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# Microwave-assisted organocatalytic intramolecular Knoevenagel/ hetero Diels-Alder reaction with *O*-(arylpropynyloxy)-salicylaldehydes. Synthesis of polycyclic embelin derivatives.

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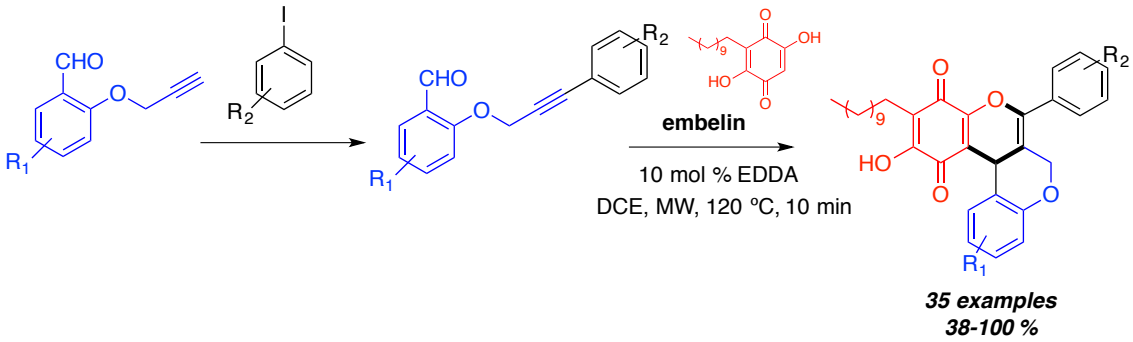



A highly efficient and regioselective approach to new polycyclic embelin derivatives through a domino Knoevenagel condensation /intramolecular hetero Diels-Alder reaction using *O*-(arylpropynyloxy)-salicylaldehydes in the presence of ethylenediamine diacetate (EDDA) is reported. This organocatalyzed protocol is compatible toward a wide range of aryl-substituted alkynyl ethers with electron-donating and electron-withdrawing groups. When other active methylene compounds were subjected to this domino reaction the corresponding adducts were obtained in high yield.

## Introduction

Natural products scaffolds have been well recognised as "privileged structures" in terms of their ability to be the basis for successful drugs.[1] An assessment of all FDA-approved new molecular entities (NMEs) reveals that natural products and their derivatives represent over one-third of all NMEs.[2] Such scaffolds can be used as cores of compound libraries. As a privileged scaffold, the benzoquinone core is ubiquitous in many bioactive natural products and pharmaceuticals.[3] Understandably, particular emphasis has been put on the development of methodologies for its synthesis, with an aim to develop facile and efficient protocols to provide benzoquinone and benzoquinone-based compound libraries.[4]

Embelin (**1**) is a naturally occurring alkyl substituted hydroxybenzoquinone and a major constituent of the Andean medicinal plant *Oxalis erythrorhiza Gillies ex Hook & Arn,* belonging to the Oxalidaceae family.[5]

It has been reported that embelin possess antidepressant,[6] antitumor,[7] anti-inflammatory,[8] analgesic,[9] antioxidant,[10] antidiabetic,[11] wound healing,[12] and antibacterial properties.[13] All these activities make embelin a "promiscuous compound"[14] due specific interactions with multiple targets such as 5-lipoxygenase,[15] the stress chaperone mortalin,[16] XIAPs,[17] NFκB,[18] STAT-3,[19] Akt[20] and mTOR,[21] and consequently an interesting scaffold for synthesizing new and more selective therapeutic agents.

Since that increased molecular complexity in natural products and diverse compounds, is associated with improved selectivity and frequency of binding,[22] the development of libraries of complex compounds with balanced physicochemical properties could led to obtain compounds having efficient binding with specific

biological targets.[23] In this sense, the use of domino reactions is a good synthetic strategy for the construction of complex polycyclic scaffolds.[24]

In recent years the domino-Knoevenagel-hetero-Diels-Alder reaction, developed by Tietze's group, has emerged as a powerful process that not only allows the efficient synthesis of complex compounds but also permits the preparation of highly diverse molecules, specially pyran and pyrano-fused carbocycles. These pyran and pyrano-fused ring systems represent important molecular frameworks, which are found in a wide range of natural and synthetic bioactive molecules.[25]

There are numerous examples of the use of unsaturated aromatic- and aliphatic aldehydes with several 1,3-dicarbonyl compounds in intramolecular domino Knoevenagel-hetero-Diels-Alder reaction (DKHDA). However, the use of alkynes as dienophiles in DKHDA reactions is limited due to their low reactivity compared to alkenes.[26] In most of cases non-activated terminal alkynes have been used. Thus the pioneer works of Balalaie *et al* reported the use of CuI as an efficient Lewis acid for activation of various non-activated alkynes using different organic solvents,[27] inclusive trifluoroethanol.[28] In these cases the formation of an intermediate copper acetylide is postulated which is consistent with the observation that only terminal acetylenes participate in the reaction, and end-capped substrates do not undergo the cycloaddition reaction. Immobilized $ZrO_2$-nanopowder in the ionic liquid 1-butyl-3-methylimidazolium nitrate [bmim][$NO_3$] was used as a suitable Lewis-acid for DKHDA reactions with unactivated terminal alkynes.[29] Parmar *et al* reported a solvent-free tetrabutylammonium-hydrogensulfate catalysed DKHDA using 2-(alkynyloxy)acetophenones with pyrazolones.[30]

Most of the examples of DKHDA with non-activated terminal alkynes use 1,3-dicarbonyl compounds such as 1,3-indanedione,[27a] Meldrum's acid and dimethyl

barbituric acid.[31] Some active methylene compounds such as 4-hydroxy-coumarin,[27c] benzoylacetonitrile,[27b] 1-phenyl-3-methyl pyrazolone,[30, 32] dihydroindole-2-thione, 4-hydroxydithiocoumarin[33] have been also used, but 2-hydroxy-1,4-benzoquinones have never been employed in this kind of transformation involving alkynes.

To the best of our knowledge, there are not any papers on intramolecular DKHDA reactions using non terminal alkynes type *O*-(arylpropynyloxy)-salicylaldehydes. Due to our interest in the preparation of bioactive embelin derivatives[13a,13b, 25c] and, since this natural benzoquinone (**1**) contains a 2-hydroxy-1,4-quinonic moiety which is a synthetic equivalent to a 1,3-dicarbonyl compound, this molecule is an adequate substrate for DKHDA reactions using the mentioned non-terminal alkynes. Thus, a series of angular polycyclic embelin derivatives with two points of diversity could be obtained and some compounds result more selective and efficient than embelin (**1**) in biological bioassays.

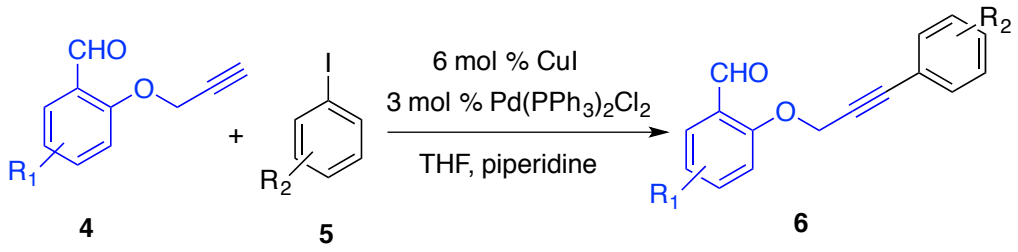
**Results and discussion**

Compounds that contain an aldehyde functionality together with a suitably placed 3-phenylprop-2-yn-1-oxy moiety are substrates which have never been studied before in the DKHDA protocol. These types of compounds were formed from the corresponding *O*-propargylated salicylaldehydes and aryl iodides *via* Sonogashira cross-coupling reactions. The starting *O*-propargylated salicylaldehydes (**4**) were obtained in excellent yields by reaction of salicylaldehyde derivatives and propargyl bromide using $K_2CO_3$ in dimethylformamide.[34]

For the Sonogashira cross-coupling reactions, initially we selected the reaction conditions published by Kwong *et al* [35] for the preparation of terminal-substituted alkynyl ethers. They used $Pd(PPh_3)_2Cl_2$ (3 mol%), Cu I (6 mol%), piperidine (2 equiv)

and dry toluene under nitrogen at 30ºC. Using these conditions in the reaction of propargylated aldehyde **4a** and 1-iodo-4-methoxybenzene (**5a**), the resulting alkynyl ether (**6a**) was obtained in 56 % yield. In order to improve this yield we carried out the reaction using other aprotic and more polar solvents such as DMSO and DMF but we did not obtain a higher yield (43% DMSO, 58% DMF), only when THF was used a 86% yield was achieved. Table 1 summarizes the yields obtained in the preparation of a variety of aryl-substituted alkynyl ethers with two points of diversity.

**Table 1.** Preparation of aryl-substituted alkynyl ethers (**6a-6ai**)




| Entry | $R_1$ | $R_2$ | product | yield (%)[a] |
|---|---|---|---|---|
| 1 | 5-Cl | 4-$OCH_3$ | **6a** | 86 |
| 2 | 5-Cl | 3-$OCH_3$ | **6b** | 97 |
| 3 | 5-Cl | 2-$OCH_3$ | **6c** | 74 |
| 4 | 5-Cl | 3-OH | **6d** | 69 |
| 5 | 5-Cl | H | **6e** | 98 |
| 6 | 5-Cl | 3-$NO_2$ | **6f** | 100 |
| 7 | 5-Cl | 3-$CF_3$ | **6g** | 96 |
| 8 | 5-Br | 4-$OCH_3$ | **6h** | 85 |
| 9 | 5-Br | 3-$OCH_3$ | **6i** | 88 |
| 10 | 5-Br | 2-$OCH_3$ | **6j** | 57 |
| 11 | 5-Br | 3-OH | **6k** | 38 |
| 12 | 5-Br | H | **6l** | 94 |

| | | | | |
|---|---|---|---|---|
| 13 | 5-Br | 3-$NO_2$ | **6m** | 88 |
| 14 | 5-Br | 3-$CF_3$ | **6n** | 82 |
| 15 | H | 4-$OCH_3$ | **6o** | 64 |
| 16 | H | 3-$OCH_3$ | **6p** | 85 |
| 17 | H | 2-$OCH_3$ | **6q** | 61 |
| 18 | H | 3-OH | **6r** | 83 |
| 19 | H | H | **6s** | 78 |
| 20 | H | 3-$NO_2$ | **6t** | 84 |
| 21 | H | 3-$CF_3$ | **6u** | 86 |
| 22 | 4-$OCH_3$ | 4-$OCH_3$ | **6v** | 82 |
| 23 | 4-$OCH_3$ | 3-$OCH_3$ | **6w** | 84 |
| 24 | 4-$OCH_3$ | 2-$OCH_3$ | **6x** | 56 |
| 25 | 4-$OCH_3$ | 3-OH | **6y** | 61 |
| 26 | 4-$OCH_3$ | H | **6z** | 87 |
| 27 | 4-$OCH_3$ | 3-$NO_2$ | **6aa** | 98 |
| 28 | 4-$OCH_3$ | 3-$CF_3$ | **6ab** | 87 |
| 29 | 4-$CO_2C_2H_5$ | 4-$OCH_3$ | **6ac** | 85 |
| 30 | 4-$CO_2C_2H_5$ | 3-$OCH_3$ | **6ad** | 97 |
| 31 | 4-$CO_2C_2H_5$ | 2-$OCH_3$ | **6ae** | 59 |
| 32 | 4-$CO_2C_2H_5$ | 3-OH | **6af** | 55 |
| 33 | 4-$CO_2C_2H_5$ | H | **6ag** | 98 |
| 34 | 4-$CO_2C_2H_5$ | 3-$NO_2$ | **6ah** | 90 |
| 35 | 4-$CO_2C_2H_5$ | 3-$CF_3$ | **6ai** | 100 |

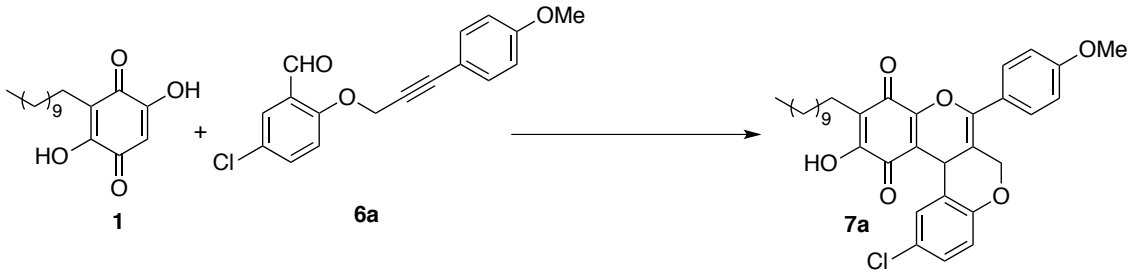
[a]Isolated yield

The reaction appeared to be quite general with respect to a wide variety of functional groups such as -Cl, -Br, -OMe, and - $CO_2C_2H_5$ in salicylaldehyde. The best

yields were obtained with iodo-benzenes having electron-withdrawing substituents as 1-iodo-3-nitrobenzene (entries 6, 13, 20, 27, 34) and 1-iodo-3-(trifluoromethyl)benzene (entries 7, 14, 21, 28, 35). However, the steric hindrance of the iodo-benzenes had significant effect on the reaction, and the yields were decreased for 1-iodo-2-methoxybenzene (entries 3, 10, 17, 24, 31). Only in one case, with the bromo-salicylaldehyde derivative (entry 10), together the formation of the corresponding aryl-substituted alkynyl ethers (**6j**, 57%), an alkyne dimer was also obtained in 26% yield.

To optimize the DKHDA reaction conditions, the reaction of compound **6a** and embelin (**1**) was chosen as a model reaction. We decided to carry out the reaction using ethylendiamine diacetate (EDDA, 10 mol %) as an effective organocatalyst for the initial Knoevenagel condensation. In the first attempt we investigated if in the absence of other additional catalyst, the DKHDA adduct could be formed. We were delighted to find that adduct **7a** was obtained in 23% in refluxing ethanol (Table 2, entry 1). A series of solvents (acetonitrile, toluene, dichloromethane, and dichloethane) were investigated (entries 2-5). Amongst the solvents tested, dichloroethane provided the best yield (entry 5). We also carried out the DKHDA reaction without EDDA (entry 6), and adduct **7a** was achieved in low yield (9%). When the reaction was performed at room temperature compound **7a** was obtained in 47% yield after 24 h (entry 7). In order to improve the yield, microwave irradiation was also used and, adduct **7a** was obtained in 93% yield in DCE at 120º C, for 10 min.

**Table 2.** Optimization of the DKHDA reaction between **1** and **6a**

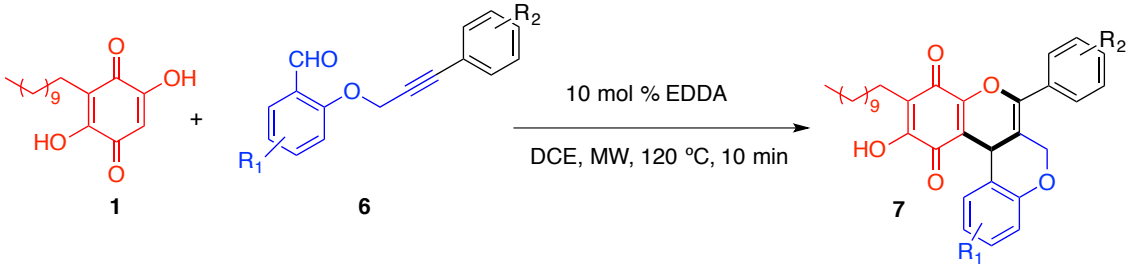


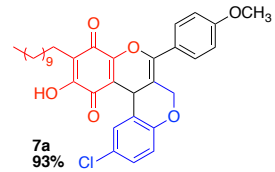

| Entry | Conditions | Yield[a] (%) |
|---|---|---|
| **1** | 10 mol% EDDA, EtOH, reflux, 3 h | 23 |
| **2** | 10 mol% EDDA, $CH_3CN$, reflux, 3 h | 48 |
| **3** | 10 mol% EDDA, toluene, reflux, 3.5 h | 50 |
| **4** | 10 mol% EDDA, DCM, reflux, 5.5 h | 66 |
| **5** | 10 mol% EDDA, DCE, reflux, 3.5 h | 68 |
| **6** | DCM, reflux, 12h | 9 |
| **7** | 10 mol% EDDA, DCM, rt, 24 h | 47 |
| **8** | 10 mol% EDDA, DCE, MW, 120°C, 10 min | 93 |

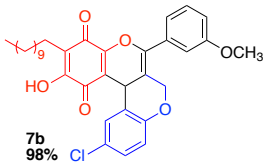
[a]Isolated yield

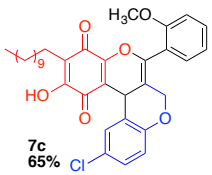
With the optimized protocol in hand, the scope of this domino process was then assessed through the variation of aryl-substituted alkynyl ethers **6** (Table 3). Diversely substituted angular embelin adducts could be prepared in good yields (up to 100%), demonstrating the versatility of this domino process. As a general trend, the DKHDA reaction is tolerant to a large variety of aryl-substituted alkynyl ethers with electron-donating and electron-withdrawing groups. This substituent diversity results very attractive for the establishment of structure-activity relationships after biological evaluation.

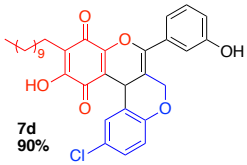
**Table 3.** Synthesis of novel tetracyclic embelin adducts

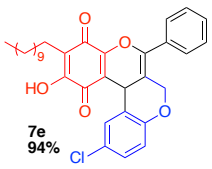


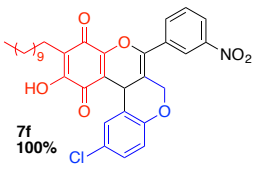



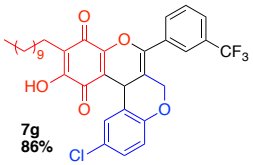



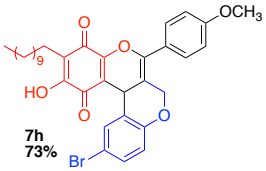



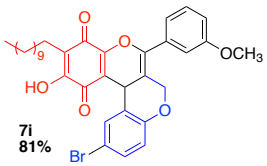



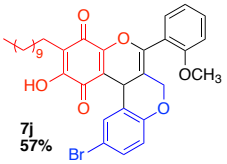



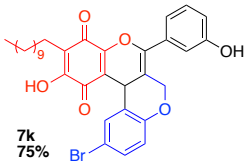



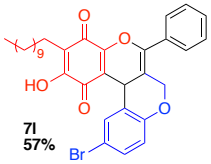



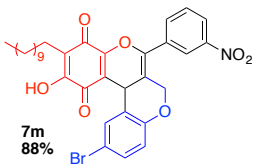



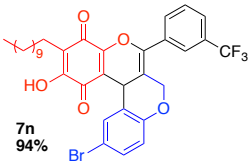



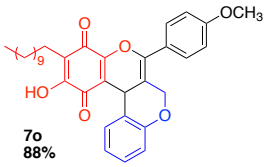



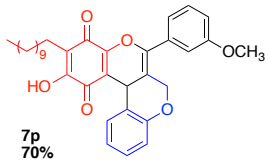



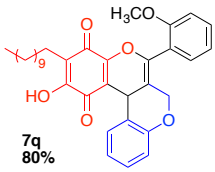



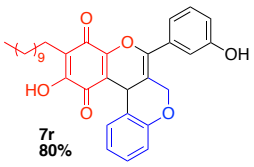



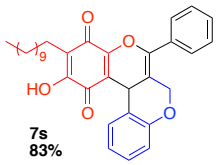



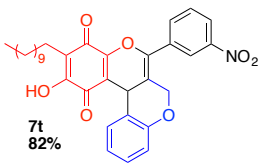



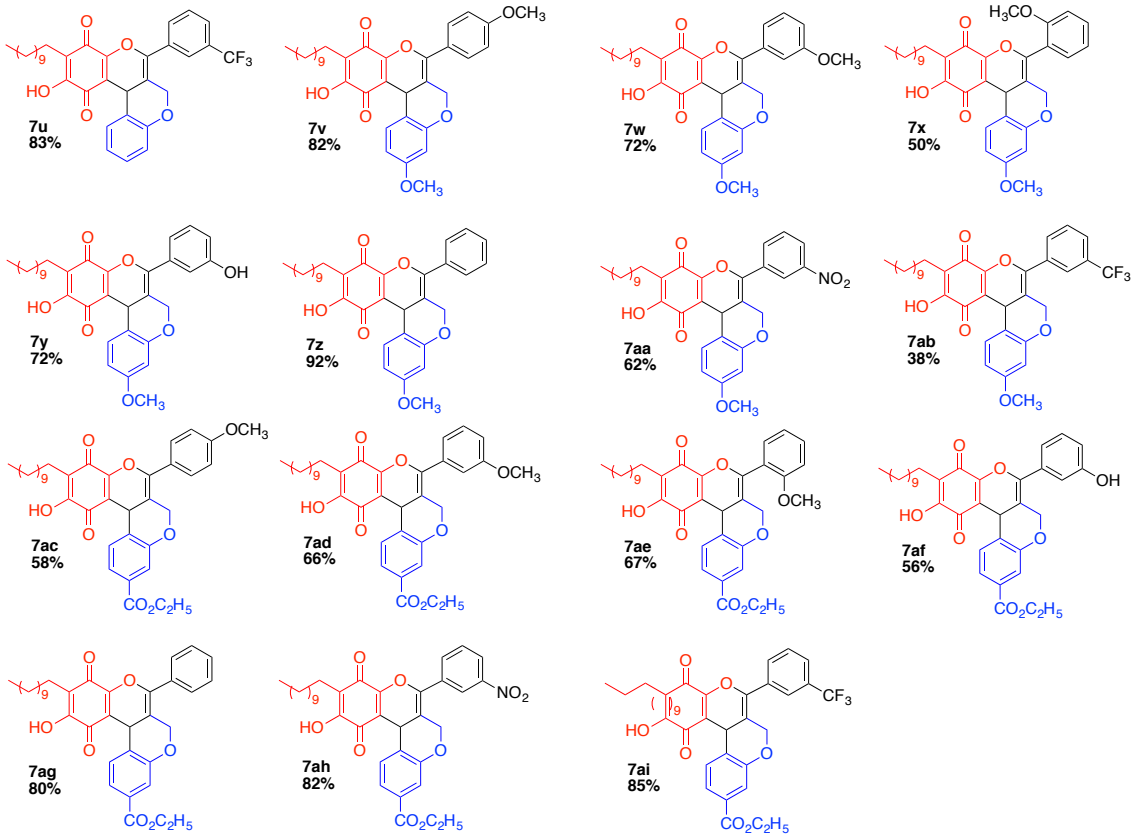



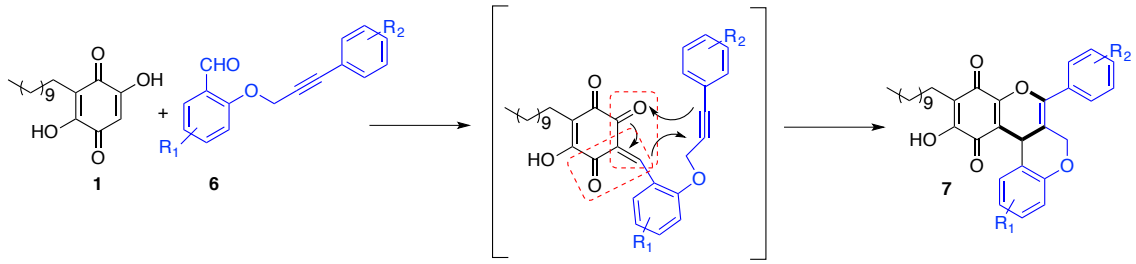






The reaction can be rationalized *via* the formation of a Knoevenagel adduct intermediate, which undergoes an intramolecular hetero-Diels-Alder reaction to form **7** (Scheme 1). The process is regioselective since only the 1,4-benzoquinone adduct is obtained from the more electron-poor heterodiene. Two new fused rings next to the benzoquinone core and three σ bonds (two C-C σ bonds and one C-O σ bond) were formed in this domino reaction. The regiosubstitution of the corresponding adducts was confirmed by the two- and three-bond correlations detected in the HMBC spectrum and also by the $^{13}C$ NMR chemical shifts of the quinone carbonyls.[4f, 13b, 25]

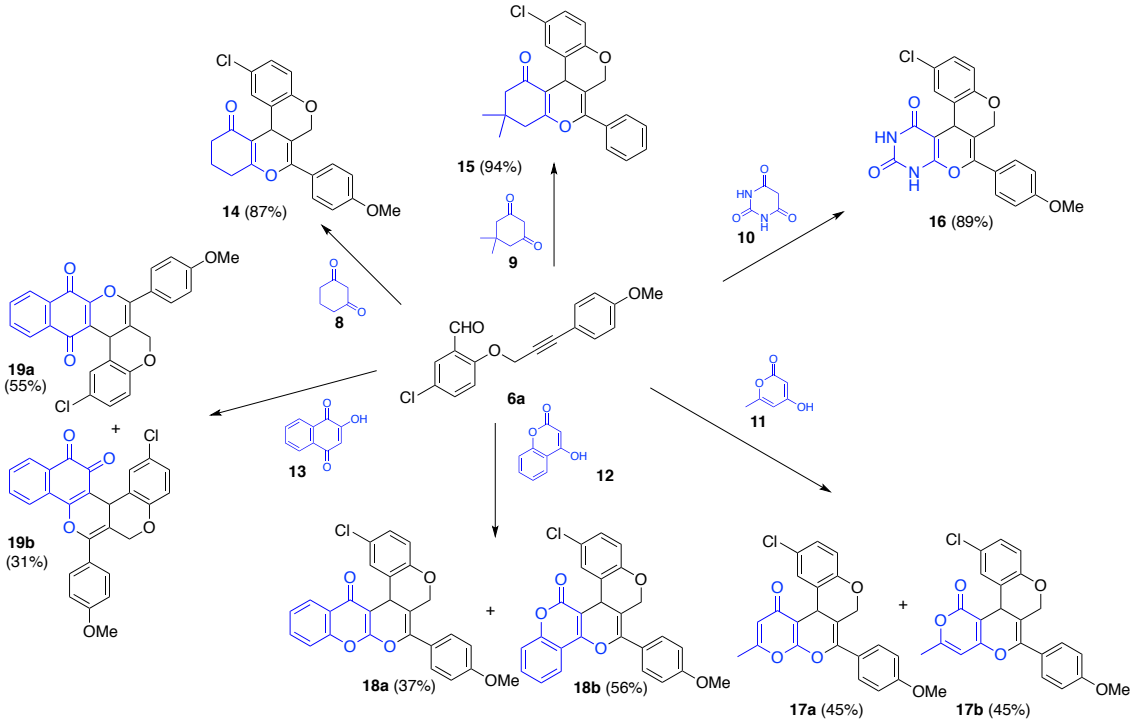
The introduction of a phenyl group in the alkyne favours the energy of HOMO of the dienophile and for this reason is not necessary an additional activation of the triple bond when aryl-end-capped alkynes are involved. In fact when the reaction of embelin was carried out with the terminal alkyne derivative **4a** (5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde) under the same reaction conditions (10 mol% EDDA, $CH_2Cl_2$, MW, 120 ºC, 10 min) the formation of the corresponding adduct was not detected.




**Scheme 1.** Plausible formation of compounds **7**

In order to see the scope of this protocol regarding the 1,3 dicarbonyl component, we carried out the DKHDA reaction with the following 1,3-dicarbonyl compounds: cyclohexanedione (**8**), dimedone (**9**) and barbituric acid (**10**). The active methylene compounds 4-hydroxy-6-methyl-2*H*-pyran-2-one (**11**), 4-hydroxycoumarin (**12**) and 2-hydroxy-1,4-naphthoquinone (**13**), which are of interest from a biological point of view, were also used. The results are summarized in Scheme 2. As we can see all enolizable symmetric cyclic 1,3-dicarbonyls annulated efficiently with 5-chloro-2-((3-phenylprop-2-yn-1-yl)oxy)benzaldehyde (**6a**) by this one-pot domino procedure. With respect to the compounds **11-13** two different products easy to separate by chromatography were obtained as a consequence of the cycloaddition reaction with the two heterodienes present in the corresponding Knoevenagel adduct intermediate. Thus from the reaction

with 4-hydroxy-6-methyl-2*H*-pyran-2-one (**11**), 4H-pyran-4-one (**17a**) and 2H-pyran-2-one (**17b**) derivatives were formed in a 1:1 ratio. In a similar way the pyrano[2,3-*c*]chromone (**18a**) and the pyrano[2,3-*c*]coumarin (**18b**) were obtained by using 4-hydroxy-coumarin (**12**). In this case the compounds were obtained in a 1:1.5 ratio in favours of the coumarin derivative formed from the heterodiene intermediate involving the keto carbonyl group instead of the lactone carbonyl group. Finally when the DKHDA between **6a** and 2-hydroxynaphthoquinone (**13**) was carried out, the corresponding 1,4-naphthoquinone (**19a**) and 1,2-naphthoquinone (**19b**) were obtained in a 1.5:1 ratio in favours of the *p*-naphthoquinone formed from the more electron-poor heterodiene. The structures of the adducts (**14**-**19**) were unequivocally determined using 1D and 2D NMR spectroscopy.




**Scheme 2.** Scope of the reaction regarding 1,3-dicarbonyl compounds.

## Conclusions

In conclusion, we have reported a microwave-assisted intramolecular approach for the synthesis of a set of new angular tetracyclic embelin derivatives. To the best of our knowledge, these are the first examples of intramolecular DKHDA reaction using *O*-(arylpropynyloxy)-salicylaldehydes. The presence of the phenyl group is essential to favours the intramolecular cycloaddition reaction. Diversely substituted embelin adducts could be prepared in good yields from a large variety of aryl-substituted alkynyl ethers with electron-donating and electron-withdrawing groups. This efficient organocatalyzed protocol was successfully applied to a variety of active methylene compounds. We expect that some of the synthesized compounds, with increased molecular complexity, result more active and selective than our starting compound, the natural benzoquinone embelin (**1**). The corresponding biological assays are in progress.

## Experimental section

**General Experimental Procedures.** IR spectra were obtained using a Fourier Transform Infrared spectrometer. NMR spectra were recorded in $CDCl_3$ or DMSO at 500 or 600 MHz for $^{1}H$ NMR and 125 or 150 MHz for $^{13}C$ NMR. Chemical shifts are given in (δ) parts per million and coupling constants (*J*) in hertz (Hz). $^{1}H$ and $^{13}C$ spectra were referenced using the solvent signal as internal standard. Melting points were taken on a capillary melting point apparatus and are uncorrected. Microwave reactions were conducted in sealed glass vessels (capacity 5 mL) using a CEM Discover microwave reactor. HREIMS were recorded using a high-resolution magnetic trisector (EBE) mass analyzer. Analytical thin-layer chromatography plates used were Polygram-Sil G/UV254. Preparative thin-layer chromatography was carried out with Analtech silica gel GF plates (20 x 20 cm, 1000 Microns) using appropriate mixtures of ethyl acetate and hexanes. All solvents and reagents were purified by standard techniques

reported[36]or used as supplied from commercial sources. All compounds were named using the ACD40 Name-Pro program, which is based on IUPAC rules. The embelin (**1**) used in the reactions was obtained from *Oxalis erythrorhiza Gillies ex Hook. & Arn.* following the procedure described in reference 5.

**General Procedure for the Synthesis of *O*-propargylated salicylaldehydes (4a-4e).** To a solution of the corresponding salicylaldehyde (1.0 mmol) in DMF (5 mL) was added anhydrous $K_2CO_3$ (152.7 mg, 1.1 mmol) followed by propargyl bromide (0.13 mL, 1.1 mmol). The reaction mixture was stirred at room temperature until disappearance of the starting salicylaldehyde. Ice water (100 mL) was then added and the product was quantitatively obtained by filtration.

*5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde (**4a**)*. Following the general procedure, to a solution of 0.5 g (3.2 mmol) of 5-chlorosalicylaldehyde and 0.49 g (3.5 mmol) of $K_2CO_3$ in dry DMF (5 mL), 0.4 mL (3.5 mmol) of propargyl bromide was added to obtain the propargylated salicylaldehyde **4a**[34a] in a quantitative yield. $^1$H-NMR (500 MHz, $CDCl_3$) δ 2.58 (1H, t, *J*=2.3 Hz), 4.83 (2H, d, *J* = 2.3 Hz), 7.09 (1H, d, *J* = 8.9 Hz), 7.51 (1H, dd, *J* = 2.7, 8.9 Hz), 7.81 (1H, d, *J*=2.7 Hz, 1H), 10.40 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 56.7 ($CH_2$), 76.9 (CH), 77.0 (C), 114.9 (CH), 126.4 (C), 127.5 (C), 128.2 (CH), 135.2 (CH), 158.1 (C), 188.2 (CH).

*5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (**4b**)*. Following the general procedure, to a solution of 0.5 g (2.5 mmol) of 5-bromosalicylaldehyde and 0.38 g (2.7 mmol) of $K_2CO_3$ in dry DMF (5 mL), 0.31 mL (2.7 mmol) of propargyl bromide was added to obtain the propargylated salicylaldehyde **4b**[34a] in a quantitative yield. $^1$H-NMR (500 MHz, $CDCl_3$) δ 2.59 (1H, t, *J* = 2.4 Hz), 4.83 (2H, d, *J* = 2.4 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.51 (dd, *J* = 2.8, 8.9 Hz, 1H), 7.81 (d, *J* =2.7 Hz, 1H), 10.41 (s, 1H); $^{13}$C-

NMR (125 MHz, $CDCl_3$) δ 55.8 ($CH_2$), 76.9 (CH), 77.2 (C), 115.0 (CH), 126.5 (C), 127.7 (C), 128.1 (CH), 135.2 (CH), 158.1 (C), 188.2 (CH).

*2-(prop-2-yn-1-yloxy)benzaldehyde (**4c**).* Following the general procedure, to a solution of 0.5 g (4.1 mmol) of salicylaldehyde and 0.62 g (4.5 mmol) of $K_2CO_3$ in dry DMF (5 mL), 0.5 mL (4.5 mmol) of propargyl bromide was added to obtain the propargylated salicylaldehyde **4c**[34a] in a quantitative yield.[1]H-NMR (500 MHz, $CDCl_3$) δ 2.57 (1H, t, *J* = 2.2 Hz), 4.83 (2H, t, *J* = 2.4 Hz), 7.09 (1H, td, *J* = 2.9, 7.7 Hz), 7.12 (dd, *J* = 1.7, 8.4 Hz, 1H), 7.57 (m, 1H), 7.86 (ddd, *J*=1.7, 3.4, 7.6 Hz, 1H), 10.49 (s, 1H); [13]C-NMR (125 MHz, $CDCl_3$) δ 56.4 ($CH_2$), 76.5 (CH), 77.7 (C), 113.2 (CH), 121.7 (CH), 125.6 (C), 128.6 (CH), 135.7 (CH), 159.8 (C), 189.5 (CH).

*4-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde (**4d**).* Following the general procedure, to a solution of 0.50 g (3.2 mmol) of 4-methoxysalicylaldehyde and 0.49 g (3.5 mmol) of $K_2CO_3$ in dry DMF (5 mL), 0.4 mL (3.5 mmol) of propargyl bromide was added to obtain the propargylated salicylaldehyde (**4d**)[34b] in a quantitative yield. [1]H-NMR (500 MHz, $CDCl_3$) δ 2.58 (1H, t, *J*=2.4 Hz), 3.88 (3H, s), 4.80 (2H, d, *J*=2.4 Hz), 6.60 (m, 2H), 7.84 (1H, d, *J*=9.1 Hz, 1H), 10.30 (1H, s); [13]C-NMR (125 MHz, $CDCl_3$) δ 55.7 ($CH_3$), 55.4 ($CH_2$), 76.6 (CH), 77.6 (C), 99.5 (CH), 106.8 (CH), 119.6 (C), 130.7 (CH), 161.5 (C), 165.9 (C), 188.1 (CH).

*Ethyl-4-formyl-3-(prop-2-yn-1-yloxy)benzoate (**4e**).* Following the general procedure, to a solution of 0.30 g (1.5 mmol) of 4-formyl-3-hydroxybenzoate and 0.24 g (1.7 mmol) of $K_2CO_3$ in dry DMF (5 mL), was added 0.15 mL (1.7 mmol) of propargyl bromide to obtain the propargylated salicylaldehyde **4e** in a quantitative yield.[34b] [1]H-NMR (500 MHz, $CDCl_3$) δ 1.39 (3H, t, *J*=7.3 Hz), 2.59 (1H, t, *J*=2.4 Hz), 4.37 (2H, q, *J*=7.2 Hz), 4.89 (1H, d, *J*=2.4 Hz), 7.17 (1H, d, *J*=8.7 Hz), 8.25 (2H, dd, *J*=2.3, 8.8 Hz, 2H), 8.51 (1H, d, *J*=2.3 Hz, 1H), 10.46 (s, 1H); [13]C-NMR (125 MHz,

$CDCl_3$) δ 14.3 ($CH_3$), 56.7 ($CH_2$), 61.2 ($CH_2$), 76.9 (CH), 77.0 (C), 113.1 (CH), 124.5 (C), 125.3 (C), 130.6 (CH), 136.8 (CH), 162.6 (C), 165.4 (C), 188.5 (CH).

**General Procedure for the Sonogashira Cross-Coupling of Aryl Iodides with Propargylated Salicylaldehydes**

To a mixture of 50 mg of the propargylated salicylaldehyde, iodobenzene (1.1 equiv), and piperidine (2.0 equiv) in 1 mL of dry THF under an Ar atmosphere, $Pd(PPh_3)_2Cl_2$ (3 mol %) and CuI (6 mol %) were added successively. The reaction mixture was stirred at 30°C until complete consumption of starting salicylaldehyde. Then the solvent was removed under reduced pressure provided, and the residue was purified by column chromatography on silica gel (hexane/EtOAc) to afford the phenyl propargylated salicylaldehyde derivative.

*5-chloro-2-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6a**).* Following the general procedure, the treatment of 50 mg (0.26 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde **4a** with 4-iodoanisole (67.2 mg, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.4 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 2.5 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 66.9 mg (86%) of compound **6a** as a yellow oil. IR (neat) $\nu_{max}$ 2256, 1696, 1632, 1523, 1474, 1432, 1325, 1225, 1202, 1187, 1154, 1122, 1032, 1010, 961, 897, 744, 705, 632 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H), 5.03 (s, 2H), 6.84 (d, $J$ = 8.2 Hz, 2H), 7.18 (d, $J$ = 8.6 Hz, 2H), 6.74 (s, 3H), 7.33 (d, $J$ = 8.6 Hz, 2H), 7.52 (dd, $J$ = 2.0, 8.6 Hz, 1H), 7.82 (d, $J$ = 1.8 Hz, 1H), 10.45 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.3 ($CH_3$), 57.8 ($CH_2$), 81.1 (C), 88.6 (C), 113.7 (C), 114.0 (CH x 2), 115.2 (CH x 2), 126.4 (C), 127.2 (C), 133.4 (CH x 2), 135.2 (CH), 158.5 (C), 160.2 (C), 188.5 (CH); EIMS *m/z* 300 ($M^+$, 4), 286 (11), 277 (16), 262 (100), 183 (48), 155

(48); HREIMS 300.0565 (calcd for $C_{17}H_{13}O_3{}^{35}Cl$ ($M^+$) 300.0553), 287.0313 (calcd. for $C_{16}H_{10}O_3{}^{37}Cl$ ($M^+$-$CH_3$) 287.0289).

*5-chloro-2-((3-(3-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6b**).* Following the general procedure, the treatment of 50 mg (0.26 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde with 3-iodoanisole (32.2 μL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.4 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol,) in dry THF (1 mL) under an Ar atmosphere at 30°C for 2.5h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 75.8 mg (97 %) of compound **6b** as a yellow oil. IR (neat) $\nu_{max}$ 1670, 1589, 1473, 1400, 1288, 1258, 1223, 1180, 1126, 995, 957, 899, 810, 752, 687, 648 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 5.04 (s, 2H), 6.90 (ddd, *J* = 0.5, 2.5, 8.3 Hz, 2H), 6.95 (dd, *J*= 1.3, 2.4 Hz, 1H), 7.01 (dt, *J*= 1.1, 7.6 Hz, 1H), 7.17 (d, *J* = 8.9 Hz, 1H), 7.22 (t, *J*= 8.1 Hz, 1H), 7.53 (dd, *J* = 2.7, 8.9 Hz, 1H), 7.82 (d, *J*= 2.7 Hz, 1H), 10.46 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.7 ($CH_2$), 57.3 ($CH_3$), 82.2 (C), 88.5 (C), 115.3 (CH), 115.6 (CH), 116.7 (CH), 122.6 (C), 124.3 (CH), 126.6 (C), 127.4 (C), 128.1 (CH), 129.5 (CH), 135.2 (CH), 158.4 (C), 159.4 (C), 188.3 (CH); EIMS *m/z* 300 ([$M^+$], 10), 270 (1), 237 (1), 145 (100), 102 (13); HREIMS 302.0513 (calcd for $C_{17}H_{13}O_3{}^{37}Cl$ ($M^+$) 302.0524), 300.0540 (calcd. for $C_{17}H_{13}O_3{}^{35}Cl$ ($M^+$) 300.0553).

*5-chloro-2-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6c**).* Following the general procedure, the treatment of 50 mg (0.26 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde with 2-iodoanisole (35.1 μL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.4 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/ EtOAc,

7:3) afforded 57.6 mg (74 %) of compound **6c**. IR (neat) $\nu_{max}$ 2222, 1678, 1593, 1477, 1438, 1396, 1265, 1223, 1184, 1126, 1045, 1003, 960, 895, 810, 744, 706, 644 $cm^{-1}$. $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.09 (s, 2H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.90 (td, *J* = 0.9, 7.5 Hz, 1H), 7.24 (d, *J*= 8.9 Hz, 1H), 7.32 (m, 1H), 7.36 (dd, *J*= 1.6, 7.5 Hz, 1H), 7.52 (dd, *J* = 2.9, 8.9 Hz, 1H), 7.82 (d, *J* = 2.7 Hz, 1H), 10.46 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.8 ($CH_2$), 58.1 ($CH_2$), 85.1 (C), 86.4 (C), 110.7 (CH), 110.8 (C), 115.6 (CH), 120.5 (CH), 126.6 (C), 127.2 (C), 127.9 (CH), 130.6 (CH), 133.7 (CH), 135.1 (CH), 158.6 (C), 160.3 (C), 188.5 (CH); EIMS *m/z* 300 ($M^+$, 4), 281 (4), 262 (3), 182 (2), 145 (100), 115 (39); HREIMS 302.0540 (calcd for $C_{17}H_{13}O_3{}^{37}Cl$ ($M^+$) 302.0524), 300.0537 (calcd. for $C_{17}H_{13}O_3{}^{35}Cl$ ($M^+$) 300.0553).

*5-chloro-2-((3-(3-hydroxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6d**)*. Following the general procedure, the treatment of 50 mg (0.26 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde with 3-hydroxyphenol (59.4 mg, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.4 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 2.5 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/ EtOAc, 7:3) afforded 51.4 mg (69 %) of compound **6d**. IR (neat) $\nu_{max}$ 1674, 1577, 1439, 1412, 1373, 1292, 1269, 1199, 1126, 1022, 987, 894, 814, 783, 744, 687 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 5.02 (s, 2H), 6.85 (dd, *J* = 2.0, 8.1 Hz, 1H), 6.90 (dd, *J*= 1.4, 2.3 Hz, 1H), 7.08 (dt, *J* = 1.3, 7.7 Hz, 1H), 7.16 (m, 2H), 7.52 (dd, *J* = 2.7, 8.8 Hz, 1H), 7.81 (d, *J* = 2.6 Hz, 1H), 10.43 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.8 ($CH_2$), 82.3 (C), 88.3 (C), 115.4 (CH), 116.7 (CH), 118.5 (CH), 122.7 (C), 124.2 (CH), 126.4 (C), 127.4 (C), 128.1 (CH), 129.7 (CH), 135.4 (CH), 155.5 (C), 158.5 (C), 188.9 (CH); EIMS *m/z* 286 ($M^+$, 13), 262 (11), 219 (60), 183 (10), 131 (100); HREIMS 288.0356

(calcd. for $C_{16}H_{11}O_3{}^{37}Cl$ ($M^+$) 288.0367), 286.0387 (calcd. for $C_{16}H_{11}O_3{}^{35}Cl$ ($M^+$) 286.0397).

*5-chloro-2-((3-phenylprop-2-yn-1-yl)oxy)benzaldehyde (**6e**).* Following the general procedure, the treatment of 50 mg (0.26 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde with iodobenzene (35.5 μL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.4 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 69.0 mg (98 %) of compound **6e**[37] as a yellow oil. IR (neat) $\nu_{max}$ 1678, 1597, 1574, 1477, 1415, 1377, 1272, 1238, 1207, 1173, 1123, 1049, 995, 895, 810, 779, 709, 687, 667 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 5.04 (s, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.32 (m, 3H), 7.41 (m, 2H), 7.52 (dd, *J* = 2,8, 8.8 Hz, 1H), 7.82 (d, *J* = 2.7 Hz, 1H), 10.45 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.3 ($CH_2$), 82.4 (C), 88.6 (C), 115.3 (CH), 121.7 (C), 126.6 (C), 127.4 (C), 128.1 (CH), 128.4 (CH x 2), 131.8 (CH x 2), 135.2 (CH), 158.5 (C), 188.3 (CH); EIMS *m/z* 270 ($M^+$, 16), 240 (2), 207 (2), 154 (3), 115 (100); HREIMS 272.0425 (calcd for $C_{16}H_{11}O_2{}^{37}Cl$ ($M^+$) 272.0418), 270.0455 (calcd. for $C_{16}H_{11}O_2{}^{35}Cl$ ($M^+$) 270.0448).

*5-chloro-2-((3-(3-nitrophenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6f**).*

Following the general procedure, the treatment of 50 mg (0.26 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde with 3-nitro-iodobenzene (67.2 mg, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.4 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 82.8 mg (100 %) of compound **6f**. IR (neat) $\nu_{max}$ 3522, 3398, 3086, 1674, 1589, 1524, 1477, 1350, 1227, 1169, 1061, 976, 902, 814,

737, 671 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 5.07 (s, 2H), 7.14 (d, *J* = 8.9 Hz, 1H), 7.52 (t, *J*=8.0 Hz, 1H), 7.55 (dd, *J*= 2.7, 8.7 Hz, 1H), 7.72 (dt, *J*= 1.2, 7.7 Hz, 1H), 7.84 (d, *J*= 2.7 Hz, 1H), 8.21 (ddd, *J*= 1.1, 2.3, 8.3 Hz, 1H), 8.28 (t, *J*= 1.8 Hz, 1H), 10.46 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.3 ($CH_2$), 85.1 (C), 85.9 (C), 115.0 (CH), 123.5 (C), 123.8 (CH), 126.5 (C), 126.6 (CH), 127.6 (C), 128.3 (C), 129.6 (C), 135.3 (CH), 137.5 (CH), 148.1 (C), 158.2 (C), 188.1 (CH); EIMS *m/z* 300 ($M^+$, 10), 270 (1), 237 (1), 145 (100), 102 (13); HREIMS 302.0513 (calcd for $C_{17}H_{13}O_3{}^{37}Cl$ ($M^+$) 302.0524), 300.0540 (calcd. for $C_{17}H_{13}O_3{}^{35}Cl$ ($M^+$) 300.0553).

*5-chloro-2-((3-(4-trifluoromethylphenyl)prop-2-yn-1-yl)oxy)benzaldehyde* (**6g**).

Following the general procedure, the treatment of 50 mg (0.26 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde with 4-trifluoromethyl-1-iododbenzene (38.9 µL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.4 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 µL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 84.9 mg (96 %) of compound **6g** as a oil yellow. IR (neat) $\nu_{max}$ 3522, 3398, 3074, 2874, 1682, 1593, 1744, 1331, 1258, 1215, 1161, 1084, 976, 899, 802, 683 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 5.06 (s, 2H), 7.15 (d, *J* = 8.9 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.54 (dd, *J* = 2,7, 8.7 Hz, 1H), 7.60 (t, *J* = 7.3 Hz, 2H), 7.68 (s, 1H), 7.83 (d, *J* = 2.8 Hz, 1H), 10.45 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.4 ($CH_2$), 84.0 (C), 86.9 (C), 115.0 (CH), 122.6 (C), 125.6 (CH, $J_{C-F}$= 2.7 Hz), 126.5 (C), 127.5 (C), 128.2 (CH x 2), 128.6 (C, $J_{C-F}$= 3.7 Hz), 129.0 (CH), 131.1 (C, $J_{C-F}$= 34.1 Hz), 134.9 (CH), 135.2 (CH), 158.2 (C), 188.1 (CH); EIMS *m/z* 338 ($M^+$, 16), 308 (3), 272 (5), 182 (100); HREIMS 302.0513 (calcd for $C_{17}H_{13}O_3{}^{37}Cl$ 302.0524), 300.0540 (calcd. for $C_{17}H_{13}O_3{}^{35}Cl$ 300.0553).

*5-bromo-2-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde* (**6h**). Following the general procedure, the treatment of 50 mg (0.21 mmol) of 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde with 4-iodoanisole (51.6 mg, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (4.4 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (42 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 4:1) afforded 58.4 mg (85 %) of compound **6h** as a yellow oil. IR (neat) $\nu_{max}$ 2218, 2203, 1678, 1597, 1508, 1474, 1400, 1292, 1254, 1238, 1192, 1254, 1238, 1192, 1123, 1029, 1018, 999, 972, 922, 879, 791, 640, 621 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.03 (s, 2H), 6.83 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 9.1 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.65 (dd, *J* = 2.5, 8.8 Hz, 1H), 7.95 (d, *J* = 2.5 Hz, 1H), 7.52 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.82 (d, *J* = 1.8 Hz, 1H), 10.45 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.3 ($CH_3$), 57.7 ($CH_2$), 81.1 (C), 88.6 (C), 113.7 (C), 114.0 (CH x 2), 114.4 (C), 115.6 (CH), 126.9 (C), 131.1 (CH), 133.4 (CH x 2), 138.1 (CH), 159.0 (C), 160.2 (C), 188.3 (CH); EIMS *m/z* 344 ($M^+$, 29), 314 (6), 262 (4), 145 (100), 102 (70); HREIMS 346.0019 (calcd for $C_{17}H_{13}O_3{}^{81}Br$ 346.0028), 344.0067 (calcd. for $C_{17}H_{13}O_3{}^{79}Br$ 344.0048).

*5-bromo-2-((3-(3-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde* (**6i**). Following the general procedure, the treatment of 50 mg (0.21 mmol) of 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde with 3-iodoanisole (26.3 μL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (4.4 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (42 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 4:1) afforded 63.7 mg (88 %) of compound **6i**[38] as a yellow oil. IR (neat) $\nu_{max}$ 1674, 1589, 1477, 1377, 1323, 1269, 1230, 1207, 1180, 1122, 1084, 1041, 1022, 1003, 987,

883, 837, 783, 702, 682, 652 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.03 (s, 2H), 6.90 (ddd, *J* = 0.8, 2.6, 8.2 Hz, 1H), 6.93 (dd, *J* = 1.6, 2.5 Hz, 1H), 7.01 (dt, *J* = 1.2, 7.7 Hz, 1H), 7.11 (d, *J* = 8.9 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.65 (dd, *J* = 2.6, 8.8 Hz, 1H), 7.96 (d, *J* = 2.6 Hz, 1H), 10.43 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.3 ($CH_3$), 57.6 ($CH_2$), 82.1 (C), 88.5 (C), 114.4 (C), 115.5 (CH), 115.6 (CH), 116.7 (CH), 122.6 (C), 124.3 (CH), 126.8 (C), 129.5 (CH), 131.1 (CH), 138.1 (CH), 158.9 (C), 159.3 (C), 188.2 (CH); EIMS *m/z* 344 ($M^+$, 14), 314 (2), 262 (2), 145 (100), 102 (30); HREIMS 346.0036 (calcd for $C_{17}H_{13}O_3{}^{81}Br$ 346.0028), 344.0050 (calcd. for $C_{17}H_{13}O_3{}^{79}Br$ 344.0048).

*5-bromo-2-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6j**).* Following the general procedure, treatment of 50 mg (0.21 mmol) of 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde with 2-methoxy-1-iodobenzene (28.7 μL, 0.22 mmol), $Pd(PPh_3)_2Cl_2$ (3% mol, 4.4 mg), CuI (6% mol, 2.5 mg) and piperidine (2 eq. 0.5 mmol, 42 μL) in dry THF (1 ml) under an Ar atmosphere at 30°C for 2.5 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/AcOEt, 7:3), afforded the corresponding product **6j** (50.7 mg, 70%) together the alkyne dimer **6j´** (13.3 mg, 25%).

**6j**: IR (neat) $\nu_{max}$ 3526, 3402, 2874, 2223, 1686, 1589, 1477, 1385, 1265, 1223, 1061, 1007, 957, 891, 810, 744, 648, 633 $cm^{-1}$;$^{1}$H-NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 3H), 5.09 (s, 2H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.90 (td, *J* = 1.2, 7.8 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.32 (ddd, *J* = 1.7, 7.9, 8.3 Hz), 7.36 (dd, *J* = 1.7, 7.6 Hz, 1H), 7.66 (dd, *J* = 2.6, 8.9 Hz, 1H), 7.96 (d, *J* = 2.7 Hz, 1H), 10.44 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.8 ($CH_3$), 58.0 ($CH_2$), 85.1 (C), 86.4 (C), 110.7 (CH), 110.8 (C), 114.4 (C), 116.0 (CH), 120.5 (CH), 126.9 (C), 130.6 (CH), 131.0 (CH), 133.7 (CH), 138.0 (CH), 159.0 (C), 160.3 (C), 188.4 (CH); EIMS *m/z* 345 ($(M+1)^+$, 3), 328 (2), 262 (30), 183 (14), 145

(100); HREIMS 346.0041 (calcd for $C_{17}H_{13}O_3{}^{81}Br$ 346.0028), 344.0052 (calcd. for $C_{17}H_{13}O_3{}^{79}Br$ 344.0048).

**6j´:** IR (neat) $\nu_{max}$ 3522, 3398, 1620, 1473, 1396, 1061, 972, 852, 806, 667 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 4.90 (s, 2H), 6.97 (d, *J* = 8.7 Hz, 1H), 7.66 (dd, *J*= 2.6, 8.8 Hz, 1H), 7.96 (d, *J* = 2.6 Hz, 1H), 10.37 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.0 ($CH_2$), 71.9 (C), 73.8 (C), 115.0 (C), 115.1 (CH), 126.8 (C), 131.4 (CH), 138.2 (CH), 158.3 (C), 187.8 (CH); ESI(+)-MS *m/z* 498 ($(M+Na)^+$, 100), 449 (52); HR-ESIMS 496.9000 (calcd. for $C_{20}H_{12}O_4{}^{79}Br_2Na$ 496.8994), 498.8980 (calcd. for $C_{20}H_{12}O_4{}^{79}Br^{81}BrNa$ 496.8994), 500.8959 (calcd. for $C_{20}H_{12}O_4{}^{81}Br_2Na$ 500.8969).

*5-bromo-2-((3-(3-hydroxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6k**).* Following the general procedure, the treatment of 50 mg (0.21 mmol) of 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde with 3-iodophenol (48.5 mg, 0.22 mmol), $Pd(PPh_3)_2Cl_2$ (4.4 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (42 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 3:7), afforded 26.7 mg (38%) of compound **6k** as a yellow oil. IR (neat) $\nu_{max}$ 1678, 1589, 1469, 1439, 1392, 1269, 1269, 1207, 1180, 1123, 1011, 991, 879, 852, 810, 771, 682, 651 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 5.03 (s, 2H), 6.84 (dd, *J* = 2.4, 8.1 Hz, 1H), 6.89 (dd, *J* = 1.2, 2.5 Hz, 1H), 6.98 (dt, *J* = 1.2, 7.6 Hz, 2H), 7.11 (d, *J* = 8.9 Hz), 7.18 (t, *J* = 7.8 Hz, 1H), 7.67 (dd, *J* = 2.6, 8.9 Hz, 1H), 7.96 (d, *J* = 2.7 Hz, 1H), 10.42 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.6 ($CH_2$), 82.3 (C), 88.2 (C), 114.5 (C), 114.9 (C), 115.7 (CH), 116.6 (CH), 118.4 (CH), 122.7 (C), 124.3 (CH), 129.7 (CH), 131.2 (CH), 138.2 (CH), 155.5 (C), 158.9 (C), 188.6 (CH); EIMS *m/z* 329 ($M^+$, 5), 277 (15), 219 (68), 199 (100), 130 (49); HREIMS 331.9885 (calcd for $C_{16}H_{11}O_3{}^{81}Br$ 331.9871), 329.9887 (calcd. for $C_{16}H_{11}O_3{}^{79}Br$ 329.9892).

*5-bromo-2-((3-phenylprop-2-yn-1-yl)oxy)benzaldehyde (**6l**).* Following the general procedure, the treatment of 50 mg (0.21 mmol) of 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde with 3-iodobenzene (29.0 μL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (4.4 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (42 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 4:1) afforded 62.1 mg (94 %) of compound **6l**[38] as a yellow oil. IR (neat) $\nu_{max}$ 2987, 2886, 2233, 1647, 1585, 1474, 1458, 1400, 1276, 1223, 1122, 1180, 1157, 1142, 1069, 995, 957, 887, 806, 752, 686, 652 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 5.04 (s, 2H), 7.13 (d, *J* = 8.9 Hz, 1H), 7.33 (m, 3H), 7.42 (m, 2H), 7.66 (dd, *J* = 2.6, 8.8 Hz, 1H), 7.97 (d, *J* = 2.6 Hz, 1H), 10.44 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.6 ($CH_2$), 82.3 (C), 88.6 (C), 114.5 (C), 115.6 (CH), 121.7 (C), 126.9 (C), 128.4 (CH x 2), 129.1 (CH), 131.2 (CH), 131.8 (CH x 2), 138.1 (CH), 158.9 (C), 188.2 (CH); EIMS *m/z* 316 ($M^+$, 55), 287 (8), 235 (7), 207 (9), 115 (100); HREIMS 315.9923 (calcd for $C_{16}H_{11}O_2{}^{81}Br$ 315.9922), 313.9933 (calcd. for $C_{16}H_{11}O_2{}^{79}Br$ 313.9942).

*5-bromo-2-((3-(3-nitrophenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6m**).* Following the general procedure, the treatment of 50 mg (0.21 mmol) of 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde with 3-nitro-1-iodobenzene (54.9 mg, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (4.4 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (42 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/ EtOAc, 7:3) afforded 66.9 mg (88 %) of compound **6m** as a yellow oil. IR (neat) $\nu_{max}$ 1682, 1589, 1524, 1466, 1393, 1342, 1273, 1219, 1177, 1119, 1018, 979, 879, 814, 733, 671, 652 $cm^{-1}$; $^1$H-NMR (500 MHz,$CDCl_3$) δ 5.07 (s, 2H), 7.09 (d, *J* = 8.9 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.66 (dd, *J* = 2.6, 8.9 Hz, 1H), 7.72 (dt, *J* = 1.3, 7.7 Hz, 1H),

7.89 (d, $J$ = 2.6 Hz, 1H), 8.21 (ddd, $J$ = 1.0, 2.3, 8.3 Hz, 1H), 8.28 (t, $J$ = 1.8 Hz, 1H), 10.44 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.3 ($CH_2$), 85.0 (C), 86.0 (C), 114.8 (C), 115.3 (CH), 123.4 (C), 123.8 (CH), 124.9 (C), 126.7 (CH), 126.9 (C), 129.6 (CH), 131.4 (CH), 137.5 (CH), 138.2 (CH), 158.6 (C), 188.0 (CH); EIMS *m/z* 360 ($M^+$, 9), 330 (3), 252 (5), 160 (100), 114 (56); HREIMS 360.9779 (calcd for $C_{16}H_{10}NO_4{}^{81}Br$ 360.9773), 358.9785 (calcd. for $C_{16}H_{10}NO_4{}^{79}Br$ 358.9793).

*5-bromo-2-((3-(3-trifluoromethylphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6n**).* Following the general procedure, the treatment of 50 mg (0.21 mmol) of 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde with 3-trifluoromethyl-1-iodobenzene 3-nitro-1-iodobenzene (31.8 µL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (4.4 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (42 µL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 66.4 mg (82 %) of compound **6n** as a yellow oil. IR (neat) $\nu_{max}$ 1682, 1589, 1470, 1435, 1393, 1331, 1273, 1219, 1177, 1157, 1115, 1099, 1076, 1007, 972, 883, 806, 690, 660 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 5.05 (s, 2H), 7.09 (d, $J$ = 8.9 Hz, 1H), 7.46 (t, $J$ = 7.8 Hz, 1H), 7.59 (dd, $J$ = 1.8, 7.7 Hz, 2H), 7.67 (m, 2H), 7.96 (d, $J$ = 2.6 Hz, 1H), 10.43 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.4 ($CH_2$), 84.0 (C), 86.9 (C), 114.6 (C), 115.3 (CH), 122.6 (C), 125.7 (CH, $J_{C\text{-}F}$= 3.7 Hz), 127.9 (C, $J_{C\text{-}F}$= 268.7 Hz), 128.6 (CH, $J_{C\text{-}F}$= 3.9 Hz), 129.0 (CH), 131.1 (C, $J_{C\text{-}F}$= 33.6 Hz), 130.4 (C), 131.3 (CH), 134.9 (CH), 138.1 (CH), 158.7 (C), 188.1 (CH); EIMS *m/z* 381 ($M^+$, 25), 352 (8), 275 (11), 182 (100); HREIMS 383.9793 (calcd for $C_{17}H_{10}F_3O_2{}^{81}Br$ 383.9796), 381.9824 (calcd. for $C_{17}H_{10}F_3O_2{}^{79}Br$ 381.9816).

*2-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6o**).* Following the general procedure, the treatment of 50 mg (0.31 mmol) of 2-(prop-2-yn-1-yloxy)benzaldehyde

with 4-iodoanisole (76.7 mg, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (6.6 mg, 3 mol %), CuI (3.6 mg, 6 mol %) and piperidine (60 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 53.0 mg (64 %) of compound **6o**[37] as a yellow oil. IR (neat) $\nu_{max}$ 3521, 3398, 2237, 1682, 1597, 1508, 1458, 1223, 1099, 1030, 957, 825, 752, 640 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.04 (s, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.08 (t, *J*= 7.5 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.57 (m, 1H), 7.87 (dd, *J* = 1.5, 7.7 Hz, 1H), 10.53 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.3 ($CH_3$), 57.5 ($CH_2$), 81.6 (C), 88.1 (C), 113.5 (CH), 113.9 (C), 114.0 (CH x 2), 121.5 (CH), 125.6 (C), 128.5 (CH), 133.4 (CH x 2), 135.7 ($CH_2$), 160.1 (C), 160.2 (C), 189.8 (CH); EIMS *m/z* 266 ($M^+$, 20), 237 (7), 145 (100), 102 (10); HREIMS 266.0945 (calcd for $C_{17}H_{14}O_3$ ($M^+$) 266.0943).

*2-((3-(3-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6p**)*. Following the general procedure, the treatment of 50 mg (0.31 mmol) of 2-(prop-2-yn-1-yloxy)benzaldehyde with 3-iodoanisole (39 μL, 0.32 mmol), $Pd(PPh_3)_2Cl_2$ (6.6 mg, 3 mol %), CuI (3.6 mg, 6 mol %) and piperidine (60 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 70.4 mg (85 %) of compound **6p** as a yellow oil. IR (neat) $\nu_{max}$ 1682, 1593, 1458, 1369, 1285, 1261, 1211, 1157, 1103, 1042, 1022, 987, 864, 833, 791, 764, 687, 648 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.04 (s, 2H), 6.89 (ddd, *J* = 0.9, 2.6, 8.3 Hz, 1H), 6.95 (dd, *J* = 1.4, 2.5 Hz, 1H), 7.02 (dt, *J* = 1.2, 7.7 Hz, 1H), 7.08 (m, 1H), 7.21 (m, 2H), 7.57 (ddd, *J* = 1.8, 7.3, 9.0 Hz, 1H), 7.87 (dd, *J* = 1.8, 7.7 Hz, 1H), 10.53 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.2 ($CH_3$), 57.3 ($CH_2$), 82.7 (C), 88.0 (C), 113.4 (CH),

115.4 (CH), 116.7 (CH), 121.5 (CH), 122.8 (C), 124.2 (CH), 125.5 (C), 128.5 (CH), 129.4 (CH), 135.7 (CH), 159.3 (C), 160.0 (C), 189.6 (CH); EIMS *m/z* 266 ($M^+$, 44), 237 (10), 145 (100), 102 (17); HREIMS 266.0958 (calcd for $C_{17}H_{14}O_3$ ($M^+$) 266.0943).

*2-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6q**).* Following the general procedure, the treatment of 50 mg (0.31 mmol) of 2-(prop-2-yn-1-yloxy)benzaldehyde with 2-iodoanisole (42.6 μL, 0.32 mmol), $Pd(PPh_3)_2Cl_2$ (6.6 mg, 3 mol %), CuI (3.6 mg, 6 mol %) and piperidine (60 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 50.0 mg (61 %) of compound **6q** as a yellow oil. IR (neat) $\nu_{max}$ 2233, 1686, 1597, 1481, 1458, 1369, 1265, 1250, 1215, 1161, 1099, 1018, 960, 833, 752, 694, 648 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.09 (s, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.89 (td, *J* = 1.0, 7.5 Hz, 1H), 7.07 (m, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.30 (ddd, *J* = 1.8, 7.5, 9.2 Hz, 1H), 7.37 (dd, *J* = 1.7, 7.6 Hz, 1H), 7.57 (ddd, *J* = 1.9, 7.3, 9.1 Hz, 1H), 7.87 (dd, *J* = 1.8, 7.7 Hz, 1H), 10.54 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.7 ($CH_3$), 57.6 ($CH_2$), 84.6 (C), 86.9 (C), 110.6 (CH), 111.0 (C), 113.7 (CH), 120.4 (CH), 121.4 (CH), 125.5 (C), 128.3 (CH), 129.5 (C), 130.4 (CH), 133.7 (CH), 135.6 (CH), 160.2 (C), 189.8 (CH); EIMS *m/z* 266 ($M^+$, 10), 249 (14), 235 (10), 145 (100), 115 (50); HREIMS 266.0935 (calcd for $C_{17}H_{14}O_3$ ($M^+$) 266.0943).

*2-((3-(3-hydroxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6r**).* Following the general procedure, the treatment of 50 mg (0.31 mmol) of 2-(prop-2-yn-1-yloxy)benzaldehyde with 3-iodophenol (72.1 mg, 0.32 mmol), $Pd(PPh_3)_2Cl_2$ (6.6 mg, 3 mol %), CuI (3.6 mg, 6 mol %) and piperidine (60 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 64.8 mg

(78 %) of compound **6r**. IR (neat) $\nu_{max}$ 3398, 2924, 1682, 1597, 1470, 1288, 1211, 1053, 787, 756, 687, 652 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 1H), 4.99 (s, 2H), 6.59 (ddd, *J* = 0.6, 2.1, 8.5 Hz, 1H), 6.67 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 1.8, 8.1 Hz, 1H), 6.93 (s, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 10.30 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.4 ($CH_2$), 82.9 (C), 87.7 (C), 113.6 (CH), 116.4 (CH), 118.4 (CH), 121.6 (CH), 123.0 (C), 124.4 (CH), 125.6 (C), 128.6 (CH), 129.7 (CH), 135.8 (CH), 155.4 (C), 160.1 (C), 189.9 (CH); HRESIMS 275.0688 (calcd. for $C_{16}H_{12}O_3Na$ 275.0684).

*2-((3-phenylprop-2-yn-1-yl)oxy)benzaldehyde (**6s**).* Following the general procedure, the treatment of 50 mg (0.31 mmol) of 2-(prop-2-yn-1-yloxy)benzaldehyde (0.31 mmol) with iodobenzene (43.1 μL, 0.32 mmol), $Pd(PPh_3)_2Cl_2$ (6.6 mg, 3 mol %), CuI (3.6 mg, 6 mol %) and piperidine (60 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 56.8 mg (78 %) of compound **6s**.[39] IR (neat) $\nu_{max}$ 1678, 1659, 1593, 1481, 1458, 1400, 1373, 1285, 1261, 1218, 1192, 1165, 1107, 1042, 995, 957, 914, 829, 756, 725, 687, 652, 609 $cm^{-1}$. $^1$H-RMN (500 MHz, $CDCl_3$) δ 5.05 (s, 2H), 7.09 (t, *J* = 7.0 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.32 (m, 3H), 7.43 (m, 2H), 7.58 (ddd, *J* = 1.8, 7.5, 9.0 Hz, 1H), 7.88 (dd, *J* = 1.7, 7.7 Hz, 1H), 10.54 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.3 ($CH_2$), 82.9 (C), 88.1 (C), 113.4 (CH), 121.5 (CH), 121.9 (C), 125.6 (C), 128.3 (CH x 2), 128.5 (CH), 128.9 (CH), 131.8 (CH x 2), 135.7 (CH), 160.1 (C), 189.7 (CH); EIMS *m/z* 236 ($M^+$, 77), 206 (50), 120 (45), 114 (100); HREIMS 236.0836 (calcd for $C_{16}H_{12}O_2$ ($M^+$) 236.0837).

*2-((3-(3-nitrophenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6t**).* Following the general procedure, the treatment of 50 mg (0.31 mmol) of 2-(prop-2-yn-1-yloxy)benzaldehyde

(0.31 mmol) with 3-nitro-1-iodobenzene (81.6 mg, 0.32 mmol), $Pd(PPh_3)_2Cl_2$ (6.6 mg, 3 mol %), CuI (3.6 mg, 6 mol %) and piperidine (60 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 73.2 mg (84 %) of compound **6t**. IR (neat) $\nu_{max}$ 1678, 1593, 1535, 1481, 1458, 1369, 1346, 1285, 1234, 1161, 1103, 1022, 999, 879, 844, 810, 764, 733, 667$cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 5.07 (s, 2H), 7.11 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.60 (ddd, *J* = 1.9, 7.3, 9.1 Hz, 1H), 7.72 (td, *J* = 1.3, 7.8 Hz, 1H), 7.88 (dd, *J* = 1.8, 7.7 Hz, 1H), 8.18 (ddd, *J* = 1.1, 2.3, 8.4 Hz, 1H), 8.26 (t, *J* = 1.8 Hz, 1H), 10.52 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 56.9 ($CH_2$), 85.5 (C), 85.6 (C), 113.2 (CH), 121.8 (CH), 123.6 (CH), 125.6 (C), 126.6 (CH), 128.7 (CH), 129.5 (CH), 130.2 (C), 135.8 (CH), 137.4 (CH), 148.1 (C), 159.8 (C), 189.4 (CH); EIMS *m/z* 281 ($M^+$, 45), 252 (14), 234 (8), 159 (100), 114 (81); HREIMS 281.0700 (calcd for $C_{16}H_{11}O_4N$ ($M^+$) 281.0688).

*2-((3-(3-trifluoromethylphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6u**).* Following the general procedure, the treatment of 50 mg (0.31 mmol) of 2-(prop-2-yn-1-yloxy)benzaldehyde (0.31 mmol) with 3-trifluoromethyl-1-iodobenzene (42.3 μL, 0.32 mmol), $Pd(PPh_3)_2Cl_2$ (6.6 mg, 3 mol %), CuI (3.6 mg, 6 mol %) and piperidine (60 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (hex/EtOAc, 7:3) afforded 81.1 mg (86 %) of compound **6u** as a yellow oil. IR (neat) $\nu_{max}$ 1678, 1597, 1481, 1458, 1396, 1331, 1288, 1219, 1157, 1119, 1072, 1011, 976, 903, 833, 798, 760, 690, 660 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 5.06 (s, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.59 (m, 3H), 7.68 (s, 1H), 7.88 (dd, *J* = 1.4, 7.7 Hz, 1H), 10.53 (s, 1H);$^{13}$C-NMR (125 MHz,

$CDCl_3$) δ 57.1 ($CH_2$), 84.6 (C), 86.4 (C), 113.3 (CH), 121.7 (CH), 122.8 (C), 123.5 (C, $J_{C-F}$= 274.6 Hz), 125.5 (CH, $J_{C-F}$= 3.5 Hz), 125.6 (C), 128.6 (CH, $J_{C-F}$= 3.8 Hz), 128.7 (CH), 128.9 (CH), 131.0 (C, $J_{C-F}$= 30.6 Hz), 134.9 (CH), 135.8 (CH), 159.9 (C), 189.5 (CH); EIMS *m/z* 304 ($M^+$, 27), 276 (7), 183 (100), 133 (3); HREIMS 304.0718 (calcd for $C_{17}H_{11}O_2F_3$ ($M^+$) 304.0711).

*4-methoxy-2-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6v**)*. Following the general procedure, the treatment of 50 mg (0.26 mmol) of of 4-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde with 4-iodoanisole (64.6 mg, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.5 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 4.5 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex: EtOAc, 7:3) afforded 63.5 mg (82 %) of compound **6v** as a yellow oil. IR (neat) $\nu_{max}$ 1666, 1601, 1504, 1454, 1439, 1381, 1315, 1288, 1265, 1207, 1169, 1111, 1057, 1011, 953, 868, 825, 794, 675 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.88 (s, 3H), 5.01 (s, 2H), 6.60 (dd, *J* = 2.2, 8.7 Hz, 1H), 6.69 (d, *J* = 2.2 Hz, 2H), 6.84 (d, *J* = 8.7, 2H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.84 (d, *J* = 8.7 Hz, 1H), 10.34 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.3 ($CH_3$), 55.7 ($CH_3$), 57.5 ($CH_2$), 81.5 (C), 88.3 (C), 99.6 (CH), 106.8 (CH), 113.9 (C), 114.0 (CH x 2), 119.6 (C), 130.5 (CH), 133.4 (CH x 2), 160.1 (C), 161.9 (C), 165.9 (C), 188.3 (CH); EIMS *m/z* 296 ($M^+$, 11), 267 (7), 237 (1), 144 (100), 102 (11); HREIMS 296.1041 (calcd for $C_{18}H_{16}O_4$ ($M^+$) 296.1049).

*4-methoxy-2-((3-(3-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6w**)*. Following the general procedure, the treatment of 50 mg (0.26 mmol) of 4-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde with 4-iodoanisole (32.8 μL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.5 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3 h, followed by evaporation of the solvent under

reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 65 mg (84 %) of compound **6w** of yellow oil. IR (neat) $\nu_{max}$ 1674, 1601, 1577, 1485, 1439, 1373, 1315, 1261, 1204, 1168, 1107, 1034, 991, 933, 860, 825, 771, 744, 683 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.88 (s, 3H), 5.02 (s, 2H), 6.60 (ddd, *J* = 0.5, 2.2, 8.9 Hz, 1H), 6.68 (d, *J*= 2.5 Hz, 1H), 6.90 (ddd, *J* = 0.9, 2.7, 8.3 Hz, 1H), 6.96 (dd, *J* = 1.5, 2.6 Hz, 1H), 7.03 (dt, *J* = 1.1, 7.5 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 10.35 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.3 ($CH_3$), 55.7 ($CH_3$), 57.3 ($CH_2$), 82.6 (C), 88.1 (C), 99.6 (CH), 106.8 (CH), 115.5 (CH), 119.7 (CH), 119.6 (C), 122.9 (C), 124.3 (CH), 129.5 (CH), 130.6 (CH), 159.3 (C), 161.8 (C), 165.9 (C), 188.3 (CH); EIMS *m/z* 296 ($M^+$, 64), 268 (67), 237 (10), 145 (100), 102 (66); HREIMS 296.1044 (calcd for $C_{18}H_{16}O_4$ ($M^+$) 296.1049).

*4-methoxy-2-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6x**).*

Following the general procedure, the treatment of 50 mg (0.26 mmol) of 4-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde with 2-iodoanisole (35.9 μL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.5 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 43.3 mg (56 %) of compound **6x**. IR (neat) $\nu_{max}$ 2839, 2233, 1674, 1597, 1493, 1435, 1258, 1161, 1107, 1014, 825, 752, 683, 644 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.89 (s, 3H), 5.07 (s, 2H), 6.60 (dd, *J*= 1.6, 8.6 Hz, 1H), 6.77 (d, *J*= 2.0 Hz, 1H), 6.87 (d, *J*= 8.6 Hz, 1H), 6.89 (t, *J*= 7.8 Hz, 1H), 7.3 (td, *J*= 1.3, 7.9 Hz, 1H), 7.40 (dd, *J*= 1.4, 7.6 Hz, 1H), 7.83 (d, J= 8.7 Hz, 1H), 10.35 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.6 ($CH_3$), 55.7 ($CH_3$), 57.6 ($CH_2$), 84.8 (C), 86.8 (C), 99.7 (CH), 107.0 (CH), 110.7 (CH), 120.4 (CH), 127.6 (C), 130.4 (CH), 130.5 (CH), 133.8 (CH), 135.2 (C), 160.4 (C), 162.0 (C), 165.9 (C), 188.4 (CH); EIMS

*m/z* 296 ($M^+$, 21), 268 (34), 262 (27), 145 (100), 115 (64); HREIMS 296.1042 (calcd for $C_{18}H_{16}O_4$ ($M^+$) 296.1049).

*4-methoxy-2-((3-(3-hydroxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6y**).* Following the general procedure, the treatment of 50 mg (0.26 mmol) of 4-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde with 3-iodoanisole (60.7 mg, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.5 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 44.7 mg (61 %) of compound **6y** as a yellow oil. IR (neat) $\nu_{max}$ 3205, 2939, 2847, 2230, 1666, 1601, 1574, 1497, 1393, 1292, 1261, 1173, 1134, 1119, 1022, 991, 864, 837, 683 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 1H), 4.99 (s, 2H), 6.59 (ddd, *J* = 0.6, 2.1, 8.5 Hz, 1H), 6.67 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 1.8, 8.1 Hz, 1H), 6.93 (s, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 10.30 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.7 ($CH_3$), 57.4 ($CH_2$), 82.5 (C), 88.1 (C), 99.6 (CH), 107.1 (CH), 116.6 (CH), 118.5 (CH), 119.4 (C), 122.8 (C), 124.0 (CH), 129.6 (CH), 130.8 (CH), 155.9 (C), 162.0 (C), 166.2 (C), 188.9 (CH); EIMS *m/z* 282 ($M^+$, 15), 254 (24), 223 (4), 151 (33), 131 (100); HREIMS 282.0880 (calcd for $C_{17}H_{14}O_4$ ($M^+$) 282.0892).

*4-methoxy-2-((3-phenylprop-2-yn-1-yl)oxy)benzaldehyde (**6z**).* Following the general procedure, the treatment of 50 mg (0.26 mmol) of 4-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde (0.26 mmol) with 3-iodobenzene (36.3 μL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.5 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 60.5 mg (87 %) of compound **6z** as a

yellow oil. IR (neat) $\nu_{max}$ 1674, 1597, 1492, 1443, 1373, 1258, 1191, 1157, 1092, 1157, 1092, 1030, 964, 822, 756, 690 $cm^{-1}$;$^1$H-NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3H), 5.02 (s, 2H), 6.60 (ddd, *J* = 0.4, 2.1, 6.5 Hz, 1H), 6.69 (d, *J* = 2.2 Hz, 1H), 7.33 (m, 3H), 7.43 (m, 2H), 7.85 (d, *J* = 8.7 Hz, 1H), 10.35 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.7 ($CH_3$), 57.3 ($CH_2$), 82.8 (C), 88.2 (C), 99.5 (CH), 106.8 (CH), 119.6 (C), 121.9 (C), 128.4 (CH x 2), 128.9 (CH), 130.6 (CH), 131.8 (CH x 2), 161.8 (C), 165.9 (C), 188.2 (CH); EIMS *m/z* 266 ($M^+$, 11), 238 (20), 207 (3), 151 (7), 115 (100); HREIMS 266.0934 (calcd for $C_{17}H_{14}O_3$ ($M^+$) 266.0943).

*4-methoxy-2-((3-(3-nitrophenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6aa**).* Following the general procedure, the treatment of 50 mg (0.26 mmol) of 4-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde with 3-iodobenzene (36.3 μL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.5 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (hex/EtOAc, 7:3) afforded 79.1 mg (98 %) of compound **6aa** as a yellow oil. IR (neat) $\nu_{max}$ 1678, 1605, 1527, 1501, 1462, 1439, 1373, 1353, 1261, 1196, 1165, 1111, 1026, 945, 906, 829, 806, 737, 671 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.89 (s, 3H), 5.04 (s, 2H), 6.63 (m, 2H), 7.51 (t, *J*= 7.9 Hz, 1H), 7.74 (dt, *J*= 1.3, 7.8 Hz, 1H), 7.86 (d, *J*= 8.4 Hz, 1H), 8.20 (ddd, *J*= 1.0, 2.3, 8.3 Hz, 1H), 8.28 (t, *J*= 1.8 Hz, 1H), 10.34 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.2 ($CH_3$), 56.9 ($CH_2$), 85.5 (C), 85.5 (C), 99.6 (CH), 106.7 (CH), 119.5 (C), 123.6 (CH), 126.6 (CH), 129.5 (CH), 130.8 (CH), 137.4 (CH), 148.0 (C), 161.4 (C), 165.9 (C), 188.0 (CH); EIMS *m/z* 311 ($M^+$, 9), 283 (84), 236 (9), 160 (100), 133 (30), 114 (75); HREIMS 311.0791 (calcd for $C_{17}H_{13}O_5N$ ($M^+$) 311.0794).

*4-methoxy-2-((3-(3-trifluoromethylphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (**6ab**).* Following the general procedure, the treatment of 50 mg (0.26 mmol) of 4-methoxy-2-

(prop-2-yn-1-yloxy)benzaldehyde (0.26 mmol) with 3-trifluoromethyl-1-iodobenzene (39.8 μL, 0.27 mmol), $Pd(PPh_3)_2Cl_2$ (5.5 mg, 3 mol %), CuI (2.9 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 75.5 mg (87 %) of compound **6ab** as a yellow oil. IR (neat) $\nu_{max}$ 1663, 1597, 1504, 1462, 1435, 1389, 1327, 1258, 1204, 1153, 1119, 1096, 1069, 1026, 999, 906, 833, 798, 740, 698, 663 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.89 (s, 1H), 5.03 (s, 2H), 6.62 (dd, *J* = 2.1, 8.7 Hz, 1H), 6.66 (d, *J* = 2.6 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 6.3 Hz, 2H), 7.70 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 10.35 (s, 1H);$^{13}$C-NMR (125 MHz, $CDCl_3$) δ 57.1 ($CH_2$), 84.6 (C), 86.44 (C), 113.3 (CH), 121.7 (CH), 122.8 (C), 123.5 (C, $J_{C-F}$= 274.6 Hz), 125.5 (CH, $J_{C-F}$= 3.5 Hz), 125.6 (C), 128.6 (CH, $J_{C-F}$= 3.8 Hz), 128.7 (CH), 128.9 (CH), 131.0 (C, $J_{C-F}$= 30.6 Hz), 134.9 (CH), 135.8 (CH), 159.9 (C), 189.5 (CH); EIMS *m/z* 334 ($M^+$, 21), 305 (78), 275 (8), 182 (100), 133 (9); HREIMS 334.0823 (calcd for $C_{18}H_{13}O_3F_3$ ($M^+$) 334.0817).

*Ethyl 4-formyl-3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)benzoate (**6ac**).* Following the general procedure, the treatment of 50 mg (0.23 mmol) of ethyl 4-formyl-3-(prop-2-yn-1-yloxy)benzoate with 4-iodoanisole (52.9 mg, 0.32 mmol), $Pd(PPh_3)_2Cl_2$ (4.8 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (51 μL, 0.5 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 3 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 61.6 mg (83 %) of compound **6ac** as a yellow oil. IR (neat) $\nu_{max}$ 3522, 3398, 2893, 2225, 1701, 1605, 1500, 1366, 1246, 1177, 1142, 1126, 1045, 1026, 829, 764, 690 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.1 Hz, 3H), 3.79 (s, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 5.09 (s, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 1H),

7.35 (d, *J* = 8.8, 2H), 8.26 (dd, *J* = 2.4, 8.8 Hz, 1H), 8.52 (d, *J* = 2.3 Hz, 1H), 10.50 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 14.3 ($CH_3$), 55.3 ($CH_3$), 57.8 ($CH_2$), 61.1 ($CH_2$), 80.9 (C), 88.9 (C), 113.3 (CH), 113.8 (C), 114.2 (CH x 2), 124.2 (C), 125.3 (C), 130.5 (CH), 133.4 (CH x 2), 136.7 (CH), 160.4 (C), 163.0 (C), 165.5 (C), 188.7 (CH); EIMS *m/z* 338 ($M^+$, 61), 309 (21), 262 (22), 145 (100), 102 (39), HREIMS 338.1171 (calcd for $C_{20}H_{18}O_5$ ($M^+$) 338.1154).

*Ethyl 4-formyl-3-((3-(3-methoxyphenyl)prop-2-yn-1-yl)oxy)benzoate (**6ad**).* Following the general procedure, the treatment of 50 mg (0.22 mmol) of ethyl 4-formyl-3-(prop-2-yn-1-yloxy)benzoate with 3-iodoanisole (26.9 μL, 0.23 mmol), $Pd(PPh_3)_2Cl_2$ (4.8 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (43 μL, 0.43 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 1.5 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 71.9 mg (97 %) of compound **6ad** as a yellow oil. IR (neat) $\nu_{max}$ 2885, 2858, 2237, 1701, 1605, 1492, 1377, 1292, 1238, 1188, 1142, 1018, 984, 849, 768, 687, 659, 629 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.2 Hz, 3H), 3.77 (s, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 5.10 (s, 2H), 6.89 (ddd, *J* = 0.8, 2.6, 8.3 Hz, 1H), 6.94 (dd, *J* = 1.2, 2.6 Hz, 1H), 7.00 (dt, *J* = 0.8, 7.5 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 8.26 (dd, *J* = 2.3, 8.8 Hz, 1H), 8.50 (d, *J* = 2.3 Hz, 1H), 10.50 (s, 1H);$^{13}$C-NMR (125 MHz, $CDCl_3$) δ 14.3 ($CH_3$), 55.3 ($CH_3$), 57.6 ($CH_2$), 61.1 ($CH_2$), 82.0 (C), 88.7 (C), 113.2 (CH), 115.7 (CH), 116.9 (CH), 122.7 (C), 124.3 (C), 124.4 (CH), 125.3 (C), 129.5 (CH), 130.6 (CH), 136.7 (CH), 159.5 (C), 162.9 (C), 165.4 (C), 188.6 (CH); EIMS *m/z* 338 ($M^+$, 65), 309 (11), 293 (11), 145 (100), 115 (24), 102 (46); HREIMS 338.1168 (calcd for $C_{20}H_{18}O_5$ ($M^+$) 338.1154).

*Ethyl 4-formyl-3-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)benzoate (**6ae**).* Following the general procedure, the treatment of 50 mg (0.22 mmol) of ethyl 4-formyl-3-(prop-2-

yn-1-yloxy)benzoate with 2-iodoanisole (26.4 μL, 0.23 mmol), $Pd(PPh_3)_2Cl_2$ (4.8 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (43 μL, 0.43 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 1.5 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 44.2 mg (59 %) of compound **6ae** as a yellow oil. IR (neat) $\nu_{max}$ 3533, 2977, 2233, 1708, 1686, 1605, 1493, 1369, 1304, 1242, 1169, 1103, 1022, 995, 941, 829, 760, 748, 694 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.2 Hz, 3H), 3.84 (s, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 5.15 (s, 2H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.89 (dd, *J* = 0.9, 7.6 Hz, 1H), 7.30 (ddd, *J* = 1.7, 7.7, 9.2 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.36 (dd, *J* = 1.7, 7.5 Hz, 1H), 8.26 (dd, *J* = 2.2, 8.7 Hz, 1H), 8.53 (d, *J* = 2.2 Hz, 1H), 10.51 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 14.3 ($CH_3$), 55.8 ($CH_3$), 58.0 ($CH_2$), 61.1 ($CH_2$), 85.5 (C), 86.2 (C), 111.0 (CH), 111.1 (C), 113.7 (CH), 120.5 (CH), 124.2 (C), 125.4 (C), 130.4 (CH), 130.6 (CH), 133.8 (CH), 136.7 (CH), 160.6 (C), 163.1 (C), 165.5 (C), 188.8 (CH); EIMS *m/z* 338 ($M^+$, 17), 320 (22), 262 (31), 183 (19), 145 (100), 115 (79); HREIMS 338.1168 (calcd for $C_{20}H_{18}O_5$ ($M^+$) 338.1154).

*Ethyl 4-formyl-3-((3-(3-hydroxyphenyl)prop-2-yn-1-yl)oxy)benzoate (**6af**).* Following the general procedure, the treatment of 50 mg (0.22 mmol) of ethyl 4-formyl-3-(prop-2-yn-1-yloxy)benzoate with 3-iodophenol (49.7 mg, 0.23 mmol), $Pd(PPh_3)_2Cl_2$ (4.8 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (43 μL, 0.43 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 1.5 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 39.5 mg (55 %) of compound **6af** as a yellow oil. IR (neat) $\nu_{max}$ 3391, 3028, 1686, 1601, 1489, 1443, 1296, 1261, 1180, 1103, 1018, 984, 957, 868, 768, 687, 656 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.3 Hz, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.95 (s, 1H), 5.09 (s, 1H), 6.83 (ddd, *J* = 1.1, 2.9, 8.3 Hz, 1H), 6.89 (dd, *J* = 1.1,

2.4 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.24 (s, 1H), 8.26 (dd, *J* = 2.2, 8.7 Hz, 1H), 8.52 (d, *J*= 2.2 Hz, 1H), 10.49 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 14.3 ($CH_3$), 57.5 ($CH_3$), 61.3 ($CH_2$), 82.0 (C), 88.5 (C), 113.2 (CH), 115.0 (C), 116.7 (CH), 118.5 (CH), 122.7 (C), 124.3 (CH), 124.9 (C), 129.7 (CH), 130.7 (CH), 137.0 (CH), 155.6 (C), 162.9 (C), 165.7 (C), 189.1 (C); EIMS *m/z* 324 ($M^+$, 22), 262 (41), 182 (24), 131 (100); HREIMS 324.1024 (calcd. for $C_{19}H_{16}O_5$ ($M^+$) 324.0998).

*Ethyl 4-formyl-3-((3-phenylprop-2-yn-1-yl)oxy)benzoate (**6ag**).* Following the general procedure, the treatment of 50 mg (0.22 mmol) of ethyl 4-formyl-3-(prop-2-yn-1-yloxy)benzoate with iodophenol (29.7 μL, 0.23 mmol), $Pd(PPh_3)_2Cl_2$ (4.8 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (43 μL, 0.43 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 1.5 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 66.2 mg (98 %) of compound **6ag** as a yellow oil. IR (neat) $\nu_{max}$ 2989, 2858, 1705, 1605, 1493, 1443, 1366, 1254, 1188, 1149, 1014, 995, 848, 756, 687, 663, 648 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.1 Hz, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 5.11 (s, 2H), 7.29 (m, 4H), 7.41 (m, 2H), 7.26 (dd, *J* = 2.2, 8.8 Hz, 1H), 8.53 (d, *J* = 2.3 Hz, 1H), 10.51 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 14.3 ($CH_3$), 57.7 ($CH_2$), 61.1 ($CH_2$), 82.3 (C), 88.8 (C), 113.3 (CH), 121.8 (C), 123.3 (C), 125.4 (C), 128.4 (CH x 2), 129.1 (CH), 130.6 (CH), 131.8 (CH x 2), 136.7 (CH), 162.9 (C), 165.4 (C), 188.6 (CH); EIMS *m/z* 308 ($M^+$, 100), 263 (27), 193 (16), 165 (10), 115 (99); HREIMS 308.1050 (calcd. for $C_{19}H_{16}O_4$ ($M^+$) 308.1049).

*Ethyl 4-formyl-3-((3-(3-nitrophenyl)prop-2-yn-1-yl)oxy)benzoate (**6ah**).* Following the general procedure, the treatment of 50 mg (0.22 mmol) of ethyl 4-formyl-3-(prop-2-yn-1-yloxy)benzoate with iodophenol (56.3 mg, 0.23 mmol), $Pd(PPh_3)_2Cl_2$ (4.8 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (43 μL, 0.43 mmol) in dry THF (1 mL) under

an Ar atmosphere at 30°C for 1.5 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (hex/EtOAc, 7:3) afforded 69.6 mg (90 %) of compound **6ah** as a yellow oil. IR (neat) $\nu_{max}$ 3521, 3398, 1686, 1609, 1531, 1366, 1057, 987, 848, 725, 667 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 1.37 (t, *J* = 7.2 Hz, 3H), 4.36 (q, *J* = 7.2 Hz, 2H), 5.14 (s, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.70 (dt, *J* = 1.2, 7.7 Hz, 1H), 8.17 (ddd, *J* = 1.0, 2.3, 8.4 Hz, 1H), 8.24 (t, *J* = 1.8 Hz, 1H), 8.26 (dd, *J* = 2.3, 8.8 Hz, 1H), 8.51 (d, *J* = 2.2 Hz, 1H), 10.49 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 14.3 ($CH_3$), 57.2 ($CH_2$), 61.1 ($CH_2$), 84.9 (C), 86.1 (C), 114.0 (CH), 123.5 (C), 123.8 (CH), 124.5 (C), 125.3 (C), 126.6 (CH), 129.5 (CH), 130.7 (CH), 136.8 (CH), 137.4 (CH), 148.2 (C), 162.6 (C), 165.3 (C), 188.4 (CH); EIMS *m/z* 353 ($M^+$, 20), 308 (11), 279 (4), 206 (7), 160 (100), 114 (36); HREIMS 353.0915 (calcd. for $C_{19}H_{15}O_6N$ ($M^+$) 353.0899).

*Ethyl 4-formyl-3-((3-(3-trifluoromethylphenyl)prop-2-yn-1-yl)oxy)benzoate (***6ai***).*

Following the general procedure, the treatment of 50 mg (0.22 mmol) of ethyl 4-formyl-3-(prop-2-yn-1-yloxy)benzoate with 3-trifluoromethyl-1-iodobenzene (56.3 mg, 0.23 mmol), $Pd(PPh_3)_2Cl_2$ (4.8 mg, 3 mol %), CuI (2.5 mg, 6 mol %) and piperidine (43 μL, 0.43 mmol) in dry THF (1 mL) under an Ar atmosphere at 30°C for 1.5 h, followed by evaporation of the solvent under reduced pressure and purification on silica gel column chromatography (Hex/EtOAc, 7:3) afforded 83.7 mg (100 %) of compound **6ai** as a yellow oil. IR (neat) $\nu_{max}$ 3514, 3402, 1712, 1689, 1612, 1434, 1385, 1319, 1061, 968, 825, 687, 667, 629 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.4 Hz, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 5.12 (s, 2H), 7.23 (d, *J* = 8.9 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.57 (s, 1H), 7.59 (s, 1H), 7.67 (s, 1H), 8.23 (dd, *J* = 2.2, 8.7 Hz, 1H), 8.53 (d, *J* = 2.2 Hz, 1H), 10.50 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 55.7 ($CH_3$), 57.1 ($CH_2$), 84.4 (C), 86.6 (C), 99.6 (CH), 106.7 (CH), 119.6 (C), 122.8 (C), 123.5 (C, $J_{C-F}$= 275.5 Hz), 125.5

(CH, $J_{C-F}$= 3.6 Hz), 128.6 (CH, $J_{C-F}$= 3.0 Hz), 129.0 (CH), 130.8 (CH), 131.0 (C, $J_{C-F}$= 33.4 Hz), 134.9 (CH), 160.6 (C), 165.9 (C), 188.1 (CH); EIMS *m/z* 376 ($M^+$, 21), 347 (8), 330 (5), 275 (4), 182 (100); HREIMS 376.0911 (calcd. for $C_{20}H_{15}O_4F_3$ ($M^+$) 376.0922).

**General Procedures for the preparation of pyran embelin derivatives via DKHDA**

A solution of embelin (30.0 mg, 0.10 mmol) in dichloroethane (5 mL), 0.15 mmol of the corresponding alkyne and 10 mol % of EDDA was placed in a microwave-special closed vial and the solution was irradiated for 10 min in a single-mode microwave oven (120 °C). The reaction mixture was then cooled to room temperature. After removal of the solvent under reduced pressure, the product was purified by preparative-TLC using Hex/EtOAc to yield the corresponding pyran derivatives.

*11-chloro-2-hydroxy-6-(4-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7a**).* Following the general procedure described above, 26.1 mg (0.09 mmol) of embelin, 40 mg (0.1 mmol) of 5-chloro-2-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.02 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^oC$. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 47.8 mg (93%) of **7a** as a brown solid. Mp: 148.8-149.4 ºC; IR (neat) $\nu_{max}$ 3348, 2923, 2853, 1687, 1651, 1619, 1608, 1513, 1479, 1400, 1345, 1323, 1305, 1248, 1220, 1172, 1116, 1085, 1023, 983, 870, 842, 814 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=6.9 Hz, 3H), 1.25 (bs, 16H), 1.50 (m, 2H), 2.50 (t, *J*=7.7 Hz, 2H), 3.83 (s, 3H), 4.82 (s, 1H), 4.86 (d, *J*=12.6 Hz, 1H), 4.89 (d, *J*=12.9 Hz, 1H), 6.65 (d, *J*=1.4 Hz, 1H), 6.76 (d, *J*=8.8 Hz, 1H), 6.93 (d, *J*=8.8 Hz, 2H), 7.09 (dd, *J*=1.9, 8.8 Hz, 1H), 7.33 (d, J=8.6 Hz, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.6 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$ x 2), 30.9 (CH), 31.9 ($CH_2$), 55.4 ($CH_3$), 67.8

($CH_2$), 106.8 (C), 110.5 (C), 113.9 (CH x 2), 118.9 (CH), 119.6 (C), 123.4 (C), 123.6 (C), 125.3 (CH), 125.9 (C), 128.2 (CH), 129.0 (C), 129.9 (CH x 2), 145.2 (C), 152.2 (C), 152.6 (C), 160.8 (C), 180.0 (C), 183.3 (C); EIMS *m/z* 576 ($M^+$, 100), 548 (22), 436 (20), 407 (39), 283 (51), 135 (87); HREIMS 578.2284 (calcd for $C_{34}H_{37}O_6{}^{37}Cl$ 578.2249), 576.2286 (calcd for $C_{34}H_{37}O_6{}^{35}Cl$ 576.2279).

*11-chloro-2-hydroxy-6-(3-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7b**).* Following the general procedure described above, 45.6 mg (0.16 mmol) of embelin, 70 mg (0.23 mmol) of 5-chloro-2-((3-(3-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 2.8 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^oC$. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 90.4 mg (98%) of **7b** as a brown solid. Mp: 81.8-82.9 ºC; IR (neat) $\nu_{max}$ 3315, 2924, 2853, 1640, 1625, 1598, 1480, 1431, 1345, 1261, 1177, 1119, 1092, 1043, 1024, 990, 887, 819 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.2 Hz, 3H), 1.26 (bs, 16H), 1.51 (m, 2H), 2.50 (t, *J*=7.7 Hz, 2H), 3.82 (s, 3H), 4.83 (s, 1H), 4.88 (s, 2H), 6.66 (d, *J* =1.5 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 6.94 (m, 3H), 7.10 (dd, *J* = 2.2, 8.7 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 (2x$CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 (2x$CH_2$), 29.7 (2x$CH_2$), 30.9 (CH), 31.9 ($CH_2$), 55.4 ($CH_3$), 67.7 ($CH_2$), 108.1 (C), 110.5 (C), 113.9 (CH), 115.8 (CH), 116.8 (C), 118.9 (CH), 119.7 (C), 120.9 (CH), 125.3 (CH), 126.0 (C), 128.3 (CH), 129.0 (C), 129.6 (CH), 132.4 (C), 145.1 (C), 152.1 (C), 152.6 (C), 159.6 (C), 179.9 (C), 183.4 (C); EIMS *m/z* 578 ($M^+$, 16), 558 (10), 481 (34), 338 (12), 135 (100); HREIMS 576.2268 (calcd for $C_{34}H_{37}O_6{}^{35}Cl$ 576.2279), 578.2264 (calcd for $C_{34}H_{37}O_6{}^{35}Cl$ 578.2249).

*11-chloro-2-hydroxy-6-(2-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7c**).* Following the general procedure described above, 32.6 mg

(0.11 mmol) of embelin, 50 mg (0.17 mmol) of 5-chloro-2-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 2.8 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 41.5 mg (65%) of **7c** as a brown solid. Mp: 121.5-122.8 ºC; IR (neat) $\nu_{max}$ 3363, 2924, 2853, 2360, 2338, 1697, 1652, 1620, 1600, 1479, 1348, 1254, 1229, 1178, 1118, 1089, 1049, 1019, 989, 820 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.1 Hz, 3H), 1.25 (bs, 16H), 1.50 (m, 2H), 2.48 (t, *J*=7.4 Hz, 2H), 3.79 (s, 3H), 4.47 (d, *J* =12.5 Hz, 1H), 4.74 (d, *J* =13.0 Hz, 1H), 4.83 (s, 1H), 6.67 (s, 1H), 6.73 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.99 (t, *J* =7.3 Hz, 1H), 7.08 (d, *J* =7.8 Hz, 1H), 7.30 (dd, *J* =1.0, 7.5 Hz, 1H), 7.39 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 ($CH_2$ x 2), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 (2x$CH_2$), 29.7 ($CH_2$ x 2), 30.8 (CH), 31.9 ($CH_2$), 55.7 ($CH_3$), 68.1 ($CH_2$), 109.3 (C), 110.5 (C), 111.4 (CH), 115.7 (C), 118.7 (CH), 119.5 (C), 120.7 (CH), 125.3 (CH), 125.5 (C), 128.1 (CH), 128.7 (C), 130.9 (CH), 131.6 (CH), 133.7 (C), 135.1 (C), 141.7 (C), 152.9 (C), 157.2 (C), 180.0 (C), 183.7 (C); EIMS *m/z* 576 ($M^+$, 35), 527 (53), 437 (26), 386 (33), 282 (37); HREIMS 576.2268 (calcd for $C_{34}H_{37}O_6{}^{35}Cl$ 576.2279).

*11-chloro-2-hydroxy-6-(3-hydroxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7d**).* Following the general procedure described above, 27.3 mg of embelin (0.09 mmol), 40 mg (0.14 mmol) of 5-chloro-2-((3-(3-hydroxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde) and 1.7 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 41.6 mg (82%) of **7d** as a brown solid. Mp: 145.6-146.1 ºC; IR (neat) $\nu_{max}$ 3335, 2921, 2852, 1645, 1613, 1584, 1480, 1400, 1346, 1328, 1273, 1250, 1220, 1194, 1168, 1117, 1089, 1029, 979, 934, 878, 912 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.26 (sa, 16H),

1.52 (m, 2H), 2.50 (t, *J*=7.7 Hz, 2H), 4.83 (s, 1H), 4.87 (s, 2H), 5.45 (bs, 1H), 6.66 (s, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.88 (m, 3H), 7.00 (dd, *J* =1.5, 8.4 Hz, 1H), 7.25 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 (2x$CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$ x 2), 30.9 (CH), 31.9 ($CH_2$), 67.7 ($CH_2$), 108.2 (C), 110.5 (C), 115.3 (CH), 117.2 (CH), 119.0 (CH), 119.7 (C), 120.9 (CH), 125.3 (CH), 126.0 (C), 128.3 (CH), 128.9 (C), 129.8 (CH), 132.5 (C), 144.9 (C), 151.2 (C), 152.1 (C), 152.6 (C), 155.8 (C), 180.1 (C), 183.3 (C); EIMS *m/z* 562 ($M^+$, 79), 548 (40), 421 (40), 268 (87), 135 (93); HREIMS 564.2114 (calcd. for $C_{33}H_{35}O_6{}^{37}Cl$ 564.2093), 562.2137 (calcd. for $C_{33}H_{35}O_6{}^{35}Cl$ 562.2122).

*11-chloro-2-hydroxy-6-phenyl-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7e**).* Following the general procedure described above, 25.3 mg (0.09 mmol) of embelin, 35 mg (0.13 mmol) of 5-chloro-2-((3-(3-phenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.6 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^{o}$C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 34.6 mg (74%) of **7e** as a brown solid. Mp: 146.2-146.7 ºC; IR (neat) $\nu_{max}$ 3338, 2921, 2851, 1653, 1481, 1401, 1347, 1325, 1249, 1218, 1170, 1116, 1091, 1069, 1020, 1009, 984, 921, 870, 814 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.26 (bs, 16H), 1.51 (m, 2H), 2.50 (t, *J* = 7.5 Hz, 2H), 4.84 (s, 1H), 4.86 (d, *J* = 12.9 Hz, 1H), 4.90 (d, *J* =12.9 Hz, 1H), 6.66 (d, *J* =1.0 Hz, 1H), 6.76 (d, *J* =8.6 Hz, 1H), 7.09 (dd, *J* =1.1, 8.9 Hz, 1H), 7.42 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 (2x$CH_2$), 28.1 ($CH_2$), 29.4 (2 x $CH_2$), 29.6 (2 x $CH_2$), 29.7 (2 x $CH_2$), 30.9 (CH), 31.9 ($CH_2$), 67.7 ($CH_2$), 107.9 (C), 110.5 (C), 118.9 (CH), 119.7 (C), 125.3 (CH), 126.0 (C), 128.3 (CH), 128.5 (2 x CH), 128.6 (2 x CH), 128.9 (C), 130.0 (CH), 131.2 (C), 145.3 (C), 151.2 (C), 152.2 (C), 152.6 (C), 179.9 (C), 183.5 (C); EIMS *m/z* 546 ($M^+$, 91), 518 (35), 405 (43), 294 (37), 252 (100);

HREIMS 546.2156 (calcd for $C_{33}H_{35}O_5{}^{35}Cl$ 546.2173), 548.2122 (calcd for $C_{33}H_{35}O_5{}^{37}Cl$ 548.2144).

*11-chloro-2-hydroxy-6-(3-nitrophenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7f**)*. Following the general procedure described above, 24.8 mg (0.08 mmol) of embelin, 40 mg of 5-chloro-2-((3-(3-nitrophenyl)prop-2-yn-1-yl)oxy)benzaldehyde (0.13 mmol) and 1.5 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^{o}$C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 50.8 mg (100%) of **7f** as a brown solid. Mp: 154.1-156.0 ºC; IR (neat) $\nu_{max}$ 3523, 3397, 2924, 2853, 1652, 1622, 1532, 1479, 1346, 1256, 1223, 1170, 1113, 1098, 1032, 987, 951, 906, 860, 813 $cm^{-1}$; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.24 (bs, 16H), 1.50 (m, 2H), 2.50 (t, *J*=8.9 Hz, 2H), 4.77 (d, *J* =12.9 Hz, 1H), 4.85 (s, 1H), 4.96 (d, *J* =13.3 Hz, 1H), 6.67 (s, 1H), 6.78 (d, *J* =8.4 Hz, 1H), 7.10 (d, *J*=7.7 Hz, 1H), 7.63 (t, *J*=7.6 Hz, 1H), 7.76 (d, *J* =7.2 Hz, 1H), 8.23 (s, 1H), 8.28 (d, *J* =8.1 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 14.0 ($CH_3$), 22.7 ($CH_2$), 22.8 ($CH_2$), 28.2 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 (2x$CH_2$), 29.7 (2x$CH_2$), 30.9 (CH), 31.9 ($CH_2$), 67.2 ($CH_2$), 110.4 (C), 110.6 (C), 119.1 (CH), 119.9 (C), 120.0 (C), 123.4 (CH), 124.7 (CH), 125.3 (CH), 126.3 (C), 128.5 (CH), 128.6 (C), 129.8 (CH), 132.9 (C), 134.2 (CH), 142.9 (C), 148.2 (C), 151.8 (C), 152.4 (C), 179.5 (C), 182.5 (C); EIMS *m/z* 591 ($M^+$, 100), 573 (70), 450 (50), 421 (43), 297 (59); HREIMS 593.1968 (calcd. for $C_{33}H_{34}NO_7{}^{37}Cl$, 593.1994), 591.2000 (calcd. for $C_{33}H_{34}NO_7{}^{35}Cl$, 591.2024).

*11-chloro-2-hydroxy-6-(3-(trifluoromethyl)phenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7g**)*. Following the general procedure described above, 23.2 mg of embelin (0.08 mmol), 40 mg of 5-chloro-2-((3-(3-trifluoromethylphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (0.12 mmol) and 1.5 mg of EDDA (10 mol %) were suspended in

2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 41.4 mg (86%) of **7g** as an amorphous brown solid. Mp: 184.3-186.0 ºC; IR (neat) $\nu_{max}$ 3774, 3534, 3357, 2925, 2854, 1707, 1650, 1619, 1481, 1395, 1336, 1216, 1166, 1066, 810 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.1 Hz, 3H), 1.26 (bs, 16H), 1.52 (m, 2H), 2.51 (t, *J* = 7.7 Hz, 2H), 4.79 (d, *J* = 12.8 Hz, 1H), 4.87 (s, 1H), 4.93 (d, *J* =12.8 Hz, 1H), 6.67 (dd, *J* =1.0, 2.5 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 7.12 (dd, *J* = 2.4, 8.7, 1H), 7.59 (m, 2H), 7.65 (s, 1H), 7.70 (dt, *J* =2.5, 7.9 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 (2x$CH_2$), 29.7 ($CH_2$), 29.8 ($CH_2$), 30.9 (CH), 31.9 ($CH_2$), 67.4 ($CH_2$), 110.5 (C), 110.6 (C), 119.1 (CH), 119.9 (C), 125.2 (CH), 125.3 (CH), 126.3 (C), 126.8 (CH, $J_{C-F}$ =3.7 Hz), 128.5 (CH), 128.7 (C), 129.3 (CH), 131.1 (C), 131.4 (C), 131.8 (CH), 132.1 (C), 143.9 (C), 151.1 (C), 151.8 (C), 152.4 (C), 179.7 (C), 183.3 (C); EIMS *m/z* 614 ($M^+$, 86), 596 (76), 444 (38), 320 (67), 173 (87); HREIMS 614.2047 (calcd for $C_{34}H_{34}O_5{}^{35}ClF_3$ 614.2047), 616.1998 (calcd for $C_{34}H_{34}O_5{}^{35}ClF_3$ 616.2017).

*11-bromo-2-hydroxy-6-(4-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7h**).* Following the general procedure described above, 23.8 mg (0.09 mmol) of embelin, 40 mg (0.12 mmol) of 5-chloro-2-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.5 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 36.7 mg (73%) of **7h** as an amorphous brown solid; Mp: 140.4-142.0 ºC; IR (neat) $\nu_{max}$ 3349, 2922, 2852, 1651, 1619, 1608, 1513, 1476, 1344, 1249, 1219, 1176, 1117, 1088, 1022, 1004, 983, 918, 841, 812 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.26 (bs, 16H), 1.51 (m, 2H), 2.50 (t, *J*=7.6 Hz, 2H), 3.83 (s, 3H), 4.82 (s, 1H), 4.86 (d, *J*=12.9 Hz, 1H),

4.89 (d, *J*=12.9 Hz, 1H), 6.71 (d, *J*=8.8 Hz, 1H), 6.78 (d, *J*=1.2 Hz, 1H), 6.93 (d, *J*=8.8 Hz, 2H), 7.23 (dd, *J*=2.1, 8.6 Hz, 1H), 7.33 (d, *J*=8.8 Hz, 2H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 (3x $CH_2$), 29.7 ($CH_2$), 30.8 (CH), 31.9 ($CH_2$), 55.4 ($CH_3$), 67.8 ($CH_2$), 106.7 (C), 110.4 (C), 113.2 (C), 113.9 (2 x CH), 119.4 (CH), 119.6 (C), 123.6 (C), 128.1 (CH), 129.5 (C), 129.9 (2 x CH), 131.2 (CH), 145.2 (C), 151.1 (C), 152.2 (C), 153.1 (C), 160.8 (C), 180.0 (C), 183.4 (C); EIMS *m/z* 622 ($M^+$, 100), 620 (84), 452 (21), 328 (29), 262 (53); HREIMS 622.1757 (calcd for $C_{34}H_{37}O_6{}^{81}Br$ 622.1753), 620.1788 (calcd for $C_{34}H_{37}O_6{}^{79}Br$ 620.1774).

*11-bromo-2-hydroxy-6-(3-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7i**).* Following the general procedure described above, 34.2 mg of embelin (0.12 mmol), 60 mg de 5-chloro-2-((3-(3-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde (0.17 mmol) and 2.1 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 58.3 mg (81%) of **7i** as a yellow oil; IR (neat) $\nu_{max}$ 3374, 3055, 2926, 2854, 2361, 2339, 1694, 1646, 1624, 1598, 1477, 1431, 1347, 1263, 1174, 1120, 1082, 1025, 988, 892, 864, 819 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.1 Hz, 3H), 1.25 (bs, 16H), 1.50 (m, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 3.82 (s, 3H), 4.82 (s, 1H), 4.88 (s, 2H), 6.70 (d, *J* =8.5 Hz, 1H), 6.79 (s, 1H), 6.95 (m, 3H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 ($CH_2$), 22.8 ($CH_2$), 28.2 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$), 29.7 ($CH_2$), 30.8 (CH), 31.9 ($CH_2$), 55.4 ($CH_3$), 67.7 ($CH_2$), 108.0 (C), 110.4 (C), 113.2 (C), 113.9 (CH), 115.8 (CH), 115.9 (C), 119.4 (CH), 119.7 (C), 120.9 (CH), 128.1 (CH), 129.4 (C), 129.6 (CH), 131.2 (CH), 132.4 (C), 145.2 (C), 152.2 (C), 153.1 (C), 159.6 (C), 179.8 (C), 183.9 (C); EIMS *m/z*

621 ($M^+$, 32), 620 (16), 481 (6), 382 (16), 135 (100); HREIMS 622.1752 (calcd for $C_{34}H_{37}O_6{}^{81}Br$ 622.1753), 620.1781 (calcd for $C_{34}H_{37}O_6{}^{79}Br$ 620.1774).

*11-bromo-2-hydroxy-6-(2-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione* (**7j**). 11.4 mg (0.04 mmol) of embelin, 20 mg (0.06 mmol) of 5-bromo-2-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 0.7 mg of EDDA (10% mol) were dissolved in 2 mL of DCE. The reaction mixture was irradiated at 120°C for 10 min. The solvent was removed under vacuum and compound **7j** (14.2 mg, 57%) was obtained as an amorphous brown solid after purification by preparative-TLC with 30% Hex/EtOAc as a yellow oil. IR $\nu_{max}$ 3518, 3402, 2924, 2854, 1620, 1477, 1350, 1057, 972, 822, 667 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.25 (bs, 16H), 1.49 (m, 2H), 2.49 (t, *J* = 7.5 Hz, 2H), 3.79 (s, 3H), 4.47 (d, *J* = 12.9 Hz, 1H), 4.74 (d, *J* = 12.9 Hz, 1H), 4.85 (s, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.80 (dd, *J* = 1.0, 2.3 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.99 (td, *J* = 0.7, 7.5 Hz, 1H), 7.23 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.30 (td, *J* = 1.5, 7.7 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 ($CH_2$ x 2), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.67 ($CH_2$ x 2), 30.7 (CH), 55.7 ($CH_3$), 68.1 ($CH_2$), 109.2 (C), 110.5 (C), 111.4 (CH), 112.8 (C), 119.2 (CH), 119.5 (C), 120.1 (C), 120.8 (CH), 128.2 (CH), 129.2 (C), 130.8 (CH), 131.1 (CH), 131.7 (CH), 151.1 (C), 152.6 (C), 153.4 (C), 157.2 (C), 180.0 (C), 183.5 (C); EIMS *m/z* 622 ($M^+$, 32), 620 (16), 481 (6), 382 (16), 135 (100); HRMS 622.1752 (calcd. for $C_{34}H_{37}O_6{}^{81}Br$ 622.1753), 620.1781 (calcd. for $C_{34}H_{37}O_6{}^{79}Br$ 620.1774).

*11-bromo-2-hydroxy-6-(3-hydroxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7k**).* 23 mg (0.08 mmol) of embelin, 40 mg (0.12 mmol) of 5-bromo-2-((3-(3-hydroxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.4 mg of EDDA

(10 mol %) were dissolved in 2 mL of DCE. The reaction mixture was irradiated at 120°C for 10 min. The solvent was removed under vacuum and compound **7k** (36.6 mg, 75%) was obtained as an amorphous brown solid after purification by preparative-TLC with Hex:AcOEt 30%. Mp: 197.2-199.0 ºC; IR $\nu_{max}$ 3518, 3398, 3255, 3061, 2951, 2923, 2854, 1620, 1531, 1477, 1350, 1057, 968, 823, 667 $cm^{-1}$;$^{1}$H-NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.26 (bs, 16H), 1.50 (m, 2H), 2.50 (t, *J*=7.8 Hz, 2H), 4.84 (s, 1H), 4.87 (d, *J*= 12.4 Hz, 2H), 4.90 (d, *J* =12.4 Hz, 1H), 5.15 (bs, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 6.78 (dd, *J* = 1.0, 2.3 Hz, 1H), 6.90 (m, 1H), 7.24 (d, *J* =2.3 Hz, 1H), 7.28 (m. 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 ($CH_2$), 22.8 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.7 (2 x $CH_2$), 30.8 (CH), 31.9 ($CH_2$), 67.6 ($CH_2$), 108.1 (C), 110.4 (C), 113.3 (C), 115.2 (CH), 117.2 (CH), 119.4 (CH), 119.7 (C), 121.0 (CH), 128.1 (CH), 129.3 (C), 129.8 (CH), 131.3 (CH), 132.5 (C), 144.9 (C), 151.1 (C), 152.1 (C), 153.1 (C), 155.7 (C), 179.9 (C), 183.3 (C); EIMS *m/z* 608 ($M^+$, 68), 580 (20), 446 (40), 314 (44), 131 (30), 68 (100); HRMS 608.1617 (calcd for $C_{33}H_{35}O_6{}^{81}Br$ 608.1597), 606.1599 (calcd for $C_{33}H_{35}O_6{}^{79}Br$ 606.1617).

*11-bromo-2-hydroxy-6-phenyl-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7l**).* Following the general procedure described above, 25.0 mg of embelin (0.09 mmol), 40 mg (0.13 mmol) of 5-chloro-2-((3-(3-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.5 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 28.5 mg (57 %) of **7l** as an amorphous brown solid. Mp: 146.2-146.7 ºC; IR (neat) $\nu_{max}$ 3342, 2920, 2851, 1653, 1619, 1478, 1446, 1398, 1346, 1325, 1249, 1218, 1168, 1117, 1091, 1070, 1008, 983, 920, 861, 811 $cm^{-1}$; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.1 Hz, 3H), 1.26 (bs, 16H), 1.52 (m, 2H), 2.51 (t, *J*=7.6 Hz, 2H), 4.85 (s, 1H), 4.87 (d, *J*=12.7 Hz, 1H), 4.90

(d, *J*=13.0 Hz, 1H), 6.72 (d, *J*=8.8 Hz, 1H), 6.80 (s, 1H), 7.24 (d, *J*=1.7, 8.5 Hz, 1H), 7.41 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$), 29.7 ($CH_2$), 30.8 (CH), 31.9 ($CH_2$), 67.7 ($CH_2$), 107.8 (C), 110.5 (C), 113.2 (C), 119.4 (CH), 119.7 (C), 128.1 (CH), 128.4 (CH x 2), 128.6 (CH x 2), 129.4 (C), 130.1 (CH), 131.2 (C), 131.2 (CH), 145.4 (C), 151.1 (C), 152.2 (C), 153.1 (C), 179.9 (C), 183.4 (C); EIMS *m/z* 592 ($M^+$, 100), 590 (73), 451 (19), 298 (60); HREIMS 592.1650 (calcd for $C_{33}H_{35}O_5{}^{81}Br$ 592.1647), 590.1659 (calcd for $C_{33}H_{35}O_5{}^{79}Br$ 590.1668).

*11-bromo-2-hydroxy-6-(3-nitrophenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7m**).* Following the general procedure described above, 16.3 mg (0.06 mmol) of embelin, 30 mg (0.08 mmol) of 5-chloro-2-((3-(3-nitrophenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.0 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^{o}$C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 31.3 mg (88 %) of **7m** as a yellow oil. IR (neat) $\nu_{max}$ 3383, 3085, 2924, 2853, 2361, 2339, 1697, 1653, 1623, 1533, 1476, 1395, 1345, 1260, 1227, 1173, 1120, 1099, 1029, 989, 952, 908, 853, 815 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.1 Hz, 3H), 1.25 (bs, 16H), 1.52 (m, 2H), 2.51 (t, *J*=7.6 Hz, 2H), 4.79 (d, *J* =12.7 Hz, 1H), 4.88 (s, 1H), 4.97 (d, *J*=12.7 Hz, 1H), 6.74 (d, *J*=8.9 Hz, 1H), 6.80 (d, *J* =1.2 Hz, 1H), 7.26 (dd, *J*=1.9, 8.6 Hz, 1H), 7.64 (t, *J*=8.0 Hz, 1H), 7.76 (dt, *J*=1.6, 7.7 Hz, 1H), 8.23 (t, *J*=1.6 Hz, 1H), 8.30 (dd, *J*=1.3, 8.3 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.6 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$), 29.8 ($CH_2$), 30.9 (CH), 31.9 ($CH_2$), 67.2 ($CH_2$), 110.3 (C), 110.6 (C), 113.7 (C), 119.6 (CH), 120.0 (C), 123.4 (CH), 124.8 (CH), 128.2 (CH), 129.0 (C), 129.9 (CH), 131.5 (CH), 132.8 (C), 134.2 (CH), 143.0 (C), 148.2 (C), 151.2 (C), 151.6 (C), 152.9 (C), 179.6 (C), 183.2 (C);

EIMS *m/z* 636 ($M^+$, 96), 635 (94), 618 (67), 501 (32), 343 (37), 149 (100); HREIMS 635.1533 (calcd for $C_{33}H_{34}O_7{}^{79}BrN$ 635.1519), 636.1481 (calcd for $C_{33}H_{33}O_7{}^{81}BrN$ 636.1420).

*11-bromo-2-hydroxy-6-(3-(trifluoromethyl)phenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7n**).* Following the general procedure described above, 30.7 mg (0.1 mmol) of embelin, 60 mg (0.16 mmol) of 5-chloro-2-((3-(3-trifluoromethylphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 2.0 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^oC$. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 64.5 mg (99 %) of **7n** as an amorphous brown solid. Mp: 76.0-77.7 ºC; IR (neat) $\nu_{max}$ 3368, 2926, 2855, 2360, 2338, 1697, 1649, 1626, 1558, 1477, 1440, 1335, 1263, 1223, 1170, 1129, 1074, 1027, 989, 909, 816 $cm^{-1}$;$^1$H-NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.1 Hz, 3H), 1.25 (bs, 16H), 1.51 (m, 2H), 2.50 (t, *J*=7.3 Hz, 2H), 4.79 (d, *J*=12.6 Hz, 1H), 4.86 (s, 1H), 4.93 (d, *J*=12.6 Hz, 1H), 6.72 (d, *J*=8.5 Hz, 1H), 6.79 (s, 1H), 7.25 (d, *J*=8.5 Hz, 1H), 7.58 (m, 2H), 7.64 (s, 1H), 7.70 (d, *J*=7.2 Hz, 1H); $^{13}$C-NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 ($CH_2$), 22.8 ($CH_2$), 28.2 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 ($CH_2$), 29.6 ($CH_2$), 29.7 (2x$CH_2$), 30.8 (CH), 31.9 ($CH_2$), 67.3 ($CH_2$), 109.4 (C), 110.5 (C), 113.5 (C), 119.5 (CH), 119.9 (C), 123.6 (C, $J_{C-F}$= 272.2Hz), 125.2 (CH, $J_{C-F}$=3.6 Hz), 126.8 (CH, $J_{C-F}$=3.2 Hz), 128.1 (CH), 129.1 (C), 129.3 (CH), 131.2 (C, $J_{C-F}$= 32.4Hz), 131.4 (CH), 131.7 (CH), 132.0 (C), 143.9 (C), 151.4 (C), 151.9 (C), 152.9 (C), 179.6 (C), 183.6 (C); EIMS *m/z* 614 ($M^+$, 86), 596 (76), 444 (38), 320 (67), 173 (87); HREIMS 658.1522 (calcd for $C_{34}H_{34}O_5{}^{79}BrF_3$ 658.1542), 660.1550 (calcd for $C_{34}H_{34}O_5{}^{81}BrF_3$ 660.1521).

*2-hydroxy-6-(4-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7o**).* Following the general procedure described above, 29.4 mg (0.10 mmol) of

embelin, 40 mg (0.16 mmol) of 5-chloro-2-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.8 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 47.8 mg (88 %) of **7o** as an amorphous brown solid. Mp: 124.7-126.0 ºC; IR (neat) $\nu_{max}$ 3341, 2924, 2854, 1687, 1650, 1607, 1513, 1485, 1452, 1403, 1355, 1304, 1249, 1223, 1175, 1113, 1085, 1023, 987, 904, 843 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.2 Hz, 3H), 1.25 (bs, 16H), 1.48 (m, 2H), 2.46 (t, *J*=7.5 Hz, 2H), 3.83 (s, 3H), 4.81 (s, 1H), 4.85 (d, *J*=12.8 Hz, 1H), 4.91 (d, *J*=12.8 Hz, 1H), 6.69 (d, *J*=7.2 Hz, 1H), 6.84 (m, 2H), 6.93 (d, *J*=8.8 Hz, 2H), 6.90 (d, *J*=8.2 Hz, 2H), 7.12 (t, *J*=7.1 Hz, 1H), 7.32 (d, *J*=8.2 Hz, 2H); $^{13}$C-NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 (2x $CH_2$), 28.2 ($CH_2$), 29.4 (2 x $CH_2$), 29.6 (2 x $CH_2$), 29.7 ($CH_2$ x 2), 30.8 (CH), 31.9 ($CH_2$), 55.4 ($CH_3$), 67.7 ($CH_2$), 107.7 (C), 111.0 (C), 113.8 (CH x 2), 117.5 (CH), 119.2 (C), 121.1 (CH), 123.8 (C), 125.2 (CH), 128.2 (C), 128.5 (CH), 128.6 (C), 129.9 (CH x 2), 132.1 (C), 144.5 (C), 153.9 (C), 160.6 (C), 180.1 (C), 183.8 (C); EIMS *m/z* 542 ($M^+$, 82), 483 (14), 402 (16), 305 (20), 135 (100); HREIMS 542.2678 (calcd for $C_{34}H_{38}O_6$ ($M^+$) 542.2668).

*2-hydroxy-6-(3-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7p**).* Following the general procedure described above, 36.8 mg of embelin (0.13 mmol), 50 mg (0.19 mmol) of 5-chloro-2-((3-(3-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 2.3 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 49.4 mg (70 %) of **7p** as an amorphous brown solid. Mp: 69.5-71.2 ºC; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.1 Hz, 3H), 1.26 (bs, 16H), 1.51 (m, 2H), 2.50 (t, *J*=7.7 Hz, 2H), 3.82 (s, 3H), 4.83 (s, 1H), 4.86 (s, 1H), 4.89 (d, *J*=13.0 Hz, 1H), 4.92 (d, *J*=13.2 Hz, 1H), 6.72 (d, *J*=7.7 Hz, 1H),

6.84 (d, *J*=8.1 Hz, 1H), 6.88 (t, *J*=7.4 Hz, 1H), 6.96 (m, 3H), 7.15 (t, *J*=7.6 Hz, 1H), 7.31 (t, *J*=7.7 Hz, 1H); IR (neat) $\nu_{max}$ 3346, 3057, 2925, 2854, 1693, 1647, 1623, 1602, 1485, 1458, 1348, 1263, 1222, 1179, 1117, 1041, 1024, 990, 866 $cm^{-1}$; $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.6 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 (2 x $CH_2$), 29.7 ($CH_2$), 30.8 (CH), 31.9 ($CH_2$), 55.4 ($CH_3$), 67.6 ($CH_2$), 108.9 (C), 111.0 (C), 113.8 (CH), 115.7 (CH), 117.6 (CH), 119.4 (C), 120.9 (CH), 121.1 (CH), 125.2 (CH), 127.5 (C), 128.2 (CH), 129.5 (CH), 132.6 (C), 144.5 (C), 151.1 (C), 152.0 (C), 153.9 (C), 159.5 (C), 180.1 (C), 183.5 (C); EIMS *m/z* 542 ($M^+$, 6), 524 (8), 387 (9), 304 (8), 135 (100); HREIMS 542.2684 (calcd for $C_{34}H_{38}O_6$ ($M^+$) 542.2668).

*2-hydroxy-6-(2-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7q**).* Following the general procedure described above, 29.4 mg (0.10 mmol) of embelin, 40 mg (0.15 mmol) of 5-chloro-2-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.8 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 43.4 mg (80 %) of **7q** as an amorphous brown solid. Mp: 74.3-75.5 ºC; IR (neat) $\nu_{max}$ 3308, 3073, 2924, 2853, 1697, 1646, 1620, 1601, 1486, 1460, 1437, 1397, 1348, 1282, 1250, 1223, 1180, 1116, 1082, 1044, 1018, 989, 863, 822 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.2 Hz, 3H), 1.26 (bs, 16H), 1.49 (m, 2H), 2.48 (t, *J*=8.0 Hz, 2H), 3.80 (s, 3H), 4.49 (d, *J*=12.8 Hz, 1H), 4.77 (d, *J*=12.8 Hz, 1H), 4.88 (s, 1H), 6.73 (d, *J*=7.5 Hz, 1H), 6.82 (d, *J*=8.4 Hz, 1H), 6.87 (t, *J*=7.5 Hz, 1H), 6.93 (d, *J*=8.4 Hz, 1H), 6.99 (t, *J*=7.5 Hz, 1H), 7.14 (t, *J*=7.5 Hz, 1H), 7.32 (dd, *J*=1.5, 7.7 Hz, 1H), 7.39 (td, *J*=1.8, 7.7 Hz, 1H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.6 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$ x 3), 30.7 (CH), 31.9 ($CH_2$), 55.6 ($CH_3$), 67.9 ($CH_2$),

110.1 (C), 111.1 (C), 111.3 (CH), 117.4 (CH), 119.2 (C), 120.3 (C), 120.7 (CH), 120.8 (CH), 125.3 (CH), 127.2 (C), 128.1 (CH), 130.9 (CH), 131.5 (CH), 141.2 (C), 151.1 (C), 152.4 (C), 154.2 (C), 157.2 (C), 180.2 (C), 183.6 (C); EIMS *m/z* 542 ($M^+$, 82), 483 (14), 402 (16), 305 (20), 135 (100); HREIMS 542.2678 (calcd for $C_{34}H_{38}O_6$ ($M^+$) 542.2668).

*2-hydroxy-6-(3-hydroxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7r**).* Following the general procedure described above, 30.0 mg (0.08 mmol) of embelin, 30 mg (0.12 mmol) of 5-chloro-2-((3-(3-hydroxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.2 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^oC$. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 38.1 mg (92 %) of **7r** as an amorphous brown solid. Mp: 80.7-81.8 ºC; IR (neat) $\nu_{max}$ 3365, 2924, 2853, 2360, 2337, 1651, 1621, 1485, 1451, 1351, 1270, 1224, 1202, 1117, 1033, 993 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.26 (bs, 16H), 1.50 (m, 2H), 2.49 (t, *J*=7.5 Hz, 2H), 4.86 (s, 1H), 4.89 (s, 2H), 6.70 (d, *J*=7.4 Hz, 1H), 6.87 (m, 5H), 7.15 (t, *J*=7.3 Hz, 1H), 7.23 (m, 1H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.6 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 ($CH_2$ x 3), 29.7 ($CH_2$), 30.8 (CH), 31.9 ($CH_2$), 67.6 ($CH_2$), 109.0 (C), 111.1 (C), 115.3 (CH), 117.1 (CH), 117.6 (CH), 119.4 (CH), 120.8 (C), 121.2 (CH), 125.2 (CH), 127.4 (CH), 128.3 (CH), 129.7 (C), 132.6 (C), 144.3 (C), 151.9 (C), 153.9 (C), 156.0 (C), 180.4 (C), 183.4 (C); EIMS *m/z* 528 ($M^+$, 62), 447 (37), 388 (18), 277 (100), 235 (52); HREIMS 528.2515 (calcd for $C_{33}H_{36}O_6$ ($M^+$) 528.2512).

*2-hydroxy-6-phenyl-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7s**).* Following the general procedure described above, 41.5 mg (0.14 mmol) of embelin, 50 mg (0.21 mmol) of 5-chloro-2-((3-phenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 2.5 mg

of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 53.1 mg (74 %) of **7s** as an amorphous brown solid. Mp: 117.6-119.0 ºC; IR (neat) $\nu_{max}$ 3344, 3065, 2923, 2852, 2359, 1897, 1654, 1616, 1485, 1450, 1404, 1348, 1326, 1249, 1217, 1180, 1115, 1089, 1071, 1017, 983, 928, 863 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.1 Hz, 3H), 1.27 (bs, 16H), 1.51 (m, 2H), 2.50 (t, *J*=7.8 Hz, 2H), 4.87 (s, 1H), 4.89 (d, *J*=12.9 Hz, 1H), 4.93 (d, *J*=12.9 Hz, 1H), 6.72 (d, *J*=7.7 Hz, 1H), 6.85 (d, *J*=7.9 Hz, 1H), 6.88 (t, *J*=7.4 Hz, 1H), 7.15 (t, *J*=7.7 Hz, 1H), 7.41 (m, 5H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.6 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 (3 x$CH_2$), 30.8 (CH), 31.9 ($CH_2$), 67.6 ($CH_2$), 108.7 (C), 111.0 (C), 117.5 (CH), 119.4 (C), 121.1 (CH), 125.2 (CH), 127.4 (C), 128.2 (CH), 128.4 (2 x CH), 128.5 (2 x CH), 129.8 (CH), 131.4 (C), 131.8 (C), 144.7 (C), 151.1 (C), 152.0 (C), 153.9 (C), 180.1 (C), 183.5 (C); EIMS *m/z* 512 ($M^+$, 43), 484 (12), 372 (14), 277 (100), 262 (39); HREIMS 512.2587 (calcd for $C_{33}H_{36}O_5$ ($M^+$) 512.2563).

*2-hydroxy-6-(3-nitrophenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7t**).* Following the general procedure described above, 41.8 mg of embelin (0.14 mmol), 50 mg (0.21 mmol) of 5-chloro-2-((3-nitrophenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 2.6 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 62.2 mg (80 %) of **7t** as an amorphous brown solid. Mp: 88.7-89.2 ºC; IR (neat) $\nu_{max}$ 3387, 2926, 2854, 1653, 1624, 1533, 1484, 1456, 1347, 1262, 1227, 1181, 1117, 1029, 992, 950, 907, 866, 812 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.1 Hz, 3H), 1.26 (bs, 16H), 1.51 (m, 2H), 2.50 (t, *J*=7.5 Hz, 2H), 4.80 (d, *J*=13.1 Hz, 1H), 4.90 (s, 1H), 4.99 (d, *J*=13.1 Hz,

1H), 6.72 (d, *J*=7.6 Hz, 1H), 6.86 (d, *J*=8.4 Hz, 1H), 6.90 (t, *J*=7.4 Hz, 1H), 7.16 (t, *J*=7.4 Hz, 1H), 7.62 (t, *J*=8.2 Hz, 1H), 7.77 (dt, *J*=1.4, 7.6Hz, 1H), 8.25 (t, *J*=1.7 Hz, 1H), 8.28 (dd, *J*=1.4, 8.3 Hz, 1H); $^{13}$C NMR (500 MHz,$CDCl_3$) δ 14.1 ($CH_3$), 22.7 (2x$CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 (2x$CH_2$), 29.7 ($CH_2$), 30.9 (CH), 31.9 ($CH_2$), 67.1 ($CH_2$), 111.2 (C), 111.3 (C), 117.7 (CH), 119.6 (C), 121.5 (CH), 123.4 (CH), 124.6 (CH), 125.2 (CH), 127.2 (C), 128.5 (CH), 129.7 (CH), 133.0 (C), 134.2 (CH), 142.3 (C), 148.1 (C), 151.2 (C), 151.5 (C), 153.7 (C), 179.8 (C), 183.3 (C); EIMS *m/z* 557 ($M^+$, 100), 512 (28), 416 (38), 388 (31), 264 (56); HREIMS 557.2440 (calcd for $C_{33}H_{35}O_7N$ ($M^+$) 557.2414).

*2-hydroxy-6-(3-(trifluoromethyl)phenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7u**).* Following the general procedure described above, 32.2 mg (0.11 mmol) of embelin, 50 mg (0.16 mmol) of 5-chloro-2-((3-(3-trifluoromethylphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 2.6 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^{o}$C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 51.1 mg (88 %) of **7u** as a yellow oil. IR (neat) $\nu_{max}$ 3347, 3071, 2925, 2854, 2361, 2338, 1695, 1648, 1624, 1485, 1457, 1399, 1335, 1259, 1221, 1169, 1127, 1073, 1027, 992, 909, 865, 810 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.1 Hz, 3H), 1.26 (bs, 16H), 1.51 (m, 2H), 2.50 (t, *J*=7.6 Hz, 2H), 4.80 (d, *J*=12.7 Hz, 1H), 4.90 (s, 1H), 4.96 (d, *J*=13.0 Hz, 1H), 6.72 (d, *J*=7.7 Hz, 1H), 6.86 (d, *J*=8.4 Hz, 1H), 6.90 (d, *J*=7.7 Hz, 1H), 7.17 (t, *J*=7.7 Hz, 1H), 7.56 (t, *J*=7.8 Hz, 1H), 7.61 (d, *J*=7.5 Hz, 1H), 7.66 (s, 1H), 7.69 (d, *J*=7.5 Hz, 1H); $^{13}$C NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.6 ($CH_2$), 29.6 ($CH_2$), 30.8 (CH), 31.9 ($CH_2$), 67.2 ($CH_2$), 110.3 (C), 111.1 (C), 117.7 (CH), 119.6 (C), 121.4 (CH), 123.7 (C, $J_{C-F}$= 273.6 Hz), 125.2 (C), 125.2 (CH), 125.3 (CH), 126.6 (CH,

$J_{C\text{-}F}$=3.6 Hz), 127.2 (C), 128.4 (CH), 129.1 (CH), 131.1 (C, $J_{C\text{-}F}$= 33.0Hz), 131.7 (CH), 132.2 (C), 143.2 (C), 151.1 (C), 151.7 (C), 153.7 (C), 179.9 (C), 183.4 (C); EIMS *m/z* 580 ($M^+$, 28), 423 (26), 359 (25), 315 (20), 172 (100); HREIMS 580.2461 (calcd for $C_{34}H_{35}O_5F_3$ ($M^+$) 580.2437).

*2-hydroxy-10-methoxy-6-(4-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7v**).* Following the general procedure described above, 26.5 mg (0.09 mmol) of embelin, 40 mg (0.14 mmol) of 5-chloro-2-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.6 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 42.5 mg (82 %) of **7v** as an amorphous brown solid. Mp: 143.1-145.1 ºC; IR (neat) $\nu_{max}$ 3517, 3398, 3348, 2925. 2853, 1613, 1501, 1464, 1357, 1303, 1061, 972 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.0 Hz, 3H), 1.26 (bs, 16H), 1.50 (m, 2H), 2.48 (t, *J*=7.7 Hz, 2H), 3.74 (s, 3H), 3.83 (s, 3H), 4.84 (m, 2H), 4.88 (d, *J*=12.5 Hz, 1H), 6.39 (d, *J*=2.3 Hz, 1H), 6.43 (dd, *J*=2.3, 8.6 Hz, 1H), 6.62 (d, *J*=8.6 Hz, 1H), 6.93 (d, *J*=8.6 Hz, 2H), 7.28 (s, 1H), 7.35 (d, J=8.8 Hz, 2H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.6 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 (2 x $CH_2$), 29.7 ($CH_2$), 30.4 (CH), 31.9 ($CH_2$), 55.3 ($CH_3$), 55.4 ($CH_3$), 67.6 ($CH_2$), 102.8 (CH), 107.3 (CH), 107.5 (C), 111.5 (C), 113.9 (CH x 2), 119.3 (C), 119.5 (C), 123.8 (C), 126.0 (CH), 130.0 (CH x 2), 144.8 (C), 151.1 (C), 152.0 (C), 154.8 (C), 159.8 (C), 160.7 (C), 180.2 (C), 183.7 (C); EIMS *m/z* 572 ($M^+$, 1), 452 (3), 336 (14), 296 (17), 145 (100); HREIMS 572.2747 (calcd for $C_{35}H_{40}O_7$ ($M^+$) 572.2774).

*2-hydroxy-10-methoxy-6-(3-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7w**).* Following the general procedure described above, 19.8 mg (0.07 mmol) of embelin, 30 mg (0.10 mmol) of 5-chloro-2-((3-(3-methoxyphenyl)prop-

2-yn-1-yl)oxy)benzaldehyde and 1.2 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^{o}$C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 27.7 mg (72 %) of **7w** as an amorphous brown solid. Mp: 88.2-89.4º C; IR (neat) $\nu_{max}$ 3314, 2924, 2853, 1361, 2338, 1694, 1617, 1500, 1461, 1435, 1347, 1255, 1210, 1160, 1118, 1081, 1029, 930, 838 cm$^{-1}$; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.1 Hz, 3H), 1.25 (bs, 16H), 1.49 (m, 2H), 2.48 (t, *J*=7.6 Hz, 2H), 3.73 (s, 3H), 3.82 (s, 3H), 4.83 (s, 1H), 4.84 (d, *J*=12.1 Hz, 1H), 4.90 (d, *J*=12.7 Hz, 1H), 6.39 (d, *J*=2.5 Hz, 1H), 6.43 (dd, *J*=2.4, 8.5 Hz, 1H), 6.62 (d, *J*=8.7 Hz, 1H), 6.96 (m, 3H), 7.32 (td, *J*=1.4, 7.6 Hz, 1H); $^{13}$C NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.6 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$ x 2), 29.7 ($CH_2$), 30.4 (CH), 31.9 ($CH_2$), 55.3 ($CH_3$), 55.4 ($CH_3$), 67.5 ($CH_2$), 102.8 (CH), 107.3 (CH), 108.7 (C), 111.4 (C), 113.9 (CH), 115.7 (CH), 119.3 (C), 119.4 (C), 121.0 (CH), 126.0 (CH), 129.5 (CH), 132.6 (C), 144.7 (C), 151.1 (C), 151.9 (C), 154.8 (C), 159.6 (C), 159.8 (C), 180.1 (C), 183.6 (C); EIMS *m/z* 572 ($M^+$, 27), 554 (100), 413 (13), 279 (12), 135 (92); HREIMS 572.2761 (calcd for $C_{35}H_{40}O_7$ ($M^+$) 572.2774).

*2-hydroxy-10-methoxy-6-(2-methoxyphenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7x**).* Following the general procedure described above, 24.5 mg (0.08 mmol) of embelin, 40 mg (0.13 mmol) of 5-chloro-2-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.5 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^{o}$C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 23.6 mg (50%) of **7x** as a yellow oil. IR (neat) $\nu_{max}$ 3312, 2924, 2852, 1706, 1600, 1496, 1460, 1437, 1348, 1281, 1248, 1162, 1116, 1019, 933, 834 cm$^{-1}$; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.1 Hz, 3H), 1.25 (bs, 16H), 1.48 (m, 2H), 2.46 (t, *J*=6.9 Hz, 2H), 3.73 (s, 3H), 3.80

(s, 3H), 4.47 (d, *J*=12.6 Hz, 1H), 4.70 (d, *J*=12.6 Hz, 1H), 4.84 (s, 1H), 6.36 (s, 1H), 6.32 (d, *J*=2.0 Hz, 1H), 6.63 (d, *J*=8.0 Hz, 1H), 6.93 (d, *J*=8.3 Hz, 1H), 6.98 (t, *J*=7.5 Hz, 1H), 7.33 (dd, *J*=1.1, 7.3 Hz, 1H), 7.38 (m, 1H); $^{13}$C NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.6 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 (2 x $CH_2$), 29.7 ($CH_2$), 30.3 (CH), 31.9 ($CH_2$), 55.3 ($CH_3$), 55.7 ($CH_3$), 67.9 ($CH_2$), 99.7 (C), 102.6 (CH), 106.9 (CH), 109.9 (C), 111.4 (CH), 119.2 (C), 119.3 (C), 120.3 (C), 120.7 (CH), 126.1 (CH), 131.0 (CH), 131.5 (CH), 141.3 (C), 151.1 (C), 152.4 (C), 155.1 (C), 157.2 (C), 159.7 (C), 180.3 (C), 183.7 (C); EIMS *m/z* 572 ($M^+$, 19), 452 (13), 335 (29), 135 (100); HREIMS 572.2755 (calcd for $C_{35}H_{40}O_7$ ($M^+$) 572.2774).

*2-hydroxy-6-(3-hydroxyphenyl)-10-methoxy-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7y**).* Following the general procedure described above, 27.8 mg (0.09 mmol) of embelin, 40 mg (0.14 mmol) of 5-chloro-2-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.7 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^{o}$C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 40.0 mg (76%) of **7y** as an amorphous brown solid. Mp: 160.2-161.4 ºC; IR (neat) $\nu_{max}$ 3514, 3397, 2923, 2852, 1617, 1500, 1443, 1349, 1154, 1113, 1076, 971 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.1 Hz, 3H), 1.25 (bs, 16H), 1.50 (m, 2H), 2.49 (t, *J*=7.7 Hz, 2H), 3.74 (s, 3H), 4.82 (m, 2H), 4.89 (d, *J*=12.7 Hz, 1H), 5.35 (bs, 1H), 6.39 (s, 1H), 6.44 (dd, *J*=1.8, 8.6 Hz, 1H), 6.61 (d, *J*=8.4 Hz, 1H), 6.88 (m, 2H), 6.93 (d, *J*=7.5 Hz, 1H), 7.24 (m, 1H); $^{13}$C NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 (2 x $CH_2$), 28.1 ($CH_2$), 29.4 (2 x $CH_2$), 29.6 (3 x $CH_2$), 29.7 ($CH_2$), 30.4 (CH), 31.9 ($CH_2$), 55.4 ($CH_3$), 67.5 ($CH_2$), 102.8 (CH), 107.4 (CH), 108.8 (C), 111.5 (C), 115.4 (CH), 116.5 (C), 110.1 (CH), 119.3 (C), 121.0 (CH), 126.0 (CH), 129.7 (CH), 132.7 (C), 144.5 (C), 151.2 (C), 151.9 (C), 154.8

(C), 155.7 (C), 159.8 (C), 180.3 (C), 183.6 (C); EIMS *m/z* 558 ($M^+$, 1), 282 (14), 254 (18), 131 (100); HREIMS 558.2609 (calcd for $C_{34}H_{38}O_7$ ($M^+$) 558.2618).

*2-hydroxy-10-methoxy-6-phenyl-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7z**).* Following the general procedure described above, 36.8 mg (0.13 mmol) of embelin, 50 mg (0.19 mmol) of 5-chloro-2-((3-phenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 2.3 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 62.4 mg (92%) of **7z** as an amorphous brown solid. Mp: 151.0-151.8 ºC; IR (neat) $\nu_{max}$ 3340, 2923, 2853, 2359, 1652, 1615, 1578, 1497, 1444, 1351, 1317, 1253, 1241, 1218, 1157, 1119, 1019, 997, 928, 903, 849 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=6.9 Hz, 3H), 1.26 (bs, 16H), 1.50 (m, 2H), 2.49 (t, *J*=7.4 Hz, 2H), 3.74 (s, 3H), 4.86 (m, 3H), 6.39 (s, 1H), 6.44 (d, *J*=8.0 Hz, 1H), 6.63 (d, *J*=8.2 Hz, 1H), 7.42 (m, 5H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.6 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$ x 2), 29.7 ($CH_2$), 30.4 (CH), 31.9 ($CH_2$), 55.4 ($CH_3$), 67.5 ($CH_2$), 102.8 (CH), 107.3 (CH), 108.5 (C), 111.5 (C), 119.3 (C), 119.4 (C), 126.1 (CH), 128.4 (CH x 2), 128.5 (CH x 2), 129.9 (CH), 131.4 (C), 151.1 (C), 151.9 (C), 154.7 (C), 159.8 (C), 180.2 (C), 183.7 (C); EIMS *m/z* 542 ($M^+$, 100), 528 (22), 402 (33), 262 (40), 249 (58); HREIMS 542.2643 (calcd for $C_{34}H_{38}O_6$ ($M^+$) 542.2668).

*2-hydroxy-10-methoxy-6-(3-nitrophenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7aa**).* Following the general procedure described above, 22.0 mg of embelin (0.08 mmol), 35 mg (0.11 mmol) of 5-chloro-2-((3-nitrophenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 2.3 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 27.2 mg (62%) of **7aa** as an

amorphous brown solid. Mp: 93.3-95.0 ºC; IR (neat) $\nu_{max}$ 3384, 3055, 2927, 2854, 2360, 1655, 1622, 1534, 1502, 1463, 1441, 1350, 1264, 1227, 1191, 1161, 1121, 1098, 1030, 951, 899, 840, 812 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.1 Hz, 3H), 1.25 (bs, 16H), 1.50 (m, 2H), 2.49 (t, *J*=7.5 Hz, 2H), 3.74 (s, 3H), 4.79 (d, *J*=12.5 Hz, 1H), 4.87 (s, 1H), 4.91 (d, *J*=13.0 Hz, 1H), 6.41 (d, *J*=1.9 Hz, 1H), 6.46 (dd, *J*=1.9, 8.3 Hz, 1H), 6.63 (d, *J*=8.5 Hz, 1H), 7.63 (t, *J*=8.1 Hz, 1H), 7.78 (d, *J*=7.7 Hz, 1H), 8.26 (s, 1H), 8.29 (d, *J*=8.3 Hz, 1H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.6 ($CH_2$), 22.7 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.7 (2x$CH_2$), 30.5 (CH), 31.9 ($CH_2$), 55.4 ($CH_3$), 67.0 ($CH_2$), 102.9 (CH), 107.8 (CH), 111.0 (C), 111.6 (C), 119.0 (C), 119.6 (C), 123.5 (CH), 124.6 (CH), 126.1 (CH), 129.8 (CH), 133.1 (C), 134.4 (CH), 132.9 (C), 142.5 (C), 148.2 (C), 151.2 (C), 151.4 (C), 154.6 (C), 159.9 (C), 179.8 (C), 183.5 (C); EIMS *m/z* 587 ($M^+$, 21), 569 (100), 540 (20), 452 (16), 294 (17), 166 (51); HREIMS 587.2530 (calcd for $C_{34}H_{37}O_8N$ ($M^+$) 587.2519).

*2-hydroxy-10-methoxy-6-(3-(trifluoromethyl)phenyl)-3-undecylchromeno[3,4-c]chromene-1,4(7H,12bH)-dione (**7ab**).* Following the general procedure described above, 17.6 mg (0.06 mmol) of embelin, 30 mg (0.09 mmol) of 4-methoxy-2-((3-(3-trifluoromethylphenyl)prop-2-yn-1-yl)oxy)benzaldehyde and 1.1 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^oC$. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 14.0 mg (38%) of **7ab** as a yellow oil. IR (neat) $\nu_{max}$ 3346, 2925, 2854, 2359, 1651, 1618, 1501, 1461, 1440, 1336, 1248, 1221, 1165, 1074, 1030, 909, 838, 808 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.25 (bs, 16H), 1.50 (m, 2H), 2.49 (t, *J*=7.6 Hz, 2H), 3.74 (s, 1H), 4.79 (d, *J*=12.5 Hz, 1H), 4.86 (s, 1H), 4.89 (d, *J*=12.8 Hz, 1H), 6.41 (d, *J*=1.5 Hz, 1H), 6.45 (d, *J*=7.7 Hz, 1H), 6.63 (d, *J*=8.5, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.62 (d, *J*=7.6 Hz, 1H), 7.66 (s, 1H), 7.69 (d, *J*=7.6 Hz, 1H); $^{13}C$ NMR (500

MHz, $CDCl_3$) δ 14.1 ($CH_3$), 22.7 (2 x $CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 ($CH_2$), 29.6 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$), 30.5 (CH), 31.9 ($CH_2$), 55.4 ($CH_3$), 67.1 ($CH_2$), 102.8 (CH), 107.6 (CH), 110.1 (C), 111.6 (C), 119.1 (C), 119.5 (C), 123.5 (C, $J_{C-F}$= 270.8 Hz), 125.4 (CH, $J_{C-F}$=3.8 Hz), 126.1 (CH), 126.6 (CH, $J_{C-F}$=3.5 Hz), 129.2 (CH), 131.2 (C, $J_{C-F}$= 32.3 Hz), 131.9 (CH), 132.2 (C), 143.5 (C), 151.1 (C), 151.6 (C), 154.6 (C), 159.9 (C), 180.0 (C), 183.6 (C); EIMS *m/z* 610 ($M^+$, 100), 469 (24), 453 (17), 317 (29), 172 (32); HREIMS 610.2564 (calcd for $C_{35}H_{37}O_6F_3$ [$M^+$] 610.2542).

*ethyl 11-hydroxy-7-(4-methoxyphenyl)-9,12-dioxo-10-undecyl-6,9,12,12b-tetrahydrochromeno[3,4-c]chromene-3-carboxylate (**7ac**).* Following the general procedure described above, 17.4 mg (0.06 mmol) of embelin, 30 mg (0.10 mmol) of ethyl 4-formyl-3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)benzoate) and 1.1 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 21.1 mg (58%) of **7ac** as a yellow oil; IR (neat) $\nu_{max}$ 3336, 2929, 2858, 2292, 1634, 1588, 1518, 1463, 1442, 1401, 1332, 1242, 1204, 1145, 1095, 1056, 1019, 994, 899, 863, 833 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.1 Hz, 3H), 1.27 (bs, 16H), 1.34 (t, *J*=7.1 Hz, 3H), 1.51 (m, 2H), 2.51 (t, *J*=7.7 Hz, 2H), 3.74 (s, 3H), 3.84 (s, 3H), 4.31 (q, *J*=7.2 Hz, 2H), 4.88 (s, 1H), 4.91 (d, *J*=12.7 Hz, 1H), 4.96 (d, *J*=12.4 Hz, 1H), 6.84 (d, *J*=8.5 Hz, 1H), 6.94 (d, *J*=8.8 Hz, 2H), 7.29 (bs, 1H), 7.34 (d, *J*=8.8 Hz, 2H), 7.44 (t, *J*=1.4 Hz, 1H), 7.28 (s, 1H), 7.84 (dd, *J*=1.6, 8.4 Hz, 1H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 14.0 ($CH_3$), 14.3 ($CH_3$), 22.7 ($CH_2$), 22.8 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.7 (2 x $CH_2$), 31.0 (CH), 31.9 ($CH_2$), 55.4 ($CH_3$), 60.7 ($CH_2$), 68.1 ($CH_2$), 106.4 (C), 111.0 (C), 114.1 (CH x 2), 117.5 (CH), 119.7 (C), 123.4 (C), 123.7 (C), 126.9 (C), 127.7 (CH), 130.03 (CH x 3), 145.7 (C), 151.3 (C), 152.2 (C), 158.1 (C), 161.1 (C), 166.1 (C), 180.0 (C), 183.6 (C); EIMS *m/z*

614 ($M^+$, 67), 586 (16), 473 (9), 321 (20), 135 (100); HREIMS 614.2898 (calcd for $C_{37}H_{42}O_8$ ($M^+$) 614.2880).

*ethyl 11-hydroxy-7-(3-methoxyphenyl)-9,12-dioxo-10-undecyl-6,9,12,12b-tetrahydrochromeno[3,4-c]chromene-3-carboxylate* **(7ad)**. Following the general procedure described above, 17.4 mg (0.06 mmol) of embelin, 30 mg (0.09 mmol) of ethyl 4-formyl-3-((3-(3-methoxyphenyl)prop-2-yn-1-yl)oxy)benzoate and 1.1 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^oC$. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 23.9 mg (66%) of **7ad** as a yellow oil. IR (neat) $\nu_{max}$ 2924, 2854, 1708, 1650, 1609, 1462, 1277, 1249, 1176, 1115, 868, 768, 698 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.1 Hz, 3H), 1.27 (bs, 16H), 1.34 (t, *J*=7.1 Hz, 3H), 1.53 (m, 2H), 2.51 (t, *J*=7.5 Hz, 2H), 3.82 (s, 3H), 4.31 (q, *J*=7.1 Hz, 2H), 4.87 (s, 1H), 4.91 (d, *J*=13.1 Hz, 1H), 4.98 (d, *J*=12.7 Hz, 1H), 6.84 (d, *J*=8.6 Hz, 1H), 6.97 (m, 3H), 7.32 (t, *J*=7.7 Hz, 1H), 7.45 (s, 1H), 7.84 (d, *J*=8.4 Hz, 1H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 14.0 ($CH_3$), 14.3 ($CH_3$), 22.7 ($CH_2$), 22.8 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$ x 2), 31.0 (CH), 31.9 ($CH_2$), 55.5 ($CH_3$), 60.7 ($CH_2$), 68.0 ($CH_2$), 107.7 (C), 111.0 (C), 114.2 (CH), 116.0 (CH), 117.5 (CH), 119.8 (C), 121.1 (CH), 123.5 (C), 126.9 (C), 127.7 (CH), 129.6 (CH), 130.1 (CH), 132.5 (C), 145.7 (C), 151.3 (C), 152.1 (C), 158.1 (C), 159.9 (C), 166.1 (C), 179.9 (C), 183.6 (C); EIMS *m/z* 614 ($M^+$, 18), 584 (13), 459 (5), 377 (14), 350 (12), 135 (100); HREIMS 614.2865 (calcd for $C_{37}H_{42}O_8$ ($M^+$) 614.2880).

*ethyl 11-hydroxy-7-(2-methoxyphenyl)-9,12-dioxo-10-undecyl-6,9,12,12b-tetrahydrochromeno[3,4-c]chromene-3-carboxylate (**7ae**).* Following the general procedure described above, 12.0 mg of embelin (0.04 mmol), 20 mg (0.06 mmol) of ethyl 4-formyl-3-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)benzoate and 0.7 mg of EDDA (10

mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 16.0 mg (67%) of **7ae** as a yellow oil. IR (neat) $\nu_{max}$ 2924, 2854, 1708, 1639, 1609, 1462, 1350, 1277, 1246, 1176, 1115, 1018, 841, 756, 659 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.0 Hz, 3H), 1.27 (bs, 16H), 1.34 (t, *J*=7.1 Hz, 3H), 1.52 (m, 2H), 2.50 (t, *J*=7.6 Hz, 2H), 3.79 (s, 3H), 4.31 (q, *J*=7.2 Hz, 2H), 4.56 (d, *J*=12.3 Hz, 1H), 4.78 (d, *J*=12.3 Hz, 1H), 4.89 (s, 1H), 6.82 (d, *J*=8.7 Hz, 1H), 6.95 (d, *J*=8.7 Hz, 1H), 6.99 (t, *J*=7.6 Hz, 1H), 7.30 (dd, *J*=1.5, 7.6 Hz, 1H), 7.39 (m, 1H), 7.46 (s, 1H), 7.83 (dd, *J*=1.5, 8.6 Hz, 1H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 14.0 ($CH_3$), 14.3 ($CH_3$), 22.7 ($CH_2$), 22.8 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$ x 3), 30.9 (CH), 31.9 ($CH_2$), 55.9 ($CH_3$), 60.7 ($CH_2$), 68.5 ($CH_2$), 109.0 (C), 111.0 (C), 111.8 (CH), 117.3 (CH), 119.6 (C), 120.5 (C), 120.9 (CH), 123.2 (C), 126.8 (C), 127.8 (CH), 130.0 (CH), 131.0 (CH), 131.7 (CH), 142.3 (C), 151.3 (C), 152.6 (C), 157.5 (C), 158.4 (C), 166.2 (C), 180.0 (C), 183.8 (C); EIMS *m/z* 614 ($M^+$, 20), 570 (15), 459 (13), 377 (25), 135 (100); HREIMS 614.2858 (calcd for $C_{37}H_{42}O_8$ ($M^+$) 614.2880).

*ethyl 11-hydroxy-7-(3-hydroxyphenyl)-9,12-dioxo-10-undecyl-6,9,12,12b-tetrahydrochromeno[3,4-c]chromene-3-carboxylate (**7af**).* Following the general procedure described above, 12.1 mg (0.04 mmol) of embelin, 20 mg (0.06 mmol) of ethyl 4-formyl-3-((3-(3-hydroxyphenyl)prop-2-yn-1-yl)oxy)benzoate and 0.8 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 °C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 13.8 mg (56%) of **7af** as a yellow oil; IR (neat) $\nu_{max}$ 3391, 2920, 2854, 1693, 1655, 1624, 1492, 1393, 1354, 1258, 1176, 1115, 960, 872, 825, 764, 660 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.25 (bs, 16H), 1.34 (t, *J*=7.0 Hz, 3H), 1.50 (m, 2H), 2.49 (t, *J*=8.0 Hz, 2H), 4.32 (q, *J*=7.2 Hz, 2H), 4.87 (s,

1H), 4.89 (d, *J*=12.8 Hz, 1H), 4.97 (d, *J*=12.8 Hz, 1H), 6.83 (d, *J*=8.5 Hz, 1H), 6.88 (m, 3H), 7.24 (m, 1H), 7.42 (t, *J*=1.2 Hz, 1H), 7.83 (dd, *J*=1.7, 8.5 Hz, 1H); $^{13}$C NMR (500 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 14.3 ($CH_3$), 22.7 (2 x $CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.7 (2x$CH_2$), 30.8 (CH), 31.9 ($CH_2$), 60.9 ($CH_2$), 67.5 ($CH_2$), 107.4 (C), 110.8 (C), 115.3 (CH), 117.3 (CH), 117.5 (CH), 119.6 (CH), 120.8 (C), 123.1 (C), 126.6 (C), 127.6 (CH), 129.8 (CH), 130.1 (CH), 132.3 (C), 145.3 (C), 151.4 (C), 151.9 (C), 155.9 (C), 157.9 (C), 166.3 (C), 180.2 (C), 183.4 (C); EIMS *m/z* 558 ($M^+$, 1), 282 (14), 254 (18), 131 (100); HREIMS 558.2609 (calcd for $C_{34}H_{38}O_7$ ($M^+$) 558.2618).

*ethyl 11-hydroxy-9,12-dioxo-7-phenyl-10-undecyl-6,9,12,12b-tetrahydrochromeno[3,4-c]chromene-3-carboxylate (**7ag**).* Following the general procedure described above, 19.1 mg (0.04 mmol) of embelin, 30 mg (0.10 mmol) of ethyl 4-formyl-3-((3-(3-phenyl)prop-2-yn-1-yl)oxy)benzoate and 1.2 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^{o}$C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 30.3 mg (80%) of **7ag** as an oil. IR (neat) $\nu_{max}$ 2924, 2845, 1709, 1655, 1620, 1450, 1350, 1288, 2346, 1177, 1115, 1018, 983, 841, 767, 698 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.1 Hz, 3H), 1.28 (bs, 16H), 1.35 (t, *J*=7.1 Hz, 3H), 1.54 (m, 2H), 2.52 (t, *J*=7.8 Hz, 2H), 4.31 (q, *J*=7.0 Hz, 2H), 4.90 (s, 1H), 4.92 (d, *J*=13.2 Hz, 1H), 4.96 (d, *J*=12.4 Hz, 1H), 6.84 (d, *J*=8.5 Hz, 1H), 7.42 (m, 6H), 7.84 (dd, *J*=1.5, 8.5 Hz, 1H); $^{13}$C NMR (500 MHz, $CDCl_3$) δ 14.0 ($CH_3$), 14.3 ($CH_3$), 22.7 ($CH_2$), 22.8 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 (2 x $CH_2$), 29.7 (2 x $CH_2$), 30.0 (CH), 31.9 ($CH_2$), 60.7 ($CH_2$), 68.0 ($CH_2$), 107.5 (C), 111.0 (C), 117.5 (CH), 119.8 (C), 123.5 (C), 126.8 (C), 127.7 (CH), 128.6 (CH x 4), 130.1 (CH x 2), 131.4 (C), 145.9 (C), 151.3 (C), 152.2 (C), 158.0

(C), 166.1 (C), 179.9 (C), 183.6 (C); EIMS *m/z* 584 ($M^+$, 86), 540 (28), 443 (19), 291 (45), 105 (100); HREIMS 584.2747 (calcd for $C_{36}H_{40}O_7$ ($M^+$) 584.2774).

*ethyl 11-hydroxy-7-(3-nitrophenyl)-9,12-dioxo-10-undecyl-6,9,12,12b-tetrahydrochromeno[3,4-c]chromene-3-carboxylate (**7ah**).* Following the general procedure described above, 16.6 mg (0.04 mmol) of embelin, 30 mg (0.085 mmol) of ethyl 4-formyl-3-((3-(3-nitrophenyl)prop-2-yn-1-yl)oxy)benzoate and 1.1 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^oC$. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 28.8 mg (82%) of **7ah** as an oil; IR (neat) $\nu_{max}$ 3379, 2924, 2854, 1709, 1654, 1623, 1531, 1477, 1389, 1288, 1245, 1177, 1119, 1026, 984, 856, 787, 768, 690 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.0 Hz, 3H), 1.27 (bs, 16H), 1.35 (t, *J*=7.1 Hz, 3H), 1.54 (m, 2H), 2.53 (t, *J*=7.8 Hz, 2H), 4.32 (q, *J*=7.2 Hz, 2H), 8.87 (d, *J*=12.8 Hz, 1H), 4.94 (s, 1H), 4.99 (d, *J*=12.8 Hz, 1H), 8.87 (d, *J*=8.6 Hz, 1H), 7.46 (t, *J*=1.5 Hz, 1H), 7.64 (t, *J*=8.2 Hz, 1H), 7.77 (d, *J*=7.8 Hz, 1H), 7.86 (dd, *J*=1.7, 8.5 Hz, 1H), 8.25 (t, *J*=1.7 Hz, 1H), 8.30 (d, *J*=8.4 Hz, 1H); $^{13}C$ NMR (500 MHz, $CDCl_3$) δ 14.0 ($CH_3$), 14.3 ($CH_3$), 22.7 ($CH_2$), 22.8 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.7 (2 x $CH_2$), 31.1 (CH), 31.9 ($CH_2$), 60.8 ($CH_2$), 67.5 ($CH_2$), 109.9 (C), 111.1 (C), 117.6 (CH), 120.1 (C), 123.6 (CH), 123.9 (C), 124.8 (CH), 126.5 (C), 127.7 (CH), 129.9 (CH), 130.3 (CH), 133.0 (C), 134.3 (CH), 143.5 (C), 148.5 (C), 151.3 (C), 151.6 (C), 157.7 (C), 166.0 (C), 179.6 (C), 183.4 (C); EIMS *m/z* 587 ($M^+$, 21), 569 (100), 540 (20), 452 (16), 294 (17), 166 (51); HREIMS 587.2530 (calcd for $C_{34}H_{37}O_8N$ ($M^+$) 587.2519).

*ethyl 11-hydroxy-9,12-dioxo-7-(3-(trifluoromethyl)phenyl)-10-undecyl-6,9,12,12b-tetrahydrochromeno[3,4-c]chromene-3-carboxylate (**7ai**).* Following the general procedure described above, 20.8 mg (0.07 mmol) of embelin, 40 mg (0.11 mmol) of

ethyl 4-formyl-3-((3-(3-trifluoromethylphenyl)prop-2-yn-1-yl)oxy)benzoate and 1.3 mg of EDDA (10 mol %) were suspended in 2 mL of DCE. The reaction mixture was irradiated for 10 min at 120 $^{o}$C. The crude was purified by preparative-TLC with 30% Hex/ EtOAc to provide 28.8 mg (82%) of **7ai** as an oil. IR (neat) $\nu_{max}$ 2928, 2854, 1709, 1639, 1616, 1477, 1335, 1288, 1246, 1169, 1123, 1072, 1026, 987, 910, 845, 810, 767, 698 cm$^{-1}$; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.0 Hz, 3H), 1.35 (t, *J*=7.1 Hz, 3H), 1.27 (bs, 16H), 1.54 (m, 2H), 2.52 (t, *J* = 7.8 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.87 (d, *J* =12.7 Hz, 1H), 4.92 (s, 1H), 4.96 (d, *J* = 13.0 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 7.46 (s, 1H), 7.58 (t, *J* =7.7 Hz, 1H), 7.62 (d, *J* =7.8, 1H), 7.66 (s, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.85 (dd, *J*=1.4, 8.6 Hz, 1H); $^{13}$C NMR (500 MHz, $CDCl_3$) δ 14.0 ($CH_3$), 14.3 ($CH_3$), 22.7 ($CH_2$), 22.8 ($CH_2$), 28.1 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.6 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$ x 2), 31.0 (CH), 31.9 ($CH_2$), 60.8 ($CH_2$), 67.6 ($CH_2$), 109.1 (C), 111.1 (C), 117.6 (CH), 119.6 (C), 123.7 (C, $J_{C\text{-}F}$= 269.7 Hz), 123.8 (C), 125.5 (CH, $J_{C\text{-}F}$=3.6 Hz), 126.6 (C), 126.6 (C), 126.9 (CH, $J_{C\text{-}F}$=3.0 Hz), 127.8 (CH), 129.3 (CH), 130.2 (CH), 131.9 (CH), 132.2 (C), 144.4 (C), 151.4 (C), 151.8 (C), 157.8 (C), 166.0 (C), 179.7 (C), 183.5 (C); EIMS *m/z* 652 ($M^+$, 63), 608 (43), 512 (21), 415 (30), 360 (38), 173 (100); HREIMS 652.2616 (calcd for $C_{37}H_{39}O_7F_3$ ($M^+$) 652.2648).

*11-chloro-6-(4-methoxyphenyl)-3,4,7,12b-tetrahydrochromeno[3,4-c]chromen-1(2H)-one* (**14**). 7.5 mg (0.07 mmol) of 1,3-cyclohexanedione, 30 mg (0.1 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde and 1.2 mg of EDDA (10 mol %) were dissolved in 2 mL of DCE. The reaction mixture was irradiated at 120$^{o}$C for 10 min. The solvent was removed under vacuum and compound **14** (23.2 mg, 87%) was obtained as an amorphous withe solid after purification by preparative-TLC with 30% Hex/EtOAc. Mp: 109.4-110.6 ºC; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 2.15 (m, 2H), 2.58 (m, 2H), 2.62 (m, 1H), 2.74 (m, 1H), 3.83 (s, 3H), 4.66 (s, 1H), 4.81 (d, *J*=12.2 Hz, 1H), 4.84 (d, *J*=

12.4 Hz, 1H), 6.69 (d, *J*=8.6 Hz, 1H), 6.71 (dd, *J*=1.2, 2.6 Hz, 1H), 6.93 (d, *J*= 8.8 Hz, 1H), 7.04 (ddd, *J*= 0.8, 2.6, 8.6 Hz, 1H), 7.28 (d, *J*=8.8 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 20.0 ($CH_2$), 27.9 ($CH_2$), 30.2 (CH), 36.9 ($CH_2$), 55.4 ($CH_3$), 67.9 ($CH_2$), 107.5 (C), 109.8 (C), 113.8 (2 x CH), 118.3 (CH), 124.4 (C), 125.5 (C), 125.7 (CH), 127.5 (CH), 129.8 (2 x CH), 130.2 (C), 144.6 (C), 152.6 (C), 160.5 (C), 168.7 (C), 198.3 (C); EIMS *m/z* 394 ($M^+$, 10), 393 (11), 362 (6), 274 (11), 135 (100); HREIMS 394.0978 (calcd. for $C_{23}H_{19}O_4{}^{35}Cl$ 394.0972), 396.0926 (calcd. for $C_{23}H_{19}O_4{}^{37}Cl$ 396.0942).

*11-chloro-6-(4-methoxyphenyl)-3,3-dimethyl-3,4,7,12b-tetrahydrochromeno[3,4-c]chromen-1(2H)-one* (**15**). 10 mg (0.07 mmol) of dimedone, 20 mg (0.1 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde and 1.2 mg of EDDA (10 mol % mol) were dissolved in 2 mL of DCE. The reaction mixture was irradiated at 120°C for 10 min. The solvent was removed under vacuum and compound **15** (28.6 mg, 94%) was obtained as an amorphous withe solid after purification by preparative-TLC with 30% n-hexanes:AcOEt. Mp: 116.0-117.4 ºC; IR (neat) $\nu_{max}$ 2959, 1678, 1601, 1512, 1477, 1373, 1254, 1169, 1026, 910, 787, 729, 648 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 1H), 1.24 (s, 1H), 2.42 (m, 2H), 2.49 (m, 1H), 2.56 (m, 1H), 3.83 (s, 3H), 4.66 (s, 1H), 4.81 (d, *J*=12.2 Hz, 1H), 4.84 (d, *J*= 12.4 Hz, 1H), 6.69 (d, *J*=8.6 Hz, 1H), 6.71 (dd, *J*=1.2, 2.6 Hz, 1H), 6.92 (d, *J*= 8.8 Hz, 1H), 7.03 (dd, *J*= 2.5, 8.7 Hz, 1H), 7.27 (d, *J*=8.8 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 27.7 ($CH_3$), 29.3 ($CH_3$), 30.3 (CH), 41.5 ($CH_2$), 50.9 ($CH_2$), 55.4 ($CH_3$), 67.9 ($CH_2$), 107.3 (C), 108.7 (C), 113.8 (2 x CH), 118.3 (CH), 124.4 (C), 125.5 (C), 125.8 (CH), 127.5 (CH), 129.7 (CH x 2), 130.6 (C), 144.7 (C), 152.4 (C), 160.4 (C), 166.9 (C), 198.3 (C); EIMS *m/z* 424 ($M^+$, 48), 421 (100), 391 (62), 338 (18), 295 (19), 135 (44); HREIMS 424.1271 (calcd. for $C_{25}H_{23}O_4{}^{37}Cl$ 424.1255), 422.1310 (calcd. for $C_{25}H_{23}O_4{}^{35}Cl$ 422.1285).

*11-chloro-6-(4-methoxyphenyl)-7,12b-dihydrochromeno[4',3':4,5]pyrano[2,3-d]pyrimidine-1,3(2H,4H)-dione* (**16**). 5.6 mg (0.044 mmol) of barbituric acid, 20 mg (0.07 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde and 0.8 mg of EDDA (10% mol) were dissolved in 2 mL of DCE. The reaction mixture was irradiated at 120 $^{o}$C for 10 min. The solvent was removed by filtration and washed with n-hexane. Compound **16** (19.1 mg, 89%) was obtained as a withe solid. Mp: 275.2-277.0 ºC; IR (neat) $\nu_{max}$ 3233, 3113, 2912, 2824, 1690, 1582, 1474, 1373, 1350, 1285, 1027, 1049, 852, 764, 675 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.66 (m, 2H), 4.99 (bs, 1H), 5.02 (d, *J*= 12.2 Hz, 1H), 6.80 (d, *J*=8.6 Hz, 1H), 7.05 (m, 3H), 7.16 (dd, *J*= 2.0, 8.3 Hz, 1H), 7.36 (d, *J*=8.7 Hz, 1H); $^{13}$C-NMR (150 MHz, $CDCl_3$) δ 30.9 (CH), 55.8 ($CH_3$), 67.6 ($CH_2$), 84.3 (C), 107.5 (C), 114.4 (CH x 2), 118.8 (CH), 123.5 (C), 124.6 (C), 126.6 (CH), 128.0 (CH), 130.2 (CH x 2), 143.9 (C), 150.1 (C), 152.8 (C), 155.9 (C), 160.8 (C), 165.3 (C), 172.5 (C); EIMS *m/z* 652 ($M^+$, 63), 608 (43), 512 (21), 415 (30), 360 (38), 173 (100); HREIMS 652.2616 (calcd. for $C_{37}H_{39}O_7F_3$ ($M^+$) 652.2648).

*11-chloro-6-(4-methoxyphenyl)-3-methyl-7,12b-dihydro-1H-pyrano[3',2':5,6]pyrano[3,4-c]chromen-1-one* (**17a**) and *11-chloro-6-(4-methoxyphenyl)-3-methyl-7,12b-dihydro-1H-pyrano[3',4':5,6]pyrano[3,4-c]chromen-1-one* (**17b**). 12 mg (0.07 mmol) of 2-methy-4-hydroxypirone, 30 mg (0.1 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde and 1.2 mg of EDDA (10 mol %) were dissolved in 2 mL of DCE. The reaction mixture was irradiated in a sealed tube at 120$^{o}$C for 10 min. The solvent was removed under vacuum and compound **17a** (19.1 mg, 45%) and **17b** (20.5 mg, 45 %) were obtained as withe solids after purification by preparative-TLC with 40% Hex/EtOAc.

**17a**: Mp: 230.1-232.1 ºC; IR (neat) $\nu_{max}$ 3522, 3402, 1693, 1666, 1601, 1477, 1427, 1246, 1169, 1076, 957, 833, 663 cm$^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 1H), 3.84 (s, 3H), 4.83 (d, *J*=12.4 Hz, 1H), 4.87 (d, *J*= 12.4 Hz, 1H), 4.94 (s, 1H), 6.23 (s, 1H),

6.72 (d, *J*=8.7 Hz, 1H), 6.94 (d, *J*= 8.5 Hz, 2H), 6.97 (s, 1H), 7.07 (d, *J*=8.5 Hz, 1H), 7.32 (d, *J*= 8.4 Hz, 2H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 19.2 ($CH_3$), 32.1 (CH), 55.4 ($CH_3$), 67.5 ($CH_2$), 97.3 (C), 107.9 (C), 113.7 (CH), 113.9 (CH x 2), 118.3 (CH), 123.3 (C), 125.9 (C), 126.2 (CH), 128.0 (CH), 129.1 (C), 129.9 (CH x 2), 144.3 (C), 152.4 (C), 160.8 (C), 161.3 (C), 161.7 (C), 179.9 (C); EIMS *m/z* 408 ($M^+$, 100), 392 (25), 376 (22), 322 (23), 294 (24); HREIMS: 408.0776 (calcd. for $C_{23}H_{17}O_5{}^{35}Cl$ 408.0765), 410.0754 (calcd. for $C_{23}H_{17}O_5{}^{37}Cl$ 410.0754).

**17b**: Mp: 260.4-261.4 ºC; IR (neat) $\nu_{max}$ 3525, 3402, 2839, 1709, 1651, 1589, 1512, 1416, 1300, 1288, 1250, 1238, 1034, 968, 930, 818, 663 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 1H), 3.84 (s, 3H), 4.75 (s, 1H), 4.82 (d, *J*=12.4 Hz, 1H), 4.86 (d, *J*=12.4 Hz, 1H), 5.92 (s, 1H), 6.73 (d, *J*=8.2 Hz, 1H), 6.94 (d, *J*= 8.8 Hz, 2H), 7.07 (m, 2H), 7.29 (d, *J*=8.8 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 20.0 ($CH_3$), 31.1 (CH), 55.4 ($CH_3$), 67.8 ($CH_2$), 96.3 (C), 99.1 (CH), 107.0 (C), 113.9 (CH x 2), 118.4 (CH), 124.0 (C), 125.6 (CH), 125.9 (C), 127.9 (CH), 129.4 (C), 129.8 (CH x 2), 144.5 (C), 152.5 (C), 160.7 (C), 162.2 (C), 162.6 (C), 164.6 (C); EIMS *m/z* 408 ($M^+$, 100), 392 (20), 376 (19), 322 (15), 294 (18); HREIMS: 408.0777 (calcd. for $C_{23}H_{17}O_5{}^{35}Cl$ 408.0765), 410.0754 (calcd. for $C_{23}H_{17}O_5{}^{37}Cl$ 410.0754).

*2-chloro-7-(4-methoxyphenyl)-6H-pyrano[2,3-b:5,4-c']dichromen-14(14bH)-one* **(18a)** and *5-chloro-14-(4-methoxyphenyl)-1H-pyrano[3,2-c:5,4-c']dichromen-7(6bH)-one* (**18b**). 14 mg (0.07 mmol) of 4-hydroxycumarin, 30 mg (0.1 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde and 1.2 mg of EDDA (10 mol %) were dissolved in 2 mL of DCE. The reaction mixture was irradiated at 120ºC for 10 min. The solvent was removed under vacuum and compound **18a** (13.6 mg, 37 %) and **18b** (21.6 mg, 56 %) were obtained as white solids after purification by preparative-TLC with 1% toluene/acetone.

**18a**: Mp: 290.6-292.1 ºC; IR (neat) $\nu_{max}$ 1709, 1612, 1570, 1477, 1423, 1242, 1053, 987, 975, 813, 756, 713, 682 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 3H), 4.88 (d, *J*=12.4 Hz, 1H), 4.95 (d, *J*=12.4 Hz, 1H), 5.10 (s, 1H), 6.75 (d, *J*=8.4 Hz, 1H), 6.95 (s, 1H), 6.97 (d, *J*= 8.8 Hz, 2H), 7.07 (dd, *J*=1.2, 8.4 Hz, 1H), 7.37 (d, *J*=8.9 Hz, 2H), 7.47 (m, 2H), 7.71 (t, *J*=7.3 Hz, 1H), 8.32 (d, *J*=7.4, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 32.5 (CH), 55.4 ($CH_3$), 67.5 ($CH_2$), 94.7 (C), 108.3 (C), 114.0 (2 x CH), 117.4 (CH), 118.3 (CH), 123.2 (C), 123.3 (C), 125.7 (CH), 125.9 (C), 126.1 (CH), 126.3 (CH), 128.0 (CH), 129.4 (C), 129.9 (CH x 2), 133.8 (CH), 144.2 (C), 152.4 (C), 153.1 (C), 160.9 (C), 161.6 (C), 178.1 (C); EIMS *m/z* 444 ([$M^+$], 100), 429 (30), 413 (43), 324 (21), 295 (2); HREIMS 446.0766 (calcd. for $C_{26}H_{17}O_5{}^{37}Cl$ ($M^+$) 446.0735), 444.0753 (calcd. for $C_{26}H_{17}O_5{}^{35}Cl$ ($M^+$) 444.0765).

**18b**: Mp: 293.8-295.1ºC; IR (neat) $\nu_{max}$ 1712, 1608, 1512, 1477, 1377, 1288, 1049, 995, 941, 814, 652 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.89 (d, *J*=12.1 Hz, 1H), 4.90 (s, 1H), 4.95 (d, *J*=12.5 Hz, 1H), 6.76 (d, *J*=8.6 Hz, 1H), 6.99 (d, *J*=8.6 Hz, 2H), 7.04 (s, 1H), 7.08 (dd, *J*=1.7, 8.6 Hz, 1H), 7.32 (t, *J*=7.7 Hz, 1H), 7.41 (d, *J*=8.7 Hz, 2H), 7.44 (d, *J*=8.2 Hz, 1H), 7.62 (t, *J*=7.7, 1H), 7.81 (d, *J*= 7.9 Hz, 1H), 7.81 (d, *J*=7.5 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 31.7 (CH), 55.4 ($CH_3$), 67.9 ($CH_2$), 98.8 (C), 107.1 (C), 109.8 (C), 114.0 (CH x 2), 116.9 (CH), 118.6 (CH), 123.0 (CH), 124.0 (C), 124.4 (CH), 125.4 (CH), 126.0 (C), 128.0 (CH), 129.3 (C), 129.8 (2 x CH), 132.7 (CH), 144.4 (C), 152.5 (C), 153.0 (C), 157.7 (C), 160.8 (C), 162.8 (C); EIMS *m/z* 444 ($M^+$, 100), 429 (28), 413 (41), 324 (20), 295 (13); HREIMS 446.0721 (calcd. for $C_{26}H_{17}O_5{}^{37}Cl$ 446.0735), 444.0791 (calcd. for $C_{26}H_{17}O_5{}^{35}Cl$ 444.0765).

*2-chloro-7-(4-methoxyphenyl)benzo[g]chromeno[3,4-c]chromene-9,14(6H,14bH)-dione (**19a**) and 5-chloro-14-(4-methoxyphenyl)benzo[h]chromeno[3,4-c]chromene-7,8(1H,6bH)-dione* (**19b**). 7.72 mg (0.044 mmol) of 2-hydroxy-1,4-naphtoquinone, 20

mg (0.07 mmol) of 5-chloro-2-(prop-2-yn-1-yloxy)benzaldehyde and 1 mg of EDDA (10 mol %) were dissolved in 2 mL of DCE. The reaction mixture was irradiated at 120°C for 10 min. The solvent was removed under vacuum and compound **19a** (11.1 mg, 55 %) and **19b** (6.1 mg, 31%) were obtained as white solids after purification by preparative-TLC with 1% DCM/MeOH.

**19a**: Mp: 164.2-165.8 ºC; IR $\nu_{max}$ 1680, 1642, 1548, 1258, 1352, 1172, 1076, 1022, 965, 825, 725 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 3.84 (s, 1H), 4.90 (d, *J*=12.4 Hz, 1H), 4.95 (d, *J*=12.8 Hz, 1H), 5.02 (s, 1H), 6.66 (d, *J*=1.4 Hz, 1H), 6.77 (d, *J*=8.6 Hz, 1H), 6.95 (d, *J*=8.8 Hz, 2H), 7.08 (dd, *J*=2.3, 8.7 Hz, 1H), 7.38 (d, *J*=8.6 Hz, 2H), 7.79 (td, *J*=1.2, 7.7 Hz, 1H), 7.83 (td, *J*=1.0, 7.4 Hz, 1H), 8.18 (d, *J*=7.7 Hz, 1H), 8.24 (d, *J*=7.6 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 31.3 (CH), 55.4 ($CH_3$), 67.9 ($CH_2$), 106.5 (C), 113.9 (2 x CH), 117.4 (C), 118.8 (CH), 123.8 (C), 125.3 (CH), 125.8 (C), 126.7 (CH x 2), 128.0 (CH), 129.5 (C), 129.9 (2 x CH), 130.8 (C), 131.6 (C), 133.9 (CH), 134.6 (CH), 144.9 (C), 152.5 (C), 152.6 (C), 160.7 (C), 177.9 (C), 184.8 (C); EIMS *m/z* 456 ($M^+$, 100), 384 (19), 282 (40), 252 (30), 135 (77); HREIMS 458.0738 (calcd. for $C_{27}H_{17}O_5{}^{37}Cl$ 458.0735), 456.0771 (calcd. for $C_{27}H_{17}O_5{}^{35}Cl$ 456.0765).

**19b:** 122.8-124.0 ºC; IR $\nu_{max}$ 1674, 1605, 1512, 1477, 1300, 1250, 1177, 1076, 1026, 983, 818, 717, 671 $cm^{-1}$; $^{1}$H-NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 1H), 4.90 (d, *J*=12.6 Hz, 1H), 4.92 (s, 1H), 4.95 (d, *J*=12.4 Hz, 1H), 6.72 (d, *J*=1.8 Hz, 1H), 6.75 (d, *J*=8.6 Hz, 1H), 7.00 (d, *J*=8.5 Hz, 2H), 7.07 (dd, *J*=2.3, 8.7 Hz, 1H), 7.40 (d, *J*=8.8 Hz, 2H), 7.64 (t, *J*=7.4 Hz, 1H), 7.71 (t, *J*=7.7 Hz, 1H), 7.87 (d, *J*=7.8 Hz, 1H), 8.23 (d, *J*=7.5 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 30.9 (CH), 55.5 ($CH_3$), 67.6 ($CH_2$), 108.2 (C), 110.8 (C), 113.6 (C), 114.6 (CH x 2), 118.6 (CH), 123.8 (C), 124.9 (CH), 125.6 (CH), 126.0 (C), 128.1 (CH), 129.6 (CH), 129.8 (CH x 2), 131.1 (C), 131.9 (CH), 133.3 (C), 135.3 (CH), 144.4 (C), 152.6 (C), 160.2 (C), 160.8 (C), 178.2 (C), 179.8 (C); EIMS *m/z*

456 ($M^+$, 9), 437 (35), 334 (11), 152 (43), 135 (100); HREIMS 458.0750 (calcd. for $C_{27}H_{17}O_5{}^{37}Cl$ 458.0735), 456.0748 (calcd. for $C_{27}H_{17}O_5{}^{35}Cl$ 456.0765).

## ASSOCIATED CONTENT

### Supporting Information.

$^1H$ and $^{13}C$ NMR spectra of compounds **6a-6ai** and **7a-7ai**. HMBC spectrum of compound **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## References

1-Harvey, A.L. *Drug Discov. Today*, **2008**, *13*, 894-900.

2- Patridge, E.; Gareiss, P.; Kinch, M.S.; Hoyer, D. *Drug Discov. Today*, **2016**, *21*, 204-207.

3-(a) Thomson, S.D. Naturally Occurring Quinones IV: Recent Advances , 1997, Chapman&Hall, Thomson Press (India). (b) Ravelo, A.G.; Estévez-Braun, A.; Chávez-

Orellana, H.; Pérez-Sacau, E.; Mesa-Siverio, D. *Curr. Topics. Med. Chem*. **2004**, *4*, 241-265.

4-(a) Tapia-Juárez, M; J. González-Campos, B.; Contreras-Celedón, C.; Corona, D.; Cuevas-Yañez, E.; Chacón-García, L. *RSC Adv.,* **2014**, *4*, 5660–5665. (b) Kitson, R.R.A.; Chang, C-H.; Xiong, R.; Williams, H. E.L.; Davis, A.L.; Lewis, W.; Dehn, D.L.; Siegel, D.; Mark Roe, S.; Prodromou, C.; Ross, D.; Moody, C.J. *Nature Chemistry* **2013**, *5*, 307-314. (c) Hong, Y.; Sengupta, S.; Hur, W.; Sim, T.*J. Med. Chem*. **2015**, *58*, 3739-3750. (d) Stahl, P.; Kissau, L.; Mazitschek, R.; Giannis, A.; Waldmann, H. Angew. *Chem. Int. Ed.* **2002**, *41*, 1174-1178. (e) Stahl, P.; Kissau, L.; Mazitschek, R.; Huwe, A.; Furet, P.; Giannis,A.; Waldmann, H.; *J. Am. Chem. Soc.* **2001**, *123*, 11586-11593. (f) Jiménez-Alonso, S.; Chavez, H.; Estévez-Braun, A.; Ravelo, A.G.; Feresin, G.; Tapia, A. *Tetrahedron* **2008**, *64*, 8938-8942. (g) Jiménez-Alonso, S.; Pérez-Lomas, A.L.; Chavez, H.; Estévez-Braun, A.; Ravelo, A.G.; Gamarro, F.; Castanys, S.; Lopez, M. *J. Med. Chem.* **2008**, *51*, 7132-7143.

5- Feresin, G. E.; Tapia, A.; Sortino, M.; Zacchino, S.; de Arias, A.R.; Inchausti, A.; Yaluff, J.; Rodriguez, G.; Theoduloz, C.; Schmeda-Hirschmann G. *J. Ethnopharmacol.* **2003**, *88*, 241-247.

6- Gupta, G.; Kazmi, I.; Afzal, Muhammad; Upadhyay, Gaurav; Singh, Rajnish; Habtemariam, Solomon. *Phytopharmacology* **2013**, *4*, 87-95.

7- Nigam, N.; Grover, A.; Goyal, S.; Katiyar, S. P.; Bhargava, P.; Wang, P-C.; Sundar, D.; Kaul, S.C.; Wadhwa, R. *PLoS One* **2015**, 10, e0138192/1-e0138192/15.

8- (a) Dhanjal, J.K.; Nigam, N.; Sharma, S.; Chaudhary, A.; Kaul, S. C.; Grover, A.; Wadhwa, R. *BMC Cancer* **2014**, *14*, 775/1-775/12. (b) Zhi-Gang, H.; Zhong-Zhi, T.; Wen-Kai, Z.; Jian-Guo, L. *Inflammation* **2015**, *38*, 527-533.

9- Mahendran, S.; Badami, S.; Ravi, S.; Thippeswamy, B. S.; Veerapur, V. P. British J. Pharm. Res. **2014**, *4*, 2182-2199.

10- Gupta, R.; Sharma, A. K.; Sharma, M. C.; Gupta, R. S. *J. Diabetes* **2012**, *4*, 248-256.

11- Naik, S. R.; Niture, N. T.; Ansari, A. A.; Shah, P.D., *Phytomedicine* **2013**, *20*, 797-804.

12- Deshmukh, P.T.; Gupta, V. B. *J. Asian Nat. Prod. Res.* **2013**, *15*, 158-165.

13- (a) Ravelo, A.G.; Estevez-Braun, A.; Jiménez Alonso, S.; Peña, R.; Machín, F.; Mendez-Alvarez, S. Spanish Patent 2013, ES 2409536 A1 20130626. (b) Pena, R.; Jimenez-Alonso, S.; Feresin, G.; Tapia, A.; Mendez-Alvarez, S.; Machin, F.; Ravelo, A. G.; Estevez-Braun, A. *J. Org. Chem.* **2013**, 78, 7977-7985. (c) Radhakrishnan, N.; Gnanamani, A.; Mandal, A.B. *Biol. Medicine* **2011**, 3, 1-7.

14- Senger, M.R.; Fraga, C.A.M.; Dantas, R.F.; Silva, F.P. *Drug Discov. Today*, **2016**, 1359-6446.

15- Filosa, R.; Peduto, A.; Schaible, A.M.; Krauth, V.; Weinigel, C.; Barz, D.; Petronzi, C.; Bruno, F.; Roviezzo, F.; Spaziano, G.; D'Agostino, B.; De Rosa, M.; Werz, O. *Eur. J. Med. Chemistry* **2015**, *94*, 132-139.

16-Nigam, N.; Grover, A.; Goyal, S.; Katiyar, S.P.; Bhargava, P.; Wang, P-C.; Sundar, D.; Kaul, S. C.; Wadhw. R. *PLoS One* **2015**, *10*, e0138192.

17- Hu, Rong; Zhu, Ke; Li, Yingchun; Yao, Kun; Zhang, Rong; Wang, Huihan; Yang, Wei; Liu, Zhuogang, *Medical Oncology* **2011**, *28*, 1584-1588.

18- Wang, Da-Guang; Sun, Ya-Bin; Ye, Fei; Li, Wei; Kharbuja, Punyaram; Gao, Ling; Zhang, David Y.; Suo, Jian. *Mol. Cell. Biochemistry* **2014**, *386*, 143-152.

19- (a) Heo, J-Y.; Kim, H-J.; Kim, S-M.; Park, K-R.; Park, S-Y.; Kim, S-W; Nam, D-W.; Jang, H-J.; Lee, S-G.; Ahn, K.-S. *Cancer Lett*. **2011**, *308*, 71-80. (b) Avisetti, D.R.; Babu, K. S.; Kalivendi, S. V. *PLoS One* **2014**, *9*, e87050/1-e87050/10.

20- Park, N.; Seok, B.H.; Chun, Y-J. *PLoS One* **2015**, *10*, e0134760/1-e0134760/17.

21-Schaible, A.M.; Traber, H.; Temml, V.; Noha, S.M.; Filosa, R.; Peduto, A.; Weinigel, C.; Barz, D.; Schuster, D.; Werz, O. *Bioch. Pharmacol.* **2013**, *86*, 476-486.

22- Clemonsa, P.A.; Bodycombea, N.E.; Carrinskia, H.A.; Wilsona, J.A.; Shamjia, A.F.; Wagnera, B.K.; Koehlera, A.N.; Schreiber, S.L. *PNAS* **2010**, *107*, 18787-18790.

23- (a) Tarcsay, A.; Keseru, G.M. *J.Med.Chem.* **2013**, *56*, 1789-1795. (b) Yongye, A.B.; Medina-Franco, J.L. *J. Chem. Inform. Mod.* **2012**, *52*, 2454-2461.

24-(a) Tietze L. F. *Domino Reactions: Concepts for Efficient Organic Synthesis*; Wiley-VCH: Weinheim, 2014. (b) Tietze, L.F.; Düfert A. *Modern Tools for the Synthesis of Complex Bioactive Molecules*; Wiley: Hoboken, NJ, 2012. (c) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley VCH: Weinheim, 2006.

25- (a) Jiménez-Alonso, S.; Pérez-Lomas, A. L.; Estévez-Braun, A.; Muñoz-Martinez, F.; Chávez-Orellana, H.; Ravelo, A. G.; Gamarro, F.; Castanys, S. López, M. *J. Med. Chem.* **2008**, *51*, 7132-7143. (b) Jiménez-Alonso, S.; Chávez-Orellana, H.; Estévez-Braun, A.; Ravelo, A. G.; Pérez-Sacau, E.; Machín, F. *J. Med. Chem.* **2008**, *51*, 6761-6772. (c) Pena, R.; Martin, P.; Feresin, G.E.; Tapia, A.; Machin, F.; Estevez-Braun, A. *J. Nat. Prod.* **2016**, *79*, 970-977. (d) McNaughton Smith, G.; Estevez Braun, A.; Jimenez Alonso, S.; Gutierrez Ravelo, A.; Fernandez-Perez, L.; Diaz Chico, Bonifacio Nicolas PCT Int. Appl. (2014), WO 2014016314 A1 20140130.

26-(a) Yamamoto, Y. *J. Org. Chem*, **2007**, *72*, 7817-7831 and references cited therein. (b) Gouverneur, V.; Reiter, M. *Chem. Eur. J.* **2005**, *11*, 5806-5815

27-(a) Khoshkholgh, M.J.; Balalaie, S.; Bijanzadeh, H.R.; Gross, J. H. *Arkivoc*, **2009**, *ix*, 114-121. (b) Mollazadeh, M.; Khoshkholgh, M.J.; Balalaie, S.; Rominger, F.; Bijanzadeh, H. R. *J. Heterocycl. Chem.* **2010**, *47*,1200-1208. (c)

Khoshkholgh, M.J.; Lofti, M.; Balalaie, S.; Rominger, F. *Tetrahedron* **2009**, *65*, 4228-4234.

28-Balalaie, S.; Azizian, J.; Shameli, A; Bijanzadeh, H. R. *J. Iran. Chem. Soc.* **2015**, *12*, 631-637.

29- Balalaie, S.; Poursaeed, A.; Malihe, J. K.; Bijanzadeh, H. R.; Wolf, E. *C.R. Chimie*, **2012**, *15*, 283-289.

30- Parmar, N.J.; Pansuriya, B.R.; Labana, B.M.; Sutariya, T.R.; Kant, R.; Gupta V. K. *Eur. J. Org. Chem* **2012**, 5953-5964.

31-Biswas, P.; Ghosh, J.; Bandyopadhyay, C. *Tetrahedron Lett.* **2014**, *55*, 6882-6886.

32-Sutariya, T.R.; Labana, B.M.; Parmar, B.D.; Parmar, N.J.; Kantb, R.; Gupta, V.K. *RSC Adv*., **2015**, *5*, 23519-23529.

33-Majumdar, K. C.; Abu, T.; Kumar, N.R. *Tetrahedron* **2012**, *68*, 5693-5718.

34-(a) Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 5970-5971.

(b) Perez-Serrano, L.; Blanco-Urgoiti, J.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *J. Org. Chem.* **2000**, *65*, 3513-3519.

35-Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2016**, *81*, 3275-3285.

36-Perrin, D. D.; Amarego, W. L. F. Purification of Laboratory Chemicals, 3rd ed.; Pergamon Press: Oxford, 1988.

37-Biju, A.T.; Wurz, N.E.; Glorius, F. *J.A.C.S* **2010**, *132*, 5970-5971.

38-Gai, R.; Prochnow, T.; Back, D. F.; Zeni, G. *Tetrahedron* **2014**, *70*, 3751-3756.

39-Rhee, J.U.; Krishe, M. J. *Org. Lett.* **2005**, *7*, 2493-2495.