Benzyloxy)-5-methoxybenzaldehyde (**24b**) as a white solid in quantitative yield. Mp: 45–47 °C. IR ν_{max} (cm^{-1}) (KBr): 2915, 2849, 1669, 1481, 1443, 1410, 1372, 1260, 1197, 1143, 1025, 1006, 719, 677, 540. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.50 (*s*, CHO), 7.42–7.33 (*m*, 5H), 7.31 (*d*, *J* = 3.1), 7.09 (*dd*, *J* = 9.1, 3.1), 6.98 (*d*, *J* = 9.1), 5.11 (*s*, 2H), 3.76 (*s*, OCH_3). EIMS *m*/*z* (%): 242 (0.8, $[M]^+$), 214 (2), 213 (2), 151 (2), 150 (2), 95 (2), 92 (10), 91 (100), 89 (2), 77 (1), 65 (28), 53 (3), 52 (3), 51 (40).

2-(Benzyloxy)-5-methylsalicylaldehyde (**24c**). Mp: 55–56 °C. IR ν_{max} (cm^{-1}) (KBr): 2919, 2864, 2760, 1677, 1606, 1490, 1453, 1381, 1280, 1244, 1154, 1110, 1025, 817, 733, 721, 686, 647. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.52 (*s*, CHO), 7.67 (*d*, *J* = 2.7), 7.43–7.28 (*m*, 6H), 6.92 (*d*, *J* = 8.5), 5.12 (*s*, 2H), 2.28 (*s*, 3H). EIMS *m*/*z* (%): 226 (2.5, $[M]^+$), 198 (4), 197 (7), 135 (9), 92 (8), 91 (100), 65 (14), 51 (4).

2-(Benzyloxy)-3-methoxybenzaldehyde (**24d**). IR ν_{max} (cm^{-1}) (KBr): 3086, 3060, 2959, 2938, 1896, 1874, 2837, 1690, 1582, 1479, 1454, 1439, 1367, 1309, 1268, 1248, 1217, 1184, 100, 1060, 963, 909, 780, 752, 696. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.23 (*s*, CHO), 7.40–7.32 (6H, *m*), 7.20–710 (2H, *m*), 5.18 (*s*, 2H), 3.94 (*s*, OCH_3). EIMS *m*/*z* (%): 242 (3, $[M]^+$), 214 (8), 213 (25), 181 (5), 151 (8), 122 (6), 92 (11), 91 (100), 77 (4), 65 (39), 63 (10), 51 (16).

2,4-Bis(benzyloxy)benzaldehyde (**24e**) as a light yellow solid in quantitative yield. Mp: 75–77 °C. IR ν_{max} (cm^{-1}) (KBr): 2949, 2925, 2846, 1664, 1601, 1452, 1381, 1324, 1178, 1094, 1008, 827, 721, 691. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.38 (*s*, CHO), 7.84 (*d*, *J* = 8.6), 7.42–7.35 (10H, *m*), 6.63 (*dd*, *J* = 8.6, 2.2), 6.59 (*d*, *J* = 2.2), 5.13 (*s*, 2H), 5.10 (*s*, 2H). EIMS *m*/*z* (%): 318 (0.5, $[M]^+$), 298 (0.7), 199 (6), 181 (3), 92 (9), 91 (100), 65 (29), 63 (6), 51 (3).

4.6. Protection of methyl salicylate and substituted salicylaldehydes with MOM group

In a typical experiment: sodium hydride (3.63 g/90.53 mmol of 60% sodium hydride in mineral oil) was placed in two-necked round bottom flask and washed with anhydrous *n*-hexane. The flask was then placed under nitrogen atmosphere and on an ice-bath. Methyl salicylate (**25**) (6.88 g/45.26 mmol) was solubilized in 60 mL of anhydrous THF and added slowly to the flask containing the sodium hydride. The mixture was allowed to stir for 15 min and MOMCl (7.288 g/90.53 mmol) was added dropwise and the flask placed under reflux for 16 h. The mixture was cooled to room temperature and poured over 100 g of crushed ice. The aqueous phase was extracted with 3 × 150 mL of ethyl acetate. The organic phase was washed with 2 × 100 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 95:5). Compound **27** was obtained as colourless oil (8.1522 g/92%).

Methyl 2-(methoxymethoxy)benzoate (**27**). IR: ν_{max} (cm^{-1}) (KBr): 2991, 2947, 2903, 2825, 1725, 1596, 1485, 1449, 1432, 1296, 1249, 1150, 1128, 1073, 984, 755. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.78 (*dd*, *J* = 7.8, 1.8), 7.44 (*ddd*, *J* = 8.4, 7.5, 1.8), 7.20 (*dd*, *J* = 8.4, 0.9), 7.05 (*ddd*, *J* = 7.8, 7.5, 0.9), 5.26 (*s*, 2H), 3.89 (*s*, OCH_3), 3.52 (*s*, OCH_3). EIMS *m*/*z* (%): 197 (16, $[M]^+$), 165 (100), 135 (26), 92 (45), 63 (34).

5-Chloro-2-(methoxymethoxy)benzaldehyde (**28a**) as a colorless oil (88%). IR ν_{max} (cm^{-1}) (KBr): 2922, 2852, 1667, 1628, 1472 1127, 866. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.43 (*s*, CHO), 7.80 (*d*, *J* = 2.8), 7.47 (*dd*, *J* = 9.0, 2.8), 7.20 (*d*, *J* = 9.0), 5.29 (*s*, 2H), 3.52 (*s*, OCH_3). EIMS *m*/*z* (%): 202 (10, $[M+2]^+$), 200 (30, $[M]^+$), 170 (16), 169 (30), 155 (35), 99 (16), 77 (30), 75 (82), 63 (100).

5-Methoxy-2-(methoxymethoxy)benzaldehyde (**28b**) as a colorless oil (78%). IR ν_{max} (cm^{-1}) (KBr): 2927, 2879 1666, 1627, 1490. 813. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.47 (*s*, CHO), 7.33 (*d*, *J* = 3.2), 7.18 (*dd*, *J* = 9.1), 7.11 (*dd*, *J* = 9.0, 3.2), 5.24 (*s*, 2H), 3.81 (*s*, OCH_3), 3.52 (*s*, OCH_3). EIMS *m*/*z* (%): 197 (18, $[M+1]^+$), 196 (100, $[M]^+$), 165 (52), 150 (98), 120 (25), 95 (36), 65 (38), 63 (58).

2-(Methoxymethoxy)-5-methylbenzaldehyde (**28c**) colorless oil (88%). IR ν_{max} (cm^{-1}) (KBr): 2925, 2853, 2790, 2665, 1627, 1450, 1386, 666. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.48 (*s*, CHO), 7.64 (*d*, *J* = 2.5), 7.34 (*dd*, *J* = 8.5, 2.5), 7.12 (*d*, *J* = 8.5), 5.27 (*s*, 2H), 3.52 (*s*, OCH_3), 2.32 (*s*, CH_3). EIMS *m*/*z* (%): 181 (10, $[M+1]^+$), 180 (34, $[M]^+$), 151 (20), 149 (45), 135 (100), 91 (44), 77 (55), 65 (25), 51 (56).

2,4-Bis(methoxymethoxy)benzaldehyde (**28e**) as white solid (56%). Mp: 44–45 °C. IR ν_{max} (cm^{-1}) (KBr): 3003, 2989, 2959, 2904, 1679, 1601, 1255, 1155, 999, 921. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.34 (*s*, CHO), 7.80 (*d*, *J* = 8.7), 6.83 (*d*, *J* = 2.2), 6.74 (*dd*, *J* = 8.7, 2.2), 5.28 (*s*, 2H), 5.22 (*s*, 2H), 3.53 (*s*, OCH_3), 3.49 (*s*, OCH_3). EIMS *m*/*z* (%): 227 (10, $[M+1]^+$), 226 (15, $[M]^+$), 181 (28), 165 (35), 151 (22), 136 (40), 77 (23), 63 (100).

4-(Diethylamino)-2-(methoxymethoxy)benzaldehyde (**28g**) as yellow oil (71%). IR ν_{max} (cm^{-1}) (KBr): 2916, 2770, 1667, 1598, 1267, 1267, 990, 798. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.17 (*s*, CHO), 7.74 (*d*, *J* = 9.4), 6.39–6.37 (*m*, 2H), 5.27 (*s*, 2H), 3.52 (*s*, OCH_3), 3.45–3.38 (*m*, 4H), 1.21 (*t*, *J* = 7.1, 6H). EIMS *m*/*z* (%): 238 (10, $[M+1]^+$), 237 (25, $[M]^+$), 222 (56), 192 (20), 178 (45), 176 (56), 162 (100), 148 (24), 134 (30), 122 (10), 77 (20), 65 (20).

4.7. Synthesis of compound 4

4.7.1. (8-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2-(methoxymethoxy) phenyl)methanone (29)

Compound **9** (1.5 g/3.74 mmol) was placed in an oven-dried three-necked round-bottom flask and solubilized in 50 mL of anhydrous THF. The mixture was then placed at −78 °C and *n*BuLi (1.6 M, 5.6 mmol) was added dropwise. The mixture was allowed

to react for 15 min at −78 °C. Then compound **27** (1.5 g/7.5 mmol) solubilized in anhydrous THF at −78 °C was added dropwise and allowed to react for 15 min at −78 °C and slowly warm to room temperature. The reaction was quenched by the addition of a saturated solution of NH_4Cl, extracted with 3 × 100 mL of ethyl acetate. The organic phase was washed 2 × 100 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2).Compound **29** was obtained as a white solid (1.25 g/68%).

(8-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2-(methoxymethoxy)phenyl)methanone (**29**). Mp: 83–84 °C. IR ν_{max} (cm^{-1}) (KBr): 2963, 2925, 2852, 1662, 1595, 1465, 1349, 1252, 1232, 1201, 1150, 1116, 1099, 1074, 994, 834, 770. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.40 (*dd*, *J* = 8.0, 1.7), 7.38 (*ddd*, *J* = 8.8, 7.5, 1.7), 7.14 (*dd*, *J* = 0.8, 8.8), 7.04 (*ddd*, *J* = 8.0, 7.5, 0.8), 7.00 (*s*), 5.05 (*s*, 2H), 3.51 (*s*, OCH_3), 3.33 (*s*, OCH_3), 2.72 (*t*, *J* = 6.6, 2H), 1.78 (*t*, *J* = 6.6, 2H), 1.38 (*s*, 6H), 1.03 (*s*, 9H), 0.17 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 195.0, 155.1, 150.4, 150.4, 137.8, 131.4, 129.3, 125.5, 123.8, 121.6, 121.3, 116.6, 114.9, 95.0, 75.6, 60.8, 55.9, 32.7, 26.9, 25.8, 22.1, 18.6. EIMS *m*/*z* (%): 486 (1, $[M]^+$), 383 (9), 309 (17), 298 (10), 297 (34), 277 (12), 264 (21), 263 (100), 253 (15), 245 (12), 223 (16), 165 (20), 121 (18), 75 (23), 73 (10).

4.7.2. (8-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2-hydroxyphenyl) methanone (30) and (8-hydroxy-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2-hydroxyphenyl)methanone (31)

To a solution of compound **29** (1.12 g, 2.3 mmol) in 30 mL of CH_3CN at 0 °C was added in one portion $NbCl_5$ (684 mg, 2.53 mmol). The mixture was stirred at 0 °C for 10 min and then allowed to warm to room temperature and let stirring for more 45 min. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$. The mixture was extracted with 3 × 100 mL of ethyl acetate. The organic phase was washed with 2 × 100 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 95:5). Compound **30** (390 mg/33%) was isolated as colorless oil and compound **31** (498 mg/67%) as a white solid

(8-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2-hydroxyphenyl)methanone (**30**). IR ν (cm^{-1}) (KBr): 3443, 2970, 2925, 2851, 1622, 1460, 1354, 1236, 1203, 1147, 1114, 1071, 830, 753. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 12.27 (OH), 7.48–7.43 (*m*, 2H), 7.02 (*dd*, *J* = 8.8, 1.2), 6.81 (*dd*, *J* = 8.2, 1.1), 6.69 (*s*), 3.69 (*s*, OCH_3), 2.75 (*t*, *J* = 6.7, 2H), 1.80 (*t*, *J* = 6.7, 2H), 1.40 (*s*, 6H), 1.04 (*s*, 9H), 0.20 (*s*, 6H). EIMS *m*/*z* (%): 443 (1, $[M]^+$), 385 (1), 330 (5), 329 (21), 298 (11), 265 (6), 210 (7), 209 (45), 195 (7), 194 (7), 122 (9), 121 (100), 89 (4), 75 (17), 65 (6), 59 (4).

(8-Hydroxy-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2-hydroxyphenyl)methanone (**31**). Mp: 173–174 °C. IR ν_{max} (cm^{-1}) (KBr): 3352, 2965, 2928, 2896, 2927, 1616, 1450, 1357, 1334, 1263, 1232, 1200, 1150, 1112, 1087, 983, 853, 759, 732, 655. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 12.22 (OH), 7.52–7.45 (*m*, 2H), 7.02 (*dd*, *J* = 8.5, 1.8), 6.84 (*ddd*, *J* = 8.1, 7.0,1.1), 6.65 (*t*, *J* = 0.7), 5.62 (*b*, OH), 3.79 (*s*, OCH_3), 2.77 (*td*, *J* = 6.7, 0.7, 2H), 1.87 (*t*, *J* = 6.7, 2H), 1.43 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 201.2, 162.8, 144.4, 143.0, 137.7, 136.3, 134.1, 123.9, 120.2, 119.9, 118.6, 117.9, 116.4, 76.3, 61.7, 32.6, 26.9, 21.7. EIMS *m*/*z* (%): 329 (0.5, $[M]^+$), 297 (14), 242 (19), 241 (99), 179 (78), 128 (21), 121 (54), 115 (24), 91 (26), 79 (27), 77 (51), 64 (100), 63 (40), 53 (31), 51 (54). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}O_5$ $[M+H]^+$: 329.13835; found: 329.13787; *m*/*z* calcd for $C_{19}H_{20}NaO_5$ $[M+Na]^+$: 351.12029; found: 351.11901.

4.7.3. 12-Methoxy-2,2-dimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2*H*)-one (32) and 12-hydroxy-2,2-dimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2*H*)-one (4)

Cyclization of benzophenone **30** and **31**.

In a typical experiment: to a solution of compound **30** (340 mg, 1.2 mmol) in DMF (5 mL) was added Cs_2CO_3 (375 mg, 1.15 mmol). The mixture was irradiated with microwaves for 15 min at 140 °C. The mixture was allowed to cool to room temperature and poured into crushed ice. The aqueous phase was then extracted with 3 × 100 mL of diethyl ether. The organic phase was washed with 2 × 30 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 7:3) and compound **4** was obtained as light yellow solid (83 mg, 36%) and compound **32** as a white solid (99 mg/32%).

Cyclization of benzophenone **31** (396 mg, 1.2 mmol) led to compound **4** as a light yellow solid (330 mg/92%).

12-Methoxy-2,2-dimethyl-3,4-dihydropyrano[3,2-b]xanthen-6(2H)-one (**32**) Mp: 173−174 °C. IR ν_{max} (cm^{-1}) (KBr): 2967, 2936, 2829, 1655, 1609, 1443, 1326, 1114, 1077, 748. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 8.32 (*dd*, *J* = 7.9, 1.6); 7.86 (*t*, *J* = 0.9), 7.70 (*ddd*, *J* = 8.4, 7.0. 1.6), 7.57 (*dd*, *J* = 8.4, 1.1), 7.36 (*ddd*, *J* = 7.9, 7.0, 1.1), 4.00 (*s*, OCH_3), 2.64 (*td*, *J* = 6.8, 0.9, 2H), 1.90 (*t*, *J* = 6.8, 2H), 1.46 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 176.6, 156.2, 153.2, 149.1, 135.7, 134.2, 126.5, 123.6, 121.5, 121.2, 119.3, 118.0, 115.2, 76.4, 61.2, 32.3, 27.0, 22.1. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{19}O_4$ $[M+H]^+$: 311,12779; found: 311,12772.

12-Hydroxy-2,2-dimethyl-3,4-dihydropyrano[3,2-b]xanthen-6(2H)-one (**4**) The spectroscopic data was in accordance with the literature[17].

4.8. Synthesis of analogues 36a–e

4.8.1. Synthesis of diarylmethanols 33e–f

In a typical experiment: Compound **9** (1.5 g/3.74 mmol) was placed in an oven-dried three-necked round-bottom flask and solubilized in 50 mL of anhydrous THF. The mixture was then placed at −78 °C and *n*BuLi (1.6 M, 5.6 mmol) was added dropwise. The mixture was allowed to react for 15 min at −78 °C. Then the 2-benzyloxy-5-chlorosalicylaldehyde (**24a**) (1.38 g/5.6 mmol) solubilized in anhydrous THF was added dropwise and allowed to react for 15 min at −78 °C and slowly warm to room temperature. The reaction was quenched by a saturated solution of NH_4Cl, extracted with 3 × 100 mL of ethyl acetate. The organic phase was washed 2 × 100 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was then purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2) and compound **33e** was obtained as light yellow oil (1.62 g/76%).

(2-(Benzyloxy)-5-chlorophenyl)(8-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanol (**33e**) as a yellow oil (1.62 g/76%). IR ν_{max} (cm^{-1}) (KBr): 3445, 2969, 2927, 2892, 2952, 1575, 1461, 1351, 1245, 1102, 1073, 1024, 1004, 944, 832, 780, 732, 694. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.43 (*d*, *J* = 8.7), 7.32–7.29 (*m*, 3H), 7.21–7.16 (*m*, 3H), 6.82 (*d*, *J* = 8.7), 6.41 (*s*), 6.26 (*s*), 5.05 (*d*, *J* = 11.8, 1H), 4.99 (*d*, *J* = 11.8, 1H), 3.57 (*s*, OCH_3), 2.61 (*t*, *J* = 6.8, 2H), 1.73 (*t*, *J* = 6.8, 2H), 1.37 (*s*, 3H),1.33 (*s*, 3H), 1.04 (*s*, 9 H), 0.18 (*s*, 3H), 0.13 (*s*, 3H). EIMS *m*/*z* (%): 198 (1), 196 (3), 167 (1), 141 (2), 92 (10), 91 (100), 89 (3), 77 (3), 75 (2), 65 (22), 63 (5), 51 (4).

(2-(Benzyloxy)-5-methoxyphenyl)(8-((*tert*-butyldimethylsilyl) oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanol (**33b**) as a colorless oil (1.9 g/98%). IR ν_{max} (cm^{-1}) (KBr): 3421, 2928, 2901, 2853, 1585, 1495, 1463, 1352, 1246, 1207, 1155, 1103, 1075, 1041, 834, 781, 734, 694. ^1H NMR (300.13 MHz, $CDCl_3$) δ

(ppm): 7.42–7.18 (*m*, 6H), 7.03 (*d*, *J* = 2.7), 6.85 (*d*, *J* = 8.7), 6.48 (*s*), 6.32 (*s*), 5.02 (*d*, *J* = 10.7, 1H), 4.93 (*d*, *J* = 11.3, 1H), 3.79 (*s*, OCH_3), 3.76 (*s*, OCH_3), 2.62 (*t*, *J* = 6.8, 2H), 1.73 (*t*, *J* = 6.8, 2H), 1.37 (*s*, 3H),1.35 (*s*, 3H), 1.05 (*s*, 9 H), 0.20 (*s*, 3H), 0.18 (*s*, 3H). EIMS *m*/*z* (%): 299 (1.5), 283 (1.3), 214 (2), 193 (13), 192 (92), 191 (3), 177 (2), 163 (19), 138 (8), 137 (76), 136 (17), 121 (10), 110 (7), 107 (7), 92 (10), 91 (100), 71 (13), 65 (41), 53 (6), 51 (13).

(2-(Benzyloxy)-5-methylphenyl)(8-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanol (**33c**) as a colorless oil (1.91 g/93%). IR ν_{max} (cm^{-1}) (KBr): 3439, 2969, 2926, 2894, 1606, 1495, 1462, 1351, 1244, 1209, 1102, 1074, 1024, 1004, 832, 779, 693. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.34–7.25 (*m*, 4H), 7.23–7.20 (*m*, 2H), 7.02 (*d*, *J* = 2.1), 6.84 (*d*, *J* = 8.4), 6.52 (*s*), 6.34 (*s*), 5.07 (*d*, *J* = 11.7, 1H), 5.03 (*d*, *J* = 11.7, 1H), 3.60 (*s*, OCH_3), 2.65 (*t*, *J* = 6.8, 2H), 2.31 (*s*, CH_3), 1.75 (*t*, *J* = 6.8, 2H), 1.39 (*s*, 3H),1.36 (*s*, 3H), 1.07 (*s*, 9 H), 0.22 (*s*, 3H), 0.20 (*s*, 3H). EIMS *m*/*z* (%): 199 (0.7), 176 (3), 175 (1), 147 (5), 135 (2), 121 (8), 119 (1), 115 (1), 92 (10), 91 (100), 79 (3), 65 (22), 51 (6).

(2-(Benzyloxy)-3-methoxyphenyl)(8-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanol (**33d**) as a yellow oil (1.9 g/90%). IR ν_{max} (cm^{-1}) (KBr): 3443, 2967, 2928, 2894, 2851, 1578, 1469, 1351, 1261, 1205, 1102, 1077, 1025, 1003, 986, 832, 78, 745, 693. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.39–7.17 (*m*, 6H), 7.06 (*d*, *J* = 8.0), 6.68 (*d*, *J* = 8.4), 6.41 (*s*), 6.25 (*b s*), 5.01 (*d*, *J* = 10.7, 1H), 4.82 (*d*, *J* = 10.7, 1H), 3.89 (*s*, OCH_3), 3.49 (*s*, OCH_3), 2.91 (*b d*, *J* = 4.1, OH), 2.57 (*t*, *J* = 6.8, 2H), 1.69 (*t*, *J* = 6.8, 2H), 1.33 (*s*, 3H),1.31 (*s*, 3H), 1.02 (*s*, 9 H), 0.16 (*s*, 3H), 0.14 (*s*, 3H). EIMS *m*/*z* (%): 283 (1.2), 214 (1.4), 193 (6), 192 (49), 163 (19), 150 (5), 145 (5), 137 (55), 131 (20), 124 (8), 121 (5), 103 (18), 92 (10), 91 (100), 79 (5), 78 (4), 77 (11), 65 (40), 51 (12).

(2,4-Bis(benzyloxy)phenyl)(8-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanol (**33e**) as a light green oil (2.2 g).

4.8.2. Synthesis of benzophenones 34a–e

In a typical experiment: Compound **33a** (1.5 g/2.6 mmol) and 20 mL of DMSO were placed in a round-bottom flask. Then it was added IBX (1.1 g/3.9 mmol). After 24 h the reaction was quenched by the addition of a 10% solution of $Na_2S_2O_3$, a saturated solution of $NaHCO_3$ and distilled water. The aqueous phase was then extracted with 3 × 150 mL of ethyl acetate. The organic phase was washed with a 2 × 100 mL solution of $Na_2S_2O_3$ 10%, 2 × 100 mL of a saturated solution of $NaHCO_3$, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 95:5) and compound **34a** was recrystallized from ethyl acetate/*n*-hexane as white solid (1.04 g/70%).

(2-(Benzyloxy)-5-chlorophenyl)(8-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanone (**34a**) as a white solid (1.04 g/70%). Mp: 123–125 °C. IR ν_{max} (cm^{-1}) (KBr): 2948, 2925, 2880, 2877, 1637, 1590, 1544, 1453, 1342, 1301, 1239, 1206, 1137, 1101, 1077, 1016, 989, 963, 872, 825, 772, 728, 688, 458. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.42 (*d*, *J* = 2.6), 7.33 (*dd*, *J* = 8.8, 2.6), 7.24–7.20 (*m*, 3H), 7.07 (*s*), 7.07–7.04 (*m*, 2H), 6.88 (*d*, *J* = 8.8), 4.98 (*s*, 2H), 3.42 (*s*, OCH_3), 2.76 (*t*, *J* = 6.7, 2H), 1.80 (*t*, *J* = 6.7, 2H), 1.38 (*s*, 6H) 1.00 (*s*, 9 H), 0.08 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 193.5, 155.1, 150.9, 150.5, 137.7, 136.3, 133.4, 130.9, 129.0, 128.2, 127.6, 126.5, 125.6, 125.1, 123.8, 116.9, 113.7, 75.6, 70.3, 60.8, 32.7, 27.0, 25.7, 22.1, 18.6. EIMS *m*/*z* (%): 355 (1), 333 (2), 331 (4), 300 (4), 299 (19), 263 (7), 245 (3), 225 (4), 223 (4), 209 (6), 207 (4), 155 (12), 105 (33), 92 (9), 91 (100), 77 (6), 75 (14), 73 (19), 65 (17), 59 (4), 51 (7).

(2-(Benzyloxy)-5-methoxyphenyl)(8-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanone (**34b**) as a white solid (1.14 g/60%). Mp: 69–70 °C. IR ν_{max} (cm^{-1}) (KBr): 2956, 2930, 2891, 2853, 1640, 1599, 1496, 1462, 1416, 1350, 1305, 1245, 1218, 1106, 1080, 1048, 996, 909, 835, 779, 733, 464. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.25–7.18 (*m*, 3H), 7.06–7.05 (*m*, 2H), 7.03 (*d*, *J* = 2.9), 7.01 (*s*), 6.93 (*dd*, *J* = 8.9, 2.9), 6.87 (*d*, *J* = 8.9), 4.91 (*s*, 2H), 3.79 (*s*, OCH_3), 3.46 (*s*, OCH_3), 2.72 (*t*, *J* = 6.7, 2H), 1.77 (*t*, *J* = 6.7, 2H), 1.36 (*s*, 6H), 0.99 (*s*, 9 H), 0.08 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 194.9, 153.5, 150.8, 150.4, 150.4, 137.7, 137.0, 132.7, 128.1, 127.4, 126.6, 125.8, 123.9, 117.2, 116.6, 114.3, 114.2, 75.5, 70.9, 60.9, 55.8, 32.7, 29.7, 27.0, 25.8, 22.1, 18.6. EIMS *m*/*z* (%): 448 (0.11), 431 (0.7), 399 (1), 355 (1), 339 (1), 327 (7), 300 (4), 299 (9), 277 (23), 263 (19), 255 (12), 241 (8), 225 (9), 219 (10), 209 (19), 207 (12), 151 (84), 121 (4), 105 (21), 92 (9), 91 (100), 75 (23), 73 (26), 65 (22), 59 (7), 51 (12).

(2-(Benzyloxy)-5-methylphenyl)(8-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanone (**34c**) as a white solid (1.14 g/64%). Mp: 110–111 °C. IR ν_{max} (cm^{-1}) (KBr): 2950, 2926, 2886, 2849, 1639, 1599, 1550, 1495, 1451, 1346, 1304, 1243, 1145, 1104, 1084, 1026, 992, 832, 799, 774, 731, 462. ^{1}H NMR (300,13 MHz, $CDCl_3$) δ (ppm): 7.29 (*d*, *J* = 2.2), 7.23–7.17 (*m*, 4H), 7.07–7.04 (*m*, 2H), 7.02 (*s*), 6.84 (*d*, *J* = 8.4), 4.96 (*s*, 2H), 3.44 (*s*, OCH_3), 2.74 (*t*, *J* = 6.7, 2H), 2.31 (*s*, CH_3), 1.79 (*t*, *J* = 6.7, 2H), 1.38 (*s*, 6H) 1.00 (*s*, 9 H), 0.09 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 195.5, 154.6, 150.2, 150.2, 137.7, 137.0, 132.1, 131.6, 130.1, 129.8, 128.1, 127.3, 126.5, 126.1, 123.7, 112.5, 75.4, 70.1, 60.8, 32.8, 27.9, 25.8, 22.1, 20.4, 18.6. EIMS *m*/*z* (%): 327 (7), 315 (2), 299 (20), 291 (4), 278 (6), 277 (26), 263 (25), 255 (13), 209 (9), 152 (10), 151 (100), 105 (22), 92 (9), 91 (92), 75 (14), 73 (15), 65 (18), 51 (6).

(2-(Benzyloxy)-3-methoxyphenyl)(8-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanone (**34d**) as a colorless oil (1.37 g/71%). IR ν_{max} (cm^{-1}) (KBr): 2972, 2929, 2892, 2854, 1658, 1594, 1578, 1562, 1469, 1349, 1312, 1259, 1210, 1116, 1064, 992, 907, 835, 780, 749, 695. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.25–7.23 (*m*, 5H), 7.11 (*dd*, *J* = 8.2, 7.3), 7.03 (*dd*, *J* = 8.2, 1.9), 7.00 (*dd*, *J* = 7.3,1.9), 6.92 (*s*), 4,93 (*s*, 2H), 3.89 (*s*, OCH_3), 3.54 (*s*, OCH_3), 2.67 (*t*, *J* = 6.6, 2H), 1.76 (*t*, *J* = 6.6, 2H), 1.37 (*s*, 6H), 1.01 (*s*, 9 H), 0.13 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 195.0, 152.8, 150.6, 150.6, 145.9, 137.6, 128.1, 128.0, 127.5, 127.0, 125.2, 124.7, 123.7, 120.9, 116.5, 114.3, 75.6, 75.5, 60.8, 56.1, 32.7, 27.0, 25.8, 22.1, 18.6. EIMS *m*/*z* (%):355 (1), 339 (2), 329 (1), 327 (1), 312 (5), 311 (14), 299 (16), 277 (16), 263 (21), 239 (7), 225 (10), 203 (16), 136 (9), 135 (100), 105 (30), 92 (8), 91 (90), 77 (5), 75 (11), 65 (15), 51(3).

(2,4-Bis(benzyloxy)phenyl)(8-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanone (**34e**) as a colorless oil (1.4 g). IR ν_{max} (cm^{-1}) (KBr): 2966, 2923, 2883, 2849, 1638, 1595, 1567, 1494, 1459, 1419, 1347, 1305, 1250, 1202, 1171, 1112, 1076, 1021, 860, 829. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.53 (*d*, *J* = 8.5), 7.45–7.34 (*m*, 5H), 7.23–7.18 (*m*, 3H), 7.04–7.01 (*m*, 2H), 6.96 (*s*), 6.60 (*dd*, *J* = 8.5, 2.2), 6.56 (*d*, *J* = 8.5), 5.09 (*s*, 2H), 4.94 (*s*, 2H), 3.44 (*s*, OCH_3), 2.73 (*t*, *J* = 6.6, 2H), 1.77 (*t*, *J* = 6.6, 2H), 1.36 (*s*, 6H), 0.98 (*s*, 9 H), 0.06 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 194.2, 162.3, 158.9, 149.8, 149.7, 136.6, 136.4, 132.1, 128.7, 128.2, 127.7, 127.4, 127.0, 126.5, 124.7, 123.1, 116.6, 105.5, 100.4, 75.3, 70.2, 69.9, 61.0, 32.8, 29.7, 27.0, 25.8, 22.8, 18.6. EIMS *m*/*z* (%): 355 (2), 327 (11), 299 (20), 271 (5), 267 (7), 263 (19), 253 (9), 241 (13), 227 (10), 225 (20), 219 (12), 211 (16), 209 (11), 207 (29), 193 (11), 151 (69), 105 (20), 92 (9), 91 (100), 75 (16), 73 (31), 65 (15), 51 (14).

4.8.3. Synthesis of benzophenones 34a–e and compound 30

In a typical experiment: Compound **34e** (750 mg/1.32 mmol) and 40 mL of anhydrous methanol/THF 3:1 were placed in a two-necked round-bottom flask and under nitrogen atmosphere. To the solution was added Pd/C 10% (15% weight/112.5 mg) in one portion. Triethylsilane (2.1 mL, 10.32 mmol) was then added dropwise. The mixture was allowed to stir for 15 min. The product was filtered over celite and washed 3 times with methanol. The methanol was evaporated and the crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 95:5). The mixture of compound **35a** and **30** was isolated as yellowish oil (564 mg). A small fraction of this mixture was purified by preparative thin layer chromatography and a small amount of compound **35a** and compound **30** was isolated.

Mixture of compounds **35a** and **30** as yellow oil (564 mg). (8-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(5-chloro-2-hydroxyphenyl)methanone (**35a**) as a green solid. Mp: 107–109 °C. IR ν_{max} (cm^{-1}) (KBr): 3434, 2943, 2879, 2840, 1614, 1582, 1452, 1346, 1238, 1183, 1102, 1062, 978, 890, 820, 769, 745, 454. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 12.15 (OH), 7.43 (*d*, *J* = 2.8), 7.39 (*dd*, *J* = 8.9, 2.8), 6.97 (*d*, *J* = 8.9), 6.72 (*s*), 3.64 (*s*, OCH_3), 2.72 (*t*, *J* = 6.7, 2H), 1.80 (*t*, *J* = 6.7, 2H), 1.41 (*s*, 6H), 1.04 (*s*, 9 H), 0.22 (*s*, 6H). EIMS *m*/*z* (%): 477 (0.6, $[M]^{+\cdot}$], 365 (9), 363 (20), 332 (15), 266 (17), 265 (81), 210 (17), 209 (100), 195 (12), 194 (15), 167 (7), 166 (12), 157 (17), 155 (58), 99 (10), 75 (48), 73 (37), 59 (17).

(8-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2-hydroxy-5-methoxyphenyl)methanone (**35b**) light yellow solid (816 mg/89%). Mp: 74–75 °C. IR ν_{max} (cm^{-1}) (KBr): 3437, 2970, 2939, 2893, 2849, 1628, 1591, 1462, 1416, 1355, 1328, 1294, 1195, 1150, 1110, 1068, 1036, 828, 780, 741, 657. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 11.90 (OH), 7.10 (*dd*, *J* = 9.1, 3.0), 6.96 (*d*, *J* = 9.1), 6.94 (*d*, *J* = 3.0), 6.71 (*s*), 3.67 (*s*, OCH_3), 3.66 (*s*, OCH_3), 2.75 (*t*, *J* = 6.7, 2H), 1.80 (*t*, *J* = 6.7, 2H), 1.40 (*s*, 6H), 1.05 (*s*, 9 H), 0.20 (*s*, 6H). EIMS *m*/*z* (%): 473 (0.5, $[M]^+$], 359 (12), 328 (9), 250 (7), 209 (28), 152 (10), 151 (100), 75 (10).

(8-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2-hydroxy-5-methylphenyl)methanone (**35c**) as a white oil (900 mg/quantitative). IR ν_{max} (cm^{-1}) (KBr): 3438, 2971, 2947, 2926, 2886, 2852, 1628, 1596, 1462, 1356, 1245, 1206, 1184, 1150, 1103, 1071, 910, 828, 778, 668. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 12.07 (OH), 7.29–7.22 (2H, *m*), 6.92 (*d*, *J* = 8.4), 6.70 (*s*), 3.62 (*s*, OCH_3), 2.76 (*t*, *J* = 6.7, 2H), 2.20 (*s*, CH_3), 1.81 (*t*, *J* = 6.7, 2H), 1.40 (*s*, 6H), 1.04 (*s*, 9 H), 0.21 (*s*, 6H). EIMS *m*/*z* (%): 457 (1, $[M]^+$], 345 (13), 312 (9), 209 (28), 136 (10), 135 (100), 77 (8), 75 (10).

(8-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2-hydroxy-3-methoxyphenyl)methanone (**35d**) as a yellow solid (717 mg/85%). Mp: 138–139 °C. IR ν_{max} (cm^{-1}) (KBr): 3454, 2967, 2918, 2878, 2843, 1617, 1599, 1447, 1348, 1249, 1106, 1084, 1050, 982, 896, 825, 774, 746, 728. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 12.55 (OH), 7.07 (*dd*, *J* = 8.1, 1.3), 7.05 (*dd*, *J* = 8.1, 1.3), 6.76 (*t*, *J* = 8.1), 6.69 (*s*), 3.93 (*s*, OCH_3), 3.67 (*s*, OCH_3), 2.74 (*t*, *J* = 6.7, 2H), 1.80 (*t*, *J* = 6.7, 2H), 1.40 (*s*, 6H), 1.04 (*s*, 9 H), 0.19 (*s*, 6H). EIMS *m*/*z* (%): 473 (0.8, $[M]^+$], 359 (13), 250 (10), 209 (14), 152 (10), 151 (100), 75 (10), 51 (12).

(8-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2,4-dihydroxyphenyl)methanone (**35e**) as a yellow oil (850 mg/quantitative). IR ν_{max} (cm^{-1}) (KBr): 3383, 2968, 2925, 2851, 1622, 1594, 1459, 1360, 1296, 1242, 1207, 1113, 1071, 985, 830, 779, 625. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 12.75 (OH), 7.35 (*d*, *J* = 8.8), 6.66 (*s*), 6.40 (*d*, *J* = 2.5), 6.28 (*dd*, *J* = 8.8, 2.5), 5.71 (OH), 3.66 (*s*, OCH_3), 2.74 (*t*, *J* = 6.7, 2H), 1.79 (*t*, *J* = 6.7, 2H), 1.39 (*s*, 6H), 1.03 (*s*, 9 H), 0.20 (*s*, 6H).

4.8.4. Synthesis of xanthones 36a–e and compound 37

To a solution of a mixture **35a** and **30** (530 mg) in DMF (10 mL) was added Cs_2CO_3 (543 mg, 1.67 mmol). The mixture was irradiated with microwaves for 15 min at 140 °C. The mixture was allowed to cool to room temperature and poured into crushed ice. The aqueous phase was then extracted with 3 × 100 mL of diethyl ether. The organic phase was washed with 2 × 50 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:1). Compound **36a** was recrystallized obtained as yellow solid (210 mg), and compound **4** as a light yellow solid (40 mg).

8-Chloro-12-hydroxy-2,2-dimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2*H*)-one (**36a**) as a yellow solid (210 mg). Mp: 225–227 °C. IR ν_{max} (cm^{-1}) (KBr): 3322, 2973, 2937, 2854, 1636, 1614, 1471, 1353, 1259, 1239, 1214, 1185, 1157, 1124, 1073, 981, 887, 808, 645. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 8.28 (*d*, *J* = 2.6), 7.67 (*t*, *J* = 1.0), 7.62 (*dd*, *J* = 9.0, 2.6), 7.53 (*d*, *J* = 9.0), 5.75 (OH), 2.91 (*td*, *J* = 6.7, 1.0, 2H), 1.92 (*t*, *J* = 6.7, 2H), 1.45 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 175.5, 154.5, 146.6, 143.1, 134.3, 132.5, 129.3, 126.0, 122.4, 119.7, 118.6, 117.1, 115.0, 77.5, 32.5, 27.0, 21.7. EIMS *m*/*z* (%): 331 (3, $[M+1]^+$), 330 (5, $[M]^+$), 275 (23), 190 (48), 184 (22), 162 (62), 155 (47), 139 (25), 128 (53), 127 (67), 126 (44), 99 (20), 77 (42), 75 (77), 74 (45), 62 (44), 53 (34), 51 (78). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{16}ClO_4$ $[M+H]^+$: 331.07316; found: 331.07271; *m*/*z* calcd for $C_{18}H_{16}NaClO_4$ $[M+Na]^+$: 353.05511; found: 353.05410.

12-Hydroxy-8-methoxy-2,2-dimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2*H*)-one (**36b**) as a white solid (478 mg/89%). Mp: decomp. IR ν_{max} (cm^{-1}) (KBr): 3232, 2975, 2931, 2841, 1647, 1613, 1591, 1490, 1467, 1438, 1370, 1253, 1208, 1122, 1075, 1029, 787. ^{1}H NMR (300.13 MHz, $CDCl_3$/DMSO-d_6 (10:1)) δ (ppm): 8.12 (*b*, OH), 7.64 (*d*, *J* = 3.1), 7.58 (*s*), 7.52 (*d*, *J* = 9.1), 7.28 (*dd*, *J* = 9.1, 3.1), 3.91 (*s*, OCH_3), 2.94 (*t*, *J* = 6.7, 2H), 1.91 (*t*, *J* = 6.7, 2H), 1.45 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$/DMSO-d_6 (10:1)): 175.5, 154.7, 150.0, 146.4, 143.3, 132.3, 123.0, 120.8, 118.5, 117.7; 115.1, 113.7, 105.1, 75.5, 55.9, 31.7, 26.1, 21.2. EIMS *m*/*z* (%): 327 (5, $[M+1]^+$), 326 (10, $[M]^+$), 272 (30), 271 (93), 270 (100), 267 (12), 255 (11), 254 (8), 242 (12), 228 (18), 215 (12), 214 (15), 171 (12), 115 (12), 77 (11), 63 (27), 62 (20), 53 (13), 51 (9). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{19}O_5$ $[M+H]^+$: 327.12270; found: 327.12371; *m*/*z* calcd for $C_{19}H_{18}NaO_5$ $[M+Na]^+$: 349.10464; found: 349.10323.

12-Hydroxy-2,2,8-trimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2*H*)-one (**36c**) as a white solid (385 mg/65%). Mp: 227–228 °C. IR ν_{max} (cm^{-1}) (KBr): 3239, 2981, 2934, 2856, 1652, 1616, 1490, 1465, 1421, 1365, 1252, 1220, 1197, 1153, 1131, 1096, 1073, 1021, 813, 783, 660. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 8.11–8.10 (m, 1H), 7.68 (*t*, *J* = 1.0), 7.49 (*dd*, *J* = 8.7, 2.0), 7.46 (*dd*, *J* = 8.7, 0.6), 5.85 (*b*, OH), 2.91 (*td*, *J* = 6.7, 1.0, 2H), 2.45 (*s*, CH_3), 1.91 (*t*, *J* = 6.7, 2H), 1.43 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 176.7; 154.4, 146.1, 143.3, 135.5, 133.3, 132.3, 126.0, 121.1, 118.0, 117.7, 117.0, 115.4, 76.6, 32.6, 27.0, 21.2, 20.8. EIMS *m*/*z* (%): 311 (3, $[M+1]^+$), 310 (8, $[M]^+$), 255 (100), 254 (74), 199 (25), 198 (24), 170 (37), 142 (33), 141 (32), 128 (26), 115 (35), 77 (28), 63 (25), 51 (30). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{19}O_4$ $[M+H]^+$: 311.12779; found: 311.12851; *m*/*z* calcd for $C_{19}H_{18}NaO_4$ $[M+Na]^+$: 333.10973, found: 333.10805.

12-Hydroxy-10-methoxy-2,2-dimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2*H*)-one (**36d**) as a light yellow solid (387 mg/83%). Mp: 207–208 °C. IR ν_{max} (cm^{-1}) (KBr): 3308, 3271, 2976, 2931, 2843, 1650, 1597, 1473, 1445, 1372, 1265, 1223, 1197, 1118, 1069, 937, 755. ^{1}H NMR (300.13 MHz, CDCl3) δ (ppm): 7.88 (*dd*, *J* = 7.8, 1.8), 7.67 (*t*, *J* = 1.0), 7.27 (*t*, *J* = 7.8), 7.20 (*dd*, *J* = 7.8, 1.8), 6.03 (*b*, OH), 4.03 (*s*, OCH_3), 2.93 (*td*, *J* = 1.0, 6.7, 2H), 1.92 (*t*, *J* = 6.7, 2H), 1.44 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 176.6,

148.6, 146.5, 146.4, 132.8, 123.0, 122.4, 118.5, 117.6, 116.7, 115.1, 114.9, 76.9, 56.4, 32.6, 26.9, 21.6. EIMS *m*/*z* (%): 327 (11, $[M+1]^+$), 326 (11, $[M]^+$), 271 (50), 270 (33), 214 (24), 200 (28), 199 (28), 185 (33), 171 (22), 157 (25), 151 (26), 144 (31), 128 (37), 116 (24), 115 (100), 89 (21), 77 (40), 75 (22), 63 (59), 62 (24), 53 (24), 51 (64). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{19}O_5$ $[M+H]^+$: 327.12270; found: 327.12325; *m*/*z* calcd for $C_{19}H_{18}NaO_5$ $[M+Na]^+$: 349.10464; found: 349.10362.

9,12-Dihydroxy-2,2-dimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2*H*)-one (**36e**) as a white solid (407 mg/71%). Mp: 262–264 °C. IR ν_{max} (cm^{-1}) (KBr): 3334, 3288, 3241, 2972, 2925, 2845, 1645, 1611, 1588, 1457, 1266, 1324, 1256, 1217, 1192, 1162, 1118, 1017, 850, 699. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.80 (*b*, OH), 9.50 (*b*; OH), 8.02 (*d*, *J* = 8.5), 7.42 (*s*), 6.89 (*d*, *J* = 2.0), 6.87 (*dd*, *J* = 8.5, 2.0), 2.87 (*t*, *J* = 6.6, 2H), 1.84 (t, *J* = 6.6, 2H), 1.38 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 174.5, 163.4, 147.2, 143.9, 133.1, 127.9, 118.4, 115.3, 114.4, 113.8, 113.5, 102.1, 75.8, 31.9, 26.6, 21.6. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}O_5$ $[M+H]^+$: 313.10705; found: 313.10696.

(2,4-dihydroxyphenyl)(8-hydroxy-7-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanone (**37**) as a white solid (125 mg, 20%). Mp: 220–222 °C. IR ν_{max} (cm^{-1}) (KBr): 3378, 3283, 2971, 2930, 2895, 2849, 1630, 1583, 1492, 1371, 1313, 1295, 1251, 1201, 1154, 1090, 1054, 983, 948, 786, 623. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 12.61 (OH), 10.90 (*b*, OH), 8.70 (*b*, OH), 7.23 (*d*, *J* = 8.6), 6.51 (*s*), 6.33 (*dd*, *J* = 2.3, 8.6), 6.30 (*d*, *J* = 2.3), 3.61 (*s*, OCH_3), 2.60 (*t*, *J* = 6.6, 2H), 1.77 (*t*, *J* = 6.6, 2H), 1.33 (*s*, 6H). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}O_6$ $[M+H]^+$: 345.13326; found: 345.13402; *m*/*z* calcd for $C_{19}H_{20}NaO_6$ $[M+Na]^+$: 367.11521; found: 36.11345.

4.9. Synthesis of analogues 41c, 41e and 41f

4.9.1. Synthesis of diarylmethanols 38c, 38e and 38f

In a typical experiment: Compound **14** (800 mg/2.7 mmol) was placed in a two-necked round-bottom flask and 25 mL of anhydrous THF was added. The mixture was then placed at −78 °C and *n*BuLi (1.6 M, 3.24 mmol) was added dropwise. The mixture was allowed to react for 15 min at −78 °C. Then the benzaldehyde **24f** (882 mg/3.24 mmol) solubilized in anhydrous THF was added dropwise and allowed to react for 1 h and 30 min at −78 °C and slowly warm to room temperature (about 6 h). The reaction was quenched by addition of a saturated solution of NH_4Cl. The aqueous phase was extracted with 3 × 50 mL of ethyl acetate. The organic phase was washed 2 × 50 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was then purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2). Compound **38f** was obtained (652 mg/48%) as yellow oil.

(2-(Benzyloxy)-5-methylphenyl)(7,8-dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanol (**38c**) as a yellow oil (730 mg/58%). IR ν_{max} (cm^{-1}) (KBr): 3474, 3442, 2975, 2931, 2860, 1494, 1463, 1343, 1241, 1106, 736. ^1H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 7.32–7.21 (*m*, 6H), 7.02 (*dd*, *J* = 8.3, 2.1), 6.81 (*d*, *J* = 8.3), 6.59 (*s*), 6.25 (*b s*), 5.03 (*d*, *J* = 11.4, 1H), 4.99 (*d*, 1H, *J* = 11.4), 3.82 (*s*, OCH_3), 3.67 (*s*, OCH_3), 3.00 (*b*, OH), 2.60 (*t*, *J* = 6.8, 2H), 2.30 (*s*, CH_3), 1.75 (*t*, *J* = 6.7, 2H), 1.37 (*s*, 3H),1.34 (*s*, 3H).

(2,4-Bis(methoxymethoxy)phenyl)(7,8-dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanol (**38e**) as a yellow oil (460 mg/38%). IR ν_{max} (cm^{-1}) (KBr): 3503, 3447, 2971, 2934, 2829, 1606, 1464, 1153, 1106, 1072, 1010, 923. ^1H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 7.23 (*d*, *J* = 8.5), 6.78 (*d*, *J* = 2.3), 6.70 (*dd*, *J* = 8.5, 2.3), 6.69 (*b s*), 6.25 (*d*, *J* = 3.7, 1H), 5.19 (*d*, *J* = 6.7, 1H), 5.15 (*s*, 2H), 5.12 (*d*, *J* = 6.7, 1H) 3.83 (*s*, OCH_3), 3.78 (*s*, OCH_3), 3.48 (*s*, OCH_3), 3.35 (*s*, OCH_3), 3.00 (*d*, *J* = 3.7, OH), 2.68 (*t*d, *J* = 6.9, 2.0, 2H), 1.74 (*t*, *J* = 6.9, 2H), 1.34 (*s*, 3H), 1.32 (*s*, 3H).

(2-(Benzyloxy)-4,5-dimethoxyphenyl)(7,8-dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanol (**38f**) as a yellow oil (652 mg/48%). IR ν_{max} (cm^{-1}) (KBr): 3518, 3493, 2965, 2926, 2832, 1537, 1504, 1457, 1337, 1202, 1104, 1019, 876. ^1H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 7.31–7.23 (*m*, 5H), 7.04 (*s*), 6.57 (*s*), 6.52 (*s*), 6.25 (*d*, *J* = 3.9, 1H), 5.00 (*d*, 1H, *J* = 11.5), 4.96 (*d*, 1H, *J* = 11.5), 3.85 (*s*, OCH_3), 3.84 (*s*, OCH_3), 3.83 (*s*, OCH_3), 3.71 (*s*, OCH_3), 3.05 (*d*, *J* = 3.9, OH), 2.59 (*t*, *J* = 6.8, 2H), 1.75 (*t*, *J* = 6.8, 2H), 1.37 (*s*, 3H),1.34 (*s*, 3H).

4.9.2. Synthesis of benzophenones 39c, 39e and 39f

In a typical experiment: Compound **38e** (450 mg/1.0 mmol) and 10 mL of DMSO were place in a round-bottom flask. Then it was added IBX (420 mg/1.5 mmol). After 12 h the reaction was quenched with the addition of a 10% solution of $Na_2S_2O_3$, a saturated solution of $NaHCO_3$ and distilled water. The aqueous phase was then extracted with 3 × 50 mL of ethyl acetate. The organic phase was washed with 2 × 50 mL of a 10% solution of $Na_2S_2O_3$, 2 × 50 mL of a saturated solution of $NaHCO_3$, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2) and compound **39e** was isolated as yellow oil (380 mg/85%).

(2-(Benzyloxy)-5-methylphenyl)(7,8-dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanone (**39c**) as a yellow solid (460 mg/66%). Mp: 114–115 °C. IR ν_{max} (cm^{-1}) (KBr): 2975, 2924, 2865, 1649, 1604, 1498, 1459, 1340, 1247, 1149, 1108, 1026, 987, 804, 734. ^1H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 7.33 (*d*, *J* = 2.3), 7.22–7.18 (*m*, 4H), 7.14 (*s*), 7.01–6.98 (*m*, 2H), 6.87 (*d*, *J* = 8.3), 4.94 (*s*, 2H), 3.71 (*s*, OCH_3), 3.52 (*s*, OCH_3), 2.73 (*t*, *J* = 6.7, 2H), 2.83 (*s*, CH_3), 1.81 (*t*, *J* = 6.7, 2H), 1.39 (*s*, 6H).

(2,4-Bis(methoxymethoxy)phenyl)(7,8-dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanone (**39e**) as a yellow oil (380 mg/85%). IR ν_{max} (cm^{-1}) (KBr): 2973, 2935, 2830, 1652, 1601, 1464, 1343, 1308, 1156, 1116, 1075, 1000, 923, 848, 793. ^1H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 7.44 (*d*, *J* = 8.5), 7.06 (*s*), 6.80 (*d*, *J* = 2.3), 6.72 (*dd*, *J* = 8.5, 1.4), 5.20 (*s*, 2H), 5.03 (*s*, 2H), 3.82 (*s*, OCH_3), 3.62 (*s*, OCH_3), 3.49 (*s*, OCH_3), 3.32 (*s*, OCH_3), 2.75 (*t*, *J* = 6.9, 2H), 1.82 (*t*, *J* = 6.9, 2H), 1.40 (*s*, 6H). EIMS *m*/*z* (%): 447 (3, $[M+1]^+$), 446 (10, $[M]^+$), 416 (25), 415 (100), 385 (38), 383 (19), 359 (12), 315 (31), 249 (12), 235 (18), 211 (26), 193 (14), 179 (12), 69 (10).

(2-(Benzyloxy)-4,5-dimethoxyphenyl)(7,8-dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanone (**39f**) as a yellow solid (580 mg/96%). Mp: 128–129 °C. IR ν_{max} (cm^{-1}) (KBr): 2973, 2930, 2843, 1642, 1604, 1513, 1450, 1404, 1341, 1276, 1210, 1111, 1026 732. ^1H NMR (400.21 MHz, CDC_{l3}) δ (ppm): 7.23–7.20 (*m*, 4H), 7.03 (*s*), 6.97–6.95 (*m*, 2H), 6.55 (*s*), 4.90 (*s*, 2H), 3.92 (*s*, OCH_3), 3.90 (*s*, OCH_3), 3.69 (*s*, OCH_3), 3.60 (*s*, OCH_3), 2.72 (*t*, *J* = 6.7, 2H), 1.79 (*t*, *J* = 6.7, 2H), 1.38 (*s*, 6H).

4.9.3. Synthesis of benzophenones 40c, 40e and 40f

Benzyl ether removal. In a typical experiment: Compound **39f** (344 mg/0.68 mmol) and 25 mL of anhydrous methanol/THF (1:1) were place in a two-necked round-bottom flask and under nitrogen atmosphere. To the solution was added Pd/C 10% (15% weight/52 mg) in one portion. Triethylsilane (1.1 mL, 6.8 mmol) was then added dropwise. The mixture was allowed to stir for 15 min. The product was filtered over celite and washed 3 times with methanol. The methanol was then evaporated and the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 8:2). Compound **40f** was isolated as yellowish oil (180 mg/67%).

(7,8-Dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2-hydroxy-5-methylphenyl)methanone (**40c**) as yellow oil (110 mg/

77%). IR ν_{max} (cm^{-1}) (KBr): 3328, 2976, 2934, 1629, 1601, 1474, 1349, 1110, 1072, 989, 828, 767, 670. ^{1}H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 12.02 (OH), 7.28 (*dd*, *J* = 8.4, 2.3), 7.21 (*d*, *J* = 2.3), 6.93 (*d*, *J* = 8.4), 6.80 (*t*, *J* = 0.8), 3.88 (*s*, OCH_3), 3.79 (*s*, OCH_3), 2.77 (*td*, *J* = 6.7, 0.8, 2H), 2.23 (*s*, CH_3), 1.85 (*t*, *J* = 6.7, 2H), 1.43 (*s*, 6H). EIMS *m*/*z* (%): 357 (12, $[M+1]^+$), 356 (1, $[M]^+$), 355 (2), 325 (16), 270 (20), 269 (100), 226 (8), 222 (10), 193 (47), 168 (11), 167 (63), 165 (10), 135 (20), 115 (10), 91 (11), 79 (11), 77 (31), 51 (11).

(7,8-Dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)(2-hydroxy-4,5-dimethoxyphenyl)methanone (**40f**) as yellow oil (180 mg/67%). IR ν_{max} (cm^{-1}) (KBr): 3473, 2974, 2936, 2857, 1619, 1505, 1461, 1350, 1268, 1203, 1153, 1110, 1071, 829. ^{1}H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 12.70 (OH), 6.86 (*s*), 6.83 (*s*), 6.51 (*s*) 3.94 (*s*, OCH_3), 3.88 (*s*, OCH_3), 3.79 (*s*, OCH_3), 3.70 (*s*, OCH_3), 2.77 (*t*, *J* = 6.7, 2H), 1.84 (*t*, *J* = 6.7, 2H), 1.42 (*s*, 6H). EIMS *m*/*z* (%): 402 (12, $[M]^+$), 372 (28), 371 (79), 355 (6), 315 (30), 281 (19), 222 (41), 209 (10), 208 (14), 207 (68), 193 (10), 191 (11), 181 (17), 168 (10), 167 (100), 166 (13), 165 (11), 147 (11), 133 (10), 96 (11), 73(22).

Methoxymethyl ether removal

To a solution of compounds **39e** (227 mg, 0.51 mmol) in 5 mL of CH_3CN at 0 °C was added in one portion $NbCl_5$ (138 mg, 0.19 mmol). The mixture was stirred at 0 °C for 10 min and then allowed to warm to room temperature and let stirring for more 45 min and the reaction mixture was quenched with a saturated solution of $NaHCO_3$. The mixture was extracted with 3 × 25 mL of ethyl acetate. The organic phase was washed with 2 × 50 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. Compound **40e** was obtained as yellow oil (172 mg/94%) and used in the next reaction without further purification

(2,4-Dihydroxyphenyl)(7,8-dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran-6-yl)methanone (**40e**). IR ν_{max} (cm^{-1}) (KBr): 3328, 2975, 2932, 2857, 1606, 1460, 1353, 1239, 1114, 989, 799. ^{1}H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 12.68 (OH), 7.34 (*d*, *J* = 8.8), 6.78 (*s*), 6.41 (*d*, *J* = 2.5), 6.30 (*dd*, *J* = 8.8, 2.5), 3.88 (*s*, OCH_3), 3.79 (*s*, OCH_3), 2.75 (*t*, *J* = 6.7, 2H), 1.83 (*t*, *J* = 6.7, 2H), 1.41 (*s*, 6H). EIMS *m*/*z* (%): 345 (5, $[M]^+$), 328 (21), 327 (100), 303 (7), 272 (10), 271 (52), 192 (26), 151 (4), 137 (42), 123 (6), 115 (5), 107 (5), 107 (5), 91 (6), 81 (13), 79 (6), 77 (7), 69 (11), 53 (10).

4.9.4. Synthesis of xanthones 41c, 41e and 41f

Synthesis of xanthones 41c, **41e** and **41f**. In a typical experiment: To a solution of compound **40c** (186 mg, 0.52 mmol) in 3 mL of DMF was added K_2CO_3 (142 mg, 1.03 mmol). The mixture was irradiated with microwave (200 W max) for 15 min at 140 °C. The mixture was allowed to cool to room temperature and poured into crushed ice. The aqueous phase was then extracted with 3 × 50 mL of diethyl ether. The organic phase was washed with 2 × 50 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2). Compound **41c** was obtained as light yellow solid (160 mg, 95%).

12-Methoxy-2,2,8-trimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2*H*)-one (**41c**) as a yellowish solid (160 mg/95%). Mp: 101–102 °C. IR ν_{max} (cm^{-1}) (KBr): 2972, 2926, 2846, 1655, 1609, 1480, 1446, 1312, 1117, 1083, 781. ^{1}H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 8.09 (*d*, *J* = 2.1), 7.85 (*t*, *J* = 1.0), 7.50 (*dd*, *J* = 8.3, 2.1), 7.46 (*d*, *J* = 8.3), 3.99 (*s*; OCH_3), 2.93 (*td*, *J* = 6.8, 1.0), 2.46 (*s*; CH_3), 1.89 (*t*, *J* = 6.8, 2H), 1.45 (*s*, 6H). ^{13}C NMR (100.63 MHz, $CDCl_3$) δ (ppm): 176.7, 154.5, 153.1, 149.2, 135.7, 135.5, 133.4, 125.9, 121.3, 121.2, 119.2, 117.8, 115.2, 76.4, 61.2, 32.4, 27.0, 22.2, 20.8. EIMS *m*/*z* (%): 325 (10, $[M+1]^+$), 324 (47, $[M]^+$), 307 (4), 293 (4), 270 (18), 269 (100), 268 (25), 267 (15), 239 (9), 197 (6), 141 (5), 115 (10), 91 (4), 77 (4). HRMS (ESI) *m*/*z* calcd for $C_{20}H_{21}O_4$ $[M+H]^+$: 325.14344; found: 325.14330.

9-Hydroxy-12-methoxy-2,2-dimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2*H*)-one (**41e**) as a white solid (64 mg/42%). Mp: 286–287 °C. IR ν_{max} (cm^{-1}) (KBr): 3227, 2973, 2940, 2840, 1646, 1611, 1574, 1444, 1349, 1202, 1116. ^{1}H NMR (400.21 MHz, DMSO-d_6) δ (ppm): 7.99 (*d*, *J* = 8.5), 7.66 (*s*), 6.87 (*dd*, *J* = 8.5, 2.3), 6.85 (*d*, *J* = 2.3), 3.87 (*s*, OCH_3), 2.89 (*t*, *J* = 6.7, 2H), 1.86 (*t*, *J* = 6.7, 2H), 1.38 (*s*; 6H). ^{13}C NMR (100.63 MHz, DMSO-d_6) δ (ppm): 174.1, 163.7, 157.5, 148.3, 147.8, 135.2, 127.8, 120.3, 119.3, 114.4, 113.8, 113.8, 102.2, 76.3, 60.7, 31.5, 26.7, 21.5. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{19}O_5$ $[M+H]^+$: 327.12270; found: 327.12258.

8,9,12-Trimethoxy-2,2-dimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2*H*)-one (**41f**) as a yellowish solid (140 mg/83%). Mp: 228–229 °C. IR ν_{max} (cm^{-1}) (KBr): 2968, 2928, 2832, 1644, 1613, 1483, 1432, 1309, 1274, 1202, 1148, 1202, 1148, 1089, 1103, 784. ^{1}H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 7.84 (*t*, *J* = 1.0), 7.66 (*s*), 7.03 (*s*), 4.02 (*s*, OCH_3), 4.00 (*s*, 2×OCH_3), 2.94 (*td*, *J* = 6.8, 1.0, 2H), 1.96 (*t*, *J* = 6.8, 2H), 1.45 (*s*, 6H). ^{13}C NMR (100.63 MHz, $CDCl_3$) δ (ppm): 175.6, 154.9, 152.5, 152.4, 149.0, 146.4, 135.7, 121.0, 119.2, 115.0, 114.5, 105.5, 100.0, 76.3, 61.2, 56.5, 56.4, 32.5, 27.0, 22.2. EIMS *m*/*z* (%): 371 (14, $[M+1]^+$), 370 (57, $[M]^+$), 355 (12), 316 (20), 315 (100), 314 (28), 313 (9), 300 (9), 299 (7), 285 (9), 170 (5). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{23}O_6$ $[M+H]^+$: 371.14891; found: 371.14872.

4.10. Synthesis of analogues 48a–c, 48e and 48g

4.10.1. Synthesis of diarylmethanols 42a–c, 42e, 42g, 43a–c, 43e and 43g

In a typical Experiment: Compound **19** (193 mg/0.87 mmol) solubilized in 5 mL of anhydrous THF and TMEDA (1.05 mmol, 121 mg) were added to a two-necked round-bottom flask under nitrogen atmosphere. The mixture was then placed at 0 °C and *n*BuLi (1.6 M, 1.05 mmol) was added dropwise. The mixture was allowed to react for 30 min at 0 °C. Then the benzaldehyde **28a** (176 mg/0.87 mmol) was added and allowed to react for 1 h 30 min at 0 °C and 6 h at room temperature. The reaction was quenched with a saturated solution of ammonium chloride, extracted with 3 × 20 mL of ethyl acetate. The organic phase was washed 2 × 25 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was then separated by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2). Compounds **42a** and **43a** were obtained as yellow oil (137 mg/38%), although compound **42a** was obtained in higher yield. The mixture was used in the next reaction without further purification.

Combined yield for compounds **42a** and **43a** (yellow oil, 137 mg/38%). (5-Chloro-2-(methoxymethoxy)phenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)methanol (**42a**). EIMS *m*/*z* (%): 422 (15, $[M+2]^+$), 420 (35, $[M]^+$), 407 (40), 405 (100), 373 (10), 345 (10), 329 (20), 327 (40), 312 (20), 297 (10), 205 (20), 155 (20). (5-Chloro-2-(methoxymethoxy)phenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl)methanol (**43a**). EIMS *m*/*z* (%):422 (20, $[M+2]^+$), 420 (65, $[M]^+$), 407 (30), 405 (75), 373 (20), 359 (35), 345 (50), 315 (25), 247 (20), 221 (65), 219 (55), 205 (100), 189 (30), 155 (62).

Combined yield for compounds **42b** and **43b** (yellow oil, 185 mg/41%). (5,6-Dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)(5-methoxy-2-(methoxymethoxy)phenyl)methanol (**42b**). EIMS *m*/*z* (%): 416 (15, $[M]^+$), 401 (20), 369 (15), 353 (15), 323 (100), 308 (20), 293 (15), 205 (15), 151 (20). (5,6-Dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl)(5-methoxy-2-(methoxymethoxy)phenyl) methanol (**43b**). EIMS *m*/*z* (%): 417 (10, $[M+1]^+$), 416 (40, $[M]^+$), 401 (25), 354 (70), 311 (100), 247 (40), 247 (35), 219 (95), 195 (35), 175 (30), 151 (70), 137 (25).

Combined yield for compounds **42c** and **43c** (yellow oil, 261 mg/45%). (5,6-Dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)(2-(methoxymethoxy)-5-methylphenyl)methanol (**42c**). EIMS *m*/*z* (%): 401 (10, $[M+1]^+$), 400 (40, $[M]^+$), 385 (90), 353 (30), 307 (100), 292 (25), 277 (20), 205 (30), 135 (55). (5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl)(2-(methoxymethoxy)-5-methylphenyl)methanol (**43c**). EIMS *m*/*z* (%): 401 (10, $[M+1]^+$), 400 (50, $[M]^+$), 385 (45), 355 (10), 325 (20), 395 (20), 247 (35), 219 (30), 205 (100), 179, 135 (65).

Combined yield for compounds **42e** and **43e** (yellow oil, 1.03 g/68%). (2,4-Bis(methoxymethoxy)phenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)methanol (**42e**). EIMS *m*/*z* (%): 447 (10, $[M+1]^+$), 446 (45, $[M]^+$), 432 (25), 431 (100), 399 (15), 353 (35), 247 (50), 205 (25), 181 (20), 151 (20). (2,4-bis(methoxymethoxy)phenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl) methanol (**43e**). EIMS *m*/*z* (%): 446 (20, $[M]^+$), 415 (25), 397 (40), 369 (20), 354 (30), 353 (100), 323 (30), 293 (35), 281 (20), 263 (80), 247 (55), 207 (30), 165 (25).

Combined yield for compounds **42g** and **43g** (yellow oil, 165 mg/33%). Both isomers were separated from the starting materials by silica gel flash chromatography but were not characterized by GC–MS since they were not sufficiently volatile.

4.10.2. Synthesis of benzophenones 44a–c, 44e, 44g, 45a–c, 45e and 45g

In a typical experiment: the two isomers, **42a** and **43a** (46.2 mg/0.11 mmol) and 1 mL of DMSO were place in two-necked round-bottom flask. Then it was added IBX (37 mg/0.132 mmol). After 12 h the reaction was quenched with the addition of a solution of $Na_2S_2O_3$ 10%, saturated $NaHCO_3$ and water. The aqueous phase was then extracted with 3×15 mL of ethyl acetate. The organic phase was washed with 2×25 mL of a 10% solution of $Na_2S_2O_3$, 2×25 mL of a saturated solution of $NaHCO_3$, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 9:1) and both benzophenones (**44a** and **45a**) were obtained as yellow oil (33.6 mg/73%).

Combined yield for compounds **44a** and **45a** (yellow oil, 137 mg/73%). (5-Chloro-2-(methoxymethoxy)phenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)methanone (**44a**). EIMS *m*/*z* (%): 420 (5, $[M+2]^+$), 418 (30, $[M]^+$), 405 (30), 403 (100), 387 (30), 373 (5), 371 (30), 359 (40), 327 (40), 327 (40). (5-chloro-2-(methoxymethoxy)phenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl)methanone (**45a**). EIMS *m*/*z* (%): 420 (10, $[M+2]^+$), 418 (70, $[M]^+$), 405 (35), 403 (100), 373 (25), 345 (35), 343 (95), 315 (25), 219 (50), 207 (40), 189 (30), 155 (70).

Combined yield for compounds **44b** and **45b** (yellow oil, 113 mg/86%). (5,6-Dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)(5-methoxy-2-(methoxymethoxy)phenyl)methanone (**44b**). EIMS *m*/*z* (%): 414 (15, $[M]^+$), 399 (40), 383 (50), 367 (95), 351 (100), 323 (50), 249 (30). (5,6-Dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl)(5-methoxy-2-(methoxymethoxy)phenyl)methanone (**45b**). EIMS *m*/*z* (%): 415 (10, $[M+1]^+$), 414 (55, $[M]^+$), 399 (60), 367 (35), 339 (100), 311 (30), 295 (35), 219 (40), 189 (35), 175 (60), 151 (90).

Combined yield for compounds **44c** and **45c** (yellow oil, 66 mg/87%). (5,6-Dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)(2-(methoxymethoxy)-5-methylphenyl)methanone (**44c**). EIMS *m*/*z* (%): 399 (5, $[M+1]^+$), 398 (40, $[M]^+$), 383 (100), 367 (60), 351 (50), 335 (55), 307 (40). (5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl)(2-(methoxymethoxy)-5-methylphenyl)methanone (**45c**). EIMS *m*/*z* (%): 399 (10, $[M+1]^+$), 398 (70, $[M]^+$), 383 (80), 353 (20), 323 (100), 135 (65).

Combined yield for compounds **44e** and **45e** (yellow oil, 870 mg/88%). (2,4-bis(methoxymethoxy)phenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)methanone (**44e**). EIMS *m*/*z* (%): 445 (10, $[M+1]^+$), 444 (45, $[M]^+$), 429 (100), 413 (40), 381 (50), 353 (20), 309 (25), 249 (15). (2,4-bis(methoxymethoxy)phenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl)methanone (**45e**). EIMS *m*/*z* (%): 445 (5, $[M+1]^+$), 444 (30, $[M]^+$), 429 (40), 400 (25), 385 (60), 369 (100), 341 (25), 205 (20).

Combined yield for compounds **44g** and **45g** (yellow oil, 135 mg/74%). Both isomers were separated by silica gel flash chromatography but were not characterized by GC–MS since they were not sufficiently volatile.

4.10.3. Synthesis of benzophenones 46a–c, 46e, 46g, 47a–c, 47e and 47g

In a typical experiment: Compounds **44a** and **45a** (80.6 mg, 0.19 mmol) and 1.5 mL of CH_3CN were place in a round-bottom flask. The solution was placed at 0 °C and $NbCl_5$ (52 mg, 0.19 mmol) was added in one portion. The mixture was stirred at 0 °C for 10 min and then allowed to warm to room temperature and let stirring for more 45 min. After this time, the reaction was quenched with saturated solution of $NaHCO_3$. The mixture was extracted with 3×15 mL of ethyl acetate. The organic phase was washed with 2×100 mL of brine, dried over sodium sulfate anhydrous and the organic solvent evaporated. The mixture of the two isomers (**46a** and **47a**) was obtained as yellow oil in quantitative yield and used in the next reaction without further purification.

Compounds **46a** and **47a** as yellow oil in quantitative yield. (5-Chloro-2-hydroxyphenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)methanone (**46a**). EIMS *m*/*z* (%): 376 (5, $[M+2]^+$), 374 (30, $[M]^+$), 361 (40), 359 (100), 343 (40), 219 (20), 164 (25), 155 (30). (5-Chloro-2-hydroxyphenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl)methanone (**47a**). EIMS *m*/*z* (%): 376 (5, $[M+2]^+$), 374 (30, $[M]^+$), 361 (40), 359 (100), 331 (20), 219 (20), 205 (20), 155 (30).

Compounds **46b** and **47b** as yellow oil in quantitative yield. (5,6-Dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)(2-hydroxy-5-methoxyphenyl)methanone (**46b**). EIMS *m*/*z* (%): 370 (20, $[M]^+$), 355 (60), 339 (100), 309 (25), 205 (20), 162 (20). (5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl)(2-hydroxy-5-methoxyphenyl)methanone (**47b**). EIMS *m*/*z* (%): 371 (10, $[M+1]^+$), 370 (40, $[M]^+$), 355 (100), 327 (20), 295 (15), 205 (20), 151 (40).

Compounds **46c** and **47c** as yellow oil in quantitative yield. (5,6-Dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)(2-hydroxy-5-methylphenyl)methanone (**46c**). EIMS *m*/*z* (%): 354 (25, $[M]^+$), 339 (90), 323 (100), 293 (40), 154 (60), 135 (50). (5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl)(2-hydroxy-5-methylphenyl)methanone (**47c**). EIMS *m*/*z* (%): 354 (35, $[M]^+$), 339 (100), 281 (30), 205 (20), 135 (40).

Combined yield for compounds **46e** and **47e** (yellow oil, 76 mg/85%). (2,4-Dihydroxyphenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-7-yl)methanone (**46e**). EIMS *m*/*z* (%): 357 (5, $[M+1]^+$), 356 (30, $[M]^+$), 341 (100), 325 (70), 295 (20), 205 (25), 176 (20), 155 (30), 137 (50). (2,4-dihydroxyphenyl)(5,6-dimethoxy-2,2-dimethyl-2*H*-benzopyran-8-yl)methanone (**47e**). EIMS *m*/*z* (%): 357 (5, $[M+1]^+$), 356 (40, $[M]^+$), 341 (100), 313 (20), 281 (30), 207 (40), 137 (60).

Combined yield for compounds **46g** and **47g** (yellow oil, 60 mg/56%). Both isomers were separated by silica gel flash chromatography but were not characterized by GC–MS since they were not sufficiently volatile.

4.10.4. Synthesis of xanthones 48a–c, 48e and 48g

With conventional heating

In a typical experiment: a solution of compound **46a** and **47a** (68 mg, 0.18 mmol) in 1 mL of DMF were place in a two-necked round-bottom flask and then it was added Cs_2CO_3 (88 mg, 0.27 mmol). The mixture was stirred at 50 °C for 21 h. The mixture was allowed to cool to room temperature and poured into crushed

ice. The aqueous phase was then extracted with 3 × 50 mL of diethyl ether. The organic phase was washed with 2 × 50 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 95:5). Compound **48a** was obtained as yellow solid (35 mg, 65%) and compound **47a** (7.1 mg) was also isolated.

9-Chloro-5-methoxy-2,2-dimethylpyrano[2,3-b]xanthen-11(2*H*)-one (**48a**) yellowish solid (35 mg/65%). Mp: 163–164 °C. IR ν_{max} (cm^{-1}) (KBr): 2954, 2913, 2846, 1644, 1603, 1478, 1435, 1256, 1116, 1079, 1017, 806, 699. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 8.31 (*d*, *J* = 2.6)), 7.69 (*dd*, *J* = 8.8, 2.6), 7.54 (*d*, *J* = 8.8), 7.48 (*s*), 6.82 (*d*, *J* = 10.8), 5.99 (*d*, *J* = 10.8), 4.09 (*s*, OCH_3), 1.51 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 175.3, 154.1, 149.3, 144.6, 143.6, 135.8, 134.5, 129.6, 126.0, 122.1, 121.9, 121.9, 119.7, 116.3, 106.7, 76.3, 62.3, 27.8. EIMS *m*/*z* (%): 344 (10, $[M+2]^+$), 342 (70, $[M]^+$), 329 (35), 327 (100), 314 (10), 312 (40), 156 (20). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{16}ClO_4$ $[M+H]^+$: 343.07316; found: 343.07304. Compound **47a** (7.1 mg).

5,9-Dimethoxy-2,2-dimethylpyrano[2,3-b]xanthen-11(2H)-one (**48b**) yellow solid (46 mg/51%). Mp: 174–175 °C. IR ν_{max} (cm^{-1}) (KBr): 2978, 2943, 2845, 1642, 1617, 1488, 1444, 1202, 1127, 783. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.72 (*d*, *J* = 3.1), 7.53 (*d*, *J* = 9.2), 7.52 (*s*), 7.36 (*dd*, *J* = 9.2, 3.1), 6.83 (*d*, *J* = 10.0), 5.98 (*d*, *J* = 10.0), 4.10 (*s*, OCH_3), 3.97 (*s*, OCH_3), 1.52 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 176.3, 155.9, 150.7, 148.8, 144.8, 143.6, 135.6, 124.7, 121.7, 121.5, 121.4, 119.4, 116.4, 106.5, 105.6, 76.2, 62.2, 55.9, 27.7. EIMS *m*/*z* (%): 338 (30, $[M]^+$), 323 (100), 308 (40), 161 (20). HRMS (ESI) *m*/*z* calcd for $C_{20}H_{19}O_5$ $[M+H]^+$: 339.12270, found: 339.12259. Compound **47b** (5 mg).

5-Methoxy-2,2,9-trimethylpyrano[2,3-b]xanthen-11(2H)-one (**48c**) yellowish solid (85 mg/72%). Mp: 181–182 °C. IR ν_{max} (cm^{-1}) (KBr): 2973, 2924, 1642, 1616, 1484, 1437, 1305, 1119. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 8.13 (*d*, *J* = 2.0), 7.56 (*dd*, *J* = 8.4, 2.0), 7.51 (*s*), 7.48 (*d*, *J* = 8.4), 6.83 (*d*, *J* = 10.1), 5.97 (*d*, *J* = 10.1), 3.98 (*s*, OCH_3), 2.38 (*s*, CH_3), 1.39 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 176.5, 154.0, 148.8, 144.7, 143.6, 135.7, 135.5, 133.6, 125.9, 122.2, 121.4, 120.9, 117.7, 116.4, 106.7, 76.1, 62.2, 27.7, 20.8. EIMS *m*/*z* (%): 323 (5, $[M+1]^+$), 322 (70, $[M]^+$), 308 (20), 307 (100), 292 (40), 153 (20). HRMS (ESI) *m*/*z* calcd for $C_{20}H_{19}O_4$ $[M+H]^+$: 323.12779, found: 323.12768. Compound **47c** (4.8 mg).

With microwave heating**.**

In a typical experiment: To a solution of compounds **46e** and **47e** (210 mg, 0.11 mmol) in 1.5 mL of DMF was added K_2CO_3 (163 mg, 1.18 mmol). The mixture was irradiated with microwave (200 W max) for 15 min at 140 °C. The mixture was allowed to cool to room temperature and poured into crushed ice. The aqueous phase was then extracted with 3 × 30 mL of diethyl ether. The organic phase was washed with 2 × 30 mL of brine, dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2). Compound **48e** was obtained as light yellow solid (87 mg, 22%).

8-Hydroxy-5-methoxy-2,2-dimethylpyrano[2,3-*b*]xanthen-11(2*H*)-one (**48e**) as a light yellow solid (87 mg/22%). Mp: 193–194 °C. IR ν_{max} (cm^{-1}) (KBr): 3112, 2975, 2936, 2845, 1609, 1435, 1234, 1101, 1005, 846, 780. ^{1}H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 8.25 (*d*, *J* = 8.7), 7.44 (*s*), 7.27 (*d*, *J* = 2.3), 7.13 (*dd*, *J* = 8.7, 2.3), 6.78 (*d*, *J* = 9.9), 5.93 (*d*, *J* = 9.9), 4.06 (*s*; OCH_3), 1.47 (*s*, 6H). ^{13}C NMR (100.63 MHz, $CDCl_3$) δ (ppm): 175.6, 161.4, 157.3, 149.1, 143.6, 135.5, 128.7, 122.4, 121.4, 116.9, 116.4, 113.9, 106.9, 103.5, 76.3, 62.4, 27.8. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}O_5$ $[M+H]^+$: 325.10705; found: 325.10695.

8-(Diethylamino)-5-methoxy-2,2-dimethylpyrano[2,3-*b*]xanthen-11(2*H*)-one (**48g**) as a yellowish solid (20 mg/44%). MP: 56–58 °C. IR ν_{max} (cm^{-1}) (KBr): 2967, 2929, 2868, 1640, 1607, 1435, 114, 1073, 813. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 8.12 (*d*, *J* = 9.1), 7.46 (*s*), 6.77 (*d*, *J* = 10.2), 6.71 (*dd*, *J* = 9.1, 2.4), 6.59 (*d*, *J* = 2.4), 5.89 (*d*, *J* = 10.2), 4.05 (*s*, OCH_3), 3.49 (*q*, *J* = 7.1, 4H), 1.47 (*s*, 6H), 1.27 (*t*, *J* = 7.1, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 174.8, 158.4, 152.4, 148.5, 144.4, 143.3, 134.7, 128.1, 122.8, 120.4, 116.6, 111.1, 109.5, 106.9, 96.1, 75.9, 62.3, 44.8, 27.6, 12.5. HRMS (ESI) *m*/*z* calcd for $C_{23}H_{26}NO_4$ $[M+H]^+$: 380.18563; found: 380.18546.

4.11. Synthesis of analogues 55a, 55f and 55g

4.11.1. Synthesis of diarylmethanols 49a, 49f, 49g, 50a, 50f and 50g

Same experimental procedure described in Section 4.10.1.

Combined yield for compounds **49a** and **50a** (yellow oil, 1.48 g/40%) Both isomers were separated from the starting materials by silica gel flash chromatography but were not characterized by GC–MS since they were not sufficiently volatile.

Combined yield for compounds **49f** and **50f** (yellow oil, 951 mg/50%) Both isomers were separated from the starting materials by silica gel flash chromatography but were not characterized by GC–MS since they were not sufficiently volatile.

Combined yield for compounds **49g** and **50g** (yellow oil, 750 mg/16%). Both isomers were separated from the starting materials by silica gel flash chromatography but were not characterized by GC–MS since they were not sufficiently volatile.

4.11.2. Synthesis of benzophenones 51a, 51f, 51g, 52a, 52f and 52g

Same experimental procedure described in Section 4.10.2.

Combined yield for compounds **51a** and **52a** (yellow oil, 1.13 g/91%). Both isomers were separated by silica gel flash chromatography but were not characterized by GC–MS since they were not sufficiently volatile.

Combined yield for compounds **51f** and **52f** (yellow oil, 489 mg/59%). Both isomers were separated silica gel flash chromatography but were not characterized by GC–MS since they were not sufficiently volatile.

Combined yield for compounds **51g** and **52g** (yellow oil, 135 mg/74%). Both isomers were separated by silica gel flash chromatography but were not characterized by GC–MS since they were not sufficiently volatile.

4.11.3. Synthesis of benzophenones 53a, 53f, 53g, 54a, 54f and 54g

In a typical experiment: Compounds **51f** and **52f** (575 mg/1.14 mmol) and 25 mL of anhydrous methanol were placed in a two-necked round-bottom flask and under nitrogen atmosphere. To the solution was added Pd/C 10% (15% weight/86 mg) in one portion. Triethylsilane (2.7 mL, 17.1 mmol) was then added dropwise. The mixture was allowed to stir for 15 min. The product was filtered over celite and washed 3 times with methanol. The methanol was then evaporated and the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 9:1). Compounds **53f** and **54f** were isolated as yellowish oil (380 mg/83%).

Combined yield for compounds **53a** and **54a** (yellow oil, 400 mg of impure mixture). From the GC–MS chromatogram we observed not only the desired compounds but also hydrodechlorinated products which we were not able to isolate.

Combined yield for compounds **53f** and **54f** (yellow oil, 380 mg/83%). (5,6-Dimethoxy-2,2-dimethyl-3,4-dihydrobenzopyran-7-yl)(2-hydroxy-4,5-dimethoxyphenyl)methanone (**53f**). EIMS *m*/*z* (%): 403 (1, $[M+1]^+$), 402 (4, $[M]^+$), 372 (20), 371 (100), 315 (7), 303 (4), 301 (5), 287 (5), 222 (3), 207 (5), 180 (9), 166 (5), 151 (4), 125 (4), 69 (5), 53 (3). (5,6-dimethoxy-2,2-dimethyl-3,4-dihy-

drobenzopyran-8-yl)(2-hydroxy-4,5-dimethoxyphenyl)methanone (**54f**). EIMS *m*/*z* (%): 403 (2, $[M+1]^+$), 402 (8, $[M]^+$), 221 (6), 207 (8), 182 (10), 181 (100), 125 (6), 110 (3), 95 (3).

Combined yield for compounds **53g** and **54g** (yellow oil, 250 mg/69%). Compounds decomposed with the conditions used in the GC–MS.

4.11.4. Synthesis of xanthones 55a, 55f and 55g

Same experimental procedure using microwave heating described in Section 4.10.4.

9-Chloro-5-methoxy-2,2-dimethyl-3,4-dihydropyrano[2,3-b]xanthen-11(2H)-one (**55a**) as a white solid (105 mg/37%). Mp: 167–168 °C. IR ν_{max} (cm^{-1}) (KBr): 2976, 2933, 1841, 1658, 1615, 1466, 1432, 1120, 1075, 942, 821. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 8.28 (*d*, *J* = 2.6), 7.65 (*dd*, *J* = 8.9, 2.6), 7.52 (*d*, *J* = 8.9), 7.48 (*s*), 4.09 (*s*, OCH_3), 2.95 (*t*, *J* = 6.8, 2H), 1.89 (*t*, *J* = 6.8, 2H), 1.40 (*s*, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 175.6, 154.0, 150.9, 146.9, 143.2, 134.4, 129.2, 125.9, 124.1, 121.9, 121.2, 119.7, 107.2, 74.4, 61.1, 31.5, 26.6, 18.2. EIMS *m*/*z* (%): 346 (2, $[M+2]^+$), 345 (9, $[M+1]^+$), 344 (16, $[M]^+$), 290 (24), 289 (51), 288 (50), 259 (34), 231 (36), 217 (51), 168 (57), 161 (29), 139 (52), 126 (84), 77 (33), 75 (58), 74 (41), 63 (100), 51 (61). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}ClO_4$ $[M+H]^+$: 345.08881, found: 345.08865.

5,8,9-Trimethoxy-2,2-dimethyl-3,4-dihydropyrano[2,3-b]xanthen-11(2H)-one (**55f**) as a light yellow solid (130 mg/46%). Mp: 216–217 °C. IR ν_{max} (cm^{-1}) (KBr): 2979, 2933, 2830, 1642, 1615, 1479, 1447, 1432, 1270, 1097, 1004, 779. ^1H NMR (400.21 MHz, $CDCl_3$) δ (ppm): 7.65 (*s*), 7.49 (*s*), 6.96 (*s*), 4.06 (*s*, OCH_3), 4.03 (*s*, OCH_3), 3.99 (*s*, OCH_3), 2.92 (*t*, *J* = 6.8, 2H), 1.86 (*t*, *J* = 6.8, 2H), 1.37 (*s*, 6H). ^{13}C NMR (100.63 MHz, $CDCl_3$) δ (ppm): 175.7, 155.2, 152.1, 150.5, 146.6, 145.9, 143.4, 122.8, 121.5, 114.3, 107.1, 105.4, 99.7, 74.3, 61.1, 56.5, 56.3, 31.8, 26.7, 18.2. EIMS *m*/*z* (%): 371 (25, $[M+1]^+$), 370 (100, $[M]^+$), 355 (8), 316 (11), 316 (62), 314 (50), 299 (8), 286 (8), 285 (26), 271 (16), 257 (10), 243 (10), 207 (7), 170 (11). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{23}O_6$ $[M+H]^+$: 371.14891; found: 371.14872.

8-(Diethylamino)-5-methoxy-2,2-dimethyl-3,4-dihydropyrano[2,3-b]xanthen-11(2H)-one (**55g**) as a light yellow solid (100 mg/48%). Mp: 126–128 °C. IR ν_{max} (cm^{-1}) (KBr): 2067, 2921, 2876, 1644, 1609, 1438, 1343, 1098, 773. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 8.12 (*d*, *J* = 9.1), 7.47 (*s*), 6.69 (*dd*, *J* = 9.1, 2.5), 6.54 (*d*, *J* = 2.5), 4.05 (*s*, OCH_3), 3.48 (*q*, *J* = 7.1, 4H), 2.92 (*t*, *J* = 6.9, 2H), 1.85 (*t*, *J* = 6.9, 2H), 1.37 (*s*, 6H), 1.27 (*t*, *J* = 7.1, 6H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 175.2, 158.3, 152.6, 150.0, 145.6, 143.3, 128.1, 122.1, 122.0, 110.8, 109.2, 107.4, 96.1, 74.0, 61.1, 44.7, 31.8, 26.7, 18.1, 12.5. HRMS (ESI) *m*/*z* calcd for $C_{23}H_{28}NO_4$ $[M+H]^+$: 382.20128; found: 382.20109.

4.12. Biological activity

4.12.1. Cell culture

The adherent cell lines MCF-7 (breast adenocarcinoma, ECACC, UK), NCI-H460 (non-small cell lung cancer, a kind gift from NCI, Bethesda, USA), A375-C5 (melanoma, ECACC, UK) and the suspension cell line HL-60 (acute myeloid leukemia, DSMZ, Germany) were routinely maintained in RPMI-1640 (with Glutamax, Lonza), supplement with 5% heat inactivated fetal bovine serum (FBS, PAA) at 37 °C in a humidified incubator with 5% CO_2. Cell number and viability were routinely determined with Trypan blue (Sigma). All the experiments were performed with cells in exponential growth and presenting more than 90% viability.

4.12.2. Cell growth inhibition assay

Cells were plated into 96-well tissue culture plates at appropriate densities (MCF-7 and NCI-H460 at 5×10^3 cells/well, A375-C5 at 7.5×10^3 cells/well and HL-60 cells at 1×10^4 cells/well) and incubated for 24 h. Cells were then treated with serial dilutions of the different compounds (ranging from 0 to 150 μM whenever possible). Following 48 h of incubation, the effect of the compounds in the growth of the different cell lines was analyzed using the Sulforhodamine B (SRB) assay, as adopted by the National Cancer Institute (NCI, USA).[42,43] Briefly, following incubation, cells were fixed in situ with ice cold trichloroacetic acid (at 10% for adherent cells and at 16.7% for the cells growing in suspension). Following SRB staining, plates were washed with 1% acetic acid, the bound dye was then solubilized with 10 mM Tris Base and absorbance was measured at 510 nm in a microplate reader (Biotek Instruments Inc, Synergy XS, Winooski, USA). The GI_{50} values for the compounds synthesized (concentration causing a 50% inhibition of cell growth) were calculated from the plotted results. Doxorubicin was used as a positive control. The effect of the vehicle solvent (DMSO) on the growth of these cell lines was evaluated in preliminary experiments, by exposing untreated control cells to the maximum concentration of DMSO used in each assay (0.25%).

4.12.3. Statistical analysis

All experimental data are presented as means ± SE from at least three independent experiments.

4.13. Lipophilicity

4.13.1. Materials

The egg yolk phosphatidylcholine (EPC), HEPES, DMSO and NaCl were acquired from Sigma–Aldrich, the hexadecylphosphocoline (HDPC) from Cayman chemicals and the water used was double-deionised with conductivity less than 0.1 μS cm^{-1}. The 96-well plate reader used was a Synergy HT from Bio-Tek Instruments and the double beam spectrophotometer was a JASCO V660. The extrusion device used was a Lipex® Extruder manufactured from Northern Lipids and the filters were acquired from Whatman. The determination of the UV-spectrum was made either in a flat-bottomed 96-well UV-plates acquired from BD Biosciences or fused quartz cuvettes of 1.4 mL from Hellma.

4.13.2. Liposome preparation

Liposomes were prepared by evaporation to dryness with a nitrogen stream of an EPC solution prepared with chloroform/methanol (9/1). The resulting dried lipid film was dispersed with a buffer (HEPES: 10 mmol L^{-1}, *I* = 0.1 mol L^{-1} with NaCl, pH 7.4) and the mixture was vortex mixed to give multilamellar liposomes (MLVs). The MLVs were extruded 10 times through polycarbonate filters with a pore diameter of 100 nm to form large unilamellar vesicles (LUVs).

4.13.3. Micelle preparation

Micelle solutions were prepared by dissolution of hexadecylphosphocholine (HDPC) in buffer (HEPES: 10 mmol L^{-1}, *I* = 0.1 mol L^{-1} with NaCl, pH 7.4) and mixed by vortex.

4.13.4. General procedure for K_p determination

The procedure used was adapted from the literature.[46] and was the following: (i) 3 μL of compound solubilized in DMSO (concentration established before in 4.11.5) was added to each well; (ii) increasing volumes of liposome or micelles were added to each well and the final concentration for 300 μL were 0 (only buffer), 50, 100, 200, 300, 400, 500, 600, 700, 800, 900 and 1000 μM. In the end, for the same concentration of xanthone, increasing concentrations of lipid were prepared; (iii) HEPES buffer was added to make up 300 μL of final volume; (iv) a blank was used for each concentration of lipid containing 1% of DMSO; (v) the plate was incubated at 37 ± 0.1 °C for 30 min and then the spectrum was traced from 240 to 600 nm. For poorly soluble compounds, the solutions were prepared with the same concentration but in

eppendorf (1.5 mL) instead. Each solution was mixed by vortex and incubated for 30 min. The spectrum ranging from 240 to 600 nm was traced individually in a double-beam spectrophotometer for each sample at 37 °C. The compound concentration used in the determination of the K_p varied from 2.5 μM for the most poorly soluble compounds to 20 μM for the most soluble.

Partition coefficient (K_p) was calculated by adjusting experimental data through a nonlinear regression of Levenberg–Marquardt in where the adjustable parameter was K_p. The program was available free of charge in the Supplementary information from.[46]

4.13.5. Statistical analysis

All experimental data are presented as means ± SE from at least three independent experiments. The linear regression analysis was calculated using the IBM SPSS Statistics 20.

4.14. Solubility

4.14.1. Materials

The HEPES, DMSO and NaCl were acquired from Sigma-Aldrich and the water used was double-deionised with conductivity less than 0.1 μS cm^{-1}. The double beam spectrophotometer was a JASCO V660. The solutions were filtered through a 0.1 μm filter from Millipore. The UV/Vis spectrum was traced with fused quartz cuvettes of 1.4 mL from Hellma.

4.14.2. Standard calibration curve determination

The standard calibration curve for each compound was prepared using a stock solution of 20 mM in DMSO. The final solutions for each standard were prepared containing 15 μL of DMSO and 1485 μL of buffer. An UV/Spectrum ranging from 240 to 500 nm was traced for each standard and a calibration curve was established using the second derivative. The concentrations of the standards ranged from 0.1 to 20 μM.

4.14.3. Solubility procedure

To 2 mL of an HEPES beffer (10 mmol L^{-1}, I = 0.1 mol L^{-1} with NaCl, pH 7.4) was added each compound until a saturated solution was obtained. The suspension of each compound (in triplicate) was agitated at 37 °C for 24 h. Each sample was filtered through a 0.1 μm filter and 1.485 μL of each filtrate was added to another eppendorf containing 15 μL of DMSO. The UV/Vis spectrum was traced in a double-beam spectrophotometer and the concentration was determined according to the standard calibration curve for each compound.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.03.079. These data include MOL files and InChiKeys of the most important compounds described in this article.

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